UNIVERSIDAD DE GRANADA

DEPARTAMENTO DE QUÍMICA ORGÁNICA

Programa de Doctorado en Química

Tesis Doctoral

Síntesis biomimética de diterpenos policíclicos

Presentada por:

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2021

Editor: Universidad de Granada. Tesis Doctorales
Autor: Álvaro Adrián Pérez Rodríguez
ISBN: 978-84-1117-201-1
URI: http://hdl.handle.net/10481/72326

AGRADECIMIENTOS

En este camino recorrido ya, miro hacia atrás y veo todo lo que he aprendido, los buenos momentos, las dificultades, los cambios. Son muchas las personas que han participado de manera directa o indirecta, pero siempre constructiva, en la culminación de este trabajo.

A mis directores Alejandro Fernández Barrero y José Francisco Quílez del Moral. He tenido mucha suerte al poder contar con vuestro conocimiento, alegría, paciencia y amistad. Cuando entré por primera vez en el despacho de Alejandro sentí que este era mi camino y no me he equivocado. Sois unas grandísimas personas y os doy las gracias por todos estos años.

A Pilar Arteaga Burón por tratarme como una segunda madre, por su cariño y amistad.

A María del Mar Herrador del Pino por todos sus buenos consejos y ayuda prestados durante mi estancia en el laboratorio.

A Azucena González Coloma y María Fe de Andrés por ayudarme y acogerme.

A mis compañeros de Madrid por su simpatía y acogerme como a uno más desde el primer momento que llevé una caja de Maritoñis. Y a Jorge por seguir acompañándome desde Colombia.

Al Dr./Guardia civil Alexis Castillo Rodríguez, por su ayuda, amistad y locura musical en los primeros años de la tesis.

A Alí Haïdour, a Irene y Antonio por su amabilidad, simpatía y ayuda con la resonancia magnética nuclear.

A Alberto Galisteo, por ser el jefe.

Al futuro Premio Nobel Juan Eduardo Martín González.

A todos mis compañeros de laboratorio que me han ayudado y me han hecho sentir integrado desde el primer momento, con alegría y buen humor.

A mi familia, porque no se puede tener una familia mejor en esta vida, apoyándome, animándome, protegiéndome, queriéndome. Sois los mejores.

A mis amigos, que son muchos y muy buenos.

A Carmen Aguirre, por guiarme sobre sus pasos, cuidarme y mantenerme cuando ya no tenía fuerzas y darme todo su amor en este camino de aprendizaje que es la vida.

Al profesor Juan Manuel Amaro-Luis por su colaboración en el aislamiento y purificación de los ácidos ent-kaurenoicos.

Esta tesis es parte del proyecto de I+D+i PID2019-106222RB-C32 "Optimización de Bioproductos: Obtención, Diversidad Molecular y Relaciones Estructura-Actividad". Referencia del proyecto, financiado por MCIN/ AEI/10.13039/501100011033/

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Abreviaturas

Abreviatura	***Descripción***
ADN	*Ácido desoxirribonucleico*
Ac.	*Acetil*
Acac.	*Acetilacetonil*
AIBN	*2, 2’-Azobisisobutironitrilo*
AMCPB	*Ácido m-cloroperbenzoico*
ARN	*Ácido ribonucleico*
Bn.	*Bencil*
Bu.	*Butil*
Bz.	*Benzoil*
CAN	*Nitrato de Amonio y Cerio*
Cat.	*Catalítica*
Cp.	*Ciclopentadienil*
DBU	*1,8-Diazabiciclo[5.4.0]undec-7-eno*
DCM	*Diclorometano*
DET	*(+)-Dietiltartrato*
DFT	*Teoría del funcional de la densidad*
DIBALH	*Hidruro de diisobutilaluminio*
DME	*1,2-dimetoxietano*
DMF	*N, N- Dimetilformamida*
DMSO	*Dimetilsulfóxido*

Abreviatura	***Descripción***
Et.	*Etil*
FabF	*β-cetoacil-ACP sintasa*
FAS	*Fatty acid Synthase*
GeGeOH	*Geranilgeraniol*
GeGePP	*Geranil geranil difosfato*
IC	*Concentración inhibitoria*
iPrCN	*Isopropil cianida*
Kcal	*Kilocaloría*
LA	*Ácido de Lewis*
LAH	*Hidruro de aluminio y litio*
LDA	*Diisopropilamida de litio*
LTA	*Tetracetato de plomo*
m-CPBA	*Ácido m-cloroperbenzoico*
MOM	*Metoximetiléter*
MsCl	*Cloruro de metansulfonilo*
Mtb	*Mycobacterium tuberculosis*
MTBE	*Metil tert-butil éter*
NCS	*N-clorosuccinimida*
Nm.	*Nanómetro*
OMS	*Organización Mundial de la Salud*

Abreviatura	*Descripción*
Otf.	*Triflato*
PDC	*Dicromato de piridinio*
PET	*Éter de petróleo*
Ph.	*Fenilo*
Ptm.	*Platensimicina*
p-TsOH	*Ácido p-toluenosulfónico*
Py	*Piridina*
S_N2	*Sustitución nucleofílica*
Sp.	*Especies*
SPIT	*Triisopropilsilano*
Ta.	*Temperatura ambiente*
TBAF	*Fluoruro de tetra-n-butilamonio*
TBDMS	*t-Butidimetilsilil*
TES	*Trietilsilano*
TFA	*Ácido trifluoroacetico*
THF	*Tetrahidrofurano*
TMS	*Tetrametilsilano*
UV	*Ultra violeta*

1 *Sintones Homoquirales y Ciclaciones Biomiméticas en la Síntesis de Terpenos Bioactivos.*

En la Introducción de la Memoria se recoge una visión general de algunas de las estrategias más empleadas en la síntesis química de terpenos bioactivos. Se comenzará con un breve recorrido sobre el uso de sintones terpénicos en la síntesis de productos naturales más complejos, describiendo sus posibilidades, ventajas y aplicaciones. Seguidamente se comentarán estrategias usadas en síntesis biomiméticas de productos naturales cíclicos, haciendo una pequeña revisión de aquellas que incluyen ciclaciones y/o reordenamientos. En cada caso se mostrarán, como ejemplo, parte de los trabajos realizados por el grupo de investigación FQM340 "Biotecnología de hongos y síntesis de moléculas bioactivas" perteneciente a la Universidad de Granada en cuyo seno se ha realizado este trabajo.

1.1 Utilización de sintones homoquirales.

I. Generalidades.

Hoy día los terpenos naturales juegan un importante papel en el mundo, impactando en muchos aspectos de nuestra vida. Saborizantes, perfumes, insecticidas o medicamentos, son algunos de los muchos usos que se le dan a este tipo de moléculas[1,2]. En los últimos 50 años el uso de terpenos homoquirales como material de partida ha permitido la síntesis parcial eficaz de compuestos terpénicos más complejos, algunos con importantes aplicaciones como consecuencia de sus bioactividades[3]. Su bajo precio en ocasiones, la posibilidad de encontrarlos en grandes proporciones en materiales renovables dentro de la naturaleza, incluso revalorizando subproductos agroindustriales y su empleo como módulos de ensamblaje quiral, son sus principales ventajas.

Se conocen numerosos terpenos que se han usado como producto de partida en la síntesis parcial de productos bioactivos. Algunos de los más empleados[4] están representados en figura 1.

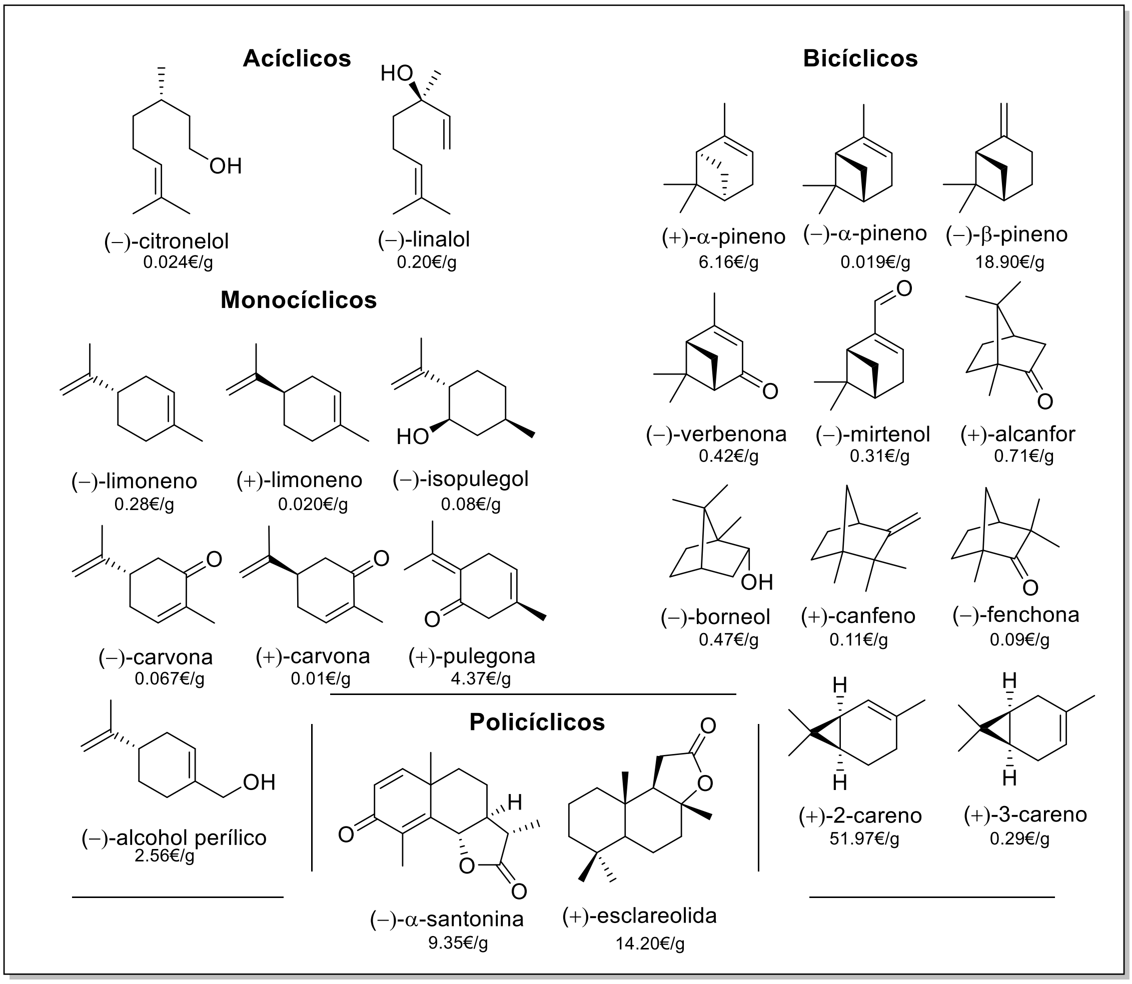


Figura 1. Sintones homoquirales más utilizados en síntesis.

Todos ellos representan bloques de construcción económicos, con una alta disponibilidad, y plasticidad en el uso, pudiéndose incluso sintetizar unos a partir de otros. Como ejemplo, dentro del grupo de los monoterpenos acíclicos, (−)-citronelol se puede transformar mediante oxidación en citronelal y este por ciclación en (−)-isopulegol, dos derivados muy utilizados en síntesis[5]. Los compuestos monoterpénicos monocíclicos son ampliamente utilizados en la síntesis de terpenos policíclicos, siendo la carvona uno de los más usados por su versatilidad. Cabe destacar α-pineno de entre los sintones bicíclicos más utilizados con fines sintéticos, siendo también uno de los más baratos.

Por otra parte, Maimone[4], en 2017 hace una clasificación de sintones quirales terpénicos, utilizados como productos de partida en la síntesis de compuestos más elaborados. Para ello, propone una clasificación en tres niveles, variando cada nivel en función de la similitud del producto de partida con la molécula objetivo de síntesis. Así pues, se engloban en un primer nivel aquellos sintones que se reconocen fácilmente dentro de la estructura final deseada, es decir, todo el esqueleto de carbono del terpeno de partida se puede reconocer ininterrumpidamente dentro del producto a sintetizar. La síntesis de eleutherobin a partir del producto natural (–)-α-felandreno[6] puede servirnos de ejemplo para ilustrar esta primera clase, puesto que se detecta claramente la estructura del producto natural de partida (figura 2). En el segundo nivel, encontramos una coincidencia parcial entre el terpeno inicial y el objetivo. Por ejemplo, la síntesis del anticancerígeno β-elemeno de Barrero y colaboradores no contiene la estructura terpenica ininterrumpida de la germacrona, pero se puede distinguir fácilmente la estructura principal de esta[7]. Por último, en las síntesis de nivel 3, la configuración estructural del producto final cambia considerablemente en comparación con la estructura del producto de partida. En este caso y debido a su dificultad, se requiere de un amplio conocimiento en química de terpenos para la comparación estructural. Un ejemplo de este tipo sería la síntesis total del taxol, uno de los productos con más repercusión del siglo XX, a partir del producto natural (–)-verbenona[4] (figura 2).

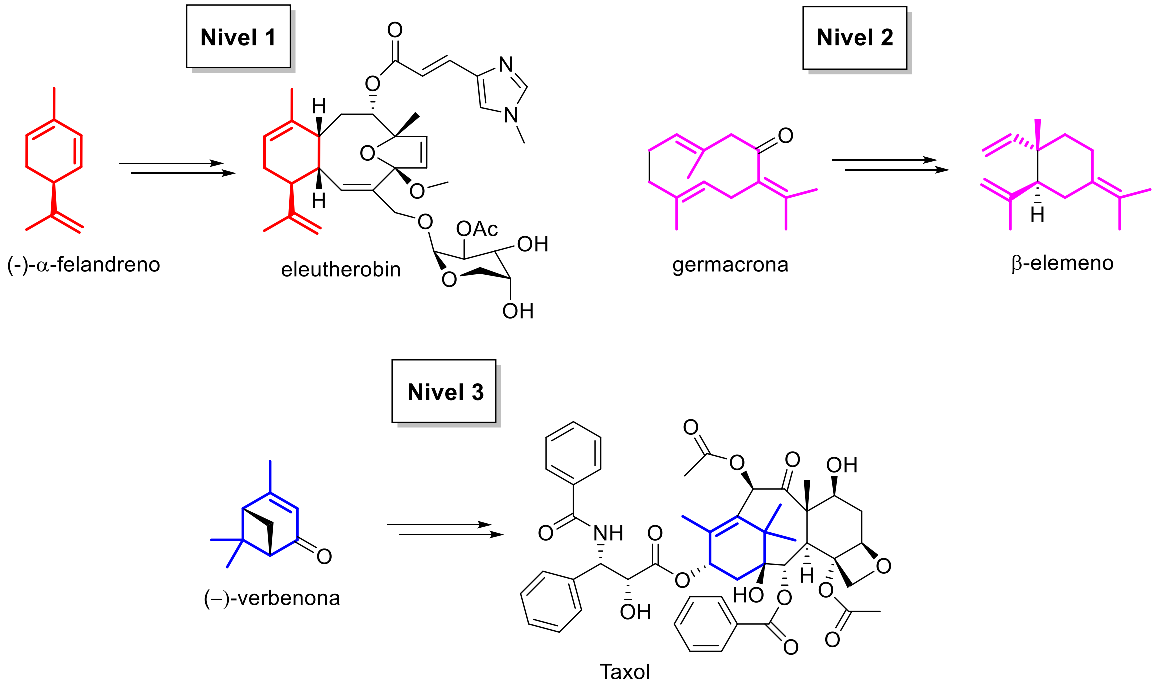


Figura 2. Niveles de clasificación en síntesis en función de la similitud del producto de partida con la molécula objetivo de síntesis.

Para dar idea de la versatilidad de esta estrategia sintética, comentaremos a modo de ejemplo el caso del uso de la carvona como uno de los sintones homoquirales más utilizados en síntesis. Este monoterpeno se encuentra en gran cantidad de aceites esenciales, sobre todo en las semillas de la planta alcaravea (*Carum carvi*), la hierbabuena (*Mentha spicata*) y el eneldo (*Anethum graveolens*). Disponible comercialmente desde 0.011€ hasta 0.067€ el gramo de producto según el enantiómero en Sigma Aldrich, son muchas las síntesis descritas a partir de este producto natural. Así podríamos destacar, la síntesis de (+)-cubiteno, un compuesto que posee un anillo de 12 miembros, descrita por Lindel et al. en 2012[8], la de (+)-crotoforbolona realizada por el grupo de Inoue en 2015[9]; o la del potente antibiótico (–)-platensimicina descrita por Nicolaou[10] y colaboradores en 2008 o por Ghosh y Xi[11], usando el mismo producto de partida, en 2009 (Figura 3).

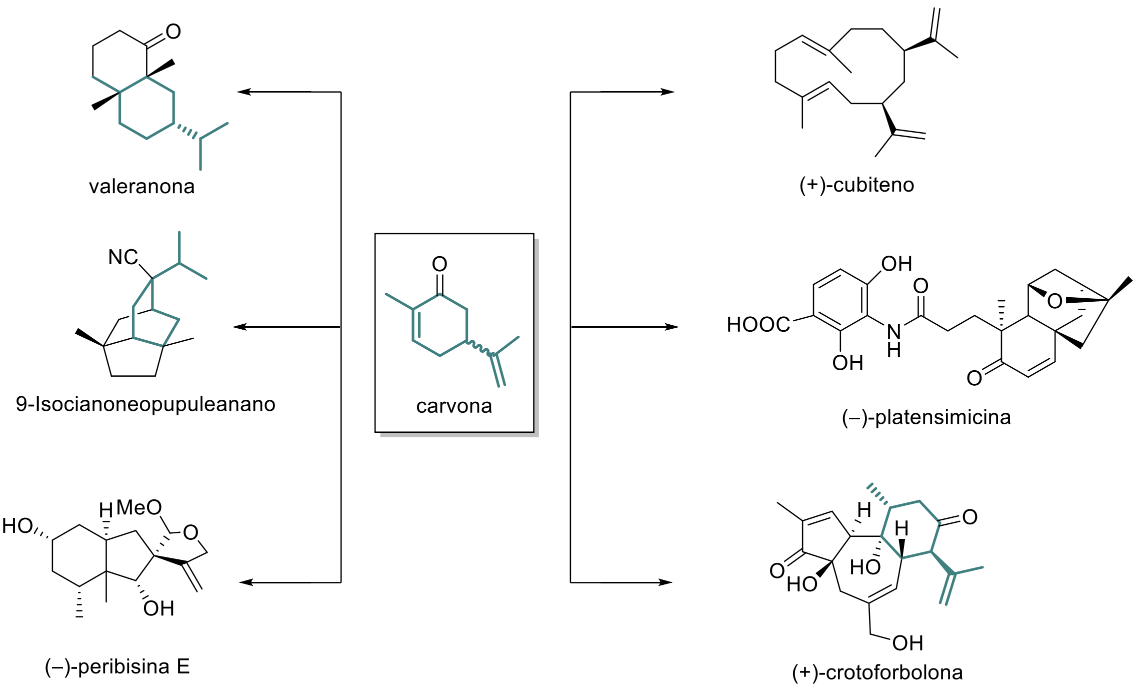


Figura 3. Ejemplos de síntesis utilizando carvona como producto de partida.

Otro ejemplo de sintón quiral usado como producto de partida de otras sustancias naturales más complejas, es (–)-isopulegol. Se encuentra desde los 8 céntimos de euro por gramo de producto en Aldrich. Este precursor de mentol, lo podemos encontrar en plantas como el eucaplipto, especies de menta o el cannabis. En 2013 el grupo de Metz[12] describió un procedimiento para sintetizar (–)-englerina A a partir del producto quiral (–)-isopulegol en 14 pasos. Otras síntesis destacadas a partir de este producto natural serían la síntesis de artemisinina[13] descrita por Schmid et al. en 1983, las síntesis de *seco*-pseudopteroxazol, (+)-Ileabetoxazol y pseudopteroxazol por el grupo de Li[14] en 2016, las síntesis de (+)-hernandulcina[15] por Cheon y colaboradores (2002), (+)-laurenditerpenol[16] por Chittiboyina et al. en 2013 y la de leubetanol[17] por el grupo de Lu en 2013 (Figura 4).

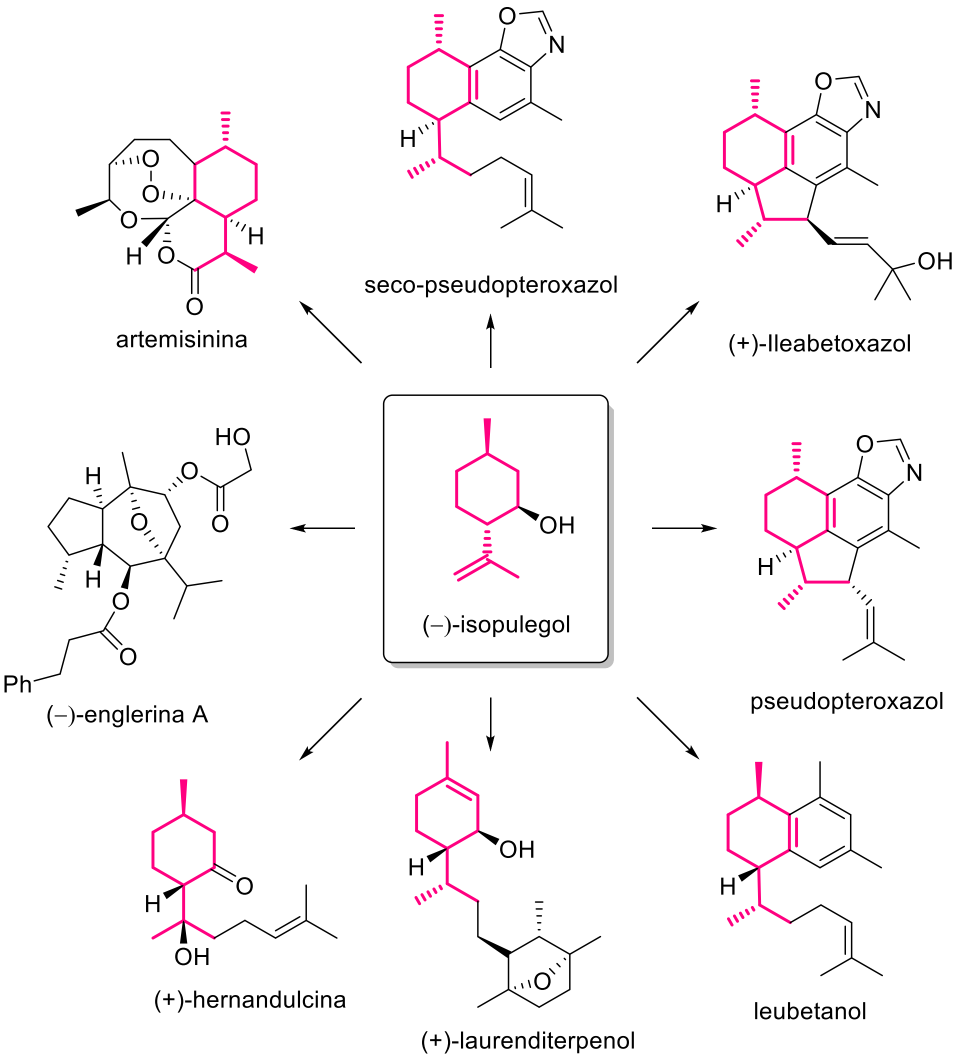


Figura 4. Ejemplos de productos naturales sintetizados desde isopulegol.

II. Aportaciones del grupo de investigación FQM 340:

En el grupo de investigación FQM 340 Biotecnología de hongos y moléculas bioactivas de la Universidad de Granada, se llevan estudiando y utilizando sintones terpénicos quirales y no quirales para el desarrollo de síntesis eficientes desde su fundación. Fruto de ello, se han realizado numerosas aportaciones en materia de artículos, libros y otras comunicaciones científicas en Congresos. Los trabajos realizados partiendo de terpenos homoquirales comienzan en su mayoría, con la extracción y purificación del producto natural de partida desde su fuente natural. Algunos de los más relevantes los encontramos descritos a continuación:

En 2015 Barrero y colaboradores publicaron la síntesis de productos naturales que comparten un núcleo común de dihidro-γ-ionona[18]. En dicha comunicación se describe las síntesis enantioselectivas de los merosesquiterpenos: siccanocromeno F, metacrominas U y V, las síntesis formales de la ambreina, fenazinomicina y la (–)-siccanina (Figuras 5–7). Todas ellas parten del producto natural (+)-3,4-dihidro-γ-ionona obtenido a partir de la degradación oxidativa del trixagol extraído de la planta *Bellardia trixago*[19,20]. El proceso desde 1kg de planta permite obtener 9.2 g de (+)-3,4-dihidro-γ-ionona.

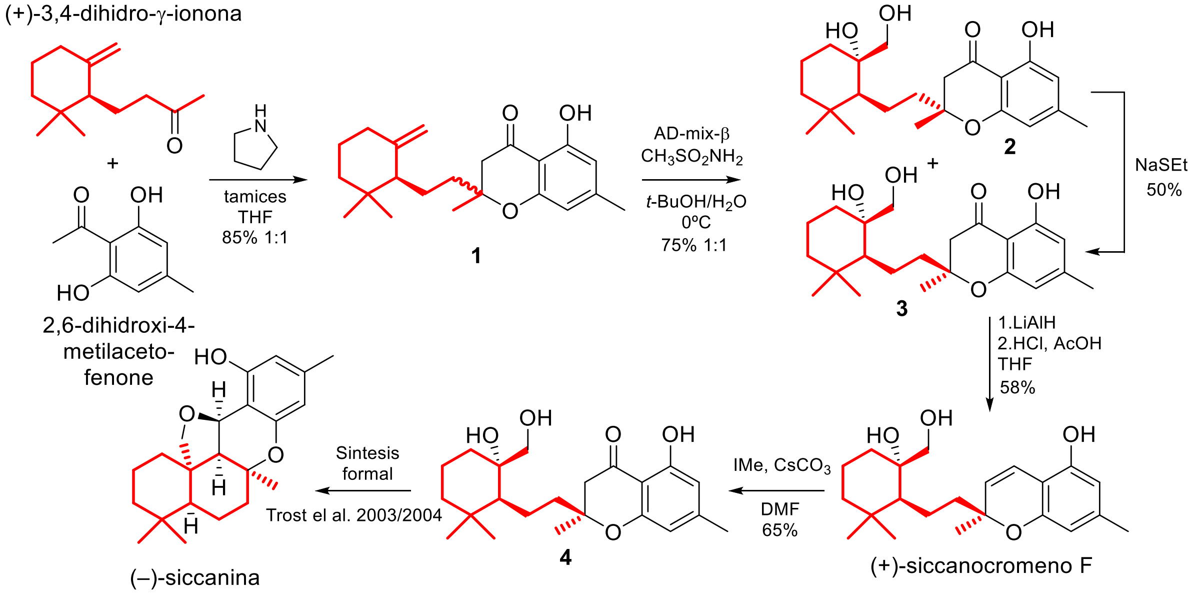


Figura 5. Síntesis de (+)-siccanocromeno F y síntesis formal de (–)-siccanina.

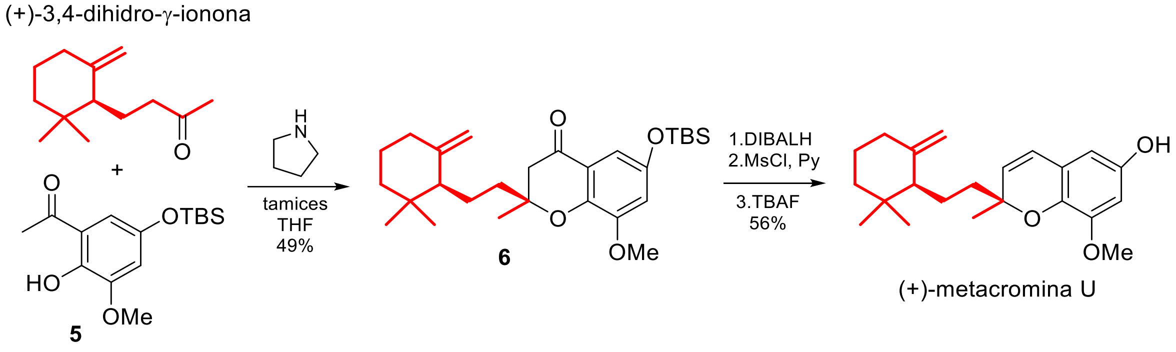


Figura 6. Síntesis de metacromina U.

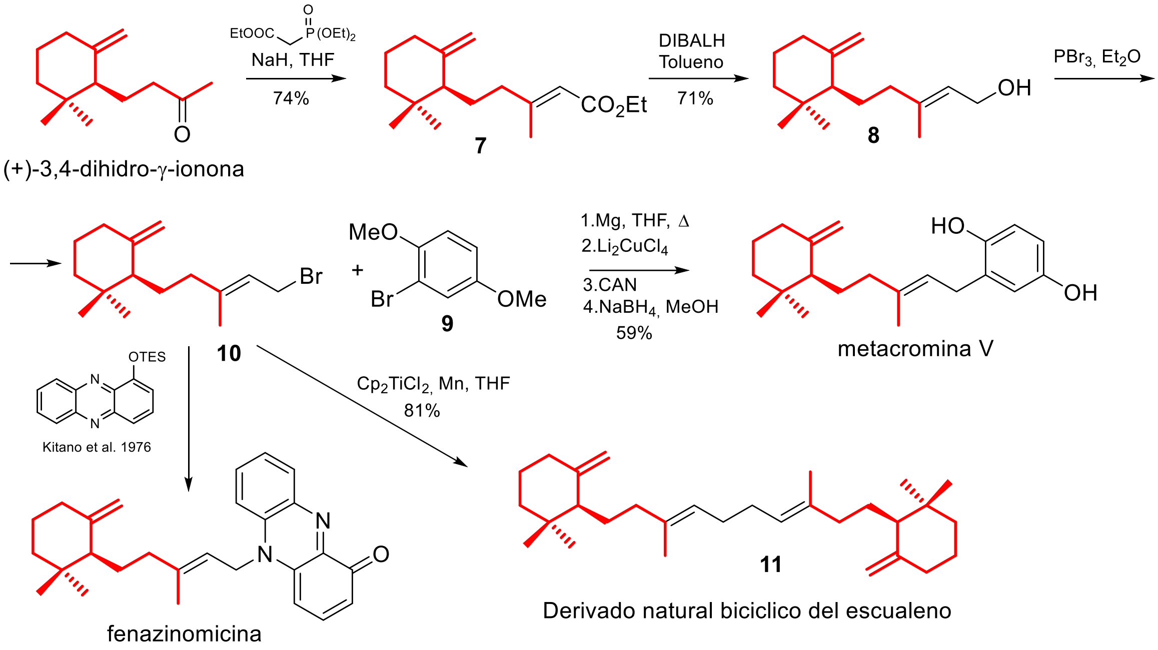


Figura 7. Síntesis de metacromina V, síntesis formal de fenacinomicina y derivado bicíclico natural del escualeno.

La síntesis formal de ambreina supuso una doble utilización de sintones homoquirales (Figura 8). Haciendo un trabajo de síntesis paralelas, utilizando por un lado, el producto natural esclareol obtenido del extracto de la planta *Salvia scl*area y por otro la (+)-3,4-dihidro-γ-ionona, preparada desde trixagol de la planta *Bellardia trixago*, se obtuvieron dos intermediarios iniciadores de la síntesis formal de la ambreina por el procedimiento descrito por Mori y Tamura en 1990[21].

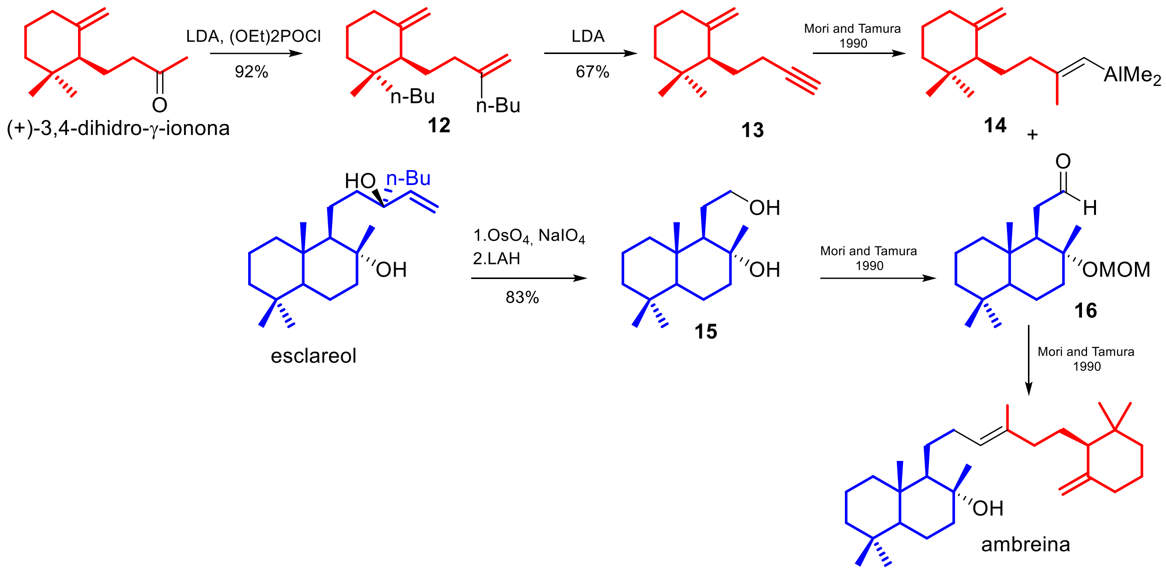


Figura 8. Síntesis formal de ambreina, utilizando (+)-3,4-dihidro-γ-ionona y esclareol.

Por último, otro ejemplo relevante es la puesta a punto de la síntesis de terpenos con anillo de furano en un solo paso, partiendo de productos naturales como la (+)-pulegona o la germacrona[22]. Esta estrategia ha supuesto la síntesis de terpenos con potente bioactividad en pocos pasos y buenos rendimientos. El uso de I_2 en dimetil sulfóxido interviene en la transformación de las α-isopropilidencetonas en anillos de furano siguiendo un enfoque biomimético. Así pues, se ha podido realizar la síntesis del monoterpeno (+)-mentofurano, un producto natural encontrado en diferentes especies de menta como *Mentha piperita* o *Mentha pulegium* con actividades antifúngicas y hepatotóxicas (Figura 9). También se han sintetizado, el sesquiterpeno curzereno presente en las raíces de la cúrcuma y con actividad antioxidante y antitumoral, atractilon e isoatractilon dos compuestos naturales con excelentes bioactividades y el producto natural linderazuleno, un pigmento natural con valor como inmunomodulador y antifúngico (Figura 10).

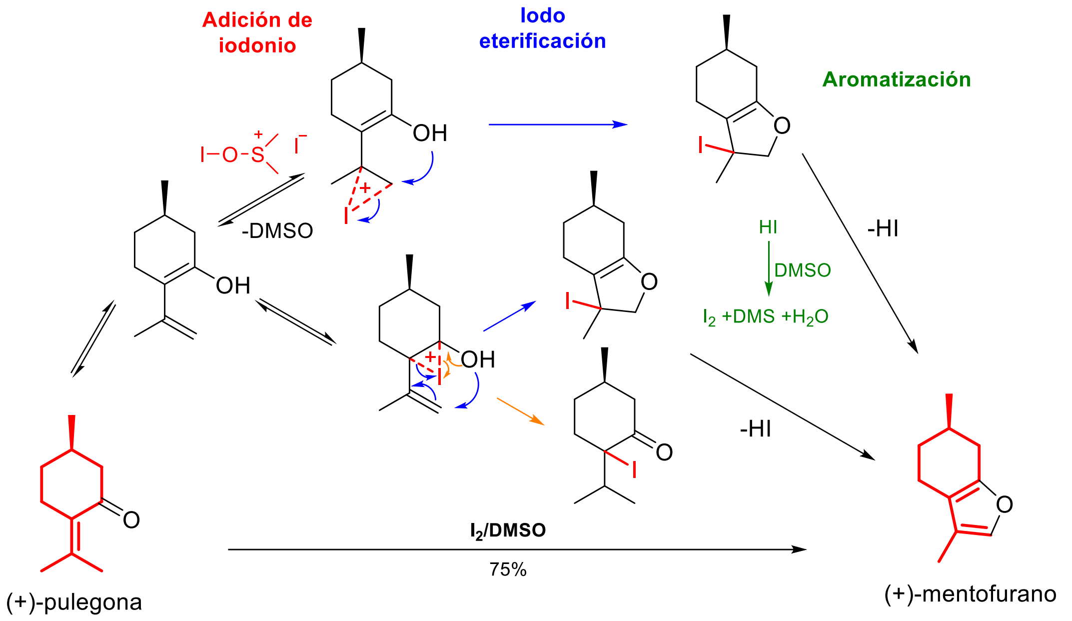


Figura 9. Síntesis y mecanismo de acción de (+)-mentofurano.

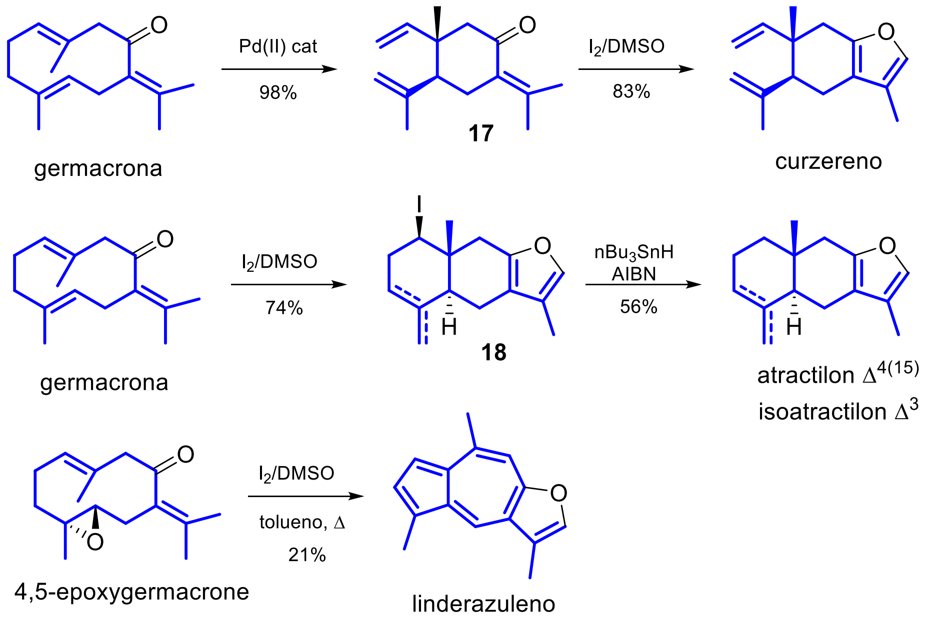


Figura 10. Síntesis de los productos naturales curzereno, atractilon e isoatractilon y linderazuleno, partiendo del producto natural germacrona.

1.2 Ciclaciones biomiméticas en Terpenos:

I. Introducción.

La diversidad que encuentra la naturaleza para producir moléculas complejas es fuente de inspiración para las estrategias de síntesis con enfoque biomimético. Las primeras síntesis biomiméticas datan de principios del siglo XX, con la preparación de compuestos fenólicos y alcaloides por Collie y Robinson[23]. Las estrategias biomiméticas permiten la construcción de productos naturales complejos en un mínimo de pasos, inspirándose en los procesos biosintéticos realizados por las enzimas presentes en la naturaleza. Este tipo de estrategias se han podido desarrollar gracias a una unión y enriquecimiento bidireccional entre los estudios anabólicos y los conocimientos en síntesis orgánica. En este sentido, los estudios de síntesis orgánica también contribuyen a confirmar o invalidar los mecanismos propuestos biosintéticamente que conducen a los esqueletos de las sustancias naturales generadas.

De entre las enzimas terpeno-sintasas encargadas de la biosíntesis de terpenos, aquellas que dan lugar a la formación de ciclos poseen una gran importancia. Esto es debido a que funcionan controlando la regio y estereoselectividad del proceso de cierre de ciclos. Estas ciclasas, actúan generando carbocationes, que desencadenan "procesos en cascada" que producen poli ciclaciones y en algunos casos reordenamientos tipo Wagner-Meerwein[24–26]. En la figura 11 pueden verse la actuación de ciclasas en biosíntesis de triterpenos a partir de escualeno[27].

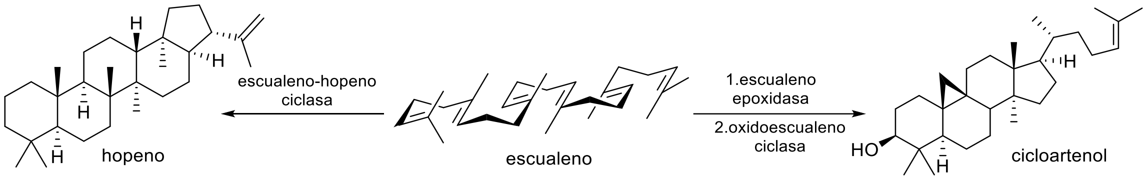


Figura 11. Esquema general de la biosíntesis de esteroides partiendo del escualeno.

El número de síntesis que incluyen reacciones biomiméticas se ha acrecentado en los últimos tiempos, demostrando el poder de estos enfoques dentro de la química contemporánea.

II. Ciclaciones catiónicas.

En la síntesis de terpenos, cabe resaltar dos variantes que tratan de imitar la acción de las terpenociclasas: las denominadas ciclaciones catiónicas y las ciclaciones radicalarias. Las ciclaciones catiónicas se basan en la generación de un carbocatión en el producto de partida poliprénico acíclico que evoluciona originando procesos de ciclación por interacción de este carbocatión con los dobles enlaces. Estos cationes pueden evolucionar hasta una olefina por desprotonación, o pueden derivar hacia alcoholes u otras estructuras en medios acuosos o nucleofílicos. La formación del carbocatión, que inicia el proceso de ciclación, puede realizarse sobre un doble enlace del polipreno o alguno de sus derivados oxidados (epóxidos o alcoholes). Las ciclaciones subsiguientes tendrán un carácter similar una vez generado el carbocatión (Figura 12).

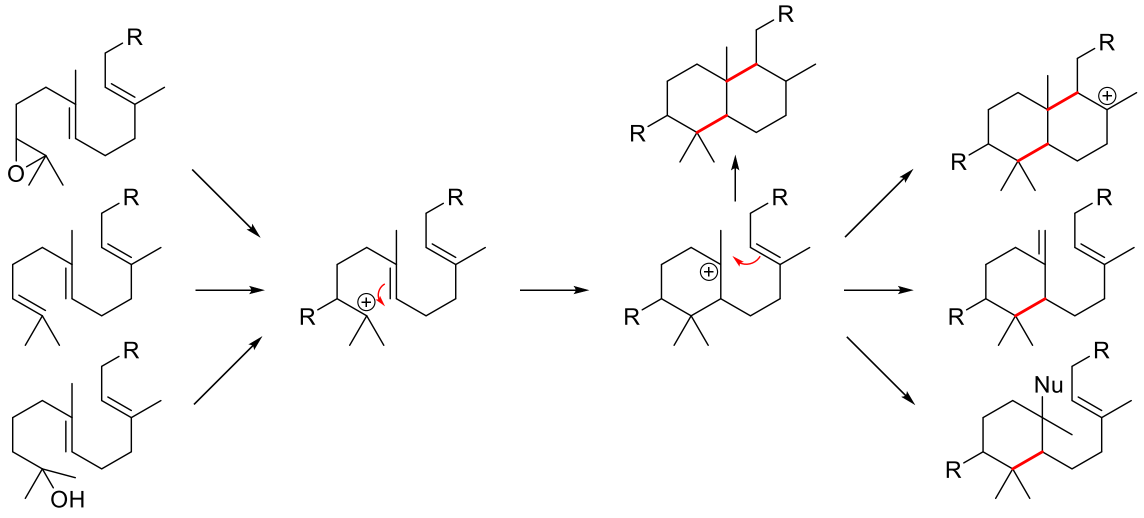


Figura 12. Mecanismo de acción de las ciclaciones catiónicas.

Es conocido que el (*S*)-2,3-oxidoscualeno es utilizado por las enzimas ciclasas, en algunas especies de plantas, durante la biosíntesis de dammarenediol[28]. En 1996 Corey utilizo un sililenoléter para dirigir la formación del anillo C durante la triciclización catiónica biomimética (Figura 13).

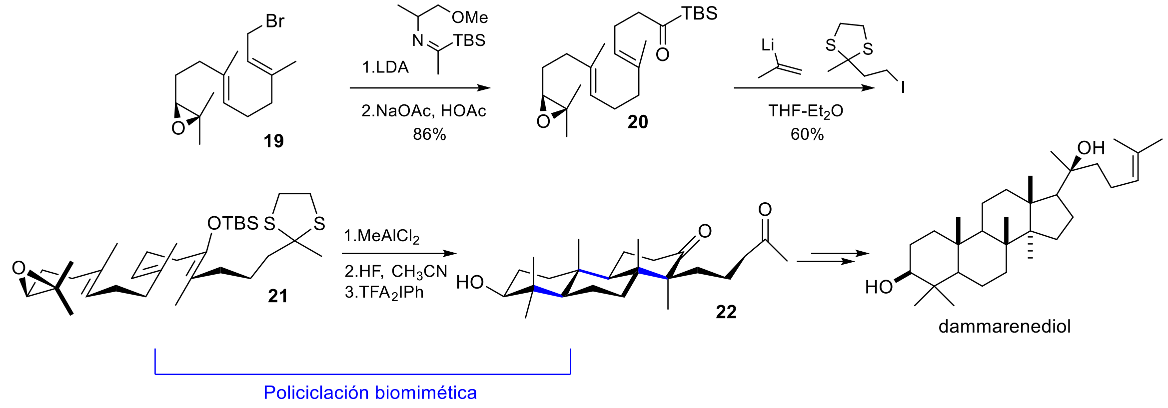


Figura 13. Síntesis total de dammarenediol de Corey.

A diferencia de Corey, Johnson en 1994, en su síntesis biomimética del sophoradiol[29], usó un átomo de flúor en C-13 para controlar la regio-selectividad del sistema pentacíclico **24** formado en presencia del ácido de Lewis $SnCl_4$ (Figura 14).

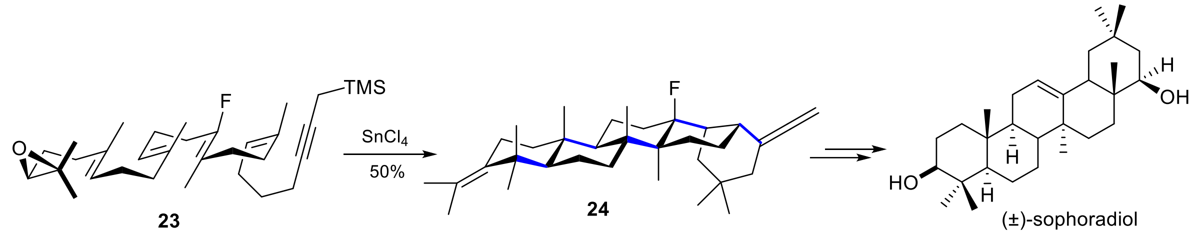


Figura 14. Sinthesis de Johnson (±)-sophoradiol usando una pentacarbociclación biomimética.

En 1999 Overman y colaboradores, describieron una tetraciclación biomimética en la síntesis hacia el adociasulfato-1, inhibidor de la proteína motora de la kinesina[30]. El ácido de Lewis utilizado para la apertura del epóxido **25** fue el triflato de escandio, este reactivo producirá la posterior tetraciclación catiónica biomimética (Figura 15).

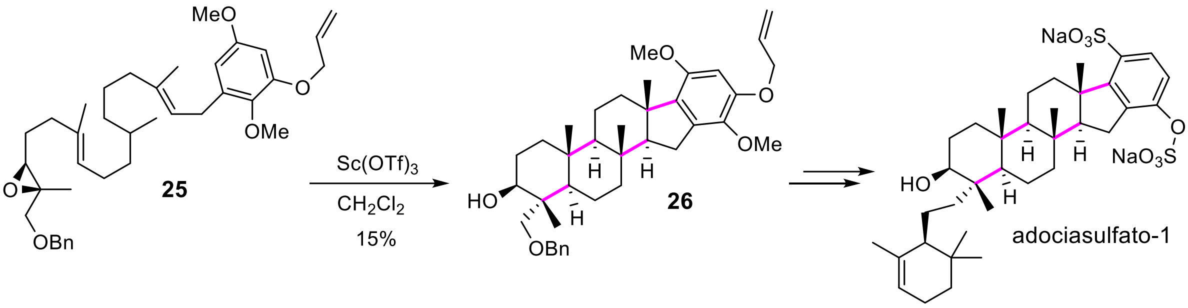


Figura 15. Paso biomimético en la síntesis de Overman del adociasulfato-1.

Otro ejemplo de la utilización de este tipo de estrategias para la producción de estructuras policíclicas, lo encontramos en la síntesis asimétrica del ácido antiochico[31] por el grupo de Loh en 2008. Estos autores describen como el ácido de Lewis $SnCl_4$ promueve la formación del oxocarbenio que es susceptible de ser atacado por el extremo alqueno del polieno, e inducir la ciclación catiónica biomimética del polieno hacia el intermedio tricíclico **29** (Figura 16).

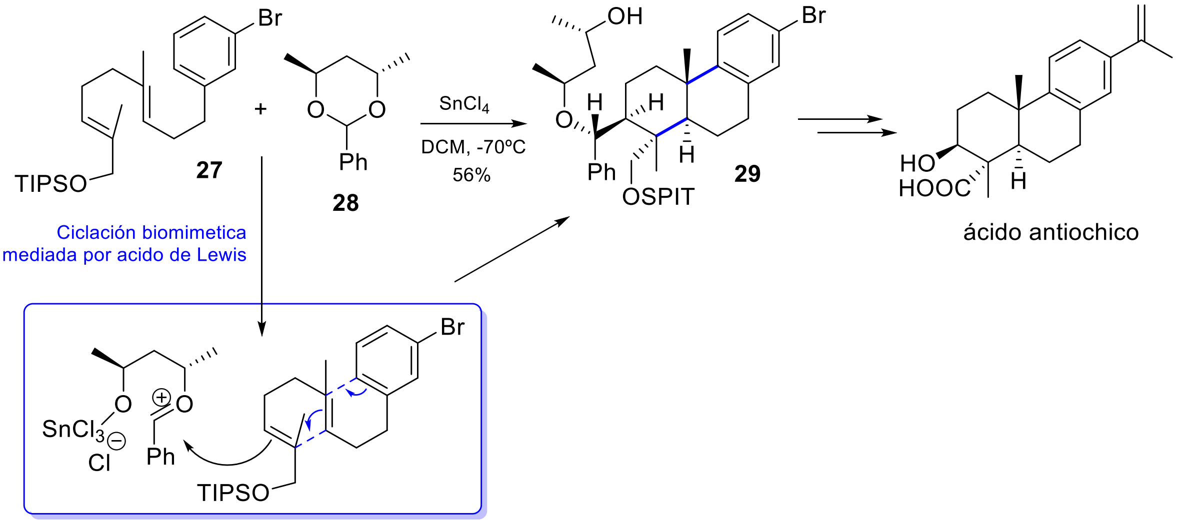


Figura 16. Cascada de ciclaciones biomiméticas mediada por ácido de Lewis en la síntesis del ácido antiochico.

III. Ciclaciones radicalarias.

Otra variante en ciclaciones biomiméticas de terpenos corresponde con las ciclaciones radicalarias. En estas ciclaciones, un radical ocupa el lugar que ocupaba el carbocatión. Su importancia radica en la posibilidad de generar estructuras policíclicas con buenos rendimientos, debido en buena parte a la suavidad de los reactivos utilizados en comparación con las ciclaciones carbocatiónicas. Ejemplos de ciclaciones radicalarias son las mostradas en la figura 17 [32–34].

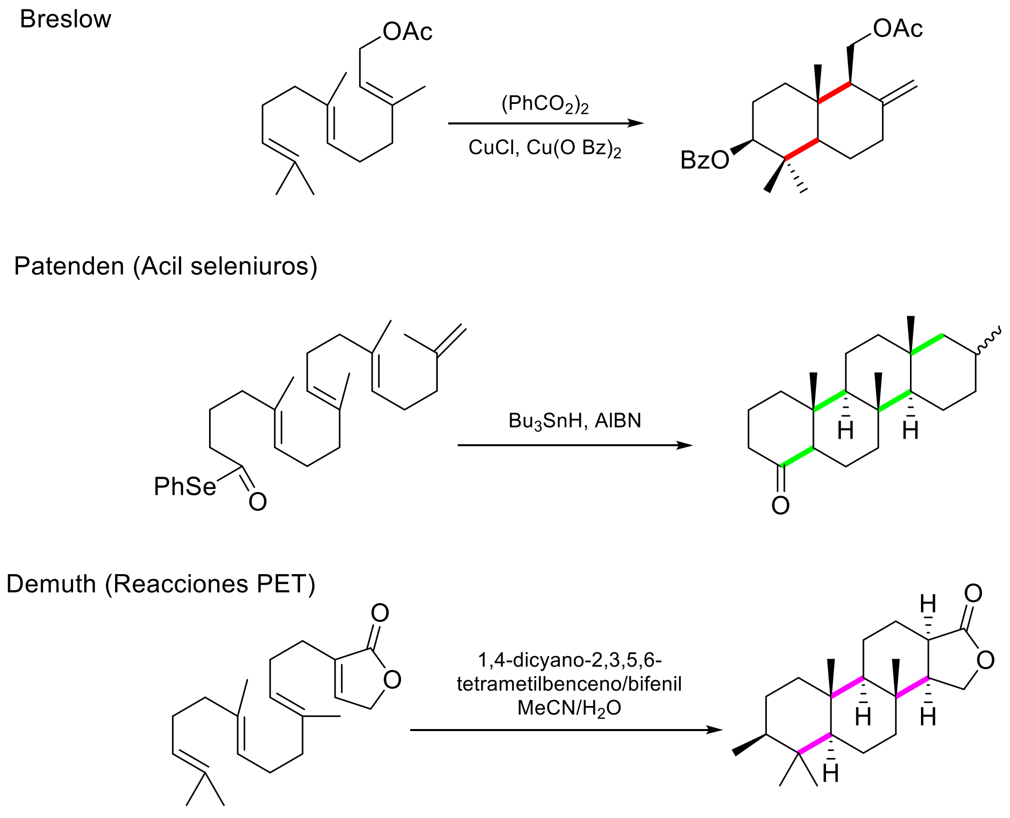


Figura 17. Ejemplos de ciclaciones radicalarias.

Un ejemplo de policiclación biomimética radiacalaria lo encontramos en la síntesis de policiclos de MacMillan en 2010[35]. A partir de un aldehído insaturado se forma la correspondiente enamina con una imidazolidinona. Esta a través de un oxidante metálico de Cu^{2+} generará un catión radical que participará en una serie de ciclaciones 6-endo-trig terminadas en el radical ciclohexadienilo. En una segunda etapa oxidativa, se producirá una rearomatización y liberación del catalizador (Figura 18).

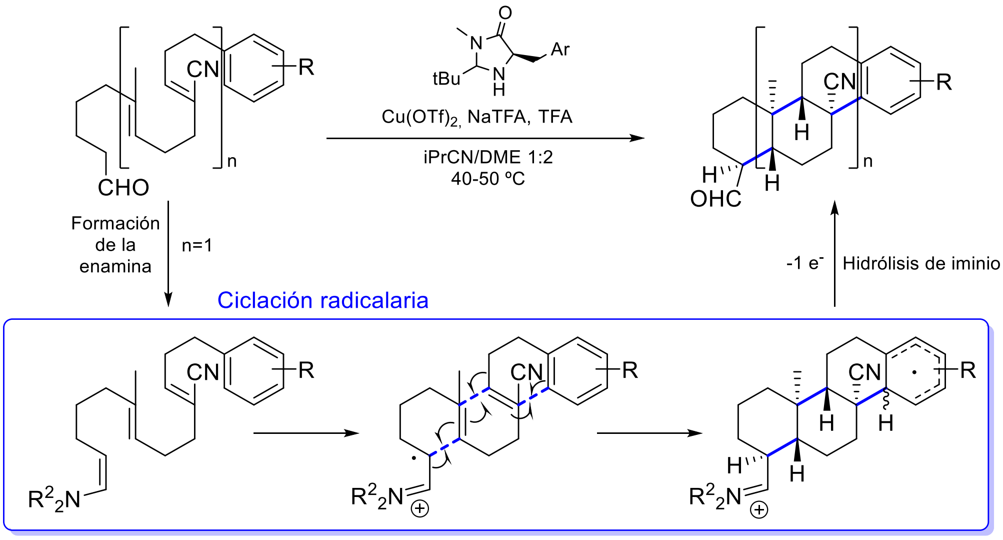


Figura 18. Síntesis de policiclos de MacMillan.

IV. Aportaciones por el grupo de investigación FQM 340 de la UGR: Empleo de sintones terpénicos en ciclaciones biomiméticas.

El grupo de investigación FQM-340 además de la línea de investigación sobre el desarrollo de sintones homoquirales y aplicaciones sintéticas también investiga innovación en ciclaciones biomiméticas. Para eso tenemos muy en cuenta las rutas biogenéticas de las moléculas que se sintetizan tratando de imitar mediante síntesis paralelas, las transformaciones producidas por las enzimas.

Los Chokoles[36] son 2,6 ciclofarnesanos con un anillo ciclopentánico como núcleo y propiedades antifúngicas. En la síntesis enantioselectiva de los chokoles K, E y B, el equipo de Barrero siguió una estrategia de síntesis del esqueleto de chokoles en 2 pasos, mediada por titanio (III), que originaba una ciclación radicalaria estereocontrolada del monoepóxido del producto natural (+)-nerolidol (**30**) (Figura 19).

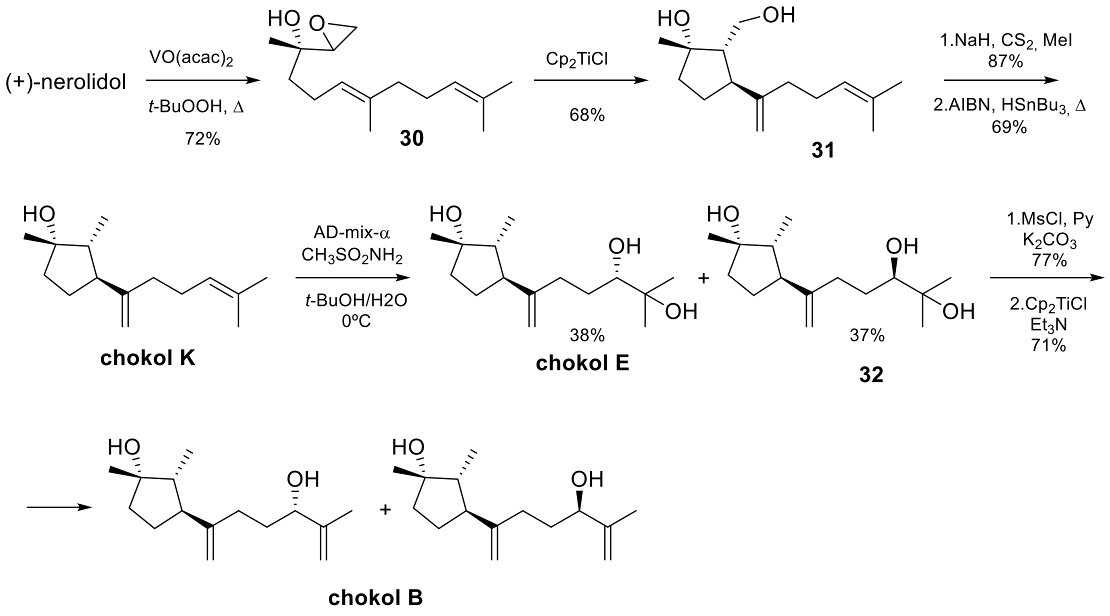


Figura 19. Síntesis enantioselectiva de los chokoles K, E y B.

Barrero et al publicaron en 2004, la síntesis de monoterpenoides con esqueleto de iridano a través de una ciclación con radicales sulfanilo[37]. El paso clave de esta estrategia de síntesis radica en una ciclación 5-*exo-trig* promovida por la adición de radicales sulfanilo al doble enlace monosustituido del derivado metoxicarbonilico de acetato de linalilo (**34**). La adición Markovnikov genera un radical centrado en C-6, que, después de la adición intramolecular al doble enlace, conducirá al ciclopentano intermedio (**36**). A continuación, la eliminación regioselectiva del grupo acetato (**37**) y la formación de la lactona dará lugar al iridano natural final (±)-deshidroiridomirmecina (Figura 20), extraído de la planta *Actinidia polygama*[38].

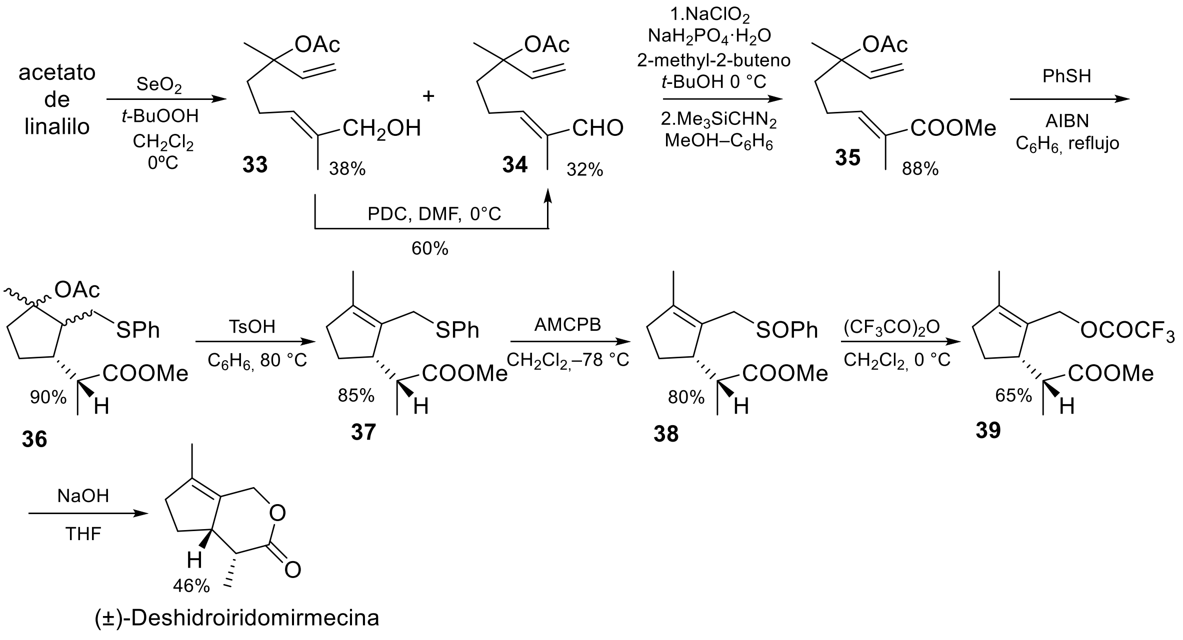


Figura 20. Sintesis de (±)-deshidroiridomirmecina.

Otro trabajo del mismo grupo de investigación, que entra dentro de las estrategias biomiméticas de ciclación radicalaria consiste en la síntesis (+)-3α-hidroxireinosina[39]. (+)-3α-hidroxireinosina se sintetizó a partir de (+)-costunolida mediante un proceso biomimético que supone una ciclación transanular mediada por Ti(III) a través de la creación de un radical terciario (Figura 21).

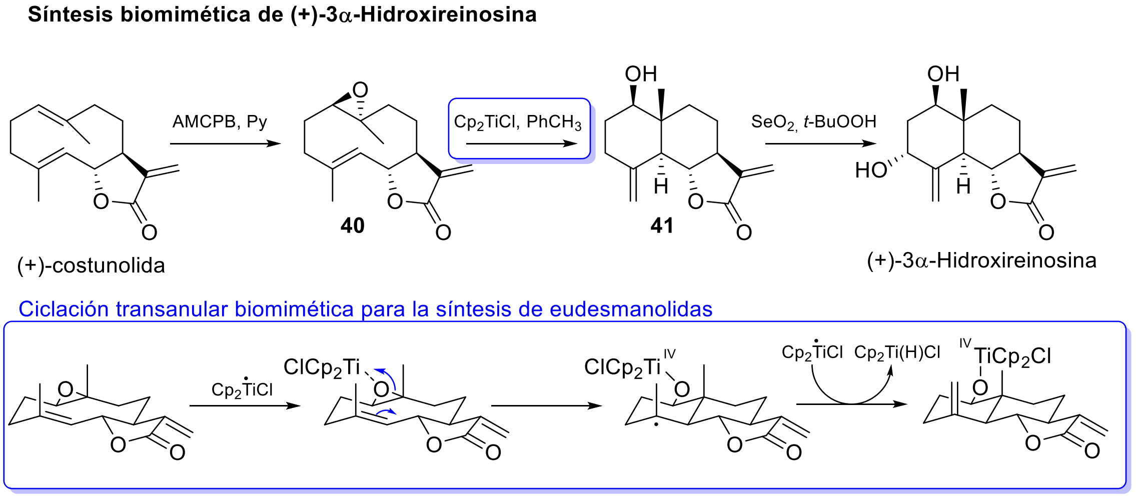


Figura 21. Mecanismo de acción radicalario en la síntesis de síntesis (+)-3α-hidroxireinosina desde el sinton quiral (+)-costunolida.

Por último, el grupo en 2009 realizó la síntesis enantioselectiva de (+)-myrrhanol A[40], un producto natural con un alto valor como antiinflamatorio. Uno de los pasos clave, es la ciclación radicalaria biomimética mediada por el cloruro de titanoceno que va a proporcionar el biciclo (**43**). Este después de varios pasos, se condensará estereoespecificamente con un yoduro de vinilo acíclico a través de un acoplamiento cruzado intramolecular de Suzuki-Miyaura (Figura 22).

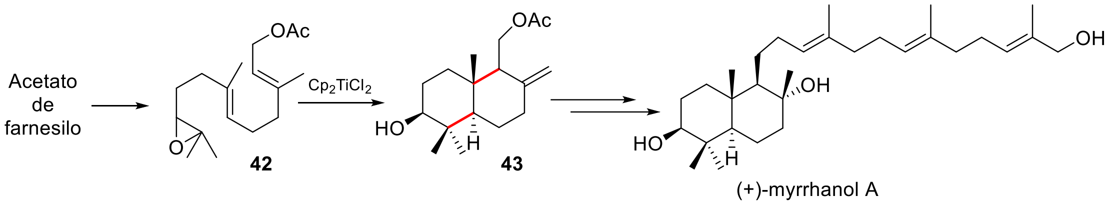


Figura 22. síntesis enantioselectiva de (+)-myrrhanol A

Todas estas reacciones muestran la utilidad del complejo Cp_2TiCl para la síntesis eficiente de productos naturales.

1.3 Procesos cascada de ciclaciones biomiméticas +/ó reordenamientos:

I. Generalidades.

Como hemos comentado anteriormente, dentro de la biogénesis, las enzimas terpeno-ciclasas son las encargadas de producir ciclaciones a partir de la generación de un carbocatión que desencadena procesos en cascada acompañados, a veces, de reordenamientos tipo Wagner-Meerwein. Estas reacciones en tándem adquieren su mayor relevancia en la biosíntesis de triterpenos, por sus múltiples ciclaciones y reordenamientos.

"A priori" no es sencillo el desarrollo de transformaciones químicas que incorporen ciclaciones y reordenamientos en un mismo paso. Sin embargo, dichas transformaciones suponen un gran avance en la química sintética, ya que al imitar las terpeno-ciclasas, se logran economizar en átomos y en número de pasos químicos.

II. Ejemplos de ciclaciones biomiméticas y/o reordenamientos catiónicos

Uno de los primeros trabajos en los que se describió una cascada de ciclaciones y reordenamientos fue el de Sharpless y Van Tamelen en 1969[41]. El tratamiento de óxido de escualeno con el ácido de Lewis $SnCl_4$ generó entre otras moléculas un alcohol tricíclico. Este es originado a través de un carbocatión malabaricano terciario intermedio, que evoluciona hacia el producto final **44** mediante un reordenamiento de metilo y de hidruro, con posterior deprotonación final (Figura 23).

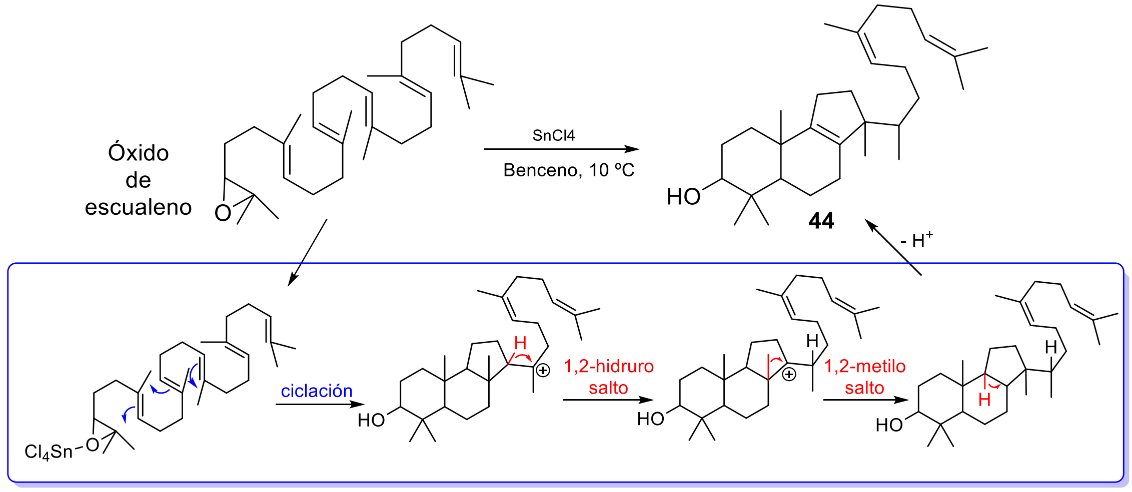


Figura 23. Cascada de ciclaciones y reordenamientos de Sharpless y Van Tamelen en el tratamiento de óxido de escualeno con ácidos de Lewis.

Durante el siglo XX y lo que llevamos del XXI, este enfoque fué ganando cada vez más fuerza como paso clave en la síntesis de terpenos. Como ejemplo de esta dupla de ciclaciones y reordenamientos en este siglo XXI, encontramos en 2008 la síntesis del potente triterpeno oleanano allobetulin desde el lupano betulin, por Salvador y colaboradores[42]. En su descripción, Salvador emplea una sal de bismuto (III) que cataliza la transformación del anillo ciclopentánico E, característico de lupanos, a ciclohexano. Este proceso, además, se desarrolla con la formación final de un anillo de tetrahidrofurano (Figura 24).

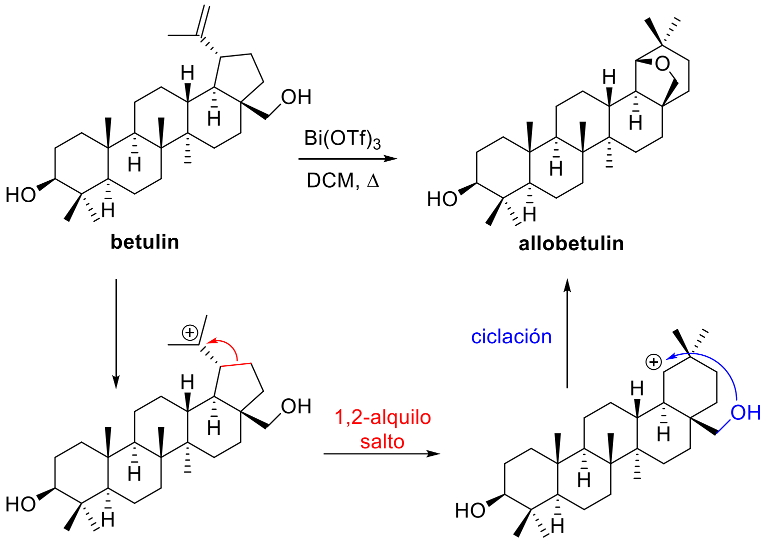


Figura 24. Síntesis del potente triterpeno oleanano allobetulin.

Los hiperjaponoles son meroterpenoides naturales que contienen una mitad fenólica proveniente de la ruta del acetato. En 2016 George et al. realizó la síntesis de (±)-hiperjaponol C a partir de (±)-hiperjapone A[43] (Figura 25).

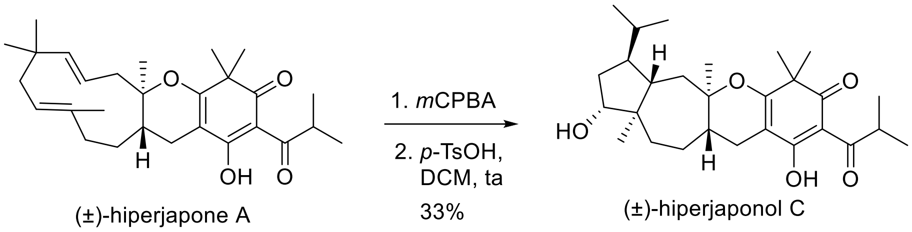


Figura 25. Síntesis de (±)-hiperjaponol C a partir de (±)-hiperjapone A.

Todo el proceso biomimético supuso una epoxidación estereo y quimioselectiva seguida de una cascada de ciclación catalizada por el ácido *p*-toluen sulfónico y un desplazamiento 1,2-alquilo (Figura 26).

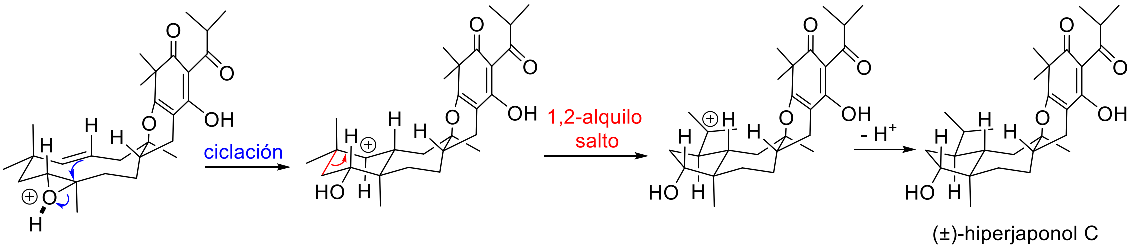
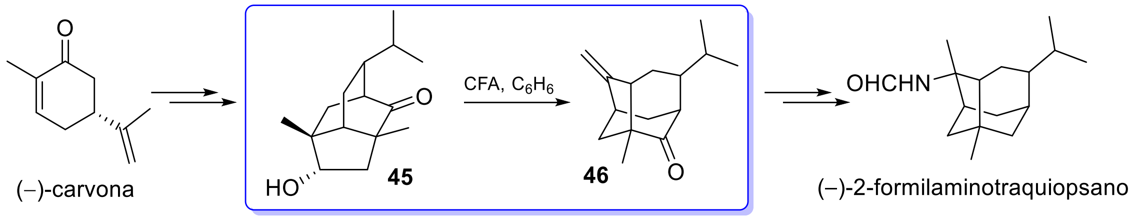


Figura 26. Mecanismo de ciclación y reordenamiento en la síntesis de (±)-hiperjaponol C.

Srikrishna et al. en la síntesis de (–)-2-formilaminotraquiopsano[44] utilizan un reordenamiento catiónico biomimético del alcohol de neopupukeanano **45** hacia el esqueleto de traquiopsano (**46**) (Figura 27).



Transposición biomimética de un isotwistano a triciclo [4.3.1.0^{3,8}] decano

Figura 27. Síntesis del sesquiterpeno bioactivo marino (–)-2-formilaminotraquiopsano.

Appendino el al en 2017[45] describen la formación del sesquiterpenoide tricíclico **47** a través de la ciclación electrofílica de zerumbona por tratamiento con el ácido de Lewis, tricloruro de aluminio ($AlCl_3$) (Figura 28).

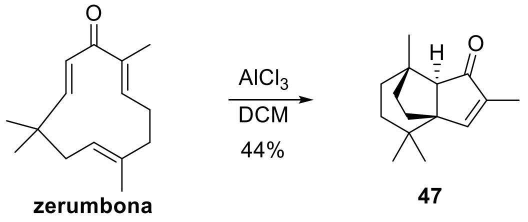


*Figura 28. Formación del compuesto tricíclico **47** a través de la ciclación de zerumbona por tratamiento con ácido de Lewis.*

La generación del compuesto tricíclico viene justificada por la activación del grupo carbonilo por el ácido de Lewis. Esto generaría un primer proceso de ciclación vía reordenamiento de Nazarov. La subsiguiente deprotonación del carbocatión alílico genera un intermedio que evoluciona a espirano por la contracción del anillo. Finalmente, el ácido induce una nueva ciclación generando el producto final (Figura 29).

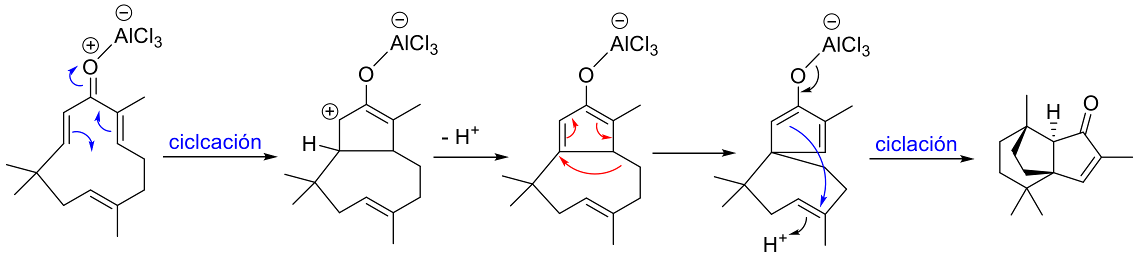


Figura 29. Mecanismo de acción de ciclación y reordenamiento catiónica a partir de la zerumbona.

Por último, en 2020 y también utilizando zerumbona como producto de partida, el grupo de Kollery[46] describió una ruta biomimética en la que se obtiene un 8-oxabiciclo[3.2.1]octano. La foto-irradiación de la zerumbona se realizó en presencia de cantidades catalíticas de ácido de Lewis (Figura 30). Según Kollery esta síntesis de un 8-oxabiciclo[3.2.1]octano **48** es un paso intermedio en la biosíntesis de moléculas que portan ese mismo esqueleto (4+7).

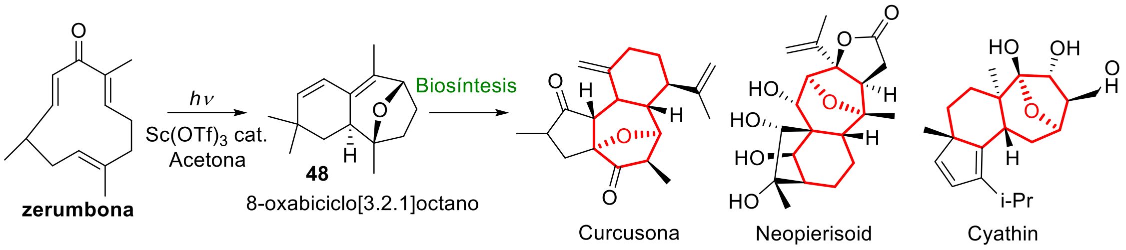


Figura 30. Síntesis del 8-oxabiciclo[3.2.1]octano.

Se postula que la radiación lumínica juega un papel importante en la isomerización de los dobles enlaces de la zerumbona. Entonces la posterior ciclación transanular mediada por el ácido de Lewis condujo un carbocatión intermedio terciario que lleva al esqueleto de 8-oxabiciclo[3.2.1]octano **48** (Figura 31).

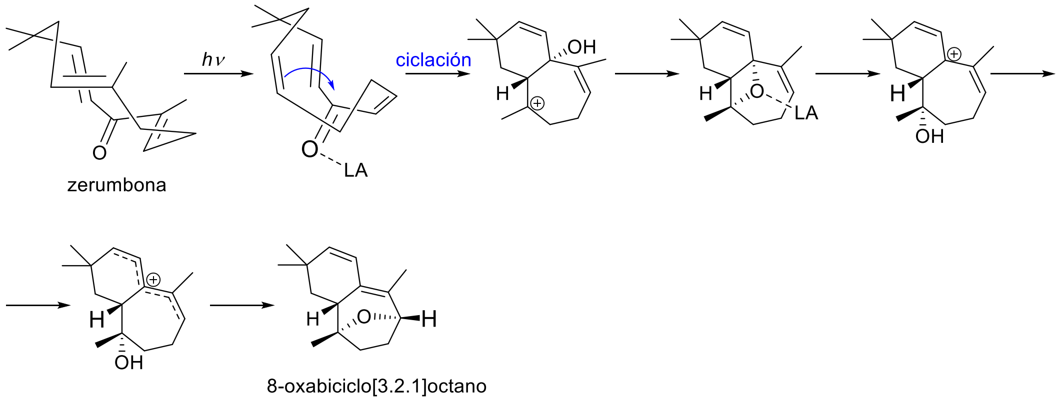


Figura 31. Mecanismo de acción en la síntesis de 8-oxabiciclo[3.2.1]octano.

III. Reordenamientos radicalarios.

Comparativamente existen pocos casos de aplicación de reordenamientos radicalarios en síntesis de terpenos. Un ejemplo está en la síntesis biomimética de las jungermannenonas. Este tipo de moléculas se han encontrado en el género de plantas Jungermannia y poseen una prometedora actividad como citotóxicos. Se postula su biosíntesis a través de reordenamientos carbocatiónicos a partir de *ent*-kaurenos. En 2019 el grupo de Lei[47] describió un proceso sintético en el que se origina un reordenamiento radicalario fotoinducido en la síntesis de (−)-jungermannenona C. Así al aplicar irradiación con luz UV de 254nm se produciría una migración fotoquímica 1,3-acilo de la cetona β,γ-insaturada (**49**) (Figura 32).

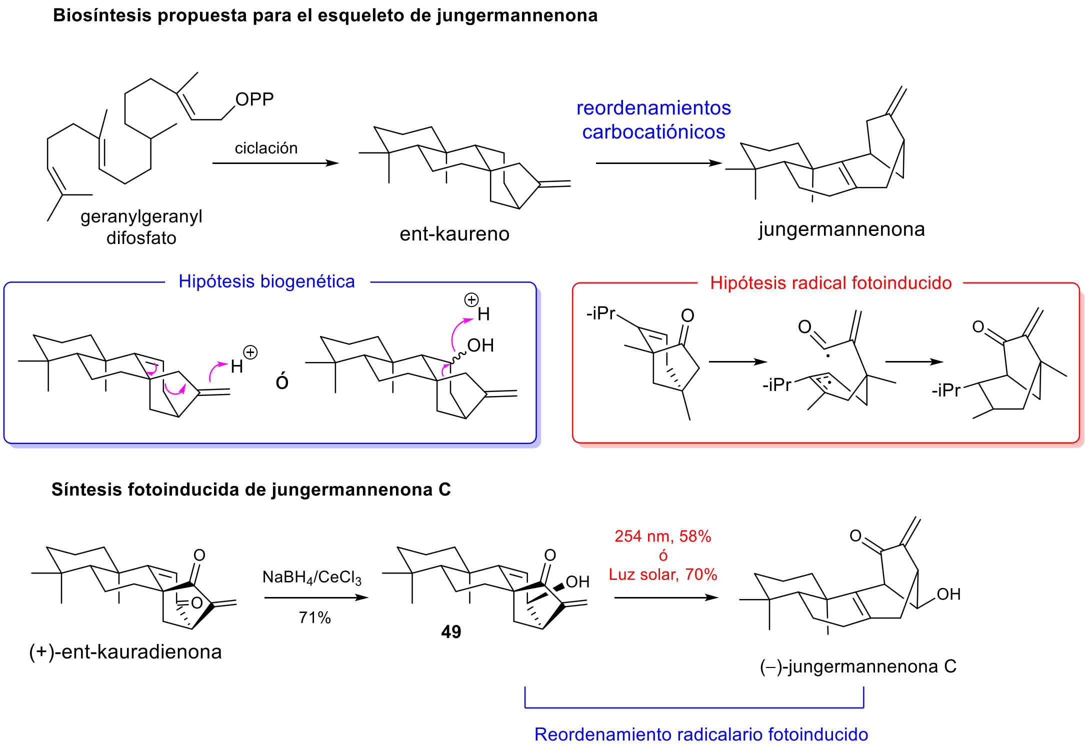


Figura 32. Biosíntesis y síntesis radicalaria fotoinducida de (−)-jungermannenona C.

IV. Ejemplos de aportaciones del grupo de investigación FQM 340 de la UGR:

El grupo llevó a cabo la síntesis de la eusdemanolida (+)-malacitanolida en 1997[48]. El planteamiento biomimético se basa en la hipótesis de que (+)-cnicina puede ser el precursor biogenético de (+)-malacitanolida. La biosíntesis se llevaría a cabo mediante una epoxidación enzimática regio- y estereoselectiva seguida de ciclación transanular estereoespecífica del 1,10-epóxido con transposición final de hidruro. Mecanismo que se ha mimetizado para la obtención de (+)-malacitanolida mediante la reacción de la (+)-cnicina con *m*-CPBA en THF en un solo paso mediante epoxidación y apertura espontánea del epóxido seguida de ciclación y reordenamiento final de hidruro, que confirmaría la relación biogenética de la (+)-cnicina con la (+)-malacitanolida (Figura 33).

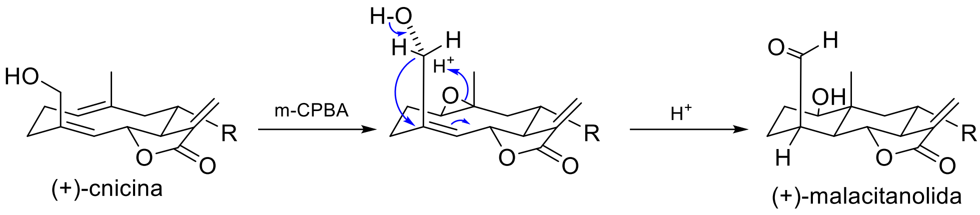


Figura 33. Ciclación y reordenamiento en la síntesis biomimética de (+)-malacitanolida.

En 2013 se publicó un estudio que muestra la generación de una gran diversidad estructural a partir de ciclaciones catiónicas transanulares partiendo del producto natural germacrona y varios derivados epoxidados de esta, germacrona-4,5-epóxido, germacrona-1,10-epóxido e isogermacrona-4,5-epóxido[49]. Germacrona fue extraída y escalada a multigramos desde la planta *Geranium macrorrhizum*. El tratamiento de germacrona con diferentes electrófilos y de sus derivados epoxidados con ácidos de Brönsted y Lewis y Ti(III) permitieron obtener con facilidad una diversidad molecular de más de 40 compuestos, correspondientes a 14 esqueletos terpénicos y varios productos naturales entre ellos (Figura 34).

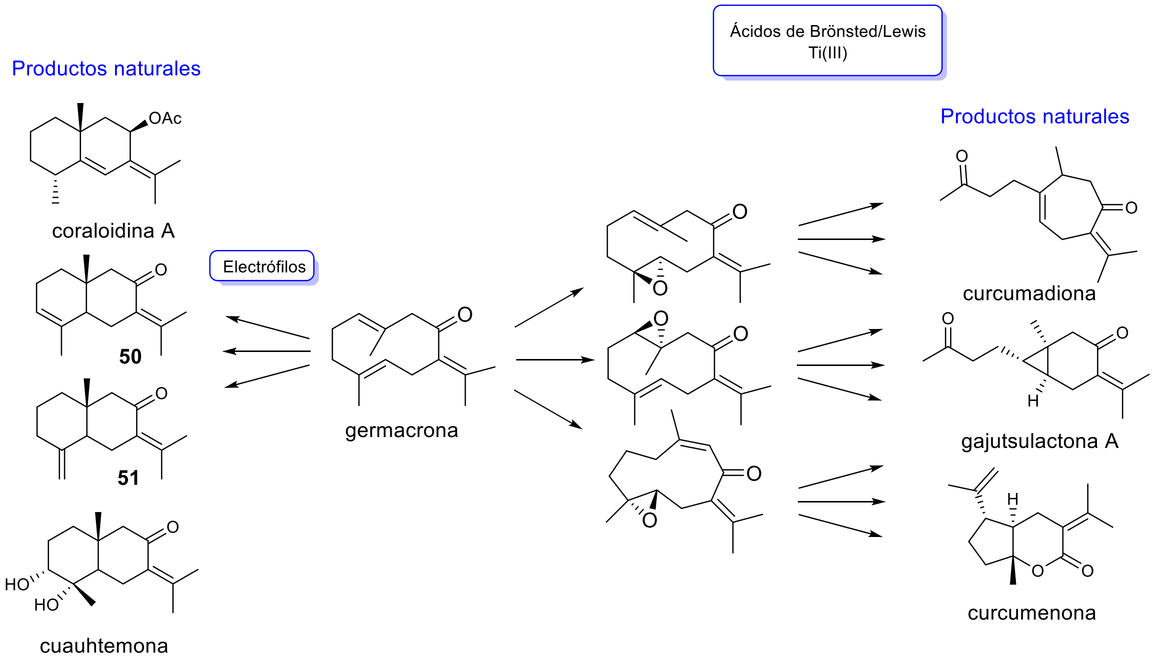


Figura 34. Diversidad estructural partiendo del producto natural germacrona y derivados epoxidados.

Entre la diversidad estructural que se genera por la aplicación del ácido de Lewis Et_2AlCl al 4,5-epóxido de la germacrona destacan 4 compuestos que se han formado a través de procesos de ciclación y reordenamiento, siendo 3 de ellos naturales y uno nuevo (**52**) (Figura 35).

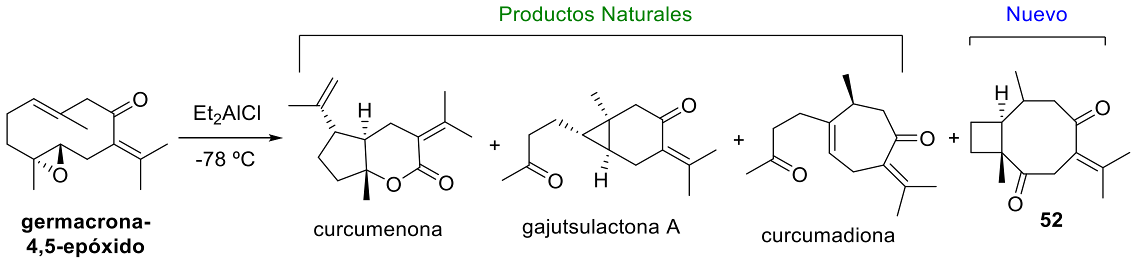


Figura 35. Diversidad estructural en el uso de Et_2AlCl sobre el 4,5-epóxigermacrona.

Se propone para la formación de los tres productos naturales un mecanismo de ciclación mediado por un carbocatión tipo guaiano (**I**), actuando como intermediario para la formación de los diferentes productos naturales a través de diferentes procesos de reordenamientos 1,2 como se observa en la figura (Figura 36).

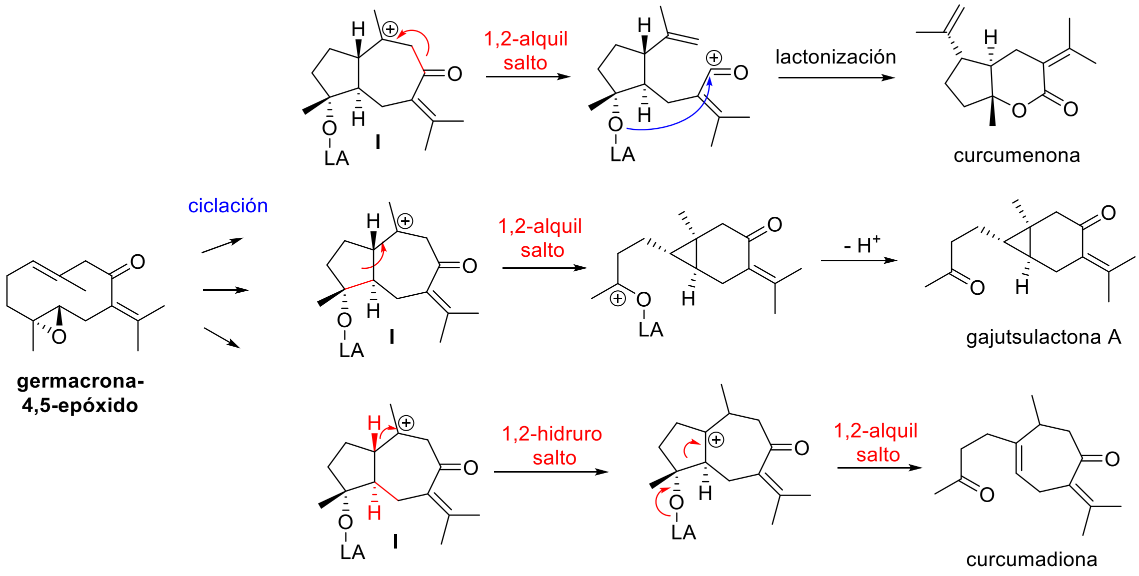


Figura 36. Mecanismo de ciclación y reordenamiento mediado por un carbocatión tipo guaiano.

La propuesta con la que se justificaría la formación del producto con un esqueleto nuevo (**52**) comenzaría con la ciclación de germacrona-4,5-epóxido para originar el carbocatión bicíclico 4+8

(**II**). Éste, tras dos reordenamientos secuenciales de hidruro 1,2 y 1,3, originaría el producto final **52** vía deprotonación (Figura 37).

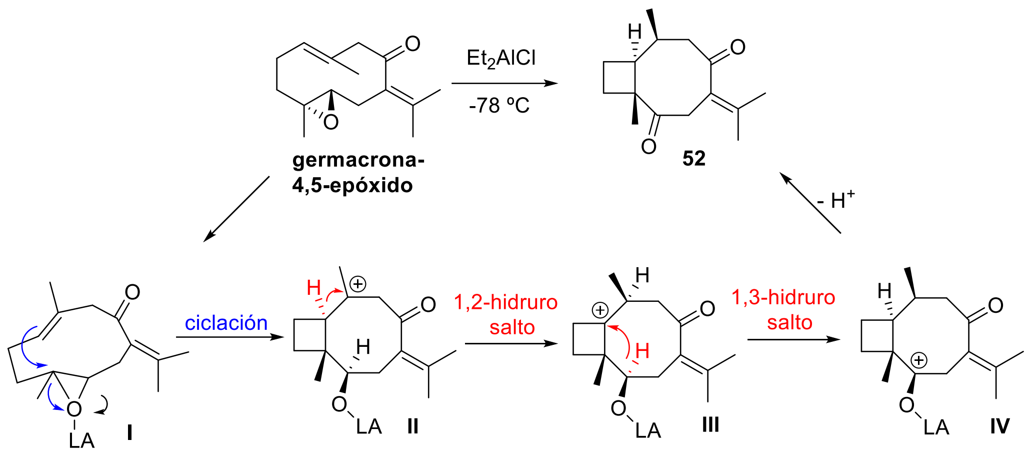


*Figura 37. Síntesis y mecanismo de ciclación y reordenamiento de **52**.*

2 *Objetivos*

Desde que se fundó el grupo de investigación FQM 340 "Biotecnología de hongos y moléculas bioactivas se han concentrado buena parte sus esfuerzos en el estudio, extracción, purificación, elucidación estructural y transformaciones químicas de productos naturales de plantas de la Península Ibérica, Sudamérica[50] y norte de África. Es de destacar, el estudio de plantas endémicas en las provincias de Granada y Almería y aquellas de zonas semidesérticas de Marruecos[51–54]. El estudio y conocimiento de la Fitoquímica de la flora silvestre, ha permitido descubrir que algunas especies de plantas actúan como una eficiente "factoría de moléculas". Así en muchos casos, estas especies proveen de grandes cantidades de productos naturales que pueden ser utilizados como sintones homoquirales en nuevas estrategias de síntesis de moléculas bioactivas más complejas. Ejemplos utilizados por el grupo de investigación, son las especies de plantas *Bellardia trixago*, de la que se obtienen grandes cantidades de trixagol y de geranilgeraniol[55], o la planta *Dittrichia viscosa*, donde encontramos varios sintones interesantes, destacando el ácido ilícico, obtenido mediante un innovador método de extracción y purificación optimizado por el grupo de investigación[56] (Barrero, A.F et al, resultados no publicados). Destaca también el caso del girasol *Helianthus annuus,* de cuyas cabezas florales se pueden extraer proporciones importantes de ácidos *ent*-kaurenoico y *ent*-traquilobánico [57,58].

Como consecuencia de ello, paralelamente al estudio fitoquímico, se desarrollaban nuevos proyectos dedicados a la síntesis de productos naturales bioactivos que trataban de resolver síntesis complejas en un menor número de etapas y facilitar así su accesibilidad. En ellos se diseñaban nuevas estrategias y procesos sintéticos para la obtención de productos complejos que en buena parte estaban fundamentados en la biosíntesis de terpenos, lo que se conoce como "estrategias biomiméticas". En este sentido es relevante la puesta a punto o utilización de procesos de ciclaciones biomiméticas catiónicas y radicalarias[48,59].

En la presente memoria se exponen los resultados obtenidos en la síntesis de los productos naturales (+)-isodaucano, (−)-2,15-valparadieno, isotuberculosinol y (−)-platensimicina. Para cada molécula objetivo, se han utilizado estrategias bioinspiradas a partir del conocimiento de los compuestos intermediarios (precursores) de la biosíntesis de la molécula final, o de procesos en cascada de ciclaciones radicalarias o catiónicas con reordenamientos. El desarrollo del trabajo se ha ordenado en los siguientes apartados:

I. *Estudio bibliográfico de síntesis biomiméticas de Terpenos mediante ciclaciones y reordenamientos.*

La naturaleza tiene sus métodos para producir moléculas complejas a través de procesos enzimáticos, lo que denominamos biosíntesis. Cabe destacar, dentro de las biogénesis de terpenos, los procesos destinados a la ciclación de moléculas por las enzimas terpenociclasas. Estas funcionan generando un carbocatión sobre un precursor acíclico poliprénico que produce las ciclaciones en cascada mediante adiciones del carbocatión a los enlaces C=C, pudiendo provocar, además, reordenamientos por migración de hidrógeno o grupos alquilo dentro de la molécula (tipo Wagner-Meerwein)[24–26] (Figura 38).

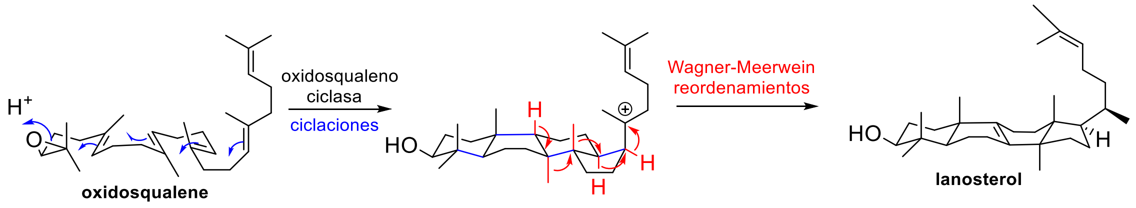


Figura 38. Ejemplo de ciclación y reordenamiento en la biosíntesis del lanosterol [60].

Estos mecanismos de ciclación y reordenamiento en una sola etapa, son muy interesantes y a la vez complicados de mimetizar en el laboratorio. Por eso se decidió hacer una revisión que recopilase la utilización de estos procesos desde principios de este siglo.

II. *Síntesis biomimética enantioselectiva de (–)-2,15 valparadieno e (+)-isodaucano:*

Los valparanos son moléculas que poseen una estructura singular dentro de la naturaleza, conteniendo un sistema tricíclico en donde el anillo A es pentacíclico, el B hexacíclico y un tercer anillo C heptacíclico. En 1990, se postuló el origen biogenético de la molécula, basado en una secuencia de ciclaciones a partir del geranil geranil difosfato como se muestra en la figura[61] (Figura 39).

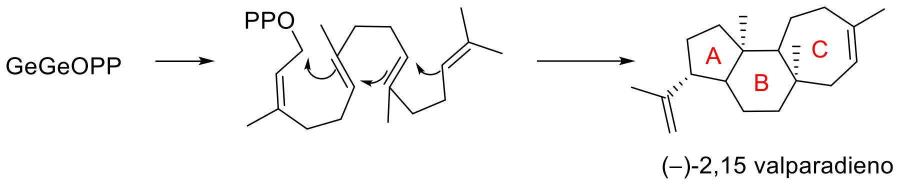


Figura 39. Biosíntesis de (–)-2,15 valparadieno.

En la actualidad, solo existe una síntesis que daba como resultado una molécula con esqueleto de valparano, el producto no natural 2,14-valparadieno[62].

En esta Tesis Doctoral, se aborda la realización de la síntesis enantioselectiva del diterpeno natural (–)- 2,15-valparadieno a partir de farnesil cetona obtenida por degradación desde el producto natural geranil geraniol extraído de la planta *Bellardia trixago*. Los pasos clave de esta estrategia sintético fueron, de una parte un proceso de ciclación biomimética radicalaria mediado por Ti(III),[63] que producirá la triciclación en un solo paso; y como segundo paso a destacar, la contracción catiónica del anillo de ciclohexano A (Figura 40). Previamente, para estudiar la policiclación en estructuras polifuncionalizadas y contracción del anillo A se pondrá a punto una metodología en una molécula más simple, con la síntesis del sesquiterpeno natural (+)-isodaucano a partir de (+)-nerolidol extraído de la planta *Dittrichia viscosa*.

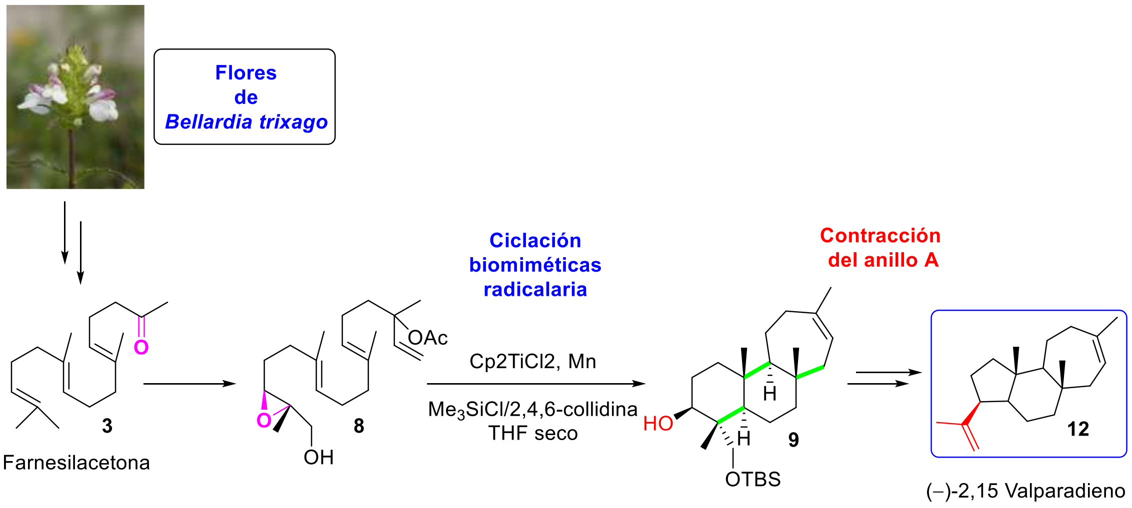


Figura 40. Pasos clave en la síntesis de (–)-2,15 valparadieno.

III. Síntesis biomimética de halimanos. Preparación de isotuberculosinol

El grupo de productos naturales perteneciente a los diterpenos halimanos se caracteriza por poseer un doble anillo de 6 miembros con una instauración entre los carbonos C5-C6, C5-C10 o C1-C10. Estas posiciones del doble enlace están relacionadas con un reordenamiento del metilo en la posición C10 desde un intermedio labdano. La biosíntesis de este grupo de moléculas está catalizada por halimano sintasas donde una diterpeno ciclasa de tipo II produciría el carbocatión bicíclico intermedio **II** desde geranil geranil difosfato y seguidamente este evolucionaría mediante reordenamientos 1,2 de tipo hidruro y metilo[64] (Figura 41).

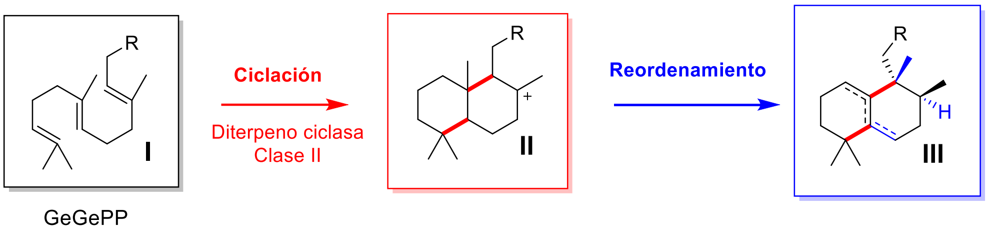


Figura 41. Biosíntesis de halimanos.

El abanico de usos biotecnológicos que se le atribuyen a este tipo de moléculas es amplio, sin haberse desarrollado hasta la fecha una síntesis de tipo biomimético. Halimanos como formosina A o angelasine C poseen un buen rango de actividad antimicrobiana[64], pero quizás el isotuberculosinol sea la molécula más representativa de este grupo, pues actúa como factor de virulencia de la bacteria *Mycobacterium tuberculosis*[65] (Figura 42).

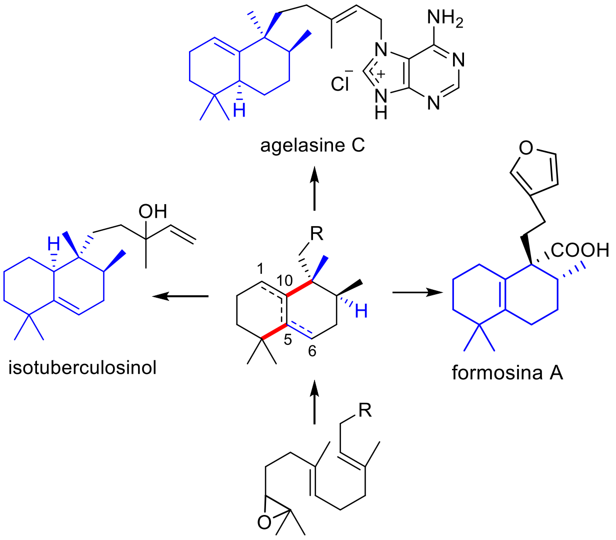
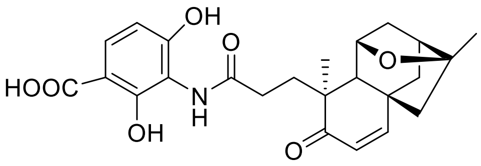


Figura 42. Ejemplos de productos naturales bioactivos con las diferentes posiciones olefinicas dentro del esqueleto halimano.

En nuestro caso proponemos como objetivo una estrategia de síntesis biomimética paralela a la que realizan las enzimas halimano-sintasas. Se ha utilizado geranilgeraniol natural como material de partida, con el objetivo de llevar a cabo procesos en cascada de ciclaciones y reordenamientos de epoxypoliprenos catalizadas por ácidos de Lewis[66]. Así abriríamos una vía de acceso a este tipo de estructuras en pocos pasos sintéticos. Una vez este establecidas las condiciones experimentales, el proceso biomimético hacia halimanos, se aplicará a la síntesis de la molécula isotuberculosinol.

IV. Síntesis bioinspirada enantioespecifica de (–)-platensimicina.

Platensimicina es un nor-diterpenoide aislado de varias cepas de *Streptomyces platensis* (Figura 43). Esta molécula fue descrita por primera vez en 2006 por científicos del grupo Merck[67], siendo uno de los mayores descubrimientos en la lucha contra las enfermedades bacterianas, en esta primera parte del siglo XXI. Destacada además de su eficacia, por su novedoso mecanismo de acción actuando como supresor de la FabF involucrada en la biosíntesis de ácidos grasos de bacterias multirresistentes a antibióticos[68,69].



(–)-platensimicina

Figura 43. Antibiótico (–)-platensimicina.

Debido a su importancia, se conoce gran parte de su origen biogenético, encontrándose como intermedios varios diterpenos con esqueleto de kaurano que sufren una degradación parcial del anillo A para formar la estructura final de la platensimicina[70–75] (Figura 44).

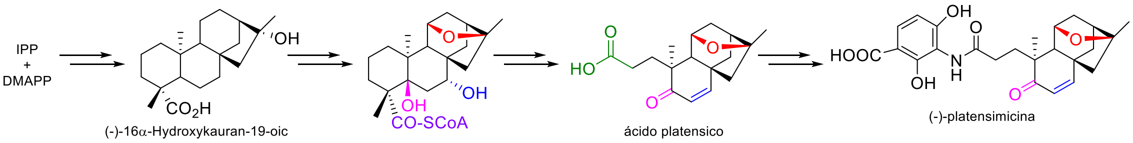


Figura 44. Pasos biosintéticos en la génesis de (–)-platensimicina.

La participación de kauranos dentro de la biogénesis de la platensimicina, inspiró la propuesta de síntesis de esta molécula como objetivo de esta memoria. Utilizando ácido *ent*-kaurenoico y ácido grandiflorenico, extraídos respectivamente de las plantas *Helianthus annuus*[76] *y Stevia lucida*[77] como sintones homoquirales de partida, se propuso en primera instancia el estudio de la degradación del anillo A en ácidos *ent*-kauranoicos. La segunda parte de nuestra propuesta sintética constituye la generación del furano característico de la molécula objetivo y la aplicación del método degradativo previamente estudiado para sintetizar ácido platensico, precursor directo de la platensimicina en la síntesis total de la molécula descrita por Nicolaou en 2006[78].

3 *Artículos de Investigación.*

3.1 *Artículo 1:* Chemical synthesis of terpenoids with participation of cyclizations plus rearrangements of carbocations: a current overview.

Quílez del Moral, J. F.; Pérez, Á.; Barrero, A. F. Chemical Synthesis of Terpenoids with Participation of Cyclizations plus Rearrangements of Carbocations: A Current Overview. *Phytochemistry Reviews* **2020**, *19* (3), 559–576. https://doi.org/10.1007/s11101-019-09646-8.

https://link.springer.com/article/10.1007/s11101-019-09646-8

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Citaciones hasta el día 20 de octubre de 2021: **6**

Chemical Synthesis of Terpenoids with Participation of Cyclizations plus Rearrangements of Carbocations. A Current Overview

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Abstract

Many terpenoids are biosynthesized after a cascade of cyclizations and rearrangements of carbocations mediated by terpenoid synthases, as exemplified in the biosynthesis of lanosterol. Although several reports of organisms or purified enzymes catalyzing this cascade of reactions in the laboratory have been described, the development of chemical transformations capable of mimicking such tandem cyclizations and rearrangements constitute a formidable challenge for organic chemists. From the very early works of Van Tamelen in the 1960s to our time, we present the Lewis or Brønsted acids-mediated cyclization-rearrangements of carbocations cascades aimed to mimic the action of enzymes. From all the achievements herein presented, the hypothesis of minimal enzymatic participation is reinforced, and this, if confirmed, promises new achievements in this area in the next future.

Key words

Biomimetic synthesis of terpenoids, tandem reactions, polyprene cyclizations, Wagner-Meerwein rearrangements, Lewis and Brønsted acids.

Introduction

The biosynthesis of terpenes is mediated by terpene synthases, and among them, the cyclases play a key role since they allow the construction of one or several cycles with high control of the regio- and stereoselectivity of the process (Cane 1999; Christianson, 2017).

The reactions mediated by these cyclases proceed via carbocations, which are often stabilized by the corresponding enzyme. The generation of these carbocations can trigger “cascade processes” where, apart from cyclizations, a series of Wagner-Meerwein rearrangements may take place (Xiao-Ming et al. 2017; Dewick, 2004; Marco 2006). These tandem reactions are involved in the biosynthesis of some mono-, sesqui-, di- and tetraterpenes. However, it is in the biosynthesis of triterpenes where these processes reach their highest relevance. Thus, some squalene or oxidosqualene cyclases produce amazing cyclizations followed by multiple rearrangements (Yoder and Johnston 2005; De la Torre and Sierra 2004; Wendt et al. 2000) (Fig. 1)

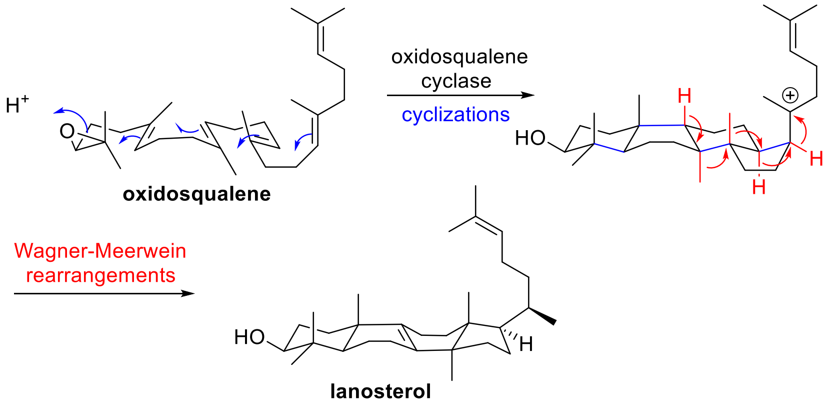
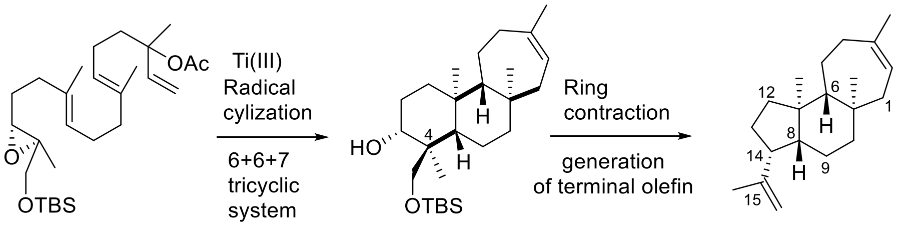


Fig. 1. Cascade of cyclizations and rearrangements of oxidosqualene to produce lanosterol

These amazing transformations have arisen the interest of many organic chemists and, as a consequence, during the second half of the twentieth century a number of processes have been developed in the laboratory aiming to mimick the action of these terpene cyclases (mainly the cyclization part) (Barret et al. 2019; Ardkhean et al. 2016; Snyder and Levinson 2014; Plesniak 2017). Thus, Barrero et al (Quilez del Moral 2019) described very recently the first synthesis of natural diterpene valparanes, a process involving a biomimetic tricyclization and a ring rearrangement. The methodology employed by these authors was based in the titanocene chloride-mediated radical opening of epoxypolyprenes followed by multiple C-C forming bonds, a protocol firstly reported by Barrero et al in 2001 (Barrero et al. 2001, Zweig et al., 2017) (Fig 2).



(-)-Valpara-2,15-diene

Fig. 2. Biomimetic synthesis of (-)-valpara-2,15-diene

The development of chemical transformations capable of achieving in only one step two kinds of processes such as cyclizations and rearrangements mimicking the action of some terpene cyclases does not seem a straightforward task. However, such a process would represent an outstanding synthetic methodology, mainly in terms of atom economy and minimal use of chemical steps.

In this sense a number of organisms or purified enzymes have been described to catalyze this cascade of reactions in the laboratory. This enzymatic approach has been revised recently (Tantillo 2017; Pemberton et al. 2013). It was postulated that the structure, functionality and the conformational and stereochemical features of the polyprenic precursor play a key role in the corresponding transformation, and that consequently, the involvement of cyclases in these processes is limited.

Together with this biotechnological approach, different Lewis or Brønsted acids also trigger this tandem sequence of reactions, either provoking the initial oxirane opening in monoepoxypolyprenes or protonating selectively any of the double bonds of polyprenes. In this regard, it should be mentioned that a number of mono and mainly sesquiterpenes were used in transformations involving cyclizations and rearrangements aiming to generate chemistry diversity from substances abundantly found in Nature. Processes involving the employ of caryopyllene, humulene and derivatives constitute nice examples of this approach (Collado et al. 1998; Yang et al. 1992; Gatilova et al. 1991). Most of these (and others) molecular rearrangements of natural terpenes were collected by Barakhash and Polivinka in 1999 (Barakhash and Polivinka 1999) and are not included here to avoid unnecessary repetitions.

This review includes the results obtained in Lewis or Brønsted acid-mediated cyclyzation-rearrangements cascades oriented to the biomimetic synthesis of terpenoids. These achievements are presented in chronological order, thus-allowing the reader to view the evolution of this strategy until the present time.

Cascade of rearrangements and cyclizations in the biomimetic synthesis of terpenoids

One of the first examples of cascade reactions including cyclizations and rearrangements were described by Van Tamelen et al (Van Tamelen et al. 1966; Van Tamelen and Sharpless 1969). This team treated to mimick the action of cyclases by reacting epoxypolyprenes with different acids. Thus, the treatment of triterpene squalene 2,3-oxide (**1**) with 0.2 mmol of $SnCl_4$ produced with poor yields, among others, the tricyclic triterpene alcohol **2**.

As shown in Fig. 3, the generation of **2** implies a triple cyclization to produce the corresponding tertiary malabaricane carbocation, which evolves to the final product after a hydride and a methyl shift, and a final deprotonation.

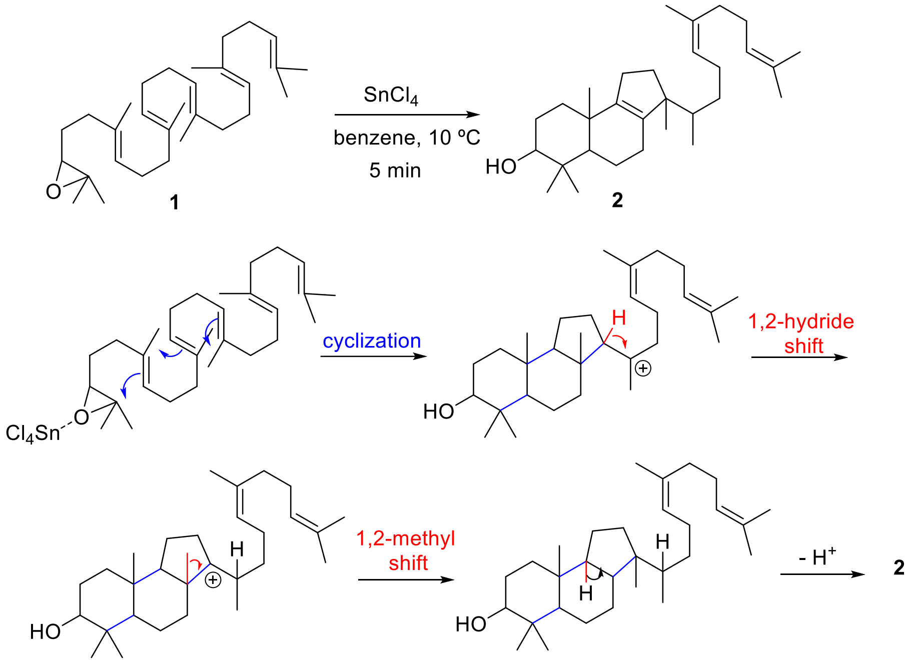


Fig. 3. Cyclyzation of oxidosqualene to give the rearranged tricyclic **2**. Mechanistical proposal

A few years later, the same author reported that, together with **2**, alcohol **3** was also produced in the reaction of **1** with $SnCl_4$ (Fig. 4). Compound **3** also presents a rearranged skeleton. In this case, three consecutive Wagner-Meerwein rearrangements were needed to produce the halimane bicyclic core present in **3** (Fig. 4). Although undoubtedly impressive, no stereochemistry was assigned in either of the corresponding manuscripts.

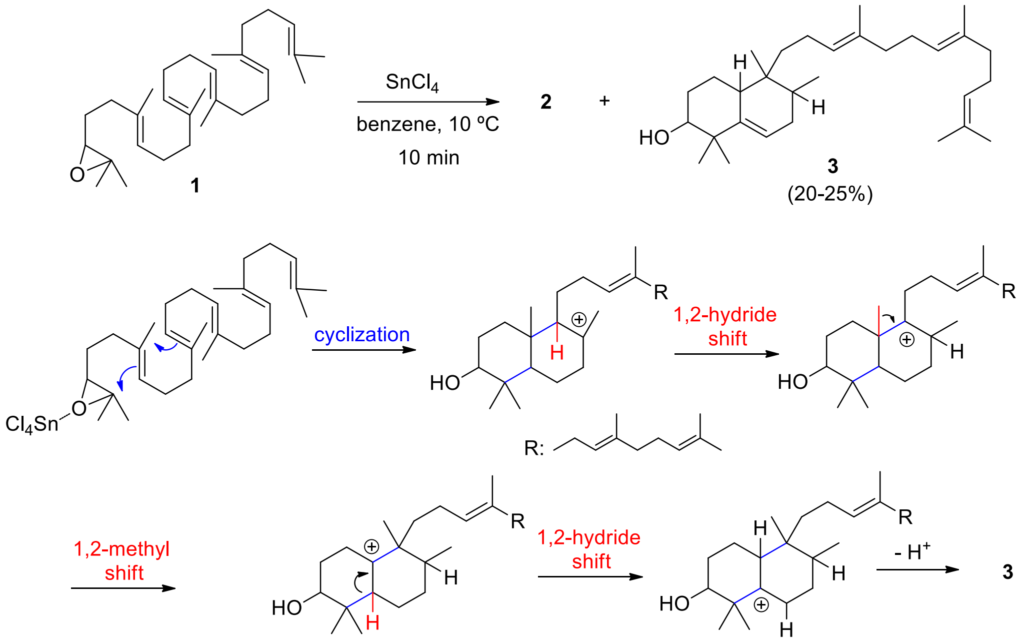


Fig. 4. Cyclization of oxidosqualene to produce compound **3** presenting the bicyclic halim-5-ene core. Mechanistical proposal

With the ultimate aim of synthesizing the tetracyclic core of natural steroid system with a five-membered ring (D ring), Johnson and Parker (Parker and Johnson 1974) devised a series of biomimetic-like olefinic cyclizations. Thus, these authors initially synthesized the monocylic polyenes **4** and **5** and then treated them with $SnCl_2$ or CF_3COOH in different experimental conditions. In the event, only one tetracyclic compound was obtained, that is, the steroidal diene **6** (no yields were provided) (Fig. 5).

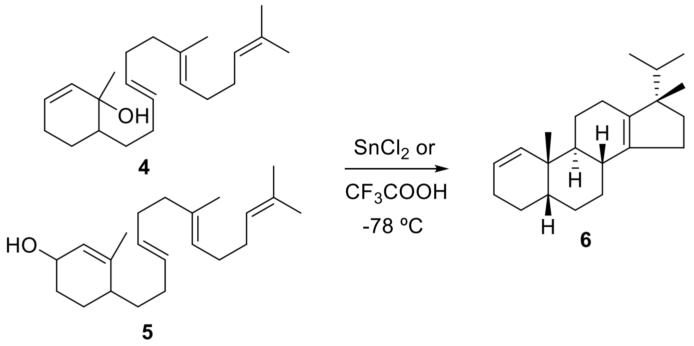


Fig. 5. Generation of tetracyclic **6** possessing the five-membered D ring present in naturally occurring steroids.

The mechanistic pathway to **6** would imply a tricyclization reaction followed by two Wagner-Meerwein rearrangements (a 1,2-hydride and 1,2-methyl transfers) to end with a deprotonation (Fig. 6).

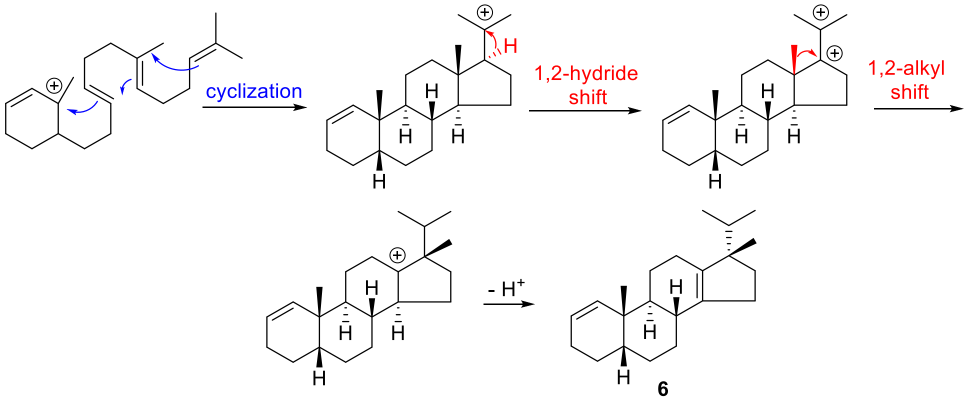


Fig. 6. Proposed cyclizations and rearrangements leading to **6**

In 1997, Corey (Corey and Roberts 1997) described the unexpected biomimetic-like cyclization and rearrangements of two monoepoxydienes, epoxypolyprene analogues **7** and **8**, when treated with BF_3 (g) and $MeAlCl_2$, respectively (Fig. 7).

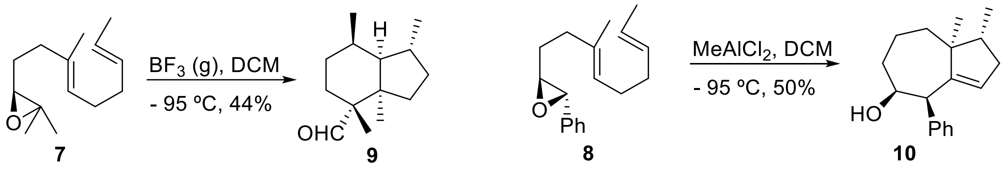


Fig. 7. Cyclization of epoxypolyprene analogues **7** and **8**

A reasonable mechanistic pathway for the generation of both compounds was proposed, where the rare intermediacy of secondary carbocations should be noticed. Remarkably, both compounds share the same steps until the formation of common intermediate **11** as shown in Fig. 8. The process initiates with a two-step cyclization with the starting material adopting a chair-boat conformation. It should be noted that in the case of **8**, a C1-C2 bond rotation in the initially-generated benzylic cation takes place before the cyclization reaction. After the two rings closure, a boat to chair flip was proposed. Then, a series of Wagner-Meerwein rearrangements (including methyl, alkyl and hydride shifts) were produced leading to the generation of common intermediate **11**. From **11**, a proton elimination generates **10**, whereas the formation of **9** involves a new 1,2-methyl shift and a ring contraction (Fig. 8). This cascade of multiple rearrangements constitutes important evidence about the influence of structural and stereochemical requirements on these tandem processes.

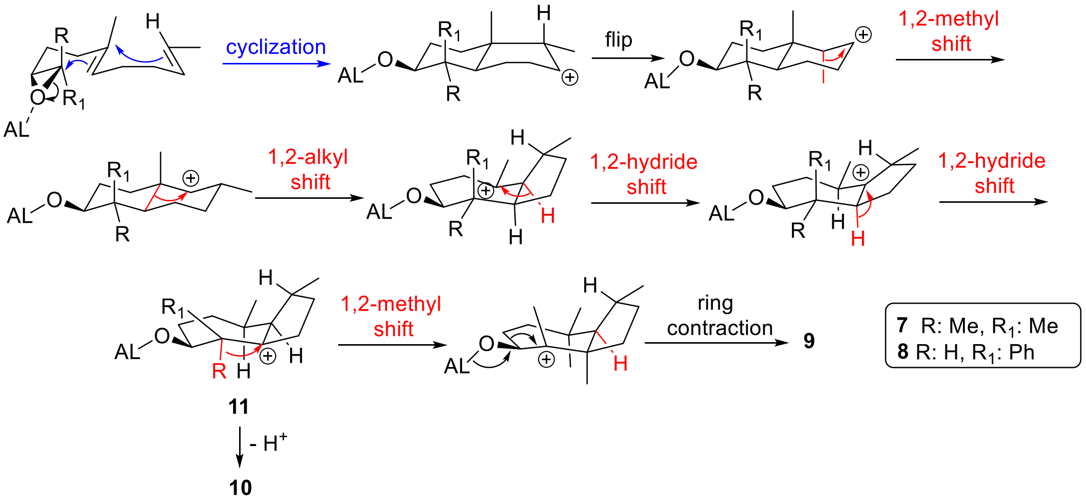


Fig. 8. Mechanistical hypothesis for the generation of **9** and **10**

During the twentieth century, this approach became more and more used as key step in the synthesis of terpenes.

Corey and Surendra described in 2008 (Surendra and Corey 2008) a very unusual example of cyclization plus 1,5-proton shift in their synthesis of the pentacyclic alcohol **6**, the key intermediate in the Ireland´s synthesis (Ireland et al. 1970) of pentacyclic triterpene germanicol **(15)** (Fig. 9). This bioactive triterpene induces selective growth inhibitory effects in human colon HCT-116 and HT29 cancer cells through induction of apoptosis, cell cycle arrest and inhibition of cell migration (Hu et al. 2016).

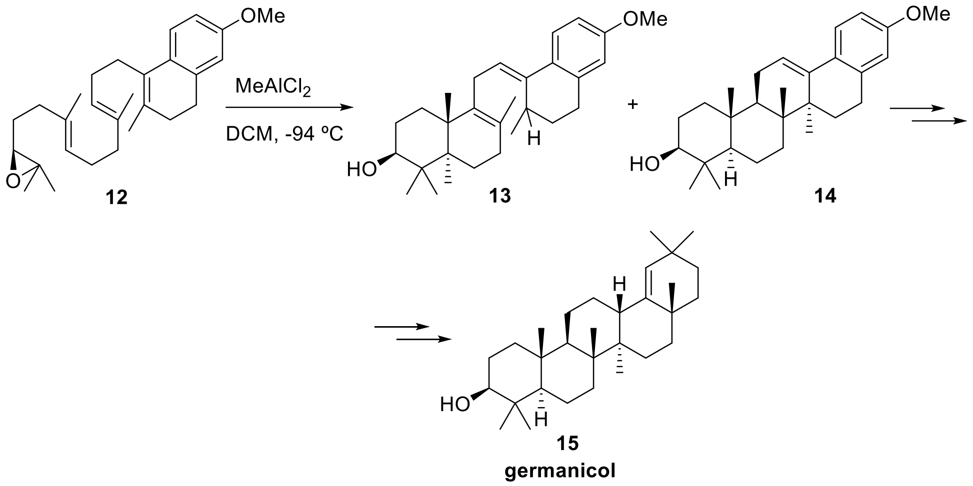


Fig. 9. Corey´s formal synthesis of germanicol (**15**)

It was postulated that the formation process of **13** included an initial cyclization reaction to produce a bicyclic carbocation which then experienced by a rare 1,5 migration of the H9 proton to generate a benzylic cation which evolved by depronation to finally afford compound **13** (Fig. 10). Isotopic ^{2}H-labeling experiment supported the mechanism proposal.

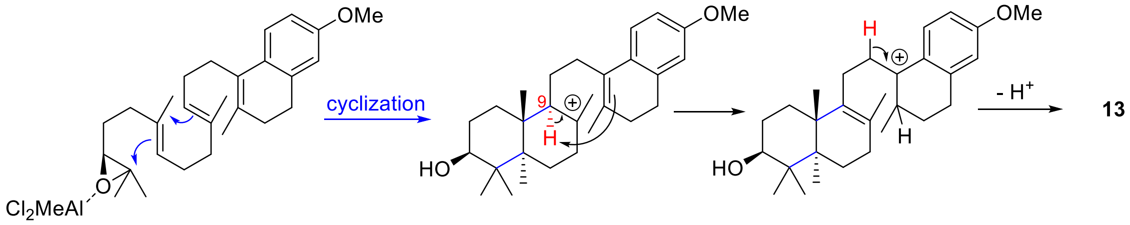


Fig. 10. Mechanistical hypothesis of the key transformation in the Corey´s synthesis of germanicol

The synthesis of the oleanane triterpenes such as allobetulin from lupanes has been described from different authors (Dehaen et al. 2011). The most representative example of this kind of transformation is the synthesis of allobetulin (**17**) using as starting material betulin (**16**) a relatively abundant natural triterpene (Fig 11). In general “allobetulins” are potent bioactive triterpenes possesing a wide spectrum of biological activities, such as cytotoxic, antiviral, antifeedant, immunotropic, antimicrobial and anti-inflammatory (Tolstikov et al. 2005)

In 2008 Salvador et al reported the employ of different bismuth(III) salts to catalyze the transformation of cyclopentane E ring of lupanes to cyclohexane, in a process involving the final generation of a tetrahydrofurane ring (Fig 11) (Salvador et al. 2008). The yield was as high as 95 when 5% mol of $Bi(OTf)_3$ was used. This transformation is known as “betulin-allobetulin rearrangement” (King and Mayo 1968) and was first described in 1922 by Schulze and Pieroh (Schulze and Pieroh 1922).

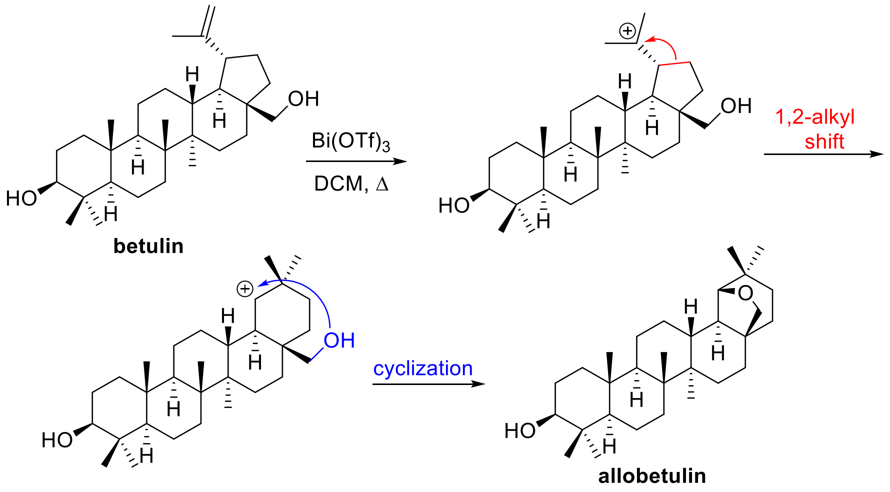


Fig. 11. Betulin-allobetulin rearrangement.

Germacrone (**17**), a natural sesquiterpene with applications in perfumery and as pesticide (Navarro-Rocha et al. 2018), is available in multigram scale from the essential oil of *Geranium macrorrhizum* (Ognyanov and Ivanov 1958). Barrero et al reported that this substance presents a remarkable proximity between its C1 and C4 carbons (smaller than the sum of the Van der Waals radii) (Barrero et al 2009). These authors argued that this spatial proximity should facilitate transanunular cyclizations. To test their hypothesis, germacrone was treated with HSO_3Cl acid in nitropropane at -78 ºC to afford the unusual skeleton present in **18-20** via a cascade of cyclizations and Wagner-Meerwein rearrangements (Fig. 12).

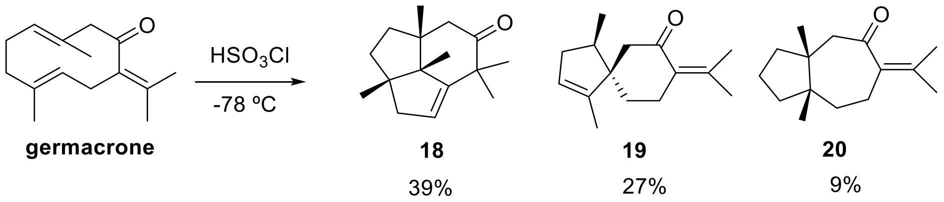


Fig. 12. Products of cyclization-rearrangement of germacrone

The mechanism proposed to reach these compounds was supported by DFT calculations. These theoretical studies revealed the tricyclic intermediate **21** to be the common intermediate to all the three structures. Its formation from germacrone involves a first cyclization process originating a C1-C4 bond forming, and a posterior concerted 1,2-alkyl shift and cyclization process (Fig. 13).

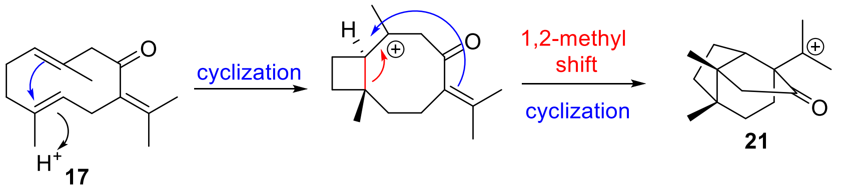


Fig. 13. Generation of intermediate **21**.

From **21**, the generation of **18** is initiated via a concerted transformation involving two 1,2-alkyl shifts and a cyclization to produce carbocation **22**, which evolves toward **18** after a third 1,2-alkyl shift and a final deprotonation (Fig. 14a). A similar sequence of rearrangements led to carbocation **23** from **21**, and, again, a third alkyl shift followed by deprotonation allowed rationalize the generation of **19** (Fig. 14b). Finally, compound **20** was postulated to be originated from **21** after a 1,2- alkyl shift followed by a deprotonation reaction (Fig. 14c).

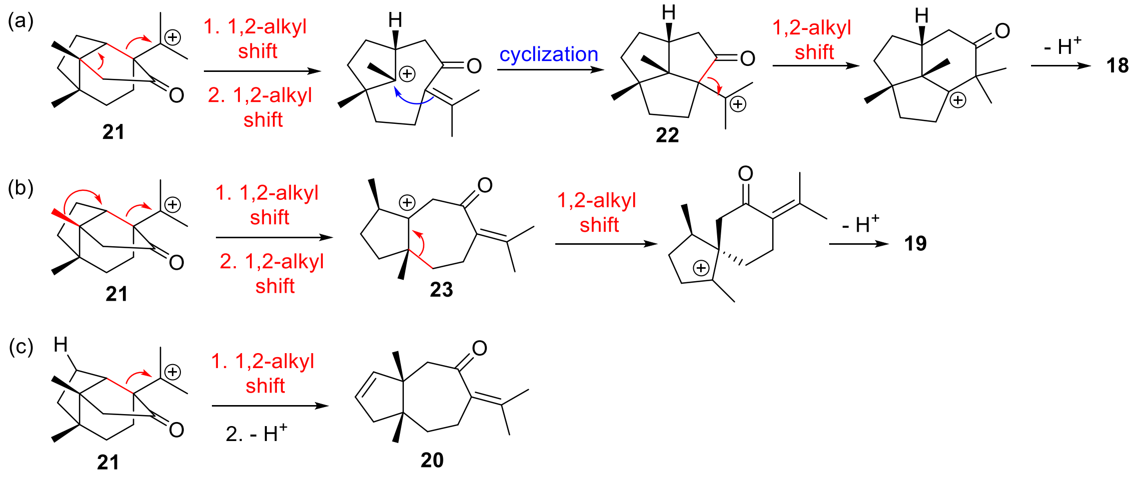


Fig. 14. Proposed cyclizations ad rearrangements leading to **18**-**20**.

The last decade has witnessed a number of examples describing cascades of cyclizations and rearrangements as key step in the multistep synthesis of potent bioactive natural terpenoids. Thus, Watanabe et al. (Watanabe et al. 2010) reported a total synthesis of (+)-stachyflin (**24**), a sesquiterpenoid alkaloid, isolated form the sponge *Smenospongia aurea*, that show good properties against influenza virus with a unique mode of action (Yoshimoto et al. 2000). Key to the synthesis was the reaction of epoxide **25** with boron trifluoride etherate that caused the generation of **26** after the epoxide opening followed by two rearrangements and a cyclization (Fig. 15).

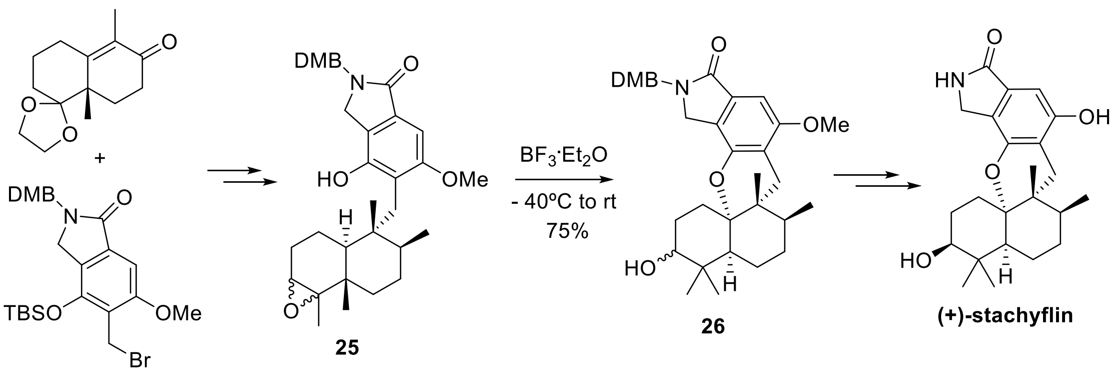


Fig. 15. Watanabe´s synthesis of (+)-stachyflin.

The Lewis acid-mediated oxirane opening generates a carbocation at C4 that undergoes a two sequential 1,2 methyl shifts and 1,2-hydride shift. Finally, the thus-generated carbocation is captured by the aromatic hydroxyl group to get the corresponding cyclization product (Fig. 16).

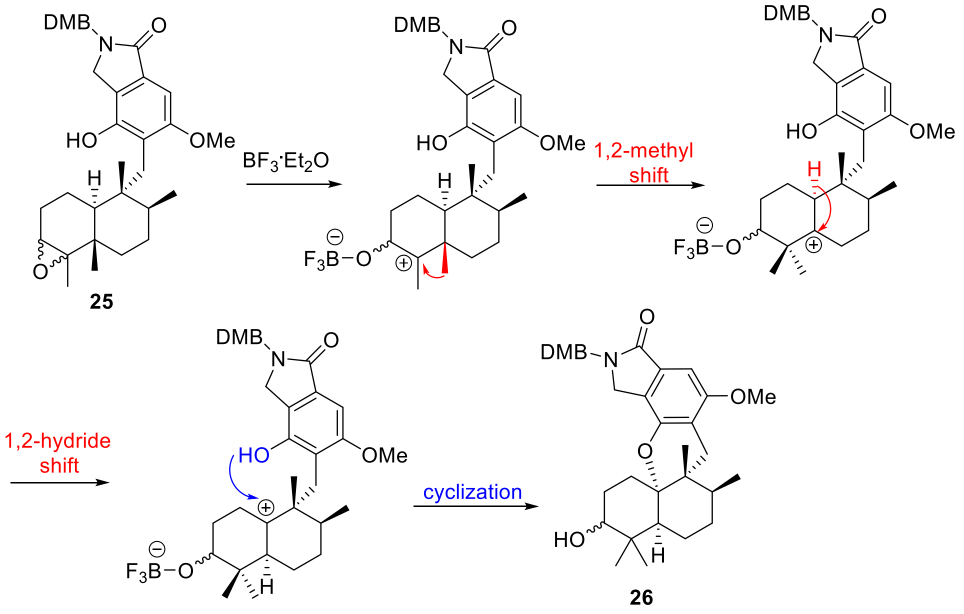


Fig. 16. Cyclization and rearrangements involve in the generation of **26**, key intermediate in the synthesis of (+)-stachyflin.

Liphagal (**27**) is a meroterpenoid natural product isolated from the sponge species *Aka coralliphaga*. This molecule has demonstrated activity as inhibitor of phosphoinositide-3-kinase as well as cytotoxic activity to LoVo (human colon), CaCo (human colon) and MDA-468 (human breast) tumor cell lines (Marion et al. 2006). George et al. (George et al. 2010) proposed the synthesis of liphagal from the natural product (+)-sclareolide (**28**) in 13 steps (Fig. 17).

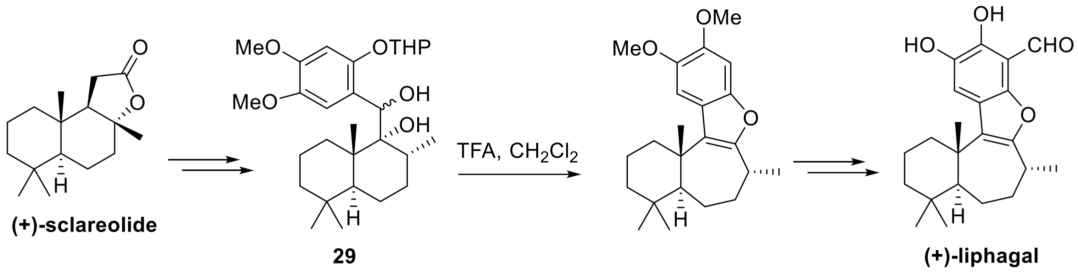


Fig. 17. Synthesis (+)-liphagal from (+)-sclareolide

Key in the synthetic approach to liphagal was the acid-mediated ring expansion of **29** via pinacol-type rearrangement of a stabilized benzylic carbocation, which was followed by a heterocyclization reaction (Fig. 18).

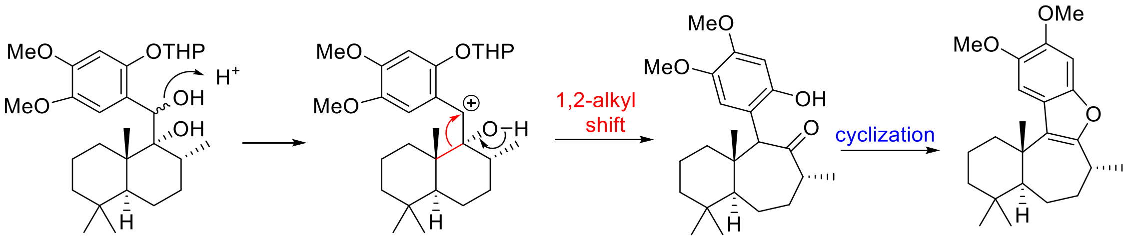


Fig. 18. Rearrangement and heterocyclization en route to (+)-liphagal

Cheilanthane sesterterpenoids are a family of natural terpenoids presents mainly in marine organisms characterized by presenting diverse and potent biological properties (Ungur and Kulciţki 2009). Aimed at synthesizing cheilanthane sesterterpenoids, Ungur et al (Ungur et al. 2002), studied the reaction of bycyclofarnesylfarnesoic methyl esters with superacids at low temperature. Thus, the treatment of the 13*Z*,17*E* ester **30** with 5 equiv of FSO_3H at –78 ºC yielded as major compound the 22(8→14)-abeo-cheilanthanic ester **31**, together with minor quantities of scalaranic ester (Fig. 19)**.**

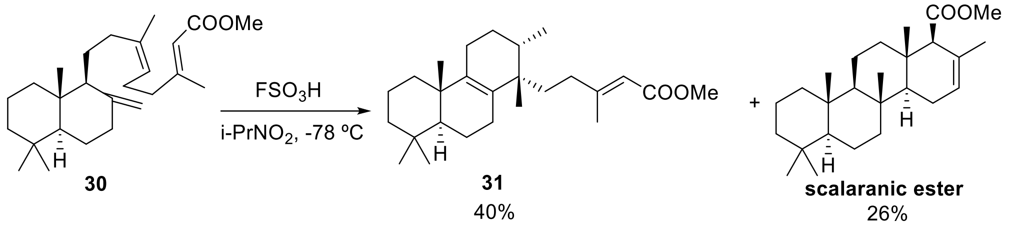


Fig. 19. Synthesis of the 22(8→14)-abeo-cheilanthanic ester **31**.

The generation of **31** involved a monocyclization process to afford the expected tricyclic carbocation that evolved via a 1,2-hydride shift and a 1,2-methyl shift to produce a carbocation at C8 which deprotonated to give the final tricyclic compound (Fig. 20).

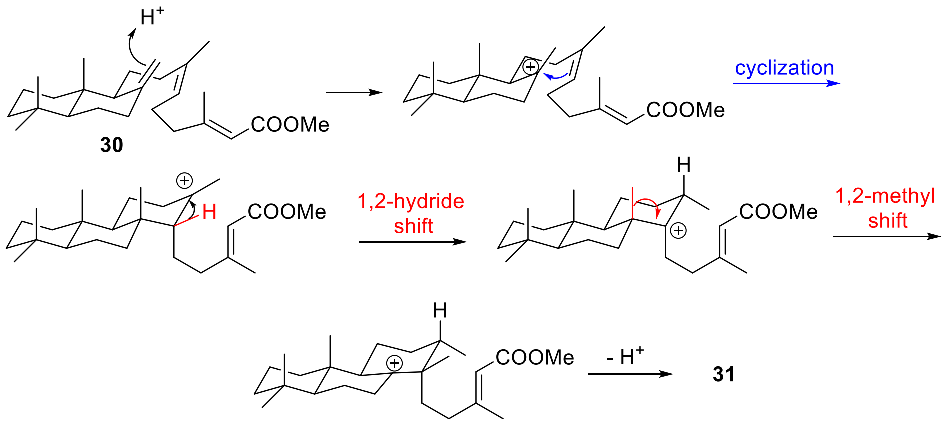


Fig. 20. Mechanistic proposal for the formation of **31**.

Duñach et al. reported different polyannulation processes on 1,6,10-trienes (Godeau et al. 2011; Godeau et al. 2012). Although neither the starting polyenes nor the final cyclized products are natural compounds, the transformation could be considered "biomimetic" as the authors claimed, thus justifying its inclusion in this review. Additionally some of these processes have been developed in order to facilitate the preparation of tricyclic core of abietane skeleton of diterpenes. In their work, the authors described how the Lewis superacid Bi(OTf)$_3$ catalyzed the cylization-rerrangement of triene **32** to afford rearranged bicyclic **33** in good yield (Fig. 21). Similarly, the arylpolyene **34** afforded quasi-quantitatively tetracyclic **35** after a final Friedel-Crafts reaction.

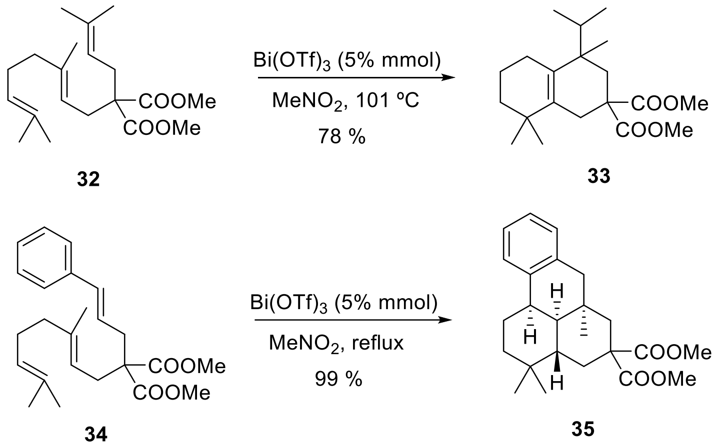


Fig. 21. Bi(OTf)$_3$-mediated biomimetic cyclization of polyenes.

Theoretical DFT calculations provided rationalization for these transformations (Fig. 22). In the case of triene **32**, the calculations indicated a step-wise cyclization process. The resulting bicyclic tertiary carbocation experienced a double Wagner-Meerwein rearrangement (1,2-hydride and 1,2-methyl shifts) to afford, after deprotonating, the final product **33**. In the case of arylpolyene **34**, the cyclization process was shown to be concerted. The corresponding bicyclic carbocation evolved to the final tetracyclic product after three sequential hydride and methyl shifts followed by a final Friedel-Craft alkylation (Fig. 22).

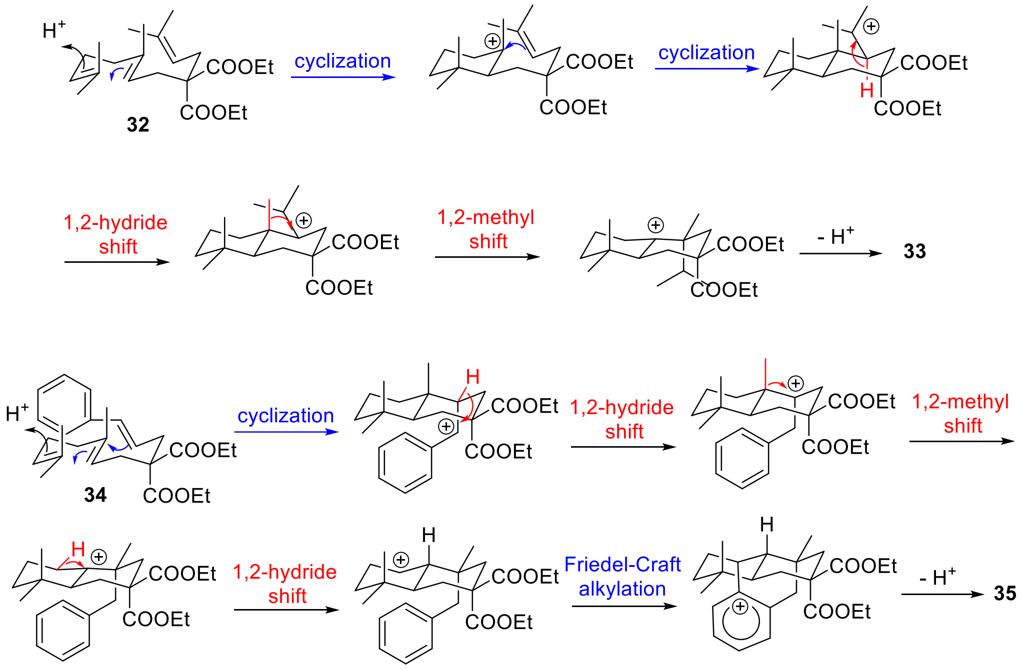


Fig. 22. Cyclizations and rearrangements leading to compounds **33** and **35**.

Shenvi and Pronin (Shenvi and Pronin 2012) described the tail-to-head (isoprene rule nomenclature) policyclization of vinyl epoxides **36** to afford mixtures of rearranged cyclic structures that eventually were converted into natural tricyclic sesquiterpenes β-funebrene (**39**) or β-cedrene (**40**). These sesquiterpenes are antimicrobial natural products identified in essential oils and barks of several conifers (Sharma et al. 2016; Barrero et al. 2005; Barrero et al. 2000) (Fig. 23).

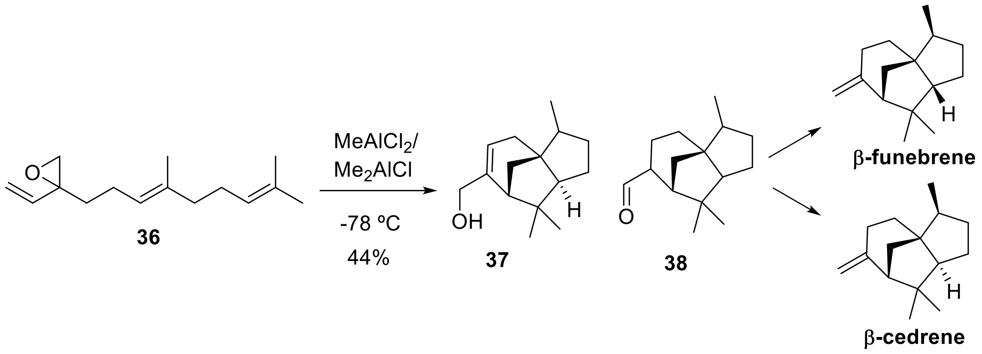


Fig. 23. Tail-to-head cyclization of **36**: synthesis of β-funebrene or β-cedrene.

The proposed reaction pathway to **37-38** involved three cyclization processes and two Wagner-Meerwein rearrangements (Fig. 24). The figure details the evolution of the 7(S)-carbocation obtained after the first cyclization and 1,2-hydride shift. The corresponding 7(*R*)-analogue was postulated to undergo the same transformations, although these are not included in the scheme to avoid repetitions.

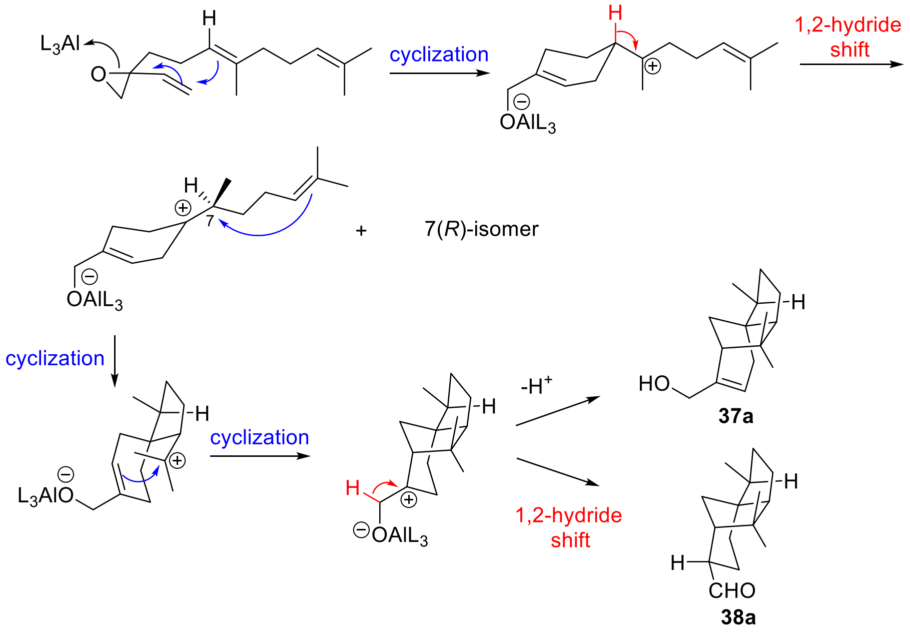


Fig. 24. Mechanistic proposal for the generation of tricyclic **37a** and **38a**

Continuing theirs studies on the chemistry of germacrone and other natural derivatives, Barrero et al reported some examples of cyclizations and rearrangements of germacrone-4,5-epoxide (**41**) (Pérez-Morales et al. 2013). Epoxide **41** is also a natural product found in the rhizomes of different species of Curcuma (Yoshihara et al. 1984). Epoxidation of germacrone with *m*CPBA affords germacrone-4,5-epoxide as the major reaction product. When this substance was treated with Et_2AlCl or $InBr_3$, a noticeable structural diversity was produced (Fig. 25). Compounds **42-44** are natural substances found in different species of Curcuma whereas diketone **45** is a new compound, although a natural substance containing the same 4 + 8 bicyclic skeleton was previously reported (Lidia-Pérez et al. 1994). Gajutsulactone A (**42**) was reported to inhibit nitric oxide production (Itokawa et al. 1979) and curcumenone (**43**) is a hepatoprotective that also presents antidiabetes activity (Morikawa et al. 2002). Both compounds (**42** and **43**) were also found by other authors in the reaction of **41** with AcOH at 100 ºC (Kuroyanagi et al. 2012).

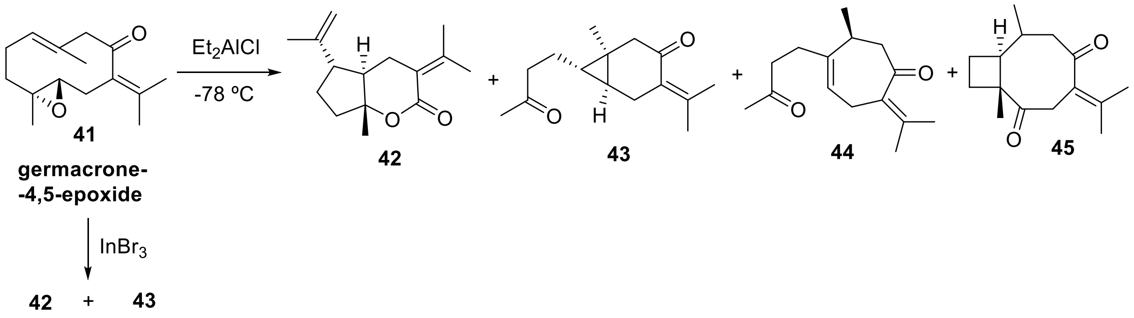


Fig. 25. Structural diversity from germacrone-4,5-epoxide.

Theoretical calculations were undertaken to support the mechanism proposed for the generation of structures **42-45**. The process starts with Lewis acid-mediated cyclization of only one of the possible conformers of **41 (41-I)** to give a guaiane carbocation, that was postulated to be a common intermediate for the formation of **42-44** (Fig. 26).

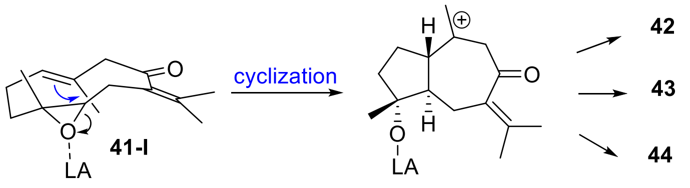


Fig. 26. Cyclization of **41**. Generation of an intermediate guaiane carbocation

Compound **42** was proposed to be formed from the key guaiane intermediate after a 1,2-alkyl shift followed by an attach of the oxygen derived from the epoxide opening to the carbonyl carbon atom (Fig. 27). From the same guaine intermediate, the generation of **43** involves a new alkyl rearrangement followed by deprotonation. Finally, the formation of **44** requires a double Wagner-Meerwein rearrangement, that is, a 1,2-hydride shift and a 1,2-alkyl shift (Fig. 27).

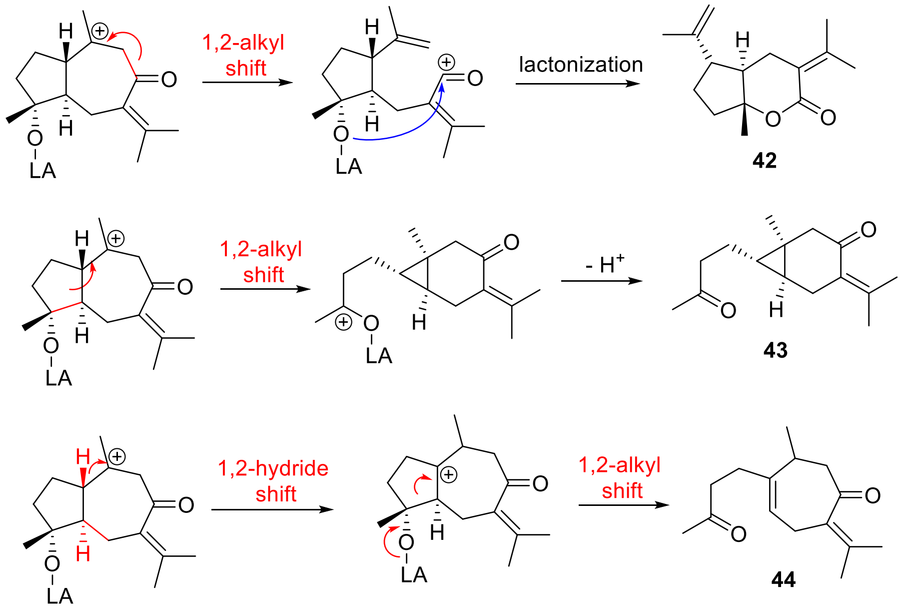


Fig. 27. Rearrangements leading to final products **42-44**.

On the other hand, the generation of diketone **45** was rationalized assuming the participation of a second conformer of **41 (41-II)**, which undergoes a first cyclization to provide a 4 + 8 bicyclic carbocation which evolves to the final product via by two sequential 1,2- and 1,3-hydride transfers and a final deprotonation (Fig. 28).

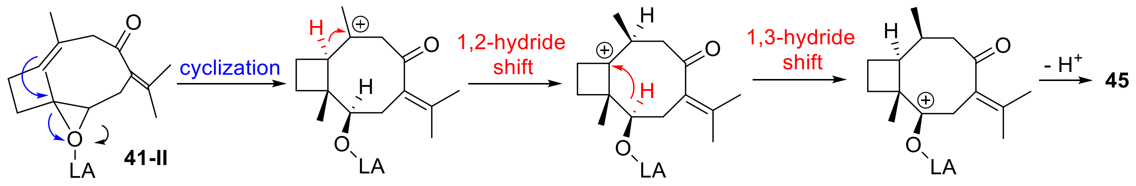


Fig. 28. Mechanistic hypothesis for the generation of **45** from germacrone-4,5-epoxide

The same authors described the generation of rearranged products (**47-49**) after treating germacrone-1,10-epoxide (**46**) with InBr$_3$ and Et$_2$AlCl (Fig. 29). It should be underlined that aldehyde **47** possesses a skeleton whose existence was not previously reported.

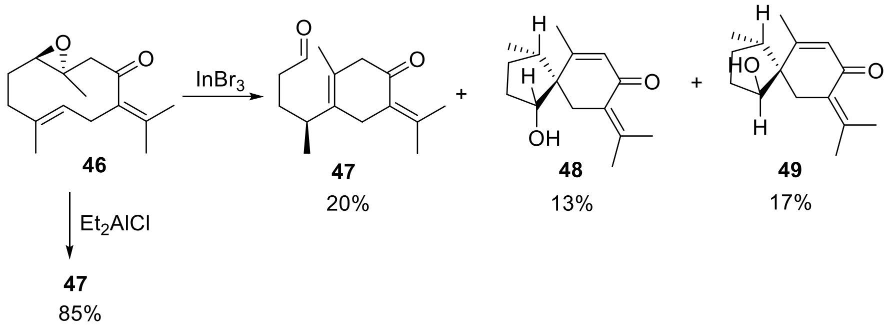


Fig. 29. Products resulting from a cascade of cyclizations and rearrangements in germacrone-1,10-epoxide (**46**)

Again, the proposed mechanism for the formation of these products was supported by theoretical calculations. Starting from the appropriate conformation of **46**, a first cyclization process leads to the corresponding eudesmane carbocation. From this intermediate, two sequential 1,2-hydride transfer and a 1,2-alkyl shift afford the monocyclic carbocation **50**. This cation was proposed to be a common intermediate for the generation of **47** and the mixture of **48** and its epimer **49**. Thus, the deprotonation of **50** produces **47** directly, whereas a second cyclization affords the rare spirojatame carbocation (as a mixture of epimers) (Hess et al. 2001), which evolves to the final products **48** and **49** via a final deprotonation (Fig. 30).

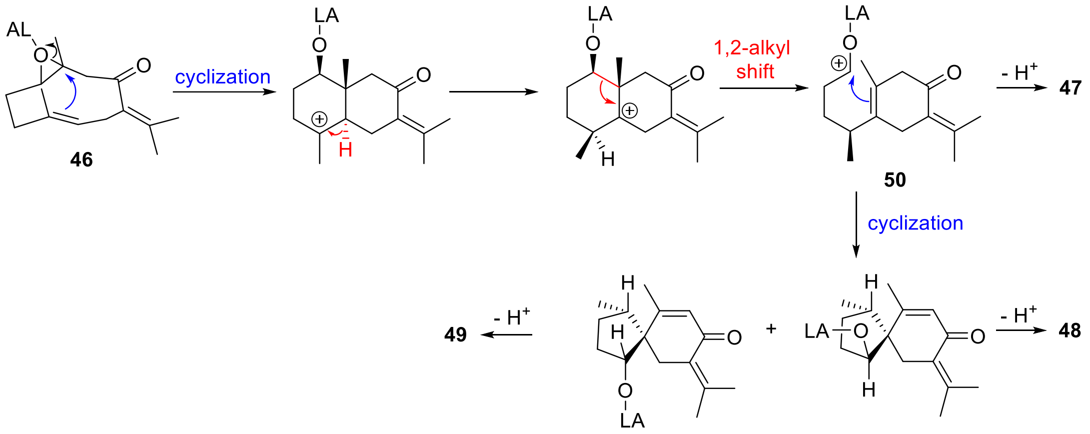


Fig. 30. Products resulting from Lewis acid-trigered cascade of cyclization-reraangements in germacrone-1,10-epoxide (**46**)

In their approach to aureole the synthesis of (±)-aureol (**53**) a cytotoxic compound isolated from *Smenospongia aurea* (Longley et al. 1993), Oltra et al. (Rosales et al. 2015) described the generation of the byproduct **54** resulting from a series of rearrangements and cyclization (Fig. 31). The action of boron trifluoride etherate in intermediate **52** was key in the synthesis of (±)-aureol (**53**),

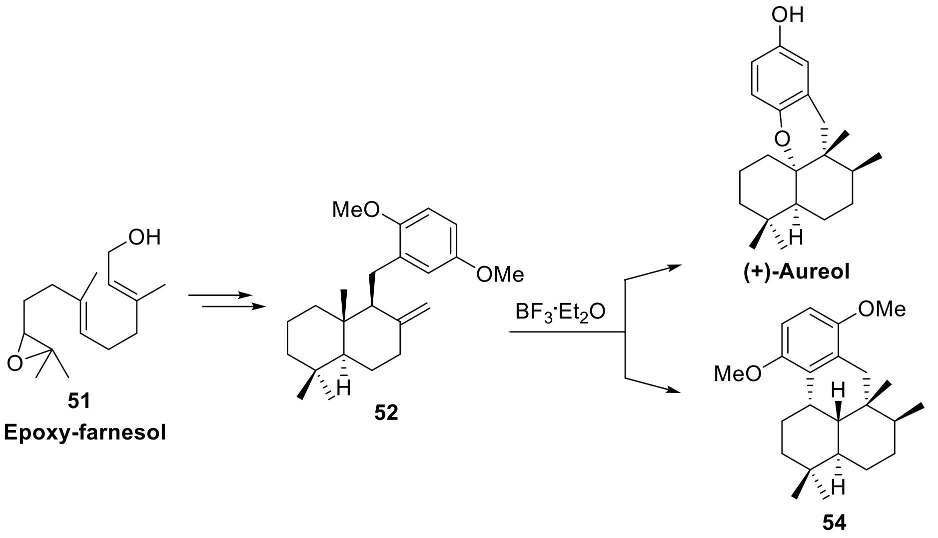


Fig. 31. Generation of aureol and **54**

The proposed mechanism to aureol and **54** involves an initial reaction of the exocyclic double bond in **52** with the Lewis acid causing the generation of the carbocation **55** and triggering three sequential Wagner-Meerwein rearrangements and a final cyclization process via an aromatic electrophilic substitution. Halymanyl carbocation **56** is a common intermediate to aureol synthesis.

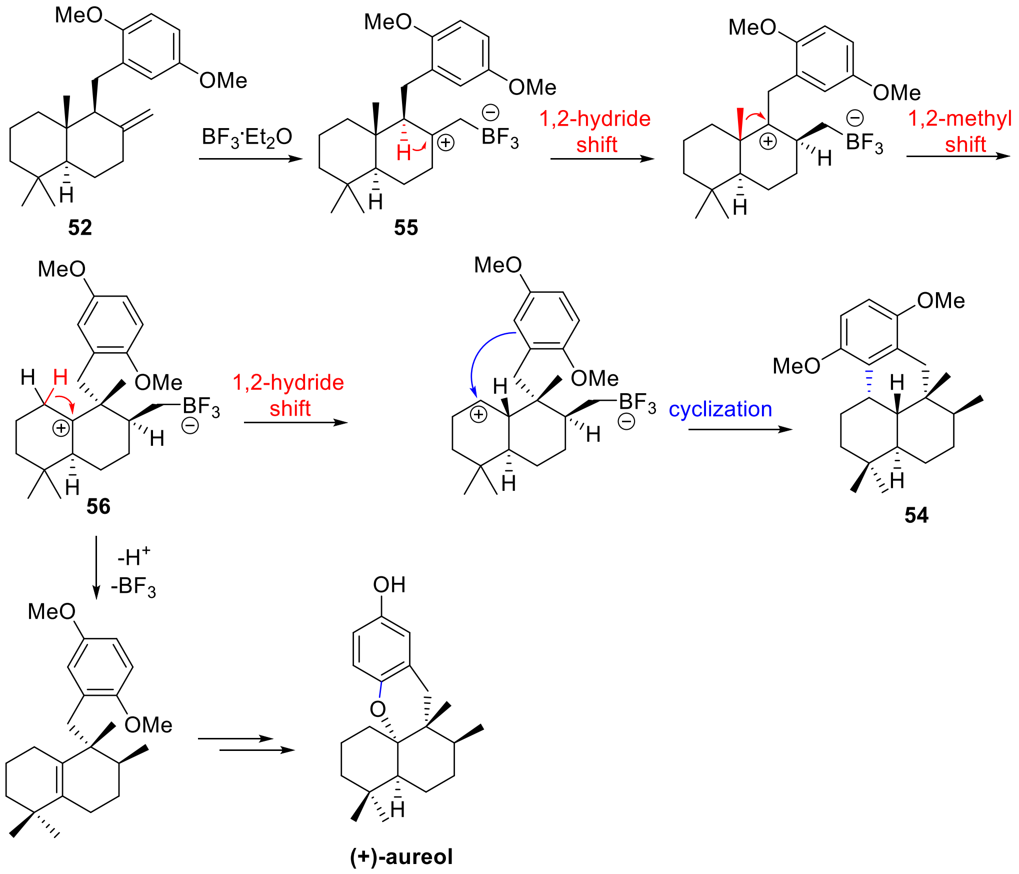


Fig. 32. Proposed mechanism for the generation of rearranged **54** in Oltra´s synthesis of (±)-aureol

Hyperjapones and hyperjaponols are natural meroterpenes containing an aromatic poliketide moiety. These substances have been found recently in *Hypericum japonicum*, a plant used in traditional medicine to treat hepatitis and some of them presented antiviral activity (Yang et al. 2016). George et al envisioned the biomimetic synthesis of hyperjaponol C (**58**) starting from hyperjapone A (**57**) (Lam et al. 2016) (Fig. 33).

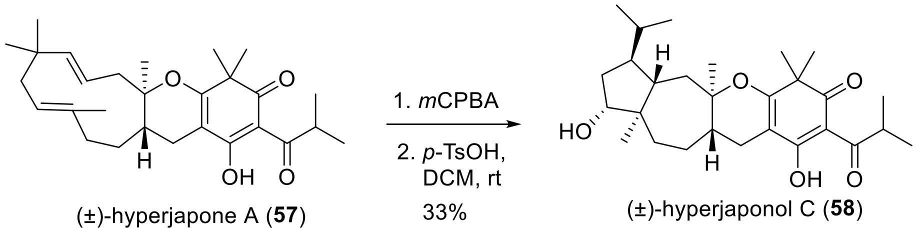


Fig. 33. Synthesis of hyperjaponol C via cyclization-rerrangement of hyperjapone A

The whole biomimetic process involved an stereo and chemoselective epoxidation followed by a cascade of an acid-catalyzed cyclization and a 1,2-alkyl shift (Fig. 34).

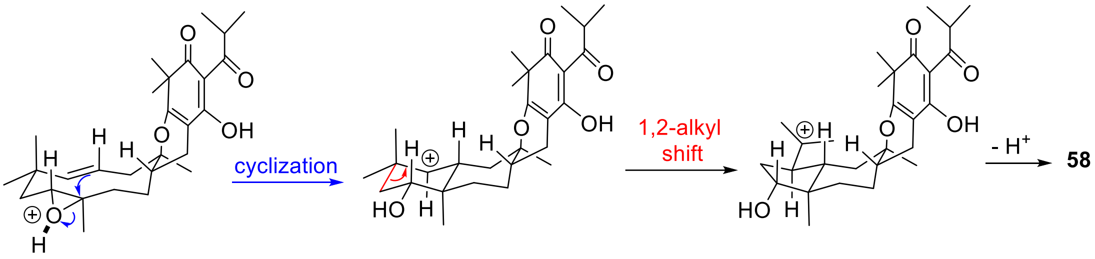


Fig. 34. Mechanistic proposal fror the generation of hyperjaponol C

Using as starting material natural zerumbone (**59**), a sesquiterpene with humulane skeleton possessing a wide range of biological properties, (Kalantari et al. 2007), Appendino et al (Minasi et al. 2017), described the formation of tricyclic sesquiterpenoid **60** (possessing a non-previously described skeleton) after the treatment zerumbone with $AlCl_3$ (Fig. 35). Natural humulanes are considerated biosynthetic intermediates toward numerous polycyclic sesquiterpenes (Cordel 1976).

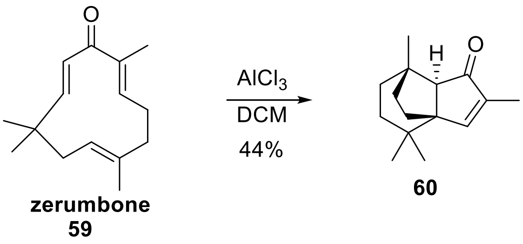


Fig. 35. Cyclization-rerrangement of zerumbone to give the tricyclic enone **60**

The generation of **60** is rationalized considering a Lewis acid activation of the carbonyl group to trigger a first cyclization process via Nazarov rearrangement. This approach supposes an alternative of the classical cyclyzation of polyenes involving the generation of a carbocation by electrophilic attack to a double bond. Deprotonation of the resulting allylic carbocation generates intermediate **61** which evolves to spirane **62** by ring contraction. A final acid-induced cyclization leads finally to **60** (Fig. 36).

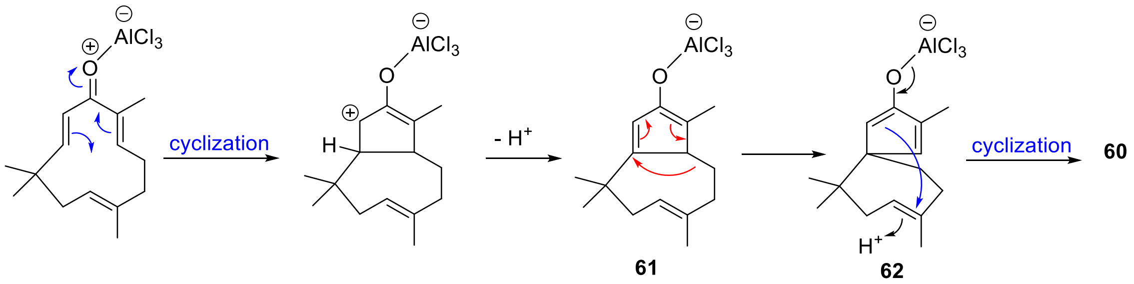


Fig. 36. Lewis-acid-mediated transformation of zerumbone

Conclusions

The cascade of cyclization-rearrangements of carbocations in the fields of the synthesis of terpenoids started to be reported as result of biomimetic studies. Nevertheless, in the last years, this approach has been used as key step in the synthesis of terpenoids with interesting biological activities. In this regard, it deserves to be underlined the synthesis of tricyclic sesquiterpenes such as beta-funebrene via an innovative tail-head cyclization followed by different rearrangements; or the formal synthesis of the germanicol using a key step a cascade of reactions including an inusual 1,5-proton shift, or the sustainable use of germacrone for the easy synthesis of natural sesquiterpenes and new sesquiterpene skeletons.

The reinforcement of the minimal assistance theory in biosynthetic processes involving cyclizations and rearrangements forecast a promising future to this methodology.

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3.2 *Artículo 2:* Access to Natural Valparanes and Daucanes: Enantioselective Synthesis of (−)-Valpara-2,15-diene and (+)-Isodaucene.

Quílez Del Moral, J. F.; Pérez, Á.; Herrador, M. D. M.; Barrero, A. F. Access to Natural Valparanes and Daucanes: Enantioselective Synthesis of (-)-Valpara-2,15-Diene and (+)-Isodaucene. *Journal of Natural Products* **2019**, *82* (1), 9–15. https://doi.org/10.1021/acs.jnatprod.8b00129.

https://pubs.acs.org/doi/10.1021/acs.jnatprod.8b00129

2019 JOURNAL IMPACT FACTOR

3.782

EDITION

Science Citation Index Expanded (SCIE)

CATEGORY

PLANT SCIENCES

32/234

JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
2019	32/234	Q1	86.54

Citaciones hasta el día 20 de octubre de 2021: **2**

Access to Natural Valparanes and Daucanes: Enantioselective Synthesis of (–)-Valpara-2,15-diene and (+)-Isodaucene

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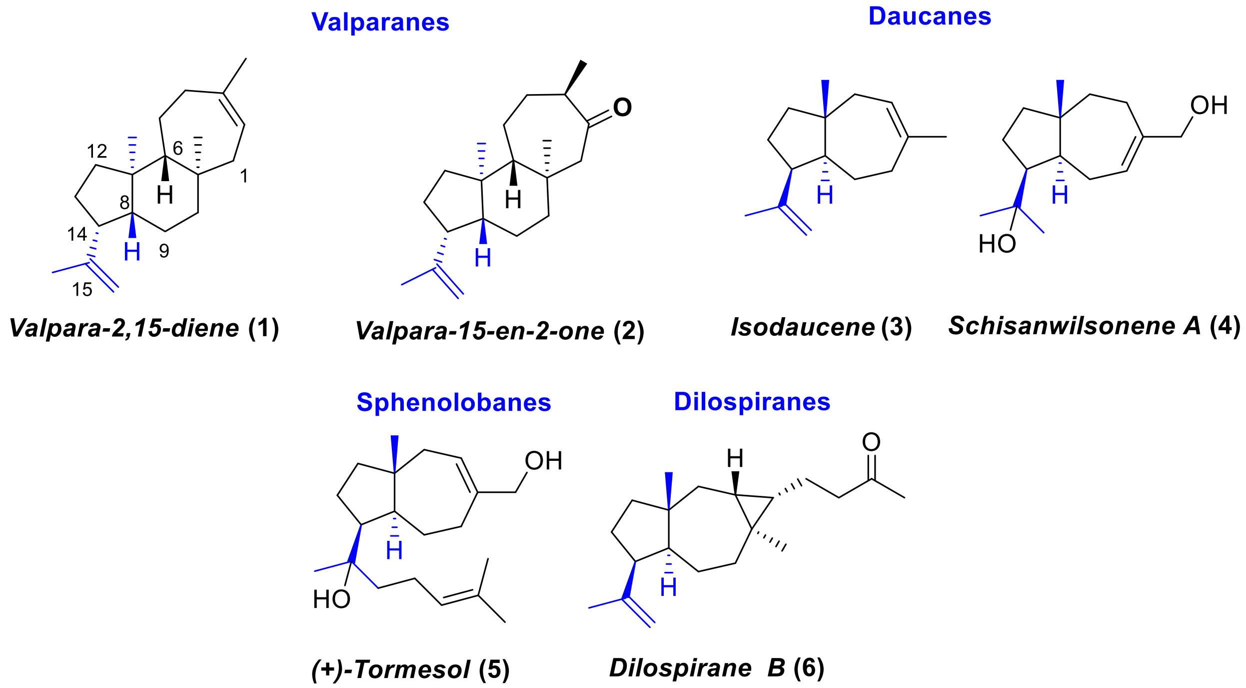
ABSTRACT: The first total synthesis of a natural diterpene valparane, (−)-valpara-2,15-diene (**1**) has been achieved from *all-trans*-geranylgeraniol (**9**), a natural renewable compound. The key steps involve a Ti(III)-mediated radical cyclization of the chiral mono-epoxypolyene (14*R*,15*R*)-14,15-epoxy,16-*tert*-butyldimethylsilyloxygeranyllinalyl acetate (**8**) to give the 6,6,7-tricyclic intermediate **7** with stereocontrolled formation of six stereocenters; a stereo- and regio-directed contraction of the A ring in **7** to produce a cyclopentane ring; and the ready generation of the target isopropenyl group. This research provides access to structurally- related natural products such as the sesquiterpene (+)-isodaucene (**3**), the synthesis of which is also reported herein.

Five-, six- and seven-membered carbocycles co-occur in natural terpenes possessing different molecular backbones. Among them, diterpene valparanes, isolated from the Cistaceae family of plants,[1] contain a cyclohexane fused between five- and seven-membered rings. A large majority of these diterpenes share the stereochemistry seen in valpara-2,15-diene (**1**) as well as the presence of an isopropenyl group at C-14 of the cyclopentane ring. Structurally related to valparanes, sesquiterpenes such as daucanes **3** and **4**,[2] and diterpenoids such as sphenolobanes (**5**)[3] and dilospiranes (**6**)[4] contain five- and seven-membered rings.



Valpara-2,15-diene **(1)** ***Valpara-15-en-2-one*** **(2)** ***Isodaucene*** **(3)** ***Schisanwilsonene A*** **(4)**

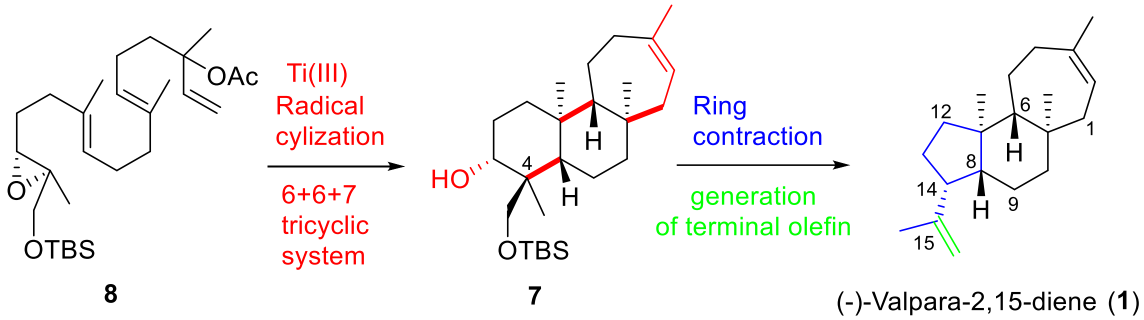
(+)-Tormesol **(5)** ***Dilospirane B*** **(6)**

Figure 1. Natural compounds containing five- and seven-membered rings.

Although the biological activities of valparanes have not been reported, some related compounds, such as those depicted in Figure 1, show interesting biological activities.[2f,5] Among them, schisanwilsonene A (**4**) is a potent antiviral[2f] while dilospirane B (**6**) possesses antitumor properties.[5i] These reported activities, together with the difficulty associated with developing synthetic approaches for producing these skeletons, particularly those of valparanes, prompted us to explore the synthesis of natural compounds containing five- and seven-membered rings in their structures. Only a few synthetic efforts toward this goal have been reported to date.[6]

Based on a study that demonstrated the radical opening of oxiranes using Nugent's reagent[7a-c] in 2001, we designed a general synthetic methodology for the production of cyclic terpenoids that involves a radical cyclization of mono-epoxypolyprenoids triggered by Cp_2TlCl.[7d] Based on the designed strategy, Justicia et al. reported the racemic synthesis of nonnatural racemic valpara-2,14-diene in 2005.[6b] Although their work represents the only reported synthetic approach for the generation of the valparane skeleton, some features of the method prevent or complicate its application for the generation of isomeric natural valpara-2,15-dienes. In fact, the literature does not describe any application of valpara-2,14-diene as an intermediate in the synthesis of natural valparanes.

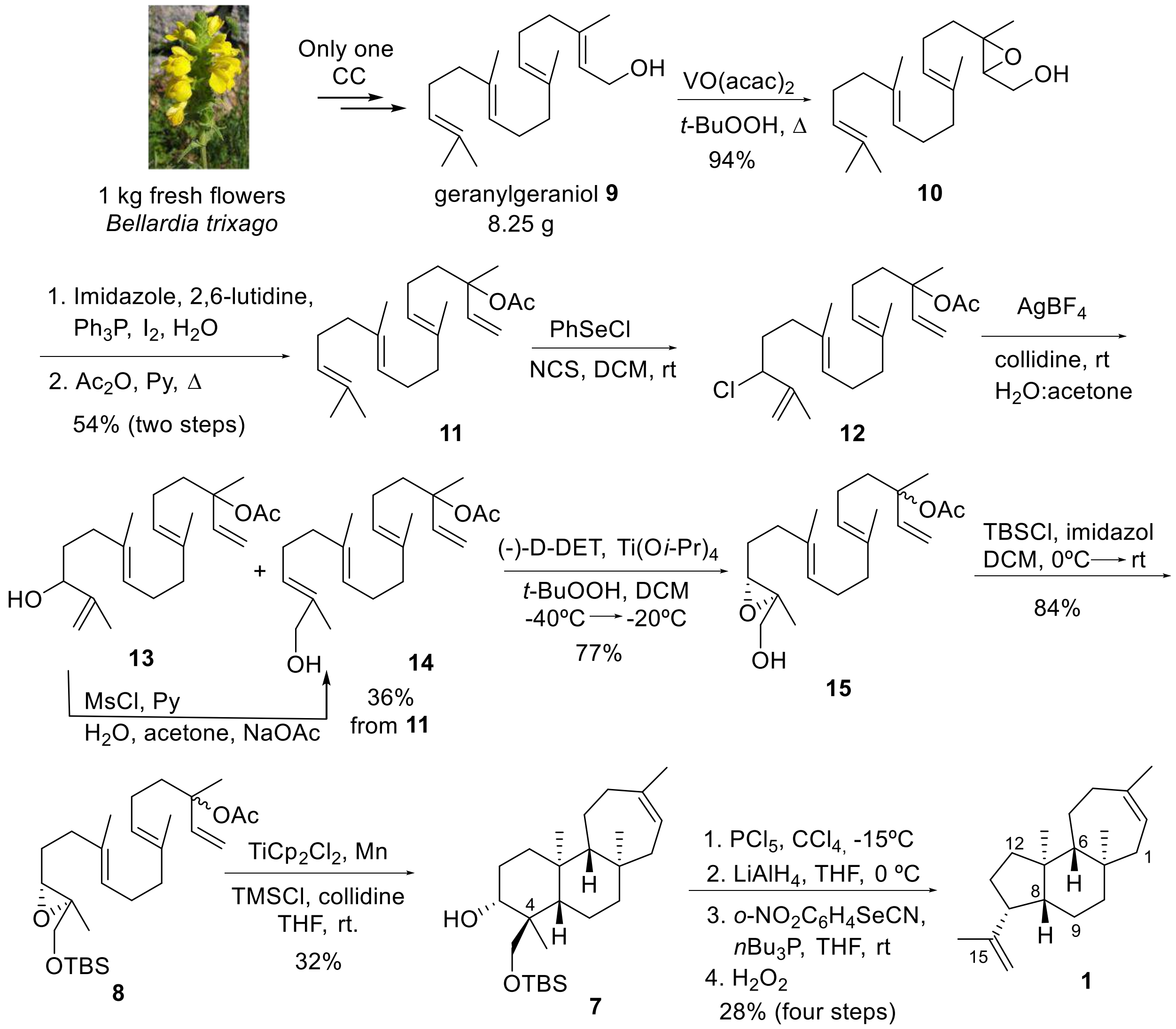
To address the ultimate goal of accessing natural valparanes, we describe herein an enantioselective route for obtaining natural (−)-valpara-2,15-diene (**1**). This synthesis has two key steps: the Ti(III)-mediated 6-*endo*-6-*endo*-7-*endo-trig* cyclization process[7,9] of acyclic silyloxymethyl oxirane **8** to afford the tricyclic intermediate **7** and the generation of target **1** from **7** through A-ring contraction, the most important transformation of this protocol[8] as shown in Scheme 1.



