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DEPARTAMENTO DE QUÍMICA ORGÁNICA

Facultad de Ciencias



TESIS DOCTORAL

*Avances en Síntesis Orgánica mediante Cloruro de
Titanoceno: Nuevas Reacciones de Desoxigenación y
Olefinación de Carbonilos.*

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2010

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Que el Licenciado en Química D. José Horacio Rodríguez Diéguez ha realizado en el Departamento de Química Orgánica de la Universidad de Granada bajo nuestra dirección, el trabajo titulado “*Avances en Síntesis Orgánica mediante Cloruro de Titanoceno: Nuevas Reacciones de Desoxigenación y Olefinación de Carbonilos*”, que presenta para optar al grado de Doctor.

Y para que así conste, firman el presente certificado en Granada, a 13 de Diciembre de 2010.

Fdo: Prof. Dr. D. Alejandro Fernández Barrero

Fdo: Dr. D. Jesús Fernández Arteaga

Avances en Síntesis Orgánica mediante Cloruro de Titanoceno: Nuevas Reacciones de Desoxigenación y Olefinación de Carbonilos

MEMORIA presentada por José Horacio Rodríguez Diéguez para optar al grado de Doctor en Química.

Granada 13 de Diciembre de 2010

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I. INTRODUCCIÓN **Y OBJETIVOS**

1. Terpenos: Biosíntesis y Ciclaciones Biomiméticas

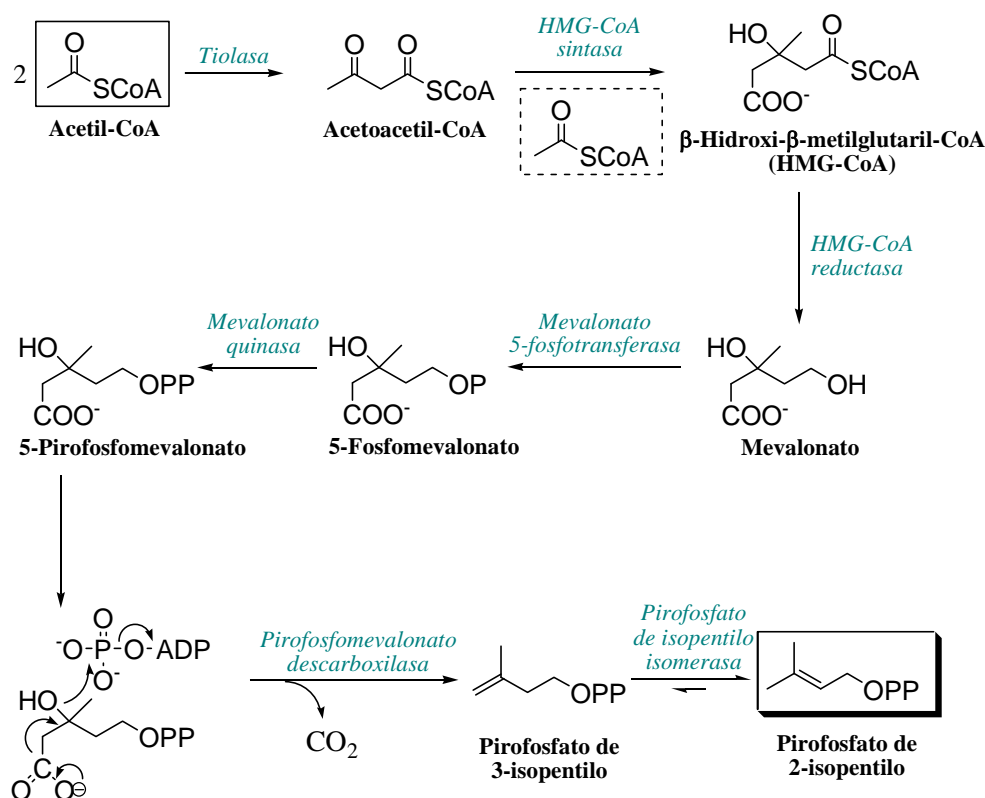
La Naturaleza, con más de 170000 moléculas, ha ofrecido y ofrece unas posibilidades inagotables en cuanto al descubrimiento de complejidad y diversidad molecular. A pesar del acelerado progreso en los métodos de síntesis orgánica y de las técnicas de automatizado robotizadas para desarrollar fácilmente librerías de compuestos, en la actualidad se considera mejor, en términos de eficacia, seleccionar “*cabezas de serie*” de origen natural para la búsqueda de nuevas moléculas bioactivas.¹

De entre las distintas familias de Productos Naturales, los terpenos constituyen probablemente el grupo con mayor número de moléculas descritas, superior a 25000,² pertenecientes a más de 400 esqueletos carbonados. Este tipo de moléculas destaca por su gran variedad de aplicaciones, desde la antigüedad

¹ *Römpp Encyclopedia of Natural Products*; W. Steglich, B. Fugmann, S. Lang-Fugmann, Eds.; Thieme-Verlag 2000, Stuttgart.

²*Dictionary of Terpenoids*; J. D. Connolly, R. A. Hill, Eds.; Vol. 1-3, Chapman and Hall 1991, London.

se usan en perfumería y cosmética, y en la actualidad también se emplean como fármacos, insecticidas, herbicidas, fitorreguladores, etc.³ Desde el punto de vista científico, su origen tiene lugar en 1887 cuando O. Wallach propone la regla del isopreno para relacionar las estructuras de mono-terpenos y L. Ruzicka a mediados del siglo pasado la redefine y emplea para establecer la estructura de sesqui-, di- y triterpenos.⁴ La regla biogenética del isopreno del Instituto Politécnico de Zurich contribuye al descubrimiento del concepto de ciclaciones de terpenoides, teniendo en cuenta las consideraciones mecánicas de Stork en 1950.⁵ Ha sido aceptado hasta hace pocos años que el ácido mevalónico era el único precursor de las unidades de isopreno C₅, difosfato de isopentenilo (IPP) o difosfato de dimetil-alilo (DMAPP), precursores biosintéticos de los terpenos (Esquema 1).



³ *Medicinal Natural Products*; P. M. Dewick, Ed.; 2nd Edition, Wiley 2002, Chichester.

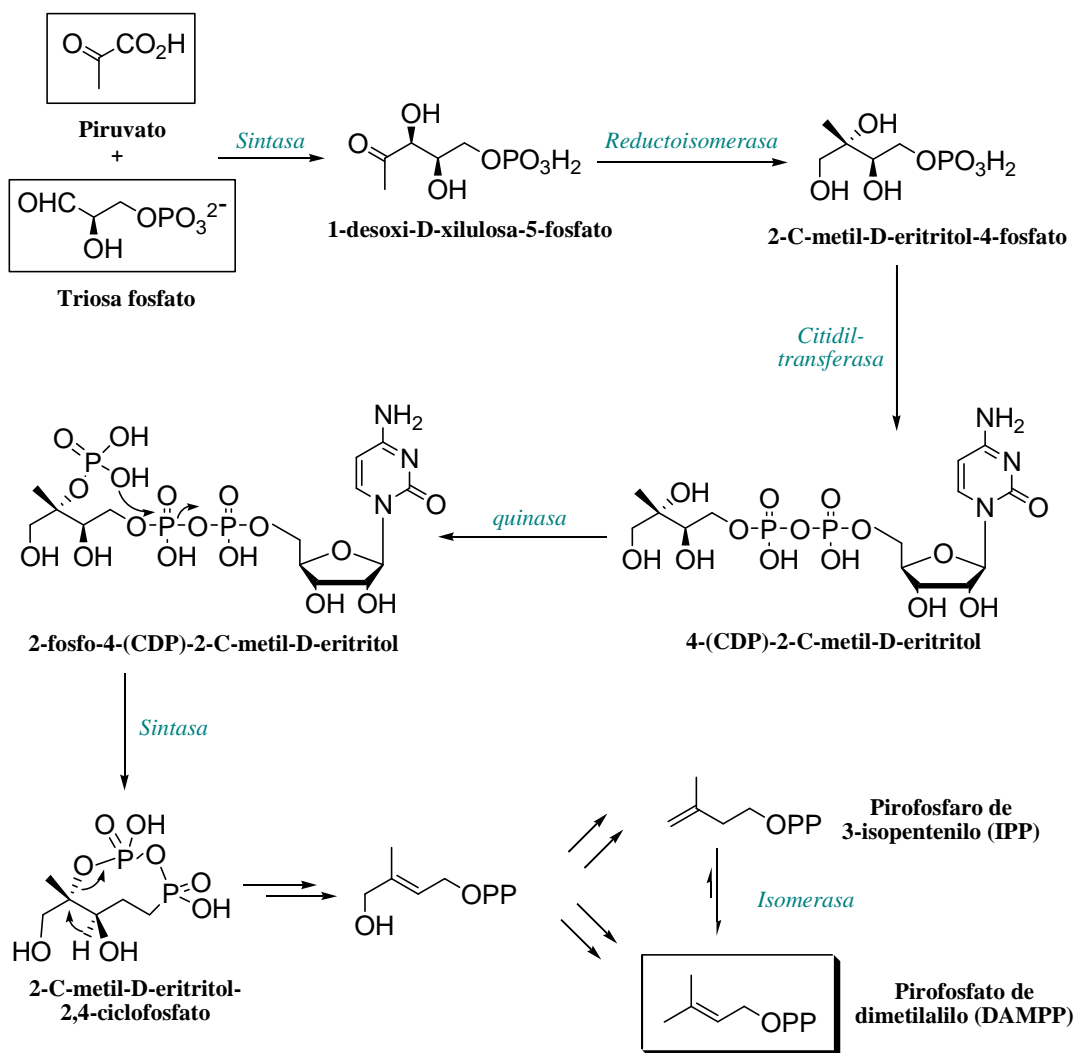
⁴ a) Ruzicka, L. *Experientia* 1959, 9, 357. b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* 1955, 38, 1890-1904.

⁵ a) Stork, G. Burgstahler, A. W. *J. Am. Chem. Soc.* 1955, 77, 5068-5077. b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta.* 1955, 38, 1890-1904.

Esquema 1. Ruta mevalónica

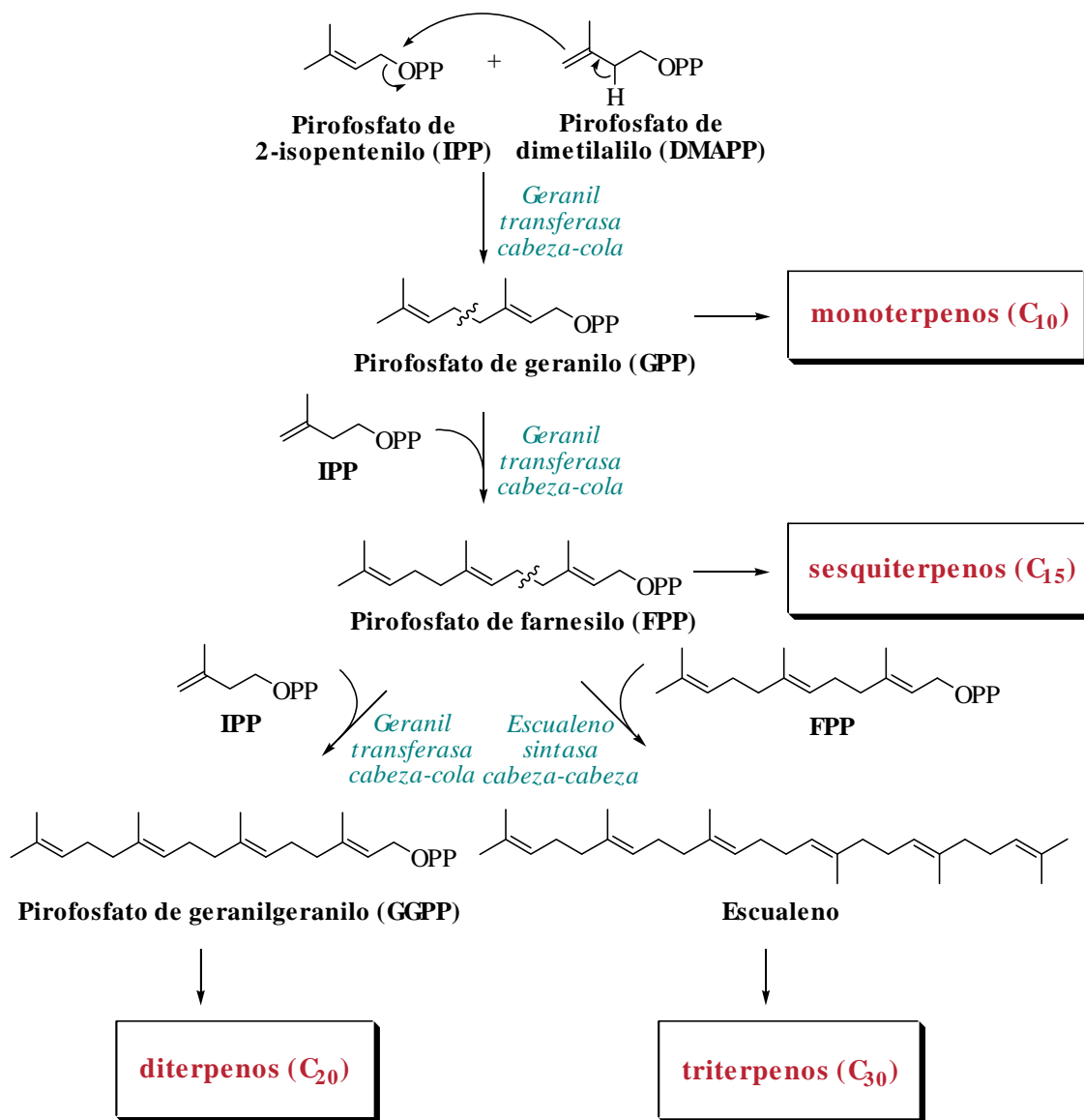
Sin embargo en 1995, M. Rohmer y D. Arigoni descubrieron una nueva vía a través del fosfato de gliceraldehído-piruvato (desoxixilulosafosfato), 1-desoxi-D-xilulosa-5-fosfato o metileritritolfosfato, inicialmente en hopanoides de bacterias (Esquema 2). Esta ruta también está presente en plantas, donde coexisten ambas, aunque separadas en compartimentos celulares bien diferenciados. En el citosol funciona la ruta mevalónica que conduce a triterpenos y esteroides, y en los cloroplastos actúa la ruta del metileritritolfosfato originando los restantes terpenos.⁶

⁶ a) Rohmer, M.; Knani, M.; Simonin, P.; Sutter, B.; Sahm, H. *Biochem. J.* **1993**, 295, 517-524. b) Rohmer, M.; Seeman, M.; Horbach, S.; Bringer-Meyer, S.; Sahm, H. *J. Am. Chem. Soc.* **1996**, 118, 2564-2566. c) Rohmer, M. *Nat. Prod. Rep.* **1999**, 16, 565-574. d) Arigoni, D.; Sagner, S.; Latzel, C.; Eisenreich, W.; Bacher, A.; Zenk, M. *Proceedings of the National Academy of Sciences of the United States of America* **1997**, 94, 10600-10605. e) Eisenreich, W.; Schwarz, M.; Cartayrade, A.; Arigoni, D.; Zenk, M. H.; Bacher, A. *Chemistry & Biology* **1998**, 5, R221-R233. f) Fellermeier, M.; Raschke, M.; Sagner, S.; Wungsintaweekul, J.; Schuhr, C. A.; Hecht, S.; Kis, K.; Radykewicz, T.; Adam, P.; Rohdich, F.; Eisenreich, W.; Bacher, A.; Arigoni, D.; Zenk, M. H. *Eur. J. Biochem.* **2001**, 268, 6302-6310. g) Kuzuyama, T.; Seto, H. *Mat. Prod. Rep.* **2003**, 20, 171-183.



Esquema 2. Ruta no mevalónica

La formación biosintética de los distintos tipos de terpenos a partir del isopreno (2-metil-butadieno), tiene lugar mediante uniones mayoritariamente *cabeza-cola* o *cabeza-cabeza* originando poliprenos acíclicos de 5, 10 (monoterpenos), 15 (sesquiterpenos), 20 (diterpenos), 25 (sesterterpenos), 30 (triterpenos), 40 (tetraterpenos), etc., carbonos (Esquema 3). Cada uno de ellos es el precursor de las distintas subfamilias de terpenos, a través de ciclaciones enzimáticas, mediante *ciclasas*.



Esquema 3

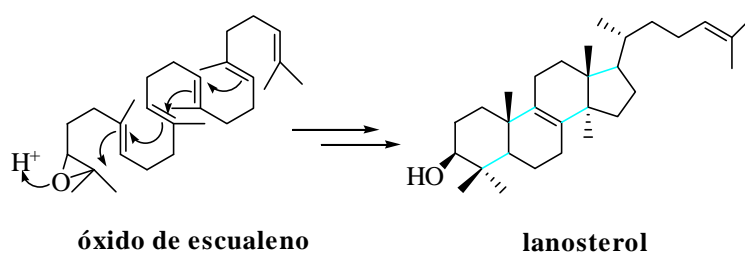
Se ha aceptado que la actuación de estas enzimas transcurre en cinco etapas:⁷

- a) Generación del carbocación.
- b) Control de la conformación del sustrato.
- c) Ciclación.
- d) Estabilización de los carbocationes intermedios.

⁷ I. Abe, G. D. Prestwich, en *Comprehensive Natural Products Chemistry*; D. Barton, K. Nakahishi, Eds.; Elsevier 1999, Vol. 2.

e) Transformación final con estabilización del carbocatión resultante de la ciclación.

Este tipo de mecanismo puede ser interpretado mediante la química de carbocationes, a través de ciclaciones y reordenamientos de Wagner-Meerwein. Así, puede haber a lo largo de los procesos migraciones de H y/o grupos alquilo, y los cationes finales pueden sufrir procesos de eliminación de H⁺ para dar olefinas, o estabilización por nucleófilos presentes en el medio. Un ejemplo clásico es la biosíntesis de lanosterol a partir de óxido de escualeno (Esquema 4). En la actualidad existen evidencias suficientes, tanto teóricas como experimentales, para interpretar este proceso de ciclación cascada desde la química de carbocationes, ya que ha sido objeto de numerosos estudios en los últimos años.⁸

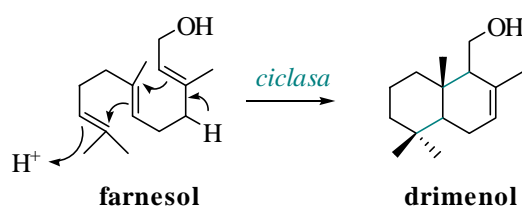


Esquema 4

El proceso se inicia en este caso (Esquema 4), previa epoxidación del precursor poliprénico escualeno hasta óxido de escualeno, mediante la enzima *oxidoescualenociclasa*, que protona selectivamente (parte ácida de la enzima) originando el carbocatión por apertura del oxirano, que cicla en cascada, provoca una serie de reordenamientos de hidrógeno y metilos y finalmente origina lanosterol por pérdida de un protón.

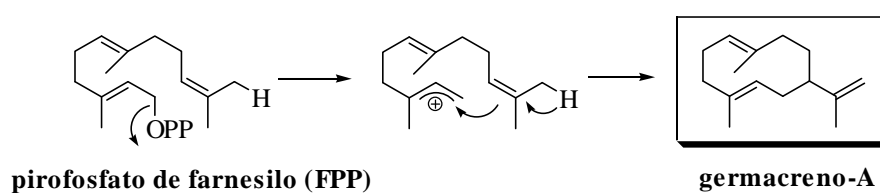
⁸ a) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025-4026. b) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171-8172. c) Corey, E. J.; Virgil, S. C.; Cheng, H.; Baker, C. H.; Matsuda, S. P. T.; Singh, V.; Sarshar, S. *J. Am. Chem. Soc.* **1995**, *117*, 11819-11820. d) Corey, E. J.; Cheng, H. *Tetrahedron Lett.* **1996**, *37*, 2709-2712.

Otra forma que ofrece la naturaleza para la biosíntesis de muchos terpenos, es la protonación directa del polipreno mediante una *ciclasa*, como la biosíntesis de drimenol a partir de farnesol (Esquema 5). En este caso, el proceso involucra la protonación del doble enlace C-10-C-11, ciclación y desprotonación final.



Esquema 5

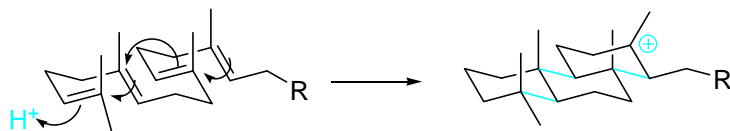
Una tercera forma de ciclación estriba en la eliminación de grupos pirofosfato de los precursores esterificados, así se genera un carbocatión alílico que puede iniciar un proceso de ciclación. Este tipo de biosíntesis está involucrado en la obtención de germacranos a partir de pirofosfato de farnesilo (Esquema 6).



Esquema 6

Una característica importante de estas ciclaciones es su estereoespecificidad. La hipótesis de Stork-Eschenmoser⁵ postula que los procesos de formación de carbocationes y ciclaciones sucesivas transcurren a través de ciclaciones *anti* sincronizadas, vía conformación silla de los

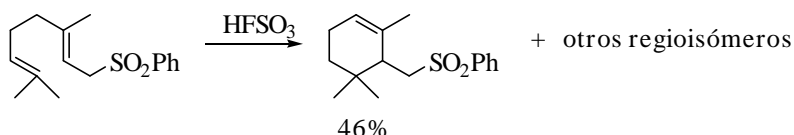
poliprenos, originando generalmente compuestos con configuraciones *anti*, *trans*, *anti*... en las uniones inter-anulares (Esquema 7).



Esquema 7

El conocimiento de estos mecanismos de biosíntesis de terpenos ha dado lugar al desarrollo de procedimientos de síntesis basados en un paso clave de "ciclación biomimética". Se han puesto a punto ciclaciones biomiméticas en su mayoría de dos clases, vía carbocationes o a través de radicales carbonados.

Ciclaciones biomiméticas carbocatiónicas se pueden inducir sobre dobles enlaces mediante protonación. Así, son bien conocidos los trabajos de Vlad⁹ con superácidos protónicos (Esquema 8).



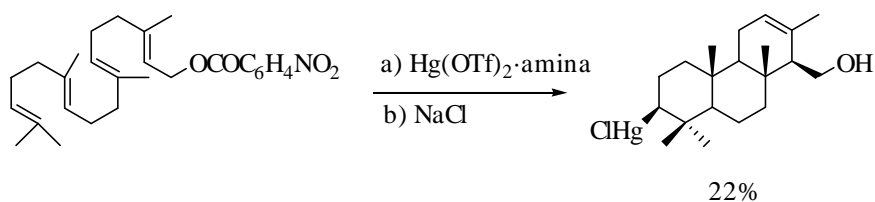
Esquema 8

También se han empleado sales mercuricas como electrófilos para inducir las ciclaciones. Los procesos son quimioselectivos, dan rendimientos aceptables, son versátiles, puesto que el mercurial intermedio se puede transformar en diferentes grupos funcionales. M. Nishizawa y colaboradores¹⁰ encontraron que el triflato mercurico complejoado con dimetil-fenilamina da los

⁹ a) Vlad, P. F.; Ungur, N. D. *Synthesis* **1983**, 3, 216-219. b) Vlad, P. F.; Ungur, N. D.; Koltza, M. N. *Tetrahedron* **1983**, 39, 3947-3958. c) Kulcitki, V.; Ungur, N.; Vlad, P. F. *Tetrahedron* **1998**, 54, 11925-11934. d) Vlad, P. F. *Pure and Applied Chemistry* **1993**, 65, 1329-1336.

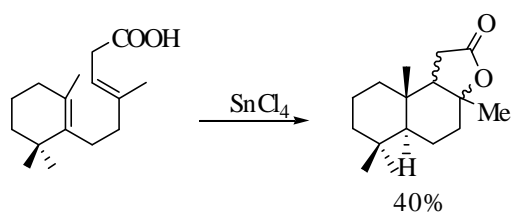
¹⁰ Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, 51, 806-813.

mejores resultados. Así cuando se emplea sobre geranilgeraniol esterificado, se obtiene, con un 22%, el producto de triple ciclación (Esquema 9). Generalmente el cloromercurial se reduce a lo largo del proceso sintético aunque se puede eliminar vía fenil-selenoéter a doble enlace o transformar en el hidroxilo correspondiente.



Esquema 9

También se pueden emplear como iniciadores de la reacción de ciclación, ácidos de Lewis. En este caso el rendimiento y la reactividad de los precursores acíclicos dependen del ácido empleado y de la funcionalización del polipreno.^{5,11} Ejemplos de ácidos de Lewis utilizados son SnCl_4 ¹² y BF_3 ¹³ (Esquema 10 y 11).



Esquema 10



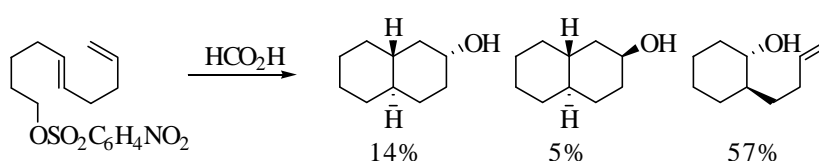
¹¹ Sadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. J. *Helv. Chim. Acta* **1957**, *40*, 2191-2198.

¹² Saito, A.; Matsushita, H.; Tsujino, Y.; Kaneko, H. *Chem. Lett.* **1981**, 757.

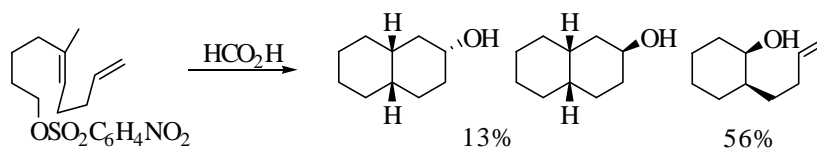
¹³ Harring, S. R.; Livinghouse, T. J. *Chem. Soc., Chem. Comm.* **1992**, 503-504.

Esquema 11

Otros tipos de ciclaciones relacionadas, son las que utilizan como iniciadores para generar el carbocatión, alcoholes o derivados, acetales etc. En este campo son bien conocidas las aplicaciones de W. S. Johnson y colaboradores,¹⁴ que pusieron de manifiesto que la reacción es estereoespecífica con respecto a la estereoquímica del alqueno¹⁵ (Esquema 12 y 13).



Esquema 12



Esquema 13

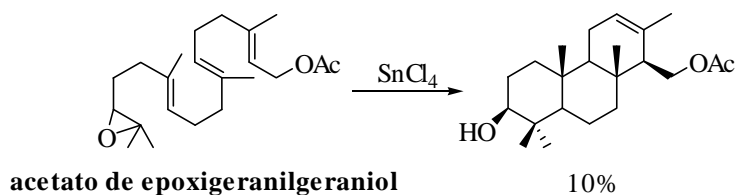
Con epoxi-poliprenos también existen trabajos de ciclaciones en medios ácidos, en este campo destacan los trabajos de E. E. van Tamelen y colaboradores,¹⁶ que emplean ácidos de Lewis. Lo más destacable es la funcionalización de las estructuras cíclicas con un hidroxilo en C-3 al iniciar la ciclación con epóxidos. En el caso del epóxido de acetato de geranilgeraniol, se obtiene un 10% del espongiario correspondiente (Esquema 14).¹⁷ El principal inconveniente es la formación de productos de reordenamiento u óxidos.

¹⁴ Johnson, W. S.; Bailey, D. M.; Owyang, R.; Bell, R. A.; Jaques, B.; Crandall, J. K. *J. A. Chem. Soc.* **1964**, 86, 1959-1966.

¹⁵ Johnson, W. S.; Lunn, W. H.; Fitz, K. *J. Am. Chem. Soc.* **1964**, 86, 1972-1978.

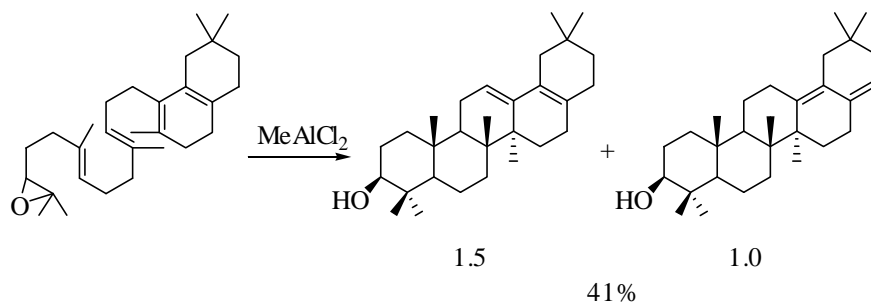
¹⁶ Van Tamelen, E. E.; James, D. R. *J. Am. Chem. Soc.* **1977**, 99, 950-952.

¹⁷ Van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, 85, 3295-3296.



Esquema 14

Cuando se emplean substratos elaborados de partida, la metodología ha servido para la síntesis de terpenos naturales. Son de destacar las síntesis de E. J. Corey y colaboradores¹⁸ en el campo de los triterpenos (Esquema 15).

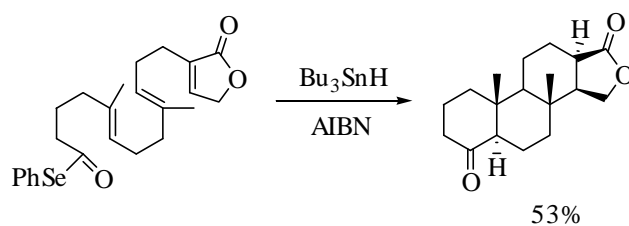


Esquema 15

También se han descrito ciclaciones biomiméticas radicalarias, entre ellas merece mencionarse el método puesto a punto por G. Pattenden y colaboradores, que emplea acilselenios.¹⁹ Mediante reducción de acilselenios con Bu_3SnH / AIBN, preparan el acil-radical que origina las ciclaciones (Esquema 16). En estos procesos aunque hay que sintetizar el precursor inicial, y la reacción de ciclación termina de manera reductora con incorporación final de hidrógeno, los rendimientos mejoran a los catiónicos. La estereoquímica de las ciclaciones es idéntica a la observada en procesos iónicos.

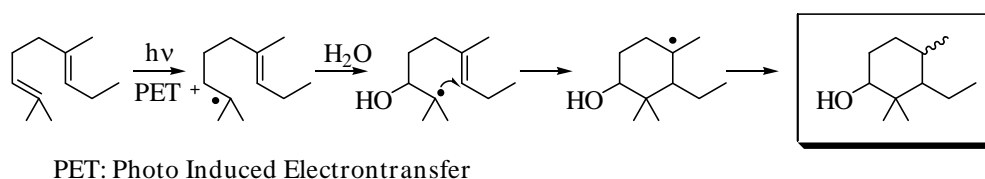
¹⁸ Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999-10003.

¹⁹ Pattenden, G.; Handa, S. *J. Chem. Soc., Perkin Trans I* **1999**, 843-847.



Esquema 16

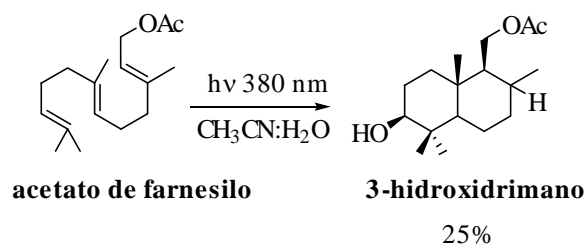
Otra metodología interesante consiste en la ciclación fotoinducida en polienos vía catión-radical, puesta a punto por H. Demuth y colaboradores.²⁰ Consiste en la irradiación de una olefina en CH₃CN:H₂O (20:1) en presencia de un aceptor de e^- como 1,4-diciano-benceno. El catión-radical intermedio es generado vía PET (*photoinduced electron transfer*) y capturado por un nucleófilo presente en el medio, normalmente agua, de manera regioselectiva (anti-Markownikoff) (Esquema 17).



Esquema 17

En el proceso, tras la adición nucleofílica de H₂O al catión-radical, se produce la ciclación, finalizando con la reducción del radical final a hidrocarburo. Cuando se aplica sobre acetato de farnesilo se obtiene un 25% del 3-hidroxi-drimano (Esquema 18).

²⁰ Hoffman, U.; Gao, Y.; Pandey, B.; Kingle, S.; Warzecha, K.; Krüger, C.; Roth, H. D.; Demuth, M. J. *Am. Chem. Soc.* **1993**, *115*, 10358-10359.



Esquema 18

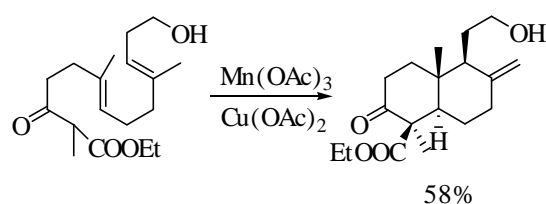
Dentro de las ciclaciones radicalarias se han usado también metales de transición²¹ como alternativa a la química radicalaria de estannanos, ya que los intermedios de estas reacciones se pueden comportar de manera diferente. Así se emplean sales de Mn^{III} ,²² o Fe^{III} [$\text{Cp}_2\text{Fe}(\text{III})\text{PF}_6$],²³ para oxidar enolatos hasta radicales.

²¹ a) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771-2788. b) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519-564.

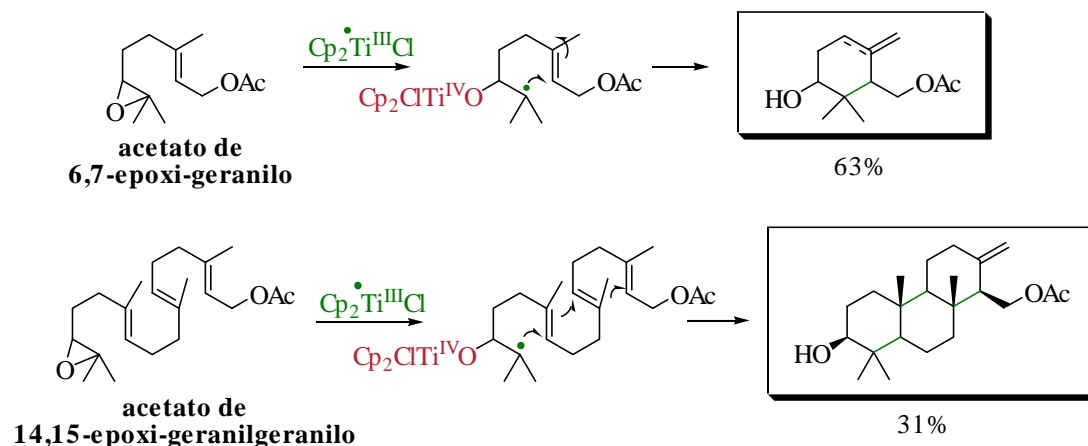
²² a) Heiba, E. I.; Dessau, R. M.; Koehl Jr., W. R. *J. Am. Chem. Soc.* **1968**, *90*, 2706-2707. b) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524-527. c) Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977-7981. d) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1974**, *96*, 3456-3462.

²³ Jahn, U.; Hartmann, I. D.; Jones, P. G. *Eur. J. Org. Chem.* **2001**, *66*, 3333-3355.

En cuanto a ciclaciones biomiméticas, nuestro grupo además de llevar a cabo ciclaciones catiónicas de epóxidos o poliprenos,²⁴ o radicalarias con $\text{Mn}(\text{OAc})_3$ (Esquema 19),²⁵ recientemente hemos puesto a punto un método general de ciclaciones radicalarias basado en la apertura homolítica de epoxi-poliprenoides mediada por Ti^{III} (Esquema 20).²⁶



Esquema 19



Esquema 20

²⁴ a) Barrero, A. F.; Sánchez, J. F.; Altarejos, J. *Tetrahedron Lett.* **1988**, 29, 3713-3717. b) Barrero, A. F.; Quintana, R.; Altarejos, J. *Tetrahedron* **1991**, 47, 4441-4455. c) Barrero, A. F.; Altarejos, J.; Álvarez-Manzaneda, E. J.; Ramos, J. M.; Salido, S. *J. Org. Chem.* **1996**, 61, 2215-2219. d) Barrero, A. F.; Oltra, J. E.; Morales V.; Álvarez, M. *J. Nat. Prod.* **1997**, 60, 1034-1035.

²⁵ Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Valdivia, M. *Org. Lett.* **2002**, 4, 1379-1382.

²⁶ a) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. *J. Org. Chem.* **2001**, 66, 4074-4078. b) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haidour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. *Chem. Eur. J.* **2004**, 10, 1778-1788.

2. Monocloruro de titanoceno (Cp_2TiCl):

Generalidades

En los últimos años uno de los grandes objetivos de nuestro Grupo de Investigación, ha sido el desarrollo de nuevas estrategias sintéticas encaminadas a la síntesis de Productos Naturales Bioactivos.²⁷ Abordar la síntesis de moléculas bioactivas es un interesante ejercicio de creatividad a través del correcto diseño de retrosíntesis, persiguiendo el empleo de estrategias cada vez más limpias, suaves y eficaces. En este sentido la química de radicales libres es actualmente una de las principales herramientas en

²⁷ a) Barrero, A. F.; Arseniyadis, S.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, J. F.; Sánchez, E. M. *Synlett* **2005**, *4*, 0591-0594; b) Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, *7*, 1627-1641; c) Barrero, A. F.; Quílez del Moral, J. F.; Herrador, M. M.; Loayza, I.; Sánchez, E. M.; Arteaga, J. F. *Tetrahedron* **2006**, *62*, 5215-5222; d) Barrero, J. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Sánchez, E. M.; Arteaga, J. F.; Piedra, M. *Eur. J. Org. Chem.* **2006**, *15*, 3434-3441; e) Barrero, A. F.; Quílez del Moral, J. F.; Herrador, M. M.; Cortés, M.; Catalán, J. V.; Sánchez, E. M.; Arteaga, J. F. *J. Org. Chem.* **2006**, *71*, 5811-5814; f) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, J. F.; Díaz, V. D.; Sánchez, E. M. *Tetrahedron* **2008**, *64*, 5111-5118; g) Arteaga, J. F.; Domingo, V.; Quílez del Moral, J. F.; Barrero, A. F. *Org. Lett.* **2008**, *10*, 1723-1726; h) Domingo, V.; Arteaga, J. F.; Quílez del Moral, J. F.; Barrero, A. F. *Nat. Prod. Rep.* **2009**, *26*, 115-134; i) Domingo, V.; Silva, L.; Diéguez, J. H.; Arteaga, J. F.; Quílez del Moral, J. F.; Barrero, A. F. *J. Org. Chem.* **2009**, *74*, 6151-6156; j) Barrero, A. F.; Herrador, M. M.; López-Pérez, J. L.; Arteaga, J. F.; Catalán, J. V. *Org. Lett.* **2009**, *11*, 4782-4785; k) Domingo, V.; Diéguez, H. R.; Morales, C. P.; Arteaga, J. F.; Quílez, J. F.; Barrero, A. F. *Synthesis* **2010**, 67-72.

síntesis orgánica,²⁸ gracias a que opera bajo condiciones suaves de reacción y a la elevada selectividad que presentan sus distintos procesos.

Las reacciones de ciclación radicalaria constituyen un grupo importante dentro de las reacciones de formación de enlaces carbono-carbono y permiten incluso la obtención de compuestos mono- y policíclicos. Son procesos que muchas veces dan buenos rendimientos, en general con alto grado de regio y estereoselectividad, y en los que puede llegar a controlarse la formación de ciclos de diferentes tamaños.²⁹ Se han empleado para sintetizar numerosos productos naturales, incluyendo terpenoides y esteroides,³⁰ lignanos y otros heterociclos oxigenados,³¹ y β -lactamas.³²

De los distintos tipos de reacciones de ciclación radicalarias existentes, destacan por su potencial sintético las secuencias en cascada, ya que permiten la

²⁸ a) *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Giese, B., Pergamon Press: Oxford, **1986**. b) *Stereochemistry of Radical Reactions*, Curran, D. P.; Porter, N. A.; Giese, B., VCH: Weinheim, **1996**. c) *Free Radicals in Organic Chemistry*, Fossey, J.; Lefort, D.; Sorba, J., Wiley: New York, **1995**. d) *Radikale und Radikationen in der Organischen Synthese*, Linker, T.; Schmittel, M., Wiley-VCH: Weinheim, **1998**; e) Bazukis, P.; Campos, O. O. S.; Bazukis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261-3264. f) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448-1449. g) Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991-4994. h) Danishefsky, S. L.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917-918. i) Chen, Y.-J.; Lin, W.-Y. *Tetrahedron Lett.* **1992**, *33*, 1749-1750.

²⁹ a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*. Pergamon Press, Oxford, **1986**. b) Curran, D. P. *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, Vol. 4, 779-831. c) Curran, D. P.; Porter, N. A.; Fieser, B. G. *Stereochemistry of Radical Reactions*. VCH, Weinheim, **1996**. d) Parsons, A. F. *An Introduction to Free Radical Chemistry*. Blackwell Science, Oxford, **2000**, Chap. 7, p. 139-159. e) *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, Vol. 2.

³⁰ Dhimane, A. L.; Fensterbank, L.; Malacria, M. *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, Vol. 2, 4.4, p. 350-382.

³¹ Lee, E. *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, Vol. 2, 4.2, p. 303-333.

³² Srikrishna, A. *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, Vol. 2, 3.1, p. 151-187.

formación de varios ciclos en un solo paso.³³ Tales reacciones son de especial interés en la síntesis de terpenoides y esteroides, debido a que mimetizan los sistemas enzimáticos involucrados en la biosíntesis de éstos compuestos.³⁴ Breslow, Julia y colaboradores, fueron los primeros en describir las polimerizaciones radicalarias de poliprenos.³⁵ Desde entonces, se ha indicado su empleo en numerosas síntesis destacando la síntesis total de hirsuteno de Curran y Rakiewicz,³⁶ y el desarrollo de diferentes métodos hacia esqueletos triquinanos.³⁷

Dentro de los reactivos que participan en Química Radicalaria, el complejo **cloruro de bis-ciclopentadieniltitanio(III)** (reactivo de Nugent)³⁸ es un reactivo suave y eficaz para la generación de radicales carbonados en síntesis orgánica, siendo muy útil su empleo en la formación de enlaces carbono-carbono e intercambio de grupos funcionales.

Este reactivo ha sido seleccionado como herramienta sintética para los trabajos aquí desarrollados, debido a sus extraordinarias cualidades para provocar la generación de radicales libres y su eficaz transformación, y a la experiencia previa adquirida por nuestro grupo en años precedentes. Esta experiencia es la base que ha permitido proponer y desarrollar en esta memoria

³³ a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.*, **1991**, *91*, 1237-1286; b) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103-13159. c) McCarroll, A. J.; Walton, J. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2224-2248. d) McCarroll, A. J.; Walton, J. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 3215-3229.

³⁴ a) Wendt, K. W.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.*, **2000**, *39*, 2812-2833. b) De la Torre, M. C.; Sierra, M. A. *Angew. Chem. Int. Ed.*, **2004**, *43*, 160-181.

³⁵ a) Breslow, R.; Barret, E.; Mohacsi, E. *Tetrahedron Lett.*, **1962**, 1207-1211. b) Breslow, R.; Groves, J. T.; Olin, S. S. *Tetrahedron Lett.*, **1966**, 4717-4719. c) Lallemand, J. Y.; Julia, M.; Mansuy, D. *Tetrahedron Lett.* **1973**, *14*, 4461-4464.

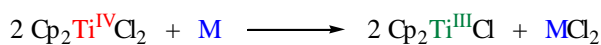
³⁶ Curran, D. P.; Rakiewicz, D. M. *Tetrahedron* **1985**, *41*, 3943-3958.

³⁷ a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925-3941. b) Dombrowski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759-2767. c) Journet, M.; Malacria, M. J. *Org. Chem.* **1992**, *57*, 3085-3093. d) Journet, M.; Malacria, M. J. *Org. Chem.* **1994**, *59*, 718-719. e) Devin, P.; Festerbank, L.; Malacria, M. J. *Org. Chem.* **1998**, *63*, 6764-6765.

³⁸ Green, M. L.; Lucas, C. R. *J. Chem. Soc.* **1972**, 1000-1003.

una serie de novedosos procesos sintéticos de interés general en Síntesis Orgánica.

El reactivo $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ se prepara *in situ* a partir de la reducción del $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ comercial con metales reductores como Mn,³⁹ Zn,⁴⁰ o Mg⁴¹ (Esquema 21). Una vez obtenido puede comportarse dando lugar a distintas especies mono-, di-⁴² y trinucleares (aunque ésta última es característica exclusivamente del estado sólido) (Figura 1).⁴³ En esas condiciones este compuesto no es caro ni tóxico, sus reacciones transcurren en condiciones suaves y son toleradas por un gran número de grupos funcionales (alcoholes, amidas, cetonas, ácidos, ésteres, etc.). Esto sugiere que puede ser un agente selectivo ideal para ser utilizado con sustratos sensibles y altamente funcionalizados. En esta memoria todas las especies de Ti^{III} citadas anteriormente serán nombradas como $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$.



Cp: Ciclopentadienilo
M: Metal reductor

Esquema 21

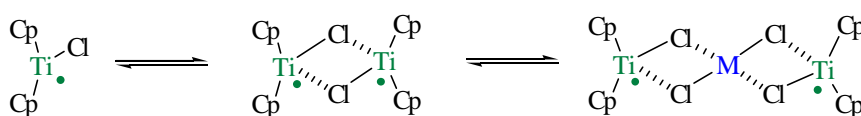


Figura 1

³⁹ Sekutowski, D. J.; Stucky, G. D. *Inorg. Chem.* **1975**, *14*, 2192-2199.

⁴⁰ Coutts, R. S.; Wailes, P. C.; Martin, R. L. *J. Organomet. Chem.* **1973**, 375-382.

⁴¹ Stephan, D. W. *Organometallics.* **1992**, *11*, 996-999.

⁴² Enemaerke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853-7864.

⁴³ Sekutowski, D. J.; Jungst, R.; Stucky, G. D. *Inorg. Chem.* **1978**, *17*, 1848-1855.

El $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ posee un electrón desapareado que le confiere un carácter reductor mono-electrónico suave.⁴⁴ Además posee una vacante electrónica que le permite funcionar como ácido de Lewis y coordinarse a distintos heteroátomos, bases de Lewis. La fácil formación de complejos con diversos grupos funcionales le transfiere la capacidad de promover procesos de transferencia mono-electrónica y originar radicales alquilo.

En los últimos años el $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ se ha utilizado ampliamente en reacciones de gran interés en síntesis orgánica. Entre ellas destacaremos las reacciones que derivan de la apertura homolítica de oxiranos⁴⁵ y las reacciones de acoplamiento pinacólico.⁴⁶ Además se ha empleado entre otras, en reacciones de reducción de bromuros de glicosilo,⁴⁷ de dibromuros vecinales,⁴⁸ de α -halocetonas,⁴⁹ en reacciones de homoacoplamiento mediante apertura de vinil-oxiranos,⁵⁰ en reacciones de ciclación de haluros de alquilo,⁵¹ así como en la formación de β -hidroxi ésteres⁵² y de alcoholes homo-alílicos.⁵³

⁴⁴ Enemaerke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *Organometallics*. **2004**, *23*, 1866-1874.

⁴⁵ Nugent, W.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561-8562.

⁴⁶ a) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484-5485 ; b) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 2673-2676; c) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 1923-1927.

⁴⁷ a) Spencer, R.; Schwartz, J. *Tetrahedron Lett.* **1996**, *37*, 4357-4360; b) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055-7057; c) Hansen, T.; Krintel, S. L.; Daasbjerg, K.; Skrydstrup, T. *Tetrahedron Lett.* **1999**, *40*, 6087-6090.

⁴⁸ a) Davies, S. G.; Thomas, S. E. *Synthesis* **1984**, 1027-1028; b) Qian, Y.; Li, G.; Zheng, X.; Huang, Y.-Z. *Synlett* **1991**, 489-490.

⁴⁹ Parrish, J. D.; Little, R. D. *Org. Lett.* **2002**, *4*, 1439-1442.

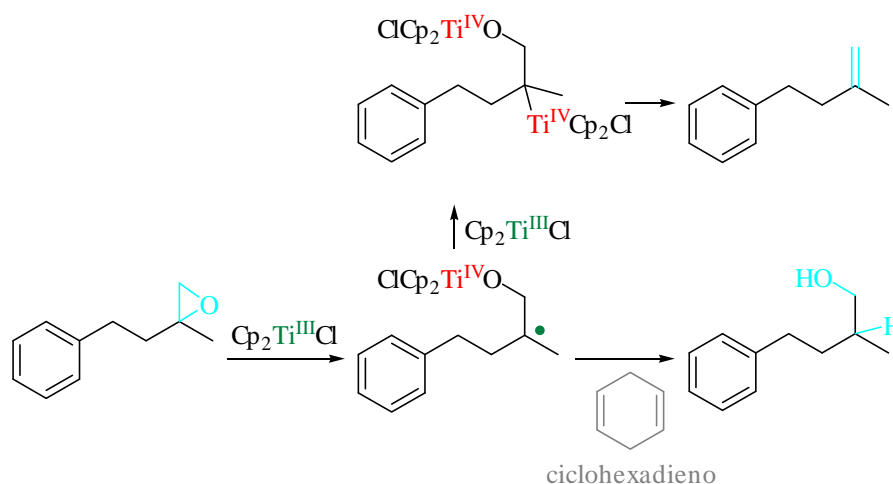
⁵⁰ Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. *Org. Lett.* **2006**, *8*, 669-672.

⁵¹ Hersant, G.; Ferjani, S. M. B.; Bennet, S. M. *Tetrahedron Lett.* **2004**, *45*, 8123-8126.

⁵² Parrish, J. D.; Shelton, D. R.; Little, R. D. *Org. Lett.* **2003**, *5*, 3615-3617.

⁵³ Rosales, A.; Óller-López, J. L.; Justicia, J.; Gansäuer, A.; Oltra, J. E.; Cuerva, J. M. *Chem. Commun.* **2004**, 2628-2629.

Referente a la apertura de los epóxidos, el reactivo fue por primera vez usado por Nugent y RajanBabu en 1988 *via* transferencia mono-electrónica.⁵⁴ El $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ origina la ruptura homolítica del enlace C-O en el oxirano para generar el radical carbonado (Esquema 22). La reacción de este radical con un segundo equivalente de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ da lugar a la formación de un complejo alquil- Ti^{IV} , que mediante eliminación de $\text{Ti}^{\text{IV}}\text{-O-Ti}^{\text{IV}}$ produce la correspondiente olefina. También es posible obtener alcoholes con buenos rendimientos mediante la adición a la mezcla de reacción de una fuente de hidrógeno tal como 1,4-ciclohexadieno.⁵⁵



Esquema 22

Actualmente la utilidad sintética de este reactivo se está centrando mayoritariamente en su reacción con sustratos que contienen epóxidos, grupos carbonilo y haluros activados.⁵⁶

⁵⁴ a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561-8562; b) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1989**, *111*, 4525-4527; c) Nugent, W.; RajanBabu, T. V. Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408-6409.

⁵⁵ RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986-997.

⁵⁶ a) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Bazdi, B.; Oltra, J. E. *Mini-Rev. Org. Chem.* **2006**, *3*, 23.

3. Objetivos:

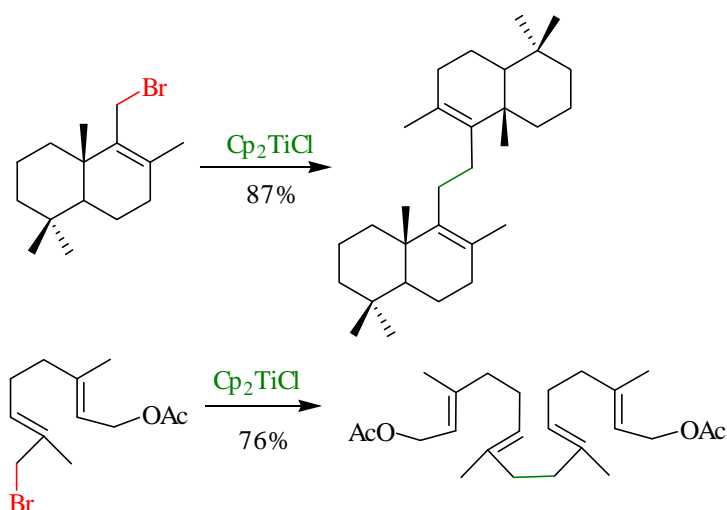
Teniendo en cuenta todo lo anteriormente expuesto, en esta Memoria se van a plantear una serie de estudios encaminados a mejorar las aplicaciones sintéticas del reactivo cloruro de titanoceno ($\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$), divididas en los siguientes objetivos perfectamente diferenciados.

1. Estudio de los acoplamientos carbono-carbono en derivados halogenados alílicos promovidos por Cp_2TiCl y por Mn/Zr(IV).

Recientemente han sido publicados con excelentes resultados (Esquema 23)⁵⁷ por nuestro Grupo de Investigación, los primeros resultados para el empleo catalítico de cloruro de titanoceno ($\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$) en el homo-acoplamiento de haluros alílicos. Esta reacción tiene lugar bajo condiciones suaves y destaca por ser quimioselectiva ante un amplio número de grupos funcionales, tales como alcoholes, aminas, cetonas, ácidos y ésteres.⁵⁸

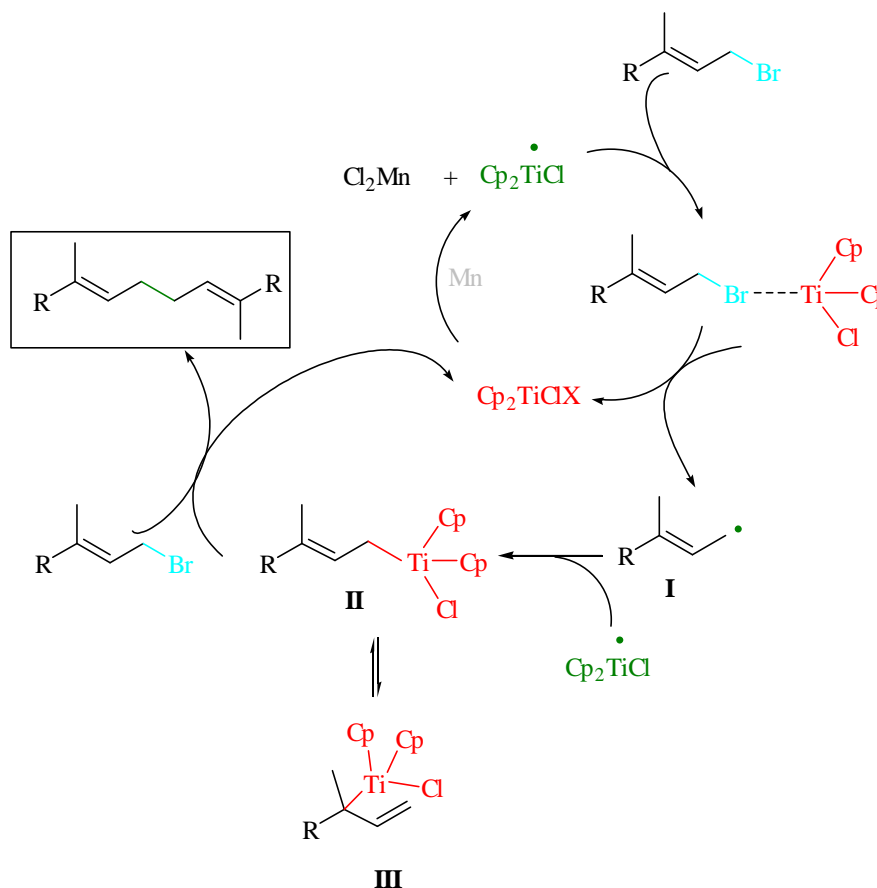
⁵⁷ Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Piedra, M.; Sánchez, E. M. *Org. Lett.* **2005**, *7*, 2301-2304.

⁵⁸ Spencer, R. P.; Cavallaro, C. L.; Schwartz, J. J. *Org. Chem.* **1999**, *64*, 3987-3995.



Esquema 23

El proceso se ha justificado mecanísticamente a través de la coordinación inicial de tipo ácido-base entre el derivado halogenado y el reactivo de Ti^{III} . Una transferencia monoeléctrica vía $\text{S}_{\text{H}}2$, conduce al correspondiente radical alílico, el cual mediante reacción con una segunda molécula de reactivo, origina los correspondientes alil-titanios (isómeros alílicos, **II** y **III**) que se acoplan con el derivado halogenado (Esquema 24). Este mecanismo permite que el método pueda ser catalítico, al eliminarse en cada etapa $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$, susceptible de reducirse en el medio por el exceso de Mn. Este hecho presenta ventajas evidentes pues la mayoría de métodos de acoplamiento de este tipo utilizan cantidades estequiométricas de reactivos, haciendo que el proceso catalítico con Ti^{III} sea más limpio, barato y menos perjudicial para el medio ambiente.

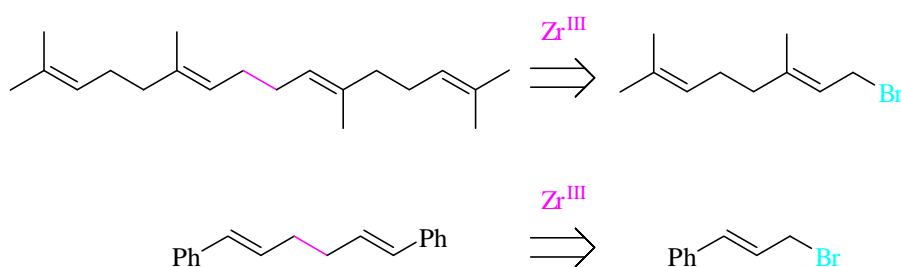


Esquema 24. Mecanismo de homo-acoplamiento de bromuros alílicos mediado/catalizado por Cp_2TiCl

Teniendo todo esto presente y debido al parecido estructural y electrónico entre el titanoceno y el zirconoceno, pensamos que mediante la elección de unas condiciones apropiadas de reacción, el reactivo $\text{Cp}_2\text{Zr}^{\text{III}}\text{Cl}$ podría ser capaz igualmente de inducir una reacción de homo-acoplamiento entre derivados halogenados alílicos.

De esta forma, ensayos iniciales para generar este acoplamiento en condiciones análogas a las empleadas con Ti^{III} , empleando $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2$ con Mn en exceso, en presencia de derivados halogenados alílicos, han conducido a homo-acoplamientos si bien nunca se ha observado en el medio el intenso color rojo característico de la presencia de Zr^{III} .

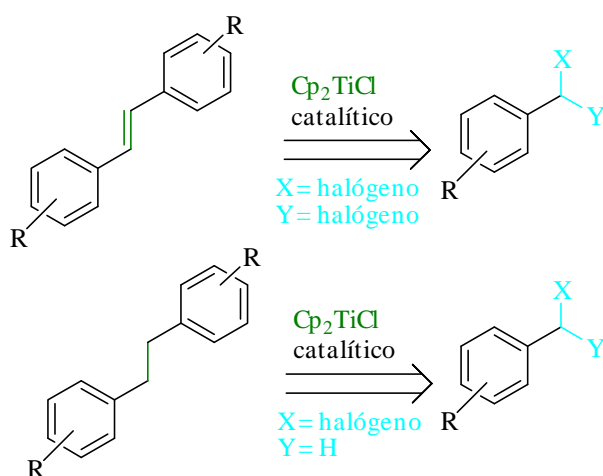
Teniendo todo esto presente, se pretende estudiar este tipo de metodología sintética hacia la formación de enlaces C-C partiendo de la hipótesis de que la reacción puede tener lugar mediante la presencia del reactivo de zirconio en forma de Zr^{IV} , actuando entonces como ácido de Lewis activando el enlace C-Halógeno, que de esta forma puede ser reducido por Mn. (Esquema 25).



Esquema 25

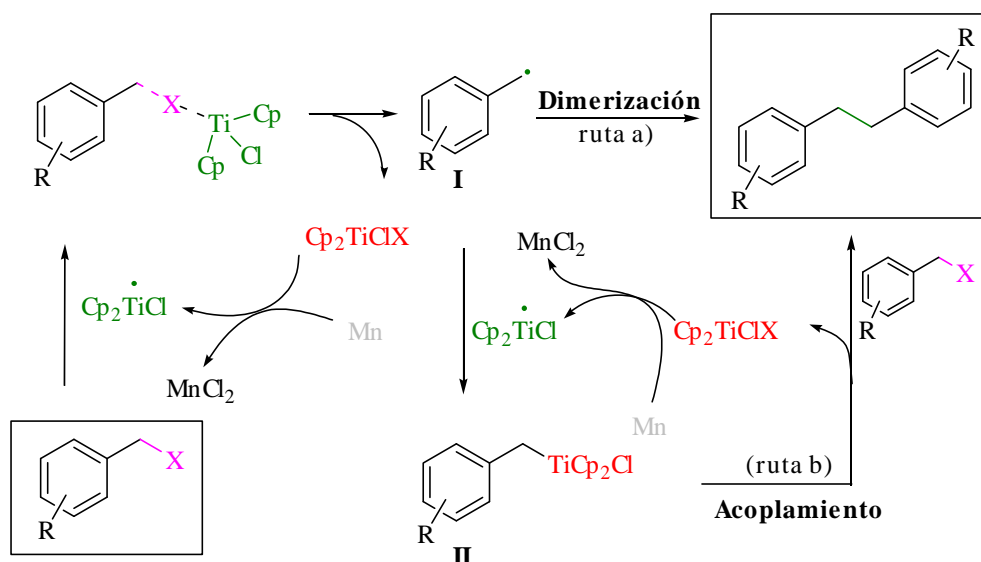
2. Estudio de los acoplamientos C-C en derivados halogenados bencílicos y *gem*-dihalogenados, y acoplamientos mixtos promovidos por metales de transición.

Se pretende en segundo lugar extender la metodología de homo-acoplamiento de derivados halogenados activados catalizada por metales de transición, generalizando su empleo hasta derivados bencílicos y *gem*-dihalogenados, viendo además la posibilidad de llevar a cabo acoplamientos cruzados con compuestos carbonílicos (Esquema 26).



Esquema 26

Considerando el mecanismo propuesto para la reacción con haluros alílicos (Esquema 24), pensamos que el $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ podría intervenir eficientemente en el homo-acoplamiento de haluros bencílicos mediante un mecanismo similar (Esquema 27).

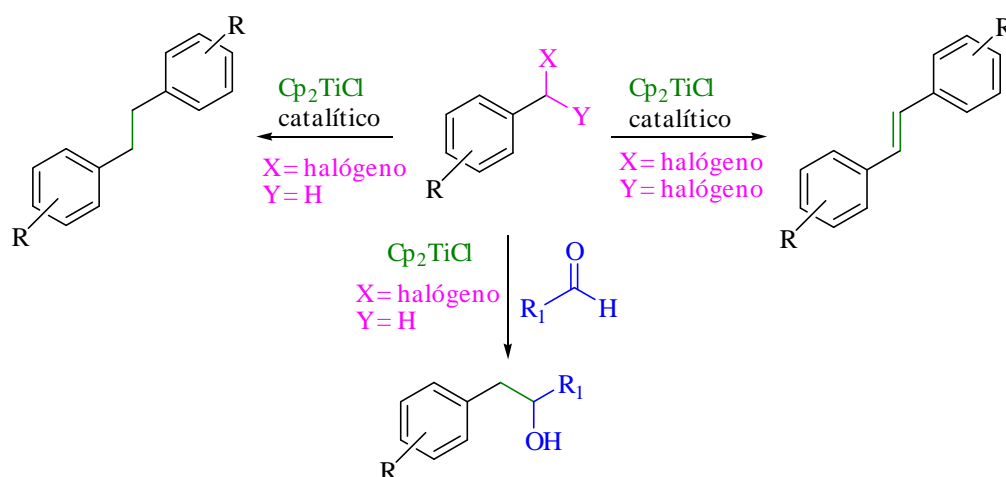


Esquema 27. Posible mecanismo de homo-acoplamiento de derivados halogenados bencílicos mediado por Cp_2TiCl .

Siguiendo el mecanismo propuesto, el exceso de Mn presente en el medio permitiría la regeneración del reactivo de Ti^{III} consiguiendo así que el proceso pueda ser también susceptible de ser catalizado con titanio. En este sentido, análisis voltamperométricos y cinéticos de la naturaleza de las especies reductoras de haluros de titanio, recientemente realizados por Skrydstrup y Daasbjerg, sugieren la ruta b) como el proceso más viable que tiene lugar en estas reacciones de acoplamiento.⁵⁹

Por lo tanto, el monocloruro de titanoceno podría catalizar el homo-acoplamiento de haluros bencílicos y asimismo de *gem*-dibromuros bencílicos para dar los correspondientes esqueletos de tipo dibencílico y estilbenílico. Por otra parte se propone que los bromuros bencílicos tratados con Ti^{III} y en presencia de aldehídos podrían conducir a productos de acoplamiento mixto tipo Barbier (Esquema 28).

⁵⁹ a) Enemærke, R. J.; *J. Am. Chem. Soc.* **2004**, *126*, 7853-7864; b) Enemærke, R. J.; *Organometallics* **2005**, *24*, 1252-1262.



Esquema 28

La principal aplicación de estos acoplamientos estriba en facilitar la síntesis de moléculas con esqueleto di-bencílico. Los compuestos que contienen este tipo de esqueleto como parte fundamental de su estructura constituyen un interesante conjunto de moléculas que han sido fundamentalmente usadas como intermedios para la síntesis de tintes, pinturas, resinas y en la formación de productos naturales tales como estilbenil o di-bencil derivados. Un número de compuestos biológicamente importantes como resveratrol y derivados,⁶⁰ combretastatinas⁶¹ y isocombretastatinas,⁶² o ácido lunulárico⁶³ también están incluidos en este grupo de moléculas.

⁶⁰ Baur, J. A.; Sinclair, D. A. *Nat. Rev. Drug Discovery* **2006**, *5*, 493-506.

⁶¹ Cirila, A.; Mann, J. *Nat. Prod. Rep.* **2003**, *20*, 558-564.

⁶² Singh, S. B.; Pettit, G. R. *Synthetic Commun.* **1987**, *17*, 877-892.

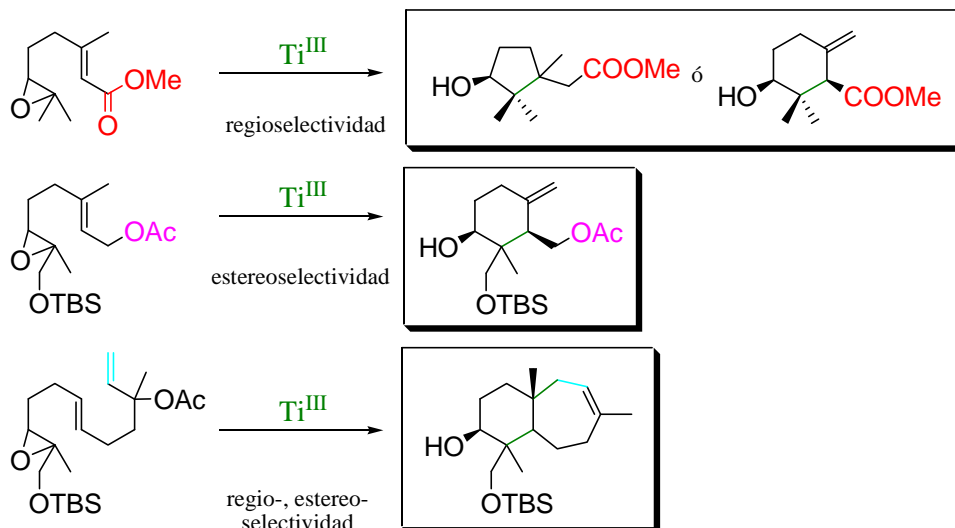
⁶³ Bracher, F.; Kreauss, J.; Bornatsch, A. *Nat. Prod. Lett.* **2000**, *14*, 305-310.

3. Diastereoselectividad en carbociclaciones radicalarias hacia ciclopentanos catalizadas por Ti^{III} . Hacia la síntesis de Toxicol A.

El tercer objetivo fundamental de esta Memoria se centra en un estudio encaminado a mejorar las aplicaciones sintéticas de $Cp_2Ti^{III}Cl$. Así, se pretende optimizar algunos aspectos de las reacciones de ciclación de epoxi-poliprenos, como son el control de la regio- y la diastereoselectividad en el cierre hacia ciclopentano-derivados. Estas ciclaciones hacia la formación de esqueletos de cinco miembros, hasta ahora habían dado mezclas de diastereoisómeros en proporción relativa 1:1, en el centro estereogénico donde se produce el cierre del anillo.

Como ya hemos comentado anteriormente, nuestro grupo de investigación viene desarrollando desde comienzos del siglo XXI una estrategia general de síntesis de terpenoides cíclicos mediante la apertura homolítica de epoxi-poliprenos promovida por el reactivo cloruro de titanoceno ($Cp_2Ti^{III}Cl$). Esta estrategia utiliza sustratos acíclicos naturales con pequeñas modificaciones y permite el cierre de ciclos de 5 a 7 eslabones en procesos catalíticos y reacciones en cascada que llevan a la construcción con un control sobre las cuestiones estereoquímicas de moléculas poli-cíclicas en una sola etapa de reacción (Esquema 29).^{26a, 27f, 64}

⁶⁴ a) Justicia, J.; Oller-Lopez, J. L.; Campaña, A. G.; Oltra, J. E.; Cuerva, J. M.; Bunuel, E.; Cardenas, D. J. *J. Am. Chem. Soc.* **2005**, *42*, 14911-14921.



Esquema 29

Por otra parte, el compuesto denominado como toxicol-A (Figura 2) es un *bis*-sulfato de hidroquinona hexaprenoide consistente en dos partes policíclicas, aislado en el Mar Rojo, de la esponja *Toxiclona toxius* (Figura 2).⁶⁵ Ha sido descrito que inhibe la *transcriptasa inversa* del virus de inmunodeficiencia humano (VIH) y que posee actividad contra *Candida albicans*. La biogénesis de este compuesto se considera mixta, con una parte procedente de la ruta mevalónica, que origina los ciclos **A-F** mediante ciclaciones irregulares, y otra procedente de la ruta del shikimato, que da lugar al ciclo **G**. Ha sido recientemente descrita la síntesis del sistema cíclico **AB** de su estructura.⁶⁶

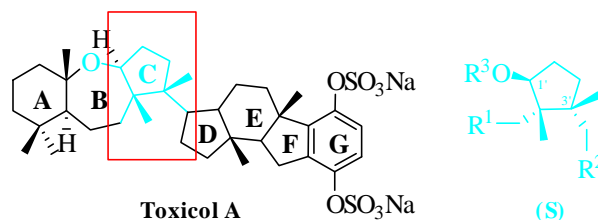
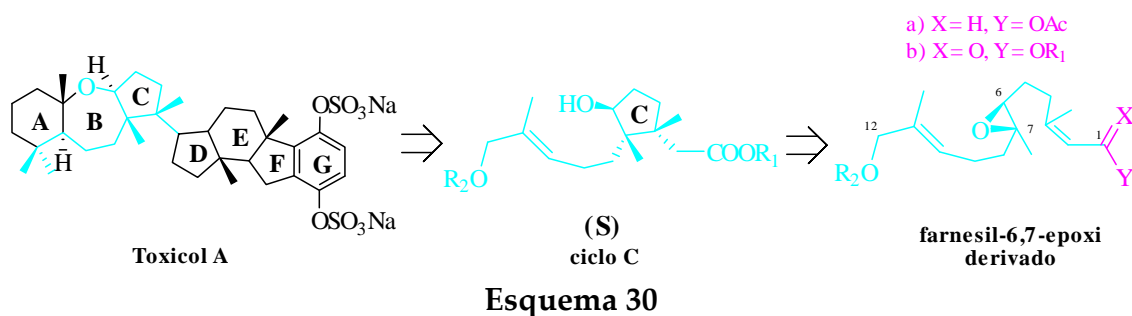


Figura 2

⁶⁵ Isaacs, S.; Hizi, A.; Kashman, Y. *Tetrahedron* **1993**, *49*, 4275-4282.

⁶⁶ Couladouris, E. A.; Vidali, V. P. *Chem. Eur. J.* **2004**, *10*, 3822-3835.

Es destacable que uno de los ciclos ubicados en el centro de la molécula, el C es un ciclopentano que posee tres centros estereogénicos de configuración relativa bien definida. Su síntesis puede ser afrontada mediante un proceso de ciclación radicalaria catalizada por Ti^{III} de un epoxi-polipreno convenientemente funcionalizado. Así, ha sido propuesto un planteamiento retrosintético dibujado en el Esquema 30. La síntesis de un sintón como S (Esquema 30) que contenga el ciclo C y que esté debidamente funcionalizado, debe permitir conectar con otros fragmentos convenientemente funcionalizados que aporten la estructura cíclica A, y con otros que aporten los ciclos E y F, facilitando de esta manera la síntesis total de Toxicol A y siendo capaces de transferir en el proceso de acoplamiento la estereoquímica absoluta adecuada para la construcción de buena parte de sus centros estereogénicos.



