UNIVERSIDAD DE GRANADA

DEPARTAMENTO DE QUÍMICA ORGÁNICA

Facultad de Ciencias

TESIS DOCTORAL

"Nuevas estrategias hacia la síntesis asimétrica de triterpenos"

Victoriano Domingo Díaz

2011

Editor: Editorial de la Universidad de Granada
Autor: Victoriano Domingo Díaz
D.L.: GR 1162-2012
ISBN: 978-84-695-1061-2

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CERTIFICAN:

Que el Licenciado en Química D. Victoriano Domingo Díaz ha realizado en el Departamento de Química Orgánica de la Universidad de Granada bajo nuestra dirección, el trabajo titulado "***Nuevas estrategias hacia la síntesis asimétrica de triterpenos***", que presenta para optar al grado de Doctor con "Mención de Doctorado Internacional".

Y para que así conste, firman el presente certificado en Granada, a 14 de Octubre de 2011.

Fdo: Prof. Dr. D. Alejandro Fernández Barrero

Fdo: Dr. D. José Francisco Quílez del Moral

"Nuevas estrategias hacia la síntesis asimétrica de triterpenos"

MEMORIA presentada por Victoriano Domingo Díaz para optar al grado de Doctor en Química con "Mención de Doctorado Internacional".

Granada 14 de Octubre de 2011

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AGRADECIMIENTOS

Al finalizar la presente memoria quiero expresar mi agradecimiento a todas las personas e instituciones que de una forma u otra han contribuido a su realización.

En primer lugar, al Prof. D. Alejandro Fernández Barrero que ha sido pilar fundamental en el desarrollo de la tesis, y donde sus años de experiencia y bagaje en la química de productos naturales han hecho posible que se haya podido llevar a cabo este trabajo. Gracias, por haber dejado a este *"artista"* pertenecer a su grupo y prestarme su ayuda siempre que la he necesitado.

Al Dr. D. José Francisco Quílez del Moral por ser algo más que un codirector, un amigo. Por todo el tiempo, conocimiento e ilusión que ha invertido en este trabajo, por su constante apoyo y por su naturalidad y sinceridad en el trato. Gracias de corazón.

Al Prof. Phil S. Baran (*The Scripps Research Institute*, CA) por haber hecho mi sueño realidad al permitirme realizar en sus laboratorios una estancia breve y por su ayuda tanto dentro como fuera del laboratorio.

A la Dra. Maria del Mar Herrador del Pino y a la Dra. Pilar Arteaga Burón por estar siempre dispuestas a ayudar en los problemas del laboratorio y hacernos más ameno el trabajo diario.

Al Prof. Pedro Joseph-Nathan por toda la información aportada en el aislamiento del compuesto natural *seco*- C- oleanano, así como por la generosa donación de una muestra y espectros originales de manera totalmente desinteresada.

Al Dr. Alí Haïdour y a la Dra. María Esther Onorato por toda la ayuda prestada en el campo de la resonancia magnética nuclear. Igualmente, al Dr. José Miguel Ramos por su asistencia en espectrometría de masas.

A todo el personal del departamento de química orgánica, a nuestro secretario José Antonio por su ayuda en cualquier tipo de trámite. A la Dra. María José de la Torre por su ayuda en la traducción de artículos al inglés.

Al Ministerio de Educación y Ciencia por la concesión de la beca F.P.U. predoctoral AP-2007-03232.

A mis compañeros de laboratorio los cuales han sido durante cinco años como mis hermanos (para lo bueno y para lo malo), por la cantidad de historias que hemos vivido juntos y que nunca olvidaré: Dr. Jesús Fernández, Dra. Elena Sánchez, Dra. Julieta Catalán, Dra. Lucia Silva, Dr. Gustavo Escobar, Dr. Abraham Mendoza, Armando López, Jesús Gil, Maria del Carmen Pérez, José A. González, las griegas Titika y Paulina, Niklas, Consuelo Prieto, y a mi amigo Alexis Castillo. Finalmente, me gustaría agradecer especialmente al Dr. Horacio Rodríguez por su amistad y transmitirme su espíritu infatigable.

A mi familia, especialmente a mis padres, José y María, que no han dudado en darme siempre la oportunidad de estudiar apoyándome económicamente incluso durante el comienzo de la tesis y que son el mejor ejemplo de sacrificio y esfuerzo. Gracias por enseñarme el valor de las cosas.

A mis amigos, a mi hermana Rocío y sobre todo a Maribel que siempre ha estado a mi lado apoyándome, que siempre me ha respetado y permitido hacer lo que más me gusta.

New reagents and reactions for use in the chemistry of Natural Products can be invented and not just discovered by hazard. First, we must recognize a reaction that would be important synthetically, but which does not yet exist in a satisfactory form. Thus, the reaction proposed either does not exist, or if it does, it is carried out under harsh conditions and is non-selective. Poor yields, uneconomic reagents and lack of stereoselectivity are other factors that spur invention. Thus, one has only to read the great syntheses of the day and ask for the yield, the conditions, the cost and the stereoselectivity at each step. It is a rare academic synthesis that does not have a weak step. It is even more unusual that new reagents or reactions are presented to alleviate the defects. Some modest efforts to help will be presented....***D. H. R. Barton***

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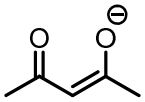
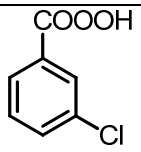
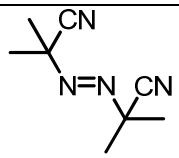
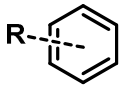
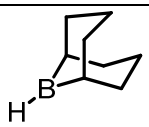
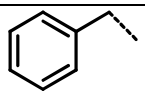
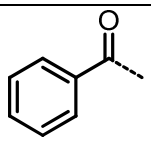
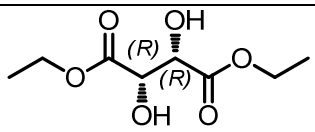
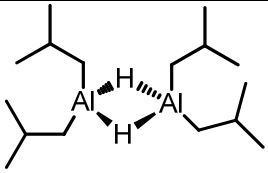
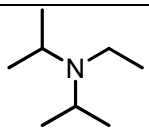
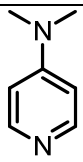
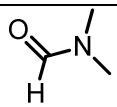
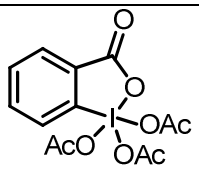
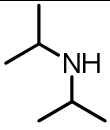
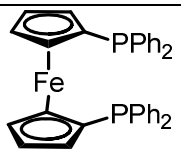
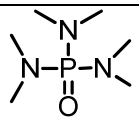
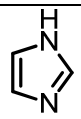
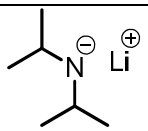
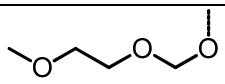
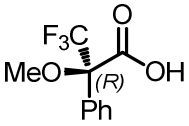
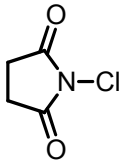
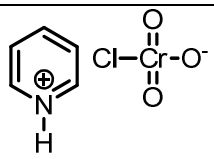
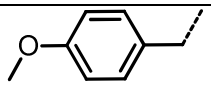
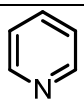
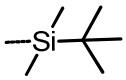
ABREVIATURAS:

Abreviatura	Nombre químico	Estructura química
Ac	Acetil	
acac	Acetilacetonil	
AMCPB	Ácido m-cloroperbenzoico	
DA	Dihidroxilación asimétrica	
AIBN	2, 2'-Azobisisobutironitrilo	
Ar	Aril (anillo aromático sustituido)	
BBN (9-BBN)	9- Borabiciclo[3.3.1]nonano	
Bn	Bencil	
Bz	Benzoil	

Cp	Ciclopentadienil	
DCM	Diclorometano	CH_2Cl_2
DET	(+)-Dietiltartrato	
DIBAL-H	Hidruro de diisobutilaluminio	
DIPEA (base de Hunig)	Diisopropiletilamina	
DMAP	*N, N*-4- Dimetilaminopiridina	
DMF	*N, N*- Dimetilformamida	
DMP	Dess-Martin periodinano	
DMSO	Dimetilsulfóxido	
DIPA	Diisoprpopilamina	

Dppf	1,1'- Bis(difenilfosfino)ferroceno	
HMPA	Hexametilfosforamida	
HPLC	High-pressure liquid chromatography	
HWE	Horner-Wadsworth-Emmons	
Imid	Imidazol	
LDA	Litio diisopropilamida	
MEM	Metoxietoximetilo	
MTPA	Ácido α-metoxi-α- trifluorometilfenil acético	
NCS	N-clorosuccinimida	
OS	Óxido de escualeno	

PDC	Dicromato de piridinio	
PMB	*p*-Metoxibencil	
Py	Piridina	
S ó SQ	Escualeno	
TBAF	Fluoruro de tetra-*n*-butilamonio	
TBDMS **(TBS)**	*t*-Butidimetilsilil	
THF	Tetrahidrofurano	

I. INTRODUCCIÓN Y OBJETIVOS

I. 1. Origen de la diversidad molecular en terpenos

El término terpeno proviene de la trementina (*lat. Balsamum terebinthinae*). La trementina, también llamada "resina de pinos", contiene los "ácidos de la resina" y algunos hidrocarburos, que son originalmente conocidos como terpenos. Tradicionalmente, todos los compuestos naturales construidos a partir de unidades de isopreno son denominados como terpenos.[1]

Los terpenos representan una de las mayores y más diversas clases de metabolitos secundarios, con alrededor de 55.000 miembros aislados hasta la fecha. Las enzimas terpeno-ciclasas son utilizadas en la naturaleza para convertir fosfatos hidrocarbonados poliénicos lineares y sencillos en una colección de esqueletos carbocíclicos quirales. Adicionalmente, reordenamientos y oxidaciones dan lugar a una gran diversidad de estructuras. Esta diversidad estructural ha venido acompañada de un amplio rango de propiedades farmacológicas que van desde actividades anti-cancerígenas y anti-maláricas a promotores tumorales y enlazantes de canales iónicos.[2] Asimismo, desde la antigüedad se conocen otras importantes aplicaciones en perfumería y cosmética y en la actualidad también se emplean como insecticidas, herbicidas, fitorreguladores, etc.[3]

Rutas biosintéticas de los precursores C5 de los terpenos:

La biosíntesis de terpenos tiene lugar a través de dos rutas diferentes que dan lugar a las unidades básicas de construcción, el dimetilalil pirofosfato (DMAPP) y el isopentenil pirofosfato (IPP). Estas dos rutas biosintéticas se denominan:

- Ruta mevalónica.[4]
- Ruta no mevalónica o ruta de la desoxixilulosa.[5a-d]

Ruta mevalónica:

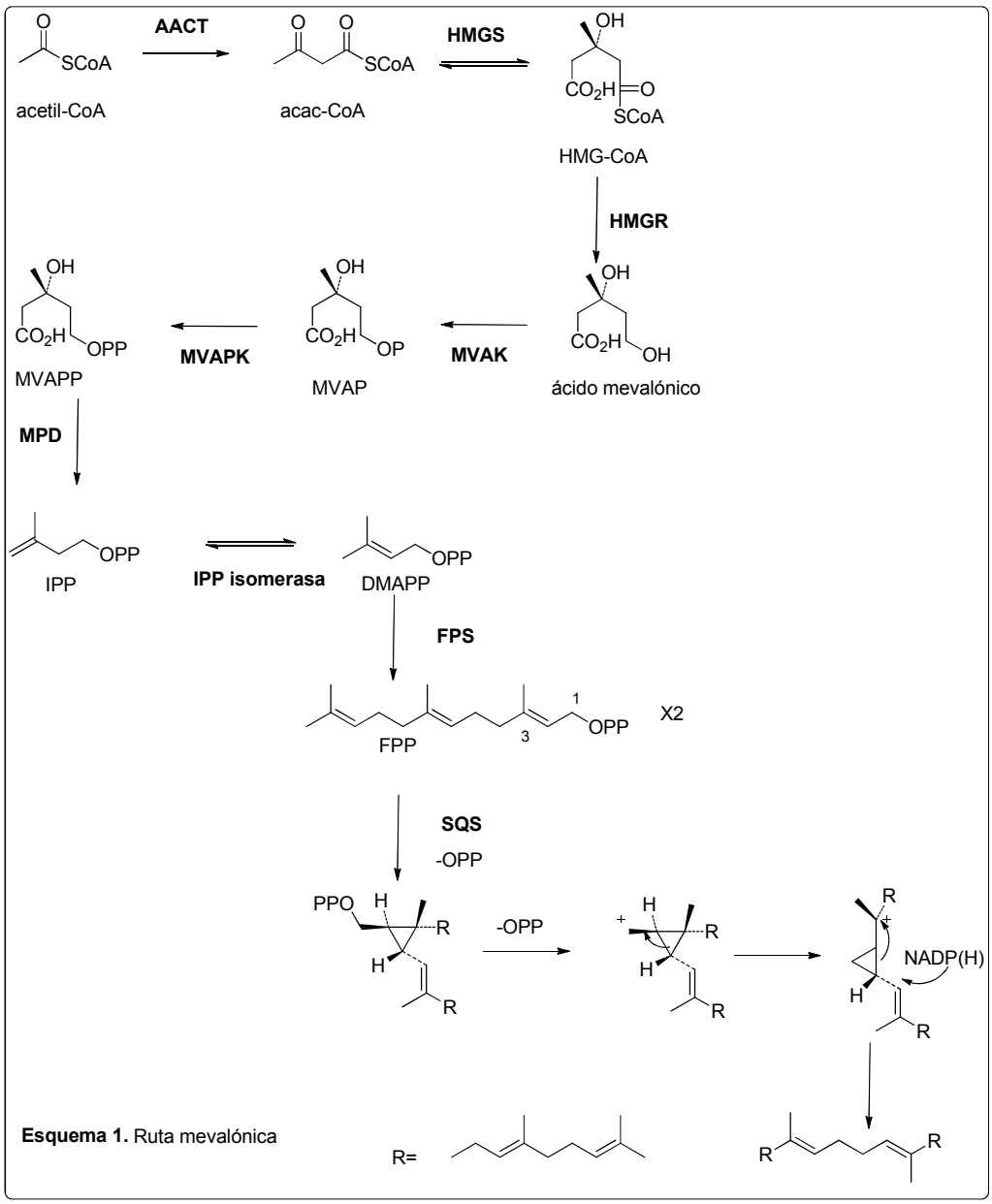
El estudio de las rutas biogenéticas de terpenos y especialmente la de triterpenos ha despertado gran interés durante las últimas décadas, habiéndose propuesto distintas hipótesis que han confluido en una primera ruta unificada, la del ácido mevalónico (MVA), que hoy día es comúnmente aceptada (Esquema 1).[6a-q]

El primer paso consiste en una condensación tipo Claisen de dos moléculas de acetil coenzima A para formar acetoacetil-coenzima A, mediada por la enzima acetoacetil-CoA tiolasa (AACT). A continuación, se incorpora una segunda molécula de acetil-CoA en un proceso tipo aldólico para producir (*S*)-3-hidroxi-3-metilglutaril-CoA bajo el control de la HMG-CoA sintasa (HMGS). El siguiente paso implica la reducción de HMG-CoA por la (*S*)-3-hidroxi-3-metilglutaril-CoA reductasa (HMGR) para originar ácido mevalónico. Esta reacción es irreversible bajo condiciones fisiológicas, constituyendo un paso clave en la biosíntesis de esteroides en eucariotas, de ahí que se sigan publicando nuevos inhibidores de la HMGR con el fin de obtener fármacos capaces de disminuir los niveles de colesterol. La conversión de (*R*)-ácido mevalónico en el isopentenil pirofosfato (IPP) requiere tres reacciones consecutivas de fosforilación vía (*3R*)-5 fosfomevalonato (MVAP) y (*3R*)-5 pirofosfatomevalonato (MVAPP), que son catalizadas por enzimas mevalonato quinasas (mevalonato-5-fosfotransferasa, MVAK, mevalonato-5-fosfato quinasa, MVAPK, y mevalonato pirofosfato anhidrodescarboxilasa, MPD). A continuación la enzima isopentenil difosfato: dimetilalil difosfato isomerasa (IPP) cataliza el reordenamiento 1,3 alílico del sustrato homoalílico IPP a su isómero alílico, el dimetilalil pirofosfato (DMAPP).

Después el DMAPP electrofílico actúa sobre IPP como la primera de las subsecuentes reacciones de transferencia de prenilos en la ruta biosintética de triterpenos. Dependiendo del número de subunidades de isopreno, se puede diferenciar entre hemi- (C5), mono-(C10), sesqui-(C15), di-(C20), sester-(C25), tri-(C30), tetra-(C40) y politerpenos $(C5)_n$ con n>8. La enzima farnesil pirofosfato sintasa (FPS) cataliza la biosíntesis del farnesil pirofosfato por una condensación inicial de IPP y DMAPP "cabeza-cola" para formar el C_{10} geranil pirofosfato (GPP). GPP a continuación sirve como sustrato alílico para una segunda condensación con IPP y originar el compuesto C_{15} farnesil pirofosfato (FPP). El mecanismo de esta reacción parece apoyarse en una ionización del grupo pirofosfato, antes de la condensación facilitada por formar complejos con cationes divalentes como el magnesio, además de ser un buen grupo saliente. Estudios mediante difracción de RX de la FPS, han revelado que existe una gran cavidad formada por diez α-hélices con secuencias enriquecidas en dos restos de aspartato, que están implicados en la unión de los grupos pirofosfato de los sustratos de la condensación, vía puente magnesio y promueven la catálisis.[6n] Además en el mismo centro activo del enzima, existen aminoácidos voluminosos como son dos fenilalaninas que juegan un papel crítico en la longitud de la cadena, determinando el

tamaño de la cadena prenilada. Una reducción en el tamaño de estos aminoácidos en la FPS puede catalizar la formación de geranilgeranilo (C_{20}) ó farnesil geranilo (C_{25}).

La síntesis del triterpeno escualeno (SQ) por unión "cabeza-cabeza" [7] tiene lugar en dos fases; condensación inicial de dos moléculas de FPP para formar el preescualeno difosfato (PSPP)[6j] y posterior reordenamiento reductivo que requiere NAD(P)H para dar SQ.



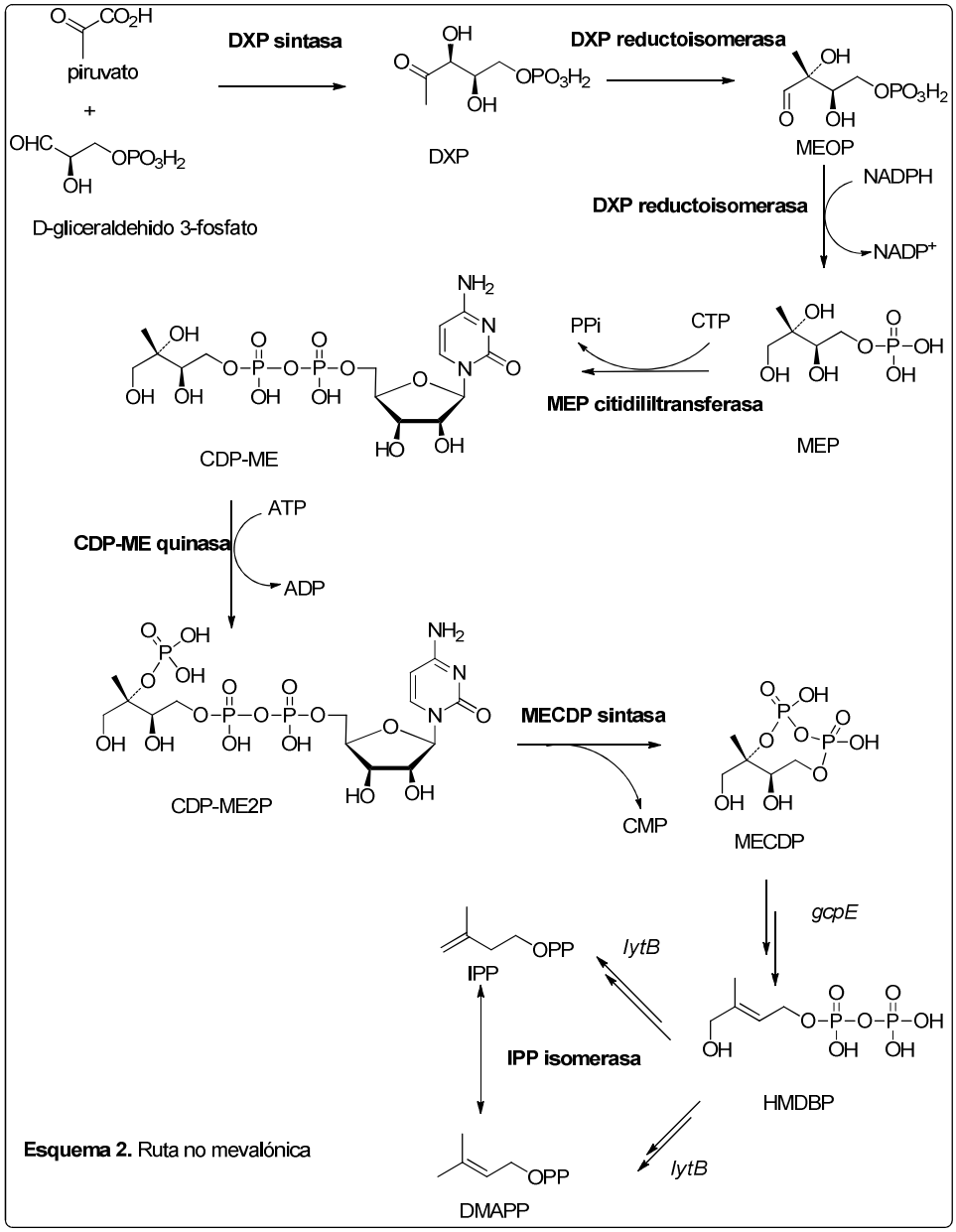
Esquema 1. Ruta mevalónica

Ruta no mevalónica:

Esta segunda ruta surge como consecuencia de una serie de hechos experimentales, no justificables mediante la ruta del mevalónico. Así entre otros, la falta de incorporación por parte de algunas bacterias, de los precursores de la ruta del mevalonato marcados isotópicamente (^{13}C-acetato) y la ausencia de actividad de algunos inhibidores de la HMGR que detienen el crecimiento de bacterias. Esta nueva ruta funciona principalmente en plantas y en algunas bacterias, pero no en arqueas y animales.

El paso inicial en la ruta no mevalónica es la formación de 1-deoxi-D-xilulosa 5-fosfato (DXP) por la condensación de piruvato y D-gliceraldehido 3-fosfato, reacción catalizada por la DXP sintasa (Esquema 2). El segundo paso consiste en el reordenamiento de DXP para dar 2-C-metileritrosa 4-fosfato (MEOP), seguido por conversión en 2-C-metil-D-eritritol 4-fosfato (MEP) mediante un proceso de reducción. Posteriormente, el MEP se convierte en 4-(citidina 5'-difosfo)-2-C-metil-D-eritritol (CDP-ME) en presencia de CTP, para a continuación en presencia de ATP convertirse en 2-fosfo-4-(citidina 5'-difosfo)-2-C-metil-D-eritritol (CDP-ME2P), reacción mediada por la CDP-quinasa. A continuación, CDP-ME2P es convertido en 2-C-metil-D-eritrol 2,4-ciclodifosfato (MECDP) con la eliminación de CMP. La conversión de este último producto por el gen *gcpE* da lugar a 1-hidroxi-2-metil-2-(E)-butenil-4-difosfato (HMBDP) que mediante posteriores transformaciones por el gen *lytB* origina IPP y DMAPP, aunque los últimos pasos no están totalmente clarificados.

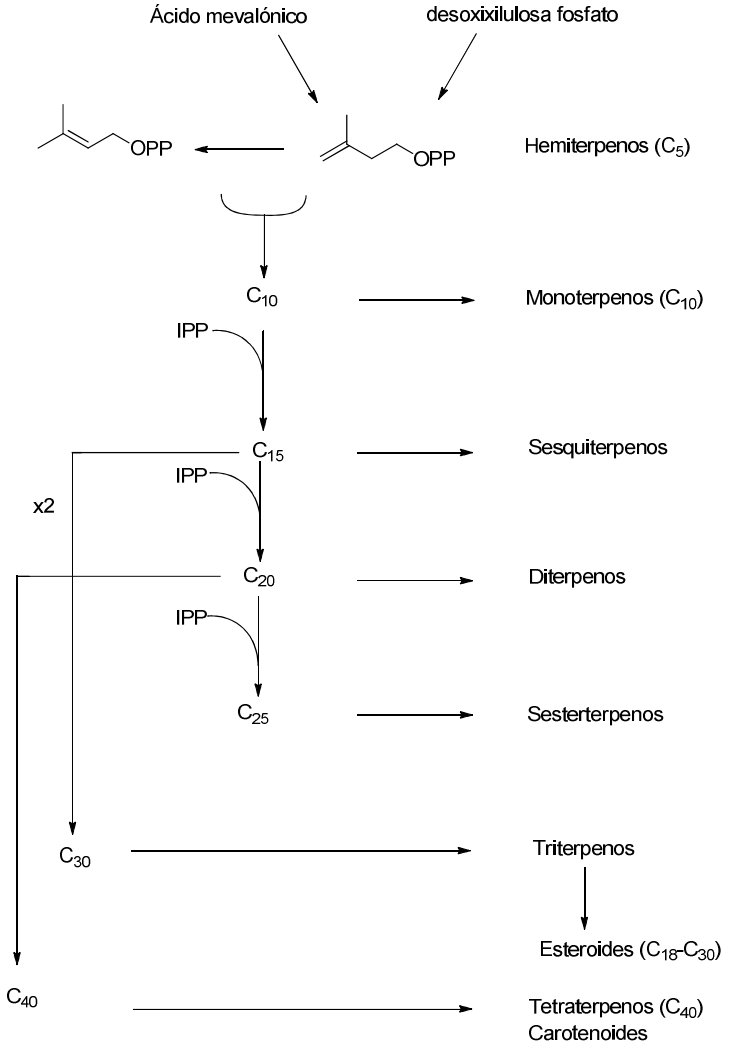
En plantas ambas rutas, mevalónica y de la desoxixilulosa, están presentes aunque en compartimentos celulares separados. En el citoplasma funciona la ruta mevalónica que conduce a triterpenos y esteroles, mientras que en plástidos como los cloroplastos actúa la ruta del metileritritolfosfato originando los restantes terpenos.[8]



Esquema 2. Ruta no mevalónica

Biosíntesis de las diferentes familias de terpenos:

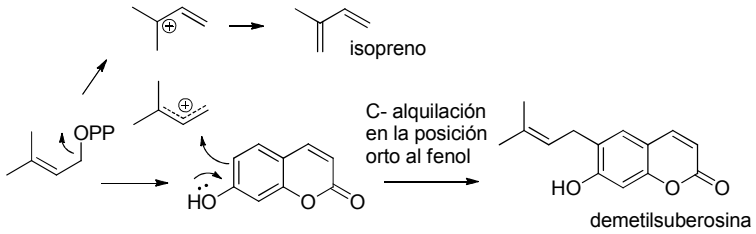
Los terpenoides pueden ser clasificados de acuerdo al número de unidades de isopreno incorporadas clasificándose como hemiterpenos, monoterpenos, sesquiterpenos, diterpenos, sesterterpenos donde la unión de unidades C5 es llevada a cabo mediante uniones cabeza-cola y triterpenos o tetraterpenos donde la unión central es cola-cola. Las estructuras de los terpenoides de cada clase pueden ser justificadas a partir de los precursores acíclicos, por mecanismos biosintéticos basados en química de carbocationes y subsiguientes reordenamientos Wagner–Meerwein (Esquema 3).[1,3,9]



Esquema 3. Biosíntesis de las diferentes familias de terpenos

A continuación se muestran algunos ejemplos representativos de estas familias de terpenoides:

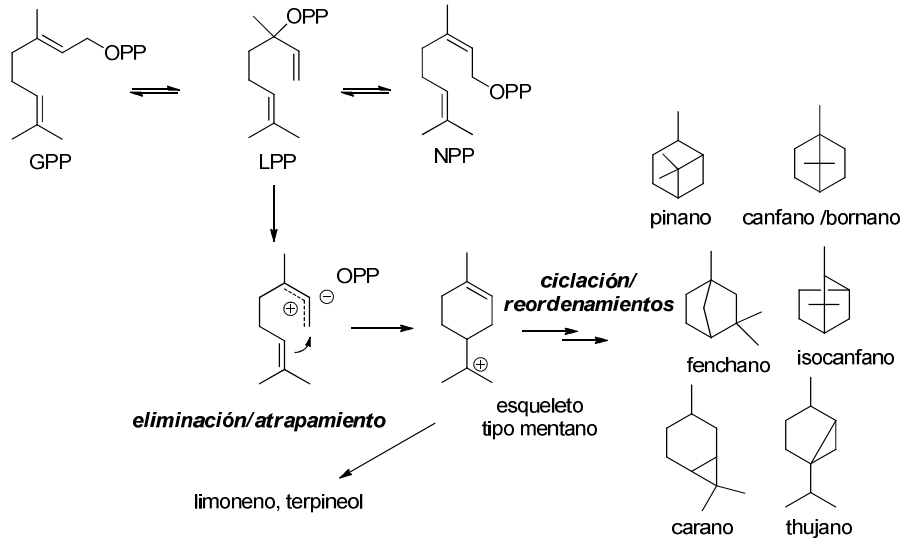
Hemiterpenos (C_5): El IPP y DMAP son los intermedios hemiterpénicos reactivos en las rutas que conducen a estructuras terpenoides más complejas. Son además usadas como agentes alquilantes en la formación de los meroterpenos. Relativamente pocos hemiterpenos verdaderos son producidos en la naturaleza.



Esquema 4. Meroterpenoides

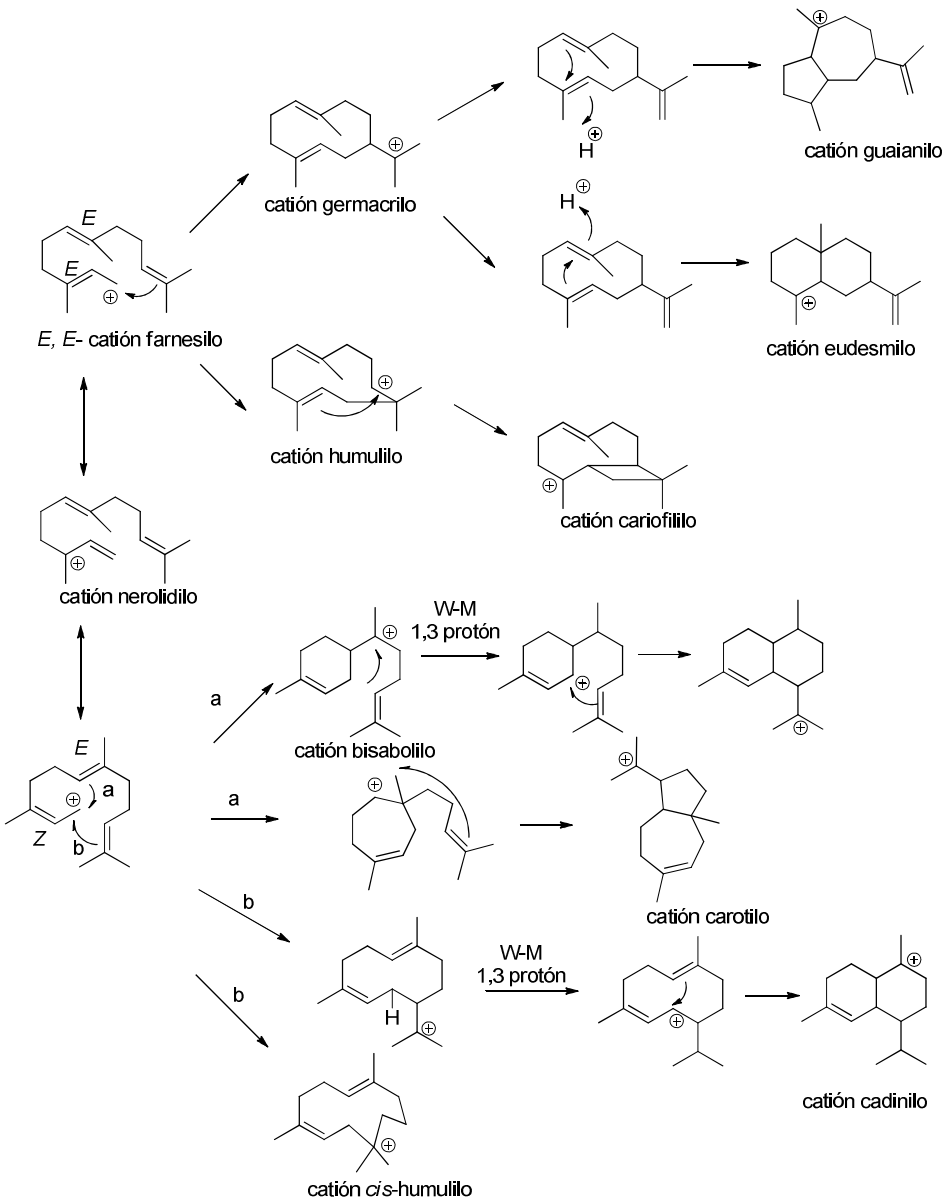
Monoterpenos (C_{10}): La combinación de DMAPP y IPP vía la enzima prenil transferasa da lugar a geranildifosfato (GPP), en el cual el doble enlace es *trans* (*E*). Su formación se piensa que tiene lugar por ionización de DMAPP a un catión alílico que se adiciona al doble enlace del IPP seguido de una pérdida de un protón. El linalil pirofosfato (LPP) y el neril pirofosfato (NPP) son isómeros del geranil pirofosfato (GPP) formados a partir de éste. Estos tres compuestos, mediante pequeños cambios funcionales pueden dar lugar a monoterpenos lineales encontrados en las fracciones volátiles de aceites usados en aromas y perfumería (ej: geranial). El rango de monoterpenos se extiende considerablemente por reacciones de ciclación. Así se pueden crear sistemas monocíclicos o bicíclicos a partir del geranil, neril o linalil pirofosfato que son aceptados por las monoterpeno ciclasas. Es conveniente además recordar que las especies implicadas en la ciclación son cationes alílicos deslocalizados y la formación de ciclos tiene lugar debido a la proximidad de los electrones π de los dobles enlaces. Los carbocationes cíclicos finalmente sufren diferentes procesos como el atrapamiento con nucleófilos (especialmente H_2O), pérdida de un protón, ciclación y posiblemente reordenamientos de Wagner-Meerwein que son característicos en la biosíntesis de terpenoides. La analogía con la química de carbocationes, está justificada debido a la alta proporción de terpenos naturales que han sufrido reordenamientos. En estos reordenamientos, generalmente migran los carbonos e hidrógenos para alcanzar una

mayor estabilidad del carbocatión o para originar una reducción de la congestión anular justificando así algunas rutas biosintéticas.



Esquema 5. Biosíntesis de algunos esqueletos de monoterpenos

Sesquiterpenos (C_{15}): La adición de una unidad C5 al geranil difosfato por parte de una prenil transferasa conduce al precursor fundamental de los sesquiterpenos, el farnesil difosfato. Las posiblidades de ciclación en estos compuestos se incrementan respecto a sus predecesores los monoterpenos encontrándose en la naturaleza una gran variedad de compuestos mono-, bi- y tricíclicos. La estereoquímica del doble enlace cercano a la unidad de pirofosfato puede adquirir la configuración *E* o *Z* por ionización dando el geranilneril pirofosfato o incluso se ha encontrado como intermedio la unidad terciaria de pirofosfato en el nerolidil pirofosfato. Como en los monoterpenos los diferentes carbocationes generados dan lugar a las diferentes estructuras encontradas en la naturaleza.



Esquema 6. Biosíntesis de algunos esqueletos de sesquiterpenos representativos

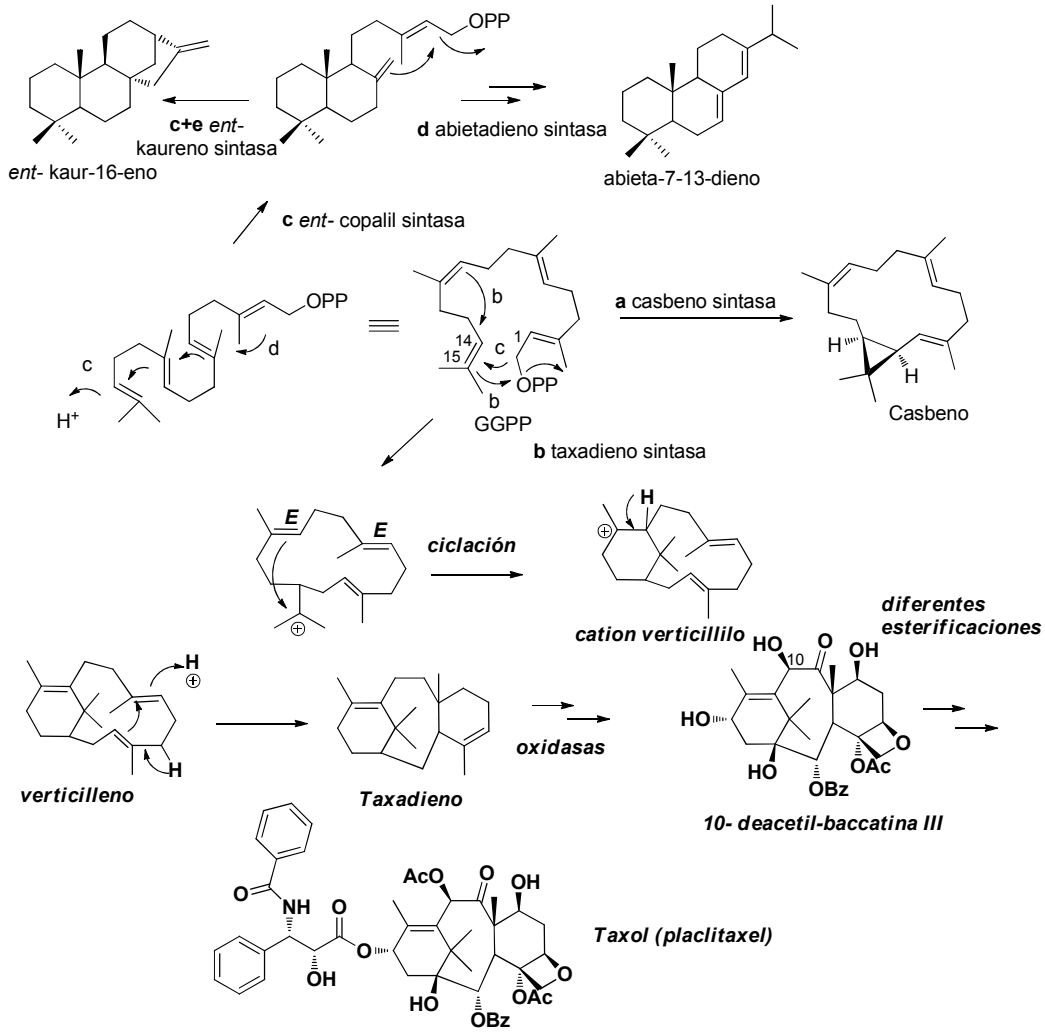
Diterpenos (C_{20}): Los diterpenos surgen a partir del geranilgeranilpirofosfato (GGPP) como consecuencia de la adición de una molécula de IPP al farnesil pirofosfato. Podemos encontrarlos en la naturaleza como diterpenos lineales como es el caso del fitol, que es una forma reducida del geranilgeraniol. Fitol es un constituyente de las clorofilas y además forma parte de fitoquinonas como la vitamina K. Como consecuencia de la adición electrofílica de protones al precursor lineal GGPP vía diterpenociclasas se originan los diterpenos cíclicos. Éstos pueden ser agrupados en función de los diferentes tipos de ciclación de GGPP que han sido verificados en diferentes estudios enzimáticos. Las sintasas son:

Casbeno sintasa:[10] Cataliza la formación de (1*S*, 3*R*)-casbeno por ionización del difosfato de GGPP y ataque del resultante ion carbonio alílico al doble enlace terminal. Se trata de una ciclación catiónica no clásica que implica los átomos C1, C14 y C15.

Ent- copalil difosfato sintasa:[11] Cataliza la formación del *ent*-copalil difosfato (*ent*-CPP) por una ciclación inducida cationicamente.

Taxadieno sintasa:[12] Cataliza la formación de taxa-4-11-dieno a través de varios pasos inducidos por la ionización del GGPP y posterior ciclación intramolecular. Existen más de 100 compuestos con esqueleto de taxano en la naturaleza donde el ejemplo más característico lo encontramos en el taxol, compuesto antitumoral aislado del tejo *Taxus baccata* (europeo) y del *Taxus brevifolia* (pacífico).

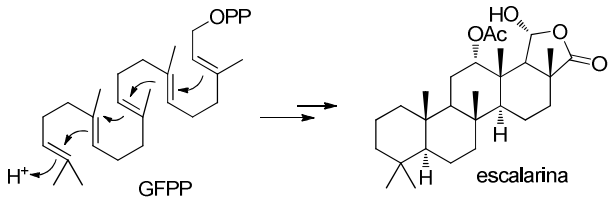
Abietano sintasa:[13] Cataliza la formación del abieta-7-13-dieno por una serie de pasos inducidos por protonación y continuados por ionización del difosfato.



Esquema 7. Biosíntesis de algunos esqueletos diterpenicos representativos

Ent-kaureno sintasa:[14] No se considera un GGPP ciclasa, pero cataliza la formación de *ent*-kaur-16-eno a partir del *ent*-CPP. En contraste con el abietadieno, el *ent*-kaur-16-eno es formado a partir de GGPP en dos pasos catalizados por dos enzimas; la *ent*-CPP sintasa y la *ent*-kaureno sintasa. Sin embargo, en 1997, se demostró que el GGPP es convertido a *ent*-kaur-16-eno vía *ent*-CPP en *Phaeosphaeria* L487 por una sencilla enzima (Esquema 7).

Sesterterpenos (C_{25}): Aunque muchos ejemplos son conocidos de este tipo de compuestos, normalmente son encontrados en hongos y en organismos marinos teniendo como origen común el geranilfarnesil pirosfosfato. El tipo más común de sesterterpenoides está ejemplificado en la escalarina. Esta estructura puede justificarse biosintéticamente como el resultado de una secuencia de ciclación concertada del geranil-farnesil pirofosfato por acción de una ciclasa, análogamente a lo que sucede con el óxido de escualeno en los triterpenos (Esquema 8).



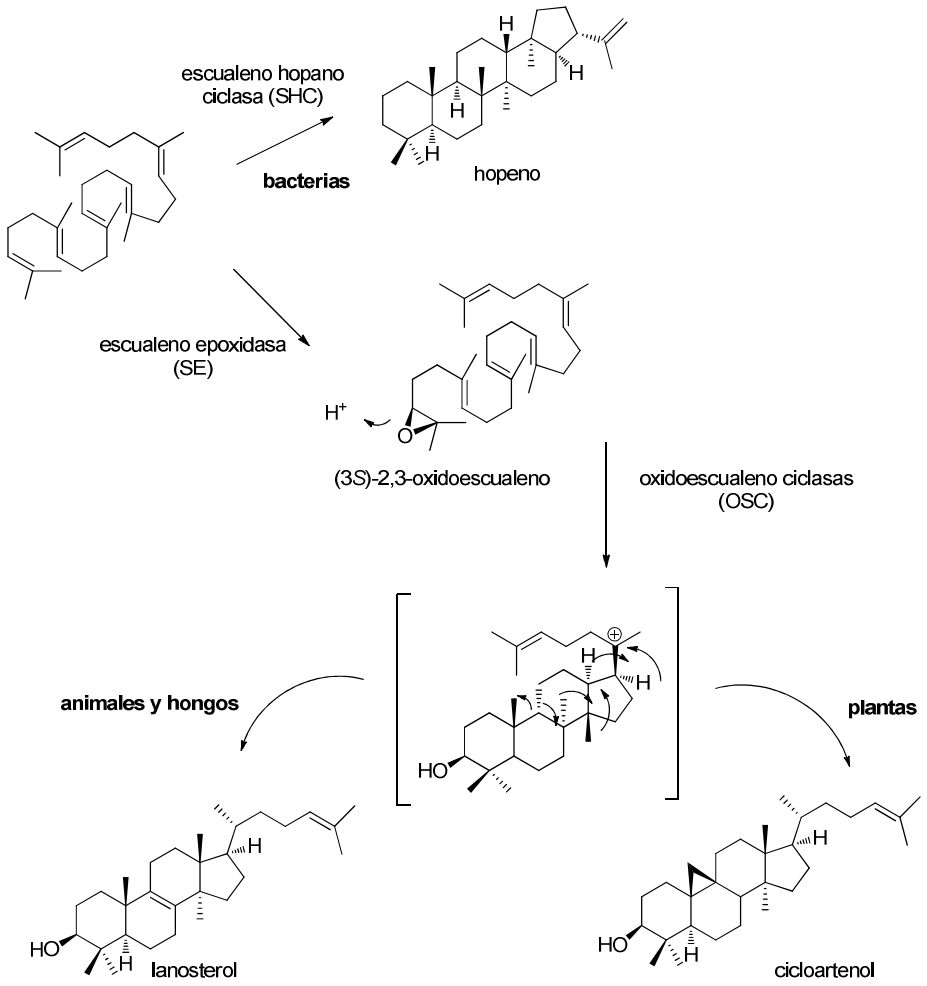
Esquema 8. Biosíntesis de la escalarina

Triterpenos (C_{30}): El SQ y OS son los precursores que dan lugar a las diferentes familias de triterpenos mediante ciclaciones inducidas enzimáticamente.[6] Por ejemplo, la ciclación del SQ por la escualeno-hopeno ciclasa da lugar al hidrocarburo pentacíclico hopeno (Esquema 9), precursor biosintético de los hopanoides bacterianos que modulan la permeabilidad de la membrana celular. Dicha enzima dimérica tiene dos dominios en cada uno de sus monómeros que adoptan un doble plegamiento α-barril. Los dos dominios se pliegan para encerrar un lugar activo central hidrofóbico. En la óxidoescualeno ciclasa encontramos dos canales diferentes, uno apolar y otro canal polar y accesible al disolvente que se dirige al centro activo de la enzima.[6q]

La epoxidación enantioselectiva de escualeno usando oxígeno molecular catalizada por la escualeno epoxidasa da lugar a (3*S*)-2,3-oxidoescualeno. Sobre este sustrato actúan un gran número de oxidoescualeno ciclasas, que son capaces de generar productos naturales mediante la formación de carbocationes intermedios. Estos intermedios carbocatiónicos experimentan reordenamientos[6e,f] (Wagner-Meerwein) que

dan lugar a diferentes esqueletos como el lanosterol (animales y hongos) y cicloartenol (plantas) (Esquema 9).[6n,o,q,15] Además estas ciclaciones pueden ser concertadas[16] o no concertadas[17], y para ello la enzima fuerza una conformación *silla-bote-silla* en la cadena del OS para la mayoría de las oxidoescualeno ciclasas. En el caso de las escualeno ciclasas la conformación forzada es en muchos casos, la *silla-silla-silla*, aunque podemos encontrar algunas excepciones.

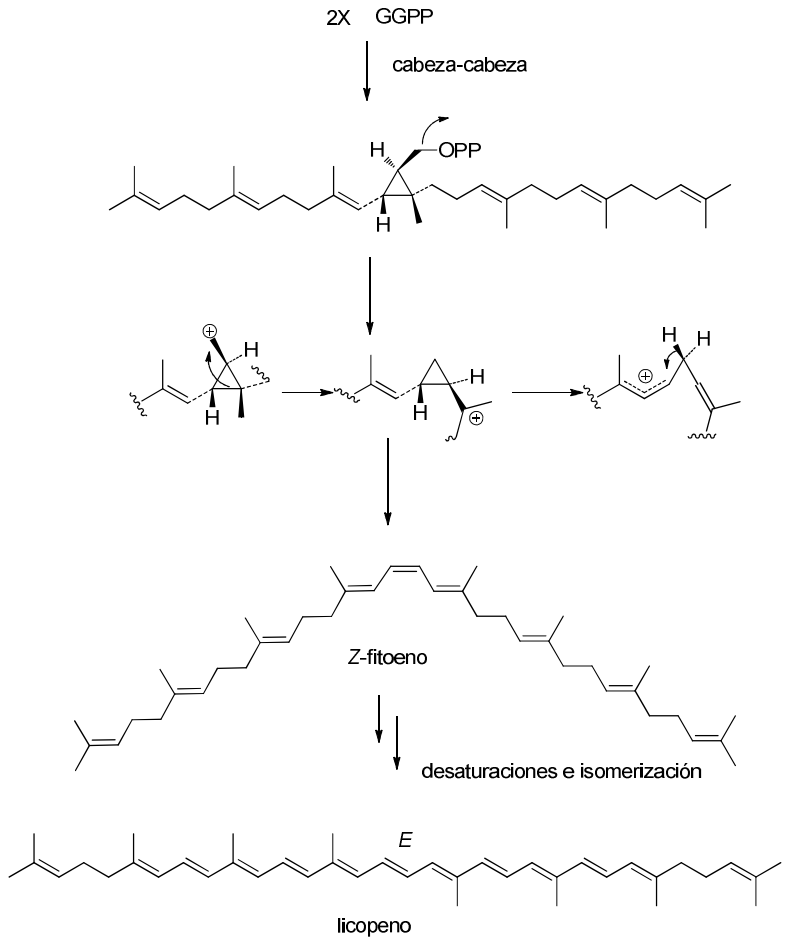
Alrededor de 20.000 triterpenos son conocidos en la naturaleza, muchos de ellos aparecen en su forma libre, mientras que otros aparecen en forma de glicósidos (saponinas) u otras combinaciones. Desde 1985, Connolly y Hill revisan anualmente los nuevos triterpenos aislados del reino de las plantas.[18] Los triterpenos comprenden un gran número de diferentes tipos de compuestos que, de acuerdo a las diversas características de sus esqueletos, pueden ser divididos en acíclicos, mono-, bi-, tri-, tetra- y pentacíclicos llegando a configurar un total de más de 100 esqueletos diferentes considerándose una de las familias de mayor diversidad dentro de los terpenos.



Esquema 9. Rutas biosintéticas de triterpenos a partir de escualeno y oxidoescualeno ciclasa

De entre toda la amplia gama de triterpenos, los más extendidos en la naturaleza son los triterpenos tetracíclicos (ej: protostanos, cicloartanos, dammaranos y eufanos) y los triterpenos pentacíclicos (ursanos, gammaceranos, lupanos, oleananos y hopanos).

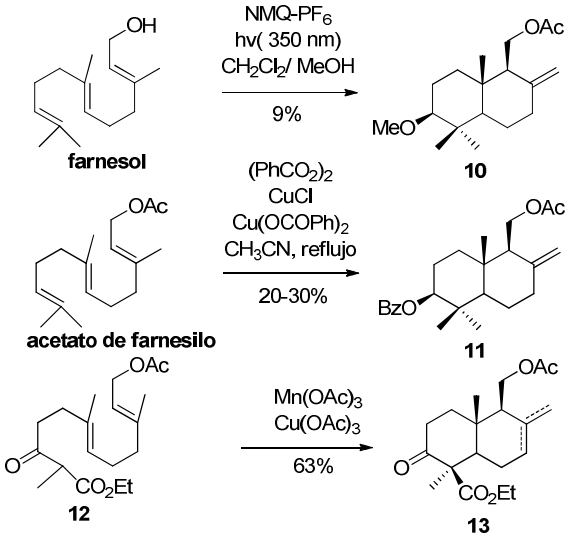
Tetraterpenos(C_{40}): Los tetraterpenos están representados mayoritariamente por un solo grupo de compuestos, los carotenoides, aunque son conocidas muchas otras variantes estructurales. La biosíntesis del esqueleto del tetraterpeno fitoeno implica el acoplamiento cabeza-cabeza de dos moléculas de geranil-geranil difosfato (GGPP), en una secuencia similar a la del escualeno en triterpenos. Sin embargo, el intermedio ciclopropánico (prefitoeno difosfato) se diferencia en que el catión alílico resultante de su ionización en lugar de aceptar un hidruro del NADPH, elimina para dar un doble enlace *Z* en plantas y hongos, mientras en bacterias da lugar a uno *E*. A continuación, la conjugación en el centro de la molécula es extendida por una secuencia de reacciones de deshidrogenación retirando pares de hidrógenos alternativamente a cada lado del sistema para dar lugar al licopeno (Esquema 10).



Esquema 10. Biosíntesis del precursor de los carotenos

I. 2. Ciclaciones biomiméticas: Cloruro de titanoceno

Desde los trabajos pioneros realizados por van Tamelen y Johnson,[19] a los recientes progresos realizados por Corey[20] sobre ciclaciones de polienos, parte de los esfuerzos de los químicos se han centrado en mimetizar a la naturaleza a nivel de laboratorio. Uno de los ejemplos más representativos de estos procesos biosintéticos es la ciclación de 2,3-(*R*)-oxidoescualeno mediante las óxido escualeno ciclasas hacia triterpenos tetra- y pentacíclicos en un sólo paso. Basadas en este proceso, se han realizado varias síntesis de triterpenos, donde la mayoría comparten una estrategia de polianelación catiónica.[15,21] El empleo de esta metodología sintética presenta un serio inconveniente, la necesidad de funcionalizar algunas posiciones en el precursor de la ciclación, con el doble objetivo de estabilizar los intermedios catiónicos y de controlar el paso de finalización del proceso.[22] Por eso otras aproximaciones similares utilizando química de radicales son más eficaces y ponen de manifiesto que los carbocationes no son únicos para llevar a cabo ciclaciones diastereoselectivas para la construcción de esqueleto de terpenoides.[23] Entre ellas merecen destacarse los procesos PET (photoinduced electron transfer) desarrollados por Demuth *et al.*[24], los trabajos de benzoiloxi radicales realizados por Breslow, donde tanto la iniciación como la terminación son procesos oxidantes,[25] o el uso de acetato de manganeso (III) vía enolatos de Mn como iniciador radicalario (Esquema 11).[26]

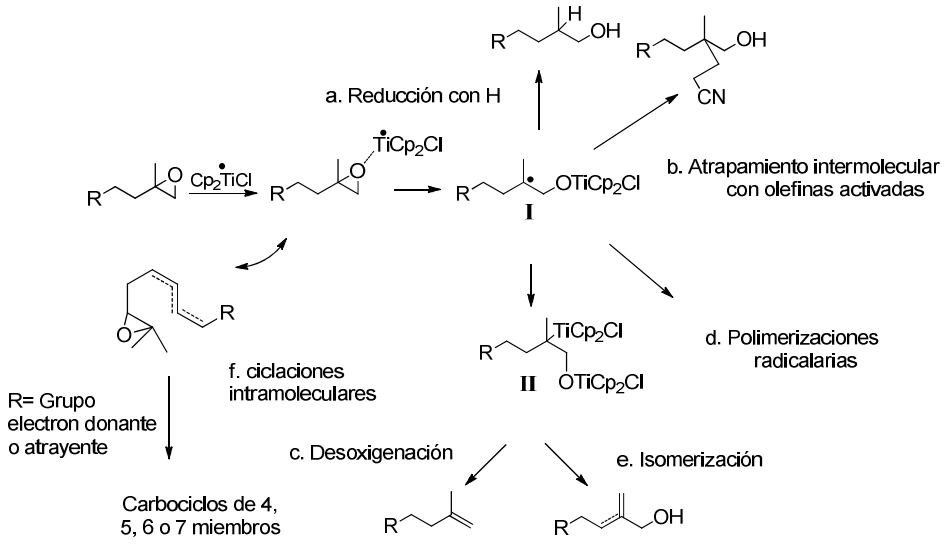


Esquema 11. Diferentes procesos radicalarios aplicados en síntesis de terpenoides

En este contexto, entre 1988 y 1994, Rajanbabu y Nugent describieron la reacción de ruptura homolítica de oxiranos mediada/catalizada por $Cp_2Ti^{III}Cl$ que origina la apertura hacia un β-titanoxi-radical.[27] La regioselectividad de la apertura del

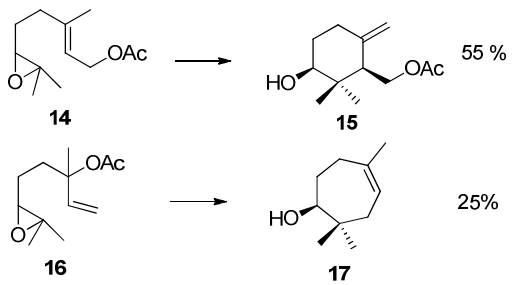
anillo oxirano vendrá definida por la estabilidad del radical formado[28] y por las interacciones estéricas entre los ligandos del catalizador y el sustrato,[29] lo que habitualmente genera el radical más sustituido.[30]

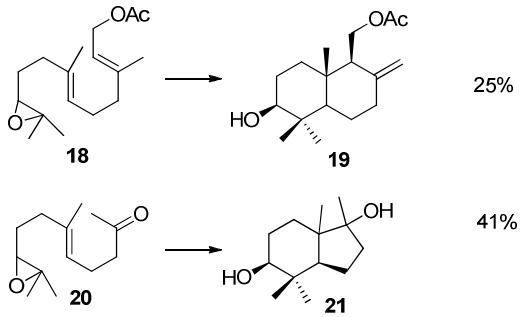
Desde entonces muchas aplicaciones han sido descritas utilizando como herramienta principal el radical carbonado que se genera. Entre otras, la reducción a alcoholes, la desoxigenación a olefinas y la formación de enlaces C-C en adiciones radicalarias inter e intramoleculares sobre insaturaciones C-C, C-O y C-N (Esquema 12).[31] Por otro lado, el desarrollo de una nueva estrategia radicalaria apropiada para la



Esquema 12. Diversas aplicaciones del cloruro de titanoceno

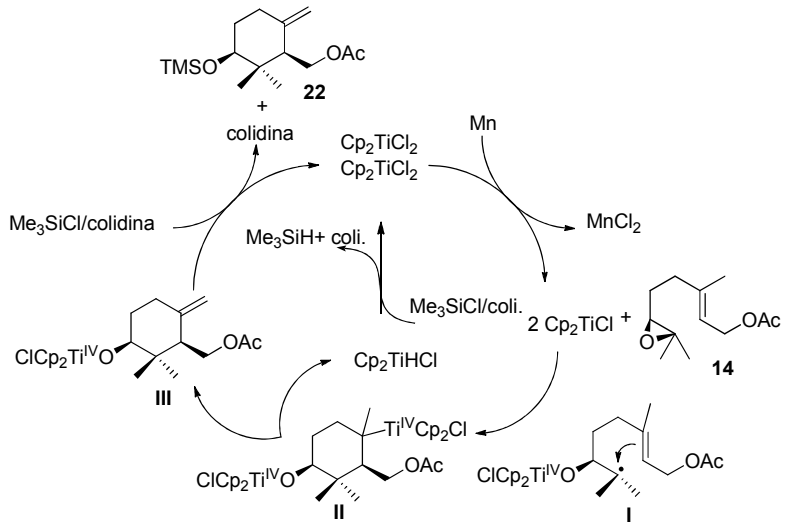
construcción de terpenos mono- y policíclicos mediante la apertura de epoxipoliprenos por cloruro de titanoceno se llevó a cabo por primera vez en nuestro grupo en 2001.[32] Inicialmente, la metodología servía para la construcción de anillos ciclohexánicos y cicloheptánicos funcionalizados en procesos de monociclación o ciclaciones en cascada (Esquema 13).





Esquema 13. Primeros resultados en síntesis de terpenoides mediante Ti (III)

Para estas ciclaciones radicalarias mediadas por Ti(III) se desarrolló una versión catalítica (Esquema 14), reduciéndose considerablemente las proporciones de Cp_2TiCl_2 empleadas y las elevadas diluciones de la versión estequiométrica.[33] Así, el empleo de la combinación de 2,4,6-colidina/TMSCl o hidrocloruro de 2,4,6-colidinio, que son compatibles con los oxiranos, regenera Cp_2TiCl_2 desde los enlaces Ti-O y Ti-C formados en el transcurso de la reacción, cerrando de esta manera el ciclo catalítico. Este protocolo catalítico es altamente quimioselectivo en la apertura del epóxido conduciendo como en el caso de la versión estequiométrica a β-titanoxi-radicales. Este ciclo catalítico permite una menor concentración de promotor y atrapador radicalario en el medio, traduciéndose en un rendimiento ligeramente mayor en el cierre de varios ciclos, dado que los intermedios radicalarios no son prematuramente atrapados.



Esquema 14. Versión catalítica en la ciclación de epoxipoliprenos

I. 3. Objetivos

Desde 1983, nuestro grupo ha estudiado el aislamiento y elucidación estructural de productos naturales de plantas medicinales o aromáticas de la Península Ibérica, con especial énfasis en aquellas endémicas de Sierra Nevada y Almería.[34] Paralelamente se fué desarrollando otra línea de investigación hacia la síntesis de terpenos bioactivos.[35] Esta última ha dado lugar al descubrimiento de nuevas reacciones de reducción, pero sobre todo es destacable la puesta a punto de procesos de ciclaciones biomiméticas iónicas y radicalarias.[36] Por otra parte, los resultados de la línea original de Productos Naturales han servido para incorporar nuevos sintones homoquirales (*chiral pool*) como materiales de partida y contribuir así a la realización de síntesis más eficientes y respetuosas con el medio ambiente.

En esta Memoria se exponen los resultados de investigación que tienen por objetivo principal demostrar que la síntesis de diferentes triterpenos se puede abordar eficazmente utilizando la estrategia de ciclaciones radicalarias, basada en la apertura de oxiranos mediante cloruro de titanoceno. Asimismo, se pondrá de manifiesto que la versatilidad de esta herramienta sintética, posibilita una nueva vía en la síntesis estereoselectiva de terpenos gamma-dioxigenados en el anillo A de terpenos. De esta forma se plantea la consecución de los siguientes objetivos concretos:

1. Estudio bibliográfico sobre triterpenos inusualmente ciclados[i]:

En la naturaleza existe un considerable número de triterpenos que poseen estructuras derivadas de procesos de ciclación diferentes de aquellos que conducen a los triterpenos tetra- o pentacíclicos. Estos triterpenos son conocidos como "*triterpenos inusualmente ciclados*". En relación con ellos, en 1989 se aisló achilleol A (**6**), y posteriormente en 1990 se aisló achilleol B (**5**).[51] Ambos triterpenos fueron aisladosr de la planta *Achillea odorata* (*Asteraceae*) por nuestro grupo de investigación. Estos dos compuestos se caracterizan por tener un esqueleto monocíclico y tricíclico respectivamente (Figura 1). Desde el punto de vista biosintético sus estructuras pueden ser clasificadas como irregulares pues contienen menos ciclos que los triterpenos originados en las ciclaciones del OS catalizados por las OS ciclasas. A partir de entonces, la sucesiva aparición de nuevos triterpenos cuyo origen biosintético también podría ser clasificado como irregular, tales como camellioles A (**8**) y C (**23**), preoleanatetraeno (**24**), *seco*-C-

[i] Durante el desarrollo de la memoria utilizaremos la terminología "*triterpenos inusualmente ciclados*" o "*triterpenos irregulares*" indistintamente refiriéndonos al mismo tipo de compuestos.

oleanano (**7**), y *seco*-C-amirina (**9**), demostraba que la existencia de estas moléculas no era puntual. Se decidió entonces revisar en esta Memoria de manera sistemática la aparición de estos *"triterpenos inusulamente ciclados"* en la naturaleza o en el laboratorio, su actividad, así como conocer su origen biosíntetico y los métodos utilizados en su síntesis química.

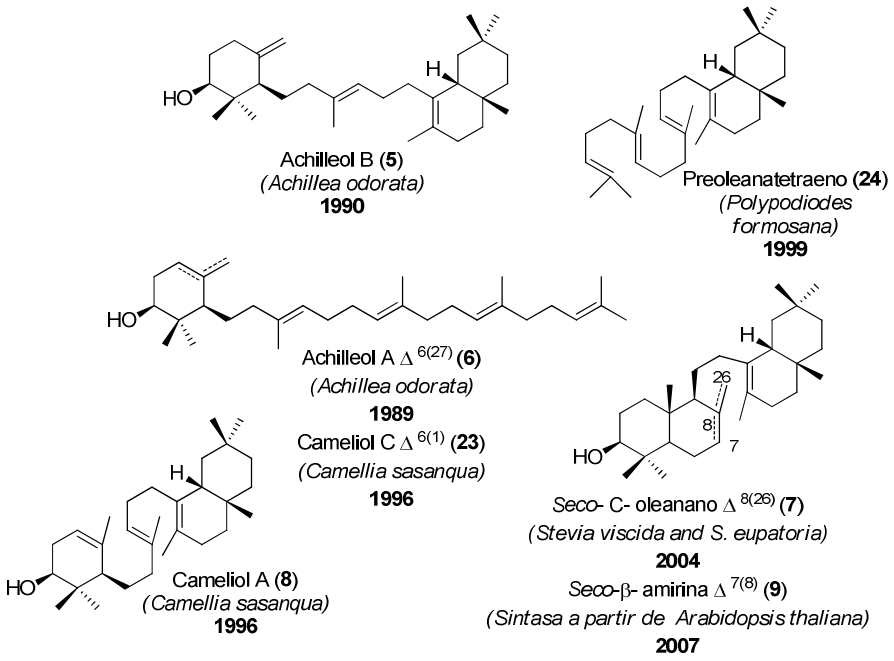


Figura 1. Triterpenos inusualmente ciclados

2. Síntesis asimétrica de triterpenos bicíclicos mediante el empleo de cloruro de titanoceno: Preparación de los componentes activos de la Mirra.

En relación con los triterpenos irregulares, nos llamó la atención la existencia de cuatro moléculas merecedoras de llevar a cabo su síntesis por su potente bioactividad: mirrhanoles A (**1**) y B (**4**) y mirrhanonas A (**2**) y B (**3**) (Figura 2). Estas sustancias deben su nombre a su fuente natural, que es la legendaria mirra (*Balsamodendron mukul*), y se caracterizan por ser antiinflamatorias, reducir el colesterol y la formación de placas en las arterias, llegando a ser incluso más potentes que la hidrocortisona y con menos efectos secundarios.[45a]

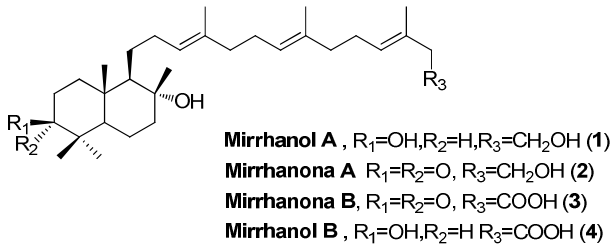


Figura 2. MOLECULAS OBJETIVO

3. Síntesis asimétrica de triterpenos irregulares mediante el empleo de cloruro de titanoceno: Síntesis de achilleol B, achilleol A, *seco*-C-oleananos.

Se pretende aplicar una nueva estrategia de carbociclación radicalaria mediante el empleo de monocloruro de titanoceno para la síntesis asimétrica de triterpenos irregulares. Dicha metodología, desarrollada en nuestros laboratorios da lugar a síntesis realmente competitivas (Esquema 15) presentando una serie de ventajas frente a los métodos descritos hasta la fecha como son:

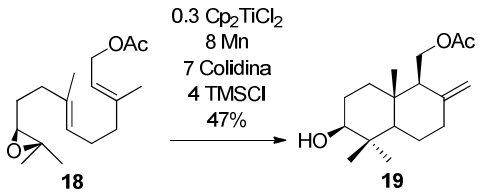
-Se puede realizar a temperatura ambiente, bajo condiciones suaves.

-Compatible con un gran número de grupos funcionales y protectores.

-Se puede realizar tanto en su versión catalítica como estequiométrica.

-Alta estereoselectividad.

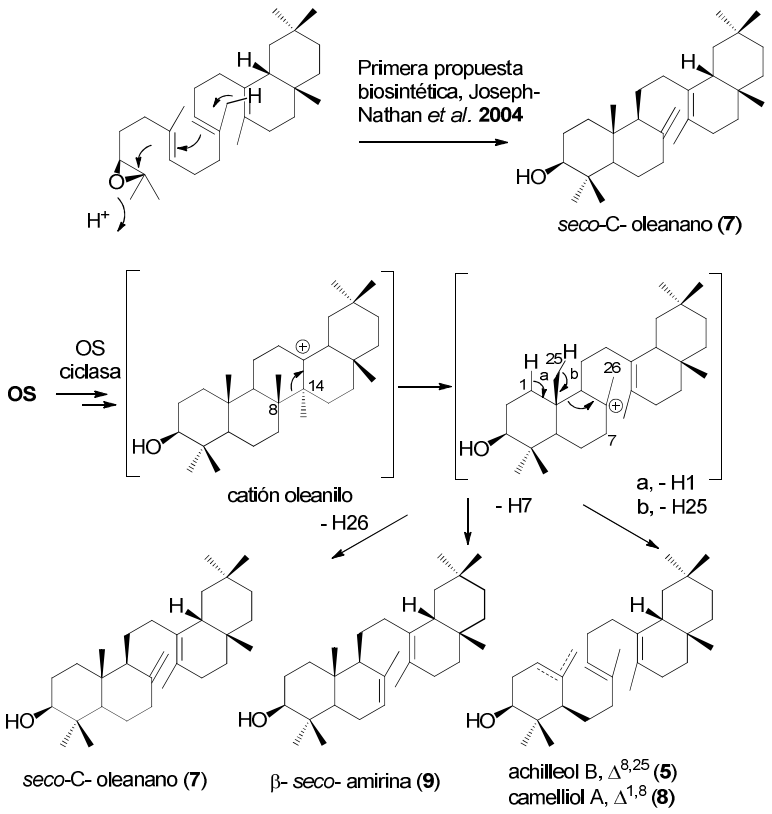
-Alta regioselectividad en el proceso de terminación.



Esquema 15. Ciclación radicalaria mediante Cp_2TiCl

Teniendo en cuenta que los triterpenos irregulares poco a poco se van revelando como más ubícuos de lo que se podría pensar, y utilizando la potencialidad de esta nueva estrategia radicalaria, se pretende aplicar en las primeras síntesis asimétricas de **achilleol B** (**5**), **achilleol A** (**6**) y ***seco*-C-oleanano** (**7**). Estas moléculas se han fijado como moléculas objetivo al presentar un desafío sintético considerable y por su peculiar estructura de *seco*- triterpenos que les confiere una relevante importancia biosintética. Además, su síntesis química nos ayudaría a asignar inequívocamente la estereoquímica relativa de la unión interanular D-E en el caso de achilleol B (**5**).

Respecto a su biosíntesis, achilleol A (**6**) se considera proveniente de una simple interrupción de la cascada de ciclaciones del OS tras el cierre del primer ciclo de 6 miembros. Por otra parte, recientemente se han descrito homólogos de OSC que además son capaces de romper anillos preformados.[37] De esta forma achilleol B (**5**) podría provenir de la ruptura de un intermedio catiónico pentacíclico mediante un proceso de retrociclación y ser considerado como un *seco*-B-C triterpeno (Esquema 16).



Esquema 16. Biosíntesis para seco-triterpenos Ebizuka *et al*. **2007**

La tercera molécula objetivo se trata del primer *seco*-C-oleanano natural (**7**) y fue aislada de *Stevia viscida* y *S. eupatoria* por el Prof. Joseph-Nathan. Su origen biosintético deriva como consecuencia de una única fragmentación a partir de la β-amirina a través del enlace C8-C14.[50]

4. Aplicación de la metodología de ciclación radicalaria hacia la síntesis de compuestos terpenoides gamma dioxigenados en el anillo A:

Entre los diferentes terpenoides bioactivos hay un gran número de ejemplos que poseen anillos gamma dioxigenados estereoquímicamente bien definidos. Algunos

ejemplos pueden verse en la figura 3 y en ellos se pone de manifiesto que el alcohol primario y secundario poseen una configuración relativa *anti*.

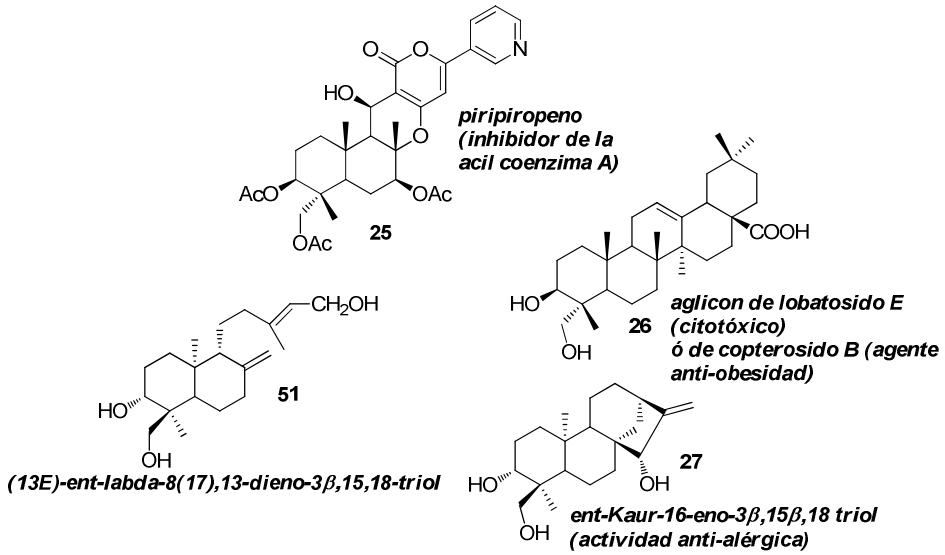
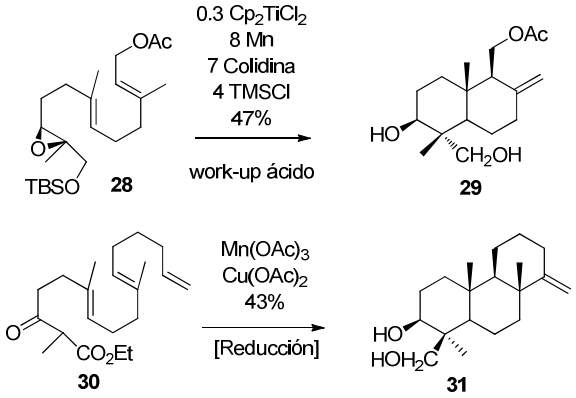


Figura 3. Ejemplos de sustancias encontradas en la naturaleza con anillo gamma dioxigenados

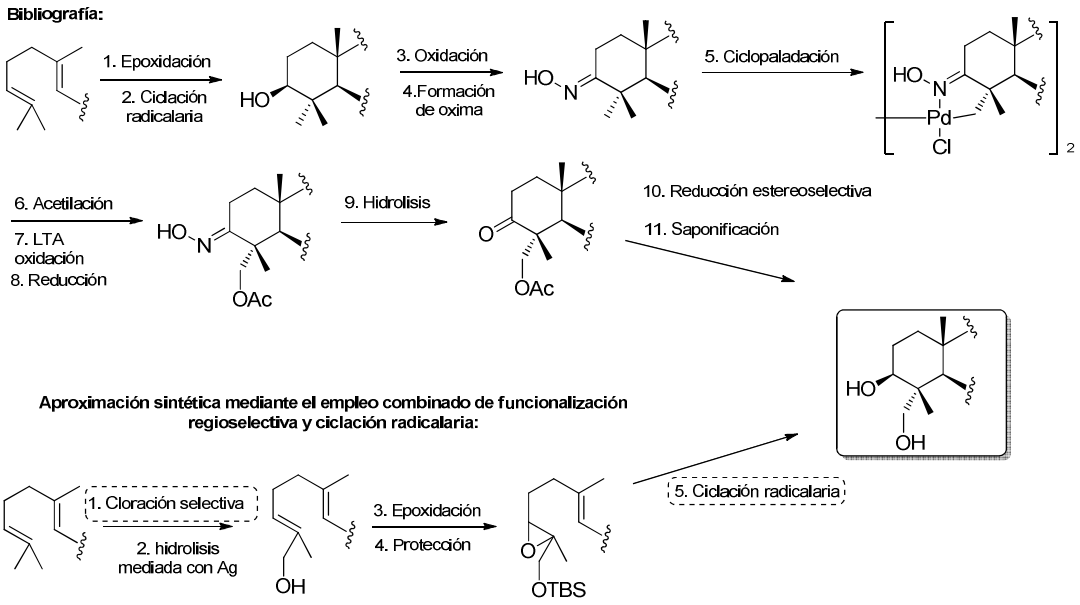
Aunque este tipo de estructuras han sido sintetizadas previamente por Snider[26a] y colaboradores utilizando $Mn(OAc)_3$ mediante la generación oxidativa de radicales, sin embargo, la estereoselectividad en este tipo de carbociclaciones conduce a una disposición relativa *syn* entre las funciones oxigenadas (Esquema 17). La utilización de la química del Cp_2TiCl, sin embargo lleva a la estereoquímica adecuada *trans*[38] y podría ser eficaz para acceder a las moléculas antes mencionadas.



Esquema 17. Carbociclación radicalaria hacia compuestos gamma dioxigenados

También se ha descrito otra estrategia para la construcción de fragmentos gamma dioxigenados mediante funcionalización remota utilizando los métodos

descritos por Baldwin.[39] Sin embargo, estos transcurren en 9 pasos y se realizan sobre sustratos más complejos (Esquema 18).



Esquema 18. Comparativa de método de Baldwin y el desarrollado en la memoria

A la vista de las consideraciones anteriores se decidió aplicar la metodología radicalaria bajo los conceptos de economía de pasos y de síntesis ideal [ii] para sintetizar el diterpeno (13*E*)-*ent*-labda-8(17),13-dieno-3β,15,18-triol (**51**) aislado de las hojas de *Rubus chingii* y de las frutas de *Rubus foliolosus*[40] (Figura 3).

[ii] "*Reacciones de construcción que no implican refuncionalizaciones intermedias y que conducen directamente a la estructura objetivo, no sólo a su esqueleto sino además a su correcta funcionalización*"

II. ANTECEDENTES BIBLIOGRÁFICOS

II. 1. Triterpenos irregulares

Los conocidos como *"triterpenos inusualmente ciclados"* mencionados en el apartado anterior de esta Memoria de acuerdo con el tipo de origen biosintético, se pueden agrupar en las siguientes clases:

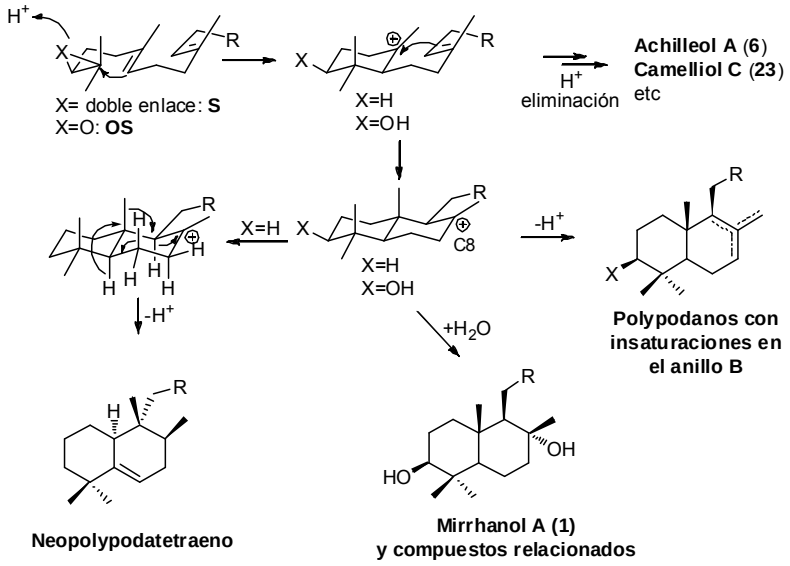
a) ***Triterpenos que provienen de una ciclación incompleta del correspondiente precursor.*** Las ciclaciones comienzan en la unidad terminal de isopropilideno o en el correspondiente epóxido y da lugar a esqueletos triterpénicos mono-, bi- y tricíclicos.

-Triterpenos monocíclicos: achillanos. Deben su nombre a achilleol A (**6**), que fue el primer triterpeno monocíclico en ser descrito, el cual fue aislado de la planta *Achillea odorata* (*Asteraceae*) en 1989 por Barrero *et al.*[41] Cabe además mencionar que recientemente se ha descrito la producción de este compuesto por mutantes de la lanosterol y cicloartenol sintasa.

Su biosíntesis tiene lugar por parada en la cascada de ciclaciones tras el primer paso de ciclación del óxido de escualeno, seguida de abstracción de un protón del metilo en α respecto del carbocatión cíclico que conduce a un doble enlace exocíclico (Esquema 19). En cuanto a su bioactividad se ha observado un efecto reforzador de las membranas celulares. Allí las interacciones de van der Waals contribuyen a estabilizarla, disminuyendo la permeabilidad del agua de las vesículas donde la longitud de la cadena parece el parámetro crítico.[42]

-Triterpenos bicíclicos: polypodanos. Su nombre proviene de la familia *Polypodaceae* donde han sido descritos.[43] Los polypodanos oxigenados en C-3 son encontrados en *Balsamodendron mukul* (*Burseraceae*)[44] y *Cratoxylum cochinchinense* (*Hypericaceae*).[45] De estos, podemos destacar mirrhanol A (**1**) y mirrhanol B (**4**), los cuales poseen unas interesantes actividades antiinflamatorias más potentes que la hidrocortisona. Así, mirrhanol A (**1**) es considerado un posible candidato como agente anti-inflamatorio y probablemente con menos efectos secundarios que esta.[44a]

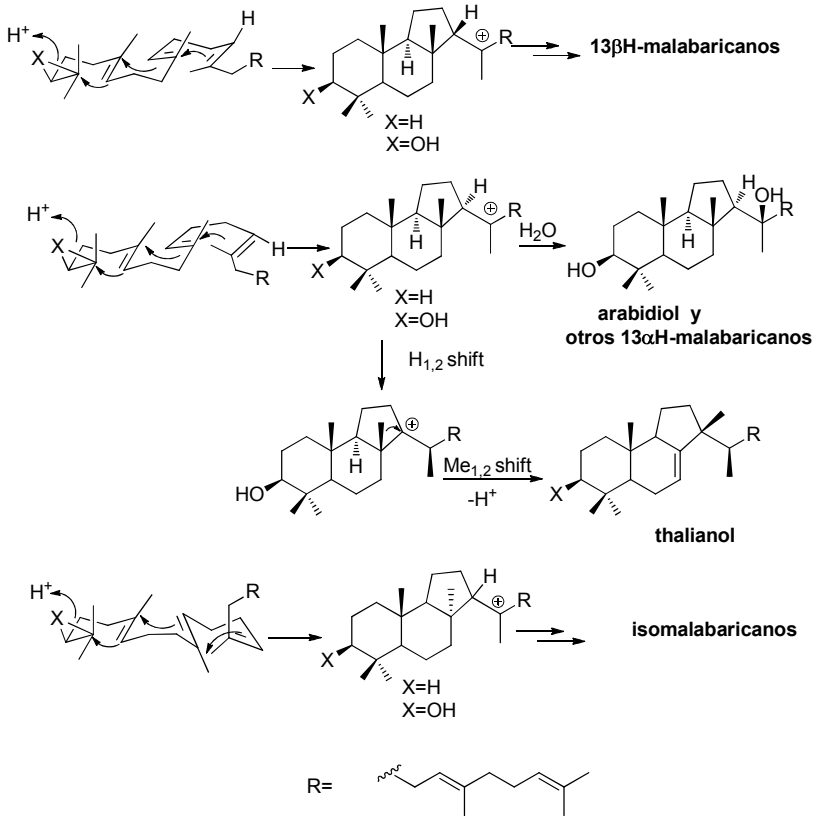
Respecto a su biosíntesis podemos decir que se originan por atrapamiento del carbocatión bicíclico en C-8 por una molécula de agua o bien por eliminación de alguno de los protones vecinales después del proceso de ciclación (Esquema 19).



Esquema 19. Biosintesis para achillanos y polypodanos

-Triterpenos tricíclicos 6,6,5: Malabaricanos, malabaricanos reordenados e isomalabaricanos reordenados. La diferencia entre malabaricanos e isomalabaricanos es la estereoquímica de la unión de los anillos B-C, siendo *trans-anti-trans* y *trans-syn-trans*, respectivamente. Los malabaricanos reordenados se diferencian de sus precursores los malabaricanos en el metilo C-30, el cual está ausente en el C-8 reordenando a la posición C-13 (Esquema 20).

Los isomalabaricanos han sido encontrados exclusivamente en esponjas marinas, la mayoría en el Pacífico, en muchos casos son los causantes de su pigmentación amarilla y se caracterizan por poseer actividades citotóxicas. Estos se pueden clasificar a su vez en tres grupos en función de su estructura y origen: esteliferinas, ácidos globosteláticos, aislados casi exclusivamente de *Rhabdastrella globostellata*, y finalmente jaspolidas-esteletinas, que se caracterizan por tener oxidadas las cadenas laterales en forma de anillos de pirona o ácidos carboxílicos.

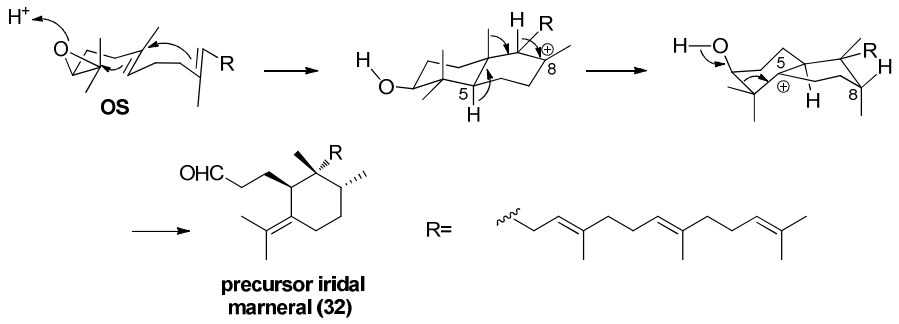


Esquema 20. Biosíntesis de malabaricanos e isomalabaricanos

b) Triterpenos que provienen de la ciclación de S o de OS hacia triterpenos policiclicos y posterior rupturas anulares del sistema preformado. Las oxidoescualeno ciclasas (OSCs) han demostrado catalizar formaciones de enlaces carbono-carbono y reordenamientos de protón o metilo para finalmente producir estructuras policíclicas. Adicionalmente, en las recientes investigaciones de Matsuda y Ebizuka se han identificado ciclasas capaces de catalizar la fragmentación de estructuras policíclicas que han dado lugar al *seco*-A-triterpeno conocido como marneral (**32**) junto con su derivado reducido marnerol[46] y otras OSCs que han dado lugar a *seco*-amirinas.[37] (Esquema 21)

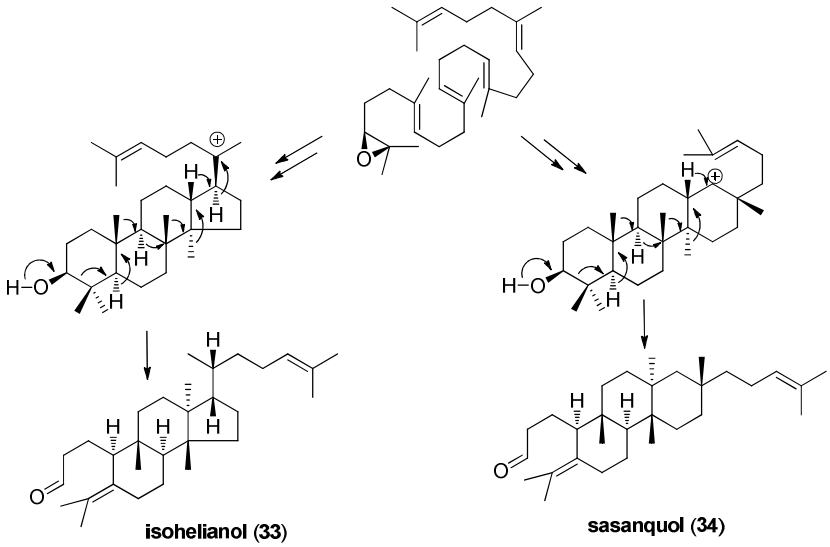
-Triterpenos *seco*-biciclicos: iridales. El esqueleto de iridal se puede definir como un 3,4-*seco*-abeo-10→9,27 polypodano. Los productos naturales que lo contienen pueden ser clasificados en cuatro grupos: iridales sencillos, espiroiridales, glicósido iridales y oxaespiroiridales. Los iridales son encontrados en plantas de la familia *Iridaceae*, del género Iris aunque también pueden ser encontradas en el género *Belamcanda* y *Tigridia*. [47b] Marner postuló que el origen biosintético de los iridales

implica intermedios similares a los polypodanos, aunque la estereoquímica indica que el doble proceso de ciclación debe proceder a través de una conformación silla-bote de OS conduciendo a un carbocatión bicíclico que tras varias migraciones 1,2 da lugar a un intermedio que mediante fragmentación de Grob produce el aldehído precursor de los iridales (**32**). (Esquema 21)[47]



Esquema 21. Biosíntesis de Iridales

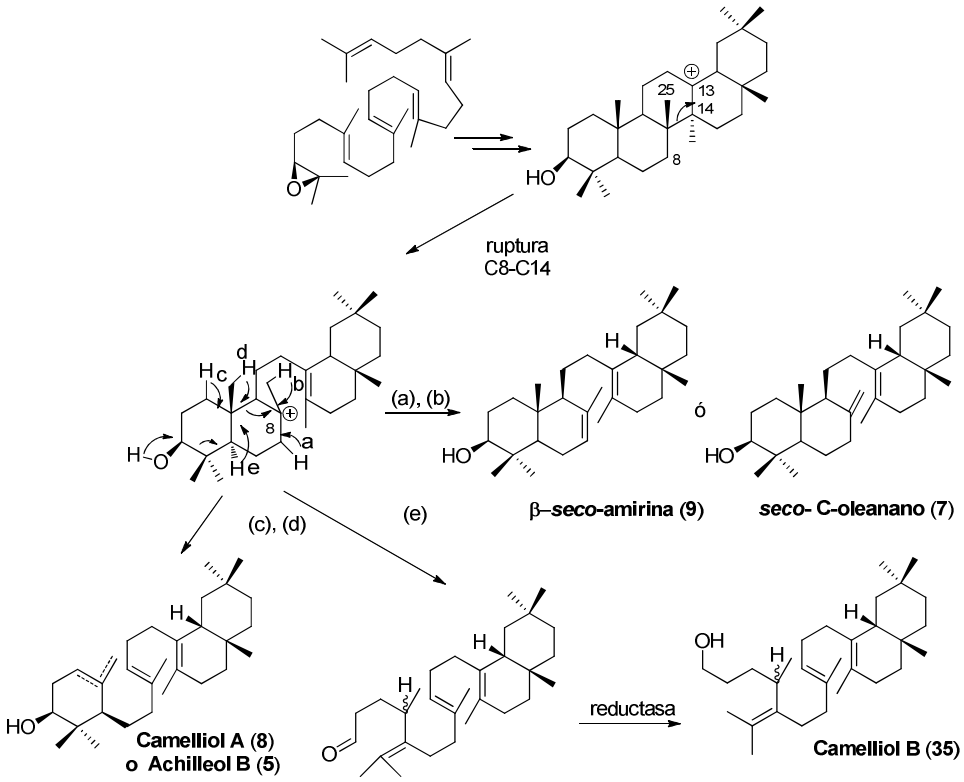
-Triterpenos *seco*-tetraciclicos. Sasanquol (**34**) aislado de la *Camellia sasanqua*[48] es el único 3,4 *seco* triterpeno proveniente de una fragmentación de Grob a partir de un intermedio catiónico de anillos fusionados 6-6-6-6. El resto provienen de cationes de anillos fusionados 6-6-6-5 como el isohelianol (**33**) aislado del polen del girasol (Esquema 22).[49]



Esquema 22. Esquema biosintético de triterpenos *seco*-tetracíclicos

-Triterpenos *seco*-pentacíclicos. Aunque las primeras propuestas biosintéticas de algunos *seco*-C-oleananos aislados de las *Asteraceas*, *Stevia viscida* y *Stevia eupatoria*

incluyeron dos procesos de ciclación diferentes para la generación de los anillos biciclicos A-B y D-E,[50] Ebizuka y colaboradores han descrito recientemente que el gen de la *A. thaliana Atlg*78500 codifica un homólogo de la OSC que tiene la capacidad de catalizar por una parte la ciclación hacia triterpenos pentacíclicos y posteriormente la consiguiente ruptura del anillo C para dar lugar a β-*seco*-amirina (**9**).[37] Además se ha propuesto que el carbocatión oleanilo podría conducir a β-*seco*-amirina (**9**) y *seco*-C-oleanano (**7**) a través de la ruptura del enlace C8-C14 y posterior eliminación de H-7 ó H-25 respectivamente (ruta a y b) (Esquema 23). Además camelliol A (**8**) o achilleol B (**5**)[51] podrían ser producidos después de un doble proceso de retrociclación por la ruptura del enlace C9-C10, seguida por desprotonación de H-1 ó H-25 (ruta c y d). Una tercera ruta que incluye una fragmentación de Grob originaría camelliol B (**35**).

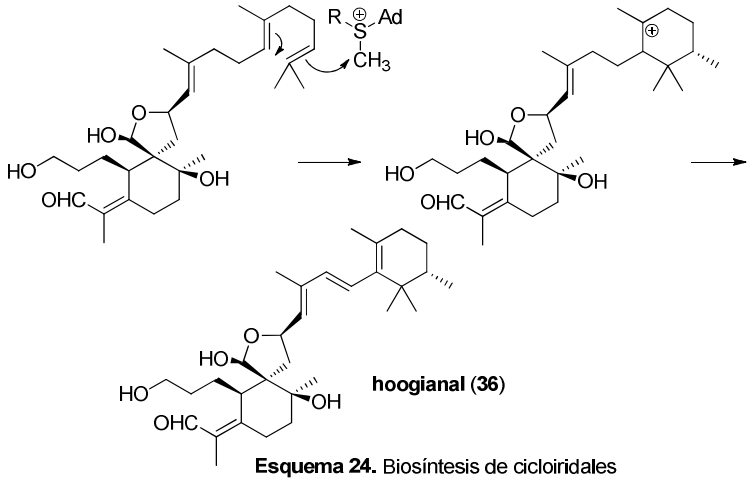


Esquema 23. Esquema biosintético de los triterpenos pentacíclicos

c) Triterpenos que provienen de dos ciclaciones independientes desde los precursores S u OS.

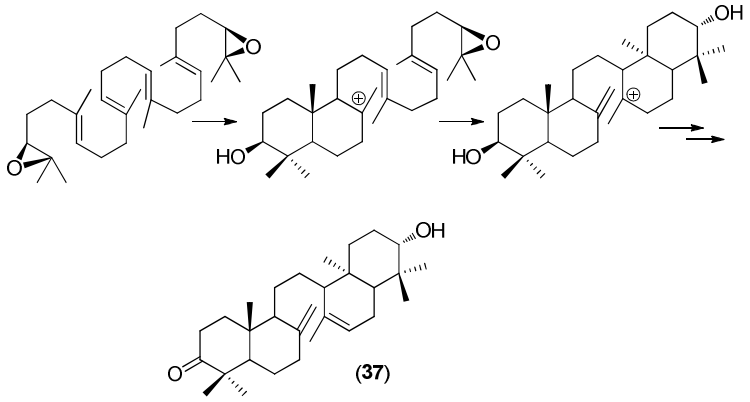
-Cicloiridales: Son derivados de los iridales en los que *S*-adenosilmetionina induce una monociclación en el doble enlace terminal de la cadena de farnesilo donde el metilo unido a sulfonio actúa como electrófilo iniciador justificándose así la presencia de carbonos adicionales en estos homotriterpenos (Esquema 24).[47a]

La degradación oxidativa de hoogianal (**36**)[52] da lugar a la β-irona, un compuesto de interés en perfumería por su fragancia a violeta.[53]



Esquema 24. Biosíntesis de cicloiridales

-2,3-22,23-Diepoxiescualeno como precursor: onoceranos. El origen de los onoceranos ocurre a través de una doble ciclación de bis-OS donde el catión bicíclico es estabilizado por desprotonación. Este compuesto bicíclico sufre a continuación un segundo proceso de ciclación en el epóxido situado al final de la cadena, formando un cabocatión tetracíclico que es el precursor de esta familia de compuestos. (Esquema 25)

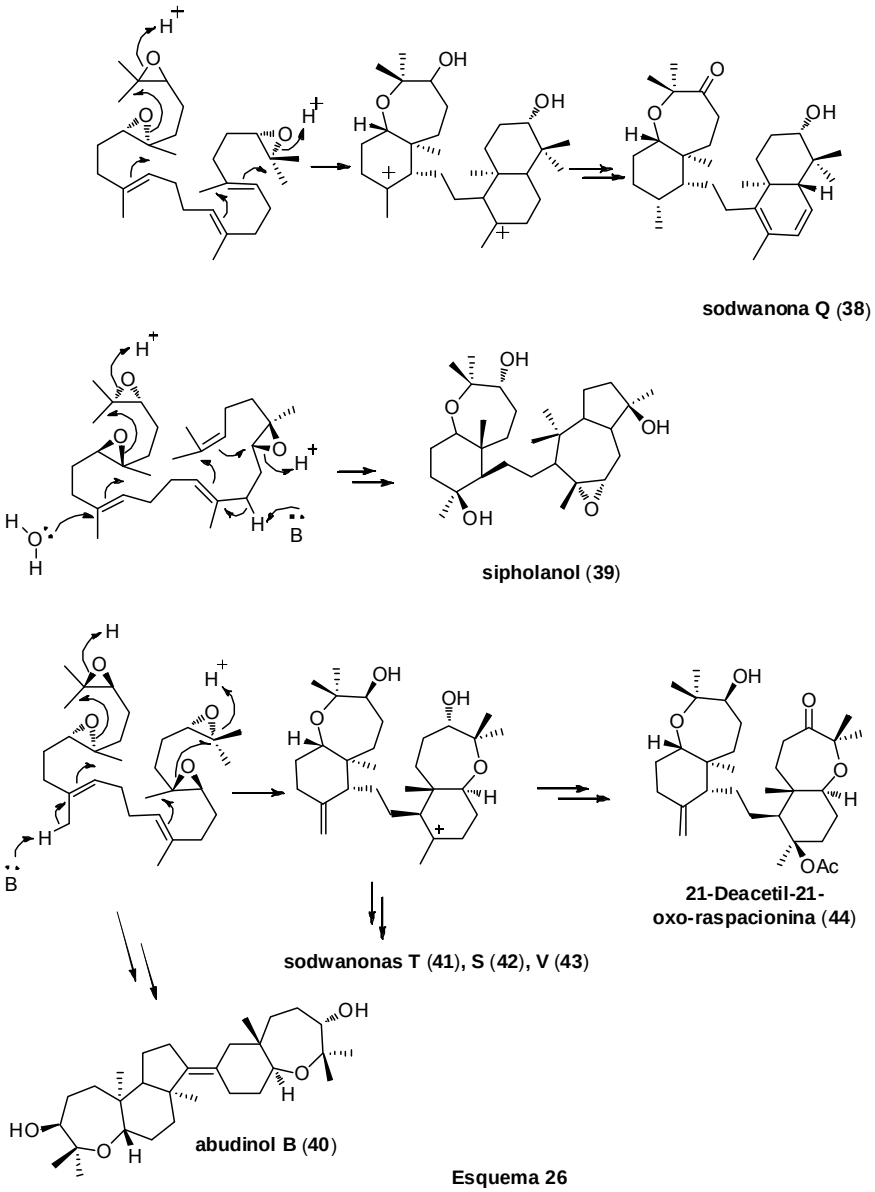


Esquema 25. Biosíntesis de onoceranos

-Otros triterpenos provenientes de la ciclación de poliepóxidos de S u OS:

Existen junto con las anteriormente explicadas otras familias de triterpenos derivadas de varios procesos distintos de ciclación procedentes de diepóxidos, triepóxidos o tetraepóxidos en diferentes posiciones de la cadena poliprenada del escualeno.[54] De este tipo se han descrito: siphonellinas como (**39**), dahabionona A o

neviotina B (2,3-6,7-diepoxiescualeno), sodwanona N (6,7-18,19-diepoxi-2,3-22,23-escualenotetraol), yardenonas (10,11-epoxi-2,3-22,23-escualenotetraol), sodwanonas (2,3-6,7-22,23-triepoxiescualeno), sipholanoles (2,3-6,7-18,19-triepoxiescualeno) como (**39**), algunas sodwanonas, raspacioninas y abudinol (2,3-6,7-18,19-22,23-tetraepoxiescualeno) (**40**) (Esquema 26).[56]



Esquema 26

II. 2. Estrategias en síntesis de triterpenos

Varias síntesis totales de triterpenos han sido descritas desde 1960, debido al interés provocado por sus desafiantes estructuras que pueden llegar a poseer hasta ocho centros quirales y por sus prometedoras actividades biológicas.[9, 55]

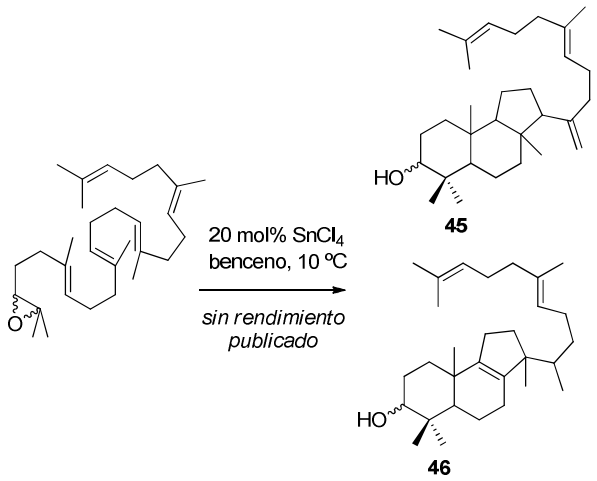
En esta Memoria se presentan en primer lugar los principales ejemplos de estas síntesis, que han sido clasificadas según se empleen ciclaciones catiónicas, radicalarias u otras aproximaciones que utilicen sintones más sencillos como materiales de partida. A continuación se expondrá una recopilación de antecedentes sobre síntesis de triterpenos irregulares.

Estrategias carbocatiónicas.

Los trabajos iniciales en el área de síntesis de terpenos biomiméticas datan de 1950 con los estudios independientes de Stork y Eschenmoser en la π–catión ciclación inducida por ácidos[15] y la propuesta de su relación en la biosíntesis de los triterpenos a partir del escualeno.

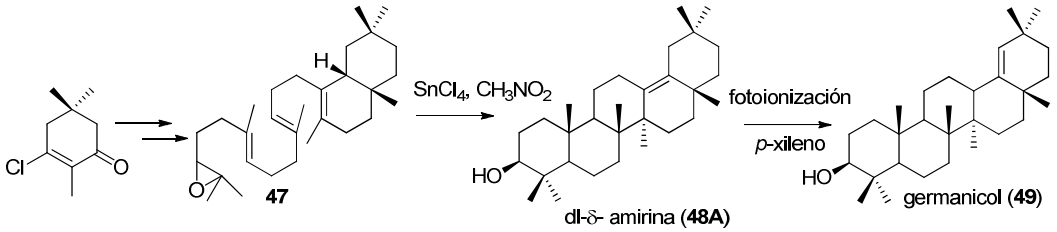
En 1961, van Tamelen utilizó el término biomimético en síntesis y se definió como *"una síntesis orgánica diseñada, al menos en los principales aspectos, en los caminos biosintéticos probados, o supuestos, para ser utilizados en la construcción natural del producto final"*. En este sentido este tipo de aproximaciones sintéticas se acercan a la *idealidad*[56] en mayor medida que otras síntesis, debido a que el esqueleto carbonado previo a la ciclación biomimética contiene el número de átomos preciso. Este precursor, tras la ciclación y una adecuada estéreo-, quimio- y regioselectividad, dará lugar al producto final en un menor número de etapas.

Con este planteamiento van Tamelen *et al.* desarrollaron trabajos en la carbociclación biomimética del OS donde el cierre del anillo C es favorecido por una adición Markovnikov 5-*exo* y en donde se observaron migraciones de metilo y protón como ocurre en la naturaleza para formar el lanosterol (Esquema 27). Se llegó a la conclusión de que dichas migraciones tienen lugar con mínima participación enzimática. Estas hipótesis fueron apoyadas en 1966 por los experimentos sínteticos utilizando ácidos de Lewis en la ciclación del OS.[57]



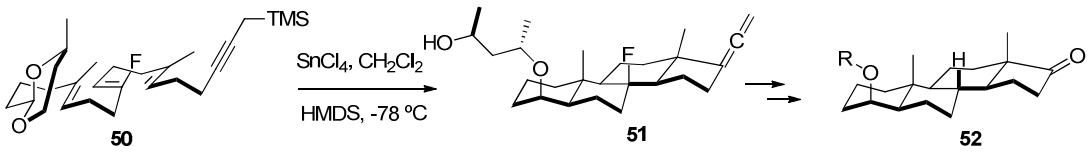
Esquema 27. Ciclación biomimética de van Tamelen

En 1972, van Tamelen *et al.* publicaron una síntesis total de δ-amirina (**48A**), en la cual los anillos D y E estaban preformados. La fotoionización de esta molécula en presencia de *p*-xileno dio lugar a germanicol (**49**) (Esquema 28).[58]



Esquema 28. Síntesis de Van Tamelen de δ- amirina y germanicol

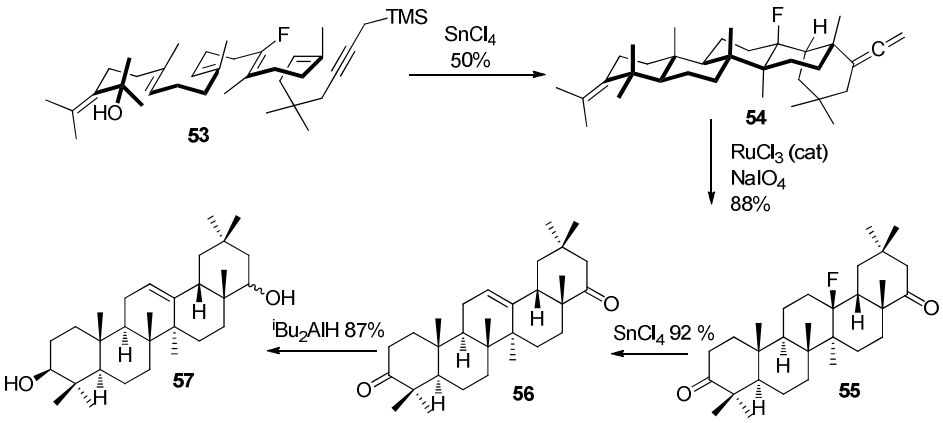
Uno de los principales contribuidores en el campo fue Johnson (Universidad de Stanford, CA) que trabajó en triterpenos y productos naturales esteroideos, desarrollando iniciadores para la ciclación (la mayoría acetales), terminadores para la ciclación (alquinos y alil silanos), y grupos estabilizadores de cationes (flúor) (Esquema 29).



Esquema 29. Trabajo de Johnson

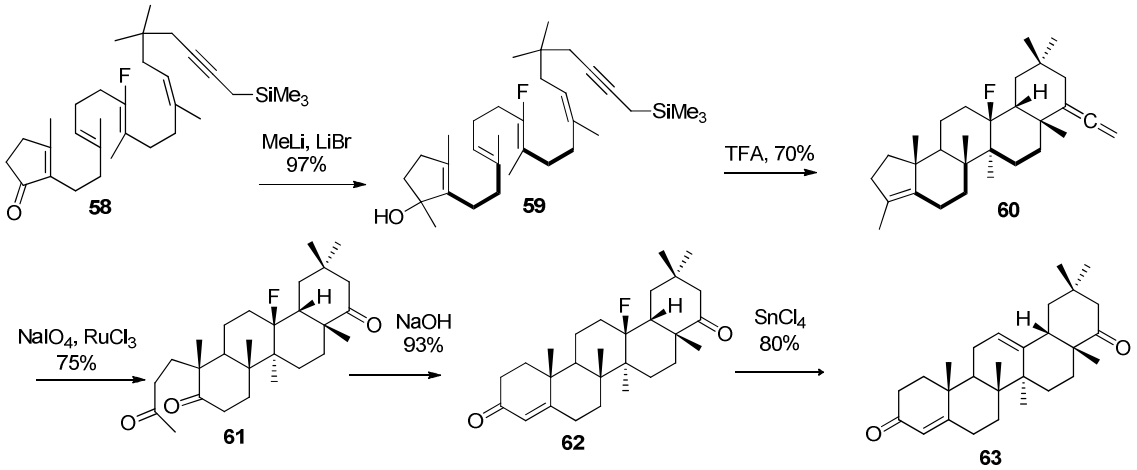
Además, fue el primero en describir una pentaciclación biomimética de polienos con flúor como grupo estabilizante y donde además el heteroátomo fue utilizado para el

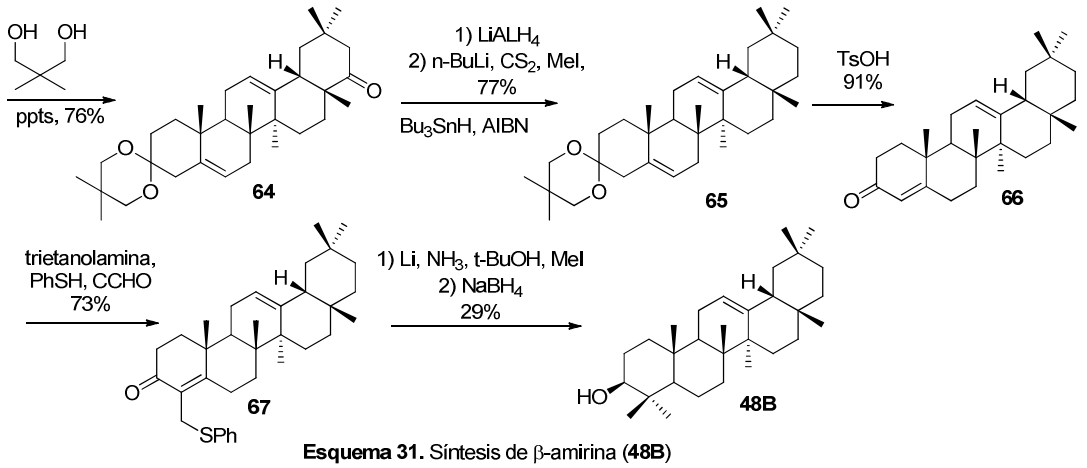
control de la regioselectividad de la ciclación. Este átomo de flúor posteriormente puede ser fácilmente retirado mediante el empleo de $SnCl_4$. La ciclación biomimética fue llevada a cabo con TFA (31 %) o con $SnCl_4$ (50%), dando lugar a la construcción de los cinco ciclos en sólo una etapa (Esquema 30). Esto supone un increíble logro en la carrera de Johnson.[59]



Esquema 30. Sintesis de (±)-Sophoradiol por Johnson

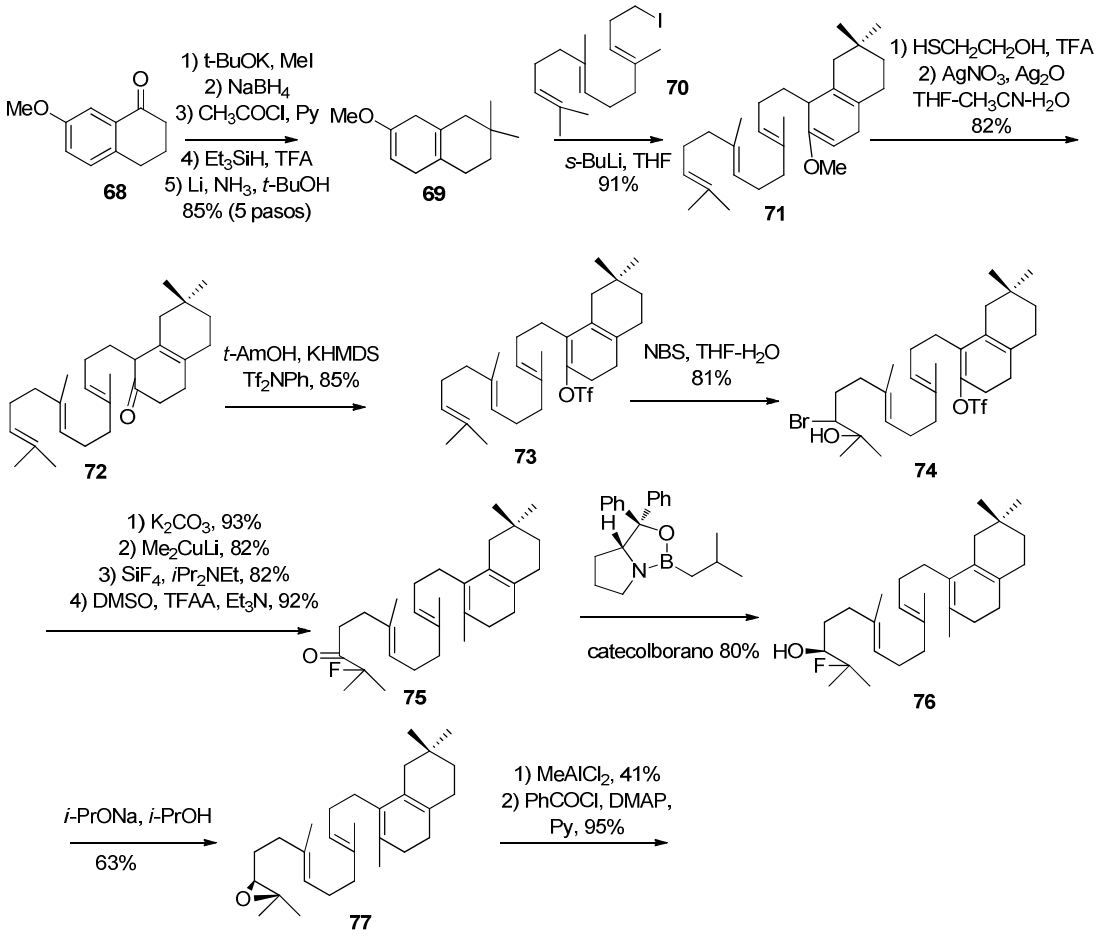
En 1993 fue publicada la síntesis racémica de β-amirina, que se llevó a cabo con un rendimiento medio de 0.2 %. La estrategia estuvo basada en una ciclación biomimética del polieno **59** donde el átomo de F juega nuevamente un papel fundamental como auxiliar estabilizante de cationes. La preparación de dicho polieno se llevó a cabo en 15 pasos partiendo del fluorodieninol **58**. Tras tratamiento ácido, se obtuvo el fluoropentaciclo **60** que contiene 5 anillos fusionados y seis de los ocho centros quirales encontrados en β-amirina (**48B**) (Esquema 31).[60]

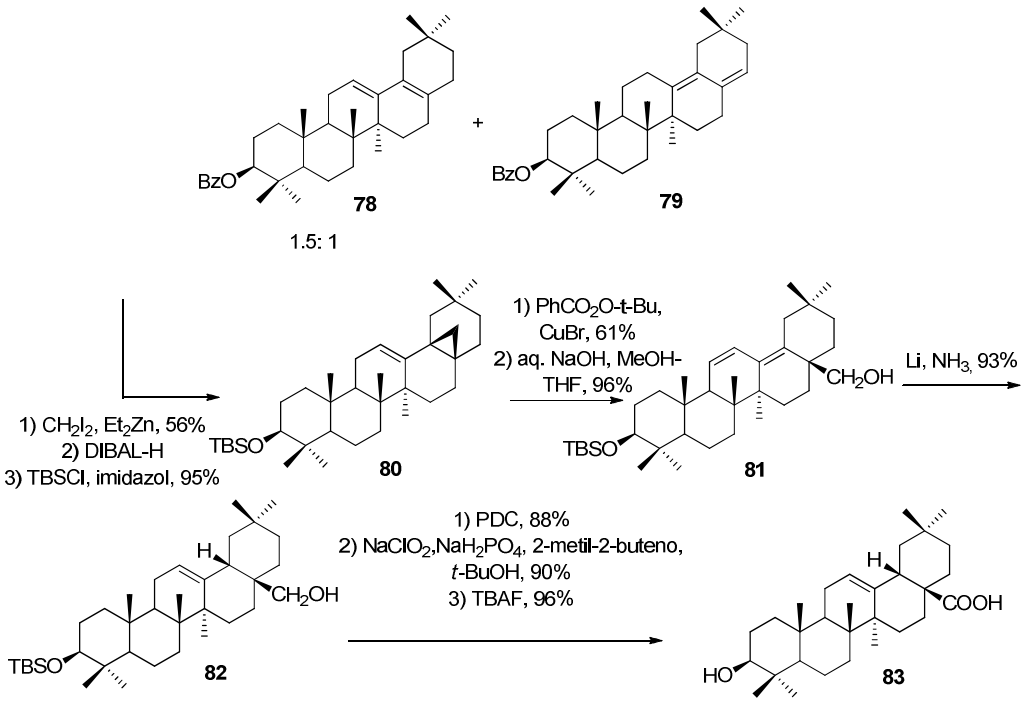




Esquema 31. Síntesis de β-amirina (**48B**)

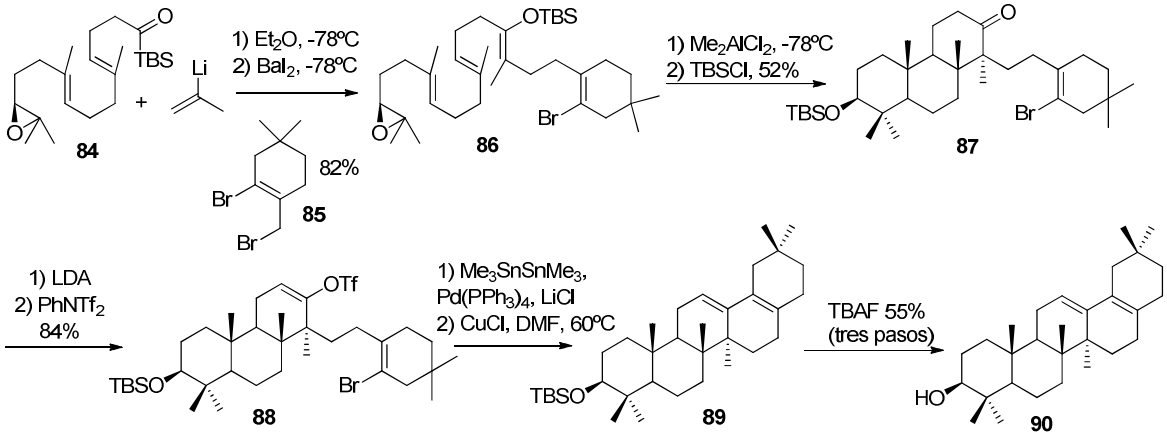
En 1993 Corey *et al.* describieron la primera síntesis asimétrica de triterpenos pentacíclicos de tipo oleanano, incluyendo el ácido oleanólico (**83**), *β*-amirina (**48B**) y eritrodiol. Como paso clave en la síntesis transformaron un epóxido quiral al pentaciclo mediante una ciclación catión- π diastereoselectiva, proceso que mimetiza a la naturaleza (Esquema 32).[15]





Esquema 32. Síntesis de Corey del ácido oleanólico (**83**)

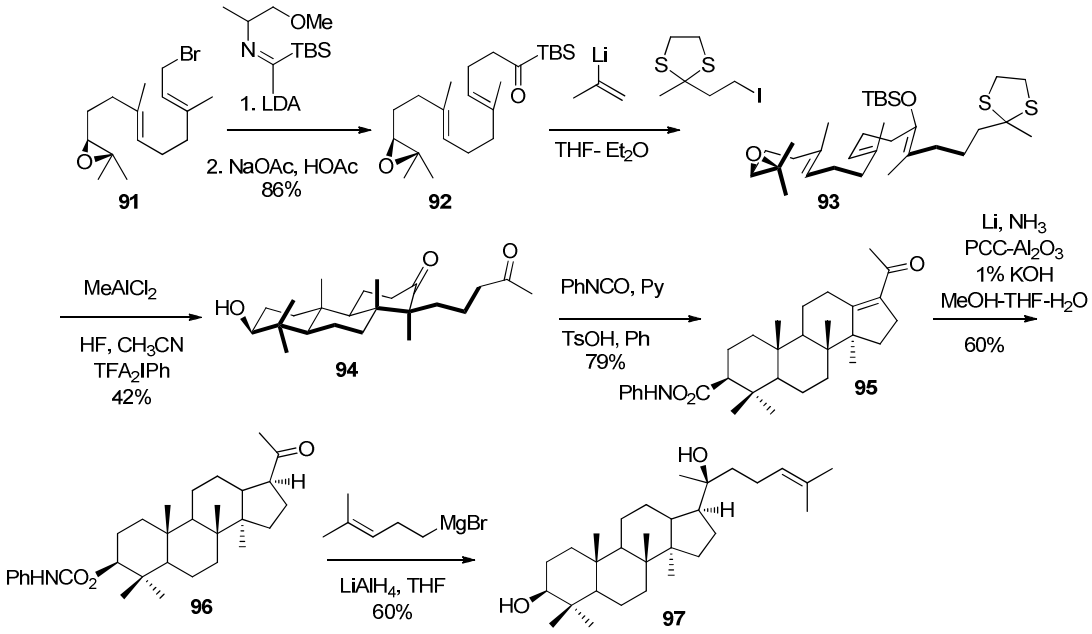
Basándose en la anterior metodología Corey *et al.* sintetizaron aegiceradienol (**90**) a partir del acilsilano **84** como intermedio clave. La ciclación catiónica del ópticamente activo epoxitetraeno y posterior sililación dio el tetraciclo **87**. Este después se transformó en un vinil triflato que mediante Cu(I) da un proceso de transmetalación sobre el grupo trimetilestannil cerrando el quinto anillo del esqueleto. Tras tratamiento con TBAF se obtuvo finalmente aegiceradienol (**90**) (Esquema 33).[15]



Esquema 33. Síntesis de Corey de aegiceradienol (**90**)

El OS es ciclado en algunas plantas para dar como producto principal dammaranediol (**97**). La primera síntesis total de este compuesto fue descrita por Corey

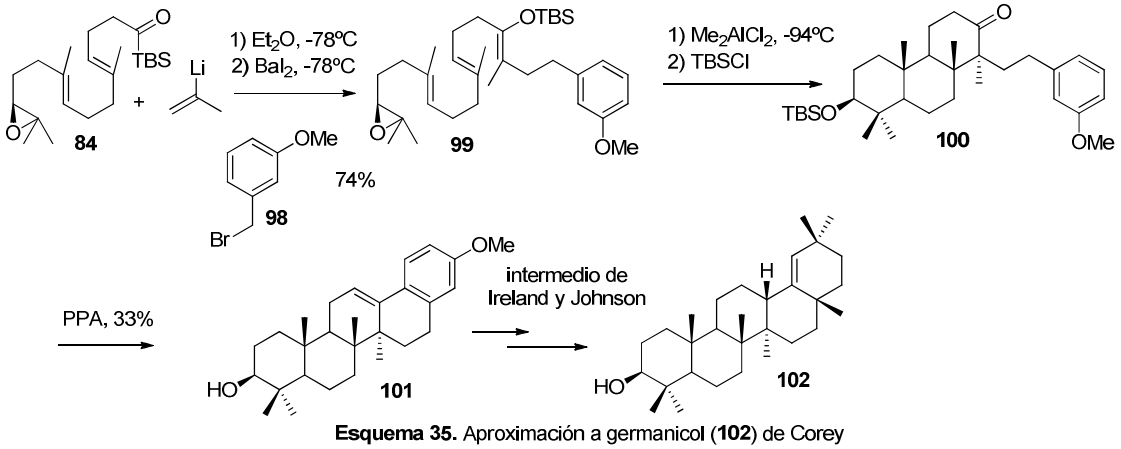
en 1996. A diferencia de Johnson que utilizó F para controlar la regioselección, la estrategia de Corey se basa en la utilización del enol silano **93** para dirigir la formación del anillo C durante la ciclación biomimética (Esquema 34).[20c]



Esquema 34. Síntesis de dammarenediol (**97**)

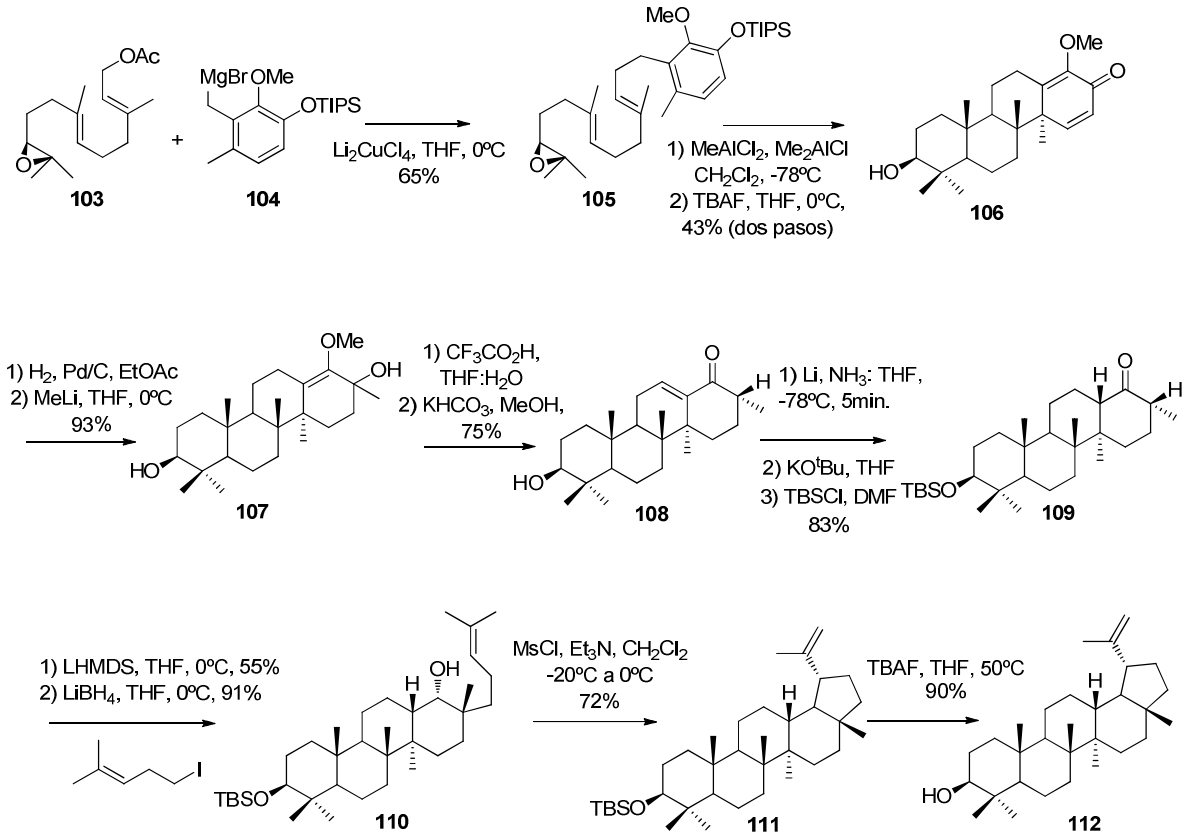
En 1999 un importante avance en estas ciclaciones biomiméticas se introdujo con la aparición del ácido quiral de Yamamoto, que controla la adición del protón sobre una de las caras del enlace π proquiral.[61] Hasta la fecha, esta impresionante transformación no ha sido aplicada en el campo de la síntesis de triterpenos.