Scheme 1. Key Steps in the Synthesis Protocol

RESULTS AND DISCUSSION

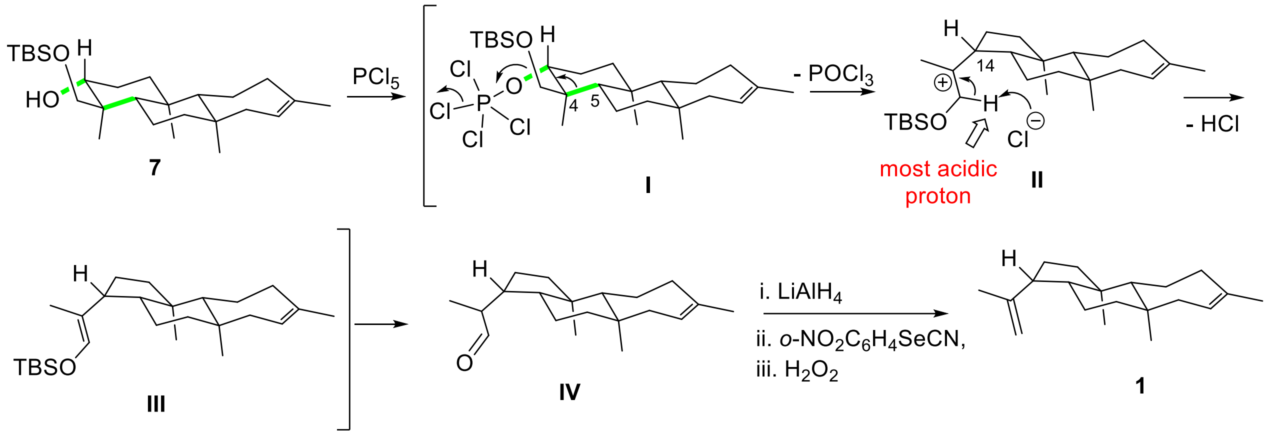
As outlined in Scheme 2, the synthesis of (-)-valpara-2,15-diene (**1**) was started with *all-trans*-geranylgeraniol **9**. As reported earlier,[7d] the geometry of the internal double bonds are fundamental to the success of the approach because only the all *E* isomer can be utilized in the planned Ti(III)-cyclization. Consequently, the ability to reliably obtain multiple grams of naturally occurring *E,E,E*-geranylgeraniol (**9**) from flowers of *Bellardia trixago* (L.) with the GeGeOH chemotype[10] constitutes one of the advantages of this approach. In this sense, considering the cost of *all-trans*-geranylgeraniol (Sigma-Aldrich Spain, 100 mg: 78.5 euros), the availability of this compound from natural sources should not be undervalued.



Scheme 2. Synthesis of (−)-Valpara-2,15-diene (1).

Epoxidation of geranylgeraniol (**9**) using the Sharpless protocol afforded its 2,3-epoxy derivative (**10**), and geranyllinalyl acetate (**11**) was obtained by subjecting epoxide **10** to Dorta's rearrangement conditions.[11] This reaction proceeds through the corresponding epoxyiodide, that undergoes reductive elimination due to the phosphine hydroxyiodide present in the reaction medium. Acetylation of the intermediate tertiary alcohol produced geranyllinalyl acetate (three steps) in 51% yield. Since there are nine allylic positions in **11**, the selective hydroxylation of this molecule at C-16 is not a straightforward transformation. In practice, it could be achieved via a highly chemoselective NCS/PhSeCl-mediated allylic chlorination followed by hydrolysis in the presence of $AgBF_4$.[12] Using this protocol, a quasi-equimolecular mixture of secondary and primary alcohols (**13** and **14**, respectively) was obtained from **11**. The secondary alcohol **13** could be recycled into **14** via mesylation and S_N2' hydrolysis, and considering this recycling, the primary alcohol **14** was obtained from **11** in a 36% overall yield. Since natural valparadiene (**1**) has been reported to be the *ent*-form,[1] chiral (–)-diethyl tartrate was used to perform the key asymmetric Sharpless epoxidation,[13] which afforded **15** in 77% yield. The silyl ether protection of the resulting asymmetric epoxy alcohol **15** afforded the key intermediate **8**. The cyclization of epoxide **8** triggered by catalytic Ti(III)[9a] yielded the tricyclic alcohol **7** in an acceptable yield of 32% and an enantiomeric excess of 87%. This result deserves to be highlighted because the domino process led to the closure of a 6,6,7 tricycle and to the stereocontrolled formation of six stereocenters. Coordination between the equatorially positioned titanoxy group at C-3 and the oxygen of the *tert*-butyldimethylsilyl ether in the transition state can be used to rationalize the final stereochemical outcome at C-4.[9d] A number of NMR resonances were key to assign the structure of **7**, namely: the signal at δ 3.60 (dd, J = 11.5, 5.0 Hz, 1H), which allowed us to establish the equatorial position of the hydroxy group at C-3; the three methyl singlets at δ 0.88, 0.83, and 0.82, confirming the cyclization process, and finally, a signal corresponding to an olefinic proton at δ 5.37–5.32 (m, 1H), that appeared as result of the loss of AcOH in the cyclization process. Next, the unprecedented contraction of the γ-dioxygenated A ring in **7** was attempted by treating this compound with PCl_5. Although different experimental conditions were assayed, complex mixtures containing silyl enol ethers and aldehydes were ultimately obtained (Scheme 3).[14] Thus, a process starting from the tricyclic alcohol **7** was developed, and the target product was obtained in a 28% yield through a four-step process that did not involve the isolation of any intermediates. The sequence involved the hydrolysis of the corresponding silyl enol ethers, followed by formyl group reduction and alcohol dehydration.[15] The spectroscopic properties and specific rotation value of + 10.1 of the synthetic compound **1** were identical to those of natural (−)-valpara-2,15-diene (**1**).[1c]

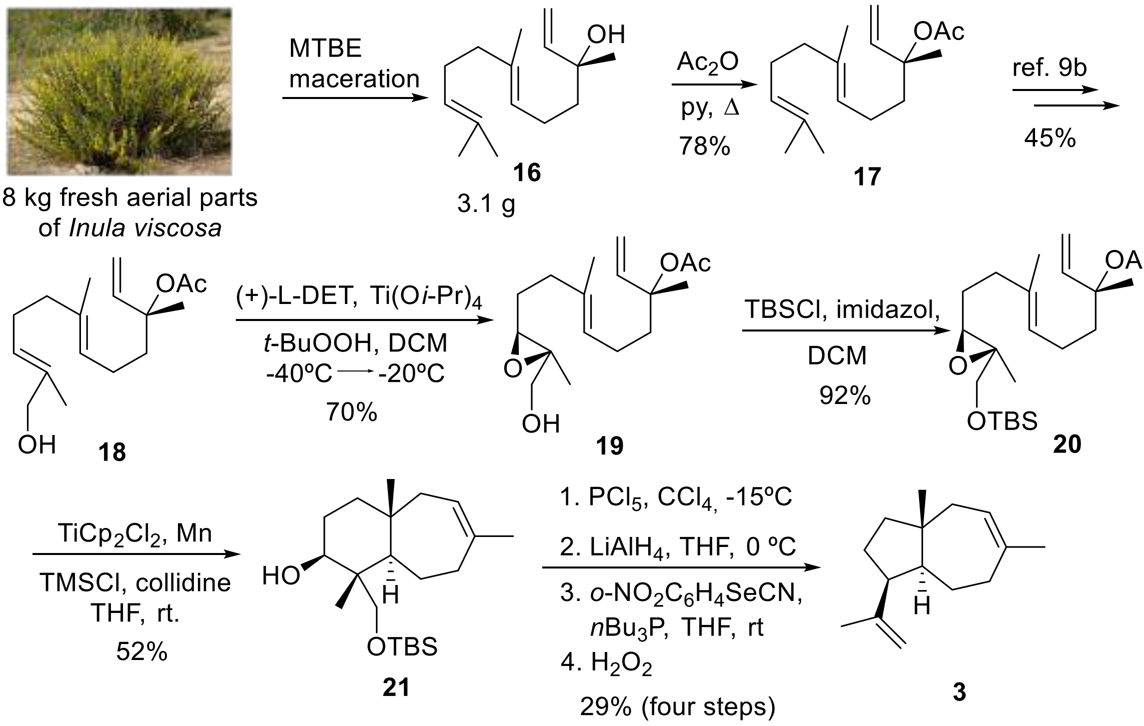
Focusing on the key A-ring contraction and the subsequent generation of **1**, the rationale behind this process is shown in Scheme 3. The equatorially-disposed primary oxygenated functional group at C-16 in compound **7** plays a key role in the success of the synthetic approach. Thus, the correct alignment of the C-4–C-5 bond and the activated hydroxy group in **I** would justify the migration of this bond to induce displacement of the leaving group and the generation of carbocation **II** with the appropriate configuration at C-14. This tertiary carbocation is converted to the corresponding silyl enol ether (**III**) by regiodirected deprotonation as a result of the higher acidity of the protons of the –CH_2OTBS moiety and the stability of aldehyde **IV**. Finally, the resulting aldehyde (**IV**) is converted into the target isopropenyl derivative **1** in a straightforward manner using standard transformations.



Scheme 3. Mechanistic Proposal for the Ring Contraction of A-ring Dioxygenated 7.

To confirm that this strategy can be used to synthesize other natural polycyclic products containing a cyclopentane moiety with an isoprenyl substituent, the synthesis of (+)-isodaucene (**3**) (Scheme 4) was addressed. As the starting material, (+)-(*E*)-nerolidol (**16**), another natural renewable compound was used. Up to 3.1 g of (+)-(*E*)-nerolidol (**16**) was isolated from the maceration of 8 kg of leaves and flowers of *Inula viscosa*.[16] The synthetic sequence toward (+)-isodaucene paralleled that of the synthesis of valpara-2,15-diene, and it is detailed in Scheme 4. The synthesis of (+)-isodaucene (**1**) began with the acetylation of **16**, and resulted in the production of nerolidyl acetate (**17**) in a 78% yield. The selective hydroxylation of nerolidyl acetate produced primary alcohol **18** through the same two-step protocol used in the synthesis of isodaucene, i.e., NCS/PhSeCl-mediated allylic halogenation followed by $AgBF_4$-mediated hydrolysis of the corresponding chlorinated derivative.[9b] Enantiocontrol was achieved through the Sharpless asymmetric epoxidation of **18** using L-(+)-diethyl tartrate to furnish the epoxide **19** in a yield of 70%. Protection of the primary hydroxy moiety to produce silyl ether **20** was achieved by treatment with TBSCl in the presence of imidazole (92%). Exposure of the epoxide **20** to catalytic Ti(III), as previously reported,[9b] led to the *trans* bicyclic alcohol **21** in an acceptable 52% yield, and only one out of the 16 possible stereoisomers was generated.

At this point, it was shown that contraction of the γ-dioxygenated A ring provided the target stereo- and regiochemistry, albeit in a modest yield. Thus, as described for the synthesis of (–)-valpara-2,15-diene (**1**), a four-step sequence that included A-ring rearrangement, formyl group reduction, and alcohol dehydration allowed the synthesis of the target natural compound from the bicyclic structure **21**. The spectroscopic properties of the synthetic compound correlated well with those published for natural isodaucene (**3**). The specific rotation of synthetic **3** was + 11.2, which is similar to that reported by Hashidoko (+ 13.0) for the same compound isolated from *Rosa rugosa*.[2g] Additionally, a study using *Cupressocyparis leylandii* that was performed by Cool led to the isolation of a compound with the same NMR data as those reported by Hashidoko, but a negative $[\alpha]_D$ value.[2d] In this regard, our synthesis permitted confirmation of the absolute configuration of the two natural enantiomers of isodaucene.



Scheme 4. Synthesis of (+)-Isodaucene (3).

In conclusion, the first access to natural valparanes is described. The key feature of the strategy is the stereo- and regio-directed contraction of the cyclohexane moiety with two hydroxy-derived substituents, which is the transformation that ultimately enabled the enantioselective synthesis of the natural valparane. Other relevant features are the availability of the starting material, which could be obtained on multigram scale from natural sources, the use of Ti(III)-mediated methodology to generate a tricyclic system with six contiguous stereocenters, and the use of a Sharpless asymmetric epoxidation to control the stereochemistry. This research may also provide access to other naturally related structures, as demonstrated by the synthesis of (+)-isodaucene (**3**).

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Silica gel SDS 60 (35-70 μm) was used for flash column chromatography. IR spectra were recorded on a Mattson Satellite FTIR spectrometer. NMR spectra were acquired with Varian Direct-Drive 600 (^{1}H 600 MHz/^{13}C 150 MHz), Varian Direct-Drive 500 (^{1}H 500 MHz/^{13}C 125 MHz), Varian Direct-Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz) and Varian Inova Unity 300 (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. Accurate mass determinations were achieved with a SYNAPT G2-Si mass spectrometer (Waters, Milford, MA, USA) equipped with high-efficiency T-Wave ion mobility and an orthogonal Z–spray™ electrospray ionization (ESI) source was used for mass analyses. MassLynx v.4.1 software was used for HRMS instrument control, peak detection, and integration. The reactions were monitored by TLC, which were performed on 0.25-mm E. Merck silica gel plates (60F-254) and involves the use of UV light for visualization and solutions of phosphomolybdic acid in EtOH and heat as the developing agents. HPLC with UV light and RI detection was also used. Semipreparative HPLC separations were conducted on a silica column (5 µm, 10 x 250 mm) at a flow rate of 2.0 mL/min using an Agilent Series 1100 instrument. The reagents were purchased at the highest quality that was commercially available and were used without further purification.

Plant Material. Aerial parts of *Bellardia trixago* of chemotype GeGeOH were collected in June 2014 in the Pantano del Cubillas zone (Granada, Spain) and identified by Prof. F. del Valle (Department of Fisiología Vegetal, University of Granada). Voucher specimens are available for inspection at the herbarium of the University of Granada. The aerial parts of *Inula viscosa* L. Greuter were collected in October 2014, in the Parque Almunia zone (Granada, Spain) and identified by Prof. F. del Valle (Department of Fisiología Vegetal, the University of Granada). Voucher specimens are available for inspection at the herbarium of the University of Granada.

Isolation of Geranylgeraniol (9) from the Extract of *Bellardia trixago*. Fresh flowers of *Bellardia trixago* (3 kg) were macerated in *tert*-butyl methyl ether (MTBE) at room temperature for 20 min to afford 55 g of extract. KOH (10% in MeOH, 10 mL) was added to a 10 g portion of this extract suspended in MeOH (50 mL). The solution was maintained at room temperature for 6 h. After removing most of the MeOH and diluting with H_2O (50 mL), the solution was extracted with MTBE (3 x 150 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude product, and the product was subjected to silica gel column chromatography using hexanes(H)/TBME mixtures of increasing polarity to afford **9**[17] (4.5 g, H/MTBE 7:3). The spectroscopic data of this compound were consistent with those previously reported.[18]

Compound 10. To a solution of 1.00 g of geranylgeraniol (**9**) (3.43 mmol) in 110 mL of toluene was added 45 mg of $VO(acac)_2$. The resulting mixture was refluxed under argon for 10 min and 1.25 mL of 5-6 M *tert*-butylhydroperoxide in decane (6.87 mmol) was added. After heating for 5 min, the mixture was diluted with EtOAc (200 mL), washed with saturated $NaHCO_3$ (3 x 100 mL) and brine, and dried over Na_2SO_4. The residue was subjected to column chromatography (H/MTBE 1:1) on silica gel to give epoxide **10** as a colorless syrup (992 mg, 94%). The spectroscopic data of this compound were consistent with those previously reported.[19]

Geranyl-linalyl Acetate (11). To a solution of **10** (2786 mg, 9.105 mmol) in 370 mL of a 3:1 mixture of benzene:1,2-dichloroethane was added imidazole (546 mg, 9.09 mmol), 2,6-lutidine (3.16 mL, 27.3 mmol), triphenylphosphine (9536 mg, 36.36 mmol), iodine (6921 mg, 27.27 mmol), and water (0.163 mL, 9.09 mmol). After stirring for 20 min under argon at room temperature, the crude reaction mixture was diluted with Et_2O, washed with saturated $Na_2S_2O_3$ (2 x 30 mL), saturated $NaHCO_3$ (2 x 30 mL), and brine, and dried over Na_2SO_4. The crude product was purified by column chromatography over silica gel (H/MTBE 8:1) to afford all *trans*-geranyllinalool (1954 mg, 74%).[20] Acetic anhydride (13 mL) and 4-dimethylaminopyridine (10 mg) were added to a solution of all *trans*-geranyllinalool (1280 mg, 4.414 mmol) in pyridine (7 mL). The mixture was heated at reflux for 8 h and poured into ice (100 g). The mixture was extracted with MTBE (3 x 100 mL). The organic layer was washed with 2N HCl (3 x 100 mL), saturated Na_2CO_3 (3 x 100 mL) and brine (3 x 100 mL), dried over Na_2SO_4, and concentrated. The resulting crude was chromatographed over silica gel (H/MTBE 97:3) to obtain acetate **11** as a colorless syrup (1055 mg, 72%). The spectroscopic data of this compound were consistent with those previously reported.[21]

3-Acetoxy-16-hydroxygeranyllinalool (14). PhSeCl (20 mg, 0.1 mmol) and NCS (154 mg, 1.10 mmol) were added to a solution of **11** (350 mg, 1.05 mmol) in dry CH_2Cl_2 (4.3 mL) under an argon atmosphere at room temperature. The mixture was stirred for 45 min, concentrated under reduced pressure, and diluted with Et_2O (150 mL). The organic layer was washed with H_2O (3 x 50 mL) and brine (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude product was dissolved in acetone-H_2O (1:2, 30 mL), and 2,4,6-collidine (0.55 mL, 4.1 mmol) and $AgBF_4$ (402 mg, 2.10 mmol) were added. The resulting mixture was heated at 60-70 ºC for 1 h. The solvent was removed *in vacuo* and the residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 25 mL). The organic layer was washed with 2N HCl (3 x 25 mL) and brine (3 x 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was separated by column chromatography (H/MTBE 3:1) on silica gel to give alcohols **13** (102 mg, 28%) and **14** (88 mg, 24%). Compound **13** was obtained as a colorless syrup: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (ddd, *J* = 17.6, 11.0, 0.9 Hz, 1H), 5.15 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.14 (bt, *J* = 6.9 Hz, 1H), 5.12 (dd, *J* = 11.0, 0.8 Hz, 1H), 4.94 (bs, 1H), 4.84 (bs, 1H), 4.04 (t, *J* = 6.4 Hz, 1H), 2.12−1.95 (m, 8H), 2.01 (s, 3H), 1.90−1.74 (m, 2H), 1.73 (s, 3H), 1.69−1.59 (m, 2H), 1.61 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H);^{13}C NMR (125 MHz,$CDCl_3$) δ 170.0, 147.5, 141.8, 135.3, 134.7, 124.6, 123.8, 113.1, 110.9, 82.9, 75.6, 39.7, 39.5, 35.6, 33.1, 26.4, 23.6, 22.2, 22.2, 17.6, 16.0, 15.9; HRMS (ESI+) calcd for $C_{22}H_{36}O_3Na$ $[M+Na]^+$ 371.2562, found 371.2541. Compound **14** was obtained as a colorless syrup: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.39 (bt, *J* = 6.4 Hz, 1H), 5.15 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.14–5.08 (m, 2H), 5.12 (dd, *J* = 11.0, 0.8 Hz, 1H), 3.98 (s, 2H), 2.16–1.94 (m, 10H), 2.00 (s, 2H), 1.90–1.69 (m, 2H), 1.66 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 170.0, 141.8, 135.3, 134.7, 134.6, 126.0, 124.4, 123.7, 113.1, 82.9, 68.9, 39.7, 39.6, 39.3, 26.5, 26.2, 23.6, 22.2, 22.2, 16.0, 15.9, 13.7; HRMS (ESI+) calcd for $C_{22}H_{36}O_3Na$ $[M+Na]^+$ 371.2562, found 371.2544.

Compound 15. A mixture of powdered, activated 4-Å molecular sieves (208 mg) and dry CH_2Cl_2 (4.5 mL) was cooled to 0 ºC. L-(+)-diethyl tartrate (0.08 mL, 0.44 mmol), titanium isopropoxide (0.11 mL, 0.36 mmol) and *tert*-butylhydroperoxide (5-6 M in decane, 0.65 mL, 3.56 mmol) were added sequentially. After 20 min, the mixture was cooled to −20 ºC, and **14** (620 mg, 1.78 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise over 15 min. After 3.5 h of stirring at −20 ºC, the reaction mixture was warmed to 0 ºC, quenched with water (10 mL), and warmed to room temperature. NaOH (5 mL, 40% aqueous solution) was added, and the mixture was stirred for 20 min and filtered through a pad of Celite®. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography over silica gel (H/MTBE 1:1) to afford epoxide **15** as a colorless syrup (500 mg, 77%): $[\alpha]_D = -9.5$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (dd, J = 17.5, 11.0 Hz, 1H), 5.19–5.09 (m, 4H), 3.67 (dd, J = 12.1, 4.5 Hz, 1H), 3.57 (dd, J = 12.1, 8.5 Hz, 1H), 3.02 (t, J = 6.3 Hz, 1H), 2.19–2.04 (m, 4H), 2.02 (s, 3H), 2.01–1.96 (m, 5H), 1.90–1.83 (m, 1H), 1.80–1.65 (m, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.55 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 141.8, 135.2, 133.9, 125.0, 123.8, 113.1, 82.9, 65.4, 60.9, 59.9, 39.7, 39.5, 36.2, 26.8, 26.5, 23.6, 22.2 (2C), 16.0, 15.9, 14.3; HRMS (ESI+) calcd for $C_{22}H_{36}O_4Na$ $[M+Na]^+$ 387.2511, found 387.2508.

Compound 8. Imidazole (238 mg, 3.50 mmol) was added to a cold (0 ºC) solution of **15** (490 g, 1.35 mmol) in dry CH_2Cl_2 (21 mL) under an argon atmosphere and stirred for 15 min, and TBSCl (405 mg, 2.69 mmol) was added. The mixture was kept to room temperature for 45 min and diluted with CH_2Cl_2 (25 mL), washed with H_2O (3 x15 mL), 2N HCl (3 x15 mL), saturated aqueous $NaHCO_3$ solution (3 x 15 mL), and brine (3 x 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography over silica gel (H/MTBE 9:1) to obtain epoxide **8** as a colorless syrup (540 mg, 84%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.19–5.09 (m, 4H), 3.59 (d, *J* = 11.4 Hz, 1H), 3.56 (d, *J* = 11.4 Hz, 1H), 2.85 (t, *J* = 6.3 Hz, 1H), 2.20−1.96 (m, 4H), 2.02 (s, 3H), 2.01–1.96 (m, 4H), 1.90–1.82 (m, 1H), 1.80–1.72 (m, 1H), 1.70–1.60 (m, 2H), 1.62 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H), 1.28 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 141.8, 135.3, 134.0, 124.8, 123.7, 113.1, 82.9, 67.9, 61.0, 60.7, 39.8, 39.6, 36.3, 27.0, 26.6, 25.8 (3C), 23.6, 22.2, 22.1, 18.3, 16.0, 15.9, 14.1, −5.4 (2C); HRMS (ESI+) calcd for $C_{28}H_{50}O_4NaSi$ $[M+Na]^+$ 501.3376, found 501.3481.

Compound 7. A mixture of Cp_2TiCl_2 (112 mg, 0.45 mmol) and Mn dust (532 mg, 9.68 mmol) in rigorously deoxygenated THF (25 mL) was stirred at room temperature until the red solution turned green. A solution of oxirane **8** (540 mg, 1.13 mmol), 2,4,6-collidine (0.91 mL, 7.91 mmol), and TMSCl (0.6 mL, 4.52 mmol) in rigorously deoxygenated THF (12 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred for 19 h, diluted with MTBE (25 mL), quenched with 2 N HCl, and extracted with MTBE (3 x 25 ml). The combined organic layers were washed with brine (3 x 30 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product obtained was purified by column chromatography over silica gel (H/MTBE, 9:1) to obtain tricycle **7** as a colorless syrup (171 mg, 36%): $[\alpha]_D$= +13.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37–5.32 (m, 1H), 3.70 (d, *J* = 9.2 Hz, 1H), 3.60 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.36 (d, *J* = 9.2 Hz, 1H), 2.12–2.04 (m, 1H), 2.00 (dd, *J* = 14.6, 6.8, 1.5 Hz, 1H), 1.89–1.82 (m, 1H), 1.83 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.73 (s, 3H), 1.68–1.58 (m, 4H), 1.52–1.42 (m, 2H), 1.28–1.10 (m, 3H), 0.99–0.89 (m, 3H), 0.92 (s, 9H), 0.88 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.3, 122.5, 76.8, 74.0, 64.5, 50.7, 46.4, 44.2, 41.7, 38.4, 37.9, 35.8, 34.6, 26.3, 25.8

(3C), 25.3, 20.5, 20.4, 19.0, 18.1, 16.2, 11.6, −5.7 (2C); HRMS (ESI+) calcd for $C_{26}H_{48}O_2SiNa$ $[M+Na]^+$ 443.3321, found 443.3317. Enantiomeric excess: 87%. The enantiomeric excess was calculated using chiral-phase liquid chromatography: column. Chiralcel OD, column size: 0.46 cm I.D. x 25 cm, eluent: Hex/IPA = 9.5/0.5, flow rate: 1.0 mL/min, temperature: 25ºC.

(–)-Valparan-2,15-diene (1). PCl_5 (150 mg, 0.72 mmol) was added to a cold (−15 ºC) solution of **7** (100 mg, 0.24 mmol) in dry CCl_4 (8 mL) under an argon atmosphere. The mixture was kept at that temperature with stirring for 25 min. The mixture was diluted with CH_2Cl_2 and quenched via dropwise addition of saturated aqueous $NaHCO_3$ solution until bubbling stopped. The organic phase was washed with brine, dried with anhydrous Na_2SO_4 and concentrated. The product crude was dissolved in dry THF (6 mL) at 0 ºC and $LiAlH_4$ (9 mg) was added under argon atmosphere and vigorous stirring. After 20 min the reaction was diluted with MTBE and water (1 drop), 6 N NaOH solution (1 drop), and water (3 drops) were successively added. The resulting mixture was stirred for 10 min and filtered through a bed of Na_2SO_4 and silica gel, washed with MTBE, and concentrated to afford a crude product which was chromatographed over silica gel (H/MTBE 9:1) to obtain a 5:1 mixture of the corresponding epimeric alcohols (21 mg, 31%, two steps). To a solution of this mixture in 1.5 mL of THF, tri-*n*-butylphosphine (10 mg, 0.048 mmol) and *o*-nitrophenylselenocyanate (11 mg, 0.048 mmol) were added. After stirring under an argon atmosphere for 35 min at room temperature, the reaction crude was diluted with MTBE and quenched with the dropwise addition of 5% NH_4Cl. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude product (33 mg) which was redissolved in dry THF (1.5 mL) under argon and 30% H_2O_2 (0.02 mL) was added. The mixture was stirred for 30 min at 45ºC and diluted with Et_2O (10 mL), washed with brine (3 x 5 mL), and worked up as usual. The crude product was column chromatographed over silica gel (H/MTBE 97:3) to afford diene **1** as a colorless syrup (17 mg, 89% after two steps): $[\alpha]_D$= + 10.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.37–5.33 (m, 1H), 4.79 (bs, 1H), 4.78 (bs, 1H), 2.70 (q, *J* = 8.7 Hz, 1H), 2.22–2.13 (m, 1H), 1.98 (dd, *J* = 14.4, 6.5 Hz, 1H), 1.91–1.77 (m, 3H), 1.75 (s, 3H), 1.73 (s, 3H), 1.67–1.42 (m, 7H), 1.37 (q, *J* = 13.4 Hz, 1H), 1.21 (td, *J* = 11.6, 4.1 Hz, 1H), 1.13–1.05 (m, 2H), 0.80 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.6, 141.0, 122.9, 110.3, 64.1, 55.4, 47.1, 46.7, 46.4, 45.1, 41.7, 34.9, 36.2, 27.3, 25.8, 25.1, 24.0, 22.2, 20.9, 16.2. The spectroscopic data of this compound were consistent with those previously reported.[1b-c]

Isolation of (+)-Nerolidol (16) from the Extract of Inula viscosa. Fresh aerial parts of *Inula viscosa* (8 Kg) were macerated two times with (MTBE (25 L) for 20 min each time. Evaporation under reduced pressure afforded 60 g of crude extract. The extract was dissolved in MTBE (2.5 L) and washed with 2 N NaOH solution (4 x 300 mL) to yield 17.4 g of neutral fraction and 39 g of an acid fraction after 2 N HCl treatment. The neutral fraction was subjected to silica gel column chromatography using H/MTBE mixtures of increasing polarity to afford (+)-nerolidol (**16**) (4.1 g, H/MTBE 7:3): colorless oil. $[\alpha]_D$= +14.2 (*c* 1.0, CH_2Cl_2). The spectroscopic data of this compound were consistent with reported data.[22]

(E)-Nerolidyl Acetate (17). Acetic anhydride (31 mL) and 4-dimethylaminopyridine (10 mg) were added to solution of nerolidol (4.10 g, 18.5 mmol) in pyridine (42 mL). The mixture was heated at reflux for 6 h and worked up as usual to give a crude product which was chromatographed over silica gel (H/MTBE 4:1) to obtain acetate **17** as a colorless oil (3.8 g, 78 %): $[\alpha]_D$ = +2.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.00 (dd, *J* = 11.0, 17.5 Hz, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.14 (d, *J* = 11.0 Hz, 1H), 5.13−5.09 (m, 2H), 2.09−1.96 (m, 8H), 2.02 (s, 3H), 1.89−1.76 (m, 2H), 1.70 (s, 3H), 1.61 (s, 6H), 1.56

(s, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 142.1, 135.6, 131.5, 124.5, 123.9, 113.2, 83.1, 40.0, 39.9, 26.9, 25.9, 23.8, 22.5, 22.4, 17.9, 16.1.HRMS (ESI+): calcd. for $C_{15}H_{25}$ $[M-CH_3CO_2H+H]^+$ 205.1956; found 205.1964.

3-Acetoxy-12-hydroxynerolidol (18). The synthesis and structural elucidation of this compound was described in reference 9b.

(R,E)-9-[(2S,3S)-3-(Hydroxymethyl)-3-methyloxiran-2-yl]-3,7-dimethylnona-1,6-dien-3-yl acetate (19). A mixture of powdered, activated 4-Å molecular sieves (990 mg) and dry CH_2Cl_2 (20 mL) was cooled to 0 ºC. L-(+)-diethyl tartrate (0.36 mL, 2.11 mmol), titanium isopropoxide (0.50 mL, 1.69 mmol), and *tert*-butylhydroperoxide (5-6 M in decane, 4.3 mL) were added sequentially. After 25 min, the mixture was cooled to −20 ºC and **19** (2.38 g, 8.50 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over 15 min. After stirring at –20 ºC for 45 min, the reaction was warmed to 0 ºC, quenched with water (22 mL) and warmed to room temperature. NaOH (5 mL, 40% aqueous solution) was added and the mixture was stirred for 20 min and filtered through a pad of Celite®. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography over silica gel (H/MTBE 1:1) to afford epoxide **19** as a colorless syrup (1.76 g, 70%): $[\alpha]_D = -7.0^o$ (*c* 1.0, CH_2Cl_2). The spectroscopic data of this compound were consistent with reported data.[9b]

(R,E)-9-[(2S,3S)-3-(Tert-butyldimethylsilyloxymethyl)-3-methyloxiran-2-yl)]-3,7-dimethylnona-1,6-dien-3-yl acetate (20). Imidazole (1.050 g, 15.44 mmol) was added to a cold (0 ºC) solution of **19** (1.76 g, 5.94 mmol) in dry CH_2Cl_2 (94 mL) under an argon atmosphere. The mixture was stirred for 15 min and TBSCl (1.790 g, 11.91 mmol) was added. The mixture was kept to room temperature for 30 min, diluted with CH_2Cl_2 (100 mL), washed with H_2O (3 x 50 mL), 2 N HCl (3 x 50 mL), saturated aqueous $NaHCO_3$ solution (3 x 50 mL), and brine (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentred *in vacuo*. The crude product was purified by column chromatography over silica gel (H/MTBE 9:1) to obtain epoxide **20** as a colorless syrup (2.24 g, 92%): $[\alpha]_D = -3.1$ (*c* 1.0, CH_2Cl_2). The spectroscopic data of this compound were consistent with reported data.[9b]

(1R,2S,4aR,9aR)-1-(Tert-butyldimethylsilyloxymethyl)-1,4a,7-trimethyl-2,3,4,4a,5,8,9,9a-octahydro-1H-benzo[7]annulen-2-ol (21). A mixture of Cp_2TiCl_2 (544 mg, 2.18 mmol) and Mn dust (2.400 g, 43.68 mmol) in rigorously deoxygenated THF (114 mL) was stirred at room temperature until the red solution turned green. A solution of **20** (2.24 g, 5.46 mmol), 2,4,6-collidine (4.15 g, 4.8 mL, 34.3 mmol) and TMSCl (2.65 g, 2.9 mL, 24.5 mmol) in rigorously deoxygenated THF (55 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred for 8 h, diluted with MTBE (100 mL), washed with 2 N HCl (3 x 50 mL), saturated aqueous $NaHCO_3$ solution (3 x 50 mL), and brine (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (H/MTBE 9:1) to obtain bicycle **21** as a colorless syrup (1.0 g, 52%): $[\alpha]_D = +15.9$ (*c* 1.0, CH_2Cl_2). The spectroscopic data of this compound were consistent with reported data.[9b]

(+)-Isodaucene (3). PCl_5 (1.54 g) was added to a cold (−15 ºC) solution of **21** (846 mg, 2.40 mmol) in dry CCl_4 (69 mL) under an argon atmosphere. The mixture was kept at that temperature for 20 min, diluted with MTBE, and quenched with the dropwise addition of saturated aqueous $NaHCO_3$ solution until bubbling stopped. The organic layer was washed with brine (3 x 20 mL), dried with anhydrous Na_2SO_4, and evaporated *in vacuo*. The crude product was dissolved in dry THF (94 mL) at 0 ºC and $LiAlH_4$ (146 mg) was added under an argon atmosphere and vigorous stirring. After 15 min the reaction was quenched by successive addition of water (4 drops), 6 N NaOH solution (4 drops), and water (12 drops). The resulting mixture was stirred for 10 min, filtered through a bed of Na_2SO_4 and silica gel, washed with MTBE, and concentrated *in vacuo* to afford a crude product which was chromatographed over silica gel (H/MTBE 3:1) to obtain a 5:1 mixture of epimeric alcohols (175 mg, 33 %, two steps). To a solution of these alcohols in THF (6 mL) was added tri-*n*-butylphosphine (350 mg, 1.75 mmol) and *o*-nitrophenylselenocyanate (400 mg, 1.75 mmol) under an argon atmosphere at room temperature. The mixture was stirred for 7 h, diluted with MTBE, and quenched with the dropwise addition of 5% NH_4Cl. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude product (355 mg) which was redissolved in dry THF (12 mL) under argon and 30% H_2O_2 (0.2 mL) was added. The mixture was stirred for 30 min at room temperature, diluted with Et_2O (20 mL), washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product obtained was purified by column chromatography over silica gel (H/MTBE 97:3) to afford diene **3** as a colorless oil (144 mg, 89% after two steps): $[\alpha]_D$= +11.2 (*c* 1.0, CH_2Cl_2);^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42−5.37 (m, 1H), 4.79 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.72 (dt, *J* = 2.5, 0.8 Hz, 1H), 2.96 (dt, *J* = 11.6, 9.1 Hz, 1H), 2.10 (dd, *J* = 14.6, 8.7 Hz, 1H), 2.10−1.97 (m, 2H), 1.86 (bd, *J* = 14.0 Hz, 1H), 1.83−1.69 (m, 3H), 1.75 (bs, 3H), 1.72 (bs, 3H), 1.57−1.48 (m, 2H), 1.39 (td, *J* = 12.2, 8.0 Hz, 1H), 1.26 (dtd, *J* = 13.5, 12.2, 2.9 Hz, 1H), 0.83 (bs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 138.8, 122.7, 112.6, 56.8, 50.4, 42.6, 42.4, 42.0, 35.4, 28.3, 27.6, 23.1 (2C), 19.3; HRMS (ESI+): calcd. for $C_{15}H_{25}$ $[M+H]^+$ 205.1956; found 205.1950. The spectroscopic data of this compound were consistent with reported data.[1g]

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **8**, **9**, **11**, **12**, **14**–**16**, **18**–**22** (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support for this work was provided by the Junta de Andalucia (P08-FQM-3596) and Ministerio de Economía y Competitividad (CTQ-2015-64049-C3-3-R). Thanks also go to Dr. Javier Moraga Galindo, from the University of Cadiz, for carrying out the chiral chromatography necessary to calculate the enantiomeric excess.

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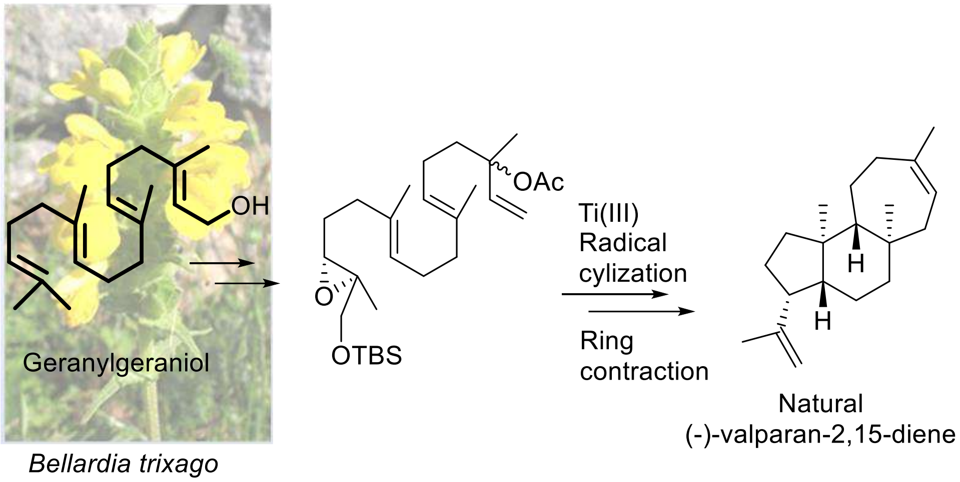

Geranylgeraniol
Bellardia trixago
OH
O
OTBS
OAc
Ti(III)
Radical
cylization
Ring
contraction
H
H
Natural
(-)-valparan-2,15-diene

3.3 *Artículo 3:* Mimicking Halimane Synthases: Monitoring a Cascade of Cyclizations and Rearrangements from Epoxypolyprenes

Quilez Del Moral, J. F.; Domingo, V.; Pérez, Á.; Martínez Andrade, K. A.; Enríquez, L.; Jaraiz, M.; López-Pérez, J. L.; Barrero, A. F. Mimicking Halimane Synthases: Monitoring a Cascade of Cyclizations and Rearrangements from Epoxypolyprenes. *Journal of Organic Chemistry* **2019**, *84* (21), 13764–13779. https://doi.org/10.1021/acs.joc.9b01996.

https://pubs.acs.org/doi/10.1021/acs.joc.9b01996

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9/57

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2019	9/57	Q1	85.09

Citaciones hasta el día 20 de octubre de 2021: **2**

Mimicking Halimane-Synthases: Monitoring a Cascade of Cyclizations plus Rearrangements from Epoxypolyprenes.

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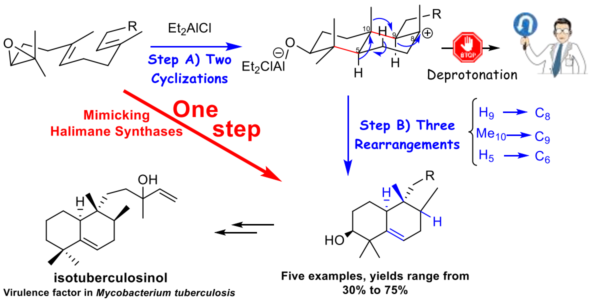


ABSTRACT: We have developed and rationalized a biomimetic transformation mimicking halimane-synthases based on a Lewis acid-catalyzed cascade of cyclizations plus rearrangements of epoxypolyprenes. Two rings, three stereogenic centers and a new double bond were generated in a single chemical operation. Based on this cascade transformation, we achieved a unified strategy

toward the stereoselective total syntheses of halimene-type terpenoids and analogues as a proof-of-concept study. This method has been applied to the rapid synthesis of diterpene isotuberculosinol, a virulence factor of *Mycobacterium tuberculosis* as representative example.

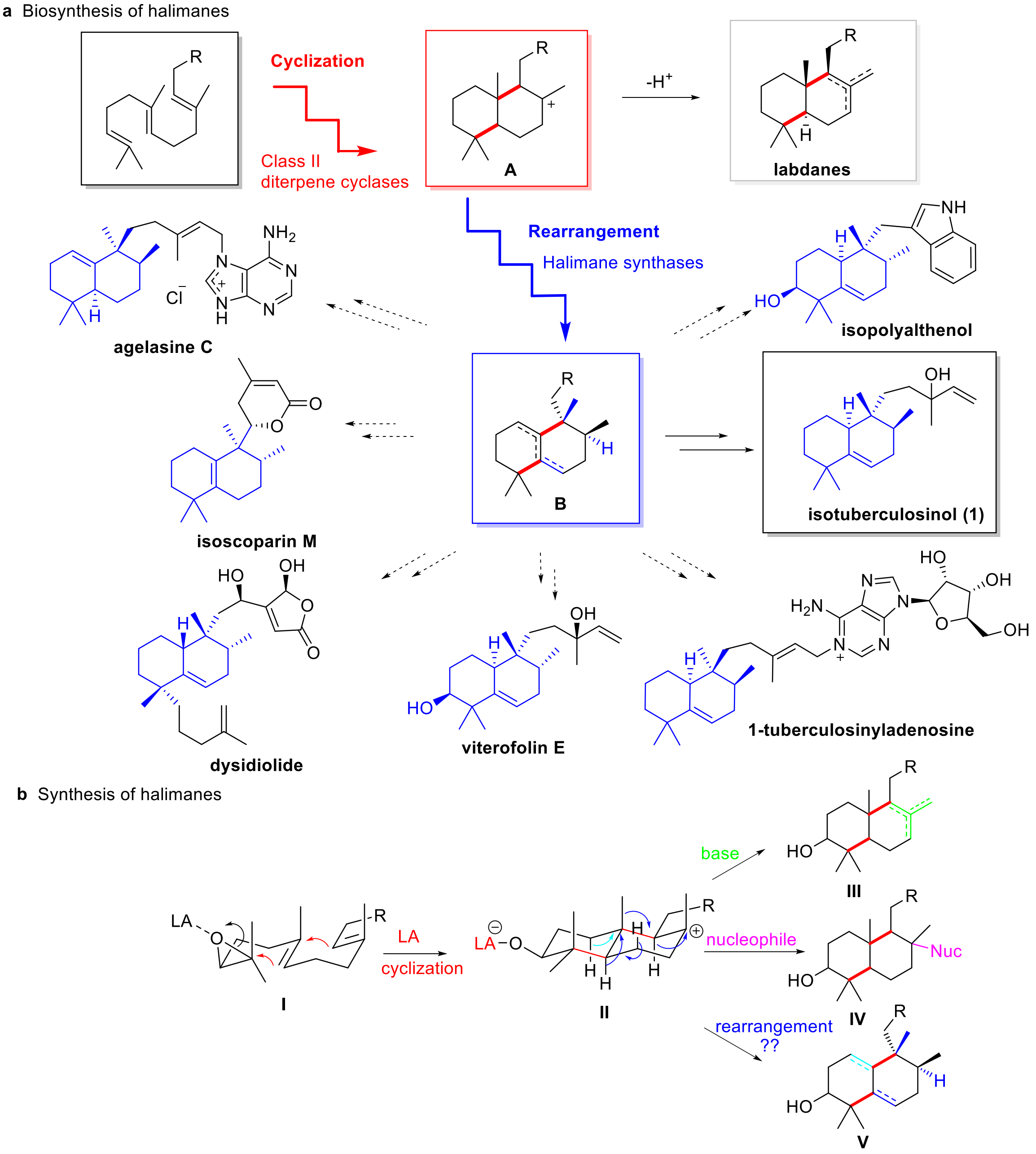
INTRODUCTION

Biomimetic strategies allow the construction of complex natural products in a minimum of steps. The benefits of these processes are recognized worldwide, with the ‘‘atom and step economy’’ approach of green chemistry which are of special interest. [1–4] In the field of terpenoid biogenesis, the generation of the hopanoid skeleton by squalene cyclases, where five new cycles and up to nine stereogenic centers are created constitutes an excellent example of the spectacular and potentiality of this process.[3,5] Challenged by these fascinating transformations, researchers have been trying to replicate the action of these enzymes for over a century.[3] Although the use of either Brönsted or Lewis acids have been by far the most common method to achieve biomimetic polycyclizations of isoprenoids in the lab,[3,6–16] other astonishing protocols including those involving enzymes[17–20] and radical cyclizations have also been reported.[21–23] An outstanding milestone in this synthetic effort was the achievement of enantioselective cyclization protocols of some polyenes.[24–29]

Often oxidosqualene- and other terpene cyclases, in addition to cyclization processes, give rise to a series of hydride and methyl shifts before releasing the final natural product. Up to seven of these rearrangements take place in the biosynthesis of triterpene cucurbitanes.[30] Obviously, the difficulty of reproducing these processes using chemical reagents involving cyclizations and rearrangements increases significantly. In this regard, van Tamelen and Sharpless reported in 1969 that the treatment of squalene 2,3-oxide with stannic chloride led to a mixture of cyclized products, including a rearranged bicyclic alcohol possessing the halimane core.[31] Apart from van Tamelen´s seminal work, to the best of our knowledge, no precedents exist on addressing rationalized synthesis of “rearranged terpenes” using this approach. However, efficient rearrangements of carbocations generated on previously cyclized structures can be found in the literature.[31–37] Some of these non-enzymatic rearrangements can be considered as nice examples of the minimal-enzymatic-assistance hypothesis,[4,38] thus encouraging the biomimetic pursuit of these complex reactions.

The bicyclic backbone **B** present in diterpene halimene–type skeleton is a common molecular fragment conserved in important biologically active natural products[39–44] (Figure 1a). Biosynthetically, it must be derived from (*E*,*E*,*E*)-geranylgeranyl diphosphate through "halimane synthases" catalysis. This process starts with a class II diterpene cyclase (DTC) mediated protonation of the terminal isopropylidene to give a bicyclic carbocation intermediate which later suffers several rearrangements of hydride and methyl groups.[45] Other common DTCs (such as copalyl synthases for example) only produce diterpenes as labdanes by deprotonation of the labda-13-en-8-yl$^+$ intermediate **A**. Among the many substances presenting the halimene framework, diterpenes such as isotuberculosinol (**1**) and 1-tuberculosinyladenosine were reported to be the virulence factors[42] isolated from *Mycobacterium tuberculosis* the causative agent of the human disease tuberculosis, a worldwide health threat responsible for approximate 1.7 million deaths annually.[46] Due to their interest and structural complexity of these substances, multistep synthesis or semi-synthesis has been developed.[47–48]

Here, we describe our efforts to know to what extent the action of "halimane synthases" can be mimicked in the laboratory *in vitro*, that is, to generate the bicyclic halimene skeleton starting from a simple acyclic epoxypolyprene in a one-step cascade process including two head-tail cyclizations and two or three 1,2-Wagner-Meerwein rearrangements (Figure 1b).



a Biosynthesis of halimanes

b Synthesis of halimanes

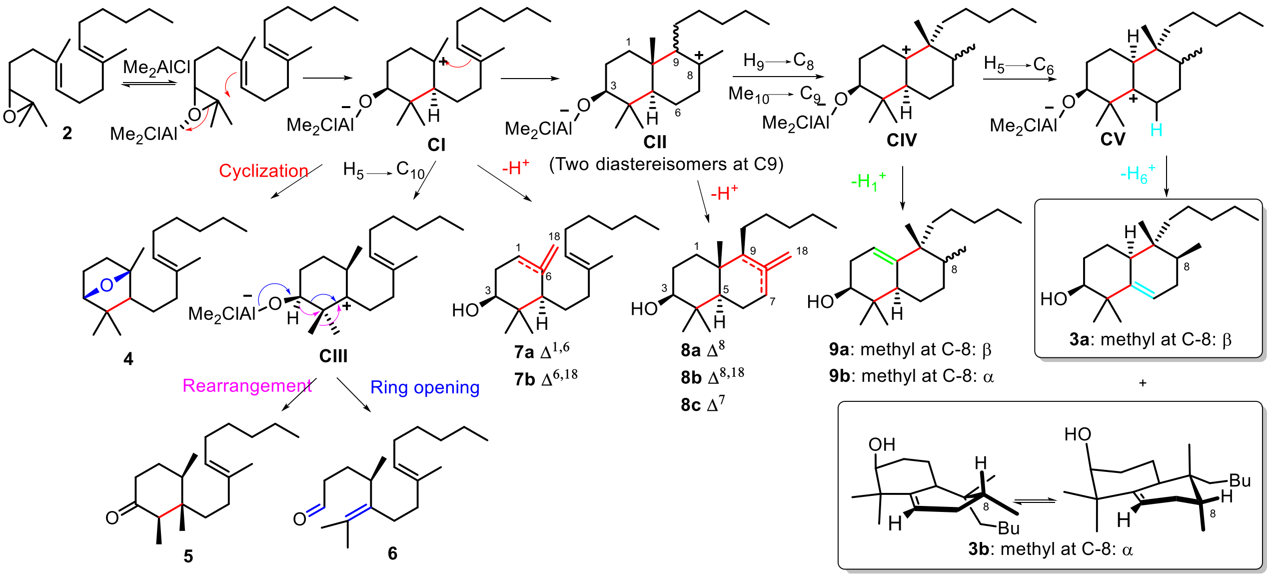
Figure 1. Accessing to the halimane skeleton. **a**, Biosynthesis of the halimanes: some representative halimane–type terpenoids. **b**, Bionspired synthesis of halimanes: Is it achievable a tandem cyclization-rearrangement process leading to halimenes?

Taking advantage of the tremendous effort devoted by chemists for decades to comprehend carbocationic polycyclizations and before starting any experimental tests, we evaluated and analysed the possible requirements that each of the agents involved in the cyclization process. Selection of the oxyrane group as an initiator is fundamental in this strategy because it must provide the selective and soft formation of the initial acyclic carbocation by oxyrane opening. Concerning the structural requirements the acyclic precursor, the presence of unsaturations in the terminal "R" moiety, as in the case of C20 geranylgeraniol derivatives or longer polyprenes, or functions containing heteroatoms located close to the C–8 carbocation **II** should be avoided since they could favour subsequent cyclizations or E1 deprotonations respectively (Figure 1b).[26,49] With regard to the reaction medium, the use of non-basic and poor nucleophilic solvents and low temperatures should help to induce the rearrangement process by avoiding the E1 processes. Finally, considering the requirements for the acid that mediates the process, it should be a Lewis acid that, after coordination to the oxirane, should permit its opening and subsequent cyclization, and most importantly, should prevent any fast ligand dissociation in the generated intermediate zwitterionic species resulting from the oxyrane opening (**II**, Figure 1b). This zwitterion possesses a carbocation and a metalanion-alkoxide, which will bear the negative charge during the whole process. Thus, when the cyclization is over, the cation at C–8 in the absence of any base or nucleophile could evolve to the rearranged products if the process is energetically favourable. Although different rearrangements could be conceivable, the series of 1,2-migrations of hydride and methyl groups leading to the different expected halimene skeletons seems to be, a priori, stereoelectronically favoured (Scheme 2). Additionally, in our opinion, the negative charge located at the metal bound to the oxygen may exert an electrostatic attraction on the bicyclic cation at C–8, thus-favouring those rearrangements that bring the charges closer. This reasoning regarding the role that the Lewis acid should exert in this process parallels the interesting rationalization provided by Shenvi to account for their results on the aluminium Lewis acids-mediated tail-to-head transformations of a nerolidol-based vinyl epoxide, mimicking class I terpene cyclases.[14] Thus, the authors claim that key to the success of their approach was the "*sequestration of the counteranion using non-dissociating ligands*". Eventually, and after prolonged reaction times, the dissociation of a chloride ion from the aluminate anion could be responsible for the ultimate deprotonation leading to the halimene skeleton.

RESULTS AND DISCUSSION

To verify the experimental viability of our hypothesis, we started this biomimetic approach by choosing the monoepoxide of farnesylbutane **2** as a simple model of a starting material. For the Lewis acid, we selected initially Me_2AlCl.[50] When **2** was made to react with 1.0 equiv of Me_2AlCl at -78 ºC in DCM (0.1 M) for 40 min, an equimolecular mixture of epimers at C–8, **3a–3b** possessing the rearranged skeleton of halima-5-ene and *syn*- halima-5-ene was obtained in 51% yield (Table 1, entry 1), together with minor proportions of the non-rearranged monocyclic (**7b**) and bicyclic products (**8b**) (3% and 2%, respectively), as well as the acyclic aldehyde **6** (1.5%). The different mechanistic steps rationalizing the generation of the products obtained in this transformation are depicted in Scheme 1.

Scheme 1. Mechanistic Steps Leading to the Generation of 3–9.



Compound **3b** turned out to present a restricted conformational equilibrium at rt on ring B and as consequence the resolution of NMR spectra, especially in ^{13}C NMR, is low. A complete characterization of this isomer was only possible after conducting the NMR experiences at 90 ºC in deuterated DMSO. Molecular Mechanics conformational search first and quantum chemical calculations then performed on **3a** and **3b** revealed the existence of two pairs of main conformers of similar stability (≤1 kcal/mol) for each epimer. The energetic barrier calculated for **3a** (7.2 Kcal/mol) supports a rapid rate of interconversion in agreement with the experimental data in NMR, whereas the interconversion barrier between the two conformers of **3b** (14.0 kcal/mol) may well account for a slow conformational equilibrium between these two species (see Supplementary Information). This phenomenon was reported in related natural products presenting the stereochemistry assigned to **3b**.[19,40a]

In order to gain a comprehensive mechanistic and energetic understanding of the different steps of the bicyclization-rearrangement cascade from **2** to **3a**–**3b**, quantum chemical calculations were carried out using 14,15-epoxygeranylcitronelene (**I**) as a diterpene model and Me_2AlCl as a catalyst. Previous inexpensive SCW calculations allowed us to find two main productive prochiral conformations (**Ia** and **Ib**) of the acyclic precursor, namely, chair-boat and chair-chair conformations, both possessing similar stabilities (difference 0.3 Kcal/mol, Figure 2). The results obtained from the computational study of the entire process are represented in Figure 2 (see Supplementary Information for details).

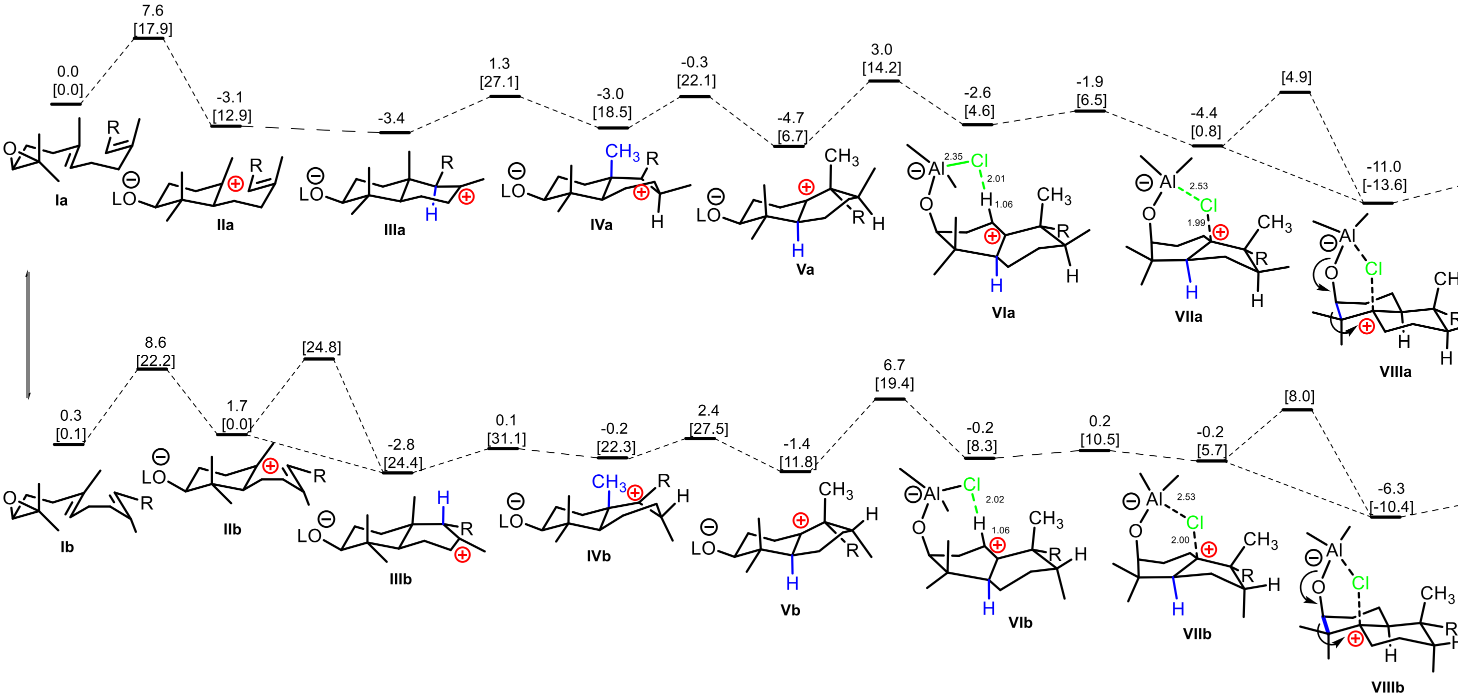
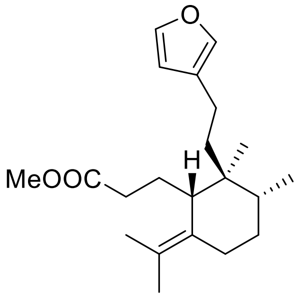


Figure 2. Energy diagram for the formation of species **I**–**X** leading to halimenes **3a**–**b**. Relative energies [kcalmo
dispersion=gd3b], in normal text for SMD solvation model by a single point energy calculation, and in brackets fo
distances in Å in TSs. For simplification of the figure, the moiety ClMe$_2$Al-O appears represented by L, and R sta

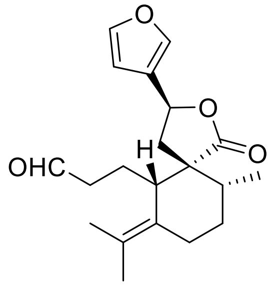
Calculations showed differing results considering the generation of the labdan-8-yl cationic intermediate **III**. Thus, whereas the calculations performed in vacuum showed that the two cyclizations were stepwise, no minimum of energy was found for this first cyclization when the calculations were performed considering the presence of CH_2Cl_2 (concerted process). Although the concerted asynchronous processes were the result obtained when the solvent was included in the calculations,[51–52] the feasibility of a stepwise scenario[53] should not be ruled out, mainly when this mechanism would well account for the generation of minor monocyclic products **4**, **5**, **7** and aldehyde **6**, found in the reaction of **2** with Me_2AlCl.

After the formation of bicyclic cations **IIIa** and **IIIb**, one 1,2 hydride $C_9 \rightarrow C_8$ shift followed by a 1,2-methyl $C_{10} \rightarrow C_9$ migration were predicted to take place, overcoming small barriers leading to the haliman-10-yl carbocations **Va** and **Vb.** Rearranged intermediates **Va** and **Vb** undergo a ring A conformational change implying a variation of the space disposition of the dimethylcholoroaluminate group from equatorial towards an axial arrangement. As consequence of this conformational change, the chlorine atom gradually approaches to C–10 carbocation, thus contributing to the stabilization of the intermediates **VII** due to the favourable electrostatic interactions between the negative charge of the chlorine atom partially detached from the alcoxyaluminate and the carbocation at C–10. In fact, the initial distance of Al–Cl, (2.27Å) when the aluminate was equatorially disposed, is gradually lengthened to 2.53Å when it is axial in both intermediates **VIIa** and **VIIb**, while the distance C10–Cl, 1.99Å, is still far from the 1.85Å of a typical C_{sp3}–Cl bond. The fact that the chlorine atom is not completely detached from the aluminate anion is of paramount importance, since it not only permits the cascade of Warner-Meerwein rearrangements of the molecule to continue; but it also favours the interconversion of carbocations **VII** to **VIII** through $C_5 \rightarrow C_{10}$ hydride shift from the alpha face of the halimane skeleton, a process thermodynamically favourable in 6 kcal/mol. Subsequently, the C3–C4 bond of **VIII** undergoes a gradual elongation until it breaks to give a 10-12 Kcal/mol more stable seco-3,4-halimane monocyclic aldehyde complex intermediates **IX**.

In this regard, a related A contraction of a halima-13*E*-en-15-PP-5-yl$^+$ intermediate was proposed to occur in the biosynthesis of premutilin, proposal that was supported by quantum chemical calculations.[54] All that led us to hypothesize that the theoretically-proposed route to aldehydes **IX** may constitute a possible biosynthetic pathway to natural 3,4-seco-halimanes such as secochiliotrin methyl ester or secochiliolide aldehyde.[67]



secochiliotrin methyl ester



secochiliolide aldehyde

The unsaturated aldehydes **IX** suffer a concerted process with activation energy near to 10 kcal/mol where A ring is regenerated through a intramolecular Prins reaction with a simultaneous proton transfer from C–6 (Hβ-6) to O–3 to produce the final $\Delta^{5,6}$ halimanes **X**. It is worth noting that the particular space orientation of the oxygen atom resulted in the Prins process in $TS_{IX–X}$, which facilitated the final proton transfer.

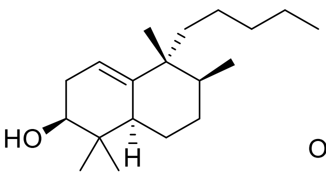
These computational calculations are consistent with those recently reported on biosynthetic studies of halimenes not oxigenated at C3[19,55] and, more significantly, they shed some light on the three most relevant figures of our cyclization-rearrangement experimental process. Thus, the solvent CH_2Cl_2 plays an important role provoking a significant decrease in the energetic barriers to cyclizations and rearrangements, probably as consequence of carbocation stabilization. Secondly, the formation of two stereoisomers at C8, **3a** and **3b,** is a consequence of the co-existence of a pre-chair-boat **Ia** acyclic precursor competing against the pre-chair-chair **Ib** precursor (both initial precursors and transition-states structures for the first cyclization step were predicted to be almost isoenergetic, see Supplementary Information). Furthermore, the role played by the oxygen and chlorine atoms in the non-detached alkoxyaluminate anion, possibilitating the A ring opening and the ensuing concerted Prins reaction and H6-deprotonation, supported the high selectivity observed toward haliman-5-enes among all the possible olefinic regioisomers and also versus other kinds of rearranged products. Finally, the recovery of the Lewis acid unaltered renders the process susceptible to catalysis by the Lewis acid.

Once we proved that the mechanism and the energetic barriers calculated for the cyclization and rearrangement processes supported the experimental results obtained with model **2**, we focused our efforts on optimizing the experimental conditions for this transformation. To this end, a screening of different Lewis acids, concentrations, temperatures and solvents was achieved (Table 1).

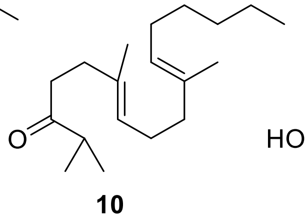
Table 1. Screen of the Cyclization-Rearrangement Experimental Conditions of Epoxide 2

entry	equiv/LA	temp (°C), C (mM)	solvent	time (min)	3a, 3b yield (ratio)	4, 5, 6 yield (ratio)	7a, 7b yield (ratio)	8a, 8b, 8c yield (ratio)
1	1/Me_2AlCl	-78, 0.03	DCM	45	51% (1:1)	2% (0:0:1)	3% (1:0)	2% (1:0:0)
2	1/Et_2AlCl	-78, 0.03	DCM	45	54% (1:1.1)	3% (1:0:0.2)	ND	10% (0:0.6:1)
3	0.1/$Bi(OTf)_3$	Reflux, 0.03	DCM	40	ND	4% (1:0:0)	4% (1:0)	23% (1:0:0)
4	1/$Cu(OTf)_2$	-78, 0.03	DCM	30	ND	ND	19% (1:0.3)	17% (5.7:0.2:1)
5[a]	1/$InBr_3$	-78, 0.03	DCM	300	27% (1:0.8)	4% (1:0:0)	ND	13% (0:0.3:1)
6[b]	1/$InBr_3$	RT, 0.03	DCM	100	37% (1:0.4)	7% (1:0:0)	9% (1:0.2)	9% (0:0.8:1)
7	**0.5/Et_2AlCl**	**-78, 0.03**	**DCM**	**100**	**53% (1:1)**	**ND**	**ND**	**ND**
8	1.5/Et_2AlCl	-78, 0.03	DCM	50	59% (1:1)	ND	3% (1:0)	2% (1:0:0)
9	**2/Et_2AlCl**	**-78, 0.03**	DCM	**45**	**71% (1:1.1)**	**6%** (1:0:1)	**ND**	**10% (0:0.6:1)**
10	3/Et_2AlCl	-78, v	DCM	40	65% (1:1)	5% (1:0:0.4)	ND	4% (0:0.3:1)
11	5/Et_2AlCl	-78, 0.03	DCM	35	59% (1:1)	ND	ND	ND
12	2/Et_2AlCl	-100, 0.03	DCM	60	34% (1:1)	ND	ND	ND
13	2/Et_2AlCl	0, 0.03	DCM	30	50% ((1:1)	7% (1:0:0.2)	ND	13% (0:0:1)
14	2/Et_2AlCl	-78, 0.3	DCM	25	63% (1:1)	ND	3% (1:0)	ND
15	2/Et_2AlCl	-78, 0.003	DCM	50	58% (1:1)	2% (1:0:0)	ND	ND
16[c]	2/Et_2AlCl	-78, 0.03	Hexane	60	27% (1:1)	ND	ND	ND
17	2/Et_2AlCl	10, 0.03	Bencene	45	54%(1:0.8)	5%(0.7:1:0)	ND	ND
18	2/Et_2AlCl	-78, 0.03	Toluene	45	68% (1:1)	2%(1:0:0)	ND	ND
19	2/Et_2AlCl	-78, 0.03	TBME	50	4% (1:1)	ND	57 (1:1.3)	21%(0:1.6:1)
20[d]	2/Et_2AlCl	-78, 0.03	THF	210	ND	4 (1:0:1)	4 (1.1:1)	ND
21	2/Et_2AlCl	-30, 0.03	DCE	30	40% (1:1.2)	ND	ND	7 (0:1:0)
22	2/Et_2AlCl	-20, 0.03	CCl_4	30	56% (1:0.8)	5%(1:0:0)	ND	3 (0:0:1)
23	2/Et_2AlCl	-60, 0.03	$CHCl_3$	70	59% (1:1.1)	2(1:0:0)	ND	7 (0:0:1)
24[e]	2/Et_2AlCl	-40, 0.03	CH_3CN	65	ND	ND	ND	22 (1:0:0)

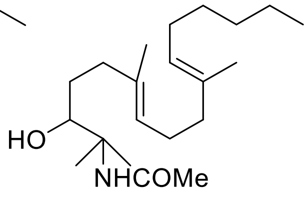
[a] Compound **9a** was obtained in 14% yield. Minor proportions of its epimer at C8 was detected by NMR from the mixture. [b] Compound **9a** was obtained in 15% yield. Its epimer at C8 was detected by NMR from the mixture. [c] 60% recovered starting material. [d] Compound **10** was obtained in 91% yield [e] Compound **11** was obtained in 43% yield.



9a



10



11

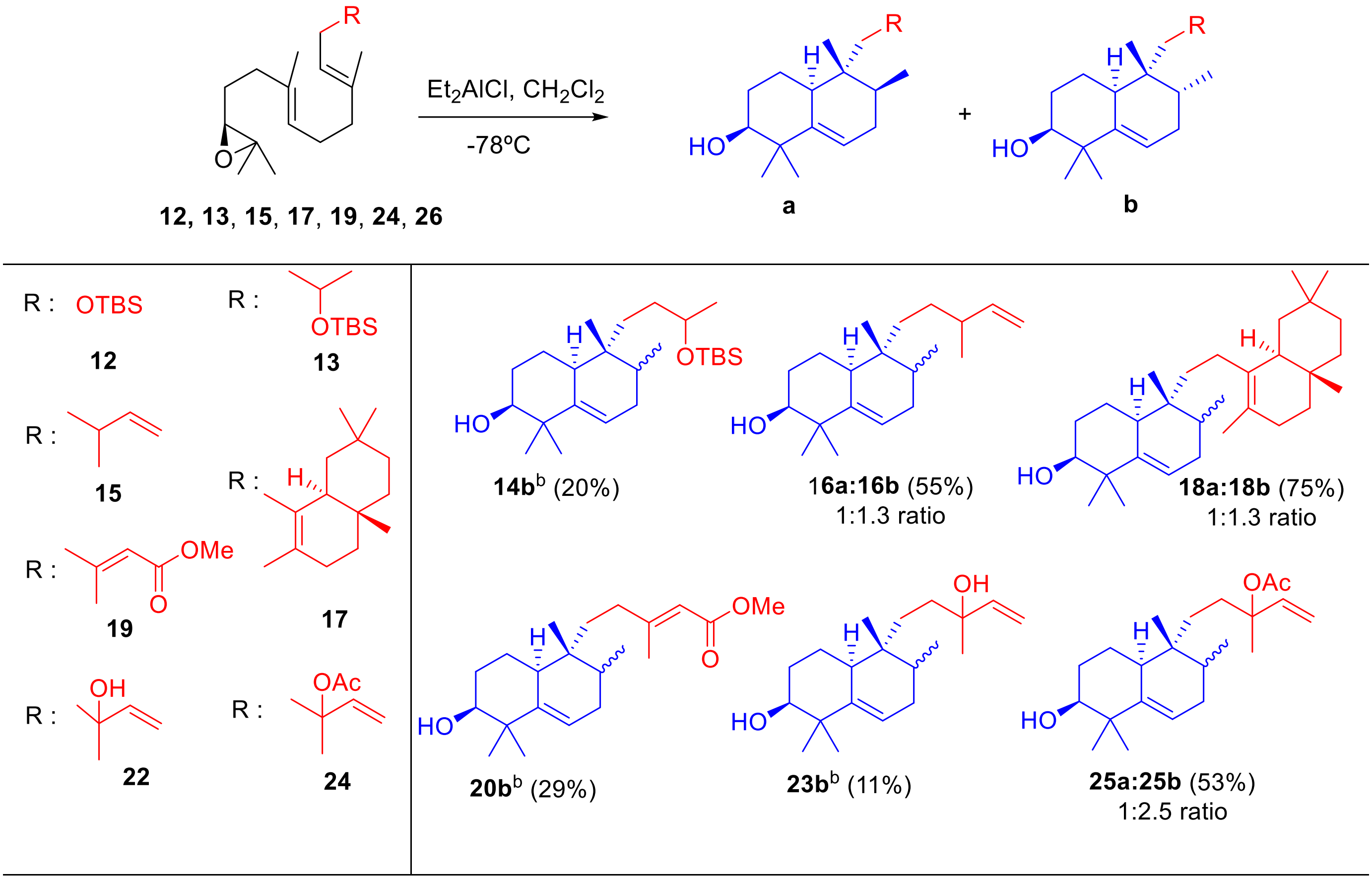
To start, several Lewis acids were tested to trigger the cyclization-rearrangement process (Table 1, entries 1–6). Although the two alkyl aluminum Lewis acids used led to acceptable yields of **3a** and **3b**, comparatively slight yield improvements were found when Et_2AlCl was used (Table 1, entry 2). Copper(II) and bismuth(III) triflates failed to produce the desired halimane derivatives, and a complex mixture of non-rearranged monocyclic and bicyclic structures was observed (Table 1, entries 3–4). The results obtained with $InBr_3$ deserve a special mention, where together with the previously generated halim-5-ene derivatives **3a** and **3b**, the formation of haliman-1(10)-enes **9a** and **9b** was observed (Table 1, entries 5–6). The greater volume of the Lewis acid in this case, hampering its approach to C–10 and therefore the stabilization of the carbocation at this position, may be postulated to rationalize these results.

All in all, Et_2AlCl was selected as catalyst of choice. Variations in the quantity of Et_2AlCl used (Table 1, entries 7–11) caused an improvement in the efficiency of the process. Thus, up to a 71% yield of the desired halim-5-enes was obtained when 2 equivalents of Lewis acid were used (Table 1, entry 9). Changes in the temperature do not produce significant yield differences (Table 1, entries 9, 12–13), with the best results being obtained when the reaction was conducted at -78º C. Furthermore, the influence of molar concentration on production of **3a** and **3b** was also moderate as can be concluded from the results obtained in entries 9, 14 and 15 of the Table 1.

Finally, significant alterations of the reaction outcome were revealed when different solvents were tested. Thus, the use of hexane as a solvent slowed down the process significantly, and after 1h, most of the starting material remained mainly unaltered (Table 1, entry 16). Good yields were obtained in benzene and toluene (54% and 68%, respectively) (Table 1, entries 17–18), probably due to the stabilization of carbocation intermediates. The effect of ethereal solvents was counter-productive and mainly regular mono- and unrearranged bicyclization products **7** and **8** were obtained (Table 1, entries 19–20). Easy deprotonation of the corresponding bicyclic cations by solvents acting as Brønsted bases may account for the observed reactivity. The use of THF provoked the production of acyclic ketone **10** as major product as result of a 1,2-hydride shift of the initial acyclic carbocation. Other halogenated solvents were also tested and, although acceptable yields of the target **3a** and **3b** were produced (Table 1, entries 21–23), the efficiency of the process was slightly worse when compared to that found when using DCM. To conclude, a polar aprotic solvent such as CH_3CN was also made to react with epoxide **2** (Table 1, entry 24) and the initial carbocation was neutralized by a molecule of acetonitrile leading to the hydroxyacetamide **11** as a major product after work-up.

Once the experimental conditions were optimized (Table 1, entry 9), we proceeded to study the scope of the process by altering the side chain of the epoxypolyprene (Table 2)

Table 2. Scope of the Biomimetic Cyclization–Rearrangement of Epoxypolyenes.[a]



12, 13, 15, 17, 19, 24, 26

a

b

12, **13**, **15**, **17**, **19**, **22**, **24**

14b[b] (20%)

16a:16b (55%) 1:1.3 ratio

18a:18b (75%) 1:1.3 ratio

20b[b] (29%)

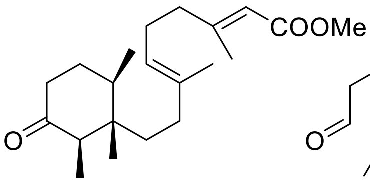
23b[b] (11%)

25a:25b (53%) 1:2.5 ratio

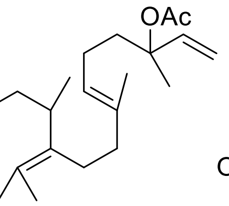
[a] Conditions: epoxypolyene (0.01 M), Et_2AlCl (2-3 equiv), CH_2Cl_2, -78ºC, 45 min. The epimeric mixtures were separated by semipreparative HPLC. [b] Minor proportions of the corresponding epimer at C8 was detected by NMR from the mixture.

First of all the reaction of the *tert*-butyldimethylsilylderivative of 10,11-epoxyfarnesol **12** with Et_2ClAl in CH_2Cl_2 only resulted in a mixture of bicyclization compounds, where no concomitant rearrangement were produced, in agreement with previous reported results.[13,56] The presence of a silyloxy group at C13 in compound **13** considerably reduced the efficiency of the process towards the halimene type products **14b** (20%), whilst when a double bond is located at C–14, as happens in **15,** an acceptable yield was again obtained (55% of halima-5-enes **16a–b**). In both cases, a certain degree of diastereoselectivity was noticed, favouring the rearranged structured derived from the chair-boat conformation of the starting epoxide (methyl groups at C8 and C9: *anti*). In the reaction of epoxypreoleanatetraene **17** with Et_2AlCl, a good 75 % of a 1:1.3 mixture of the corresponding tetracyclic derivatives (**18a–b**) was obtained, which evidenced a high energetic barrier for a third cyclization in this case.[57]

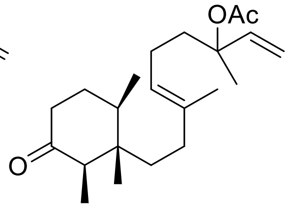
When the monoepoxy derivative of methyl geranylgeraniate (**19**) was used as a starting material, the diastereomer **20b** resulting from the expected cyclization-rearrangement was obtained in a 29% yield. It should be noted that the monocyclic ketone **21** (5.5%) was also obtained.



21



26

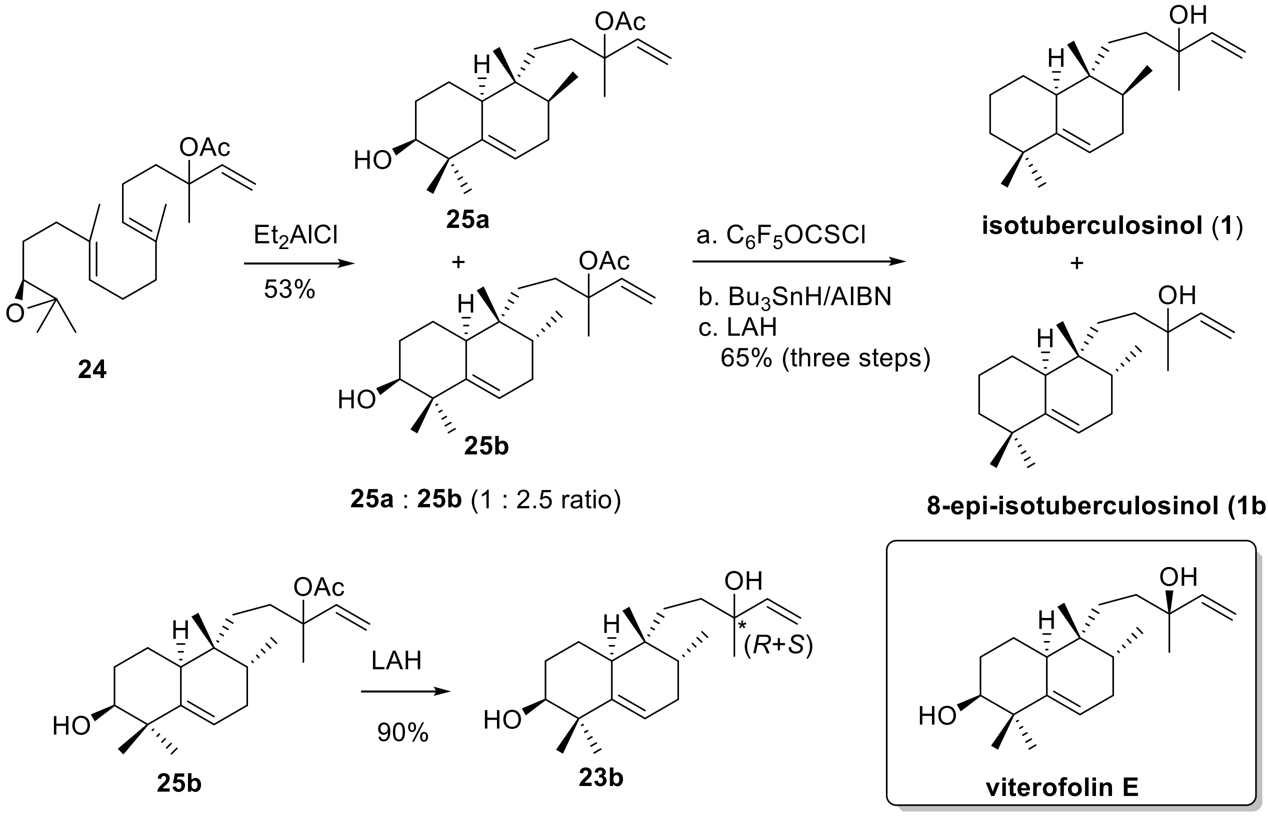


27

Perhaps the most elegant demonstration of the utility of this cascade of cyclizations plus rearrangements strategy is displayed in the straightforward synthesis of the interesting halim-5-ene isotuberculosinol (**1**). We also anticipated that, while addressing the synthesis of tuberculosinol, the natural halimene viterofolin E,[59] isolated from *Vitex rotundifolia*, could be produced en route (Scheme 2). With these targets in mind, we treated the monoepoxy derivative of geranyllinalool (**22**) with Et_2ClAl in DCM at -78 ºC. Unsurprisingly, the presence of a free hydroxyl group prevented the cyclization-rearrangement process to take place efficiently, and only 12% of the corresponding halim-5-enes (**23**) were produced. However, if the monoepoxy derivative of geranyllinalool acetate **24** was subjected to the same conditions, an acceptable 53% yield of diastereoisomers **25** (1: 2.5) was obtained, together minor proportions of **26** and **27**. Of these two diastereomers, compound **25a** presents the same stereochemistry at C–8 and C–9 as that exhibited by isotuberculosinol (**1**) (Scheme 2), whereas the second distereomer, **25b**, shares the stereochemistry at C–8 and C–9 with viterofolin E. Reduction of **25b** with LAH allowed to complete the synthesis of viterofolin E as a mixture of epimers at C–13 (**23b**) in only two steps and 34% yield from epoxide **24**.

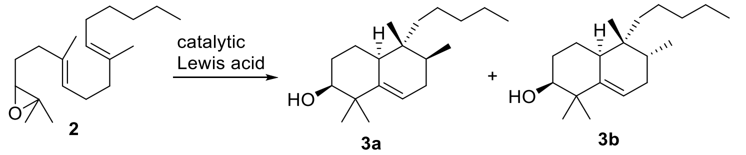
Continuing with the synthesis of isotuberculosinol, the pair of epimers **25** was deoxygenated following the modified Barton-McCombie procedure, and then reduced with LAH. Isotuberculosinol **1** was thus obtained in 65% yield for the last three steps and in an overall 10% yield from monoepoxyderivative **24**. The spectroscopic data of synthetic isotuberculosinol matched completely with those reported for the natural substance.[47] Together with isotuberculosinol, its 8-epi-isomer **1b** was isolated in 25% yield. Although this substance has not been described as natural product so far, it was enzymatically produced.[60]

Scheme 2. Synthesis of (±) isotuberculosinol.



Once we proved that rearranged diterpenes can be produced after a tandem process of cyclization and rearrangements, we turned back (our attention) to one of the conclusions inferred from the computational calculations, namely, (that) the process is susceptible to catalysis by the Lewis acid. Thus, we treated epoxide to substoichiometric quantities of different Lewis acids (Table 3). Although the use of 50% mmol of dimethylaluminium chloride also produced **3a** and **3b** with acceptable yield (table 3, entry 1), when the quantity of dimethylaluminium chloride was lowered up to 0.2 equiv, the process showed no completion after 5h of reaction time, and 31% of starting material remained unaltered (Table 3, entry 2). We decided then to test different gallium[66] and indium halides. Although the use of indium halides (Table 3, entries 3–4) led to low yields of the rearranged products **3a** and **3b**, the use of 0.2 equiv of different gallium halides led, gratifyingly, to acceptable yields of the desired halim-5-ene derivatives (Table 3, entries 5–7). We finally found that the quantity of $GaCl_3$ could be reduced to 0.01 equiv without decreasing the yield of the halim-5-enes produced (Table 3, entry 8).

Table 3. Generation of Halim-5-enes derivatives (3a–3b) from Epoxide 2 Using Catalytic Quantities of Lewis Acids[a]

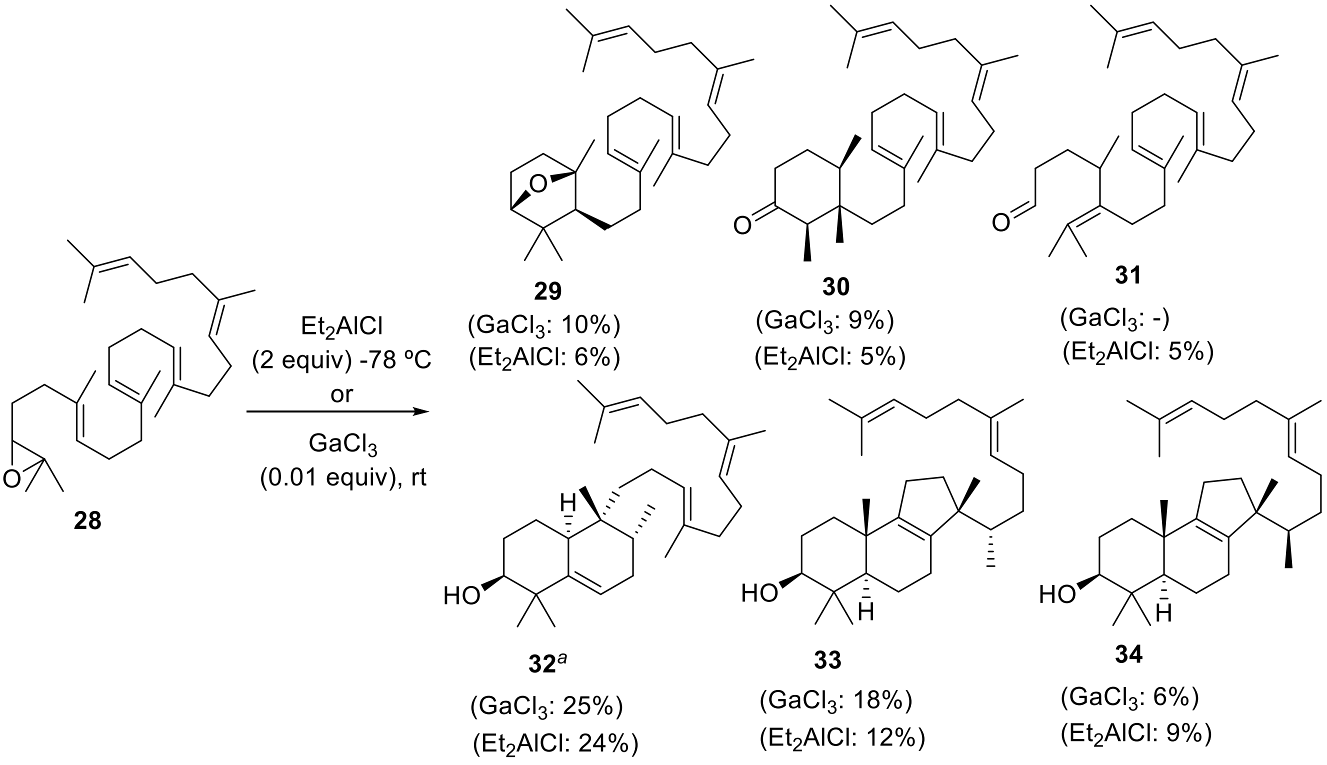


entry	equiv/LA	temp (ºC), time (min)	3a, 3b yield (ratio)
1	0.5/Me_2AlCl	-78, 100	53% (1:1)
2[b]	0.2/Me_2AlCl	-78, 180	32% (1:1.7)
3	0.2/InI_3	rt, 15	28 %(1:0.8)
4	0.2/$InCl_3$	rt, 55	12% (1:2)
5	0.2/$GaCl_3$	rt, 5	56% (1:1)
6	0.2/GaI_3	rt, 5	53% (1:1)
7	0.2/$GaBr_3$	rt, 5	54% (1:1)
8	0.1/$GaCl_3$	rt, 5	55% (1:1)
9	0.01/$GaCl_3$	rt, 5	51% (1:1)

[a] DCM was used as solvent, 0.03 C (mM). [b] ·31% of starting material was recovered.

Finally, considering both the enormous biosynthetic importance of the cyclization of squalene-2,3-oxide and the fact that its cyclization with $SnCl_4$ supposed the only precedent so far reported of cyclization and rearrangement to produce halim-5-enes, we decided to study the behavior of squalene-2,3-oxide (**28**) in the presence of aluminium and gallium Lewis acids. The results obtained are summarized in Scheme 3.

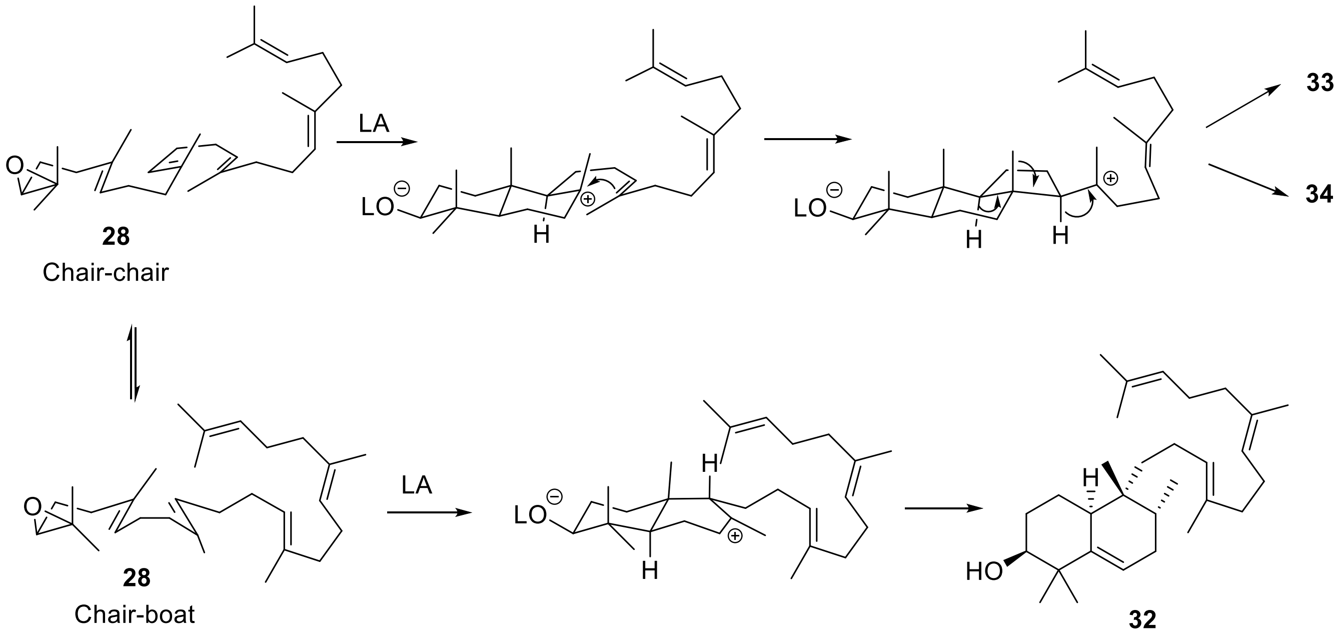
Scheme 3. Cyclization of oxidoaqualene with Et_2AlCl and $GaCl_3$.



[a] Minor proportions of the corresponding epimer at C8 was detected by NMR from the mixture.

Although no reported by van Tamelen, monocycles **29** and **30** were found previously in the cyclizations of **28**, either triggered by different acids or in processes involving cyclases.[62,63] Aldehyde **31** was described for the first time. Halim-5-ene **32** presented the same ^{1}H NMR signals to that of the halimene described by van Tamelem, which allowed us to assign unambiguously the stereochemistry of the product reported by these authors. It should be noted that van Tamelen and Sharpless suggested the opposite configuration at C9 for this compound in their seminal contribution. Finally, the rearranged malabaricanes thalianol (**33**) and 14-epithalianol (**34**) were also produced in these transformations.[64,68] Although van Tamelen amazingly assigned in 1966 the same rearranged malabaricane to the tricyclic compound generated in the reaction of squalene-2,3-oxide with $SnCl_4$, our work suggest that the same mixture of thalianol and 14-epithalianol could have been generated in the $SnCl_4$-mediated cyclization. To conclude, the yields of **32-34** and their corresponding stereochemistries seem to indicate that, on the one hand, the bicyclic cation derived from the chair-chair conformation of squalene-2,3-oxide evolves via a third cyclization to produce the rearranged malabaricanes **33** and **34**, after a hydride and methyl shift, and a proton elimination (Scheme 4). On the other hand, the bicyclic intermediated derived from chair-boat conformation of the acyclic precursor would undergo the corresponding 1,2-shifts to generate the halim-5-ene derivative **32**.

Scheme 4. Formation of 32-34 from epoxide 28.



CONCLUSIONS

Nature produces numerous examples of rearranged diterpenes and triterpenes. In this regard, we prove that rearranged halima-5-enes can be produced in a single synthetic step by reacting monoepoxy-geranylgeraniol derivatives with appropriate Lewis acids, via a cascade of two cyclizations and three rearrangements. The fact that we were capable to generate “in vitro” the halima-5-ene skeleton constitutes a nice illustration of the theory of “minimal enzymatic assistance”, which was postulated to define the action of cyclases in the generation of related natural products. Quantum chemical calculations revealed, on the one hand, that the energetic barriers calculated for the cyclization and rearrangements processes were low enough to support our mechanistic proposal and, on the other hand, that the process was susceptible to catalysis by the Lewis acid. This last inference was confirmed experimentally, and acceptable yields of rearranged halim-5-ene derivatives could be produced after employing 0.01 equiv of $GaCl_3$.

EXPERIMENTAL SECTION

General Remarks.

All air- and water-sensitive reactions were performed in flaks flame-dried under a positive flow of argon and conducted under an argon atmosphere. The solvents used were purified according to standard literature techniques and stored under argon. Anhydrous dichloromethane was distilled from calcium hydride (5 % w/v) under positive pressure of nitrogen. THF was freshly distilled immediately prior to use from sodium/benzophenone and strictly deoxygenated for 30 min under Argon. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated. Silica gel SDS 60 (35-70 μm) was used for flash column chromatography. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and solutions of phosphomolybdic acid in ethanol. HPLC with UV detection was used. Semi-preparative HPLC separation were carried out on a column (5 μm Silica, 10 X 250 mm) at a flow rate of 2.0 mL/min in an Agilent Series 1100 instrument. NMR spectra were performed with a Varian Direct Drive 600 (^{1}H 600 MHz/^{13}C 150 MHz), Varian Direct Drive 500 (^{1}H 500 MHz/^{13}C 125 MHz), Varian Direct Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz) and Varian Inova Unity (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. High-resolution MS were determined on an Autospec-Q VG-Analytical (FISONS) mass spectrometer. DEPT 135 and two-dimensional

(COSY, HSQC, HMBC, NOESY) NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

Preparation of polyenic precursors 35–38.

*(6E,10E)-2,6,10-Trimethylhexadeca-2,6,10-triene (**35**).* To a solution of farnesyl acetate (1000 mg, 3.78 mmol) in 20 mL of THF cooled at 0ºC was added 3.8 mL of Li_2CuCl_4 (0.38 mmol). The resulting solution was cooled at -30 ºC and then, 2.83 mL of butylmagnesium chloride were added dropwise (5.67 mmol). After stirring for 4 h, the reaction mixture was diluted with *tert*butyl methyl ether (MTBE) (120 mL) and then washed with saturated aqueous NH_4Cl and brine. The organic layer was then dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography with hexane (H) provided 971 mg of compound **35** (97%). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15–5.08 (m, 3H), 2.11–2.04 (m, 4H), 2.01–1.97 (m, 6H), 1.68 (s, 3H), 1.60 (s, 9H), 1.36–1.26 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 134.8 (C), 134.7 (C), 131.2 (C), 124.8 (CH), 124.4 (CH), 124.3 (CH), 39.7 (CH_2), 39.7 (CH_2), 31.5 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 25.7 (CH_3), 22.6 (CH_2), 17.7 (CH_3), 16.0 (CH_3), 15.9 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}$ 263.2739, found 263.2732.

*Tert-butyldimethyl(((5E,9E)-6,10,14-trimethylpentadeca-5,9,13-trien-2-yl)oxy)silane (**36**).* To a solution of farnesyl ketone (1147 mg, 4.38 mmol) in 24 mL of THF cooled at 0ºC was added 141 mg of LAH (3.72 mmol). The resulting solution was stirred for 20 min, and then, diluted with MTBE. To this solution, 0.1 mL of H_2O, 0.1 mL of 5N NaOH and 0.3 mL of H_2O were added successively. The resulting mixture was filtrated through a pad Na_2SO_4 and silica gel and concentrated under reduced pressure. To a stirred solution of this reaction crude oil in 70 mL of DMF were added imidazole (627 mg, 9.2 mmol) and TBSCl (1384 mg, 9.2 mmol). After consumption of the starting product (12 h), the mixture was diluted with MTBE and water and extracted with MTBE. The combined organic layer was washed with 2N HCl and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (H:MTBE, 3:1) afforded 1460 mg of compound **36**

(88%). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17–5.08 (m, 3H), 3.80 (sext, J = 6.1 Hz, 1H), 2.12–1.92 (m, 10H), 1.69 (s, 3H), 1.61 (s, 9H), 1.53–1.67 (m, 2H), 1.14 (d, J = 6.1 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 135.0 (C), 134.9 (C), 131.2 (C), 124.4 (CH), 124.3 (CH), 124.2 (CH), 68.4 (CH), 39.9 (CH_2), 39.7 (CH_2), 39.7 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 25.9 (3 x CH_3), 25.7 (CH_3), 24.3 (CH_2), 23.8 (CH_3), 18.2 (C), 17.7 (CH_3), 16.0 (CH_3), 16.0 (CH_3), -4.4 (CH_3), -4.7 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{47}OSi$ 379.3396, found 379.3391.

*(6E,10E)-3,7,11,15-Tetramethylhexadeca-1,6,10,14-tetraene (**37**).* A mixture of Cp_2TiCl_2 (4124 mg, 16.56 mmol) and Mn dust (3163 mg, 57.61 mmol) in deoxygenated THF 100 mL) was stirred at rt until the red solution turned green, under an argon atmosphere. Then, a solution of geranylgeraniol (2092 mg, 7.2 mmol) in strictly deoxygenated THF (5.0 mL) was added to the solution of Cp_2TiCl_2. The reaction mixture was refluxed for 20 h. Then, the solution was diluted with MTBE, filtrated and the solid washed with ethyl acetate. The organic layer was washed with HCl 2N, then with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting crude was flash chromatographed (H) to give 1007 mg (51%) of compound **37**. Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (ddd, J = 17.2, 10.3, 7.5 Hz, 1H), 5.16–5.08 (m, 3H), 4.96 (ddd, J = 17.2, 2.0, 1.2 Hz, 1H), 4.92 (ddd, J = 10.3, 2.0, 0.9 Hz, 1H), 2.17–1.96 (m, 11H), 1.68 (s, 3H), 1.60 (s, 9H), 1.38–1.27 (m, 2H), 0.97 (d, J = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 145.0 (CH), 135.1 (C), 131.5 (C), 124.8 (CH), 124.7 (CH), 124.5 (CH), 118.5 (C), 112.7 (CH_2), 46.0 (CH), 40.0 (CH_2), 37.6 (CH_3), 37.0 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.0 (CH_3), 25.9 (CH_2), 20.4 (CH_3), 17.9 (CH_3), 16.3 (CH_3), 16.3 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{35}$ 275.2739, found 275.2727.

*Methyl (2E,6E,10E)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenoate (**38**).* To a stirred solution of geranylgeraniol (1000 mg, 3.45 mmol) in 40 mL in CH_2Cl_2 under Argon was added Dess-Martin reagent (2925 mg, 6.9 mmol). After 2 h at rt the reaction was quenched with a saturated solution of $Na_2S_2O_3$–$NaHCO_3$ that was added slowly to the mixture, the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

Filtration on silica gel (H: MTBE, 1:2) afforded the allylic aldehyde, which was dissolved in 30 mL of *tert*-butyl alcohol and 15 mL of 2-methyl-2-butene. A solution of sodium chlorite (1910 mg, 21.22 mmol) and sodium dihydrogenphosphate (2200 mg, 15.92 mmol) in 15 mL of water was added dropwise over a 25 min period. The pale yellow reaction mixture was stirred at room temperature for 2 h. Volatile components were then removed under vacuum. The residue was dissolved in 150 mL of water and extracted with two 100 mL portions of MTBE. The combined organic layers were washed with brine, dried and concentrated. To a stirred solution of this reaction crude oil in 8.5 mL of benzene and 2.1 mL of MeOH, 1.6 mL (3.2 mmol) of a 2M solution of $TMSCH_2N_2$ in hexanes was added dropwise. After consumption of the starting product (30 min), the mixture was concentrated under reduced pressure. Purification by flash chromatography (H/MTBE, 10:1) afforded 556 mg of compound **38** (51%). The spectroscopic data of compound **38** coincide with those reported in the literature.[58]

General procedure for the synthesis of epoxy-derivatives 2, 13, 15 and 19

Powdered NBS (1.1 mmol) was added to a solution of the corresponding polyene (**35–38**) (1.0 mmol) in a mixture of THF:H_2O (12 mL, 5:1) at 0 ºC. The mixture was stirred for 30 min, diluted with MTBE, washed with water, dried with anhydrous Na_2SO_4 and the solvent concentrated under reduced pressure. The residue was dissolved in 8 mL of MeOH containing 1.2 mmol of K_2CO_3 (20 mL) and stirred for 10 min. The methanolic solution was then diluted with MTBE, washed with water, brine, dried with anhydrous $Na_2SO_4$and the solvent removed, giving a residue which was flash chromatographed to give the corresponding epoxides.

*(3-((3E,7E)-3,7-Dimethyltrideca-3,7-dien-1-yl)-2,2-dimethyloxirane (**2**).* Following the general procedure, successive reaction of polyene **28** with NBS and K_2CO_3/MeOH provided compound **2** (45%). This compound was separated by flash chromatography (H:MTBE, 95:5). Colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.17–5.11 (m, 2H), 2.70 (t, J = 6.2 Hz, 1H), 2.19–2.06 (m, 4H), 2.04–1.94 (m, 4H), 1.70–1.63 (m, 2H), 1.62 (s, 3H), 1.59 (s, 3H), 1.33–1.27 (m, 6H), 1.30 (s, 3H), 1.26 (s,

3H), 0.88 (t, *J* = 6.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 134.5 (C), 133.9 (C), 124.9 (CH), 124.9 (CH), 64.2 (CH), 58.3 (C), 39.6 (CH_2), 36.3 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 27.9 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 24.9 (CH_3), 22.6 (CH_2), 18.7 (CH_3), 16.0 (CH_3), 15.9 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, found 279.2681.

*Tert-butyl(((5E,9E)-12-(3,3-dimethyloxiran-2-yl)-6,10-dimethyldodeca-5,9-dien-2-yl)oxy)dimethyl silane (**13**).* Following the general procedure, successive reaction of polyene **29** with NBS and K_2CO_3/MeOH provided compound **13** (45%). This compound was separated by flash chromatography (H:MTBE, 95:5). Colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 5.17 (bt, *J* = 6.8 Hz, 1H), 5.13 (bt, *J* = 6.9 Hz, 1H), 3.80 (sext, *J* = 6.0 Hz, 1H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.19–1.92 (m, 8H), 1.71–1.57 (m, 2H), 1.63 (s, 3H), 1.61 (s, 3H), 1.53–1.39 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.6 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 134.9 (C), 134.0 (C), 124.9 (CH), 124.4 (CH), 68.4 (CH), 64.2 (CH), 58.3 (C), 39.8 (CH_2), 39.6 (CH_2), 36.3 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 25.9 (3 x CH_3), 24.9 (CH_3), 24.3 (CH_2), 23.8 (CH_3), 18.8 (CH_3), 18.2 (C), 16.0 (CH_3), 16.0 (CH_3), -4.4 (CH_3), -4.7 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{47}O_2Si$ 395.3345, Found 395.3355.

*2,2-Dimethyl-3-((3E,7E)-3,7,11-trimethyltrideca-3,7,12-trien-1-yl)oxirane (**15**).* Following the general procedure, successive reaction of polyene **30** with NBS and K_2CO_3/MeOH provided compound **15** (58%). This compound was separated by flash chromatography (H:MTBE, 95:5). Colourless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.74–5.63 (m, 1H), 5.17–5.08 (m, 2H), 4.97–4.89 (m, 2H), 2.69 (t, *J* = 6.2 Hz, 1H), 2.15–2.04 (m, 6H), 2.00–1.92 (m, 5H), 1.66–1.63 (m, 2H), 1.61 (s, 3H), 1.58 (s, 1H), 1.35–1.30 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 145.0, 135.0, 134.2, 125.1, 124.9, 112.7, 64.4, 58.5, 39.9, 37.6, 37.0, 36.6, 27.7, 26.8, 25.9, 25.1, 20.4, 19.0, 16.3, 16.2; HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{35}O$ 291.2688, Found 291.2677.

*Methyl (2E,6E,10E)-13-(3,3-dimethyloxiran-2-yl)-3,7,11-trimethyltrideca-2,6,10-trienoate (**19**).* Following the general procedure, successive reaction of polyene **31** with NBS and K_2CO_3/MeOH provided compound **19** (34%). This compound was separated by flash chromatography (H:MTBE, 10:1). Colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.68 (bs, 1H) 5.15 (bt, J = 6.9 Hz, 1H), 5.10 (m, 1H), 3.69 (s, 3H), 2.71 (t, J = 6.2 Hz, 1H), 2.19–1.97 (m, 10H), 2.17 (d, J = 1.3 Hz, 3H), 1.67–1.59 (m, 2H), 1.62 (s, 3H), 1.61 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 167.2 (C), 160.1 (C), 136.1 (C), 134.1 (C), 124.7 (CH), 122.9 (CH), 115.2 (CH), 64.2 (CH), 58.3 (C), 50.8 (CH$_3$), 40.9 (CH$_2$), 39.6 (CH$_2$), 36.3 (CH$_2$), 27.5 (CH$_2$), 26.6 (CH$_2$), 25.9 (CH$_2$), 24.9 (CH$_3$), 18.8 (CH$_3$), 18.7 (CH$_3$), 16.0 (CH$_3$), 16.0 (CH$_3$); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{35}O_3$ 335.2586, Found 335.2593.

Epoxides **12**, **17**, **22**, **24** and **28** were obtained following methods previously reported in the literarure.[13, 57, 61, 65]

General procedure for the cyclization plus rearrangement of epoxypolyprenes 2, 12, 13, 15, 17, 19, 24 and 26.

A solution of starting material (0.5 mmol) in dry DCM (50 mL) was cooled at -78 ºC, To a separate flask was added dry DCM (15 mL) followed by 1 mL of a 1M solution Et_2AlCl in DCM (1 mmol). This solution of Et_2AlCl was slowly added to a cooled solution of starting material (approximately for 1h). The reaction crude oil was further stirred until disappearance of the starting material. Then, 1.5 mL of Et_3N and 0.7 mL of a 4:1 mixture of $MeOH/H_2O$ were added. The reaction mixture was taken out of the cooling bath and a saturated solution of NH_4Cl (60 mL) was then added. After separation of the organic layer, the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layer was washed with brine (3 x 50 mL), dried over Na_2SO_4, concentrated under reduced pressure and then purified by column chromatography.

Cyclization of epoxypolyprene 2

Using DCM as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl at -78 ºC for 1 h provided after flash chromatography (H:MTBE, 6:1) compounds **3a** and **3b** (71%, 1:1 ratio), compound **4** (3%), compound **6** (3%) and compounds **8b** and **8c** (10%, 0.6:1 ratio). Ratios were determined by integration of the ^{1}H NMR spectrum of the mixture.

*(2S,4aS,5R,6S)-1,1,5,6-Tetramethyl-5-pentyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**3a**).* A fraction enriched in **3a** was subjected to HPLC (normal phase, H:TBME 19:1, Rt = 50.1 min) to give pure **3a**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.53 (dt, *J* = 5.1, 2.2 Hz, 1H), 3.47 (t, *J* = 2.8 Hz, 1H), 2.27 – 2.22 (m, 1H), 1.92 – 1.85 (m, 2H), 1.79 (dddd, *J* = 17.7, 10.6, 3.5, 2.3 Hz, 1H), 1.70 (dq, *J* = 14.0, 3.5 Hz, 1H), 1.57–1.45 (m, 3H), 1.36 – 1.17 (m, 8H), 1.14 (s, 3H), 1.06 (s, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.66 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 142.4 (C), 120.8 (CH), 76.4 (CH), 41.3 (C), 38.8 (CH), 37.0 (C), 36.8 (CH_2), 33.5 (CH), 32.8 (CH_2), 31.8 (CH_2), 28.3 (CH_3), 28.3 (CH_2), 25.5 (CH_3), 22.7 (CH_2), 22.2 (CH_2), 20.0 (CH_2), 16.3 (CH_3), 15.1 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2682.

*(2S,4aS,5R,6R)-1,1,5,6-Tetramethyl-5-pentyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**3b**).* A fraction enriched in **3b** was subjected to HPLC (normal phase, H:MTBE 19:1, Rt = 50.1 min) to give pure **3b**. Colourless oil. ^{1}H NMR (600 MHz, DMSO–*d*$_6$, 85 ºC): δ 5.27 (bt, *J* = 3.9 Hz, 1H, H6), 3.32 (t, *J* = 3.1 Hz, 1H, H3), 2.06 (bd, *J* = 17.4 Hz, 1H, H7a), 1.98 (bd, *J* = 12.2 Hz, 1H, H10), 1.92 (tdd, *J* = 13.2, 4.9, 2.6 Hz, 1H, H2a), 1.68 – 1.55 (m, 3H, H7b, H8, H2b), 1.52 – 1.40 (m, 2H, H1), 1.31 – 1.13 (m, 8H, H11, H12, H13, H14), 1.01 (s, 3H, H19), 0.98 (s, 3H, H18), 0.85 (t, *J* = 7.1 Hz, 3H, H15), 0.78 (s, 3H, H20), 0.75 (d, *J* = 6.7 Hz, 3H, H17); $^{13}C\{^1H\}$ NMR (150 MHz, DMSO–*d*$_6$, 85 ºC): δ 148.6 (C6), 121.7 (C5), 80.2 (C3), 45.8 (C4), 45.1 (C10), 41.0 (C9), 39.7 (C11), 37.8 (C8), 37.7 (CH_2), 36.0 (C7), 34.8 (C2), 32.3 (C18), 30.2 (C19), 27.6 (CH_2), 27.2 (CH_2), 27.0 (C20), 26.7 (C1), 19.7 (C17), 19.0 (C15); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688; Found 279.2679.

*(1R,4S)-1,3,3-Trimethyl-2-((E)-3-methylnon-3-en-1-yl)-7-oxabicyclo[2.2.1]heptane (**4**).* Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.17 (tm, *J* = 6.9 Hz, 1H), 3.70 (d, *J* = 5.4 Hz, 1H),

2.00 – 1.86 (m, 5H), 1.69 – 1.63(m, 1H), 1.57 (s, 3H), 1.50 – 1.22 (m, 10H), 1.31 (s, 3H), 1.17 (dd, *J* = 8.7, 5.8 Hz, 1H), 1.03 (s, 3H), 1.00 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 135.0 (C), 133.8 (C), 125.0 (CH), 88.7 (C), 86.0 (CH), 55.1 (CH), 45.2 (C), 39.8 (CH_2), 39.0 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 26.1 (CH_2), 26.1 (CH_3), 25.7 (CH_2), 23.9 (CH_3), 22.6 (CH_2), 18.9 (CH_3), 15.9 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2710.

*(R,E)-4,8-Dimethyl-5-(propan-2-ylidene)tetradec-8-enal (**6**).* Aldehyde **6** was purified and characterized as its primary alcohol derivative **6a**. To a solution of a fraction enriched in **6** (18 mg) in 5 mL of MeOH:H_2O (4:1 ratio) was added 3 mg of $NaBH_4$ and the mixture was stirred for1 h 30 min at 0ºC. The reaction was concentrated under reduced pressure and the residue dissolved in MTBE and washed with water, quenched with acetone, and concentrated under reduced pressure. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting crude was purified by HPLC (H:MTBE, 6:1) to afford 12 mg of primary alcohol **6a**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (t, *J* = 7.1 Hz, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 2.71 (h, *J* = 7.1 Hz, 1H), 2.06 – 1.93 (m, 4H), 1.68 (s, 3H), 1.65 (s, 3H) 1.63 (s, 3H), 1.55 – 1.25 (m, 10 H), 0.98 (d, *J* = 6.9 Hz, 3H),0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 135.7 (C), 135.6 (C), 125.2 (C), 124.3 (CH), 63.4 (CH_2), 40.4 (CH_2), 35.6 (CH), 31.6 (CH_2), 31.6 (CH_2), 31.2 (CH_2), 29.6 (CH_2), 27.9 (CH_2), 27.0 (CH_2), 22.6 (CH_2), 21.0 (CH_3), 20.1 (CH_3), 19.7 (CH_3), 16.0 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{19}H_{35}$ 263.2739, Found 263.2745.

*(2S,4aR,5S,8aR)-1,1,4a-Trimethyl-6-methylene-5-pentyldecahydronaphthalen-2-ol (**8b**).* A fraction enriched in **8b** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 22.7 min) to give pure **8b**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.83 (d, *J* = 1.7 Hz, 1H), 4.53 (d, *J* = 1.7 Hz, 1H), 3.27 (dd, *J* = 11.8, 4.4 Hz, 1H), 2.43 – 2.38 (m, 1H), 1.99 (td, J = 13.1, 5.0 Hz, 1H), 1.81 (dt, *J* = 13.1, 3.6 Hz, 1H), 1.77 – 1.06 (m, 15H), 1.01 (s, 3H), 0.92 (s, 1H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.78 (s, 3H), 0.68 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 148.4 (C), 106.5 (CH_2), 78.9 (CH), 56.6 (CH),

54.6 (CH), 39.3 (C), 39.1 (C), 38.2 (CH_2), 37.1 (CH_2), 32.5 (CH_2), 28.4 (CH_2), 28.3 (CH_3), 28.0 (CH_2), 24.0 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 15.4 (CH_3), 14.4 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2597.

*(2S,4aR,5S,8aR)-1,1,4a,6-Tetramethyl-5-pentyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-2-ol (**8c**).* A fraction enriched in **8c** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 21.5 min) to give pure **8c**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.39 (bs, 1H), 3.26 (dd, *J* = 11.2, 4.5 Hz, 1H), 2.00 – 1.94 (m, 2H), 1.91 (dt, *J* = 13.3, 3.6 Hz, 2H), 1.69 (s, 3H), 1.67 – 1.57 (m, 3H), 1.52 (s, 2H), 1.42 – 1.10 (m, 8H), 0.98 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 3H), 0.76 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 135.6 (C), 121.7 (CH), 79.2 (CH), 54.9 (CH), 49.6 (CH), 38.7 (C), 37.3 (CH_2), 36.5 (C), 32.5 (CH_2), 31.9 (CH_2), 27.9 (CH_3), 27.4 (CH_2), 27.2 (CH_2), 23.5 (CH_2), 22.6 (CH_2), 21.9 (CH_3), 15.1 (CH_3), 14.1 (CH_3), 13.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2608.

Using MTBE as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl, using MTBE as a solvent for 1 h provided after flash chromatography (H:MTBE, 9:1) compounds **3a** and **3b** (4%, 1:1 ratio), compounds **7a** and **7b** (57%, 1:1.3 ratio) and compounds **8b** and **8c** (21%, 1.6:1 ratio). Ratios were determined by integration of the ^{1}H NMR spectrum of the mixture.

*(1S,5R)-4,6,6-Trimethyl-5-((E)-3-methylnon-3-en-1-yl)cyclohex-3-en-1-ol (**7a**).* A fraction enriched in **7a** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 20.8 min) to give pure **7a**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.23 (bs, 1H), 5.13 (t, *J* = 6.8 Hz, 1H), 3.45 (dd, *J* = 8.1, 5.5 Hz, 1H), 2.26 – 2.19 (m, 1H), 2.15 (ddd, *J* = 15.1, 10.9, 5.2 Hz, 1H), 1.99 – 1.93 (m, 4H), 1.75 – 1.68 (m, 1H), 1.71 (s, 4H), 1.63 (bs, 1H), 1.60 (s, 3H), 1.37 – 1.23 (m, 7H), 0.95 (s, 3H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.82 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 137.1 (C), 135.0 (C), 125.3 (CH), 118.2 (CH), 75.0 (CH), 48.8 (CH), 42.0 (CH_2), 38.1 (C), 31.8 (CH_2), 31.6 (CH_2), 29.5 (CH_2),

27.9 (CH_2), 27.2 (CH_2), 27.0 (CH), 25.3 (CH_3), 22.6 (CH_3), 16.2 (CH_3), 16.0 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2690.

*(1S,3R)-2,2-Dimethyl-4-methylene-3-((E)-3-methylnon-3-en-1-yl)cyclohexan-1-ol (7**b**).* A fraction enriched in **7b** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 22.6 min) to give pure **7b**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.10 (t, *J* = 7.3 Hz, 1H), 4.88 (s, 1H), 4.61 (s, 1H), 3.41 (dd, *J* = 9.9, 4.2 Hz, 1H), 2.33 (dt, *J* = 13.2, 4.8 Hz, 1H), 2.08 (ddd, *J* = 13.6, 9.6, 4.2 Hz, 2H), 2.02–1.94 (m, 3H), 1.88 – 1.77 (m, 2H), 1.67 – 1.46 (m, 4H), 1.59 (s, 3H), 1.35 – 1.24 (m, 6H), 1.03 (s, 3H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.72 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 149.9 (C), 137.7 (C), 127.6 (CH), 111.0 (CH_2), 80.0 (CH), 53.4 (CH), 43.2 (C), 41.2 (CH_2), 35.8 (CH_2), 34.9 (CH_2), 34.2 (CH_2), 32.2 (CH_2), 30.5 (CH_2), 28.5 (CH_3), 26.3 (CH_2), 25.3 (CH_2), 18.6 (CH_3), 18.1 (CH_3), 16.8 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2578.

Using benzene as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl, using benzene as a solvent at 10ºC for 45 minutes provided after flash chromatography (H:MTBE, 9:1) compounds **3a** and **3b** (54%, 1:0.8 ratio), compound **4** (2%) and compound **5** (3%). Ratios were determined by integration of the ^{1}H NMR spectrum of the mixture.

*(2R,3S,4R)-2,3,4-Trimethyl-3-((E)-3-methylnon-3-en-1-yl)cyclohexan-1-one (**5**).* Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.16 (t, *J* = 7.1 Hz, 1H), 2.50 (q, *J* = 6.7 Hz, 1H), 2.37 – 2.33 (m, 2H), 2.14 – 1.80 (m, 6H), 1.68 – 1.55 (m, 1H), 1.63 (s, 3H), 1.48 – 1.23 (m, 8H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 10.2 Hz, 3H), 0.91 (t, *J* = 3.5 Hz, 3H), 0.59 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 214.1 (C), 134.8 (C), 124.9 (CH_2), 50.5 (CH), 43.5 (C), 41.6 (CH_2), 36.1(CH), 36.0 (CH_2), 32.6 (CH_2), 31.6 (CH_2), 31.0(CH_2), 29.5(CH_2), 28.0 (CH_2), 22.6 (CH_2), 16.2 (CH_3), 15.4 (CH_3), 15.0 (CH_3), 14.1 (CH_3), 7.6 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2687.

Using THF as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl, using THF as a solvent for 1 h provided after flash chromatography (H:MTBE, 9:1) in silica column compounds **6** and **4** (4%, 1:1 ratio), compounds **7a** and **7b** (4%, 1:1.3 ratio) and compound **10** (91%). Ratios were determined by integration of the ^1H NMR spectrum of the mixture.

*(6E,10E)-2,6,10-Trimethylhexadeca-6,10-dien-3-one (**10**).* Colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 5.15 – 5.10 (m, 1H), 2.61 (hept, *J* = 6.9 Hz, 1H), 2.56 – 2.51 (m, 2H), 2.24 (t, *J* = 7.8 Hz, 2H), 2.08 (q, *J* = 7.3 Hz, 2H), 2.01 – 1.94 (m, 2H), 1.37 – 1.24 (m, 6H), 1.60 (d, *J* = 8.0 Hz, 6H), 0.89 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 135.0 (C), 133.8 (C), 125.0 (CH), 88.7 (C), 86.0 (CH), 55.1 (CH), 45.2 (C), 39.8 (CH_2), 39.0 (CH_2), 31.5 (CH_2), 29.5 (CH_2), 27.8 (CH_2), 26.1 (CH_2), 26.1 (CH_3), 25.7 (CH_2), 23.9 (CH_3), 22.6 (CH_2), 18.9 (CH_3), 15.9 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{35}O$ 279.2688; Found 279.2706.

Using CH_3CN as solvent

Following the general procedure, reaction of epoxide **2** with Et_2AlCl, using acetonitrile as a solvent at -40 ºC for 1 h provided after chromatography in silica column, using mixtures of H and MTBE of increasing polarity, compound **8a** (H:MTBE, 95:5, 22%) and compound **11** (H:MTBE, 2:1. 43%). Ratios were determined by integration of the ^1H NMR spectrum of the mixture.

*(2S,4aS,8aR)-1,1,4a,6-tetramethyl-5-pentyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-2-ol (**8a**).* A fraction enriched in **8a** was subjected to HPLC (normal phase, H:TBME 5:1, Rt = 13.1 min) to give pure **8a**. Colourless oil.^1H NMR (500 MHz, $CDCl_3$): δ 3.25 (dd, *J* = 11.7, 4.7 Hz, 1H), 2.10 – 1.94 (m, 3H), 1.88 – 1.81 (m, 2H), 1.75 – 1.56 (m, 3H), 1.57 (s, 3H), 1.46 (ddd, *J* = 24.4, 12.4, 6.3 Hz, 1H), 1.38 – 1.24 (m, 6H), 1.11 (dd, *J* = 12.4, 2.0 Hz, 1H), 1.01 (s, 3H), 0.95 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.81 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 140.5 (C), 125.6 (C), 79.0 (CH), 51.1 (CH), 38.8 (C), 38.7 (C), 35.0 (CH_2), 33.8 (CH_2), 32.8 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 28.1 (CH_3), 27.8 (CH_2), 22.5 (CH_2), 20.1 (CH_3), 19.4 (CH_3), 18.8 (CH_2), 15.5 (CH_3), 14.1 (CH_3); HRMS (ESI–

QTOF) m/z: $[M - OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2584. A fraction enriched in **8a** was subjected to HPLC (normal phase, H:TBME 5:1, Rt = 13.1 min) to give pure **8a**. Colourless oil.^{1}H NMR (500 MHz, $CDCl_3$): δ 3.25 (dd, J = 11.7, 4.7 Hz, 1H), 2.10–1.94 (m, 3H), 1.88 – 1.81 (m, 2H), 1.75 – 1.56 (m, 3H), 1.57 (s, 3H), 1.46 (ddd, J = 24.4, 12.4, 6.3 Hz, 1H), 1.38 – 1.24 (m, 6H), 1.11 (dd, J = 12.4, 2.0 Hz, 1H), 1.01 (s, 3H), 0.95 (s, 3H), 0.90 (t, J = 7.0 Hz, 3H), 0.81 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 140.5 (C), 125.6 (C), 79.0 (CH), 51.1 (CH), 38.8 (C), 38.7 (C), 35.0 (CH_2), 33.8 (CH_2), 32.8 (CH_2), 30.4 (CH_2), 28.2 (CH_2), 28.1 (CH_3), 27.8 (CH_2), 22.5 (CH_2), 20.1 (CH_3), 19.4 (CH_3), 18.8 (CH_2), 15.5 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{19}H_{33}$ 261.2582, Found 261.2584.

*N-((6E,10E)-3-hydroxy-2,6,10-trimethylhexadeca-6,10-dien-2-yl)acetamide (**11**).* Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (t, J = 6.9 Hz, 1H), 5.14 (t, J = 7.1 Hz, 1H), 4.01 (dd, J = 9.9, 3.7 Hz, 1H), 2.24 – 1.93 (m, 8H), 1.98 (s, 3H), 1.73 – 1.56 (m, 2H), 1.63 (s, 3H), 1.60 (s, 3H), 1.37 – 1.24 (m, 6H), 1.28 (s, 3H), 1.12 (s, 3H), 0.89 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 163.9 (C), 134.6 (C), 133.8 (C), 125.1 (CH), 125.0 (CH), 88.7 (CH), 66.6 (C), 39.6 (CH_2), 36.7 (CH_2), 31.6 (CH_2), 29.6 (CH_2), 29.1 (CH_3), 28.6 (CH_2), 27.9 (CH_2), 26.6 (CH_2), 22.8 (CH_3), 22.6 (CH_2), 16.0 (CH_3), 15.9 (CH_3), 14.3 (CH_3), 14.1 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{21}H_{38}NO$ 320.2983, Found 320.2953.

Cyclization of epoxypolyprene 12

Following the general procedure, reaction of epoxide **12** with Et_2AlCl for 1 h provided a mixture which was a complex mixture of drimanes structures, in good agreement with the results described by Corey *et al.*[13]

Cyclization of epoxypolyprene 13

Following the general procedure, reaction of epoxide **13** with Et_2AlCl for 1 h provided after flash chromatography (H:MTBE, 6:1) compounds **14a** and **14b** (30% combined, 1:2 ratio). Ratios were determined by integration of the ^{1}H spectrum of the mixture.

*(2S,4aS,5R,6R)-5-(3-((Tert-butyldimethylsilyl)oxy)butyl)-1,1,5,6-tetramethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**14b**).* Compound **14b** was purified and characterized as its alcohol derivative **14b´**. A fraction enriched in **14b** was desilylated with TBAF (3 equiv) for 13 h and the resulting crude subjected to HPLC (normal phase, H:MTBE 1:1, Rt = 21.1 min) to give pure **14b´**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.46 (t, J = 3.9 Hz, 1H), 3.72 (dq, J = 11.9, 6.0 Hz, 1H), 3.44 (m, 1H), 2.20 – 2.00 (m, 2H), 1.91 (tdd, J = 14.0, 4.4, 2.5 Hz, 1H), 1.79 – 1.12 (m, 9H), 1.20 (d, J = 6.2 Hz, 3H), 1.13 (s, 6H), 0.83 (s, 3H), 0.80 (d, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): only distinguishable signals δ 76.8 (CH), 69.1 (CH), 40.0 (CH), 35.8 (CH), 33.3 (CH_2), 32.8 (CH_3), 23.6 (CH_3), 22.2 (CH_3), 14.6 (CH_3). HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{33}O_2$ 281.2481, Found 281.2462.

Cyclization of epoxypolyprene 15

Following the general procedure, reaction of epoxide **15** with Et_2AlCl for 1 h provided after flash chromatography (H:TBME, 6:1) compounds **16a** and **16b** (55% combined, 1:1.2 ratio). Ratios were determined by integration of the ^{1}H spectrum of the mixture. These two compounds were produced as a mixture of epimers at C–13).

*(2S,4aS,5R,6S)-1,1,5,6-Tetramethyl-5-(3-methylpent-4-en-1-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen -2-ol (**16a**).* A fraction enriched in **16a** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 37.8 min) to give pure **16a**. Colourless oil.^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74-5.66 (m, 1H), 5.54 (m, 1H), 4.99 – 4.91 (m, 2H), 3.48 – 3.47 (m, 1H), 2.22 (m, 1H), 2.06 – 1.99 (m, 1H), 1.90 – 1.68 (m, 4H), 1.54-1.49 (m, 3H), 1.37-1.20 (m 4H), 1.14 (s, 3H), 1.06 (s, 3H), 1.02 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H) (epimer I), (0.81, d, J = 6.8 Hz, 3H) (epimer II), 0.66 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 144.9 (CH) (epimer I), 144.8 (CH) (epimer II), 142.4 (C) (epimer I), 142.3 (C) (epimer II), 120.8 (CH) (epimer II), 120.8 (CH) (epimer I), 112.6 (CH_2) (epimer II), 112.6 (CH_2) (epimer I), 76.4 (CH), 41.3 (C), 38.7 (CH) (epimer II), 38.7 (CH) (epimer I), 38.6 (CH) (epimer II), 38.5 (CH) (epimer I), 37.0 (C) (epimer II), 36.9 (C) (epimer I), 34.1 (CH_2), 33.4 (CH) (epimer I), 33.4 (CH) (epimer II), 31.9 (CH_2), 29.5 (CH_2), 28.4 (CH_3), 28.3 (CH_2), 25.6 (CH_3), 20.3

(CH_3) (epimer II), 20.3 (CH_3) (epimer I), 19.8 (CH_2) (epimer II), 19.8 (CH_2) (epimer I), 16.3 (CH_3), 15.0 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{20}H_{33}$ 273.2582, Found 273.2589.

*(2S,4aS,5R,6R)-1,1,5,6-Tetramethyl-5-(3-methylpent-4-en-1-yl)-1,2,3,4,4a,5,6,7-octahydro naphthalen-2-ol (**16b**).* A fraction enriched in **16b** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 38.9 min) to give pure **16b**. Colourless oil. ^{1}H NMR (500 MHz, DMSO-D$_6$, 78 ºC): δ 5.76–5.67 (m, 1H), 5.29 – 5.26 (m, 1H), 4.97 – 4.88 (m, 2H), 3.32 (t, *J* = 3.1 Hz, 1H), 2.11–1.94 (m, 3H), 1.87 – 1.79 (m, 1H), 1.68 – 1.39 (m, 5H), 1.36 – 1.11 (m 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.97 (d, *J* = 4.9 Hz, 3H) (epimer I), 0.95 (d, *J* = 4.9 Hz, 3H) (epimer II), 0.78 (s, 3H) (epimer I), 0.77 (s, 3H) (epimer II), 0.76 (d, *J* = 6.6 Hz, 3H) (epimer I), 0.74 (d, *J* = 6.6 Hz, 3H) (epimer II); $^{13}C\{^1H\}$ NMR (125 MHz DMSO–D$_6$): δ 149.9 (CH) 121.5 (CH), 117.7 (CH_2) (epimer I), 117.6 (CH_2) (epimer II), 80.1 (CH), 46.3 (C), 45.0 (CH), 43.0 (CH) (epimer I), 42.9 (CH) (epimer II), 40.8 (C) 37.7 (CH) (epimer I), 37.7 (CH) (epimer II), 35.9 (CH_2), 35.0 (CH_2), 34.6 (CH_2), 32.3 (CH_3), 30.2 (CH_3), 26.9 (CH_3) (epimer I), 26.89 (CH_3) (epimer II), 26.6 (CH_2) 25.1 (CH_3), 19.6 (CH_3) (epimer I), 19.61 (CH_3) (epimer II); HRMS (ESI–QTOF) m/z: $[M - OH]^+$ Calcd for $C_{20}H_{33}$ 273.2582, Found 273.2589.

Cyclization of epoxypolyprene 17

Following the general procedure, reaction of epoxide **17** with Et_2AlCl for 30 min provided after flash chromatography (H:MTBE, 9:1) compounds **18a** and **18b** (75% combined, 1:1 ratio). Ratios were determined by integration of the ^{1}H spectrum of the mixture.

*(2S,4aS,5R,6S)-1,1,5,6-Tetramethyl-5-(2-((4aS,8aR)-2,4a,7,7-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**18a**).* A fraction enriched in **18a** subjected to HPLC (normal phase, H:TBME 6:1, Rt = 18.9 min) to give pure **18a**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (m, 1H), 3.48 (t, *J* = 2.9 Hz, 1H), 2.22 (bd, *J* = 12.1 Hz, 1H), 2.12 (dt, *J* = 13.1, 8.4 Hz, 1H), 2.01 – 1.66 (m, 8H), 1.62 – 1.44 (m, 6H), 1.56 (s, 3H), 1.40 – 0.96 (m, 7H), 1.14 (s, 3H), 1.08 (s, 3H), 0.89 (s, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 3H), 0.83 (s, 3H), 0.67 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 142.5 (C), 133.8 (C), 123.5 (C), 120.9

(CH), 76.5 (CH), 43.2 (CH_2), 42.5 (CH), 41.5 (C), 38.6 (CH), 37.1 (C), 36.6 (CH_2), 35.2 (CH_2), 34.6 (CH_2), 33.6 (CH), 33.2 (CH_3), 31.9 (CH_2), 31.5 (C), 31.1 (C), 29.6 (CH_2), 28.5 (CH_2), 28.5 (CH_3), 27.1 (CH_3), 26.6 (CH_2), 25.6 (CH_3), 24.7 (CH_2), 24.2 (CH_3), 20.4 (CH_2), 18.6 (CH_3), 16.3 (CH_3), 15.4 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OH]^+$ Calcd for $C_{30}H_{49}$ 409.3834, Found 409.3829.

(2S,4aS,5R,6R)-1,1,5,6-Tetramethyl-5-(2-((4aS,8aR)-2,4a,7,7-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol ***(18b)****.* A fraction enriched in **18b** subjected to HPLC (normal phase, H:MTBE 6:1, Rt =20.2 min) to give pure **18b**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): only distinguishable signals δ 5.46 (t, *J* = 3.8 Hz, 1H), 3.45 (m, 1H), 2.12 (m, 1H), 2.06 (dt, *J* = 12.6, 4.9 Hz, 1H), 2.00 – 1.80 (m, 7H), 1.77 – 1.64 (m, 3H), 1.61 – 0.92 (m, 10H), 1.51 (s, 3H), 1.10 (m, 3H), 0.89 (m, 3H), 0.88 (m, 9H), 0.82 (m, 3H), 0.81 (m, 3H).; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): only distinguishable signals δ 134.0 (C), 123.2 (C), 120.7 (CH), 76.6 (CH), 43.1 (CH_2), 42.5 (CH), 39.9 (CH), 36.5 (CH_2), 35.9 (C), 34.6 (CH_2), 33.1 (CH_3), 32.7 (CH), 31.5 (CH_2), 31.0 (C), 29.4 (CH_2), 29.2 (CH_2), 26.9 (CH_3), 26.5 (CH_2), 25.1 (CH_2), 24.8 (CH_3), 24.1 (CH_3), 22.6 (CH_2), 22.2 (CH_3), 18.3 (CH_3), 14.5 (CH_3), 14.1 (CH_3); HRMS (FAB) m/z: $[M – OH]^+$ Calcd for $C_{30}H_{49}$ 409.3834, Found 409.3831.

Cyclization of epoxypolyprene 19

Following the general procedure, reaction of epoxide **13** with Et_2AlCl for 50 min provided after flash chromatography (H:MTBE, 4:1) compound **21** (5.5%) and compounds **20a** and **20b** (32%, 1:9 ratio). Ratios were determined by integration of the ^{1}H spectrum of the mixture.

Methyl (2E,6E)-3,7-dimethyl-9-((1S,2R,6R)-1,2,6-trimethyl-3-oxocyclohexyl)nona-2,6-dienoate ***(21)****.* A fraction enriched in **21** was subjected to HPLC (normal phase, H:MTBE 6:1, Rt = 20.9 min) to give pure **21**. Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.68 (bs, 1H), 5.14 – 5.08 (m, 1H), 3.70 (s, 3H), 2.49 (q, *J* = 6.7 Hz, 1H), 2.37 – 2.33 (m, 2H), 2.20 – 2.16 (m, 7H), 2.06 – 1.97 (m, 2H), 1.90 – 1.81 (m, 2H), 1.67 – 1.60 (m, 1H), 1.64 (s, 3H), 1.43 (ddd, *J* = 14.6, 12.4, 4.8 Hz, 1H), 1.36 (ddd, *J* = 14.4, 13.0, 4.4 Hz, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.59 (s, 3H);

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 213.9 (C), 167.2 (C), 159.9 (C), 136.4 (C), 122.9 (CH), 115.4 (CH), 50.8 (CH_3), 50.5 (CH), 43.4 (C), 41.6 (CH_2), 40.9 (CH_2), 32.7 (CH), 29.3 (CH_2), 24.6(CH_3), 22.2 (CH_3), 19.1 (CH_3), 14.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M]^+$ Calcd for $C_{21}H_{34}O_3$ 334.2508, Found 334.2513.

*Methyl (E)-5-((1R,2R,6S,8aS)-6-hydroxy-1,2,5,5-tetramethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1-yl)-3-methylpent-2-enoate (**20b**).* A fraction enriched in **20b** was subjected to HPLC (normal phase, H:MTBE 4:1, Rt = 26.5 min) to give pure **20b**. Colourless oil. ^1H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.66 (bs, 1H), 5.45 (t, *J* = 3.3 Hz, 1H), 3.68 (s, 3H), 3.45 (bs, 1H), 2.15 (s, 3H), 2.13 – 1.98 (m, 3H), 1.91 (tdd, *J* = 14.1, 4.7, 2.6 Hz, 1H), 1.77 – 1.64 (m, 3H), 1.70 – 1.29 (m, 4H), 1.10 (s, 6H), 0.81 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): only distinguishable signals δ 167.3 (C), 161.7 (C), 120.7 (CH), 114.9 (CH), 76.5 (CH), 50.8 (CH_3), 40.0 (CH), 35.3 (CH_2), 32.7 (CH), 29.3 (CH_2), 24.6 (CH_3), 22.2 (CH_3), 19.1 (CH_3), 14.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OH]^+$ Calcd for $C_{21}H_{33}O_2$ 317.2481, Found 317.2486.

Cyclization of epoxypolyprene 22

Following the general procedure, reaction of epoxide **22** with Et_2AlCl for 40 min provided after flash chromatography (H:MTBE, 2:1) compound **23a** and **23b** (12%, 1:9 ratio). Ratios were determined by integration of the ^1H spectrum of the mixture.

*(2S,4aS,5R,6R)-5-(3-Hydroxy-3-methylpent-4-en-1-yl)-1,1,5,6-tetramethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (**23b**).* Colourless oil. ^1H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.87 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.44 (t, *J* = 3.3 Hz, 1H), 5.18 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.04 (dd, *J* = 10.7, 1.2 Hz, 1H), 3.43 (bs, 1H), 2.09 – 2.01 (m, 1H), 1.89 (tdd, *J* = 13.9, 4.7, 2.6 Hz, 1H), 1.71 (ddd, *J* = 15.0, 7.2, 3.6 Hz, 1H), 1.64 (dq, *J* = 13.6, 6.6 Hz, 1H), 1.50 – 1.32 (m, 3H), 1.40 (td, *J* = 12.9, 3.9 Hz, 1H), 1.26 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 0.80 (s, 3H), 0.78 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): only distinguishable signals δ 145.2 (CH), 111.7 (CH_2), 76.5 (CH), 39.9 (CH), 36.0 (CH_2), 32.8 (CH), 29.3 (CH_2), 27.8 (CH_3), 24.7 (CH_3), 22.1 (CH_3), 14.6 (CH_3).

Cyclization of epoxypolyprene 24

Following the general procedure, reaction of epoxide **24** with Et_2AlCl for 50 min provided after column chromatography aldehyde **26** (H:MTBE, 5:1) (4%), compound **27** (H:MTBE, 5:1) (6%) and compounds **25a** and **25b** (H:MTBE, 4:1) (53% combined, 1:2.5 ratio). Compounds **25a** and **25b** were obtained as a pair of diastereomers. **25a1** and **25a2**, and **25b1** and **25b2**, respectively.

*Compound **25a1***. A mixture of **25a** and **25b** was subjected to HPLC (normal phase, H:MTBE 9:1), to give pure **25a1** (Rt = 47.7 min). Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.98 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.52 (dt, *J* = 5.0, 2.2 Hz, 1H), 5.14 (dd, *J* = 17.6, 0.9 Hz, 1H), 5.12 (dd, *J* = 11.0, 0.9 Hz, 1H), 3.47 (t, *J* = 2.9 Hz, 1H), 2.22 – 2.17 (m, 1H), 2.00 (s, 3H), 1.91 – 1.83 (m, 2H), 1.81 – 1.66 (m, 4H), 1.52 (s, 3H), 1.51 – 1.42 (m, 3H), 1.38 – 1.31 (m, 1H), 1.25 (ddd, *J* = 14.2, 11.6, 6.0 Hz, 1H), 1.13 (s, 3H), 1.05 (s, 3H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.66 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 169.9 (C), 142.2 (CH), 141.9 (C), 120.7 (CH), 113.1 (CH_2), 83.2 (C), 76.3 (CH), 41.3 (C), 38.5 (CH), 36.8 (C), 33.2 (CH), 32.8 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 28.5 (CH_3), 28.2 (CH_2), 25.5 (CH_3), 23.7 (CH_3), 22.2 (CH_3), 19.8 (CH_2), 16.3 (CH_3), 14.9 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2518.

*Compound **25a2***. A mixture of **25a** and **25b** was subjected to HPLC (normal phase, H:MTBE 9:1), to give pure **25a2 (**Rt = 53.6 min). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.93 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.52 (dt, *J* = 5.9, 1.9 Hz, 1H), 5.16 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.12 (dd, *J* = 11.0, 1.0 Hz, 1H), 3.47 (t, *J* = 3.0 Hz, 1H), 2.23 – 2.17 (m, 1H), 2.01 (s, 3H), 1.91 – 1.75 (m, 4H), 1.71 – 1.57 (m, 2H), 1.54 (s, 3H), 1.54 – 1.43 (m, 3H), 1.33 (dt, *J* = 13.5, 4.0 Hz, 1H), 1.25 (ddd, *J* = 14.4, 12.8, 4.9 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.66 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 169.9 (C), 142.2 (CH), 141.9 (C), 120.7 (CH), 113.1 (CH_2), 83.2 (C), 76.3 (CH), 41.3 (C), 38.5 (CH), 36.8 (C), 33.2 (CH), 32.8 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 28.5 (CH_3), 28.2 (CH_2), 25.5 (CH_3), 23.7 (CH_3), 22.2 (CH_3),19.8 (CH_2), 16.3 (CH_3), 14.9 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2527.

*Compound **25b1**.* A mixture of **25a** and **25b** was subjected to HPLC (normal phase, H:MTBE 9:1), to give pure **25b1 (**Rt = 41.8 min). Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.92 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.44 (t, *J* = 3.7 Hz, 1H), 5.12 (d, *J* = 17.5, 1H), 5.10 (d, *J* = 11.0 Hz, 1H), 3.43 (bs, 1H), 2.09 – 2.01 (m, 1H), 1.99 (s, 3H), 1.90 (tdd, *J* = 13.9, 4.7, 2.4 Hz, 1H), 1.81 (bt, *J* = 13.0 Hz, 1H), 1.75 – 1.68 (m, 1H), 1.67 – 1.60 (m, 2H), 1.51 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 0.80 (s, 3H), 0.77 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): only distinguishable signals δ 169.8 (C), 141.9 (CH), 113.1 (CH_2), 76.5 (CH), 39.9 (CH), 33.6 (CH_2), 32.8 (CH), 29.2 (CH_2), 24.7 (CH_3), 23.6 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 14.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2524.

*Compound **25b2**.* A mixture of **25a** and **25b** was subjected to HPLC (normal phase, H:MTBE 9:1), to give pure **25b2 (**Rt = 43.7 min). Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.95 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.45 (t, *J* = 3.5 Hz, 1H),5.13 (d, *J* = 17.6, 1H), 5.10 (dd, *J* = 11.1, 1H), 3.44 (bs, 1H), 2.07 – 2.01 (m, 1H), 1.98 (s, 3H), 1.91 (tdd, *J* = 14.0, 4.5, 2.5 Hz, 1H), 1.75 – 1.68 (m, 3H),1.64 (dq, *J* = 14.1, 7.4 Hz, 1H), 1.50 (s, 3H), 1.09 (s, 6H), 0.80 (s, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): only distinguishable signals δ 169.8 (C), 142.0 (CH), 113.1 (CH_2), 76.5 (CH), 39.8 (CH), 33.6 (CH_2), 32.8 (CH), 29.3 (CH_2), 24.8 (CH_3), 23.6 (CH_3), 22.2 (CH_3), 22.0 (CH_3), 14.5 (CH_3); HRMS (ESI–QTOF) m/z: $[M - OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2530.

*(E)-3,7,11-Trimethyl-13-oxo-10-(propan-2-ylidene)trideca-1,6-dien-3-yl acetate (**26**).* Aldehyde **26** was purified and characterized as its primary alcohol derivative **26a**. To a solution of a fraction enriched in **26** (44 mg) in 22 mL of MeOH:H_2O (4:1 ratio) was added 15 mg of $NaBH_4$ and the mixture was stirred for 30 min at 0ºC. The reaction was concentrated under reduced pressure and the residue dissolved in MTBE and washed with water, quenched with acetone, and concentrated under reduced pressure. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The resulting crude was purified by column chromatography (H/MTBE, 3:1) to afford 21 mg of primary alcohol **26a**. Colourless oil. ^{1}H NMR

(500 MHz, $CDCl_3$): δ 5.99 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.17 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.13 (dd, *J* = 11.0, 0.9 Hz, 1H), 5.15–5.10 (m, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.71 (sext, *J* = 7.1 Hz, 1H), 2.06 – 1.85 (m, 7H), 2.02 (s, 3H), 1.82–1.76 (m, 2H), 1.82 – 1.76 (m, 2H), 1.68 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.56 (s, 3H), 1.38 – 1.32 (m, 2 H), 0.97 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.0 (C), 141.8 (CH), 136.3 (C), 135.5 (C), 125.3 (C), 123.1 (CH), 113.1 (CH_2), 82.9 (C), 63.4 (CH_2), 40.2 (CH_2), 39.8 (CH_2), 35.6 (CH), 31.6 (CH_2), 31.2 (CH_2), 26.8 (CH_2), 23.6 (CH_3), 22.2 (CH_2), 22.2 (CH_3), 20.9 (CH_3), 20.1 (CH_3), 19.6 (CH_3), 16.0 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OAc]^+$ Calcd for $C_{20}H_{35}O$ 291.2693, Found 291.2693.

*(E)-3,7-Dimethyl-9-((1S,2R,6R)-1,2,6-trimethyl-3-oxocyclohexyl)nona-1,6-dien-3-yl acetate (**27**).* Colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 5.99 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.17 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.14 (dd, *J* = 11.0, 0.8 Hz, 1H), 5.15 – 5.10 (m, 1H), 2.49 (q, *J* = 6.7 Hz, 1H), 2.38 – 2.33 (m, 2H), 2.05 – 1.95 (m, 4H), 2.02 (s, 3H), 1.91 – 1.75 (m, 4H), 1.67 – 1.58 (m, 1H), 1.62 (s, 3H), 1.55 (s, 3H), 1.46 – 1.32 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.59 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 213.9 (C), 169.9 (C), 141.8 (CH), 135.5 (C), 123.8 (CH), 113.1 (CH_2), 82.9 (C), 50.5 (CH), 43.4 (C), 41.6 (CH_2), 39.7 (CH_2), 36.1 (CH), 35.9 (CH_2), 32.5 (CH_2), 31.0 (CH_2), 23.6 (CH_3), 22.3 (CH_2), 22.2 (CH_3), 16.1 (CH_3), 15.4 (CH_3),15.0 (CH_3), 7.6 (CH_3); HRMS (ESI–QTOF) m/z: $[M – OAc]^+$ Calcd for $C_{20}H_{33}O$ 289.2537, Found 289.2533.

Cyclization of epoxypolyprene 2 using Br_3In as Lewis acid

To a solution of starting material (0.5 mmol) in dry DCM (10 mL) was added indium tribromide (0.5 mmol) at room temperature. The reaction mixture was further stirred until disappearance of the starting material. Then, solvent was removed under reduced pressure and the crude reaction mixture passed through a short plug of silica gel and celite (4:1) which was washed with EtOAc:H (9:1). Finally the crude resultant was concentrated under reduced pressure and then purified by flash chromatography in silica column (H:MTBE, 95:5), to obtain compounds **3a** and **3b** (37%, 1:0.45

ratio), compound **4** (7%), compounds **7a** and **7b** (9%, 1:0.2 ratio), compounds **8b** and **8c** (9%, 1:0.8 ratio) and compounds **9a** and **9b** (25%, 1:0.7 ratio).

(2S,5R,6S,8aR)-1,1,5,6-Tetramethyl-5-pentyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-2-ol ***(9a)****.* A fraction enriched in **9a** was subjected to HPLC (normal phase, H:MTBE 9:1, Rt = 13.4 min) to give **9a** together with some proportion of **3a**. Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.28 (t, *J* = 4.0 Hz, 1H), 3.40 (dd, *J* = 6.2, 4.9 Hz, 1H), 2.33 (dtd, *J* = 17.5, 4.6, 2.0 Hz, 1H), 2.10 (dddd, *J* = 17.5, 5.9, 3.6, 2.1 Hz, 1H), 1.88 – 1.79 (m, 1H),1.71 (d, *J* = 13.5 Hz, 1H), 1.57 – 1.36 (m, 3H), 1.37 – 1.15 (m, 8H), 1.05 – 0.98 (m, 1H), 1.00 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 145.1 (C), 113.9 (CH), 74.9 (CH), 43.9 (CH), 43.1 (CH), 42.3 (C), 36.5 (C), 32.8 (CH_2), 31.5 (CH_2), 30.7 (CH_2), 29.1 (CH_2), 26.6 (CH_3), 23.2 (CH_2), 22.7 (CH_3), 22.7 (CH_2), 19.3 (CH_3), 16.5 (CH_3), 14.2 (CH_3); HRMS (ESI–QTOF) m/z: [M + H]$^+$ Calcd for $C_{19}H_{35}O$ 279.2688, Found 279.2679.

Catalytic assays of cyclization plus rearrangement of epoxide 2

Using Et_2AlCl as Lewis acid

The reactions were performed following the general procedure and only varying the quantity of catalyst.

Using indium or gallium halides as Lewis acids

To a solution of starting material (0.5 mmol) in dry DCM (15 mL) was added the Lewis acid (0.2-0.01 mmol) at room temperature. The reaction mixture was further stirred until disappearance of the starting material. Then, solvent was removed under reduced pressure and the crude reaction mixture passed through a short plug of silica gel and celite (4:1) which was washed with MTBE. Finally the crude resultant was concentrated under reduced pressure and then column chromatographed to afford the corresponding mixtures of **3a** and **3b** (H:MTBE, 6:1).

Synthesis of isotuberculosinol (1)

A solution of 110 mg (0.31 mmol) of **25a** and **25b** in 3 mL of DCM was treated with 0.09 mL (0.62 mmol) of pentafluorophenyl chlorothionoformate (0.153 mmol) and 115 mg (0.9 mmol) of DMAP. After stirring for 7h at rt, the mixture was concentrated under vacuum and column chromatographed (H:MTBE, 20:1) to afford 151 mg of the corresponding xanthates. To a solution of 88 mg (0.15 mmol) of this mixture in 5 mL of degassed toluene, 9 mg of AIBN and 0.24 mL of tributyltin hydride (0.92 mmol) were added. The mixture was refluxed for 1h and then column chromatographed (H:MTBE, 15:1) to afford 85 mg of a mixture of deoxygenated products. This mixture was dissolved in 2 mL of THF and treated at rt with 38 mg of LAH at 0ºC. The mixture was then stirred for 12 h. After the usual work-up, 58 mg (0.20 mmol) of a mixture of **1** and **1b** (1:2.5 ratio) were obtained (65%). This mixture was subjected to HPLC (normal phase H:MTBE, 10:1) to give **1** (Rt = 24.3 min) and **1b** (Rt = 26.1 min). Compounds **1** and **1b** were obtained both as a pair of diastereomers.

*Isotuberculosinol (**1**).* Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.92 (dd, *J* = 17.4, 10.8 Hz, 2H), 5.43 (bd, *J* = 5.5 Hz, 2H), 5.22 (bd, *J* = 17.3 Hz, 2H), 5.07 (bd, *J* = 10.8 Hz, 2H), 2.13 (dm, *J* = 13.1 Hz, 2H), 1.83 (dt, *J* = 17.7, 5.5 Hz, 2H), 1.74 – 1.68 (m, 4H), 1.60 – 1.33 (m, 14H), 1.30 (s, 6H), 1.29 – 1.17 (m, 4H), 1.06 (s, 6H), 1.01 (qd, *J* = 12.9, 4.2 Hz, 2H), 1.00 (s, 6H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.62 (s, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 146.0, 146.0 (C), 145.1, 145.1 (CH), 116.2, 116.1 (CH), 111.8, 111.8 (CH_2), 73.5, 73.3 (C), 40,9 (CH_2), 39.7 (CH), 36.7 (C), 36.1 (C), 35.2, 35.1 (CH_2), 33.3 (CH), 31.7 (CH_2), 30.1 (CH_2), 29.8 (CH_3), 29.1 (CH_3), 27.7, 27.6 (CH_3), 27.3 (CH_2), 22.2 (CH_2), 16.2, 16.2 (CH_3), 15.0, 15.0 (CH_3).

*8-Epi-isotuberculosinol (**1b**).* Colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$): only distinguishable signals δ 5.91 (ddd, *J* = 17.4, 10.8, 6.9 Hz, 1H), 5.33 (bs, 1H), 5.21 (dd, *J* = 17.1, 2.9 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 1.96 (bd, *J* = 12.9 Hz, 1H), 1.79 – 1.00 (m, 14H), 1.28 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.79 (s, 3H), 0.77 (m, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): only distinguishable signals δ 145.3, 145.3 (CH), 114.3 (CH), 111.7, 111.6 (CH_2), 73.5, 73.5 (C), 41,9 (CH_2), 40.8, 40.8 (CH), 36.0 (CH_2), 32.9, 32.9 (CH), 29.5 (CH_3), 27.7 (CH_3), 23.0 (CH_2), 22.0 (CH_3), 14.6 (CH_3).

Cyclization of epoxypolyprene 28

Using Et$_2$AlCl as Lewis acid

Following the general procedure, reaction of epoxide **28** with Et$_2$AlCl for 50 min provided after flash column chromatography (H:MTBE, 95:5) aldehyde **31** (5%), compound **29** (6%), compound **30** (5%), compound **32** (24%) and compounds **33** (12%) and **34** (9%).

*(R,8E,12E,16E)-4,8,13,17,21-pentamethyl-5-(propan-2-ylidene)docosa-8,12,16,20-tetraenal (**31**). Colourless* oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.73 (t, *J* = 1.8 Hz, 1H), 5.27 – 5.08 (m, 4H), 2.74 (tq, *J* = 7.4, 6.9 Hz, 1H), 2.34 (td, *J* = 7.4, 1.9 Hz, 2H), 2.12 – 1.95 (m, 16H), 1.70 (s, 6H), 1.67 (q, *J* = 7.4 Hz, 2H), 1.66 (s, 6H), 1.63 (s, 3H), 1.62 (s, 6H), 1.02 (d, *J* = 6.9 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, CDCl$_3$) δ 202.9 (CH), 135.8, 135.2, 134.9, 134.5, 131.3, 126.6 (C), 124.4, 124.3, 124.3, 124.0 (CH), 42.5, 40.4, 39.8, 39.8 (CH$_2$), 35.3 (CH), 28.3, 28.3, 27.8, 26.9, 26.8, 26.7 (CH$_2$), 25.7, 21.0, 20.1, 19.6, 17.7, 16.1, 16.1, 16.0 (CH$_3$). HRMS (ESI–QTOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{50}O$ 427,3862, Found 427.3930.

*(1R,2S,4S)-1,3,3-trimethyl-2-((3E,7E,11E)-3,8,12,16-tetramethylheptadeca-3,7,11,15-tetraen-1-yl)-7-oxabicyclo[2.2.1]heptane (**29**)*. Colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.19 – 5.10 (m, 4H), 3.74 (d, *J* = 5.4 Hz, 1H), 2.14 – 1.88 (m, 16H), 1.70 (s, 3H), 1.62 (s, 12H), 1.51 – 1.39 (m, 4H), 1.35 (s, 3H), 1.20 (dd, *J* = 8.6, 5.7 Hz, 1H), 1.07 (s, 3H), 1.04 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, CDCl$_3$) δ 135.39, 135.21, 134.94, 131.27 (C), 124.5, 124.4, 124.3, 124.3 (CH), 86.7 (C), 86.1 (CH), 55.2 (CH), 45.3 (C), 39.8, 39.8, 39.8, 39.0, 28.3, 28.2, 26.8, 26.7, 26.2 (CH$_2$), 26.1 (CH$_3$), 25.8 (CH$_2$), 25.7, 23.4, 18.9, 17.7, 16.1, 16.0, 16.0 (CH$_3$).

*(2R,3S,4R)-2,3,4-trimethyl-3-((3E,7E,11E)-3,8,12,16-tetramethylheptadeca-3,7,11,15-tetraen-1-yl)cyclohexan-1-one (**30**)*. Colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.22 – 5.09 (m, 4H), 2.51 (q, *J* = 6.7 Hz, 1H), 2.40 – 2.34 (m, 2H), 2.13 – 1.98 (m, 15H), 1.92 – 1.81 (m, 2H), 1.70 (s, 3H), 1.65 (s, 3H), 1.63 (s, 9H), 1.47 – 1.36 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.60 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, CDCl$_3$) δ 214.0, 135.3, 135.2, 135.0, 131.3 (C), 124.4, 124.4, 124.3, 124.2,

50.5 (CH), 43.5(C), 41.6, 39.8, 39.8, 36.2 (CH), 36.0, 32.6, 31.0, 28.3, 28.2, 26.8, 26.7 (CH$_2$), 25.7, 17.7, 16.2, 16.1, 16.0, 15.4, 15.1, 7.6 (CH$_3$).

(2S,4aS,5R,6R)-1,1,5,6-tetramethyl-5-((3E,7E)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-ol (32). Colourless oil. A fraction enriched in **32** was subjected to HPLC (normal phase, H:MTBE 95:5, Rt = 26.8 min) to give pure **32**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.30 (dt, *J* = 3.9, 2.0 Hz, 1H), 5.14 – 5.08 (m, 3H), 3.34 (q, *J* = 3.5 Hz, 1H), 2.12 – 1.81 (m, 14H), 1.66 (s, 3H), 1.65 – 1.60 (m, 2H), 1.58 (s, 9H), 1.54 – 1.44 (m, 2H), 1.37 – 1.27 (m, 1H), 1.25 – 1.16 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 0.84 (s, 3H), 0.79 (d, *J* = 6.6 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, DMSO) δ 143.7, 134.8, 134.0, 130.9 (C), 125.9, 124.7, 124.5, 117.0, 75.46 (CH), 41.6 (C), 39.7 (CH), 39.6 (CH$_2$), 36.3 (C), 35.0 (CH$_2$), 33.0 (CH), 31.3, 30.0, 30.0 (CH$_2$), 27.4 (CH$_3$), 26.8, 26.5(CH$_2$), 25.7, 25.3 (CH$_3$), 22.2, 22.2 (CH$_2$), 22.1, 17.9, 16.3, 16.1, 14.9 (CH$_3$).

Thalianol (33). A fraction enriched in **33** was subjected to HPLC (normal phase, H:MTBE 95:5, Rt = 45.3 min) to give pure **33**. Colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.12 (bt, *J* = 6.9 Hz, 1H), 5.10 (bt, *J* = 6.9 Hz, 1H), 3.26 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.21 – 1.82 (m, 9H), 1.78 – 1.70 (m, 5H), 1.69 (bs, 3H), 1.66 – 1.62 (m, 2H), 1.61 (bs, 6H), 1.57 – 1.42 (m, 3H), 1.35 (ddd, *J* = 9.9, 6.6, 2.8 Hz, 1H), 1.31 – 1.21 (m, 2H), 1.09 – 1.04 (m, 1H), 1.02 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H), 0.82 (s, 3H), 0.71 (d, *J* = 6.6 Hz, 3H). ^{13}C {^{1}H} NMR (126 MHz, cdcl$_3$) δ 143.2, 138.2, 134.7, 131.3 (C), 125.0, 124.4, 79.2 (CH), 52.6 (C), 51.5 (CH), 39.7 (CH$_2$), 38.7 (C), 38.4 (CH), 35.7 (C), 35.6, 31.7, 30.8 (CH$_2$), 28.2 (CH$_3$), 27.9, 27.8, 26.8, 26.6 (CH$_2$), 25.7 (CH$_3$), 25.2 (CH$_2$), 23.4 (CH$_3$), 19.4 (CH$_2$), 19.0, 17.7, 16.0, 15.5, 14.7 (CH$_3$).

14-Epi-thalianol (34). A fraction enriched in **34** was subjected to HPLC (normal phase, H:MTBE 95:5, Rt = 38.3 min) to give pure **34**. Colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.11 (bt, *J* = 6.9 Hz, 1H), 5.10 (bt, *J* = 6.9 Hz, 1H), 3.28 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.22 – 1.83 (m, 10H), 1.79 – 1.71 (m, 5H), 1.71 (bs, 3H), 1.69 – 1.64 (m, 3H), 1.62 (d, *J* = 6.1, 1.4 Hz, 6H), 1.47 (ddd, *J* = 12.1, 6.4, 1.8 Hz, 1H), 1.35 – 1.26 (m, 3H), 1.09 (dd, *J* = 12.3, 1.5 Hz, 1H), 1.04 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 6H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, CDCl$_3$) δ 143.4, 138.0, 134.9, 131.3

(C), 125.0, 124.4, 79.3 (CH), 52.8 (C), 51.6 (CH), 39.8 (CH_2), 38.8 (C), 38.2(CH), 35.8, 35.6 (C), 32.2, 30.8 (CH_2), 28.2(CH_3), 27.9, 27.6, 26.8, 26.5 (CH_2), 25.7, 25.2(CH_3), 23.4 (CH_2), 19.5 (CH_3), 19.0 (CH_2), 17.7, 16.0, 15.5, 14.3 (CH_3).

Using $GaCl_3$ as Lewis acid

To a solution of starting material **28** (1 mmol) in dry DCM (30 mL) was added gallium trichloride (0.01 mmol) at room temperature. The reaction mixture was further stirred until disappearance of the starting material. Then, solvent was removed under reduced pressure and the crude reaction mixture passed through a short plug of silica gel which was washed with TBME. Finally the crude resultant was concentrated under reduced pressure and then purified by flash chromatography in silica column (H:MTBE, 95:5) to obtain compound **29** (10%), compound **30** (9%), compound **32** (25%) and compounds **33** (18%) and **34** (6%).

ASSOCIATED CONTENT

Supporting Information.

This material is available free of charge via on the ACS Publications website at DOI:

Copies of ^{1}H and ^{13}C NMR spectra, and computational data (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support for this work was provided by the Junta de Andalucia (P08-FQM-3596) and Ministerio de Economía y Competitividad (CTQ-2015-64049-C3-3-R).

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3.4 ***Artículo 4:*** Bioinspired Synthesis of Platensimycin from Natural *ent*-Kaurenoic acids.

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Pendiente de publicación.

Bioinspired Synthesis of Platensimycin from Natural *ent*-Kaurenoic acids.

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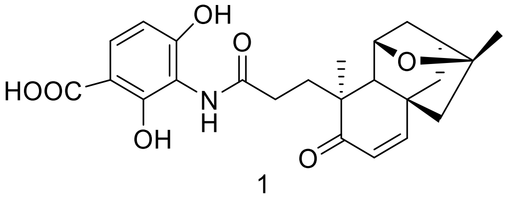
ABSTRACT: The biomimetic formal synthesis of the multidrug-resistant bacteria antibiotic platensymicyn was accomplished starting either from *ent*-kaurenoic acid or grandiflorenic acid, both natural compounds available in multigram scale from their natural sources. Apart from the natural origin of the selected precursors, key in the herein described approach was the long-distant functionalization of *ent*-kaurenoic acid at C11 and the efficient protocol miss a point for the A-ring degradation the diterpene framework.

INTRODUCTION

The proliferation of antibiotic-resistant bacteria and fungi is revealing as one of the major health issues in developed countries. According to CDC estimations, more than 2.8 million are infected by antibiotic-resistant pathogens each year in the United Sates, resulting in at least 35,000 deaths, a number of deaths which is very similar in Europe[1]. In this context, the search of new antibiotics presenting new modes of action to fight against resistant bacteria is becoming a global pressing need. In 2006, (-)-platensimycin (PTM), a meroditerpenoid from *Streptomyces platensis* was isolated by Merck researchers[2]. Since then, this nor-diterpenoid has been the subject of numerous studies[3]. Its activity has been tested with a powerful activity range, against Gram-positive bacteria including methicillinresistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate S*taphylococcus aureus* (VISA) and vancomycin-resistant *enterococci* (VRE) among others[4,5]. Additionally this substance possesses a unique mode of action as a suppressor of β-ketoacyl-(acyl-carrier protein) synthase II (FabF) engaged in the mechanism of fatty acid biosynthesis[2,3]. This unique mode of action, its challenging structural and functional architecture along with the complexity of finding biotechnological protocols for producing PTM in multigram scale attracted the attention of many synthetic chemists and consequently a number of synthetic strategies have been developed to complete the synthesis of PTM and analogues[6–16].



1

(-)-Platensimycin

Fungi and plants as *Fusarium fujikuroi* or *Stevia subpubescens* contain diterpenes sharing the same furan ring substructure found in PTM[17,18]. Recent studies proved that *ent*-kauran-16α-ol and other *ent*-kauranes[19–23] are involved as intermediates in the PTM tricyclic core biosynthesis. Thus, in 2016, Rudolf and co-workers revealed[23] the biosynthetic origin of the 11*S*,16*S* platensimycin ether ring, which proved to be crucial in the high selectivity for FabF, which makes it a powerful tool against FabF bacteria. These authors proposed that (-)-16α-hydroxykauran-19-oic acid is transformed by the cytochrome P450 monooxygenase PtmO5, that inserts a hydroxyl group in C-11 position. The resulting diol is directly involved in the 11*S*,16*S* ether ring formation by cyclization in the aforementioned enzyme PtmO5 (Figure 1).

Recent works attributed the generation of characteristic PTM enone moiety to the action of PtmO3/PtmO6 (α-ketoglutarate-dependent dioxygenases), which hydroxylate C-7 in β–disposition[16], and the nonheme diiron monooxygenase PtmU3[24] that inserts C-5 *β*-hydroxyl group, involved in the A ring degradation and the final constitution of platensimycin α,β-unsaturated ketone (Figure 1).

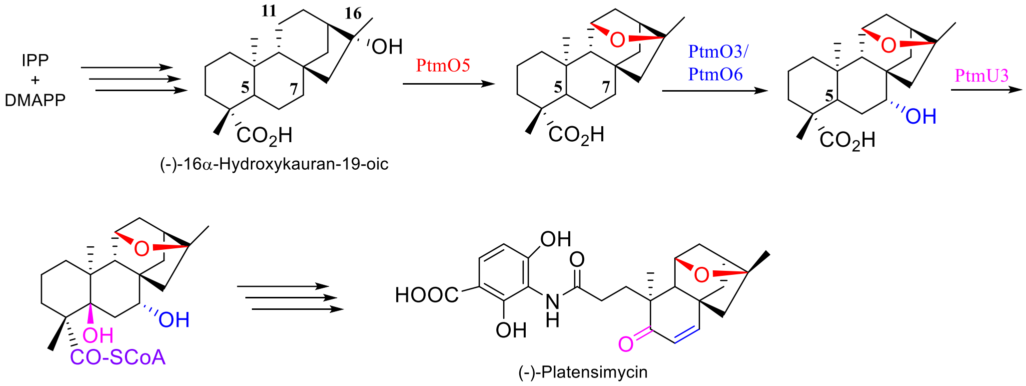


Figure 1. Biosynthetic route and enzymes involved in the pathway to PTM

RESULTS AND DISCUSSION

Based on this biosynthetic evidence, it was anticipated that natural *ent*-kaurenoic and grandiflorenic contain the structural and stereochemical requirements to eventually afford PTM. Thus, both compounds include in their structure not only the C-17 tricyclic carbon framework of PTM, but also present the appropriate stereochemistry at C8, C9, C10 and C13. Furthermore, the exocyclic methylene at C16 (together with C9-C11 double bond in the case of grandiflorenic acid) should enable the generation of the furane moiety. Finally, the presence of the carboxylic acid at C4 will be key to develop a new A ring degradation protocol which should involve the loss of C4, C19 and C20 (Figure 2).

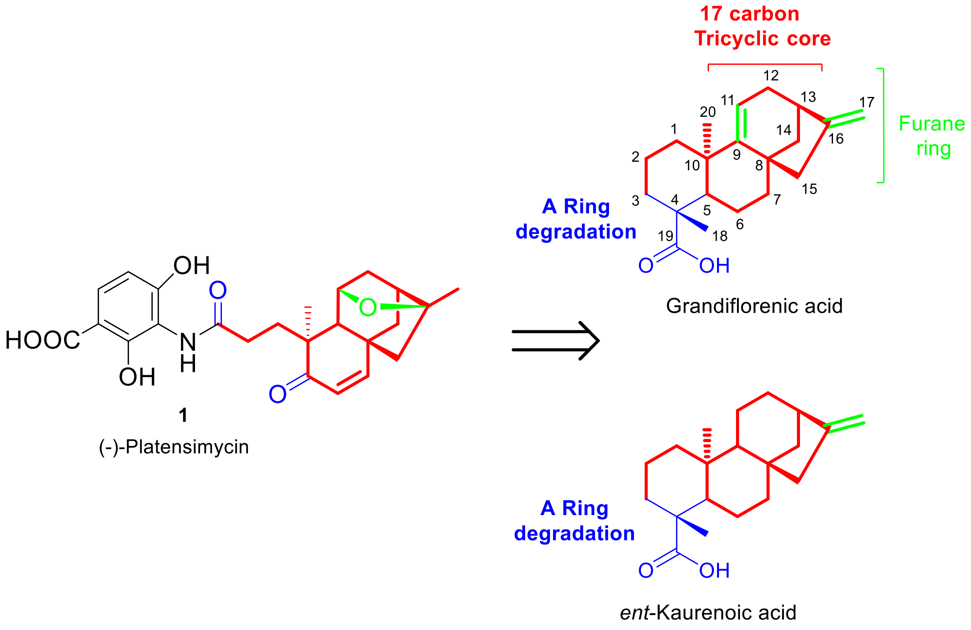
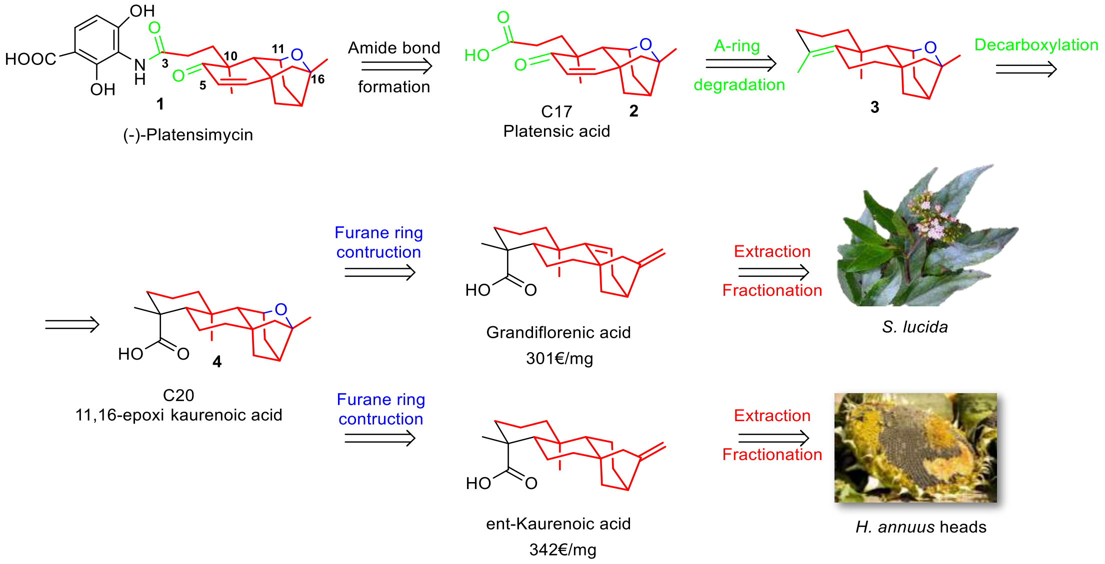


Figure 2. Recognition of the kaurene diterpene moiety in PTM. Evaluation of the structural features of grandiflorenic and *ent*-kaurenoic acids enabling the synthesis of PTM.

The use of these starting materials will depend on their availability and easy accessibility in multigram quantities. Since both *ent*-kaurenoic and grandiflorenic acids are commercially available from Sigma Aldrich with expensive prices ranging from 301€ of grandiflorenic acid to 342€ ent-kaurenoic acid per milligram, the search of suitable natural sources of these compounds supposes a determinant requisite for the success of this strategy. In this regard, plants as *Helianthus annuus* (sunflower) and *Stevia lucida* were reported to possess a good accumulation in kaurenoic acid (sunflower)[25,26] and *ent*-kaurenoic and grandiflorenic acids in *S. lucida*[27]. In addition, since the production of sunflower oil in 2020 was over 55 million tons worldwide [28], the use of the residue of sunflower heads would constitute a nice example of turning agricultural residues into ecological and economic assets[29].

The retrosynthetic planning of our work is shown in Scheme 1. The first disconnection, that is, the amide bond formation from platensic acid (**2**) to get PTM (**1**) was described by Nicolaou and coworkers in 2009[16]. The synthesis of acid **2** was proposed to occur via the oxidative degradation of the olefin present on the A ring of **3,** which in turn will be obtained by oxidative decarboxylation of **4**. The generation of **4** from grandiflorenic would involve a double regio-and setereoselective hydration to generate the 11,16-diol formation, which after dehydration of the primary alcohol and subsequent acid cyclization would produce the ether bridge present in **4**. Moreover, the methylene anti-Markownikoff hydration of kaurenoic acid would enable us to obtain **4** through a long-distance functionalization mediated by lead tetraacetate (LTA) (Scheme 1). Both, grandiflorenic acid and *ent*-kaurenoic acid will be obtained from *Helianthus annuus* heads and the aerial parts from *Stevia lucida*, respectively.

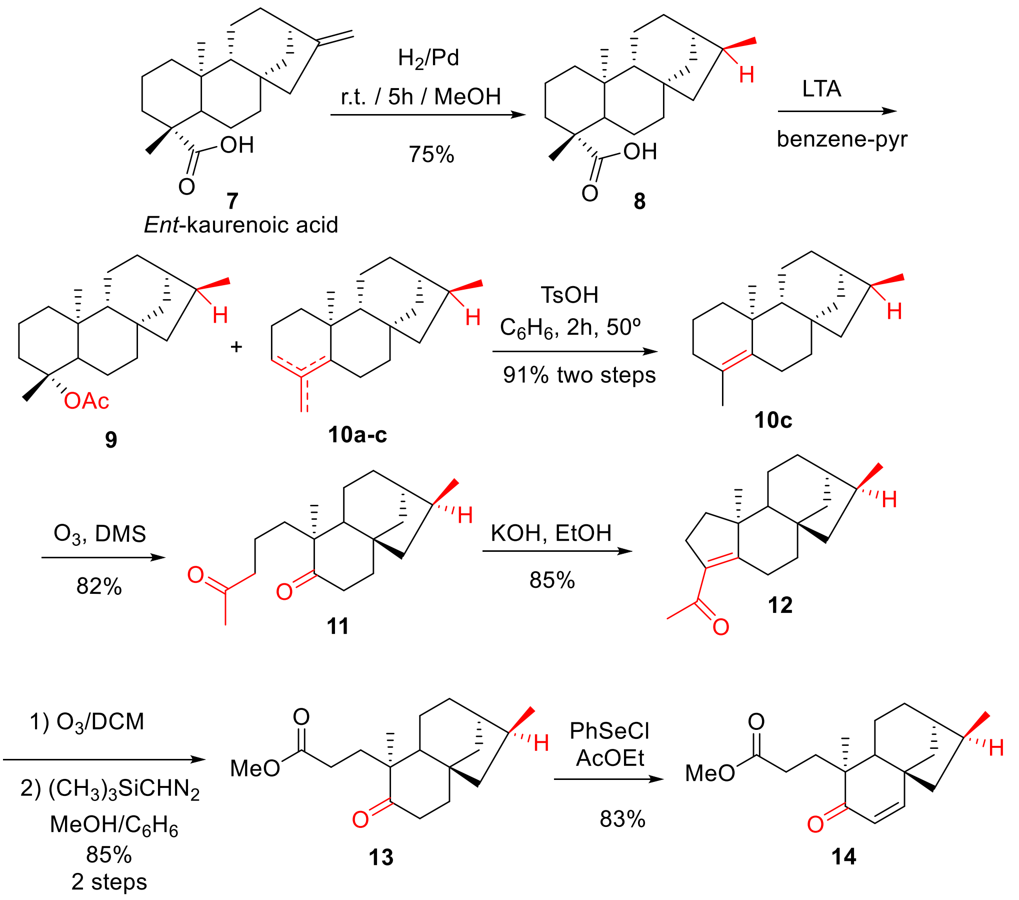


Scheme 1. Retrosynthetic analysis of PTM.

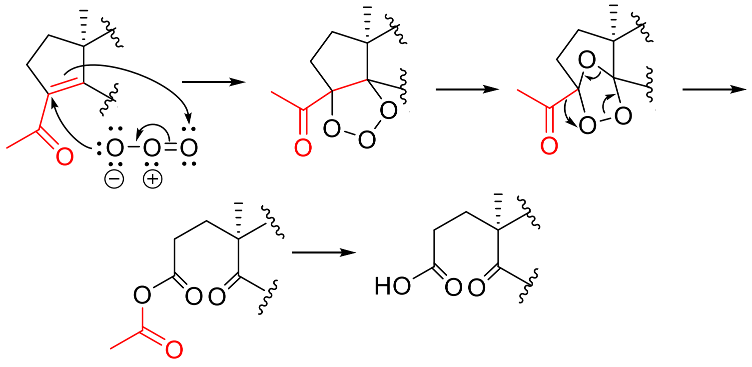
As above-mentioned, the availability of starting materials from cheap and accessible natural sources constitutes a crucial feature of our strategy. For this reason, we started by developing an appropriate procedure for the extraction of *ent*-kaurenoic acid from sunflower heads. Thus, seedless floral heads were macerated in *tert*-butyl methyl ether. Then, the resulting extract was subjected to an alkaline extraction with 2N NaOH. The organic phase was separated as an emulsion, where kaurenoic acid was present as its sodium salt. This emulsion was broken after addition of water acidulated at pH 2.5 and after addition of hexane. The resulting organic phase was then extracted with

NaOH 2N, and the aqueous player acidified and reextracted with *tert*-butyl methyl ether to give a mixture of kaurenoic and trachilobanoic acids in a 4:1 ratio, and a final yield of 0.05% (Barrero et al 2021, unpublished results). On the other hand, acids from *Stevia lucida* aerial parts were obtained via Soxhlet extraction and fractionation following Amaro´s procedure[27].

Once we have multigram of our starting materials in our hands, we decided to study the key step of A ring degradation using the product of hydrogenation of *ent*-kaurenoic acid (**8**) as a simple model. Thus, the synthetic procedure started with the reduction of *ent*-kaurenoic acid by catalytic hydrogenation to afford **8** in 75% yield. Oxidative decarboxylation of **8** with lead tetraacetate[30,31] afforded a variable mixture of the acetylated compound **9** and the regioisomers **10a**-**c**. Treatment of this mixture with *p*-toluensulfonic acid caused both acetic acid elimination plus olefin isomerization to afford only the desired tetrasubstituted olefin **10c** in 91% yield in two steps (Scheme 2). A ring opening was accomplished then by bubbling ozone through a solution of **10a** in dichloromethane at 0°C to furnish diketone **11** in 82% yield. The intramolecular aldolic condensation of **11** provided the pentacyclic methyl ketone **12** (Scheme 2). Noteworthy, exposure of **12** to ozone caused the opening of the cyclopentene ring to afford after esterification the ketoester **13** in 85% yield. As required two carbon atoms were lost during the process, which should involve degradation of the initially formed α-diketone. A mechanism to rationalize this transformation is proposed (Scheme 3). Finally, the α-β unsaturated ketone **14** was obtained via treating **13** with phenyl selenium chloride in EtOAc and subsequent elimination of the corresponding selenoxide generated after addition of H_2O_2 (83% yield; Scheme 2).

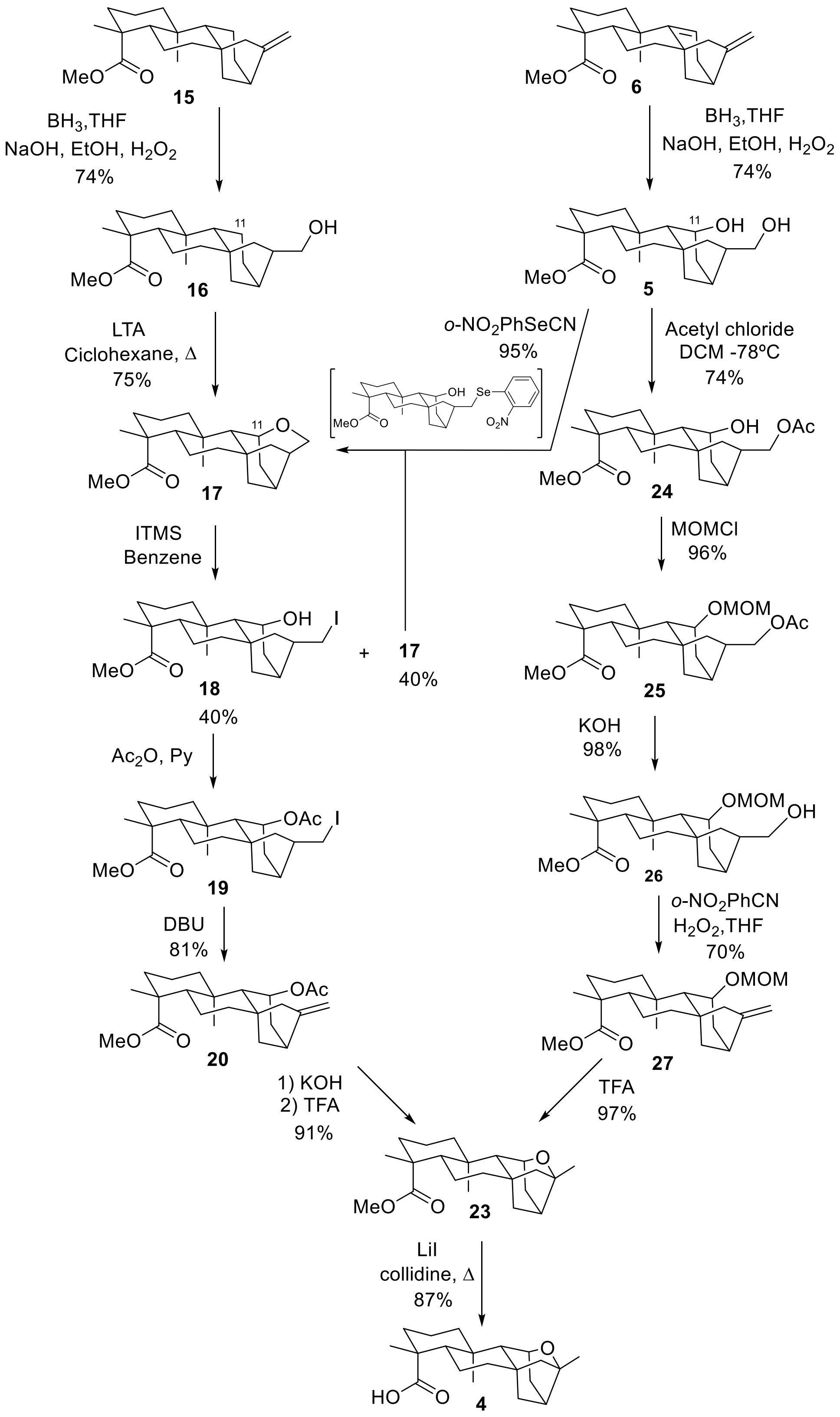


Scheme 2. *Ent*-kaurenoic Ring A degradation Model.



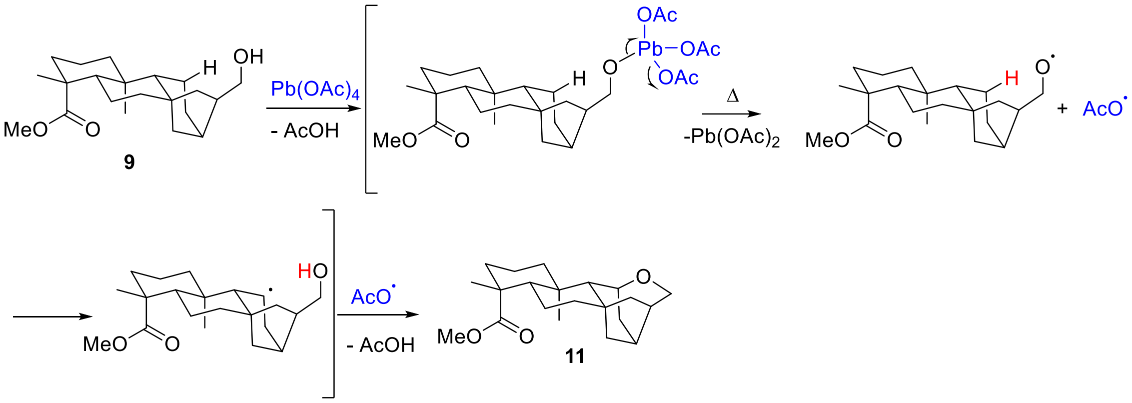
Scheme 3. *Ent*-kaurenoic ring A degradation. Mechanistic proposal

Once the appropriate experimental conditions for the A-ring degradation were found, we focused our efforts to develop a strategy for the construction of the furane ring in PTM using both the methyl esters of *ent*-kaurenoic and grandiflorenic acids as starting materials (see Schemes 4 and 5). The two parallel approaches starting from each one of these precursors converged in the generation of the pyran derivative **4** (Scheme 4).



Scheme 4. Ether Ring Synthesis

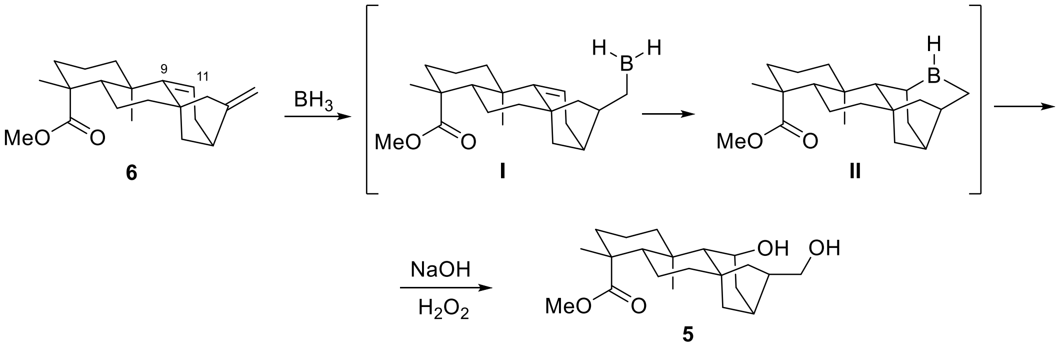
Starting from the methyl ester of *ent*-kaurenoic acid (**15**), our first approach to PTM began with the regio-and stereoselective hydration by the most accessible α face of the olefin present in **15** using BH_3 in THF as hydroborating agent and H_2O_2/KOH as oxidant. Primary alcohol **16** was thus obtained in a 74 % yield. The required oxygenation at C-11 was accomplished by treating **16** with LTA in refluxing cyclohexane[32–34] to produce **17** in a remarkable 75% yield. This good yield is the result of spatial proximity of C17-hydroxyl with H11β (Scheme 5).