Los pasos iniciales de esta propuesta sintética pasan por el estudio del comportamiento de epóxidos ubicados en el doble enlace interior de la cadena de un derivado de farnesilo (6,7-epoxi-farnesil derivados) frente a la apertura homolítica con $Cp_2Ti^{III}Cl$ que generará un radical en C7. No existen antecedentes en bibliografía de química radicalaria sobre este tipo de ciclaciones y debido a ello, es conveniente comprobar cómo se comportan derivados con un grupo acetilo en C1, que se presupone deben conducir a procesos 6-endo-*trig* y formación de los correspondientes ciclohexano-derivados. Posteriormente se estudiará el comportamiento en procesos 5-exo-*trig*, favorecidos si se ubica un grupo éster sobre C1. Este estudio requiere

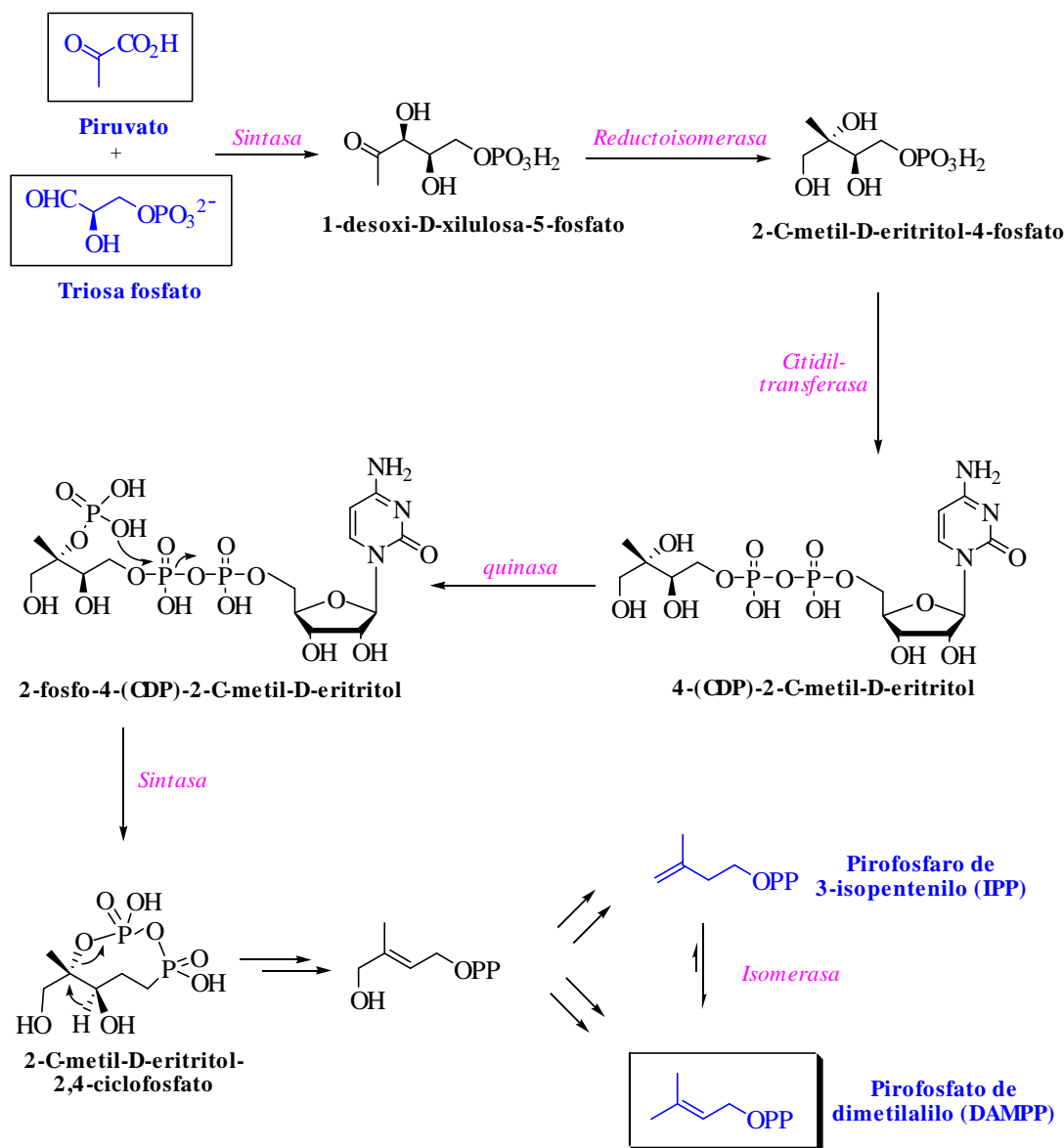
además el control de la estereoselectividad en la construcción de los diferentes estereocentros del ciclopentano.

4. Biomimetización de las desoxigenaciones en la ruta no-mevalónica hacia terpenos: Nuevo proceso en una sola etapa para la desoxigenación-reducción de alcoholes mediada/catalizada por Cp_2TiCl .

En esta parcela del trabajo de Tesis Doctoral se tratará de explorar la posibilidad de mimetizar la desoxigenación catalizada por la enzima *IspH* en la ruta no-mevalónica de terpenos para el proceso de desoxigenación-reducción de alcoholes, mediante el empleo de Cp_2TiCl .

Recientemente se ha puesto de manifiesto que las últimas etapas hacia la biosíntesis de los precursores C_5 , IPP y DMAPP, en la ruta no-mevalónica hacia terpenoides, conocida como la ruta de la 1-desoxi-D-xilulosa-5-fosfato o del metil-eritritol, están catalizadas por las enzimas *IspG* y *IspH* (Esquema 31).⁶⁷

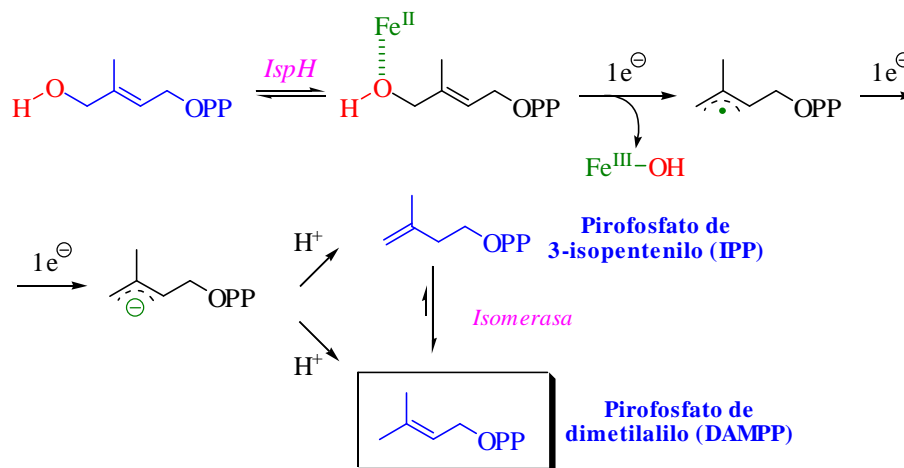
⁶⁷ a) M. Seemann, B. T. S. Bui, M. Wolff, D. Tritsch, N. Campos, A. Boronat, A. Marquet, M. Rohmer, *Angew. Chem. Int. Ed.* **2002**, *41*, 4337-4339; b) M. Rohmer, *Nat. Prod. Rep.* **1999**, *16*, 565-574.



Esquema 31. Ruta no-mevalónica hacia IPP y DAMPP

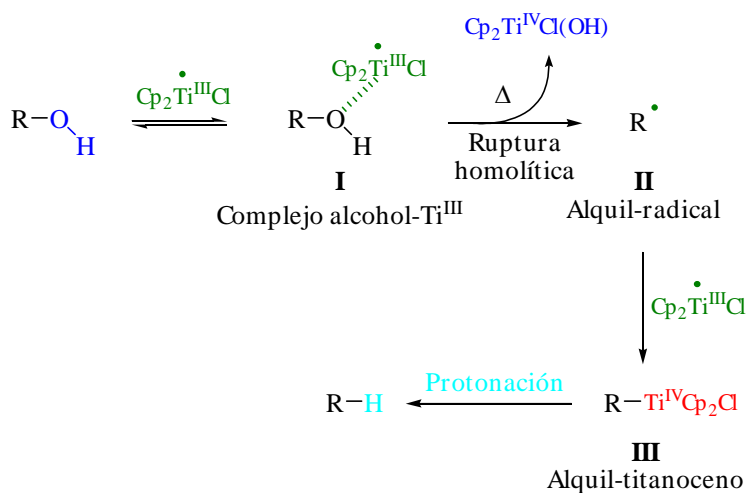
Los detalles mecanísticos no se conocen completamente, pero se ha sugerido que la actividad de las enzimas radica en sendos cluster $\text{Fe}^{\text{II}}\text{-S}$. La enzima *IspH* actúa gracias a la formación de un complejo hidroxilo- Fe^{II} con el 4-hidroxi-3-metil-buten-1-il pirofosfato provocando la ruptura homolítica del enlace C-O por transferencia mono-electrónica y generando un radical alílico. Este radical se reduce mediante una segunda transferencia mono-electrónica

desde otro Fe^{II} al carbanión alílico, que es protonado produciendo una mezcla de IPP y DMAPP (Esquema 32).⁶⁸



Esquema 32. Mecanismo propuesto para la reacción de desoxigenación catalizada por la enzima *IspH*

Tratando de mimetizar a *IspH* pensamos que la interacción entre un alcohol y el Cp_2TiCl podría generar un complejo alcohol- Ti^{III} (I) que activaría el enlace C-O y bajo unas adecuadas condiciones podría inducirse la ruptura homolítica que generaría un alquil-radical centrado en el carbono (II) (Esquema 33).



⁶⁸ W. Eisenreich, A. Bacher, D. Arigoni, F. Rohdich, *Cell. Mol. Life Sci.* **2004**, *61*, 1401-1426.

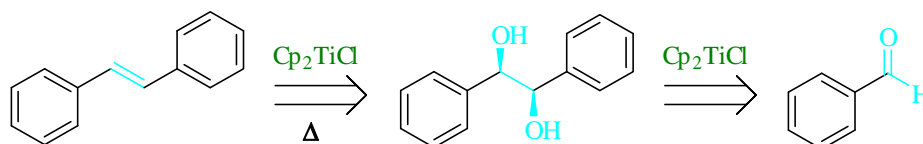
Esquema 33. Mecanismo propuesto para la desoxigenación-reducción de alcoholes con Ti^{III} .

La formación de **II** (Esquema 33) supondría un paso clave para la desoxigenación de alcoholes, y permitiría el desarrollo de nuevas aplicaciones sintéticas. Por ejemplo, el radical **II** evolucionaría hacia el hidrocarburo correspondiente, si es atrapado por una segunda molécula del reactivo generando un alquil-titanoceno (**III**, Esquema 33) que podría ser protonado en el medio de reacción hasta el hidrocarburo correspondiente.

5. Nuevos procesos sintéticos para la reducción-olefinación de carbonilos mediados/catalizados por Ti^{III} .

Hasta la fecha, los tres tipos principales de aplicaciones sintéticas que emplean el cloruro de titanoceno ($Cp_2Ti^{III}Cl$), las reacciones con oxiranos, carbonilos o derivados halogenados, se llevan a cabo de manera general a temperatura ambiente, y utilizando como disolvente THF en la mayoría de los casos.²⁷ Únicamente en algunas ciclaciones por apertura de oxiranos se ha llegado a calentar la disolución bien en THF o en mezclas de THF-benceno o THF-tolueno para acelerar los procesos de reacción.

Teniendo todo esto presente, en el objetivo anterior se plantea la posibilidad de que calentando la disolución de un alcohol en presencia de Ti^{III} se pueda forzar la ruptura homolítica del enlace C-OH. En el caso de dioles vecinos, la evolución de la etapa de desoxigenación puede conducir hacia la formación de compuestos con una nueva insaturación (Esquema 34).



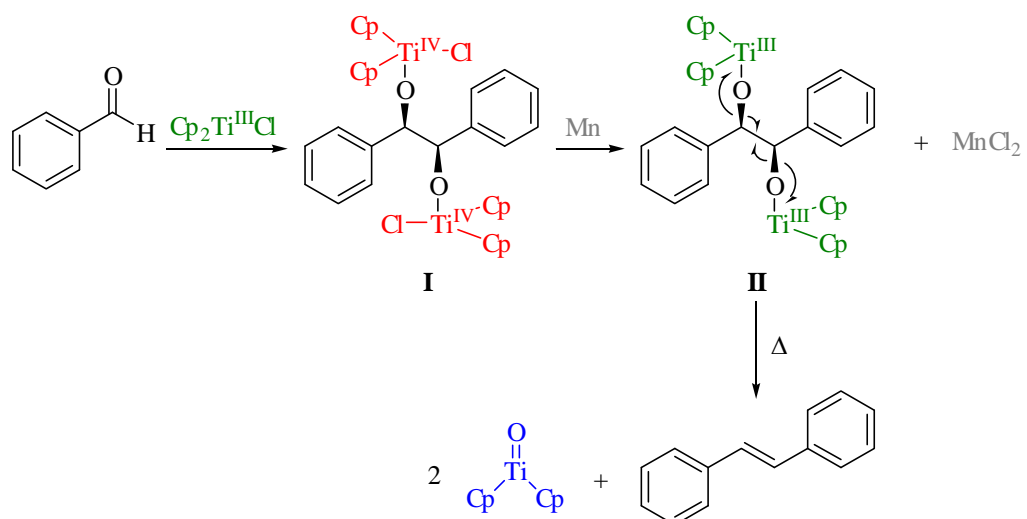
Esquema 34

Dado que es bien conocido el empleo del cloruro de titanoceno ($Cp_2Ti^{III}Cl$), para dar acoplamientos pinacolónicos mediante la generación en el medio de reacción un radical carbonado (a partir del correspondiente carbonilo

que en las condiciones adecuadas puede producir homo-acoplamiento generando un nuevo enlace C-C). Se estudiará el empleo del mismo reactivo de Nugent para generar en un único proceso en cascada, una etapa inicial de homo-acoplamiento seguido de una segunda etapa de desoxigenación (Esquema 35). Este proceso permite abrir la posibilidad de estudiar el empleo del $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ como precursor de otra reacción de gran importancia en Síntesis Orgánica como es la Olefinación de Carbonilos, conocida generalmente como “acoplamiento de McMurry”.⁶⁹

Así, se propone que el reactivo de Nugent podría ser capaz de promover procesos generales de olefinación de carbonilos, como resultado de la ruptura homolítica de los enlaces C-O pertenecientes a las especie pinacolato de Ti^{III} , (Esquema 35, II) originadas por reducción de los pinacولات de Ti^{IV} (Esquema 35, I) con exceso de metal reductor. Dichos pinacولات de Ti^{IV} son justamente el resultado del acoplamiento pinacolínico de los correspondientes carbonilos precursores. Esta metodología presentaría fundamentalmente la gran ventaja de poder llevarse a cabo en un proceso “one pot” y en condiciones más suaves que las empleadas actualmente.

⁶⁹ a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-24; b) Fürstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed.* **1996**, *35*, 2442-2449. c) Wirth, T. *Angew. Chem. Int. Ed.* **1996**, *35*, 61-63. d) Ephritikhine, M. *Chem. Commun.* **1998**, 2549-54.



Esquema 35. Mecanismo propuesto para la olefinación de carbonilos mediada por $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$.

II. ANTECEDENTES

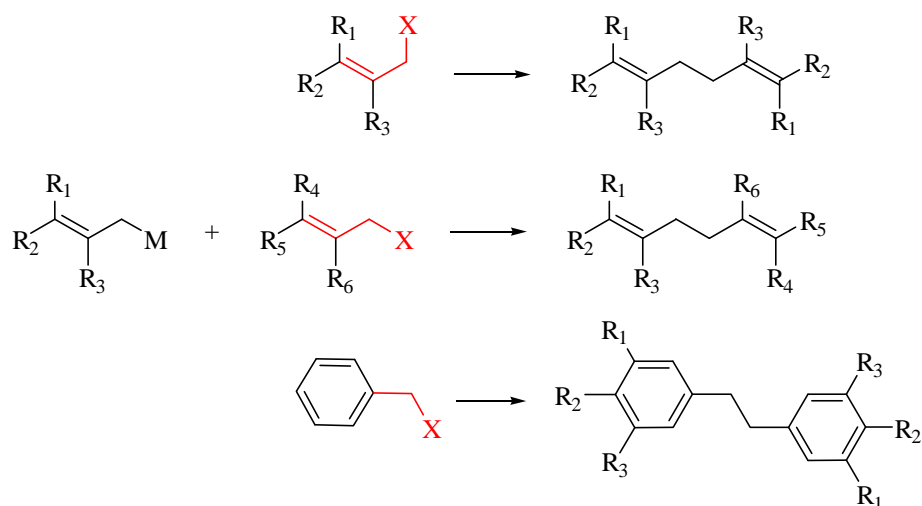
BIBLIOGRÁFICOS

**II.1. ACOPLAMIENTOS C-C EN DERIVADOS
HALOGENADOS ALÍLICOS Y BENCÍLICOS
CATALIZADOS POR METALES DE TRANSICIÓN.**

Los procesos que conducen al acoplamiento de derivados halogenados, constituyen una buena metodología para la formación de enlaces carbono-carbono en síntesis orgánica.⁷⁰

Dentro de este conjunto de reacciones, los acoplamientos de derivados halogenados alílicos y bencílicos (Esquema 36) resultan de enorme interés, puesto que permiten el acceso sencillo a estructuras de 1,5-dienos y dibencilos. Estas unidades estructurales tienen gran importancia, pues están presentes en un gran número de terpenoides y otros productos naturales.

⁷⁰ Para una revisión, ver: Baker, R. *Chem. Rev.* **1973**, *73*, 487-530.



Esquema 36

Hasta la fecha, aparece descrito en bibliografía el empleo de diferentes métodos para el homo- y hetero-acoplamiento derivados halogenados alílicos y bencílicos. Desde que E. J. Corey en el año 1964 llevara a cabo reacciones de acoplamiento en presencia de Ni(CO)₄,⁷¹ han sido descritas importantes contribuciones para el desarrollo de esta metodología. Entre ellas aparecen por ejemplo, metodologías de homo-acoplamiento electroquímico,⁷² y métodos de homo-acoplamiento y acoplamiento mixto, mediante el empleo de distintos tipos de metales.⁷³

Es conocido que los haluros alílicos y bencílicos reaccionan rápidamente en presencia de SmI₂,⁷⁴ (agente reductor muy útil en síntesis orgánica, introducido en 1980 por Girard, Namy y Kagan)⁷⁵ originando exclusivamente los productos de homoacoplamiento con buenos rendimientos. De esta forma el cloruro de cinamilo (**1a**, Esquema 37) condujo en 30 minutos, a la mezcla de los

⁷¹Corey, E. J.; Hamanaka, E. J. *Am. Chem. Soc.* **1964**, *86*, 1641-1642.

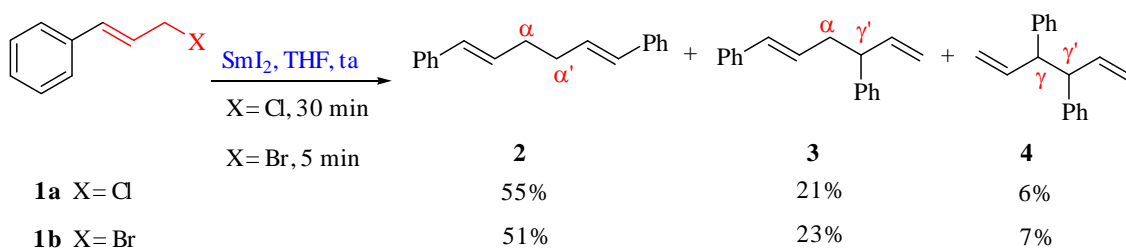
⁷²a) Yoshida, J.; Funahashi, H.; Iwasaki, H.; Kawabata, N. *Tetrahedron Lett.* **1986**, *27*, 4469-4472.
b) Tokuda, M.; Endate, K.; Sugimoto, H. *Chem. Lett.* **1988**, 945-948.

⁷³ Coupling Reactions Between sp³ Carbon Centers en *Comprehensive Organic Synthesis*; Trost, B. M.; Patenden, G., Eds.; Pergamon Press: Oxford, **1991**; Vol. 3, 413-434.

⁷⁴ Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307-338.

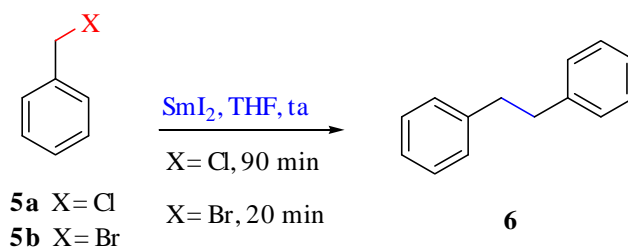
⁷⁵ Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693-2698

productos de acoplamiento $\alpha\alpha'$, $\alpha\gamma'$ y $\gamma\gamma'$ (**2**, **3**, **4**, Esquema 37) con un 51%, 23% y 7% de rendimiento respectivamente. Cuando se empleó bromuro de cinamilo (**1b**, Esquema 37), en tan sólo 5 minutos, se obtienen los mismos productos de acoplamiento: $\alpha\alpha'$, $\alpha\gamma'$ y $\gamma\gamma'$ (**2**, **3**, **4**) con rendimientos parecidos (55%, 21% y 6%) (Esquema 37).



Esquema 37

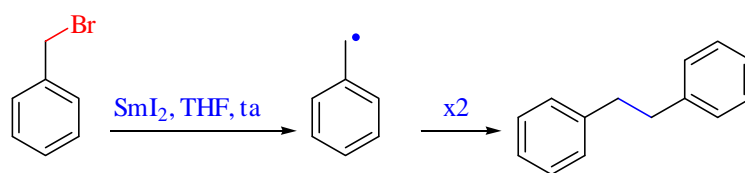
De la misma forma, la reacción de cloruro de bencilo (**5a**) con SmI_2 , condujo al di-bencilo (**6**) con un 67% de rendimiento en 90 minutos, mientras que el bromuro de bencilo (**5b**) en las mismas condiciones, originó (**6**) con un 82% de rendimiento en tan sólo 20 minutos (Esquema 38).



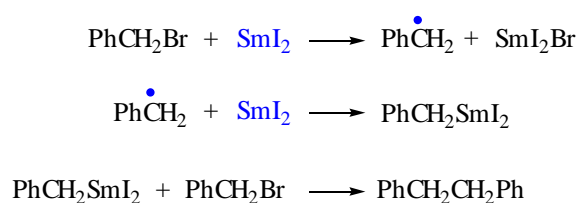
Esquema 38

El mecanismo por el cual se produce la formación de los correspondientes productos de homo-acoplamiento en presencia de este reactivo, no está hasta la fecha bien definido. H. B. Kagan propone la formación de los mismos a través de colisión de radicales (Esquema 39). Por otra parte

Denis P. Curran,⁷⁶ propone la existencia de evidencias que apoyan que los productos de acoplamiento, no se originan mediante combinación de radicales, sino que tiene lugar la formación de un alil-samarario (mediante un proceso de segunda transferencia electrónica) que reacciona posteriormente con otra molécula de derivado halogenado, dando lugar así a los correspondientes productos de homo-acoplamiento (Esquema 40).

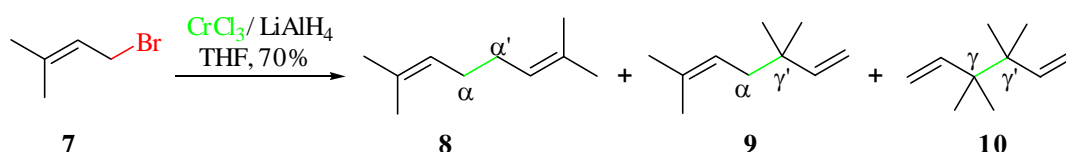


Esquema 39



Esquema 40

Los haluros alílicos también sufren procesos de homo-acoplamiento en presencia del reactivo de transferencia electrónica Cr^{II} .⁷⁷ Así cuando el bromuro alílico (**7**, Esquema 41) se trata con $\text{CrCl}_3/\text{LiAlH}_4$, se obtienen tanto los productos de acoplamiento $\alpha\alpha'$, como $\alpha\gamma'$ y $\gamma\gamma'$ (**8**, **9**, **10**) con un 70% de rendimiento y en proporción 72:22:6 (Esquema 41).

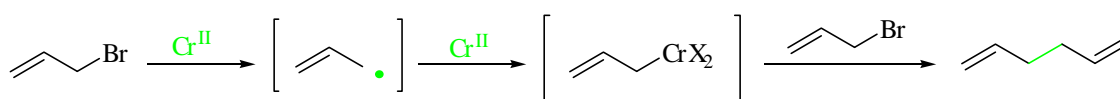


⁷⁶ Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 12, 943-961.

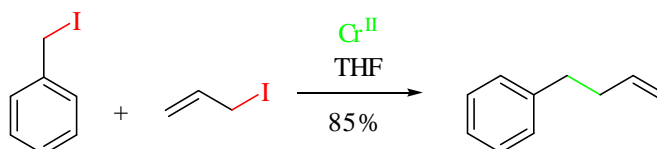
⁷⁷ Para una revisión de este reactivo, ver: Fürstner, A. *Chem. Rev.* **1999**, 99, 991-1045.

Esquema 41

Desde un punto de vista mecanístico, esta reacción se puede explicar a través de la formación en primer lugar de un radical de tipo alílico, el cual se reduciría rápidamente en presencia de un exceso de Cr^{II} para dar el correspondiente intermedio alil-cromo, que reaccionaría con los derivados halogenados alílicos de partida originando los productos de homoacoplamiento (Esquema 42).

**Esquema 42**

Este reactivo de Cr^{II} también ha sido empleado por Sustmann *et al.*⁷⁸ en reacciones de acoplamiento mixto, por ejemplo mediante la adición de un derivado halogenado alílico sobre un bencil-cromo formado previamente (Esquema 43).

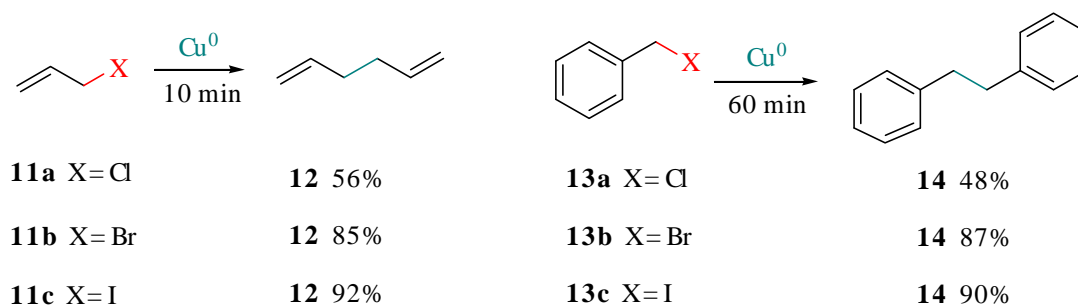
**Esquema 43**

El cobre metálico ha sido empleado también en reacciones de homoacoplamiento. Así, Ebert *et al.*,⁷⁹ observaron que cloruros, bromuros y yoduros de alilo (**11**) y bencilo (**13**) reaccionaban en presencia de Cu^0 , generado *in situ* mediante la reducción con naftalenuro de litio de complejos de Cu^{I} con

⁷⁸ Sustmann, R.; Altevogt, R. *Tetrahedron Lett.* **1981**, 22, 5167-5170.

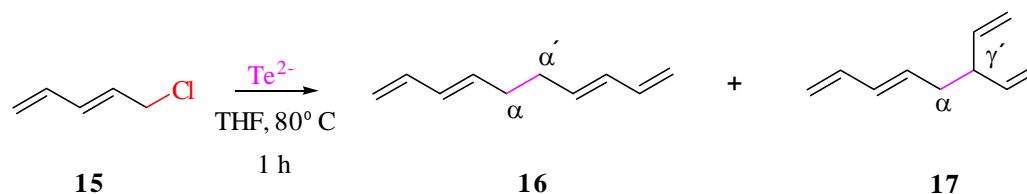
⁷⁹ Ginah, F. O.; Donovan, T. A.; Suchan, S. D.; Pfenning, D. R.; Ebert, G. W. *J. Org. Chem.* **1990**, 55, 584-589.

trialquil-fosfinas ($\text{CuI}\cdot\text{PR}_3$), para dar lugar a los respectivos productos de homocoplamiento con buenos rendimientos: 1,5-hexadieno (**12**) y di-bencilo (**14**) (Esquema 44).



Esquema 44

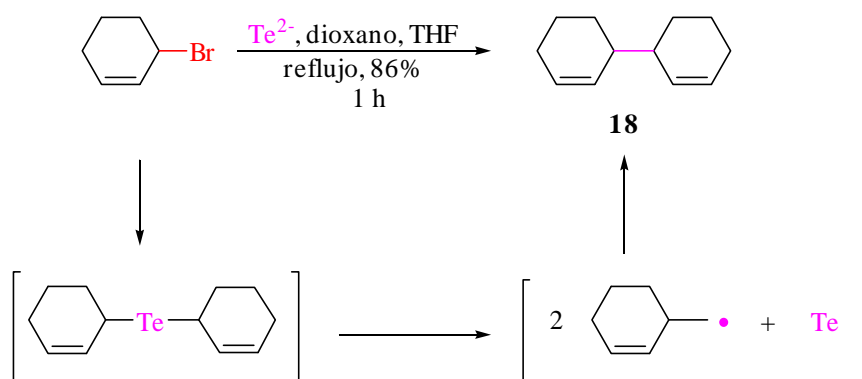
Clive *et al.*⁸⁰ llevaron a cabo en 1982 el acoplamiento de una gran variedad de haluros alílicos (bromo y cloro-derivados) en presencia de Te^{2-} [generado *in situ* a partir de la reducción de telurio metálico en polvo con $\text{LiB}(\text{C}_2\text{H}_5)_3\text{H}$] bajo condiciones de reacción suaves, conduciendo con buenos rendimientos a los correspondientes productos de acoplamiento: 1,5-dienos. Por ejemplo, el derivado clorado alílico (**15**) en presencia de Te^{2-} , condujo con un 82% de rendimiento a la mezcla de los productos de acoplamiento $\alpha\alpha'$ y $\alpha\gamma'$ (**16**, **17**) en proporción 1.3:1 (Esquema 45).



Esquema 45

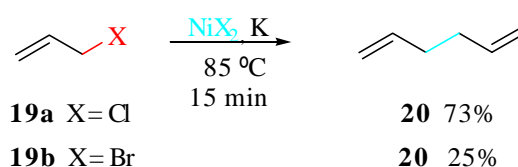
⁸⁰ Clive, D. L. J.; Anderson, P. C.; Moss, N.; Singh, A. *J. Org. Chem.* **1982**, *47*, 1641-1647.

Estudios mecanísticos han establecido la existencia de un intermedio de telurio *bis*-alílico que origina los radicales alílicos, los cuales dimerizan formando así el producto de homo-acoplamiento (**18**) (Esquema 46).



Esquema 46

Rieke *et al.*,⁸¹ llevaron a cabo el homo-acoplamiento de cloruro y bromuro de alilo (**19a** y **19b**) por formación del compuesto $(\pi\text{-alil-NiX})_2$, obteniendo 1,5-hexadieno (**20**) con un 73% y un 25% de rendimiento respectivamente (Esquema 47).



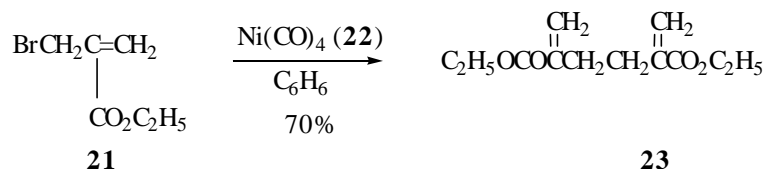
Esquema 47

Los complejos $(\pi\text{-alil-NiX})_2$ ⁸² se preparan normalmente a partir de un derivado halogenado alílico y de especies de Ni⁰, tales como Ni(CO)₄ (**22**). El procedimiento más común implica el tratamiento de un bromuro alílico con

⁸¹ a) Rieke, R. D.; Kavaliunas, A. V.; Rhyne, L. D.; Fraser, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 246-248. b) INab, S.; Matsumoto, H.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 2093-2098.

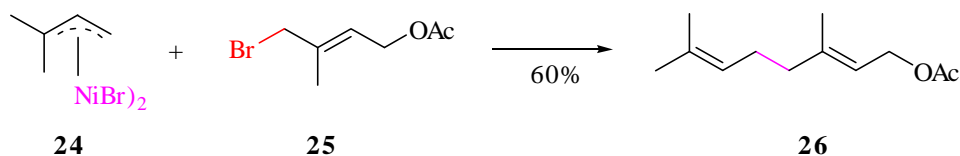
⁸² Para una revisión sobre el uso sintético de este reactivo, ver: Billington, D. C. *Chem. Soc. Rev.* **1985**, *14*, 93-120.

$\text{Ni}(\text{CO})_4$ a 50-70 °C.⁸³ Cuando el bromuro alílico **21** se puso en presencia de $\text{Ni}(\text{CO})_4$ (**22**) en benceno a 50 °C, se formó el producto de acoplamiento **23** con un 70% de rendimiento (Esquema 48).



Esquema 48

Se han llevado a cabo reacciones de acoplamiento mixto con rendimientos razonables, en presencia de este reactivo. En ellas el complejo de níquel (**24**) reacciona con el derivado bromado alílico (**25**), originando un 60% del producto de acoplamiento mixto, el monoterpeno acetato de geranilo (**26**), formándose solamente pequeñas cantidades de los correspondientes productos de homo-acoplamiento (Esquema 49).

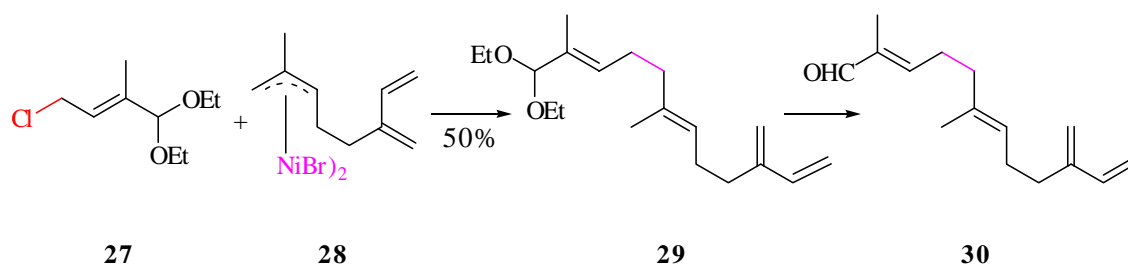


Esquema 49

Siguiendo este método, el aldehído sesquiterpénico β -sinensal (**30**), ha sido preparado a partir del cloruro alílico (**27**) y el complejo $(\pi\text{-alil-NiX})_2$ (**28**).⁸⁴ Además de la formación de un 50% del producto de acoplamiento mixto deseado (**29**), se formaron como productos minoritarios los correspondientes productos de homo-acoplamiento (20% y 26%) (Esquema 50).

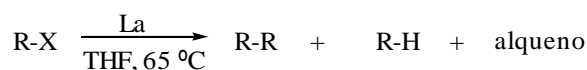
⁸³ Semmelhack, M. F.; Helquist, P. M. *Org. Synth.* **1972**, *52*, 115-121.

⁸⁴ Sato, K.; Inoue, S.; Watanabe, K. *J. Chem. Soc., Perkin Trans 1* **1981**, *9*, 2411-2414.



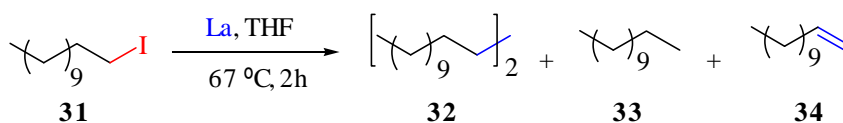
Esquema 50

Más recientemente, Sonoda *et al.*⁸⁵ han investigado el empleo de lantano metálico en síntesis orgánica. La reacción de derivados halogenados alquílicos no activados R-X en presencia de lantano, conduce mayoritariamente al producto de homo-acoplamiento R-R, junto con producto de reducción R-H y la correspondiente olefina sobre todo cuando se utilizan derivados halogenados secundarios y terciarios (Esquema 51).



Esquema 51

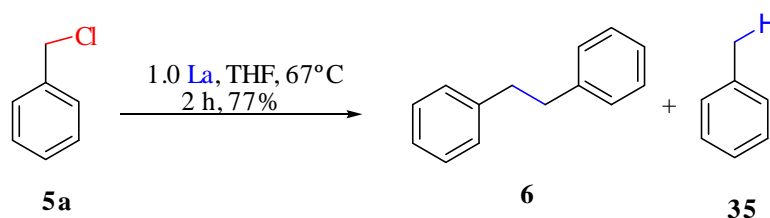
Cuando la reacción se llevó a cabo con 1-iodododecano (**31**) en presencia de cantidades estequiométricas de lantano, se obtuvo un 70% de (**32**), producto correspondiente a la reacción de dimerización, además de un 18% del producto de reducción (**33**) y un 6% de la olefina (**34**) (Esquema 52).



⁸⁵ Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 966-969.

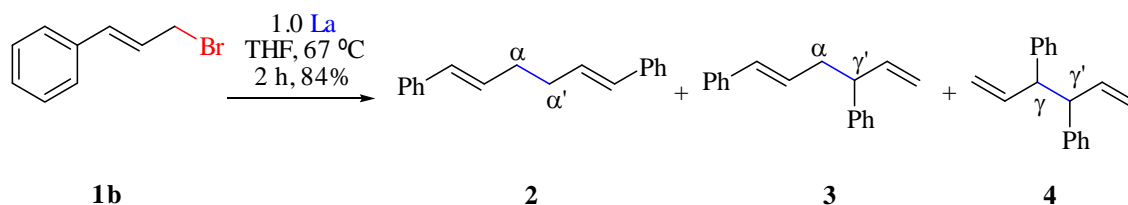
Esquema 52

Esta reacción en presencia de lantano metálico también ha sido aplicada a derivados halogenados alílicos y bencílicos, de forma que se ha llevado a cabo la dimerización reductiva de cloruro de bencilo (**5a**) y bromuro de cinamilo (**1b**) para obtener eficientemente los correspondientes productos de homocoplamiento. En el caso del cloruro de bencilo, se obtiene un 77% de di-bencilo (**6**) junto con un 6% del correspondiente producto de reducción (**35**) (Esquema 53).



Esquema 53

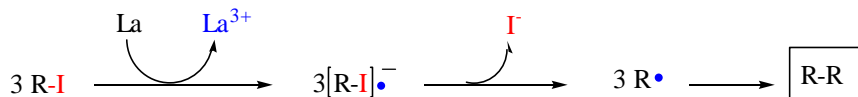
En el caso de bromuro de cinamilo, se obtienen los productos de acoplamiento $\alpha\alpha'$, $\alpha\gamma'$ y $\gamma\gamma'$ (**2**, **3**, **4**) en una proporción relativa 33:48:19 con un 84% de rendimiento, junto con un 4% del producto de reducción (Esquema 54).



Esquema 54

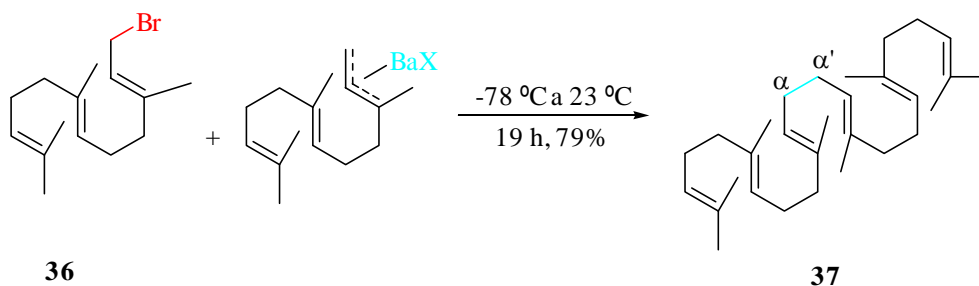
Desde un punto de vista mecanístico, los autores proponen que los radicales formados a través de la transferencia electrónica del lantano al

derivado halogenado, son las especies implicadas en el proceso de homo-acoplamiento (Esquema 55).



Esquema 55

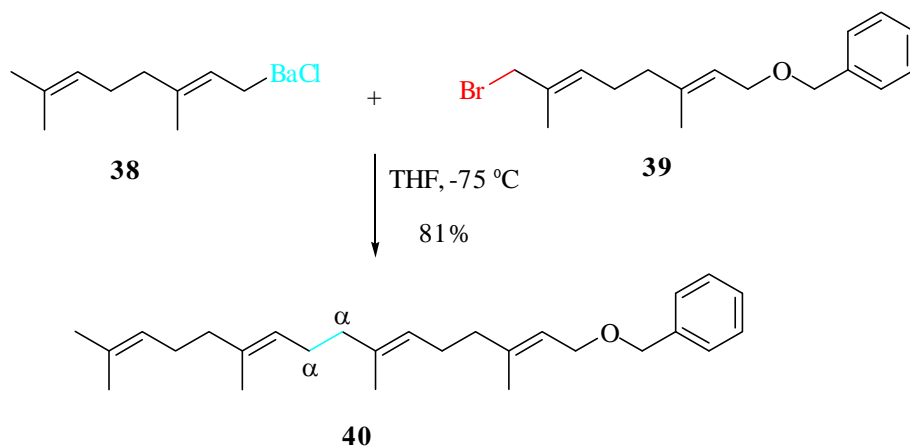
Otro metal utilizado en procesos de homo-acoplamiento ha sido Ba. En el campo de los terpenoides, la reacción de homo-acoplamiento de haluros alílicos usando Ba, origina exclusivamente los productos de acoplamiento $\alpha\alpha'$. Este proceso llevado a cabo por Corey *et al.*,⁸⁶ representó la primera síntesis directa del triterpeno escualeno (**36**) con un 79% de rendimiento mediante el acoplamiento de dos unidades de *E,E*-farnesilo (**37**) (Esquema 56).



Esquema 56

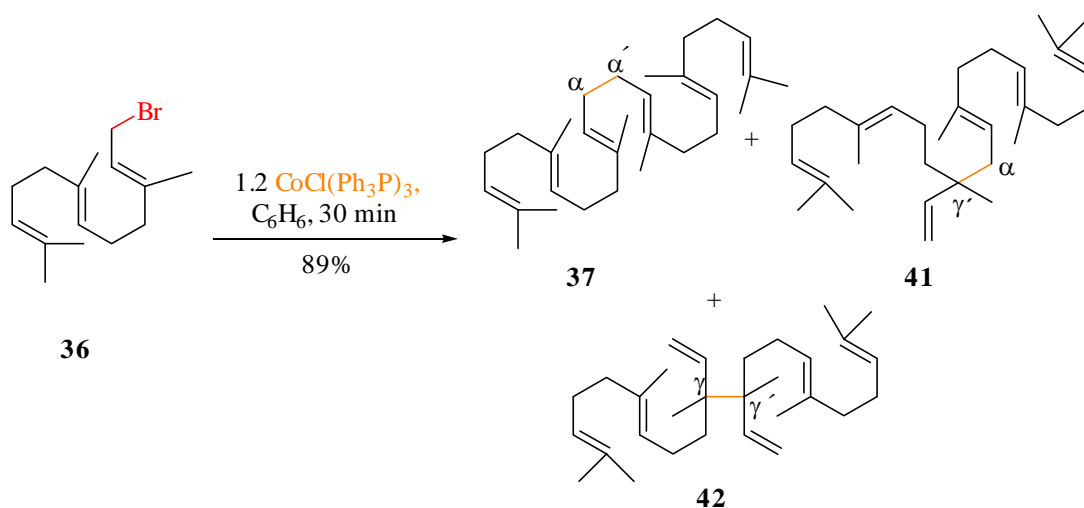
La síntesis de dienos asimétricos a través del acoplamiento mixto regioselectivo $\alpha\alpha'$ de derivados halogenados alílicos, también se ha abordado mediante el empleo de este reactivo. Así el bencil éter de geranilgeraniol (**40**), se obtuvo con un 81% de rendimiento mediante el tratamiento del bromuro alílico (**39**) con el geranil-bario (**38**) a $-75\text{ }^{\circ}\text{C}$ en THF (Esquema 57).

⁸⁶ Corey, E. J.; Shieh, W.-C. *Tetrahedron Lett.* **1992**, 33, 6435-6438.



Esquema 57

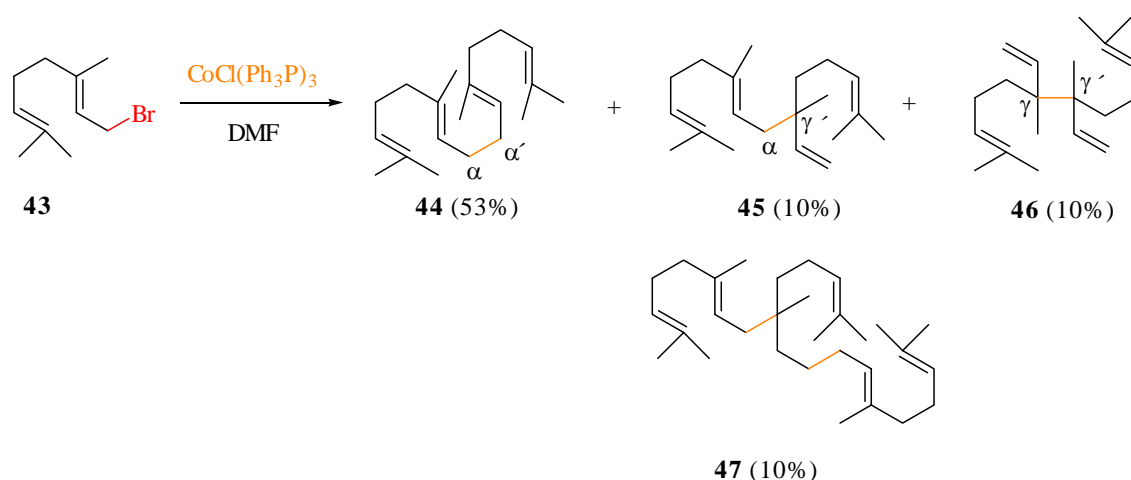
A partir de bromuro de farnesilo se puede sintetizar escualeno, el proceso fue llevado a cabo por Yamada *et al.*,⁸⁷ empleando el reactivo cloro-tris(trifenilfosfina)cobalto(I) [CoCl(Ph₃P)₃]. Esta reacción se llevó a cabo bajo condiciones suaves de reacción, obteniéndose escualeno en un 55%, además de los productos de acoplamiento $\alpha\gamma'$ y $\gamma\gamma'$ (**41**, **42**) con un 22% y 12% de rendimiento respectivamente (Esquema 58).



Esquema 58

⁸⁷ Momose, D.; Iguchi, K.; Sugiyama, T.; Yamada, Y. *Tetrahedron Lett.* **1983**, 24, 921-924.

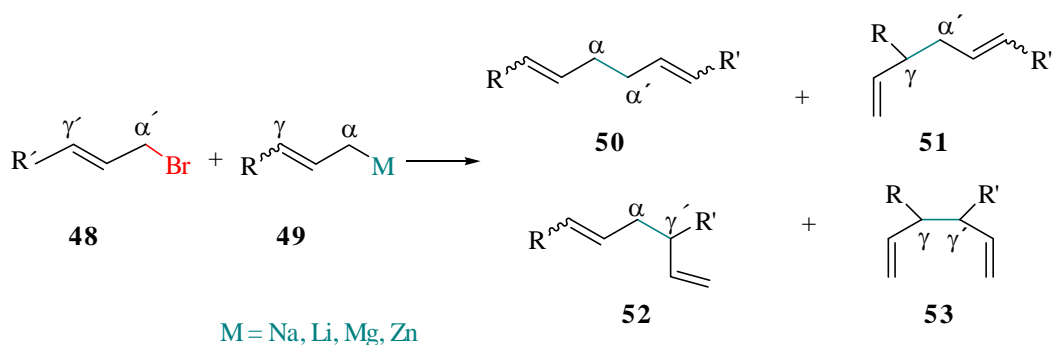
Cuando la reacción se llevó a cabo con bromuro de geranilo (**43**) en presencia de un disolvente polar aprótico tal como *N,N*-dimetilformamida (DMF) y hexametil-fosforamida, se formó una especie trimérica (**47**) además de los correspondientes productos de acoplamiento $\alpha\alpha'$ (**44**), $\alpha\gamma'$ (**45**) y $\gamma\gamma'$ (**46**) (Esquema 59). Los autores explican la formación del trímero (**47**) mediante la adición del radical geranilo a la posición menos impedida de la olefina presente en el producto de acoplamiento $\alpha\gamma'$ (**45**).



Esquema 59

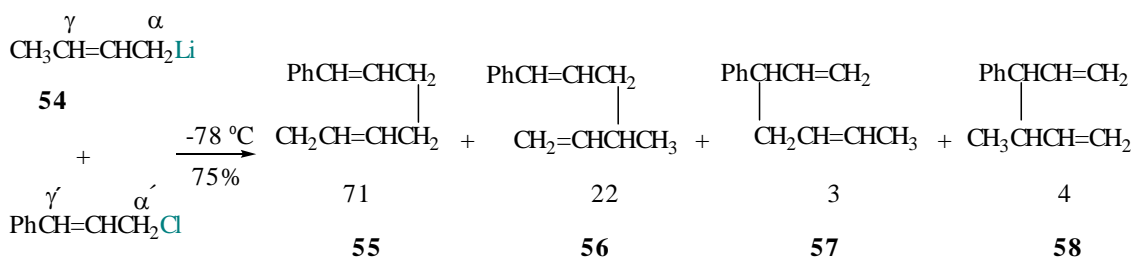
Yamamoto *et al.*,⁸⁸ demostraron que la reacción de haluros alílicos tales como (**48**) y de organometálicos alílicos del tipo (**49**), donde $\text{M} = \text{Na}, \text{Li}, \text{Mg}, \text{Zn}$, conduce generalmente a la mezcla de los cuatro productos de acoplamiento $\alpha\alpha'$, $\alpha\gamma'$, $\gamma\alpha'$ y $\gamma\gamma'$ (**50, 51, 52, 53**) (Esquema 60).

⁸⁸ Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 6282-6284.



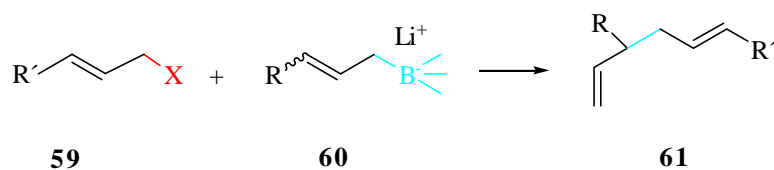
Esquema 60

Por ejemplo, el organometálico alílico (54), en presencia de cloruro de cinamilo a $-78\text{ }^{\circ}\text{C}$, originó un 75% de la mezcla de productos de acoplamiento, $\alpha\alpha'$, $\gamma\alpha'$, $\alpha\gamma'$ y $\gamma\gamma'$ (55, 56, 57, 58) en proporción 71:22:3:4 (Esquema 61).



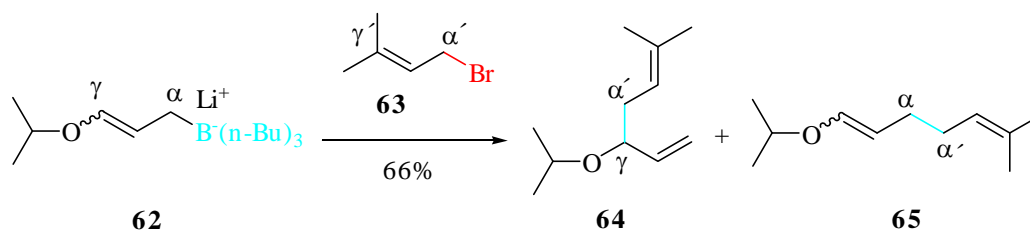
Esquema 61

Sin embargo, cuando se emplearon alilboratos de litio (preparados por la adición de alquil-boranos a una solución de un alil-litio), tales como (60), mostraron una alta regioselectividad hacia la formación de los productos de acoplamiento $\gamma\alpha'$ (61) (Esquema 62).



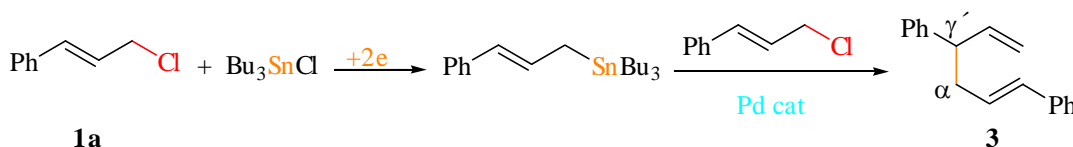
Esquema 62

Cuando se lleva a cabo la reacción del alil-borato de litio (**62**) en presencia del bromuro alílico (**63**), se obtiene mayoritariamente (**64**), resultante del acoplamiento $\gamma\alpha'$, frente a (**65**) resultante del acoplamiento $\alpha\alpha'$ en proporción 81:19 (Esquema 63).



Esquema 63

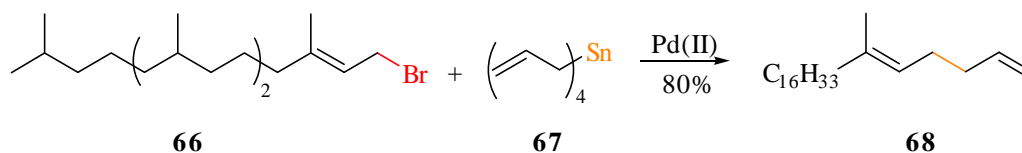
También se han llevado a cabo reacciones de homo-acoplamiento y de acoplamiento mixto, empleando complejos de Pd. El método consiste en la reacción entre un derivado halogenado alílico y un alil-estannano. Este alil-estannano se puede generar *in situ*⁸⁹, mediante la reducción electroquímica del haluro orgánico con cloruro de tributil-estaño, que en presencia de paladio catalítico conduce al producto $\alpha\gamma'$ como único regioisómero. Cuando cloruro de cinamilo (**1a**) se puso a reaccionar en estas condiciones, condujo con un 89% de rendimiento al producto de acoplamiento $\alpha\gamma'$ (**3**) como único producto de reacción (Esquema 64).



Esquema 64

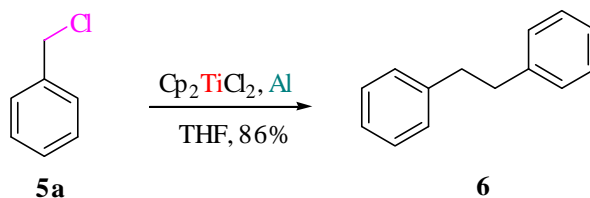
⁸⁹ Yoshida, J.; Funahashi, H.; Iwasaki, H.; Kawabata, N. *Tetrahedron Lett.* **1986**, 27, 4469-4472

Cuando el alil-estanano (67) se acopla con el bromuro alílico (66), se obtiene exclusivamente el producto de acoplamiento mixto (68) (Esquema 65).⁹⁰



Esquema 65

Respecto de acoplamientos de derivados halogenados arílicos, Yanlong y colaboradores⁹¹ reducen haluros alílicos y bencílicos con cantidades equimoleculares de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ a temperatura ambiente, obteniendo así los correspondientes productos de homo-acoplamiento. Di-bencilo (6) se obtiene con un 86% de rendimiento cuando el cloruro de bencilo (5a) se añade a una solución de Ti^{III} en THF (Esquema 66).

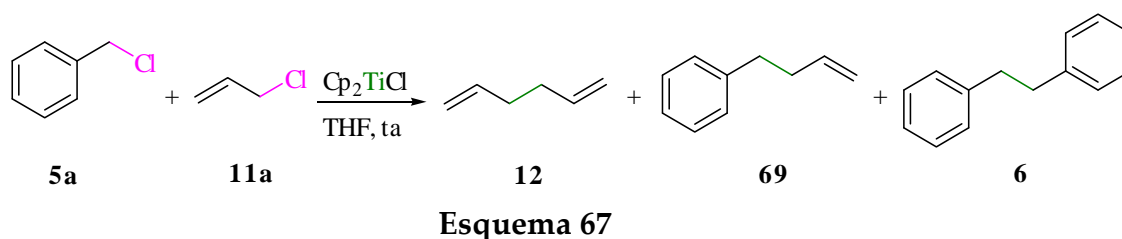


Esquema 66

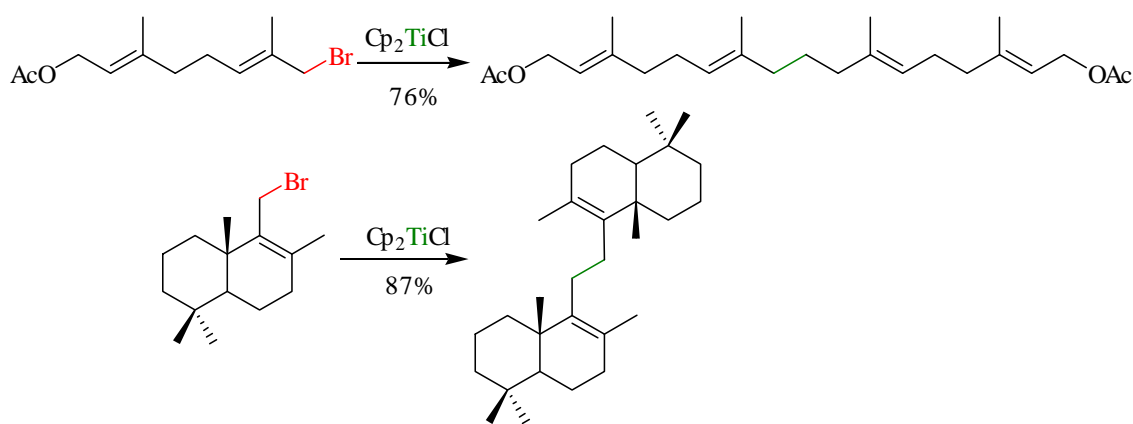
Por otro lado el producto de acoplamiento mixto (69) se obtiene con un 32%, cuando el cloruro de alilo (11a) se pone en presencia de cloruro de bencilo (5a) y dos equivalentes de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$. Además se forman productos de homo-acoplamiento: 1,5-hexadieno (12) 33% y dibencilo (6) 35% (Esquema 67).

⁹⁰ Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, 21, 2599-2602

⁹¹ Yanlong, Q.; Guisheng, L.; Huang, Y. J. *Organometallic Chem.* **1990**, 381, 29-34.



Finalmente, y tal y como indicamos en el apartado de Introducción y Objetivos (Esquema 24), nuestro Grupo de Investigación ha desarrollado una metodología para el homo-acoplamiento de haluros alílicos mediante el empleo catalítico de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ con excelentes resultados (Esquema 68).⁵⁷ Esta reacción se caracteriza fundamentalmente por tener lugar bajo condiciones suaves y destaca por ser quimioselectiva ante un amplio número de grupos funcionales tales como alcoholes, aminas, cetonas, ácidos y ésteres.⁹²



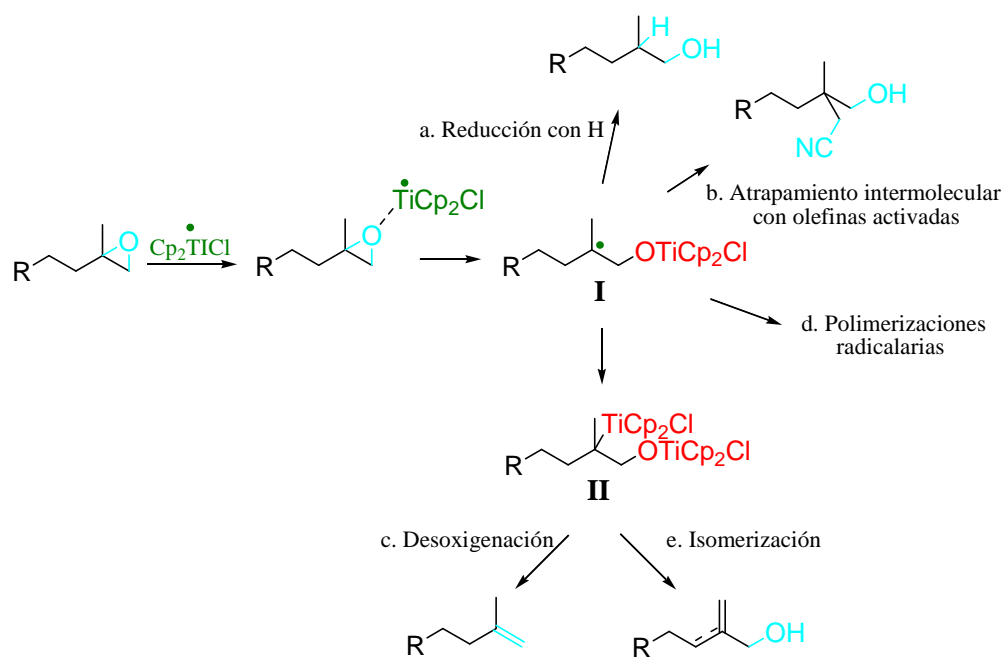
⁹² Spencer, R. P.; Cavallaro, C. L.; Schwartz, J. J. *Org. Chem.* **1999**, *64*, 3987-3995.

II.2. CICLACIONES DE EPOXI-POLIPRENOS
MEDIADAS POR Cp_2TiCl .

En el caso de epóxidos, entre 1988 y 1994 Rajanbabu y Nugent describieron la reacción de ruptura homolítica mediada/catalizada por $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ que origina la apertura hacia un β -titanoxi-radical y las primeras aplicaciones.⁹³ Desde entonces, muchas otras han sido descritas utilizando como herramienta principal el carbono radical que se genera, tales como la reducción a alcoholes, desoxigenación a olefinas y formación de enlaces C-C en adiciones radicalarias inter e intramoleculares sobre insaturaciones C-C, C-O y C-N (Esquema 69).⁹⁴

⁹³ a) Nugent, W. A.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561-8562. b) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525-4527. c) Rajanbabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408-6409. d) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986-997.

⁹⁴ a) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103-2112. b) Nugent, W. A.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561-8562. c) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525-4527. d) Rajanbabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408-6409. e) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986-997. f) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 101-103. g) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849-12859. h) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Synthesis* **2001**, 2500-2520. i) Fernández-Mateos, A.; Martín de la Nava, E.; Pascual



Esquema 69

La regioselectividad de la apertura del anillo oxirano vendrá definida por la estabilidad del radical formado⁹⁵ y por las interacciones estéricas entre los ligandos del catalizador y el sustrato,⁹⁶ lo que habitualmente genera el radical más sustituido (Figura 3).⁹⁷

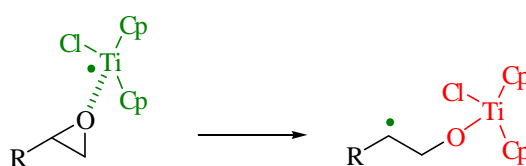


Figura 3

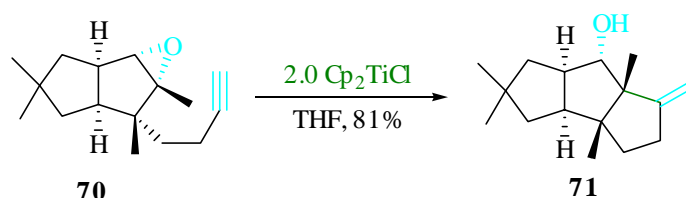
Coca, G.; Ramos Silvo, A.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607-609. j) Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silvo, A. I.; Rubio González, R. *Synlett* **2004**, 1011-1014. Review reference 27.

⁹⁵ Zipse, H.; *Top. Curr. Chem.* **2006**, *263*, 163-189.

⁹⁶ Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359-1371.

⁹⁷ Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771-2788.

El β -titanoxi-radical así generado puede dar lugar a reacciones de formación de enlaces C-C mediante la adición inter- o intramolecular a olefinas activadas o a grupos carbonilo.⁹⁸ Este tipo de adiciones pueden generar, con sustratos epoxi-olefínicos o epoxi-alquinos y condiciones de reacción adecuadas, las atractivas reacciones de ciclación radicalaria que cierran un solo ciclo u otras en cascada que permiten acceder fácilmente a innumerables esqueletos de Productos Naturales mono- y policíclicos.²⁷ Así entre otras ha dado lugar a ciclaciones 5-*exo* en numerosas aplicaciones llevadas a cabo por RajanBabu,⁹⁹ Clive¹⁰⁰ y Roy,¹⁰¹ permitiendo la síntesis directa de derivados ciclopentánicos funcionalizados tal como la de triquinanos (Esquema 70).



Esquema 70

Fernández-Mateos *et al.* estudiaron la influencia de la longitud de la cadena carbonada en la ciclación de epoxi-alquenos inducida por Ti^{III} , observando que sólo se producían procesos de ciclación 5-*exo* y 6-*exo*.¹⁰² Los productos obtenidos son consecuencia de la reducción final de las especies de alquil-titanio generadas. Es destacable que la presencia de un grupo carbonilo

⁹⁸ a) Fernández-Mateos, A.; Martín de la Nava, E.; Pascual, G.; Ramos, A.; Rubio, R. *Org. Lett.* **1999**, *1*, 607-609; b) Fernández-Mateos, A.; Herrero, P.; Mateos, L. Rabanedo, R.; Rubio, R. *J. Org. Chem.* **2007**, *72*, 9973-9982.

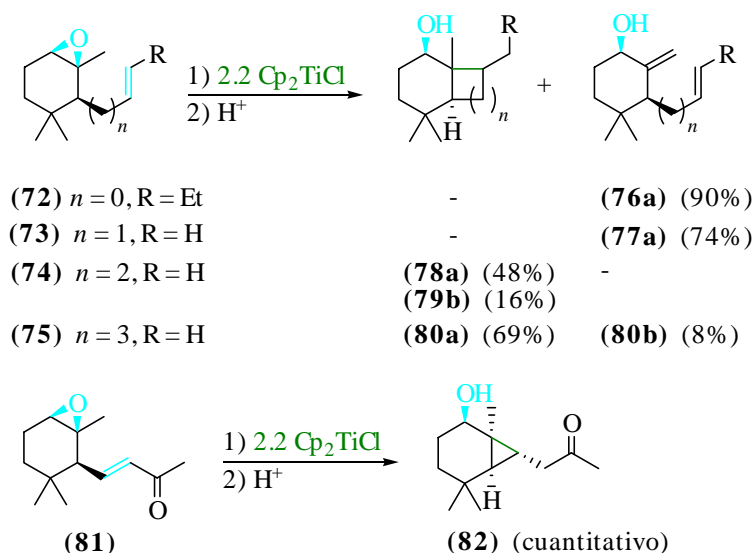
⁹⁹ RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986-997.

¹⁰⁰ a) Clive, D. L. J.; Magnusson, S. R. *Tetrahedron Lett.* **1995**, *36*, 15-18; b) Clive, D. L. J.; Magnusson, S. R.; Manning, H. W.; Mayhew, D. L. *J. Org. Chem.* **1996**, *61*, 2095-2108.

¹⁰¹ a) Maiti, G.; Chandra Roy, S. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 403-404; b) Mandal, P. K.; Maiti, G.; Chandra Roy, S. C. *J. Org. Chem.* **1998**, *63*, 2829-2834.

¹⁰² Fernández-Mateos, A.; Mateos Burón, L.; Martín de la Nava, E.; Rabanedo Clemente, R.; Rubio González, R.; Sanz González, F. *Synlett* **2004**, 2553-2557.

conjugado con el doble enlace produce una aceleración en el proceso de ciclación. Así, cuando se emplea **81** como sustrato, el proceso 3-*exo* hacia la formación de **82** se produce de manera cuantitativa (Esquema 71).¹⁰³



Esquema 71

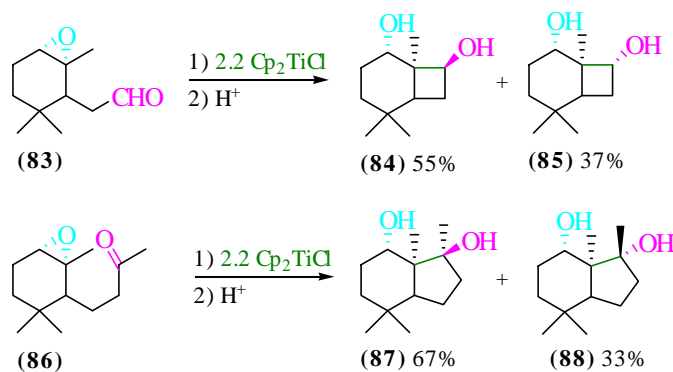
Relacionado con lo anterior, A. Gansäuer *et al.* establecieron, mediante una combinación de estudios teóricos y experimentales de ciclaciones 3-*exo* catalizadas por Cp_2TiCl_2 , que ambas reacciones son termodinámicamente favorables y que la eficacia del proceso depende, de la facilidad con la que los radicales de ciclopropano son atrapados por una segunda molécula de Cp_2TiCl_2 .¹⁰⁴

Se ha empleado también epoxi-aldehídos, epoxi-cetonas y epoxi-nitrilos como sustratos en ciclaciones catalizadas por Ti^{III} . Cuando se emplean epoxi-carbonil derivados (**83**, **86**, Esquema 72) se obtienen cicloalcanoles (**84**, **85**, **87**, **88**,

¹⁰³ a) Fernández-Mateos, A.; Martín de la Nava, E.; Pascual Coca, G.; Ramos Silvo, A.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607-609; b) Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silvo, A. I.; Rubio González, R. *Synlett* **2004**, 1011-1014.

¹⁰⁴ Friedrich, J.; Dolg, M.; Gansäuer, A.; Geich-Gimbel, D.; Lauterbach, T. *J. Am. Chem. Soc.* **2005**, *127*, 7071-7077.

Esquema 72), mientras que se obtienen cicloalcanonas, si los sustratos son epoxi-nitrilos. En lo referente a experimentos con derivados de epoxi-carbonilos, se obtienen productos desde ciclopropanoles hasta ciclohexanoles con buenos rendimientos especialmente altos en el caso los hidroxiciclopropanos.



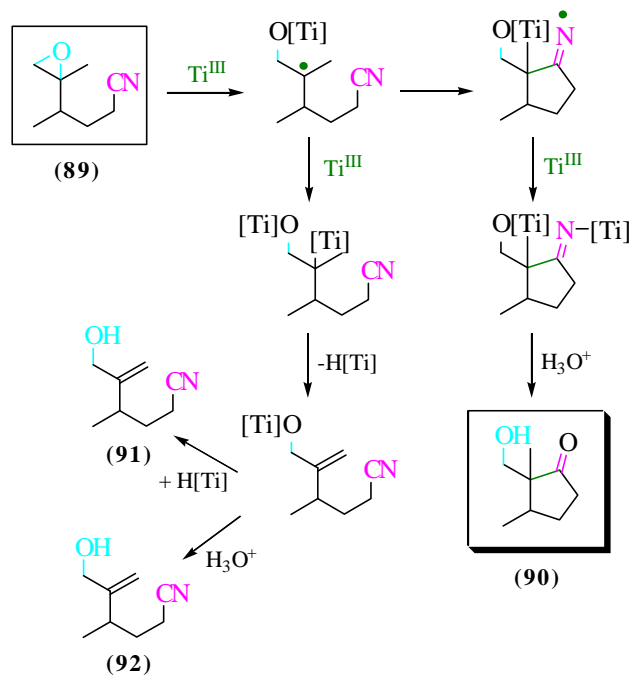
Esquema 72

La pérdida de eficacia detectada en los procesos 6-*exo* es debida a la competencia con la β -eliminación de hidrógeno del radical carbonado resultante de la apertura homolítica inicial del epóxido.¹⁰⁵

En cuanto al comportamiento de los epoxi-nitrilos, este método conduce con buenos rendimientos a compuestos resultantes de procesos de ciclaciones 4-, 5- y 6-*exo-dig*.¹⁰⁶ El mecanismo propuesto requiere la adición de un β -titanoxi radical al nitrilo para dar lugar a un radical de iminio que evoluciona hasta la correspondiente cetona (Esquema 73).

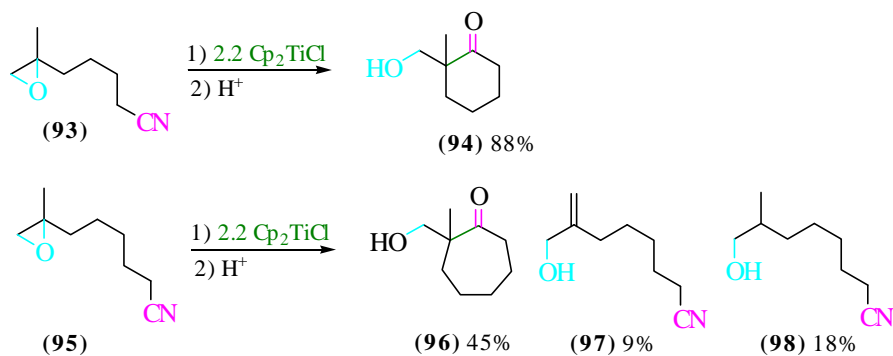
¹⁰⁵ Fernández-Mateos, A.; Martín de la Nava, E.; Pascual Coca, G.; Ramos Silvo, A.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607-609.

¹⁰⁶ Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silvo, A. I.; Rubio González, R. *Synlett* **2004**, 1011-1014.



Esquema 73

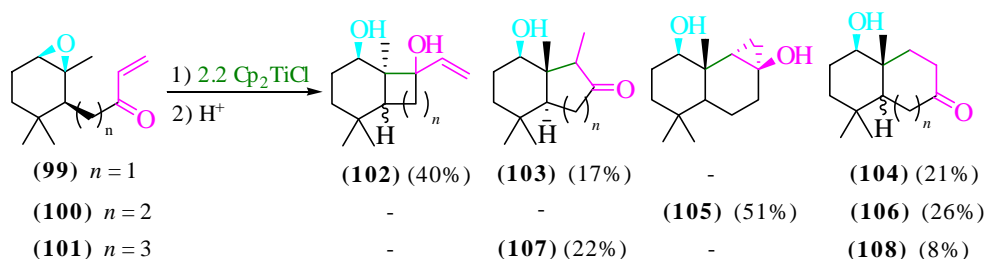
En el caso de los β -epoxi-nitrilos se ha observado la pérdida del grupo nitrilo, mientras que en el caso de los ϵ -epoxi-nitrilos, se produce la competencia entre la eliminación del β -titanoxi-radical intermedio y la ciclación 7-*exo-dig* (Esquema 74).