En 2008 el grupo de Corey desarrolló dos rutas sintéticas cortas, utilizando el mismo sustrato de partida que en síntesis anteriores, para originar el pentaciclo intermedio **101**. Este intermedio fue usado previamente por los grupos de Ireland y Johnson para la obtención de germanicol (**102**) (Esquema 35).[20d]

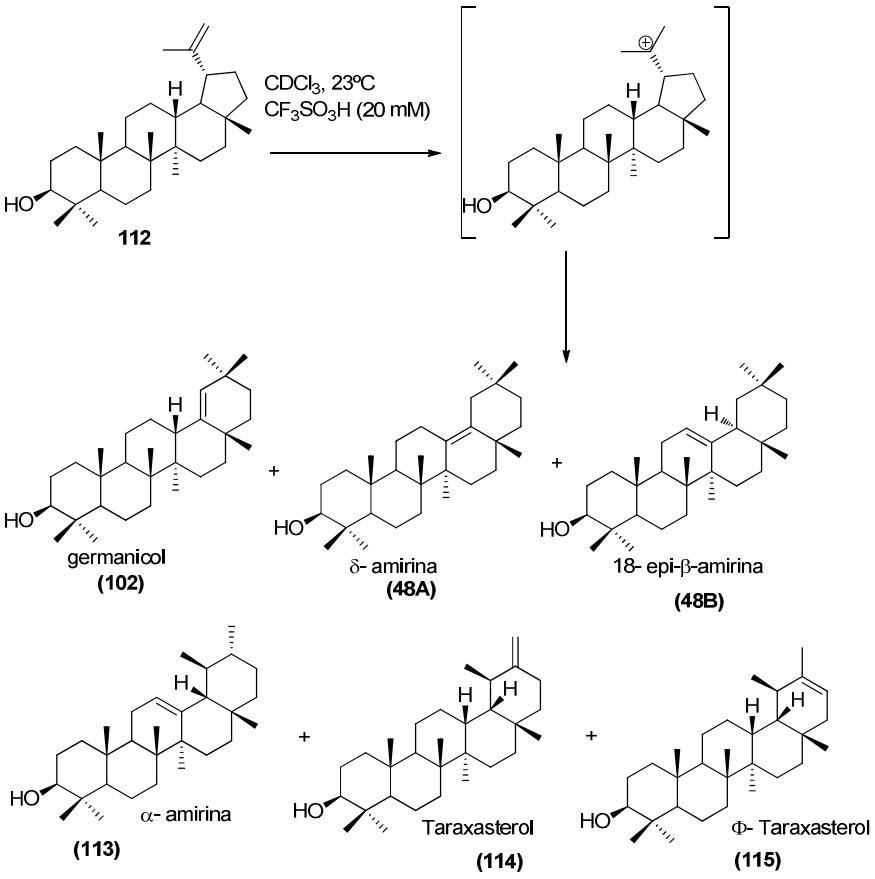


Esquema 35. Aproximación a germanicol (**102**) de Corey

Recientemente, en 2009, Corey sintetizó lupeol (**112**) (Esquema 36), que fue empleado posteriormente en un estudio biomimético mediante el cual transformó en un sólo paso lupeol en los triterpenos pentacíclicos germanicol (**102**), δ-amirina (**48A**), 18-epi-β-amirina (**48B**), α-amirina (**113**), taraxasterol (**114**) y ψ-taraxasterol (**115**) a través de intermedios carbocatiónicos. [20e] La investigación tuvo su origen en parte por los trabajos computacionales desarrollados en sus laboratorios. Para comprobar esta hipótesis llevaron a cabo experimentos bajo condiciones ácidas utilizando lupeol sintético como material de partida y generando inicialmente el lupanil catión (Esquema 37).[62]



Esquema 36. Síntesis de lupeol



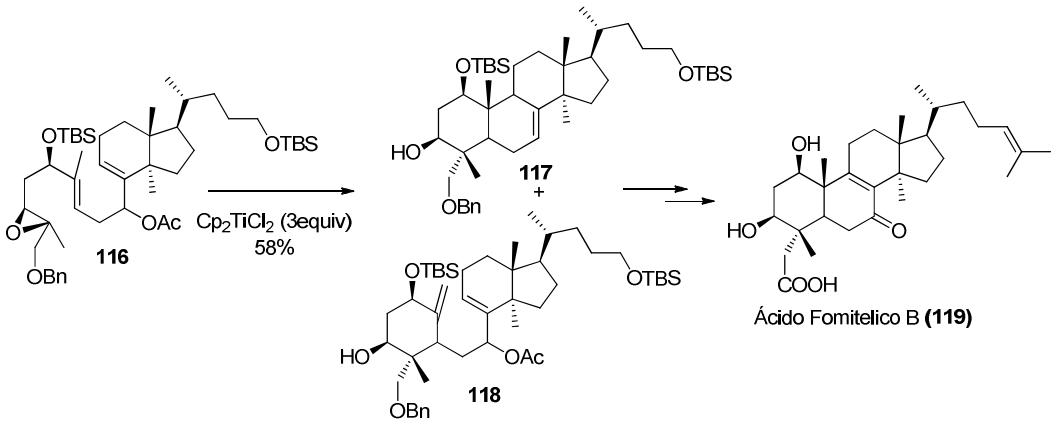
Esquema 37

Estrategias radicalarias.

Hace aproximadamente unos 40 años Breslow *et al.* propusieron la hipótesis de que las ciclaciones radicales de poliprenos podrían ser biosintéticamente una alternativa en la naturaleza en la biosíntesis de terpenos, aunque posteriormente esta propuesta fue desmentida por los mismos autores.[63] Así se demostró que se podía acceder a esqueletos terpénicos mediante ciclaciones radicales que tienen lugar, en muchos casos, con mejores rendimientos y estereoselectividades que las ciclaciones catiónicas.

Las estrategias radicalarias han sido poco utilizadas en la síntesis de la familia de terpenos. El primer precedente es la síntesis racémica de achilleol A (**6**) [70] (ver síntesis de triterpenos irregulares), que constituye una de las primeras aplicaciones de la estrategia general de síntesis de terpenos puesta a punto por nuestro grupo mediante apertura de oxiranos con Ti(III). Recientemente, S. Kobayashi *et al.* han descrito la primera síntesis total del ácido fomitélico B (**119**)[64], triterpeno con estructura tipo

lanostano que es un potente inhibidor de la DNA polimerasa. Esta síntesis tiene por paso clave otra aplicación de la estrategia de ciclación radicalaria en cascada inducida por Ti(III) para construir el esqueleto carbocíclico. Posteriormente se procede a la isomerización del doble enlace trisustituido seguida por una oxidación alílica, dando lugar a la enona del producto natural (Esquema 38).

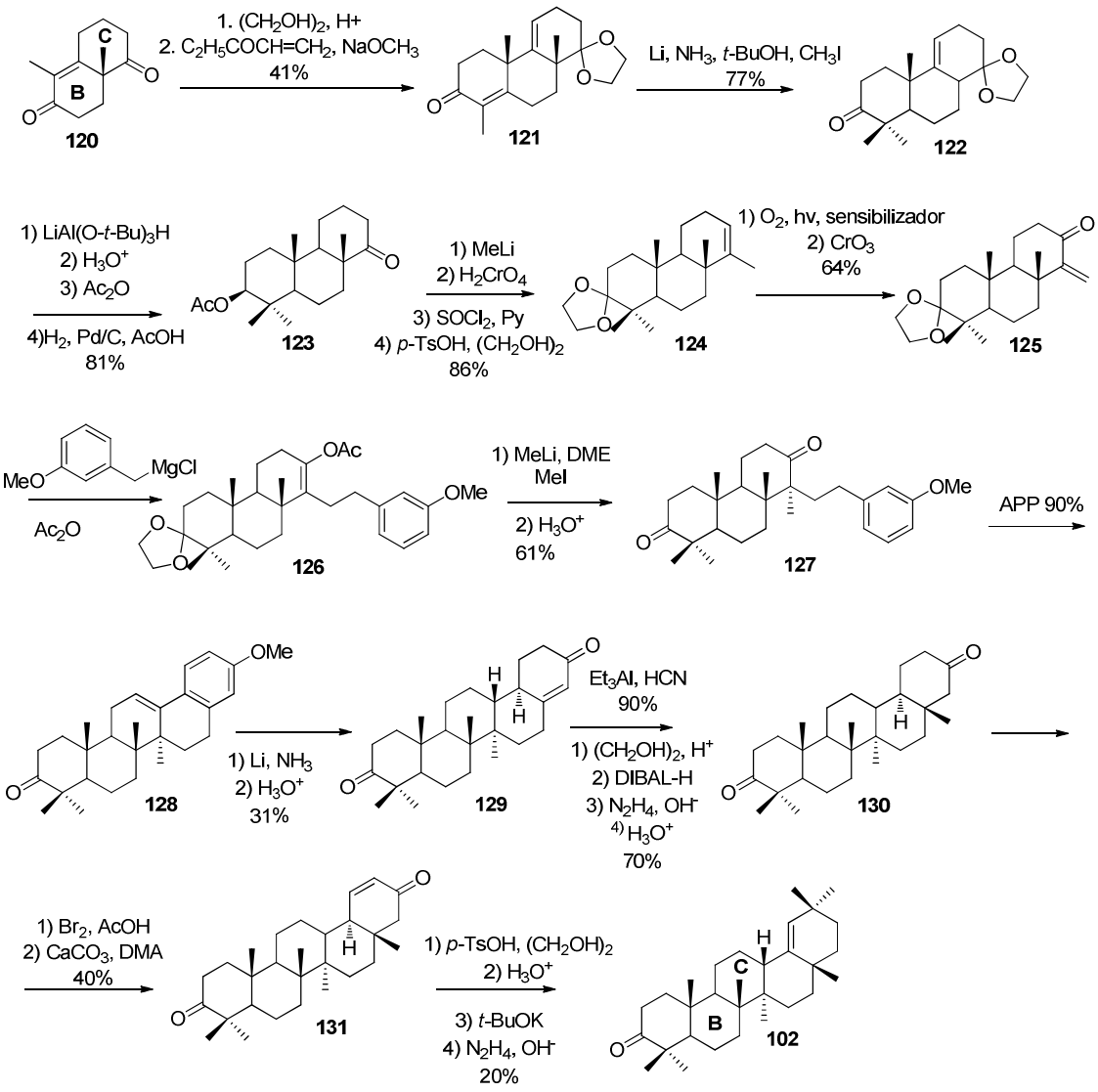


Esquema 38. Síntesis de ácido fomitélico

Otras estrategias sintéticas.

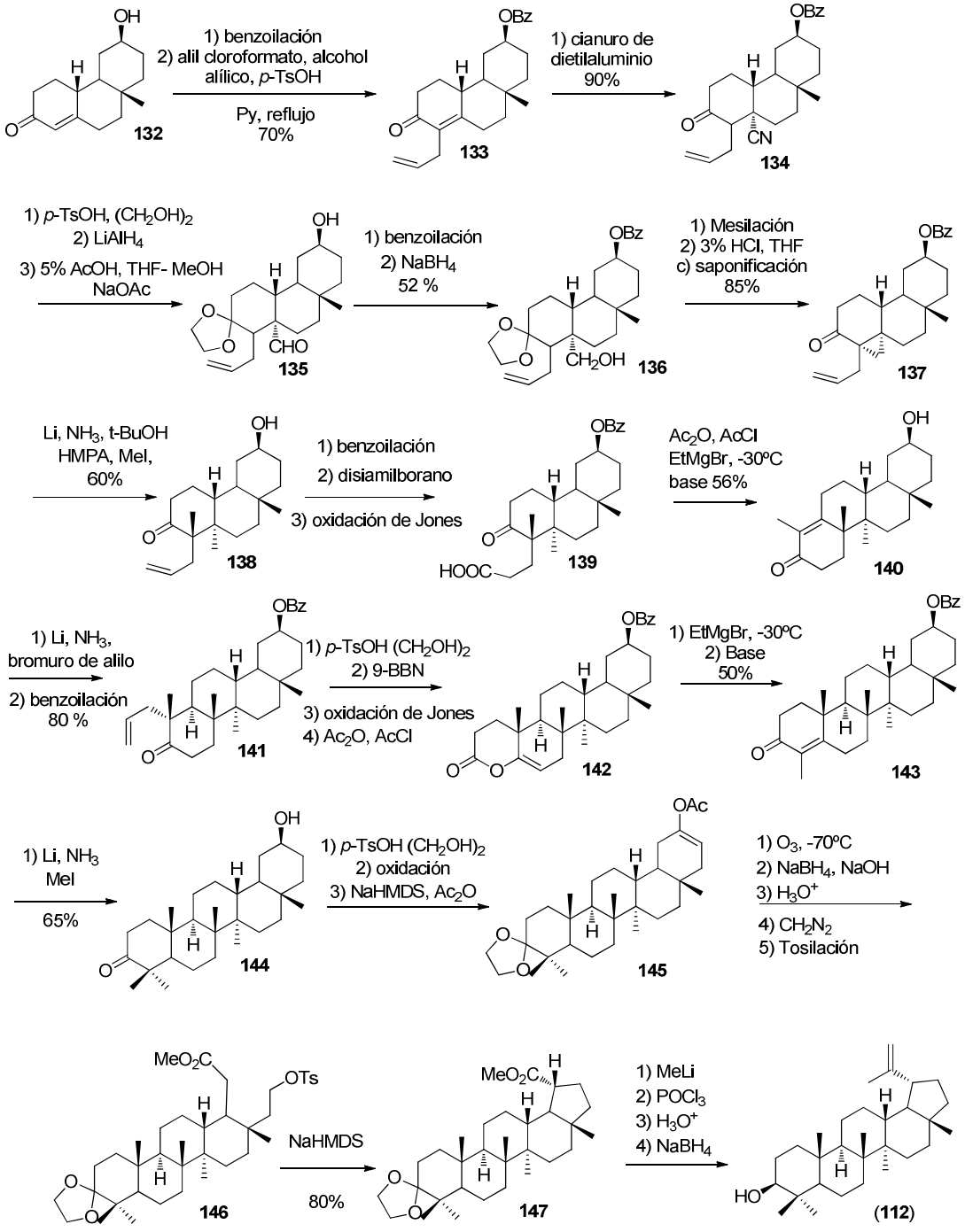
Además de síntesis totales "biomiméticas" según la definición de van Tamelen, muchos otros esfuerzos sintéticos se han utilizado para acceder a este tipo de moléculas, aunque con el inconveniente de precisar de un mayor número de etapas y siendo el rendimiento global menor. Sin embargo, cabe destacar el gran mérito en estas aproximaciones, puesto que estas síntesis fueron realizadas durante los años 70 donde los medios técnicos eran mucho menores.

En 1970, los grupos de investigación de R. E. Ireland y W. S. Johnson describieron la síntesis total racémica de germanicol (**102**). Esta síntesis consta de 31 pasos con un rendimiento medio de 0.1 % (Esquema 39).[65]



Esquema 39. Sintesis racémica de germanicol por Ireland y Johnson

En 1971 Stork *et al.* llevaron a cabo la síntesis de lupeol (**112**), triterpeno frecuentemente encontrado en plantas, tomando como punto de partida la construcción de los anillos D y E al comienzo de la secuencia sintética. A partir de una enona tricíclica racémica **132**, tras 37 pasos de reacción, dio lugar al acetal precursor del lupeol **(112)**. Este, mediante tratamiento con exceso con metil litio, seguido de deshidratación con oxicloruro de fósforo en piridina, retirada del grupo protector acetal y reducción con borohidruro sódico da lugar al producto natural (**112**) (Esquema 40).[66]



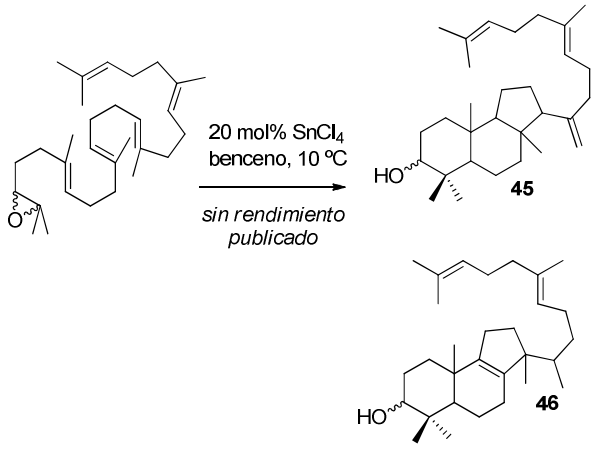
Esquema 40. Síntesis total de lupeol por Stork

II. 3. Síntesis de triterpenos irregulares

Estrategias catiónicas:

Síntesis de malabaricanos y malabaricanos reordenados (van Tamelen 1966):

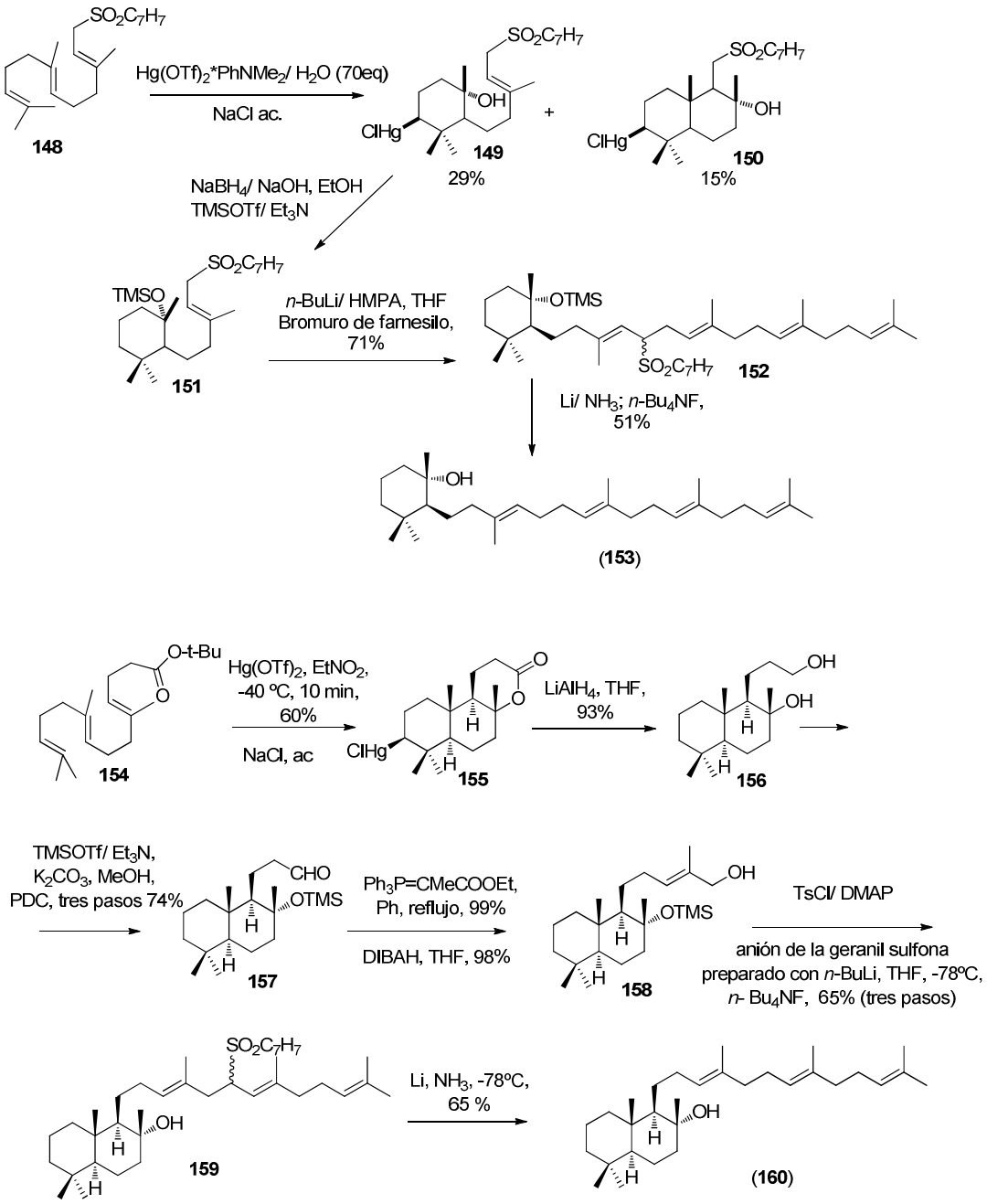
Van Tamelen *et al.*[51] realizan la ciclación biomimética del OS para obtener malabaricanos y malabaricanos reordenados (Esquema 41). Estos resultados sugieren que los reordenamientos de metilos en las ciclaciones de este precursor requieren mínima asistencia enzimática, de forma que el papel enzimático se limitaría a evitar el atrapamiento prematuro del carbocatión por moléculas de agua así como a favorecer el reordenamiento del anillo C de un anillo de 5 miembros a un anillo de 6 miembros.



Esquema 41. Ciclación biomimética de van Tamelen

Síntesis de (±) 6α-hidroxiachilla-9,13,17,21 tetraeno (153) y (±)-8αhidroxipolypoda-13, 17, 21-Trieno (160) (Nishizawa 1994):

Nishizawa *et al.*[67] sintetizan 6 α-hidroxiachilla-9,13,17,21-tetraeno (**153**), aislado de *Polypoides formosana*. Utilizan, como paso clave, una ciclación de la farnesil sulfona mediada por triflato de mercurio (II) (Esquema 42). Los cationes intermedios que se generan experimentan atrapamiento intermolecular por una molécula de agua.

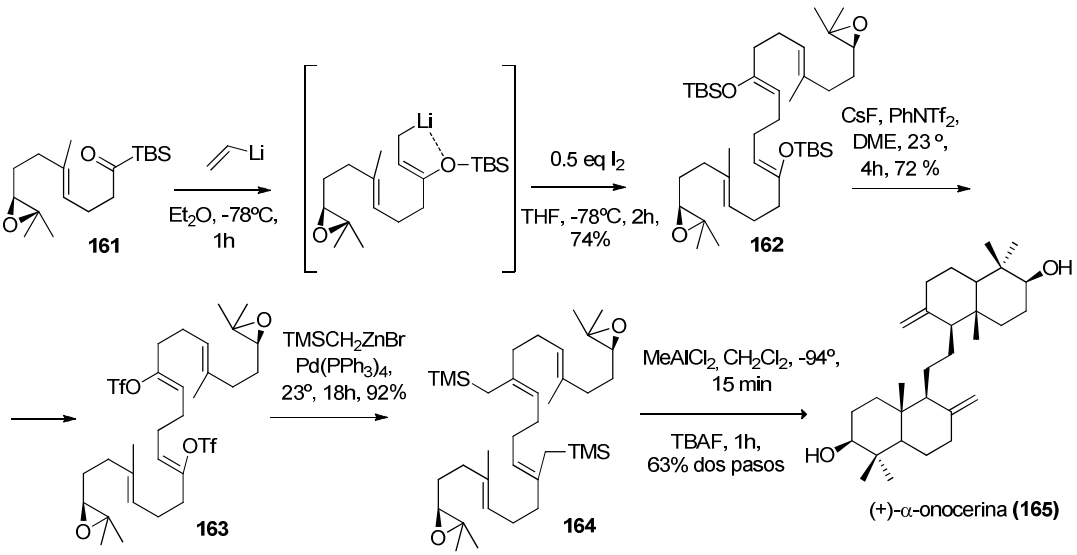


Esquema 42. Síntesis de (±) 6 -hidroxiachilla-9,13,17,21 tetraeno (**153**) y (±)-8-hidroxipolypoda-13, 17, 21-trieno (**160**)

En esta reacción se obtienen los productos monocíclico **149** y bicíclico **150**, en un 29% y un 15%, respectivamente. El organomercurial monocíclico **149** se reduce con $NaBH_4$ y se acopla con bromuro de farnesilo. Finalmente, la desulfonación reductiva seguida de desprotección del sililo en **152** conduce a la obtención del triterpeno **153**. Esta estrategia se emplea igualmente con el compuesto bicíclico para obtener **160**.

Síntesis de (+)-α-onocerina (Corey 2002):

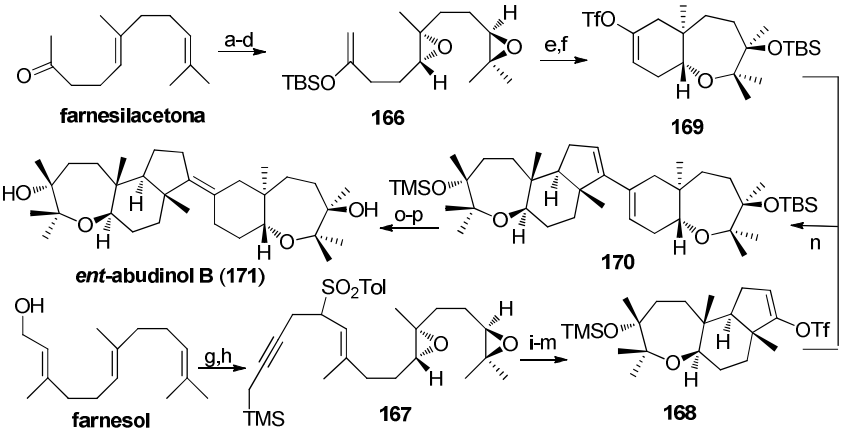
La síntesis de (+)-α-onocerina por Corey[68] fue llevada a cabo mediante acoplamiento de cuatro componentes y posterior tetraciclación. El acil silano derivado del acetato de farnesilo fue tratado con vinil litio, que da lugar a la formación estereoespecífica del (*Z*)-silil enol éter como resultado de un reordenamiento de Brook espontáneo. En la misma reacción, una disolución de I_2 fue adicionada para obtener el diepóxido deseado **162** por dimerización oxidativa. Por último, este diepóxido fue expuesto a 2.5 equivalentes de $MeAlCl_2$ para inducir la cascada catiónica que, tras desprotección con TBAF, dio lugar al producto tetracíclico (**165**) (Esquema 43).



Esquema 43. Síntesis de α-onocerina de Corey

***Ent*-abudinol B (McDonald 2006):**

McDonald *et al.*[69] llevaron a cabo la primera síntesis de *ent*-abudinol B (**171**) usando una ciclación en cascada de diepóxidos para construir los diferentes carbociclos de la estructura por separado. El acoplamiento de los correspondientes enol-triflatos **168** y **169** origina finalmente el esqueleto pentacíclico (Esquema 44). El paso clave fue un acoplamiento cruzado de las unidades ABC **168** y DE **169**, mediado por Pd, que tuvo lugar en un 70 %. Tras la hidrogenación del dieno **170** y desprotección final se obtuvo la estructura del compuesto *ent*-abudinol B (**171**) (Esquema 44).



(a) $NaBH_4$, MeOH, 0º C, 90%; (b) catalizador Shi, oxone, K_2CO_3, Na_2EDTA, DMM/MeCN/H_2O, 0º C, 95%; (c) SO_3-piridina, DMSO, Et_3N, DCM, 0º C, 95%; (d) KHMDS, TBSCl, THF, -78º C, 87%; (e) TBSOTf, DTBMP, DCM, -78º C, 60%; (f) KHMDS, THF, -78º C, luego $PhNTf_2$, -78º C, 95%; (g) Ph_3P, NBS, THF, 0º C, luego cat. Bu_4NI, $NaSO_2Tol$, 99%; (h) *n*-BuLi, THF, -78 to -40º C, luego 1-bromo-4-trimetilsilil-2-butino, -78 to 20 ºC, 92%; (**i**) catalizador Shi , oxone, K_2CO_3, Na_2EDTA, DMM/MeCN/H_2O, 0º C, 76%; (j) $Cl_2Pd(dppp)$, $LiEt_3BH$, THF, 0º C, 71%; (k) TMSOTf, DTBMP, DCM, -78º C, 75%; (l) Bu_4NF, THF, 99%; (m) O_3, DCM, -78º C, luego Me_2S, -78 to 20º C, 88%; (f) 95%; (n) **A** $Cl_2Pd(PPh_3)_2$, Ph_3P, PhOK, bis(neopentilglicolato)diboro, toluene, 50º C, luego **B**, $Cl_2Pd(dppf)$, K_3PO_4, DMF, 80º C, 70%; (o) 10% Pd-C, tolueno, H_2, 0º C, 30%; (p) Bu_4NF, THF, 60º C, 84%.

Esquema 44. Síntesis de *ent*-abudinol por McDonald

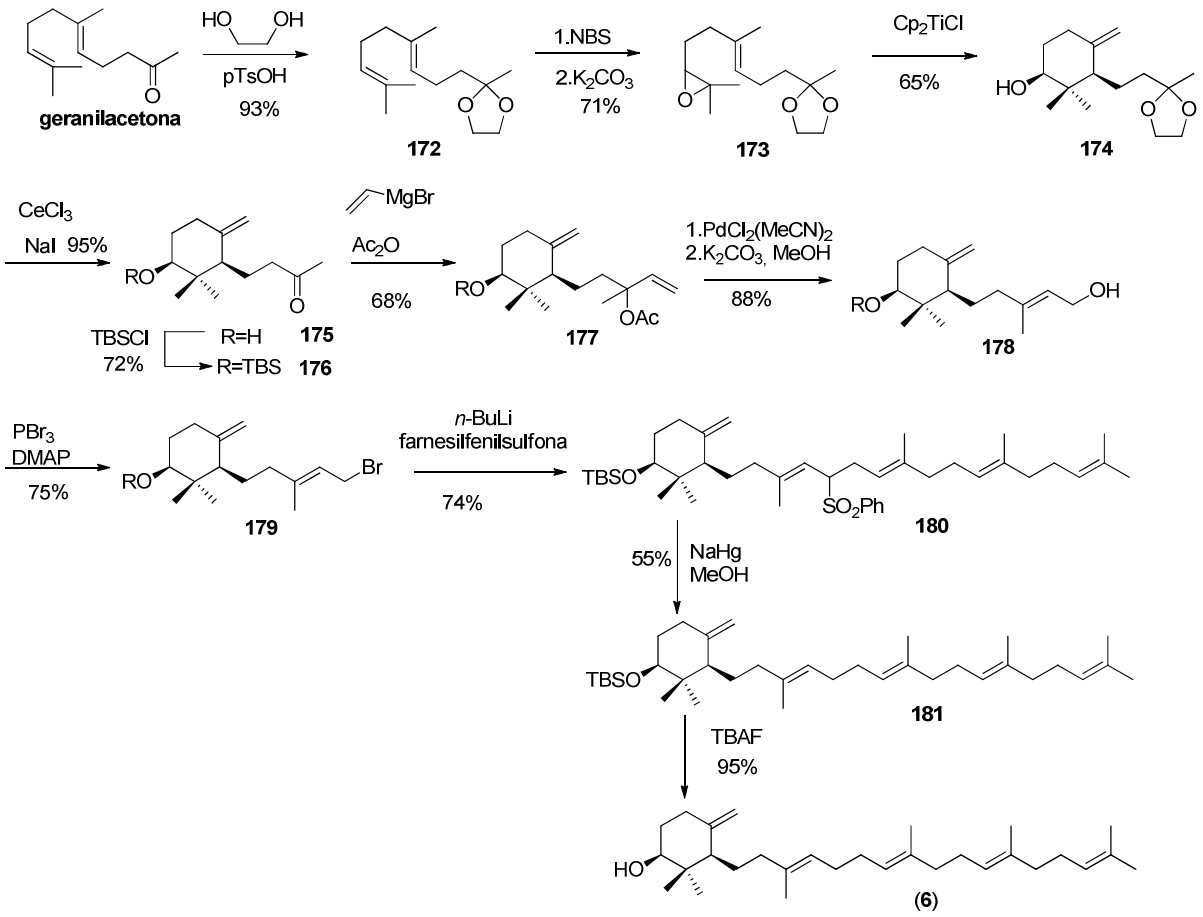
Estrategias radicalarias:

(±) Achilleol A (Barrero 2002):

La síntesis racémica de esta molécula fue descrita por Barrero *et al.*[70] usando como paso clave la metodología de carbociclación de epoxipoliprenos mediada por titanio (III). La aproximación sintética a esta molécula se basa en una estrategia convergente C_{15}+C_{15}.

En el esquema 45 se desarrolla la metodología aplicada. En la síntesis de la parte monocíclica se parte de geranil acetona, que se transforma en el etilenglicol acetal **172** para evitar el atrapamiento radical por parte del grupo carbonilo en la reacción de carbociclación. El tratamiento con NBS acuosa y K_2CO_3 genera el oxirano **173** que da lugar al metilenciclohexanol **174** tras tratamiento con Cp_2TiCl. Tras la desprotección del grupo carbonilo, la cetona **175** se hace reaccionar con bromuro de vinil magnesio. El correspondiente alcohol terciario sufre un reordenamiento hasta alcohol primario en el siguiente paso de reacción por tratamiento con Pd (II). Se llega así al silil derivado de elegansidiol **178**, sintón que, transformado en el bromuro alílico **179**, se hace reaccionar con el anión derivado de la farnesil sulfona para dar el esqueleto triterpénico de achilleol A **180**. Para finalizar, la desulfonación reductiva de **180** mediante amalgama

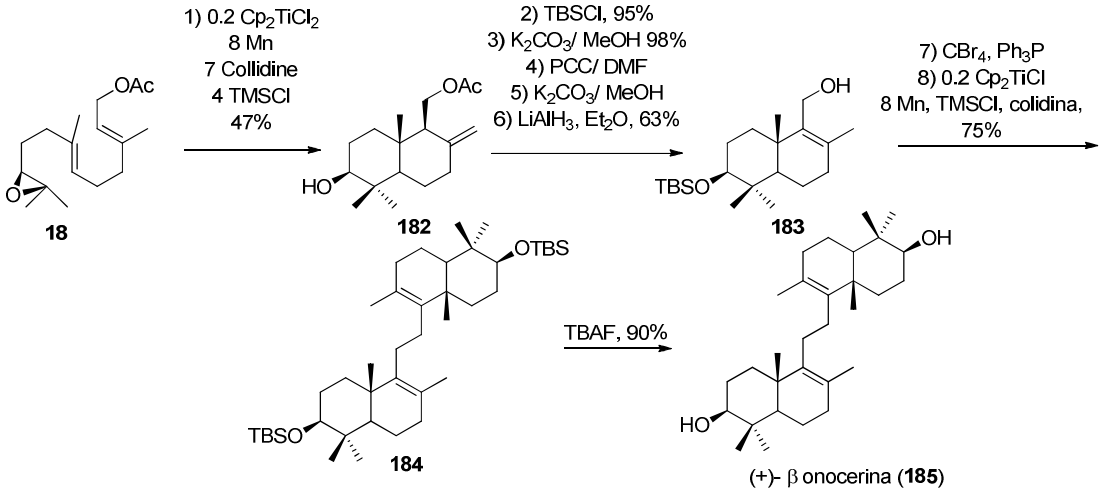
Na/Hg en metanol, seguida de la desprotección de **181** mediante TBAF, origina el alcohol deseado (**6**) (Esquema 45).



Esquema 45. Primera síntesis total de achilleol A

Onoceranos (Barrero 2005):

En 2005 Barrero *et al.* llevaron a cabo la síntesis de (+)-onocerina (**185**) donde dos fueron los pasos clave: el primero, una ciclación radicalaria con Ti (III), y el segundo, la utilización de este mismo reactivo para promover una dimerización por acoplamiento de haluros alílicos (Esquema 46).[71]

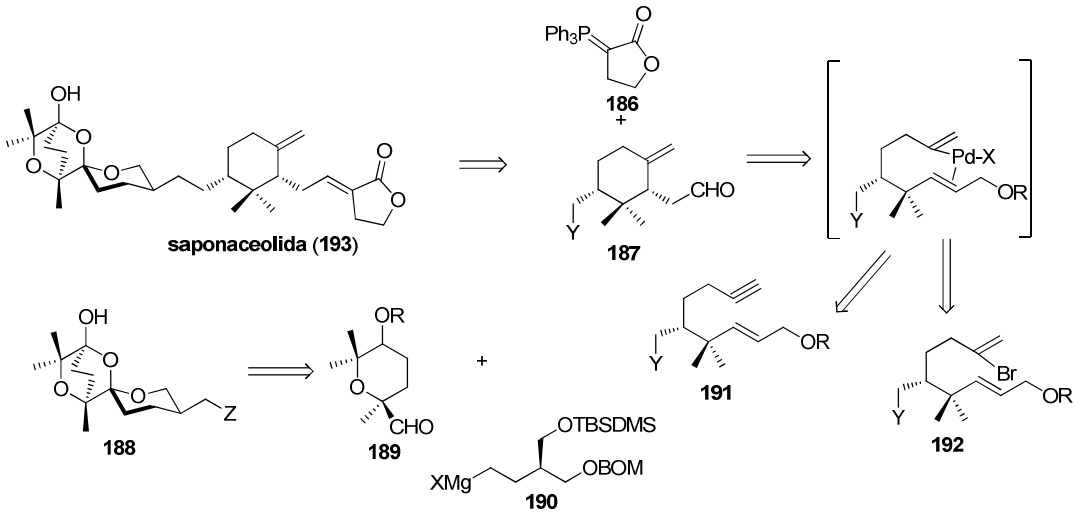


Esquema 46. Síntesis de β-onocerina

Otras aproximaciones sintéticas:

(+)-Saponaceolida B (B. Trost 1999):

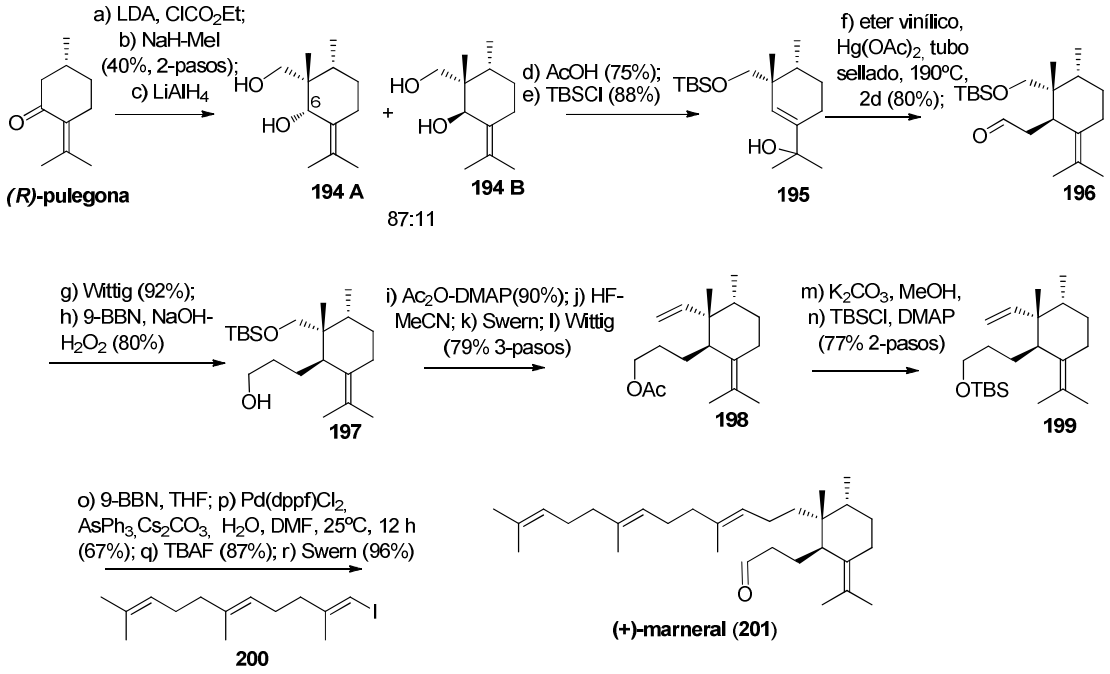
Las saponaceolidas A-D fueron descubiertas en el norte de Italia del hongo *Tricholoma saponaceum* poseyendo actividad antitumoral en 60 líneas de cáncer humano.[72] La etapa clave fue la construcción del anillo ciclohexánico mediante una reacción de Heck intramolecular entre un bromuro vinílico y la correspondiente olefina (Esquema 47).



Esquema 47. Análisis retrosintético de la saponaceolida

(+)-Marneral (Arseniyadis 2008):

En 2008 se sintetizó por primera vez de manera convergente (+)-marneral (**201**). Así, mediante una reacción de B-alquil Suzuki-Miyaura se llevó a cabo el acoplamiento un ioduro vinílico (**200**) y una parte monocíclica quiral (**199**). Esta última fue construida a partir de la (*R*)-pulegona mediante un reordenamiento de Claisen catalizado con mercurio a partir del alcohol alílico (Esquema 48).[73]

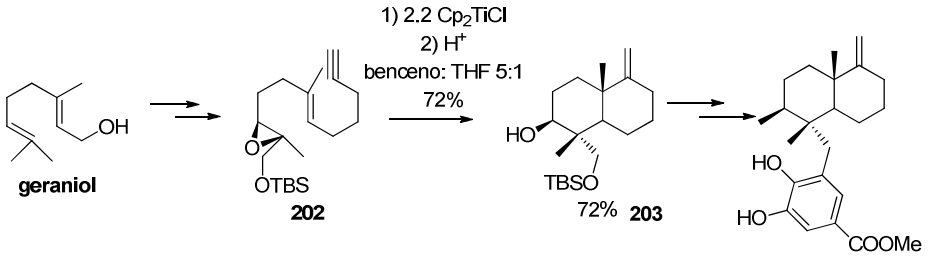


Esquema 48. Síntesis de marneral (**201**)

II. 4. Empleo del cloruro de titanoceno en ciclaciones de epoxipoliprenos

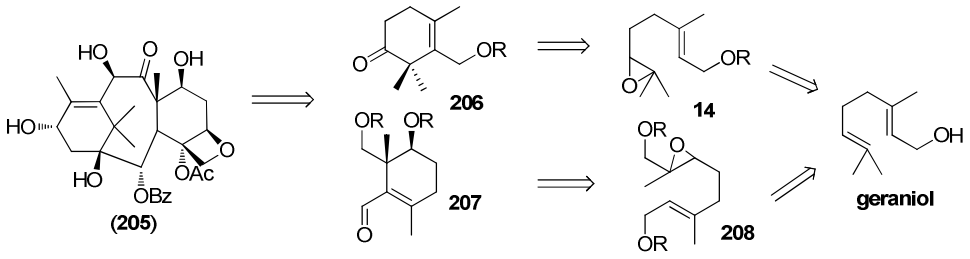
Debido a la bondad del método radicalario con cloruro de titanoceno en la construcción de terpenoides, esta metodología ha sido ampliamente utilizada. Destacamos aquí entre los siguientes ejemplos:

Síntesis del (+)-smenospondiol (**204**) en 2001 (Esquema 49):[74]



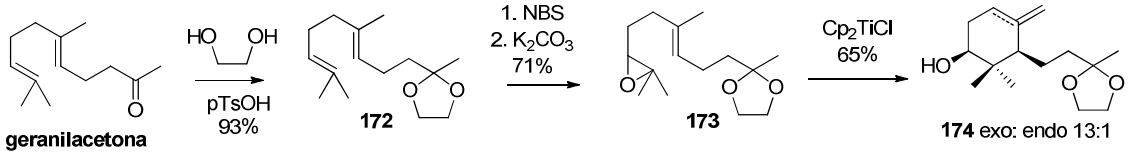
Esquema 49. Síntesis de smenospondiol

Síntesis de los anillos A y C del paclitaxel en 2001 (Esquema 50):[75]



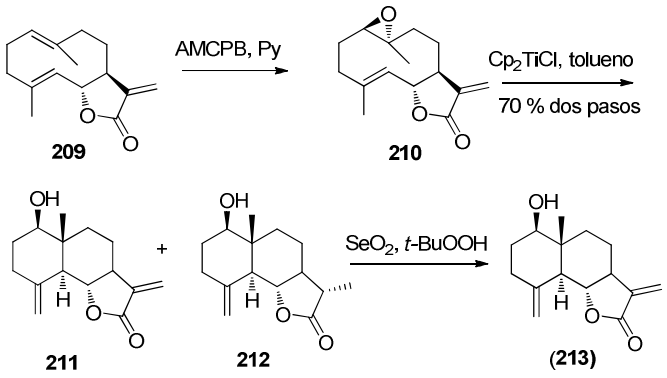
Esquema 50. Síntesis de los anillos A y C del paclitaxel

Síntesis del anillo de ciclohexano del (±)-achilleol A (**6**) (Esquema 51):[70]



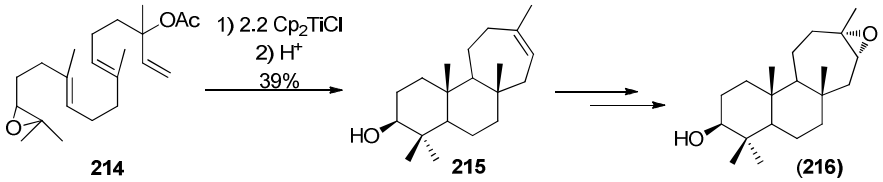
Esquema 51. Síntesis del anillo de 6 miembros en el achilleol A

Ciclaciones transanulares de epoxigermacrolidas hacia eudesmanolidas: Síntesis de (+)-3α- hidroxireynosin (**213**) (Esquema 52):[76]



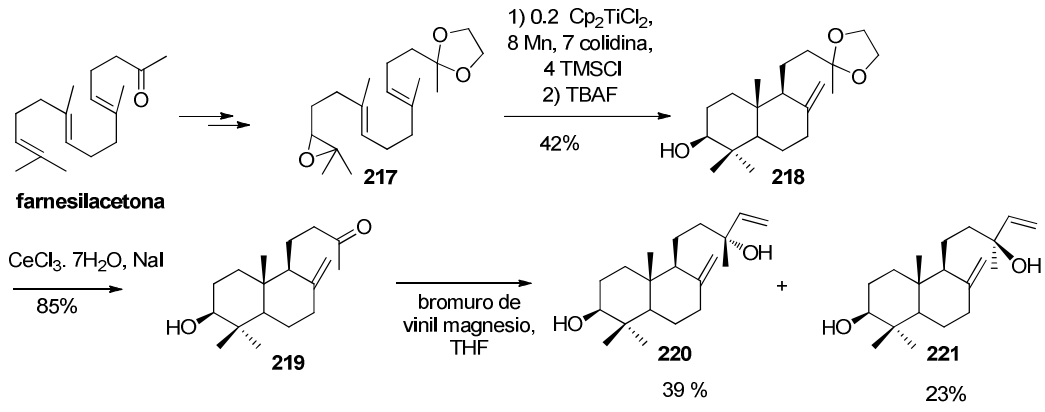
Esquema 52. Síntesis de eudesmanolidas

Síntesis de barekóxido (**216**) obtenido a partir de una ciclación 6+6+7 del epoxigeranillinalil acetato **214** (Esquema 53):[77]



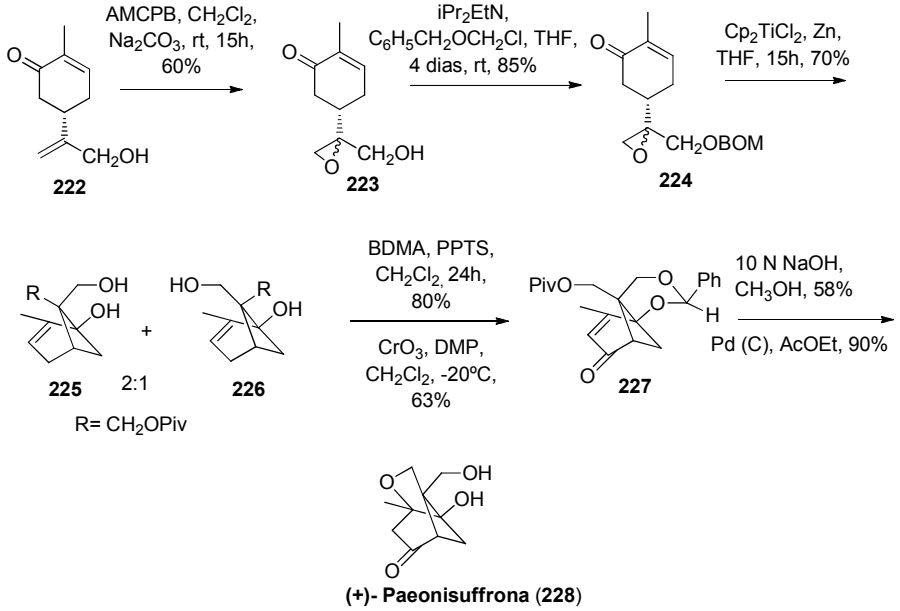
Esquema 53. Síntesis de barekóxido

La versatilidad de esta estrategia, esta vez en su versión catalítica, para la rápida preparación de diferentes terpenoides bicíclicos se pone de manifiesto en la síntesis de 3β-hidroximanool (**220**) (Esquema 54), labdano aislado de *Gleichenia japónica*. Así, la apertura y ciclación del epoxiderivado **217** dio el compuesto bicíclico en un 42 %, que posteriormente se convirtió en el producto natural.[78]



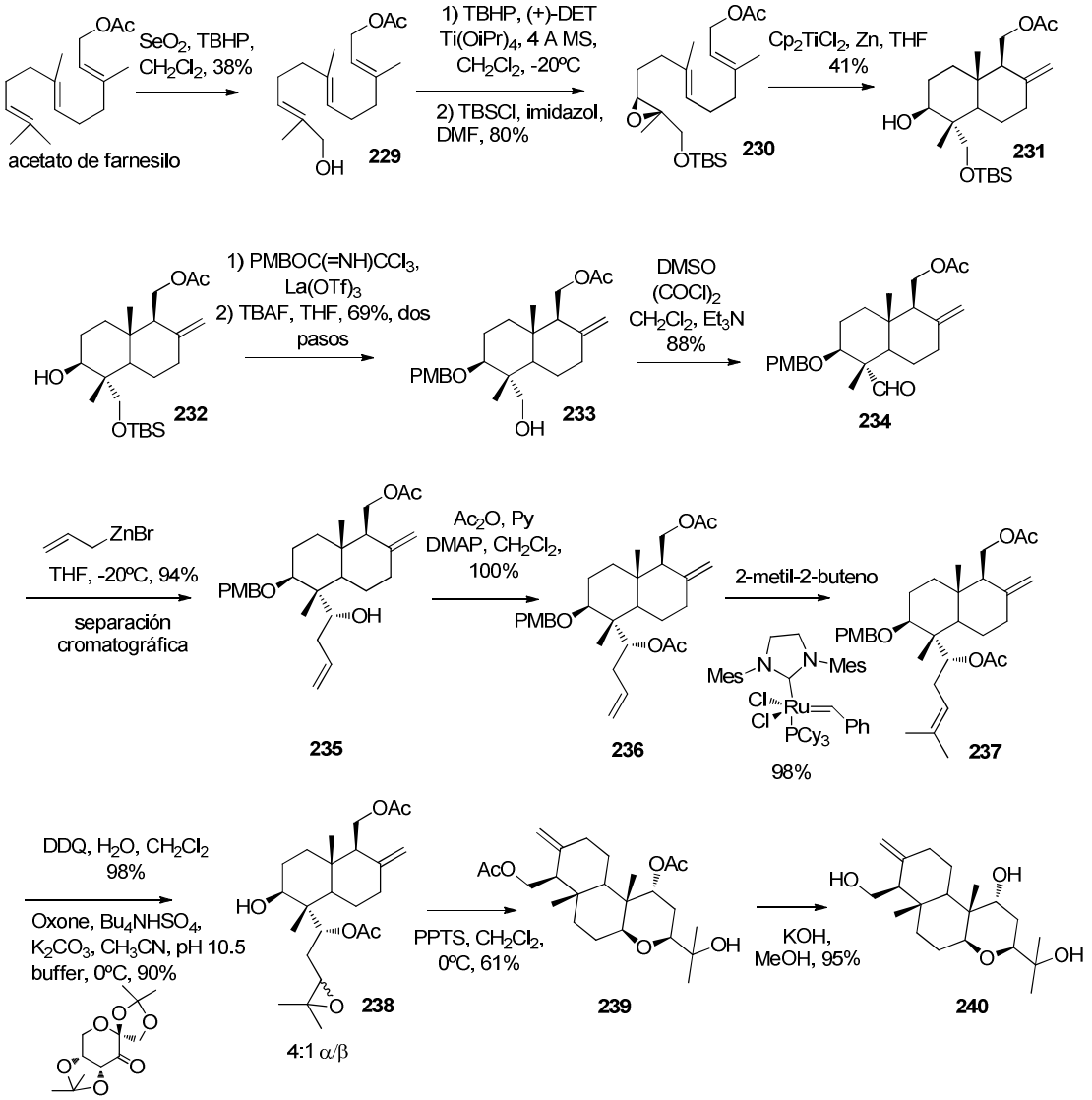
Esquema 54. 3 β-hidroximanool

En 2008 Bermejo *et al.* realizaron la semisíntesis de (+)-paeonisuffrona (**228**), compuesto aislado de las raíces de *Paeonia albiflora* y *Paeonia suffructicosa*. Partiendo como material de partida de (+)-10-hidroxicarvona **222**, el paso clave de la estrategia sintética fue la ciclación estereoselectiva mediada por Ti (III) para acceder al esqueleto oxigenado de pinano (Esquema 55).[79]



Esquema 55. Semisíntesis para la obtención de paeonisuffrona

Más recientemente, en 2011, se ha llevado a cabo la síntesis de los anillos DEF de terpendol E **240**. Los anillos D-E se construyeron mediante ciclación radicalaria con Ti(III), mientras que el anillo F tetrahidropiránico fue construido por ciclación inducida por ácido del intermedio **238**. Dicho sustrato fue preparado previamente mediante metátesis cruzada seguida por epoxidación de Shi (Esquema 56).[80]



Esquema 56. Síntesis de los anillos D y E de terpendol E

III. ARTICULOS DE INVESTIGACIÓN

Artículo 1: *Unusually cyclized triterpenes: occurrence, biosynthesis and chemical synthesis, Domingo, V.; Arteaga, J. F.; Quilez del Moral, J. F.; Barrero, A. F., Natural Product Reports,* ***2009****, 26, 115-134.*

REVIEW www.rsc.org/npr | Natural Product Reports

Unusually cyclized triterpenes: occurrence, biosynthesis and chemical synthesis

Victoriano Domingo, Jesús F. Arteaga, José F. Quílez del Moral and Alejandro F. Barrero*

Received 24th July 2008
First published as an Advance Article on the web 29th October 2008
DOI: 10.1039/b801470c

Covering: 1998 to 2008

The biosynthetic origin of most of triterpenes lies in cascade cyclizations and rearrangements of the acyclic precursors squalene (S) and 2,3-oxidosqualene (OS), processes leading to tetra- and pentacyclic triterpene skeleta. Apart from these, a number of triterpenoid structures derived from cyclization processes, that are different from those leading to tetra- and pentacyclic triterpenes, are also found in Nature. We have defined these processes as unusual cyclizations, and grouped them in three blocks, namely, incomplete cyclizations of the corresponding S-derived precursors, cyclizations of S or OS towards polycyclic triterpenes and subsequent cleavage of the preformed ring systems, and two independent cyclizations of the S- or OS-derived precursor. Apart from the molecules obtained from intact organisms, we will also consider the compounds obtained from *in vitro* cyclizations promoted by enzyme systems. After establishing which compounds could unambiguously be grouped under the term 'unusually cyclized triterpenes', this review moves on to the advances achieved in this kind of structure during the last ten years. These advances are presented in three parts. The first one presents the structure and biological properties of the unusual triterpenes reported in the last decade. The second part considers the main biosynthetic pathways which justify the formation of these triterpenes from their corresponding acyclic precursors. Finally, we look at the achievements made in different synthetic strategies directed at some of these molecules. One hundred and twenty-three references are cited.

1 Introduction
2 Occurrence and biological activities of unusually cyclized triterpenes
2.1 Triterpenes resulting from incomplete cyclizations of S and OS
2.2 Triterpenes derived from processes of cyclization of S or OS towards polycyclic triterpenes and subsequent retrocyclization reactions from pentacyclic carbocation intermediates
2.3 Triterpenes deriving from two independent cyclization processes of S or OS derivatives
3 Biosynthesis of unusually cyclized triterpenes
3.1 Biosyntheses mediated by OSC and SC. Triterpenes originating from a single cyclization
3.2 Biosynthesis of triterpenes *via* processes of cyclization of S or OS towards polycyclic triterpenes and subsequent retrocyclization reactions
3.3 Biosynthesis of triterpenes involving two independent cyclization processes
4 Chemical syntheses of unusually cyclized triterpenes
4.1 Achillanes
4.2 Polypodanes
4.3 Malabaricanes
4.4 Marneral
4.5 *ent*-Abudinol B
5 Conclusions
6 References

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1 Introduction

Triterpenes are one of the most structurally diverse groups of terpenes, with more than 100 skeleta described as natural products.[1–4] The origin of this diversity is the type of mechanism that takes part in their biosynthesis – the enzymatic systems generically named terpenoid synthases act on acyclic polyprene precursors generating carbocations that, by electrophilic additions on double bonds, produce processes of cyclization and rearrangements. In the specific case of the triterpenes, the triterpenoid synthases act on the most common precursors – squalene (S) and oxidosqualene (OS) – and biosynthesis is initiated by enzymatic protonation of the terminal double bond or the oxirane respectively. As those precursors contain five or six double bonds, the possibilities of cyclization accompanied by rearrangement are theoretically very great.[5–7] This has generated a good deal of interest amongst scientists. In this context, the hypothesis of isoprene as a biogenetic precursor for triterpenes by Ruzicka, Eschenmoser, Arigoni *et al.*[8,9] was a significant milestone which was complemented by the characterization of

some thirty OS cyclases (OSCs) and various studies of mutations on the genes involved in these cyclization processes.[5,10–12]

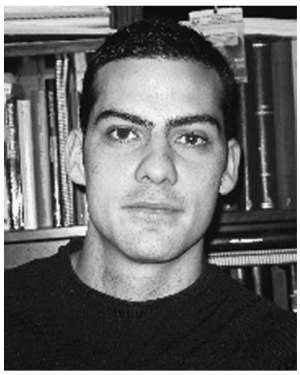
Most of the triterpenes contain tetra- or pentacyclic skeletons, but together with these a number of triterpenoid structures derived from cyclization processes different to those leading to tetra- and pentacyclic triterpenes have also been reported from Nature. We have named these structures 'unusually cyclized triterpenes', and have grouped them as follows:

a) Triterpenes arising *via* an incomplete cyclization of the corresponding S-derived precursors. These processes start at the terminal isopropylidene unit or at its corresponding epoxide and lead to mono-, bi- and tricyclic triterpenic skeletons.

b) Triterpenes arising *via* cyclization of S or OS towards polycyclic triterpenes and subsequent cleavage of the preformed ring systems.

c) Triterpenes arising *via* two independent cyclizations of the S- or OS-derived precursor.

The aim of this review is to cover the structure, biological properties, biosynthesis and chemical synthesis of the unusually cyclized triterpenes described in the last ten years. Apart from the molecules obtained from live organisms, compounds obtained

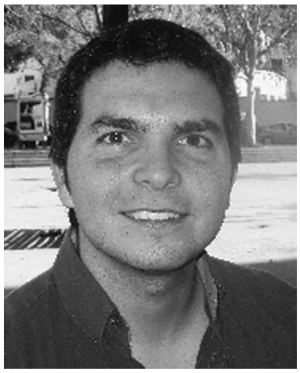


Victoriano Domingo

Victoriano Domingo was born in Granada (Spain) in 1981 and graduated in Chemistry in 2006 at the University of Granada. He is a Ph.D. student at the same University under the supervision of Prof. Alejandro F. Barrero and Dr José F. Quílez. Currently, he is in the process of completing the total synthesis of various triterpenes. His interests lie in modern synthetic methodologies with application in the field of bioactive natural products.

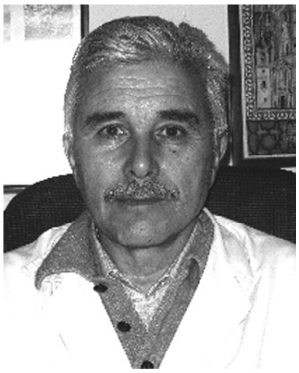
José F. Quìlez del Moral

José F. Quílez del Moral was born in Linares (Spain) in 1967 and studied Chemistry at the University of Granada, where he graduated in 1990. He received his Ph.D. degree in 1996 under the supervision of Prof. A. F. Barrero. In 1997, he started a 20 month post-doctoral fellowship with Prof. S. Arseniyadis at the Institut de Chimie des Substances Naturelles at Gif-sur Yvette (France) working on the total synthesis of taxol. He returned to Granada as an assistant professor and joined Prof. A. F Barrero's group in 1998. He is currently a Senior Lecturer and his research interests are directed towards the development of new methods for the synthesis of molecules having biological activity.



Jesús F. Arteaga

Jesús F. Arteaga was born in Salamanca (Spain) in 1979 and he graduated in Chemistry in 2002 at the University of Granada. He received his Ph. D. degree in 2006 under the supervision of Prof. Alejandro F. Barrero at the same university. From 2006–2007 he formed part of a post-doctoral team at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette, France) with Prof. Simeon Arseniyadis working on the total synthesis of biologically active natural products. He is currently a post-doctoral investigator at the University of Huelva (Spain). His research interests are mainly focused on the development of new applications of free-radical chemistry in the synthesis of natural products and homogeneous catalysis.



Alejandro F. Barrerro

Alejandro F. Barrerro was born in Orense (Spain) in 1949. He obtained his Ph.D. degree in 1975 at the University of Salamanca under the guidance of Professors Joaquín Pascual de Teresa, Arturo San Feliciano and Inés Sánchez Bellido. After working as a research scientist at the Compañía Española de Petróleos Research Center in San Fernando de Henares (Spain), he returned to the University of Salamanca as a Lecturer. He moved to the University of Granada as Full Professor in 1983, where he is Head of the Organic Chemistry Department. He is also President of the Natural Product Group of the Royal Spanish Society of Chemistry. His work includes the direction of more than 40 doctoral theses. His current interests are the chemistry and biotechnology of terpenoids and the application of both radical cyclization reactions and new couplings catalyzed by transition metals to the synthesis of natural bioactive products.

from *in vitro* cyclizations of S or OS promoted by enzymatic systems are also included.

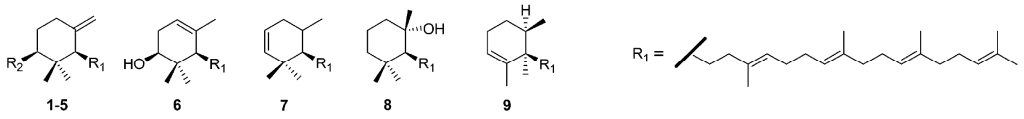
2 Occurrence and biological activities of unusually cyclized triterpenes

2.1 Triterpenes resulting from incomplete cyclizations of S and OS

Monocyclic triterpenes: Achillanes and neoachillane. Although achilleol A **1**, the first monocyclic triterpene to be described, was isolated from the plant *Achillea odorata* (Asteraceae) in 1989,[13] it is worth noting the recently described production of this compound by a number of mutants of lanosterol and cycloartenol synthase (Table 1). Compound **1** and some derivatives were also found in other species of the Umbelliferae,[17] Asteraceae,[18] Theaceae,[19] and Gramineae.[20] Camelliol C **6**, first found in *Camellia sasanqua* (Theaceae),[19] has also been isolated from *in vitro* cyclizations promoted by enzymatic systems.

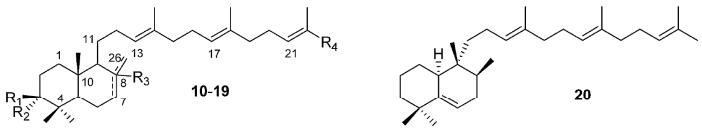
Monocyclosqualene **7** was isolated from the herb *Ligularia fischeri* var. *spiciformis* (Compositae),[30] and 3-deoxyachilleol A **5** from a squalene hopene cyclase (SCH) mutant of the prokaryotic bacterium *Alicyclobacillus acidocaldarius*.[29] Only camelliol C **6** was reported to present a slight inhibitory effect

Table 1 Monocyclic triterpenes with the achillane skeleton



Compound	R^2	Source
Achilleol A (**1**)	OH	*Bupleurum spinosum*,[17] *Santolina elegans*,[18] *Camellia sasanqua*, *C. japonica*,[19] wheat germ oil and rice bran oil,[20] SHC mutant [*Alicyclobacillus acidocaldarius* ΔG600],[21] OSLC mutant [*S. cerevisiae* H234 (M/Y/F), Y510 (A/K/W/H),[22,23] V454A, V454G],[24] CAS1 mutant [*Arabidopsis thaliana* I481 (A/G),[25] Y410C Y532H[26]], Gene expression: CAMS1 [*At1g78955*],[27] BARS1 [*At4g15370*][28]
Achilleol A esterified derivative (**2**)	$CH_3(CH_2)_{10}COO$	*B. spinosum*,[17] *S. elegans*,[18] *C. sasanqua*,[19] *C. japonica*,[19] wheat germ oil and rice bran oil[20]
Achilleol A esterified derivative (**3**)	$CH_3(CH_2)_{12}COO$	
Achilleol A esterified derivative (**4**)	$CH_3(CH_2)_{14}COO$	
3-Deoxyachilleol (**5**)	H	SHC Mutant [*Alicyclobacillus acidocaldarius* D377 (C/N), Y612A][29]
Camelliol C (**6**)	—	*C. sasanqua*,[19] *C. japonica*,[19] OSLC mutant: [*S. cerevisiae* Y510 (K/W)],[22] CAS1 [*Arabidopsis thaliana* I481 (A/G)],[25] Gene expression: CAMS1 [*At1g78955*],[27] BARS1[*At4g15370*][28]
Monocyclosqualene (**7**)	—	*Ligularia fischeri*[30]
6α-Hydroxyachilla-9,13,17,21-tetraene (**8**)	—	SHC mutants [*Alicyclobacillus acidocaldarius* L607(F/W)][31]
Neoachillapentaene (**9**)	—	SHC mutants [*Alicyclobacillus acidocaldarius* L607(F/W), Y420W][31]

Table 2 Bicyclic triterpenes with the polypodane skeleton

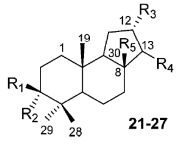


Compound	Δ	R^1	R^2	R^3	R^4	Source
α-Polypodatetraene (**10**)	$\Delta^{8(26)}$	H	H	—	H	SHC mutants [*A. acidocaldarius*Y420A, Y609F][34,35]
γ-Polypodatetraene (**11**)	Δ^7	H	H	—	H	SHC mutants [*A. acidocaldarius* F365A,[36] Y420A,[34] Y609 (A/L/C/S),[37,38] Y612A,[37] L607K[39,40]]
3β-Hydroxy γ-polypodatetraene (**12**)	Δ^7	OH	H	—	H	*Cratoxylum cochinchinense*[41]
Myrrhanol A (**13**)	—	OH	H	α-OH	CH_2OH	*Balsamodendron mukul*[33,42]
Myrrhanone A (**14**)	—	O	O	α-OH	CH_2OH	*B. mukul*[33,42]
Myrrhanone A acetate (**15**)	—	O	O	α-OH	CH_2OAc	*B. mukul*[43]
Myrrhanol B (**16**)	—	OH	H	α-OH	COOH	*B. mukul*[43]
Myrrhanone B (**17**)	—	O	O	α-OH	COOH	*B. mukul*[43]
21,22-Dihydro α-polypodatetraene (**18**)	$\Delta^{8(26)}$	H	H	—	H	*Tetrahymena pyriformis*[44]
21,22-Dihydro γ-polypodatetraene (**19**)	Δ^7	H	H	—	H	*T. pyriformis*[44]
Neopolypodatetraene (**20**)	—	—	—	—	—	SHC mutant [*A. acidocaldarius* F365A][37]

on the HIV transcriptase.[14] It is possible that these compounds may have a biological role as reinforcers of the cell membranes.[15,16]

Bicyclic triterpenes: Polypodanes. Table 2 lists the structures of eleven bicyclic triterpenes with the polypodane skeleton. Herein, neopolypodatetraene **20**, a rearranged polypodane described in SHC mutants from *Alicyclobacillus acidocaldarius*,[37] is also included. Although previously described in species of the Polypodaceae family,[32] α- and γ-polypodatetraene have also been isolated recently from mutated enzymes. The polypodanes oxygenated at C-3 (**12–17**) were found in *Balsamodendron mukul* (Burseraceae),[33,42] and *Cratoxylum cochinchinense* (Hypericaceae).[41] Of these, myrrhanol A **13** and myrrhanol B **16** possess interesting anti-inflammatory activity in various assays. The former is more potent than hydrocortisone, and is considered a plausible candidate as an anti-inflammatory agent, and probably with fewer side effects.[33]

Table 3 Triterpenes with the malabaricane skeleton



21-27

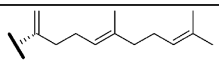
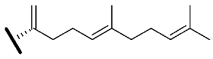
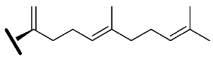
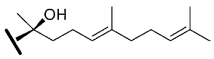
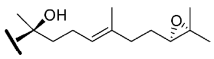
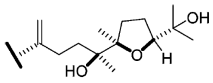
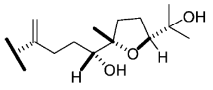
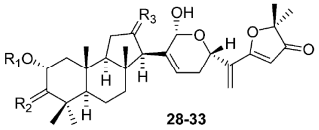
Compound	R^1	R^2	R^3	R^4	R^5	Source
Malabarica-14(27),17,21-trien-3-ol (**21**) (13*R* or 13*S*)	OH	H	H		Me	SHC mutant [*A. acidocaldarius* ΔG600],[21] Gene expression: BARS1[*At4g15370*][28]
13β-Malabaricatriene (**22**)	H	H	H		Me	SHC mutant [*A. acidocaldarius* F601A][45]
13α-Malabaricatriene (**23**)	H	H	H		Me	SHC mutants [*A. acidocaldarius* F601A, Y420A, I261A],[31,45,46] sediment lake Cadagno[47]
Arabidiol (**24**)	OH	H	H		Me	Gene expression: [*At4g15340*],[48] SHC mutant [*A. acidocaldarius* ΔG600][21]
Arabidiol 20,21-epoxide (**25**)	OH	H	H		Me	Gene expression: [*At4g15340*][48]
26	O	O	H		Me	*Caloncoba echinata*[49]
27	O	O	H		Me	*C. echinata*[49]

Table 4 Triterpenes with the malabaricane skeleton (sodagnitins)



28-33

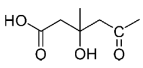
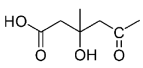
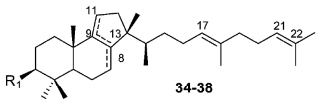
Compound	R^1	R^2	R^3	Source
Sodagnitin A (**28**)	H	O	H_2	*Cortinarius sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]
Sodagnitin B (**29**)	H	O	O	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]
Sodagnitin C (**30**)		O	H_2	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*, *C. cf. calochrous*[50]
Sodagnitin D (**31**)		O	O	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]
Sodagnitin E (**32**)	H	H, β-OH	H_2	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]
Sodagnitin F (**33**)	H	H, β-OH	O	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]

Table 5 Triterpenes with the rearranged malabaricane skeleton



34-38

Compound	R^1	Source
Thalianol (**34**), podioda-8,17,21-trien-3β-ol	OH	Gene expression: [*At5g48010*],[51] SHC mutant [*A. acidocaldarius* ΔG600][21]
(21*S*)-21,22-Epoxy-malabarica-8,17-dien-3-ol (**35**)	OH	Gene expression: [*At5g48010*][51]
Podioda-9(11)-17,21-trien-3β-ol (**36**)	OH	SHC mutant [*A. acidocaldarius* ΔG600][21]
7,17,21-Podiodatriene (**37**)	H	SHC mutant [*A. acidocaldarius* F605A],[52,53] Gene expression: BARS1 [*At4g15370*][28]
8,17,21-Podiodatriene (**38**)	H	SHC mutant [*A. acidocaldarius* F605A][52,53]

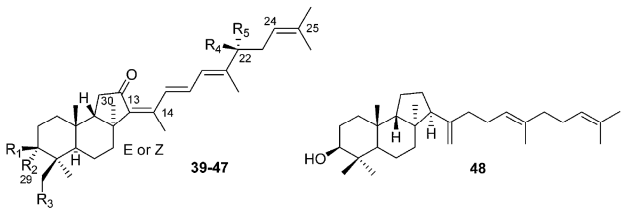
Tricyclic 6,6,5 triterpenes: Malabaricanes and rearranged isomalabaricanes. Tricyclic triterpenes containing the fused 6,6,5 system are grouped in malabaricanes (Table 3 and Table 4) (**21–33**), rearranged malabaricanes (Table 5) (**34–38**), and isomalabaricanes (Tables 6–8) (**39–76**). The difference between malabaricanes and isomalabaricanes is the stereochemistry of the B–C ring junction – *trans-anti-trans* and *trans-syn-trans* respectively – while in the rearranged malabaricanes Me-30 is absent at C-8 but at C-13. Table 4 displays a group of malabaricanes of marine origin possessing a similar side chain named sodagnitins. In two cases, compounds **30–31**, esters of hydroxymethylglutaric acid were found at C-2. The side chain of these molecules presents different degrees of oxidation. Thus, up to four oxygens can be found in this moiety, mostly as hydroxyls or tetrahydrofurans. Compounds **26–27**, isolated from *Caloncoba echinata* (Flacourtiaceae),[49] inhibited *Plasmodium falciparum*, while sodagnitins A and C are active against *Bacillus subtilis*, *B. brevis*, and *Nematospora coryli.*[50]

Isomalabaricanes have been found exclusively in marine sponges, mostly from the Pacific, and in many cases form their yellow pigmentation. The substances possessing this skeleton are characterised structurally by a carbonyl group on C-12, an *E* or *Z* double bond on C-13 (which can undergo light-induced isomerization), and highly unsaturated systems on the side chain, which in many cases are four and five double bonds conjugated with the carbonyl on C-12. Moreover, oxygenated functions are frequently present on the ring at C-3 and on the C-29 methyl group.

They have been classified into three groups according to their structure and origin. Stelliferins (Table 6) have a methylene on C-23, and an oxygenated function on C-22. The second group comprises globostellatic acids (Table 7), isolated almost exclusively from *Rhabdastrella globostellata*. Most of these compounds contain a carboxylic acid or a methyl ester on C-29 and a highly unsaturated side chain with 4 or 5 conjugated double bonds. The third group – jaspolides and stelletins (Table 8) – either contain side chains with terminal pyrone rings (**66–67**) or a carboxylic acid in place of one of the terminal methyls of the side chain (**70–72**), or are *nor*-triterpenes that have lost the last carbon of the side chain, forming methylketones (**73–76**).

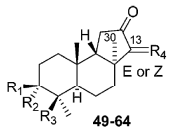
Numerous examples of isomalabaricanes have been found with cytotoxic activity. Mixtures of 29-hydroxystelliferin

Table 6 Triterpenes with the isomalabaricane skeleton (stelliferins)



Compound	Δ^{13}	R^1	R^2	R^3	R^4	R^5	Source
3-*Epi*-29-hydroxystelliferin A (**39**)	*Z*	H	OH	OH	OH	H	*Stelleta globostellata*[55]
Stelliferin G (**40**)	*Z*	H	H	OH	OAc	H	*Jaspis* species [54]
29-Hydroxystelliferin E (**41**)	*Z*	OAc	H	OH	OAc	H	*Jaspis* species,[54] *S. globostellata*[55]
29-Hydroxystelliferin A (**42**)	*Z*	OAc	H	OH	OH	H	*Jaspis* species[54]
29-Hydroxystelliferin D (**43**)	*Z*	OH	H	OH	OH	H	*S. globostellata*[55]
Stelliferin riboside E (**44**)	*Z*	H	OAc	H	H or O-ribose	O-ribose or H	*R. globostellata*[56]
3-*O*-Deacetyl-13*Z*-stelliferin riboside (**45**)	*Z*	H	OH	H	H or O-ribose	O-ribose or H	*R. globostellata*[56]
Stelliferin riboside (**46**)	*E*	H	OAc	H	H or O-ribose	O-ribose or H	*R. globostellata*,[56] *G. globostellifera*[57]
3-Hydroxy-13*E*-stelliferin riboside (**47**)	*E*	H	OH	H	H or O-ribose	O-ribose or H	*R. globostellata*,[56] *G. globostellifera*[57]
13α*H*-Isomalabarica-14(27),17*E*,21-trien-3β-ol (**48**)	—	—	—	—	—	—	OSLC [*S. cerevisiae* H234 (L/M/N/D),[58,59] F445 (C/M/N/T/D),[60] Y510(F/H)[23,61,62]]

Table 7 Triterpenes with the isomalabaricane skeleton (globostellatic acids)



49-64

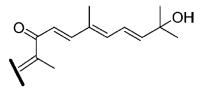
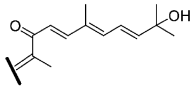
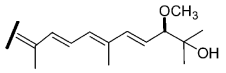
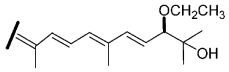
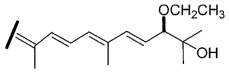
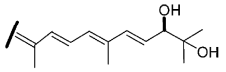
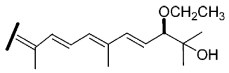
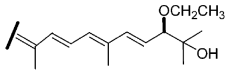
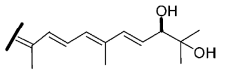
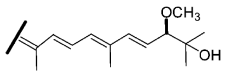
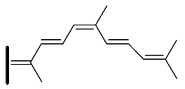
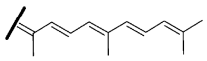
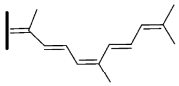
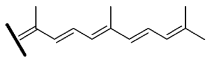
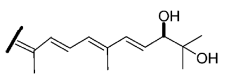
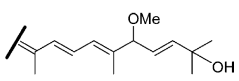
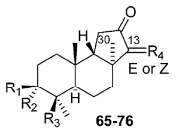
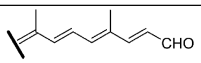
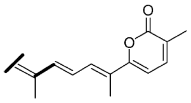
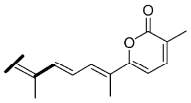
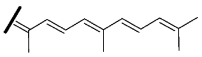
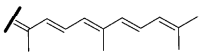
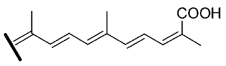
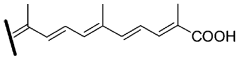
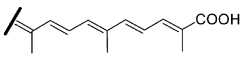
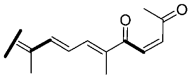
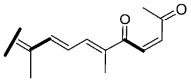
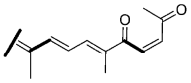
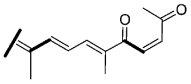
Compound	Δ^{13}	R^1	R^2	R^3	R^4	Source
Globostellatic acid F (**49**)	*Z*	H	OH	COOH		*R. globostellata*[56]
Globostelletin (**50**)	*Z*	H	OH	CH_3		*R. globostellata*[56]
Globostellatic acid G (**51**)	*Z*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid I (**52**)	*Z*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid K (**53**)	*Z*	H	OAc	COOH		*R. globostellata*[56]
Globostellatic acid M (**54**)	*Z*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid H (**55**)	*E*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid J (**56**)	*E*	H	OAc	COOH		*R. globostellata*[56]
Globostellatic acid L (**57**)	*E*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid E (**58**)	*Z*	H	OAc	$COOCH_3$		*Jaspis* species[63]
13*Z*,17*Z*-Globostellatic acid X methyl ester (**59**)	*Z*	H	OAc	$COOCH_3$		*R. globostellata*[64]
13*Z*,17*E*-Globostellatic acid X methyl ester (**60**)	*Z*	H	OAc	$COOCH_3$		*R. globostellata*[64]
13*E*,17*Z*-Globostellatic acid X methyl ester (**61**)	*E*	H	OAc	$COOCH_3$		*R. globostellata*[64]
13*E*,17*E*-Globostellatic acid X methyl ester (**62**)	*E*	H	OAc	$COOCH_3$		*R. globostellata*[64]
Globostellatic acid F methyl ester (**63**)	*E*	H	OAc	$COOCH_3$		*R. globostellata*[64]
Globostellatic acid B methyl ester (**64**)	*E*	H	OAc	$COOCH_3$		*R. globostellata*[64]

Table 8 Triterpenes with the isomalabaricane skeleton (jaspolides-stelletins)



65-76

Compound	Δ^{13}	R^1	R^2	R^3	R^4	Source
3-*O*-Acetyl-jaspiferal B methyl ester (**65**)	*Z*	H	OAc	$COOCH_3$		*Jaspis* species[63]
Jaspolide A (**66**)	*Z*	OH	H	CH_3		*Jaspis* species[65]
Jaspolide B (**67**)	*E*	OH	H	CH_3		*Jaspis* species [65]
Stelletin J (**68**)	*Z*	OH	H	CH_2OH		*R. globostellata*[66]
Stelletin K (**69**)	*Z*	OH	H	COOH		*R. globostellata*[66]
Stelletin I (**70**)	*Z*	OAc	H	CH_3		*R. globostellata*[67]
Stelletin L (**71**)	*E*	OH	H	CH_3		*Stelletta tenuis*[68]
Stelletin M (**72**)	*Z*	OH	H	CH_3		*S. tenuis*[68]
Isogeoditin A (23*Z*) (**73**)	*Z*,*E*	O	O	CH_3		*R.* aff. *distincta*[69]
Isogeoditin B (23*Z*) (**74**)	*Z*	OAc	H	CH_3		*R.* aff. *Distincta*[69]
Geoditin A (23*E*) (**75**)	*Z*	O	O	CH_3		*R.* aff. *distincta*,[69] *G. japonica*[70]
Geoditin B (23*E*) (**76**)	*Z*	OAc	H	CH_3		*R.* aff. *distincta*,[69] *G. japonica*[70]

A/29-hydroxystelliferin B and stelliferin G/13 E-stelliferin G showed antiproliferative activity against melanoma cells (MALME-3M),[104] with an IC_{50} value of 0.11 and 0.23 μg/mL respectively. Stelliferin riboside **44** and 3-*O*-deacetyl-13, 14 *Z*-stelliferin riboside **45** showed potent activity against the mouse lymphoma cell line L5178Y.[56]

Stelliferin riboside **44** and the 3-*epi*-acetate derivative of 29-hydroxystelliferin **E 41** were shown to induce 29% and 23% DNA-polymerase β binding, respectively, at 28 μg/mL. These compounds displayed varying levels of activity toward the A2780 ovarian cancer cell line, revealing structure-based effects on both the level of cytotoxicity and DNA-polymerase β binding.[66]

Globostellatic acids E–M showed potent activity against the mouse lymphoma cell lne L5178Y, with ED_{50} values of 0.3–10.4 nM. They were weakly active or inactive against a human cervix carcinoma HeLa and rat pheochromocytoma PC-12 cell lines.[56] Six globostellatic acids methyl esters **59–64**, especially those with 13*E* geometry **61–64**, exhibited a high selective index value in antiangiogenic activity, inhibiting proliferation of human umbilical vein endothelial cells selectively in comparison with other cell lines.[64]

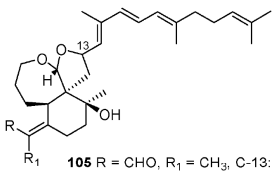
Stelletins L and M (**71–72**) also showed interesting cytotoxic activity against stomach cancer.[68] Some isomalabaricanes possess antimicrobial activities, thus stelliferin ribosides **44–46** show activity against *E. coli*, presenting an inhibition zone of 12 mm at a loading concentration of 10 μg. Globostelletin (**50**) and globostellatic acids G and I (**51–52**) show moderate activities against *E. coli*, and globostelletin also inhibits *Bacillus subtilis*,

with inhibition zones of 12 and 13 mm at concentrations of 5 and 10 μg.[56]

2.2 Triterpenes derived from processes of cyclization of S or OS towards polycyclic triterpenes and subsequent retrocyclization reactions from pentacyclic carbocation intermediates

Oxidosqualene cyclases (OSCs) have been recognized to catalyze carbon-carbon bond formations and rearrangements including hydride and methyl groups to finally produce different polycyclic structures. However, recent reports by Matsuda and Ezibuka's groups of the identification of a marneral synthase yielding the A-ring-*seco*-triterpene marneral on one hand, and an OSCs yielding *seco*-amyrins revealed that OSCs have the ability to cleave preformed ring systems in addition to forming multiring systems. Bearing these findings in mind, we have established a new group of triterpenes which includes those structures derived from an OSC-mediated annulation of S or OS to give, in an earlier part of the reaction, a carbenium ion intermediate possessing bi-, tetra- or pentacyclic systems, which in a later process undergo fragmentations of the previously generated rings to produce *seco*-bi-, tetra- and pentacyclic triterpenes. However, those *seco*-triterpenoids arising from postcyclization steps,[71,72] are not included here.

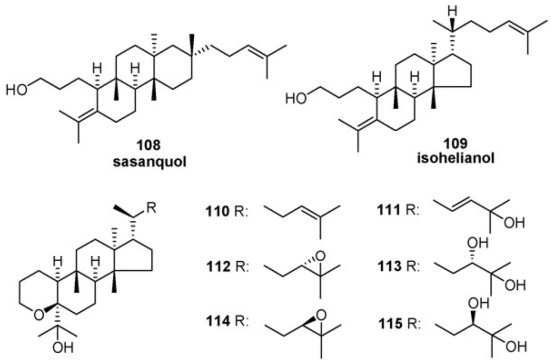
***Seco*-bicyclic triterpenes: Iridals.** The iridal skeleton is a 3,4-*seco*-abeo-10→9,27 polypodane, and most of the iridals are characterized by a carbonyl function on position C-1, and an alcohol, ester, or glucoside on C-3, often accompanied by different epoxide-, alcohol-, ketone-type oxygenated functions (Table 9). They can be classified into four broad groups: simple iridals **77–91**, spiroiridals **92–97**, glycoside iridals **98–104**, and oxaspiroiridals **105–107**. Iridals are found only in plants of the family Iridaceae, mainly in the genus *Iris*, although some were found in the genera *Belamcanda* and *Tigridia*. Marneral (**77**) and marnerol (**78**) were produced by a new OSC encoded by the gene *At5g42600* of *Arabidopsis thaliana*.[72]



105 R = CHO, R_1 = CH_3, C-13: *S*
106 R = CHO, R_1 = CH_3, C-13: *R*
107 R = CH_3, R_1 = CHO, C-13: *S*

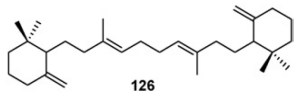
***Seco*-tetracyclic triterpenes.** Sasanquol (**108**) was isolated from sasanqua oil, obtained from the seeds of *Camellia sasanqua*.[84] The remaining 3,4-*seco* tetracyclic triterpenes reported (**109–115**) were isolated from the diethyl ether extract of the pollen grains of sunflower (*Helianthus annuus*). Compounds **109–115** showed potent inhibitory effects of the induction of Epstein-Barr virus early antigen induced by the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate.[85]

***Seco*-pentacyclic triterpenes.** Ten compounds listed in Table 10 have been considered as *seco*-pentacyclic triterpenes. Eight of them were isolated from plants of the families Asteraceae and Polypodaceae, and two were obtained in the laboratory using *Arabidopsis thaliana* OSC mutants.[87] The structures of **116** and **117** were confirmed by X-ray diffraction analysis of the corresponding ketone at C-3.[86]



2.3 Triterpenes deriving from two independent cyclization processes of S or OS derivatives

Bis-(6,11-cyclofarnesa-2,7(14)-diene) **126**, isolated from an anoxic sulfur-rich sediment, is a unique example of the cycloachillane skeleton.[90]



Cycloiridals. Although a number of cycloiridals were reported before 1998, only two of these triterpenes have been described in the last ten years, namely, hoogianal (**127**) from *Iris hoogiana*[91] and iridotectoral B (**128**) from *Iris tectorum*.[80]

The oxidative degradation of hoogianal yielded β-irone, a compound of interest in perfumery due to its violet aroma.[91]

Onoceranes. Two onoceranes (**129–130**), tetracyclic triterpenes with a symmetrically substituted bisdecalin skeleton, and one *seco*-onocerane (**131**) were isolated in 2002 from the fruit peel of *Lansium domesticum*.[92]

These triterpenoids exhibited mild toxicity against brine shrimp (*Artemia salina*).[92]

Sipholanes. Kashman *et al.* defined the sipholane skeleton as the assembling of two tetramethyl perhydrogenated bicyclic

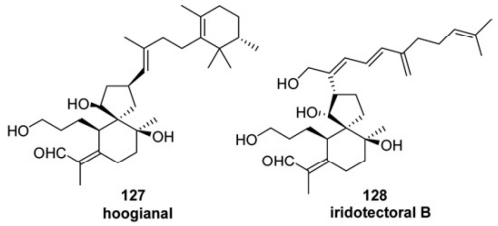
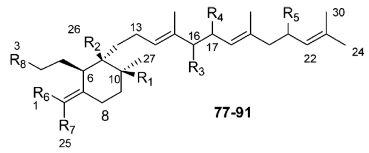
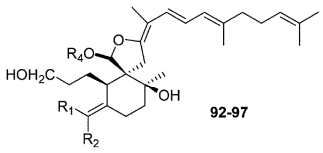
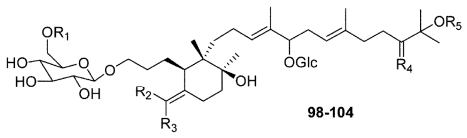


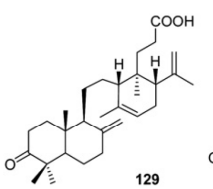
Table 9 *Seco*-Bicyclic triterpenes with the iridal skeleton

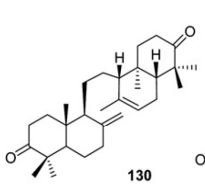


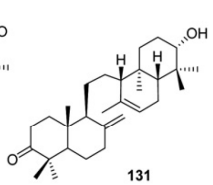




Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Source
Marneral (**77**)	H	CH_3	H	H	H	CH_3	CH_3	CHO	Gene expression: [*At5g42600*][72]
Marnerol (**78**)	H	CH_3	H	H	H	CH_3	CH_3	CH_2OH	Gene expression: [*At5g42600*][72]
23-Hydroxyiridal (**79**)	OH	CH_3	H	H	Δ^{21}	CHO	CH_3	CH_2OH	*I. variegata*[73]
18,19-Epoxy-10- deoxyiridal (**80**)	H	CH_3	H	H	H	CHO	CH_3	CH_2OH	*I. germanica*[74]
18,19-Epoxyiridal (**81**)	OH	CH_3	H	H	H	CHO	CH_3	CH_2OH	*I. versicolor*[75]
16,26-Dihydroxyiridal (**82**)	OH	CH_2OH	OH	H	H	CHO	CH_3	CH_2OH	*I. versicolor*[75]
22,23-Epoxi-21-hydroxyiridal (**83**)	OH	CH_3	H	H	OH	CHO	CH_3	CH_2OH	*I. cristata*[76]
22,23-Epoxyiridal (**84**)	OH	CH_3	H	H	H	CHO	CH_3	CH_2OH	*I. cristata*[76]
22,23-Epoxy-10-deoxy-21-hydroxyiridal (**85**)	H	CH_3	H	H	OH	CHO	CH_3	CH_2OH	*I. cristata*[76]
Iritectol A (**86**)	OH	CH_3	OH	H	H	CHO	CH_3	CH_2OH	*I. tectorum*[77]
Iritectol B (**87**)	OH	CH_3	O	H	H	CHO	CH_3	CH_2OH	*I. tectorum*[77]
Iridobelamal A (**88**)	OH	CH_3	α-OH	H	H	CH_3	CHO	CH_2OH	*B. chinensis*,[79] *I. tectorum*[77]
3-*O*-Decanoyl-16-*O*-acetylisoiridogermanal (**89**)	OH	CH_3	β-OAc	H	H	CHO	CH_3	Myristic acid	*B. chinensis*[78]
3-*O*-Tetradecanoyl-16-*O*-acetylisoiridogermanal (**90**)	OH	CH_3	β-OAc	H	H	CHO	CH_3	Capric acid	*B. chinensis*[78]
Iristectorone K (**91**)	—	—	—	—	—	—	—	—	*I. germanica*[79]
Iridotectoral A (**92**)	CH_3	CHO	—	H	—	—	—	—	*I. tectorum*,[80]
(13*R*)-Iridotectoral C (**93**)	CHO	CH_3	—	CH_3	—	—	—	—	*I. tectorum*[81]
(13*R*)-Iridotectoral D (**94**)	CH_3	CHO	—	CH_3	—	—	—	—	*I. tectorum*[81]
(13*S*)-Iridobelamal B (**95**)	CHO	CH	—	CH_3	—	—	—	—	*B. chinensis*[80]
Belachinal (**96**)	CHO	CH_3	—	H	—	—	—	—	*B. chinensis*[78]
Tigridal (**97**)	CHO	CH_3	—	H	—	—	—	—	*Tigridia pavonea*[82]
98	Glc	CHO	CH_3	O	H	—	—	—	*I. spuria*[83]
22-Oxo-23-hydroxy-iridal-3,16-di-β-D-glucopyranoside (**99**)	H	CHO	CH_3	O	H	—	—	—	*I. spuria*[83]
22,23-Dihydroxy-iridal-3,16-di-β-D-glucopyranoside (**100**)	H	CHO	CH_3	H,OH	H	—	—	—	*I. spuria*[83]
22-Oxo-isoiridal-3,16,23-tri-β-D-glucopyranoside (**101**)	H	CH_3	CHO	O	Glc	—	—	—	*I. spuria*[83]
102	Glc	CH_3	CHO	O	H	—	—	—	*I. spuria*[83]
22-Oxo-23-hydroxy-isoiridal-3,16-di-β-D-glucopyranoside (**103**)	H	CH_3	CHO	O	H	—	—	—	*I. spuria*[83]
22,23-Dihydroxy-isoiridal-3,16-di-β-D-glucopyranoside (**104**)	H	CH_3	CHO	H,OH	H	—	—	—	*I. spuria*[83]



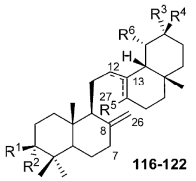




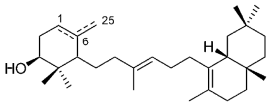
systems, namely a benzoxepine and a *cis*-azulene linked by a two carbon bridge. The structure of the sipholane skeleton was established by X-ray diffraction analysis.[93] In the last ten years, four sipholenols (**132–135**) were isolated, as for the rest of the sipholanes, from the Red Sea sponge *Siphonochalina siphonella*.[94–96]

Siphonellines. Two recently reported siphonellines were also isolated *S. siphonella*.[95,96] Their structures coincide in the

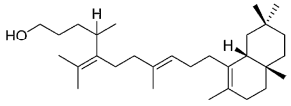
Table 10 *Seco*-pentacyclic triterpenes



116-122

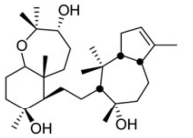


123-124

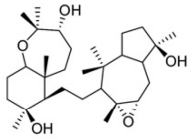


125

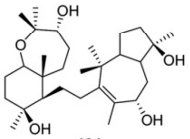
Compound	Δ	R^1	R^2	R^3	R^4	R^5	R^6	Source
8,14-*Seco*-oleana-8(26),13-dien-3β-ol (**116**)	$\Delta^{14(27)}$	OH	H	CH_3	CH_3	CH_3	H	*Stevia viscida*[86]
8,14-*Seco*-oleana-8(26),13-dien-3β-acetyl (**117**)	$\Delta^{14(27)}$	OAc	H	CH_3	CH_3	CH_3	H	*S. eupatoria*[86]
β-*Seco*-amyrin (**118**)	Δ^{7},$\Delta^{14(27)}$	OH	H	CH_3	CH_3	CH_3	H	Gene expression: [*At1g78500*][87]
α-*Seco*-amyrin (**119**)	Δ^{7},$\Delta^{14(27)}$	OH	H	CH_3	H	CH_3	CH_3	Gene expression: [*At1g78500*][87]
8,14-*Seco*taraxastane (**120**)	$\Delta^{8(26)}$,Δ^{12}	OH	H	H	CH_3	CH_3	CH_3	*Koelpinia linearis*[88]
8,14-*Seco*taraxastane (**121**)	$\Delta^{8(26)}$,Δ^{13} isomer	OH	H	H	CH_3	CH_3	CH_3	*K. linearis*[88]
8,14-*Seco*-20-hydroxy-taraxastane (**122**)	Δ^{12}	OH	H	OH	CH_3	H	CH_3	*K. linearis*[88]
Achilleol B (**123**)	$\Delta^{6(25)}$	—	—	—	—	—	—	*Achillea odorata*[89]
Camelliol A (**124**)	$\Delta^{1(6)}$	—	—	—	—	—	—	*Camellia sasanqua*[19]
Camelliol B (**125**)	—	—	—	—	—	—	—	*C. sasanqua*[19]



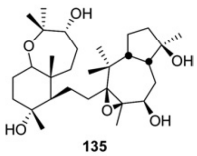
132
sipholenol F



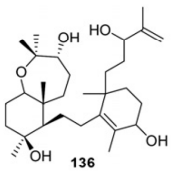
133
sipholenol G



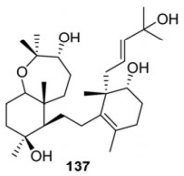
134
sipholenol H



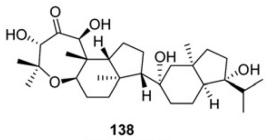
135
sipholenol I



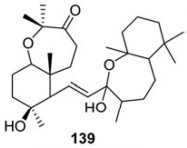
136
siphonellinol B



137
siphonellinol C



138
neviotine B



139
dahabinone A

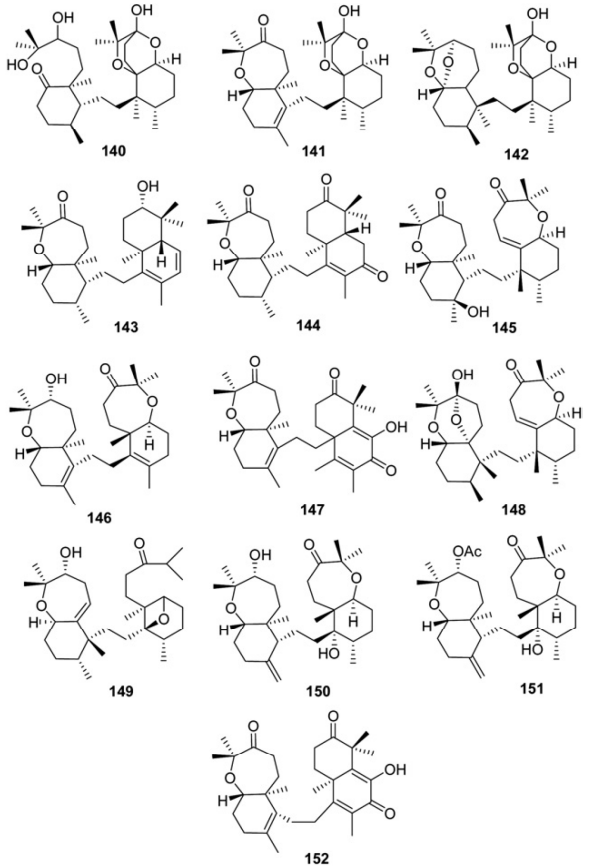
presence of a decahydrotetramethylbenzooxepine linked by an ethylene bridge to a cyclohexenol derivative. No significant bioactivities were reported for these siphonellines.

Neviotines and dahabinone A. Structurally related to sipholanes and siphonellines, neviotine B (**138**) and dahabinone A (**139**) are, respectively, pentacyclic and tetracyclic triterpenes isolated from *S. siphonella*.[95]

Sodwanones. Six new sodwanones (**140–145**) were isolated from the marine sponge *Axinella weltneri* and seven from an unnamed species of *Axinella* collected in the Indo-Pacific (**146–152**).[97,98,99] With structural similarities to sipholanes, both carbo- and heterocyclic rings are present in the skeleta of the different sodwanones that have been described – their number varying from four to six. However, two different ring systems are always present in this kind of compound. The structures of some sodwanones were confirmed by X-ray diffraction analysis.[100]

A number of sodwanones have been found to possess cytotoxic activity against different cell lines. The cytotoxic activities of sodwanone S (**145**) were evaluated against 13 human tumor lines.[98] Sodwanone V (**148**) inhibited hypoxia-induced HIF-1 activation in T47D breast tumor cells and PC-3 prostate tumor cells (IC_{50} 15 μM).[99]

Yardenones. Yardenones are pentacyclic triterpenes isolated from three Red Sea sponges belonging to the same Axenilledae family, namely, *Ptilocaulis spiculifer*, *Axinella cf. bidderi* and a new species of *Axinella* (Table 11).[97,99,101,102] These compounds are similar to other marine terpenes in that they are comprised of two halves, the left one being again a perhydro-tetramethylbenzooxepine. Yardenone A and B showed weak activity with the human lung carcinoma cell line NSCLC-N6.[102]



Abudinols and muzitone. Abudinol A (**158**) and B (**159**) are two pentacyclic structures also isolated from *P. spiculifer*.[97,101] It is also found in the same species muzitone (**160**), which is a tetracyclic triterpene thought to be derived from abudinol B.

Raspacionins. Eight raspacionins (**161–168**) have been isolated from *Raspaciona aculeata*, a Mediterranean sponge collected on the Sicilian coast (Table 12).[103] These compounds are comprised of two benzoxepine-derived moieties linked by an ethylene bridge. The structure of the first raspacionin reported was confirmed by X-ray analysis.[104] Raspacionins possess moderate antifeedant and cytotoxic activities.[103]

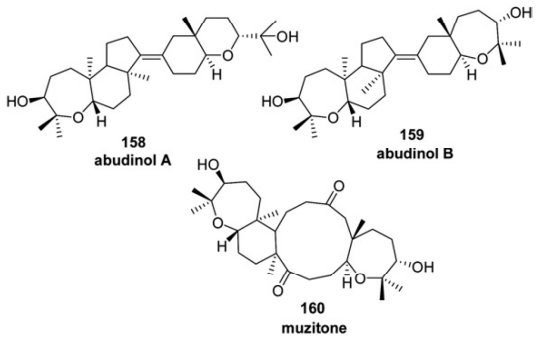
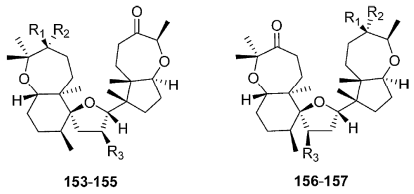


Table 11 Triterpenes with the yardenone skeleton



Compound	R^1	R^2	R^3	Source
Yardenone (**153**)	O	O	H	*Ptilocaulis spiculifer*,[97] Axinella *species,*[99] Axinella cf. bidderi[102]
Yardenone A (**154**)	O	O	OH	*A. cf. bidderi*[102]
Yardenone B (**155**)	H	OH	H	*A. cf. bidderi*[102]
Dihydroyardenone (**156**)	H	OH	H	*P. spiculifer*[97,101]
12*R*-Hydroxyyardenone (**157**)	O	O	OH	*Axinella* species[99]

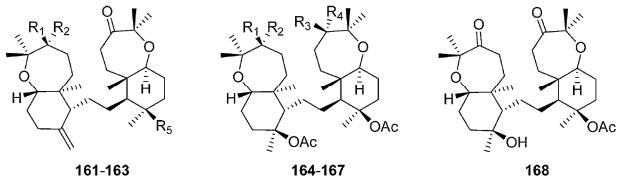
3 Biosynthesis of unusually cyclized triterpenes

Since the postulation of the isoprene biogenetic rule by Ruzicka *et al.*,[8,9] considerable progress has been made in understanding the biogenesis of the more than 100 known triterpene skeletons.[4–7,10,105,106] The cyclization mechanism is initiated by protonation of S or OS or other related initiators. The carbocation thus formed triggers a cascade of cyclizations by electrophilic addition to olefins, generating carbocations. The corresponding cyclic cations are stabilized by loss of a proton or by addition of water or other nucleophiles, just after the cyclization or after going through different 1,2-antiperiplanar rearrangements. The interest in this type of mechanism has led to the involvement of molecular biology, genetics, biochemistry, etc. in this topical scientific field, thus more than 30 OSCs and SCs have been characterized. Cloning of different OSCs and SCs has led to the identification of poly- and monofunctional cyclases that yield a single product or various, and experiments of directed mutagenesis have shown that changes in a single amino acid can cause profound alterations in their specificity.[27,87,105,107]

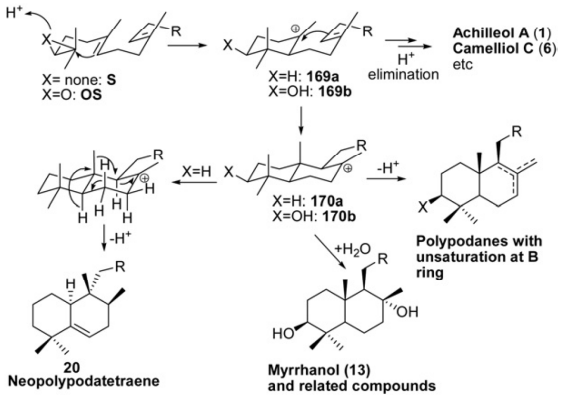
It is currently accepted that in the mechanism of cyclizations[105] mediated by OSC and SC, the cyclases provide a template that folds the flexible acyclic substrate and the carbocation intermediates in a series of conformations which define the regio- and stereospecificity of the process. The carbocation intermediates generated are stabilized with electron-rich environments, namely cation-π interactions with aromatic residues of Phe, Tyr, and Trp. This stabilization favours the cyclization kinetics, making the process more selective.[52,108,109] Finally, the terminal carbocations are neutralised either by the selective loss of a proton from a basic center of the enzyme or by addition of water.

In this review, we have highlighted summarized schemes of the main biosynthetic routes, either established or proposed, towards unusually cyclized triterpenes. In this context, the most recent advances in the enzymatic synthesis of cyclic triterpenes have been reviewed by Abe.[105]

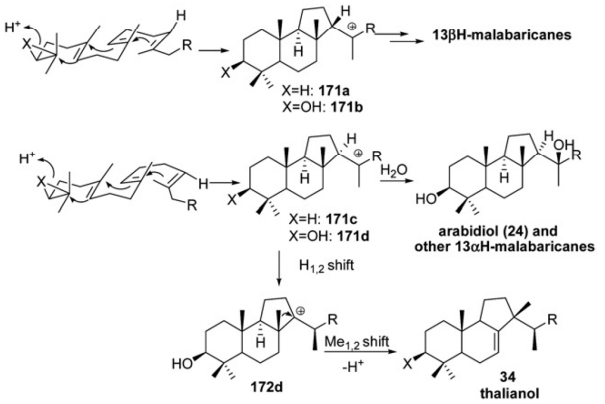
Table 12 Triterpenes with the raspacionin skeleton



Compound	R^1	R^2	R^3	R^4	R^5
21-Deacetyl-21-oxoraspacionin (**161**)	OH	H	—	—	OAc
15-Deacetyl-21-oxoraspacionin (**162**)	OH	H	—	—	OH
4,21-Dioxoraspacionin (**163**)	O	O	—	—	OAc
10-Acetoxy-4-acetyl-21-oxo-28-hydroraspacionin (**164**)	OAc	H	O	O	—
10-Acetoxy-4-acetyl-28-hydroraspacionin (**165**)	OAc	H	H	OAc	—
10-Acetoxy-28-hydroraspacionin (**166**)	OH	H	H	OAc	—
10-Acetoxy-21-deacetyl-4-acetyl-21-oxo-28-hydroraspacionin (**167**)	OAc	H	H	OH	—
10-Hydroxy-4,21-dioxo-28-hydroraspacionin (**168**)	—	—	—	—	—



Scheme 1 Proposed biosynthesis of achillanes and polypodanes.



Scheme 2 Proposed biosynthesis of malabaricanes.

3.1 Biosyntheses mediated by OSC and SC. Triterpenes originating from a single cyclization

Monocyclic triterpenes. It has been proposed that achillanes are biosynthesized as a result of a monocyclization of OS either towards achilleol A and derivatives **1–4**, or towards camelliol C **6**, *via* the monocyclic carbocation **169** (Scheme 1).[13,19,20] At the same time, 3-deoxyachilleol A **5**, monocyclosqualene **7**, and **8** would be formed in a similar transformation by monocyclization from S. More recently, Matsuda *et al.* reported that the *Arabidopsis thaliana* gene *Atl78955* encodes an enzyme that transforms OS mainly into camelliol C **5**, together with small amounts of achilleol A **1** and β-amyrin. This enzyme was named camelliol C synthase (CAMS1).[27] Sequence alignments show that nearly all plant cyclases contain Val or Ile at the position corresponding to Ala484 in CAMS1. The decreased steric bulk at this position is postulated to justify the formation of the monocycle.

It has also been found that several mutants of SHC,[21] lanosterol synthase,[24] and cycloartenol synthase[25,26] produce achilleol A **1** or camelliol C **6**. Mutants of *Alicyclobacillus acidocaldarius* generate achillanes **5**, **7** and **8**.[31]

Bicyclic triterpenes. The formation of all the bicyclic triterpenes, polypodanes with or without an oxygenated function on C-3, should involve a cyclization of either OS or S, respectively. The acyclic precursors are postulated to adopt a chair-chair conformation, that would produce after the cyclization process, carbocation intermediates **170a** and **170b**. From these, deprotonations, hydrations, rearrangement-deprotonations and, in some cases oxidations, would lead to all the known polypodanes (Scheme 1).

While it has not been demonstrated experimentally that an OSC makes polypodanes, SHC mutants from *A. acidocaldarius*[29,34,38,40,110] produce polypodatetraenes **10** and **11**, as well as from the rearranged derivative **20**.

Tricyclic triterpenes. The malabaricane tricyclic triterpenes are thought to be formed in a triple cyclization of OS or S *via* chair-chair-chair conformations or chair-chair-boat conformations

leading to the tricyclic 6,6,5 carbocations **171a–171d** (Scheme 2). Deprotonations or hydration of tricyclic cations **171a–171b**, accompanied in some cases by epoxidations of the side chain and opening of epoxides to tetrahydrofuran derivatives produce the natural 13β-H malabaricanes. Similarly, intermediates **171c** and **171d** can evolve to either 13α-H malabaricanes or, after hydride- and methyl-shifts, to the so-called rearranged malabaricanes such as thalianol **34**.

It has been found that two *A. thaliana* genes, namely *At4g15340* and *At5g4810*, encode OSCs that produce arabidiol **24** and its 20,21-epoxide **25**, and thalianol **34** and its 21,22 epoxide **35**, respectively.[48,51] The mechanism of their formation is rationalized *via* the tricyclic carbenium ion **168d**, which either rearranges to **172d** and, by a subsequent H-9 elimination, affords **34**, or undergoes stereospecific addition of water to give **24**. In an *A. acidocaldarius* SHC elimination of the residue Gly600, which is located close to the place of formation of ring D, generated a mutant that was incubated with OS to produce malabaricanes **21** and **24** and rearranged malabaricanes **34** and **36**, together with achilleol A **1**.[21] Similarly, a number of malabaricanes and rearranged malabaricanes have been obtained by site-directed mutagenesis of *A. acidocaldarius* SCH, which includes point mutants of Phe601, Ile261, Tyr420, etc.[11,105]

Isomalabaricanes, the other large group of 6,6,5 tricyclic triterpenes, have the opposite stereochemistry at C-8 and C-9 to that of the malabaricanes. The biogenetic origin of these compounds is thought to involve cyclizations of chair-boat conformations of S or OS leading to the tricyclic carbocations **173a,b**. Deprotonation of H-13, oxidation on C-12 to carbonyl group, and different dehydrogenations and oxidations, mainly on the side chain, generate the great variety of natural isomalabaricanes (Scheme 3). Tyr510 mutants were proved to afford isomalabaricatrienol **48**, which is considered a putative precursor of isomalabaricane triterpenoids in sponges.[23]

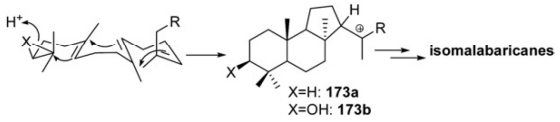
3.2 Biosynthesis of triterpenes *via* processes of cyclization of S or OS towards polycyclic triterpenes and subsequent retrocyclization reactions

***Seco*-bicyclic triterpenes: Iridals.** Marner postulated that the biosynthetic origin of iridals present in the *Iris* family involves an intermediate similar to that of polypodanes, although the stereochemistry of the majority of 10-deoxyiridals indicates that the double cyclization must proceed *via* a chair-boat conformation of OS leading to bicyclic cation **173c**. A series of 1,2-shifts would lead to **173d**, which would then undergo a Grob fragmentation to produce the aldehyde precursor of iridals (Scheme 4).[111,112]

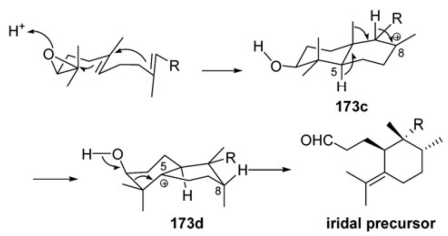
Reduction of the aldehyde group, oxidation by monooxygenases at C-1 and/or C-25, C-10, C-16, C-17, C-26, and C-13, or dehydrogenation on the side chain, would give rise to many of the iridals described. In support of Marner's hypothesis, it has recently been established that the *A. thaliana* gene *At5g42600* encodes a new OSC (called marneral synthase)[72] that catalyses the formation of the iridal marneral 77 and its reduction product marnerol **78**. Analysis of the sequence alignments for marneral synthase showed that this cyclase contains Gly at the position corresponding to Cys456 in other OSCs. The crystal structure of HLC showed that Cys456 is linked by a hydrogen bond to the Asp455 catalytic center which protonates the oxirane. This change may facilitate the mobility of Asp455 and would then help the deprotonation of H-5 and the fragmentation of the A ring.

***Seco*-tetracyclic triterpenes.** Sasanquol (**105**) is the only 3,4-*seco* triterpene thought to be biosynthesized by Grob fragmentation from a 6-6-6-6-fused ring cationic intermediate (**175**). The rest of the 3,4-*seco* tetracyclic triterpenes that have been reported arise from the corresponding 6-6-6-5-ring-fused cations (**174**) (Scheme 5).[87]

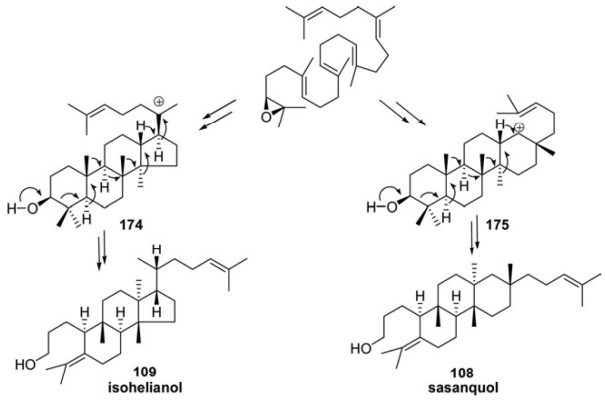
***Seco*-pentacyclic triterpenes.** Although preliminary reports on the biosynthetic proposal of some *seco*-oleananes isolated from *Stevia viscida* and *Stevia eupatoria* (**113–114**) include two different cyclization proccesses for the generation of the A–B and D–E bicyclic systems,[86] Ebizuka *et al.* have recently reported that the *A. thaliana* gene *At1g78500* encodes an OSC-homologue that is able to catalyse both the cyclization of OS leading to pentacyclic triterpenes and the subsequent cleavage of the C ring to afford α-*seco*-amyrin and β-*seco*-amyrin.[87] It was thus proposed that the pentacyclic oleanyl carbocation **171a** could lead to β-*seco*-amyrin (**115**) and the *seco*-oleanane **113** through C-8–C-14 bond cleavage and subsequent elimination of H-7 or H-25,



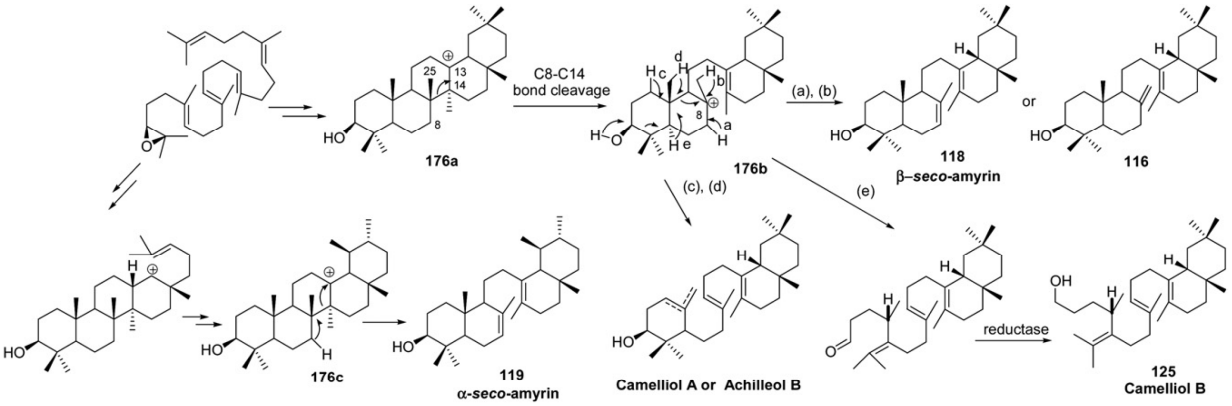
Scheme 3 Proposed biosynthesis of isomalabaricanes.



Scheme 4 Proposed biosynthesis of iridals.



Scheme 5 Proposed *seco*-tetracyclic triterpene biosynthesis.