Scheme 4. Long distance funtionalization mechanism to form **11**.

Trimethylsilyl iodide-mediated opening of the cyclic ether **17** produced, after acetylation of the resulting unstable iodoalcohol **18**, primary iodide **19** and starting **17** in 40% and 43% yield, respectively, in one-pot reaction. Additionally, we obtained a minor product (**20**) in 13% yield, with a double bond at C-11, as a result of the secondary hydroxyl group elimination. It should be noticed that the presence of **17** derives from cyclization of the intermediate iodoalcohol and not from unaltered starting material. Iodine elimination of **19** with DBU produced the exocyclic olefin **21** in 81% yield, along with minor proportions of cyclic ether **17** (6%) yield. Hydrolysis of the acetate **21** and subsequent treatment of the corresponding alcohol with TFA caused the desired regioselective cyclization to generate the targeted furan derivative **23** in a combined 91% yield. Finally, treatment of **23** with lithium iodide in collidine at reflux, afforded acid **4** in 87% yield (Scheme 4).

The route from grandiflorenic acid started with the double regio- and selective hydroboration of the olefinic bonds of methyl gradiflorenate (**6**) to give diol **5**. The selectivity of this double hydration process is noteworthy, mainly if we considered that the diol obtained after a stepwise hydroboration is **5b**, the C11 epimer of diol **5**. To rationalize this facial selectivity, the steric hindrances around both faces of the trisubstituted C9-C11 double bond and around the β-face of the exocyclic olefin must be considered. Thus, it is proposed that the BH_3/THF reagent initially binds selectively by the α-face to the exocyclic olefin to produce an alkylborane complex (**I**), which evolve towards the cyclic dialkylborane **II** after an intramolecular hydroboration of the C9-C11 double bond by the β-face (Scheme 5).

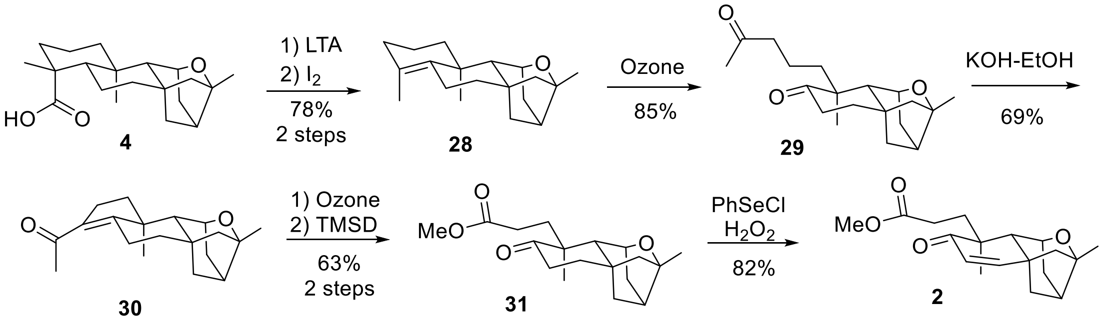


Scheme 5. Selective double hydroboration -oxidation of **6**.

Once we got diol **5** in our hands, selective dehydration of primary alcohol was tried using Grieco´s dehydration procedure[35]. In the event, the pyran derivative **17** was again formed, most likely due to the spatial proximity of the hydroxyl groups which tends to collapse towards the stable six-membered heterocyclic ring via a SN_2 displacement of the corresponding seleno intermediate. Although at this point, cyclic ether **17** is an intermediate in the kaurenic approach to the furan derivative **4**, we devoted ourselves to establish an alternative route to target **4**.

Our new approach from diol **5** involved some protecting groups manipulation. Thus, selective acetylation of primary alcohol of **5** was accomplish using acetyl chloride at -78 ºC to afford acetate **24** in a 74% yield. Secondary alcohol was then protected with methoxymethyl chloride (MOMCl) to give **25** in 96% yield. Alkaline deprotection of the acetate group led to the primary alcohol **26**, which was now successfully eliminated following Grieco´s protocol[35] to furnish olefin **27** (84% yield, two steps). Finally, pyran derivative **23** was produced in 97% yield by treating **27** with TFA, after a one pot deprotection-cyclization process.

One we succeeded in making converge our two approached in the furan derivative **4**, our next goal was to applied to **4** the A ring degradation experimental conditions that were optimized with the reduced derivative of kaurenoic acid (**8**). Following the above-detailed procedure, decarboxylation of carboxylic acid **4** was conducted using lead tetraacetate. The resulting reaction mixture was then made react with *p*TsOH to obtain olefin **28** in low yields. Gratifyingly, when the mentioned crude was treated with molecular iodine, the desired tetrasubstituted **28** was obtained in 78% yield over the two steps. Ozonolysis led to the A ring cleavage affording diketone **29** in 85% yield (Scheme 6).



Scheme 6. Synthesis of methyl platensinoate (**2**).

Intramolecular aldol condensation of compound **29** with potassium hydroxide in ethanol provided the enone **30** in 69% yield. Ozonolysis of **30** caused, as previously described (Scheme 3), the loss of two carbon atoms and the generation of methyl ester **31** after methylation with trimethylsilyl diazomethane of the corresponding acid (63% yield, two steps). Finally, the dehydrogenation of **31** to produce methyl platensinoate (**2**) was accomplished in an 83% yield using the same PhSeCl/H_2O_2 protocol previously described in the model study. Since compound **2** constitutes an intermediate in the PTM synthesys described by Nicolaou in 2009 [16], the herein described synthetic approach constitutes a formal enantioselective synthesis of PTM. It should be noted that the specroscopic data of our methyl platensinoate (**2**) matches completely with those described by Nicolau et al for the same product.

In conclusion, we have investigated two approaches to **2**, resulting in the formal bioinspired synthesis of synthesis of PTM, a multidrug- resistant antibiotic possessing a unique mode of action as suppressor of the fatty acid biosynthesis in bacteria. The use of renewable starting materials was essential in our strategy. The use of *ent*-kaurenoic acid present in sunflower, whose oil production in 2020 was over 55 million tons worldwide, features the harnessing of agricultural of residues for the production of added value chemicals. Also key in our strategy was the unprecedent protocol described for the A-ring degradation of kaurene diterpenoids, which additionally enabled the required loss of two carbon atoms for the synthesis of methyl platensinoate. All in all, the synthetic route herein competes favourably with other synthetic approaches, resulting in fact in the shortest sequence to this natural product. Finally, our protocol is flexible enough to be applicable to the synthesis of other PTM analogues in the search of more active antibiotics.

Acknowledgment. This work has been supported by grants MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD, PID2019-106222RB-C32/SRA (State Research Agency, 10.13039/501100011033).

Supporting Information Available: Complete experimental procedures, copies of ^{1}H NMR and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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4 Discusión de los resultados.

4.1 Estudio bibliográfico de síntesis biomiméticas de Terpenos mediante ciclaciones y reordenamientos.

Uno de los objetivos marcados en el desarrollo de la presente memoria consiste en la recopilación de artículos publicados desde principio de siglo sobre estrategias sintéticas hacia terpenos que implican mecanismos de ciclación y reordenamiento. Estos imitan los procesos enzimáticos que realiza la naturaleza.

El interés en este tema está ligado a nuestra investigación acerca de la síntesis de halimanos, cuya planificación a seguir engloba este tipo de estrategias. Como hemos comentado anteriormente, las etapas sintéticas que implican ciclación y reordenamiento dirigidos en sólo paso suponen una alta dificultad. Su gran ventaja es que suelen mejorar el rendimiento global en síntesis por economizar en átomos y número de pasos sintéticos. Aunque existen varias revisiones de organismos o enzimas que pueden catalizar este tipo de transformaciones en el laboratorio, nosotros hemos puesto el foco en el desarrollo de transformaciones químicas que imitan esta serie de procesos en tándem. Así pues, se presenta el artículo **número 1**, como primer objetivo de esta memoria en donde se describen ejemplos de este tipo de reacciones incluyendo los mecanismos de reacción de estas transformaciones. Está siempre presente un carbocatión iniciador de los procesos de ciclación y transposición ya sea de metilo, alquilo en general o de hidruro o ambos.

Las estrategias planteadas en esta revisión, suponen el empleo del uso de diferentes ácidos de Lewis o Brønsted para iniciar el proceso en cascada de ciclaciones y reordenamientos a través de la apertura de un oxirano o reaccionando selectivamente con alguno de los dobles enlaces presentes en los poliprenos.

Cabe destacar el uso de varios tipos de monoterpenos y principalmente sesquiterpenos naturales como productos de partida utilizados para lograr las transformaciones que implican ciclaciones y reordenamientos.

La revisión llevada a cabo utilizando SciFinder CAS (Copyright © 2021 American Chemical Society). ha conducido a encontrar 62 artículos científicos sobre el tema. Un ejemplo representativo de ellos lo encontramos en la síntesis de (+)-liphagal[108] (Figura 45) a partir del producto natural (+)-esclareolida, en la síntesis se genera un intermedio (**61**) cuyo reordenamiento de 1,2- de alquilo y posterior ciclación dará lugar a la molécula **62**.

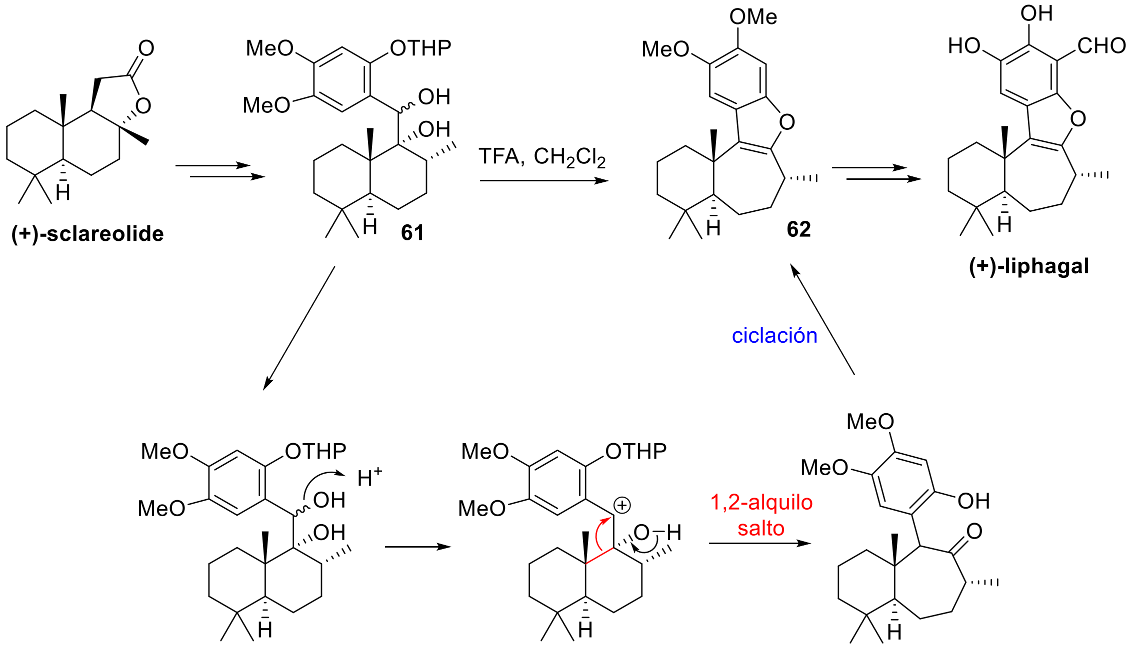


Figura 45. Reordenamientos y ciclación en la síntesis de (+)-liphagal.

4.2 Síntesis enantioselectiva de (–)-2,15-valparadieno e (+)-isodaucano.

El segundo objetivo marcado en la tesis es realizar una propuesta de ruta biomimética de síntesis para (–)-2,15 valparadieno, un producto natural cuya síntesis se describe por primera vez en esta memoria. El desarrollo de esta ruta sintética permitirá estudiar su viabilidad y planteará la posibilidad de emplearse de forma general para la síntesis de otros valparanos naturales.

La estructura de valparano incluye tres ciclos fusionados de diferente tamaño (5+6+7), lo que supone un claro desafío sintético. Para abordar este reto, partíamos de resultados previos de nuestro grupo de investigación, en los que se habían encontrado las condiciones estructurales-funcionales que debían reunir los sustratos de partida para poder controlar la formación de ciclos de 5, 6 ó 7 miembros, en procesos de ciclación radicalaria mediados por Ti(III)[63,109]. Cabe destacar cómo los diferentes regioisómeros del acetato alílico terminal en un polipreno, pueden determinar la predominancia del cierre 7-*endo* sobre el 6-*endo*, generando por tanto los anillos de cicloheptano que se encuentran en las moléculas objetivo (Figura 46).

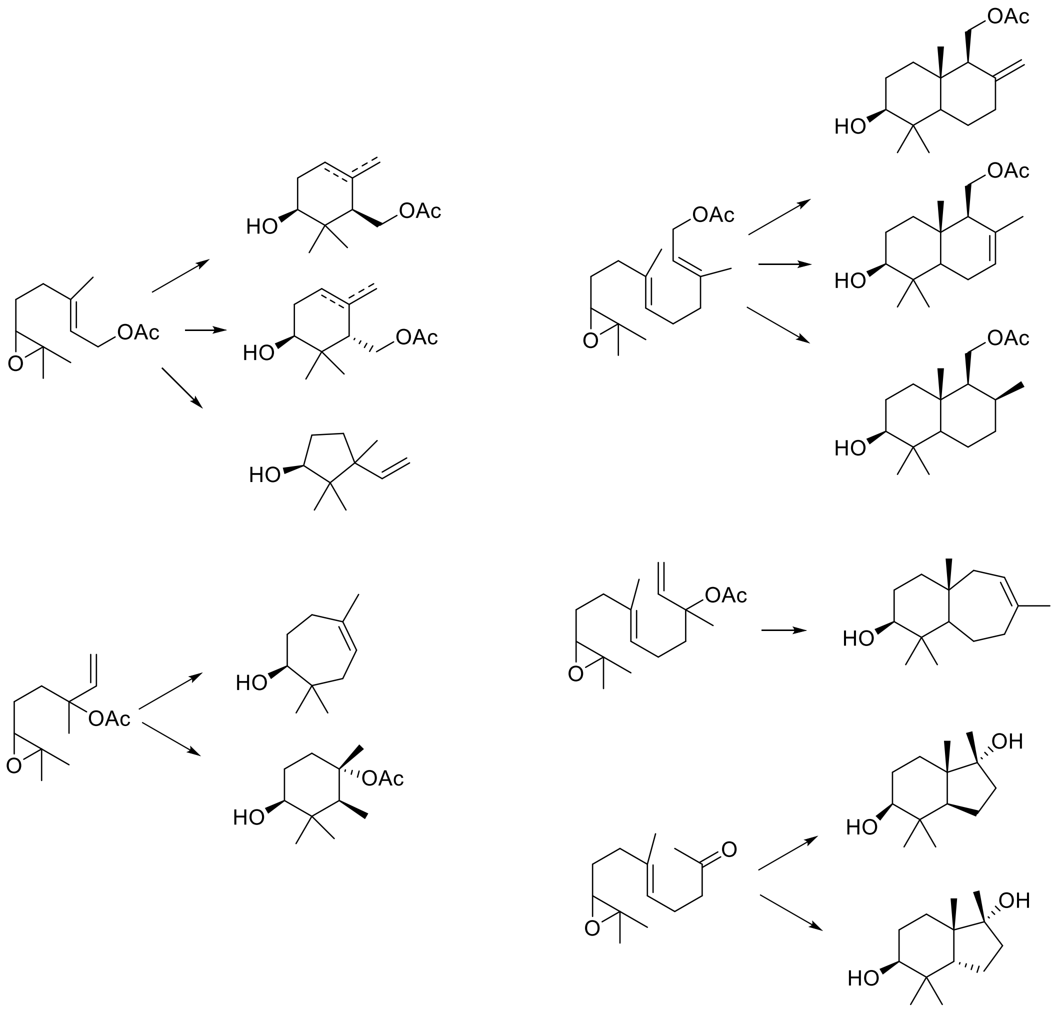


Figura 46. Estudio del grupo de Barrero en la formación de ciclos de 5 de 6 y de 7 a través de ciclaciones catiónicas con Ti(III).

Con esta información previa en mente, el esquema retrosintético ideado para la síntesis de (–)2,15-valparadieno (**12**) utilizará como producto de partida (Figura 47), el producto natural extraído de las flores de *Bellardia trixago*, geranilgeraniol **1**. Los pasos clave para el desarrollo de dicha síntesis, son la formación del compuesto **10** con un anillo ciclopentánico producto de una contracción de anillo desde el compuesto **9** y la policiclación radicalaria inducida por Ti (III) del compuesto **8**. El compuesto **8**, posee los grupos funcionales epóxido y acetato que van a definir el inicio y el final de la ciclación con Ti (III) hasta el compuesto **9.** Además **8** posee un grupo OTBS, clave en la estrategia, sobre el metilo (C-16) que habrá de introducirse gracias a una oxidación selectiva desde el producto de partida **1** extraído de la planta *Bellardia trixago*.

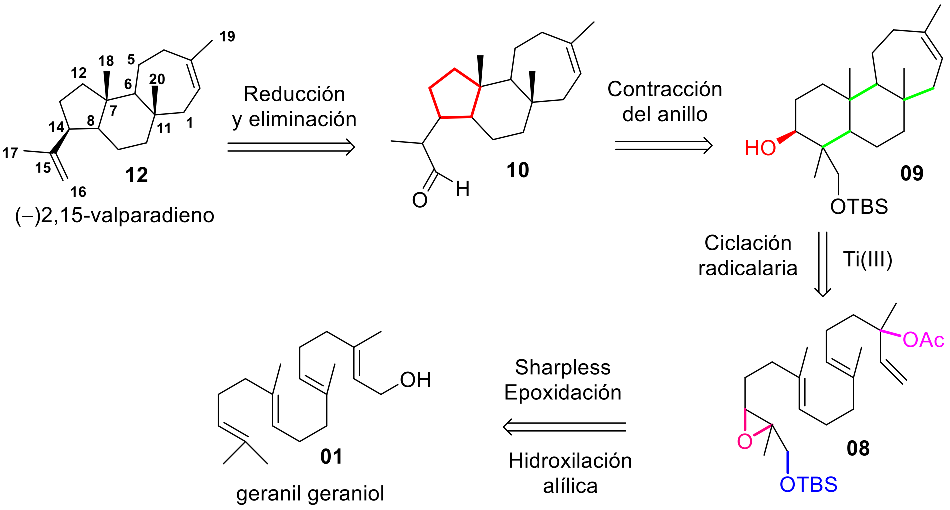


Figura 47. Esquema retrosintético de (–)-2,15 valparadieno.

I. *Puesta a punto del proceso sobre un modelo sencillo. Síntesis de (+)-isodaucano.*

Antes de realizar la síntesis de (–)-2,15-valparadieno, se estudió el proceso de ciclación con Ti(III) en sustratos polifuncionalizados, usando un producto de partida más simple como el epóxido **17.** Esto a la vez permite completar la síntesis del sesquiterpeno natural (+)-isodaucano. Este es un biciclo que cuenta con una estructura similar a valparanos con una configuración de doble anillo de 5+7 y el doble enlace en posición terminal igual que nuestra molécula objetivo (Figura 48).

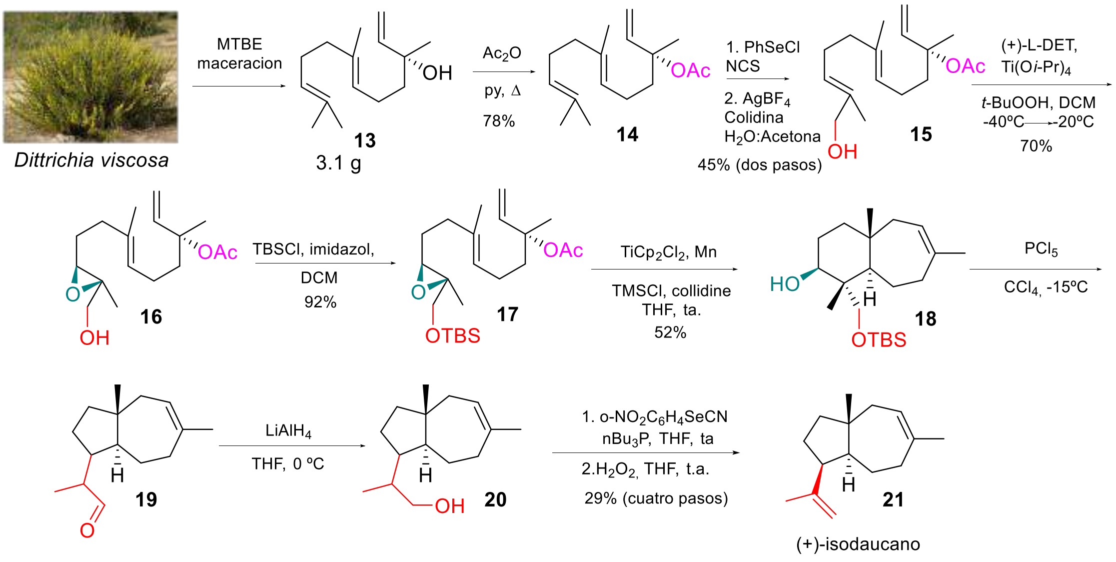


Figura 48. Modelo de síntesis de (+)-isodaucano a partir de (+)-nerolidol.

La síntesis del epóxido **17** comenzó a partir del producto natural (+)-nerolidol, extraído de la planta *Dittrichia viscosa* (Figura 4). La acetilación de nerolidol genera el acetato terciario alílico **14** (78% rendimiento), que posee los requerimientos estructurales necesarios para la generación del ciclo de siete miembros en el proceso de ciclación radicalaria. El isopropilideno terminal del compuesto acetilado **14,** sufre una oxidación posicionalmente selectiva sobre el doble enlace trisustituido más accesible, usando de nuevo un sistema desarrollado previamente por el grupo de investigación[110], y que supone el empleo de PhSeCl/NCS. La sustitución del cloro alílico así obtenido usando tetrafluroroborato de plata, dió como resultado el compuesto hidroxilado **15** con un 45% de rendimiento. La funcionalización del isopropilideno va a ser el paso clave en la formación regioselectiva del doble enlace terminal del producto natural. Para la obtención del epoxialcohol **16**, el producto **15** se sometió a una epoxidación enantioselectiva siguiendo el protocolo descrito por Sharpless[111,112] para la obtención de epoxialcoholes alílicos. La estereoquímica del epóxido resultante está determinada por el diastereómero (+)-dietil tartrato utilizado en la reacción y la enantioselectividad está garantizada por el catalizador formado a partir del tetraisopropóxido de titanio y el dietil tartrato, en presencia de tamices moleculares de 4Å dando el producto **16** en un 70% de rendimiento.

Una vez formado el epóxido y la posterior protección del alcohol como *tert*butildimetilsilil éter, el tratamiento de **17** con Ti(III) en condiciones subestequiométricas usando el sistema TMSCl/colidina como regenerador dio lugar, mediante una biciclación en cascada 6-*endo* y 7-*endo*, al alcohol bicíclico **18** con un 52% de rendimiento. La contracción catiónica del anillo A hasta ciclopentano se desarrolla mediante la acción del pentacloruro de fosforo según el mecanismo propuesto en la figura 49.

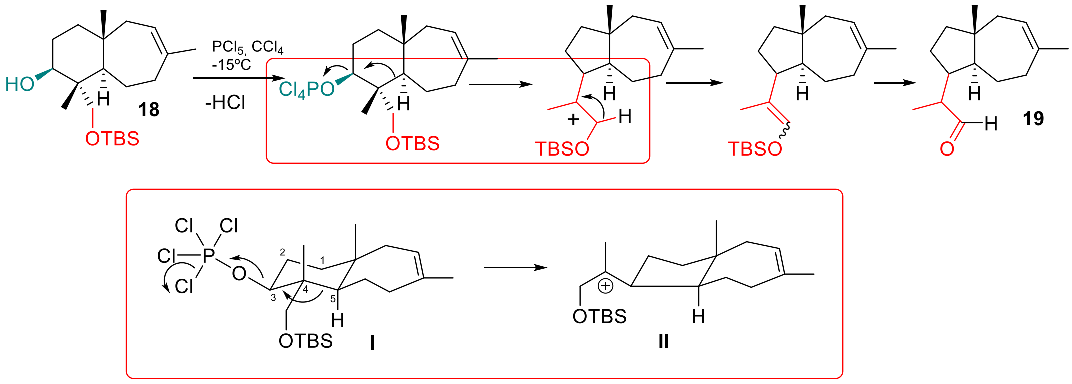


Figura 49. Mecanismo de contracción catiónica del anillo A.

La disposición ecuatorial del grupo oxigenado primario en C-16 juega un papel fundamental en el éxito de esta estrategia de síntesis. La correcta alineación *anti* del enlace C-4-C-5 y el grupo hidroxilo activado en **I**, justificaría la migración de este enlace para inducir el desplazamiento del grupo saliente y la generación del carbocatión **II** con la configuración apropiada. A continuación, se genera selectivamente un sililenoléter desde el carbocatión terciario debido a la eliminación regiodirigida por la mayor acidez del protón en C-13. Este sililenoléter evoluciona hacia el aldehído correspondiente en el medio ácido generado (HCl) y conduce finalmente a **19**.

A continuación, la reducción del aldehído **19** formado, con hidruro de aluminio-litio y posterior eliminación del alcohol resultante (**20**), mediante el protocolo descrito por Grieco[107], dio como resultado la olefina terminal (**21**), siendo el rendimiento para estos cuatro últimos pasos del 29%.

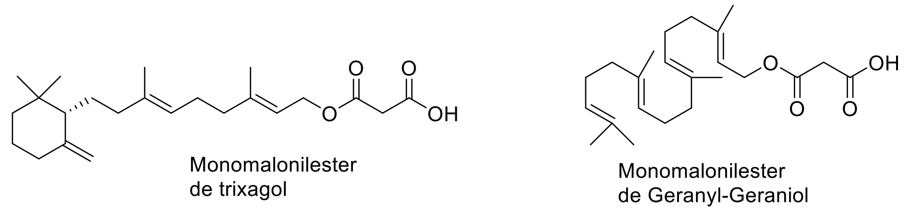
La síntesis del producto final (+)-isodaucano se llevó a cabo en 10 pasos sintéticos y un 3% de rendimiento global.

II. Comparación de la propuesta sintética actual hacia 2,15-valparadieno con la síntesis publicada de 2,14-valparadieno.

La propuesta de síntesis que planteamos, presenta una serie de innovaciones sustanciales sobre el planteamiento descrito por Justicia y colaboradores en 2005[62], en el que sintetizaban el producto no natural 2,14-valparadieno. En primer lugar, se ha utilizado como producto de partida geranilgeraniol (GeGeOH), un producto natural renovable, abundante y fácil de obtener desde la planta *Bellardia trixago*. Otra mejora con respecto a la síntesis de 2005 es la funcionalización del metilo en C-16 del isopropilideno terminal. Este es el paso clave para el acceso a valparanos naturales con doble enlace terminal. Finalmente, esta entrada de grupo hidroxilo en C-16 va a permitir llevar a cabo una epoxidación enantioselectiva del doble enlace vecinal y, por lo tanto, conseguir así la síntesis asimétrica de la molécula final.

III. Obtención del material de partida, geranilgeraniol (GeGeOH).

Para iniciar la ruta de síntesis desde el geranilgeraniol, se trabajó con los extractos de la planta *Bellardia trixago,* esta especie es conocida como gallocresta o boca de dragón, es una planta terófita propia de climas secos y terrenos pobres o poco estructurados[113]. Posee una alta concentración de aceites esenciales, es utilizada para la obtención de aromas y productos naturales, útiles para la síntesis de compuestos bioactivos. De entre los productos que se pueden extraer, destacan los diterpenos trixagol y geranil-geraniol (Figura 50), ya que son utilizados como material de partida en la síntesis de compuestos de interés[114–116]. En nuestra Comunidad Autónoma (Andalucía) existen por el momento, tres quimiotipos diferentes de esta especie, siendo uno de ellos muy rico en monomalonil éster de geranilgeranilo [55], cuya saponificación va a dar el producto de partida deseado.



Monomalonilester de trixagol

Monomalonilester de Geranyl-Geraniol

Figura 50. Monomalonil ester de trixagol y el geranil-geraniol, productos encontrados en la planta Bellardia trixago.

El extracto obtenido del *B. trixago* supone el 7% del peso seco de la planta. El monomalonil éster de geranilgeranilo se encuentra en un 20 % de concentración dentro del extracto. Este se somete a saponificación en metanol e hidróxido potasico al 10% (Figura 51), generando el polipreno geranilgeraniol puro, en un 57% de rendimiento, tras cromatografía en columna de gel de silice[117].

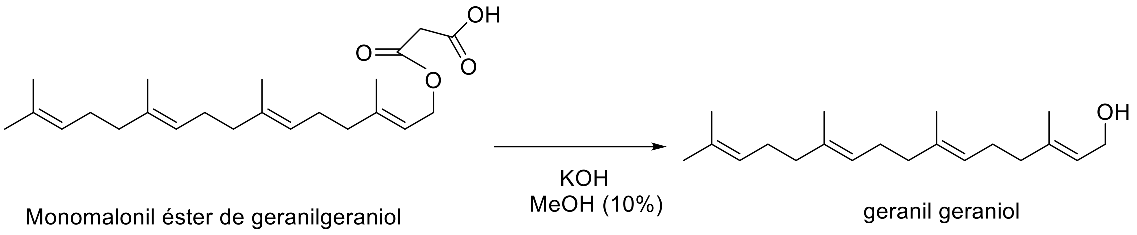


Figura 51. Reacción de saponificación del monomalonil ester de geranilgeranilo para dar geranil geraniol.

IV. Síntesis de (–)-2,15-valparadieno

Una vez puesta a punto la estrategia sintética con la preparación de (+)-isodaucano, el protocolo fue aplicado a la síntesis del compuesto natural (–)-2,15-valparadieno. Para ello se utilizó, como se ha comentado, el producto natural geranilgeraniol (**1**) extraído de la planta *Bellardia trixago* como producto de partida. La epoxidación selectiva del doble enlace vecinal al alcohol alílico del geranil geraniol y el posterior tratamiento con ácido peryódico nos permitió obtener la farnesil cetona **3** (94% rendimiento en 2 pasos) (Figura 52). El geranil linalol **4** se obtiene por la adición de bromuro de vinil magnesio al carbonilo. La derivación del alcohol del geranil linalol **4** para formar acetato de geranillinalilo **5** (56% de rendimiento desde farnesil cetona **3**), paso importante, como hemos comentado, en el cierre 7-*endo* del triciclo.

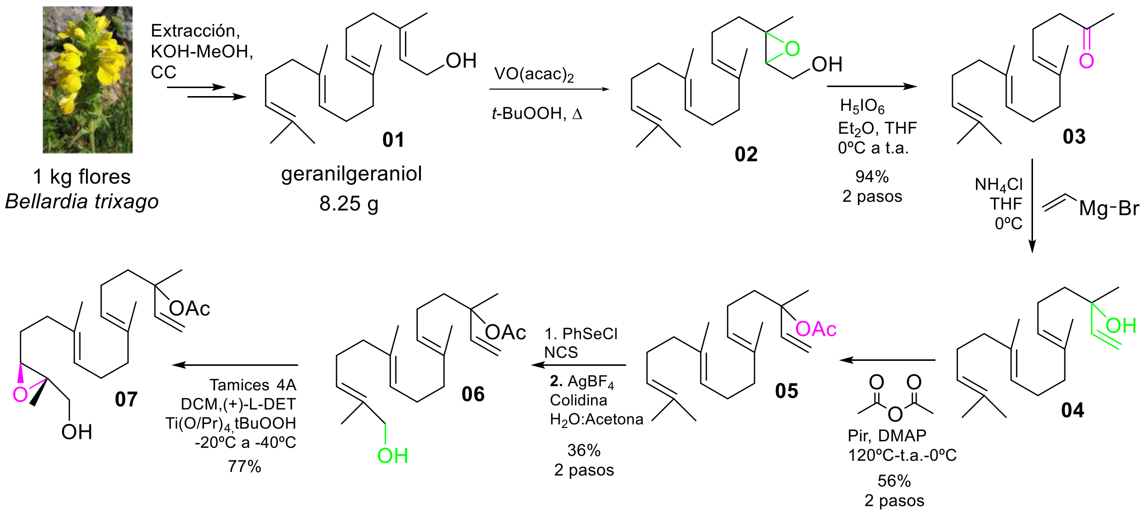


Figura 52. Primera parte de la síntesis de (–)-2,15-valparadieno

A partir del compuesto acetilado, se aplican los mismos pasos que para la síntesis de (+)-isodaucano. Así pues, se procedió a la oxidación del isopropilideno terminal y a continuación la formación del epóxido de manera enantioselectiva y posterior protección del alcohol con cloruro de *tert*butildimetilsililo (TBSCl) con rendimientos del 77 y el 84%. La triciclación dará lugar mediante el tratamiento con Cp_2TiCl_2 a un sistema tricíclico 6+6+7, después de dos ciclaciones 6-*endo* y una ciclación 7-*endo*. La obtención del alcohol tricíclico **9** con un rendimiento moderado del 32% ha de valorarse teniendo en cuenta la formación de 3 ciclos y 6 centros estereogénicos contiguos en un solo paso a partir de una molécula polifuncionalizada (Figura 53).

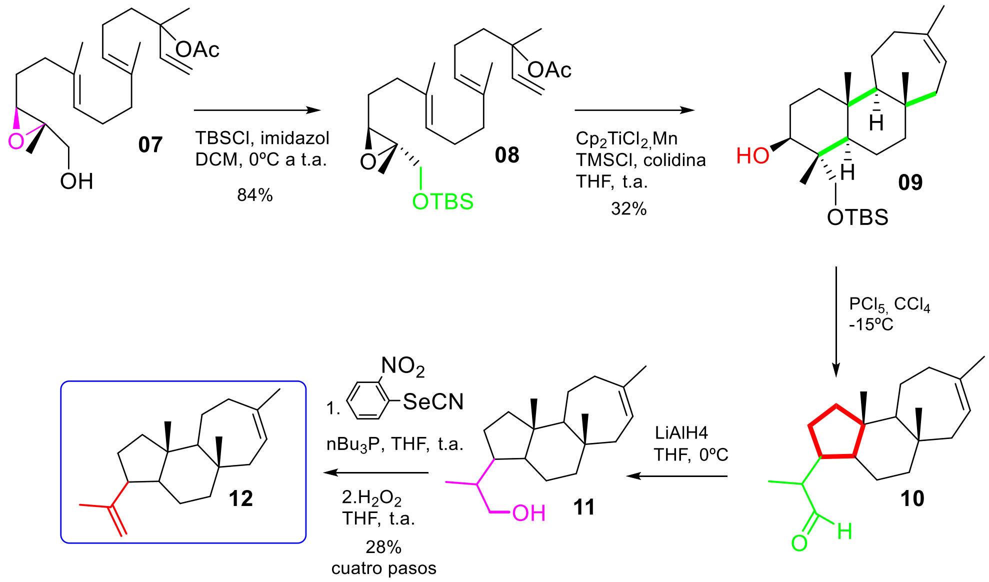


Figura 53. Segunda y última parte en la síntesis de (–)-2,15-valparadieno.

El mecanismo propuesto para la formación del triciclo a partir del epóxido **8** se muestra en la Figura 54. La rotura homolítica del enlace O-C del epóxido más sustituído, propicia la formación de un radical terciario (a). Este genera un primer proceso de ciclación 6-*endo* para dar lugar a un segundo radical (b), que se va se adicionar al doble enlace próximo en un proceso *6*-endo para dar lugar a un tercer radical (c). Este nuevo radical evoluciona regioselectivamente por un proceso 7-*endo*, favorecido sobre el 6-endo por el efecto Thorpe-Ingold del grupo metilo y el acetato sobre el carbono C-3. Se genera así el tercer anillo presente en el intermedio radical (d), que es atrapado por otra molécula de Cp_2TiCl_2 y posteriormente evoluciona mediante un proceso de eliminación β de acetato, obteniéndose el alcohol tricíclico **9**.

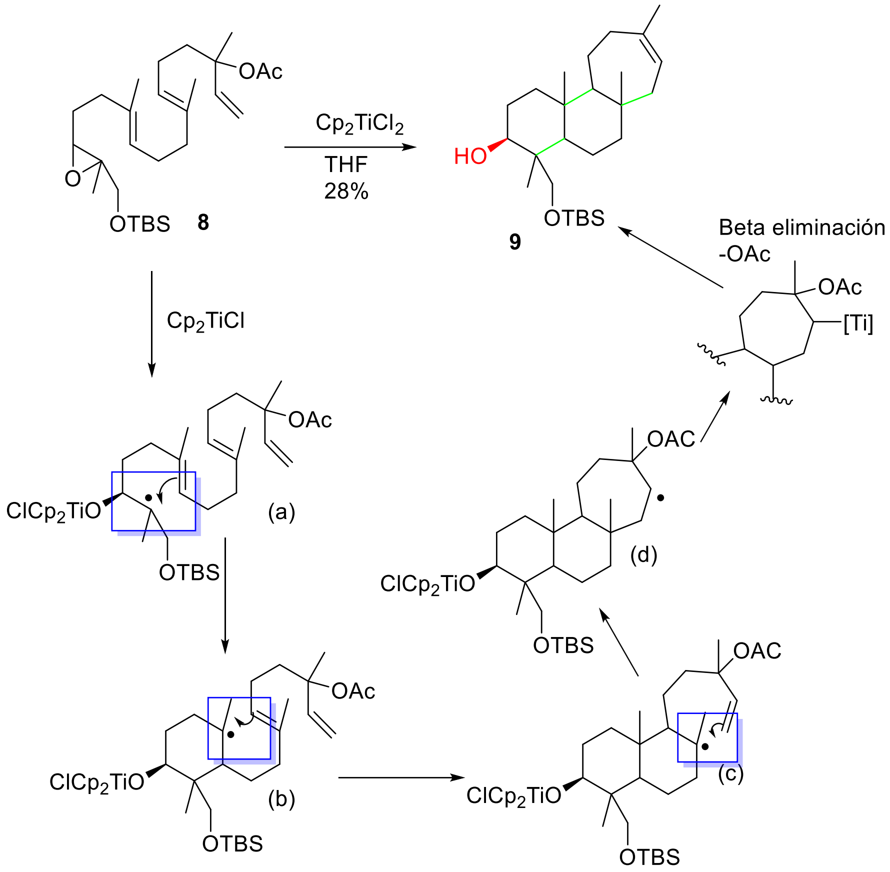


Figura 54. Mecanismo de triciclación radicalario mediado por Ti(III)

A partir de **9**, el paso clave de la aproximación sintética, supone la contracción catiónica del anillo A mediante el mismo proceso descrito en la síntesis de (+)-isodaucano que ahora conduce al aldehído **10**. La reducción del aldehído con hidruro de aluminio y litio ($LiAlH_4$) generará dos alcoholes epímeros (**11**), siendo el protocolo descrito por Grieco[107] para la eliminación de alcoholes, el utilizado para la formación de nuestra molécula final (–)-2,15-valparadieno (**12**) (Figura 9). Los últimos cuatro pasos se consiguen con un rendimiento total del 28%, siendo el global para la síntesis de (–)-2,15-valparadieno del 1,1% de rendimiento.

4.3 Síntesis biomimética de halimanos. Preparación de isotuberculosinol.

Los diterpenos que presentan esqueleto de halimano constituyen un grupo de productos naturales cuya biosíntesis se podría clasificar intermedia entre aquellos de tipo labdano y los de tipo clerodano. El halimano isotuberculosinol aislado de *Mycobacterium tuberculosis* constituye un ejemplo interesante pues actúa como su factor de virulencia[65,118].

Además de encontrarse en la planta Cistacea *Halimium viscosum* de donde proviene su nombre, encontramos este tipo estructuras en plantas y poríferos marinos, siendo el género de esponjas Angelas sp. y Raspalia sp. característicos por su contenido en halimanos bioactivos[64]. En la actualidad, existe un buen número de productos naturales con esqueleto de halimano que no han sido evaluados biológicamente, aunque varios de ellos presentan potentes y variadas bioactividades antibacteriana, antifúngica, antipalúdica y citotóxica. Incluso varios muestran actividad antiincrustante contra macroalgas, siendo una alternativa de gran utilidad en la industria pesquera ante el uso de productos antiadherentes que incluyen sustancias nocivas para el medio marino. Diferentes ejemplos los podemos encontrar en la Figura 55.

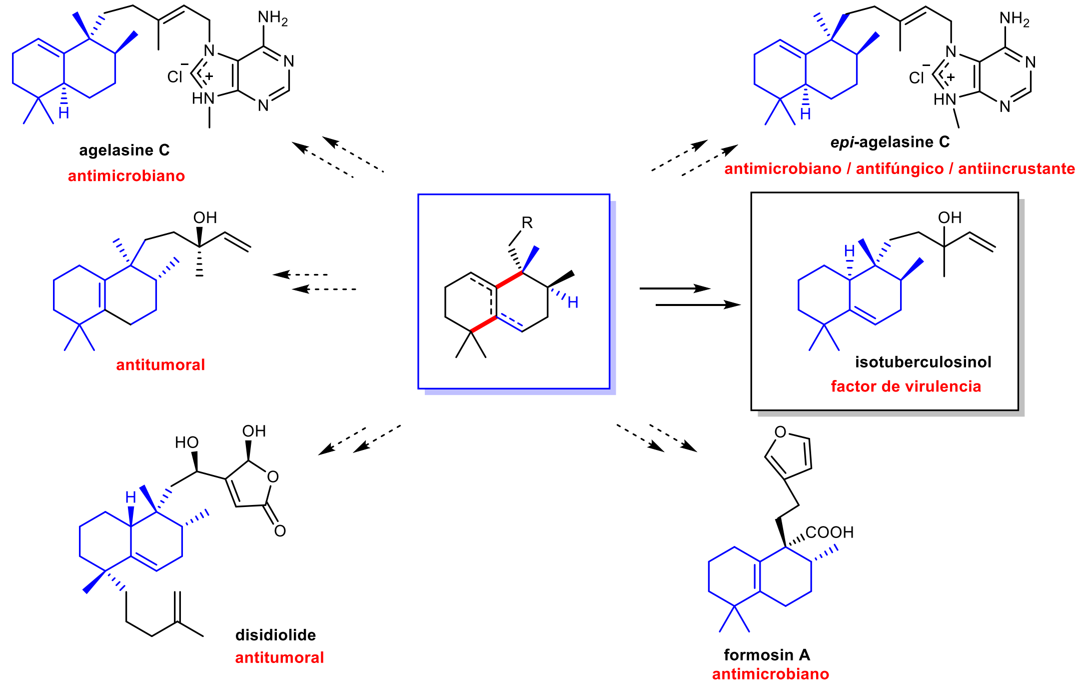


Figura 55. Ejemplos de moléculas bioactivas con esqueleto halimano.

I. Síntesis de halimanos.

En la biosíntesis de halimanos a partir de geranil geranil difosfato interviene una diterpeno ciclasa de tipo II originando un carbocatión bicíclico labdanilo intermedio que mediante reordenamientos 1,2 de metilo y de hidruro conduce hasta el esqueleto característico de halimano [64]. En base a ese proceso se ha diseñado una estrategia de síntesis biomimética que se va a poner a punto desde el monoepoxido de farnesil butano (R=butil). Se trata de una sola etapa, a través de dos ciclaciónes 6-*endo* y tres reordenamientos carbocatiónicos 1,2 con desprotonación final a la estructura típica de halima-5-eno. El proceso estará mediado por ácidos de Lewis (Figura 56).

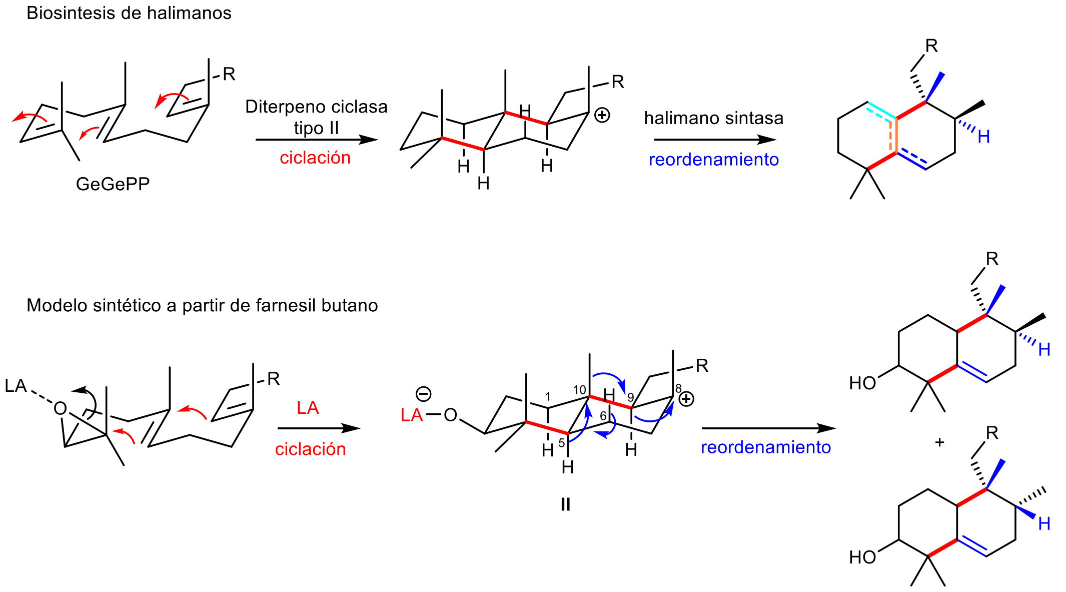


Figura 56. Comparación de la biosíntesis de halimanos con nuestro modelo biomimético.

La apertura del epóxido de farnesilbutano mediante el ácido de Lewis provocará la formación del biciclo que cierra con un carbocatión en C-8. Este intermedio sufre tres reordenamientos, el primero 1,2 de hidruro del hidrogeno en C-9 hacia C-8, el segundo del metilo en C-10 hasta C-9 pasando el carbocatión a C-10 y el tercero salto del hidrogeno en C-5 a C-10. Finalmente, la pérdida de un protón en C-6 formará la olefina correspondiente.

Como puede observarse la estereoquimica relativa de los grupos que emigran es *anti* y su disposición axial sobre el ciclohexano correspondiente. Adicionalmente, esta hipótesis está soportada mediante cálculos computacionales. Así los valores de las barreras para el epoxifarnesilbutano, usando como disolvente diclorometano que están en su mayoría por debajo de las 10 kcal/mol, son propicios para la formación del carbocatión inicial y llevar a cabo los procesos en tándem de ciclaciones y reordenamientos. Esto debe permitir llevar a cabo el proceso en condiciones normales reacción (Figura 57).

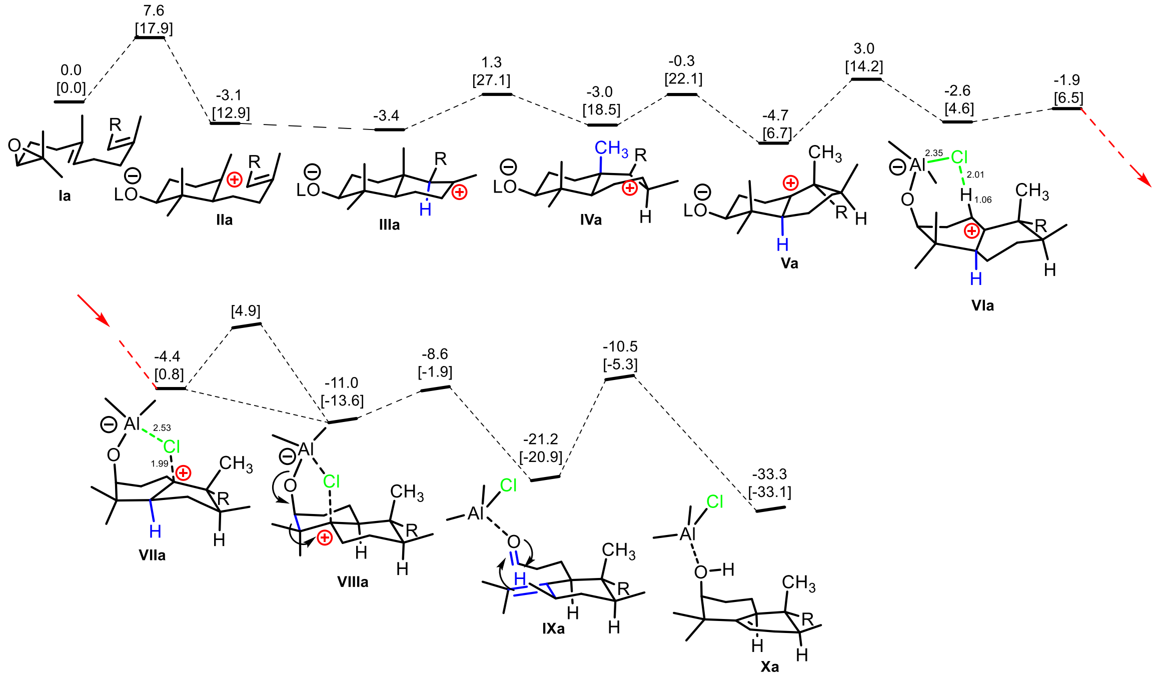
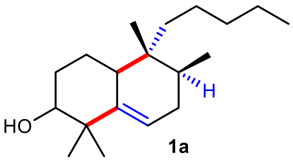


*Figura 57. Análisis computacional de la formación del diastereoisomero **1a**, las barreras energéticas en el vacío se muestran entre corchetes y se comparan con las calculadas en diclorometano para el proceso de síntesis.*

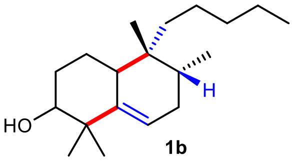
El estudio del proceso de ciclación+reordenamiento (Figura 57) se inició mediante la reacción del epóxido de farnesil butano con Me_2AlCl que condujo a la formación de los diasteroisomeros **1a** y **1b** en proporciones 1:1 con un 51% de rendimiento (Tabla 1, Entrada 1). Para la optimización se variaron las condiciones de reacción, utilizando para ello diferentes disolventes, ácidos de Lewis, concentraciones, temperatura y tiempo. Como resultado se obtuvieron mayoritariamente los productos de ciclación y reordenamiento y en menor proporción, productos de ciclación normal monocíclicos y bicíclicos. Finalmente, y después de más de treinta experimentos se llegó a la conclusión de que las condiciones óptimas para la síntesis de halimanos a partir del uso de ácidos de Lewis (Tabla 1), eran las definidas en la entrada 9. En condiciones rigurosamente anhidras y atmosféra de argón, empleo de 2 equivalentes de cloruro de dietilaluminio, en diclorometano a una concentración de 0.03 mM y un tiempo no superior a

45 minutos, se obtienen los productos de ciclación-reordenamiento a **1a** y **1b** en proporciones 1:1.1 y en un 71% de rendimiento.

Tabla 1. Variaciones en la optimización del modelo de síntesis. En azul se muestra el mejor registro.



1a



1b

Entrada	*Equiv, LA*	*Temp (ºC), C (mM)*	*Disolvente*	*Tiempo (min)*	*1a, 1b rendimiento,(Ratio)*
1	1/Me$_2$AlCl	-78, 0.03	DCM	45	51% (1:1)
2	1/Et$_2$AlCl	-78, 0.03	DCM	45	54% (1:1.1)
3	0.1/Bi(OTf)$_3$	Reflujo, 0.03	DCM	40	ND
4	1/Cu(OTf)$_2$	-78, 0.03	DCM	30	ND
5	1/InBr$_3$	-78, 0.03	DCM	300	27% (1:0.8)
6	1/InBr$_3$	TA, 0.03	DCM	100	37% (1:0.4)
7	0.5/Et$_2$AlCl	-78, 0.03	DCM	100	53% (1:1)
8	1.5/Et$_2$AlCl	-78, 0.03	DCM	50	59% (1:1)
9	2/Et$_2$AlCl	-78, 0.03	DCM	45	71% (1:1.1)
10	3/Et$_2$AlCl	-78, 0.03	DCM	40	65% (1:1)
11	5/Et$_2$AlCl	-78, 0.03	DCM	35	59% (1:1)
12	2/Et$_2$AlCl	-100, 0.03	DCM	60	34% (1:1)
13	2/Et$_2$AlCl	0, 0.03	DCM	30	50% ((1:1)
14	2/Et$_2$AlCl	-78, 0.3	DCM	25	63% (1:1)
15	2/Et$_2$AlCl	-78, 0.003	DCM	50	58% (1:1)
16	2/Et$_2$AlCl	-78, 0.03	Hexano	60	27% (1:1)
17	2/Et$_2$AlCl	10, 0.03	Benceno	45	54% (1:0.8)
18	2/Et$_2$AlCl	-78, 0.03	Tolueno	45	68% (1:1)
19	2/Et$_2$AlCl	-78, 0.03	TBME	50	4% (1:1)
20	2/Et$_2$AlCl	-78, 0.03	THF	210	ND
21	2/Et$_2$AlCl	-30, 0.03	DCE	30	40% (1:1.2)
22	2/Et$_2$AlCl	-20, 0.03	CCl$_4$	30	56% (1:0.8)
23	2/Et$_2$AlCl	-60, 0.03	CHCl$_3$	70	59% (1:1.1)
24	2/Et$_2$AlCl	-40, 0.03	CH$_3$CN	65	ND
25	0.5/Me$_2$AlCl	-78, cat	DCM	100	53% (1:1)
26	0.2/Me$_2$AlCl	-78, cat	DCM	180	32% (1:1.7)
27	0.2/InI$_3$	TA, cat	DCM	15	28 % (1:0.8)
28	0.2/InCl$_3$	TA, cat	DCM	55	12% (1:2)
29	0.2/GaCl$_3$	TA, cat	DCM	5	56% (1:1)
30	0.2/GaI$_3$	TA, cat	DCM	5	53% (1:1)
31	0.2/GaBr$_3$	TA, cat	DCM	5	54% (1:1)
32	0.1/GaCl$_3$	TA, cat	DCM	5	55% (1:1)
33	0.01/GaCl$_3$	TA, cat	DCM	5	51% (1:1)

De manera adicional, las condiciones descritas en las entradas 5 y 6 permitieron la obtención del halimano **3** con doble enlace en posición C1-C10 en un 14 y 15% de rendimiento respectivamente (R=butil) (Figura 58).

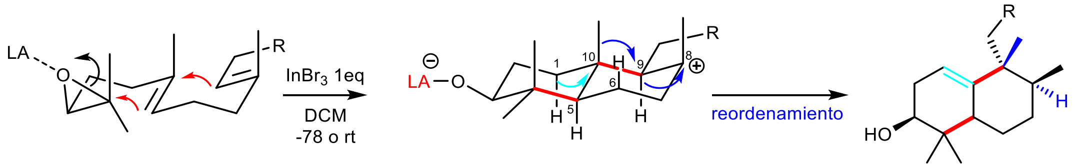


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Figura 58. Síntesis de halimanos con doble enlace en C1-C10.

II. Isotuberculosinol.

Como se ha mencionado anteriormente, isotuberculosinol actúa como factor de virulencia de la bacteria *Mycobacterium tuberculosis*[65]. Esta bacteria es conocida por producir la tuberculosis, una gran fuente de morbilidad y mortalidad produciendo alrededor de 2 millones de muertos al año[64]. La aparición y el aumento de cepas multirresistentes, tanto a antibióticos como a fármacos ha suscitado una gran preocupación en la comunidad médica, necesitándose nuevos métodos para hacer frente a la enfermedad. Una de las nuevas terapias que se están investigando hoy día son aquellas dirigidas a anular el factor de virulencia de la bacteria. El factor de virulencia está ligado a mecanismos utilizados por la bacteria para evadir el sistema inmunológico humano y llevar a cabo su ciclo vital. Se cree que la bacteria se encierra y replica dentro de los macrófagos alveolares, encapsulándose utilizando restos del fagosoma en el que la bacteria fue envuelta. Isotuberculosinol tiene la función fisiológica de servir como agente inmunomodulador en la supresión de la maduración fagosómica y del compartimento endocítico, impidiendo que la bacteria sea digerida por el lisosoma dentro del macrófago alveolar infectado (Figura 59) y así, continuar con su ciclo de vida[65]. El descubrimiento de isotuberculosinol, abre una puerta al reconocimiento del sitio de unión de esta molécula con el macrófago huésped y así crear un mecanismo para anularla.

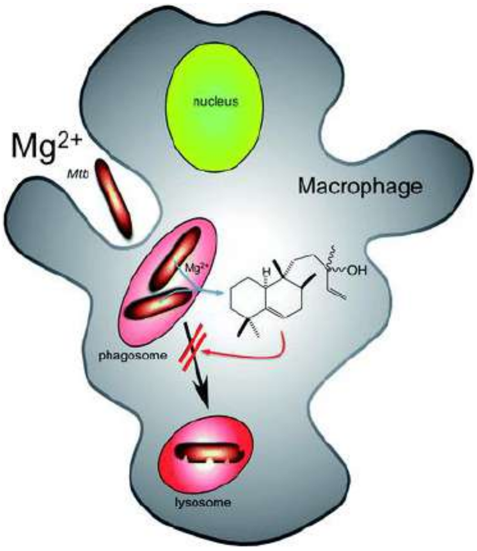

Figura 59. Ilustración tomada de Mann and Peters 2012[65]*. En ella se aprecia la envoltura fagocítica de la bacteria Mycobacterium tuberculosis (Mtb) y como la liberación de isotuberculosinol impide la digestión de la misma interrumpiendo el proceso de maduración lisosomal dentro del macrófago.*

III. Síntesis biomimética de isotuberculosinol.

El producto de partida del proceso sintético es el geranilgeraniol extraído de la planta *Bellardia trixago*, de la cual se obtuvo y siguiendo el protocolo descrito en la síntesis del producto natural (–)-2,15-valparadieno se sintetizó acetato de geranillinalilo. Este fue epoxidado con NBS en agua y medio básico para obtener el compuesto **4.** Poniendo en práctica las condiciones optimizadas para la síntesis de halimanos y utilizando como producto de partida el derivado monoepoxidado del acetato de geranil linalilo **4**, se consiguió obtener un 53% de mezcla de diastereomeros (**2a** y **2b**) provenientes de procesos de ciclación y reordenamiento, encontrándose en una proporción 1:2.5 (Figura 60). De los dos isómeros, **2a** presenta la misma estereoquímica en C-8 y C-9 que isotuberculosinol. El par de epimeros **2a** y **2b** fue desoxigenado mediante el procedimiento de Barton-McCombie y reducido con LAH generando isotuberculosinol y su epímero en 8 en un 65% de rendimiento en los últimos 3 pasos y 10% de rendimiento global. Por otra parte, el diastereómero **2b** comparte la misma estereoquímica en C-8 y C-9 que el producto natural viterofolin E. La reducción con hidruro de aluminio y litio permitió la síntesis completa de viterofolin E como una mezcla de epímeros en C-13 (**5b**), y con un 34% de rendimiento desde el epóxido **4**.

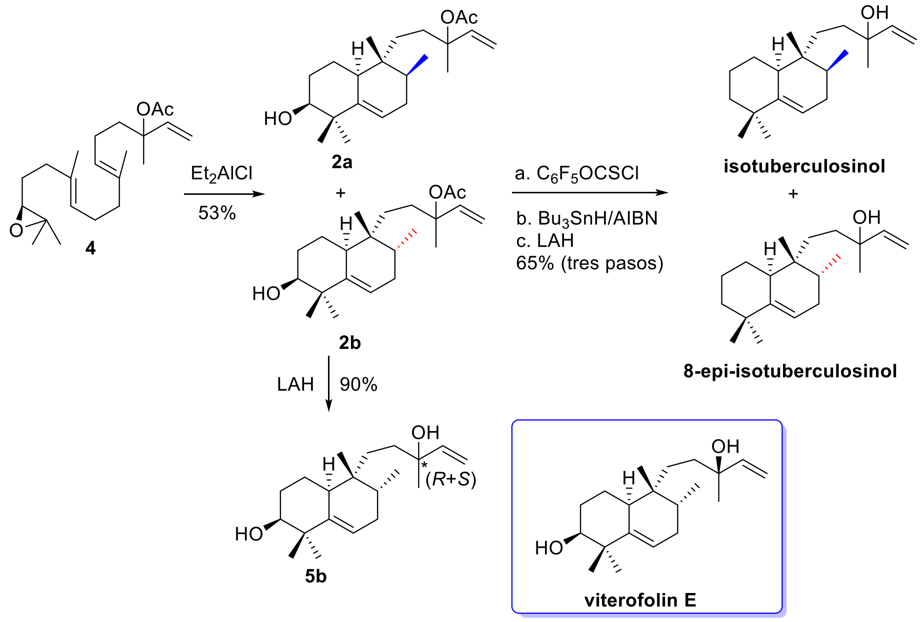

Figura 60. Síntesis de isotuberculosinol, 8-epi-tuberculosinol y viterofolin E.

4.4 Síntesis bioinspirada de (–)-platensimicina.

Hoy en día existe una gran preocupación de cara al futuro de los antibióticos, pues ya sea por una mala praxis en el uso de antibióticos o por mutación genética, van apareciendo nuevas cepas de bacterias polirresistentes a los medicamentos que tenemos para combatirlas. En 2017, la organización mundial de la salud emitió una lista de bacterias, para las que se necesitan urgentemente nuevos antibióticos, debido a la aparición de cepas multirresistentes peligrosas para la salud humana. Esta lista está dividida en tres categorías según prioridad (Tabla 2). Apareciendo de la siguiente manera[119].

Tabla 2. Lista OMS de patógenos prioritarios para la I+D de nuevos antibióticos.

Prioridad 1: CRÍTICA	
Acinetobacter baumannii	Resistente a los carbapenémicos.
Pseudomonas aeruginosa	Resistente a los carbapenémicos.
Enterobacteriaceae	Resistente a los carbapenémicos, productoras de ESBL.
Prioridad 2: ELEVADA	
Enterococcus faecium	Resistente a la vancomicina
Staphylococcus aureus	Resistente a la meticilina, con sensibilidad intermedia y resistencia a la vancomicina
Helicobacter pylori	Resistente a la claritromicina
Campylobacter spp	Resistente a las fluoroquinolonas
Salmonellae	Resistente a las fluoroquinolonas
Gonorrhoeae	Resistente a la cefalosporina, resistente a las fluoroquinolonas
Prioridad 3: MEDIA	
Streptococcus pneumoniae	Sin sensibilidad a la penicilina
Haemophilus influenzae	Resistente a la ampicilina
Shigella spp.	Resistente a las fluoroquinolonas

Actualmente los mecanismos de acción de los antimicrobianos son variados, actuando en distintas áreas de la célula objetivo. Algunos de estos agentes antibióticos los podemos encontrar actuando en contra de la formación de la pared celular bacteriana, interfiriendo en la síntesis de peptidoglucanos, elementos básicos para la creación de la pared bacteriana. Estos déficits de peptidoglucanos llevarían finalmente a la lisis de la célula bacteriana. A este grupo pertenecen los antibióticos beta-lactámicos, glucopéptidos (vancomicina, teicoplanina y avoparcina), bacitracina y estreptograminas (virginiamicina, quinupristina-dalfopristina). Las poliximinas, actúan como agentes activos rompiendo las membranas fosfolipídicas de las bacterias Gram-negativas. Otros poseen un mecanismo de actuación interfiriendo en la síntesis de proteínas a nivel del complejo ribosómico, como las tetraciclinas o el cloranfenicol y otros actúan directamente en la formación de los ácidos nucleicos o impidiendo el superenrollamiento del ADN bacteriano. En la figura 61 se muestran las diferentes estructuras bacterianas y algunos de los ejemplos de antimicrobianos que actúan a esos niveles[120].

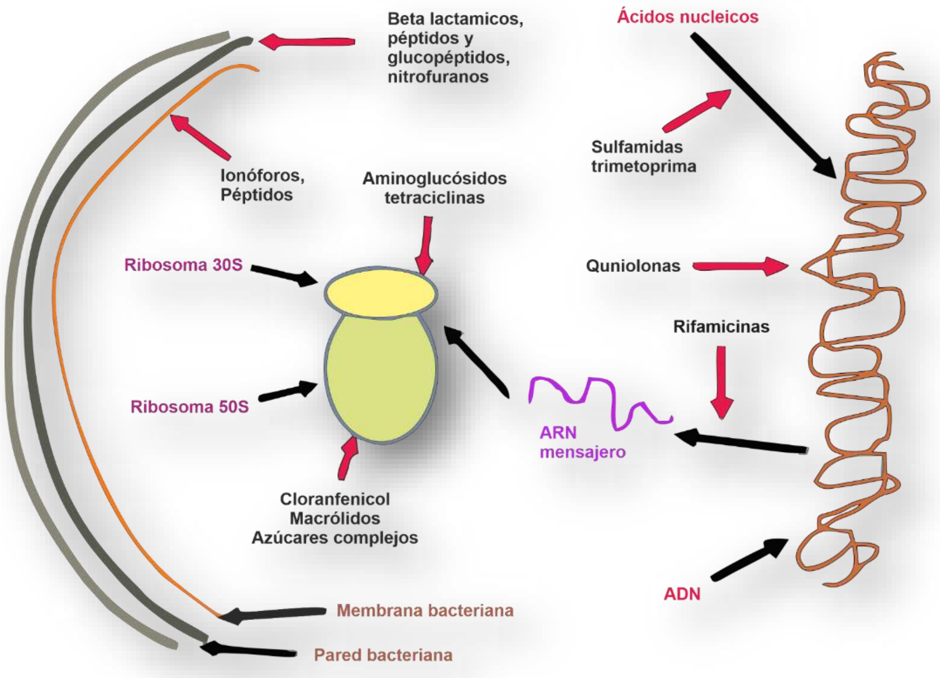

Figura 61. Flecha negra. Partes de la célula bacteriana. Flecha roja. Estrategias de acción de los antibióticos frente a los diferentes orgánulos de la célula bacteriana. Fuente www.who.int.

IV. (−)-Platensimicina, mecanismo de acción.

La platensimicina (Ptm), desde su descubrimiento en 2006 en la bacteria *Streptomyces platensis*, puede que haya sido el antibiótico más estudiado en los últimos 15 años. Aparece entre cientos de comunicaciones científicas, en el título de 22 artículos de revisión, ya sean de síntesis totales[4,11,78,89,90,93], formales[92,121,122], mencionando la biogénesis[70–75,123] o el mecanismo de acción[124–127]. Y es que no es escasa la importancia que posee, puesto que su novedoso mecanismo de acción abre una nueva puerta a la búsqueda de nuevas estrategias contra las bacterias más resistentes a los antibióticos actuales. Ptm para algunas bacterias es letal a concentraciones mínimas, presentando en el caso de *Staphyloccocus aureus* una inhibición de la enzima FabF con un IC_{50} de 48 nanomolar. Esta enzima es crucial en la síntesis de ácidos grasos.

El acceso a la cadena de síntesis de ácidos grasos (FASII), inhibiendo la β-cetoacil-ACP sintasa (FabF) impide la condensación de malonil-ACP con Acetil-CoA para formar β-cetobutiril-ACP y dióxido de carbono, siendo este proceso de condensación esencial para biosíntesis de ácidos grasos (Figura 62).

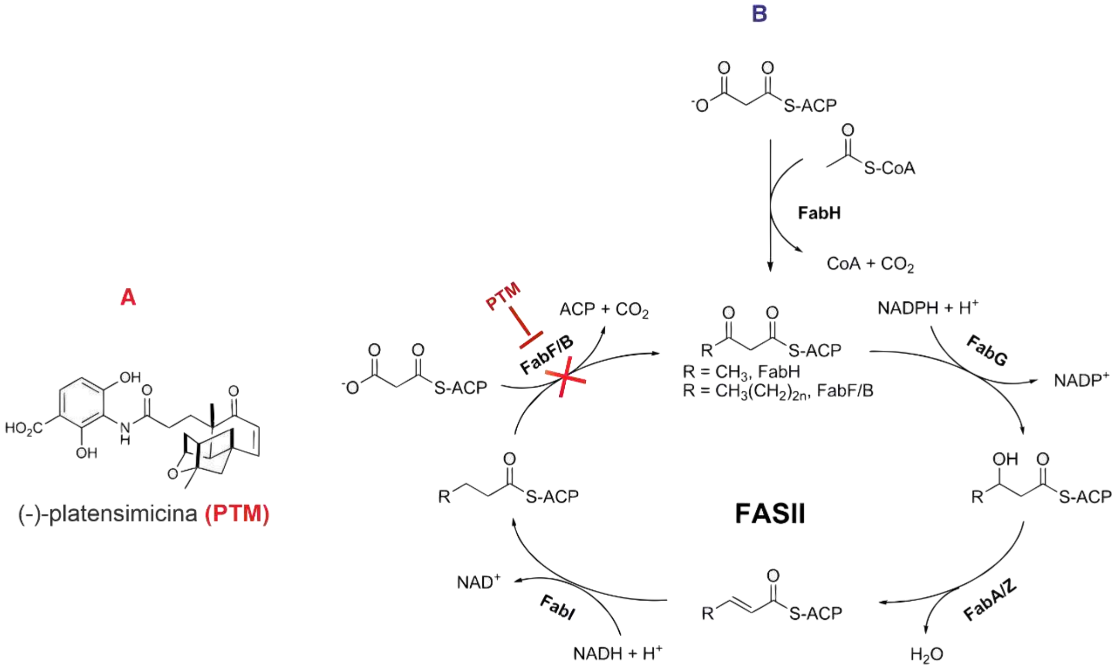

Figura 62. Mecanismo de acción de la platensimicina (PTM) sobre FabF. Fuente Peterson et al. 2014[125].

La figura muestra el mecanismo de acción de la Ptm sobre el complejo enzimático FASII involucrado en la síntesis de ácidos grasos de las bacterias.

II. Biosíntesis de Platensimicina.

Debido a la gran potencia antimicrobiana demostrada por Ptm, su nula toxicidad en mamíferos[127] y su novedoso mecanismo de acción se han desarrollado investigaciones centradas en conocer los mecanismos biosintéticos utilizados por *S. platensis*. Ello redundaría en la búsqueda de nuevas estrategias biotecnológicas o de síntesis química que supongan una mayor rentabilidad que la escasa producción ofrecida por la bacteria. Como resultado, hasta el momento se conoce gran parte del proceso biogenético, así como las enzimas y moléculas intermedias implicadas en el mismo[70–74,82,97,123] (Figura 63).

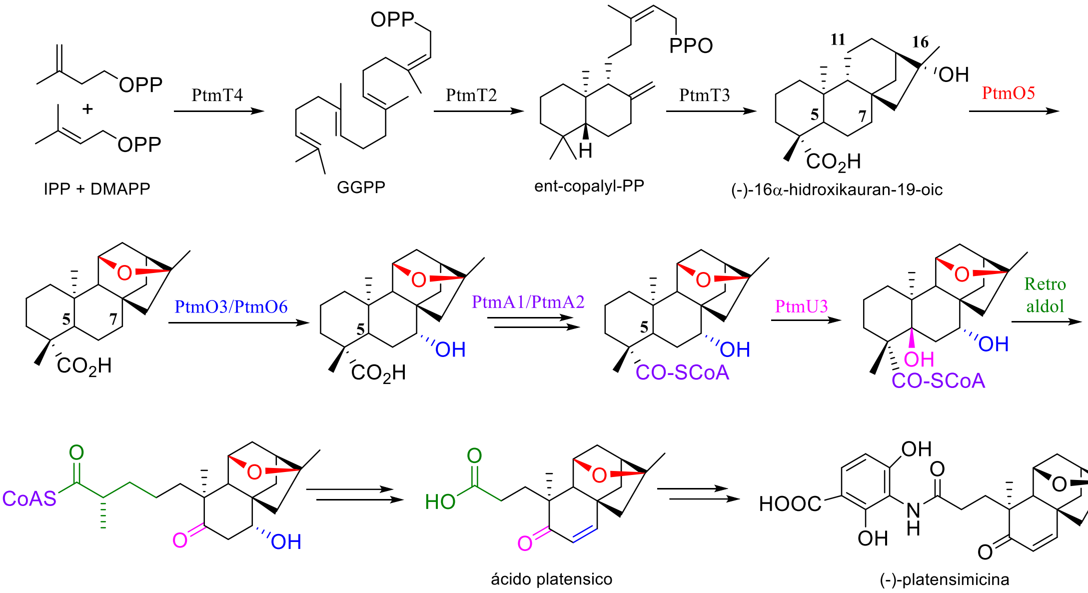

Figura 63. Esquema biosintético de (–)-platensimicina.

La ruta biosintética de la platensimicina, en lo referente a la parte terpénica, sigue la ruta no mevalónica del metileritritol que origina los intermedios C-5, isopentenil pirofosfato y dimetilalil pirofosfato. Estos van a sufrir una serie de transformaciones enzimáticas que incluyen preniltransferasas y ciclasas para formar el kaurano hidroxilado en C-16. En estos pasos es de destacar la acción enzimática de PtmT3 sobre pirofosfato de *ent*-copalilo. A continuación, la enzima PtmO5, conducirá a la formación del O-heterociclo furánico característico de Ptm, a través del cierre del diol formado en C-11 y C-16. La hidroxilación en el carbono C-7 por las enzimas PtmO3 y PtmO6 está relacionado con el doble enlace que formará la cetona α–β insaturada del producto natural final, por otro lado, la enzima PtmU3 hidroxilará en C-5, funcionalización involucrada en la apertura del anillo A para el que se propone un mecanismo retro aldólico.

III. *Síntesis bioinspirada de (–)-platensimicina.*

La estrategia de síntesis de Ptm planteada aquí fue resultado del conocimiento de la participación de moléculas con esqueleto de kaurano como intermedios en su biosíntesis. A partir de ahí se pensó en la forma de llevar a cabo la degradación del anillo A y la formación del furano típicos de esta molécula. Las moléculas que se adecuaban como materiales de partida con los requerimientos necesarios, tanto en funcionalidad como en estructura y estereoquímica, fueron los diterpenos ácido *ent*-kaurenoico y ácido grandiflorénico (Figura 64). Estos productos naturales contaban, además, con la posibilidad de ser obtenibles desde fuentes vegetales accesibles, como son la especie de planta sudamericana *Stevia lucida* que proporcionaba ambos sintones homoquirales en cantidades aceptables,[77] y el girasol. Este último, *Helianthus annuus*, es una de las plantas cultivadas en mayor cantidad en todo el mundo, alcanzando una producción anual de unos 48 millones de toneladas[128]. El desgranado de la pipa genera mayoritariamente un residuo constituido por las cabezas florales, en donde se ha publicado la presencia de ácido kaurenoico[76,99]. Se descartó la compra directa de estos sintones por su más que elevado precio comercial, que llega a superar los 300€ por miligramo de cada producto natural, y en su lugar se obtuvieron a partir de *Stevia lucida* proveniente de Venezuela (colaboración con el Prof. J.M. Amaro, Universidad de los Andes (Mérida, Venezuela), y por la puesta a punto de un proceso de extracción y fraccionamiento desde cabezas de girasol.

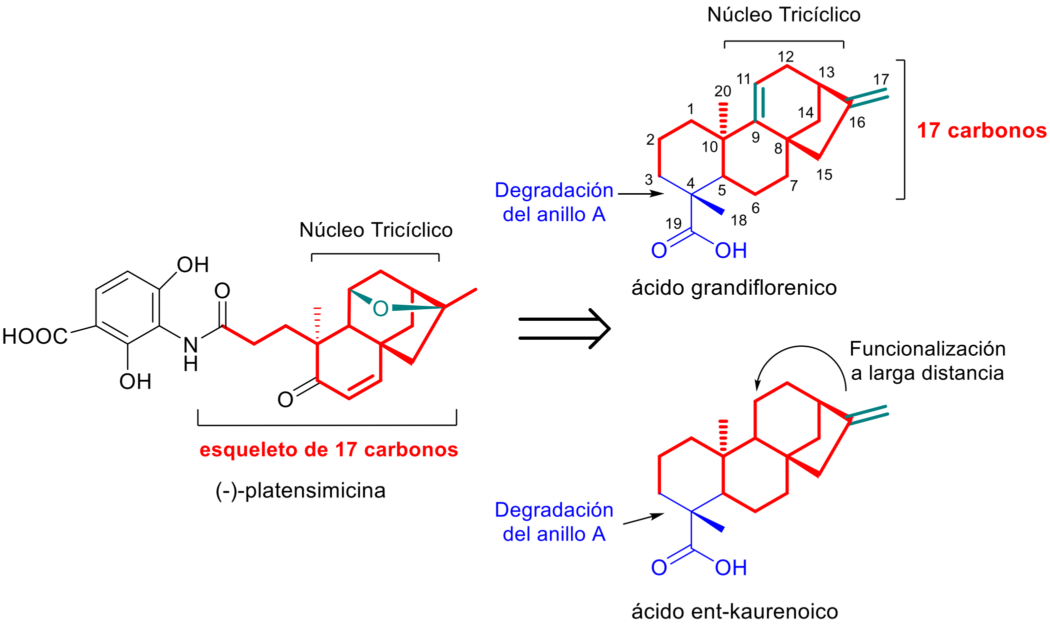

Figura 64. Similitudes entre platensimicina y los acidos grandiflorénico y ent-kaurenoico.

La estrategia sintética ideada permitió definir un esquema retrosintético con los pasos a seguir en la sintesis del antibiotico (–)-Ptm (Figura 65). El último de los pasos es la formación de la amida, que está descrita por Nicolaou en su sintesis total de Ptm en 2006 a partir del ácido platensico[78]. Por lo tanto la obtención de éste constituiría una síntesis formal de Ptm. Ácido platlaténsico se obtendría por degradación de la olefina **22** generada al descarboxilar el ácido carboxilico **16**. En este intermedio previamente se ha formado el anillo de furano via hidroboracion de las olefinas presentes en acido grandiflorenico o hidroboracion y tratamiento con tetracetato de plomo en la vía de síntesis que parte del ácido *ent*-kaurenoico.

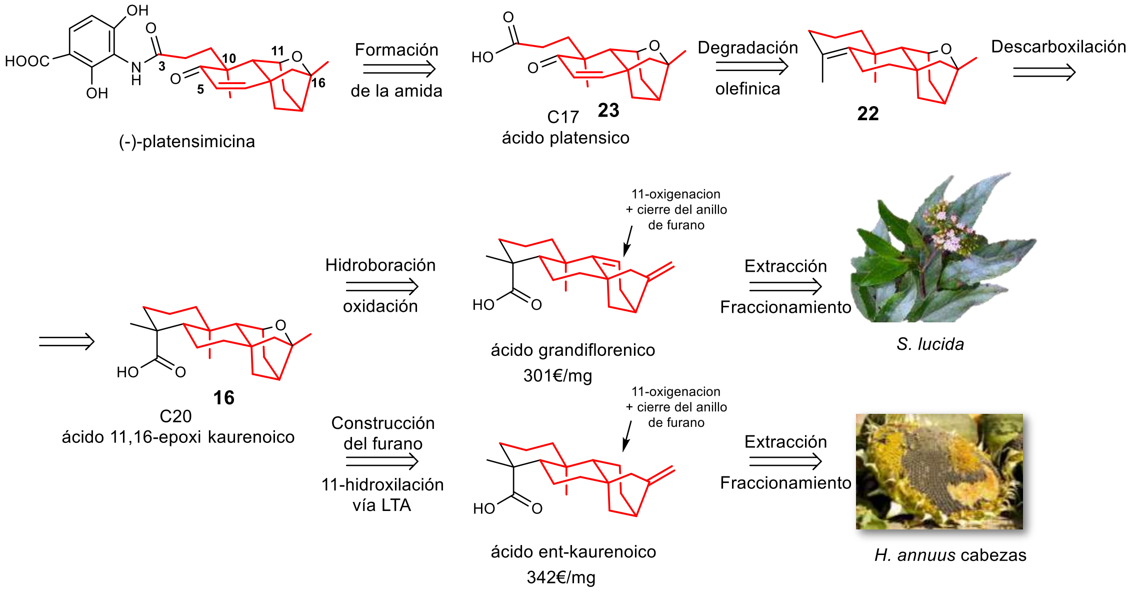

Figura 65. Esquema retrosintético en la síntesis de (–)-platensimicina.

Previamente al inicio del desarrollo de la síntesis se llevó a cabo un estudio para el aislamiento selectivo de ácido *ent*-kaurenoico desde las cabezas florales de *Helianthus annuus* (Barrero, A.F. et al, resultados no publicados). El proceso permite la extracción y obtención mediante fraccionamiento de una mezcla de ácidos kaurenoico y trachilobanoico con un rendimiento próximo al 50% sobre el peso de extracto.

El protocolo diseñado para abrir y degradar el anillo A de la molécula es un paso crucial en la síntesis de Ptm. Durante el proceso, no sólo han de eliminarse los carbonos C-4, C-19 y C-20 del esqueleto de kaurano, sino que además han de obtenerse los grupos funcionales cetona y ácido propios del ácido platénsico en los carbonos C-5 y C-3 del diterpeno. Para la puesta a punto de este proceso se decidió utilizar el dihidroderivado del ácido *ent*-kaurenoico (**1**) como modelo. La descarboxilación mediada por tetracetato de plomo (LTA) de este dihidroderivado originó una mezcla de tres olefinas isomericas y el acetoxiderivado correspondiente con buen rendimiento. Esta mezcla se isomerizó en medio ácido con *p*TsOH con rendimiento próximo a cuantitativo a la olefina tetrasustituida **4**. A continuación, se consiguió llevar a cabo la ruptura oxidativa del anillo por tratamiento del metil ciclohexeno **4** con ozono del anillo para dar la dicetona A rinde **5** (Figura 66). La condensación aldólica intramolecular que sufre 5 por tratamiento en medio básico dio lugar a la ciclopentenona **6**. A partir de **6**, merece ser destacada el resultado de su reacción con ozono, que supuso, no sólo la eliminación requerida de dos átomos de carbono, sino también la instalación las funciones ácido y cetona, anticipadas en el diseño sintético. Se obtuvo así el éster **7**, una vez tratado con diazometano el crudo de reacción. La deshidrogenación de este éster metilico con PhSeCl/H_2O_2 permitió acceder al 16,17-dihidro derivado del ácido platensico **8**. En su conjunto se abrió un camino eficiente para la degradación de ácidos kaurenoicos en el anillo A en seis etapas y un rendimiento global del 53%.

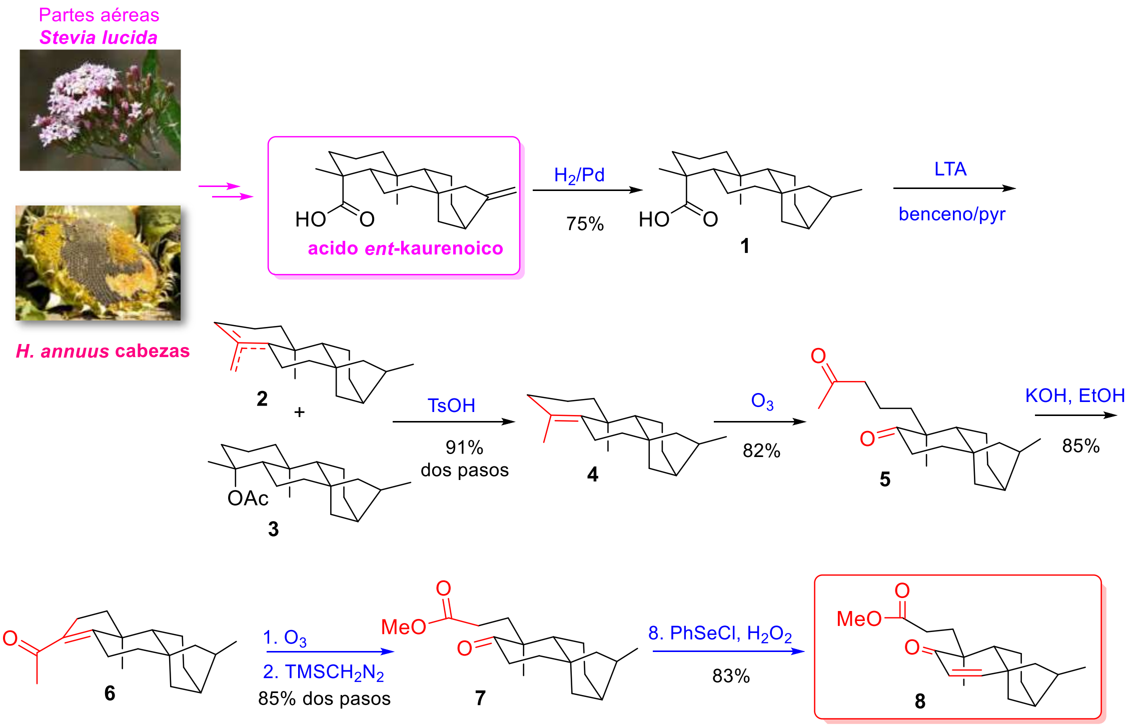

Figura 66. Modelo de degradación del anillo A.

Cabe destacar que el modelo ideado de síntesis de degradación del anillo A, es aplicable para la síntesis de todas aquellas moléculas que posean dicho anillo degradado y originariamente posean en su estructura un anillo A hexacíclico con un ácido carboxílico derivado del ácido propanoico (Figura 67).

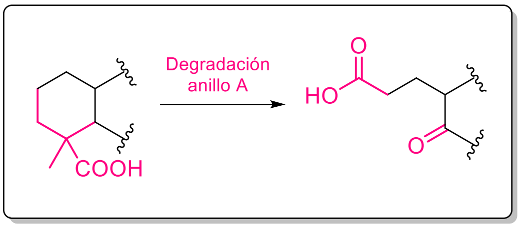

Figura 67. Aplicación del modelo de degradación del anillo A.

Una vez optimizadas las condiciones para la degradación del anillo A de derivados del ácido *ent*-kaurenoico, se comenzó la síntesis hacia el ester metílico del ácido platensico (síntesis formal de Ptm), utilizando los ácidos kaurenoico y grandiflorénico (Figura 68) como productos de partida. Las síntesis, que en comienzo evolucionan en paralelo a partir de los dos ácidos mencionados, confluirán en el intermedio **11** que posee un anillo tetrahidropiránico.

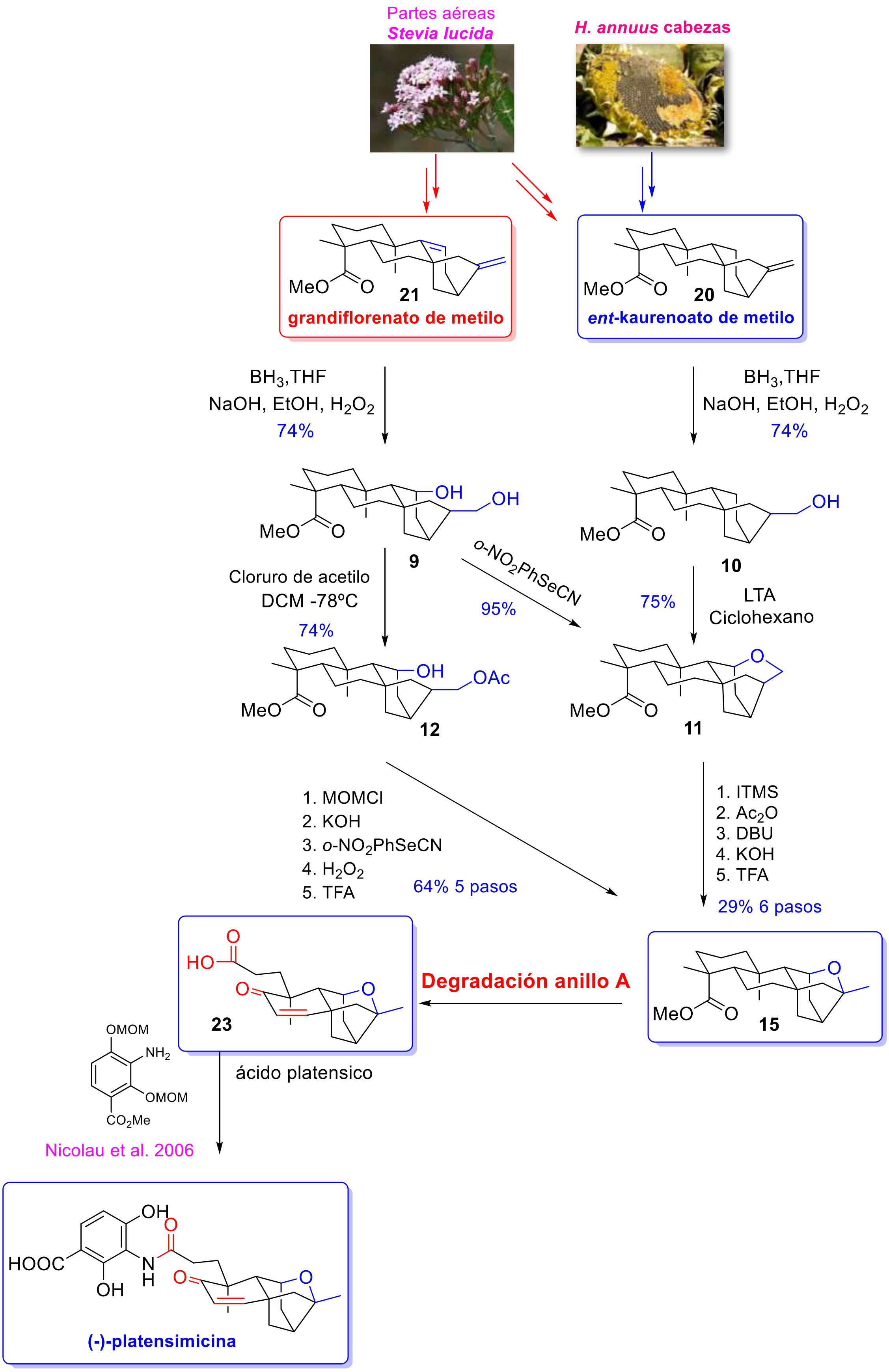

Figura 68. Rutas de síntesis de (–)-platensimicina.

La síntesis de ácido platénsico a partir de ácido *ent*-kaurenoico comienza con la obtención del derivado metilado **20**. El tratamiento de **20** con BH_3/THF seguido de oxidación transcurre de manera regio- y estereoselectiva por la cara menos impedida α para dar el alcohol primario **10** (74%). La funcionalización a larga distancia requerida para formar el tetrahidropirano **11** se logró por la acción del reactivo tetracetato de plomo en ciclohexano a reflujo (75 % de rendimiento). El mecanismo propuesto para esta transformación se recoge en la Figura 69.

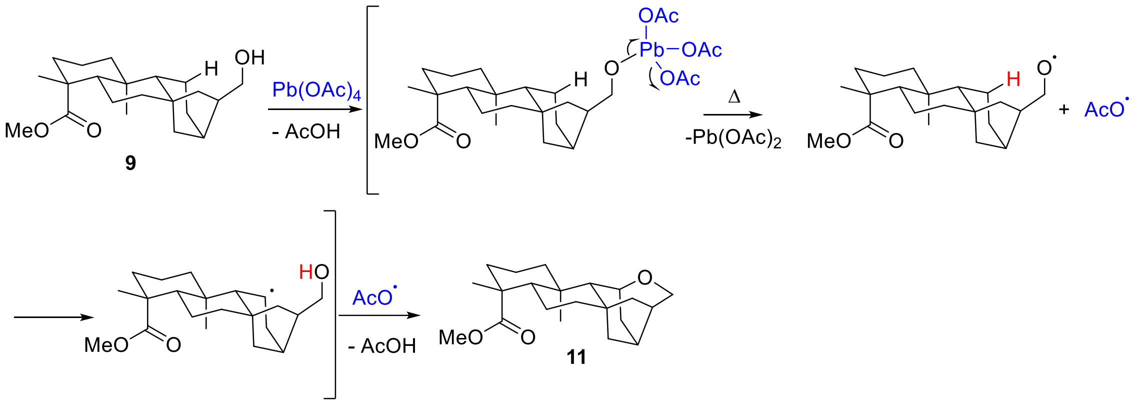

Figura 69. Mecanismo propuesto para la funcionalización a larga distancia con tetracetato de plomo.

Tras mucha experimentación, se consiguió la apertura del heterociclo **11** con yoduro de trimetil sililo para generar, tras acetilación del intermedio iodoalcohol **12** inestable, el iodoacetato **13** con un 43% de rendimiento. La eliminación del iodo con DBU produjo la olefina exocíclica **14** al 81% de rendimiento. Finalmente, la hidrolisis del acetato y posterior tratamiento del alcohol con ácido trifluoroacético supuso la formación del tetrahidrofurano **15** con un rendimiento del 91%. El tratamiento con ioduro de litio permitió obtener el ácido **16** (Figura 70).

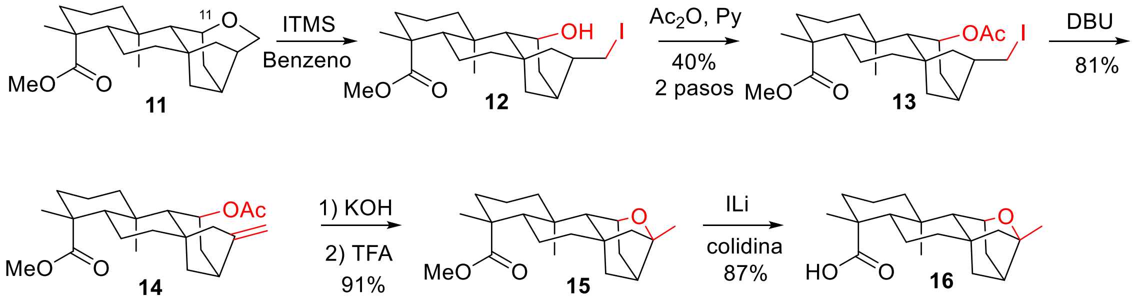

*Figura 70. Síntesis del furano **16** a partir del piranoderivado **11**.*

La ruta del ácido grandiflorénico hacia el intermedio común **16** se inició con la doble hidroboración regioselectiva de los enlaces olefínicos del metil grandiflorenato (**21**). Teniendo en cuenta los impedimentos estéricos en ambas caras del enlace trisustituido entre los carbonos C9-C11 y sobre la cara β del metileno, proponemos que el complejo BH_3/THF reacciona primero selectivamente con la cara α de la olefina exocíclica creando un complejo alquil-borano (**I**). Este evoluciona a través de un dialquil-borano cíclico (**II**), después de una hidroboración intramolecular del doble enlace en C9-C11 que sólo es posible por la cara β (Figura 71).

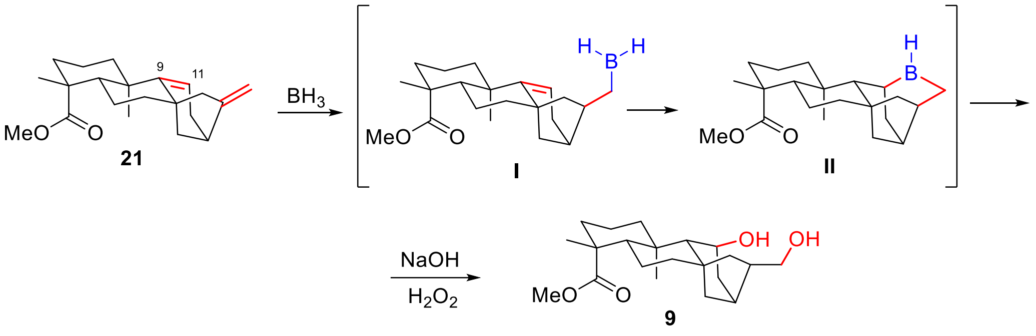

*Figura 71. Mecanismo propuesto para la formación del diol **9**.*

A partir de **9**, se intentó la deshidratación selectiva del alcohol primario utilizando el protocolo de Grieco. Sin embargo, el resultado de la reacción fue de la obtención de nuevo del pirano derivado **11**, el cual se forma como consecuencia de la proximidad espacial de los hidroxilos que colapsan a través de un desplazamiento SN_2 del *o*-nitrofenilseleno derivado. Aunque el éter cíclico **11** es un intermedio en la ruta del ácido kaurenoico para obtener el furano derivado **16**, nos propusimos desarrollar una aproximación alternativa hacia el intermedio clave **16**.

La nueva ruta a partir del diol **9** supone el uso de varios grupos protectores. Comenzamos así con la acetilación selectiva del alcohol primario con cloruro de acetilo a -78 ºC para obtener el acetato **12** (74% de rendimiento), seguida de la protección del alcohol secundario con MOMCl para dar **17** al 96%. La desprotección del acetato en medio básico y posterior eliminación del alcohol primario **18** siguiendo el protocolo de Grieco[107] dio lugar a la formación de la olefina exocíclica **19** con un rendimiento del 68% en tres pasos. Finalmente, el tratamiento con ácido trifluoroacético produjo en un solo paso la desprotección del alcohol secundario y la posterior ciclación hacia el deseado tetrahidrofurano **15** (Figura 72).

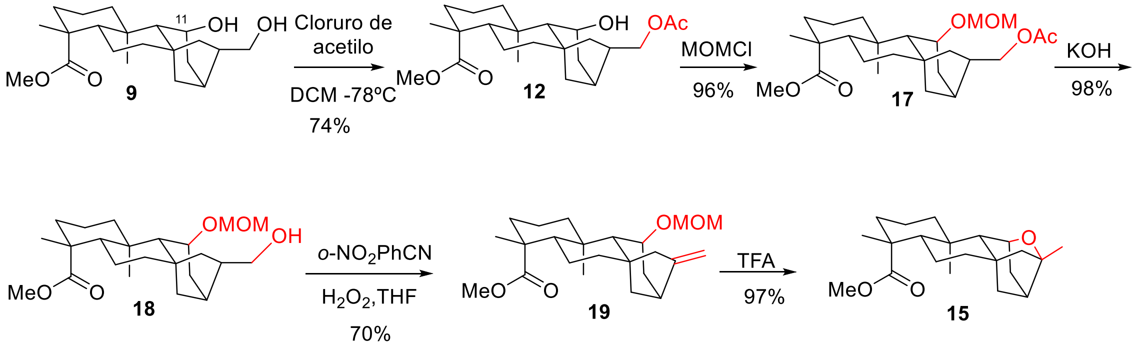

*Figura 72. Ruta alternativa para la síntesis del compuesto **15**.*

Una vez obtenido el ácido **16**, el siguiente paso consiste en aplicar a este compuesto (**16**) las condiciones experimentales optimizadas en la degradación del anillo A en el derivado reducido del ácido kaurenoico (**1**). Siguiendo el procedimiento detallado anteriormente, se llevó a cabo la descarboxilación del ácido carboxílico **16** usando tetraacetato de plomo. A continuación, la mezcla de reacción resultante se hizo reaccionar con *p*TsOH para obtener la olefina **24** con bajos rendimientos. Afortunadamente, cuando el crudo mencionado se trató con yodo molecular, se obtuvo el tetrasustituido **24** deseado con un rendimiento del 78% en las dos etapas. La ozonólisis condujo a la escisión del anillo A proporcionando dicetona **25** con un rendimiento del 85% (Figura 73).

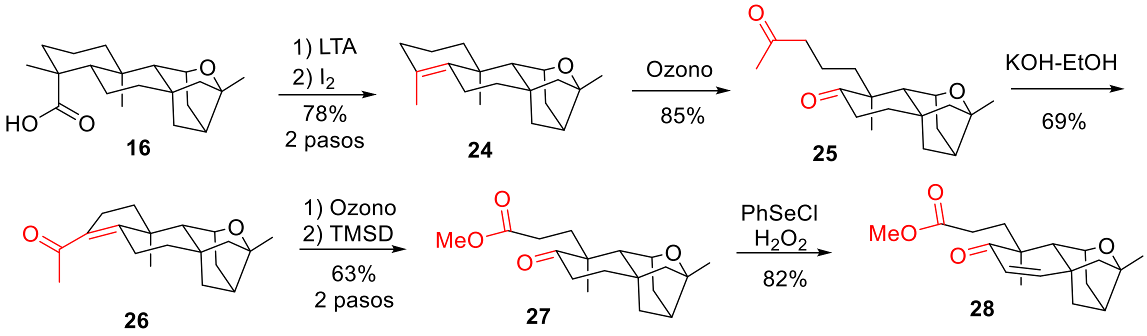

*Figura 73. Síntesis de metil platensinoato (**23**).*

La condensación aldólica intramolecular del compuesto **25** con hidróxido de potasio en etanol proporcionó la enona **26** con un rendimiento del 69%. La ozonolisis de **26** provocó la pérdida de dos átomos de carbono y la generación del éster metílico **27** después de la metilación con trimetilsilil diazometano del ácido correspondiente (rendimiento del 63%, dos etapas). Finalmente, la deshidrogenación de **27** para producir metil platensinoato (**28**) se logró con un rendimiento del 83% utilizando el mismo protocolo PhSeCl / H_2O_2 descrito previamente en el estudio modelo. Dado que el compuesto **28** constituye un intermedio en la síntesis de PTM descrita por Nicolaou en 2009, el enfoque sintético aquí descrito constituye una síntesis enantioselectiva formal de PTM. Cabe señalar que los datos espectroscópicos de nuestro platensinoato de metilo (**28**) coinciden completamente con los descritos por Nicolau et al para el mismo producto.

Se puede concluir que la síntesis de platensinoato de metilo (**28**) desde ácido ent-kaurenoico se describe en 16 etapas con un 3,4% de rendimiento global y desde ácido grandiflorénico en 16 etapas con un rendimiento del 6,5% global.

5 *Conclusiones.*

1. Se ha llevado a cabo una revisión acerca de las estrategias en las que intervienen, síntesis biomiméticas de terpenos con participación de mecanismos de ciclación y reordenamiento, descritas en los últimos 20 años.

2. Se ha desarrollado un proceso biomimético para la síntesis del sesquiterpeno (+)-isodaucano partiendo del sintón natural extraído de *Dittrichia viscosa*, (+)-nerolidol. En este proceso se han buscado las condiciones para por un lado llevar a cabo una doble ciclación radicalaria 6-endo, 7-endo mediante Ti(III) desde un epoxiderivado de nerolidol convenientemente funcionalizado. Sobre el biciclo formado se ha inducido la contracción del anillo de 6 a 5 eslabones mediante PCl_5 que facilita la síntesis. La síntesis del producto final (+)-isodaucano se llevó a cabo en 10 pasos sintéticos y un 3% de rendimiento global.

3. Basado en la misma estrategia anterior se ha llevado a cabo por primera vez la síntesis biomimética y enantioselectiva, de un valparano natural, (–)-2,15-valparadieno, en 12 pasos con un 1,1% de rendimiento. Para ello se ha empleado con éxito el complejo Cp_2TiCl para inducir la ciclación radicalaria biomimética de un epoxigeranillinalol derivado, funcionalizado con OTBS. La reacción origina una cascada de tres ciclaciones con formación de los 3 ciclos en un solo paso. En el proceso de contracción del anillo A con PCl_5, se ha conseguido una formación totalmente regioselectiva del doble enlace terminal inducida por la presencia de la función OTBS que aumenta la acidez del protón correspondiente. La síntesis del producto natural (–)-2,15-valparadieno se ha llevado a cabo en 13 pasos sintéticos y un 1,1% de rendimiento global.

4. Se ha logrado poner a punto y optimizado un proceso dirigido hacia la síntesis biomimética de halimanos, imitando la biosíntesis y el modo de acción de las enzimas sintasas de halimanos, realizando la síntesis con biciclación y tres reordenamientos en una sola etapa con un 71% de rendimiento en el mejor de los casos. Como modelo para esta estrategia se ha empleado mono epóxido de farnesilbutano y diferentes ácidos de Lewis como catalizadores.

5. Las condiciones optimizadas anteriores se han logrado aplicar con éxito para la síntesis biomimética del diterpeno isotuberculosinol, factor de virulencia de *Mycobacterium tuberculosis* en sólo 5 pasos con un 10% de rendimiento total.

6. Se ha desarrollado con éxito un proceso de degradación del anillo A para moléculas con estructuras de ácidos *ent*-kaurenoicos. Utilizando acido 6,17-dihidro kaurenoico consta seis etapas y un rendimiento global del 53%.

7. A partir de los sintones homoquirales ácido grandiflorénico y ácido *ent*-kaurenoico obtenidos desde fuentes naturales, la planta *Stevia lucida* y las cabezas de girasol *Helianthus annuus* se ha llevado la síntesis de platensinoato de metilo, por lo tanto, la síntesis formal bioinspirada del antibiótico natural (–)-platensimicina[78] (Nicolaou en 2006 y 2009). El proceso se ha desarrollado en 16 etapas con un 6,5% de rendimiento global.

6 *Anexos*

6.1 *Supporting information Artículo 2:*

Access to Natural Valparanes and Daucanes: Enantioselective Synthesis of (−)-Valpara-2,15-diene and (+)-Isodaucene.

Access to Natural Valparanes and Daucanes: Enantioselective Synthesis of (–)-Valpara-2,15-diene and (+)-Isodaucene

José F. Quílez del Moral,* Álvaro Pérez, María del Mar Herrador and Alejandro F. Barrero*

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*Corresponding authors: E-mails: afbarre@ugr.es; jfquilez@ugr.es

Supporting Information

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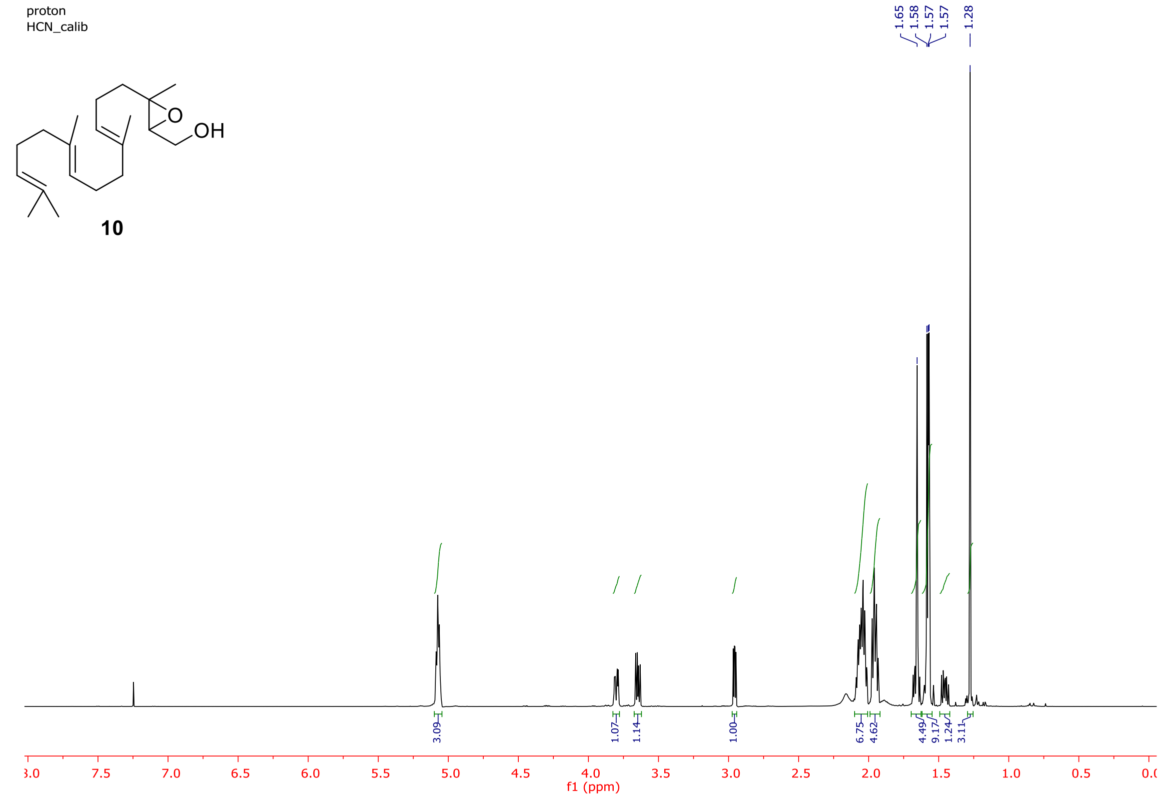
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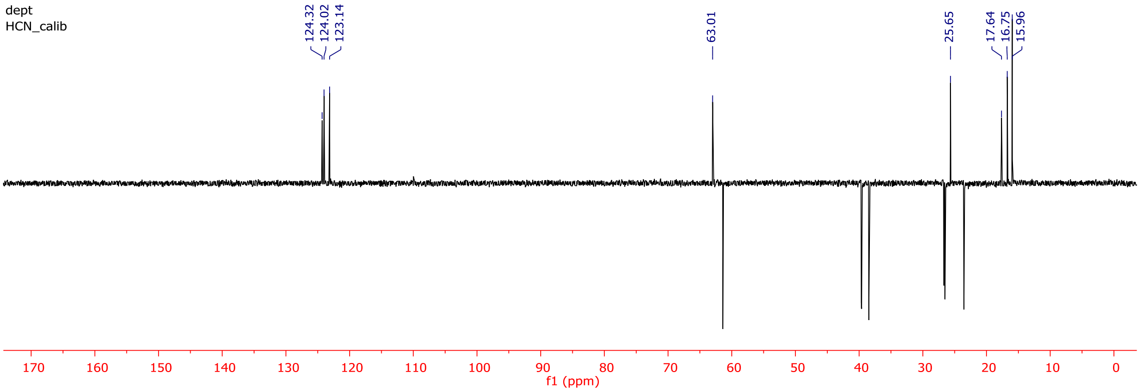
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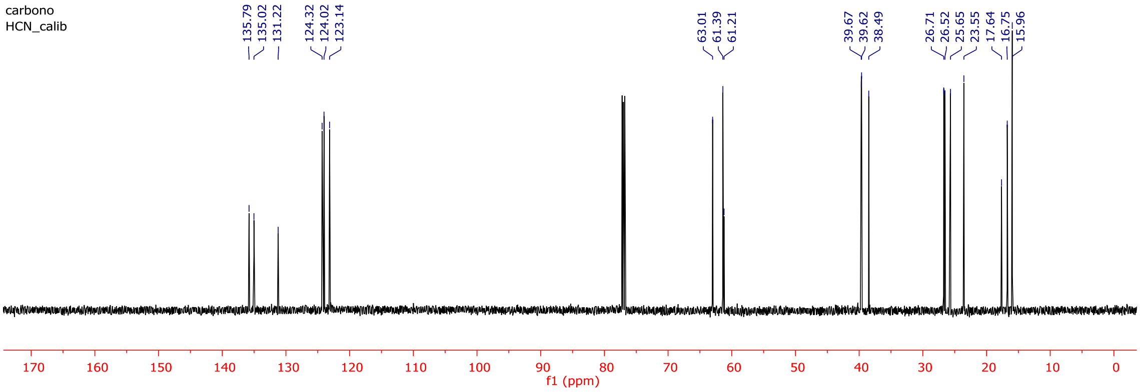
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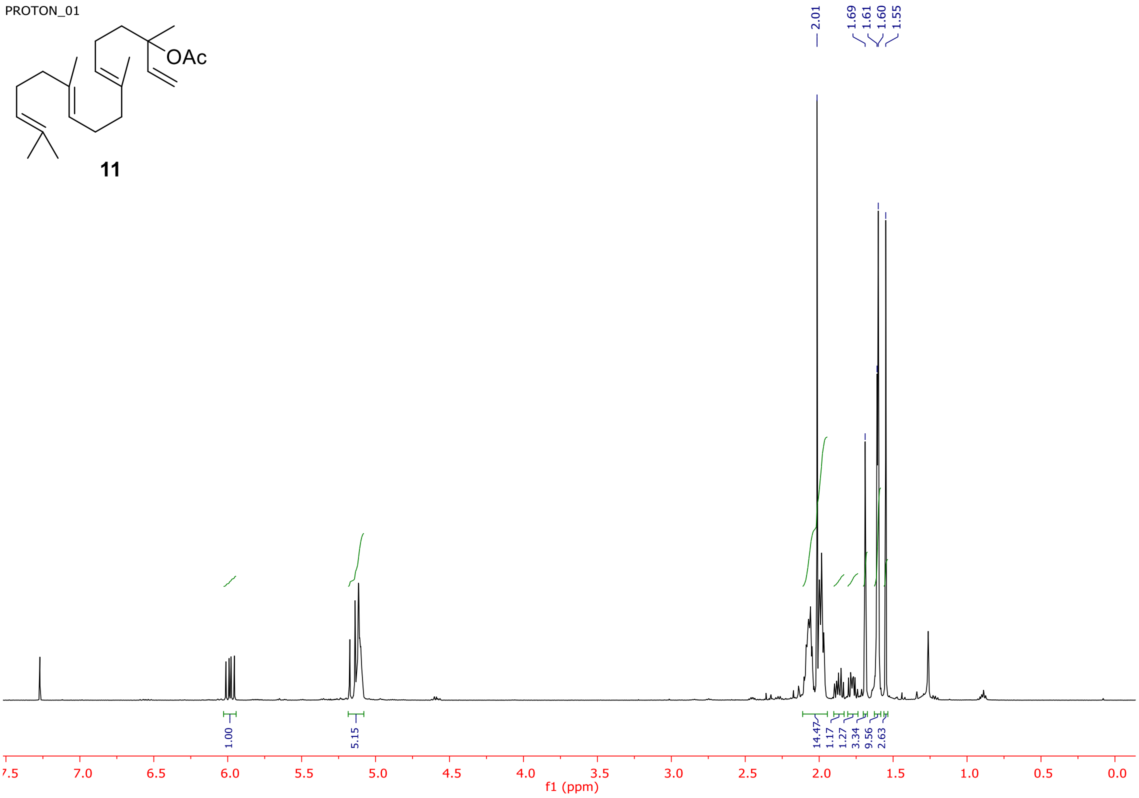
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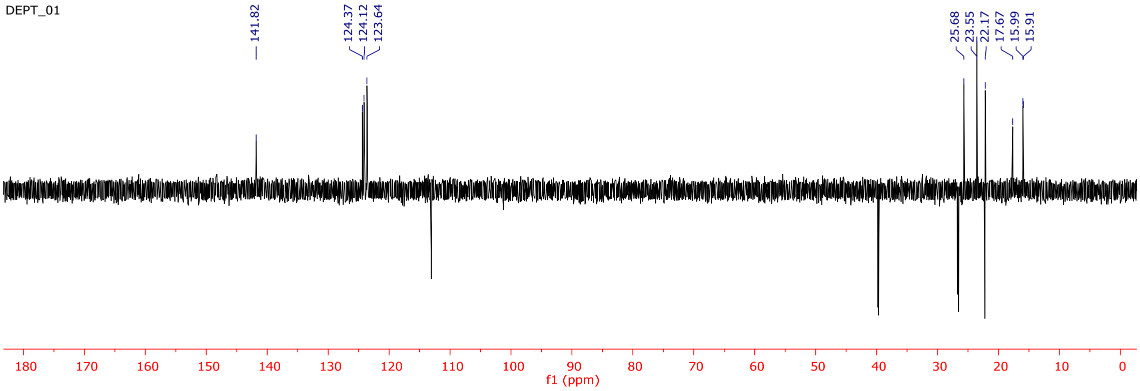
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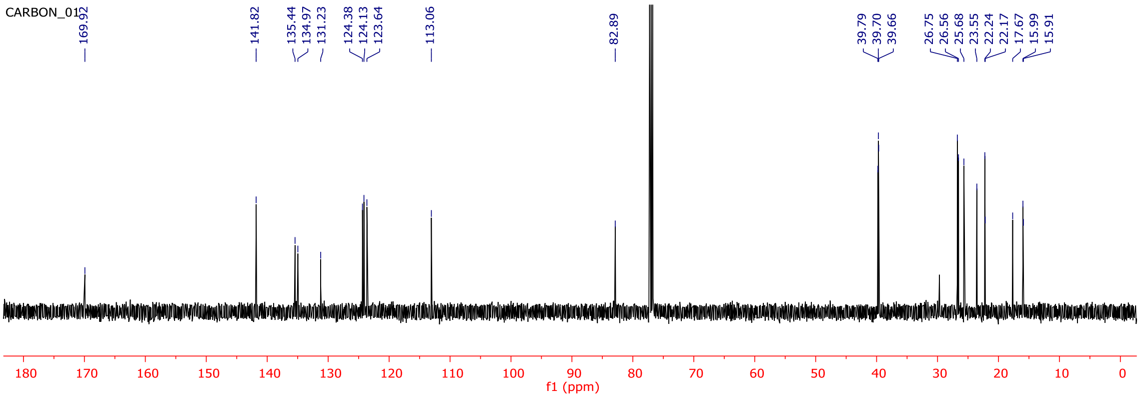
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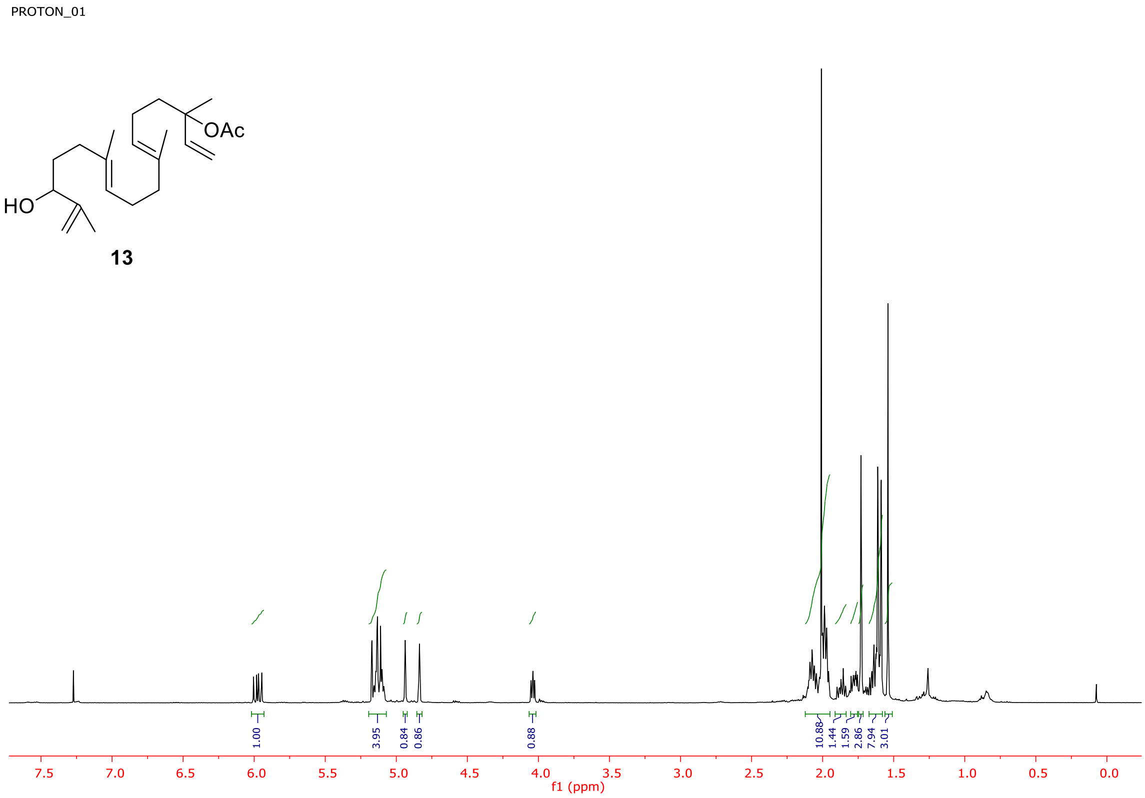
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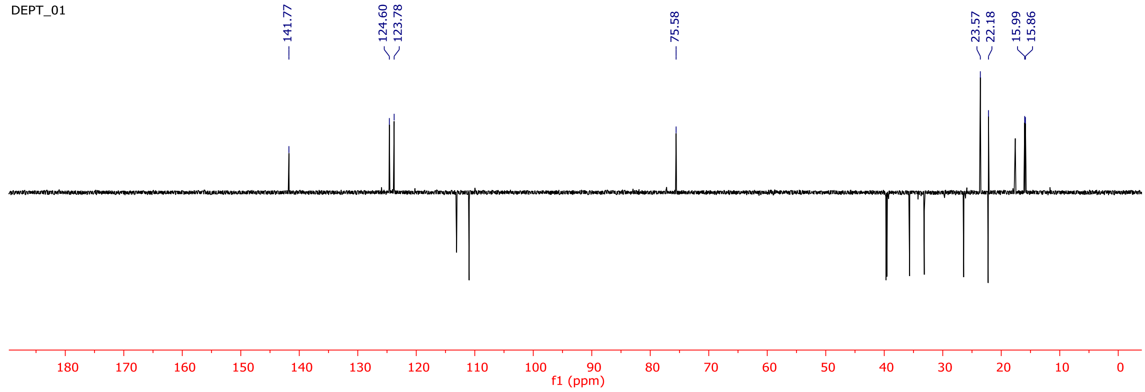
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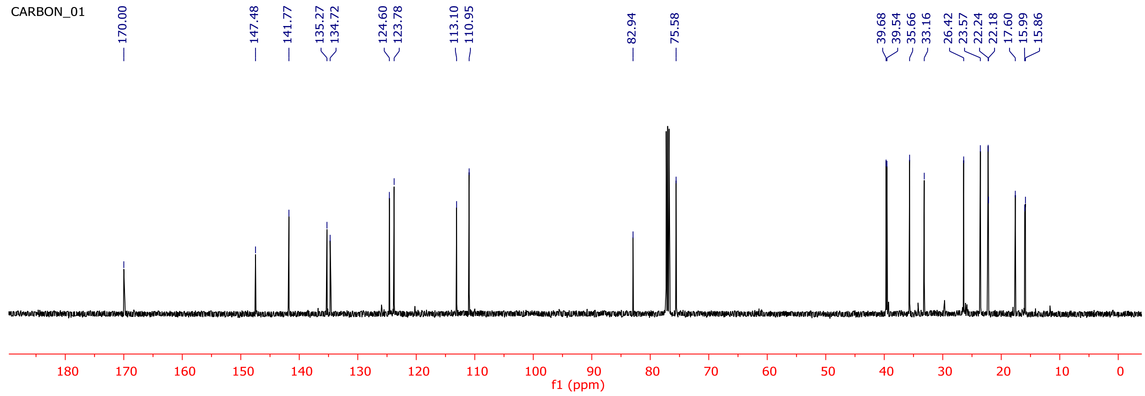
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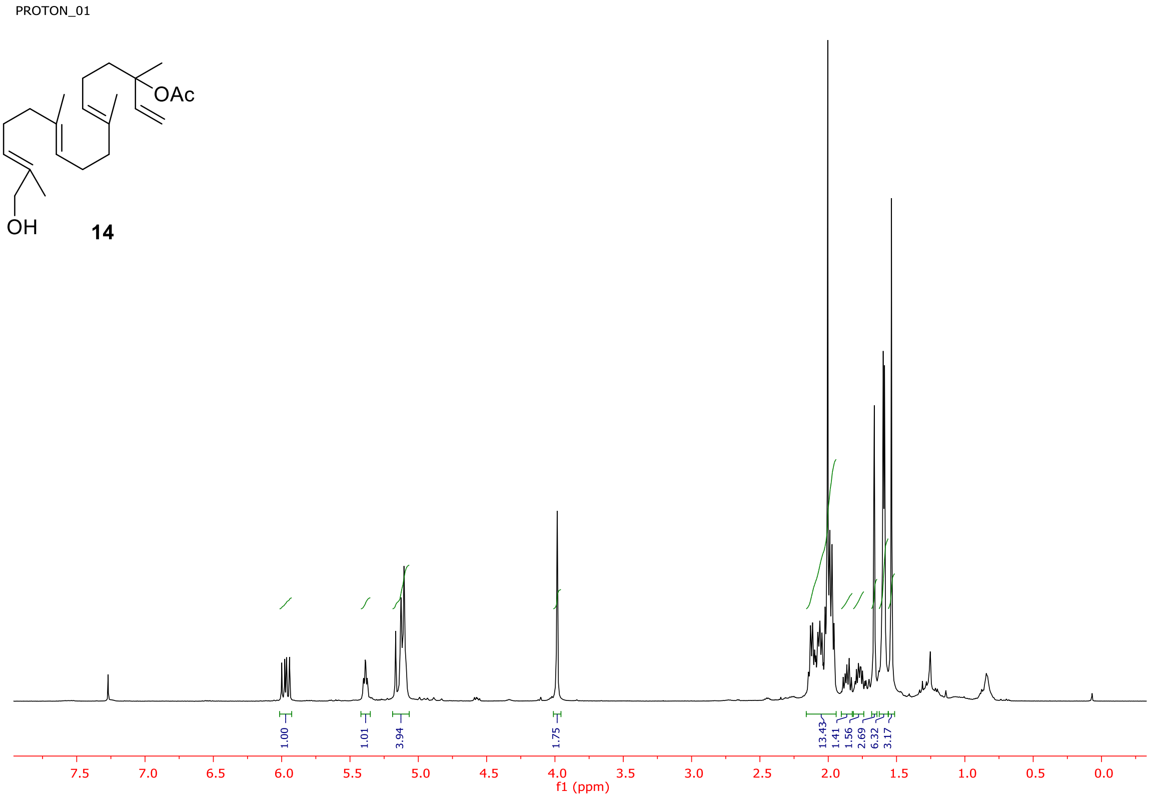
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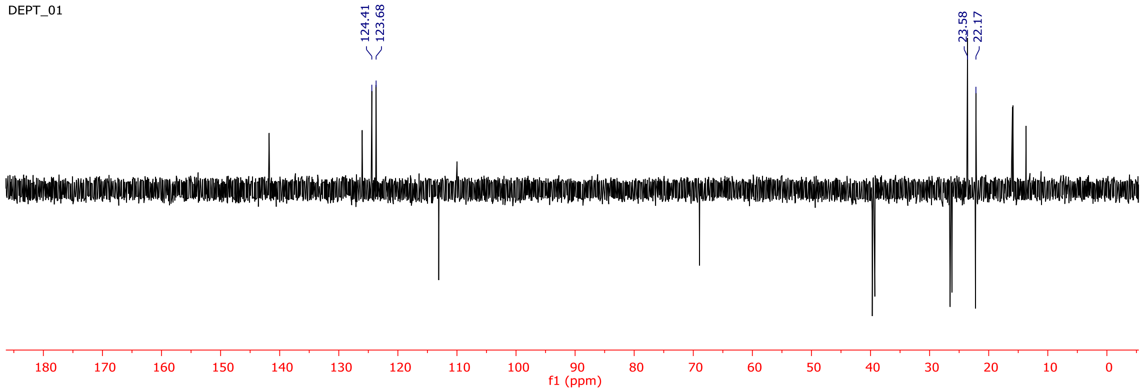
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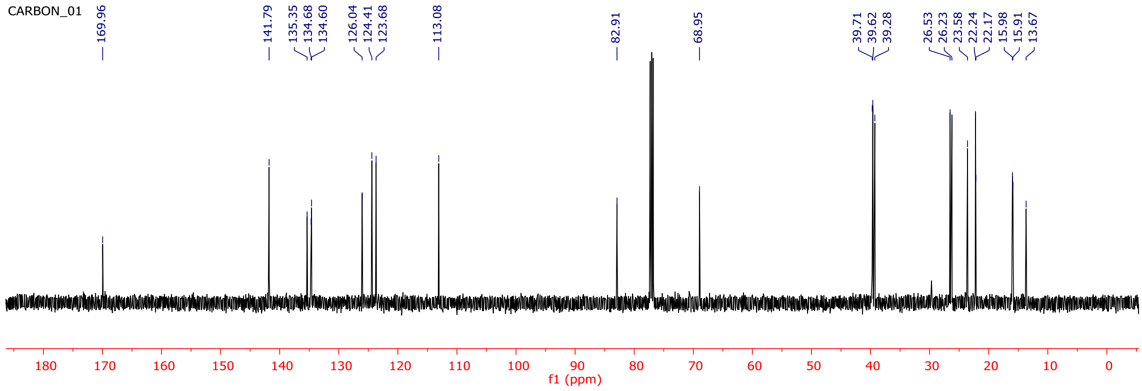
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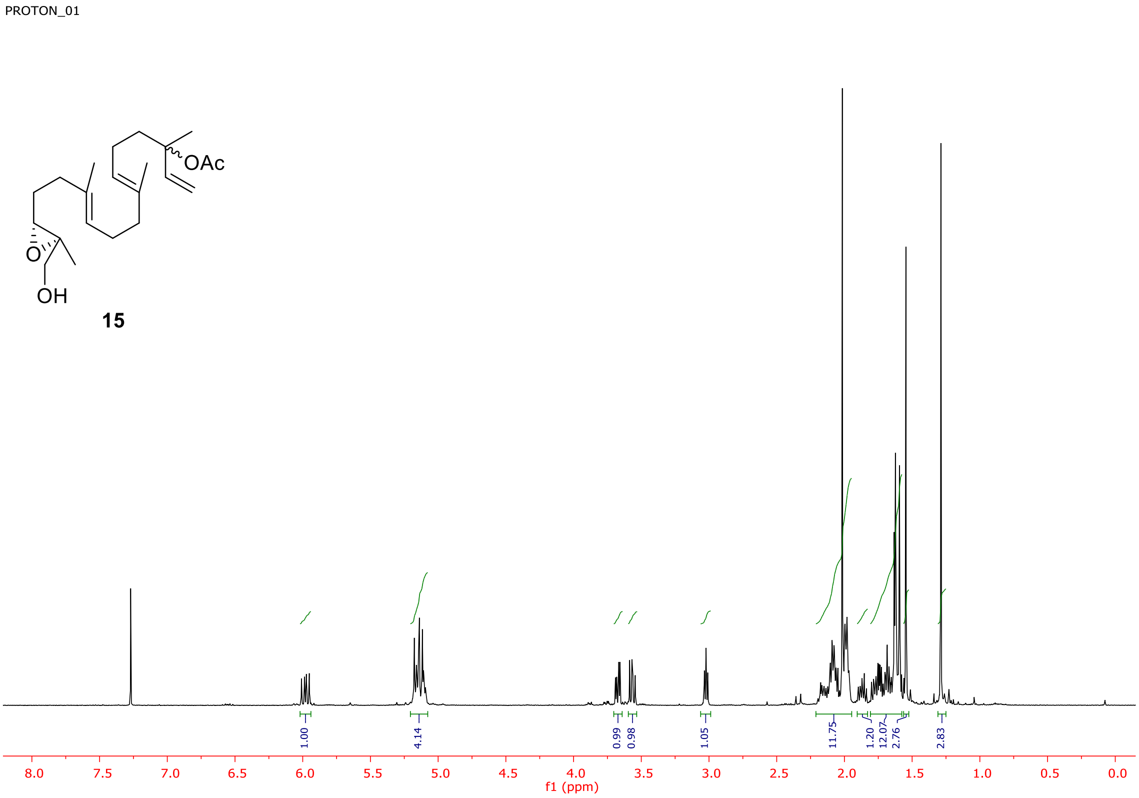
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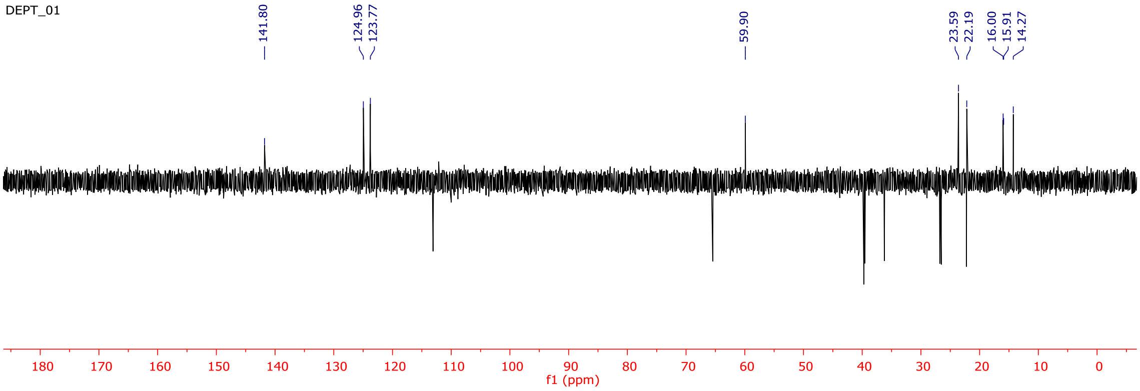
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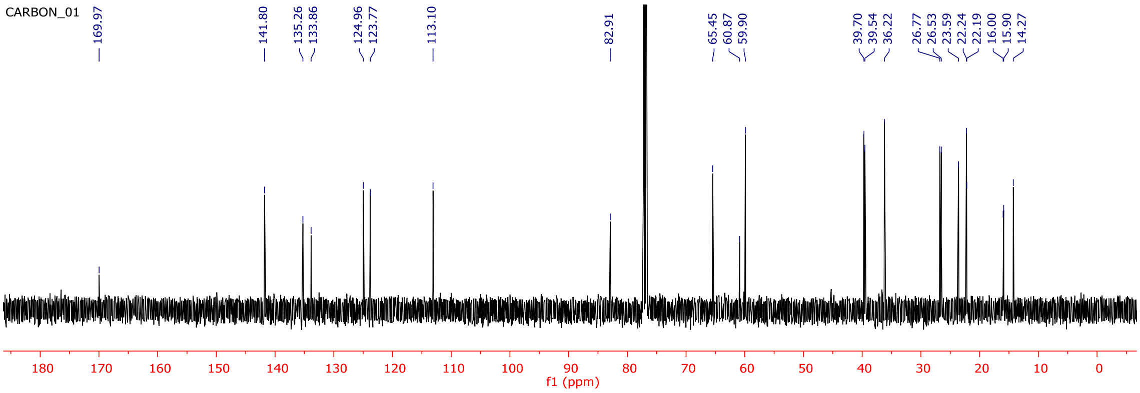
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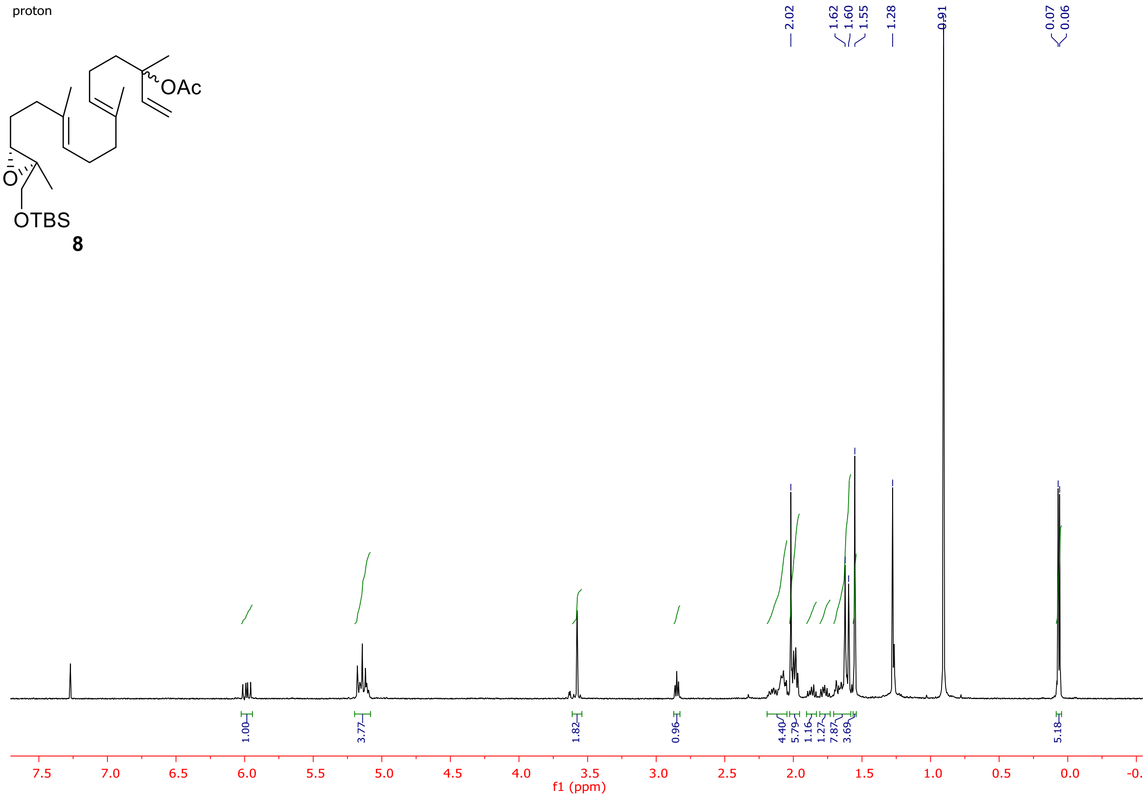
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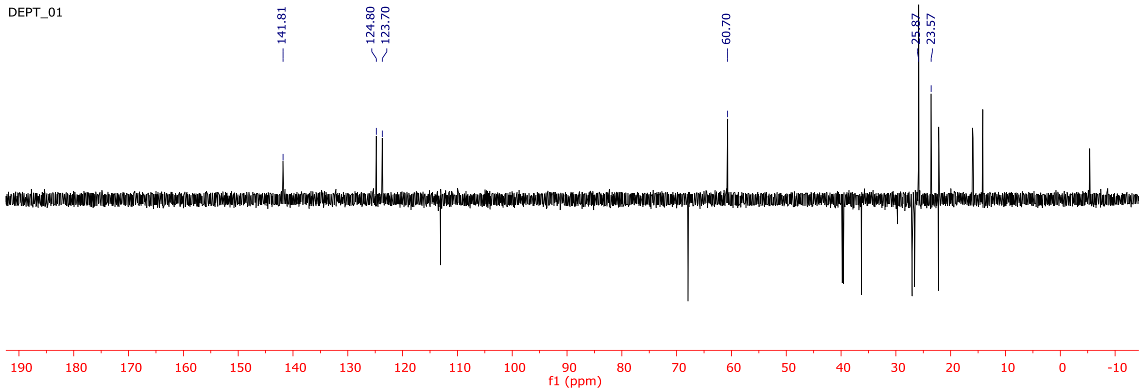
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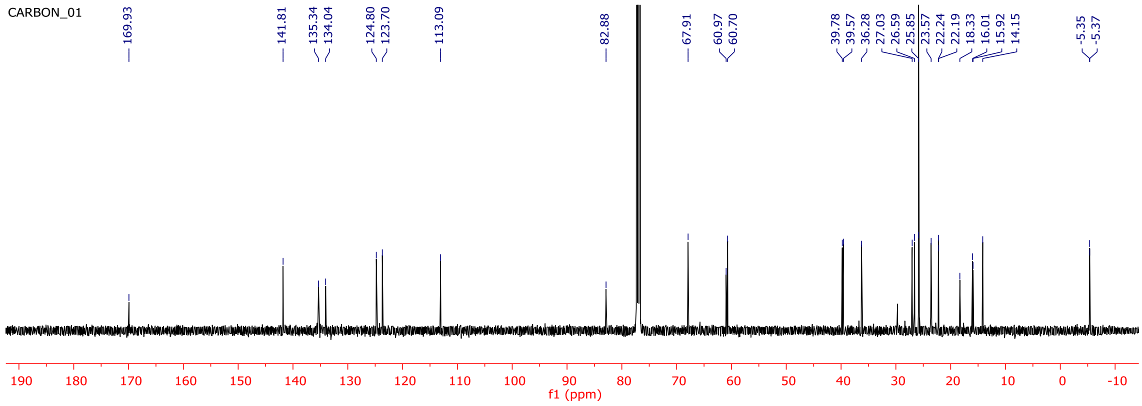
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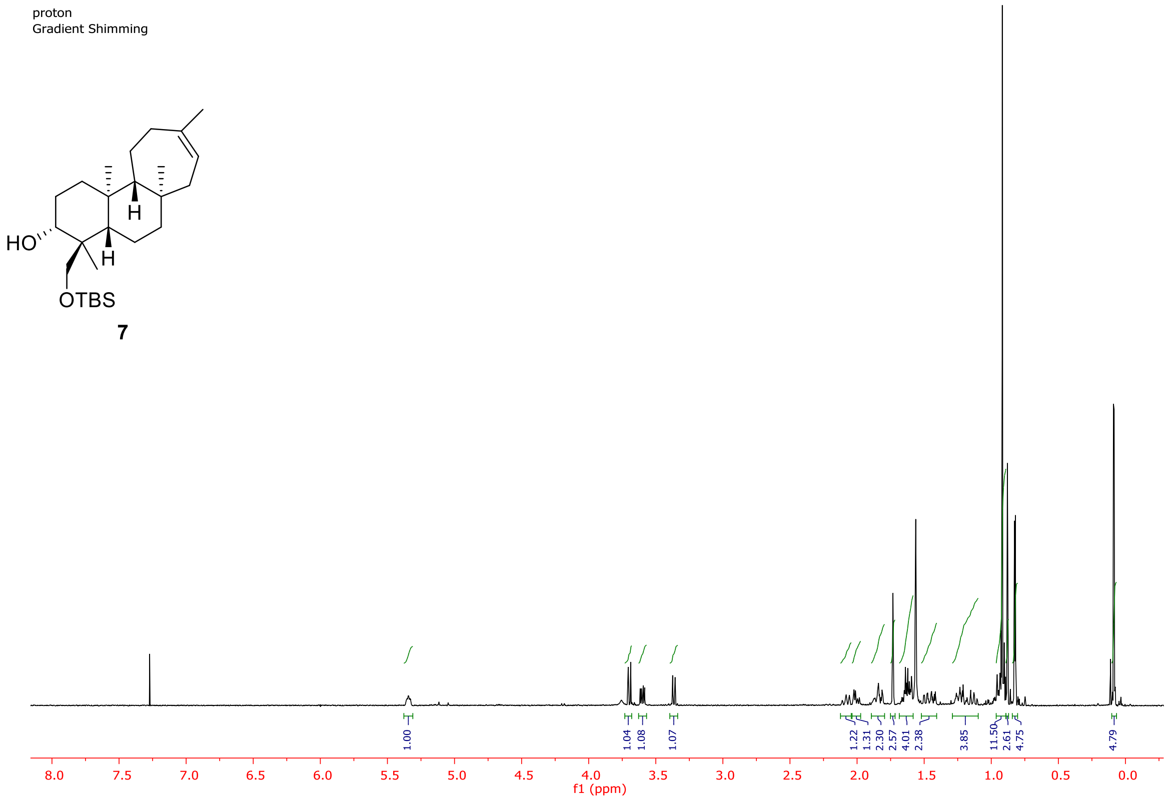
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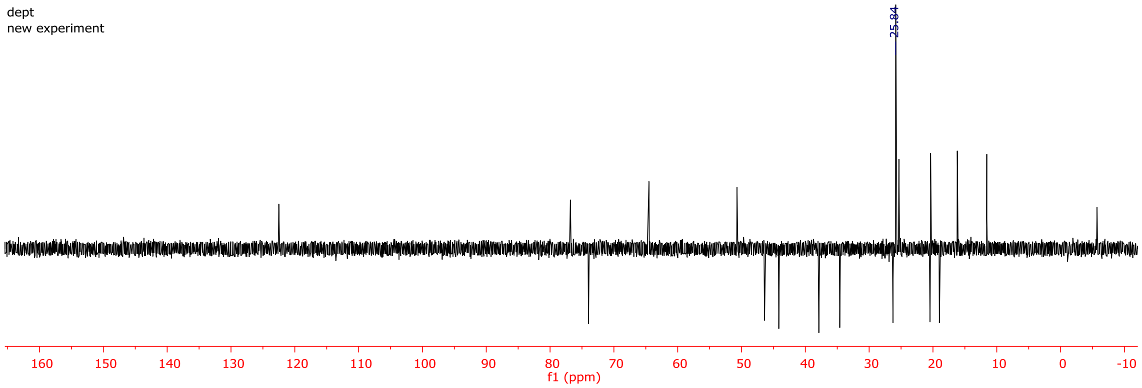
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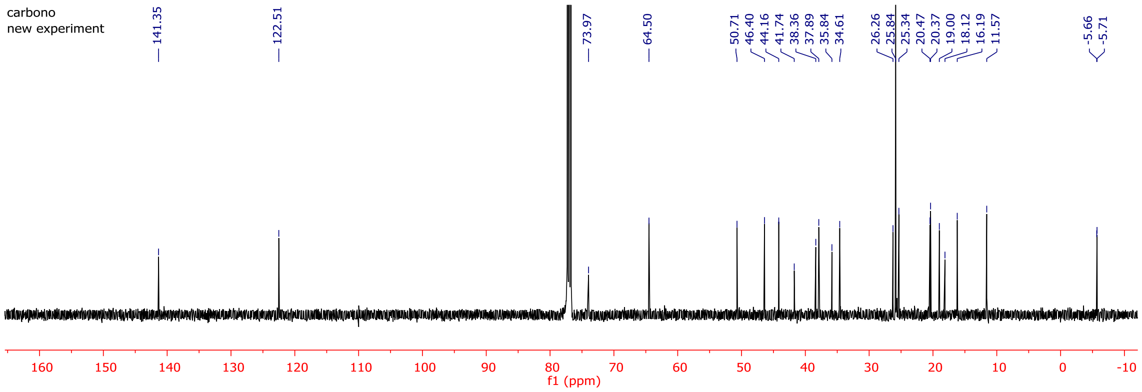
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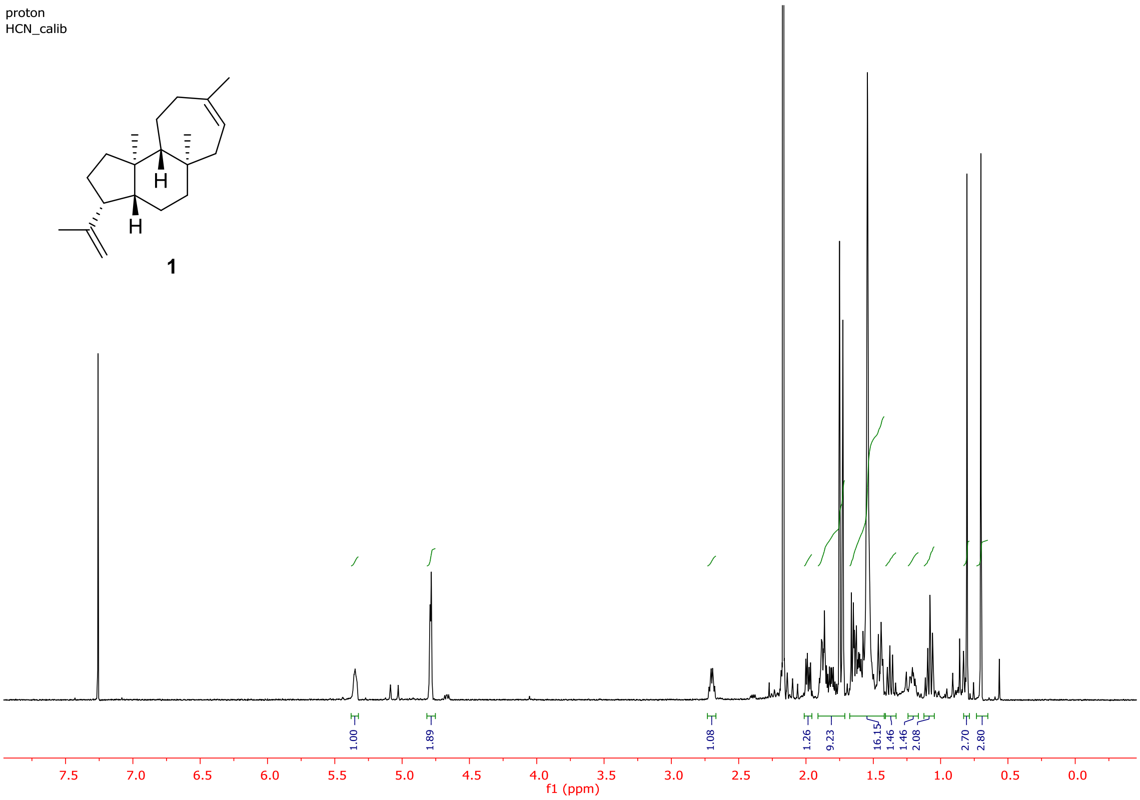
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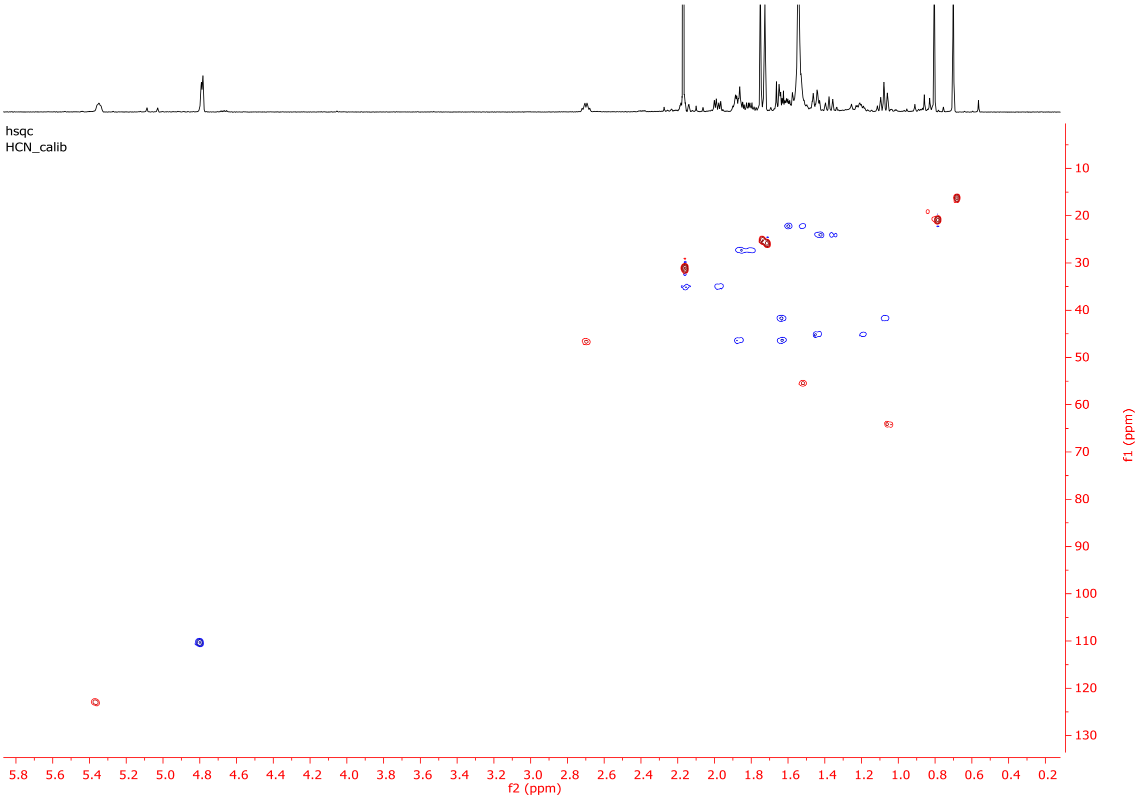
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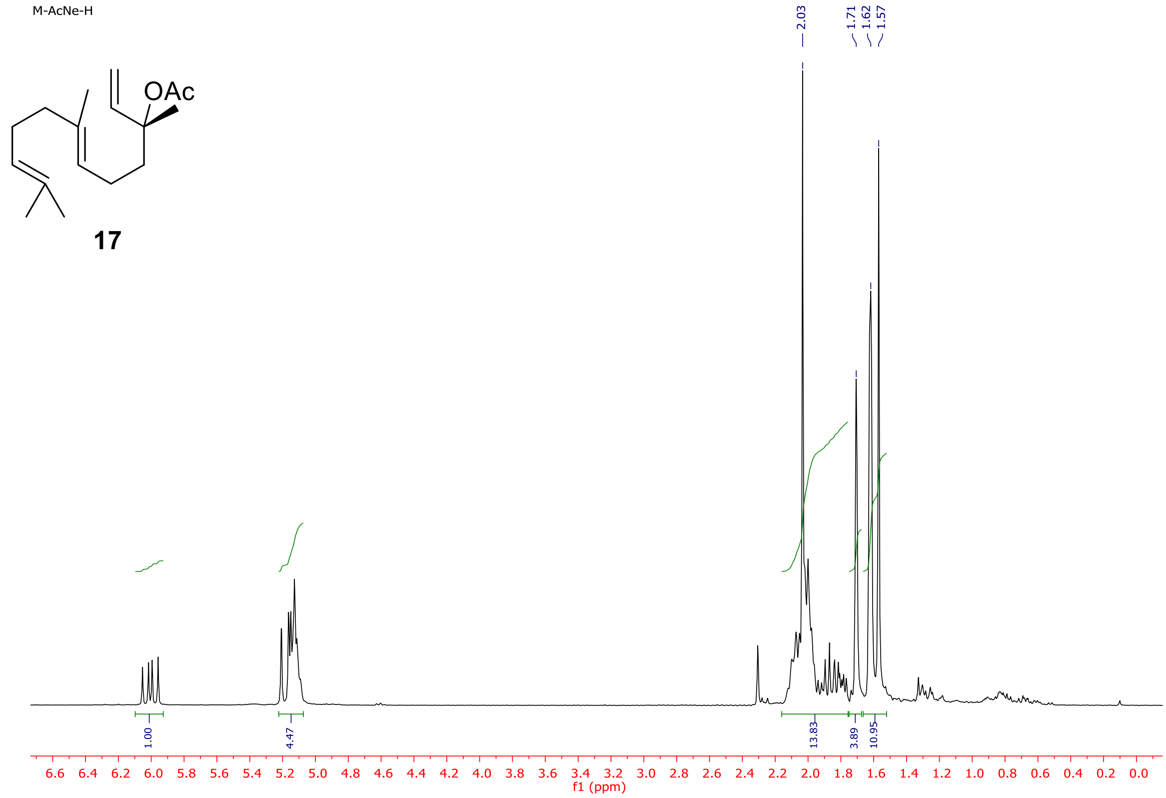
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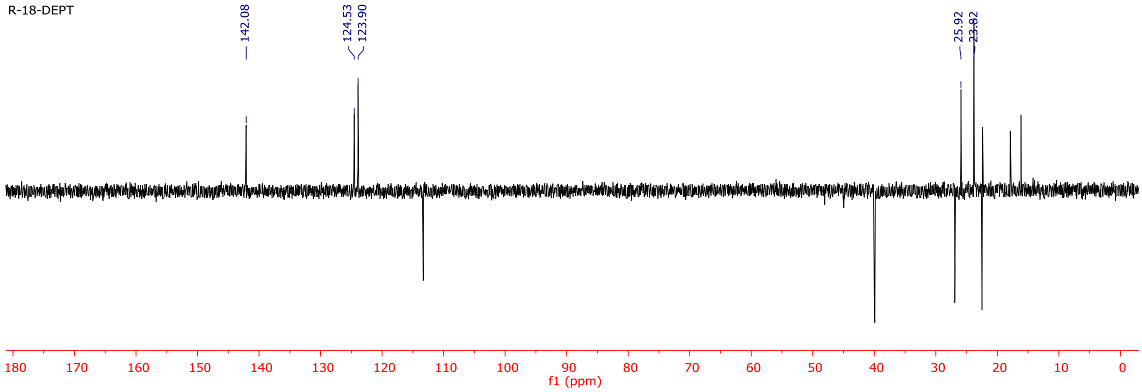
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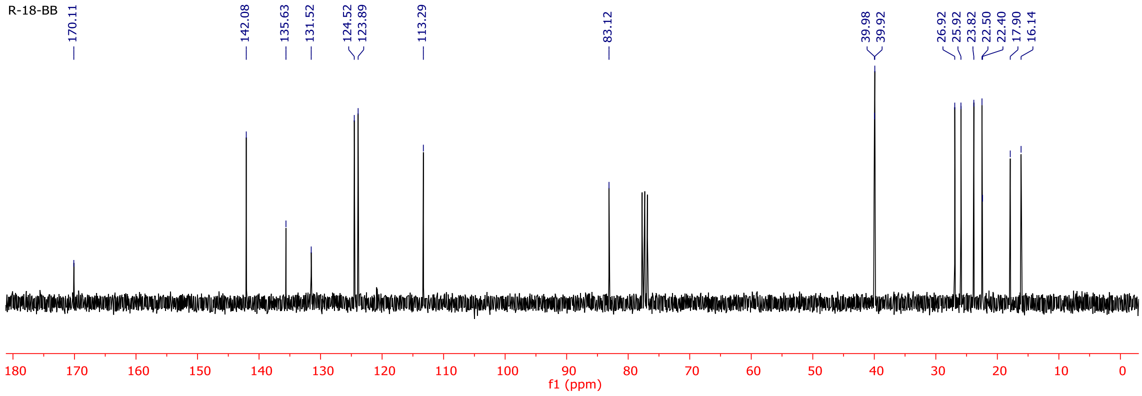
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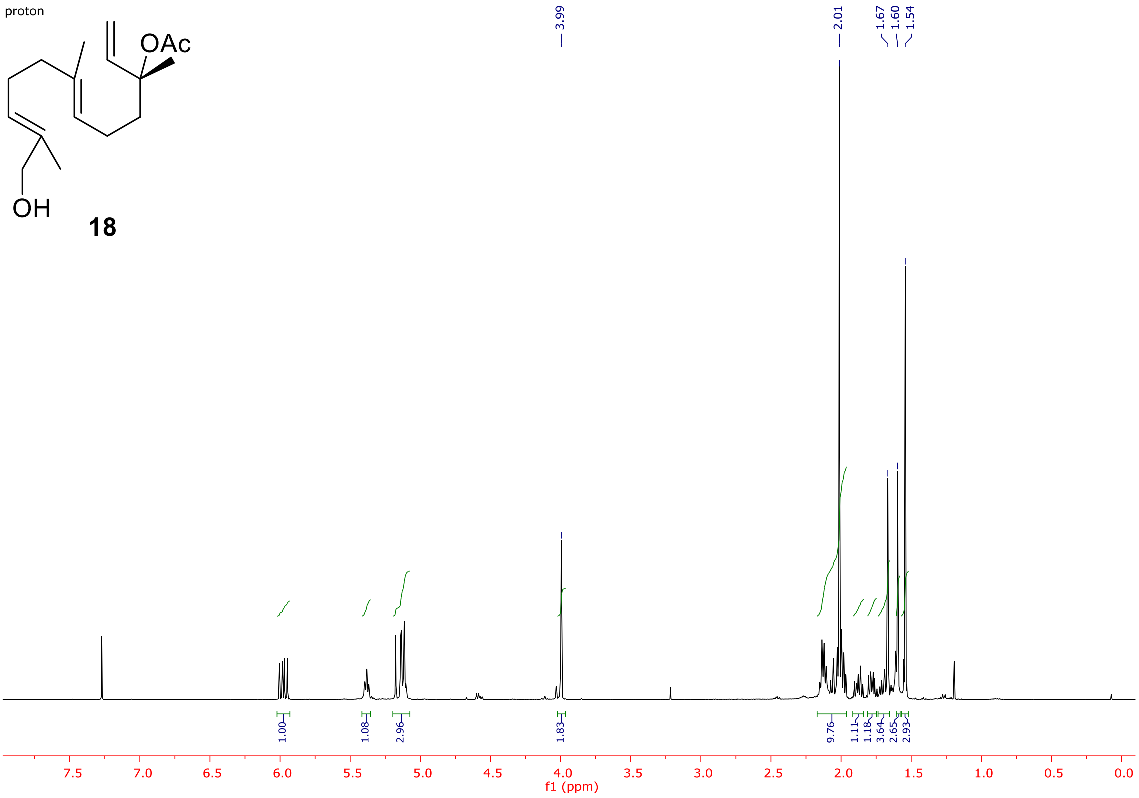
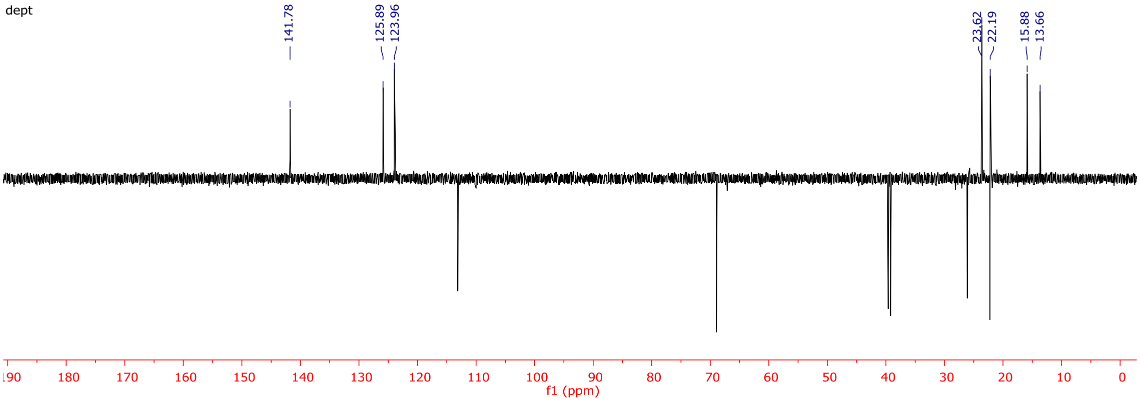
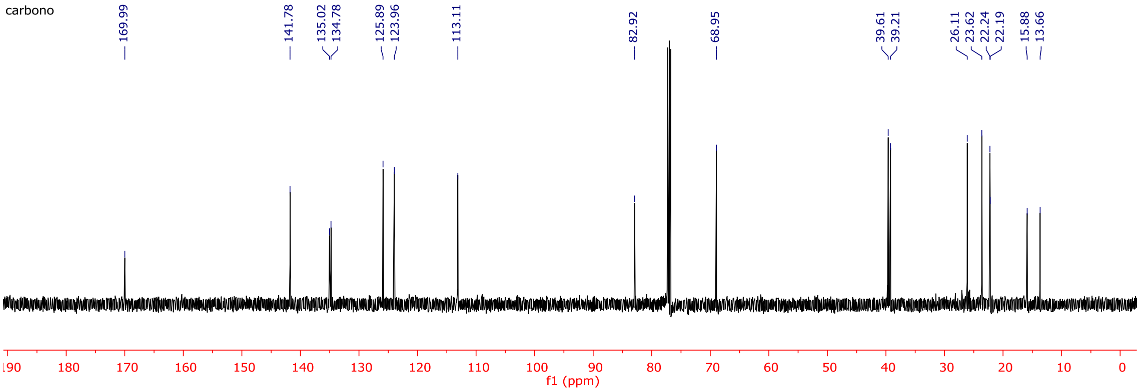
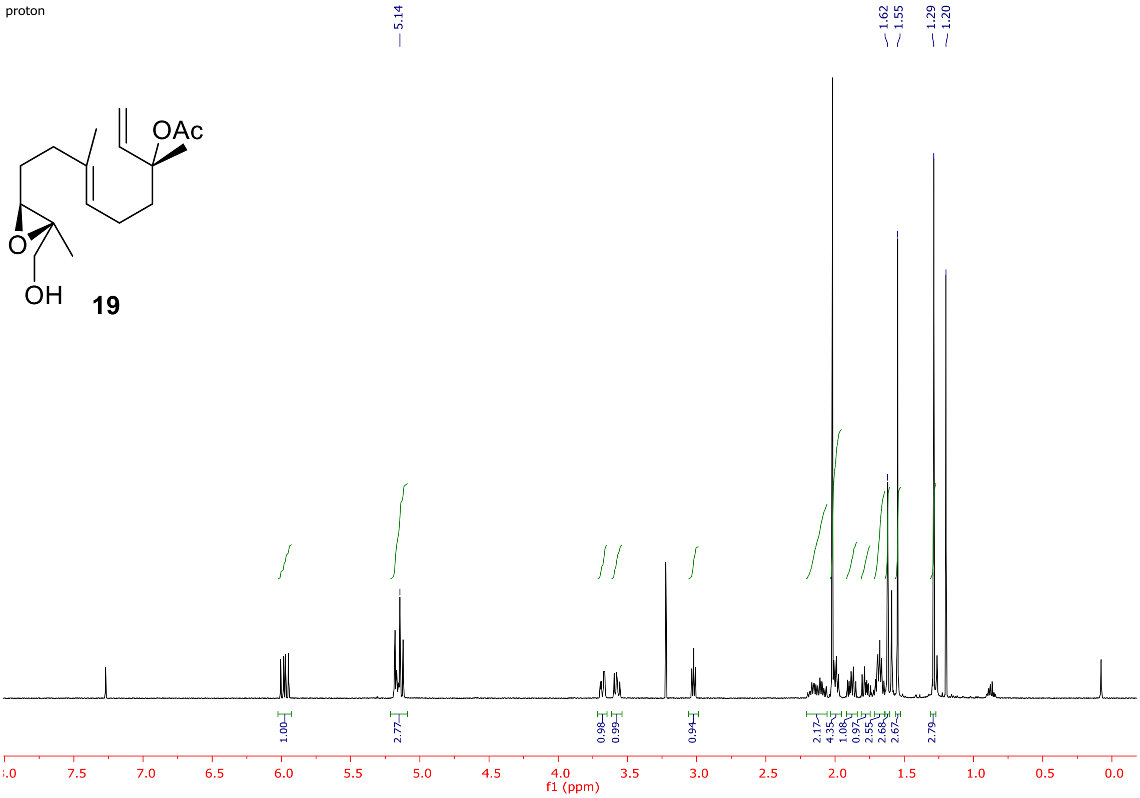
170.11
142.08
135.63
131.52
124.52
123.89
113.29
83.12
39.98
39.92
26.92
25.92
23.82
22.50
22.40
17.90
16.14
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

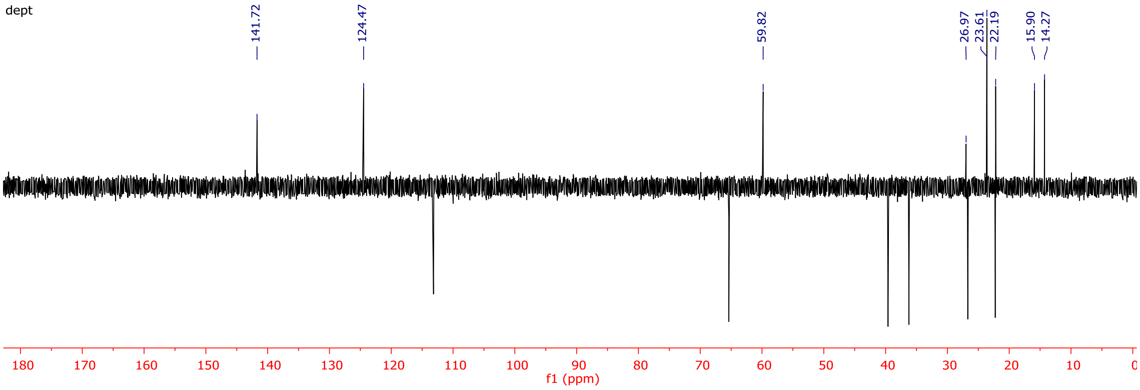

proton
OAc
OH
3.99
2.01
1.67
1.60
1.54
1.00
1.08
2.96
1.83
9.76
1.11
1.18
3.64
2.65
2.93
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

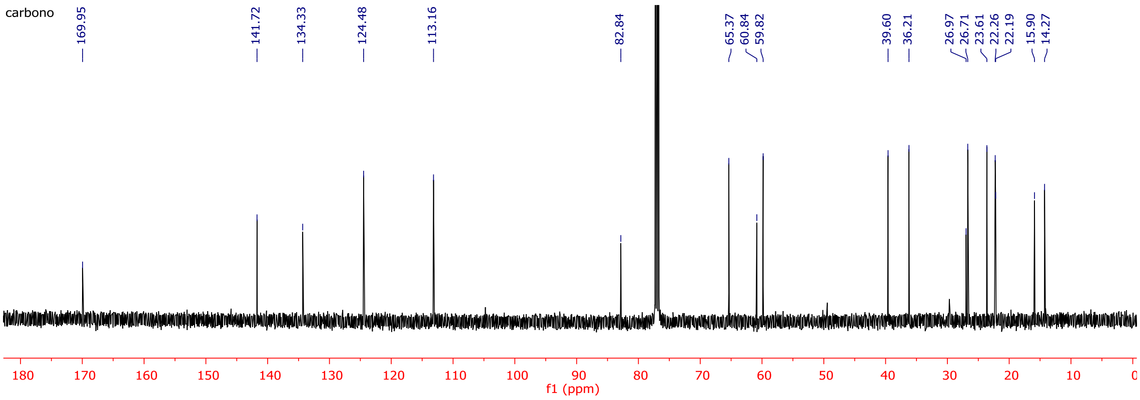
18

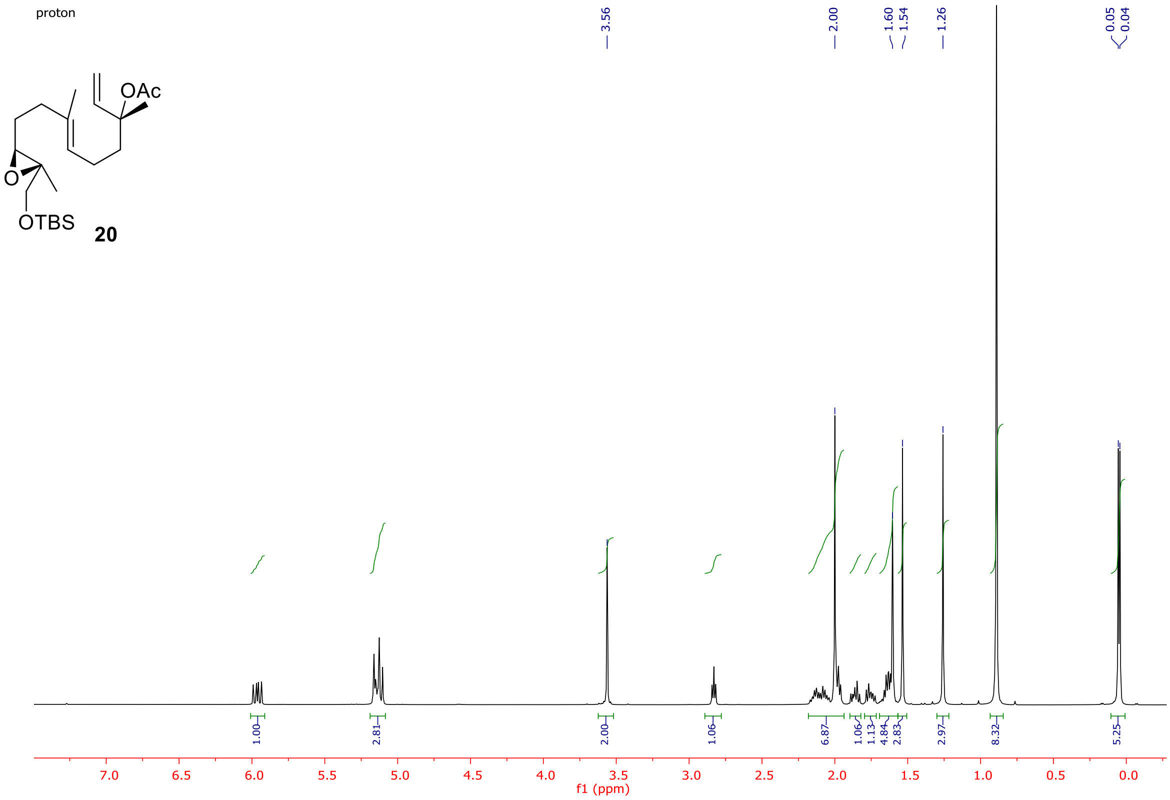

dept
141.78
125.89
123.96
23.62
22.19
15.88
13.66
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

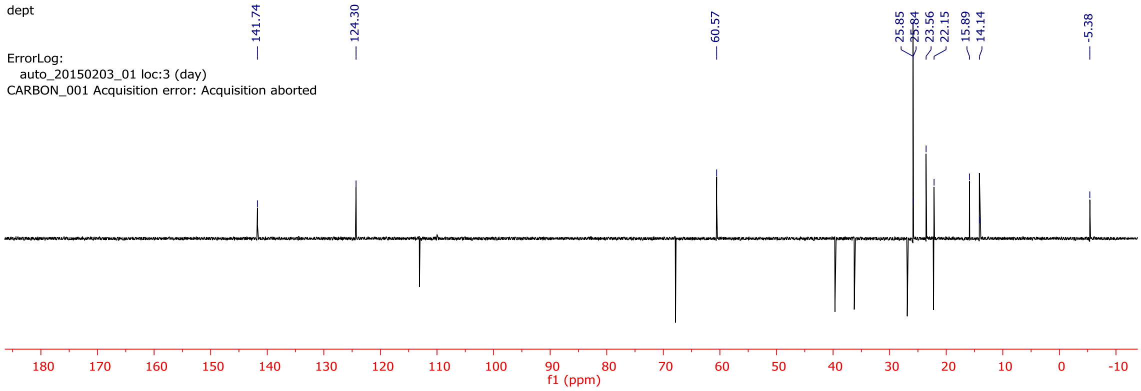

carbono
169.99
141.78
135.02
134.78
125.89
123.96
113.11
82.92
68.95
39.61
39.21
26.11
23.62
22.24
22.19
15.88
13.66
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

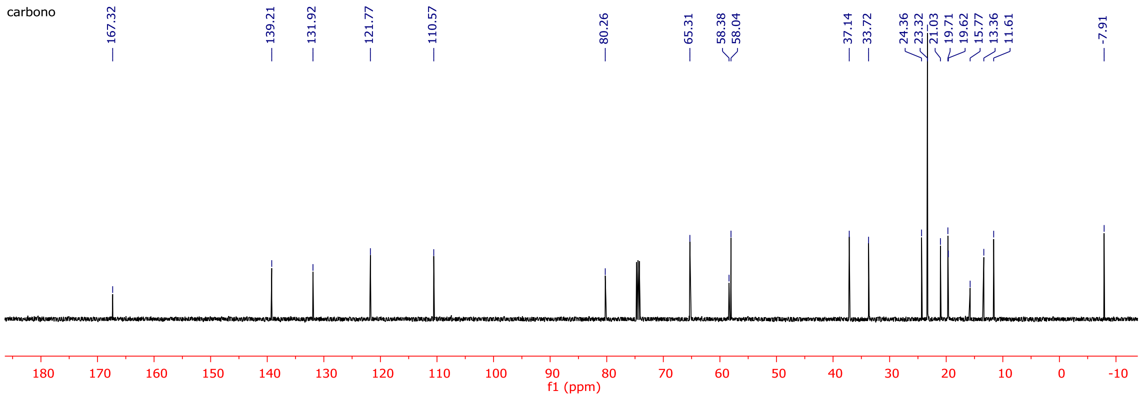

proton
5.14
1.62
1.55
1.29
1.20
OAc
O
OH
19
1.00
2.77
0.98
0.99
0.94
2.17
4.35
1.08
0.97
2.55
2.68
2.67
2.79
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

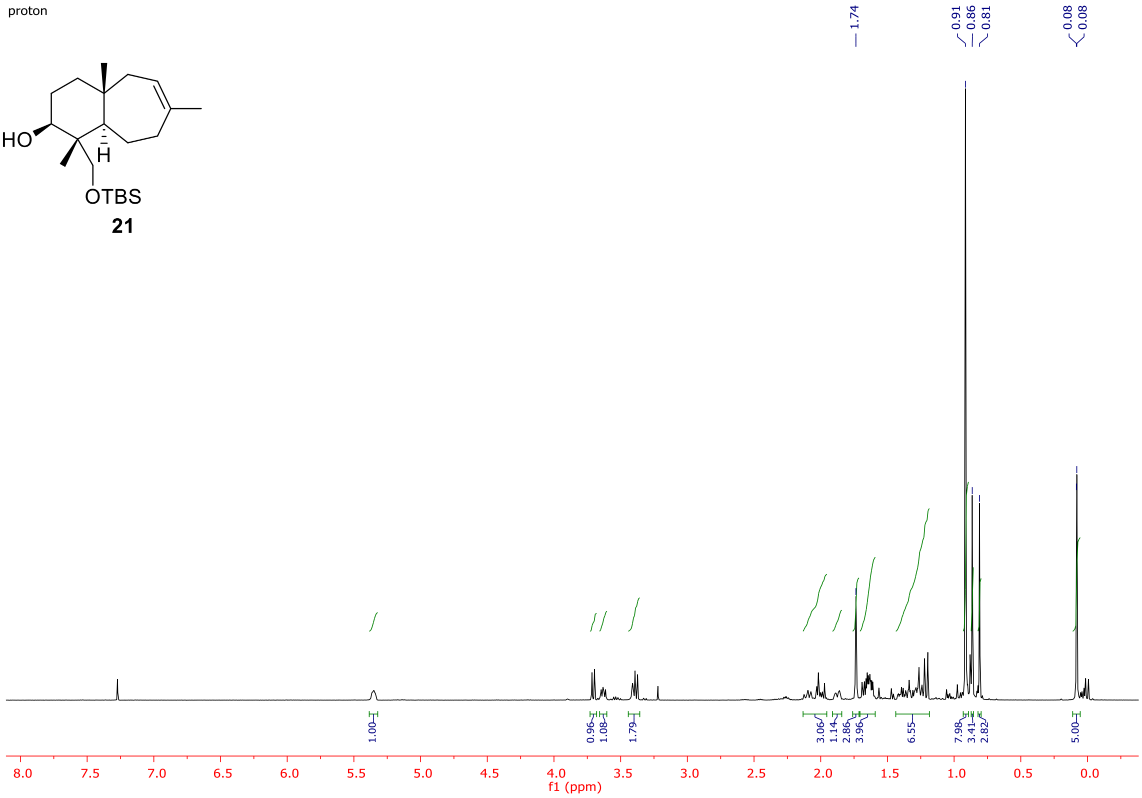

dept
141.72
124.47
59.82
26.97
23.61
22.19
15.90
14.27
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

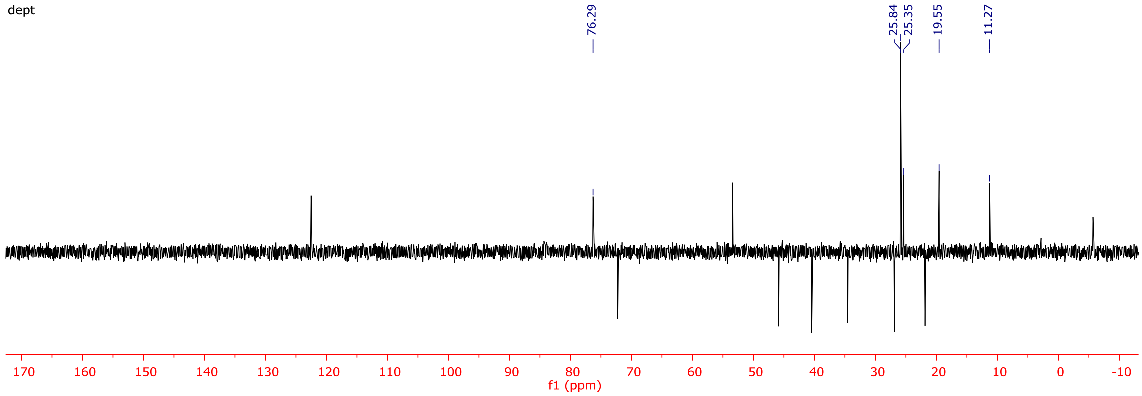

carbono
169.95
141.72
134.33
124.48
113.16
82.84
65.37
60.84
59.82
39.60
36.21
26.97
26.71
23.61
22.26
22.19
15.90
14.27
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

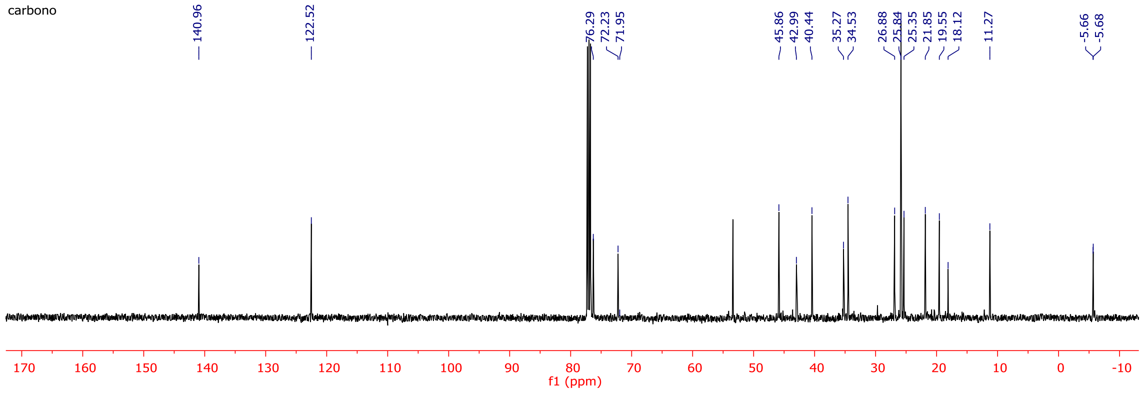

proton
OAc
O
OTBS
20
3.56
2.00
1.60
1.54
1.26
0.05
0.04
1.00
2.81
2.00
1.06
6.87
1.06
1.13
4.84
2.83
2.97
8.32
5.25
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

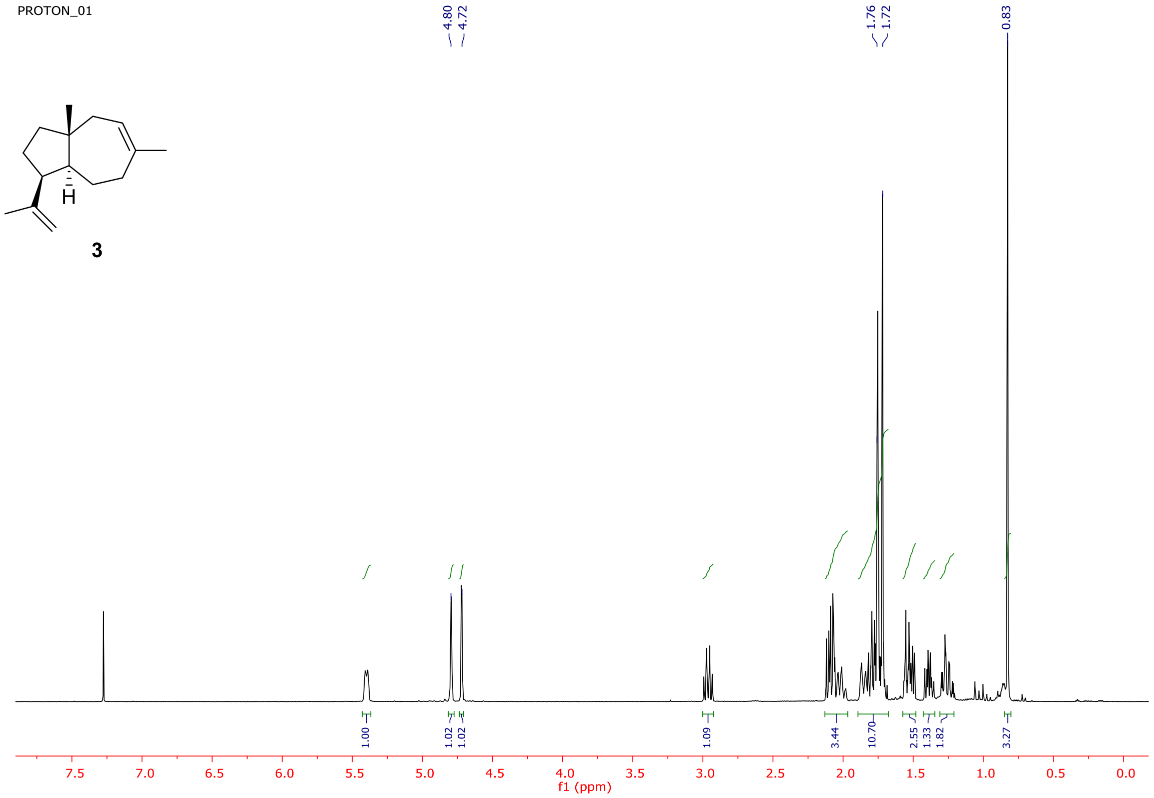

dept
ErrorLog:
auto_20150203_01 loc:3 (day)
CARBON_001 Acquisition error: Acquisition aborted
141.74
124.30
60.57
25.85
25.84
23.56
22.15
15.89
14.14
-5.38
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

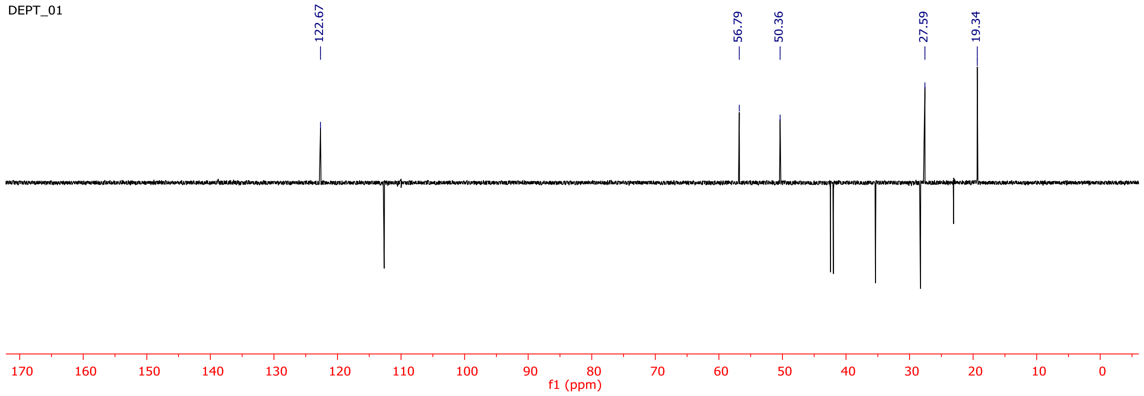

carbono
167.32
139.21
131.92
121.77
110.57
80.26
65.31
58.38
58.04
37.14
33.72
24.36
23.32
21.03
19.71
19.62
15.77
13.36
11.61
-7.91
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

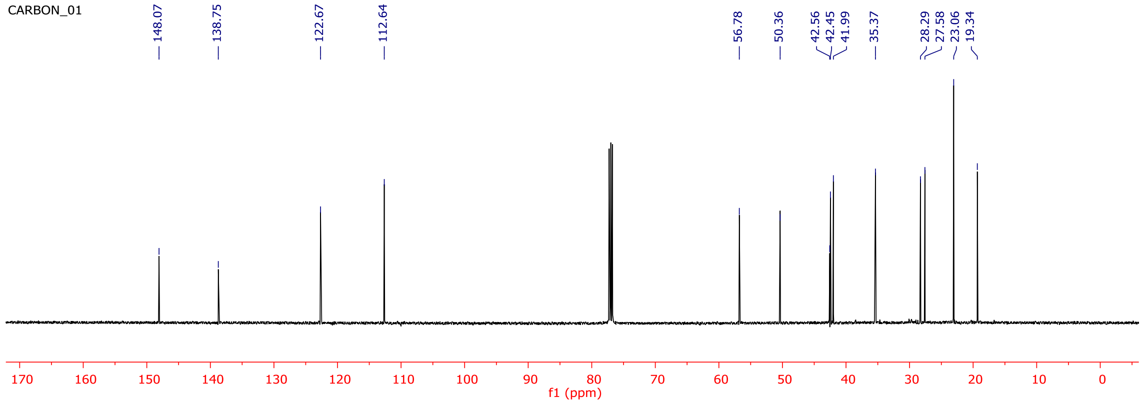

proton
HO
H
OTBS
21
1.74
0.91
0.86
0.81
0.08
0.08
1.00
0.96
1.08
1.79
3.06
1.14
2.86
3.96
6.55
7.98
3.41
2.82
5.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


dept
76.29
25.84
25.35
19.55
11.27
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


carbono
140.96
122.52
76.29
72.23
71.95
45.86
42.99
40.44
35.27
34.53
26.88
25.84
25.35
21.85
19.55
18.12
11.27
-5.66
-5.68
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

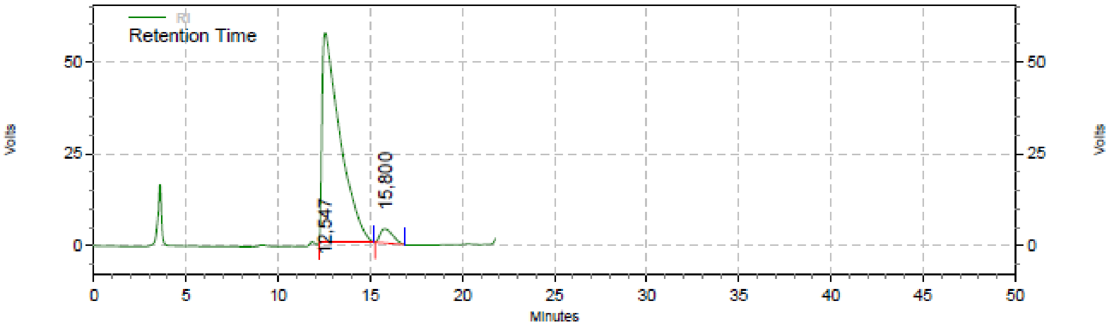

PROTON_01
H
3
4.80
4.72
1.76
1.72
0.83
1.00
1.02
1.02
1.09
3.44
10.70
2.55
1.33
1.82
3.27
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


DEPT_01
122.67
56.79
50.36
27.59
19.34
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CARBON_01
148.07
138.75
122.67
112.64
56.78
50.36
42.56
42.45
41.99
35.37
28.29
27.58
23.06
19.34
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Area % Report

Data File: C:\Documents and Settings\Administrador\Escritorio\JaviMoraga\M-53A 7.dat
Method: C:\EZChrom Elite\Projects\Tesis MK\Method\Moraga\Isocratico Iso Hex IR Analitica quiral.met
Acquired: 24/07/2015 11:31:26
Printed: 24/07/2015 12:01:30



RI Results

Retention Time	Area	Area %	Height	Height %
12,547	30681881	95,47	454789	93,62
15,800	1454799	4,53	30978	6,38
Totals	32136680	100,00	485767	100,00

Comment:

Column	: CHIRACEL OD
Column size	: 0.46cmI.D. x 25cm
Eluent	: Hex/IPA=9.5/0.5
Flow rate	: 1.0ml/min
Temp.	: 25 C

6.2 *Supporting information Artículo 3:*

Mimicking Halimane Synthases: Monitoring a Cascade of Cyclizations and Rearrangements from Epoxypolyprenes.