Esquema 74

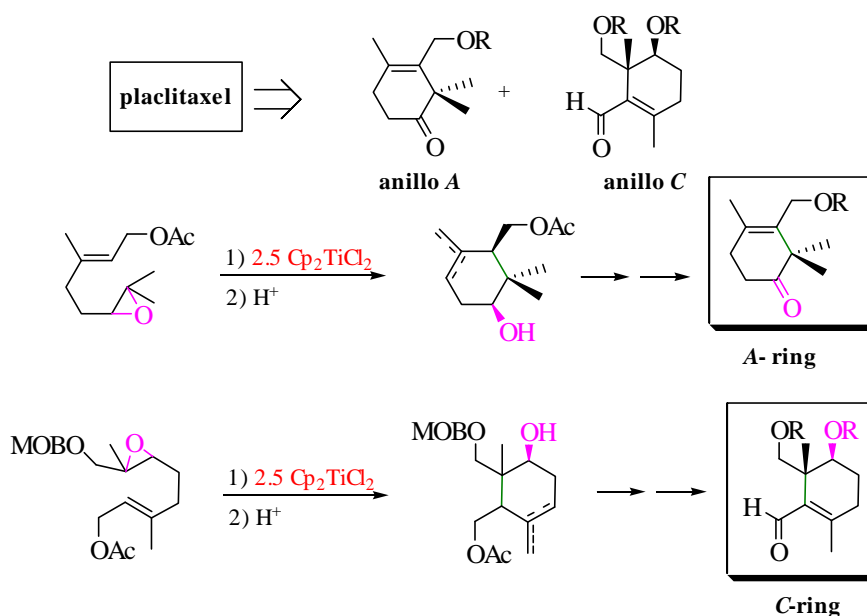
Un conjunto de estudios llevados a cabo sobre series de epoxi-cetonas conjugadas con dobles enlaces mono-sustituidos mostraron únicamente buenos rendimientos en las ciclaciones quimioselectivas hacia el ciclopropil-derivado

correspondiente cuando se emplean β -cetonas como material de partida (Esquema 75).¹⁰⁷ En el resto de series se obtiene mezclas de ciclaciones sobre los dobles enlaces o carbonilos.



Esquema 75

Las ciclaciones *6-endo* catalizadas por Ti^{III} han sido empleadas en numerosas secuencias sintéticas. En sus estudios hacia la síntesis de paclitaxel, T. Takahashi *et al.* prepararon los sintones cíclicos A- y C de su estructura comenzando a partir de geraniol (Esquema 76).¹⁰⁸

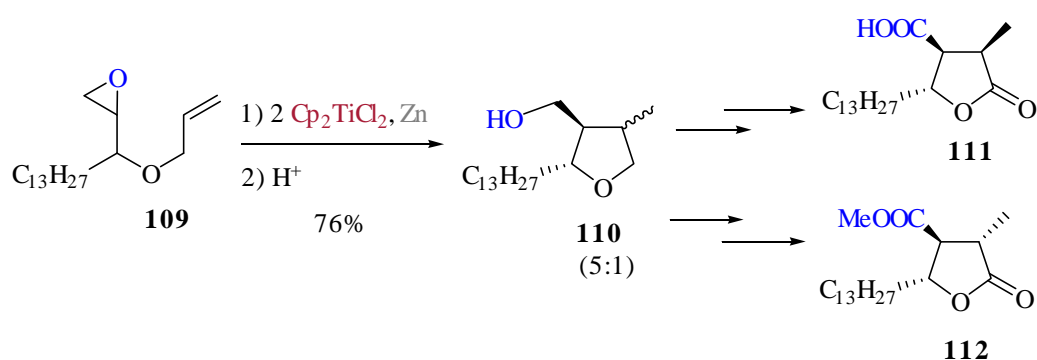


Esquema 76

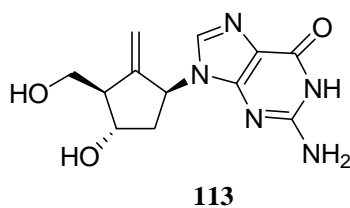
¹⁰⁷ Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silvo, A. I.; Rubio González, R. *Synlett* **2004**, 1011-1014.

¹⁰⁸ Nakai, K.; Kamoshita, M.; Doi, T.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **2001**, *42*, 7855-7857.

Se ha indicado el empleo de Ti^{III} en ciclaciones 5-*exo*-dig y 5-*exo*-trig para la síntesis de lignanos y productos naturales derivados de tetrahidrofurano, como son γ -lactonas. Así, dos potentes antibióticos: el ácido (\pm)-dihidroprotolichesterínico (**111**) y el ácido (\pm)-rocellárico (**112**) se han sintetizado eficientemente empleando el epoxi-alqueno **109** como producto de partida (Esquema 77).¹⁰⁹

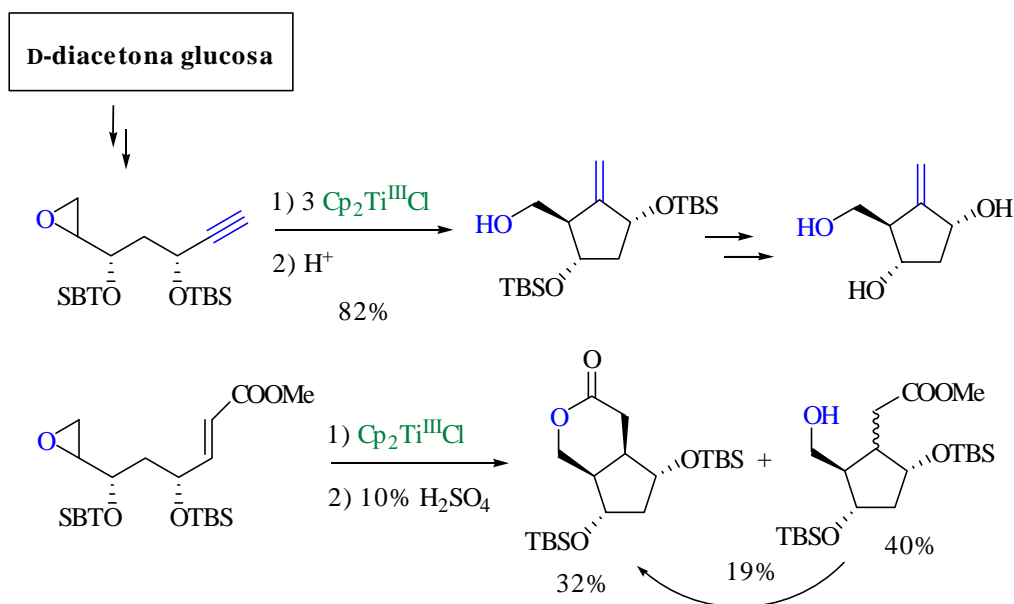


Ziegler ha descrito dos aproximaciones a la síntesis de uno de los ciclos de entecavir (**113**), un nucleósido sintético activo contra el virus de la hepatitis B, a partir de *D*-diacetona glucosa (Esquema 78).¹¹⁰



¹⁰⁹ Mandal, P. K.; Roy, S. C. *Tetrahedron*, **1999**, 55, 11395-11398.

¹¹⁰ Ziegler, F. E.; Sarpong, M. A. *Tetrahedron*, **2003**, 59, 9013-9018.



En relación con todas estas temáticas, en los últimos años se han publicado nuevas reacciones de mono-ciclación ó ciclaciones en cascada: por ejemplo las que utilizan epoxi-esteres, epoxi-enonas,¹¹¹ epoxi-nitrilos,¹¹² síntesis de ciclobutanos mediante ciclaciones 4-*exo*,¹¹³ y síntesis de ciclopentitoles.¹¹⁴ Se han desarrollado nuevas síntesis de compuestos heterocíclicos del tipo de las β -lactamas¹¹⁵ y anillos oxigenados desde 4 a 8 eslabones que incluyen lactonas

¹¹¹ Martín-Rodríguez, M.; Galán-Fernández, R.; Marcos-Escribano, A.; Bermejo, F. A. *J. Org. Chem.* **2009**, *74*, 1798-01.

¹¹² a) Fernández-Mateos, A.; Teijon, P. H.; Clemente, R. R.; González, R. R.; González, F. S. *Synlett* **2007**, 2718-22; b) Monleón, L. M.; Grande, M.; Anaya, J. *Tetrahedron* **2007**, *63*, 3017-3025.

¹¹³ Friedrich, J.; Walczak, K.; Dolg, M.; Piestert, F.; Lauterbach, T.; Worgull, D.; Gansauer, A. *J. Am. Chem. Soc.* **2008**, *130*, 1788-96

¹¹⁴ Chiara, J. L.; Bobo, S.; Sesmilo, E. *Synthesis* **2008**, 3160-66.

¹¹⁵ a) Monleon, L. M.; Grande, M.; Anaya, J. *Synlett* **2007**, 1243-46; b) Monleón, L. M.; Grande, M.; Anaya, J. *Tetrahedron* **2007**, *63*, 3017-25.

como las dihidro-isocumarinas etc.¹¹⁶ Se han estudiado reacciones de reducción de oxazinas, ácidos hidroxámicos y *N*-hidroxi-carbamatos.¹¹⁷

Otro aspecto relevante de la química de **monocloruro de titanoceno** son nuevas reacciones de acoplamiento C-C incluyendo homo-acoplamientos-dimerizaciones,¹¹⁸ acoplamientos entre epóxidos y nitrilos,¹¹⁹ metodologías de acoplamiento pinacolínico y acoplamientos cruzados-alilaciones.

También se pusieron a punto nuevas metodologías que incluyen la síntesis de 2-ene-1,4-dioles a través de una apertura en cascada de 1,3-diepóxidos,¹²⁰ síntesis de C-cuaternarios mediante apertura de 2,3-epoxialcoholes,¹²¹ hidrogenación de alquenos y alquinos mediada por **Cp₂Ti^{III}Cl**/metales de transición, apertura de oxetanos catalizada por **Ti^{III}**.¹²²

¹¹⁶ a) Banerjee, B.; Roy, S. C. *Eur. J. Org. Chem.* **2006**, 489-97; Mandal, S. K.; Roy, S. C. *Tetrahedron* **2007**, *63*, 11341-48; b) Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2007**, *48*, 4131-34; c) Mandal, S. K.; Roy, S. C. *Tetrahedron Lett.* **2008**, *49*, 11050-57; d) Xu, L.; Huang, X. *Tetrahedron Lett.* **2008**, *49*, 500-03.

¹¹⁷ Cesario, C.; Tardibono, L. P. Jr.; Miller, M. J. *J. Org. Chem.* **2009**, *74*, 448-51.

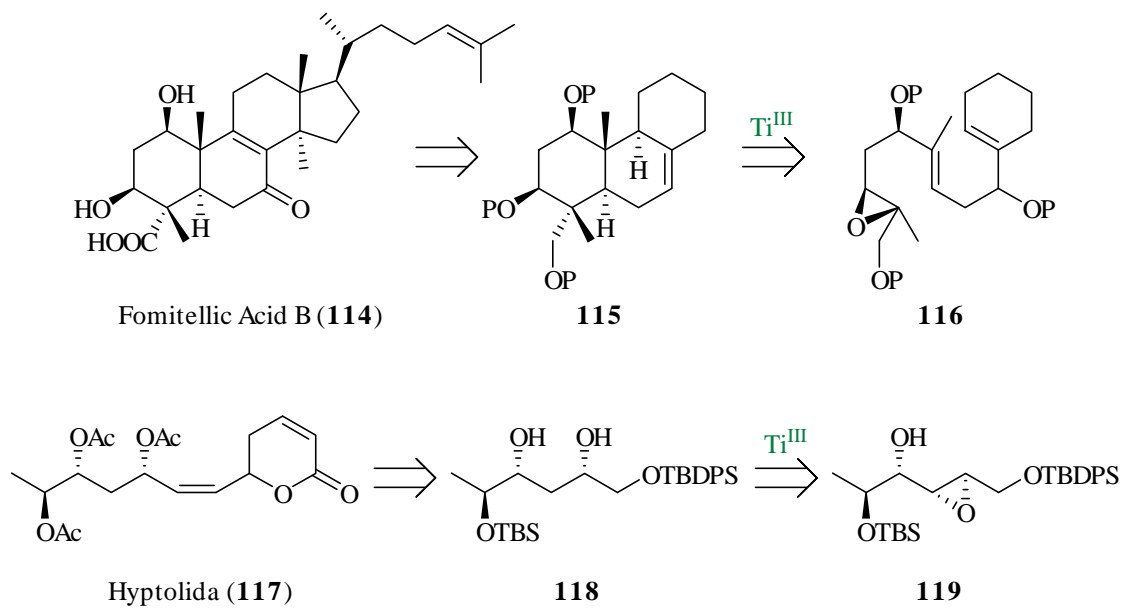
¹¹⁸ Ramesh, N.; Prakash, C.; Sureshababu, R.; Dhayalan, V.; Mohanakrishnan, A. K. *Tetrahedron* **2008**, *64*, 2071-79.

¹¹⁹ Fernández-Mateos, A.; Madrazo, S. E.; Teijon, P. H.; González, R. R. *J. Org. Chem.* **2009**, *74*, 3913-18.

¹²⁰ Aldegunde, M. J.; Castedo, L.; Granja, J. R. *Chem. Eur. J.* **2009**, *15*, 4785-87.

¹²¹ Chakraborty, T. K.; Samanta, R.; Das, S. *J. Org. Chem.* **2006**, *71*, 3321-24.

¹²² Gansäuer, A.; Ndene, N.; Lauterbach, T.; Justicia, J.; Winkler, I.; Mück-Lichtenfeld, C.; Grimme, S. *Tetrahedron* **2008**, *64*, 11839-44.



Esquema 79

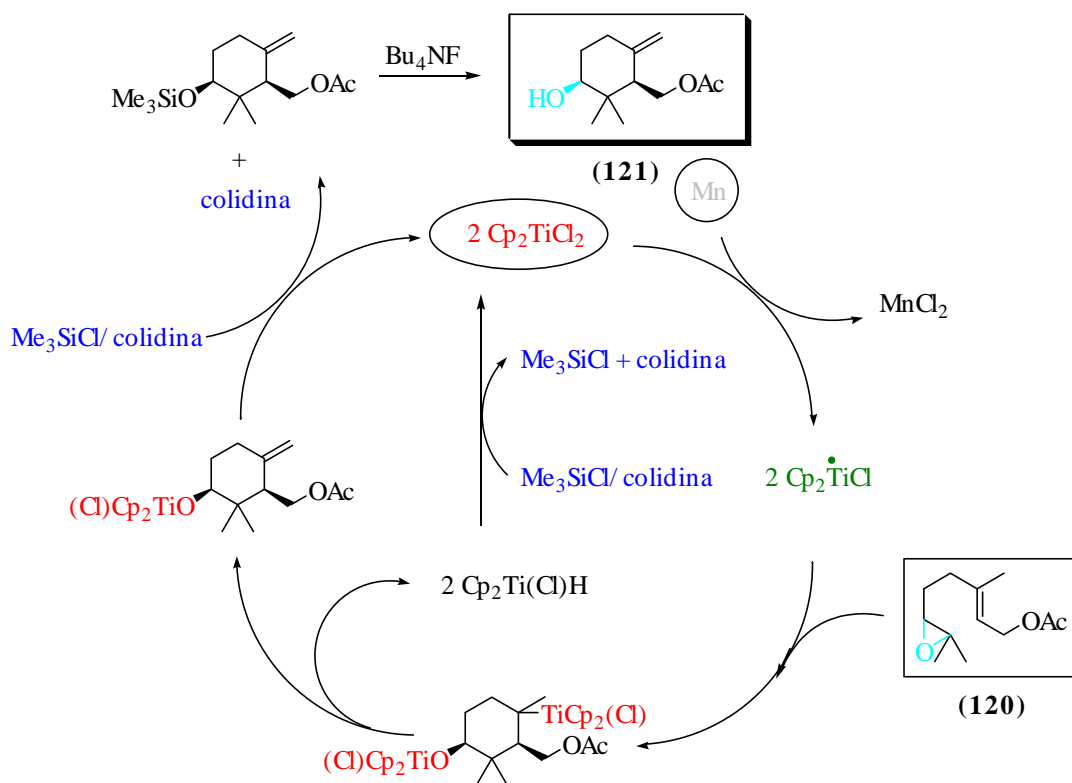
Junto a estos tipos de nuevas reacciones, recientemente se ha utilizado $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ como paso clave en síntesis totales de Productos Naturales,¹²³ especialmente los terpenoides como el ácido fomitólico B (114) e hyptolida (117) (Esquema 79).

Para las ciclaciones radicalarias ha sido desarrollada una versión catalítica (Esquema 80), reduciéndose considerablemente las proporciones de Cp_2TiCl_2 empleadas y las elevadas diluciones de la versión estequiométrica.¹²⁴ Así, el empleo de la combinación de 2,4,6-colidina/TMSCl o hidrocioruro 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. Además la alta tolerancia a diferentes grupos funcionales se mantiene en la versión catalítica respecto a la estequiométrica.

Gansaeuer, Andreas; Justicia, Jose; Rosales, Antonio; Worgull, Dennis; Rinker, Bjoern; Cuerva, Juan Manuel; Oltra, Juan Enrique. **Transition-metal-catalyzed allylic substitution and titanocene-catalyzed epoxypolyene cyclization as a powerful tool for the preparation of terpenoids.** *European Journal of Organic Chemistry* (2006), (18), 4115-4127. CODEN: EJOCHF ISSN:1434-193X. CAN 146:8123 AN 2006:991058 CAPLUS

¹²³ a) Yamaoka, M.; Fukatsu, Y.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett.* **2009**, *50*, 3849-52; b) Chakraborty, T. K.; Purkait, S. *Tetrahedron Lett.* **2008**, *49*, 5502-04; c) Bermejo, F. A.; Fernández Mateos, A.; Marcos Escribano, A.; Martín Lago, R.; Mateos Burón, L.; Rodríguez López, M.; Rubio González, R. *Tetrahedron* **2006**, *62*, 8933-42.

¹²⁴ a) Gansäuer, A. *Synlett* **1998**, 801-809; b) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2909-2910; c) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771-2788; d) Gansäuer, A.; Narayan, S. *Adv. Synth. Cat.* **2002**, *344*, 465-475; e) Gansäuer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem. Eur. J.* **2003**, *9*, 531-542; f) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556-5573; g) Gansäuer, A.; Barchuk, A.; Fielenbach, D. *Synthesis* **2004**, 2567-2573; h) Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Org. Lett.* **2003**, *5*, 1935-1938; i) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849-12859; j) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Synthesis* **2001**, 2500-2520; k) Gansäuer, A.; Justicia, J.; Rosales, A.; Worgull, D.; Rinker, B.; Cuerva, J. M.; Oltra, J. E. *Eur. J. Org. Chem.* **2006**, *18*, 4115-4127.

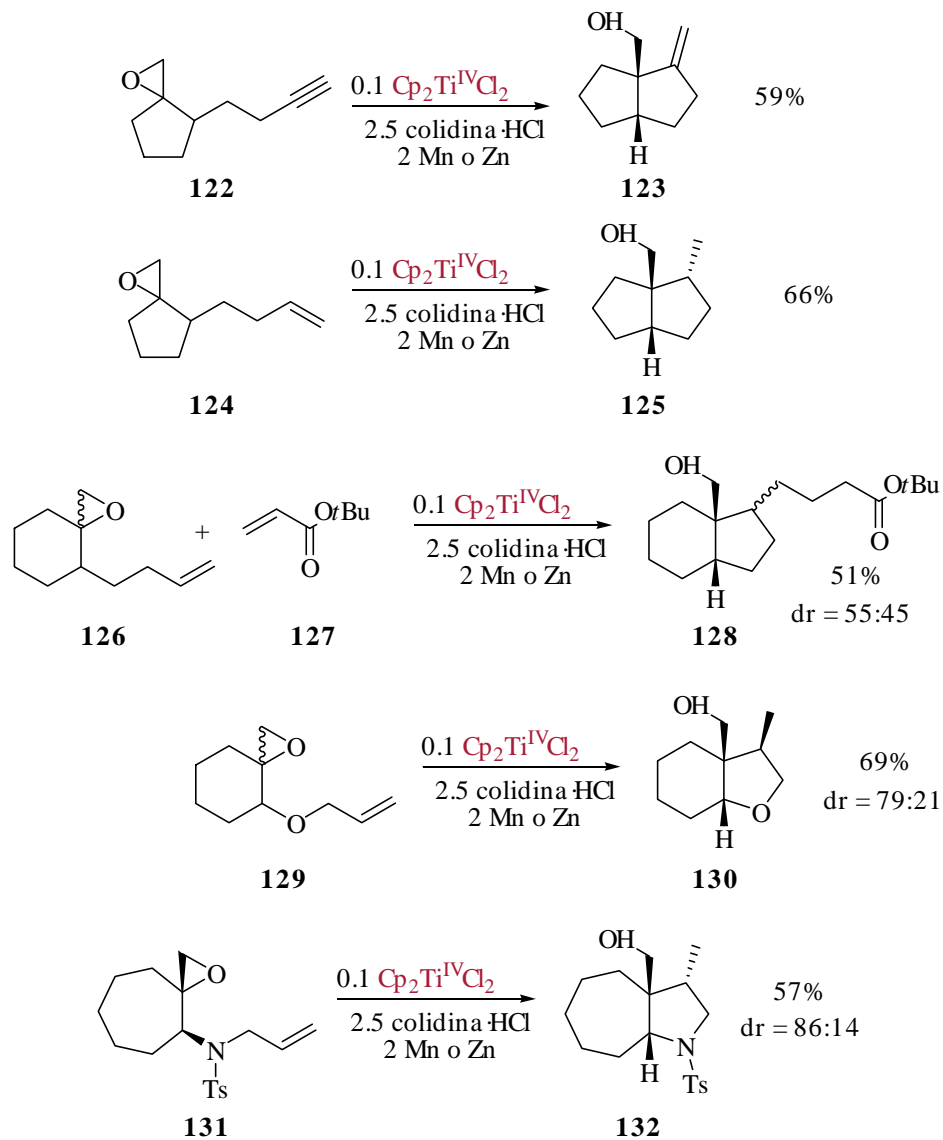


Esquema 80

Gansäuer y colaboradores utilizaron una versión catalítica para obtener ciclaciones 5-*exo* hacia ciclopentanos, tetrahidrofuranos y pirrolidinas con excelentes resultados (Esquema 81).¹²⁵ Siguiendo esta idea, luego desarrollaron la captura intermolecular del radical formado después de la ciclación con compuestos carbonílicos α,β -insaturados.¹²⁶

¹²⁵ a) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 101-103. b) Gansäuer, A.; Pierobon, M. *Synlett* **2000**, 1357-1359. c) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849-12859. d) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Synthesis* **2001**, 2500-2520.

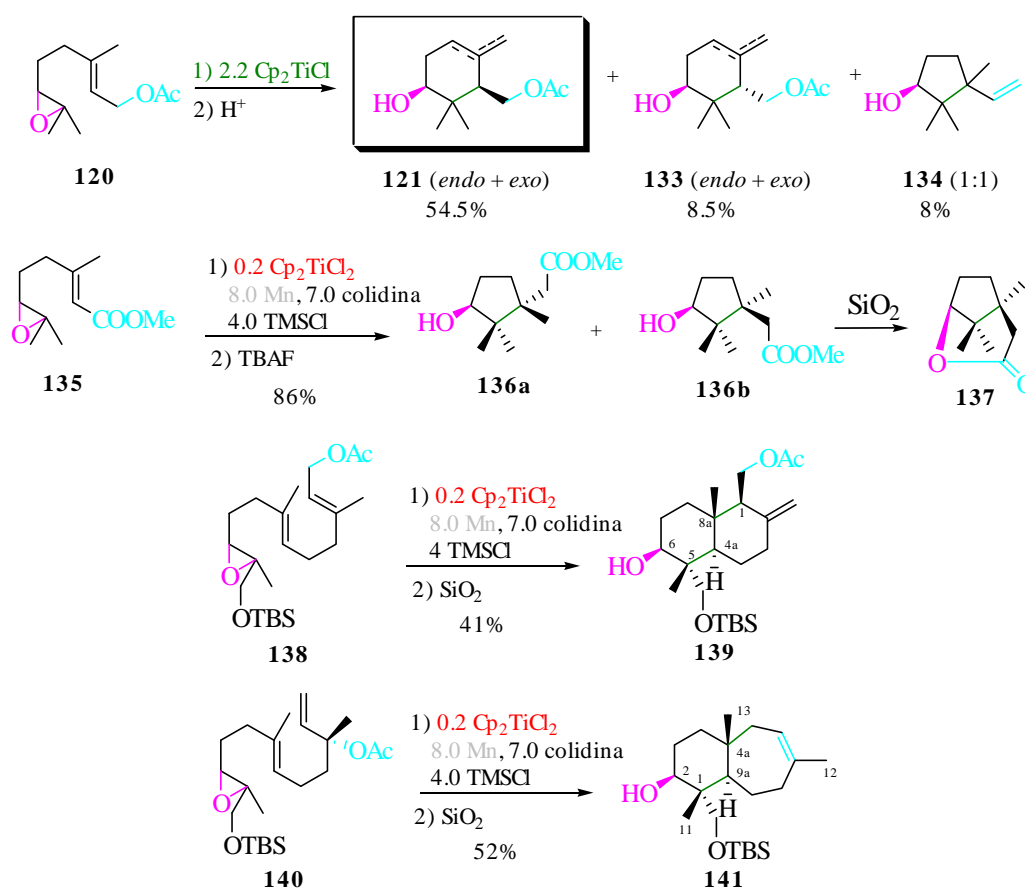
¹²⁶ Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3206-3208.



Esquema 81

En este terreno nuestro Grupo de Investigación como ya se ha mencionado, desde comienzos del siglo XXI diseñó una estrategia general de síntesis de terpenoides cíclicos, mediante la apertura homolítica de epoxi-

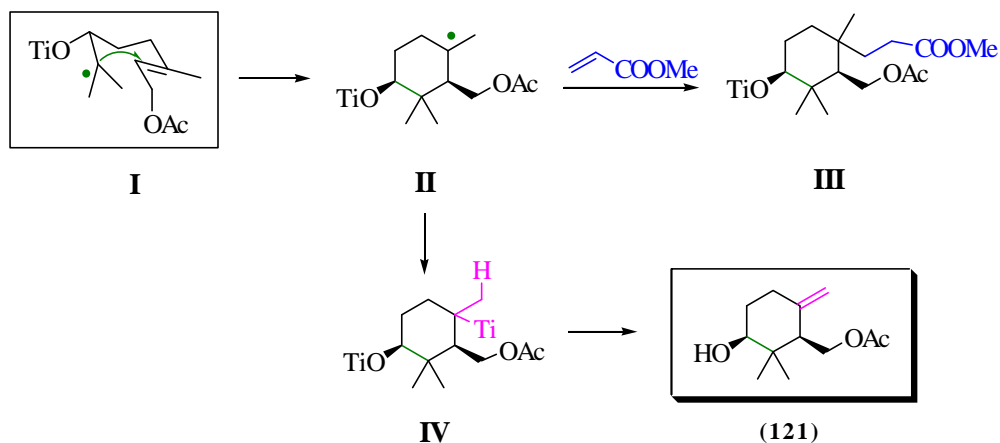
poliprenos promovida por cloruro de titanoceno.²⁶ Esta estrategia se caracteriza por utilizar sustratos acíclicos naturales, con pequeñas modificaciones y permite el cierre de ciclos de 5 a 7 eslabones, tanto en procesos de monociclación como en reacciones en cascada. De esta forma llevan a la construcción de moléculas policíclicas en una sola etapa de reacción con un buen control sobre las cuestiones estereoquímicas (Esquema 82).⁶⁴



Esquema 82

La relación *cis* observada en estos procesos de ciclación entre el grupo hidroxilo generado y el grupo acetoxi-metilo para los productos mayoritarios, es consecuencia del estado de transición tipo silla que se atraviesa en la etapa de ciclación (Esquema 83). La formación de **III** cuando la reacción se lleva a cabo en presencia de **acrilato de metilo**, sirve para apoyar la propuesta de este mecanismo. La facilidad del intermedio cíclico de alquil-titanio para producir

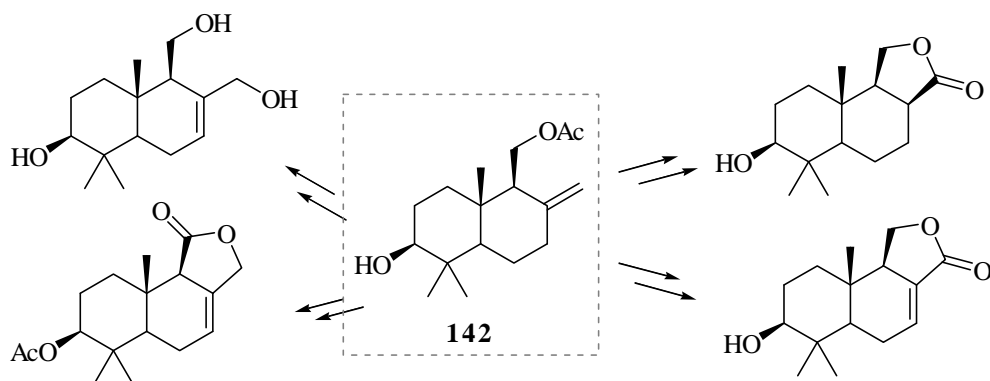
$\text{Cp}_2\text{Ti}(\text{Cl})\text{H}$ por una **eliminación syn** podría justificar la eliminación regioselectiva hacia el **doble enlace exocíclico** observada.



Esquema 83

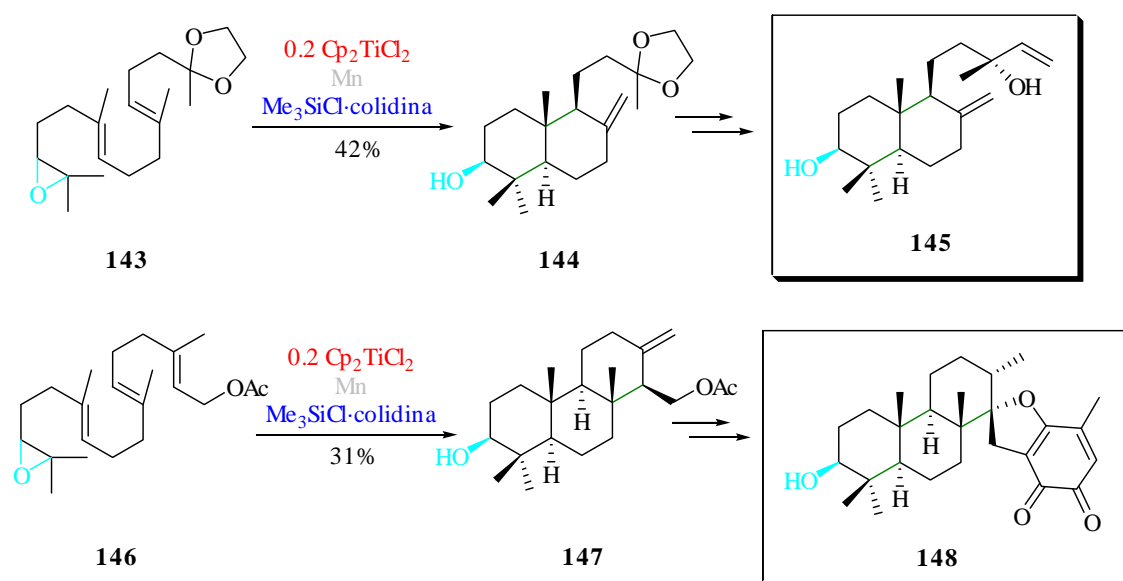
Comparativamente la eficacia del proceso de ciclación radicalaria por apertura de oxiranos promovida por $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, se mejoró considerablemente con la versión catalítica de la reacción. Así, por ejemplo, para el biciclo drimánico **142** se consiguió aumentar el rendimiento para su formación con un 15% extra. En consecuencia, con las condiciones catalíticas se han sintetizado diferentes drimanos naturales con actividad insecticida (Esquema 84).¹²⁷

¹²⁷ a) Justicia, J.; Oltra, J. E.; Barrero, A. F.; Guadaño, A.; González-Coloma, A.; Cuerva, J. M. *Eur. J. Org. Chem.* **2005**, 712-718; b) Justicia, J.; Álvarez de Cienfuegos, L.; Estévez, R. E.; Paradas, M.; Lasanta, A. M.; Oller, J. L.; Rosales, A.; Cuerva, J. M.; Oltra, J. E. *Tetrahedron*, **2008**, *64*, 11938-11943; c) Justicia, J.; Campana, A. G.; Bazdi, B.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *Adv. Synth. Catalysis*, **2008**, *4*, 571-576; d) Cuerva, J. M.; Justicia, J.; Oller, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63-91.



Esquema 84

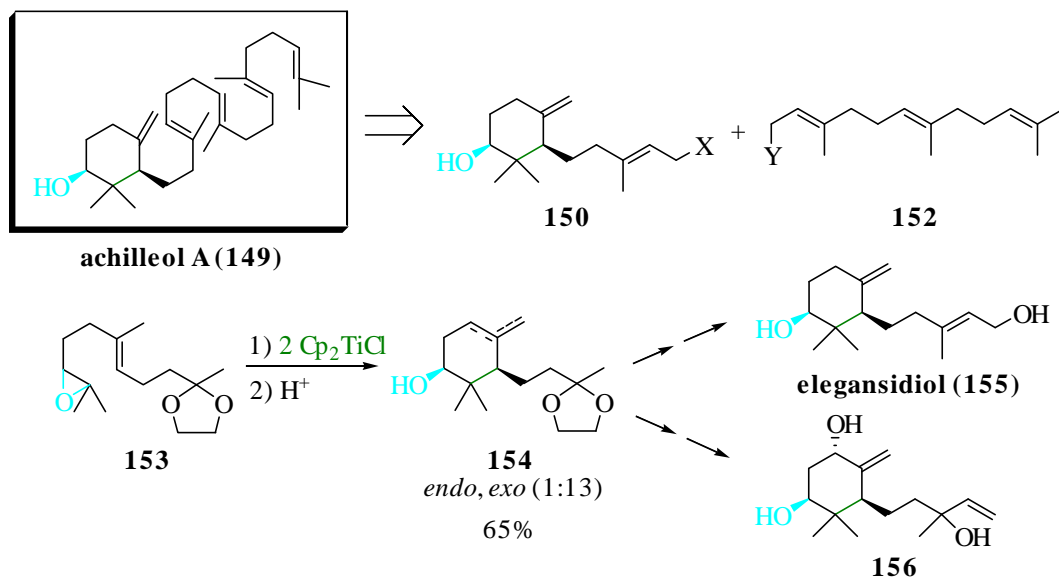
El protocolo catalítico también ha sido utilizado como paso clave para llevar a cabo la síntesis de numerosos terpenoides,²⁷ entre ellos estructuras bicíclicas como las de 3 β -hidroxi-manool (**145**), y tricíclicas tales como el metabolito marino Stypoldiona (**148**) (Esquema 85).



Esquema 85

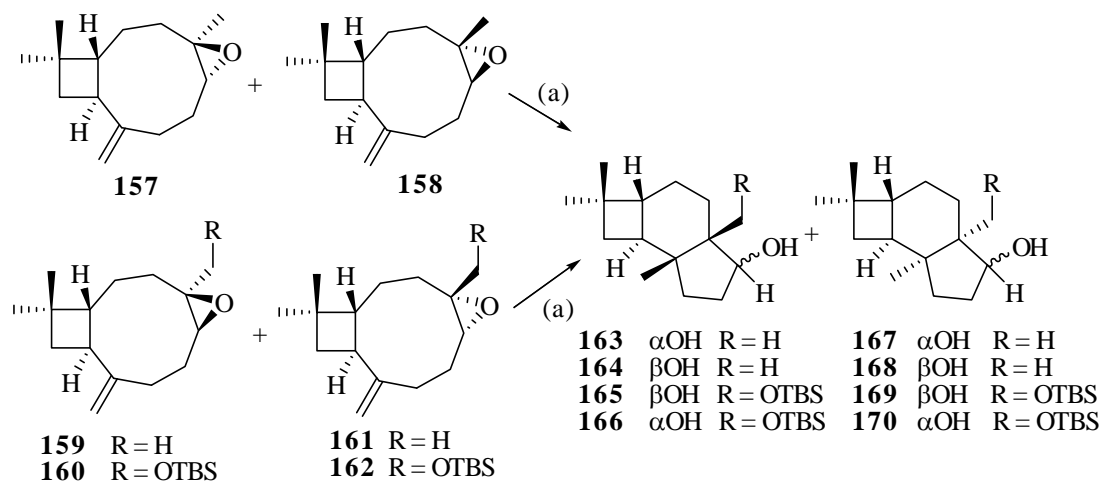
Otro interesante ejemplo de la aplicación de este método fue la primera síntesis del triterpeno monocíclico achilleol-A (**149**) en nuestros laboratorios.⁶⁴ En esta síntesis convergente, el sintón monocíclico (**150**) se prepara a partir del

epóxido (**153**), obtenido previamente a partir de geranilacetona comercial (Esquema 86).



Esquema 86

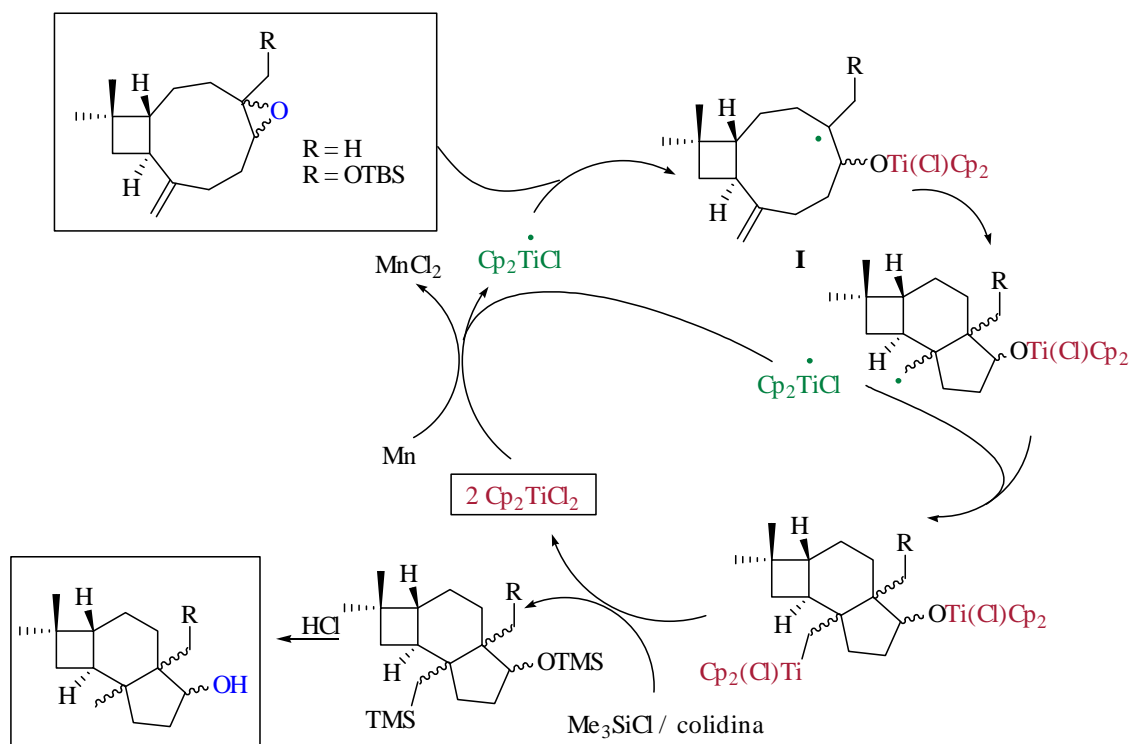
También hemos desarrollado una metodología de ciclaciones transanulares en cariofileno-derivados catalizadas por Cp₂Ti^{III}Cl. La ciclación transanular de los epoxi-cariofilenos **157-162** catalizada por Cp₂Ti^{III}Cl conduce a los alcoholes tricíclicos **163-170** (Esquema 87).²⁷



(a) Cp₂TiCl₂ (0.2 eq.), Mn (polvo), 2,4,6-colidina, TMSCl, THF, t.a., 40 min.

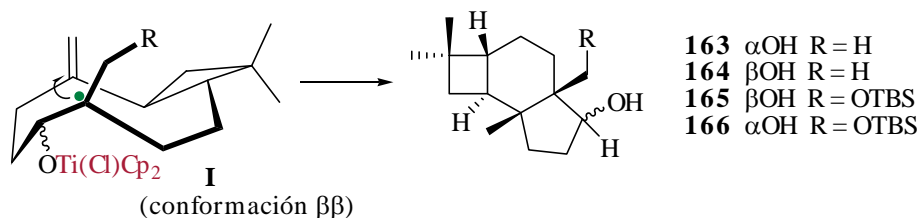
Esquema 87

La ciclación transcurre con altos rendimientos (>80%) vía las conformaciones $\alpha\alpha$ o $\beta\beta$ del radical intermedio I (Esquema 88).



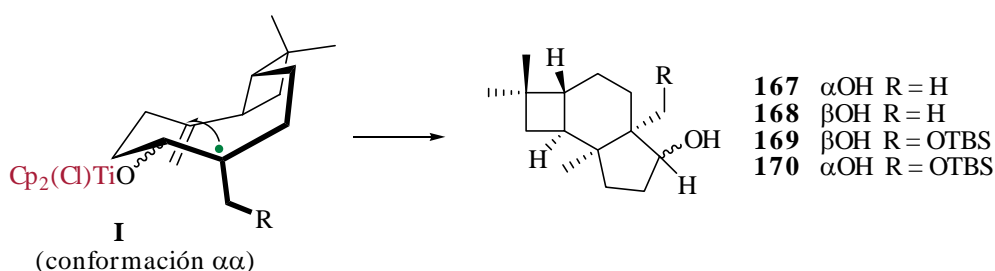
Esquema 88

La conformación $\beta\beta$ origina los alcoholes **163**, **164**, **165** y **166** (Esquema 89), mientras que la $\alpha\alpha$ conduce a los alcoholes **167**, **168**, **169** y **170** (Esquema 90).



Esquema 89

La ciclación radicalaria transcurre con marcada estereoselectividad hacia la formación de diferentes isómeros hidroxilados. Esta estereoselectividad está determinada por la facilidad de que se produzca la ciclación en las diferentes conformaciones que adopta el anillo de 9 miembros del radical intermedio **I**. En el conformero $\beta\beta$ la proximidad del radical al grupo metileno exocíclico es mayor que en el conformero $\alpha\alpha$ (Esquemas 89 y 90).

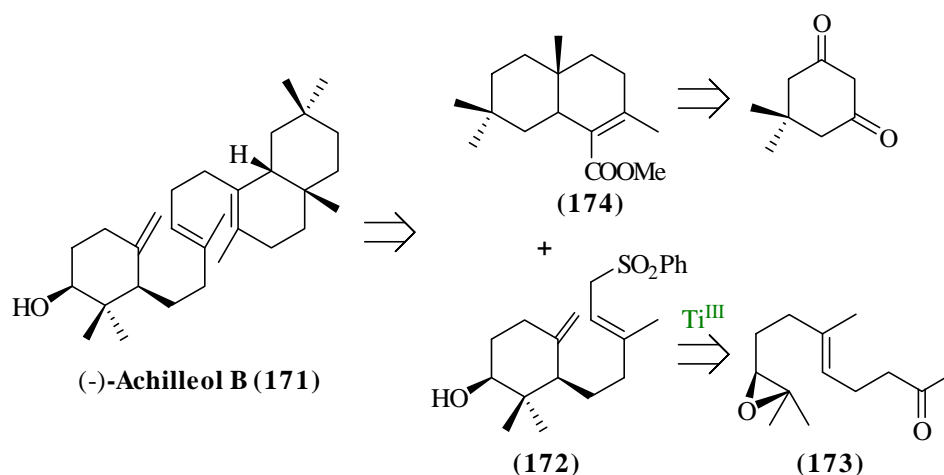


Esquema 90

Relacionado estructuralmente con achilleol A, se sintetizó por primera vez el achilleol B (**171**),^{27g} triterpeno aislado por primera vez en 1990 de la planta *Achillea odorata*¹²⁸. Este posee un “esqueleto irregular” caracterizado por poseer menos ciclos que los esperados a partir de la ciclación del óxido de escualeno por las *óxido-escualeno ciclasas*. Se ha sintetizado a través de una secuencia lineal de 14 etapas, con un acoplamiento final de una mitad monocíclica (**172**), obtenida a través de una ciclación radicalaria catalizada por Ti^{III} de un mono-epóxido quiral (**173**)^{27b, 129} y de la correspondiente mitad bicíclica (**174**) construida mediante el empleo de una anelación de Robinson como etapa clave (Esquema 91).^{27a}

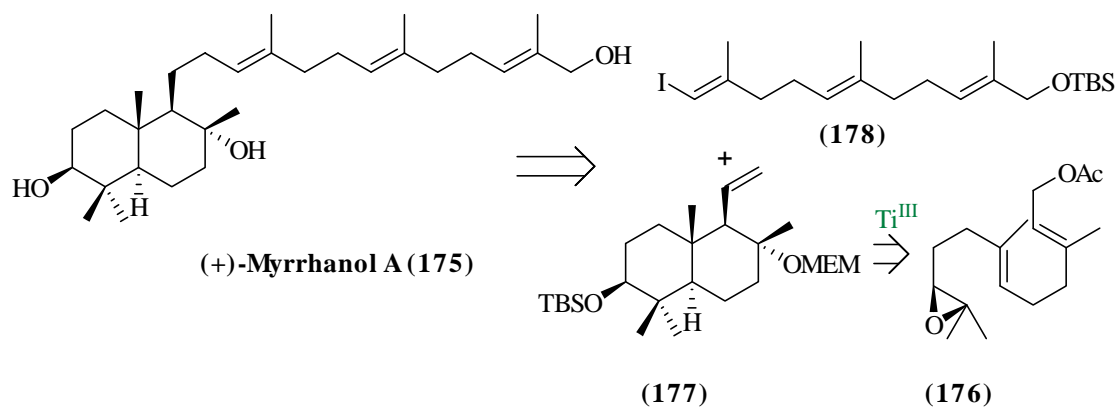
¹²⁸ Barrero, A. F.; Manzaneda, E. A.; Manzaneda, R. A.; Arseniyadis, S.; Guittet, E. *Tetrahedron* **1990**, *46*, 8161.

¹²⁹ a) 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; b) Barrero, A. F.; Quílez, J. F.; Herrador, M. M.; Sánchez, E. M.; Arteaga, J. F. *J. Mex. Chem. Soc.* **2006**, *4*, 149.



Esquema 91

La metodología ha sido también empleada para la síntesis de (+)-myrrhanol A (175),²⁷ⁱ compuesto natural aislado de la mirra con esqueleto de triterpeno de la clase de los polipodanos,¹³⁰ a través de una secuencia cuyos pasos clave son una ciclación radicalaria catalizada por Ti^{III} del mono-epóxido quiral (176)¹³¹ que da lugar al esqueleto bicíclico clave (177) y su correspondiente acoplamiento con el iodolvinil-derivado (178) (Esquema 92).

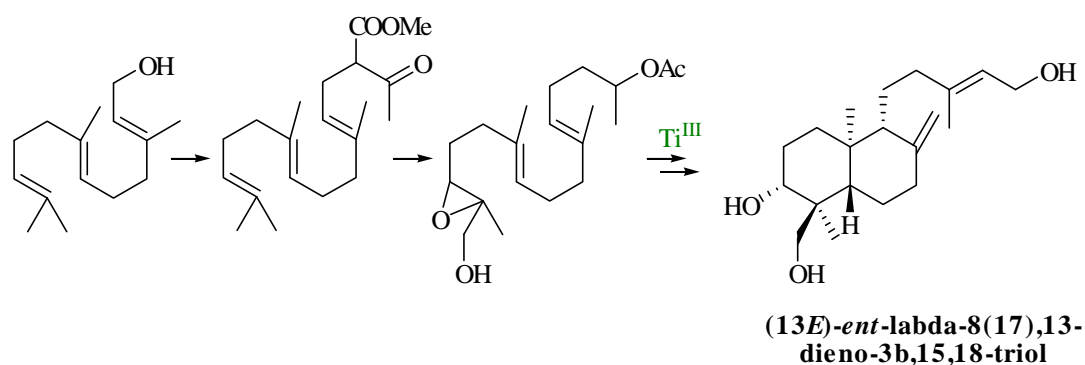


Esquema 92

¹³⁰ 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; b) Matsuda, H.; Morikawa, T.; Ando, S.; Oominami, H.; Murakami, T.; Kimura, I.; Yoshikawa, M. *Bioorg. Med. Chem.* **2004**, *12*, 3037.

¹³¹ a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8560; and references 26a, 27b, 57, 124h.

Más recientemente se ha llevado a cabo la síntesis del (13*E*)-*ent*-labda-8(17),13-dieno-3 β ,15,18-triol,^{27k} compuesto diterpénico que procede de la corteza de *Suregada multiflora*,¹³² destacando por poseer actividades antialérgicas y que pertenece a este conjunto de productos, mediante el empleo de dos metodologías novedosas de síntesis orgánica, como son la cloración alílica selectiva de olefinas catalizada por compuestos de Se,^{27e} así como la ciclación radicalaria catalizada por Ti^{III} de estructuras de epoxi-poliprenos convenientemente funcionalizados (Esquema 93).^{26a, 27b}



Esquema 93

¹³² Cheepracha, S.; Yodsaoue, O.; Karalai, C.; Ponglimanont, C.; Subhadhirasakul, S.; Tewtrakul, S.; Kanjana-opas, K.; *Phytochemistry* **2006**, *67*, 2630.

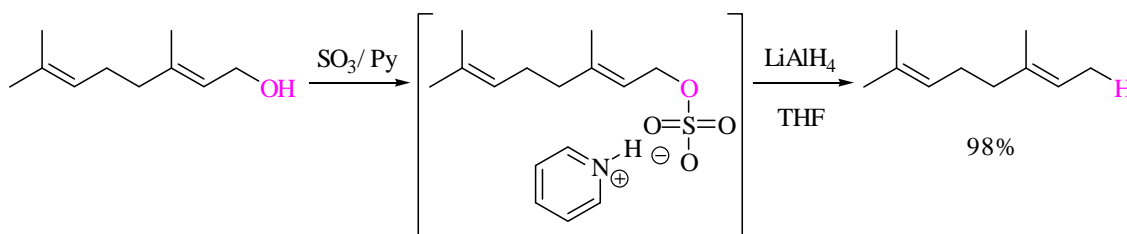
II.3. DESOXIGENACIÓN DE ALCOHOLES.

La desoxigenación de alcoholes constituye una poderosa herramienta sintética empleada especialmente en síntesis complejas de productos naturales.¹³³ La mayor parte de los procesos de desoxigenación conocidos, tienen lugar a través de varias etapas, siendo la metodología de Barton-McCombie la más empleada. Especialmente para el caso de alcoholes secundarios, debido a su compatibilidad con una amplia gama de grupos funcionales.¹³⁴ Hasta la fecha han sido descritos pocos procedimientos de desoxigenación en una única etapa, por lo que es necesario y conveniente investigar en este campo.

¹³³ a) Zard, S. Z. Xanthates and Related Derivatives as Radical Precursors. en *Radicals in Organic Synthesis*, Vol. 1; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, **2001**; pp 90-108; b) McCombie, W. S. en *Comprehensive Organic Synthesis*, Vol. 8; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., **1991**; pp 811-833.

¹³⁴ a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672-685; b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C.; Joseph, C. J. *Org. Chem.* **1993**, *58*, 6838-6842; c) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C.; Joseph, C. *Synlett* **1991**, 435-438; d) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743-745.

Así, basándose en la idea de que los derivados activados de alcoholes más comúnmente empleados en síntesis, cloruros, bromuros y aril-sulfonatos, pueden ser suficientemente reactivos para una desoxigenación, pero a menudo presentan problemas. Tratando de superarlos Corey durante el desarrollo de la síntesis total del sesquiterpeno sesquicarene, desarrolló una metodología que emplea el complejo piridina-trióxido de azufre, como reactivo para la activación del hidroxilo y llevó a cabo la etapa de reducción, sin aislar el mono-éster sulfato intermedio (Esquema94).¹³⁵



Esquema 94

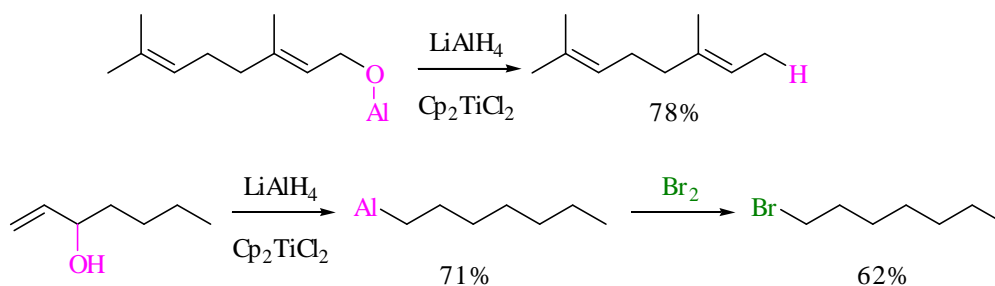
Otra posibilidad para afrontar el proceso de desoxigenación, radica en el empleo de reactivos de Ti de baja valencia y LiAlH_4 . Así, tras estudios iniciales llevados a cabo tanto por J. E. McMurry¹³⁶ como por Tkatchenko y Young,¹³⁷ se desarrolló un proceso de desaluminoxidación de alcóxidos de aluminio alílicos o bencílicos y desoxigenación de éteres alílicos, empleando catalizadores de Ti (TiCl_4 o Cp_2TiCl_2) sin especificar con detalle el mecanismo del proceso.¹³⁸ En el caso de alcoholes alílicos con dobles enlaces terminales, la reducción del doble enlace tiene lugar simultáneamente además de la desoxigenación (Esquema 95).

¹³⁵ Corey, E. J.; Achiwa, K. *J. Org. Chem.* **1969**, *34*, 3667–3668

¹³⁶ McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, *43*, 3249–3254.

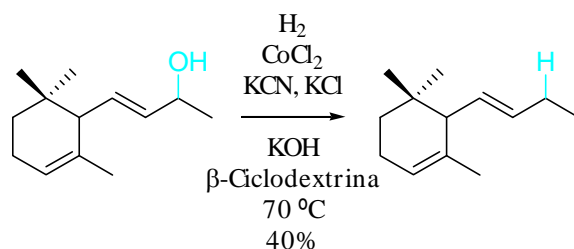
¹³⁷ Ledon, H.; Tkatchenko, I.; Young, D. *Tetrahedron Lett.* **1979**, *20*, 173–176.

¹³⁸ Sato, F.; Tomuro, Y.; Ishikawa, H.; Oikawa, T.; Sato, M. *Chem. Lett.* **1980**, 103–106.



Esquema 95

Posteriormente se ha empleado de manera similar un anión hidrocobaltato¹³⁹ generado *in situ*, para inducir la desoxigenación de alcoholes alílicos. Este método emplea además β -ciclodextrina como agente de transferencia de fase, seguido por tratamiento con hidrógeno (Esquema 96).¹⁴⁰ El método se restringe fundamentalmente a olefinas *trans* y a alcoholes alílicos primarios y secundarios.



Esquema 96

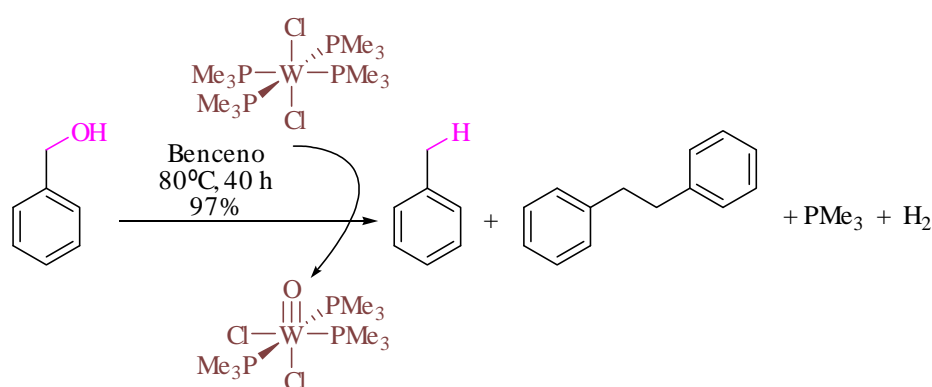
Más recientemente Mayer, J. M. puso a punto una metodología para la homólisis de enlaces C-O a través del empleo de alcóxidos de W.¹⁴¹ Así, los reactivos $\text{WCl}_2(\text{PMe}_3)_4$ y $\text{WH}_2\text{Cl}_2(\text{PMe}_3)_4$ reaccionan con alcoholes dando lugar a la formación de $\text{W}(\text{O})\text{Cl}_2(\text{PMe}_3)_3$ junto con PMe_3 , los correspondientes hidrocarburos y H_2 (Esquema 97). La distribución de productos obtenidos

¹³⁹ Lee, J.T.; Alper, H., *J. Org. Chem.* **1990**, *55*, 1854-1859.

¹⁴⁰ Lee, J. T.; Alper, H. *Tetrahedron Lett.* **1990**, *31*, 4101-4104.

¹⁴¹ Crevier, T. J.; Mayer, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 8485-8491.

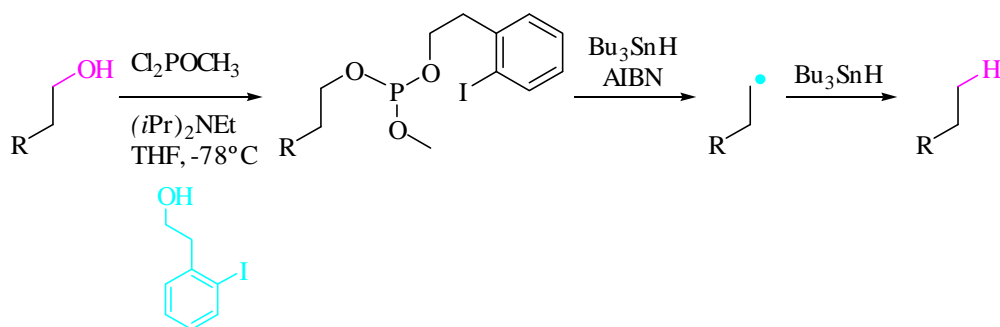
indica la existencia de un mecanismo que pasa por la formación de alquilradicales. Asimismo, estudios cinéticos igualmente sugieren que el proceso tiene lugar a través de la formación de especies de alcóxidos de tungsteno intermedias. Los radicales alquílicos se forman por homólisis de los enlaces C-O del complejo alcóxido y dan lugar a la aparición de compuestos de *oxo*-W estables. También se ha probado la eficacia en procesos de desulfuración de tioles.



Esquema 97

En 2004 Zhang y Koreeda pusieron a punto una metodología para la desoxigenación de alcoholes, en este caso mediante el empleo de fosfitos en una secuencia de dos etapas.¹⁴² El correspondiente alcohol es inicialmente convertido en un derivado de fósforo trivalente que genera un radical arílico por tratamiento con un iniciador de radicales. Este ataca intra-molecularmente al átomo de P evolucionando a través de una β -escisión a un radical alquílico que por abstracción de hidrógeno, conduce hasta el correspondiente hidrocarburo (Esquema 98). Esta metodología es altamente eficiente incluso para alcoholes impedidos y terciarios.

¹⁴² Zhang, L.; Koreeda, M. *J. Am. Chem. Soc.* **2004**, *126*, 13190–13191.



Esquema 98

Spiegel *et al.* han puesto a punto otra novedosa estrategia de desoxigenación que emplea el agua como fuente de átomos de hidrógeno.¹⁴³ En este caso se emplea agua-trialquilborano en mezclas de disolventes y ausencia de hidruros metálicos, transcurriendo el proceso probablemente a través de la formación de complejos de trialquilborano-H₂O.

¹⁴³ Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513–12515.

II.4. OLEFINACIÓN DE CARBONILOS.

La reacción de **olefinación de carbonilos** catalizada por reactivos de Ti de baja valencia, conocida generalmente por el nombre de acoplamiento de McMurry¹⁴⁴ ha sido extensamente empleada en Síntesis Orgánica por su habilidad para dar buenos resultados tanto en acoplamientos inter- como intra-moleculares. Esta reacción es una de las más conocidas debido a sus numerosas aplicaciones. Entre otras destacan procesos

¹⁴⁴ a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513-24; b) Fürstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed.* **1996**, *35*, 2442-2449; c) Wirth, T. *Angew. Chem. Int. Ed.* **1996**, *35*, 61-63; d) Ephritikhine, M. *Chem. Commun.* **1998**, 2549-54.

de acoplamiento tanto inter- como intra-moleculares, que han sido ampliamente descritos debido a su alta eficiencia.¹⁴⁵

La bien conocida oxofilia del Ti que origina enlaces Ti-O muy estables, es la fuerza motriz de estos acoplamientos. En la década de los setenta los grupos de Mukaiyama, Tyrlik y McMurry publican casi simultáneamente que aldehídos y cetonas dan acoplamientos a olefinas en presencia de reactivos de Titanio de baja valencia generados a partir de TiCl_4/Zn , TiCl_3/Mg y $\text{TiCl}_4/\text{LiAlH}_4$, respectivamente.¹⁴⁶

Normalmente esta clase de reacciones transcurren en dos etapas; primero se prepara el reactivo de titanio de baja valencia, mediante reducción de TiCl_4 o TiCl_3 , para después realizar la adición del carbonilo correspondiente. Han sido descritos numerosos agentes reductores del reactivo de titanio: Li, Na, K, Mg, Zn, KC_8 , $\text{Zn}(\text{Cu})$, LiAlH_4 , etc.; así como distintos protocolos en el intento de mejorar los problemas de reproducibilidad asociados a esta reacción.¹⁴⁷

Es destacable indicar que los protocolos para llevar a cabo esta metodología sintética, presentan problemas de reproducibilidad. Para evitarlos

¹⁴⁵ a) McMurry J. E. *Chem. Rev.* **1989**, 89, 1513-1524; b) Robertson G. M. en *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I, Pattenden, G., Eds.; Pergamon: Oxford, **1991**, Vol. 3, pp. 563; c) Dushin R. en *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed., Pergamon: Oxford, **1995**, Vol. 3, pp. 1071; d) Lectka T. In *Active Metals: Preparation, Characterization, Applications*; Fürstner, A., Ed.; Wiley-VCH: Weinheim, Germany, **1995**, pp. 85; e) Fürstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2442-2449; f) Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 61-63; g) Ephritikhine, M. *Chem. Comm.* **1998**, 2549-2554.

¹⁴⁶ a) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, 96, 4708-09; b) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041-44; c) Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147-48.

¹⁴⁷ a) McMurry J. E. *Chem. Rev.* **1989**, 89, 1513-1524; b) Robertson G. M. en *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I, Pattenden, G., Eds.; Pergamon: Oxford, **1991**, Vol. 3, pp. 563; c) Dushin R. en *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed., Pergamon: Oxford, **1995**, Vol. 3, pp. 1071; d) Lectka T. en *Active Metals: Preparation, Characterization, Applications*; Fürstner, A., Ed.; Wiley-VCH: Weinheim, Germany, **1995**, pp. 85; e) Fürstner A., Bogdanovic B. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2442-2449; f) Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 61-63; g) Ephritikhine, M. *Chem. Commun.* **1998**, 2549-2554.

McMurry recomienda el empleo de $\text{TiCl}_3\text{-Zn(Cu)}$,¹⁴⁸ mientras que Fürtsner *et al.* posteriormente pusieron a punto el denominado método instantáneo, donde el carbonilo se añade conjuntamente con TiCl_3/Zn , considerando que sólo es posible reducir el Ti^{III} cuando se encuentra coordinado al carbonilo.¹⁴⁹ También se ha publicado un método catalítico en Ti empleando TiCl_3/Zn en presencia de TMSCl como regenerador, habiéndose comprobado que la presencia de TMSCl permite hacer olefinaciones con polvo de Ti.¹⁵⁰

Desde un punto de vista mecanístico, en esta metodología sintética son tres las etapas a considerar:

- Formación de la especie de titanio de baja valencia.
- Reacción de acoplamiento.
- Reacción de desoxigenación para dar la olefina correspondiente.

Respecto de la primera, en los primeros años desde la puesta a punto de estas reacciones, se pensó que la especie reductora era Ti^0 , siendo necesario ese estado del metal para provocar acoplamientos. Evidencias aportadas por Corey *et al.*¹⁵¹ y por Bogdanovic *et al.*¹⁵² demuestran que especies hasta de Ti^{II} también pueden efectuar la reacción.

En cuanto a la etapa de acoplamiento tres son los caminos que se han propuesto,¹⁵³ el primero pasa por la dimerización de titanoxi-radicales que conduce a pinacولات intermedios. Estos se pueden aislar operando a bajas

¹⁴⁸ McMurry, J. E.; Letcka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748-49.

¹⁴⁹ a) Fürtsner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991-10; b) Fürtsner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215-29.

¹⁵⁰ Furstner, A.; Hupperts, A. *J. Am. Chem. Soc.*, **1995**, *117*, 4468-75.

¹⁵¹ Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260-65.

¹⁵² Bogdanovic, B.; Bolte, A. *J. Organomet. Chem.* **1995**, *502*, 109.

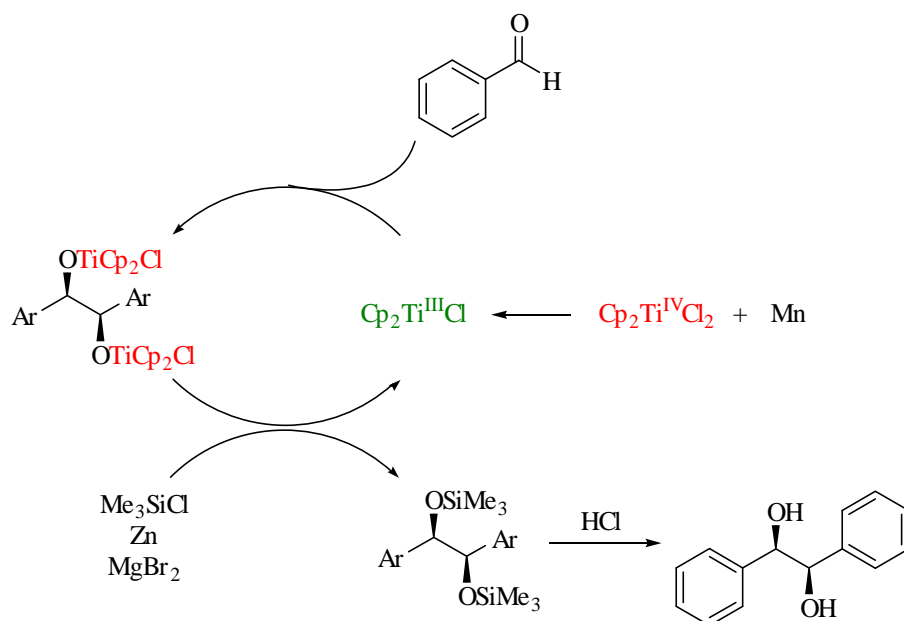
¹⁵³ Villiers, C.; Ephritikhine, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2380-82.

temperaturas, de la misma manera que es bien conocido que **monocloruro de titanoceno**, conduce a pinacoles con buenos rendimientos tanto en condiciones estequiométricas como catalíticas. Sin embargo en condiciones de reducción enérgicas, se ha postulado el acoplamiento a través de oxa-titanaciclos ó a través de carbenos. Igualmente para esta segunda etapa de acoplamiento, se han propuesto como intermedios los acil-radicales y/o carbenos en la formación del correspondiente pinacolato. La participación de un intermedio u otro viene condicionada en cada caso por la naturaleza del grupo carbonilo, las especies de titanio involucradas y el agente reductor usado. Actualmente todavía existen dudas sobre el mecanismo de la tercera etapa de desoxigenación; aunque generalmente hayan sido aceptadas las especies de Ti^{II} y/o Ti^0 como las responsables de esta etapa de reducción.

Respecto a la etapa de desoxigenación, está generalmente bien aceptado que los pinacولات tanto abiertos como cíclicos necesitan por lo menos que el titanio esté como Ti^{II} para poder evolucionar hacia la olefina.

Es por otra parte destacable que hasta la fecha, la reacción más relevante que emplea el **$Cp_2Ti^{III}Cl$** para reaccionar con grupos carbonilo conduce al acoplamiento pinacolínico,¹⁵⁴ un ejemplo de las cuales puede verse en el Esquema 99.

¹⁵⁴ a) Dunlap, M. S.; Nicholas, K. M. *J. Organomet. Chem.* **2001**, 630, 125-131; b) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, 28, 5717-5720; c) Barden, M. C.; Schwartz, J. J. *Am. Chem. Soc.* **1996**, 118, 5484; d) Gansauer, A. *Chem. Comm.* **1997**, 457; e) Gansauer, A.; Bauer, D. *J. Org. Chem.* **1998**, 63, 2070; f) Gansauer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 2673; g) Gansauer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 1923; i) Dunlap, M. S.; Nicholas, K. M. *Synth. Commun.* **1999**, 29, 1097; j) Hirao, T.; Hatano, B.; Asahara, M.; Muguruma, Y.; Ogawa, A. *Tetrahedron Lett.* **1998**, 39, 5247; k) Yamamoto, Y.; Hattori, R.; Itoh, K. *Chem. Commun.* **1999**, 825; l) Yamamoto, Y.; Hattori, R.; Miwa, T.; Nakagai, Y.; Kubota, T.; Yamamoto, C.; Okamoto, Y.; Itoh, K. *J. Org. Chem.* **2001**, 66, 3865-3870.



Esquema 99. Ciclo catalítico propuesto para el acoplamiento pinacolínico catalizado por Ti^{III} .

III. ARTÍCULOS DE INVESTIGACIÓN

Artículo 1:

*Mild Ti^{III}- and Mn/Zr^{IV}-Catalytic Reductive Coupling
of Allylic Halides: Efficient Synthesis of Symmetric Terpenes.*

Journal of Organic Chemistry **2007**, 72, 2998-2995

JOC Article

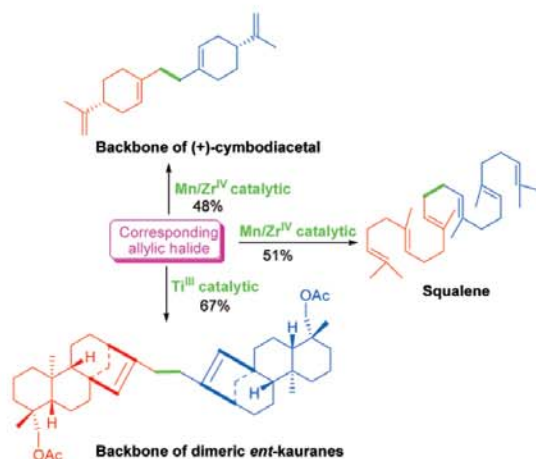
Mild Ti^{III} - and Mn/Zr^{IV} -Catalytic Reductive Coupling of Allylic Halides: Efficient Synthesis of Symmetric Terpenes[†]

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Two new efficient methods for the regioselective homocoupling of allylic halides using either catalytic Ti^{III} or the combination Mn/Zr^{IV} catalyst have been developed. The regio- and stereoselectivity of the process proved to increase significantly when the Mn/Zr^{IV} catalyst is used as the coupling reagent and when cyclic substituted allylic halides are used as substrates. The use of Lewis acids such as collidine hydrochloride allowed the quantity of catalyst to be lowered up to 0.05 equiv. We have proved the utility of these protocols with the synthesis of different terpenoids such as (+)- β -onoceradiene (**1**), (+)- β -onocerine (**2**), squalene (**5**), and advanced key-intermediates in the syntheses of (+)-cymbodiactal (**3**) and dimeric *ent*-kauranoids as xindongnin M (**4a**).

Introduction

Several publications have described methods to achieve the homocoupling of both alkyl and allylic halides, including the electrochemical coupling of allylic halides by using a copper anode,¹ the coupling of two allylic moieties via the reaction of allylic or benzylic halides with SmI_2 in THF,² the reduction of organic halides with lanthanum metal,³ the reaction of allylic

organometallic compounds with allylic halides,⁴ the coupling of π -methallylnickel(I) bromide with halides,⁵ the homocoupling of alkyl halides via activated copper,⁶ the reductive coupling of allylic halides by chlorotris(triphenylphosphine) cobalt(I),⁷ the coupling of allylic halides promoted by Te^{2-} species,⁸ and so on. Within the field of terpenoid synthesis, the homocoupling

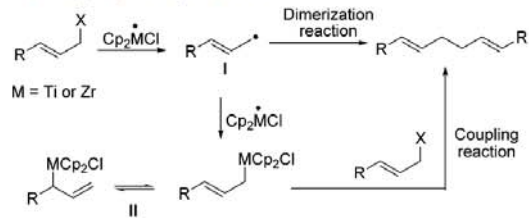
[†] Dedicated to Professor Miguel Yus on the occasion of his 60th birthday.
 (1) Tokuda, M.; Endate, K.; Sugimoto, H. *Chem. Lett.* **1988**, 945–948.
 (2) Krief, A.; Laval, A. *Chem. Rev.* **1999**, *99*, 745–777.
 (3) Nishino, T.; Watanabe, T.; Okada, M.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 966–969.