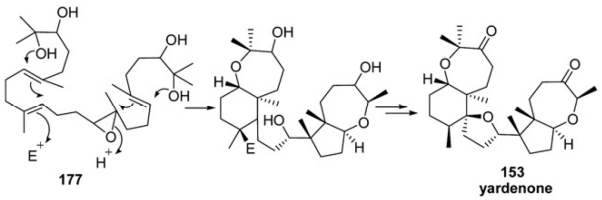
Scheme 6 Proposed biosynthesis of *seco*-pentacyclic triterpenes.

respectively (Scheme 6, pathway (a) and (b)). Moreover, camelliol A (**121**) or achilleol B (**120**) could be produced after a double retrocyclization process (Scheme 6, pathway (c) and (d)). The fragmentation of the B ring of these compounds could involve cleavage of the C-9–C-10 bond triggered by deprotonation of H-1 or H-25. A third pathway, which could include a Grob fragmentation, could lead to camelliol B **122**. On the other hand, the biogenesis of α-*seco*-amyrin (**116**) could involve the existence of intermediate **171c**, produced after the corresponding cyclization and methyl-shift.

3.3 Biosynthesis of triterpenes involving two independent cyclization processes

Cycloiridals are considered to be derived from iridals. It has been suggested that the biosynthesis of hoogianal proceeds *via* the corresponding iridals, which suffer a *S*-adenosylmethionine-mediated monocyclization initiated on the terminal double bond of the farnesyl side chain (Scheme 7). This proposal may well account for the presence of the additional carbon in these homotriterpenes.[111]

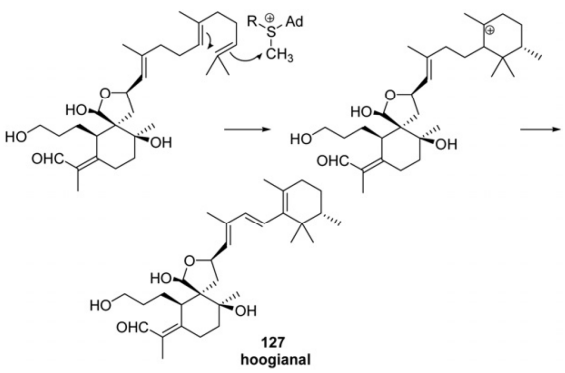
10,11-Epoxy-2,3-22,23-squalenetetraol as precursor. As seems to happen with most marine triterpenoids, the yardenone skeleton is presumably obtained after two separate cyclizations. In this case the precursor would be a squalene derivative dihydroxylated at both terminal isopropylidene moieties and possessing an epoxide at C-10–C-11 (**177**). Thus, the right and left parts formed during the biogenesis are proposed to start after activation of the internal 10,11-epoxide and the Δ^{14} double bond, respectively (Scheme 8).[94]



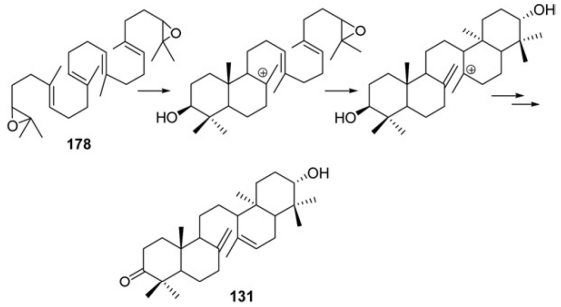
Scheme 8 Proposed biosynthesis of yardenones.

2,3-22,23-Diepoxysqualene as precursor. The origin of onoceranes such as **131** is thought to occur through an initial cyclization of bis-OS (**178**) to afford a bicyclic cation that is stabilized by deprotonation (Scheme 9). The bicyclic compounds which then arise could undergo a second process of cyclization at the epoxide located at the end of the chain, forming the tetracyclic carbocation, precursors of the natural product.

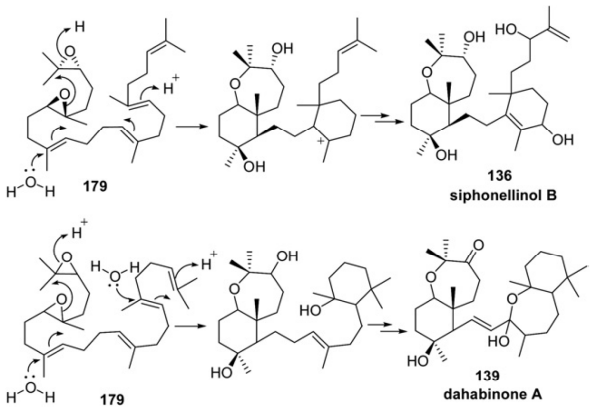
2,3-6,7-Diepoxysqualene as precursor. In the case of siphonellines (**136–137**) and dahabinone A (**139**), the two cyclizations



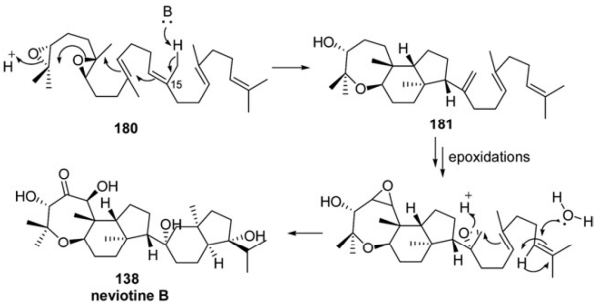
Scheme 7 Proposed biosynthesis of cycloiridals.



Scheme 9 Proposed biosynthesis of onoceranes.



Scheme 10 Proposed biosynthesis of siphonellinol B and dahabinone.



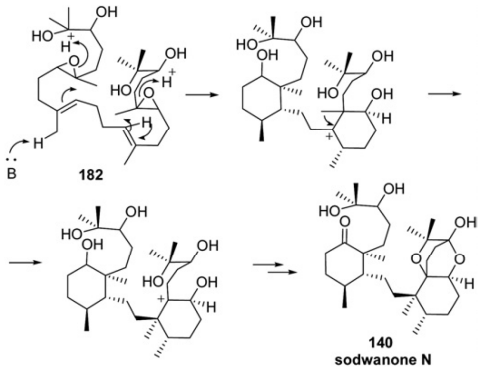
Scheme 11 Proposed biosynthesis of neviotine B.

which make up their skeleton take place in a common diepoxysqualene precursor (**179**) (Scheme 10).[94] It is worth noting that whereas the cyclization of the left part of this molecule would start from a terminal epoxide for both skeleta, the second cyclization could arise after protonation of an internal double bond in the case of the siphonellines, whereas the protonation could take place in the terminal isopropylidene for dahabinone A.

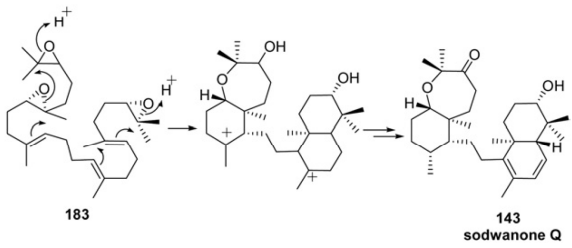
A more complex pathway seems to be involved in the biogenesis of neviotine B (**138**) (Scheme 11).[94] Thus, starting from the same diepoxide (**180**), a first cyclization could occur to give the intermediate tricyclic structure **181**. Then, the epoxide resulting derived from the methylene at C-15 could undergo a proton-induced opening, leading after a cascade cyclization process to the neviotane skeleton.

6,7-18,19-Diepoxy-2,3-22,23-squalenetetraol as precursor. Most of the sodwanones are thought to be derived from tri- or tetraepoxides. Nevertheless, in some of these natural products, i.e., sodwanone N (**140**), the left and right hand cyclizations may be limited to the formation of one cyclohexane ring which is formed after the acid activation of the corresponding epoxide (**182**) (Scheme 12).

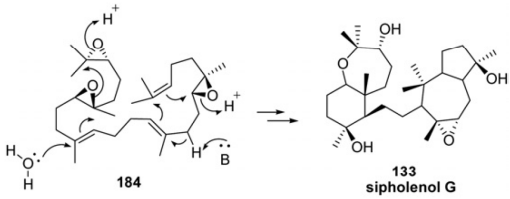
2,3-6,7-22,23-Triepoxysqualene as precursor. A significant number of sodwanones are biosynthesized after protonation of both terminal epoxides of a triepoxysqualene precursor (**183**) (Scheme 13).



Scheme 12 Proposed biosynthesis of sodwanone N.

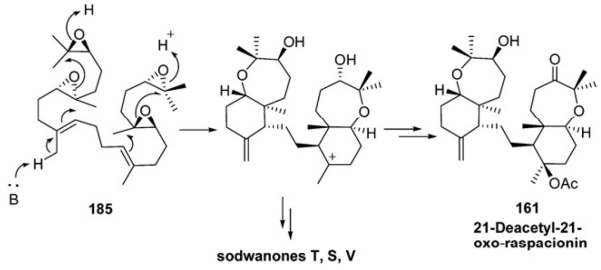


Scheme 13 Proposed biosynthesis of sodwanone Q.

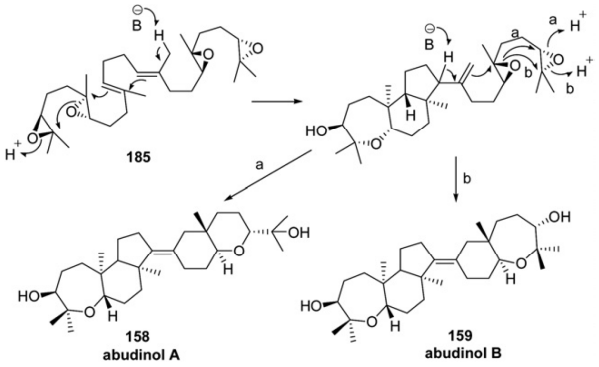


Scheme 14 Proposed shipolenol G biosynthesis.

2,3-6,7-18,19-Triepoxysqualene as precursor. Although the sipholanes share with siphonellines and some sodwanones the proposal for the origin of the left part, interestingly, the biogenesis of the right part would be induced by the protonation of an internal epoxide (**184**) (Scheme 14).



Scheme 15 Proposed biosynthesis of raspacionin.



Scheme 16 Proposed biosynthesis of abudinol.

2,3-6,7-18,19-22,23-Tetraepoxysqualene as precursor. The biogenesis of a number of tetracyclic sodwanones and all the reported raspacionins are thought to involve the presence of a tetraepoxy precursor (**185**). Symmetric acid-induced opening of the epoxides located at the terminal position of each C-15 subunit could lead to the corresponding tetracyclic structure (Scheme 15).

It has been proposed that the biosynthesis of abudinols involves the same tetraepoxyderivative of squalene (**185**). Once the first tandem cyclization takes place, abstraction of H-14 could trigger the generation of the tricyclic moiety (Scheme 16).

Kashman *et al.* proposed that abudinol B (**159**) could be involved in the biosynthesis of muzitone (**160**).[94]

4 Chemical syntheses of unusually cyclized triterpenes

Although a number of impressive syntheses of unusually cyclized triterpenes has been achieved in the last ten years,[113] we have included here only the syntheses of compounds whose occurrence has been reported since 1998 (shown in section 2).

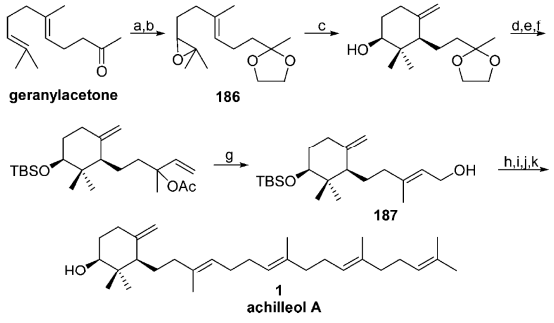
4.1 Achillanes

The synthesis of achilleol A **1** was planned on the basis of a C_{15}-C_{15} convergent strategy (Scheme 17).[114] The monocyclic sesquiterpenic elegansidiol (**187**) was obtained through a Ti-mediated radical cyclization of oxirane **186**, prepared from commercially available geranylacetone. Alcohol **175** was converted into allylic bromide which was then coupled with farnesylsulfone. Desulfonation with NaHg in MeOH and deprotection of the silyl ether with TBAF led to achilleol A **1**.

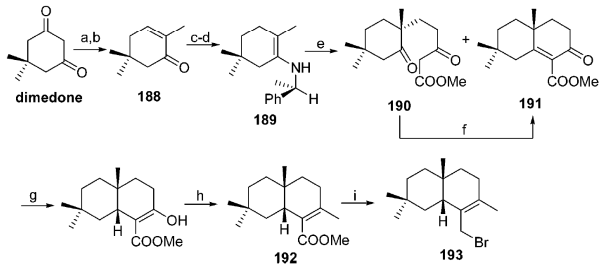
Very recently, our research group carried out the first total synthesis of (−)-achilleol B,[115] an achievement that led us to reassign the relative stereochemistry of the interannular junction as *cis*. The key steps employed in our synthesis were an enantioselective Robinson annelation for the construction of the bicyclic moiety,[116] and a Ti(III)-mediated cyclization of a chiral monoepoxide to construct the monocyclic moiety.

Scheme 18 summarizes the formation of the bicyclic synthon. Thus, based on the work of Heathcock,[117] ketone **188** was prepared from dimedone. Treatment of **188** with (*S*)-phenylethylamine led to enamine **189** which reacts with freshly prepared Nazarov reagent to obtain a mixture of the desired keto ester and its acyclic precursor **190**, which was converted into the keto ester by treatment with KF in MeOH. Reduction with H_2-Pd/C and treatment with the corresponding enol triflate with MeLi in the presence of $CuBr{\cdot}SMe_2$ gave the *cis*-decalin **192**. Subsequent reduction with $LiAlH_4$ and treatment with PBr_3 led to the allylic bromide **193**.

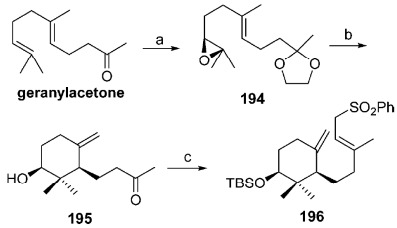
The monocyclic synthon was synthesized starting from geranylacetone (Scheme 19). Sharpless asymmetric dihydroxylation of this acyclic precursor led to the corresponding asymmetric diol. Protection of the carbonyl group, and



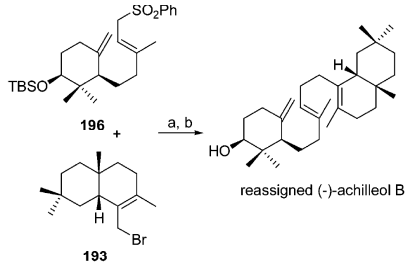
Scheme 17 *Reagents and conditions*: (a) Ethylene glycol, TsOH, 93%; (b) NBS, K_2CO_3, 71%; (c) Cp_2TiCl, 65%; (d) $CeCl_3$, NaI, 95%; (e) TBSCl, imidazole, DMAP, 72%; (f) i. allylmagnesium bromide; ii. Ac_2O, 68%; (g) i. $PdCl_2(MeCN)_2$; ii. K_2CO_3, MeOH, 88%; (h) PBr_3, DMAP, 75%; (i) *n*BuLi, $PhSO_2$-farnesyl, 74%; (j) NaHg, MeOH, 55%; (k) TBAF, 95%.



Scheme 18 *Reagents and conditions*: (a) i. NaOH, CH_3I, H_2O; ii. LAH, Et_2O; (b) PDC, DCM; (c) H_2, Pd/C, EtOAc; (d) (*S*)-phenylethylamine, PhH, 74%; (e) methyl 3-oxo-4-pentenoate, PhH, 41%; (f) KF, MeOH, 99%; (g) H_2, Pd/C, EtOAc, 91%; (h) i. Tf_2O, iPr_2EtN; ii. $CuBr{\cdot}SMe_2$, MeLi, 91%; (i) i. DIBALH, 94%; ii. PBr_3, 90%.



Scheme 19 *Reagents and conditions*: (a) i. AD-mix-β, $CH_3SO_2NH_2$, *t*BuOH/H_2O, 0 °C, 67%, ii. ethylene glycol, TsOH, 82%; iii. MsCl, Py, DMAP, K_2CO_3, MeOH, 74%, (b) i. Cp_2TiCl, 77%; ii. $CeCl_3$, NaI, 95%; (c) i. TBSCl, imidazole, DMAP, 91%; ii. diethyl phosphonoacetate, NaH, DIBALH, 74%; iii. PBr_3, DMAP, 75%; iii. $NaSO_2Ph$, DMF, 72%.



Scheme 20 *Reagents and conditions*: (a) i. *n*BuLi, THF, 71%; (b) i. Li, $EtNH_2$, THF; ii. TBAF, 86%.

treatment of the corresponding diol with mesyl chloride and subsequent treatment with base gave rise to oxirane **194**. Ti(III)-mediated cyclization of this epoxide led after deprotection of the ketyl group led to ketoalcohol **195**. Application of the Horner–Wadsworth–Emmons protocol to the corresponding silyl derivative provided the requisite two-carbon homologation. The corresponding unsaturated ester was converted to bicyclic sulfone **196** following straightforward transformations.

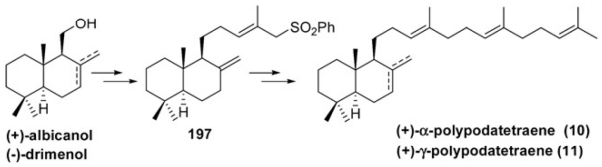
Finally, the target (−)-achilleol B was efficiently assembled as shown in Scheme 20.

4.2 Polypodanes

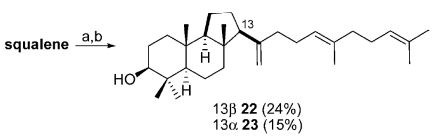
Akita *et al.* reported the synthesis of (+)-α-polypodatetraene **10** and (+)-γ-polypodatetraene **11**.[118] Starting from (+)-albicanol and (−)-drimenol respectively, the hydrocarbon chain was lengthened following straightforward transformations, including a Wittig reaction (Scheme 21). The subsequent formation of sulfone **197** enabled coupling with geranyl bromide to give, after desulfonation, the desired final products.[119]

4.3 Malabaricanes

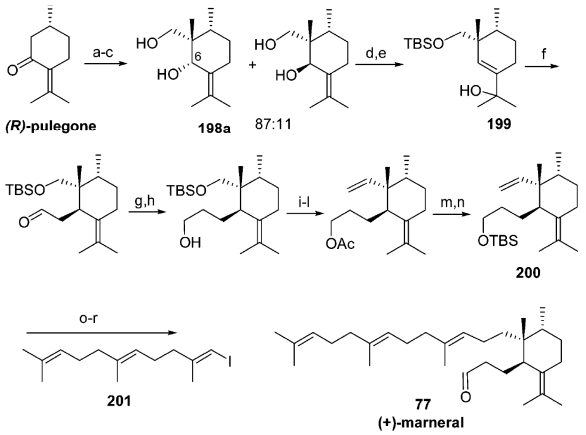
In our laboratories malabaricanes **22** and **23** were prepared through a titanocene-catalyzed cyclization of 2,3-oxidosqualene, mimicking the enzyme lanosterol synthase.[120] Treatment of OS with a catalytic quantity of Cp_2TiCl_2 led to a mixture of 13α- and 13β- malabaricanes in 39% yield (Scheme 22).



Scheme 21



Scheme 22 *Reagents and conditions*: (a) i. NBS, $MeOH/H_2O$; ii. K_2CO_3, MeOH; (b) Cl_2TiCp_2, Mn, TMSCl, collidine, THF, 39%.



Scheme 23 *Reagents and conditions*: (a) LDA, $ClCO_2Et$; (b) NaH-MeI (40%, 2 steps); (c) $LiAlH_4$; (d) AcOH (75%); (e) TBSCl (88%); (f) vinyl ether, $Hg(OAc)_2$, sealed tube, 190 °C, 2 d (80%); (g) Wittig (92%); (h) 9-BBN, NaOH-H_2O_2 (80%); (i) Ac_2O-DMAP (90%); (j) HF-MeCN; (k) Swern; (l) Wittig (79%, 3 steps); (m) K_2CO_3, MeOH, (n) TBSCl, DMAP (77%, 2 steps), (o) 9-BBN, THF, (p) $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, H_2O, DMF, 25 °C, 12 h (67%), (q) TBAF (87%); (r) Swern (96%).

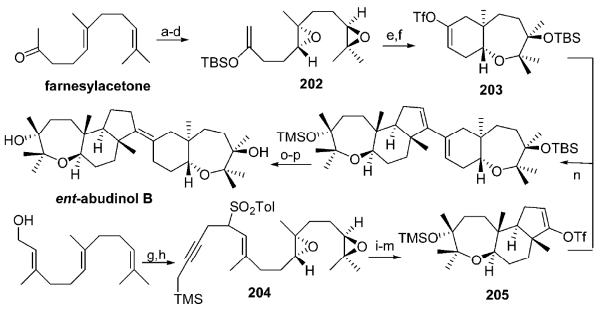
4.4 Marneral

In 2008, Arseniyadis *et al.* reported the convergent synthesis of (+)-marneral (Scheme 23).[121] This achievement was based on the B-alkyl Suzuki–Miyaura coupling of vinyl iodide **201** and the corresponding monocyclic counterpart **200**. Central to the elaboration of the monocyclic moiety was the mercury-catalyzed Claisen rearrangement of the allylic alcohol **199**, efficiently prepared from commercially available (*R*)-pulegone. X-Ray analysis of intermediate **198a** established the relative configuration of the final product.

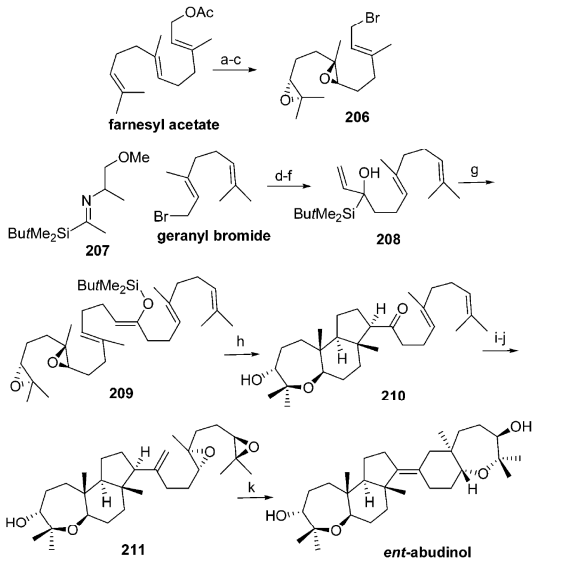
4.5 *ent*-Abudinol B

McDonald *et al.*[122] carried out the first synthesis of *ent*-abudinol B inspired by the biosynthesis proposed for abudinols A (**158**) and B (**159**), using cascade cyclizations of di-epoxides coupled to the corresponding enol-silane **202** or ene-propargylsilane **204** to construct the different carbocycles of the structure (Scheme 24). The key step was the Pd-catalyzed cross-coupling of ABC (**205**) and DE (**203**) units, which proceeded in 70% yield. Hydrogenation of the diene occurred in low yield (30%). Final desilylation provided the structure corresponding to *ent*-abudinol B.

In 2008 the same research group reported a total synthesis of the same triterpene *ent*-abudinol (Scheme 25).[123] The synthesis relies on Lewis acid promoted tandem oxa- and carbacyclizations of the squalene-like substrate **209**. This 29-carbon substrate was prepared by coupling of diepoxybromide **206** with the Brook rearrangement product of the lithium alkoxide of **207**. Compounds **206** and **208** were prepared from farnesyl acetate and geranyl bromide, respectively (Scheme 25). Me_3SiOTf-promoted tandem cyclization of **209** afforded tricyclic ketone **210** as the major product. Ketone **210** was converted to diepoxide **211** by methylenation and double enantioselective epoxidation of the



Scheme 24 *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0 °C, 90%; (b) Shi catalyst, Oxone, K_2CO_3, Na_2EDTA, DMM/MeCN/H_2O, 0 °C, 95%; (c) SO_3-pyridine, DMSO, Et_3N, DCM, 0 °C, 95%; (d) KHMDS, TBSCl, THF, −78 °C, 87%; (e) TBSOTf, DTBMP, DCM, −78 °C, 60%; (f) KHMDS, THF, −78 °C, then $PhNTf_2$, −78 °C, 95%; (g) Ph_3P, NBS, THF, 0 °C, then cat. Bu_4NI, $NaSO_2Tol$, 99%; (h) *n*BuLi, THF, −78 to −40 °C, then 1-bromo-4-trimethylsilyl-2-butyne, −78 to 20 °C, 92%; (i) Shi catalyst, Oxone, K_2CO_3, Na_2EDTA, DMM/MeCN/H_2O, 0 °C, 76%; (j) $Cl_2Pd(dppp)$, $LiEt_3BH$, THF, 0 °C, 71%; (k) TMSOTf, DTBMP, DCM, −78 °C, 75%; (l) Bu_4NF, THF, 99%; (m) O_3, DCM, −78 °C, then Me_2S, −78 to 20 °C, 88%; (f) 95%; (n) **205**, $Cl_2Pd(PPh_3)_2$, Ph_3P, PhOK, bis(neopentylglycolato)diboron, toluene, 50 °C, then **203**, $Cl_2Pd(dppf)$, K_3PO_4, DMF, 80 °C, 70%; (o) 10% Pd/C, toluene, H_2, 0 °C, 30%; (p) Bu_4NF, THF, 60 °C, 84%.



Scheme 25 *Reagents and conditions*: a) D-Epoxone (0.5 equiv), Oxone, pH 10.5 buffer, DMM/MeCN/H_2O, −5 °C, 54%; b) K_2CO_3, MeOH, 99%; c) MsCl, Et_3N, −40 °C, then LiBr, THF, 0 °C, 60%; d) LDA, THF, −30 °C, then **207**; e) NaOAc, HOAc, 84% (2 steps); f) $H_2C{=}CHMgCl$, Et_2O, 0 °C, then HCl, 88%; g) *n*BuLi, hexane/THF, −78 °C, then **206**, 50%. DMM = dimethoxymethane; h) Me_3SiOTf, DTBMP, CH_2Cl_2, −78 °C, then Bu_4NF, 50%; i) Ph_3PMeBr, KO*t*Bu, benzene, 80 °C, 30% (+55% C-14 epimer); j) D-Epoxone (0.5 equiv), Oxone, pH 10.5 buffer, DMM/MeCN/H_2O,−5 °C, 50%; k) Me_3SiOTf, DTBMP, CH_2Cl_2, −78 °C, then Bu_4NF.

trisubstituted double bonds. Again, trimethylsilyl triflate promoted a tandem oxa- and carbocyclization of **211** to provide *ent*-abudinol in modest yield.

5 Conclusions

There has been an increase in the description of new natural triterpenes derived from partial cyclization of squalene or 2,3-oxidosqualene in the last few years. In addition, the confirmation of the existence of OSCs specific for the formation of these compounds seems to indicate that these molecules are more widely distributed in Nature than might be expected *a priori*. At the same time, the biosynthetic proposals that suggest new retrocyclization mechanisms are involved in the biosynthesis of these molecules seem to widen the range of structural diversity in these irregular triterpenes, a possibility that should be explored in the future.

Marine organisms, mainly sponges, prove to be a remarkable source of triterpenes, which are structurally distant from those having a terrestrial origin. Many of these compounds, which often possess interesting biological properties, derive from cyclization of polyepoxides of squalene or 2,3-oxidosqualene. In our opinion, the scientific research into these unusually cyclized triterpenes constitutes a valid strategy for the advance in the understanding of the metabolism of natural products. This research should also contribute to the discovery of new bioactive molecules with potential applications.

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Artículo 2: *Enantioselective Total Synthesis of the Potent Anti-inflammatory (+)-Myrrhanol A, Domingo, V.; Silva, L.; Dieguez, H. R.; Arteaga, J. F.; Quilez del Moral, J. F.; Barrero, A. F., Journal of Organic Chemistry,* ***2009****, 74, 6151-6156.*

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Enantioselective Total Synthesis of the Potent Anti-inflammatory (+)-Myrrhanol A

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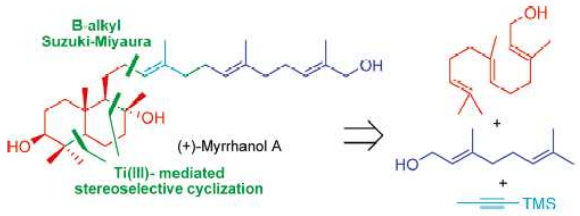
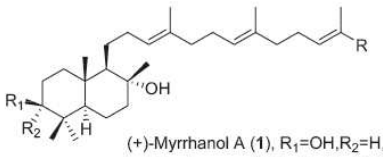
Received May 14, 2009



The first total synthesis of potent anti-inflammatory polypodanes (+)-myrrhanol A (**1**), (+)-myrrhanone A (**2**), (+)-myrrhanone B (**3**), and (+)-myrrhanol B (**4**) has been achieved. Key steps in our convergent, highly stereocontrolled route are a Ti(III)-mediated radical cyclization of a chiral monoepoxide to furnish a bicyclic synthon that combines stereospecifically with an acyclic vinyl iodide via an intermolecular B-alkyl Suzuki−Miyaura cross-coupling.

Introduction

(+)-Myrrhanol A (**1**), (+)-myrrhanone A (**2**), (+)-myrrhanone B (**3**), and (+)-myrrhanol B (**4**) are polypodane triterpenes isolated from guggul-gum resin.[1] Although most of the triterpenes contain a tetra- or pentacyclic skeleton as a result of cascade cyclizations and rearrangements of the acyclic precursors squalene (S) and 2,3-oxidosqualene (OS), these bicyclic polypodane triterpenes derive from incomplete cyclization of S or OS. Compounds **1**−**4** could be then encompassed in a group of triterpenes defined as "unusually cyclized triterpenes", characterized by deriving from cyclization proccesses different from those leading to tetra- and pentacyclic triterpenes. It is worth mentioning that there has been an increase in the description of this kind of natural compound in the past few years.[2]



(+)-Myrrhanol A (**1**), R_1=OH,R_2=H,R=CH_2OH
(+)-Myrrhanone A (**2**), R_1=R_2=O, R=CH_2OH
(+)-Myrrhanone B (**3**), R_1=R_2=O, R_1=COOH
(+)-Myrrhanol B (**4**), R_1=OH,R_2=H R=COOH

The resin from *B. mukul* is used in several alternative-medicine preparations including products prescribed or sold for the prevention of inflammation, lowering cholesterol, and reduction of plaque buildup in the arteries. In connection with this, myrrhanol A (**1**) and myrrhanone A (**2**) were shown to display a potent anti-inflammatory effect on exudative pouch fluid, angiogenesis, and granuloma weights in adjuvant-induced air-pouch granuloma of mice, their effects being more marked than those of hydrocortisone.[1]

Moreover, myrrhanol A (**1**), myrrhanone A (**2**), and myrrhanol B (**4**) were characterized as significant NO production inhibitors due to their inhibitory activities against

(1) (a) Kimura, I.; Yoshikawa, M.; Kobayashi, S.; Sugihara, Y.; Suzuki, M.; Oominami, H.; Murakami, T.; Matsuda, H.; Doiphode, V. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 985–989. (b) Matsuda, H.; Morikawa, T.; Ando, S.; Oominami, H.; Murakami, T.; Kimura, I.; Yoshikawa, M. *Bioorg. Med. Chem.* **2004**, *12*, 3037–3046.

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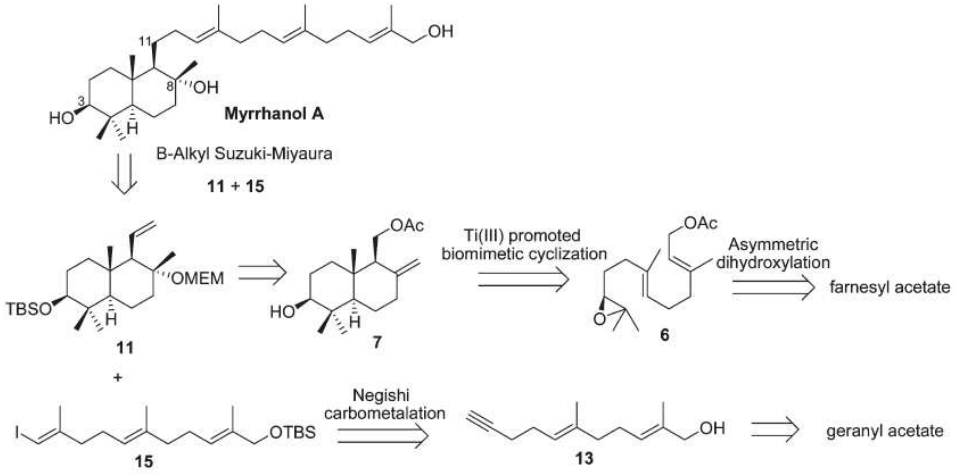
DOI: 10.1021/jo90101 1m Published on Web 07/06/2009

SCHEME 1. Retrosynthetic Analysis Based on a Ti(III)-Promoted Radical Cyclization and a B-Alkyl Suzuki−Miyaura Cross-Coupling

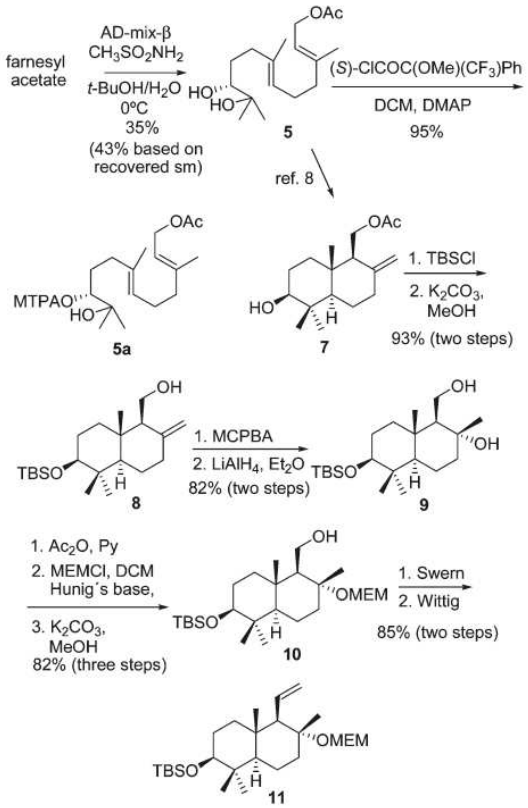


iNOS induction in LPS-activated macrophages, which substantiates the traditional effects of this herbal medicine for the treatment of inflammation.[1,3] The unusual triterpenoid structures of these compounds together with their potent biological activities prompted us to address their total synthesis.[4]

Results and Discussion

In designing a synthetic route toward (+)-myrrhanol A (**1**) we envisioned a convergent approach based on the coupling of a chiral synthon C16, namely, **11** with a polyprenated (*E*)-vinyl iodide, **15**, based on the retrosynthetic analysis outlined in Scheme 1. In our opinion, this approach will overcome the steric hindrance posed by C-11 in carbon−carbon coupling when the bicyclic synthon possesses 15 carbon atoms. In this regard, preliminary tests carried out in our laboratories proved the steric problems associated with the C15 + C15 coupling of related derivatives.

SCHEME 2. Synthesis of Bicyclic Synthon 11



The key steps involved a Ti(III)-mediated cyclization[5] of a chiral monoepoxide **6** and a B-alkyl Suzuki−Miyaura coupling of the synthons **11** and **15**.[6]

As shown in Scheme 2, the synthesis of the required boronate precursor **11** was projected in accordance with

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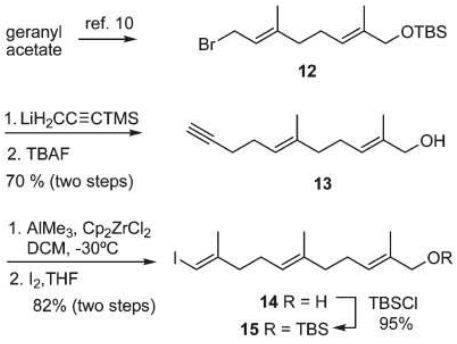
SCHEME 3. Synthesis of Acyclic Synthon 15

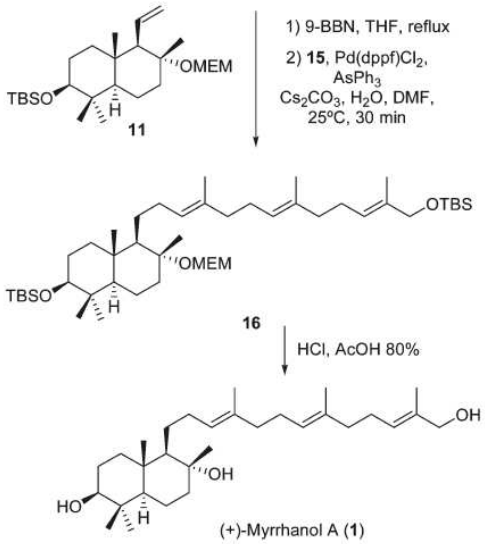


the absolute configuration found in the natural polypodanes, that is, 3*S*,5*R*,8*R*,9*R*,10*S* (myrrhanol A numbering).

The element of enantiocontrol in the synthesis was based on the Sharpless asymmetric terminal dihydroxylation[7] of *E*,*E*-farnesyl acetate to access enantioselectively key bicyclic **7**, already reported by us in our asymmetric synthesis of onocerane triterpenes.[8] This reaction proceeded with acceptable selectivity and efficiency to diol **5** in a 43% yield based on recovered starting material. The enantiopurity of this alcohol was established as 96% on the basis of the ^{1}H NMR spectrum of the corresponding (*S*)-Mosher ester **5a**.[9] Chiral diol **5** was efficiently converted into the isodrimenediol skeleton **7** via Ti(III)-mediated radical cyclization of the corresponding oxirane as previously described by us.[8] Protection of the 3-hydroxyl group of bicyclic **7** as its *tert*-butyldimethylsilylether and deprotection of the primary acetoxy group led to alcohol **8** in a 93% yield. Oxidation of the exocyclic double bond by MCPBA followed by reductive opening with $LiAlH_4$ of the oxirane ring generated the quaternary stereocenter at C-8 with the appropriate configuration, thus affording diol **9** in an 82% yield as the only diastereoisomer detected. The primary alcohol in **9** was selectively acetylated, whereas the tertiary hydroxyl group was protected as its MEM ether. At this point, the presence of orthogonal protecting groups at C-3, C-8, and C-11 positions provides the opportunity to extend the chain at C11 via a selective acetoxy-deprotection of the latter. Swern oxidation of the primary alcohol **10** and Wittig olefination of the corresponding sterically hindered aldehyde allowed us to achieve the required one-carbon homologation to afford the bicyclic synthon **11** in an 85% yield over two steps.

Turning our attention to the synthesis of the synthon **15**, we started the linear sequence from the commercially available geranyl acetate (Scheme 3). Based on the work of Corey, allylic bromide **12** was obtained from geranyl acetate.[10]

SCHEME 4. Palladium-Catalyzed Cross-Coupling Reaction



Three carbons were then introduced via coupling with 1-trimethylsilyl propargyl lithium, which after deprotection gave **13** in a 70% overall yield. The *E*-vinyl iodide key intermediate **15** was then installed by a Negishi carbometalation.[11] This protocol proved to proceed with remarkably high regio- and stereoselectivity.

The target (+)-myrrhanol A was efficiently assembled as follows. Treatment of olefin **11** with 9-BBN in THF under reflux, followed by addition of $Pd(dppf)Cl_2$ and the geometrically pure vinyl iodide **15**, afforded the desired coupling product **16** in a 90% isolated yield as shown in Scheme 4. As expected, the alkene geometry of the acyclic partner was maintained in the Suzuki coupling product. Harsh conditions were necessary in the hydroboration reaction due to the sterically congested environment of the vinyl group in **11** (Scheme 4).

Concomitant deprotection of the three ethers present in **15** was achieved in only one step after treating this compound with a mixture of AcOH and HCl in THF to afford (+)-myrrhanol A (**1**). Considerable experimentation was needed to avoid both alkene isomerization and dehydration of the tertiary alcohol. MS and ^{1}H and ^{13}C NMR of our synthetic coincide completely with those of the natural product. The sign of the optical rotation $[\alpha]_D$ of both synthetic (+8.2°, *c* 1.0, MeOH) and natural myrrhanol A (+12.2°, *c* 1.0, MeOH) matched, thus confirming the absolute configuration of the natural compound.

Once the enantioselective synthesis of (+)-myrrhanol A was achieved, we decided to address the synthesis of its congeners (+)-myrrhanone A (**2**), (+)-myrrhanone B (**3**), and (+)-myrrhanol B (**4**) (Scheme 5), which although present in the resin of *B. mukul* in minor concentration also presented a significant NO production inhibitory activity. Thus, regioselective protection of the primary alcohol in **1** as its corresponding *tert*-butyldimethylsilylether and subsequent

(7) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *10*, 2768–2771.

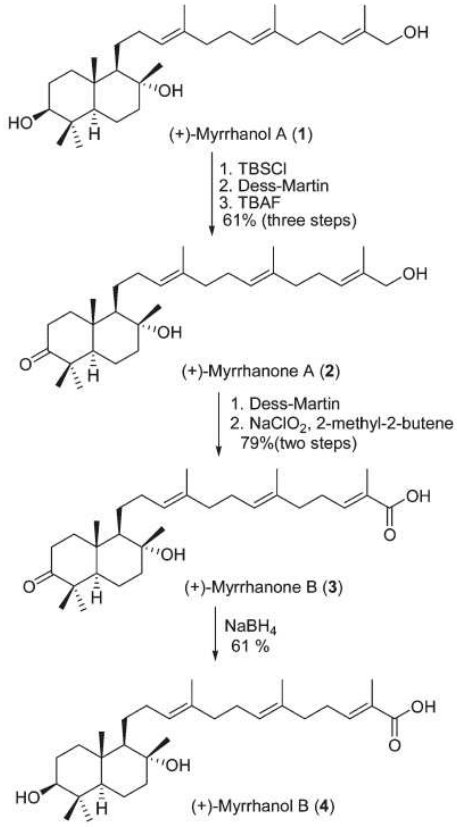
(8) For the preparation of racemic **7**: (a) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074–4078. (b) Justicia, J.; Rosales, A.; Bunuel, E.; Oller-Lopez, J. L.; Valdivia, M.; Haidour, A.; Oltra, J. E.; Barrero, A. F.; Cardenas, D. J.; Cuerva, J. M. *Chem.—Eur. J.* **2004**, *10*, 1778–1788. (c) Justicia, J.; Oltra, J. E.; Cuerva, J. M. *J. Org. Chem.* **2005**, *70*, 8265−8272. For the enantioselective preparation of **7**, see: Barrero, A. F.; Herrador, M. M.; Quilez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Piedra, M.; Sanchez, E. M. *Org. Lett.* **2005**, *7*, 2301–2304.

(9) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215–3216.

(10) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742–1744.

(11) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.

SCHEME 5. Synthesis of (+)-Myrrhanone A (2), (+)-Myrrhanone B (3), and (+)-Myrrhanol B (4)



Dess−Martin oxidation at C3 provided after TBAF deprotection (+)-myrrhanone A (**2**) (Scheme 5). From myrrhanone A, the synthesis of (+)-myrrhanone B (**3**) requires the oxidation of the primary allylic alcohol to carboxylic acid. This transformation was uneventfully achieved using the Dess−Martin periodinane to afford the corresponding aldehyde, which was oxidized to the desired carboxylic acid **3** with sodium chlorite.[12] Finally, chemo- and stereoselective reduction of **3** afforded the target (+)-myrrhanol B (**4**).

Conclusion

In summary, we report a brief and convergent first total synthesis of the potent anti-inflammatory (+)-myrrhanol A and its also bioactive congeners (+)-myrrhanone A (**2**), (+)-myrrhanone B (**3**), and (+)-myrrhanol B (**4**), starting from commercially available geranyl and farnesyl acetate. The synthesis of these unusually cyclized triterpenes illustrates the versatility of the Ti(III)-mediated radical cyclization of asymmetric monoepoxides of polyprenes in the enantioselective synthesis of polycyclic natural structures. In our opinion, this radical approach complements conveniently the cationic version of these cyclizations used by Corey and others in the synthesis of polycyclic triterpenes.[13]

(12) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
(13) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869.

Experimental Section

(*R*,2*E*,6*E*)-10,11-Dihydroxy-3,7,11-trimethyldodeca-2,6-dienyl Acetate (5). To a mixture of *tert*-butanol (225 mL) and water (225 mL) were added 40.05 g of AD-mix-β (85.65 mmol $K_3Fe(CN)_6$, 85.65 mmol of K_2CO_3, 0.04 mmol of $[K_2OsO_2(OH)_4]$, and 0.3 mmol of $(DHQD)_2$-PHAL ligand (hydroquinidine 1,4-phthalazinediyl diether). The resulting mixture was stirred mechanically at 25 °C until two clear phases were obtained. Then, $CH_3SO_2NH_2$ (2.715 g, 28.50 mmol) was added, and the mixture was cooled to 0 °C. The resulting heterogeneous slurry was stirred vigorously at 0 °C, as farnesyl acetate (7.50 g, 28.50 mmol) was added at once. Stirring was continued at 0 °C for 24 h. At this time the oxidation was completed, and solid sodium sulphite (37.20 g) was added. The mixture was allowed to warm to room temperature and stirred until two clear phases were obtained. Ethyl acetate (150 mL) and water (45 mL) were added, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (3 × 100 mL). The combined organic extract was washed with a 2 N aqueous NaOH solution (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. This crude product was purified by flash chromatography (hexane/*t*-BuOMe, 1:3) to afford 1.5 g (5.71 mmol) of starting material and 2.97 g (9.9 mmol) of **5** as a clear colorless viscous oil. $[\alpha]^{20}_D$ = +12.1 (*c* 1.0, $CHCl_3$).[14] IR (film) 3446, 2971, 2930, 1735, 1717, 1437, 1365, 1229, 1159, 1074, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (dt, J = 7.2, 1.2 Hz, 1H), 5.14 (dt, J = 6.8, 0.9 Hz, 1H), 4.56 (d, J = 6.8 Hz, 2H), 3.32 (dd, J = 10.5, 1.8 Hz, 1H), 2.40 (d, J = 4.5 Hz, 1H), 2.25−2.18 (m, 1H), 2.13−2.0 (m, 4H), 2.03 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.58−1.53 (m, 1H), 1.42−1.34 (m, 1H), 1.17 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 141.8, 135.2, 124.2, 118.4, 78.0, 72.9, 61.3, 39.3, 36.6, 29.5, 26.3, 25.9, 23.2, 20.9, 16.3, 15.8. HRFABMS: calcd for $C_{17}H_{30}O_4Na$ $[M+Na]^+$ 321.2042, found 321.2071.

(*S*)-MTPA Ester 5a. To a solution of **5** (9 mg, 0.03 mmol) in dry CH_2Cl_2 (1.2 mL) were added (*S*)-(+)-methoxy-α-(trifluoromethyl)phenylacetyl chloride (11 μL, 0.06 mmol) and DMAP (15 mg, 1.2 mmol). The resulting mixture was then stirred for 1 h at rt. The mixture was diluted with CH_2Cl_2 and then passed through a column of silica gel. The eluent was concentrated to give the desired (*S*)-MTPA ester **5a** (15 mg, 0.029 mmol) as a colorless oil. ^1H NMR (C_6D_6, 500 MHz), *R* enantiomer δ 7.82 (bd, J = 7.8 Hz, 2H), 7.09 (bt, J = 7.8 Hz, 2H), 7.02 (bt, J = 7.3 Hz, 1H), 5.40 (bt, J = 6.8 Hz, 1H), 5.08 (bt, J = 6.8 Hz, 1H), 5.00 (dd, J = 9.7, 2.4 Hz, 1H), 4.58 (d, J = 7.0 Hz, 2H); 3.51 (s, 3H), 2.02 (m, 2H), 1.94−1.84 (m, 4H), 1.66 (s, 3H), 1.55−1.40 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 0.98 (s, 3H), 0.89 (s, 3H); *S* enantiomer δ 3.44 (s, 3H).

(2*S*,4a*S*,5*S*)-Decahydro-2-hydroxy-1,1,4a-trimethyl-6-methylenenaphthalen-5-yl)methyl Acetate (7). A mixture of Cp_2TiCl_2 (276 mg, 1.11 mmol) and Mn dust (2438 mg, 44.32 mmol) in strictly deoxygenated THF (70 mL) and Ar atmosphere was stirred at rt until the red solution turned green. Then, a solution of 1550 mg (5.54 mmol) of epoxide **4** and 2,4,6-collidine (5.1 mL, 38.78 mmol) and Me_3SiCl (2.8 mL, 22.16 mmol) were added. The reaction mixture was stirred for 2 h (TLC monitoring), quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in THF (20 mL) and stirred with Bu_4NF (6.7 mL, 6.67 mmol) for 3 h. Then, THF was removed, and the mixture was diluted with *t*-BuOMe, washed with brine, and dried over anhydrous Na_2SO_4 and the solvent was removed. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 1:1) to afford 732 mg (47%) of **7**.[9]

(14) Vidari, G; Dapiaggi, A.; Zanoni, G.; Gaslaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485–6488.

(2*E*,6*E*,10*E*)-11-Iodo-2,6,10-trimethylundeca-2,6,10-trien-1-ol (14). To a solution of zirconocene dichloride (125 mg, 428 mmol) in CH_2Cl_2 (3.4 mL) at rt under an argon atmosphere was added dropwise a solution of trimethylaluminum in heptane (2 M in heptane, 2.6 mL, 5.14 mmol). After 15 min, the solution was cooled to 0 °C, and a solution of alkyne **13** (325 mg, 1.69 mmol) dissolved in CH_2Cl_2 (3.4 mL) was added to the above lemon yellow solution. The reaction mixture was stirred at 0 °C for 6 h and then cooled to −30 °C. Iodine (869 mg, 3.42 mmol) was added as a solution in 2 mL of THF. The resulting brown slurry was warmed to 0 °C and poured slowly with stirring into an iced saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4. Concentration followed by flash chromatography on silica gel with 1:2 hexane/ether as eluent provided the desired product **14** as a colorless oil (464 mg, 1.39 mmol, 82%). IR 3419, 2919, 2850, 1644, 1442 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.86 (s, 1 H), 5.37 (t, J = 6.9 Hz, 1H), 5.07 (t, J = 6.9 Hz, 1H), 3.99 (s, 2H), 2.22 (t, J = 7.9 Hz, 2H), 2.10 (m, 4H), 2.01 (t, J = 7.2 Hz, 2H), 1.83 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.5, 136.4, 135.5, 126.6, 123.9, 75.1, 69.3, 39.6, 39.4, 28.2, 26.3, 24.1, 16.1, 13.7. HRFABMS: calcd for $C_{14}H_{23}IONa$ $[M+Na]^+$ 357.0691, found 357.0698.

Compound 16. To olefin **11** (240 mg, 0.527 mmol) was added a solution of 9-BBN (3.16 mL, 0.5 M in THF), and the solution was stirred at reflux for 4 h. This solution was transferred by cannula to another flask containing a mixture of vinyl iodide **15** (292 mg, 0.652 mmol), $Pd(dppf)Cl_2$, CH_2Cl_2 (53 mg, 0.065 mmol), $AsPh_3$ (29 mg, 0.097 mmol), Cs_2CO_3 (664 mg, 2.04 mmol), and water (0.375 mL, 15 mmol) in DMF (7.5 mL). After 30 min, the brown reaction mixture was diluted with water and extracted three times with *t*-BuOMe. The organic layer was washed with water and brine and dried over Na_2SO_4. Concentration followed by silica gel flash-chromatography (hexane/*t*-BuOMe, 12:1) yielded 368 mg (90%) of **16**. $[\alpha]^{20}_D = +1.5$ (*c* 1.0, CH_2Cl_2); IR (film) 2952, 2930, 2856, 1598, 1448, 1253, 1101, 1067, 1039, 835, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.38 (t, J = 7.0 Hz, 1H), 5.14 (t, J = 7.2 Hz, 1H), 5.11 (t, J = 7.1 Hz, 1H), 4.86 (t, J = 7.7 Hz, 1H), 4.73 (t, J = 7.7 Hz, 1H), 3.99 (s, 2H), 3.74−3.62 (m, 2H), 3.54 (t, J = 4.8 Hz, 2H), 3.38 (s, 3H), 3.19 (dd, J = 11.2, 4.5 Hz, 1H), 2.14−1.90 (m, 10H), 1.70−0.84 (m, 12H), 1.60 (s, 3H), 1.59 (s, 6H), 1.18 (s, 3H), 0.90 (s, 9H), 0.88 (s, 12H), 0.80 (s, 3H), 0.71 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 134.4, 134.2, 125.2, 124.4, 124.4, 88.8, 80.2, 79.3, 71.9, 68.7, 66.4, 59.2, 58.9, 54.9, 40.1, 39.7, 39.4, 39.3, 38.6, 38.0, 31.4, 28.5, 27.5, 26.7, 26.2, 26.1, 26.0 (3C), 25.9 (3C), 20.7, 19.9, 18.4, 18.1, 16.1, 16.0, 15.9, 15.8, 13.4, −3.8, −4.9, −5.3 (2C). HRFABMS: calcd for $C_{46}H_{88}O_5Si_2Na$ $[M+Na]^+$ 799.6067, found 799.6054.

(+)-Myrrhanol A (1). To a solution of **12** (211 mg, 0.271 mmol) and 80% aqueous AcOH (4.2 mL) in THF (2.8 mL) was gradually added 2 M HCl (0.7 mL) at room temperature for 30 min, and the whole mixture was stirred for 3.5 h at the same temperature. The reaction mixture was diluted with brine and extracted with *t*-BuOMe. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (hexane/*t*-BuOMe, 1:2) to give (+)-myrrhanol A (**1**) (99 mg, 80%). Colorless oil, $[\alpha]^{25}_D = +8.2$ (*c* 1.0, MeOH); IR(film) 3429, 2928, 1640, 1448, 1364, 1037 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.39 (t, J = 7.0 Hz, 1H), 5.16 (t, J = 7.1 Hz, 1H), 5.11 (t, J = 7.0 Hz, 1H), 3.99 (s, 2H), 3.21 (dd, J = 11.4, 4.6 Hz, 1H), 2.15−1.86 (m, 10H), 1.83 (bd, J = 11.6 Hz, 1H), 1.73−1.08 (m, 9H), 1.65 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H), 1.12 (s, 3H), 1.02 (t, J = 3.7 Hz, 1H), 0.98 (s, 3H), 0.89 (bd, J = 11.2 Hz, 1H), 0.79 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 134.7, 134.6, 126.0, 125.0, 124.5, 78.7, 73.9, 68.9, 61.2, 55.0, 44.4, 39.6, 39.3, 38.81 (2C), 37.8, 31.3, 28.1, 27.1, 26.5, 26.1, 25.1, 23.7, 20.2, 16.2, 16.0, 15.5, 15.3, 13.7. HRFABMS: calcd for $C_{30}H_{52}O_3Na$ $[M+Na]^+$ 483.3813, found 483.3825.

(+)-Myrrhanone A (2). To a stirred solution of (+)-myrrhanol A (73 mg, 0.159 mmol) in DMF (3 mL) were added imidazole (16 mg, 0.238 mmol) and TBSCl (36 mg, 0.238 mmol) at rt. The reaction progress was monitored by TLC, and after consumption of the starting product (20 min), the mixture was diluted with *t*-BuOMe and water and extracted with *t*-BuOMe. The combined organic layer was washed with 2 N HCl and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was dissolved in dry CH_2Cl_2 (4.1 mL) under Ar, and Dess−Martin reagent (118 mg, 0.278 mmol) was added. 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, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was dissolved in THF (2 mL) and stirred with TBAF 1 M (0.25 mL, 0.25 mmol) for 30 min (TLC monitoring). Then, THF was removed, the mixture was diluted with *t*-BuOMe, washed with brine, and dried over anhydrous Na_2SO_4, and the solvent removed. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 1:1) to afford 45 mg (61% over three steps) of (+)-myrrhanone A (**2**). Colorless oil, $[\alpha]^{25}_D = +6.9$ (*c* 1.0, MeOH); IR (film) 3406, 2935, 2862, 1702, 1456, 1385, 1078, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (t, J = 7.0 Hz, 1H), 5.08 (t, J = 7.2 Hz, 1H), 5.04 (t, J = 6.8 Hz, 1H), 3.9 (s, 2H), 2.51 (ddd, J = 16.0, 11.7, 7.0 Hz, 1H), 2.32 (ddd, J = 16.0, 6.3, 3.4 Hz, 1H), 2.08−1.80 (m, 11H), 1.58−1.21 (m, 8H), 1.58 (s, 3H), 1.52 (s, 6H), 1.11 (s, 3H), 1.04 (t, J = 3.9 Hz, 1H), 1.02 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9, 135.4, 134.7, 134.6, 125.9, 124.8, 124.5, 73.7, 68.9, 60.3, 55.1, 47.5, 43.8, 39.6, 39.3, 38.6, 38.3, 33.9, 31.1, 26.5, 26.3, 26.1, 25.7, 23.6, 21.4, 21.3, 16.2, 16.0, 14.81, 13.7. HRFABMS: calcd for $C_{30}H_{50}O_3Na$ $[M+Na]^+$ 481.3657, found 481.3667.

(+)-Myrrhanone B (3). To a mixture of (+)-myrrhanone A (37 mg, 0.080 mmol) in CH_2Cl_2 (2 mL) under Ar was added Dess−Martin reagent (67 mg, 0.16 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, and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Filtration on silica gel (hexane/*t*-BuOMe 1:2) afforded the allylic aldehyde, which was dissolved in 2 mL of *tert*-butyl alcohol and 1 mL of 2-methyl-2-butene. A solution of sodium chlorite (29 mg, 0.32 mmol) and sodium dihydrogenphosphate (33 mg, 0.24 mmol) in 0.5 mL of water was added dropwise over a 10 min period. The pale yellow reaction mixture was stirred at room temperature overnight. Volatile components were then removed under vacuum. The residue was dissolved in 30 mL of water and extracted with two 15 mL portions of hexane. The aqueous layer was acidified to pH 3 with HCl and extracted with three 20 mL portions of ether. The combined ether layers were washed with 50 mL of cold water, dried, and concentrated. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 2:1) to give 30 mg (79% overall yield) of (+)-myrrhanone B (**3**). Colorless oil, $[\alpha]^{25}_D = +7.1$ (*c* 1.0, MeOH); IR (film) 3423, 2936, 1687, 1643, 1457, 1385 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (bt, J = 7.3 Hz, 1H), 5.06 (t, J = 7.0 Hz, 1H), 5.04 (t, J = 6.8 Hz, 1H), 2.53 (ddd, J = 16.0, 11.7, 7.0 Hz, 1H), 2.33 (ddd, J = 16.0, 6.4, 3.5 Hz, 1H), 2.24 (q, J = 7.1 Hz, 2H), 2.05−1.76 (m, 9H), 1.76 (s, 3H), 1.57−1.14 (m, 8H), 1.54 (s, 3H), 1.52 (s, 3H), 1.16 (s, 3H), 1.08 (t, J = 3.9 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6, 171.4, 134.6, 144.1, 133.4, 126.9, 125.4, 125.1, 74.4, 60.4, 55.1, 47.4, 43.6, 39.3, 38.6, 38.2, 37.9, 33.9, 31.3, 26.8, 26.2, 25.9, 25.7, 23.5, 21.3 (2 C), 16.0, 15.7, 14.7, 12.0. HRFABMS: calcd for $C_{30}H_{48}O_4Na$ $[M+Na]^+$ 495.3450, found 495.3441.

(+)-Myrrhanol B (4). To a solution of (+)-myrrhanone B (10 mg, 0.021 mmol) in dry MeOH was added $NaBH_4$, and the mixture was stirred for 2 h. The reaction was quenched with acetone and concentrated under reduced pressure. The residue was dissolved in 10 mL of water, and this was acidified to pH 3 with HCl and extracted with three 10 mL portions of EtOAc, washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude was purified by HPLC (hexane/*t*-BuOMe, 1:1) to afford 6 mg (60%) of (+)-myrrhanol B (**4**). Colorless oil, $[\alpha]^{28}_D = +6.2$ (*c* 1.0, MeOH); IR (film) 3453, 2930, 2862, 1709, 1650, 1456, 1385, 1080, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (bt, J = 7.2 Hz, 1H), 5.04 (t, J = 7.0 Hz, 1H), 5.02 (t, J = 7.1 Hz, 1H), 3.18 (dd, J = 11.6, 4.6 Hz, 1H), 2.21 (q, J = 6.8 Hz, 2H), 2.08−1.72 (m, 9H), 1.74 (bs, 3H), 1.64−1.02 (m, 9H), 1.53 (s, 3H), 1.51 (s, 3H), 1.10 (s, 3H), 0.98 (t, J = 3.8 Hz, 1H), 0.92 (s, 3H), 0.84 (bd, J = 11.9 Hz, 1H), 0.73 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 143.6, 137.0, 133.2, 126.9, 125.5, 125.4, 78.8, 75.1, 61.4, 55.0, 44.3, 39.3, 38.8 (2C), 37.9, 37.8, 31.6, 28.1, 27.1, 26.5, 25.7, 25.6, 23.6, 20.2, 16.0, 15.7, 15.5, 15.3, 12.1. HRFABMS calcd for $C_{30}H_5O_4Na$ $[M + Na]^+$ 497.3607, found 497.3625.

Acknowledgment. This research was supported by the Spanish Ministry of Science and Technology, Project CTQ2006-15575-C02-01. V.D. thanks the Spanish Ministry of Science and Technology for a predoctoral grant enabling him to pursue these studies.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **6**, **8**−**11**, **13**, **15**, and ^1H and ^{13}C NMR spectra of **1**-**11**, and **13**-**16**. This material is available free of charge at http://pubs.acs.org.This material is available free of charge via the Internet at http://pubs.acs.org.

Artículo 3: *First Total Synthesis of (-)-Achilleol B: Reassignment of Its Relative Stereochemistry, Arteaga, J. F.; Domingo, V.; Quilez del Moral, J. F.; Barrero, A. F. Organic Letters,* ***2008****, 10, 1723-1726.*

ORGANIC LETTERS

2008
Vol. 10, No. 9
1723−1726

First Total Synthesis of (−)-Achilleol B: Reassignment of Its Relative Stereochemistry

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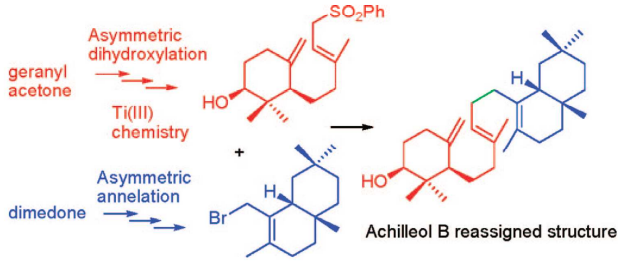
Received February 13, 2008

ABSTRACT



The first total synthesis of (−)-achilleol B was achieved using a convergent approach with a longest linear sequence of 14 steps. Three key steps were employed, including an enantioselective Robinson annelation for the construction of the bicyclic moiety. The monocyclic synthon was prepared through a Ti(III)-mediated cylization of a chiral monoepoxide obtained via asymmetric dihydroxylation of geranylacetone. The asymmetric preparation of these subunits also permitted us to achieve the enantioselective synthesis of elegansidiol, achilleol A, and farnesiferol B.

Achilleol B (**1**) is a triterpene isolated in 1990 from *Achillea odorata* (Asteraceae).[1] It possesses a tricyclic skeleton which could be encompass in a group of triterpenes which could be described as irregular. Other examples of these irregular triterpenes are achilleol A (**2**),[2] camelliols C and A (**3** and **4**),[3] preoleanatetraene (**5**),[4] *seco*-oleananes **6** and **7**,[5] and *seco*-amyrins **8** and **9** (Figure 1).[6] All are structurally characterized by possessing less rings than those usually found in the oxidosqualene (OS) cyclizations catalyzed by OS cyclases. Thus, in the case of **2** and **5**, their biosynthesis could be rationalized by considering an incomplete cyclization of OS[7] initiated at the oxirane ring. In this sense, it was recently proven that the *Arabidopsis thaliana* OS cyclase At1g78955 mainly makes camelliol C (**3**) and minor quantities of achilleol A and β-amyrin (**10**) (0.2%).[8] Recently, a new biosynthetic mechanism toward *seco*-triterpenes such as compounds **6**−**9** has been proposed. This new route involves a first cyclization and subsequent rearrangements to the corresponding pentacyclic structure present in the oleanane or ursane skeletons, followed by a retrocyclization process starting from a carbenium ion located at C-13 which

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10.1021/ol800326n CCC: $40.75
Published on Web 04/02/2008

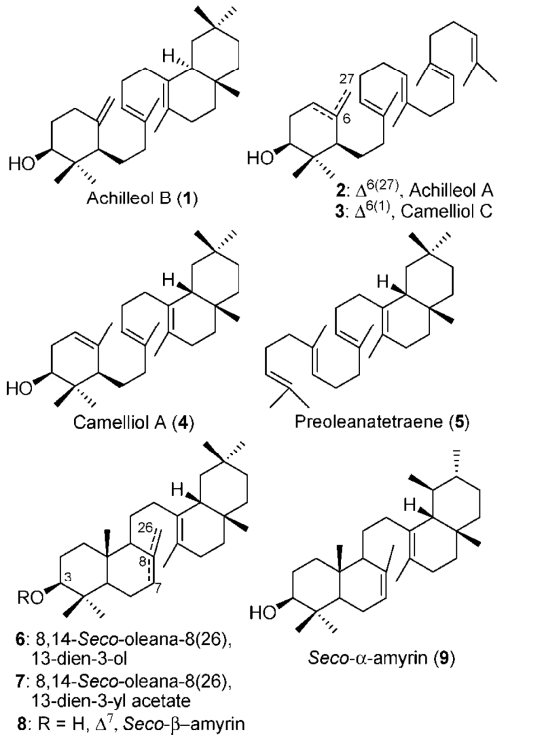


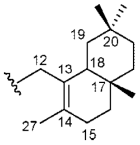
Figure 1. Irregular triterpenes.

would provoke the breaking of the C8−C14 bond.[6] In this sense, a triple rethrocyclization process initiated at the oleanyl cation would account for the biosynthesis of preoleanatetraene (**6**).

Our interest of this kind of molecule, together with the discrepancy observed in the interannular ring junction stereochemistry present in achilleol B and in structures **4–9** prompted us to re-examine the stereochemistry assigned to achilleol B.[1] This stereochemistry was initially described as trans due to the lack of NOE effect between the methyl and proton located at the interannular carbons. To help clarify this point, a comparative study of the ^{13}C NMR chemical shifts of the carbons of the bicyclic system present in **4**−**6** and **1** was undertaken.

Following this comparison (Table 1), it was suspected that the actual stereochemistry of the bicyclic system in achilleol B (**1**) was cis. With the aim of both confirming this hypothesis and establishing unambiguously the structure and absolute stereochemistry of achilleol B, the enantioselective synthesis of this compound was addressed. Thus, we anticipated that the tricyclic achillane skeleton might arise from the coupling of two C15 chiral synthons, namely, **A** (nucleophilic where X = phenylsulfone) and **B** (electrophilic with Y = Br) (Scheme 1).

Table 1. ^{13}C Chemical Shifts of the C−D Rings



carbon	achilleol B (**1**)	camelliol A (**4**)	preoleana-tetraene (**5**)	*seco*-C oleanane (**6**)
12	31.6	31.6	31.7	30.8
13	133.7	133.9	133.6	134.3
14	123.9	123.9	123.9	123.5
15	26.6	29.5	29.5	29.5
17	31.4	31.4	31.4	31.5
18	42.3	42.3	42.3	42.9
19	43.0	43.0	43.0	42.9
20	31.0	31.0	31.0	31.0
27	18.6	18.7	18.6	18.8

The syntheses of **A** and **B** were projected in accordance to the absolute configuration found in the normal enantiomeric series in triterpenes, that is, 3*S*,5*R*,17*R*,18*R*; the numbering of the target product was considered. Synthon **A** could be disconnected along the olefin bond through a Horner−Emmons condensation. The enantioselective synthesis of the monocyclic C-13 moiety would involve a radical carbocyclization of the oxirane intermediate **C**. This Cp_2TiCl-mediated reaction would lead to the hoped-for methylenecyclohexanol with the lateral chain possessing the appropriate stereochemistry. Further retrosynthesis of oxirane **C** through an asymmetric dihydroxylation indicated commercially available geranylacetone as a suitable starting material. The use of the premixed catalyst AD-mix-β would originate, after selective mesylation and basic treatment, the 3*S* monoepoxide, which after Ti(III)-induced cyclization should lead to the corresponding 3*S*-hydroxymonocycle.

Once we had the required **A** synthon in hand, the asymmetric synthesis of related natural products such as elengasidiol (**11**),[9] its coumarine derivative farnesiferol B (**12**),[10] and achilleol A **2**[2] could be easily achieved after straightforward transformations.

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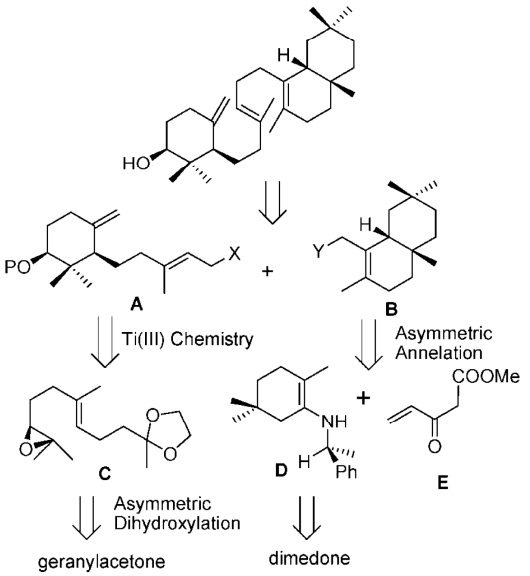
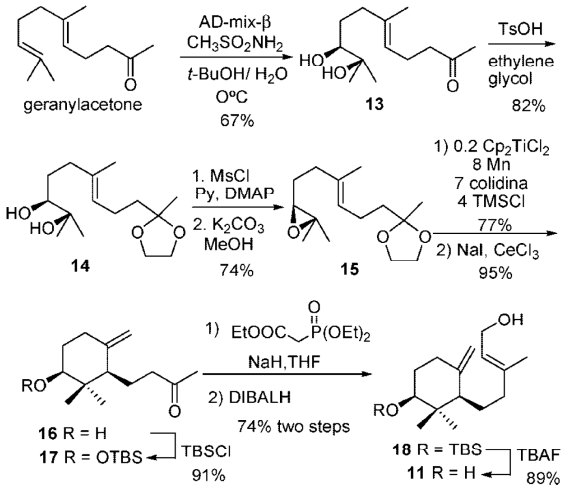
(15) Tsangarakis, C.; Arkoudis, E.; Raptis, C; Stratakis, M. *Org. Lett.* **2007**, *9*, 583–586.
(16) Barrero, A. F.; Cuerva, J. M.; Alvarez-Manzaneda, E. J.; Oltra, J. E.; Chahboun, *Tetrahedron Lett.* **2002**, *43*, 2793–2796.
(17) Yields obtained in the preparation of B synthon were improved with respect to those obtained in ref 11. In particular, the efficiency in the generation of the alcohol derivative of **23** by reduction of the corresponding α,β-unsaturated ester improves from 79% to 94% yield when DIBALH is used instead of LAH.
(18) Alvarez-Manzaneda, R. Doctoral Thesis, **1989**, University of Granada.

Scheme 1. Rethrosynthetic Analysis for Achilleol B

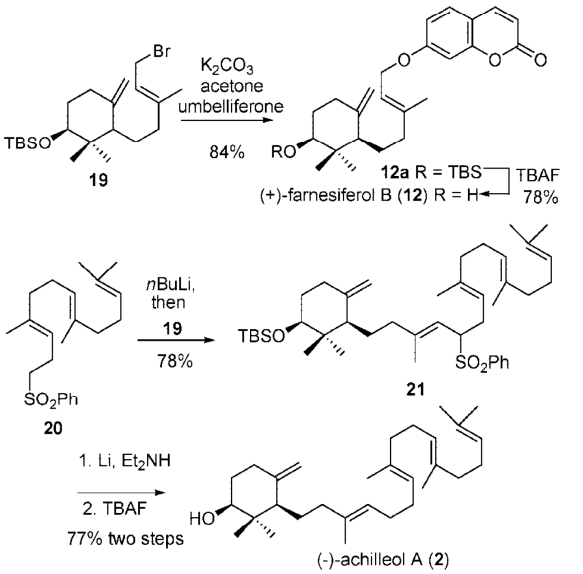


On the other hand, synthon **B** would derive from an interesting enantioselective variant of the Robinson annulation using the Nazarov reagent and a chiral enamine.[11] In this sense, the use of 2*S*-phenylethylamine should permit access to the bicyclic system with the appropriate stereochemistry.

Scheme 2. Synthesis of A Synthon



Scheme 3. Enantioselective Synthesis of (−)-Achilleol A and (+)-Farnesiferol B



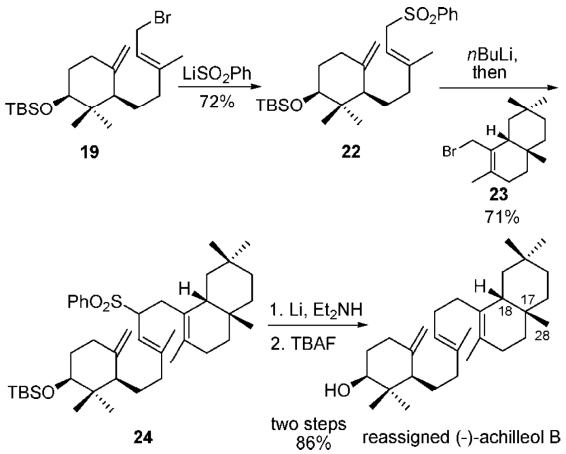
Sharpless asymmetric dihydroxylation[12] of geranylacetone led, with acceptable selectivity and efficiency, to diol **13**.[13] Protection of the carbonyl group led only to 85% of the ketal **14** (based on recovered starting material). Reaction of diol **14** with mesyl chloride and subsequent treatment with base gave rise to oxirane **15** in 74% global yield. When this epoxide was reacted with 0.2 equiv of Cp_2TiCl_2 and Mn in excess (8 equiv) in the presence of 7 equiv of the Ti(III) regenerator TMSCl-collidine,[14] the cyclization took place efficiently and the monocyclic alcohol was obtained after acid workup. Only the exocyclic isomer was detected. Deprotection of the ketyl group led to ketoalcohol **16**. Application of the Horner−Wadsworth−Emmons protocol to the silyl derivative **17** furnished the requisite two-carbon homologation. The corresponding unsaturated ester was reduced with DIBALH to give **18**, thus completing the synthesis of the **A** synthon. Simple deprotection of the silylether in **18** led to the natural sesquiterpene (−)-elegansidiol (**11**) (Scheme 2).

The targeted (−)-achilleol B and (+)-farnesiferol B were efficiently assembled as follows. Alcohol **18** was brominated with PBr_3 to give the allylic bromide **19**. Then, alkylation of the potassium salt of commercial umbelliferone with bromide **19** afforded the silyl ether derivative of farnesiferol B which, after TBAF-mediated deprotection, yielded (+)-farnesiferol B (**11**). On the other hand, and as anticipated, the coupling process between **19** and the lithium derivative from farnesylphenylsulfone (**20**) proceeded smoothly in 78% yield. Reductive elimination of the phenylsulfonyl group using Li-ethylamine and subsequent deprotection of the silyl group with TBAF afforded (−)-achilleol A (**2**) in a yield of 77% for the two steps. Although racemic protocols to farnesiferol B[15] and achilleol A[16] have been reported, our synthesis supposes the first enantioselective preparation of these two natural compounds. These stereocontrolled syntheses proved the absolute configuration of both compounds. In this sense, the stereostructure of natural (+)-farnesiferol B (**12**) is the opposite of that described by Caglioti and coworkers.[10]

The **B** synthon preparation was previously communicated by us in our enantioselective synthesis of preoleanatetraene.[17] Following a synthetic route parallel to that used with achilleol A, we proceeded to make allylic bromide **23** react with the corresponding anion of phenylsulfone **22** to gratifyingly obtain the desired diasteromeric mixture of sulfones **24** in good yield. Finally, exposure of **24** to Li-$EtNH_2$ and subsequent deprotection of the silyl ether led to the formation of **25**. MS and ^1H and ^{13}C NMR of our synthetic achilleol B coincide completely with those of the natural product. Noteworthy is the existence of a NOE effect between H-18 and the CH_3−C17. The sign of the optical rotation $[\alpha]_D$ of synthetic achilleol B (−10.9, *c* 0.9, $CHCl_3$) matched that of the natural compound (−8.1, *c* 1.1, $CHCl_3$).

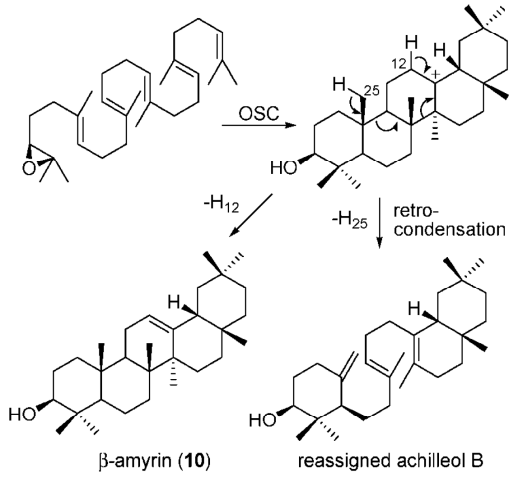
All of the above allowed us both to reassign the stereochemistry of the interannular junction of the bicyclic system in achilleol B and also to establish absolute stereochemistry of the natural product as that shown is Scheme 4.

Scheme 4. Synthesis of Reassigned Achilleol B



With regard to the biosynthetic origin of achilleol B, a cyclization−rearrangement−retrocondensation[6] process is proposed, a hypothesis that is supported by the coexistence

Scheme 5. Biogenetic Proposal for Achilleol B



in *Achillea odorata* of achilleol B and the oleanane β-amyrin (Scheme 5).[18]

In conclusion, the first enantioselective synthesis of achilleol B has been efficiently completed with a longest linear sequence of 14 steps. This work has also allowed us to reassign the structure of this natural triterpene. Furthermore, this asymmetric protocol enabled us to complete the synthesis of achilleol A, elegansidiol, and farnesiferol B in 10, 8, and 9 steps and 12, 17, and 13% overall yield, respectively.

Acknowledgment. This research was supported by the Spanish Ministry of Science and Technology, Projects BQU 2002-03211 and CTQ2006-15575-C02-01.

Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ^1H and ^{13}C NMR spectra of **12**−**18**, **22**, and those of natural and synthetic (−)-elegansiol (**11**), (−)-achilleol (**2**), and (−)-achilleol B. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800326N

Artículo 4: *Total Synthesis of (+)-seco-C Oleanane Via Stepwise Controlled Radical Cascade Cyclization, Domingo, V.; López Pérez J., Peláez R., Arteaga, J. F.; Quilez del Moral, J. F.; Barrero, A. F., Submitted,* ***2011****.*

Total Synthesis of (+)-seco-C Oleanane Via Stepwise Controlled Radical Cascade Cyclization

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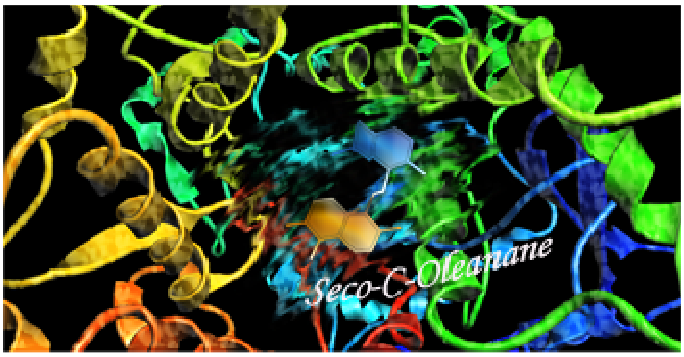


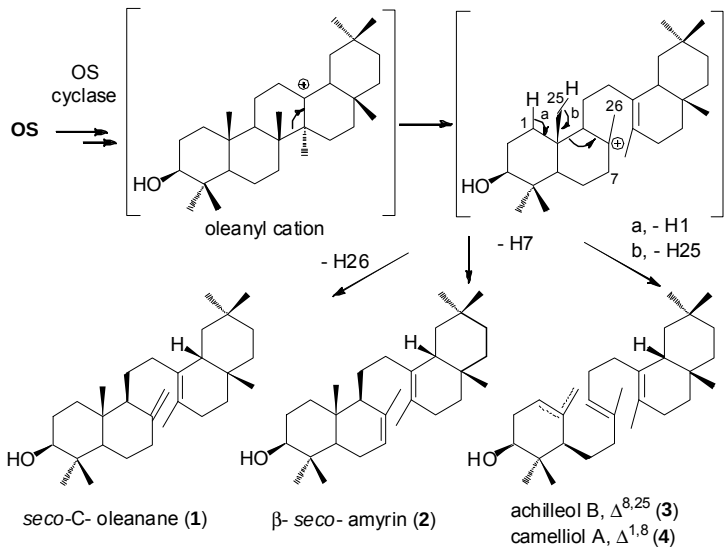
Abstract:

An asymmetric concise total synthesis of (+)-*seco*-C-oleanane (**1**) was accomplished. The successful route to this natural products involves as key step a stepwise, regio- and stereo- controlled catalytic radical polyene cascade cyclization from preoleanatetraene oxide (**16**), a process mediated by Cp_2TiCl. The use of this single electron transfer complex permits mild cyclization conditions without using unnecessary prefunctionalizations and stops the process at the bicyclic level. Theoretical data revealed high activation energy for the third ring closure, which would account for the control of the cyclization. This process also led as to natural (-)-achileol A, camelliol A and (+)-*seco*-β amyrin as minor compounds.

Introduction

The biosynthesis of β-amyrin where 2, 3-oxidosqualene (OS) possessing one stereogenic center is transformed into a pentacyclic triterpene containing eight stereogenic centers constitutes one of the most impressive examples of efficiency in organic synthesis. Over the last 20 years, remarkable progress has been achieved in the understanding of the fascinating mechanism of triterpene formation, although the degree of enzymatic assistance still remains difficult to determine.[1] The potential of metabolic engineering to produce alternative natural products or to increase the yields of those of "commercial value" has renewed the interest of this kind of compounds.[2] In this sense, the recent report by Ebizuka *et al.* describing an OS cyclase-homologue that is capable of cleaving preformed ring systems, in addition to produce polycyclic systems, further increases the diversity of structures produced by OS cyclases.[3] In this context, some triterpenes from higher plants or mutagenesis studies such as the *seco*-C oleananes (**1**)[4] and (**2**),[3] achilleol B (**3**)[5] and camelliol A (**4**)[6] are proposed to derive from the oleanyl cation which suffers rethrocyclization processes (Scheme 1).[7]

SCHEME 1. Natural triterpenes 1-4 and their proposed biosynthetic origin.



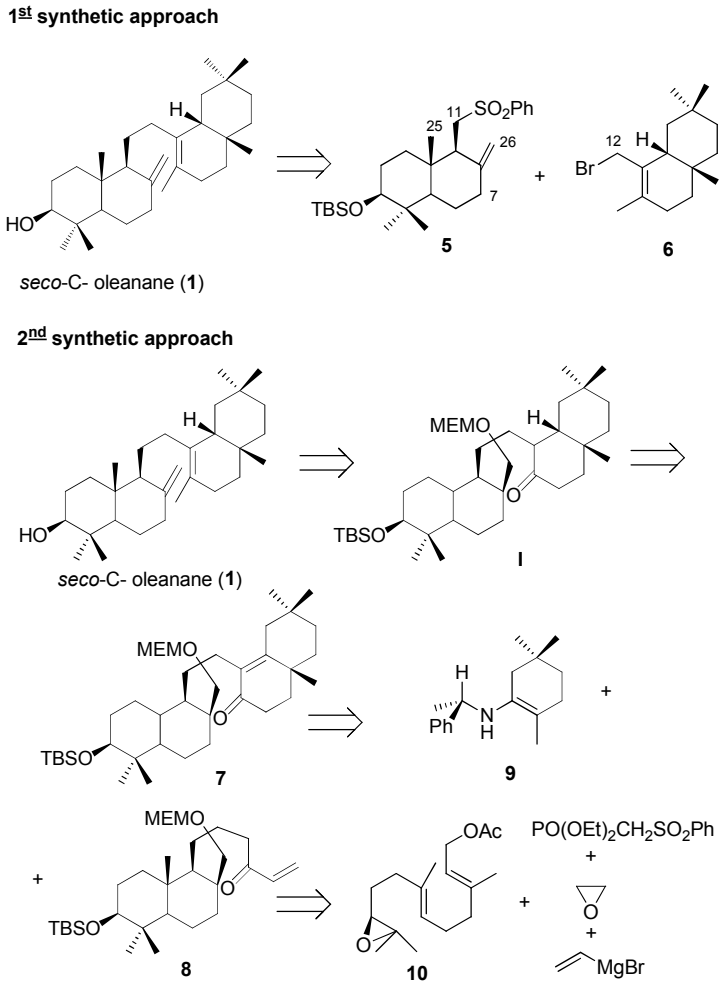
During the writing of this manuscript, Hoshino *et al*. reported the existence of achilleol B synthase, an enzyme encoded by AK070534 gene from *Oryza sativa*.[8] This *seco*-type triterpene cyclase produces achilleol B (**3**) as main product (*ca.* 90%).

Results and Discussion

From the work of pioneers that including those of van Tamelen and Johnson,[9] to the recent progresses reported by Corey,[10] chemists´ efforts to mimick the enzymatic cyclization of 2,3-(*R*)-OS in tetra- and pentacyclic triterpenes in a single step have culminated in a number of impressive syntheses of triterpenes, most of them sharing a cation-olefin polyannulation strategy.[11] Nevertheless, this synthetic strategy involves certain drawbacks, such as the need to attach extra groups to the polyene substrate to stabilize carbocationic intermediates, and the control of the termination steps.[12] In contrast to these acid-catalyzed cyclizations, other approaches using radical transformations exploited successfully in several polycarbocyclizations have received less attention.[13] In this sense, it has been established that the Ti(III)-mediated opening of epoxypolyprenes – a strategy reported by our group[14a] – may well be efficiently used for the preparation of polycyclic structures.[14j-o] Interested in the so called "unusually cyclized triterpenes",[7] we report herein the enantioselective synthesis of the *seco*-C-oleanane **1**, a metabolite isolated from *Stevia viscida* and *S. eupatoria*,[4] and collaterally those of *seco*-triterpenes **2**-**4**.

In our efforts to synthesize **1**, two “dead-end” routes were tried prior to the successful approach (Scheme 2).

SCHEME 2. Unsuccessful approaches to (+)-*seco* C oleanane.(1).

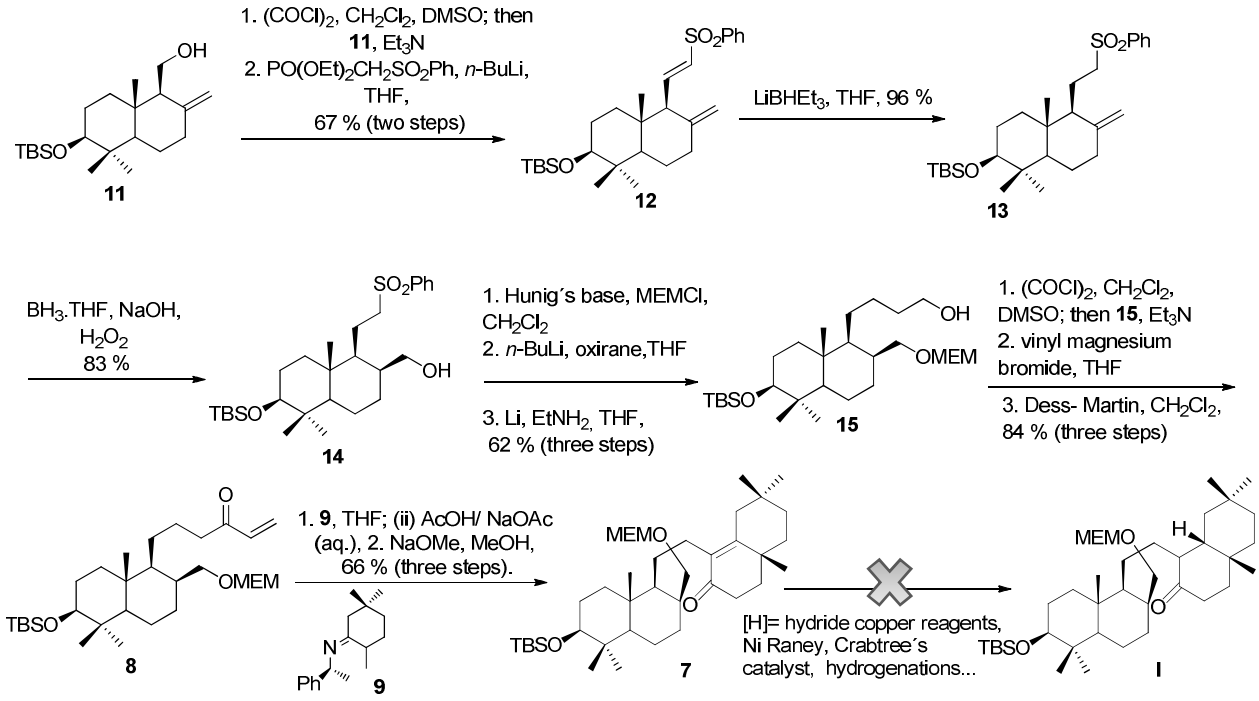


The first of them was based on the convergent coupling of two C15 synthons, **5** and **6**, which we previously prepared in an enantiopure form.[15] This strategy failed most likely due to the large steric repulsions originated in the C11–C12 approaching.

In order to overcome this steric hindrance posed by C11 and C12 in the carbon-carbon coupling, we planned a second route where target *seco*-C oleanane could be obtained from ketone **I**, after incorporation of a methyl group from the corresponding enol triflate. Ketone **I** would be produced after stereoselective *cis* hydrogenation of enone **7**. The construction of the tetracyclic backbone in **7** would be the result of an

enantioselective variation of the Robinson annulation, employing bicyclic compound **8** as the chiral Michael acceptor and enamine **9**. Finally, compound **8** was envisaged as being accessible by C5 homologation of the C15 bicyclic compound resulting from the Ti(III)-mediated cyclization of the chiral monoepoxiderivative of farnesol, **10**, a transformation previously reported by some of us.[14o]

SCHEME 3. Second approach to (+)-*seco*-C oleanane.

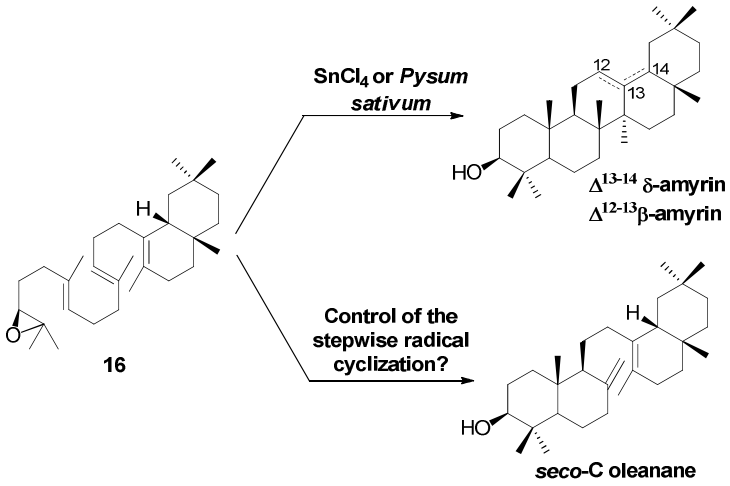


Our synthesis of (+)-*seco*-C oleanane started from bicyclic **11**, produced after Ti(III)-catalyzed cyclization of **10** (Scheme 3). In order to overcome the steric hindrance posed by C-11 in carbon-carbon coupling when the bicyclic synthon possesses 15 carbon atoms, alcohol **11** was subjected to Swern oxidation conditions and then to Horner-Wadsworth-Emmons reaction with phenylsulfonylmethyl phosphonate to furnish the vinyl sulfone **12** in a 67 % yield over two steps. The required C16 primary sulphone

was obtained in 96% yield by treatment of **12** with superhydride. Since our strategy involved as key transformation the stereoselective hydrogenation of enone **I**, the exocyclic double in **13** was thought to be masked as the corresponding protected primary alcohol derivative. In the event, the treatment of compound **13** to standard hydroboration-oxidation protocol led to the primary alcohol **14** as the only detectable diastereoisomer. Moving forward with the synthetic planning, the required C4 homologation to generate the key enone **8** was envisaged as being accessible after a double C-2 homologation.[15] Thus, we proceeded to react ethylene oxide with the lithium derivative of the bicyclic sulphone to afford as anticipated the C-2 homologated primary alcohol **15**. The second C-2 homologation was achieved after Swern oxidation of **15** and treatment of the corresponding aldehyde with vinyl magnesium bromide to afford after Dess-Martin oxidation the desired enone in a 85% yield over the three steps. With the assumption of *seco*-C oleanane (**1**) possessing an absolute configuration *R* at C19, enamine **9** was prepared by treating the corresponding ketone with (*S*)-phenylethylamine.[16] Satisfactorily, the asymmetric Michael addition took place after treating **9** with enone **8** to produce, after hydrolisys with AcOH/NaOAc and subsequent exposure to NaOMe, the advanced tetracyclic intermediate **7** in 66% overall yield. Unfortunately, we were unable to progress with our synthetic proposal since we failed in achieving the stereoselective conjugate reduction of the tetrasubstituted conjugated enone to produce the desired *cis*-decalin **I**. This substrate remained unaltered versus a variety of reducing reagents and conditions, including copper hydrides generated in situ,[17a,b] commercial Stryker´s reagent,[17c] nickel Raney,[17d] Crabtree´s catalyst[17e] and dozens of hydrogenations with varying loads of catalyst (Pd or Pt), solvent, pH or pressure.[17f]

Finally, after getting enough topological information from our unsuccessful routes, we anticipated that target **1** could be produced via cyclization of epoxypreoleanatetraene **16** assuming that the process would stop after the second cyclization (Scheme 4). Two reasons led us to envision this truncated cyclization, on the one hand, the recently reported theoretical calculations supporting the nonconcerted nature of the radical cyclization of a C15-epoxypolyprene,[18] and on the other, the existence of different examples where the Ti(III)-promoted cyclization failed when the acceptor double bond possessed a *Z* geometry.[14a] Contrarily to what we expected using radical chemistry, at this point, it should be reminded that van Tamelen *et al*. described the racemic epoxide **16** which was transformed into *dl*-δ-amyrin by treatment with stannic chloride-CH_3NO_2 at 0 ºC.[19] In the same sense, the transformation of **16** by a cyclase from *Pysum sativum* led directly to *β*-amyrin[20] (Scheme 4). These results coincided with recent experimental[10a,b] and theoretical[21] data in that the carbocationic cyclization of polyprenes leads to tricyclic structures without the intermediacy of mono- or bicyclic carbocations. With all these data in mind, the crux of our strategy was to know whether the radical cyclization of key intermediate **16** would lead to the desired bicyclization process, or the cyclization would progress to produce the pentacyclic oleanane skeleton (Scheme 4).

SCHEME 4. Carbocationic versus radical cyclizations starting from 16.



In order to gain more data to evaluate the feasibility of our radical approach, theoretical studies were undertaken to provide reaction and activation energies of the radicals which are intermediates along the pathway connecting the starting bicyclic radical **I**, resulting from the Ti(III)-mediated homolytic opening of the oxirane ring in **16**, to the potential pentacyclic radical **IV**.

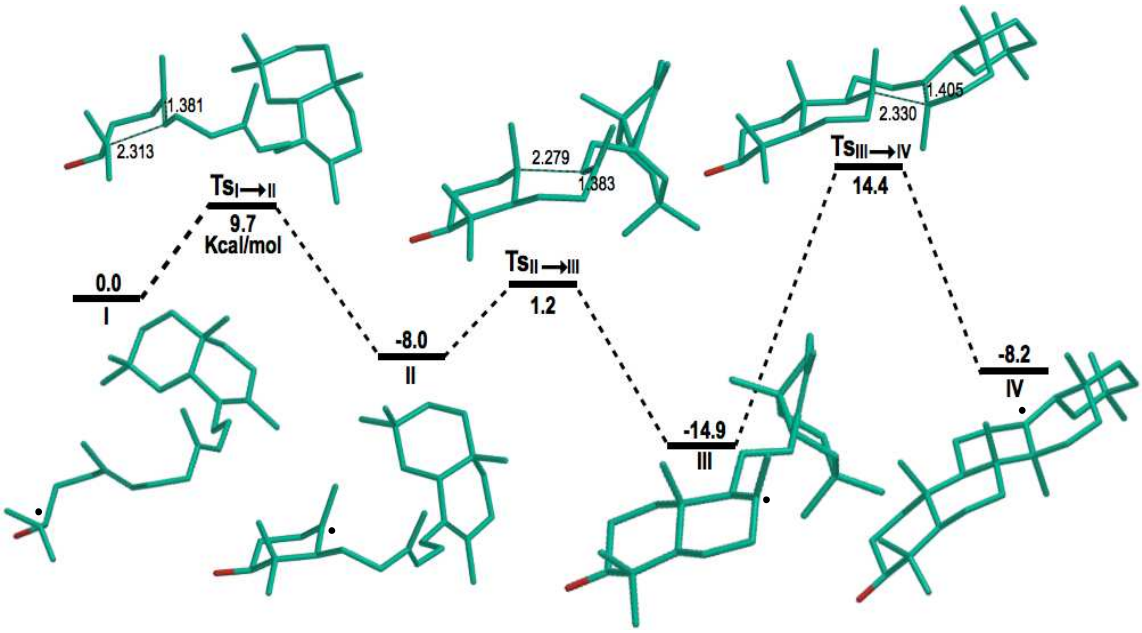


FIGURE 1. Energy profile of the radical cyclization reaction from bicyclic radical I to the oleanyl radical IV. Optimized geometries by UB3LYP/6-31+G(d). Relative energies

to that of I (kcal/mol) including zero-point energy corrections are shown. Distances given in Å.

Focussing on the third key radical cyclization, the computational studies showed not only that this process is thermodynamically unfavourable by 6.7 Kcal/mol, but also that the activation energy for cyclization is higher than 29 kcal/mol, which is a considerable energetic barrier, not easily reachable at room temperature. This high barrier is most likely due to an important increase of the steric hindrance and steric congestion when evolving from the most stable conformer of radical **III** to pentacyclic radical **IV**. In this sense, it should be noticed that the approach of carbons 8 and 14 in the transition state leading from **III** to **IV** forced a rotation of C11-C12 bond (Figure 1). Furthermore, the theoretical calculations also showed a slight D-ring rotation in the transition state conformation when compared to that of **IV**, which results in a destabilizing decrease in the Me-26-Me-28 distance (Figure 2).

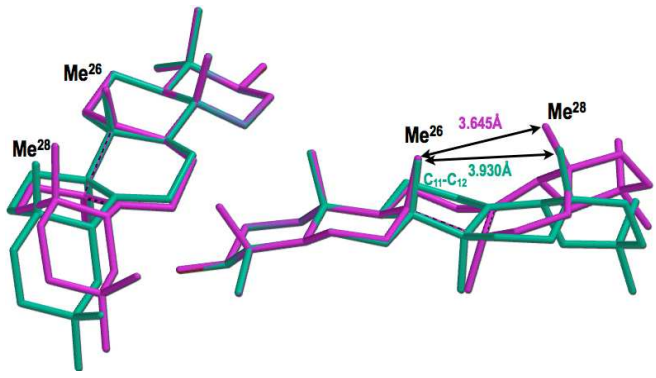
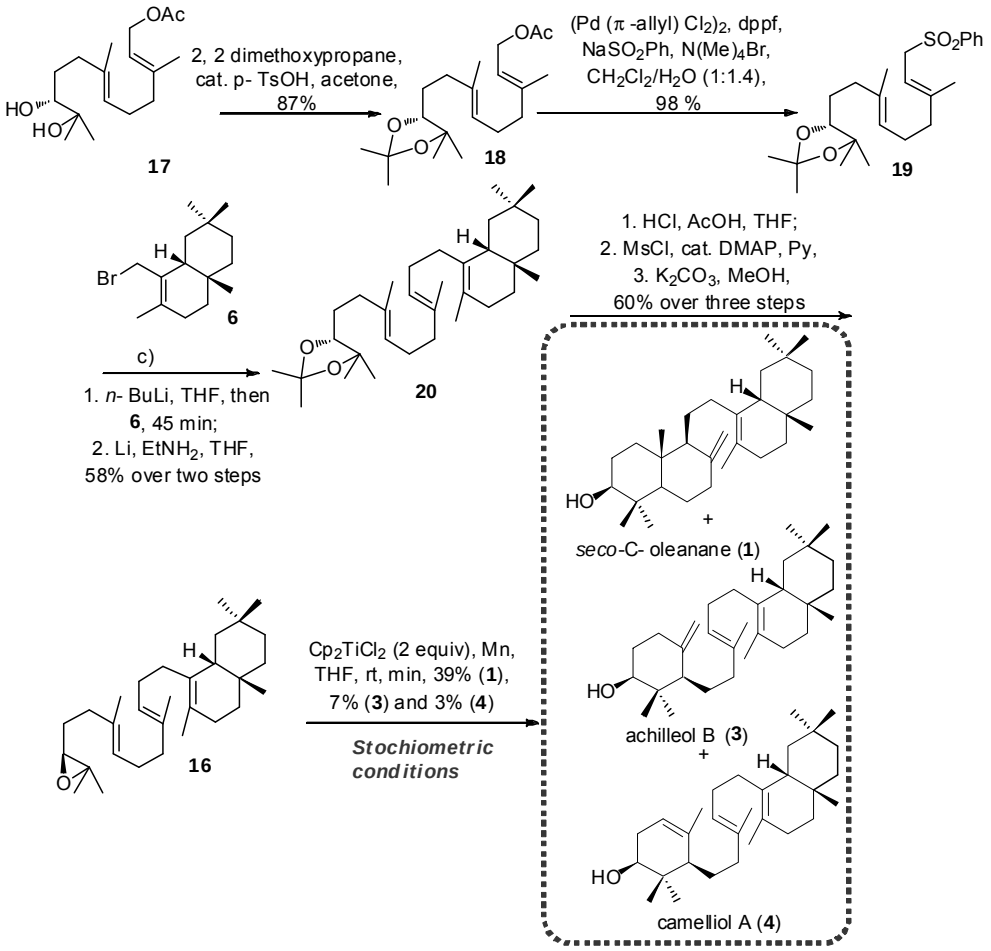


FIGURE 2. Superposition of radical **IV** (green) and the **III** to **IV** transition state (pink) structures.

Encouraged by the computational results, we went on to address the experimental studies that should corroborate the applicability of our synthetic proposal. In designing a synthetic route toward key intermediate **16** we envisioned a convergent approach based on the coupling of two chiral synthons, namely bicyclic allyl bromide **6** and polyprenated (*E*)-allyl sulphone **19** (Scheme 4). The route to **19** commenced from commercially available farnesol, which was protected as its acetate form and exposed to asymmetric dihydroxylation conditions to afford the corresponding chiral diol in a 43% yield, based on recovered starting material (96% ee).[14o] After acetonide protection with 2, 2 dimethoxypropene, exposure of **18** to palladium catalyzed allylic sulphonation conditions[22] led to the formation of **19** as a single isomer in 98% yield on a gram scale. Anionic alkylation of the asymmetric intermediate **6**[16] with acyclic moiety **19** afforded gratifyingly the diasteromeric mixture of sulfones which after reductive desulphonation furnished **20** in 58% overall yield. Deprotection of acetonide **20** in acidic conditions, treatment of the corresponding diol with mesyl chloride and subsequent oxirane closure with base gave rise to enantiopure preoleanatetraene oxide (**16**) in 60% global yield (Scheme 5).

SCHEME 5. Synthesis of (+)-*seco*-C oleanane using stochiometric Ti(III).



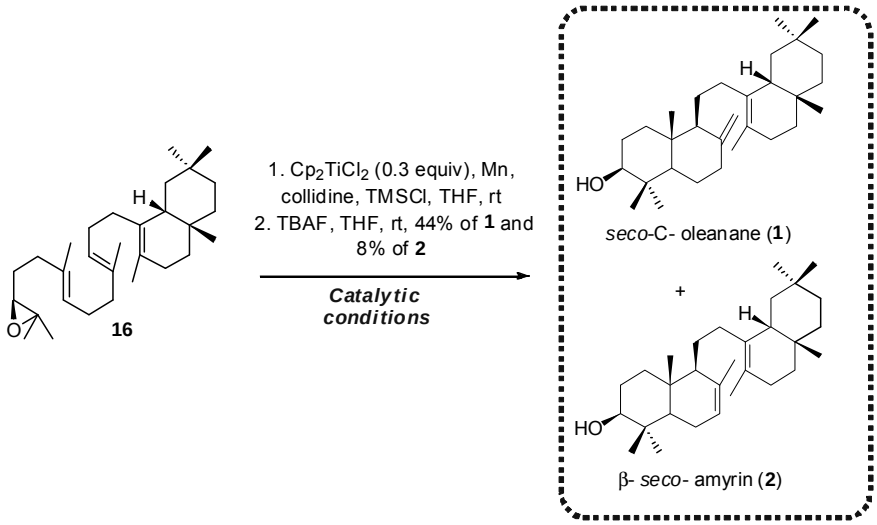
With this polyprene precursor in our hands without the use of further functionalizations to promote the radical cascade, we proceeded to achieve the key Ti(III)-mediated cyclization. Gratifyingly, exposure of **16** to 2 equiv of Cp_2TiCl led to *seco*-oleanane C (**1**) as the major product (39%), along with minor tricyclic triterpenes, achilleol B (**3**), and camelliol A (**4**), in 7 and 3%[23] respectively. The physical and spectral properties of synthetic **1** turned out to be identical with those of an authentic sample. Achilleol B (**3**) was firstly isolated by our group from *Achillea odorata*[5]

whereas camelliol A (**4**) was identified from *Camellia sasanqua*.[6] Both achilleol B (**3**) and camelliol A (**4**) were formed as a consequence of a premature trapping of the achilleyl radical **II** (Figure 1) by a second molecule of Cp_2TiCl, followed by a β-elimination process. Whereas previous to this work one enantioselective synthesis of achilleol B (**3**) was reported,[14n] the minor camelliol A (**4**) has not been prepared before.

At this point, the feasibility of overcoming the energy barrier leading to the pentacyclic skeleton was testing by conducting the cyclization reaction at refluxing THF-toluene. In the event, no pentacyclic compound was detected, with the results obtained being comparable to those obtained at room temperature.

Finally, and bearing in mind that it has been reported that in some cases the use of catalytic Ti(III) improved in some degree the results obtained with the stochiometric protocol,[14j-p,18] we decided to treat epoxide **16** with 0.2 equiv of Cp_2TiCl_2 and Mn in excess (8 equiv) in the presence of 7 equiv of the Ti(III) regenerator TMSCl-collidine.[14i] Under these conditions, the efficiency of the cyclization increased and the targeted *seco*-C-oleanane (**1**) was obtained in a 44% yield after TBAF mediated desilylation (Scheme 6). Together with **1**, a minor isomer (8%), C-ring *seco*-β amyrin (**2**), was also obtained in the cyclization. Compound **2** was recently reported to be produced by a triterpene synthase encoded by *Atl*g78500, one of the OSC homologous genes of *Arabidopsis thaliana*.[3] The formation of **2** in the cyclization of epoxypolyprene **16** also permitted to confirm the structure and stereochemistry of this *seco* triterpene.

SCHEME 6. Synthesis of (+)-*seco*-C oleanane using cataliytic Ti(III).



Conclusion

We have achieved the first enantioselective synthesis of *seco*-C-oleanane (**1**) and related *seco*-triterpenes **2-4**. The use of a Ti(III)-mediated radical polyannulation reaction as key step to produce these molecules demonstrated the synthetic efficiency of this strategy where the cationic version of these cyclizations or other approaches failed. In addition to a minimal use of protecting group chemistry and high stereocontrol over the six stereocenters created, we supported these results with radical computational calculations, which also confirmed the non-concerted nature of these radical cyclizations.

Experimental section

((2*S*,4a*S*,5*S*)-Decahydro-1,1,4a-trimethyl-6-methylene-5((phenylsulfonyl)methyl) naphthalen-2-yloxy)(*tert*-butyl)dimethylsilane (5). A mixture of alcohol **11** (529 mg, 1.5 mmmol) and diphenyldisulfide (981 mg, 4.5 mmol) in pyridine (1.5 mL) was stirred at room temperature for 1 h before tributylphosphine (1.11 mL, 4.5 mmol) was added. After stirring for an additional 4 h, EtOAc (100 mL) and water (50 mL) were added and

the resulting layers separated. The organic layer was washed with 10% HCl (aq) (25 mL), 10% NaOH (aq) (25 mL) and brine (25 mL), dried (Na_2SO_4) and evaporated under vacuum. The resulting crude was purified by column chromatography on silica gel 5:1 (hexane/*t*-BuOMe) to afford the corresponding sulphide (521 mg, 78%). To a solution of this sulfide (215 mg, 0.484 mmol) in DCM (12 mL) at -78 ºC was dropwise added a 0.1 *M* solution of MCPBA (0.5 mL, 1.21 mmol). The resulting mixture was stirred for 45 min until starting material consumption (TLC analysis). Then, the reaction was diluted with DCM and the organic layer was washed with $NaHCO_3$ (3 × 80 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel 5:1 (hexanes/*t*-BuOMe) to afford the corresponding sulfone **5** (166 mg, 72%). White foam, TLC (hexanes/*t*-BuOMe, 2:1 v/v) R_f = 0.62; $[\alpha]_D$= +15.2 (*c* 1, CH_2Cl_2); IR (film): ν_{max} 2948, 2855, 1737, 1648, 1472, 1446, 1307, 1252, 1144, 1100, 885, 774, 731, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, *J* = 8 Hz, 2H), 7.62 (t, *J*= 7.6 Hz, 1H), 7.48 (t, *J*=7.6 Hz, 2H), 4.73 (brs, 1H), 4.42 (brs, lH), 3.35 (dd, *J* = 14.6, 8.8 Hz, 1H), 3.23-3.16 (m, 2H), 2.37 (bt, *J* = 9.8 Hz, 1H), 1.97 (bt, *J*= 13.2, 4.6 Hz, 1H), 1.73 (dt, *J* = 13.2, 2.8 Hz, 1H), 1.59-1.52 (m, 4H), 1.38-1.21 (m, 2H), 1.15 (dd, *J* = 13.2, 2.8 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 9H), 0.70 (s, 3H), 0.61 (s, 3H), -0.04 (s, 6H);^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.53, 140.32, 133.61, 129.25 (2C), 128.28 (2C), 107.97, 78.96, 54.46, 52.53, 50.58, 39.87, 39.56, 37.56, 36.71, 28.69, 28.09, 26.05 (3C), 23.80, 18.25, 15.90, 15.18, -3.65, -4.77. HRFABMS: calcd. $C_{28}H_{46}NaO_3SSi$ $[M+Na]^+$ 513.2835, found 513.2841.

((2*S*,4a*S*,5*S*)-Decahydro-1,1,4a-trimethyl-6-methylene-5-((*E*)-2-(phenylsulfonyl) vinyl)naphthalene-2-yloxy)(*tert*-butyl)dimethylsilane (12). Oxalyl chloride (3.8 mL, 2.0 M in CH_2Cl_2, 7.5 mmol) was added to a solution of dry DMSO (1.2 mL, 15 mmol) in dry CH_2Cl_2 (27 mL) at –60 °C, under Argon. The mixture was stirred for 30 min and

a solution of alcohol **11** (880 mg, 2.5 mmol) in CH_2Cl_2 (9 mL) was added. After additional stirring for 30 min at –60 °C, Et_3N (3.5 mL, 25 mmol) was added, and the mixture was allowed to warm up to 0 °C. The reaction mixture was then poured into ice cold water, diluted with CH_2Cl_2 (150 mL) and washed with brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the corresponding crude which was directly used in the next step. To a solution of diethyl (phenylsulfonylmethyl) phosphonate (870 mg, 3.0 mmol) in THF (7 mL) was added *n*-butyllithium (2M solution in hexanes, 1.5 mL, 3.0 mmol) at –78ºC. The resulting yellow mixture was stirred for 10 min and then, a solution the aldehyde in THF (7 mL) was added dropwise. The mixture was stirred for 12 h until starting material consumption (TLC analysis), then diluted with *t*-BuOMe and quenched with NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with *t*-BuOMe (3 × 80 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel 3:1 (hexanes/*t*-BuOMe) to afford the corresponding vinyl sulfone **12** (813 mg, 67%).White solid, TLC (hexanes/*t*-BuOMe, 3:1 v/v) R_f = 0.50; $[\alpha]_D$= +31.5 (*c* 1, CH_2Cl_2); IR (film): 2934, 2854, 1639, 1319, 1146, 1088, 835, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ =7.87 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.04 (dd, *J* = 15.0, 10.6 Hz, 1H), 6.3 (d, *J* = 15.0 Hz, 1H), 4.78 (brs, 1H), 4.36 (brs, lH), 3.17 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.41 (bd, *J* = 11.2 Hz, 1H), 1.99 (dt, *J* = 13.8, 5.5 Hz, 1H), 1.70 (dt, *J* = 13.1, 2.6 Hz, 1H), 1.61-1.39 (m, 4H), 1.33 (dt, *J* = 13.3, 3.3 Hz, 1H), 1.08-0.98 (m, 2H), 0.91 (s, 3H), 0.89 (s, 3H), 0.87 (s, 9H), 0.76 (s, 3H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.2, 145.5, 140.8, 133.3, 132.7, 129.4 (2C), 127.6 (2C), 109.3, 79.2, 59.6, 53.7, 39.9, 39.2, 38.4, 28.7, 27.9, 25.9 (3C), 22.9, 18.1, 17.1, 16.1, 15.0, -3.7, -4.9.

((2*S*,4a*R*,5*S*)-Decahydro-1,1,4a-trimethyl-6-methylene-5-(2-(phenylsulfonyl)ethyl) naphthalen-2-yloxy)(*tert*-butyl)dimethylsilaneompound (13): A solution 1M of $LiBH(Et)_3$ in THF (1.77 mL, 1.7 mmol) was added to a solution of vinyl sulphone **12** (702 mg, 1.4 mmol) in THF (40 mL) at 0 ºC under Argon, then the resulting yellow mixture was stirred for 3 h to rt before quenching with water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under vacuum. The resulting crude was purified by flash column chromatography on silica gel 3:1 (hexanes/*t*-BuOMe) to afford the corresponding sulfone **13** (634 mg, 96%) as a white foam. TLC (hexanes/*t*-BuOMe, 3:1 v/v) R_f = 0.55; $[\alpha]_D$= +14.6 (*c* 1, CH_2Cl_2); IR (film):2952, 2934, 2854, 1641, 1461, 1307, 1150, 1088, 835, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ =7.82 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J*= 7.4 Hz, 1H), 7.48 (t, *J*=7.4 Hz, 2H), 4.70 (brs, 1H), 4.19 (brs, lH), 3.18 (ddd, *J*= 14.4, 10.4, 4.4 Hz, 1H), 3.11 (dd, *J* = 9.6, 5.7, 1H), 2.81 (ddd, *J* = 14.1, 9.9, 6.0 Hz, 1H), 2.26 (ddd, *J* = 12.9, 4.0, 2.3 Hz, 1H), 1.89 (m, 1H), 1.80 (dt, *J* =13.0, 5.0 Hz, 1H), 1.67-1.46 (m, 6H), 1.27 (dt, *J* = 12.7, 4.1 Hz, 1H), 1.09-1.03 (m, 1H), 0.94 (dd, *J* = 12.5, 2.6 Hz, 1H), 0.80 (s, 9H), 0.81 (s, 3H), 0.64 (s, 3H), 0.57(s, 3H), -0.03(s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 147.1, 139.9, 133.6, 129.3(2C), 127.9 (2C), 107.0, 79.1, 55.3, 54.6, 39.7, 39.4, 37.9, 36.9, 28.7, 28.2, 27.0, 25.9 (3C), 24.1, 18.1, 17.1, 15.9, 14.3, -3.7, -4.9. HRFABMS: calcd. $C_{28}H_{46}NaO_3SSi$ $[M+Na]^+$ 513.2835, found 513.2841.

Compound 14: A solution of **13** (789 mg, 1.6 mmol) in anhydrous THF (69 mL) was cooled to 0 ºC under Argon and treated with $BH_3 \cdot THF$ (3.2 mL, 1M in THF, 3.2 mmol). The reaction mixture was allowed to warm slowly to rt over 4 h. It was then cooled to 0 ºC, and treated with a premixed solution of 3M NaOH (1.3 mL, 3.9 mmol) and 30%

aqueous H_2O_2 (1.3 mL, 3.9 mmol). After 1 h at 0 ºC, the reaction mixture was stirred for 3 h at rt and quenched with saturated NH_4Cl solution (25 mL). The mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic extracts were washed with brine (15 mL) and dried. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel with *t*-BuOMe to afford the corresponding hydroxy sulfone **14** (675 mg, 83%) as a white foam. TLC (EtOAc/*t*-BuOMe, 1:1 v/v) R_f = 0.75; $[\alpha]_D$ = +12.6 (*c* 1, CH_2Cl_2); IR (film): 3453, 2931, 2854, 1642, 1469, 1447, 1304, 1145, 1085, 835, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.90 (d, *J* = 7.3 Hz, 2H), 7.65 (t, *J*= 7.4 Hz, 1H), 7.56 (t, *J*=7.9 Hz, 2H), 3.54-3.48 (m, 2H), 3.22 (ddd, *J* = 13.7, 11.4, 5 Hz, 1H), 3.12 (dd, *J* = 10.8, 5.2, 1H), 2.96 (ddd, *J* = 13.7, 11.0, 4.9 Hz, 1H), 1.99-1.92 (m, 2H), 1.71-1.45 (m, 7H), 1.36-1.27 (m, 2H), 1.23 (dt, *J* = 11.3, 4 Hz, 1H), 0.93 (dt, *J* = 12.8, 4.5 Hz, 1H), 0.76 (brd, *J* = 9.7 Hz, 1H), 0.87 (s, 12H), 0.70 (s, 3H), 0.67(s, 3H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 139.5, 133.7, 129.3 (2C), 128.0 (2C), 79.1, 61.3, 55.5, 55.3, 52.01, 39.6, 39.2, 37.8, 37.4, 29.5, 28.5, 27.7, 25.9 (3C), 18.7, 18.1, 17.6, 15.9, 15.7, -3.7, -4.9. HRFABMS: calcd. $C_{28}H_{48}NaO_4SSi$ $[M+Na]^+$ 531.2940, found 531.2945.

Compound 15: Hydroxysulfone **14** (383 mg, 0.76 mmol) was dissolved in 15.8 mL of CH_2Cl_2 and *N*,*N*-diisopropylethylamine (0.40 mL, 2.28 mmol) and MEMCl (0.23 mL, 1.98 mmol) were added at 0 ºC. The mixture was stirred for 3 h at rt, and then partitioned between H_2O (50 mL) and DCM (50 mL). The aqueous layer extracted with DCM (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. To a solution of the crude residue obtained above in THF (6.7 mL) at –78 ºC was added a 2.5M solution of *n*-BuLi (0.5 mL, 0.84 mmol). The resulting yellow mixture was stirred for 30 min, and then oxirane (30 equiv) was added. The reaction mixture was stirred for 10 min and then quenched

by the dropwise addition of a saturated aqueous solution of NH_4Cl (3 mL). The reaction mixture was partitioned between EtOAc (50 mL), and H_2O (50 mL), and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). Evaporation of the organic solvent gave a mixture of diastereomers which were used directly without further purification. A solution of lithium (9 mg, 1.2 mmol) in ethylamine (10 mL) at –78 ºC under Argon was stirred for 30 min until the solution turned dark blue. Then, the crude bishomologated compound obtained above in THF (6 mL) at –78 ºC was added. The mixture was stirred for 10 min (TLC monitoring), then the reaction was quenched by dropwise addition of a saturated aqueous solution of NH_4Cl (3 mL). The resulting mixture was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with H_2O (25mL), brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel 1:1 (hexanes/ *t*-BuOMe) to afford the primary alcohol **15** (236 mg, 62%) as a colorless oil. TLC (*t*-BuOMe) R_f =0.50; $[\alpha]_D$ = +14.3 (*c* 1, CH_2Cl_2); IR (film): 3422, 2933, 2856, 1461, 1253, 1095, 1053, 835, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 4.71 (d, *J* = 6.8, 1H), 4.69 (d, *J* = 6.8, 1H), 3.73-3.55 (m, 7H), 3.44 (t, *J* = 9.7 Hz, 1H), 3.39 (s, 3H), 3.15 (dd, *J* = 11.1, 4.7 Hz, 1H), 1.96 (m, 2H), 1.64 (dt, *J* =13.0, 3.3 Hz, 1H), 1.60-1.15 (m, 12H), 0.94 (dt, *J* = 13.1, 3.8 Hz, 1H), 0.88 (s, 3H), 0.87(s, 9H), 0.79 (brd, *J* = 9.2 Hz, 1H), 0.73 (s, 3H), 0.71 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 95.6, 79.4, 71.9, 67.0, 66.7, 62.8, 59.1, 55.7, 52.9, 39.6, 37.6, 37.5, 36.1, 33.1, 30.1, 28.6, 27.9, 25.9 (3C), 25.2, 24.1, 18.2, 17.8, 15.9 (2C), -3.7, -4.8. HRFABMS: calcd. $C_{28}H_{56}NaO_5Si$ $[M+Na]^+$ 523,3795, found 523.3799.