Mimicking Halimane-Synthases: Monitoring a Cascade of Cyclizations plus Rearrangements from Epoxypolyprenes.

José F.Quilez del Moral[†,*], *Victoriano Domingo*[†], *Álvaro Pérez*[†], *Kevin A. Martínez Andrade*[†], *Lourdes Enríquez*[‡], *Martín Jaraiz*[‡], *José Luis López-Pérez*[ǁ,*], *and Alejandro F. Barrero*[†,*]

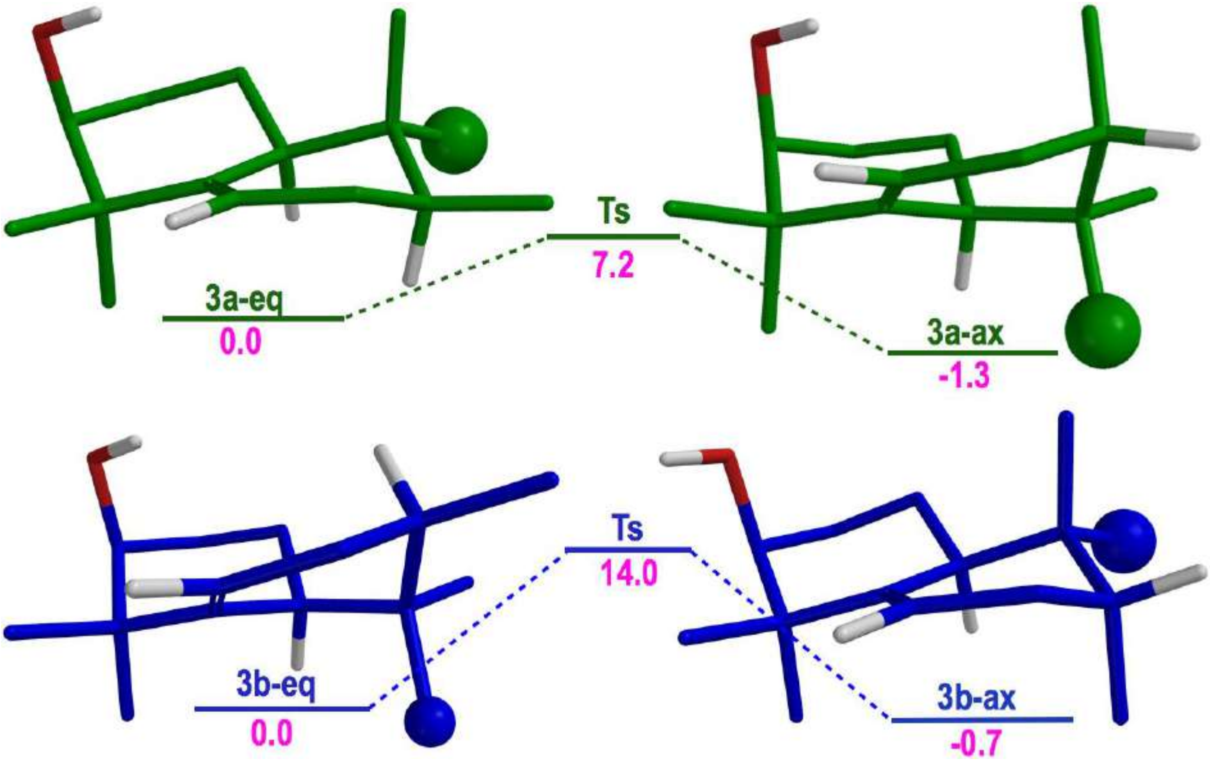
- [†]Dr. Victoriano Domingo; Álvaro Pérez; Kevin A. Martínez Andrade, Dr. J. F. Quílez del Moral, Prof. A. F. Barrero.
  Department of Organic Chemistry, Institute of Biotechnology, University of Granada, Avda.Fuente Nueva, s/n, 18071 Granada, Spain
- [‡]Lourdes Enríquez, Prof. M. Jaraiz.
  Department of Electronics, University of Valladolid, Campus M. Delibes, 47011, Valladolid, Spain
- [ǁ]Prof. José Luis López-Pérez.
  Department of Pharmaceutical Sciences, IBSAL-CIETUS, University of Salamanca, Avda.Campo Charro, s/n, 37007 Salamanca, Spain. Department of Pharmacology, Faculty of Medicine, University of Panama, Republic of Panama

Contents:

Computational chemistry methodology

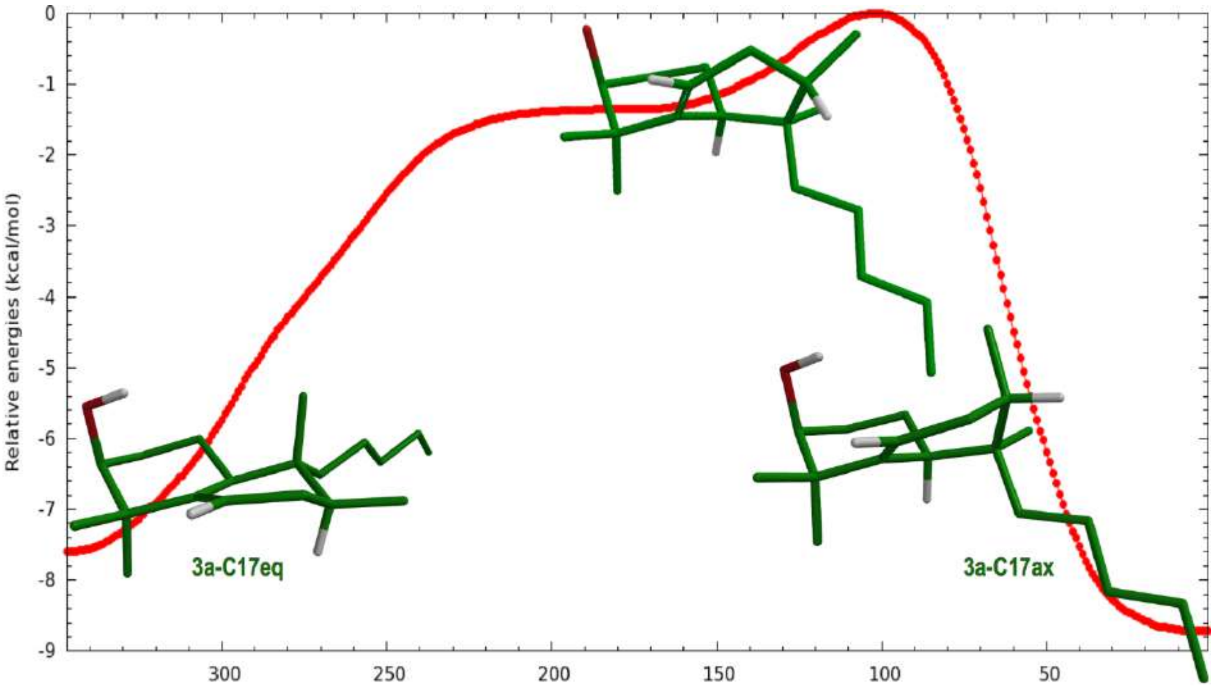
Geometry optimizations and energy calculations were performed with GAUSSIAN 09[1] using DFT[2-4] at the B3LYP/6-31+g(d,p)[5-10] level of theory *in vacuo*. The D3 dispersion-correction scheme,[11] applying the Becke–Johnson damping,[12-14] was included for all calculation. To simulate the solvent effect used in the experimental reactions (dichloromethane), a single point calculation was performed at the same level described before, using the SMD continuum model.[25] Also, the temperature used in experimental conditions (195.15º K) have been taken into account.Intermediates and products and the saddle points of the reactions were located by means of GRRM[16] (Global Reaction Route Mapping) program, linked to GAUSSIAN 09, with the routines SCW[17] and 2PSHS.[18] Transition state structures were optimized as saddle points at the same level of calculation with the routine SADDLE implemented also in GRRM. A vibrational analysis was performed at the same level of theory *in vacuo* in order to determine the zero-point vibrational energy and to characterize each stationary point as a minimum or transition state structure. Transition states were identified by the presence of a single imaginary frequency that corresponds to the expected motion along the reaction coordinate. The reported energies are expressed in Kcal/mol. The same energies expressed in Kcal/mol as relative energies appear in the Plot of IRC, but do not include zero-point energy corrections. To verify that the TSs correspond to the expected reactant and product wells, intrinsic reaction coordinate (IRC)[19-22] calculations were performed at the same level B3LYP/6-31+g(d,p). Structural drawings were produced with Spartan08.[23]

Figure S1. Interconversion barriers for the main conformers of epimers at C-8 3a and 3b. Free relative energies are represented in kcal/mol. The linear chain has been replaced by a ball for simplification of the structures and to facilitate the visualization of the spatial arrangement of the four conformers.*



*The two pairs of main conformers for each epimer were obtained after a conformational search with Molecular Mechanics (MMFF) followed by an optimization with DFT B3LYP/6-31+g(d.p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)

Plot of IRC interconversion of conformers **3a** (B3LYP/6-31+g(d,p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)



Cartesian Coordinates and Energies of **3a-eq**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform) //# MIN/B3LYP/6-31+g(d,p)) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)

Charge = 0 Multiplicity = 1

\---

C	-0.743292141683	1.015082035508	1.235674714537
C	-1.909714291859	1.996387840165	1.355407523921
C	-3.249104456864	1.273080276188	1.201724999412
C	-3.345079250228	0.499210623832	-0.140419139974
C	-2.121252565858	-0.418512468381	-0.303697638513
C	-2.239745430578	-1.701796299148	-0.680269499824
C	-1.076978703219	-2.559421736972	-1.086833269323
C	0.164964741778	-1.718256408455	-1.400924100272
C	0.469813574060	-0.742153092369	-0.225295725627
C	-0.753726926170	0.233778036590	-0.098383702176

```
C     1.717430484435      0.128852948428     -0.561837360962
C     3.098319539284     -0.381950236218     -0.125710295042
C     4.236003078239      0.479547702990     -0.683892716519
C     5.626022293551      0.021446393957     -0.230165464386
C     6.758312123637      0.881358091610     -0.797194557831
C     1.322804196199     -2.618596108920     -1.844400461632
C     0.677523026136     -1.530087200531      1.084073101996
C    -4.684854038116     -0.254242466081     -0.183821147254
C    -3.360958489565      1.517526903403     -1.308654095981
H    -0.797320148345      0.309027595694      2.070870543408
H     0.204755086744      1.549631056072      1.350598570350
H    -1.889615722377      2.490440524027      2.333343537768
H    -1.827458580244      2.783381637474      0.597010657914
H    -4.070724861371      1.996318339900      1.243057500681
H    -0.628817657580      0.978414282284     -0.899620326320
H    -3.225457979851     -2.146080718671     -0.782940070594
H    -0.846148832692     -3.312302113842     -0.318110471396
H    -1.359858929064     -3.134515351585     -1.978865285312
H    -0.092551701808     -1.079427828710     -2.259582428602
H     1.724654125875      0.297601208483     -1.647892512819
H     1.589858738848      1.121392672357     -0.113679252765
H     3.252556935520     -1.418792503955     -0.440973434398
H     3.159850708087     -0.382718880431      0.969760541610
H     4.193744668956      0.468366311183     -1.782844559009
H     4.084165770122      1.526465118457     -0.382756355993
H     5.776057481346     -1.024932745963     -0.530285757935
H     5.669972866299      0.035184962076      0.867653503878
H     6.756666873396      0.864108953369     -1.894178601419
H     7.739482999846      0.527364085853     -0.460484452883
H     6.656484767738      1.927346506313     -0.482789785927
H     1.687260552760     -3.254451416874     -1.030375260118
H     2.167987755683     -2.043936991580     -2.232696572935
H     0.984761065799     -3.282732052209     -2.648902420260
H    -0.257963845293     -1.975345392489      1.435572573423
H     1.058587126701     -0.891169675921      1.884517225588
H     1.399585776075     -2.340097507221      0.950139472798
H    -4.854048210595     -0.704773263130     -1.166704858112
H    -5.503642217857      0.449211356651      0.003723783317
H    -4.746183188535     -1.041214760179      0.571331878002
H    -3.499950375577      0.988841209059     -2.257268552103
H    -4.192350187800      2.222146734196     -1.187966065369
H    -2.439873943771      2.098503150067     -1.384407408004
O    -3.481955998867      0.403873454615      2.325544869561
H    -2.922580728692     -0.381232440152      2.223962153189
----------------------------------------------------------------
Thermochemistry at  298.150 K,    1.000 Atm
E(el)          = -514508.434460  kcal/mol
ZPVE            = 312.732803  kcal/mol
Enthalpie(0K)   = -514195.701657  kcal/mol
E(tr)          = 0.888732  kcal/mol
E(rot)          = 0.888732  kcal/mol
E(vib)          = 324.694879  kcal/mol
```

H-E(el) = 327.064831 kcal/mol
Enthalpie = -514181.369628 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000068155947
S(rot) = 0.000054686072 (Symmetry number= 1)
S(vib) = 0.000117527769
G-E(el) = 282.093585 kcal/mol
Free Energy = -514226.414875 kcal/mol

Cartesian Coordinates and Energies of Barrier **3a-eq / 3a-ax**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform) //# SADDLE/B3LYP/6-31+g(d,p)) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)

Charge = 0 Multiplicity = 1

C	-1.623614461116	-0.491361705079	1.995748291491
C	-2.737435370466	0.563508529027	2.150293777584
C	-3.527450815680	0.832359030759	0.857536181298
C	-2.603038907948	1.169666414767	-0.369559247009
C	-1.595189726019	0.025175752827	-0.383481323552
C	-1.689448474252	-1.042008129143	-1.191579664011
C	-0.952438519661	-2.317415217911	-0.891813484075
C	0.459521524821	-2.145521678656	-0.289971795619
C	0.638773831571	-0.843127082791	0.586684531795
C	-0.696623350515	-0.062897674541	0.833455046884
C	1.545488853414	0.142928976277	-0.212955623990
C	2.995232539756	-0.288387173214	-0.466055440070
C	3.714467809744	0.642564103784	-1.448856062202
C	5.182388315475	0.270535637929	-1.681438449762
C	5.885896540940	1.196634076668	-2.676774933739
C	0.867523340265	-3.463907621109	0.380979259543
C	1.303524422332	-1.117230501188	1.947087979042
C	-3.449904391582	1.258080684232	-1.648441089746
C	-1.947013916467	2.551721783874	-0.164698605617
H	-2.052598978529	-1.482984084434	1.802838119753
H	-1.075133965317	-0.561424309136	2.939616752802
H	-3.451911216813	0.255382834979	2.921506185047
H	-2.286250565457	1.502882388240	2.493529894955
H	-4.211841825690	1.673516236503	1.015496810150
H	-0.370956911392	0.947056702917	1.101793047589
H	-2.387782972240	-1.050071397889	-2.023683842243
H	-1.566767287704	-2.897878952261	-0.184012464184
H	-0.877668957128	-2.940618916262	-1.790205001441
H	1.126971686346	-2.022547212047	-1.148874226018
H	1.061708410059	0.337781389864	-1.178700096338
H	1.568023924055	1.104161818880	0.318307234797
H	3.031371213702	-1.312607332382	-0.859835629400
H	3.551620304573	-0.302765796604	0.479314641506
H	3.181998152688	0.632710503296	-2.410924293182

H	3.658600845147	1.676823405468	-1.078960191980
H	5.238784381183	-0.765758811419	-2.042695105867
H	5.716786295278	0.291166489428	-0.721502315036
H	5.392578140890	1.171309515268	-3.656147988573
H	6.933058894593	0.908484401318	-2.824423409441
H	5.872641222879	2.236239334255	-2.326665077474
H	0.253650330490	-3.678833933812	1.263149637321
H	1.916713864723	-3.469019297916	0.690002856832
H	0.729563337302	-4.293767263049	-0.322588876802
H	0.722250873025	-1.804590733642	2.566214658819
H	1.413129837344	-0.179180034352	2.505417269354
H	2.301232395725	-1.547013590100	1.833699074532
H	-2.813738955448	1.480679406091	-2.511983258304
H	-4.182590640664	2.066884999702	-1.551631648505
H	-4.005357945501	0.342127614506	-1.856407186743
H	-1.254002631957	2.765158322933	-0.985822161963
H	-2.716505263876	3.331654082802	-0.163332775155
H	-1.390634396471	2.639647844542	0.769718594230
O	-4.385271073948	-0.281418682774	0.565900242387
H	-3.827740324585	-1.001022721473	0.227785143856

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Thermochemistry at 298.150 K, 1.000 Atm
E(el) = -514500.834293 kcal/mol
ZPVE = 312.139372 kcal/mol
Enthalpie(0K) = -514188.694921 kcal/mol
E(tr) = 0.888732 kcal/mol
E(rot) = 0.888732 kcal/mol
E(vib) = 323.813509 kcal/mol
H-E(el) = 326.183461 kcal/mol
Enthalpie = -514174.650832 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000068155947
S(rot) = 0.000054640807 (Symmetry number= 1)
S(vib) = 0.000116718920
G-E(el) = 281.372012 kcal/mol
Free Energy = -514219.462280 kcal/mol

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Cartesian Coordinates and Energies of **3a-ax**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform) //# MIN/B3LYP/6-31+g(d,p)) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)
Charge = 0 Multiplicity = 1

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C	-1.460294146069	-0.293067587650	2.105084360567
C	-2.681000294695	0.629745868814	2.224683513204
C	-3.545907813885	0.623088686805	0.961859268373
C	-2.734201163917	0.988141616003	-0.317567279332
C	-1.538883360706	0.027792159614	-0.383076451892
C	-1.335144459502	-0.808070154067	-1.414215991878

C	-0.192591713186	-1.782661350436	-1.513345130437
C	0.434900665453	-2.095728730355	-0.145817438773
C	0.691657077449	-0.772528838784	0.632978845049
C	-0.629725221624	0.038290507189	0.841617332083
C	1.632482868738	0.155454603342	-0.196153258841
C	2.966773170403	-0.423002460359	-0.680161184905
C	3.826003451186	0.629438306111	-1.390568260038
C	5.169525322163	0.088061265267	-1.889339298991
C	6.021277970378	1.149767560425	-2.589891526705
C	-0.419526788186	-3.145194119251	0.584211706130
C	1.380441633093	-1.063409013822	1.976992389233
C	-3.663954060121	0.901281228414	-1.538377894354
C	-2.253005775576	2.455560282258	-0.226906591347
H	-1.787604897188	-1.336887441155	2.089222698465
H	-0.842524332923	-0.176203415164	2.999556788760
H	-3.304601632587	0.322348550291	3.071882818505
H	-2.352057080973	1.655496893188	2.429696139915
H	-4.364621449479	1.343154934037	1.070573949484
H	-0.304895096220	1.077549826581	0.988296216623
H	-2.012597190659	-0.785682791011	-2.262990652603
H	-0.546394124577	-2.710671999333	-1.981253666147
H	0.564726435735	-1.379447737223	-2.200889489557
H	1.415125768954	-2.557456008995	-0.314581405490
H	1.083894988678	0.537521151043	-1.064678289079
H	1.847995606486	1.032528631408	0.429658000648
H	2.793707778987	-1.258193515162	-1.370048402729
H	3.533993809087	-0.831696742563	0.165648132939
H	3.264587560537	1.042181310494	-2.241490417626
H	4.008218709242	1.471233992986	-0.706996104037
H	4.988983642956	-0.749411820414	-2.577392882050
H	5.728498911267	-0.327304277145	-1.039437019060
H	5.502294012815	1.557700649848	-3.466065231499
H	6.977663028773	0.737681345011	-2.931803274075
H	6.241354706435	1.987138815935	-1.916196679351
H	-1.470814693086	-2.848259237049	0.643592378540
H	-0.066767806093	-3.344848375599	1.599609226198
H	-0.382241452158	-4.092273977060	0.033544950029
H	0.767476343042	-1.671041360361	2.645733951605
H	1.616803514986	-0.129721563140	2.501072197013
H	2.320082743130	-1.603074018997	1.819335667219
H	-3.143620198713	1.209281145402	-2.451165356560
H	-4.513982998068	1.577629675206	-1.395074261253
H	-4.065155094494	-0.102850188219	-1.689954578991
H	-1.727709132484	2.730797871510	-1.147728402716
H	-3.112002643583	3.127269943506	-0.115264460997
H	-1.575781708822	2.642149305550	0.608066067157
O	-4.203637145539	-0.648194581515	0.814366675221
H	-3.548558844366	-1.292078355831	0.502754298600

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Thermochemistry at  298.150 K,    1.000 Atm
E(el)          = -514509.546300  kcal/mol
ZPVE           = 312.632542  kcal/mol
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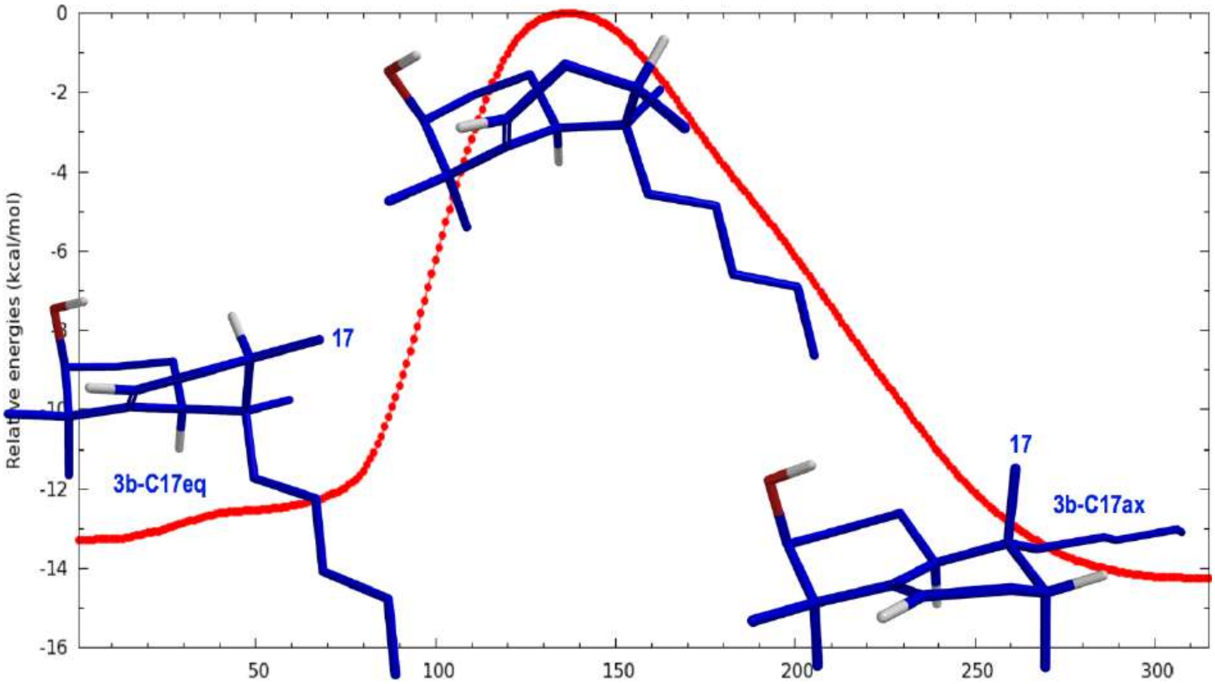
Enthalpie(0K)   = -514196.913758  kcal/mol
E(tr)          = 0.888732  kcal/mol
E(rot)          = 0.888732  kcal/mol
E(vib)          = 324.672178  kcal/mol
H-E(el)         = 327.042130  kcal/mol
Enthalpie       = -514182.504170  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000068155947
S(rot)          = 0.000054522878 (Symmetry number= 1)
S(vib)          = 0.000119020456
G-E(el)         = 281.822146  kcal/mol
Free Energy     = -514227.724154  kcal/mol
-----------------------------------------------------------------
```

Plot of IRC interconversion of conformers **3b** (B3LYP/6-31+g(d,p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)



Cartesian Coordinates and Energies of **3b-eq**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform) //# MIN/B3LYP/6-31+g(d,p)) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)

Charge = 0 Multiplicity = 1

C	-2.981729893787	-1.859733369176	-1.035018954226
C	-3.647559843399	-0.991249866446	0.038290967605
C	-2.650575064810	-0.555856786752	1.158939009248
C	-1.474272932151	0.114854648745	0.443280831453
C	-0.736045793464	-0.769520844878	-0.556133169231
C	-1.739722676752	-1.199381796985	-1.651398479212
C	-1.185446990343	1.420352117496	0.574164827360
C	-0.121107053936	2.128706538666	-0.217749382480
C	0.312261232189	1.332445381609	-1.453441850922
C	0.608315930877	-0.143194735780	-1.056751722047
C	3.013200453444	0.307767424271	0.010814925602
C	1.612362042347	-0.306527449162	0.122487666250
C	1.393652864964	2.075803619708	-2.248568959867
C	-3.378442074440	0.370043183342	2.146780959067
C	-2.192913045903	-1.794539310731	1.962360357462
O	-4.273282160437	0.152893007356	-0.567662328486
C	1.136185091919	-0.938265759555	-2.262292711726
H	-0.451850941103	-1.694078490703	-0.036909021384
C	3.955481173977	-0.214966126656	1.101488415717
C	5.348975935342	0.420257021196	1.060700657330

C	6.285766581793	-0.115547083799	2.146240831599
H	-3.723548567202	-2.070921104528	-1.813199669396
H	-2.702634932902	-2.824170389525	-0.594659162146
H	-4.472577954334	-1.543764679813	0.501656647126
H	-2.036816744979	-0.327390597662	-2.248018655564
H	-1.272646584624	-1.906597411031	-2.342447026519
H	-1.740024158661	2.028120865246	1.283627600298
H	-0.497575093435	3.113211645773	-0.526776326731
H	0.750239684827	2.337122290009	0.422093964246
H	-0.563121585786	1.282233951713	-2.116798045846
H	2.954283098522	1.398498586514	0.094765821538
H	3.454574904516	0.094565219788	-0.970439325723
H	1.732263480180	-1.389508666271	0.269606277743
H	1.149292860454	0.065296458272	1.043230179273
H	1.681441641930	1.532337628503	-3.153370166474
H	1.006439587543	3.051530881135	-2.566302897079
H	2.298958306402	2.259908078933	-1.666074222050
H	-3.761872948454	1.274592488186	1.670936555163
H	-2.715527343572	0.663705301484	2.967605469107
H	-4.233382409422	-0.160146491191	2.580816565068
H	-3.057427163701	-2.272691446256	2.436993491404
H	-1.689715640804	-2.549755979965	1.356815526523
H	-1.500475705665	-1.488672952245	2.754046800919
H	-3.574004822907	0.781050254464	-0.809541978964
H	0.528152707864	-0.778448308268	-3.158310760610
H	1.138201611722	-2.013011846783	-2.043938354638
H	2.162258081613	-0.654412179854	-2.510667599107
H	3.504990722349	-0.034171247318	2.088529595734
H	4.052225062047	-1.306117112047	1.004547936957
H	5.252316981630	1.509737076978	1.166097385614
H	5.796247164418	0.245721464063	0.072176892156
H	5.879189869408	0.073046769564	3.147504318831
H	7.273518428988	0.356533578838	2.093829365987
H	6.428685282277	-1.198550140456	2.046239127411

Thermochemistry at 298.150 K, 1.000 Atm
E(el) = -514509.527075 kcal/mol
ZPVE = 312.396903 kcal/mol
Enthalpie(0K) = -514197.130172 kcal/mol
E(tr) = 0.888732 kcal/mol
E(rot) = 0.888732 kcal/mol
E(vib) = 324.503885 kcal/mol
H-E(el) = 326.873837 kcal/mol
Enthalpie = -514182.653238 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000068155947
S(rot) = 0.000054563202 (Symmetry number= 1)
S(vib) = 0.000119757216
G-E(el) = 281.508468 kcal/mol

Free Energy = -514228.018607 kcal/mol

Cartesian Coordinates and Energies of Barrier **6b-eq / 6b-ax**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform) //# SADDLE/B3LYP/6-31+g(d,p)) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)
Charge = 0 Multiplicity = 1

C	-2.814624992964	-1.963648419337	-0.896917439463
C	-3.517270424740	-1.152596030596	0.207061215183
C	-2.514575786612	-0.471335712074	1.211874547306
C	-1.541188171071	0.258909724506	0.295472119111
C	-0.714734817059	-0.629589322144	-0.611960036513
C	-1.717323220117	-1.185962902477	-1.653126300356
C	-1.632204777496	1.562074783535	-0.014869870497
C	-0.957269859383	2.099712373242	-1.248239307077
C	0.470849671071	1.552763900153	-1.485008990412
C	0.635056271609	0.026190637428	-1.080622399379
C	3.128445390825	-0.222501004427	-0.169882996204
C	1.619559342577	-0.170690979582	0.121033142495
C	1.461110103277	2.538083241270	-0.838629108657
C	-3.281766959734	0.461686553680	2.160696861421
C	-1.835498712915	-1.548300749661	2.084104539817
O	-4.396068103465	-0.182144898407	-0.381737371092
C	1.164865532905	-0.741863961430	-2.303871517704
H	-0.403995889078	-1.513948411062	-0.050444459874
C	3.961027453707	-0.171629168206	1.115154343384
C	5.469145258766	-0.293712501812	0.873470193662
C	6.290124090267	-0.246714141982	2.164678643268
H	-3.584870635216	-2.312059090705	-1.593687101847
H	-2.365894791317	-2.859509019014	-0.450002003693
H	-4.180161857297	-1.813034571169	0.777756219797
H	-2.156699699446	-0.376012910057	-2.248337587934
H	-1.227629117930	-1.866809075001	-2.355988155169
H	-2.282456262987	2.229499426051	0.543386774905
H	-1.588595880906	1.842055949860	-2.111922902343
H	-0.925285228827	3.194089754340	-1.223613110529
H	0.650364522765	1.607079495374	-2.565191073713
H	3.442358437277	0.593275387913	-0.828476239900
H	3.363747182457	-1.150149984484	-0.706835433240
H	1.373041235444	-1.122423997073	0.606468752214
H	1.419791272804	0.596598181643	0.876158812674
H	2.505813273222	2.263608472149	-0.993528534714
H	1.319684796597	3.529468289954	-1.283872826836
H	1.291065249281	2.638005213003	0.238664699973
H	-3.830322755756	1.245693522144	1.636927708111
H	-2.592289021111	0.935858505396	2.867725821981

H	-4.012609395188	-0.115859312053	2.737474781515
H	-2.577057847755	-2.020122933598	2.738270053103
H	-1.357479664404	-2.341450386049	1.507314773136
H	-1.069442288083	-1.090612257891	2.719433147352
H	-3.845866344923	0.530985385768	-0.744554879253
H	0.480675997959	-0.649790319681	-3.153037452833
H	1.292222432060	-1.809976704316	-2.088353978323
H	2.134328182781	-0.348780642137	-2.624737482100
H	3.755070046749	0.771129707840	1.642475195147
H	3.636918083302	-0.976818167369	1.790912541382
H	5.793925100144	0.514822756501	0.203790044102
H	5.675483978864	-1.233744020479	0.343058765669
H	6.125184810580	0.693900055087	2.704645630434
H	7.364020869042	-0.328978789663	1.961555460640
H	6.015096126234	-1.067749768788	2.838198089667

Thermochemistry at 298.150 K, 1.000 Atm
E(el) = -514496.259932 kcal/mol
ZPVE = 312.338023 kcal/mol
Enthalpie(0K) = -514183.921909 kcal/mol
E(tr) = 0.888732 kcal/mol
E(rot) = 0.888732 kcal/mol
E(vib) = 323.943217 kcal/mol
H-E(el) = 326.313169 kcal/mol
Enthalpie = -514169.946763 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000068155947
S(rot) = 0.000054576119 (Symmetry number= 1)
S(vib) = 0.000112568661
G-E(el) = 282.290303 kcal/mol
Free Energy = -514213.969629 kcal/mol

Cartesian Coordinates and Energies of **6b-ax**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform) //# MIN/B3LYP/6-31+g(d,p)) empiricaldispersion=gd3b scrf=(smd,solvent=chloroform)
Charge = 0 Multiplicity = 1

C	-2.195576930457	-2.369261829567	0.300480265446
C	-3.409760730051	-1.472462917947	0.057438111419
C	-3.193215150505	-0.034395407691	0.598752071138
C	-1.881767161578	0.541779870775	0.038815183869
C	-0.639304306207	-0.339282242918	0.175288368349
C	-0.934785801164	-1.773223825248	-0.326328066723

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C     -1.809726569971      1.788573214278      -0.454296929303
C     -0.526133853595      2.477110926762      -0.825324651008
C      0.696454034514      1.798188535970      -0.187543239455
C      0.652538900519      0.267857634883      -0.468270539745
C      3.262898896377      0.067458801023      -0.280133930644
C      1.883681528012     -0.448319467755       0.145966213491
C      0.793277772895      2.154398350953       1.303430158525
C     -4.430790785921      0.812678856230       0.257868833154
C     -3.092263149774     -0.088300613886       2.144813559513
O     -3.755860172618     -1.462952073128      -1.340219041617
C      0.662491619041      0.054787852202      -1.998700278261
H     -0.434167298739     -0.431960758359       1.252074539648
C      4.404282234787     -0.768535035292       0.309447984360
C      5.796886542145     -0.281291597991      -0.103759932651
C      6.928809952398     -1.130265426738       0.480434724559
H     -2.399408366078     -3.356897863214      -0.128259545336
H     -2.056007372455     -2.511722496901       1.378126348224
H     -4.291048084120     -1.896873992249       0.550291346143
H     -1.054129620256     -1.765997857053      -1.415242735509
H     -0.080680462641     -2.423680071999      -0.117025559073
H     -2.715041630097      2.380481746539      -0.551552490258
H     -0.417931331366      2.520717512313      -1.917968790167
H     -0.577630272528      3.523992128821      -0.497277767729
H      1.591790479600      2.195812079191      -0.680380139521
H      3.390712654804      1.111437652542       0.032610767435
H      3.346098189786      0.059521451107      -1.374399689498
H      1.827427009252     -1.511881755823      -0.115111542431
H      1.817064276160     -0.405557472613       1.240274548292
H      1.695412510096      1.744463614565       1.766919733764
H      0.827814767902      3.242738800280       1.427483979748
H     -0.070710485263      1.787848183394       1.866478289190
H     -4.549446858443      0.962862064334      -0.817759647783
H     -4.386246662660      1.793396713386       0.741324440538
H     -5.330576219228      0.305424968773       0.623550081995
H     -3.973778337025     -0.585757038880       2.566645917420
H     -2.207482727793     -0.620954437116       2.498921845833
H     -3.051312861047      0.928372783680       2.548630909491
H     -3.093879335104     -0.937852973092      -1.815056023696
H     -0.304537635385      0.292791975374      -2.451031688070
H      0.903621306771     -0.980609741262      -2.256851815846
H      1.414440072422      0.693161450495      -2.473522413961
H      4.330440914480     -0.762974975932       1.406826073529
H      4.283428509105     -1.816811992144      -0.000200552021
H      5.922909488525      0.763731285941       0.211511162178
H      5.867911753421     -0.282005945513      -1.200277739594
H      6.902908501566     -1.124383931152       1.577224907108
H      7.911836716599     -0.758904575721       0.168877783912
H      6.849283077626     -2.174305482081       0.153258143278
-------------------------------------------------------------
Thermochemistry at  298.150 K,    1.000 Atm
E(el)          = -514510.498482  kcal/mol
ZPVE           = 312.714536  kcal/mol
```
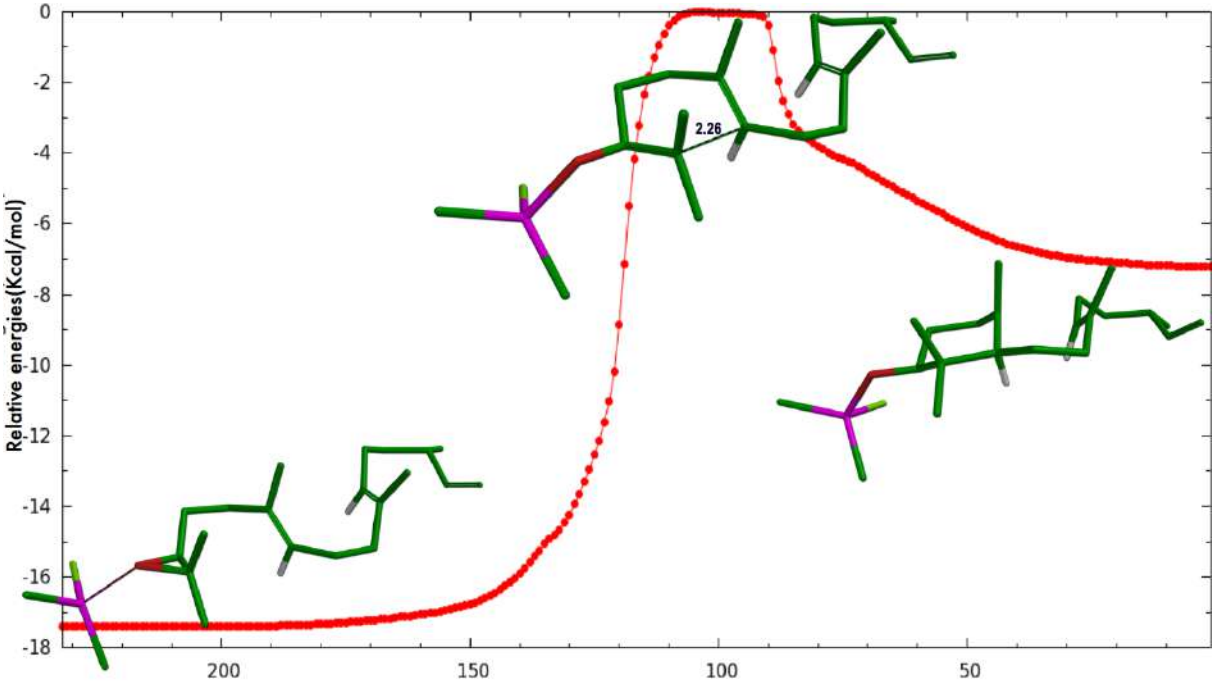

```
Enthalpie(0K)   = -514197.783946  kcal/mol
E(tr)           = 0.888732  kcal/mol
E(rot)          = 0.888732  kcal/mol
E(vib)          = 324.771402  kcal/mol
H-E(el)         = 327.141354  kcal/mol
Enthalpie       = -514183.357127  kcal/mol
S(el)           = 0.000000000000
S(tr)           = 0.000068155947
S(rot)          = 0.000054576174 (Symmetry number= 1)
S(vib)          = 0.000120023797
G-E(el)         = 281.723682  kcal/mol
Free Energy     = -514228.774799  kcal/mol
---------------------------------------------------------------
```

1.1.Steps in the formation of Xa from Ia

Plot of IRC transformation of **Ia** in to **IIa** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **Ia**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.616922944995	1.319449314699	-0.606904731320
C	2.074457912942	1.060636047361	-1.050362867117
C	2.793947304750	0.254077532396	-0.006025838814
C	2.974130678562	-1.210331161904	0.007461133439
C	-0.429781714219	-0.514672032932	0.696817955802
C	-1.221951039788	-1.757445344329	0.993293314675
C	-2.692201483169	-1.438572014795	1.384735831300
C	-3.509954097472	-0.923890934148	0.222508360833
C	-3.750339853752	0.389039890289	0.090677603531
C	-0.203756608727	0.050417677827	-0.499889768092
C	-4.500891498446	1.101207643250	-0.999209352750
C	-5.722345754432	1.897503476827	-0.497407628552
C	-6.979665790492	1.057612936143	-0.195919266414
C	-6.767624669719	0.032690547934	0.888426256812
C	-7.138707216995	-1.248062663470	0.814871667341
C	-8.147372329072	1.986811241549	0.191752953690
C	-4.021387204243	-1.982936195824	-0.717308752981
C	2.517424160102	-2.079329149146	-1.135618380115
C	3.131337656295	-1.915768180407	1.330082249117
C	-0.709749109059	-0.497803993156	-1.809166158697
H	0.155192579069	2.004303140519	-1.328568753822
H	0.626654810427	1.838751413339	0.358559432213

H	2.106772151660	0.553766309423	-2.017873565556
H	2.609148292189	2.008808650683	-1.165894726841
H	2.837454447275	0.734914016019	0.971510841241
H	-0.047469678823	0.007399569811	1.575590493666
H	-1.216194104805	-2.445487777103	0.140950717070
H	-0.752539903797	-2.293961064167	1.827611737060
H	-3.152182279561	-2.352397206498	1.784715087037
H	-2.685106079403	-0.700781632708	2.195004249226
H	-3.348562039073	1.047567698385	0.862538078909
H	-3.812600110098	1.812181141390	-1.479514112579
H	-4.821288424991	0.406997029361	-1.783047692447
H	-5.992752275332	2.644609743769	-1.253945864510
H	-5.442957767284	2.461425112310	0.404297111856
H	-7.260584336427	0.523841391720	-1.115251729253
H	-6.317011220497	0.404485217621	1.809589954849
H	-7.000234899534	-1.932162143330	1.646965642940
H	-7.591751205540	-1.655971002415	-0.086324220510
H	-8.330309792707	2.732021844093	-0.590733696610
H	-7.924119748437	2.523907306322	1.121426806193
H	-9.066420704373	1.414538635150	0.347801794196
H	-3.250527737872	-2.732305858343	-0.932305512508
H	-4.372870164197	-1.580901927333	-1.668976009937
H	-4.864352535491	-2.511345421839	-0.251164974433
H	3.174537293372	-2.949495433577	-1.226514019121
H	2.524035383735	-1.542675538164	-2.083856107424
H	1.500884738424	-2.429444943753	-0.935049965372
H	3.481406239911	-1.242321970567	2.112378752620
H	3.834178624159	-2.750025668100	1.243320256470
H	2.156132181058	-2.318555716588	1.622880417780
H	0.081258391675	-0.512905488266	-2.568056109311
H	-1.511296617200	0.144135672138	-2.194958760320
H	-1.116236134774	-1.506079820570	-1.721147529528
O	4.097304176153	-0.309952369337	-0.380155804395
Al	5.836403838689	0.306956032385	0.301101766465
C	5.817267600631	0.125197117274	2.266399979182
C	7.092753196525	-0.711040628232	-0.814752362172
H	6.696355155521	0.639791138455	2.676881892182
H	5.871241657092	-0.916782703683	2.606916286737
H	4.942913244499	0.592670880374	2.737830364411
H	6.921236925522	-0.531462920844	-1.882855862610
H	8.132190052949	-0.431159463355	-0.601091665944
H	7.009535381630	-1.792576435381	-0.640494617090
Cl	5.536687770517	2.397998484923	-0.281999787041

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029479.143086 kcal/mol
ZPVE = 357.556602 kcal/mol
Enthalpie(0K) = -1029121.586484 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 365.454503 kcal/mol
H-E(el) = 367.005722 kcal/mol

Enthalpie = -1029112.137364 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000056401401 (Symmetry number= 1)
S(vib) = 0.000121538754
G-E(el) = 337.095366 kcal/mol
Free Energy = -1029142.047720 kcal/mol

Cartesian Coordinates and Energies of **Transition state Ia-IIa**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.632518444022	1.054241928471	-1.227469022314
C	2.121223794520	0.745712036958	-1.498490658132
C	2.731913263735	0.021854395032	-0.303628154316
C	2.090220991242	-1.308669373518	0.061820442233
C	-0.059003623571	-0.700070175598	0.393655350440
C	-0.852638041575	-1.866342549004	0.912266596744
C	-2.266055901509	-1.409843270279	1.373414871909
C	-3.133766961701	-0.910801010776	0.241578535321
C	-3.308864907693	0.407079408515	0.056441134126
C	-0.064853663950	-0.233551252547	-0.898205151329
C	-4.094218545144	1.109537722826	-1.014613785923
C	-5.245512827834	1.982136438717	-0.473907432040
C	-6.511386074551	1.213617618319	-0.044898070659
C	-6.272739547345	0.257779976760	1.095867584999
C	-6.695955074187	-1.008229225339	1.136604066563
C	-7.620799111829	2.212009789941	0.341957526648
C	-3.770858100160	-1.984801730157	-0.598478947626
C	2.065953066788	-2.397701175289	-0.967414755612
C	2.327321367647	-1.771213892879	1.467250947420
C	-0.640359231226	-0.984771809405	-2.056403626937
H	0.174698588875	1.521951915325	-2.104881623114
H	0.559300758441	1.755862495819	-0.390399412550
H	2.247881581956	0.142117736416	-2.403732576930
H	2.681050363900	1.672894703716	-1.642633494059
H	2.656571808812	0.692201914379	0.569063007666
H	0.249882503978	0.016558072918	1.152819437801
H	-0.945391638575	-2.655041279864	0.159548381742
H	-0.342689518669	-2.307358413154	1.773815093218
H	-2.750075687622	-2.261688634795	1.868375014311
H	-2.148402431288	-0.625781156101	2.129704156140
H	-2.825113167077	1.078327094529	0.768574885084
H	-3.406258695608	1.768847184317	-1.564015565189
H	-4.494176675871	0.401609396806	-1.748035698791
H	-5.535298939467	2.699678035795	-1.251013704642
H	-4.882095536740	2.579265156825	0.374584258530
H	-6.864373302463	0.630165751969	-0.907416651417
H	-5.757303056694	0.674766204243	1.962343671404

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H     -6.537930470445       -1.636090420953        2.008639186123
H     -7.219368829553       -1.458301123914        0.295628420500
H     -7.825535048635        2.906808063801       -0.480271404933
H     -7.324032157047        2.803842852965        1.216041594887
H     -8.547358241232        1.687295963448        0.591565675055
H     -3.058619906049       -2.782514354511       -0.839280813149
H     -4.185919105675       -1.610223616853       -1.535409193733
H     -4.594155526923       -2.446424131055       -0.037168442924
H      3.044517630123       -2.888909580694       -0.930945794060
H      1.922349790344       -2.028591650866       -1.981448884933
H      1.308255428003       -3.149272799978       -0.730181770739
H      2.071997494771       -1.016297375866        2.212690270365
H      3.411664425536       -1.924757023864        1.538072276622
H      1.834822881049       -2.718473609728        1.692821107690
H      0.007983051816       -0.903299744646       -2.934357802537
H     -1.597095812975       -0.517337702787       -2.319108651098
H     -0.832502110139       -2.036693874848       -1.846025884491
O      4.038171294102       -0.399145405307       -0.542603287289
Al     5.442869007554        0.420208397021        0.320371024613
C      5.402810218777       -0.091044452444        2.245504879640
C      7.070415007521        0.044684646600       -0.733906260658
H      6.198027262359        0.433836420764        2.791481323547
H      5.566699816939       -1.167040110307        2.408367300292
H      4.458909864483        0.181741871995        2.737611664809
H      6.966452593375        0.389299687487       -1.770431736283
H      7.948124143757        0.548416479684       -0.308237091637
H      7.294099751982       -1.030907168718       -0.763426199583
Cl     4.814095693687        2.568610308373        0.194482953894
--------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029471.232203  kcal/mol
ZPVE           = 357.122125  kcal/mol
Enthalpie(0K)   = -1029114.110078  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 364.993997  kcal/mol
H-E(el)         = 366.545216  kcal/mol
Enthalpie       = -1029104.686986  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)          = 0.000056109775 (Symmetry number= 1)
S(vib)          = 0.000120883439
G-E(el)         = 336.750821  kcal/mol
Free Energy     = -1029134.481382  kcal/mol
--------------------------------------------------------------
```

Cartesian Coordinates and Energies of **IIa**

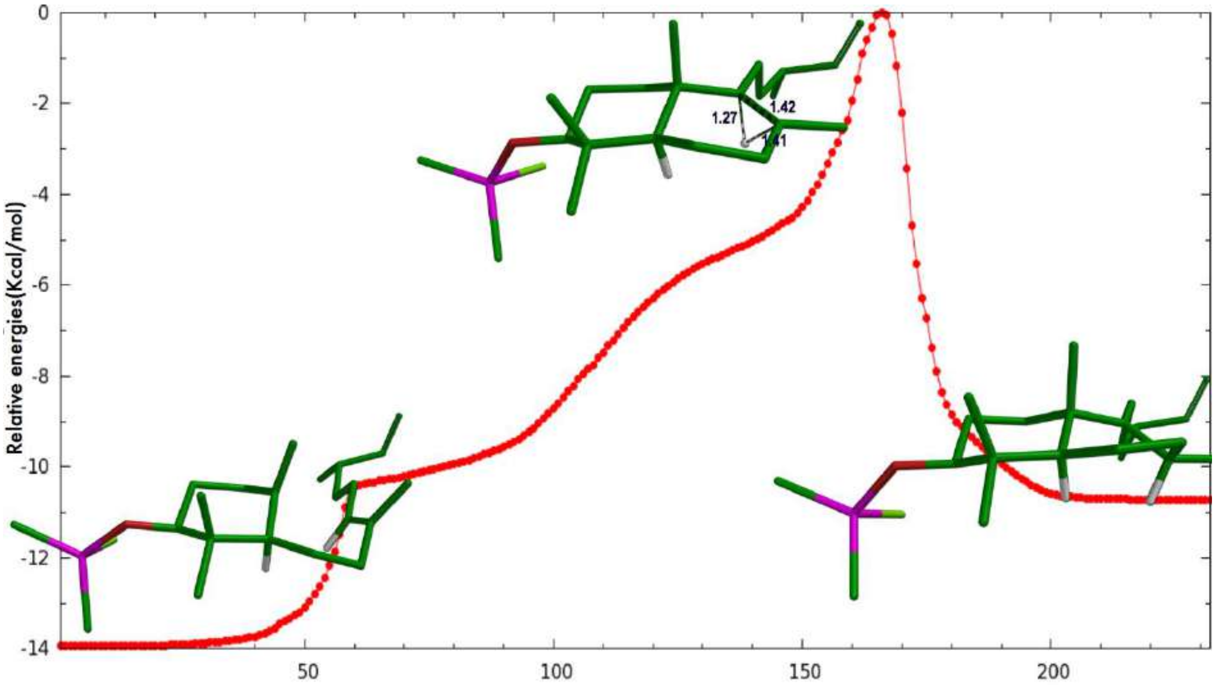
#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.177395887679	0.748411318814	-1.135976268165
C	1.723110127282	0.518801848747	-1.342683250162
C	2.354878101752	-0.214733057839	-0.154487605217
C	1.678334454559	-1.591294464348	0.139223959653
C	0.101237102914	-1.300527607740	0.292745495315
C	-0.754001491608	-2.487374527470	0.725415830987
C	-2.147690859608	-1.978388900703	1.173387543570
C	-2.820096242097	-1.206615624177	0.070932474436
C	-2.653453350873	0.138559734969	-0.019179378491
C	-0.346360576558	-0.613047519262	-0.941659516477
C	-3.253717825273	1.081319419807	-1.018508638782
C	-4.161859474319	2.153137271550	-0.379391206553
C	-5.551799659941	1.664842805419	0.073122435030
C	-5.490481138056	0.636326611114	1.173162913382
C	-6.174588969708	-0.510785132541	1.190623133163
C	-6.397899895162	2.867755700916	0.536250603058
C	-3.656433205609	-2.014324822988	-0.876775229857
C	2.015174965471	-2.627713576661	-0.935964539464
C	2.200144163323	-2.093577324218	1.493516038587
C	-0.763457600982	-1.339183428121	-2.175570923878
H	-0.246330831020	1.250607979480	-2.008302550235
H	0.060788651645	1.374046162245	-0.247885870494
H	1.922465438162	-0.021508186617	-2.273015360915
H	2.181566957263	1.509492603716	-1.418174011272
H	2.159874546611	0.411439715453	0.739881779847
H	0.078706067468	-0.555995052559	1.097975514514
H	-0.852284700532	-3.225610089275	-0.076311413758
H	-0.278575874817	-2.999852698358	1.563511115158
H	-2.769032196639	-2.830746485290	1.469148220223
H	-2.018111729806	-1.344501275549	2.056501217936
H	-2.104431145504	0.622626019991	0.787558660121
H	-2.438004248250	1.609467965556	-1.530440541451
H	-3.813940037254	0.543643191440	-1.789595863919
H	-4.305635388654	2.956425857238	-1.110895780406
H	-3.641471121010	2.608278367306	0.474845353521
H	-6.052292259314	1.208215101233	-0.792762522388
H	-4.874846216124	0.900858375300	2.034874884991
H	-6.131106773287	-1.190235598468	2.036769838827
H	-6.815070078453	-0.800638291375	0.360067555011
H	-6.470965610794	3.620982692197	-0.255722764497
H	-5.947655678798	3.345148586185	1.414367537292
H	-7.408528215626	2.550808373685	0.807731146905
H	-3.221935570616	-3.004641069528	-1.046649587658
H	-3.817394930288	-1.532655811772	-1.842081315144
H	-4.641831094141	-2.167570714948	-0.416905213909
H	3.096414101484	-2.779630879605	-0.924002434230
H	1.756062682502	-2.307153995368	-1.947021402753
H	1.523157890124	-3.586154670840	-0.738674161639
H	1.863542727672	-1.458318347770	2.319516651829
H	3.291365530904	-2.041287541024	1.460644776506
H	1.908620634106	-3.127994550140	1.697355861804
H	0.087658018172	-1.333171788242	-2.867629113951

```
H     -1.567552507850      -0.797499032798      -2.681305386492
H     -1.060344060038      -2.371503925250      -2.006496821519
O      3.707421672243      -0.380705118213      -0.381363253236
Al     4.909185976363       0.755401272136       0.375045455443
C      4.911512279786       0.456966413206       2.344605204003
C      6.612551793945       0.642995986506      -0.622978762800
H      5.527494087180       1.203572308729       2.863053309213
H      5.309907162698      -0.533621479814       2.609167029062
H      3.901705825050       0.529086189562       2.773263189962
H      6.465910521190       0.854107475909      -1.690384699415
H      7.349530574700       1.364735731934      -0.246623302764
H      7.065037493683      -0.355700357566      -0.544175281027
Cl     3.927807273253       2.778210411410       0.049585992177
------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029483.659309  kcal/mol
ZPVE           = 359.061546  kcal/mol
Enthalpie(0K)   = -1029124.597763  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 367.006285  kcal/mol
H-E(el)        = 368.557505  kcal/mol
Enthalpie      = -1029115.101804  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055733467 (Symmetry number= 1)
S(vib)         = 0.000125250662
G-E(el)        = 338.274388  kcal/mol
Free Energy    = -1029145.384921  kcal/mol
------------------------------------------------------------
```

2. Plot of IRC transformation of **IIa** in to **IVa** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **IIa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.283931110659	0.445716699055	-0.617079785443
C	1.199093371453	0.544988138419	-1.140019759222
C	2.171034333942	-0.221765920129	-0.235451877981
C	1.798066748288	-1.730785108804	-0.080096750167
C	0.260371485144	-1.771256930757	0.403973922803
C	-0.294029902350	-3.149283062760	0.753269860137
C	-1.627810050217	-2.988341577883	1.528996221747
C	-2.623585436066	-2.185945969214	0.735338202433
C	-2.667765818161	-0.832476284530	0.847886201424
C	-0.528817503368	-1.005054698457	-0.585507617145
C	-3.600155689607	0.094795128078	0.114779928580
C	-3.635992296827	1.501602828738	0.721883108806
C	-4.518027564407	2.489908357151	-0.065941808138
C	-5.951037882504	2.026380534225	-0.109105358838
C	-6.635154643375	1.725342079196	-1.215803098488
C	-4.422252464106	3.899174706802	0.543730745204
C	-3.516704373343	-2.955148845792	-0.197343592484
C	2.061280354740	-2.514352375192	-1.368552894679
C	2.661372572308	-2.316941172293	1.046267299771
C	-1.070298091807	-1.608351544284	-1.835158970589
H	-0.962746992733	0.980748050649	-1.285118983163
H	-0.302995410010	0.896699060288	0.377328270822
H	1.282820251064	0.194712279901	-2.173115804817
H	1.472772675955	1.604228358340	-1.114103322557

```
H     2.066016403814      0.217194760884      0.777485834930
H     0.289792697340     -1.174428260363      1.323671020738
H    -0.442051704664     -3.764183330119     -0.139913827334
H     0.417832964370     -3.684397574902      1.384100994048
H    -2.035036579735     -3.979436067410      1.756929539504
H    -1.415755249594     -2.493150719341      2.481959417686
H    -2.039000448467     -0.374580828384      1.609580694983
H    -3.302961120415      0.174808387985     -0.943405537803
H    -4.612691671220     -0.322601928220      0.094483951358
H    -2.617247826481      1.905511770971      0.773220275577
H    -3.996965950642      1.440962935971      1.757848072420
H    -4.141550760669      2.532310427978     -1.098328855947
H    -6.446860886579      1.949673855118      0.861113844359
H    -7.673646525356      1.410090415977     -1.178226626044
H    -6.179077945446      1.797579203113     -2.200963562387
H    -5.011334629795      4.615775986806     -0.035462930726
H    -3.383481103253      4.245445060659      0.566649602860
H    -4.801604019113      3.904688785562      1.572290882960
H    -3.964538177815     -2.334806948693     -0.975516907388
H    -4.335466635891     -3.406661704858      0.378511672836
H    -2.978364431536     -3.781645695029     -0.673293903372
H     3.129996727663     -2.449966134290     -1.583293907110
H     1.541513960192     -2.109725220478     -2.239676737841
H     1.787746061336     -3.569352612858     -1.260604786903
H     2.410578053420     -1.879659364685      2.018285508936
H     3.700575891933     -2.058527981564      0.827359740695
H     2.581510581599     -3.405895263446      1.113342918372
H    -0.432043572928     -1.285662198720     -2.666307891563
H    -2.064839455686     -1.206157218312     -2.050802893096
H    -1.104498908045     -2.695029977771     -1.826625119251
O     3.456642515026     -0.089850405406     -0.722390296440
Al    4.590151212447      1.126540796281      0.016078443180
C     5.045973547501      0.540615371168      1.864490543452
C     6.050999195300      1.498680179179     -1.263414158762
H     5.641634652517      1.300251471974      2.387816351900
H     5.633362933829     -0.389349846246      1.865092812681
H     4.151400247894      0.364006841848      2.478540156468
H     5.660119995633      1.852117179850     -2.226510493568
H     6.732396183668      2.272023141736     -0.884786375776
H     6.654836375408      0.601907091332     -1.462193946230
Cl    3.248658465089      2.947017692056      0.247877339478
----------------------------------------------------------------
        Thermochemistry at  195.150 K,    1.000 Atm
        E(el)           = -1029483.851220  kcal/mol
        ZPVE            = 358.855396  kcal/mol
        Enthalpie(0K)   = -1029124.995824  kcal/mol
        E(tr)           = 0.581707  kcal/mol
        E(rot)          = 0.581707  kcal/mol
        E(vib)          = 366.500864  kcal/mol
        H-E(el)         = 368.052084  kcal/mol
        Enthalpie       = -1029115.799136  kcal/mol
        S(el)           = 0.000000000000
        S(tr)           = 0.000066308847
        S(rot)          = 0.000055909435 (Symmetry number= 1)
        S(vib)          = 0.000117363073
```

G-E(el) = 338.713320 kcal/mol
Free Energy = -1029145.137899 kcal/mol

Cartesian Coordinates and Energies of **Transition state IIa-IVa**

FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	-0.226311528618	0.506504336485	-0.910568431066
C	1.236858023305	0.518856977209	-1.347686748267
C	2.124482288457	-0.202900812062	-0.328302180867
C	1.710513956712	-1.694771608021	-0.143619850200
C	0.191362155828	-1.727045891851	0.207325973989
C	-0.365479800628	-3.128173828317	0.479403706897
C	-1.703544365701	-3.037708858673	1.214460692056
C	-2.599114890916	-1.904178516985	0.791948438616
C	-2.170469014968	-0.885024060615	-0.095532662613
C	-0.771799621787	-0.931931218741	-0.734045924415
C	-3.180461868161	0.146594637091	-0.579632396479
C	-3.301445872803	1.389455122803	0.324361000009
C	-4.477846637871	2.301699179718	-0.083729542227
C	-5.795842022577	1.623712896393	0.188940906284
C	-6.657744467387	1.195770515298	-0.737656563318
C	-4.391188032459	3.646917881207	0.655407038446
C	-3.998338246828	-1.940850017822	1.339105516598
C	2.109999654360	-2.532912123689	-1.369226351633
C	2.502264558471	-2.236020499238	1.064078249598
C	-1.007161653012	-1.581564343596	-2.121279418704
H	-0.843210268506	1.064857005492	-1.623564990545
H	-0.290821294769	1.031374828447	0.051988513529
H	1.370538490028	0.077292767912	-2.341804825516
H	1.584990189875	1.552631393134	-1.406462394969
H	1.917731786147	0.281241591132	0.649170660990
H	0.144819710643	-1.179381988380	1.166202544589
H	-0.486055798734	-3.683612291271	-0.454655347930
H	0.329622642005	-3.703145811262	1.092567591742
H	-2.309300245730	-3.946209977939	1.090634130520
H	-1.555052255007	-2.948921465308	2.299933644484
H	-1.978172348743	-0.691580278461	1.142710459730
H	-2.869427861027	0.473297833151	-1.572736885468
H	-4.162641063585	-0.319218044330	-0.695651636230
H	-2.368378183936	1.958601558538	0.285071692993
H	-3.438473528588	1.089014202692	1.373838388359
H	-4.399705714385	2.489392191270	-1.163415221103
H	-6.041548212012	1.490985750874	1.245278575994
H	-7.597515719150	0.722772033911	-0.468703256474
H	-6.460264540143	1.326101999118	-1.799389737990
H	-5.211919135466	4.306152945887	0.359527873667
H	-3.446230740453	4.153538710478	0.435870540255
H	-4.451270389660	3.501848433713	1.740546799607

H	-4.591349035222	-2.562605921540	0.655649667237
H	-4.479369380610	-0.965298526373	1.390517985075
H	-4.018542781044	-2.416966823413	2.321891478660
H	3.197686649696	-2.501718541995	-1.458307556744
H	1.709511609117	-2.151214286365	-2.309630971066
H	1.799684885727	-3.579132562131	-1.263336242301
H	2.179809382378	-1.765634526397	2.000674674418
H	3.555997131742	-1.989321256529	0.923835920899
H	2.418759370318	-3.323326637304	1.170663064530
H	-0.093795221141	-1.539379083478	-2.709604774917
H	-1.777416706698	-1.041762020014	-2.680030633738
H	-1.316868066415	-2.627129768180	-2.047562906989
O	3.460121778599	-0.089900027359	-0.672531061623
Al	4.526791494936	1.098366663555	0.178684679483
C	4.846569571817	0.491031415426	2.053475583352
C	6.102769354856	1.489564054338	-0.955818467899
H	5.419889729946	1.238235884699	2.618841835009
H	5.412191495665	-0.451704284112	2.093205842817
H	3.906228123341	0.332802405470	2.600599401907
H	5.801349505048	1.863582345132	-1.943286796738
H	6.749886347310	2.251865496018	-0.501419817524
H	6.718704551327	0.593245590358	-1.118031196560
Cl	3.209264077071	2.944101254787	0.359750719834

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029480.569682 kcal/mol
ZPVE = 357.643941 kcal/mol
Enthalpie(0K) = -1029122.925741 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 365.101151 kcal/mol
H-E(el) = 366.652371 kcal/mol
Enthalpie = -1029113.917311 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055665351 (Symmetry number= 1)
S(vib) = 0.000117559201
G-E(el) = 337.319481 kcal/mol
Free Energy = -1029143.250202 kcal/mol

Cartesian Coordinates and Energies of **IVa**

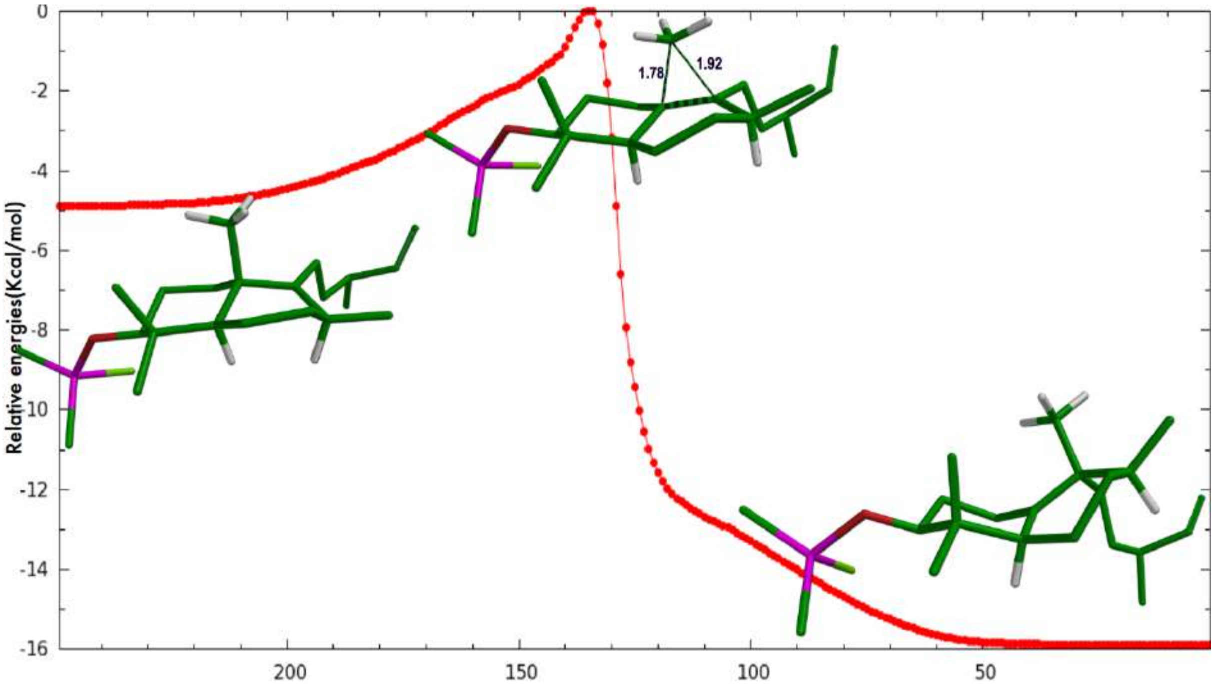
#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.210552037513	0.518093290692	-0.913658031827
C	1.258744685314	0.480342650647	-1.334426030385
C	2.112337016846	-0.226011019623	-0.279892137872
C	1.687066240755	-1.711220731197	-0.082236664923

C	0.162313666525	-1.729454388047	0.256387139641
C	-0.398644366865	-3.138489669680	0.525825949766
C	-1.922400425455	-3.135615180250	0.756296518340
C	-2.498280513185	-1.713368485549	1.038702351761
C	-2.146272288069	-0.829668380439	-0.099248978630
C	-0.781662662714	-0.921172809715	-0.682878687792
C	-3.140503571009	0.120014589240	-0.626576137767
C	-3.245473724218	1.377079765683	0.303278585498
C	-4.438390864382	2.271348586822	-0.103510043440
C	-5.748044835193	1.565326147095	0.121472440403
C	-6.592167351903	1.179825117041	-0.839642781885
C	-4.379487761825	3.592181956559	0.683415549545
C	-3.970700555528	-1.775433462937	1.452579541180
C	2.107412171224	-2.559679162515	-1.294721487292
C	2.461256968047	-2.243899238531	1.140669156010
C	-1.011128175569	-1.601869742534	-2.081445002631
H	-0.814667567371	1.052988685501	-1.653584905369
H	-0.272045924133	1.073875975940	0.028405990779
H	1.399555490210	0.009810635505	-2.313276727679
H	1.614868821216	1.511458312635	-1.419564467780
H	1.893535213422	0.278549016253	0.682324262634
H	0.111942483873	-1.184702290320	1.210937313681
H	-0.155335268380	-3.808043395502	-0.303304165046
H	0.105030707291	-3.544906515012	1.405131390822
H	-2.459984204578	-3.539522981823	-0.108834197220
H	-2.194768377993	-3.766013228330	1.607455777941
H	-1.903875713700	-1.313524910418	1.882658066363
H	-2.882721445158	0.466981131762	-1.627996385027
H	-4.131919612393	-0.345645447718	-0.654976631483
H	-2.318692887715	1.949697156085	0.230052138619
H	-3.354709256737	1.075556957411	1.350144366491
H	-4.342163173348	2.495429070617	-1.174320167779
H	-6.002913302208	1.368929498082	1.164930718095
H	-7.528036074162	0.679364943317	-0.610398879878
H	-6.381516519350	1.370242731257	-1.889730434592
H	-5.197553287006	4.253499546333	0.384642268073
H	-3.433359048143	4.112996326801	0.506162720646
H	-4.469433435352	3.410821210116	1.760673516829
H	-4.582995123003	-2.219301549290	0.660722573107
H	-4.388969783398	-0.797340628650	1.695709408862
H	-4.068302995486	-2.408624000428	2.338047469526
H	3.189912105580	-2.469817050119	-1.405832241595
H	1.666813358680	-2.231601446522	-2.237501368170
H	1.862210069265	-3.617803083126	-1.155450458123
H	2.149236801807	-1.737850397502	2.062192690909
H	3.524160331493	-2.038274823607	0.998437231620
H	2.335110496165	-3.323219495164	1.276080595092
H	-0.091205080880	-1.504506178499	-2.654454917292
H	-1.809296000286	-1.112449766879	-2.643332255479
H	-1.247511677149	-2.662377008786	-1.986273934147
O	3.457320003352	-0.120444238262	-0.603139217666
Al	4.525824656441	1.131494472809	0.129053621605
C	5.083051319759	0.533052341542	1.957107147966
C	5.973649241304	1.609103284720	-1.142170395640
H	5.663007767554	1.313705795709	2.464762723717

```
H      5.702860177175        -0.372141845876         1.901604800058
H      4.205891582613         0.309348309687         2.578335048530
H      5.555857372016         1.976725369154        -2.088086980249
H      6.619921412082         2.396071879163        -0.733197127809
H      6.606027456135         0.739784550130        -1.368128748748
Cl     3.146446874072         2.898090691383         0.442177317723
--------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029485.950966  kcal/mol
ZPVE           = 359.997874  kcal/mol
Enthalpie(0K)   = -1029125.953092  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 367.206017  kcal/mol
H-E(el)         = 368.757237  kcal/mol
Enthalpie       = -1029117.193729  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)          = 0.000055622370 (Symmetry number= 1)
S(vib)          = 0.000110060157
G-E(el)         = 340.347931  kcal/mol
Free Energy     = -1029145.603035  kcal/mol
--------------------------------------------------------------
```

Plot of IRC transformation of **IVa** in to **Va**$_1$ (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **IVa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.098022558187	-0.537020095146	-0.900162195479
C	-1.362833525382	-0.403249098783	-1.329294429233
C	-2.166913671860	0.374995142733	-0.286991389597
C	-1.641335271188	1.829859039425	-0.108463661917
C	-0.116515080253	1.753423667262	0.225688200749
C	0.536712066231	3.128553934811	0.456858840064
C	2.056476407593	3.032242658786	0.694696753539
C	2.542470722555	1.581907787702	0.999232614923
C	2.126407401338	0.693546471196	-0.113071436379
C	0.769018130275	0.861447915238	-0.695441105699
C	3.049950533037	-0.339277632219	-0.612265055871
C	3.058717235917	-1.571326471148	0.355758915152
C	4.194857029026	-2.555619614684	-0.003515192056
C	5.545254608655	-1.933697472896	0.227643292231
C	6.429150624222	-1.629911527759	-0.727023965573
C	4.031556236409	-3.845729920288	0.818864134991
C	4.018709668188	1.559407542486	1.403632639767
C	-2.008710114103	2.690900170946	-1.329537393020
C	-2.374589039857	2.426432730601	1.110245814170
C	1.048415394351	1.497215810330	-2.106753889230
H	0.665032334742	-1.129841197691	-1.625079143669
H	0.115084374715	-1.076120101731	0.053499694461
H	-1.466635085888	0.061957292898	-2.315134257034
H	-1.790539295721	-1.407750773150	-1.401701984714
H	-1.984923869338	-0.131271686051	0.681727723904
H	-0.098218636940	1.230237094110	1.193445527792

H	0.339747705265	3.786246819494	-0.393578082727
H	0.058538797657	3.593845350364	1.321067687754
H	2.621809172982	3.389546709232	-0.173194821615
H	2.364710638688	3.656055899708	1.538322880357
H	1.930393989336	1.236275957968	1.855024513198
H	2.766964037628	-0.695606523905	-1.603604363871
H	4.072755236795	0.051358068608	-0.651613728845
H	2.096951998877	-2.083091138522	0.284511034400
H	3.172863509103	-1.245587066126	1.394899588080
H	4.102632375634	-2.803534660510	-1.069422214759
H	5.795828481987	-1.728553768857	1.270416681716
H	7.392486301692	-1.187183796451	-0.492898402476
H	6.223704841683	-1.832477354990	-1.775902873224
H	4.807935126548	-4.569523351764	0.555805537451
H	3.055552666054	-4.306351001992	0.637208176900
H	4.113531461636	-3.638547362584	1.892057503610
H	4.652708959590	1.940470765277	0.596314562112
H	4.375371808218	0.563735946167	1.672569532035
H	4.163299683961	2.209599320062	2.270166515583
H	-3.095493503114	2.676841306541	-1.433555273395
H	-1.599205695500	2.320008033812	-2.270670890179
H	-1.687627042214	3.730621881863	-1.206028400978
H	-2.094658035522	1.910087149546	2.036381947144
H	-3.449220653632	2.290918786888	0.972269674055
H	-2.176542805412	3.496257878044	1.234244789025
H	1.403876686736	2.525880578357	-2.032572848880
H	0.113219710782	1.497207191706	-2.663023722660
H	1.776590633327	0.912961594730	-2.673090440734
O	-3.515760420655	0.358198506874	-0.610653727702
Al	-4.673257881750	-0.802536849888	0.136974141564
C	-5.222194562589	-0.123138973280	1.939262602835
C	-6.130781205498	-1.221247342874	-1.144398923855
H	-4.344215516558	0.062588362932	2.571713433993
H	-5.857403280189	-0.854349312923	2.454533529947
H	-5.785168941351	0.815968756027	1.850957286664
H	-5.724333615276	-1.637770252058	-2.074855252204
H	-6.830251621365	-1.955952153079	-0.725816438800
H	-6.704485661066	-0.320186807470	-1.400597039279
Cl	-3.415599844987	-2.644453065644	0.518063189099

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029486.021154 kcal/mol
ZPVE = 360.363096 kcal/mol
Enthalpie(0K) = -1029125.658058 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 367.466484 kcal/mol
H-E(el) = 369.017704 kcal/mol
Enthalpie = -1029117.003451 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055621739 (Symmetry number= 1)
S(vib) = 0.000106963688
G-E(el) = 340.987664 kcal/mol
Free Energy = -1029145.033490 kcal/mol

Cartesian Coordinates and Energies of **Transition State IVa– Va$_1$**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.072243145379	-0.682369456713	-0.636616704990
C	-1.335517542337	-0.502551665490	-1.194986813189
C	-2.218892688962	0.279542619465	-0.217252482952
C	-1.637523485080	1.695736599277	0.075665072361
C	-0.164968861627	1.541334733863	0.585075317549
C	0.463024616505	2.880076020841	1.056240414796
C	1.919415381873	3.117066715414	0.648177550063
C	2.772033441161	1.844690747499	0.678646514759
C	2.150028782100	0.723087863528	-0.136004820516
C	0.739247853717	0.638312539887	-0.263264346156
C	3.051175843233	-0.413173905101	-0.539482284655
C	3.341611254883	-1.310275552258	0.684075207987
C	4.283681907887	-2.481138013259	0.328120786459
C	5.635691953314	-1.969759664653	-0.096381486934
C	6.166040450748	-2.102259469819	-1.314851508452
C	4.410517300173	-3.439065492915	1.524477366001
C	4.238708577621	2.144226020946	0.343984792920
C	-1.787402871887	2.587148018814	-1.169429302132
C	-2.470825478767	2.312196573982	1.214457407253
C	1.349424569080	1.390309887797	-1.753369145649
H	0.692940779092	-1.271412054320	-1.313937814336
H	0.002542006301	-1.253808190400	0.299467660033
H	-1.318049817391	-0.004670974362	-2.172187011385
H	-1.793248884109	-1.483413863202	-1.338929278832
H	-2.169624729253	-0.269064330378	0.746322965272
H	-0.264078857821	0.907423475481	1.480177150872
H	-0.135864267412	3.715963629279	0.690333505663
H	0.390582962081	2.921786829365	2.146964162233
H	1.978235347720	3.552386027198	-0.356622947523
H	2.372772417756	3.855867706411	1.315614292458
H	2.728284805972	1.441758226568	1.704973623943
H	2.594350474059	-1.026014830154	-1.316153479075
H	3.990681032382	-0.031807963953	-0.942977307467
H	2.400857051360	-1.712325362423	1.075573846191
H	3.795890066998	-0.720321693616	1.489594504922
H	3.839529094152	-3.029677095421	-0.513544822548
H	6.207890618571	-1.459072583400	0.681344840873
H	7.153884489548	-1.719096449505	-1.552156796319
H	5.633798286261	-2.615593534530	-2.112697404351
H	5.052464383097	-4.288025193328	1.273868878994
H	3.430638932622	-3.825972750835	1.822441799785
H	4.850615399763	-2.928231829310	2.388988238397
H	4.354270478323	2.454977568237	-0.700964741979
H	4.899469000854	1.292714711075	0.519493254312
H	4.589172926235	2.969289818677	0.969517649397
H	-2.853715845041	2.722788082585	-1.359852302052
H	-1.376722639438	2.133822690404	-2.076291819299

H	-1.335542511124	3.577244974452	-1.034579811539
H	-2.341194872050	1.751988823035	2.147516823897
H	-3.526368661861	2.254441329459	0.943753111065
H	-2.216982042225	3.361104091751	1.401216286855
H	0.593249074933	2.165972679661	-1.824734039727
H	1.245430161298	0.608360935385	-2.498244405560
H	2.323249689677	1.875361261930	-1.857751639117
O	-3.514884237630	0.360168694535	-0.690713426809
Al	-4.799183361283	-0.728488810055	-0.016864716046
C	-5.201607254706	-0.189103500490	1.860224515697
C	-6.294856016190	-0.835990089855	-1.310073214048
H	-4.296854288754	-0.162583957471	2.484229807008
H	-5.893731241203	-0.895683766559	2.337643671530
H	-5.665104255807	0.807104919982	1.913395681330
H	-5.952439484528	-1.190792172969	-2.291212706958
H	-7.077700106096	-1.526508443876	-0.968853299473
H	-6.769055450013	0.144272571570	-1.462516949842
Cl	-3.733524804202	-2.730786727642	0.135338129080

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029481.445234 kcal/mol
ZPVE = 360.348837 kcal/mol
Enthalpie(0K) = -1029121.096396 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 368.213966 kcal/mol
H-E(el) = 369.765186 kcal/mol
Enthalpie = -1029111.680048 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055691122 (Symmetry number= 1)
S(vib) = 0.000128117068
G-E(el) = 339.136239 kcal/mol
Free Energy = -1029142.308995 kcal/mol

Cartesian Coordinates and Energies of **Va$_1$**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.017940198461	-0.917241590235	-0.540868145939
C	-1.381963846231	-0.503975608318	-1.111612061871
C	-2.189184751281	0.201177112490	-0.027541015270
C	-1.481663088782	1.491849802105	0.480443266339
C	0.033093293535	1.082095363765	0.942071311724
C	0.836553227908	2.255066097783	1.524288837878
C	1.754987747019	2.900575925595	0.492333424069
C	2.742586490322	1.872406558895	-0.056762223807
C	2.010530270147	0.678525925447	-0.747976648854
C	0.713033607490	0.296485010984	-0.093874050417
C	2.962042652485	-0.565560179311	-0.764319582872
C	3.138811721947	-1.281115901026	0.578909887726
C	4.322280955351	-2.273915792511	0.578849184811

C	5.631687224501	-1.542577205285	0.434613293832
C	6.469333815221	-1.644632579189	-0.600478367752
C	4.313261082340	-3.122346437918	1.861181015196
C	3.802382603503	2.543778173961	-0.940441645065
C	-1.477983437815	2.583485983493	-0.591680825504
C	-2.243873707496	1.985725380135	1.713705742985
C	1.654646142232	1.023480811487	-2.231755299707
H	0.587475724574	-1.498585304910	-1.263187222465
H	-0.208795961529	-1.552056902575	0.326130079934
H	-1.285590680818	0.131493146980	-1.996330309488
H	-1.895512628306	-1.426003384352	-1.397761046875
H	-2.227583657670	-0.488987257475	0.840920540866
H	-0.208165134945	0.348858656431	1.728399136474
H	0.151623266689	2.989975041885	1.948659906472
H	1.446392175864	1.890602069537	2.360274877006
H	1.172187848407	3.338215164056	-0.326472427144
H	2.308955256423	3.725331324095	0.953411665834
H	3.270078745836	1.450421613697	0.808138419158
H	2.629098848958	-1.284737717799	-1.518590357383
H	3.932960098507	-0.198770922620	-1.108096068694
H	2.226994861891	-1.832637379784	0.836778900680
H	3.298812800322	-0.552701988233	1.384935837852
H	4.204850195596	-2.944316658835	-0.284044771012
H	5.890070107087	-0.880993595878	1.264470819579
H	7.403464434097	-1.092046434399	-0.635343548400
H	6.252986292667	-2.296869319275	-1.443791880653
H	5.132706403996	-3.846546027562	1.856135898765
H	3.370674170132	-3.671037624145	1.961192422451
H	4.430392096862	-2.488679560442	2.748504159554
H	3.349058387483	3.116649251977	-1.755068066080
H	4.506785149594	1.829389621690	-1.375985248839
H	4.384604538506	3.244382593261	-0.334380464679
H	-2.514550311911	2.749443401295	-0.893802999025
H	-0.914769809629	2.301226153977	-1.484681977997
H	-1.072038374340	3.524725572469	-0.210501091269
H	-2.190999797426	1.267321667725	2.537926732768
H	-3.294281844437	2.075691277228	1.424689349986
H	-1.901593672895	2.961001289143	2.069698456556
H	1.109851335420	1.966170050255	-2.305139638515
H	1.056721455600	0.239020511238	-2.697293226889
H	2.586742038269	1.114437244557	-2.792438110076
O	-3.448576777813	0.504495911868	-0.501837136935
Al	-4.861306482687	-0.568178742286	-0.080220244436
C	-5.245919881489	-0.343771139057	1.861144533396
C	-6.305177548136	-0.281540898005	-1.398047354255
H	-4.354828815306	-0.519318124673	2.479997040146
H	-6.013750937016	-1.049114088523	2.204572345951
H	-5.608693114671	0.669680279042	2.086348554003
H	-5.957943503103	-0.468403276650	-2.422530662395
H	-7.155857139403	-0.951304250828	-1.215432910028
H	-6.688408462917	0.748011244506	-1.362736711190
Cl	-3.957171543620	-2.637077039046	-0.312844464178

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Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029489.241720  kcal/mol
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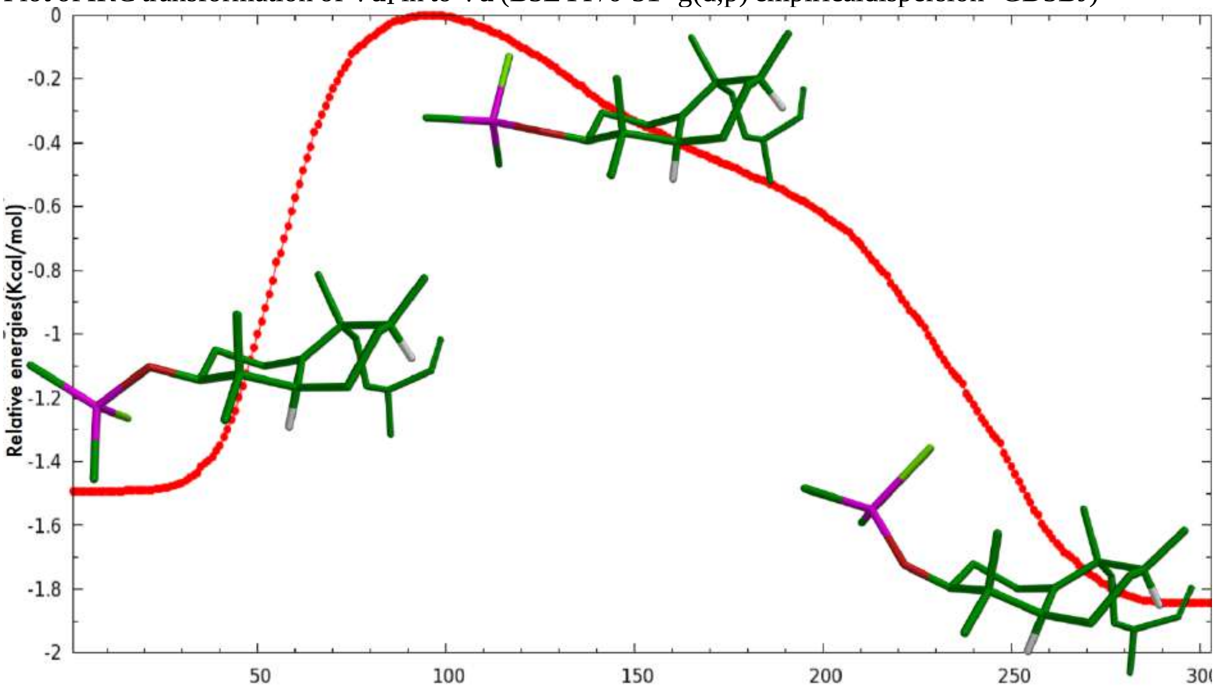
```
ZPVE            = 360.932917  kcal/mol
Enthalpie(0K)   = -1029128.308802  kcal/mol
E(tr)           = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 367.998738  kcal/mol
H-E(el)         = 369.549958  kcal/mol
Enthalpie       = -1029119.691762  kcal/mol
S(el)           = 0.000000000000
S(tr)           = 0.000066308847
S(rot)          = 0.000055541037 (Symmetry number= 1)
S(vib)          = 0.000107793977
G-E(el)         = 341.428124  kcal/mol
    Free Energy     = -1029147.813595  kcal/mol
    ---------------------------------------------------------------
```

Plot of IRC transformation of **Va$_1$** in to **Va** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



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Cartesian Coordinates and Energies of **Va$_1$**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.170435269389	-1.126240850615	0.766173347616
C	-1.362120397215	-1.112448061925	0.481322479235
C	-2.056336252311	-0.001852920629	1.267818450742
C	-1.460980940291	1.408685410189	0.942182548887
C	0.185671042374	1.325077973085	1.106616914674
C	0.895193878832	2.666168998386	0.868677839749
C	1.433402659438	2.800640546810	-0.552298660561
C	2.397647894815	1.661708571535	-0.880829122744
C	1.718326676539	0.261858131386	-0.740102535748
C	0.726430659595	0.183367111120	0.380370791888
C	2.821427335538	-0.830107977263	-0.546764413718
C	3.492274288820	-0.865249513092	0.830502444141
C	4.758392666351	-1.749170353659	0.857660004166
C	5.838896901360	-1.163393255886	-0.014130608217
C	6.352707143266	-1.736884667878	-1.105105322886
C	5.262953600788	-1.922830873115	2.300040113183
C	3.064283479128	1.889487062432	-2.244044675479
C	-1.857802043981	1.890391375372	-0.451471143587
C	-1.983218807154	2.392399436487	1.993439536015
C	0.914166123710	-0.107744298273	-2.035061862563
H	0.649842611282	-1.960713989876	0.258197446696
H	0.288999784478	-1.255889416832	1.850443266700
H	-1.566390367478	-1.004157275631	-0.586059894593
H	-1.755611996718	-2.086024882052	0.783496349944
H	-1.839386623152	-0.179155615439	2.345403422310
H	0.231796989227	1.039181366180	2.168888724010
H	0.216979747398	3.487601540861	1.103605326314
H	1.731948305100	2.750489646001	1.573596349530
H	0.612225471515	2.815977775426	-1.276893291338
H	1.956456926058	3.757326615059	-0.657998748395
H	3.193060365516	1.693833658393	-0.125194395462
H	2.415384775486	-1.819211721024	-0.779351142462
H	3.578851149606	-0.634962496023	-1.310503212737
H	2.791196600793	-1.244818837213	1.583570889357
H	3.770988037938	0.147642115275	1.150018354892
H	4.492787638096	-2.738422953535	0.459512305185
H	6.216287590192	-0.188493569944	0.302537744722
H	7.139894337668	-1.261794719482	-1.682807574090
H	6.008407389587	-2.709095767923	-1.450905300777
H	6.143859569298	-2.570191326866	2.331067162043
H	4.488462231515	-2.366078267159	2.935439042149
H	5.541976219627	-0.955214140270	2.734172619619
H	2.324780389870	2.009476346711	-3.041289366942
H	3.741519081865	1.078536842537	-2.526318121887
H	3.656437790571	2.808837512024	-2.206356842617
H	-2.944297983080	1.979811432388	-0.486170214175
H	-1.581329984448	1.193078557777	-1.242930784908
H	-1.430812140271	2.873787283752	-0.665725685499
H	-1.612197740783	2.154889671857	2.996584817749
H	-3.072243024093	2.290135861283	2.000447181899
H	-1.740179382861	3.433055575956	1.764233388851
H	0.221031543173	0.683213848337	-2.321280482617
H	0.346867359080	-1.031151218721	-1.914098042655

H	1.634011332829	-0.256506006972	-2.842151441625
O	-3.412410011667	0.037751653238	1.057382496690
Al	-4.552070939768	-0.878469774200	-0.020400686837
C	-4.526933904219	-2.821063298148	0.426076203764
C	-6.274099025665	0.089871623552	0.033239980050
H	-3.609102639084	-3.330958232373	0.103595598573
H	-4.645801214443	-2.996221164740	1.504953941890
H	-5.358971308231	-3.332128052467	-0.077622987142
H	-6.150662529827	1.147266562817	-0.236361117913
H	-6.728328905695	0.057635276616	1.033415194203
H	-6.999639235212	-0.340117755795	-0.669720101866
Cl	-3.659271506149	-0.686315920885	-2.102565930732

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029487.518110 kcal/mol
ZPVE = 360.778930 kcal/mol
Enthalpie(0K) = -1029126.739180 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 368.004723 kcal/mol
H-E(el) = 369.555942 kcal/mol
Enthalpie = -1029117.962167 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055329604 (Symmetry number= 1)
S(vib) = 0.000111567215
G-E(el) = 340.997936 kcal/mol
Free Energy = -1029146.520174 kcal/mol

Cartesian Coordinates and Energies of **Transition State Va$_1$- Va**

FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.124297782107	-1.010247486746	0.291739139319
C	-1.383726691828	-0.855779882976	-0.096596631997
C	-2.073848460126	0.121230998579	0.854796962999
C	-1.396704117532	1.528831876204	0.811482550113
C	0.212549364736	1.337208290719	1.078365043393
C	0.992567758073	2.659533265645	1.132962813010
C	1.664175524104	2.999005676421	-0.193560771182
C	2.619462075505	1.884276786523	-0.618574970958
C	1.881915301901	0.516421071439	-0.780811378496
C	0.772434132459	0.305540237342	0.205887332723
C	2.918719226635	-0.649562520036	-0.655514807743
C	3.436318038596	-0.932516372742	0.758082684997
C	4.610496902592	-1.935352245404	0.777876263232
C	5.815138246585	-1.366008664255	0.073697078567
C	6.372424754882	-1.860842111255	-1.034295434740
C	4.961646088349	-2.322453488689	2.224374035534
C	3.429104262270	2.298932271725	-1.854214077152
C	-1.670459032663	2.232862723517	-0.519800219316

C	-1.975172678303	2.359822266076	1.960381674605
C	1.217740391374	0.399950222702	-2.195015131804
H	0.606816115592	-1.769769836634	-0.319948145448
H	0.127699342815	-1.341683885318	1.339018344019
H	-1.504312035548	-0.538246999564	-1.133680527120
H	-1.830387162277	-1.849528434657	-0.026004001835
H	-1.918091272934	-0.265399565909	1.888712694347
H	0.170968091199	0.868635760316	2.074855344839
H	0.326209187867	3.464842592498	1.444396512184
H	1.763098056461	2.583728697059	1.910336771820
H	0.914654832101	3.168690084802	-0.974484173023
H	2.223581070656	3.935531171738	-0.094105629874
H	3.334345784009	1.752121325110	0.203673429301
H	2.501969366738	-1.567871897731	-1.080080653365
H	3.759524541893	-0.380905656363	-1.300446534047
H	2.630672745130	-1.336322618704	1.383508409895
H	3.766552501187	-0.003047086751	1.239988781435
H	4.294500040174	-2.841148055016	0.241931432673
H	6.249223524700	-0.476461073140	0.535779571643
H	7.249142386734	-1.405218854448	-1.484729590051
H	5.974821280331	-2.747911209552	-1.522366977395
H	5.768777372975	-3.059966453823	2.246573238340
H	4.092853274187	-2.748698351612	2.737744978826
H	5.292410714800	-1.445115520021	2.793088700276
H	2.779470005361	2.590830369763	-2.684786994817
H	4.099081447942	1.509693292047	-2.206702597026
H	4.049688704578	3.164838945966	-1.604745699748
H	-2.752563362772	2.307537327916	-0.641448032377
H	-1.284778103730	1.681371176683	-1.380163818041
H	-1.247847096704	3.241397745233	-0.532502600822
H	-1.697121925776	1.949783950406	2.937520252742
H	-3.063469201025	2.304403134698	1.866817562167
H	-1.680591127411	3.411633386024	1.922604884342
H	0.589234685620	1.263109778211	-2.417244102271
H	0.611696935133	-0.502285814217	-2.286418305134
H	2.016354110271	0.347472194421	-2.937398413202
O	-3.407340847818	0.286581667740	0.576168274366
Al	-4.647625014061	-0.958344387576	0.104948580232
C	-4.394656289472	-2.569077622227	1.257371621054
C	-6.404022238310	-0.051325713351	0.107634197775
H	-3.410317570681	-3.048029815384	1.156249245321
H	-4.530097590327	-2.322225661845	2.320464408447
H	-5.138587895889	-3.337312801197	1.006740480207
H	-6.389075534836	0.844585390586	-0.527087143819
H	-6.699704335319	0.264831257173	1.117793944507
H	-7.197631904537	-0.705680576780	-0.276252971661
Cl	-4.081560478764	-1.525246271375	-2.001626904783

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029487.910602 kcal/mol
ZPVE = 360.035070 kcal/mol
Enthalpie(0K) = -1029127.875533 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 367.360954 kcal/mol

H-E(el) = 368.912173 kcal/mol
Enthalpie = -1029118.998429 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055553551 (Symmetry number= 1)
S(vib) = 0.000112445544
G-E(el) = 340.219184 kcal/mol
Free Energy = -1029147.691418 kcal/mol

Cartesian Coordinates and Energies of **Va**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.084366597315	-0.876635783870	-0.606715977644
C	-1.347508625239	-0.473512478688	-1.101949322264
C	-2.131754812772	0.153509493479	0.045620809183
C	-1.436788080490	1.433193798281	0.595664534871
C	0.099203280873	1.029549251772	0.991808255029
C	0.895875567590	2.179398627961	1.626463263091
C	1.766045356672	2.915888687428	0.613686654524
C	2.752635782198	1.951380202199	-0.041994264025
C	2.021652995289	0.791092561019	-0.789354747115
C	0.762571638131	0.328386865739	-0.112544761574
C	3.002056527831	-0.420002198315	-0.940980311601
C	3.265187117594	-1.231829823047	0.332057705522
C	4.482690017224	-2.172535507012	0.197972464169
C	5.756643966244	-1.381337813602	0.052030354770
C	6.556471158337	-1.387900236021	-1.017409240639
C	4.567947894436	-3.117873786402	1.407962394549
C	3.765884900901	2.707359455557	-0.912278972411
C	-1.488339250447	2.576510958159	-0.419986003371
C	-2.169883897467	1.849347307442	1.874294146221
C	1.597078208300	1.232097832221	-2.229284791025
H	0.641580713614	-1.398432630292	-1.382168700045
H	-0.092608493355	-1.566665314298	0.229177740890
H	-1.300609387793	0.209191325590	-1.954781702585
H	-1.847260769241	-1.393480047816	-1.417234851603
H	-2.122331012981	-0.580985453688	0.877540760922
H	-0.106978425114	0.244223752226	1.736289376403
H	0.210374024896	2.867607408309	2.122324678674
H	1.541184091104	1.772175475935	2.414875800482
H	1.147154995789	3.400703630083	-0.150016290335
H	2.320925066153	3.716048151498	1.115337789797
H	3.319703359734	1.481876675609	0.772087147532
H	2.652678055151	-1.089862240376	-1.732627739621
H	3.944957941267	0.000653611339	-1.300523840008
H	2.386899832277	-1.838058123120	0.583235748769
H	3.436123993281	-0.564125221308	1.186935203379
H	4.347413390523	-2.778008333507	-0.709136983315
H	6.024249113417	-0.764306859076	0.912736143975
H	7.469046800061	-0.800358672601	-1.051668222967
H	6.329270840754	-1.993755116652	-1.891848420442

H	5.412774777490	-3.805200184339	1.308889386769
H	3.652292682710	-3.710704820757	1.506468840470
H	4.703482307961	-2.550383811427	2.336470160032
H	3.272269178987	3.322491751307	-1.670727065829
H	4.471475191711	2.042139445063	-1.417983032757
H	4.352150035668	3.379723483292	-0.278797656812
H	-2.537708424977	2.740286485875	-0.675782556373
H	-0.954243205827	2.348588540379	-1.345671723899
H	-1.082946476158	3.504345442193	-0.006599118720
H	-2.073223171931	1.095399425978	2.661956019420
H	-3.230792037010	1.925250204741	1.621838247982
H	-1.840200984154	2.815861174242	2.264180611873
H	1.037691843221	2.168483689430	-2.214909835538
H	0.990953182724	0.471710987135	-2.723478999443
H	2.503987781659	1.375912657309	-2.819665751937
O	-3.414283206513	0.448217671717	-0.368732908007
Al	-4.783965287497	-0.680565810773	0.048661883779
C	-5.110636888908	-0.557984061528	2.009700595267
C	-6.278693700059	-0.370813319687	-1.205754249383
H	-4.203656415176	-0.763686636769	2.595351116165
H	-5.468727712378	0.441443780584	2.296805541334
H	-5.868475462603	-1.281901723006	2.336562152454
H	-5.962730587096	-0.503511624157	-2.248633579538
H	-6.683487880388	0.646695160266	-1.111226489278
H	-7.107293339946	-1.068227206671	-1.025193955102
Cl	-3.836320831413	-2.711237965020	-0.311810290776

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Thermochemistry at  195.150 K,    1.000 Atm
E(el)           = -1029489.244412  kcal/mol
ZPVE            = 360.659630  kcal/mol
Enthalpie(0K)   = -1029128.584781  kcal/mol
E(tr)           = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 367.784889  kcal/mol
H-E(el)         = 369.336109  kcal/mol
Enthalpie       = -1029119.908303  kcal/mol
S(el)           = 0.000000000000
S(tr)           = 0.000066308847
S(rot)          = 0.000055543343 (Symmetry number= 1)
S(vib)          = 0.000106667619
G-E(el)         = 341.351925  kcal/mol
Free Energy     = -1029147.892486  kcal/mol
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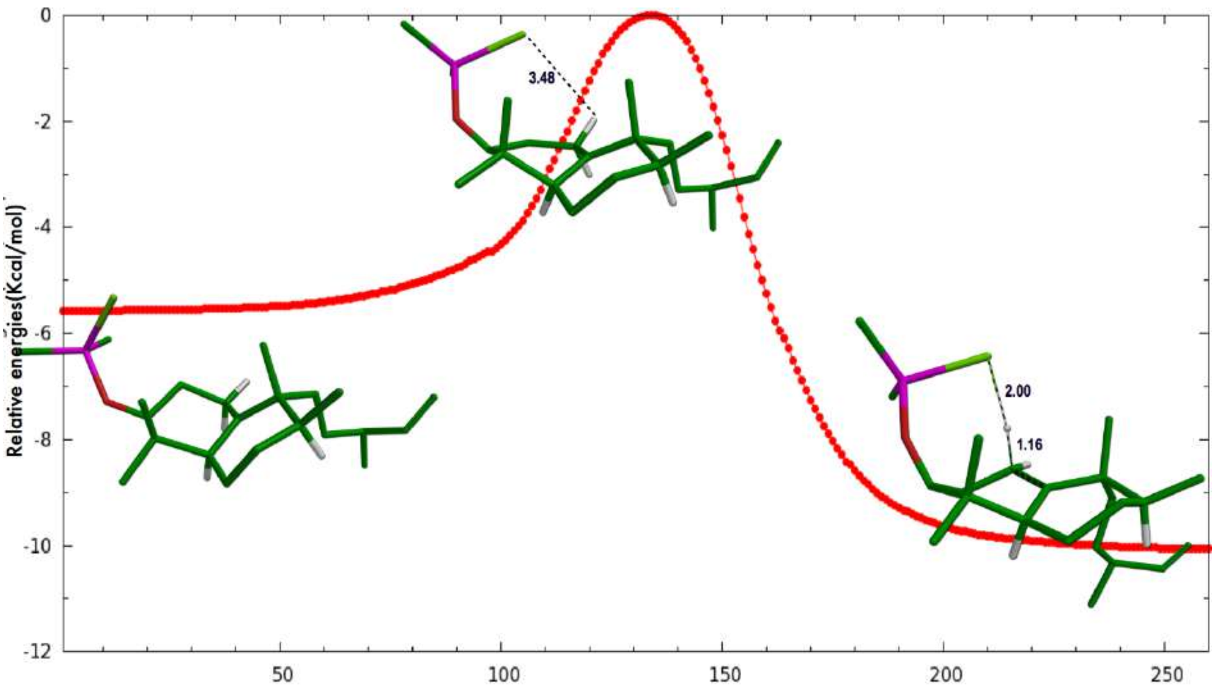
Plot of IRC transformation of **Va** in to **VIa** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **Va**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.212242503354	-1.045139159031	-0.896628422764
C	1.314973699354	-1.134027118769	-0.594933667963
C	2.068768963308	0.033329284014	-1.230415628301
C	1.523778168530	1.417882369568	-0.745547030159
C	-0.118211663858	1.427406631335	-0.951790062452
C	-0.777660092066	2.762296730621	-0.575099785325
C	-1.347694999380	2.755152198144	0.839711435819
C	-2.368583593428	1.630866147463	1.009049057279
C	-1.741059629683	0.227853753316	0.727050186206
C	-0.722610685453	0.234343467713	-0.372278108680
C	-2.881938003953	-0.785893750790	0.383548921575
C	-3.506915109228	-0.639113238592	-1.007769320828
C	-4.850081256694	-1.389678677443	-1.144288150442
C	-5.902225779847	-0.762633863345	-0.266574267707
C	-6.497345973043	-1.350931381245	0.774098363836
C	-5.310001094914	-1.410117952057	-2.611384549880
C	-3.066091010082	1.730720376102	2.372051234531
C	1.903872757021	1.702691072065	0.705698513966
C	2.115732727371	2.498546950180	-1.655139194726
C	-0.991076944625	-0.319382562956	1.990729212660
H	-0.736069875907	-1.910961980278	-0.496456135154
H	-0.315954015499	-1.043665428765	-1.990234831501
H	1.506706051103	-1.168206321020	0.479762946038
H	1.670303440182	-2.079620990852	-1.011083565159
H	1.866031753377	-0.003519527264	-2.324684007907
H	-0.151944460986	1.266494348543	-2.040628062009
H	-0.060167184626	3.574368606553	-0.699735798526

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H     -1.591669615892      2.963185557008     -1.283055553441
H     -0.547293496583      2.644675945310      1.578857588551
H     -1.830427189197      3.716435209923      1.046804322598
H     -3.138662458827      1.782658555088      0.241353827039
H     -2.527458417127     -1.812178765707      0.518583230330
H     -3.654259499779     -0.636467076533      1.142717934774
H     -2.819598132374     -1.018396061929     -1.773374804147
H     -3.677584513357      0.419882837367     -1.242740408453
H     -4.697192915017     -2.426067164090     -0.812041549560
H     -6.181243012489      0.259847160601     -0.530671889351
H     -7.255756073029     -0.841466208988      1.360959018247
H     -6.251942379882     -2.369408738598      1.067014723453
H     -6.248521585942     -1.960996782318     -2.719639390821
H     -4.557566740124     -1.884373754750     -3.250850069541
H     -5.473697248564     -0.391256892149     -2.982622267880
H     -2.345362351944      1.729657903507      3.195093893553
H     -3.781632095492      0.921752297155      2.543341669008
H     -3.621202598462      2.672160431852      2.424545331493
H      2.992067784905      1.717357017823      0.778362270119
H      1.560855766340      0.932272761511      1.396746255198
H      1.527749386893      2.676693779236      1.030628383720
H      1.755506048223      2.408989165723     -2.685928600705
H      3.198311546552      2.342164719251     -1.658704261734
H      1.919271009020      3.513026693672     -1.299188356296
H     -0.285469956912      0.409223434789      2.390401614467
H     -0.446515153570     -1.239934697880      1.777511775390
H     -1.740659390765     -0.539837136077      2.753392579555
O      3.420901617991     -0.007575339589     -0.995439265540
Al     4.490363877889     -1.125646003513     -0.042661270039
C      4.316784661352     -2.995835328131     -0.716076936202
C      6.279577419601     -0.287937233326     -0.002561755673
H      3.417103013658     -3.507167957538     -0.348159628141
H      4.303160992009     -3.039206613268     -1.814729251326
H      5.173892209234     -3.596517516756     -0.381672032911
H      6.234914687755      0.739092814396      0.383573981616
H      6.729700240471     -0.242269391860     -1.004085848568
H      6.971321691254     -0.846013602305      0.642008386303
Cl     3.613962429394     -1.113001611681      2.054055231760
--------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029487.557033  kcal/mol
ZPVE           = 360.620618  kcal/mol
Enthalpie(0K)   = -1029126.936415  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 368.110699  kcal/mol
H-E(el)        = 369.661918  kcal/mol
Enthalpie      = -1029117.895115  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055320987 (Symmetry number= 1)
S(vib)         = 0.000113987905
G-E(el)        = 340.808533  kcal/mol
Free Energy     = -1029146.748500  kcal/mol
--------------------------------------------------------------
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Cartesian Coordinates and Energies of **Transition State Va- VIa**

FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

\---

C	-0.090213783731	-0.899598763383	-0.877872647151
C	1.359269608250	-1.022283079998	-1.406782026232
C	2.235971630829	0.260833071266	-1.476590744311
C	1.660324351766	1.524091577174	-0.750299271834
C	0.052392355354	1.565184180056	-1.076088859358
C	-0.649643462472	2.912373244592	-0.858595074310
C	-1.279550637093	3.032247742228	0.525561652061
C	-2.277260918605	1.895911252009	0.758575914861
C	-1.596964689401	0.493168312335	0.656807932672
C	-0.554547845994	0.417301047397	-0.419969277905
C	-2.680986521691	-0.618088844144	0.463661784738
C	-3.500884963130	-0.584818215112	-0.829610737378
C	-4.662350518671	-1.604502103994	-0.813817056424
C	-5.682490756587	-1.235734553868	0.232567566404
C	-5.988324045385	-1.962711673958	1.309999175932
C	-5.320084535247	-1.693177437581	-2.201034168860
C	-3.056887567109	2.107330948758	2.062811449069
C	1.966367795013	1.530371782894	0.746707984465
C	2.311562503310	2.755270924016	-1.392144931474
C	-0.838964692945	0.144119893333	1.990305027237
H	-0.301984104158	-1.673920877176	-0.139419279163
H	-0.792810923648	-1.094469079181	-1.710388924717
H	1.847470036819	-1.722506395563	-0.732290040627
H	1.347078389306	-1.491917470059	-2.393051728787
H	2.271866960357	0.558970863019	-2.542908274683
H	0.088963657779	1.321753798655	-2.151005392433
H	0.047307028537	3.729708052729	-1.044869650398
H	-1.442626381863	3.011578389674	-1.611237854472
H	-0.510672542300	3.029856662959	1.305656500747
H	-1.801920106432	3.991344388909	0.610471775648
H	-3.001976607943	1.951323568929	-0.062982195608
H	-2.223916592238	-1.605232519517	0.577180926093
H	-3.362965942708	-0.518799669525	1.311611100982
H	-2.870053682930	-0.799790153337	-1.700727565560
H	-3.923525819405	0.413428037671	-0.996304206598
H	-4.249537335965	-2.590728481779	-0.559966052665
H	-6.200336934846	-0.288669347089	0.064951677496
H	-6.742361974056	-1.639007212456	2.021182802081
H	-5.498559726962	-2.912700144550	1.512147493143
H	-6.128237702797	-2.430015486689	-2.203695293917
H	-4.589003865326	-1.983161112413	-2.963635360072
H	-5.746143436509	-0.725882730922	-2.493146066868
H	-2.389175220081	2.181115153945	2.926090220268
H	-3.779603371719	1.310574425902	2.258531434213
H	-3.615926425441	3.046003457692	2.000513490443
H	3.044927952117	1.633231759244	0.874735260049
H	1.688876801338	0.600666022503	1.241203082380
H	1.485776929234	2.377382750828	1.244661500690

H	1.984351112057	2.911273297718	-2.425814443388
H	3.389019434056	2.562291260809	-1.398636433528
H	2.137545102951	3.671009085600	-0.821009591634
H	-0.255749490948	0.990270344174	2.349661757957
H	-0.164612445795	-0.707613155091	1.881676268369
H	-1.595250219424	-0.106112170347	2.737133528658
O	3.516498665264	0.030904503822	-1.030297956837
Al	4.306810323203	-1.163893123083	0.080245560354
C	4.734311081846	-2.835285901013	-0.900839698674
C	5.732538664675	-0.205967717790	1.061067336906
H	3.848930080259	-3.276112536512	-1.379421148115
H	5.476242730482	-2.656669904794	-1.691639478221
H	5.147658572013	-3.597488848681	-0.227249273109
H	5.337724068746	0.647108891927	1.629379797004
H	6.499208686978	0.183533021266	0.376944499423
H	6.238323601180	-0.864364693786	1.779403432468
Cl	2.695289667855	-1.770936310612	1.621102772496

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029480.257748 kcal/mol
ZPVE = 360.805073 kcal/mol
Enthalpie(0K) = -1029119.452675 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 368.028806 kcal/mol
H-E(el) = 369.580026 kcal/mol
Enthalpie = -1029110.677723 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055242502 (Symmetry number= 1)
S(vib) = 0.000110090818
G-E(el) = 341.213483 kcal/mol
Free Energy = -1029139.044265 kcal/mol

Cartesian Coordinates and Energies of **VIa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.321357547542	-0.837635444378	-0.272822469093
C	1.092527043000	-0.882723238150	-1.580308499135
C	2.130130505361	0.257123427227	-1.659385965851
C	1.533612310625	1.629512144056	-1.119290594672
C	-0.036621848307	1.530604660919	-0.883781171962
C	-0.714181454282	2.870644176117	-0.523267715473
C	-1.228978818205	2.905136917174	0.910445523149
C	-2.215807443546	1.760660897711	1.135430826828
C	-1.499018300429	0.380522829377	1.011540152585
C	-0.409672199052	0.369854508123	-0.037174548917
C	-2.549530048202	-0.717668433866	0.638398854345
C	-3.038382945290	-0.701700480084	-0.813092267564
C	-4.245954063432	-1.634268144328	-1.051725024720

C	-5.460583781894	-1.138178310782	-0.310912919539
C	-6.075007410462	-1.775875006574	0.688548799232
C	-4.542812123342	-1.758670023682	-2.555431148174
C	-2.995099286171	1.943184149480	2.444149086687
C	2.194661559725	2.043983768856	0.205212821166
C	1.827999454203	2.695581829750	-2.188158825411
C	-0.837619754103	-0.023825458017	2.362063304158
H	1.115391692419	-0.825735926321	0.576123798936
H	-0.220980397735	-1.747993044364	-0.009658828896
H	1.613105757152	-1.835944746543	-1.680262173152
H	0.385569925936	-0.807034954134	-2.419431202609
H	2.336565217548	0.408201479084	-2.731411685478
H	-0.425930425374	1.191199827141	-1.866029934750
H	-0.017337270771	3.690815323748	-0.693716290075
H	-1.558458339819	3.044340953326	-1.201028658002
H	-0.394901305620	2.828769774803	1.620083348050
H	-1.720056081545	3.864880754604	1.104748898305
H	-2.948556104581	1.813291749134	0.319443270271
H	-2.138392695787	-1.705618883761	0.870134123994
H	-3.401378046155	-0.578029692714	1.309682770880
H	-2.227602931500	-1.009035168974	-1.486071346369
H	-3.321211962052	0.315991960820	-1.113335239521
H	-3.989273690002	-2.629833437962	-0.663428455018
H	-5.848345604802	-0.172717316158	-0.643674561575
H	-6.952802421337	-1.361945212144	1.175721685602
H	-5.722505252342	-2.740069277275	1.048114611236
H	-5.381800197685	-2.437163097222	-2.734353078775
H	-3.670089301562	-2.141338553351	-3.095671645588
H	-4.802656379643	-0.782821187616	-2.983203216148
H	-2.325967108819	2.070156427030	3.300284395663
H	-3.665672780945	1.105258693889	2.656950250423
H	-3.611639351144	2.844631184296	2.373469557891
H	3.269163855208	2.155807179365	0.058109237347
H	2.062743953921	1.296231073526	0.990511469769
H	1.789110089779	2.999983786514	0.553116859660
H	1.282524998741	2.497620004831	-3.118263736718
H	2.898034326707	2.664794339503	-2.415134945443
H	1.593696665297	3.712662075654	-1.862045138264
H	-0.132764719329	0.734521764908	2.710597729629
H	-0.294876999664	-0.965632182793	2.284269153499
H	-1.620360425729	-0.144904621817	3.112603058544
O	3.314838469969	-0.042707002460	-1.020344899745
Al	4.049338911971	-1.284132184269	0.018592204336
C	3.916724205978	-3.129043433720	-0.704091398690
C	5.766866967357	-0.615334469619	0.718020961957
H	2.885981133362	-3.505964782402	-0.752008540751
H	4.339195134239	-3.199413874668	-1.716386743514
H	4.476282458872	-3.831657415738	-0.072095449989
H	5.653896226486	0.381311061652	1.163955313338
H	6.522599230537	-0.534808513521	-0.075255760689
H	6.176105908965	-1.276297089960	1.492946528415
Cl	2.583495367452	-1.310905356457	1.857875965805

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Thermochemistry at  195.150 K,    1.000 Atm
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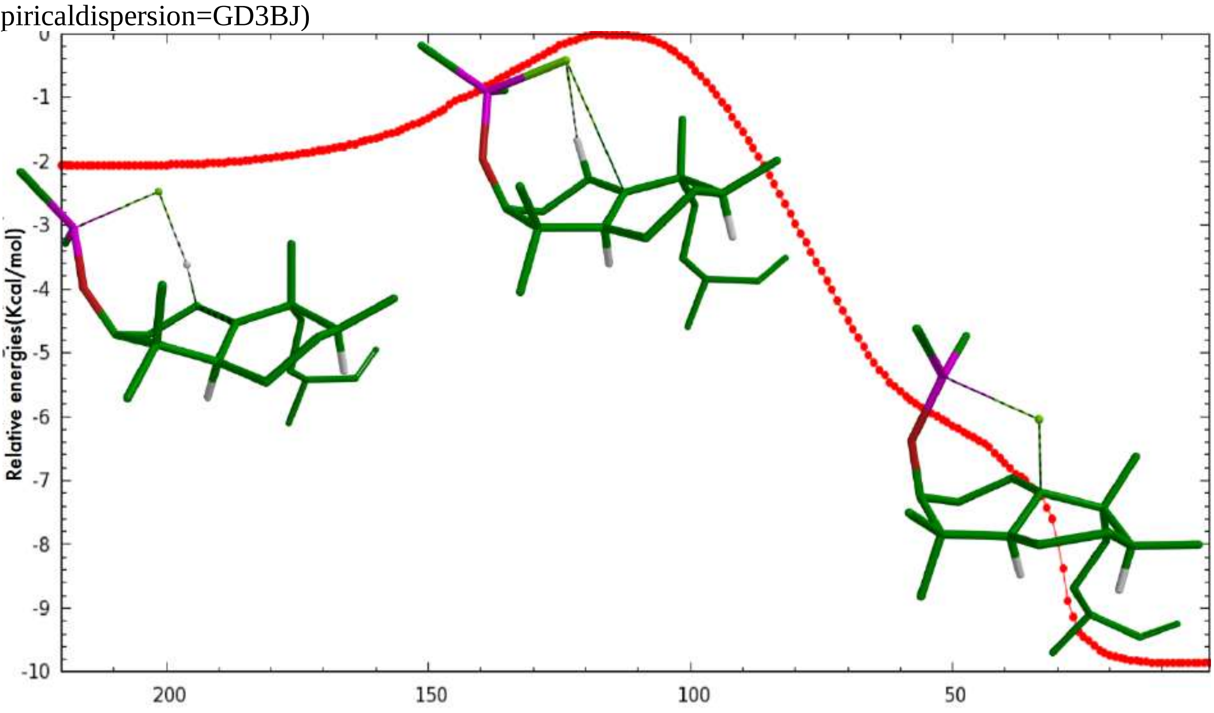
E(el) = -1029484.395044 kcal/mol
ZPVE = 359.382244 kcal/mol
Enthalpie(0K) = -1029125.012800 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 366.597953 kcal/mol
H-E(el) = 368.149173 kcal/mol
Enthalpie = -1029116.245871 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055071752 (Symmetry number= 1)
S(vib) = 0.000110824052
G-E(el) = 339.713749 kcal/mol
Free Energy = -1029144.681295 kcal/mol

Plot of IRC transformation of **VIa** in to **VIIa** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **VIa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	-0.265836672987	0.107646598293	0.998229711046
C	-0.745768658244	1.463913693137	1.484569981471
C	-1.751405083292	2.090608229389	0.495338397948
C	-1.287427000286	1.891894778870	-1.013195420672
C	0.203789038052	1.337941890778	-1.092663575465
C	0.799175934711	1.294509768300	-2.516680282053
C	1.001040486022	-0.124769761137	-3.032417794979
C	1.904010658467	-0.903359717762	-2.076789718324
C	1.215947845450	-1.083592453039	-0.687761496607
C	0.390662931422	0.113934145422	-0.274811875876
C	2.304406991486	-1.338143795468	0.405757625619
C	3.124713416383	-0.112818057078	0.819782437288
C	4.299565662864	-0.462437155547	1.758872926951
C	5.320238033330	-1.312188124693	1.047119005806
C	5.644743699919	-2.567483904555	1.366260394158
C	4.949838364748	0.818993289369	2.306966442167
C	2.385773018203	-2.215465865829	-2.708768724929
C	-2.207940469394	0.913334665466	-1.759441219718
C	-1.361953363156	3.271123312732	-1.689687692818
C	0.255553188183	-2.310442499094	-0.703813721357
H	-1.217372677803	-0.525647951108	0.794640161977
H	0.218524693756	-0.520580496469	1.748568683879
H	-1.227108756218	1.368502759885	2.458544057721
H	0.120374625943	2.129580601340	1.612466163665
H	-1.730888849949	3.175974368495	0.686104776392
H	0.780726350837	2.069549596494	-0.490680883674
H	0.161376657382	1.856606195402	-3.198455572887
H	1.769272240920	1.805931645397	-2.518124433824
H	0.035420743737	-0.635097215906	-3.141411734639
H	1.453363893475	-0.094381455457	-4.029704814166
H	2.794954782120	-0.282929792165	-1.912554599643
H	1.831656650471	-1.773006958728	1.292528996496
H	2.974494189178	-2.108240312453	0.013916139295
H	2.481699528232	0.615753848018	1.330654995414
H	3.528297212732	0.397705644125	-0.064607190293
H	3.900338874377	-1.039564618638	2.604464469911
H	5.821790139229	-0.831192766111	0.204266706478
H	6.397575496687	-3.120732033562	0.812756266719
H	5.171202896435	-3.081560118763	2.199701458143
H	5.765808035129	0.580987138498	2.995284274629
H	4.216156508656	1.431429404401	2.842416190389
H	5.363678353085	1.424773789533	1.491743628483
H	1.550036161113	-2.826568744493	-3.062389462479
H	2.983146657587	-2.821529654378	-2.021260313050
H	3.015165735703	-1.988590691675	-3.574877817306
H	-3.228805579160	1.296213849907	-1.754213176777
H	-2.240947309008	-0.071400877051	-1.288485126922
H	-1.883263050195	0.800632110865	-2.799386145735
H	-0.634488125789	3.972194357309	-1.264207755874
H	-2.361859065486	3.680838604029	-1.517141647512
H	-1.209447435463	3.230096686878	-2.771553615435
H	-0.495788365724	-2.226909583182	-1.492201767134
H	-0.271880073246	-2.427664978638	0.242482112992

H	0.845297777164	-3.212156171999	-0.876723899426
O	-3.041707718464	1.636019015243	0.671802821414
Al	-3.959060120437	0.435823845945	1.609798149708
C	-3.626183651510	0.514380749674	3.566759935998
C	-5.803337736952	0.334612002351	0.921284734885
H	-2.615036158615	0.189511837361	3.847782192801
H	-3.767729679562	1.529360653084	3.964264360649
H	-4.324249347369	-0.142022464450	4.103415005469
H	-5.816906212062	0.213714825922	-0.169516631111
H	-6.372660254983	1.244138796936	1.156882816563
H	-6.350973824379	-0.513788865630	1.351658464449
Cl	-2.926232812873	-1.578041095960	0.968560751119

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029484.333908 kcal/mol
ZPVE = 358.828630 kcal/mol
Enthalpie(0K) = -1029125.505277 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 365.767231 kcal/mol
H-E(el) = 367.318450 kcal/mol
Enthalpie = -1029117.015458 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055081570 (Symmetry number= 1)
S(vib) = 0.000104054893
G-E(el) = 339.710765 kcal/mol
Free Energy = -1029144.623142 kcal/mol

Cartesian Coordinates and Energies of **Transition State VIa- VIIa**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.334909774376	0.137784378496	1.312987379824
C	-0.623948589894	1.586196262450	1.690770317734
C	-1.635674141803	2.196426976692	0.708882876266
C	-1.091373441842	2.104108397171	-0.779946097560
C	0.107525335186	1.079726572438	-0.950308800786
C	0.510533050326	0.798481070238	-2.416536960742
C	0.578009957623	-0.693869649856	-2.711577996443
C	1.579186133087	-1.349200561978	-1.760805805312
C	1.061553635729	-1.270395686192	-0.290335601290
C	0.238931205454	-0.039376559336	-0.012532250722
C	2.289535788555	-1.243978923318	0.689350704845
C	3.058915267871	0.076474588497	0.776472670456
C	4.415463246484	-0.062229699825	1.501626278669
C	5.358545790024	-0.931540493668	0.710714401995
C	5.851569877501	-2.106111284446	1.110860437553
C	5.035084489068	1.323214345340	1.749686879926
C	1.958303211922	-2.763492276828	-2.215096465504
C	-2.252231072518	1.732457121061	-1.719314466937
C	-0.538246484415	3.486617212634	-1.173832595184

C	0.203105847051	-2.518734566411	0.069602447796
H	-1.307449633515	-0.394573073315	1.167023121681
H	0.181511878625	-0.438580130039	2.082157838887
H	-1.047242136913	1.618561127658	2.696540042248
H	0.312711625034	2.163065404034	1.699338961629
H	-1.700918114926	3.273103363062	0.936449571729
H	0.969314252013	1.612638999207	-0.463617636975
H	-0.197383220920	1.287872684803	-3.082444401323
H	1.488960785129	1.247785463247	-2.622563201629
H	-0.415049960672	-1.148060452394	-2.591502001248
H	0.882856371742	-0.856274356727	-3.750691786744
H	2.496972997107	-0.747087371099	-1.809435111204
H	1.958717668799	-1.536301277653	1.690607535232
H	2.961405260054	-2.034622362397	0.342692777907
H	2.460678947571	0.825277901475	1.311856523185
H	3.245040759616	0.483111975075	-0.227047513382
H	4.235289229040	-0.543032252601	2.473046485663
H	5.646584590117	-0.538677109946	-0.266935620248
H	6.535340624068	-2.678917532111	0.491652908412
H	5.592247549018	-2.530033881414	2.078433082311
H	5.983129086235	1.237417867117	2.288079866962
H	4.360762780503	1.953806531867	2.339407421406
H	5.233090659210	1.836479500638	0.800871859346
H	1.078259892467	-3.400941217602	-2.337365383725
H	2.644517080155	-3.257374047826	-1.520319255323
H	2.461484955106	-2.705579431960	-3.185164928220
H	-3.119650569702	2.339182588398	-1.454768546732
H	-2.548987079993	0.688285781757	-1.607728913078
H	-2.005651164669	1.933215686745	-2.765600488453
H	0.207891007561	3.841347895024	-0.451551005124
H	-1.352744443792	4.216362979808	-1.195551329550
H	-0.073108460166	3.477500904741	-2.165580461618
H	-0.628851638567	-2.647359651136	-0.622609278833
H	-0.218927053164	-2.446902692872	1.071442606524
H	0.848446918042	-3.397906151332	0.035400633362
O	-2.884713249571	1.645098768312	0.860782338196
Al	-3.848302521806	0.237018681117	1.363572817574
C	-3.366058757846	-0.387977397692	3.195152906610
C	-5.749437553975	0.554474360188	0.945621602176
H	-2.312369245352	-0.671872955188	3.326893275507
H	-3.585739332980	0.386694414691	3.943855952673
H	-3.961090605382	-1.271674365364	3.462303255824
H	-5.882890004356	0.835422539201	-0.107076045583
H	-6.169716561278	1.364252850517	1.557593707906
H	-6.357387985872	-0.341901840227	1.124150203022
Cl	-3.092197445579	-1.435609788178	-0.037665193672

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Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029484.185477 kcal/mol
ZPVE = 359.871477 kcal/mol
Enthalpie(0K) = -1029124.314000 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 367.083331 kcal/mol

H-E(el) = 368.634550 kcal/mol
Enthalpie = -1029115.550926 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054862461 (Symmetry number= 1)
S(vib) = 0.000110512816
G-E(el) = 340.262870 kcal/mol
Free Energy = -1029143.922607 kcal/mol

Cartesian Coordinates and Energies of **VIIa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.346369101977	0.111321312658	1.650002674791
C	-0.421579980863	1.627310175779	1.863035924530
C	-1.452549673134	2.271340988034	0.940046489440
C	-0.989756919070	2.162072644565	-0.549700611634
C	-0.208864054051	0.818927568692	-0.852423341367
C	-0.421721890413	0.320547091836	-2.303047627475
C	0.046312997997	-1.120914188704	-2.552410957758
C	1.193955840343	-1.510803657117	-1.626637201939
C	0.782963104014	-1.454794552300	-0.112224064063
C	-0.292997124137	-0.322782103105	0.167800946672
C	2.105612752648	-1.200874757757	0.689114835139
C	2.803718312272	0.159469128248	0.613150145169
C	4.206530385594	0.137666922687	1.261651056928
C	5.150627587591	-0.740528288224	0.482913602278
C	5.737053750738	-1.850128852060	0.938924062145
C	4.768304829413	1.565577441686	1.370993744998
C	1.802385029574	-2.853137730034	-2.055490315207
C	-2.219250752420	2.393753360503	-1.446553444966
C	0.000452284257	3.314673114202	-0.827803832711
C	0.263808323905	-2.817456700918	0.392251148517
H	-1.197123959320	-0.358174558387	2.139579773380
H	0.525460682303	-0.277534507896	2.172609565267
H	-0.691144563772	1.821898363224	2.905978787343
H	0.557423999582	2.090789240251	1.695263339280
H	-1.500092428151	3.347632220894	1.166481039814
H	0.851917393933	1.085224736794	-0.770136756310
H	-1.477289298650	0.391655876942	-2.561433863211
H	0.110228906532	1.006955318376	-2.971509132173
H	-0.784484839222	-1.820944250068	-2.415812724121
H	0.366488916625	-1.228092347717	-3.594996888791
H	1.977272885879	-0.754996641742	-1.768786261482
H	1.950170484000	-1.457209250074	1.742793123981
H	2.808728436654	-1.953032548457	0.319981812072
H	2.211880998089	0.931148265494	1.113667560032
H	2.917461162983	0.483968683826	-0.428934145540
H	4.109693781058	-0.276368208341	2.275335029568
H	5.353590731042	-0.414208073761	-0.539633831344
H	6.413845641417	-2.433614973793	0.321765370714
H	5.560321094190	-2.209561799727	1.950276203743

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H     5.749016136038      1.566507587938      1.855867247857
H     4.095754819016      2.205490666861      1.952699724594
H     4.883986072908      2.015495888302      0.377569021713
H     1.051894875934     -3.649663132535     -2.068405879783
H     2.625291156846     -3.172699512489     -1.409243882966
H     2.201526572752     -2.762150149649     -3.070967701280
H    -2.759047775622      3.275192869382     -1.088011726514
H    -2.920418626066      1.559917509500     -1.424847606441
H    -1.926275942076      2.577851510624     -2.484343656234
H     0.844304589424      3.307572586885     -0.129094253798
H    -0.499861052733      4.284762137360     -0.741573982371
H     0.407917649777      3.239211188952     -1.842141227937
H    -0.503067878734     -3.236719093842     -0.260120075742
H    -0.167674427547     -2.719767260525      1.392447928688
H     1.087189214039     -3.532782306129      0.453193345240
O    -2.723527579787      1.744255599916      1.169205829102
Al   -3.701951345621      0.314791916890      1.190545901567
C    -3.818434181450     -0.683026399607      2.889677728062
C    -5.244463477693      0.267221553468     -0.030832393129
H    -2.931127127751     -0.598146842637      3.528483941961
H    -4.669098152648     -0.312290933272      3.478379430379
H    -3.999930188017     -1.751307955099      2.713119194498
H    -5.011587261318      0.632977274226     -1.037154501780
H    -6.056903500711      0.895217952778      0.359946578280
H    -5.648423400153     -0.748580919744     -0.129810613174
Cl   -2.091973356887     -1.103593532188     -0.163243370925
--------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)           = -1029481.643010  kcal/mol
ZPVE            = 362.600923  kcal/mol
Enthalpie(0K)   = -1029119.042087  kcal/mol
E(tr)           = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 369.356479  kcal/mol
H-E(el)         = 370.907699  kcal/mol
Enthalpie       = -1029110.735311  kcal/mol
S(el)           = 0.000000000000
S(tr)           = 0.000066308847
S(rot)          = 0.000054428012 (Symmetry number= 1)
S(vib)          = 0.000099029638
G-E(el)         = 343.995432  kcal/mol
Free Energy     = -1029137.647578  kcal/mol
--------------------------------------------------------------
```
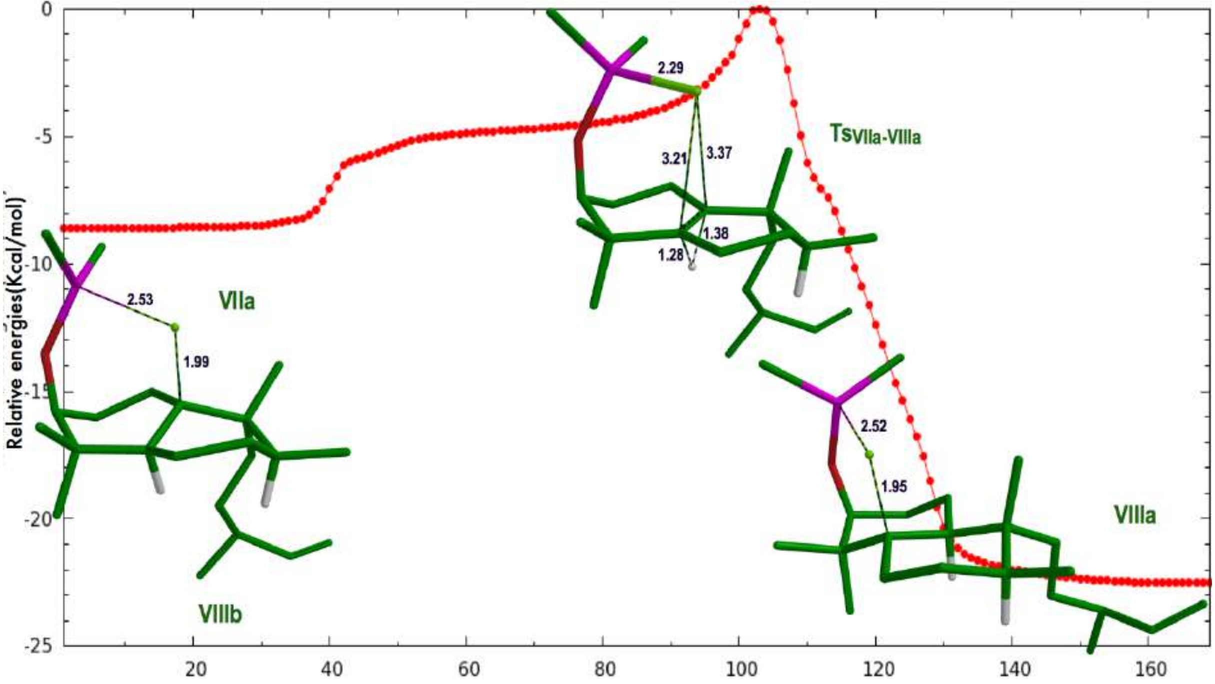

Plot of IRC transformation of **VIIa** in to **VIIIa** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **VIIa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.693077017506	-1.439097920506	-1.008029990472
C	0.745449252437	-2.723169585980	-0.172731094255
C	-0.315154669180	-2.726686735265	0.925115925658
C	-0.005840652685	-1.617734685879	1.982869781702
C	0.628871953977	-0.316527040517	1.341566524533
C	0.229353848682	0.975063639624	2.095938471549
C	0.544272146795	2.274798099617	1.339806045956
C	1.742138142127	2.115963295149	0.408031548704
C	1.505425684214	1.022429365113	-0.693121669696
C	0.558904800091	-0.141540583150	-0.179398716749
C	2.925099741424	0.479833933472	-1.079490999549
C	3.709947779160	-0.391669613382	-0.095365996011
C	5.166409024483	-0.633868162102	-0.551449283980
C	5.958019801379	0.647522306634	-0.543343181912
C	6.523407573260	1.220443669609	-1.608723970780
C	5.839041500845	-1.685616911798	0.347680118174
C	2.174698218017	3.476882595081	-0.154955104481
C	-1.290377525794	-1.364490278897	2.792508358274
C	1.047016254733	-2.175449505364	2.966622616703
C	0.941405226656	1.627793415987	-1.995600219440
H	-0.127405956691	-1.505583593721	-1.719885936606
H	1.590080209610	-1.382297593928	-1.621966467995
H	0.588613024018	-3.580134676020	-0.835420960040
H	1.736622053423	-2.847182156770	0.278997409821
H	-0.255431910474	-3.685468299436	1.462905794248

```
H     1.710120341182     -0.433413503058      1.481052087832
H    -0.837330844480      0.953350754419      2.315848951062
H     0.747157233040      0.969255374838      3.061628957279
H    -0.326491470643      2.599484429750      0.760879854987
H     0.747809414767      3.077049261132      2.058131419595
H     2.573312537806      1.760900688652      1.031001678311
H     2.868847550724     -0.041898847295     -2.041180291817
H     3.523536898064      1.373139613387     -1.281355855393
H     3.229670121447     -1.366135163614      0.031156180162
H     3.739701406010      0.070378642559      0.899652428967
H     5.144934603752     -1.018766878265     -1.580755672250
H     6.064306295702      1.122809843610      0.434443489215
H     7.089200343948      2.143859529861     -1.527910229366
H     6.440919205159      0.779502003961     -2.599726696529
H     6.861375960994     -1.890689713442      0.016686201927
H     5.277255487267     -2.626108024205      0.334815582980
H     5.885353832208     -1.336741201525      1.386409360477
H     2.469353475447      4.134872866837      0.668977918151
H     1.358050541180      3.968709460258     -0.692649105133
H     3.029436094674      3.401091213865     -0.833686377934
H    -1.708698157529     -2.326712952157      3.102778641173
H    -2.061311809587     -0.854607161527      2.215358268034
H    -1.084927372802     -0.781186576159      3.694961427688
H     1.951729163668     -2.513260481258      2.449662932155
H     0.642730619604     -3.023898016791      3.528182377947
H     1.343812208876     -1.408092437819      3.690277080905
H     0.071663357751      2.261395594802     -1.818215347506
H     0.640318427003      0.837545501485     -2.689250232500
H     1.706272225723      2.231005815117     -2.490090652474
O    -1.596979129175     -2.637565008355      0.381554607837
Al   -2.661385889411     -1.713812947942     -0.625805796048
C    -2.650436137846     -2.104150650084     -2.561304398268
C    -4.329937426151     -1.069039329995      0.195257840299
H    -2.843856089032     -1.200575538194     -3.154206499841
H    -1.716096726636     -2.547802909318     -2.925802166092
H    -3.453595375449     -2.814923741717     -2.800483521198
H    -4.180346989233     -0.614809204475      1.181446256737
H    -5.034871605896     -1.901234676058      0.327828008685
H    -4.830188616306     -0.327412791476     -0.440874989326
Cl   -1.320180353140      0.428356986031     -0.487804233447
-------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)           = -1029481.650041  kcal/mol
ZPVE            = 362.456902  kcal/mol
Enthalpie(0K)   = -1029119.193139  kcal/mol
E(tr)           = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 369.245067  kcal/mol
H-E(el)         = 370.796286  kcal/mol
Enthalpie       = -1029110.853755  kcal/mol
S(el)           = 0.000000000000
S(tr)           = 0.000066308847
S(rot)          = 0.000054427592 (Symmetry number= 1)
S(vib)          = 0.000099298864
G-E(el)         = 343.851103  kcal/mol
```

Free Energy = -1029137.798938 kcal/mol

Cartesian Coordinates and Energies of **Transition State VIIa– VIIIa**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.880934816901	-1.577864410565	-0.830292088219
C	0.697144596201	-2.865720691851	-0.037048630977
C	-0.447497878970	-2.696844707395	0.970880535989
C	-0.101108895071	-1.575634137197	2.004195786369
C	0.471167996535	-0.309870008759	1.312988221246
C	0.352873621789	1.002333507280	2.064396917907
C	0.677325235988	2.232189328204	1.226230156164
C	1.933403830676	2.027597340480	0.381793568663
C	1.736209142530	0.859129620798	-0.632424353735
C	1.011514556002	-0.336523947021	0.002905608984
C	3.134495591792	0.390068600263	-1.144747975116
C	3.987716605174	-0.415924052145	-0.160874314449
C	5.446472088851	-0.601782120759	-0.634476463064
C	6.175886465794	0.716461800700	-0.656305050834
C	6.666111381892	1.314782771723	-1.744546445364
C	6.180926790678	-1.610404458180	0.264585796751
C	2.360073452240	3.349438499527	-0.269769251119
C	-1.370015240236	-1.256482183377	2.818032215025
C	0.974500230969	-2.086932140629	2.995720956860
C	0.898404010334	1.302743277100	-1.856583743310
H	-0.030782824547	-1.398907950532	-1.415383741061
H	1.698652381841	-1.655245380322	-1.546476408128
H	0.438627091792	-3.673772751302	-0.726052107763
H	1.633235231330	-3.148380180954	0.461435310651
H	-0.519557494633	-3.625480654288	1.564403258628
H	1.711872965980	-0.580270294454	1.166670113570
H	-0.685032371138	1.053276114523	2.394368727001
H	0.969305544216	0.956372130372	2.970587339969
H	-0.175125263226	2.449579751534	0.575960104049
H	0.807732034963	3.095592619444	1.886890299813
H	2.743397058376	1.727581073318	1.063494589186
H	3.011560001452	-0.189827666359	-2.065163562177
H	3.683918598997	1.287700837889	-1.437446855554
H	3.554035205314	-1.413030767222	-0.007785069661
H	4.009855416815	0.070389402455	0.824650314291
H	5.422763423349	-0.999595478989	-1.658483769173
H	6.300907466731	1.196573524277	0.316790645632
H	7.189826823105	2.264257965728	-1.686923919226
H	6.564534199575	0.868637334326	-2.731383689909
H	7.205925496425	-1.770569498933	-0.081818746838
H	5.665265401232	-2.577028310460	0.270558805172
H	6.229015484773	-1.247873313715	1.298587006448
H	2.635867579213	4.065296815351	0.510858339586
H	1.541315122533	3.791087549624	-0.845138528947
H	3.223150027635	3.239965641147	-0.932010874885
H	-1.809570864673	-2.204357746470	3.140374873363

H	-2.116652781435	-0.731745224674	2.224049876361
H	-1.139304772076	-0.671444951339	3.713443485841
H	1.889061204581	-2.414296156069	2.490245635211
H	0.578386507115	-2.940041618136	3.553722346776
H	1.244653622376	-1.313819739979	3.722235498939
H	-0.079842911164	1.684745832779	-1.562913311384
H	0.732396711087	0.470065716966	-2.542957414124
H	1.447330496821	2.073721699438	-2.401669744612
O	-1.639626138057	-2.478102582406	0.329922666731
Al	-2.713066436526	-1.511476819938	-0.707206893409
C	-2.274670845051	-1.699725752654	-2.645173120353
C	-4.587298623338	-1.819420046901	-0.166498437350
H	-1.393022798039	-1.140139206440	-2.988155011404
H	-2.124742677982	-2.751662249271	-2.927183465038
H	-3.118512909317	-1.326749944734	-3.242061906551
H	-4.736176324880	-1.611160641698	0.901312935224
H	-4.894684342764	-2.859798417218	-0.341053891253
H	-5.280268053350	-1.175044727977	-0.723351039748
Cl	-2.205475483892	0.660538465163	-0.173084179493

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029484.180965 kcal/mol
ZPVE = 359.426223 kcal/mol
Enthalpie(0K) = -1029124.754742 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 366.735366 kcal/mol
H-E(el) = 368.286585 kcal/mol
Enthalpie = -1029115.894380 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054664206 (Symmetry number= 1)
S(vib) = 0.000110532540
G-E(el) = 339.936767 kcal/mol
Free Energy = -1029144.244198 kcal/mol

Cartesian Coordinates and Energies of **VIIIa**

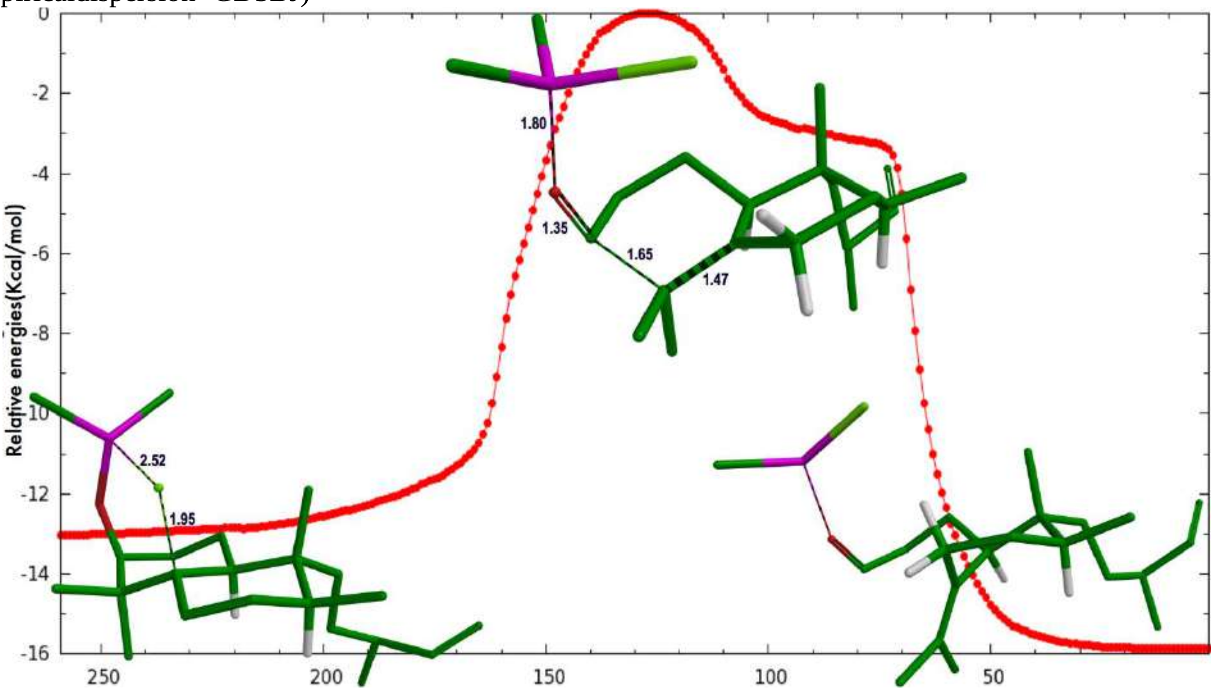
#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.864769902742	-1.651105409755	-0.716212919877
C	0.542958389209	-2.906951622397	0.094673752026
C	-0.660103640310	-2.711809402073	1.027555538671
C	-0.477418929226	-1.459337322833	1.953352099543
C	-0.055395736475	-0.181095225079	1.146581411663
C	0.182014761676	1.046235969493	2.025111378549
C	0.695121111577	2.261899449172	1.258945122422
C	1.977409531781	1.947774422927	0.476979435696
C	1.759707136315	0.792069662922	-0.551087634346
C	1.125299143862	-0.438781116989	0.189710015064
C	3.136389124785	0.349746997806	-1.134932327635

C	4.114390437259	-0.369181917754	-0.199807445820
C	5.542158758734	-0.467225169603	-0.781971245232
C	6.184156767228	0.892777314641	-0.868344627126
C	6.556082259692	1.509401166789	-1.992876988611
C	6.407881127525	-1.414622483028	0.066159293328
C	2.544855719384	3.239284101398	-0.128057716009
C	-1.764700270286	-1.253681485606	2.771568860823
C	0.642021026566	-1.799888274166	2.975867386071
C	0.931151893886	1.283093014564	-1.757516045262
H	0.045926706834	-1.432529369743	-1.404664317270
H	1.741343981018	-1.841512407511	-1.339733611413
H	0.314619252158	-3.743375549226	-0.573428996334
H	1.422681944457	-3.199051147515	0.682648930623
H	-0.701633651994	-3.573077188511	1.711967098537
H	1.903010703491	-0.743696805845	0.900604062184
H	-0.723210336300	1.288569352885	2.585644620891
H	0.944236672952	0.758846442639	2.758127987857
H	-0.078730951158	2.641422140632	0.582880815136
H	0.897339793392	3.066877454878	1.975067972218
H	2.709068306573	1.583335777086	1.212977454502
H	2.960785368419	-0.289040287353	-2.008440840928
H	3.627325775927	1.241192726301	-1.533139660152
H	3.763556725938	-1.387314586655	0.009248737141
H	4.174807476082	0.140706953952	0.771288396461
H	5.469972928771	-0.878285291093	-1.798795389757
H	6.345851043796	1.392543173606	0.089475948622
H	7.018852314186	2.491833679781	-1.979822743035
H	6.410630403662	1.047289186670	-2.966790040304
H	7.414069858160	-1.511378840652	-0.352686247767
H	5.958211185511	-2.412407051888	0.116781281105
H	6.505491217788	-1.038277311702	1.091841106296
H	2.741855780554	3.965215285324	0.668146855062
H	1.835005644135	3.700153943578	-0.822332761654
H	3.484855726630	3.077947685456	-0.661791024699
H	-2.001955978552	-2.186385285582	3.292687750091
H	-2.621305900678	-1.004525559687	2.148476353369
H	-1.641378236614	-0.473410695252	3.527932766542
H	1.635985068263	-1.879457597337	2.532232954740
H	0.409938122364	-2.766155000785	3.433319603657
H	0.686864758823	-1.064683658483	3.782628164250
H	0.039969792527	1.839567924118	-1.468877602445
H	0.606978703993	0.445995495518	-2.380411250414
H	1.545340082160	1.935199560705	-2.385571142509
O	-1.859426809551	-2.700771044571	0.315620266076
Al	-2.740465557534	-1.704616450314	-0.800604976414
C	-2.246320156977	-1.731373132071	-2.712587080845
C	-4.594050595169	-1.288962990777	-0.290888604286
H	-1.894517341171	-0.750532427819	-3.059252933957
H	-1.458249375294	-2.460091147428	-2.937385185612
H	-3.116726337893	-1.989475853469	-3.329923675129
H	-4.702931386092	-1.097910463721	0.783041339782
H	-5.261307804023	-2.125260762715	-0.540364948801
H	-4.974327554329	-0.410092899047	-0.827737537419
Cl	-1.587922904262	0.361564144094	0.073334492857

```
Thermochemistry at  195.150 K,    1.000 Atm
E(el)           = -1029495.535357  kcal/mol
ZPVE            = 362.438051  kcal/mol
Enthalpie(0K)   = -1029133.097305  kcal/mol
E(tr)           = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 369.892062  kcal/mol
H-E(el)         = 371.443282  kcal/mol
Enthalpie       = -1029124.092075  kcal/mol
S(el)           = 0.000000000000
S(tr)           = 0.000066308847
S(rot)          = 0.000054602599 (Symmetry number= 1)
S(vib)          = 0.000112675549
G-E(el)         = 342.838579  kcal/mol
Free Energy     = -1029152.696778  kcal/mol
-----------------------------------------------------------------
```

Plot of IRC transformation of **VIIIa** in to **IXa** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **VIIIa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.234536321085	0.625555671892	-1.355787057962
C	0.893688004080	2.005049141864	-1.331225673250
C	2.078896388977	2.069221773115	-0.359080696121
C	1.670948990871	1.605871432832	1.082058148213
C	0.903826061954	0.237133861564	1.070271913867
C	0.438293456844	-0.216233152849	2.452748817181
C	-0.394883007798	-1.493759614592	2.433672909775
C	-1.612938439205	-1.373907460641	1.508222467716
C	-1.195062611251	-1.050997761572	0.038015464580
C	-0.242669486726	0.198219597080	0.039390304876
C	-2.462733495629	-0.694297378611	-0.796747916905
C	-3.185188505369	0.618879859675	-0.479766451277
C	-4.576740850423	0.716353643678	-1.144414968531
C	-5.529318481259	-0.290525862647	-0.554720220420
C	-6.110113759397	-1.294762045144	-1.216003361987
C	-5.145061359194	2.138448886857	-0.999265358608
C	-2.501958346177	-2.616028876278	1.660175763111
C	2.926764079038	1.583441280599	1.971771878011
C	0.735805937816	2.696631284954	1.673736756427
C	-0.582169189473	-2.293578520352	-0.641743849881
H	0.932789556148	-0.113598088417	-1.754088183986
H	-0.612278298289	0.643832730878	-2.045630139767
H	1.265040889307	2.267030336981	-2.327018097621
H	0.148762912000	2.763689876556	-1.058206436089
H	2.373164253544	3.124579347725	-0.250854716117
H	-0.879620107390	1.010496038987	0.412070491054
H	1.294117605108	-0.317245731604	3.123523026847
H	-0.185060790557	0.592316694020	2.851149524086
H	0.223842209758	-2.348546837590	2.139680300883
H	-0.737353481670	-1.702120223175	3.454084914947
H	-2.193806199920	-0.512188414822	1.868600321787
H	-2.196377728692	-0.693971985499	-1.860240945186
H	-3.173023043164	-1.517506291971	-0.685742644645
H	-2.588435761587	1.474384661528	-0.819228235440
H	-3.313878663582	0.743918196642	0.603916493512
H	-4.461331829327	0.495067371032	-2.214850818441
H	-5.745331450933	-0.159380038998	0.508086987293
H	-6.794579802074	-1.981364979946	-0.726507536689
H	-5.920165103994	-1.460942161462	-2.274102786147
H	-6.120575598841	2.225539977877	-1.487064918780
H	-4.469045309510	2.875598952663	-1.446418010730
H	-5.273380792959	2.399170223049	0.058412451007
H	-2.805075877909	-2.726653491038	2.706893656464
H	-1.966880547230	-3.528016081163	1.377022216592
H	-3.414353781558	-2.559043151353	1.060932327202
H	3.407795332370	2.565190032650	1.922774983671
H	3.658828847358	0.847664565864	1.645524037159
H	2.675801878888	1.389036174273	3.018218678630
H	-0.245176237272	2.743423724459	1.197807645599
H	1.211748536007	3.672261265750	1.538182510387
H	0.587148223000	2.556692621823	2.746881771480

H	0.167136893291	-2.792465096313	-0.028080536804
H	-0.107624799492	-2.031078080687	-1.590271621842
H	-1.370578394039	-3.018479059421	-0.865346348709
O	3.185440923600	1.387589907415	-0.864541567737
Al	3.735706097526	-0.228637485042	-1.180435220490
C	3.136155137923	-1.141199813984	-2.826693691461
C	5.469545961250	-0.709052998394	-0.385136164491
H	2.567903283245	-0.480160317417	-3.492214383559
H	3.997776411852	-1.515932945522	-3.394459827385
H	2.501081427542	-2.009790245594	-2.607565104613
H	5.601122744785	-0.293758676488	0.620811771778
H	6.296962440573	-0.332127254455	-1.001701053203
H	5.596064071132	-1.797460431095	-0.317180546252
Cl	2.191743650137	-1.145108724725	0.588597715976

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029495.581653 kcal/mol
ZPVE = 362.284678 kcal/mol
Enthalpie(0K) = -1029133.296975 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 369.538405 kcal/mol
H-E(el) = 371.089625 kcal/mol
Enthalpie = -1029124.492029 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054605563 (Symmetry number= 1)
S(vib) = 0.000112977824
G-E(el) = 342.447542 kcal/mol
Free Energy = -1029153.134111 kcal/mol

Cartesian Coordinates and Energies of **Transition State VIIIa– IXa**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.382630774394	0.251465357183	-1.409014047189
C	1.134361290836	1.552939789002	-1.636419890119
C	2.107767878193	1.907478144509	-0.500623305674
C	1.328980011907	1.815207833827	0.955045110225
C	0.545028768834	0.570452713097	1.035227850346
C	0.685567369149	-0.291706433077	2.220266787676
C	-0.259063146999	-1.483068611388	2.324789050643
C	-1.603608015640	-1.190850519105	1.650979869398
C	-1.391968604134	-0.942223134059	0.130236826916
C	-0.412985755152	0.267959621930	-0.052122168322
C	-2.728793736363	-0.572904605585	-0.568500892897
C	-3.591844708114	0.514348545356	0.081098596109
C	-4.832522126351	0.882713192507	-0.760272570349
C	-5.770750310052	-0.289813881972	-0.883137907322
C	-6.115057987515	-0.893587612513	-2.022932333951
C	-5.562216135154	2.090507496959	-0.147049463518
C	-2.624972710549	-2.283530589351	1.986652552739

```
C       2.381565936128        1.990326957510        2.055103403746
C       0.355158468982        3.034531006579        1.006270205486
C      -0.855265355893       -2.212824056972       -0.562715901942
H       1.066265227539       -0.596364730665       -1.403532592743
H      -0.347670483571        0.088766330826       -2.205823246934
H       1.734937554220        1.471207995182       -2.547671045427
H       0.425480234287        2.375877615349       -1.790290711066
H       2.337279367853        2.986757318494       -0.551178040663
H      -1.029656370021        1.174067159193       -0.128618854653
H       1.741086212453       -0.598753878281        2.264342766336
H       0.569985685835        0.385700158006        3.084016658624
H       0.207313903180       -2.363875977503        1.875577411053
H      -0.411935431718       -1.716536721919        3.383847416843
H      -1.979978222043       -0.247919851053        2.078510356359
H      -2.499821803300       -0.266696294830       -1.598534935883
H      -3.327521120708       -1.483067321429       -0.670812108340
H      -3.009418631990        1.431636013565        0.241875617492
H      -3.931382014775        0.194049722088        1.074218262009
H      -4.493359802943        1.156413676567       -1.769313102976
H      -6.191829690331       -0.650406766232        0.058148674858
H      -6.804369089773       -1.732470834876       -2.039301088354
H      -5.717406004307       -0.565437758091       -2.980689438471
H      -6.423507422576        2.380440708544       -0.756059379680
H      -4.891355199039        2.953369696534       -0.067011809927
H      -5.927182406250        1.854797720707        0.859906947434
H      -2.810076652435       -2.299199628234        3.065753339008
H      -2.258770744928       -3.275160446223        1.705217784368
H      -3.584836124136       -2.125993878594        1.488045049083
H       2.961960613451        2.892353266362        1.845158166133
H       3.083729660096        1.157387858722        2.081083170215
H       1.920489617630        2.111020013853        3.041565148265
H      -0.325757591535        3.075379299479        0.156936876002
H       0.960396768464        3.944575447425        1.005175290716
H      -0.234982063664        3.021973214139        1.928334328709
H       0.170020430829       -2.453655384202       -0.277586754361
H      -0.872625942068       -2.098415690732       -1.649563903710
H      -1.493455589610       -3.067721225954       -0.326345433357
O       3.256490557698        1.203877777084       -0.475558773803
Al      4.001487933165       -0.366091415225       -0.951534706087
C       3.675091583599       -0.781260823942       -2.866713665370
C       5.847423042420       -0.385852863860       -0.257878451287
H       2.613955530504       -0.898989412940       -3.122630698855
H       4.086846413526       -0.001936432073       -3.523354053977
H       4.170952896031       -1.722771740511       -3.138237778742
H       5.878407831627       -0.150409112492        0.813994132852
H       6.480565576901        0.349951679792       -0.772333825077
H       6.317461700166       -1.369231695097       -0.388217079447
Cl      2.779194153538       -1.859484001910        0.263867309062
---------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029491.734882  kcal/mol
ZPVE           = 360.338352  kcal/mol
Enthalpie(0K)   = -1029131.396530  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
```

E(vib) = 367.501013 kcal/mol
H-E(el) = 369.052233 kcal/mol
Enthalpie = -1029122.682649 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054920684 (Symmetry number= 1)
S(vib) = 0.000107146186
G-E(el) = 341.085694 kcal/mol
Free Energy = -1029150.649187 kcal/mol

Cartesian Coordinates and Energies of I**Xa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.486983481512	0.233476203067	-1.322106120299
C	1.396226347319	1.452297898367	-1.569916088289
C	2.435385653896	1.652890869815	-0.510764491898
C	0.547738274324	2.146145168359	1.513544753820
C	0.386916805185	0.860453752851	1.103170310332
C	0.939928654772	-0.337457292532	1.825721592654
C	-0.238135802280	-1.133346957227	2.446067341082
C	-1.581532877823	-0.863317713007	1.736691721331
C	-1.397415758714	-0.774009769625	0.191959588497
C	-0.440592021969	0.456117745894	-0.103802266179
C	-2.746674789965	-0.521654135801	-0.529288584500
C	-3.618289250925	0.629082004857	-0.016041613895
C	-4.917403717525	0.815251163124	-0.830329289070
C	-5.819853639724	-0.382907543997	-0.691625563341
C	-6.212673948946	-1.181176302263	-1.687082312497
C	-5.653004663351	2.092302041381	-0.388453045678
C	-2.633775503924	-1.875183674675	2.205759277687
C	1.403680607212	2.544175878969	2.693259141374
C	-0.126981396485	3.342340253411	0.882149057914
C	-0.845155473013	-2.107672964870	-0.352480536955
H	1.110585602717	-0.651527378298	-1.187352571661
H	-0.114818537603	0.061695467090	-2.220250444428
H	1.946718868430	1.299854918235	-2.507740753308
H	0.807869240413	2.368728093778	-1.665983095103
H	2.523092659992	2.637304255849	-0.036927477989
H	-1.088620573168	1.291556774523	-0.369686568040
H	1.470713094398	-0.970806334333	1.109832684542
H	1.668142766835	-0.078167752756	2.593305389795
H	-0.007112983645	-2.203969142444	2.418605131577
H	-0.350076714484	-0.863998160723	3.502743881655
H	-1.916452805087	0.130589091069	2.063478858928
H	-2.531028779853	-0.347430463076	-1.593561259862
H	-3.334988393632	-1.444692117206	-0.502042618500
H	-3.063807252660	1.575312703773	-0.039537905664
H	-3.891136540980	0.466309847572	1.034036073857
H	-4.646772638188	0.918737826107	-1.890757497052
H	-6.167844319939	-0.588455702606	0.323251549961
H	-6.870474155144	-2.028019156418	-1.515121424284

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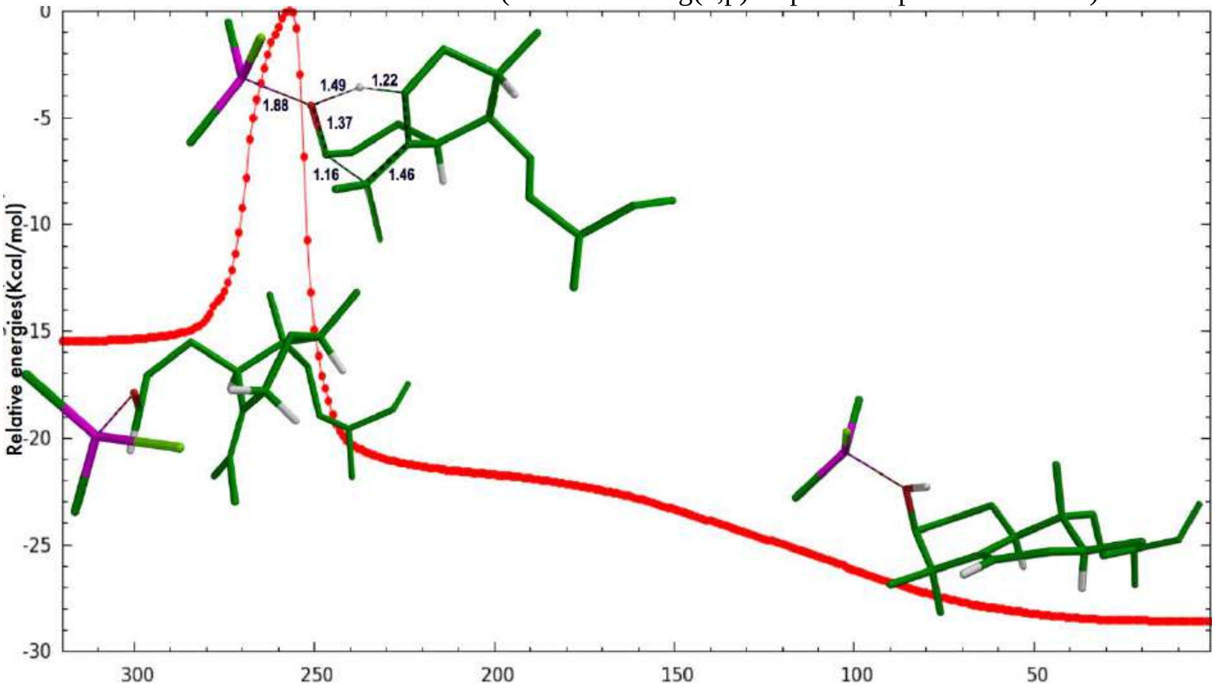
H     -5.885617614051      -1.012809541221      -2.710781218030
H     -6.560074127651       2.249559447990      -0.979814360504
H     -5.009843542690       2.972142712315      -0.502920889740
H     -5.946315568302       2.026917234287       0.666313913422
H     -2.721306019510      -1.841535648727       3.297392314447
H     -2.359361567504      -2.899430789025       1.934228997562
H     -3.624043498365      -1.672887344307       1.788566990982
H      2.058841946208       3.382720833391       2.421949031298
H      2.033024966160       1.740430014490       3.072038797452
H      0.773098703853       2.901543788781       3.518021462029
H     -0.873929503077       3.091915330416       0.129710012708
H      0.610424766085       4.010118673777       0.413185660694
H     -0.620029067560       3.938707205371       1.659593203873
H      0.154495505540      -2.344831840730       0.013828523917
H     -0.799424850781      -2.100083316078      -1.445106763582
H     -1.509941683307      -2.928463104597      -0.070523902063
O      3.316762625792       0.821244867632      -0.231273980200
Al     4.251073352842      -0.701313168518      -1.039917772353
C      4.106051309703      -0.347241436795      -2.978317900077
C      5.969202186507      -0.638513530621      -0.093145633378
H      3.109811558296      -0.564598372221      -3.382860237261
H      4.366988282281       0.685873294935      -3.246779616498
H      4.807800517463      -0.996914154521      -3.518044298751
H      5.828615965536      -0.702807245320       0.993007875780
H      6.521175104018       0.287299001712      -0.302040292305
H      6.614586156727      -1.476575021912      -0.385231198652
Cl     3.035207637062      -2.433110516424      -0.455015885471
--------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029502.703981  kcal/mol
ZPVE           = 359.816413  kcal/mol
Enthalpie(0K)   = -1029142.887568  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 367.706868  kcal/mol
H-E(el)        = 369.258088  kcal/mol
Enthalpie      = -1029133.445893  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055238301 (Symmetry number= 1)
S(vib)         = 0.000122022381
G-E(el)        = 339.430939  kcal/mol
Free Energy    = -1029163.273042  kcal/mol
--------------------------------------------------------------
```

Plot of IRC transformation of **IXa** in to **Xa** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **IXa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.323242116553	1.187387031595	2.035585021674
C	1.373152828881	0.198978463106	2.566090302967
C	2.309553753276	-0.337432550129	1.530385648790
C	0.356262855585	-1.575008962038	0.053966512640
C	0.014918578647	-0.257273266946	0.059052326594
C	0.455936373833	0.655916502026	-1.069102610948
C	-0.281288149326	1.999118187529	-1.086121826376
C	-1.765251745161	1.780552126446	-0.785355464184
C	-1.969654096288	1.282213300871	0.684512079683
C	-0.733764803305	0.427622242615	1.182734847323
C	-3.250605772984	0.406910305126	0.747393345895
C	-3.220451359139	-0.951387666533	0.039156778603
C	-4.618862446990	-1.591375868874	-0.105912318326
C	-5.481272135226	-0.799382198172	-1.053218015924
C	-6.628491335019	-0.191464502390	-0.741154056539
C	-0.079333021988	-2.595790482429	1.076418843669
H	0.828677573401	1.967176460549	1.461110534622
H	-0.150762245789	1.672559274558	2.890982840673
H	2.013744733656	0.711492051407	3.298620580457
H	0.893103259115	-0.638103050575	3.081075124961
H	2.543089111052	-1.408007948556	1.524195042735
H	-1.149168660268	-0.321842092356	1.861635990248
H	1.539741988339	0.813940284201	-1.026999254647
H	0.276892479535	0.150920370401	-2.025058113061
H	0.148778817580	2.706882350555	-0.367442058054
H	-0.156985246660	2.460333104538	-2.071687199177

```
H    -2.086088132970      0.963793715635     -1.445021972778
H    -4.076761945006      0.998046852137      0.335656717166
H    -3.501313758184      0.237217783589      1.804323531712
H    -2.777496069850     -0.864044569024     -0.960579184853
H    -2.583746056123     -1.649890999393      0.589499856379
H    -1.408710532437      3.214898151035      1.585431294909
H    -2.281293750303      2.124592424295      2.675610863105
H    -3.147400980591      2.970977569033      1.400874149350
H    -2.527369150454      3.181940431279     -2.244091945215
H    -3.670730051357      2.862672640426     -0.937937205515
H    -2.268901417324      3.909622444711     -0.657265774323
H     0.456119783924     -2.505933716538     -1.885643572307
H     1.690292591171     -3.063739723184     -0.760601614890
H     1.856715666642     -1.486174075878     -1.538320862696
H    -0.636949344048     -3.399037575698      0.577623681693
H    -0.707634785264     -2.198612072449      1.873429361117
H     0.791871331253     -3.076934139797      1.540804273007
O     2.992708702565      0.428988525721      0.820092695809
C    -2.206714684708      2.468592253256      1.638587853630
C    -2.609467870826      3.002510461163     -1.167044833039
H    -5.109351073970     -0.736890198554     -2.078428281289
C    -4.492469407765     -3.046845963081     -0.588631632115
H    -3.884805926127     -3.636184333798      0.107195139053
H    -5.474146947334     -3.521944484214     -0.676202031807
H    -4.009421545994     -3.087881542653     -1.572454463602
C     1.140683254062     -2.176992308432     -1.090930319154
H    -7.202934035954      0.359090767393     -1.480328544320
H    -7.032753491964     -0.227875739996      0.268158892737
Al    4.621426907771     -0.041789599209     -0.165438411971
C     5.884827836380      1.315565998480      0.485747078137
H     5.507645405894      2.331138565106      0.313908840375
H     6.084340682350      1.211524981764      1.560678438811
H     6.849394475393      1.237813025257     -0.031900635743
C     4.863972111690     -1.961302758423      0.244200565582
H     4.024002914285     -2.587789228571     -0.081210490665
H     5.747931248907     -2.333248457094     -0.290166446781
H     5.040052971628     -2.158123651612      1.311021849287
H    -5.103575904697     -1.592310323634      0.880785368598
Cl    3.981917956547      0.277392739009     -2.232347637268
---------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029505.124125  kcal/mol
ZPVE           = 359.588821  kcal/mol
Enthalpie(0K)  = -1029145.535304  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 367.683501  kcal/mol
H-E(el)        = 369.234720  kcal/mol
Enthalpie      = -1029135.889405  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055181790 (Symmetry number= 1)
S(vib)         = 0.000128220348
G-E(el)        = 338.655498  kcal/mol
Free Energy    = -1029166.468627  kcal/mol
```

Cartesian Coordinates and Energies of **Transition State IXa–Xa**

```
# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1
```

C	0.334501296154	1.000456631727	2.119440317297
C	1.365154163047	-0.060917145898	2.532715521292
C	1.988566794173	-0.749590243941	1.315099761391
C	0.772410969864	-1.512359742161	0.412694077698
C	0.022515096877	-0.292469966145	0.105980405710
C	0.499851100293	0.545355361606	-0.933729694337
C	-0.135708677122	1.919055077633	-1.076098984207
C	-1.639706708414	1.830034215291	-0.781474214873
C	-1.917200991278	1.313616772926	0.671570333362
C	-0.767843902462	0.366065511033	1.192957809640
C	-3.238424745252	0.495941141209	0.665159384230
C	-3.214147149228	-0.849160987077	-0.068349783407
C	-4.606609329080	-1.507031450684	-0.187838281578
C	-5.516367294479	-0.693052407520	-1.070547099163
C	-6.661648546441	-0.121577831397	-0.690575550839
C	0.090436111645	-2.570574918935	1.289477643277
H	0.844102631574	1.818946551542	1.605583694278
H	-0.146098896977	1.419130113195	3.005331169903
H	2.174710542482	0.417028919160	3.093492373591
H	0.907564867255	-0.801367044791	3.196869801084
H	2.618636592949	-1.608142734845	1.577813807839
H	-1.245885709987	-0.393094746954	1.815002181812
H	1.603138654291	0.591235456693	-0.403130110315
H	0.797566557993	0.054929582722	-1.860574423614
H	0.336842522437	2.642397904571	-0.399846239799
H	0.031672071243	2.295965153460	-2.088713925289
H	-2.024188745111	1.066251100329	-1.468344121138
H	-4.025061096286	1.122860746292	0.230570071407
H	-3.538795584964	0.315407982366	1.706874101707
H	-2.802238264536	-0.736053709003	-1.079433881574
H	-2.553192369202	-1.552358299967	0.451193666978
H	-1.259972412130	3.170608157458	1.655799704816
H	-2.241946080644	2.108680588033	2.676638228672
H	-3.004434776774	3.053464331785	1.403865955210
H	-2.231417158046	3.344980193374	-2.205534800416
H	-3.432204472029	3.080897869173	-0.939309758246
H	-1.953039467577	3.989957417794	-0.585647027369
H	0.672769924368	-2.599061603902	-1.458123809889
H	2.027983907904	-3.059374000243	-0.417988274817
H	2.111100140522	-1.567044012289	-1.344406226243
H	-0.606456012495	-3.155190501593	0.680805567362
H	-0.459578037820	-2.170935164983	2.140486957434
H	0.845625510670	-3.261376843792	1.676372985783
O	2.670777092377	0.153195585274	0.543130915622
C	-2.108905823795	2.480898890955	1.655762710042
C	-2.357275079526	3.136114284712	-1.138322180217
H	-5.185138292343	-0.583225541915	-2.105658981425

C	-4.475677602117	-2.940925264507	-0.729758805682
H	-3.832600362594	-3.546032551975	-0.080871243999
H	-5.452826443990	-3.428192821159	-0.795812890696
H	-4.032719252454	-2.938014226091	-1.733018027328
C	1.439586936123	-2.211563788503	-0.778849726609
H	-7.274735494220	0.445989738707	-1.384328416584
H	-7.026045701456	-0.207227226981	0.330822995740
Al	4.403491298543	0.052937726451	-0.176371607124
C	5.332400859966	1.691212407663	0.406399668563
H	4.753542449970	2.589467708505	0.154909621875
H	5.505299301016	1.702465879447	1.491447209068
H	6.311139029876	1.793625682490	-0.079761783610
C	5.112271063834	-1.731396836507	0.311243603611
H	4.498857365686	-2.558831661048	-0.067876163457
H	6.114787466458	-1.866437857234	-0.115401342275
H	5.214829870282	-1.862338386061	1.398210669614
H	-5.052392433104	-1.553305830842	0.815780170405
Cl	3.901875724036	0.167074665356	-2.339196710234

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Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029492.269375 kcal/mol
ZPVE = 359.552644 kcal/mol
Enthalpie(0K) = -1029132.716731 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 366.965909 kcal/mol
H-E(el) = 368.517128 kcal/mol
Enthalpie = -1029123.752247 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055059088 (Symmetry number= 1)
S(vib) = 0.000114064534
G-E(el) = 339.686431 kcal/mol
Free Energy = -1029152.582944 kcal/mol

\--

Cartesian Coordinates and Energies of **Xa**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

\--

C	-0.081103462380	-0.206803370891	1.464502451556
C	1.005983220940	-1.218452912579	1.837947428192
C	2.031060364468	-1.343359092201	0.721268687210
C	1.415547365063	-1.764792404889	-0.628558518898
C	0.333201239730	-0.737204521437	-0.994315740668
C	0.270299342211	-0.190677476982	-2.219074393370
C	-0.883311357469	0.634157689027	-2.706979541657
C	-2.114395781691	0.484224402197	-1.805588452599
C	-1.707315278912	0.705127254355	-0.317656960669
C	-0.722609185261	-0.447979519304	0.075792636959
C	-2.951545858617	0.694775300728	0.605515513444
C	-3.818905987684	-0.567804243682	0.598094183963
C	-5.135240991140	-0.400810847568	1.389990760290

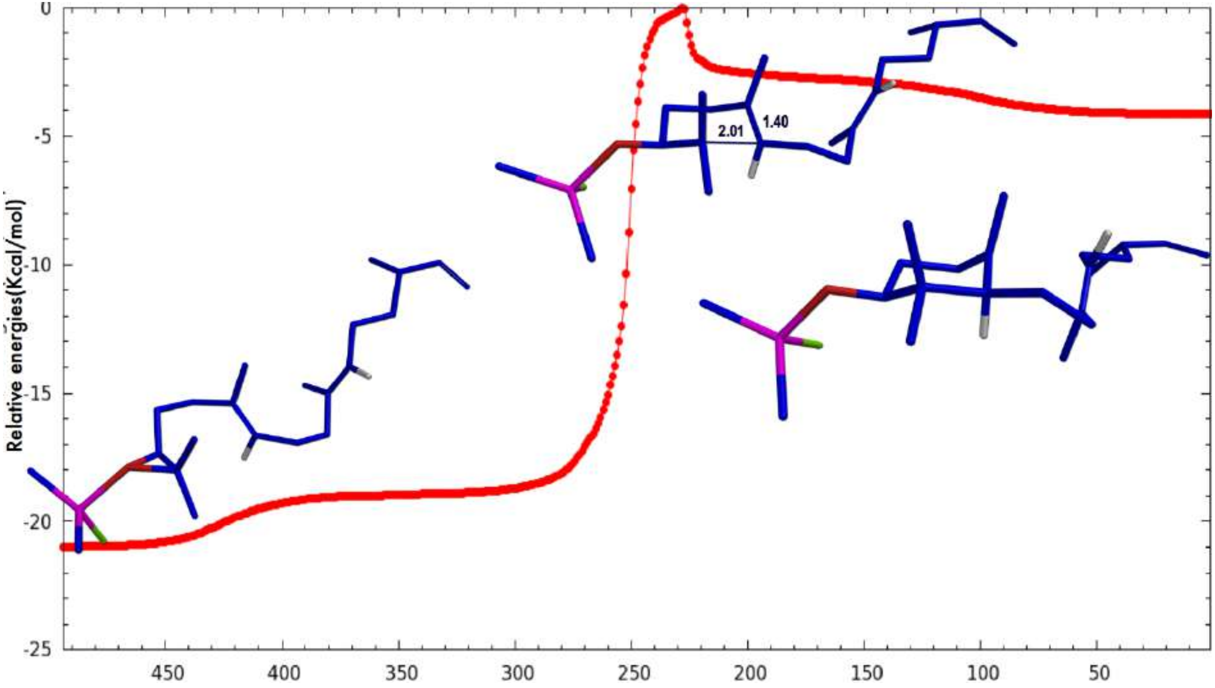
C	-6.054316769731	0.579680886930	0.709375002892
C	-6.454462417285	1.750789822647	1.210624506579
C	0.769963344651	-3.164252807596	-0.480337546764
H	0.369811229491	0.788492243039	1.491411675987
H	-0.859853370366	-0.211703824505	2.232449940184
H	1.512040098237	-0.901119226545	2.755802435968
H	0.580962430462	-2.207974079049	2.035784552708
H	2.848040573273	-2.015012285971	0.993966348060
H	-1.327052238794	-1.360967801018	0.163363711166
H	2.212836158046	0.466204775018	-0.162625398990
H	1.052287893589	-0.399128700765	-2.942369790295
H	-0.595743258762	1.691566056986	-2.799113852181
H	-1.134990682486	0.313465943534	-3.726564937512
H	-2.438418507418	-0.562385630756	-1.892889111126
H	-3.574687068117	1.554471564819	0.339154251097
H	-2.629375788205	0.885319835662	1.636518691907
H	-4.069298775060	-0.863680414265	-0.428855013926
H	-3.266032720191	-1.409960729251	1.032156713488
H	-0.034797378861	2.116469335184	-0.598756592743
H	-0.944986195162	2.367102885234	0.893758848538
H	-1.634067273672	2.865608581670	-0.640680278055
H	-3.452148492679	1.158841722000	-3.368263213063
H	-4.196008507415	1.181298617629	-1.767316510923
H	-3.031950646731	2.430477744672	-2.220774618321
H	2.145220559111	-2.278814093586	-2.619484416445
H	3.290470482587	-2.597674775760	-1.315481625886
H	3.043290844726	-0.943816688213	-1.880491295977
H	0.414489596161	-3.499690853970	-1.458397329518
H	-0.079676347515	-3.175567517938	0.203778102273
H	1.507238763768	-3.889972747858	-0.118639469285
O	2.668393590269	-0.031685450388	0.541379980515
C	-1.035467439409	2.087719639006	-0.158986574817
C	-3.264525484969	1.364177166519	-2.308603547644
H	-6.407361381348	0.277052393733	-0.279107115094
C	-5.837301064957	-1.758332427006	1.563965291292
H	-5.185411576926	-2.470991934917	2.081394659270
H	-6.760761196359	-1.654453746642	2.141608543754
H	-6.096778605007	-2.188644911533	0.589004000887
C	2.537524853158	-1.890401685079	-1.675994212173
H	-7.122885019406	2.408365775770	0.662666277075
H	-6.125047437281	2.090090221901	2.190242658786
Al	4.547078359472	0.501531500819	0.765128442596
C	4.559348825832	1.610014464338	2.387430129903
H	3.828730132085	2.425963797615	2.325049362784
H	4.325554632931	1.021673641491	3.285233208152
H	5.541823412222	2.070345682007	2.552363649659
C	5.549816461004	-1.189516388820	0.658149921471
H	5.357766508958	-1.732062373089	-0.274825309952
H	6.628537783462	-0.989453932878	0.693493704412
H	5.332179388421	-1.866952867788	1.495287828984
H	-4.888640245606	-0.005435225319	2.385578787367
Cl	4.539416358133	1.673356334740	-1.093715450928

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029517.043471 kcal/mol

```
ZPVE            = 361.925056  kcal/mol
Enthalpie(0K)   = -1029155.118415  kcal/mol
E(tr)           = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 369.422500  kcal/mol
H-E(el)         = 370.973720  kcal/mol
Enthalpie       = -1029146.069750  kcal/mol
S(el)           = 0.000000000000
S(tr)           = 0.000066308847
S(rot)          = 0.000055376606 (Symmetry number= 1)
S(vib)          = 0.000117623982
G-E(el)         = 341.668256  kcal/mol
Free Energy     = -1029175.375215  kcal/mol
----------------------------------------------------------------
```

Scheme S1. Proposed formation mechanism of Xb from Ib.

Plot of IRC transformation of **Ib** in to **IIb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **Ib**.