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Ti^{III}- and Mn/Zr^{IV}-Catalytic Reductive Coupling

JOC Article

SCHEME 1. Possible Mechanistic Pathways for the Homocoupling of Allylic Halides



reaction of allylic halides using Rieke barium⁹ is very interesting, giving satisfactory results in the coupling of (*E,E*)-farnesyl barium with farnesyl bromide. This process represents the first direct synthesis of squalene by the coupling of two *E,E*-farnesyl units. Most of the above-mentioned methods use stoichiometric quantities of reducing species.

Titanocene chloride¹⁰ has been widely used through SET processes in the homolytic opening of oxiranes¹¹ and in pinacol coupling reactions.¹² It has also been used in the reduction of glycosyl bromides¹³ and vic-dibromides¹⁴ and in the homocoupling of allylic and benzylic halides¹⁵ with satisfactory results. These reactions take place under mild conditions and are tolerated by a large number of functional groups, such as alcohols, amines, amides, ketones, acids, and esters.^{13d} By comparison with their Ti^{III} analogues, Zr^{III} complexes have been much less used in organic synthesis. Zirconocene chloride can be obtained by reduction of Cp₂ZrCl₂ with sodium-amalgam in THF or toluene.^{16b,c,17} Cp₂ZrCl has been used to achieve pinacolic couplings with aliphatic aldehydes.¹⁷ These pinacolic couplings have also been successfully achieved using catalytic amounts of Cp₂ZrCl₂ in the presence of Mg and TMSCl.¹⁸ Cp₂ZrCl also provokes the slow reduction of glycosyl halides to glycals,^{10,13d} although when this reagent was prepared

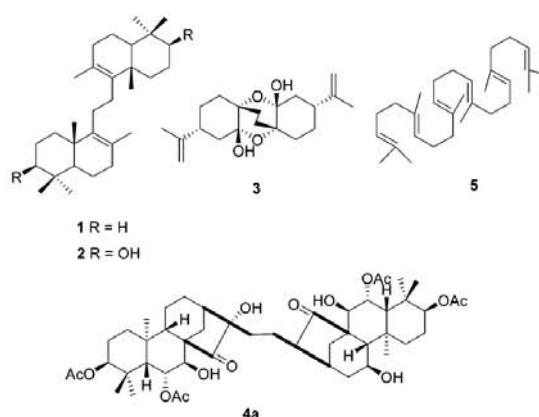


FIGURE 1. Natural dimeric structures.

in situ, it proved to be more efficient than Cp₂TiCl for the reduction of aliphatic halides.

Bearing in mind the mechanism proposed for the reactions mediated by these two reagents, we surmised that these species could well intervene efficiently in the homocoupling of allylic halides (Scheme 1).

In a previous paper^{19a} we described the first results of a new catalytic method for the homocoupling of allylic bromides mediated by Ti^{III}, including the enantioselective preparation of onocerane derivatives **1** and **2**. We describe here the complete development of the process, the ability of Zr^{IV} to catalyze these homocouplings in the presence of manganese metal (to our knowledge no precedence of Zr^{IV} catalyzing these kind of processes can be found in the literature), and finally, new applications toward the synthesis of symmetric terpenes, such as the preparation of advanced key-intermediates in the syntheses of (+)-cymbodiacetal (**3**)²⁰ and dimeric *ent*-kauranoids (**4**), such as xindongnin M (**4a**),²¹ and an improved synthetic way to prepare squalene (**5**) (Figure 1).

Results and Discussion

The development of these synthetic methods began with the use of geranyl bromide (**6**) and its geometric stereoisomer neryl bromide (**7**).^{19a} The treatment of **6** and **7** in THF with an excess of Cp₂TiCl led rapidly to the formation of the homocoupling products being the αα' coupling (**8** and **9**) (Figure 2). Digeranyl and isodigeranyl, regioisomers derived from the coupling of **6** (obtained with 57% and 32%, respectively), are naturally occurring terpenes found in the commercially available bergamot oil.²²

According to these results, we surmised that the process may well begin with a fast single-electron transfer (SET) from Cp₂-

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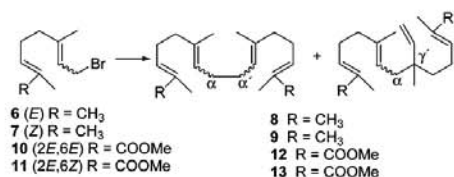


FIGURE 2. Coupling of allylic bromides using Cp₂TiCl₂/Mn.

TiCl (generated in situ) to the corresponding halogenated derivative to give an allylic radical species (I). This would then either dimerize to give the coupling products or suffer a second SET process to give an allyltitanium species (II), which would react with a molecule of unaltered halogenated derivative to also produce the coupling products (Scheme 1).

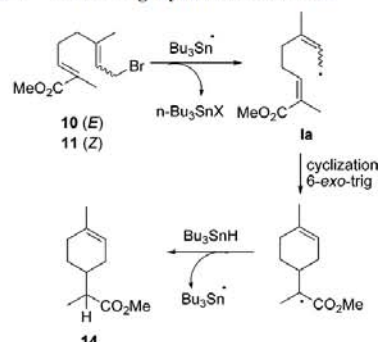
To provide more data about the mechanistic aspects of this coupling, we carried out the reaction with the compounds **10** and **11**, in which the α,β -unsaturated methyl ester group ought to favor the radical cyclization process.²³ The treatment of **10** and **11** with Ti^{III} produced similar results to those obtained with **6** and **7**, and the homocoupling products **12** and **13** were obtained in yields of 84% and 60%, respectively, and no cyclization products were observed. On the other hand, when **10** and its geometric stereoisomer **11** were treated with *n*-Bu₃SnH/AIBN in benzene at 80 °C under free-radical-forming conditions, the corresponding cyclization product, methyl 1-*p*-menthen-9-oate (**14**),²⁴ was formed via a 6-*exo*-trig process involving allylic radical **Ia** (Scheme 2). In both cases the cyclization yields were about 70%, together with a 10% yield of coupling products. Thus, the tendency of **Ia** to cyclize rather than to dimerize seems to confirm the involvement of an allyltitanium species in the formation of the coupling compounds. Additionally, this process constitutes an efficient and new mild method for the biomimetic preparation of *p*-menthanes starting from geraniol or nerol.

Once we had established the presence of the allyltitanium species as intermediates in this reaction and bearing in mind that in this double SET process Cp₂TiClBr is released, we anticipated that the excess of Mn in the medium ought to permit the regeneration of Ti^{III} from Cp₂TiClBr and thus render the process susceptible to catalysis by titanium. Gratifyingly, when **6** was made to react with 0.4 equiv of Cp₂TiCl₂ and an excess of Mn, the hoped-for conversion took place efficiently, producing 88% coupling products **8**. To our knowledge this protocol constitutes the only catalytic process involving the reduction of allylic halides.

To find out the extent to which the quantity of Ti^{III} could be reduced in this catalytic process, we made several assays lowering the proportion of Cp₂TiCl₂ used and deduced that the minimum quantity necessary for the reaction to take place was 0.2 equiv. Experiments made with lesser quantities of Ti^{III} invariably showed the presence of unaltered starting material even after prolonged reaction times.

To widen the scope of this catalytic procedure, apart from the previously reported allylic terpenic halides **6**, **7**, **10**, **11**, and **21**,^{19a} other structurally varied allylic bromides such as **15**, **17**, **19**, and **23** and the secondary chloro derivative **25** (which is

SCHEME 2. 6-*Exo*-Trig Cyclization Reaction



easily obtained by regioselective chlorination of β -pinene)²⁵ were made to react with only 0.2 equiv of Cp₂TiCl₂ and an excess of Mn. It was then found that these reactions took place rapidly (5–15 min) to form the hoped-for coupling products (**8**, **9**, **12**, **13**, **16**, **18**, **20**, **22**, and **24**) (Table 1, entries 1, 2, 4–11), with acceptable selectivity and yields ranging from good to excellent (64–98%). The results obtained with compound **19** deserve special consideration. In this case, the starting material was recovered after 23 h of reaction (Table 1, entry 3). Nevertheless, when the concentration of the coupling reaction of **19** was increased from 0.07 to 0.8 M, 85% of the coupling products **20** was yielded in only 5 min (Table 1, entry 4). The need for a higher concentration in this case compared with the rest of the allylic halides studied may be attributed to the greater stability of the intermediate radical. This concentration effect may suggest that compounds **20** are formed by radical dimerization.

The results shown in Table 1 allowed us to extend the catalytic coupling reaction to different structures deriving from allylic halides and are in accordance with the proposed absence of radicals during the coupling process, given that under these catalytic conditions the concentration of radical **I** (Scheme 1) would be much lower and the probability of coupling would fall significantly versus the much more favorable cyclization process (Table 1, entries 5–9).

Once we had established the catalytic process, we began to study the possibility of further decreasing the quantities of Cp₂TiCl₂ and Mn by using electrophilic salts such as 2,4,6-collidine hydrochloride and LiCl (Table 2).

With allylic bromide **10** as the starting material, we reduced the initial quantity of Cp₂TiCl₂ to 0.1 equiv, obtaining 31% of homocoupling products and recovering 27% of **10** after 90 min (Table 2, entry 2). When using 0.05 equiv of Ti^{III} and 1.5 equiv of Mn, no reaction took place and the starting material was recovered after 90 min (Table 2, entry 3). Nevertheless, when 2,4,6-collidine hydrochloride (2.5 equiv) was added to the reaction medium, the homocoupling of **10** or **11** completed in 20 min (Table 2, entries 4 and 5), although the corresponding reduction product was formed to some extent (12%). If 2,4,6-collidine hydrochloride is replaced by LiCl (2.5 equiv) (Table 2, entry 6), the hoped-for homocoupling products **12** (38%) were now accompanied by the formation of the trans-halogenated derivative **27** (17%). It is believed that 2,4,6-collidine hydro-

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


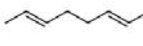
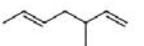



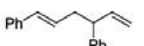
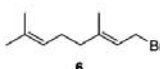
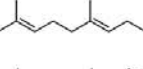
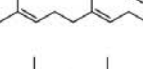
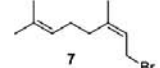
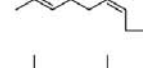
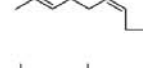
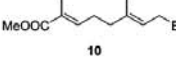
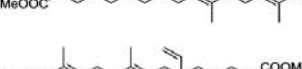

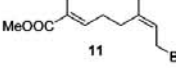


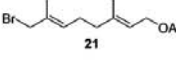
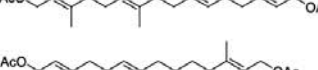
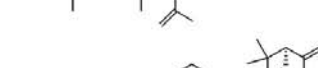

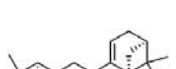
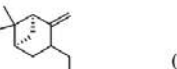

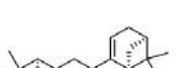
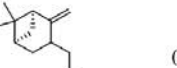
(24) Compound **14** was obtained as a mixture of diastereoisomers at a 1:1 ratio.

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Ti^{III}- and Mn/Zr^{IV}-Catalytic Reductive Coupling

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TABLE I. Coupling of Allylic Halides^a under Catalytic Conditions^b of Ti^{III}

Entry	Allylic Halide	[M] ^c	Compounds	Ratio ^d ($\alpha\alpha'$: $\alpha\gamma'$) ^e	Yield ^f (%)
1		0.07			98 ^g
2		0.07	 	(76:24)	85 ^g
3		0.07	no reaction	–	–
4		0.8	 	(45:55)	85 ^g
5		0.07	 	(64:36)	89
6		0.07	 	(73:27)	90
7		0.07	 	(74:26)	85
8		0.07	 	(81:19)	64
9		0.07	 	(80:20)	76
10		0.07	 	(61:39)	70
11		0.07	 	(52:48)	90

^a Prepared by the reaction of the corresponding alcohols with Ph₃P/CBr₄ in benzene except for the commercially available **6**, **15**, **17**, and **19** and for the secondary chloro derivative **25**, which is easily obtained by regioselective chlorination of β -pinene. ^b 0.2 equiv of Cp₂TiCl₂ and 8.0 equiv of Mn, THF, rt. ^c Molar concentration compared to the starting material. ^d Determined by GC–MS analysis. ^e A certain degree of *E/Z* isomerization was observed. In most cases the different isomers obtained in each coupling process could be isolated either by column chromatography on AgNO₃ (20%)–silica gel or by HPLC. ^f Isolated yield after column chromatography. ^g Determined by GC–MS analysis. ^h This yield includes 15% of the $\gamma\gamma'$ regioisomer.

TABLE 2. Effect of 2,4,6-Collidine Hydrochloride and LiCl on the Reductive Coupling of Allylic Bromides

entry	allylic bromide	equiv of Cp ₂ TiCl ₂	equiv of Mn	concn ^a (M)	time (min)	equiv of LiCl	equiv of 2,4,6-collidine hydrochloride	compd (yield, %)
1	10	0.2	8.0	0.07	10	0	0	12 (85)
2	10	0.1	8.0	0.07	90	0	0	12 (31) ^b
3	10	0.05	1.5	0.07	90	0	0	no reaction
4	10	0.05	1.5	0.07	20	0	2.5	12 (58) ^c
5	11	0.05	1.5	0.07	20	0	2.5	13 (55) ^d
6	10	0.05	1.5	0.07	60	2.5	0	12 (38) ^e

^a Molar concentration of the starting material. ^b 27% of **10** was recovered. ^c A 12% yield of the reduced product was obtained. ^d A 12% yield of the reduced product was obtained. ^e A 17% yield of the trans-halogenated compound **27** was also obtained.

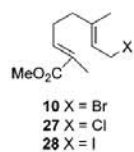
TABLE 3. Coupling of Allylic Bromides under Catalytic Conditions of Zr^{IV}

entry	allylic halide	Cp ₂ ZrCl ₂	concn ^a (M)	time	coupling products	ratio ^b (αα'/αγ')	yield ^c (%)
1	23	0.2	0.07	28 h	no reaction		
2	23	0.2	0.8	21 h	24		35 ^d
3	23	0.3	0.8	10 min	24	70:30	65
4	6	0.3	0.8	20 min	8	81:19	84
5	19	0.3	0.8	30 min	20	48:52	82 ^e
6	10	0.3	0.8	20 min	12	82:18	78
7	25	0.3	0.8	24 h	no reaction		

^a Molar concentration compared to the starting material. ^b Determined by GC–MS analysis. ^c Isolated yield after column chromatography. ^d Even after 21 h, 32% of starting material **23** was recovered. ^e This yield includes 14% of the γγ' regioisomer.

chloride or LiCl establish a Lewis acid–base interaction with the allylic bromide, which facilitates its reduction and subsequent coupling. Thus we conclude that the quantity of Cp₂TiCl₂ and Mn used in the standard protocol (3.0 and 8.0 equiv, respectively) can be considerably reduced to 0.05 equiv of Cp₂TiCl₂ and 1.5 equiv of Mn with no significant loss of efficiency in the process.

Another factor that has been analyzed during this work is the influence of the type of C–X bond (X = Cl, Br, I) upon the coupling reactions. As expected, the main difference observed was the lesser reactivity of the chloro derivative, **27**, compared to the bromo and iodo derivatives, **10** and **28**. Thus, while with **10** and **28** the coupling reaction completed in 10 and 5 min with yields of 85% and 84%, **27** generated 57% coupling products **12** in 75 min, with 10% of the starting material being recovered. The differences in reactivity found can be attributed to the different speeds at which radical **I** was formed due to the different dissociation energies of the C–X.²⁶



We then turned our attention to the behavior of the Zr^{III} species analogous to those of Ti^{III}. Bearing in mind both the antecedents of Zr^{III} chemistry and the similar electronic structure of Zr and Ti, we presumed that the Zr^{III} species could also affect the homocoupling of allylic halides. We began this study by making myrtenyl bromide (**23**) react under the standard catalytic conditions used with Ti^{III}, namely, 0.2 equiv of Cp₂ZrCl₂, 8 equiv of Mn, and THF (0.07 M). After 28 h, no coupling product was formed and **23** was recovered unaltered (Table 3, entry 1).

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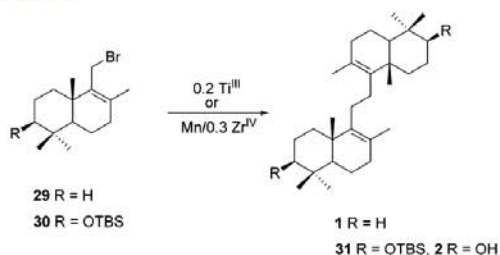
Nevertheless, an increase to 0.8 M in the concentration of the starting material led to a 35% yield of the coupling products **24** with 32% of the starting material being recovered (Table 3, entry 2). However, although it has been reported that THF solutions of Cp₂ZrCl are deep red,^{16b,17} in our case, the combination of Cp₂ZrCl₂ and Mn in THF remained colorless, which suggests that Zr^{III} species were not originated. Thus, with the aim of gaining an insight into the real active species in this process, we proceeded to reduce Cp₂ZrCl₂ with Na(Hg) amalgam^{16b} to obtain a deep red solution, thus confirming the presence of Zr^{III} species. Addition of myrtenyl bromide to this Zr^{III} solution did not lead to any coupling adduct in our hands. Considering that Mn itself is not able to reduce allylically halogenated derivatives, an activation of the C–X bond by Cp₂ZrCl₂ (acting as an efficient Lewis acid) is proposed as the preliminary step to trigger this Cp₂ZrCl₂/Mn-mediated transformation.²⁷ The thus-activated C–X bond is now susceptible to be reduced by Mn to give the corresponding organomanganese derivatives (species represented in Scheme 1 by **II** with M now being Mn).

Additionally, we found that the yield of this process could be further improved when the reaction was carried out at the same molar concentration but increasing the quantity of Zr^{IV} from 0.2 to 0.3 equiv (Table 3, entry 3). In this case, the conversion is total, and **23** gave rise to the corresponding coupling products **24** after only 10 min with a 65% yield. ¹H NMR and GC–MS analyses of the coupling adducts showed a distribution of regioisomers 70:30 favoring the αα' regioisomer. When these data were compared to those obtained with Ti^{III} (Table 1, entry 10), a noticeable increase of the reaction regioselectivity was observed when the combination Mn/Zr^{IV} catalyst was used, while the efficiency of the coupling showed

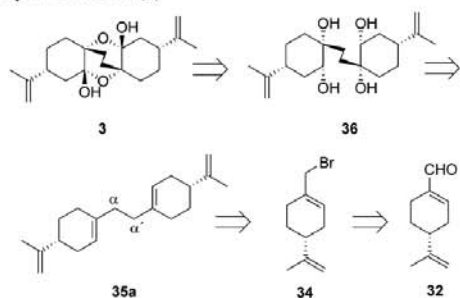
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Ti^{III} - and Mn/Zr^{IV} -Catalytic Reductive Coupling

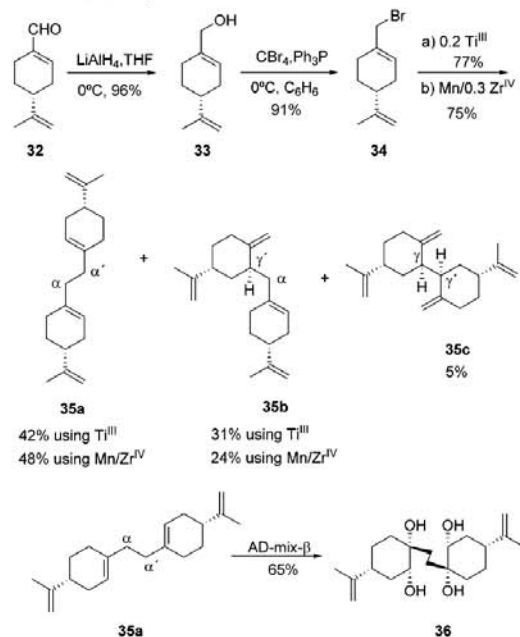
SCHEME 3



SCHEME 4. Approach to the Synthesis of (+)-Cymbodiactal (3)



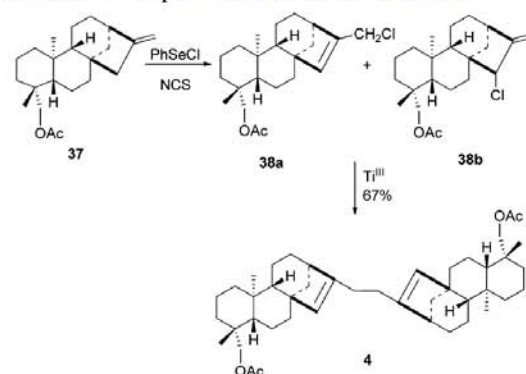
SCHEME 5. Homocoupling Reaction of (*R*)-Perillyl Bromide (34): Synthesis of the Advanced Intermediate 36



no substantial alteration. Similar results were found when either geranyl bromide (6) (Table 3, entry 4) or cinnamyl bromide (19) (Table 3, entry 5) was treated with 0.3 equiv of Zr^{IV} , which seems to confirm the increase of regioselectivity derived from the use of this reagent in all cases. Furthermore, a thorough analysis of the 1H NMR and GC-MS of the homocoupling products now showed an almost complete geometric purity of the $\alpha\alpha'$ and $\alpha\alpha'$ adducts, thus improving significantly the results

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SCHEME 6. Preparation of Dimeric *ent*-Kauranoids



obtained with Ti^{III} . In fact, when geranyl bromide was used as the substrate, the 6:1 ratio of (6*E*, 10*E*) and (6*Z*, 10*E*) $\alpha\alpha'$ isomers obtained with Ti^{III} improved by up to 50:1 when Zr^{IV}/Mn mediated the coupling process. This seems to indicate that geometric isomerization (trans to cis) of the allylic manganese should be kept to a minimum during the coupling conditions, which makes this process particularly advantageous. Finally, as happened to be with the Ti^{III} -mediated reactions of allylic bromides 6 and 10, when these compounds were exposed to the combination Mn/Zr^{IV} catalyst, only the corresponding homocoupling products were obtained (Table 3, entries 4 and 6). The absence of cyclization adducts seems to confirm again that these homocoupling processes should proceed via allylic manganese rather than via radical dimerization (Scheme 1).

When the secondary allylic chloride 25 was treated under these catalytic procedure conditions, the homocoupling products 24 were not formed and the starting material was recovered unaltered even after prolonged reaction times (Table 3, entry 7). When 25 was exposed to catalytic Ti^{III} , a 90% yield of homocoupling products 24 was obtained in only 5 min (Table 1, entry 11).

Although we have already reported the synthesis of (+)- β -onoceradiene (1) and (+)- β -onocerine (2) via Ti^{III} -induced homocoupling of key intermediates 29 and 30,^{19a} we considered that these homocoupling products could also be achieved using Mn and catalytic Cp_2ZrCl_2 , which would also allow the utility of this method to be tested. Thus, when 29 and 30 were treated using the combination Mn/Zr^{IV} catalyst, (+)- β -onoceradiene and (+)- β -onocerine were obtained in comparable yields to those obtained with Ti^{III} (Scheme 3).

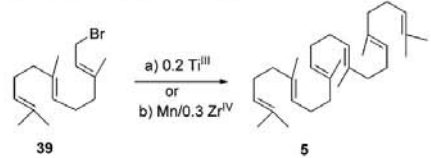
We present here new applications of these catalytic homocoupling protocols, such as the preparation of compound 36, an advanced key-intermediate in the enantioselective synthesis of (+)-cymbodiactal (3) (Scheme 5), and the straightforward access to the framework of naturally occurring dimeric *ent*-kauranoids 4 (Scheme 6).

(+)-Cymbodiactal (3) is a dihemiacetal bis-monoterpenoid isolated from the essential oil of *Cymbopogon martini*.²⁰ Several varieties of this plant are cultivated for use in soaps and perfumes. The enantioselective synthesis of (+)-cymbodiactal (3) was designed starting from (*R*)-perillyl aldehyde (32) (Scheme 4). The key step of this strategy rests on the homocoupling reaction of (*R*)-perillyl bromide (34) catalyzed by Ti^{III} or Zr^{IV} to obtain the key intermediate 7,7'-bis((4*R*)-1,8-*p*-menthadiene) (35a).

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TABLE 4. Synthesis of Squalene (5)



entry	allylic bromide ^a	Ti ^{III}	Zr ^{IV}	concn (M)	time (min)	coupling products yield (%)	squalene yield (%)
1	39	0.2	0	0.07	10	63	43
2	39	0	0.3	0.8	60	62	51

^a Prepared by reaction of *trans,trans*-farnesol with Ph₃P/CBr₄ in C₆H₆.

Allylic bromide **34** was obtained by reduction of commercially available (*R*)-perillyl aldehyde (**32**) with LiAlH₄/THF and subsequent bromination with CBr₄/Ph₃P. (*R*)-Perillyl bromide (**34**) in the presence of 0.2 equiv of Ti^{III} or 0.3 equiv of Zr^{IV} underwent the expected homocoupling reaction to give 77% and 75%, respectively, of the corresponding coupling adducts, with the $\alpha\alpha'$ regioisomer **35a** being the major reaction product (Scheme 5). Moving forward with the synthetic planning, we found that compound **35a** could be chemo- and stereoselectively hydroxylated to efficiently lead to tetrol **36** as the only detectable stereoisomer using AD-mix- β ,²⁸ as evidenced by the NOE effect observed between H2 and H4, both protons in an axial disposition in the most stable chair conformation of the cyclohexane ring in **36**. Even though preliminary dihemiacetal formation assays (PDC and Dess–Martin oxidations) were disappointing in that they furnished unacceptably low yields (approximately 5%) of the desired natural product **3**, the four-step sequence illustrated above for the preparation of **36** appears sufficiently promising to warrant completion of the synthesis.

Recently, the isolation of bioactive dimeric *ent*-kauranoids, such as xindongnins M–O,²¹ lushanrubescensin J,²⁹ and bis-rubescensins A–C³⁰ from different species of *Isodon rubescens*, called our attention. It was then envisioned that the dimeric framework of these structures could be easily constructed via the Ti^{III}- or Zr^{IV}/Mn-mediated homocoupling of the corresponding allylic halides (Scheme 6). We chose as the starting material *ent*-kaur-16-en-19-ol isolated from *Odontites longiflora*.³¹ When its acetate derivative **37** was treated with PhSeCl and NCS,²⁵ the mixture of allylic chlorides **38** was obtained. When this mixture was exposed to catalytic Ti^{III}, we found the octacyclic structure **4**, although unreacted starting material **38** remained unaltered even after prolonged reaction times. It was nevertheless found that when 1.1 equiv of Cp₂TiCl was used, the reaction was completed after only 5 min and a 67% yield of dimer **4** was obtained.

Finally, we previously reported that squalene (**5**) can be prepared from *trans,trans*-farnesyl bromide (**39**) using 0.2 equiv of Ti^{III} in only one step in 43% yield (Table 4, entry 1). Bearing

in mind the higher degree of regioselectivity and geometric purity of the Mn/Zr-mediated couplings, we hoped that this yield could be improved using these metals. Gratifyingly, the exposure of **39** to 0.3 equiv of Zr^{IV} and 8 equiv of Mn led to a 51% yield of squalene (Table 4, entry 2). In fact, the ¹H NMR and GC–MS analyses of the coupling products in both cases showed that the 66:22:12 ratio of $\alpha\alpha'$ (*EE*)/ $\alpha\alpha'$ (*ZE*)/ $\alpha\gamma'$ (*E*) regioisomers obtained with Ti^{III} improved considerably in the Zr^{IV}-mediated process, where no *E/Z* isomerization was noticed and a 82:18 ratio of $\alpha\alpha'$ (*EE*)/ $\alpha\gamma'$ (*E*) regioisomers was obtained. This catalytic process probably constitutes one of the easiest and most efficient synthetic ways to prepare squalene.

Conclusion

In conclusion, we present new catalytic methods for the homocoupling of allylic halides mediated either by Ti^{III} or by Mn/Zr^{IV} species with good to excellent yields. Thus, on the one hand, the range of applicability of the previously published Cp₂-TiCl-protocol coupling has been widened with the successful homocoupling of a number of allylic halides. Furthermore, it was found that the use of Lewis acids such as 2,4,6-collidine hydrochloride allows for the lowering of the quantity of Ti^{III} up to 0.05 equiv. On the other hand, the results obtained in the use of the combination Mn and Cp₂ZrCl₂ catalyst are presented. Both methods are very mild and should tolerate most functional groups. It is noteworthy that the regioselectivity of the process increases significantly when the combination Mn/Zr^{IV} catalyst is used as the reagent and when cyclic substituted allylic halides are used as substrates. These reagents have been employed in the efficient synthesis of symmetric terpenes, such as the onocerane derivatives (**1** and **2**), the preparation of an advanced key-intermediate in the enantioselective synthesis of (+)-cymbodiacetal (**3**), the framework of dimeric *ent*-kauranoids (**4**), and the synthesis of squalene (**5**).

Experimental Section

Homocoupling Reactions. Catalytic Protocol with Ti^{III}. A mixture of Cp₂TiCl₂ (190 mg, 0.74 mmol) and Mn dust (1620 mg, 29.44 mmol) in thoroughly deoxygenated THF (50 mL) and under Ar atmosphere was stirred at rt until the red solution turned green. The corresponding allylic halide (3.68 mmol) in strictly deoxygenated THF (1 mL) was then added to the Cp₂TiCl solution. The reaction mixture was stirred for 15 min, quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel to afford the corresponding coupling products.

Representative Example. (*R*)-Perillyl bromide (**34**) (2644 mg, 12.3 mmol) was subjected to the Ti^{III} catalytic procedure conditions (631 mg, 2.46 mmol of Cp₂TiCl₂ and 5412 mg, 98.4 mmol of Mn), and the resulting crude product was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 50:1) to afford 1275 mg (77% yield) of a mixture of the corresponding coupling products **35** ($\alpha\alpha'$ ($\alpha\gamma'$ + $\gamma\gamma'$) at a 54:46 ratio). The corresponding mixture was subjected to flash column chromatography on AgNO₃ (20%)–silica gel (hexane/*t*-BuOMe, 99:1), and two fractions were obtained, the first containing the $\alpha\alpha'$ coupling product 7,7'-bis((4*R*)-1,8-*p*-menthadiene) (**35a**) and the second containing the $\alpha\gamma'$ coupling product (4*R*)-7-((2*R*,4*R*)-1(7),8-*p*-menthadien-2-yl)-1,8-*p*-menthadiene (**35b**). Finally, *t*-BuOMe was added and the $\gamma\gamma'$ coupling product (**35c**) could be isolated.

Catalytic Protocol with Zr^{IV}. A mixture of Cp₂ZrCl₂ (462 mg, 1.58 mmol) and Mn dust (2323 mg, 42.20 mmol) in deoxygenated THF (9 mL) and under Ar atmosphere was stirred at rt. The

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corresponding allylic bromide (5.28 mmol) in strictly deoxygenated THF (1 mL) was then added (TLC monitoring). The reaction mixture was quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel to afford the corresponding coupling products **35**.

Representative Example. (*R*)-Perillyl bromide (**34**) (240 mg, 0.95 mmol) was subjected to the Zr^{IV}/Mn catalytic procedure conditions (56 mg, 0.19 mmol of Cp₂ZrCl₂ and 421 mg, 7.67 mmol of Mn), and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 50:1) to afford 192 mg (75% yield) of a mixture of the corresponding coupling products **35** ($\alpha\alpha'$ ($\alpha\gamma'$ + $\gamma\gamma'$)) at a 63:37 ratio).

7,7'-Bis((4*R*)-1,8-*p*-menthadiene) (35a). [α]_D +75.9 (*c* 2.65, CH₂Cl₂); ν (film) 3080, 2962, 2921, 2854, 1644, 1455, 1436, 1373, 886 cm⁻¹; δ _H (400 MHz, CDCl₃) 1.48 (2H, ddd, *J* = 5.6, 11.3, 17.1 Hz), 1.75 (6H, s), 1.80–1.85 (2H, m), 1.87–2.15 (10H, m), 2.06 (4H, bs), 4.73 (4H, bs), 5.43 (2H, bs) ppm; δ _C (100 MHz, CDCl₃) 20.9, 28.0, 29.0, 30.9, 36.1, 41.3, 108.5, 120.3, 137.6, 150.3 ppm; EIMS (70 eV) *m/z* (relative intensity) 270 (15), 227 (35), 187 (22), 159 (18), 145 (32), 134 (25), 119 (55), 105 (61), 93 (95), 91 (100), 79 (73), 67 (42), 44 (45).

7,7'-Bis(1(*R*),2(*R*)-dihydroxy-8-*p*-menthene) (36). 7,7'-Bis-((4*R*)-1,8-*p*-menthadiene) (**35a**) (285 mg, 1.06 mmol) was added to a solution of AD-mix- β (2968 mg) and CH₃SO₂NH₂ (207 mg, 2.11 mmol) in *t*-BuOH/H₂O 1:1 (10 mL) at 0 °C and stirred. After 7 h, Na₂S₂O₃ (2385 mg) was added to the reaction mixture while stirring for 10–20 min was continued at rt. The *t*-BuOH was removed and extracted with EtOAc. The organic phase was washed with 6 N NaOH (3 \times 100 mL) and brine, then dried over anhydrous Na₂SO₄, and concentrated under reduced pressure, with the crude product thus obtained being purified by column chromatography on silica gel (*t*-BuOMe) to give **36** (230 mg, 65%). [α]_D +9.96 (*c* 0.5, MeOH); ν (film) 3399, 3327, 2941, 2916, 2854, 1642, 1441, 1261, 1161, 1062, 880, 749 cm⁻¹; δ _H (400 MHz, DMSO) 1.10–1.65 (16H, m), 1.66 (6H, s), 1.80–1.90 (2H, m), 3.20 (2H, m), 4.22 (2H, d, *J* = 6.7 Hz), 4.63 (2H, s), 4.64 (2H, s) ppm; δ _C (100 MHz, DMSO) 20.7, 25.7, 32.3, 33.5, 35.3, 43.2, 71.6, 72.9, 108.4, 149.5 ppm; HRFABMS calcd for C₂₀H₃₄O₄Na [M + Na]⁺ 361.2355, found 361.2354.

17,17'-Bis(19-acetoxy-*ent*-isokaurene) (4). A mixture of Cp₂-TiCl₂ (37 mg, 0.14 mmol) and Mn dust (53 mg, 0.96 mmol) in strictly deoxygenated THF (1 mL) was stirred at room temperature until the red solution turned green. Then **38a** and **38b** (46 mg, 0.12

mmol) in strictly deoxygenated THF (1 mL) were added to the solution of Cp₂TiCl₂. The reaction mixture was stirred for 5 min, quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 20:1) to afford a 67% yield of the coupling product **4**. [α]_D -42.0 (*c* 1.0, CH₂Cl₂); ν (film) 2926, 2865, 1739, 1456, 1371, 1238, 1031 cm⁻¹; δ _H (400 MHz, CDCl₃) 0.94 (6H, s), 1.04 (6H, s), 1.20–1.90 (36H, m), 2.04 (6H, s), 2.20 (4H, s), 2.39 (2H, bs), 3.87 (1H, d, *J* = 11.0 Hz), 4.22 (2H, d, *J* = 11.0 Hz), 5.07 (2H, bs) ppm; δ _C (100 MHz, CDCl₃) 18.3, 18.5, 19.1, 19.7, 21.3, 25.8, 27.7, 28.1, 36.6, 37.3, 39.6, 40.2, 40.7, 43.8, 44.0, 49.1, 49.3, 56.8, 67.4, 134.3, 147.0, 171.6 ppm; HRFABMS calcd for C₄₄H₆₆O₄ [M + Na]⁺ 681.4859, found 681.4857.

Procedure for Radical Cyclization Reaction of 10 and 11. A solution of tributyltin hydride (228 mg, 0.76 mmol) and AIBN (7 mg, 0.04 mmol) in dry, degassed benzene (14 mL) was added dropwise (10 mL/h) to a solution of the bromide (**10** or **11**) (100 mg, 0.38 mmol) in dry, degassed benzene (136 mL) heated to 80 °C under an atmosphere of argon. After the addition time plus an additional hour (TLC monitoring), the cooled mixture was evaporated under reduced pressure, and the residue was dissolved in diethyl ether. An aqueous saturated KF solution (5 mL) was added, and the mixture was stirred for 2 h at rt. After filtration through Celite, the biphasic filtrate was extracted with diethyl ether. The aqueous layer was extracted with diethyl ether after separation. The combined organic extracts were concentrated under reduced pressure, and the crude product was purified by column chromatography (petroleum ether/diethyl ether, 20:1) on silica gel to afford 50 mg (72%) of the cyclized compound methyl 1-*p*-menthen-9-oate (**14**).

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Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ¹H and ¹³C NMR spectra of **4**, **8b**, **14**, **20a**, **20b**, **23**, **24**, **25**, **27**, **34**, **35a–c**, **36**, **38a**, and **39**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Artículo 2:

*Couplings of Benzylic Halides Mediated by Titanocene
Chloride: Synthesis of Bibenzyl Derivatives.*

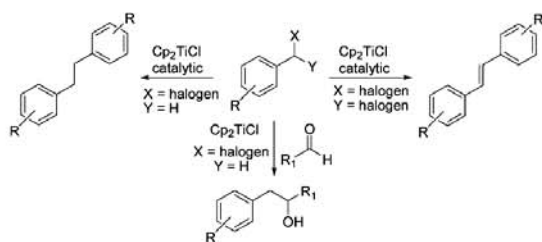
Journal of Organic Chemistry **2006**, 72, 2251-2254.

JOC Note

Couplings of Benzylic Halides Mediated
by Titanocene Chloride: Synthesis
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Titanocene monochloride catalyzes the homocoupling of benzylic halides and benzylic *gem*-dibromides to give the corresponding bibenzyl and stilbenyl systems. Exposure of benzylic bromides to Ti(III) in the presence of aldehydes gave rise to the Barbier-type products. Examples of the utility of the herein described processes are included.

Compounds containing the bibenzyl moiety as the core of their structure constitute an interesting group of molecules. These molecules have been used as key intermediates both for the synthesis of dyes, paints, and resins, and for the preparation of a number of natural products as stilbenyl or bibenzyl derivatives. A number of biologically important compounds such as the well-known resveratrol and derivatives,¹ combretastatins² and isocombretastatins,³ or lunularic acid⁴ are included among this group of compounds.

Different methods have already been developed to achieve the synthesis of compounds of this type, among them, the homocoupling of benzylic halides mediated mostly by equi-

molecular quantities of reducing systems such as Ni,⁵ Mg,⁶ In,⁷ Mn/CuCl₂,⁸ Zn/Cu,⁹ SmI₂,¹⁰ CrCl₂,¹¹ Ti(III)citrate/vitamin B₁₂ cat.,¹² and salts and carbonyl complexes of Ni, Mn, or Fe.¹³ The Pd/C-catalyzed¹⁴ coupling of benzylic chloride, 1-(dichloromethyl)-, and 1-(trichloromethyl)benzene leading to the corresponding bibenzyl systems with uneven yields has also been described. McMurry coupling reaction of different benzaldehydes was used to synthesize a series of stilbenoids.¹⁵ There has also been a very recent description of the stereoselective synthesis of hydroxystilbenoids by ruthenium-catalyzed cross-metathesis.¹⁶ One precedent of the reaction of benzylic and allylic halides using equimolecular quantities of Ti(III) to give the corresponding homocoupling products has been reported by Yanlong et al.¹⁷ Heterocoupling of benzylic halides with benzaldehyde or derivatives has also been reported to be achieved using conventional methods such as Wittig synthesis,¹⁸ condensation via sulfones,¹⁹ and either SmI₂,¹⁰ CrCl₂,¹¹ or Mn-mediated²⁰ carbon-carbon bond forming processes, among others.

As a result of our research into the use of Cp₂TiCl in the synthesis of bioactive natural products, we have recently developed novel processes of homocoupling of allylic halides²¹ and vinyl epoxides catalyzed by titanocene chloride.²² Subsequently, we wanted to explore the feasibility of accomplishing Ti(III)-mediated homo- and heterocoupling of benzylic halides. Thus, considering the mechanism proposed for the reaction with allylic halides and vinyl epoxides, we surmised that titanocene could well intervene efficiently in the homocoupling of benzylic halides (Scheme 1). Following this mechanistical proposal,

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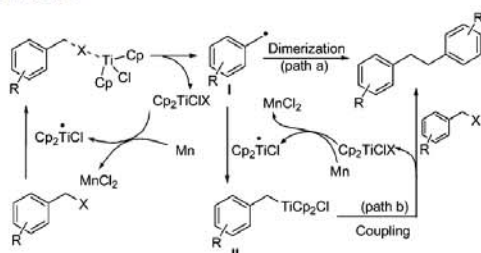
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JOC Note

SCHEME 1



Cp₂TiClX should be released after a SET process; consequently, the excess of Mn present in the medium should permit the regeneration of Ti(III), and thus the process would be susceptible to catalysis by titanium. In this sense, voltammetric and kinetic analyses of the nature of reducing species in titanocene halide-promoted reactions carried out by Skrydstrup and Daasbjerg suggest path b as the most likely process taking place in this coupling reaction.²³

We started our study by making benzyl bromide (**1a**) react with 0.2 equiv of Cp₂TiCl₂ and 8.0 equiv of Mn in dry and deoxygenated THF (*c* 0.07 M)—conditions which had been previously reported to promote homocoupling reactions of allylic bromides in short reaction times (10–20 min).²¹ Under these conditions, the reaction was completed after 8 h, and bibenzyl (**2a**) was obtained in a 73% yield (Table 1, entry 1). The marked lesser reactivity of **1a** when compared to that of allylic bromides could be attributed to the higher stability of the intermediate benzylic radical (**I**, Scheme 1). When the molar concentration of **1a** was increased around 10 times (*c* 0.8 M), a remarkable increase of the reaction rate was noticed (Table 1, entry 2). Furthermore, whereas no reaction was detected after 24 h when benzyl chloride (**1b**) was forced to react under diluted conditions (Table 1, entry 3), a 52% yield of bibenzyl (**2a**) was obtained when the concentration was increased up to 0.8 M (Table 1, entry 4). Additionally, 2-(bromomethyl)naphthalene (**3**) behaved similarly, and a 60% yield of 1,2-bis(naphthyl)ethane (**4a**) was obtained when the concentration used was 0.07 M (Table 1, entry 5).

With the aim of widening the scope of this reaction, the influence of different oxygenated substituents on the aromatic ring was then tested. Thus, the presence of an electron-donating substituent as the methoxy group in *para* position to the bromomethyl moiety made the corresponding methoxybenzyl derivative **5** react within a few minutes to afford **6a** in a 77% yield (Table 1, entry 6). On the other hand, an electron-withdrawing substituent as the carboxymethyl group slowed down the homocoupling process (57%) (Table 1, entry 7), and more concentrated experimental conditions (*c* 0.8 M) were needed to reach satisfactory results (72%) (Table 1, entry 8). Furthermore, good yields were also detected when two or three methoxy groups were present in the starting benzylic bromide (Table 1, entries 9–12). The formation of **12a**, a dimer isolated from *Frullania brittoniae* spp. *Truncatifolia*²⁴ and comprised in a patented antitumoral composition, constituted a direct synthetic application of this process.

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TABLE 1. Homocoupling Reactions of Benzylic Bromides Mediated by Ti(III)

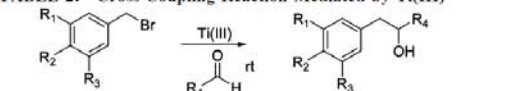
Chemical structures of benzylic bromides **1a** through **12a** and their corresponding homocoupling products **2a** and **2b**. The structures show various substituents R₁, R₂, and R₃ on the aromatic ring.


entry	benzylic halide	<i>c</i> (M)	time	compounds (yield) ^d
1	1a	0.07	8 h	2a (73%)
2	1a	0.8	2 h	2a (74%)
3	1b	0.07	24 h	
4	1b	0.8	8 h	2a (52%) ^b
5	3	0.07	20 h	4a (60%)
6	5	0.07	5 min	6a (77%)
7	7	0.07	7 h	8a (57%) ^c
8	7	0.8	30 min	8a (72%)
9	9	0.07	75 min	10a (74%)
10	9	0.8	35 min	10a (70%)
11	11	0.07	8 h	12a (40%) ^d
12	11	0.8	35 min	12a (70%)
13 ^e	1a	0.07	25 min	2a (12%) + 2b (85%) ^f
14 ^e	1a	0.07	20 min	2a (3%) + 2b (89%) ^f
15 ^e	9	0.07	15 min	10a (15%) + 10b (83%)

^a Isolated yield after column chromatography. ^b A 30% yield of starting material was recovered. ^c A 23% yield of starting material was recovered. ^d A 37% yield of starting material was recovered. ^e Conditions: 1.0 equiv of Cp₂TiCl₂, 8.0 equiv of Mn, 5.0 equiv of 1,4-cyclohexadiene, THF, rt. ^f Calculated by NMR. ^g Conditions: 1.0 equiv of Cp₂TiCl₂, 8.0 equiv of Mn, 5.0 equiv of *t*-BuSH, THF, rt.

To gain an insight into the mechanism of this process, benzyl bromide (**1a**) was treated with 1.0 equiv of Ti(III) in the presence of radical reductors such as 1,4-cyclohexadiene or *t*-BuSH (5.0 equiv). In the event, the main product of both reactions was toluene (**2b**), while only minor amounts of bibenzyl (**2a**) were detected (Table 1, entries 13 and 14). This seems to denote that the initially formed benzylic radical is stable enough to be trapped by a proton donor before evolving to the benzylyltitanium species. This result was confirmed after noticing that, in the reaction of bromide **9** with 1.0 equiv of Ti(III) and 5.0 equiv of 1,4-cyclohexadiene, the corresponding reduction product **10b** was obtained in a 83% yield (Table 1, entry 15). Since in our previous work on Ti(III)-mediated homocoupling of terpenic allylic halides²¹ we postulated that the reacting intermediates were allyltitanium species, we considered that the result of the treatment of allylic halides with titanocene in the presence of hydrogen radical donors would add new evidence to help clarify the mechanistic nature of these two processes. Thus, when geranyl bromide was exposed to 1.0 equiv of Ti(III) in the presence of 5.0 equiv of *t*-BuSH or 1,4-cyclohexadiene, only the corresponding homocoupling product was detected in excellent yields (>90%). It could then be inferred that, in the case of terpenic allylic halides, the rate of reduction of the allylic radical to the allylic titanium is faster than any other collateral process; hence, allyltitanium species are mainly the species involved in the coupling process, while when benzylic halides are considered, the intermediacy of benzylic radicals should not be ruled out.

TABLE 2. Cross-Coupling Reaction Mediated by Ti(III)



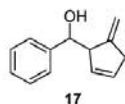
1a R₁ = R₂ = R₃ = H
5 R₁ = H, R₂ = OMe, R₃ = H
9 R₁ = R₂ = OMe, R₃ = H
9 R₁ = R₂ = OMe, R₃ = H
13 R₁ = R₂ = R₃ = H, R₄ = C₆H₅
14 R₁ = H, R₂ = OMe, R₃ = H, R₄ = C₆H₅
15 R₁ = R₂ = OMe, R₃ = H, R₄ = C₆H₅
16 R₁ = R₂ = OMe, R₃ = H, R₄ = 

entry	benzylic halide	time	compounds (yield) ^a
1 ^b	1a	3 h	13 (38%) + 2a (5%)
2 ^c	1a	5 min	13 (35%) + 2a (24%)
3 ^d	1a	10 min	13 (57%) + 2a (15%)
4 ^d	5	5 min	14 (50%) + 6a (15%) + 17 (19%)
5 ^d	9	10 min	15 (58%) + 17 (20%)
6 ^d	9	15 min	16 (60%)

^a Isolated yield after column chromatography. ^b Conditions: 0.2 equiv of Cp₂TiCl₂, 8.0 equiv of Mn, 7.0 equiv of collidine, 4.0 equiv of TMSCl, THF, rt. ^c Conditions: 2.0 equiv of Cp₂TiCl₂, 8.0 equiv of Mn, THF, rt. ^d For entries 3–6, 1.0 equiv of Cp₂TiCl₂ was used.

Encouraged by the good yields found in the homo C–C bond forming, we decided then to explore the feasibility of accomplishing crossed C–C bonds between benzylic bromides and aldehydes.

In this sense, there have been recent descriptions of Barbier-type reactions—mostly allylations—mediated by titanocene monochloride using either catalytic quantities²⁵ or 2 equiv of this reagent.²⁶ In our hands, when benzyl bromide (**1a**) was reacted with benzaldehyde using catalytic Ti(III) in the presence of the combination Mn/collidine/TMSCl, the cross-coupling adduct **13** was the main reaction product (Table 2, entry 1). On the other hand, when an excess of Ti(III) (2.0 equiv) was added to **1a** and benzaldehyde, the result was similar (Table 2, entry 2). We focused then our efforts to improve the experimental conditions for this cross-coupling. In the event, the use of only 1 equiv of Ti(III) together with the quick and simultaneous addition of the aldehyde and the corresponding benzyl bromide, as well as the employment of an excess of aldehyde due to its tendency to undergo pinacol coupling reactions in the presence of SET reagents, allowed yields of the Barbier-type adducts ranging from 50 to 60% yield (Table 2, entries 3–6). In entries 4 and 5, apart from the corresponding cross-coupling products, a byproduct possessing structure **17** could also be isolated in 19 and 20% yield, respectively. The formation of **17** seems to indicate an unprecedented transference of a cyclopentadienyl moiety from Cp₂TiCl.

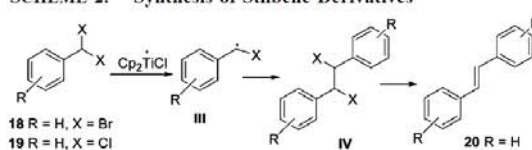
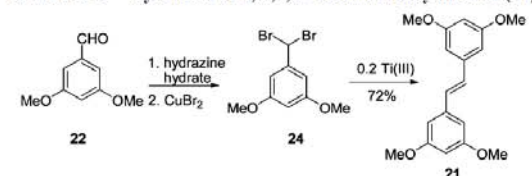


Once we had postulated the intermediacy of radical species in the reaction of benzylic bromides with Ti(III), it was envisioned that stilbene and derivatives could be prepared from the corresponding 1,1-dihalobenzyl derivatives after treatment

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SCHEME 2. Synthesis of Stilbene Derivatives

SCHEME 3. Synthesis of 3,3',5,5'-Tetramethoxystilbene (**21**)

with catalytic quantities of Ti(III) (Scheme 2). Thus, the benzylic radical initially formed (**III**), now further stabilized by the presence of the halogen atom at α , would dimerize to give the 1,2-dihalodibenzyl derivative (**IV**), which could further evolve to give rise to the formation of the corresponding stilbene derivatives via a Ti(III)-mediated reductive dehalogenation.²⁷

Thus, we caused 1,1-dibromobenzyl (**18**) to react with 0.2 equiv of Cp₂TiCl₂ and an excess of Mn (*c* 0.8 M) and found that the reaction took place after 35 min, yielding 74% of *trans*-stilbene (**20**). Under identical experimental conditions, 1,1-dichlorobenzyl (**19**) led after 18 h only to a 32% yield of **20**, with 50% of unaltered starting material being recovered. In our opinion, it deserves to be underlined the ability of catalytic quantities of Ti(III) to promote in an one-pot reaction two chemical transformations, namely, a carbon–carbon bond forming process and the reduction of 1,2-dibromides to the corresponding olefins.

At this juncture, we felt that naturally occurring 3,3',5,5'-tetramethoxystilbene (**21**), isolated from *Centipeda minima*,²⁸ could be efficiently synthesized using this catalytic protocol. Compound **21** is contained in a pharmaceutical composition used in the prevention of carcinogenesis,²⁹ while its tetrahydroxy derivative showed significantly lower IC₅₀ values against COX-2 than clinically established celecoxib.³⁰ This synthesis was designed starting from commercially available 3,5-dimethoxybenzaldehyde (**22**). When this compound was treated with hydrazine hydrate following the conditions described by Takeda et al.,³¹ considerable quantities of the corresponding azine were formed. The reduction of the quantity of hydrazine from 20 to 2.5 equiv led efficiently to the corresponding hydrazone, which was converted into dibromide **24** by reaction with Et₃N/CuBr₂.³¹ Gratifyingly, exposure of **24** to catalytic Ti(III) led to natural product **21** in a 72% yield (Scheme 3).

In summary, the reduction of benzylic halides and benzylic gem-dibromides with Cp₂TiCl resulted in good yields of the

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JOC Note

corresponding bibenzyls and stilbenes. Cp_2TiCl also proved to mediate the heterocoupling reaction of benzylic halides and aldehydes. The synthesis of different bibenzyls and stilbenes illustrates the utility of these processes.

Experimental Section

General Procedure for the Catalytic Homocoupling Reaction of Benzylic Bromides Mediated by Ti(III). A mixture of Cp_2TiCl_2 (190 mg, 0.74 mmol) and Mn dust (1620 mg, 29.44 mmol) in thoroughly deoxygenated THF (50 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. The corresponding benzylic bromide (3.68 mmol) in strictly deoxygenated THF (2 mL, $C_f = 0.07$ M) was then added to the Cp_2TiCl solution (TLC monitoring). Then, THF was removed, and the reaction was quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products (**2a**, **4a**, **6a**, **8a**, **10a**, and **12a**). The same procedure was followed when the molar concentration was 0.8.

General Procedure for the Cross-Coupling Reaction Mediated by Ti(III). A mixture of Cp_2TiCl_2 (333 mg, 1.30 mmol) and Mn dust (572 mg, 10.40 mmol) in thoroughly deoxygenated THF (18 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. Then, the corresponding benzylic bromide (1.30 mmol, 1.0 equiv) and the corresponding aldehyde (2.60 mmol, 2.0 equiv) were added simultaneously to the Cp_2TiCl solution (TLC monitoring). THF was removed, and the reaction mixture was quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding alcohols (**13**, **14**, **15**, **16**, and **17**). In some cases, minor quantities of homocoupling products were obtained. Please see Table 2.

General Procedure for the Catalytic Homocoupling Reaction of Benzylic *gem*-Dihalides Mediated by Ti(III). A mixture of Cp_2TiCl_2 (61 mg, 0.24 mmol) and Mn dust (528 mg, 9.60 mmol) in thoroughly deoxygenated THF (2 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. The corresponding benzylic *gem*-dihalide (1.2 mmol) in strictly deoxygenated THF (1 mL) was then added to the Cp_2TiCl solution (TLC monitoring). Then, THF was removed, and the reaction was quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding stilbene derivatives (**20**, **21**).

Synthesis of 3,3',5,5'-Tetramethoxystilbene (21). 1-(3,5-Dimethoxybenzylidene)hydrazine (**23**): Finely powdered 4 Å molecular sieves (2 g) were placed in a flask under argon atmosphere. MeOH (5 mL) and hydrazine hydrate (160 mg, 5.0 mmol) were added successively. After 20 min, a methanol solution (5 mL) of 3,5-dimethoxybenzaldehyde (**22**) (332 mg, 2.0 mmol) was added dropwise to the reaction mixture for 5 min at room temperature (TLC monitoring). Then, molecular sieves were filtered off and washed with *t*-BuOMe. The solvent was concentrated under reduced pressure at 0 °C to obtain 310 mg of **23**. Compound **23** was directly used in the following reaction without purification.

1-(Dibromomethyl)-3,5-dimethoxybenzene (24): Copper(II) bromide (670 mg, 3.0 mmol) was dissolved in MeOH (6 mL) under argon atmosphere. Then, Et_3N (0.15 mL) was added, and the mixture was stirred for 20 min at room temperature. Then, 1-(3,5-dimethoxybenzylidene)hydrazine (**23**) (180 mg, 1.0 mmol) was added dropwise in 3 mL of MeOH for 5 min at 0 °C (TLC monitoring). After being stirred for 5 min, the reaction was quenched by addition of 3.5% NH_3 aqueous solution, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure to afford **24**: IR (film) 2961, 2936, 2838, 1596, 1461, 1427, 1349, 1323, 1298, 1203, 1158, 1064, 697 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.73 (6H, s), 6.31 (1H, t, $J = 2.2$ Hz), 6.48 (1H, s), 6.62 (1H, d, $J = 2.2$ Hz), 6.63 (1H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 41.0, 55.6 (2C), 101.9, 104.8 (2C), 143.8, 160.7 (2C).

3,3',5,5'-Tetramethoxystilbene (21): According to the general procedure described for the homocoupling of benzylic *gem*-dihalides, the resulting crude was purified by column chromatography using hexane as eluent on silica gel to afford 72% of **21**³² as a colorless solid: Mp 129–130 °C, lit.³² 130–132 °C; ^1H NMR (300 MHz, CDCl_3) δ 3.75 (12H, s), 6.33 (2H, t, $J = 2.3$ Hz), 6.60 (4H, d, $J = 2.3$ Hz), 6.94 (2H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 55.5, 100.3, 104.8, 129.3, 139.3, 161.1.

Acknowledgment. This research was supported by the Spanish Ministry of Science and Technology, Project BQU 2002-03211. Thanks go to Dr. M. J. de la Torre for revising our English text.

Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ^1H and ^{13}C NMR spectra of **2**, **4**–**17**, **20**, **21**, and **24**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO062492P

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Artículo 3:

“Control of the Regio- and Diastereoselectivity on the Radical Cyclization of Acyclic Epoxy-poliprenoids to Cyclopentane Derivatives”

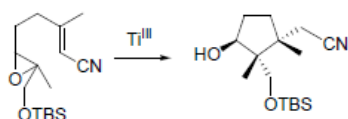
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TET-D-10-01932

Graphical Abstract

**Control of the regio- and diastereoselectivity
on the radical cyclization of acyclic
epoxypolyprenoids to cyclopentane
derivatives**

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Jesús F. Arteaga^b, Horacio R. Diéguez^a, José A. G. Delgado^a, José F. Quílez del Moral^a, Alejandro F. Barrero^a
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Control of the regio- and diastereoselectivity on the radical cyclization of acyclic epoxypropenoids to cyclopentane derivatives

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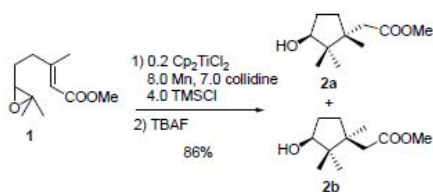
ABSTRACT

The titanocene-mediated cyclization of acyclic epoxypropenes conveniently functionalized leads with high yields and good stereochemical control to functionalized cyclopentanes possessing three contiguous stereogenic centers. These cyclopentanes can be considered as useful intermediates in the synthesis of toxicol A.

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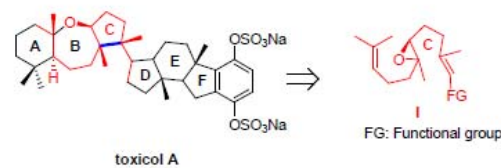
1. Introduction

The titanocene-mediated radical cyclization of acyclic mono-epoxypropenoids is a powerful synthetic tool which permits the construction of rings with different sizes.¹ In contrast to what is reported for cyclizations involving carbocations,² this kind of radical cyclization is employed in cascade processes to originate different-sized rings, after properly modulating the electronic distribution of the double bonds involved. In this regard, a few years ago, our research group reported that the Ti(III)-mediated cyclization of methyl 6,7-epoxygeranate (**1**) led to an equimolecular ratio of **2a** and **2b**,³ via a 5-*exo-trig* process (Scheme 1).



Scheme 1

The control of the diastereoselectivity of this reaction may derive into a good method to generate advanced intermediates in the synthesis of natural terpenoids. Among these intermediates, a toxicol-A C subunit (Scheme 2) could be accessible using the mentioned approach. Toxicol A is a hexaprenoid hydroquinone sulfate isolated from the Red Sea sponge *Toxiclona toxius*,⁴ and was reported to inhibit the reverse transcriptase of human immunodeficiency virus (HIV) and to possess activity against *Candida albicans*. Thus, synthon **I**, easily available from commercial farnesyl acetate, and containing the C ring subunit, adequately functionalized (Scheme 2), should permit further transformations with the ultimate goal of incorporating the A, D, E and F rings to achieve the total synthesis of toxicol A.

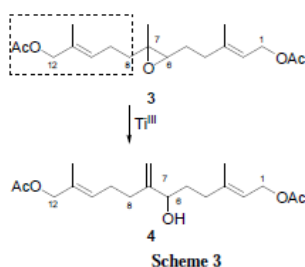


Scheme 2

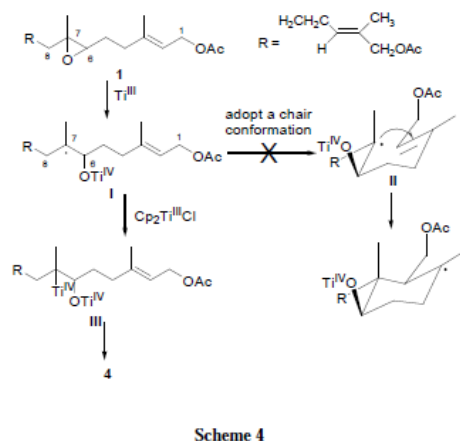
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2. Results and discussion

We started the development of our idea by studying the reactivity of different 6,7-epoxy-farnesyl derivatives with $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$. In this sense, we must mention the absence of precedents in radical cyclizations of epoxy-polyprenes presenting the oxirane located in an intermediate position of an acyclic chain. Thus, when compound **3**, obtained from farnesyl acetate via standard transformations and which possesses two acetate groups located at C1 and C12 positions, was made to react with catalytic $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$,¹⁴ the reaction crude showed almost exclusively the formation of the opened allylic alcohol **4** (Scheme 3, Table 1, entry 1).



Contrarily to what was the case with 6,7-epoxygeranyl acetate, which after treatment with Ti(III) produced the 6-*endo*-trig cyclization product,⁵ the isoprenic chain at C8 in **3** prevented the formation of the chair-like transition state **II** needed to complete the cyclization process (Scheme 4).



When the epoxyfarnesyl derivative **5**,⁶ which possesses an isopropenyl at the end of the acyclic moiety was made to react with catalytic $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, the resulting products were the acyclic allylic alcohol **6** (39.7%), together with the cyclization product **7** (13.3%), originated via a 6-*endo*-trig process (Scheme 5, Table 1, entry 2). The formation of this highly functionalized cyclohexane is rationalized by considering that the radical initially originated after the homolytic opening of the oxirane adds to the $\Delta^{2,3}$ double bond. Comparing these results with those obtained with **3**, the formation now of a significant quantity of cyclization product seems to suggest a higher conformational freedom in the intermediate radical which allows an easier achievement of the chair-like transition state leading to the cyclization process.

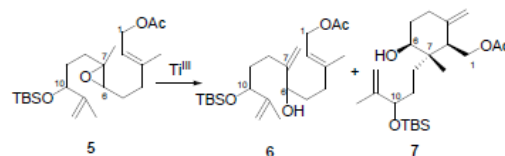
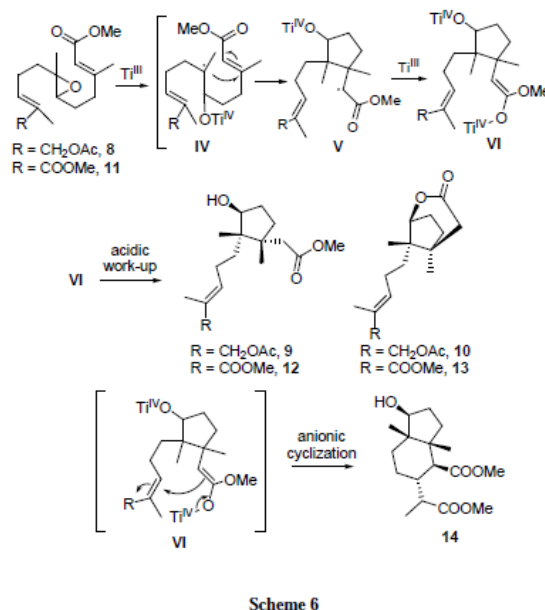


Table 1. Ti(III)-mediated cyclizations of 6,7-epoxy-farnesyl derivatives

Entry	Starting material	Reaction product	Time min.	Yield %	Ratio a:b
1	3	4	70	56	
2	5	6 + 7	50	53	3:1
3	8	9 + 10	25	95	8:7
4	11	12 + 13 + 14	200	90	4:7:2

Reaction of acetoxyester **8** with Ti(III) following the catalytic protocol afforded after 25 min a 50.7 and 44.3% yield of cyclopentanes **9** and **10**, respectively (Table 1, entry 3, Scheme 6). Compound **10** was obtained as a result of a spontaneous lactonization after work-up of the reaction mixture.



When diester **11** was treated with catalytic quantities of Ti(III), cyclopentanes **12** and **13** were obtained in 27.7 and 48.5% yield, respectively, together with a distereomeric mixture of hydriindane derivatives (13.8%), from which compound **14** could be isolated. The stereochemistry of **14** was established by NOE diff experiences (Figure 1) and also by the coupling constant

value $J=12$ Hz between H-2, H-10, which suggests an *anti* relationship between these two protons.

These hydrindane derivatives were probably generated as a result of a cascade process involving a radical cyclization and a Michael addition (Scheme 6), the second step being caused through the intermediate enolate-radical produced after the first cyclization.

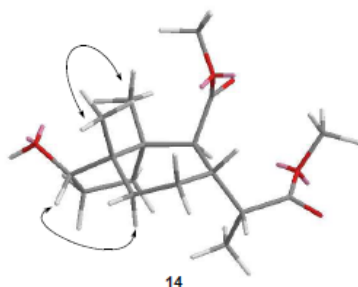


Figure 1.

Considering the lack of stereoselectivity obtained in the closure of the cyclopentane ring of these C15 precursors, then we focused our efforts on improving the stereochemical outcome of the radical 5-*exo-trig* cyclization by using C10 epoxyolyprenes derived from commercial geraniol (15-19) (Table 2).

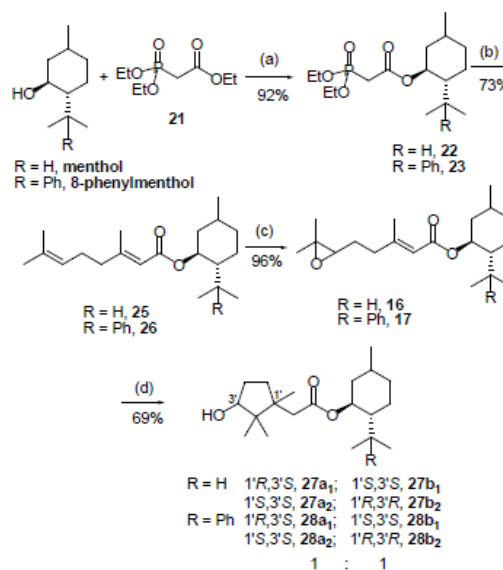
Table 2. 5-*Exo-trig* cyclizations catalyzed by Ti(III).

Entry	Starting material	R ₁	R ₂	Reaction product	Yield %	Ratio a:b
1	1	COOMe	H	2	86	1:1
2	15 ⁷	COO <i>t</i> -Bu	H	20	81	1:1
3	16	COO(-)-menthyl	H	27	71	1:1
4	17	COO-8-phenyl(-)-menthyl	H	28	69	1:1
5	18 ⁸	COOEt	COOEt	29	94	2:1
6	19	CN	H	30	99	4:1

At this point, it has to be said that the preparation of the menthyl esters **25** and **26**, precursor of epoxides **16** and **17**, could not be achieved using standard esterification or transesterification transformations,⁹ but employing a convergent methodology via the corresponding 2-diethylfosonoacetates (**22** and **23**) and subsequent Wadsworth-Emmons condensation¹⁰ with commercially available 5-methylhex-4-en-2-one (**24**) (Scheme 7).¹¹

Unfortunately, none of the epoxyderivatives **15-17** showed diastereoselection in their reaction with Ti(III) (Table 2). Thus, in the reaction of the menthyl esters **16** and **17**, two couples of

diastereomers in a 1:1 ratio were obtained in each case, which were distinguished in ¹H NMR as **27a** (*trans*)-**27b** (*cis*) y **28a** (*trans*)-**28b** (*cis*), respectively, in a 1:1 ratio.



(a) **21**, DMAP, toluene, 120 °C, 140 h. (b) **24**, NaH, THF, 25 °C.
(c) *m*-CPBA, DCM, 0 °C, 20 min. (d) 0.2 Cp₂Ti^{IV}Cl₂, 8.0 Mn, 7.0 2,4,6-collidine, 4.0 TMSCl, THF, 25 °C, 80 min.

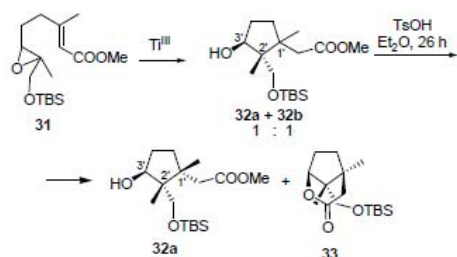
Scheme 7

The next step in our work plan led us to test an epoxyderivative possessing a diester at the start of the chain such as compound **18**. This substrate offers the possibility of introducing an additional alkoxy carbonyl group at C2, that is, at the position adjacent to the ring closing. Thus, treatment of diester **18** with Cp₂Ti^{III}Cl following the catalytic protocol afforded a 94% (Table 1, entry 5) of cyclization products (**29**), showing for the first time in this work a stereoselectivity towards the desired product **29a** (2:1 ratio), which possessed a relative *cis* disposition between the hydroxyl and the methyl group at C3 (Table 2, entry 5).

Basing ourselves in previous works by Fernández-Mateos *et al.*,¹² we also studied the Ti(III)-mediated cyclization of the 6,7-epoxy derivative of geranyl nitrile (**19**). Remarkably, it was observed that the yield was nearly quantitative to give the mixture of cyclopentanes **30** (Table 2, entry 6) with a diastereoselectivity of 4:1 in favour of **30a**. Most likely, the coordination of the Ti(III) species to the nitrile moiety should be responsible for the observed selectivity.

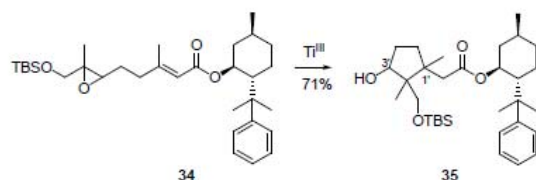
At this point, we turned our efforts to test the influence of oxygenated functions at the methyl groups located in α position to the oxirane ring in this kind of cyclizations. The steric requirements of this new functionalization, which is also necessary to extend the chain in synthon **I** towards toxicol A (Scheme 1), could also affect the stereochemical outcome of the process. Thus, the cyclization of **31** (Scheme 8) using catalytic quantities of Cp₂Ti^{III}Cl led to the mixture of diastereomers **32**, which could be resolved after lactonization of **32b** in acid medium to give **33**. Unfortunately, diastereomers **32** were produced in a 1:1 ratio, which proved that although the formation of the new stereogenic center at C2' proceeded with total

stereochemical control, no diastereoselectivity was generated in the formation of C1'.



Scheme 8

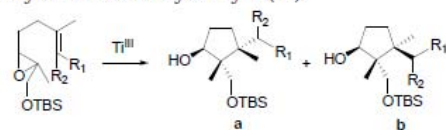
Continuing with this study, the cyclization of the phenylmenthyl epoxide **34** using $Cp_2Ti^{III}Cl$ led to a 71% of the cyclopentane derivatives **35** (Scheme 9; Table 3, entry 2), as a mixture of four diastereomers ($1'S,3'S$; $1'R,3'R$; $1'R,3'S$; and $1'S,3'R$), which are differentiated in NMR H^1 as two couples, namely **35a** (*trans*) y **35b** (*cis*), in a relative ratio of 1.3:1 (Scheme 9).



Scheme 9

Subsequently, we tested the behavior of the epoxy derivatives **36** and **38**, which possess an additional ester at C2. Thus, the reaction of **36** with $Cp_2Ti^{III}Cl$ resulted in the formation of a 92% yield of cyclization product **37**, showing a stereoselectivity 2.5:1 in favour of the desired compound **37a**, which presents a *cis* relative disposition between the hydroxyl group and the methyl at C3 (Table 3, entry 3).

Table 3. 5-*Exo-trig* cyclization reactions of epoxyterpenoids hydroxylated at C8 catalyzed by $Ti(III)$.



Entry	Starting material	R ₁	R ₂	Reaction product	Yield %	Ratio a:b
1	31	COOMe	H	32	76	1:1
2	34	COO-8-phenyl-(-)-menthyl	H	35	71	1.3:1
3	36	COOEt	COOEt	37	92	2.5:1
4	38	H	CN	39	95	4:1

Finally, cyclization of **38**, an oxirane possessing an unsaturated nitrile, led in nearly quantitative yield to cyclopentanes **39**. The diastereoselectivity in the ring closing was then acceptable as the formation of the desired isomer **39a** was 4.5 times higher than that of the isomer presenting the undistorted stereochemistry **39b** (Table 3, entry 4).

In conclusion, with the present work we have shown that, in radical cyclizations of epoxyterpenoids catalyzed by Cp_2TiCl , it is possible to control both the regioselectivity of the process towards cyclopentanes, and the stereoselectivity in the cyclization process by using malonyl derivatives or nitriles α,β -unsaturated as radical acceptors. Thus, the use of epoxyterpenoids conveniently functionalized provokes 5-*exo-trig* ring closures with excellent yields and good stereochemical control on the three stereogenic centres created. This methodology permits an easy access to highly functionalized cyclopentanes, potential intermediates in the synthesis of toxicol A.