Compound 8: Oxalyl chloride (0.76 mL, 2.0M in CH_2Cl_2, 1.52 mmol) was added to a solution of dry DMSO (0.23 mL, 3.04 mmol) in dry CH_2Cl_2 (5.4 mL) at –60 °C, under

Argon. The mixture was stirred for 30 min, and a solution of alcohol **15** (254 mg, 0.50 mmol) in CH_2Cl_2 (1.8 mL) was added. After additional stirring for 30 min at –60 °C, Et_3N (0.7 mL, 5 mmol) was added. The mixture was allowed to warm up to 0 °C, poured into ice cold water, diluted with CH_2Cl_2 and worked up in the usual way to give the corresponding crude aldehyde, directly used in the next step. To a solution of the aforementioned aldehyde dissolved in THF (4.4 mL) at 0 ºC, vinyl magnesium bromide (0.557 mL) was added dropwise. The reaction mixture was stirred for 10 minutes at 0 ºC and then quenched by dropwise addition of a saturated aqueous solution of NH_4Cl (2 mL). The aqueous layer was separated and extracted with *t*-BuOMe (2 x 20 mL). The combined organic layer was washed with brine (25 mL) and dried over Na_2SO_4 to give a mixture of epimers which were used in the next step without purification. To a solution of the allylic alcohols in CH_2Cl_2 (16 mL) was added Dess-Martin periodinane (299 mg, 0.70 mmol) at 0 ºC. The ice bath was removed and the solution was stirred at rt while the reaction progress was monitored by TLC. After TLC analysis indicated consumption of the starting alcohol (30 min), the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3 \cdot NaHCO_3$ (5 mL), diluted in CH_2Cl_2 (20 mL) and the organic layer was washed with a saturated solution of $NaHCO_3$ (20 mL), brine (25 mL) and dried over Na_2SO_4. Volatiles were removed *in vacuo* and the crude material purified by silica gel flash chromatography1:1 (hexanes/*t*-BuOMe) to afford enone **8** (224 mg, 84%) as yellowish oil. TLC (hexanes/*t*-BuOMe, 1:1 v/v) R_f = 0.55, $[\alpha]_D$= +10.9 (*c* 1, CH_2Cl_2); IR (film): 2932, 2853, 1640, 1461, 1252, 1111, 1087, 1052, 835, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ =6.33 (dd, *J* =17.6, 10.5 Hz, 1H), 6.19 (dd, *J* = 17.6, 1.1 Hz, 1H), 5.79 (dd, *J* = 10.5, 1.1 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 3.69-3.53 (m, 5H), 3.46 (t, *J* = 9.6 Hz, 1H), 3.38 (s, 3H), 3.14 (dd, *J* = 11.1, 4.9 Hz, 1H), 2.56 (dt, *J* = 7.5, 3.1 Hz, 2H), 1.96 (brt, *J* = 7.4 Hz, 2H), 1.75-1.68 (m, 1H), 1.60

(dt, *J* = 9.4 ,3.5 Hz, 1H), 1.54-1.15 (m, 10 H) 0.94 (dt, *J* = 13.1, 3.9 Hz, 1H), 0.87 (s, 12H), 0.78 (brt, *J* = 5.8 Hz, 1H), 0.71 (s, 3H), 0.68 (s, 3H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 201.5, 136.6, 127.9, 95.6, 79.3, 71.9, 66.9, 66.7, 59.1, 55.6, 52.9, 39.9, 39.6, 37.6, 37.5, 36.3, 31.5, 30.0, 28.6, 27.8, 25.9 (3C), 25.2, 22.6, 18.2, 17.7, 15.9, -3.7, -4.8. HREIMS (m/z): [M-H]+ calcd. for $C_{30}H_{56}O_5Si$ 523.3897 found 523.3819.

Compound 7: To a solution of compound **8** (224 mg, 0.43 mmol) in THF (1.5 mL), imine **9**[15] (207 mg, 0.85 mmol) at 0 °C was added. The resulting mixture was stirred for 17 h at the same temperature, and concentrated under reduced pressure. H_2O (6.0 mL) and AcOH (1.0 mL) were added to the residue at rt. The mixture was then stirred for 4 h, poured into brine (25 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was treated with a NaOMe 30% wt/wt solution (0.17 mL, 0.94 mmol) in MeOH (1 mL) at reflux for 5 h, while the reaction progress was monitored by TLC. After TLC analysis indicated consumption of the starting diketone, the solvent was remove *in vacuo*, partitioned between saturated aqueous 2N HCl (50 mL) and *t*-BuOMe (50 mL) and the aqueous layer extracted with *t*-BuOMe (2 x 25 mL). The combined organic layers were washed a saturated solution of $NaHCO_3$ (50 mL), brine (50 mL) and dried over Na_2SO_4. Volatiles were removed under reduced pressure and the crude material purified by silica gel flash chromatography1:1 (hexanes/*t*-BuOMe) to afford enone **7** (183 mg, 66% overall yield). TLC (hexanes/*t*-BuOMe, 1:1 v/v) R_f = 0.45, $[\alpha]_D$= + 0.3 (*c* 1, CH_2Cl_2); IR (film): 2930, 2855, 1665, 1459, 1252, 1112, 1086, 1051, 835, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.79 (d, *J* = 6.7 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 3.77-3.54 (m, 6H), 3.4 (s, 3H), 3.15 (dd, *J* = 10.9, 5.2 Hz, 1H), 2.48 (dd, *J* = 14.5, 5.4

Hz, 1H), 2.45 (dd, *J* = 14.5, 5.4 Hz, 1H), 2.40-2.31 (m, 2H), 2.03-1.96 (m, 4H), 1.79 (dt, *J* = 13.5, 4.2 Hz, 1H), 1.73 (ddd, *J* = 8.4, 5.3, 3.1 Hz, 1H), 1.66-1.20 (m, 11 H), 1.19 (s, 3H), 1.05 (s, 3H), 1.01-0.94 (m, 1H) 0.89 (s, 3H), 0.88 (s, 3H), 0.87 (s, 9H), 0.82 (s, 3H), 0.72 (s, 3H), 0.67 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125MHz): δ =198.5, 161.6, 135.3, 95.8, 79.4, 71.9, 67.3, 66.7, 59.1, 55.7, 53.7, 40.9, 39.6, 38.4, 37.8, 37.6, 37.5, 36.5, 35.6, 34.8, 34.2, 33.8, 32.5, 30.1, 28.6, 27.8, 26.0 (3C), 25.7, 25.1, 24.2, 22.7, 18.2, 17.8, 16.0, 15.9, -3.7, -4.8. HREIMS (m/z): [M-H]+ calcd. for $C_{39}H_{70}O_5Si$ 645.4993, found 645.4994.

(2*E*,6*E*)-3,7-dimethyl-9-((*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)nona-2,6-dienyl acetate (18): 2, 2- Dimethoxypropane (2.9 mL, 24 mmol) was added to a cooled (0ºC) solution of **16**[14] (500 mg, 1.6 mmol) and cat *p*-TsOH in acetone (30 mL). The reaction was removed from the ice bath and stirred at rt for 30 min. It was then quenched with saturated aqueous $NaHCO_3$. The resulting solution was poured into *t*-BuOMe (150 mL) and the aqueous layer was extracted *t*-BuOMe (2 x 50 mL). The combined organic extract was washed with water (150 mL), brine (150 mL), dried over Na_2SO_4 .Volatiles were removed under vacuum and the crude material purified by silica gel flash chromatography (hexanes/*t*-BuOMe 1:2) to afford acetonide **17** (535 mg, 87%). TLC (hexanes/*t*-BuOMe, 1:1 v/v) R_f = 0.75; $[\alpha]_D$= + 3.3 (*c* 1, MeOH); IR (film): 2982, 1742, 1377, 1369, 1232, 1114, 1023, 1003 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ =5.33 (dt, *J* = 7.1, 1.2 Hz, 1H); 5.14 (dt, *J* = 6.9, 1.1 Hz, 1H), 4.6 (d, *J* = 7.1 Hz, 2H), 3.65 (dd, *J* = 9.2, 3.6 Hz, 1H), 2.22-1.98 (m, 6H), 2.05 (s, 3H), 1.70 (s, 3H), 1.64-1.57 (m, 1H), 1.61 (s, 3H), 1.49-1.43 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.2, 142.2, 134.9, 124.2, 118.4, 106.5, 82.9, 80.2, 61.5, 39.6, 36.7, 28.6, 27.8, 26.9, 26.3, 26.2, 23.0, 21.1, 16.6, 16.1.

(R)-2,2,4,4-tetramethyl-5-((3E,7E)-3,7-dimethyl-9-(phenylsulfonyl)nona-3,7-dienyl) -1,3-dioxolane (19): A solution of (Pd(π-allyl)Cl)$_2$ (23 mg, 0.06 mmol) and dppf (102 mg, 0.18 mmol) in 3.5 mL CH_2Cl_2 was added to a flask containing $NaSO_2Ph$ (854 mg, 5.2 mmol), tetramethylammonium bromide (42 mg, 0.27 mmol), and **17** (1.19 g, 3.06 mmol), in a mixture of degassed water (10 mL) and CH_2Cl_2 (7 mL). The reaction was stirred at rt for 2.5 h, at which time the layers were separated. The aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and purified via silica gel flash chromatography 2:1 (hexanes/*t*-BuOMe) to afford the corresponding sulphone **18** (1.26 g, 98 %). TLC (hexanes/*t*-BuOMe, 1:1 v/v) R_f = 0.62; $[\alpha]_D$= + 0.63 (*c* 1, CH_2Cl_2); IR (film): 2979, 2932, 2855, 1.447, 1371, 1234, 1150, 1128, 100, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ =7.84 (d, *J* = 7.4 Hz, 2H); 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 5.17 (t, *J* = 7.9 Hz, 1H), 5.07 (bt, *J* = 6.3 Hz, 1H), 3.77 (d, *J* = 7.9 Hz, 2H), 3.61 (dd, *J* = 9.3, 3.3 Hz, 1H), 2.20-2.15 (m, 1H), 2.03-1.96 (m, 5H), 1.61-1.53 (m, 1H), 1.58 (s, 3H), 1.47-1.41 (m, 1H), 1.39 (s, 3H), 1.29 (s, 6H), 1.21 (s, 3H), 1.07(s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 146.3, 138.7, 135.1, 133.5, 129.0 (2C), 128.546 (2C), 123.7, 110.3, 106.4, 82.9, 80.1, 56.1, 39.6, 36.7, 28.6, 27.7, 26.9, 26.1, 26.0, 22.9, 16.2, 16.0. HRFABMS: calcd. $C_{24}H_{36}NaO_4S$ $[M+Na]^+$ 443.2232, found 443.2235.

(R)-5-((3E,7E)-10-((4aS,8aR)-1,2,3,4,4a,5,6,8a-octahydro-2,2,4a,7-tetramethyl naphthalen-8-yl)-3,7-dimethyldeca-3,7-dienyl)-2,2,4,4-tetramethyl-1,3-dioxolane (20): To a solution of sulphone **18** (850 mg, 2.02 mmol) in THF (9.6 mL) was added *n*-butyllithium (2M solution in hexane, 1.01 mL, 2.02 mmol) at –78 ºC. The resulting yellow mixture was stirred for 10 min and a solution of bromide **6** (192 mg, 0.67 mmol) in THF (20 mL) was added dropwise. The mixture was allowed to warm for 4 h, and then diluted with *t*-BuOMe (100 mL) and quenched with water. The organic layer was

washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica chromatography (hexane: *t*-BuOMe, gradient from 3:1 to 1:1) afforded the corresponding epimeric mixture of sulphones (326 mg, 78%). To a solution of Li (10 mg) in $EtNH_2$ (15 mL) was added at –78 ºC a solution of the sulphones (326 mg, 0.522 mmol) in THF (8 mL). The mixture was stirred for 20 min. Saturated NH_4Cl was then added slowly, and the mixture was further stirred for 10 min. The aqueous layer was extracted with *t*-BuOMe (2 x 100 mL), and the combined organic extract was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The crude material was purified by silica gel flash chromatography 5:1 (hexanes/*t*-BuOMe) to afford acetonide **19** (187 mg, 74%). TLC (hexanes/*t*-BuOMe, 4:1 v/v) R_f = 0.85; $[\alpha]_D$= + 5.3 (*c* 1, CH_2Cl_2); IR (film): 2969, 2914, 2857, 1458, 1369, 1215, 1113, 1002 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ =5.09 (t, *J* = 8.1 Hz, 1H), 5.08 (t, *J* = 7.3 Hz, 1H), 3.59 (dd, *J* = 9.2, 3.5 Hz, 1H), 2.17-2.10 (m, 2H), 2.04-1.77 (m, 10H), 1.66-1.56 (m, 2H), 1.55 (s, 3H), 1.54 (s, 3H), 1.50 (s, 3H), 1.45-1.36 (m, 3H), 1.35 (s, 3H), 1.32 (d, *J* = 2.5 Hz, 1H), 1.31 (d, *J* = 2.7 Hz, 1H), 1.30 (m, 1H), 1.25 (s, 3H), 1.17 (s, 3H), 1.13 (t, *J* = 3.2 Hz, 1H), 1.03 (s, 3H), 0.89 (t, *J* = 13 Hz, 1H), 0.88 (d, *J* = 9.2 Hz, 1H), 0.82 (s, 3H), 0.80 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ =134.8, 134.4, 133.8, 125.0, 124.9, 124.1, 106.6, 83.1, 80.2, 43.2, 42.6, 39.9, 36.8 (2C), 34.8, 32.3, 31.9, 31.6, 31.1, 29.7, 28.7, 28.0, 27.3, 27.1, 27.0, 26.8 (2C), 26.3, 24.4, 23.1, 18.7, 16.1 (2C). HREIMS (m/z): $[M]^+$ calcd. for $C_{33}H_{56}O_2$ 484.4280 found 484.4277.

Preoleanatetraene oxide (16): To a solution of **19** (127 mg, 0.26 mmol) and 80% aqueous AcOH (2.5 mL) in THF (4 mL) was gradually added 2M HCl (2 mL) at rt for 30 min, and the whole mixture was stirred for 12 h at the same temperature. The reaction mixture was diluted with brine and extracted with *t*-BuOMe (100 mL). The

combined organic extract was washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL) and dried over Na_2SO_4. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (hexane/*t*-BuOMe, 2: 1) to give the corresponding diol (92 mg, 80%). To a solution of the aforementioned diol (142 mg, 0.32 mmol) and catalytic DMAP in anhydrous pyridine (5 mL) cooled at -12º C under argon atmosphere, was added dropwise MsCl (0.15 mL, 1.92 mmol). After 40 minutes (TLC monitoring), the mixture was diluted with *t*-BuOMe and treated with sat $NaHCO_3$ solution. After additional 15 minutes stirring at rt, the mixture was extracted with Et_2O (3 x 50 mL), the organic layer washed with HCl 1N (1x 50 mL), brine (1x 50 mL) and dried over anhydrous Na_2SO_4 and finally concentrated under reduced pressure. The mesylated crude was dissolved in 5 mL of MeOH and K_2CO_3 (176 mg, 1.25 mmol) was added. After stirring for 20 minutes, the formation of epoxide was complete (TLC monitoring). Then, the reaction was quenched by diluting with H_2O and *t*-BuOMe. The organic layer washed with 1 *N* HCl (2 x 50 mL), saturated $NaHCO_3$ (2 x 50 ml) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 1:2) to afford 101 mg of the corresponding epoxide **20** (74% yield over two steps). Colorless oil, TLC (hexanes/*t*-BuOMe, 1:2 v/v) R_f = 0.50; $[\alpha]_D$= +2.9 (*c* 1, CH_2Cl_2); IR (film): 2944, 2917, 2858, 1451, 1377, 1121, 1033, 967, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ =5.16 (t, *J*= 6.6 Hz, 1H), 5.15 (t, *J*=6.6 Hz, 1H), 2.69 (t, *J*=6.3 Hz, 1H), 2.22-1.83 (m, 14H), 1.73-1.64 (m, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.48 (dt, *J*=13.7, 4.3 Hz, 1H), 1.41-1.33 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 1.23-1.09 (m, 1H), 0.95 (t, *J*= 13 Hz, 1H), 0.94 (d, *J*= 9.2 Hz, 1H), 0.89 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ =134.6, 133.9, 133.5, 124.9, 124.7, 123.8, 64.1, 58.2, 42.9, 42.2, 39.6, 36.5, 36.3, 34.6, 33.1, 31.6, 31.4, 30.9, 29.5, 27.5, 27.1, 26.9,

26.6, 26.5, 24.9, 24.2, 18.7, 18.6, 16.0, 15.9. HREIMS (m/z): [M+H]+ calcd. for $C_{30}H_{50}O$ 427.3861 found 427.3948.

***Seco*-C-oleanane (1), achilleol B (3) and camelliol A (4)**: A mixture of Cp_2TiCl_2 (138 mg, 0.557 mmol) and Mn dust (61 mg, 1.11 mmol) in a strictly deoxygenated mixture THF (6 mL) under Ar atmosphere was stirred at rt until the red solution turned green. Then, a solution of 119 mg (0.278 mmol) of preoleanatetraene oxide in THF (6 mL) was added. The reaction mixture was stirred for 20 minutes (TLC monitoring), quenched with 1N HCl, extracted with *t*-BuOMe (50 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel using mixtures of hexanes and *t*-BuOMe as eluent (gradient from 10:1 → 4:1 hexanes: *t*-BuOMe v/v) to afford 51 mg (49 %) of an inseparable mixture of triterpenes by classic chromatography, namely, *seco*- C- oleanane (**1**), achilleol B (**3**) and camelliol A (**4**) in a 81%, 13% and 6% ratio, respectively, calculated by GC-MS analyses. TLC (hexanes/*t*-BuOMe, 4:1 v/v) R_f = 0.30. This mixture was subjected to column chromatography on $AgNO_3$ (20%)-silica gel using mixtures of hexanes and *t*-BuOMe as eluent (gradient from 5:1 → 2:1 hexanes: *t*-BuOMe v/v) to afford two main fractions, the first constituted by a mixture of the three triterpenes (hexanes/*t*-BuOMe, 3:1 v/v), and a second one enriched in *seco*-C oleanane (**1**) and achilleol B (**3**) (hexanes/*t*-BuOMe, 2:1 v/v) This fraction was subjected to HPLC (6:1 hexanes: *t*-BuOMe) to obtain pure *seco*-C oleanane (**1**) and achilleol B (**3**) (t_r= 25.3 min and 26.2 min, respectively). *Seco*-C oleanane (**1**): White solid: mp 134-135 ^oC; $[\alpha]_D$= +23, (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 3610, 3450, 1644, 1384, 892 cm-1; 1H NMR ($CDCl_3$, 500 MHz): δ= 4.86 (1H, d, *J* = 1.5 Hz, H-26), 4.63 (1H, d, *J* = 1.0 Hz, H- 26'), 3.25 (1H, dd, *J* = 11.7, 4.4 Hz, H-3), 2.41 (1H, dq, *J* = 12.7, 2.4 Hz, H-7), 2.32 (1H, m, H-12), 1.99 (1H, m, H-7'), 1.99 (1H, m, H-15), 1.88 (1H, m, H-15'),

1.89 (1H, m, H-16), 1.79 (1H, m, H-1), 1.75 (1H, m, H-6), 1.69 (1H, m, H-2), 1.60 (1H, m, H-9), 1.59 (1H, m, H-2'), 1.55 (1H, m, H-18), 1.56 (3H, s, Me-27), 1.49 (1H, m, H-11), 1.48 (1H, m, H-22), 1.47 (1H, m, H-12'), 1.38 (1H, m, H-6'), 1.33 (1H, m, H-11'), 1.33 (1H, m, H-21), 1.33 (1H, m, H-19), 1.21 (1H, m, H-22'), 1.17 (1H, m, H-1'), 1.12 (1H, m, H-21'),1.10 (1H, m, H-5), 0.93 (1H, m, H-19'), 0.99 (3H, s, Me-23), 0.88 (3H, s, Me-30), 0.87 (3H, s, Me-29), 0.85 (3H, s, Me-28), 0.81 (1H, m, H-16'), 0.77 (3H, s, Me- 24), 0.67 (3H, s, Me-25); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 148.3, 134.2, 123.5, 106.5, 78.9, 56.9, 54.6, 42.9, 42.9, 39.5, 39.1, 38.2, 36.8, 36.5, 34.5, 33.1, 31.5, 30.9, 30.8, 29.4, 28.3 27.9, 27.2, 26.4, 24.0, 24.0, 22.8, 18.7, 15.3, 14.4; HREIMS *m/z* 426.3868 (calcd for $C_{30}H_{50}O$, 426.3865). Achilleol B (**3**): $[\alpha]_D$= -10.9º (c 0.9, $CHCl_3$); IR ($CHCl_3$): 3394, 3080, 1662, 1644, 1385, 1365, 1195, 1085, 892. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.12 (1H, t, *J* = 7.0 Hz), 4.88 (1H, bs), 4.62 (1H, bs), 3.40 (1H, dd, *J* = 10.0, 4.5 Hz), 2.32 (1H, dt, *J* = 13.2, 4.5 Hz), 2.21 (1H, ddd, *J* = 13.1, 10.0, 6.6 Hz), 2.08 (1H, ddd, *J* = 13.2, 10.3, 3.8 Hz), 2.02-1.82 (7H, m), 1.80-1.44 (8H, m), 1.61 (3H, s), 1.58 (3H, s), 1.39 (1H, ddd, *J* = 13.0, 3.7, 2.6 Hz), 1.35 (1H, dd, *J* = 13.8, 3.9 Hz), 1.23 (1H, dt, *J* = 13.3, 3.5 Hz), 1.12 (1H, m), 1.04 (3H, s), 0.97 (1H, t, *J* = 13.0 Hz), 0.90 (3H, s), 0.88 (3H, s), 0.82 (3H, s), 0.82 (1H, m), 0.72 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 147.5, 135.2, 133.8, 124.8, 124.1, 108.6, 77.5, 51.3, 43.2, 42.5, 40.8, 38.9, 36.8, 34.8, 33.4, 33.3, 32.4, 31.9, 31.6, 31.2, 29.7, 27.4, 27.2, 26.7, 26.1, 24.4, 24.0, 18.9, 16.2, 15.7.

***Seco*-C-oleanane (1) and C-ring *seco*-β amyrin** (**2**): A mixture of Cp_2TiCl_2 (18 mg, 0.071 mmol) and Mn dust (104 mg, 1.896 mmol) in strictly deoxygenated THF (4 mL) under Argon atmosphere was stirred at rt until the red solution turned green. Then, a solution of 101 mg (0.237 mmol) of preoleanatetraene oxide **16** and 2, 4, 6-collidine (0.220 mL, 1.659 mmol) and Me_3SiCl (0.12 mL, 0.946 mmol) were added. The reaction

mixture was stirred for 3.30 h (TLC monitoring), quenched with 1N HCl , extracted with *t*-BuOMe (50 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in THF (3 mL) and stirred with Bu_4NF (0.704 mL, 0.704 mmol) for 30 min. Then, THF was removed, and the mixture was diluted with *t*-BuOMe (50 mL), washed with brine (50 mL), and dried over anhydrous Na_2SO_4 and the solvent was removed. The resulting crude was purified by column chromatography on silica gel using mixtures of hexanes:*t*-BuOMe of increasing polarity as eluents to afford 59 mg (51%) of the *exo* and *endo* isomers, *seco*-C oleanane (**1**) and *seco*-β amyrin (**2**) in a 7:1 ratio respectively (NMR integration). TLC (hexanes/*t*-BuOMe, 4:1 v/v) R_f = 0.30. This mixture was subjected to column chromatography on $AgNO_3$ (20%)-silica gel using mixtures of hexanes and *t*-BuOMe as eluent (gradient from 5:1 → 2:1 hexanes: *t*-BuOMe v/v) to obtain a fraction enriched in *seco*-β amyrin (**2**) (hexanes/*t*-BuOMe, 2:1 v/v) and19 mg of **1** (hexanes/*t*-BuOMe, 2:1 v/v). The fraction enriched in *seco*-β amyrin (**2**) was subjected to HPLC (4:1 hexanes: *t*-BuOMe) to obtain pure *seco*-β- amyrin (**2**) (t_r= 17.3 min): $[\alpha]_D$= +10.1, (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 3610, 3450, 1644, 1384, 892 cm-1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ= 5.40 (1H, brs, H-7), 3.25 (1H, dd, J = 10.9, 4.9 Hz, H-3), 2.41 (1H, dt, J = 13.0, 5.8 Hz, H-12), 1.98 (1H, m, H-15), 1.97 (1H, m, H-6, H-6'), 1.92 (1H, m, H-1), 1.87 (1H, m, H-15'), 1.75 (3H, brs, Me-26), 1.70-1.55 (2H, m, H-2, H-2'), 1.63 (1H, m, H-18), 1.58 (1H, m, H-9), 1.58 (1H, m, H-12'), 1.57 (3H, s, Me-27), 1.51 (1H, m, H-22), 1.42 (1H, m, H-11), 1.38 (1H, m, H-19), 1.35 (1H, m, H-21), 1.23 (1H, m, H-22'),1.20 (1H, m, H-5), 1.19 (1H, m, H-1'), 1.14 (1H, m, H-11'), 1.13 (1H, m, H-21'), 0.98 (1H, m, H-19'), 0.98 (3H, s, Me-23), 0.88 (3H, s, Me-29), 0.88 (3H, s, Me-30), 0.86 (3H, s, Me-24), 0.84 (3H, s, Me-28), 0.76 (3H, s, Me-25); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 135.40, 134.3, 123.6 ,121.8, 79.2, 55.7, 49.7, 43.0, 42.8, 38.7, 37.2, 37.0, 36.5, 34.9, 34.6, 33.2,

31.5, 31.0, 29.4, 27.9, 27.5, 27.1, 26.5, 26.0, 24.0, 23.5, 22.1, 18.8, 15.1, 13.7. HREIMS *m/z* 426.3855 (calcd for $C_{30}H_{50}O$, 426.3862).

Acknowledgment. This research was supported by the Spanish Ministry of Science and Technology, Project CTQ2010-16818 (BQU) V.D. thanks the Spanish Ministry of Science and Technology for a predoctoral grant enabling him to pursue these studies. We thank Prof. P. Joseph-Nathan (Centro de Investigacion y de Estudios Avanzados del IPN., Mexico) for providing NMR spectra and sample of *seco*-C oleanane (**1**).

Supporting Information Available. Experimental procedures and spectroscopic data for compound **5**, computational calculations and ^{1}H and ^{13}C NMR spectra of **1**-**4**, **8**-**9**, **12**-**16**, and **18**-**20**. This material is available free of charge at http://pubs.acs.org.

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Artículo 5: *Expedient access to A-ring-γ-dioxygenated terpenoids: the first synthesis of (13E)-ent-labda-8(17),13-diene-3β,15,18-triol, Domingo, V.; Dieguez, H. R.; Morales, C. P.; Arteaga, J. F.; Quilez del Moral, J. F.; Barrero, A. F., Synthesis,* ***2010****, 67-72.*

Expedient Access to A-Ring-γ-Dioxygenated Terpenoids: The First Synthesis of (13*E*)-*ent*-Labda-8(17),13-diene-3β,15,18-triol

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Received 24 July 2009; revised 2 September 2009

Abstract: A simple approach to A-ring-γ-dioxygenated terpenoids is described which involves two key steps, namely, selenium-catalyzed selective allylic chlorination of polyprenoids and titanocene-mediated radical cyclization of epoxypolyprenes. We have applied this synthetic route to the first synthesis of the diterpene, (13*E*)-*ent*-labda-8(17),13-diene-3β,15,18-triol. A stereoselective approach to this synthesis is also described.

Key words: diterpene, radical cyclizations, oxiranes, stereoselective synthesis, titanocene

Among naturally occurring bioactive terpenoids there are numerous examples which possess a stereochemically defined γ-dioxygenated A-ring (Figure 1).[1] Representatives include the labdane-type diterpene, (13*E*)-*ent*-labda-8(17),13-diene-3β,15,18-triol (**1**), the common aglycone of the natural glycosides goshonosides-F1, -F2 and -F3 which were isolated from the leaves of *Rubus chingii* and the fruits of *Rubus foliolosus*,[2] *ent*-kaur-16-ene-3β,15β,18-triol (**2**) isolated from the bark of *Suregada multiflora*[3] which displays anti-allergic activity, the meroterpenoid pyripyropene A (**3**) from the fungus *Aspergillus fumigatus* which proved to be an inhibitor of acyl-coenzyme A:cholesterol acyltransferase,[4] the aglycone of lobatoside E (**4**) isolated from *Actinostemma lobatum* which displays cytotoxicity and may induce apoptosis of tumor cells,[5] and the lupene triterpene (**5**) obtained from *Mimusops elengi*[6] (Figure 1).

There are a number of reports describing the preparation of A-ring-dioxygenated terpenoids starting from the corresponding C-3 alcohols using a γ-oxidation protocol following Baldwin's method, which involves cyclopalladation of the equatorial methyl group at C-4 of an intermediate oxime.[7] This protocol requires a multistep sequence as shown in Scheme 1. Moreover, when total synthetic approaches are considered, the carbocyclic core also needs to be prepared,[8] which increases the complexity of the overall sequence.

Bearing in mind the recently introduced concepts of step-economy,[9] and of an ideal synthesis as that which includes: 'construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality',[10] we described, in a preliminary paper, a method to access directly five- to seven-membered polyfunctional terpene carbocycles via titanocene(III)-catalyzed radical cyclizations of the appropriate epoxypolyprenes.[11] In this work, we reported that, although acceptable yields of cyclization products could be obtained when a silyloxy function was located in an α position with respect to the oxirane ring, good stereoselectivities were only obtained when the initial cyclization led to a cyclohexane ring. Prior to our work, Takahashi et al. reported the titanocene(III)-mediated cyclization of various epoxy derivatives of geranyl acetate hydroxylated on one of the methyl groups adjacent to the oxirane ring.[12]

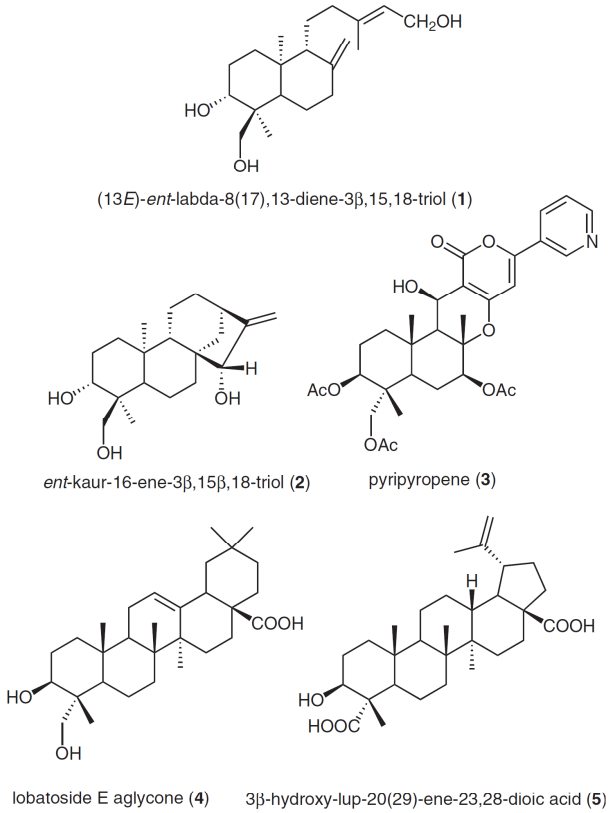


Figure 1 Examples of natural products containing a γ-dioxygenated A ring

SYNTHESIS 2010, No. 1, pp 0067–0072
Advanced online publication: 03.11.2009
DOI: 10.1055/s-0029-1217094; Art ID: Z15709SS

Confirmation of the stereochemical outcome of these cyclizations would render this method an expedient protocol for the preparation of A-ring-γ-dioxygenated terpenoids. This would involve as key transformations, selective positional functionalization of the starting polyprene and stereoselective cyclization of the corresponding oxirane. This strategy would improve on known methods in terms of efficiency and number of steps (Scheme 1).

To test this idea, we investigated the stereoselective synthesis of the labdane-type diterpene (13*E*)-*ent*-labda-8(17),13-diene-3β,15,18-triol (**1**) (Scheme 2).[2]

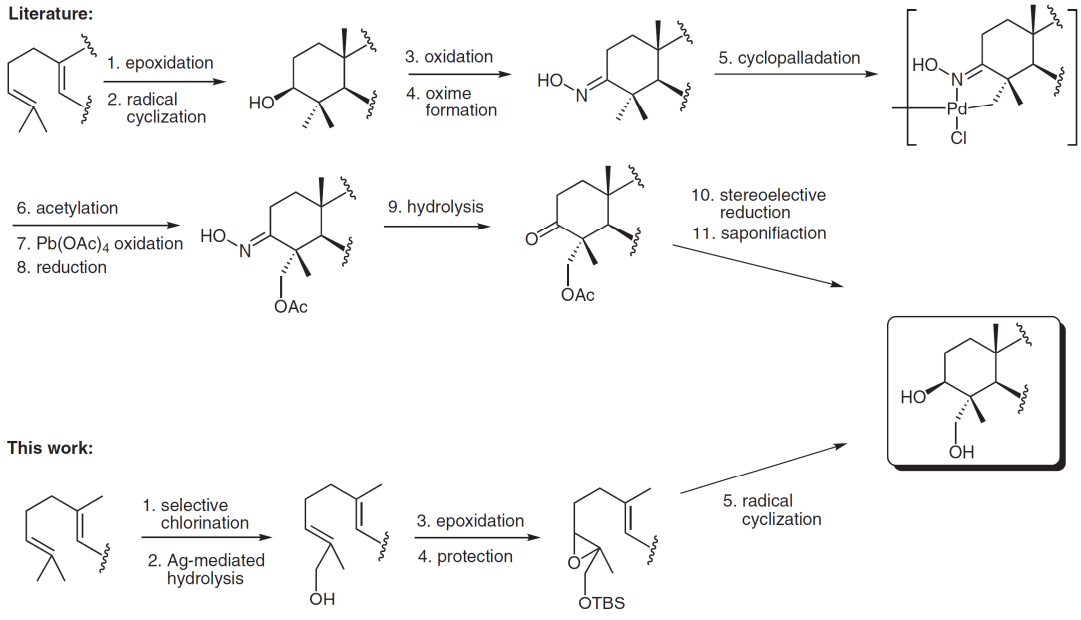
Since the correct alkene geometry is essential in the radical cyclization of epoxypolyprenes, pure (*E*,*E*)-farnesylacetone (**8**) was obtained from commercially available farnesol (**6**) through alkylation of farnesyl bromide (prepared via bromination of **6**) with methyl acetoacetate and subsequent Krapcho decarboxylation.[13] The carbonyl group of **8** needed to be protected in order to avoid the generation of a third ring during the titanium(III)-mediated cyclization.[14] When this carbonyl was protected as a ketal, partial deprotection was observed in the key selenium-mediated regioselective halogenation of the terminal isopropylidene unit of the polyprene; this method was developed in our laboratory and was based on a previous report by Tunge and Mellegard.[15] Thus, farnesylacetone (**8**) was efficiently transformed into acetate **9** in two steps. Treatment of **9** with *N*-chlorosuccinimide and a catalytic amount of phenylselenyl chloride (PhSeCl) led to the corresponding allyl chloride derivative, silver tetrafluoroborate mediated hydrolysis of which gave rise to a quasi-equimolecular mixture of primary and secondary alcohols **10a** and **10b**. The secondary alcohol could be recycled into **10a** via mesylation and subsequent hydrolysis with acetone–H_2O. Thus, primary alcohol **10a** was obtained in a good 70% yield overall.

Hydroxy-directed epoxidation of **10a** using Sharpless conditions[16] gave the key intermediate **11** in 90% yield. Protection of the primary alcohol group as its *tert*-butyldimethylsilyl ether and subsequent reaction with titanocene dichloride (Cp_2TiCl_2, 0.2 equiv) and excess manganese (8 equiv) in the presence of the titanocene(III) regenerator, trimethylsilyl chloride–2,4,6-collidine (7 equiv),[17] led to efficient radical cyclization occurring to afford the A-ring-γ-dioxygenated key intermediate **12** after acid work-up. Gratifyingly, the reaction, in which up to four contiguous stereogenic centers were created, proceeded with high stereocontrol. Next, ketone **13** was obtained in stereoisomerically pure form following protection of the diol in **12** and subsequent regeneration of the carbonyl group.

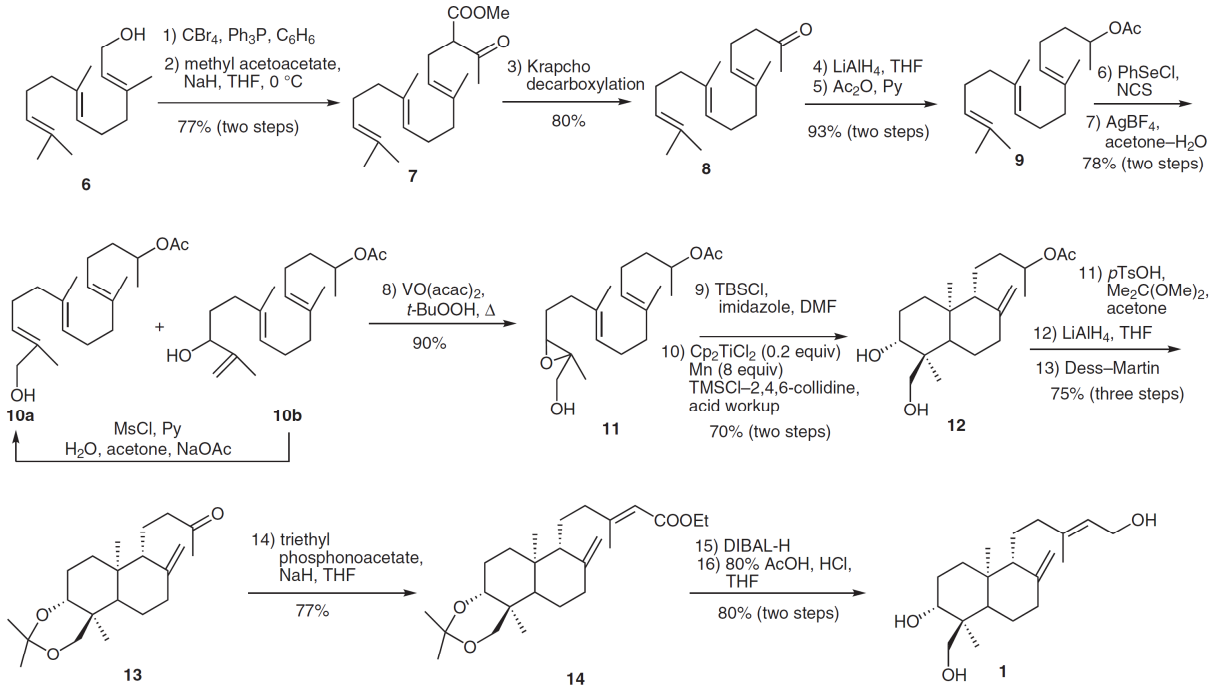
An interaction between the oxygen of the *tert*-butyldimethylsilyl ether and the titanoxy group at C-3 in the proposed transition state can be invoked to rationalize the stereochemical outcome of the cyclization (Scheme 3).[11,12]

Horner–Wadsworth–Emmons reaction of the acetonide **13** with triethyl phosphonoacetate furnished the requisite two-carbon homologue **14** in 77% yield. The corresponding unsaturated ester was reduced with diisobutylaluminum hydride at –20 °C, thus avoiding acetal opening, to give, after acid-mediated diol deprotection, (13*E*)-*ent*-labda-8(17),13-diene-3β,15,18-triol (**1**) (Scheme 2). Spectroscopic data of synthetic **1** were identical with those of the natural product.

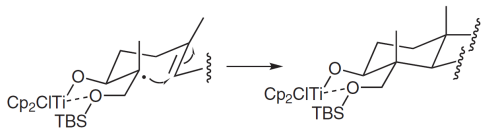
An enantioselective version of this sequence was easily envisaged via Sharpless asymmetric epoxidation of the allylic alcohol intermediate **10a**.[18] This transformation proceeded in an acceptable 71% yield (Scheme 4), however, the enantiomeric excess was not measured. Importantly,



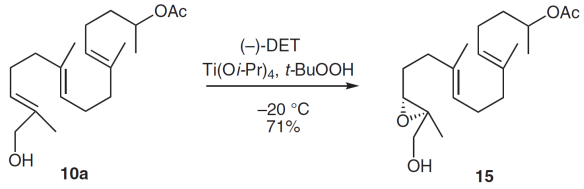
Scheme 1 Comparison between existing methods to access to terpenoids polyfunctionalized on the A ring and this work



Scheme 2 Synthesis of (13*E*)-*ent*-labda-8(17),13-diene-3β,15,18-triol (**1**)



Scheme 3 Proposed conformation of the transition state leading to a dioxygenated polycyclic terpenoid



Scheme 4 Enantioselective synthesis of oxirane **15**

the synthesis of both enantiomeric series can be achieved by choosing the appropriate chiral tartrate.

In summary, we have reported a short stereoselective synthesis of (13*E*)-*ent*-labda-8(17),13-diene-3β,15,18-triol (**1**) starting from commercially available farnesol. The synthesis of labdane **1** demonstrates the utility of the two key reactions, namely, the selenium-catalyzed selective allylic hydroxylation of the polyprenoid and the titanocene(III)-mediated radical cyclization of the monoepoxide of the polyprene, and should be applicable for the preparation of a number of bioactive terpenoids. Moreover, this method can be easily adapted for asymmetric synthesis via Sharpless asymmetric epoxidation of the corresponding allylic alcohol intermediates.[19]

All air- and moisture-sensitive reactions were performed in flame-dried flasks under a positive flow of Ar. THF was freshly distilled immediately prior to use from Na/benzophenone and strictly degassed for 30 min under Ar for the Cp_2TiCl_2/Mn reaction. Reagents were purchased from commercial sources and used without further purification, unless otherwise stated. Silica gel SDS 60 (35–70 μm) was used for flash column chromatography. IR spectra were recorded with a Mattson model Satellite FTIR instrument using NaCl plates. NMR studies were performed with Varian Direct Drive 500 MHz spectrometer. Accurate mass determinations were carried out using an AutoSpec-Q mass spectrometer arranged in an EBE geometry (Micromass Instrument, Manchester, UK) and equipped with a FAB (LSIMS) source. The instrument was operated at 8 kV accelerating voltage and Cs^+ was used as primary ions. Reactions were monitored by TLC performed on 0.25 mm Merck silica gel plates (60F–254) using UV light for visualization and a soln of phosphomolybdic acid in EtOH with heat as the developing agent.

Methyl (4*E*,8*E*)-2-Acetyl-5,9,13-trimethyltetradeca-4,8,12-trienoate (7)

CBr_4 (11.60 g, 35 mmol) and Ph_3P (9.18 g, 35 mmol) at 0 °C under an Ar atmosphere were added to a stirred solution of allylic alcohol (3.89 g, 17.5 mmol) in 90 mL of benzene. The solution was stirred at the same temperature for 2 h (TLC monitoring), and hexane (90 mL) was then added. The reaction mixture was filtered to remove any triphenylphosphine oxide. The filtrate was concentrated under reduced pressure and the resulting crude was purified by column chromatography on silica gel (hexane–*t*-BuOMe, 10:1) to afford the corresponding bromo derivative. A 60% dispersion of NaH in mineral oil (2.10 g, 52.5 mmol) was washed with hexane (3 × 10 mL) and then suspended in THF (50 mL). Methyl acetoacetate (5.8 mL, 54 mmol) was added dropwise at 0 °C. After 30 min, the soln was treated with the crude of the bromination reaction and stirred for 4 h. The reaction mixture was quenched with H_2O (50 mL), extracted with EtOAc (3 × 100 mL) and the combined organics were washed with H_2O (4 × 50 mL). The organic layer was dried over anhyd

Na_2SO_4 and concentrated. Column chromatography (Et_2O–hexane, 1:19) afforded **7** as a colorless oil; yield: 4.35 g (77%).

IR (film): 2919, 2855, 1747, 1720, 1436, 1150 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.10–5.01 (m, 3 H), 3.71 (s, 3 H), 3.45 (t, *J* = 7.5 Hz, 1 H), 2.54 (t, *J* = 7.5 Hz, 2 H), 2.20 (s, 3 H), 2.05–1.97 (m, 8 H), 1.67 (s, 3 H), 1.62 (s, 3 H), 1.59 (s, 3 H), 1.57 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.1, 170.2, 138.8, 135.4, 131.5, 124.6, 124.1, 119.8, 59.8, 52.5, 39.9 (2 C), 29.3, 27.0, 26.7, 26.6, 25.8, 17.9, 16.2, 16.0.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{32}NaO_3$: 343.2249; found 343.2244.

(*E*,*E*)-Farnesylacetone (8)

A soln of ester **7** (1.136 g, 3.55 mmol), H_2O (0.26 mL) and LiBr (0.463 g, 5.33 mmol) in DMSO (10 mL) was heated at reflux for 3 h (TLC monitoring). The soln was diluted with EtOAc (200 mL) and washed with H_2O (3 × 75 mL) and brine (100 mL). The organic layer was dried over anhyd Na_2SO_4 and concd under reduced pressure. Rapid filtration through silica gel (hexane–MTBE, 3:1) gave ketone **8** as a colorless oil; yield: 0.745 g (80%).

^1H NMR (500 MHz, $CDCl_3$): δ = 4.99 (m, 3 H), 2.35 (t, *J* = 7.6 Hz, 2 H), 2.16 (q, *J* = 7.6 Hz, 2 H), 2.03 (s, 3 H), 1.99–1.85 (m, 8 H), 1.58 (s, 3 H), 1.52 (s, 3 H), 1.51 (s, 3 H), 1.49 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.2, 136.6, 135.3, 131.4, 124.6, 124.3, 122.7, 43.9, 39.9, 30.1, 26.9, 26.8, 25.8 (2 C), 22.7, 17.9, 16.2 (2 C).

(5*E*,9*E*)-6,10,14-Trimethylpentadeca-5,9,13-trien-2-yl Acetate (9)

To a soln of farnesylacetone (**8**) (2.048 g, 7.81 mmol) in THF (45 mL) at 0 °C was added $LiAlH_4$ (0.265 g, 6.64 mmol). After stirring for 10 min, the reaction was quenched by diluting with MTBE (25 mL) followed by addition of 5 M NaOH (0.25 mL) and H_2O (0.25 mL). The resulting mixture was stirred for 10 min and then filtered through a bed of Na_2SO_4 and silica gel, washed with *t*-BuOMe (3 × 50 mL), and concentrated under reduced pressure to afford the desired alcohol. A mixture of the alcohol (1.958 g, 7.42 mmol), pyridine (26 mL, 0.32 mmol), Ac_2O (0.935 mL, 1.00 mmol) and DMAP (cat.) was stirred at r.t. for 2 h. The reaction mixture was poured onto ice (100 g) and extracted with MTBE (3 × 50 mL). The combined organic phase was successively washed with 2 M HCl (3 × 50 mL), 5% aq $NaHCO_3$ soln (3 × 30 mL) and H_2O (3 × 30 mL), and then dried over anhyd Na_2SO_4. After evaporation of the solvent the crude residue was chromatographed on silica gel (hexane–MTBE, 3:1) to afford acetate **9** as a colorless oil; yield: 2.23 g (93% over two steps).

IR (film): 2971, 2921, 2856, 1739, 1448, 1372, 1241, 1131, 1020, 837 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.09 (br t, *J* = 6.8 Hz, 3 H), 4.88 (sext, *J* = 6.9 Hz, 1 H), 2.09–1.95 (m, 10 H), 2.02 (s, 3 H), 1.68 (s, 3 H), 1.65–1.47 (m, 2 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.58 (s, 3 H), 1.21 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 135.9, 135.2, 131.4, 124.6, 124.4, 123.6, 70.9, 39.9 (2 C), 36.2, 26.9, 26.8, 25.8, 24.1, 21.5, 20.2, 17.9, 16.1 (2 C).

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{34}NaO_2$: 329.2457; found: 329.2434.

Primary and Secondary Alcohols 10a and 10b

Commercially available PhSeCl (203 mg, 1.06 mmol) was dissolved in anhyd CH_2Cl_2 (92 mL) under an Ar atm. To this soln were added acyclic polyprenoid **9** (3.26 g, 10.64 mmol) followed by NCS (1.56 g, 11.70 mmol) at r.t. The mixture was stirred for 1.5 h (TLC monitoring) at r.t, concd under vacuum, and then suspended in Et_2O (300 mL). The organic layer was decanted from the solid, washed with H_2O (2 × 100 mL) and brine (100 mL), dried over anhyd Na_2SO_4 and then concd under reduced pressure. The resulting crude was dissolved in acetone–H_2O (1:1, 160 mL), after which 2,4,6-collidine (4.5 mL, 34 mmol) and $AgBF_4$ (5.0 g, 25.5 mmol) were added. The resulting mixture was heated at 60–70 °C for 4 h (TLC monitoring). The acetone was removed under reduced pressure and the residue was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with 2 M HCl (3 × 50 mL) and brine (100 mL), dried over anhyd Na_2SO_4, and concd under reduced pressure. The residue was purified by column chromatography (hexane–MTBE, 5:1) on silica gel to afford **10b**; yield: 0.918 g (27%, 2.84 mmol; colorless oil) and **10a**; yield: 1.122 g (33%, 3.47 mmol; colorless oil).

(5*E*,9*E*,13*E*)-15-Hydroxy-6,10,14-trimethylpentadeca-5,9,13-trien-2-yl Acetate (10a)

IR (film): 3448, 2978, 2921, 2854, 1727, 1448, 1374, 1019, 739 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.38 (t, *J* = 7.0 Hz, 1 H), 5.10 (br t, *J* = 6.7 Hz, 1 H), 5.09 (br t, *J* = 7.0 Hz, 2 H), 4.87 (sext, *J* = 6.6 Hz, 1 H), 3.98 (br s, 2 H), 2.14–1.96 (m, 10 H), 2.01 (s, 3 H), 1.66 (s, 3 H), 1.65–1.46 (m, 2 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.20 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 135.9, 134.9, 134.8, 126.3, 124.6, 123.6, 70.9, 69.2, 39.9, 39.5, 36.2, 26.7, 26.4, 24.1, 21.6, 20.2, 16.2, 16.1, 13.9.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{34}NaO_3$: 345.2406; found: 345.2401.

(5*E*,9*E*)-13-Hydroxy-6,10,14-trimethylpentadeca-5,9,14-trien-2-yl Acetate (10b)

IR (film): 3440, 2974, 2933, 2856, 1737, 1447, 1373, 1244, 897 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.13 (t, *J* = 6.9 Hz, 1 H), 5.08 (t, *J* = 7.0 Hz, 1 H), 4.92 (br s, 1 H), 4.87 (sext, *J* = 6.6 Hz, 1 H), 4.82 (br s, 1 H), 4.02 (t, *J* = 6.0 Hz, 1 H), 2.10–1.96 (m, 8 H), 2.01 (s, 3 H), 1.72 (s, 3 H), 1.70–1.46 (m, 4 H), 1.60 (s, 3 H), 1.57 (s, 3 H), 1.20 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 147.7, 135.8, 134.9, 124.8, 123.7, 111.1, 75.8, 70.9, 39.8, 36.1, 35.9, 33.4, 26.6, 24.1, 21.6, 20.2, 17.9, 16.2, 16.1.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{34}NaO_3$: 345.2406; found: 345.2405.

Conversion of 10b into 10a

To a soln of **10b** (164 mg, 0.51 mmol) in pyridinc (5 mL) at 0 °C was added DMAP (cat.). After 10 min, MsCl (0.88 mL, 3.0 mmol) was added. The reaction mixture was stirred for 1 h and then quenched with sat. aq $NaHCO_3$ soln (15 mL) and extracted with MTBE (2 × 20 mL). The organic extract was washed with 1 M HCl (15 mL), sat. aq $NaHCO_3$ soln (15 mL), and brine (15 mL), dried over anhyd Na_2SO_4, and concd under reduced pressure. The residue was dissolved in acetone (5 mL) and H_2O (4 mL), NaOAc (100 mL) was added, and the mixture was heated at reflux for 2 h. The resulting crude was purified by column chromatography (hexane–MTBE, 2:1) on silica gel to afford **10b**; yield: 59 mg (38%) and **10a**; yield: 64 mg (41%).

(5*E*,9*E*)-12-[3-(Hydroxymethyl)-3-methyloxiran-2-yl]-6,10-dimethyldodeca-5,9-dien-2-yl Acetate (11)

A mixture of allylic alcohol **10a** (280 mg, 0.87 mmol) and $VO(acac)_2$ (8 mg) in benzene (33 mL) was heated at reflux for 10

min under Ar. Next, *t*-BuOOH in decane (0.2 mL, 1.40 mmol) was added and stirring was continued at reflux for 20 min. After cooling, the mixture was diluted with EtOAc (50 mL) and washed with sat. aq $NaHCO_3$ soln (2 × 25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, evaporated under reduced pressure and chromatographed on silica gel (hexane–MTBE, 1:1) to give the desired epoxide as a colorless oil; yield: 264 mg (90%).

IR (film): 3455, 2973, 2930, 2861, 1736, 1448, 1374, 1244, 1131, 1040, 868 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.14 (t, *J* = 5.7 Hz, 1 H), 5.08 (t, *J* = 6.0 Hz, 1 H), 4.87 (sext, *J* = 6.1 Hz, 1 H), 3.65 (br d, *J* = 12.0 Hz, 1 H), 3.55 (dd, *J* = 12.0, 7.3 Hz, 1 H), 3.00 (t, *J* = 6.4 Hz, 1 H), 2.16–1.96 (m, 8 H), 2.02 (s, 3 H), 1.72–1.46 (m, 4 H), 1.61 (s, 3 H), 1.58 (s, 3 H), 1.28 (s, 3 H), 1.21 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7, 135.4, 133.8, 124.8, 123.4, 70.6, 65.6, 61.1, 60.0, 39.5, 36.1, 35.8, 26.7, 26.4, 23.8, 21.3, 19.9, 15.9, 15.8, 14.1.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{34}NaO_4$: 361.2355; found: 361.2371.

3b,18-Dihydroxy-14,15-dinor-*ent*-labda-8(17)-en-13-yl Acetate (12)

To a stirred soln of **11** (0.774 g, 2.29 mmol) in CH_2Cl_2 (28 mL), imidazole (0.669 g, 9.85 mmol) and TBSCl (1.48 g, 4.9 mmol) were added at r.t. After stirring for 1 h (TLC monitoring), the mixture was extracted with MTBE (2 × 50 mL). The combined organic layer was washed with 2 M HCl (3 × 50 mL) and brine (50 mL), dried over anhyd Na_2SO_4 and concd under reduced pressure. The residue was purified by column chromatography (hexane–MTBE, 4:1) on silica gel to afford the corresponding silylated derivative; yield: 0.954 mg (95%).

A mixture of Cp_2TiCl_2 (0.276 g, 1.11 mmol) and Mn dust (0.244 g, 44.32 mmol) in strictly deoxygenated THF (70 mL) under an Ar atm was stirred at r.t. until the red soln turned green. Next, a soln of the silyl derivative of epoxide **11** (0.243 g, 5.50 mmol), 2,4,6-collidine (5.1 mL, 38.8 mmol) and Me_3SiCl (2.8 mL, 22.16 mmol) were added. The reaction mixture was stirred for 5 h (TLC monitoring), then diluted with MTBE (150 mL) and quenched with 2 M HCl (50 mL). After further stirring for 2 h, the mixture was extracted with MTBE (2 × 100 mL), the combined organics washed with brine (100 mL), dried over anhyd Na_2SO_4 and concd under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–MTBE, 1:3) to afford the desired diol **12** (colorless oil) as a 1:1 mixture of diastereoisomers; yield: 0.843 g (45%).

IR (film): 3385, 2936, 2874, 1735, 1642, 1449, 1373, 1245, 1032, 889 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ () = 4.84–4.80* (m, 4 H), 4.52 (br s, 1 H), 4.47 (br s, 1 H), 3.65–3.62* (m, 4 H), 3.40* (d, *J* = 10.4 Hz, 2 H), 2.36* (ddd, *J* = 12.9, 4.0, 2.5 Hz, 2 H), 2.02 (s, 3 H), 2.01 (s, 3 H), 1.95* (dt, *J* = 13.0, 4.9 Hz, 2 H), 1.78–1.10* (m, 24 H), 1.19 (d, *J* = 5.3 Hz, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H), 0.84* (s, 6 H), 0.70* (s, 6 H); * indicates signals common to both diastereoisomers.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 170.8, 147.5, 147.4, 107.0, 106.8, 76.2*, 71.4*, 71.5, 71.1, 56.5, 56.0, 48.9*, 42.2*, 39.3, 39.2, 37.8*, 36.7, 36.6, 34.9, 34.8, 27.4*, 24.0, 23.9, 21.4, 21.3, 20.1, 19.8, 19.4, 19.3, 14.8, 14.7, 11.3*; * indicates signals common to both diastereoisomers.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{34}NaO_4$: 361.2355; found: 361.2371.

3β,18-Isopropylidenedioxy-14,15-dinor-*ent*-labda-8(17)-en-13-one (13)

To a soln of **12** (101 mg, 0.30 mmol) and *p*-TsOH (cat.) in anhyd acetone (5.3 mL) at r.t. under an Ar atm, was added dropwise 2,2-dimethoxypropane (0.5 mL). After 2.5 h (TLC monitoring), $NaHCO_3$ was added, acetone was removed under reduced pressure and the residue was extracted with MTBE (3 × 10 mL). The combined organic layer was washed with H_2O (10 mL) and brine (10 mL), dried over anhyd Na_2SO_4 and finally concd under reduced pressure. To a soln of the resulting protected diol in THF (7 mL) was added $LiAlH_4$ (13 mg, 0.36 mmol). After 10 min, the reaction was quenched by adding 5 M NaOH (0.1 mL) and H_2O (0.1 mL). The mixture was filtered through Na_2SO_4 and silica gel to afford the desired alcohol. The resulting crude alcohol was dissolved in anhyd CH_2Cl_2 (7.3 mL) under Ar and Dess–Martin periodinane (254 mg, 0.60 mmol) was added. After stirring for 2 h at r.t. the reaction was quenched with a sat. aq soln of $Na_2S_2O_3$–$NaHCO_3$ (5 mL). The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhyd Na_2SO_4 and concd under reduced pressure. Flash column chromatography on silica gel (hexane–MTBE, 1:1) afforded **13** as a colorless oil; yield: 65 mg (75%, over three steps).

IR (film): 2988, 2936, 2853, 1715, 1642, 1459, 1379, 1109, 863 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.84 (br s, 1 H), 4.46 (br s, 1 H), 3.54 (dd, *J* = 11.7, 3.8 Hz, 1 H), 3.45 (d, *J* = 10.6 Hz, 1 H), 3.42 (d, *J* = 10.6 Hz, 1 H), 2.56 (ddd, *J* = 17.6, 8.3, 4.7 Hz, 1 H), 2.39–2.29 (m, 2 H), 2.10 (s, 3 H), 1.95–1.81 (m, 3 H), 1.65–1.22 (m, 7 H), 1.44 (s, 3 H), 1.41 (s, 3 H), 1.12 (dd, *J* = 12.4, 3.2 Hz, 1 H), 1.03 (s, 3 H), 0.73 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.1, 147.1, 107.2, 98.8, 72.5, 56.0, 50.7, 42.3, 39.5, 37.6, 37.2, 36.9, 30.0, 29.8, 29.6, 24.2, 23.0, 19.2, 17.3, 15.4, 12.3.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{34}NaO_3$: 357.2406; found: 357.2418.

Ethyl (13*E*)-3β,18-Isopropylidenedioxy-*ent*-labda-8(17),13-dienoate (14)

To a suspension of a 60% dispersion of NaH in mineral oil (20 mg, 0.490 mmol) in THF (1.5 mL) at 0 °C was added dropwise triethyl phosphonoacetate (0.1 mL, 0.49 mmol) under an inert atm. After stirring for 5 min, ketone **13** (43 mg, 0.13 mmol) in anhyd THF (0.5 mL) was added. The soln was stirred for 6 h and then diluted with ether (15 mL), washed with H_2O (10 mL) and brine (10 mL), dried over anhyd Na_2SO_4 and concd under reduced pressure. The resulting crude was purified by column chromatography on silica gel (hexane–MTBE, 6:1) to afford **14** as a colorless oil; yield: 42 mg (77%).

IR (film): 2937, 2852, 1714, 1646, 1446, 1380, 1145, 863, 735 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.62 (br s, 1 H), 4.86 (br s, 1 H), 4.52 (br s, 1 H), 4.14 (q, *J* = 6.4 Hz, 2 H), 3.53 (dd, *J* = 11.8, 3.8 Hz, 1 H), 3.50 (d, *J* = 10.0 Hz, 1 H), 3.45 (d, *J* = 10.0 Hz, 1 H), 2.38 (ddd, *J* = 12.9, 4.2, 2.4 Hz, 1 H), 2.28 (ddd, *J* = 13.8, 9.4, 3.8 Hz, 1 H), 2.15 (s, 3 H), 1.93 (m, 2 H), 1.83 (dt, *J* = 13.1, 3.4 Hz, 1 H), 1.69–1.20 (m, 8 H), 1.45 (s, 3 H), 1.41 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.12 (dd, *J* = 12.4, 3.3 Hz, 1 H), 1.03 (s, 3 H), 0.73 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 160.4, 147.2, 115.7, 107.4, 99.0, 77.3, 72.7, 59.6, 56.1, 50.9, 39.6, 39.5, 37.7, 37.4, 37.1, 29.9, 24.4, 23.2, 21.5, 19.3, 18.9, 15.7, 14.4, 12.4.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{25}H_{40}NaO_4$: 427.2824; found: 427.2841.

(13*E*)-*ent*-Labda-8(17),13-diene-3β,15,18-triol (1)

To a soln of dienoate **14** (27 mg, 0.064 mmol) in toluene (1 mL) at –78 °C was added DIBAL-H (1 M soln in hexanes, 0.31 mL, 0.31 mmol). After 10 min, the reaction was quenched by the addition of H_2O (1 mL) dropwise. The mixture was filtered through Na_2SO_4

and silica gel to afford the desired alcohol. To a soln of this alcohol (21 mg, 0.06 mmol) and 80% aq AcOH (0.84 mL) in THF (0.6 mL) was slowly added 2 M HCl (0.1 mL) at r.t. over 30 min. The resulting soln was stirred for 2 h at the same temperature and then diluted with brine (5 mL) and extracted with MTBE (20 mL). The organic layer was washed with sat. aq $NaHCO_3$ soln (2 × 10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was chromatographed on silica gel (hexane–MTBE, 1:2) to give **1** as colorless prisms. Yield: 16 mg (80% over two steps); mp 141–142 °C.

IR (film): 3419, 2935, 1640, 1422, 1115, 888, 736 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.37 (t, *J* = 5.8 Hz, 1 H), 4.85 (br s, 1 H), 4.53 (br s, 1 H), 4.13 (d, *J* = 6.9 Hz, 2 H), 3.69 (d, *J* = 10.0 Hz, 1 H), 3.68 (dd, *J* = 11.6, 4.6 Hz, 1 H), 3.42 (d, *J* = 10.0 Hz, 1 H), 2.38 (ddd, *J* = 12.9, 4.2, 2.4 Hz, 1 H), 2.15 (m, 1 H), 1.96 (dt, *J* = 12.7, 4.9 Hz, 1 H), 1.85–1.28 (m, 9 H), 1.67 (s, 3 H), 1.26–1.14 (m, 2 H), 0.86 (s, 3 H), 0.73 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.6, 140.4, 123.3, 107.0, 76.4, 71.7, 59.5, 56.1, 49.0, 42.4, 39.3, 38.3, 38.0, 36.9, 27.7, 24.1, 22.0, 16.4, 15.0, 11.4.

HRMS–FAB: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{34}NaO_3$: 345.2406; found: 345.2422.

Asymmetric Epoxidation of 10a

To a suspension of powdered activated 3 Å MS (250 mg) in CH_2Cl_2 (5 mL), were added (–)-DET (54 mg, 0.26 mmol), $Ti(OiPr)_4$ (62 mg, 0.22 mmol) and *t*-BuOOH (3.5 M in toluene, 1.24 mL, 4.34 mmol) at –20 °C. After stirring for 20 min at –20 °C, the mixture was cooled to –40 °C, and a soln of alcohol **10a** (685 mg, 2.13 mmol) in CH_2Cl_2 (2.5 mL) was added over 20 min. The resulting mixture was stirred for 2 h at –30 °C, warmed to 0 °C, and treated with H_2O (5 mL). The mixture was stirred for 20 min at 0 °C, warmed to r.t. and treated with 30% aq NaOH soln (5 mL) and brine (5 mL). After stirring for 30 min, the resulting suspension was filtered through Celite (washing with CH_2Cl_2). The aq layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organics concd under reduced pressure. The residue was purified by silica gel column chromatography (hexane–MTBE, 1:1) to afford epoxide **15** as a colorless oil; yield: 577 mg (81%).[20]

Acknowledgment

This research was supported by the Spanish Ministry of Science and Technology, Project CTQ2006-15575-C02-01. V.D. thanks the Spanish Ministry of Science and Technology for a predoctoral grant enabling the pursuit of these studies.

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IV. DISCUSIÓN DE LOS RESULTADOS

IV. 1. *Estudio bibliográfico sobre triterpenos inusualmente ciclados:*

Uno de los objetivos propuestos para el desarrollo de esta tesis consiste en la recopilación de la aparición y distribución en la naturaleza de los triterpenos irregulares. Así se han presentado en el artículo de revisión **nº1** las estructuras y propiedades biológicas de estos compuestos que han surgido durante la última década. Allí se pone de manifiesto que en los últimos años existe un incremento considerable en el número de artículos científicos sobre la descripción de estos nuevos triterpenos naturales derivados de la ciclación parcial de escualeno ó 2,3-óxido de escualeno. Cabe destacar que los organismos marinos, principalmente las esponjas, son una fuente importante de triterpenos irregulares, que además presentan por lo general unas interesantes propiedades biológicas. Si tenemos en cuenta que el ser humano solamente ha podido explorar hasta 1 km de profundidad en el océano, pero que recientemente esta barrera tecnológica está siendo superada, se pronostica que un gran número de triterpenos irregulares bioactivos aparecerán en un futuro cercano procedentes de los fondos marinos.

El segundo objetivo comprendía el estudio de las rutas biosintéticas de estos triterpenos irregulares a partir de sus precursores lineales, este objetivo se ha alcanzado sistematizando su estudio en una clasificación en diferentes familias según su origen biosintético. Además, la confirmación de la existencia de OSCs específicas para la formación de estas moléculas indica que su distribución en la naturaleza es mayor de lo que se podría esperar *a priori*. Al mismo tiempo, las propuestas biosintéticas sugieren nuevos mecanismos de retrociclación que están implicados en la biosíntesis de estas sustancias, dando lugar a una amplia diversidad estructural en estos triterpenos irregulares. Por citar un ejemplo representativo, recientemente, *Hoshino et al.*[81] han descubierto los genes que codifican en *Oryza sativa* la formación de achilleol B. Esta achilleol B sintasa es capaz de producir este triterpeno irregular en un 90% (Figura 1). De este modo, se ha descrito la tercera *seco*-triterpeno sintasa hasta la fecha, lo cual parece indicar que este campo de estudio tiene una gran potencialidad.

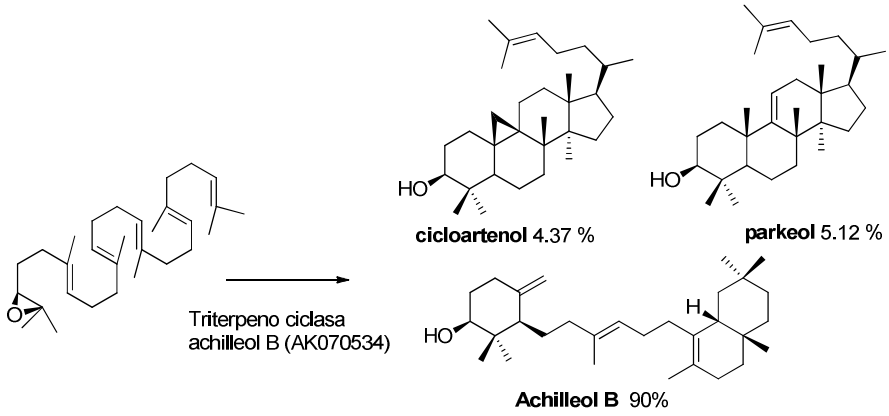


Figura 1

Finalmente, dentro de este mismo estudio de triterpenos irregulares se ha hecho en su último apartado un resumen bibliográfico de las diferentes estrategias dirigidas hacia la síntesis de estos compuestos.

IV. 2. *Síntesis total enantioselectiva de el potente anti-inflamatorio (+)-mirrhanol A.*

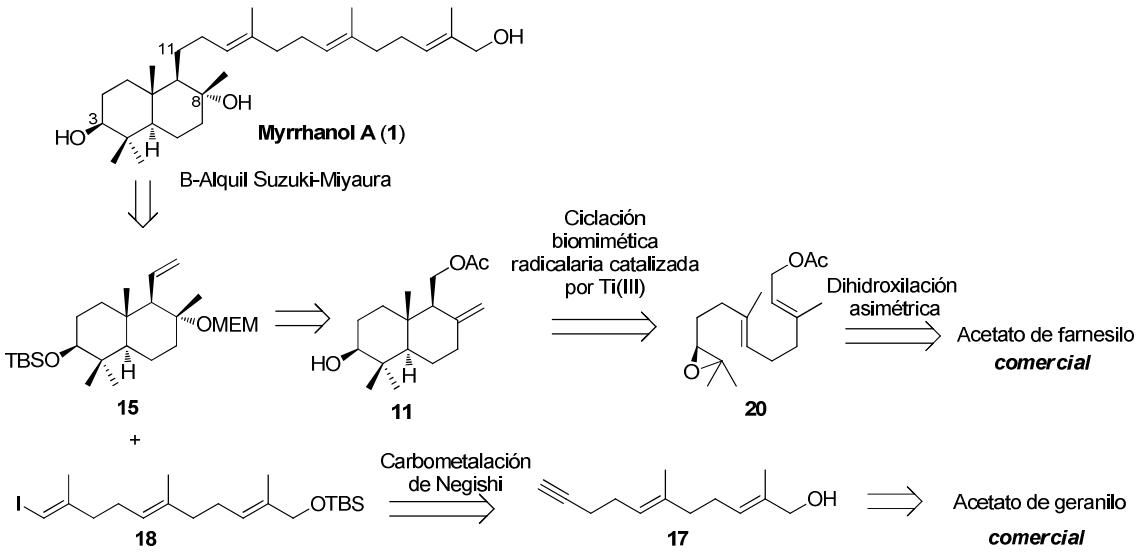
Introducción y análisis retrosintético:

Dentro de la revisión bibliográfica de triterpenos irregulares se encontraron descritos en la "Mirra" los mirrhanoles, una serie de compuestos con interesante bioactividad antiinflamatoria.

Las resinas de la mirra son prescritas en la forma de mezclas directas con polvos o extractos de otros fármacos para su uso contra la obesidad, como antiinflamatorios, antibacterianos o anticoagulantes en la medicina popular de la India. Los fármacos sin elaborar proceden de las resinas naturales que secretan *Balsamodendron (Commiphora) mukul* y *mirra*. Así, el 50% de extracto acuoso metanólico de estas resinas exhibe un potente efecto antiinflamatorio sobre el granuloma de ratón inducido por bolsas de aire, donde el triterpeno irregular mirrhanol A (**1**) era el compuesto no esteroideo e hidrofílico responsable de la actividad.[44a]

En el diseño retrosintético hacia mirrhanol A (**1**) (Esquema 1), se planteó una aproximación convergente basada en el acoplamiento de Suzuki-Miyaura[82] de un alquil borano obtenido a partir del sintón quiral C16 **15**, y un sintón acíclico, el vinil ioduro poliprenado **18**. Basándonos en estudios previos de nuestro laboratorio, esta síntesis fue diseñada utilizando un fragmento C16, dado que su menor impedimento estérico con

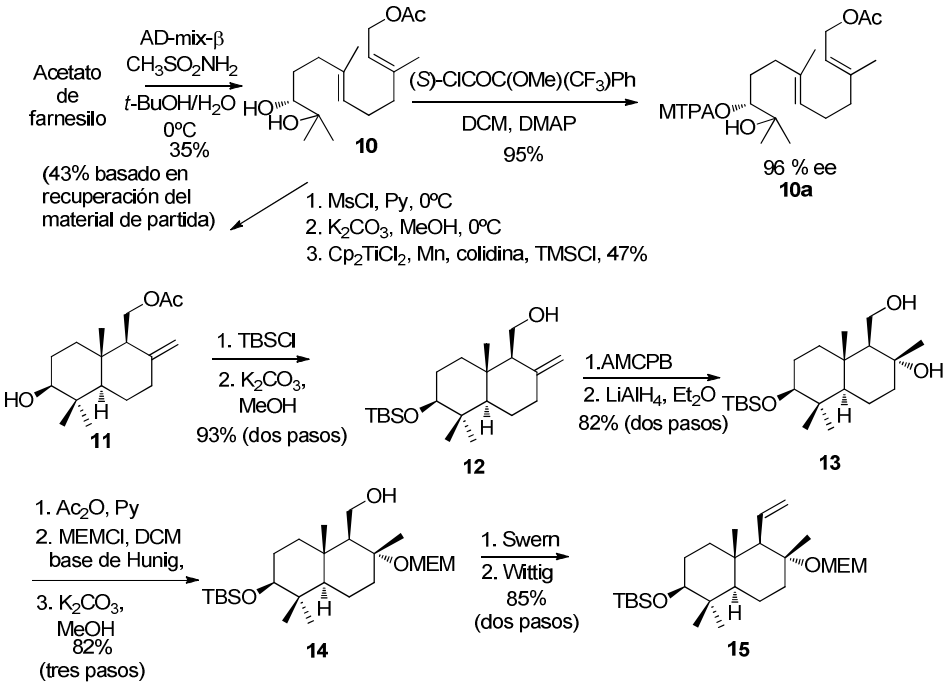
relación a su análogo C15 debería permitir la reacción de acoplamiento. En este punto cabe resaltar que para la consecución de la síntesis se seleccionaron grupos protectores ortogonales, pero con la característica de que todos pudieran ser retirados en un solo paso mediante tratamiento ácido. De este modo, se diseñó una síntesis nuevamente convergente y económica desde el punto de vista de las etapas (Esquema 1).



Esquema 1. Análisis retrosintético de mirrhanol A

Obtención del sintón bicíclico 15:

La etapa clave para la contrucción del esqueleto de isodrimenodiol **11** fue la cascada radicalaria del epoxipolipreno quiral **20**, reacción promovida por cantidades catalíticas de Cp_2TiCl. El epóxido **20** proviene de hacer reaccionar acetato de farnesilo en condiciones de dihidroxilación asimétrica de Sharpless, reaccción de la que se obtiene el diol quiral **10** (96% ee, determinado mediante análisis de Mosher). El diol se transforma vía mesilato en el epóxido correspondiente que, mediante una ciclación radicalaria 6-*endo-trig* mediada por Ti (III) en condiciones catalíticas, origina el compuesto bicíclico **11** con un 47% (Esquema 2). Cabe destacar que la configuración de los cuatro nuevos estereocentros creados en este proceso coinciden con los de la molécula objetivo.



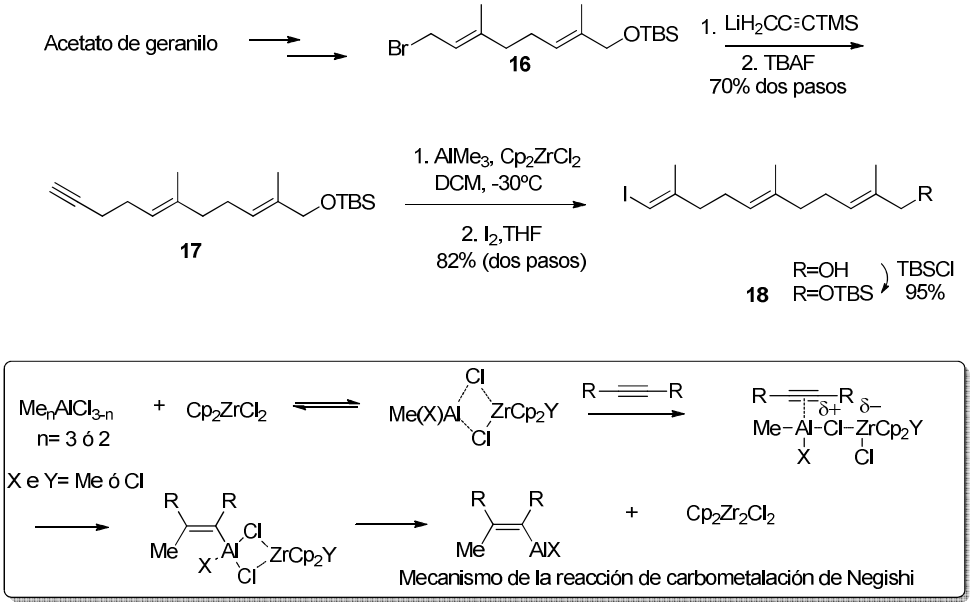
Esquema 2

Se protegió entonces el compuesto **11** en forma de su *tert*-butildimetilsilil derivado y se saponificó para liberar el alcohol primario **12** con un 93% para los dos pasos. Con objeto de introducir el alcohol terciario en C-8 se epoxidó la olefina mediante AMCPB, donde el ataque electrofílico tuvo lugar estereoselectivamente por la cara menos impedida (cara alfa), de forma que la apertura reductiva con $LiAlH_4$ del correspondiente epóxido condujo al alcohol **13** con un 82% para los dos pasos. Previa a la introducción del grupo vinilo, se obtuvo el alcohol primario **14** utilizando química de grupos protectores. Así los alcoholes primario y terciario del diol **13** se protegieron de forma ortogonal, introduciendo selectivamente primero el grupo acetato y después el grupo metoxietoximetilo para, tras la desprotección del éster, obtener **14** con un 82% (tres pasos). La oxidación del alcohol primario **14** utilizando las condiciones de Swern y subsiguiente olefinación de Wittig del correspondiente aldehído con bromuro de metil trifenilfosfonio condujeron al intermedio **15** con un 85% de rendimiento para los dos últimos pasos. Con esta homologación de un átomo de carbono se deja el sintón bicíclico preparado para la reacción de acoplamiento.

Preparación del sintón acíclico 18:

Para construir el sintón de 14 átomos **18** (Esquema 3) partimos de acetato de geranilo comercial, que se transforma en el bromo derivado **16** mediante métodos

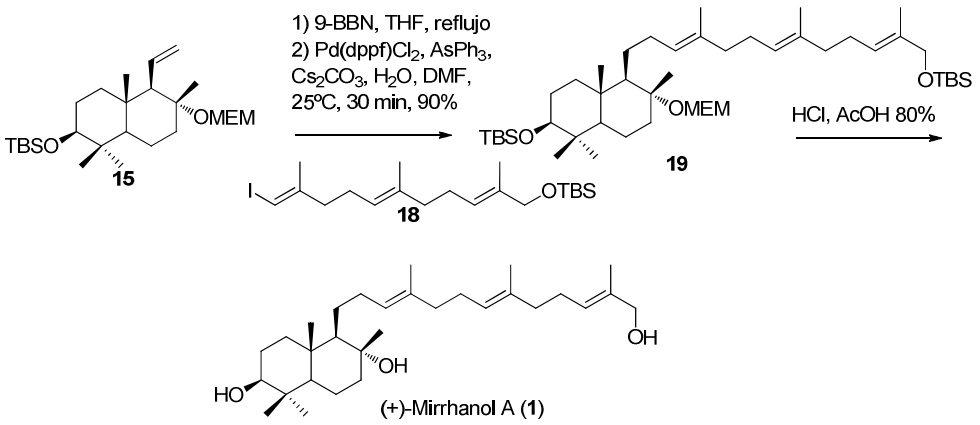
conocidos.[83] El tratamiento de **16** con el reactivo acetilénico trimetilsililpropargil-litio permitió no sólo homologar la cadena en tres carbonos, sino también introducir el alquino terminal (**17**) tras desprotección del trimetilsililo (70%, dos pasos). A continuación, una carbometalación de Negishi,[84] seguida del desplazamiento electrofílico del correspondiente carboalano por yodo, da lugar de manera regio- y estereoselectiva al ioduro vinílico *E* (82%), intermedio clave para el acoplamiento. La protección final del alcohol primario como su silil éter en un 95% condujo al compuesto **18**.



Esquema 3. Preparación del sintón acíclico

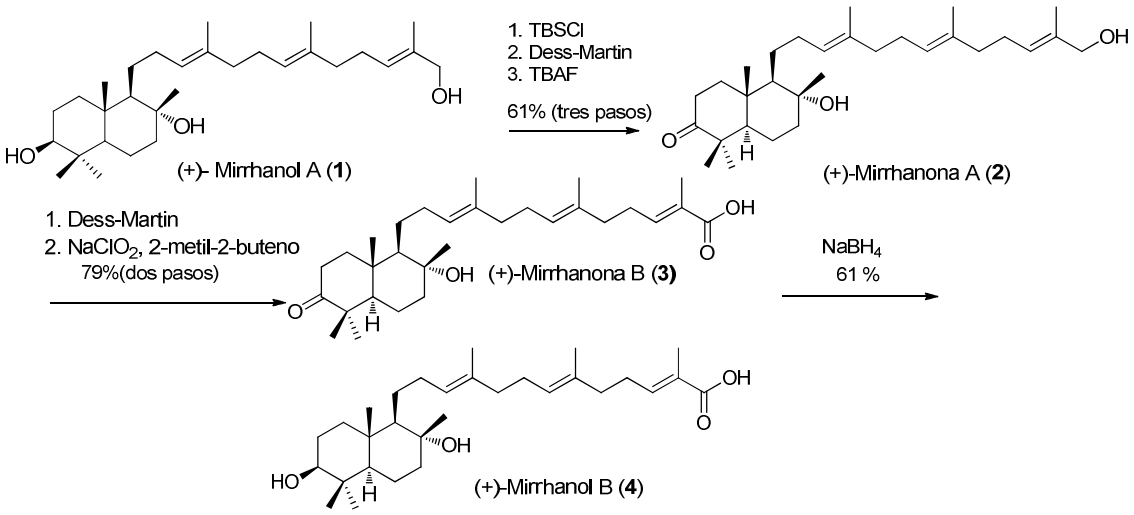
Acoplamiento de Suzuki-Miyaura. Síntesis de mirrhanoles:

Para obtener el esqueleto de polypodano, se necesitó hacer previamente reaccionar la olefina bicíclica **15** con BBN a reflujo durante 4 h, una muestra evidente de los impedimentos estéricos de esta posición. Entonces se llevó a cabo el acoplamiento catalizado por $Pd(dppf)Cl_2$ entre el correspondiente alquilborano derivado con, y el ioduro vinílico geométricamente puro **18** para obtener el producto en un magnífico 90% (Esquema 4). La desprotección de los tres éteres en un sólo paso por tratamiento con una mezcla de AcOH y HCl originó mirrhanol A (**1**) (80%). El espectro de masas, signo de $[\alpha]_D$, espectros de RMN de ^1H y ^{13}C de nuestro mirrhanol (**1**) sintético coincidió completamente con los descritos para el producto natural.[44]



Esquema 4. Acoplamiento de los sintones cíclico y acíclico, síntesis de mirrhanol A

Como se ha comentado anteriormente, la resina de mirra contiene, además de mirrhanol A, otros derivados de esta molécula que igualmente presentan actividad antiinflamatoria, aunque menor. Oxidaciones en diferentes posiciones de mirrhanol A (**1**) dieron lugar a los diferentes derivados de la familia. Así, se obtuvo (+)-mirrhanona A (**2**) cuando se oxidó el alcohol en C3 con reactivo de Dess-Martin hasta la cetona correspondiente (Esquema 5). Por otro lado, la oxidación en dos estapas del alcohol primario de la cadena poliprenada de (+)-mirrhanona A (**2**) hasta ácido carboxílico, primero con Dess-Martin, y luego con clorito sódico, condujo a mirrhanona B (**3**). Por último se preparó (+)-mirrhanol B (**4**) al llevar a cabo la reducción quimio- y estereoselectiva de la cetona de **3** con borohidruro sódico (60%). La comparación de todos los datos espectroscópicos y rotaciones ópticas de estas moléculas con las de los correspondientes productos naturales confirmaron las estructuras y estereoquímicas asignadas a estas sustancias.



Esquema 5. Síntesis de los congeneres del mirrhanol A

En resumen, se completó una síntesis breve de estos polypodanos bioactivos a partir de sus derivados lineales comerciales como son el acetato de geranilo y el acetato de farnesilo. Así, la síntesis de estos triterpenos irregulares demuestra la versatilidad de la ciclación radicalaria de epoxipoliprenos quirales mediada por Ti(III).

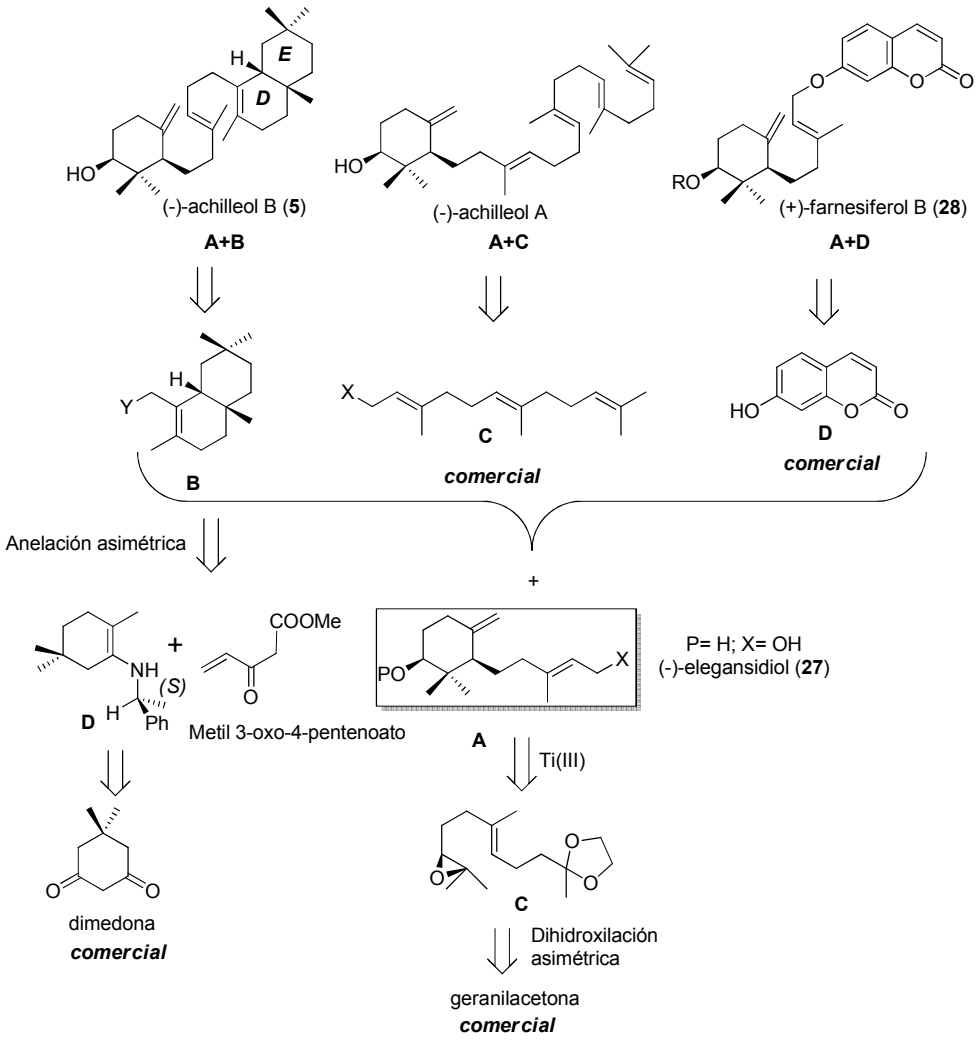
Muy recientemente, se ha descrito que el compuesto (8*R*)-3β,8-dihidroxipolypoda-13*E*,17*E*,21-trieno (mirrhanol C), estructuralmente idéntico a mirrhanol A (**1**) pero sin funcionalización en C-29, desencadena la apoptosis en células cancerígenas de próstata humanas quimioresistentes PC-3 *in vitro* e *in vivo*. Estos datos sugieren que este tipo de sustancias podrían servir como nuevos agentes para el tratamiento del cáncer de próstata resistente a fármacos.[85] Esta circunstancia revaloriza el interés de la nueva estrategia desarrollada.

IV. 3. *Primera síntesis total de (-)-achilleol B: Reasignación de su estereoquímica relativa.*

Introducción y análisis retrosintético

Achilleol B (**5**) es un triterpeno tricíclico con cuatro centros quirales aislado de *Achillea odorata* (*Asteraceae*),[51] de donde se obtuvieron 60 mg a partir de 1580 gr de planta seca. De este triterpeno no se ha descrito ninguna síntesis total hasta la fecha, esta circunstancia, junto con nuestro interés en confirmar sus estereoquímicas relativa y absoluta nos llevó a realizar su síntesis.

Se diseñó entonces una síntesis convergente de la molécula (Esquema 6), donde los pasos clave planteados serían, por una parte, una reacción de anelación de Robinson enantioselectiva para la construcción del fragmento bicíclico **B** (anillos D-E), mientras que el sintón monocíclico **A** sería obtenido mediante ciclación mediada con Ti(III) de un monoepóxido quiral que a su vez procedería vía dihidroxilación asimétrica de la geranilacetona. La preparación asimétrica de estas subunidades permitiría además acceder fácilmente a la síntesis de otro triterpeno irregular (-)-achilleol A (**6**) y los sesquiterpenos (-)-elegansidiol (**27**), y (+)-farnesiferol B (**28**), tal y como se planteó en su análisis retrosintético (Esquema 6).



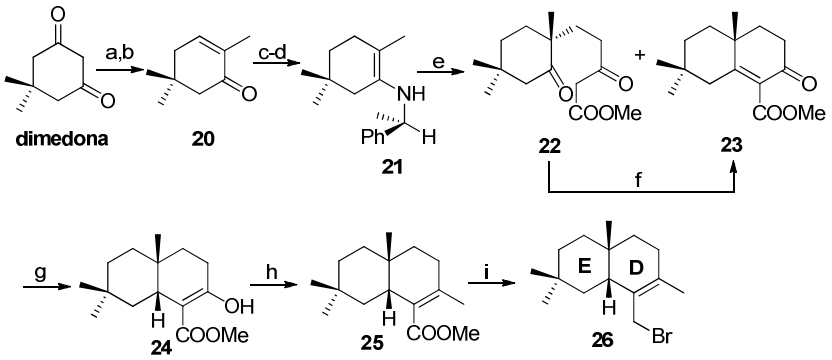
Esquema 6. Análisis retrosintético de achilleol B, achilleol A y farnesiferol B

Construcción del sintón bicíclico B:

La síntesis de los anillos D-E comienza utilizando como producto de partida un sustrato comercial de bajo coste como es la dimedona (Esquema 7). A continuación se metila en condiciones básicas y se procede a su filtrado y posterior recristalización en EtOAc dando lugar a cristales blancos de alta pureza con un 55% de rendimiento. A continuación se reduce y deshidrata la dimedona metilada en un sólo paso mediante la utilización de $LiAlH_4$ para dar el alcohol α,β insaturado, que es oxidado con PCC para obtener la enona **20** (en un 88% para las dos etapas). Esta enona se redujo mediante hidrogenación con Pd/C en AcOEt, o bien con Pd/C en EtOH con catálisis ácida ($HClO_4$), obteniendo el carbonilo saturado con un 50%. Hay que destacar que para la manipulación desde **20** se hubo de utilizar Et_2O como disolvente para realizar los procesados y columnas puesto que la sustancia tenía una alta volatilidad. Posteriormente, se genera la base de Schiff **21** derivada de la (*S*)-feniletilamina manteniendo a reflujo con tamices la cetona reducida y la amina quiral. La selección de este auxiliar quiral se hizo basándonos en los trabajos de D'Angelo[86] sobre reacciones de Michael asimétricas.

A continuación, sobre el reactivo de Nazarov (metil 3-oxo-4 pentanoato) tiene lugar la adición de Michael del compuesto **21**. Esta reacción descrita por primera vez en la síntesis de preoleanatetraeno,[87] fue optimizada cambiándose el disolvente, utilizando THF y realizándose a baja temperatura (0ºC). En el mismo medio de reacción se hidroliza en un sólo paso mediante el uso del tampón NaOAc, H_2O, AcOH (pH=5) durante 4 horas, para obtener en el mejor de los casos un rendimiento del 60% de **22**. El exceso enantiomérico de la condensación se determinó más adelante de la secuencia sintética mediante la formación del correspondiente lactato derivado del alcohol primario resultante de la reducción de **25**, al tratarlo con cloruro de (*S*)-lactilo en presencia de DMAP/Et_3N. La integración de las señales de los lactatos diasterómeros por ^{1}H-RMN determinó un exceso enantiomérico del 85%.

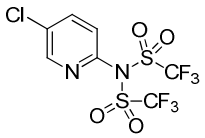
El compuesto **22** se trató con una base débil como es el KF dando lugar a la decalina correspondiente **23** tras posterior condensación aldólica intramolecular. El derivado β-cetoéster **23** se somete nuevamente a hidrogenación con Pd/C dando con excelente estereoselectividad la *cis* decalina **24** (34% desde **20**).



(a) i. NaOH, CH_3I, H_2O, 55% (varias cristalizaciones); ii. LAH, Et_2O, 95%; (b) PDC, DCM, 82%; (c) H_2-Pd/C, EtOAc, 12 h, 50%, ; (d) (*S*)-feniletilamina, PhH, 24h, 74%; (e) Metil 3-oxo-4-pentenoato, THF, 60% (85%ee); (f) KF, MeOH, 99% ; (g) H_2-Pd/C, EtOAc, 91%; (h) i. Tf_2O, (*i*-Pr)$_2$EtN; ii. CuBr·SMe_2, MeLi, 91%; (i) i. DIBALH, 94%; ii. PBr_3, 90%.

Esquema 7

Gracias a que el β-cetoéster está en equilibrio con el correspondiente enol **24**, se formó el enol triflato del correspondiente enol **24** en condiciones suaves, bien por tratamiento con anhídrido tríflico o con el correspondiente reactivo de Comin. Este último presentó frente al anterior grandes ventajas de estabilidad así como condiciones más suaves (Figura 2). Este enol triflato es tratado con el dimetilcuprato de litio (reactivo de Gilman) generado *in situ* mediante la adición de 2 equivalentes de MeLi sobre CuBr.SMe_2. Esta metilación permite acceder a **25** (91%) y completar el esqueleto carbonado del sintón bicíclico situando una olefina tetrasustituida conjugada con el éster. Posteriormente, se reduce el éster α,β insaturado **25** al correspondiente alcohol, y finalmente se halogena para dar el haluro alílico **26** de 15 átomos de carbono (92% para las dos etapas).

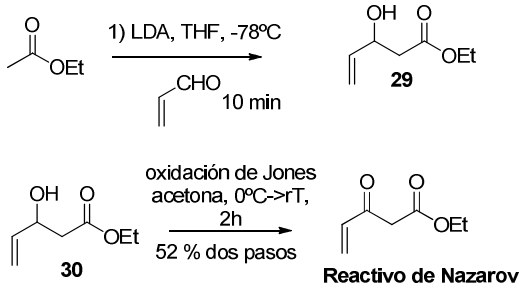


Reactivo de Comin
N-(5-Cloro-2-piridil)triflimida

Figura 2

Ahora se abre un pequeño paréntesis, para comentar que la reacción de anelación del esquema anterior fué optimizada, de manera que se ha podido obtener el compuesto **25** de forma totalmente reproducible a escala de gramos. El principal inconveniente del proceso estribaba en la preparación del reactivo de Nazarov. Este compuesto normalmente se obtiene por reacción de eliminación de su precursor 5-metoxi-3-oxovalerato de metilo, proceso llevado a cabo mediante destilación a elevada temperatura en medio ácido. Estas condiciones junto con la alta reactividad inherente

del producto de eliminación, hace que en muchas ocasiones se deteriore el producto buscado, disminuyendo el rendimiento y dificultando la reproducibilidad. Además cabe comentar el alto coste del precursor (5 ml, 188 €). Para solventar este problema se accedió al reactivo de Nazarov mediante la siguiente secuencia sintética, previamente descrita,[3] que parte de productos de partida baratos como son el acetato de etilo y la acroleína (500 ml, 110 €) (Esquema 8).



Esquema 8

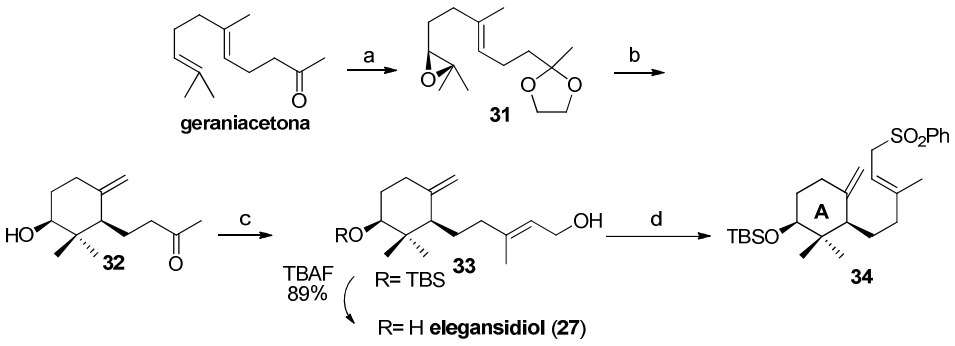
Construcción del sintón monocíclico de esqueleto terpenoide A:

Para la construcción del fragmento quiral monocíclico **A** se comenzó la secuencia sintética con una dihidroxilación asimétrica de Sharpless sobre geranilacetona como elemento de enantiocontrol del proceso (Esquema 9). Se obtuvo el diol quiral en un 67% (*ee* 97%), que posteriormente es convertido en tres pasos en el epóxido quiral **31**. Para ello se protegió el grupo carbonilo en forma de su etilenglicol acetal, después se llevó a cabo la formación del mesilato y bajo tratamiento en condiciones básicas se generó el epóxido quiral **31**. A continuación, se procedió a la apertura radicalaria del oxirano con Ti (III) como etapa clave, así bajo las condiciones catalíticas en Ti[33] y reacción a temperatura ambiente, el radical β-titanoxi generado se adiciona 6-*endo*-*trig* y da lugar al sintón **32** en un 77% de manera totalmente regio- y estereoselectiva. La estereoquímica de los dos centros quirales creados, así como la formación del doble enlace terminal, es la misma que se presenta en el producto natural.

Las etapas finales de la preparación del sintón monocíclico **A** (**34**) consistieron en la regeneración de la cetona y protección del alcohol como su silil derivado, ambas conseguidas en un 91%. Mediante reacción de olefinación de Horner-Wadsworth-

[3] Protocolo para la preparación del reactivo: *Organic Syntheses*, Coll. Vol. 9, p.432 (1998); Vol. 71, p.236 (1993)

Emmons a partir del carbanión generado del trietil fosfonoacetato con *n*-BuLi se consiguió obtener la correspondiente olefina estereoselectivamente con configuración *E*. Entonces, la reducción del éster α,β insaturado y posterior desprotección del silil derivado **33** dio lugar al sesquiterpeno elegansidiol (**27**), molécula aislada hace más de una década de *Santolina elegans*.[88] El alcohol se trató posteriormente con PBr_3 originando el bromuro alílico en un 75% que, tras desplazamiento nucleofílico por la sal de fenilsulfinato sódico, dio lugar a la sulfona **34**, sintón clave de 15 átomos de carbono.



(a) i. AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/ H_2O, 0ºC, 67%, ii. Etilenglicol, TsOH, 82%; iii. MsCl, Py, DMAP, K_2CO_3, MeOH, 74%, (b) i. Cp_2TiCl, 77%; ii. $CeCl_3$, NaI, 95%; (c) i. TBSCl, imidazol, DMAP, 91%; ii. dietilfosfonoacetato, NaH, iii DIBALH, 74% (dos pasos); d) i. PBr_3, DMAP, 75%; ii. $NaSO_2Ph$, DMF, 72%.

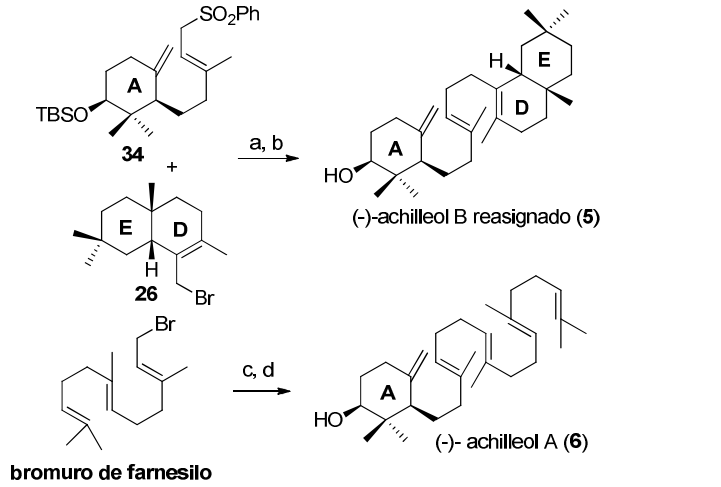
Esquema 9

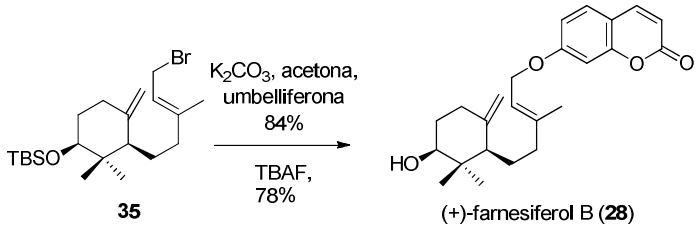
Síntesis de achilleol B:

Finalmente, el acoplamiento de ambos sintones **26** y **34** se realizó mediante una reacción de alquilación clásica. Se genera el anión de la sulfona **34** sobre el que se adicionó lentamente el bromuro **26** a -78ºC, obteniéndose la mezcla de diastereoisómeros en un 71% (Esquema 10). La posterior desulfonación mediante Li/ $EtNH_2$ y desprotección mediante fluoruro dio el compuesto natural objetivo, achilleol B (**5**), en un 86% para los dos últimos pasos. El espectro de masas, signo y valor de $[\alpha]_D$, espectros de RMN ^1H y ^{13}C de achilleol B (**5**) sintético coincidieron completamente con los descritos para el producto natural. Además en este caso se pudo confirmar la existencia de efecto NOE entre el H-18 y el CH3-C17. Como originariamente se asignó una configuración relativa *trans* a la decalina, debido a la ausencia de efecto NOE en un espectro NOESY, este trabajo ha permitido además la reasignación de la estereoquímica relativa de (-)-achilleol B. También con posterioridad este trabajo ha servido como ejemplo modelo en los estudios computacionales DP4 para asignación de la estereoquímica de compuestos naturales. [89]

La construcción del sintón monocíclico no sólo nos permitió acceder a achilleol B, sino también de forma asimétrica a otros compuestos naturales que contenía esta subunidad en su estructura, tales como el triterpeno (-)-achilleol A (**6**) y el meroterpeno (+)-farnesiferol B (**28**) (Esquema 10).[90]

Así, la sulfona monocíclica **34** se pudo acoplar con bromuro de farnesilo en un 78%. La desulfonación del producto de acoplamiento y posterior desprotección en las mismas condiciones anteriores dio lugar a (-)-achilleol A (**6**). Por otro lado el bromuro **35** se condensó con umbeliferona y después de desproteger se obtuvo (+)-farnesiferol B (**28**).[88]





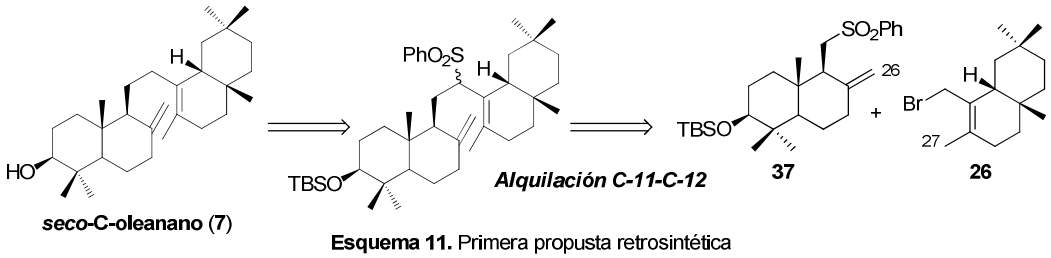
Esquema 10

IV. 4. *Síntesis total de (+)- seco- C-Oleanano vía ciclación radicalaria controlada en cascada.*

Primeras aproximación: Acoplamiento C15+C15

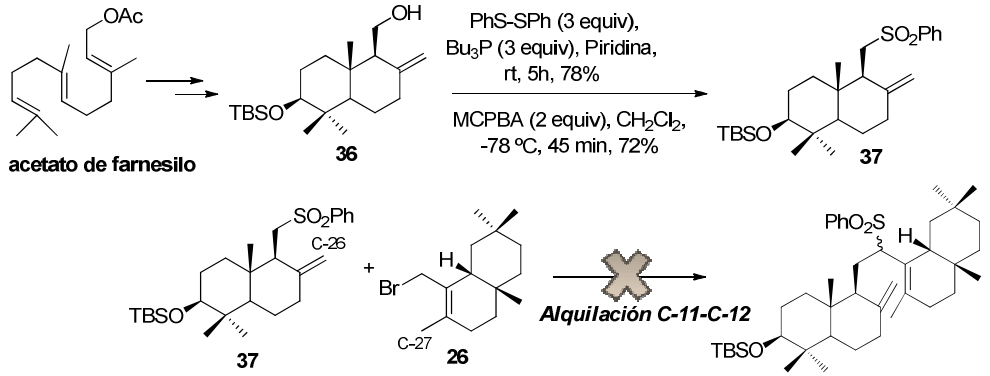
Otra molécula seleccionada como objetivo de nuestro estudio hacia la síntesis de triterpenos inusualmente ciclados es el *seco*-C-oleanano (**7**), que también proviene biosintéticamente de un proceso de ciclación-retrociclación.

Una primera aproximación sintética se diseñó basada en un acoplamiento convergente de dos sintones C15, la sulfona bicíclica **37** y el haluro alílico **26** (Esquema 11).



Esquema 11. Primera propusta retrosintética

Esta sulfona **37** se construyó de forma sencilla a partir del alcohol procedente de **36**, previamente sintetizado como intermedio de la síntesis de mirrhanol A (**1**). El biciclo **36** se convirtió en el fenilsulfuro derivado en un 78% que, tras oxidación quimioselectiva controlada con AMCPB, dio la correspondiente sulfona **37** en un 72% (Esquema 12). El carbanión de litio de la sulfona se puso a reaccionar con el haluro alílico **26** en diferentes condiciones pero sin éxito, ya que se recuperó únicamente el producto de partida. Esta estrategia no tuvo éxito debido a las grandes repulsiones estéricas procedentes de la interacción entre C-27 y C-26 (Esquema 12).

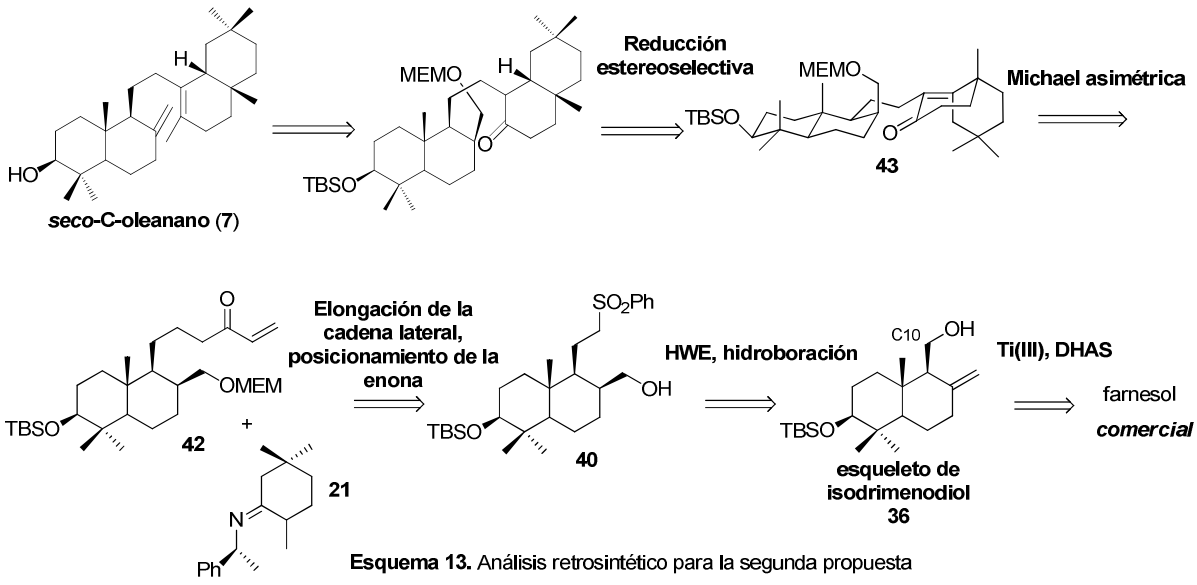


Esquema 12

Segunda aproximación: Construcción del esqueleto *seco*-C-oleanano (7) por anelación de Robinson.

Para intentar superar el impedimento estérico que aparece en la primera aproximación, se planteó una segunda ruta que se basa en la construcción del intermedio avanzado con esqueleto tetracíclico **43** mediante una reacción de Michael asimétrica

(Esquema 13). Para ello se emplearía la enona **42** y la imina quiral **21**, esta última ya empleada anteriormente en la síntesis de achilleol B, y que va a permitir generar los anillos D y E con la estereoquímica deseada. La preparación del aceptor de Michael lineal **42** se podría llevar a cabo mediante alargamiento de la cadena lateral de **40**, mientras que **40** se podría sintetizar usando una reacción de olefinación HWE y posterior reducción de la correspondiente vinil sulfona a partir del aldehído derivado de **36** en posición C-10. Como una de las reacciones clave comprende la reducción del doble enlace tetrasustituido en el intermedio **43** mediante hidrogenación estereoselectiva, se hacía necesaria la protección el doble enlace disustituido en el intermedio **36**, generado tras la ciclación con Ti (III). Para ello, se transformaría dicha insaturación en el correspondiente alcohol primario mediante una reacción de hidroboración-oxidación que conduciría al compuesto **40**.

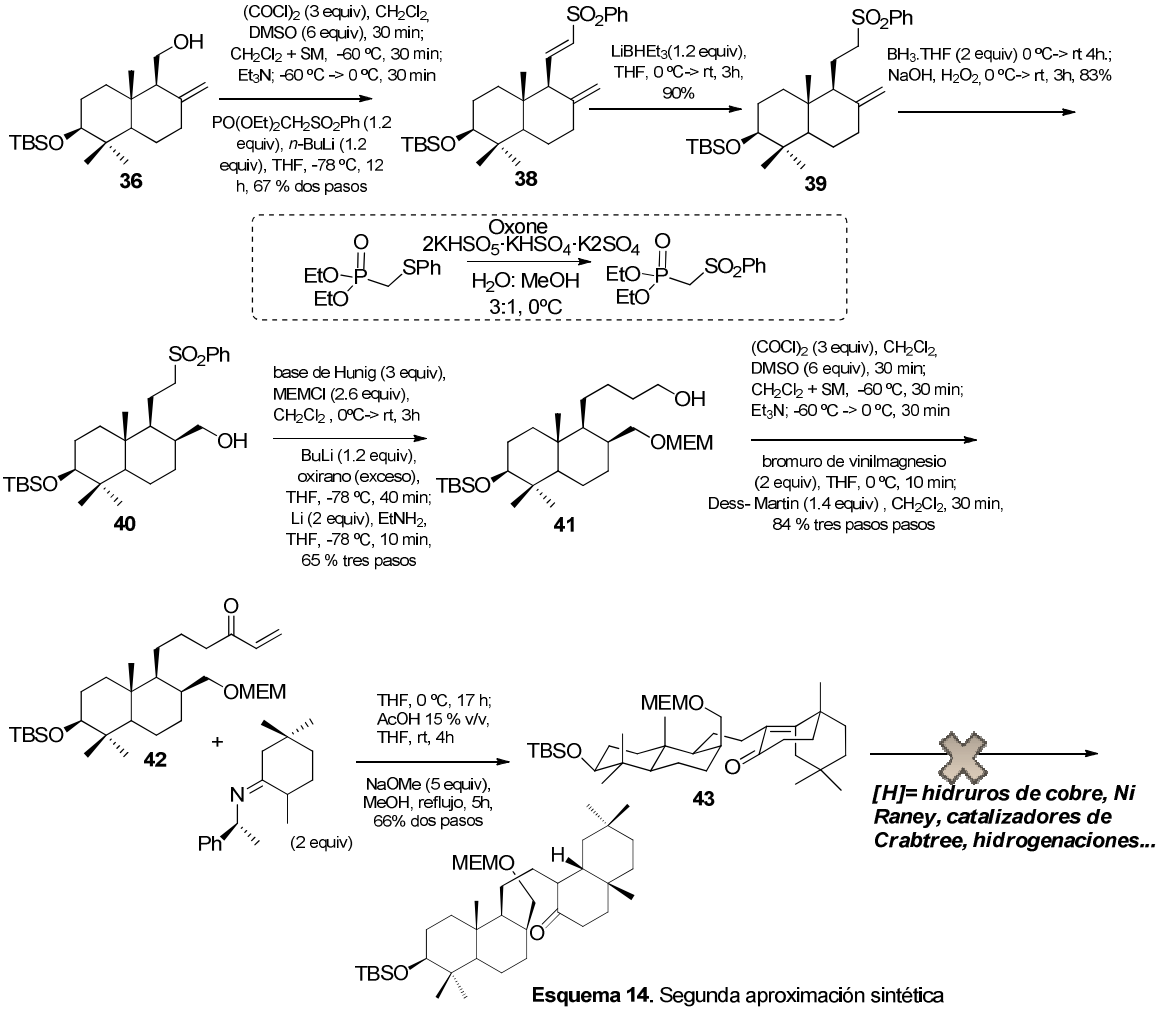


Esquema 13. Análisis retrosintético para la segunda propuesta

Construcción de la enona tetracíclica 43

La ruta sintética comienza con el mismo intermedio, el derivado de isodrimenodiol **36**, clave en la primera aproximación planteada (Esquema 14). Este fue oxidado hasta aldehído bajo las condiciones de Swern, y el crudo fue tratado con dietil (fenilsulfonil)metilfosfonato para obtener la vinil sulfona **38** correspondiente con un 67% para los dos pasos. De este modo se consiguió en una sola reacción homologar y situar la función sulfona. La vinilsulfona **38** fue reducida quimioselectivamente a alquil sulfona **39** mediante el empleo de superhidruro. Se obtuvo un 90% mediante un

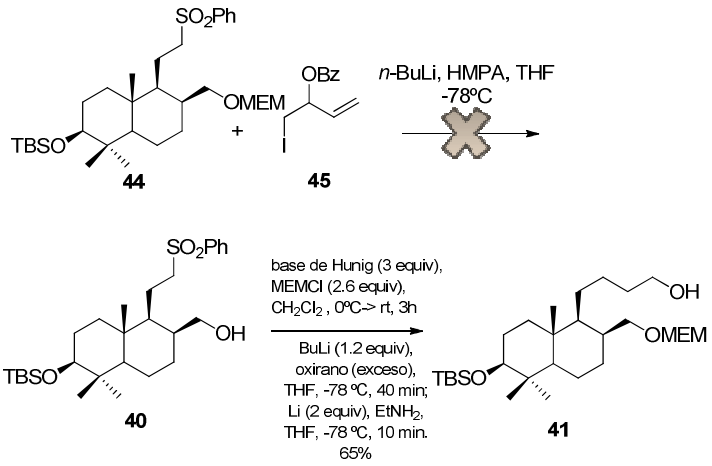
mecanismo tipo Michael y permaneció inalterado el doble enlace exocíclico. Este doble enlace exocíclico en posteriores etapas de la ruta se podría hidrogenar, por lo que se decidió enmascarar transformándolo al correspondiente alcohol primario **40** con un 83%, mediante hidroboración-oxidación. Se obtuvo un único estereoisómero, el correspondiente a la entrada por la cara menos impedida α. A continuación, el alcohol primario de **40** se protegió en forma de éter **44** utilizando el cloruro de metoxietoximetilo.



Esquema 14. Segunda aproximación sintética

Para acceder a la enona **42** se precisa agregar cuatro átomos de carbono sobre **40**. Con esta idea el carbanión de litio de la sulfona **44** se intentó primero alquilar directamente con el ioduro de alquilo **45** (Esquema 15). Sin embargo, no se obtuvo el resultado deseado, probablemente debido a impedimentos estéricos. Se intentó entonces alquilar a través de varias etapas. Así, cuando la sal de litio de **44** se trató con oxirano,

se obtuvo satisfactoriamente la bishomologación, para tras desulfonación reductiva obtener el compuesto buscado **41** en un 65%.

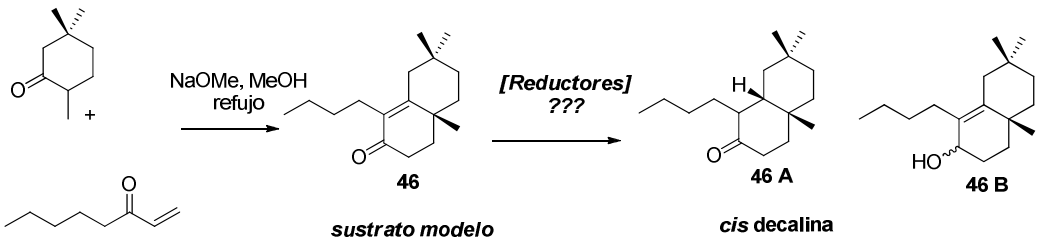


Esquema 15. Alargamiento de la cadena lateral

Una oxidación de Swern sobre **41** dio el aldehído que, por tratamiento con el Grignard, bromuro de vinil magnesio y posterior oxidación con el reactivo de Dess-Martin, condujo a la enona **42** en un 84% para los tres pasos (Esquema 14). Esta enona se trató con la imina quiral derivada de la feniletilamina a 0ºC en THF durante 17 horas para, tras una reacción de Michael asimétrica, originar el producto de acoplamiento. Este intermedio se trató en medio básico a reflujo (NaOMe) cerrando el anillo D, de forma que se obtuvo el correspondiente carbonilo α,β insaturado **43** en un 66%.

Reducción de la enona tetracíclica: Optimización sobre el sustrato modelo 46.

Esta enona intermedia **43** debía de ser reducida para obtener la correspondiente *cis* decalina, para ello se puso a punto el sustrato modelo **46** (Esquema 16). Con este objetivo en mente, se probaron aquellos reductores que según la bibliografía daban lugar a una configuración relativa *cis* tras el proceso de reducción. Entre ellos podemos mencionar: hidruros de cobre, bien generados *in situ*[91] o comerciales, como el reactivo de Stryker (hexámero de hidruro de cobre trifenilfosfina),[92] Nickel Raney previamente ensayado en nuestros laboratorios,[93] o el catalizador de Crabtree, indicado en la reducción de enonas tetrasustituidas.[94] Sin embargo, únicamente se obtuvieron productos de reducción mediante la utilización de hidrogenación heterogénea con Pd/C.[95]



Esquema 16. Ensayos de reducción sobre el sustrato modelo

Se realizaron los siguientes ensayos de hidrogenación sobre el sustrato **46** para intentar optimizar las condiciones de reacción.[4]

Entrada	CATALIZADOR 8% wt/wt	DISOLVENTE	PRESIÓN de H_2 (atm)	TIEMPO	RENDIMIENTO producto 46A
1	Pd/C 5%	AcOEt	1	2 días	NR
2	Pd/C 5%	Py	1	3 días	NR
3	Pd/C 10%	EtOH	1	14 horas	45%
4	Pd/C 10%	AcOEt	1	1 día	45%
5	Pd/C 10%	EtOH	1	1 día	53%
6	Pd/C 5%	EtOH ($HClO_4$ cat)	1	1 día	60%
7	Pd/C 10%	MeOH	2	1 día	30% **(46B)**
8	Pd/C 10%	*t*BuOH: EtOH (6:1)	2	1 día	NR.
9	Pd/C 10%	EtOH	4	1 día	37% **(46B)**
10	Pd/C 10%	Py	4	3 días	NR
11	PtO_2 3mol%	MeOH (AcOH cat)	1	2 días	NR
12	Pd/C 10%	Py	4	3 días	NR

Al llevar a cabo las distintas experiencias se observó la existencia de dos procesos competitivos, con formación de la cetona hidrogenada **46A** y del alcohol **46B**.

[4] En la tabla de resultados se ha representado entre paréntesis los casos en los que la reducción tiene lugar sobre el grupo carbonilo.

La proporción de cada una de estas moléculas dependió del tipo de disolvente utilizado (menos voluminoso y prótico favorecía la reducción del carbonilo) y de la cantidad de catalizador (se realizaron ensayos de competición donde el doble de carga desplazaba el equilibrio hacia la formación de reducción del doble enlace frente al del carbonilo, aunque no de una manera espectacular). Aunque las condiciones descritas en los ensayos **5** y **6** fueron las que condujeron a mayor proporción del producto de reducción deseado, finalmente seleccionamos las de la entrada **5**. Esta selección fue debida a que en este caso se recuperó producto de partida, mientras que en las de **6** se formaba también el dieno debido a la deshidratación del alcohol, con lo que en este caso no cabía la posibilidad de reutilizar el producto de partida.

Con el fin de confirmar la estereoquímica del producto de reducción 1,4 deseado, llevamos a cabo estudios NOE-diff sobre esta sustancia. Estos estudios nos permitieron confirmar que, al contrario de lo esperado inicialmente, la configuración de la decalina era *trans* (Figura 3).

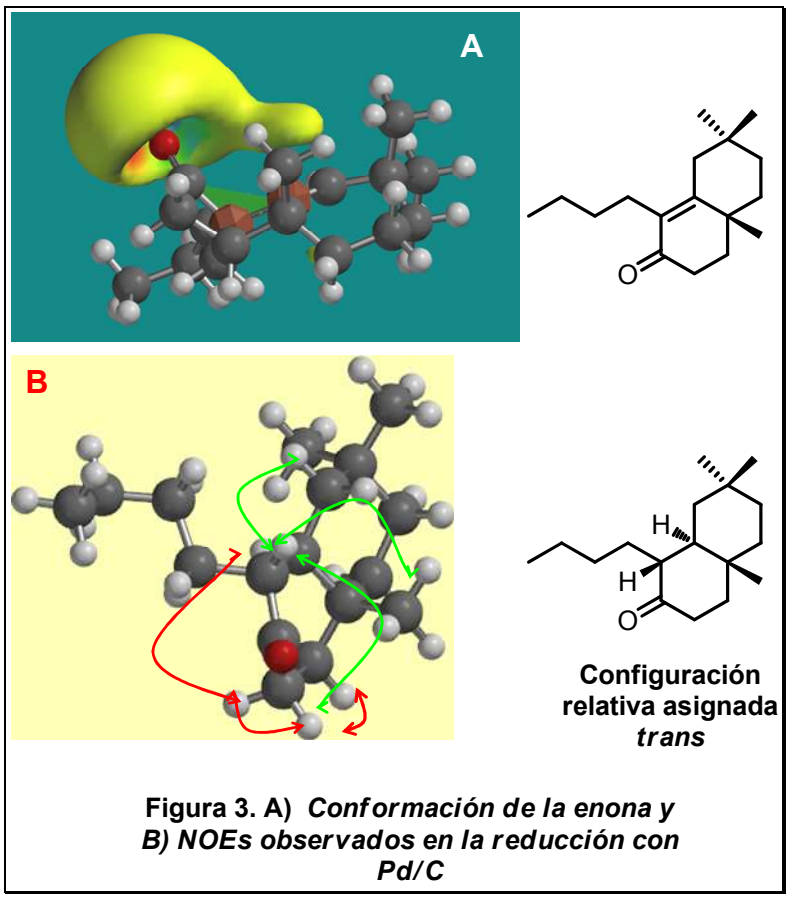


Figura 3. A) ***Conformación de la enona y B) NOEs observados en la reducción con Pd/C***

Esta estereoselectividad, diferente a lo descrito en bibliografía en la reducción de decalinas con catalizadores heterogéneos,[96] se podría atribuir al gran impedimento que ejerce el segundo metilo que se sitúa por la cara beta axial (Figura 3). Forzando así a que el catalizador de superficie se sitúe por la cara alfa, cara por la que resulta la hidrogenación.