```
#        FREQ/B3LYP/6-31+g(d,p)        empiricaldispersion=GD3BJ        scrf=(smd,
solvent=dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1
---------------------------------------------------------------
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C	-0.959078622114	-1.832075577601	-0.102258947168
C	-2.272089134551	-1.534984465573	-0.861728390411
C	-3.072200473512	-0.499295274369	-0.121209129925
C	-3.068496389314	0.953898376500	-0.375614940735
C	0.061531783447	0.103372242016	1.066631090304
C	0.904446324337	1.327430759694	1.295608337228
C	2.217162769852	1.053946583053	2.076131834388
C	3.174426085680	0.140213969889	1.330238189596
C	3.981351335535	0.653095147839	0.387283015958
C	-0.026348179835	-0.639027183880	-0.049249886751
C	4.959906147749	-0.067740699729	-0.496726260977
C	6.417042762104	0.323872461255	-0.189803667557
C	7.442402057196	-0.245659502071	-1.180037683322
C	8.844495167802	0.276316356921	-0.966513953719
C	9.274949871315	1.064790419778	0.022710040124
C	7.467919170916	-1.787711388962	-1.176239239982
C	3.111154287362	-1.318297684794	1.705566317602
C	-2.310309941683	1.564312317627	-1.525385687821
C	-3.378873153369	1.893539124491	0.762138572335
C	0.758496150460	-0.382791318440	-1.310233040222
H	-0.460761803372	-2.676510831820	-0.594295614230

H	-1.204939627953	-2.158046855006	0.915011907703
H	-2.068070422957	-1.209402526610	-1.884435760968
H	-2.872940258810	-2.448832309894	-0.930820690254
H	-3.364997877157	-0.789739976178	0.887302355631
H	-0.522888115910	-0.221575189209	1.929189143472
H	1.167474337350	1.804757631654	0.346343669855
H	0.316330366344	2.059377256978	1.865745077432
H	2.699685267048	2.018719535237	2.270292674655
H	1.968670089745	0.620724884064	3.052907735106
H	3.945179420103	1.734511924177	0.236063202757
H	4.835612963943	-1.149983448337	-0.409709849695
H	4.744707653060	0.184359385437	-1.546350148077
H	6.491755053168	1.418563643392	-0.190731803599
H	6.664894193990	-0.003105911035	0.828427652921
H	7.138707597250	0.070194129860	-2.191824102777
H	9.568267295362	-0.061557392250	-1.709920568033
H	10.315920839019	1.367888985959	0.082684624897
H	8.616584602136	1.435322423849	0.802504547742
H	6.505869370385	-2.207761407975	-1.484164421680
H	7.702607865332	-2.161828551767	-0.173157576816
H	8.231056836873	-2.169703395517	-1.862513154917
H	2.094447915076	-1.704780148045	1.572322544206
H	3.360672234632	-1.445276241964	2.766979308521
H	3.794656148842	-1.941177499816	1.125811687658
H	-2.852123762986	2.437969061671	-1.899744879442
H	-2.173954116585	0.863665650725	-2.348837799990
H	-1.327420390141	1.890489154321	-1.173910931335
H	-4.007635897300	1.420888528573	1.518014157707
H	-3.880215946281	2.793140908798	0.394536507026
H	-2.432497920678	2.192927163041	1.225091283807
H	1.289572367318	0.569387873896	-1.296683186282
H	0.112791302849	-0.408253794431	-2.195856932863
H	1.511219884172	-1.170448226086	-1.444771016126
O	-4.205886882047	0.102078724475	-0.839474576582
Al	-6.117352170933	-0.012062277166	-0.406782686332
C	-6.660227697740	-1.554664746007	-1.497968660949
C	-6.743521222117	1.826510826974	-0.727023450589
H	-7.703243336886	-1.832615293020	-1.300025989448
H	-6.048821382396	-2.439513543223	-1.279371381438
H	-6.575087230193	-1.347951693119	-2.572669483740
H	-6.402826436369	2.209641332615	-1.698480536389
H	-7.840068199638	1.870995513309	-0.734307417018
H	-6.401805268576	2.522930015250	0.047838145652
Cl	-5.995974432981	-0.528739031360	1.732402160158

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029478.423143 kcal/mol
ZPVE = 357.651020 kcal/mol
Enthalpie(0K) = -1029120.772123 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 365.745218 kcal/mol

H-E(el) = 367.296438 kcal/mol
Enthalpie = -1029111.126705 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000056622282 (Symmetry number= 1)
S(vib) = 0.000127061674
G-E(el) = 336.682705 kcal/mol
Free Energy = -1029141.740438 kcal/mol

Cartesian Coordinates and Energies of **Transition state Ib-IIb**

\# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	-0.929814517631	-1.578153086581	-0.172004158443
C	-2.332458530715	-1.349635714668	-0.800804824129
C	-2.952350674843	-0.065836989227	-0.252535610151
C	-2.106952202811	1.197496085446	-0.499019164191
C	-0.335168393812	0.777267628597	0.362054285549
C	0.569022604334	1.988692021169	0.357953909217
C	1.754215402415	1.843601940625	1.344931401853
C	2.666564572719	0.663469564414	1.051166571607
C	3.586372639392	0.763375024155	0.078005361407
C	-0.138459719533	-0.346088594541	-0.442087209635
C	4.563495125068	-0.274800867218	-0.396069499076
C	6.018916474361	0.119742517981	-0.082076462314
C	7.069716680197	-0.813020047164	-0.699987794789
C	8.488494044263	-0.326406786335	-0.514150325950
C	8.897848761242	0.734517245314	0.187263260332
C	6.953455987746	-2.258488739999	-0.175366971992
C	2.451261971012	-0.559604565953	1.907348417232
C	-1.882826608687	1.582305757607	-1.940007770891
C	-2.543473000314	2.359977624449	0.361613454204
C	0.707140782186	-0.355726309386	-1.667446183768
H	-0.452110909340	-2.456715626742	-0.614615321509
H	-1.051577598265	-1.742239601567	0.903067807354
H	-2.276747535496	-1.304288881812	-1.893408518152
H	-2.987525733558	-2.181716347544	-0.532839478496
H	-3.038055248434	-0.188946383384	0.842758491949
H	-0.777435140981	0.556979303196	1.333286805954
H	0.962345987276	2.182624490872	-0.643403597867
H	-0.004992347158	2.871050619999	0.651696919656
H	2.326803608762	2.776738974299	1.305771687336
H	1.357537562905	1.763351045655	2.364322089028
H	3.663131542701	1.724142161023	-0.436409145085
H	4.338393733030	-1.251341086448	0.040079445848
H	4.461953894462	-0.389124687598	-1.486427028462
H	6.189817588438	1.140320020103	-0.446395039991
H	6.148368203291	0.152726839466	1.007291378531
H	6.887011831480	-0.846913452572	-1.786711876839

H	9.242312624688	-0.942724960433	-1.006069520649
H	9.952541333846	0.981272271056	0.261192205253
H	8.209744441023	1.391911324681	0.709902685578
H	5.990033387602	-2.707068860121	-0.435472891059
H	7.061058699713	-2.278863056366	0.915060087033
H	7.737895387785	-2.893300714682	-0.599906689179
H	1.406831709804	-0.892791259056	1.876906652548
H	2.665911116459	-0.325007370019	2.957712846738
H	3.081890678789	-1.402444055111	1.620327524237
H	-2.833429823112	1.982274446501	-2.306673557401
H	-1.620499761085	0.739410199257	-2.579138298239
H	-1.124902130939	2.365156533088	-2.033498771219
H	-2.494420193909	2.140560479042	1.430026882029
H	-3.602067708515	2.506270336619	0.116236323358
H	-2.008399956104	3.284754511926	0.139138829832
H	0.985639574941	0.635278755230	-2.022332409028
H	0.220230427054	-0.921631785048	-2.467753897290
H	1.634100062370	-0.887935634500	-1.415847405716
O	-4.174312392065	0.207116696765	-0.849065638253
Al	-5.715497540768	-0.076579795065	0.100366627571
C	-7.210251156288	-0.196394198222	-1.186240287195
C	-5.809766590215	1.266827384103	1.569813860972
H	-8.157102215036	-0.427827759312	-0.681005700541
H	-7.035876650826	-0.984312454332	-1.929992401625
H	-7.353728331548	0.747070702804	-1.731387448630
H	-5.889049446989	2.296981521310	1.191274181688
H	-6.691980194803	1.090832511023	2.199526348565
H	-4.938641916582	1.225407359145	2.238979476306
Cl	-5.277227271385	-2.064588226484	1.063810078615

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Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029470.139873  kcal/mol
ZPVE           = 356.909750  kcal/mol
Enthalpie(0K)   = -1029113.230123  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 364.294184  kcal/mol
H-E(el)        = 365.845404  kcal/mol
Enthalpie      = -1029104.294469  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000056273963 (Symmetry number= 1)
S(vib)         = 0.000115848322
G-E(el)        = 336.647495  kcal/mol
Free Energy     = -1029133.492378  kcal/mol
---------------------------------------------------------------
```

Cartesian Coordinates and Energies of **IIb**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

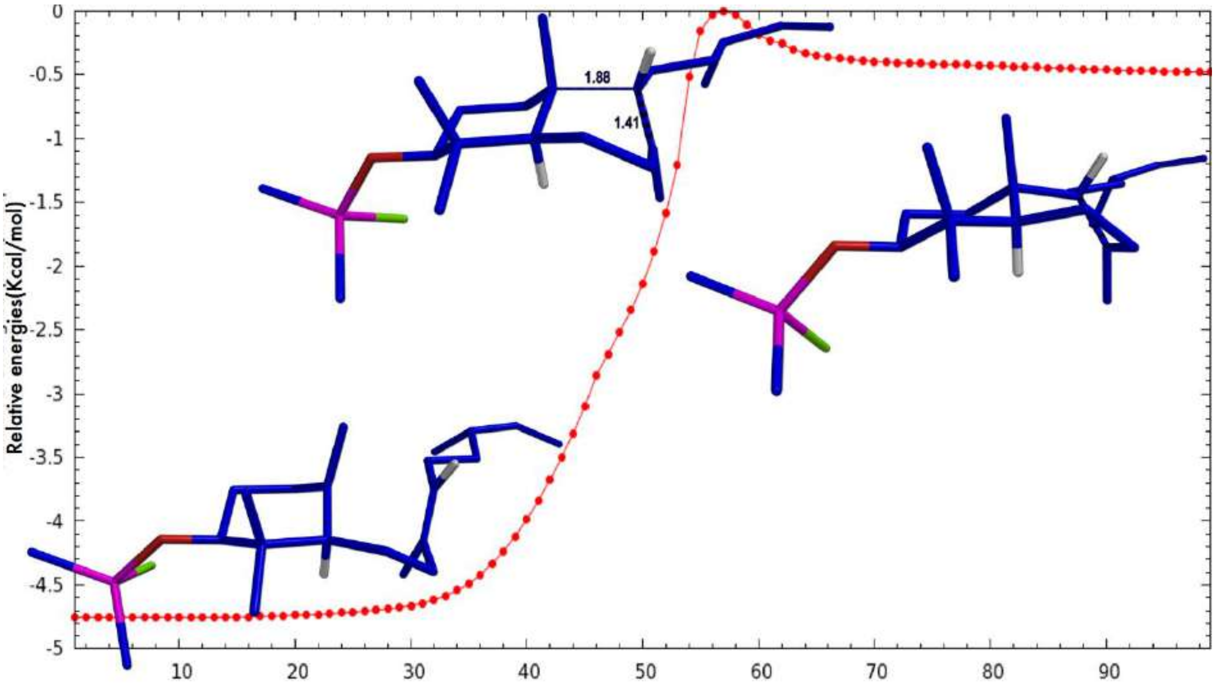
Charge = 0 Multiplicity = 1

```
-----------------------------------------------------------
C     -0.081431477064      -0.800909459052      -0.565920251416
C     -1.613060567714      -0.846637345975      -0.984570209542
C     -2.452727003376       0.227379305929      -0.278497458263
C     -1.912941157580       1.677744779464      -0.500505026688
C     -0.360822729451       1.622095985985      -0.080548276338
C      0.417520053237       2.936691981647      -0.019348033223
C      1.629259547691       2.768753921822       0.942524598765
C      2.218037077489       1.369110245350       0.911345942938
C      2.894389842126       0.932233811742      -0.176973900850
C      0.276669333250       0.574488394021      -0.903355352889
C      3.532578573683      -0.411732322424      -0.373621381484
C      5.035133345011      -0.388187871669      -0.028248230080
C      5.763738766557      -1.701114271452      -0.347864712290
C      7.261265969520      -1.612152333621      -0.163248393242
C      7.959609803476      -0.582408418880       0.323176199931
C      5.218196816468      -2.888402540438       0.471119395611
C      1.992556677009       0.531199990377       2.137789861647
C     -2.171709136759       2.173108311225      -1.924779180114
C     -2.626483718479       2.610682056375       0.488026932280
C      0.791987302703       0.822749649607      -2.279889946248
H      0.485661076828      -1.551808990290      -1.119648629059
H     -0.033971532892      -0.997850494292       0.507899420153
H     -1.720420903669      -0.758621479884      -2.069642067430
H     -1.989119112034      -1.827867661694      -0.678673339410
H     -2.353274186083       0.035774284586       0.809192147168
H     -0.437481363182       1.228813700482       0.938347472304
H      0.759167051399       3.237651418891      -1.013270151029
H     -0.222461828930       3.742603685762       0.343401850578
H      2.398294000818       3.507532262590       0.690969909327
H      1.300726777228       2.990442137441       1.962568721518
H      3.075768932564       1.657279082474      -0.970172229656
H      3.022368378926      -1.173022367720       0.221527442492
H      3.422652100346      -0.712218113609      -1.425263518787
H      5.509475963562       0.431187714553      -0.581730386736
H      5.148990377544      -0.152569278864       1.037434594551
H      5.588148637937      -1.930228428772      -1.411638883100
H      7.801970288383      -2.514374167085      -0.451404540173
H      9.039039631611      -0.638338476404       0.423759077372
H      7.493064341423       0.346248827091       0.637906760269
H      4.166956033484      -3.091637595874       0.245646515346
H      5.309714843227      -2.685650749203       1.544130650833
H      5.781164449837      -3.802027312065       0.256125237051
H      0.925072023029       0.461685334186       2.382455635692
H      2.467857452795       1.016354372552       2.999477940906
H      2.395504650354      -0.478545913422       2.056482772567
H     -3.251228583958       2.273254292041      -2.053790906680
H     -1.834477912044       1.478464672619      -2.696631225818
H     -1.704849862034       3.148289540128      -2.102633087635
H     -2.356872964977       2.386873088598       1.525384747100
H     -3.700854833698       2.438917029725       0.382588356573
H     -2.422967547874       3.666808276824       0.287624792656
```

H	1.054110829381	1.859725982756	-2.477580474672
H	-0.007715827165	0.537617142386	-2.975440537452
H	1.635813383197	0.167674008580	-2.504787421892
O	-3.763160423772	0.126980043425	-0.701529039734
Al	-4.986717758072	-0.735530779839	0.333568447317
C	-6.534277790394	-1.237907560640	-0.789235008434
C	-5.287932696881	0.333834632835	1.986465604845
H	-7.274592197337	-1.817818296444	-0.222427787965
H	-6.225340548517	-1.852336704353	-1.644971800470
H	-7.050228743764	-0.353292651447	-1.188639522131
H	-5.779068037318	1.293193419414	1.766491785444
H	-5.928544322700	-0.202251355362	2.699031261996
H	-4.349954265312	0.559131359433	2.513695929253
Cl	-3.834515549946	-2.585328437939	0.980939790465

```
-------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029477.261069  kcal/mol
ZPVE           = 358.706907  kcal/mol
Enthalpie(0K)   = -1029118.554162  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 366.005752  kcal/mol
H-E(el)        = 367.556971  kcal/mol
Enthalpie      = -1029109.704098  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055986662 (Symmetry number= 1)
S(vib)         = 0.000113477042
G-E(el)        = 338.684628  kcal/mol
Free Energy     = -1029138.576441  kcal/mol
-------------------------------------------------------------
```

Plot of IRC transformation of **IIb** in to **IIIb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **IIb**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	-0.034391273193	-0.798349539758	-0.677094741766
C	-1.563371530091	-0.822914840410	-1.110917635111
C	-2.428710259519	0.142614434690	-0.288814652009
C	-1.914766273408	1.618660327584	-0.326770569148
C	-0.364602322753	1.539403321144	0.103125403164
C	0.385735204255	2.850931279798	0.338253039272
C	1.571213190162	2.588928369796	1.309638575315
C	2.223171377434	1.234963513336	1.090213479594
C	2.925214406247	0.987989008224	-0.039620205447
C	0.295317963862	0.614821428028	-0.838489755263
C	3.628787107022	-0.283935145431	-0.413047036605
C	5.122238254891	-0.244184051179	-0.031796480023
C	5.919349771152	-1.461938543792	-0.519677381334
C	7.405668246181	-1.338613914886	-0.274020093771
C	8.042388007403	-0.364343880560	0.381804571560
C	5.407429556110	-2.781398076925	0.092769605527
C	2.026601841768	0.222828333663	2.183388868969
C	-2.165116197513	2.284801918187	-1.680881345390
C	-2.658624144156	2.408768029278	0.758725280530
C	0.820398205364	1.040895043086	-2.166720080479
H	0.550328059690	-1.463255917648	-1.315878617010
H	0.010405569001	-1.126162982235	0.364082206996
H	-1.665987309364	-0.609138011703	-2.178689435822
H	-1.918382250340	-1.841697767182	-0.927320850383
H	-2.333818210133	-0.177008427489	0.768750438617
H	-0.443024520134	1.021458432025	1.064830028275
H	0.751912993251	3.268792594677	-0.603126442454

```
H    -0.278708664971     3.599841597972     0.772298385282
H     2.312761161133     3.388523246072     1.202004883241
H     1.199303919927     2.639973190128     2.337760704203
H     3.071345356297     1.824534994108    -0.722687671071
H     3.550975240383    -0.434814051842    -1.499015128416
H     3.144046139117    -1.144059906677     0.055566245297
H     5.566588106225     0.667697104889    -0.448593631919
H     5.205029479574    -0.161198028420     1.059153009010
H     5.783383083936    -1.534750094075    -1.611188283008
H     7.995200032947    -2.164356256897    -0.674091986080
H     9.120227718235    -0.389427447211     0.508521548633
H     7.525322409767     0.486783626995     0.814551022450
H     4.375776864139    -2.995013857927    -0.202363891213
H     6.022081247062    -3.626620680234    -0.232190050115
H     5.452842712126    -2.737726062625     1.186791157158
H     0.961224322545     0.077122342659     2.402307803118
H     2.471075668888    -0.748416622245     1.963878212713
H     2.476285647102     0.598304237886     3.111099458154
H    -3.245129650119     2.364195623005    -1.820511509677
H    -1.785910370727     1.711897196925    -2.529189067269
H    -1.731420843174     3.290308166061    -1.716564469934
H    -2.400784149144     2.060830567692     1.764357579719
H    -3.727607009547     2.232905035674     0.612770539768
H    -2.472120881404     3.484876932552     0.695049412967
H     0.049938183569     0.796646586916    -2.909212427189
H     1.699483532138     0.455179437287    -2.443303185316
H     1.034995198644     2.104541877335    -2.240990541917
O    -3.733841049418     0.071644473590    -0.733177512796
Al   -4.950290665032    -0.932228650406     0.175524681997
C    -6.464398625729    -1.347502436006    -1.025662258763
C    -5.310210247957    -0.062736795288     1.930895779740
H    -6.993640195373    -0.437633828388    -1.342265066156
H    -7.201046879496    -1.998738927135    -0.536941983826
H    -6.125363899390    -1.863298002533    -1.933538040037
H    -5.968288934055    -0.681297384480     2.555425434480
H    -5.803033603688     0.912984024861     1.808328036832
H    -4.391529030345     0.103929864032     2.511248465768
Cl   -3.757034111480    -2.811098436128     0.635987041513
------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)         = -1029477.163542  kcal/mol
ZPVE           = 359.475640  kcal/mol
Enthalpie(0K)   = -1029117.687902  kcal/mol
E(tr)         = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 367.054653  kcal/mol
H-E(el)        = 368.605872  kcal/mol
Enthalpie      = -1029108.557670  kcal/mol
S(el)         = 0.000000000000
S(tr)         = 0.000066308847
S(rot)         = 0.000055992653 (Symmetry number= 1)
S(vib)         = 0.000114599413
```

G-E(el) = 339.595352 kcal/mol
Free Energy = -1029137.568190 kcal/mol

Cartesian Coordinates and Energies of **Transition state IIb-IIIb**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.143970538011	-0.761871357559	-0.704691247295
C	-1.338997029222	-0.789814472465	-1.156939641143
C	-2.241941712222	0.146409067766	-0.339132625780
C	-1.751721919511	1.632966833781	-0.342427680314
C	-0.255889611366	1.569891684855	0.104337966975
C	0.465114694336	2.879050921361	0.441806835666
C	1.586181783316	2.522926095351	1.466351530649
C	2.103103401302	1.145090355971	1.217132713389
C	2.368385483799	0.775512215712	-0.115554951907
C	0.624751488625	0.671236106181	-0.773935939128
C	3.160269993569	-0.476290557934	-0.441282022133
C	4.654794831931	-0.288281395110	-0.138196681575
C	5.517938995206	-1.503504066813	-0.505349377607
C	7.000454547334	-1.244437890229	-0.367639337684
C	7.593596103122	-0.146465854424	0.108927355958
C	5.139494609228	-2.756107776300	0.310954084285
C	2.116188391970	0.186417102270	2.344679750970
C	-2.032675748909	2.327423084364	-1.682550730067
C	-2.546824831455	2.380855854245	0.744590895778
C	0.885757038623	1.138154410814	-2.204485456344
H	0.743707851481	-1.422093846901	-1.337610104886
H	0.192018258285	-1.139956783250	0.323442365997
H	-1.432727389101	-0.551191523715	-2.221357821862
H	-1.717312962804	-1.806403773024	-1.018939177962
H	-2.149942923529	-0.184840175591	0.715853352113
H	-0.345277281570	1.031963246733	1.060210840363
H	0.880754492841	3.354848583401	-0.450990348209
H	-0.203729634028	3.604924306380	0.904946949341
H	2.426318744078	3.227600617962	1.379591517198
H	1.204196366689	2.597921699900	2.488201969406
H	2.665003822470	1.638565780567	-0.712444341713
H	3.038850563502	-0.710704738044	-1.503702269231
H	2.755593527850	-1.329936979004	0.105634947799
H	5.016127407221	0.589085462006	-0.689010220317
H	4.789601939381	-0.060830794623	0.928388762085
H	5.332826659441	-1.736552732707	-1.566200973600
H	7.630274467959	-2.075784569830	-0.685506725731
H	8.675102496667	-0.080115067241	0.172826689743
H	7.037446700596	0.721577417877	0.450333357679
H	4.110766017339	-3.074858012363	0.118763794758
H	5.793022203264	-3.596824492477	0.059405932004
H	5.249889028988	-2.561033755457	1.383940072017

H	1.070916982257	-0.095994671441	2.554906859261
H	2.686436064494	-0.721035915689	2.154282035911
H	2.474719775957	0.677904784696	3.255750764440
H	-3.111370993961	2.465005388878	-1.777410242281
H	-1.721982244135	1.745273972832	-2.550218696937
H	-1.551592338019	3.311917634090	-1.732177021374
H	-2.286875423398	2.032812819585	1.751415585689
H	-3.608740057091	2.177233637988	0.594011106529
H	-2.394817318953	3.464838602792	0.697784372557
H	0.015722092595	0.905742085080	-2.817826552406
H	1.734881630562	0.609835003848	-2.644531150736
H	1.064121072669	2.213309231340	-2.271502694068
O	-3.546347290691	0.048934424224	-0.787096512587
Al	-4.760528045844	-0.943432642854	0.119904711028
C	-6.222474221386	-1.479282361518	-1.101576858819
C	-5.247655893505	0.001133216987	1.810390536023
H	-6.766944199622	-0.605627432369	-1.487490969591
H	-6.955310980389	-2.123054212150	-0.597168231471
H	-5.839705162934	-2.036083708579	-1.967000623103
H	-5.936673015604	-0.602386704571	2.416096365295
H	-5.743945253727	0.961796129920	1.608826331552
H	-4.368319226422	0.207199343363	2.436604705377
Cl	-3.549259357553	-2.757037858889	0.760481170019

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029479.004365 kcal/mol
ZPVE = 359.638322 kcal/mol
Enthalpie(0K) = -1029119.366043 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 367.549418 kcal/mol
H-E(el) = 369.100638 kcal/mol
Enthalpie = -1029109.903727 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055704739 (Symmetry number= 1)
S(vib) = 0.000124608099
G-E(el) = 338.899727 kcal/mol
Free Energy = -1029140.104638 kcal/mol

Cartesian Coordinates and Energies of **IIIb**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.151966759663	-0.789073882897	-0.719167530675
C	-1.327153528038	-0.795211745478	-1.160977047412
C	-2.211842883207	0.131643398311	-0.315835670559
C	-1.701676536186	1.607865338949	-0.278965000235
C	-0.208686791832	1.523976188983	0.144260979323

C	0.517756058082	2.826483633092	0.512922066586
C	1.614511003501	2.445536733752	1.546012960230
C	2.129354010001	1.076156955782	1.284902551528
C	2.264552184388	0.694121143346	-0.101107317446
C	0.699444744670	0.638137539549	-0.747587525628
C	3.109962948928	-0.533205303323	-0.429427535548
C	4.605669857210	-0.282961984073	-0.194891211963
C	5.499250470847	-1.477925501027	-0.554980876106
C	6.975345885830	-1.157558936675	-0.509020762430
C	7.548663098802	-0.020258389793	-0.106054733915
C	5.216438587276	-2.706659163605	0.333332129705
C	2.295527174640	0.142822476472	2.413841904419
C	-1.986259644338	2.347993181919	-1.595282013196
C	-2.486996425615	2.327222671852	0.836053567436
C	0.901041964841	1.127977541975	-2.189392542898
H	0.736262070833	-1.450795497615	-1.366372289635
H	0.207621692703	-1.195557256564	0.299360631788
H	-1.428274292406	-0.524606988847	-2.217327118622
H	-1.718808589425	-1.811060417857	-1.055967213049
H	-2.131018779101	-0.232006461404	0.727109410145
H	-0.281185551217	0.964689226269	1.092383220121
H	0.948639243882	3.310407535736	-0.368710958058
H	-0.150305480319	3.553538796081	0.976035671048
H	2.471440660717	3.138497064283	1.489114310711
H	1.229594758409	2.511509258663	2.568726745087
H	2.650981769530	1.573503477552	-0.632847932780
H	2.958196877722	-0.793412104270	-1.481433077257
H	2.756539602487	-1.393078449323	0.144822367864
H	4.909271669452	0.584461885472	-0.794764776718
H	4.784143795734	-0.007049138695	0.853947885717
H	5.268342408124	-1.766105280486	-1.593037316520
H	7.620327356284	-1.976118236145	-0.829891959068
H	8.628512470978	0.089911105355	-0.103777363681
H	6.976616217253	0.838369610165	0.232702620256
H	4.192221630946	-3.071298360607	0.212317858272
H	5.888630476951	-3.532722203162	0.082038292097
H	5.377041539425	-2.459606864966	1.389235617888
H	1.293248413268	-0.276410175455	2.620977189683
H	2.961095722118	-0.694632563467	2.207961685470
H	2.594569963814	0.665235776079	3.327864146358
H	-3.062718143926	2.508861596600	-1.678865088563
H	-1.687250894659	1.787223810186	-2.480482811362
H	-1.487363412390	3.324599718682	-1.618236398831
H	-2.221795951752	1.944845993046	1.829547342367
H	-3.552897203220	2.143114083162	0.686432704903
H	-2.324023729513	3.410641418417	0.825629231443
H	0.032229153272	0.897009325844	-2.801840794309
H	1.759514482172	0.628044301069	-2.647664258441
H	1.068073789881	2.207448665503	-2.239291932635
O	-3.522388427293	0.064936290625	-0.765227341462
Al	-4.790007579879	-0.948328480806	0.010365302283
C	-6.045612422744	-1.655765613180	-1.356595166011

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C      -5.617905243014         0.092720120124         1.513856687319
H      -6.562112153795        -0.839533929461        -1.879227290581
H      -6.807838785401        -2.299313302012        -0.899882457197
H      -5.507249480813        -2.250506081114        -2.105397774716
H      -6.359575196481        -0.517073215123         2.043763771331
H      -6.118149527868         0.992038659508         1.130840463304
H      -4.850897278585         0.400889610761         2.235571836346
Cl     -3.633108843213        -2.632796616143         0.961591022380
------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029481.084458  kcal/mol
ZPVE           = 359.972866  kcal/mol
Enthalpie(0K)   = -1029121.111592  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)          = 0.581707  kcal/mol
E(vib)          = 367.938268  kcal/mol
H-E(el)         = 369.489487  kcal/mol
Enthalpie       = -1029111.594970  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)          = 0.000055691086 (Symmetry number= 1)
S(vib)          = 0.000125517416
G-E(el)         = 339.178894  kcal/mol
Free Energy     = -1029141.905563  kcal/mol
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```
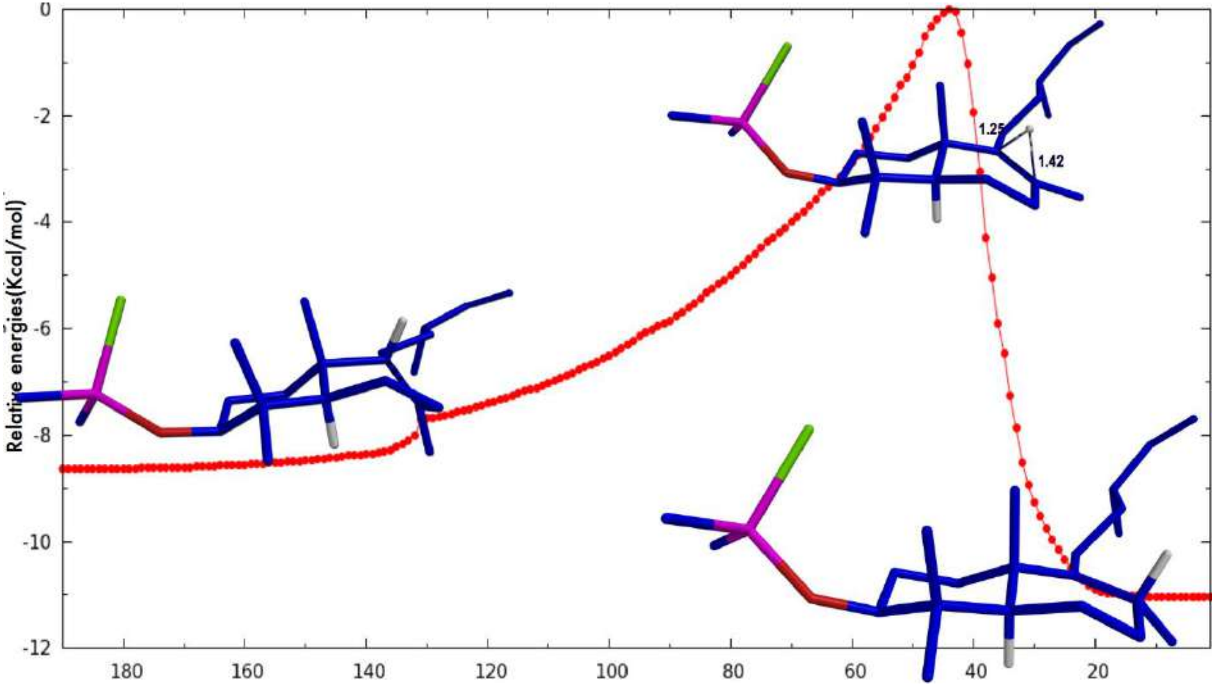

Plot of IRC transformation of **IIIb** in to **IVb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **IIIb**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	-0.208234485503	-0.496132648643	-0.962220689888
C	1.323314465218	-0.593720851218	-1.045996983968
C	2.071935380371	0.752570570417	-0.978018293647
C	1.612518151862	1.690978789508	0.204571159537
C	0.062204844314	1.673286954878	0.208928708842
C	-0.647936591843	2.658024468638	1.148335404409
C	-2.037561505887	2.952533174242	0.516493064693
C	-2.565199306472	1.766137899717	-0.197728904539
C	-2.273277011842	0.481286980876	0.390300100261
C	-0.592438473418	0.275799240709	0.304197524937
C	-3.062208300359	-0.729828592297	-0.098207408221
C	-4.518547025922	-0.700321457600	0.384680218101
C	-5.343094887377	-1.920631053267	-0.046626598646
C	-6.712320231685	-1.972108934155	0.591191026953
C	-7.276911447495	-1.052473001061	1.378679944719
C	-5.491107136849	-2.014037500702	-1.578936695875
C	-3.187279699370	1.937392234463	-1.525665229161
C	2.276981817730	1.311213616178	1.538296231401
C	2.088755540015	3.114829857594	-0.154467410671
C	-0.271969305579	-0.528993664411	1.572885444948
H	-0.636163549197	-1.503277852953	-0.960148268631
H	-0.600959197404	0.024068625357	-1.847572421571
H	1.698726642336	-1.252047915763	-0.260443266676
H	1.593617164065	-1.071560541707	-1.993277504223
H	1.797168723772	1.312022589327	-1.897249062160
H	-0.186763087599	2.023411396810	-0.808531538408

H	-0.745196628127	2.243584476952	2.156279906599
H	-0.109833644201	3.601721944122	1.246229336807
H	-2.767528690447	3.211682246745	1.302698106762
H	-1.992861375317	3.811970272312	-0.160429974195
H	-2.383514981353	0.595205626355	1.476611530533
H	-2.584363813784	-1.637663844860	0.281252016280
H	-3.006341996669	-0.795735220640	-1.187840009882
H	-4.516533821555	-0.638805586225	1.480246360376
H	-5.018018171562	0.211745790064	0.028000252080
H	-4.803157443154	-2.822004205700	0.284463998252
H	-7.286364954731	-2.866475303166	0.347040823851
H	-8.278973512704	-1.193452833503	1.771365263917
H	-6.772381374086	-0.134460858905	1.665228733990
H	-5.974219480747	-1.111495440958	-1.971464652340
H	-4.524455959386	-2.137378999237	-2.075960649962
H	-6.113299515169	-2.869486707434	-1.859087407138
H	-3.867281476608	1.131778663707	-1.801477480169
H	-2.363269529630	1.934615542834	-2.262192475157
H	-3.677605262847	2.910474245198	-1.620524401849
H	3.328560034947	1.601585189200	1.503597392626
H	2.269414215572	0.244532594661	1.746782224577
H	1.807039993892	1.845491765233	2.373136312350
H	1.529901871994	3.530951325184	-1.002818235795
H	3.142994309561	3.061710778200	-0.437069057900
H	2.002210311447	3.806794742237	0.690191364882
H	0.725000652024	-0.964145144833	1.524468741750
H	-0.976041920477	-1.358160378476	1.688380301209
H	-0.323333215396	0.090717886918	2.472016774126
O	3.440377965404	0.589573400956	-0.946802961588
Al	4.578587155447	-0.752962376022	-0.610843842996
C	6.311508026959	0.048325731588	-0.060877159312
C	4.633519992837	-2.025659525040	-2.158685029386
H	6.734146759390	0.663503415707	-0.866451458343
H	7.044285076826	-0.727168769907	0.194339875750
H	6.181147122357	0.688579663526	0.821079715701
H	4.893731083715	-1.500811313388	-3.086976547198
H	5.393408909829	-2.795027144004	-1.972039177677
H	3.672323184407	-2.533427686955	-2.305242685145
Cl	3.766676531432	-1.942962535568	1.142154333220

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029479.072185 kcal/mol
ZPVE = 359.817520 kcal/mol
Enthalpie(0K) = -1029119.254664 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 366.791640 kcal/mol
H-E(el) = 368.342859 kcal/mol
Enthalpie = -1029110.729325 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055622288 (Symmetry number= 1)

S(vib) = 0.000102206564
G-E(el) = 340.895302 kcal/mol
Free Energy = -1029138.176882 kcal/mol

Cartesian Coordinates and Energies of **Transition state IIIb-IVb**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.123780370194	-0.252486382064	-1.388633659573
C	1.385446830681	-0.477030115590	-1.261126729820
C	2.216543649355	0.796869263038	-1.027911942735
C	1.654786217688	1.739345129491	0.096501230654
C	0.114246767315	1.837776005591	-0.066973729419
C	-0.585155608383	2.812085823141	0.885088062354
C	-1.906407171704	3.234405145507	0.252197785926
C	-2.715942138544	2.078495905270	-0.267110394059
C	-2.172457099138	0.765057958488	-0.334444222118
C	-0.661470472195	0.489386737252	-0.132860142404
C	-3.066133068091	-0.393766070179	-0.775196955561
C	-4.144698559591	-0.779369378856	0.254473184420
C	-4.941910269154	-2.028417519949	-0.144066076463
C	-5.881984162809	-2.497637830392	0.942319843776
C	-6.126311846081	-1.910420704792	2.116771198530
C	-5.728209135153	-1.827526400302	-1.454821426151
C	-4.125130170807	2.404007552589	-0.673075669624
C	2.114575115221	1.312275544815	1.500153978532
C	2.265721243140	3.132427811385	-0.173171566971
C	-0.541440881042	-0.420027011478	1.112590132279
H	-0.606542255541	-1.225098365775	-1.519258495583
H	-0.352354856361	0.347701735398	-2.280954218671
H	1.587943362586	-1.192587160522	-0.462091352880
H	1.748620789970	-0.946056573608	-2.181178864493
H	2.127306599904	1.393478970743	-1.961532770356
H	-0.019514113166	2.266162796340	-1.075396518736
H	-0.764874011736	2.351566718480	1.864482347340
H	0.023697956865	3.698736160418	1.065592495671
H	-2.537948444198	3.833375666148	0.920690175130
H	-1.713608843882	3.870695059060	-0.624537743427
H	-2.629784384405	1.116119921261	0.779407356912
H	-2.433319917904	-1.263147736205	-0.943527441422
H	-3.512797261794	-0.146315162564	-1.743042191202
H	-3.648812873306	-0.968659302771	1.214392973849
H	-4.842726827706	0.050806505196	0.418309297948
H	-4.219976916966	-2.842228214078	-0.314785441034
H	-6.415837823627	-3.417022636062	0.701833379050
H	-6.833907909475	-2.340573281767	2.818183679516
H	-5.635993262115	-0.994100268990	2.432520989041
H	-6.420836015603	-0.982895825305	-1.361753732482
H	-5.065925536571	-1.645398832163	-2.306598930575

H	-6.321481541355	-2.716021499069	-1.689982315494
H	-4.720878163638	2.711402782302	0.192105225255
H	-4.635800585655	1.599514609327	-1.196620913969
H	-4.068208101261	3.276340789469	-1.333726227817
H	3.185984402958	1.498882804999	1.589832053062
H	1.983017037664	0.253489092921	1.707719994108
H	1.604385014605	1.898866117533	2.274578018480
H	1.853360195464	3.591555233684	-1.081267634282
H	3.341883916774	3.006980859404	-0.317023758896
H	2.120113662427	3.825487274736	0.663186408713
H	0.450356480588	-0.858239282901	1.197033291086
H	-1.251789700876	-1.251068282345	1.052451055620
H	-0.741931466269	0.131455582283	2.036959774405
O	3.546315036888	0.511480467758	-0.795695429492
Al	4.477030707410	-0.957743250793	-0.333399492840
C	6.151413672368	-0.340217980159	0.528285931445
C	4.607308290595	-2.238918627486	-1.852559899629
H	6.769411549406	0.248209700995	-0.164697414684
H	6.762004599516	-1.182565556468	0.879858653581
H	5.941741416985	0.294782692806	1.399820236108
H	5.065781800633	-1.771927154322	-2.736432661791
H	5.222054984387	-3.109808568717	-1.586878519287
H	3.624734153850	-2.625572903869	-2.157699050605
Cl	3.246660311015	-2.061726538319	1.266074782020

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029473.895771 kcal/mol
ZPVE = 358.801298 kcal/mol
Enthalpie(0K) = -1029115.094474 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 366.258750 kcal/mol
H-E(el) = 367.809970 kcal/mol
Enthalpie = -1029106.085802 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055613648 (Symmetry number= 1)
S(vib) = 0.000116361560
G-E(el) = 338.630072 kcal/mol
Free Energy = -1029135.265699 kcal/mol

Cartesian Coordinates and Energies of **IVb**

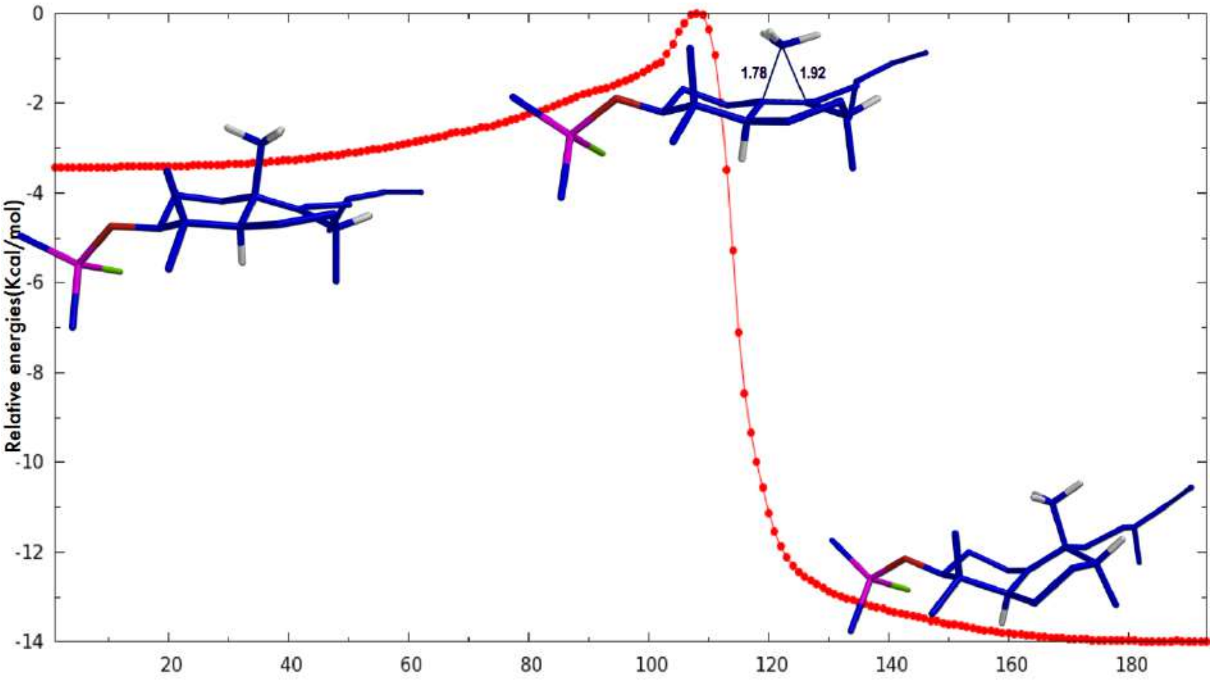
#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.143360276674	-0.279468903024	-1.421460305213
C	1.351782715174	-0.535406212779	-1.231101652184
C	2.180418731446	0.742756741924	-1.057919472496
C	1.638879088383	1.707929794730	0.052902735917

C	0.094770096179	1.855917064052	-0.096340626343
C	-0.560416083369	2.800276127860	0.916206298482
C	-1.927505565534	3.219532134991	0.391645936012
C	-2.848676688337	2.024054390910	0.094325677003
C	-2.179079306922	0.761960025374	-0.342380567728
C	-0.720284904316	0.531428224449	-0.221350065251
C	-3.069026783429	-0.350562546289	-0.769992068475
C	-4.149435305389	-0.745775860928	0.274171971180
C	-4.912798009691	-2.010718593222	-0.137513794120
C	-5.857670136835	-2.494940743133	0.939202007216
C	-6.137858988617	-1.902262963578	2.102788097433
C	-5.683547477224	-1.825290643526	-1.458688698203
C	-4.017064478514	2.461935581218	-0.822714433730
C	2.099234420835	1.274178247204	1.456283846201
C	2.284551929433	3.083511272117	-0.226475978678
C	-0.678565348388	-0.382826419451	1.073892790513
H	-0.652261946652	-1.238509805924	-1.545959240451
H	-0.316333274362	0.304647535905	-2.334874174078
H	1.521215337741	-1.203895330263	-0.385173098804
H	1.729798636660	-1.066020612304	-2.111775542728
H	2.076124803549	1.310255555187	-2.005822024135
H	-0.037117551417	2.332322534838	-1.081530157536
H	-0.652144560382	2.324605933766	1.899320519069
H	0.058341363380	3.687848541746	1.061340418460
H	-2.446575910275	3.883099119593	1.091646166147
H	-1.790411886988	3.791474054643	-0.534866017951
H	-3.302017821029	1.704996174929	1.055150783136
H	-2.488433229735	-1.234850264437	-1.026989099167
H	-3.568421403285	-0.021117929599	-1.692419863452
H	-3.653860154278	-0.921631602685	1.234198020351
H	-4.857796154591	0.074295973846	0.422603928970
H	-4.174295058653	-2.812254944734	-0.295660079262
H	-6.361080860930	-3.431468510153	0.699022605231
H	-6.845603256934	-2.344719266359	2.796380765638
H	-5.680459211638	-0.968196754406	2.415419351894
H	-6.393151892234	-0.994232963582	-1.376397691825
H	-5.012112120762	-1.629219120309	-2.300620564421
H	-6.254500537619	-2.725765699533	-1.703416111391
H	-4.455928007396	3.374956344241	-0.412748106907
H	-4.809231881802	1.717699327607	-0.909345071609
H	-3.641382534662	2.692861127137	-1.824103315513
H	3.173711853610	1.445102807006	1.542607714326
H	1.953636868806	0.216799460288	1.666779453895
H	1.603134293780	1.865464881578	2.233701885734
H	1.887130267099	3.540490928062	-1.141492500709
H	3.359166774178	2.936233542344	-0.360362099502
H	2.142972097814	3.787779008272	0.600007266415
H	0.349033938509	-0.715705601806	1.212321555084
H	-1.297888861034	-1.273239452585	0.951935597575
H	-0.995177218731	0.156302137197	1.968005680860
O	3.518728194145	0.456387774345	-0.853735484990
Al	4.490579468214	-0.946718952435	-0.316726712350

```
C     6.125218876086     -0.238334348297      0.573167260812
C     4.760423832617     -2.227123811451     -1.825916505889
H     6.713332786228      0.369801523154     -0.126370797053
H     6.759969575286     -1.055221341282      0.937302574707
H     5.856013784528      0.390201838484      1.431290694848
H     5.258828154429     -1.739698046020     -2.674041769720
H     5.372302516060     -3.082278876410     -1.513119656035
H     3.794316439123     -2.616298310338     -2.174632467818
Cl    3.300381332072     -2.084178005114      1.255675983488
-----------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029480.163949  kcal/mol
ZPVE           = 360.612081  kcal/mol
Enthalpie(0K)   = -1029119.551869  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 368.178462  kcal/mol
H-E(el)        = 369.729681  kcal/mol
Enthalpie      = -1029110.434268  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055615439 (Symmetry number= 1)
S(vib)         = 0.000116804082
G-E(el)        = 340.495374  kcal/mol
Free Energy     = -1029139.668576  kcal/mol
-----------------------------------------------------------------
```

Plot of IRC transformation of **IVb** in to **Vb$_1$** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **IVb**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent=dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	-0.097375766126	-0.877166428943	0.793750980259
C	1.363239724287	-0.849913391562	1.240291164300
C	2.197554685705	0.058492281983	0.335374855561
C	1.704674685666	1.534631756344	0.398121397058
C	0.195373451918	1.553105651815	-0.002013610837
C	-0.393546783030	2.978597672268	-0.066724098273
C	-1.934789374730	3.036203614152	-0.081630360343
C	-2.590204827835	1.740622382144	-0.573694108859
C	-2.073385405584	0.531528516272	0.109595726135
C	-0.735806299259	0.538255123755	0.751663767416
C	-2.885464844372	-0.704330091922	0.104731966279
C	-4.401002250447	-0.593947493361	-0.091001030315
C	-5.104024404607	-1.952709501972	0.045403658166
C	-6.610805008304	-1.839734662254	0.037698458336
C	-7.342354146435	-0.741673690725	-0.169770057215
C	-4.655641878482	-2.952485255388	-1.039302608206
C	-2.407400363984	1.532196478434	-2.117141815899
C	2.028417911975	2.149630184136	1.770218639565
C	2.492843905349	2.322671080364	-0.666142753750
C	-1.087208721045	0.964718474775	2.233669170526
H	-0.672618226273	-1.536876480028	1.452836076824
H	-0.135257843604	-1.313689017199	-0.212172890835
H	1.471883272676	-0.535716681036	2.284638269704
H	1.767622188578	-1.862992200212	1.169576774663
H	2.009142512259	-0.278958174658	-0.703248248308
H	0.206875871335	1.160750045059	-1.027592127586

H	-0.031685367421	3.572477483407	0.776414492998
H	0.000887219160	3.461052894644	-0.963611190559
H	-2.319698488554	3.242240677257	0.921877988035
H	-2.650205897084	-1.290846797467	1.000660412346
H	-2.435031617261	-1.308482941161	-0.705836105165
H	-4.806443040052	0.093828015972	0.660260122735
H	-4.633780102347	-0.169987107457	-1.073774271172
H	-4.822043343269	-2.379082392129	1.021550292210
H	-7.128758124777	-2.783988160483	0.205752701577
H	-8.426748960867	-0.785602257900	-0.165721663335
H	-6.902431636687	0.234561207433	-0.351313358945
H	-4.858072354118	-2.550138276127	-2.038179801827
H	-3.588860289389	-3.187086172459	-0.968268582175
H	-5.199933245575	-3.896687421845	-0.945042371598
H	-2.869234364407	2.386640675391	-2.618879841576
H	-1.353393735055	1.495612335338	-2.393346961711
H	-2.894666389749	0.619701345461	-2.467331764866
H	3.097252034247	2.014102875244	1.950117510127
H	1.500374323829	1.676516842791	2.599385360523
H	1.810905306077	3.222223672907	1.799835821365
H	2.260435577388	1.969266397407	-1.677894102431
H	3.559728509792	2.159112967793	-0.501435171104
H	2.295067640068	3.398421548926	-0.617927488219
H	-1.227215724737	2.039262699578	2.334686323894
H	-0.250194298694	0.657864390539	2.860583306539
H	-1.980525516530	0.451855288639	2.603774909189
O	3.542865859145	-0.045295793594	0.655823984635
Al	4.669945458818	-1.076386142444	-0.300058219073
C	6.166901735954	-1.688028720765	0.851502242467
C	5.163863499004	-0.106430978627	-1.982475593830
H	6.741314508983	-0.834885823676	1.237305149865
H	6.858096851720	-2.333978341337	0.295548934317
H	5.791870980157	-2.258540494258	1.710594686799
H	4.265471152452	0.161241555547	-2.553807577991
H	5.796245980227	-0.732029389553	-2.624336350490
H	5.713193007936	0.816809643638	-1.754060526765
H	-2.284135126584	3.860569959789	-0.711455232630
H	-3.672311240473	1.790785881727	-0.409080337278
Cl	3.392518619262	-2.828319119639	-0.934910673916

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Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029483.423626 kcal/mol
ZPVE = 360.982399 kcal/mol
Enthalpie(0K) = -1029122.441227 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 368.557274 kcal/mol
H-E(el) = 370.108494 kcal/mol
Enthalpie = -1029113.315132 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055713443 (Symmetry number= 1)

S(vib) = 0.000114018072
G-E(el) = 341.203355 kcal/mol
Free Energy = -1029142.220271 kcal/mol

Cartesian Coordinates and Energies of **Transition state IVb-Vb$_1$**

\# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.045684085609	-1.067305546809	0.096558902899
C	1.303090751058	-1.086486132978	0.808022466131
C	2.254000129379	-0.039667855808	0.218223106522
C	1.669967747916	1.400037313155	0.341391978697
C	0.255880232070	1.431721735466	-0.329134064553
C	-0.352924866643	2.858449781243	-0.405030771606
C	-1.853248133515	2.960749238993	-0.105430503131
C	-2.654376558505	1.762944747834	-0.619808599933
C	-2.094295297140	0.443140951994	-0.135068966826
C	-0.701834788180	0.308916637605	0.096340683131
C	-3.001066002664	-0.763743181732	-0.214377499517
C	-4.482222785779	-0.526548020244	0.101621085019
C	-5.276384066583	-1.837093261955	0.207244903825
C	-6.700560767737	-1.630535918880	0.666993107178
C	-7.330331834786	-0.469610953393	0.865897287620
C	-5.270469060349	-2.630664128235	-1.114924647625
C	-2.684184691081	1.693917551729	-2.165361885524
C	1.678930809362	1.840314073497	1.815633192602
C	2.592591588564	2.344012619060	-0.450961722903
C	-1.480844748321	0.571707579845	1.676639984124
H	-0.712299455491	-1.833998736785	0.495030739095
H	0.111911848425	-1.315268795133	-0.963058211614
H	1.185969906889	-0.924868378561	1.886562432574
H	1.767022088020	-2.065944185499	0.674667466537
H	2.306194159817	-0.250141144427	-0.870273681703
H	0.452296645125	1.117260678774	-1.366339686485
H	0.177114193701	3.520067738712	0.282255354077
H	-0.155397994907	3.256515691308	-1.403670148416
H	-2.021131984630	3.059404589672	0.972317577539
H	-2.617930087654	-1.565151273874	0.419263139867
H	-2.881319456330	-1.132650839088	-1.242497199288
H	-4.570060419684	0.013670224960	1.052845388800
H	-4.941573483384	0.106680429354	-0.665304018719
H	-4.784887101012	-2.465303521843	0.967485382367
H	-7.254917156975	-2.555080251503	0.828733164270
H	-8.366951820617	-0.445670225640	1.186307030121
H	-6.851053048081	0.493870879893	0.719722654360
H	-5.692272609246	-2.026833386276	-1.926208145512
H	-4.261723564660	-2.943346138922	-1.401470819202
H	-5.877459811013	-3.536289083136	-1.025366650774
H	-3.063506896045	2.642446239685	-2.555103240865

H	-1.686632478424	1.532325672552	-2.582892038252
H	-3.338752535936	0.896182802576	-2.525785820707
H	2.717215607164	1.866060737777	2.152004832793
H	1.164092748312	1.139109039100	2.478403168771
H	1.248922077770	2.838796194182	1.959237793161
H	2.579178661450	2.105160320279	-1.520581306005
H	3.616284327725	2.205340851498	-0.099927473307
H	2.322778341748	3.397902663684	-0.326601776907
H	-0.813563626191	1.342717465645	2.046340170310
H	-1.354150579344	-0.390203870665	2.163459129807
H	-2.504826707415	0.922935655266	1.830603475444
O	3.498730017152	-0.124151842364	0.812088346400
Al	4.869028608569	-0.941346847067	-0.049126119197
C	6.257204154563	-1.436677873197	1.272847305575
C	5.407584451707	0.160359515711	-1.622224640273
H	6.690117941005	-0.549858529088	1.757745014160
H	7.083847556232	-1.986760321882	0.803616108353
H	5.847655162621	-2.077265362193	2.065139141870
H	4.559314863223	0.366760992509	-2.290489621107
H	6.167900337380	-0.352206234423	-2.226696452315
H	5.830306198889	1.130097609490	-1.320664726961
H	-2.262104731694	3.872772786040	-0.551876883339
H	-3.686304479769	1.857297034818	-0.270228199168
Cl	3.885619559528	-2.800742202321	-0.906009992257

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029479.658244 kcal/mol
ZPVE = 360.150514 kcal/mol
Enthalpie(0K) = -1029119.507730 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 367.429710 kcal/mol
H-E(el) = 368.980930 kcal/mol
Enthalpie = -1029110.677314 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055730768 (Symmetry number= 1)
S(vib) = 0.000114089027
G-E(el) = 340.064980 kcal/mol
Free Energy = -1029139.593264 kcal/mol

Cartesian Coordinates and Energies of **Vb$_1$**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

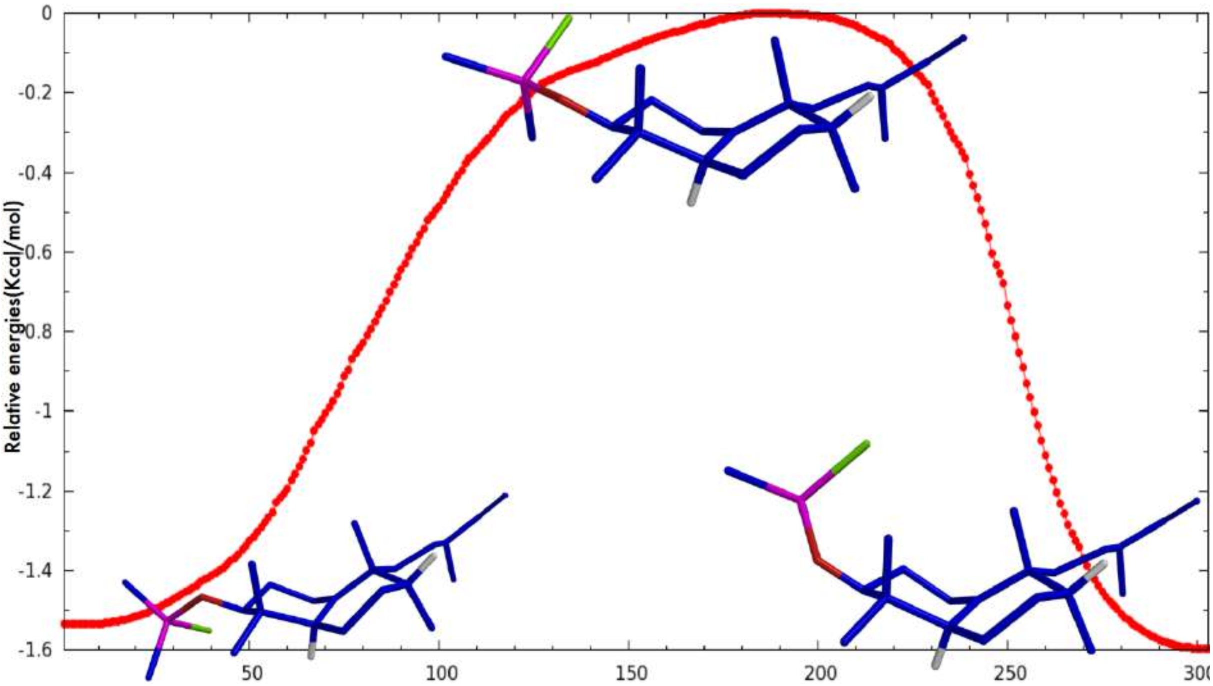
C	-0.010612997687	-1.022078642623	-0.482824650594
C	1.254631141799	-1.066595220140	0.449083893195
C	2.260872144805	-0.013565497651	-0.002143164385
C	1.675739994407	1.426384823987	0.058969490827

C	0.252225664495	1.431357683883	-0.751697081105
C	-0.389151656228	2.830460424723	-0.841794949782
C	-1.651393718141	2.989695196335	0.003240847494
C	-2.622958445212	1.829153495725	-0.235621016383
C	-1.992718887392	0.477486303036	0.220607095374
C	-0.614255125316	0.307142456625	-0.356534441798
C	-2.921231218866	-0.727423224087	-0.129194349712
C	-4.374049632451	-0.589886733940	0.343705089465
C	-5.202860996543	-1.859958901085	0.090598618954
C	-6.582638816155	-1.798205455780	0.704130740016
C	-7.154908941918	-0.758414857749	1.317219337976
C	-5.328004957150	-2.193186006177	-1.410173414218
C	-3.073251296909	1.791230445782	-1.707002179401
C	1.517540655251	1.905997293570	1.502688486851
C	2.643362394152	2.355407470943	-0.683445562727
C	-1.776191209644	0.479010555975	1.774682270107
H	-0.690978687425	-1.839040651453	-0.261633235843
H	0.386725725513	-1.156632723571	-1.498090983140
H	0.985449687260	-0.923353296652	1.499456460043
H	1.696789496873	-2.060543203729	0.335499609450
H	2.469114128683	-0.215463935093	-1.073620334922
H	0.622486345988	1.129408389074	-1.744261385028
H	0.342548410855	3.586554037286	-0.556623546292
H	-0.628666493091	3.032111699174	-1.890799954332
H	-1.391965013207	3.057847364799	1.064048834717
H	-2.515896321280	-1.633597863081	0.328991895143
H	-2.895611452678	-0.889292402670	-1.210541171429
H	-4.393941806871	-0.378614287215	1.417704135552
H	-4.868049435618	0.253023805261	-0.150101875499
H	-4.680535728876	-2.703734696460	0.569369994215
H	-7.158371498544	-2.718531187640	0.600832485317
H	-8.165006821281	-0.828573834178	1.708414679714
H	-6.650453538825	0.193312759112	1.454668570389
H	-5.782183714627	-1.355360713357	-1.951386972747
H	-4.356408704913	-2.412080104881	-1.862324475761
H	-5.964393685380	-3.070422497866	-1.561777265001
H	-3.384811695520	2.789266976421	-2.030251955390
H	-2.266867396607	1.467354628218	-2.374170809830
H	-3.916337327982	1.116834290369	-1.866706307503
H	2.514946991095	1.994175755093	1.937463071979
H	0.961949113749	1.201599490675	2.123894140024
H	1.028661920703	2.884063042697	1.554084428645
H	2.700035644439	2.115335190442	-1.750063909556
H	3.635860705515	2.190748603199	-0.255957546324
H	2.394611117321	3.414014143754	-0.571840581015
H	-1.087583469368	1.252617419304	2.104205635415
H	-1.401907591082	-0.488311301878	2.116503562312
H	-2.745400469152	0.664194475292	2.242930604246
O	3.399779531997	-0.095662471647	0.771279479419
Al	4.868254450484	-0.989392894553	0.162494019964
C	5.978193083677	-1.525800674828	1.706455776236
C	5.678451645840	0.092053193342	-1.300176267074

H	6.349063779020	-0.652355468508	2.261163160063
H	6.854866909036	-2.107513055205	1.392493666857
H	5.411427956090	-2.146785156337	2.412382993967
H	4.953231165684	0.323143868680	-2.092907581629
H	6.513131904255	-0.437280861810	-1.777805480951
H	6.070328773904	1.047627237308	-0.922352510231
H	-2.144053294500	3.934187160965	-0.251912028574
H	-3.508066618770	1.988274724650	0.389629999116
Cl	3.928525605650	-2.802332905891	-0.825755427461

```
------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029484.928971  kcal/mol
ZPVE           = 359.892792  kcal/mol
Enthalpie(0K)   = -1029125.036179  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 367.339785  kcal/mol
H-E(el)        = 368.891005  kcal/mol
Enthalpie      = -1029116.037966  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055699508 (Symmetry number= 1)
S(vib)         = 0.000113878958
G-E(el)        = 340.004608  kcal/mol
Free Energy     = -1029144.924363  kcal/mol
------------------------------------------------------------
```

Plot of IRC transformation of **Vb$_1$** in to **Vb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **Vb$_1$**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	1.066173191008	-1.053837470466	-0.679752147822
C	-0.428190659248	-0.597565287140	-0.858019319845
C	-1.257239006966	-1.096266944568	0.320590699584
C	-0.747630936518	-0.533698912216	1.678197644856
C	0.856753025544	-0.826013954974	1.784043423142
C	1.466365402626	-0.386511819750	3.131659226748
C	2.409354898467	0.811083767423	3.029809418025
C	3.420507593839	0.621253834141	1.895087489102
C	2.697275933648	0.551699233955	0.515857926687
C	1.574404305033	-0.447500687539	0.552668383094
C	3.705012288112	0.253212413144	-0.638704932312
C	4.939444931677	1.163570845574	-0.674026541977
C	5.800350490149	0.946807024844	-1.929543536832
C	6.919834982540	1.953264677223	-2.062721153868
C	7.280265003284	2.890131569500	-1.181353515427
C	6.386103625631	-0.478057604535	-2.002459455754
C	4.298861452809	-0.616222106498	2.150886469109
C	-1.070488022491	0.955369673100	1.820004841475
C	-1.445538667806	-1.315492781889	2.797740129661
C	1.999864429162	1.921145922314	0.198510384124
H	1.657275931198	-0.823651150988	-1.561145514632
H	1.009074038272	-2.144839134684	-0.565021497169
H	-0.509216473782	0.488471567788	-0.958777838685
H	-0.791188346653	-1.061118852730	-1.779723539359
H	-1.110706619962	-2.195537014922	0.367950990512
H	0.836793983500	-1.926578849507	1.732983369493
H	0.666087741063	-0.165648910944	3.838221620981

H	2.008607377155	-1.237582959761	3.555940392645
H	1.838763035113	1.732846556163	2.881366516328
H	2.945485862408	0.933276242488	3.977243454916
H	4.070638419579	1.502133772513	1.862724752670
H	4.016802677486	-0.793212543558	-0.575360907731
H	3.189884011225	0.366181970232	-1.596710150656
H	5.565358777287	1.005932404747	0.210222860463
H	4.625932192273	2.212180280923	-0.652330537261
H	5.150432517844	1.077738098641	-2.809645686550
H	7.491419045682	1.865271655499	-2.987187026480
H	8.116844459765	3.552173479421	-1.381529100203
H	6.765952612888	3.035899334560	-0.236286332625
H	5.603043581070	-1.238776264546	-2.072467683109
H	6.994240895877	-0.686266525387	-1.114846398189
H	7.030043542470	-0.589771311088	-2.880200804193
H	4.696421900528	-0.589765765463	3.170152643393
H	3.733546066741	-1.548647726134	2.044277813753
H	5.148657282215	-0.672474590171	1.468444396883
H	-2.156492686861	1.060906731464	1.856176288242
H	-0.722315469982	1.545906702171	0.970794383804
H	-0.650165596610	1.377145833060	2.738792790732
H	-1.144268331713	-2.368094181150	2.806262926554
H	-2.518760007234	-1.280561079177	2.592206027211
H	-1.273132605200	-0.890952395800	3.790382669267
H	1.236710685454	2.185046206064	0.926166858903
H	1.544005412215	1.905362437500	-0.793807448529
H	2.768977372055	2.696691013775	0.216000177428
O	-2.580943110391	-0.757603878444	0.134451332361
Al	-3.766896942525	-1.956899139852	-0.556879713764
C	-4.143901518748	-3.317390085543	0.847952125622
C	-5.263982479577	-0.975047870310	-1.392583754782
H	-4.773033205739	-4.131271878854	0.464765146223
H	-3.222199637024	-3.779461215658	1.228477119728
H	-4.669587722752	-2.873022539993	1.705568470337
H	-5.824044597250	-0.382275439293	-0.655743194177
H	-5.978150366713	-1.658765170459	-1.870085881532
H	-4.907415382704	-0.284189093479	-2.167716138000
Cl	-2.513307274648	-2.997230293165	-2.135789278334

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Thermochemistry at 195.150 K, 1.000 Atm

E(el) = -1029485.038446 kcal/mol

ZPVE = 360.782620 kcal/mol

Enthalpie(0K) = -1029124.255826 kcal/mol

E(tr) = 0.581707 kcal/mol

E(rot) = 0.581707 kcal/mol

E(vib) = 367.942238 kcal/mol

H-E(el) = 369.493458 kcal/mol

Enthalpie = -1029115.544989 kcal/mol

S(el) = 0.000000000000

S(tr) = 0.000066308847

S(rot) = 0.000055704845 (Symmetry number= 1)

S(vib) = 0.000105928459

G-E(el) = 341.580013 kcal/mol
Free Energy = -1029143.458433 kcal/mol

Cartesian Coordinates and Energies of **Transition state Vb$_1$-Vb**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	1.201452506018	-1.589459258880	-0.109207769727
C	-0.314163623850	-1.364851442153	-0.459319408467
C	-1.166111506482	-1.540763978014	0.797270722630
C	-0.760276709801	-0.527854616026	1.911640291428
C	0.863806710918	-0.605201459438	2.134296007206
C	1.362366863253	0.308661245492	3.271458785140
C	2.158079815625	1.519377415019	2.787216968845
C	3.245898647280	1.101597337501	1.791684628190
C	2.610457295326	0.487912144507	0.507404044988
C	1.596679348007	-0.564119839907	0.860187769076
C	3.703006871266	-0.064513107283	-0.460518435900
C	4.829260181745	0.919864250711	-0.803720372387
C	5.797402458722	0.363928201128	-1.860562595514
C	6.803250091592	1.385757689838	-2.338023752269
C	6.987968971824	2.624545016029	-1.873457930343
C	6.544120683893	-0.894835345352	-1.374188100649
C	4.254037657189	0.148040108386	2.457439495463
C	-1.221000954153	0.888708832503	1.559307346015
C	-1.434182892691	-0.971912084749	3.214877923133
C	1.793501129553	1.582071994640	-0.268243633971
H	1.808502669563	-1.605106512316	-1.009345808744
H	1.244387252151	-2.578558069415	0.366886594384
H	-0.481884595231	-0.386427247868	-0.913344555652
H	-0.573705306976	-2.103693424866	-1.220206555690
H	-0.941559190070	-2.556324646155	1.196432742369
H	0.942560910083	-1.659685756463	2.443111112089
H	0.515578609416	0.641429126153	3.872031903789
H	1.984881205707	-0.288901144660	3.945096790561
H	1.488252445622	2.255005198391	2.332280165320
H	2.621732801647	2.017214309181	3.645702217200
H	3.785007547528	1.999820354100	1.472080229127
H	4.126347759114	-0.976968703141	-0.030822384492
H	3.229780217421	-0.354049546890	-1.402674175583
H	5.400722911708	1.186325490986	0.091302679427
H	4.400606679273	1.850112866821	-1.190017345248
H	5.201529140457	0.070762817856	-2.739680107222
H	7.449135940713	1.034030761778	-3.143201129239
H	7.756613418607	3.267550835153	-2.290552634524
H	6.390266125211	3.047025456011	-1.071354344754
H	5.860127879184	-1.724814938570	-1.173896884627
H	7.104039738824	-0.676951115376	-0.457588817174
H	7.260576116301	-1.236779951416	-2.127431898030

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H      4.582686890044        0.560461250455        3.416401680234
H      3.817152857811       -0.836737501213        2.656894344185
H      5.144133181586       -0.009718365011        1.845788816978
H     -2.311787616597        0.903748004145        1.576547189730
H     -0.920275170147        1.192306644130        0.555499390428
H     -0.851896178369        1.625418348315        2.279743003751
H     -1.034766529860       -1.926131783962        3.575478905280
H     -2.494393873156       -1.111717198550        2.985412284058
H     -1.352118495003       -0.232180655828        4.015357886250
H      0.959305860809        1.973415541187        0.307987814395
H      1.409648259413        1.187919763184       -1.211456615716
H      2.474373814060        2.408077435837       -0.485332843248
O     -2.507320139359       -1.378083693687        0.548232405915
Al    -3.485849033939       -2.223483923335       -0.734412451656
C     -2.839119058616       -4.108839562137       -0.838910084320
C     -5.392111720036       -1.868299481095       -0.351040400865
H     -3.376217322000       -4.662148153987       -1.620738938966
H     -1.769510766634       -4.192306874781       -1.081319309718
H     -3.001712940276       -4.645767441804        0.107095323162
H     -5.713544177292       -2.336829415317        0.589621731054
H     -6.041920557339       -2.252863953982       -1.147971827494
H     -5.586541627597       -0.790981988767       -0.266819440761
Cl    -2.879682703347       -1.201480183888       -2.648056974240
-----------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029484.237101  kcal/mol
ZPVE           = 361.050514  kcal/mol
Enthalpie(0K)   = -1029123.186587  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 368.239986  kcal/mol
H-E(el)        = 369.791206  kcal/mol
Enthalpie      = -1029114.445895  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055734370 (Symmetry number= 1)
S(vib)         = 0.000112131241
G-E(el)        = 341.114563  kcal/mol
Free Energy     = -1029143.122538  kcal/mol
-----------------------------------------------------------------
```

Cartesian Coordinates and Energies of **Vb**

```
#FREQ/B3LYP/6-31+g(d,p)    empiricaldispersion=GD3BJ    scrf=(smd,    solvent=
dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1
-----------------------------------------------------------------
C      1.426601253824       -2.061592519828        0.453463345001
C     -0.057212841173       -2.119270135099       -0.045390677967
C     -1.032673729521       -2.033933232138        1.128670253504
C     -0.818882162240       -0.753714001130        2.004956597576
C      0.802383146676       -0.567107191183        2.308642348766
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C	1.117572417454	0.659014812800	3.186744604370
C	1.768606342955	1.813153299786	2.424787338155
C	2.932161151910	1.322928994269	1.555489527376
C	2.428613358768	0.327621322694	0.463257537733
C	1.593348957731	-0.749003110824	1.090724606049
C	3.610799320250	-0.263345659638	-0.364836738379
C	4.583974445117	0.773877336531	-0.940652166958
C	5.606392040755	0.156492665200	-1.908170144386
C	6.462226044644	1.189218316075	-2.604622753792
C	6.478979356055	2.508080440613	-2.393053616066
C	6.518435717358	-0.879925238526	-1.220939227469
C	4.043649875337	0.712025978060	2.427022987855
C	-1.415670141632	0.488183185255	1.344000510970
C	-1.504458770484	-0.989688157740	3.356007006292
C	1.469615496887	1.066408557559	-0.540049961339
H	2.113567088440	-2.245864293384	-0.367257250851
H	1.538144102525	-2.855978554720	1.202230371353
H	-0.262808676057	-1.331814013698	-0.773349299003
H	-0.180403176021	-3.072281789892	-0.566520650763
H	-0.810267546993	-2.898052924476	1.792511985495
H	0.966861623770	-1.490297956118	2.882110741940
H	0.207591488635	1.004816257439	3.678182476564
H	1.784501548662	0.334161639048	3.992403004988
H	1.026596275514	2.326788957325	1.807766925084
H	2.138639006592	2.556010541718	3.139922776705
H	3.347925287041	2.185148186968	1.023538674005
H	4.159448972621	-0.979715538042	0.254080328290
H	3.199413963122	-0.827665135831	-1.206999040119
H	5.125282960893	1.285966346116	-0.138215224190
H	4.025271001449	1.543324287710	-1.482182929334
H	5.045556838098	-0.372595437949	-2.695143135016
H	7.144951810042	0.775970057367	-3.347851096629
H	7.149849495702	3.153935219867	-2.950810774032
H	5.833078739175	2.995185862878	-1.668778764321
H	5.950135631151	-1.731851653694	-0.835840172138
H	7.060218726998	-0.418567225257	-0.387290351089
H	7.260790126198	-1.271906279292	-1.923183181575
H	4.297803612819	1.393706771704	3.244620275864
H	3.733769839099	-0.238121008940	2.876580015383
H	4.957779134454	0.520970414740	1.861978579968
H	-2.503035179271	0.418500886185	1.403393360848
H	-1.178786584245	0.561889720120	0.284018301951
H	-1.110832917246	1.403537672215	1.860489803847
H	-1.021807257370	-1.789049314238	3.928753292618
H	-2.530303981648	-1.299136835384	3.134761918704
H	-1.549070063073	-0.090243652602	3.975705526586
H	0.583982547568	1.470373022655	-0.060268971700
H	1.144650336755	0.403917375951	-1.343982104154
H	2.032034833983	1.895949653261	-0.973941259823
O	-2.347297291522	-2.067864312207	0.727938300332
Al	-3.183028755315	-2.046676249796	-0.883455290407
C	-2.750775259775	-3.695184346041	-1.913842863814

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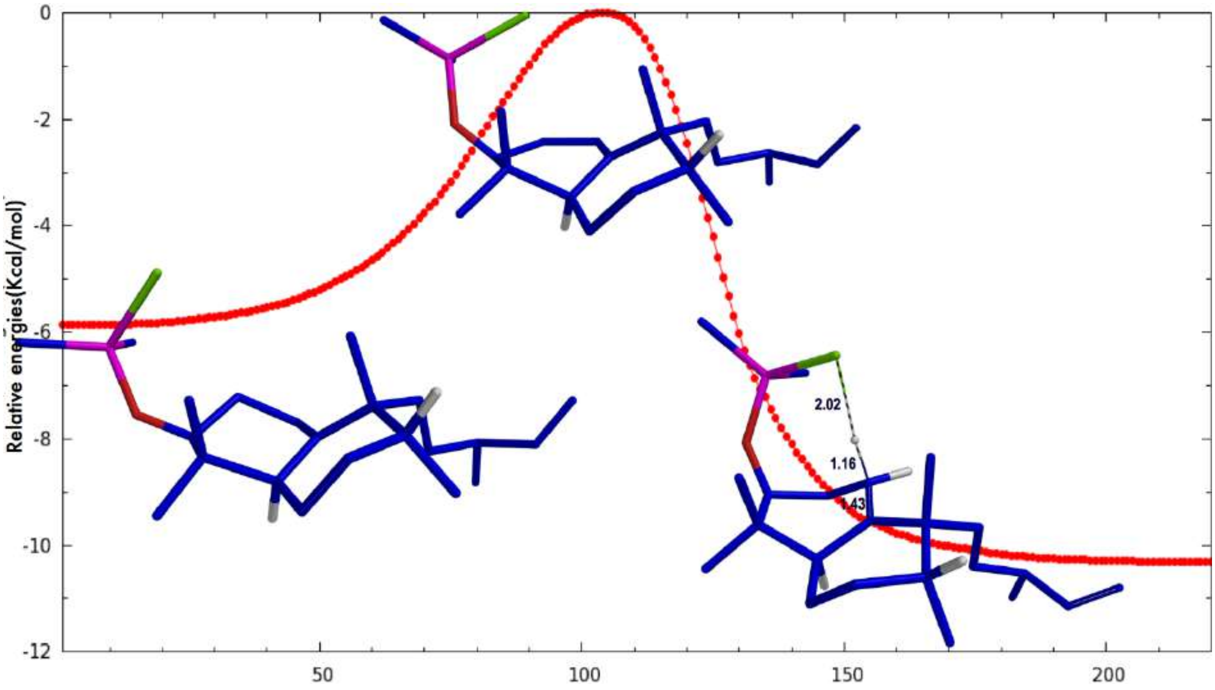
C       -5.073990755227         -1.597034090978         -0.527883518083
H       -3.367122707960         -3.747660530960         -2.821762685069
H       -1.704596815181         -3.740268564114         -2.246075770904
H       -2.953794336228         -4.604544449602         -1.330558590489
H       -5.570355035725         -2.371410228595          0.073323221347
H       -5.645673858906         -1.488234329789         -1.458795312606
H       -5.164249556694         -0.649247302042          0.019597352302
Cl      -2.231997232988         -0.321514828623         -2.038595349495
--------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029482.892459  kcal/mol
ZPVE           = 361.386978  kcal/mol
Enthalpie(0K)   = -1029121.505481  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 368.804181  kcal/mol
H-E(el)        = 370.355401  kcal/mol
Enthalpie      = -1029112.537058  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055440185 (Symmetry number= 1)
S(vib)         = 0.000110892603
G-E(el)        = 341.866465  kcal/mol
Free Energy    = -1029141.025994  kcal/mol
--------------------------------------------------------------
```

Plot of IRC transformation of **Vb** in to **VIb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ



Cartesian Coordinates and Energies of **Vb**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.363037840951	1.224310287195	1.163557582132
C	-1.143528426679	0.887957325402	1.356017542735
C	-2.017678758603	1.683147717518	0.388607212928
C	-1.619119122438	1.434512538072	-1.103484429509
C	0.008080649680	1.658586707367	-1.255405075237
C	0.509055611313	1.496937700059	-2.700221210261
C	1.142687918383	0.129730525382	-2.953253167210
C	2.298120207901	-0.136893534953	-1.979895807451
C	1.791886456775	-0.101130033142	-0.500659867696
C	0.757213706078	0.935927704038	-0.228611808680
C	2.971553446875	-0.060844621107	0.525731504526
C	3.572431491676	1.302336816777	0.895538577925
C	4.912215147372	1.165470955218	1.654814840784
C	5.994066885957	0.632333657802	0.751563201859
C	6.591187886567	-0.556119642288	0.872027515447
C	5.329592593258	2.517554903065	2.256704714471
C	3.486332788968	0.786566973666	-2.294322525762
C	-2.031096707376	0.041889156454	-1.578174217568
C	-2.322481600296	2.496232327775	-1.956005101512
C	1.039691312319	-1.464775062246	-0.221951690004
H	0.971704310000	0.694416735329	1.893527276225
H	0.472971996380	2.304904065635	1.334683945712
H	-1.327378906126	-0.181916892293	1.237993238878
H	-1.403606999692	1.141512999088	2.386662458750
H	-1.817446697878	2.762236989863	0.577733282312
H	0.065387187607	2.712669081958	-0.937653314976
H	-0.318229842283	1.657886283568	-3.391924695127

H	1.235341382683	2.287909960098	-2.915575919511
H	0.382961888010	-0.651959755109	-2.865827352586
H	1.516959233082	0.080444862171	-3.981263361056
H	2.651404240049	-1.162845707181	-2.140687369003
H	2.660841290587	-0.559771426450	1.449529060781
H	3.752252943399	-0.699330200431	0.098890428088
H	2.878701158126	1.856967745614	1.535266468105
H	3.732892649649	1.923052943635	0.009209265624
H	4.765981671429	0.449460304707	2.475804551733
H	6.296309171012	1.299086158955	-0.058865721161
H	7.370979376099	-0.875505617712	0.187135414712
H	6.326126976286	-1.245946770596	1.670264864454
H	6.264747174278	2.425202465715	2.816341690008
H	4.559296530480	2.897950509405	2.936205595190
H	5.482199624434	3.264644964752	1.468564428381
H	3.257324078324	1.842307272904	-2.121713753901
H	3.749664580644	0.678186294281	-3.351273924311
H	4.372194050578	0.533688018805	-1.709217347615
H	-3.118599393371	-0.029135463991	-1.533396510680
H	-1.645612269393	-0.756934539614	-0.944695818662
H	-1.723646847601	-0.131977308287	-2.613174339202
H	-1.951263568540	3.504726081249	-1.742223881202
H	-3.382147147060	2.460005130395	-1.688186351314
H	-2.236788764226	2.310023705705	-3.029595180621
H	0.278448957420	-1.675117556175	-0.970556069037
H	0.571350654577	-1.487009898532	0.762816723620
H	1.802992554032	-2.246816562705	-0.261244445641
O	-3.356215886367	1.416253837131	0.532227285424
Al	-4.328251659788	0.253781957540	1.532222363436
C	-4.116150096660	0.661525278227	3.470524260464
C	-6.142120944604	0.229957081400	0.746765832209
H	-3.113581192127	0.433436501494	3.857572838549
H	-4.324354072657	1.718882662553	3.687758120903
H	-4.822025227263	0.063626823458	4.063181697653
H	-6.110520086290	-0.026639557490	-0.320733669532
H	-6.638413454290	1.206499631993	0.834417016729
H	-6.786769294098	-0.510789917137	1.237743933561
Cl	-3.361212087171	-1.777360557064	1.188616795448

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------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029485.091615  kcal/mol
ZPVE           = 361.257734  kcal/mol
Enthalpie(0K)   = -1029123.833881  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 368.590342  kcal/mol
H-E(el)        = 370.141562  kcal/mol
Enthalpie      = -1029114.950053  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055327967 (Symmetry number= 1)
S(vib)         = 0.000110747832
```

G-E(el) = 341.684096 kcal/mol
Free Energy = -1029143.407519 kcal/mol

Cartesian Coordinates and Energies of **Transition state Vb-VIb**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.181706749327	1.272900885176	1.073932636636
C	-1.248339014975	1.778382561008	1.365635585798
C	-2.224592334123	1.988175164614	0.171364244028
C	-1.732677624738	1.480733256232	-1.230609152567
C	-0.130200973886	1.772357779162	-1.336611267831
C	0.465236334345	1.712683547359	-2.753215747633
C	1.145785609259	0.379405285388	-3.059130563303
C	2.220918481234	0.049489755348	-2.014129562254
C	1.593074676654	-0.050615115757	-0.586633235431
C	0.560360835297	0.989203127497	-0.312815765119
C	2.683820123761	-0.186589737504	0.530816355549
C	3.374269648999	1.057549109930	1.110395108090
C	4.727523234808	0.712056600343	1.778735868343
C	5.760753188134	0.309495898633	0.759105853866
C	6.288006508292	-0.910614490136	0.628547352891
C	5.231000327259	1.902229359207	2.612083274493
C	3.403380172583	1.023340693089	-2.132252334957
C	-2.071960423989	0.012182305846	-1.480432142266
C	-2.450260636078	2.334081385154	-2.287267577977
C	0.793296898786	-1.416827054081	-0.509680470398
H	0.454511089078	0.445941124565	1.732619440792
H	0.900461537438	2.079501868962	1.313751333508
H	-1.684177564479	1.032733918338	2.026935660422
H	-1.192362520344	2.707774005447	1.937778916621
H	-2.316137223779	3.083480688585	0.040625953565
H	-0.112447685364	2.809803721081	-0.961314200229
H	-0.313177024001	1.913810875454	-3.488767158162
H	1.191873463364	2.525492729795	-2.859679816084
H	0.398602517764	-0.417261782097	-3.102386888414
H	1.608524540216	0.420582600614	-4.050896781869
H	2.612487150780	-0.952101912285	-2.230447193140
H	2.267018675672	-0.760329616600	1.364668909723
H	3.444944444954	-0.835583506769	0.083487351881
H	2.745761440766	1.514252455273	1.880614133840
H	3.540095192566	1.827256548263	0.350128870809
H	4.561028672632	-0.139690126191	2.452949231097
H	6.092587173048	1.106217039062	0.090191511987
H	7.037814067047	-1.131174346590	-0.125348012357
H	5.992677244929	-1.728746657214	1.281781121332
H	6.176469811562	1.662311296412	3.106817125833
H	4.501536375422	2.177493140263	3.381264365697
H	5.397939126259	2.779953141223	1.976007333478

H	3.137279342132	2.044788490934	-1.842469562047
H	3.741953048269	1.056038961877	-3.172910116182
H	4.251425645963	0.709560331895	-1.522503403666
H	-3.156795738801	-0.085854114822	-1.542494637307
H	-1.749688017954	-0.639439729603	-0.670237783868
H	-1.648069866815	-0.330880467338	-2.429371317194
H	-2.097124476923	3.371159839478	-2.296933523370
H	-3.510956174777	2.334845952128	-2.017766711541
H	-2.363243164485	1.921064727766	-3.295776232211
H	0.160632090964	-1.568762370435	-1.380098105809
H	0.171038760438	-1.491959283320	0.384487371957
H	1.552922485320	-2.202969390014	-0.482571229257
O	-3.470748671201	1.464497744953	0.432576387559
Al	-4.114575011442	0.141269693899	1.486584292574
C	-4.447602834240	0.818567939115	3.322013904347
C	-5.570757438419	-0.764088387370	0.500456942081
H	-3.547990229836	1.251457772436	3.780950173147
H	-5.220053647641	1.600421299035	3.322834243010
H	-4.791853004095	0.015460044203	3.986932696074
H	-5.222205363362	-1.187267122972	-0.451221961091
H	-6.391607413983	-0.071149389949	0.268907209138
H	-5.995415847236	-1.591440156747	1.083979929334
Cl	-2.390669550383	-1.386448119598	1.720368656817

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029476.671655 kcal/mol
ZPVE = 360.798519 kcal/mol
Enthalpie(0K) = -1029115.873137 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 367.946750 kcal/mol
H-E(el) = 369.497970 kcal/mol
Enthalpie = -1029107.173685 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000055145711 (Symmetry number= 1)
S(vib) = 0.000108792710
G-E(el) = 341.302245 kcal/mol
Free Energy = -1029135.369411 kcal/mol

Cartesian Coordinates and Energies of **VIb**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	-0.190130824351	0.654636956561	0.909396631701
C	-0.978971040017	1.914873579724	1.225227922895
C	-2.125212004685	2.127835769129	0.215316357140
C	-1.659398702741	1.810575273451	-1.273268693883
C	-0.084884699455	1.616711784028	-1.369476224770

C	0.444760508836	1.474859333748	-2.815772255287
C	1.065904664696	0.109113882825	-3.096652325765
C	2.165676314868	-0.215713250546	-2.079361219696
C	1.542089951147	-0.343259928129	-0.651906277567
C	0.435997524544	0.639153683179	-0.379081227300
C	2.624853424859	-0.291417695233	0.476996403436
C	3.073750492228	1.089118821171	0.975280796040
C	4.323620143309	1.014715788639	1.880421166480
C	5.538435592951	0.599710653092	1.091451157263
C	6.215298900795	-0.540521973972	1.249583258502
C	4.567295225116	2.366292220394	2.572475530949
C	3.343707549406	0.760521676598	-2.228109914970
C	-2.332861386614	0.537083483967	-1.810767926748
C	-2.082607983378	3.010123068820	-2.138160460123
C	0.879296308010	-1.762361651690	-0.559470126393
H	-0.964168509175	-0.204668535587	0.825794704826
H	0.434185825403	0.271969860754	1.717546876403
H	-1.404687932347	1.853168636869	2.227489262545
H	-0.297827737172	2.778144790937	1.211889011492
H	-2.362930289796	3.203650668840	0.242958986594
H	0.324737842564	2.553748522480	-0.935273889234
H	-0.370616911949	1.646410821051	-3.517710628233
H	1.176548089245	2.263322354346	-3.015085698521
H	0.284843835315	-0.658686283117	-3.069022654381
H	1.481998445710	0.093139003661	-4.109784508882
H	2.563409563490	-1.211451269998	-2.309865845374
H	2.260738725238	-0.863553912398	1.336812705807
H	3.489257302874	-0.845341966760	0.096895123536
H	2.267997338123	1.559610274530	1.549696840434
H	3.286624711434	1.763660556876	0.140864016504
H	4.140257117411	0.255819975199	2.654144899112
H	5.870778977622	1.314961740065	0.335943076135
H	7.089338253119	-0.774149695236	0.648976185993
H	5.919945838944	-1.276148528820	1.994417725697
H	5.435633155854	2.316335794813	3.235790450243
H	3.697001312781	2.663310204412	3.167571671061
H	4.754458764159	3.154318260408	1.832970306513
H	3.074102762148	1.793276349837	-1.990510778391
H	3.688994400101	0.745752061549	-3.267265081898
H	4.190237232189	0.481072814409	-1.597869182335
H	-3.416011036436	0.657681702374	-1.783349003504
H	-2.100754864749	-0.345058660754	-1.210847163358
H	-2.029368693360	0.350715162132	-2.846359644059
H	-1.544247953564	3.922432744083	-1.855718530891
H	-3.150017753517	3.188712021363	-1.976765582649
H	-1.937763629840	2.843495685343	-3.209115710733
H	0.132026464859	-1.919179461185	-1.339059827439
H	0.395033869354	-1.929863464660	0.402505019104
H	1.675345164555	-2.501768076765	-0.684476305552
O	-3.263991518643	1.417322238141	0.533671289050
Al	-3.840569945003	0.171177418808	1.663076509084
C	-3.506610217077	0.603621267097	3.572654300238

C	-5.616270087243	-0.463206270561	1.087243919013
H	-2.440839077469	0.591111308257	3.839105001003
H	-3.900394283570	1.594588364118	3.839393720926
H	-4.000156681501	-0.126739464563	4.227661933392
H	-5.615747477517	-0.751994456848	0.028302476511
H	-6.381600442890	0.314873453162	1.213183405550
H	-5.942173399406	-1.337931772355	1.664770212252
Cl	-2.357847122568	-1.606870878736	1.245790085700

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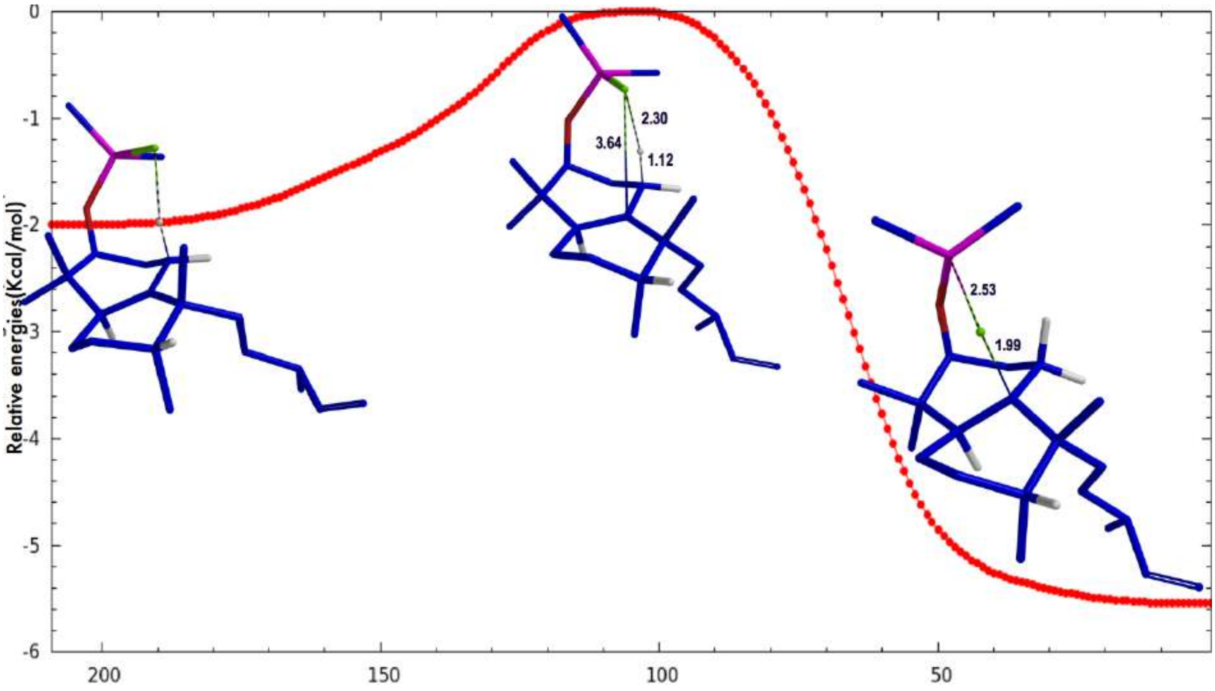
--------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029481.638661  kcal/mol
ZPVE           = 360.051515  kcal/mol
Enthalpie(0K)   = -1029121.587146  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 367.453787  kcal/mol
H-E(el)        = 369.005007  kcal/mol
Enthalpie       = -1029112.633655  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055037412 (Symmetry number= 1)
S(vib)         = 0.000120433573
G-E(el)        = 339.397021  kcal/mol
Free Energy     = -1029142.241640  kcal/mol
--------------------------------------------------------------
```

Plot of IRC transformation of **VIb** in to **VIIb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **Transition state VIb-VIIb**

FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

\---

C	-0.267325035820	0.141318228389	1.184823948889
C	-0.525124863794	1.601632108818	1.551180468727
C	-1.581144691332	2.202648327012	0.615437914928
C	-1.134194688262	2.062343847510	-0.903383672058
C	0.020484325187	1.005554997536	-1.137478867400
C	0.267891480534	0.643648710102	-2.623152383180
C	0.513469311251	-0.847493281996	-2.835914293057
C	1.619266502097	-1.355872461673	-1.905129854398
C	1.128140988111	-1.250323101922	-0.425434609915
C	0.260623300721	-0.053643479420	-0.151611058659
C	2.308642350898	-1.285054160816	0.606949943780
C	3.020949734651	0.035553564366	0.920257360440
C	4.311462437359	-0.169053095293	1.744666829984
C	5.368530532320	-0.864644370857	0.926329024177
C	5.846351262682	-2.090432642830	1.155131746748
C	4.834348052213	1.178208169661	2.269727402374
C	2.961872332189	-0.686544555404	-2.243031701439
C	-2.375735288478	1.714410552451	-1.746604791179
C	-0.575116664678	3.421811281840	-1.366678363642
C	0.254040985070	-2.516626375483	-0.131933528492
H	-1.257181710827	-0.375433996412	1.059111361043
H	0.257283586135	-0.433233460310	1.947615740773
H	-0.894799800969	1.652890572702	2.576931882295
H	0.416560692656	2.167394972719	1.501112389242
H	-1.616360651511	3.286370183796	0.816026201162

H	0.950098153736	1.533812933934	-0.776364559285
H	-0.600215194912	0.948423954961	-3.202999614869
H	1.108576745266	1.227294734219	-3.008232228624
H	-0.418806533364	-1.392989259762	-2.648910796524
H	0.785005374852	-1.033473714035	-3.880323453572
H	1.758963332554	-2.427938711074	-2.086680550582
H	1.936239462121	-1.705391938027	1.546422485833
H	3.027679061911	-2.013049883309	0.219127271479
H	2.353941507154	0.691101830035	1.492283946205
H	3.275671477223	0.576722543649	0.003745677034
H	4.066858886131	-0.807168341671	2.605444180722
H	5.757133405922	-0.290934407406	0.082255342004
H	6.614390264682	-2.530658546861	0.526220419085
H	5.489112830067	-2.691815637238	1.988168705502
H	5.734210932849	1.039612738730	2.875842779257
H	4.078823660381	1.677500059535	2.885901472573
H	5.088808976870	1.848118657071	1.439500567836
H	2.949656711591	0.397399253175	-2.099784279665
H	3.192176777131	-0.869627363996	-3.297708791311
H	3.785578845400	-1.092546121690	-1.652392449653
H	-3.207555771447	2.334932151004	-1.411143887444
H	-2.681647772412	0.674962666361	-1.611245999817
H	-2.212027975764	1.915225116431	-2.809124794537
H	0.230595926465	3.770639438490	-0.708060588875
H	-1.368847454157	4.174117201087	-1.347690161091
H	-0.183452867682	3.377122122877	-2.388922382039
H	-0.560617993900	-2.625287388841	-0.847354214515
H	-0.189353008586	-2.493845740844	0.863315227688
H	0.916584693690	-3.383725901823	-0.202979026609
O	-2.827420988678	1.675571766594	0.856421441813
Al	-3.759241225858	0.309367856299	1.512511147672
C	-3.155654698910	-0.197813478158	3.343264427041
C	-5.681201912424	0.604554674505	1.185012766722
H	-2.093216842075	-0.471586644989	3.411918713199
H	-3.322731203692	0.623135039598	4.055395066628
H	-3.723945698326	-1.062867296623	3.710557337359
H	-5.875293330322	0.813256929004	0.124929876784
H	-6.065444675901	1.456126402998	1.763011836028
H	-6.278355404919	-0.274734936980	1.459396611793
Cl	-3.083450599880	-1.450157050988	0.172068889138

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Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029481.389615  kcal/mol
ZPVE           = 360.499846  kcal/mol
Enthalpie(0K)   = -1029120.889769  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 367.863229  kcal/mol
H-E(el)        = 369.414448  kcal/mol
Enthalpie      = -1029111.975166  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
```

S(rot) = 0.000054847557 (Symmetry number= 1)
S(vib) = 0.000113821393
G-E(el) = 340.639430 kcal/mol
Free Energy = -1029140.750185 kcal/mol

Cartesian Coordinates and Energies of **VIIb**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.247462073443	0.166387441415	1.690316182174
C	-0.302570646105	1.688020230260	1.865802590486
C	-1.348955712489	2.319946522556	0.951113752471
C	-0.925601766256	2.170046055393	-0.547135153338
C	-0.171570563416	0.809604505190	-0.836984442267
C	-0.434500181854	0.267681760708	-2.264863906717
C	-0.046167891239	-1.206423863808	-2.470711431463
C	1.159355099402	-1.604149582349	-1.619113856872
C	0.840258293354	-1.433085846579	-0.079012099354
C	-0.228782809728	-0.301055928450	0.216226017792
C	2.169691357976	-1.193795730596	0.717786565753
C	2.856966664551	0.177597885597	0.755280768188
C	4.262505572038	0.104184860816	1.395787403505
C	5.225728395579	-0.647734199576	0.514927682561
C	5.800223429072	-1.816638186344	0.809946732214
C	4.793700079837	1.518283762322	1.685245971378
C	2.421639634846	-0.931549639763	-2.193254909073
C	-2.173545199212	2.400932207980	-1.418057579673
C	0.074147679591	3.300690614270	-0.877001916741
C	0.330811114957	-2.798298026940	0.438162604701
H	-1.096961126987	-0.277446162176	2.204722359929
H	0.624653403766	-0.225752343602	2.209552014113
H	-0.546655995671	1.911803738199	2.909173800487
H	0.675386646035	2.138703812437	1.663123325566
H	-1.378396111613	3.402008693823	1.152141644824
H	0.894798000360	1.064011757178	-0.791697382455
H	-1.492336369448	0.371729564675	-2.501700107295
H	0.104406176424	0.907140458321	-2.971935081172
H	-0.896249826398	-1.848544525879	-2.230094120114
H	0.177993204358	-1.382060627579	-3.528928723649
H	1.324066109136	-2.681013806461	-1.750294282075
H	2.010307155868	-1.513295063968	1.754054789704
H	2.878561912427	-1.921955834290	0.311403152481
H	2.264770018881	0.888340588301	1.335995137934
H	2.955958840260	0.609893920814	-0.242932633229
H	4.176182816009	-0.436367147421	2.349130612439
H	5.454125226961	-0.169921010772	-0.440145534104
H	6.490200437313	-2.303056268542	0.126715170560
H	5.600440307393	-2.324163664470	1.751115853163
H	5.778064519431	1.479602620719	2.161292653979

H	4.111923833368	2.062663884855	2.347756808792
H	4.891641427879	2.095014236274	0.757470563355
H	2.351495689589	0.159188847800	-2.221922834955
H	2.544878907908	-1.269375850862	-3.227938505852
H	3.332173659551	-1.201308960486	-1.655435602488
H	-2.689736964857	3.299232756652	-1.066663595750
H	-2.887510148372	1.579774857080	-1.359846788151
H	-1.903541971298	2.556799201723	-2.466679692534
H	0.935247581935	3.297028785243	-0.199731150318
H	-0.409197270046	4.280251700653	-0.801950568468
H	0.454606502162	3.194903744093	-1.899234696537
H	-0.452274701859	-3.209558335055	-0.200821267482
H	-0.069239582252	-2.721348080559	1.453442807702
H	1.163502447421	-3.508102529491	0.453034112948
O	-2.619538539166	1.814290841363	1.224530924253
Al	-3.613831438639	0.397919023839	1.307115146773
C	-3.708453061207	-0.545293130169	3.038236069635
C	-5.181556290093	0.332195438226	0.118682743095
H	-2.800387554028	-0.468166221782	3.648333260073
H	-4.530465773291	-0.134079126937	3.640590149627
H	-3.924303613006	-1.612566668045	2.897911960871
H	-4.965054581569	0.661439662274	-0.903807278898
H	-5.977715584619	0.983497271485	0.504832112387
H	-5.600408440487	-0.680805777891	0.061400054743
Cl	-2.050471732844	-1.082038088334	-0.027321139923

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Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029477.100352  kcal/mol
ZPVE           = 362.958257  kcal/mol
Enthalpie(0K)   = -1029114.142095  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 369.900547  kcal/mol
H-E(el)        = 371.451767  kcal/mol
Enthalpie      = -1029105.648586  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000054352861 (Symmetry number= 1)
S(vib)         = 0.000102086292
G-E(el)        = 344.174390  kcal/mol
Free Energy     = -1029132.925962  kcal/mol
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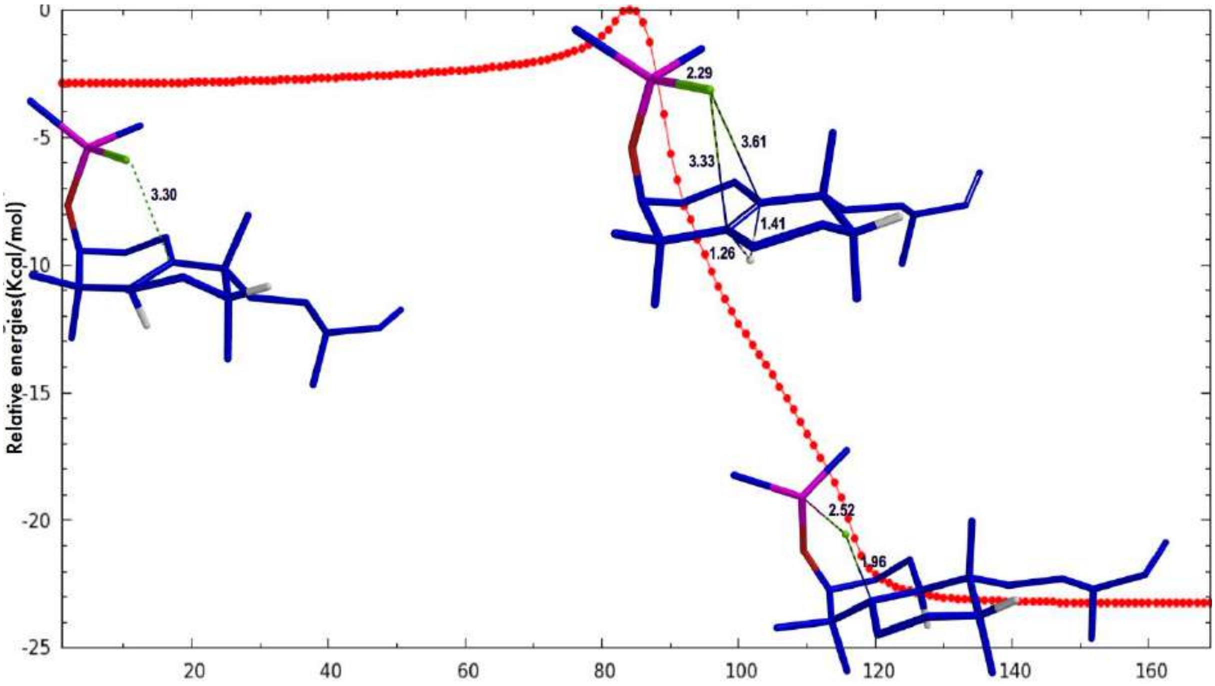
Plot of IRC transformation of **VIIb** in to **VIIIb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **VIIb**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	-0.365305753627	-0.795913910818	1.163675401395
C	-1.151956145211	-0.233045251497	2.347045341180
C	-2.385149400158	0.526115775730	1.841287319127
C	-1.957193712292	1.753100166913	0.968441652181
C	-0.750621919303	1.435357667529	0.000083662495
C	-0.899794881162	1.954174695295	-1.460942040588
C	0.103114824845	1.349946973321	-2.447135551069
C	1.452449442278	1.052529117852	-1.786014796743
C	1.245857160476	-0.035772066186	-0.681073550924
C	-0.012868748705	0.176437891894	0.129984184320
C	2.444929299682	-0.028021314965	0.337378300835
C	3.797640664726	-0.406209061787	-0.278726366913
C	4.969531314298	-0.265160324705	0.721481139638
C	6.203086059887	-0.916612293956	0.151029969788
C	6.832982585814	-1.967865244827	0.680384607253
C	5.263686847313	1.203436572594	1.077669906463
C	2.142588834416	2.360245625434	-1.351567751427
C	-3.204425440556	2.249483702825	0.219482968386
C	-1.486110872345	2.891248959902	1.901789730701
C	1.139924970531	-1.443971725905	-1.339517016143
H	-1.039804172407	-1.490174991127	0.620127170083
H	0.475350177833	-1.422725663139	1.460927490916
H	-1.477186755374	-1.065633784651	2.975458167415
H	-0.506790895717	0.411204777809	2.956117215531
H	-2.895124463275	0.956138321723	2.720264175671
H	0.108058783015	2.032478233729	0.401399938163
H	-1.904823964408	1.690724168194	-1.784429062818

H	-0.827423864822	3.045229593595	-1.437478896134
H	-0.317654140626	0.426739655570	-2.851385157730
H	0.245014393551	2.032834449058	-3.291256559768
H	2.105283034029	0.593811020483	-2.536671030566
H	2.501478814636	0.961700067711	0.799125855206
H	2.246408531638	-0.735147727596	1.145776299810
H	4.014838610425	0.199890499098	-1.165711870159
H	3.759807208812	-1.446492640833	-0.614573813989
H	4.698348347270	-0.801117294357	1.642014394360
H	6.588346986993	-0.470802628284	-0.768217546223
H	7.719490597377	-2.393469358980	0.220123353318
H	6.481371923492	-2.438104426111	1.596142298552
H	4.394839868368	1.702130860141	1.518270638016
H	5.558170918874	1.766276111988	0.183664185683
H	6.085162911473	1.266959462863	1.796909361700
H	2.200759832537	3.028325757335	-2.216703696627
H	1.602320493281	2.903139598378	-0.569671542690
H	3.160890787564	2.201651052920	-0.993533199958
H	-4.001889590756	2.419334303742	0.948961805570
H	-3.571877584314	1.510843598530	-0.491650368696
H	-3.013749140542	3.194446936328	-0.298512824423
H	-0.650405091070	2.585155133459	2.541548124870
H	-2.302565818592	3.217195739602	2.553038663949
H	-1.160561191967	3.761915045290	1.319558927443
H	0.214178102234	-1.543717375275	-1.906942278866
H	1.161152143781	-2.238202132451	-0.589728042262
H	1.989357177907	-1.585188156110	-2.010211385102
O	-3.265310612785	-0.313910975451	1.193343428250
Al	-3.478512265396	-1.683262342634	0.090555474467
C	-2.469974999842	-3.326451983181	0.674773372874
C	-5.388523017728	-1.917368698085	-0.337845198371
H	-1.525095003267	-3.524497286199	0.151865858630
H	-2.272341127597	-3.360341952642	1.754991006973
H	-3.122330141354	-4.181790239466	0.447323841573
H	-5.832391515647	-0.981549467910	-0.700278740372
H	-5.961260252227	-2.232043098667	0.545120620179
H	-5.539411188954	-2.676307413576	-1.116258288853
Cl	-2.402777496271	-1.009498114356	-1.819063852483

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029481.907919 kcal/mol
ZPVE = 360.318717 kcal/mol
Enthalpie(0K) = -1029121.589202 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 367.445418 kcal/mol
H-E(el) = 368.996638 kcal/mol
Enthalpie = -1029112.911282 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054955941 (Symmetry number= 1)
S(vib) = 0.000107299145

G-E(el) = 341.007051 kcal/mol
Free Energy = -1029140.900868 kcal/mol

Cartesian Coordinates and Energies of **Transition state VIIb-VIIIb**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	-0.256160166463	-0.391659292850	1.559110272152
C	-1.257962903170	0.219975692839	2.531728291566
C	-2.521196354863	0.665519862146	1.786577948754
C	-2.170787489274	1.775446261294	0.745807137819
C	-0.942608456682	1.373398238867	-0.117053460745
C	-0.856634577455	1.987269067736	-1.502773468861
C	0.241678803187	1.410506761479	-2.393233269530
C	1.523757501654	1.154728333794	-1.599267533408
C	1.261596620657	0.072174787645	-0.509041526757
C	-0.002362222291	0.391716981720	0.306243870681
C	2.496602739094	-0.059508639487	0.431699805572
C	3.821254405024	-0.350976314735	-0.285078900662
C	5.000508272840	-0.594523012311	0.684173976720
C	6.216836226609	-1.018435046509	-0.098190361443
C	6.822347372674	-2.204233924754	-0.000773238597
C	5.324526215284	0.646441713846	1.535676418982
C	2.106516669824	2.478573909097	-1.069205687857
C	-3.418984973541	2.038704388614	-0.117847045993
C	-1.820824117868	3.099040598870	1.470801001091
C	0.982444242309	-1.306467440637	-1.174349808980
H	-0.670121444891	-1.335931142694	1.174149849815
H	0.675360934459	-0.644932985826	2.062120613735
H	-1.534706182549	-0.535166578495	3.271884301138
H	-0.799566267128	1.055359039695	3.075103194406
H	-3.194272234236	1.150743134694	2.515778735984
H	0.041135309184	1.780709582695	0.557057341425
H	-1.825217937645	1.788976982443	-1.961970591660
H	-0.773433329916	3.075462026351	-1.401734342910
H	-0.121664630111	0.480294089403	-2.835446067353
H	0.440731849989	2.101978458967	-3.218372671871
H	2.265162201383	0.723810298784	-2.280142448302
H	2.589439666806	0.848636163982	1.037996719586
H	2.326454457827	-0.882939417169	1.130166171749
H	4.093980940332	0.468579111241	-0.960010701892
H	3.708720689726	-1.242331856980	-0.909861749917
H	4.724942326358	-1.418395838259	1.357303714547
H	6.610924939994	-0.274627648132	-0.793900572706
H	7.696302833769	-2.449413485001	-0.596684105762
H	6.461905745310	-2.971416656552	0.681022568057
H	4.482439376888	0.937478789873	2.170994240706
H	5.575601823417	1.500583536190	0.894524404708
H	6.182569793044	0.453585807284	2.185942365040

H	2.204825916402	3.188493883770	-1.896454880471
H	1.471857420743	2.960989472525	-0.316224080740
H	3.094543767163	2.353333122425	-0.623333327539
H	-4.268672322592	2.178854773777	0.556389549959
H	-3.648533648818	1.197960027317	-0.769979188642
H	-3.312297642381	2.948304802644	-0.716171465593
H	-0.977235377288	2.993627630105	2.161079671198
H	-2.684412585916	3.437123245635	2.050692638745
H	-1.576135928754	3.889323501076	0.753254811167
H	-0.008390562140	-1.356649137142	-1.626138784377
H	1.053441574486	-2.110714989729	-0.437827872274
H	1.730857358534	-1.487903449326	-1.949664415353
O	-3.162557970712	-0.405008029356	1.218935033378
Al	-3.297244641436	-1.778443406703	0.100362234036
C	-2.084427212509	-3.290473914543	0.593077441879
C	-5.205360982970	-2.215038243428	-0.157804660821
H	-1.053523925395	-3.208341093051	0.222900101486
H	-2.036702508048	-3.448321944650	1.680470509143
H	-2.485060295354	-4.217085055675	0.158893496972
H	-5.782461278126	-1.332385658904	-0.463232522522
H	-5.660849343713	-2.598750551677	0.765718062512
H	-5.344219057392	-2.979631636180	-0.933494216593
Cl	-2.508748423335	-0.976296688049	-1.895674524573

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029481.111854 kcal/mol
ZPVE = 358.931306 kcal/mol
Enthalpie(0K) = -1029122.180548 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 365.995413 kcal/mol
H-E(el) = 367.546633 kcal/mol
Enthalpie = -1029113.565221 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054992992 (Symmetry number= 1)
S(vib) = 0.000103694586
G-E(el) = 339.993918 kcal/mol
Free Energy = -1029141.117936 kcal/mol

Cartesian Coordinates and Energies of **VIIIb**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

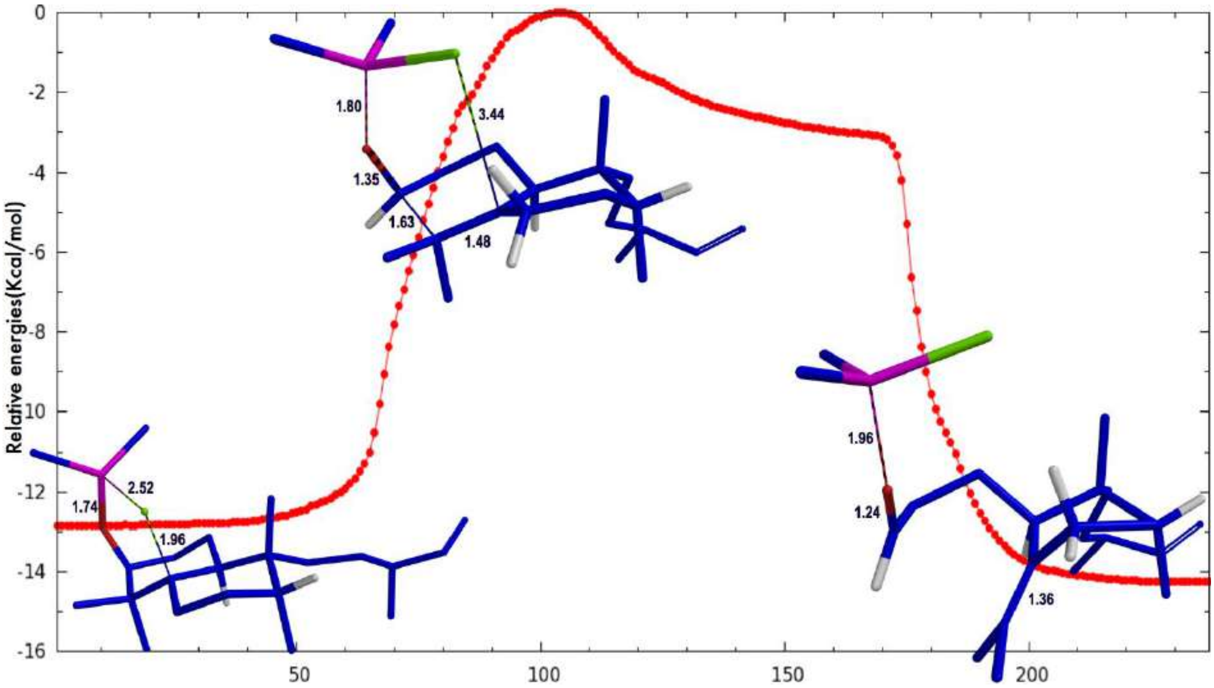
C	-0.314823106660	-0.637496363933	1.381703055753
C	-1.265627792270	-0.032146961682	2.417023170269
C	-2.546680383404	0.545866482736	1.797814884213
C	-2.231202703828	1.537020347140	0.622454909996
C	-1.195298289065	0.945148543429	-0.394347416529

C	-0.879833906802	1.876771104109	-1.565067212666
C	0.235245737928	1.360811805219	-2.473245070239
C	1.525202895466	1.084404239390	-1.684710502385
C	1.289777932077	-0.016140860170	-0.601031790047
C	0.068467329455	0.389464886062	0.302936814090
C	2.533018008131	-0.116764614518	0.333060171181
C	3.880557363900	-0.392756720312	-0.347749812520
C	5.073938981565	-0.410936109869	0.635107184945
C	6.309717709526	-0.902388721721	-0.072859889273
C	6.986209865670	-2.013061614402	0.230044208968
C	5.342564636431	0.970190945047	1.260783947297
C	2.106302708198	2.402516697896	-1.137712673367
C	-3.550816420794	1.955487694532	-0.050319026873
C	-1.635671040266	2.824734128258	1.255887196033
C	1.101734446427	-1.385177401801	-1.286939645160
H	-0.768349193130	-1.514759991636	0.915425629073
H	0.580852108212	-0.994720112440	1.893611826072
H	-1.564711014061	-0.790507397940	3.147509767051
H	-0.739484610362	0.754355101137	2.973552017877
H	-3.042888783100	1.159482469540	2.565398313730
H	0.428998260389	1.274491310218	0.843406583164
H	-1.788571466708	2.071752017582	-2.137638671497
H	-0.571245983364	2.834395947365	-1.135475505044
H	-0.096818037475	0.458429092437	-2.993579013883
H	0.434047563080	2.109255968088	-3.248900649547
H	2.257645880549	0.679962113650	-2.394278671681
H	2.602183169501	0.803791524603	0.922193166250
H	2.368129746894	-0.923217252234	1.054928862573
H	4.088049763548	0.348732545505	-1.129232424776
H	3.846875374211	-1.364799848513	-0.849146562469
H	4.840814592616	-1.119540859852	1.442571198656
H	6.655894377322	-0.278137915434	-0.899562199255
H	7.870376487559	-2.312693205562	-0.324828420051
H	6.675534261564	-2.661870664768	1.046231223378
H	4.478282178298	1.339105673588	1.820955062105
H	5.580425096205	1.707148789562	0.483753871231
H	6.192797299052	0.923481836406	1.947800392068
H	2.137397797633	3.154144793443	-1.933949036754
H	1.510531514950	2.820259937496	-0.320274277024
H	3.124558934742	2.279887442311	-0.764432459488
H	-4.250357088401	2.288825538205	0.721992829853
H	-4.026436159251	1.135616138975	-0.585451505171
H	-3.399238372169	2.786729602054	-0.744852821042
H	-0.673732623707	2.669533010912	1.746988456433
H	-2.334314446193	3.189285490010	2.014596343905
H	-1.518111228594	3.621877815505	0.518567443826
H	0.259046855497	-1.405332590259	-1.974104880846
H	0.940158552203	-2.175854615209	-0.548413889645
H	1.996969983178	-1.644095750627	-1.858669915627
O	-3.444971547020	-0.459834852562	1.441961738611
Al	-3.581238836385	-1.765018508694	0.304104744657
C	-2.605114247094	-3.447070548102	0.645438781977

C	-5.243830720097	-1.806099714859	-0.745179487965
H	-1.908972057088	-3.687459633995	-0.169289080194
H	-2.025174215544	-3.421395680199	1.575632748744
H	-3.305541524071	-4.289379703980	0.719239015405
H	-5.575913453813	-0.805399785979	-1.045276671559
H	-6.058978492283	-2.256870942202	-0.162817271291
H	-5.133920453312	-2.410055330366	-1.655259174592
Cl	-2.077699053026	-0.547066553307	-1.311202278822

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029492.863300 kcal/mol
ZPVE = 362.767095 kcal/mol
Enthalpie(0K) = -1029130.096204 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 370.178684 kcal/mol
H-E(el) = 371.729904 kcal/mol
Enthalpie = -1029121.133396 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054864183 (Symmetry number= 1)
S(vib) = 0.000110200418
G-E(el) = 343.396269 kcal/mol
Free Energy = -1029149.467031 kcal/mol

Plot of IRC transformation of **VIIIb** in to **IXb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **VIIIb**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.973798529318	-1.819790888900	-0.766018091820
C	0.729816704479	-3.042354001796	0.119671795415
C	-0.525876294857	-2.898195941776	0.994217928779
C	-0.520914457927	-1.560747489575	1.816411337453
C	-0.178188890098	-0.317351908506	0.924527999985
C	-0.144419107606	1.007090842864	1.686437940021
C	0.288273245874	2.194024247073	0.824561104792
C	1.671315725126	1.968530488500	0.189835846723
C	1.675840538249	0.683878538767	-0.703934967101
C	1.088546644303	-0.538894178832	0.072843344546
C	3.128722817062	0.348897088348	-1.174937498351
C	4.050444562065	-0.489438381253	-0.276612383349
C	5.516606610260	-0.486427348363	-0.767300155981
C	6.151801336531	0.864453036212	-0.565920629264
C	6.573667525581	1.680725613720	-1.534886522127
C	6.330190492800	-1.571502829533	-0.041363984878
C	2.764921823106	2.046224292238	1.269935096700
C	-1.868640764129	-1.419572788456	2.546044616882
C	0.562439783702	-1.697832695731	2.921124440989
C	0.902416955659	1.014760009638	-2.001674007918
H	0.166030200101	-1.715782505887	-1.492761392638
H	1.885349436957	-1.964837542225	-1.350632666543
H	0.604489264731	-3.941028528034	-0.492532787325
H	1.607227526847	-3.211278944526	0.757824351970
H	-0.505177980972	-3.699817027800	1.748422089550
H	1.832356707200	-0.743485759457	0.851598420325
H	-1.115154463164	1.198238533234	2.147978441805

H	0.571969263442	0.880354538397	2.503974778822
H	-0.464394161830	2.381499362443	0.054322800899
H	0.317592778753	3.093309627120	1.450394175678
H	1.859514390117	2.807136483731	-0.494400125589
H	3.064054542568	-0.170511304711	-2.138997204731
H	3.620284952124	1.303626379737	-1.396631800269
H	3.706577491124	-1.529853124554	-0.253810805915
H	4.036425245465	-0.142149450644	0.760958878367
H	5.518840232503	-0.710788304923	-1.843312192785
H	6.264436246286	1.174551645775	0.475426549458
H	7.027245766512	2.642698333475	-1.314817204851
H	6.480429858347	1.409650037044	-2.584176543797
H	5.891655114294	-2.562001130289	-0.204985005637
H	6.346621106987	-1.386451549324	1.039713838306
H	7.365884485902	-1.591139560275	-0.393930593319
H	2.637505019003	2.966423927883	1.850586991696
H	2.730444742117	1.210028177738	1.975825548744
H	3.764859385191	2.072416538716	0.832812706481
H	-2.053977613431	-2.330976831653	3.122595841764
H	-2.704446482598	-1.295453411415	1.860278022041
H	-1.859797964289	-0.579156294465	3.246016170542
H	1.581031325732	-1.760271203675	2.534649438470
H	0.368917176621	-2.616955397531	3.481791117374
H	0.518246322421	-0.870964704143	3.633779556279
H	-0.076332957440	1.456198387562	-1.820201390839
H	0.753530197429	0.125007271118	-2.618673551215
H	1.488363212115	1.729551987327	-2.590367233822
O	-1.689833994985	-3.073989658182	0.245829490129
Al	-2.588632044416	-2.283856444156	-1.012775842310
C	-1.971909593573	-2.444039653046	-2.882390348903
C	-4.501104490732	-2.007576375507	-0.647329901517
H	-1.099210834824	-3.099912796688	-2.986040757806
H	-2.768388853639	-2.855571467376	-3.516126091838
H	-1.702170302284	-1.468866201820	-3.309358905139
H	-5.066854735588	-2.932018462774	-0.826884048023
H	-4.931508538658	-1.240770706139	-1.304546283038
H	-4.694545391656	-1.706600893518	0.388898087613
Cl	-1.681821926444	-0.045159906689	-0.294463776403

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029492.716306 kcal/mol
ZPVE = 362.720442 kcal/mol
Enthalpie(0K) = -1029129.995864 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 369.396929 kcal/mol
H-E(el) = 370.948148 kcal/mol
Enthalpie = -1029121.768158 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054531497 (Symmetry number= 1)
S(vib) = 0.000096338790

G-E(el) = 344.352727 kcal/mol
Free Energy = -1029148.363580 kcal/mol

Cartesian Coordinates and Energies of **Transition state VIIIb-IXb**

FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.860303387884	-1.675356492771	-0.880893538111
C	0.557255265433	-2.960588305122	-0.129166864020
C	-0.531981655753	-2.789501096845	0.942622521428
C	-0.199041555859	-1.508721227062	1.903565549595
C	0.250553351040	-0.340269826102	1.117269810018
C	-0.320248656270	0.979763996709	1.395253017201
C	0.360502711200	2.205968854329	0.771441548934
C	1.816610132516	1.931635863062	0.369365743288
C	1.872487709837	0.721387883433	-0.609850373131
C	1.306546833761	-0.540486379843	0.100143922757
C	3.336719546424	0.467198042672	-1.093664558697
C	4.231312314937	-0.503385588280	-0.309847526506
C	5.708656998942	-0.446075904893	-0.760622803457
C	6.344905166583	0.859206607082	-0.359326216766
C	6.797842644294	1.794589176550	-1.197694741806
C	6.498784784185	-1.629507770883	-0.176934258386
C	2.712080748938	1.804428137088	1.613005227892
C	-1.427638986008	-1.252792437872	2.785998879742
C	0.989274224410	-1.936637633641	2.827078442167
C	1.045008739577	1.078010797317	-1.865811185295
H	-0.011043990882	-1.334309042462	-1.439787741882
H	1.676187204130	-1.823225431880	-1.594499090355
H	0.194344352440	-3.722144692259	-0.825985950873
H	1.475006231405	-3.350771554279	0.329062886011
H	-0.460320235065	-3.633344803883	1.652097774451
H	2.122416599073	-0.996919572563	0.676513835540
H	-1.359848921328	0.881605475305	1.022046075319
H	-0.447009434782	1.069457287441	2.481602176602
H	-0.213326230351	2.531675323055	-0.097541459688
H	0.323830045462	3.028972785154	1.492477891101
H	2.173212396374	2.802514640578	-0.194881605571
H	3.300858404630	0.100105051285	-2.125858472367
H	3.834682924590	1.441962931929	-1.150584046525
H	3.878526166158	-1.532963822560	-0.453049367359
H	4.195224272510	-0.310924428528	0.769115559938
H	5.733254461598	-0.517538207025	-1.856936150524
H	6.432931973100	1.023686053189	0.717015535911
H	7.253056993288	2.712437021052	-0.837640465548
H	6.731786557547	1.668848381853	-2.276110019900
H	6.058244789641	-2.583613133741	-0.486428807907
H	6.495332601489	-1.597393484790	0.919478945696
H	7.540936138129	-1.608854338248	-0.509086210593

H	2.576025138940	2.677655619191	2.259460227133
H	2.481976250351	0.917917784219	2.216052663509
H	3.769620740331	1.756295626756	1.345220398630
H	-1.746720736094	-2.201913635141	3.223385372018
H	-2.266990382143	-0.868506534996	2.206068618792
H	-1.203660623883	-0.564257911665	3.607995620826
H	1.850502326188	-2.303088541604	2.268276920263
H	0.629580813079	-2.741147856570	3.473606790998
H	1.310278505730	-1.108082031398	3.466240719097
H	-0.025764192047	1.146996566541	-1.671527018068
H	1.176991171874	0.328228014146	-2.648918808367
H	1.391161830455	2.036086738096	-2.269102636496
O	-1.795130905897	-2.712222189969	0.467788214104
Al	-2.821763065255	-2.195419337211	-0.912478309136
C	-2.193987891963	-2.965800049561	-2.633511637880
C	-4.706807821763	-2.428700707892	-0.379941724297
H	-1.172782367857	-2.672388343092	-2.909618062862
H	-2.225265410923	-4.064269195962	-2.612186234024
H	-2.848504293840	-2.642232810529	-3.453733843244
H	-4.961513253546	-3.488153340361	-0.240133630501
H	-5.393236743623	-2.024076580288	-1.135060872341
H	-4.923889419018	-1.913337046825	0.564950468826
Cl	-2.418233055205	0.054465776740	-1.024192466884

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029489.315476 kcal/mol
ZPVE = 360.234405 kcal/mol
Enthalpie(0K) = -1029129.081071 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 367.125606 kcal/mol
H-E(el) = 368.676826 kcal/mol
Enthalpie = -1029120.638650 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054811832 (Symmetry number= 1)
S(vib) = 0.000101651093
G-E(el) = 341.396538 kcal/mol
Free Energy = -1029147.918938 kcal/mol

Cartesian Coordinates and Energies of **IXb**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.687087130972	-1.648416980521	-0.851704939775
C	0.204045199956	-2.955133393861	-0.195747857800
C	-0.939864464832	-2.765199058439	0.751353376009
C	0.538991690055	-1.209830212173	2.514521987806
C	0.461795602378	-0.490621237125	1.363407267262

C	-0.470669028110	0.668221868127	1.161258274959
C	0.362931523941	1.978142024460	1.077524180543
C	1.821227410659	1.767739030375	0.585661756896
C	1.893178292372	0.626530673397	-0.476977585974
C	1.376102090514	-0.715658185500	0.171723840932
C	3.347837467342	0.460062559419	-1.024621255616
C	4.315883517070	-0.507335508768	-0.328408030969
C	5.781544219865	-0.313717499226	-0.777984988747
C	6.337021671718	0.988993065776	-0.264476555814
C	6.728076918697	2.020463198365	-1.016873668435
C	6.651755390779	-1.489257525991	-0.301136937832
C	2.793399462152	1.611054600100	1.766922692305
C	-0.407994020622	-1.011793382186	3.676217379282
C	1.607075048210	-2.233095789449	2.824101451119
C	1.050197748267	1.089513526700	-1.688527307439
H	-0.164881912495	-1.152848532536	-1.320939401045
H	1.390158316319	-1.896927142187	-1.653889730111
H	-0.164849906586	-3.630201960092	-0.979193251911
H	1.020126663332	-3.457649692049	0.329604086944
H	-0.866607965144	-3.188844039399	1.759343465449
H	2.251900986443	-1.252698965475	0.527467709175
H	-1.025273124696	0.523683686807	0.230397652242
H	-1.218224716524	0.758191384074	1.948601540983
H	-0.158877069337	2.680218089508	0.420330189687
H	0.395044891246	2.445346361286	2.067671118163
H	2.122552910090	2.684459888890	0.062130104008
H	3.286524675706	0.143529640024	-2.073626536220
H	3.800889274778	1.458439955844	-1.049707125415
H	4.029943171432	-1.542486358451	-0.555214131062
H	4.273431522827	-0.410150007303	0.762200647862
H	5.803326859694	-0.287139600192	-1.876568545716
H	6.415345586946	1.065370263783	0.822350925394
H	7.123537690265	2.931209193541	-0.576839648778
H	6.666155925045	1.985565665668	-2.102314532569
H	6.270935180890	-2.439482532892	-0.691818264637
H	6.652301542560	-1.552875838585	0.793967626033
H	7.688680982851	-1.372853051845	-0.630517401305
H	2.661918538665	2.444270516505	2.465736154232
H	2.623190111753	0.686481116905	2.326399185709
H	3.834369665257	1.627911555779	1.434984693803
H	-0.649671736324	-1.977113393575	4.138016562530
H	-1.346546069475	-0.534281860744	3.395991777325
H	0.063247910533	-0.402241505485	4.459102625455
H	2.405513492108	-2.288255189233	2.084810851324
H	1.176691023241	-3.239185522100	2.931398408262
H	2.063414630919	-1.998163240616	3.794017356856
H	-0.002983378413	1.250660019265	-1.460124231821
H	1.095648169069	0.371610047401	-2.511257231129
H	1.459980024008	2.034302404043	-2.063082193074
O	-2.045488280460	-2.297349455205	0.424973684155
Al	-3.147987106352	-2.039280126255	-1.173084376470
C	-2.476153632664	-3.399540417943	-2.440002291671

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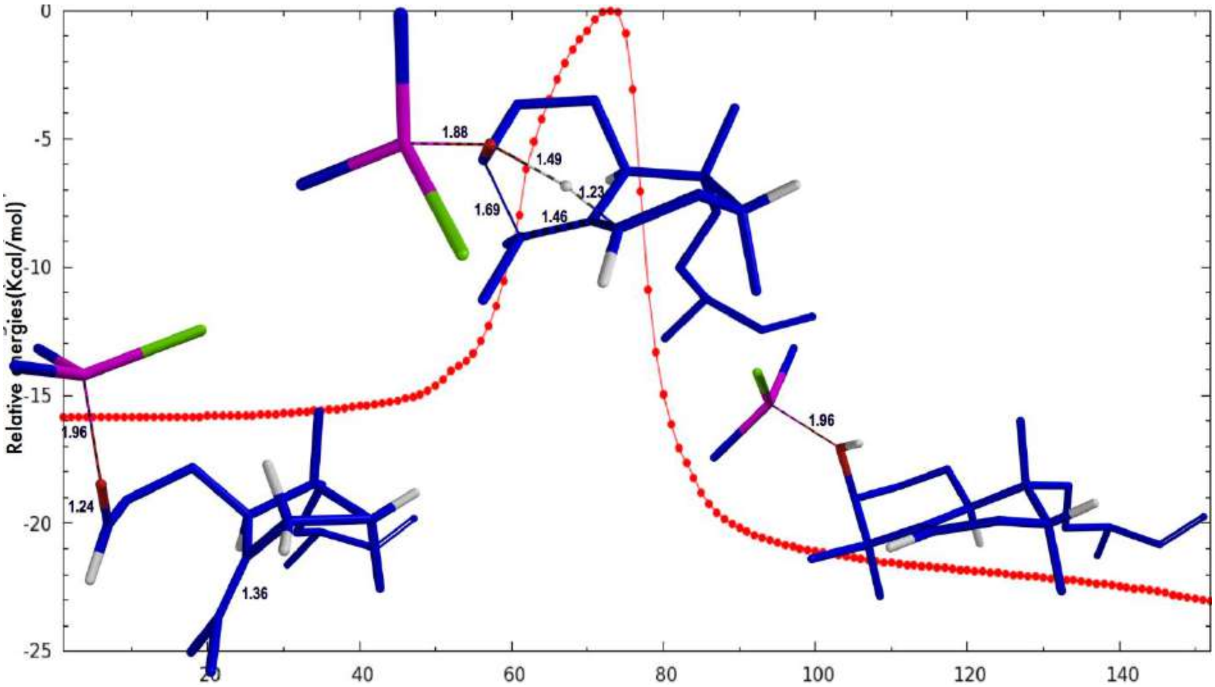
C     -4.953873509028        -2.137570285447        -0.409988488335
H     -1.503656588742        -3.139961113799        -2.876113543327
H     -2.395784594280        -4.401365381313        -1.995625957338
H     -3.178723738279        -3.486522546105        -3.279506974343
H     -5.164005348110        -3.123758855131         0.024547107871
H     -5.718591927943        -1.947946987552        -1.173865611416
H     -5.094362370415        -1.389939714254         0.380499333665
Cl    -2.620180605397        -0.013841803326        -1.832590855340
---------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029498.187634  kcal/mol
ZPVE           = 359.926495  kcal/mol
Enthalpie(0K)   = -1029138.261139  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 367.754754  kcal/mol
H-E(el)        = 369.305974  kcal/mol
Enthalpie       = -1029128.881660  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055123202 (Symmetry number= 1)
S(vib)         = 0.000121450846
G-E(el)        = 339.562909  kcal/mol
Free Energy     = -1029158.624725  kcal/mol
---------------------------------------------------------------
```

Plot of IRC transformation of I**Xb** in to **Xb** (B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ)



Cartesian Coordinates and Energies of **IXb**.

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ

Charge = 0 Multiplicity = 1

C	0.715047330996	-1.309712936739	-1.988340327273
C	0.000549419931	-2.564903112328	-1.460386446492
C	-0.978770471700	-2.311277837060	-0.358003091518
C	0.877676593885	-1.294077298141	1.423164015529
C	0.935534524425	-0.488817737735	0.327553877129
C	0.112342719643	0.782745691828	0.258210103243
C	0.614039435837	1.763482681565	-0.811695010170
C	2.147568439533	1.781753357019	-0.852647118988
C	2.670988576672	0.393367155870	-1.371325300322
C	1.727521329097	-0.799633133658	-0.925582151693
C	4.131603915290	0.106256441592	-0.920465582537
C	4.388430193444	-0.447365622405	0.488703057738
C	5.873968654051	-0.358245704830	0.904780227389
C	6.291927086195	1.069722984752	1.138751677041
C	7.196652693362	1.744234692481	0.424782229492
C	6.128937819500	-1.200798884982	2.166379961155
C	2.697895783069	2.290834677654	0.490454712350
C	0.042649355912	-0.914219094196	2.627587284205
C	1.681261742795	-2.555041372939	1.624830457081
C	2.734104465778	0.497797164732	-2.911334642332
H	-0.033850569806	-0.554130151565	-2.237474526408
H	1.228646437418	-1.573993649464	-2.914904291860
H	-0.587756019705	-3.014699513367	-2.273366224928
H	0.726885372510	-3.312488604344	-1.128615569750
H	-0.976261060271	-2.963052190809	0.522927234510
H	2.385796079600	-1.650803002112	-0.743699627977
H	-0.939441003552	0.535913499567	0.071788077861