3. Experimental

3.1. General

NMR spectra were performed with a Varian Direct-Drive 600 (1H 600 MHz/ ^{13}C 150 MHz), 500 (1H 500 MHz/ ^{13}C 125 MHz), Bruker ARX 400 (1H 400 MHz/ ^{13}C 100 MHz) and Varian Inova Unity 300 (1H 300 MHz/ ^{13}C 75 MHz) spectrometers. The accurate mass determination was carried out with an 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^+ was used as primary ion. 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 a solution of phosphomolybdic acid in ethanol and heat as developing agent. GC-MS analyses were carried out in a Hewlett Packard 6890 chromatograph connected to a Hewlett-Packard 5988A mass spectrometer using an ionization voltage of 70 eV. The GC conditions were: HP-1 methylsilicone capillary column (25 m x 0.2 mm); He 1.9 mL/min; the injection and detector heater temperature was 250 °C; temperature program from 50 °-300 °C at 10 °C/min. Quantitative chromatographic analysis were carried out on Hewlett Packard 6890 chromatograph equipped with a flame ionization detector (FID) and coupled to an integrator HP-3390A. The column and experimental conditions were the same as those described above, except that the detector heater temperature was 300 °C and the inlet head was 20 psi. The percentage compositions were computed from the GC peak areas without correction factors. HPLC with UV and RI detection was used. Semipreparative 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. All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an argon atmosphere. The solvents used were purified according to standard literature techniques and stored under argon. 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 reactions. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated.

Preparation of all varieties of epoxy-polyprenes used in cyclization reactions involving known procedures are described in the Supplementary Material part.

3.2. Experimental general procedure for catalytic cyclization of epoxy-poliprenes mediated by Ti(III).

A mixture of Cp_2TiCl_2 (70.7 mg, 0.275 mmol) and Mn dust (778.7 mg, 7.34 mmol) in strictly deoxygenated THF (5 mL) and argon atmosphere was stirred at room temperature until the red solution turned green. Then, a solution of the corresponding epoxide (0.918 mmol), 2,4,6-collidine (0.85 mL, 6.12 mmol) and TMSCl (0.46 mL, 3.67 mmol) in strictly deoxygenated THF (2.0 mL) was added and stirred until disappearance of the starting material (25-200 min). The reaction was quenched with HCl 2 N (dropwise addition of 20 mL), extracted with *t*-BuOMe (3x40 mL), washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The resulting crude was diluted in THF (40.0 mL) and stirred at room temperature. Then TBAF 1M in THF (5.7 mmol) was added and stirred for 1 h.¹³ At this point the mixture was concentrated under reduced pressure, rediluted in H_2O , extracted with EtOAc (4x10 mL), washed with brine and concentrated under reduced pressure. Final purifications and isolations of the resulting compounds were carried out through SiO_2 column chromatography eluting with hexane:*t*-BuOMe mixtures.

3.3. Experimental general procedure for stoichiometric cyclization of epoxy-poliprenes mediated by Ti(III).

A mixture of Cp_2TiCl_2 (707.0 mg, 2.75 mmol) and Mn dust (778.7 mg, 7.34 mmol) in strictly deoxygenated THF (5.0 mL) and argon atmosphere was stirred at room temperature until the red solution turned green. Then, a solution of the corresponding epoxide (0.918 mmol) in strictly deoxygenated THF (2.0 mL) was added and stirred until disappearance of the starting material (25-200 min). The reaction was quenched with HCl 2 N (dropwise addition of 20 mL), extracted with *t*-BuOMe (3x40 mL), washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. Final purifications and isolations of the resulting compounds were carried out through SiO_2 column chromatography eluting with hexane:*t*-BuOMe mixtures.

3.4. Radical Cyclization of 3.

After subjecting **3** (320 mg, 0.918 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1, 2:1) on silica gel to afford 173 mg (0.514 mmol, 56%) of non-cyclized **4**.

3.4.1. (2*E*,10*E*)-6-Hydroxy-3,11-dimethyl-7-methylenedodeca-2,10-diene-1,12-diyol diacetate (**4**). Colourless oil; 1H NMR ($CDCl_3$, 400 MHz): δ 5.49 (1H, t, $J=7.4$ Hz), 5.38 (1H, t, $J=7.3$ Hz), 5.07 (1H, s), 4.88 (1H, s), 4.60 (2H, d, $J=7.2$ Hz), 4.45 (2H, s), 4.07 (1H, m), 2.08 (3H, s), 2.05 (3H, s), 1.72 (3H, s), 1.69 (3H, s); FABHRMS calcd for $C_{19}H_{30}O_5Na$ [M+Na]⁺ 361.1985, found 361.1983.

3.5. Radical Cyclization of 5.

After subjecting **5** (220 mg, 0.536 mmol) to the catalytic procedure conditions, the resulting crude was treated with TBAF in THF (3.3 mmol) for 3h. The corresponding diol derivatives of **6** and **7**, that is **6a** and **7a** were purified by column chromatography (hexane/*t*-BuOMe, 4:1, 2:1) on silica gel to afford 88 mg of **6a** (39.7%) and 29 mg of **7a** (13.3%).

3.5.1. (E)-6,10-Dihydroxy-3,11-dimethyl-7-methylenedodeca-2,11-dienyl acetate (**6**). Colourless oil, 1H NMR ($CDCl_3$, 500 MHz): δ 5.37 (1H, t, $J=7.4$ Hz), 5.05 (1H, s), 4.96 (1H, s), 4.90 (1H, s), 4.85 (1H, s), 4.58 (2H, d, $J=7.0$ Hz), 4.10 (2H, m), 2.19-2.05 (5H, m), 2.05 (3H, s), 1.74 (3H, s), 1.71 (3H, s), 1.70-1.40 (3H, m) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.6, 150.1, 144.2, 135.3, 120.7, 113.7, 113.2, 77.9, 77.8, 63.9, 38.2, 36.0, 35.9, 29.6, 23.7, 20.2, 19.4 ppm; FABHRMS calcd for $C_{17}H_{28}O_4Na$ [M+Na]⁺ 319.1880, found: 319.1812.

3.5.2. [(1*R*,2*S*,3*S*)-3-Hydroxy-2-(3-hydroxy-4-methylpent-4-enyl)-2-methyl-6-methylenecyclohexyl]methyl acetate (**7a**). Colourless oil, 1H NMR ($CDCl_3$, 500 MHz): δ 4.98 (1H, m), 4.85 (1H, s), 4.84 (1H, s), 4.64 (1H, s), 4.57 (1H, dd, $J=13.2$, 7.0 Hz), 4.35 (1H, dd, $J=11.2$, 3.9 Hz), 4.07 (1H, m), 3.61 (1H, s), 2.54 (1H, dt, $J=13.3$, 4.0 Hz), 2.18 (1H, dd, $J=10.6$, 3.8 Hz), 2.00 (3H, s), 1.83 (1H, m), 1.74 (3H, s), 1.65-1.15 (6H, m), 0.88 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.0, 150.1, 145.0, 114.6, 113.9, 79.2, 74.8, 65.8, 54.6, 33.2, 33.0, 30.7, 30.4, 23.7, 20.4, 16.0 ppm; FABHRMS calcd for $C_{17}H_{28}O_4Na$ [M+Na]⁺ 319.1880, found: 319.1862.

3.6. Radical Cyclization of 8.

After subjecting **8** (350 mg, 1.08 mmol) to the catalytic procedure conditions, the resulting crude 332 mg (95%) was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford **9** (169 mg, 50.7%) and **10** (133 mg, 44.3%).

3.6.1. Methyl [(1*R*,2*S*,3*S*)-2-((E)-5-acetoxy-4-methylpent-3-enyl)-3-hydroxy-1,2-dimethylcyclopentyl]acetate (**9**). Colourless oil, 1H NMR ($CDCl_3$, 500 MHz): δ 5.45 (1H, t, $J=7.2$ Hz), 4.39 (2H, s), 3.83 (1H, dd, $J=7.2$, 2.2 Hz), 3.58 (3H, s), 2.16 (2H, dd, $J=17.0$, 13.0 Hz), 2.05-1.10 (8H, m), 2.00 (3H, s), 1.60 (3H, m), 1.06 (3H, s), 0.75 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.8, 171.2, 130.4, 130.2, 81.1, 76.9, 70.35, 51.4, 50.6, 45.8, 43.1, 36.7, 32.3, 30.2, 23.7, 22.3, 20.9, 14.1 ppm; FABHRMS calcd for $C_{18}H_{30}O_5Na$ [M+Na]⁺ 349.1985, found: 349.1977.

3.6.2. (E)-2-methyl-5-((1*S*,5*S*,8*S*)-5,8-dimethyl-3-oxo-2-oxabicyclo[3.2.1]octan-8-yl)pent-2-enyl acetate (**10**). Colourless oil, 1H NMR ($CDCl_3$, 500 MHz): δ 5.35 (1H, t, $J=7.2$ Hz), 4.38 (1H, s), 4.37 (2H, t, $J=4.2$ Hz), 2.48 (1H, dd, $J=18.9$, 3.4 Hz), 2.26 (1H, d, $J=18.9$ Hz), 2.11-1.85 (4H, m), 2.01 (3H, s), 1.66 (1H, m), 1.60 (3H, m), 1.33-1.15 (3H, m), 1.00 (3H, s), 0.87 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 171.1, 131.1, 128.8, 86.7, 70.1, 46.3, 45.5, 43.2, 36.3, 33.1, 29.8, 22.4, 21.2, 19.1, 14.2, 13.5 ppm; FABHRMS calcd for $C_{17}H_{26}O_4Na$ [M+Na]⁺ 317.1723, found: 317.1727.

3.7. Radical Cyclization of 11.

After subjecting **11** (297 mg, 0.92 mmol) to the stoichiometric procedure conditions, the resulting crude (280 mg, 90%) was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford **12** (79 mg, 27.7%), **13** (125 mg, 48.5%) and **14** (40 mg, 13.8%).

3.7.1. Methyl (E)-5-((1*S*,2*R*,5*S*)-5-hydroxy-2-methoxycarbonylmethyl-1,2-dimethylcyclopentyl)-2-methylpent-2-enoate (**12**). Colourless oil, 1H NMR ($CDCl_3$, 300 MHz): δ 6.80 (1H, dt, $J=7.4$, 1.4 Hz), 3.91 (1H, dd, $J=7.3$, 1.3 Hz), 3.72 (3H, s), 3.67 (1H, m), 3.63 (3H, s), 2.27-2.13 (3H, m), 1.85-1.10 (6H, m), 1.84 (3H, s), 1.11 (3H, s), 0.81 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 168.8, 143.0, 127.5, 80.8, 51.8, 51.3, 50.4, 45.7, 43.0, 36.6, 32.5, 29.4, 24.6, 22.2, 20.8, 12.4 ppm; FABHRMS calcd for $C_{17}H_{26}O_5Na$ [M+Na]⁺ 335.1829, found: 335.1834.

3.7.2. Methyl (E)-2-methyl-5-((1S,5S,8S)-5,8-dimethyl-3-oxo-2-oxa-bicyclo[3.2.1]octan-8-yl)pent-2-enoate (13). Colourless oil, ¹H NMR (CDCl₃, 300 MHz): δ 6.72 (1H, t, *J*=7.4 Hz), 4.43 (1H, d, *J*=4.1 Hz), 3.74 (3H, s), 2.59 (1H, dd, *J*=14.5, 1.4 Hz), 2.36 (1H, d, *J*=14.5 Hz), 2.35-1.13 (8H, m), 1.83 (3H, s), 1.04 (3H, s), 0.95 (3H, s) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 171.3, 168.1, 141.4, 128.7, 86.7, 51.8, 46.6, 45.7, 43.4, 36.6, 33.1, 29.8, 28.3, 19.8, 14.6, 12.5 ppm; FABHRMS calcd for C₁₆H₂₄O₄Na [M+Na]⁺ 303.1719, found 303.1716.

3.7.3. Methyl (1S,3aR,4S,5S,7aS)-5-(1-methoxycarbonyl)ethyl-octahydro-1-hydroxy-3a,7a-dimethyl-1H-indene-4-carboxylate (14). Colourless oil, ¹H NMR (CDCl₃, 300 MHz): δ 4.36 (1H, dd, *J*=9.1, 7.2 Hz), 3.67 (3H, s), 3.64 (3H, s), 2.50 (1H, dq, *J*=7.1, 2.3 Hz), 2.48 (1H, d, *J*=12.0 Hz), 2.19-1.23 (8H, m), 1.90 (1H, m), 1.13 (3H, d, *J*=7.1 Hz), 0.91 (3H, s), 0.79 (3H, s) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 178.3, 177.1, 77.5, 54.6, 54.5, 54.4, 47.9, 48.2, 43.1, 41.9, 35.3, 32.6, 32.3, 24.5, 20.6, 20.1, 18.2 ppm; FABHRMS calcd for C₁₇H₂₈O₅Na [M+Na]⁺ 335.1834, found: 335.1812.

3.8. Radical Cyclization of 15.

After subjecting **15** (571 mg, 2.38 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel yielding 455 mg (1.93 mmol, 81%) of an equimolecular mixture of **20a** and **20b**. A solution of this mixture (61 mg, 0.25 mmol) in Et₂O was treated with an excess of TsOH during 26 h at room temperature. Then, the reaction mixture was washed with saturated aqueous NaHCO₃ (2x25 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford to afford 21 mg (0.12 mmol) of the lactone derived from **20b** and 30 mg (0.12 mmol) of **20a**.

3.8.1. *t*-Butyl 2-((1R,3S)-3-hydroxy-1,2,2-trimethylcyclopentyl)acetate (20a). Colourless oil; ¹H NMR (CDCl₃, 400 MHz): δ 3.86 (1H, dd, *J*=8.4, 5.2 Hz), 2.21-2.08 (1H, m), 2.07 (2H, s), 1.90-1.79 (1H, m), 1.68-1.48 (2H, m), 1.45 (9H, s), 1.04 (3H, s), 0.85 (3H, s), 0.80 (3H, s) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 172.6, 81.4, 80.2, 47.3, 44.8, 43.7, 34.2, 31.0, 28.2, 22.8, 21.6, 17.4 ppm.

3.8.2. (1S,5S)-5,8,8-Trimethyl-2-oxa-bicyclo[3.2.1]octan-3-one. (lactone derived from **20b**), colourless oil; ¹H NMR (CDCl₃, 300 MHz): δ 4.16 (1H, d, *J*=4.5 Hz), 2.48 (1H, dd, *J*=18.8, 3.2 Hz), 2.30 (1H, d, *J*=18.8 Hz), 2.11-1.89 (2H, m), 1.88-1.63 (2H, m), 0.95 (3H, s), 0.86 (3H, s), 0.82 (3H, s) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 171.5, 89.1, 44.9, 43.6, 41.9, 36.1, 29.7, 20.5, 19.2, 16.8 ppm; FABHRMS: calcd for C₁₀H₁₆O₂Na [M+Na]⁺ 191.1048, found: 191.1060.

3.9. Synthesis of epoxide 16.

3.9.1. (1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl, 2-(diethoxyphosphoryl)acetate (22). A solution of (-)-menthol (600 mg, 3.84 mmol) in anhydrous toluene (10.0 mL), DMAP (142 mg, 1.15 mmol) and (EtO)₂P(O)CH₂CO₂Et (**21**) (2.34 mL, 11.54 mmol), was refluxed under argon atmosphere. After 27 h the solvent was removed under reduced pressure and the crude filtrated through silica gel eluting with hexane (100 mL) and *t*-BuOMe (200 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel afforded 1243 mg (3.72 mmol, 97%) of **22** as colourless oil, ¹H NMR (CDCl₃, 400 MHz): δ 4.68 (1H, td, *J*=10.9, 10.9, 4.4 Hz), 4.12 (4H, q, *J*=7.1 Hz), 2.91 (2H, d, *J*=21.7 Hz), 2.00-1.88 (2H, m), 1.67-1.60 (2H, m), 1.48-1.35 (2H, m), 1.30 (6H, t, *J*=7.1 Hz),

1.06-0.92 (2H, m), 0.90-0.80 (1H, m), 0.87 (3H, d, *J*=2.7 Hz), 0.85 (3H, d, *J*=3.2 Hz), 0.71 (3H, d, *J*=7.0 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 165.4, 75.6, 62.6, 62.5, 46.9, 40.6, 35.2, 34.1, 33.9, 31.4, 25.8, 23.1, 22.0, 20.8, 16.3, 16.0 ppm.

3.9.2. ((1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl (E)-3,7-dimethylocta-2,6-dienoate (25). A mixture of NaH (163 mg, 4.07 mmol) and anhydrous THF (15.0 mL) was stirred and cooled to 0 °C under argon atmosphere. Then, **22** (1236 mg, 3.70 mmol) in anhydrous THF (3.0 mL) was added and stirred for 7 min. At this point commercial **24** (5-methylhex-4-en-2-one) (*E:Z* mixture of isomers, 7.7:2.3) (0.6 mL, 4.07 mmol) was added and the solution stirred at rt for 4 h. The reaction was diluted with *t*-BuOMe (50 mL), saturated aqueous NH₄Cl was added dropwise, and finally quenched with H₂O (60 mL). The aqueous layer was extracted with *t*-BuOMe (3x80 mL). The aqueous layer was extracted with *t*-BuOMe (3x80 mL). The resulting organic mixture was then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel afforded 780 mg (2.70 mmol, 73%) of condensation product **25** as colourless oil, ¹H NMR (CDCl₃, 300 MHz): δ 5.62 (1H, s), 5.07 (1H, m), 4.68 (1H, td, *J*=10.8, 10.8, 4.4 Hz), 2.62 (td, *J*=7.8, 7.8, 1.6 Hz), 2.14 (3H, s), 2.00 (1H, d, *J*=11.7 Hz), 1.92-0.75 (12H, m), 1.86 (3H, s), 1.67 (3H, s), 1.59 (3H, s), 0.89 (3H, d, *J*=2.2 Hz), 0.87 (3H, d, *J*=2.6 Hz), 0.75 (3H, d, *J*=7.0 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 166.6, 166.0[†], 159.7[†], 159.4, 132.5, 132.0[†], 123.8[†], 123.2, 116.8[†], 116.1, 73.2, 47.2, 41.3, 41.1, 34.4, 33.5, 31.5, 29.8, 26.9, 26.4, 26.2, 25.7, 25.4, 23.7, 22.1, 20.8, 18.9, 17.7, 16.5 ppm; FABHRMS: calcd for C₂₀H₃₄O₂Na [M+Na]⁺ 329.2456; found: 329.2461.

3.9.3. ((1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl (E)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enoate (16). To a solution of **25** (400 mg, 1.31 mmol) in DCM (7.0 mL) at 0 °C under argon atmosphere, was dropwisely added *m*-CPBA (271 mg, 1.57 mmol) in DCM (7 mL) and the mixture stirred until disappearance of starting material. Then the mixture was diluted with DCM (25 mL), washed with NaOH 2 N (3x40 mL) and brine (2x40 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel affording 409 mg (1.27 mmol, 97%) of **16** as colourless oil, ¹H NMR (CDCl₃, 300 MHz): δ 5.66 (1H, s), 4.68 (1H, td, *J*=10.8, 10.8, 4.4 Hz), 2.69 (1H, t, *J*=6.2 Hz), 2.28 (2H, m), 2.16 (3H, d, *J*=1.2 Hz), 1.98 (1H, d, *J*=11.7 Hz), 1.92-0.75 (10H, m), 1.28 (3H, s), 1.24 (3H, s), 0.89 (3H, d, *J*=2.2 Hz), 0.87 (3H, d, *J*=2.6 Hz), 0.75 (3H, d, *J*=7.0 Hz) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 166.3, 158.2, 116.6, 73.3, 63.7, 58.6, 47.2, 41.2, 37.6, 34.4, 31.5, 27.0, 26.3, 24.8, 23.6, 22.1, 20.8, 18.9, 18.8, 16.5 ppm; FABHRMS: calcd for C₂₀H₃₄O₃Na [M+Na]⁺ 345.2406, found: 345.2407.

3.10. Radical Cyclization of 16.

After subjecting **16** (322 mg, 1.00 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1, 1:1) on silica gel to afford 230 mg (71%) of a diastereomeric mixture (1'*R*,3'*S*; 1'*S*,3'*S*; 1'*S*,3'*R*; y 1'*R*,3'*R*) showing in ¹H NMR two representative groups of signals corresponding to **27a** (*trans*) and **27b** (*cis*) in equimolecular ratio.

3.10.1. Compounds 27a₁+27a₂+27b₁+27b₂. Pale yellow oil, ¹H NMR (CDCl₃, 300 MHz): δ 4.63 (2H, tdd, *J*=10.8, 10.8, 4.3, 1.4 Hz), 3.96 (1H, ddd, *J*=9.1, 7.4, 2.3 Hz), 3.85[†] (1H, ddd, *J*=8.1, 5.3, 1.9 Hz), 2.33 (1H, dd, *J*=13.1, 4.5 Hz), 2.20-1.75 (31H, m), 1.03[†] (3H, s), 0.92 (3H, d, *J*=2.1 Hz), 0.87 (6H, s), 0.84 (12H, s),

0.78 (6H, dd, $J=4.4, 1.7$ Hz), 0.71 (6H, d, $J=7.0$ Hz) ppm; ^{13}C NMR (CDCl₃, 75 MHz): δ 172.8, 172.7, 81.3, 81.2, 74.1, 74.0, 49.4, 47.3, 47.2, 47.0, 46.5, 46.5, 44.8, 44.7, 44.2, 44.1, 42.8, 42.7, 42.7, 42.6, 41.0, 34.3, 34.3, 34.2, 34.0, 31.4, 31.0, 30.9, 30.0, 30.0, 27.0, 26.2, 23.3, 23.3, 22.8 ppm. († : signal corresponding to diastereomeric couple **27a**).

3.11. Synthesis of epoxide **17**.

3.11.1. (1S,2R,5S)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(diethoxyphosphoryl)acetate (23). A solution of (-)-8-phenylmenthol (1000 mg, 4.30 mmol) in anhydrous toluene (10.0 mL), DMAP (158 mg, 1.29 mmol) and (EtO)₂P(O)CH₂CO₂Et (**21**) (2.61 mL, 12.91 mmol) was refluxed under argon atmosphere. After 140 h the solvent was removed under reduced pressure and the crude filtrated through silica gel eluting with hexane (100 mL) and *t*-BuOMe (200 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel afforded 1720 mg (4.17 mmol, 97%) of **23** as colourless oil. ^1H NMR (CDCl₃, 300 MHz): δ 7.23 (4H, m), 7.07 (1H, m), 4.79 (1H, td, $J=10.8, 10.8, 4.4$ Hz), 4.08-3.91 (4H, m), 2.35 (1H, dd, $J=21.3, 14.3$ Hz), 2.03 (1H, dd, $J=21.3, 14.4$ Hz), 2.00 (1H, m), 1.79 (2H, tq, $J=13.4, 13.4, 3.4$ Hz), 1.63 (1H, dt, $J=12.9, 2.8, 2.8$ Hz), 1.40 (1H, m), 1.30-0.80 (3H, m), 1.25 (9H, m), 1.15 (3H, s), 0.83 (3H, d, $J=6.5$ Hz) ppm; ^{13}C NMR (CDCl₃, 75 MHz): δ 165.0, 151.7, 127.9 (2C), 125.3, 125.0, 75.1, 62.4, 62.3, 50.2, 41.3, 39.4, 34.7, 34.4, 33.0, 31.2, 29.1, 26.2, 23.2, 21.7, 16.3, 16.2 ppm.

3.11.2. (1S,5S)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl (E)-3,7-dimethylocta-2,6-dienoate (26). A mixture of NaH (172 mg, 4.31 mmol) and anhydrous THF (20.0 mL), was stirred and cooled to 0 °C under argon atmosphere. Then, **23** (1615 mg, 3.92 mmol) in anhydrous THF (3.0 mL) was added and stirred for 7 min. At this point commercial **24** (*E:Z* mixture of isomers, 7.7:2.3) (0.64 mL, 4.31 mmol) was added and the solution stirred at rt for 4 h. The reaction was diluted with *t*-BuOMe (50 mL), saturated aqueous NH₄Cl was added dropwise, and finally quenched with H₂O (60 mL). The aqueous layer was extracted with *t*-BuOMe (3x80 mL). The resulting organic mixture was then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel afforded 1093 mg (2.86 mmol, 73%) of condensation product **26** as colourless oil. ^1H NMR (CDCl₃, 300 MHz): δ 7.23 (4H, m), 7.07 (1H, m), 5.12 † (0.22H, m), 5.05 (0.77H, m), 4.99 (1H, s), 4.78 (1H, td, $J=10.7, 10.7, 4.3$ Hz), 2.68-2.48 (m), 2.07 (3H, s), 1.92-0.75 (12H, m), 1.78 (s), 1.68 (3H, s), 1.61 (3H, s), 1.30 (3H, s), 1.22 (3H, s), 0.85 (3H, d, $J=6.5$ Hz) ppm; ^{13}C NMR (CDCl₃, 75 MHz): δ 166.1, 159.4 † , 159.0 † , 151.8, 132.4, 128.0, 125.6, 125.0, 123.9 † , 123.3, 116.9 † , 116.2, 73.4, 73.3 † , 50.8, 42.1, 40.9, 39.9, 34.8, 33.3 † , 31.4, 27.3, 26.9, 26.8, 26.3 † , 26.1, 25.9, 25.7, 25.2 † , 21.9, 18.8, 17.8 ppm; FABHRMS: calcd for C₂₆H₃₈O₂Na [M+Na] $^+$ 405.2770; found: 405.2771. [† : signals corresponding to minor diastereoisomer (*Z*)].

3.11.3. (1S,2R,5S)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl (E)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enoate (17). To a solution of **26** (1073 mg, 2.81 mmol) in DCM (9.0 mL) at 0 °C under argon atmosphere, was dropwisely added *m*-CPBA (582 mg, 3.37 mmol) in DCM (9.0 mL) and the mixture stirred until disappearance of starting material. Then the mixture was diluted with DCM (25 mL), washed with NaOH 2 N (3x40 mL) and brine (2x40 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel affording 1085 mg (2.73 mmol, 97%) of **17** as pale yellow oil, ^1H

NMR (CDCl₃, 300 MHz): δ 7.23 (4H, m), 7.07 (1H, m), 5.02-4.96 (1H, m), 4.78 (1H, td, $J=10.8, 10.8, 4.2$ Hz), 2.67 (1H, t, $J=6.2$ Hz), 2.28-1.93 (2H, m), 2.08 (3H, s), 1.92 (1H, d, $J=12.3$ Hz), 1.70-1.56 (5H, m), 1.52-1.40 (2H, m), 1.29 (6H, m), 1.26 (3H, s), 1.21 (3H, s), 1.16-1.03 (2H, m), 0.85 (3H, d, $J=6.5$ Hz) ppm; ^{13}C NMR (CDCl₃, 75 MHz): δ 165.8, 157.6, 151.8, 127.9, 125.5, 124.9, 116.6, 116.5, 73.5, 63.6, 58.4, 50.7, 42.0, 39.8, 37.4, 34.7, 31.4, 27.7, 27.4, 26.9, 26.7, 25.6, 25.4, 25.1, 24.9, 21.9 ppm; FABHRMS: calcd for C₂₆H₃₈O₃Na [M+Na] $^+$ 421.2719; found: 421.2717.

3.12. Radical Cyclization of **17**.

3.12.1. Compounds 28a₁+28a₂. After subjecting **17** (398 mg, 1.00 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1, 1:1) on silica gel to afford 276 mg (69%) of a diastereomeric mixture (1'*R*,3'*S*; 1'*S*,3'*S*; 1'*S*,3'*R*; y 1'*R*,3'*R*) showing in ^1H NMR two representative groups of signals corresponding to **28a** (*trans*) and **28b** (*cis*), in equimolecular ratio. General structure of this mixture was determined after isolation of *trans* diastereomeric couple (**28a**) as pale yellow oil. ^1H NMR (CDCl₃, 300 MHz): δ 7.28 (4H, m), 7.13 (1H, m), 4.78 (2H, td, $J=10.7, 10.7, 4.3$ Hz), 3.71 (1H, dd, $J=8.2, 4.8$ Hz), 2.11-1.95 (2H, m), 1.89-1.78 (2H, m), 1.73-1.65 (1H, m), 1.62 (1H, d, $J=13.0$ Hz), 1.57-1.39 (4H, m), 1.35-1.15 (3H, m), 1.29 (3H, s), 1.18 (3H, s), 0.98-0.84 (1H, m), 0.94 (3H, s), 0.87 (3H, d, $J=6.5$ Hz), 0.80 (3H, s), 0.66 (3H, s) ppm; ^{13}C NMR (CDCl₃, 75 MHz): δ 172.4, 152.3, 128.0, 125.4, 124.8, 81.3, 73.9, 50.3, 47.2, 42.3, 41.8, 39.5, 34.7, 34.0, 31.4, 30.9, 29.5, 26.4, 23.2, 22.8, 21.9, 21.5, 17.2 ppm.

3.14. Radical Cyclization of **18**.

After subjecting **18** (260 mg, 0.91 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 4:1) on silica gel yielding 241 mg (94%) of a mixture 2:1 of **29a** and **29b**. A solution of this mixture (241 mg, 0.84 mmol) in Et₂O was treated with an excess of TsOH during 26 h at room temperature. Then, the reaction mixture was washed with saturated aqueous NaHCO₃ (2x25 mL) and brine (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford 154.6 mg (0.54 mmol, 64.3%) of **29a** and 61.1 mg (0.27 mmol, 32.1%) of the lactone derived from **29b**.

3.14.1. Diethyl 2-((1R,3S)-3-hydroxy-1,2,2-trimethylcyclopentyl)malonate (29a). Colourless oil; ^1H NMR (CDCl₃, 500 MHz): δ 4.18 (4H, m), 3.76 (1H, dd, $J=3.6, 3.6$ Hz), 3.46 (1H, s), 2.19 (1H, m), 1.84 (2H, m), 1.61 (1H, m), 1.34 (3H, s), 1.28 (3H, t, $J=7.0$ Hz), 1.25 (3H, t, $J=7.0$ Hz), 0.95 (6H, s) ppm; ^{13}C NMR (CDCl₃, 125 MHz): δ 169.0, 168.8, 83.5, 61.2, 61.1, 58.1, 48.6, 48.2, 36.8, 31.1, 24.6, 19.1, 18.6, 14.3, 14.2 ppm; FABHRMS: calcd for C₁₅H₂₆O₅Na [M+Na] $^+$ 309.1672; found: 309.1667.

3.14.2. Ethyl (1S,4R,5S)-5,8,8-Trimethyl-3-oxo-2-oxa-bicyclo[3.2.1]octane-4-carboxylate (lactone derived from **29b**). Colourless oil, ^1H NMR (CDCl₃, 500 MHz): δ 4.26 (1H, m), 4.24 (2H, dd, $J=7.1, 7.1$ Hz), 3.48 (1H, d, $J=2.2$ Hz), 2.34 (1H, ddd, $J=13.9, 9.2, 4.2$ Hz), 2.08 (2H, m), 1.61 (1H, m), 1.31 (3H, t, $J=7.1$ Hz), 1.06 (3H, s), 1.05 (3H, s), 0.95 (3H, s) ppm; ^{13}C NMR (CDCl₃, 125 MHz): δ 169.0, 167.8, 89.1, 61.7, 58.3, 46.1, 45.5, 30.3, 29.7, 20.9, 18.0, 17.0, 14.4 ppm; FABHRMS: calcd for C₁₃H₂₀O₄Na [M+Na] $^+$ 263.1254; found: 263.1252.

3.15. Radical Cyclization of 19.

After subjecting **19** (165 mg, 1.00 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 5:1, 2:1) affording 131.2 mg (79.2%) of **30a** and 32.8 mg (19.8%) of **30b**.

3.15.1. *2-((1R,3S)-3-Hydroxy-1,2,2-trimethylcyclopentyl)acetoneitrile (30a)*. ¹H NMR (CDCl₃, 500 MHz): δ 5.12 (1H, m), 3.95 (1H, dd, *J*=8.2, 6.4 Hz), 2.18 (2H, m), 1.75 (1H, t, *J*=7.2 Hz), 1.61 (1H, m), 1.50 (2H, m), 1.18 (3H, s), 0.93 (3H, s), 0.89 (3H, s) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 119.4, 81.1, 46.6, 44.5, 34.8, 30.4, 27.3, 22.7, 22.4, 17.7 ppm.

3.15.2. *2-((1S,3S)-3-Hydroxy-1,2,2-trimethylcyclopentyl)acetoneitrile (30b)*. ¹H NMR (CDCl₃, 500 MHz): δ 5.19 (1H, m), 3.93 (1H, dd, *J*=7.6, 4.6 Hz), 2.70 (1H, d, *J*=16.5 Hz), 2.29 (1H, d, *J*=16.5 Hz), 2.18 (1H, m), 1.90 (1H, m), 1.88-1.50 (2H, m), 1.10 (3H, s), 0.90 (3H, s), 0.89 (3H, s) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 118.4, 80.0, 45.6, 43.1, 33.6, 29.2, 25.7, 21.7, 21.3, 15.9 ppm.

3.16. Radical Cyclization of 31.

After subjecting **31** (594 mg, 1.81 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to afford 455 mg (1.38 mmol, 76%) of an equimolecular mixture of **32a** and **32b**. A solution of this mixture (53 mg, 0.16 mmol) in Et₂O was treated with an excess of TsOH for 26 h at rt. Then the reaction was quenched with saturated aqueous NaHCO₃ and washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 14 mg of lactone **33**, 29 mg of **32a**, and 7 mg corresponding to a mixture of both compounds.

3.16.1. *Methyl 2-((1R,2R,3S)-3-hydroxy-2-(*t*-butyldimethylsilyloxy)-1,2-dimethylcyclopentyl)acetate (32a)*. ¹H NMR (CDCl₃, 400 MHz): δ 4.20 (1H, dd, *J*=8.6, 6.8 Hz), 3.64 (3H, s), 3.54 (1H, d, *J*=9.6 Hz), 3.46 (1H, d, *J*=9.6 Hz), 2.25 (2H, q, *J*=13.2 Hz), 2.17-2.05 (1H, m), 1.86-1.74 (1H, m), 1.65-1.46 (2H, m), 1.07 (3H, s), 0.92 (3H, s), 0.88 (9H, s), 0.04 (6H, s) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 173.3, 78.2, 68.7, 51.4, 50.6, 44.8, 41.5, 34.1, 30.1, 25.9 (3C), 22.6, 18.2, 13.1, -5.6 (2C) ppm; FABHRMS: calcd for C₁₇H₃₄O₄SiNa [M+Na]⁺ 353.2124, found: 353.2106.

3.16.2. *(1S,5S,8R)-8-(*t*-Butyldimethylsilyloxymethyl)-5,8-dimethyl-2-oxa-bicyclo[3.2.1]octan-3-one (33)*. Colourless oil, ¹H NMR (CDCl₃, 400 MHz): δ 4.51 (1H, d, *J*=4.5 Hz), 3.39 (2H, dd, *J*=11.9, 10.2 Hz), 2.49 (1H, dd, *J*=18.5, 2.9 Hz), 2.24 (1H, d, *J*=17.7 Hz), 1.98 (2H, m), 1.75 (2H, m), 1.05 (3H, s), 0.86 (3H, s), 0.84 (9H, s), 0.00 (3H, s), -0.01 (3H, s) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 171.4, 86.2, 65.5, 49.0, 45.5, 41.5, 36.6, 29.6, 25.9 (3C), 19.0, 18.3, 12.2, -5.6 (2C) ppm; FABHRMS: calcd for C₁₆H₃₀O₃SiNa [M+Na]⁺ 321.1862, found: 321.1855.

3.17. Radical Cyclization of 34.

After subjecting **34** (391 mg, 0.74 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to afford 278 mg (0.54 mmol, 71%) of a diastereomeric mixture **35** (1'*R*,3'*S*; 1'*S*,3'*S*; 1'*S*,3'*R*; y 1'*R*,3'*R*). **35** was saponified by reaction with KOH/MeOH, and the corresponding crude treated with TMSCHN₂ to obtain a mixture of compounds **32a** and **33** in a 1.3:1 ratio.

3.18. Radical Cyclization of 36.

After subjecting **36** (216 mg, 0.72 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1; 2:1) on silica gel affording 145 mg (0.47 mmol, 65.7%) of **37a** and 58 mg (0.19 mmol, 26.3%) of **37b**.

3.18.1. *Diethyl 2-[(1R,2R,3S)-2-(*t*-Butyldimethylsilyloxymethyl)-3-hydroxy-1,2-dimethylcyclopentyl]malonate (37a)*. Colourless oil, ¹H NMR (CDCl₃, 500 MHz): δ 4.16 (4H, m), 4.02 (1H, d, *J*=9.9 Hz), 3.96 (1H, dd, *J*=8.2, 4.2 Hz), 3.47 (1H, d, *J*=9.9 Hz), 3.45 (1H, s), 2.14 (1H, m), 1.78 (2H, m), 1.65 (1H, m), 1.39 (3H, s), 1.28 (3H, t, *J*=7.1 Hz), 1.25 (3H, t, *J*=7.1 Hz), 0.95 (3H, s), 0.89 (9H, s), 0.06 (3H, s), 0.05 (3H, s) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 174.3, 174.2, 88.0, 71.3, 66.7, 66.5, 63.5, 58.2, 53.0, 44.7, 35.2, 31.4 (3C), 25.5, 23.6, 23.4, 19.7, 19.6, -5.6 (2C) ppm; FABHRMS: calcd for C₂₁H₄₀O₆SiNa [M+Na]⁺ 439.2492, found 439.2517.

3.18.2. *Diethyl 2-[(1S,2R,3S)-2-(*t*-Butyldimethylsilyloxymethyl)-3-hydroxy-1,2-dimethylcyclopentyl]malonate (37b)*. Colourless oil, ¹H NMR (CDCl₃, 500 MHz): δ 4.16 (5H, m), 3.69 (1H, s), 3.59 (1H, d, *J*=9.9 Hz), 3.48 (1H, d, *J*=9.9 Hz), 2.16 (1H, m), 1.95 (1H, m), 1.63 (1H, ddd, *J*=15.2, 9.5, 2.6 Hz), 1.56 (1H, m), 1.32 (3H, s), 1.26 (6H, m), 0.92 (3H, s), 0.90 (9H, s), 0.06 (3H, s), 0.05 (3H, s) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 174.5, 174.4, 84.4, 74.9, 66.7, 66.6, 62.5, 57.7, 53.4, 42.4, 37.2, 31.6 (3C), 26.0, 23.9, 23.7, 19.8, 19.7, 0.0 (2C) ppm; FABHRMS: calcd for C₂₁H₄₀O₆SiNa [M+Na]⁺ 439.2492, found 439.2517.

3.19. Radical Cyclization of 38.

After subjecting **38** (502 mg, 1.81 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1; 3:1) on silica gel affording 381.6 mg (1.38 mmol, 76%) of **39a** and 95.4 mg (0.34 mmol, 19%) of **39b**.

3.19.1. *2-[(1R,2R,3S)-2-(*t*-Butyldimethylsilyloxymethyl)-3-hydroxy-1,2-dimethylcyclopentyl]acetoneitrile (39a)*. Colourless oil, ¹H NMR (CDCl₃, 500 MHz): δ 4.02 (1H, dd, *J*=7.9, 4.2 Hz), 3.73 (1H, d, *J*=10.1 Hz), 3.58 (1H, d, *J*=10.1 Hz), 2.81 (1H, d, *J*=16.5 Hz), 2.41 (1H, d, *J*=16.5 Hz), 2.19 (1H, m), 1.98 (1H, m), 1.62 (2H, m), 1.12 (3H, s), 0.93 (3H, m), 0.90 (9H, s), 0.08 (6H, s) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 119.4, 81.4, 65.1, 50.6, 43.9, 36.4, 30.8, 26.5, 25.9 (3C), 23.2, 19.1, 18.1, -5.6 (2C) ppm; FABHRMS: calcd for C₁₆H₃₁NO₂Na [M+Na]⁺ 320.2022, found 320.1974.

3.19.2. *2-[(1S,2R,3S)-2-(*t*-Butyldimethylsilyloxymethyl)-3-hydroxy-1,2-dimethylcyclopentyl]acetoneitrile (39b)*. Colourless oil, ¹H NMR (CDCl₃, 500 MHz): δ 4.18 (1H, t, *J*=8.0 Hz), 3.53 (1H, d, *J*=10.1 Hz), 3.48 (1H, d, *J*=10.1 Hz), 2.39 (2H, d, *J*=1.7 Hz), 2.14 (1H, m), 1.75 (2H, m), 1.59 (1H, m), 1.19 (3H, s), 0.94 (3H, m), 0.89 (9H, s), 0.06 (3H, s), 0.06 (3H, s) ppm; ¹³C NMR (CDCl₃, 125 MHz): δ 119.3, 76.8, 68.1, 50.0, 44.3, 35.0, 29.9, 27.1, 25.9 (3C), 23.5, 18.2, 13.5, -5.6 (2C) ppm; FABHRMS: calcd for C₁₆H₃₁NO₂Na [M+Na]⁺ 320.2022, found: 320.1974.

Acknowledgments

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spectroscopical data of epoxyolyprenes **3**, **5**, **8**, **11**, **15**, **18**, **19**, **31**, **34**, **36** and **38**.

Supplementary Material

Supplementary data associated with this article can be found in the online version. These data include preparation and

Artículo 4:

*Weakening C-O Bonds: Ti(III), a New Reagent
for Alcohol Deoxygenation and Carbonyl Coupling
Olefination.*

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Weakening C–O Bonds: Ti(III), a New Reagent for Alcohol Deoxygenation and Carbonyl Coupling Olefination

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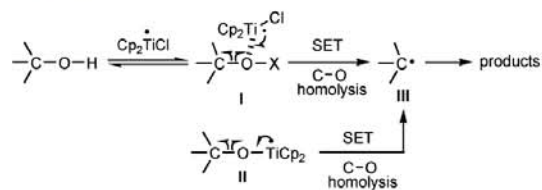
Abstract: Investigations detailed herein, including density functional theory (DFT) calculations, demonstrate that the formation of either alkoxy- or hydroxy-Ti(III) complexes considerably decreases the energy of activation for C–O bond homolysis. As a consequence of this observation, we described two new synthetic applications of Nugent's reagent in organic chemistry. The first of these applications is an one-step methodology for deoxygenation–reduction of alcohols, including benzylic and allylic alcohols and 1,2-dihydroxy compounds. Additionally, we have also proved that Ti(III) is capable of mediating carbonyl coupling–olefination. In this sense, and despite the fact that for over 35 years it has been widely accepted that either Ti(II) or Ti(0) was the active species in the reductive process of the McMurry reaction, the mechanistic evidence presented proves the involvement of Ti(III) pinacolates in the deoxygenation step of the herein described Nugent's reagent-mediated McMurry olefination. This observation sheds some light on probably one of the mechanistically more complex transformations in organic chemistry. Finally, we have also proved that both of these processes can be performed catalytically in Cp₂TiCl₂ by using trimethylsilyl chloride (TMSCl) as the final oxygen trap.

Introduction

It is well-known that Cp₂TiCl (Nugent's reagent) is a mild reductant, useful through monoelectronic transfer and widely employed in organic synthesis.¹ Its applications arise from the interaction of titanocene dichloride, acting as a Lewis acid, with the heteroatoms of different functional groups, which behave as Lewis bases. This interaction leads to a balanced complex that may evolve into different products. Recent research revealing mechanistic details about this interaction has been reported.² In this sense, evidence showing that H₂O and methanol can act, via the corresponding Ti(III) complexes, as an efficient hydrogen-atom donor has been published.^{2c,d}

With these considerations in mind, it would be reasonable to postulate that the interaction of an alcohol and Cp₂TiCl would

Scheme 1. Proposed Mechanism for Ti(III)-Promoted C–O Bond Homolysis



produce the alcohol complex **I**. The formation of this species, or of the titanocene alkoxy derivative **II**, could weaken the corresponding C–O bond allowing under suitable conditions and by means of monoelectronic transfer their homolytic cleavage to give rise to the C-centered radical **III**, which would finally evolve to the corresponding products (Scheme 1).

To validate this approach, we chose two synthetic transformations including C–O cleavages as key processes, namely, deoxygenation–reduction of alcohols and carbonyl coupling–olefinations.

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- (1) The single electron transfer bis(cyclopentadienyl)-titanium(III)chloride, Nugent's reagent, can be generated in situ by stirring commercial Cp₂TiCl₂ with dust Mn or Zn. For pioneering reports on the use of this reagent, see: (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997 and references cited therein. For pertinent reviews on the use of this reagent, see: (b) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788. (c) Gansäuer, A.; Pierobon, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 207–220. (d) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556–5573. (e) Barrero, A. F.; Quílez del Moral, J. F.; Sanchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627–1641. (f) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Bazdi, B.; Oltra, J. E. *Mini-Rev. Org. Chem.* **2006**, *3*, 23–35.

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Alcohol deoxygenation constitutes a powerful synthetic tool especially used in complex natural product synthesis.³ Most of the known synthetic procedures take place via a number of steps, the Barton–McCombie methodology being the most commonly used, mainly for secondary alcohols, due to its compatibility with different functional groups.⁴ Few procedures involving one-step deoxygenations have been described,⁵ which in our opinion makes necessary further efforts in this subject.

On the other hand, the reductive coupling of carbonyls into olefins by use of low-valent titanium species (LVT), known as the McMurry reaction, has been extensively used in organic synthesis, and both inter- and intramolecular couplings have been described to proceed with remarkable efficiency.⁶ This kind of reaction is usually carried out in two consecutive steps, namely, reduction of TiCl₄ or TiCl₃ followed by addition of the carbonyl compound. In this regard, a number of reducing agents such as Li, Na, K, Mg, Zn, KC₈, Zn(Cu), LiAlH₄, and others were used, in an attempt to overcome the reproducibility problems usually associated with this reaction. To this end, different improved protocols have been reported.⁷ From a mechanistic point of view, there are three main features to consider: formation of the LVT species, coupling reaction, and finally, deoxygenation of the intermediates leading to the olefin. In the coupling step, the involvement of acyl radical and/or carbenoid intermediates in the metallopinacolate formation is accepted, although their structure is claimed to be influenced by the nature of the carbonyl group, the titanium species, and the reducing agent.^{6g} In this sense, even more uncertainties exist about the actual mechanism of the deoxygenation of these metallopinacolate intermediates, although it has been widely

Scheme 2. Proposed Mechanism for Ti(III)-Mediated Alcohol Deoxygenation–Reduction

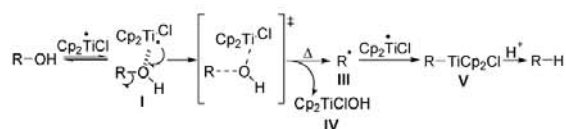








Table 1. Calculated^a ΔG^\ddagger and ΔG_{rxn} Values for C–O Bond Homolytic Cleavage of Different Alcohols

substrate	ΔG^\ddagger	ΔG_{rxn}
	30.0	2.3
	29.0	2.7
	29.9	4.9
	31.7	6.3
	41.7	19.8
	52.3	36.7

^a Calculated via UM05/Ahlich-VZDZ.

accepted that species with low valence states of Ti, either Ti(II) or Ti(0), were required in this reductive process.

Results and Discussion

A. Deoxygenation–Reduction of Alcohols. i. Mechanistic Proposal and DFT Calculations. The mechanistic proposal for deoxygenation–reduction of alcohols is depicted in Scheme 2. Thus, the C-centered radical **III**, originating from homolysis of the corresponding C–O bond, could evolve to the corresponding hydrocarbon after being trapped by another molecule of Cp₂TiCl₃, generating alkyltitanium **V**, which would then be protonated easily to afford the alkane. In this regard, the direct reduction of the radical **III** by species such as **I**, **IV**, or the solvent should not be ruled out.

To verify this hypothesis, density functional theory (DFT; UM05/Ahlich-VZDZ)⁸ calculations were carried out. Thus, the energy barriers (ΔG_{rxn} and ΔG^\ddagger) for homolytic cleavage of the C–O bond in the alcohol complex **I** were calculated for different types of alcohols (Table 1 and Figure 1).

Although the calculated values were endothermic for all compounds studied (**1–6**), the allylic and benzylic alcohols showed, as expected, lower activation and reaction energies

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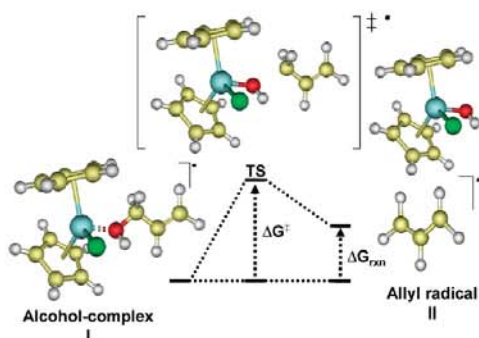


Figure 1. Energy diagram for C–O bond homolytic cleavage in allylic alcohol **1** (activation energy ΔG^\ddagger and reaction energy ΔG_{rxn}).

(Table 1). In any case, when these data were compared with those calculated theoretical and experimentally for the uncomplexed homolytic C–O bond dissociation,⁹ significant higher values were found for the uncomplexed species, which clearly show that this homolytic cleavage is strongly affected by coordination to Ti(III).

In light of these observations, we surmised that the necessary energy for this homolysis could be obtained by simply heating organic solutions of the corresponding alcohol– Cp_2TiCl complexes. Thus, a solution of benzylic alcohol **4** in THF (0.2 M) was treated with 2.1 equiv of TiCp_2Cl_2 and 8.0 equiv of Mn in THF. After the mixture was refluxed for 45 min, the reaction was proven to be completed, and gratifyingly, only toluene was obtained in an excellent yield of 93%.

Variations on the quantities of Nugent's reagent were carried out in order to gain further insight into the course of the reaction. Thus, when only 1.1 equiv of Cp_2TiCl_2 was used, the reaction stopped when approximately half the starting material **4** remained unaltered, toluene being obtained in a 47% yield. This fact suggests that the C-centered radical (**III**) is efficiently trapped by a second equivalent of Ti(III) leading to the formation of a benzyl–titanium intermediate (**V**). Consequently, 2.0 equiv of Ti(III) is required to drive the reaction to completion. With respect to the reducing agent, its quantity can be lowered up to 1.5 equiv, and the transformation still remains efficient (92%).

ii. Scope of the Reaction. We devoted our efforts to investigate the scope of this transformation (Table 2). Ti(III) (2.0 equiv), 1.5 equiv of reducing agent, and tetrahydrofuran (THF) as solvent were used, except for entry 19, where toluene was employed. Thus, different benzylic alcohols were transformed efficiently into the corresponding deoxygenated–reduced compounds (Table 2, entries 1–5). Allylic alcohols reacted in a similar way producing the expected deoxygenated–reduced products (Table 2, entries 6–12). Thus, farnesol **19** gave rise mainly to hydrocarbon **20** (Table 2, entry 7). In this case, the absence of cyclization products resulting from an intermediate allylic radical also supports the fast reduction of this species (Scheme 2). This result is in good accordance with previous results by some of us, which reported the high tendency of allylic radicals to evolve to allyltitanium species in presence of excess

(9) Complementary calculations on nonmediated homolytic C–O bond cleavages gave values larger than 56 kcal mol^{-1} in any case. The reported experimental value for MeOH is $102 \text{ kcal mol}^{-1}$; Kerr, J. A. *Chem. Rev.* **1966**, *66*, 465–500. For supplementary data, see Supporting Information.

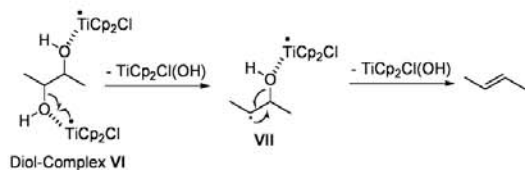
Table 2. Ti(III)-Mediated Deoxygenation–Reduction of Alcohols^a

entry	substrate	product	<i>t</i> (min)	yield (%)
1			60	79 ^c
2			60	91 ^c
3			50	90 ^c
4			90	60 ^c
5			55	83 ^c
6			50	91 ^c
7			60	80 ^c
8			55	92 ^b
9		-	240	-
10			60	70 ^c
11			50	87 ^c
12			120	38 ^c
13			240	85 ^b
14			65	94 ^c
15			60	79 ^c
16			90	86 ^b
17			90	68 ^c
18			90	92 ^c
19			120	90 ^c

^a 2.0 equiv of Ti(III) and 1.5 equiv of reducing agent per mole of starting material were used; THF was used as solvent. ^b 0.3 equiv of Ti(III), 4.0 equiv of TMSCl equiv, and 8 equiv of reducing agent per mole of starting material were used; THF was used as solvent. ^c Toluene was used as solvent.

Cp_2TiCl .¹⁰ The conversion of 4-hydroxy-3-methylbut-2-enyl benzoate **22** to isopentenyl benzoate **23** (Table 2, entry 10) deserved to be emphasized, since it mimicks the function of

- (10) (a) Seemann, M.; Bui, B. T. S.; Wolff, M.; Tritsch, D.; Campos, N.; Boronat, A.; Marquet, A.; Rohmer, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4337–4339. (b) Rohmer, M. *Nat. Prod. Rep.* **1999**, *16*, 565–574. (c) Eisenreich, W.; Bacher, A.; Arigoni, D.; Rohdich, F. *Cell. Mol. Life Sci.* **2004**, *61*, 1401–1426. (d) Xiao, J.; Chu, L.; Samakis, Y.; Liu, P. *J. Am. Chem. Soc.* **2009**, *131*, 9931–9933.
(11) (a) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Diéguez, H. R.; Sánchez, E. M. *J. Org. Chem.* **2007**, *72*, 2988–2995. (b) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Piedra, M.; Sánchez, E. M. *Org. Lett.* **2005**, *7*, 2301–2304.

Scheme 3. Proposed Mechanism for Ti(III)-Promoted Deoxygenation of 1,2-Diols

the IspH enzyme in the natural biosynthesis of C5 units of the terpenoids through the deoxyxylulose phosphate pathway.¹¹ With respect to 1,2-diols, treatment of 1,2-diphenylethane-1,2-diol **28** with 2.1 equiv of TiCp_2Cl_2 and 1.5 equiv of Mn led almost quantitatively to *trans*-stilbene **29** (Table 2, entry 14). Other 1,2-diols such as tetradecane-1,2-diol **32** and pinanediol **34** were easily deoxygenated to **33** and β -pinene **35**, respectively, in high yield (Table 2, entries 17 and 18). The stoichiometry of the reagents and good yield seem to indicate that the double bond would be formed via an initial deoxygenation from the diol complex **VI** leading to the C-centered radical **VII** (Scheme 3). The presence of this first radical would facilitate the second C–O cleavage to lead to the corresponding olefin.

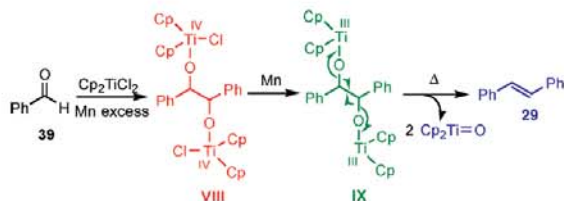
When nonactivated alcohols such as octadecanol **36** were used as starting material, no reaction was observed (see ΔG_{rxn} in Table 1). To overcome this unreactivity, other solvents with higher boiling point were tested. Thus, when a mixture of Nugent's reagent and **36** were heated in toluene at reflux, **37** and **38** (1:1) were obtained as result of deoxygenation–reduction and dehydration processes, respectively (Table 2, entry 19).

When we focused our attention on the presence of different functional groups in the alcohols to be deoxygenated, good yields of the corresponding deoxygenation products were also obtained in the presence of hydroxyls protected as methyl ethers (Table 2, entries 3 and 4), although the acid-labile silyl ethers did not tolerate the reaction conditions. Other hydroxyl protecting groups such as acetate also decompose under the reaction conditions. However, most robust esters such as the benzoate or, even more efficiently, the pivalate proved to be appropriate protecting groups in our deoxygenation protocol (Table 2, entries 10 and 11). Furthermore, alcohols containing carboxylic acids protected as methyl esters, as well as chloro derivatives, also deoxygenated in acceptable yields (Table 2, entries 5 and 15). Finally, although in a low-yield, nonoptimized process, a primary allylic alcohol was deoxygenated in the presence of a carbonyl group (Table 2, entry 12), which in our opinion widens promisingly the possibilities of this transformation.

B. Carbonyl Coupling–Olefination. i. Mechanistic Proposal.

On the basis of the above findings, namely, the dramatic decrease in the calculated homolytic C–O bond dissociation energy for $\text{RH}_2\text{C–OH}$ compared to that calculated for the complex $\text{Cp}_2\text{Ti}^{\text{III}}(\text{Cl})\text{HO–CH}_2\text{R}$ and the observed double-bond formation upon treatment of diols **28**, **30**, **32**, and **34** with titanocene(III), we surmised that the Nugent's reagent (Cp_2TiCl) would be able to promote carbonyl olefinations via homolysis of the carbon–oxygen bonds present in the Ti(III) pinacolates (**IX**, Scheme 4). Species **IX** would originate after reduction of the corresponding Ti(IV) pinacolates (**VIII**, Scheme 4), which are described as intermediates in Ti(III)-mediated pinacol coupling of carbonyls.¹²

To test the validity of this hypothesis, we began by examining whether homolytic cleavage of the C–O bond in the species $\text{PhCH}_2\text{OTi}^{\text{III}}\text{Cp}_2$ could be obtained by treating sodium benzoxide

Scheme 4. Proposed Mechanism for Ti(III)/Mn-Promoted Carbonyl Olefination

with Cp_2TiCl in refluxing THF.¹³ Gratifyingly, after this mixture was heated for 3 h, gas chromatographic (GC) analysis of the crude product proved the generation of toluene, which seemed to confirm the first premise of our hypothesis.^{2d} Encouraged by this result, we made benzaldehyde **39** react with 2 equiv of titanocene(III) in THF at reflux. Stilbene **29** was thus obtained with high efficiency (93% yield) after 1 h (Table 3, entry 1). Considering that the system $\text{Cp}_2\text{TiCl}_2/\text{Mn}$ was previously reported to mediate pinacol coupling of aldehydes and ketones,¹² we focused our efforts to gain an insight into the real species participating in the deoxygenation step.

To this end, we subjected benzaldehyde **39** to the same experimental conditions described above but now maintained the temperature at 25 °C. After 10 min of stirring at this temperature, analysis of an aliquot taken from the green reaction mixture revealed complete consumption of the starting material, benzopinacol being the only product formed. Excess Mn was then removed from the remaining reaction mixture, and the filtrate was heated at reflux for 1 h to afford again stilbene **29**. It is worth noting the progressive color change, from green to blue, during the heating. At this point, it was reasonable to assume the involvement of a Ti(III) pinacolate in this olefination process, according to the mechanistic proposal depicted in Scheme 4. The excess Mn present in the reaction medium would reduce the initially generated Ti(IV) pinacolate species¹² to the corresponding Ti(III) species. The fact that, to the best of our knowledge, Mn is not able to reduce Ti to a valence lower than 3 at room temperature, together with the green color of the solution, constitutes a strong hint to confirm the presence of this Ti(III) metalpinacol.¹⁴

A final piece of evidence to denote the involvement of Ti(III) pinacolates in the deoxygenation step was derived from the following experience. Thus, addition of only 0.5 equiv of Zn or Mn to a solution of 1 equiv of Cp_2TiCl_2 in THF at room temperature, after 5 min of stirring, caused the expected color change in the solution, which turned from red to green, thus confirming the reduction of the Ti(IV) species to Ti(III). Addition at this point of 1 equiv of benzaldehyde **39** caused the solution to show an orange hue within a few minutes, most likely due to the presence of Ti(IV) pinacolates. NMR analysis of an aliquot confirmed the disappearance of benzaldehyde and

- (12) (a) Barden, M. C.; Schwarz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484–5485. Enemärke, R. J.; Larsen, J.; Hjøllund, G. H.; Troels Skrydstrup, T.; Daasbjerg, K. *Organometallics* **2005**, *24*, 1252–126. (b) Paradas, M.; Campaña, A. G.; Estévez, R. E.; Álvarez de Cienfuegos, L.; Jiménez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2009**, *74*, 3616–3619 and references cited therein.
- (13) For the preparation of biscyclopentadienyl titanium alkoxides, see: Huffman, J. C.; Moloy, K. G.; Marsella, J. A.; Caulton, K. G. *J. Am. Chem. Soc.* **1980**, *102*, 3009–3014.
- (14) Villiers and Ephritikhine postulated the involvement of U(III) analogues in the reductive coupling of ketones: Villiers, C.; Ephritikhine, M. *Chem.—Eur. J.* **2001**, *14*, 3043–3051.

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Table 3. Titanocene(III)-Mediated Reductive Carbonyl Coupling^a

entry	substrate	product	yield (%)
1			93 ^d
2			87 ^d
3			94 ^d
4			93 ^d
5			74 ^d
6			95 ^b
7			65 ^d
8			76 ^d
9			74 ^d
10			73 ^d
11			71 ^d
12			62 ^d
13			65 ^e
14			77 ^e

^a 1.2 equiv of Ti(III) and 2.4 equiv of reducing agent per mole of starting material were used; THF was used as solvent. ^b 0.3 equiv of Ti(III), 4.0 equiv of TMSCl equiv, and 8 equiv of reducing agent per mole of starting material were used; THF was used as solvent. ^c For details, see text.

the sole presence of benzopinacol as reaction product. This orange solution remained unaltered for hours, in both color and composition. At this point, addition of a further 0.5 equiv of Zn or Mn led the reaction mixture to recover its former green color (15 min), which was rationalized by assuming a new reduction from the corresponding Ti(IV) to Ti(III) pinacolate (Scheme 4). At this moment, benzopinacol was again proven to be the only component of the reaction mixture. As happened previously, no change in the color or composition was observed after several hours of stirring. However, gentle heating until refluxing temperature was reached produced the formation of stilbene **29**, as well as a last color change, in this case, from green to dark blue, which was attributed to the production of titanocene oxide as a result of the deoxygenation step.

ii. Scope of the Reaction. Once we obtained conclusive evidence confirming the involvement of Ti(III) species in the

deoxygenation process, we devoted our effort to investigate the scope of this transformation. Thus, excellent to good yields and reproducibility were also found with other aromatic and conjugated aldehydes (Table 3, entries 1–10). This protocol proved also to be applicable, less efficiently, to aromatic and aliphatic ketones (Table 3, entries 11 and 12), where longer reaction times were necessary to complete the reductive coupling.¹⁵ Different aliphatic and aromatic aldehydes bearing additional functional groups led efficiently to the coupling products, which increases substantially the potential of this transformation. Thus, aldehydes containing hydroxyl groups protected as ethers or esters, and even unprotected hydroxyl derivatives, coupled efficiently (Table 3, entries 2, 4, and 10). Methoxycarbonyl and halogen derivatives also reacted with acceptable yields (Table 3, entries 3 and 5).

With the aim of widening the scope of this transformation, we checked the ability of titanocene(III) to promote intermolecular cross-coupling reaction between dissimilar ketones. Thus, we submitted benzophenone **60** and excess (4 equiv) cyclohexanone **59** to the standard reaction conditions to obtain the intermolecular cross coupling adduct **61** at 65% yield (Table 3, entry 13). Similar results were obtained with a mixture of citral **49** and benzaldehyde **39** in excess (Table 3, entry 14). It was thus proven that unsymmetrical olefins can be generated by reaction of aromatic and aliphatic carbonyls.

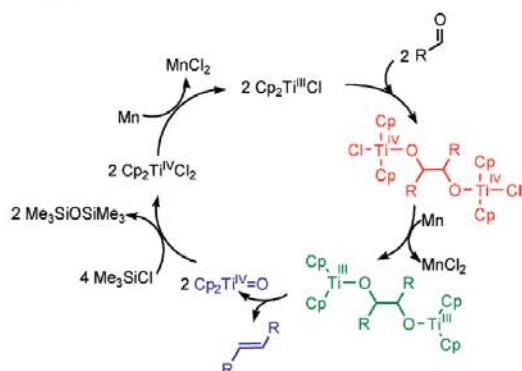
C. Catalytic Processes in Titanium. Our final efforts were devoted to render these processes catalytic. Among the types of reagents that have been described to regenerate Cp₂TiCl₂ from species of oxygen-bonded titanium,¹⁶ chlorosilanes were claimed to promote carbonyl coupling reactions catalytic in titanium by regenerating TiCl₃ from the corresponding titanium oxide, namely, ClTi=O, and accumulating the corresponding hexamethyldisiloxane, which is finally removed in vacuum. Since we propose the formation of titanocene oxides or hydroxytitanocene derivatives in the deoxygenation step of these processes, we decided to make farnesol **19** react with 0.3 equiv of Cp₂TiCl₂ (2 equiv is required in the noncatalytic route) in the presence of excess Mn and 4 equiv of trimethylsilyl chloride (TMSCl). To our delight, the deoxygenation product was obtained after 55 min in an exceptional 92% yield (Table 2, entry 8). The deoxygenation of diol **30** could also be achieved by employing substoichiometric quantities of Ti and TMSCl as regenerator. The yield of the corresponding alkene (86%) was again higher than that obtained in the stoichiometric version (Table 2, entry 16).

Additionally, this catalytic protocol could also be used to promote the reductive coupling of benzylic aldehydes, and thus, by using only 0.3 mmol of Cp₂TiCl₂ and 4 equiv of TMSCl, **46** was transformed into **31** in 95% yield (Table 3, entry 6), which again meant an increase in the efficiency of transformation when compared to the stoichiometric version.

The catalytic protocol for this McMurry reaction can be rationalized as depicted in Scheme 5. Thus, the titanium oxo species resulting from the deoxygenation step would react with TMSCl in view of the pronounced oxophilicity of silicon. Consequently, hexamethyldisiloxane, which can be easily removed, would be the final acceptor of oxygen. In this sense, the fact that TMSCl, a known regenerator of titanium chloride from titanium oxides, is capable of regenerating the final

(15) Although in these cases, other reductive coupling mechanisms possibly coexist, it should be noted that the corresponding pinacols deriving from acetophenone **55** and geranylketone **57** could be isolated.

(16) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475.

Scheme 5. Proposed Catalytic Cycle for Reductive Carbonyl Olefination

titanium species produced in this transformation strongly supports the proposed formation of $\text{Cp}_2\text{Ti}=\text{O}$ in the deoxygenation process.

A final piece of evidence of the potential of this protocol was obtained when the keto alcohol **26** was subjected to catalytic conditions, giving an excellent 85% yield of the deoxygenated compound. The yield improved significantly on that obtained in the stoichiometric version, an increase that was noticed in all cases where both versions were compared.

Conclusion

We describe two new synthetic applications of Nugent's reagent in organic chemistry as a direct consequence of the dramatic decrease in homolytic C–O bond dissociation energy for $\text{RH}_2\text{C}-\text{OH}$ compared to that for the complex $\text{Cp}_2\text{Ti}^{\text{III}}(\text{Cl})\text{HO}-\text{CH}_2\text{R}$. The first of these applications is an easy and reproducible deoxygenation–reduction procedure for alcohols and 1,2-diols. This method complements alternative previously reported deoxygenations and is of general interest to organic synthesis. Its application on the allylic terpenoid alcohol **22** deserved to be emphasized, since it mimicks the

function of the IspH enzyme in the natural biosynthesis of C5 units of the terpenoids through the deoxyxylulose phosphate pathway.¹¹

We have also described that Nugent's reagent has the capability to induce reductive carbonyl coupling in reasonable short reaction times and with total reproducibility. The mechanistic evidence presented, proving the involvement of Ti(III) pinacولات in the deoxygenation step of this McMurry olefination, is particularly noteworthy since, in our opinion, it casts some light on one of the mechanistically more obscure transformations in organic chemistry.

Additionally, we have proven how these processes can be performed catalytically in Cp_2TiCl_2 by using TMSCl as the final oxygen trap. In this sense, we should underscore the fact that keto alcohol **26** was efficiently transformed into the corresponding deoxygenated compound **27** by using the catalytic protocol, a process where the less reactive aliphatic keto group was completely discriminated in favor of the allylic alcohol.

Our current interest is focused to gain a comprehensive understanding of the overall reactions and to widen the scope of these innovative processes. We are also engaged in testing the applicability of these processes in the synthesis of bioactive natural products.

Acknowledgment. This research was supported by the Spanish Ministry of Science and Innovation, Project CTQ2006-15575-C02-01. We also thank the "Centro de Servicios de Informática y Redes de Comunicaciones" (CSIRC), University of Granada, for allowing us to use its supercomputing facilities (UGRGrid). V.D. thanks the Spanish Ministry of Science and Technology for a predoctoral grant enabling him to pursue these studies.

Supporting Information Available: Computational details, experimental procedures, spectroscopic data, and ^1H and ^{13}C NMR spectra for compounds **8**, **10**, **12**, **14**, **16**, **18**, **20**, **23**, **25**, **27**, **29**, **31**, **33**, **41**, **43**, **45**, **48**, **50**, **52**, **54**, **56**, **58**, **61**, and **62** and complete ref 8a. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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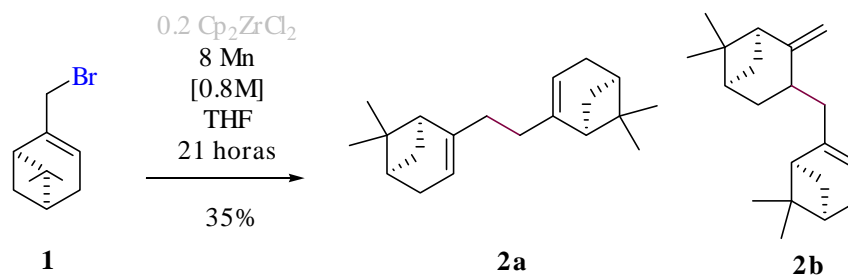
IV. DISCUSIÓN DE **RESULTADOS**

**1. ACOPLAMIENTOS C-C EN
DERIVADOS HALOGENADOS
ALÍLICOS Y BENCÍLICOS.**

1.1 Acoplamiento catalítico de derivados halogenados alílicos mediante Mn/Zr^{IV}.

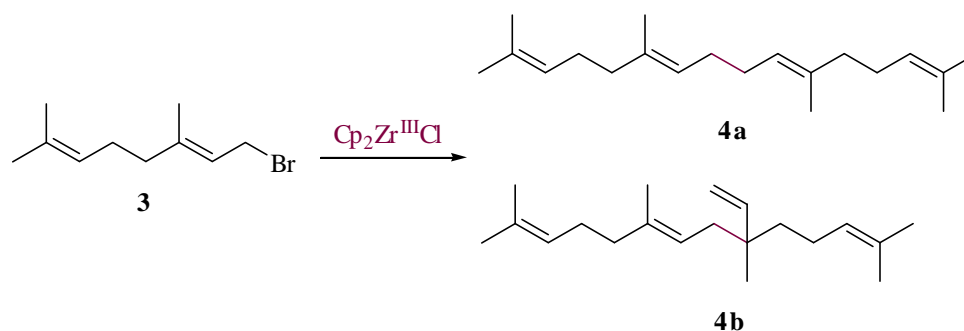
Como se ha indicado en el apartado de introducción, uno de los objetivos que persigue nuestro Grupo de Investigación es llevar a cabo un estudio comparativo de las especies de $\text{Cp}_2\text{Zr}^{\text{III}}\text{Cl}$ análogas a las de Ti^{III} para comprobar su comportamiento químico en reacciones radicalarias. Teniendo en cuenta la estructura electrónica similar del Zr y el Ti, se pensó que las especies de $\text{Cp}_2\text{Zr}^{\text{III}}\text{Cl}$ podrían también originar acoplamiento con los haluros alílicos.

Nuestro estudio empezó haciendo reaccionar el bromuro de mirtenilo (**1**) bajo las mismas condiciones catalíticas usadas con el Ti^{III} :⁵⁷ 0.2 equivalentes de $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2$, 8 equivalentes de Mn y THF (0.07 M), pero después de 28 horas no se había producido acoplamiento. Tras este primer intento, se incrementó la concentración de producto de partida hasta 0.8 M obteniéndose un rendimiento en productos de acoplamiento (**2a** + **2b**) del 35% quedando un 32% de material de partida sin reaccionar (Esquema 1).



Esquema 1

Se comprobó entonces en bibliografía que las disoluciones de $\text{Cp}_2\text{Zr}^{\text{III}}\text{Cl}$ en THF son de color **rojo intenso**.^{155,156} Sin embargo, en nuestro caso la combinación de $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2$ y Mn en THF producía disoluciones incoloras, lo cual indica que la especie $\text{Cp}_2\text{Zr}^{\text{III}}\text{Cl}$ no se forma. Entonces se procedió a reducir $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2$ con un metal de mayor potencial reductor, como Na en forma de amalgama con Hg, y se obtuvo una disolución de color rojo intenso, que confirmaba la presencia de la especie $\text{Cp}_2\text{Zr}^{\text{III}}\text{Cl}$. Sobre esta disolución de color rojo se adicionó el bromuro de geranilo (**3**) obteniéndose un 85% de productos de acoplamiento (**4a** + **4b**, Esquema 2).