En este contexto, se decidió someter la enona modelo **46** a las condiciones de reducción de Birch, condiciones que están descritas que originan productos de reducción *trans*,[94] comprobando que efectivamente se obtenía el mismo producto de hidrogenación con decalina *trans*.

Síntesis de *seco*-C-oleanano (7) por ciclación radicalaria en cascada sobre el óxido de preoleanatetraeno.

Introducción y análisis retrosintético

Finalmente, después de obtener la suficiente información topológica de nuestras rutas sin éxito, y teniendo en cuenta la primera propuesta biosintética del *seco*-C-oleanano (**7**) a partir del óxido de preoleanatetraeno **47**,[50] se decidió cambiar de estrategia. Se consideró entonces que nuestro compuesto objetivo podría ser obtenido directamente por la ciclación radicalaria sobre el sustrato **47** (Figura 5), compuesto que se caracteriza por contener todos los átomos de carbono necesarios del producto final (**7**).

Cabe destacar que van Tamelen había ensayado la ciclación catiónica del compuesto **47** en su forma racémica, dando como resultado la amirina.[58a] El quid de nuestra estrategia era entonces comprobar si el radical generado tras la apertura homolítica del oxirano superaría la barrera energética de cierre del anillo C para obtener el mismo resultado que van Tamelen, o por el contrario, que se interrumpiese la cascada a nivel bicíclico, de manera que se originaría directamente el producto que queríamos sintetizar (Figura 5).

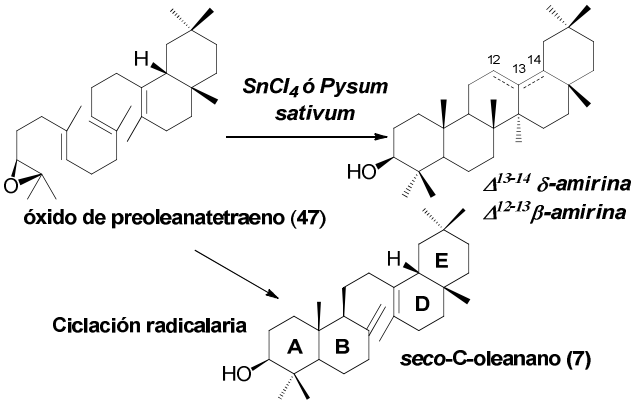


Figura 5

Cálculos teóricos

Ante esta circunstancia, se decidió estudiar a nivel computacional UB3LYP/6-31+G(d) el perfil de energías de los intermedios por los que debería pasar el radical una vez se iniciase la ciclación radicalaria (Figura 6). La primera conclusión que se extrae de estos cálculos es que el cierre de estos anillos no es concertado como sucede en el caso de las ciclaciones catiónicas.[15] Por otra parte, los datos teóricos también revelaron que el cierre del anillo C a partir del *seco*-C-oleanil radical se mostraba como un proceso termodinámicamente desfavorable de +29 kcal/mol, mientras que el cierre de los dos primeros anillos es un proceso favorable y espontáneo. Estos datos parecían indicar que la ciclación se podría detener tras el cierre del anillo B en el estado de transición **III**.

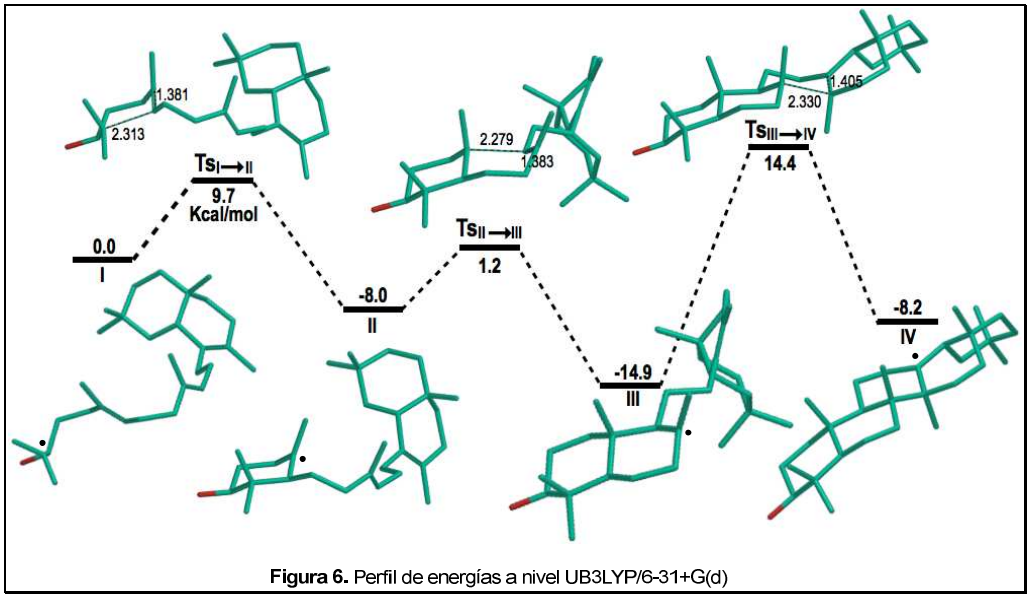
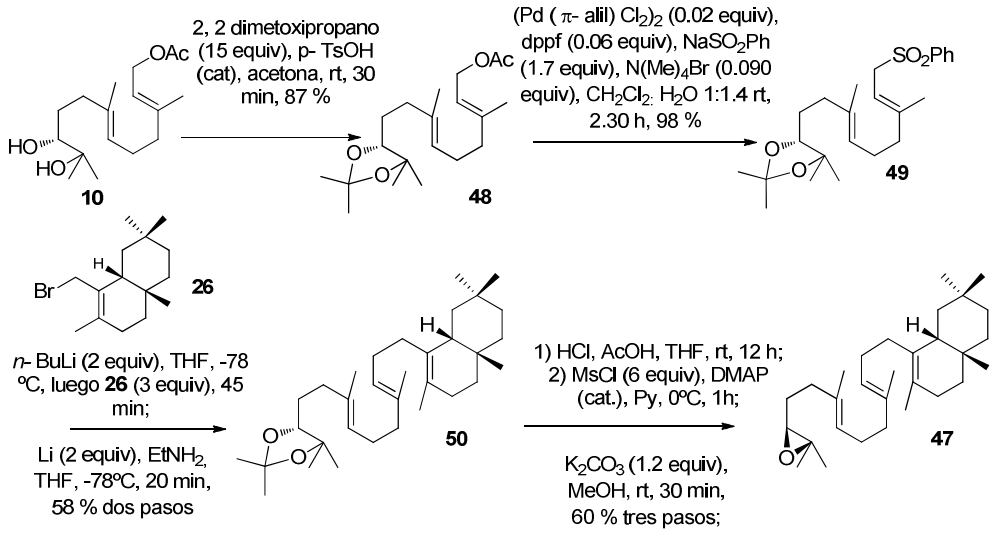


Figura 6. Perfil de energías a nivel UB3LYP/6-31+G(d)

Obtención del epóxido clave 47:

Animados por estos resultados se sintetizó el compuesto **47** mediante una estrategia convergente, que suponía el acoplamiento de la sulfona **48** con el sintón bicíclico **26**, compuesto preparado previamente por nosotros para la síntesis de (-)-achilleol B (**5**).

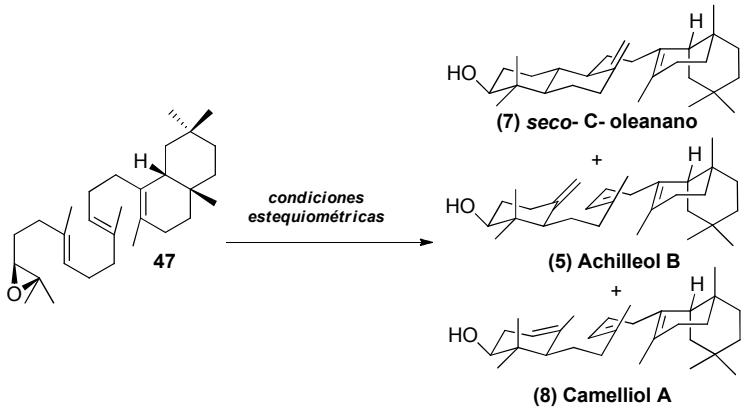
Se desarrolló entonces la secuencia sintética que se detalla en el esquema 17. A partir del acetato de farnesilo, bajo condiciones de dihidroxilación asimétrica de Sharpless, se forma el diol óptimamente puro **10**, que se protege en forma de acetónido para dar **48**. A continuación la sulfona se introdujo mediante la formación de una especie de π-alil paladio con un excelente rendimiento de 98%, originando **49**.[97] Posteriormente se procedió a la alquilación del compuesto acíclico **49**, que en este caso, y al contrario de lo sucedido en la primera aproximación descrita para esta molécula, sí originó el acoplamiento esperado con **26**. El producto obtenido sometido a la correspondiente desulfonación originó el precursor del óxido de preoleanatetraeno **50** (58%, dos pasos). La desprotección en medio ácido del acetónido liberó el correspondiente diol que, tras transformaciones convencionales, dio el epoxipolipreno **47** en un 60% para los tres pasos.



Esquema 17. Síntesis del óxido de preoleanatetraeno

Síntesis de *seco*-C-oleanano (7):

Una vez obtenido el intermedio clave **47**, se procedió a inducir la cascada radicalaria mediante el empleo de cloruro de titanoceno en condiciones estequiométricas utilizando 2 equivalentes de la especies de Ti (Esquema 18). Satisfactoriamente, conseguimos como producto mayoritario la molécula objetivo *seco*-C-oleanano (**7**) en un más que aceptable 39% de rendimiento, considerando los rendimientos obtenidos para este tipo de procesos. Se completaba así la primera síntesis total de este producto natural. El espectro de masas, signo de $[\alpha]_D$, y datos de ^1H y ^{13}C de nuestro producto sintético (**7**) coincidieron completamente con los de una muestra natural suministrada por el profesor Joseph-Nathan. Junto a *seco*-C-oleanano, se obtuvieron pequeñas proporciones de achilleol B (**5**) (7%) previamente sintetizado en esta Memoria y camelliol A (**8**) (3%) producto natural aislado de *Camellia sasanqua*.



Esquema 18. Ciclación estequiométrica: Cp_2TiCl_2 (2 equiv), Mn (4 equiv), 1:2 THF: Tolueno, reflujo, 20 min, 49% ((3): (4): (1) en 2.2 :1: 13.5 proporción de productos)

Es importante destacar que esta es la primera vez que se prepara el triterpeno natural camelliol A. La formación de achilleol B y camelliol A fue el resultado de la captura radical intermedio achilleílo, obtenido tras la primera ciclación, por una segunda molécula de titanoceno (Figura 7).

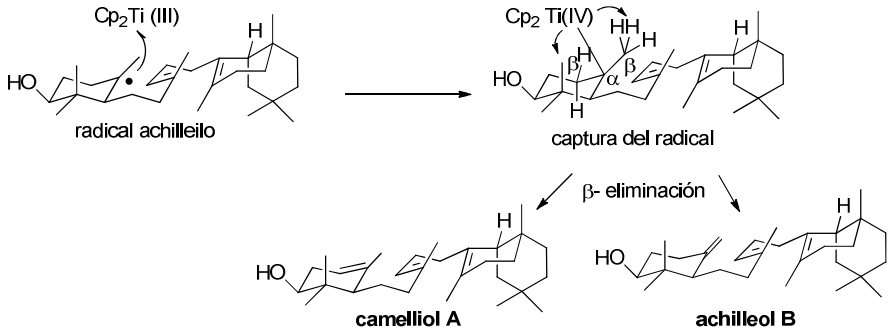
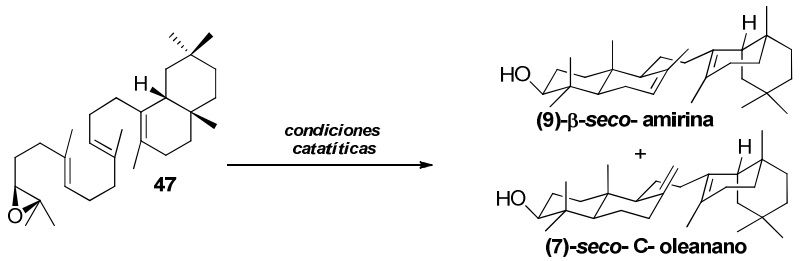


Figura 7. Captura del radical achilleilo

La composición de la mezcla de triterpenos obtenida fue establecida mediante el empleo de CG-EM, experimentos TOCSY en RMN, y mediante la utilización de la base de datos espectroscópica NAPROC-13 RMN utilizando listados de los desplazamientos de carbonos.

Llegado a este punto, y con el fin de minimizar la formación de productos de monociclación, se sometió al epoxipolipreno **47** a condiciones de ciclación catalíticas. Conforme a lo anticipado, se obtuvo en un excelente 44 % el producto *seco*-C-oleanano (**7**) (Esquema 19). También se formó de manera minoritaria un 8% del isómero con doble en enlace endocíclico trisustituido, conocido como *seco*-β-amirina (**9**). Recientemente, se ha descrito que este producto es producido por la triterpeno sintasa *Atl*g78500. Finalmente, y al igual que sucediá con camelliol A, esta es la primera vez que se obtiene *seco*-β-amirina mediante un proceso sintético.



Esquema 19. Ciclación catalítica: a) Cp_2TiCl_2 (0.3 equiv), Mn (8 equiv), colidina (7 equiv), TMSCl (4 equiv), THF, rt, 3.30 h, b) TBAF (3 equiv), THF, rt, 30 min, 51% dos pasos ((1): (2) in a 7:1 proporción de productos)

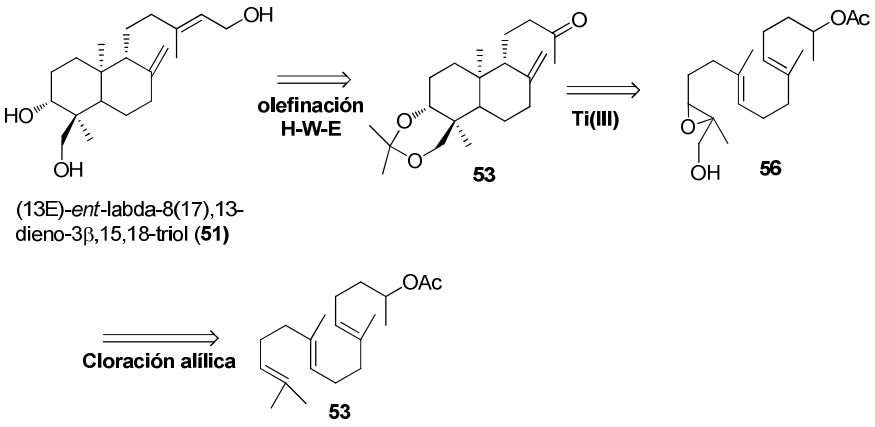
IV. 5. *Acceso a terpenoides γ dioxigenados: Primera síntesis de (13E)-ent-labda-8(17),13-dieno-3β,15,18-triol.*

Introducción y análisis retrosintético

Otro de los objetivos de esta Memoria consiste en aplicar la metodología radicalaria de ciclación para obtener, con una estereoquímica relativa definida y desde un precursor acíclico determinado, terpenoides gamma-dioxigenados en el anillo A. En concreto, esta doble funcionalización sitúa un grupo hidroxilo en C-3 una posición ecuatorial, mientras que un segundo hidroxilo se localiza en el metilo en posición ecuatorial sobre el carbono C-4. Esta estereoquímica relativa *trans* está presente en diferentes productos naturales bioactivos, por lo que el desarrollo de esta idea permitirá abrir un nuevo acceso a este tipo de productos.

Para demostrar la viabilidad del método nos planteamos la síntesis de (13*E*)-*ent*-labda-8(17),13-dieno-3β,15,18-triol (**51**) (Esquema 19), diterpeno aislado de las hojas de *Rubus chingii* y de los frutos de *Rubus foliolosus*.

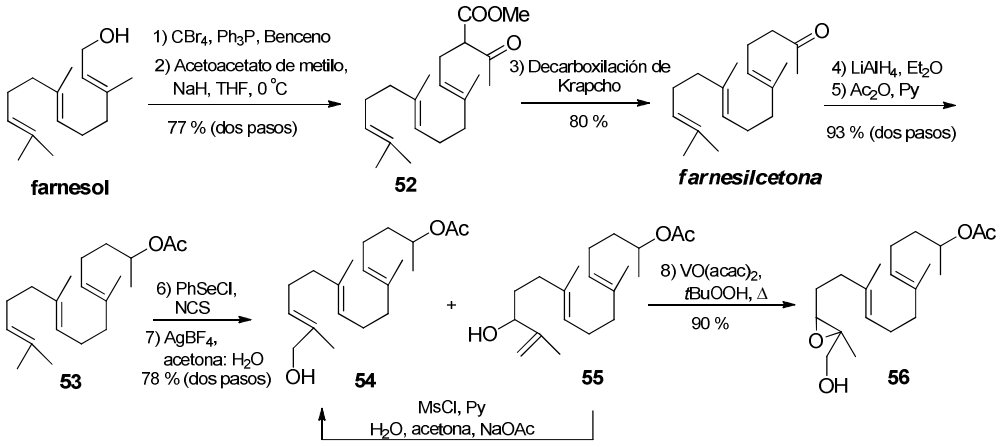
Dos son los pasos claves propuestos para la síntesis de esta molécula, por una parte, la ciclación radicalaria estereoselectiva del epoxialcohol **56**, y por otra, la obtención de este epoxialcohol. Para esto último se requiere un método de funcionalización selectiva de uno de los metilos del isopropilideno terminal.



Esquema 19. Retrosíntesis compuesto **51**

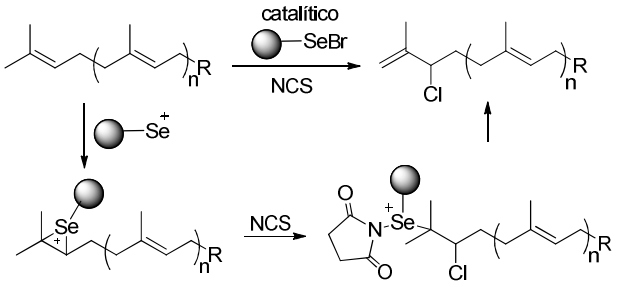
Síntesis del precursor acíclico 56:

Debido a que la geometría del correspondiente polipreno es fundamental para el resultado de la posterior reacción radicalaria, la secuencia sintética (Esquema 20) comienza con la obtención de farnesilacetona estereoisoméricamente pura a partir de *E*, *E*-farnesol, producto comercial. Inicialmente *E,E*-farnesol se bromó mediante el empleo de tetrabromuro de carbono-trifenilfosfina. El correspondiente haluro alílico se desplaza nucleofílicamente por el carbanión generado del acetoacetato de metilo para dar el beta cetoéster **52** en un 77 %. Se procede entonces a la descarboxilación dando la farnesilcetona en un 80 %. Dada la capacidad del grupo carbonilo para sufrir adiciones radicalarias, que generaría un ciclo adicional a los deseados en la correspondiente ciclación con Ti(III), se "protege" la cetona en forma de acetato mediante reducción y acetilación, originando **53** con un 93% para ambos pasos.



Esquema 20. Síntesis del precursor **56**

En este punto, para funcionalizar selectivamente uno de los metilos del isopropilideno situado en el extremo de la cadena acíclica, se utilizó un método de cloración altamente regioselectivo de poliprenos terpénicos. Este proceso, desarrollado previamente en nuestro grupo de investigación, se produce por la acción de especies de Se^{+} (Esquema 21). Mecanísticamente, esta acusada selectividad de dobles enlaces muy parecidos se puede justificar atendiendo tanto al gran tamaño del electrófilo (PhSeCl), como a su pequeña concentración (subestequiométrica) en el medio de reacción.[98]



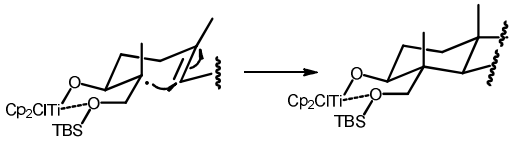
Esquema 21. Mecanismo de la cloración alílica

Así, el tratamiento de **53** con la mezcla NCS/PhSeCl permitió obtener el correspondiente cloro alílico y doble enlace terminal sobre el doble enlace trisustituido del extremo de la molécula. Este cloroderivado, tras hidrólisis mediada por tetrafluoroborato de plata/nitrato de plata, dio lugar a una mezcla casi equimolecular de alcoholes primario (**54**) y secundario (**55**) en un más que aceptable 78 %, sobre todo si tenemos en cuenta que el alcohol secundario puede ser transformado en el primario vía mesilación e hidrólisis (Esquema 20).

La introducción de este alcohol en posición alílica permitió, además, la epoxidación selectiva de este doble enlace utilizando hidroperóxido de *tert*-butilo en presencia de acetil acetonato de vanadilo para dar el epoxipolipreno **56**. Este intermedio ya era susceptible de ser ciclado utilizando la metodología radicalaria basada en el uso de especies de Ti(III).

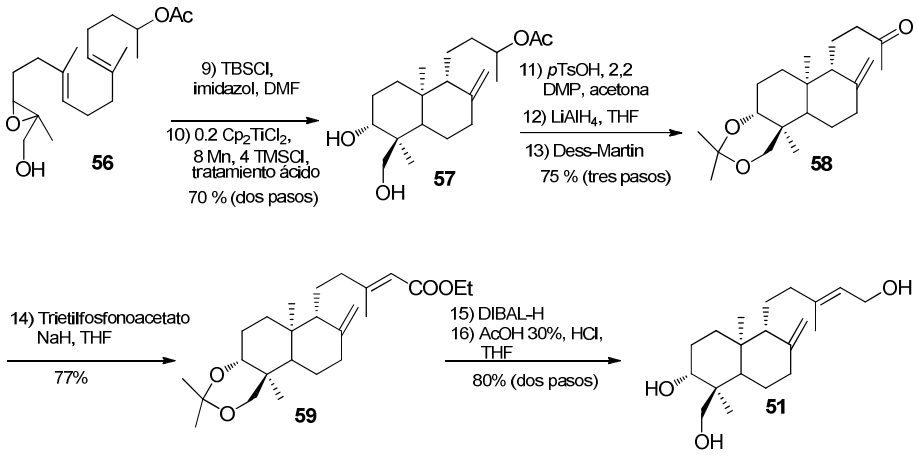
Ciclación en cascada para la construcción del esqueleto del *ent*-labdano diol:

Al llevar a cabo la reacción de ciclación radicalaria inducida por Ti(III) bajo condiciones catalíticas sobre el silil derivado de **56** destaca sobremanera el alto estereocontrol con que esta se produce, pues se crean 4 nuevos estereocentros en posición contigua y con la estereoquímica adecuada. El tratamiento ácido del crudo de ciclación condujo al compuesto **57** en un 70 % para los dos pasos (Esquema 23). El resultado estereoquímico de la reacción se podría justificar suponiendo una interacción en el estado de transición entre el éter de silicio y el resto titanoxi presente en C-3 (Esquema 22).



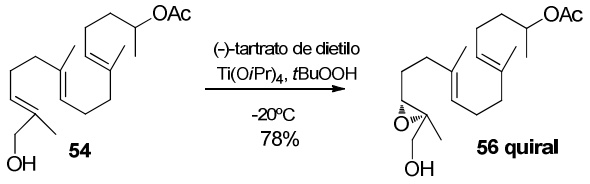
Esquema 22

Una vez conformada la decalina *trans* del esqueleto de labdano para regenerar el grupo carbonilo en C-13, se protegió el diol en forma de acetónido, se desprotegió el acetato y se oxidó el alcohol en C-13 mediante reactivo de Dess-Martin para obtener en un 75% el compuesto **58**. La presencia del carbonilo en **58** permitió completar los 15 átomos del esqueleto labdánico mediante olefinación de Horner-Wadsworth-Emmons con trietilfosfonoacetato para dar el correspondiente éster α,β insaturado **59** con un 77%. La reducción del éster con DIBAL-H, y posterior tratamiento ácido originó en un 80% el producto natural deseado **51**.



Esquema 23. Síntesis de (13E)-ent-labda-8(17),13-dieno-3β,15,18-triol

Finalmente, este método puede ser fácilmente adaptado para la síntesis enantioselectiva mediante la utilización de la epoxidación asimétrica de Sharpless de los alcoholes alílicos intermedios del tipo **54** (Esquema 24).



Esquema 24. Aproximación asimétrica a **51**

V. CONCLUSIONES

1. Se ha presentado una revisión de las estructuras y propiedades biológicas de los triterpenos inusualmente ciclados que se han publicado durante la última década. Se ha estructurado según los diferentes tipos de familias, biosíntesis y aparición, y se han recopilado las síntesis descritas hasta la fecha.

2. Se ha empleado una estrategia sintética de ciclación radicalaria de epoxipoliprenos desarrollada previamente por nuestro grupo, para acceder a productos naturales triterpénicos. Las moléculas objetivo son biosintetizadas a través de procesos de retrociclación o de ciclaciones irregulares desde óxido de escualeno. Los procesos sintéticos han permitido un buen control de la regio- y estereoselectividad en las carbociclaciones. Así, y a modo de ejemplo, se han generado dos nuevos anillos de seis eslabones, 4 centros esterogénicos definidos y dos nuevos enlaces C-C en un sólo paso a partir de una estructura lineal sencilla.

3. Se ha diseñado una ruta convergente y rápida hacia el triterpeno irregular mirrhanol A (**1**) y sus congéneres. Estas moléculas destacan por sus importantes actividades como antiinflamatorios y reductores de los niveles de colesterol previniendo la formación de placas en las arterias. El uso combinado de la dihidroxilación asimétrica de Sharpless, la ciclación radicalaria de epoxipoliprenos en cascada para dar lugar a esqueletos drimánicos (6+6), junto con la reacción de acoplamiento boro alquil Suzuki-Miyaura en la formación de enlaces carbono-carbono, ha permitido la síntesis asimétrica de **1** y sus derivados en pocas etapas. Esta estrategia permite el acceso sintético fácil a nuevos agentes para el tratamiento del cáncer de próstata.

4. El empleo de reacciones asimétricas en las secuencias sintéticas, como la dihidroxilación de Sharpless y la anelación enantioselectiva de Robinson, mediadas por iminas quirales, ha permitido conseguir la inducción de quiralidad con altos excesos enantioméricos. De esta forma se han generado centros estereogénicos de configuración definida, correspondientes a la serie enantiomérica de los productos naturales objetivo.

5. Se han conseguido optimizar las condiciones de reacción en la anelación enantioselectiva de Robinson en la construcción de *cis*-decalinas llegando a obtener este fragmento molecular a escala de gramos de manera más económica y eficiente.

6. Haciendo uso de la estrategia de ciclación radicalaria, se ha llevado a cabo la síntesis enantioselectiva del triterpeno irregular achilleol B (**5**), compuesto aislado por nuestro grupo en los años 90. Se trata de una síntesis convergente, donde la secuencia lineal más larga fue de 14 pasos. La síntesis ha permitido la reasignación de la estereoquímica relativa de la molécula.

Además aprovechando el sintón monocíclico se completaron las síntesis de achilleol A (**6**), del sesquiterpeno elegansidiol (**27**) y de farnesiferol B (**28**) en 10, 8 y 9 pasos con un rendimiento medio de 12, 17 y 13%, respectivamente.

7. Se ha intentado la síntesis de *seco*-C-oleanano (**7**) mediante dos rutas convencionales fallidas que han servido para conocer mejor la topología molecular de la sustancia abriendo el camino hacia su síntesis definitiva. Un diseño retrosintético basado en una ciclación radicalaria de óxido de preoleanatetraeno ha permitido la síntesis eficiente de *seco*-C-oleanano (**7**), obteniéndose además achilleol B (**5**), *seco*-β-amirina (**9**) y camelliol A (**8**) como productos minoritarios. La síntesis de *seco*-C-oleanano demuestra la eficiencia sintética de esta estrategia donde la versión catiónica de estas ciclaciones no resulta adecuada. Finalmente, estos resultados han sido apoyados por resultados computacionales que confirman la naturaleza no concertada de las ciclaciones radicalarias.

8. Se ha abierto a una nueva ruta hacia terpenos gamma-dioxigenados mediante el empleo de metodologías sintéticas altamente eficaces como son, la cloración alílica selectiva catalizada por cloruro de fenilselenio, y la ciclación radicalaria mediada por Ti (III). Se ha demostrado la viabilidad de esta ruta en la síntesis racémica de (13*E*)-*ent*-labda-8(17),13-dieno-3β,15,18-triol (**51**).

VI. ANEXOS

Supporting Information[5]

Enantioselective Total Synthesis of the Potent Anti- Inflammatory (+)-Myrrhanol A

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^{1}H and ^{13}C NMR spectra of **11**

^{1}H and ^{13}C NMR spectra of **13**

[5] La numeración de los compuestos en la parte experimental se corresponde con la numeración de los compuestos de los artículos de investigación.

^{1}H and ^{13}C NMR spectra of **14**

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^{1}H and ^{13}C NMR spectra of **3**

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General Experimental Section:

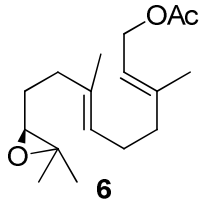
All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an atmosphere of argon. Tetrahydrofuran (THF) was freshly distilled immediately prior to use from sodium/benzophenone and strictly deoxygenated for 30 min under argon for the Cp_2TiCl_2/Mn reaction. 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.

Farnesyl acetate: Obtained from commercially available farnesol.

(2*E*,6*E*)-3,7-dimethyl-9-((S)-3,3-dimethyloxiran-2-yl)nona-2,6-dienyl acetate (6).

To a solution of **5** (3.621 g, 0.0121 mol) and catalytic DMAP in anhydrous pyridine (170 mL) cooled at - 12º C under Argon atmosphere, was added dropwise MsCl (5.635 mL, 0.073 mol). After 40 minutes (TLC monitoring), the mixture was diluted with *t*-BuOMe and treated with sat $NaHCO_3$ solution. After additional 15 minutes stirring at room temperature, the mixture was extracted with Et_2O (3 x 10 mL), the organic layer washed with HCl 1N (1x 10mL), brine and dried over anhydrous Na_2SO_4 and finally concentrated under reduced pressure. The mesylated crude was dissolved 184 mL of methanol and 6.67 g of K_2CO_3 were added. After stirring for 20 minutes, the formation of epoxide was complete (TLC monitoring). Then, the reaction was quenched by diluting with H_2O and *t*-BuOMe. The organic layer washed with 1N HCl (2 x 10 mL), sat.$NaHCO_3$ (2 x 10 ml) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 3:1) to afford 2 g of the corresponding epoxide (74% yield in two steps). This epoxide (2 g, 8.915 mmol), pyridine (4.4 mL) and Ac_2O (1.10 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into an ice bath and extracted with *t*-BuOMe (3 x 20 mL). The organic phase was successively washed with 2 M HCl (3 x 20 mL), 5% aqueous $NaHCO_3$ (3 x 30 mL), water (3 x 30 mL), and dried over anhydrous sodium sulfate. After Filtration of the crude through silica gel (hexane/*t*-BuOMe, 2:1) afforded 2.065 g (87%) of epoxyacetate **6** as a colourless oil. $[\alpha]^{20}_D = -2.8$ (c 1.0, $CHCl_3$); IR (film):

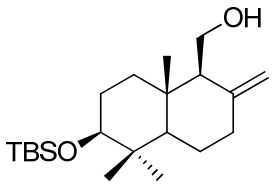
1720, 1365, 1230 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$): δ 5.32 (dt, *J* = 7.5, 1.0 Hz, 1H), 5.13 (dt, *J* = 7.0, 1.0 Hz, 1H), 4.56 (d, *J* = 7.5 Hz, 2H), 2.68 (t, *J* = 6.5 Hz, 1H), 2.02-2.15 (m, 6H), 2.03 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H), 1.55-1.64 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H). ^{13}C NMR: δ 170.9, 141.9, 134.5, 124.2, 118.4, 64.1, 61.3, 58.2, 39.4, 36.2, 27.4, 26.1, 24.9, 21.0, 18.7, 16.5, 16.0.



6

((2S,4a*S*,5*S*)-decahydro-2-*tert*-butyldimethylsilyloxy-1,1,4a-trimethyl-6-methylenenaphthalen-5-yl)methanol (8).

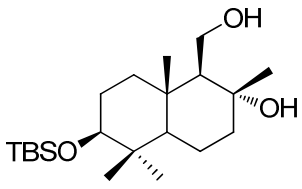
To a stirred solution of **7** (230 mg, 1.13 mmol) in DMF (13 mL), imidazole (335 mg, 4.9 mmol) and TBSCl (742 mg, 4.9 mmol) were added at room temperature. After stirring for 16 h (TLC monitoring), the mixture was diluted with *t*-BuOMe and water and extracted with *t*BuOMe. The combined organic layer was washed with 2N HCl, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 95:5) on silica gel to afford 336 mg (91%) of the corresponding silylated derivative. This compound was dissolved in MeOH (6 mL) and then K_2CO_3 (249 mg, 1.810 mmol) was added. The mixture was stirred for 2 h (TLC monitoring) at room temperature, concentrated under vacuum, washed with water and extracted with *t*-BuOMe. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 293 mg (98%) of the primary alcohol **8**. $[\alpha]^{20}_D$ = + 9.2 (c 1.0, $CHCl_3$). IR(film) ($CHCl_3$): 3620, 3450, 1650, 1100, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.84 (bs, 1H), 4.55 (bs, lH), 3.72-3.72 (m, 2H), 3.15 (dd, *J* = 10.5, 5.4 Hz, 1H), 2.33(bd, *J* = 12.9 Hz, 1H) 1.96-1.16 (m, 8H), 1.01 (dd, *J* = 12.5, 2.6 Hz, 1H), 0.94 (s, 3H), 0.80 (s, 9H), 0.65 (s, 3H), 0.63 (s, 3H), -0.04 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4, 106.6, 79.2, 58.9, 58.7, 54.5, 39.7, 38.6, 37.8, 36.9, 28.7, 28.1, 25.9 (3C), 23.9, 18.1, 15.9, 15.3 ,-3.7, -4.9.



8

(2*S*,4a*S*,5*S*,6*R*)-Decahydro-5-(hydroxymethyl)-1,1,4a,6-tetramethylnaphthalene-2-*tert*-butyldimethylsilyloxy,6-ol (9).

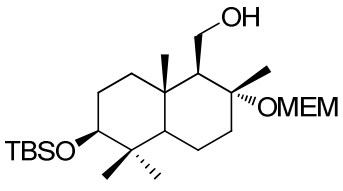
To a solution of **6** (695 mg, 1.97 mmol) in CH_2Cl_2 (9 mL) *m*-chloroperbenzoic acid (579 mg, 3.36 mmol) was added. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted with ether and the organic layer was washed with 10% aqueous $Na_2S_2O_3$, 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the organic solvent gave a residue, which was reacted in the next step. To a suspension of the crude in Et_2O (5 ml) $LiAlH_4$ was added at 0ºC (85 mg, 2.24 mmol), The mixture was stirred for 1.5 h at room temperature, and then worked-up as usual. Evaporation of the organic layer gave **9** in 82 % overall yield. $[\alpha]^{20}_D$= +5.4 (c 1.0, CH_2Cl_2); IR (film): 3326, 2937, 2855, 1460, 1383, 1252, 1062, 935, 834, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.89 (bs, 2H), 3.16 (dd, *J* = 11.1, 4.8 Hz,1H), 1.86 (bd, *J* = 12.4 Hz, 1H), 1.76-1.46 (m, 7H), 1.31 (s, 3H), 1.30-1.25 (m, 1H), 1.17 (bt, *J* = 13.1 Hz, 1H), 0.89 (s, 3H), 0.68 (s, 9H), 0.77 (s, 3H), 0.70 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.9, 73.1, 60.8, 60.1, 54.9, 44.2, 39.4, 38.1, 37.1, 28.6, 27.6, 25.9 (3C), 24.2, 20.1, 18.1, 16.0, 16.0, -3.8, -4.9; HRFABMS: calcd. for $C_{21}H_{42}O_3SiNa$ [M+Na]+ 393.2800, found 393.2803.



9

((2*S*,4a*S*,5*S*,6*R*)-decahydro-2-*tert*-butyldimethylsilyloxy,6-(2-methoxyethoxy)methoxy-1,1,4a,6-tetramethylnaphthalen-5-yl)methanol (10).

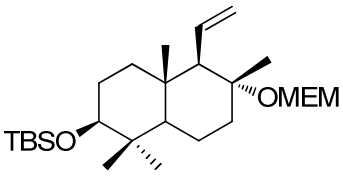
Diol **7** (554 mg, 1.495 mmol), pyridine (5 mL), Ac_2O (0.18 mL) and DMAP (cat.) were stirred at room temperature for 2 h. The reaction mixture was poured into an ice bath and extracted with *t*-BuOMe (3 x 20 mL). The organic phase was successively washed with 2 M HCl (3 x 20 mL), 5% aqueous $NaHCO_3$ (3 x 30 mL), water (3 x 30 mL), and dried over anhydrous sodium sulfate. After evaporating the solvent, the acetylated crude was dissolved in 3.3 mL of DMF and MEMCl (260 mg, 2.09 mmol) and N,N-diisopropylethylamine (312 mg, 2.41 mmol) were added. The mixture was stirred for 2.5 h at 80 ºC, and then was diluted with brine and extracted with Et_2O. The organic layer was dried over Na_2SO_4. Evaporation of the organic solvent gave a crude product, which was chromatographed on silica gel (hexane/*t*-BuOMe, 10:1) to afford 400 mg of the corresponding ether. This compound was dissolved in MeOH (6 mL) and then K_2CO_3 (249 mg, 1.810 mmol) was added. The mixture was stirred for 2 h (TLC monitoring) at room temperature, concentrated under vacuum, washed with water and extracted with *t*-BuOMe. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 1:2) on silica gel to afford 263 mg (98%) of the corresponding hydroxy-derivative **10**. $[\alpha]^{20}_D$= +3.4 (c 1.0, CH_2Cl_2); IR (film):3449, 2930, 2855, 1651, 1462, 1387, 1252, 1098, 1034, 835, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.84 (d, *J* = 7.8 Hz, 1H), 4.77 (d, *J* = 7.8 Hz, 1H), 3.84 (dd, *J* = 11.2, 7.3 Hz, 1H), 3.74-3.60 (m, 3H), 3.51 (t, *J* = 4.6 Hz, 2H), 3.35 (s, 3H), 3.17 (dd, *J* = 10.8, 4.8 Hz, 1H), 1.94 (dt, *J* = 12.3, 2.9 Hz, 1H), 1.77 (dt, *J* = 13.2, 3.4 Hz, 1H), 1.69-1.46 (m, 6H), 1.31-1.18 (m, 2H), 1.30 (s, 3H), 0.87 (s, 3H), 0.85 (s, 9H), 0.78 (s, 3H), 0.69 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 88.7, 81.7, 78.9, 71.7, 67.2, 60.5, 60.1, 58.9, 54.7, 39.6, 39.3, 38.2, 37.5, 28.5, 27.5, 25.8 (3C), 21.4, 19.8, 18.0, 16.4, 15.9, -3.8, -4.9; HRFABMS: calcd. for $C_{25}H_{50}O_5SiNa$ [M+Na]+ 481.3325, found 481.3328.



10

((2*S*,4a*S*,5*R*,6*R*)-6-((2-methoxyethoxy)methoxy)-decahydro-1,1,4a,6-tetramethyl-5-vinylnaphthalen-2-yloxy)(*tert*-butyl)dimethylsilane (11).

Oxalyl chloride (1 mL, 2.0 M in CH_2Cl_2, 1.93 mmol) was added to a solution of dry DMSO (0.3 mL, 3.86 mmol) in dry CH_2Cl_2 (7 mL) at - 60 °C, under argon. The mixture was stirred for 30 min and a solution of the unprotected alcohol **10** (295 mg, 0.64 mmol) in CH_2Cl_2 (5 mL) was added. Upon 30 min additional stirring at -60 °C, Et_3N (0.9 mL, 6.43 mmol) was added, and the mixture was allowed to warm up to 0 °C, poured into ice cold water, diluted with CH_2Cl_2 and worked up in the usual way to give the corresponding crude aldehyde, directly used in the next step. A solution of potassium *tert*-butoxide (205 mg, 1.83 mmol) in 3.8 mL of dry toluene was stirred under argon at room temperature as methyltriphenylphosphonium bromide (653 mg, 1.83 mmol) was added. The resulting bright yellow solution was stirred for 1 h, cooled to 0 °C before the aldehyde (0.610 mmol) was added in dry toluene (2.5 mL). The ice bath was removed and the solution was stirred at room temperature while the reaction progress was monitored by TLC. After TLC analysis indicated consumption of the starting aldehyde (45 min), the reaction mixture was diluted with hexane and worked up as usual. Rapid filtration on silica gel with hexane as eluent afforded 248 mg (85% over two steps) of a colourless oil compound **11**. $[\alpha]^{20}_D$= -5.4 (c 1.0, CH_2Cl_2); IR (film): 3443, 2933, 2855, 2096, 1641, 1461, 1387, 1251, 1130, 1096, 1040, 916, 834, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (dt, *J* = 16.7, 10.3 Hz, 1H), 5.13 (dd, *J* = 10.3, 2.5 Hz, 1H), 4.99 (dd, *J* = 16.7, 2.5 Hz, 1H), 4.80 (d, *J* = 7.8 Hz, 1H), 4.71 (d, *J* = 7.8 Hz, 1H), 3.65 (m, 2H), 3.51 (t, *J* = 4.8, 2H), 3.36 (s, 3H), 3.18 (dd, *J* = 11.3, 4.4 Hz, 1H), 1.92 (m, 1H), 1.80 (d, *J* = 7.8 Hz, 1H), 1.68-1.24 (m, 6H), 1.28 (s, 3H), 0.99-0.80 (m, 2H), 0.89 (s, 6H), 0.87 (s, 9H), 0.72 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8, 119.0, 89.0, 79.3, 78.6, 71.9, 66.3, 64.4, 58.9, 54.6, 40.4, 39.4, 38.9, 37.5, 28.6, 27.5, 25.9 (3C), 21.3, 19.9, 18.1, 16.3, 15.9, -3.81, -4.96. HRFABMS: calcd. for $C_{26}H_{50}O_4SiNa$ [M+Na]+ 477.3375, found 477.3376.

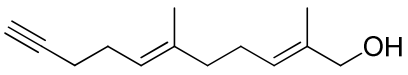


11

Geranyl acetate: commercially available.

(2*E*,6*E*)-2, 6-dimethyl-11-(trimethylsilyl)undeca-2,6-dien-10-yn-1-ol (13).

To a solution of 1-(Trimethylsilyl)-1- propyne (3 mL, 19.8 mmol) in THF (12 mL) at -20 ºC was added *n*BuLi (2.0 M, 9.9 mL, 19.8 mmol) dropwise. After 30 minutes, bromide **12**[6] (836 mg, 2.4 mmol) in THF (5.6 mL) was added to the above solution and the temperature was raised to 0 ºC slowly. The reaction mixture was stirred for 5 minutes at 0 ºC and then quenched with H_2O. The aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 15 mL), brine (15 mL) and dried over Na_2SO_4. The resulting crude was treated with TBAF (1.0 M in THF, 1.7 mL) at room temperature for 30 minutes followed by quenching with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O (2 × 20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 15 mL), brine (15 mL) and dried over Na_2SO_4. Concentration followed by flash chromatography on silica gel with a 1:1 mixture of hexane/Et_2O as eluent provided the desired product **13** as a colorless oil (322 mg, 1.68 mmol) (70% two steps). IR (film): 3350, 3034, 2919, 2857, 1668, 1436, 1383 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.37 (t, 1H, *J* = 6.4 Hz), 5.18 (t, 1H, *J* = 6.9 Hz), 3.97 (s, 2H), 2.25-2.01 (m, 6H), 1.93 (t, *J* = 2.5 Hz, 2H), 1.65 (s, 3H), 1.62 (s, 3H), 1.57(s, 1H);^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.3, 134.8, 125.8, 122.8, 84.5, 68.9, 68.2, 39.2, 27.1, 26.0, 18.9, 16.0, 13.7. HRFABMS: calcd. for $C_{13}H_{20}ONa$ [M+Na]+ 215.1412, found 215.1402

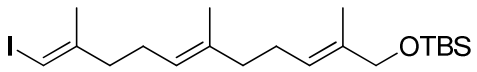


13

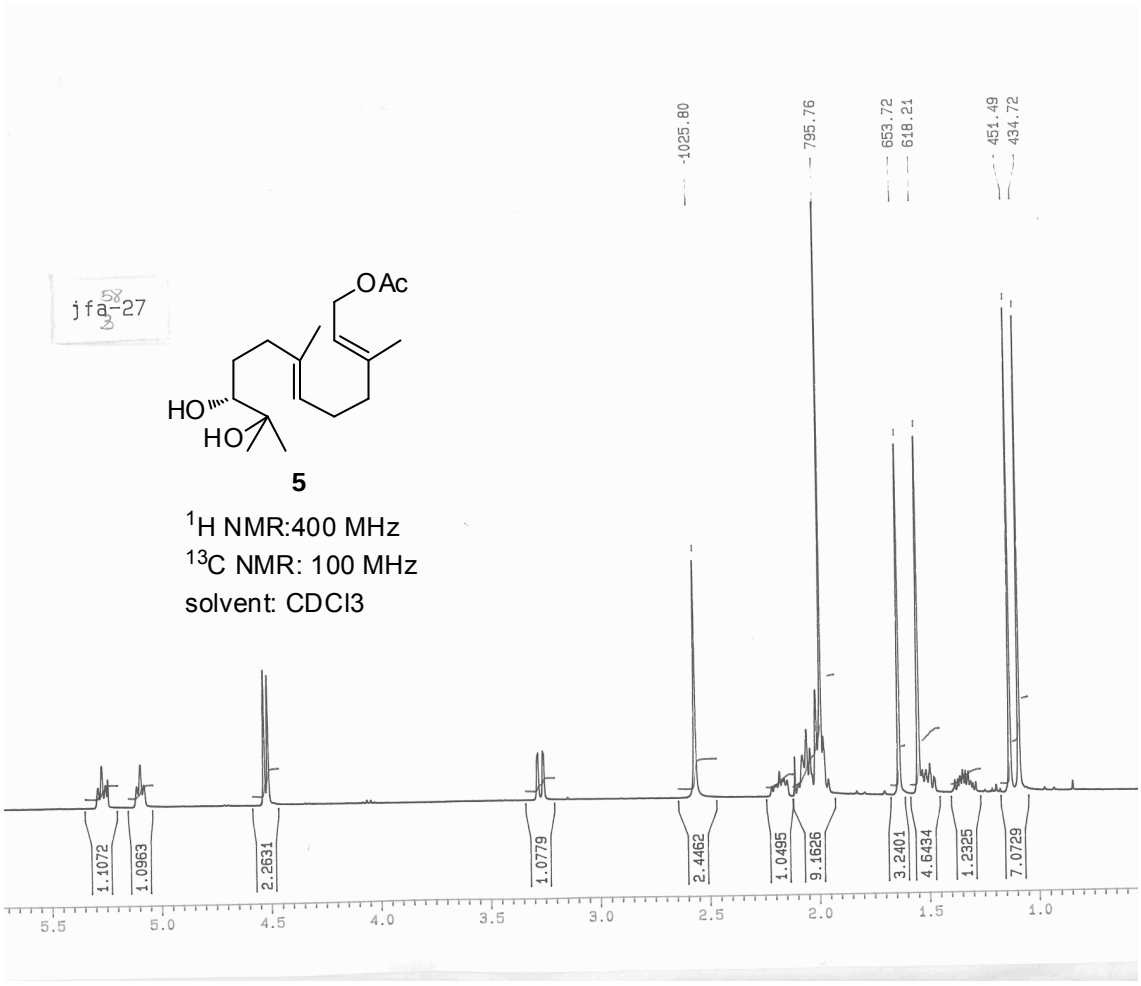
((2*E*,6*E*,10*E*)-11-)Iodo-2,6,10-trimethylundeca-2,6,10-trien-1-oxy)(*tert*-buthyl)dimethylsilane (15).

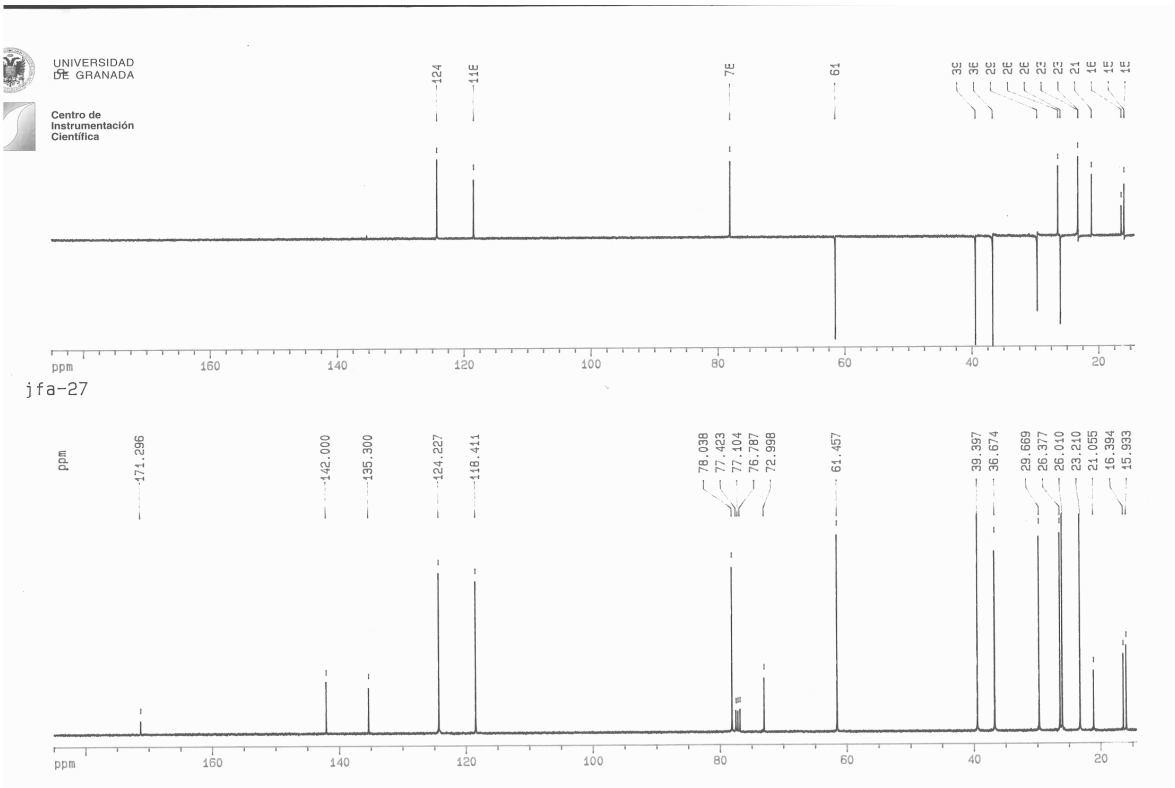
[6] Bogenstaetter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.*, **1999**, *121*, 12206-12207.

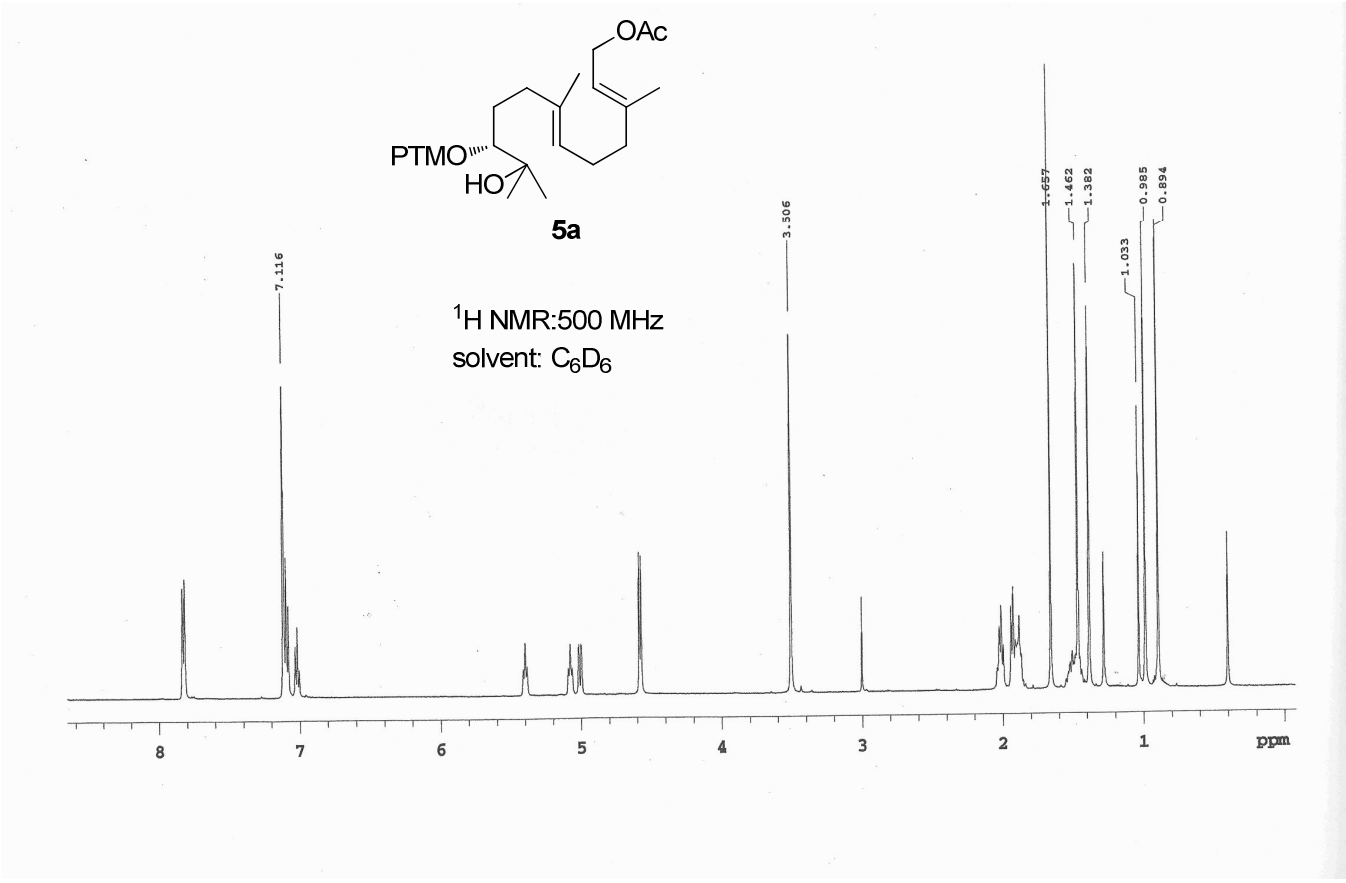
To a stirred solution of the vinyl iodide 14 (437 mg, 1.31 mmol) in DMF (3.9 mL), imidazole (118 mg, 2.6 mmol), DMAP (29 mg, 0.26 mmol) and TBSCl (392 mg, 2.6 mmol) were added at room temperature. After stirring for 30 minutes (TLC monitoring), the mixture was diluted with water and extracted with *t*BuOMe (3 × 50 mL). The combined organic layer was washed with 2N HCl, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Concentration followed by flash chromatography on silica gel with 5:1 hexane/ *t*-BuOMe as eluent provided the desired product **15** as a colorless oil (558 mg, 1.25 mmol, 95%). IR(film): 3056, 2953, 2928, 2855, 1461, 1262, 1109, 1068, 836, 775 and 667 cm^{-1}. ^1H NMR $CDCl_3$, 500 MHz) δ 5.86 (s, 1 H), 5.37 (t, *J* = 6.9 Hz, 1H), 5.07 (t, *J* =6.9 Hz, 1H), 3.99 (s, 2H), 2.22 (t, *J* = 7.9 Hz, 2H) ,2.1 (q, *J*= 15.1, 7.5 Hz ,4H), 2.01 (t, *J* = 7.2 Hz, 2H), 1.83 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H);^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.78, 135.86, 134.38, 124.20, 123.09, 74.69, 68.63, 39.47, 39.33, 26.12, 26.11, 25.95(3C), 23.93, 18.41, 15.97, 13.44, -5.26,(2C). HRFABMS: calcd. for $C_{20}H_{37}IOSiNa$ [M+Na]+ 471.1555, found 471.1547.

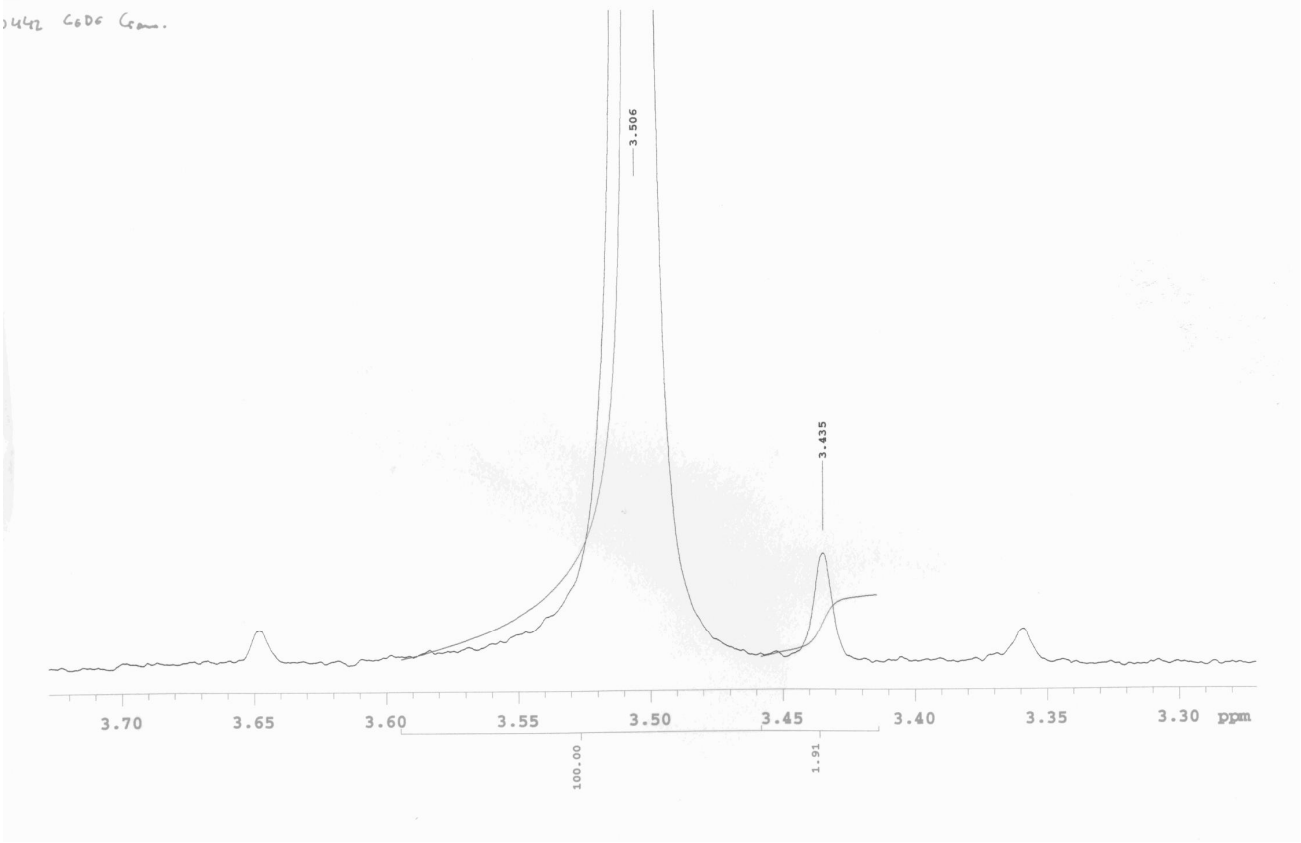


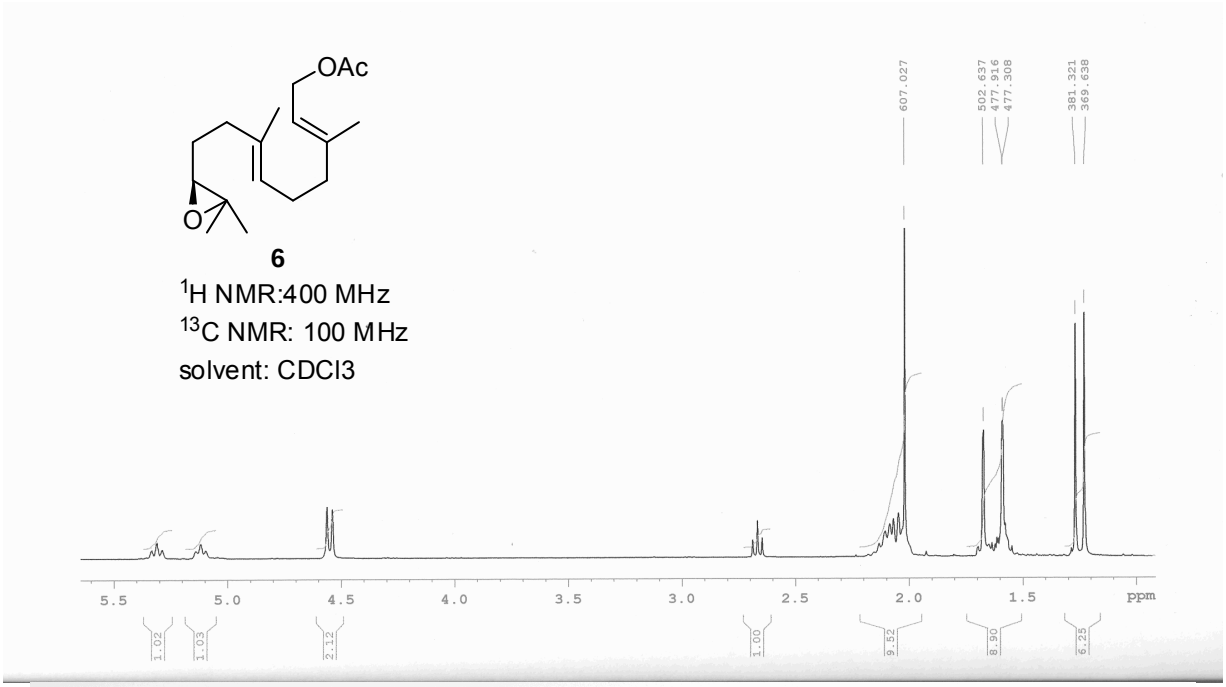
15

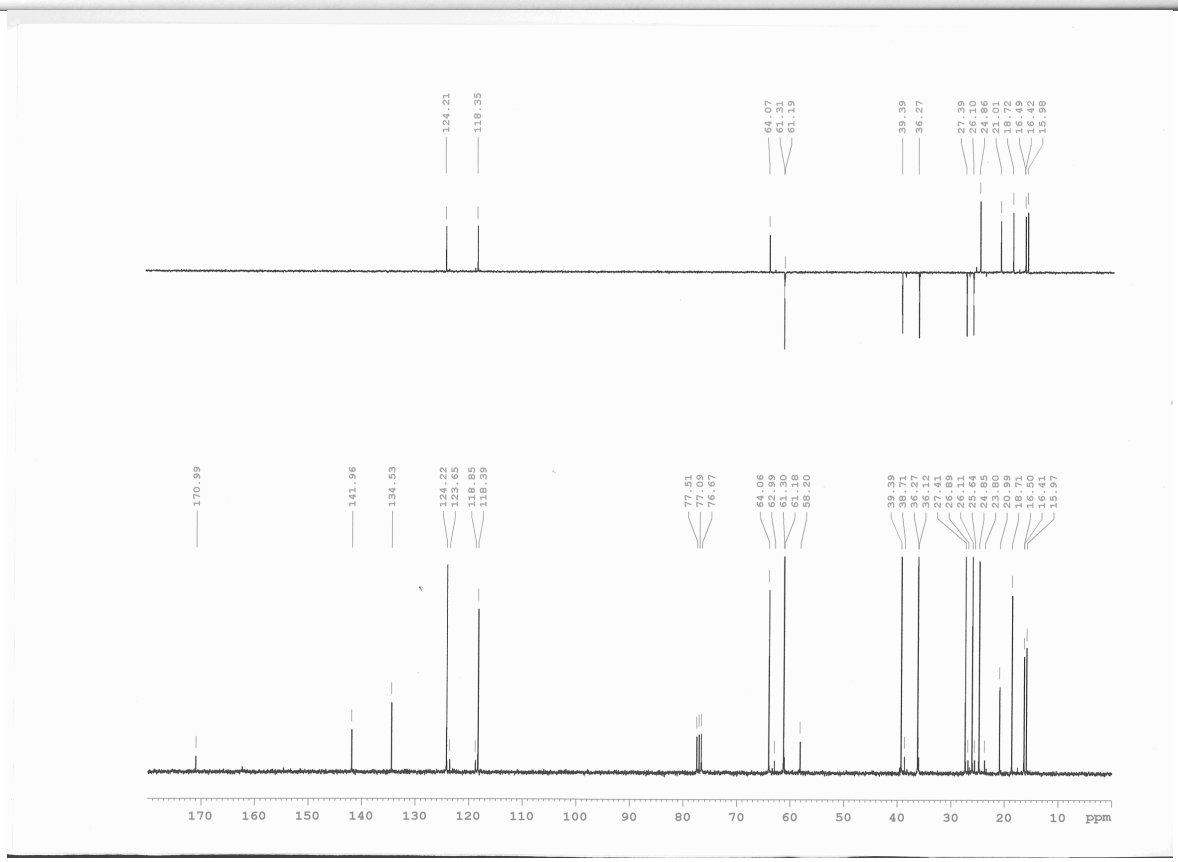

jfa-27
OAc
HO
HO
5
1H NMR:400 MHz
13C NMR: 100 MHz
solvent: CDCl3
1025.80
795.76
653.72
618.21
451.49
434.72
1.1072
1.0963
2.2631
1.0779
2.4462
1.0495
9.1626
3.2401
4.6434
1.2325
7.0729
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

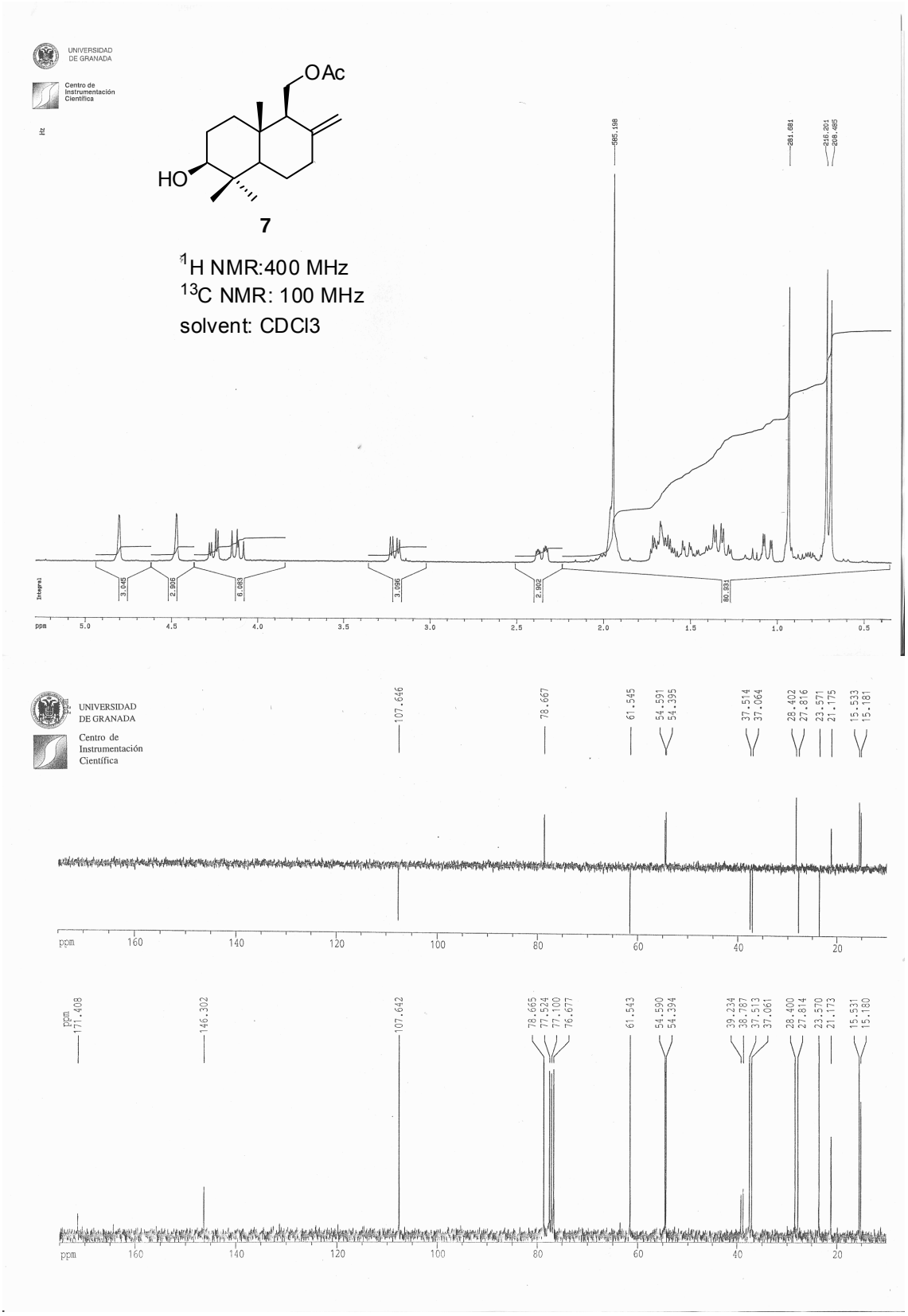

UNIVERSIDAD DE GRANADA
Centro de Instrumentación Científica
124
118
78
61
ppm
160
140
120
100
80
60
40
20
jfa-27
171.296
142.000
135.300
124.227
118.411
78.038
77.423
77.104
76.787
72.998
61.457
39.397
36.674
29.669
26.377
26.010
23.210
21.055
16.394
15.933

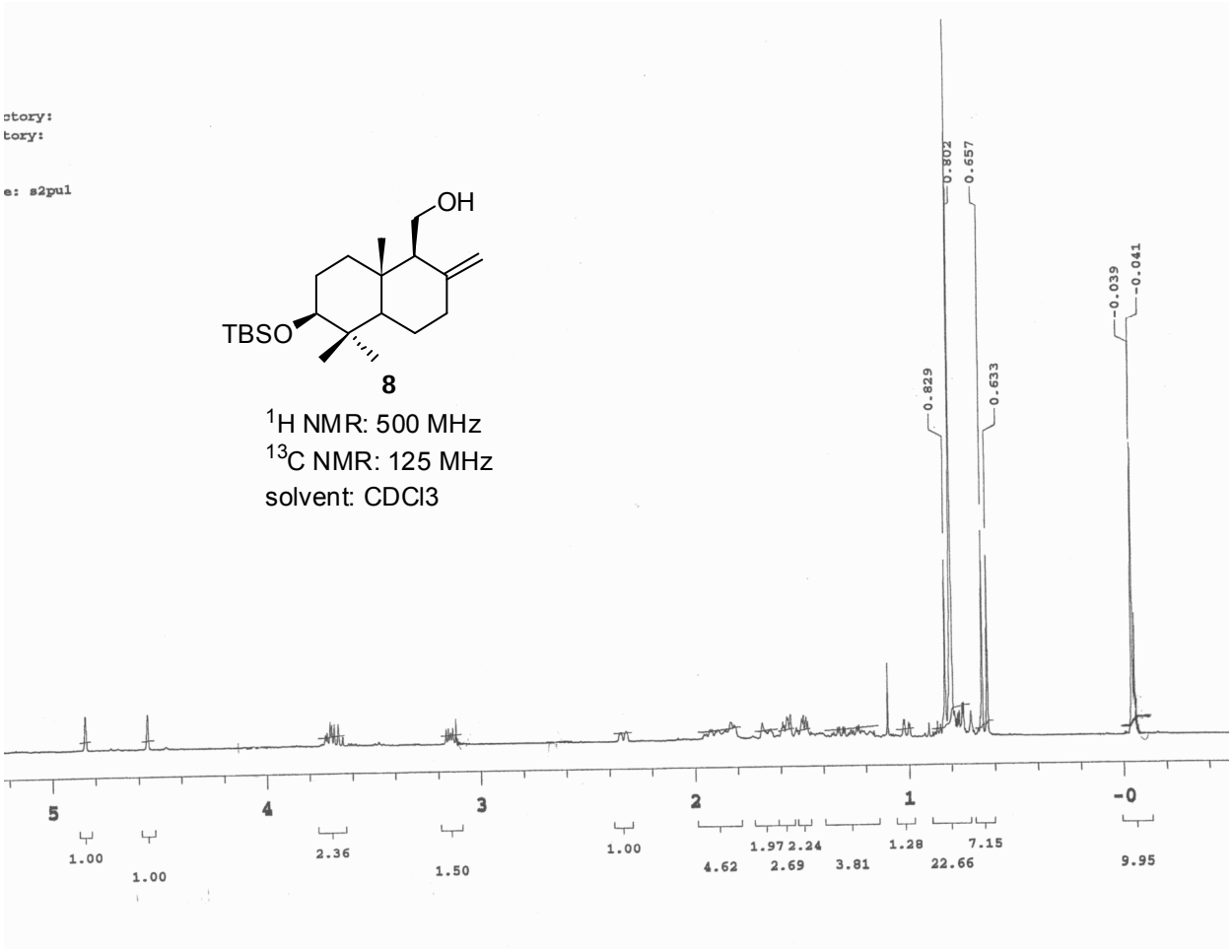

OAc
PTMO
HO
5a
1H NMR:500 MHz
solvent: C6D6
7.116
3.506
1.657
1.462
1.382
1.033
0.985
0.894
8
7
6
5
4
3
2
1
ppm

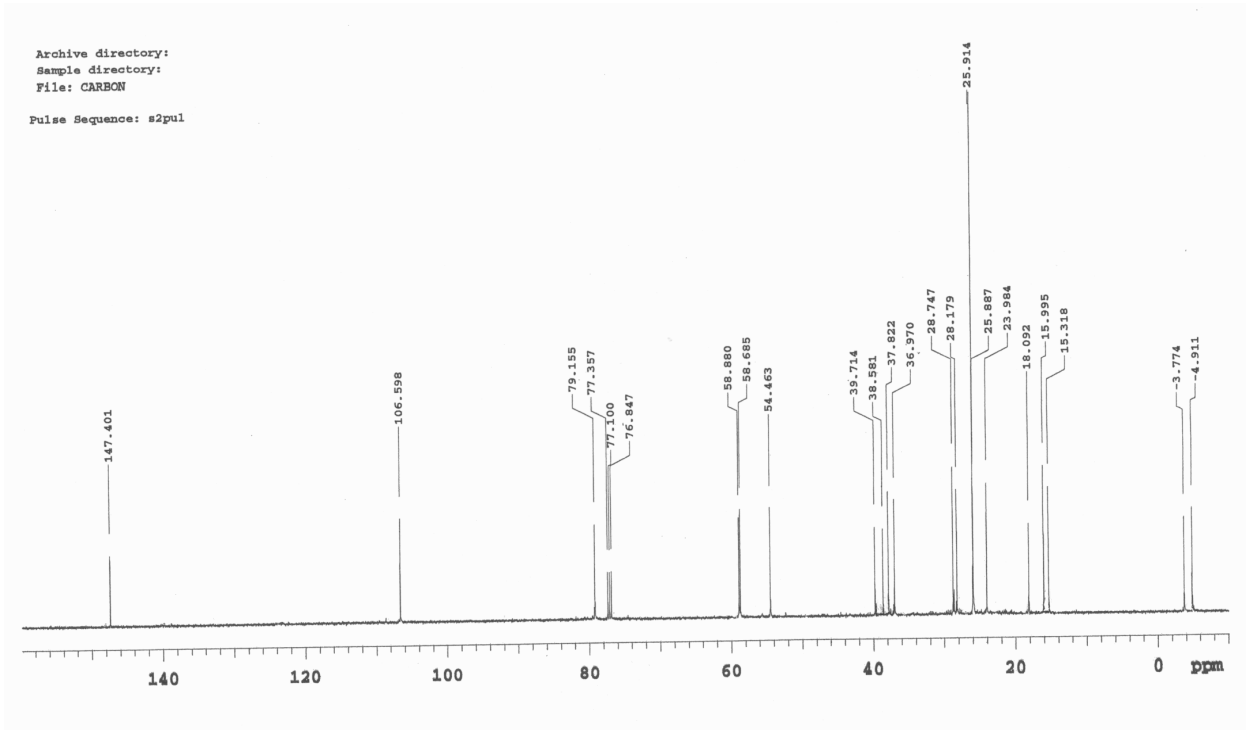

3.506
3.435
3.70
3.65
3.60
3.55
3.50
3.45
3.40
3.35
3.30
ppm
100.00
1.91


OAc
O
6
1H NMR:400 MHz
13C NMR: 100 MHz
solvent: CDCl3
607.027
502.637
477.366
477.308
381.321
369.638
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.02
1.03
2.12
1.00
9.52
8.90
6.25


124.21
118.35
64.07
61.31
61.19
39.39
36.27
27.39
26.10
24.86
21.01
18.72
16.49
16.42
15.98
170.99
141.96
134.53
124.22
123.65
118.85
118.39
77.51
77.09
76.67
64.06
62.99
61.30
61.18
58.20
39.39
38.71
36.27
36.12
27.41
26.89
26.11
25.64
24.85
23.80
20.99
18.71
16.50
16.41
15.97
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

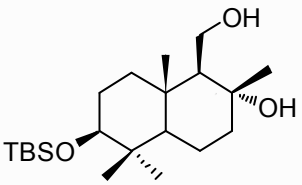

UNIVERSIDAD DE GRANADA
Centro de Instrumentación Científica
OAc
HO
7
1H NMR:400 MHz
13C NMR: 100 MHz
solvent: CDCl3
UNIVERSIDAD DE GRANADA
Centro de Instrumentación Científica


OH
TBSO
8
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
0.829
0.657
0.633
-0.039
-0.041
1.00
1.00
2.36
1.50
1.00
4.62
1.97
2.24
2.69
3.81
1.28
22.66
7.15
9.95


Archive directory:
Sample directory:
File: CARBON
Pulse Sequence: s2pul
147.401
106.598
79.155
77.357
77.100
76.847
58.880
58.685
54.463
39.714
38.581
37.822
36.970
28.747
28.179
25.914
25.887
23.984
18.092
15.995
15.318
-3.774
-4.911
ppm

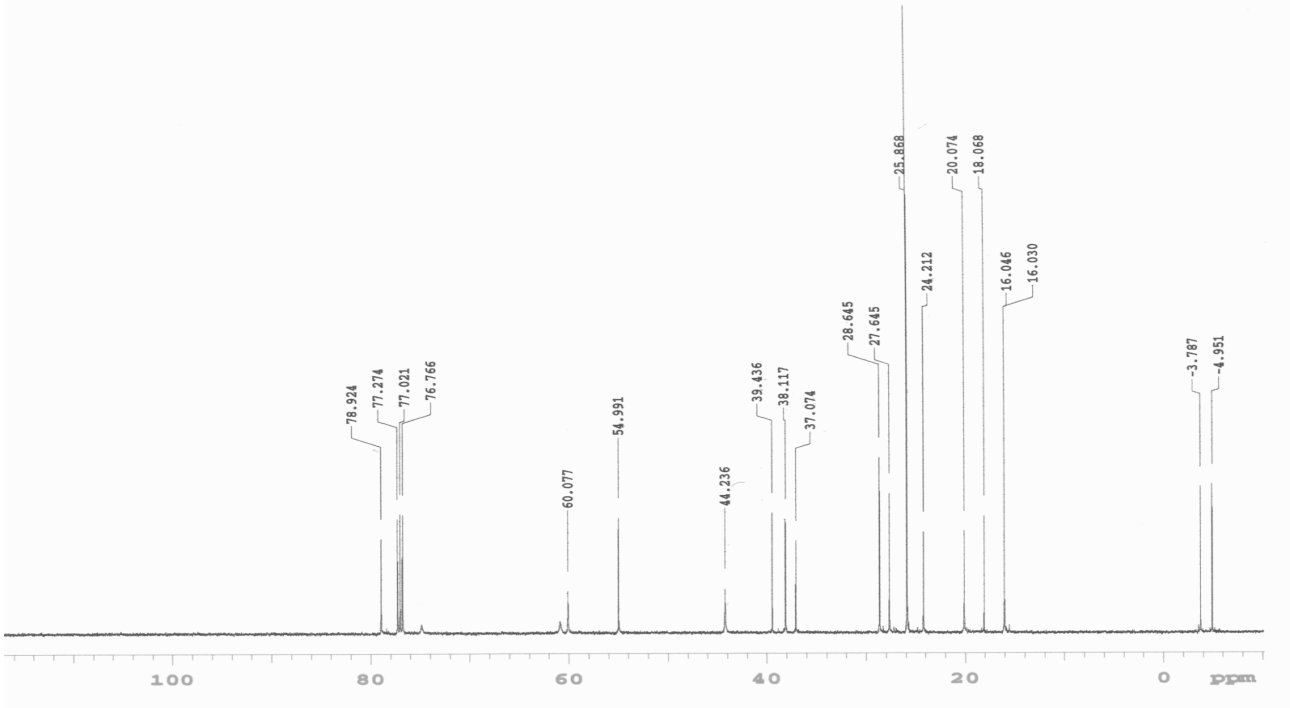
VD-349_15-10-08
File: xp
Sample id: tmpstudy

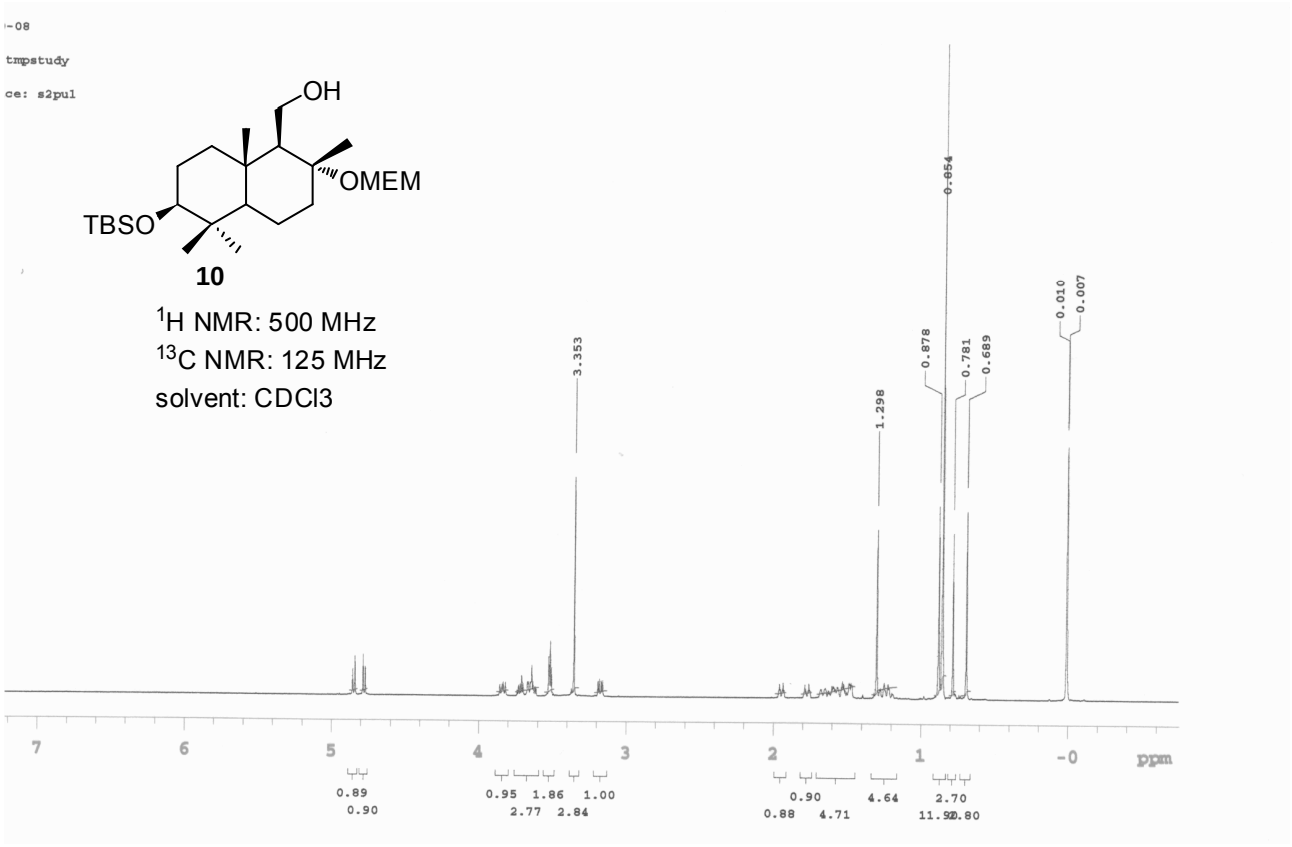
Pulse Sequence: s2pul

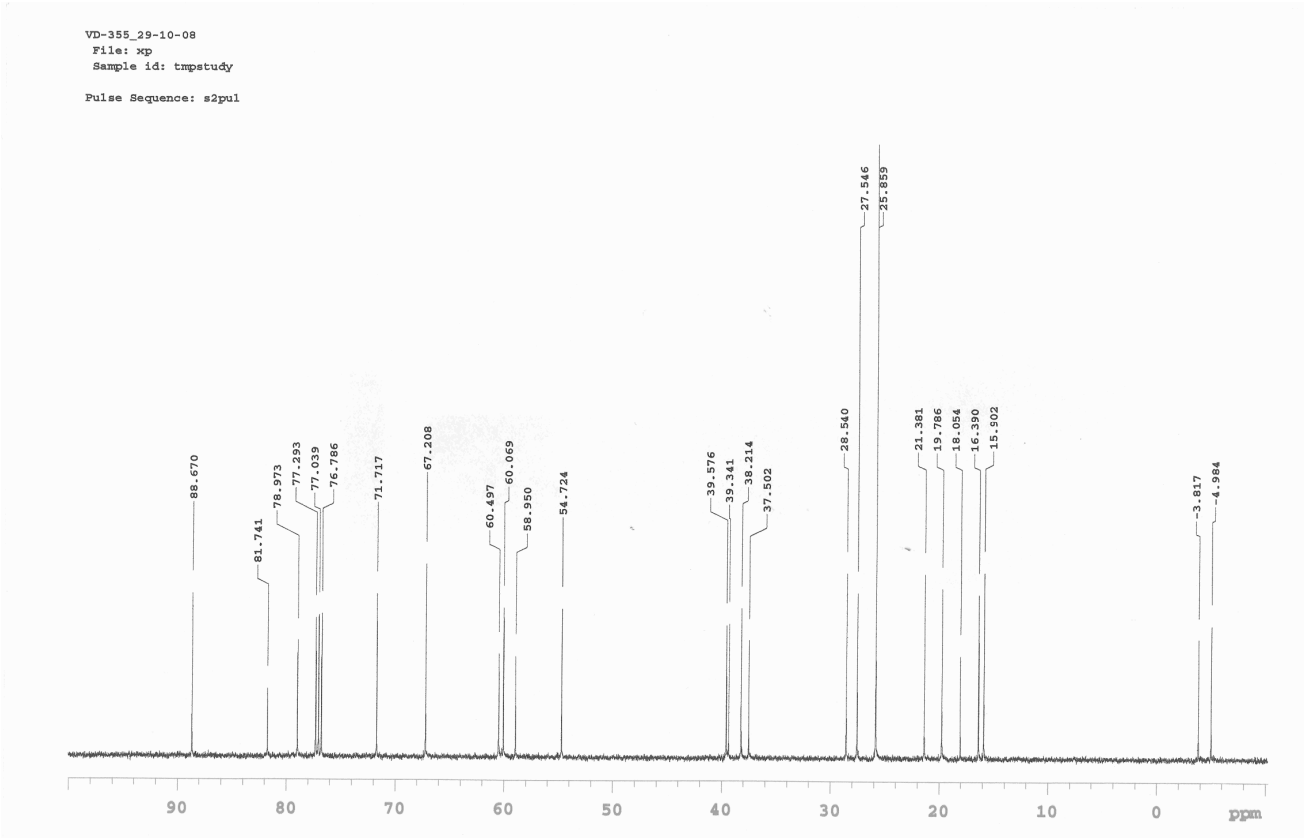


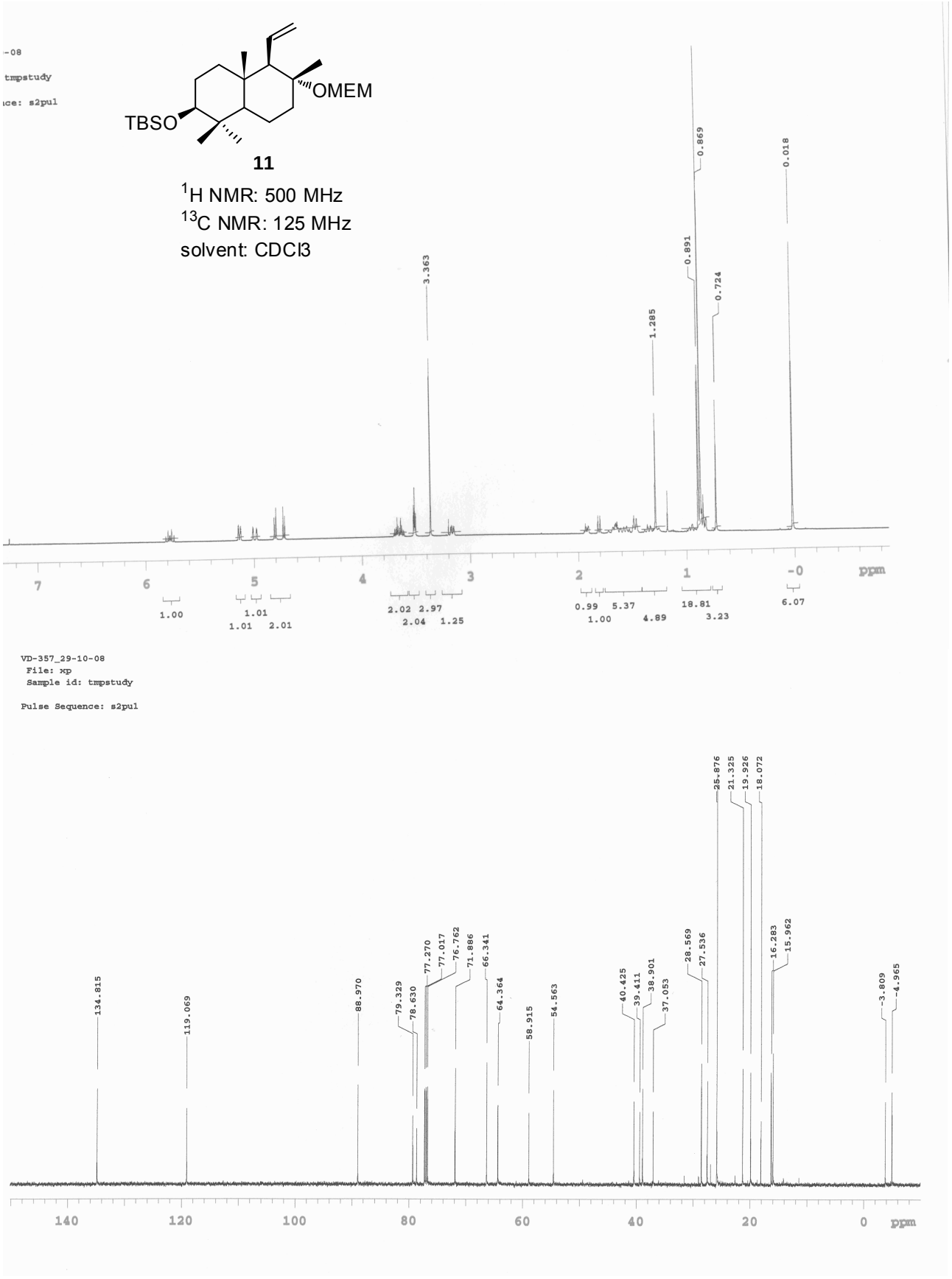
9

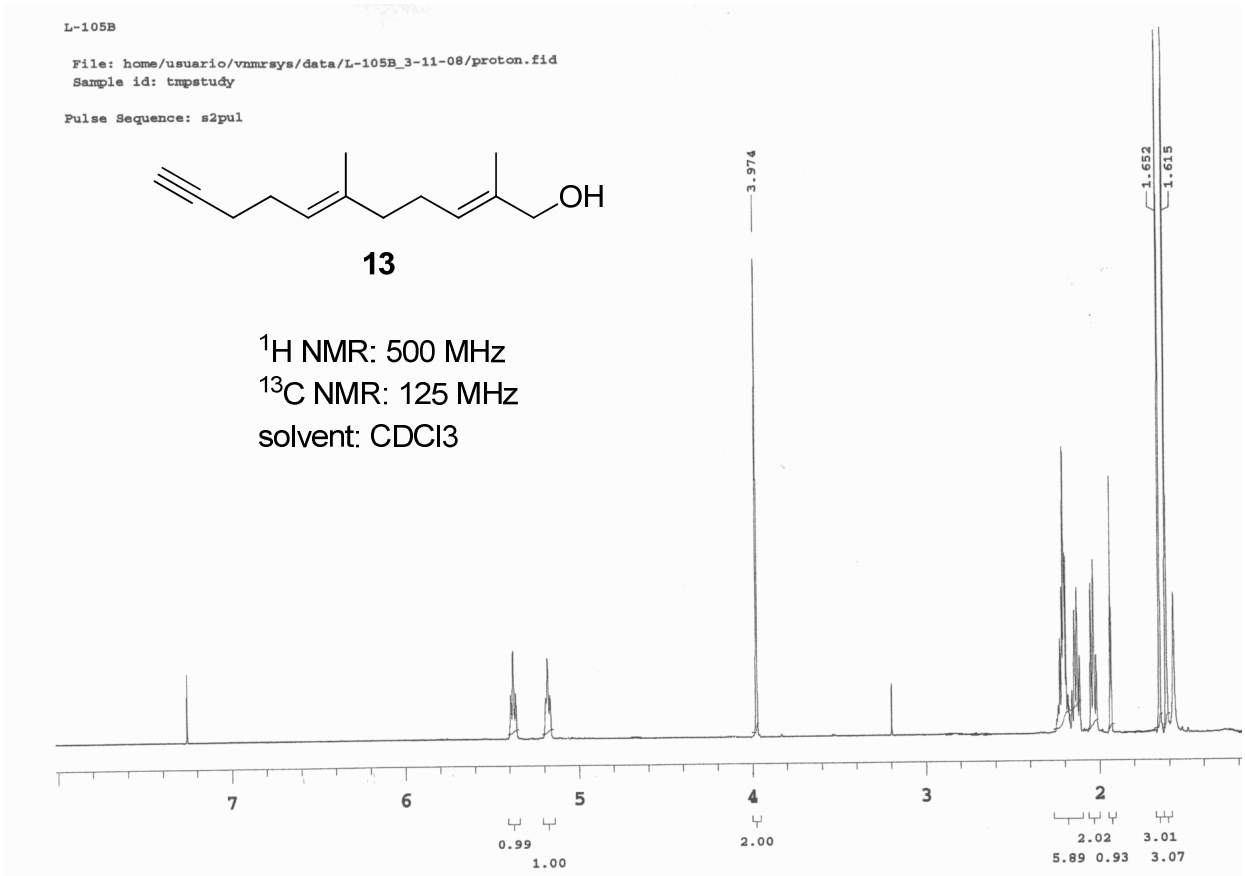
^{1}H NMR: 500 MHz
^{13}C NMR: 125 MHz
solvent: CDCl3

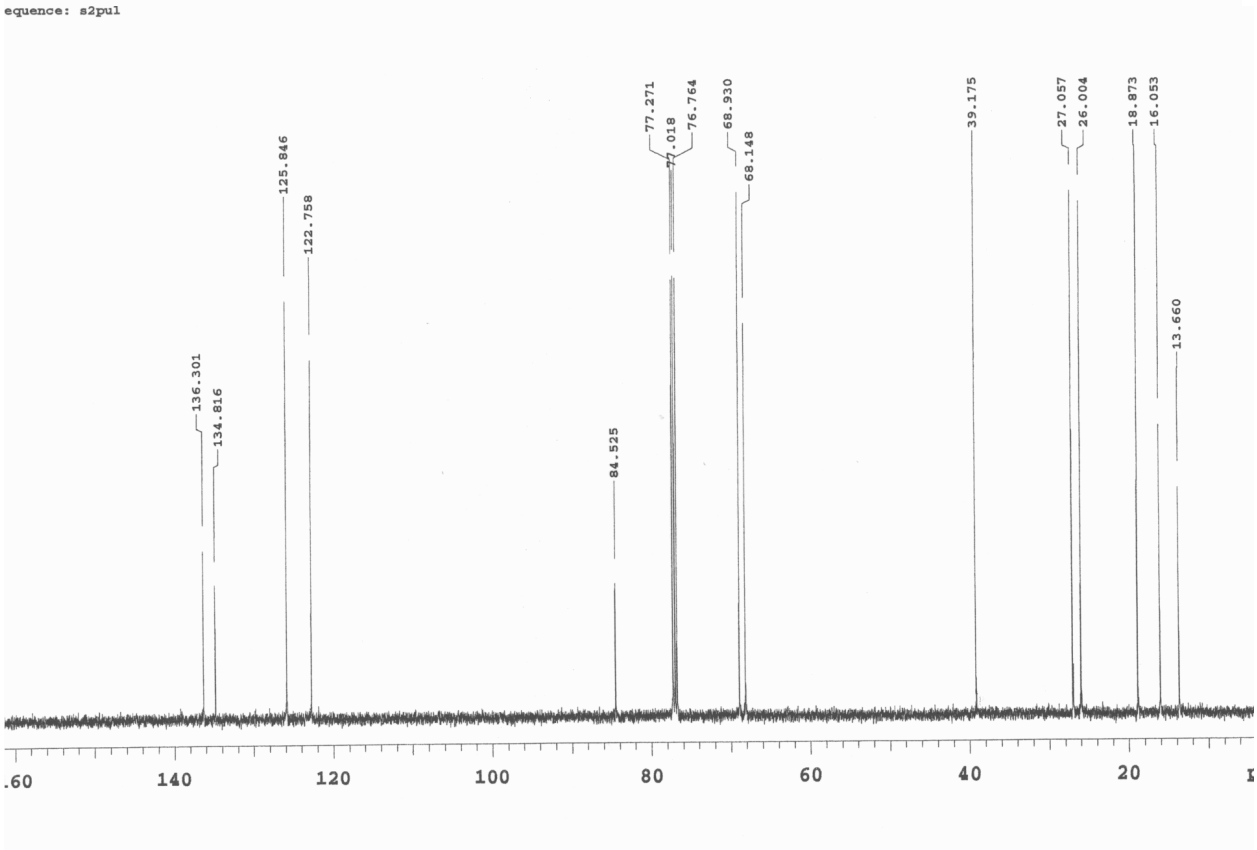


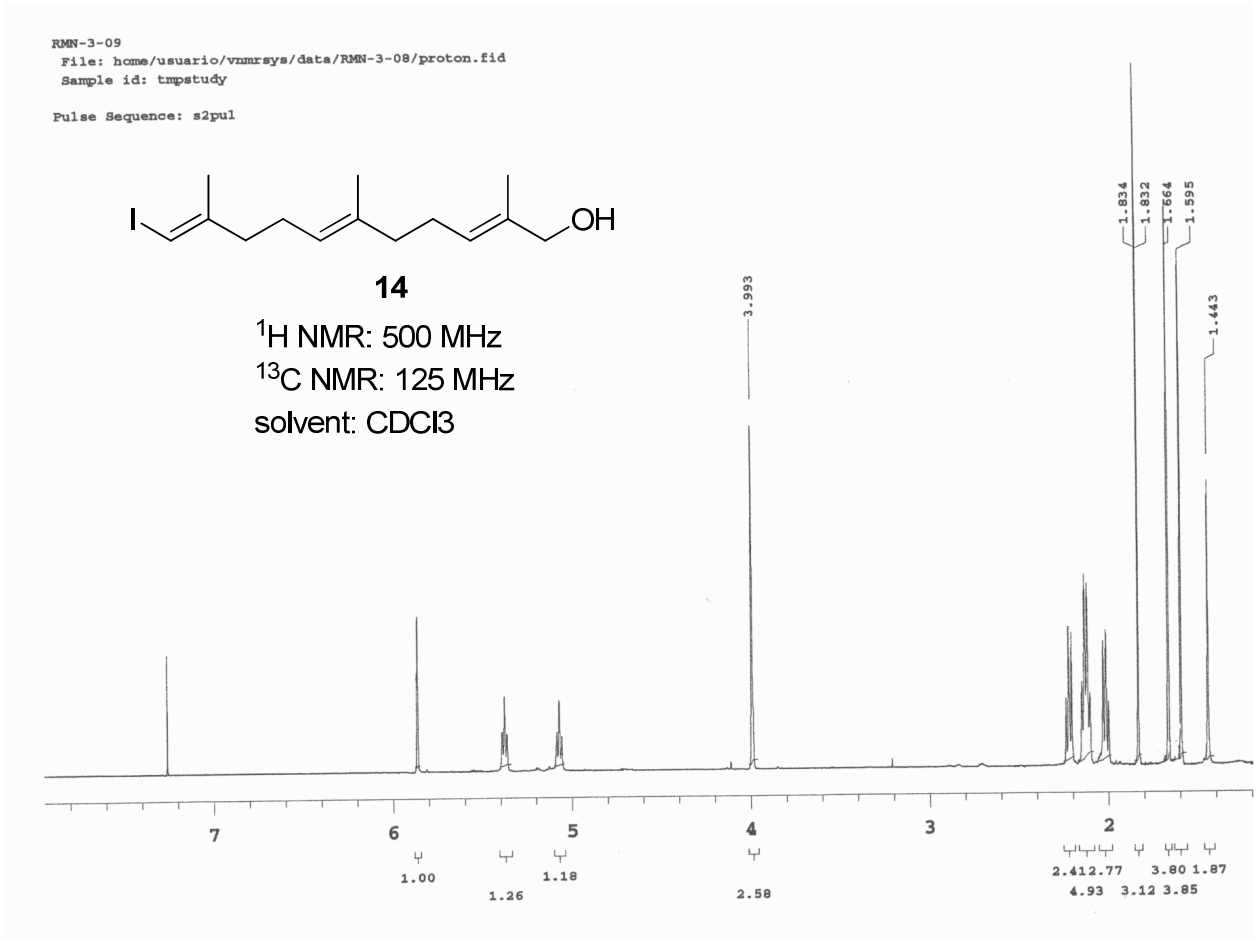

-08
tmpstudy
ce: s2pul
OH
OMEM
TBSO
10
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
3.353
1.298
0.878
0.854
0.781
0.689
0.010
0.007
7
6
5
4
3
2
1
-0
ppm
0.89
0.90
0.95
1.86
1.00
2.77
2.84
0.90
4.64
0.88
4.71
2.70
11.92
0.80

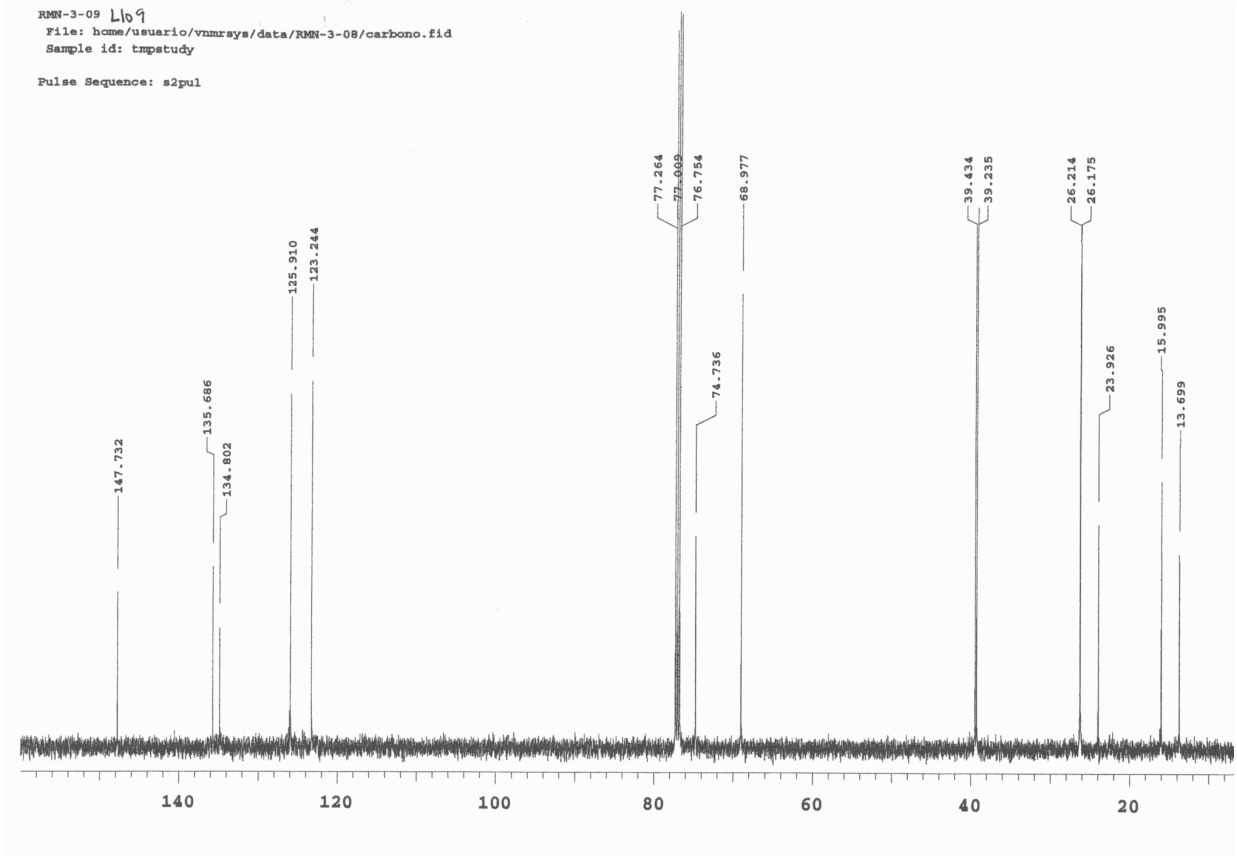

VD-355_29-10-08
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
88.670
81.741
78.973
77.293
77.039
76.786
71.717
67.208
60.497
60.069
58.950
54.724
39.576
39.341
38.214
37.502
28.540
27.546
25.859
21.381
19.786
18.054
16.390
15.502
-3.817
-4.984
90
80
70
60
50
40
30
20
10
0
ppm

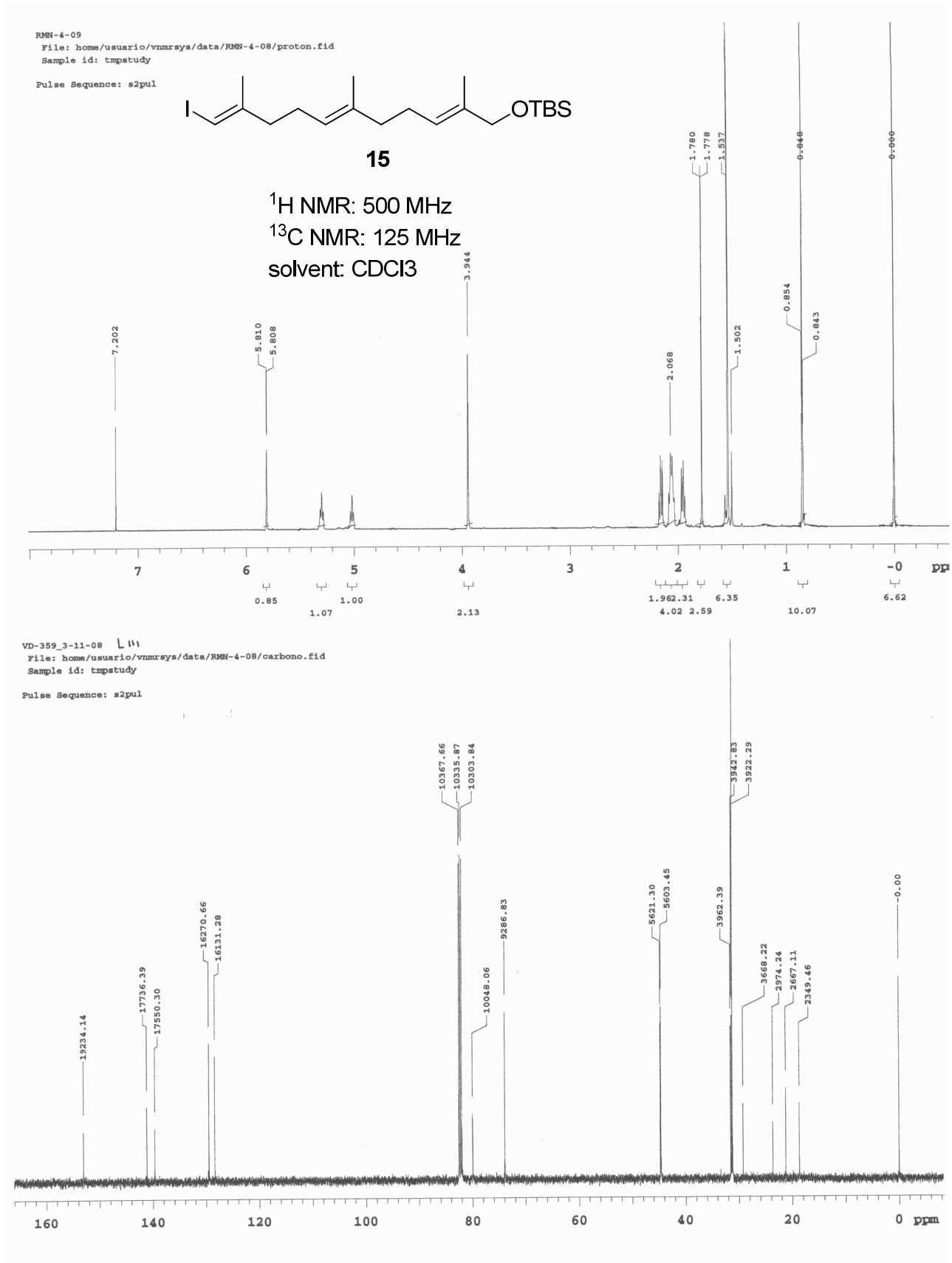

TBSO
OMEM
11
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
0.869
0.018
0.891
0.724
3.363
1.285
ppm
1.00
1.01
1.01
2.01
2.02
2.97
2.04
1.25
0.99
5.37
1.00
4.89
18.81
3.23
6.07
VD-357_29-10-08
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
25.876
21.325
19.926
18.072
16.283
15.962
28.569
27.536
40.425
39.411
38.901
37.053
77.270
77.017
76.762
71.886
66.341
64.364
58.915
54.563
88.970
79.329
78.630
134.815
119.069
-3.809
-4.965
140
120
100
80
60
40
20
0
ppm

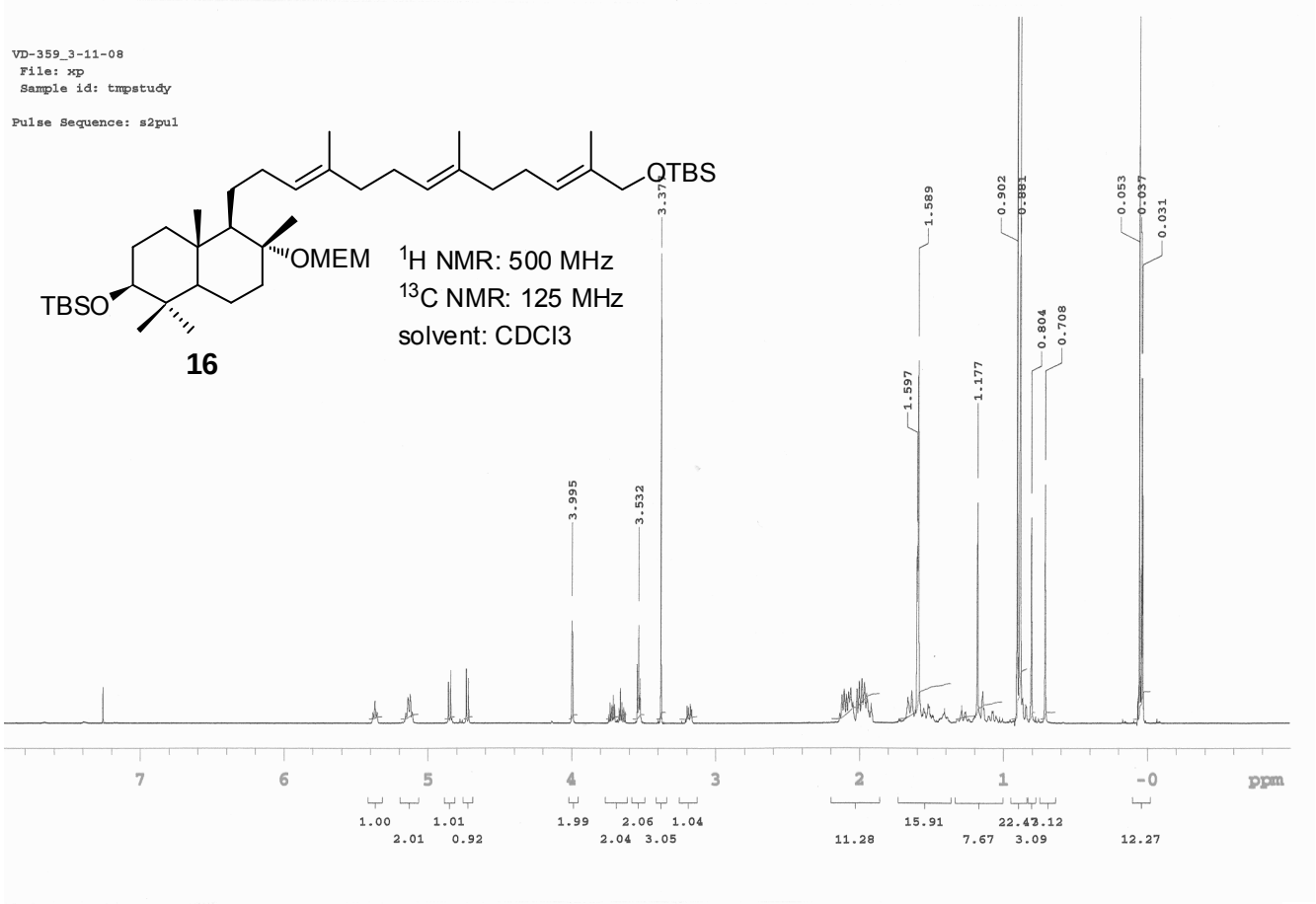

L-105B
File: home/usuario/vnmrsys/data/L-105B_3-11-08/proton.fid
Sample id: tmpstudy
Pulse Sequence: s2pul
OH
13
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
3.974
1.652
1.615
7
6
5
4
3
2
0.99
1.00
2.00
2.02
3.01
5.89
0.93
3.07

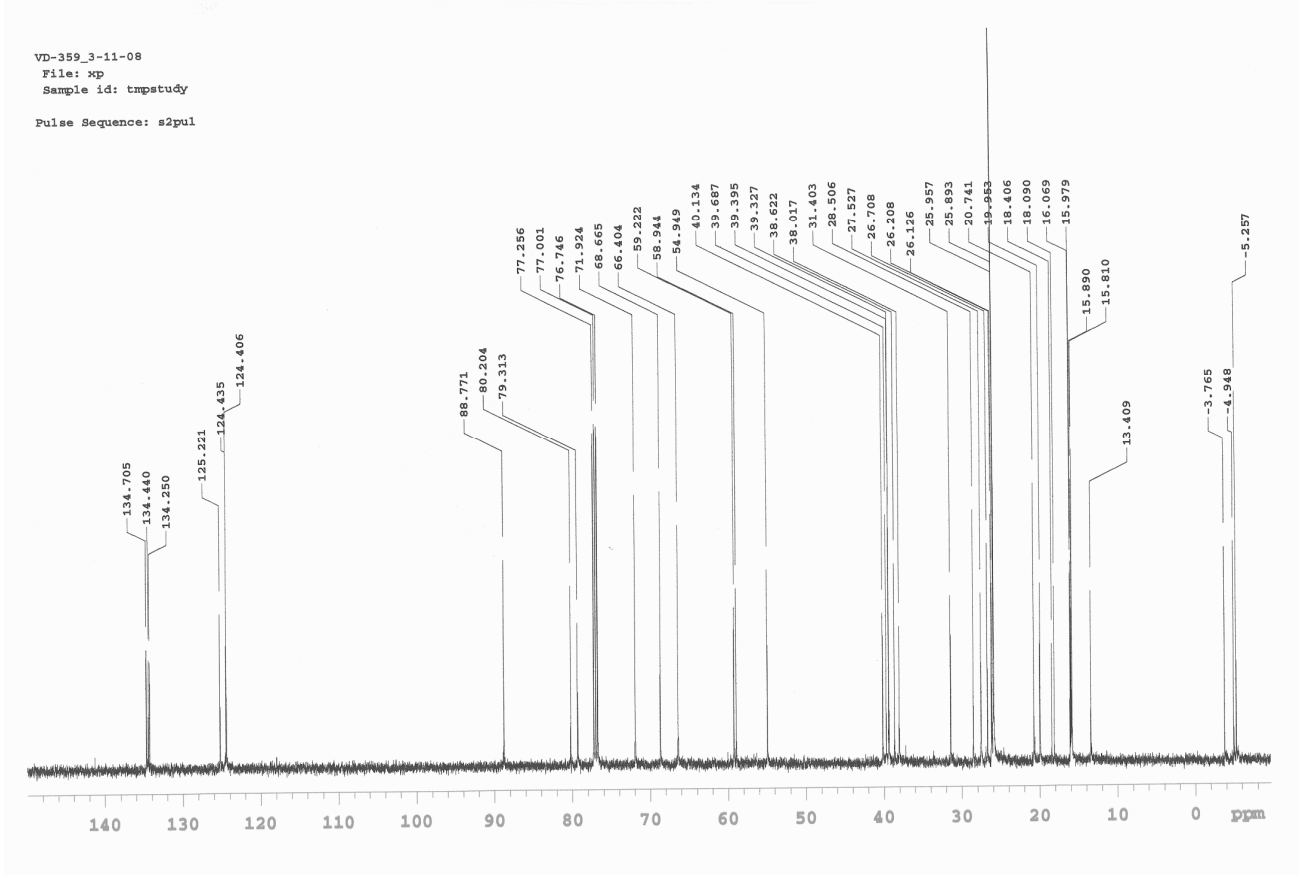

equence: s2pul
136.301
134.816
125.846
122.758
84.525
77.271
77.018
76.764
68.930
68.148
39.175
27.057
26.004
18.873
16.053
13.660
.60
140
120
100
80
60
40
20

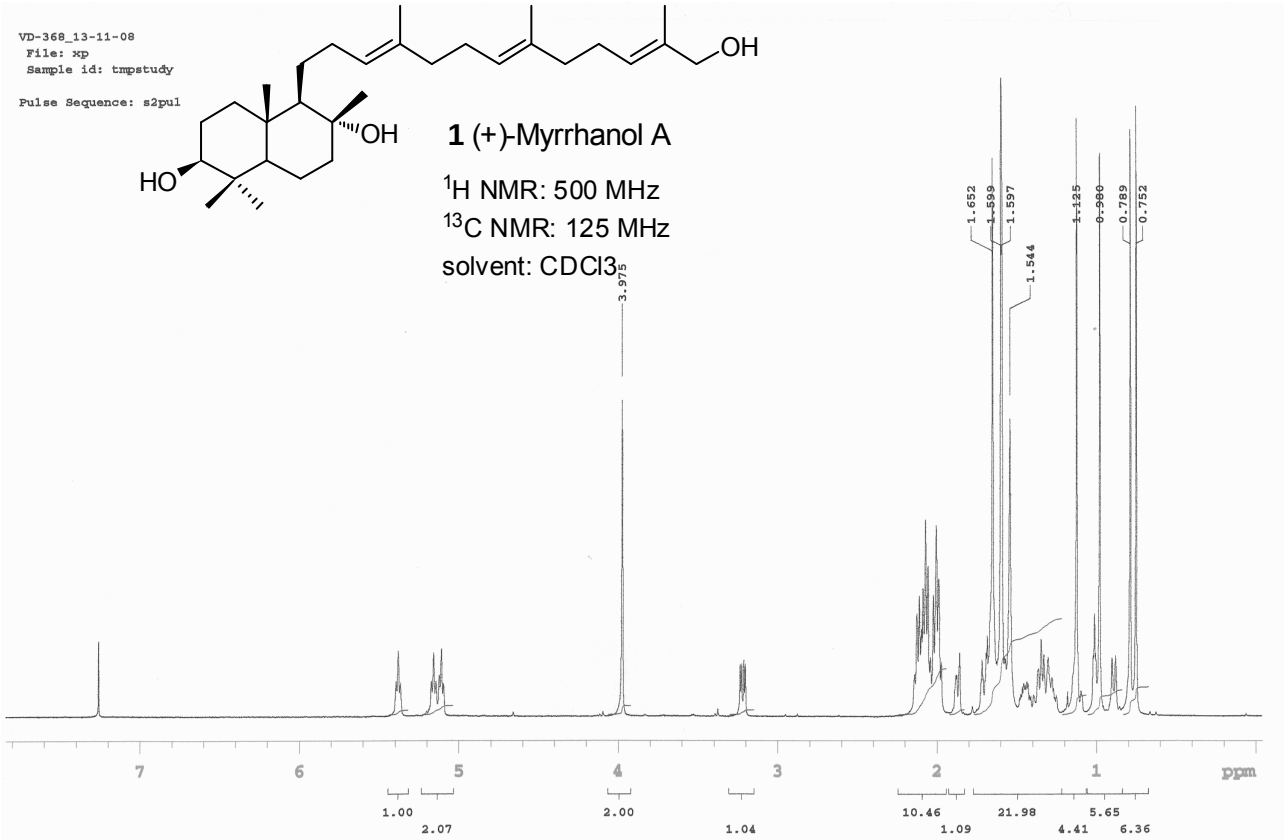

RMN-3-09
File: home/usuario/vnmrsys/data/RMN-3-08/proton.fid
Sample id: tmpstudy
Pulse Sequence: s2pul
I
OH
14
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
1.834
1.832
1.664
1.595
3.993
1.443
7
6
5
4
3
2
1.00
1.26
1.18
2.58
2.41
2.77
3.80
1.87
4.93
3.12
3.85