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H     0.116368044427     1.275076602646     1.233760611987
H     0.218821362746     1.497316127262    -1.797536423028
H     0.226650549867     2.763911696990    -0.591827251864
H     2.460652242768     2.519686490891    -1.602559550025
H     4.564039690947    -0.612656274008    -1.630468756498
H     4.706399328380     1.029785099670    -1.054773339108
H     4.098060329740    -1.501928252762     0.528846804898
H     3.779838866637     0.059972354474     1.241538356343
H     6.484672029814    -0.764052720823     0.085580210269
H     5.794931626378     1.569190209974     1.972971914282
H     7.452327678289     2.774649708797     0.653693846087
H     7.714675716931     1.283970192752    -0.413805873229
H     5.853097073148    -2.247745672390     1.997970928982
H     5.532840395477    -0.828450665188     3.008482540636
H     7.182420717943    -1.165648379506     2.460072483243
H     2.284184528687     3.285891579968     0.688740800319
H     3.785870384908     2.382466792691     0.480703471612
H     2.419837365974     1.650709714204     1.331456892214
H    -0.183704525383    -1.793266108859     3.237969211317
H    -0.902142079949    -0.435226374266     2.364607443075
H     0.596934444246    -0.213832685301     3.268281964458
H     2.283373804713    -2.847307584631     0.765397118493
H     1.020845054886    -3.394873285832     1.877233070997
H     2.356679231707    -2.430749995256     2.481199002423
H     1.780426228954     0.808035484297    -3.348161979227
H     3.028339362118    -0.450376235758    -3.372667378898
H     3.484682868809     1.243439856718    -3.193465462734
O    -1.926360785360    -1.513662777068    -0.511404993935
Al   -3.571792971180    -1.437378497152     0.552712509809
C    -4.952049195205    -1.556349358511    -0.840999194274
C    -3.319422660857    -2.878708096191     1.883291027657
H    -5.956764498600    -1.455380840050    -0.411198671525
H    -4.838922976386    -0.760632730988    -1.587439087397
H    -4.921040281581    -2.517880800777    -1.370685815222
H    -3.248436730308    -3.877889971461     1.430957476531
H    -4.187149655321    -2.903607382563     2.555407635485
H    -2.440482867037    -2.734706822143     2.524155522306
Cl   -3.402682538964     0.547604424291     1.454516017221
------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029501.740035  kcal/mol
ZPVE           = 360.587553  kcal/mol
Enthalpie(0K)   = -1029141.152481  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 368.392113  kcal/mol
H-E(el)        = 369.943333  kcal/mol
Enthalpie      = -1029131.796702  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055083179 (Symmetry number= 1)
S(vib)         = 0.000117758340
```

G-E(el) = 340.657348 kcal/mol
Free Energy = -1029161.082687 kcal/mol

Cartesian Coordinates and Energies of **Transition state IXb-Xb**

# FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# SADDLE /B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	0.735001101503	-1.525795410201	-1.886693893663
C	0.015156491076	-2.713103471330	-1.230129203537
C	-0.656705387467	-2.307901007212	0.085745385726
C	0.516463641878	-1.741017289258	1.167972695667
C	0.954757600983	-0.614167311096	0.340558805301
C	0.163589070576	0.560988185012	0.331482294946
C	0.493469890409	1.610928512845	-0.718997252478
C	2.019752415626	1.723362922652	-0.885314438843
C	2.609331994814	0.351798023426	-1.386917185024
C	1.769554017283	-0.888632762830	-0.884748121224
C	4.090268877877	0.147236739580	-0.956524240909
C	4.376534137717	-0.346313230535	0.470270968043
C	5.856291328029	-0.175051671453	0.882377763436
C	6.211962708343	1.278221121772	1.058213528694
C	7.081651584417	1.962754477120	0.311146673924
C	6.147343296064	-0.954981081014	2.175854300344
C	2.619412078559	2.336177592486	0.391163282368
C	-0.190038280060	-1.376864432185	2.480304422800
C	1.527398679655	-2.861624820405	1.440631642014
C	2.616966458705	0.409434313951	-2.928568771156
H	-0.002658136607	-0.784171347395	-2.200493136101
H	1.267430352386	-1.857196276677	-2.780141334315
H	-0.767151439071	-3.080447016412	-1.902002678087
H	0.712093519504	-3.541184185504	-1.064356988042
H	-1.060973408611	-3.159135957749	0.646978713349
H	2.473982515146	-1.694045816988	-0.680617083389
H	-0.825289178843	-0.101355139251	0.030875728233
H	-0.187750028815	0.925937568754	1.295587025433
H	0.030393252602	1.347438393866	-1.676023535690
H	0.066034350139	2.573745769794	-0.427480758068
H	2.217626793273	2.444198400407	-1.687827698064
H	4.540590837919	-0.577777434242	-1.648113967474
H	4.625166752896	1.087451077286	-1.128941743892
H	4.132705822539	-1.411508641466	0.552158402938
H	3.747621655557	0.162963871021	1.207276378753
H	6.483136013111	-0.586747041683	0.078710869485
H	5.701046101745	1.787016292464	1.878198607569
H	7.295240272201	3.010765239819	0.499437428302
H	7.613747481911	1.493202575300	-0.513325667553
H	5.919735239900	-2.019159143859	2.049361579348
H	5.535565677336	-0.576497759878	3.003822936390
H	7.198024230427	-0.860410364365	2.465667299196

H	2.192785992268	3.334292544192	0.536952958765
H	3.703337332833	2.447191684262	0.329140526966
H	2.389284862209	1.754224296221	1.288058958745
H	-0.533793108806	-2.290227534791	2.973073153686
H	-1.058565002415	-0.733653039943	2.344356863438
H	0.513116257372	-0.875743407880	3.154139101531
H	2.118592142352	-3.158672459361	0.575548762461
H	0.996626777139	-3.748105941196	1.800672264879
H	2.217824041006	-2.547497042054	2.229417036885
H	1.632629976358	0.651796759685	-3.339637623509
H	2.946504712274	-0.535967355274	-3.370339271342
H	3.314428706337	1.185858863340	-3.258823928993
O	-1.615530224347	-1.353980998350	-0.132498414873
Al	-3.393378283809	-1.271741630655	0.469724501044
C	-4.508831638264	-1.070032124872	-1.143393249695
C	-3.650680508865	-2.819112335215	1.679562520738
H	-5.559281105681	-0.881035249621	-0.887349013016
H	-4.172530822777	-0.228584428817	-1.762954290926
H	-4.484471154585	-1.972284046627	-1.770272110650
H	-3.559185652558	-3.783599786984	1.159605272193
H	-4.656969408642	-2.793665365599	2.117418716529
H	-2.944224134711	-2.824233473825	2.519426047135
Cl	-3.289006580728	0.634527829844	1.608433367390

Thermochemistry at 195.150 K, 1.000 Atm
E(el) = -1029488.475347 kcal/mol
ZPVE = 359.121920 kcal/mol
Enthalpie(0K) = -1029129.353427 kcal/mol
E(tr) = 0.581707 kcal/mol
E(rot) = 0.581707 kcal/mol
E(vib) = 365.984878 kcal/mol
H-E(el) = 367.536098 kcal/mol
Enthalpie = -1029120.939249 kcal/mol
S(el) = 0.000000000000
S(tr) = 0.000066308847
S(rot) = 0.000054955313 (Symmetry number= 1)
S(vib) = 0.000101986503
G-E(el) = 340.197166 kcal/mol
Free Energy = -1029148.278180 kcal/mol

Cartesian Coordinates and Energies of **Xb**

#FREQ/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ scrf=(smd, solvent= dichloromethane)//# MIN/B3LYP/6-31+g(d,p) empiricaldispersion=GD3BJ
Charge = 0 Multiplicity = 1

C	1.270810520886	-1.484929887334	-0.597682876508
C	0.546596228463	-2.625152610610	0.121014474704
C	-0.585283414234	-2.079676977701	0.980456757878
C	-0.125758150602	-1.046648996779	2.029476183202
C	0.619167311453	0.079121629220	1.294621838630

C	0.359122150857	1.373134610225	1.538780583112
C	1.180428478075	2.512586499002	1.007259548944
C	2.562719007538	2.049076630322	0.516682727073
C	2.402089793779	0.818177753773	-0.427946230413
C	1.741109369673	-0.359278445827	0.353531369924
C	3.777866454733	0.401252729303	-1.033525509386
C	4.661432849711	-0.598078503806	-0.272911338426
C	6.083149653835	-0.708028701504	-0.867361778238
C	6.865256440083	0.559553745765	-0.640689974513
C	7.322336396642	1.374583027713	-1.594491129246
C	6.829049741346	-1.909680814255	-0.261869453702
C	3.510369861589	1.838282509311	1.706975027581
C	-1.350853177076	-0.565915130092	2.829227806710
C	0.833678414549	-1.734698090739	3.031100437889
C	1.515716296564	1.271034819325	-1.612685861578
H	0.587234279861	-1.073802659320	-1.344493216338
H	2.127770877714	-1.879013044851	-1.152381770389
H	0.132529205998	-3.329111681556	-0.608580969455
H	1.231597434224	-3.194259933817	0.758183400274
H	-1.149275423670	-2.881611418571	1.461799574615
H	2.518142581466	-0.797627653179	0.992450530418
H	-1.371156230197	-0.470172398699	0.032700924388
H	-0.458737929966	1.639974791058	2.200590907314
H	0.633019967675	3.031611934525	0.209346650230
H	1.302259892001	3.258473794711	1.803071756982
H	2.991333338773	2.854676828665	-0.094108734709
H	3.604585136323	-0.025740723986	-2.029254553873
H	4.351105794854	1.319826492865	-1.208046023544
H	4.205448718095	-1.595077663212	-0.303233019804
H	4.750214595477	-0.338149675871	0.786662416460
H	5.991644450942	-0.865406108931	-1.951433177816
H	7.061320683344	0.805021483047	0.405555226486
H	7.885386336253	2.272526682371	-1.357513066456
H	7.148128087323	1.167007480775	-2.647966245405
H	6.281325498693	-2.840818323206	-0.444854145349
H	6.937815314598	-1.792554554843	0.823305326672
H	7.830799661270	-2.009669414546	-0.690448241979
H	3.520910936590	2.734896567971	2.336133621581
H	4.536617821635	1.661611202305	1.378356204935
H	3.202032142978	0.999492185333	2.339478865973
H	-1.855947220746	-1.428883409585	3.273631005434
H	-2.082100290391	-0.035093166265	2.215033450588
H	-1.046223265273	0.095068004044	3.644637998713
H	1.762632725567	-2.075336939967	2.571379021387
H	0.347141875057	-2.600420394683	3.494551247907
H	1.092913967999	-1.026788982578	3.823078971686
H	0.477844254361	1.444504717691	-1.316295632022
H	1.511018386226	0.534526755436	-2.419349681813
H	1.905400685996	2.205011561685	-2.032561525917
O	-1.553094776548	-1.426052449572	0.088794428524
Al	-3.426400804346	-1.877858959234	-0.293469522400
C	-3.389126200935	-2.662738593046	-2.094615098684

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C     -4.017441195934      -2.922486182974       1.268093531749
H     -4.401559387136      -2.866753382476      -2.465713015382
H     -2.909622630013      -1.993492558495      -2.819574138381
H     -2.843808737814      -3.616393476692      -2.110730685189
H     -3.460019268498      -3.862012389046       1.386050076137
H     -5.072769888307      -3.201893056142       1.152310350150
H     -3.938249552288      -2.362977294426       2.207503635292
Cl    -4.032930137295       0.233412999229      -0.263486364535
------------------------------------------------------------
Thermochemistry at  195.150 K,    1.000 Atm
E(el)          = -1029514.581907  kcal/mol
ZPVE           = 361.797523  kcal/mol
Enthalpie(0K)   = -1029152.784384  kcal/mol
E(tr)          = 0.581707  kcal/mol
E(rot)         = 0.581707  kcal/mol
E(vib)         = 369.028619  kcal/mol
H-E(el)        = 370.579838  kcal/mol
Enthalpie      = -1029144.002069  kcal/mol
S(el)          = 0.000000000000
S(tr)          = 0.000066308847
S(rot)         = 0.000055302351 (Symmetry number= 1)
S(vib)         = 0.000110401872
G-E(el)        = 342.167876  kcal/mol
Free Energy    = -1029172.414031  kcal/mol
------------------------------------------------------------
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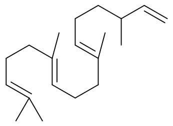

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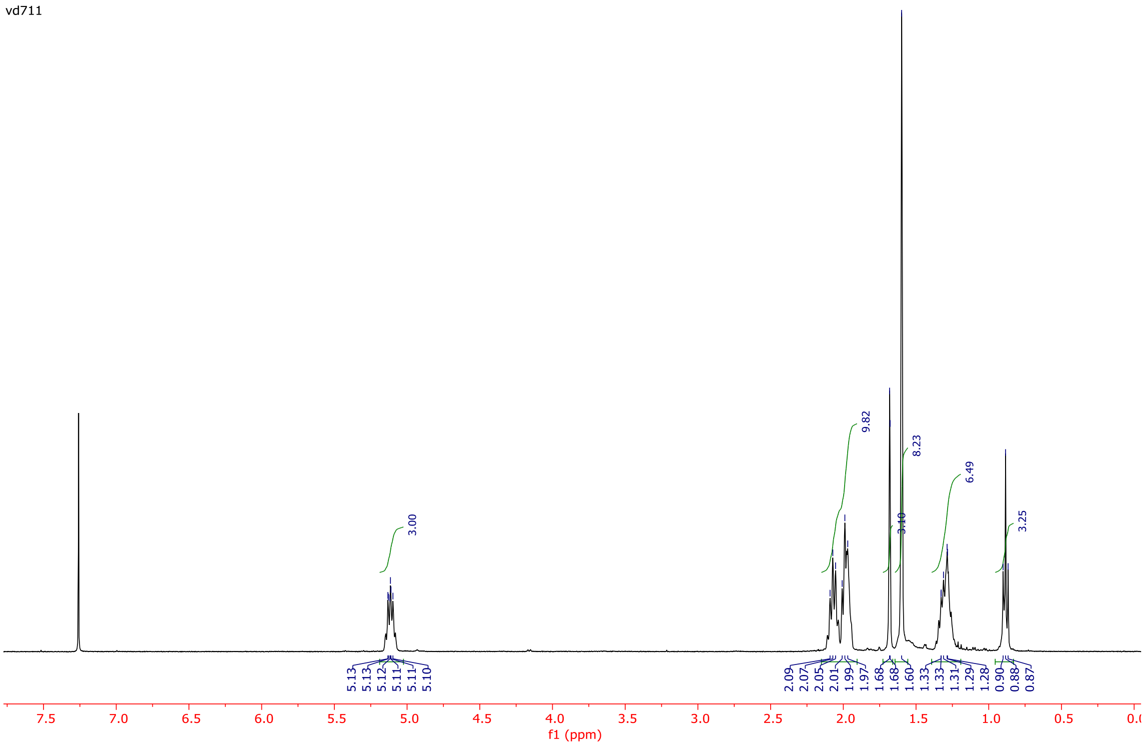
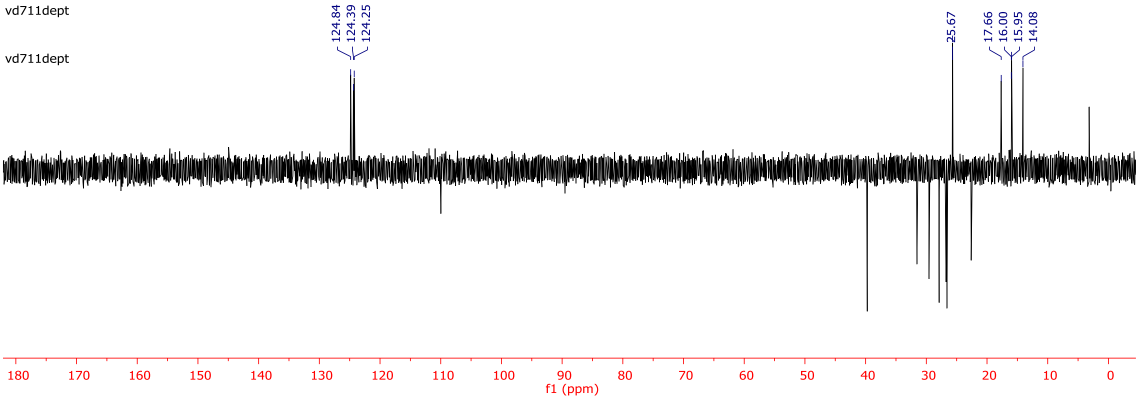
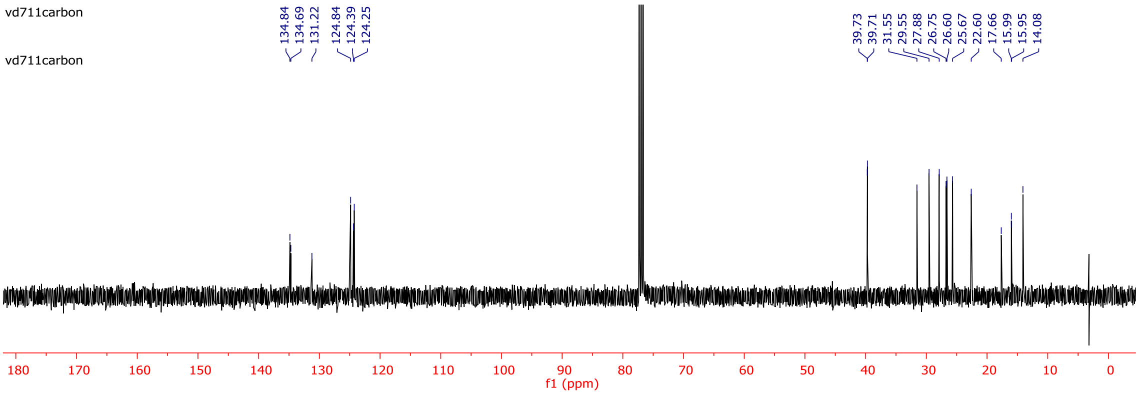
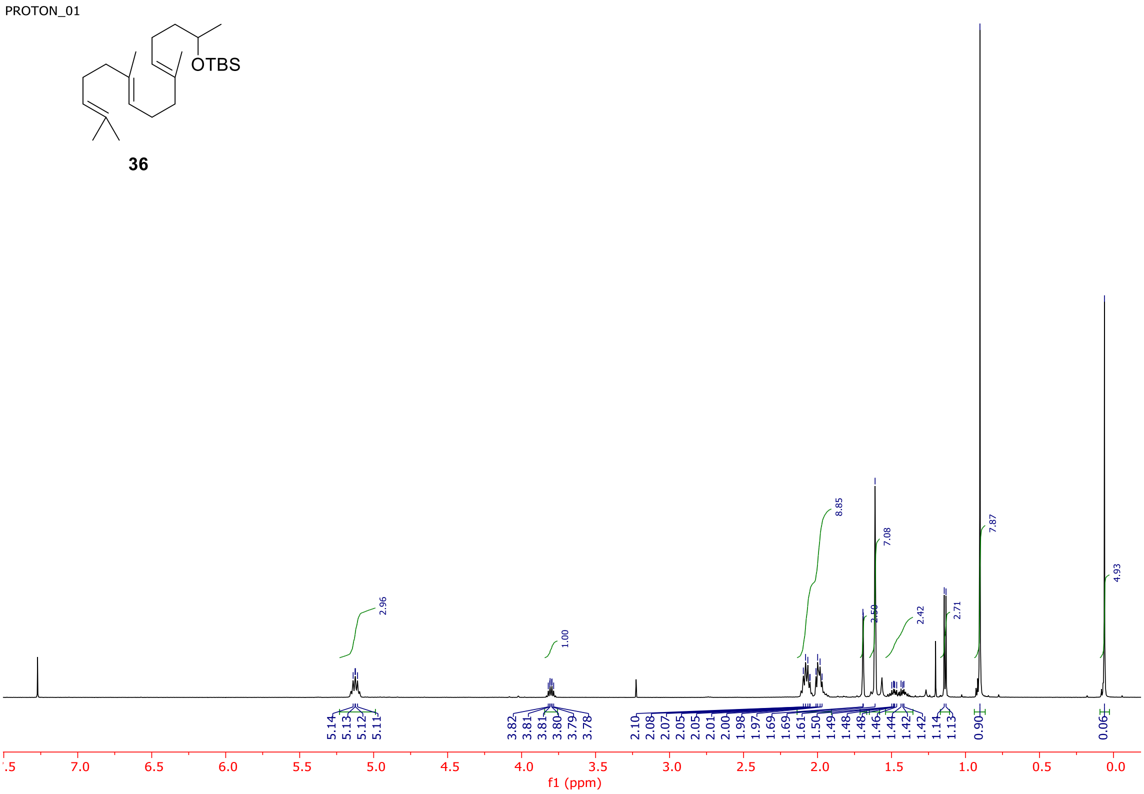
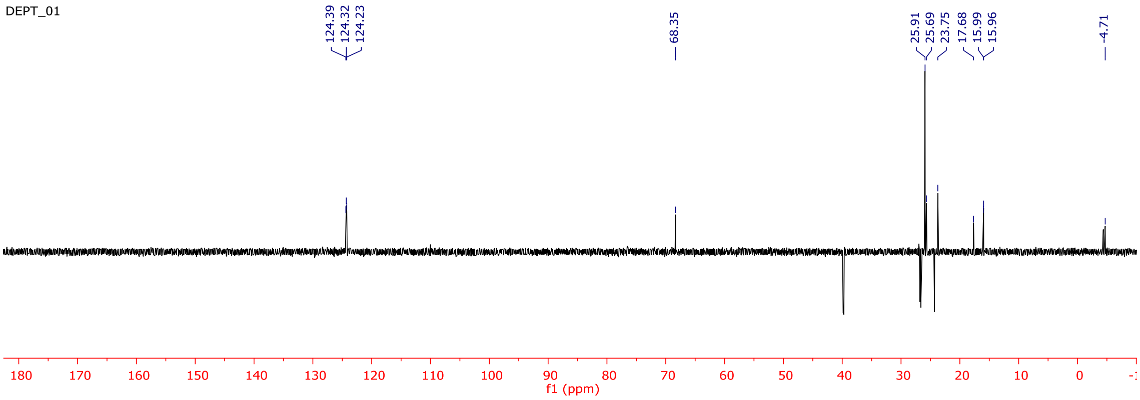
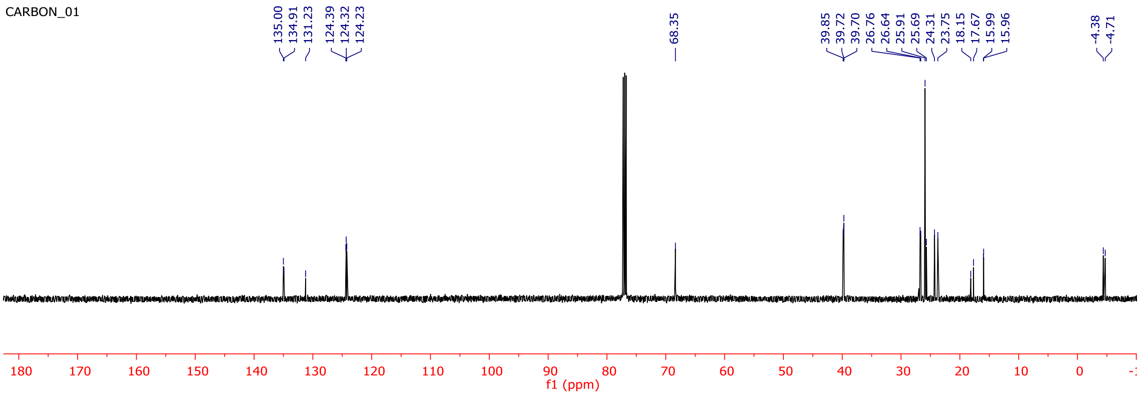

vd711
vd711
3.00
9.82
3.10
8.23
6.49
3.25
5.13
5.13
5.12
5.11
5.11
5.10
2.09
2.07
2.05
2.01
1.99
1.97
1.68
1.68
1.60
1.33
1.33
1.31
1.29
1.28
0.90
0.88
0.87
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

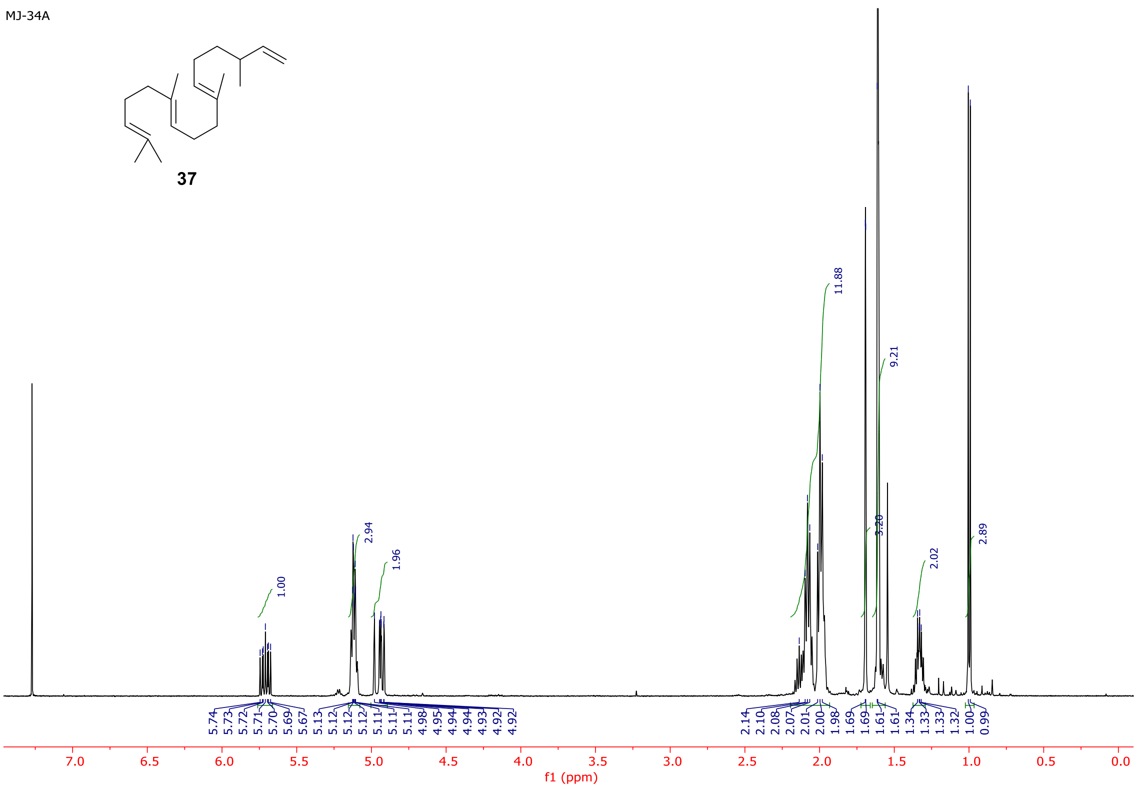

vd711dept
vd711dept
124.84
124.39
124.25
25.67
17.66
16.00
15.95
14.08
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

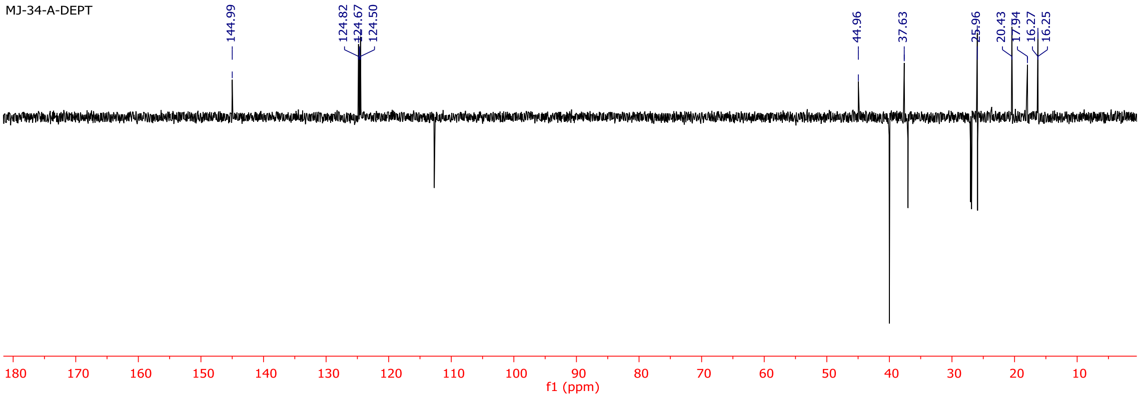

vd711carbon
vd711carbon
134.84
134.69
131.22
124.84
124.39
124.25
39.73
39.71
31.55
29.55
27.88
26.75
26.60
25.67
22.60
17.66
15.99
15.95
14.08
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

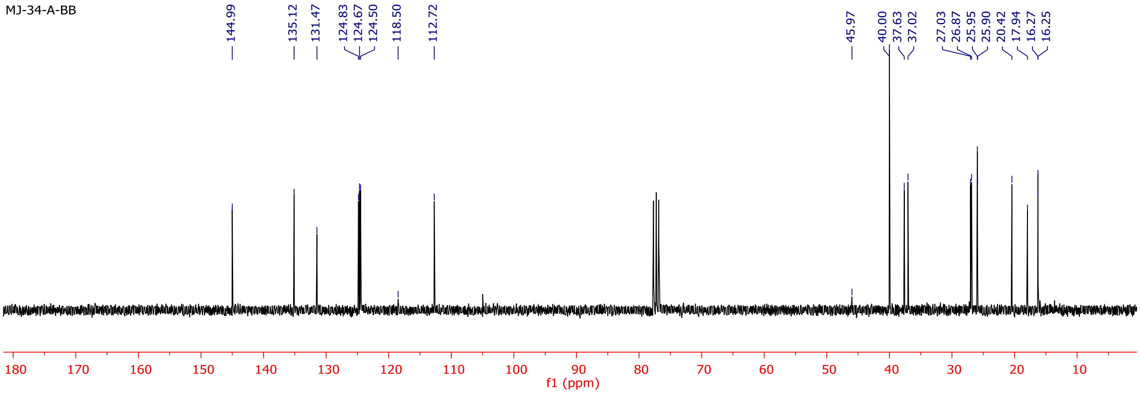

PROTON_01
OTBS
36
2.96
1.00
8.85
7.08
2.50
2.42
2.71
7.87
4.93
5.14
5.13
5.12
5.11
3.82
3.81
3.81
3.80
3.79
3.78
2.10
2.08
2.07
2.05
2.05
2.01
2.00
1.98
1.97
1.69
1.69
1.61
1.50
1.49
1.48
1.48
1.46
1.44
1.42
1.42
1.14
1.13
0.90
0.06
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

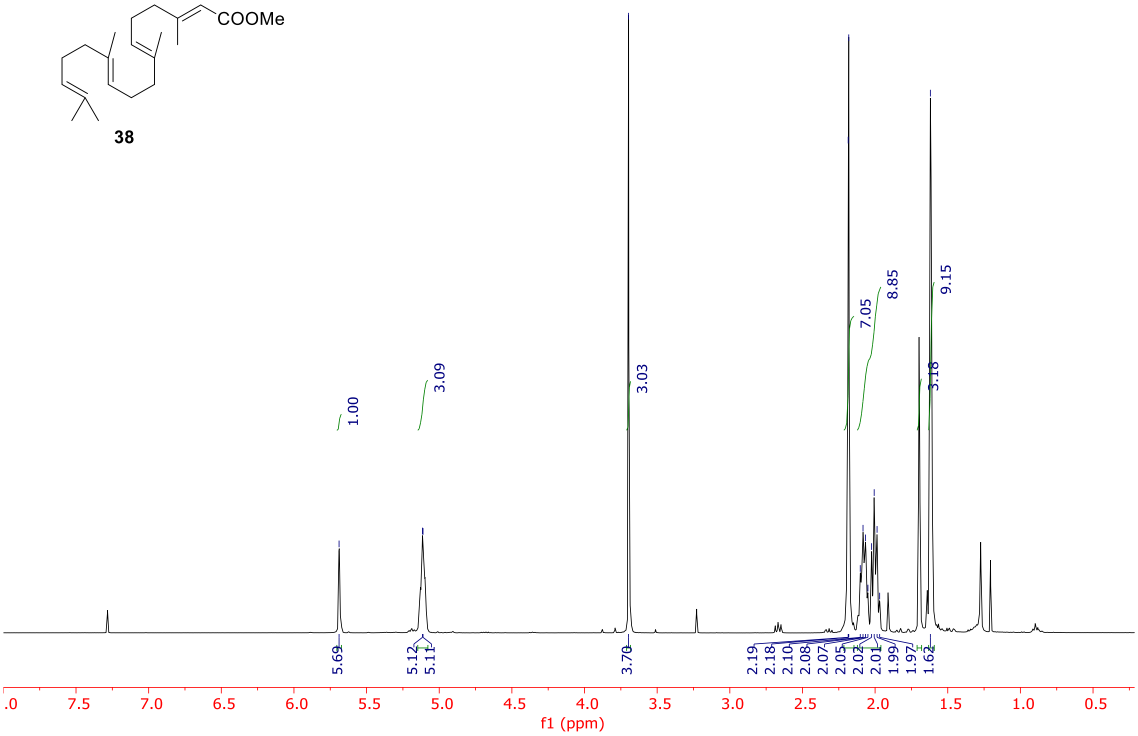

DEPT_01
124.39
124.32
124.23
68.35
25.91
25.69
23.75
17.68
15.99
15.96
-4.71
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

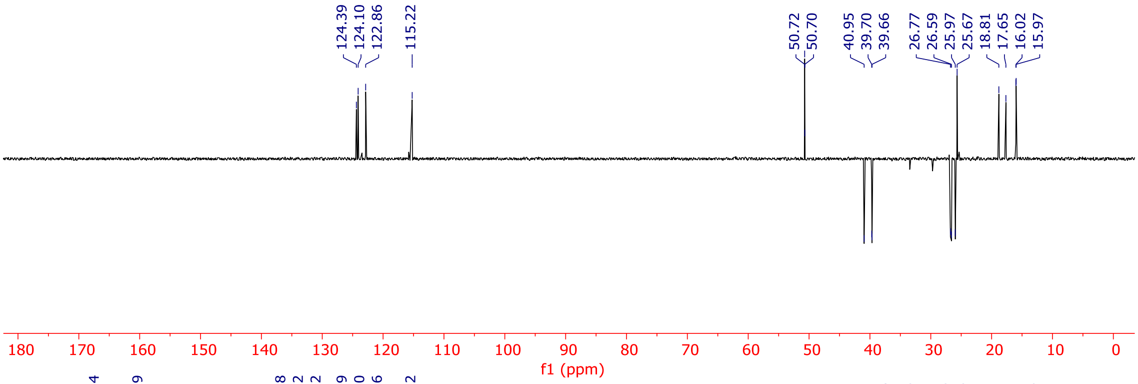

CARBON_01
135.00
134.91
131.23
124.39
124.32
124.23
68.35
39.85
39.72
39.70
26.76
26.64
25.91
25.69
24.31
23.75
18.15
17.67
15.99
15.96
-4.38
-4.71
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

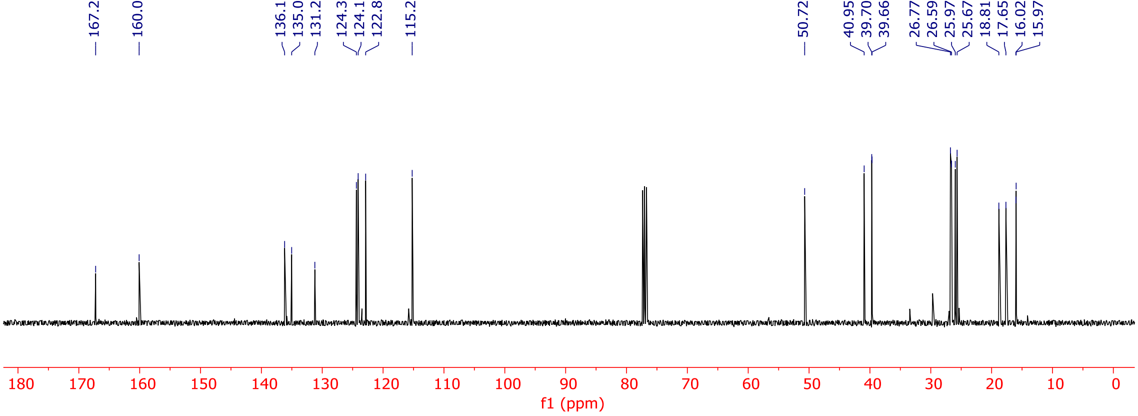

MJ-34A
37
1.00
2.94
1.96
11.88
9.21
3.20
2.02
2.89
5.74
5.73
5.72
5.71
5.70
5.69
5.67
5.13
5.12
5.12
5.12
5.11
5.11
5.11
4.98
4.95
4.94
4.94
4.93
4.92
4.92
2.14
2.10
2.08
2.07
2.01
2.00
1.98
1.69
1.69
1.61
1.61
1.34
1.33
1.33
1.32
1.00
0.99
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

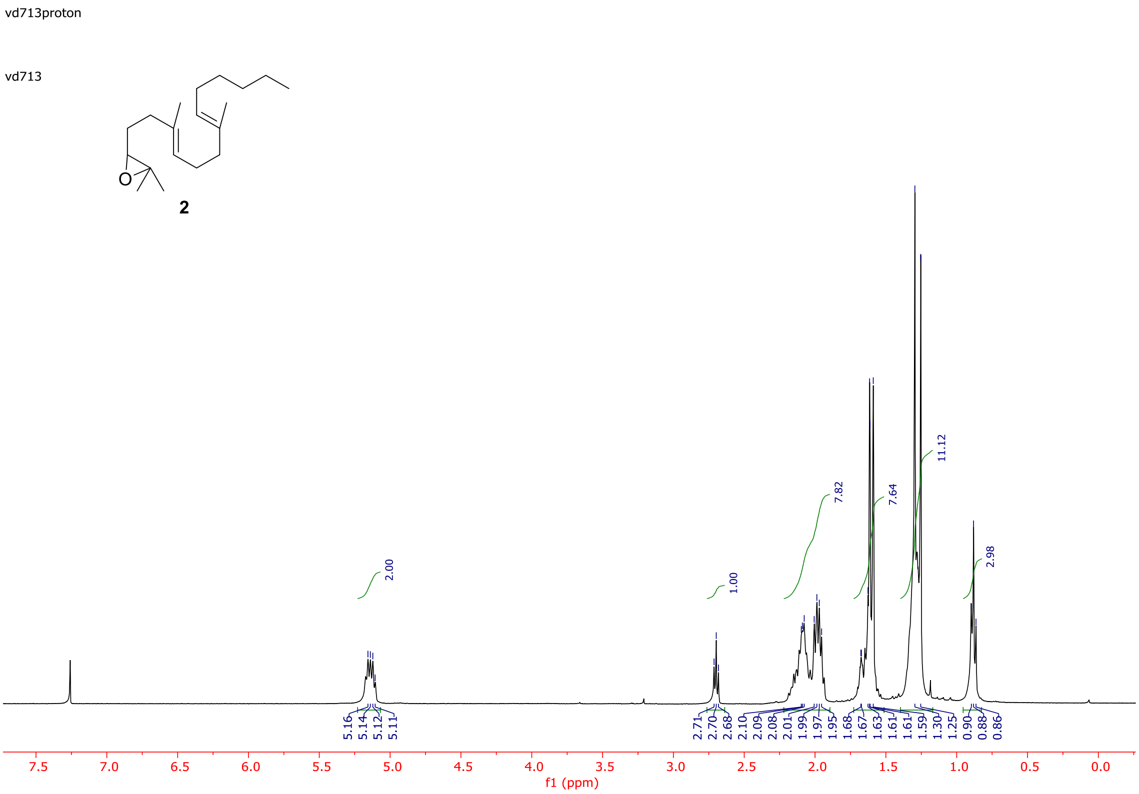

MJ-34-A-DEPT
144.99
124.82
124.67
124.50
44.96
37.63
25.96
20.43
17.94
16.27
16.25
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

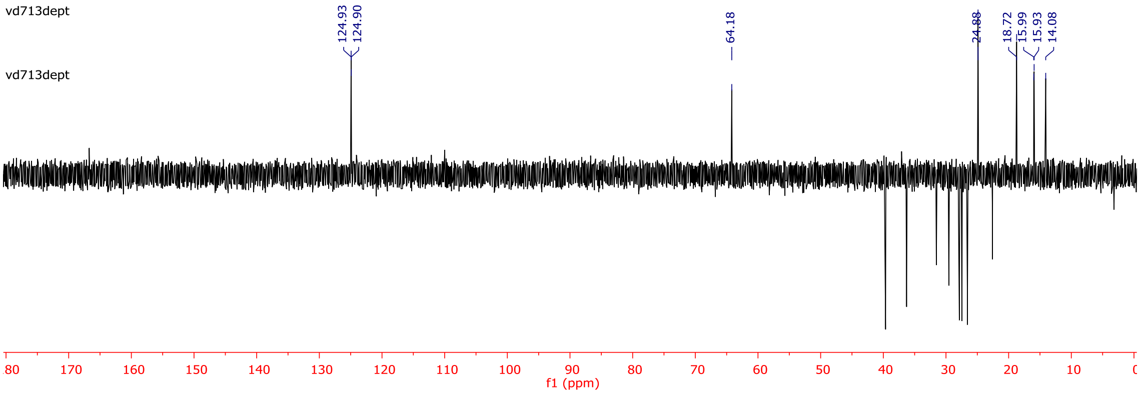

MJ-34-A-BB
144.99
135.12
131.47
124.83
124.67
124.50
118.50
112.72
45.97
40.00
37.63
37.02
27.03
26.87
25.95
25.90
20.42
17.94
16.27
16.25
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

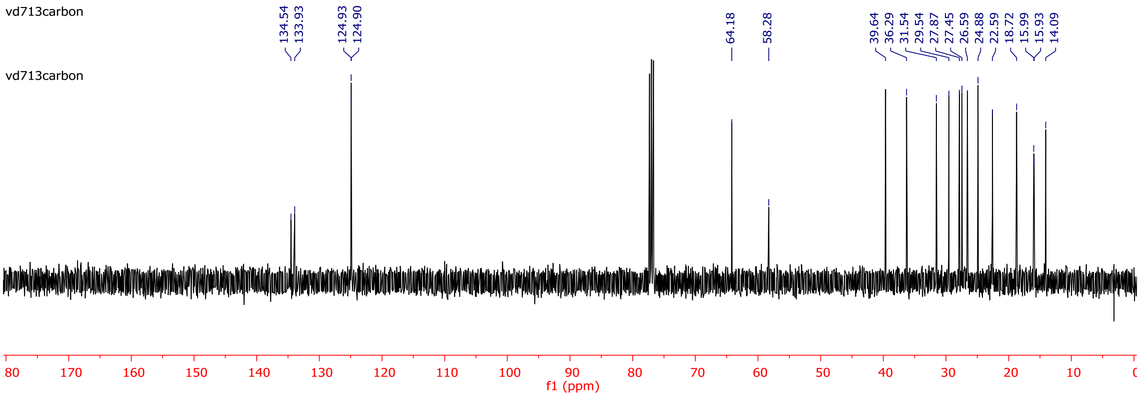

COOMe
38
1.00
3.09
3.03
7.05
8.85
3.18
9.15
5.69
5.12
5.11
3.70
2.19
2.18
2.10
2.08
2.07
2.05
2.02
2.01
1.99
1.97
1.62
.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

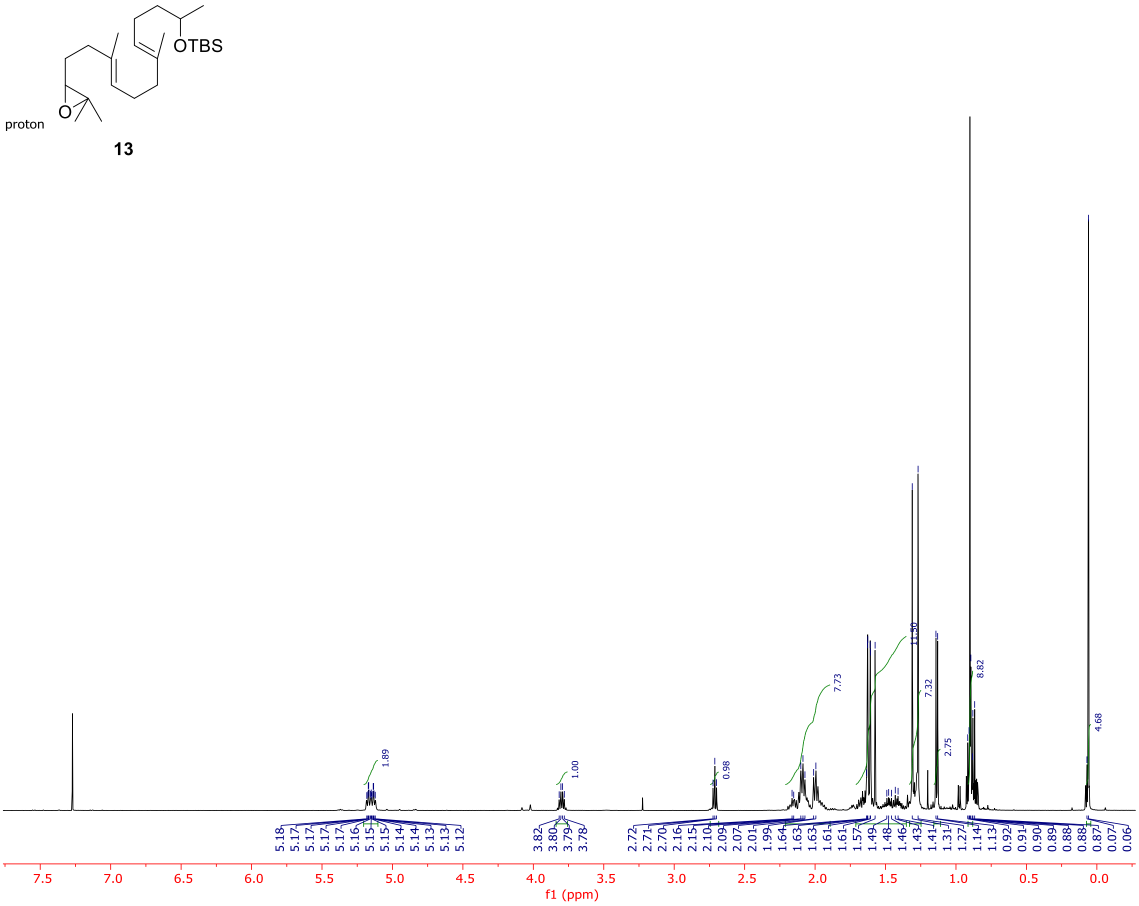

124.39
124.10
122.86
115.22
50.72
50.70
40.95
39.70
39.66
26.77
26.59
25.97
25.67
18.81
17.65
16.02
15.97
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

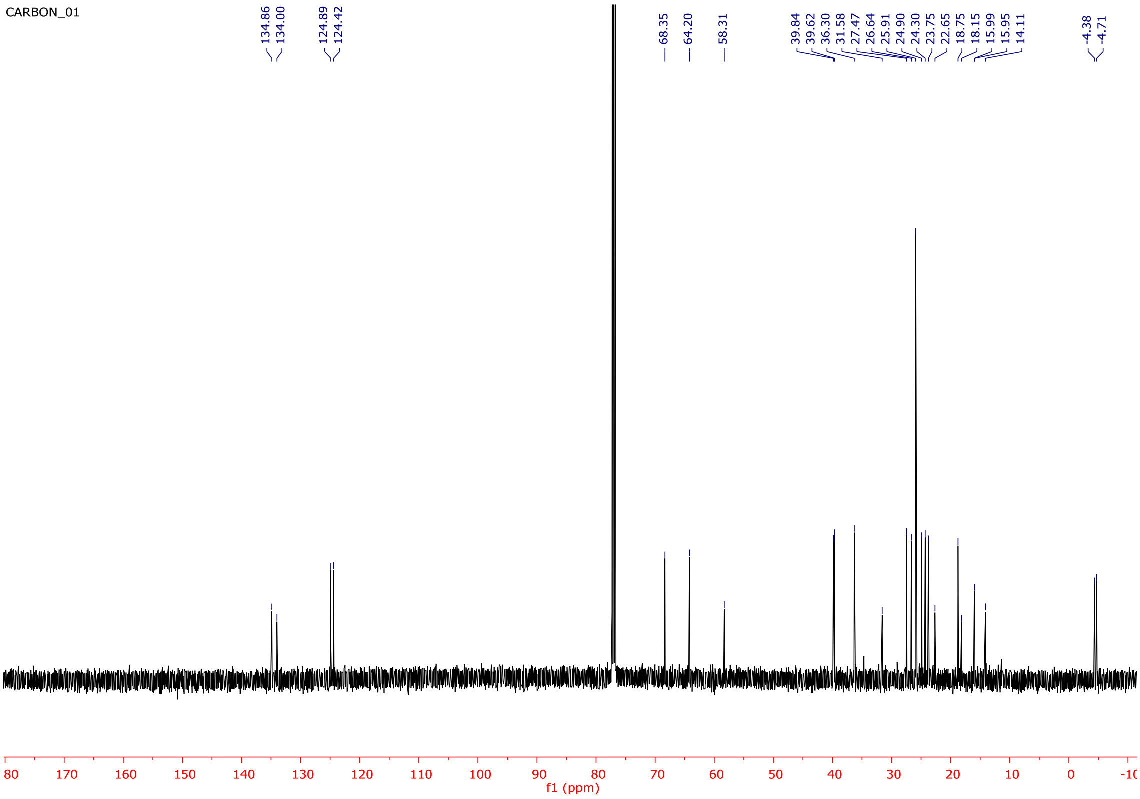

167.24
160.09
136.18
135.02
131.22
124.39
124.10
122.86
115.22
50.72
40.95
39.70
39.66
26.77
26.59
25.97
25.67
18.81
17.65
16.02
15.97
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


vd713proton
vd713
O
2
2.00
1.00
7.82
7.64
11.12
2.98
5.16 5.14 5.12 5.11
2.71 2.70 2.68 2.10 2.09 2.08 2.01 1.99 1.97 1.95 1.68 1.67 1.63 1.61 1.61 1.59 1.30 1.25 0.90 0.88 0.86
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

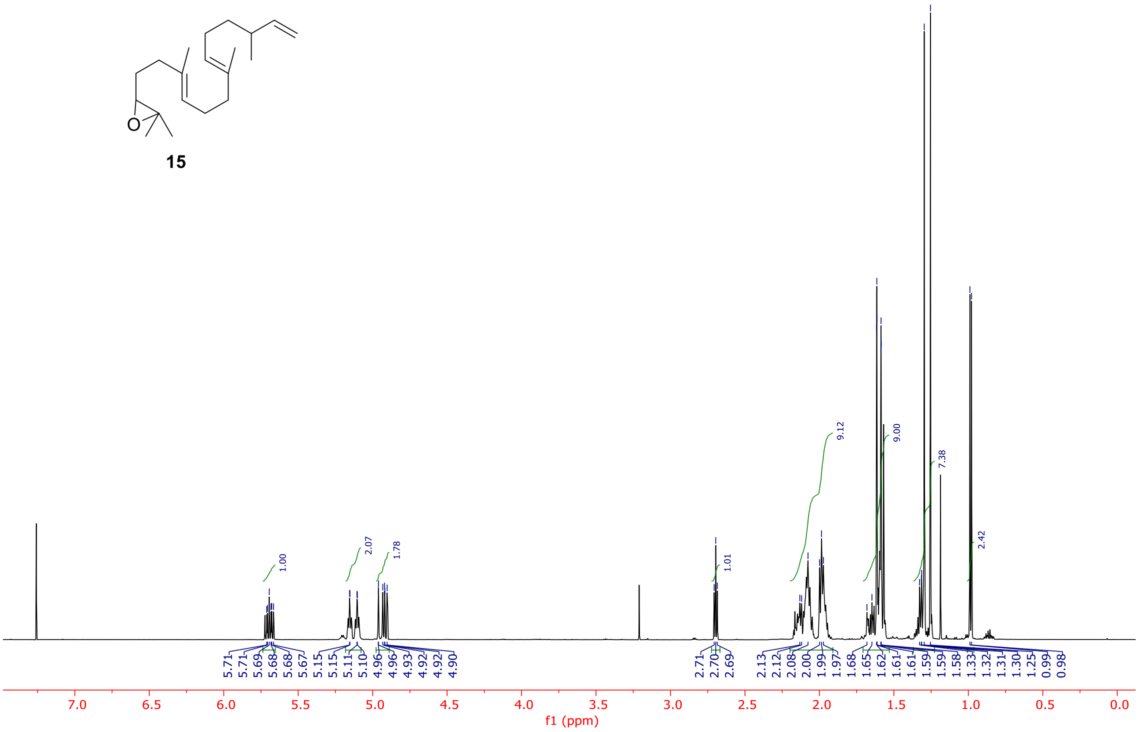

vd713dept
vd713dept
124.93 124.90
64.18
24.88
18.72 15.99 15.93 14.08
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


vd713carbon
vd713carbon
134.54 133.93
124.93 124.90
64.18
58.28
39.64 36.29 31.54 29.54 27.87 27.45 26.59 24.88 22.59 18.72 15.99 15.93 14.09
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

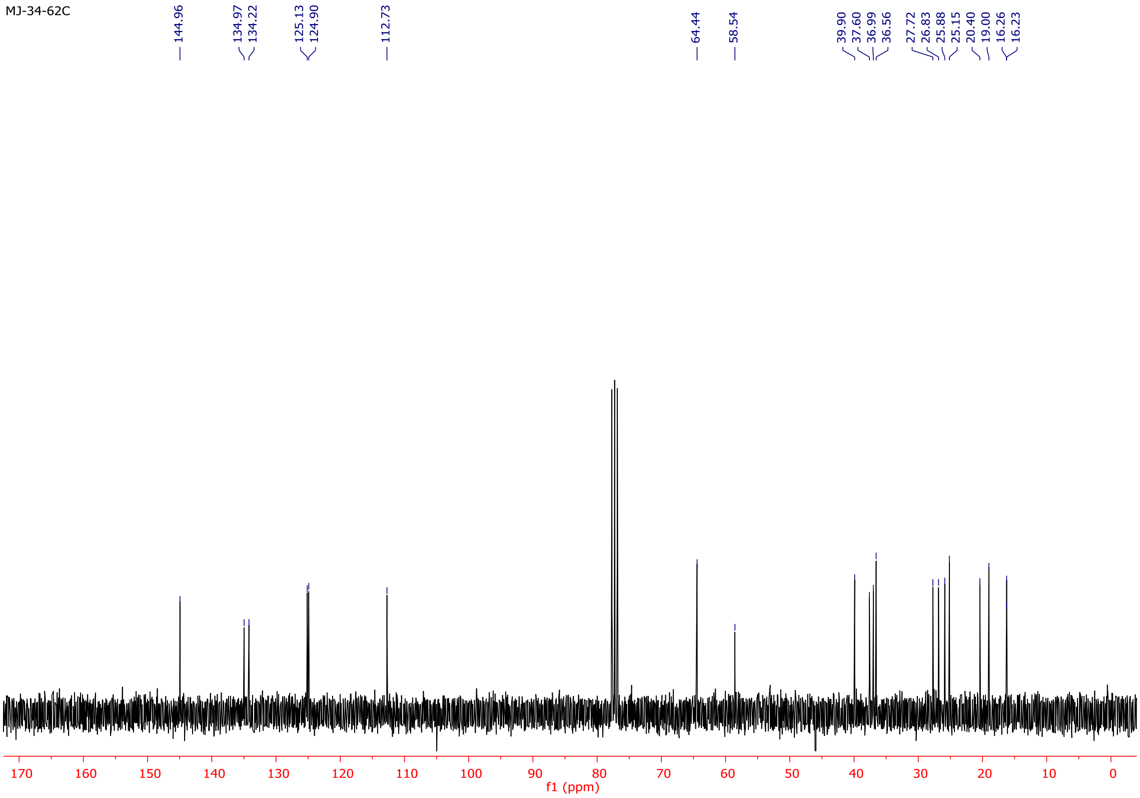

OTBS
O
proton
13
1.89
1.00
0.98
7.73
11.30
7.32
2.75
8.82
4.68
5.18
5.17
5.17
5.17
5.16
5.15
5.15
5.14
5.14
5.13
5.13
5.12
3.82
3.80
3.79
3.78
2.72
2.71
2.70
2.16
2.15
2.10
2.09
2.07
2.01
1.99
1.64
1.63
1.63
1.61
1.61
1.57
1.49
1.48
1.46
1.43
1.41
1.31
1.27
1.14
1.13
0.92
0.91
0.90
0.89
0.88
0.88
0.87
0.07
0.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CARBON_01
134.86
134.00
124.89
124.42
68.35
64.20
58.31
39.84
39.62
36.30
31.58
27.47
26.64
25.91
24.90
24.30
23.75
22.65
18.75
18.15
15.99
15.95
14.11
-4.38
-4.71
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

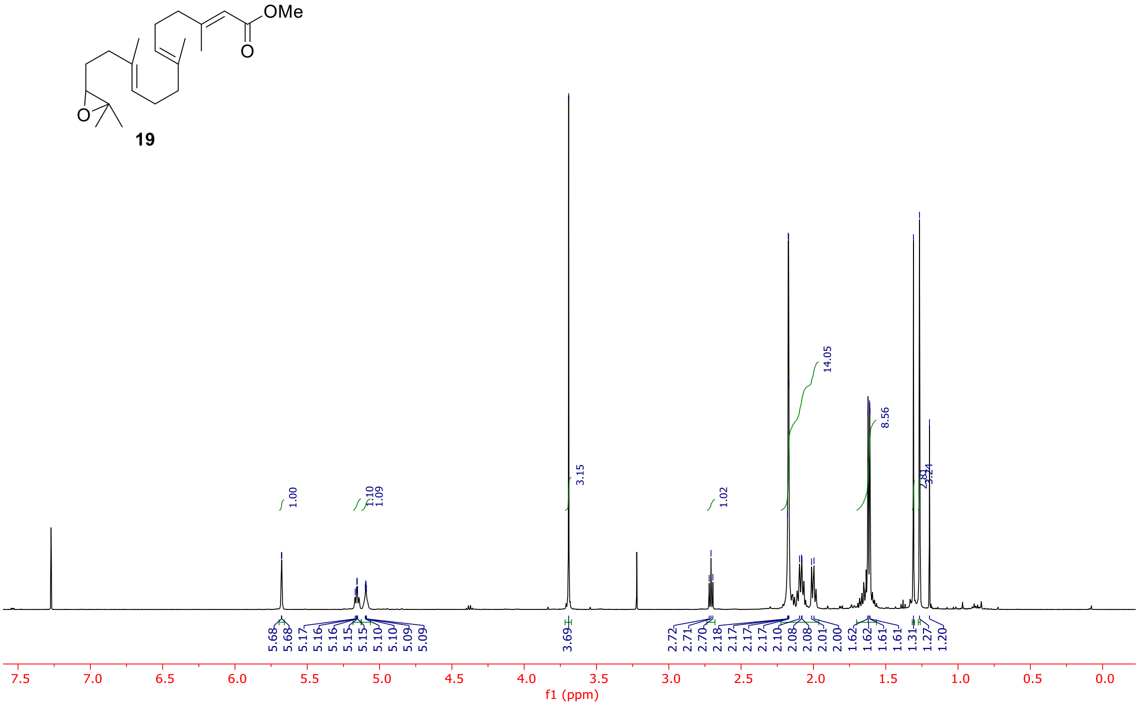
proton
13-25740_FJL-507



MJ-34-62C



PROTON_01



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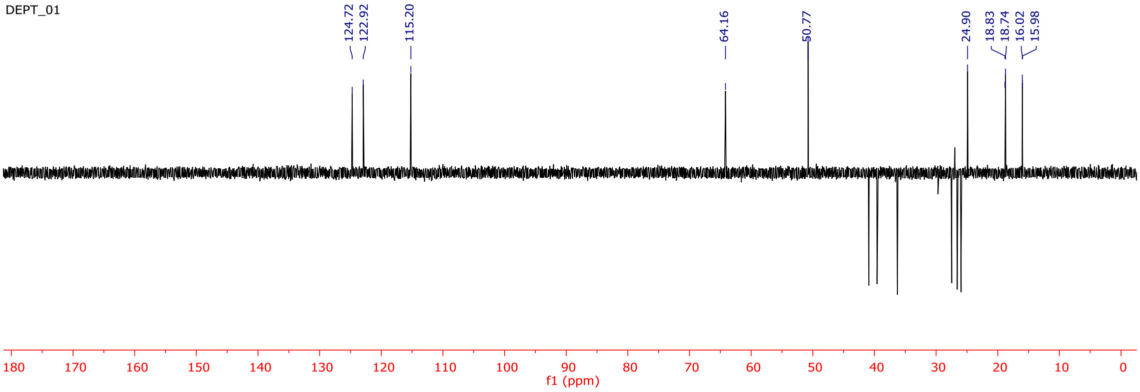
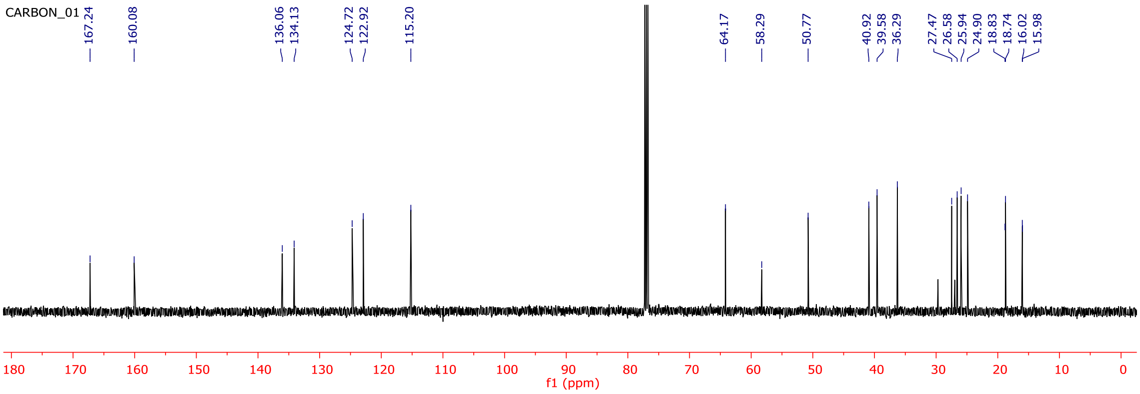
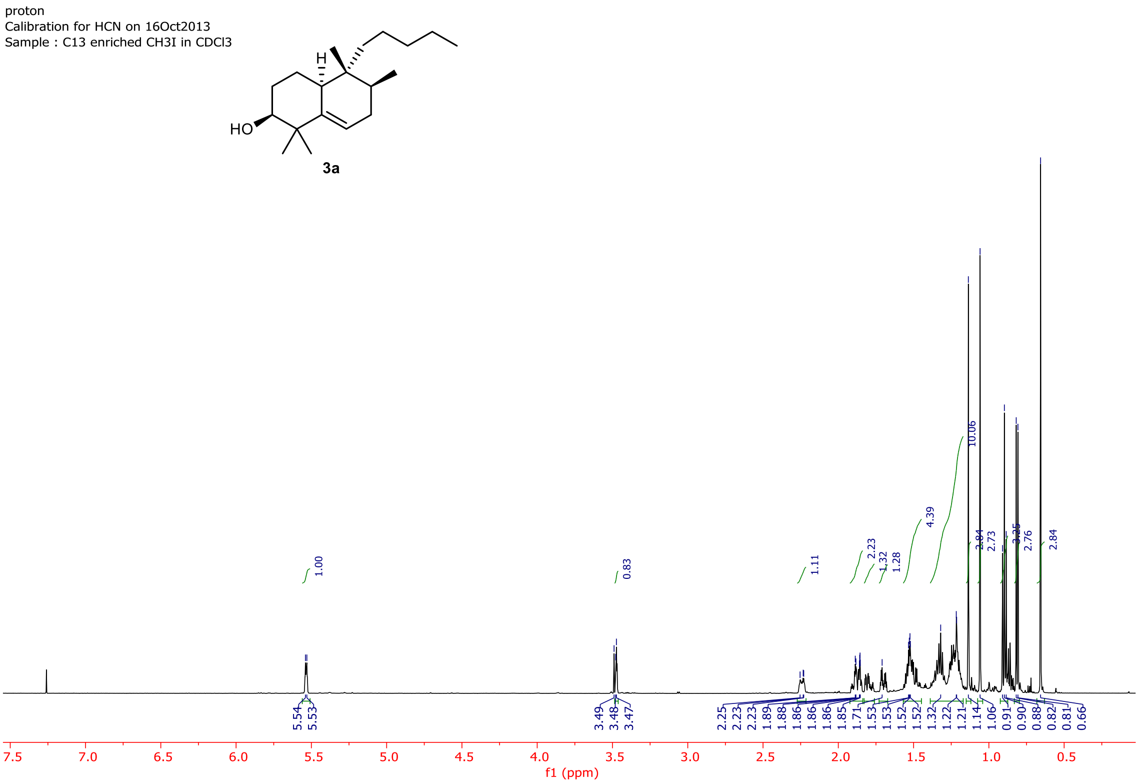
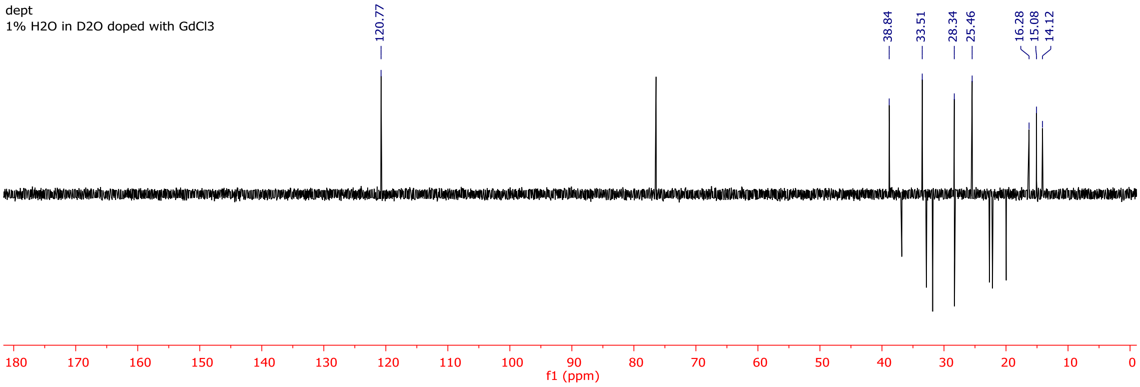
DEPT_01

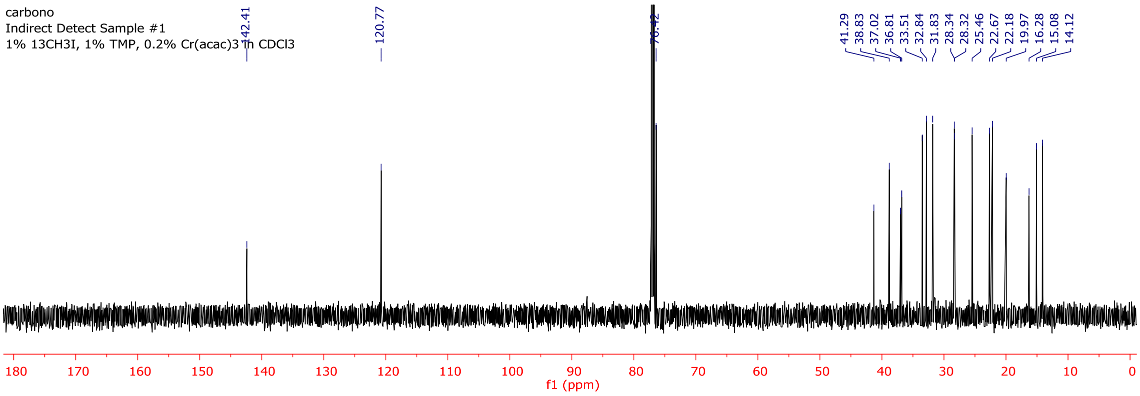


CARBON_01

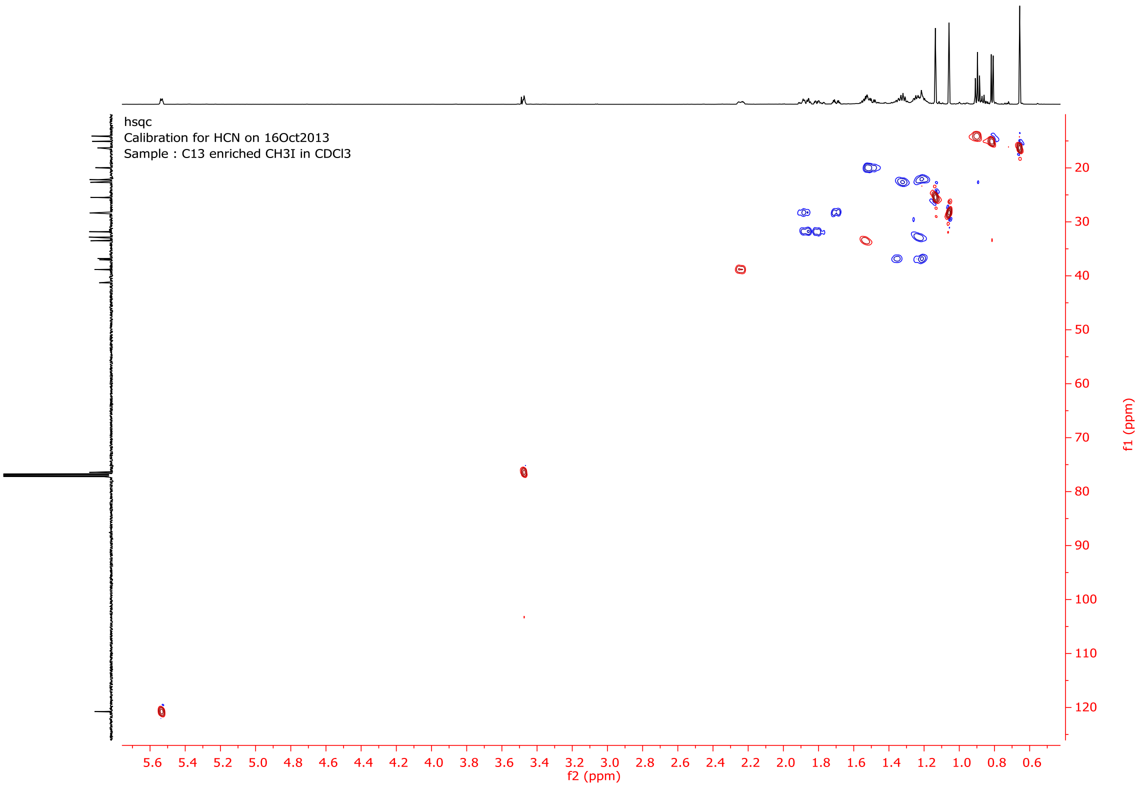


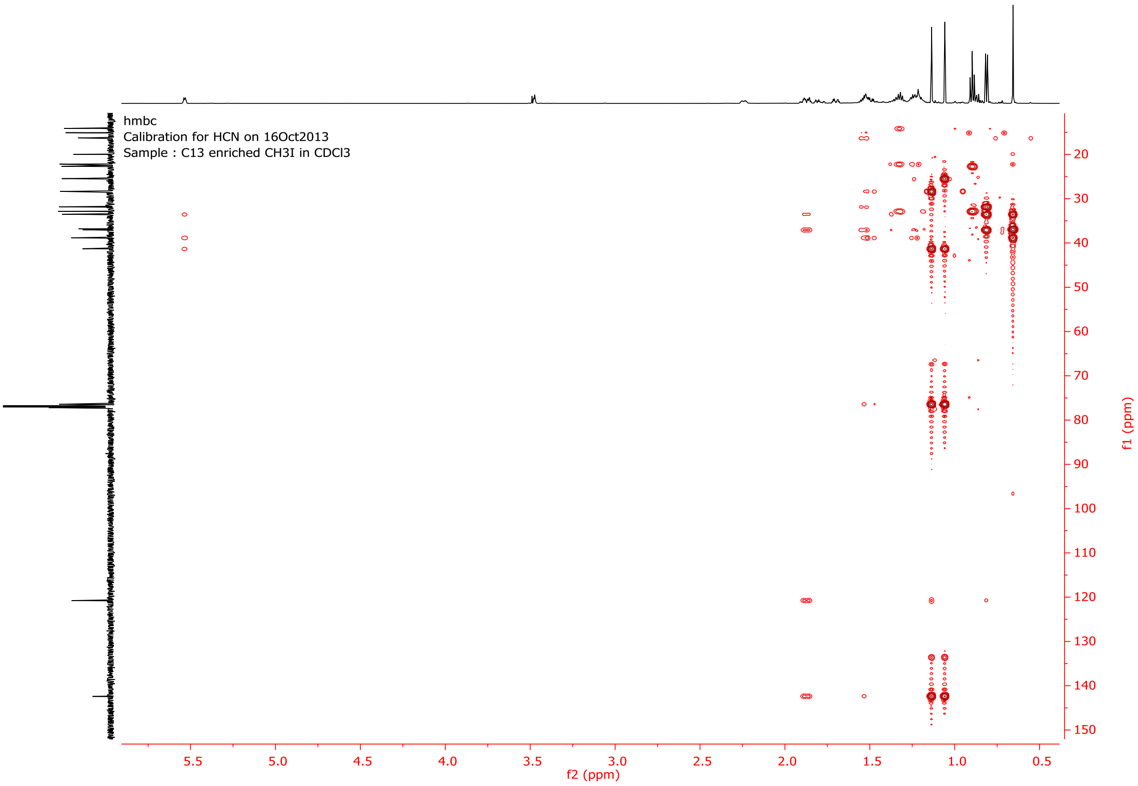

proton
Calibration for HCN on 16Oct2013
Sample : C13 enriched CH3I in CDCl3
H
HO
3a
1.00
0.83
1.11
2.23
1.32
1.28
4.39
10.06
2.84
2.73
3.25
2.76
2.84
5.54
5.53
3.49
3.48
3.47
2.25
2.23
2.23
1.89
1.88
1.86
1.86
1.86
1.85
1.71
1.53
1.53
1.52
1.52
1.32
1.22
1.21
1.14
1.06
0.91
0.90
0.88
0.82
0.81
0.66
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

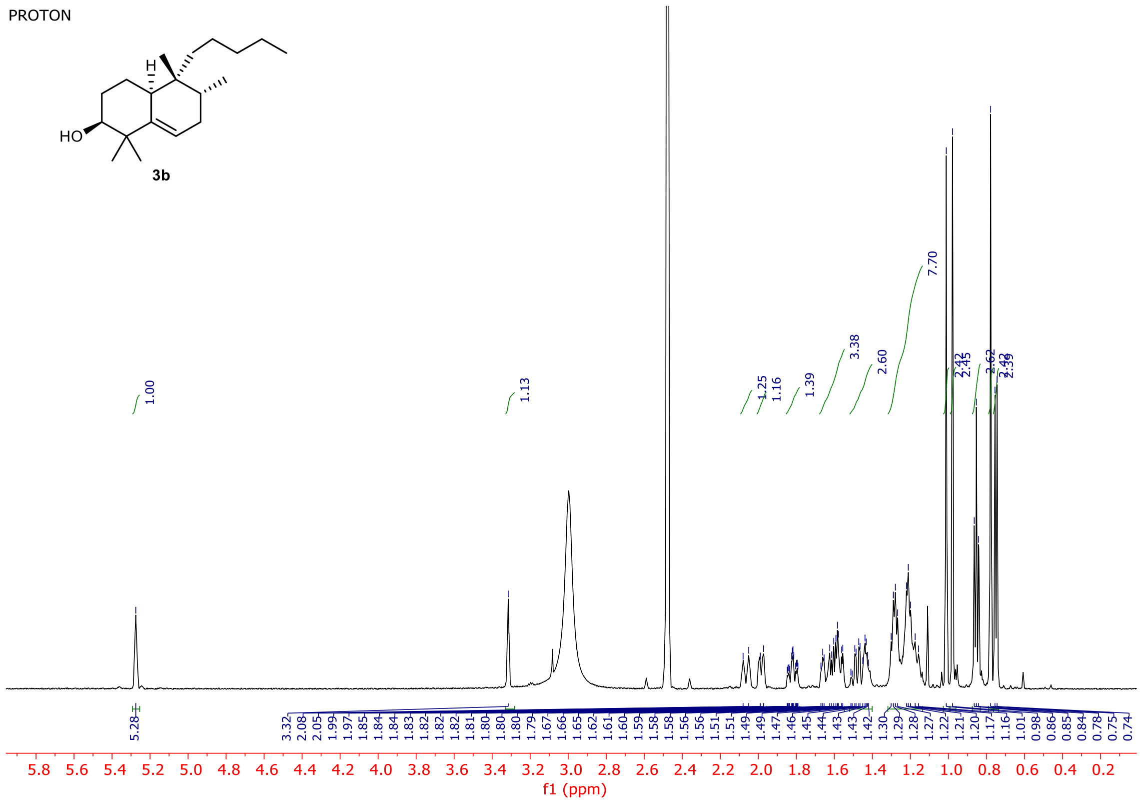

dept
1% H2O in D2O doped with GdCl3
120.77
38.84
33.51
28.34
25.46
16.28
15.08
14.12
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

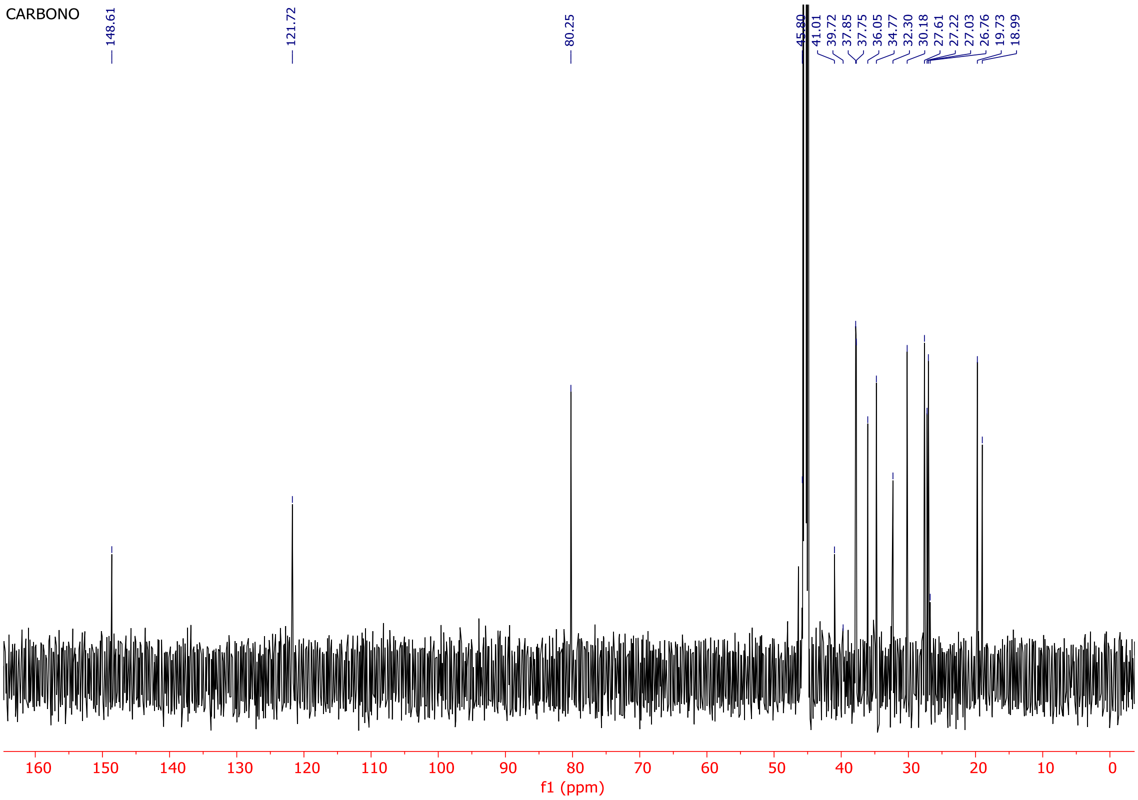

carbono
Indirect Detect Sample #1
1% 13CH3I, 1% TMP, 0.2% Cr(acac)3 in CDCl3
142.41
120.77
76.42
41.29
38.83
37.02
36.81
33.51
32.84
31.83
28.34
28.32
25.46
22.67
22.18
19.97
16.28
15.08
14.12
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

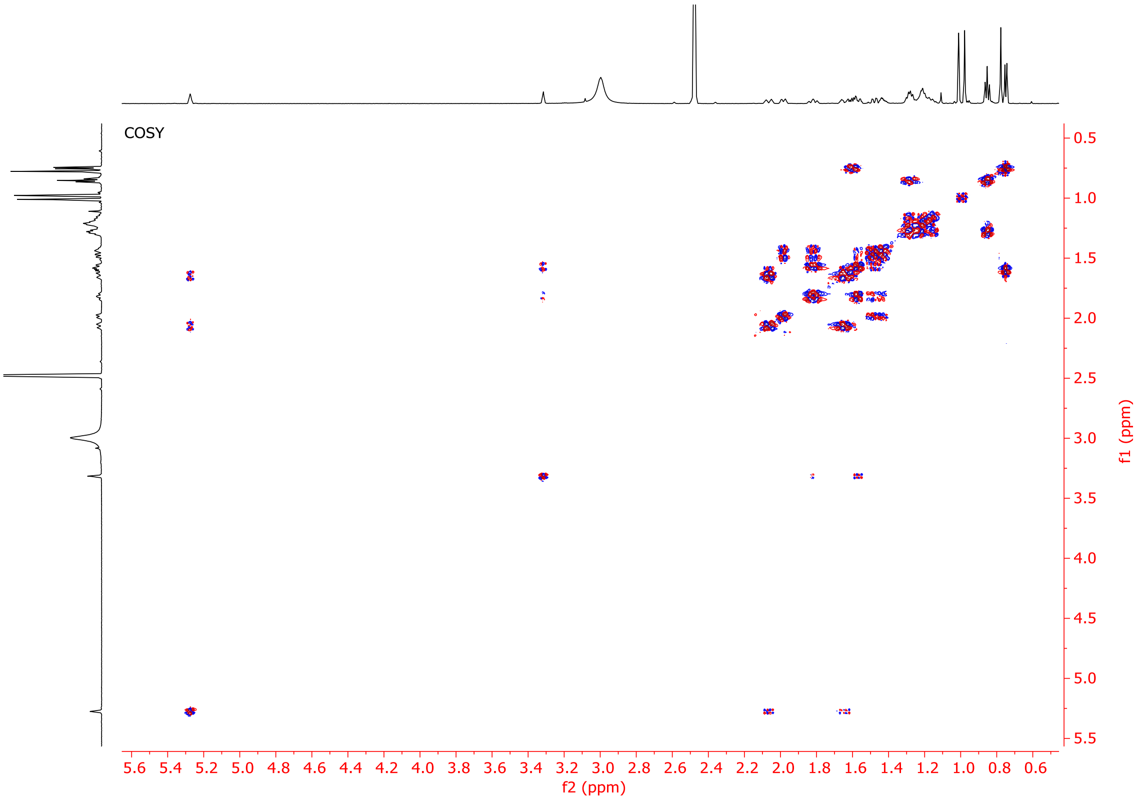

cosydqf
Calibration for HCN on 16Oct2013
Sample : C13 enriched CH3I in CDCl3
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f2 (ppm)
0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
f1 (ppm)

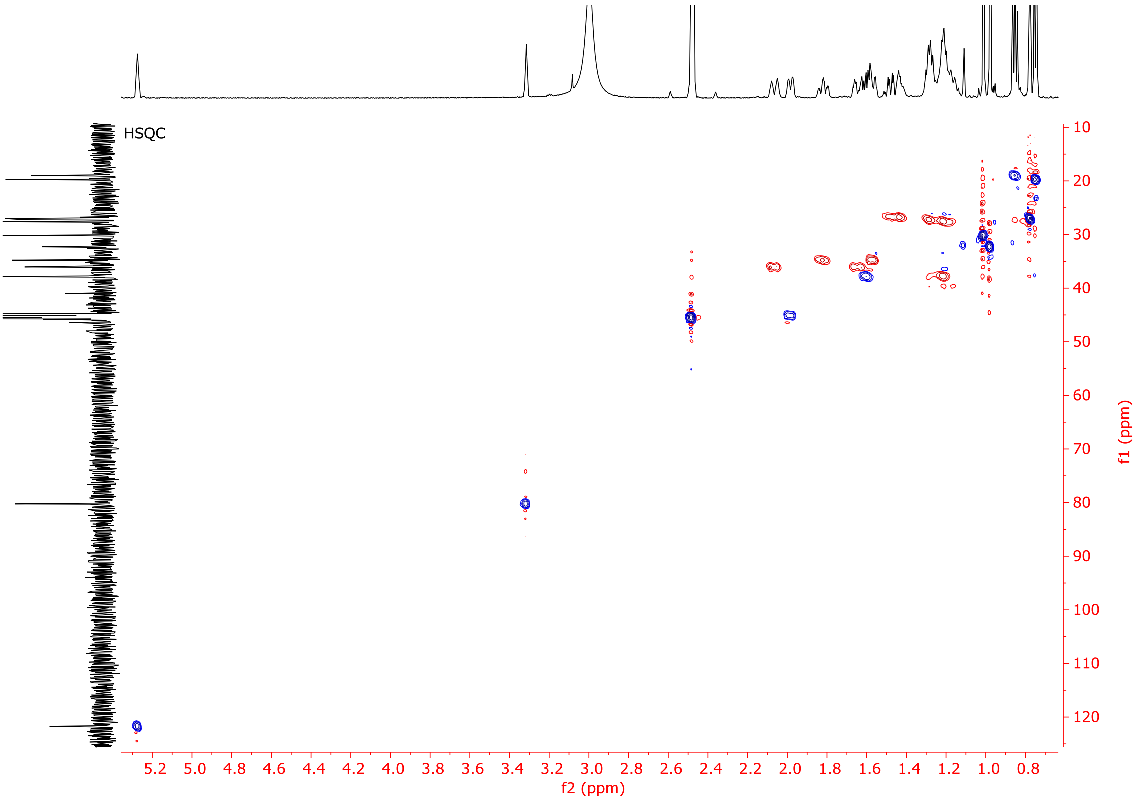

hsqc
Calibration for HCN on 16Oct2013
Sample : C13 enriched CH3I in CDCl3
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f2 (ppm)
20 30 40 50 60 70 80 90 100 110 120
f1 (ppm)

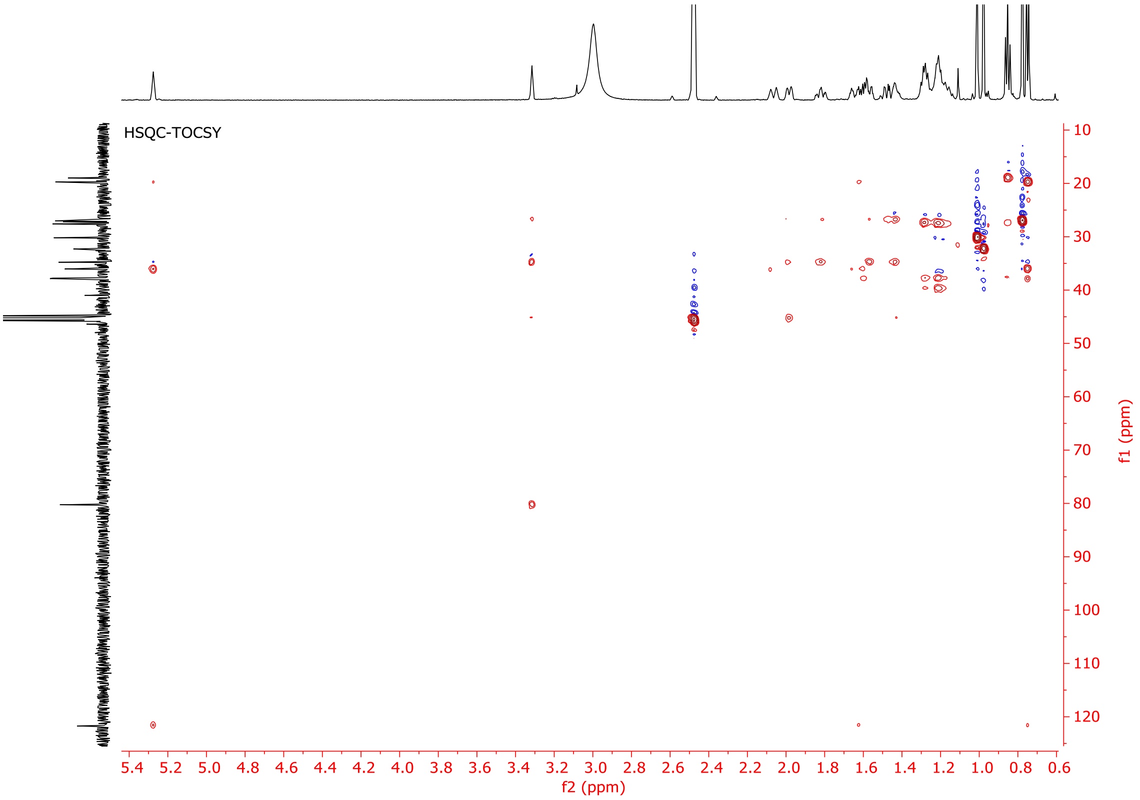

hmbc
Calibration for HCN on 16Oct2013
Sample : C13 enriched CH3I in CDCl3
f2 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150

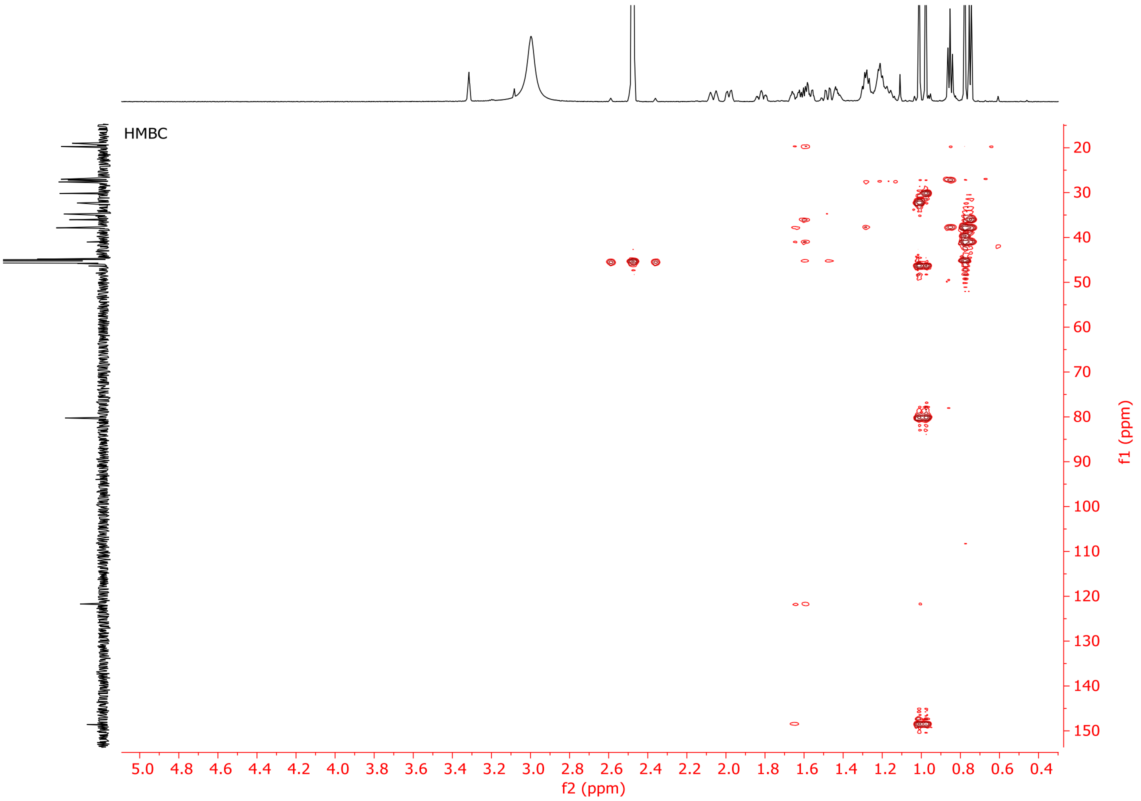

PROTON
H
HO
3b
1.00
1.13
1.25
1.16
1.39
3.38
2.60
7.70
2.42
2.45
2.62
2.42
2.39
5.28
3.32
2.08
2.05
1.99
1.97
1.85
1.84
1.83
1.82
1.82
1.81
1.80
1.80
1.79
1.67
1.66
1.65
1.62
1.61
1.60
1.59
1.58
1.58
1.56
1.56
1.51
1.51
1.49
1.49
1.47
1.46
1.45
1.44
1.43
1.43
1.42
1.30
1.29
1.28
1.27
1.22
1.21
1.20
1.17
1.16
1.01
0.98
0.86
0.85
0.84
0.78
0.75
0.74
f1 (ppm)
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2


CARBONO
148.61
121.72
80.25
45.80
41.01
39.72
37.85
37.75
36.05
34.77
32.30
30.18
27.61
27.22
27.03
26.76
19.73
18.99
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

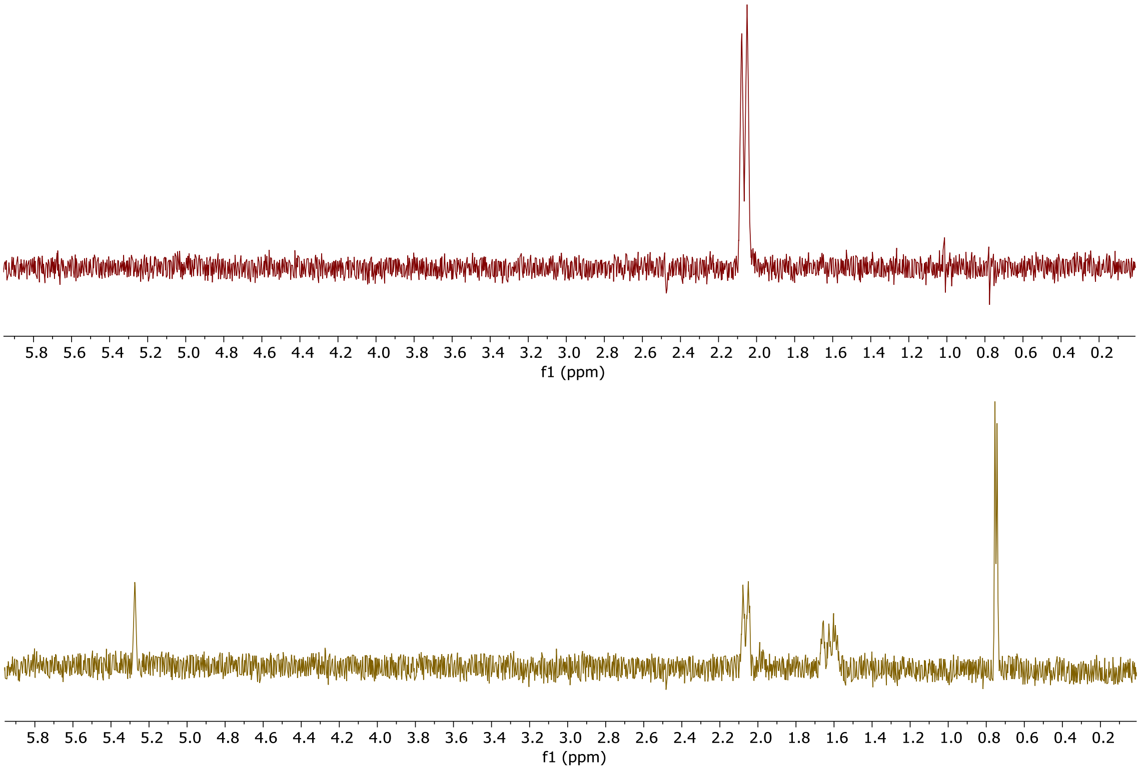

COSY
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
f1 (ppm)
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
f2 (ppm)


HSQC
f2 (ppm)
f1 (ppm)
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
10
20
30
40
50
60
70
80
90
100
110
120

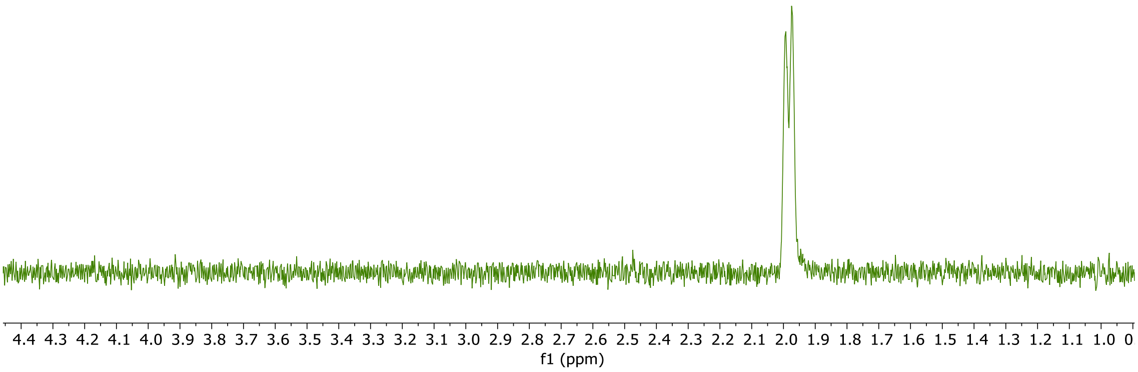

HSQC-TOCSY
f2 (ppm)
f1 (ppm)
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
10
20
30
40
50
60
70
80
90
100
110
120

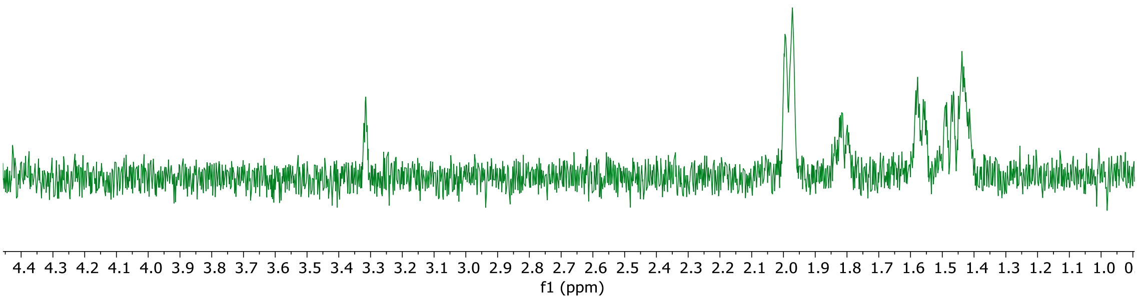

HMBC
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
f2 (ppm)

TOCSY

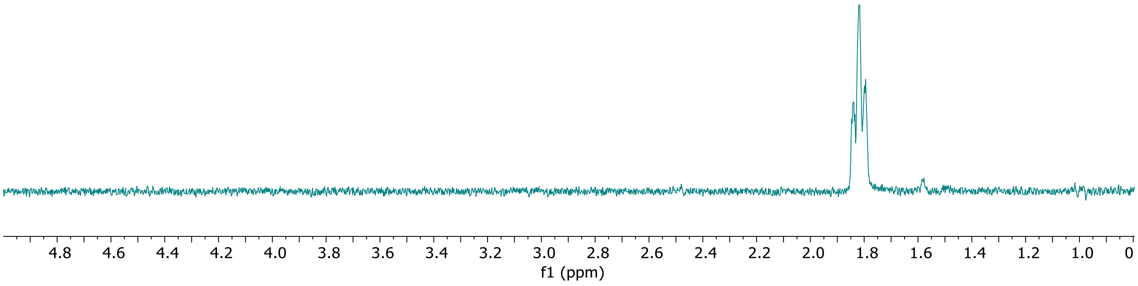

5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
f1 (ppm)
5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2
f1 (ppm)

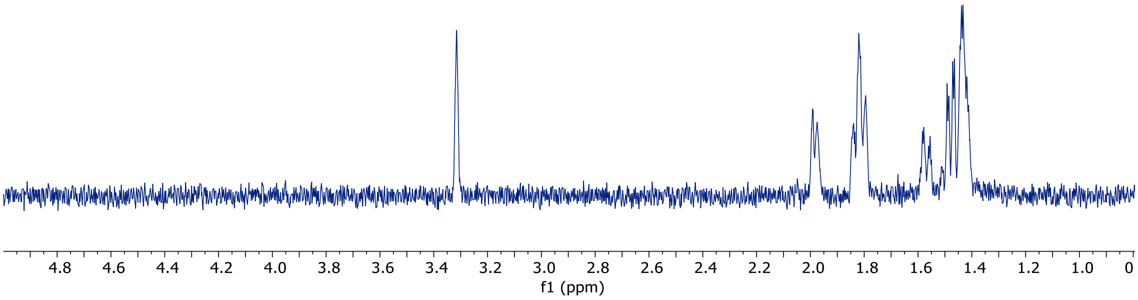
TOCSY


4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0
f1 (ppm)

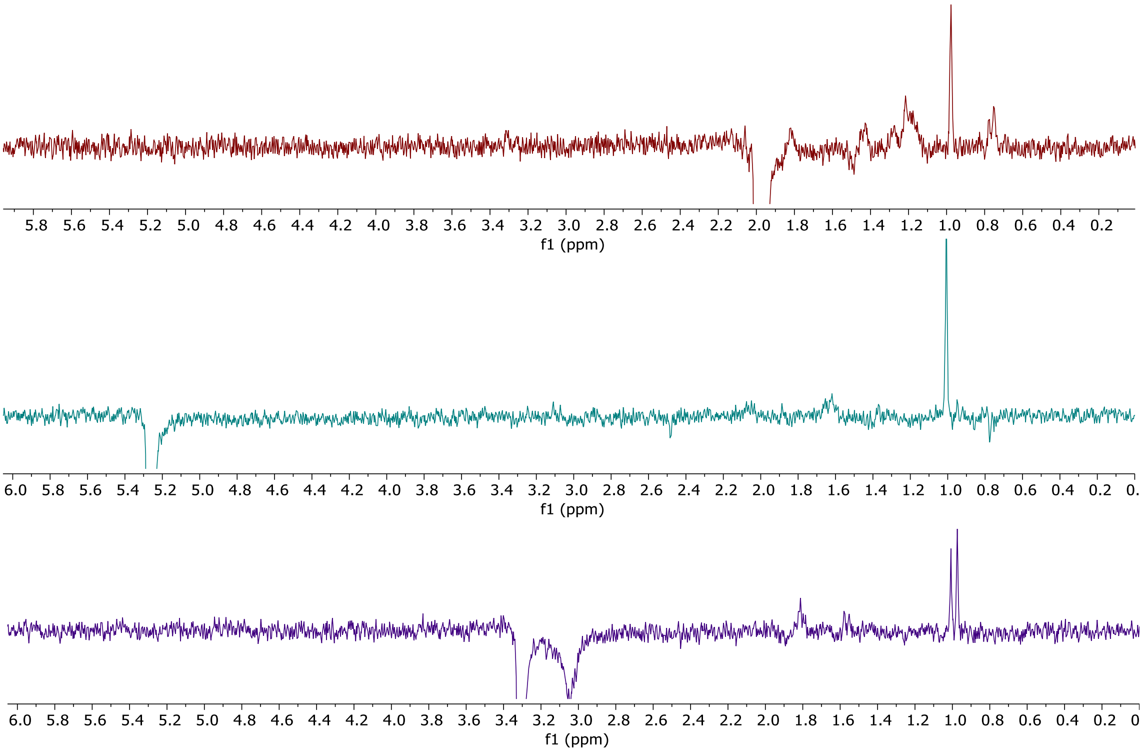

4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0
f1 (ppm)

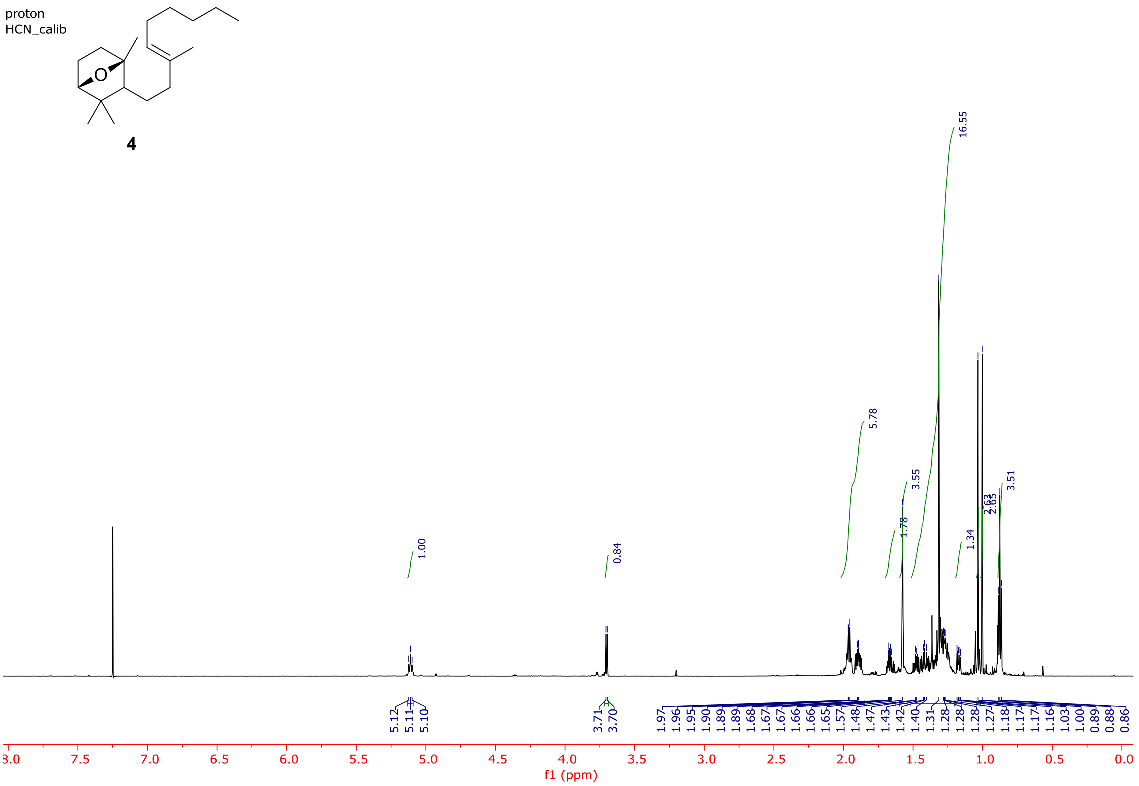
TOCSY

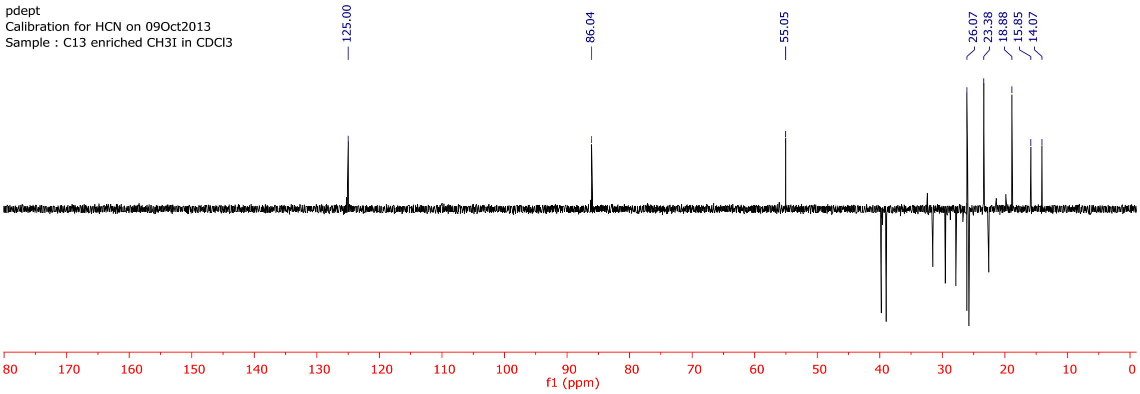

4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0
f1 (ppm)

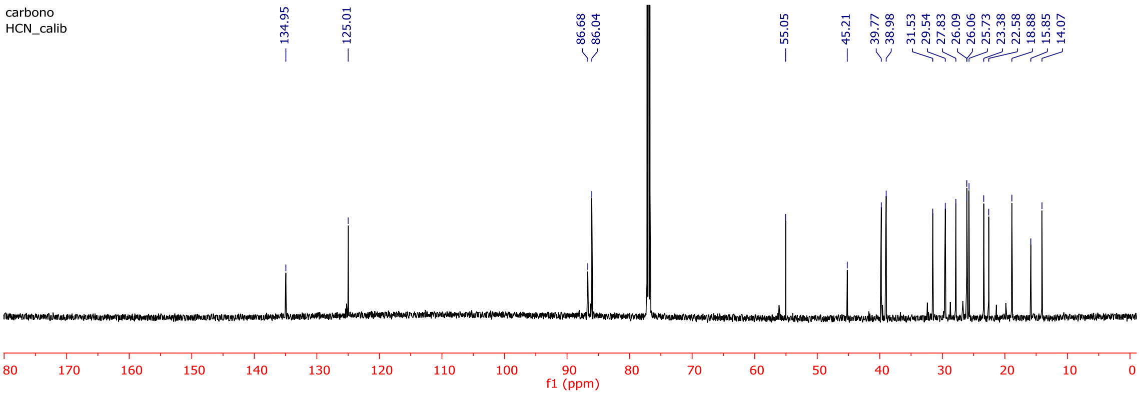

4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0
f1 (ppm)

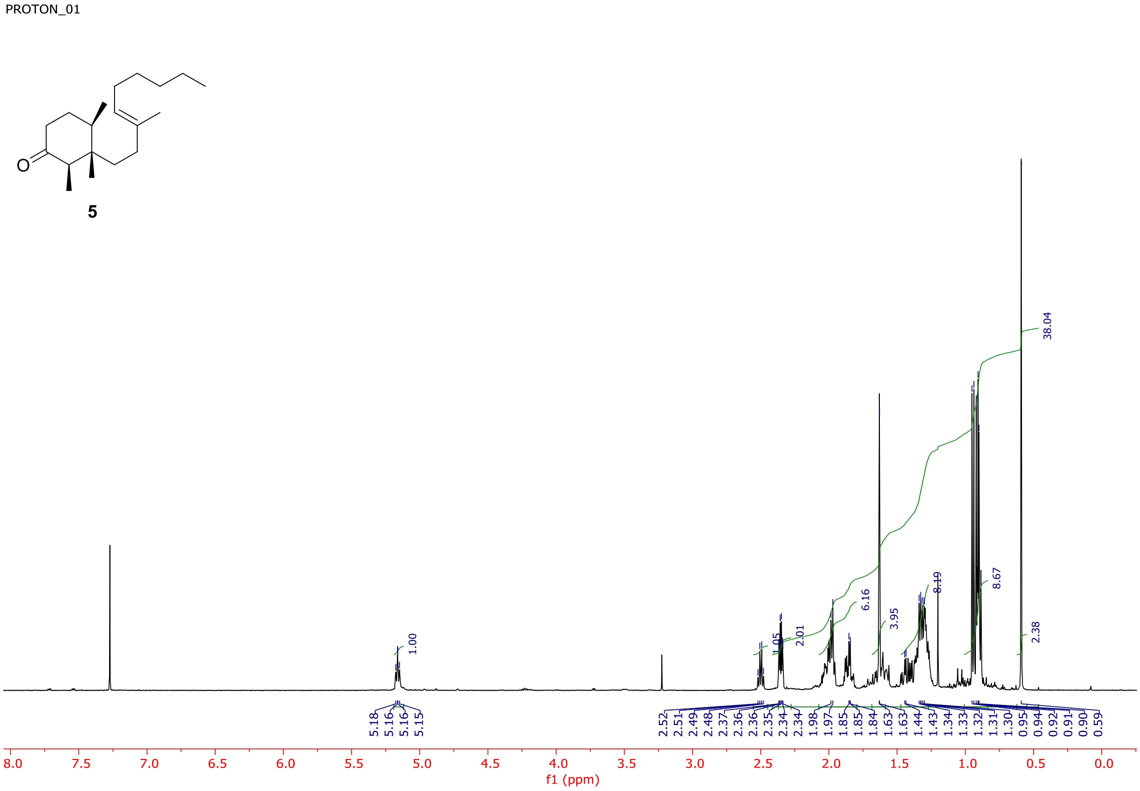
NOESY

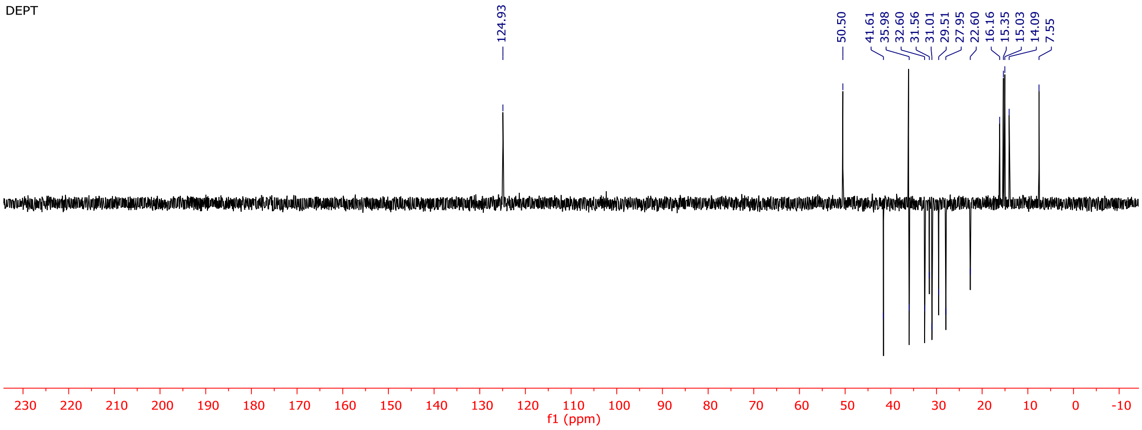

f1 (ppm)
f1 (ppm)
f1 (ppm)

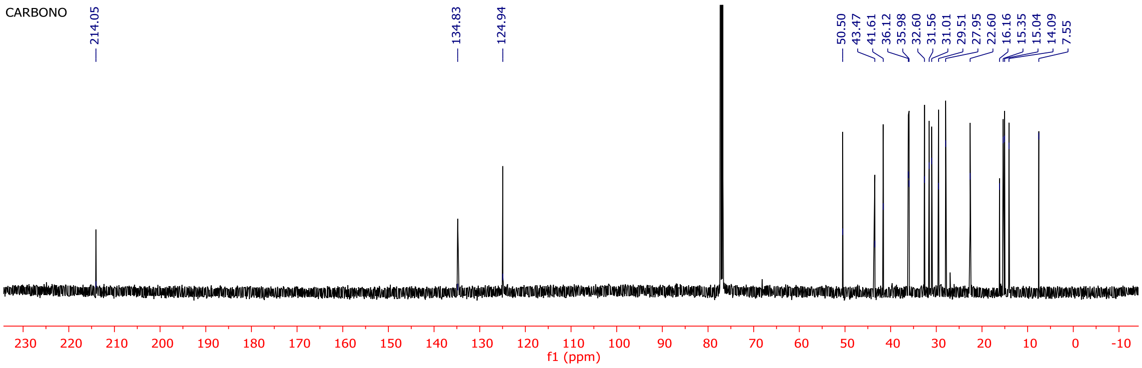

proton
HCN_calib
O
4
1.00
0.84
5.78
1.78
3.55
16.55
1.34
2.63
3.51
5.12
5.11
5.10
3.71
3.70
f1 (ppm)

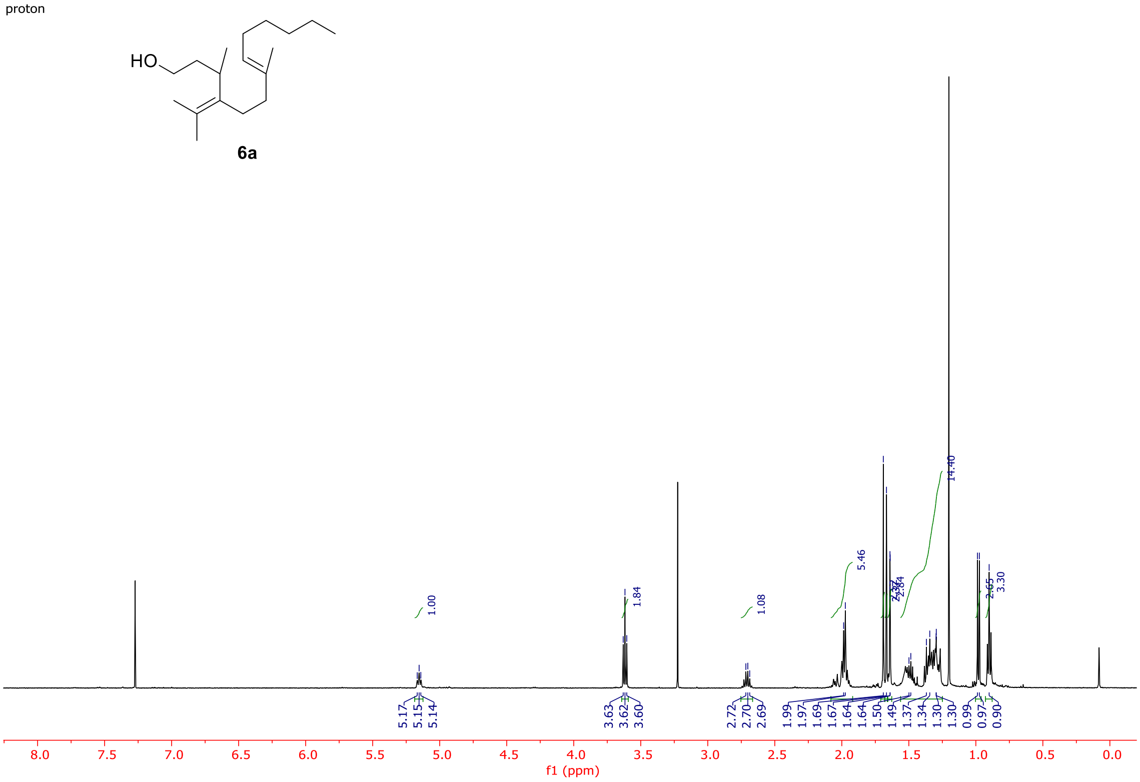

pdept
Calibration for HCN on 09Oct2013
Sample : C13 enriched CH3I in CDCl3
125.00
86.04
55.05
26.07
23.38
18.88
15.85
14.07
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


carbono
HCN_calib
134.95
125.01
86.68
86.04
55.05
45.21
39.77
38.98
31.53
29.54
27.83
26.09
26.06
25.73
23.38
22.58
18.88
15.85
14.07
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

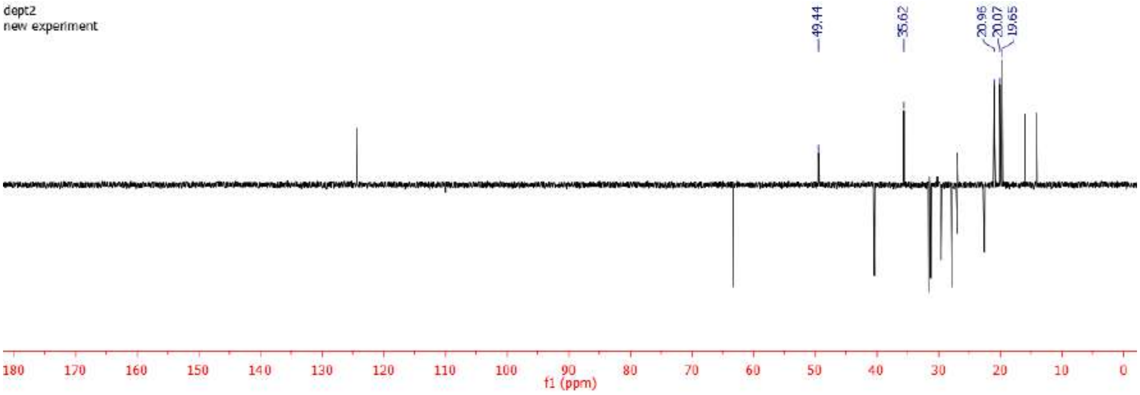

PROTON_01
O
5
1.00
1.05
2.01
6.16
3.95
8.19
8.67
2.38
38.04
5.18
5.16
5.16
5.15
2.52
2.51
2.49
2.48
2.37
2.36
2.36
2.35
2.34
2.34
1.98
1.97
1.85
1.85
1.84
1.63
1.63
1.44
1.43
1.34
1.33
1.32
1.31
1.30
0.95
0.94
0.92
0.91
0.90
0.59
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

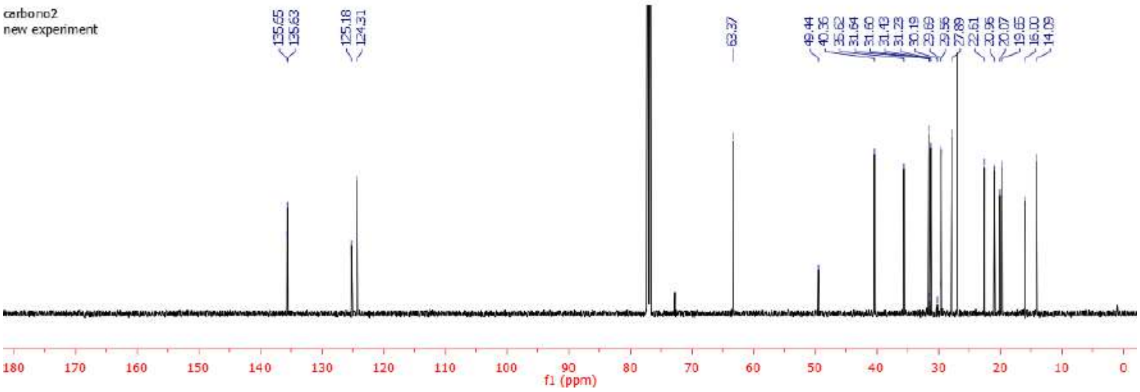

DEPT
124.93
50.50
41.61
35.98
32.60
31.56
31.01
29.51
27.95
22.60
16.16
15.35
15.03
14.09
7.55
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

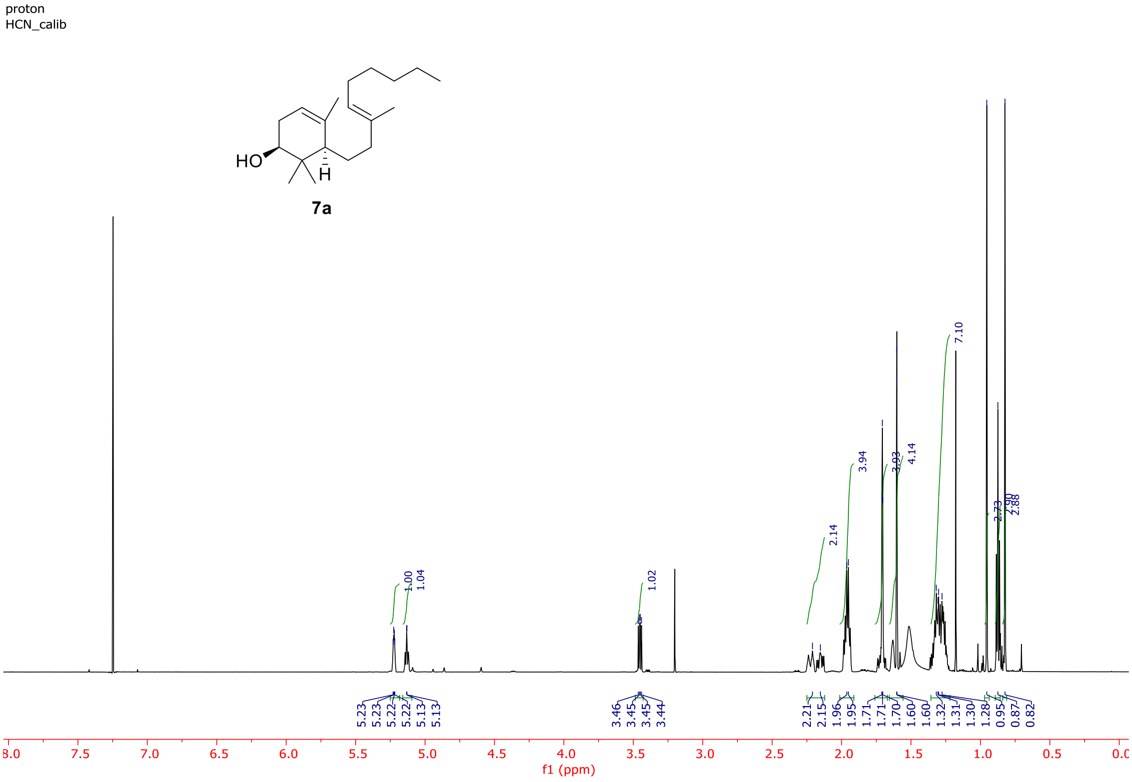

CARBONO
214.05
134.83
124.94
50.50
43.47
41.61
36.12
35.98
32.60
31.56
31.01
29.51
27.95
22.60
16.16
15.35
15.04
14.09
7.55
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

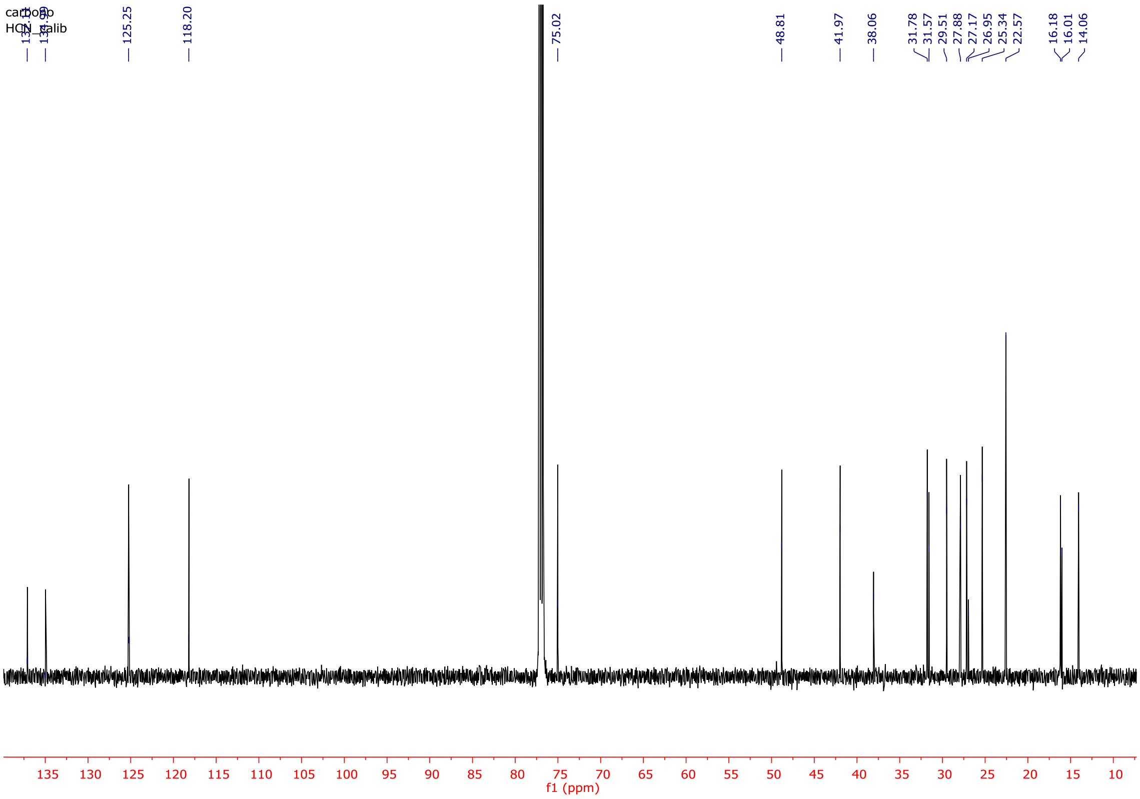

proton
HO
1.00
1.84
1.08
5.46
2.27
2.24
14.40
2.65
3.30
5.17
5.15
5.14
3.63
3.62
3.60
2.72
2.70
2.69
1.99
1.97
1.69
1.67
1.64
1.64
1.50
1.49
1.37
1.34
1.30
1.30
0.99
0.97
0.90
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

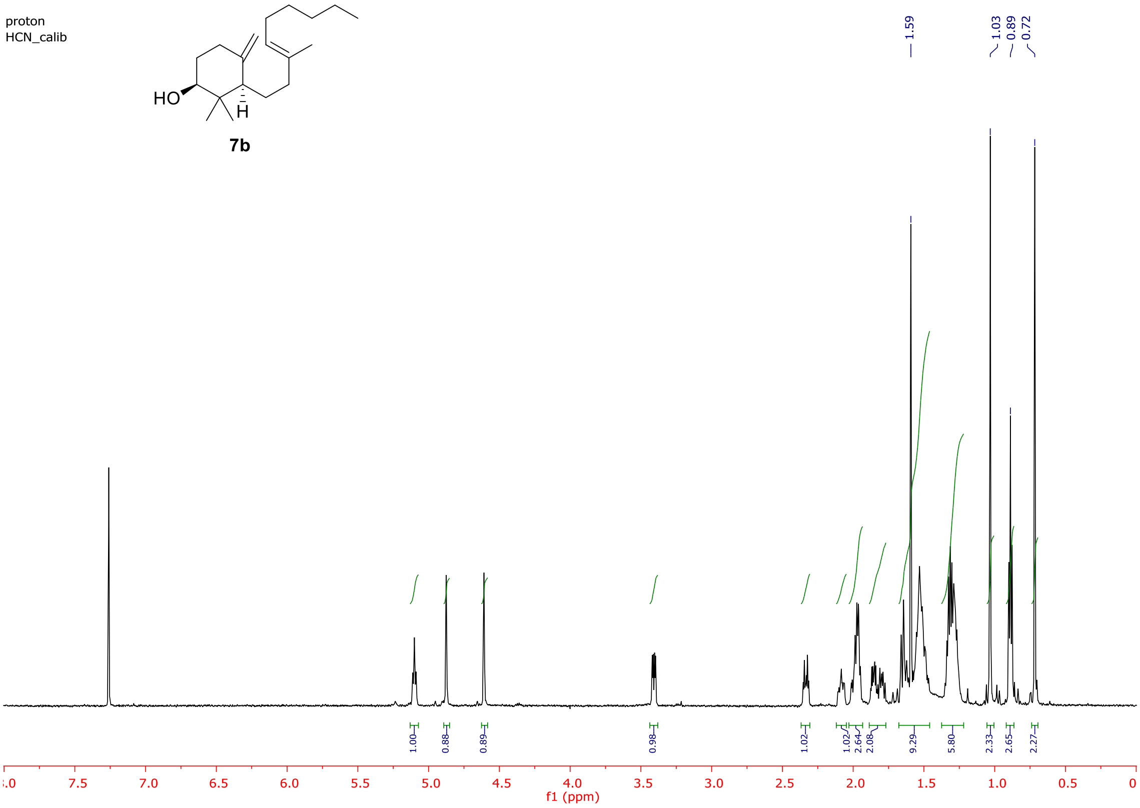
6a


dept2
new experiment
49.44
35.62
20.96
20.07
19.65
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

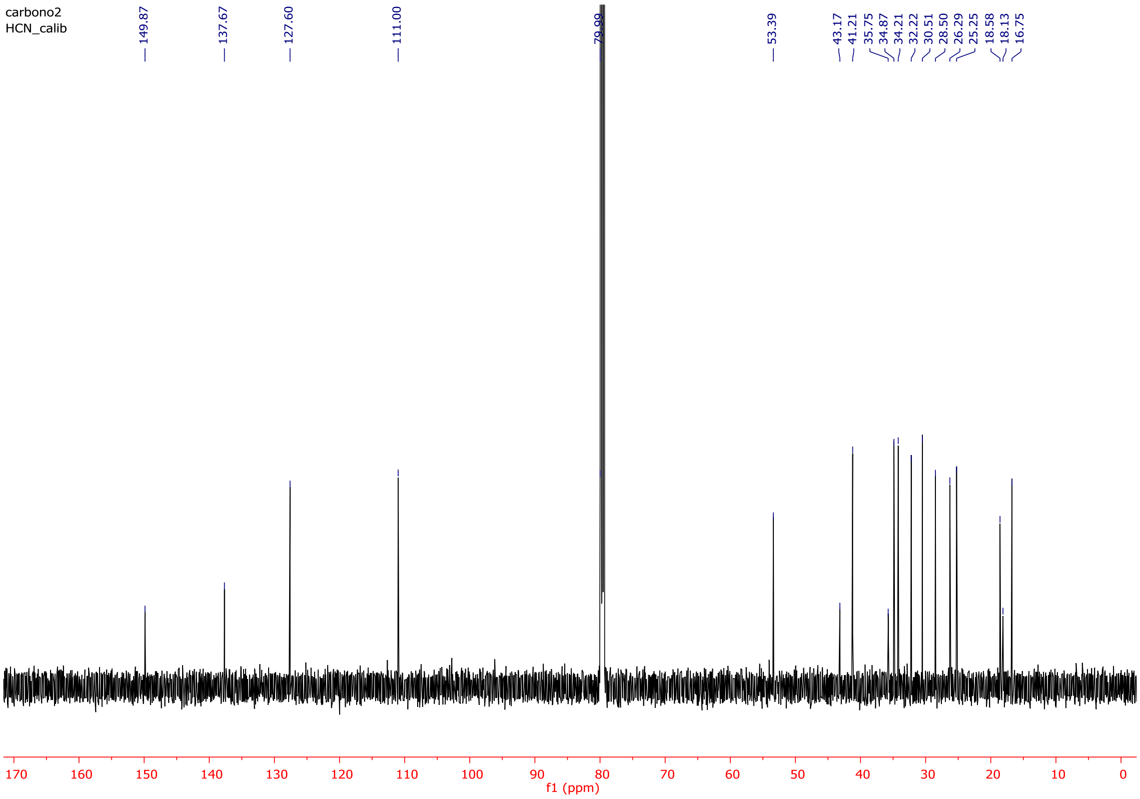

carbono2
new experiment
135.65
135.63
125.18
124.31
63.37
49.44
40.36
35.62
31.64
31.60
31.43
31.23
30.19
29.69
29.56
27.89
22.61
20.96
20.07
19.65
16.00
14.09
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

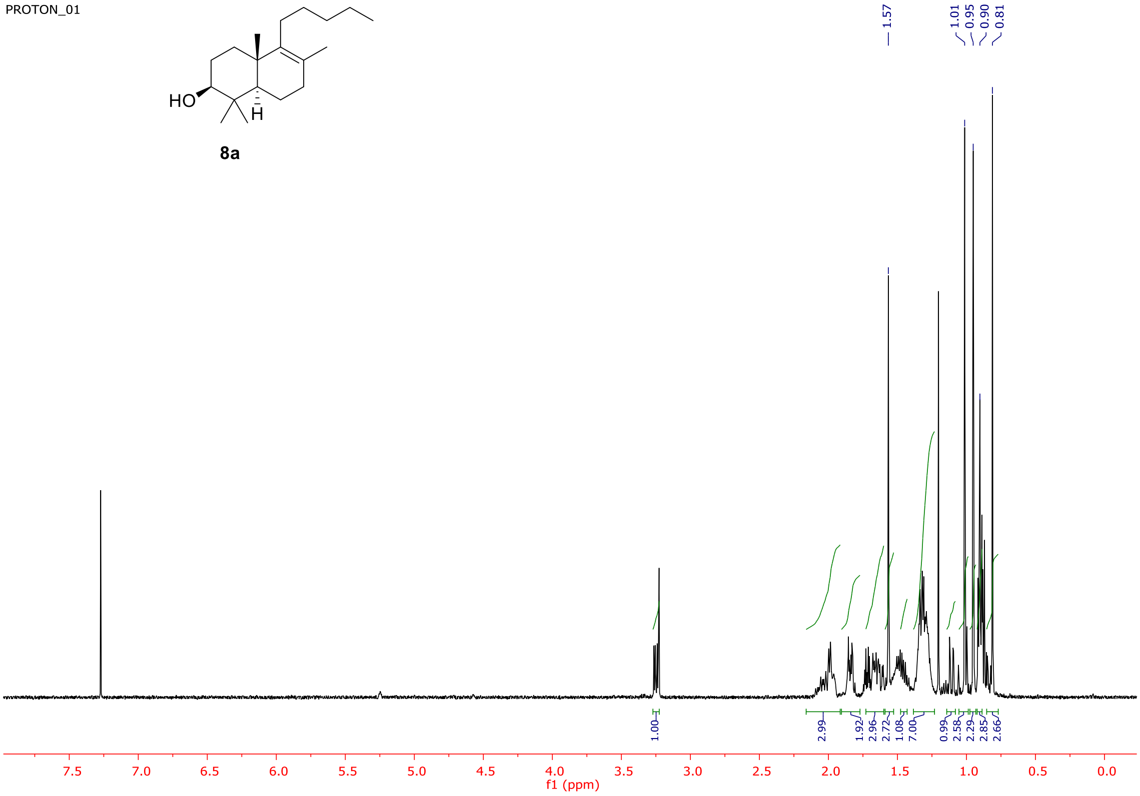

proton
HCN_calib
HO
H
7a
1.00
1.04
1.02
2.14
3.94
3.93
4.14
7.10
2.73
2.90
2.88
5.23
5.23
5.22
5.22
5.13
5.13
3.46
3.45
3.45
3.44
2.21
2.15
1.96
1.95
1.71
1.71
1.70
1.60
1.60
1.32
1.31
1.30
1.28
0.95
0.87
0.82
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

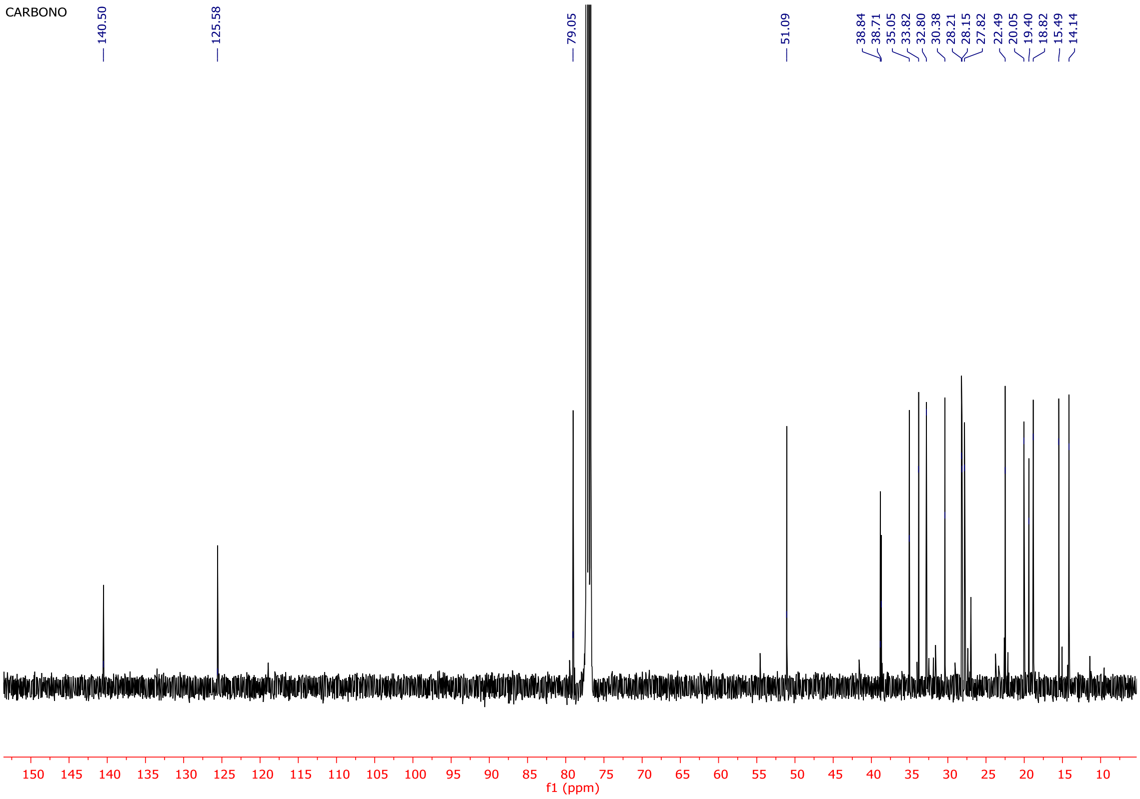

carbono
HCN_calib
137.11
134.99
125.25
118.20
75.02
48.81
41.97
38.06
31.78
31.57
29.51
27.88
27.17
26.95
25.34
22.57
16.18
16.01
14.06
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

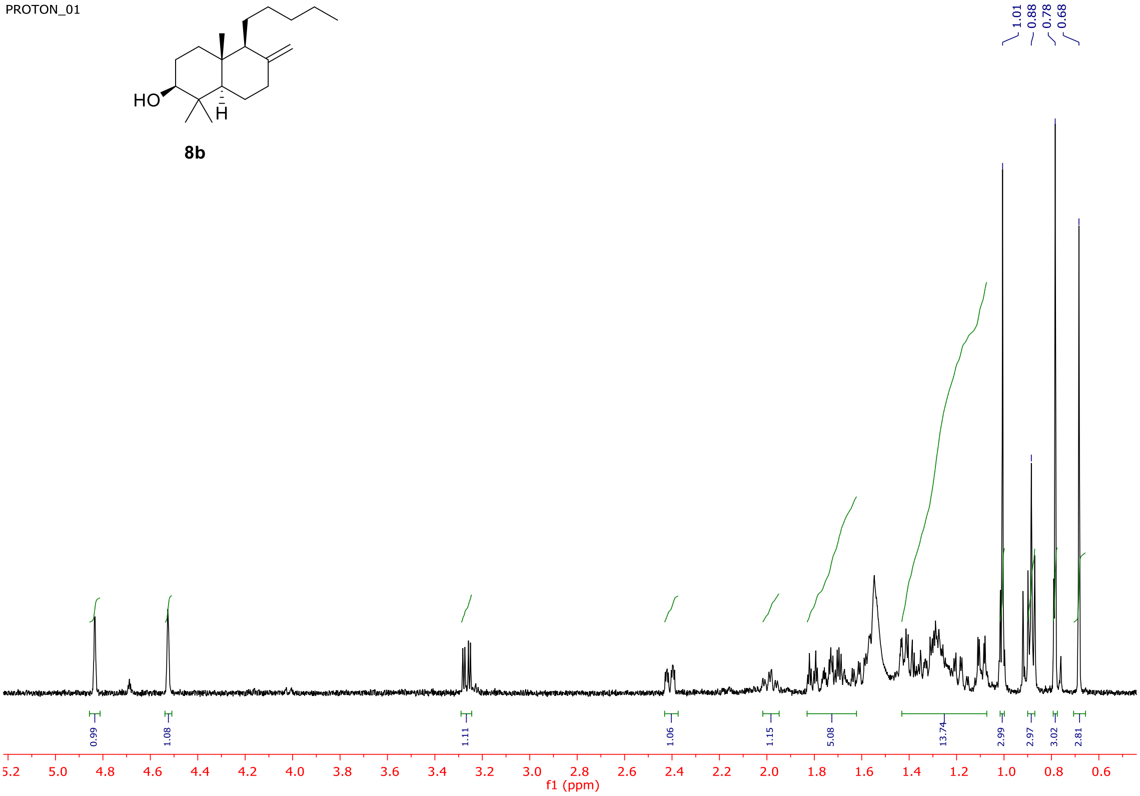

proton
HCN_calib
HO
H
1.59
1.03
0.89
0.72
1.00
0.88
0.89
0.98
1.02
1.02
2.64
2.08
9.29
5.80
2.33
2.65
2.27
.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

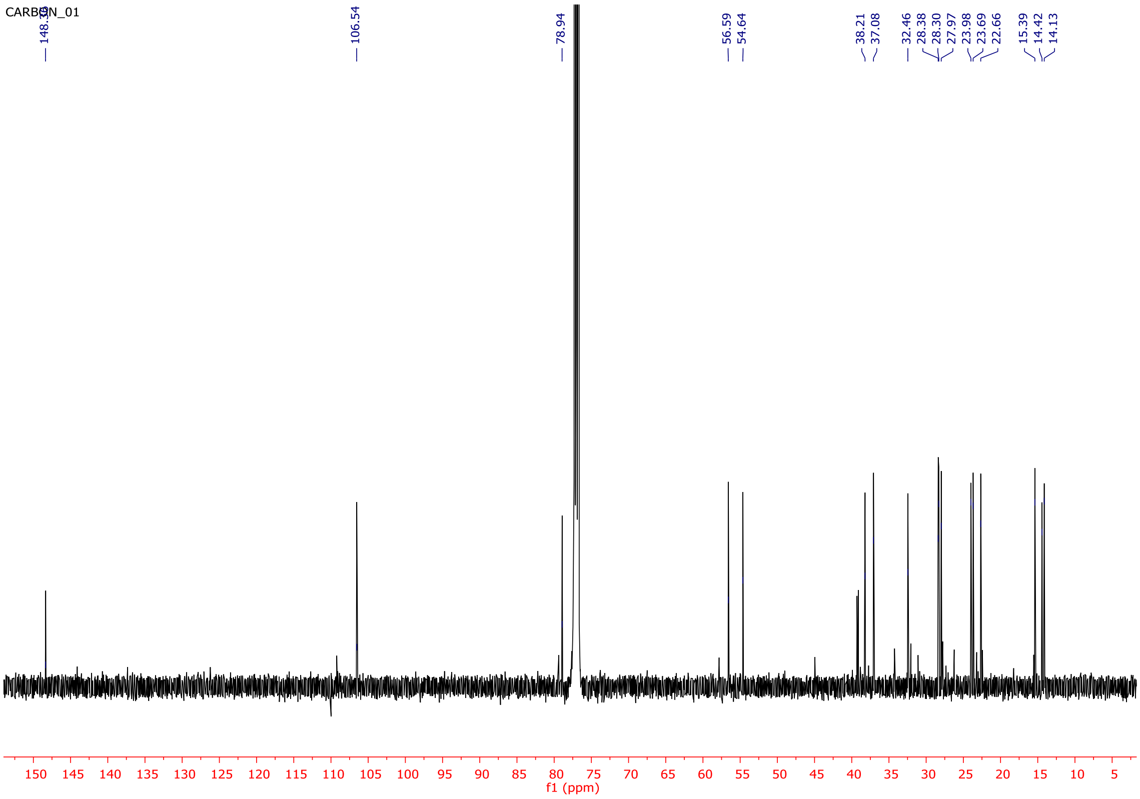
7b

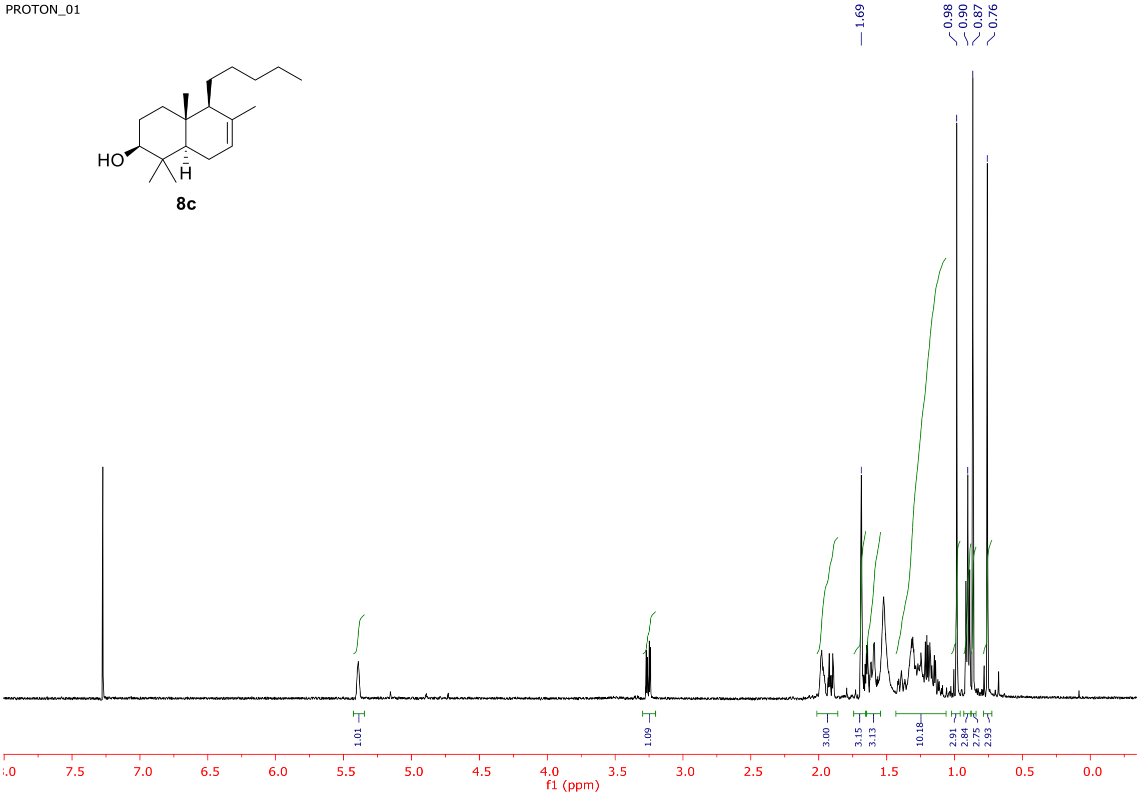

carbono2
HCN_calib
149.87
137.67
127.60
111.00
79.99
53.39
43.17
41.21
35.75
34.87
34.21
32.22
30.51
28.50
26.29
25.25
18.58
18.13
16.75
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

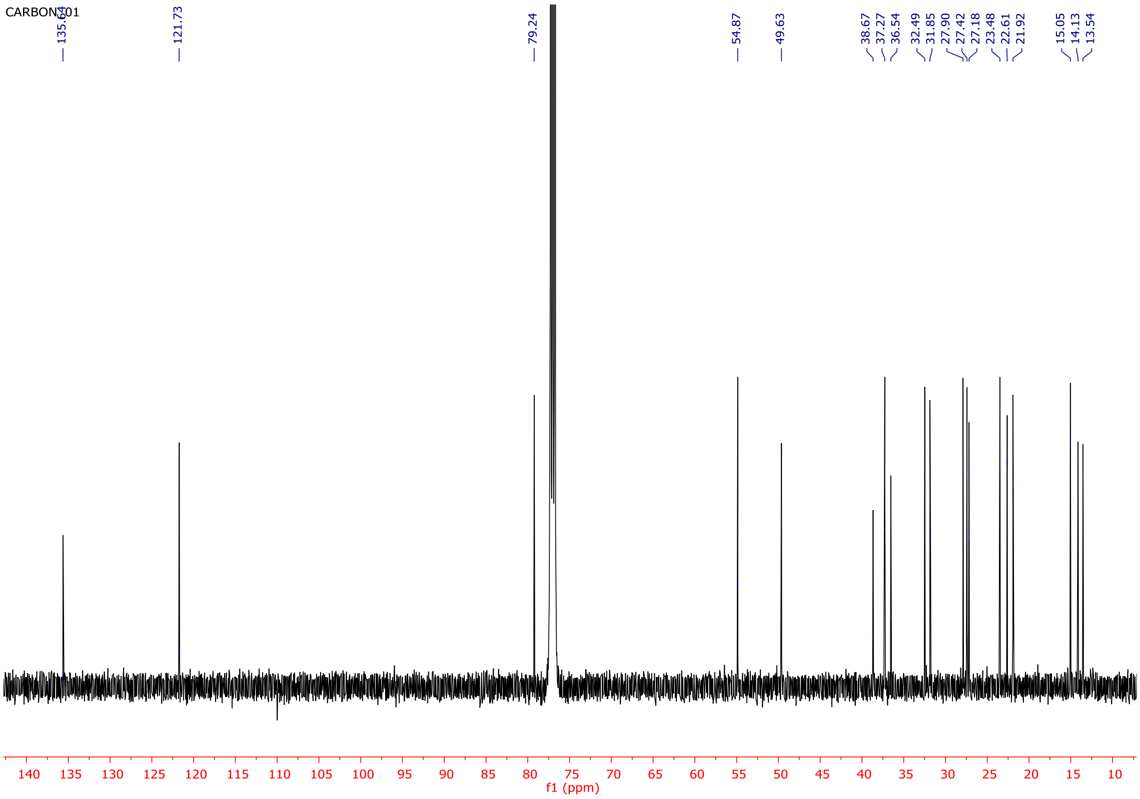

PROTON_01
HO
H
8a
1.57
1.01
0.95
0.90
0.81
1.00
2.99
1.92
2.96
2.72
1.08
7.00
0.99
2.58
2.29
2.85
2.66
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

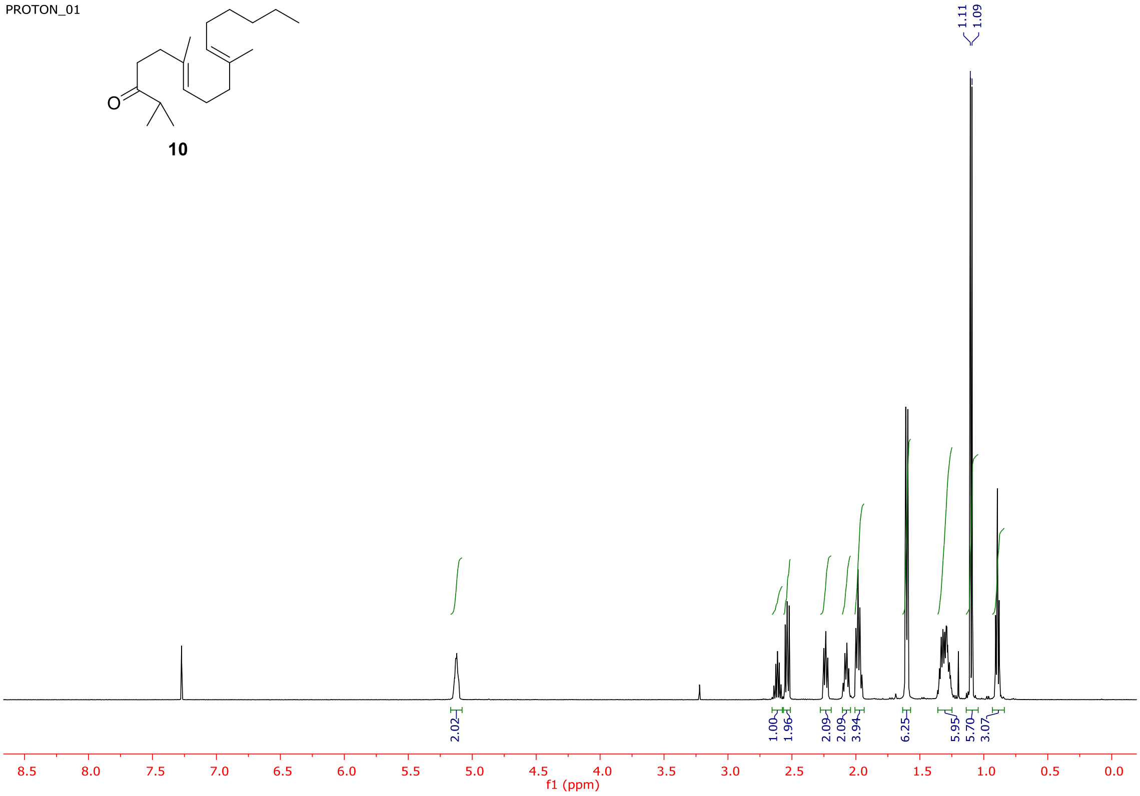

CARBONO
140.50
125.58
79.05
51.09
38.84
38.71
35.05
33.82
32.80
30.38
28.21
28.15
27.82
22.49
20.05
19.40
18.82
15.49
14.14
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

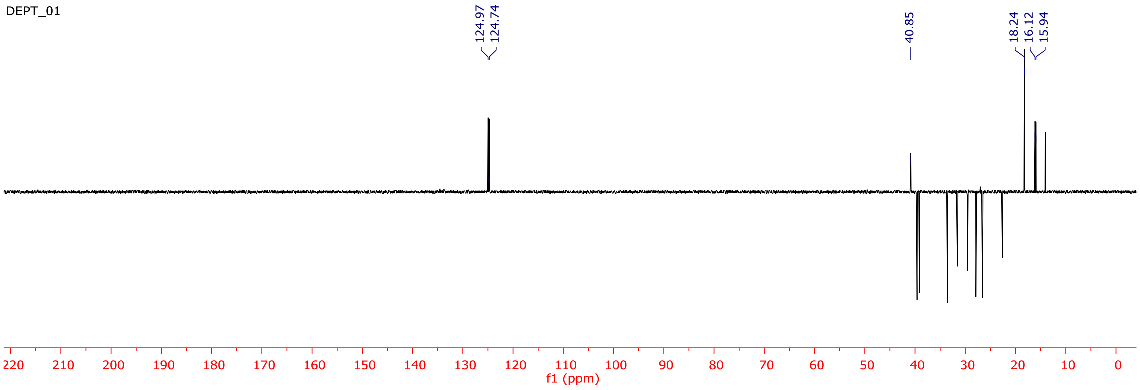

PROTON_01
HO
H
8b
1.01
0.88
0.78
0.68
0.99
1.08
1.11
1.06
1.15
5.08
13.74
2.99
2.97
3.02
2.81
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)

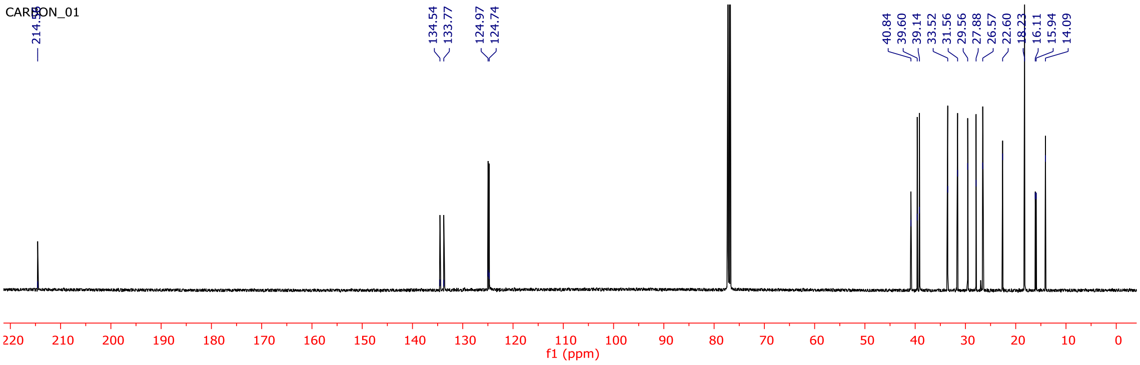

CARBON_01
148.36
106.54
78.94
56.59
54.64
38.21
37.08
32.46
28.38
28.30
27.97
23.98
23.69
22.66
15.39
14.42
14.13
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5
f1 (ppm)

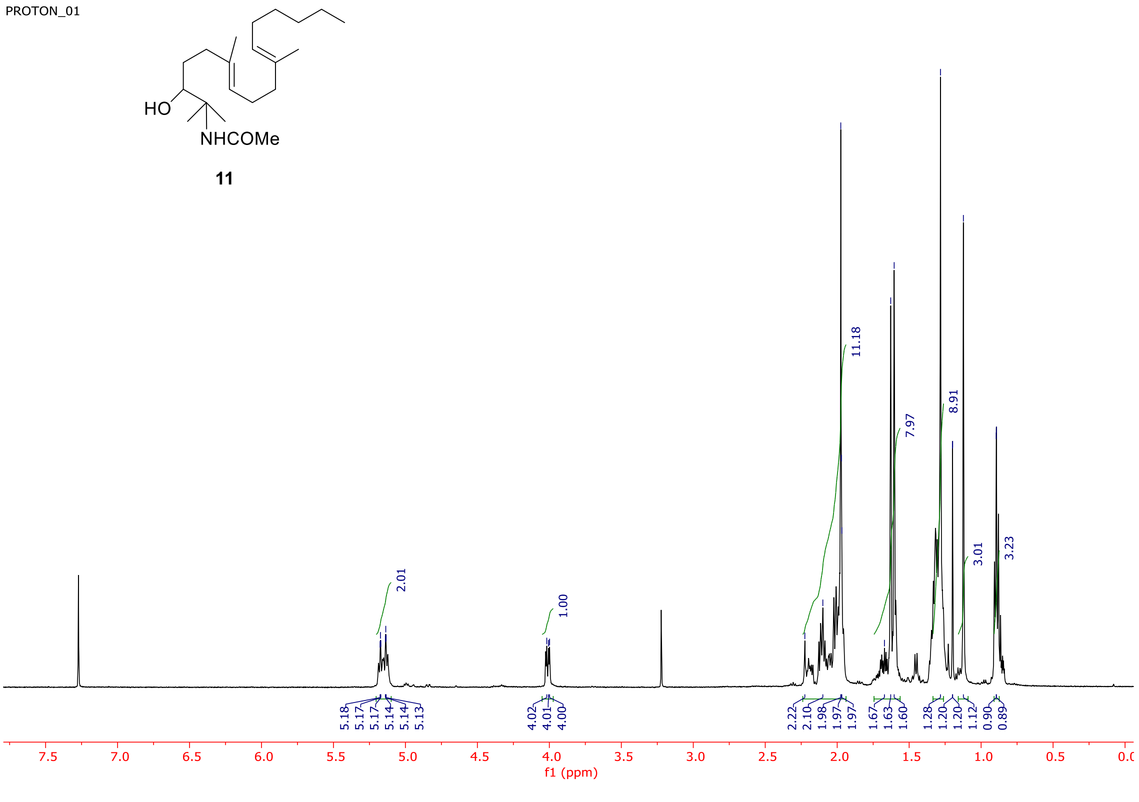

PROTON_01
HO
H
8c
1.69
0.98
0.90
0.87
0.76
1.01
1.09
3.00
3.15
3.13
10.18
2.91
2.84
2.75
2.93
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CARBON_01
135.64
121.73
79.24
54.87
49.63
38.67
37.27
36.54
32.49
31.85
27.90
27.42
27.18
23.48
22.61
21.92
15.05
14.13
13.54
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)

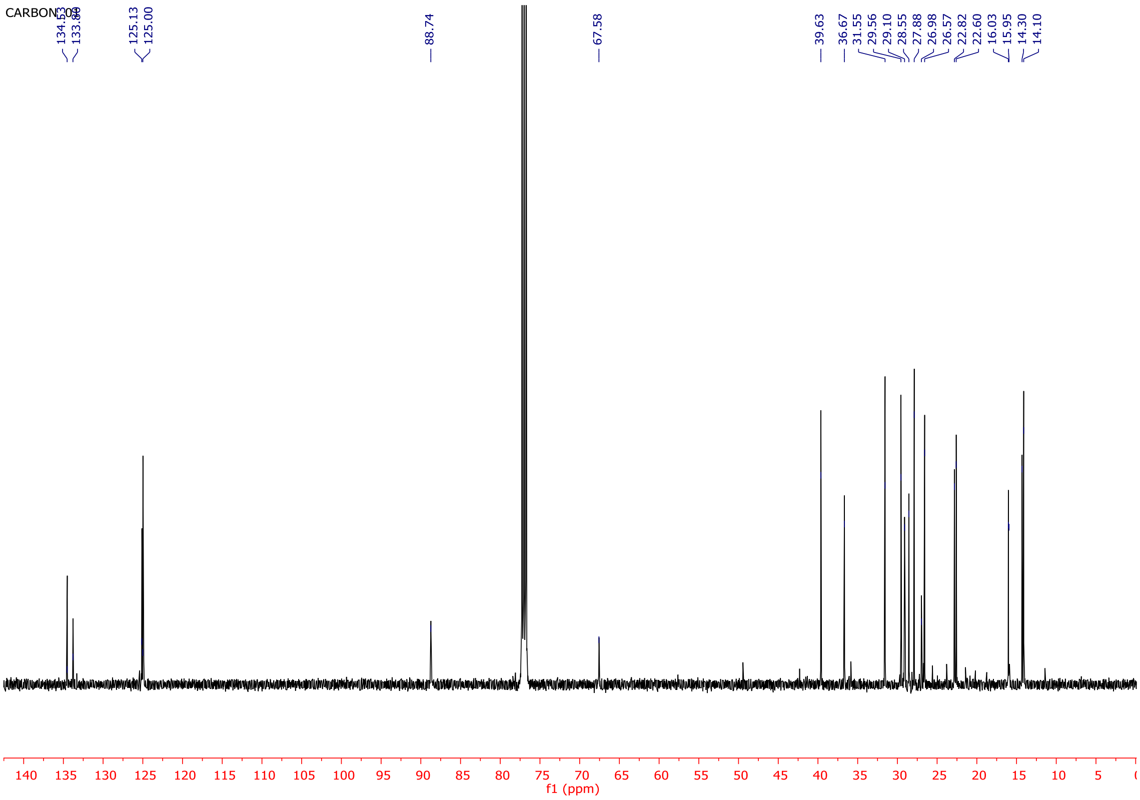

PROTON_01
O
10
1.11
1.09
2.02
1.00
1.96
2.09
2.09
3.94
6.25
5.95
5.70
3.07
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

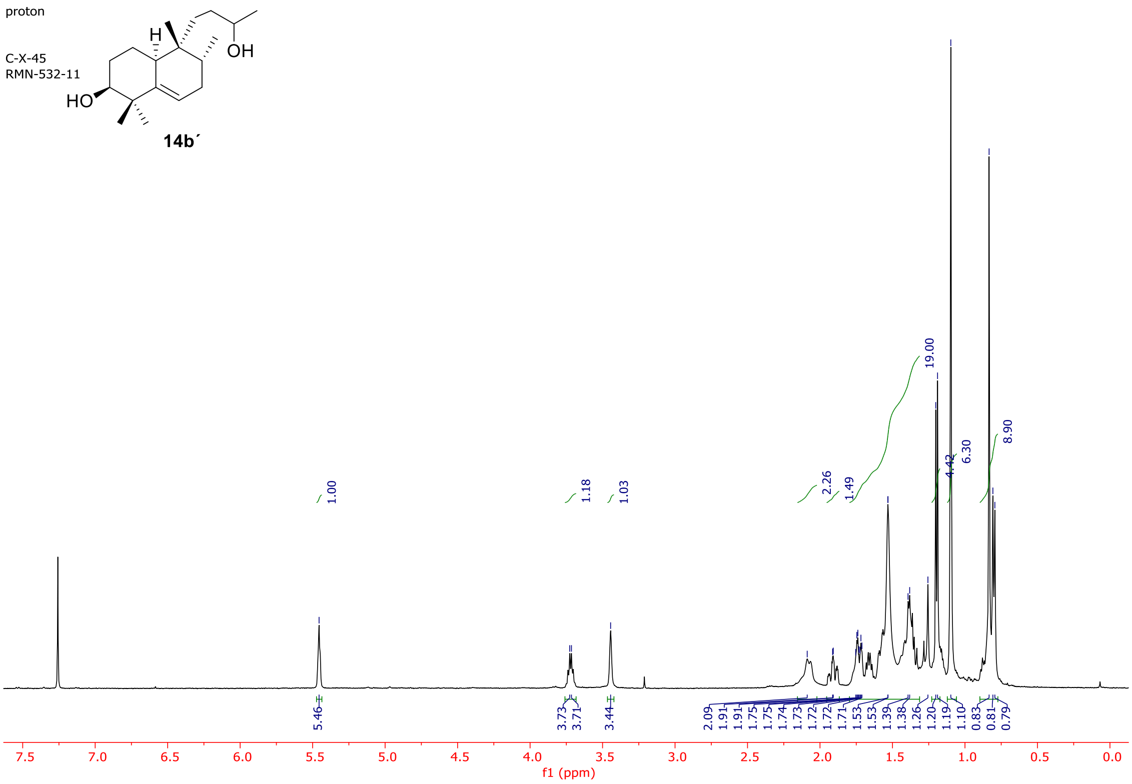

DEPT_01
124.97
124.74
40.85
18.24
16.12
15.94
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

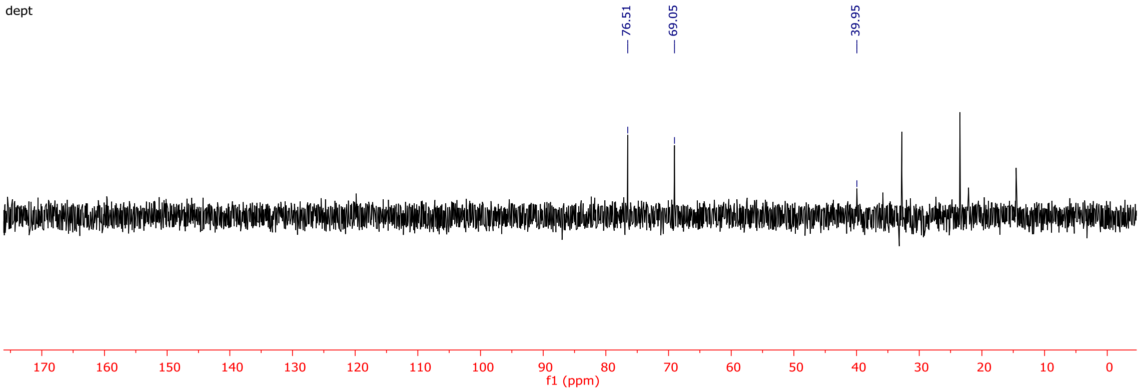

CARBON_01
214.
134.54
133.77
124.97
124.74
40.84
39.60
39.14
33.52
31.56
29.56
27.88
26.57
22.60
18.23
16.11
15.94
14.09
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

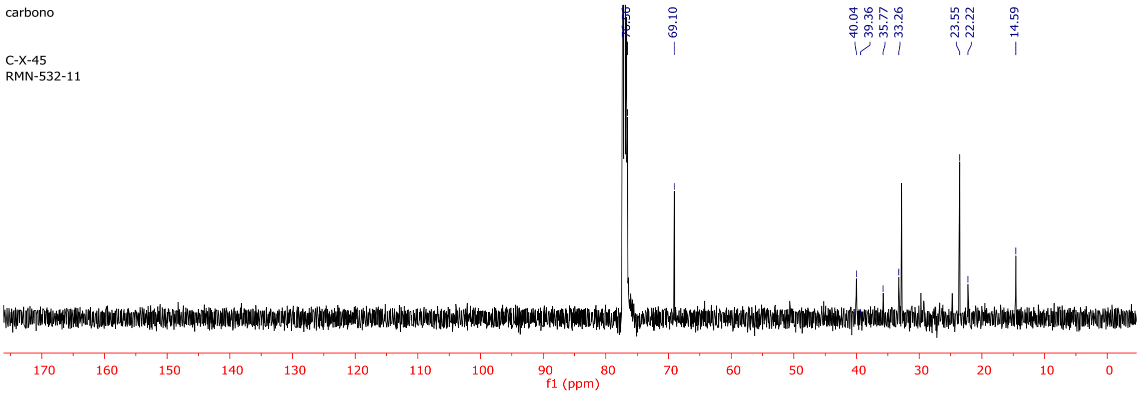

PROTON_01
HO
NHCOMe
2.01
1.00
11.18
7.97
8.91
3.01
3.23
5.18
5.17
5.14
5.14
5.13
4.02
4.01
4.00
2.22
2.10
1.98
1.97
1.97
1.67
1.63
1.60
1.28
1.20
1.20
1.12
0.90
0.89
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

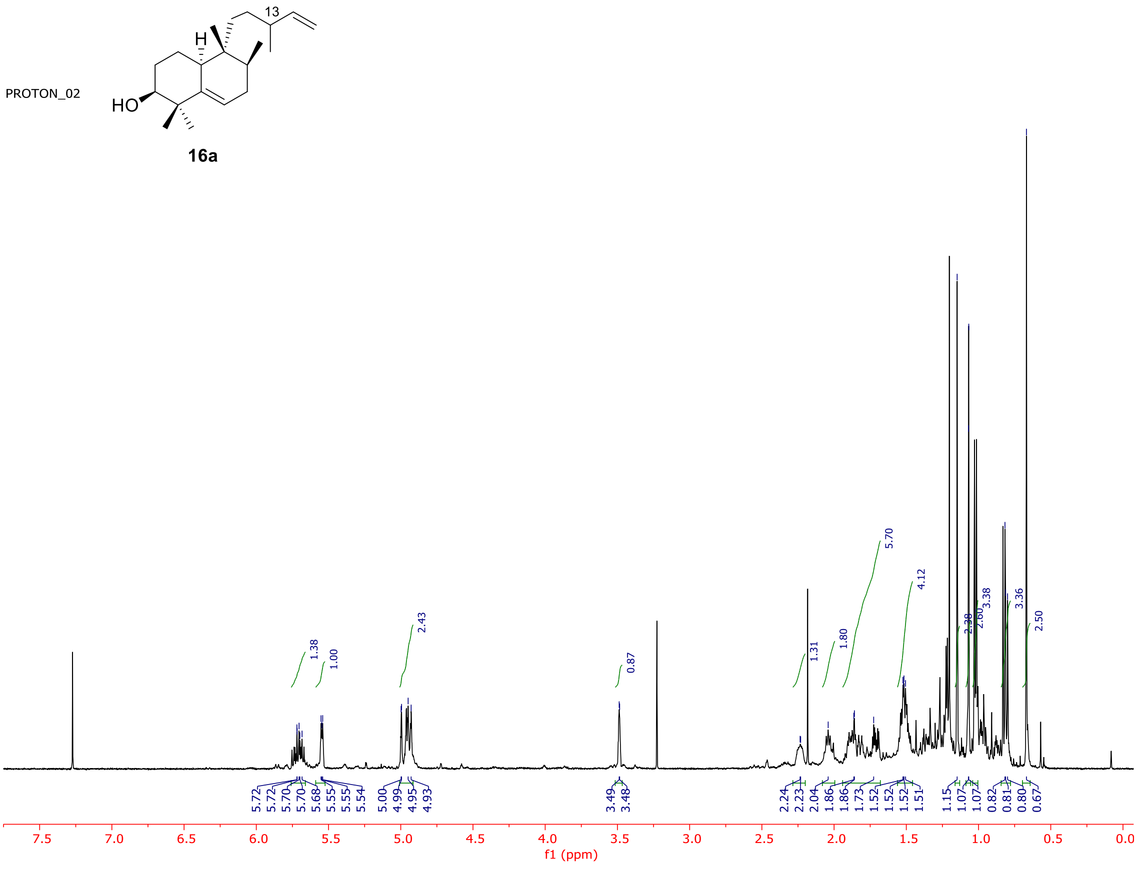
11


CARBON_01
134.53
133.80
125.13
125.00
88.74
67.58
39.63
36.67
31.55
29.56
29.10
28.55
27.88
26.98
26.57
22.82
22.60
16.03
15.95
14.30
14.10
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)

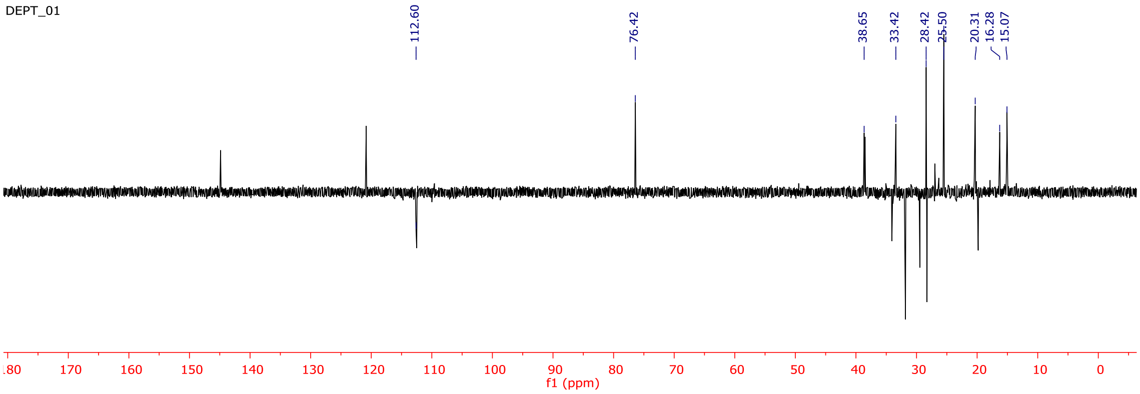

proton
C-X-45
RMN-532-11
H
OH
HO
14b´
1.00
1.18
1.03
2.26
1.49
19.00
4.42
6.30
8.90
5.46
3.73
3.71
3.44
2.09
1.91
1.91
1.75
1.75
1.74
1.73
1.72
1.72
1.71
1.53
1.53
1.39
1.38
1.26
1.20
1.19
1.10
0.83
0.81
0.79
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

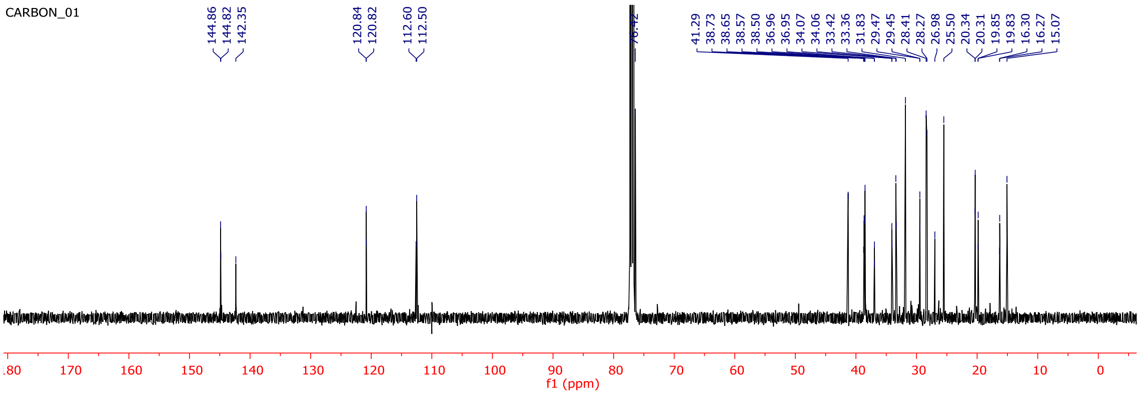

dept
76.51
69.05
39.95
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

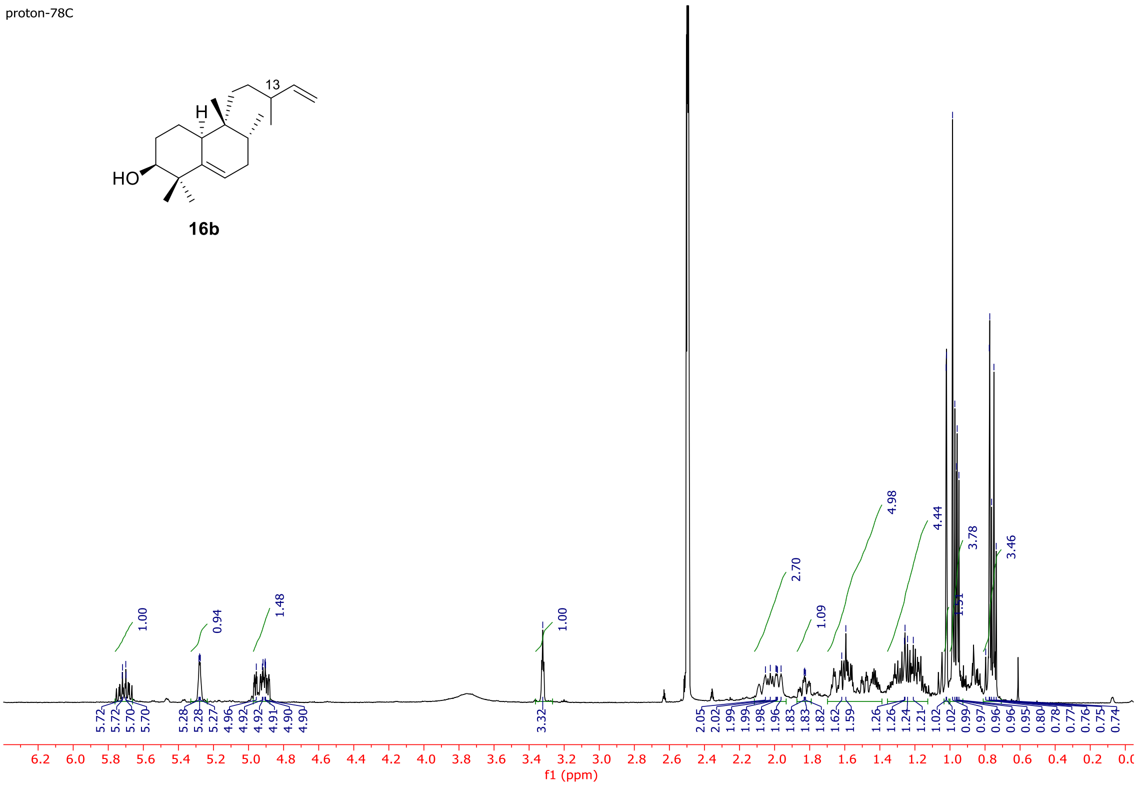

carbono
C-X-45
RMN-532-11
76.90
69.10
40.04
39.36
35.77
33.26
23.55
22.22
14.59
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

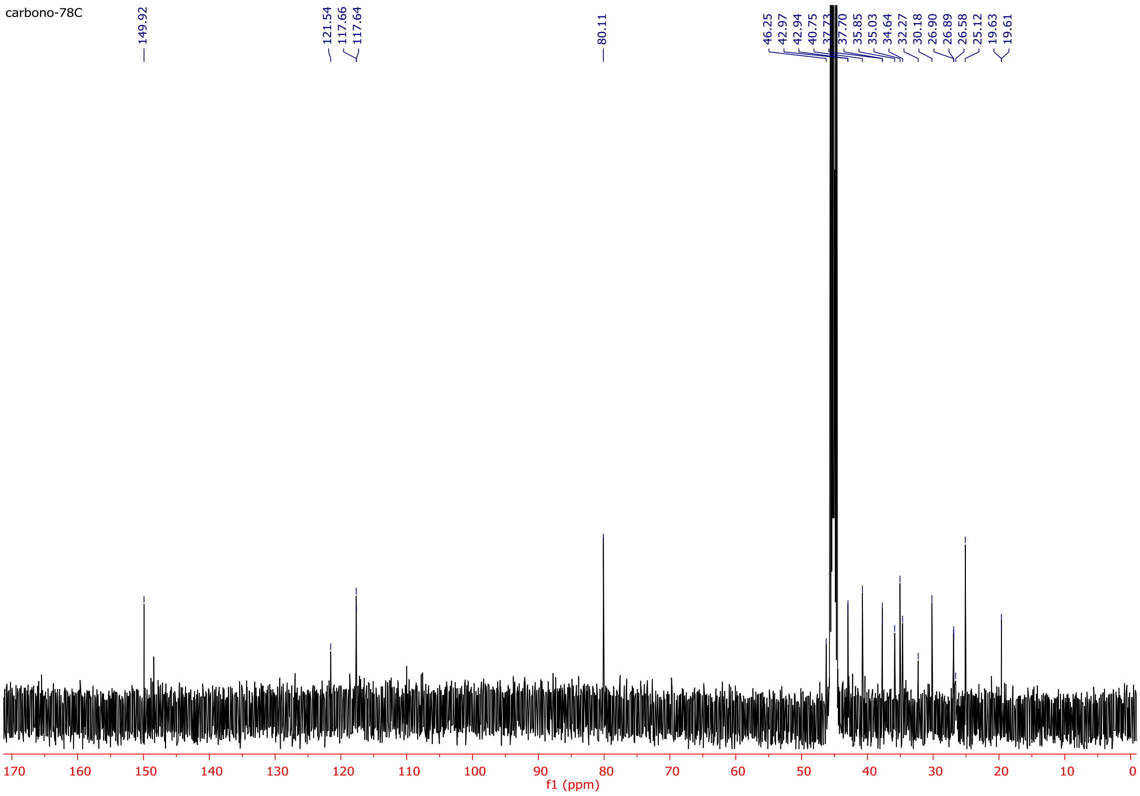

PROTON_02
13
H
HO
1.38
1.00
2.43
0.87
1.31
1.80
5.70
4.12
2.38
2.60
3.38
3.36
2.50
5.72
5.72
5.70
5.68
5.55
5.55
5.54
5.00
4.99
4.95
4.93
3.49
3.48
2.24
2.23
2.04
1.86
1.86
1.73
1.52
1.52
1.51
1.15
1.07
1.07
0.82
0.81
0.80
0.67
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

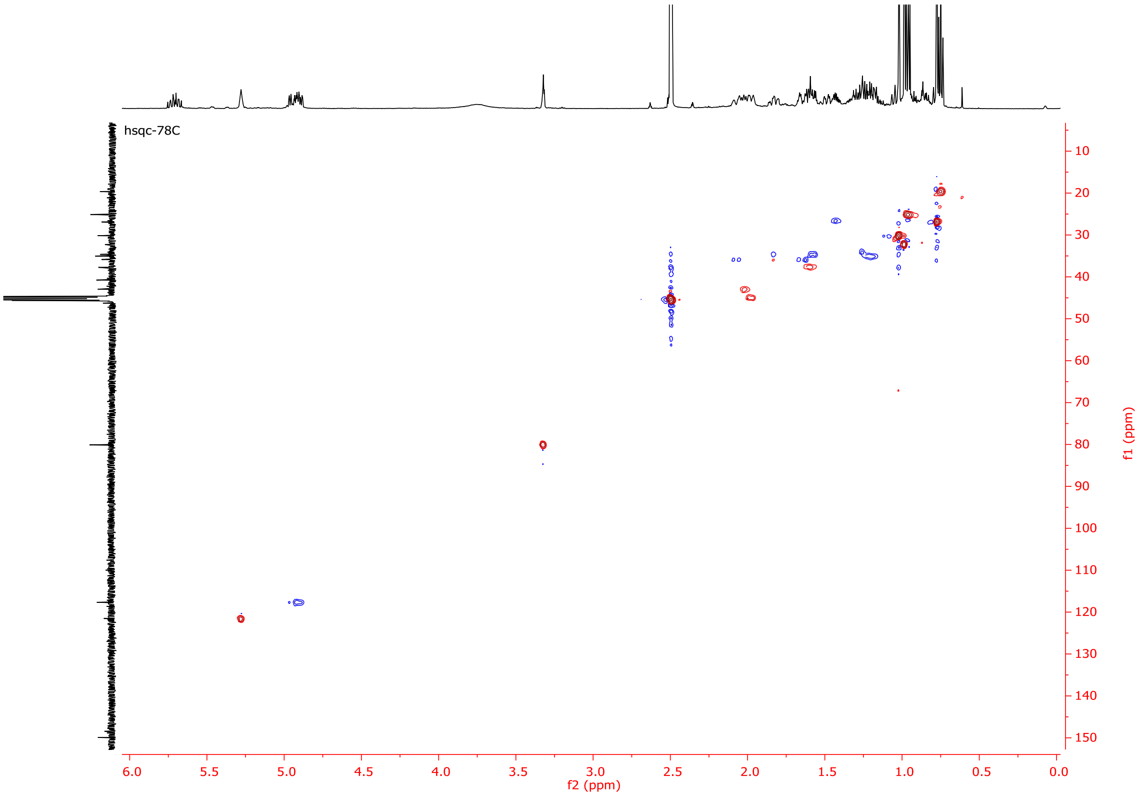
16a

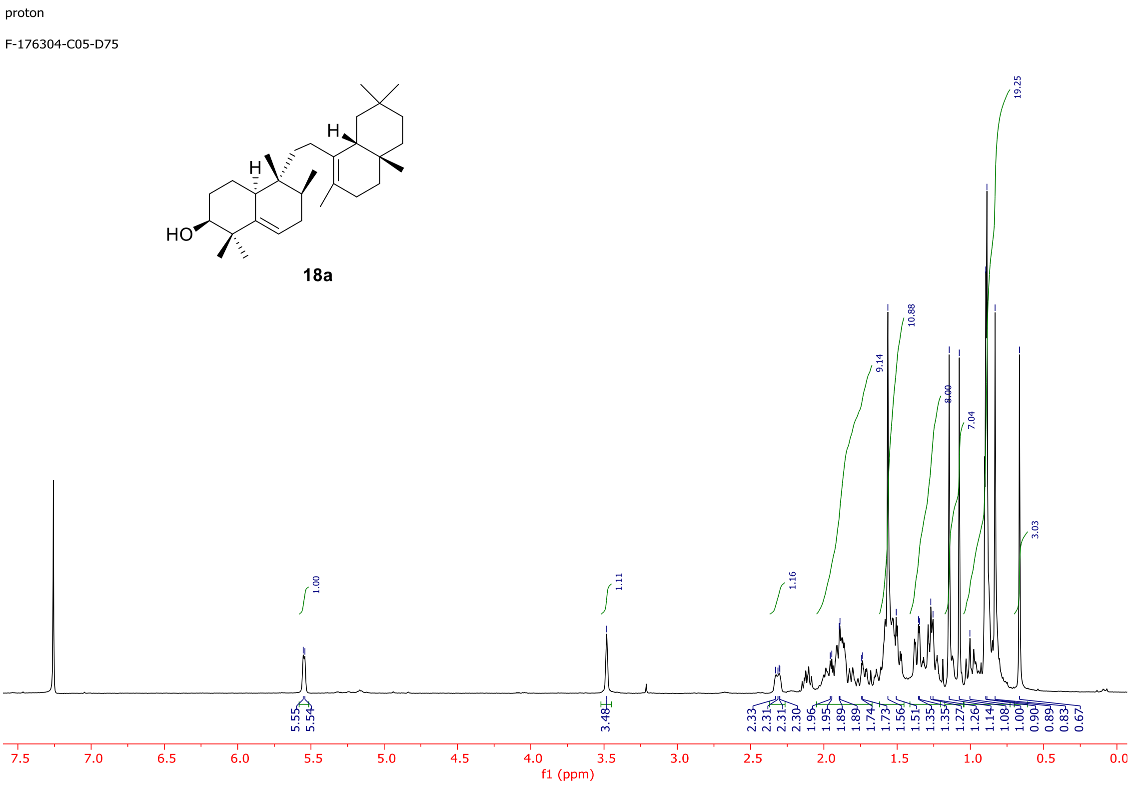

DEPT_01
112.60
76.42
38.65
33.42
28.42
25.50
20.31
16.28
15.07
.80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

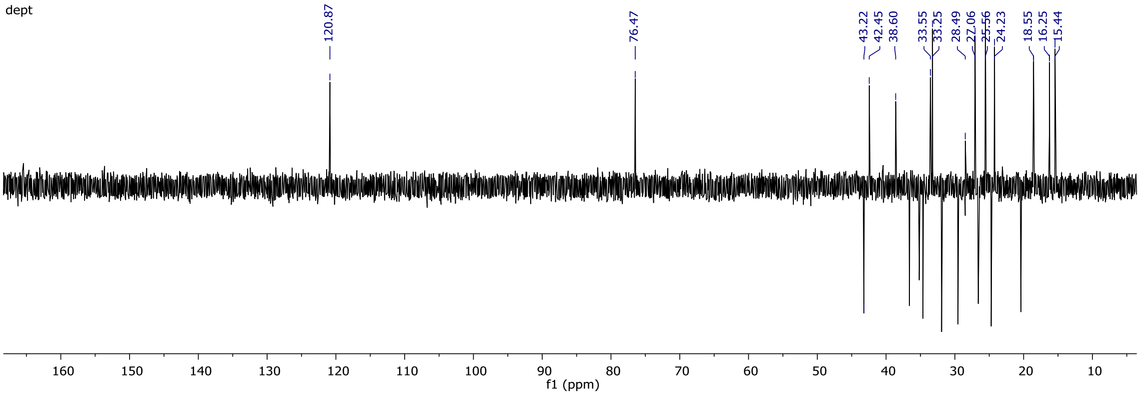

CARBON_01
144.86
144.82
142.35
120.84
120.82
112.60
112.50
76.42
41.29
38.73
38.65
38.57
38.50
36.96
36.95
34.07
34.06
33.42
33.36
31.83
29.47
29.45
28.41
28.27
26.98
25.50
20.34
20.31
19.85
19.83
16.30
16.27
15.07
.80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

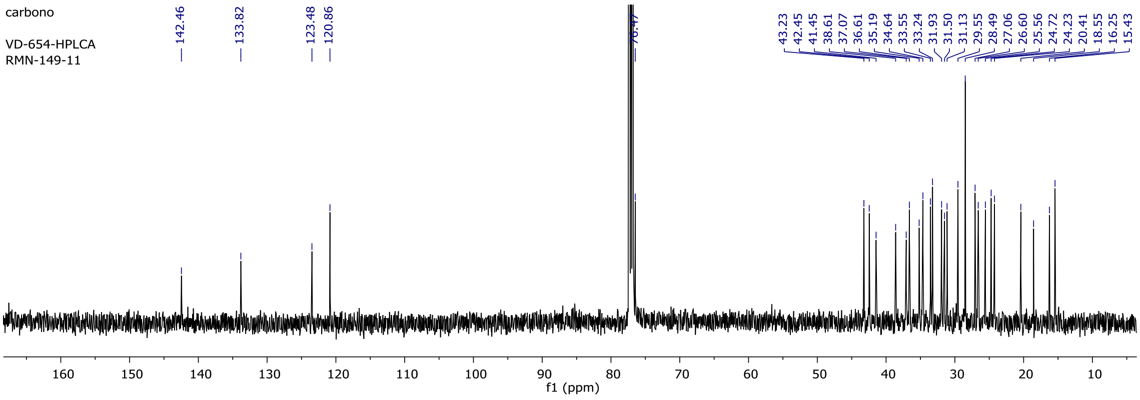

proton-78C
13
H
HO
16b
1.00
0.94
1.48
1.00
2.70
1.09
4.98
4.44
1.51
3.78
3.46
5.72
5.72
5.70
5.70
5.28
5.28
5.27
4.96
4.92
4.92
4.91
4.90
4.90
3.32
2.05
2.02
1.99
1.99
1.98
1.96
1.83
1.83
1.82
1.62
1.59
1.26
1.26
1.24
1.21
1.02
1.02
0.99
0.97
0.96
0.96
0.95
0.80
0.78
0.77
0.76
0.75
0.74
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.(
f1 (ppm)

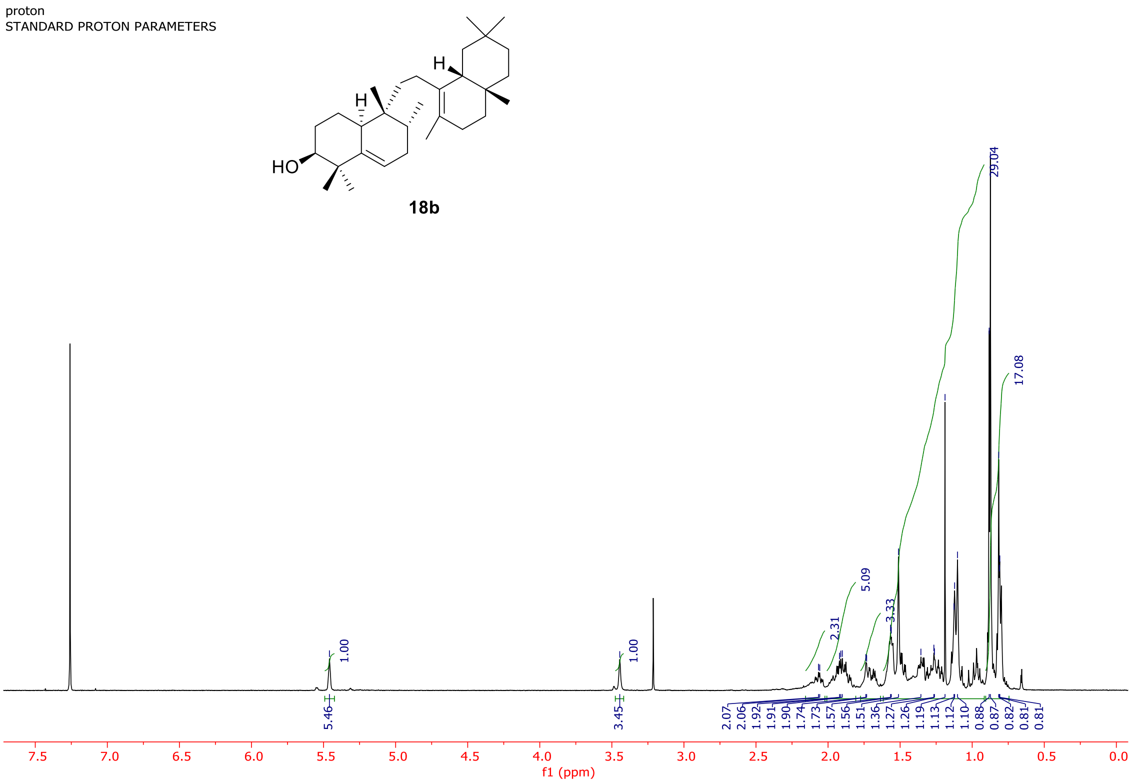

carbono-78C
149.92
121.54
117.66
117.64
80.11
46.25
42.97
42.94
40.75
37.73
37.70
35.85
35.03
34.64
32.27
30.18
26.90
26.89
26.58
25.12
19.63
19.61
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


hsqc-78C
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
f1 (ppm)
6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)

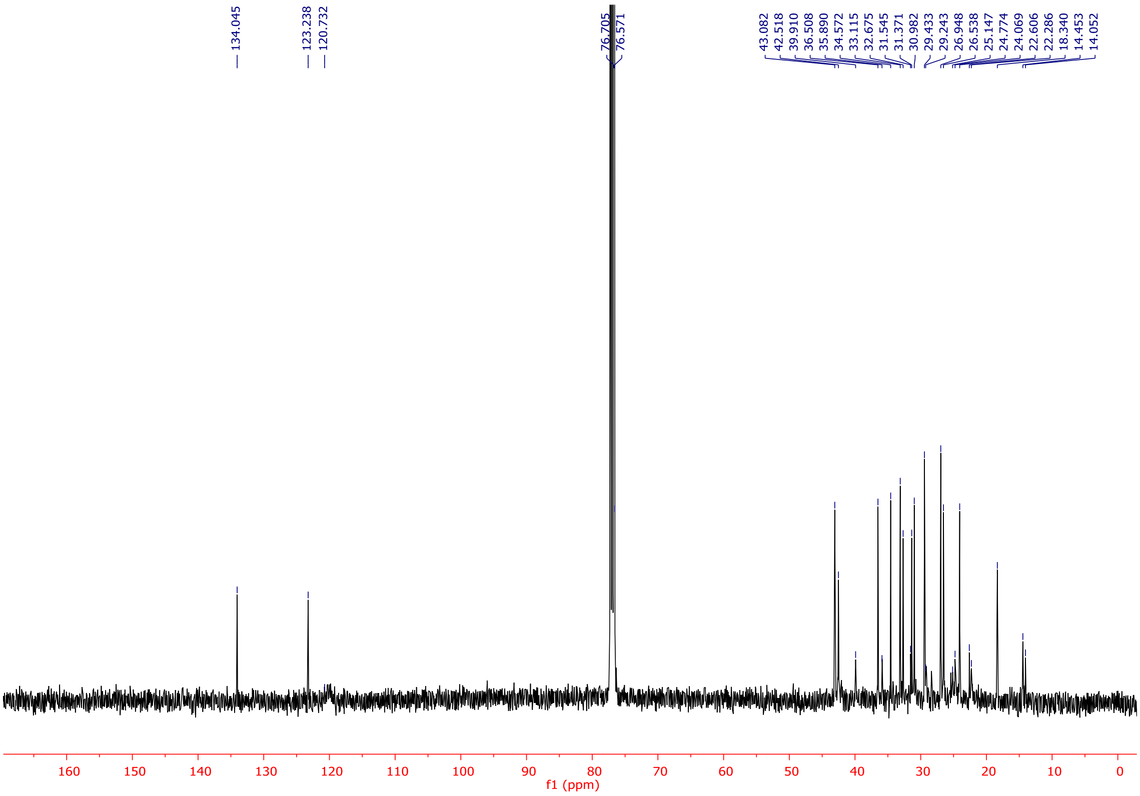

proton
F-176304-C05-D75
H
H
HO
18a
1.00
1.11
1.16
9.14
10.88
8.00
7.04
19.25
3.03
5.55
5.54
3.48
2.33
2.31
2.31
2.30
1.96
1.95
1.89
1.89
1.74
1.73
1.56
1.51
1.35
1.35
1.27
1.26
1.14
1.08
1.00
0.90
0.89
0.83
0.67
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

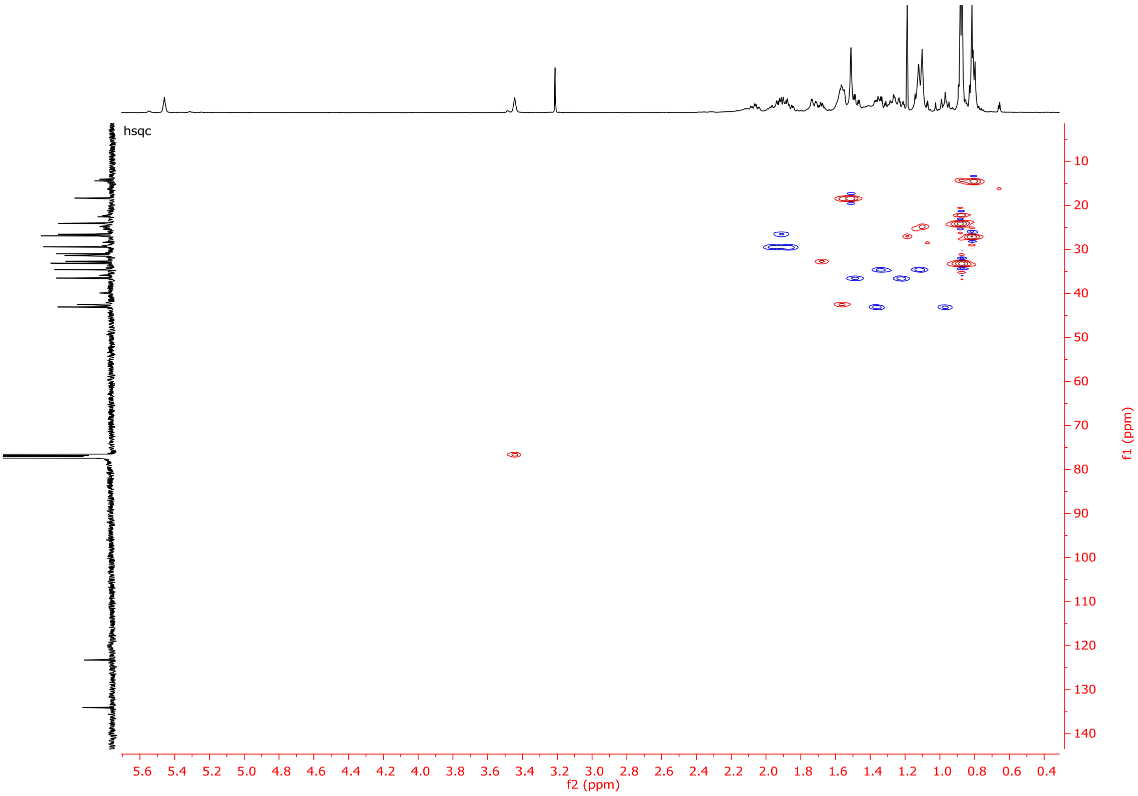

dept
120.87
76.47
43.22
42.45
38.60
33.55
33.25
28.49
27.06
25.56
24.23
18.55
16.25
15.44
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

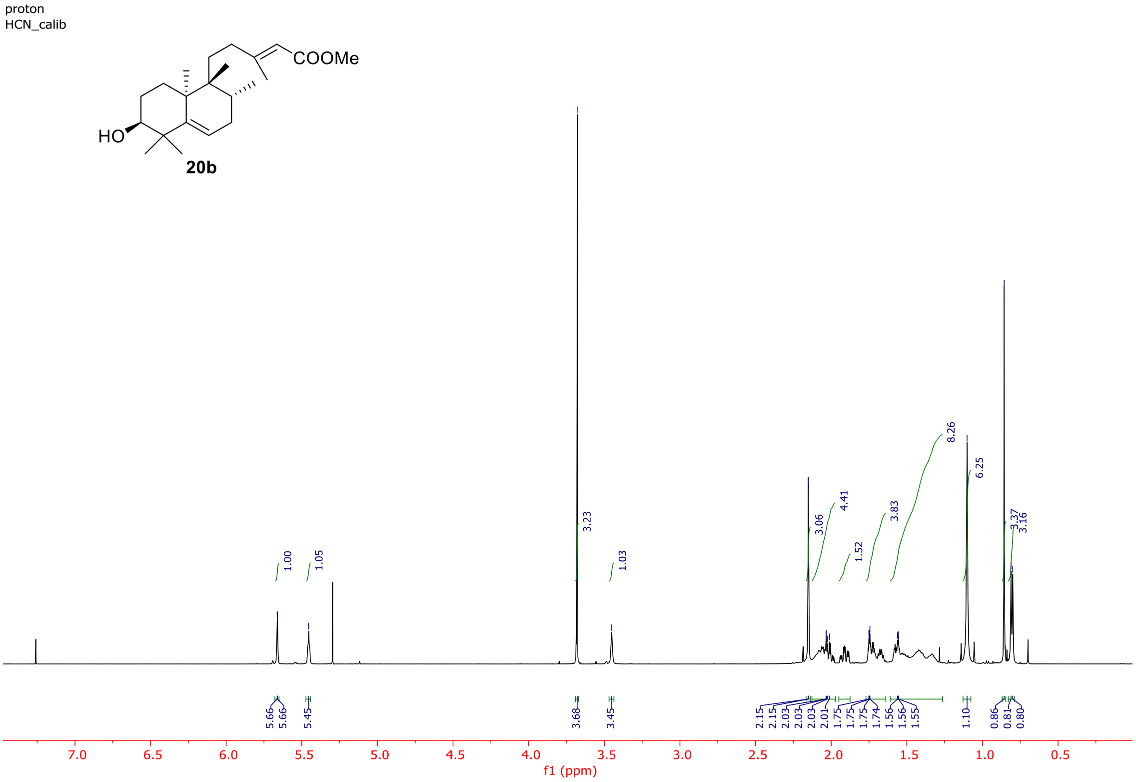

carbono
VD-654-HPLCA
RMN-149-11
142.46
133.82
123.48
120.86
76.47
43.23
42.45
41.45
38.61
37.07
36.61
35.19
34.64
33.55
33.24
31.93
31.50
31.13
29.55
28.49
27.06
26.60
25.56
24.72
24.23
20.41
18.55
16.25
15.43
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

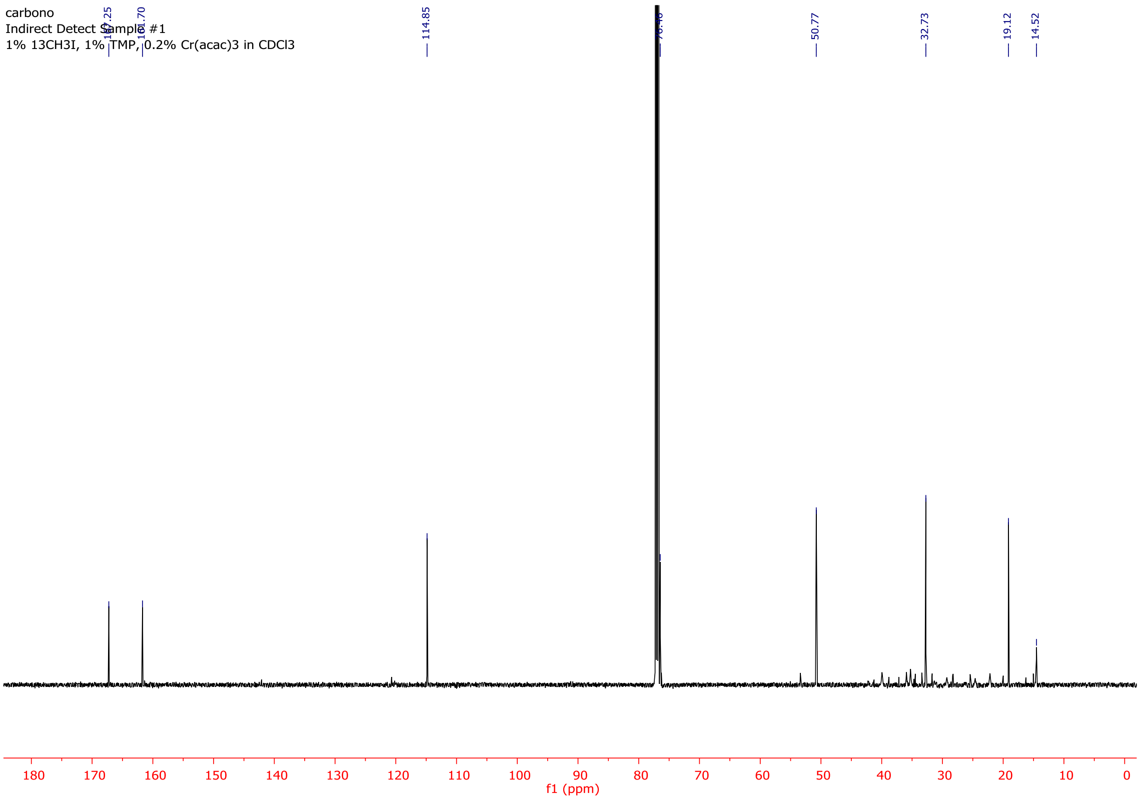

proton
STANDARD PROTON PARAMETERS
H
H
HO
1.00
1.00
2.31
5.09
3.33
29.04
17.08
5.46
3.45
2.07
2.06
1.92
1.91
1.90
1.74
1.73
1.57
1.56
1.51
1.36
1.27
1.26
1.19
1.13
1.12
1.10
0.88
0.87
0.82
0.81
0.81
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

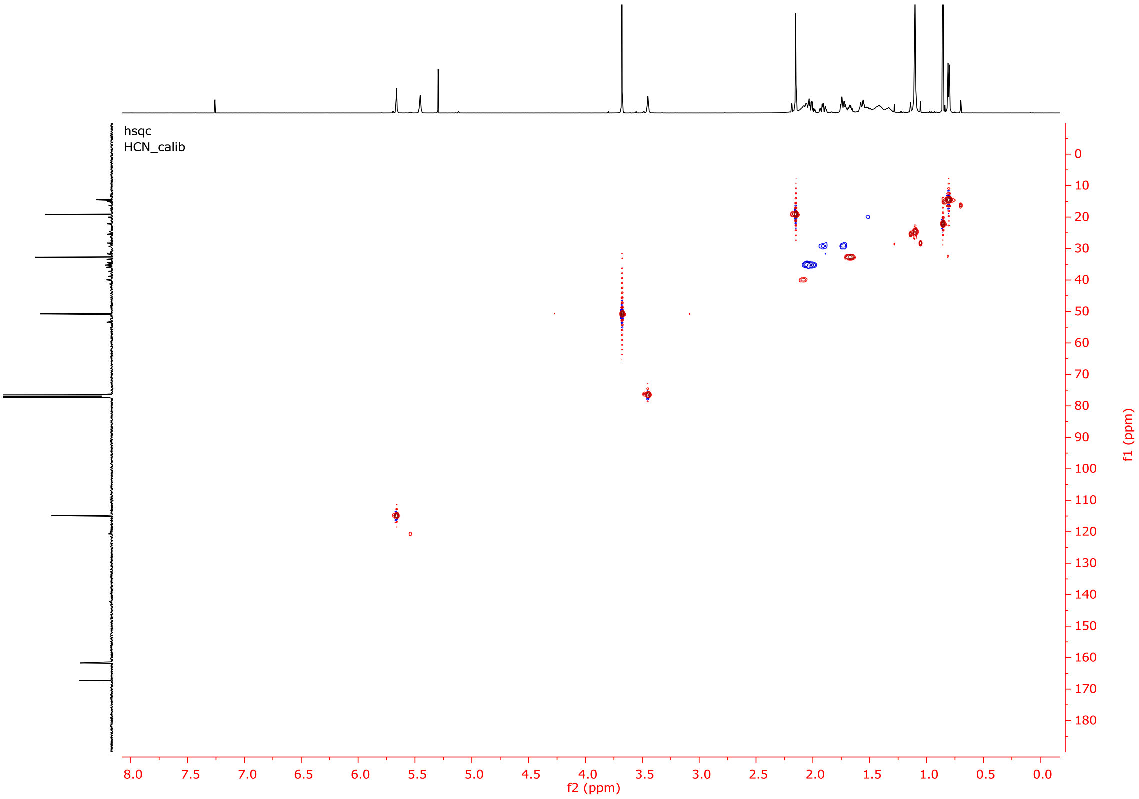
18b

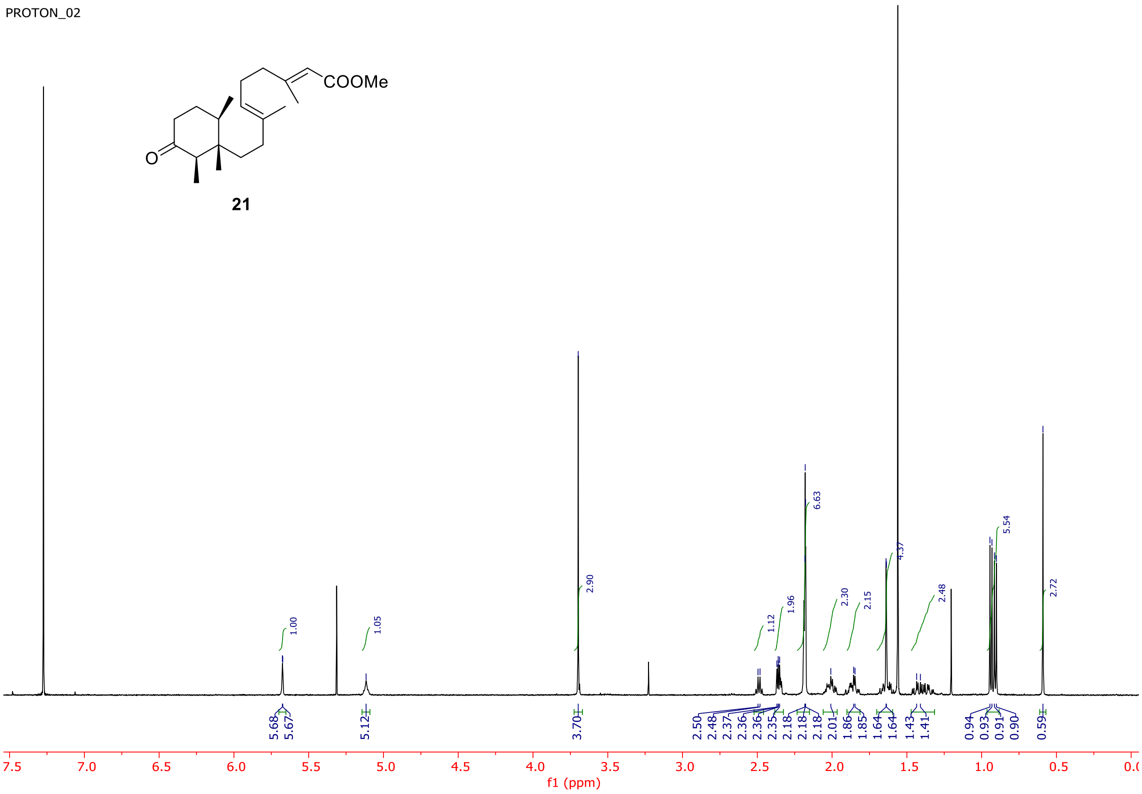

134.045
123.238
120.732
76.705
76.571
43.082
42.518
39.910
36.508
35.890
34.572
33.115
32.675
31.545
31.371
30.982
29.433
29.243
26.948
26.538
25.147
24.774
24.069
22.606
22.286
18.340
14.453
14.052
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

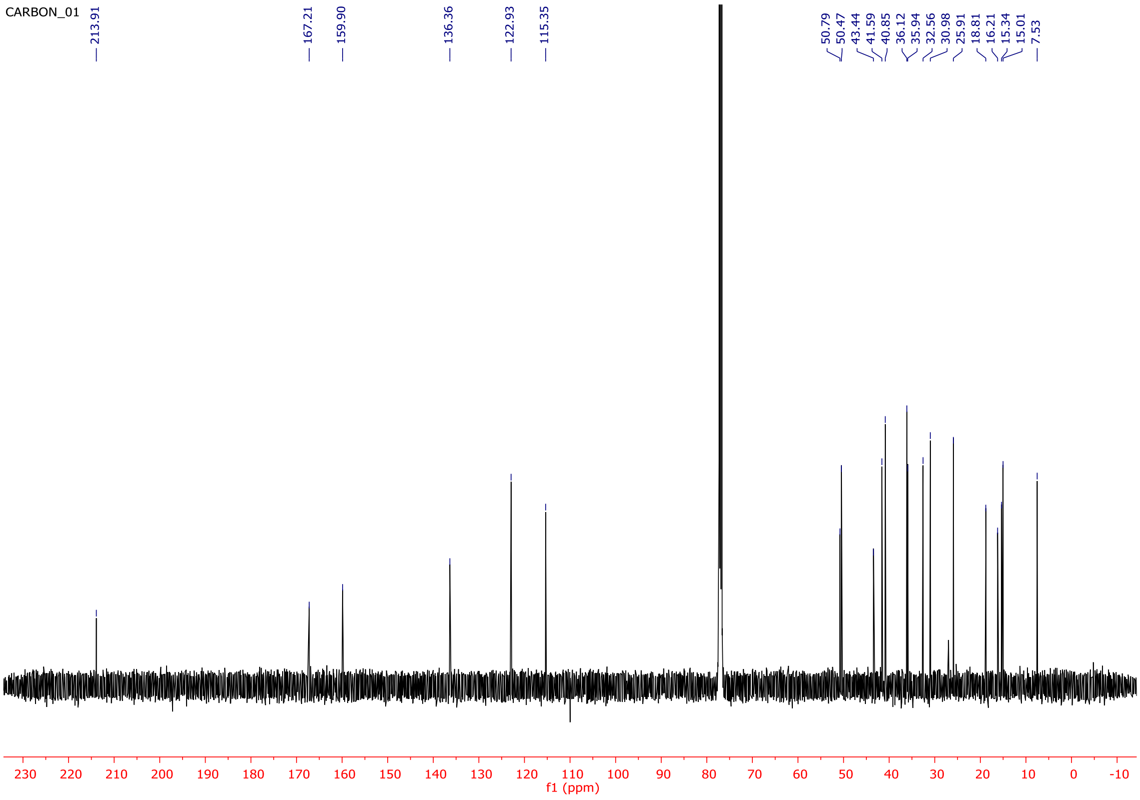

hsqc
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
f2 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)

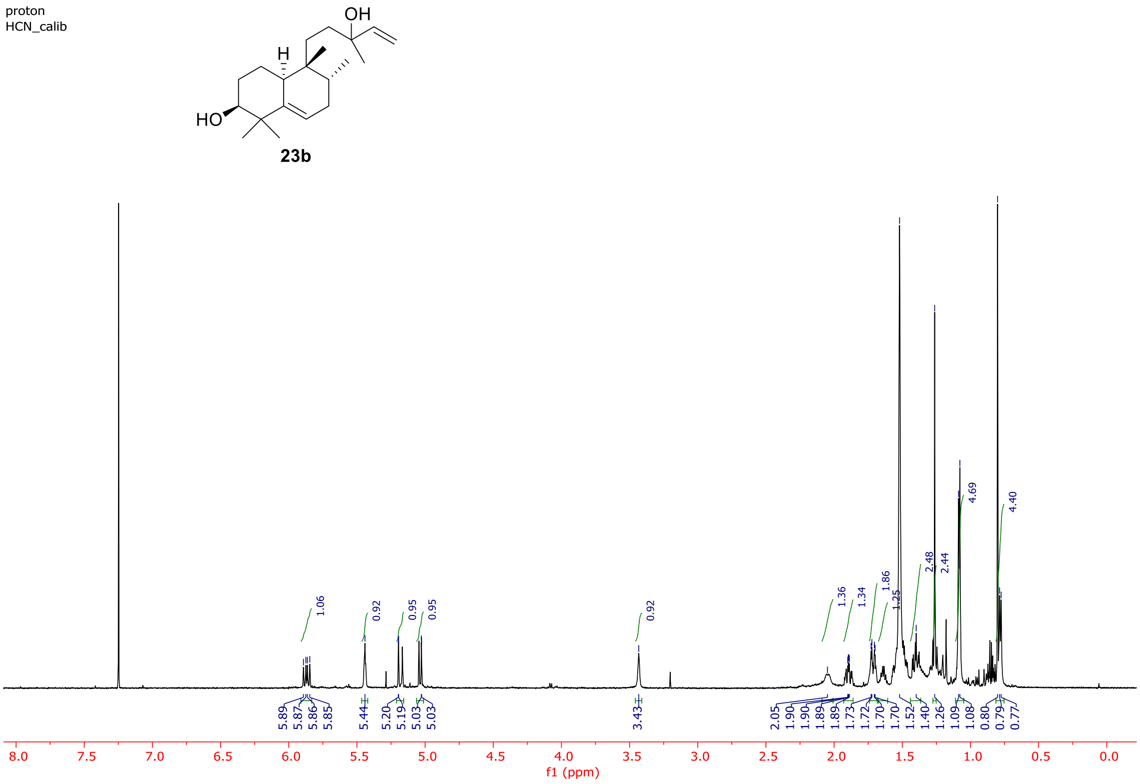

proton
HCN_calib
COOMe
HO
20b
1.00
1.05
3.23
1.03
3.06
4.41
1.52
3.83
8.26
6.25
3.37
3.16
5.66
5.66
5.45
3.68
3.45
2.15
2.15
2.03
2.03
2.03
2.01
1.75
1.75
1.75
1.74
1.56
1.56
1.55
1.10
0.86
0.81
0.80
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

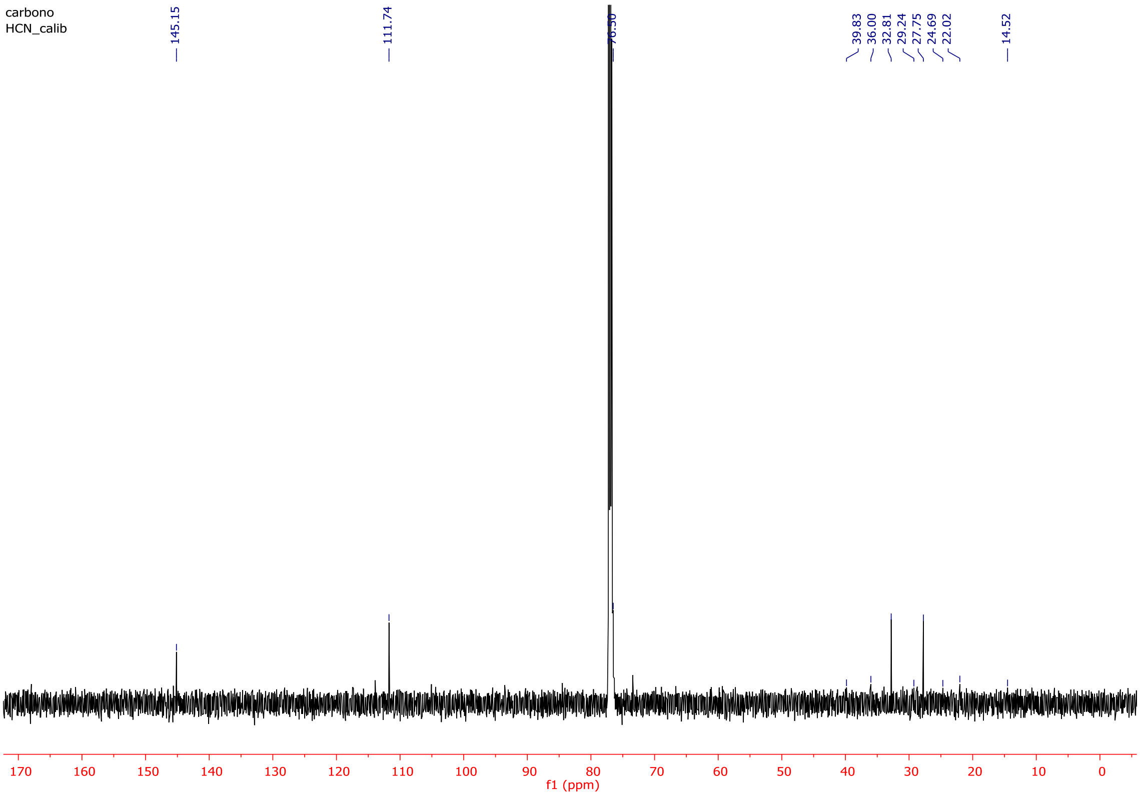

carbono
Indirect Detect Sample #1
1% 13CH3I, 1% TMP, 0.2% Cr(acac)3 in CDCl3
167.25
161.70
114.85
50.77
32.73
19.12
14.52
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

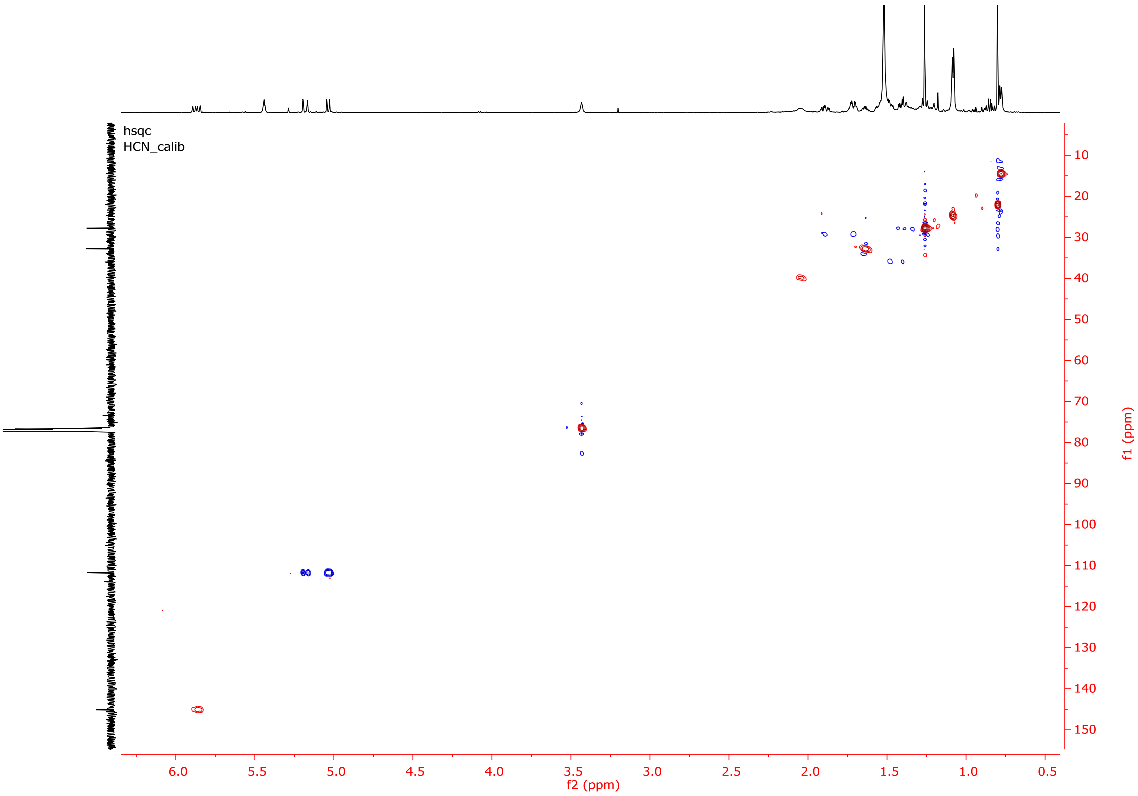

hsqc
HCN_calib
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)

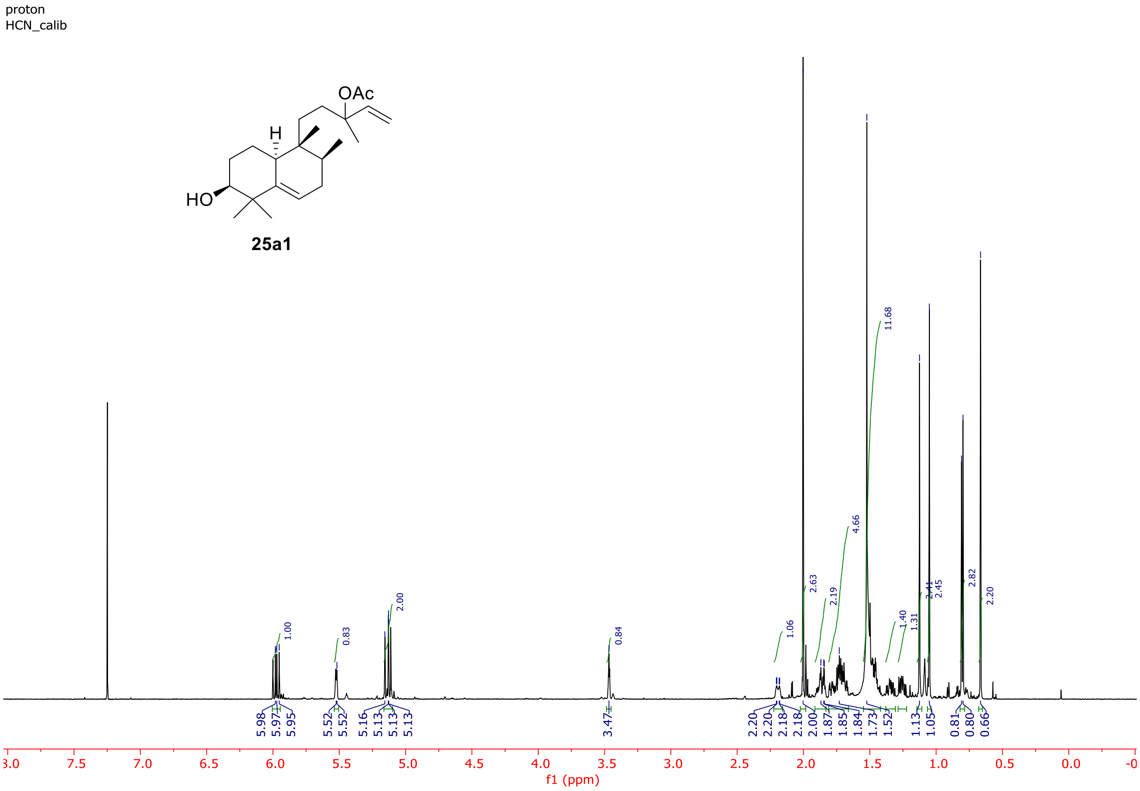

PROTON_02
COOMe
O
21
1.00
1.05
2.90
1.12
1.96
6.63
2.30
2.15
4.37
2.48
5.54
2.72
5.68
5.67
5.12
3.70
2.50
2.48
2.37
2.36
2.36
2.35
2.18
2.18
2.18
2.01
1.86
1.85
1.64
1.64
1.43
1.41
0.94
0.93
0.91
0.90
0.59
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

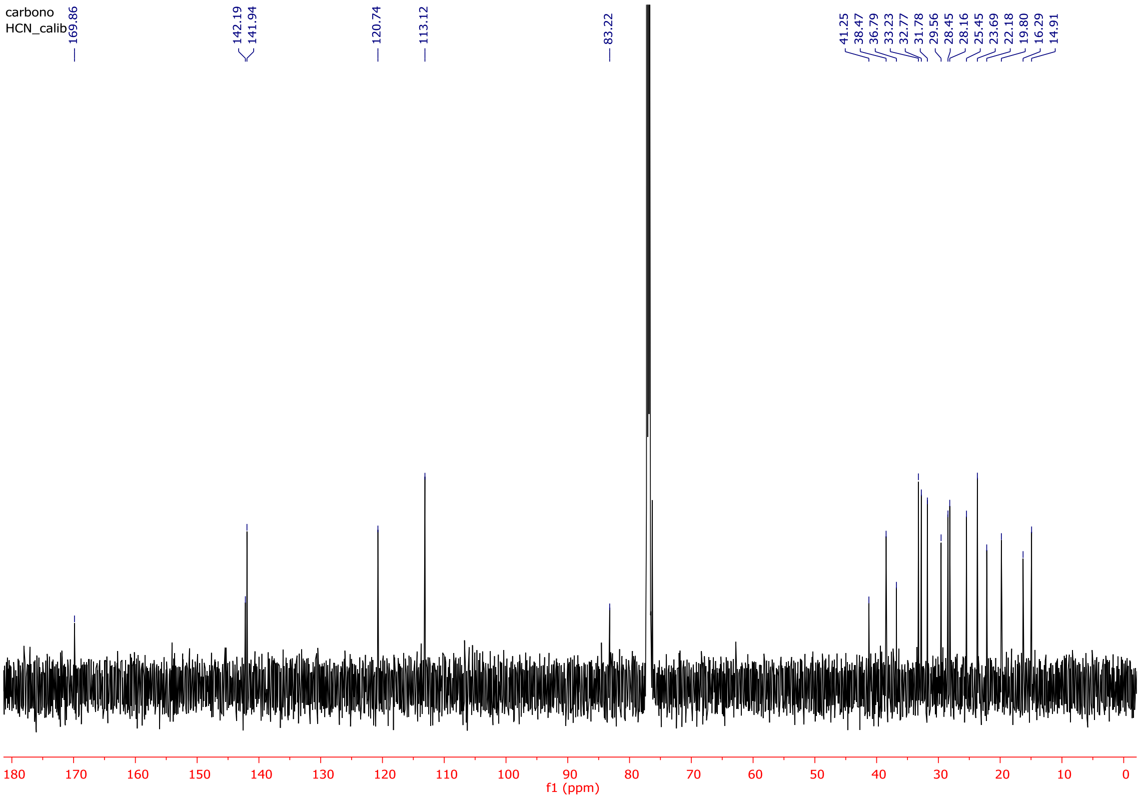

CARBON_01
213.91
167.21
159.90
136.36
122.93
115.35
50.79
50.47
43.44
41.59
40.85
36.12
35.94
32.56
30.98
25.91
18.81
16.21
15.34
15.01
7.53
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

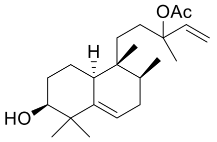

proton
HCN_calib
OH
H
HO
23b
1.06
0.92
0.95
0.95
0.92
1.36
1.34
1.86
1.25
2.48
2.44
4.69
4.40
5.89
5.87
5.86
5.85
5.44
5.20
5.19
5.03
5.03
3.43
2.05
1.90
1.90
1.89
1.89
1.73
1.72
1.70
1.70
1.52
1.40
1.26
1.09
1.08
0.80
0.79
0.77
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


carbono
HCN_calib
145.15
111.74
76.50
39.83
36.00
32.81
29.24
27.75
24.69
22.02
14.52
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

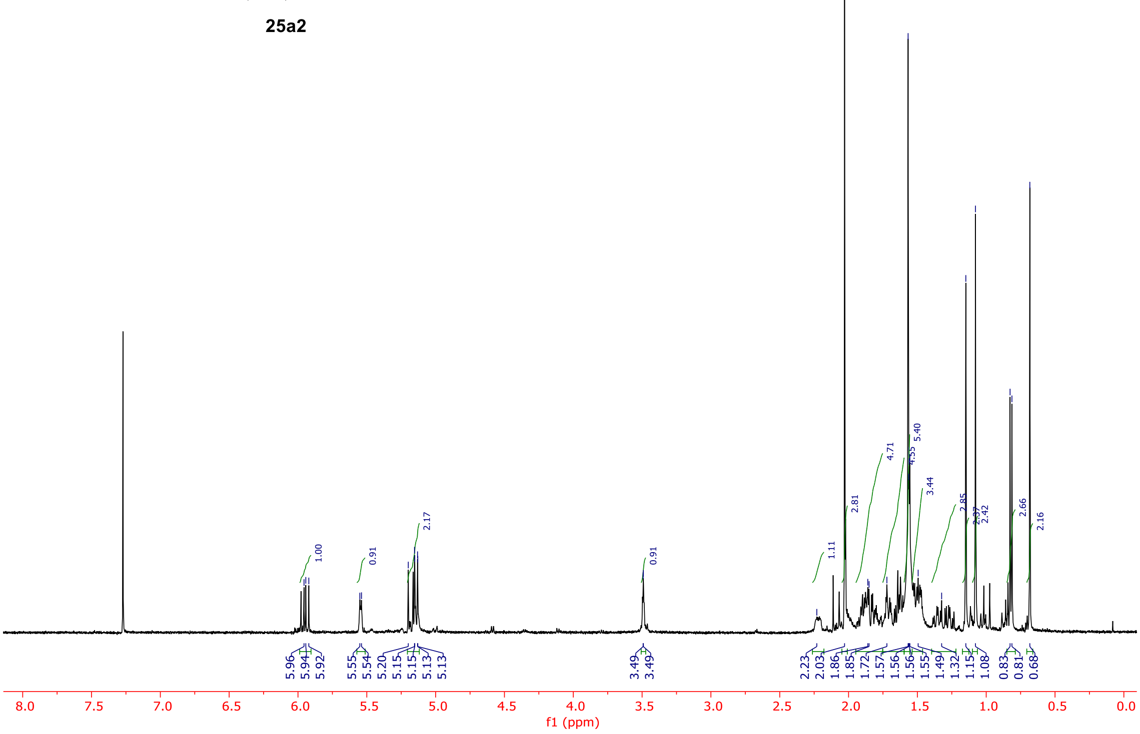

hsqc
HCN_calib
f2 (ppm)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

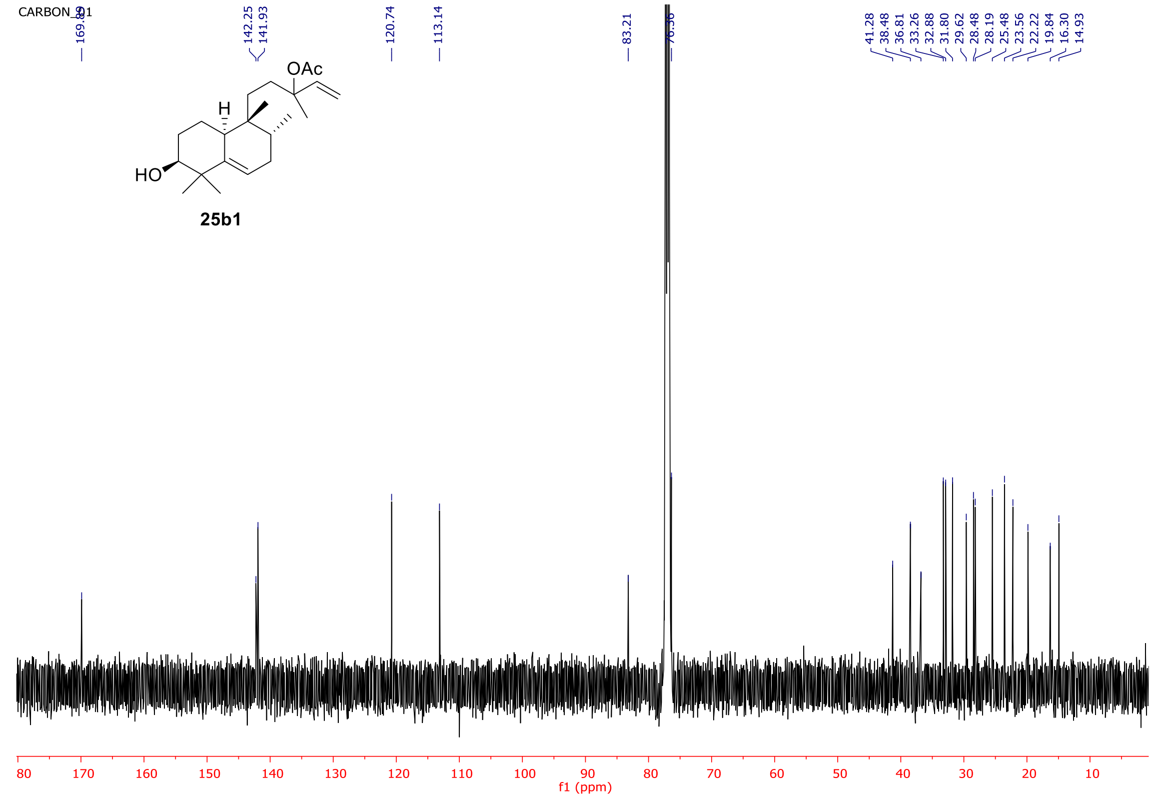

proton
HCN_calib
OAc
H
HO
25a1
1.00
0.83
2.00
0.84
1.06
2.63
2.19
4.66
11.68
1.40
1.31
2.41
2.45
2.82
2.20
5.98
5.97
5.95
5.52
5.52
5.16
5.13
5.13
5.13
3.47
2.20
2.20
2.18
2.00
1.87
1.85
1.84
1.73
1.52
1.13
1.05
0.81
0.80
0.66
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0
f1 (ppm)


carbono
HCN_calib
169.86
142.19
141.94
120.74
113.12
83.22
41.25
38.47
36.79
33.23
32.77
31.78
29.56
28.45
28.16
25.45
23.69
22.18
19.80
16.29
14.91
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

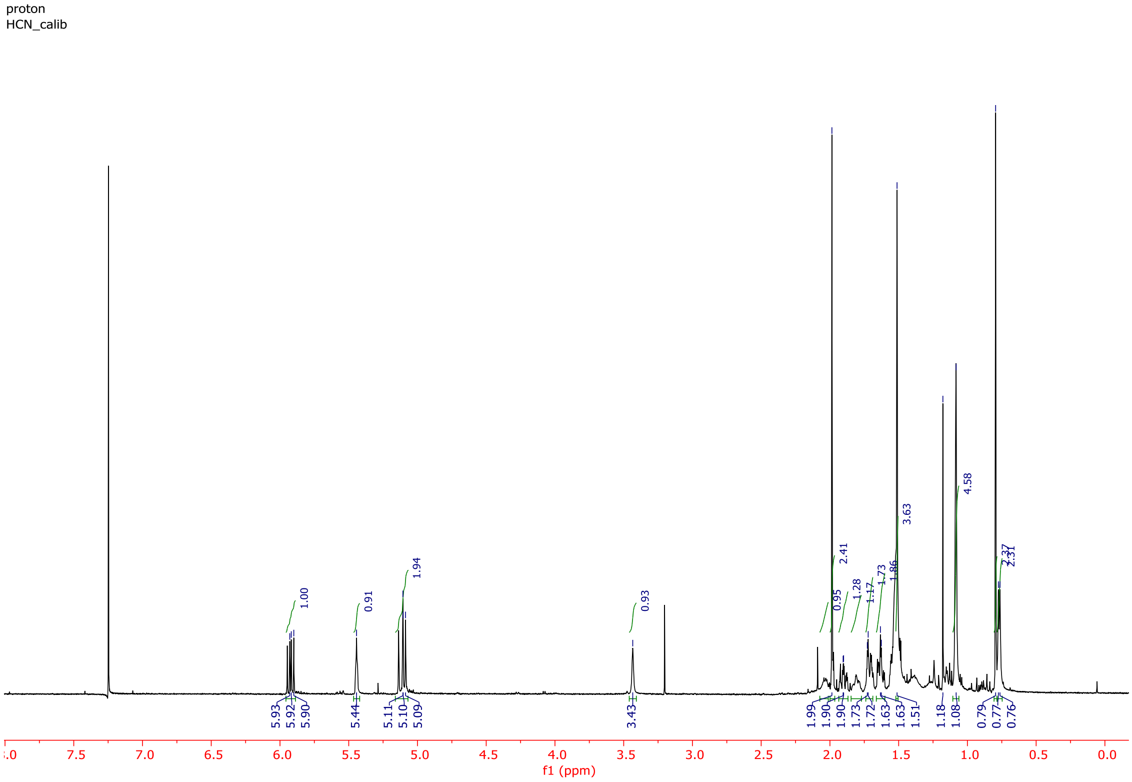

OAc
H
HO

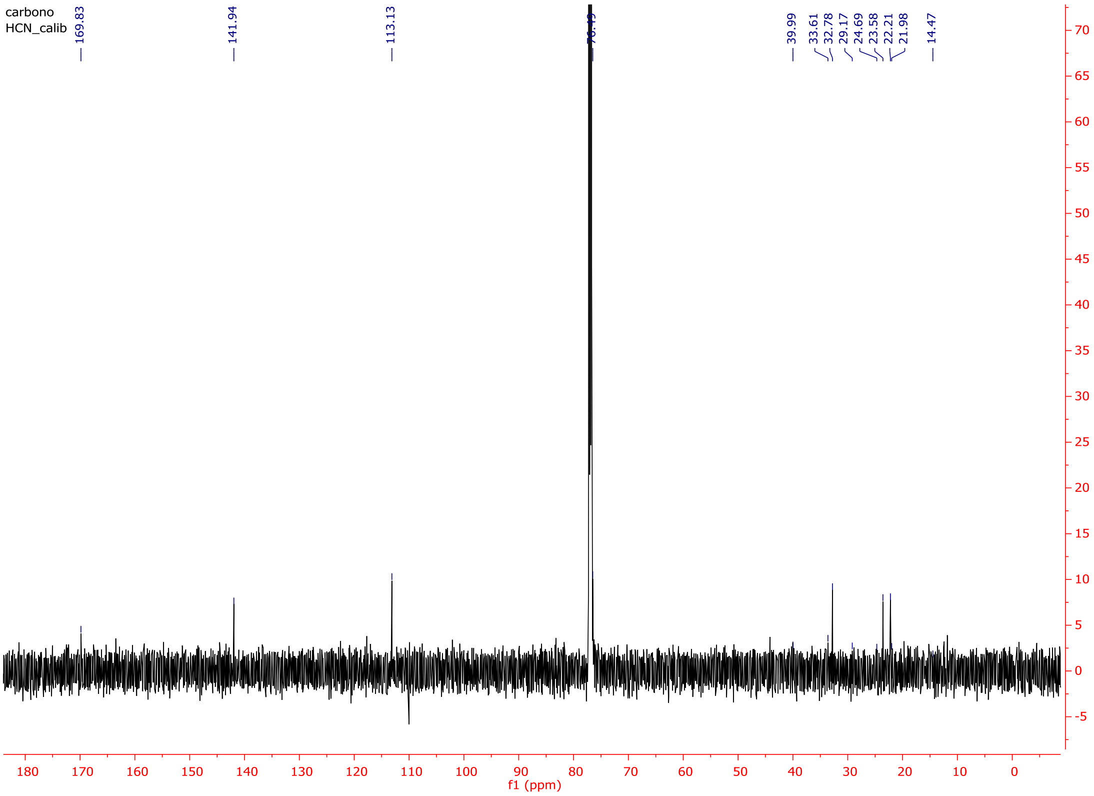
25a2

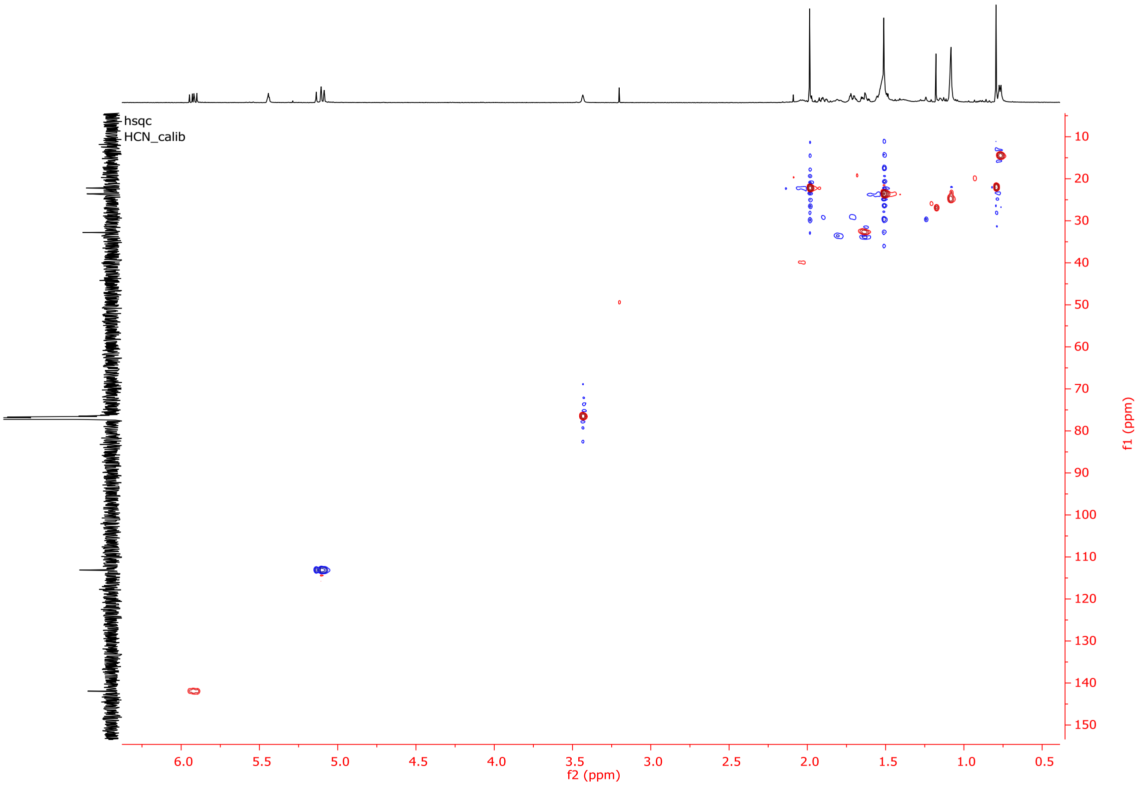

PROTON_01
1.00
0.91
2.17
0.91
1.11
2.81
4.71
4.55
5.40
3.44
2.85
2.37
2.42
2.66
2.16
5.96
5.94
5.92
5.55
5.54
5.20
5.15
5.15
5.13
5.13
3.49
3.49
2.23
2.03
1.86
1.85
1.72
1.57
1.56
1.56
1.55
1.49
1.32
1.15
1.08
0.83
0.81
0.68
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

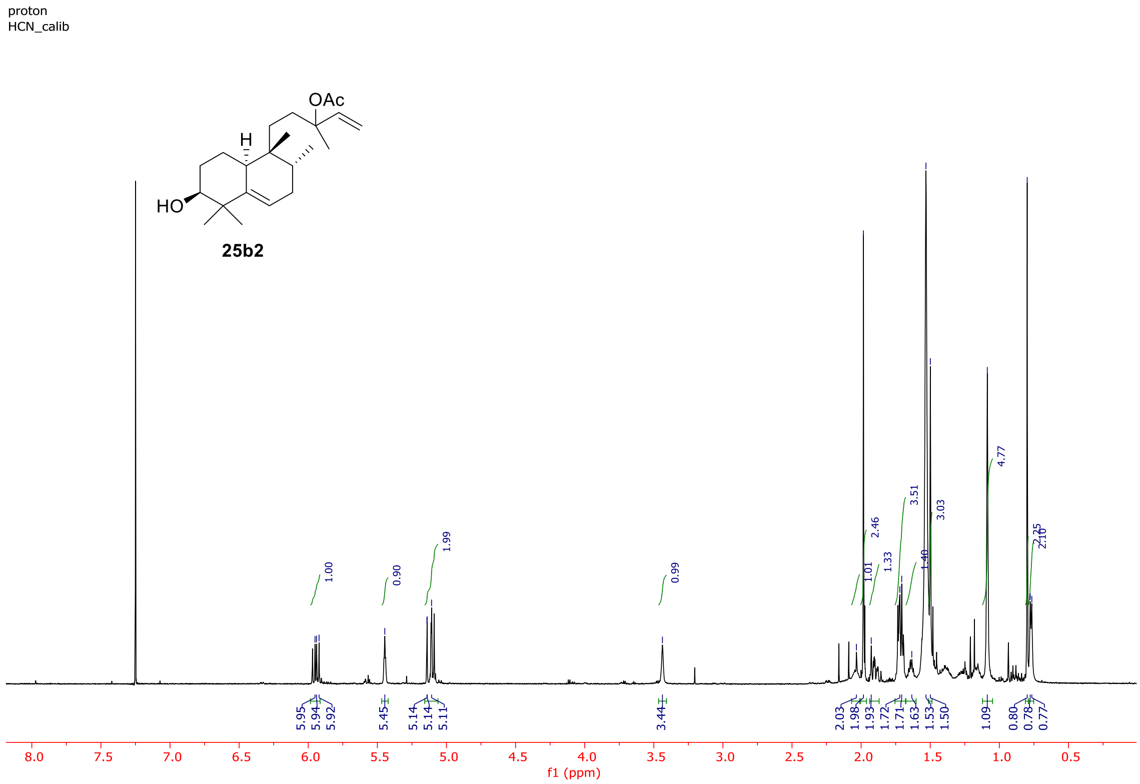

CARBON_01
169.89
142.25
141.93
120.74
113.14
83.21
76.36
41.28
38.48
36.81
33.26
32.88
31.80
29.62
28.48
28.19
25.48
23.56
22.22
19.84
16.30
14.93
OAc
H
HO
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

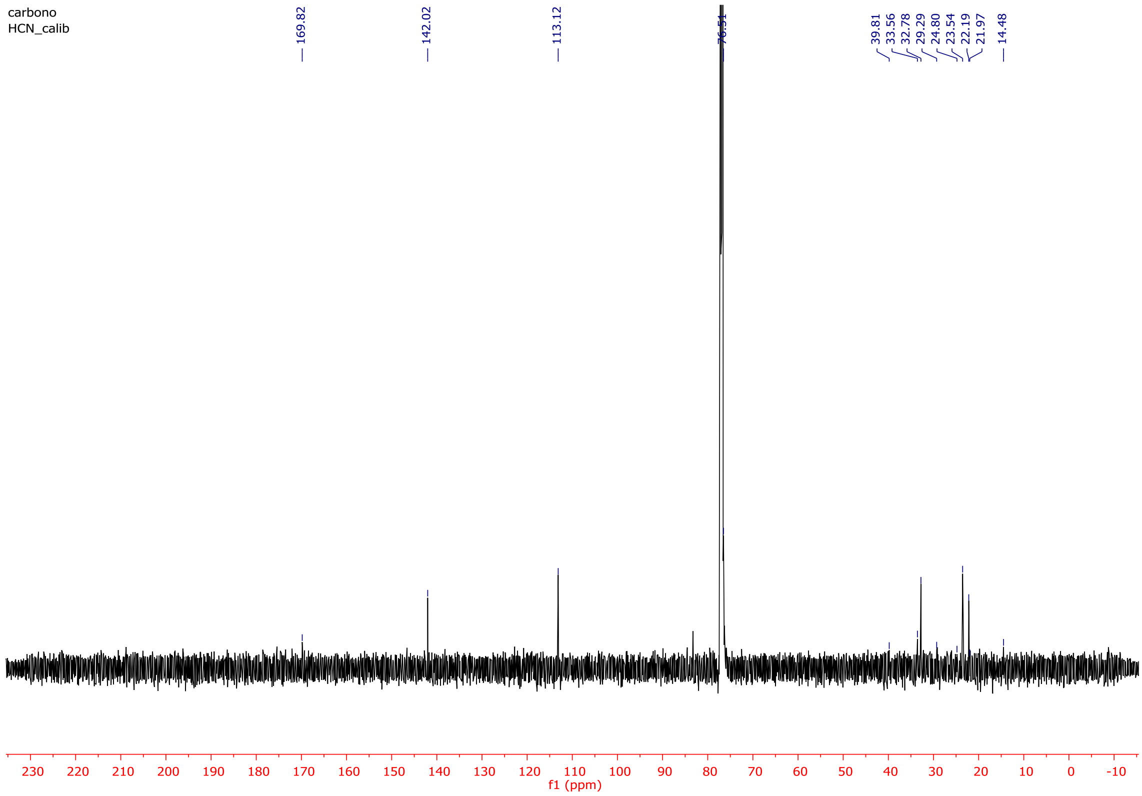
25b1

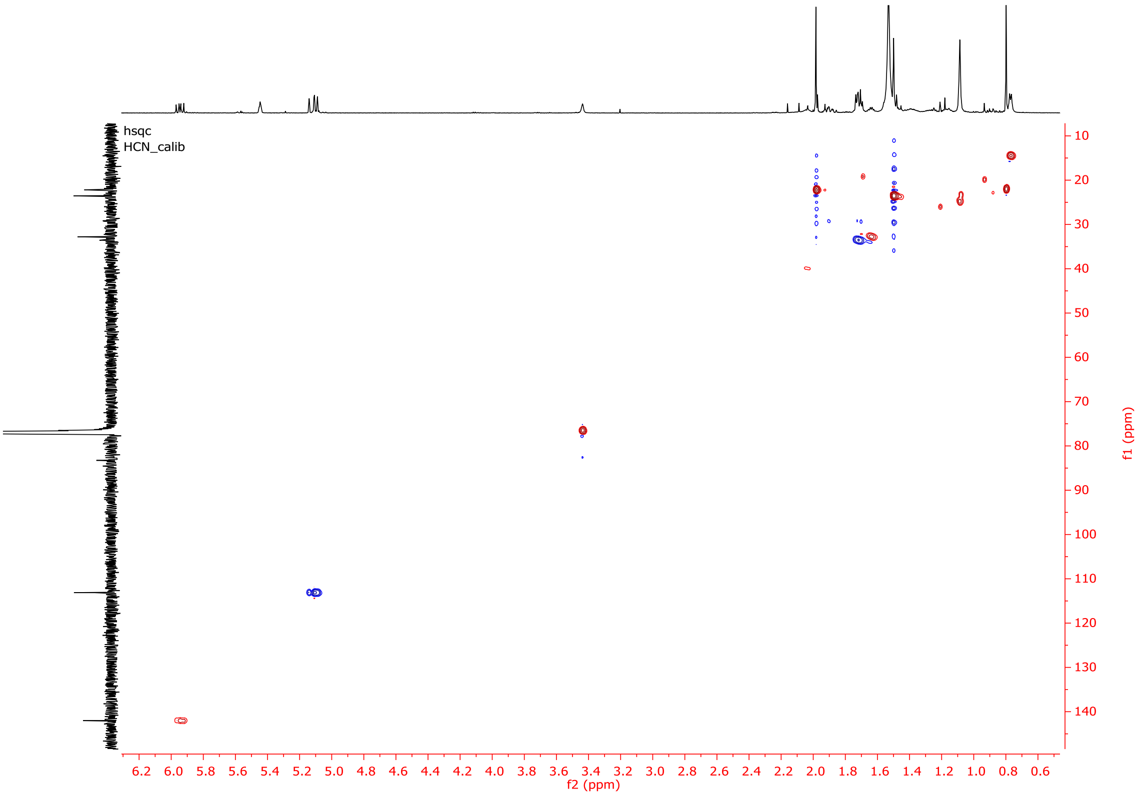

proton
HCN_calib
1.00
0.91
1.94
0.93
0.95
2.41
1.28
1.17
1.73
1.86
3.63
4.58
2.37
2.31
5.93
5.92
5.90
5.44
5.11
5.10
5.09
3.43
1.99
1.90
1.90
1.73
1.72
1.63
1.63
1.51
1.18
1.08
0.79
0.77
0.76
.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

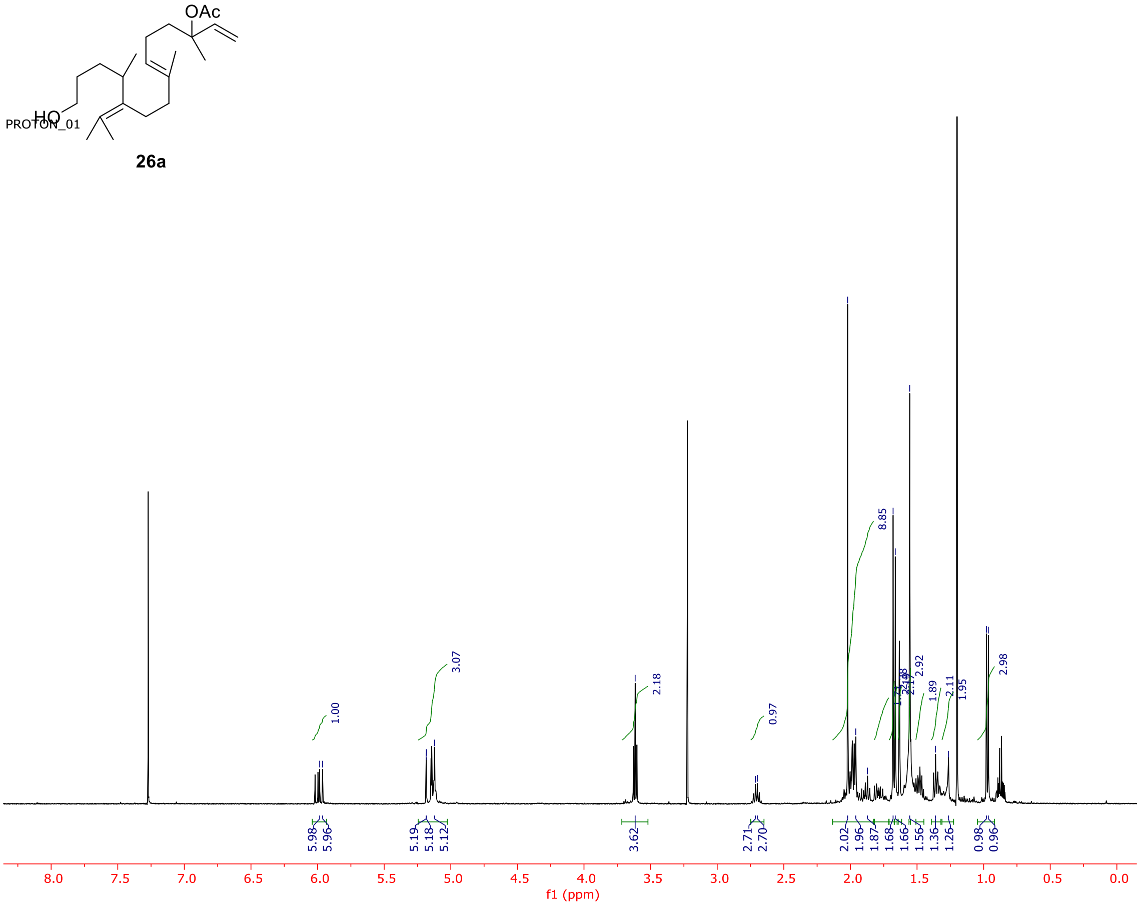

carbono
HCN_calib
169.83
141.94
113.13
76.49
39.99
33.61
32.78
29.17
24.69
23.58
22.21
21.98
14.47
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


hsqc
HCN_calib
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

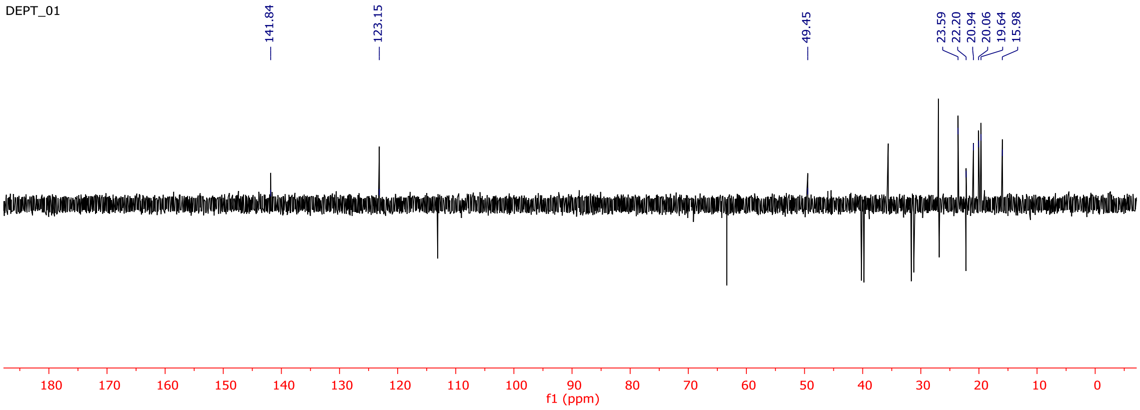

25b2
proton
HCN_calib
OAc
H
HO
1.00
0.90
1.99
0.99
1.01
2.46
1.33
3.51
1.40
3.03
4.77
2.25
2.10
5.95
5.94
5.92
5.45
5.14
5.14
5.11
3.44
2.03
1.98
1.93
1.72
1.71
1.63
1.53
1.50
1.09
0.80
0.78
0.77
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

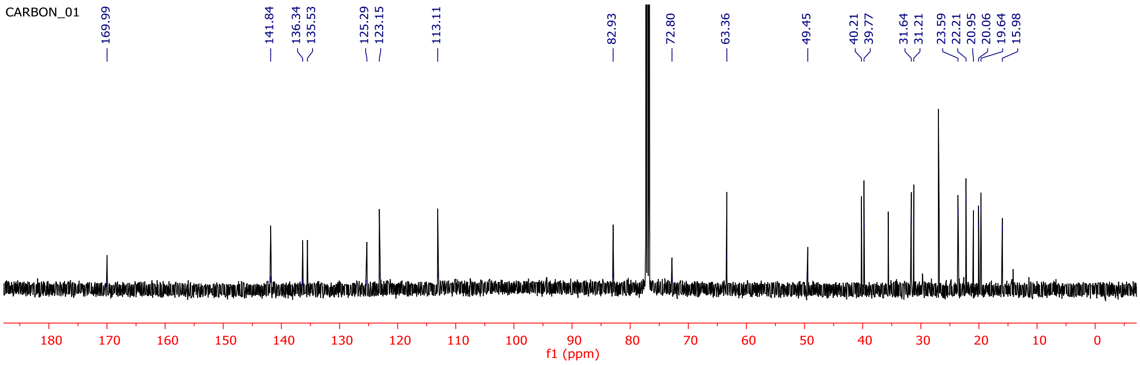

carbono
HCN_calib
169.82
142.02
113.12
76.51
39.81
33.56
32.78
29.29
24.80
23.54
22.19
21.97
14.48
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

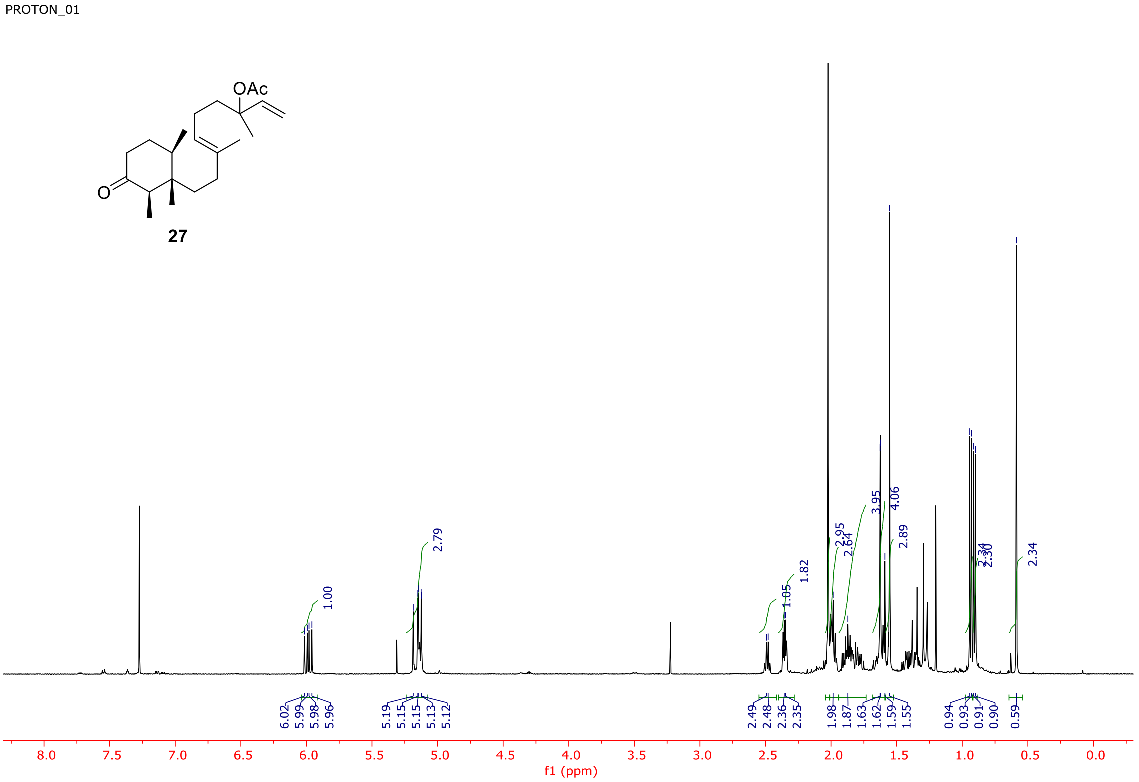

hsqc
HCN_calib
f2 (ppm)
f1 (ppm)
6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
10 20 30 40 50 60 70 80 90 100 110 120 130 140

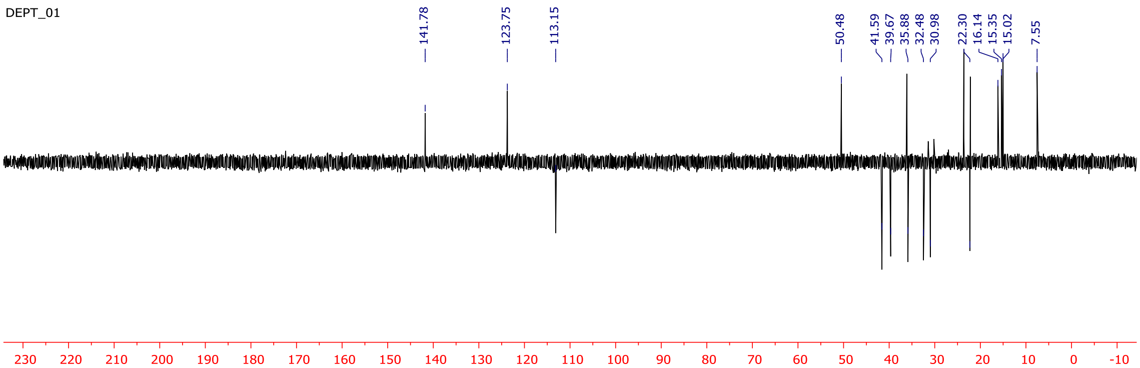

OAc
HO
PROTON_01
1.00
3.07
2.18
0.97
8.85
2.92
1.89
2.11
1.95
2.98
5.98
5.96
5.19
5.18
5.12
3.62
2.71
2.70
2.02
1.96
1.87
1.68
1.66
1.56
1.36
1.26
0.98
0.96
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

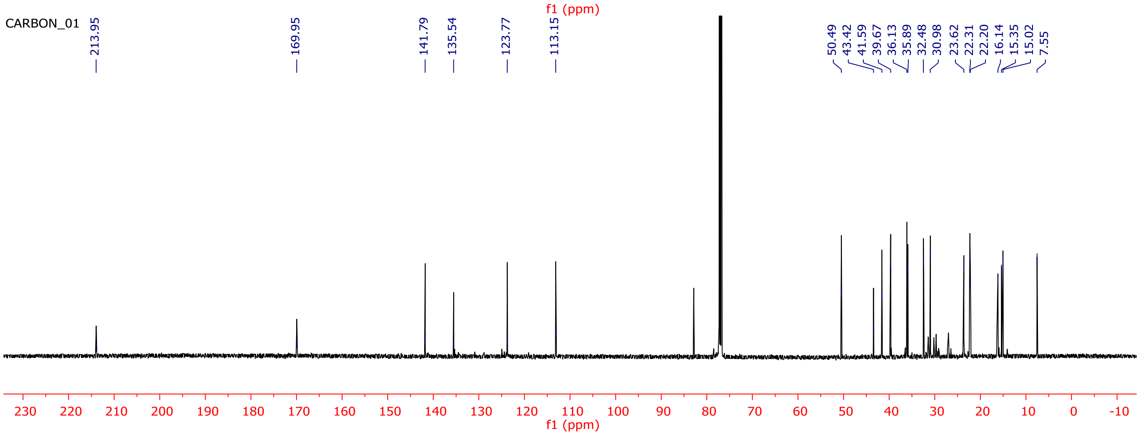
26a


DEPT_01
141.84
123.15
49.45
23.59
22.20
20.94
20.06
19.64
15.98
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

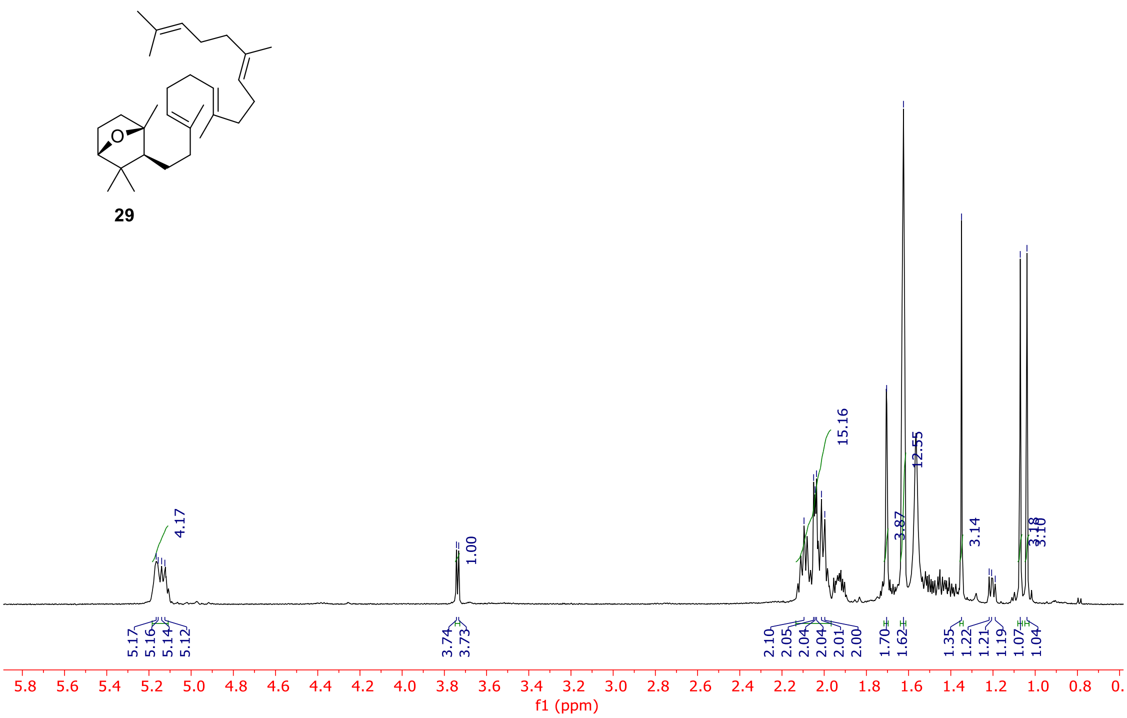

CARBON_01
169.99
141.84
136.34
135.53
125.29
123.15
113.11
82.93
72.80
63.36
49.45
40.21
39.77
31.64
31.21
23.59
22.21
20.95
20.06
19.64
15.98
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

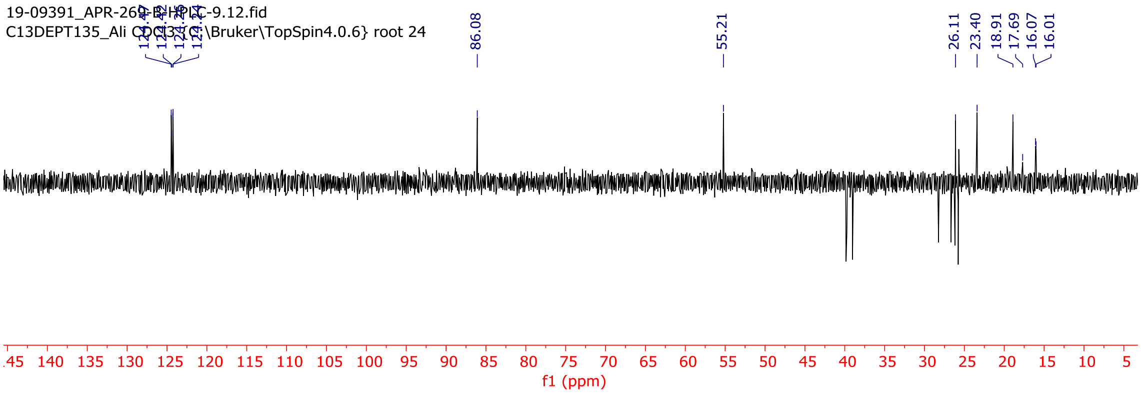

PROTON_01
OAc
O
27
1.00
2.79
1.05
1.82
2.95
2.64
3.95
4.06
2.89
2.34
2.30
2.34
6.02
5.99
5.98
5.96
5.19
5.15
5.15
5.13
5.12
2.49
2.48
2.36
2.35
1.98
1.87
1.63
1.62
1.59
1.55
0.94
0.93
0.91
0.90
0.59
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

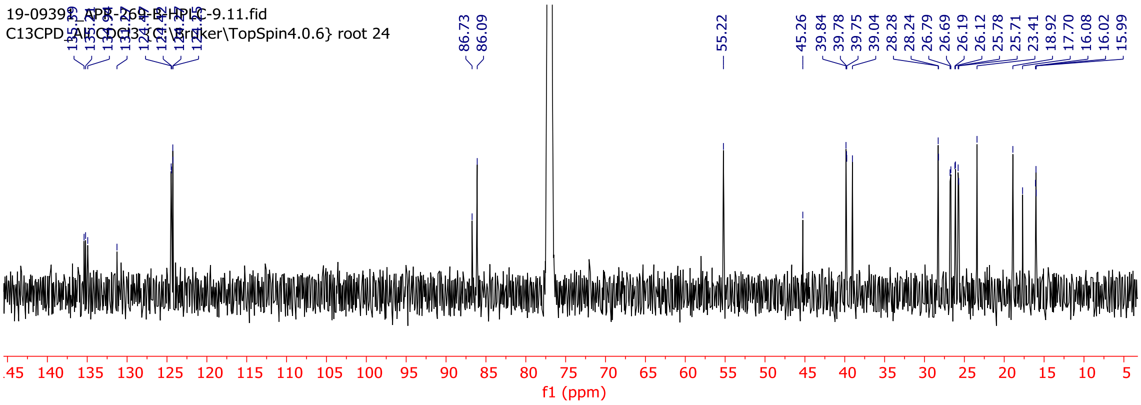


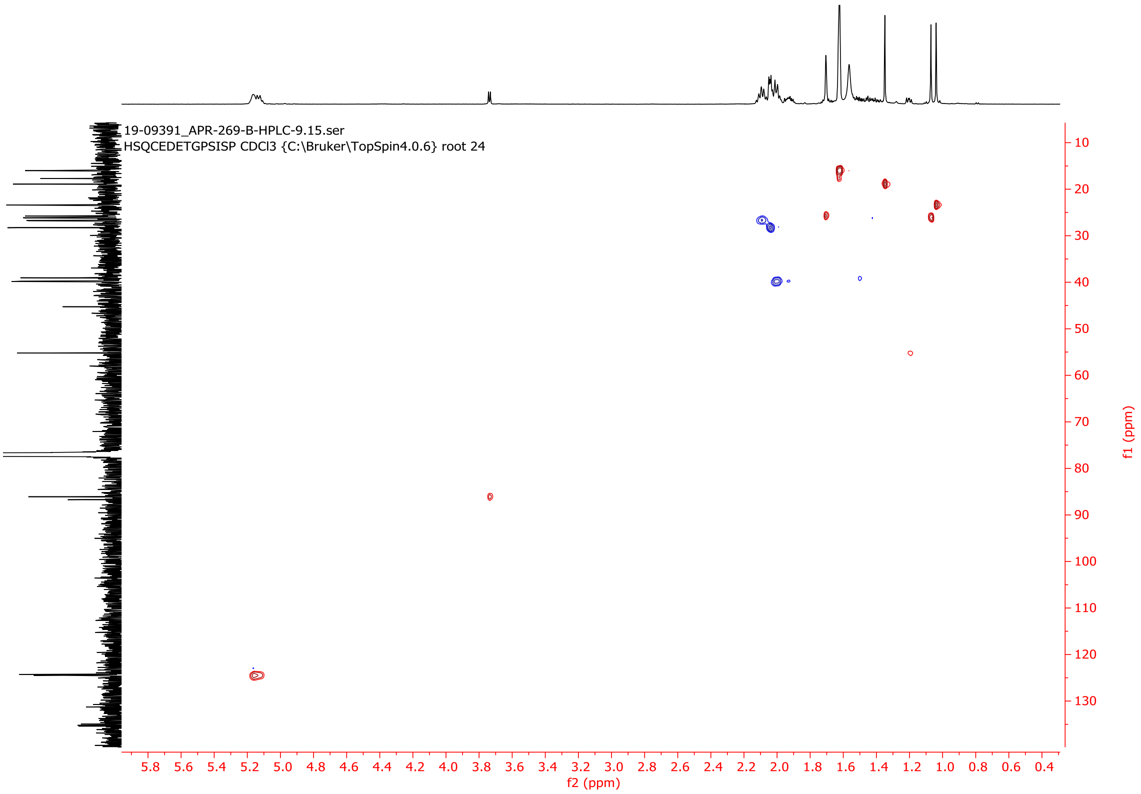


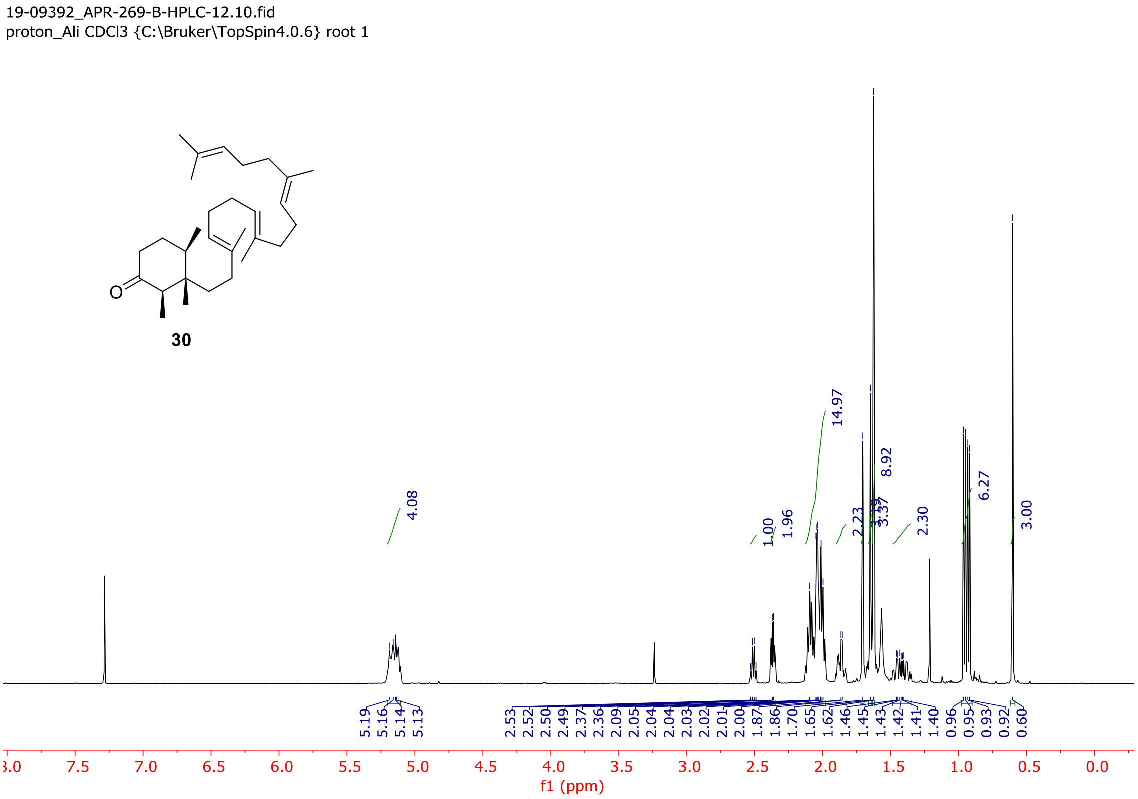
19-09391_APR-269-B-HPLC-9.10.fid
proton_Ali CDCl3 {C:\Bruker\TopSpin4.0.6} root 24

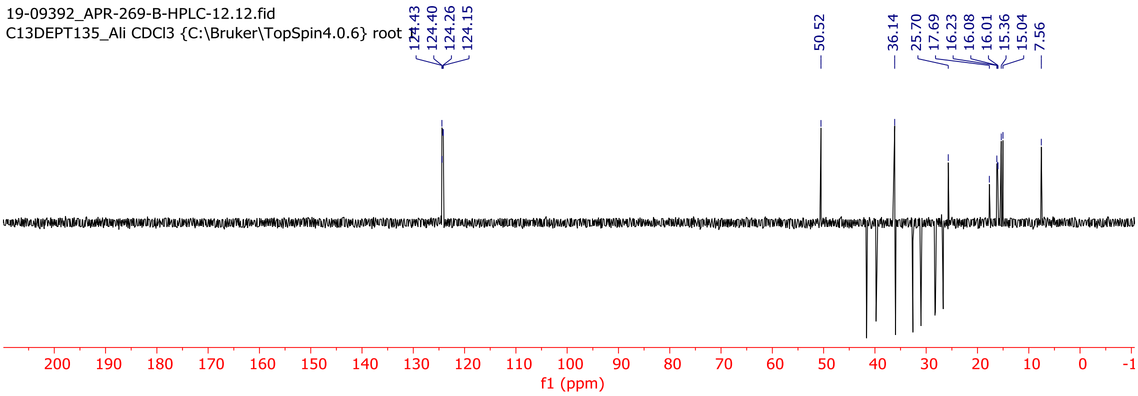


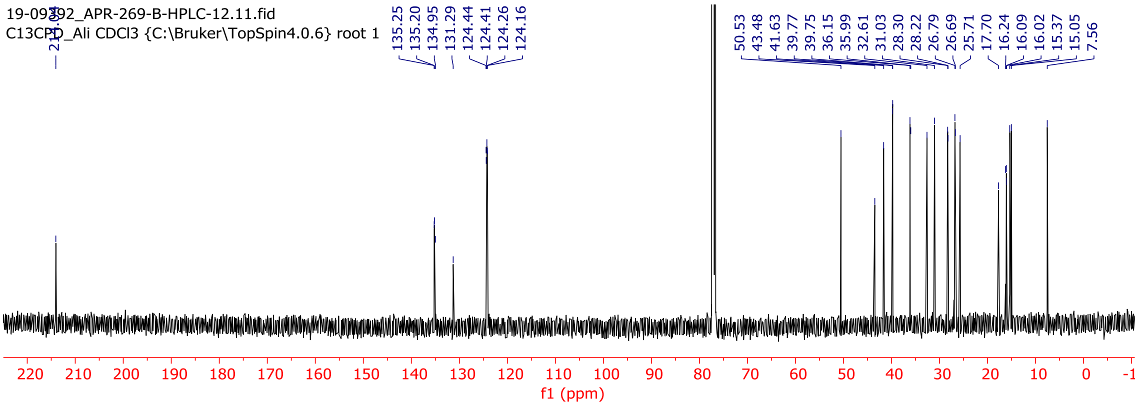

19-09391_APR-269-B-HPLC-9.12.fid
C13DEPT135_Ali CDCl3 {C:\Bruker\TopSpin4.0.6} root 24
124.47
124.42
124.26
124.24
86.08
55.21
26.11
23.40
18.91
17.69
16.07
16.01
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)


19-09391_APR-269-B-HPLC-9.11.fid
C13CPD_Ali CDCl3 {C:\Bruker\TopSpin4.0.6} root 24
135.39
135.21
134.94
131.27
124.47
124.42
124.27
124.25
86.73
86.09
55.22
45.26
39.84
39.78
39.75
39.04
28.28
28.24
26.79
26.69
26.19
26.12
25.78
25.71
23.41
18.92
17.70
16.08
16.02
15.99
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)

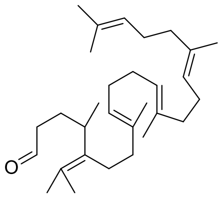

19-09391_APR-269-B-HPLC-9.15.ser
HSQCEDETGPSISP CDCl3 {C:\Bruker\TopSpin4.0.6} root 24
10
20
30
40
50
60
70
80
90
100
110
120
130
f1 (ppm)
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
f2 (ppm)


19-09392_APR-269-B-HPLC-12.10.fid
proton_Ali CDCl3 {C:\Bruker\TopSpin4.0.6} root 1
O
30
4.08
1.00
1.96
14.97
2.23
3.19
3.37
8.92
2.30
6.27
3.00
5.19
5.16
5.14
5.13
2.53
2.52
2.50
2.49
2.37
2.36
2.09
2.05
2.04
2.04
2.03