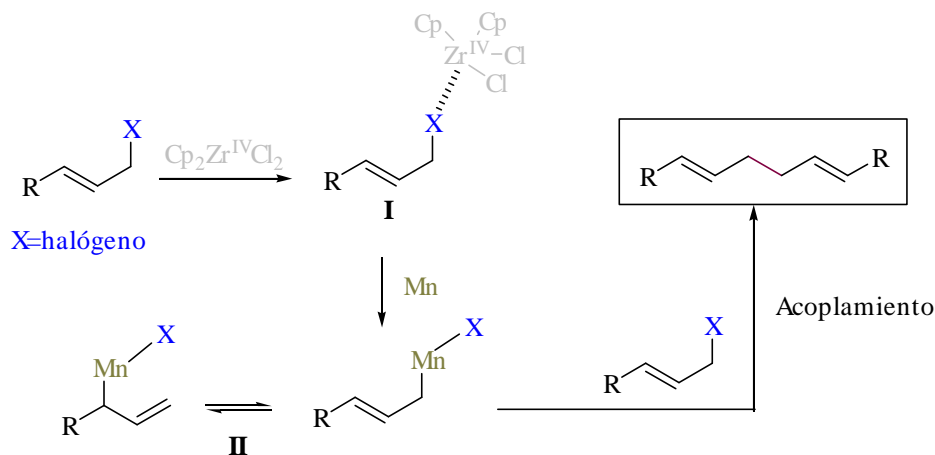
Esquema 2

Este resultado hace pensar que la reacción con $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2/\text{Mn}$ del Esquema 1, considerando que el Mn por sí sólo no es capaz de llevar a cabo la

¹⁵⁵ Cuenca, T.; Royo, P. J. *Organomet. Chem.* **1985**, 293, 61-67

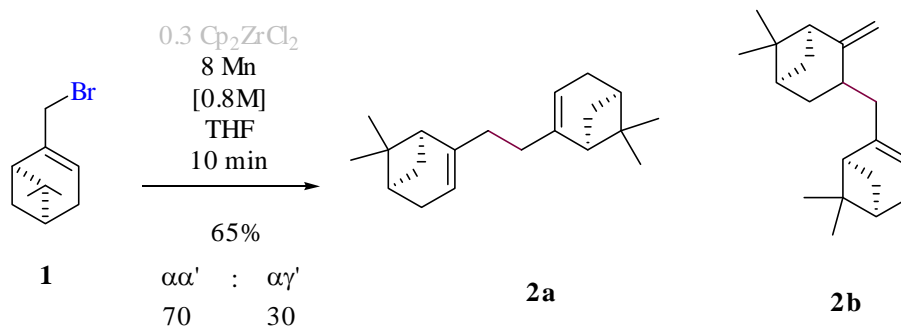
¹⁵⁶ Barden, M. C.; Schwartz, J. J. *Org. Chem.* **1997**, 62, 7520-7521

reducción de los halógeno-derivados alílicos, se produce mediante una activación del enlace C-X por parte del $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2$, actuando como un buen ácido de Lewis.¹⁵⁷ Así el enlace C-X activado, es ahora susceptible de ser reducido con Mn para dar el correspondiente organomanganeso derivado (especie representada en el Esquema 3 por II).



Esquema 3. Posible mecanismo para el homo-acoplamiento de haluros alílicos.

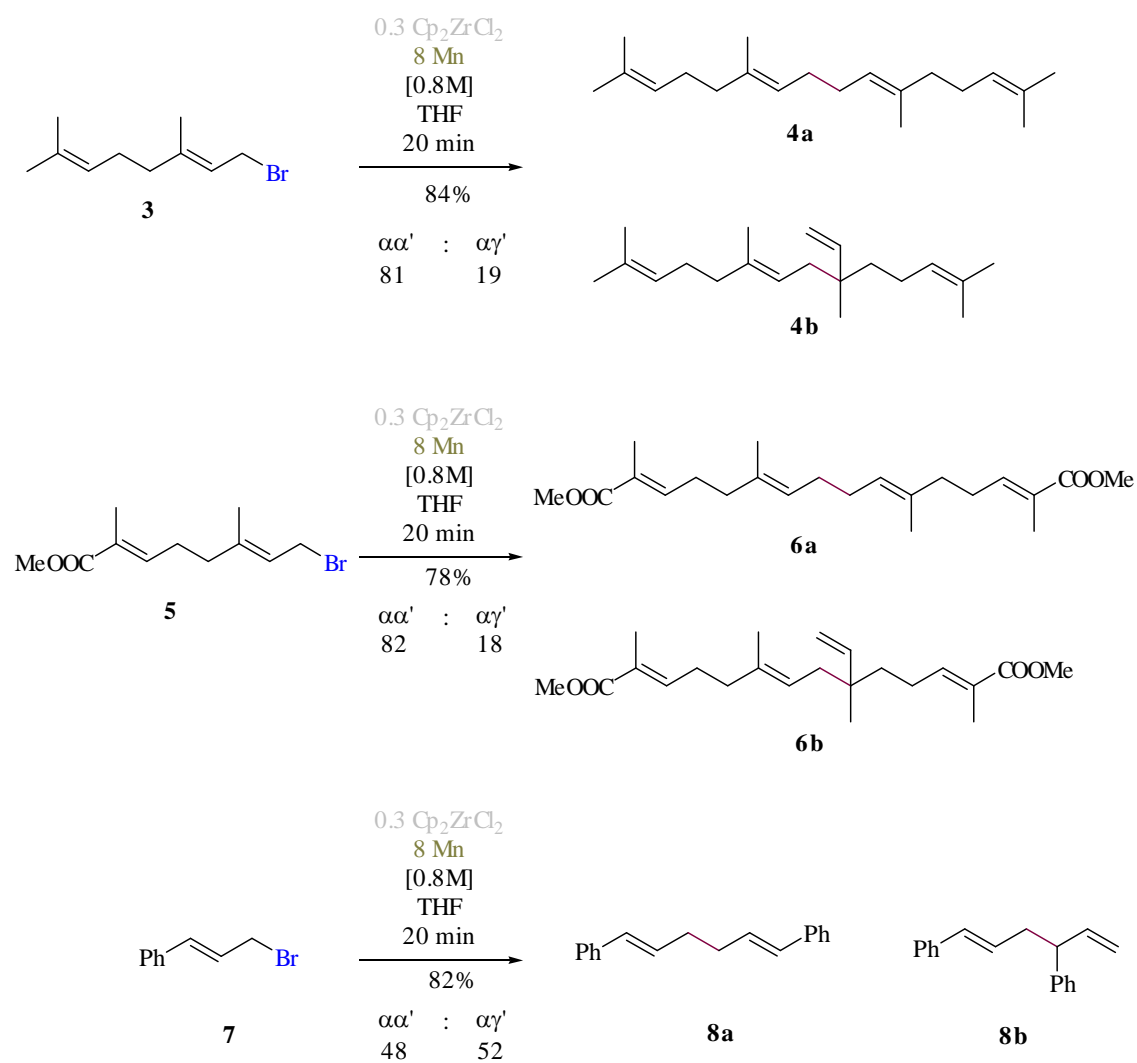
Posteriormente se comprobó que el rendimiento de este proceso podía ser optimizado, cuando la reacción se llevaba a cabo incrementando la cantidad de Zr^{IV} de 0.2 a 0.3 equivalentes. Así la conversión de (1) hasta los correspondientes productos de acoplamiento (2) fue total después de sólo 10 minutos con un rendimiento del 65% (Esquema 4).



¹⁵⁷ a) Ma, J.; Chan, T.-H. *Tetrahedron Lett.* **1998**, 39, 2499-2502; b) Li, C.-J.; Meng, Y.; *J. Org. Chem.* **1998**, 63, 7498-7504; c) Kim, S.-H.; Hiyama, T. *Organomet.* **1982**, 1, 1249-1251; d) Cahiez, G.; *Tetrahedron Lett.* **1989**, 30, 7373-7376; e) Suh, Y.; Lee, J.-S. *J. Organomet. Chem.* **2003**, 684, 20-36.

Esquema 4

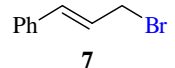
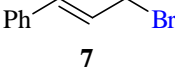
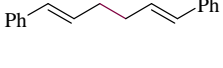
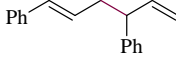
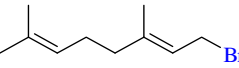
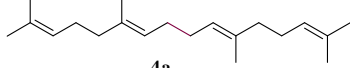
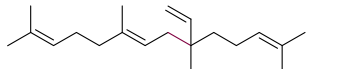
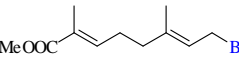
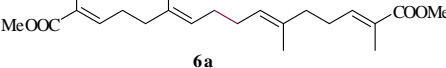
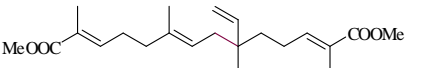
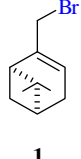
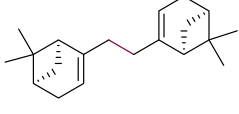
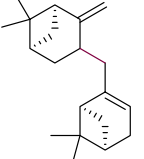
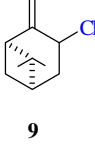
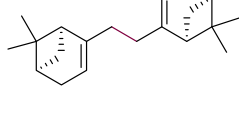
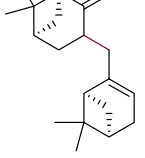
En el siguiente esquema se ilustran el resto de las reacciones de homocoplamiento con $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2/\text{Mn}$ que se han realizado para generalizar el método (Esquema 5). Los productos de acoplamiento fueron analizados en cada reacción mediante espectroscopia de ^1H RMN y CG/EM, obteniéndose las correspondientes distribuciones de regioisómeros que se indican en los esquemas correspondientes. Además se han aislado en cada caso los correspondientes productos mediante cromatografía en columna y HPLC semi-preparativo en fase normal con sílica gel.



Esquema 5

A efectos comparativos, a continuación se exponen en la siguiente tabla los resultados previos a este trabajo, correspondientes a las reacciones de homoacoplamiento mediante el empleo de Ti^{III} sobre los mismos sustratos que se han utilizado para el estudio del proceso con $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2/\text{Mn}$ (Tabla 1).

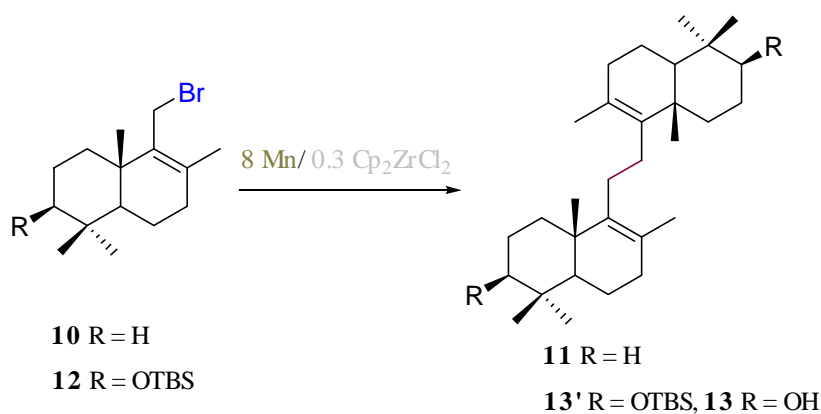
TABLA 1. Acoplamiento de haluros alílicos bajo condiciones catalíticas de Ti^{III} .

Caso	Haluro alílico	[M] ^c	Compuesto	Proporción ($\alpha\alpha'$: $\alpha\gamma'$)	Rend. (%)
1		0.07	No reacciona	–	–
2		0.8	 	(45:55)	85
3		0.07	 	(64:36)	89
4		0.07	 	(74:26)	85
5		0.07	 	(61:39)	70
6		0.07	 	(52:48)	90

^c Concentración molar en THF.

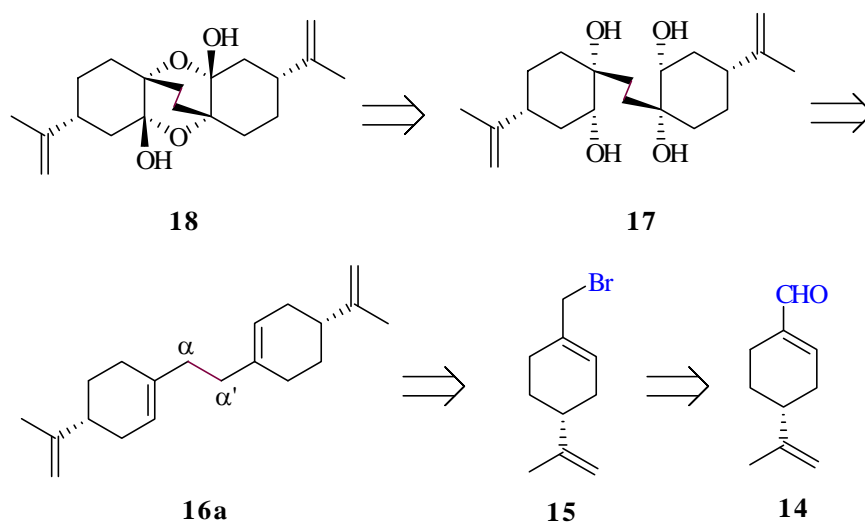
La comparación de estos resultados con los anteriormente expuestos de $Cp_2Zr^{IV}Cl_2/Mn$, pone de manifiesto por un lado que los rendimientos globales de homo-acoplamiento son de la misma magnitud. En segundo lugar se observa una **mayor regioselectividad** hacia la formación de productos resultado del acoplamiento $\alpha\alpha'$ mayoritaria en todos los casos cuando se emplea la mezcla reactiva $Cp_2Zr^{IV}Cl_2/Mn$. Esta mayor regioselectividad llega a hacerse muy acusada en la síntesis del diterpeno digeranilo, donde se pasa de un balance ($\alpha\alpha'$: $\alpha\gamma'$) de 64/36 con el empleo de Ti^{III} a 81/19 en este caso.

Posteriormente se han llevado a cabo diversas aplicaciones de esta metodología de homo-acoplamiento catalítico, dentro de diversas síntesis en multi-etapas. Se eligieron síntesis en las que la reacción constituye una etapa clave para la eficacia del procedimiento sintético global. En la síntesis de los triterpenos (+)- β -onoceradieno (**11**) y (+)- β -onocerina (**13**) se realizó el homo-acoplamiento de los sintones triterpénicos bicíclicos **10** y **12**,⁵⁷ mediante el empleo de Mn y $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2$ como catalizador, obteniéndose los correspondientes productos de acoplamientos con buenos rendimientos, rendimientos del 75% y 80% respectivamente (Esquema 6).



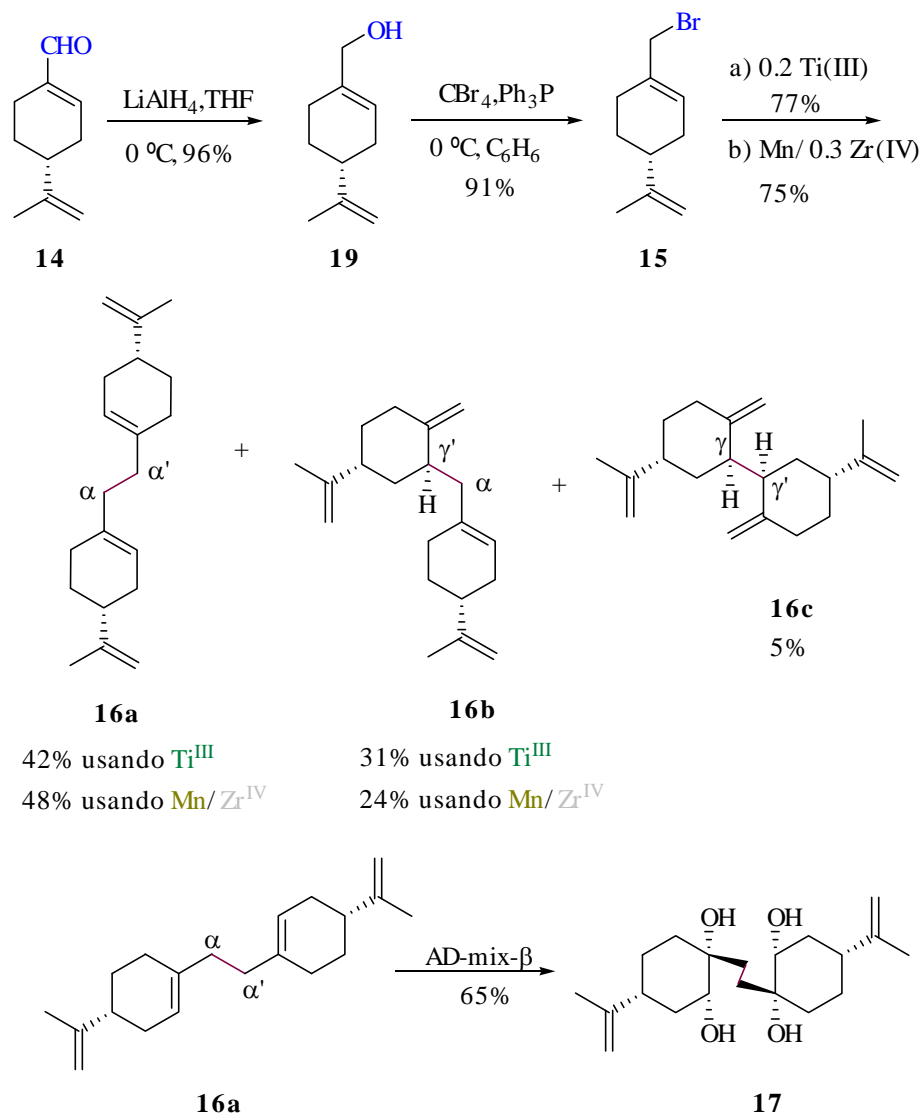
Esquema 6. Síntesis del (+)- β -onoceradieno (**11**) y de la (+)- β -onocerina (**13**).

Otro ejemplo se ha centrado en la síntesis del diterpeno natural (+)-cimbodiacetal (**18**) (Esquema 7). En este caso el esquema retrosintético muestra como intermedio clave la formación del compuesto (**16a**) que se puede obtener aplicando nuestra metodología por homo-acoplamiento del bromuro alílico (**15**) (bromuro de perillilo).



Esquema 7. Aproximación a la síntesis de (+)-cimodiacetal (18).

El bromuro alílico **15** fue obtenido a partir de perillaldehído comercial (**14**) en dos etapas mediante reducción hasta el correspondiente alcohol alílico **19** con hidruro de aluminio y litio a 0 °C y posterior bromación con tetrabromuro de carbono en presencia de trifenilfosfina (Esquema 8). Se obtiene así el bromuro de perillilo con más del 87% de rendimiento global. La reacción de homo-acoplamiento de **15** se realizó primero con Ti^{III} obteniéndose un balance de regioselectividad de 42% $\alpha\alpha'$ frente a 31% $\alpha\gamma'$, y posteriormente empleando el reactivo $\text{Cp}_2\text{Zr}^{\text{IV}}\text{Cl}_2/\text{Mn}$ resultando un 48% $\alpha\alpha'$ frente a un 24% $\alpha\gamma'$. En este caso se comprueba como nuevamente el nuevo reactivo mostró una mejor regioselectividad (Esquema 8).



Esquema 8. Homo-acoplamiento de bromuro de (*R*)-perillilo (**15**): síntesis del compuesto **17**.

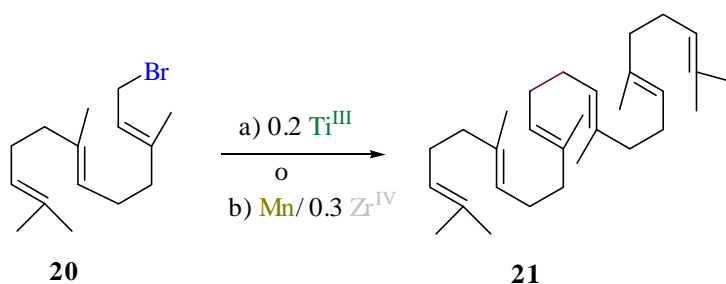
Dentro del esquema sintético, el producto de homo-acoplamiento **16a** se hizo reaccionar con los reactivos de la dihidroxilación asimétrica de Sharpless¹⁵⁸

¹⁵⁸ Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; et al., *The Osmium-Catalyzed Asymmetric*

con AD-mix- α obteniéndose con un buen rendimiento y completa diastereoselección el compuesto tetra-hidroxilado **17**. Este último paso deja expedita la ruta hacia el producto natural **18**.

Finalmente un tercer ejemplo ha estribado en la síntesis del triterpeno comercial escualeno (**21**). Este producto puede ser preparado a partir del bromuro de *trans, trans*-farmesilo (**20**), mediante el empleo de 0.2 equivalentes de Ti^{III} en sólo una etapa y con un rendimiento del 43% (Tabla 2, Entrada 1). Teniendo en cuenta los resultados anteriores de esta memoria, pensamos que el rendimiento podría mejorarse mediante el uso de $Cp_2Zr^{IV}Cl_2/Mn$. Afortunadamente, el tratamiento de **20** con 0.3 equivalentes de $Cp_2Zr^{IV}Cl_2$ y 8 equivalentes de Mn dio como resultado un rendimiento del 51% de escualeno (Tabla 2, Entrada 2) como consecuencia de la mejor regioselectividad que se venía observando a lo largo de todo este estudio.

TABLA 2. Síntesis del escualeno (**21**)



Caso	Bromuro Alílico	Ti^{III}	Zr^{IV}	[M]	t (min)	Escualeno (%)
1 ¹⁵⁹	20	0.2	0	0.07	10	21 (43%)

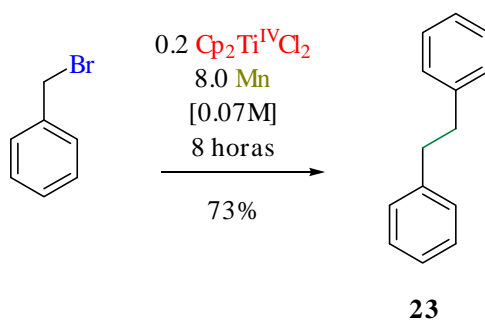
Dihydroxylation: A New Ligand Class and a Process Improvement. *J. Org. Chem.* **1992**, *57*, 2768-2771.

¹⁵⁹ "Mild Ti(III)- and Mn/Zr(IV)-Catalytic Reductive Coupling of Allylic Halides: Efficient Synthesis of Symmetric Terpenes" *J. Org. Chem.* **2007**, *72*, 2988-2995.

2	20	0	0.3	0.8	60	21 (51%)
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1.2 Acoplamiento de derivados halogenados bencílicos mediante Ti^{III}: Síntesis de derivados dibencílicos.

Empezamos nuestro estudio haciendo reaccionar el bromuro de bencilo (**22**) con 0.2 equivalentes de $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ y 8.0 equivalentes de Mn en THF seco y desoxigenado (c 0.07 M). Estas condiciones son las que se habían empleado previamente para las reacciones de homo-acoplamiento de bromuros alílicos en tiempos reducidos (10-20 minutos). Bajo estas condiciones, la reacción se completó después de 8 horas y el dibencilo (**23**) se obtuvo con un 73% de rendimiento (Esquema 9).

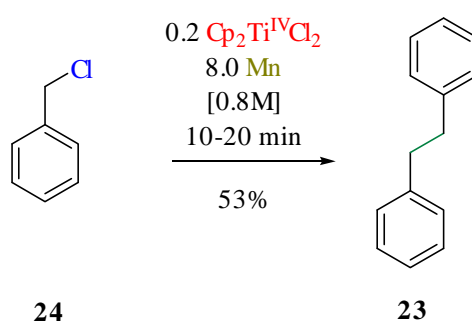


Esquema 9

La notoria reactividad inferior de (**22**) comparada con la de los bromuros alílicos, podría atribuirse a la elevada estabilidad del radical bencílico intermedio debido al efecto resonante del anillo aromático. Cuando la

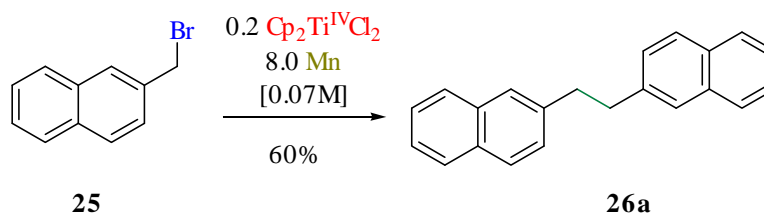
concentración de reactivo se elevó cerca de 10 veces (c 0.8 M), se incrementó notoriamente la velocidad de reacción.

Cuando se cambia el bromo por cloro, se observa que tras 24 horas el cloruro de bencilo (**24**) no da reacción empleando $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ en condiciones diluidas. Sin embargo se obtuvo un 53% de rendimiento de dibencilo (**23**), cuando la concentración se incrementó hasta 0.8M (Esquema 10).



Esquema 10

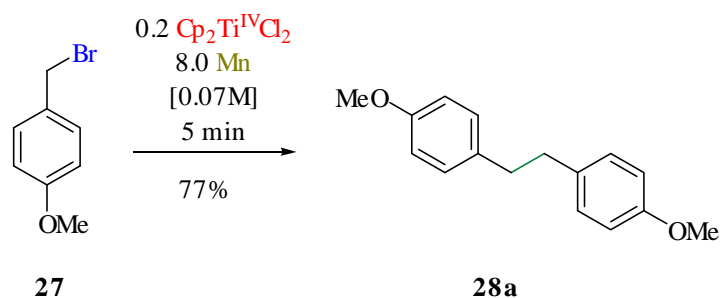
Adicionalmente, el 2-(bromometil)naftaleno (**25**) se comporta de manera similar, y se obtiene 1,2-bis(naftil)etano (**26a**) con un 60% de rendimiento cuando se realiza el proceso con una concentración de 0.07 M (Esquema 11).



Esquema 11

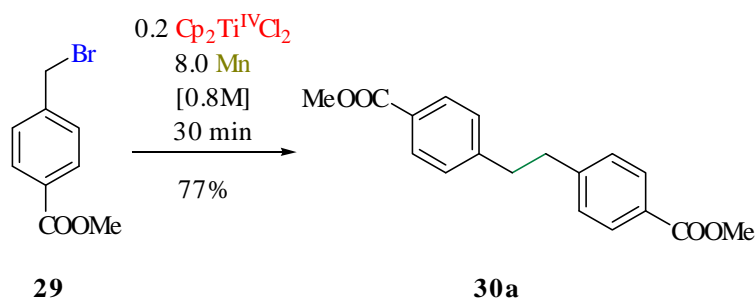
Con el objetivo de intentar aumentar el alcance de este tipo de reacciones y generalizar el método, se examinó la influencia de diferentes sustituyentes oxigenados en el anillo aromático. Así la presencia de sustituyentes electrón-donantes, tales como el grupo metoxi- en posición *para* respecto del bromo-

metileno en el bencil-derivado (**27**), hace que este reaccione rápidamente y en pocos minutos origina el producto (**28a**) con un 77% de rendimiento (Esquema 12).



Esquema 12

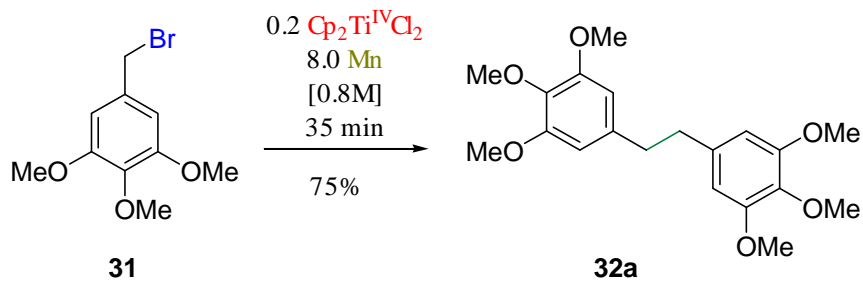
En el caso opuesto, cuando se coloca un grupo electrón-atrayente como sustituyente en *para*, se observa una disminución notable del rendimiento en la formación del producto de homo-acoplamiento (57%). En este caso usando condiciones de mayor concentración (c 0.8M) se obtuvieron resultados satisfactorios (73%) (Esquema 13).



Esquema 13

También se obtuvieron buenos resultados cuando se introdujeron tres grupos metoxi- en el anillo aromático del bromuro bencílico de partida. El derivado (**31**) conduce a un 40% de (**32a**) tras 8 horas de reacción, en condiciones de baja concentración [0.07M]. Sin embargo, elevando la concentración [0.8M] el rendimiento obtenido es de un 70% de (**32a**) en 35 minutos, y constituye una síntesis directa de este producto natural aislado de

Frullania brittoniae subsp. *truncatifolia*¹⁶⁰ que entra a formar parte de la composición de un antitumoral patentado (Esquema 14).



Esquema 14

¹⁶⁰ Asakawa, Y.; Tanikawa, K.; Aratani, T. *Phytochemistry* **1976**, *15*, 1057-1059.

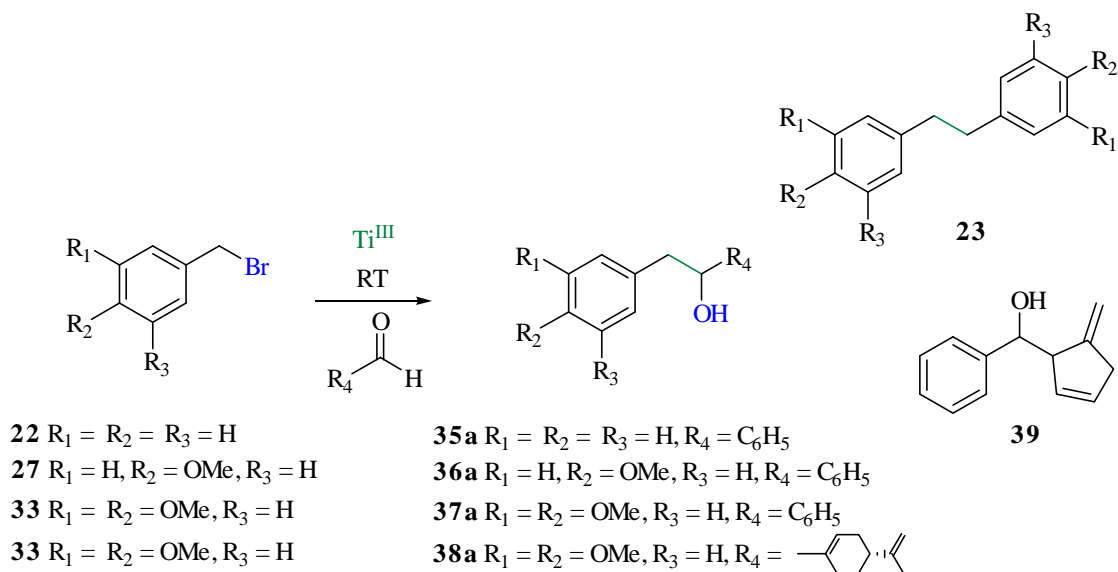
1.3 Acoplamiento mixto entre derivados halogenados bencílicos y aldehídos catalizados por Ti^{III}.

Animados por los excelentes resultados anteriores, se decidió explorar la viabilidad de la formación de enlaces C-C por reacción entre bromuros de bencilo y aldehídos (Esquema 15, Tabla 3).

Cuando el bromuro de bencilo (**22**) se hace reaccionar con benzaldehído usando 0.2 equivalentes de Ti^{III} en presencia de la mezcla de reactivos Mn/colidina/TMSCl, el producto de acoplamiento mixto (**35a**) fue el mayoritario (Tabla 3, Entrada 1; Esquema 15). Siguiendo con el estudio, cuando se añade un exceso de Ti^{III} (2.0 equivalentes) sobre una disolución de (**22**) y benzaldehído, se obtiene un resultado similar (Tabla 3, Entrada 2).

TABLA 3. Reacciones de acoplamiento mixto mediadas por Ti^{III}

Entrada	Haluro de bencilo	T (min)	Compuesto (%)
1	22	180	35a (38%) + 23 (5%)
2	22	5	35a (35%) + 23 (24%)
3	22	10	35a (57%) + 23 (15%)
4	27	5	36a (50%) + 28a (15%) + 39 (19%)
5	33	10	37 (58%) + 39 (20%)
6	33	15	38a (60%)



Esquema 15

Tras estos resultados preliminares, enfocamos nuestros esfuerzos en intentar mejorar las condiciones experimentales de estos acoplamientos mixtos. En este sentido se experimentaron los siguientes factores: el uso de un solo equivalente de Ti^{III} , la rápida y simultánea adición del aldehído (2.0 equiv.) y del bromuro de bencilo correspondiente (1.0 equiv), así como el empleo de un exceso de aldehído (2.0 equiv) (debido a la tendencia de producirse acoplamiento pinacolínico en presencia de este conjunto de reactivos). Estas modificaciones permitieron que los rendimientos de la reacción tipo Barbier estuvieran cerca del 60% (Tabla 3, casos 3-6). En los casos 4 y 5, además de los correspondientes productos de acoplamiento mixto, se obtuvo de forma minoritaria otro producto con una estructura peculiar (compuesto **39**, Figura 1) que se aisló con un rendimiento del 19% y 20% respectivamente.

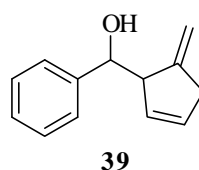
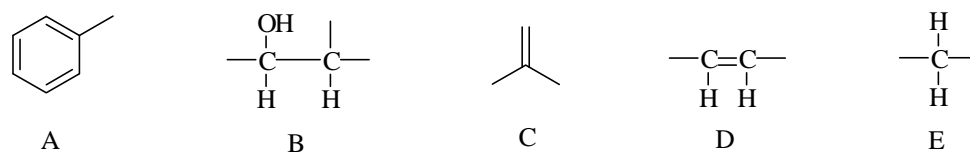


Figura 1

Este compuesto presenta una fórmula molecular $C_{13}H_{14}O$ según su espectro de masas de alta resolución. La función oxigenada se trata de un hidroxilo, pues presenta absorción a 3400 y 1033 cm^{-1} en el IR, dónde asimismo, se observan bandas de doble enlace y anillo bencénico. En su espectro de ^1H -RMN se pone de manifiesto la presencia de un anillo bencénico monosustituido, por la existencia de cinco protones aromáticos, lo cual se corrobora con las señales y δ correspondientes en ^{13}C -RMN. Además se comprueba la presencia de dos dobles enlaces en ^1H -RMN; uno de ellos terminal di-sustituido con dos señales singlete ancho entre 5.0 y 5.2 ppm y otro 1,2-di-sustituido con estereoquímica *Z* a 5.4 y 5.8 ppm con un acoplamiento de 4.8 Hz. Las restantes señales se asignan a un protón de un alcohol secundario (4.4 ppm, $J = 7.4$ Hz) acoplado con otro protón sobre carbono secundario (3.4 ppm, $J = 7.4$ Hz), un sistema AB centrado a 3.0 ppm y el protón del hidroxilo. Este resultado indica la existencia en la molécula de las siguientes agrupaciones estructurales (Figura 2):

**Figura 2**

Dada la fórmula molecular con un índice de insaturación de siete, el compuesto además del anillo aromático posee otro ciclo, y para realizar las conectividades entre las agrupaciones mencionadas, resultaron imprescindibles el espectro COSY donde se pone de manifiesto la existencia de acoplamientos directos entre las agrupaciones (E y D) y a larga distancia (alílico) entre (E y C) y (C y B). Por otro lado el espectro HMQC ha permitido localizar los carbonos

acoplados a cada señal del espectro de protones, mientras que el espectro HMBC presenta acoplamiento a larga distancia, claves para identificar la estructura (Figura 3).

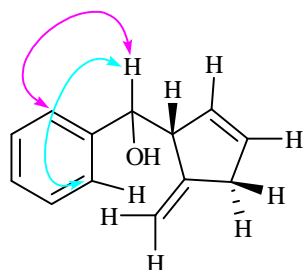


Figura 3

El acoplamiento a larga distancia del protón del alcohol secundario con los carbonos bencénicos, unido a su δ , indica su naturaleza bencílica. Esta conexión, por otra parte implica la presencia de un ciclopenteno existiendo entonces las posibilidades estructurales I y II (Figura 4):

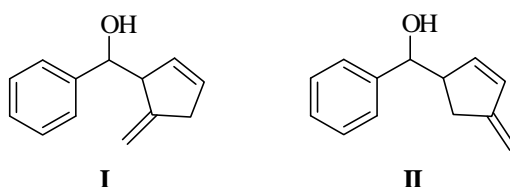


Figura 4

Diferentes experiencias de NOE *dif* que están resumidas en la figura siguiente (Figura 5), confirman inequívocamente la estructura I.

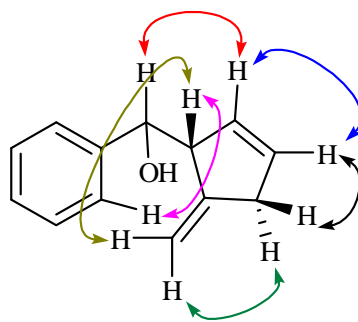
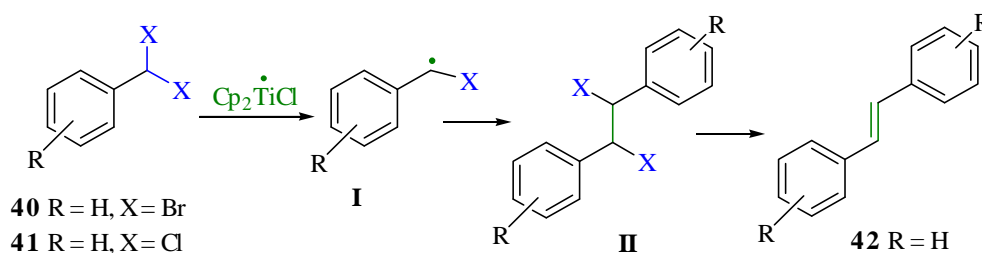


Figura 5

Este subproducto podría provenir del acoplamiento de un anión ciclopentadienilo del reactivo $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ con el benzaldehído, pero esta hipótesis no aclara la procedencia del carbono adicional que forma el metileno unido al ciclopentano.

1.4 Homo-acoplamientos de *gem*-dibromuros bencílicos catalizados por Ti^{III}.

Una vez postulada la intermediación de las especies radicalarias en la reacción de los bromuros bencílicos con Ti^{III}, se pensó que el estilbena y sustancias relacionadas podrían ser preparados a partir de los correspondientes 1,1-dihalo-bencil derivados, después del tratamiento con cantidades catalíticas de Ti^{III} (Esquema 16). Así, el radical bencílico formado inicialmente (I), puede estabilizarse adicionalmente por la presencia de un átomo de halógeno en α , y podría dimerizar para dar el correspondiente 1,2-dihalo-dibencil derivado (II), que evolucionaría para dar el correspondiente estilbena derivado vía deshalogenación reductiva mediante Ti^{III}.¹⁶¹

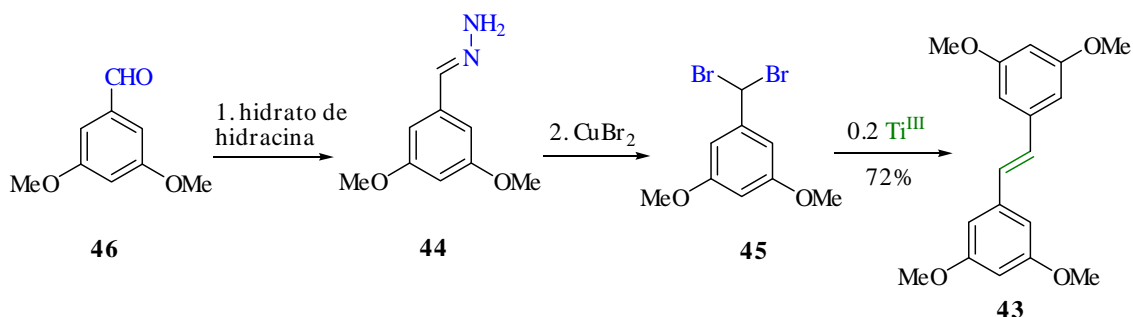


Esquema 16. Síntesis de estilbena derivados.

¹⁶¹ Davies, S.G.; Thomas, S. E. *Synthesis* **1984**, 1027-1029

Cuando se puso a reaccionar 1,1-dibromobenzilo (**40**) con 0.2 equivalentes de $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2$ y un exceso de Mn (c 0.8 M,) la reacción se completó en 35 minutos dando un rendimiento del 74% de *trans*-estilbeno (**42**).

Se procedió entonces a aplicar esta metodología para llevar a cabo la síntesis del estilbeno natural **43**. Para la consecución de este objetivo se utilizó como sustrato de partida el 3,5-dibenzaldehído (**46**) disponible comercialmente. Cuando se trató **46** con hidracina hidratada, siguiendo las condiciones descritas por Takeda *et al*,¹⁶² se obtuvo la correspondiente acina. La reducción del número de equivalentes de hidracina empleados, de 20 a 2.5 equivalentes, condujo a la obtención de la correspondiente hidrazona, que fue transformada en dibromuro **45** mediante tratamiento con $\text{Et}_3\text{N}/\text{CuBr}_2$. Rápidamente, se realizó sobre el compuesto **45** el proceso catalítico con Ti^{III} , obteniéndose el producto natural **43** con un rendimiento del 72% (Esquema 17).

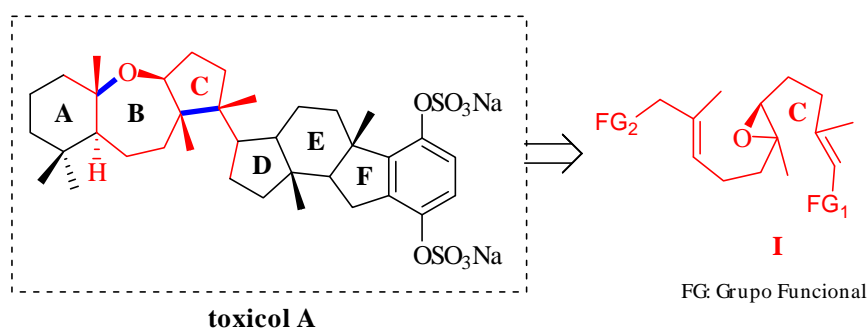


Esquema 17. Síntesis del 3,3',5,5'-tetrametoxi-estilbeno (**43**)

¹⁶² Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, 53, 557-566.

2. CONTROL DE LA
DIASSTEREOSELECTIVIDAD EN
CARBOCICLACIONES RADICALARIAS
HACIA CICLOPENTANOS CATALIZADAS
POR Ti^{III}.

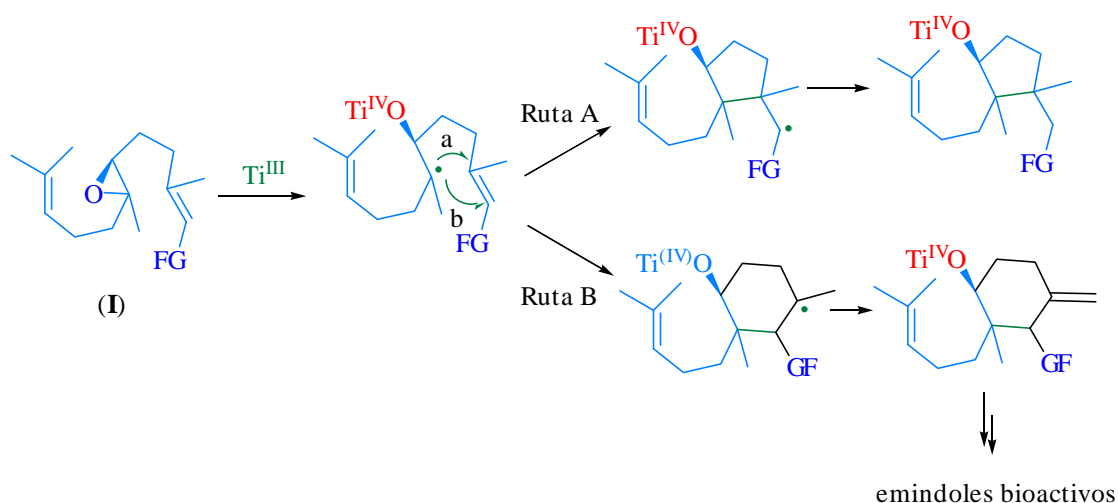
Para la aproximación a la síntesis de Toxicol A, se ha propuesto un planteamiento retrosintético que implica su construcción a partir de un sintón sesquiterpénico convenientemente funcionalizado (dibujado I en el Esquema 18). Así, la síntesis de I (Esquema 18) debe permitir conectar con otros fragmentos que aporten el ciclo A y los ciclos E y F respectivamente, facilitando la síntesis total de Toxicol A y transfiriendo la estereoquímica absoluta adecuada para la construcción de buena parte de sus centros estereogénicos.



Esquema 18

Considerando la estrategia propuesta, los pasos iniciales de este trabajo se han centrado en el estudio del comportamiento de diversos 6,7-epoxi-farsenil derivados tipo I (Esquema 18) frente a la apertura homolítica del enlace C-O del anillo oxiránico mediante empleo de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$. Aunque para este tipo de ciclaciones de epoxi-poliprenos que presentan el oxirano situado en un doble

enlace intermedio no hay antecedentes en bibliografía, el epoxi-farnesil derivado más simple (I con $FG_1 = OAc$ y $FG_2 = H$, Esquema 19), debería conducir, según nuestra experiencia previa en ciclaciones radicalarias catalizadas por $Cp_2Ti^{III}Cl$,¹⁶³ a la formación de ciclohexano-derivados *vía* ciclaciones 6-*endo*-trig (Ruta B, Esquema 19), un proceso que tendría un interés alternativo para la síntesis de emindoles bioactivos.¹⁶⁴



Esquema 19

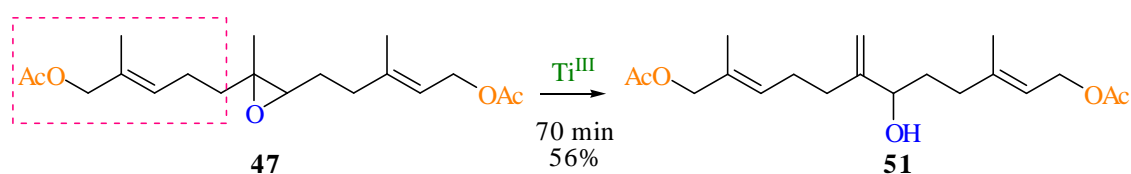
De esta forma, se ha tratado de favorecer los procesos de ciclación 5-*exo*-trig (Ruta A, Esquema 19) variando la funcionalización sobre C-1 en el correspondiente epoxi-farnesil derivado (por ej. $FG_1 = COOMe$ y $FG_2 = H$ en I, Esquema 19). Además se ha prestado especial atención respecto a la estereoselectividad en la construcción de los diferentes centros estereogénicos del ciclohexano, con el objetivo final de ajustar la estereoquímica de nuestros

¹⁶³ El empleo combinado de $Me_3SiCl/2,4,6$ -colidina ha sido publicado previamente por nuestro Grupo para la regeneración de Cp_2TiCl_2 a partir de $Cp_2Ti(Cl)H$ y oxi-titanio derivados.

¹⁶⁴ a) Nozawa, K.; Yuyama, M.; Nakajima, S.; Kawai, K.; Udagawa, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2155; b) Nozawa, K.; Udagawa, S.; Nakajima, S.; Kawai, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1157; c) Nozawa, K.; Nakajima, S.; Kawai, K.; Udagawa, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1689; d) Hosoe, T.; Itabashi, T.; Kobayashi, N.; Udagawa, S.-I.; Kawai, K.-I. *Chem. Pharm. Bull.* **2006**, 54, 185-187.

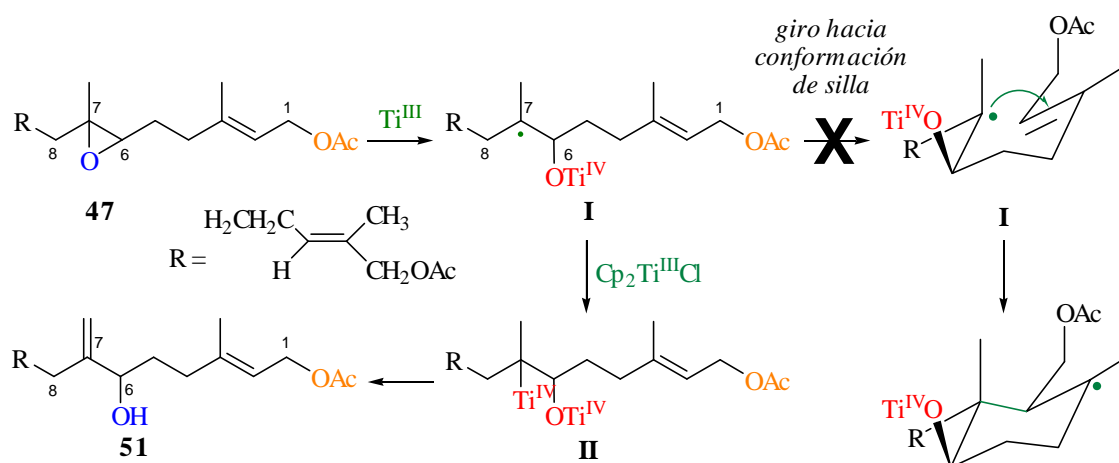
intermedios a aquellas que presenta en su estructura el producto natural toxicol A.

Inicialmente se prepararon diversos 6,7-epoxi-derivados sesquiterpénicos (**47-50**), funcionalizados en los extremos, a partir de farnesol comercial. Cuando en los carbonos C1 y C12 de la molécula se sitúan dos grupos acetato, como se muestra en el compuesto **47**, preparado desde acetato de 12-acetoxi-farnesilo por tratamiento con AMCPB, la reacción con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ conduce casi exclusivamente a la formación del alcohol alílico abierto **51** (Esquema 20; Tabla 4, Entrada 1).



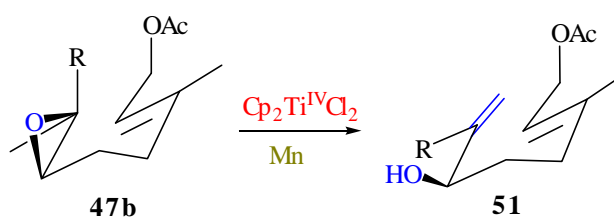
Esquema 20

Lo que probablemente puede suceder, es que el resto isoprénico de 5 carbonos que alarga el sustrato acetato de epoxi-geranilo (señalado entre puntos en el Esquema 20) habitual en nuestras experiencias previas de ciclaciones de epóxidos, impida alcanzarse fácilmente el estado de transición tipo silla necesario para que se complete satisfactoriamente el proceso de ciclación (Esquema 21).²⁶ De esta forma, el radical inicialmente formado (**I**) evoluciona por reducción hasta alquil-titanio (**II**) y posteriormente elimina formando el doble enlace terminal (**51**) de manera regioselectiva. Esta regioselectividad está de acuerdo con aquella observada para los procesos de terminación de las ciclación que conducen habitualmente a doble enlace exocíclico.



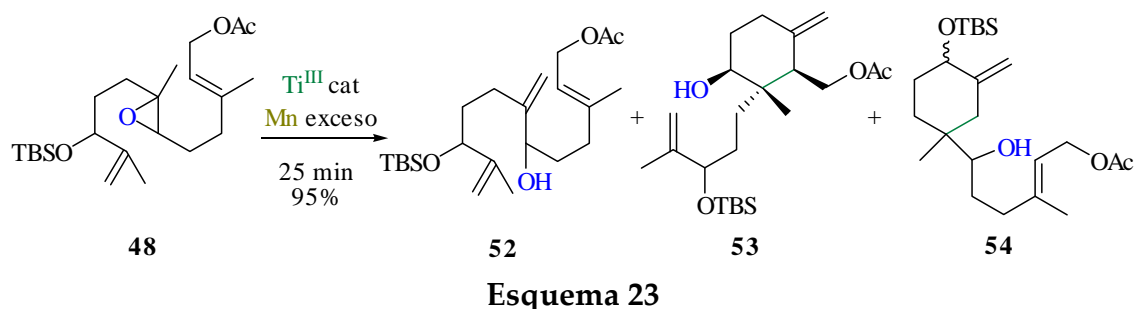
Esquema 21

Con el fin de comprobar la influencia de la cadena situada en C7 sobre el proceso de ciclación, se preparó el otro 6,7-epóxido (**47b**) estereoisómero de **1**, mediante dihidroxilación asimétrica de acetato de 12-acetoxi-farnesilo, posterior mesilación y tratamiento con base. Desafortunadamente, la reacción del epóxido **47b** con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ no produjo ciclación, obteniéndose exclusivamente el compuesto abierto **51** (Esquema 22; Tabla 4, Entrada 2).



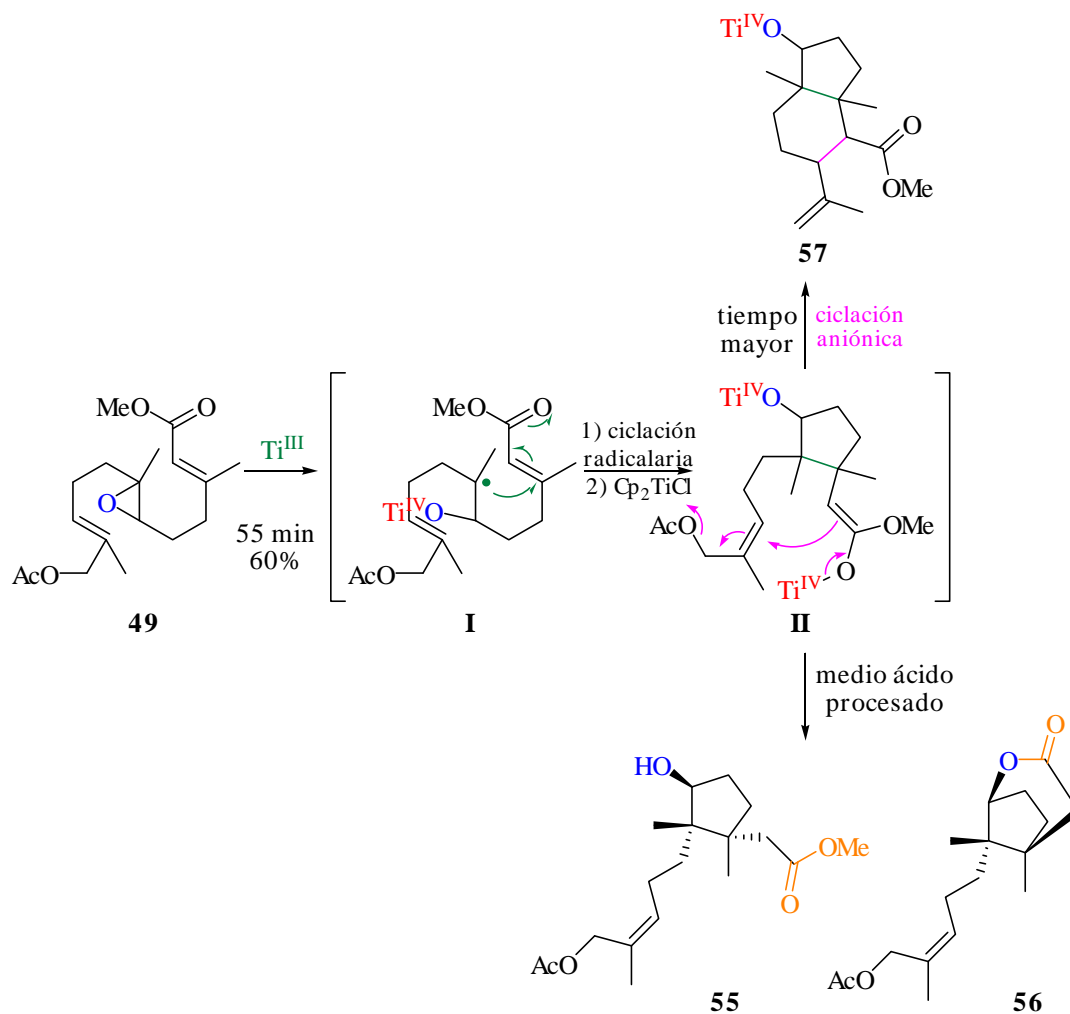
Esquema 22

Cuando se modifica la cadena, colocando un metileno terminal en C11-C12, como es el caso de **48**,^{27e} la reacción con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ conduce al derivado acíclico **52**, junto con dos productos de ciclación **53** y **54** originados por sendos procesos de ciclación 6-*endo*-trig (Esquema 23, Tabla 4, Entrada 3). El radical producido como consecuencia de la ruptura homolítica del oxirano en C6-C7, evoluciona adicionándose tanto al doble enlace del inicio de la cadena $\Delta^{2,3}$ como al metileno terminal $\Delta^{11,12}$, dando lugar a dos productos ciclohexánicos altamente funcionalizados diferentes, **53** y **54**. Comparando estos resultados respecto a la reacción de los compuestos **47** ó **47b**, el hecho de que se produzca un porcentaje significativo de ciclación hacia el doble enlace $\Delta^{2,3}$ indica la existencia de una mayor facilidad para el proceso de ciclación. El cambio en las funciones sobre C10-C12 debe permitir ahora, una mayor libertad conformacional, para alcanzar más fácilmente el estado de transición tipo silla necesario.



Para favorecer la formación de ciclos de cinco miembros a través de procesos 5-*exo-trig*, frente a 6-*endo-trig* en el proceso de ciclación radicalaria, se modificó la estructura electrónica de la cadena carbonada situando un potente aceptor de radicales como un éster metílico α,β -insaturado. Así se ubicó dicha función bien únicamente en el comienzo (C1, **49**), o bien en el comienzo y final de la cadena carbonada (C1 y C12, **50**). Los resultados previamente descritos del empleo de ésteres α,β -insaturados como aceptores radicalarios en procesos de ciclación intramolecular, nos permitían anticipar la posible obtención de buenos resultados en este tipo de procesos.^{165, 27c} La reacción de **49** con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ condujo mayoritariamente a los productos monocíclicos con anillo ciclopentánico **55** y **56** (Esquema 24; Tabla 4, Entradas 4 y 5).

¹⁶⁵ a) Gansauer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem. Eur. J.* **2003**, *9*, 531-542.



Esquema 24

Es destacable que el aumento en el tiempo de reacción supone la formación de proporciones cada vez mayores de los correspondientes derivados hidrindánicos tipo **57** (Esquema 24, Tabla 4, Entrada 5).

Los rendimientos hacia la formación de los ciclopentanos deseados alcanzan hasta el 60%, pero sin embargo no se observa diastereoselectividad en el cierre del ciclo. Resulta destacable que la obtención de los derivados hidrindánicos bicíclicos tipo **57** es el resultado de un proceso de ciclación cascada radical-aniónico con participación de los dos dobles enlaces de ambos extremos de la molécula de partida. Inicialmente se produce el cierre del ciclopentano y posteriormente el radical intermedio resultante, ubicado en α del

éster, debe reducirse hasta enolato de titanio (Esquema 24), que puede evolucionar mediante un proceso SN_2' con desplazamiento del acetato.

Al situar doble función éster en la estructura cambia el comportamiento en el proceso de ciclación. Así, la reacción del di-éster **50** mejora sensiblemente el rendimiento de ciclación (95%, Tabla 4, Entrada 6) obteniéndose los monocarbociclos **58** y **59** en un 35% de rendimiento junto con una mezcla de hidrindanos estereoisómeros de la cual se pudo aislar **60** (Esquema 25). Este último es formado nuevamente como resultado de una cascada de ciclaciones la primera radicalaria y la segunda probablemente una Michael aniónica. Su estereoquímica relativa se ha podido establecer mediante experiencias de nOe y medida de las J (Figura 6).

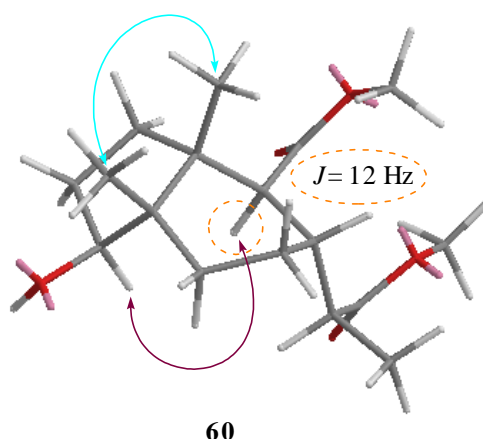
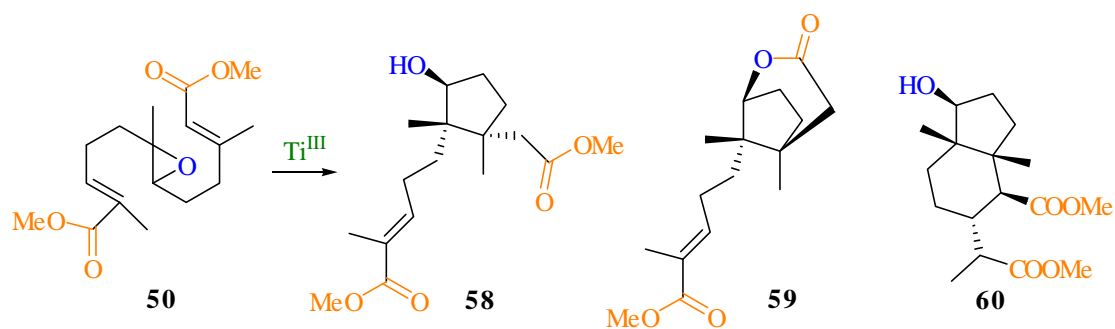


Figura 6. Principales efectos nOe observados en **60**.

El compuesto **50** también se hizo reaccionar empleando cantidades estequiométricas de $Cp_2Ti^{III}Cl$, obteniendo los mismos productos de reacción, pero con peores rendimientos (Tabla 4, Entrada 7).



Esquema 25

TABLA 4. Reacciones de ciclación 5-*exo*-trig catalizadas por Ti^{III}

Entrada	P.P.	P.F.	Tiempo (min)	Rend. (%)	Ratio
1	47	51	70	56%	a
2	47b	51	70	58%	a
3	48	52 + 53	50	53%	3:1
4	49	55 + 56	25	95%	8:7
5	49	55 + 56 + 57	300	55%	15:25:20
6 ^b	50	58 + 59 + 60	200	90%	4:7:2
7 ^c	50	58 + 59 + 60	200	65%	20:25:20

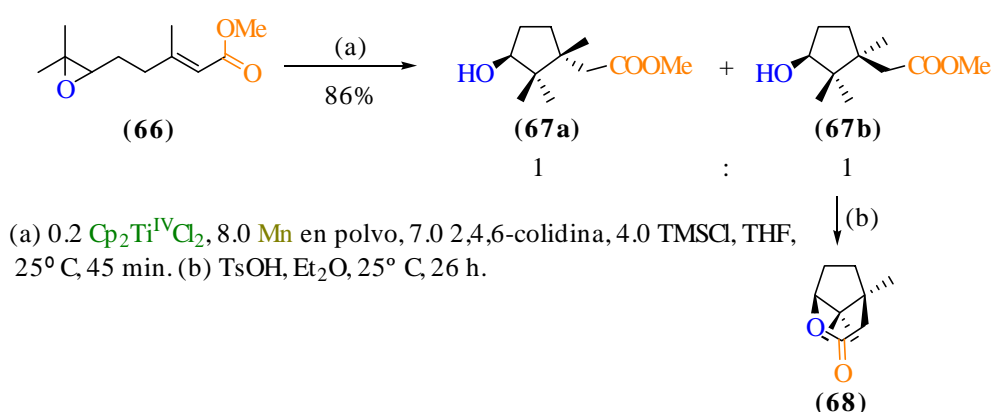
P.P. = Producto de Partida, P. F. = Producto Final

^a Sólo se observan trazas del producto ciclado; ^b Experimento empleando cantidades catalíticas en Ti^{III} ; ^c Experimento realizado empleando cantidades estequiométricas en Ti^{III} .

Considerando la baja diastereoselectividad obtenida en el cierre de los anillos ciclopentánicos, centramos a continuación nuestros esfuerzos en la mejora del comportamiento estereoquímico en la ciclación radicalaria 5-*exo*-trig.

Para ello como materiales de partida se emplearon epoxi-poliprenos derivados de geraniol comercial (61-65). Este estudio se diseñó teniendo presente la experiencia previa de la reacción de 6,7-epoxigeraniato de metilo (66),^{27c} molécula que posee un éster α,β -insaturado como aceptor con $Cp_2Ti^{III}Cl$

catalítico en presencia de exceso de Mn (Tabla 5, Entrada 1).¹⁶⁶ La reacción condujo en sólo 10 minutos y posterior desprotección del trimetilsilileter, a los productos de ciclación 5-*exo*-trig **67a** y **67b** en un rendimiento del 86% (Esquema 26). Estas mezclas presentan la ventaja de ser fácilmente resueltas ya que **67b** se transforma cuantitativamente en **68**, por lactonización espontánea en sílica gel o reacción con TsOH en DCM (Esquema 26). Esta transformación permite asignar inequívocamente las configuraciones relativas de **67a** y **67b**.

**Esquema 26**

Teniendo en cuenta este precedente, se pensó que un aumento del impedimento estérico sobre el éster situado en C1, podría conducir al incremento en el control estereoquímico de la reacción. De acuerdo con esto, se prepararon los correspondientes *tert*-butil- (**61**), (-)-mentil- (**62**) y 8-fenilmentil- (**63**) ésteres.¹⁶⁷ Para la preparación de geraniato de *tert*-butilo (**61**) fueron empleadas diferentes metodologías¹⁶⁸ hasta conseguir su obtención de manera eficiente empleando KO*t*-Bu en Et₂O anhidro,¹⁶⁹ obteniendo con esta última metodología buenos resultados (81%).

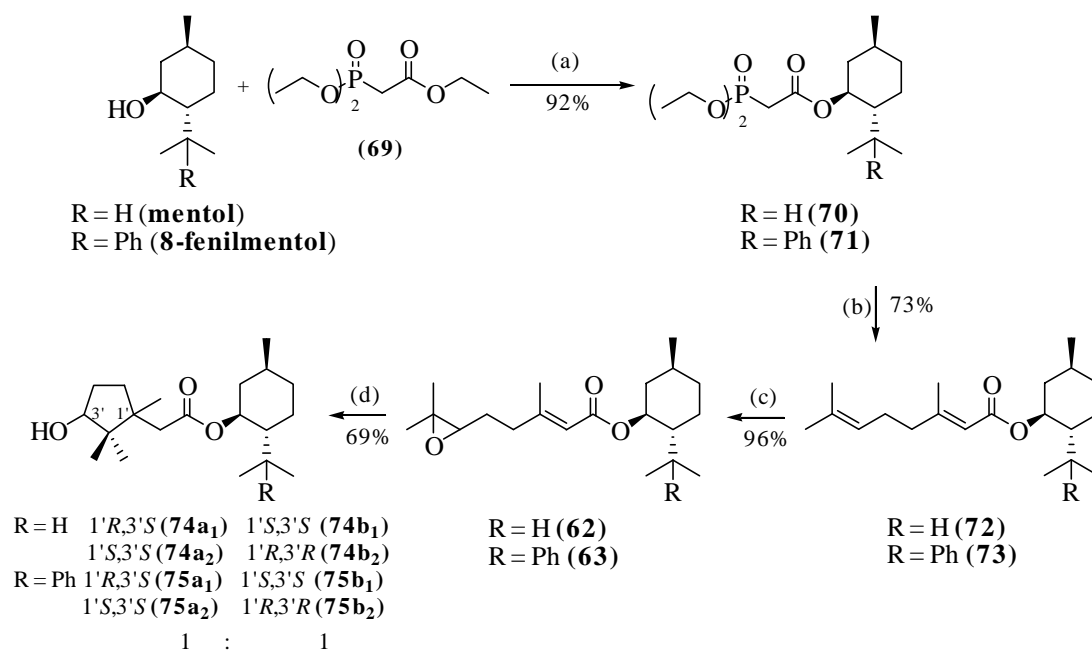
¹⁶⁶ El empleo combinado de Me₃SiCl/2,4,6-colidina ha sido publicado previamente por nuestro Grupo para la regeneración de Cp₂TiCl₂ a partir de Cp₂Ti(Cl)H y oxi-titanio derivados.

¹⁶⁷ Vasin, V. A.; Razin, V. V. *Synlett* **2001**, 5, 658-660.

¹⁶⁸ a) Wiener, H. *J. Mol. Cat.* **1986**, 37, 45-52. b) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 19, 4475-4478. c) Wipf, P.; Stephenson, C. R. *J. Org. Lett.* **2003**, 5, 2449-2452.

¹⁶⁹ Vasin, V. A.; Razin, V. V. *Synlett* **2001**, 5, 658-660.

Cabe destacar que la preparación de los ésteres mentílicos **62** y **63** no pudo completarse por procesos de esterificación o trans-esterificación convencionales,¹⁷⁰ sino a partir de una metodología convergente *vía* los correspondientes 2-dietilfosfonoacetatos (**70** y **71**) y posterior condensación de Wadsworth-Emmons¹⁷¹ con el producto comercial 5-metilhex-4-en-2-ona (**76**) para obtener así los geraniato de (-)-mentilo (**72**) y de (-)-8-fenilmentilo (**73**) deseados. La formación de **70** y **71** se lleva a cabo por acoplamiento de 2-dietilfosfonato de etilo (**69**) y mentol u 8-fenilmentol (97% de rendimiento en ambos casos) (Esquema 27).¹⁷²



(a) 3.0 **69**, 0.3 DMAP, tolueno, 120° C, 140 h. (b) 1.1 **76**, 1.1 NaH, THF, 25° C, 5 h. (c) 1.1 AMCPB, DCM, 0° C, 20 min. (d) 0.2 Cp₂Ti^{IV}Cl₂, 8.0 Mn en polvo, 7.0 2,4,6-colidina, 4.0 TMSCl, THF, 25° C, 80 min.

Esquema 27

¹⁷⁰ a) Wiener, H. *J. Mol. Cat.* **1986**, 37, 45-52. b) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 19, 4475-4478. c) Wipf, P.; Stephenson, C. R. *J. Org. Lett.* **2003**, 5, 2449-2452. d) Yang, D.; Xu, M. *Org. Lett.* **2001**, 3, 1785-1788. e) Kasai, Y.; Taji, H.; Fujita, T.; Yamamoto, Y.; Akagi, M.; Sugio, A.; Kuwahara, S.; Watanabe, M.; Harada, N.; Ichikawa, A.; Schurig, V. *Chirality* **2004**, 16, 569-585. f) Kamalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett.* **2002**, 43, 879-882. g) Chavan, S. P.; Kale, R. R.; Shivasankar, K.; Chandake, S. I.; Benjamin, S. B. *Synthesis* **2003**, 17, 2695-2698. h) Matsukawa, Y.; Isobe, M.; Kotsuki, H.; Ichikawa, Y. *J. Org. Chem.* **2005**, 70, 5339-5341.

¹⁷¹ Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, 83, 1733-1738.

¹⁷² Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, 28, 2713-2716.

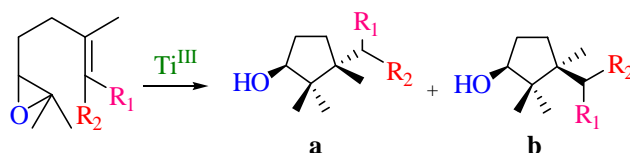
Una vez preparados los epóxidos, primero se hizo reaccionar el éster *t*-butílico (**61**) con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ se obtuvieron buenos rendimientos de ciclación (**78**) pero sin mejoría del control estereoquímico en el cierre del ciclo (Tabla 5, Entrada 2). En el caso del éster mentílico, la ciclación catalizada por $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ de **62** da lugar con un 71% (Tabla 4, Entrada 3), a una mezcla de cuatro diastereoisómeros (Esquema 27, $1'S,3'S$; $1'R,3'R$; $1'R,3'S$; y $1'S,3'R$) que se distinguen en ^1H -RMN como dos parejas, **74a** (*trans*) y **74b** (*cis*), en una proporción 1:1. Posteriormente se estudió el comportamiento del geraniato de 8-fenil(-)-mentilo **63**, cuya distribución del producto de ciclación es igualmente de 1:1 entre dos parejas de diastereoisómeros, **75a** (*trans*) y **75b** (*cis*) (Esquema 27; Tabla 5, Entrada 4).

A continuación se llevó a cabo el estudio del comportamiento de un epoxi-derivado que posea un di-éster en el inicio de la cadena $\text{R}_1=\text{R}_2=\text{COOMe}$ (**64**). Esta opción permite introducir así un grupo alcoxi-carbonil adicional sobre C2 y de esta manera se ubica una ramificación sobre la posición adyacente al cierre del ciclo. Por otra parte esta distribución electrónica del doble enlace $\Delta^{2,3}$, lo convierte en un más potente aceptor de radicales. La reacción de (**64**) con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ condujo a un 94% (Tabla 5, Entrada 5) de producto de ciclación (**79**), y por primera vez obteniéndose una apreciable estereoselectividad 2:1, hacia el producto deseado (**a**, Esquema 28) que posee una disposición relativa *cis* entre hidroxilo y metilo en C3.

Basado en resultados previos descritos en bibliografía,¹⁷³ se probó finalmente el comportamiento del epoxi-derivado de geraniol con un grupo nitrilo, también α,β -insaturado (excelente aceptor de radicales) en el comienzo

¹⁷³ a) Fernández-Mateos, A.; Herrero-Teijón, P.; Mateos-Burón, L.; Rabanedo-Clemente, R.; Rubio-González, R. *J. Org. Chem.* **2007**, *72*, 9973-9982; b) Fernández-Mateos, A.; Herrero-Teijón, P.; Rabanedo-Clemente, R.; Rubio-González, R.; Sanz-Gonzalez, F. *Synlett* **2007**, *17*, 2718-2722.

de la cadena carbonada (**65**), frente a las condiciones de ciclación radicalaria. Se observó que el rendimiento en el proceso deseado es muy elevado hacia **80** (Tabla 5, Entrada 6) y que la distribución de compuestos ciclados muestra una mayor proporción de diastereoisómero deseado (**a**, Esquema 28) que en los diferentes casos anteriores.