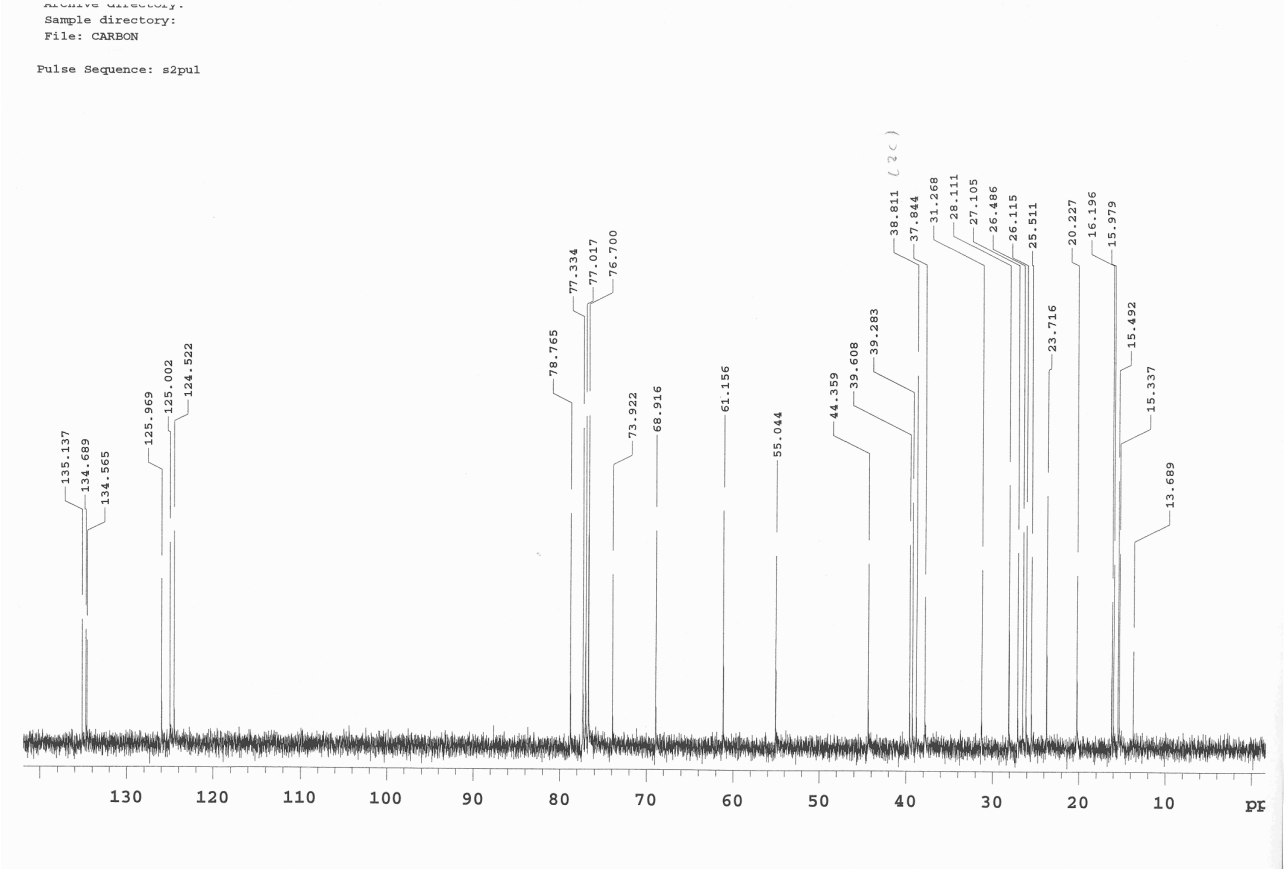

RMN-3-09 LL09
File: home/usuario/vnmrsys/data/RMN-3-08/carbono.fid
Sample id: tmpstudy
Pulse Sequence: s2pul
147.732
135.686
134.802
125.910
123.244
77.264
77.009
76.754
74.736
68.977
39.434
39.235
26.214
26.175
23.926
15.995
13.699
140
120
100
80
60
40
20


RMN-4-09
File: home/usuario/vnmrsys/data/RMN-4-08/proton.fid
Sample id: tmpstudy
Pulse Sequence: s2pul
I
OTBS
15
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
7.202
5.810
5.808
3.944
2.068
1.780
1.778
1.537
1.502
0.854
0.843
0.848
0.000
0.85
1.07
1.00
2.13
1.96
2.31
4.02
2.59
6.35
10.07
6.62
VD-359_3-11-08
File: home/usuario/vnmrsys/data/RMN-4-08/carbono.fid
Sample id: tmpstudy
Pulse Sequence: s2pul
10367.66
10335.87
10303.84
3942.83
3922.29
19234.14
17736.39
17550.30
16270.66
16131.28
10048.06
9286.83
5621.30
5603.45
3962.39
3668.22
2974.24
2667.11
2349.46
-0.00
ppm


VD-359_3-11-08
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
OTBS
OMEM
TBSO
16
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
3.37
1.589
0.902
0.881
0.053
0.037
0.031
0.804
0.708
1.597
1.177
3.995
3.532
7
6
5
4
3
2
1
-0
ppm
1.00
1.01
1.99
2.06
1.04
15.91
3.12
2.01
0.92
2.04
3.05
11.28
7.67
3.09
12.27


VD-359_3-11-08
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
77.256
77.001
76.746
71.924
68.665
66.404
59.222
58.944
54.949
40.134
39.687
39.395
39.327
38.622
38.017
31.403
28.506
27.527
26.708
26.208
26.126
25.957
25.893
20.741
18.406
18.090
16.069
15.979
15.890
15.810
13.409
-3.765
-4.948
-5.257
88.771
80.204
79.313
134.705
134.440
134.250
125.221
124.435
124.406
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


VD-368_13-11-08
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
HO
OH
OH
1 (+)-Myrrhanol A
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
1.652
1.599
1.597
1.544
1.125
0.980
0.789
0.752
3.975
7
6
5
4
3
2
1
ppm
1.00
2.07
2.00
1.04
10.46
1.09
21.98
5.65
4.41
6.36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76.700
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61.156
55.044
44.359
39.608
39.283
38.811
37.844
31.268
28.111
27.105
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26.115
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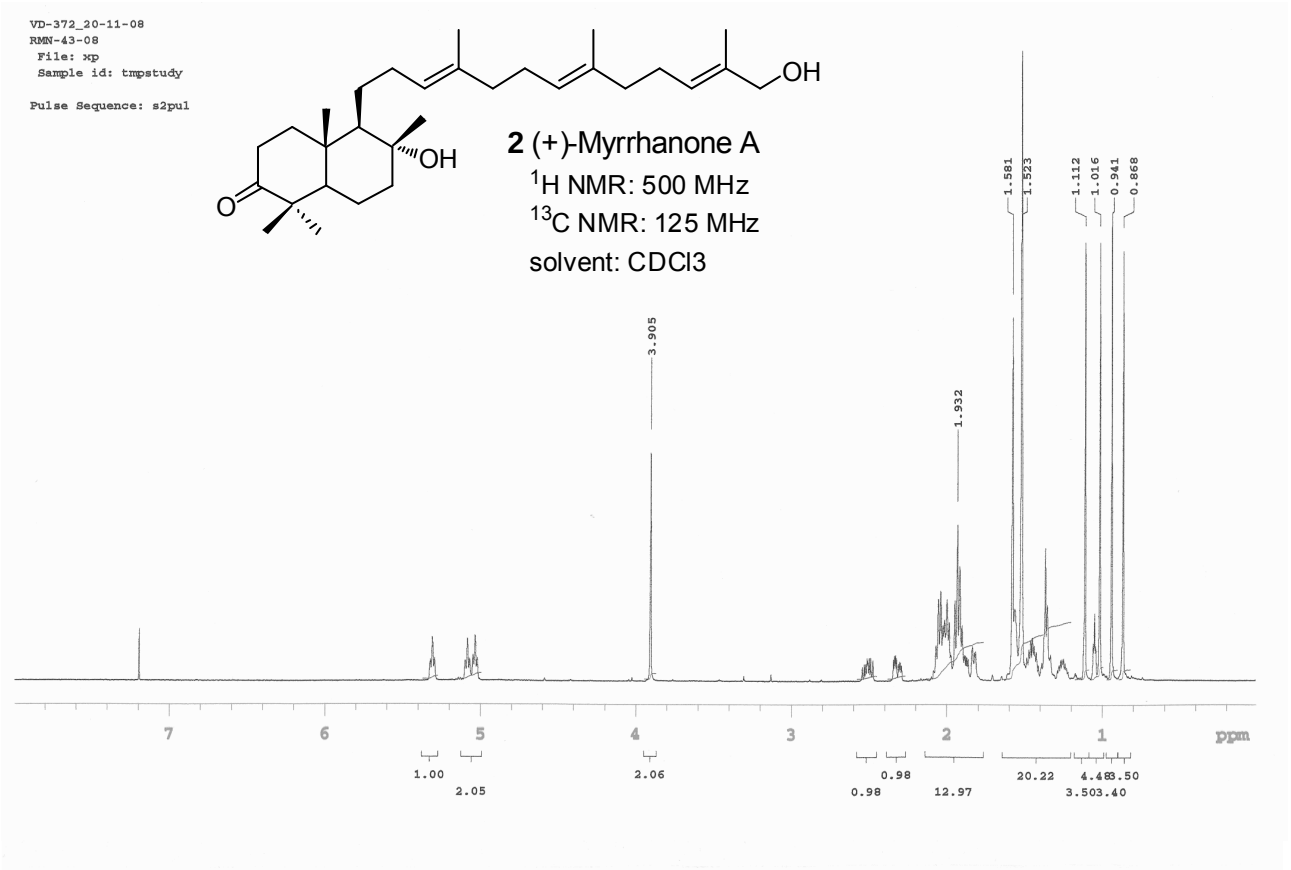
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13C NMR: 125 MHz
solvent: CDCl3
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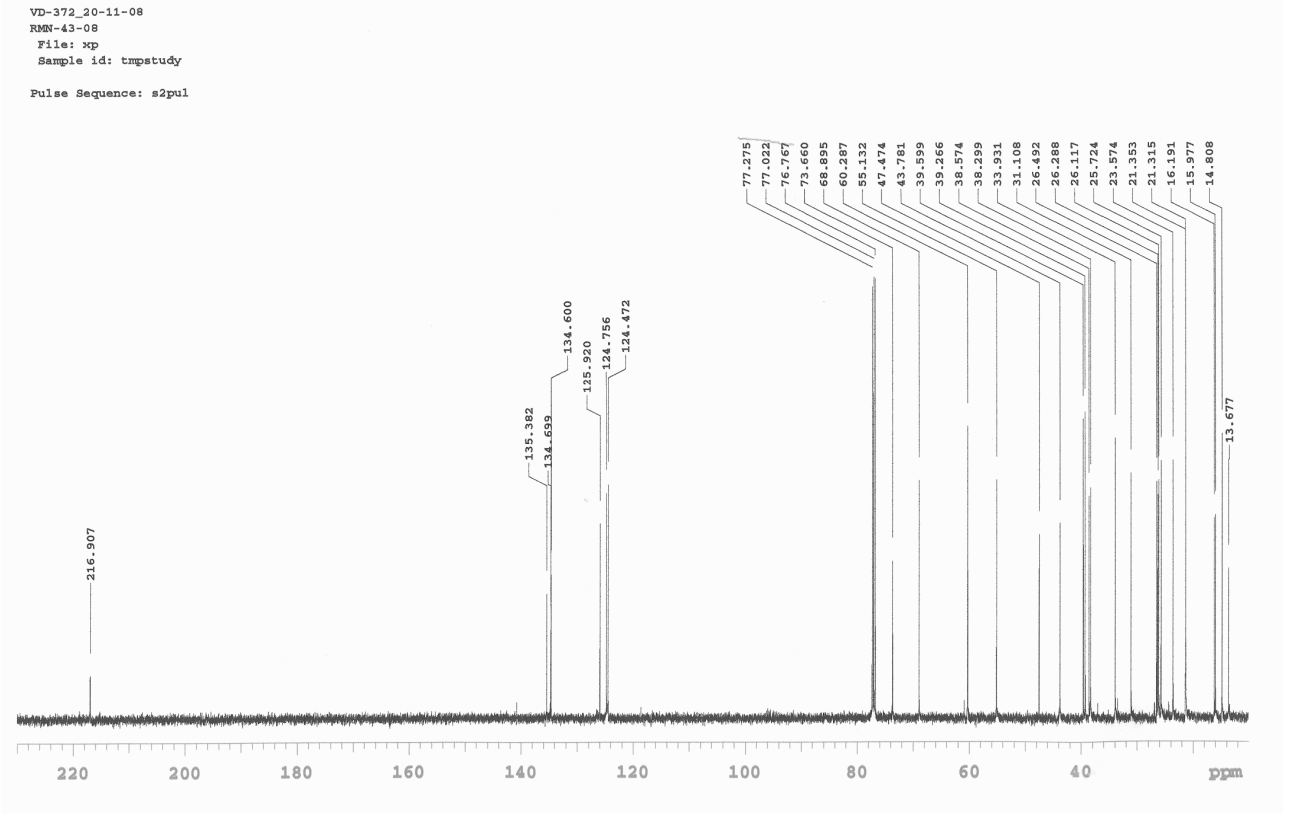
1.523
1.112
1.016
0.941
0.868
3.905
1.932
7
6
5
4
3
2
1
ppm
1.00
2.05
2.06
0.98
0.98
12.97
20.22
3.50
3.40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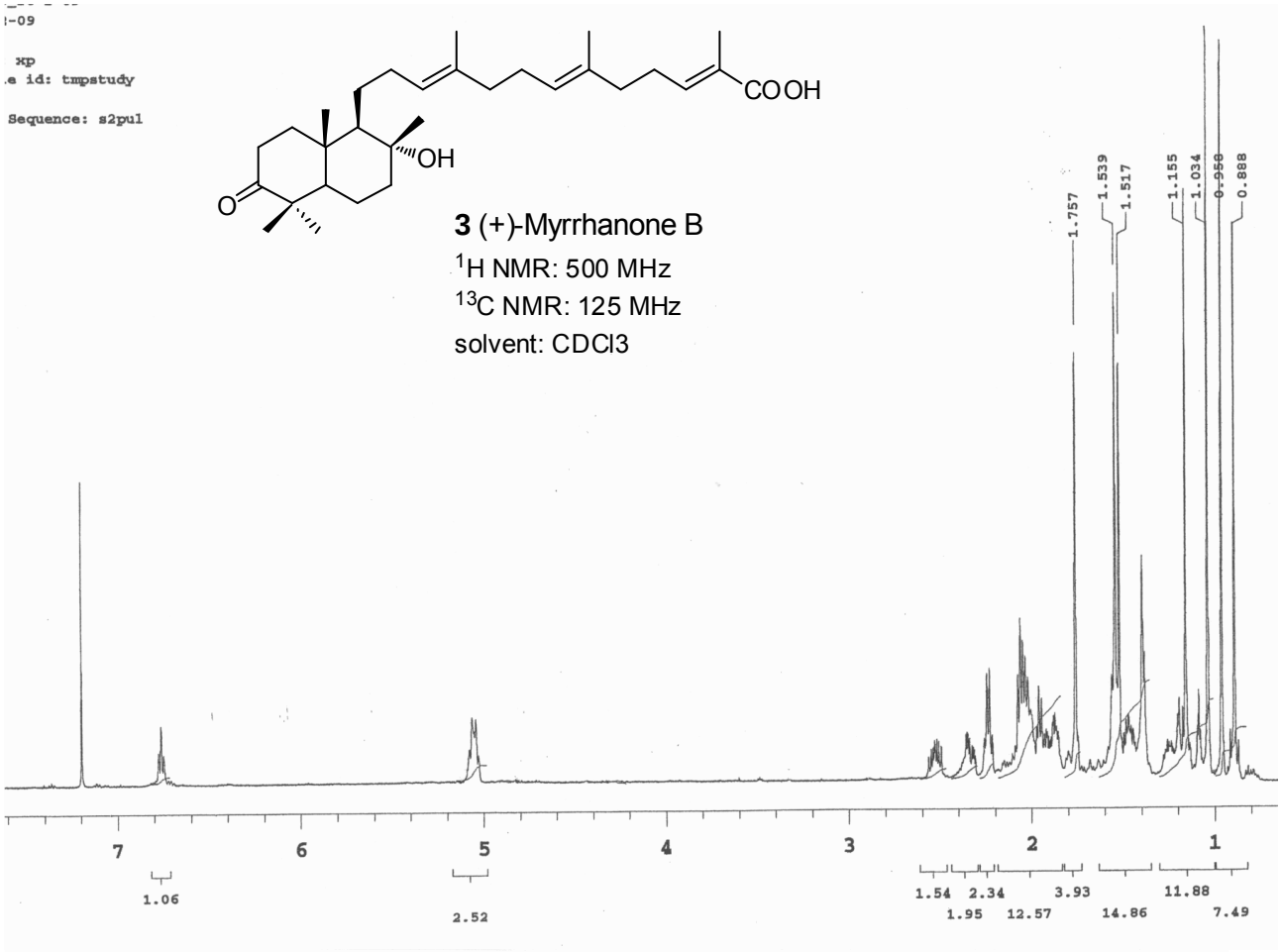
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O
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^{13}C NMR: 125 MHz
solvent: CDCl3
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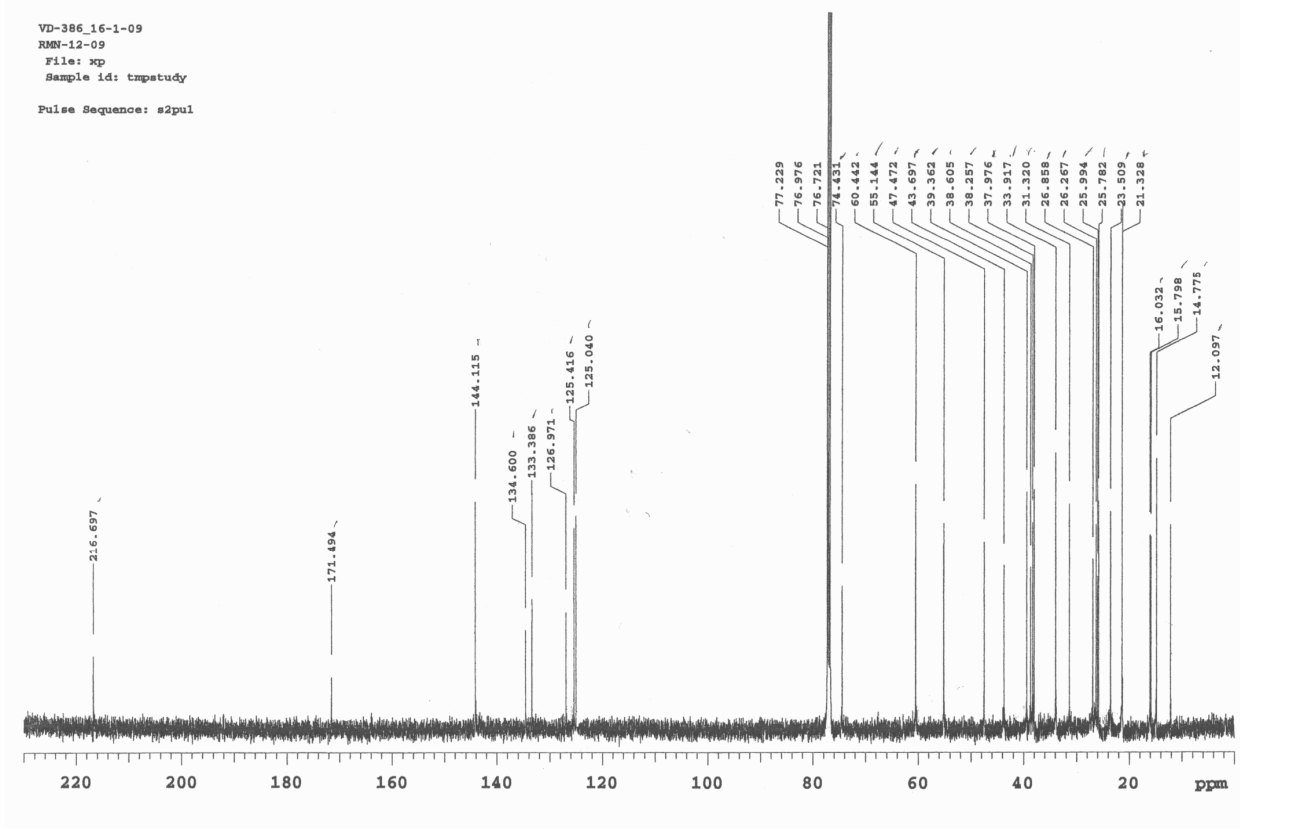
1.517
1.155
1.034
0.950
0.888
1.06
2.52
1.54
2.34
3.93
11.88
1.95
12.57
14.86
7.49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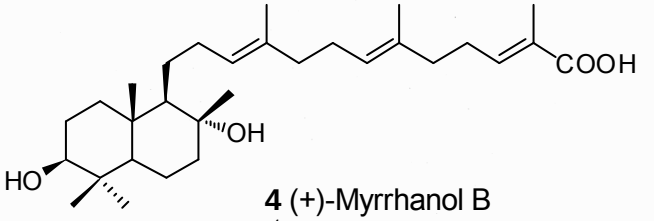
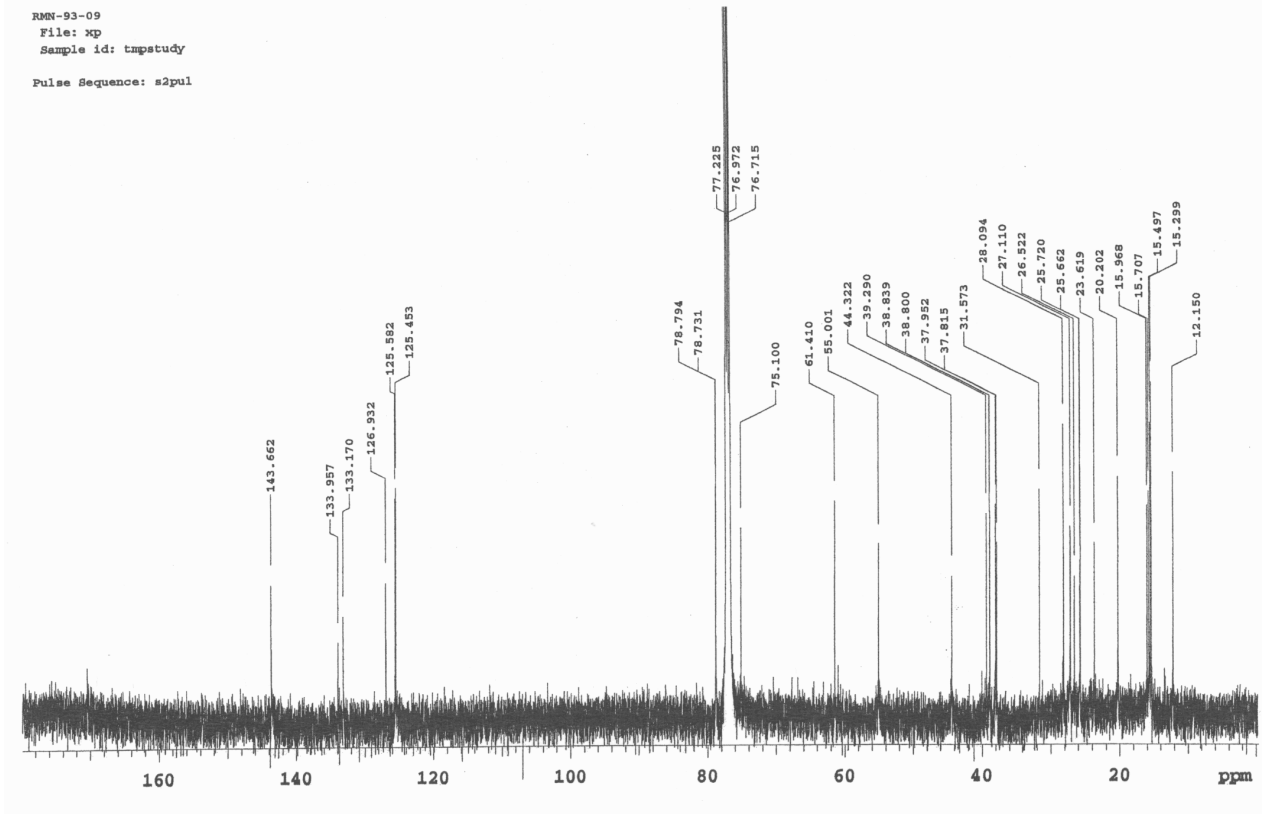
ppm



4 (+)-Myrrhanol B
^{1}H NMR: 500 MHz
^{13}C NMR: 125 MHz
solvent: CDCl3



Supporting Information

First Total Synthesis of Achilleol B: Reassignment of its Relative Stereochemistry

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General Experimental Section:

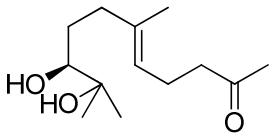
All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an atmosphere of argon. Tetrahydrofuran (THF) was freshly distilled immediately prior to use from sodium/benzophenone and strictly deoxygenated for 30 min under argon for the Cp_2TiCl_2/Mn reaction. 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. Optical rotations were measured on a Perkin-Elmer 141 polarimeter, using $CHCl_3$ as the solvent. IR spectra were recorded with a Mattson model Satellite FTIR instrument as NaCl plates (films). NMR studies were performed with Varian Direct Drive 400 MHz, 500 MHz and Bruker ARX 400 spectrometers. The accurate mass determination was carried out with a AutoSpec-Q mass spectrometer arranged in a EBE geometry (Micromass Instrument, Manchester, UK) and equipped with a FAB (LSIMS) source. The instrument was operated at 8 KV of accelerating voltage and Cs+ were used as primary ions. 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 a solution of phosphomolybdic acid in ethanol and heat as developing agent.

Geranylacetone: Commercially available.

(*R*,*E*)-9,10-dihydroxy-6,10-dimethylundec-5-en-2-one (13).

To a mixture of *tert*-butanol (15 mL) and water (15 mL) was added 2.67 g of AD-mix-β (5.712 mmol $K_3Fe(CN)_6$, 5.712 mmol of K_2CO_3, 0.003 mmol $[K_2OsO_2(OH)_4]$ and 0.02 mmol $(DHQD)_2$-PHAL ligand (hydroquinidine 1,4-phtalazinediyl diether)). The resulting mixture was stirred mechanically at 25 °C, until two clear phases were obtained. Then, $CH_3SO_2NH_2$ (0.181 g, 1.904 mmol) was added and the mixture was cooled to 0 °C. The resulting heterogeneous slurry was stirred vigorously at 0 °C, as geranyl acetone (0.370 g, 1.90 mmol) was added at once. Stirring was continued at 0 °C for 24 h. At this time the oxidation was completed and solid sodium sulphite (2.48

g) was added. The mixture was allowed to warm to room temperature and stirred until two clear phases were obtained. Ethyl acetate (50 mL) and water (15 mL) were added, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with a 2 N aqueous NaOH solution (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. This crude product was purified by flash chromatography (hexane/Et_2O, 1:3) to afford 151 mg of starting material and 173 mg (0.76 mmol) of **13** as a clear colourless viscous oil. $[\alpha]_D^{20}$ = + 4.71º (*c* 1.30, $CHCl_3$); IR (film): $\nu_{máx}$ 3424, 2970, 1709, 1376, 1163, 1078, 760 cm^{-1}; ^1H RMN ($CDCl_3$, 300 MHz): δ 5.00 (1H, t, *J* = 7.0 Hz), 3.19 (1H, d, *J* = 8.3 Hz), 2.39 (2H, m), 2.17 (2H, m), 2.03 (3H, s), 1.98-1.82 (2H, m), 1.55 (3H, s), 1.50-1.40 (2H, m), 1.07 (3H, s), 1.01 (3H, s); ^{13}C RMN ($CDCl_3$, 75 MHz): δ 208.6, 135.6, 123.6, 79.9, 68.4, 43.9, 34.0, 31.0, 27.5, 23.9, 22.5, 23.8, 18.4 ppm; HRFABMS: calcd. for $C_{13}H_{25}O_3$ $[M+H]^+$ 229.1804, found: 229.1805.



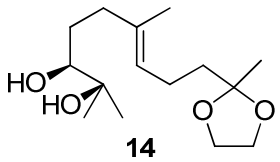
13

(*R*,*E*)-2,6-dimethyl-9-(2-methyl-1,3-dioxolan-2-yl)non-6-ene-2,3-diol (14).

To a solution of **13** (173 mg, 0.76 mmol) in ethylene glycol (4.5 mL), 4Å molecular sieves and *p*TsOH (145 mg, 0.76 mmol) were added. The mixture was stirred at room temperature for 1h. Aqueous sodium carbonate was then added, and the resulting mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.The residue was flash-chromatrographed to afford 137 mg (0.51 mmol) of diol **14**[7] together with 32 mg of starting ketone. Compound **14** was isolated as a colourless oil. $[\alpha]_D^{20}$ = + 1.15º (*c* 1.0, $CHCl_3$); IR (film): $\nu_{máx}$ 3415, 2976, 2928, 1712, 1384, 1251, 1136, 1056, 947, 860 cm^{-1}; ^1H RMN (300 MHz, $CDCl_3$): δ 5.13 (1H, t, *J* = 6.9 Hz), 3.92 (4H, m), 3.28 (1H, d, *J* = 8.3 Hz), 2.22-1.95 (4H, m), 1.63-1.29 (4H, m), 1.58 (3H, s), 1.32 (3H, s), 1.17 (3H, s), 1.14 (3H, s); ^{13}C RMN (75 MHz, $CDCl_3$): δ 135.4, 125.2, 110.4, 78.5, 73.3, 65.0 (2C), 39.4,

[7] Rapoport, H.; Snyder, C.; Bondinell, W. *J. Org. Chem.* **1971**, *36*, 3951-3960.

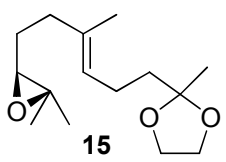
37.1, 30.0, 26.8, 24.1, 23.7, 23.1, 16.2; HRFABMS: calcd. for $C_{15}H_{28}O_4Na$ $[M+Na]^+$ 295.1885, found: 295.2001.



14

2-methyl-2-((*E*)-4-methyl-6-((*R*)-3,3-dimethyloxiran-2-yl)hex-3-enyl)-1,3-dioxolane (15).

To a solution of **14** (111mg, 0.41 mmol) and catalytic DMAP in anhydrous pyridine (5mL) cooled at -12º C under Argon atmosphere, was added dropwise MsCl (0.24 mL, 2.45 mmol). After 40 minutes (TLC monitoring), the mixture was diluted with *t*-BuOMe and treated with sat $NaHCO_3$ solution. After additional 15 minutes stirring at room temperature, the mixture was extracted with Et_2O (3 x 10 mL), the organic layer washed with HCl 1N (1x 10mL), brine and dried over anhydrous Na_2SO_4 and finally concentrated under reduced pressure. The mesylated crude was dissolved 15 mL of methanol and 225 mg of K_2CO_3 were added. After stirring for 10 minutes, the formation of epoxide was complete (TLC monitoring). Then, the reaction was quenched by diluting with H_2O and *t*-BuOMe. The organic layer washed with 1N HCl (2 x 10 mL), sat.$NaHCO_3$ (2 x 10 ml) and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 3:1) to afford 78 mg (74% yield in two steps) of the monoepoxide **15**.[8] $[\alpha]_D^{20}$ = -11.8º (*c* 1.2, $CHCl_3$); IR (film): $\nu_{máx}$ 3726, 3627, 2959, 2928, 2877, 1450, 1376, 1249, 1220, 1124, 1056, 947, 863 cm^{-1}; ^1H RMN (400 MHz, $CDCl_3$): δ 5.17 (1H, t, *J* = 7.0 Hz), 3.95 (4H, m), 2.69 (1H, t, *J* = 6.9 Hz), 2.20-2.03 (4H, m), 1.65-1.53 (4H, m), 1.62 (3H, s), 1.32 (3H, s), 1.29 (3H, s), 1.25 (3H, s); ^{13}C RMN (100 MHz, $CDCl_3$): δ 134.3, 124.6, 109.9, 64.6, 64.2, 58.3, 55.9, 39.0, 36.3, 27.4, 24.9, 23.8, 22.6, 18.7, 15.9; HRFABMS: calcd. for $C_{15}H_{26}O_3Na$ $[M+Na]^+$ 277.1780, found: 277.1788.

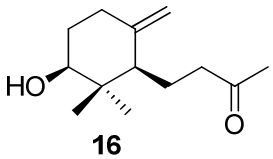


15

[8] Barrero, A. F.; Cuerva, J. M.; Alvarez-Manzaneda, E. J.; Oltra, J. E.; Chahboun, R. *Tetrahedron Lett.* **2002**, *43*, 2793-2796.

(1*S*,3*R*)-2,2-dimethyl-3-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-4-methylenecyclohexanol (16).

A mixture of Cp_2TiCl_2 (62 mg, 0.24 mmol) and Mn dust (532 mg, 9.68 mmol) in strictly deoxygenated THF (7 mL) was stirred at room temperature until the red solution turned green. Then, a solution of the oxirane **15** (305mg, 1.20 mmol), 2,4,6-collidine (1.1 mL, 8.33 mmol), and TMSCl (0.6 mL, 4.76 mmol) in strictly deoxygenated THF (3 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred for 2 h, and then quenched with 2 N aq HCl. The aqueous layer was then extracted with *t*-BuOMe. The combined organic layers were washed with brine dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The mixture was purified by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to afford 196 mg (77%) of the corresponding monocyclic alcohol. A suspension of this alcohol (100 mg, 0.39 mmol) and $NaI\cdot 2H_2O$ (372 mg, 2.0 mmol) in acetonitrile (30 mL) was added $CeCl_3\cdot 7H_2O$ (560 mg, 1.5 mmol), and the resulting mixture was stirred for 15 h at room temperature. The reaction mixture was diluted with ether and washed with H_2O (2 x 40ml). The organic layer was separated, and the aqueous layer was extracted with ether (1x 40 mL). The combined organic layers were washed once with saturated brine solution and dried over anhydrous sodium sulfate. The extracts were then concentrated under reduced pressure and the the residue was purified through flash chromatography to give 78 mg (95%) of the corresponding hydroxy ketone **16**[9] as a colourless oil. $[\alpha]_D$= -13.9º (*c* 1.0, CH_2Cl_2); ^{1}H RMN (400 MHz, $CDCl_3$) δ: 4.84 (1H, s), 4.5 (1H, s), 3.38 (1H,dd, *J* = 4.1, 8.9 Hz), 2.51 (1H, ddd, *J* = 5.0, 9.1, 14.3 Hz), 2.35-2.23 (2H, m), 2.08 (3H, s), 2.00-1.4 (6H, m), 1.01 (3H, s), 0.74 (3H, s).^{13}C RMN (100 MHz, $CDCl_3$) δ: 209.3, 147.2, 108.8, 76.9, 52.0, 43.0, 40.6, 32.2, 32.0, 26.1, 19.7, 16.2.



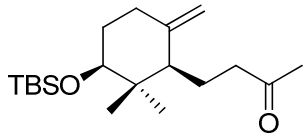
16

4-((1*R*,3*S*)-3-tert-butildimetilsililoxy-2,2-dimethyl-6-methylenecyclohexyl)butan-2-one (17).

To a stirred solution of **16** (230 mg, 1.13 mmol) in DMF (13 mL), imidazole (335 mg, 4.9 mmol) and TBSCl (742 mg, 4.9 mmol) were added at room temperature. After stirring for 16 h (TLC

[9] Tsangarakis, C.; Arkoudis, E.; Raptis, C.; Stratakis, M. *Org. Lett.* **2007**, *9*, 583-586.

monitoring), the mixture was diluted with *t*BuOMe and water and extracted with *t*BuOMe. The combined organic layer was washed with 2N HCl, brine, dried over anhydrous Na_2 SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 95:5) on silica gel to afford 336 mg (91%) of the corresponding silylated derivative **17**. $[\alpha]_D$= +11.3º (*c* 1.0, CH_2Cl_2); ^{1}H RMN (400 MHz, $CDCl_3$), δ: 4.80 (1H), 4.48 (1H), 3.38 (1H, dd, *J* = 3.6, 7.1 Hz), 2.44 (1H, ddd, *J* = 17.1, 7.4, 7.1 Hz), 2.3 (1H, m), 2.21 (1H, ddd, *J* = 17.1, 8.1, 4.6 Hz), 2.08 (3H, s), 1.96 (1H, m), 1.84 (1H, m), 1.65 (1H, m), 1.6 (1H, m), 1.51 (2H, m), 0.91 (3H, s), 0.88 (9H, s), 0.81 (3H, s), 0.02 (6H, s); ^{13}C RMN (100 MHz, $CDCl_3$) δ: 209.7, 148.1, 109.1, 76.9, 52.4, 43.2, 40.4, 32.0, 29.8, 29.9, 27.1, 25.9, 25.8, 21.0, 18.0, -4.9.

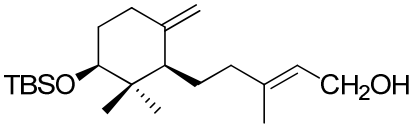


17

(1*S*,3*R*)-1-*tert*-butildimetilsililoxy -3-((*E*)-5-hydroxy-3-methylpent-3-enyl)-2,2-dimethyl-4-methylenecyclohexanol (18).

To a suspension of NaH (7 mg, 0.266 mmol) in THF (1 mL) cooled at 0ºC, triethylphosphonoacetate (0.05 ml, 0.266 mmol) was added dropwise under inert atmosphere. After stirring for 5 min, ketone **17** (43 mg, 0.133 mmol) in anhydrous THF (0.5 mL) was added. The solution was stirred for 24h and then diluted with ether, washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. To an ice cooled solution of the Horner-Wadsworth-Emmons adduct **18** in toluene (15 mL) DIBALH (1M solution in hexanes, 1 mL, 1 mmol) was added. The mixture was stirred for 10 min. After usual work-up, the residue was purified by column chromatography to give 35 mg (74% two steps) of **18**. $[\alpha]_D$= -5.5º (*c* 1, $CHCl_3$); IR (film): $\nu_{máx}$ 3560, 2960, 2925, 2856, 1645, 1097, 1022, 804 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.38 (1H, t, *J* = 6.9 Hz), 4.80 (1H, s), 4.54 (1H, s), 4.12 (2H, d, *J* = 6.9 Hz), 3.37 (1H, dd, *J* = 7.2, 3.6 Hz), 2.34 (1H, ddd, *J* = 12.3, 7.5, 4.7 Hz), 1.90 (1H, ddd, *J* = 12.9, 8.3, 4.3 Hz), 1.80-1.45 (7H, m), 1.65 (3H, s),0.91 (3H, s), 0.87 (9H, s), 0.78 (3H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR ($CDCl_3$, 100

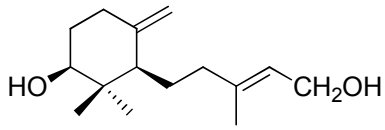
MHz): δ 148.3, 141.8, 123.0, 108.7, 77.1, 59.4, 52.4, 40.5, 38.9, 32.2, 29.5, 27.1, 26.0, 25.9, 24.9, 24.8, 24.1, 18.2, 16.4; -4.1, -4.9; HRFABMS: calcd. for $C_{21}H_{40}O_2SiNa$ $[M+Na]^+$ 375.2695, found 375.2701.



18

(-)-Elegansidiol (11):

To a magnetically stirred solution **18** (40 mg, 0.11 mmol) was added tetrabutylammonium fluoride (1 M solution in THF, 0.32 mL, 0.32 mmol) at room temperature. The reaction was stirred at 60 °C for 1h. After dilution with EtOAc, the mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting was flash-chromatographed to afford 24 mg (89%)of **(-)-elegansidiol**.[10] $[\alpha]_D$= -3.2º (*c* 0.9, $CHCl_3$); IR (film): $\nu_{máx}$ 3384, 2930, 2852, 1717, 1645, 1449, 1379, 1261, 1183, 1082, 1023, 890 cm^{-1}; EIMS m/z 238 $[M^+]$,(1), 220 (8), 205 (35), 187 (27), 175 (24), 159 (18), 134 (27),119 (45), 107 (62), 96 (100), 81 (64), 67 (44), 55 (54), 43(85), 41 (83); ^1H NMR (500 MHz, $CDCl_3$): δ 5.40 (1H, tq, *J* = 6.9 Hz), 4.88 (1H, bs, 1H), 4.60 (1H, bs), 4.15 (2H, d, *J* = 6.9 Hz), 3.42 (1H, dd, *J* = 9.6, 4.2 Hz), 2.33 (1H, dt, *J* = 13.1, 4.4 Hz), 2.13 (1H, m), 1.99 (1H, dt, *J* = 12.1, 4.8 Hz), 1.88-1.79 (2H, m), 1.70-1.44 (5H, m), 1.68 (3H, s), 1.03 (3H, s), 0.73 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.1, 140.1, 123.1, 108.3, 77.2, 59.3, 51.2, 40.4, 38.7, 32.7, 32.0, 26.0, 23.8, 16.2, 15.7; HRFABMS: calcd. for $C_{15}H_{27}O_2$ $[M+H]^+$ 239.2011, found 239.2014.

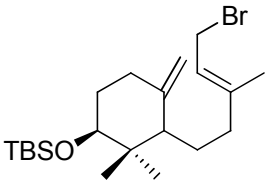


11

[10] Barrero, A.; Alvarez-Manzaneda, E.; MarHerrador, M.; Alvarez-Manzaneda, R.; Quilez, J.; Chahboun, R.; Linares, P.; Rivas, A. *Tetrahedron Lett.* **1999**, *40*, 8273-8276.

((1*S*,3R)-3-((*E*)-5-bromo-3-methylpent-3-enyl)-2,2-dimethyl-4-methylenecyclohexyloxy)(*tert*-butyl)dimethylsilane (19).

To a solution of **15** (35 mg, 0.1 mmol) in dry Et_2O (1.5 mL) cooled at 0ºC was added of PBr_3 (4 μL, 0.04 mmol). The resulting solution was stirred at 0ºC for 10 min, and then diluted with Et_2O and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting bromide **20** (39 mg) was used in the next reaction without purification.

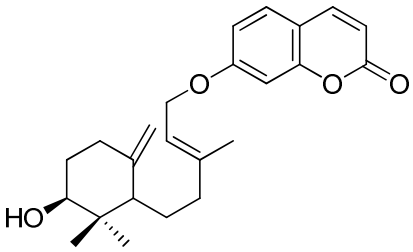


19

(+)-Farnesirerol B (12):

Bromide **19** (72 mg, 0.175 mmoles) alkylated the potassium salt of 7-hydroxycoumarin, which was prepared in situ from 7-hydroxycoumarin (57 mg, 0.35 mmoles) and K_2CO_3 (73 mg, 0.525 mmoles) in dry acetone (2 mL). The reaction was complete after 12 h at room temperature. The mixture was then concentrated under reduced pressure, extracted with *t*-BuOMe and washed with brine. Purification of the resulting crude by flash chromatography (hexane/ *t*-BuOMe, 3:1) afforded 73 mg of the silyl derivative of farnesiferol B **12a**. To a solution of the resulting crude in 4 mL of THF was added tetrabutylammonium fluoride (0.60 mL) at room temperature. The reaction was stirred at 60 °C for 1h. After dilution with EtOAc, the mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/ *t*-BuOMe, 1:1) to afford 43 mg (78%) of **(+)-farnesiferol B**. $[\alpha]_D$= +8.5 (*c* 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (1H, d, *J* = 9.5 Hz), 7.35 (1H, d, *J* = 8.5 Hz), 6.85 (1H, dd, *J* = 8.5, 2.4 Hz), 6.82 (1H, d, *J* = 2.4 Hz), 6.25 (1H, d, *J* = 9.5 Hz), 5.45 (1H, t, *J* = 7.0 Hz), 4.88 (1H, s), 4. 61 (2H, d, *J* = 7.0 Hz), 4.59 (1H, s), 3.39 (1H, dd, *J* = 9.5 Hz, 4.0 Hz), 2.33 (1H, td, *J* = 13.0, 5.0 Hz), 2.19 (1H, m), 1.82-1.96 (3H, m), 1.76 (3H, s), 1.46-1.72 (4H, m), 1.02 (3H, s), 0.74 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 161.3, 155.9, 147.1, 143.5, 142.8, 128.7, 118.4,

113.4, 113.0, 112.4, 108.6, 101.6, 77.1, 65.5, 51.0, 40.5, 38.4, 32.7, 32.1, 26.0, 23.4, 16.8, 15.9. HRFABMS: calcd. for $C_{24}H_{31}O_4$ $[M+H]^+$ 383.2222; found 383.2220.

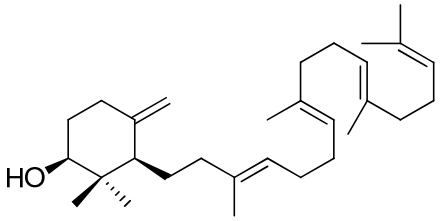


12

(-)-Achilleol A (2):

To a solution of farnesylphenylsulphone **20** (180 mg, 0.52 mmol) in THF (7 mL) was added *n*-butyllithium (2.5 M solution in hexane, 0.2 mL, 0.5 mmol) at -78ºC. The resulting yellow mixture was stirred for 10 min and a solution of bromide **19** (53 mg, 0.13 mmol) in THF (7 mL) was added dropwise. The mixture was allowed to warm for 4 h, and then diluted with *t*-BuOMe and quenched with water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (hexane: *t*-BuOMe, 10:1) afforded the epimeric mixture of sulphones **21** (64 mg, 78%). To a solution of Li (19 mg) in $EtNH_2$ (0.6 mL) was added at –78 ºC a solution of **21** (13 mg, 0.02 mmol) in THF (1 mL). The mixture was stirred for 30 min. MeOH and saturated NH_4Cl was then added, and the mixture was further stirred for 10 min. The aqueous layer was extracted with *t*-BuOMe (2 x 5 ml), and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in a vacuum. Purification by flash chromatography (hexane: *t*-BuOMe, 6:1) afforded 9 mg (83%) of the silylated derivative of achilleol A **2a**. To a solution of the silyl derivative **2a** (16 mg, 0.03 mmol) in THF (1 mL) was added tetrabutylammonium fluoride (1M solution in THF, 0.18 mL, 0.18 mmol) at room temperature. The reaction was stirred at 60 °C for 24 h. After dilution with EtOAc, the mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1) to afford 12 mg (94%) of **(-)-achilleol A (2)**. $[\alpha]_D$= -6.9º (c 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)= δ 5.15-5.05 (4H, m), 4.86 (1H, bs), 4.59 (1H, bs), 3.39 (1H, dd, *J* = 9.9, 4.3 Hz), 2.31 (1H, dt, *J* = 13.1, 4.7 Hz), 2.10-1.95

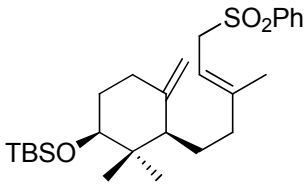
(14H, m), 1.88-1.76 (2H, m), 1.70-1.46 (4H, m), 1.66 (3H, s), 1.59 (12H, s), 1.01 (3H, s), 0.70 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$; DEPT) δ 147.3, 135.5, 135.2, 135.0, 131.3, 124.5,124.5, 124.4, 124.4, 108.5, 77.4, 51.0, 40.6, 39.9, 39.8, 38.7, 33.3, 32.3, 28.4, 28.3, 26.9, 26.8, 26.0, 25.8, 23.8, 17.8, 16.2, 16.1, 16.1, 15.6.



2

((1*S*)-2,2-dimethyl-3-((*E*)-3-methyl-5-(phenylsulfonyl)pent-3-enyl)-4-methylenecyclohexyloxy) (tert-butyl) dimethylsilane (22):

To a stirred solution of **19** (210 mg, 0.5 mmol) in dry DMF (5 mL) was added at 0ºC phenylsulfinate sodium (123 mg, 0.75 mmol). After stirring for 3h the reaction was diluted with *t*-BuOMe, washed with HCl 2 N (2 x 5 ml), brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel 3:1 (hexane/*t*-BuOMe) to afford 171 mg (72 %) of the corresponding sulfone **22**. IR (film): $\nu_{máx}$ 2951, 2935, 2856, 1646, 1472, 1447, 1387, 1317, 1253, 1151, 1086, 888, 835, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (2H, bd, *J* = 7.4 Hz), 7.62 (1H, bt, *J* = 7.4 Hz), 7.52 (2H, bt, *J* = 7.4 Hz), 5.15 (1H, dt, *J* = 6.9, 1.0 Hz), 4.80 (1H, s), 4.50 (1H, s), 3.80 (2H, d, *J* = 7.9 Hz), 3.37 (1H, dd, *J* = 7.3, 3.6 Hz), 2.30 (1H, ddd, *J* = 12.9, 8.0, 4.6 Hz), 2.05-1.97 (1H, m), 1.91 (1H, ddd, *J* = 12.9, 8.3, 4.7 Hz), 1.80-1.47 (6H, m), 1.31 (3H, s), 0.91 (3H, s), 0.88 (9H, s), 0.77 (3H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.3, 141.8, 123.0, 108.7, 77.1, 59.4, 52.4, 40.5, 38.9, 32.2, 29.5, 27.1, 26.0, 25.9, 24.9, 24.8, 24.1, 18.2, 16.4; HRFABMS: calcd. for $C_{27}H_{44}O_3SSiNa$ $[M+Na]^+$ 499.2678, found 499.2686.



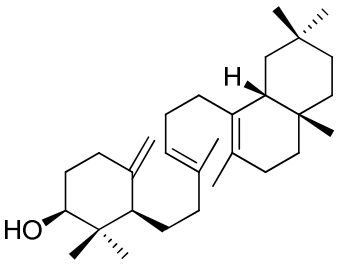
22

(-)-Achilleol B

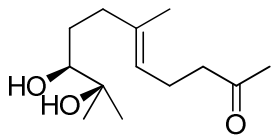
To a solution of **23** (162 mg, 0.33 mmol), in THF (2 mL) was added *n*-butyllithium (2 M solution in hexane, 0.16 mL, 0.32 mmol) at -78ºC. The resulting yellow mixture was stirred for 10 min and a solution of **21** (31 mg, 0.11 mmol) of bromide **23**[11] in THF (5 mL) was added dropwise. The mixture was allowed to warm for 2 h. The mixture was then diluted with *t*-BuOMe and quenched with water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (hexane: *t*-BuOMe, 10:1) afforded the epimeric mixture of sulphones **24** (53 mg, 71 %). To a solution of Li (32 mg) in $EtNH_2$ (4 mL) was added at –78 ºC a solution of **24** (22 mg, 0.032 mmol) in THF (2 mL). The mixture was stirred for 30 min. MeOH and saturated NH_4Cl was then added, and the mixture was further stirred for 10 min. The aqueous layer was extracted with *t*-BuOMe (2 x 10 ml), and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in a vacuum. Purification by flash chromatography (hexane: *t*-BuOMe, 10:1) afforded 15 mg (87%) of the silylated derivative of (-)-achilleol B. To a solution of the silyl derivative of achilleol B (26 mg, 0.05 mmol) in THF (1 mL) was added tetrabutylammonium fluoride (1M solution in THF, 0.15 mL, 0.15 mmol) at room temperature. The reaction was stirred at 60 °C for 12 h. After dilution with EtOAc, the mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 8 mg of starting material and 16 mg (98 %) of **(-)-achilleol B**. $[\alpha]_D$= -10.9º (c 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)= δ 5.12 (1H, t, *J* = 7.0 Hz), 4.88 (1H, bs), 4.62 (1H, bs), 3.40 (1H, dd, *J* = 10.0, 4.5 Hz), 2.32 (1H, dt, *J* = 13.2, 4.5 Hz), 2.21 (1H, ddd, *J* = 13.1, 10.0, 6.6 Hz), 2.08 (1H, ddd, *J* = 13.2, 10.3, 3.8 Hz), 2.02-1.82 (7H, m), 1.80-1.44 (8H, m), 1.61 (3H, s), 1.58 (3H, s), 1.39 (1H, ddd,

[11] Barrero, A. F.; Arseniyadis, S.; Quilez del Moral, J. F.; Herrador, M. M.; Rosellón, A. *Synlett* **2005**, 789-792.

J = 13.0, 3.7, 2.6 Hz), 1.35 (1H, dd, *J* = 13.8, 3.9 Hz), 1.23 (1H, dt, *J* = 13.3, 3.5 Hz), 1.12 (1H, m), 1.04 (3H, s), 0.97 (1H, t, *J* = 13.0 Hz), 0.90 (3H, s), 0.88 (3H, s), 0.82 (3H, s), 0.82 (1H, m), 0.72 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 135.2, 133.8, 124.8, 124.1, 108.6, 77.5, 51.3, 43.2, 42.5, 40.8, 38.9, 36.8, 34.8, 33.4, 33.3, 32.4, 31.9, 31.6, 31.2, 29.7, 27.4, 27.2, 26.7, 26.1, 24.4, 24.0, 18.9, 16.2, 15.7.

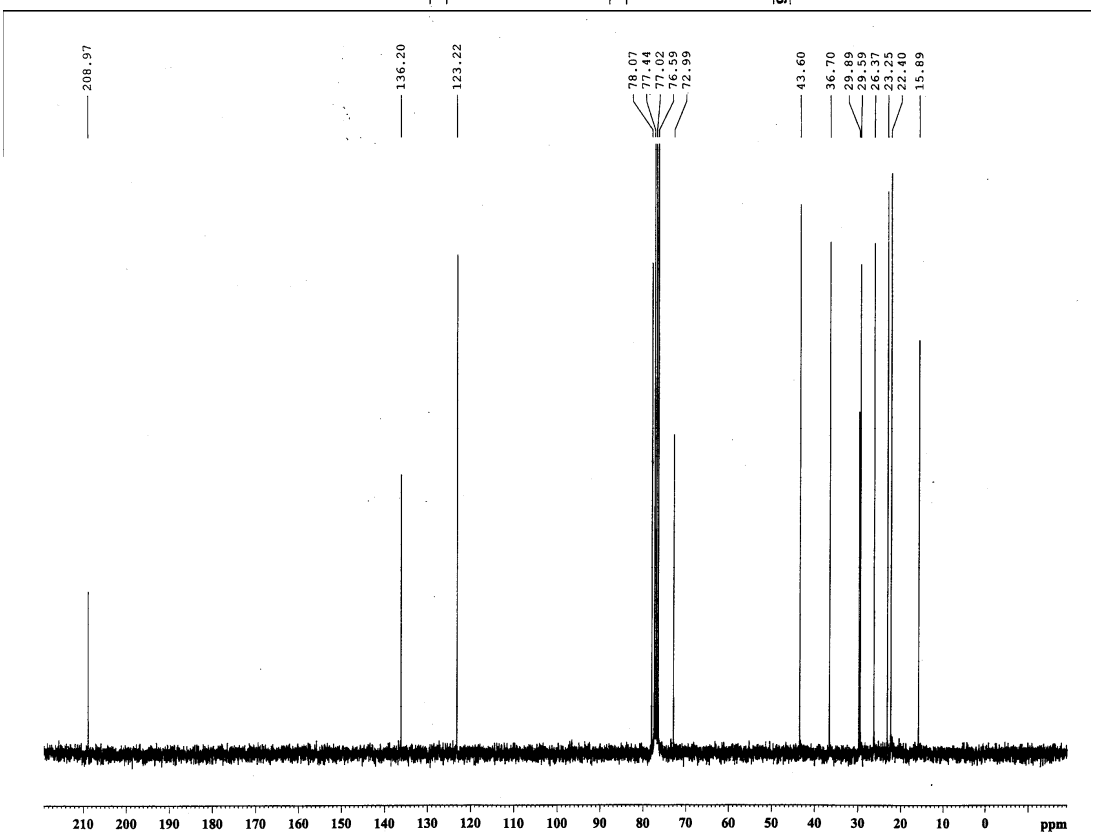


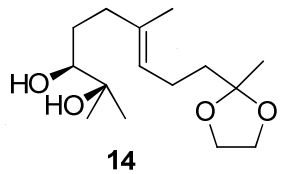
reassigned achilleol B



13

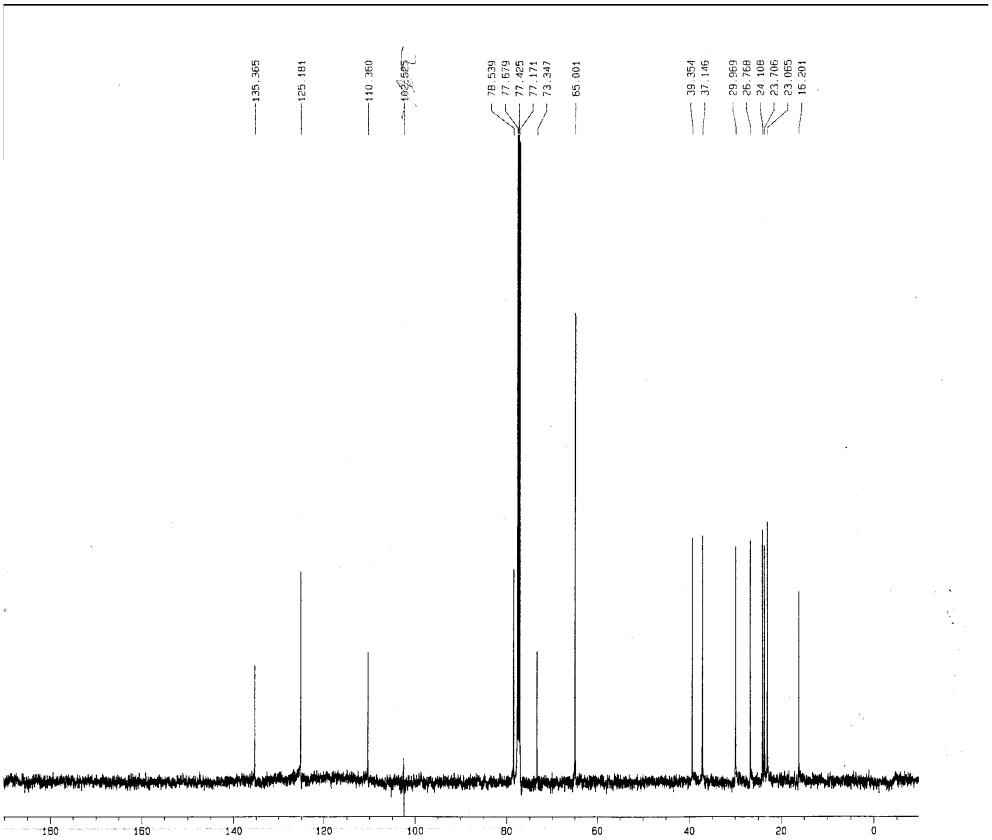
^{1}H NMR: 300 MHz
^{13}C NMR: 75 MHz
solvent: $CDCl_3$

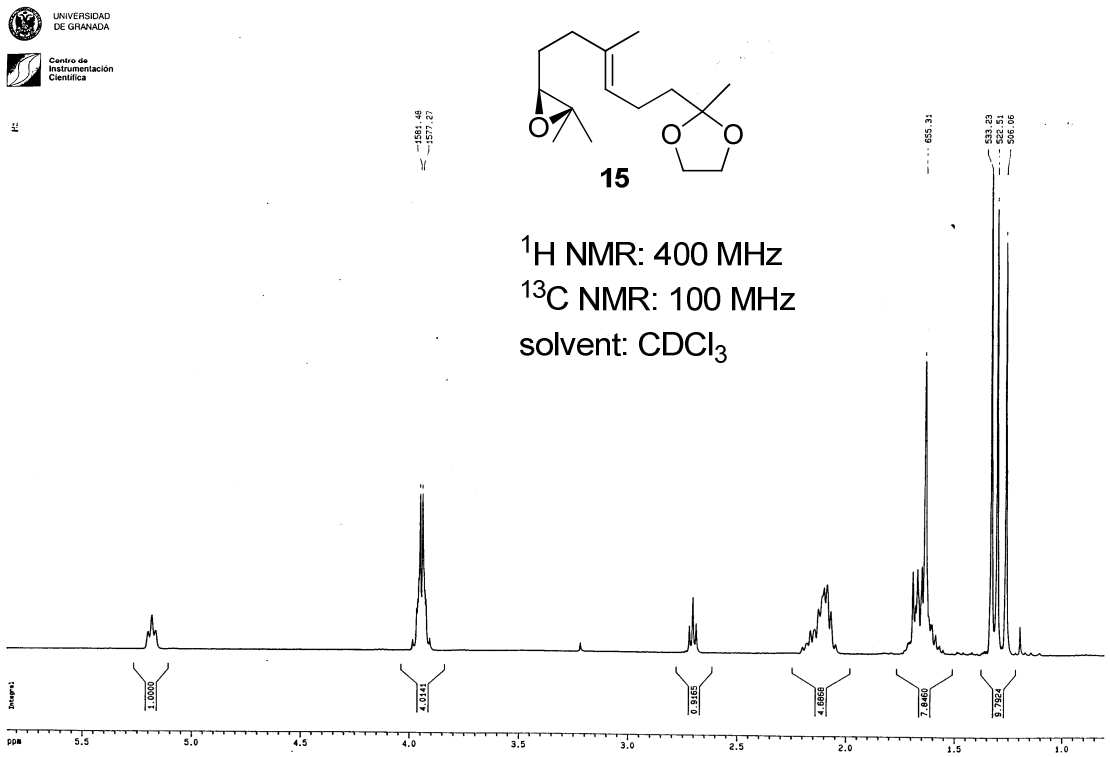




14

^{1}H NMR: 300 MHz
^{13}C NMR: 75 MHz
solvent: $CDCl_3$

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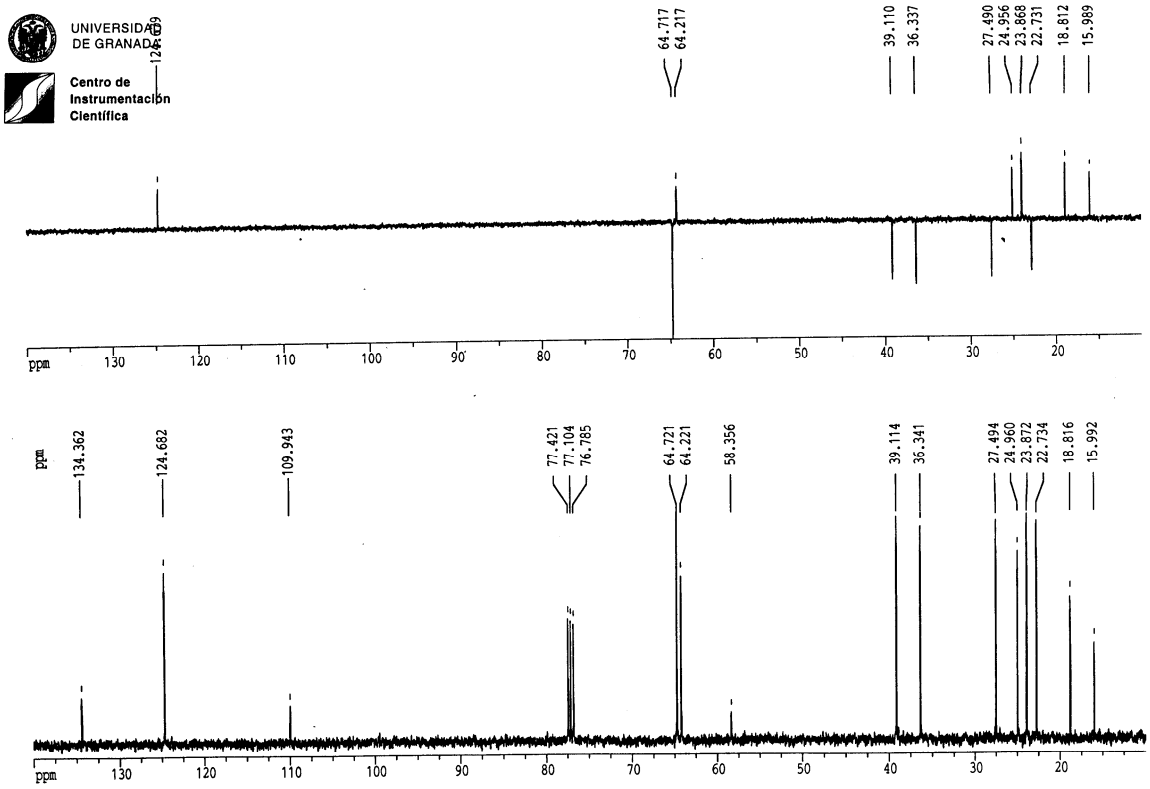
Centro de Instrumentación Científica
15
1H NMR: 400 MHz
13C NMR: 100 MHz
solvent: CDCl3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Centro de Instrumentación Científica
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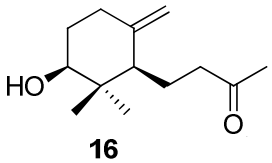
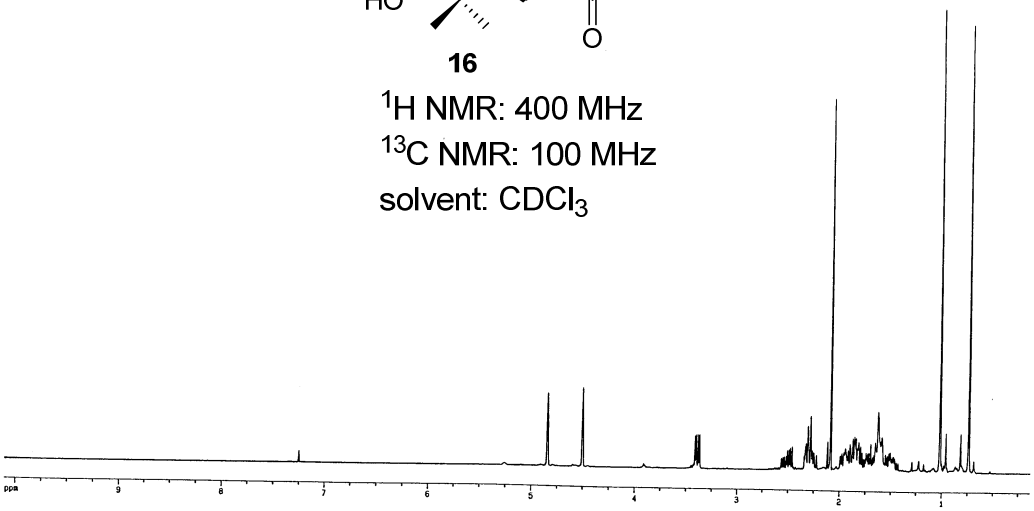


16

^{1}H NMR: 400 MHz

^{13}C NMR: 100 MHz

solvent: $CDCl_3$



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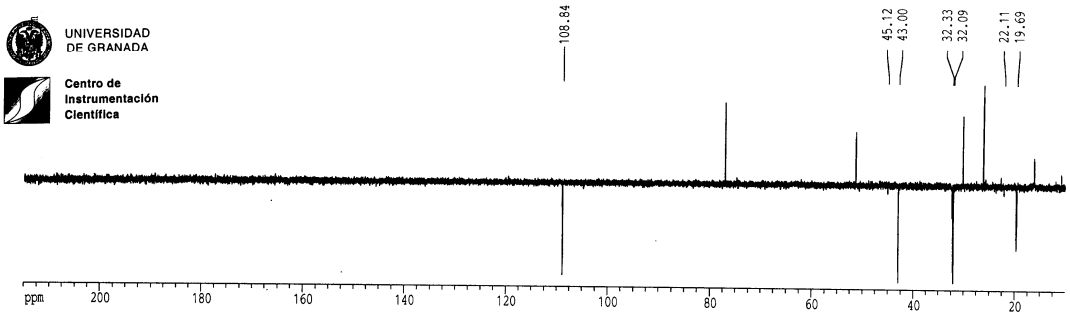

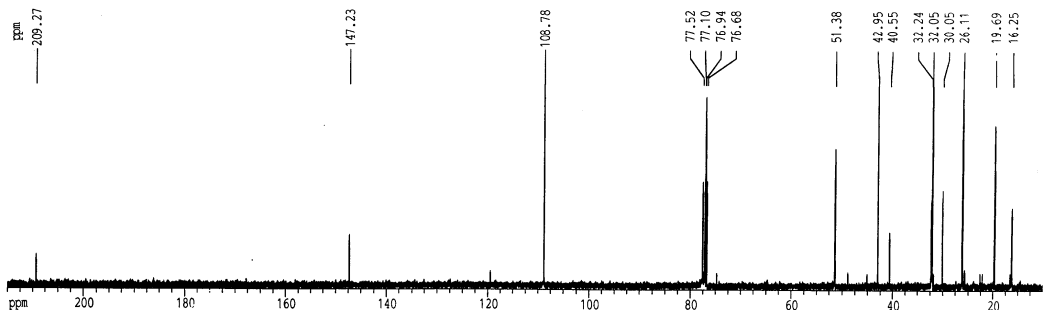

Jesus 65-6
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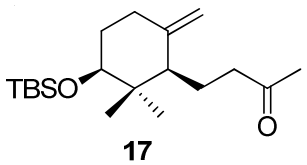
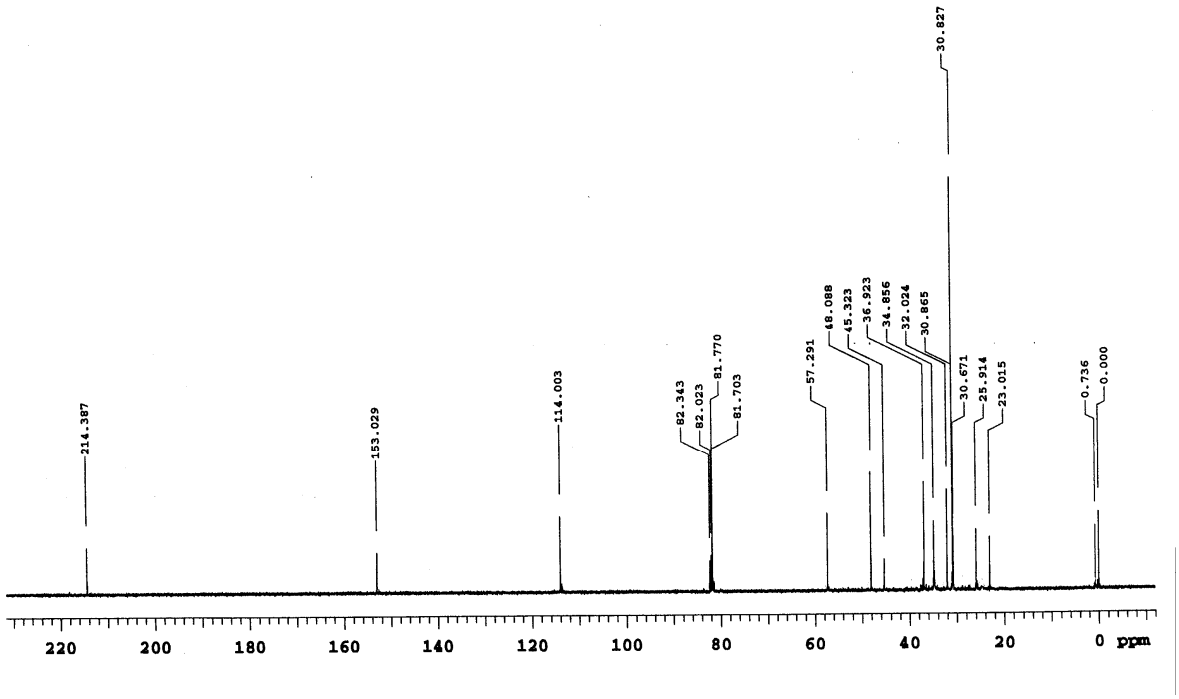
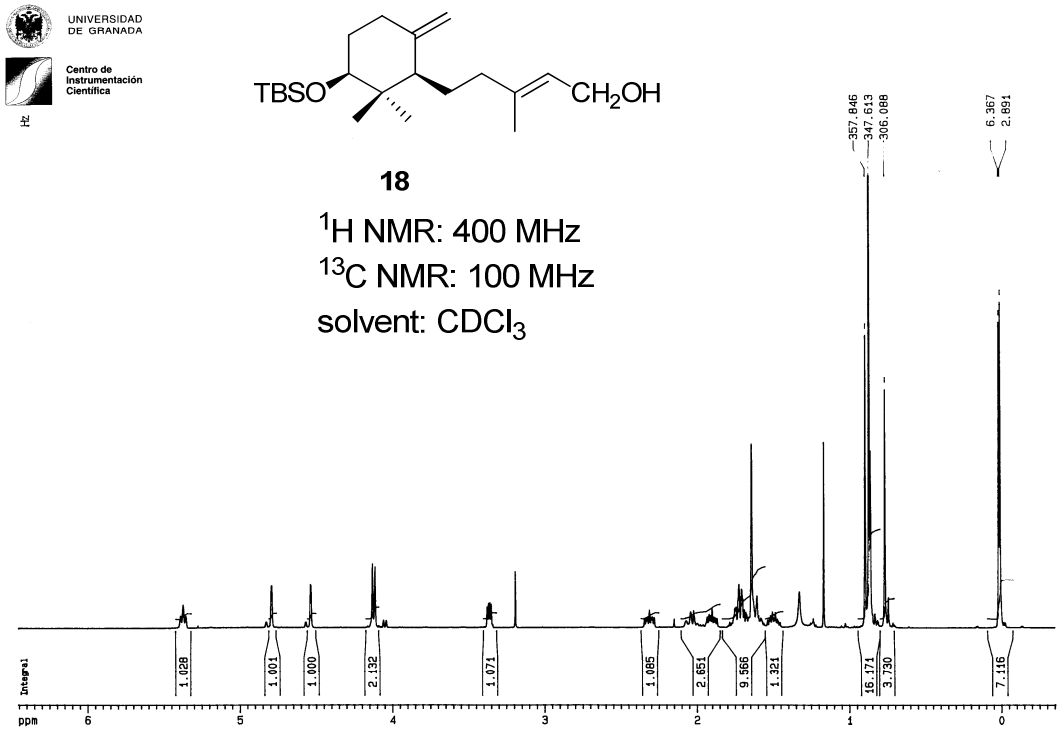
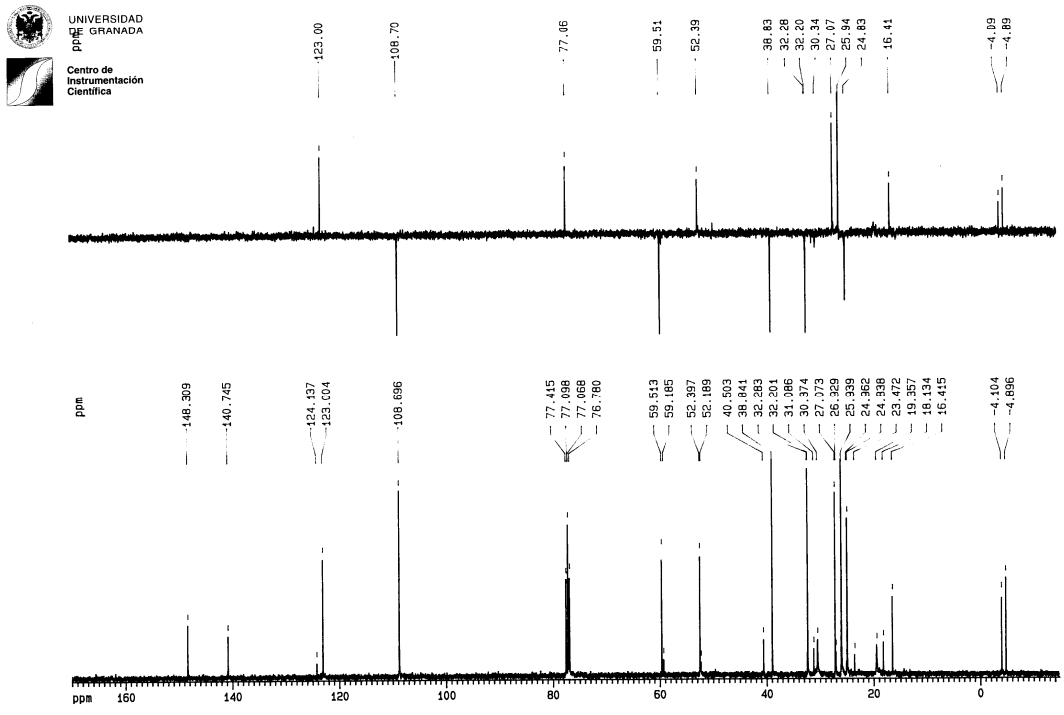


17

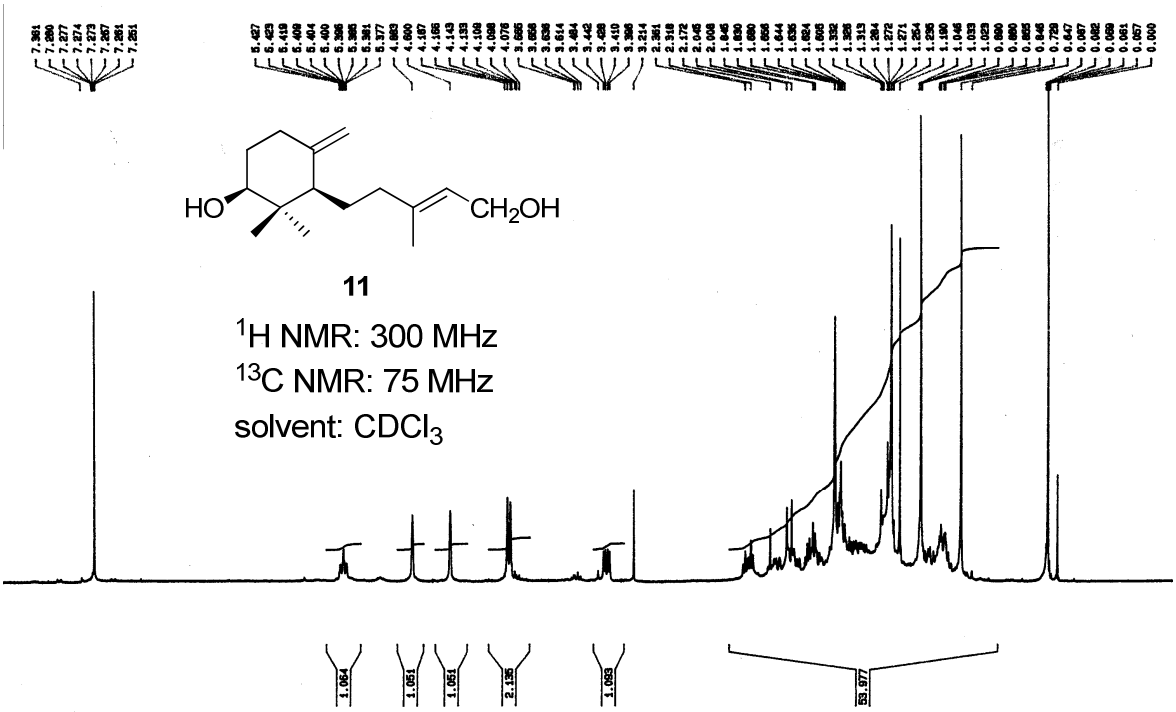
^{1}H NMR: 400 MHz
^{13}C NMR: 100 MHz
solvent: $CDCl_3$







Natural elegansidiol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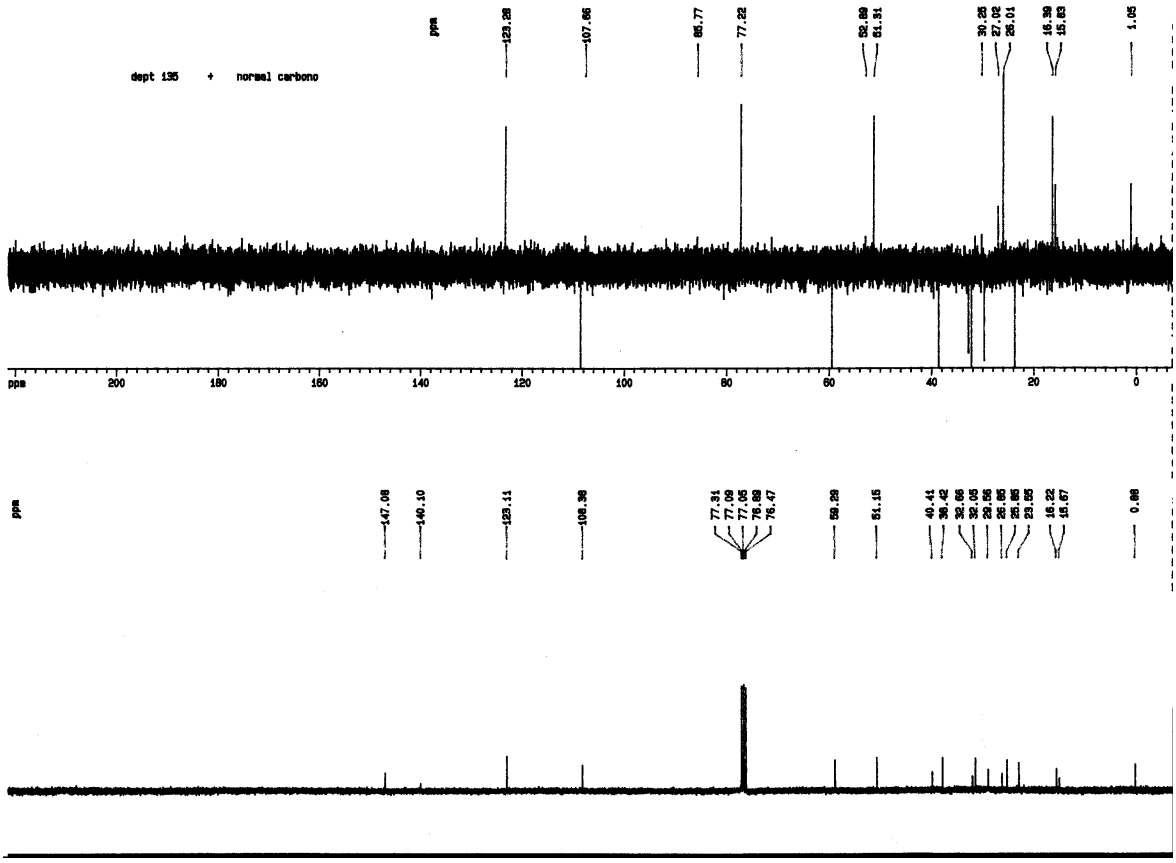
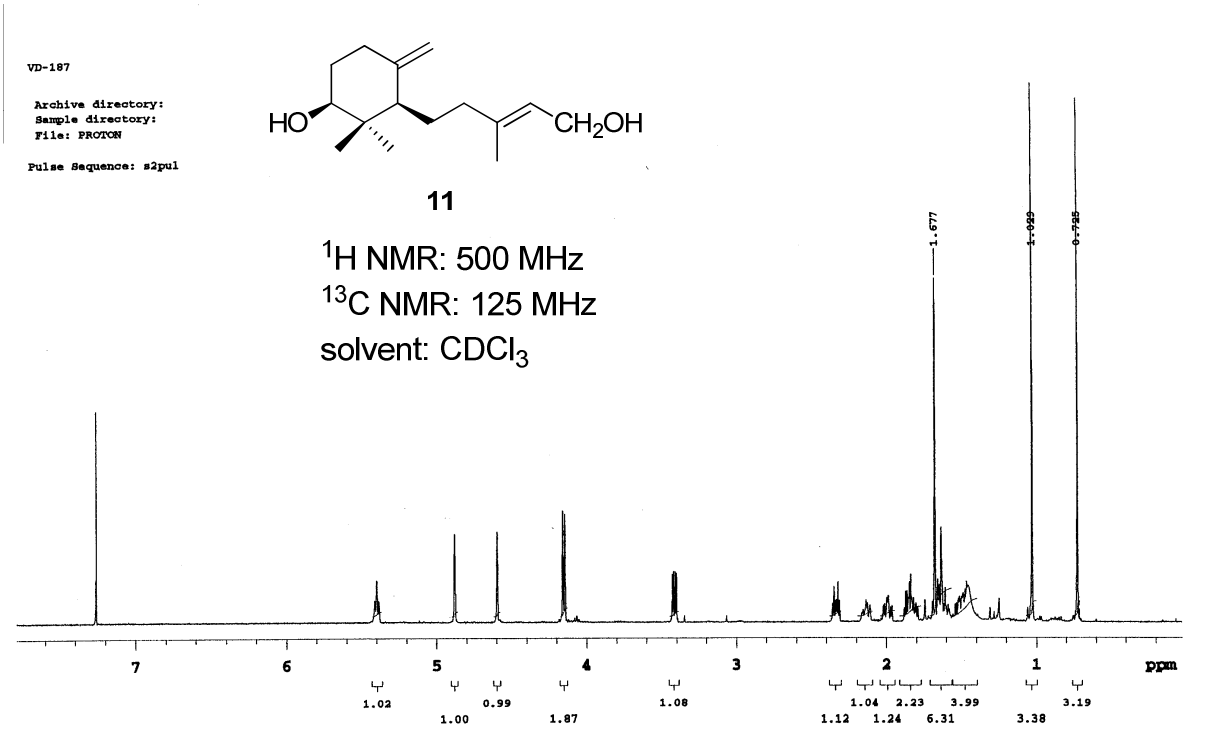
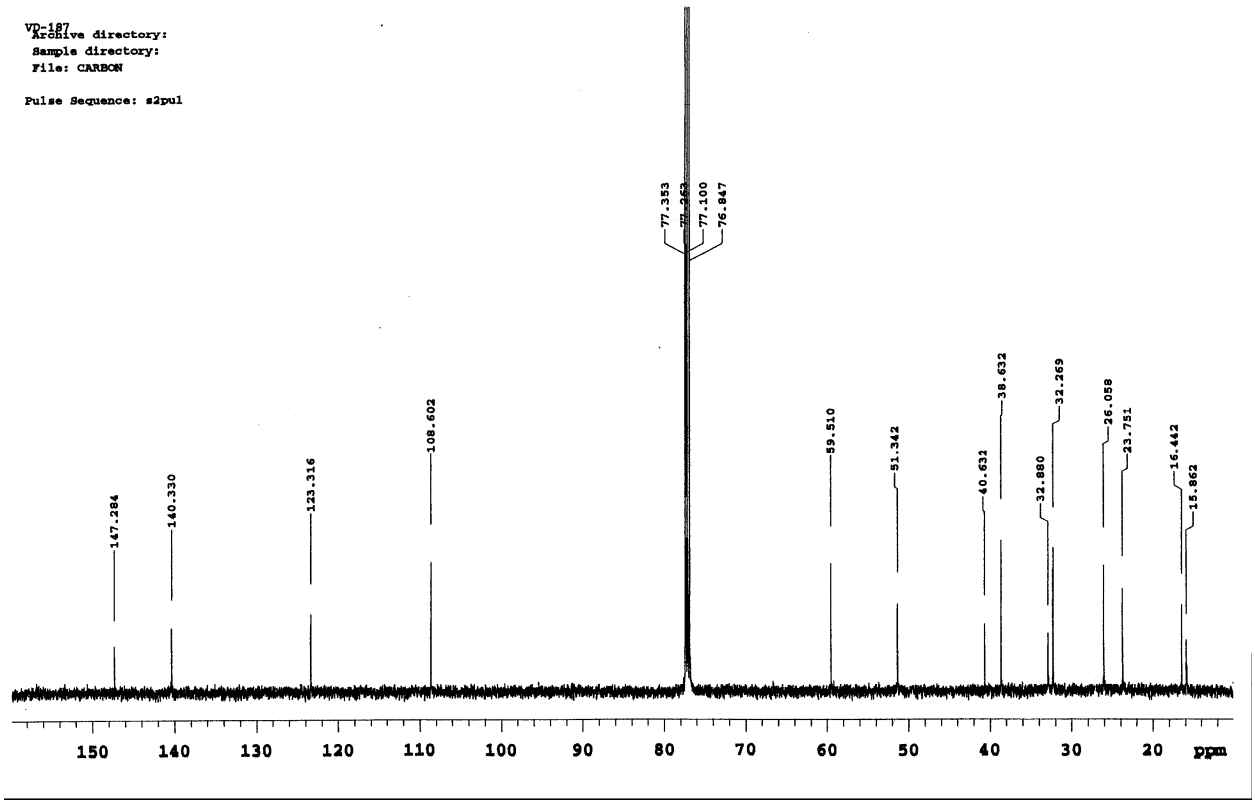
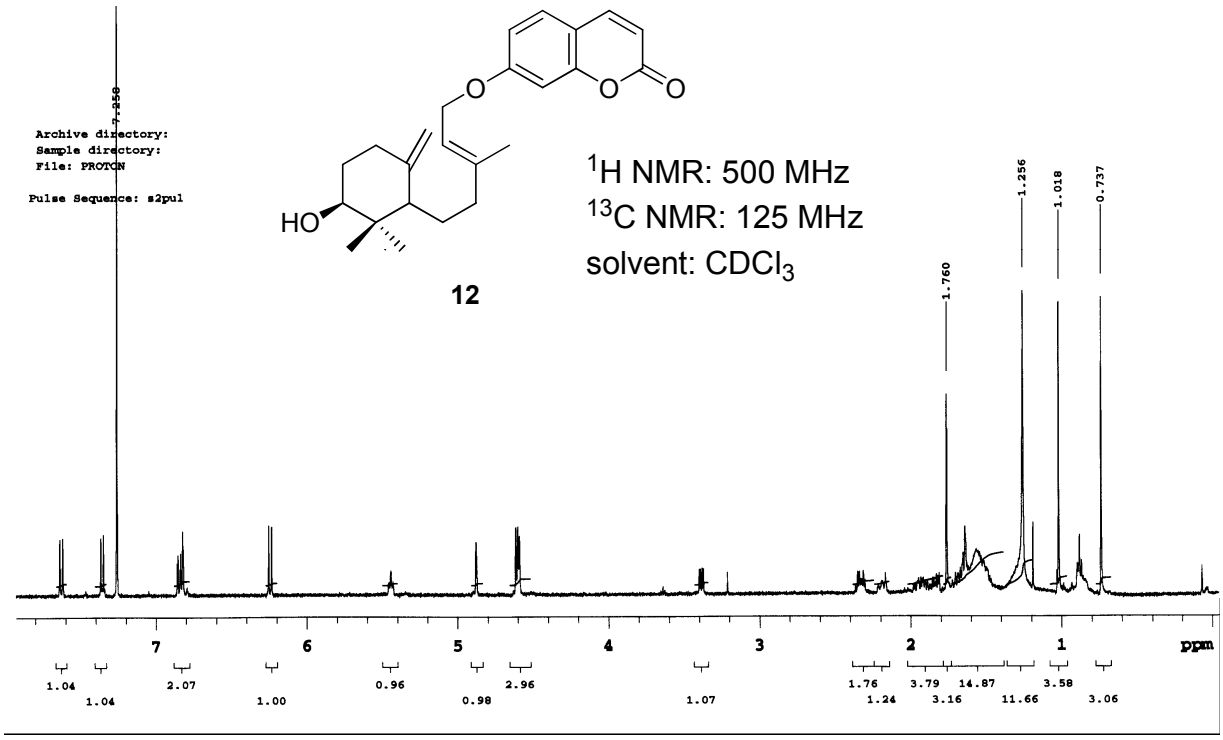
CH2OH
11
1H NMR: 300 MHz
13C NMR: 75 MHz
solvent: CDCl3


dept 135 + normal carbono
ppm

Synthetic elegansidiol



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O
O
O
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^{13}C NMR: 125 MHz
solvent: $CDCl_3$
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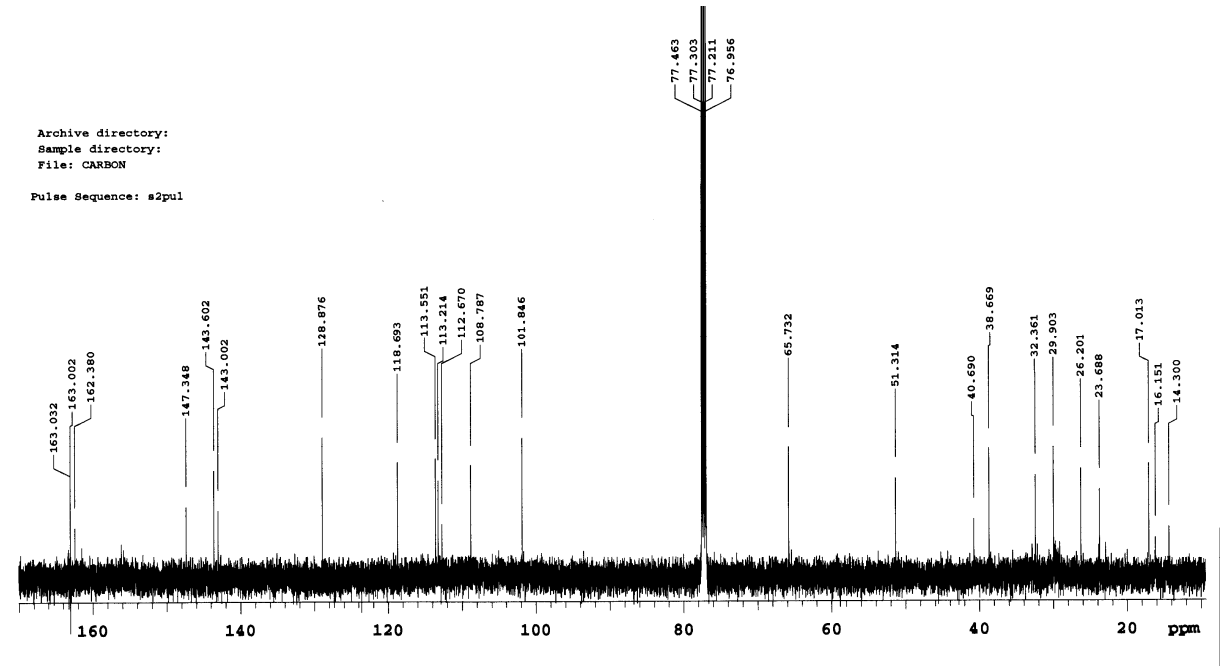
1.760
1.256
1.018
0.737
7
6
5
4
3
2
1
ppm
1.04
1.04
2.07
1.00
0.96
0.98
2.96
1.07
1.76
1.24
3.79
3.16
14.87
11.66
3.58
3.06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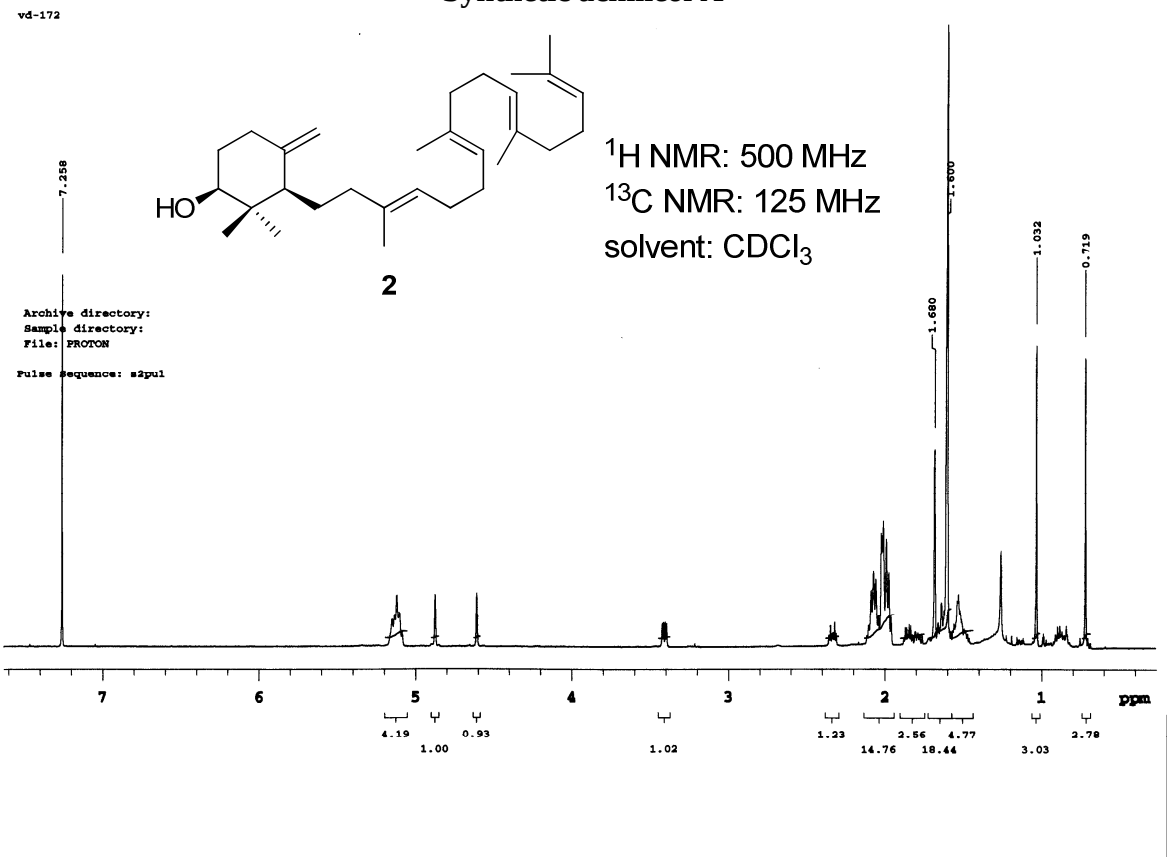
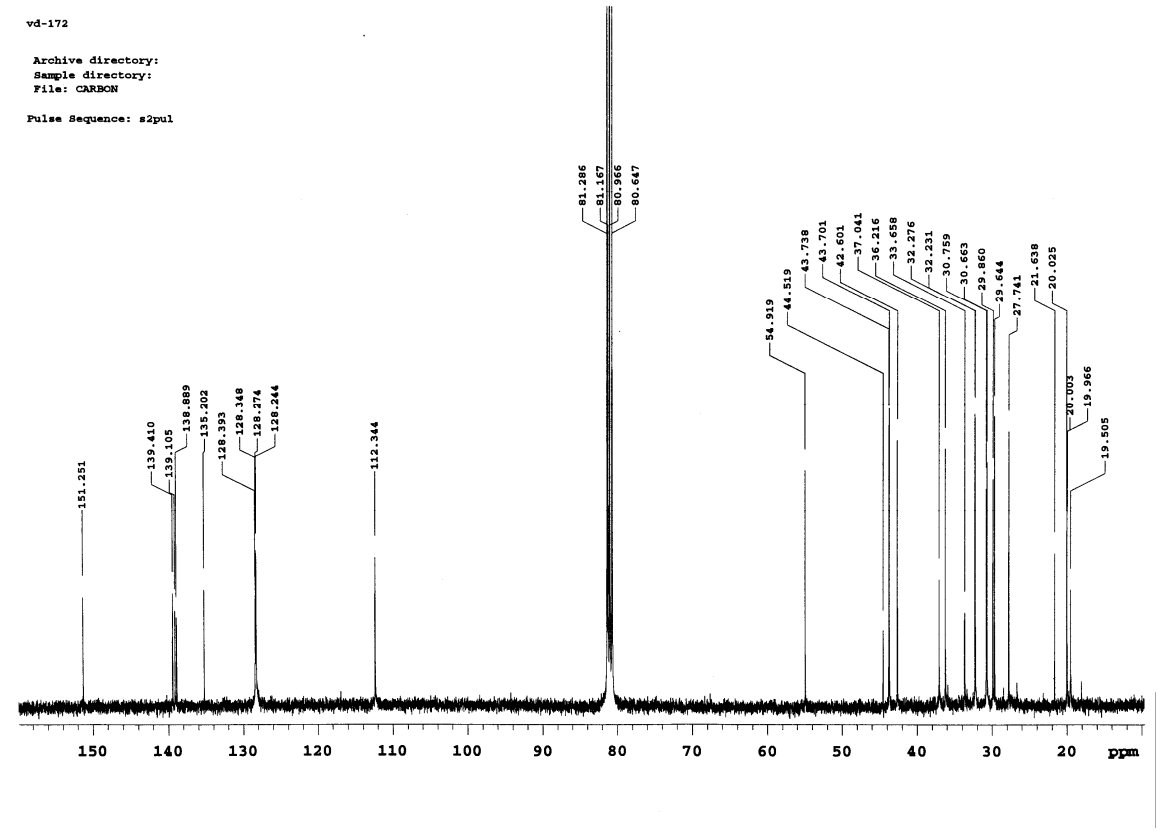
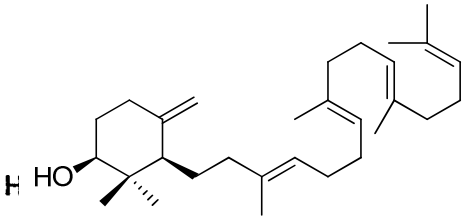
118.693
113.551
113.214
112.670
108.787
101.846
65.732
51.314
40.690
38.669
32.361
29.903
26.201
23.688
17.013
16.151
14.300
160
140
120
100
80
60
40
20
ppm

Synthetic achilleol A



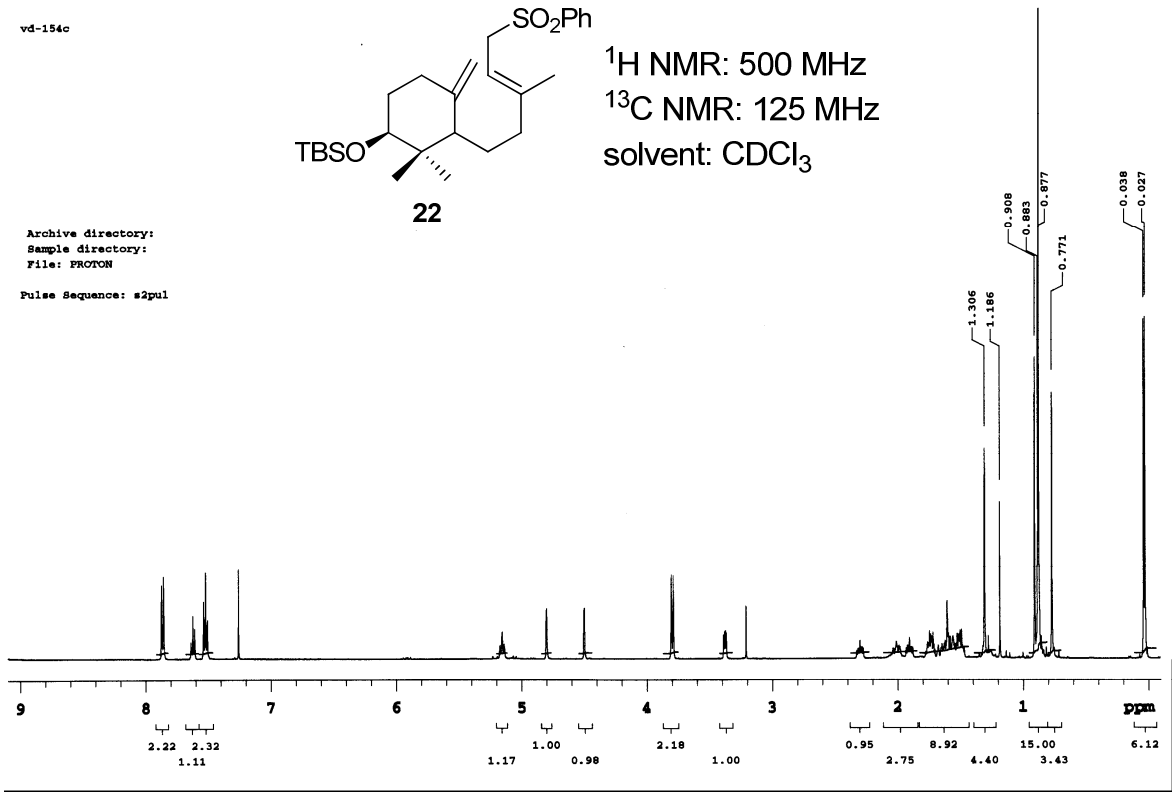


Natural achilleol A



2

^{1}H NMR: 500 MHz
^{13}C NMR: 125 MHz
solvent: $CDCl_3$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TBSO
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13C NMR: 125 MHz
solvent: CDCl3
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9
8
7
6
5
4
3
2
1
ppm
2.22
2.32
1.11
1.17
1.00
0.98
2.18
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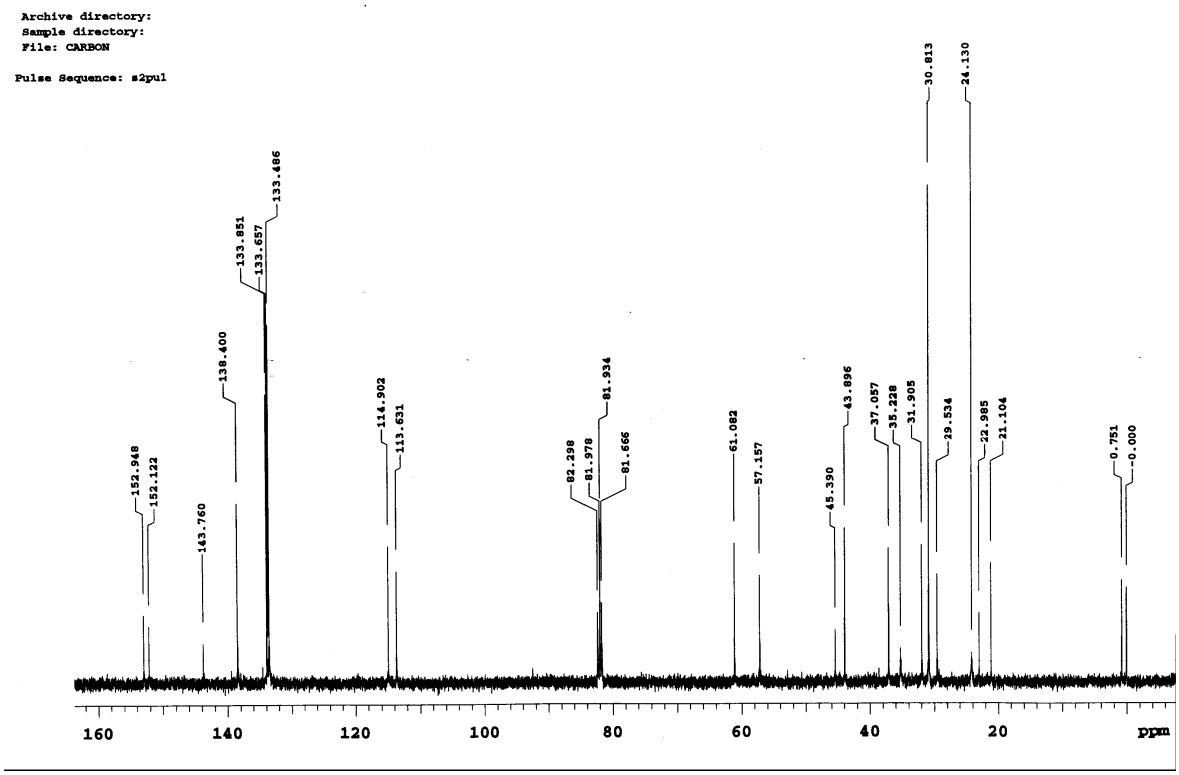
2.75
4.40
15.00
3.43
6.12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57.157
45.390
43.896
37.057
35.228
31.905
29.534
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21.104
152.948
152.122
143.760
0.751
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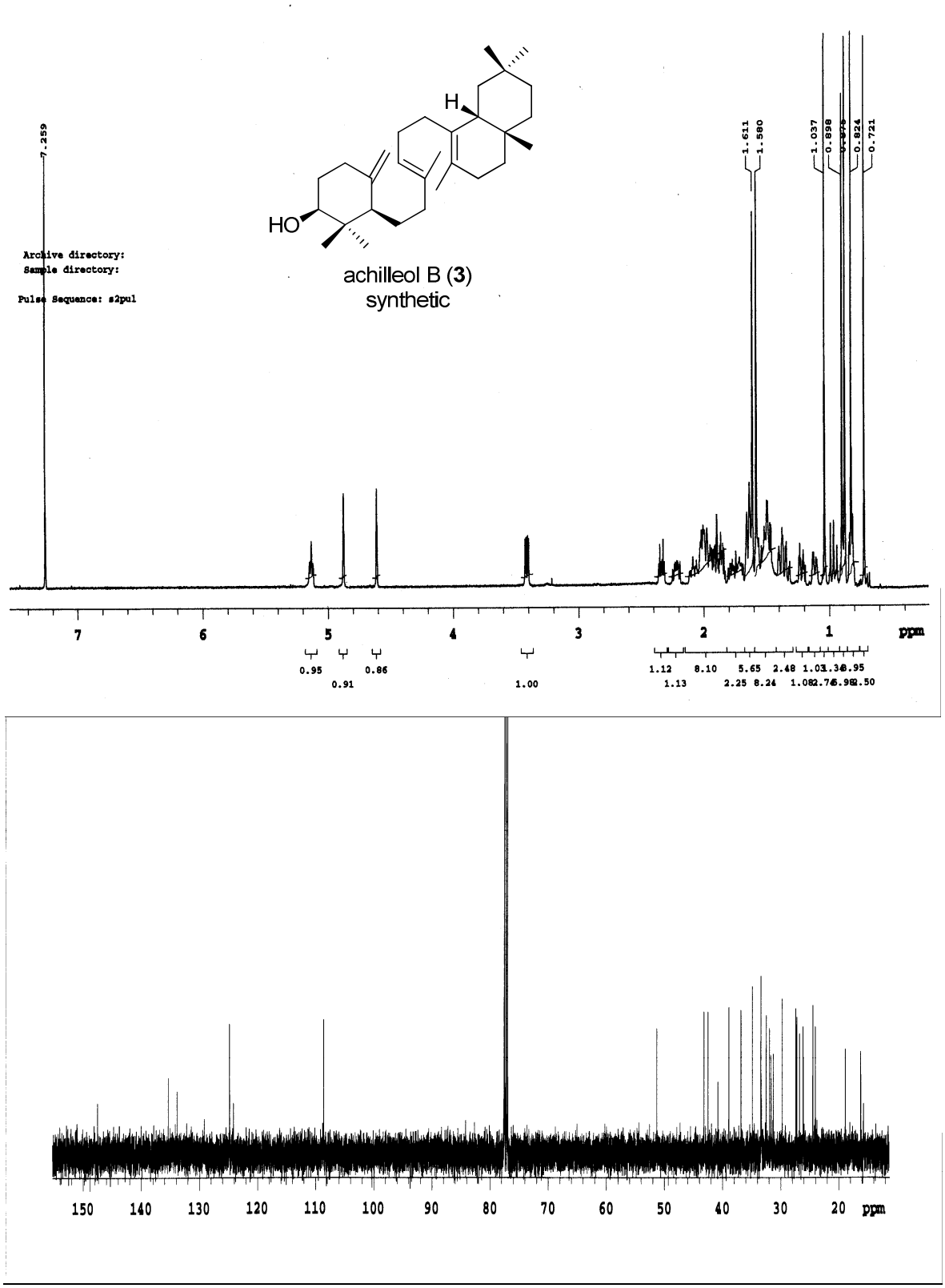
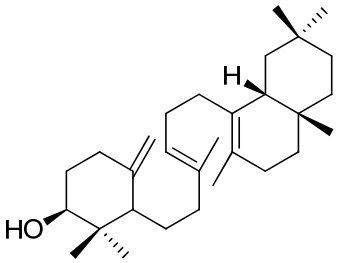
140
120
100
80
60
40
20
ppm

Synthetic achilleol B

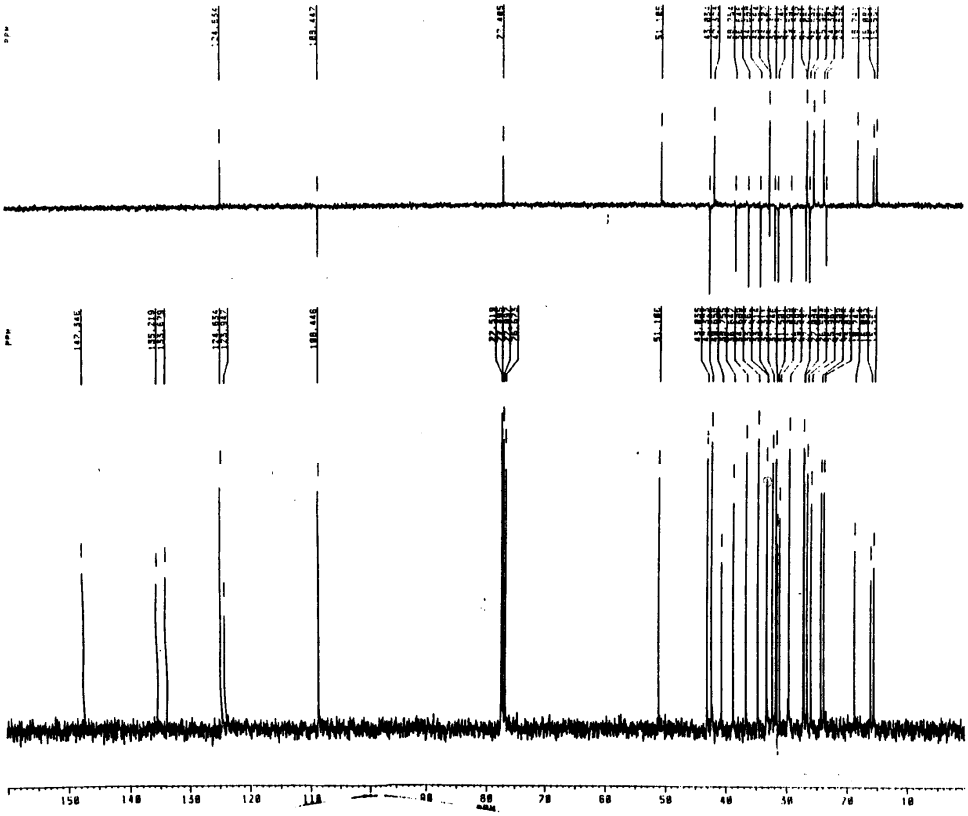


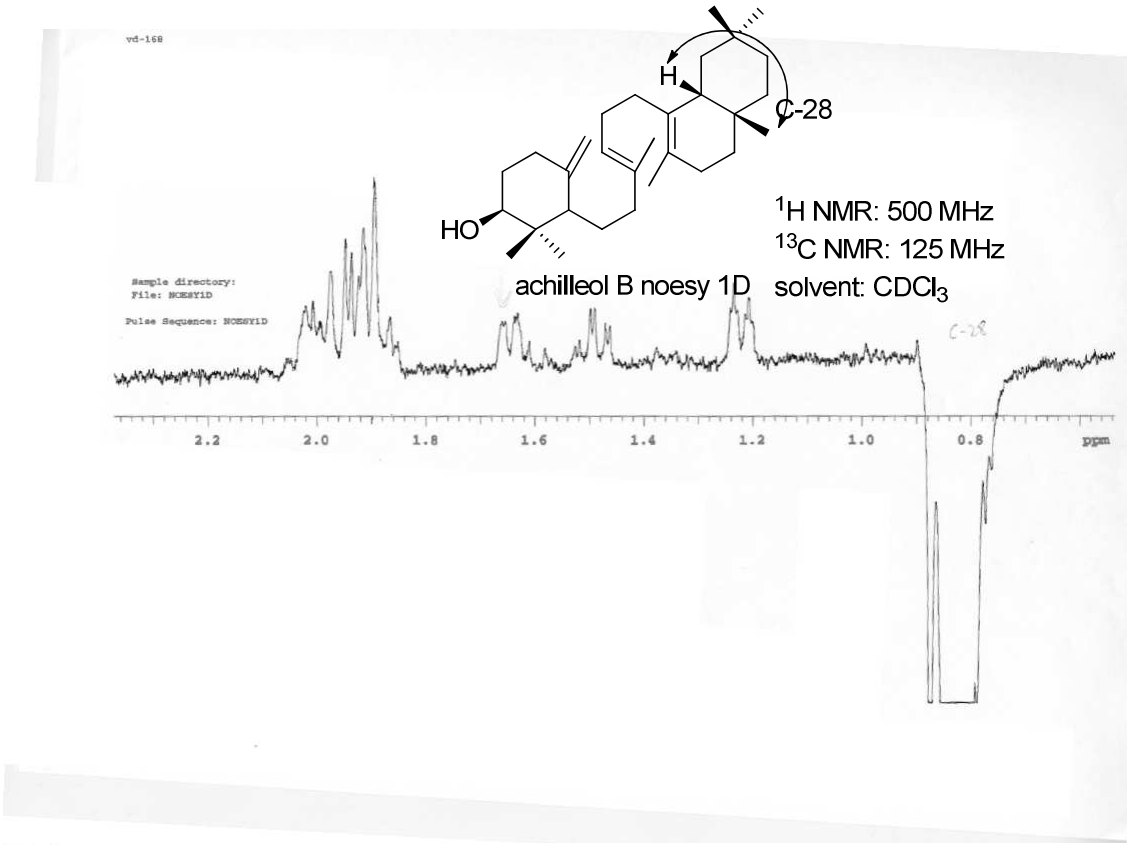
Natural achilleol B



reassigned achilleol B

^{1}H NMR: 300 MHz
^{13}C NMR: 75 MHz
solvent: $CDCl_3$




H
C-28
HO
achilleol B noesy 1D
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
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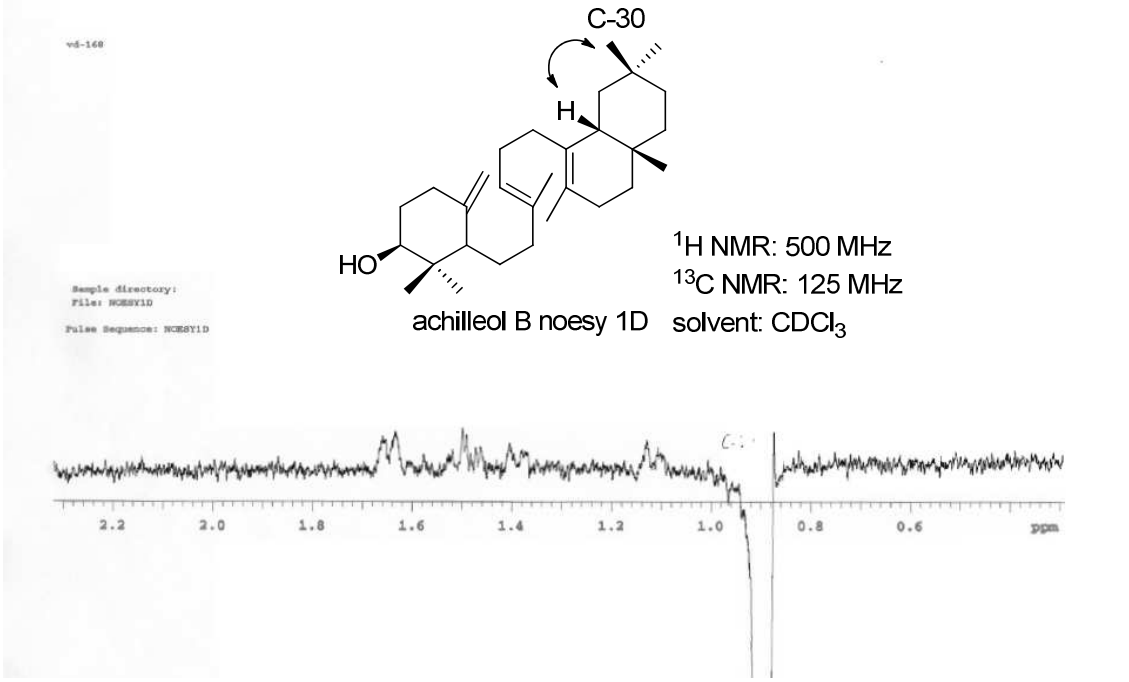
2.0
1.8
1.6
1.4
1.2
1.0
0.8
ppm


C-30
H
HO
achilleol B noesy 1D
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
ppm

Total Synthesis of (+)-seco-C Oleanane Via Stepwise Controlled Radical Cascade Cyclization

Victoriano Domingo,[†] Jesús F. Arteaga,[‡] José Luis López Pérez,[§] Rafael Pelaez,[§] José F. Quílez del Moral,[†,*] and Alejandro F. Barrero[†,*]

[†]Department of Organic Chemistry, Institute of Biotechnology, Faculty of Sciences, University of Granada, Campus de Fuente Nueva, s/n,18071 Granada, Spain, [‡]Department of Chemistry Engineering, Physique Chemistry and Organic Chemistry, Faculty of Experimental Sciences, University of Huelva, Campus el Carmen, 21071 Huelva, Spain, [§]Department of Pharmacy, University of Salamanca, Spain.

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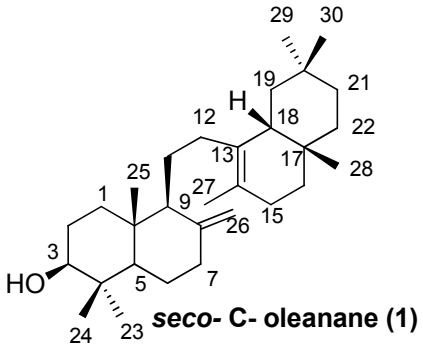
Supporting Information

General Details

The solvents used were purified according to standard literature techniques and stored under Argon. THF and toluene were freshly distilled immediately prior to use from sodium/benzophenone and strictly deoxygenated for 30 min under Argon for each of the Cp_2TiCl_2/Mn or Zn reactions. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. IR spectra were recorded on a Mattson Satellite FTIR spectrometer. NMR spectra were performed with a Varian Direct-Drive 500 (^{1}H 500 MHz/^{13}C 125 MHz), Bruker ARX 400 (^{1}H 400 MHz/^{13}C 100 MHz) and Varian Inova Unity 300 (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. The accurate mass determination was carried out with a AutoSpec-Q mass spectrometer arranged in a EBE geometry (Micromass

Instrument, Manchester, UK) and equipped with a FAB (LSIMS) source. The instrument was operated at 8 KV of accelerating voltage and Cs+ were used as primary ions. Optical rotations were measured on a Perkin-Elmer 141 polarimeter, using $CHCl_3$ as the solvent. 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 or acidic mixture of anisaldehyde and heat as developing agents. HPLC with UV and RI detection was used. Semi-preparative HPLC separations 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. GC-MS analysis was performed on a CARLO ERBA 8000 Series mod. 8060, with a split ratio of 1: 100, 1ml/ min helium flow. Column temperature was held at 240 ºC for 2 min, then increased to 330 ºC with a rate of 20 ºC/min, followed by keeping at 330 ºC for 15 min. A ZB-5ms (30 mx0.25 mm I.D., 0.25 μm film thickness, Phenomenex Inc., Torrance, CA, USA) column was used. The mass spectrometer ionization mode was electron impact (EI+), the acquisition mode was full scan (m/z range 45–500 Da), and the detector voltage was 70 eV. 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 following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, pent = pentet, hex = hexet, br = broad.