2.02
2.01
2.00
1.87
1.86
1.70
1.65
1.62
1.46
1.45
1.43
1.42
1.41
1.40
0.96
0.95
0.93
0.92
0.60
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

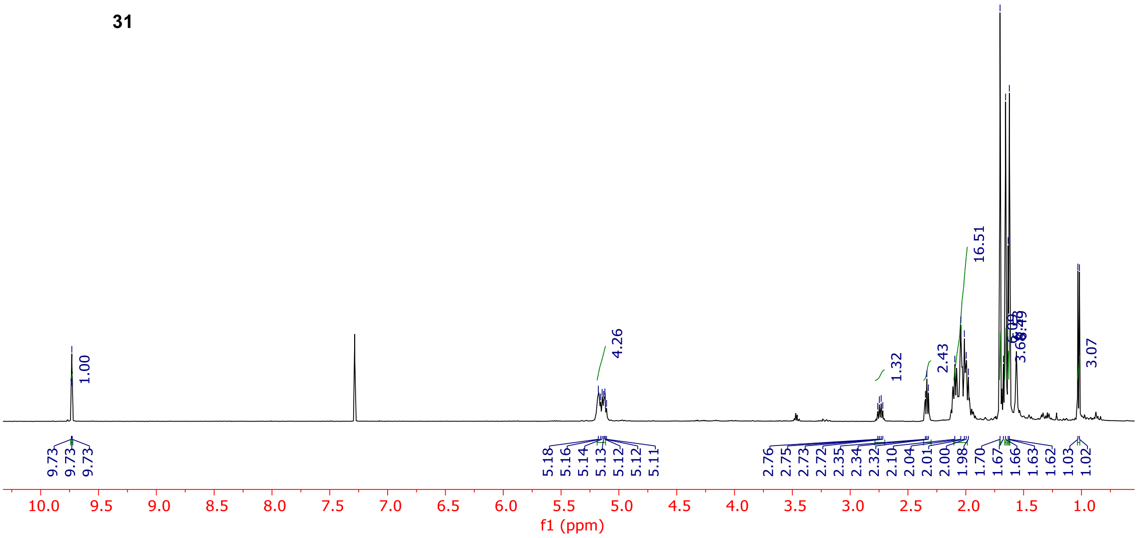

19-09392_APR-269-B-HPLC-12.12.fid
C13DEPT135_Ali CDCl3 {C:\Bruker\TopSpin4.0.6} root 1
124.43
124.40
124.26
124.15
50.52
36.14
25.70
17.69
16.23
16.08
16.01
15.36
15.04
7.56
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

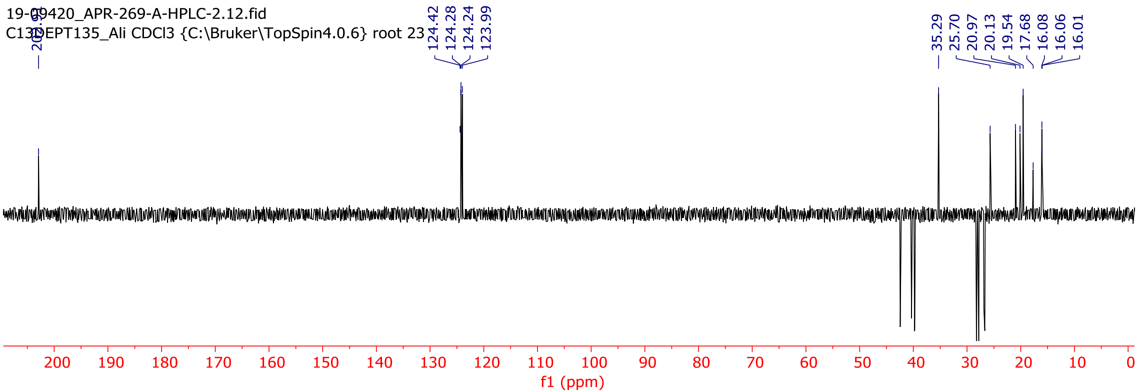

19-09392_APR-269-B-HPLC-12.11.fid
C13CPD_Ali CDCl3 {C:\Bruker\TopSpin4.0.6} root 1
214.04
135.25
135.20
134.95
131.29
124.44
124.41
124.26
124.16
50.53
43.48
41.63
39.77
39.75
36.15
35.99
32.61
31.03
28.30
28.22
26.79
26.69
25.71
17.70
16.24
16.09
16.02
15.37
15.05
7.56
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

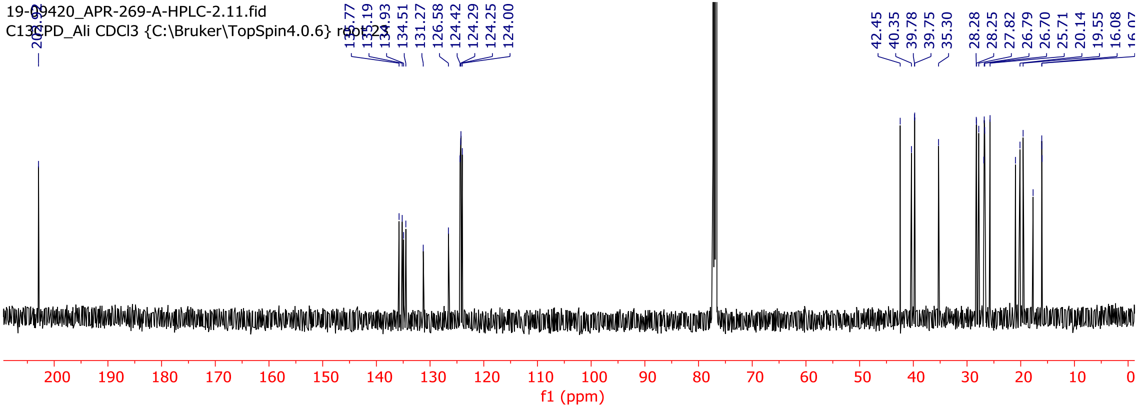
19-09420_APR-269-A-HPLC-2.10.fid
proton_Ali CDCl3 {C:\Bruker\TopSpin4.0.6} root 23

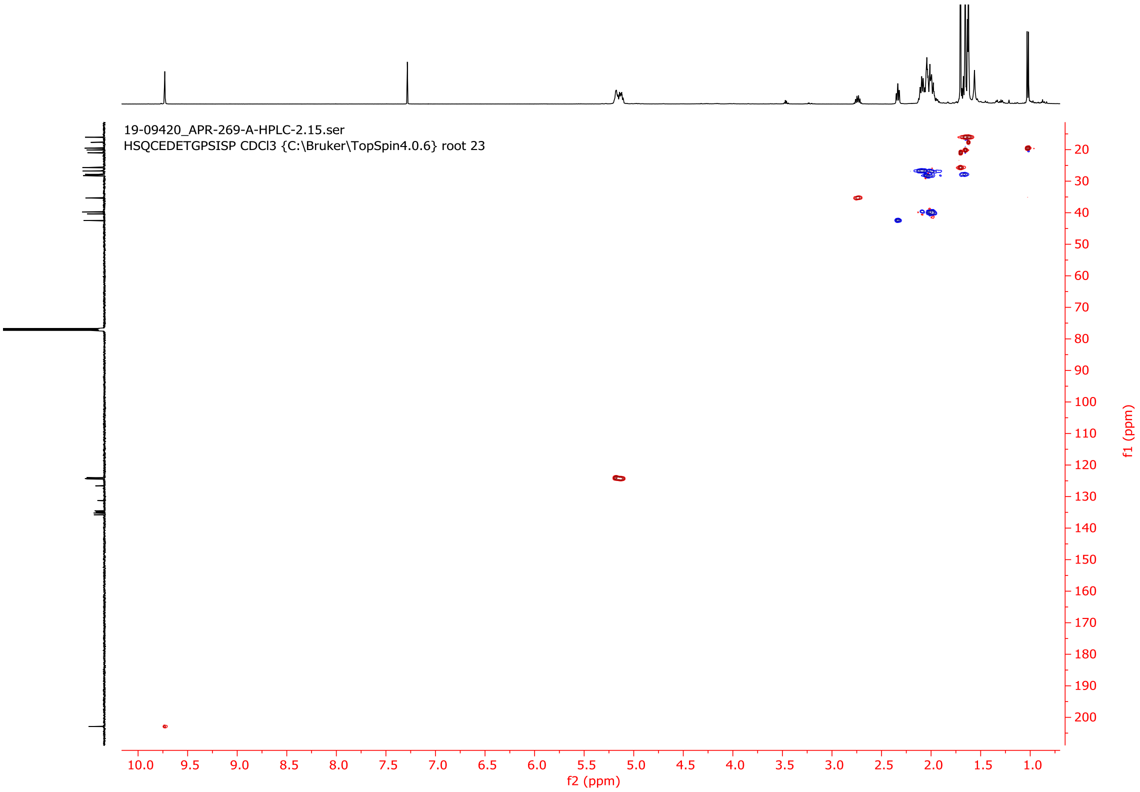


31

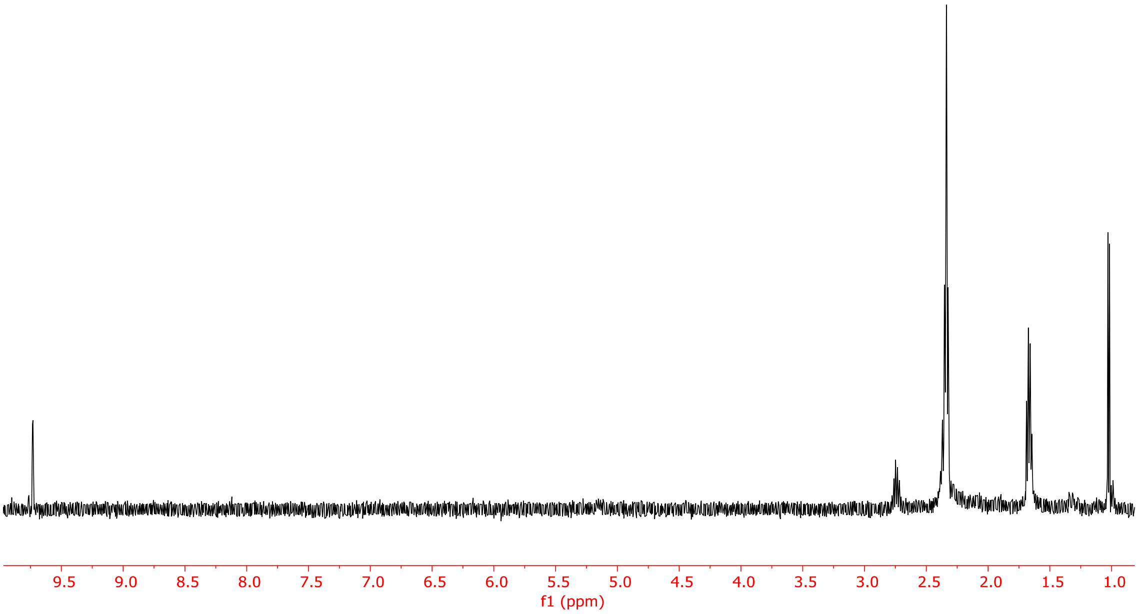


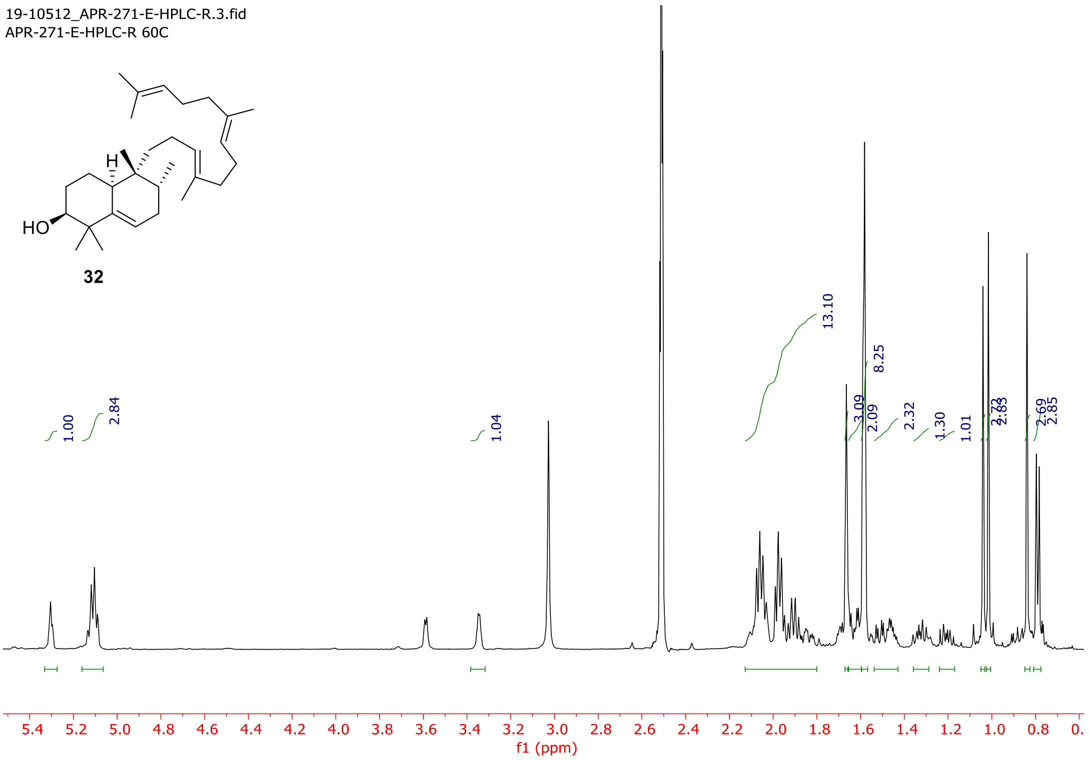


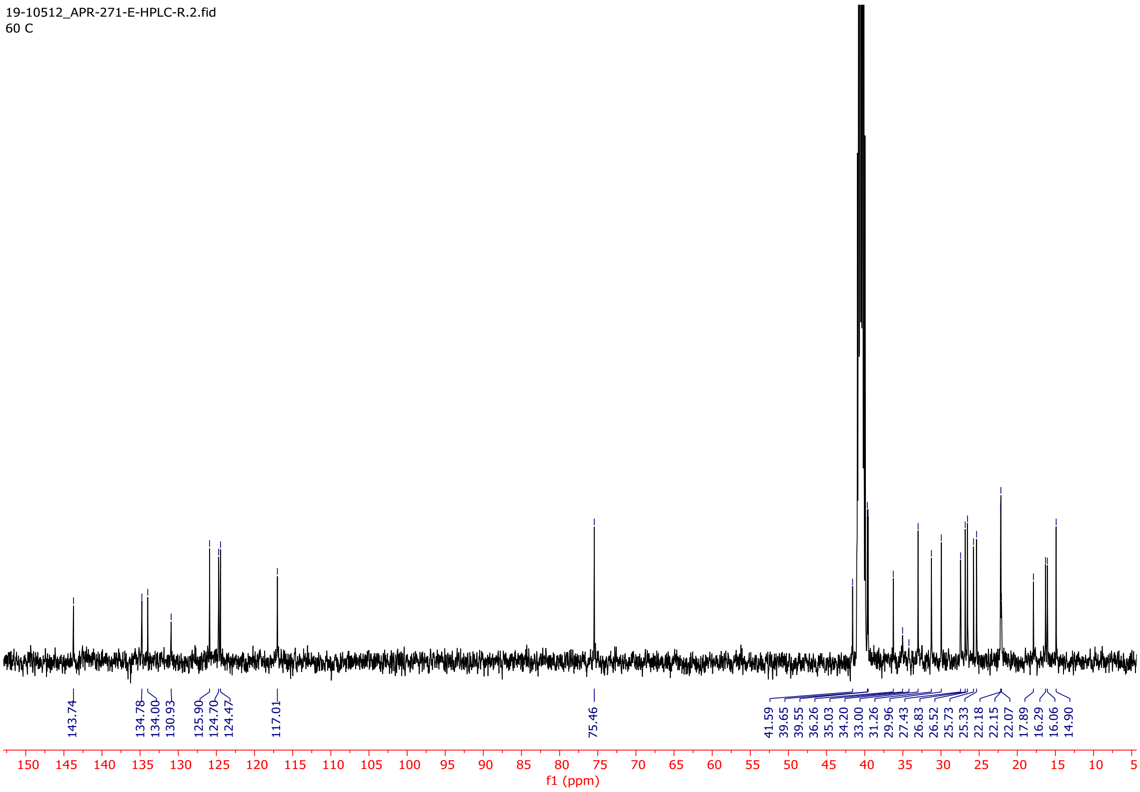



19-09420_APR-269-A-HPLC-2.15.ser
HSQCEDETGPSISP CDCl3 {C:\Bruker\TopSpin4.0.6} root 23
f1 (ppm)
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f2 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

1D-TOCSY


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


19-10512_APR-271-E-HPLC-R.3.fid
APR-271-E-HPLC-R 60C
H
HO
32
1.00
2.84
1.04
13.10
8.25
3.09
2.09
2.32
1.30
1.01
2.73
2.83
2.69
2.85
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.
f1 (ppm)


19-10512_APR-271-E-HPLC-R.2.fid
60 C
143.74
134.78
134.00
130.93
125.90
124.70
124.47
117.01
75.46
41.59
39.65
39.55
36.26
35.03
34.20
33.00
31.26
29.96
27.43
26.83
26.52
25.73
25.33
22.18
22.15
22.07
17.89
16.29
16.06
14.90
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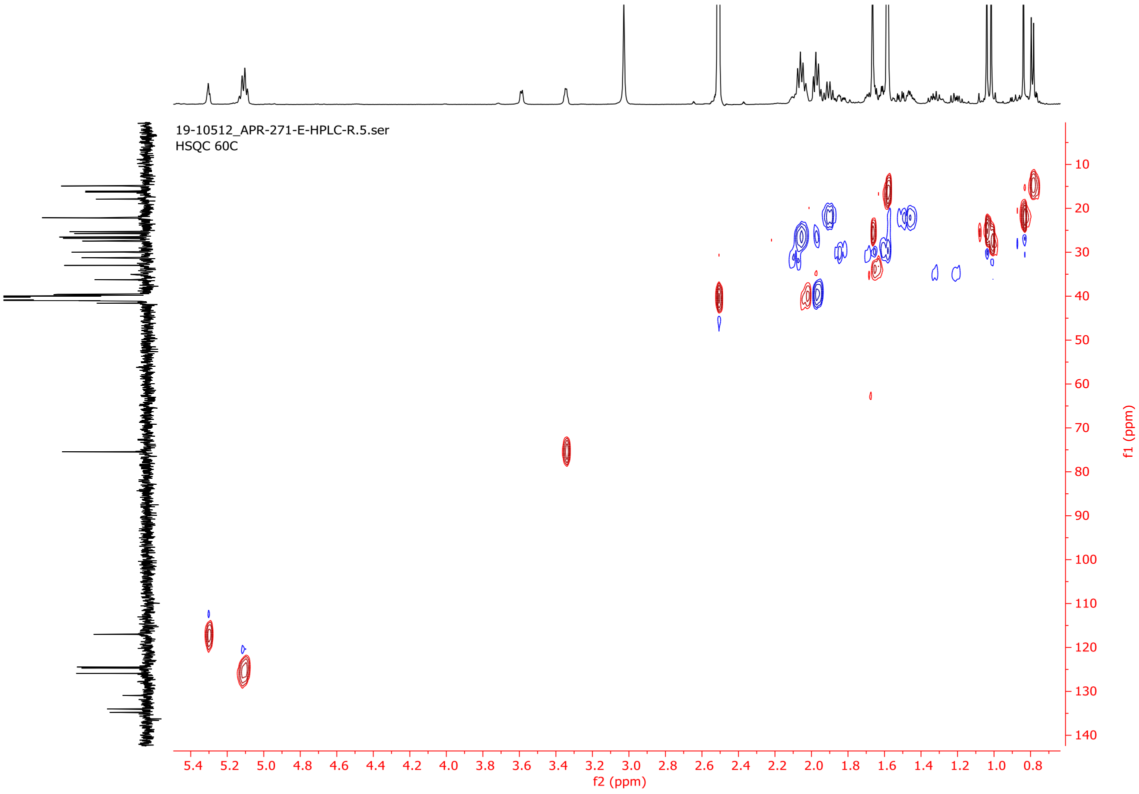
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f2 (ppm)
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f1 (ppm)
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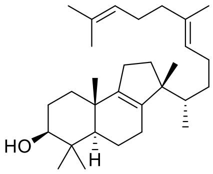
proton



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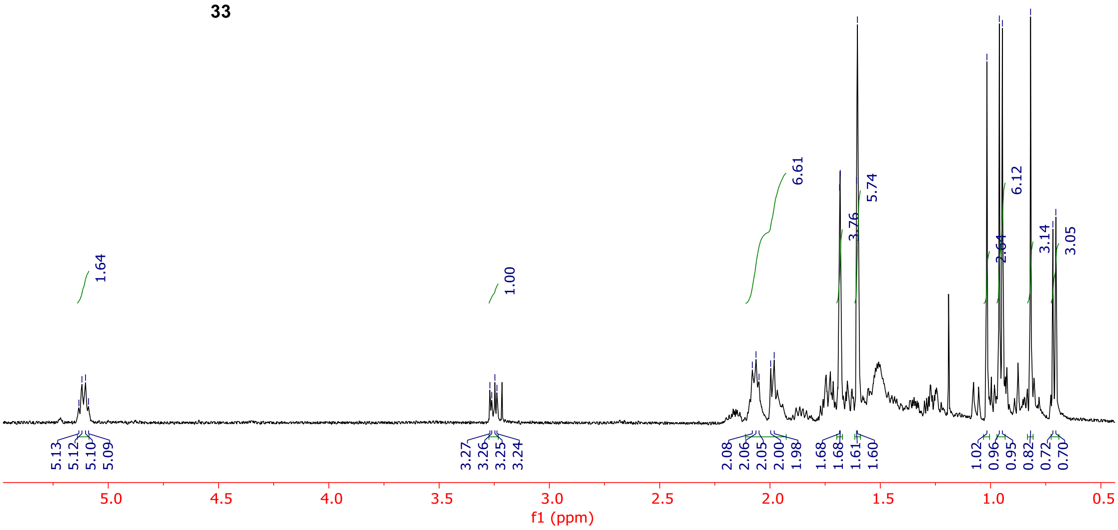
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6.61
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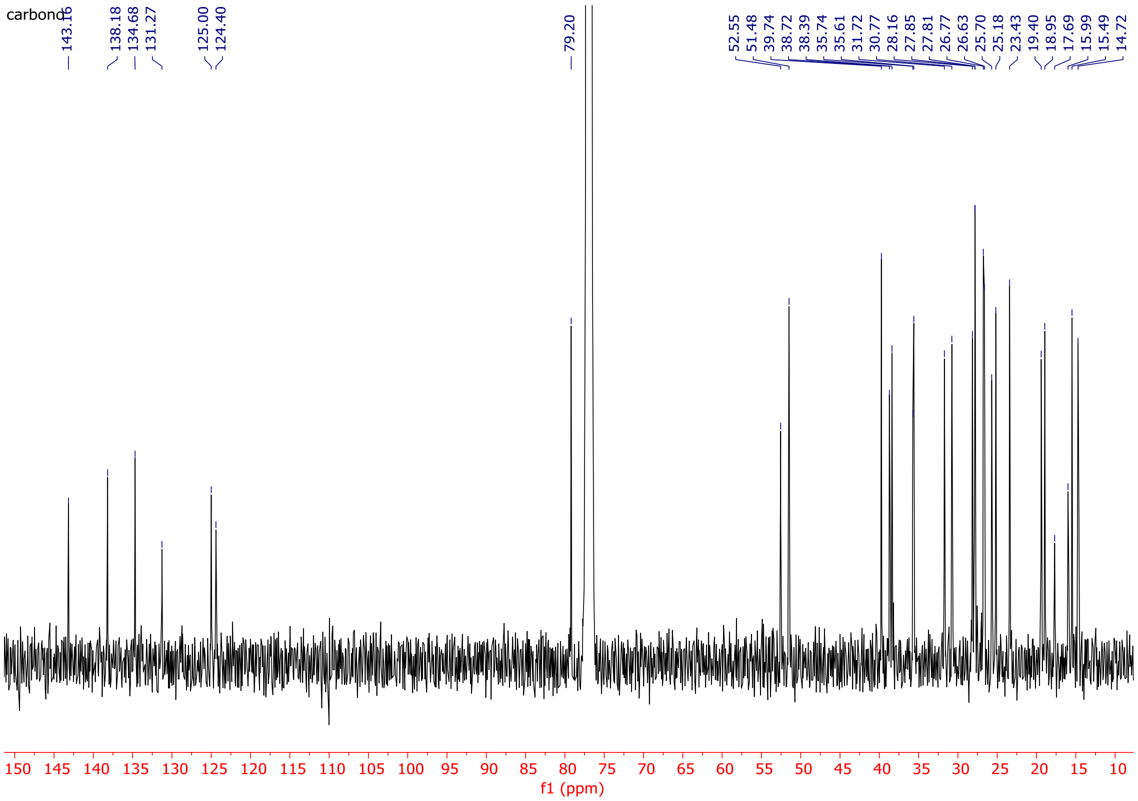
5.74
2.64
6.12
3.14
3.05
5.13
5.12
5.10
5.09
3.27
3.26
3.25
3.24
2.08
2.06
2.05
2.00
1.98
1.68
1.68
1.61
1.60
1.02
0.96
0.95
0.82
0.72
0.70
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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79.20
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51.48
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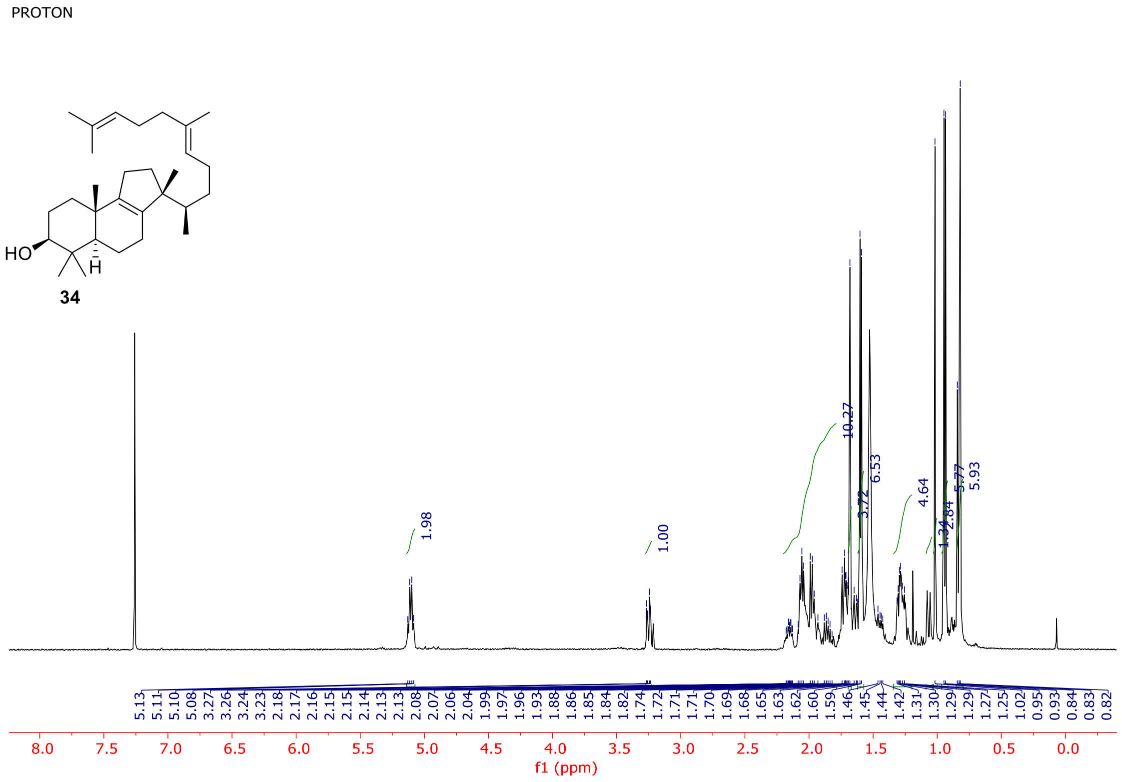
38.39
35.74
35.61
31.72
30.77
28.16
27.85
27.81
26.77
26.63
25.70
25.18
23.43
19.40
18.95
17.69
15.99
15.49
14.72
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)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H
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1.24
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5.77
5.93
5.13
5.11
5.10
5.08
3.27
3.26
3.24
3.23
2.18
2.17
2.16
2.15
2.14
2.13
2.13
2.08
2.07
2.06
2.04
1.99
1.97
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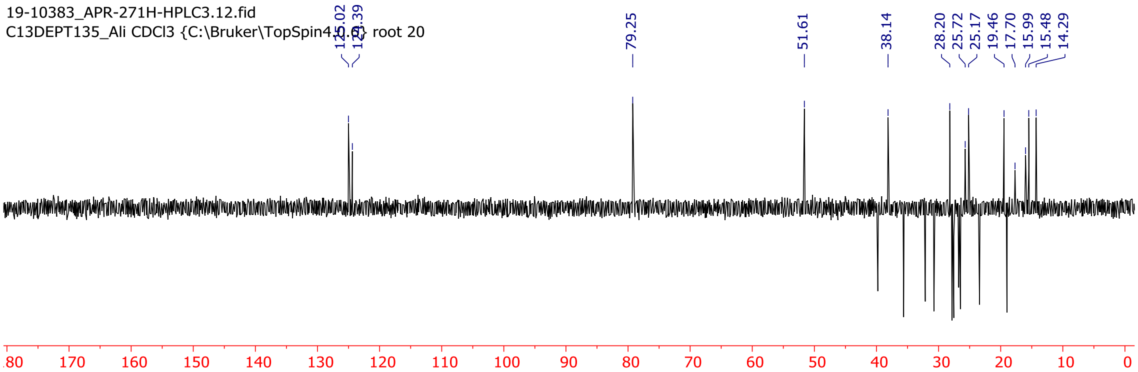
1.86
1.85
1.84
1.82
1.74
1.72
1.71
1.71
1.70
1.69
1.68
1.65
1.63
1.62
1.60
1.59
1.46
1.45
1.44
1.42
1.31
1.30
1.29
1.29
1.27
1.25
1.02
0.95
0.93
0.84
0.83
0.82
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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79.25
51.61
38.14
28.20
25.72
25.17
19.46
17.70
15.99
15.48
14.29
80
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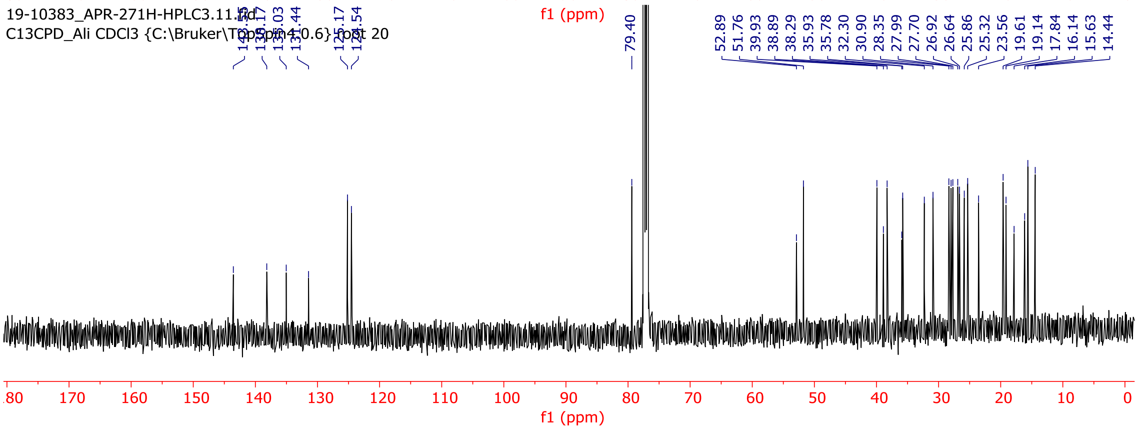
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


f1 (ppm)
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135.03
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125.17
124.54
79.40
52.89
51.76
39.93
38.89
38.29
35.93
35.78
32.30
30.90
28.35
27.99
27.70
26.92
26.64
25.86
25.32
23.56
19.61
19.14
17.84
16.14
15.63
14.44
80
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150
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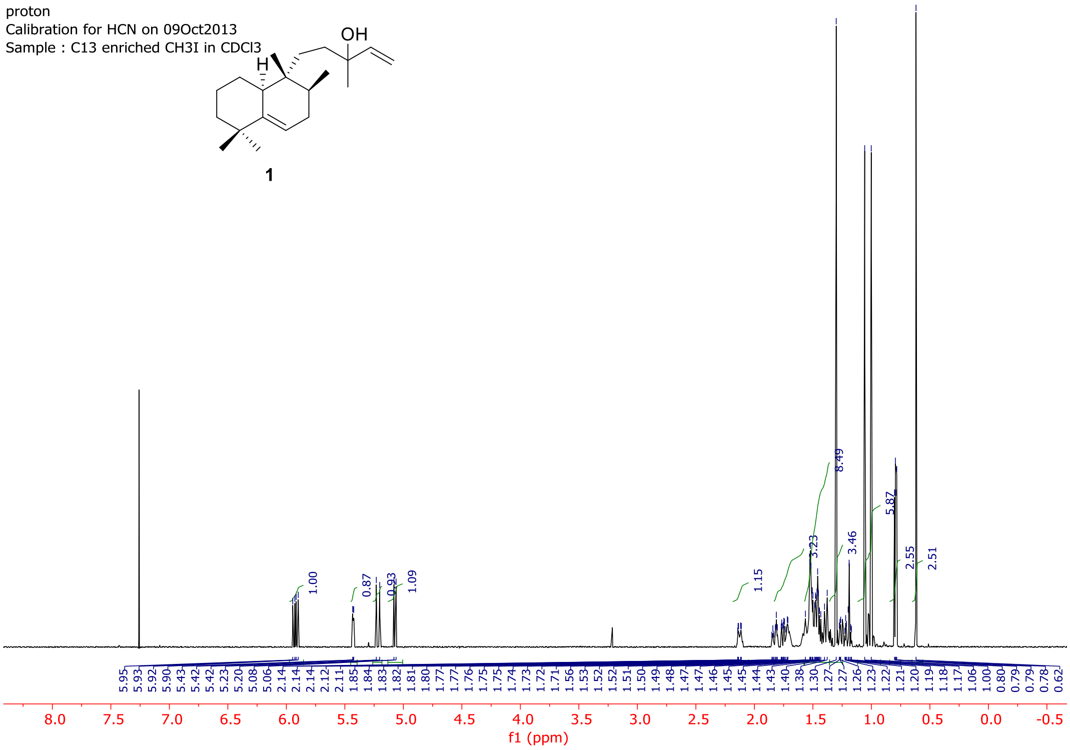
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


proton
Calibration for HCN on 09Oct2013
Sample : C13 enriched CH3I in CDCl3
OH
H
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0.93
1.09
1.15
3.23
8.49
3.46
5.87
2.55
2.51
5.95
5.93
5.92
5.90
5.43
5.42
5.23
5.20
5.08
5.06
2.14
2.14
2.12
2.11
1.85
1.84
1.83
1.82
1.81
1.80
1.77
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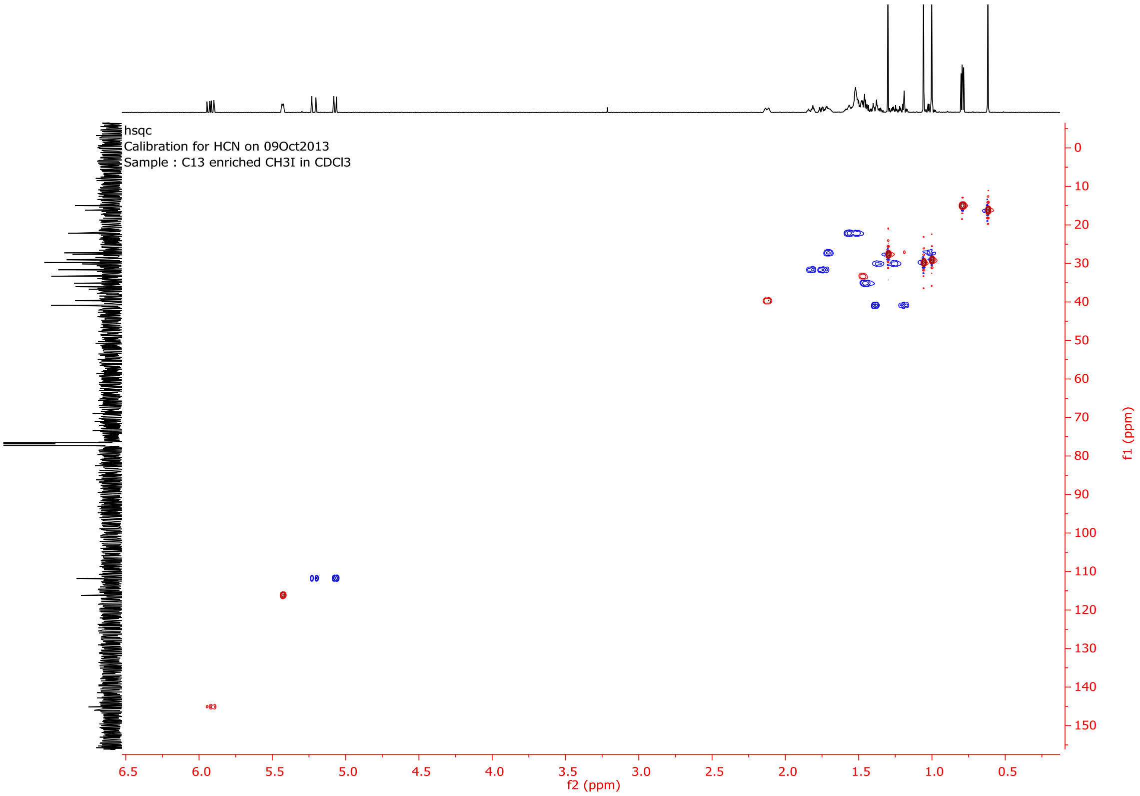
1.27
1.26
1.23
1.22
1.21
1.20
1.19
1.18
1.17
1.06
1.00
0.80
0.79
0.79
0.78
0.62
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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Calibration for HCN on 09Oct2013
Sample : C13 enriched CH3I in CDCl3
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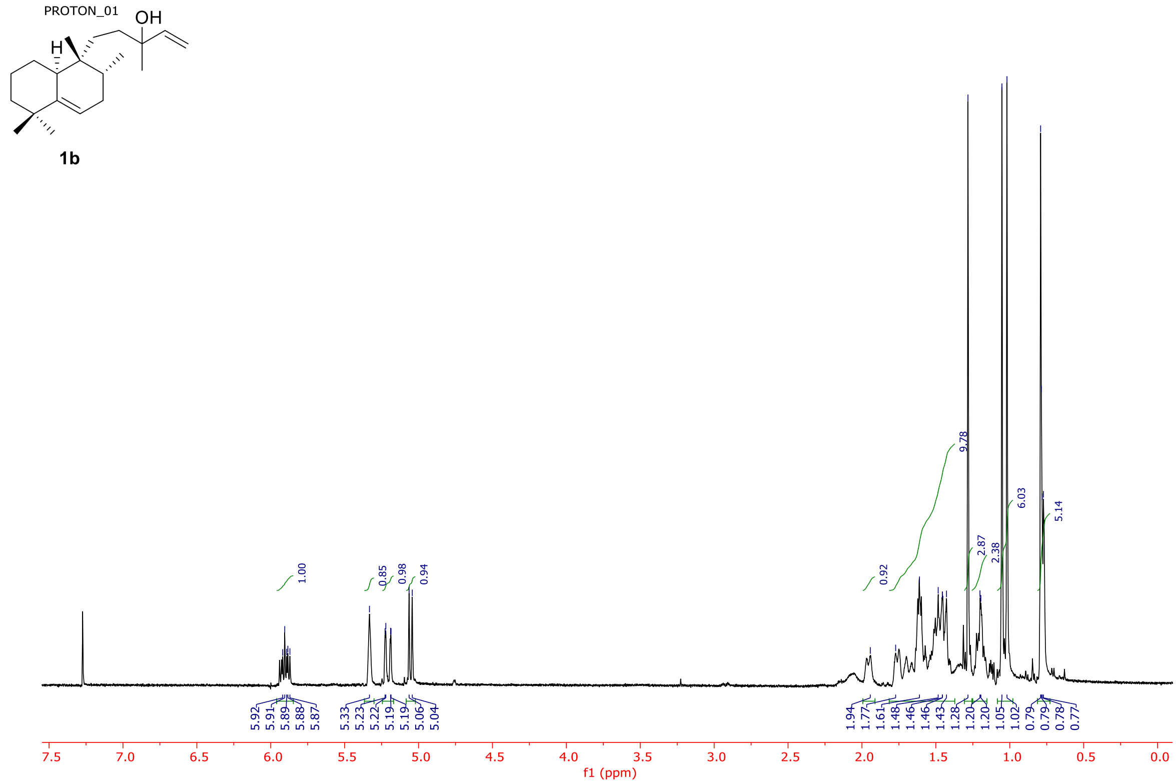
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)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H
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0.92
9.78
2.87
2.38
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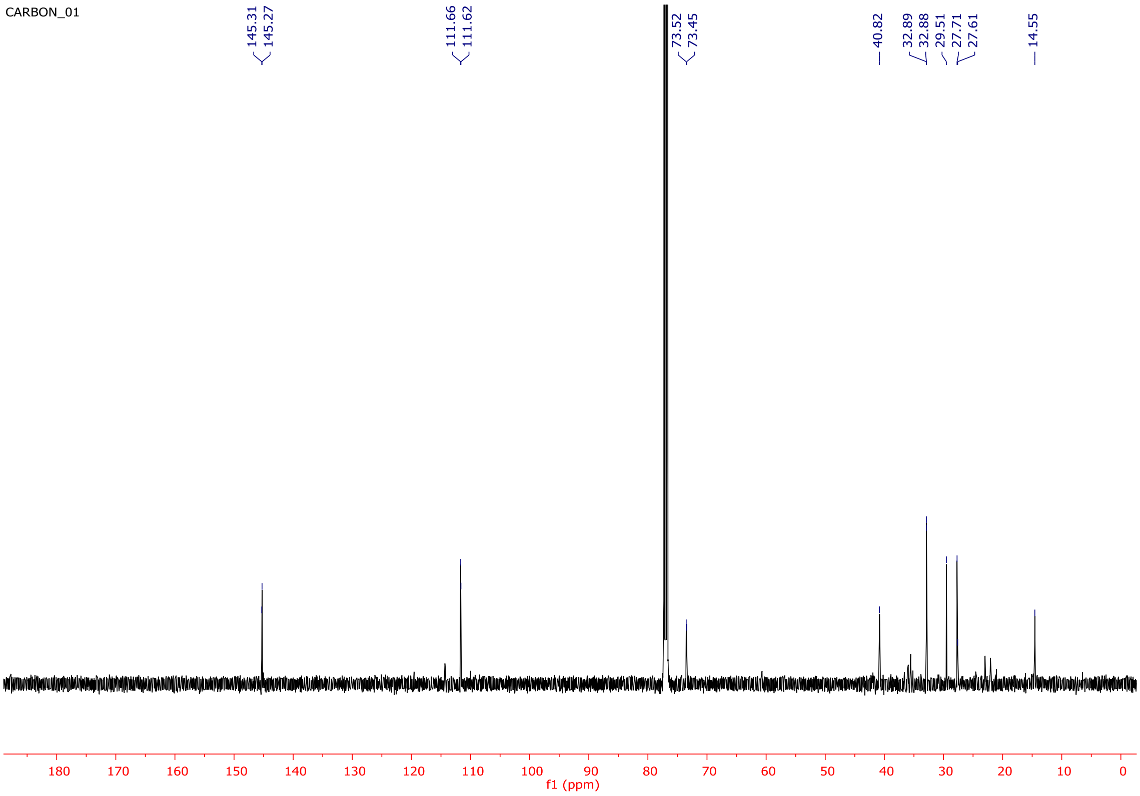
5.92
5.91
5.89
5.88
5.87
5.33
5.23
5.22
5.19
5.19
5.06
5.04
1.94
1.77
1.61
1.48
1.46
1.46
1.43
1.28
1.20
1.20
1.05
1.02
0.79
0.79
0.78
0.77
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

1b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145.27
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111.62
73.52
73.45
40.82
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32.88
29.51
27.71
27.61
14.55
180
170
160
150
140
130
120
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100
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80
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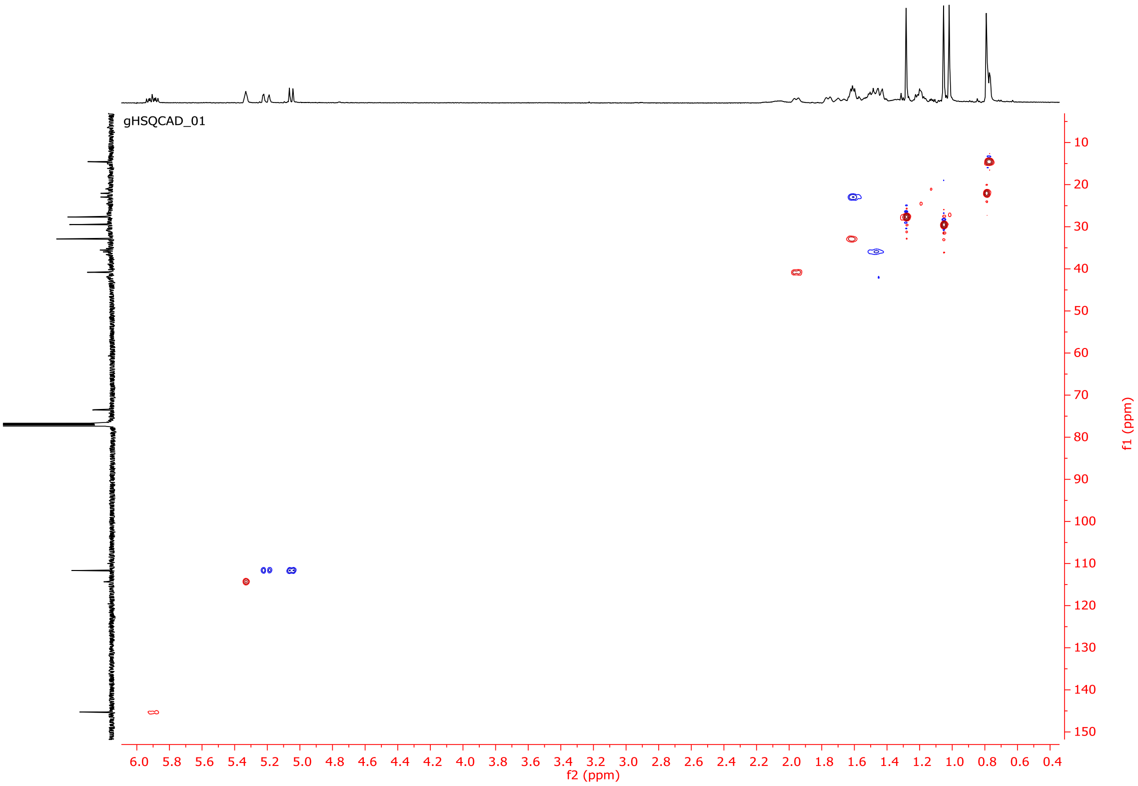
50
40
30
20
10
0
f1 (ppm)


gHSQCAD_01
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5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

6.3 Supporting information Artículo 4:

Bioinspired Synthesis of Platensimycin from Natural ent-Kaurenoic acids.

Bioinspired Synthesis of Platensimycin from Natural *ent*-Kaurenoic acids.

Álvaro Pérez†, José F.Quílez del Moral†* and Alejandro F. Barrero†*

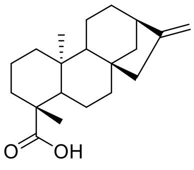
†Department of Organic Chemistry, Institute of Biotechnology, University of Granada, 18071 Granada, Spain.

Table of Contents

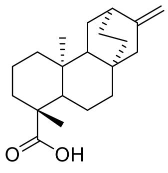
Materials and Methods

All air- and water-sensitive reactions were performed in flaks flame-dried under a positive flow of argon and conducted under an argon atmosphere. The solvents used were purified according to standard literature techniques and stored under argon. Anhydrous dichloromethane was distilled from calcium hydride (5% w/v) under positive pressure of nitrogen. THF, Cyclohexane, Benzene and Toluene were freshly distilled immediately prior to use from sodium/benzophenone and strictly deoxygenated for 30 min under argon. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated. Silica gel SDS 60 (35−70 µm) was used for flash column chromatography. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and solutions of phosphomolybdic acid in ethanol. Ozonizations were carried out with ECO-DE Ozonator plus with an O_3 stream (500mg/h, 0,17 mmol/min). HPLC with UV detection was used. Semipreparative HPLC separation was carried out on a column (5 µm Silica, 10 × 250 mm^2) at a flow rate of 4.0 mL/ min in an Agilent Series 1100 instrument. NMR spectra were recorded with Varian Direct Drive 600 (^{1}H NMR 600 MHz/^{13}C NMR 150 MHz), Varian Direct Drive 500 (^{1}H NMR 500 MHz/^{13}C NMR 125 MHz), Varian Direct Drive 400 (^{1}H NMR 400 MHz/^{13}C NMR 100 MHz), and Varian Inova Unity (^{1}H NMR 300 MHz/^{13}C NMR 75 MHz) spectrometers. High-resolution mass spectra (HRMS) were determined on an Autospec-Q VG-Analytical (FISONS) mass spectrometer. Distortionless enhancement by polarization transfer 135 and two-dimensional (correlated spectroscopy, heteronuclear single-quantum correlation spectroscopy, heteronuclear multiple bond correlation, nuclear Overhauser enhancement spectroscopy) NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

Plant material and isolation of starting material.

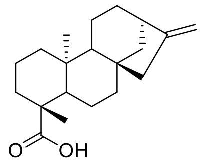


ent-kaurenoic acid

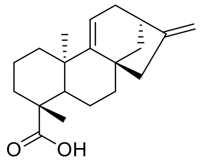


trachilobanoic acid

Helianthus annuus were collected in Villalobos, Zamora, Spain in July 2019. Sunflower heads (25 kg), without seeds, were extracted by maceration in MTBE, two times 15 minutes each. The resultant extract (25 g) was extracted with aqueous 50% $NaHCO_3$, the aqueous phase was removed and the organic layer was then extracted with aqueous 5% Na_2CO_3 removing the aqueous layer. Repeating the same previous process, we made a serial of fractionated extractions with NaOH 0.5N, NaOH 2N, NaOH 0.5N and finally NaOH 4N. The resultant crude, rich in sodium kaurenoate, was solved in *tert*-butyl methyl ether (MTBE) and acidulated with HCl 2N to pH 2,5, then we added hexane (H). The sodium salts were precipitated in the aqueous phase and the organic layer was extracted with NaOH 0.25 N, the aqueous phase, which contains the acid fraction, was acidulated to pH 2,5 and extracted with MTBE. The organic layer was evaporated obtaining a mixture (11974 mg) 80:20 *ent*-kaurenoic acid and trachilobanoic acid. Ratios were determined by integration of the ^{1}H spectrum of the mixture. Spectroscopic data match with those reported on bibliography[1].

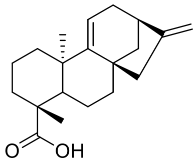


ent-Kaurenoic acid



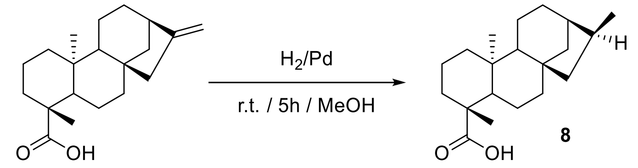
Grandiflorenic acid

Stevia lucida was collected in Páramo de la Negra, close to El Delgadito (Merida, Venezuela) in March 2019. Dried aerial parts (22 Kg) were milled to powder and extracted in a Soxhlet using EtOH. The resultant extract (5657 g) was redissolved on MeOH, adsorbed on silica gel and extracted with hexane. The solvent was evaporated in vacuo and the concentrate (682 g), then solved in hot methanol (MeOH) and stayed 12 hours at 4ºC. The mixture was centrifugated and evaporated the supernatant, obtaining 613 g of extract which was absorbed on celite and purified in a silica gel chromatography column using increasing gradients of ethyl acetate (EtOAc) in H. *Ent*-kaurenoic acid (6277 mg) and grandiflorenic acid (5940 mg) were separated on silica gel/$AgNO_3$ column. Spectroscopic data match with those reported on bibliography[2].



Grandiflorenic acid

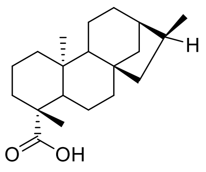
Grandiflorenic acid. White crystals. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.26 (t, *J* = 3.5 Hz, 1H), 4.94 (s, 1H), 4.82 (s, 1H), 2.79 (s, 1H), 2.63 (d, *J* = 15.6, 2.4 Hz, 1H), 2.54 – 2.40 (m, 2H), 2.25 – 2.15 (m, 2H), 2.05 – 1.83 (m, 5H), 1.70 – 1.60 (m, 2H), 1.56 – 1.44 (m, 3H), 1.33 – 1.29 (m, 1H), 1.27 (s, 3H), 1.05 (s, 3H), 1.04 – 0.99 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.11(C), 158.58(C), 155.95(C), 114.91(CH), 105.48(CH_2), 50.32(CH_2), 46.58(CH), 44.95(CH_2), 44.70(C), 42.28(C), 41.25(CH), 40.76(CH_2), 38.80(C), 38.31(CH_2), 37.93(CH_2), 29.67(CH_2), 28.24(CH_3), 23.62(CH_3), 20.16(CH_2), 18.48(CH_2). HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{29}O_2$ 301.2168, found 301.2169.



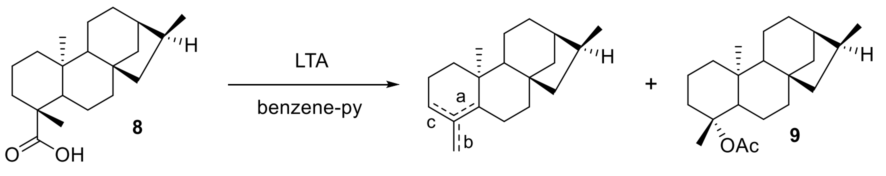
***ent*-Kaurenoic acid**

8

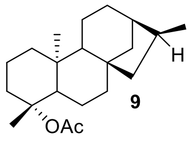
Hydrogenation of *ent*-kaurenoic acid to give *ent*-kauran-19-oic acid (8). To a stirred solution of ent-kaurenoic acid (204 mg, 0.68 mmol) in dry methanol (9.5 mL) was added a catalytic amount of palladium in activated carbon. The flask was tightly closed and sealed. The mixture was stirred for 7h ar rt under a hydrogen balloon pressure. After that, the reaction mixture was diluted with MTBE (50 mL) and filtered through celite. The resultant crude was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography with H/MTBE, 4:1 provided 152 mg of compound **8** (74%) as a white solid. The spectroscopic data of compound **8** match with those reported in the literature[3,4]. (**Can. J. Chem.97:568–575(2019)dx.doi.org/10.1139/cjc-2018-0369; Henrick C. A. and Jefferies P. R. Aust. J. Chem. 1964, 17, 915** Harnessing the Biocatalytic Potential of PtmO6, an α-Ketoglutarate-Dependent Dioxygenase from Platensimycin Biosynthesis, for the Chemoenzymatic Synthesis of Highly Oxidized ent-Kaurane Diterpenes) Falta poner mezcla de isomeros 3:1



*Ent-kauran-19-oic acid (**8**).* White solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.17 (bd, *J* = 12.3 Hz, 1H), 2.05 (h, 1H), 1.99 (d, *J* = 11.3 Hz, 1H), 1.95 – 1.75 (m, 5H), 1.64 (t, *J* = 12.5 Hz, 1H), 1.60 – 1.38 (m, 7H), 1.25 (s, 3H), 1.10 – 1.00 (m, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.97 (s, 3H), 0.97 – 0.78 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.29(C), 57.09(CH), 56.60(CH), 48.76(CH_2), 44.82(C), 43.70(C), 42.20(CH_2), 40.81(CH_2), 40.77(CH_2), 40.06(CH), 39.66(C), 37.93(CH_2), 34.42(CH), 28.96(CH_3), 25.93(CH_2), 22.14(CH_2), 19.11(CH_2), 19.00(CH_2), 15.80(CH_3), 15.55(CH_3). $[\alpha]_D$ -32.1. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{33}O_2$ 305.2481, found 305.2467.

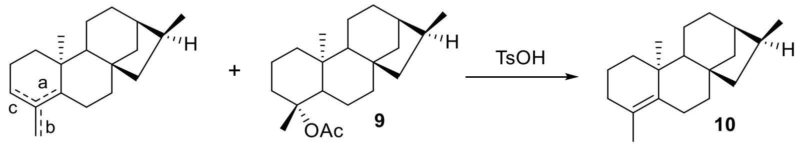


Decarboxylation of 8 to give compound 9 and the mixture of isomers 10a-c. To a dry, flamed and argon-filled flask containing 200 mg (0.66 mmol) of stirred **8** in anhydrous bencene (2 mL), 0.2 mL of distilled Pyidine (Py) was added followed by $Cu(OAc)_2$ (5 mg, 0.028 mmol) and lead tetracetate (LTA) (368 mg, 0.83 mmol)[5]. The mixture was refluxed for 2 h and after the consumption of the starting product, cooled to room temperature. The resulting mixture was diluted with MTBE (50 mL) and filtered through a short plug of silica gel, which was washed with ethyl acetate. The mixture was washed with 2N HCl, saturated $NaHCO_3$ and brine, and dried with anhydrous Na_2SO_4. The solvent was removed, giving a residue, which was flash chromatographed (H/MTBE, 9:1) to give **9** (49 mg, 0.15 mmol) in 23.4% yield, and the mixture of isomers **10a-c** in a 1.4:1:1 proportion (103mg, 0.4 mmol, 60.7% yield). Ratios were determined by integration of the ^{1}H spectrum of the mixture.

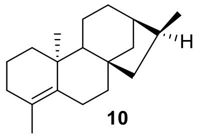


9

Compound ***9***. White solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.58 (d, *J* = 11.0 Hz, 1H), 2.02 (h, 1H), 1.95 (s, 1H), 1.93 (s, 3H), 1.92 – 1.88 (m, 1H), 1.79 – 1.42 (m, 13H), 1.41 (s, 3H), 1.32 (td, *J* = 12.1, 4.3 Hz, 1H), 1.06 (d, *J* = 7.0 Hz, 1H), 1.00 (d, *J* = 2.0 Hz, 3H), 0.99 (s, 3H), 0.98 – 0.91 (m, 2H), 0.85 – 0.78 (m, 1H); ^{13}C {^{1}H} NMR (126 MHz, cdcl$_3$) δ 170.41(C), 86.29 (C), 57.31(CH), 54.71(CH), 48.83(CH$_2$), 44.64(C), 41.31(CH$_2$), 40.84(CH$_2$), 40.14(CH), 39.98 (C), 39.20(CH$_2$), 37.39(CH$_2$), 34.31(CH), 25.92(CH$_2$), 22.89(CH$_3$), 19.87(CH$_2$), 19.19(CH$_2$), 19.01(CH$_3$), 18.72(CH$_2$), 17.55(CH$_3$), 15.77(CH$_3$).

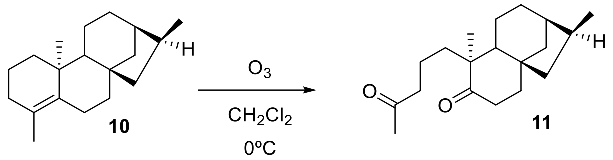


Synthesis of 10a. To a solution of the previous crude (227 mg) in 10 mL of benzene was added *p*-toluenesulfonic acid (TsOH) (30 mg, 0.18 mmol) under argon. The reaction was heated at 50 ºC for 2.5 h, and then diluted with 100mL of MTBE. The resulting mixture as washed with saturated Na$_2$CO$_3$ and brine, and dried with anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure obtaining 202 mg of crude which was purified by flash chromatography with H/MTBE, 9:1 to afford 200 mg (0.774mmol, 94% yield) of pure **10a**.

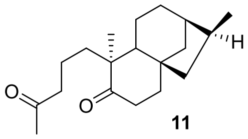


10

Compound ***10a***. Colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.47 (dt, *J* = 13.6, 3.4 Hz, 1H), 2.11 (d, *J* = 11.9 Hz, 1H), 2.05 (h, *J* = 12.7, 6.6 Hz, 1H), 1.96 – 1.78 (m, 6H), 1.61 (s, 3H), 1.61 – 1.50 (m, 6H), 1.49 – 1.33 (m, 3H), 1.12 (s, 3H), 1.09 – 1.04 (m, 2H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.90 (td, *J* = 6.5, 1.7 Hz, 1H); ^{13}C {^{1}H} NMR (126 MHz, CD$_3$OD) δ 137.21(C), 123.75(C), 56.19(CH), 48.29(CH$_2$), 45.04(C), 41.16(CH$_2$), 40.42(CH$_2$), 40.09(CH), 39.68(CH$_2$), 39.45(C), 34.63(CH), 33.01(CH$_2$), 26.03(CH$_2$), 24.37(CH$_2$), 22.81(CH$_3$), 19.76(CH$_2$), 19.62(CH$_3$), 18.91(CH$_2$), 15.89(CH$_3$). $[\alpha]_D$ -80.1. HRMS (ESI-QTOF) m/z: $[M - H]^+$ calcd for $C_{19}H_{29}$ 257.2269 , found 257.2266.

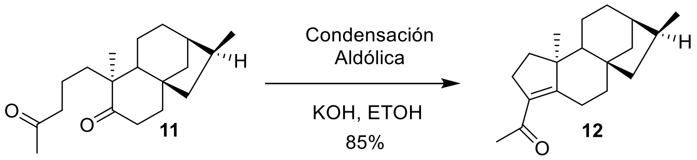


Ozonolysis of 10. Compound **10** (44 mg, 0,17 mmol) was solved in dichloromethane (DCM) (11 mL) and Py (0.06mL) in a two-neck flask at 0ºC of temperature. Then, an O_3 stream (500mg/h, 0,17 mmol/min) was bubbled in the stirring mixture[6]. After 1 hour, 3 mL of dimethyl sulfide was added and the resulting mixture was diluted with 50 mL of DCM. The organic layer was washed with brine and dried over Na_2SO_4. The crude was purified via flash chromatography (5:1 H/MTBE), to give an 82% of pure **11** (40 mg, 0.138mmol).

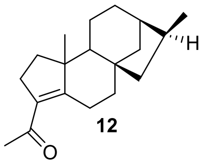


11

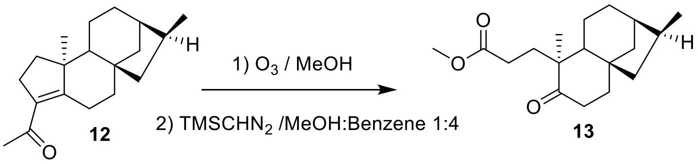
*Compound **11**.* Colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.61 (td, *J* = 14.8, 5.9 Hz, 1H), 2.50 – 2.30 (m, 2H), 2.26 (ddd, *J* = 15.1, 4.4, 2.8 Hz, 1H), 2.13 (s, 3H), 2.10 (h, *J* = 12.7, 6.6 Hz, 1H), 2.07 – 2.01 (m, 2H), 1.84 – 1.59 (m, 6H), 1.52 – 1.43 (m, 2H), 1.34 – 1.25 (m, 3H), 1.23 (dd, *J* = 11.6, 5.6 Hz, 2H), 1.18 (s, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 1.04 – 1.03 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.31(C), 209.24(C), 52.47(C), 47.22(CH_2), 46.56(CH), 44.34(CH_2), 43.88(C), 39.78(CH), 39.69(CH_2), 37.43(CH_2), 37.28(CH_2), 37.21(CH_2), 34.56(CH), 29.87(CH_3), 25.43(CH_2), 24.37(CH_3), 20.00(CH_2), 19.46(CH_2), 15.70(CH_3). $[\alpha]_D$ -94.9. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{31}O_2$ 291.2324 , found 291.2326.



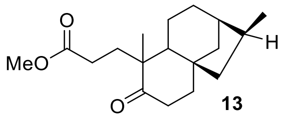
Synthesis of compound 12. Compound **11** (65 mg, 0.22 mmol) was solved in EtOH (5mL). Potassium hydroxide (KOH) (840 mg, 15 mmol) was added, turning the reaction from white to yellow color. After the consumption of the starting material, the reaction was diluted in MTBE, washed with brine and dried over Na_2SO_4. The crude was concentrated and purified by flash chromatography (H/MTBE, 9:1) to obtain getting 51 mg (0.19 mmol) of purified **12** (85% yield).


12

*Compound **12***. Colorless syrup. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.29 (dt, *J* = 14.2, 3.4 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.53 (ddt, *J* = 15.5, 9.5, 1.5 Hz, 1H), 2.23 (s, 3H), 2.14 – 2.05 (m, 1H), 2.02 (d, *J* = 11.5 Hz, 1H), 1.98 (q, *J* = 4.9, 4.3 Hz, 1H), 1.85 – 1.79 (m, 1H), 1.74 (q, *J* = 13.9, 7.2 Hz, 1H), 1.68 (t, 1H), 1.65 – 1.59 (m, 1H), 1.58 – 1.24 (m, 6H), 1.14 (s, 3H), 1.10 (ddt, *J* = 11.4, 4.1, 1.8 Hz, 1H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.93 – 0.86 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.43(C), 163.66(C), 131.52(C), 55.33(CH), 53.72(C), 47.25(CH_2), 44.31(C), 40.78(CH_2), 39.94(CH), 39.50(CH_2), 39.50(CH_2), 34.38(CH), 30.84(CH_2), 30.57(CH_3), 25.36(CH_2), 23.50(CH_2), 20.99(CH_3), 20.84(CH_2), 15.70(CH_3).

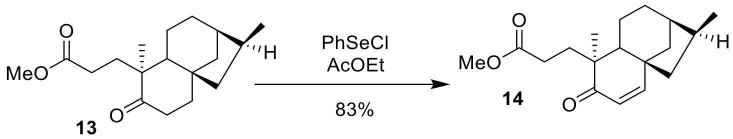


Synthesis of 13. A O_3 stream (500 mg/h, 0.17 mmol/min) was bubbled into a solution of methyl ketone **12** (83 mg, 0.30 mmol) in MeOH (5 mL) for 45 min at 0ºC. The solvent was completely removed and 2.5 mL of a 4:1 mixture of benzene/MeOH was added to the residue. To this solution, 0.16 mL (0.34 mmol) of trimethylsilyldiazomethane ($TMSCHN_2$) was added. The mixture was stirred for 15 min and then, the solvent was concentrated under reduced pressure and the crude was purified via flash chromatography using H:MTBE 6:1 as eluent to furnish **13** (75 mg, 0.26 mmol) in 85% yield (2 steps).

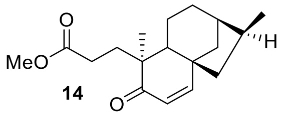


13

*Compound **13***. Colorless syrup. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.65 (s, 3H), 2.63 (td, *J* = 14.6, 5.9 Hz, 1H), 2.30 – 1.87 (m, 7H), 1.80 – 1.46 (m, 9H), 1.26 – 1.23 (m, 1H), 1.23 (s, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 1.03 – 0.99 (m, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 215.77(C), 174.26(C), 51.88(C), 51.54(CH$_3$), 47.31(CH), 47.26(CH$_2$), 43.89(C), 39.67(CH$_2$), 39.67(CH), 37.56(CH$_2$), 37.15(CH$_2$), 34.49(CH), 32.36(CH$_2$), 29.97(CH$_2$), 25.37(CH$_2$), 23.61(CH$_3$), 20.05(CH$_2$), 15.68(CH$_3$).

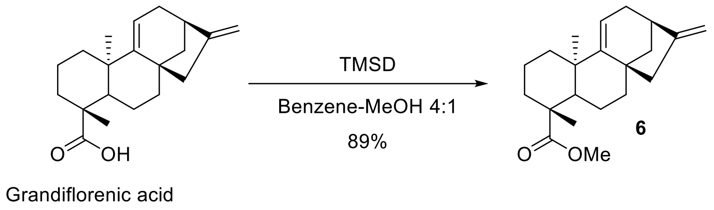


Synthesis of 14. To a solution of **13** (23 mg, 0.08 mmol) in 2.5 mL of EtOAc, PHSeCl (24 mg, 0.13 mmol) was added. The solution was stirred for 22 h at room temperature under argon until the consumption of starting material. The solvent was then removed. The resulting crude was dissolved in 0.01 mL of Pyidine and 2.5 mL of DCM. Finally, 0.01 mL of H_2O_2 was added at 0ºC. The 0ºC bath was then removed and the mixture heated for 10 min. The mixture was purified via flash chromatography using H:EtOAc 6:1 as eluent to obtain **14** (20mg, 0.07 mmol) in 83% yield.

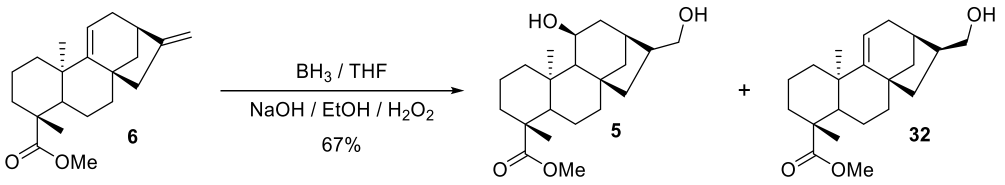


14

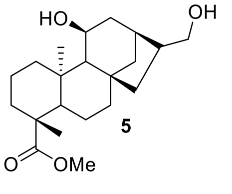
Compound ***14***. Colorless syrup. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.60 (d, *J* = 10.0 Hz, 1H), 5.80 (d, *J* = 10.0 Hz, 1H), 3.58 (s, 3H), 2.19 – 1.95 (m, 5H), 1.80 (m, 2H), 1.73 – 1.55 (m, 4H), 1.44 – 1.37 (m, 2H), 1.19 (s, 1H), 1.16 – 1.14 (m, 1H), 1.13 (s, 3H), 1.02 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 204.39(C), 174.01(C), 159.03(CH), 126.69(CH), 51.59(CH$_3$), 48.73(C), 48.36(CH$_2$), 45.55(C), 42.99(CH), 40.87(CH$_2$), 39.31(CH), 35.11(CH), 32.08(CH$_2$), 29.70(CH$_2$), 25.30(CH$_2$), 23.82(CH$_3$), 18.48(CH$_2$), 15.56(CH$_3$). [α]$_D$ -7.4. HRMS (ESI-QTOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{27}O_3$ 291.1960, found 291.1954.



Synthesis of methyl grandiflorenate (6). To a solution of grandiflorenic acid (2958 mg, 9.85 mmol) in 60 mL of benzene/MeOH (4:1) TMSCHN$_2$ (1340 mg, 11,8 mmol) was added. After consumption of starting material, the solvent was removed under reduced pressure to give methyl ester **6** (2774 mg, 8.82 mmol) in 89.6% yield. Spectroscopic data match with those reported on bibliography[3,7].

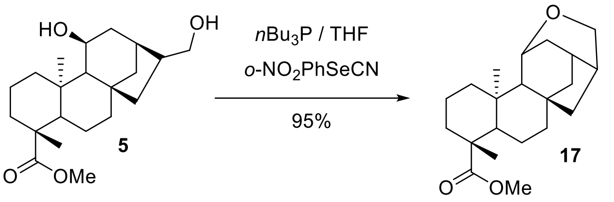


Synthesis of compound 5. To a solution of 2774 mg (8.82 mmol) of **6** in dry tetrahydrofuran (THF) (100 mL), 2.5 mL of a 1M borane-THF solution was added dropwise at 0ºC under inert gas (Ar). After 15 min, the 0ºC bath was removed and the mixture was stirred for 1 h until consumption of the starting material. Then, the reaction was cooled (0ºC) and EtOH (33 mL), NaOH 4N (24 mL) and 30 mL of H$_2$O$_2$ were added. The resulting mixture was then diluted with 150 mL of EtOAc, washed with water and brine and dried over Na$_2$SO$_4$. The solvent was evaporated over reduced pressure and the crude was chromatographed via silica gel column using H:TBME 1:1 as eluent to afford **5** (2071 mg, 5.92 mmol) in 67% yield, and **28** (401 mg, 1.21 mmol) in 13% yield. Spectroscopic data of compound **5** and **28** match with those reported in the literature[8].

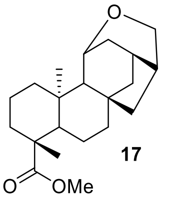


*Compound **5***. White crystals. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 3.94 – 3.85 (m, 3H), 3.64 (s, 3H), 2.22 – 2.14 (m, 2H), 2.11 (dh, *J* = 11.9, 6.6, 5.9 Hz, 1H), 2.00 – 1.74 (m, 8H), 1.67 (q, *J* = 13.4

Hz, 1H), 1.62 – 1.40 (m, 4H), 1.22 (bs, 1H), 1.18 (s, 3H), 1.12 – 1.00 (m, 3H), 0.71 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 177.97(C), 72.86(C), 66.84(CH), 65.59(CH), 63.11(CH_2), 56.77(CH), 51.18(CH_3), 43.82(C), 42.79(CH), 42.15(CH_2), 40.23(CH_2), 40.01(CH_2), 39.91(CH_2), 38.40(C), 37.98(CH_2), 37.78(CH), 35.37(CH_2), 28.72(CH_3), 21.86(CH_2), 19.01(CH_2), 14.88(CH_3). [α]$_D$ -28.9. HRMS (ESI-QTOF) m/z: [M - OH]$^+$ calcd for $C_{21}H_{33}O_3$ 333.2430, found 333.2429.

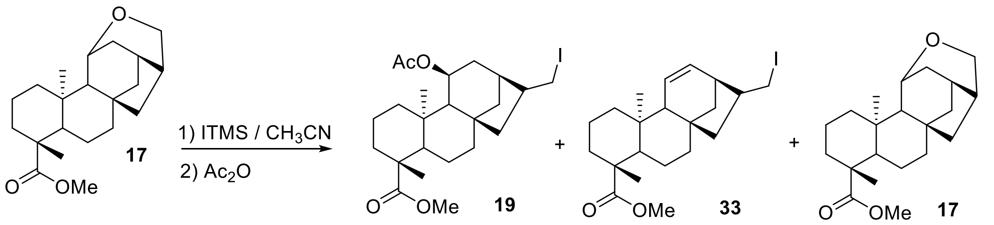


Synthesis of compound 17. A solution of 2-nitrophenyl selenocyanate (o-NO_2PhSeCN) (379 mg, 1.67 mmol) in dry THF (7.5 mL) was added dropwise to a solution of **5** (390 mg, 1.11 mmol) in dry THF (32.5 mL). After that, 0.43 mL (1.67 mmol) of *n*-tributylphosphine (n-Bu_3P) was added dropwise. The mixture was stirred at room temperature under argon for 2 h. After this time, the reaction was diluted with MTBE, washed with NH_4Cl, brine and the organic layer dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude was purified by flash chromatography (H/MTBE (1:1)). Pure **17** (341mg, 1.03mmol) was obtained in 95% yield[9,10].

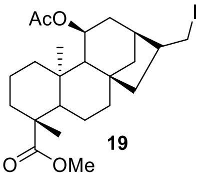


17

*Compound **17**.* White crystals. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.94 (bs, 1H), 3.77 (d, *J* = 10.0 Hz, 1H), 3.54 (s, 3H), 3.44 (dd, *J* = 10.0, 1.8 Hz, 1H), 2.25 – 1.97 (m, 4H), 1.84 (dt, *J* = 13.4, 3.8 Hz, 1H), 1.80 – 1.48 (m, 5H), 1.45 – 1.32 (m, 5H), 1.19 (bs, 1H), 1.09 (s, 3H), 1.09 – 1.04 (m, 1H), 1.03 – 0.88 (m, 3H), 0.66 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.20(C), 69.11(CH), 64.74(CH_2), 62.87(CH), 57.27(CH), 51.19(C), 48.85(CH_2), 43.80(C), 42.54(CH_2), 42.19(C), 40.70(CH_2), 39.80(CH_2), 38.00(CH_2), 37.67(C), 35.63(CH_3), 32.51(CH), 31.25(CH_2), 29.00(CH_3), 22.32(CH_2), 19.24(CH_2), 16.12(CH_3). [α]$_D$ -26.0. HRMS (ESI-QTOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{33}O_3$ 333.2430, found 333.2432.

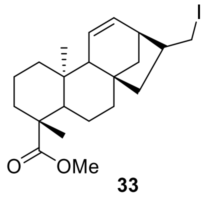


Synthesis of 19. To a solution of **17** (71mg, 0.21 mmol) in 5 mL of dry acetonitrile, trimethylsilyl iodide (ITMS) (0.03 mL, 0.25 mmol) was added dropwise at 0ºC under argon. After 15 minutes the 0ºC bath was removed and the solution heated to 40ºC for 45 min. The mixture was then cooled to room temperature and Ac_2O (0.36 mL) was added. After stirring for 10 min, the mixture was cooled to 0ºC, diluted with 50 mL of MTBE and washed with 2N HCl, saturated $NaCO_3$ and brine. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude was purified via flash chromatography in (H/MTBE (10:1)) to afford a 40% of **19** (39mg, 0.086 mmol), a 13% yield of **20** (12mg, 0.03mmol), and a 43% of **17** (31 mg, 0.09 mmol).



19

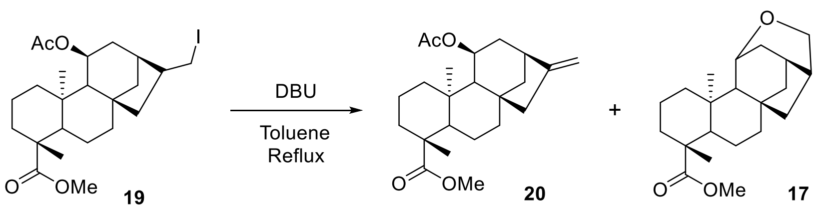
*Compound **19***. White crystals. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.14 (d, *J* = 6.4 Hz, 1H), 3.66 (s, 3H), 3.42 (dt, *J* = 47.1, 9.0 Hz, 2H), 2.47 – 2.36 (m, 1H), 2.28 (q, 1H), 2.19 (dt, 1H), 2.07 (s, 3H), 2.02 (d, *J* = 11.7 Hz, 2H), 1.88 – 1.74 (m, 3H), 1.66 – 1.60 (m, 2H), 1.23 – 1.21 (m, 1H), 1.19 (s, 3H), 1.09 – 1.05 (m, 1H), 1.02 (td, 1H), 0.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.78(C), 169.25(C), 68.27(CH), 63.29(CH), 56.67(CH), 51.25(CH_3), 45.02(CH_2), 44.17(C), 43.83(C), 43.81(CH), 41.89(CH_2), 40.18(CH_2), 39.67(CH_2), 39.15(CH), 38.54(C), 37.92(CH_2), 32.18(CH_2), 28.77(CH_3), 21.74(CH_3), 21.66(CH_2), 18.95(CH_2), 15.18(CH_3), 9.24(CH_2). APR_338-22-26-HPLC-11.. $[\alpha]_D$ -10.3. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{36}O_4I$ 503.1658, found 503.1650.



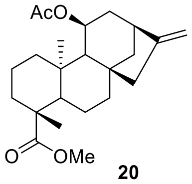
33

*Compound **33***. Pale oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.94 (ddt, *J* = 9.5, 6.3, 1.5 Hz, 1H), 5.69 (dd, *J* = 9.8, 3.8 Hz, 1H), 3.65 (s, 3H), 3.23 – 3.11 (m, 2H), 2.65 – 2.44 (m, 2H), 2.19 (dt, 1H), 2.01 (d, *J* = 11.0 Hz, 1H), 1.89 – 1.78 (m, 3H), 1.74 – 1.61 (m, 3H), 1.53 – 1.41 (m, 3H), 1.20 (s, 3H), 1.15 – 1.01 (m, 4H), 0.93 (ddd, *J* = 13.6, 7.6, 1.8 Hz, 1H), 0.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.87(C), 130.39(CH), 128.44(CH), 62.12(CH), 55.87(CH), 51.17(CH_3), 50.48(CH), 48.95(CH_2), 44.09(C), 43.88(C), 41.69(CH), 41.40(CH_2), 39.87(CH_2), 38.86(C), 37.99(CH_2),

37.38(CH$_2$), 28.71(CH$_3$), 21.77(CH$_2$), 18.9(CH$_2$)9, 15.27(CH$_3$), 11.04(CH$_2$). [α]$_D$ -101.1. HRMS (ESI-QTOF) m/z: [M + H]$^+$ calcd for $C_{21}H_{32}O_2I$ 443.1447, found 443.1441.

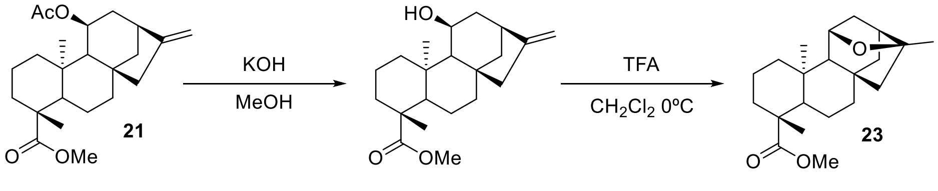


Synthesis of 20. To a solution of **19** (198 mg, 0.39 mmol) in anhydrous toluene (5 mL), 0.19 mL (1.3 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The mixture was heated to reflux under inert atmosphere for 19 h, and then column chromatographed using H/MTBE (3:1) as eluent. Compound **20** (119 mg, 0.32 mmol) was obtained in 81% yield and **17** (8 mg, 0.02 mmol) in 6% yield.

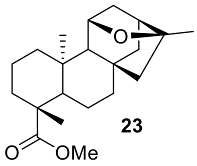


20

*Compound **20***. Colourless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.05 (d, *J* = 5.2, 1.5 Hz, 1H), 4.84 (s, 1H), 4.70 (s, 1H), 3.66 (s, 3H), 2.64 (dt, *J* = 3.8 Hz, 1H), 2.50 (d, *J* = 15.1 Hz, 1H), 2.20 (dt, *J* = 9.7 Hz, 1H), 2.08 – 1.96 (m, 2H), 1.95 (s, 3H), 1.91 – 1.63 (m, 6H), 1.62 – 1.44 (m, 3H), 1.32 (s, 1H), 1.20 (s, 3H), 1.19 – 1.17 (m, 1H), 1.11 (dd, *J* = 12.1, 2.3 Hz, 1H), 1.07 – 0.90 (m, 2H), 0.80 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 177.85(C), 170.06(C), 155.17(C), 103.11(CH$_2$), 69.35(CH), 60.83(CH), 56.88(CH), 51.24(CH$_3$), 47.80(CH$_2$), 43.85(C), 43.04(C), 42.23(CH), 41.13(CH$_2$), 40.24(CH$_2$), 39.50(CH$_2$), 39.15(CH$_2$), 38.32(C), 37.96(CH$_2$), 28.81(CH$_3$), 21.70(CH$_3$), 21.68(CH$_2$), 19.02(CH$_2$), 15.29(CH$_3$). [α]$_D$ -76.3. HRMS (ESI-QTOF) m/z: [M + H]$^+$ calcd for $C_{23}H_{35}O_4$ 375.2535, found 375.2531.

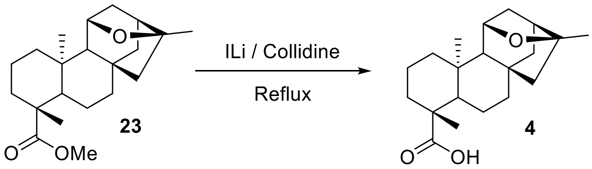


Synthesis of 23. A solution of **20** (119 mg, 0.32 mmol) in 14 mL of 10% KOH/MeOH was stirred at room temperature for 19 h. After this time, the solvent was evaporated under reduced pressure and the crude was dissolved in MTBE (50 mL), washed with NH$_4$Cl, water and brine and dried over Na$_2$SO$_4$. The resulting crude after evaporation of the solvent was dissolved in DCM (14 mL) and cooled to 0ºC. After that, trifluoroacetic acid (TFA) (1,13 mL, 14.7 mmol) was added and the mixture was stirred at 0ºC for 45 min under argon. Then, the solution was diluted with MTBE (50 mL), washed with Na_2CO_3 and brine and dried over Na_2SO_4. Finally, the organic layer was concentrated under reduced pressure and the crude was purified via flash chromatography (H/MTBE 2:1). **23** (96 mg, 0.29 mmol) was obtained in a 91% yield (two steps). The spectroscopic data of compound **23** match with those reported in the literature[1,11]

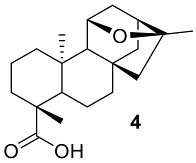


23

*Compound **23**.* Colorless oil. ^1H NMR (600 MHz, Chloroform-*d*) δ 4.28 (bt, *J* = 3.5 Hz, 1H), 3.57 (s, 3H), 2.14 (t, *J* = 6.5 Hz, 1H), 2.12 – 2.10 (m, 1H), 1.93 (d, *J* = 11.2 Hz, 1H), 1.87 (dd, *J* = 11.7, 3.6 Hz, 1H), 1.84 – 1.66 (m, 4H), 1.61 – 1.53 (m, 1H), 1.45 (d, *J* = 3.6 Hz, 1H), 1.44 (s, 1H), 1.39 – 1.33 (m, 3H), 1.27 (s, 3H), 1.27 (s, 1H), 1.19 – 1.15 (m, 1H), 1.10 (s, 3H), 1.05 – 0.92 (m, 3H), 0.80 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 178.17(C), 85.67(C), 76.89(CH), 58.28(CH), 57.47(CH), 56.94(CH_2), 51.23(CH_3), 45.46(CH), 45.05(C), 43.66(C), 43.44(CH_2), 41.38(CH_2), 40.49(CH_2), 38.28(CH_2), 38.00(CH_2), 36.94(C), 28.94(CH_3), 23.24(CH_3), 21.61(CH_2), 19.05(CH_2), 17.42(CH_3). $[\alpha]_D$ -56.8. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{33}O_3$ 333.2430, found 333.2427.



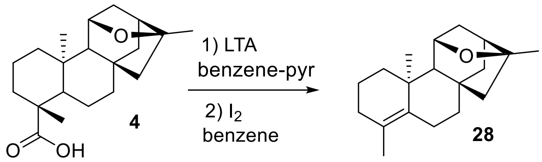
Synthesis of 4. To a solution of **23** (330 mg, 0.99 mmol) in dry collidine (13.9 mL), lithium Iodide (1328 mg, 9.93 mmol) was added. The mixture was heated to reflux under argon inert for 3 h. The reaction crude was cooled to 0ºC and quenched with distilled water and MTBE. The mixture was acidulated to pH 3 with HCl 2N and extracted several times with MTBE (70 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ and dried over Na_2SO_4. The solvent was evaporated over reduced pressure and the resultant crude was purified by flash chromatography (H/EtOAc, (5:1)) to afford **4** (275 mg, 0.86 mmol) in 87% yield. The spectroscopic data of compound **4** match with those reported in the literature[1].



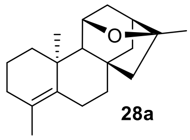
4

*Compound **4**.* Whyte crystals. ^1H NMR (500 MHz, Chloroform-*d*) δ 4.40 (t, *J* = 3.5 Hz, 1H), 2.27 – 2.18 (m, 2H), 2.04 (d, *J* = 11.3 Hz, 1H), 1.99 (dd, *J* = 11.7, 3.5 Hz, 1H), 1.95 – 1.68 (m, 5H), 1.57

(dd, *J* = 11.2, 3.4 Hz, 1H), 1.54 (bs, 1H), 1.50 – 1.42 (m, 3H), 1.39 – 1.35 (m, 1H), 1.37 (s, 3H), 1.31 – 1.26 (m, 1H), 1.26 (s, 3H), 1.16 – 1.02 (m, 3H), 1.00 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.87(C), 85.84(C), 76.91(CH), 58.23(CH), 57.43(CH), 56.90(CH_2), 45.48(CH), 45.05(C), 43.55(C), 43.45(CH_2), 41.31(CH_2), 40.46(CH_2), 38.23(CH_2), 37.72(CH_2), 37.16(C), 29.15(CH_3), 23.20(CH_3), 21.53(CH_2), 18.97(CH_2), 17.66(CH_3). $[\alpha]_D$ -49.8. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{30}O_3$ 319.2273, found 319.2268.

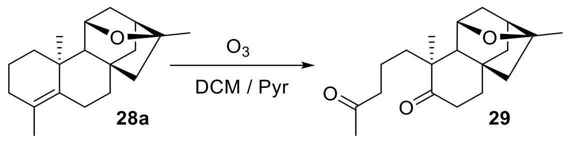


Synthesis of 28. To a dry, flamed and argon-filled flask with 258 mg (0.81 mmol) of **17** in anhydrous benzene (4 mL) was added 0.25 mL of distilled Py, $Cu(OAc)_2$ (11 mg, 0.065 mmol) and lead tetracetate (LTA) (934 mg, 2.1 mmol). The mixture was refluxed for 4 h and then cooled to room temperature, diluted in MTBE (50 mL) and filtered through a short plug of silica gel, which was washed with ethyl acetate. The resultant mixture was washed with 2N HCl, saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. This reaction crude was treated with I_2 (15 mg, 0.06 mmol) at room temperature and inert atmosphere (Ar). After 3 h, the reaction mixture was quenched with MTBE and washed with aqueous 10% $Na_2S_2O_3$, brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo and purified by flash column chromatography (H/EtOAc 5:1)) to give **28** (198 mg, 0.72 mmol) in 78% yield (2 steps).

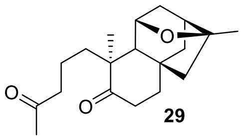


28a

*Compound **28**.* Colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.30 (t, 1H), 2.36 (dt, *J* = 13.4, 3.4 Hz, 1H), 2.17 (t, *J* = 6.5, 1.1 Hz, 1H), 2.03 (dd, *J* = 3.5 Hz, 1H), 2.00 (d, *J* = 11.2 Hz, 1H), 1.96 – 1.74 (m, 4H), 1.70 (dt, 1H), 1.53 (s, 3H), 1.53 (bs, 1H), 1.50 – 1.47 (m, 2H), 1.45 (dd, *J* = 11.1, 3.7 Hz, 1H), 1.29 (s, 3H), 1.36 – 1.20 (m, 5H), 1.11 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.09(C), 123.78(C), 85.83(C), 77.56(CH), 57.33(CH), 56.50(CH_2), 45.38(CH), 45.25(C), 42.86(CH_2), 40.35(CH_2), 39.87(CH_2), 37.16(CH_2), 36.87(C), 32.66(CH_2), 24.95(CH_3), 23.40(CH_2), 23.29(CH_3), 19.47(CH_3), 18.71(CH_2). $[\alpha]_D$ -31.0. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{29}O$ 273.2218, found 273.2216.

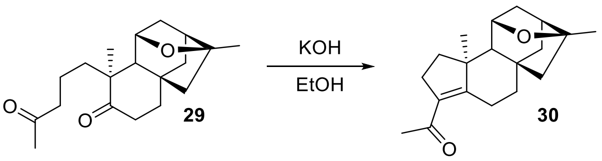