Esquema 28

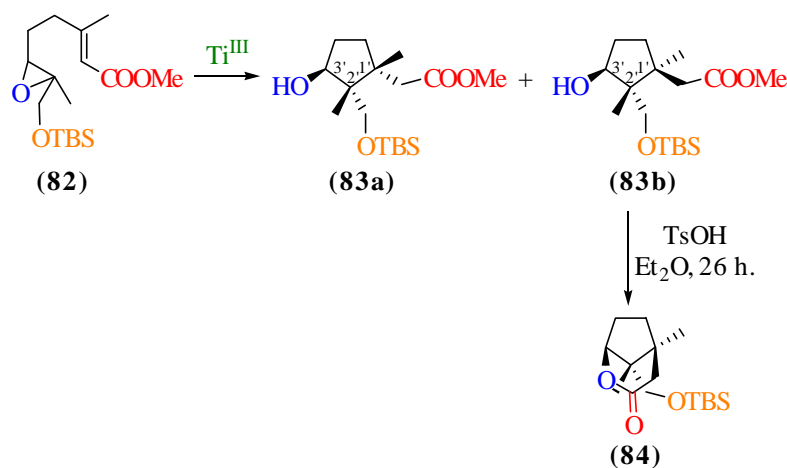
TABLA 5. Reacciones de ciclación 5-*exo*-trig catalizadas por Ti^{III}

Entrada	P.P.	R ₁	R ₂	P.F.	Rend. (%)	Ratio (a:b)
1	66	COOMe	H	67	86%	1:1
2	61	COO <i>t</i> -Bu	H	78	81%	1:1
3	62	COO(-)-mentilo	H	74	71%	1:1
4	63	COO-8-fenil(-)-mentilo	H	75	69%	1:1
5	64	COOEt	COOEt	79	94%	2:1
6	65	CN	H	80	99%	4:1

P.P. = Producto de Partida, P. F. = Producto Final

Llegado a este punto, se consideró que la funcionalización con un hidroxilo de uno de los metilos del extremo final de la cadena carbonada (adyacentes al grupo oxirano), y su posterior protección con un grupo *tert*-butildimetilsililo (TBS), podría suponer un aporte extra de condicionamiento estérico que originara control estereoquímico en la ciclación hacia el anillo de cinco eslabones. Además hay que tener en cuenta que el diseño de la síntesis de toxicol-A, implica necesariamente la funcionalización de ese metilo, para que sirva de unión con el sintón que permita la construcción de los anillos A-B.

La epoxidación y subsiguiente protección con TBSCl sobre (2*E*,6*E*)-8-hidroxi-3,7-dimetilocta-2,6-dienoato de metilo (**81**) conduce a (2*E*)-6,7-epoxi-8-*tert*-butildimetilsililoxi-3,7-dimetioct-2-enoato de metilo (**82**) (Esquema 29). La ciclación de éste empleando cantidades catalíticas de Cp₂Ti^{III}Cl, conduce a la mezcla de estereoisómeros **83** nuevamente con una distribución de 1:1 (Esquema 29; Tabla 6 Entrada 1), lo cual demuestra un buen control estereoquímico en la formación del C-2', mientras que es nulo para C-1'.



Esquema 29

La lactonización empleando TsOH de **83** hasta **84** (Esquema 29), junto con experimentos de nOe dif. en su espectro de ¹H-RMN, permiten asignar la configuración relativa de los diferentes carbonos de **83a** (Figura 7).

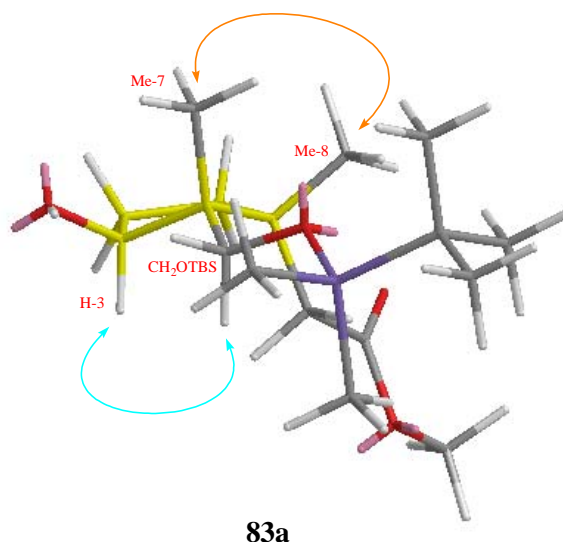
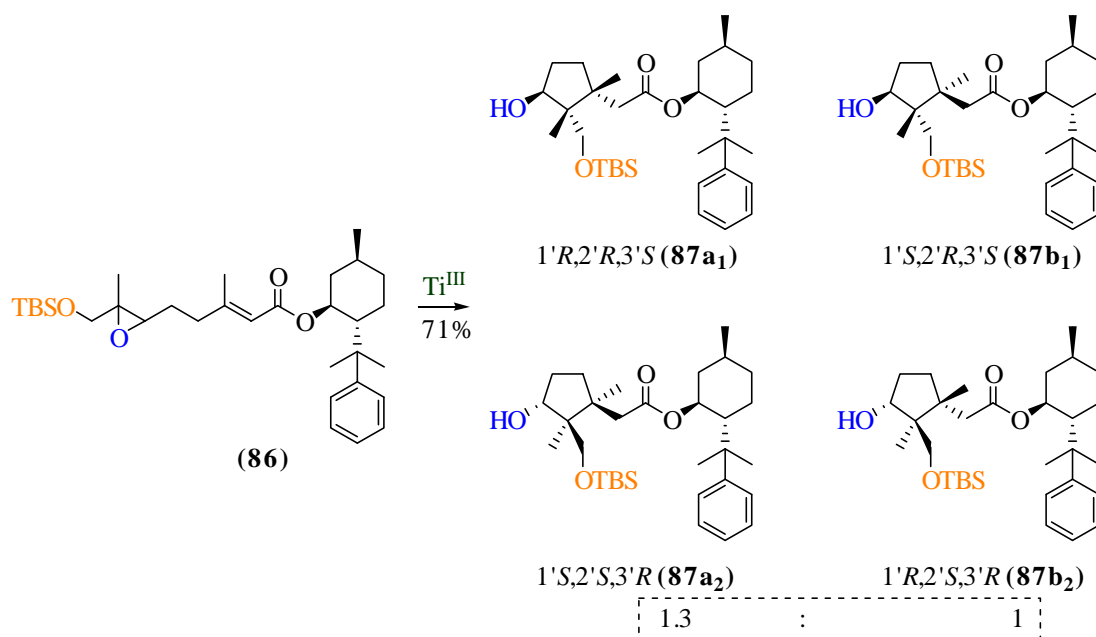


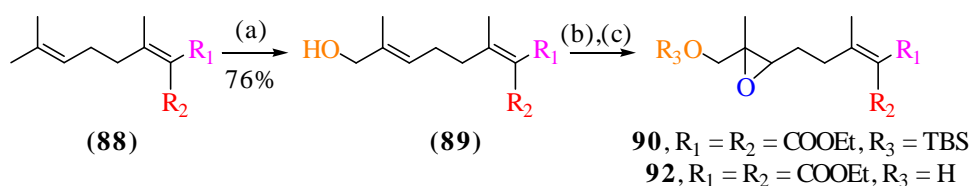
Figura 7. Efectos nOe más representativos observados en **83a**

Se emplea a continuación un éster más voluminoso, siguiendo el mismo razonamiento que en los derivados no funcionalizados anteriormente estudiados. La oxidación alílica con SeO_2 de geraniato de 8-fenil(-)-mentilo (**65**), seguida de epoxidación y protección con TBSCl, permite llegar con buenos rendimientos hasta **86** (Esquema 30). La ciclación empleando $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ del epóxido **86** conduce en un 71% de rendimiento al conjunto de productos ciclopentánicos **87** (Esquema 30; Tabla 6, Entrada 2). **87** consiste en una mezcla de cuatro diastereoisómeros ($1'S,3'S$; $1'R,3'R$; $1'R,3'S$; y $1'S,3'R$), que se diferencian en ^1H -RMN como dos parejas, **87a** (*trans*) y **87b** (*cis*), en una proporción relativa de 1.3:1 (Esquema 30). La asignación de las configuraciones relativas de los diferentes estereocentros ha sido en este caso realizada por comparación con los casos precedentes.



Esquema 30

Al igual que en los productos no funcionalizados en el extremo de la cadena C8, se llevó a cabo el estudio del comportamiento de un epoxi-derivado que posea un di-éster en el inicio de la cadena (**90**, Esquema 31; $R_1 = R_2 = \text{COOMe}$, $R_3 = \text{TBS}$) y función en C8. La reacción de **90** con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ condujo a un 92% de producto de ciclación (**91**) obteniéndose una estereoselectividad 2.5:1 hacia el producto deseado que posee una disposición relativa *cis* entre hidroxilo y metilo en C3 (Tabla 6, Entrada 3).

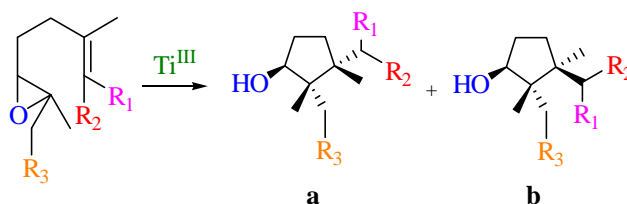


- (a) 0.5 SeO_2 , 2.0 *t*-BuOOH, DCM, 0° C, 2 horas.
 (b) 1.2 AMCPB, DCM, 0° C, 40 minutos.
 (c) 2.0 TBSCl, 2.6 imidazol, DCM, 0° C, 45 minutos.

Esquema 31

El compuesto con -OH libre en C8 (**92**, Esquema 31) todavía mejora este balance hasta un 3:1 (Tabla 6, Entrada 4), probablemente debido a la coordinación inicial del Ti^{III} con el hidroxilo libre.

Por otra parte, si se lleva a cabo la ciclación sobre **94**, molécula que contiene un nitrilo insaturado en lugar de un éster en el inicio de la cadena carbonada, se obtiene un rendimiento del producto de ciclación (**95**) prácticamente cuantitativo y una significativa relación de 4.5:1 a favor del estereoisómero buscado (Tabla 6, Entrada 5).



Esquema 32

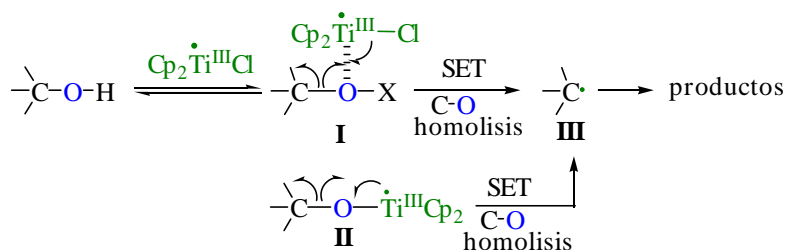
TABLA 6. Reacciones de ciclación 5-*exo*-trig catalizadas por Ti^{III} de compuestos funcionalizados en el final de la cadena carbonada.

Entrada	P.P.	R ₁	R ₂	R ₃	P.F.	Rend. (%)	Ratio (a:b)
1	81	COOMe	H	OTBS	83	76	1:1
2	86	COO-8-fenil-(-)-mentilo	H	OTBS	87	71	1.3:1
3	90	COOEt	COOEt	OTBS	91	92	2.5:1
4	92	COOEt	COOEt	OH	93	90	3:1
5	94	H	CN	OTBS	95	95	4:1

P.P. = Producto de Partida, P. F. = Producto Final

**3. MIMETIZACIÓN DE LA RUTA NO
MEVALÓNICA HACIA TERPENOS: NUEVA
METODOLOGÍA EN UNA SOLA ETAPA
PARA LA REDUCCIÓN DE ALCOHOLES A
ALCANOS CATALIZADA POR Ti^{III}.**

Teniendo presente nuestra experiencia previa en la química del reactivo de Nugent $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$,²⁷ junto con evidencias anteriores donde se comprobó que H_2O y MeOH pueden actuar como donadores de hidrógeno a través de los correspondientes complejos con Ti^{III} ,¹⁷⁴ se puede plantear que la interacción de un alcohol o alcóxido con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ podría producir el complejo alcohólico I (Esquema 33).



Esquema 33

La formación de este tipo de especies o las derivadas del alcóxido de titanio (II, Esquema 33), puede producir el debilitamiento del correspondiente enlace C-O permitiendo que se produzca, bajo las condiciones adecuadas, la

¹⁷⁴ a) Enemrke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853-7864; b) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359-1371; c) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-López, J. L.; Robles, R.; Cardenas, D. J.; Buñuel, E.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5522-5526; d) Jin, J.; Newcomb, M. *J. Org. Chem.* **2008**, *73*, 7901-7905.

ruptura homolítica a través de una transferencia mono-electrónica para producir el radical carbonado **III** (Esquema 33), que finalmente evoluciona hacia la formación de los productos de reacción.

Para verificar nuestra hipótesis mecanística, se realizaron estudios teóricos¹⁷⁵ preliminares por métodos DFT (UM05/Ahlich-VDZ).¹⁷⁶ En estos estudios se calcularon las barreras de energía para la etapa clave de ruptura homolítica del alcohol-complex **I** del mecanismo de reducción (Figura 8). Los resultados obtenidos se muestran en la Figura 8 y la Tabla 7.

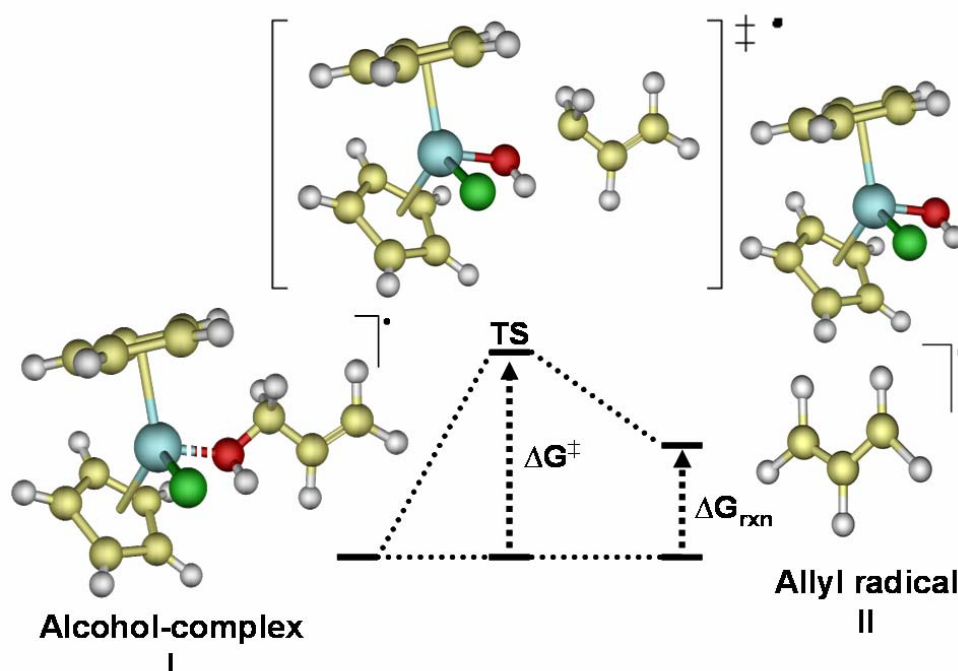


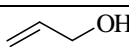
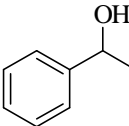
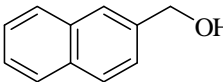
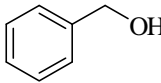
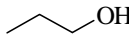
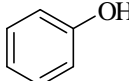
Figura 8. Ruptura homolítica (energía de activación ΔG^\ddagger y energía de reacción ΔG_{rxn}) para la primera etapa del mecanismo de reacción propuesto con el alcohol bencílico (**96**).

¹⁷⁵ M. J. Frisch, et al., Gaussian 03, Revision E.01, Gaussian, Inc., Wallingford CT, 2004. For complete reference, see supporting information.

¹⁷⁶ a) Y. Zhao, N. E. Schultz, D. G. Truhlar, *J. Chem. Phys.* **2005**, *123*, 161103/1-161103/4; b) A. Schaefer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571-2577; c) D. Feller, *J. Comp. Chem.* **1996**, *17*, 1571-1586; d) K. L. Schuchardt, B. T. Didier, T. Elsethagen, L. Sun, V. Gurumoorthi, J. Chase, J. Li, T. L. Windus, *J. Chem. Inf. Model.* **2007**, *47*, 1045-1052.

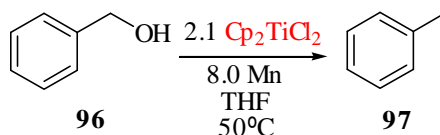
Los resultados mostraron que aunque la ruptura homolítica sea una etapa endotérmica para todos los compuestos estudiados (Tabla 7, Casos 1-6), se produce una clara diferencia en las energías de Gibbs ya que los alcoholes alílicos y bencílicos mostraron tal y como se esperaba energías de activación y reacción menores (Tabla 7). En cualquier caso al comparar estos valores con los calculados teóricamente y experimentalmente para la disociación homolítica de enlaces C-O, se encontraron valores significativamente mayores para las especies no-complejadas, lo que viene claramente a demostrar que esta ruptura homolítica se ve fuertemente afectada por la coordinación con Ti^{III} .

Tabla 7. Valores de ΔG^\ddagger y ΔG_{rxn} calculados para la ruptura homolítica de enlaces C-O de diferentes alcoholes.

Compuesto	ΔG^\ddagger	ΔG_{rxn}
	30.0	2.3
	29.0	2.7
	29.9	4.9
	31.7	6.3
	41.7	19.8
	52.3	36.7

Para validar esta hipótesis, en una primera reacción se utilizó alcohol bencílico **96** como producto de partida y THF como disolvente (Esquema 34). Se preparó un montaje equipado con refrigerante de reflujo. Se tuvieron todas las precauciones propias de las reacciones habituales con el reactivo $Cp_2Ti^{III}Cl$:

destilación y estricta desoxigenación del disolvente, creación de atmósfera inerte en el matraz de reacción, etc.



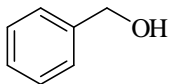
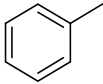
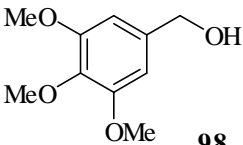
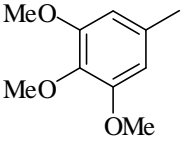
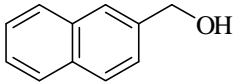
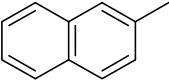
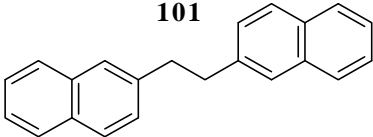
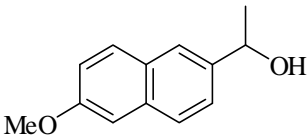
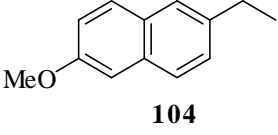
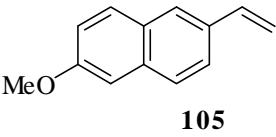
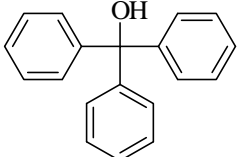
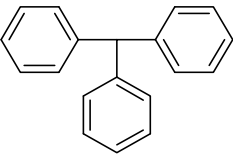
Esquema 34

De esta forma, inicialmente se trató un equivalente de alcohol bencílico (96) con 2.1 equivalentes de Cp₂Ti^{III}Cl y 8.0 equivalentes de Mn como reductor en una disolución de 0.2 M en THF (Tabla 8, Entrada 1; Esquema 34). No se observó transformación a temperatura ambiente, por lo que se calentó a 50 °C durante 6 horas. Tras el procesado, se detectó producto de desoxigenación-reducción, tolueno (97), con un 35% de rendimiento (Tabla 8, Entrada 1a). A la vista de este resultado, se repitió el ensayo a reflujo y la reacción se completó en 45 minutos. En este caso se produjo una transformación del 93% hacia tolueno (Tabla 8, Entrada 1b). Posteriormente se realizó otro ensayo con 1.1 equivalentes de Cp₂Ti^{III}Cl pero la reacción terminó con un 50% de material de partida sin reaccionar (Tabla 8, Entrada 1c).

Con respecto a la cantidad de metal reductor se pudo disminuir la proporción hasta 1.5 equivalentes de Mn o Zn por equivalente de alcohol. En estos casos la transformación fue del 92% y 87% respectivamente (Tabla 8, Entradas 1d y 1e).

Una vez puesto a punto el método, se realizó un estudio del alcance del proceso usando los diferentes alcoholes bencílicos (96, 98, 100, 103 y 106) que aparecen en la Tabla 8.

Tabla 8. Desoxigenación-reducción de alcoholes bencílicos catalizada por Ti^{III} .^a

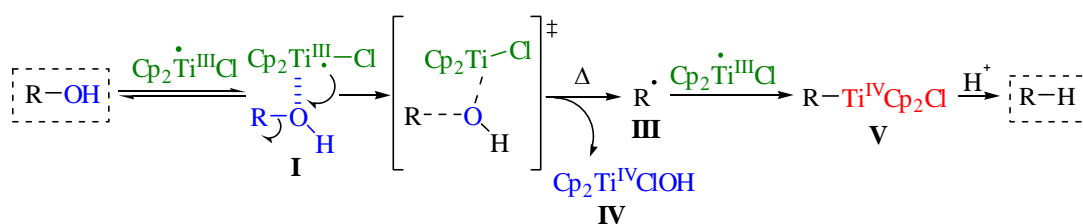
Entrada	Substrato	Producto	t (min)	Rend. (%)	
1	 96	 97	360	a 35	
			45	b 93	
			60	c 50	
			60	d 92	
			60	e 87	
2	 98	 99	50	90	
3	 100	 101		79	
			 102	60	trazas
4	 103	 104		77	
			 105	90	8
5	 106	 107	60	91	

^a Se emplearon 2.0 equiv de Ti^{III} , 1.5 equiv de agente reductor por mol de material de partida y THF como disolvente.

En todos los casos se observaron elevados rendimientos y tiempos relativamente cortos de reacción. Hay que destacar la formación de trazas de producto de dimerización (**102**) en la Entrada 3 probablemente generado a causa de la alta estabilidad del radical formado. En el caso del alcohol bencílico

secundario **103** (Tabla 8, Entrada 4), se generó mayoritariamente el producto de desoxigenación-reducción **104**, junto con una pequeña cantidad del derivado vinílico **105** fruto de un proceso de eliminación.

Considerando conjuntamente los resultados obtenidos con los diferentes alcoholes junto con la ausencia de formación de productos de acoplamiento, puede proponerse para estas transformaciones el mecanismo representado en el Esquema 35. La debilitación del enlace C-O en **I** provoca su homólisis al calentar dando el radical **III**.¹⁷⁷ Así, el radical centrado en el carbono (**III**) es atrapado por una segunda molécula de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ generándose el intermedio bencil-titanio (**IV**, $\text{R} = \text{PhCH}_2-$), apoyándose de esta manera la necesidad de emplear 2.1 equivalentes de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$.



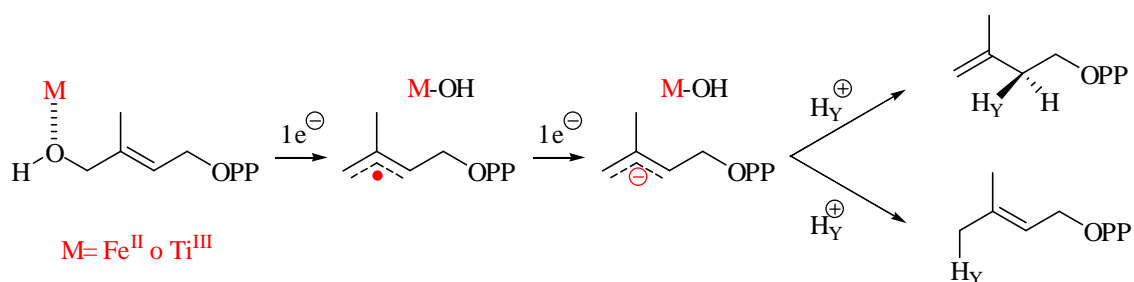
Esquema 35. Mecanismo propuesto para la reacción de desoxigenación-reducción catalizada por Ti^{III} .

Una vez demostrada la viabilidad del método para desoxigenaciones a partir de alcoholes bencílicos, se pasó a realizar ensayos análogos con diferentes alcoholes alílicos (Tabla 9). Inicialmente, el alcohol alílico **108** fue tratado bajo las mismas condiciones que los que alcoholes bencílicos: 2.1 equivalentes de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, 1.5 equivalentes de metal reductor en THF a reflujo. La reacción de desoxigenación-reducción se dio en 1 hora dando mayoritariamente isopentenil

¹⁷⁷ Otro mecanismo alternativo hacia **III** basado en la homólisis inicial del enlace O-H está siendo investigado en nuestro Grupo de Investigación, con evidencias claras de formación de un alcóxido de Ti^{IV} que se reduce a alcóxido de Ti^{III} con exceso de Mn antes de la homólisis.

benzoato (**109**) junto con una pequeña proporción del dimetilalil benzoato (**110**) (Tabla 9, Entrada 1).

Este proceso mimetiza la biosíntesis natural de la unidad C5 isoprénica en la ruta *no-mevalónica* (Esquema 36), que transcurre mediante dos transferencias mono-electrónicas que dan como resultado el proceso natural de desoxigenación-reducción. El último paso de dicha ruta es mediado por *IspH*, y está basado en la formación de un complejo entre Fe^{II} y el OH, a través del cual se transfiere un primer electrón que provoca la homólisis del enlace C-O y origina un radical alílico. La reducción monoelectrónica de éste lleva a un carbanión alílico que es protonado hacia una mezcla de IPP y DMAPP.



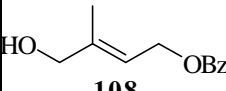
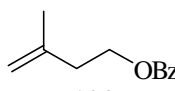
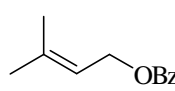
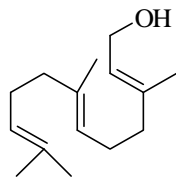
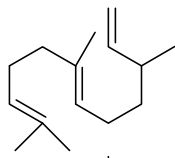
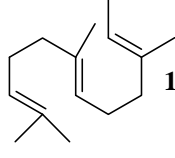
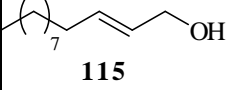
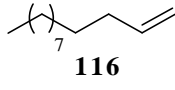
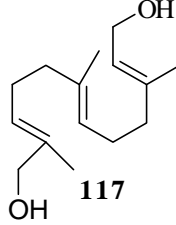
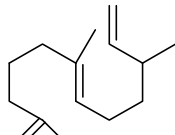
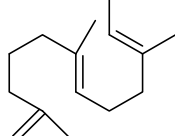
Esquema 36. Mecanismo de la reacción catalizada por *IspH*.

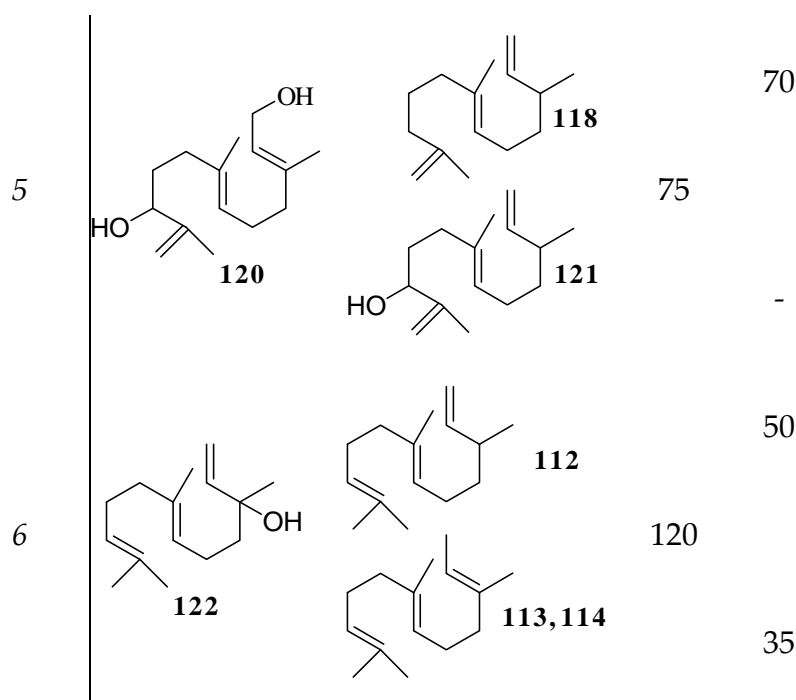
Como queda recogido en la Tabla 8, se realizaron ensayos para los distintos tipos de sustituyentes en alcoholes alílicos (primarios, secundarios y terciarios). En todos los casos los rendimientos fueron de buenos a excelentes en tiempos relativamente cortos de reacción. En el caso del farnesol (**111**) la reacción tuvo lugar en una hora, dando mayoritariamente como resultado el hidrocarburo **112**, fruto de la desoxigenación en C1 y la incorporación de un hidrógeno en C3, junto con los isómeros **113** y **114** (Tabla 9, Entrada 2). La ausencia de productos de ciclación o dimerización en este caso, avala la rápida reducción del radical alílico intermedio por una segunda molécula de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$.

Los derivados dihidroxilados del farnesol (**117** y **120**) se prepararon para estudiar la selectividad del método. Debido a la presencia de dos funciones hidroxilo en el mismo sustrato, en este caso se emplearon 4.2 equivalentes de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ y 3 equivalentes de Mn (Tabla 9, Entradas 4 y5). Se comprobó que la cinética de la reacción se ve afectada por la sustitución del grupo hidroxilo, siguiendo el siguiente orden:

Alcohol primario > Secundario > Terciario

Tabla 9. Desoxigenación-reducción de alcoholes alílicos catalizada por Ti^{III} .^a

Entrada	Substrato	Producto	t (min)	Rend. (%)
1	 108	 109	60	70
		 110		3
2	 111	 112	60	80
		 113, 114		10
3	 115	 116	50	91
4	 117	 118	70	65
		 119		20



^a Todas las reacciones fueron llevadas a cabo con 2.1 equivalentes de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, 1.5 equivalentes de Mn en THF como disolvente a reflujo. Excepto las entradas 4-5 donde se usaron 4.2 equivalentes de Cp_2TiCl_2 y 3 equivalentes de Mn

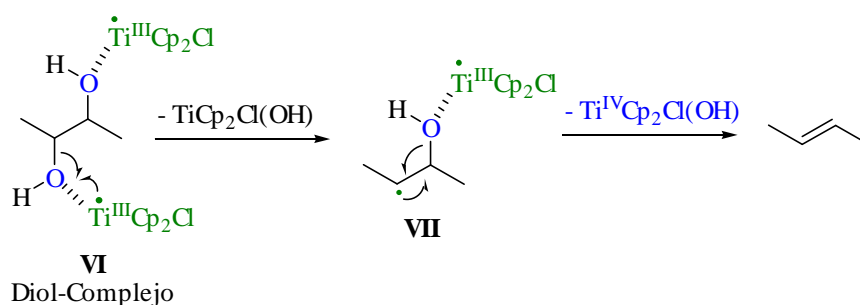
Para verificar estos resultados se repitió un ensayo con el sustrato **120** (Tabla 9 Entrada 5), demostrando que se puede aislar el compuesto **118**, fruto de la desoxigenación-reducción selectiva del alcohol primario, en tiempos cortos de reacción. El estudio finalizó con el alcohol terciario nerolidol (**122**, Tabla 9, Entrada 6), utilizado para avalar la viabilidad y eficacia del método en todo tipo de alcoholes alílicos.

Una vez realizada la primera parte de los ensayos, el estudio de los resultados demuestra que el método es totalmente efectivo para todo tipo de alcoholes activados. Por lo tanto, se pasó a una segunda etapa de ensayos con otro tipo de funciones hidroxiladas, tales como 1,2-dihidroxi-derivados y alcoholes no activados (Tabla 10).

La desoxigenación del 1,2-dihidroxitetradecano **123** fue llevada a cabo usando 2.1 equivalentes de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, y 1.5 equivalentes de Mn produciendo

cuantitativamente el hidrocarburo insaturado **124** (Tabla 10, Entrada 1). Este resultado se confirmó con los sustratos **125** y **127** (Tabla 10, Entradas 2 y 3) con buenos rendimientos, mostrando la viabilidad del método también para la 1,2-desoxigenación.

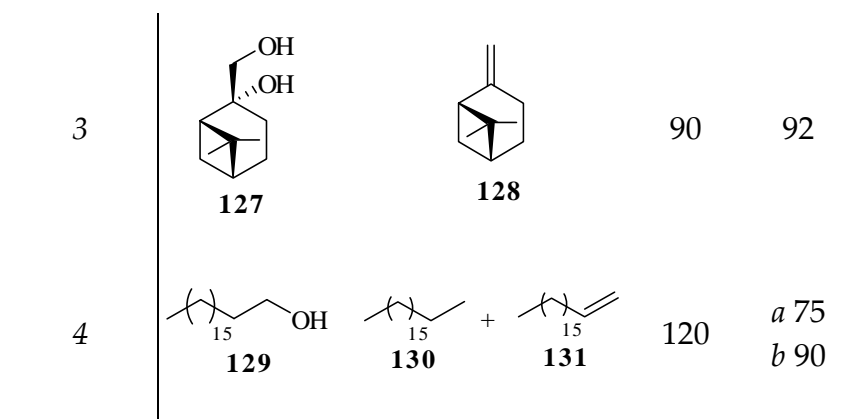
La estequiometría de los reactivos y el excelente rendimiento observado, indican que probablemente el doble enlace se forma tras una primera desoxigenación de hidroxilo secundario del diol-complejo **IV** (Esquema 37), que conlleva a la homólisis del segundo enlace C-O.



Esquema 37.

Tabla 10. Desoxigenación-reducción de compuestos dihidroxilados mediada/catalizada por Ti^{III} .

Entrada	Substrato	Producto	t (min)	Rend. (%)
1			90	98
2			65	94



Con respecto a los alcoholes no activados, cuando se puso a reaccionar el 1-octadecanol **129** (Tabla 10, Entrada 4), en las mismas condiciones; 2.1 equivalentes de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ y 1.5 equivalentes Mn en THF at reflujo, no se observó reacción.

Pensando que ahora la Energía de Activación es más alta que para alcoholes activados y tratando de poder aplicar el método a alcoholes no activados, se utilizaron otros disolventes con mayor punto de ebullición. Con dioxano a reflujo se produjo una transformación del 75% hacia producto de desoxigenación-reducción **131** (Tabla 10, Entrada 4a), pero el resultado no es fácilmente reproducible. Con tolueno se produjo una excelente transformación del 90% y mostrando una total reproducibilidad (Tabla 10, Entrada 4b).

Estas nuevas condiciones fueron llevadas a cabo con otros alcoholes alifáticos de distinta naturaleza, demostrándose la eficacia de la metodología en todos los casos. Esto supone otra innovación, porque hasta donde nosotros sabemos, es la primera vez que se utiliza tolueno como disolvente para aplicaciones sintéticas con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$.

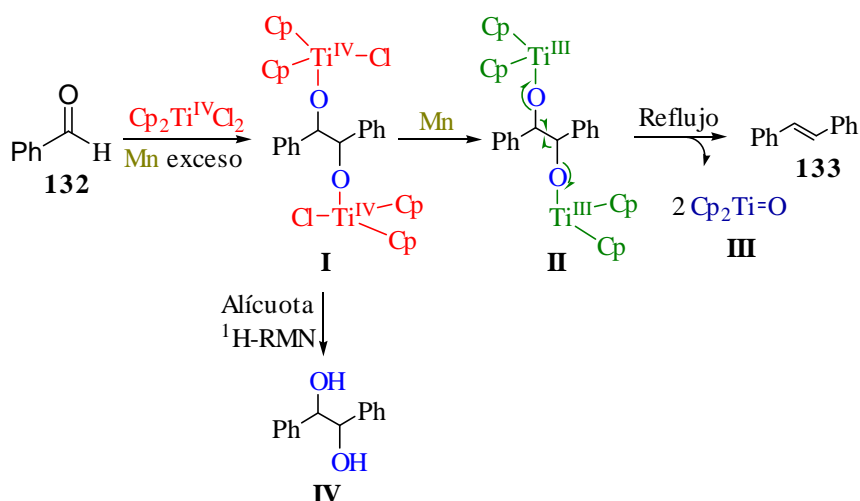
Para demostrar la eficacia del tolueno en este tipo de reacciones, se repitieron algunos de los ensayos con el alcohol activado **115** y 1,2-diol **125**.

Comparativamente, las reacciones fueron más rápidas y con rendimientos sensiblemente superiores (ver desarrollo experimental). En contraste, no se produjo la transformación del fenol bajo ninguna de las condiciones fijadas.

Es destacable reseñar que estas mismas reacciones y procesos pueden igualmente llevarse a cabo empleando cantidades subestequiométricas de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, obteniendo resultados en cuanto a distribución de productos y rendimientos similares. Para emplear este método catalítico en $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ es necesario el uso de TMSCl como atrapador final de oxígeno.

4. OLEFINACIÓN DE CARBONILOS
CATALIZADA POR Ti^{III}.

Tal y como se indicó en la introducción y se ha demostrado en el apartado anterior, la energía de disociación necesaria para la ruptura homolítica del enlace C-O en el complejo $\text{Cp}_2\text{Ti}^{\text{IV}}(\text{Cl})\text{O}-\text{CH}_2\text{R}$ experimenta un notable descenso con respecto a la registrada para el alcohol libre correspondiente. Esta información junto con el hecho de que diferentes dioles evolucionen hasta la formación de los correspondientes dobles enlaces, nos hizo pensar que el reactivo de Nugent ($\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$), podría ser válido para promover reacciones de olefinación de carbonilos. Este proceso se originaría a través de la ruptura homolítica de los enlaces C-O presentes en los pinacولاتos (**II**, Esquema 38) inicialmente formados.



Esquema 38. Mecanismo propuesto para la olefinación de carbonilos promovida por $\text{Ti}^{\text{III}}/\text{Mn}$.

Los pinacولات de Ti^{III} tipo II, que generan las insaturaciones por ruptura homolítica, podrían originarse a partir de la correspondiente reducción de los pinacولات de Ti^{IV} (I, Esquema 38), que son conocidos al haber sido ampliamente descritos como intermedios en los acoplamientos pinacolínicos de carbonilos catalizados por Ti^{III} .¹⁷⁸

Esta hipótesis teórica podría ser demostrada por tratamiento de benzóxido sódico con $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ en THF a reflujo para conseguir la formación de la especie intermedia $\text{PhCH}_2\text{OTi}^{\text{III}}\text{Cp}_2$.¹⁷⁹ Si se produce la homólisis del enlace C-O, quedaría demostrada nuestra hipótesis sobre la viabilidad del Ti^{III} para dar procesos de olefinación a partir de carbonilos. Afortunadamente, después de calentar la mezcla durante 3 horas, análisis de cromatografía de gases (GC)

¹⁷⁸ a) Barden, M. C.; Schwarz, J. J. *Am. Chem. Soc.* **1996**, *118*, 5484–5485; b) Enemærke, R. J.; Larsen, J.; Hjøllund, G. H.; Troels Skrydstrup, T.; Daasbjerg, K. *Organometallics* **2005**, *24*, 1252–126; c) Paradas, M.; Campaña, A. G.; Estévez, R. E.; Álvarez de Cienfuegos, L.; Jiménez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2009**, *74*, 3616–3619.

¹⁷⁹ Huffman, J. C.; Moloy, K. G.; Marsella, J. A.; Caulton, K. G. *J. Am. Chem. Soc.* **1980**, *102*, 3009–3014.

demonstraron la formación de tolueno, avalando definitivamente la validez de nuestra hipótesis.

Animados por este resultado, se trató posteriormente el benzaldehído **132** con 2.0 equivalentes de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ en THF a reflujo. La reacción finalizó tras una hora con un rendimiento del 93% para la formación de estilbena **133** (Tabla 11, Entrada 1). Teniendo presente que la mezcla de reactivos $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2/\text{Mn}$ ha sido ampliamente descrita como catalizadora del proceso de acoplamiento pinacólico de aldehídos y cetonas, nuestro principal esfuerzo se ha centrado en descubrir las verdaderas especies que participan en el proceso de desoxigenación.

En busca de este fin, se diseñaron distintos ensayos para la elucidación del mecanismo de este nuevo proceso de olefinación (Tabla 11). En otro ejemplo, se puso a reaccionar benzaldehído **132** en las mismas condiciones a las mencionadas en el caso anterior, pero ahora a una temperatura de 25 °C. Después de agitar durante 10 minutos, el análisis de una alícuota de la mezcla de reacción **verde** mostró el consumo completo del material de partida, siendo el benzo-pinacol la única especie formada. En este punto, se eliminó el exceso de **Mn** de la mezcla resultante, y el líquido filtrado se calentó a reflujo durante 1 hora, produciéndose, de nuevo, la transformación total a estilbena **133**. Vale la pena destacar el viraje progresivo de la disolución, del color **verde** habitual hacia **azul oscuro**, durante la etapa a reflujo de desoxigenación-olefinación. De esta forma resulta razonable proponer la implicación de la especie de pinacolato de Ti^{III} (**II**, Esquema 38) como responsable de este paso.

Así, el exceso de **Mn** presente en el medio de reacción reduciría la especie de pinacolato de Ti^{IV} (**I**, Esquema 38) hasta la correspondiente especie de pinacolato de Ti^{III} reducida (**II**, Esquema 38). El hecho de que hasta la fecha no

se ha demostrado que el Mn sea capaz de reducir al Ti hasta una valencia menor que III a temperatura ambiente, junto con el color verde de la disolución antes de calentar, constituyen argumentos suficientemente relevantes para confirmar la presencia de estos pinacولات de Ti^{III} .¹⁸⁰

Para completar el estudio mecanístico de este proceso, la evidencia final de la existencia de la especie II fue obtenida del siguiente ensayo estratégicamente diseñado. A una disolución de 1.0 equivalente de $Cp_2Ti^{IV}Cl_2$ en THF se le adicionaron 0.5 equivalentes de Mn, cantidad necesaria estequiométricamente para producir la reducción hasta $Cp_2Ti^{III}Cl$. Después de 15 minutos, la reacción viró a verde (Figura 9), confirmando así reducción de Ti^{IV} a Ti^{III} . En ese momento se adicionó 1.0 equivalentes de benzaldehído **132**, virando rápidamente a color naranja-rojizo (Figura 9), probablemente debido a la presencia de la especie I de pinacolato de Ti^{IV} . Análisis de RMN de una alícuota mostraron la desaparición del material de partida **132** y la formación de benzopinacol (**IV**, Esquema 38) como único producto de reacción. Esta disolución permaneció estable en color y composición durante 4 horas a temperatura ambiente. Para apoyar nuestra hipótesis, se volvieron a adicionar 0.5 equivalentes de Mn, provocando el viraje a verde en 15 minutos (Figura 9). Es razonable asumir entonces que se produzca una nueva reducción de la especies de pinacolato de Ti^{IV} hasta las correspondientes especies de pinacolato de Ti^{III} . De nuevo, se dejó agitar la mezcla de reacción a temperatura ambiente durante varias horas, y la mezcla permaneció inalterada. Sin embargo, calentando la reacción a reflujo se produjo la transformación hasta estilbena **133** y se observó asimismo el viraje de la disolución de verde a azul oscuro, Este último cambio de color se atribuye a la formación de óxido de titanoceno (**III**, Esquema 38) resultante de la etapa de desoxigenación (Figura 9).

¹⁸⁰ Villiers y Ephritikhine postularon la implicación de análogos de U^{III} en el acoplamiento reductor de cetonas: Villiers, C.; Ephritikhine, M. *Chem. Eur. J.* **2001**, *14*, 3043–3051.

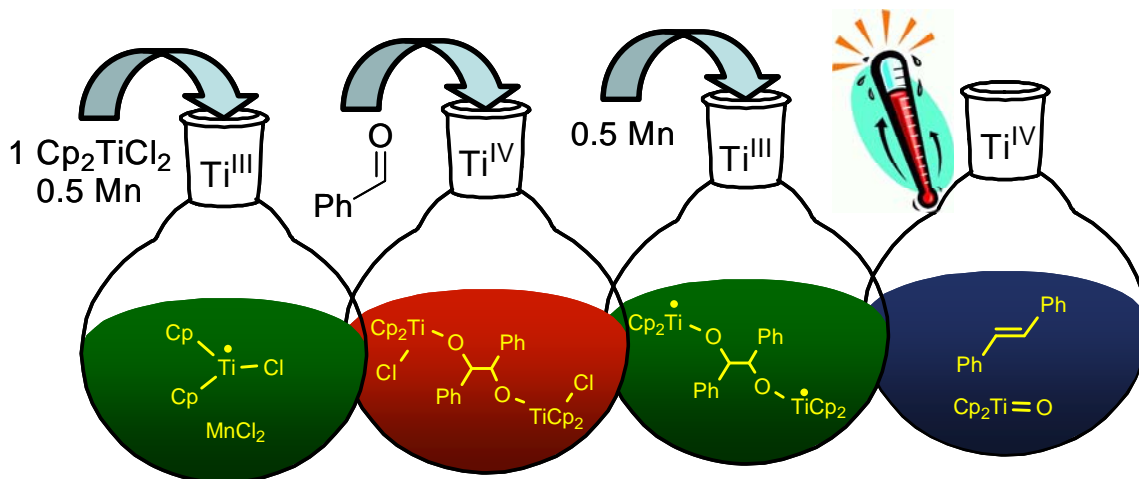


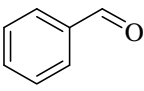
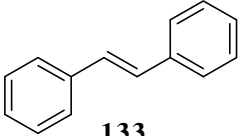
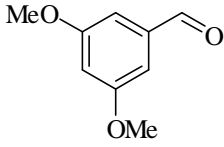
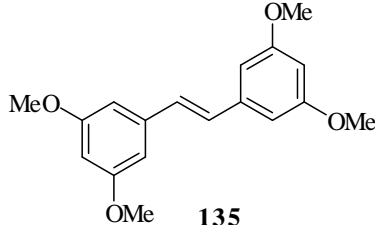
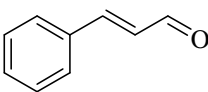
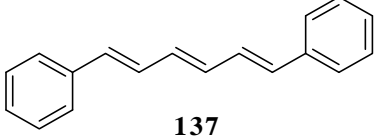
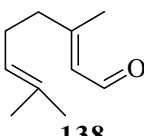
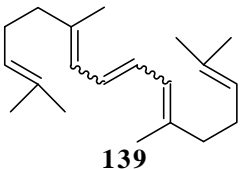
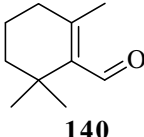
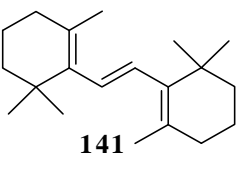
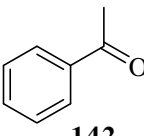
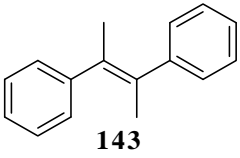
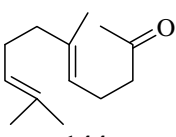
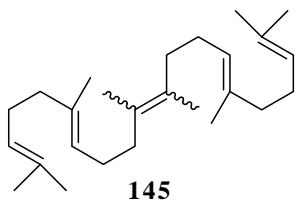
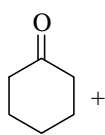
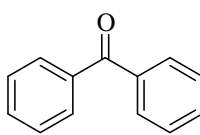
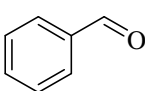
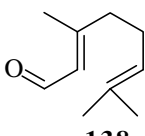
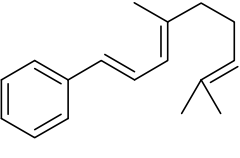
Figura 9.

Una vez que obtuvimos la prueba que confirma la participación de especie Ti^{III} en el proceso de desoxigenación, nos centramos en determinar el alcance de la reactividad de este nuevo proceso sintético de la química radicalaria. Para ello, se escogieron los diferentes tipos de carbonilos que aparecen en la Tabla 11.

Como podemos observar, se han obtenido excelentes rendimientos y total reproducibilidad cuando utilizamos aldehídos conjugados y aldehídos bencílicos como material de partida (Tabla 11, Entradas 1-5). También hemos demostrado la viabilidad del proceso en cetonas aromáticas y alifáticas (Tabla 11, Entradas 6-7), donde fueron necesarios mayores tiempos de reacción.

Tabla 11. Olefinación de carbonilos promovida por Ti^{III} /Mn.

Entrada	Substrato	Producto	Rend.
---------	-----------	----------	-------

		(%)	
1	 132	 133	93
2	 134	 135	87
3	 136	 137	65
4	 138	 139	76
5	 140	 141	74
6	 142	 143	71
7	 144	 145	62
8	 146	 147	65
9	 132	 138	77
		 149	

Para aumentar el rango de aplicación de este proceso de olefinación, comprobamos la eficacia del $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ para promover la reacción de acoplamiento-olefinación intermolecular entre distintos carbonilos (Tabla 11, Entradas 8-9). Al tratar, en las condiciones de acoplamiento-olefinación fijadas la benzofenona (**147**) con un exceso de ciclohexanona (**146**), se obtuvo el producto de acoplamiento **148** con un 65% de rendimiento. Resultados similares fueron obtenidos con una mezcla de citral (**138**) y benzaldehído (**132**). Con estos resultados se demuestra que este método es totalmente eficaz para la generación de olefinas asimétricas a partir de carbonilos aromáticos y alifáticos.

Es destacable reseñar que estas mismas reacciones y procesos pueden igualmente llevarse a cabo empleando cantidades subestequiométricas de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ obteniendo resultados en cuanto a distribución de productos y rendimientos similares. Para emplear este método catalítico en $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ es necesario el uso de TMSCl como atrapador final de oxígeno.

V. CONCLUSIONES

- Se ha desarrollado un nuevo método catalítico para el homo-acoplamiento de haluros alílicos, mediado por las especies Mn/Cp₂ZrCl₂ con rendimientos de buenos a excelentes, tratándose de un método suave y tolerado por un amplio rango de grupos funcionales. Es destacable que la regioselectividad del proceso frente a otros reactivos similares como el Cp₂TiCl, se ve incrementada significativamente cuando se usa la combinación Mn/Zr(IV) y especialmente cuando se emplea el método sobre haluros alílicos cíclicos. Este reactivo han sido empleado satisfactoriamente en la síntesis de terpenos simétricos tales como diversos derivados onoceránicos, la preparación de sintones avanzados en la síntesis enantioselectiva del (+)-cimodiacetal y el escualeno.

- Se ha puesto de manifiesto que el homo-acoplamiento de haluros de bencilo y *gem*-dibromuros bencílicos catalizado por Cp₂TiCl, produce muy buenos rendimientos en la obtención de di-bencilos y estilbenos. Se han conseguido además resultados interesantes en acoplamientos mixtos tipo Barbier entre halogenuros bencílicos y aldehídos, ampliando así la aplicación de este método hacia acoplamientos mixtos.

- En las ciclaciones radicalarias de epoxi-poliprenos catalizada por Cp₂Ti^{III}Cl, es posible controlar la regioselectividad hacia ciclopentanos y la estereoselectividad del proceso de ciclación utilizando malonil-derivados o nitrilos α,β -insaturados como aceptores radicalarios. El empleo de epoxi-poliprenos convenientemente funcionalizados induce cierres 5-*exo*-trig con

excelentes rendimientos y con un buen control estereoquímico sobre los tres estereocentros formados. Por tanto, esta metodología permite un sencillo acceso a un intermedio ciclopentánico altamente funcionalizado clave para la síntesis del compuesto Toxicol A.

- Se ha desarrollado un novedoso método de desoxigenación-reducción de alcoholes en una sola etapa. Se ha demostrado la efectividad con alcoholes activados, no activados y 1,2-dihidroxi-derivados, mediante el empleo de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ en THF o tolueno a reflujo. Se ha postulado que el proceso se basa en la formación de un alcohol-complejo de Ti^{III} que produce una considerable disminución en la energía de activación de la homólisis del enlace C-O. Esta ruptura homolítica genera un radical centrado en el carbono que es el intermedio clave del proceso.

Esta novedosa metodología presenta unos rendimientos de buenos a excelentes y se producen en tiempos relativamente cortos de reacción. Estas características justifican la eficacia de este nuevo método frente a los ya existentes en bibliografía, y lo hacen tremendamente interesante en síntesis orgánica. Otro punto novedoso a su favor es que presenta carácter biomimético.

Estas mismas reacciones y procesos pueden igualmente llevarse a cabo empleando cantidades subestequiométricas de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, obteniendo resultados en cuanto a distribución de productos y rendimientos similares. Para emplear este método catalítico en $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ es necesario el uso de TMSCl como atrapador final de oxígeno.

- Se ha comprobado además, que el reactivo de Nugent's (Cp_2TiCl) es capaz de inducir el acoplamiento reductivo de carbonilos con rendimientos de buenos a excelentes, en tiempos cortos de reacción y con una excelente reproducibilidad.

Se han aportado pruebas mecanísticas que demuestran la participación de la especie pinacolato de Ti(III) en la etapa de desoxigenación de este proceso de acoplamiento-olefinación tipo McMurry. Estos datos son especialmente relevantes, ya que alguna luz sobre la que es, probablemente, una de las transformaciones mecanísticas más oscuras en la Química Orgánica. Nuestro grupo de investigación sigue trabajando en futuras aplicaciones de este nuevo proceso en la síntesis de productos naturales bioactivos.

Estas mismas reacciones y procesos pueden igualmente llevarse a cabo empleando cantidades subestequiométricas de $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$, obteniendo resultados en cuanto a distribución de productos y rendimientos similares. Para emplear este método catalítico en $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$ es necesario el uso de TMSCl como atrapador final de oxígeno.

ANEXO 1

Supporting Information Artículo 1

*Supporting Information***Mild Ti^{III}- and Mn/Zr^{IV} Catalytic Reductive Coupling of Allylic Halides: Efficient Synthesis of Symmetric Terpenes**

Alejandro F. Barrero, M. Mar Herrador, José F. Quiroz del Moral, Pilar Arteaga, Jesús F. Arteaga, Horacio R. Diéguez and Elena M. Sánchez

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¹H and ¹³C NMR spectra of **1**, **2**, **5**, **7**, **9**, **10**, **11**, **12**, **13**, **21**, **22** and **31** were included in *Org. Lett.* **2005**, *7*, 2301-2304.

General Details

Optical rotations were determined using CHCl₃ or CH₂Cl₂ as the solvents. IR spectra were recorded as NaCl plates (films). NMR studies were performed with a 400 (¹H 400 MHz/¹³C 100 MHz) spectrometer. Accurate mass determination was carried out with a mass spectrometer arranged in an EBE geometry and equipped with a FAB (LSIMS) source. The spectrometer was operated at 8 KV accelerating voltage and Cs⁺ were used as primary ions. The low resolution mass spectra were obtained in quadrupolar mass spectrometer equipped with a solids probe for the introduction of the sample. GC/MS analysis was done with a mass spectrometer coupled to a gas chromatograph and equipped with an EI source at 70 eV. The analyses were performed on a capillary column (30 m × 0.25 mm × 0.25 μm) inserted directly into the ion source. The temperature program was: 60°C (4 min), 10°C/min to 180°C and 4°C/min to 250°C, then isothermal for 15 min. The carrier gas was helium with a flow rate of 1 mL/min. HPLC with UV detection was used. Semi-preparative HPLC separations were carried out on a column (5 μm Silica, 10 × 250 mm) at a flow rate of 2.0 mL/min. All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an argon atmosphere. Tetrahydrofuran (THF) was freshly distilled immediately prior to use from sodium/benzophenone. The rest of the solvents used were purified according to standard literature techniques and stored under argon.

General procedure for bromination reaction of allylic alcohols (7, 10, 11, 21, 23, 34): CBr₄ (2.0 mmol) and Ph₃P (2.0 mmol) at 0°C under an Ar atmosphere were added to a stirred solution of allylic alcohol (1.0 mmol) in 7 mL of benzene. The solution was stirred at the same temperature for 2 h (TLC monitoring), and hexane (10 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 purified by column chromatography on silica gel to afford the corresponding bromo-derivative.

Geranyl bromide (6): Commercially available.

Neryl bromide (7): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 99% of **7**.¹

Methyl (2*E*,6*E*)-8-bromo-2,6-dimethyl-2,6-octadienoate (10): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 96% of **10**.²

Methyl (2*E*,6*Z*)-8-bromo-2,6-dimethyl-2,6-octadienoate (11): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 90% of **11**.²

Allyl bromide (15): Commercially available.

Crotyl bromide (17): Commercially available.

Cinnamyl bromide (19): Commercially available.

(2*E*,6*E*)-8-Bromo-3,7-dimethyl-2,6-octadienyl acetate (21): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 98% of **21**.³

(-)-Myrtenyl bromide (23): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel to afford 97% of **23**.⁴

(*R*)-Perillyl bromide (34): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel to afford 91% of **34**. $[\alpha]_D + 33.5$ (c 1.2, CH₂Cl₂); ν (film) 3079, 2923, 2921, 2856, 2838, 1662, 1644, 1434, 1375, 1209, 1164, 890, 816, 649, 601 cm⁻¹; δ_H (400 MHz; CDCl₃) 1.45-1.58 (1H, m), 1.74 (3H, s), 1.85-2.04 (2H, m), 2.10-2.27 (4H, m), 3.96 (2H, s), 4.72 (1H, s), 4.74 (1H, s), 5.91 (1H, bs) ppm; δ_C (100 MHz; CDCl₃) δ 20.8, 26.9, 27.4, 30.9, 39.2, 40.6, 109.0, 127.7, 134.5, 149.4 ppm.

Preparation of 27 and 28

¹ Haibo, X.; Shao, Y.; Becker, J. M.; Naidor, F.; Gibbs, R. A. *J. Org. Chem.* **2000**, *65*, 8552-8563.

² Barreiro, A. F.; Herrador, M. M.; Quiles del Moral, J. F.; Arteaga, P.; Arteaga, J.; Piedra, M.; Sánchez, E. M. *Org. Lett.* **2005**, *7*, 2301-2304.

³ Oshlischlager, A. C.; Wong, J. W.; Varigin, V. G.; Pierce, H. D. *J. Org. Chem.* **1963**, *48*, 5009-5017.

⁴ a) Hoy, B.; Wei, H. K.; Lecomte, J.; Rogge, R. *Bull. Soc. Chim. France* **1946**, 148-150; b) Harwood, L. M.; Julia, M. *Synthesis* **1980**, *6*, 456-457.

Methyl (2E,6E)-8-chloro-2,6-dimethyl-2,6-octadienoate (27): A mixture of the corresponding hydroxy-ester (245 mg, 1.24 mmol) and triphenylphosphine (455 mg, 1.73 mmol) in CCl_4 (1.24 mL, dried over 4Å sieves) under argon was refluxed for 1 h (TLC monitoring) before being cooled to room temperature. Hexane (20 mL) was added and the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and the resulting crude purified by column chromatography on silica gel (hexane/*t*-BuOMe, 5:1) to afford 240 mg (90%) of the corresponding chloro-derivative 27.⁵

Methyl (2E,6E)-8-iodo-2,6-dimethyl-2,6-octadienoate (28): The corresponding hydroxy-ester (300 mg, 1.51 mmol) was dissolved in a mixture of acetonitrile (7.5 mL) and toluene (30 mL) under argon. Triphenylphosphine (596 mg, 2.27 mmol), imidazole (154 mg, 2.27 mmol) and iodine (576 mg, 2.27 mmol) were added. The mixture was heated at 60°C for 10 min (TLC monitoring) before being cooled to room temperature. The mixture was diluted with ethyl acetate and washed with an aqueous saturated sodium thiosulfate solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was filtered through a short pad of silica gel (hexane/*t*-BuOMe, 2:1) to afford 400 mg (86%) of the corresponding iodo-derivative 28.

Homocoupling reactions

a. Catalytic Protocol with Ti^{III} (1, 4, 5, 8, 9, 12, 13, 16, 18, 20, 22, 24, 31, 35): A mixture of Cp_2TiCl_2 (190 mg, 0.74 mmol) and Mn dust (1620 mg, 29.44 mmol) in thoroughly deoxygenated THF (50 mL) and under Ar atmosphere was stirred at rt until the red solution turned green. The corresponding allylic halide (3.68 mmol) in strictly deoxygenated THF (1 mL) was then added to the Cp_2TiCl_2 solution. The reaction mixture was stirred for 15 min, quenched with 1N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products.

⁵ Kato, T.; Hirano, T.; Hoshikawa, M.; Uyehara, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 221-228.

b. Catalytic Protocol with Zr^{IV} (1, 5, 8, 12, 20, 24, 31, 35): A mixture of Cp₂ZrCl₂ (462 mg, 1.58 mmol) and Mn dust (2323 mg, 42.20 mmol) in deoxygenated THF (9 mL) and under Ar atmosphere was stirred at rt. The corresponding allylic bromide (5.28 mmol) in strictly deoxygenated THF (1 mL) was then added, (TLC monitoring). The reaction mixture was quenched with 1N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products.

Compounds 8: After subjecting geranyl bromide (6) to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford a yield of 89% ($\alpha\alpha'$: $\alpha\gamma'$ at a 64:36 ratio) and 84% ($\alpha\alpha'$: $\alpha\gamma'$ at a 81:19 ratio), respectively, of a mixture of coupling products. This mixture was subjected to flash column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent and two main fractions being obtained, the first containing the $\alpha\alpha'$ coupling products as a mixture of (6*E*,10*E*) and (6*Z*,10*E*) isomers at a 6:1 ratio and the second containing the $\alpha\gamma'$ coupling products as a mixture of (6*E*) and (6*Z*) isomers at a 14:1 ratio when Ti^{III} was used. In the presence of 0.3 equiv of Zr^{IV} the $\alpha\alpha'$ coupling products are presented as a mixture of (6*E*,10*E*) and (6*Z*,10*E*) isomers at a 50:1 ratio, whilst isomerization 6*E*/6*Z* in the $\alpha\gamma'$ coupling products was not observed. The fraction containing $\alpha\alpha'$ coupling products was re-subjected to column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent to isolate the (6*E*,10*E*)-2,6,11,15-tetramethylhexadeca-2,6,10,14-tetraene (8a) isomer in a pure state.⁶ The fraction containing $\alpha\gamma'$ coupling products was re-subjected to column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent to isolate the 2,6,9,13-tetramethyl-9-vinyltetradeca-2,6*E*,12-triene (8b): ν (film) 2966, 2924, 2855, 1637, 1449, 1375, 1105, 1001, 910 cm⁻¹; δ_{H} (300 MHz; CDCl₃) δ 0.88 (3H, s), 1.20-1.30 (2H, m), 1.51 (6H, s), 1.52 (3H, s), 1.60 (6H, s), 1.78-1.90 (2H, m), 1.92-2.08 (6H, m), 4.86 (1H, dd, J = 1.5, 17.5 Hz), 4.94 (1H, dd, J = 1.5, 10.8 Hz), 5.00-5.14 (3H, m), 5.70 (1H, dd, J = 10.8, 17.5 Hz) ppm; δ_{C} (75 MHz, CDCl₃) 16.3, 17.7, 17.8, 22.7, 23.0, 25.8, 26.7, 30.0, 39.0, 40.1, 40.4, 111.5, 121.0, 124.5, 125.2, 131.1, 131.3, 136.4, 147.3 ppm; EIMS (70 ev)

⁶ Hoshino, T.; Kumai, Y.; Kudo, I.; Nakano, S.; Ohashi, S. *Org. Biomol. Chem.* 2004, 2, 2650-2657.

m/z (relative intensity) 274 [M]⁺ (1), 259 (1), 205 (3), 137 (6), 95 (12), 81 (30), 69 (100).

1,6-diphenyl-1,5-hexadiene (20a) and 1,4-diphenyl-1,5-hexadiene (20b): Cinnamyl bromide (19) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}) and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 8:1) to afford 85% ($\alpha\alpha'$: $\alpha\gamma'$: $\gamma\gamma'$ at a 45:40:15 ratio) and 82% yield ($\alpha\alpha'$: $\alpha\gamma'$ at a 48:38:14 ratio), respectively, of a mixture of coupling products. The corresponding mixtures were subjected to flash column chromatography on AgNO₃ (20%)–Si gel (hexane/*t*-BuOMe, 97:3), two main fractions being obtained, the first containing the $\alpha\alpha'$ coupling product (1,6-diphenyl-1,5-hexadiene)^{7,8} (20a) and the second containing the $\alpha\gamma'$ coupling product (1,4-diphenyl-1,5-hexadiene)⁸ (20b).

1,2-bis((1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethane (24a): Myrtenyl bromide (23) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}) and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 20:1) to afford a 70% yield ($\alpha\alpha'$, $\alpha\gamma'$ + $\gamma\gamma'$ at a 61:39 ratio) and a 65% ($\alpha\alpha'$, $\alpha\gamma'$ + $\gamma\gamma'$ at a 70:30 ratio), respectively, of a mixture of coupling products. The corresponding mixtures were subjected to flash column chromatography on silica gel using hexane as eluent to isolate 1,2-bis((1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethane (24a).⁹ When the secondary allylic chloride 25¹⁰ was subjected to the catalytic procedure conditions (Ti^{III}) and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 40:1), a 90% yield ($\alpha\alpha'$, $\alpha\gamma'$ + $\gamma\gamma'$ at a 61:39 ratio) of a mixture of coupling products 24 was obtained. However when 25 was treated under catalytic procedure conditions (Zr^{IV}) the homocoupling products 24 were not formed and the starting material was recovered unaltered even after prolonged reaction times.

Compounds 35: (*R*)-Perillyl bromide (34) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 50:1) to afford a 77% yield ($\alpha\alpha'$, $\alpha\gamma'$ +

⁷ Clive, D. L. J.; Anderson, P. C.; Moss, N.; Singh, A. *J. Org. Chem.* **1982**, *47*, 1641-1647.

⁸ Orita, A.; Watanabe, A.; Tsuchiya, H.; Otera, J. *Tetrahedron* **1999**, *55*, 2889-2898.

⁹ Fillard, C.; Villeneuve, J. J.; Prevot, J. *Bull. Soc. Chim. France* **1979**, 473-478.

¹⁰ Compound 25 was obtained from selective allylic chlorination of β -pinene in a 77% yield in only 5 min.

$\gamma\gamma'$ at a 54:46 ratio) and a 75% ($\alpha\alpha'$, $\alpha\gamma' + \gamma\gamma'$ at a 63:37 ratio), respectively, of a mixture of coupling products. The corresponding mixtures were subjected to flash column chromatography on AgNO_3 (20%)-Si gel (hexane/*t*-BuOMe, 99:1), and two fractions were obtained, the first containing the $\alpha\alpha'$ coupling product 7,7'-bis((4*R*)-1,8-*p*-menthadiene) (**35a**) and the second containing the $\alpha\gamma'$ coupling product (4*R*)-7-((2*R*,4*R*)-1(7),8-*p*-menthadien-2-il)-1,8-*p*-menthadiene (**35b**). Finally, *t*-BuOMe was added and $\gamma\gamma'$ coupling product (**35c**) could be isolated.

7,7'-bis((4*R*)-1,8-*p*-menthadiene) (35a): $[\alpha]_{\text{D}} + 75.9$ (c 2.65, CH_2Cl_2); ν (film) 3080, 2962, 2921, 2854, 1644, 1455, 1436, 1373, 886 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 1.48 (2H, ddd, $J = 5.6, 11.3, 17.1$ Hz), 1.75 (6H, s), 1.80-1.85 (2H, m), 1.87-2.15 (10H, m), 2.06 (4H, bs), 4.73 (4H, bs), 5.43 (2H, bs) ppm; δ_{C} (100 MHz; CDCl_3) 20.9, 28.0, 29.0, 30.9, 36.1, 41.3, 108.5, 120.3, 137.6, 150.3 ppm; EIMS (70 eV) m/z (relative intensity) 270 (15), 227 (35), 187 (22), 159 (18), 145 (32), 134 (25), 119 (55), 105 (61), 93 (95), 91 (100), 79 (73), 67 (42), 44 (45).

(4*R*)-7-((2*R*,4*R*)-1(7),8-*p*-menthadien-2-il)-1,8-*p*-menthadiene (35b): $[\alpha]_{\text{D}} + 55$ (c 0.85, CH_2Cl_2); ν (film) 3069, 2964, 2929, 2854, 1644, 1438, 1374, 1259, 887, 806 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 1.30 (1H, ddd, $J = 4.8, 12.3, 17.1$ Hz), 1.37-1.50 (2H, m), 1.71 (3H, s), 1.74 (3H, s), 1.75-2.27 (12H, m), 2.55 (1H, m), 4.62 (1H, bs), 4.64 (1H, bs), 4.66-4.76 (4H, m), 5.43 (1H, bs) ppm; δ_{C} (100 MHz; CDCl_3) 20.9, 21.1, 28.0, 28.7, 30.9, 31.1, 33.1, 35.9, 38.9, 40.9, 41.2, 41.3, 107.6, 108.5, 108.5, 122.4, 135.8, 150.2, 150.3, 152.0 ppm; EIMS (70 eV) m/z (relative intensity) 270 (10), 255 (9), 227 (40), 187 (20), 159 (12), 145 (18), 134 (22), 119 (40), 107 (48), 93 (100), 92 (95), 91 (78), 79 (82), 77 (95), 67 (98), 55 (81).

2,2'-bis((2*R*,4*R*)-1(7),8-*p*-menthadiene) (35c): $[\alpha]_{\text{D}} + 39.1$ (c 0.9, CH_2Cl_2); ν (film) 3068, 2929, 2856, 1645, 1441, 1374, 887 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 1.28 (2H, ddd, $J = 4.7, 12.7, 17.2$ Hz), 1.44 (2H, dt, $J = 1.7, 13.0$ Hz), 1.72 (6H, s), 1.80-1.90 (2H, m), 1.95 (2H, bd, $J = 13.5$ Hz), 2.10-2.30 (6H, m), 2.69 (2H, bs), 4.55 (2H, bs), 4.63 (2H, bs), 4.70 (4H, s) ppm; δ_{C} (100 MHz; CDCl_3) 20.9, 31.1, 33.5, 34.0, 38.9, 42.4, 108.3, 108.7, 150.1, 150.5 ppm; EIMS (70 eV) m/z (relative intensity) $[\text{M}^+ - 43]$ 227 (3), 159 (8), 145 (9), 134 (25), 105 (32), 93 (48), 91 (100), 79 (78), 67 (93), 55 (48).

7,7'-bis(1*R*),2*R*)-dihydroxy-8-*p*-mentheno (36): 7,7'-bis((4*R*)-1,8-*p*-menthadiene) (**35a**) (285 mg, 1.06 mmol) was added to a solution of AD-mixβ (2968 mg) and CH₃SO₂NH₂ (207 mg, 2.11 mmol) in *t*-BuOH:H₂O 1:1 (10 mL) at 0°C and stirred. After 7 h Na₂S₂O₃ (2385 mg) was added to the reaction mixture whilst keeping on stirring for 10 min and 20 min at rt. The *t*-BuOH was removed and extracted with EtOAc. The organic phase was washed with NaOH 6N (3 × 100 mL) and brine, then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure, the crude thus obtained being purified by column chromatography on silica gel (*t*-BuOMe) to give **36** (230 mg, 65%). [α]_D + 9.96 (c 0.5, MeOH); ν (film) 3399, 3327, 2941, 2916, 2854, 1642, 1441, 1261, 1161, 1062, 880, 749 cm⁻¹; δ_H (400 MHz; DMSO) 1.10-1.65 (16H, m), 1.66 (6H, s), 1.80-1.90 (2H, m), 3.20 (2H, m), ¹¹ 4.22 (2H, d, *J* = 6.7 Hz), 4.63 (2H, s), 4.64 (2H, s) ppm; δ_C (100 MHz; DMSO) 20.7, 25.7, 32.3, 33.5, 35.3, 43.2, 71.6, 72.9, 108.4, 149.5 ppm; HRFABMS calcd for C₂₀H₃₄O₄Na [M+Na]⁺ 361.2355, found 361.2354.

β-onoceradiene (1): 11-bromo-8-drimene (**29**) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 4:1) to afford 87% yield and 73%, respectively, of the homocoupling product **1**.²

(2*S*,4*aS*,8*aR*)-5,5'-ethylene-bis[2-(*tert*-butyldimethylsilyloxy)-1,1,4*a*,6-tetramethyl-1,2,3,4,4*a*,7,8,8*a*-octahydronaphthalene] (31): Compound **30** was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), and the resulting crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 1:8) to afford 75% yield and 68%, respectively, of the homocoupling product **31**.²

Allylic chlorination of 19-acetoxy-*ent*-kaur-16-ene (37): PhSeCl (21 mg, 0.10 mmol) was dissolved in DCM (2 mL). To this solution was added 19-acetoxy-*ent*-kaur-16-ene (70 mg, 0.21 mmol) at rt. To this mixture was added *N*-chlorosuccinimide (31 mg, 0.23 mmol) and stirred for 3 h (TLC monitoring). The solution was concentrated and suspended with diethyl ether. The organic layer was decanted from the solid, washed with H₂O and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced

¹¹ dd (*J* = 4.6, 11.0 Hz) when the ¹H NMR spectrum was made in DMSO + D₂O

pressure. Then, the resulting crude was dissolved in DCM (5 mL), silica gel was added and heated at reflux for 15 min. The solvent was removed and the crude was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 18:1) to afford 19-acetoxy-17-chloro-*ent*-isokaurene (**38a**) together with 19-acetoxy-15-chloro-*ent*-kaur-16-ene (**38b**) (50 mg, 65%) in variable proportions (from 1:4 to 1:2).