Experimental



***seco*- C- oleanane (1)**

Table 1. [1]H NMR data comparison between synthetic *seco*- C- oleanane (**1**), and natural *seco*- C- oleanane (**1**) reported data[12].

Synthetic *seco*- C- oleanane (**1**) [1]H NMR ($CDCl_3$, 500 MHz) (δ, multiplicity, coupling constant (Hz))	Natural *seco*- C- oleanane (**1**) [1]H NMR ($CDCl_3$, 300 MHz) (δ, multiplicity, coupling constant (Hz))
4.86 (1H, d, *J* = 1.5 Hz, H-26)	4.87 (1H, d, *J* = 1.5 Hz, H-26)
4.63 (1H, d, *J* = 1.0 Hz, H- 26')	4.62 (1H, d, *J* = 1.0 Hz, H- 26')
3.25 (1H, dd, *J* = 11.8, 4.4 Hz, H-3)	3.24 (1H, dd, *J* = 11.7, 4.4 Hz, H-3)
2.41 (1H, ddd, *J* = 12.8, 4.2, 2.6 Hz, H-7)	2.39 (1H, dq, *J* = 12.7, 2.4 Hz, H-7)
1.99 (1H, m, H-7')	1.97 (1H, m, H-7')
2.32 and 1.47 (1H each, m, H-12, H-12')	2.32 and 1.47 (1H each, m, H-12, H-12')
1.99 and 1.88 (1H each, m, H-15, H-15')	1.97 and 1.87 (1H each, m, H-15, H-15')
1.89 and 0.81 (1H each, m, H-16, H-16')	1.89 and 0.80 (1H each, m, H-16, H-16')
1.79 (1H, t, *J* = 3.4 Hz) and 1.17 (1H, m), (H-1, H-1')	1.77 and 1.15 (1H each, m, H-1, H-1')
1.75 and 1.38 (1H each, m, H-6, H-6')	1.74 and 1.37 (1H each, m, H-6, H-6')
1.69 and 1.59 (1H each, m, H-2, H-2')	1.68 and 1.58 (1H each, m, H-2, H-2')
1.60 (1H, m, H-9)	1.59 (1H, m, H-9)
1.55 (1H, m, H-18)	1.55 (1H, m, H-18)
1.56 (3H, s, Me-27)	1.55 (3H, s, Me-27)
1.49 and 1.33 (1H each, m, H-11, H-11')	1.48 and 1.32 (1H each, m, H-11, H-11')
1.48 and 1.21 (1H each, m, H-22, H-22')	1.47 and 1.21 (1H each, m, H-22, H-22')

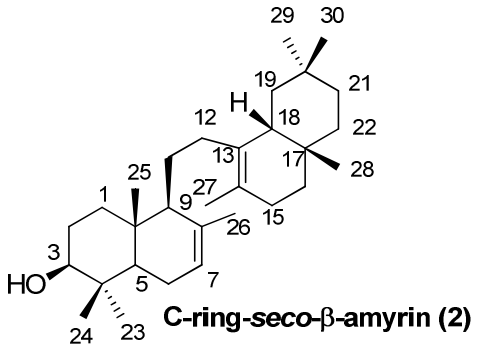
[12] Roman, L. U.; Guerra-Ramirez, D.; Moran, G.; Martinez, I.; Hernandez, J. D.; Cerda-Garcia-Rojas, C. M.; Torres-Valencia, J. M.; Joseph-Nathan, P., *Org. Lett.*, **2004**, *6*, 173-176.

1.34 and 0.93 (1H each, m, H-19, H-19')	1.33 and 0.92 (1H each, m, H-19, H-19')
1.33 and 1.12 (1H each, m, H-21, H-21')	1.32 and 1.10 (1H each, m, H-21, H-21')
1.10 (1H, dt, *J* = 12.8, 2.83Hz, , H-5)	1.06 (1H, m, H-5)
0.99 (3H, s, Me-23)	0.98 (3H, s, Me-23)
0.88 (3H, s, Me-30)	0.87 (3H, s, Me-30)
0.87 (3H, s, Me-29)	0.86 (3H, s, Me-29)
0.85 (3H, s, Me-28)	0.84 (3H, s, Me-28)
0.77 (3H, s, Me- 24)	0.76 (3H, s, Me- 24)
0.67 (3H, s, Me-25)	0.66 (3H, s, Me-25)

Table 2. ^{13}C NMR data comparison between synthetic *seco*- C- oleanane (**1**), and natural *seco*- C-oleanane (**1**) reported data.

Carbon no.	Synthetic *seco*- C- oleanane (**1**) ^{13}C NMR ($CDCl_3$, 150 MHz) (δ)	Natural *seco*- C- oleanane (**1**) ^{13}C NMR ($CDCl_3$, 75 MHz) (δ)
1	36.8	36.8
2	27.9	28.0
3	78.9	78.9
4	39.1	39.1
5	54.6	54.7
6	24.0	24.1
7	38.2	38.2
8	148.3	148.3
9	56.9	56.9
10	39.5	39.5
11	22.8	22.9
12	30.8	30.8
13	134.2	134.3

14	123.5	123.5
15	29.4	29.5
16	26.4	26.4
17	31.5	31.5
18	42.9	42.9
19	42.9	42.9
20	30.9	31.0
21	34.5	34.6
22	36.5	36.5
23	28.3	28.3
24	15.3	15.4
25	14.4	14.5
26	106.5	106.6
27	18.7	18.8
28	27.2	27.2
29	33.1	33.1
30	24.0	24.1



C-ring-seco-β-amyrin (2)

Table 1. Comparison between ^{1}H NMR data of synthetic C- ring- *seco*- β- amyrin (**2**), and those of natural C- ring- *seco*- β- amyrin (**2**) reported data[13].

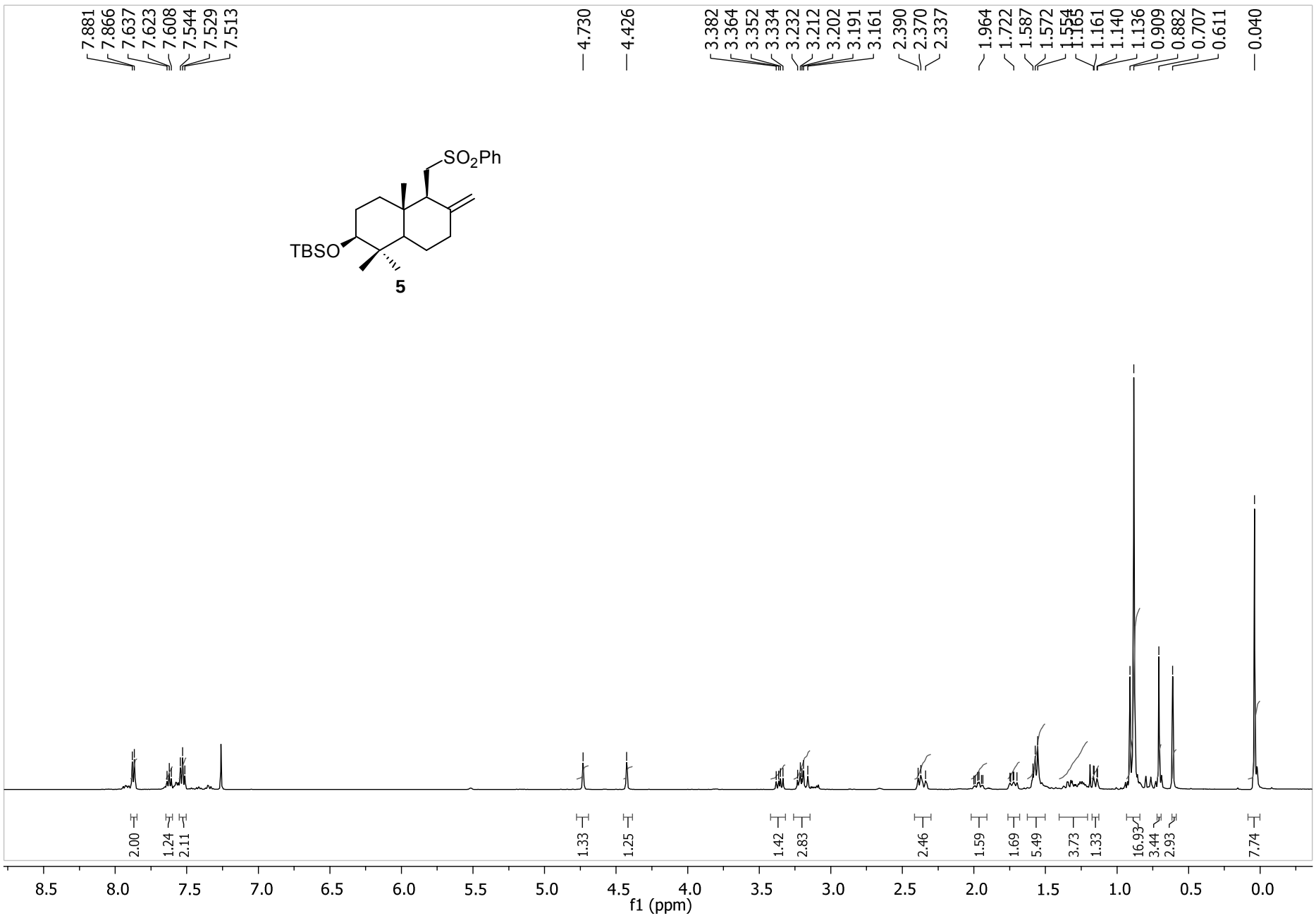
[13] Shibuya M.; Xiang T.; Katsube Y.; Otsuka M.; Zhang H.; Ebizuka Y. *J. Am. Chem. Soc.*, **2007**, *129*, 1450-1455.

Synthetic C- ring- *seco*- β- amyrin (**2**) ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, multiplicity, coupling constant (Hz))	Natural C- ring- *seco*- β- amyrin (**2**) ^{1}H NMR ($CDCl_3$, 500 MHz) (δ, multiplicity, coupling constant (Hz))
1.92, 1.19 (1H each, m, H-1, H-1')	1.92, 1.19 (1H each, m, H-1, H-1')
1.55-1.70 (1H each, m, H-2, H-2')	1.55-1.70 (1H each, m, H-2, H-2')
3.25 (1H, dd, *J* = 10.9, 4.9 Hz, H-3)	3.25 (1H, dd, *J* = 11.1, 4.8 Hz, H-3)
1.20 (1H, m, H-5)	1.20 (1H, m, H-5)
1.97 (1H each, m, H-6, H-6')	1.97 (1H each, m, H-6, H-6')
5.40 (1H, brs, H-7)	5.40 (1H, brs, H-7)
1.58 (1H, m, H-9)	1.58 (1H, m, H-9)
1.42, 1.14 (1H each, m, H-11, H-11')	1.42, 1.14 (1H each, m, H-11, H-11')
2.41 (1H, dt, *J* = 13.0, 5.8 Hz, H-12), 1.58 (1H, m, H-12')	2.41 (1H, dt, *J* = 12.8, 5.7 Hz, H-12), 1.58 (1H, m, H-12')
1.98, 1.87 (1H each, m, H-15, H-15')	1.98, 1.87 (1H each, m, H-15, H-15')
1.63 (1H, m, H-18)	1.63 (1H, m, H-18)
1.38, 0.98 (1H each, m, H-19, H-19')	1.38, 0.98 (1H each, m, H-19, H-19')
1.35, 1.13 (1H each, m, H-21, H-21')	1.35, 1.13 (1H each, m, H-21, H-21')
1.51, 1.23(1H each, m, H-22, H-22')	1.51, 1.23(1H each, m, H-22, H-22')
0.98 (3H, s, Me-23)	0.98 (3H, s, Me-23)
0.86 (3H, s, Me-24)	0.86 (3H, s, Me-24)
0.76 (3H, s, Me-25)	0.76 (3H, s, Me-25)
1.75 (3H, brs, Me-26)	1.75 (3H, brs, Me-26)
1.57 (3H, s, Me-27)	1.57 (3H, s, Me-27)
0.84 (3H, s, Me-28)	0.84 (3H, s, Me-28)
0.88 (3H, s, Me-29)	0.88 (3H, s, Me-29)
0.88 (3H, s, Me-30)	0.88 (3H, s, Me-30)

Table 2. Comparison between ^{13}C NMR data of synthetic synthetic C- ring- *seco*- β- amyrin (**2**), and those of natural C- ring- *seco*- β- amyrin (**2**) reported data.

Carbon no.	Synthetic C- ring- *seco*- β- amyrin (**2**) ^{13}C NMR ($CDCl_3$, 150 MHz) (δ)	Natural C- ring- *seco*- β- amyrin (**2**) ^{13}C NMR ($CDCl_3$, 125 MHz) (δ)
1	37.2	37.1
2	27.5	27.5
3	79.2	79.2
4	38.7	38.6
5	49.7	49.7
6	23.5	23.5
7	121.8	121.8
8	135.40	135.4
9	55.7	55.7
10	37.0	36.9
11	26.0	26.0
12	34.9	34.9
13	134.3	134.2
14	123.6	123.6
15	29.4	29.4
16	26.5	26.4
17	31.5	31.4
18	42.8	42.7
19	43.0	43.0
20	31.0	31.0
21	34.6	34.5
22	36.5	36.5
23	27.9	27.9
24	15.1	15.0
25	13.7	13.7
26	22.1	22.1
27	18.8	18.8

28	27.1	27.0
29	33.2	33.1
30	24.0	24.0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3.334
3.232
3.212
3.202
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1.722
1.587
1.572
1.554
1.165
1.161
1.140
1.136
0.909
0.882
0.707
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0.040
SO2Ph
TBSO
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1.24
2.11
1.33
1.25
1.42
2.83
2.46
1.59
1.69
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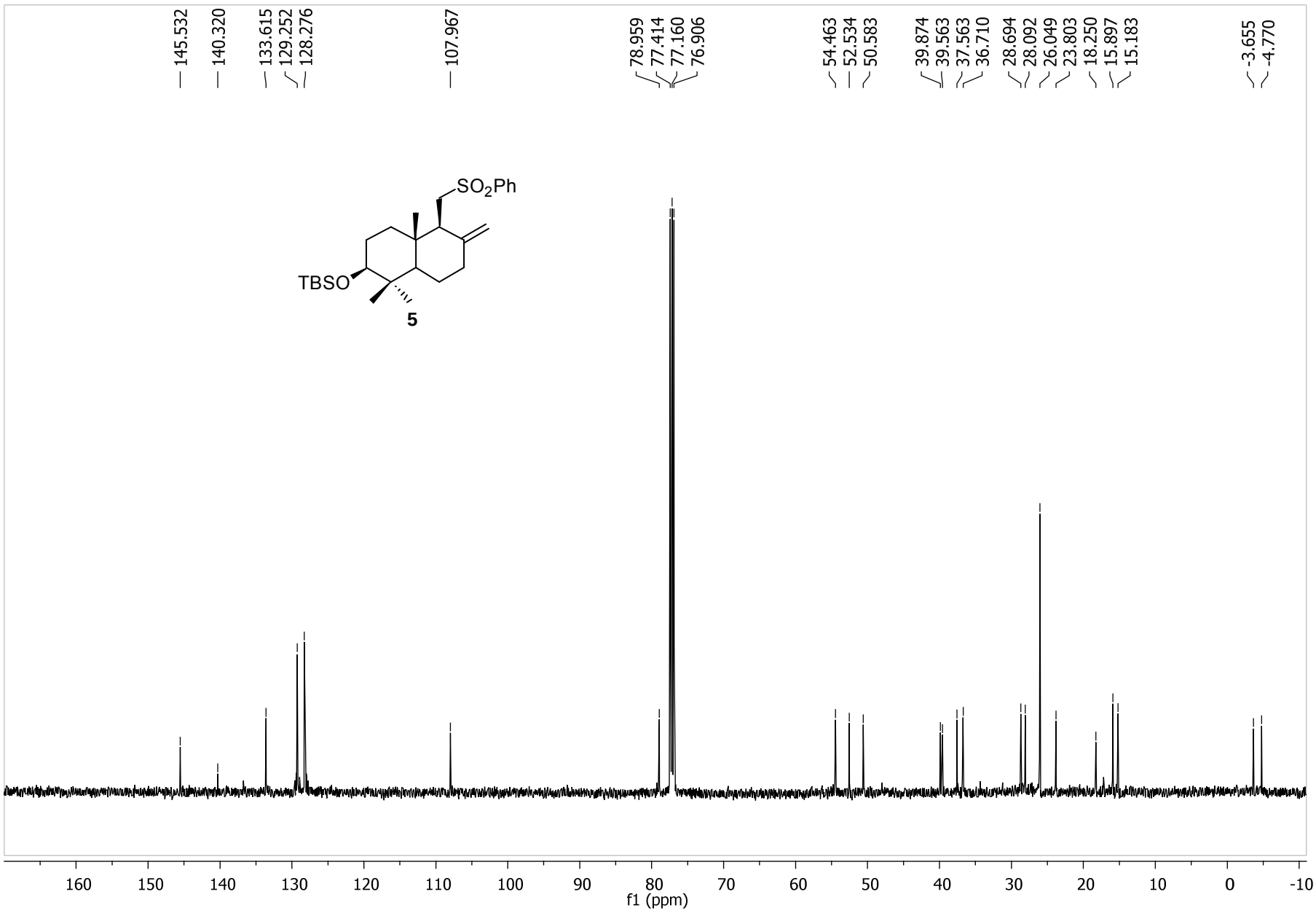
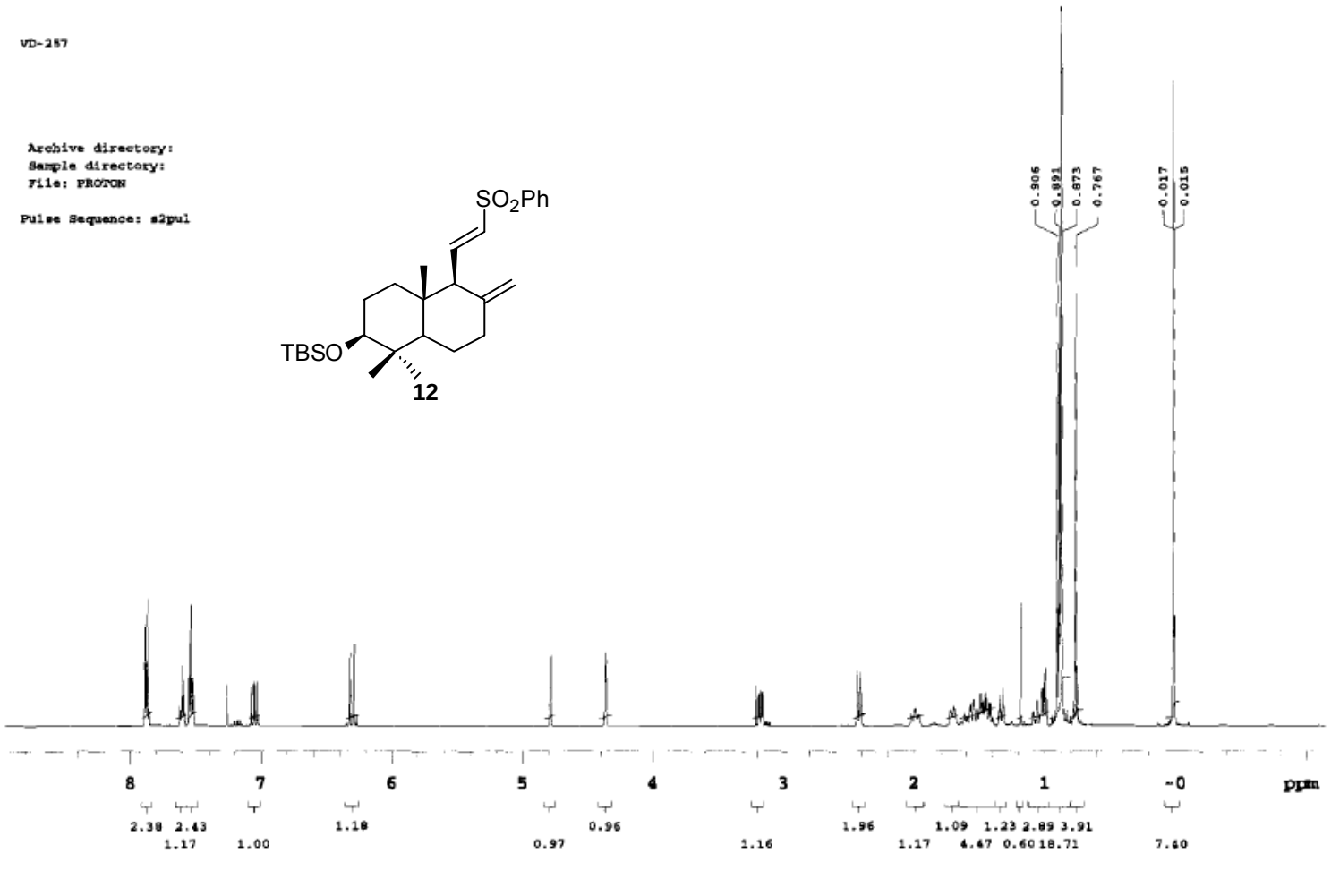
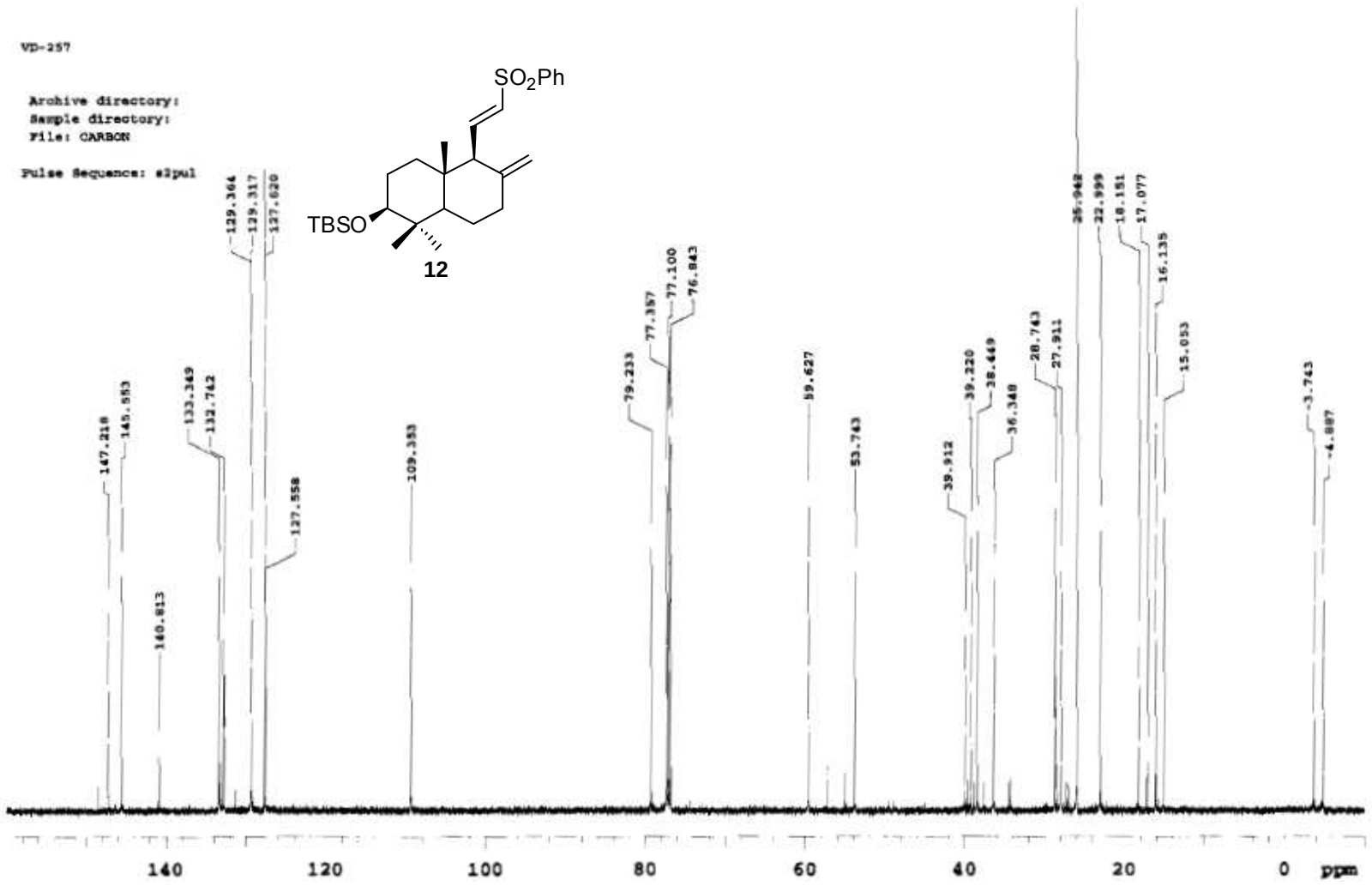
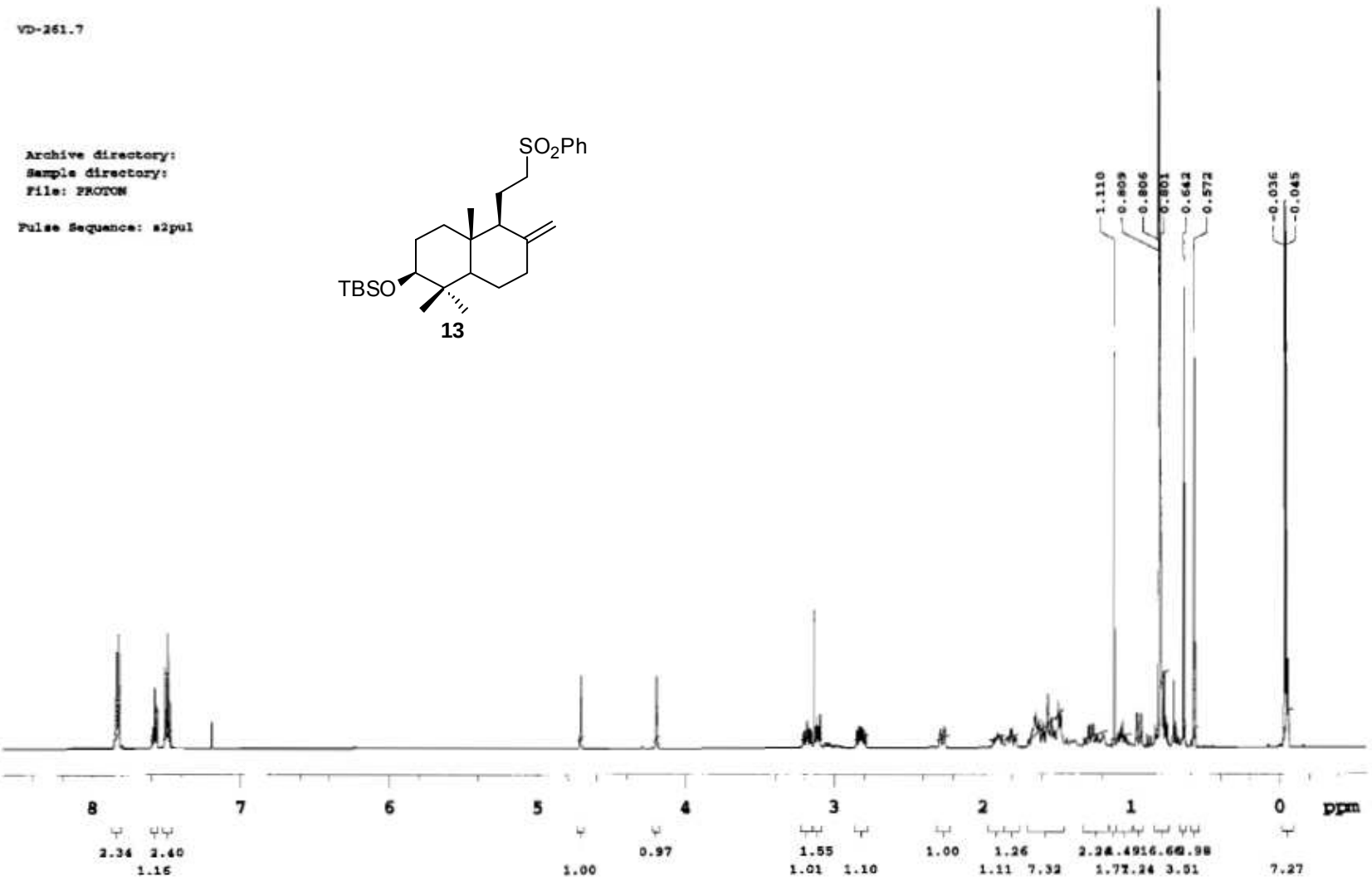
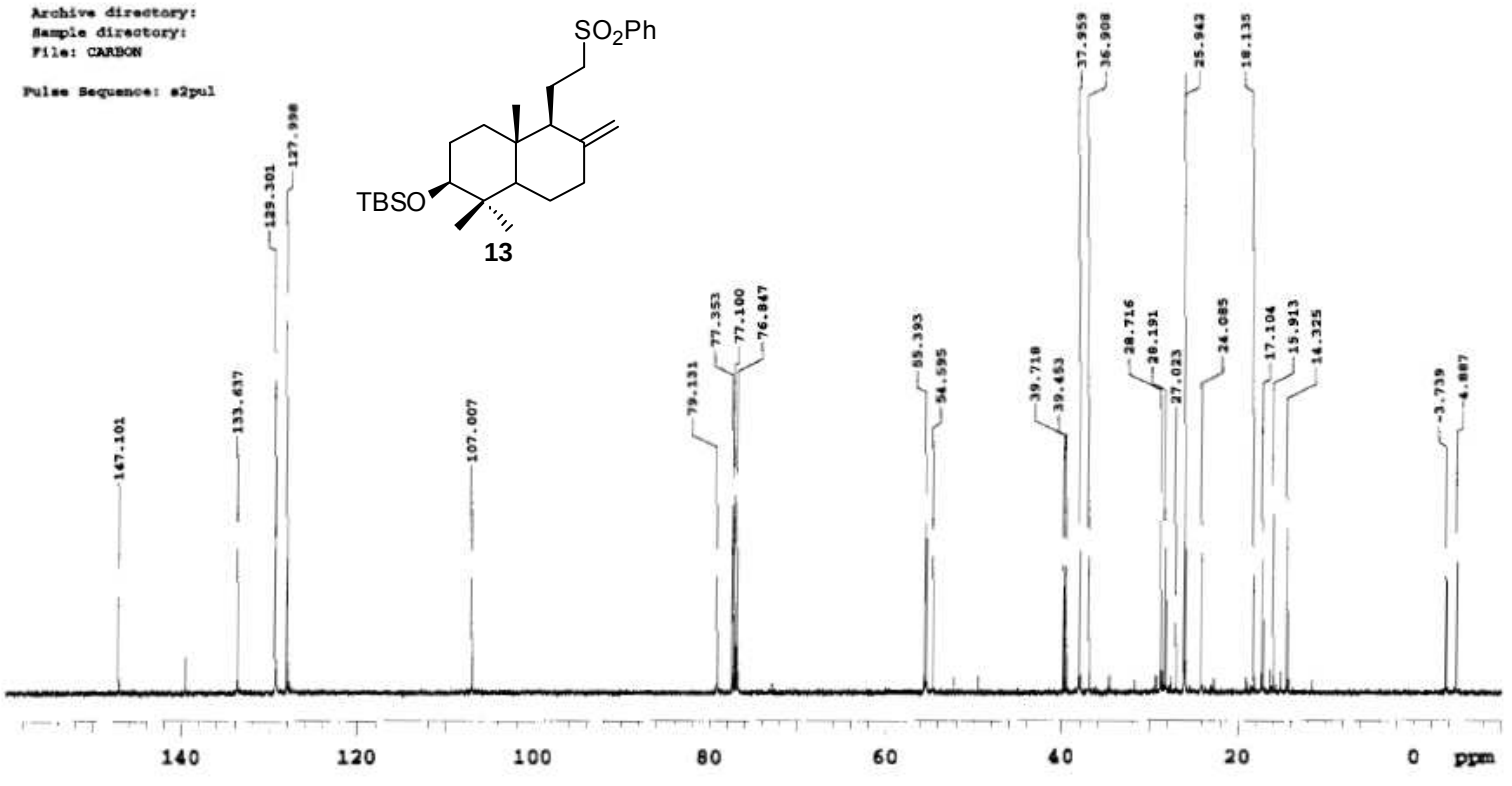
1.33
16.93
3.44
2.93
7.74
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

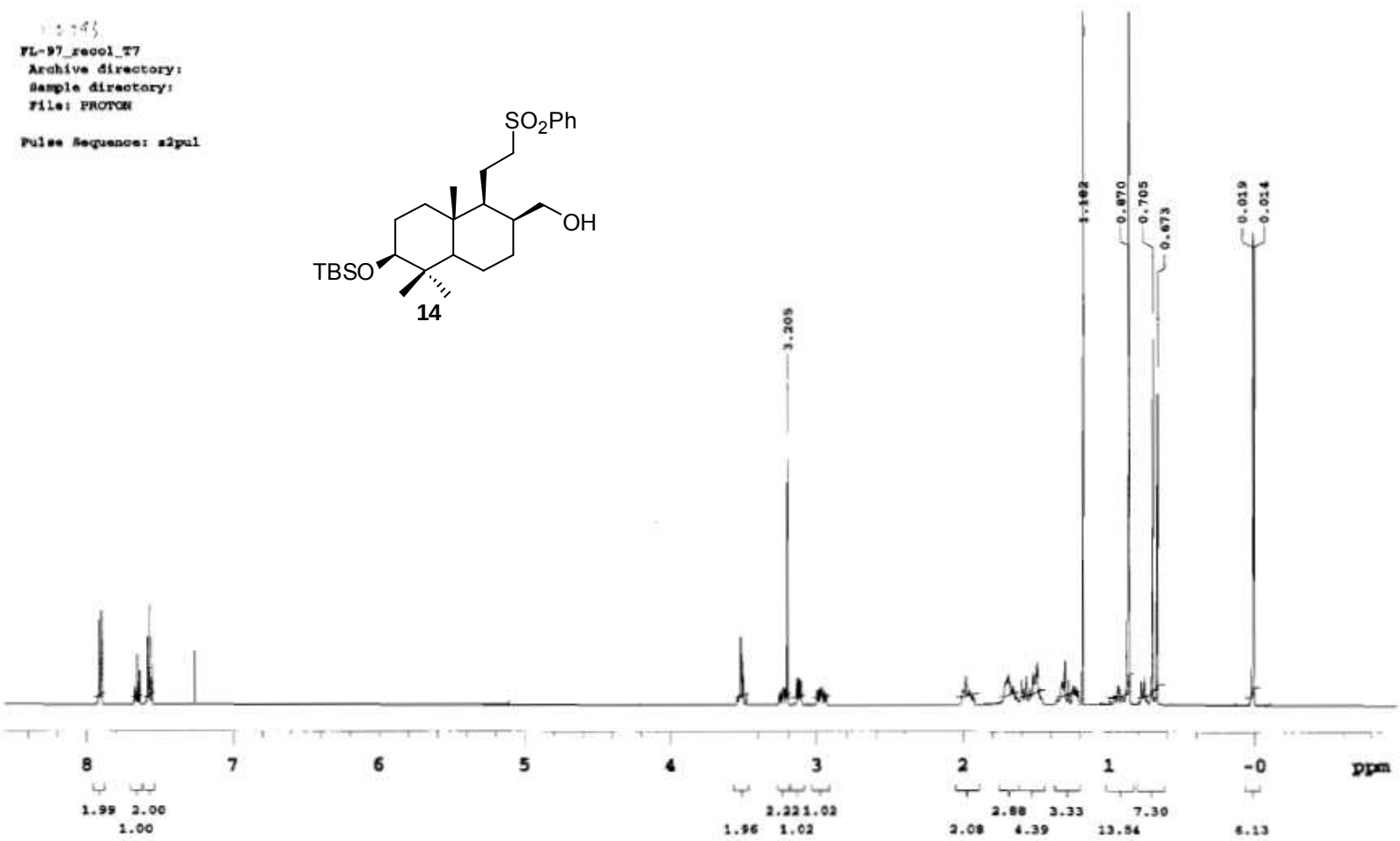

145.532
140.320
133.615
129.252
128.276
107.967
78.959
77.414
77.160
76.906
54.463
52.534
50.583
39.874
39.563
37.563
36.710
28.694
28.092
26.049
23.803
18.250
15.897
15.183
-3.655
-4.770
SO2Ph
TBSO
5
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

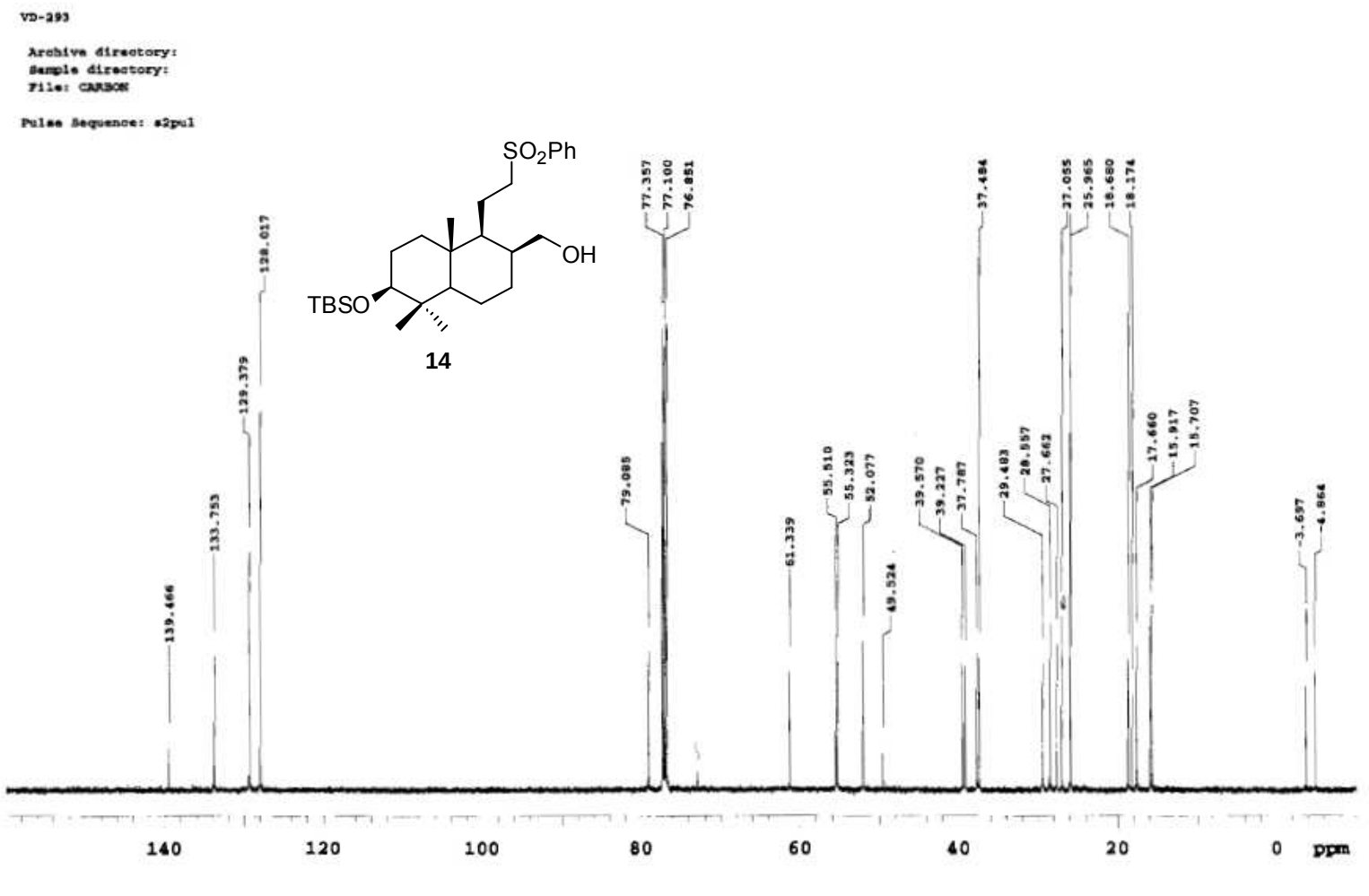

VD-257
Archive directory:
Sample directory:
File: PROTON
Pulse Sequence: s2pul
SO2Ph
TBSO
12
0.906
0.891
0.873
0.767
0.017
0.015
8
7
6
5
4
3
2
1
-0
ppm
2.38 2.43
1.17
1.00
1.18
0.97
0.96
1.16
1.96
1.17
1.09 1.23 2.89 3.91
4.47 0.60 18.71
7.40

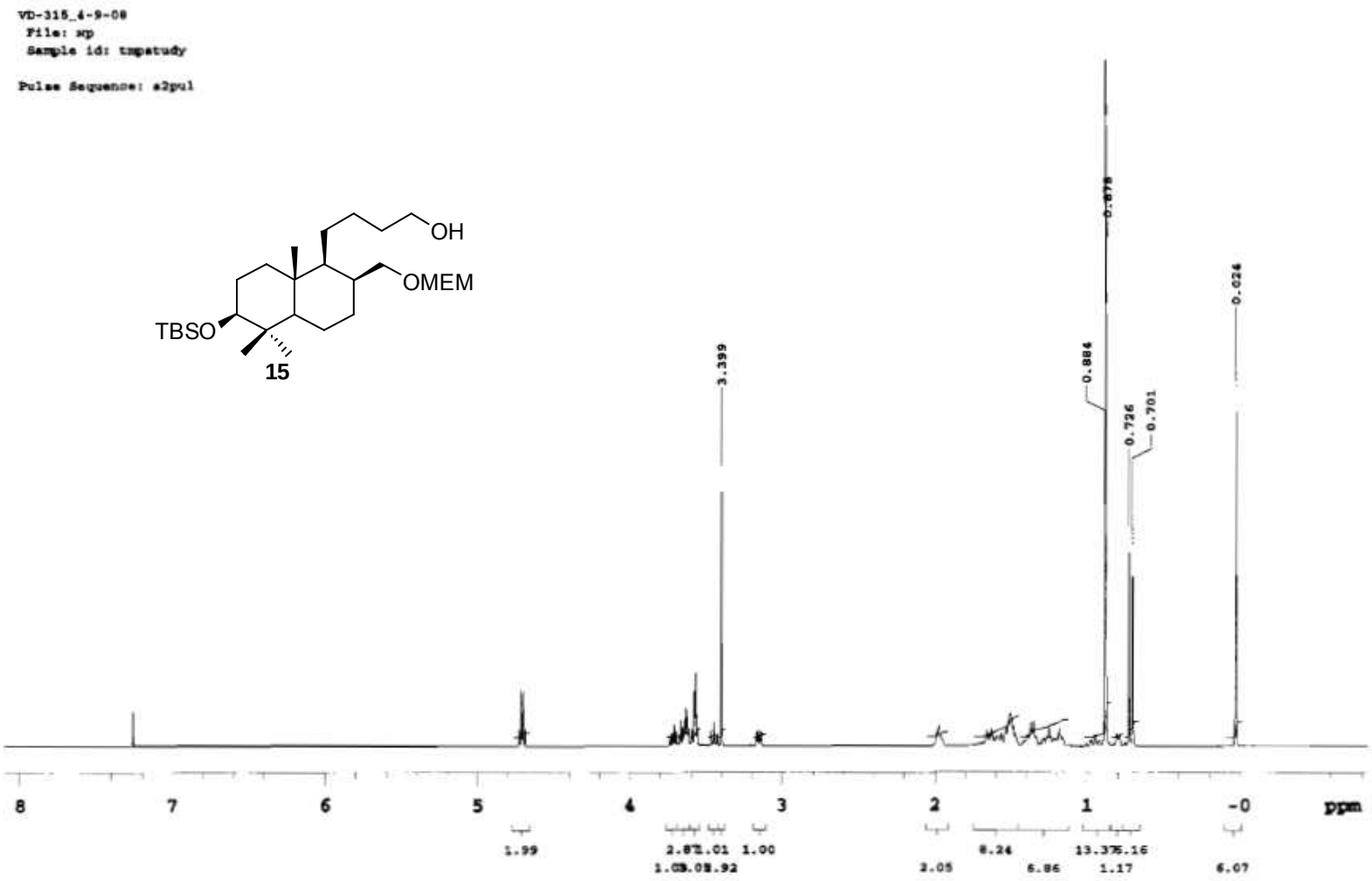

VD-257
Archive directory:
Sample directory:
File: CARBON
Pulse Sequence: s2pul
SO2Ph
TBSO
12
147.218
145.553
140.813
133.349
132.742
129.364
129.317
127.620
127.558
109.353
79.233
77.357
77.100
76.843
59.627
53.743
39.912
39.220
38.449
36.348
28.743
27.911
25.962
22.999
18.151
17.077
16.135
15.053
-3.743
-4.887
140
120
100
80
60
40
20
0
ppm

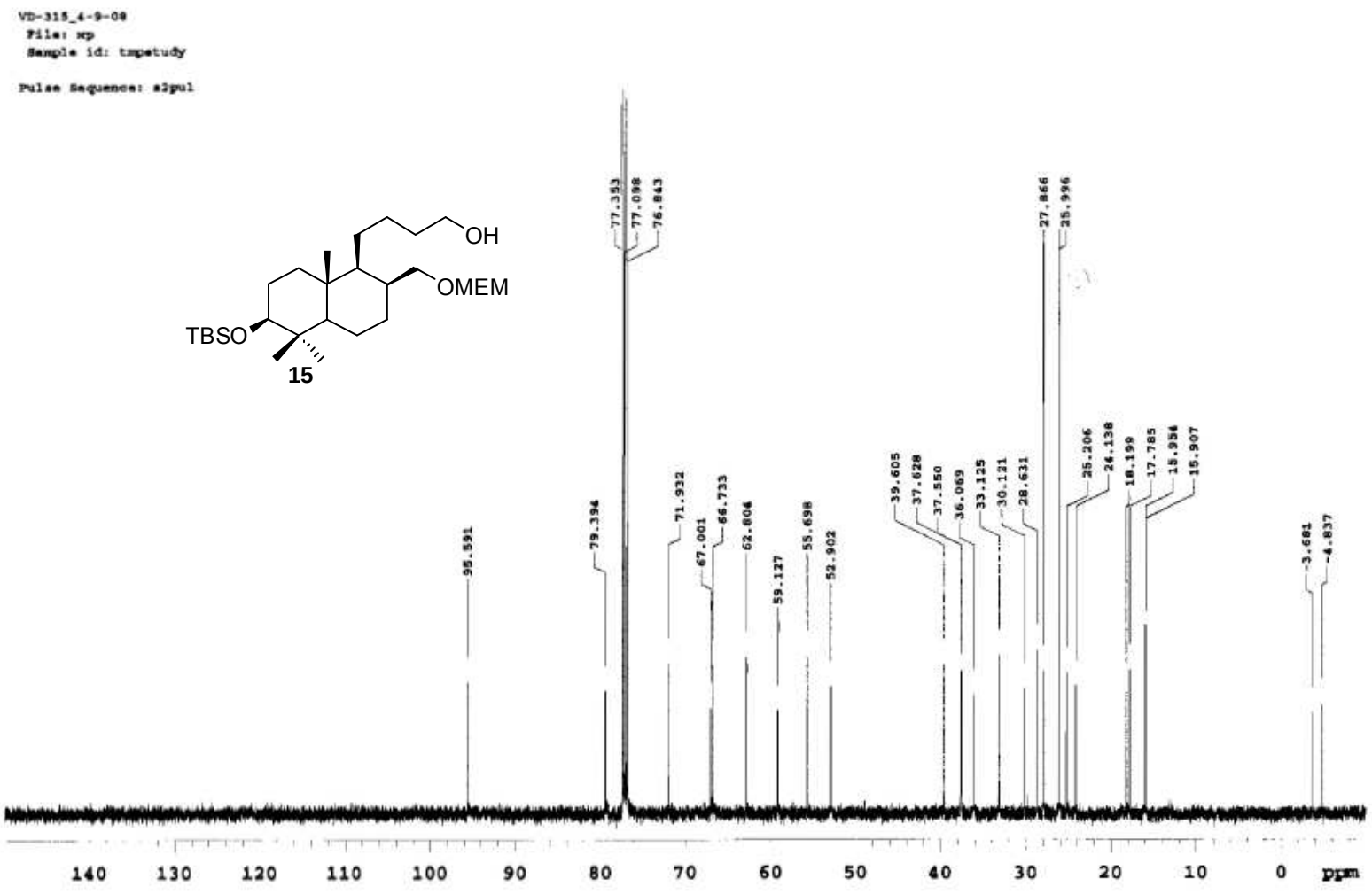

VD-261.7
Archive directory:
Sample directory:
File: PROTON
Pulse Sequence: s2pul
SO2Ph
TBSO
13
1.110
0.809
0.806
0.801
0.642
0.572
-0.036
-0.045
8
7
6
5
4
3
2
1
0
ppm
2.34
2.40
1.16
1.00
0.97
1.55
1.01
1.10
1.00
1.26
1.11
7.32
1.77
1.24
3.51
7.27

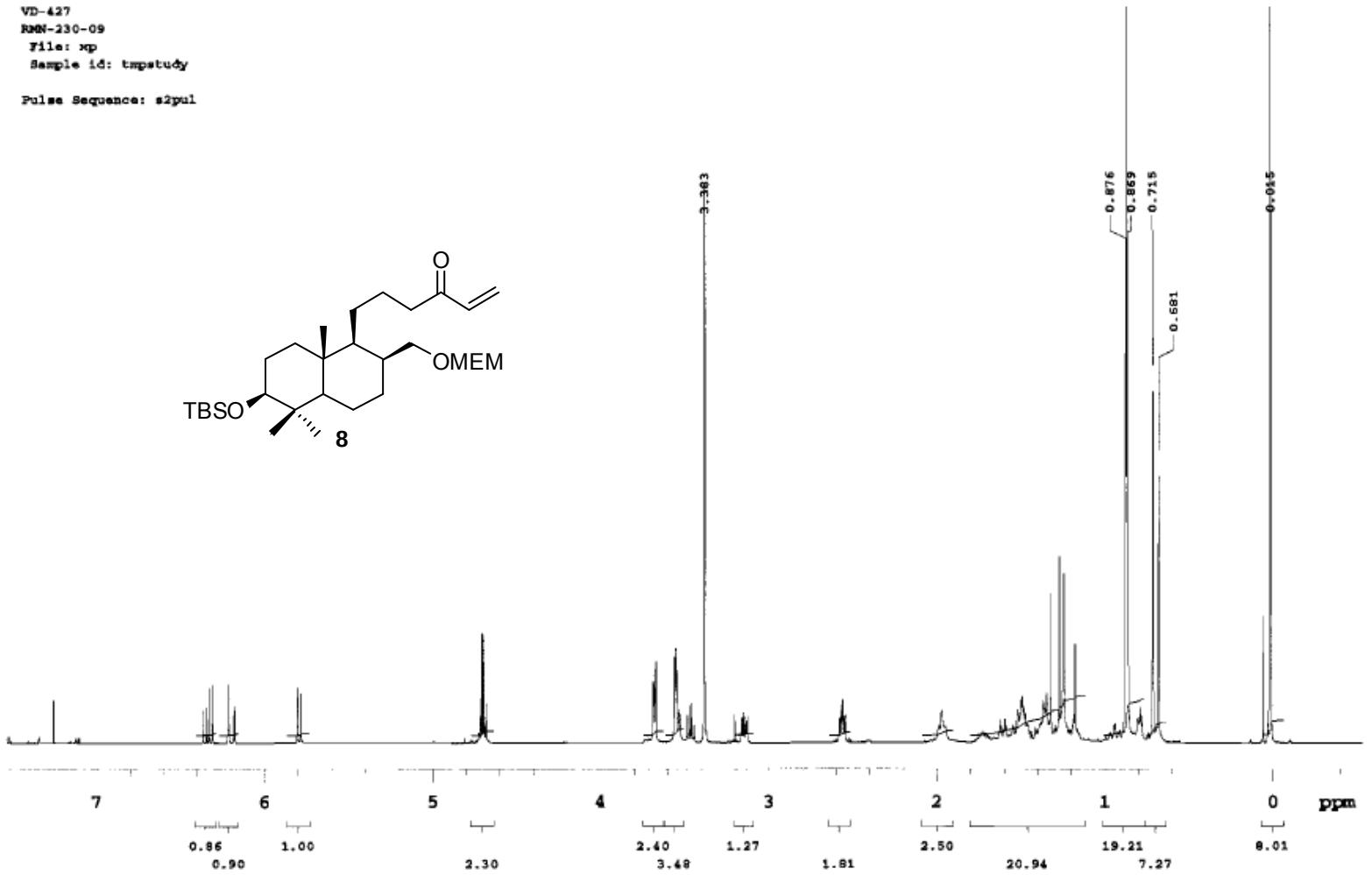

VD-261.7
Archive directory:
Sample directory:
File: CARBON
Pulse Sequence: s2pul
SO2Ph
TBSO
13
147.101
133.637
129.301
127.958
107.007
79.131
77.353
77.100
76.847
55.393
54.595
39.718
39.453
37.959
36.908
28.716
28.191
27.023
25.942
24.085
18.135
17.104
15.913
14.325
-3.739
-4.887
140
120
100
80
60
40
20
0
ppm

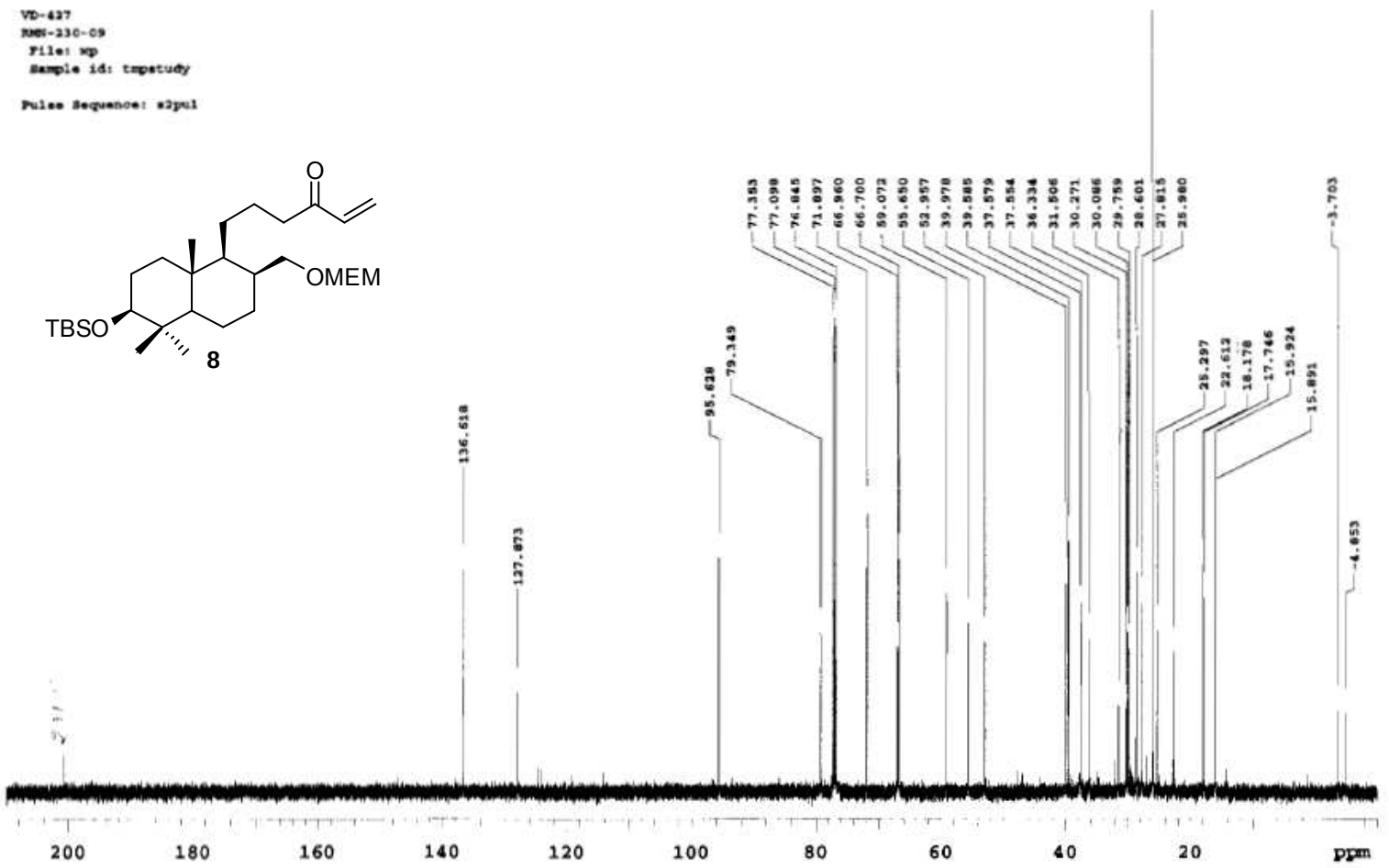

FL-97_recol_T7
Archive directory:
Sample directory:
File: PROTON
Pulse Sequence: s2pul
SO2Ph
OH
TBSO
14
3.209
1.102
0.870
0.705
0.673
0.019
0.014
8
7
6
5
4
3
2
1
-0
ppm
1.99 2.00
1.00
1.96 2.22 1.02
1.02
2.08 2.88 3.33
4.39
13.54 7.30
6.13

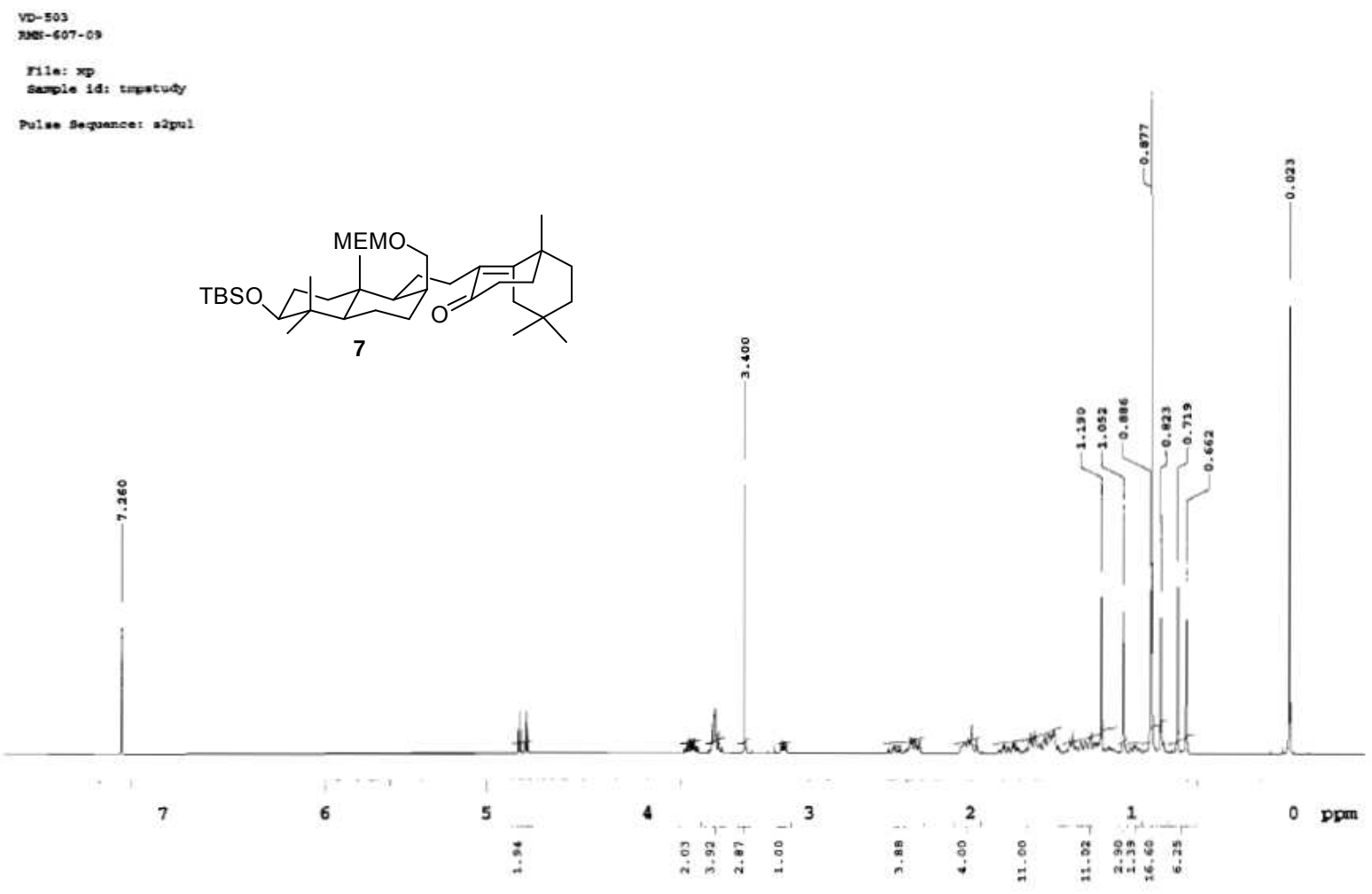

VD-293
Archive directory:
Sample directory:
File: CARBON
Pulse Sequence: s2pul
SO2Ph
OH
TBSO
14
139.466
133.753
129.379
128.617
79.085
77.357
77.100
76.851
61.339
55.810
55.323
52.077
49.524
39.570
39.227
37.787
37.484
29.483
28.557
27.662
27.055
25.965
18.680
18.174
17.660
15.917
15.707
-3.697
-4.864
140
120
100
80
60
40
20
0
ppm

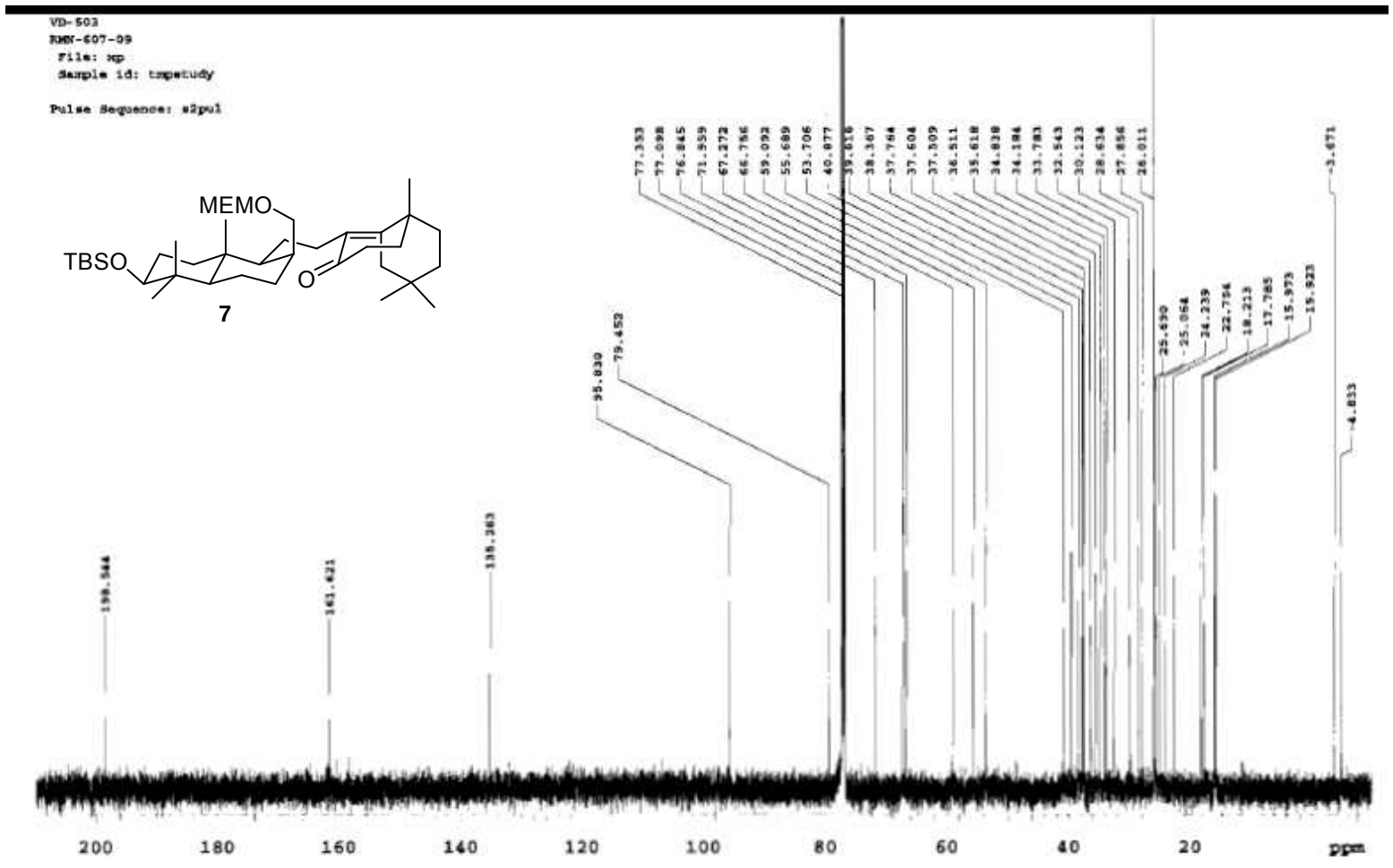

VD-315_4-9-08
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
OH
OMEM
TBSO
15
3.399
0.884
0.878
0.736
0.701
0.024
8
7
6
5
4
3
2
1
-0
ppm
1.99
2.87
1.01
1.00
8.24
13.37
5.16
1.03
3.08
1.92
2.05
6.86
1.17
6.07

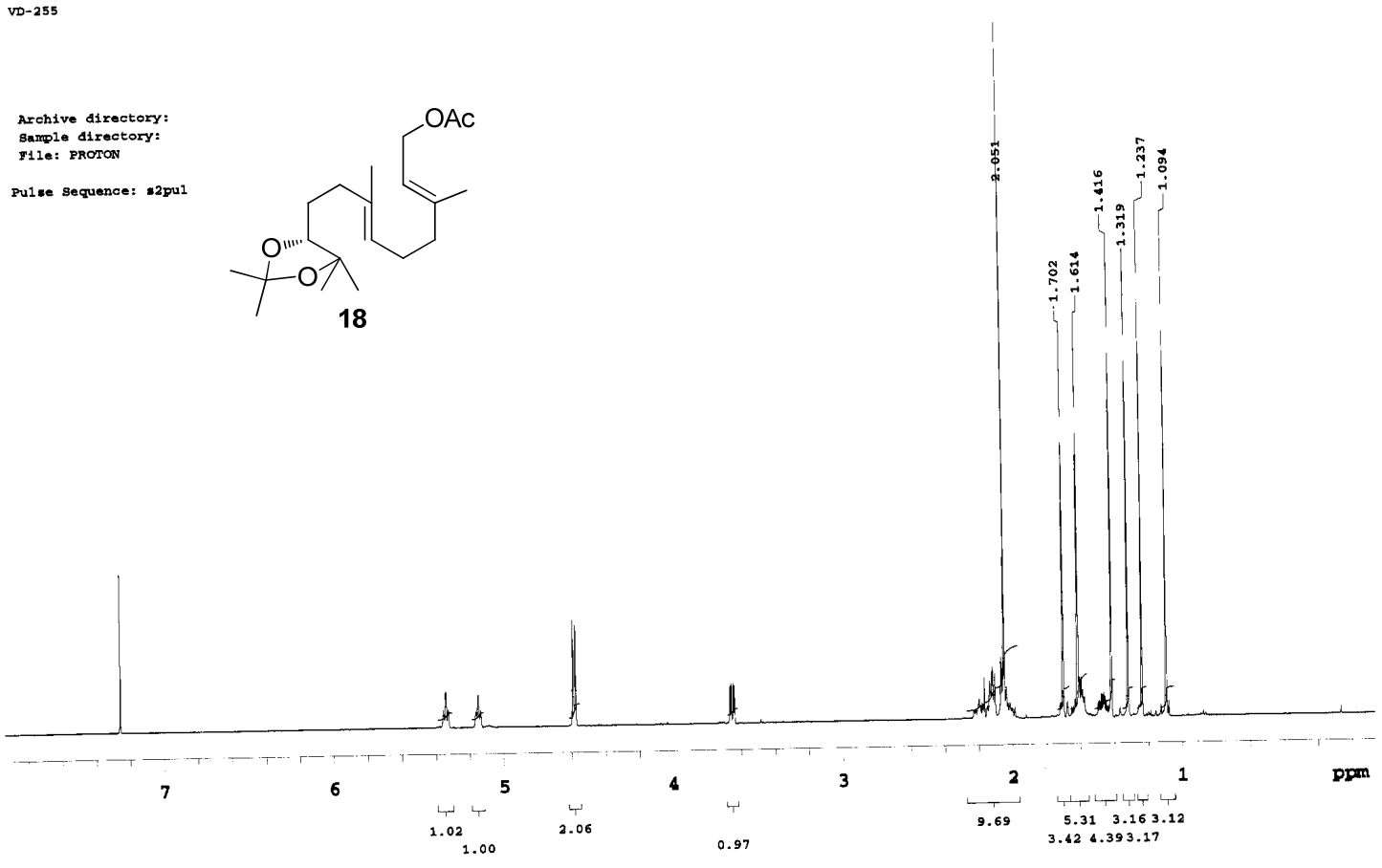

VD-315_4-9-08
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
OH
OMEM
TBSO
15
77.353
77.098
76.843
27.866
25.996
98.591
79.394
71.932
67.001
66.733
62.804
59.127
55.698
52.902
39.605
37.628
37.550
36.069
33.125
30.121
28.631
25.206
24.138
18.199
17.785
15.954
15.907
-3.681
-4.837
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

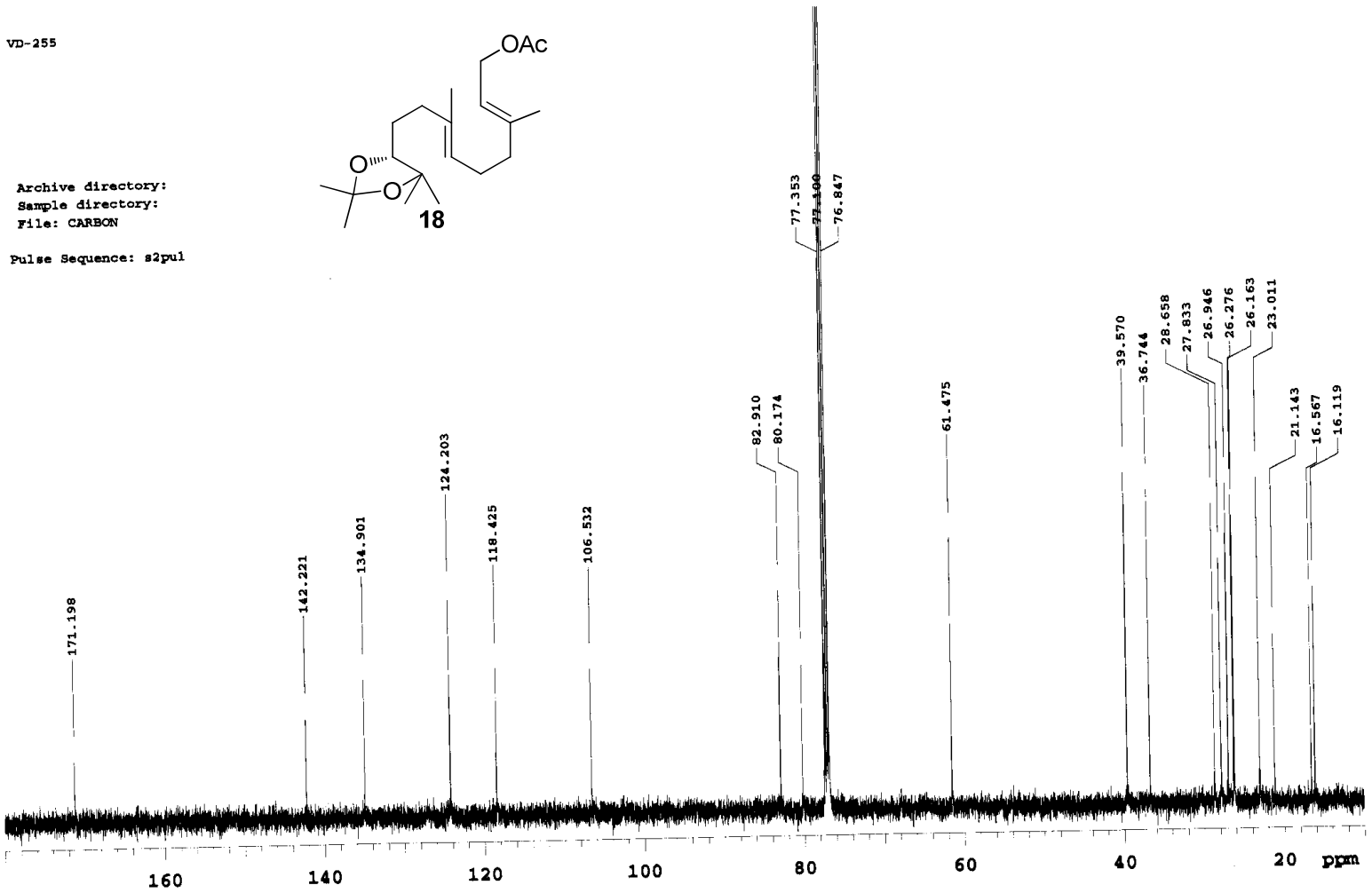

VD-427
RMN-230-09
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
O
OMEM
TBSO
8
3.383
0.876
0.869
0.715
0.681
0.015
7
6
5
4
3
2
1
0
ppm
0.86
1.00
2.40
1.27
2.50
19.21
8.01
0.90
2.30
3.48
1.81
20.94
7.27

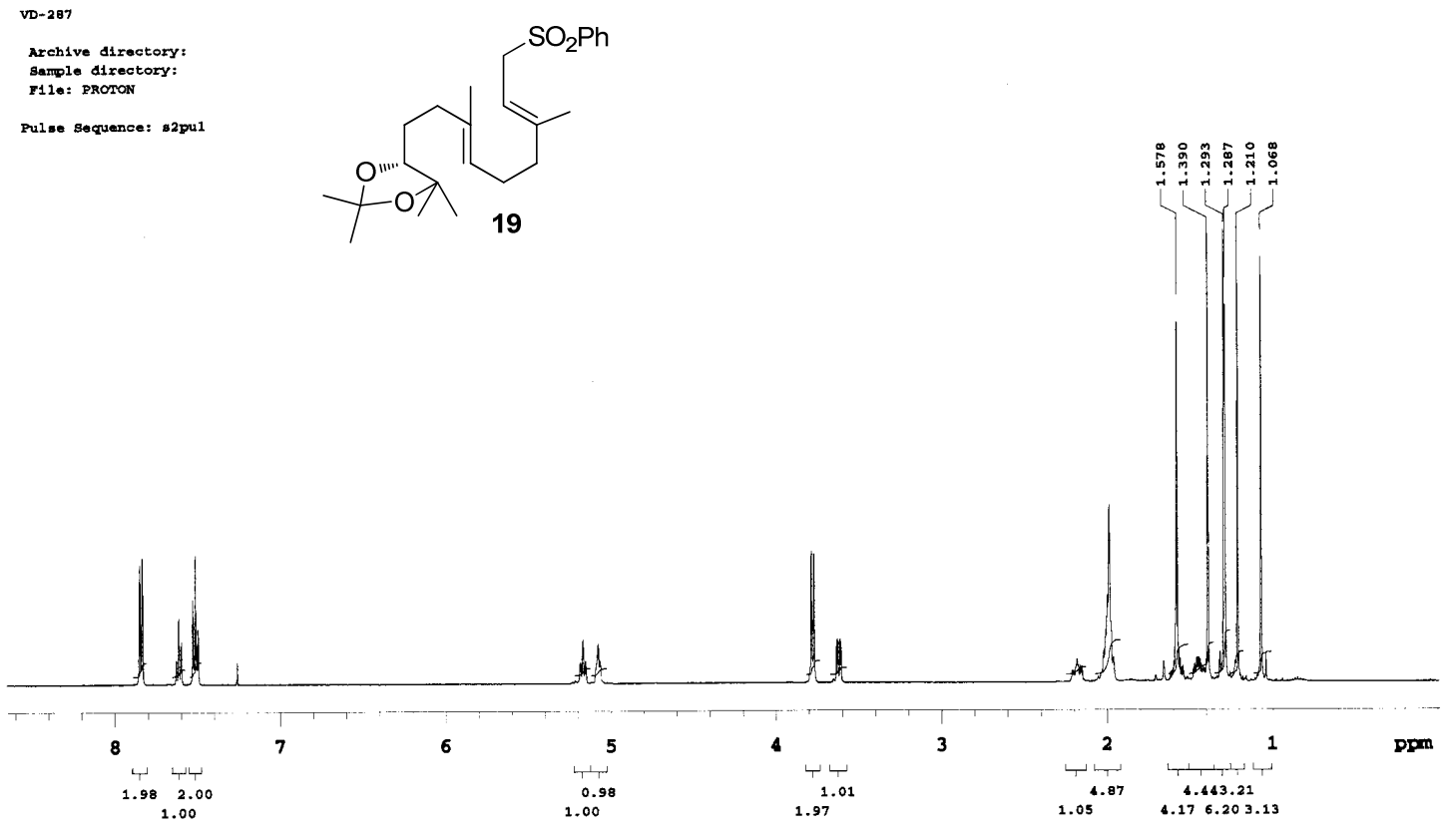

VD-427
RMN-230-09
File: wp
Sample id: tmpstudy
Pulse Sequence: s2pul
O
OMEM
TBSO
8
136.618
127.873
95.628
79.349
77.383
77.098
76.845
71.897
66.960
66.700
59.072
55.650
52.957
39.978
39.585
37.579
37.554
36.334
31.506
30.271
30.086
29.759
28.601
27.815
25.980
25.297
22.612
18.178
17.746
15.924
15.891
-3.703
-4.653
200
180
160
140
120
100
80
60
40
20
ppm

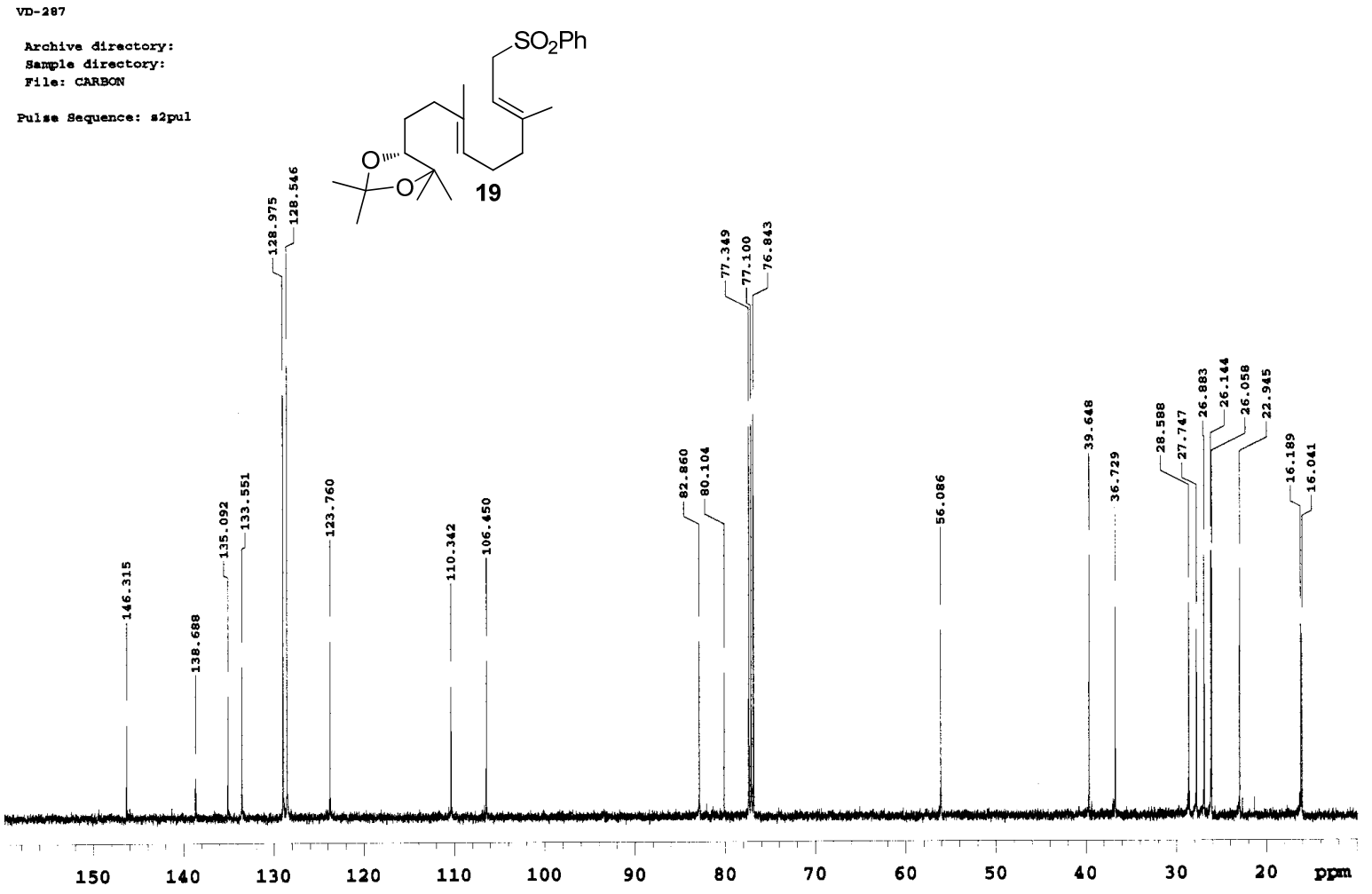

VD-503
RMN-607-09
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
MEMO
TBSO
O
7
7.260
3.400
1.190
1.052
0.886
0.877
0.823
0.719
0.662
0.023
7
6
5
4
3
2
1
0
ppm


VD-503
RMN-607-09
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
MEMO
TBSO
O
7
77.353
77.098
76.845
71.959
67.272
66.786
59.092
55.689
53.706
40.877
39.616
38.367
37.764
37.604
37.309
36.511
35.618
34.838
34.184
33.783
32.543
30.123
28.634
27.856
26.011
25.630
25.064
24.239
22.754
18.213
17.785
15.973
15.923
-3.671
-4.833
95.830
79.452
199.544
161.421
135.363
200
180
160
140
120
100
80
60
40
20
ppm


VD-255
Archive directory:
Sample directory:
File: PROTON
Pulse Sequence: s2pul
OAc
O
O
18
2.051
1.702
1.614
1.416
1.319
1.237
1.094
7
6
5
4
3
2
1
ppm
1.02
1.00
2.06
0.97
9.69
5.31
3.42
4.39
3.16
3.17
3.12

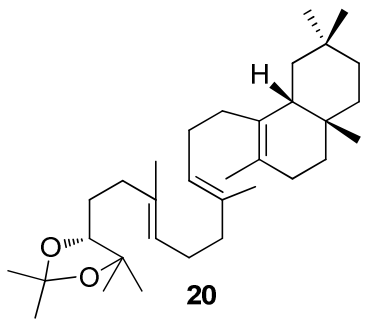

VD-255
OAc
O
O
18
Archive directory:
Sample directory:
File: CARBON
Pulse Sequence: s2pul
171.198
142.221
134.901
124.203
118.425
106.532
82.910
80.174
77.353
77.100
76.847
61.475
39.570
36.744
28.658
27.833
26.946
26.276
26.163
23.011
21.143
16.567
16.119
160
140
120
100
80
60
40
20
ppm


VD-287
Archive directory:
Sample directory:
File: PROTON
Pulse Sequence: s2pul
SO2Ph
O
O
19
1.578
1.390
1.293
1.287
1.210
1.068
8
7
6
5
4
3
2
1
ppm
1.98
2.00
1.00
0.98
1.00
1.01
1.97
4.87
1.05
4.443.21
4.17 6.20 3.13

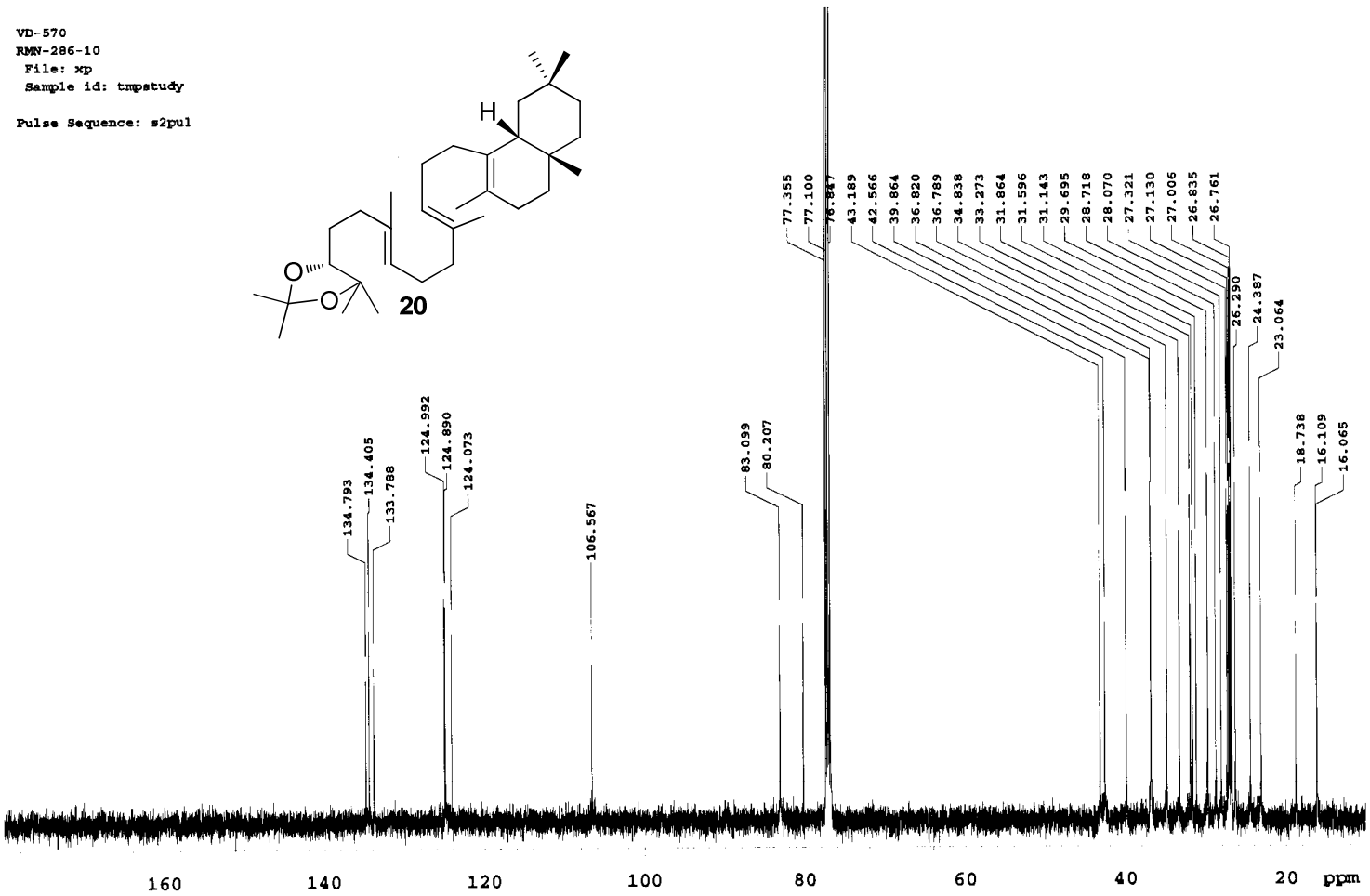

VD-287
Archive directory:
Sample directory:
File: CARBON
Pulse Sequence: s2pul
SO2Ph
O
O
19
146.315
138.688
135.092
133.551
128.975
128.546
123.760
110.342
106.450
82.860
80.104
77.349
77.100
76.843
56.086
39.648
36.729
28.588
27.747
26.883
26.144
26.058
22.945
16.189
16.041
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

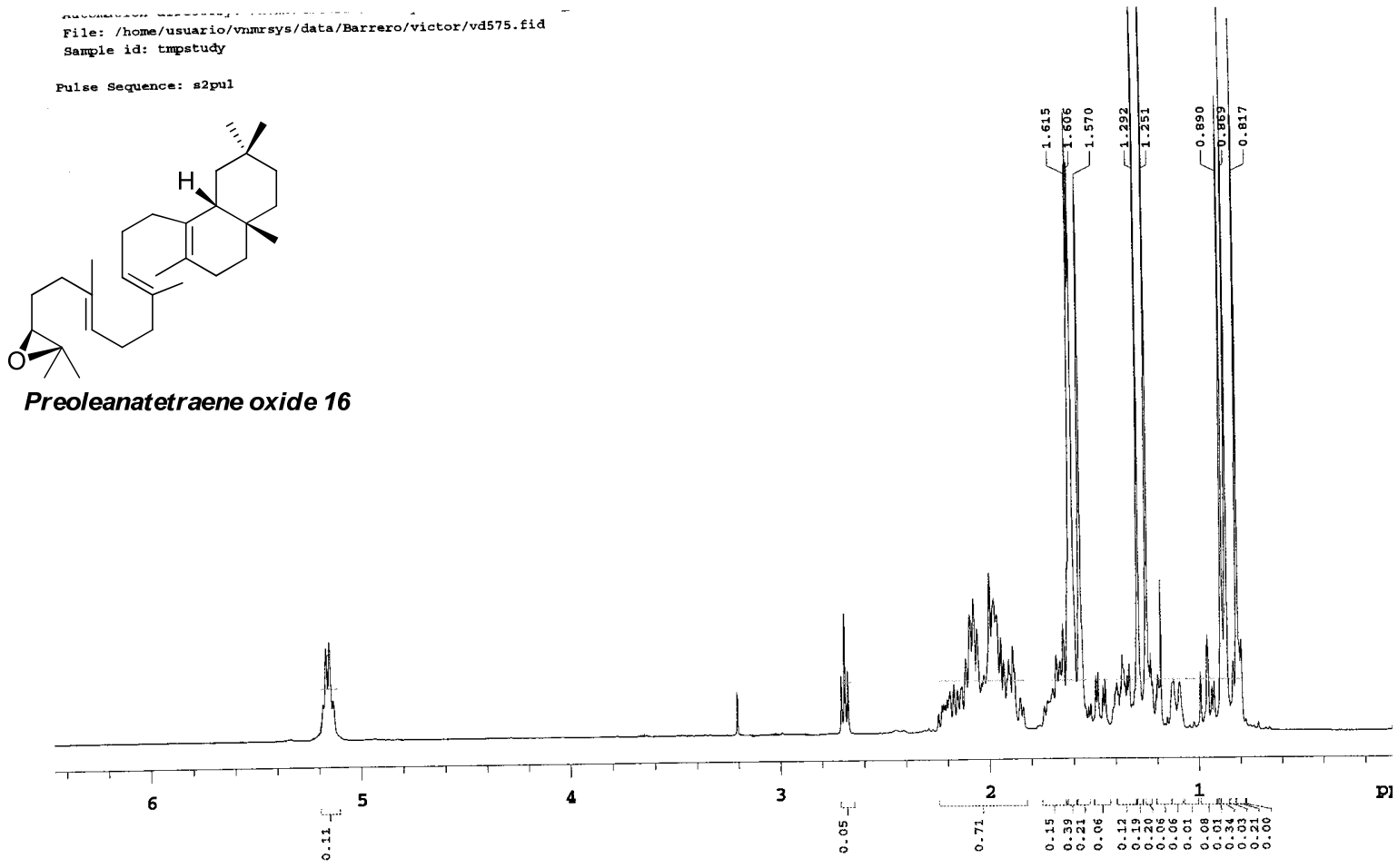
VD-570
RMN-286-10
File: xp
Sample id: tmpstudy

Pulse Sequence: s2pul

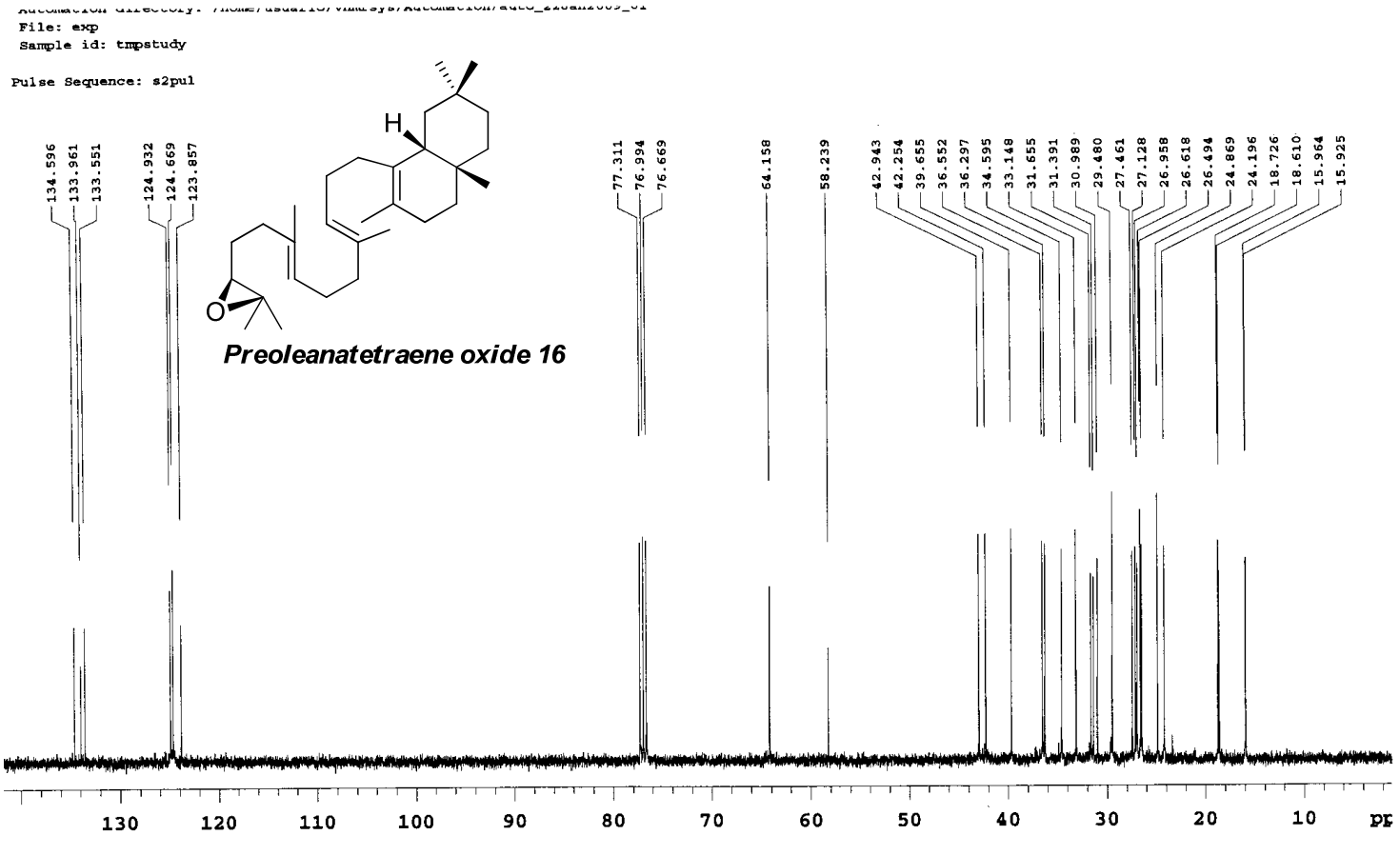


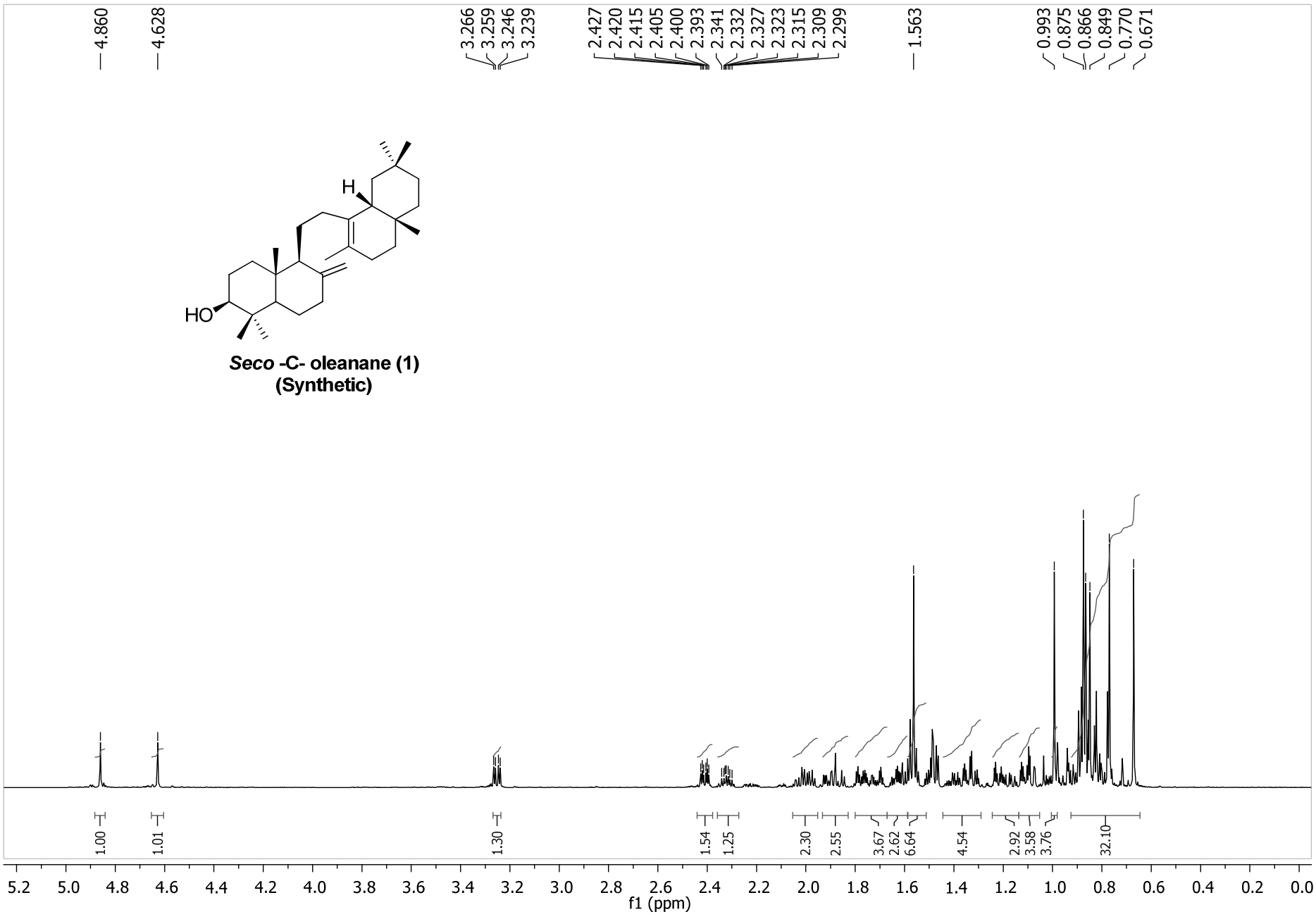
20


VD-570
RMN-286-10
File: xp
Sample id: tmpstudy
Pulse Sequence: s2pul
H
O
O
20
77.355
77.100
76.847
43.189
42.566
39.864
36.820
36.789
34.838
33.273
31.864
31.596
31.143
29.695
28.718
28.070
27.321
27.130
27.006
26.835
26.761
26.290
24.387
23.064
18.738
16.109
16.065
134.793
134.405
133.788
124.992
124.890
124.073
106.567
83.099
80.207
160
140
120
100
80
60
40
20
ppm

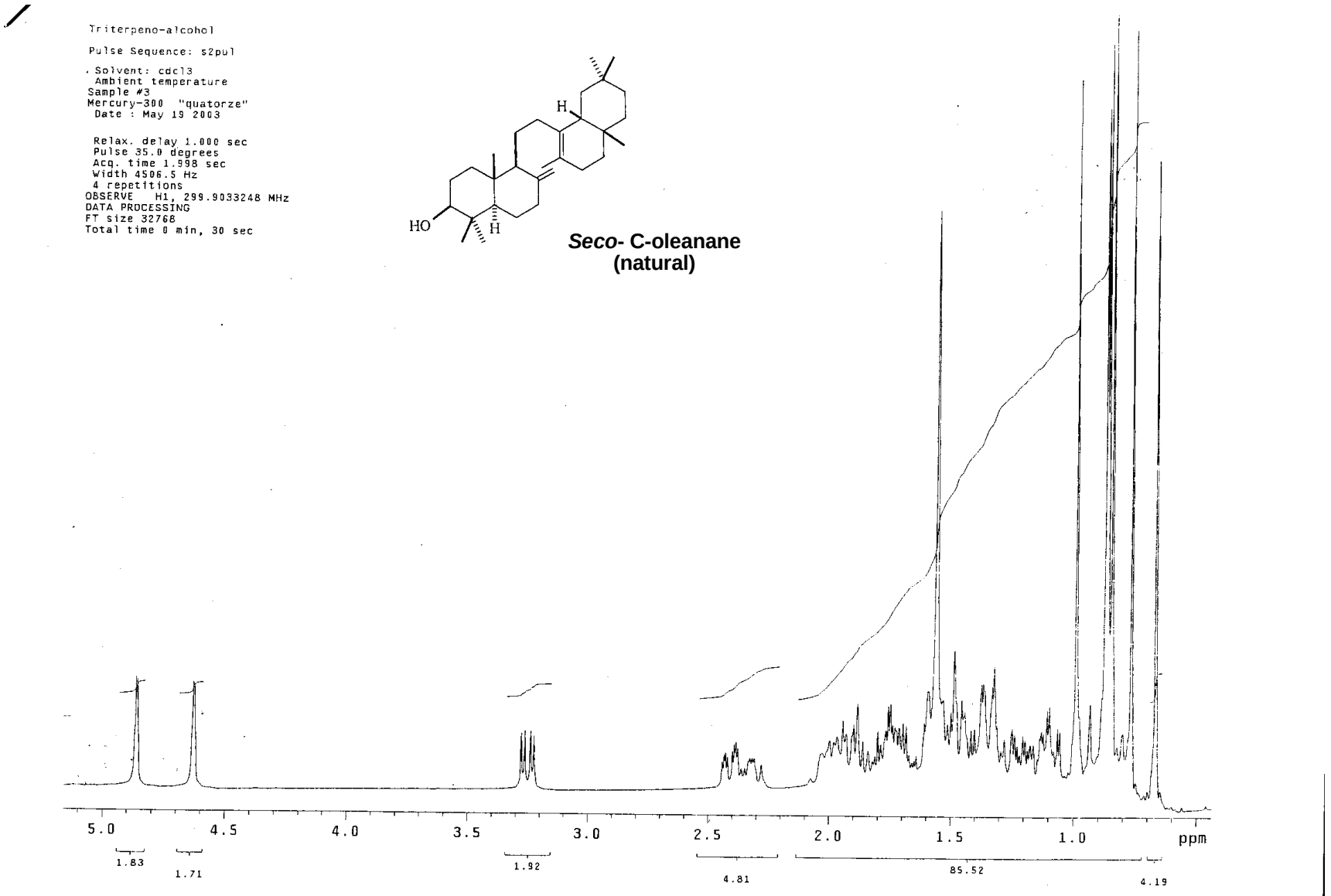


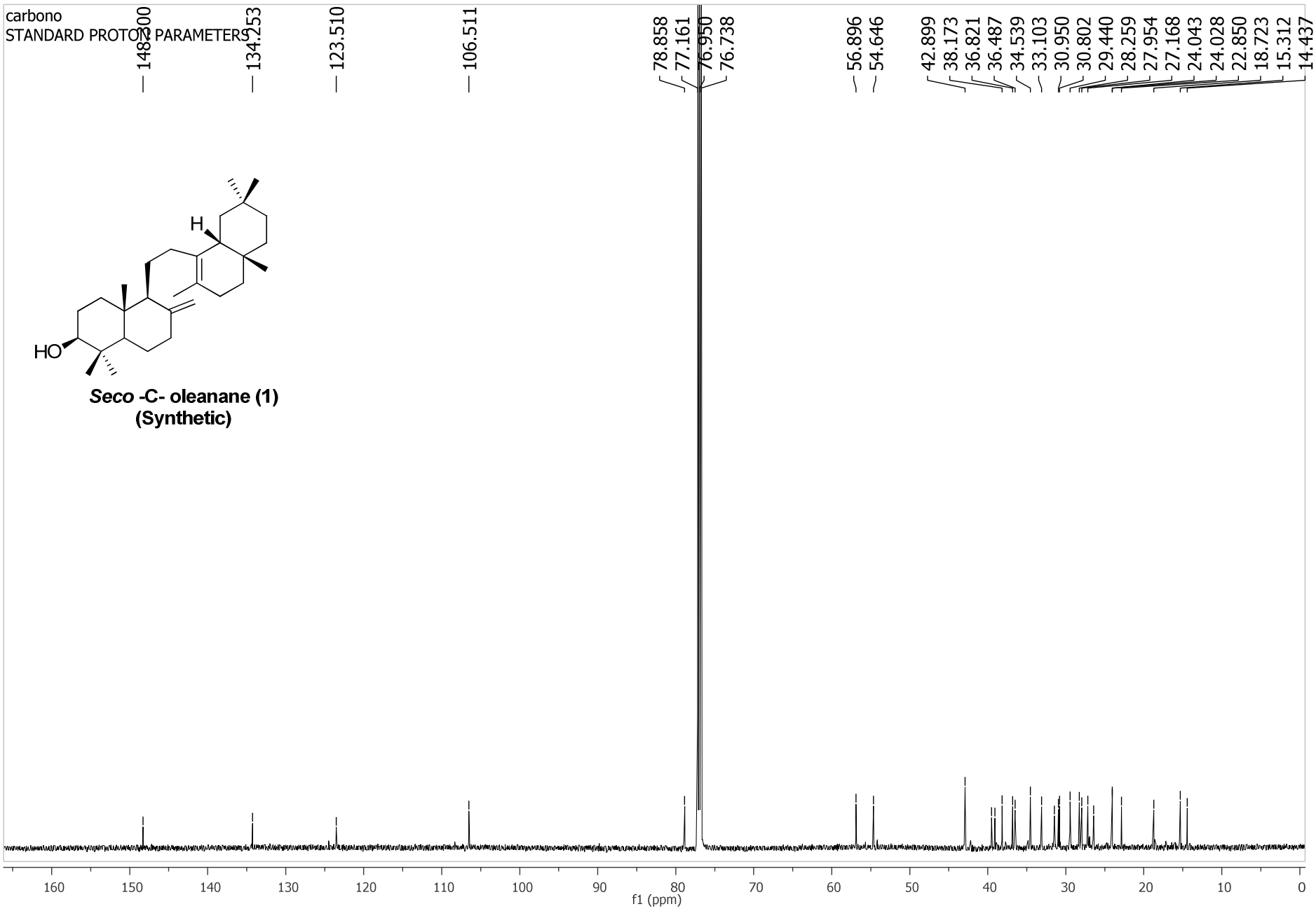
Preoleanatetraene oxide 16


File: exp
Sample id: tmpstudy
Pulse Sequence: s2pul
H
O
Preoleanatetraene oxide 16
134.596
133.961
133.551
124.932
124.669
123.857
77.311
76.994
76.669
64.158
58.239
42.943
42.254
39.655
36.552
36.297
34.595
33.148
31.655
31.391
30.989
29.480
27.461
27.128
26.958
26.618
26.494
24.869
24.196
18.726
18.610
15.964
15.925
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



***Seco* -C- oleanane (1)**
(Synthetic)


Triterpeno-alcohol
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #3
Mercury-300 "quatorze"
Date : May 19 2003
Relax. delay 1.000 sec
Pulse 35.0 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
4 repetitions
OBSERVE H1, 299.9033248 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 30 sec
HO
H
H
Seco- C-oleanane
(natural)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.83
1.71
1.92
4.81
85.52
4.19

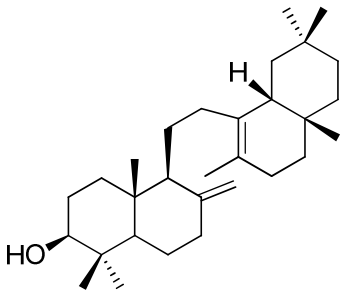


***Seco* -C- oleanane (1)**
(Synthetic)

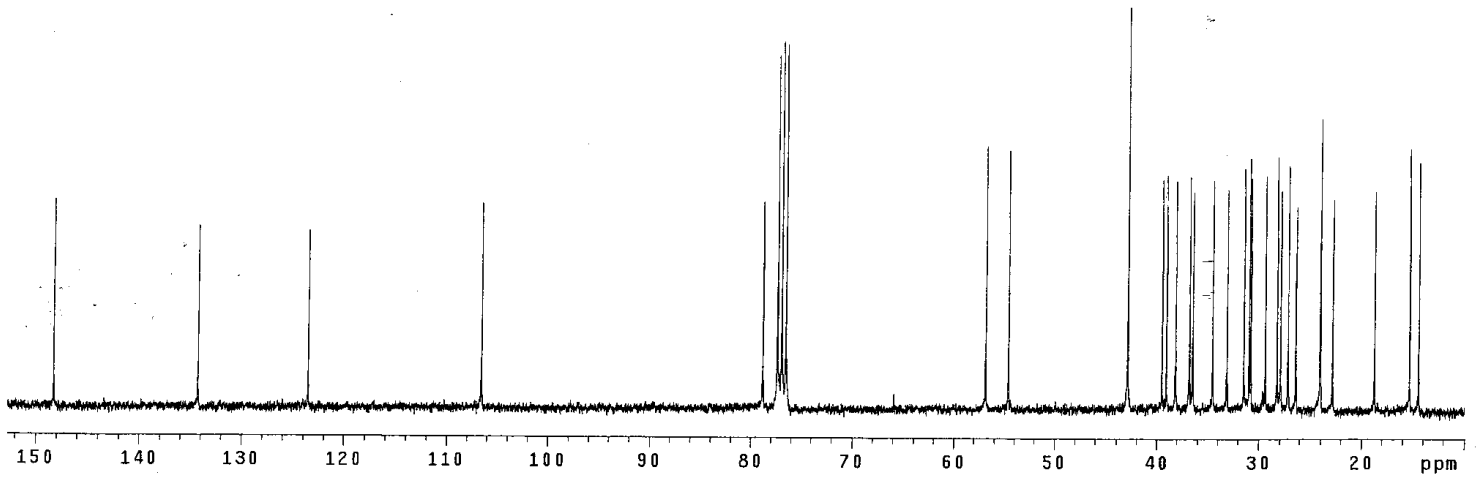
Triterpeno alcohol

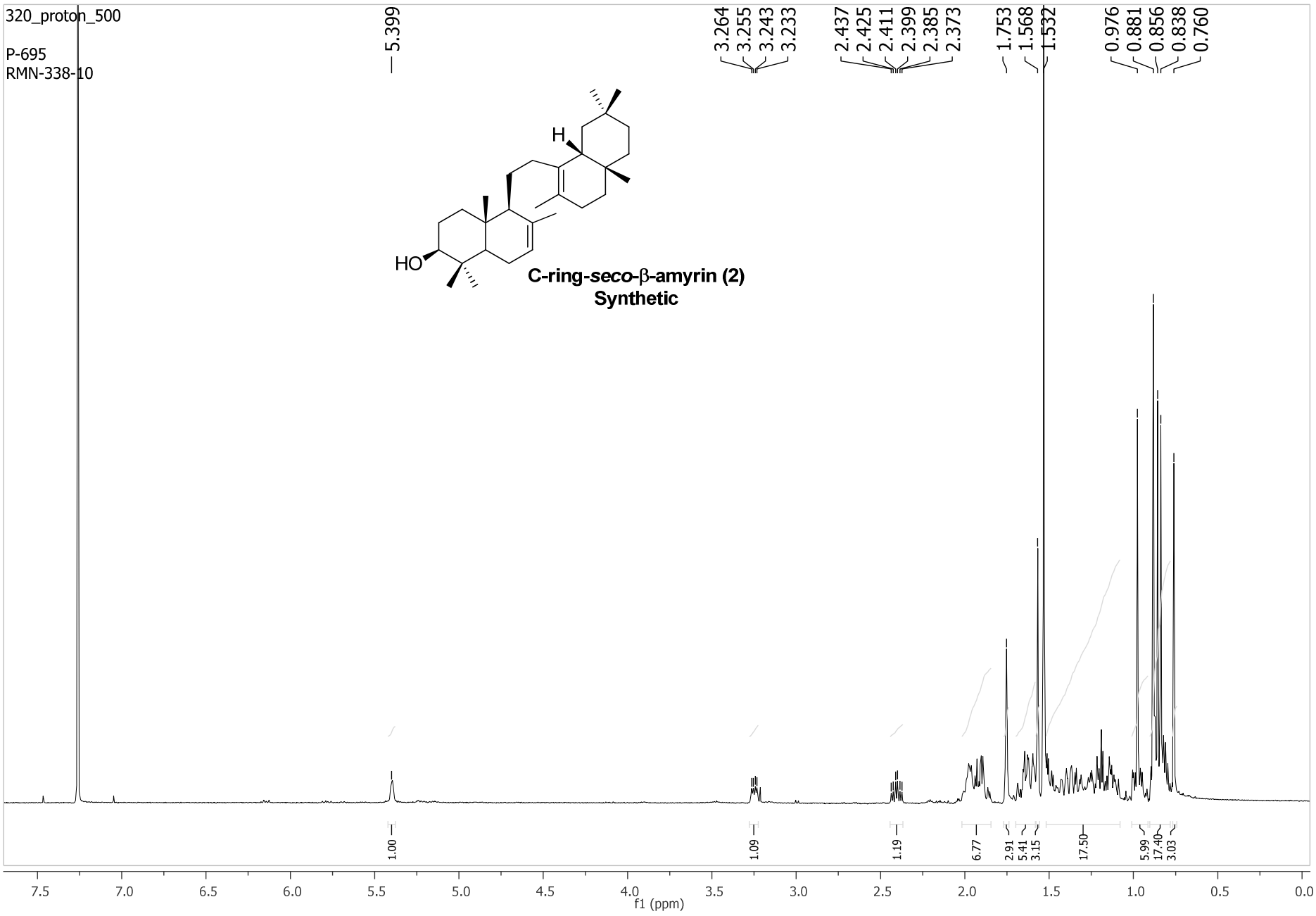
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
Sample #3
File: Ctriterp-ol
Mercury-300BB "nathan"
Date :May 20 2003

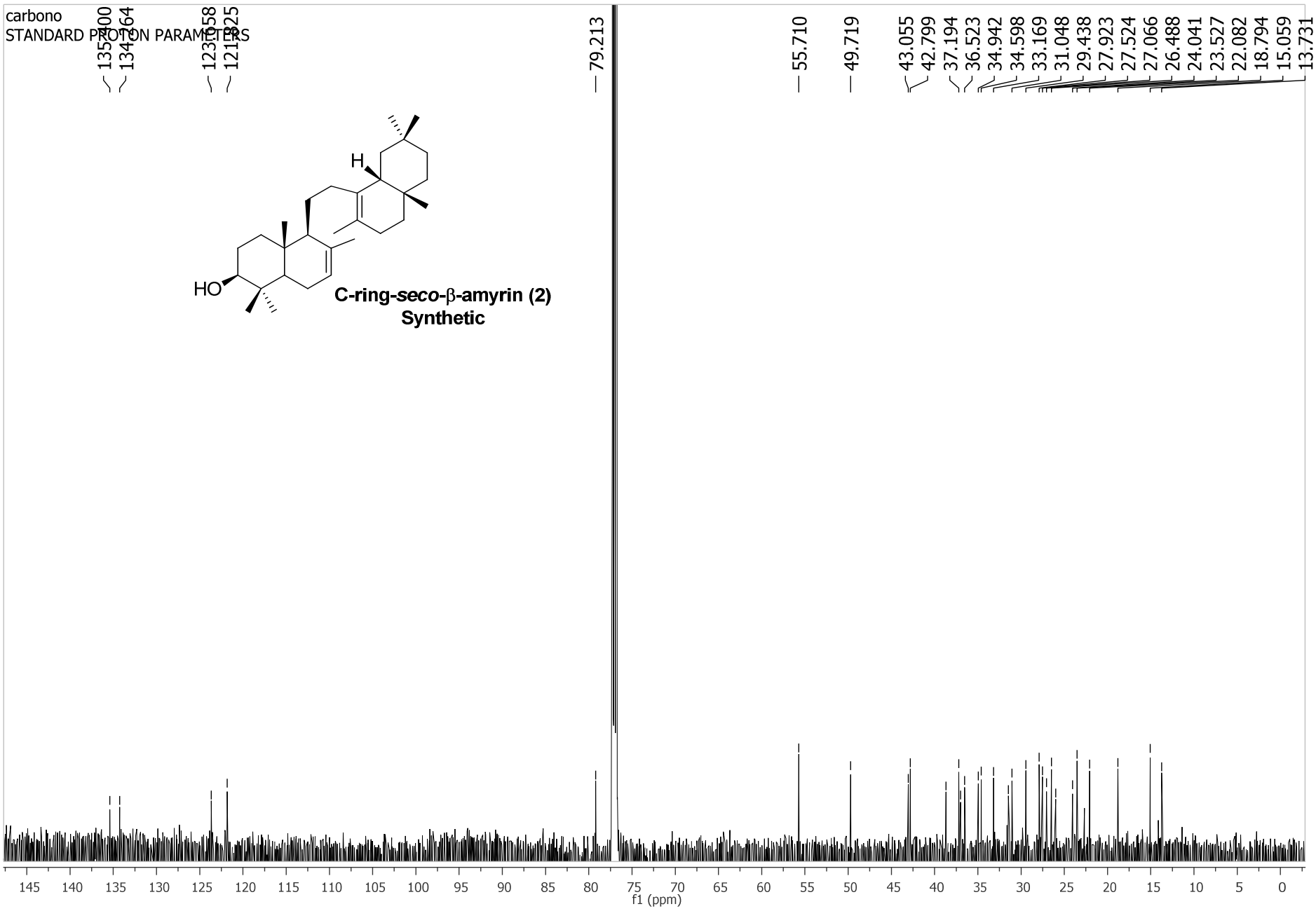
Relax. delay 2.000 sec
Pulse 39.0 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
672 repetitions
OBSERVE C13, 75.4107522 MHz
DECOUPLE H1, 299.9048450 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 57 hr, 7 min, 18 sec