Ozonolysis of 28. A O_3 stream (500 mg/h, 0.17 mmol/min) was bubbles into a solution of **28a** (66mg, 0,17mmol) in 16 mL of DCM and 0.07 mL of Py . After stirring for 1 h, 15 mL of dimethyl sulfide was added and the resulting mixture was diluted in 50 mL of DCM. The organic layer was washed with brine and dried over Na_2SO_4. The crude was purified via flash chromatography (H/MTBE, 1:4) to give 63 mg (0,21 mmol) of pure **29** (85% yield).

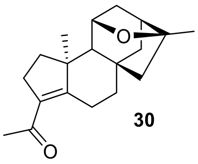


29

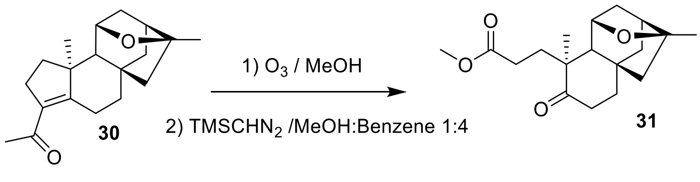
*Compound **29**.* Colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.32 (t, *J* = 3.5 Hz, 1H), 2.55 (ddd, *J* = 15.1, 13.4, 6.2 Hz, 1H), 2.43 (q, *J* = 7.4 Hz, 2H), 2.36 – 2.26 (m, 2H), 2.16 (s, 1H), 2.14 (s, 3H), 2.05 – 1.93 (m, 3H), 1.87 (td, *J* = 13.6, 5.2 Hz, 1H), 1.67 (td, *J* = 10.8, 10.4, 3.1 Hz, 1H), 1.64 – 1.53 (m, 3H), 1.49 – 1.42 (m, 4H), 1.41 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.25(C), 208.70(C), 86.31(C), 77.24(CH), 55.05(CH_2), 49.82(CH), 49.60(C), 44.77(CH), 44.39(C), 44.07(CH_2), 42.73(CH_2), 40.72(CH_2), 38.05(CH_2), 36.30(CH_2), 33.51(CH_2), 29.79(CH_3), 23.60(CH_3), 23.08(CH_3), 19.07(CH_2). $[\alpha]_D$ -47.4. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{29}O_3$ 305.2117, found 305.2110.



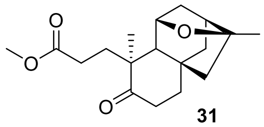
Synthesis of compound 30. To a solution of **29** (48 mg, 0.16 mmol) in EtOH (5mL), KOH (840mg, 15 mmol) was added. The mixture was stirred for 30 min at room temperature. It was then diluted with MTBE, washed with brine and dried over Na_2SO_4. The crude was concentrated and purified by flash chromatography (H/MTBE, 2:1) to give 31mg (0.11 mmol) of purified **30** (69% yield).



*Compound **30**.* Pale syrup. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.25 (t, *J* = 3.5 Hz, 1H), 3.33 (dt, *J* = 13.9, 3.5 Hz, 1H), 2.74 – 2.58 (m, 2H), 2.30 (t, *J* = 6.5 Hz, 1H), 2.25 (s, 3H), 2.10 (d, *J* = 11.4 Hz, 1H), 2.05 (dd, *J* = 11.8, 3.4 Hz, 1H), 2.02 – 1.95 (m, 2H), 1.86 (ddd, *J* = 12.5, 7.8, 2.2 Hz, 1H), 1.82 (s, 1H), 1.69 (q, 1H), 1.56 (td, *J* = 10.6, 9.9, 3.7 Hz, 1H), 1.52 – 1.48 (m, 2H), 1.43 (d, *J* = 11.1 Hz, 1H), 1.39 (s, 3H), 1.38 – 1.34 (m, 1H), 1.17 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.52(C), 162.99(C), 131.11(C), 86.05(C), 77.85(CH), 57.12(CH), 55.87(CH_2), 50.23(C), 45.22(CH), 44.86(C), 42.25(CH_2), 40.07(CH_2), 40.06(CH_2), 36.11(CH_2), 31.49(CH_2), 30.55(CH_3), 23.26(CH_3), 23.15(CH_3), 22.57(CH_2). $[\alpha]_D$ -48.7. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{27}O_2$ 287.2011, found 287.2014.

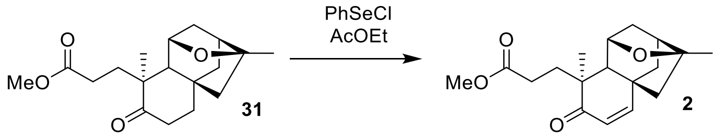


Synthesis of compound 31. A O_3 stream (500mg/h, 0,17 mmol/min) was bubbled into a solution of methyl ketone **30** (31 mg, 0.11 mmol) in MeOH (7.2 mL) at 0ºC. After 15 min, the reaction was heated to room temperature and stirred for further 45 min. Then, the solvent was evaporated and 2 mL of benzene/MeOH (4:1) was added to the mixture. To this solution, 0.06 mL of trimethylsilyldiazomethane (0.13 mmol) was added and the mixture was stirred for 15 min. Then, the solvent was concentrated under reduced pressure and the crude was purified via flash chromatography using (H/MTBE 6:1) as eluent to furnish a 63% yield of **31** (21 mg, 0.07 mmol) (2 steps).

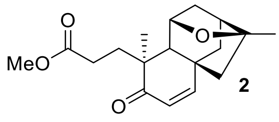


31

*Compound **31**.* White solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.33 (t, *J* = 3.5 Hz, 1H), 3.68 (s, 3H), 2.59 (td, *J* = 14.2, 6.1 Hz, 1H), 2.40 – 2.25 (m, 3H), 2.11 – 1.96 (m, 5H), 1.86 (td, *J* = 13.9, 5.1 Hz, 1H), 1.80 – 1.73 (m, 1H), 1.70 – 1.59 (m, 2H), 1.52 – 1.44 (m, 2H), 1.41 (s, 3H), 1.33 – 1.24 (m, 1H), 1.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.63(C), 173.95(C), 86.28(C), 77.11(CH), 55.15(CH_2), 51.66(CH_3), 50.13(CH), 49.08(C), 44.78(CH), 44.44(C), 42.65(CH_2), 40.67(CH_2), 36.20(CH_2), 33.91(CH_2), 32.92(CH_2), 29.56(CH_2), 23.48(CH_3), 23.05(CH_3). $[\alpha]_D$ -32.5. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{27}O_4$ 307.1909, found 307.1913.

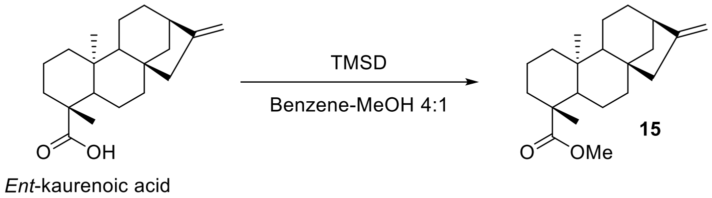


Synthesis of 2. To a solution of **31** (21mg, 0.07mmol) in EtOAc (2.5 mL), PHSeCl (21 mg, 0.11 mmol) was added. The solution was stirred for 22 h at room temperature under inert atmosphere. The solvent was then removed and the resulting crude was dissolved in 0.01mL of Py and 2.5 mL of DCM. To this solution, 0.01mL of H_2O_2 was added at 0ºC. The 0ºC bath was removed and the mixture heated for 10 min. The mixture was purified via flash chromatography using H/AcOEt (3:1) as eluent to give **2** (17 mg, 0.06 mmol) in 82% yield. Spectroscopic data match with those reported on literature[12].



2

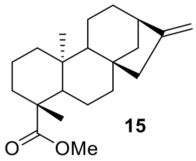
*Compound **2**.* Pale syrup. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.48 (d, *J* = 10.1 Hz, 1H), 5.90 (d, *J* = 10.0 Hz, 1H), 4.41 (t, 1H), 3.68 (s, 3H), 2.42 (t, *J* = 6.5 Hz, 1H), 2.37 (s, 1H), 2.34 – 2.20 (m, 3H), 2.14 – 2.00 (m, 3H), 1.88 (dd, *J* = 11.1, 3.6 Hz, 1H), 1.83 – 1.71 (m, 2H), 1.63 (d, *J* = 11.1 Hz, 1H), 1.46 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.24(C), 173.79(C), 153.51(CH), 127.26(CH), 86.98(C), 76.48(CH), 54.94(CH_2), 51.65(CH_3), 46.33(C), 45.98(CH), 45.98(C), 44.66(CH), 43.18(CH_2), 40.58(CH_2), 30.79(CH_2), 29.14(CH_2), 24.51(CH_3), 23.03(CH_3). $[\alpha]_D$ -39.5. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{25}O_4$ 305.1753, found 305.1745.



Ent-kaurenoic acid

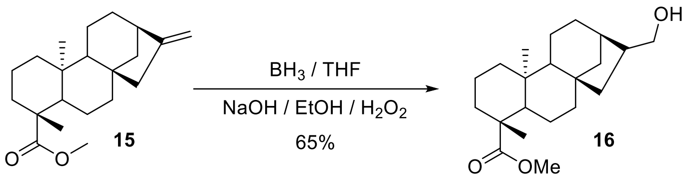
15

Synthesis of *ent*-kaur-16-en-18-oic acid, methyl ester (15). To a solution of *ent*-kaurenoic acid (5000 mg, 16.53 mmol) in 100 mL of a 4:1 mixture of benzene/MeOH, $TMSCHN_2$ (2266 mg, 20mmol) was added. The mixture was stirred room temperature conditions for 15 minutes. After consumption of starting material, the solvent was removed under reduced pressure to give **15** (4813mg, 15.21 mmol) in 92% yield. Spectroscopic data match with those reported on bibliography[1].

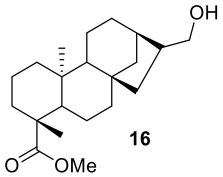


15

*Kaur-16-en-18-oic acid, methyl ester (**15**).* White solid. ^1H NMR (500 MHz, Chloroform-*d*) δ 4.82 (s, 1H), 4.76 (s, 1H), 3.66 (s, 3H), 2.65 (s, 1H), 2.19 (d, *J* = 13.2, 2.8 Hz, 1H), 2.09 – 2.05 (m, 2H), 1.99 (dd, *J* = 11.4, 2.3 Hz, 1H), 1.91 – 1.74 (m, 4H), 1.67 – 1.42 (m, 7H), 1.19 (s, 3H), 1.15 (dd, *J* = 11.3, 5.0 Hz, 1H), 1.09 – 1.03 (m, 2H), 1.02 (d, *J* = 4.4 Hz, 1H), 0.85 (s, 3H), 0.82 (d, *J* = 4.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.15(C), 155.95(C), 102.98(CH_2), 57.08(CH), 55.10(CH), 51.13(CH_3), 48.97(CH_2), 44.24(C), 43.85(CH), 43.83(C), 41.32(CH_2), 40.79(CH_2), 39.70(CH_2), 39.45(C), 38.13(CH_2), 33.13(CH_2), 28.78(CH_3), 21.95(CH_2), 19.17(CH_2), 18.42(CH_2), 15.43(CH_3). HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{33}O_2$ 317.2481, found 317.2466.

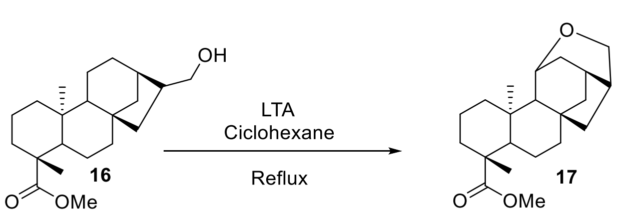


Synthesis of 16 . To a solution of 2600 mg (8.22 mmol) of **15** in dry THF (100 mL), 2.3 mL of a 1M borane-THF solution was added dropwise at 0ºC under inert gas (Ar). After 15 min, the 0ºC bath was removed and the mixture was stirred for 1 h until consumption of the starting material. Then, the reaction was cooled (0ºC) and EtOH (32 mL), NaOH 4N (22.5 mL) and 29 mL of H_2O_2 were added. The resulting mixture was then diluted with 150 mL of EtOAc, washed with water and brine and dried over Na_2SO_4. The solvent was evaporated over reduced pressure and the crude was chromatographed via silica gel column (H/MTBE 5:1) to afford **16** (1339 mg, 4.00 mmol) in 65% yield. The spectroscopic data of compound **16** match with those reported in the literature[8,13,14].



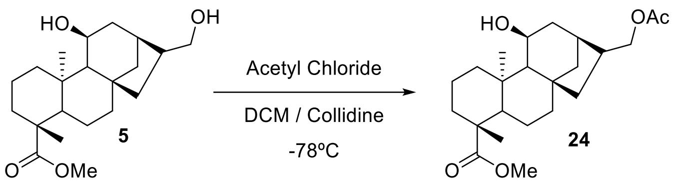
16

*Compound **16**.* White foam. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.64 (dd, *J* = 7.3, 6.0 Hz, 2H), 3.57 (s, 3H), 2.16 – 2.06 (m, 3H), 1.92 (d, *J* = 11.1 Hz, 1H), 1.83 – 1.72 (m, 3H), 1.64 (qd, *J* = 13.6, 3.0 Hz, 1H), 1.54 – 1.32 (m, 8H), 1.09 (s, 3H), 1.01 – 0.88 (m, 5H), 0.75 (s, 3H), 0.70 (dd, *J* = 13.8, 4.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.16(C), 64.29(CH_2), 56.99(CH), 56.42(CH), 51.13(CH_3), 44.25(C), 43.82(C), 43.62(CH_2), 43.23(CH), 42.09(CH_2), 40.76(CH_2), 40.36(CH_2), 39.43(C), 38.10(CH_2), 36.94(CH), 28.73(CH_3), 26.02(CH_2), 22.22(CH_2), 19.16(CH_2), 19.12(CH_2), 15.36(CH_3). $[\alpha]_D$ -60.2. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{35}O_3$ 335.2586, found 335.2591.

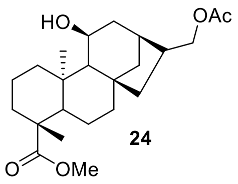


Synthesis of 17 . To a solution of **16** (730 mg, 2.18 mmol) in dry cyclohexane (137 mL), LTA (6580 mg, 14.84 mmol) was added. The reaction was heated to reflux under inert atmosphere[15].

After 24 h, the reaction was cooled to room temperature and passed through a small column of celite/silica gel (1:1) that was washed with MTBE. The solvent was evaporated under reduced pressure and the resultant crude was purified via column chromatography (H/MTBE 7:1) to afford **17** (542 mg, 1.630 mmol) in a 75% yield.

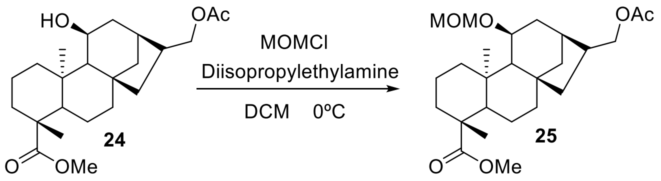


Synthesis of 24. To a solution of **5** (802 mg, 2.29 mmol) at -78ºC in 76 mL dry dichloromethane (76 mL) and 1.1 mL of anhydrous collidine (8.47 mmol) acetyl chloride (0.15 mL, 2.13 mmol) was added dropwise under argon. The mixture was stirred for 20 min. After this time, the mixture was diluted with MTBE and washed with HCl 2N. The aqueous phase was extracted several times with MTBE and the combined organic layer was dried over anhydrous Na_2SO_4 and then, concentrated in vacuo. Column chromatography (H/EtOAc5:1) provided **24** (712 mg, 1.81 mmol) in 79% yield.

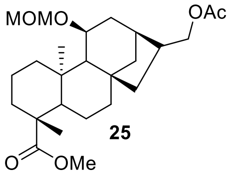


24

Compound ***24***. White solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.37 (dd, *J* = 10.8, 8.3 Hz, 1H), 4.23 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.79 (d, *J* = 6.5 Hz, 1H), 3.53 (s, 3H), 2.17 – 2.04 (m, 3H), 1.93 (s, 3H), 1.83 (dt, *J* = 12.5, 3.2 Hz, 1H), 1.78 – 1.70 (m, 5H), 1.66 – 1.32 (m, 7H), 1.08 (s, 3H), 1.06 (s, 1H), 0.98 (dd, *J* = 12.2, 2.3 Hz, 1H), 0.96 – 0.90 (m, 2H), 0.61 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 177.93(C), 171.41(C), 66.69(CH), 66.53(CH_2), 65.61(CH), 56.78(CH), 51.18(CH_3), 43.82(C), 42.95(C), 41.98(CH_2), 41.53(CH_2), 40.04(CH_2), 39.56(CH_2), 39.49(CH), 38.36(C), 37.97(CH_2), 37.12(CH), 35.27(CH_2), 28.71(CH_3), 21.92(CH_2), 21.13(CH_3), 18.99(CH_2), 14.89(CH_3). $[\alpha]_D$ -57.3. HRMS (ESI-QTOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{36}O_5Na$ 415.2460, found 415.2453.

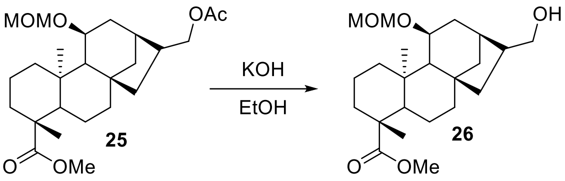


Synthesis of 25. To a solution of **24** (712 mg, 1.81 mmol) in dry DCM (12 mL) at 0ºC, diisopropylethylamine (830 mg, 6.42 mmol) was added under inert atmosphere. After 5 minutes stirring, chloromethyl methyl ether (MOMCl) (0.45 mL, 5.90 mmol) was added. The reaction mixture was then let to warm to room temperature. After stirring for 2h, the reaction was cooled (0ºC) and diluted with MTBE (60 mL). Then, it was washed with HCl 2N, water, $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (H/MTBE 2:1) afforded **25** (763 mg, 1.75 mmol) in 96% yield.

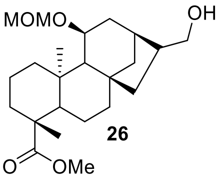


25

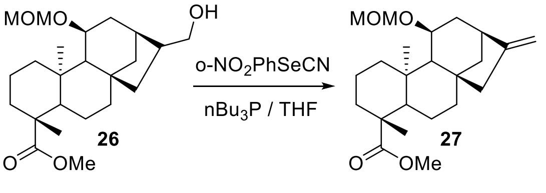
*Compound **25***. Pale syrup. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.52 (s, 2H), 4.34 (dd, J = 10.8, 8.3 Hz, 1H), 4.20 (dd, J = 10.8, 6.4 Hz, 1H), 3.64 (d, J = 6.6 Hz, 1H), 3.56 (s, 3H), 3.27 (s, 3H), 2.17 – 2.06 (m, 3H), 1.96 (s, 3H), 1.92 – 1.71 (m, 5H), 1.63 – 1.32 (m, 7H), 1.19 (s, 1H), 1.10 (s, 3H), 1.04 – 0.86 (m, 4H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 177.93(C), 171.32(C), 93.40(CH_2), 69.25(CH), 66.35(CH_2), 63.45(CH), 56.90(CH), 55.44(CH_3), 51.17(CH_3), 43.89(C), 43.11(C), 42.09(CH_2), 40.91(CH_2), 40.17(CH_2), 40.04(CH_2), 39.72(CH), 38.22(C), 38.00(CH_2), 37.02(CH), 32.36(CH_2), 28.77(CH_3), 21.96(CH_2), 21.13(CH_3), 19.09(CH_2), 15.17(CH_3). $[\alpha]_D$ -44.5. HRMS (ESI-QTOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{40}O_6Na$ 459.2723, found 459.2721.



Synthesis of 26. A solution of **25** (763 mg, 1.75 mmol) in 68 mL of 10% KOH/MeOH was stirred at room temperature for 10 min. After this time, the solvent was evaporated under reduced pressure and the crude was dissolved in MTBE (60 mL), washed with NH_4Cl, water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure affording **26** (673 mg, 1.71 mmol) 98% yield.

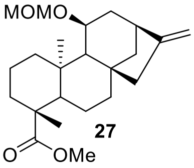


Compound ***26***. Pale syrup.^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.61 (s, 2H), 3.91 (dd, *J* = 10.5, 7.8 Hz, 1H), 3.84 (dd, *J* = 10.7, 6.2 Hz, 1H), 3.74 (d, *J* = 6.8 Hz, 1H), 3.65 (s, 3H), 3.36 (s, 3H), 2.26 – 2.06 (m, 3H), 2.01 – 1.78 (m, 5H), 1.73 – 1.40 (m, 7H), 1.28 (s, 1H), 1.19 (s, 3H), 1.14 – 0.97 (m, 4H), 0.74 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 177.95(C), 93.37(CH_2), 69.44(CH), 64.01, (CH_2) 63.56(CH), 56.88(CH), 55.50(CH_3), 51.18(CH_3), 43.89(C), 43.73(CH), 42.99(C), 42.21(CH_2), 40.45(CH_2), 40.19(CH_2), 40.16(CH_2), 38.26(C), 38.00(CH_2), 37.09(CH), 32.51(CH_2), 28.77(CH_3), 21.93(CH_2), 19.09(CH_2), 15.19(CH_3). $[\alpha]_D$ -36.2. HRMS (ESI-QTOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{38}O_5Na$ 417.2617, found 417.2619.



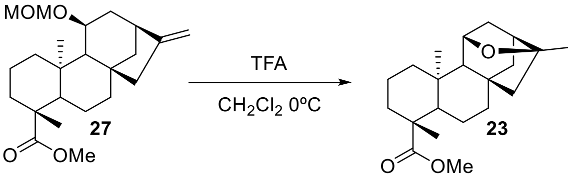
Synthesis of 27. To a solution of **26** (120mg, 0.21 mmol) in dry THF (10 mL) in a dry flamed flask, a solution of *o*-NO2PhSeCN (207 mg, 0.912 mmol) in dry THF (5 mL) was added dropwise. After that, 0.23 mL (0.91 mmol) of *n*-Bu_3P was added. The reaction mixture was stirred at room temperature for 2 h. After this time, the reaction was diluted with MTBE, washed with NH_4Cl

and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The resulting crude was dissolved in dry THF (5.6 mL) at room temperature under inert gas. Then, 0.16 mL (7.38 mmol) of H_2O_2 was added to the mixture and heated for 10 minutes. The reaction was then diluted with MTBE 40 mL, washed with distilled water and brine and dried over Na_2SO_4. Flash chromatography (H/MTBE 9:1) afforded **27** (120 mg, 0.32 mmol) in 70% yield.



27

*Compound **27**.* White crystals. ^1H NMR (500 MHz, Chloroform-*d*) δ 4.77 (s, 1H), 4.56 (s, 1H), 4.52 (d, *J* = 7.0 Hz, 1H), 4.44 (d, *J* = 6.9 Hz, 1H), 3.71 (d, *J* = 5.5 Hz, 1H), 3.57 (s, 3H), 3.25 (s, 3H), 2.53 (dt, *J* = 3.9 Hz, 1H), 2.44 (dd, *J* = 16.7, 2.5 Hz, 1H), 2.16 – 2.10 (m, 1H), 1.97 – 1.34 (m, 11H), 1.30 (s, 1H), 1.12 (s, 3H), 1.06 – 0.91 (m, 4H), 0.67 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.00(C), 155.64(C), 102.73(CH_2), 93.57(CH_2), 70.29(CH), 61.69(CH), 57.02(CH), 55.21(CH_3), 51.19(CH_3), 47.41(CH_2), 43.90(C), 43.00(C), 42.70(CH), 41.43(CH_2), 40.18(CH_2), 39.62(CH_2), 38.20(CH_2), 38.16(C), 38.02(CH_2), 28.81(CH_3), 21.76(CH_2), 19.15(CH_2), 15.23(CH_3). $[\alpha]_D$ -52.7. HRMS (ESI-QTOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{37}O_4Na$ 377.2692, found 377.2676.



Synthesis of 27. To a cooled (0ºC) solution of **27** (317mg, 0.84mmol) in dry DCM, TFA (3.0 mL, 39.18 mmol) was added under argon. The mixture was stirred at 0ºC for 10 min. Then, the solution was diluted with MTBE (50 mL, washed with Na_2CO_3 and brine and dried over Na_2SO_4. The organic layer was then concentrated under vacuo and the crude was purified via flash chromatography (H/MTBE 2:1) to afford **23** (271 mg, 0.82 mmol) in a 97% yield.

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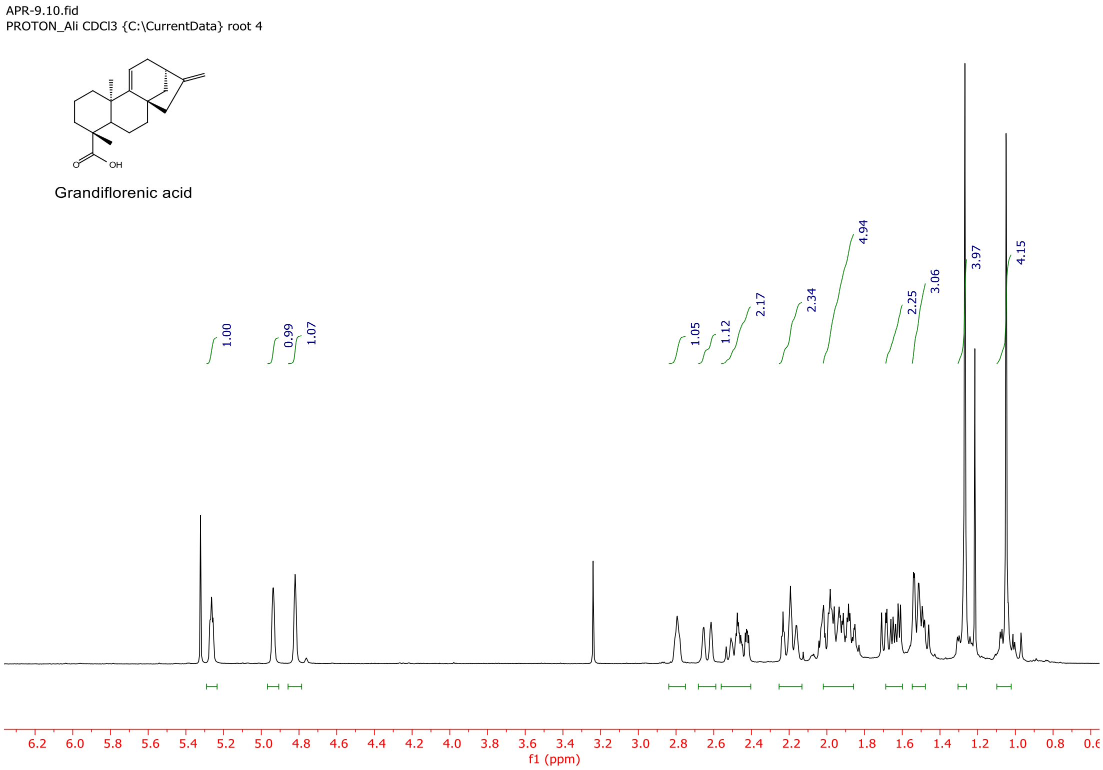
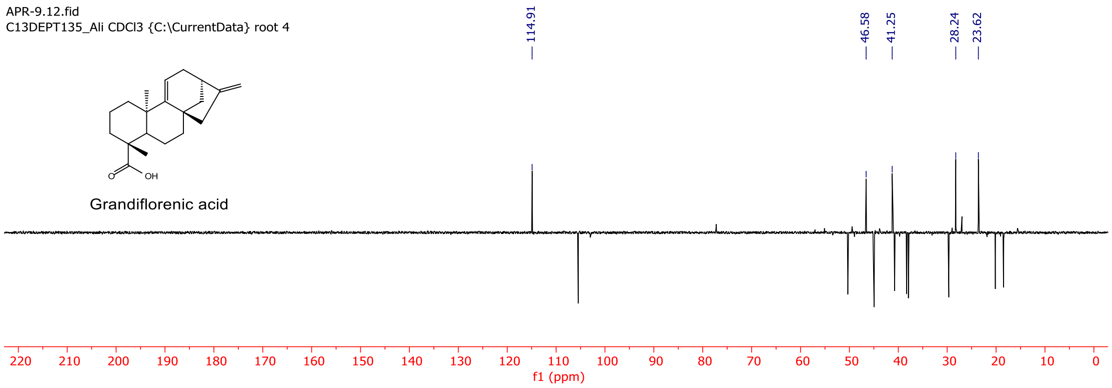
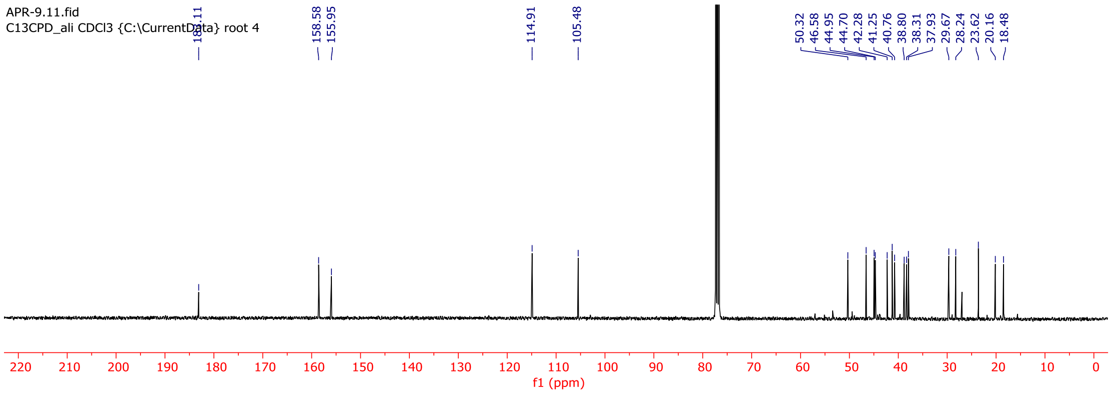
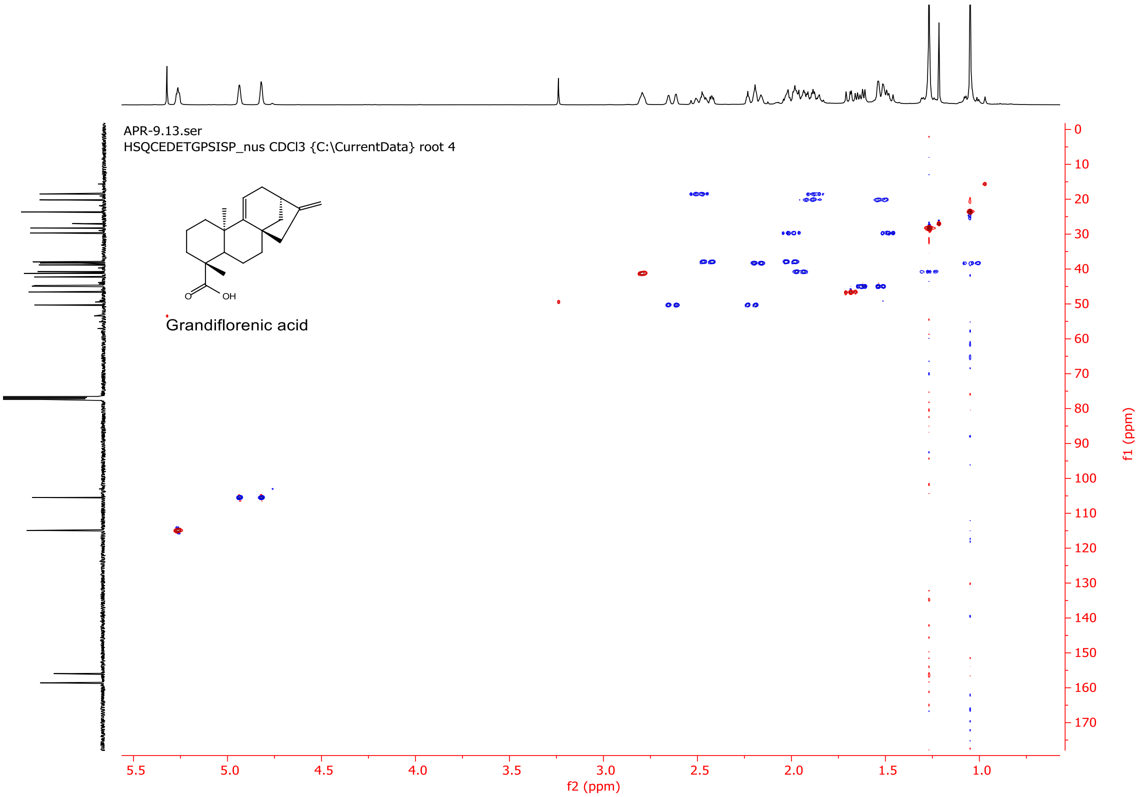
Proton and Carbon NMR Spectra:





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40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)
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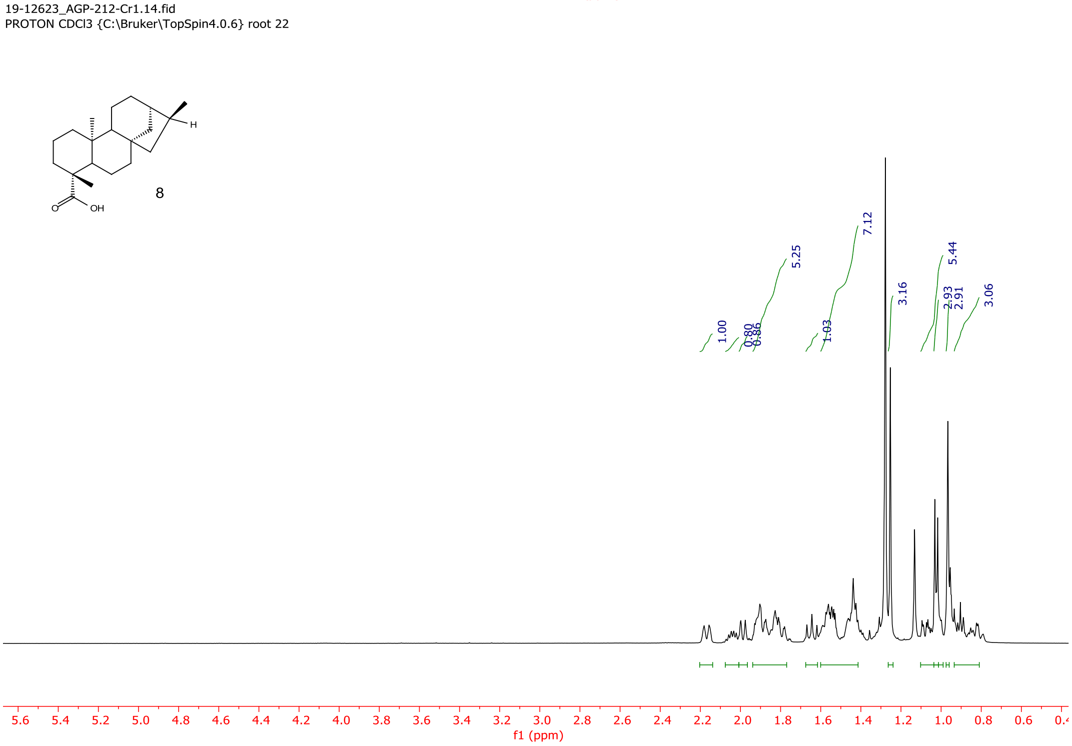
f2 (ppm)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2.93
2.91
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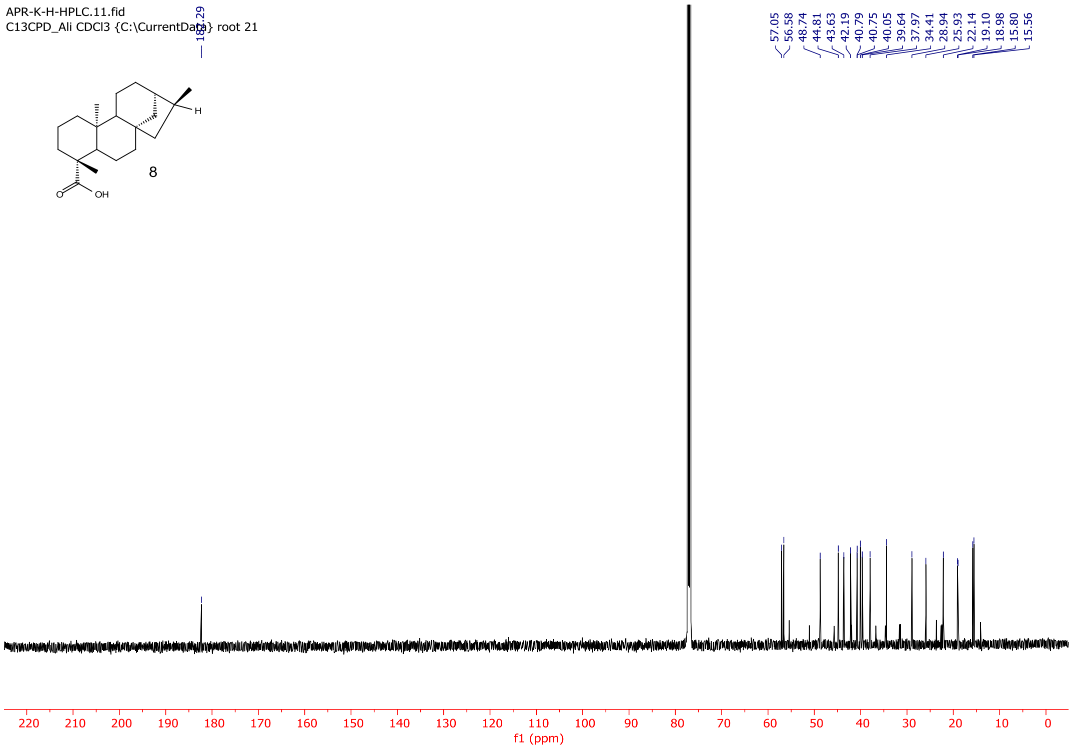
f1 (ppm)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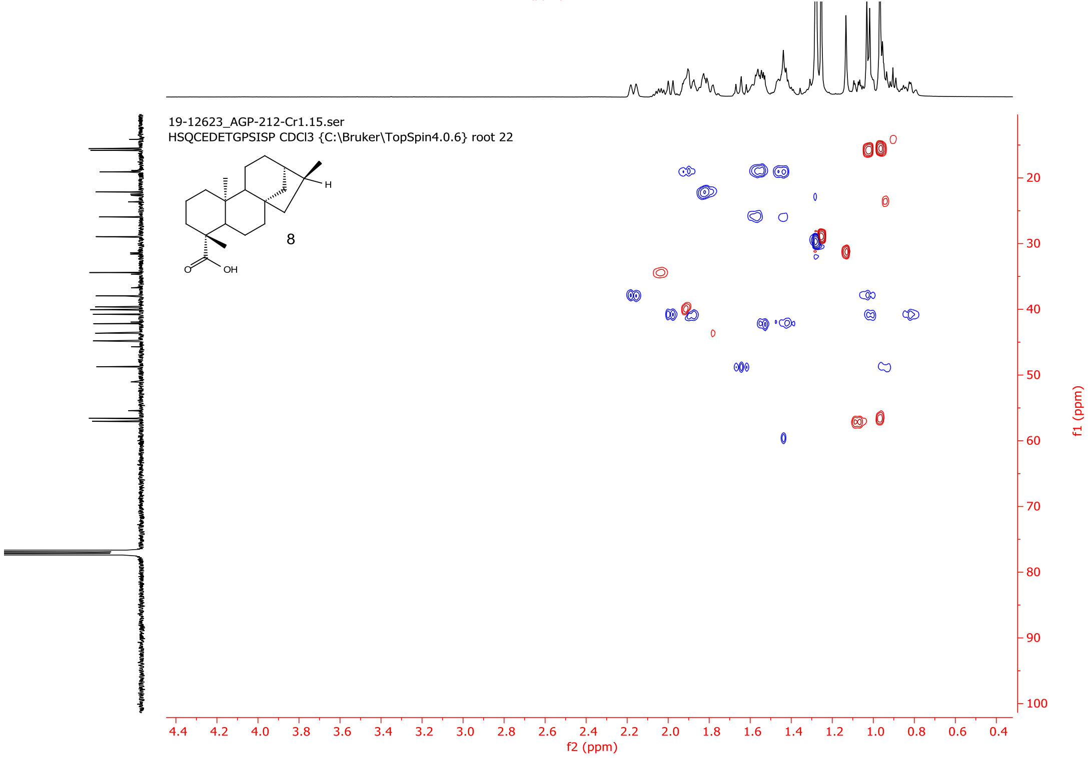
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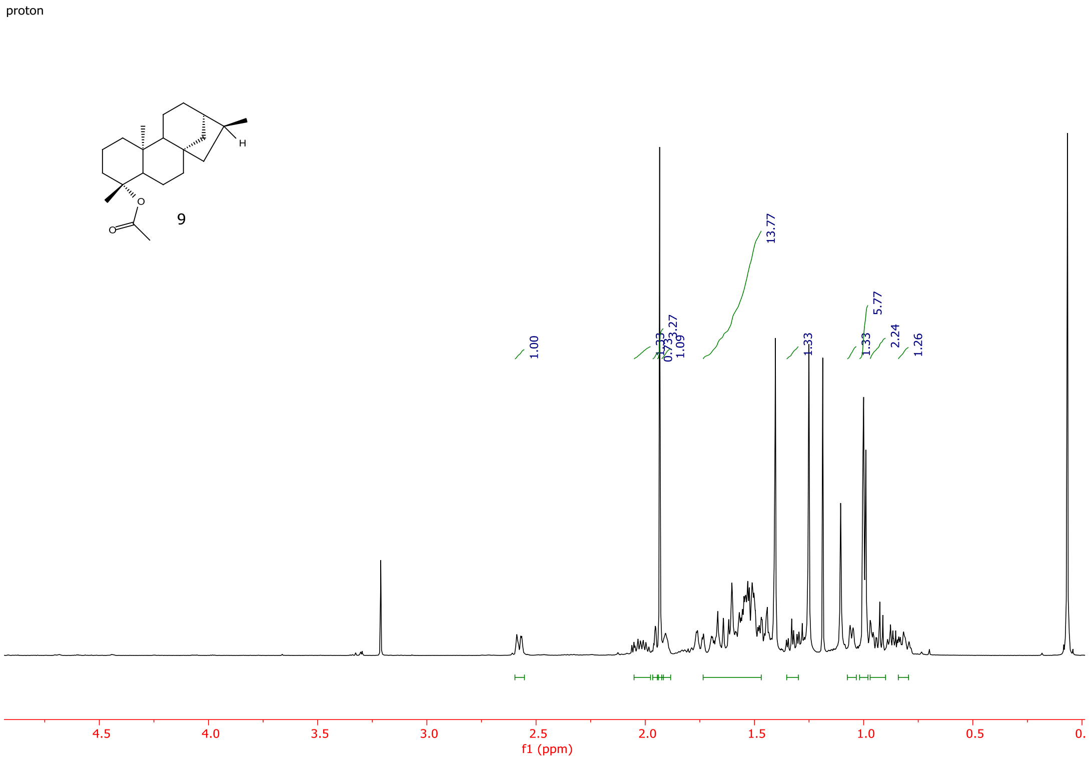
f2 (ppm)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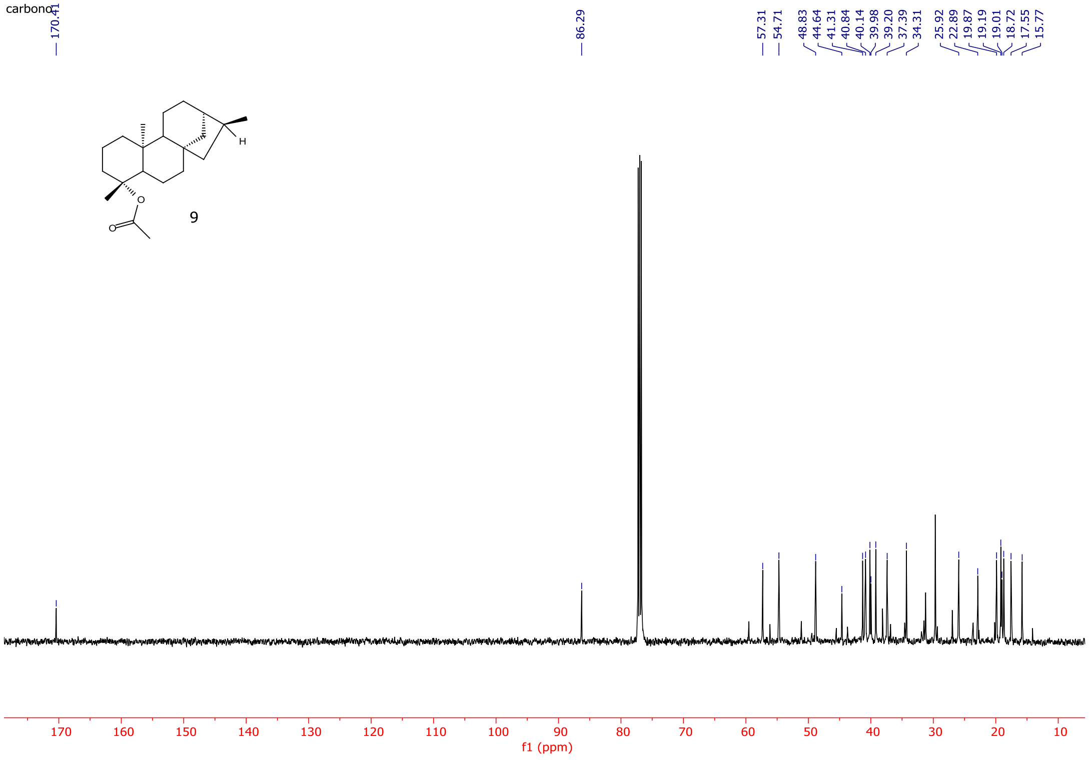
f1 (ppm)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34.31
25.92
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19.87
19.19
19.01
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9
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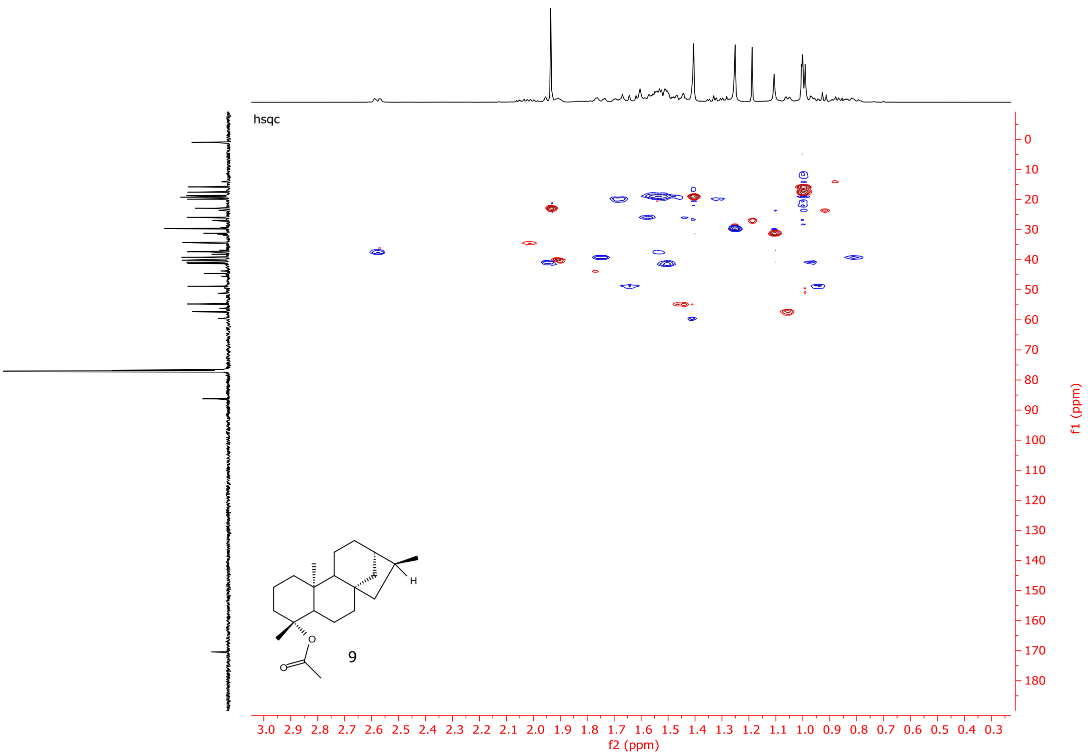
f1 (ppm)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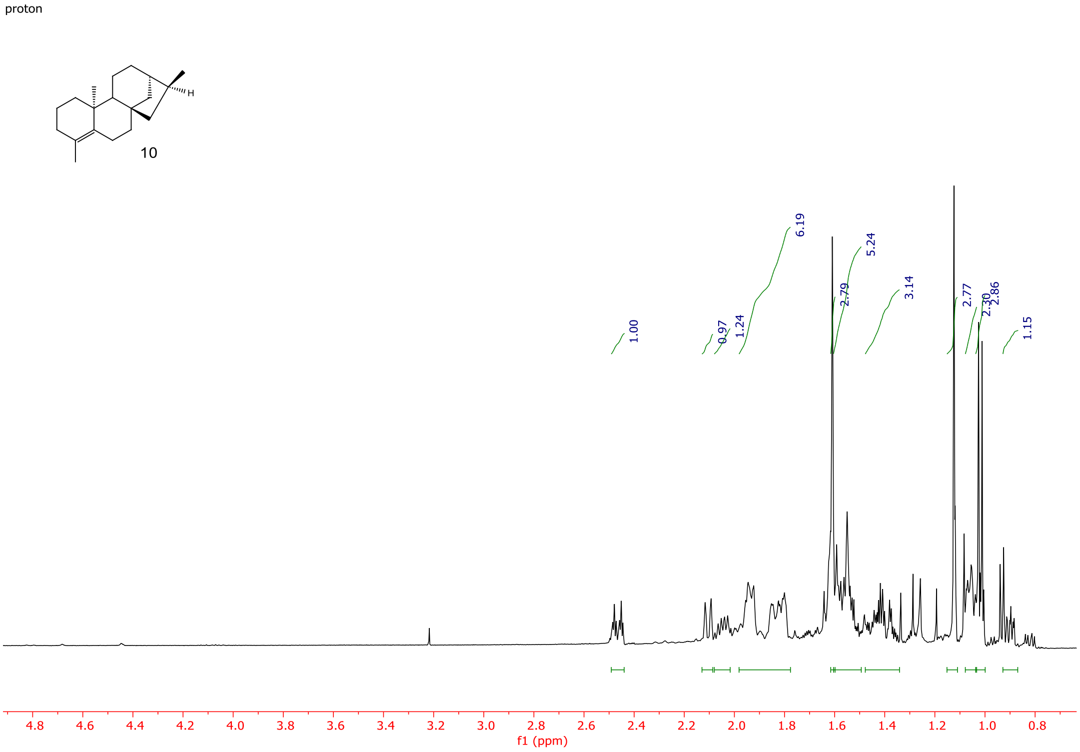
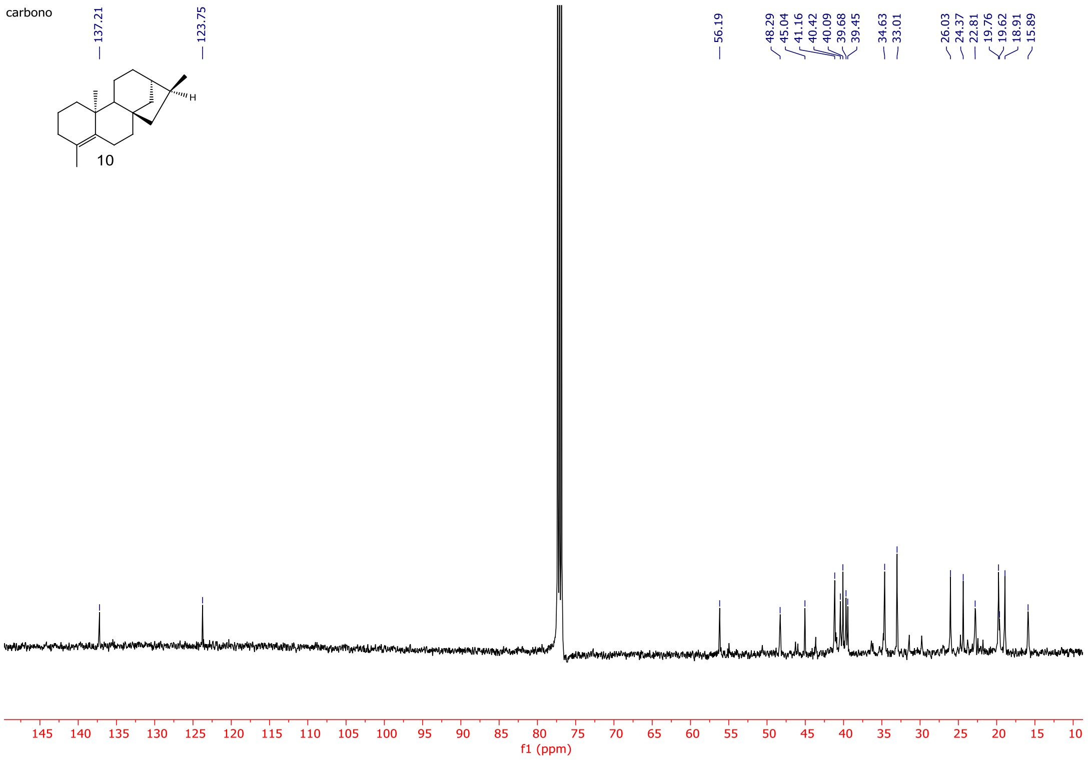
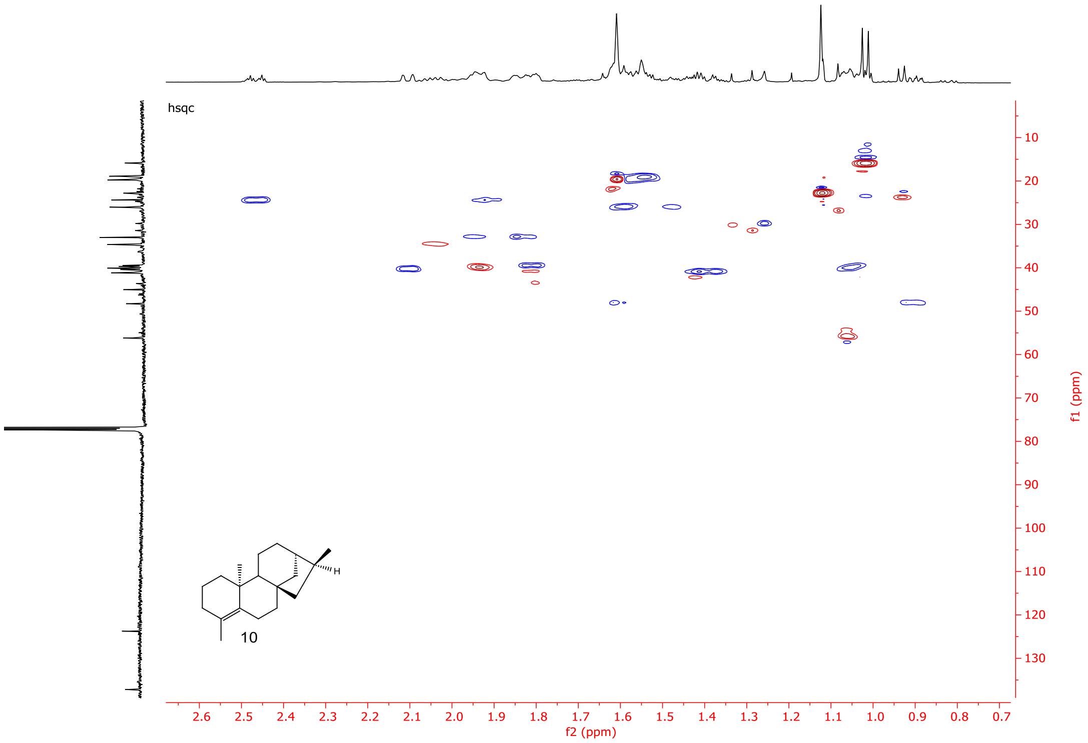
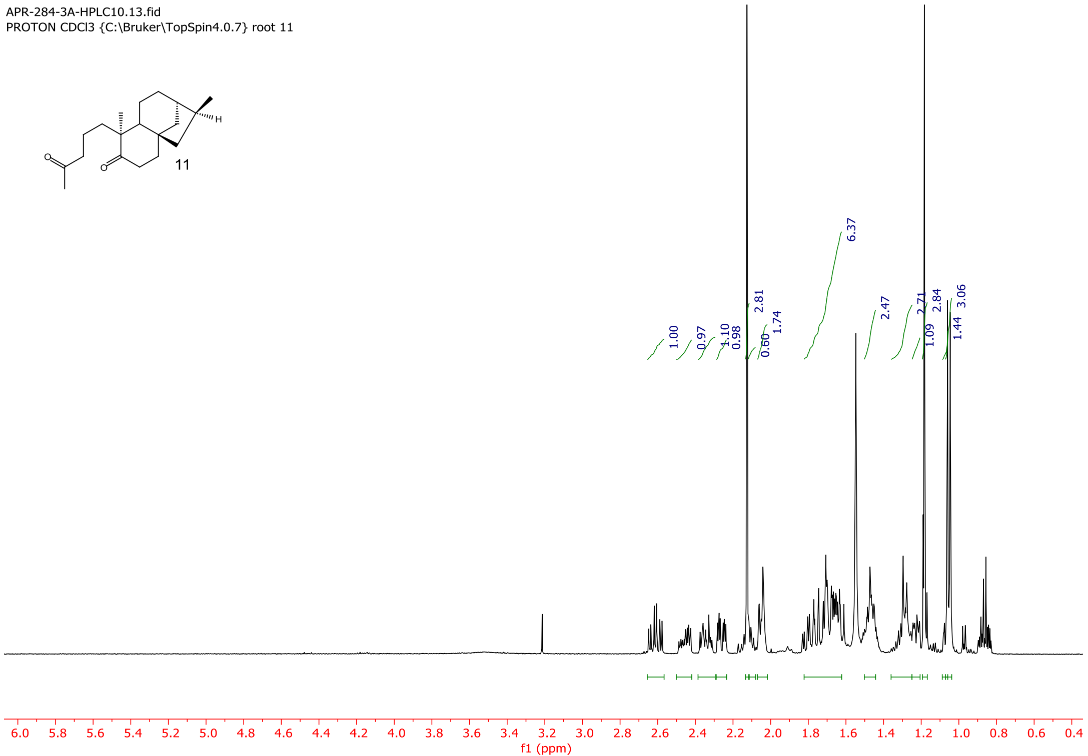
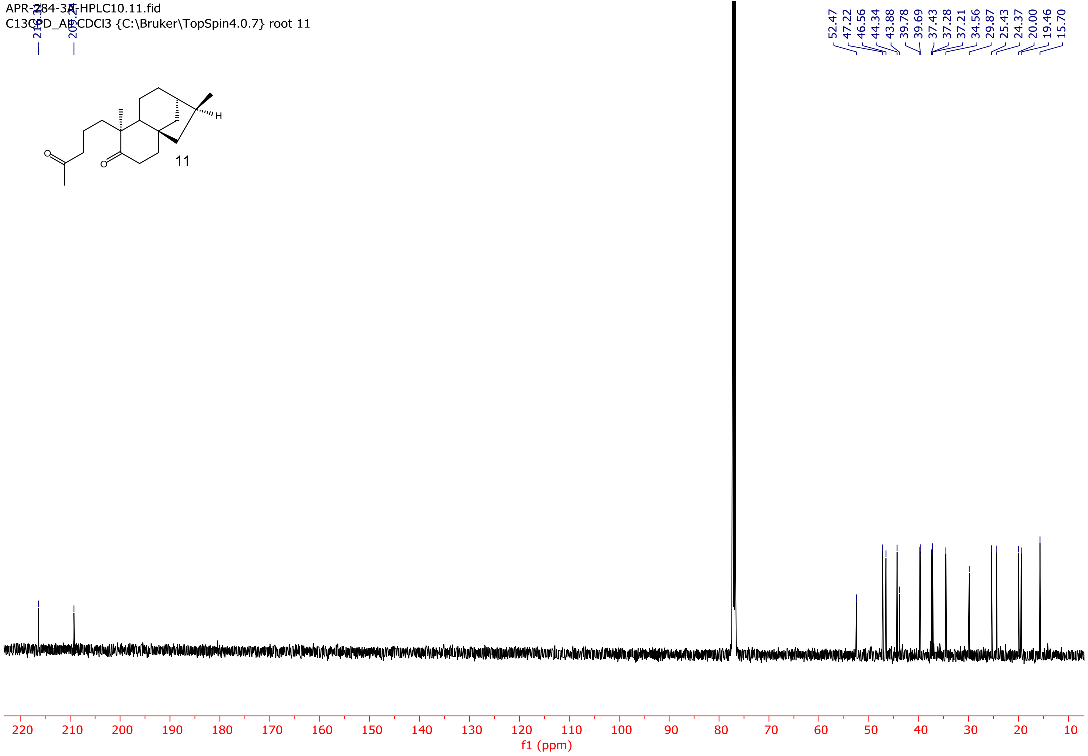
3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)
H
O

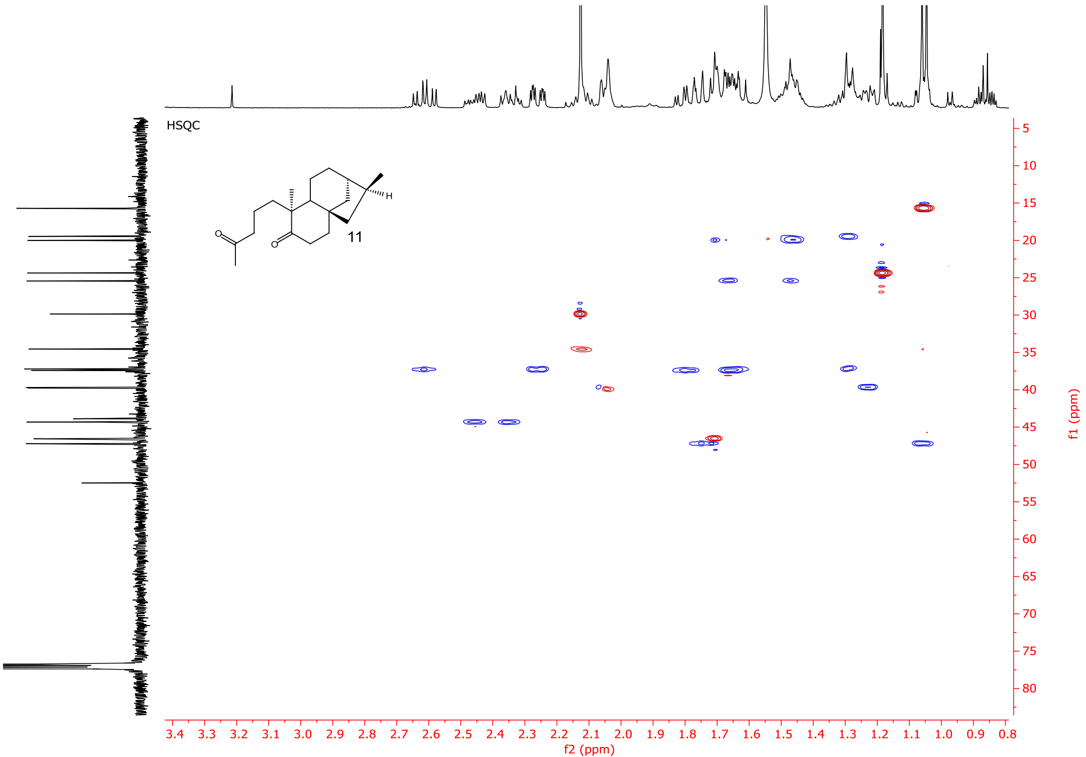

proton
10
H
1.00
0.97
1.24
6.19
2.79
5.24
3.14
2.77
2.30
2.86
1.15
4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)

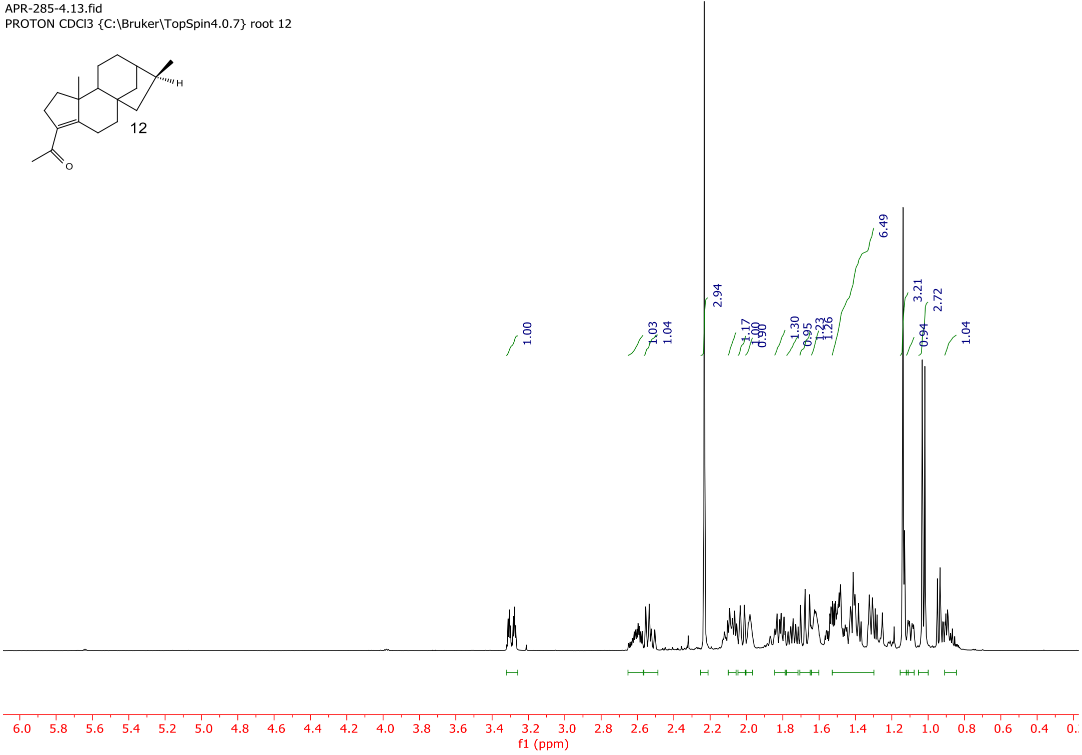

carbono
137.21
123.75
56.19
48.29
45.04
41.16
40.42
40.09
39.68
39.45
34.63
33.01
26.03
24.37
22.81
19.76
19.62
18.91
15.89
10
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

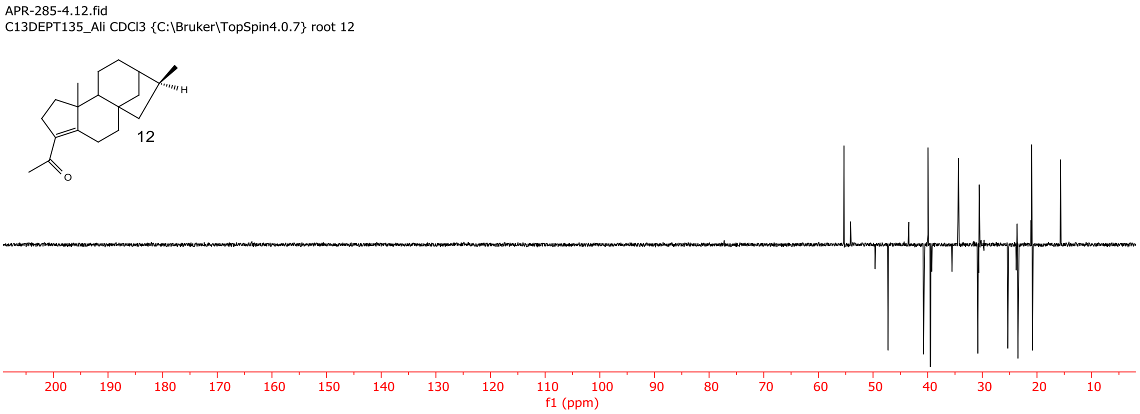

hsqc
10
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7
f2 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130
f1 (ppm)

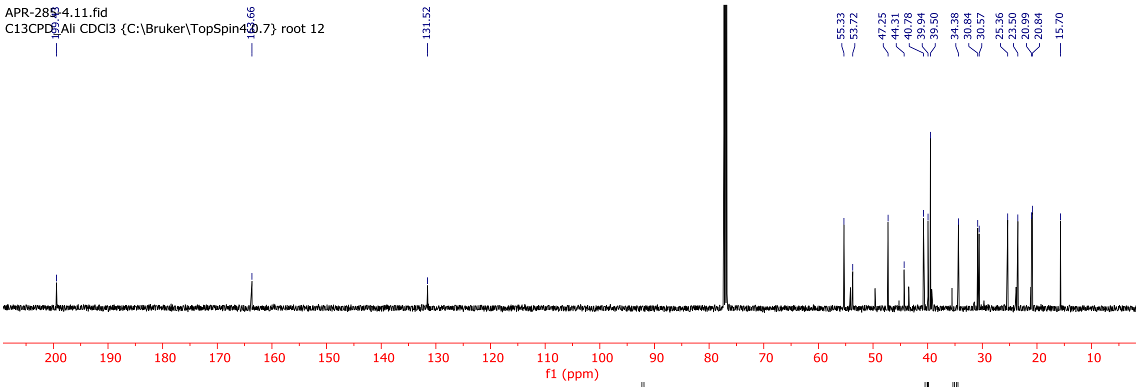

APR-284-3A-HPLC10.13.fid
PROTON CDCl3 {C:\Bruker\TopSpin4.0.7} root 11
11
1.00
0.97
1.10
0.98
2.81
0.60
1.74
6.37
2.47
2.71
1.09
2.84
1.44
3.06
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
f1 (ppm)

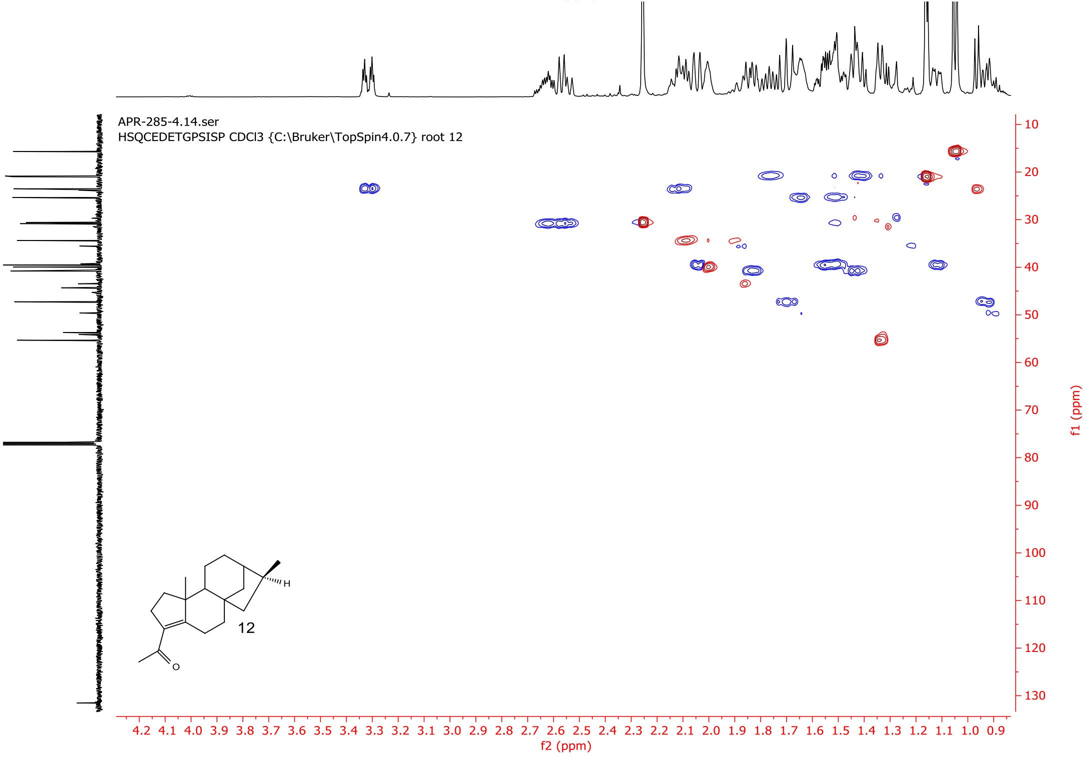

APR-284-3A-HPLC10.11.fid
C13CPD_AP CDCl3 {C:\Bruker\TopSpin4.0.7} root 11
216.31
209.24
11
52.47
47.22
46.56
44.34
43.88
39.78
39.69
37.43
37.28
37.21
34.56
29.87
25.43
24.37
20.00
19.46
15.70
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

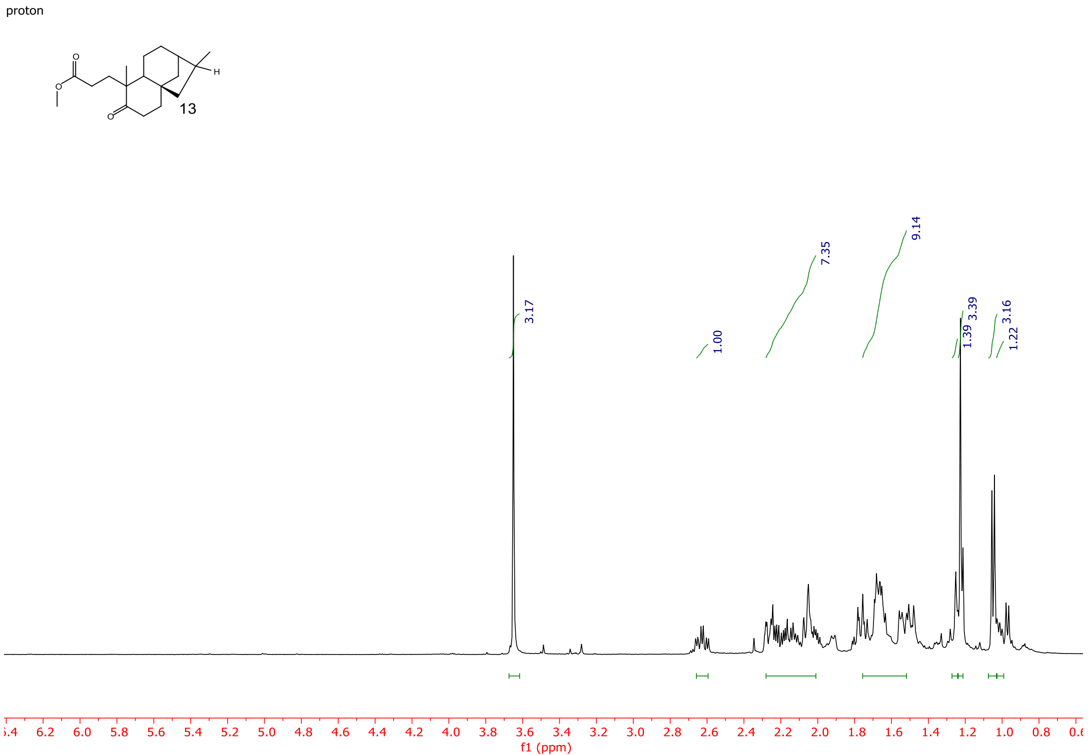

HSQC
11
3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8
f2 (ppm)
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80
f1 (ppm)

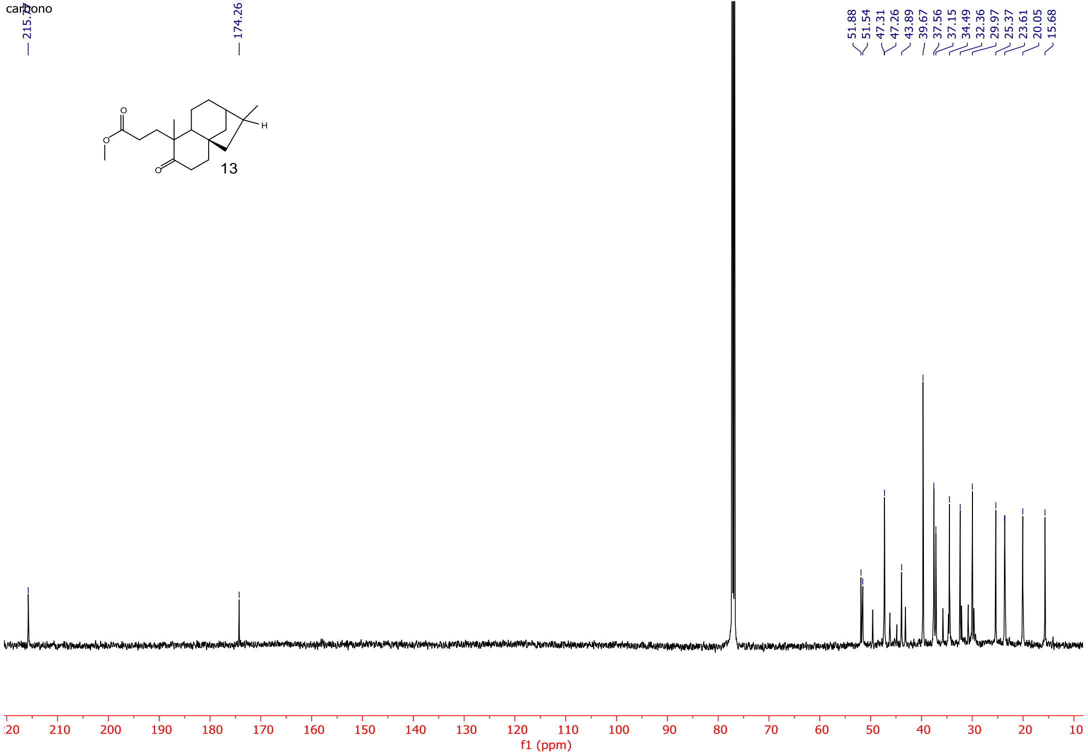

APR-285-4.13.fid
PROTON CDCl3 {C:\Bruker\TopSpin4.0.7} root 12
12
1.00
1.03
1.04
2.94
1.17
1.00
0.90
1.30
0.95
1.23
1.26
6.49
3.21
0.94
2.72
1.04
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.
f1 (ppm)

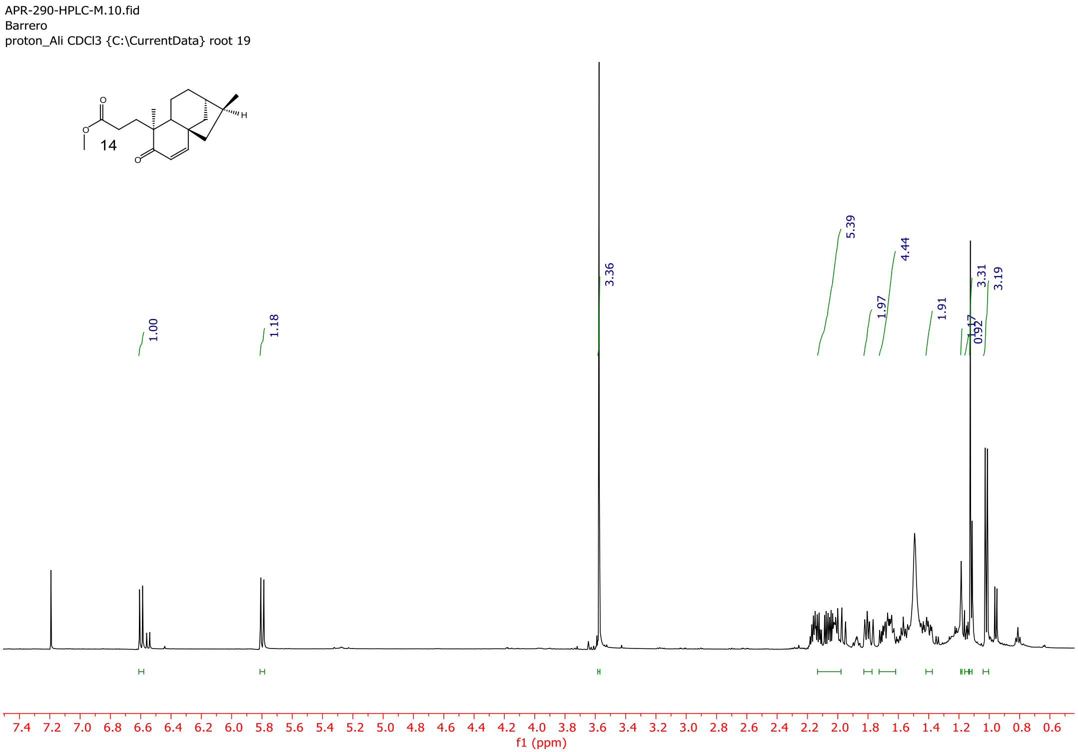

APR-285-4.12.fid
C13DEPT135_Ali CDCl3 {C:\Bruker\TopSpin4.0.7} root 12
H
O
12
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

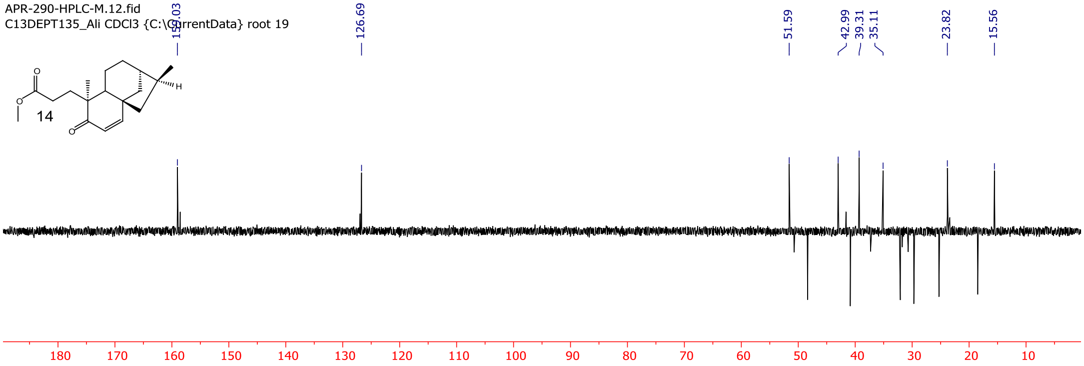

APR-285-4.11.fid
C13CPD_Ali CDCl3 {C:\Bruker\TopSpin4.0.7} root 12
131.52
55.33
53.72
47.25
44.31
40.78
39.94
39.50
34.38
30.84
30.57
25.36
23.50
20.99
20.84
15.70
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

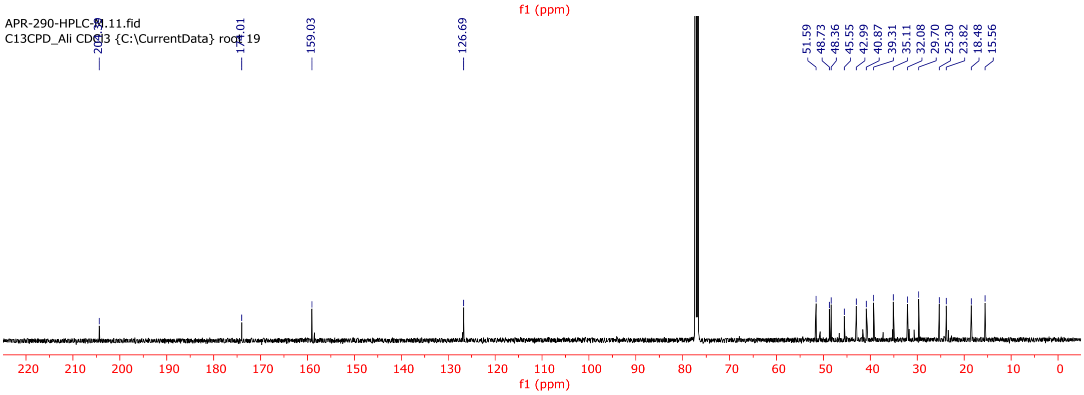

APR-285-4.14.ser
HSQCEDETGPSISP CDCl3 {C:\Bruker\TopSpin4.0.7} root 12
H
O
12
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
f1 (ppm)

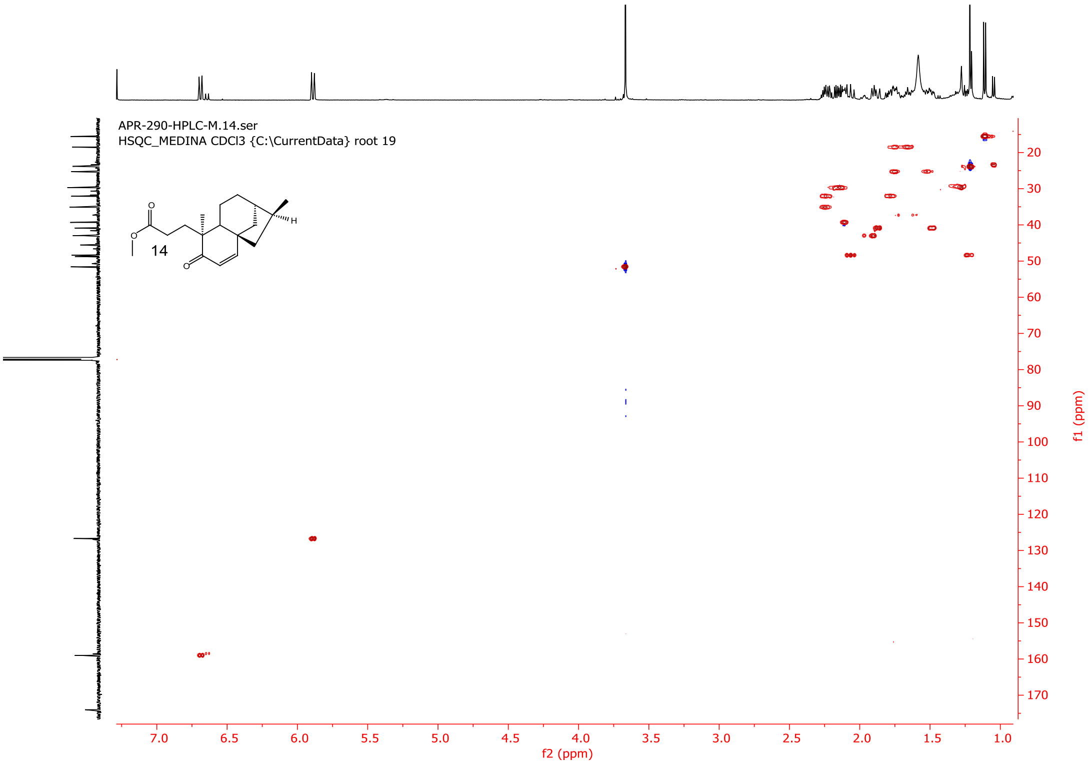

proton
13
3.17
1.00
7.35
9.14
1.39
3.39
3.16
1.22
.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.
f1 (ppm)

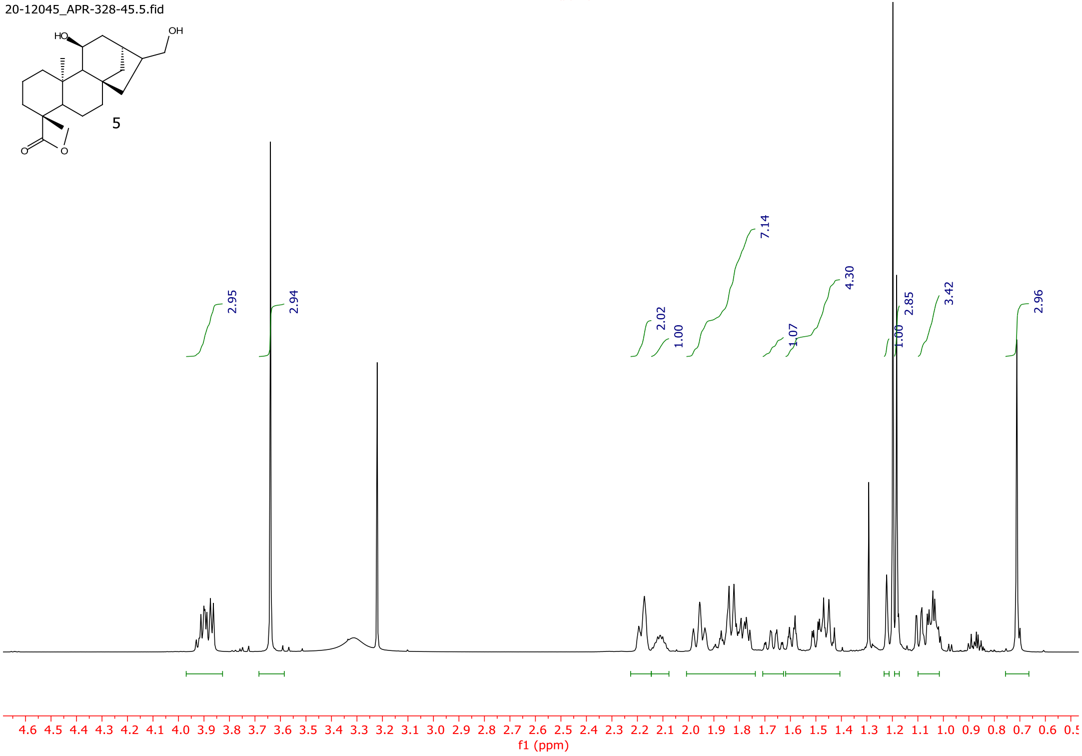

carbono
215.77
174.26
13
51.88
51.54
47.31
47.26
43.89
39.67
37.56
37.15
34.49
32.36
29.97
25.37
23.61
20.05
15.68
20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

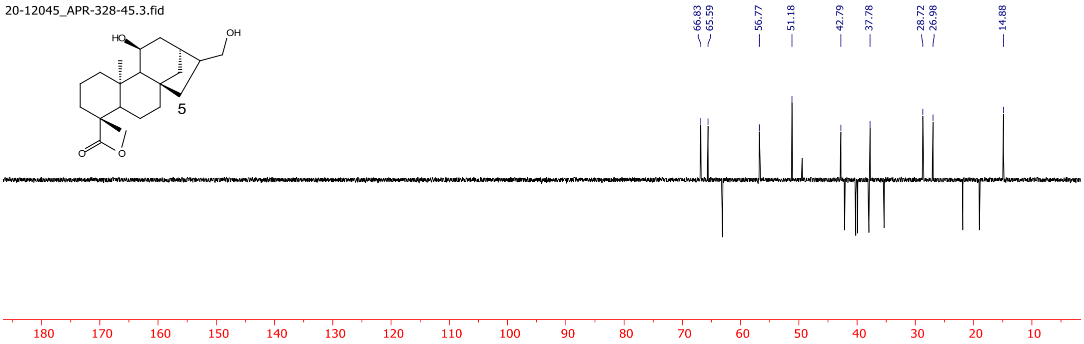

APR-290-HPLC-M.10.fid
Barrero
proton_Ali CDCl3 {C:\CurrentData} root 19
O
O
H
O
14
1.00
1.18
3.36
5.39
1.97
4.44
1.91
1.17
0.92
3.31
3.19
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)

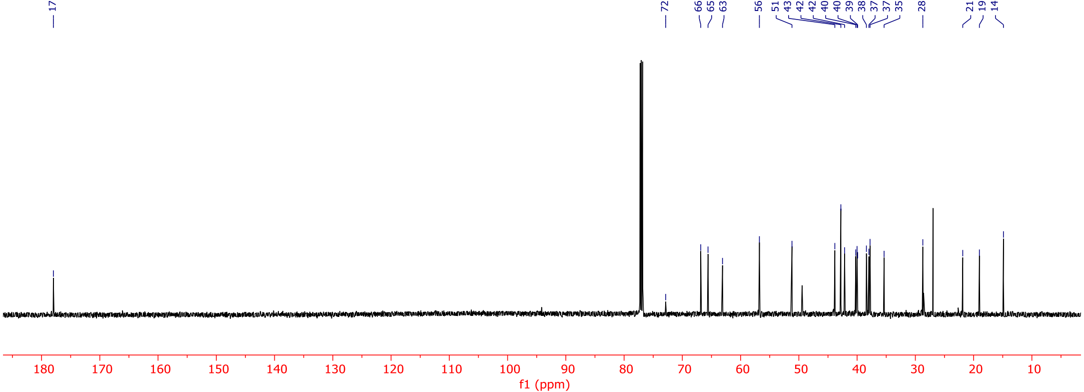

APR-290-HPLC-M.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 19
159.03
126.69
51.59
42.99
39.31
35.11
23.82
15.56
O
O
H
O
14
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

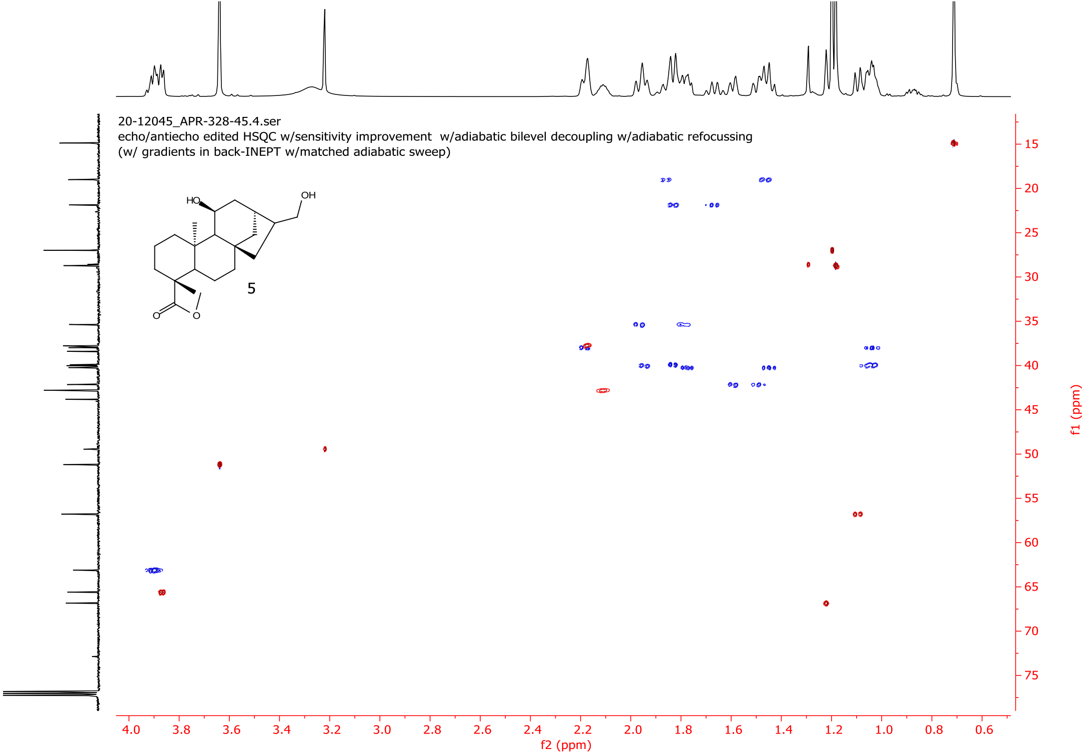

APR-290-HPLC-M.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 19
204.39
174.01
159.03
126.69
51.59
48.73
48.36
45.55
42.99
40.87
39.31
35.11
32.08
29.70
25.30
23.82
18.48
15.56
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


APR-290-HPLC-M.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 19
14
f2 (ppm)
f1 (ppm)
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170

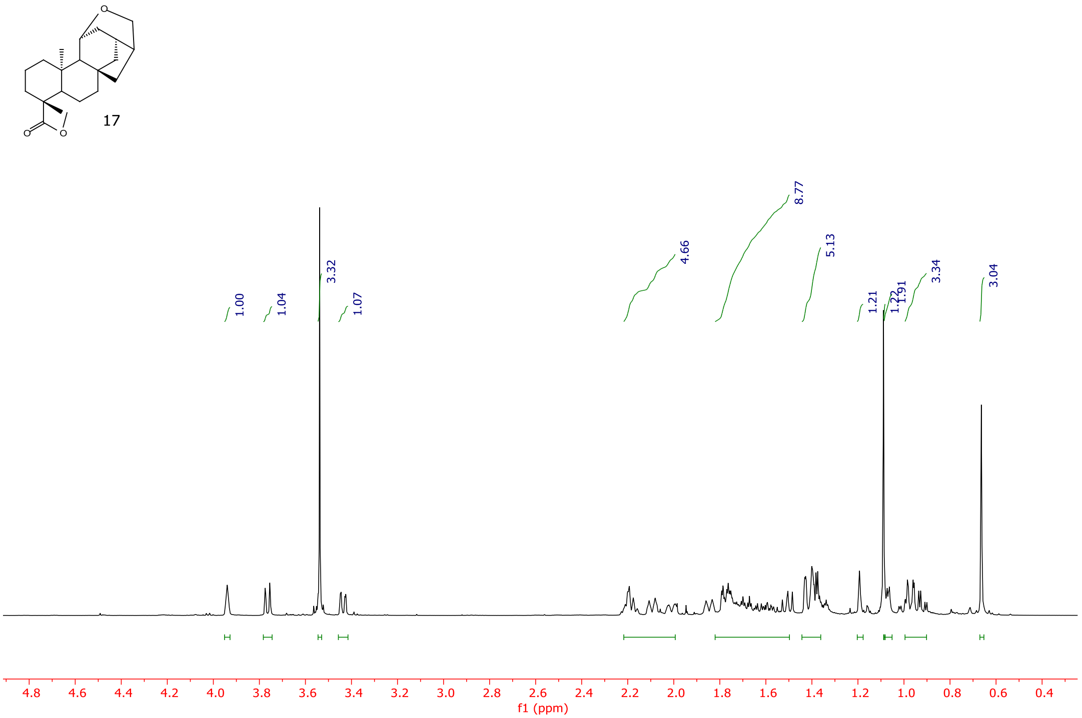

20-12045_APR-328-45.5.fid
HO
OH
5
2.95
2.94
2.02
1.00
7.14
1.07
4.30
1.00
2.85
3.42
2.96
4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5
f1 (ppm)


20-12045_APR-328-45.3.fid
HO
OH
5
O
O
66.83
65.59
56.77
51.18
42.79
37.78
28.72
26.98
14.88
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

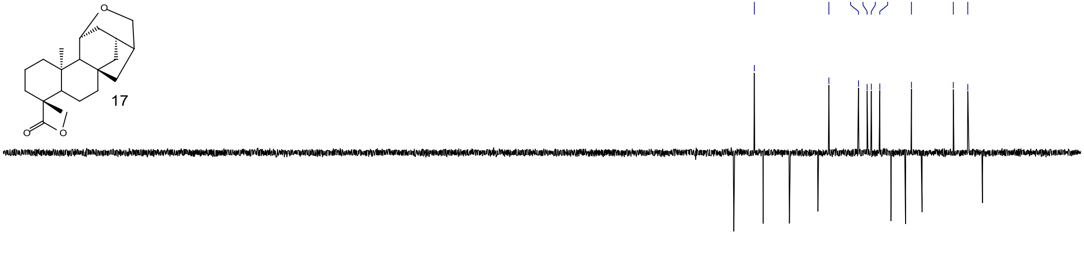

20-12045_APR-328-45.2.fid
177.7
72.86
66.84
65.59
63.11
56.77
51.18
43.82
42.79
42.15
40.23
40.01
39.91
38.40
37.98
37.78
35.37
28.72
21.86
19.01
14.88
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


20-12045_APR-328-45.4.ser
echo/antiecho edited HSQC w/sensitivity improvement w/adiabatic bilevel decoupling w/adiabatic refocussing
(w/ gradients in back-INEPT w/matched adiabatic sweep)
HO
OH
5
O
O
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
f2 (ppm)
15
20
25
30
35
40
45
50
55
60
65
70
75
f1 (ppm)

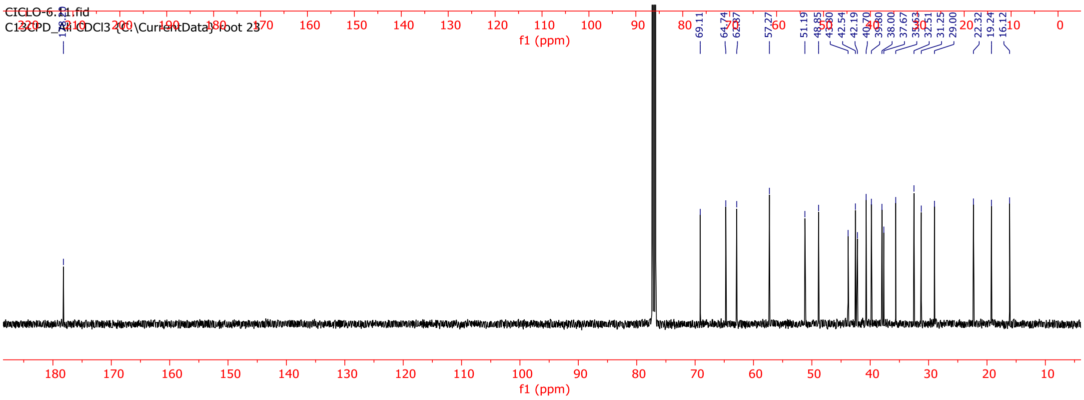
CICLO-6.13.fid
proton_Ali CDCl3 {C:\CurrentData} root 23

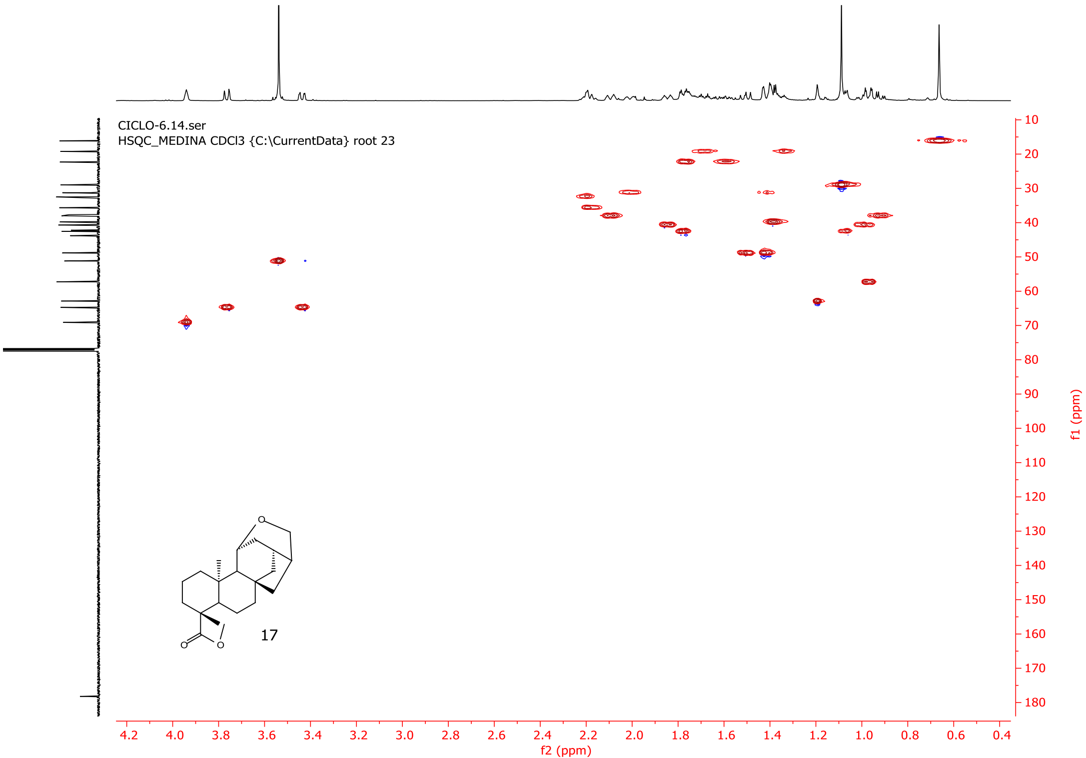


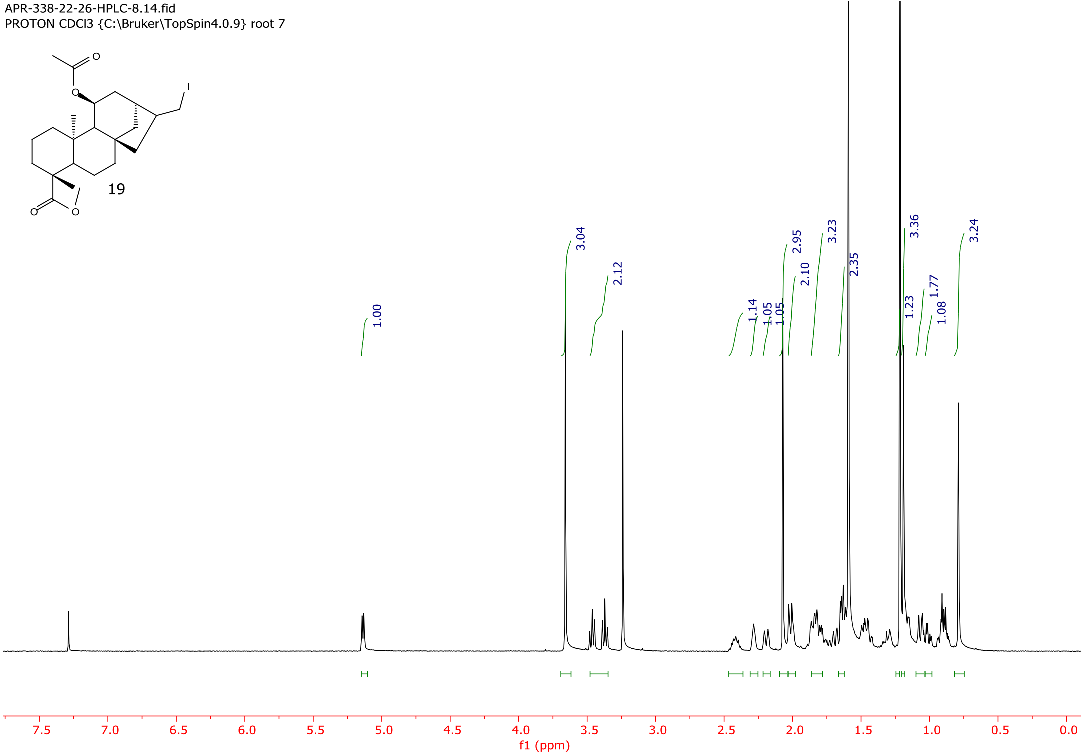
CICLO-6.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 23

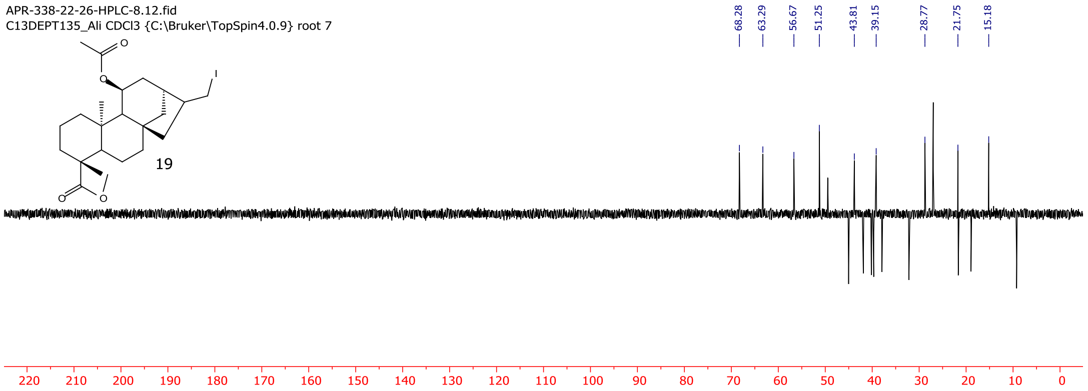


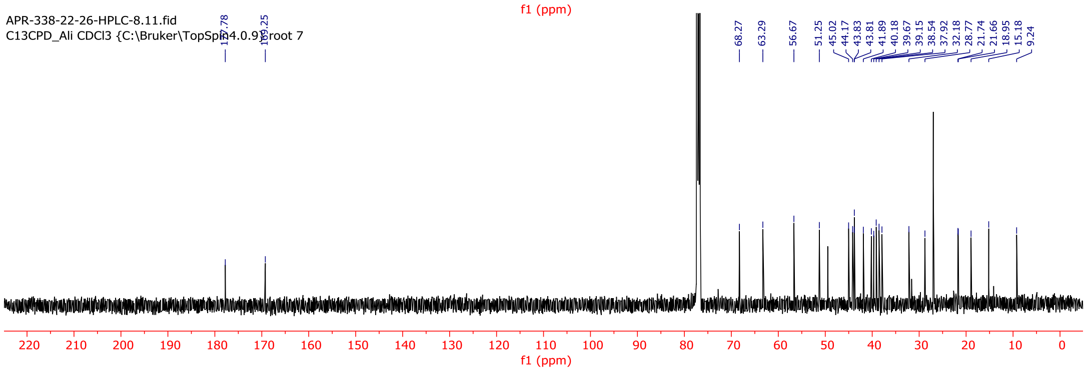
CICLO-6.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 23

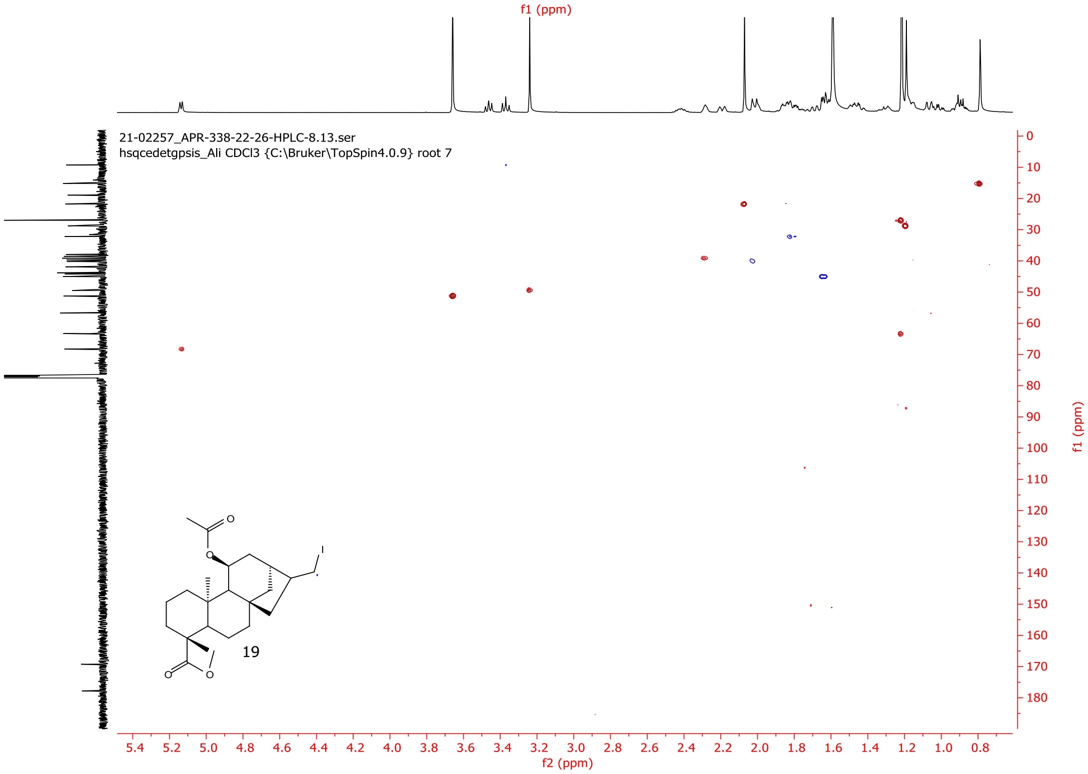


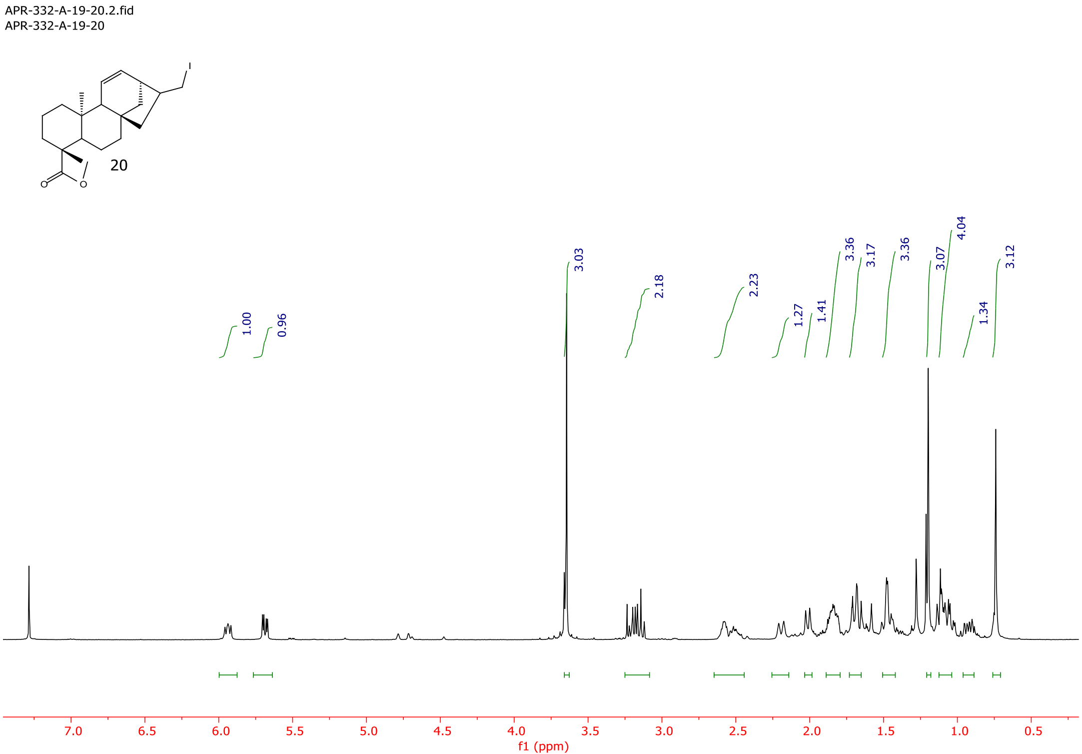

CICLO-6.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 23
17
f2 (ppm)
f1 (ppm)
4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180

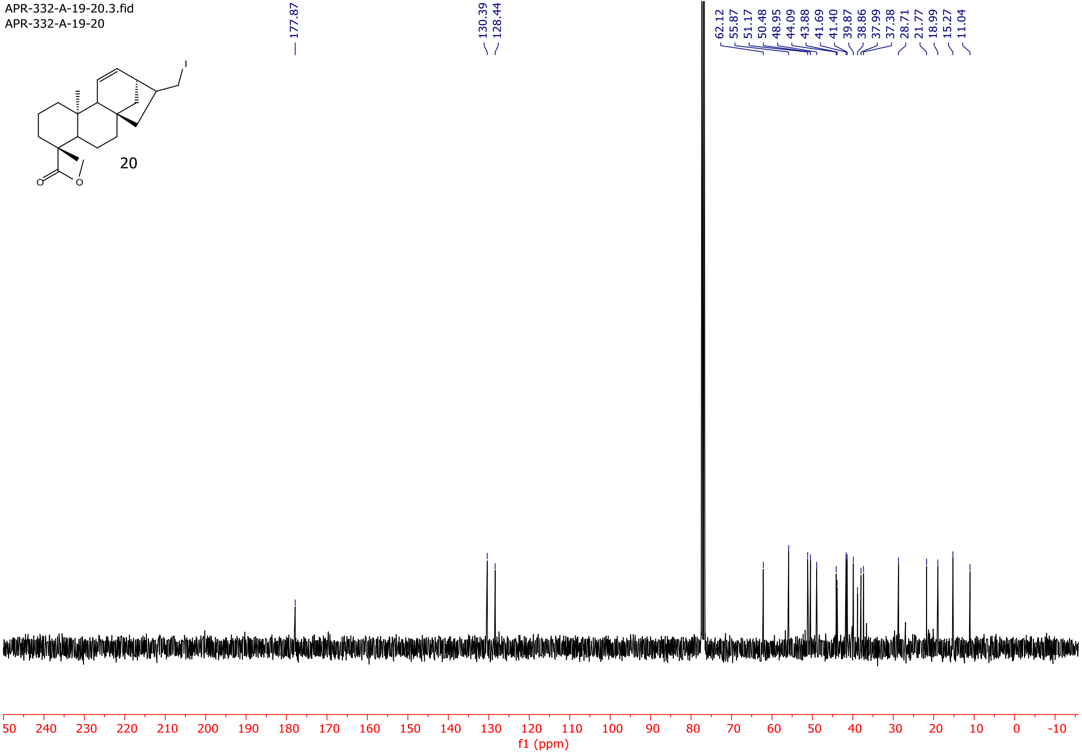

APR-338-22-26-HPLC-8.14.fid
PROTON CDCl3 {C:\Bruker\TopSpin4.0.9} root 7
19
1.00
3.04
2.12
1.14
1.05
1.05
2.95
2.10
3.23
2.35
1.23
3.36
1.08
1.77
3.24
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

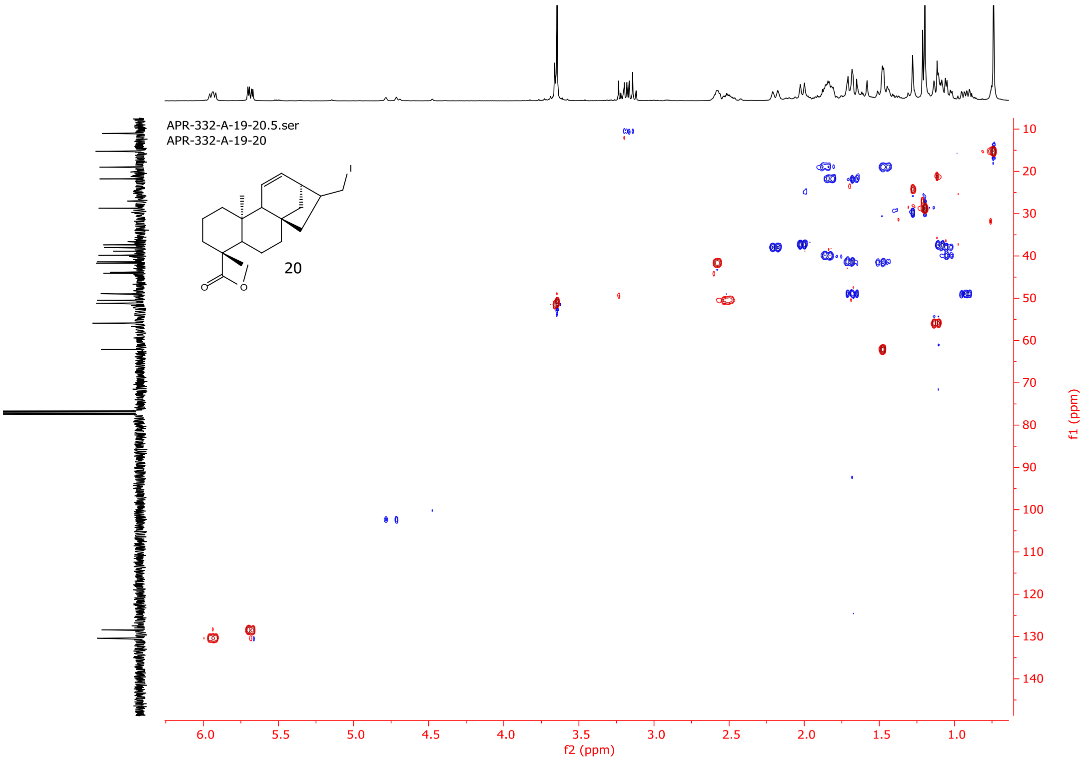

APR-338-22-26-HPLC-8.12.fid
C13DEPT135_Ali CDCl3 {C:\Bruker\TopSpin4.0.9} root 7
68.28
63.29
56.67
51.25
43.81
39.15
28.77
21.75
15.18
O
O
I
O
O
19
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

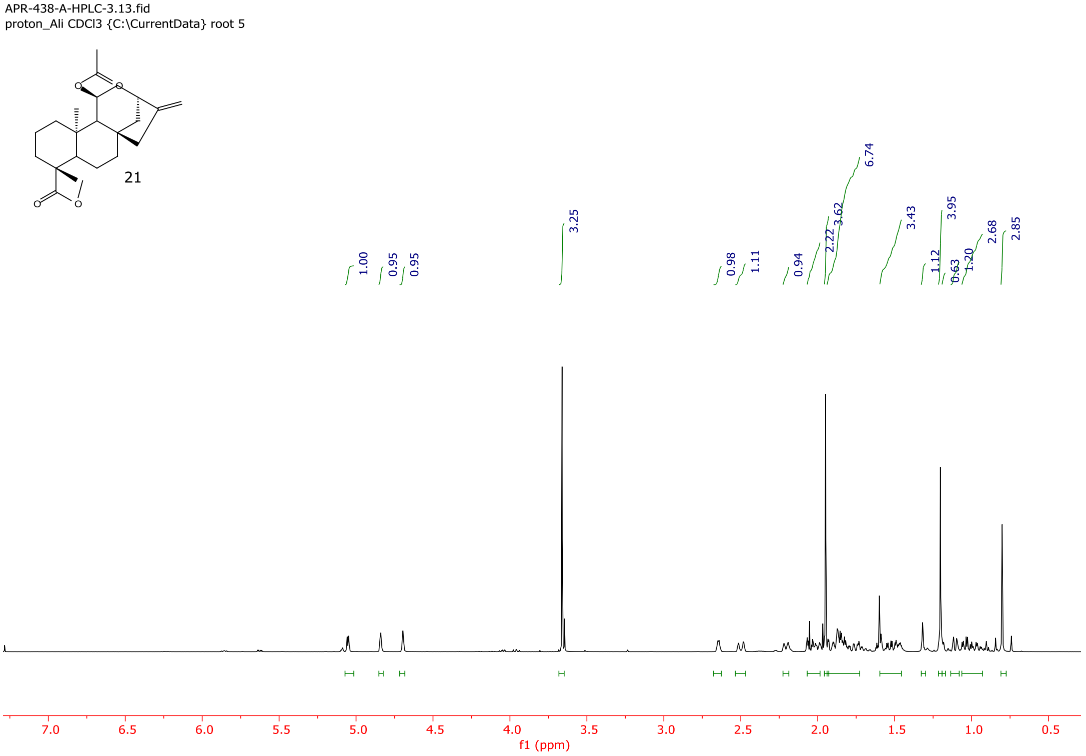

APR-338-22-26-HPLC-8.11.fid
C13CPD_Ali CDCl3 {C:\Bruker\TopSpin4.0.9} root 7
177.78
169.25
68.27
63.29
56.67
51.25
45.02
44.17
43.83
43.81
41.89
40.18
39.67
39.15
38.54
37.92
32.18
28.77
21.74
21.66
18.95
15.18
9.24
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

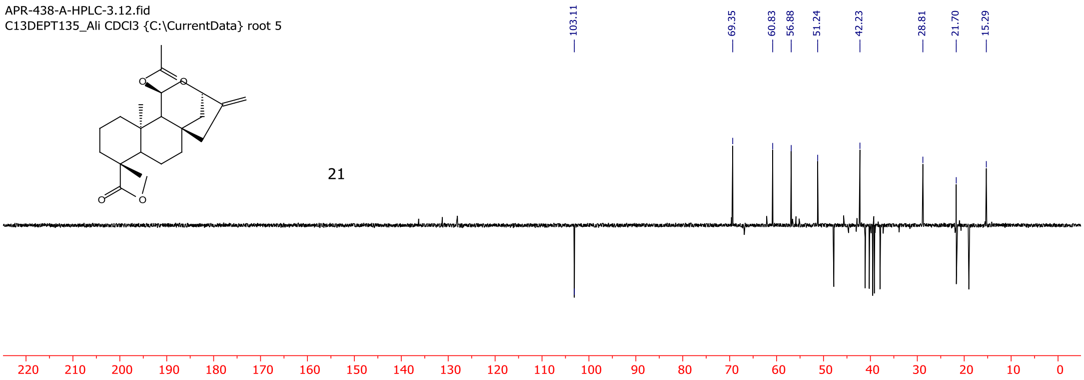

21-02257_APR-338-22-26-HPLC-8.13.ser
hsqcedetgpsis_Ali CDCl3 {C:\Bruker\TopSpin4.0.9} root 7
O
O
I
O
O
19
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)

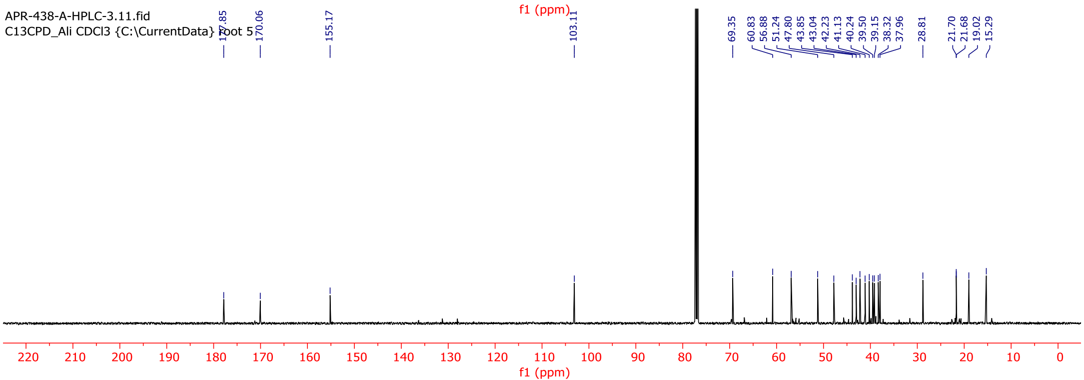

APR-332-A-19-20.2.fid
APR-332-A-19-20
20
1.00
0.96
3.03
2.18
2.23
1.27
1.41
3.36
3.17
3.36
3.07
4.04
1.34
3.12
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

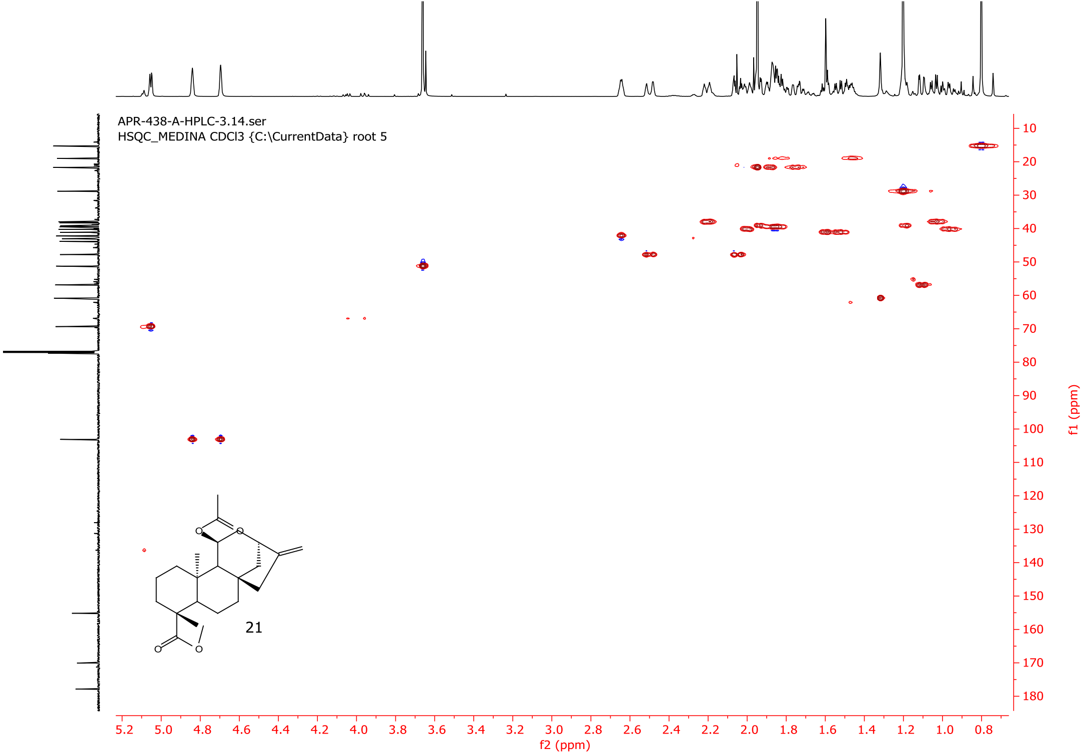

APR-332-A-19-20.3.fid
APR-332-A-19-20
20
177.87
130.39
128.44
62.12
55.87
51.17
50.48
48.95
44.09
43.88
41.69
41.40
39.87
38.86
37.99
37.38
28.71
21.77
18.99
15.27
11.04
50
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

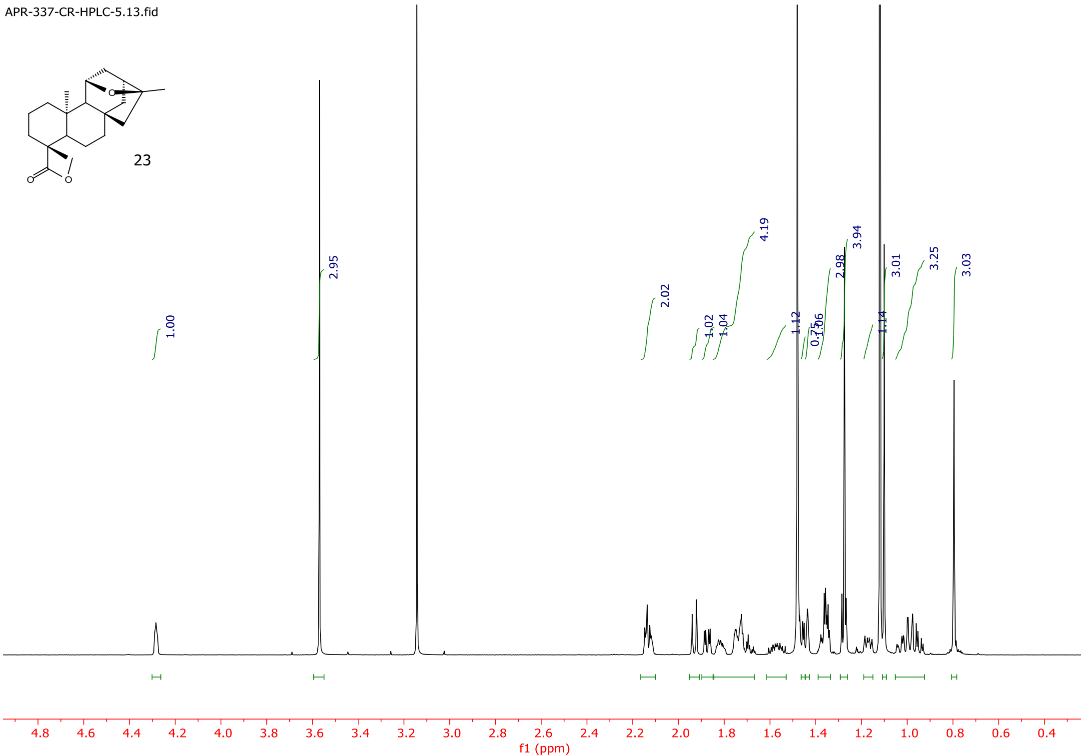

APR-332-A-19-20.5.ser
APR-332-A-19-20
20
f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

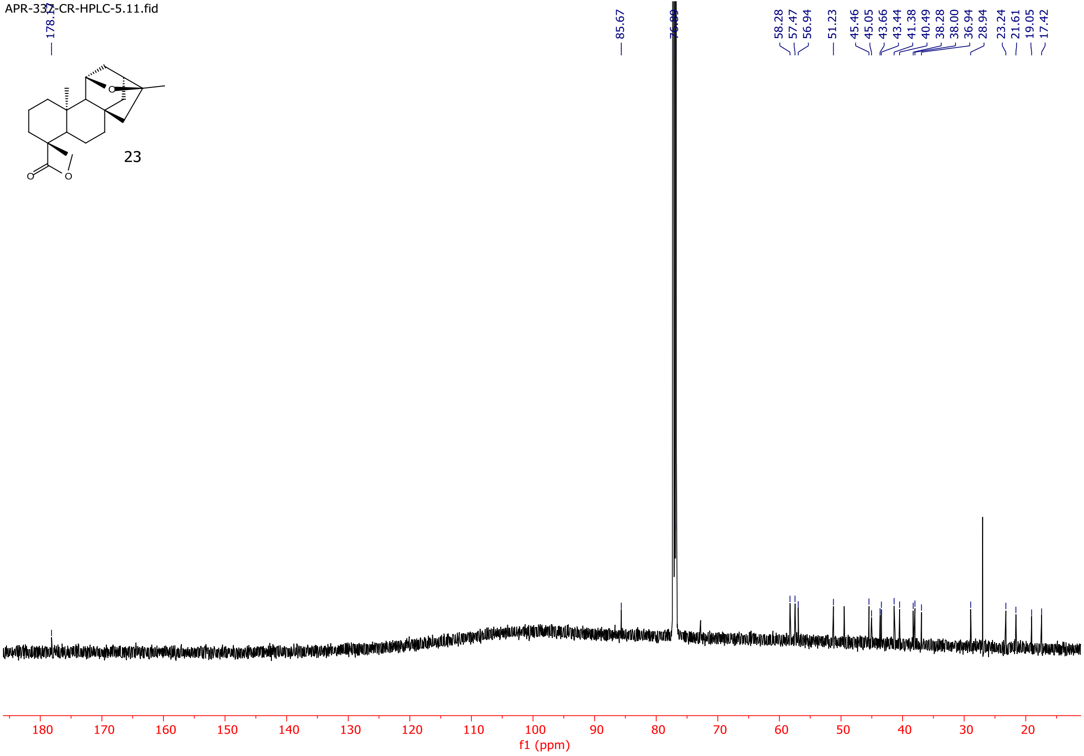

APR-438-A-HPLC-3.13.fid
proton_Ali CDCl3 {C:\CurrentData} root 5
21
1.00
0.95
0.95
3.25
0.98
1.11
0.94
2.22
3.62
6.74
3.43
1.12
3.95
0.63
1.20
2.68
2.85
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

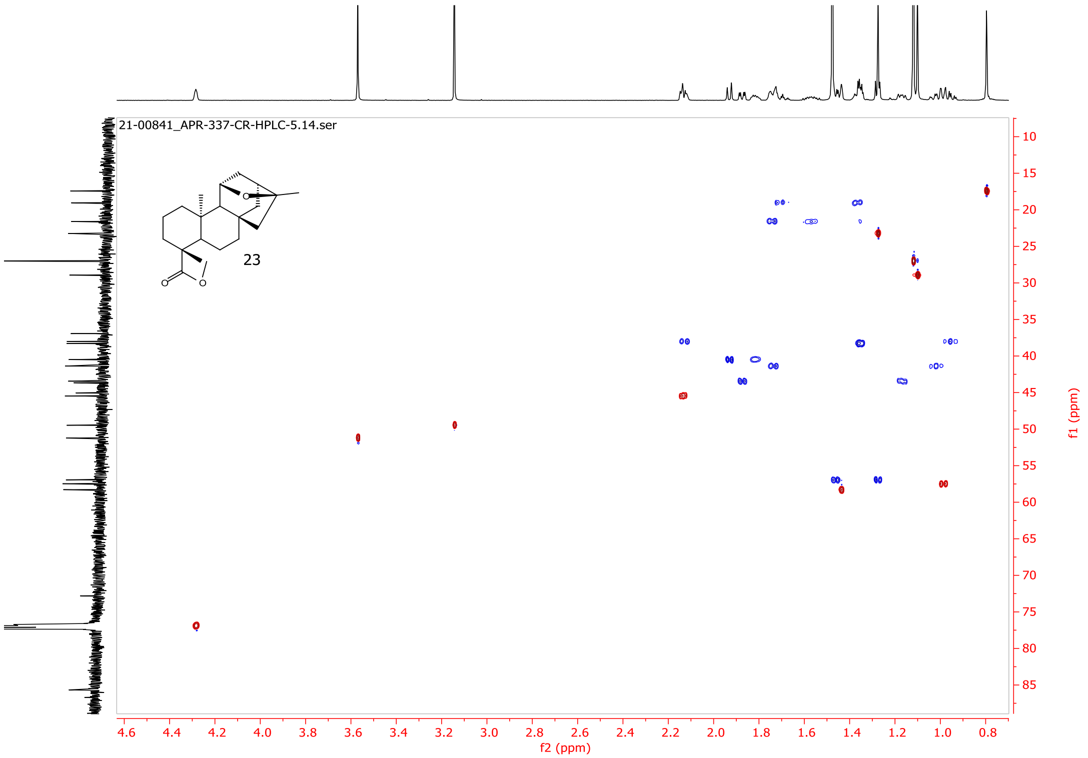

APR-438-A-HPLC-3.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 5
103.11
69.35
60.83
56.88
51.24
42.23
28.81
21.70
15.29
21
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


APR-438-A-HPLC-3.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 5
177.85
170.06
155.17
103.11
69.35
60.83
56.88
51.24
47.80
43.85
43.04
42.23
41.13
40.24
39.50
39.15
38.32
37.96
28.81
21.70
21.68
19.02
15.29
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

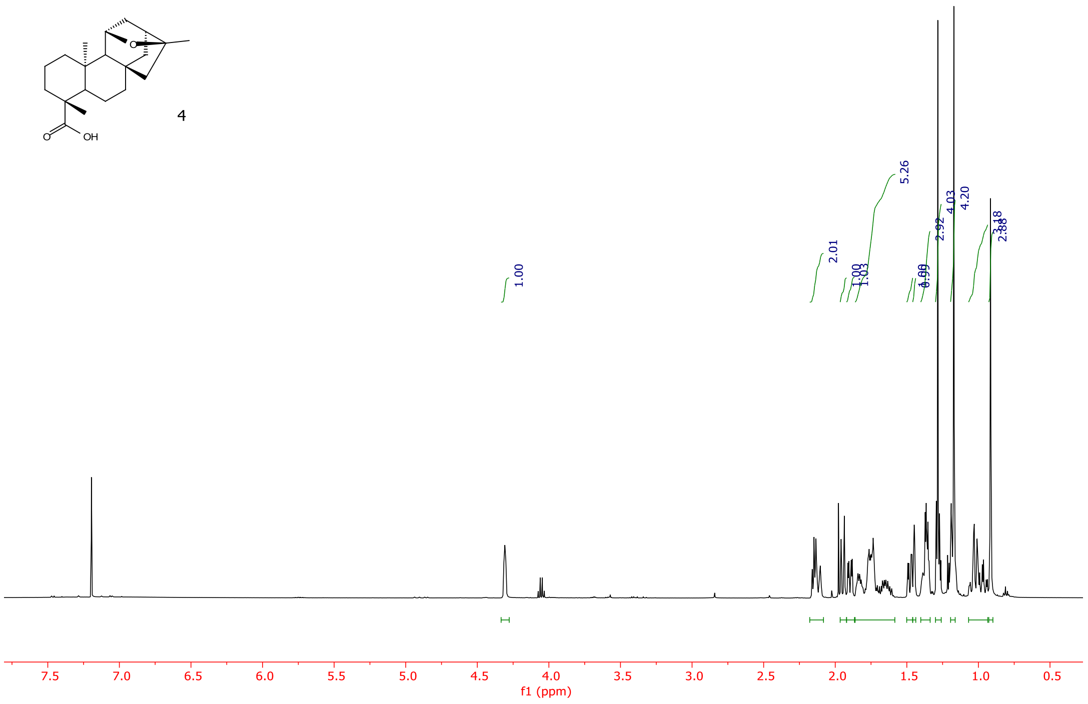

APR-438-A-HPLC-3.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 5
21
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)

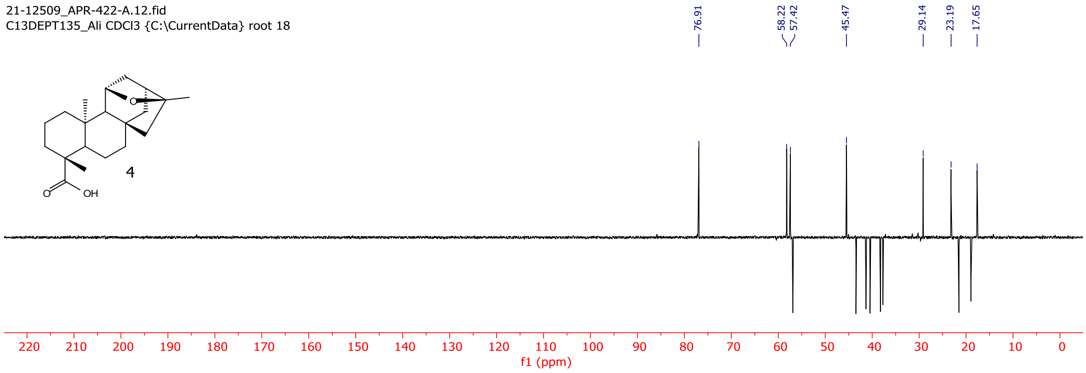

APR-337-CR-HPLC-5.13.fid
23
1.00
2.95
2.02
1.02
1.04
4.19
1.12
0.75
1.06
2.98
3.94
1.14
3.01
3.25
3.03
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
f1 (ppm)

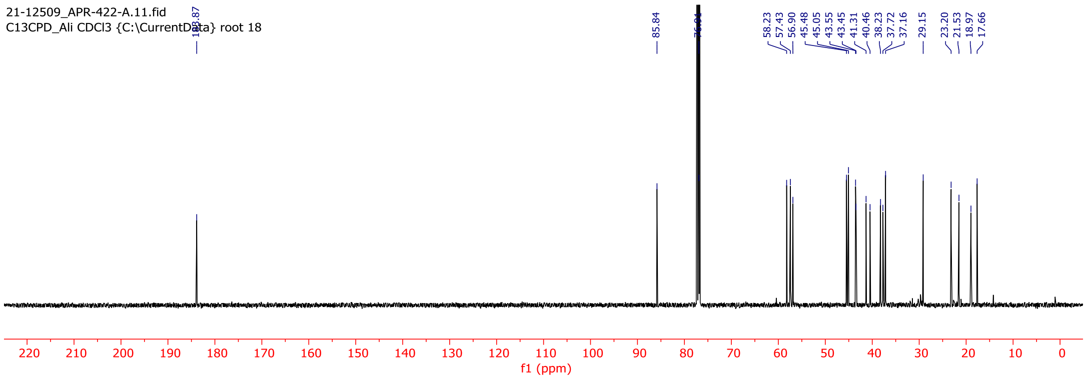

APR-337-CR-HPLC-5.11.fid
23
178.17
85.67
76.80
58.28
57.47
56.94
51.23
45.46
45.05
43.66
43.44
41.38
40.49
38.28
38.00
36.94
28.94
23.24
21.61
19.05
17.42
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

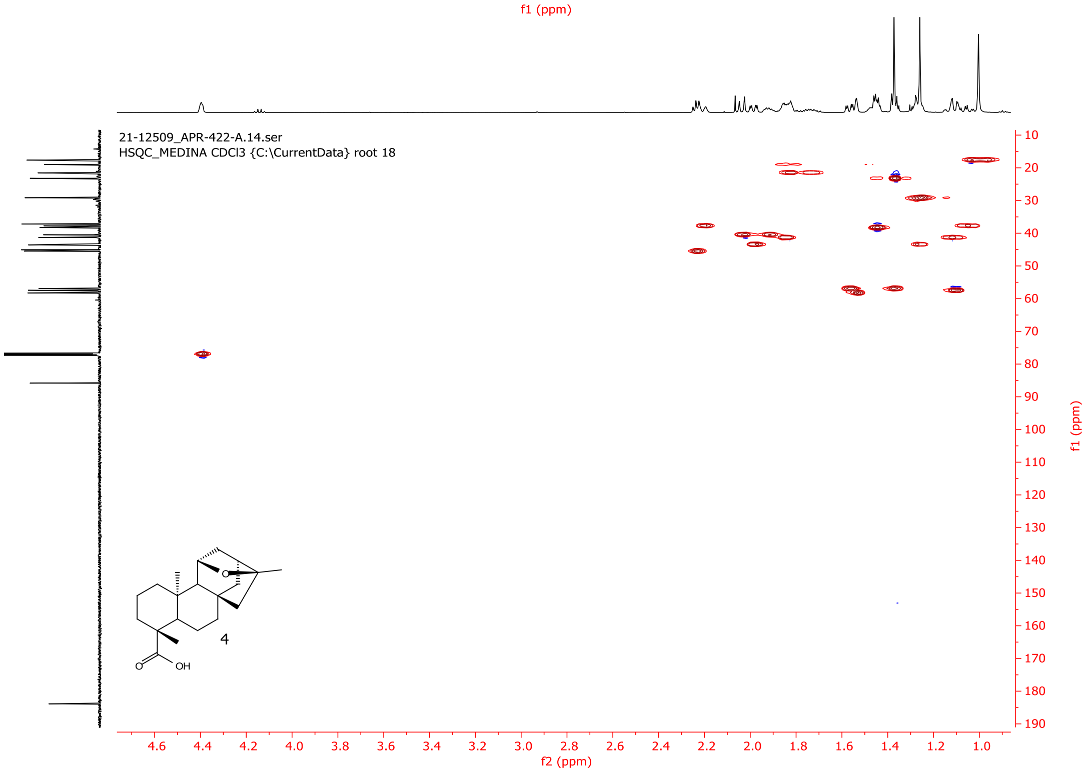


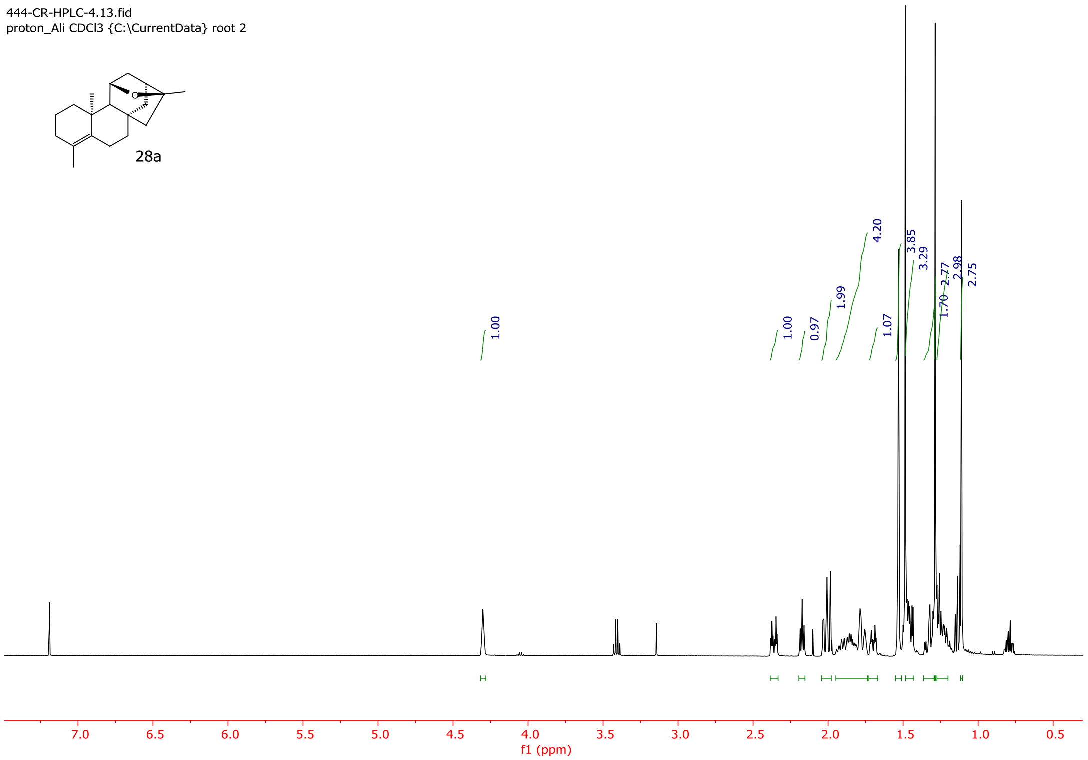
21-12509_APR-422-A.13.fid
proton_Ali CDCl3 {C:\CurrentData} root 18

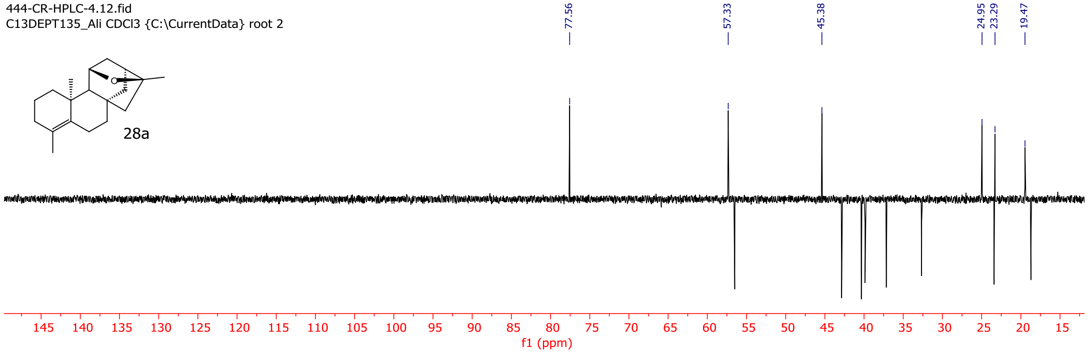


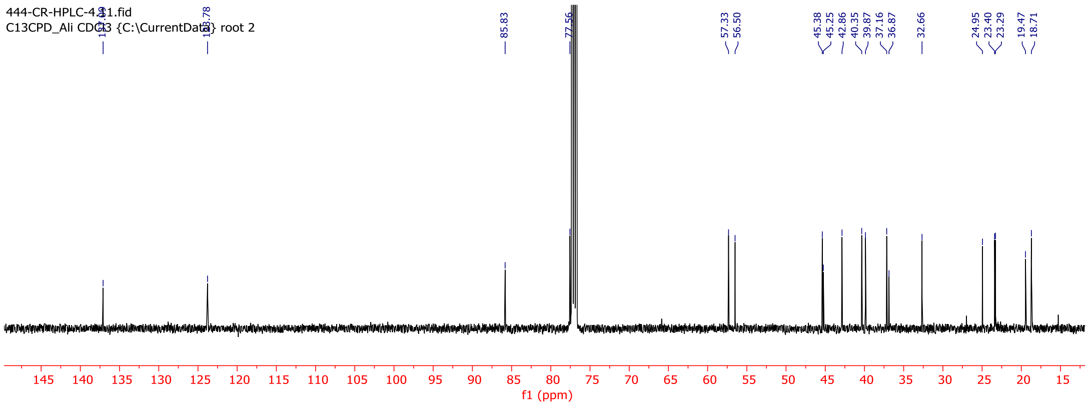

21-12509_APR-422-A.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 18
76.91
58.22
57.42
45.47
29.14
23.19
17.65
4
O
OH
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

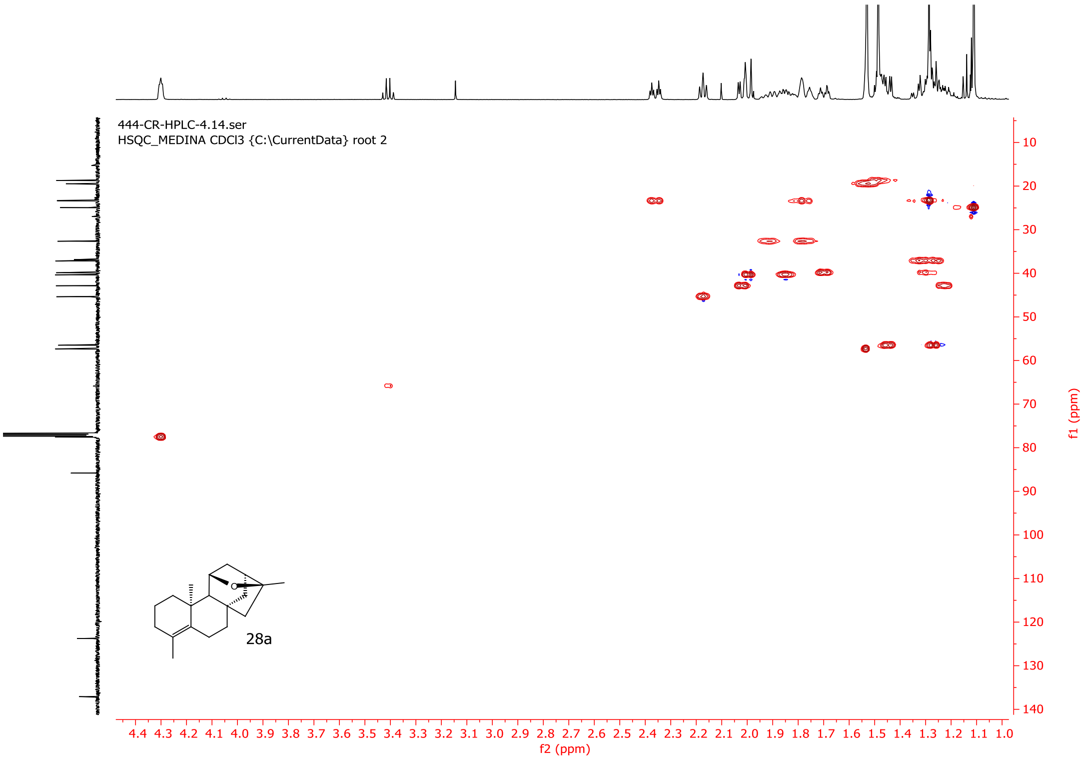

21-12509_APR-422-A.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 18
183.87
85.84
76.91
58.23
57.43
56.90
45.48
45.05
43.55
43.45
41.31
40.46
38.23
37.72
37.16
29.15
23.20
21.53
18.97
17.66
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

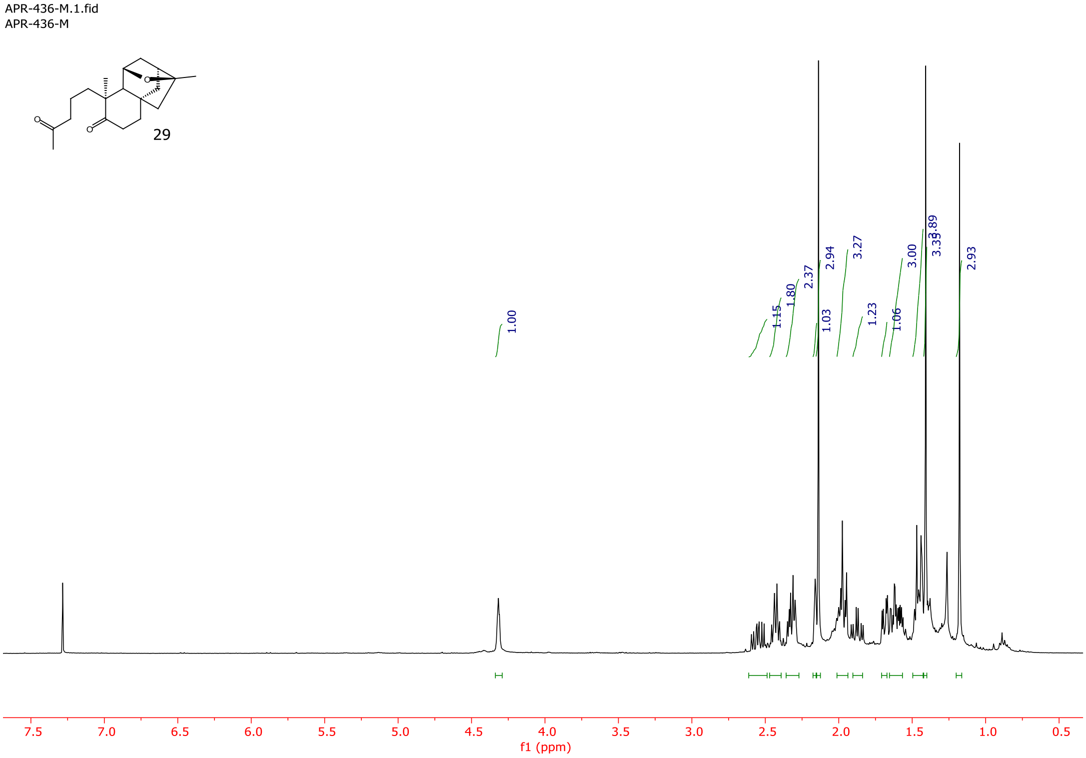

21-12509_APR-422-A.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 18
4
O
OH
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f2 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190
f1 (ppm)

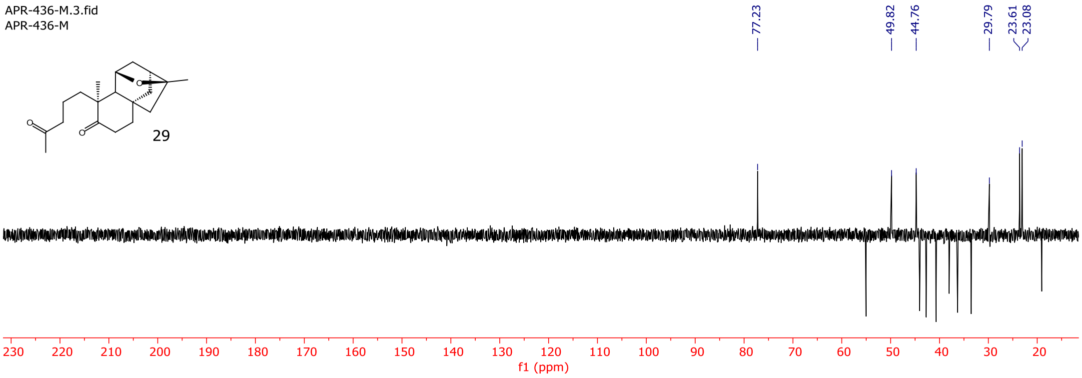

444-CR-HPLC-4.13.fid
proton_Ali CDCl3 {C:\CurrentData} root 2
28a
1.00
1.00
0.97
1.99
4.20
1.07
3.85
3.29
1.70
2.77
2.98
2.75
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

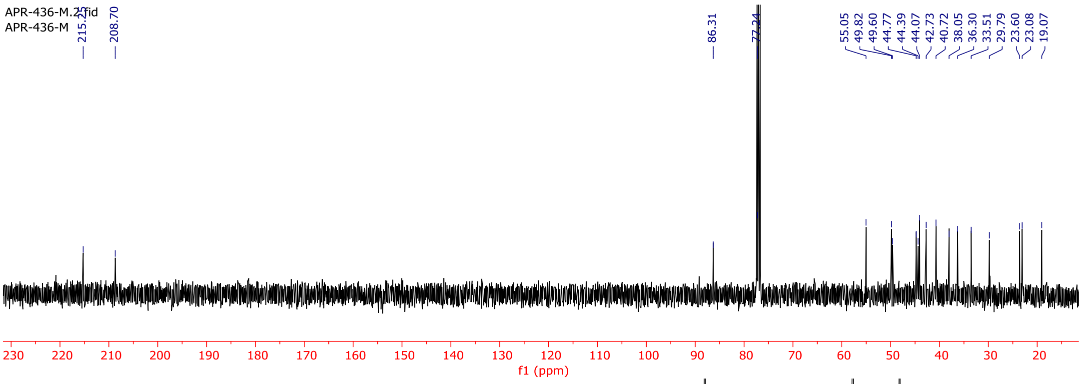

444-CR-HPLC-4.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 2
28a
77.56
57.33
45.38
24.95
23.29
19.47
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)

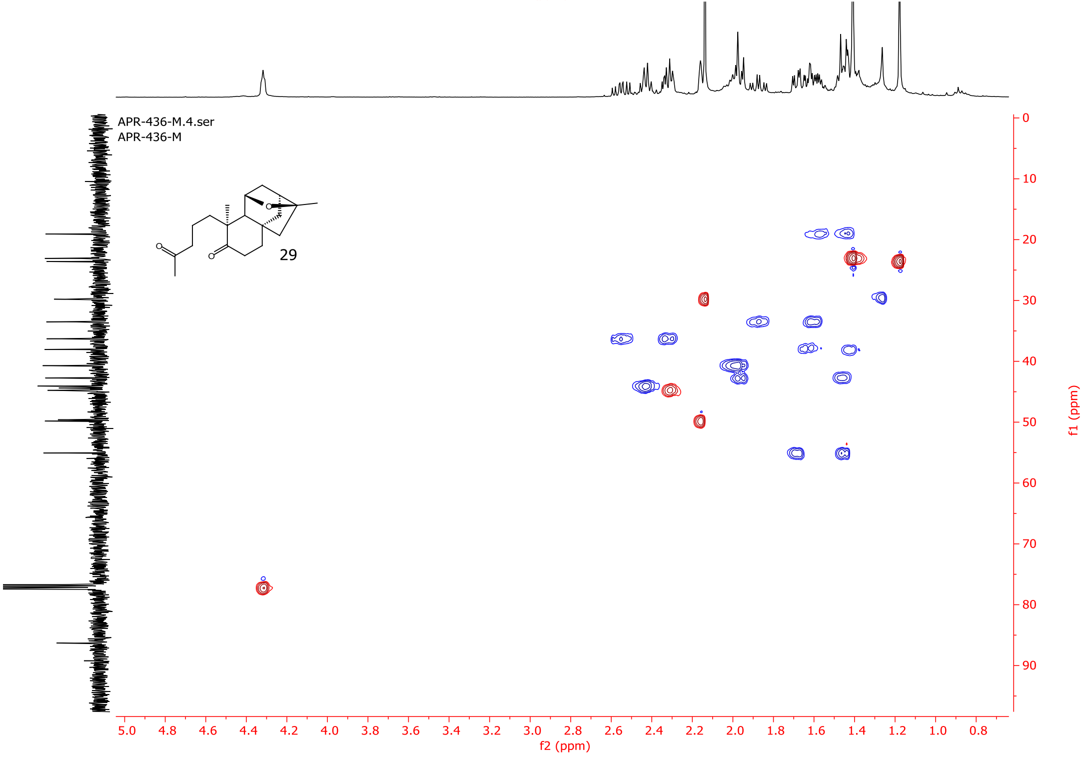

444-CR-HPLC-4.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 2
137.09
123.78
85.83
77.56
57.33
56.50
45.38
45.25
42.86
40.35
39.87
37.16
36.87
32.66
24.95
23.40
23.29
19.47
18.71
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)

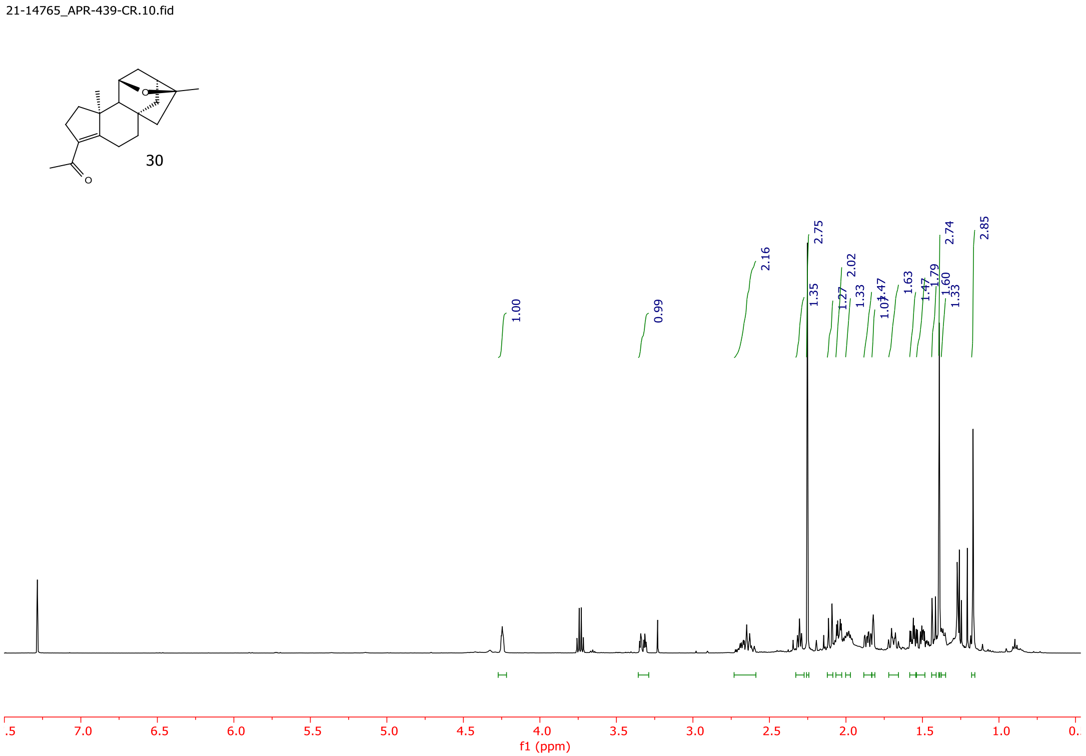

444-CR-HPLC-4.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 2
28a
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0
f2 (ppm)
10 20 30 40 50 60 70 80 90 100 110 120 130 140
f1 (ppm)

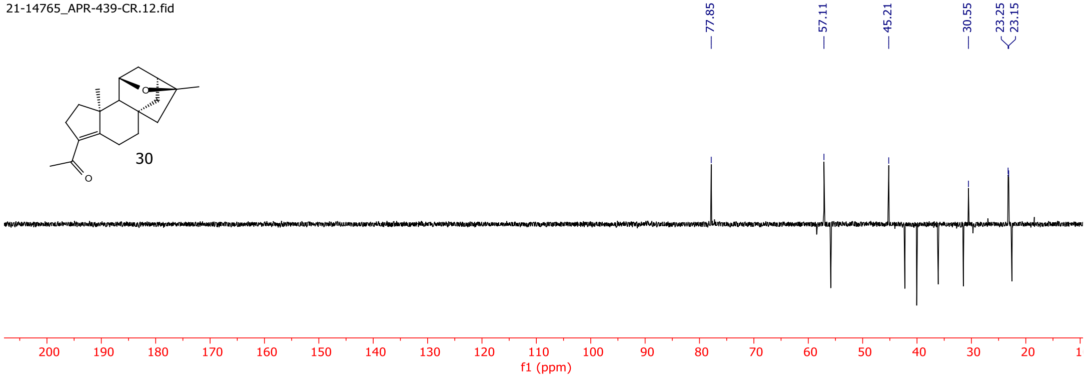

APR-436-M.1.fid
APR-436-M
29
1.00
1.15
1.80
2.37
1.03
2.94
3.27
1.23
1.06
3.00
3.33.89
2.93
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

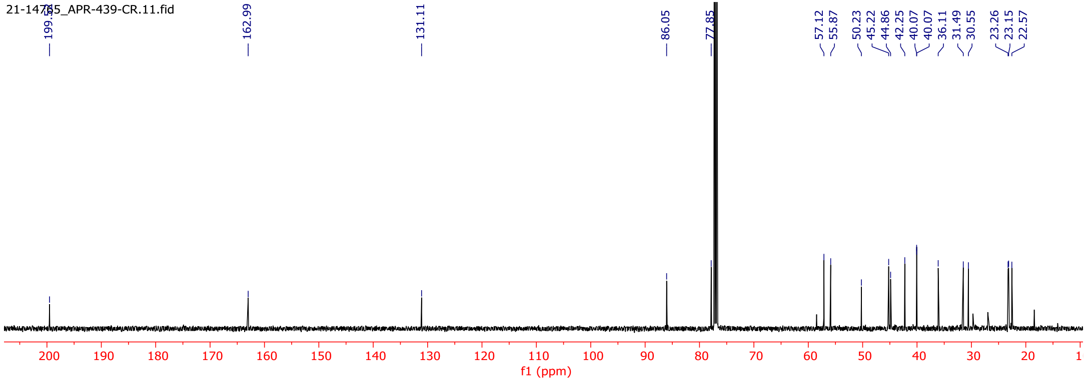

APR-436-M.3.fid
APR-436-M
29
77.23
49.82
44.76
29.79
23.61
23.08
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

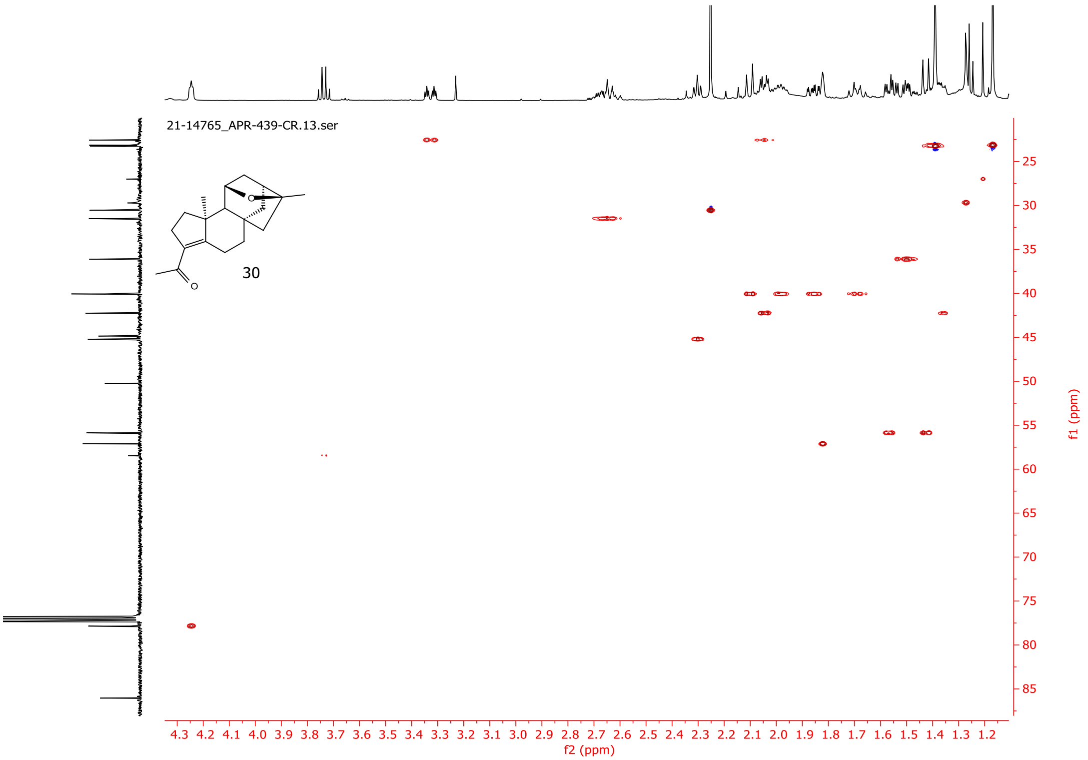

APR-436-M.2.fid
APR-436-M
215.25
208.70
86.31
77.24
55.05
49.82
49.60
44.77
44.39
44.07
42.73
40.72
38.05
36.30
33.51
29.79
23.60
23.08
19.07
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

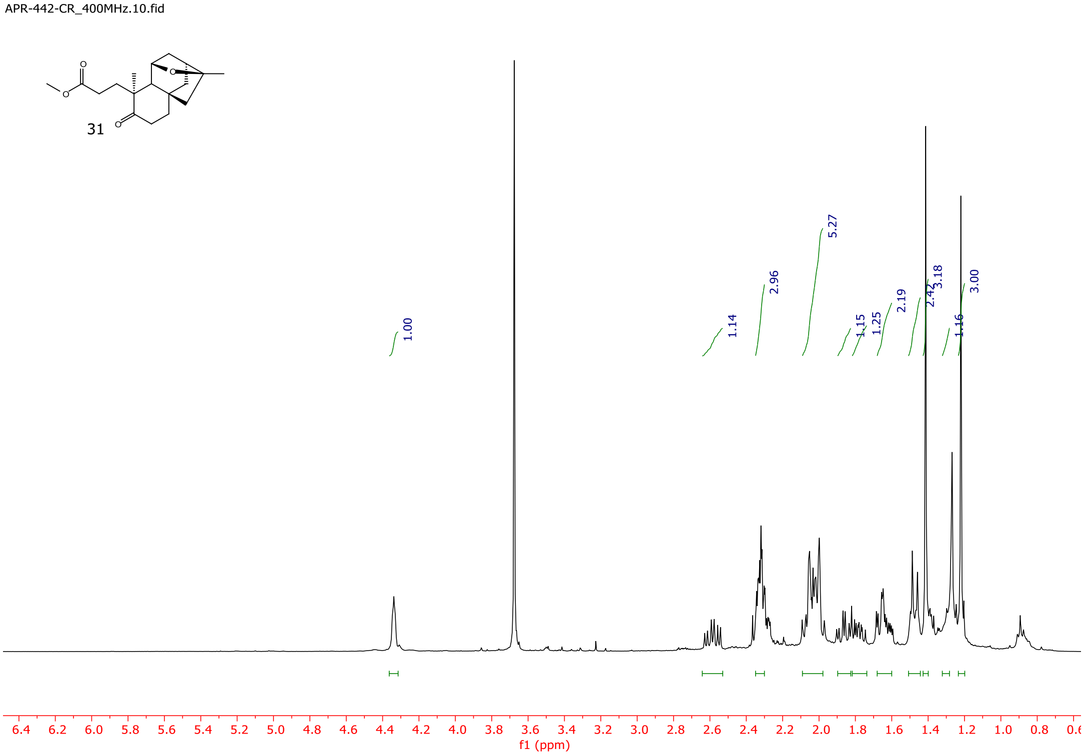

APR-436-M.4.ser
APR-436-M
29
0
10
20
30
40
50
60
70
80
90
f1 (ppm)
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
f2 (ppm)

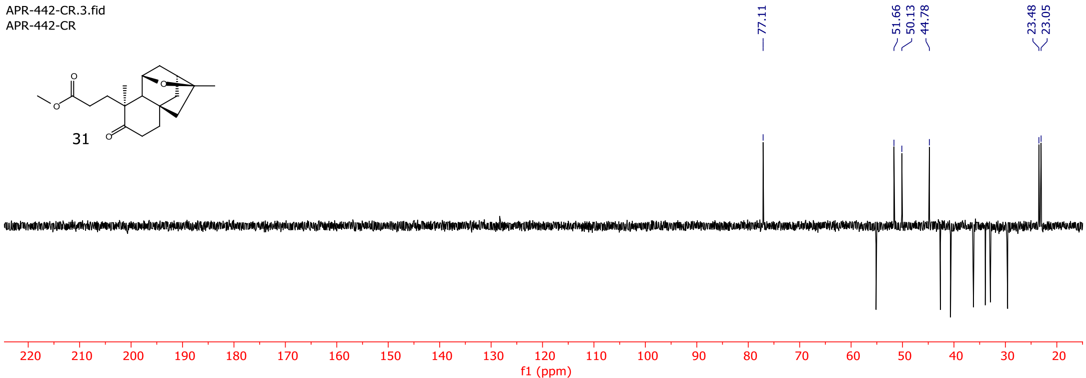

21-14765_APR-439-CR.10.fid
30
1.00
0.99
2.16
1.35
2.75
1.27
2.02
1.33
1.07
1.47
1.63
1.47
1.79
2.74
1.60
1.33
2.85
.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.
f1 (ppm)

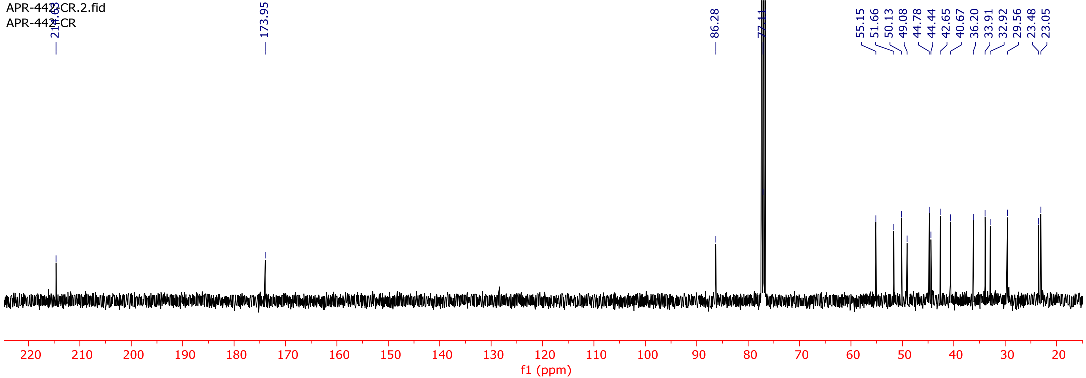

21-14765_APR-439-CR.12.fid
77.85
57.11
45.21
30.55
23.25
23.15
30
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
1
f1 (ppm)

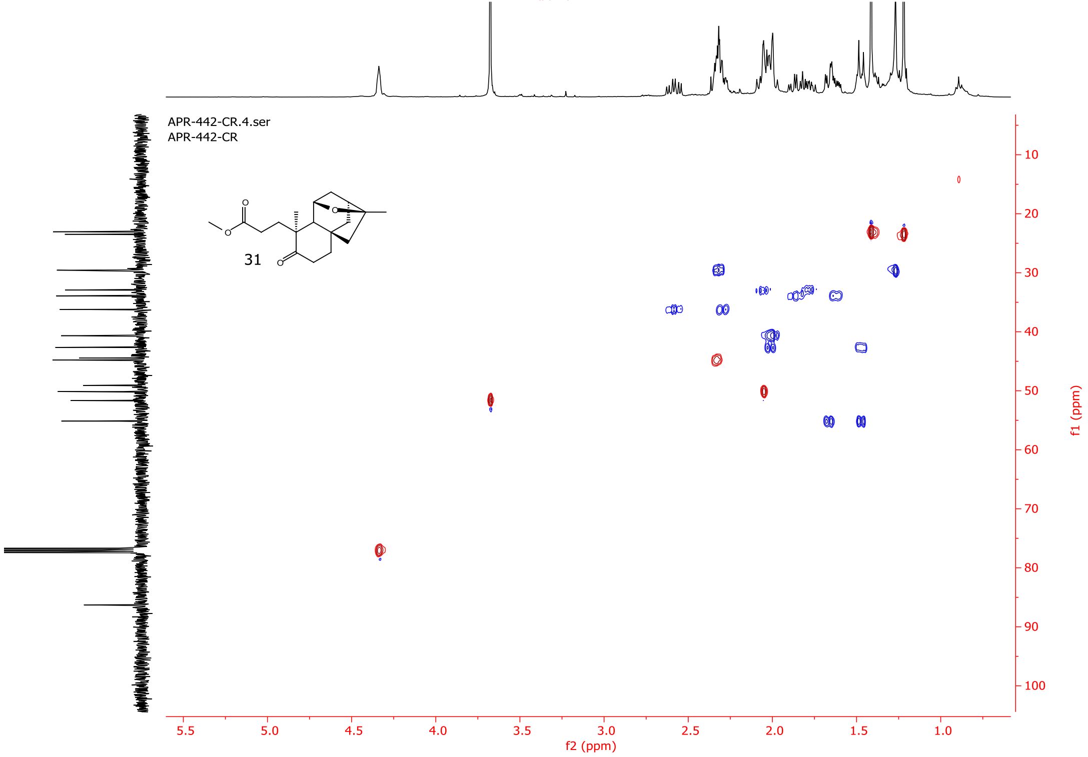

21-14765_APR-439-CR.11.fid
199.05
162.99
131.11
86.05
77.85
57.12
55.87
50.23
45.22
44.86
42.25
40.07
40.07
36.11
31.49
30.55
23.26
23.15
22.57
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
1
f1 (ppm)

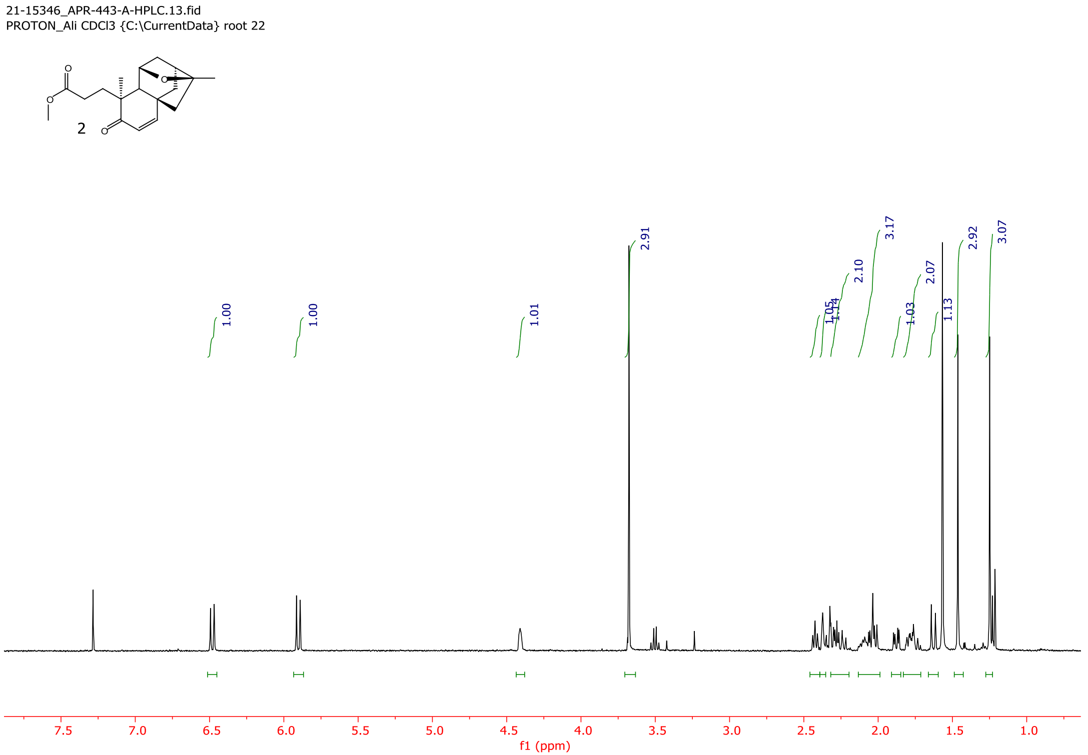

21-14765_APR-439-CR.13.ser
30
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2
f2 (ppm)
25 30 35 40 45 50 55 60 65 70 75 80 85
f1 (ppm)

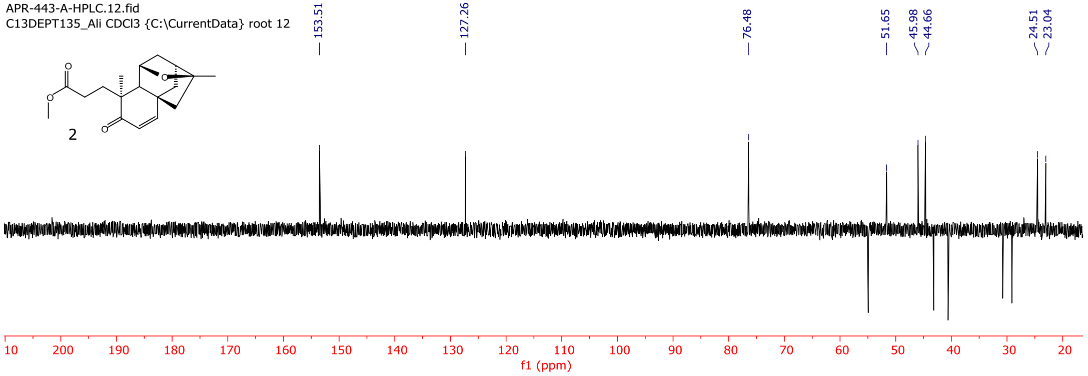

APR-442-CR_400MHz.10.fid
31
1.00
1.14
2.96
5.27
1.15
1.25
2.19
2.42
3.18
1.16
3.00
6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)

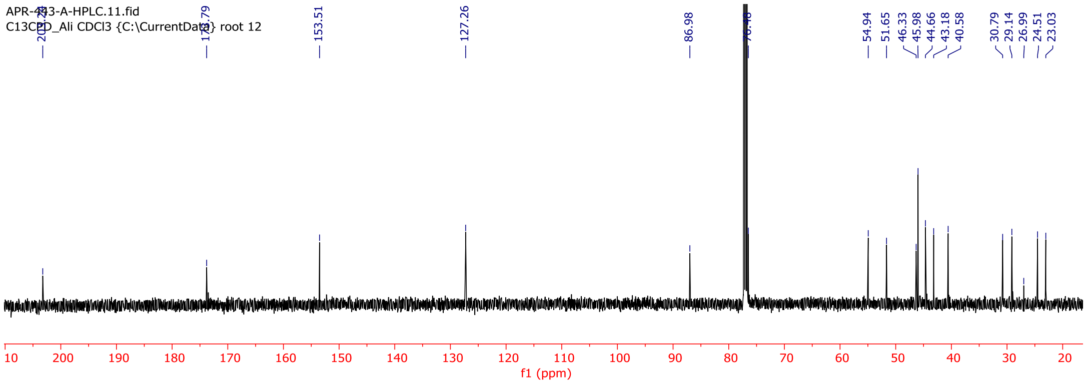

APR-442-CR.3.fid
APR-442-CR
31
77.11
51.66
50.13
44.78
23.48
23.05
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

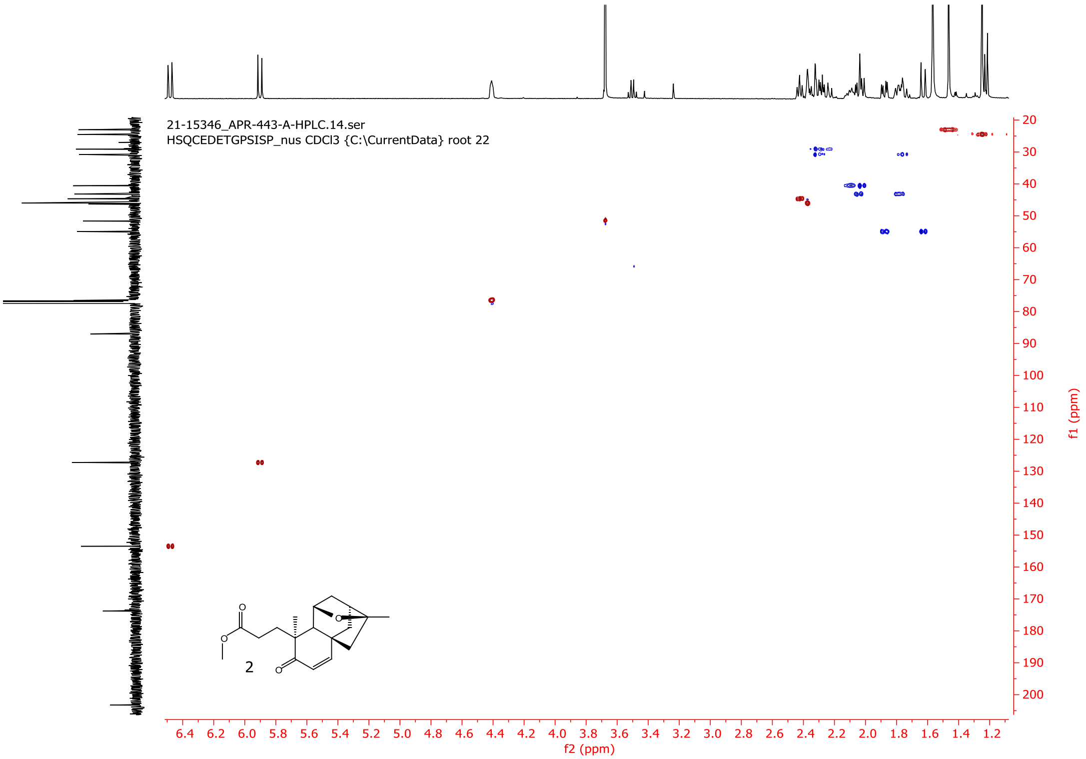

APR-442-CR.2.fid
APR-442-CR
214.63
173.95
86.28
77.11
55.15
51.66
50.13
49.08
44.78
44.44
42.65
40.67
36.20
33.91
32.92
29.56
23.48
23.05
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


APR-442-CR.4.ser
APR-442-CR
31
10
20
30
40
50
60
70
80
90
100
f1 (ppm)
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

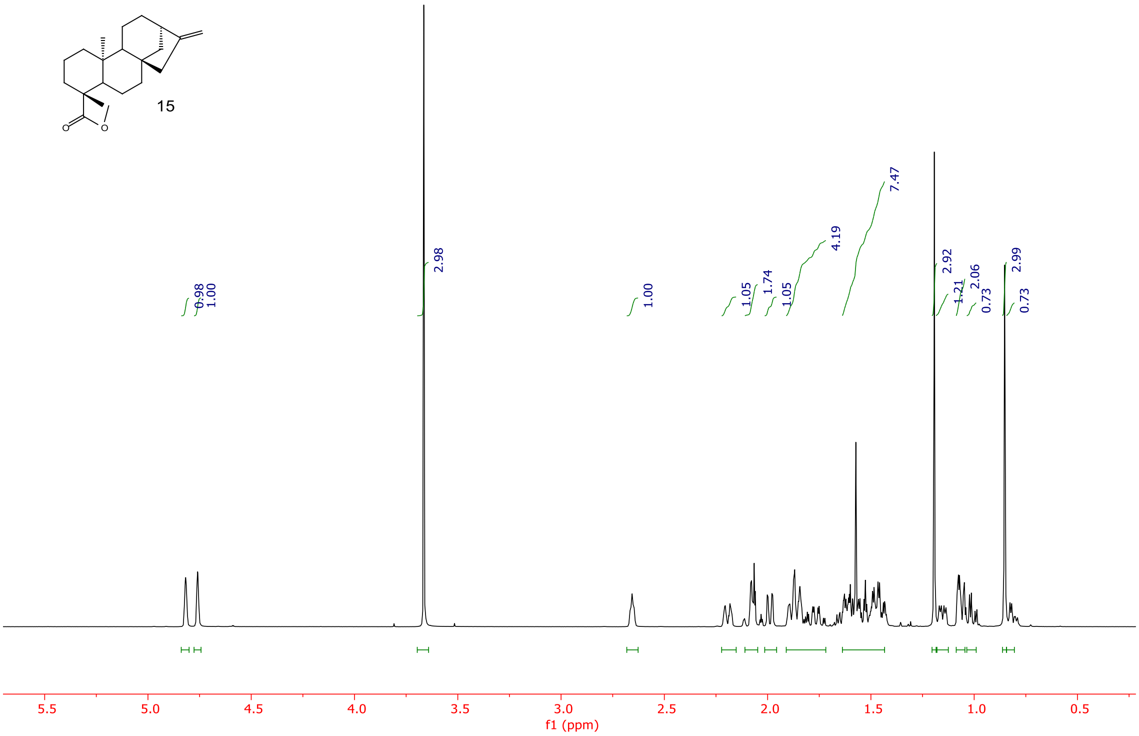

21-15346_APR-443-A-HPLC.13.fid
PROTON_Ali CDCl3 {C:\CurrentData} root 22
2
1.00
1.00
1.01
2.91
1.05
1.14
2.10
3.17
1.03
2.07
1.13
2.92
3.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

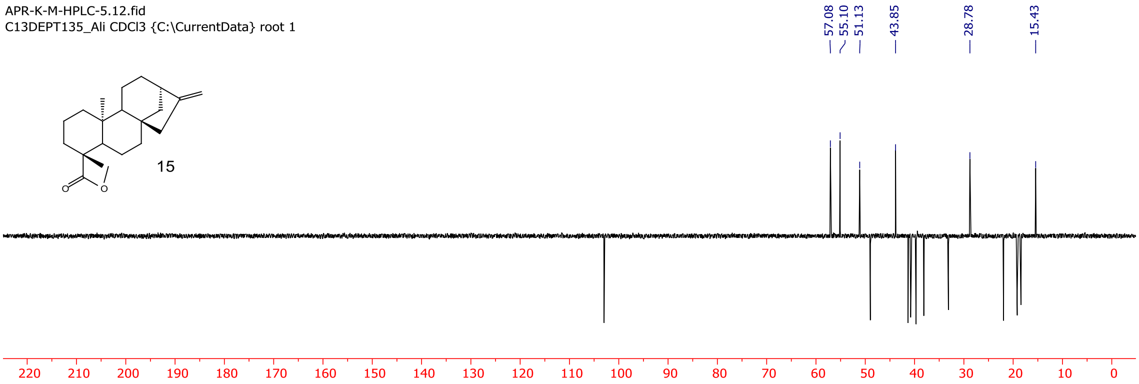

APR-443-A-HPLC.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 12
2
153.51
127.26
76.48
51.65
45.98
44.66
24.51
23.04
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

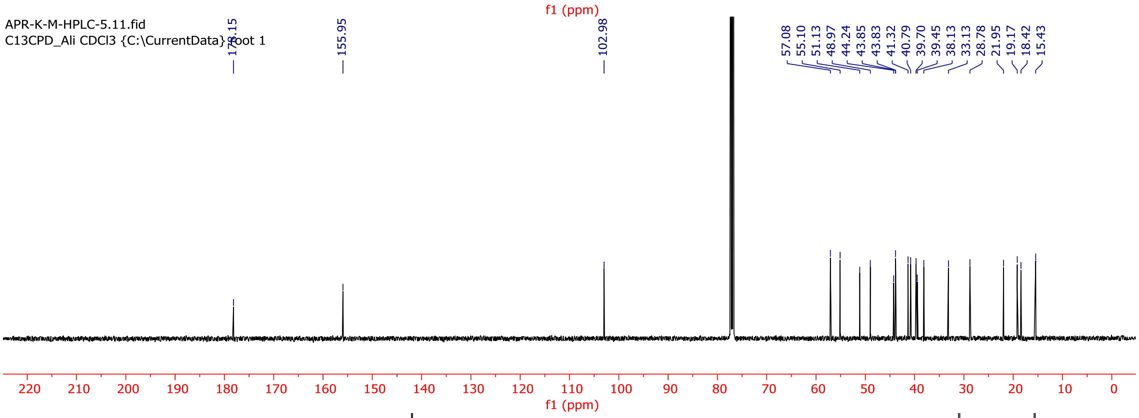

APR-443-A-HPLC.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 12
173.79
153.51
127.26
86.98
54.94
51.65
46.33
45.98
44.66
43.18
40.58
30.79
29.14
26.99
24.51
23.03
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

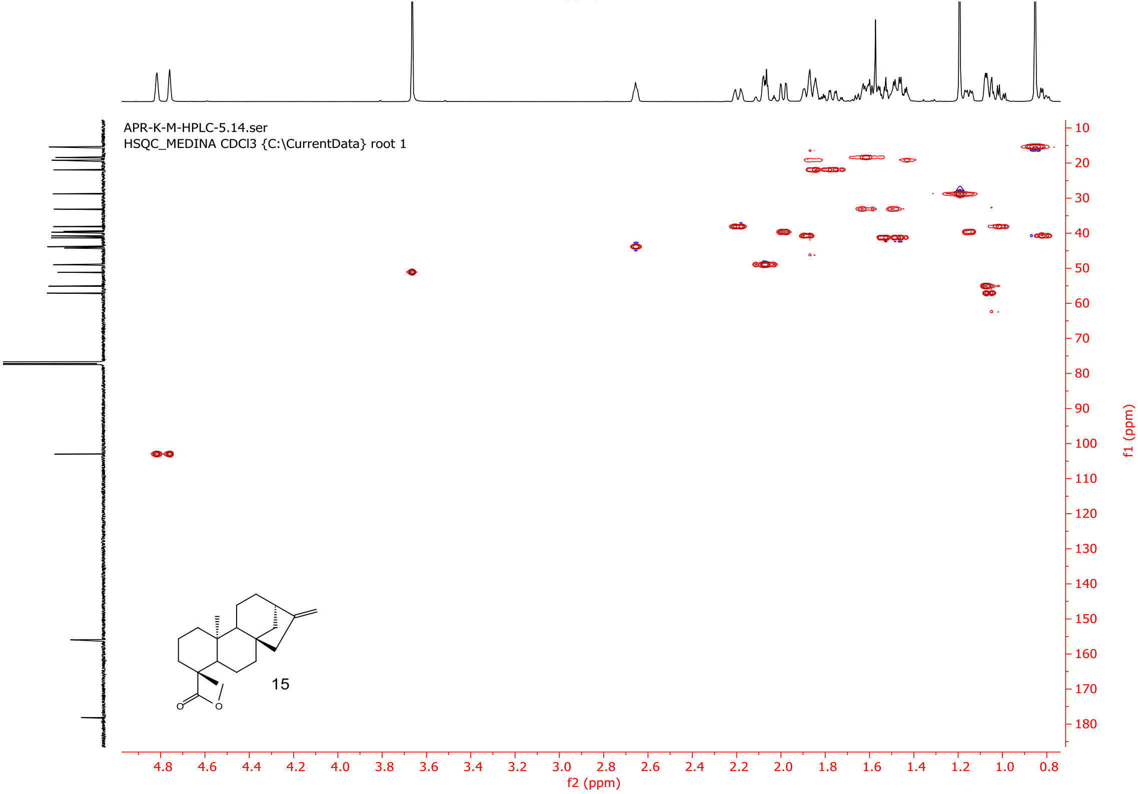


APR-K-M-HPLC-5.13.fid
proton_Ali CDCl3 {C:\CurrentData} root 1

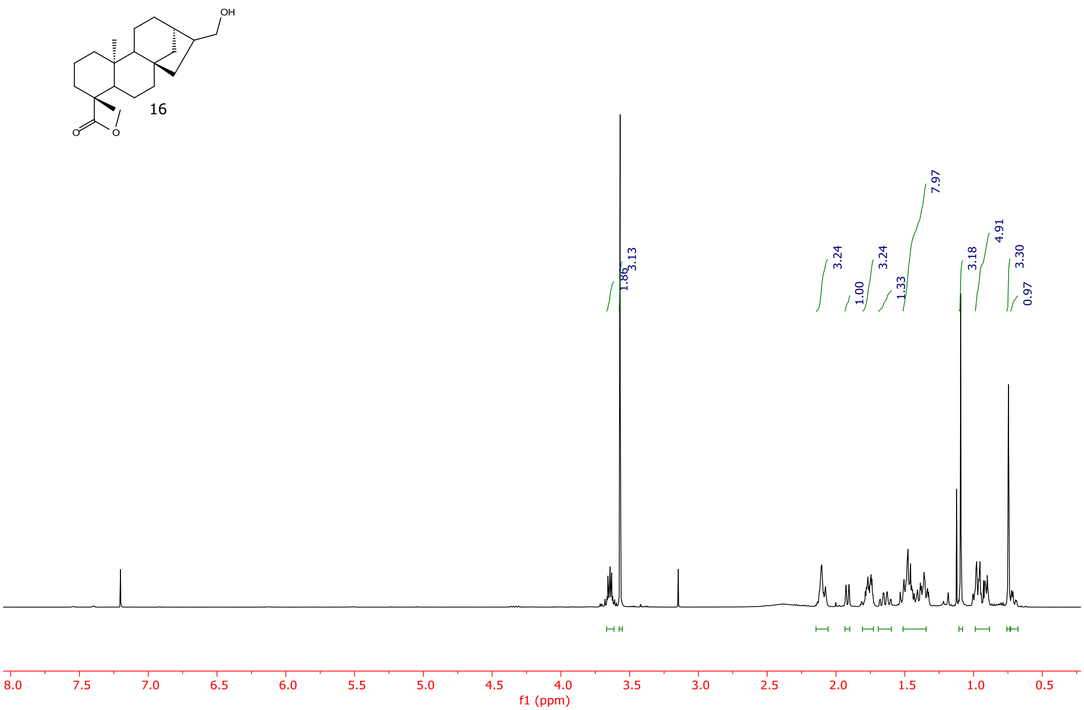



APR-K-M-HPLC-5.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 1
57.08
55.10
51.13
43.85
28.78
15.43
15
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

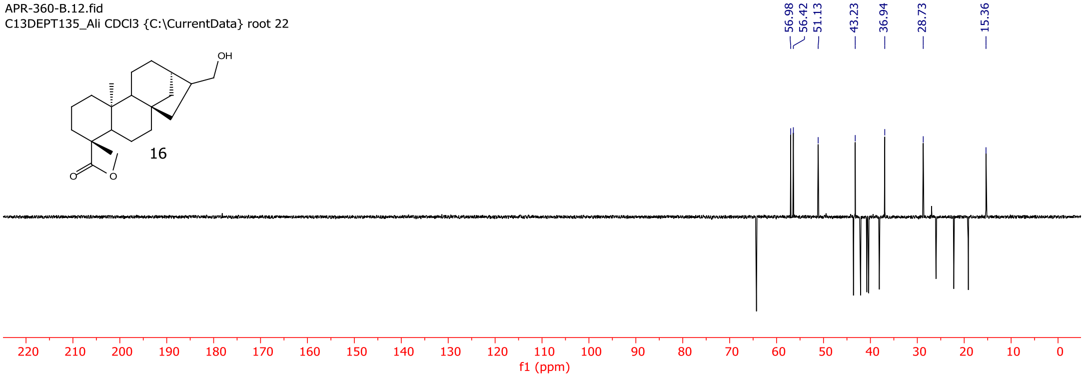

APR-K-M-HPLC-5.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 1
178.15
155.95
102.98
57.08
55.10
51.13
48.97
44.24
43.85
43.83
41.32
40.79
39.70
39.45
38.13
33.13
28.78
21.95
19.17
18.42
15.43
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


APR-K-M-HPLC-5.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 1
15
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)
4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)

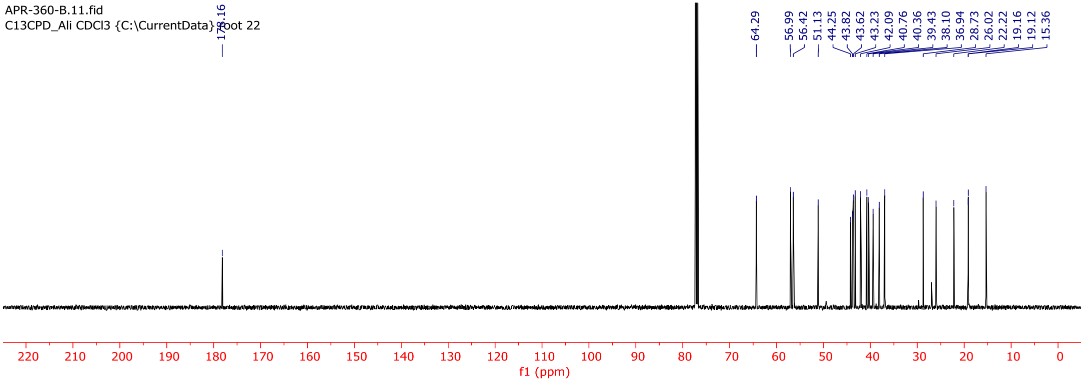
APR-360-B.13.fid
PROTON CDCl3 {C:\CurrentData} root 22

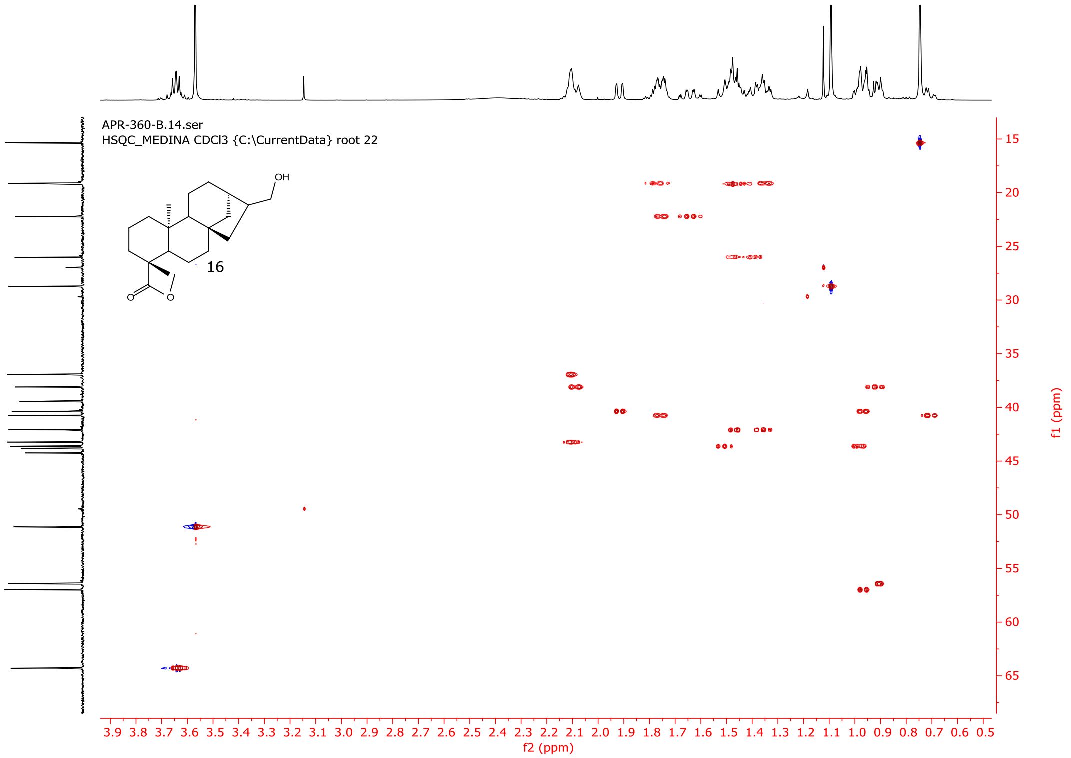


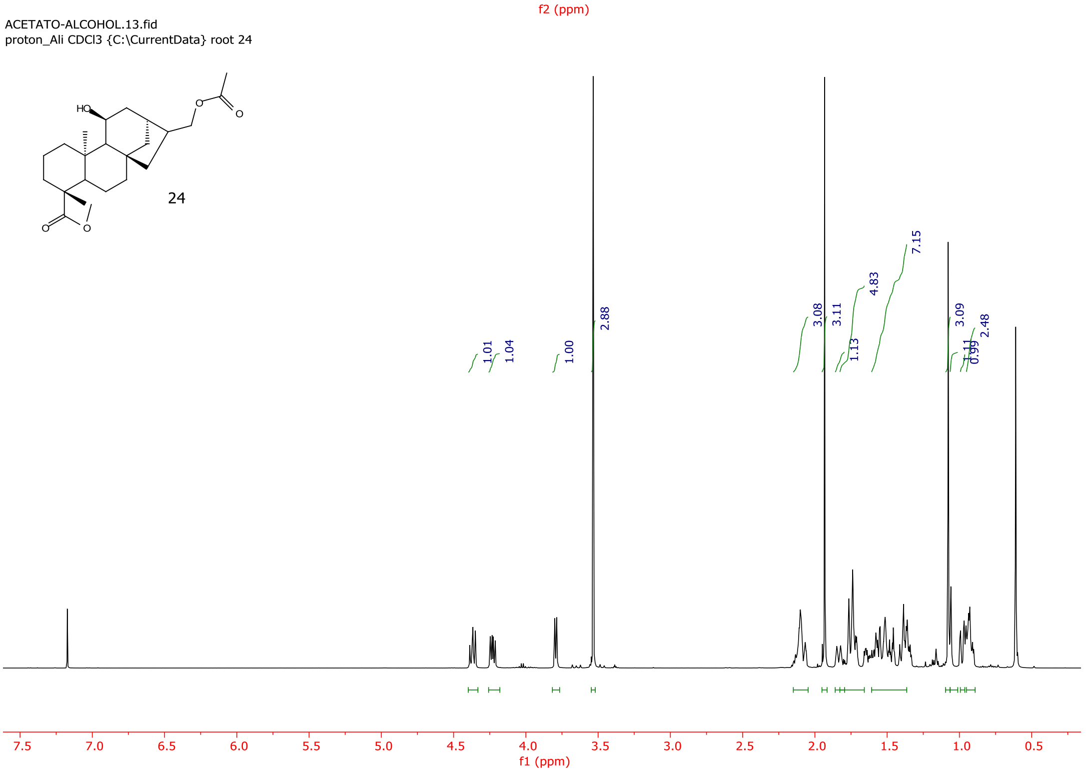
APR-360-B.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 22

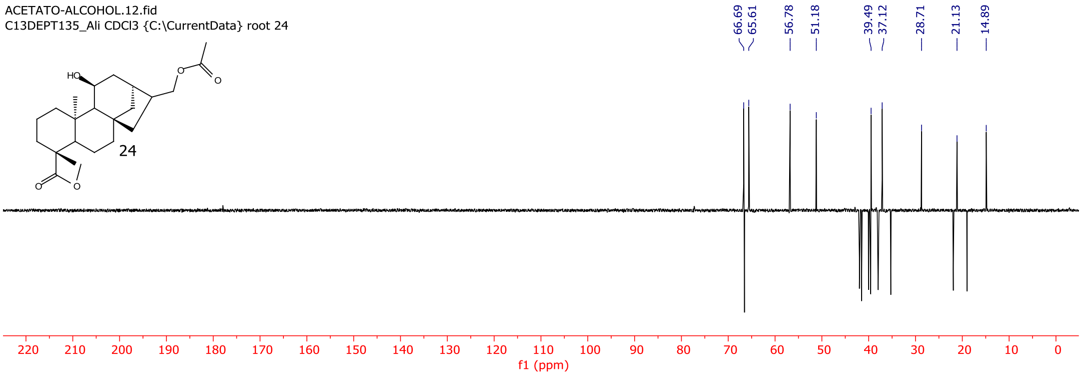


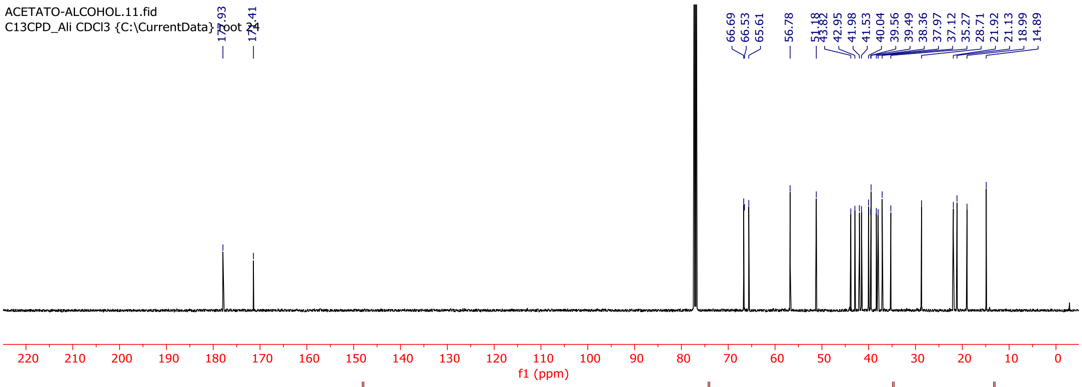
APR-360-B.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 22

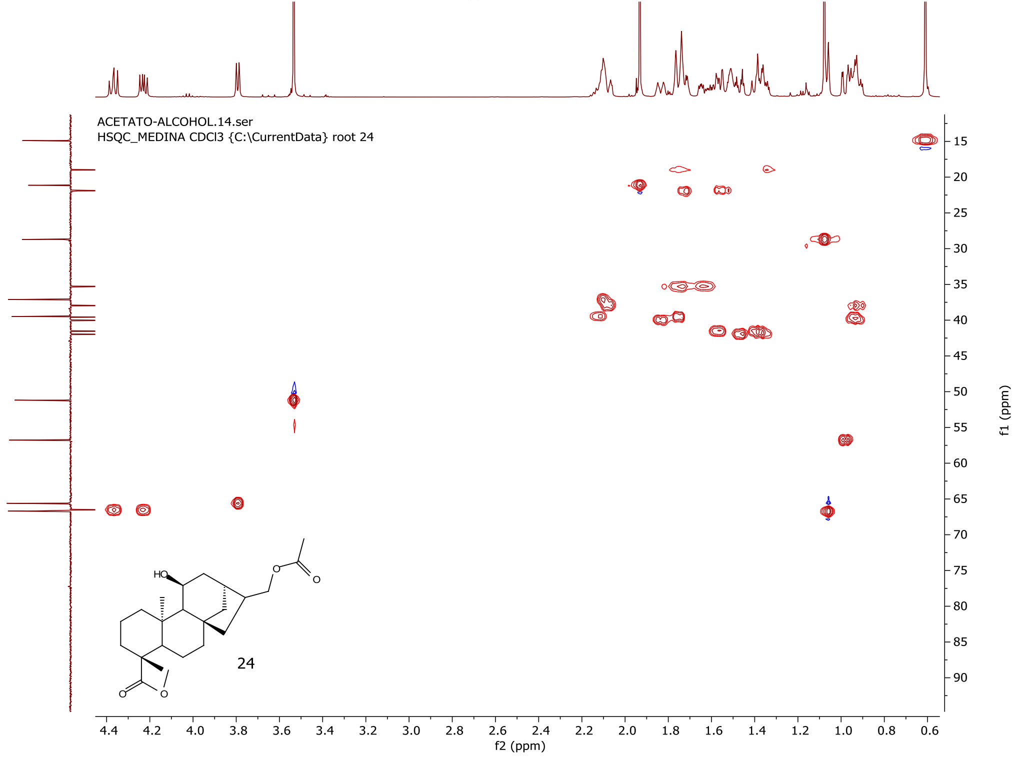


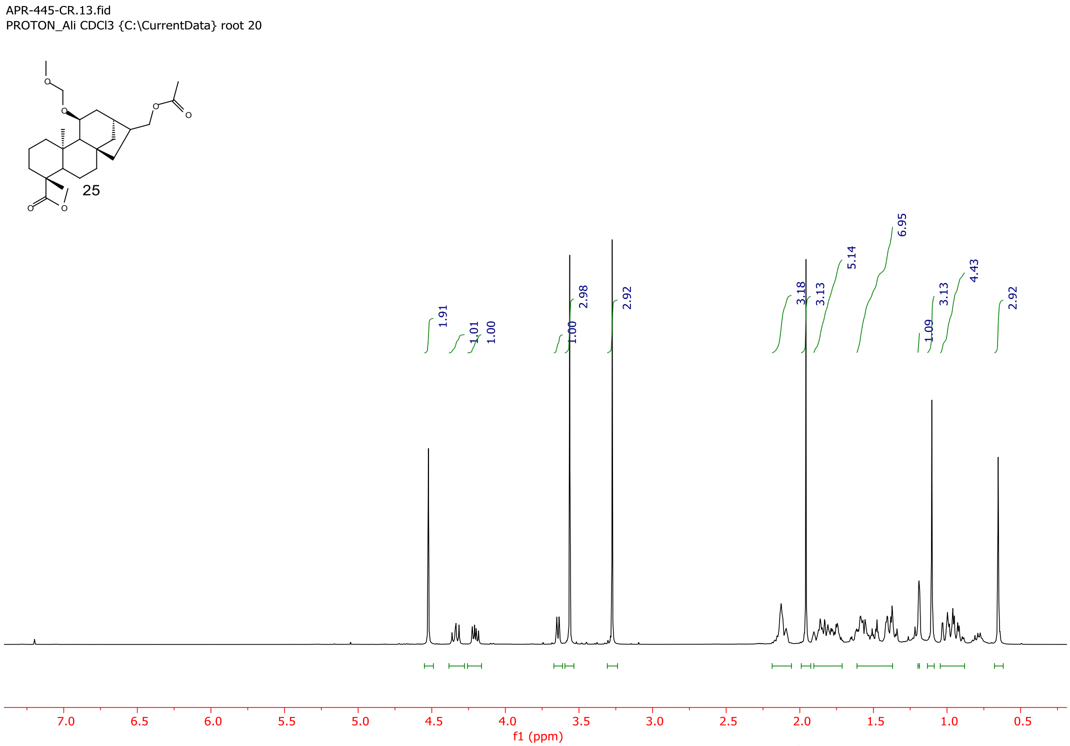

APR-360-B.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 22
OH
16
3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 0.6 0.5
f2 (ppm)
15 20 25 30 35 40 45 50 55 60 65
f1 (ppm)

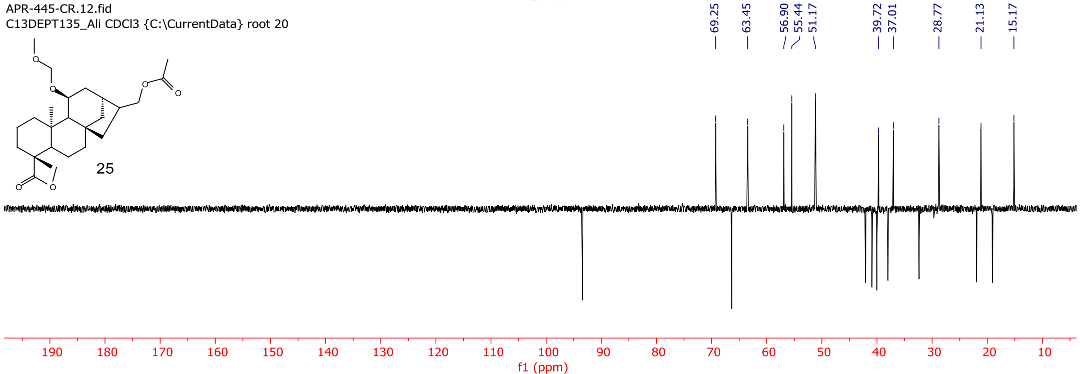

ACETATO-ALCOHOL.13.fid
proton_Ali CDCl3 {C:\CurrentData} root 24
HO
24
1.01
1.04
1.00
2.88
3.08
3.11
1.13
4.83
7.15
3.09
1.11
0.99
2.48
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

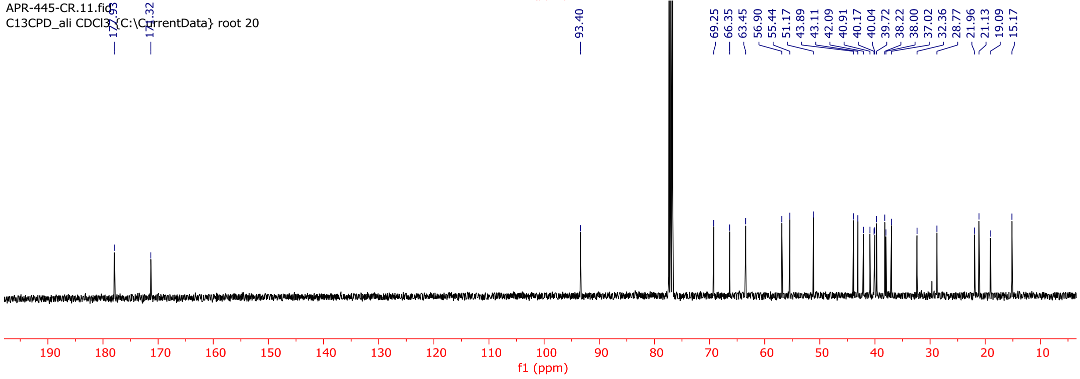

ACETATO-ALCOHOL.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 24
66.69
65.61
56.78
51.18
39.49
37.12
28.71
21.13
14.89
HO
24
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

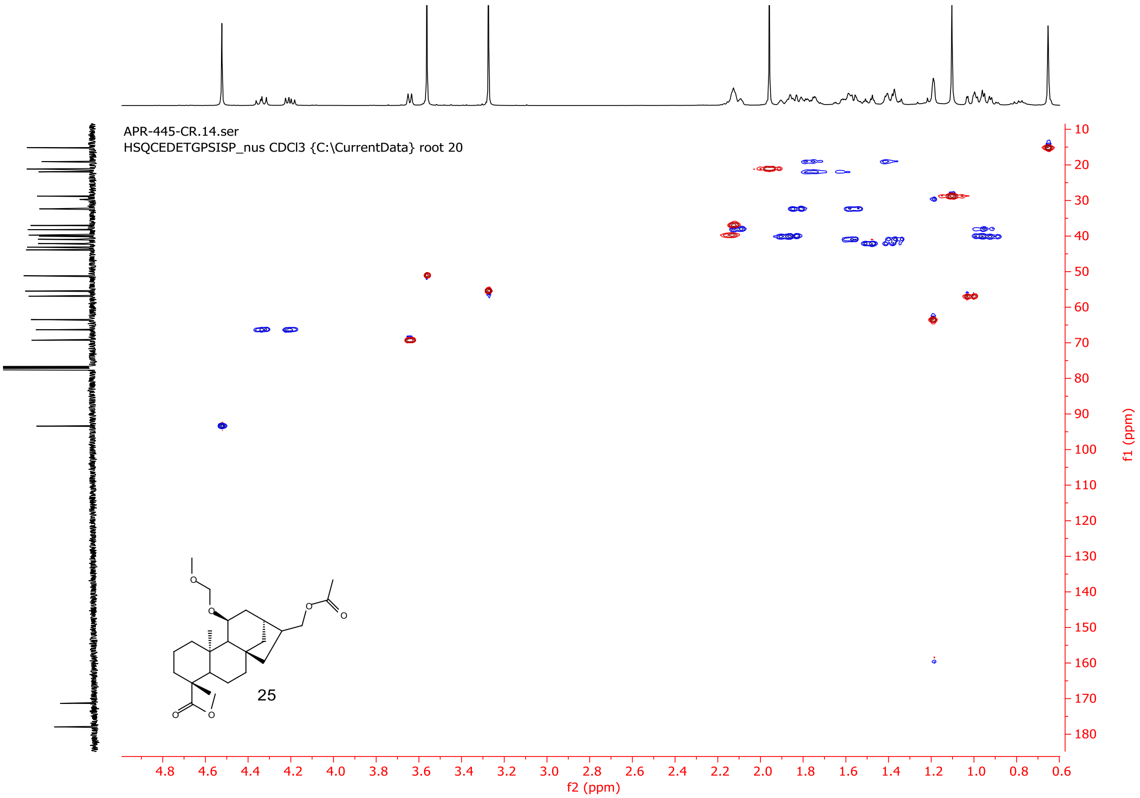

ACETATO-ALCOHOL.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 24
177.93
171.41
66.69
66.53
65.61
56.78
51.18
43.82
42.95
41.98
41.53
40.04
39.56
39.49
38.36
37.97
37.12
35.27
28.71
21.92
21.13
18.99
14.89
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

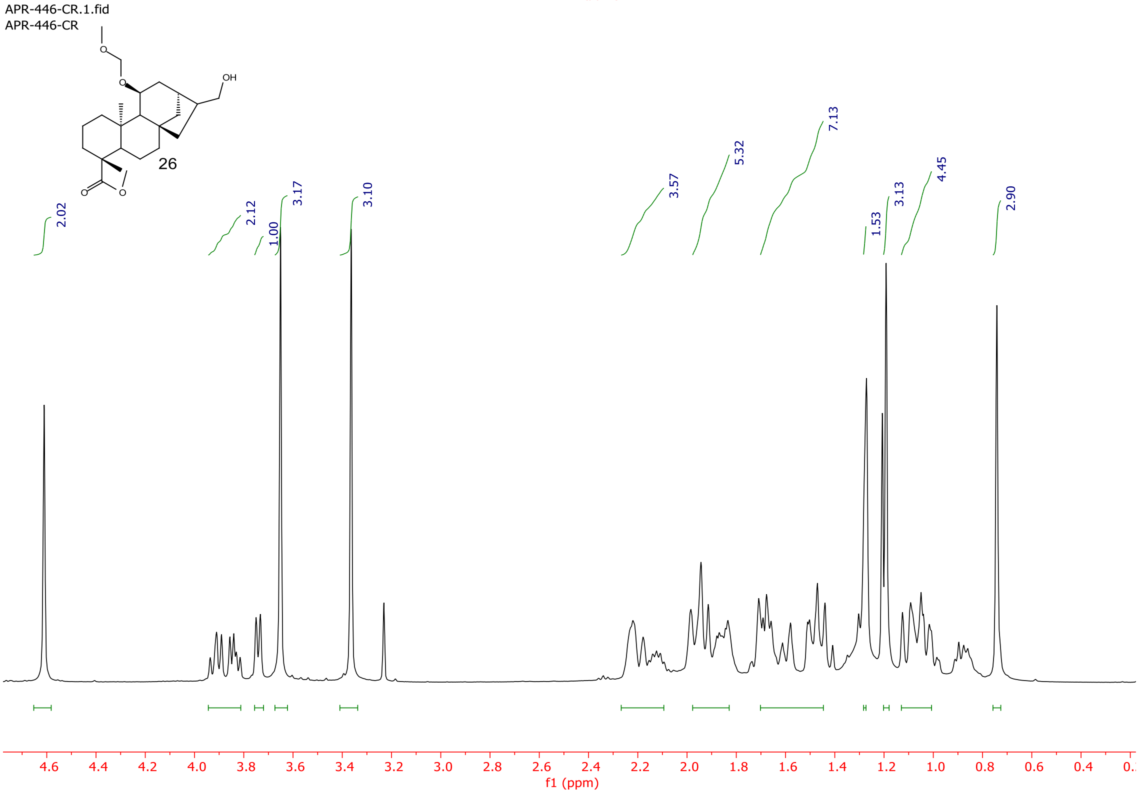

ACETATO-ALCOHOL.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 24
HO
24
f2 (ppm)
4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)
15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90

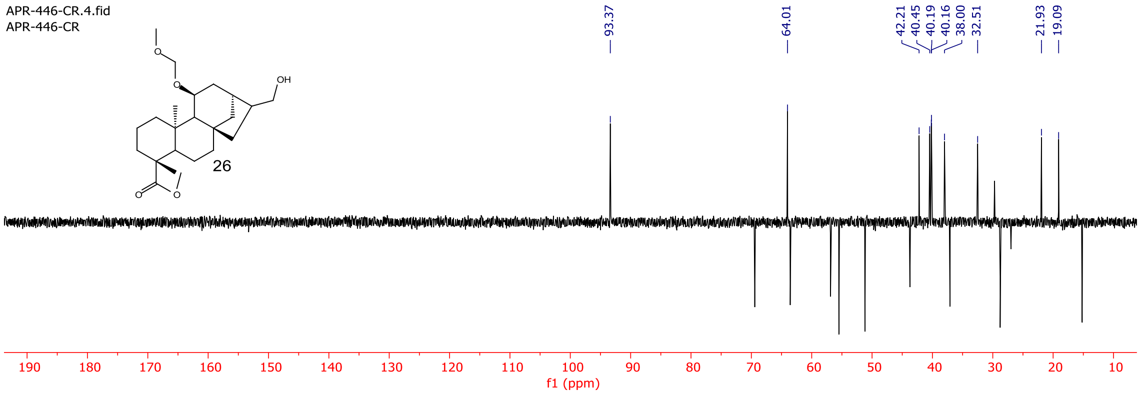

APR-445-CR.13.fid
PROTON_Ali CDCl3 {C:\CurrentData} root 20
25
1.91
1.01
1.00
1.00
2.98
2.92
3.18
3.13
5.14
6.95
1.09
3.13
4.43
2.92
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

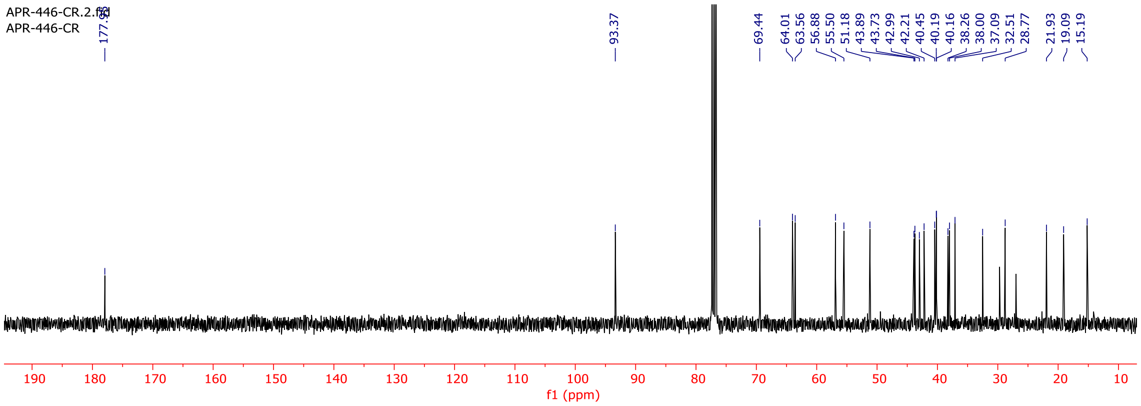

APR-445-CR.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 20
25
69.25
63.45
56.90
55.44
51.17
39.72
37.01
28.77
21.13
15.17
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

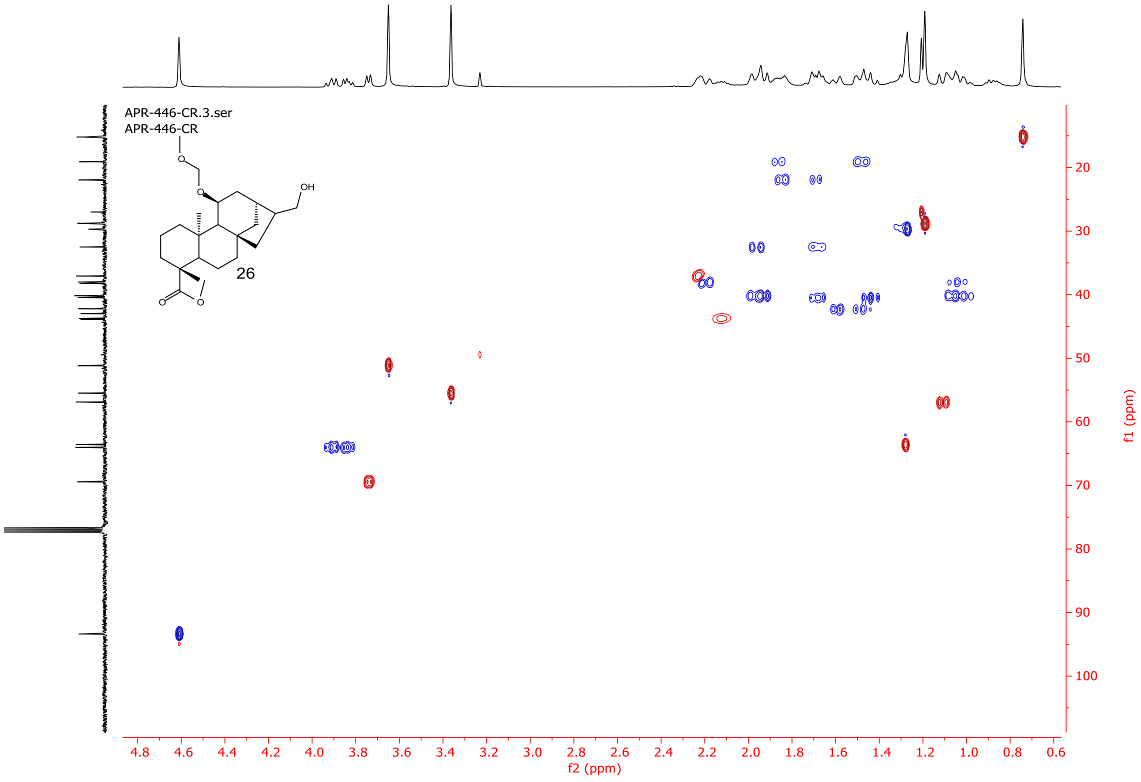

APR-445-CR.11.fid
C13CPD_ali CDCl3 {C:\CurrentData} root 20
177.93
171.32
93.40
69.25
66.35
63.45
56.90
55.44
51.17
43.89
43.11
42.09
40.91
40.17
40.04
39.72
38.22
38.00
37.02
32.36
28.77
21.96
21.13
19.09
15.17
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

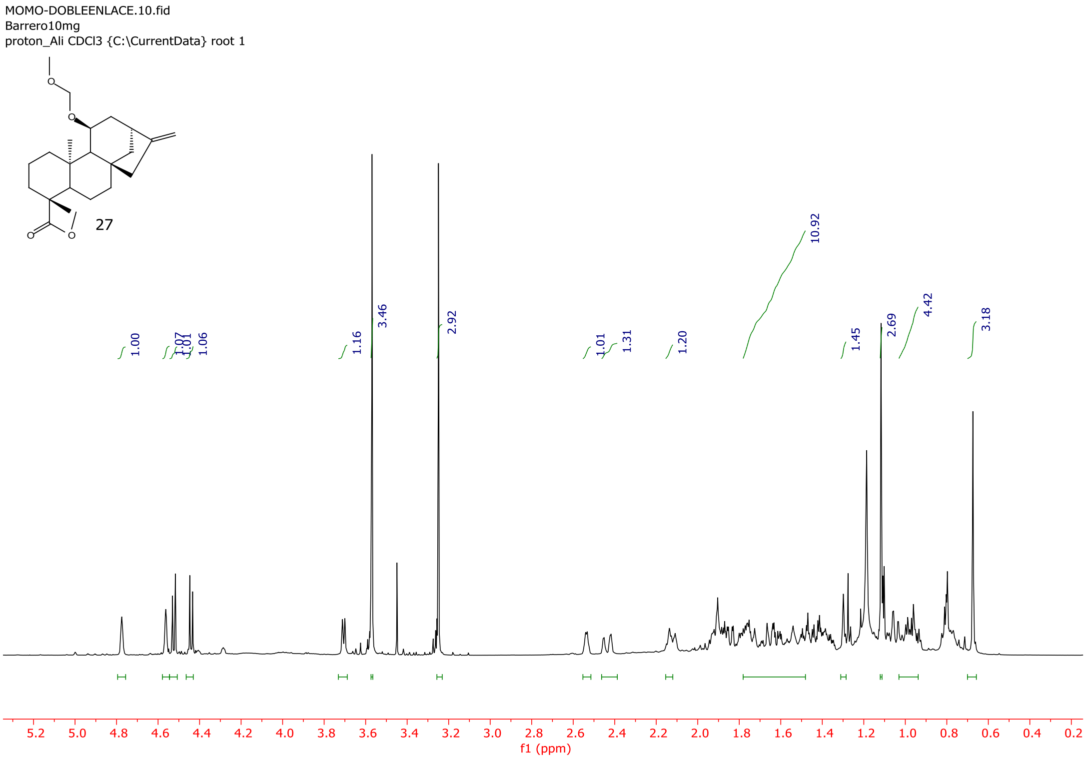

APR-445-CR.14.ser
HSQCEDETGPSISP_nus CDCl3 {C:\CurrentData} root 20
25
f1 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
f2 (ppm)

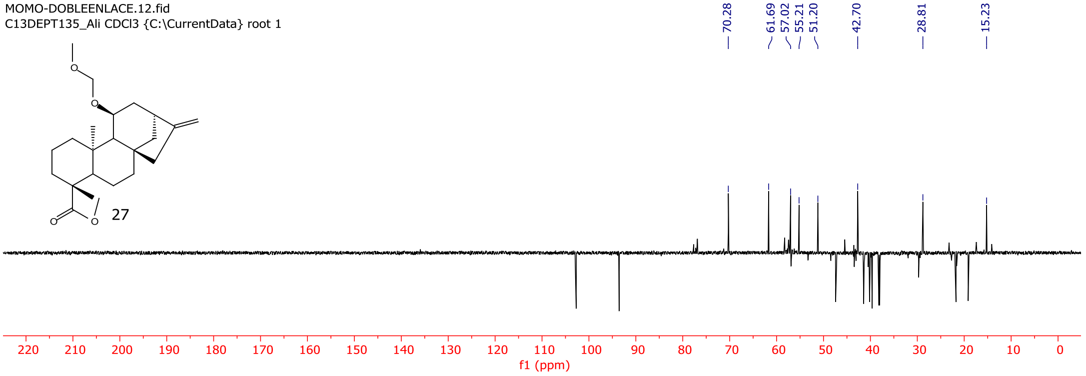

APR-446-CR.1.fid
APR-446-CR
OH
26
2.02
2.12
1.00
3.17
3.10
3.57
5.32
7.13
1.53
3.13
4.45
2.90
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
f1 (ppm)

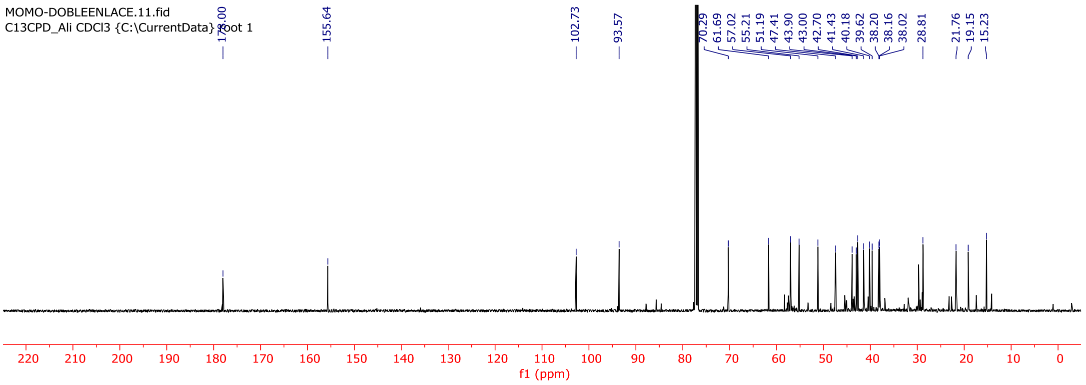

APR-446-CR.4.fid
APR-446-CR
OH
26
93.37
64.01
42.21
40.45
40.19
40.16
38.00
32.51
21.93
19.09
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

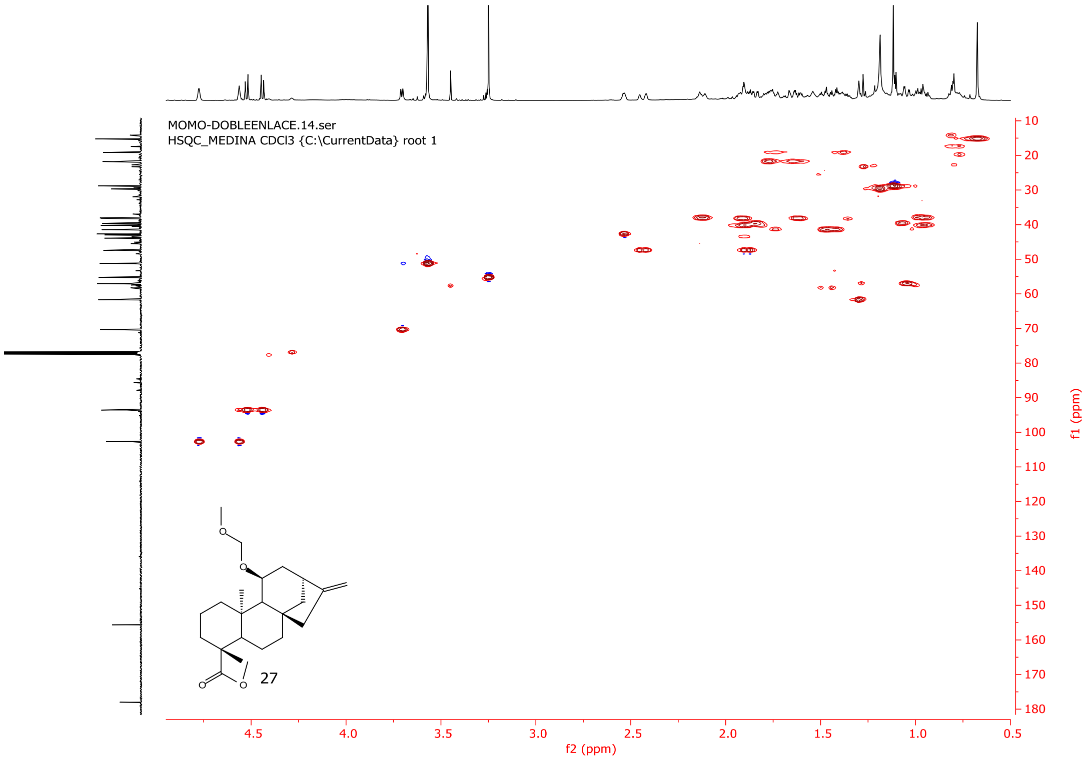

APR-446-CR.2.fid
APR-446-CR
177.95
93.37
69.44
64.01
63.56
56.88
55.50
51.18
43.89
43.73
42.99
42.21
40.45
40.19
40.16
38.26
38.00
37.09
32.51
28.77
21.93
19.09
15.19
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


APR-446-CR.3.ser
APR-446-CR
OH
26
20
30
40
50
60
70
80
90
100
f1 (ppm)
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
f2 (ppm)


MOMO-DOBLEENLACE.10.fid
Barrero10mg
proton_Ali CDCl3 {C:\CurrentData} root 1
27
1.00
1.07
1.01
1.06
1.16
3.46
2.92
1.01
1.31
1.20
10.92
1.45
2.69
4.42
3.18
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
f1 (ppm)


MOMO-DOBLEENLACE.12.fid
C13DEPT135_Ali CDCl3 {C:\CurrentData} root 1
70.28
61.69
57.02
55.21
51.20
42.70
28.81
15.23
27
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MOMO-DOBLEENLACE.11.fid
C13CPD_Ali CDCl3 {C:\CurrentData} root 1
178.00
155.64
102.73
93.57
70.29
61.69
57.02
55.21
51.19
47.41
43.90
43.00
42.70
41.43
40.18
39.62
38.20
38.16
38.02
28.81
21.76
19.15
15.23
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MOMO-DOBLEENLACE.14.ser
HSQC_MEDINA CDCl3 {C:\CurrentData} root 1
27
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

7 Referencias.

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