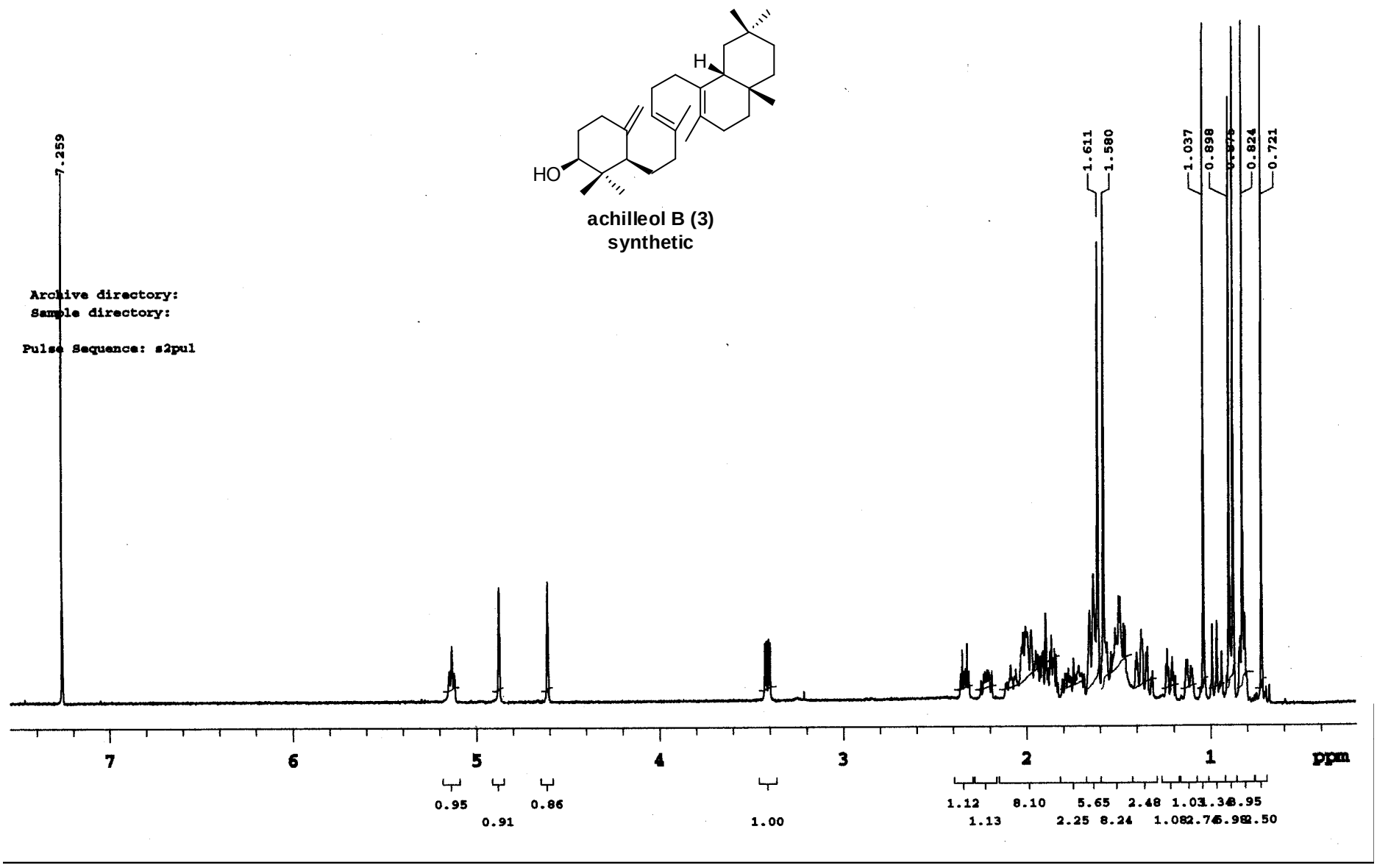


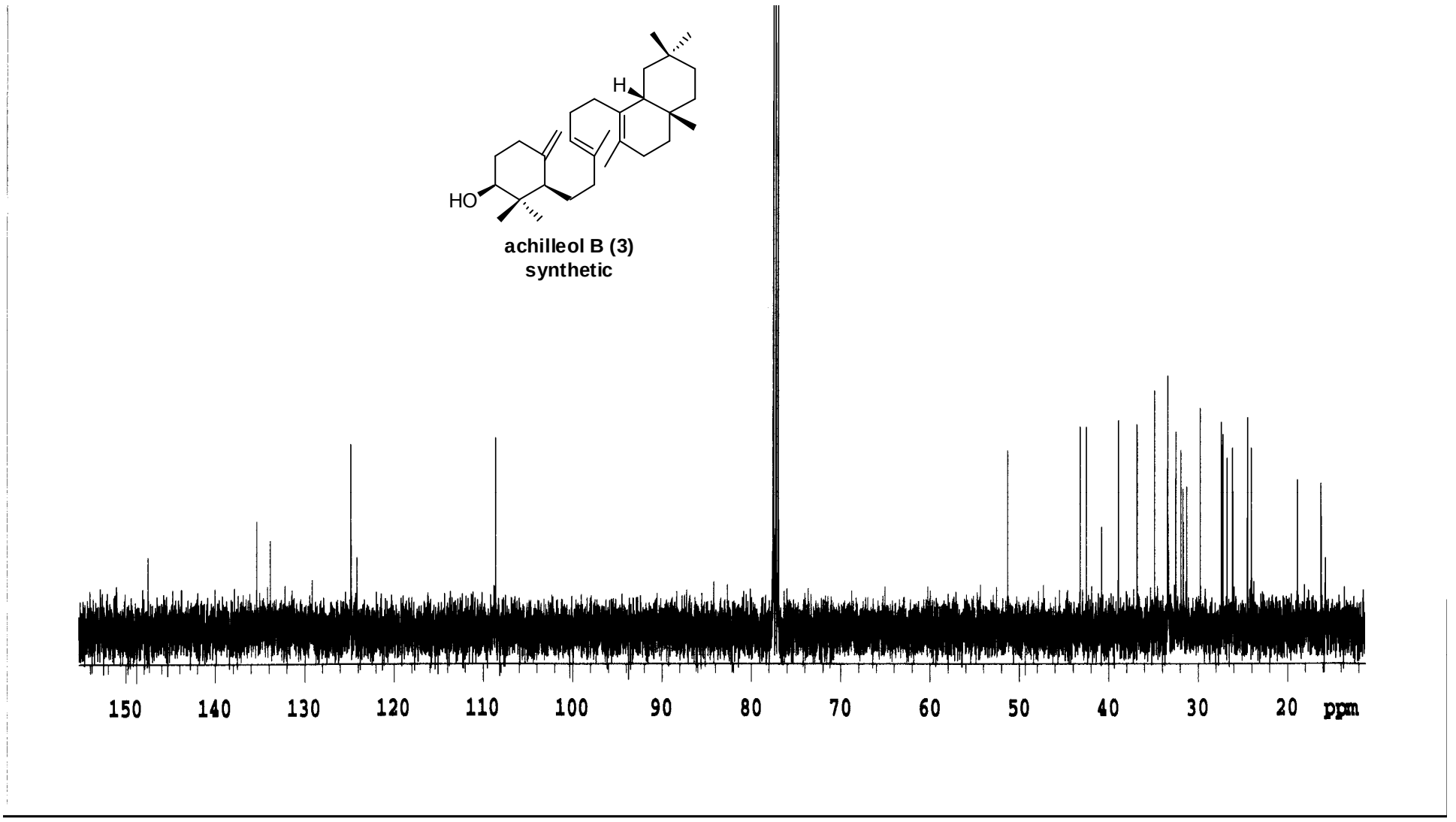
***Seco* -C- oleanane (1)**
(natural)

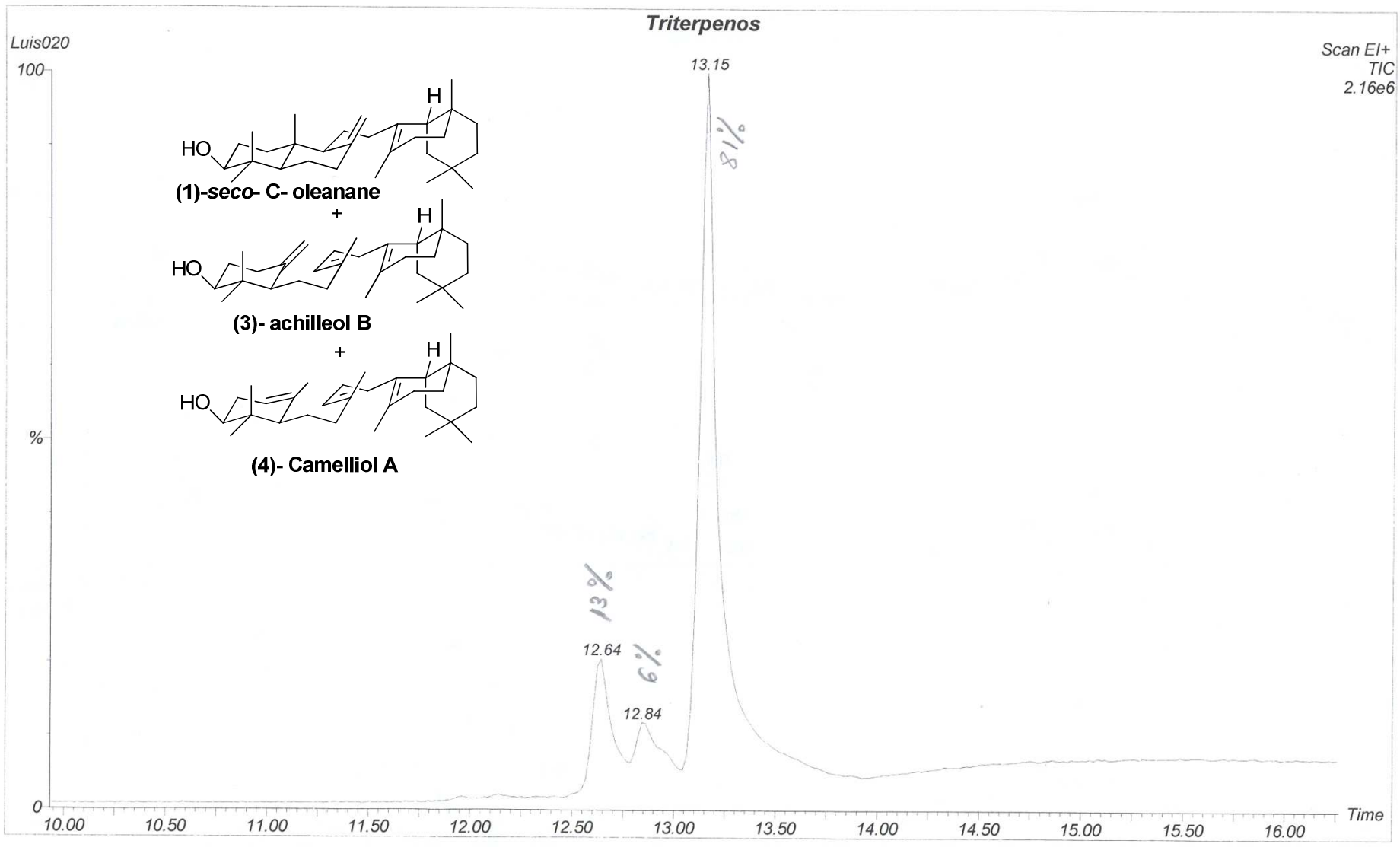



320_proton_500
P-695
RMN-338-10
5.399
3.264
3.255
3.243
3.233
2.437
2.425
2.411
2.399
2.385
2.373
1.753
1.568
1.532
0.976
0.881
0.856
0.838
0.760
H
HO
C-ring-seco-β-amyrin (2)
Synthetic
1.00
1.09
1.19
6.77
2.91
5.41
3.15
17.50
5.99
17.40
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


carbono
STANDARD PROTON PARAMETERS
135.400
134.764
123.658
121.825
79.213
55.710
49.719
43.055
42.799
37.194
36.523
34.942
34.598
33.169
31.048
29.438
27.923
27.524
27.066
26.488
24.041
23.527
22.082
18.794
15.059
13.731
H
HO
C-ring-seco-β-amyrin (2)
Synthetic
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 0
f1 (ppm)


HO
H
achilleol B (3)
synthetic
Archive directory:
Sample directory:
Pulse Sequence: s2pul
7.259
1.611
1.580
1.037
0.898
0.824
0.721
7
6
5
4
3
2
1
ppm
0.95
0.91
0.86
1.00
1.12
1.13
8.10
5.65
2.25
2.48
8.24
1.03
1.08
1.34
2.74
8.95
5.98
2.50


H
HO
achilleol B (3)
synthetic
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



HO H

(1)-*seco*- C- oleanane

\+

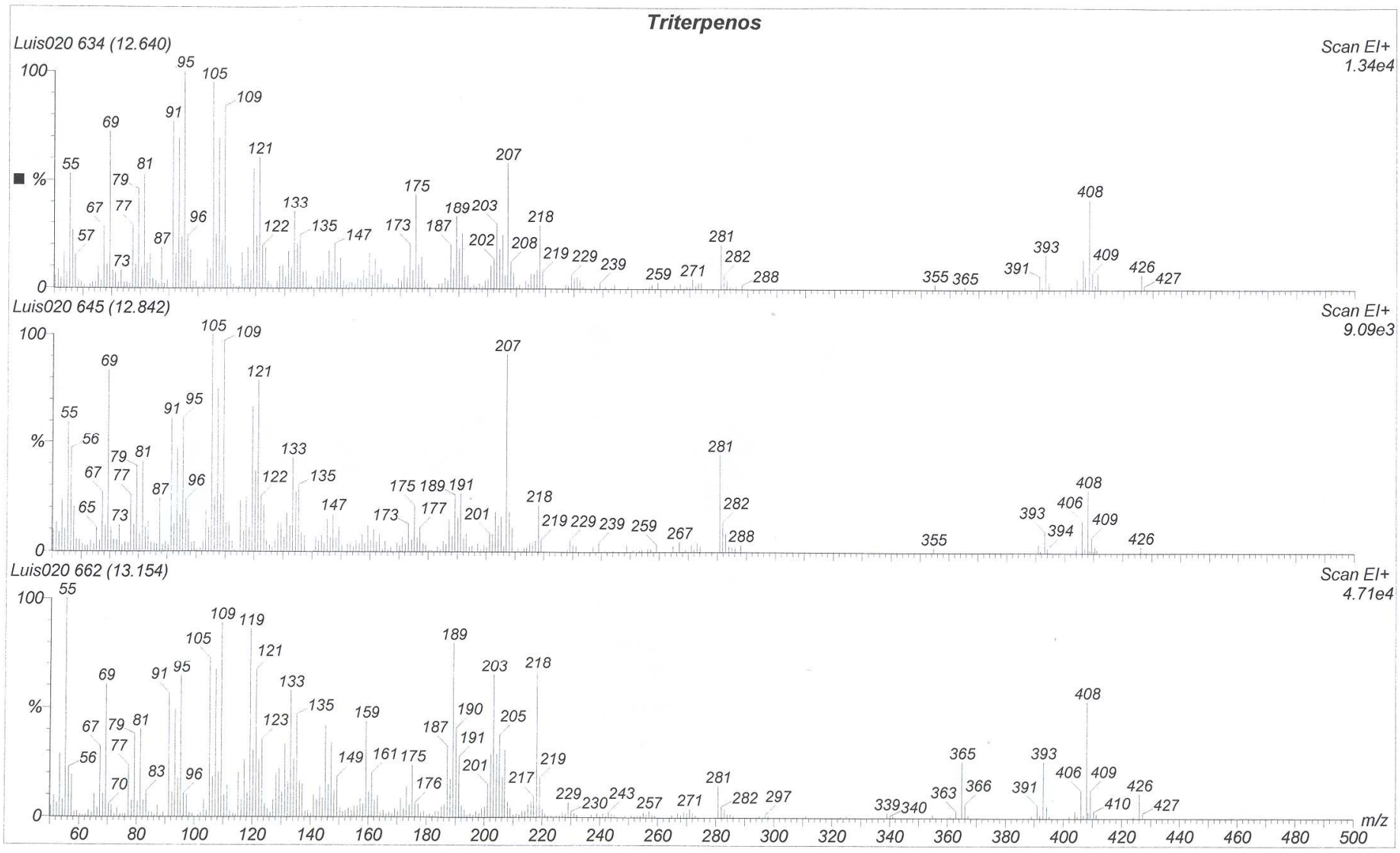
HO H

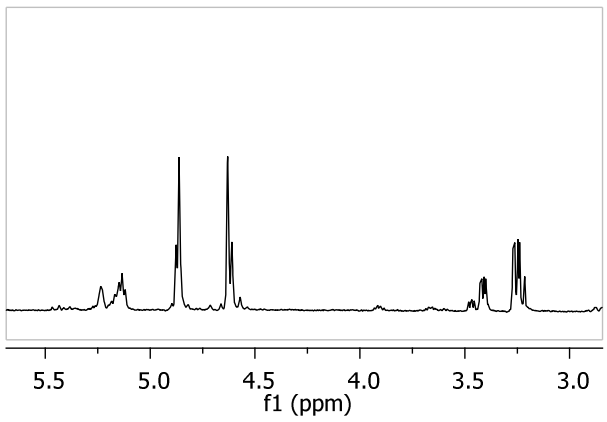
(3)- achilleol B

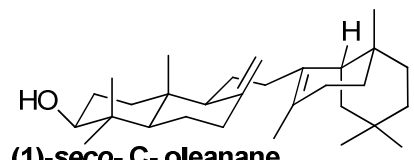
\+

HO H

(4)- Camelliol A


Triterpenos
Luis020 634 (12.640)
Scan EI+
1.34e4
Luis020 645 (12.842)
Scan EI+
9.09e3
Luis020 662 (13.154)
Scan EI+
4.71e4
100
%
0
m/z
60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480 500



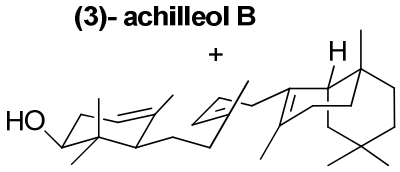


(1)-*seco*- C- oleanane

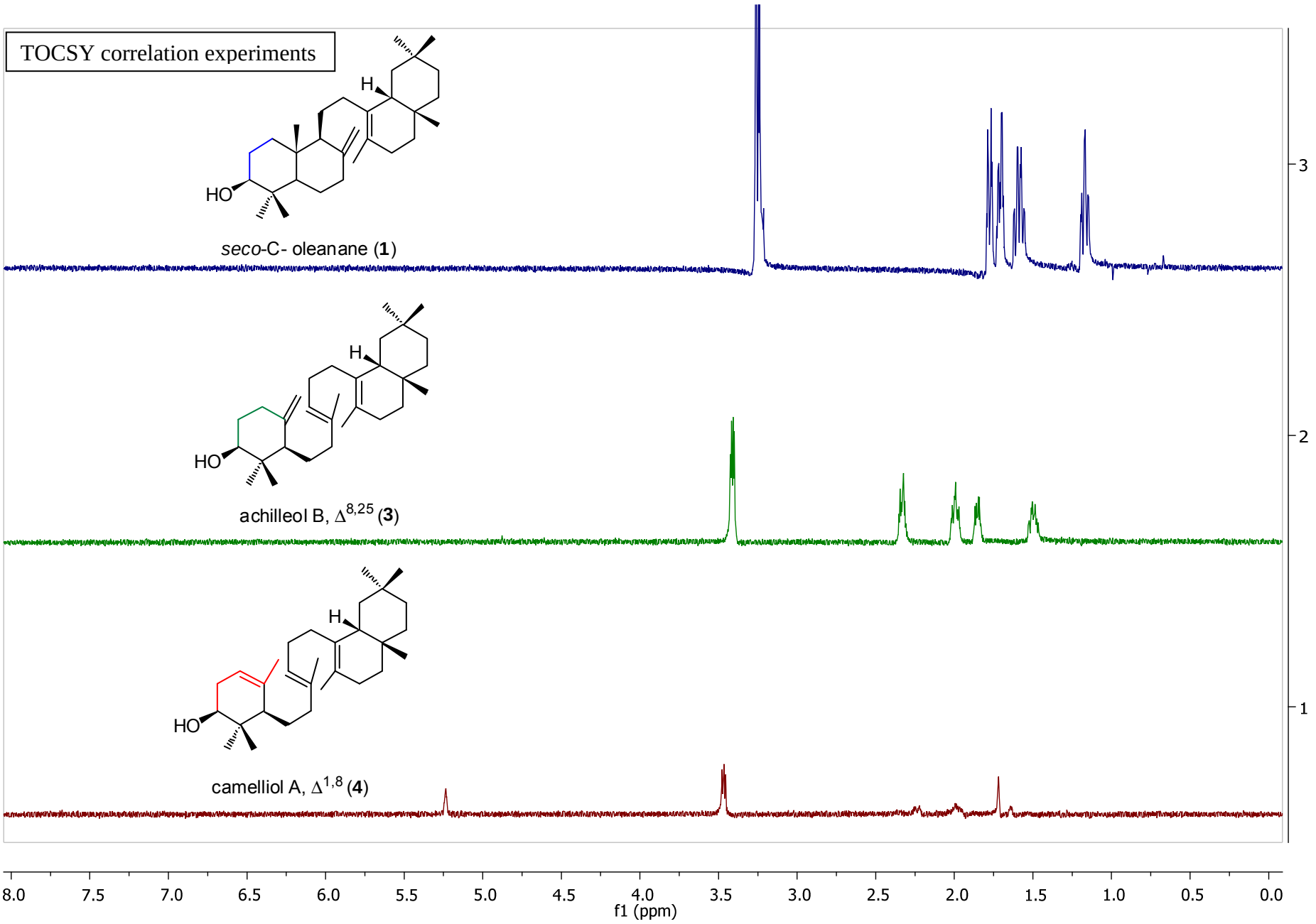
+

(3)- achilleol B

+

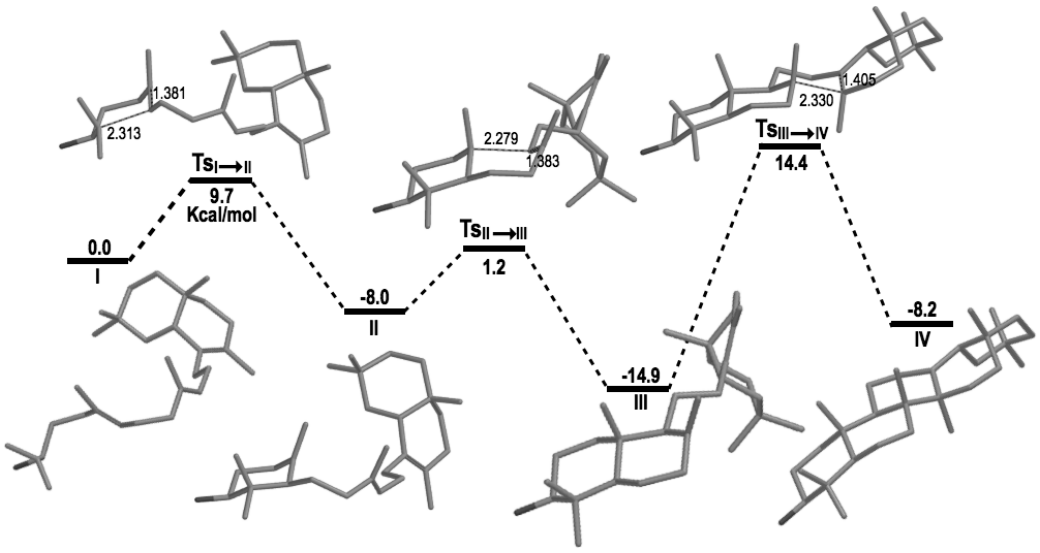


(4)- Camelliol A


TOCSY correlation experiments
HO
H
seco-C- oleanane (1)
achilleol B, Δ8,25 (3)
camelliol A, Δ1,8 (4)
3
2
1
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)

Computational Details

Conformational studies were performed for **I** to **IV** with Spartan 08[14] previous to quantum mechanical optimization. The minimum energy conformations for **I** to **IV** depicted in figure 2 are the ones closer to the transition state structures and were found to be the lowest energy conformations in THF. Geometry optimizations and energy calculations were performed with GAUSSIAN 09W[15] using DFT[16] method with ub3lyp/6-31+g(d)[17] basis set *in vacuo*. Transition state structures were optimized as saddle points at the same level b3lyp/6-31+g(d). A vibrational analysis was performed at the same level of theory in order to determine the zero-point vibrational energy and to characterize each stationary point as a minimum or transition state structure. The reported energies are expressed en Hartrees (au). The same energies expressed in Kcal/mol as relative energies appear in Figure 1.



[14] Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio, R. A.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Van Voorhis, T.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C. P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P.; Lee, A. M.; Lee, M. S.; Liang, W.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E.; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock, H. L.; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon, M., *Phys. Chem. Chem. Phys.* **2006,** *8*, 3172-3191

[15] Frisch, M. J. et al. Gaussian 09, revision A.02; Gaussian, Inc.; Wallingford, CT, 2009.

[16] (a) Lynch, B. J.; Zhao, Y.; Truhlar, D. G., *J. Phys. Chem. A* **2003,** *107*, 1384-1388. (b) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*,Wiley-VCH,Weinheim, Germany, 2nd edn., **2000**, pp. 117–259. (c) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*, Clarendon Press, Oxford, UK, **1989.**

[17] (a) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J., *J. Phys. Chem.* **1994,** *98*, 11623-11627. (b) Kim, K., Jordan, K.D.; *J. Phys. Chem* **1994**, *.98*, 10089-10094. (c) Becke, A. D., *J. Chem. Phys.* **1993,** *98*, 5648-5652. (d) Becke, A. D., *J. Chem. Phys.* **1993,** *98*, 1372-1377. (f) Lee, C.; Yang, W.; Parr, R. G., *Phys. Rev. B* **1988,** *37*, 785-789 .

Cartesian Coordinates and Energies of I

# opt freq ub3lyp/6-31+g(d) geom=connectivity
Charge = -1 Multiplicity = 2

C	5.830680000	1.444508000	1.355355000
C	4.530982000	2.052985000	0.733168000
C	3.318449000	1.102668000	0.572397000
C	3.425025000	-0.001310000	-0.461919000
C	3.693055000	0.467302000	-1.873940000
C	-0.106663000	-3.093680000	0.038762000
C	0.808947000	-3.049867000	-0.946071000
C	2.220257000	-3.553032000	-0.710270000
C	3.343627000	-2.519657000	-0.984376000
C	3.260268000	-1.291977000	-0.114639000
C	6.622223000	0.572327000	0.374799000
H	4.232916000	2.859843000	1.418349000
H	2.437584000	1.716143000	0.307069000
H	3.096852000	0.651691000	1.550266000
H	4.727056000	0.820467000	-1.964356000
H	3.540175000	-0.313076000	-2.626924000
H	3.042980000	1.317483000	-2.127804000
H	4.302349000	-3.033406000	-0.804885000
H	5.452925000	0.739337000	2.155161000
C	-1.535553000	-2.616750000	0.020677000
H	-2.204126000	-3.432183000	0.335934000
H	-1.851042000	-2.335719000	-0.990328000
C	-1.760899000	-1.410670000	0.973584000
H	-1.475584000	-1.704790000	1.990281000
H	-1.056228000	-0.621446000	0.686363000
H	3.347335000	-2.256491000	-2.048259000
H	2.400345000	-4.426854000	-1.359028000
H	2.307732000	-3.909328000	0.324784000
C	-4.188647000	-1.348536000	1.686239000
C	-4.041167000	-2.459097000	2.702009000
H	-3.026655000	-2.857378000	2.771147000
H	-4.710711000	-3.298274000	2.458979000
H	-4.333992000	-2.111140000	3.704006000
C	-3.181298000	-0.872523000	0.925469000
C	-5.616015000	-0.851420000	1.552015000
H	-6.025872000	-0.650283000	2.554061000
H	-6.229792000	-1.679582000	1.158823000
C	-3.395225000	0.260400000	-0.077609000
C	-4.867305000	0.373826000	-0.568778000
C	-5.790360000	0.393321000	0.669068000
H	-5.580730000	1.287554000	1.267344000
H	-6.838726000	0.477558000	0.347424000
C	-5.222501000	-0.830090000	-1.466656000
H	-6.265248000	-0.764265000	-1.807075000

H	-5.093276000	-1.786380000	-0.950452000
H	-4.583257000	-0.848660000	-2.358853000
C	-5.056086000	1.657486000	-1.418071000
H	-6.127790000	1.781963000	-1.635553000
C	7.331909000	1.243329000	-0.770084000
H	8.368496000	1.531343000	-0.509799000
H	6.828345000	2.167490000	-1.078309000
H	7.404894000	0.574256000	-1.647507000
C	7.294402000	-0.662474000	0.902045000
H	7.566400000	-1.360624000	0.091686000
H	6.650516000	-1.201615000	1.611832000
H	8.236870000	-0.426875000	1.439896000
O	6.665734000	2.401525000	1.838533000
H	-4.570738000	1.502938000	-2.392083000
H	-2.774643000	0.032082000	-0.958228000
C	-2.863862000	1.590009000	0.526399000
H	-3.386373000	1.775788000	1.475005000
H	-1.805201000	1.467486000	0.788577000
C	-3.022465000	2.837973000	-0.374416000
C	-4.508540000	2.945400000	-0.787070000
H	-5.100745000	3.203521000	0.103078000
H	-4.639278000	3.780655000	-1.490998000
C	-2.624657000	4.089308000	0.430921000
H	-3.247022000	4.197690000	1.328858000
H	-2.743763000	4.999665000	-0.172077000
H	-1.577083000	4.037282000	0.753122000
C	-2.105997000	2.749757000	-1.613184000
H	-2.325650000	1.881609000	-2.243030000
H	-1.053711000	2.678605000	-1.311757000
H	-2.213938000	3.646592000	-2.237701000
C	0.542929000	-2.513258000	-2.333540000
H	1.058264000	-1.554952000	-2.481099000
H	0.931749000	-3.202796000	-3.096495000
H	-0.519756000	-2.354655000	-2.536870000
H	0.221993000	-3.487462000	1.003726000
H	3.096000000	-1.502902000	0.944646000
H	4.770190000	2.542356000	-0.222921000

SCF Done: E(UB3LYP) = -1248.50041066 A.U. after 3 cycles

Zero-point correction= 0.734613 (Hartree/Particle)
Thermal correction to Energy= 0.770956
Thermal correction to Enthalpy= 0.771901
Thermal correction to Gibbs Free Energy= 0.662841
Sum of electronic and zero-point Energies= -1247.765797
Sum of electronic and thermal Energies= -1247.729454
Sum of electronic and thermal Enthalpies= -1247.728510
Sum of electronic and thermal Free Energies= -1247.837570

Cartesian Coordinates and Energies of TSI-->II

# opt=(calcfc,ts) freq b3lyp/6-31+g(d) geom=connectivity
Charge = -1 Multiplicity = 2

C	5.944463000	-2.094574000	0.079952000
C	5.025369000	-2.257700000	1.332350000
C	3.583392000	-1.713770000	1.169559000
C	3.568015000	-0.223711000	0.912148000
C	3.421136000	0.665736000	2.119748000
C	0.623397000	1.475570000	-0.880302000
C	1.631222000	2.366202000	-0.863650000
C	2.905913000	2.100020000	-1.638357000
C	4.127982000	1.631634000	-0.788907000
C	4.045204000	0.195854000	-0.319968000
C	6.182385000	-0.616860000	-0.319055000
H	5.515526000	-1.793265000	2.200939000
H	4.991574000	-3.336989000	1.540026000
H	2.982586000	-1.957452000	2.061427000
H	3.116805000	-2.244942000	0.322821000
H	4.293737000	0.607515000	2.795758000
H	3.283413000	1.721759000	1.861456000
H	2.550320000	0.360910000	2.721568000
H	0.771079000	0.575893000	-1.481569000
H	5.009203000	1.751273000	-1.431891000
H	3.922568000	-0.516247000	-1.140117000
H	5.333006000	-2.531244000	-0.771976000
C	-0.688049000	1.512301000	-0.142047000
H	-0.796186000	2.424680000	0.454661000
H	-0.716320000	0.675720000	0.572776000
C	-1.912052000	1.383964000	-1.087367000
H	-1.939089000	2.257051000	-1.748753000
H	-1.746223000	0.518285000	-1.743026000
H	4.279748000	2.320442000	0.051855000
H	3.196104000	3.021307000	-2.170288000
H	2.717480000	1.338943000	-2.406515000
C	1.618915000	3.658597000	-0.078346000
H	2.440669000	3.681687000	0.650163000
H	0.688133000	3.825328000	0.471524000
H	1.773014000	4.517981000	-0.748002000
C	-4.001708000	2.217521000	0.074873000
C	-3.718793000	3.678671000	-0.194309000
H	-4.572513000	4.152100000	-0.701912000
H	-2.830559000	3.848962000	-0.806627000
H	-3.577795000	4.227034000	0.749530000
C	-3.215362000	1.199239000	-0.331006000
C	-5.232329000	2.001275000	0.935284000
H	-6.074090000	2.577277000	0.519663000
H	-5.039357000	2.458969000	1.920255000
C	-3.561452000	-0.255914000	-0.019820000

C	-4.447602000	-0.416105000	1.248216000
C	-5.656410000	0.536438000	1.118072000
H	-6.272953000	0.231108000	0.264385000
H	-6.297722000	0.444788000	2.006976000
C	-3.637993000	-0.062720000	2.513337000
H	-4.260616000	-0.171643000	3.412006000
H	-3.252652000	0.960926000	2.489723000
H	-2.777185000	-0.734413000	2.622971000
C	-4.914218000	-1.887394000	1.392538000
H	-5.642632000	-1.948998000	2.214889000
C	6.644769000	-0.445763000	-1.745295000
H	5.943680000	-0.913598000	-2.453974000
H	7.617995000	-0.943322000	-1.881455000
H	6.766686000	0.612298000	-2.025169000
C	6.923464000	0.250562000	0.671982000
H	6.867669000	1.315271000	0.394592000
H	7.988169000	-0.029913000	0.709833000
H	6.527892000	0.143409000	1.688492000
O	7.153773000	-2.683298000	0.226726000
H	-4.053908000	-2.493052000	1.710548000
H	-2.612214000	-0.775771000	0.181660000
C	-4.192911000	-0.916204000	-1.276454000
H	-5.084258000	-0.340821000	-1.563071000
H	-3.494614000	-0.824116000	-2.119203000
C	-4.598745000	-2.399931000	-1.110720000
C	-5.520917000	-2.505984000	0.125604000
H	-6.473636000	-2.009351000	-0.109550000
H	-5.767470000	-3.561077000	0.315982000
C	-5.373589000	-2.849790000	-2.363717000
H	-6.270976000	-2.236157000	-2.518651000
H	-5.694285000	-3.896641000	-2.274101000
H	-4.751560000	-2.766865000	-3.264652000
C	-3.356791000	-3.302598000	-0.961618000
H	-2.713496000	-3.228672000	-1.848096000
H	-3.651090000	-4.355287000	-0.854907000
H	-2.744086000	-3.042087000	-0.093124000

SCF Done: E(UB3LYP) = -1248.48391655 A.U. after 29 cycles
Imag. Freq. -371.7099 cm^{-1}

Zero-point correction= 0.733597 (Hartree/Particle)
Thermal correction to Energy= 0.767303
Thermal correction to Enthalpy= 0.768247
Thermal correction to Gibbs Free Energy= 0.668976
Sum of electronic and zero-point Energies= -1247.750319
Sum of electronic and thermal Energies= -1247.716613
Sum of electronic and thermal Enthalpies= -1247.715669
Sum of electronic and thermal Free Energies= -1247.814941

Cartesian Coordinates and Energies of II

# opt freq ub3lyp/6-31+g(d) geom=connectivity
Charge = -1 Multiplicity = 2

C	5.811586000	-2.088593000	0.138280000
C	4.849838000	-2.320336000	1.346082000
C	3.437274000	-1.713773000	1.132551000
C	3.553099000	-0.252199000	0.814402000
C	3.302097000	0.714341000	1.933906000
C	0.768747000	1.270438000	-0.853956000
C	1.779764000	2.155888000	-0.903588000
C	3.026354000	1.863588000	-1.718095000
C	4.319416000	1.494063000	-0.938392000
C	4.385649000	0.041391000	-0.411842000
C	5.858246000	-0.515846000	-0.237804000
H	5.312756000	-1.895478000	2.249562000
H	4.781892000	-3.405767000	1.507685000
H	2.796449000	-1.877933000	2.014531000
H	2.964019000	-2.248767000	0.289673000
H	3.485547000	1.758645000	1.662031000
H	2.260000000	0.646940000	2.290713000
H	3.936970000	0.498488000	2.814574000
H	0.902170000	0.339781000	-1.409754000
H	5.148384000	1.639198000	-1.639273000
H	3.972736000	-0.593862000	-1.219713000
H	5.248338000	-2.529954000	-0.751205000
C	-0.534171000	1.356749000	-0.104107000
H	-0.601360000	2.271450000	0.494627000
H	-0.589205000	0.519995000	0.609464000
C	-1.766635000	1.280748000	-1.044707000
H	-1.742643000	2.139966000	-1.724026000
H	-1.651790000	0.394605000	-1.683459000
H	4.492433000	2.216958000	-0.130274000
H	3.245957000	2.756135000	-2.327973000
H	2.813318000	1.051009000	-2.425424000
C	1.777385000	3.496476000	-0.204107000
H	2.662529000	3.606213000	0.435407000
H	0.895427000	3.660199000	0.421385000
H	1.824670000	4.311702000	-0.941975000
C	-3.792493000	2.267010000	0.108189000
C	-3.388278000	3.701226000	-0.149520000
H	-4.175998000	4.235175000	-0.702301000
H	-2.458422000	3.799551000	-0.713441000
H	-3.257083000	4.242296000	0.799753000
C	-3.085078000	1.191034000	-0.294396000
C	-5.053181000	2.146928000	0.944270000
H	-5.835995000	2.792994000	0.516849000
H	-4.843635000	2.579863000	1.936941000
C	-3.549911000	-0.233847000	0.003635000

C	-4.473331000	-0.329014000	1.251978000
C	-5.597988000	0.719243000	1.102652000
H	-6.216034000	0.472743000	0.230985000
H	-6.266262000	0.671820000	1.974898000
C	-3.662872000	-0.048459000	2.534720000
H	-4.310517000	-0.105251000	3.420478000
H	-3.191027000	0.938583000	2.521416000
H	-2.864701000	-0.791056000	2.659283000
C	-5.062016000	-1.757439000	1.378673000
H	-5.810473000	-1.760349000	2.185319000
C	6.639113000	-0.442592000	-1.562541000
H	6.042376000	-0.841613000	-2.397341000
H	7.525345000	-1.078302000	-1.448272000
H	6.961942000	0.575322000	-1.828646000
C	6.649337000	0.243869000	0.838482000
H	6.876175000	1.278439000	0.535297000
H	7.589399000	-0.295675000	1.004663000
H	6.117774000	0.287196000	1.797040000
O	7.022484000	-2.624479000	0.324388000
H	-4.262396000	-2.433231000	1.712352000
H	-2.648358000	-0.827067000	0.220789000
C	-4.204955000	-0.838982000	-1.268956000
H	-5.037815000	-0.190457000	-1.574388000
H	-3.481590000	-0.804656000	-2.094661000
C	-4.735639000	-2.284487000	-1.118737000
C	-5.690496000	-2.322060000	0.096982000
H	-6.597655000	-1.752854000	-0.153308000
H	-6.020517000	-3.355912000	0.276852000
C	-5.516854000	-2.665908000	-2.390537000
H	-6.355510000	-1.978421000	-2.562316000
H	-5.926508000	-3.682108000	-2.311764000
H	-4.870342000	-2.634302000	-3.277379000
C	-3.575488000	-3.287610000	-0.945525000
H	-2.907394000	-3.261751000	-1.815975000
H	-3.960142000	-4.311999000	-0.851825000
H	-2.964215000	-3.083763000	-0.060934000

SCF Done: E(UB3LYP) = -1248.51568276 A.U. after 3 cycles

Zero-point correction= 0.737103 (Hartree/Particle)
Thermal correction to Energy= 0.771880
Thermal correction to Enthalpy= 0.772824
Thermal correction to Gibbs Free Energy= 0.668270
Sum of electronic and zero-point Energies= -1247.778580
Sum of electronic and thermal Energies= -1247.743803
Sum of electronic and thermal Enthalpies= -1247.742859
Sum of electronic and thermal Free Energies= -1247.847413

Cartesian Coordinates and Energies of TSII-->III

# opt=(calcfc,ts) freq b3lyp/6-31+g(d) geom=connectivity
Charge = -1 Multiplicity = 2

C	-4.652388000	-2.313074000	-0.519670000
C	-3.528402000	-2.049783000	-1.568363000
C	-2.369235000	-1.170138000	-1.029512000
C	-2.904594000	0.152960000	-0.537682000
C	-3.037744000	1.211905000	-1.608339000
C	-1.303729000	1.048925000	0.800107000
C	-1.968927000	2.139848000	1.335442000
C	-3.213432000	1.849353000	2.140373000
C	-4.363510000	1.285139000	1.258836000
C	-3.977979000	-0.025976000	0.534577000
C	-5.195000000	-0.908168000	0.055795000
H	-3.977955000	-1.590443000	-2.461080000
H	-3.138611000	-3.027741000	-1.883982000
H	-1.597944000	-1.023270000	-1.802889000
H	-1.892791000	-1.714863000	-0.196514000
H	-3.472641000	2.146134000	-1.239702000
H	-2.056482000	1.449155000	-2.043950000
H	-3.669809000	0.865536000	-2.440805000
H	-1.404526000	0.111110000	1.349356000
H	-5.224790000	1.100622000	1.911343000
H	-3.507637000	-0.664524000	1.305893000
H	-4.093572000	-2.743402000	0.377939000
C	-0.037398000	1.126591000	-0.024557000
H	-0.086027000	1.940568000	-0.758679000
H	0.072054000	0.201660000	-0.603963000
C	1.233127000	1.312987000	0.849347000
H	1.158680000	2.265104000	1.385532000
H	1.219499000	0.537539000	1.626663000
H	-4.686800000	2.050834000	0.540198000
H	-3.561957000	2.756028000	2.658927000
H	-2.996665000	1.102844000	2.920702000
C	-1.770275000	3.567178000	0.894019000
H	-2.657345000	3.959686000	0.367839000
H	-0.912512000	3.697460000	0.225275000
H	-1.615443000	4.230255000	1.761489000
C	3.102247000	2.255366000	-0.572159000
C	2.559788000	3.666516000	-0.552102000
H	3.309101000	4.368186000	-0.154849000
H	1.650743000	3.775922000	0.042728000
H	2.328502000	4.006285000	-1.573247000
C	2.524520000	1.209159000	0.054572000
C	4.337762000	2.105983000	-1.439635000
H	5.060295000	2.897372000	-1.184458000
H	4.050523000	2.314851000	-2.483998000
C	3.120188000	-0.197636000	-0.011079000

C	4.019597000	-0.426783000	-1.258840000
C	5.028591000	0.737797000	-1.351171000
H	5.685294000	0.724735000	-0.473086000
H	5.680934000	0.593898000	-2.225049000
C	3.152432000	-0.468702000	-2.534404000
H	3.778933000	-0.621463000	-3.424324000
H	2.579442000	0.452356000	-2.675819000
H	2.433702000	-1.296421000	-2.488032000
C	4.758233000	-1.786075000	-1.155350000
H	5.490138000	-1.850890000	-1.974474000
C	-6.083973000	-1.274802000	1.260598000
H	-5.477434000	-1.624193000	2.109793000
H	-6.730311000	-2.101584000	0.944170000
H	-6.713247000	-0.442482000	1.608928000
C	-6.090013000	-0.234770000	-0.997342000
H	-6.581805000	0.671013000	-0.609793000
H	-6.856260000	-0.961738000	-1.289618000
H	-5.550160000	0.042125000	-1.909438000
O	-5.620141000	-3.113093000	-0.978452000
H	4.033726000	-2.590892000	-1.340352000
H	2.276773000	-0.900527000	-0.086229000
C	3.859936000	-0.503501000	1.320625000
H	4.630107000	0.265471000	1.473342000
H	3.155053000	-0.392539000	2.154905000
C	4.530864000	-1.894436000	1.403710000
C	5.465415000	-2.047385000	0.181778000
H	6.306953000	-1.349885000	0.300697000
H	5.902673000	-3.056798000	0.172844000
C	5.366500000	-1.969891000	2.695919000
H	6.136667000	-1.187658000	2.718328000
H	5.872799000	-2.941091000	2.782511000
H	4.735134000	-1.842933000	3.585499000
C	3.478744000	-3.022180000	1.445786000
H	2.816029000	-2.902867000	2.312499000
H	3.967052000	-4.002353000	1.532540000
H	2.844986000	-3.049869000	0.554331000

SCF Done: E(UB3LYP) = -1248.50078888 A.U. after 31 cycles
Imag. Freq. -381.2253 cm^{-1}
Zero-point correction= 0.736962 (Hartree/Particle)
Thermal correction to Energy= 0.770539
Thermal correction to Enthalpy= 0.771483
Thermal correction to Gibbs Free Energy= 0.671795
Sum of electronic and zero-point Energies= -1247.763827
Sum of electronic and thermal Energies= -1247.730250
Sum of electronic and thermal Enthalpies= -1247.729306
Sum of electronic and thermal Free Energies= -1247.828994

Cartesian Coordinates and Energies of III

# opt freq ub3lyp/6-31+g(d) geom=connectivity
Charge = -1 Multiplicity = 2

C	-4.467047000	-2.231405000	-0.721925000
C	-3.374632000	-1.787280000	-1.739402000
C	-2.215171000	-0.992076000	-1.119449000
C	-2.664095000	0.295562000	-0.383976000
C	-3.047388000	1.365970000	-1.431756000
C	-1.467035000	0.856154000	0.519334000
C	-1.927140000	2.038848000	1.336202000
C	-3.069259000	1.732954000	2.258885000
C	-4.257774000	1.119260000	1.473263000
C	-3.820782000	-0.088919000	0.618438000
C	-5.015212000	-0.933489000	0.054838000
H	-3.857670000	-1.221217000	-2.549591000
H	-2.982040000	-2.701345000	-2.206519000
H	-1.478381000	-0.737232000	-1.897166000
H	-1.693051000	-1.641092000	-0.396836000
H	-3.573115000	2.221826000	-0.995273000
H	-2.148762000	1.751104000	-1.931841000
H	-3.689742000	0.950737000	-2.210454000
H	-1.281441000	0.034553000	1.234687000
H	-5.030236000	0.808689000	2.186237000
H	-3.328019000	-0.786641000	1.319894000
H	-3.876199000	-2.769729000	0.093485000
C	-0.128019000	1.068682000	-0.218284000
H	-0.180765000	1.908878000	-0.922647000
H	0.084673000	0.182680000	-0.825230000
C	1.064947000	1.294289000	0.742430000
H	0.941221000	2.243163000	1.274465000
H	1.022348000	0.515647000	1.516557000
H	-4.714076000	1.895846000	0.844244000
H	-3.393316000	2.631445000	2.805561000
H	-2.754248000	0.994201000	3.017024000
C	3.044478000	2.277510000	-0.504776000
C	2.524938000	3.696780000	-0.467230000
H	3.262060000	4.369515000	-0.002827000
H	1.585607000	3.802815000	0.078615000
H	2.359225000	4.076688000	-1.486949000
C	2.410032000	1.217284000	0.037721000
C	4.332629000	2.139920000	-1.296429000
H	5.050341000	2.904567000	-0.959591000
H	4.114712000	2.402464000	-2.345562000
C	3.000461000	-0.191274000	-0.037190000
C	3.961185000	-0.392973000	-1.243551000
C	4.994396000	0.755342000	-1.234167000
H	5.606765000	0.692476000	-0.326745000
H	5.687461000	0.636724000	-2.080163000

C	3.166193000	-0.372064000	-2.565608000
H	3.840456000	-0.498306000	-3.424120000
H	2.612225000	0.561316000	-2.702339000
H	2.437175000	-1.191415000	-2.592042000
C	4.664527000	-1.771305000	-1.146270000
H	5.430060000	-1.833967000	-1.934412000
C	-5.850149000	-1.490603000	1.229541000
H	-5.205783000	-1.936873000	2.002171000
H	-6.489169000	-2.283932000	0.824823000
H	-6.486143000	-0.733054000	1.712095000
C	-5.988356000	-0.164734000	-0.857476000
H	-6.509834000	0.643923000	-0.321975000
H	-6.726386000	-0.886692000	-1.224883000
H	-5.505536000	0.273555000	-1.735408000
O	-5.429758000	-2.982113000	-1.266314000
H	3.928672000	-2.552375000	-1.382901000
H	2.157854000	-0.885867000	-0.172357000
C	3.672579000	-0.539206000	1.319877000
H	4.442930000	0.215269000	1.531733000
H	2.929549000	-0.441328000	2.122539000
C	4.323094000	-1.941028000	1.398570000
C	5.305796000	-2.083225000	0.213302000
H	6.158389000	-1.409679000	0.383572000
H	5.721496000	-3.101773000	0.196158000
C	5.103156000	-2.057488000	2.722009000
H	5.881299000	-1.286110000	2.794578000
H	5.592806000	-3.037377000	2.806036000
H	4.435852000	-1.942616000	3.586444000
C	3.254077000	-3.053535000	1.370776000
H	2.567559000	-2.952843000	2.221151000
H	3.724567000	-4.043781000	1.438007000
H	2.646785000	-3.039293000	0.460565000
C	-1.690750000	3.471376000	0.958984000
H	-0.814568000	3.611924000	0.317497000
H	-1.552903000	4.097808000	1.854856000
H	-2.550718000	3.907663000	0.415283000

SCF Done: E(UB3LYP) = -1248.53006160 A.U. after 4 cycles

Zero-point correction= 0.740525 (Hartree/Particle)
Thermal correction to Energy= 0.773659
Thermal correction to Enthalpy= 0.774604
Thermal correction to Gibbs Free Energy= 0.677491
Sum of electronic and zero-point Energies= -1247.789537
Sum of electronic and thermal Energies= -1247.756402
Sum of electronic and thermal Enthalpies= -1247.755458
Sum of electronic and thermal Free Energies= -1247.852570

Cartesian Coordinates and Energies of TSIII-->IV

# opt=(calcfc,ts) freq b3lyp/6-31+g(d) geom=connectivity
Charge = -1 Multiplicity = 2

C	-5.629023000	1.230966000	-0.586547000
C	-4.806323000	2.204511000	0.309503000
C	-3.281868000	2.034945000	0.207958000
C	-2.787991000	0.602559000	0.550824000
C	-2.899688000	0.405517000	2.082917000
C	-1.269500000	0.445810000	0.060581000
C	-0.756502000	-0.991771000	0.142703000
C	-1.633219000	-1.961046000	-0.617023000
C	-3.106042000	-1.852333000	-0.146308000
C	-3.633294000	-0.412041000	-0.305941000
C	-5.192339000	-0.280861000	-0.253263000
H	-5.152670000	2.098373000	1.348124000
H	-5.079348000	3.225177000	0.007374000
H	-2.782223000	2.768720000	0.859400000
H	-2.972408000	2.272845000	-0.822676000
H	-2.965593000	-0.644049000	2.383676000
H	-2.035525000	0.843814000	2.598288000
H	-3.788533000	0.904773000	2.474598000
H	-1.347815000	0.686969000	-1.009134000
H	-3.711269000	-2.541087000	-0.746452000
H	-3.395747000	-0.127936000	-1.347460000
H	-5.191053000	1.384161000	-1.630011000
C	-0.282963000	1.469139000	0.658875000
H	-0.043946000	1.225969000	1.701963000
H	-0.748531000	2.460090000	0.676154000
C	1.042307000	1.594494000	-0.139434000
H	0.799615000	2.008965000	-1.130912000
H	1.661539000	2.354673000	0.356247000
H	-3.196370000	-2.193967000	0.893462000
H	-1.266208000	-2.992883000	-0.503384000
H	-1.631558000	-1.733515000	-1.690429000
C	-0.332245000	-1.528961000	1.490048000
H	0.323363000	-0.846408000	2.037023000
H	0.185639000	-2.490317000	1.379720000
H	-1.199618000	-1.725975000	2.135306000
C	1.265456000	-0.776761000	-0.976221000
C	0.667061000	-0.520676000	-2.359607000
H	0.080858000	0.396532000	-2.431143000
H	0.038750000	-1.349091000	-2.699566000
H	1.495821000	-0.434996000	-3.082033000
C	1.812185000	0.296554000	-0.248043000
C	1.992576000	-2.125128000	-0.913013000
H	1.846197000	-2.665172000	-1.857906000
H	1.537497000	-2.761012000	-0.143530000
C	3.216356000	0.286293000	0.358830000
C	3.836732000	-1.127370000	0.582352000

C	3.502953000	-2.010495000	-0.641681000
H	3.995486000	-1.601883000	-1.534501000
H	3.926349000	-3.015371000	-0.489427000
C	3.273173000	-1.771103000	1.865068000
H	3.721843000	-2.761866000	2.025168000
H	2.192148000	-1.893440000	1.834919000
H	3.511462000	-1.154354000	2.741789000
C	5.374953000	-1.046957000	0.795033000
H	5.777631000	-2.070807000	0.774089000
C	-5.819086000	-1.138780000	-1.374701000
H	-5.301717000	-0.982400000	-2.333480000
H	-6.857236000	-0.807647000	-1.493170000
H	-5.813022000	-2.217297000	-1.155991000
C	-5.844178000	-0.726896000	1.068137000
H	-5.671958000	-1.794973000	1.274608000
H	-6.921248000	-0.548286000	0.976018000
H	-5.500367000	-0.157899000	1.936612000
O	-6.948068000	1.438472000	-0.526449000
H	5.564151000	-0.677665000	1.812808000
H	3.191485000	0.795593000	1.336439000
C	4.090030000	1.164175000	-0.598583000
H	3.989933000	0.758791000	-1.615060000
H	3.661467000	2.174058000	-0.636509000
C	5.597665000	1.265377000	-0.272588000
C	6.151909000	-0.172384000	-0.193838000
H	6.111849000	-0.616827000	-1.199100000
H	7.215083000	-0.152107000	0.090504000
C	6.306256000	2.025923000	-1.409653000
H	6.163928000	1.520837000	-2.373837000
H	7.387191000	2.095602000	-1.223782000
H	5.916457000	3.047865000	-1.506898000
C	5.836864000	2.034561000	1.043418000
H	5.455122000	3.060884000	0.963734000
H	6.910648000	2.094650000	1.268861000
H	5.343704000	1.568546000	1.902291000

SCF Done: E(UB3LYP) = -1248.48476763 A.U. after 4 cycles
Imag. Freq. -423.7102 cm^{-1}
Zero-point correction= 0.741907 (Hartree/Particle)
Thermal correction to Energy= 0.773059
Thermal correction to Enthalpy= 0.774003
Thermal correction to Gibbs Free Energy= 0.684914
Sum of electronic and zero-point Energies= -1247.742861
Sum of electronic and thermal Energies= -1247.711709
Sum of electronic and thermal Enthalpies= -1247.710765
Sum of electronic and thermal Free Energies= -1247.799853

Cartesian Coordinates and Energies of IV

# opt freq ub3lyp/6-31+g(d) geom=connectivity
Charge = -1 Multiplicity = 2

C	-5.476284000	1.243378000	-0.732357000
C	-4.828032000	2.094578000	0.400811000
C	-3.298385000	1.976236000	0.496074000
C	-2.788332000	0.516995000	0.692888000
C	-3.135734000	0.096836000	2.145760000
C	-1.225654000	0.500760000	0.401769000
C	-0.528138000	-0.896410000	0.190147000
C	-1.395927000	-1.794775000	-0.727733000
C	-2.888611000	-1.798718000	-0.369021000
C	-3.466090000	-0.371780000	-0.409310000
C	-5.019888000	-0.288652000	-0.562905000
H	-5.313785000	1.833399000	1.352469000
H	-5.099540000	3.141891000	0.207899000
H	-2.923716000	2.616641000	1.310058000
H	-2.863218000	2.373521000	-0.435127000
H	-3.225737000	-0.985194000	2.281230000
H	-2.385021000	0.460630000	2.857473000
H	-4.090399000	0.530029000	2.450261000
H	-1.164510000	1.010428000	-0.568755000
H	-3.410165000	-2.435730000	-1.092334000
H	-3.099864000	0.065812000	-1.355973000
H	-4.907758000	1.562267000	-1.670218000
C	-0.394373000	1.346930000	1.387491000
H	-0.393229000	0.888014000	2.382849000
H	-0.846272000	2.337133000	1.508281000
C	1.064378000	1.527104000	0.923901000
H	1.065758000	2.275430000	0.106034000
H	1.656790000	1.986906000	1.730321000
H	-3.052121000	-2.264829000	0.611739000
H	-0.999519000	-2.820999000	-0.713008000
H	-1.326961000	-1.454832000	-1.767346000
C	-0.357327000	-1.637667000	1.543654000
H	0.402535000	-1.171279000	2.178597000
H	-0.065948000	-2.683638000	1.394171000
H	-1.290351000	-1.652446000	2.107084000
C	0.929121000	-0.647214000	-0.462192000
C	0.830936000	0.052628000	-1.861056000
H	1.808875000	0.040771000	-2.353789000
H	0.514297000	1.096550000	-1.797575000
H	0.133365000	-0.465009000	-2.526721000
C	1.735020000	0.263400000	0.458716000
C	1.661511000	-2.001831000	-0.711888000
H	1.268556000	-2.450140000	-1.633417000
H	1.431408000	-2.713658000	0.084033000
C	3.251442000	0.227829000	0.539510000
C	3.844825000	-1.206683000	0.396510000

C	3.190750000	-1.892483000	-0.825537000
H	3.461465000	-1.351334000	-1.741871000
H	3.611955000	-2.903228000	-0.938495000
C	3.554201000	-2.019547000	1.676721000
H	3.917755000	-3.051585000	1.572694000
H	2.489036000	-2.059345000	1.914829000
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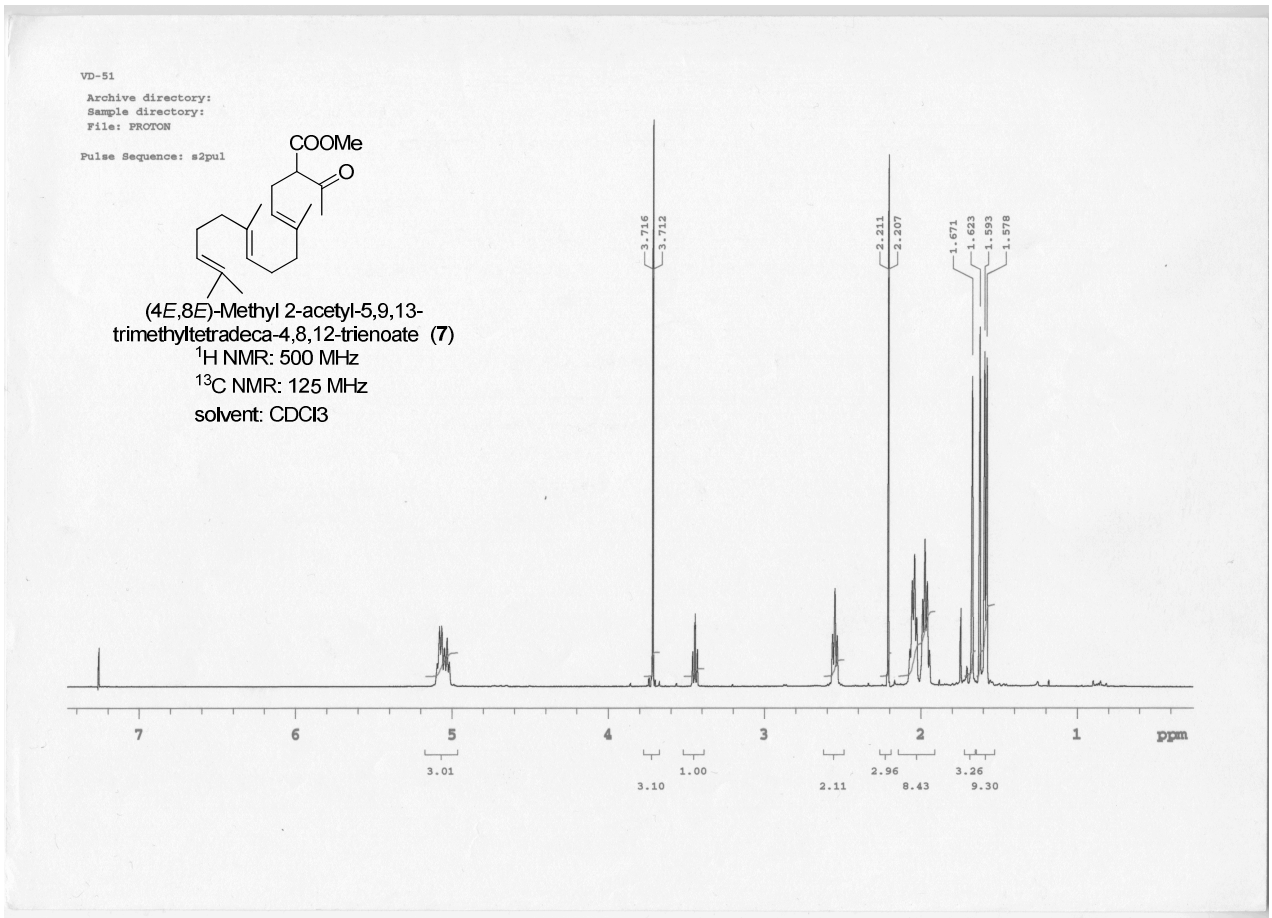
C	5.388459000	-1.161068000	0.240088000
H	5.743499000	-2.169428000	-0.020981000
C	-5.442165000	-0.983694000	-1.876380000
H	-4.805463000	-0.669666000	-2.717446000
H	-6.469024000	-0.668044000	-2.094036000
H	-5.413518000	-2.082374000	-1.818677000
C	-5.829563000	-0.948265000	0.568361000
H	-5.615485000	-2.025436000	0.654114000
H	-6.890926000	-0.810496000	0.334384000
H	-5.660155000	-0.492647000	1.548126000
O	-6.799583000	1.407584000	-0.829686000
H	5.831111000	-0.937047000	1.220865000
H	3.523121000	0.592634000	1.544641000
C	3.873844000	1.243776000	-0.472611000
H	3.508905000	1.014099000	-1.480774000
H	3.491371000	2.245739000	-0.235735000
C	5.418921000	1.287071000	-0.526839000
C	5.923043000	-0.150643000	-0.782027000
H	5.620807000	-0.450612000	-1.795993000
H	7.023517000	-0.168116000	-0.773810000
C	5.854228000	2.193263000	-1.694613000
H	5.460292000	1.825252000	-2.650784000
H	6.949408000	2.232982000	-1.776193000
H	5.491165000	3.220341000	-1.556873000
C	6.010209000	1.866060000	0.775600000
H	5.660448000	2.894966000	0.932044000
H	7.107549000	1.890264000	0.726552000
H	5.731734000	1.288474000	1.662581000

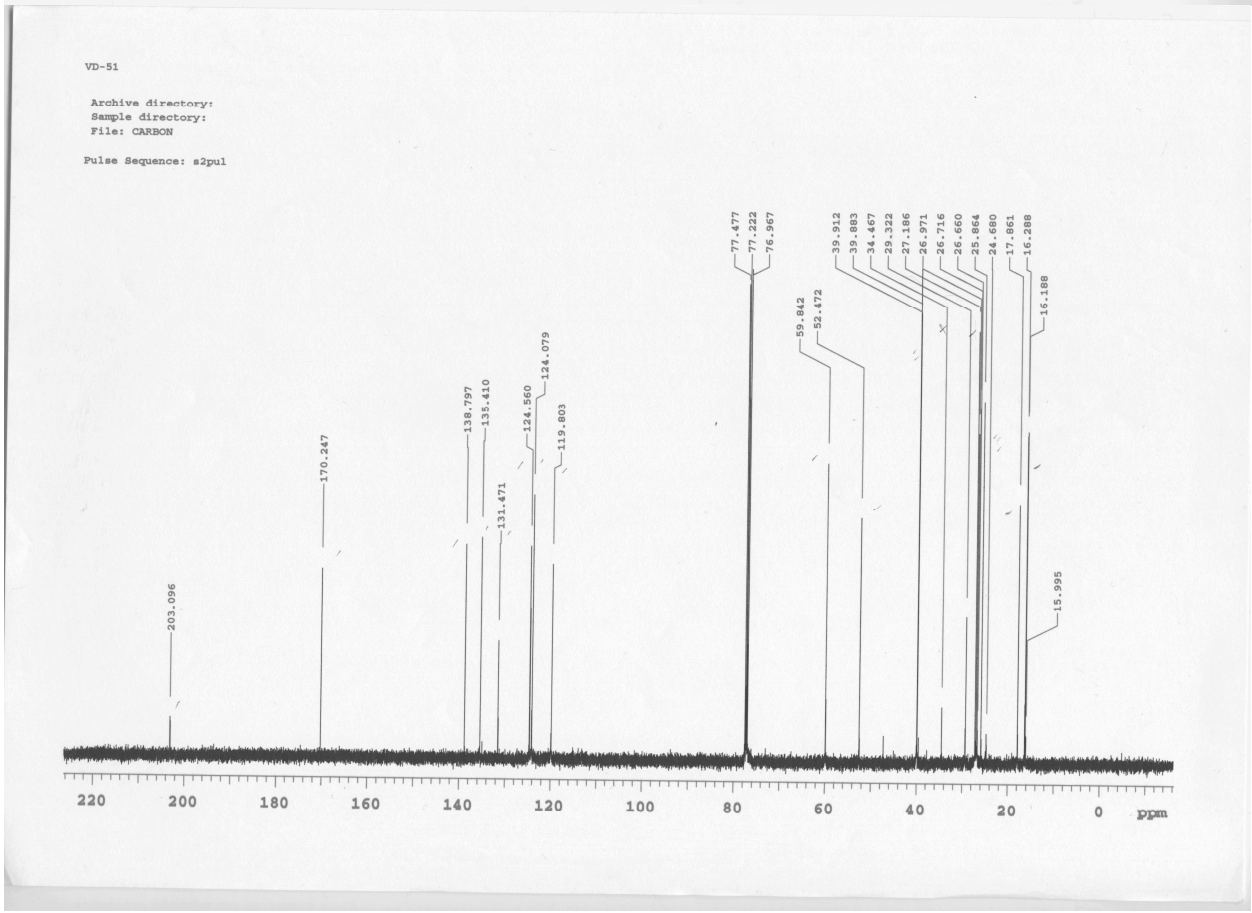
SCF Done: E(UB3LYP) = -1248.52332550 A.U. after 3 cycles

Zero-point correction= 0.744737 (Hartree/Particle)
Thermal correction to Energy= 0.775792
Thermal correction to Enthalpy= 0.776737
Thermal correction to Gibbs Free Energy= 0.687850
Sum of electronic and zero-point Energies= -1247.778589
Sum of electronic and thermal Energies= -1247.747533
Sum of electronic and thermal Enthalpies= -1247.746589
Sum of electronic and thermal Free Energies= -1247.835475

Spectra of compounds

Expedient Access towards Terpenoids γ-Dioxygenated in the A Ring: First Synthesis of (13E)-ent-labda-8(17),13-diene-3β,15,18-triol.


VD-51
Archive directory:
Sample directory:
File: PROTON
Pulse Sequence: s2pul
COOMe
O
(4E,8E)-Methyl 2-acetyl-5,9,13-trimethyltetradeca-4,8,12-trienoate (7)
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
3.716
3.712
2.211
2.207
1.671
1.623
1.593
1.578
7
6
5
4
3
2
1
ppm
3.01
3.10
1.00
2.11
2.96
8.43
3.26
9.30


VD-51
Archive directory:
Sample directory:
File: CARBON
Pulse Sequence: s2pul
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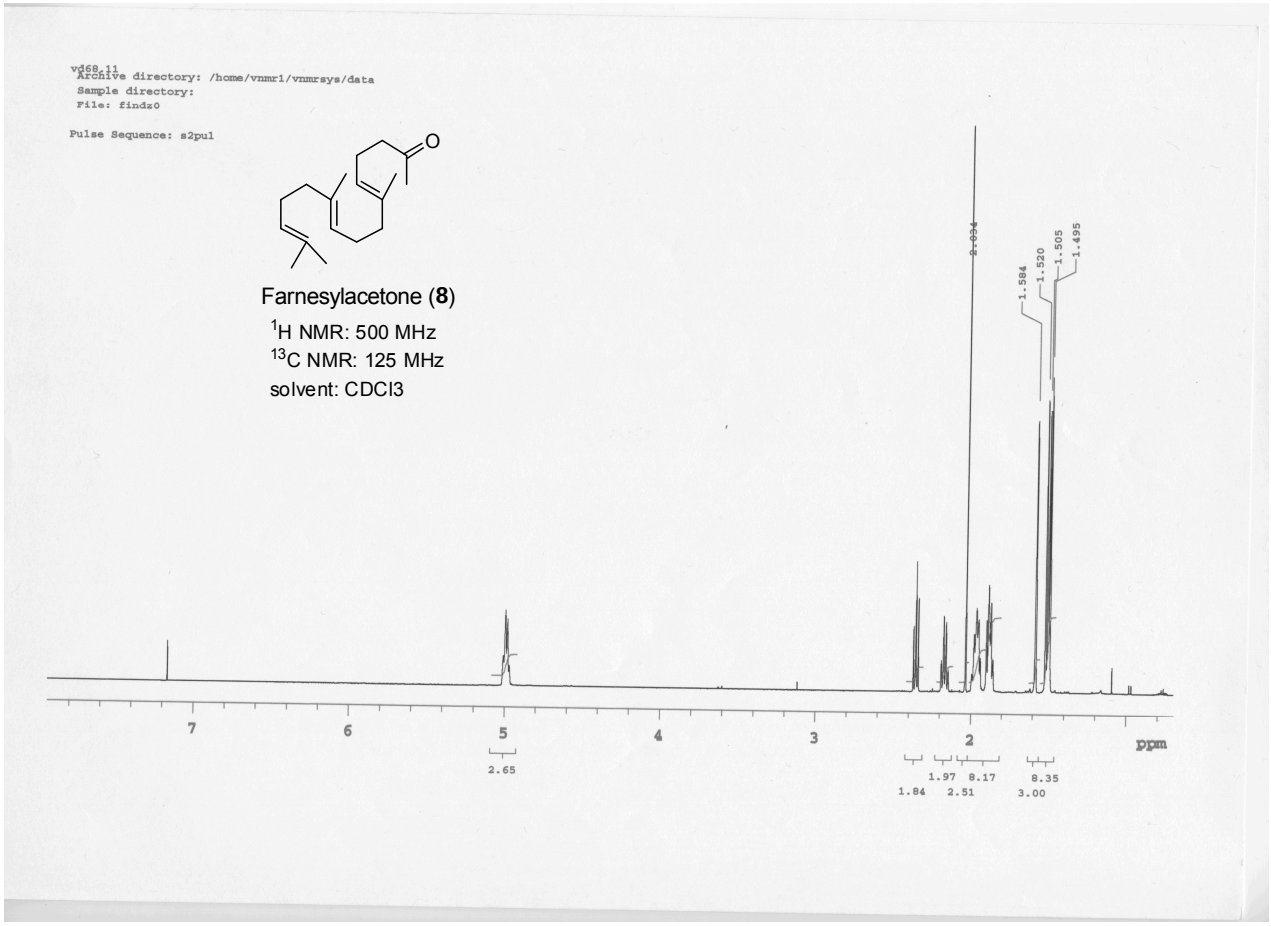
77.222
76.967
39.912
39.883
34.467
29.322
27.186
26.971
26.716
26.660
25.864
24.680
17.861
16.288
16.188
59.842
52.472
203.096
170.247
138.797
135.410
131.471
124.560
124.079
119.803
15.995
220
200
180
160
140
120
100
80
60
40
20
0
ppm

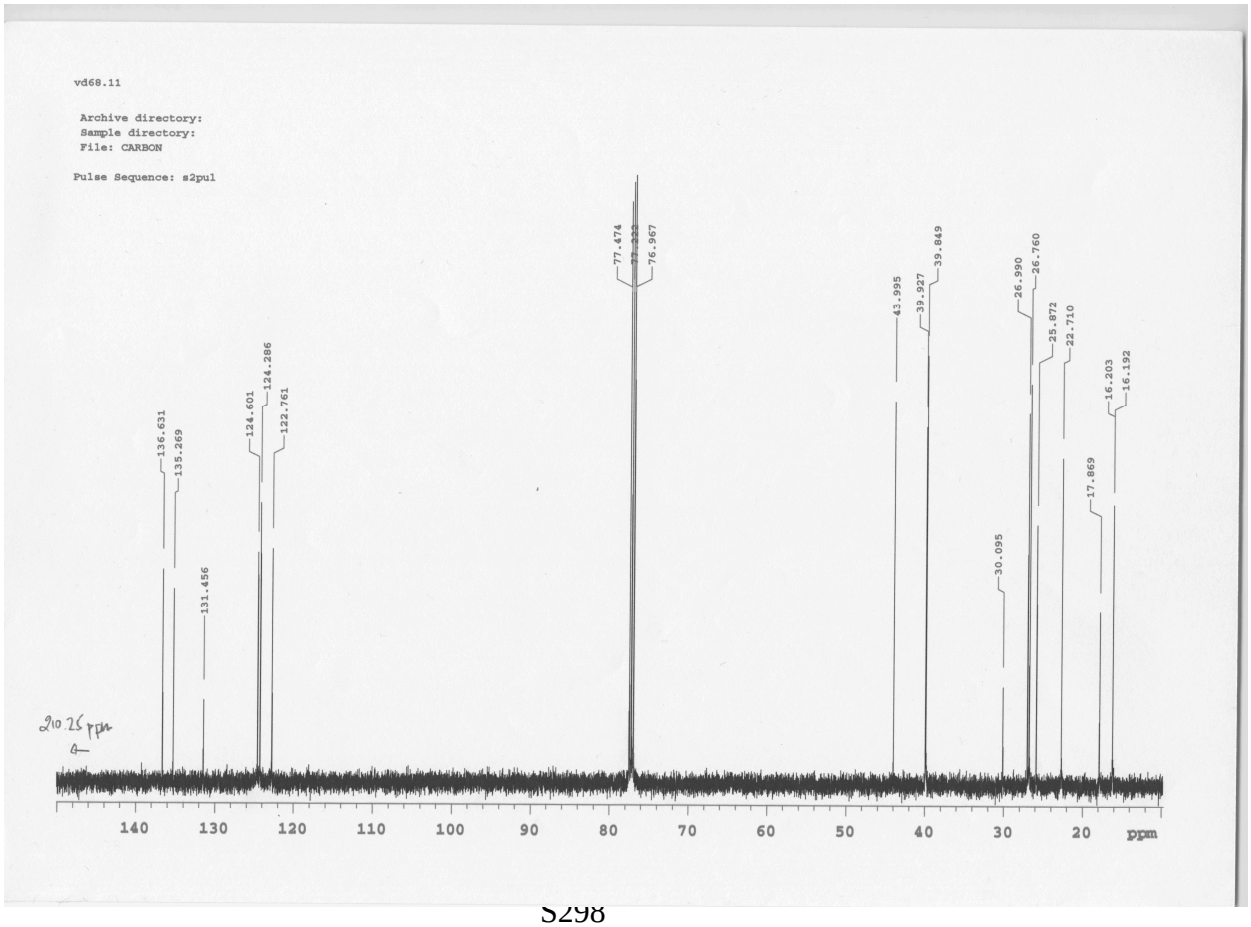


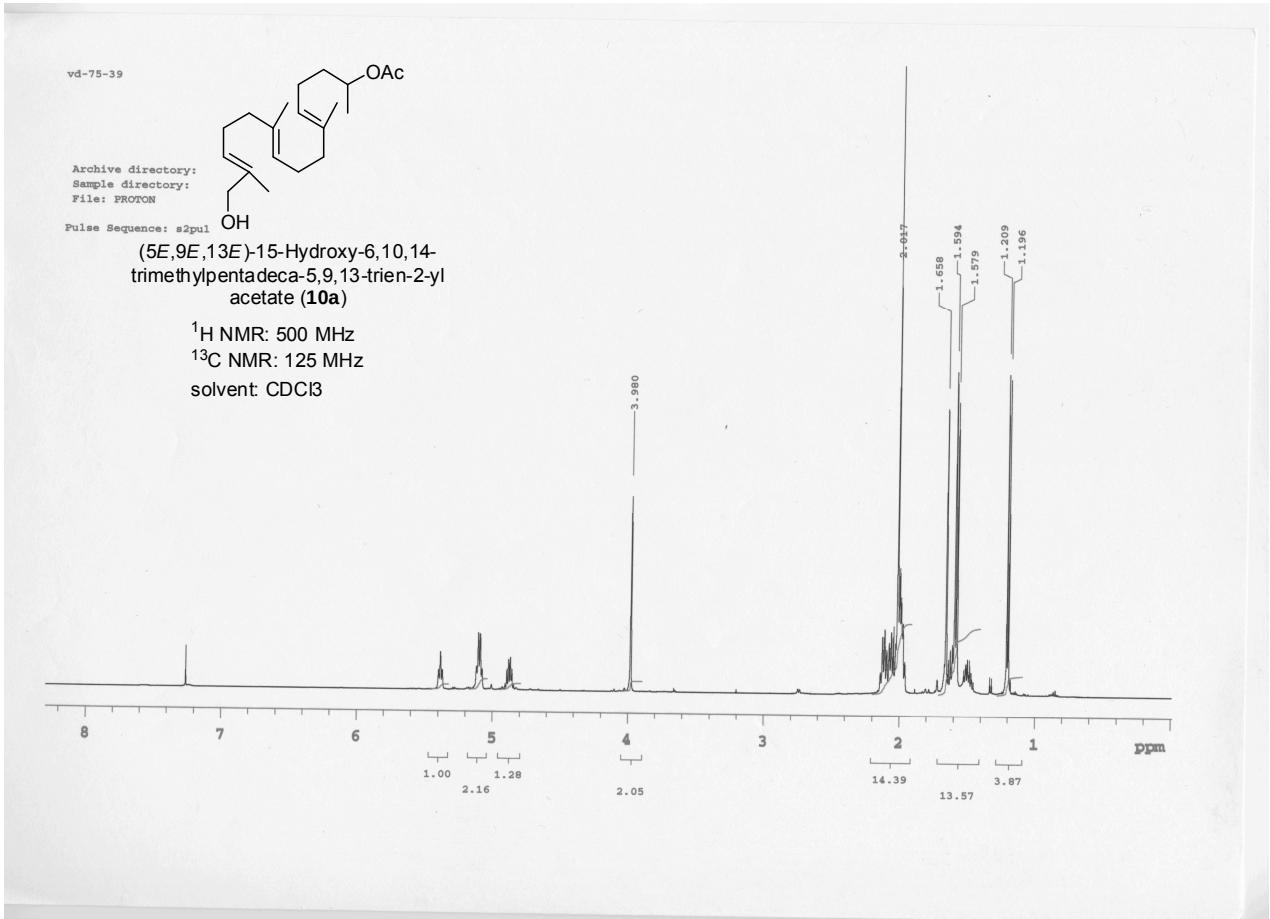
Farnesylacetone (**8**)

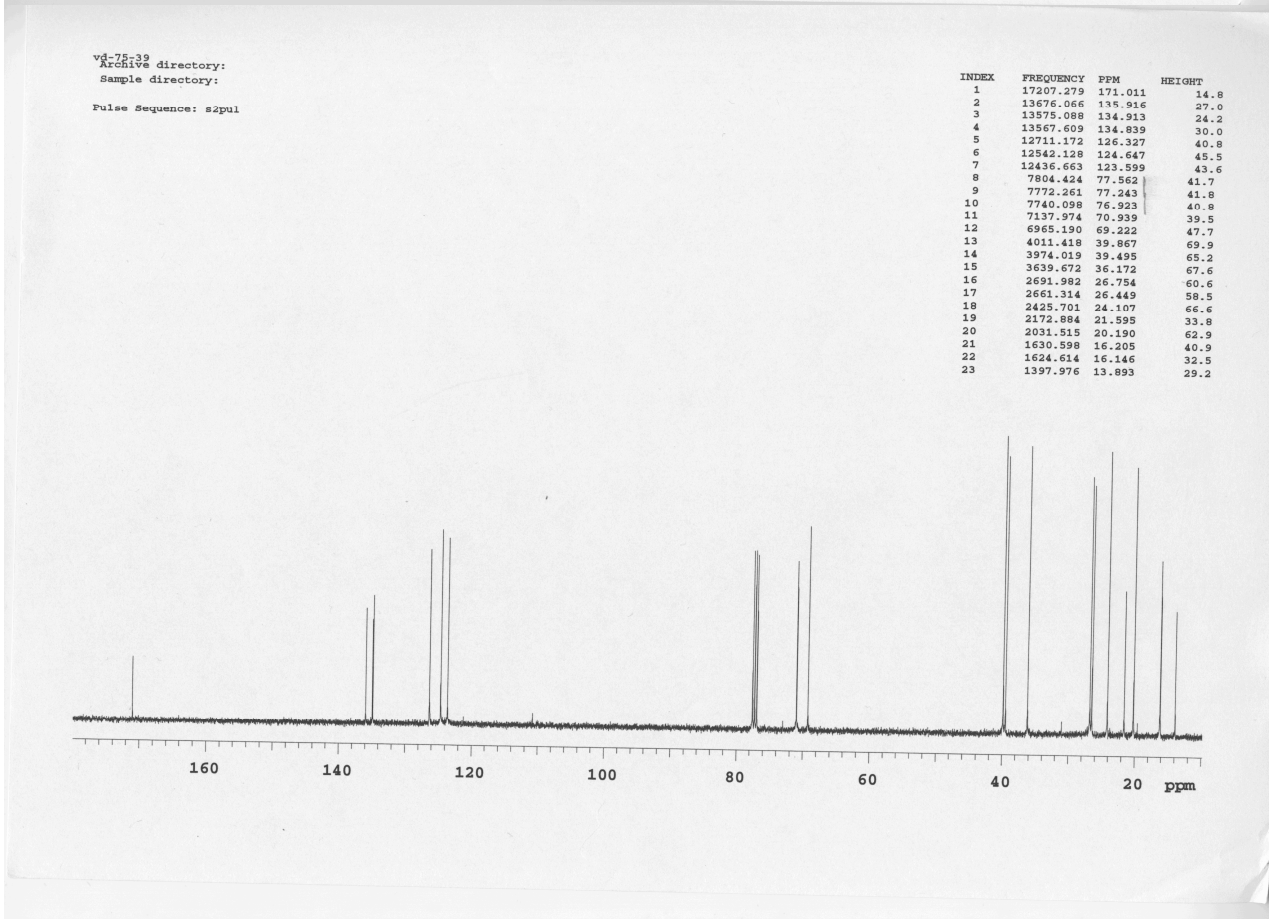
^{1}H NMR: 500 MHz

^{13}C NMR: 125 MHz

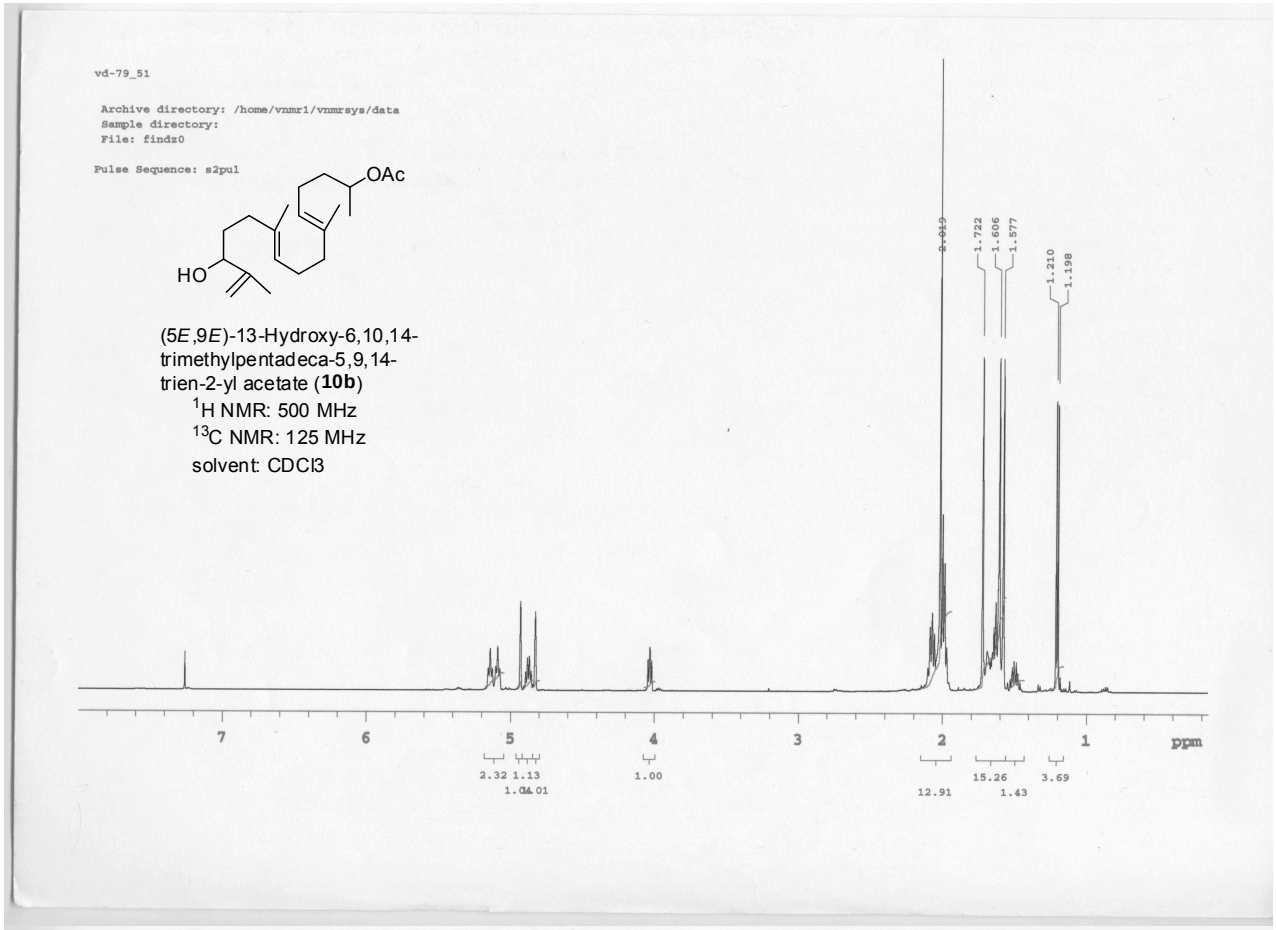
solvent: CDCl3







INDEX	FREQUENCY	PPM	HEIGHT
1	17207.279	171.011	14.8
2	13676.066	135.916	27.0
3	13575.088	134.913	24.2
4	13567.609	134.839	30.0
5	12711.172	126.327	40.8
6	12542.128	124.647	45.5
7	12436.663	123.599	43.6
8	7804.424	77.562	41.7
9	7772.261	77.243	41.8
10	7740.098	76.923	40.8
11	7137.974	70.939	39.5
12	6965.190	69.222	47.7
13	4011.418	39.867	69.9
14	3974.019	39.495	65.2
15	3639.672	36.172	67.6
16	2691.982	26.754	60.6
17	2661.314	26.449	58.5
18	2425.701	24.107	66.6
19	2172.884	21.595	33.8
20	2031.515	20.190	62.9
21	1630.598	16.205	40.9
22	1624.614	16.146	32.5
23	1397.976	13.893	29.2

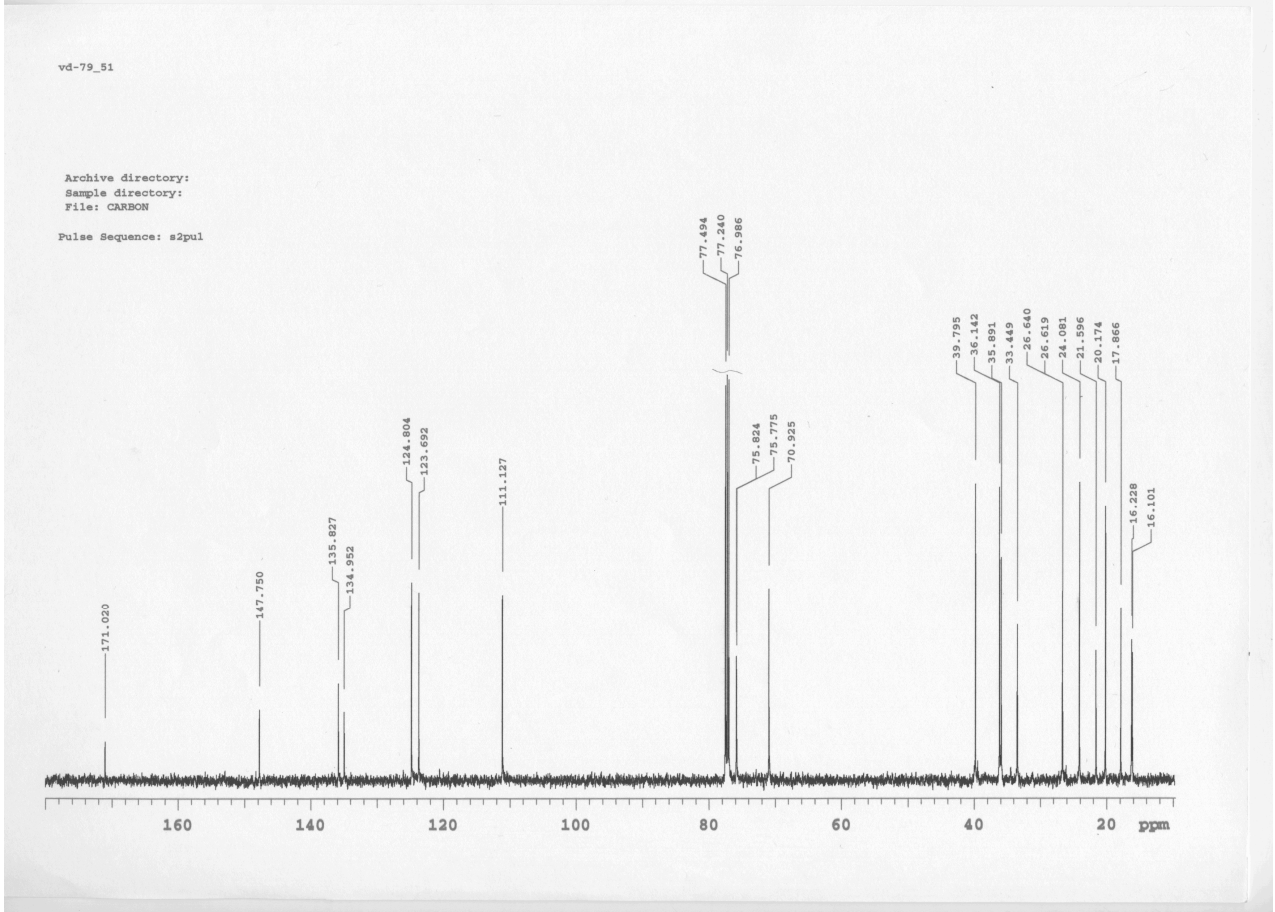


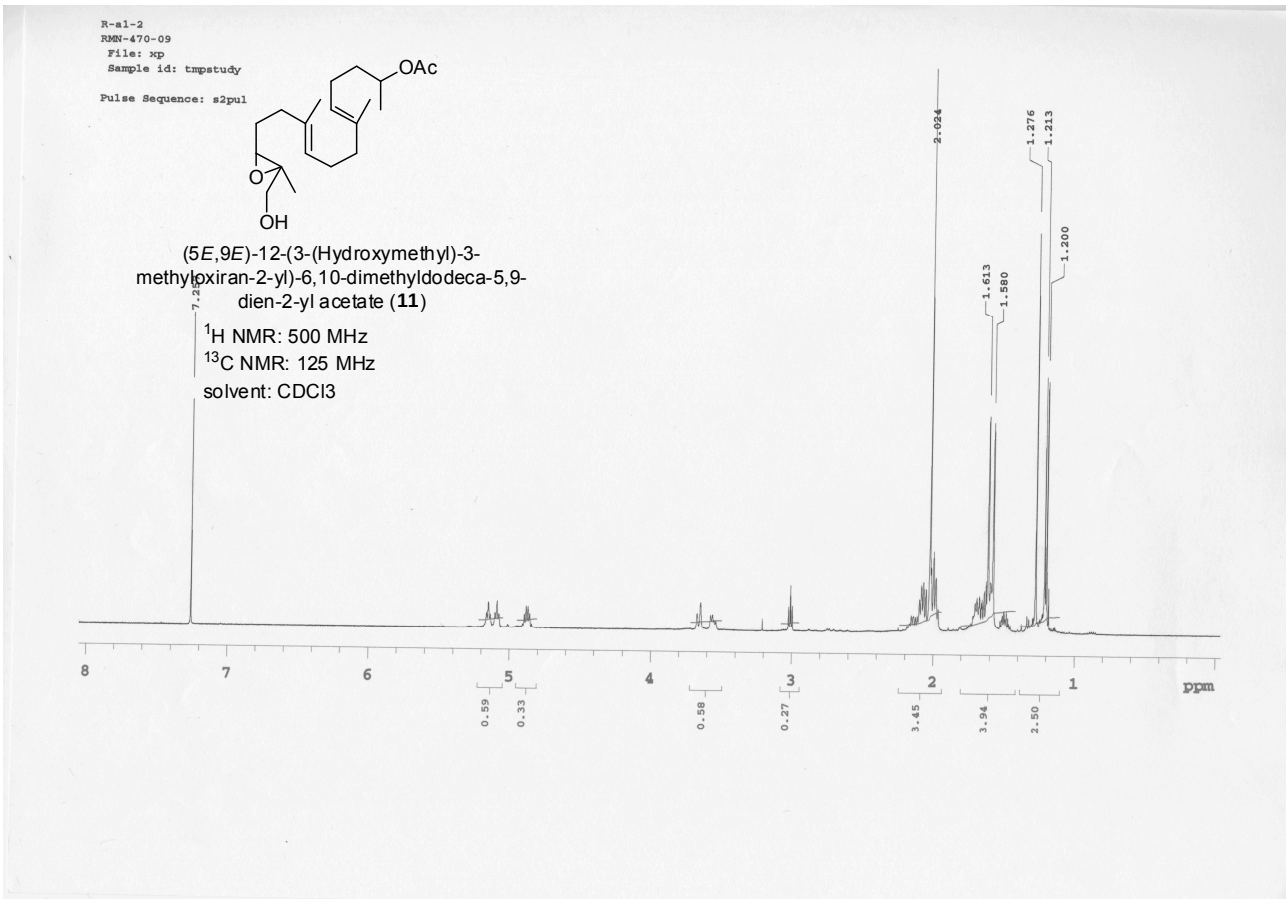
(5*E*,9*E*)-13-Hydroxy-6,10,14-trimethylpentadeca-5,9,14-trien-2-yl acetate (**10b**)

^{1}H NMR: 500 MHz

^{13}C NMR: 125 MHz

solvent: CDCl3



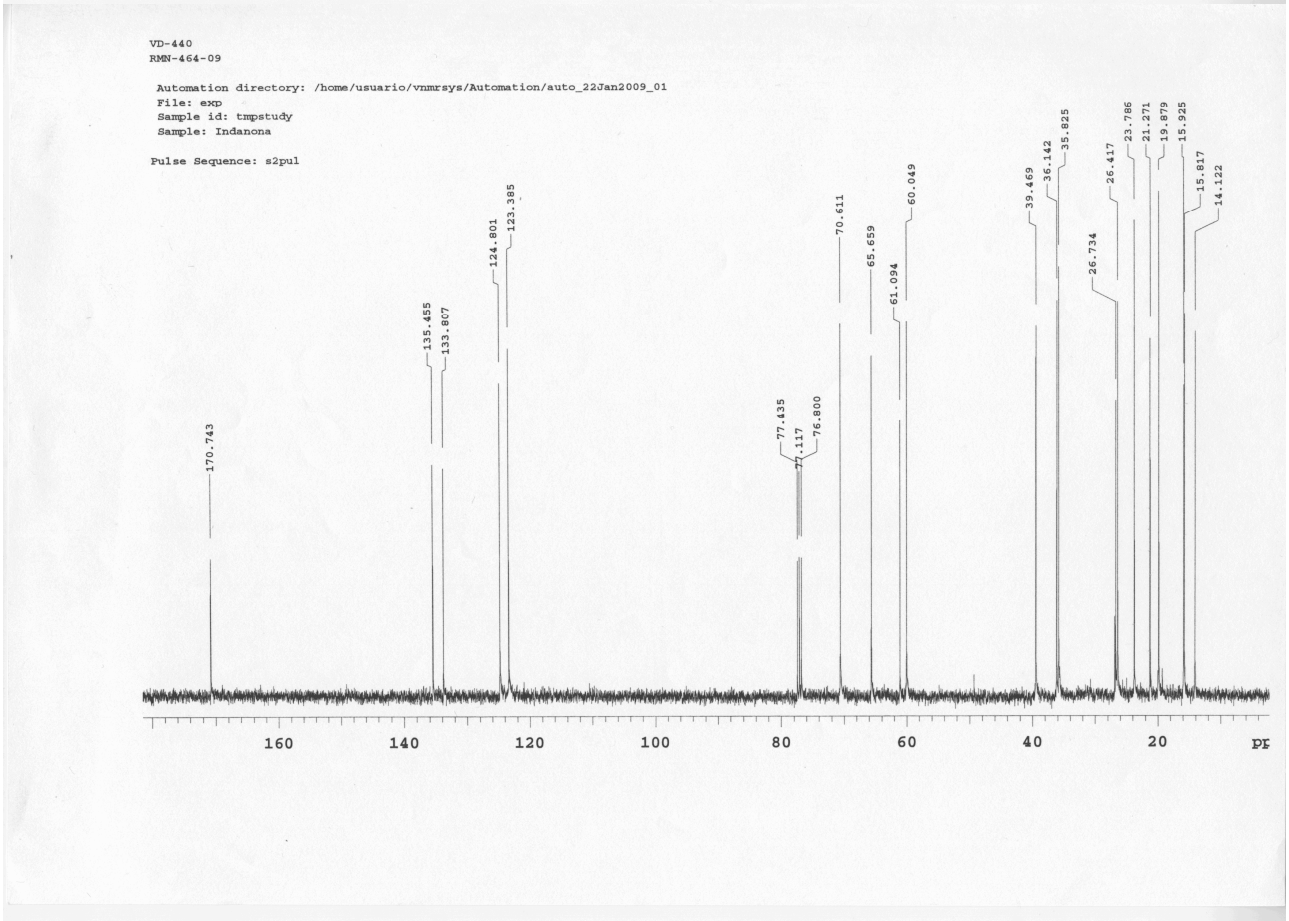


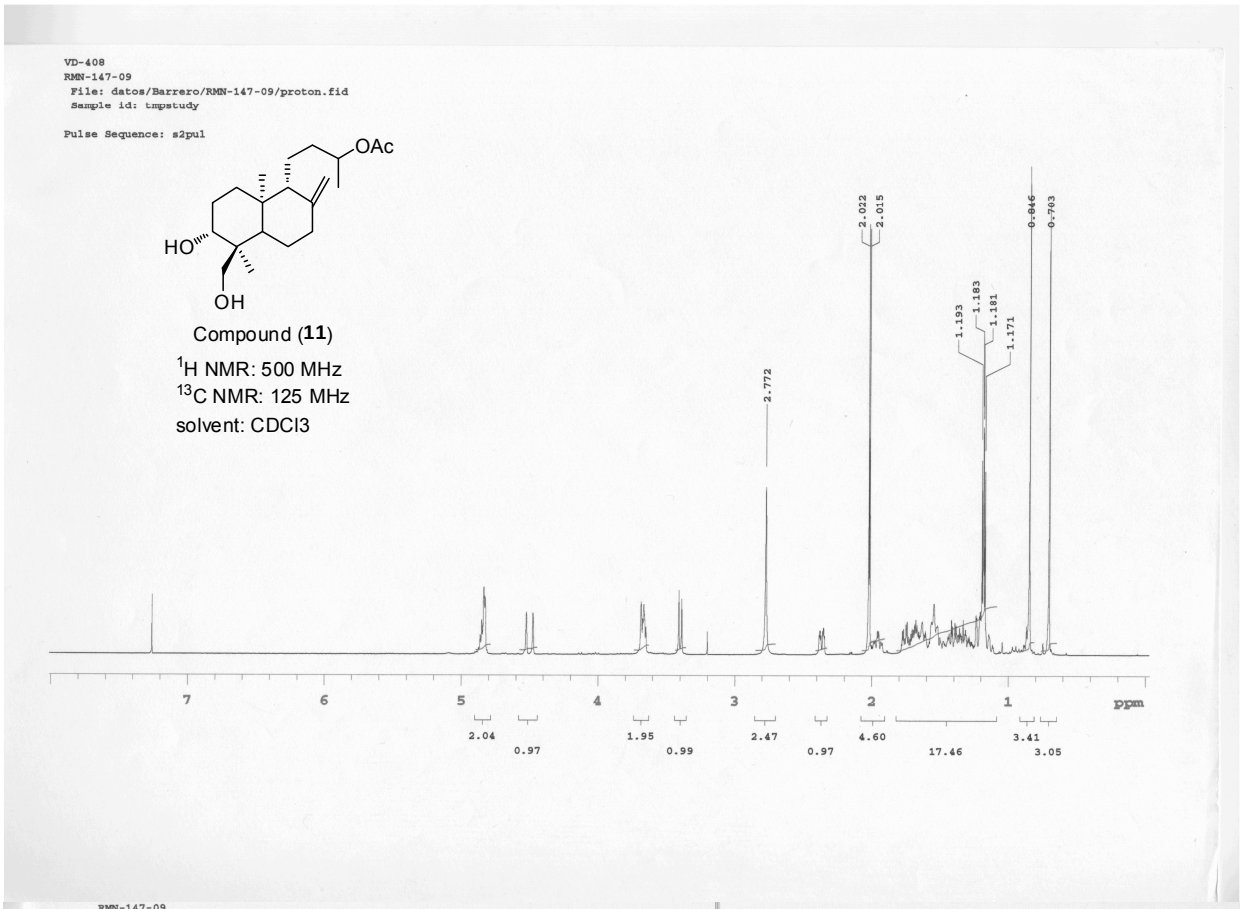
(5*E*,9*E*)-12-(3-(Hydroxymethyl)-3-methyloxiran-2-yl)-6,10-dimethyldodeca-5,9-dien-2-yl acetate (**11**)

^{1}H NMR: 500 MHz

^{13}C NMR: 125 MHz

solvent: CDCl3




VD-408
RMN-147-09
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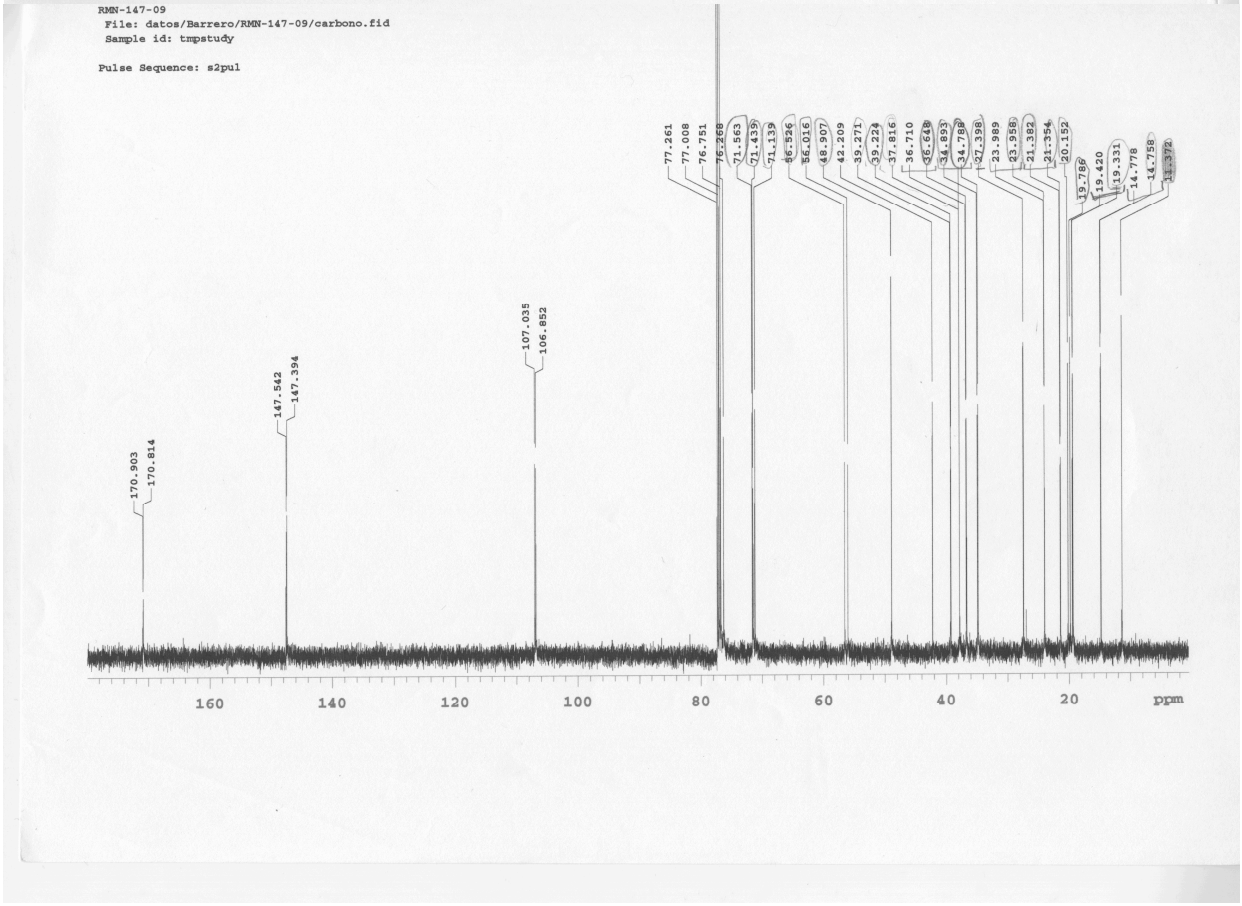
Sample id: tmpstudy
Pulse Sequence: s2pul
OAc
HO
OH
Compound (11)
1H NMR: 500 MHz
13C NMR: 125 MHz
solvent: CDCl3
2.772
2.022
2.015
1.193
1.183
1.181
1.171
0.846
0.763
7
6
5
4
3
2
1
ppm
2.04
0.97
1.95
0.99
2.47
0.97
4.60
17.46
3.41
3.05


RMN-147-09
File: datos/Barrero/RMN-147-09/carbono.fid
Sample id: tmpstudy
Pulse Sequence: s2pul
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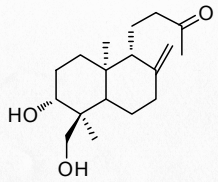
147.542
147.394
107.035
106.852
77.261
77.008
76.751
76.268
71.563
71.439
71.139
66.526
56.016
48.907
42.209
39.271
39.224
37.816
36.710
35.649
34.893
34.788
27.398
23.989
23.958
21.382
21.354
20.152
19.786
19.420
19.331
14.778
14.758
11.372
160
140
120
100
80
60
40
20
ppm

VD-416-B

File: xp
Sample id: tmpstudy

Pulse Sequence: s2pul



3 ,18-isopropylidendioxy-14,15-dinor-ent-labd-8(17)-en-13-one (**13**)

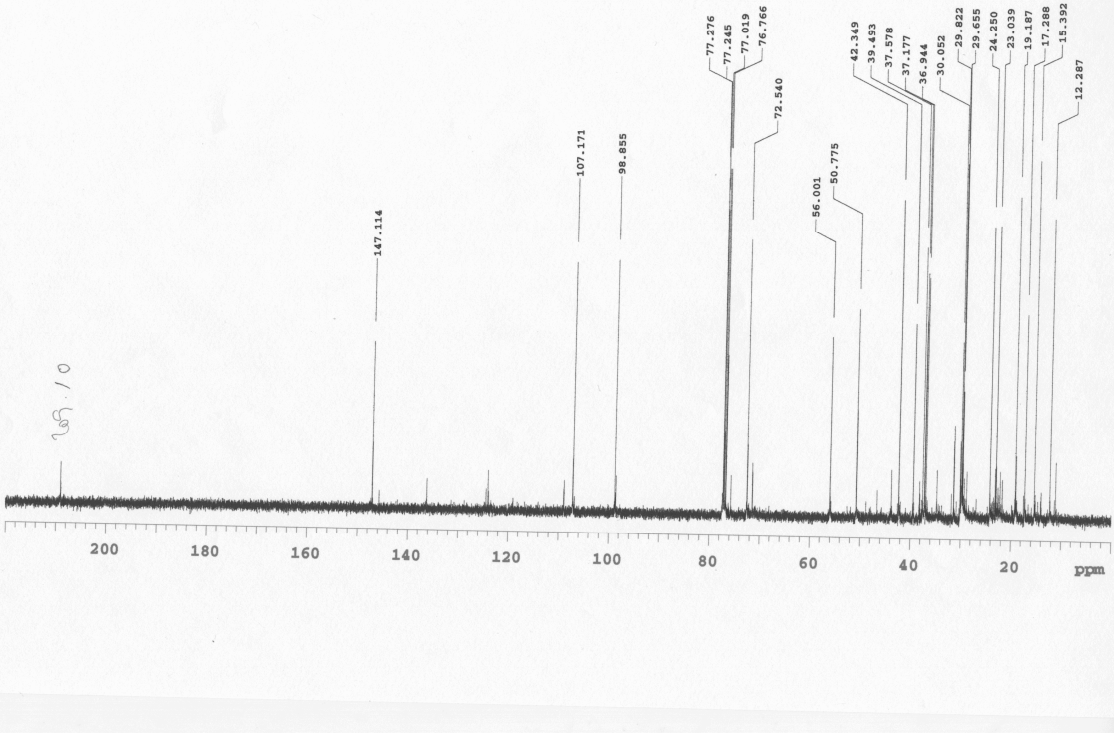
^{1}H NMR: 500 MHz

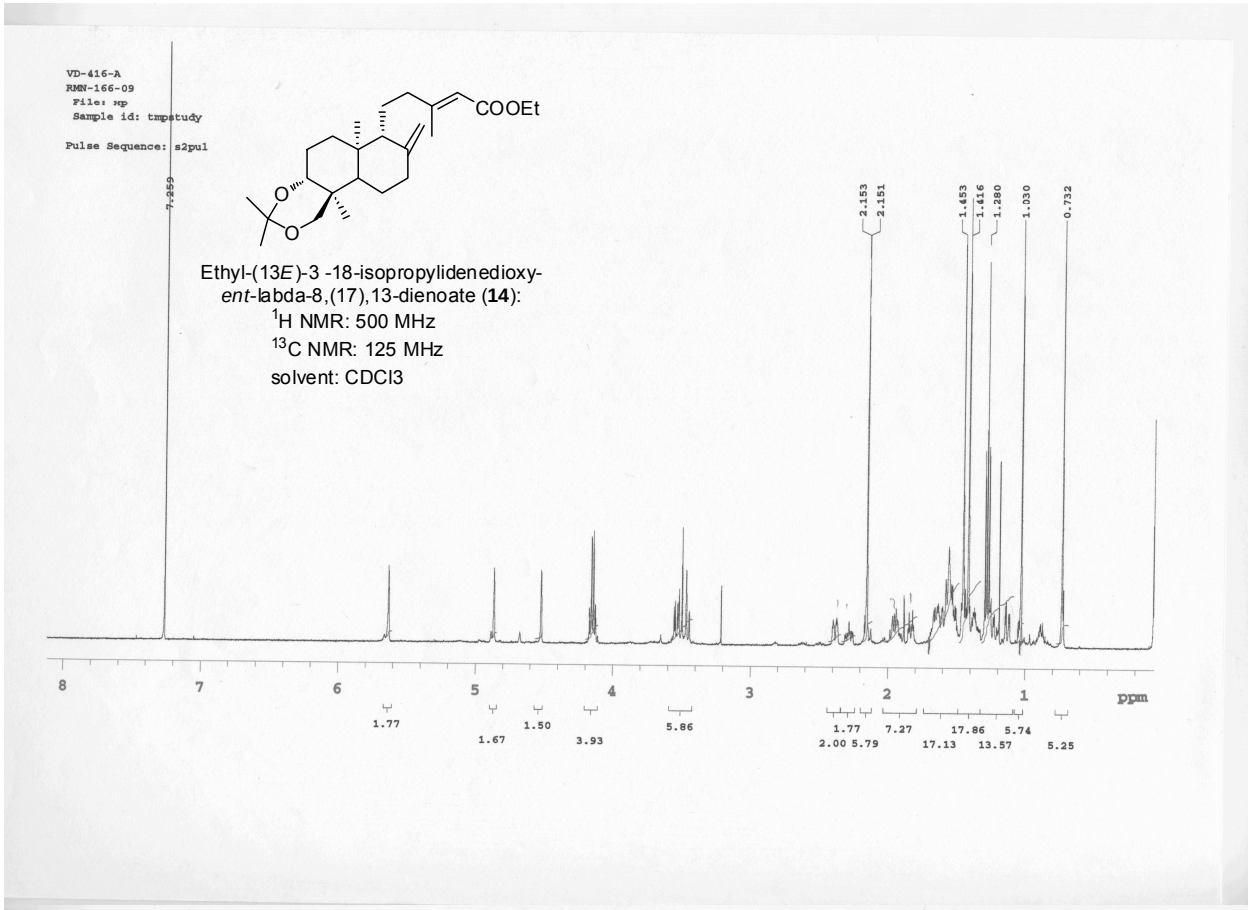
^{13}C NMR: 125 MHz

solvent: CDCl3

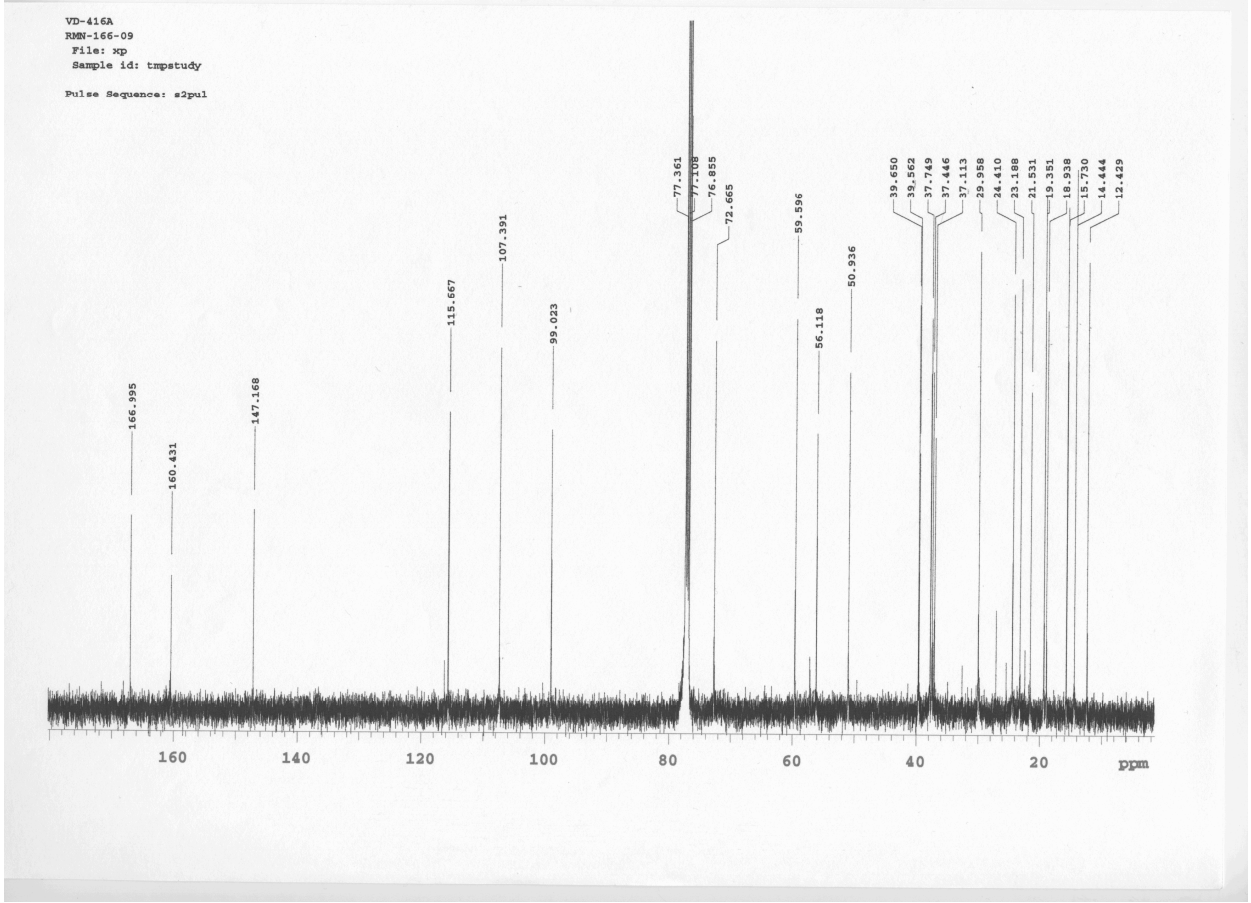
VD-415
RMN-158-09
File: xp
Sample id: tmpstudy

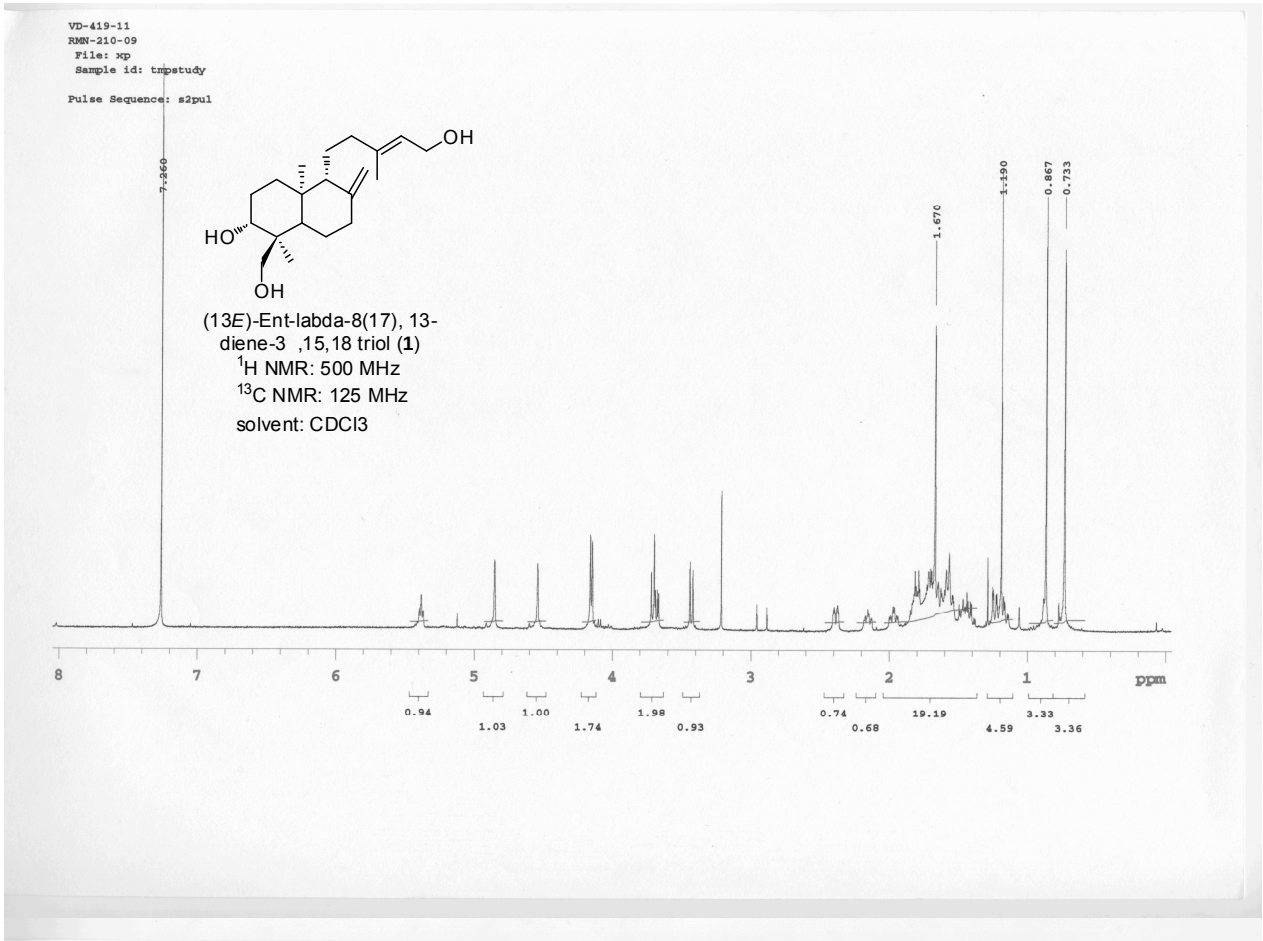
Pulse Sequence: s2pul



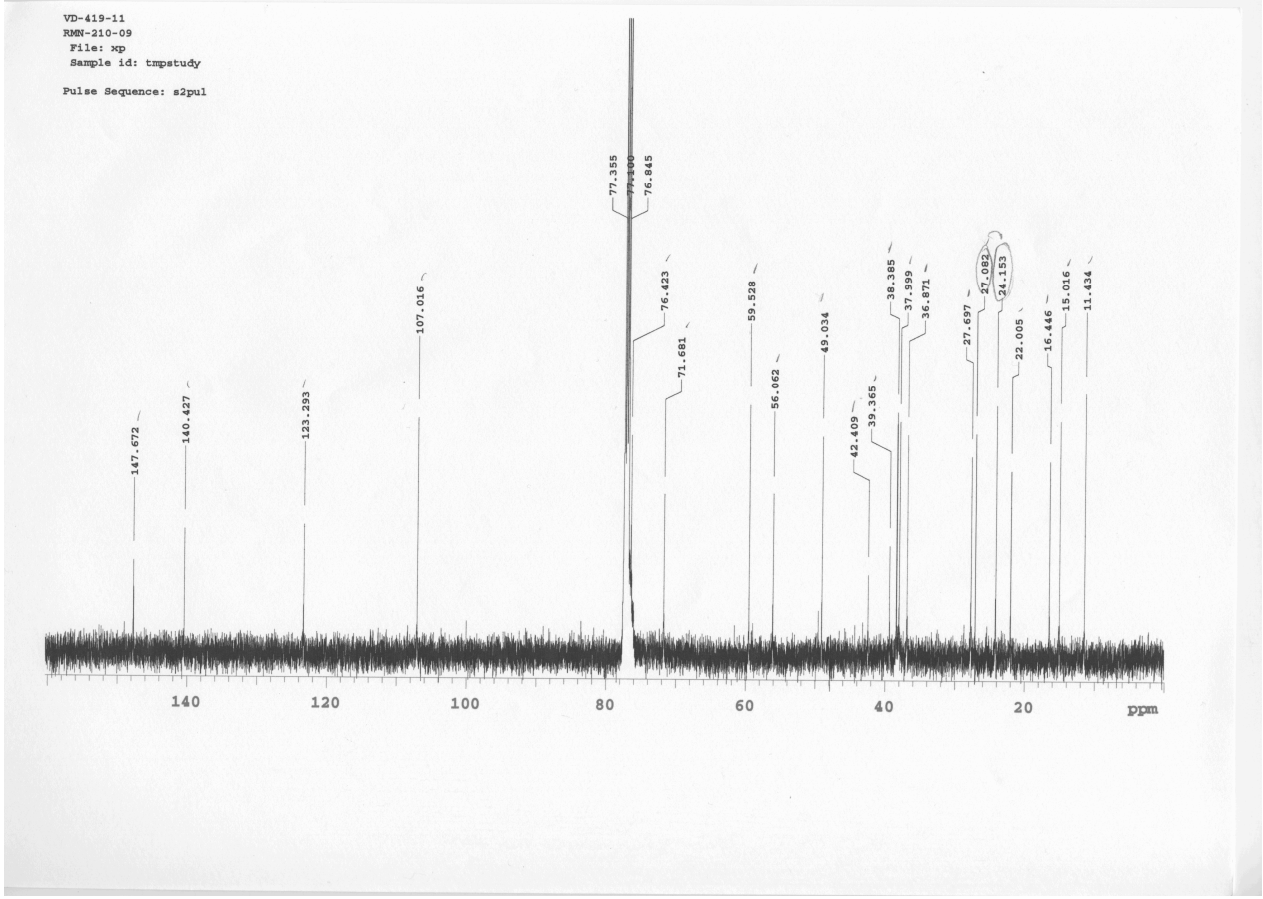


Ethyl-(13*E*)-3 -18-isopropylidenedioxy-*ent*-labda-8,(17),13-dienoate (**14**):
^{1}H NMR: 500 MHz
^{13}C NMR: 125 MHz
solvent: CDCl3





(13*E*)-Ent-labda-8(17), 13-diene-3 ,15,18 triol (**1**)
^{1}H NMR: 500 MHz
^{13}C NMR: 125 MHz
solvent: CDCl3



VI. REFERENCIAS

1 *Terpenes: Flavors, Fragances, Pharmaca, Pheromones*; Breitmaier E., 1st Edition, Wiley **2008**.

2 Maimone, T. J.; Baran, P. S., *Nat. Chem. Biol.*, **2007**, *3*, 396-407.

3 (a) *Medicinal Natural Products*; P. M. Dewick, Ed.; 2nd Edition, Wiley **2002**, Chichester. (b) *Química de los productos naturales*; J. Alberto Marco, Síntesis **2006**, Madrid.

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