19-acetoxy-15-chloro-*ent*-kaur-16-ene (38a): ν (film) 2932, 2868, 1738, 1653, 1457, 1390, 1371, 1239, 1032 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 0.96 (3H, s), 1.04 (3H, s), 1.13-1.92 (18H, m), 2.05 (3H, s), 2.80 (1H, bs), 3.88 (1H, d, $J = 11.0$ Hz), 4.22 (1H, d, $J = 11.0$ Hz), 4.36 (1H, bs), 5.15 (1H, bs), 5.29 (1H, bs) ppm; δ_{C} (100 MHz; CDCl_3) 18.2, 18.3, 18.5, 20.1, 21.2, 27.8, 33.0, 35.9, 36.4, 37.2, 38.6, 39.9, 40.6, 42.4, 48.3, 55.5, 56.6, 67.3, 73.9, 111.0, 157.3, 171.6 ppm.

Homocoupling reaction of 38a and 38b

17,17'-bis(19-acetoxy-*ent*-isokaurene) (4): A mixture of Cp_2TiCl_2 (37 mg, 0.14 mmol) and Mn dust (53 mg, 0.96 mmol) in strictly deoxygenated THF (1 mL) was stirred at room temperature until the red solution turned green. Then **38a** and **38b** (46 mg, 0.12 mmol) in strictly deoxygenated THF (1 mL) were added to the solution of Cp_2TiCl_2 . The reaction mixture was stirred for 5 min, quenched with 1N HCl, extracted with *t*-BuOMe, washed with 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, 20:1) to afford a 67% yield of the coupling product **4**. $[\alpha]_{\text{D}} - 42.0$ (c 1.0, CH_2Cl_2); ν (film) 2926, 2865, 1739, 1456, 1371, 1238, 1031 cm^{-1} ; δ_{H} (400 MHz; CDCl_3) 0.94 (6H, s), 1.04 (6H, s), 1.20-1.90 (36H, m), 2.04 (6H, s), 2.20 (4H, s), 2.39 (2H, bs), 3.87 (1H, d, $J = 11.0$ Hz), 4.22 (2H, d, $J = 11.0$ Hz), 5.07 (2H, bs) ppm; δ_{C} (100 MHz; CDCl_3) 18.3, 18.5, 19.1, 19.7, 21.3, 25.8, 27.7, 28.1, 36.6, 37.3, 39.6, 40.2, 40.7, 43.8, 44.0, 49.1, 49.3, 56.8, 67.4, 134.3, 147.0, 171.6 ppm; HR FABMS calcd for $\text{C}_{44}\text{H}_{66}\text{O}_4$ $[\text{M} + \text{Na}]^+$ 681.4859, found 681.4857.

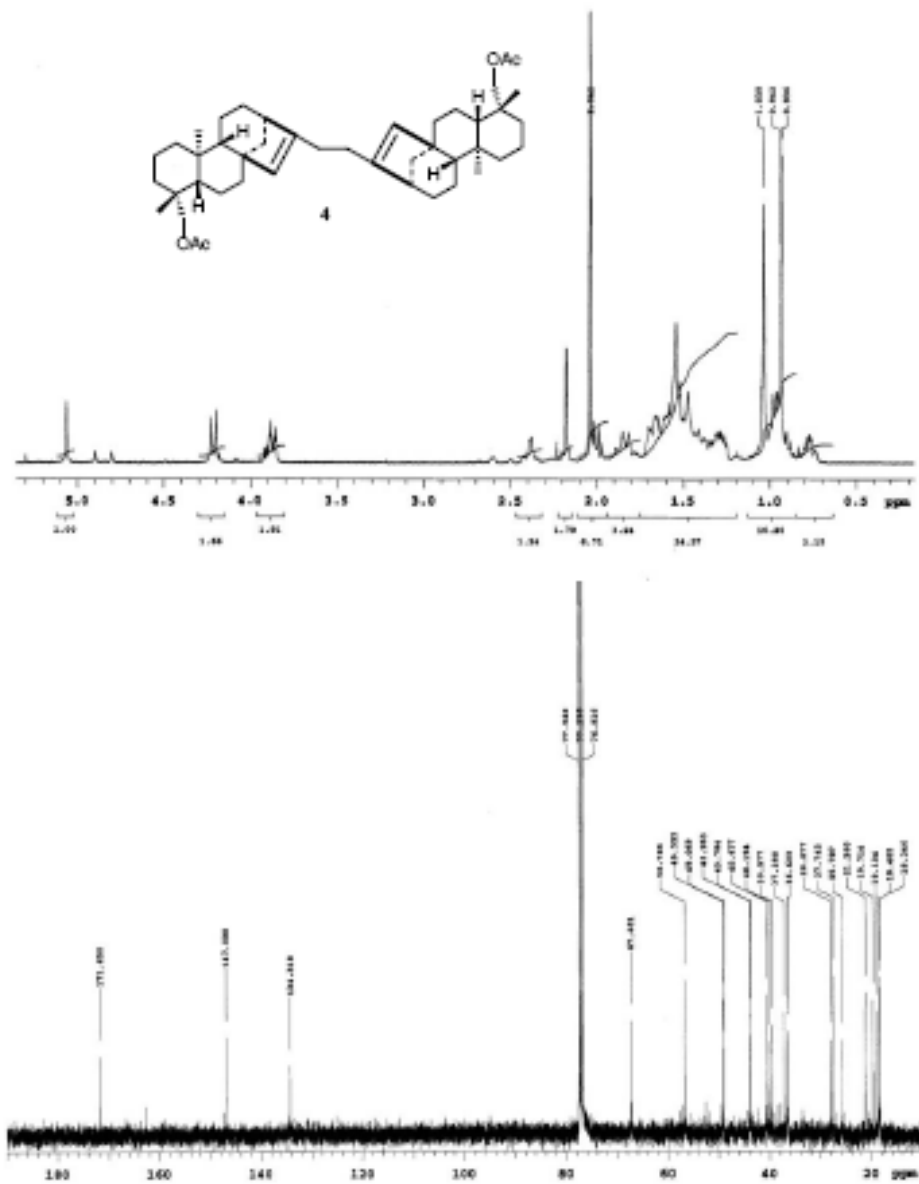
Squalene (5): *Trans, trans*-farnesyl bromide (**39**) was subjected to the catalytic procedure conditions (Ti^{III} and Zr^{IV}), and the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford a 63% yield ($\alpha\alpha'$ (*EE*): $\alpha\alpha'$ (*EZ*): $\alpha\gamma'$ at a 66:22:12 ratio) and 62% ($\alpha\alpha'$: $\alpha\gamma'$ at a 82:18 ratio), respectively, of a mixture of coupling products. The $\alpha\alpha'$ coupling products could be

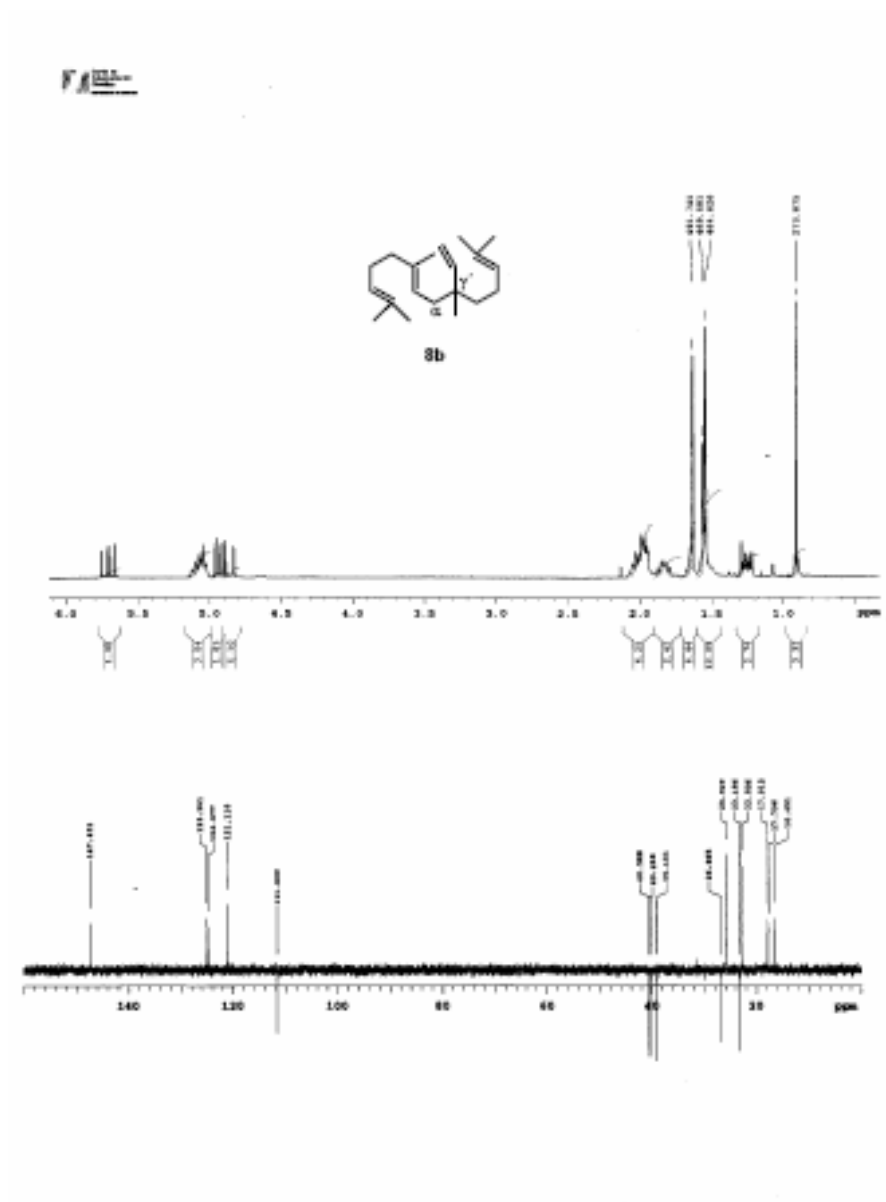
separated from the $\alpha\gamma'$ coupling products as a mixture of (6*E*,10*E*,14*E*,18*E*) and (6*E*,10*Z*,14*E*,18*E*) by column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent at a 3:1 ratio, whilst the $\alpha\gamma'$ coupling products are presented as a mixture of isomers at a 10:1 ratio when Ti^{III} is used. Fractions enriched with the major isomer were re-subjected to column chromatography on AgNO₃ (20%)-Si gel using hexane as eluent to isolate **5**.¹² In the presence of 0.3 equiv of Zr^{IV} isomerization *E/Z* was not observed.

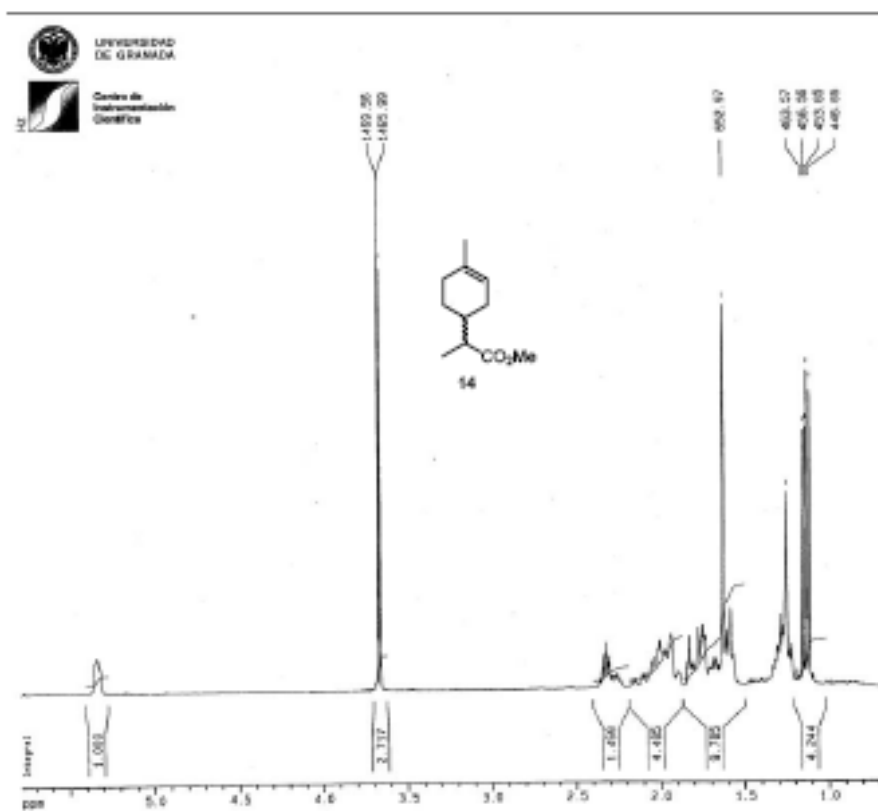
Procedure for radical cyclization reaction of 10 and 11: A solution of tributyltin hydride (228 mg, 0.76 mmol) and AIBN (7 mg, 0.04 mmol) in dry, degassed benzene (14 mL) was added dropwise (10 mL/h) to a solution of the bromide (**10** or **11**) (100 mg, 0.38 mmol) in dry, degassed benzene (136 mL) heated to 80°C under an atmosphere of argon. After the addition time plus an additional hour (TLC monitoring), the cooled mixture was evaporated under reduced pressure and the residue dissolved in diethyl ether. An aqueous saturated KF solution (5 mL) was added and the mixture stirred for 2 h at rt. After filtration through celite, the biphasic filtrate was extracted with diethyl ether. The aqueous layer was extracted with diethyl ether after separation. The combined organic extracts were concentrated under reduced pressure and the crude was purified by column chromatography (petroleum ether/diethyl ether, 20:1) on silica gel to afford 50 mg (72%) of the cyclized compound methyl 1-*p*-menthen-9-oate (**14**).¹³ δ_{H} (400 MHz; CDCl₃) 1.12 (3H, d, *J* = 7.0 Hz), 1.56 (3H, s), 1.50-2.40 (8H, m), 3.65 (3H, s), 5.30-5.40 (1H, m) ppm; (only distinctive signals) δ 1.14 (3H, d, *J* = 7.0 Hz), 3.66 (3H, s) ppm; EIMS (70 eV) *m/z* (relative intensity) 182 [*M*⁺] (5), 150 (15), 95 (47), 94 (81), 88 (100), 79 (75), 67 (40); HR EIMS calcd for C₁₁H₁₈O₂ [*M*]⁺ 182.1307, found 182.1311.

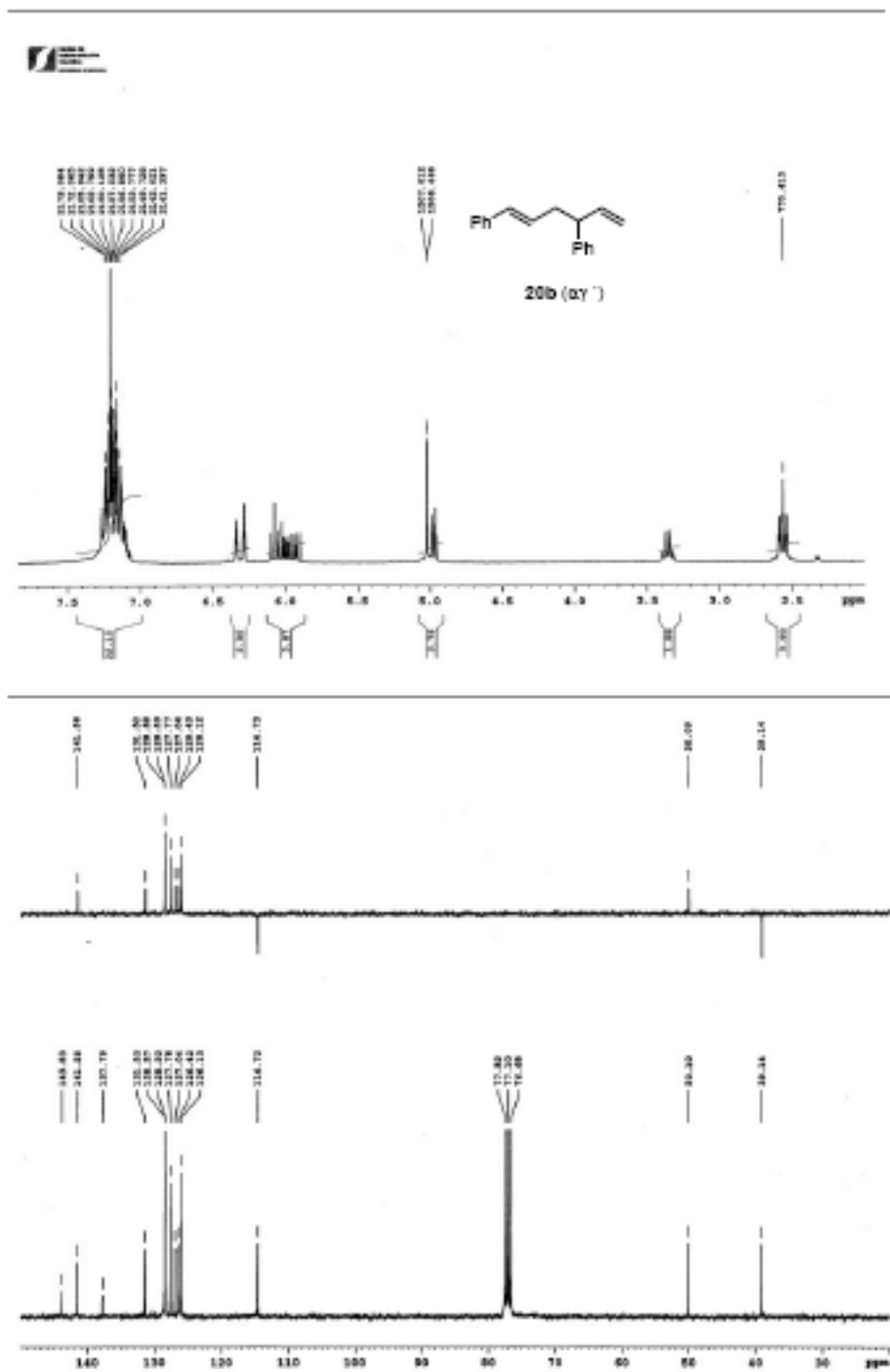
¹² Ho, H.; Cai, Y.; Sun, M.; Cocks, H. *J. Agric. Food Chem.* 2002, 50, 363-372.

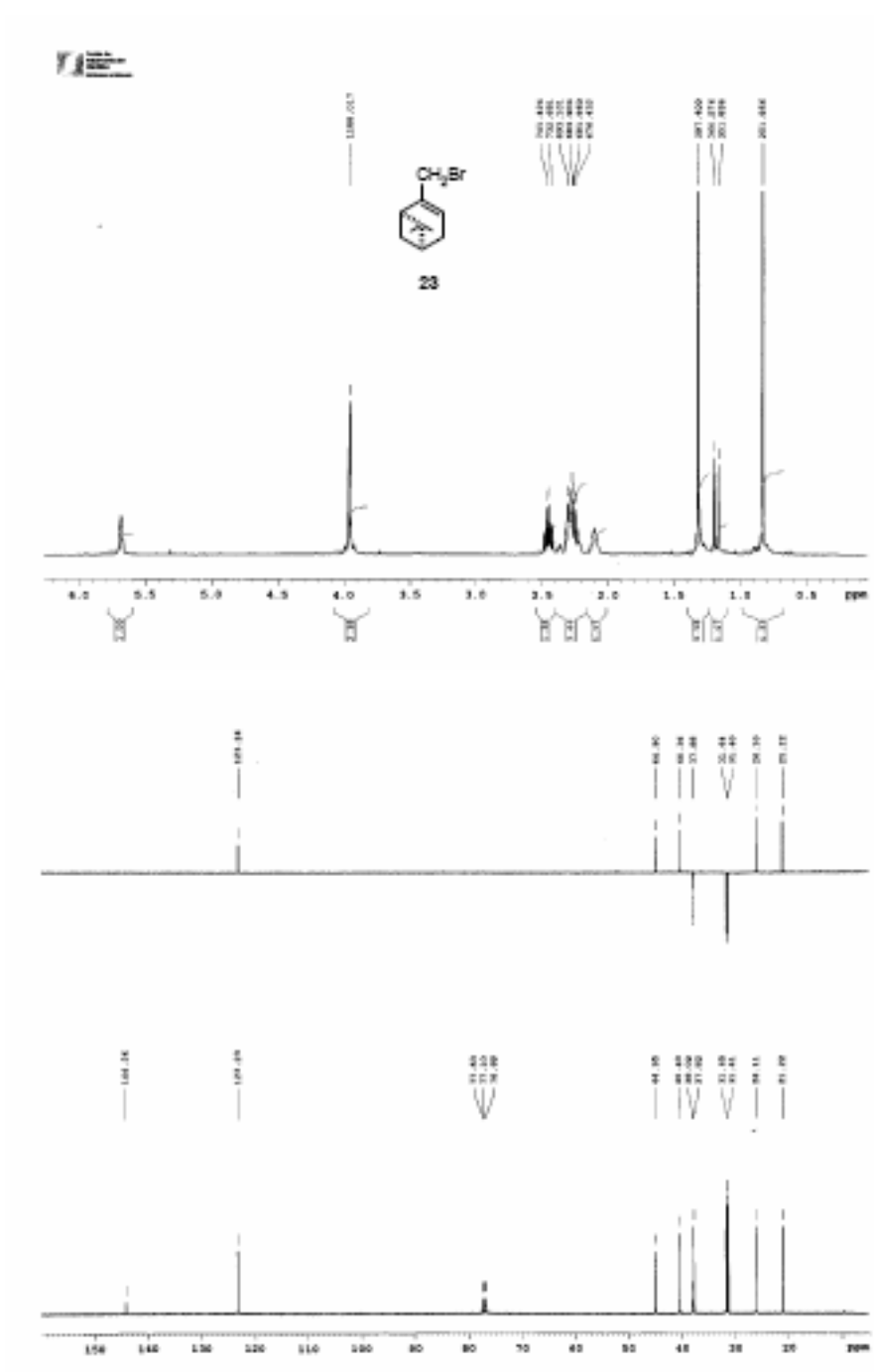
¹³ Guth, H. *Helv. Chim. Acta* 1996, 79, 1559-1571.

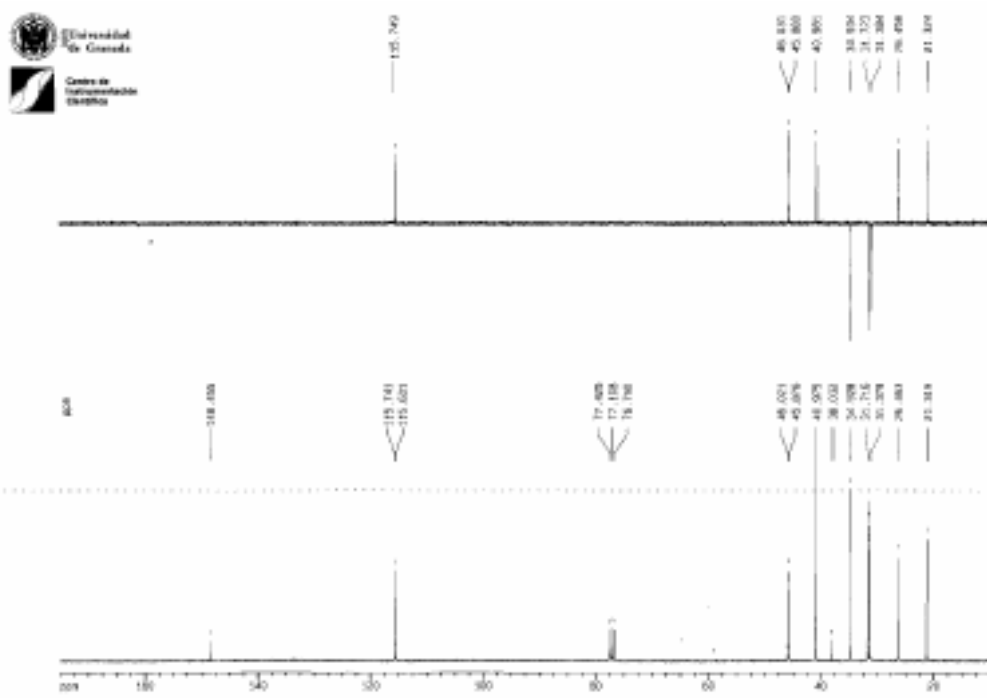
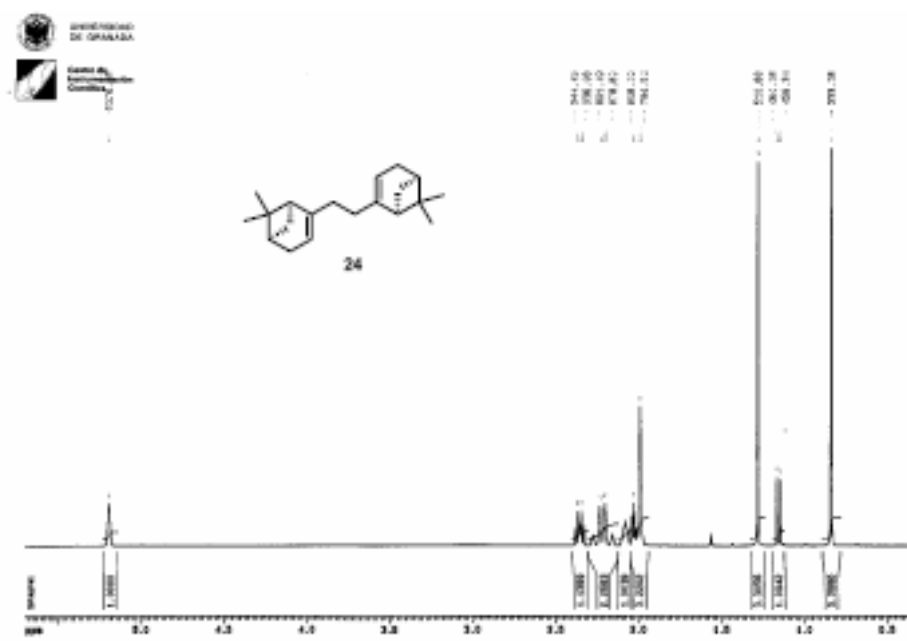


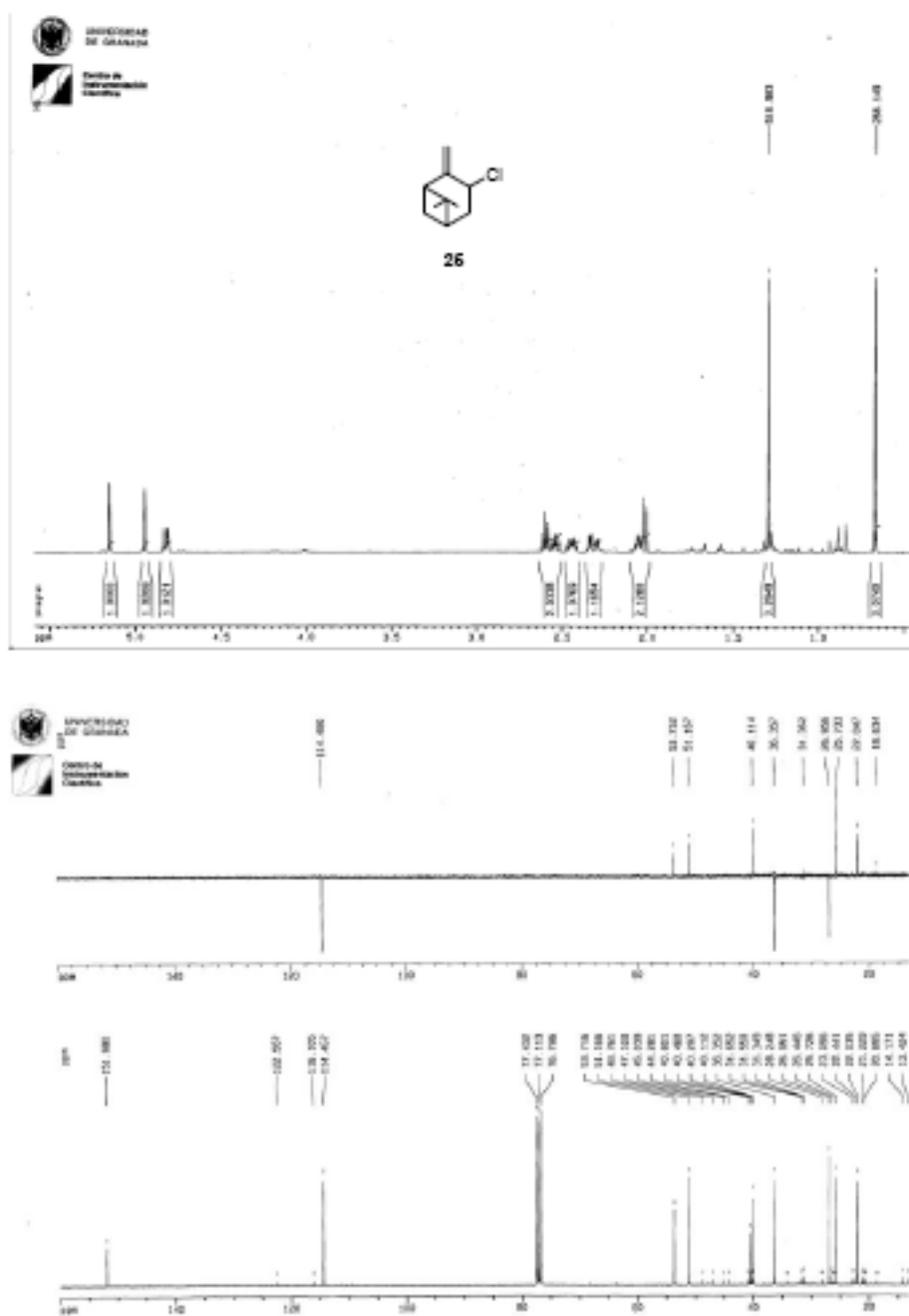


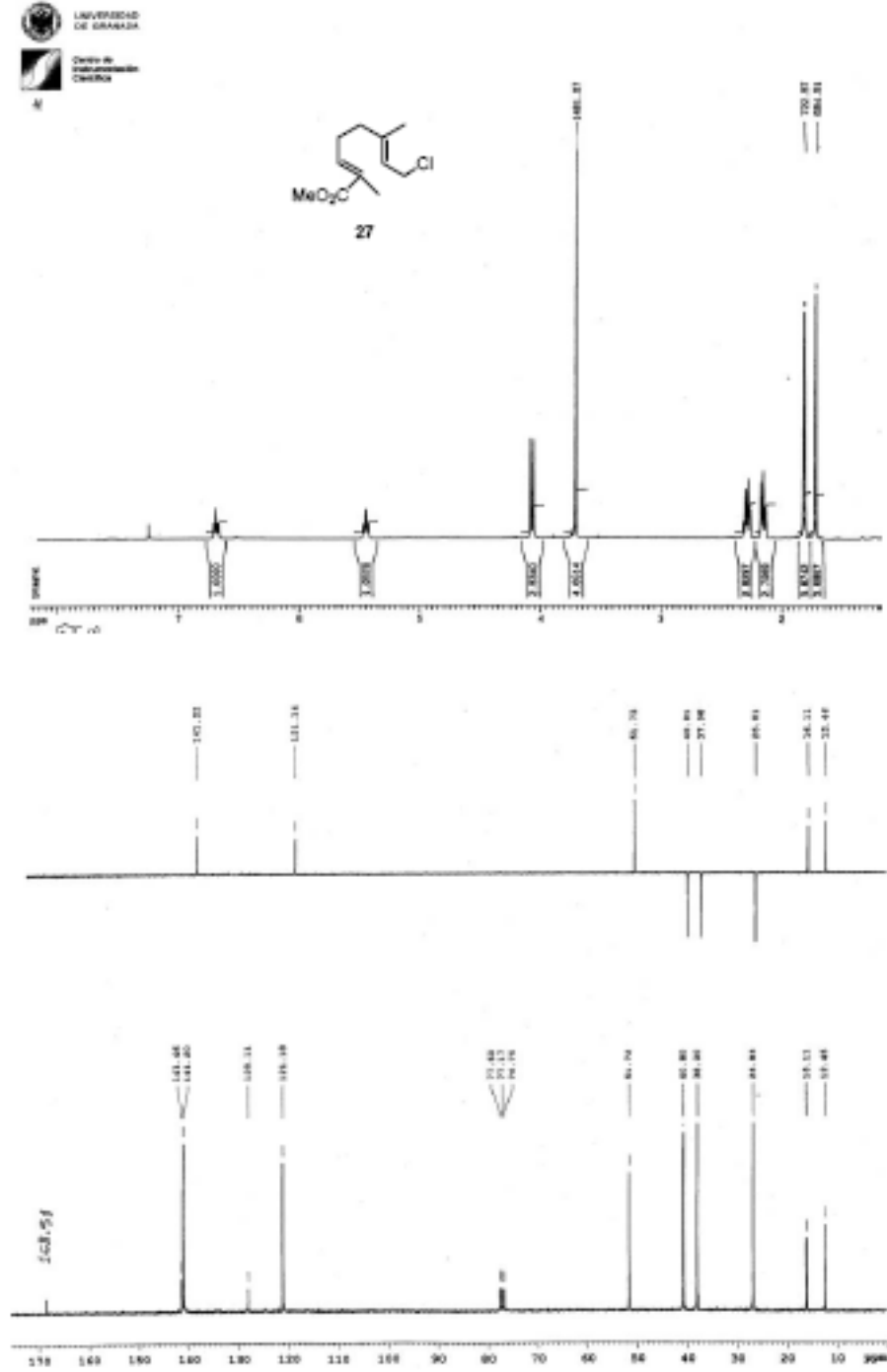


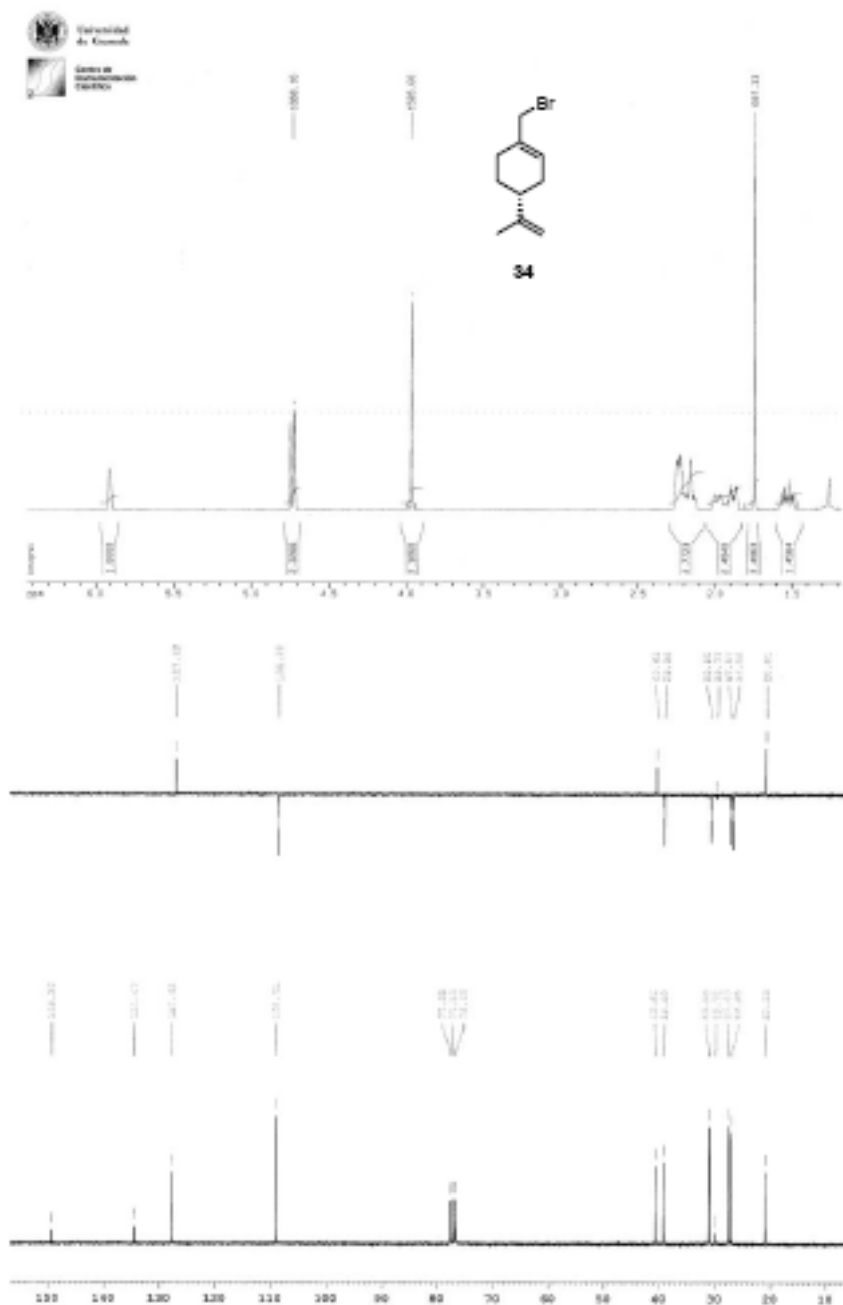


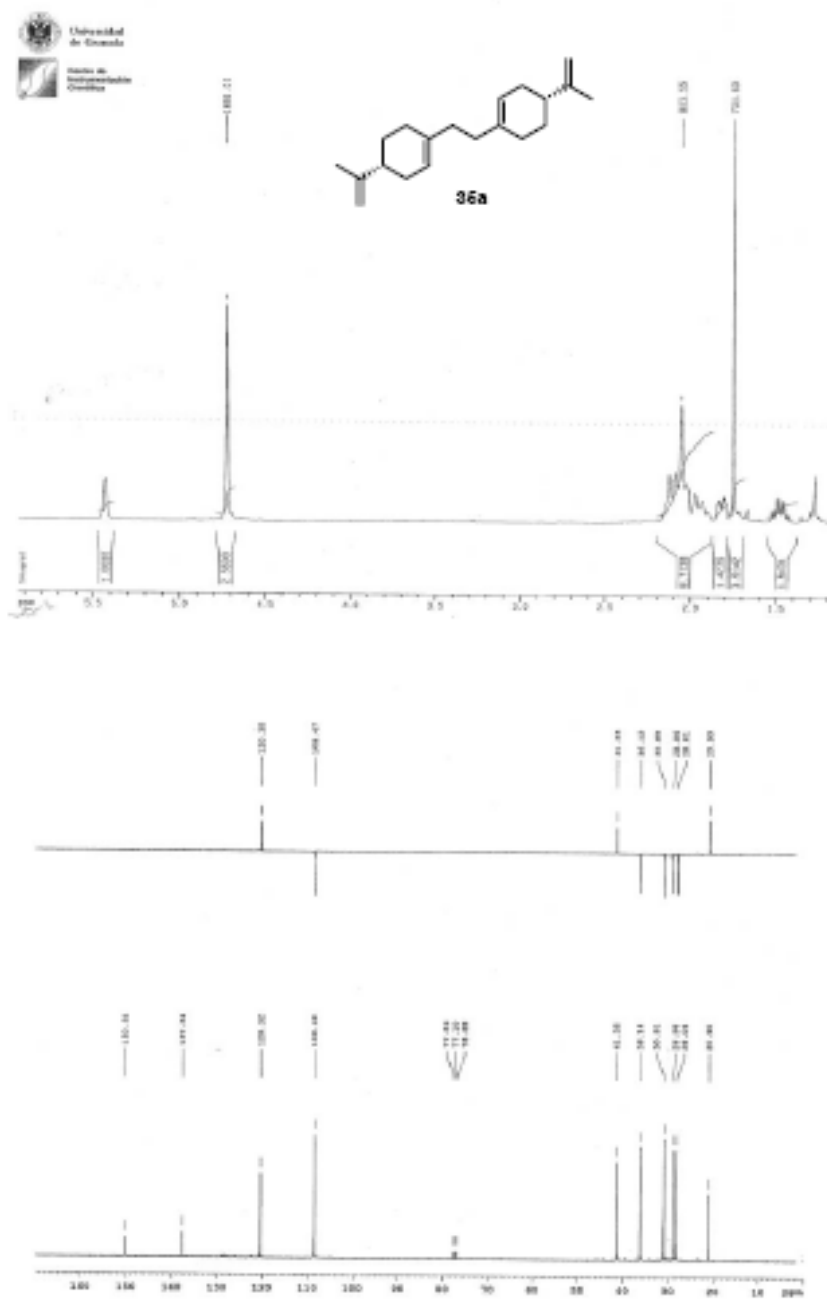


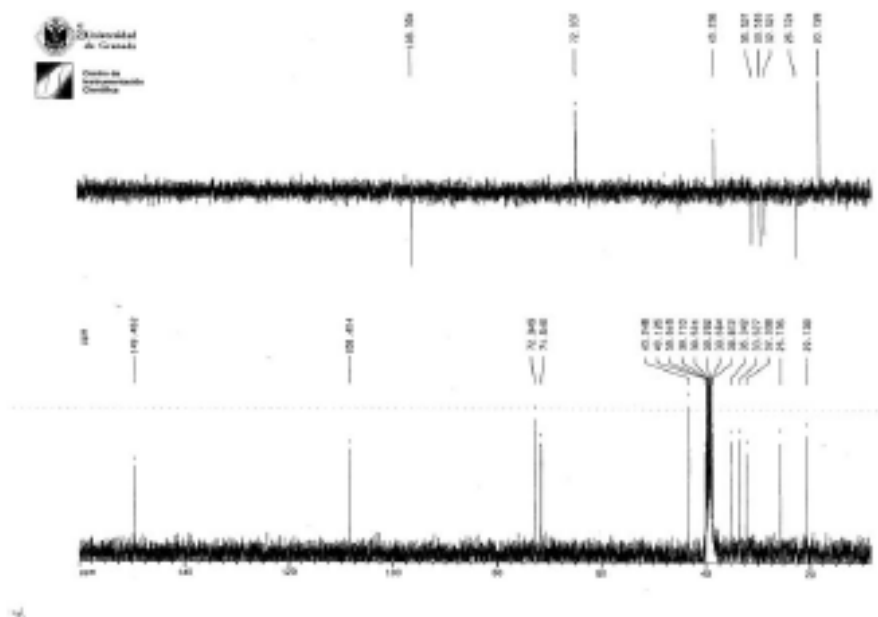
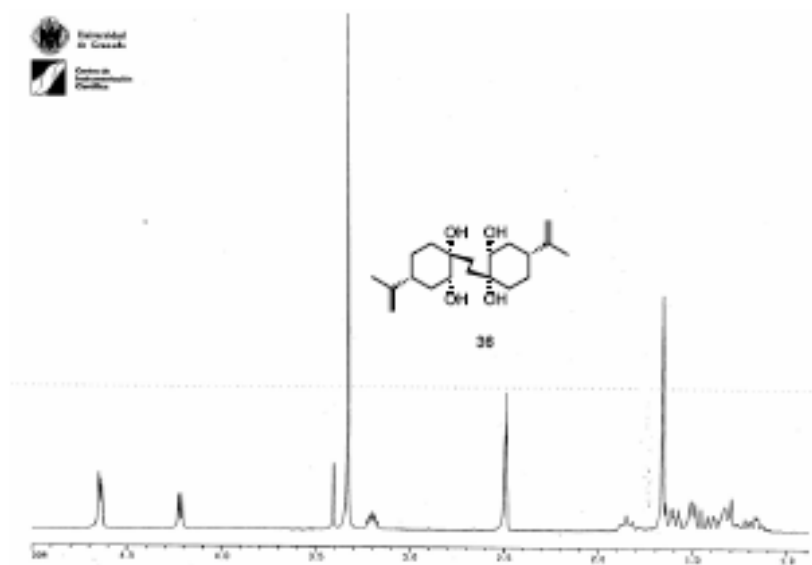


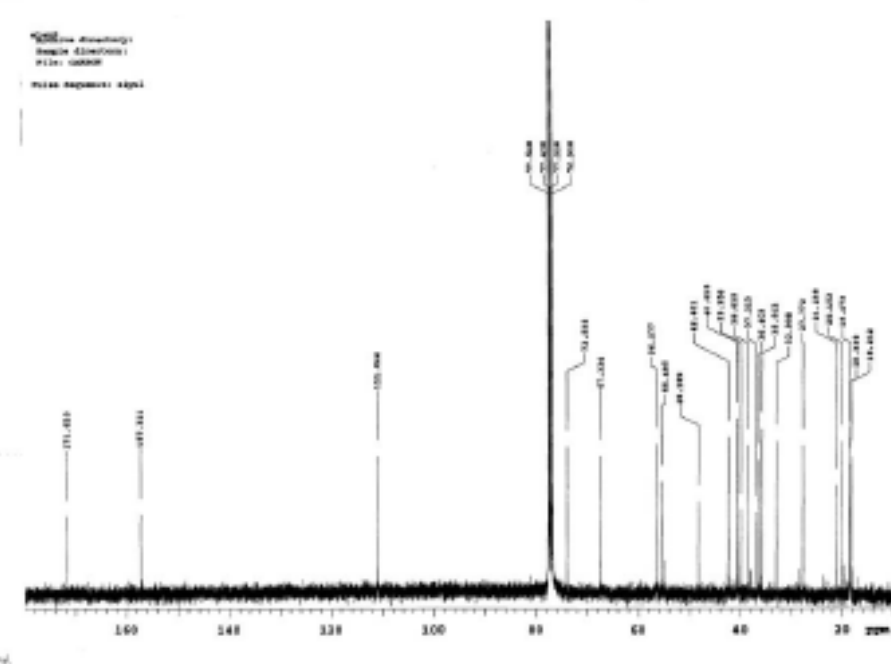
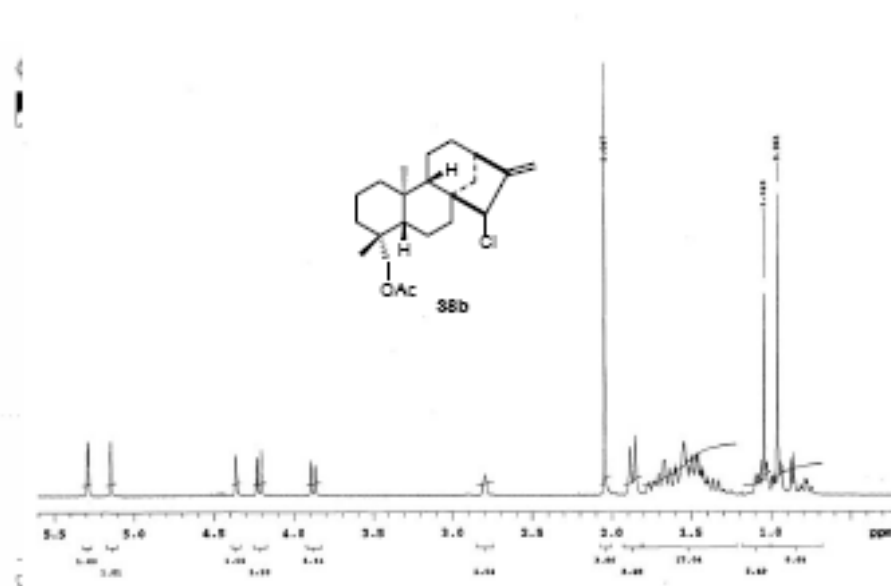


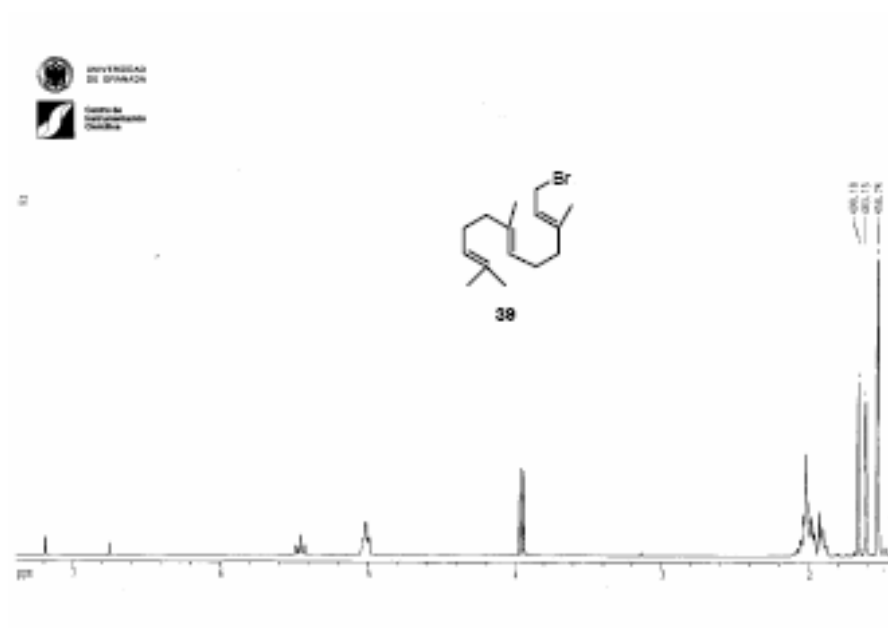












ANEXO 2

Supporting Information Artículo 2

Supporting Information**Couplings of Benzylic Halides Mediated by Titanocene Chloride:
Synthesis of Bibenzyl Derivatives**

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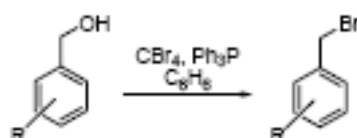
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General Details

All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an argon atmosphere. Tetrahydrofuran (THF) was freshly distilled immediately prior to use from sodium/benzophenone and thoroughly deoxygenated for 30 min under argon for each of the Cp₂TiCl₂/Mn reactions. The rest of the solvents used were purified according to standard literature techniques and stored under argon. Analytical TLC was performed on layers of silica gel 0.25 mm thick, using a 7% phosphomolybdic acid solution (EtOH) to visualize the spots. Silica gel (35-70 μm) was used for column chromatography.

Experimental procedures

General procedure for bromination reaction of benzylic alcohols



CBr₄ (2.0 mmol) and Ph₃P (2.0 mmol) at 0°C under an Ar atmosphere were added to a stirred solution of benzylic alcohol (1.0 mmol) in 7 mL of benzene. The solution was stirred at the same temperature for 2 h (TLC monitoring), and hexane (10 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 purified by column chromatography on silica gel to afford the corresponding benzylic bromo-derivative (**5**, **7**, **9** and **11**).

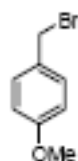
Benzyl bromide (1a): Commercially available.

Benzyl chloride (1b): Commercially available.

2-(Bromomethyl)naphthalene (3): Commercially available.

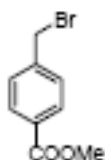
4-Methoxybenzyl bromide (5): According to the general procedure described above, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to afford 96% of **5** as a yellowish oil.¹

¹ Brindley, C. R.; Jauz, R. *Eur. J. Org. Chem.* 2005, 755-758.



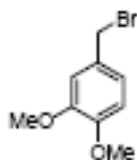
5

Methyl 4-(bromomethyl)benzoate (7): According to the general procedure for the bromination of benzylic alcohols, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 92% of **7**² as a white solid. Mp 47 - 48 °C, lit.² 47 - 49 °C.



7

3,4-Dimethoxybenzyl bromide (9): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 94% of **9**^{3a} as a yellowish solid. Mp 46 - 48 °C, lit.^{3b} 47 - 50 °C.

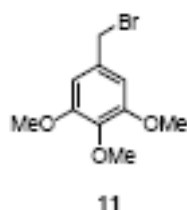


9

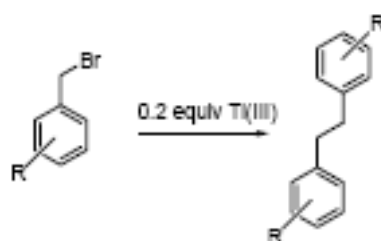
3,4,5-Trimethoxybenzyl bromide (11): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 90% of **11**^{4a} as a white solid. Mp 74 - 75 °C, lit.^{4b} 71 - 73 °C.

² Schaper, K.; Abdollah Madzmi Moberakeh, S.; Gewer, C. *Eur. J. Org. Chem.* **2002**, 1037-1046.

³ (a) Yadav, J. S.; Kumar Mishra, R. *Tetrahedron Lett.* **2002**, *43*, 5419-5422. (b) TenBrink, R. E. *J. Heterocycl. Chem.* **1981**, *18*, 821-824.



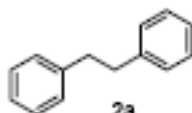
General procedure for catalytic homocoupling reaction of benzylic bromides mediated by Ti(III)



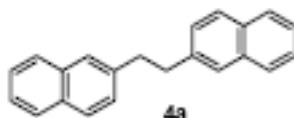
A mixture of Cp_2TiCl_2 (190 mg, 0.74 mmol) and Mn dust (1620 mg, 29.44 mmol) in thoroughly deoxygenated THF (50 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. The corresponding benzylic bromide (3.68 mmol) in strictly deoxygenated THF (2 mL, $C_f = 0.07$ M) was then added to the Cp_2TiCl_2 solution (TLC monitoring). Then, THF was removed and the reaction was quenched with 1N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products (2a, 4a, 6a, 8a, 10a and 12a). The same procedure was followed when the molar concentration was 0.8.

⁴ (a) Kong, Y.; Grembecka, Y.; Edler, M. C.; Humel, E.; Mooberry, S. L.; Sabat, M.; Rieger, J.; Brown, M. L. *Chem. & Biol.* **2005**, *12*, 1007-1014. (b) Ohta, A.; Tomozura, Y.; Sawaki, J.; Sato, N.; Akiike, H.; Ikuta, M.; Shimazaki, M. *Heterocycles* **1991**, *32*, 965-973.

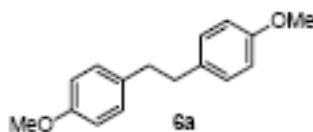
1,2-Diphenylethane (2a): According to the general procedure described above, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel to afford 73% of **2a**^{5a} as a white solid. Mp 50 - 51 °C (methanol), lit.^{5b,c} 50 - 53 °C.



1,2-Bis(naphthyl)ethane (4a): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel to afford 60% of **4a**⁶ as a white solid. Mp 180 - 181 °C (ethanol/ethyl acetate), lit.⁶ 183 - 184 °C.



1,2-bis(4-methoxyphenyl)ethane (6a): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 20:1) on silica gel to afford 77% of **6a**⁷ as a white solid. Mp 123 - 125 °C (ethanol), lit.⁷ 125 - 126 °C.

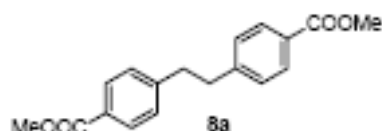


⁵ (a) Yanlong, Q.; Guisheng, L.; Huzang, Y. *J. Organomet. Chem.* **1990**, *381*, 29-34. (b) Mc Murry, J. E.; Silvestri, M. *J. Org. Chem.* **1975**, *40*, 2687-2688. (c) Proffitt, J. A.; Ong, H. H. *J. Org. Chem.* **1979**, *44*, 3972-3974.

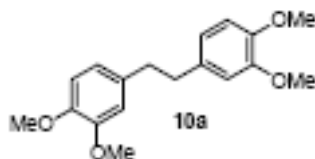
⁶ Inaba, S.; Matsumoto, H.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 2093-2098.

⁷ Ki-Bong, O.; Soo-Hwan, K.; Jaekwang, L.; Woon-Jea, C.; Taebo, L.; Sanghee, K. *J. Med. Chem.* **2004**, *47*, 2418-2421.

1,2-bis(4-methoxycarbonylphenyl)ethane (8a): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel to afford 72% of **8a**^{8a} as a yellow solid. Mp 117 - 118 °C, lit.^{8b} 118.5 - 119.5 °C.



1,2-bis(3,4-dimethoxyphenyl)ethane (10a): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to afford 74% of **10a**^{9a} as a white solid. Mp 109 - 111 °C, lit.^{9b} 110.5 - 111 °C.

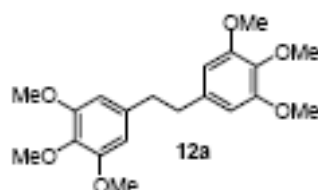


1,2-bis(3,4,5-trimethoxyphenyl)ethane (12a): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to afford 70% of **12a**^{9a} as a white solid. Mp 137 - 138 °C (ethanol), lit.^{9b} 138 - 139 °C.

⁸ (a) Suh, Y.; Lee, J.; Kim, S.; Rieke, R. D. *J. Organomet. Chem.* **2003**, *684*, 20-36. (b) Bellatre, J. L.; Splezner, E. G. *Synth. Commun.* **1986**, *16*, 575-584.

⁹ (a) Pincock, J. A.; Wedge, P. J. *J. Org. Chem.* **1994**, *59*, 5587-5595. (b) Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans 1: Org. & Bio-Org. Chem.* **1977**, 120-122.

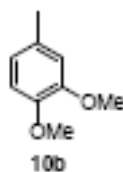
^{9b} Iwakuma, T. *Heterocycles* **1981**, *15*, 1115-1118.



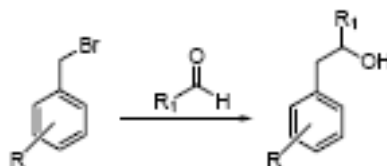
Procedure for the reaction of benzylic bromides with Ti(III) in the presence of proton donors

A mixture of Cp_2TiCl_2 (249 mg, 1.0 mmol) and Mn dust (440 mg, 8.0 mmol) in thoroughly deoxygenated THF (15 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. Benzyl bromide (1a) (1.0 mmol) and 1,4-cyclohexadiene (400 mg, 5.0 mmol) or *t*-BuSH (451 mg, 5.0 mmol) were then added to the Cp_2TiCl_2 solution and the reaction mixture was stirred for 20 min (TLC monitoring). Then, THF was filtered through a pad of silica gel and the resulting crude was proven to contain by NMR mainly toluene together with minor quantities of 1,2-diphenylethane. Yields were calculated by combining NMR integrals and the quantities of bibenzyl (2a) obtained after silica gel chromatography of the reaction crude.

The same procedure was followed when 3,4-dimethoxybenzyl bromide (9) was used as starting material. In this case the corresponding reduction product **10b**¹¹ (83%) together with a 15% yield of **10a** were isolated after usual work up and column chromatography (petroleum ether/diethyl ether, 20:1).

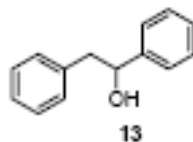


¹¹ Janssen, R. H. A. M.; Wijkens, P.; Kruk, C.; Biessels, H. W. A.; Menichini, F.; Theuns, H. G. *Phytochemistry* **1990**, *29*, 3331-3339.

General procedure for cross-coupling reaction mediated by Ti(III)

A mixture of Cp_2TiCl_2 (333 mg, 1.30 mmol) and Mn dust (572 mg, 10.40 mmol) in thoroughly deoxygenated THF (18 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. Then, the corresponding benzylic bromide (1.30 mmol, 1.0 equiv) and the corresponding aldehyde (2.60 mmol, 2.0 equiv) were added simultaneously to the Cp_2TiCl_2 solution (TLC monitoring). THF was removed and the reaction mixture was quenched with 1N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding alcohols (**13**, **14**, **15**, **16** and **17**). In some cases minor quantities of homocoupling products were obtained. Please, see Table 2 in the article body.

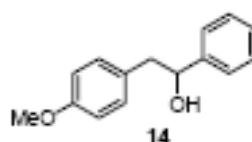
1,2-Diphenylethanol (13): According to the general procedure described above, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 10:1) on silica gel to afford 57% of **13**¹² as a yellowish solid, mp 65 - 66 °C (hexane), lit.¹² 64 - 65 °C, together with a 15% yield of the homocoupling product 1,2-diphenylethane (**2a**).



¹² Kim, S.; Riecke, R. D. *J. Org. Chem.* 2000, 65, 2322-2330.

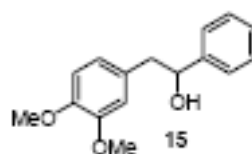
Following the general procedure but using 2.0 equiv of Ti(III) (996 mg, 4.0 mmol), reaction of benzyl bromide (**1a**) (342 mg, 2.0 mmol) with benzaldehyde (424 mg, 4.0 mmol) afforded after usual work up and column chromatography (hexane/*t*-BuOMe, 10:1) a 35% yield of **13** (140 mg) and a 24% yield of **2a** (43 mg).

2-(4-Methoxyphenyl)-1-phenylethanol (14): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 50% of **14**¹³ as a yellow solid, mp 60 - 61 °C, lit.¹³ 62 °C, together with a 15% yield of the homocoupling product 1,2-bis(4-methoxyphenyl)ethane (**6a**) and a 19% yield of **17**.

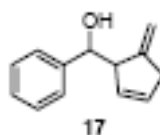


2-(3,4-Dimethoxyphenyl)-1-phenylethanol (15): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 58% of the alcohol **15** as a yellow oil together with a 20% yield of **17** as a yellow oil. Compound **15**: IR (film) 3483, 2935, 2834, 1590, 1515, 1452, 1418, 1262, 1236, 1155, 1139, 1028, 762, 700 cm⁻¹; ¹H NMR (400 MHz; CDCl₃) δ 2.95 (1H, dd, *J* = 7.9, 13.7 Hz), 3.01 (1H, dd, *J* = 5.1, 13.7 Hz), 3.81 (3H, s), 3.87 (3H, s), 4.88 (1H, dd, *J* = 5.1, 7.9 Hz), 6.63 (1H, d, *J* = 1.7 Hz), 6.77 (1H, dd, *J* = 1.7, 8.1 Hz), 6.82 (1H, d, *J* = 8.1 Hz), 7.20-7.40 (5H, m); ¹³C NMR (100 MHz; CDCl₃) δ 45.7, 55.8, 56.0, 75.4, 111.2, 112.7, 121.6, 126.0 (2C), 127.7, 128.5 (2C), 130.3, 143.8, 147.9, 148.9; HR FABMS calcd for C₁₆H₁₈O₃Na [M+Na]⁺ 281.1153, found 281.1150.

¹³ Noyce, D. S.; Hartner, D. R.; Miles, F. B. *J. Am. Chem. Soc.* **1968**, *90*, 3794-3796.



(5-Methylenecyclopent-2-enyl)(phenyl)methanol (17): IR (film) 3418, 3061, 3030, 2882, 1655, 1514, 1453, 1263, 1033, 892 cm^{-1} ; ^1H NMR (400 MHz; CDCl_3) δ 2.40 (1H, bs), 2.98 (1H, m), 3.06 (1H, m), 3.48 (1H, d, $J = 7.4$ Hz), 4.47 (1H, d, $J = 7.4$ Hz), 5.08 (1H, bs), 5.14 (1H, bs), 5.46 (1H, dd, $J = 2.3, 6.0$ Hz), 5.85 (1H, bd, $J = 6.0$ Hz), 7.25-7.37 (5H, m); ^{13}C NMR (100 MHz; CDCl_3) δ 39.0, 58.2, 76.6, 110.1, 126.9 (2C), 127.6, 128.2 (2C), 131.2, 131.7, 142.4, 149.9; HR FABMS calcd for $\text{C}_{13}\text{H}_{14}\text{ONa}$ $[\text{M}+\text{Na}]^+$ 209.094235, found 209.094513.

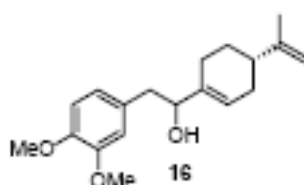


2-(3,4-Dimethoxyphenyl)-1-[(4R)-4-(1-methylethenyl)cyclohex-1-enyl]ethanol (16): According to the general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 60% of **16** (white solid) as a mixture of diastereoisomers at a 3:1 ratio. IR (film) 3500, 3078, 2919, 2835, 1643, 1590, 1515, 1463, 1262, 1236, 1156, 1141, 1029, 887, 805 cm^{-1} ; HR FABMS calcd for $\text{C}_{19}\text{H}_{26}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 325.1779, found 325.1771.

Major diastereoisomer: ^1H NMR (400 MHz; CDCl_3) δ 1.43-1.63 (1H, m), 1.75 (3H, s), 1.85-2.35 (7H, m), 2.74 (1H, dd, $J = 8.4, 13.5$ Hz), 2.82 (1H, dd, $J = 4.4, 13.5$ Hz), 3.88 (3H, s), 3.89 (3H, s), 4.20 (1H, dd, $J = 4.4, 8.4$ Hz), 4.69-4.75 (2H, m), 5.71 (1H, bs), 6.74-6.80 (2H, m), 6.83 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz; CDCl_3) δ 20.8, 24.4,

27.7, 30.6, 41.4, 41.8, 55.9, 56.0, 76.9, 108.7, 111.3, 112.5, 121.3, 122.3, 123.2, 131.1, 139.2, 147.7, 148.9, 149.8.

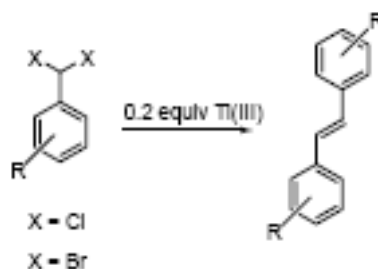
Minor diastereoisomer: ^1H NMR (400 MHz; CDCl_3) (only distinctive signals) δ 2.71 (1H, dd, $J = 8.6, 13.5$ Hz); ^{13}C NMR (100 MHz; CDCl_3) (only distinctive signals) δ 20.9, 25.0, 27.6, 30.5, 41.3, 42.0, 77.0, 112.6, 121.4, 130.9, 138.8, 149.9.



Procedure for cross-coupling reaction catalyzed by Ti(III)

A mixture of Cp_2TiCl_2 (100 mg, 0.4 mmol) and Mn dust (880 mg, 16.0 mmol) in thoroughly deoxygenated THF (28 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. Then, benzaldehyde (424 mg, 4.0 mmol), benzyl bromide (**1a**) (342 mg, 2.0 mmol), 2,4,6-collidine (1697 mg, 14.0 mmol) and Me_3SiCl (870 mg, 8.0 mmol) were added to the Cp_2TiCl_2 and the reaction mixture was stirred for 3 h (TLC monitoring). THF was removed and the reaction mixture was dissolved in *t*-BuOMe (200 mL), quenched with 1N HCl and stirred for 1 h. Then, the organic layer 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, 10:1) on silica gel to afford **13** (150 mg, 38%) and **2a** (10 mg, 5%).

General procedure for catalytic homocoupling reaction of benzylic *gem*-dihalides mediated by Ti(III)

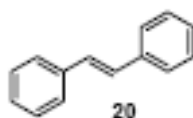


A mixture of Cp_2TiCl_2 (61 mg, 0.24 mmol) and Mn dust (528 mg, 9.60 mmol) in thoroughly deoxygenated THF (2 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. The corresponding benzylic *gem*-dihalide (1.2 mmol) in strictly deoxygenated THF (1 mL) was then added to the Cp_2TiCl_2 solution (TLC monitoring). Then, THF was removed and the reaction was quenched with 1N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding stilbene-derivatives (20, 21).

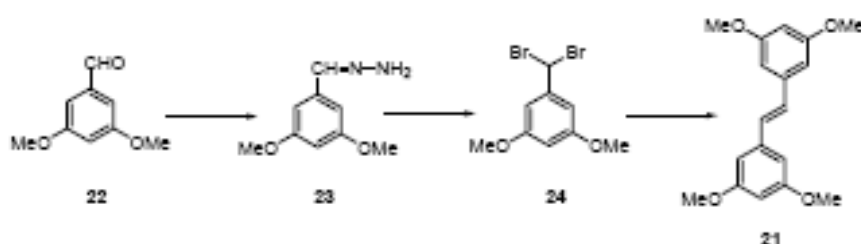
α, α' -Dibromotoluene (18): Commercially available.

α, α' -Dichlorotoluene (19): Commercially available.

Trans-stilbene (20): According to the general procedure described above, the resulting crude was purified by column chromatography using hexane as eluent on silica gel to afford 74% of 20^{56} as a white solid. Mp 120 - 121 °C (ethanol), lit.⁵⁶ 124 - 125 °C.



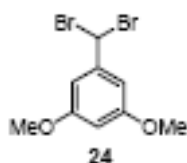
Synthesis of 3,3',5,5'-tetramethoxystilbene (21)



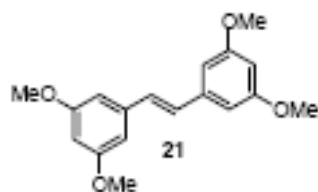
1-(3,5-Dimethoxybenzylidene)hydrazine (23): Finely powdered molecular sieves 4Å (2 g) were placed in a flask under argon atmosphere. MeOH (5 mL) and hydrazine hydrate (160 mg, 5.0 mmol) were added successively. After 20 min, a methanol solution (5 mL) of 3,5-dimethoxybenzaldehyde (22) (332 mg, 2.0 mmol) was added dropwise to the reaction mixture for 5 min at room temperature (TLC monitoring). Then, molecular sieves were filtered off and washed with *t*-BuOMe. The solvent was concentrated under reduced pressure at 0°C to obtain 310 mg of 23. Compound 23 was directly used in the following reaction without purification.

1-(Dibromomethyl)-3,5-dimethoxybenzene (24): Copper(II) bromide (670 mg, 3.0 mmol) was dissolved in MeOH (6 mL) under argon atmosphere. Then Et₃N (0.15 mL) was added and the mixture was stirred for 20 min at room temperature. Then, 1-(3,5-dimethoxybenzylidene)hydrazine (23) (180 mg, 1.0 mmol) was added dropwise in 3 mL of MeOH for 5 min at 0°C (TLC monitoring). After being stirred for 5 min, the reaction was quenched by addition of 3.5% NH₃ aqueous solution, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced

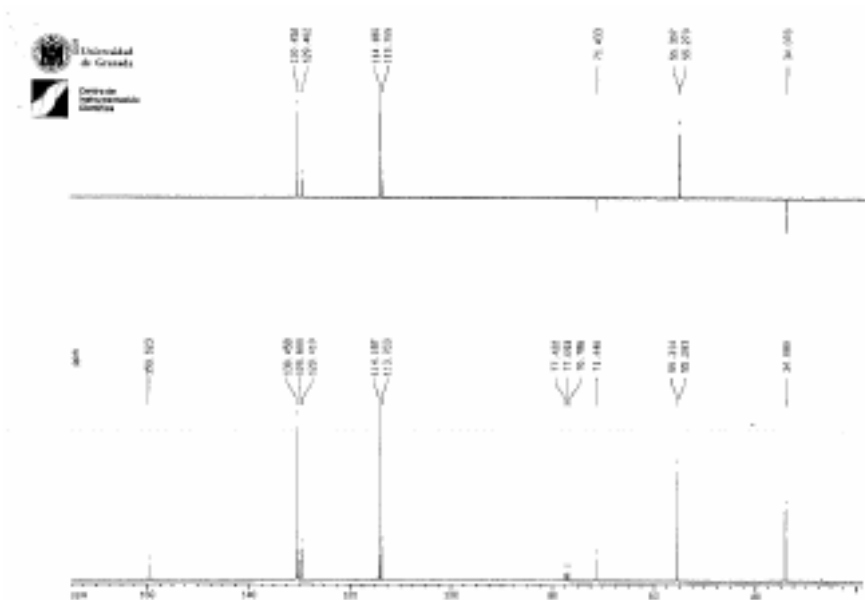
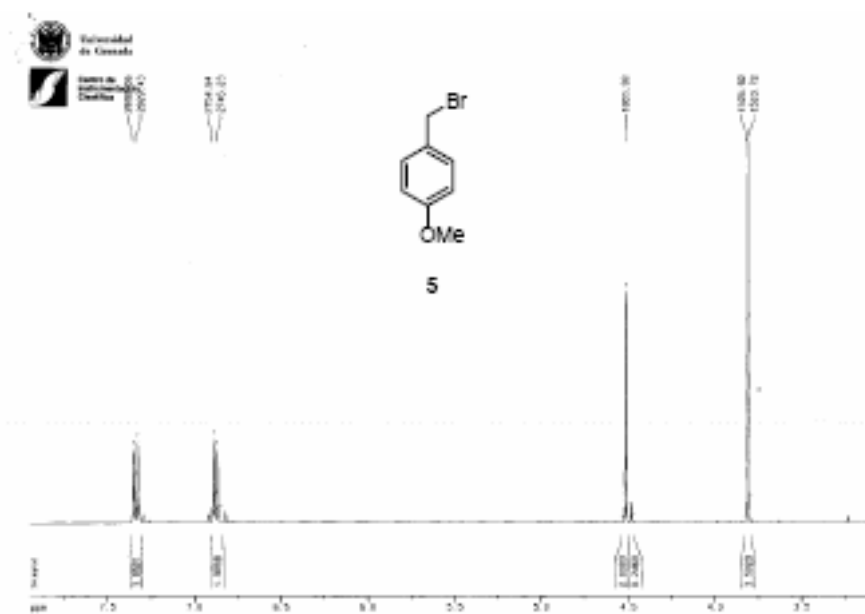
pressure to afford **24** as a yellow oil. IR (film) 2961, 2936, 2838, 1596, 1461, 1427, 1349, 1323, 1298, 1203, 1158, 1064, 697 cm^{-1} ; ^1H NMR (300 MHz; CDCl_3) δ 3.73 (6H, s), 6.31 (1H, t, $J = 2.2$ Hz), 6.48 (1H, s), 6.62 (2H, d, $J = 2.2$ Hz); ^{13}C NMR (75 MHz; CDCl_3) δ 41.0, 55.6 (2C), 101.9, 104.8 (2C), 143.8, 160.7 (2C); HR EIMS calcd for $\text{C}_9\text{H}_{10}\text{O}_2\text{Br}_2$ $[\text{M}]^+$ 307.9047, found 307.9049.

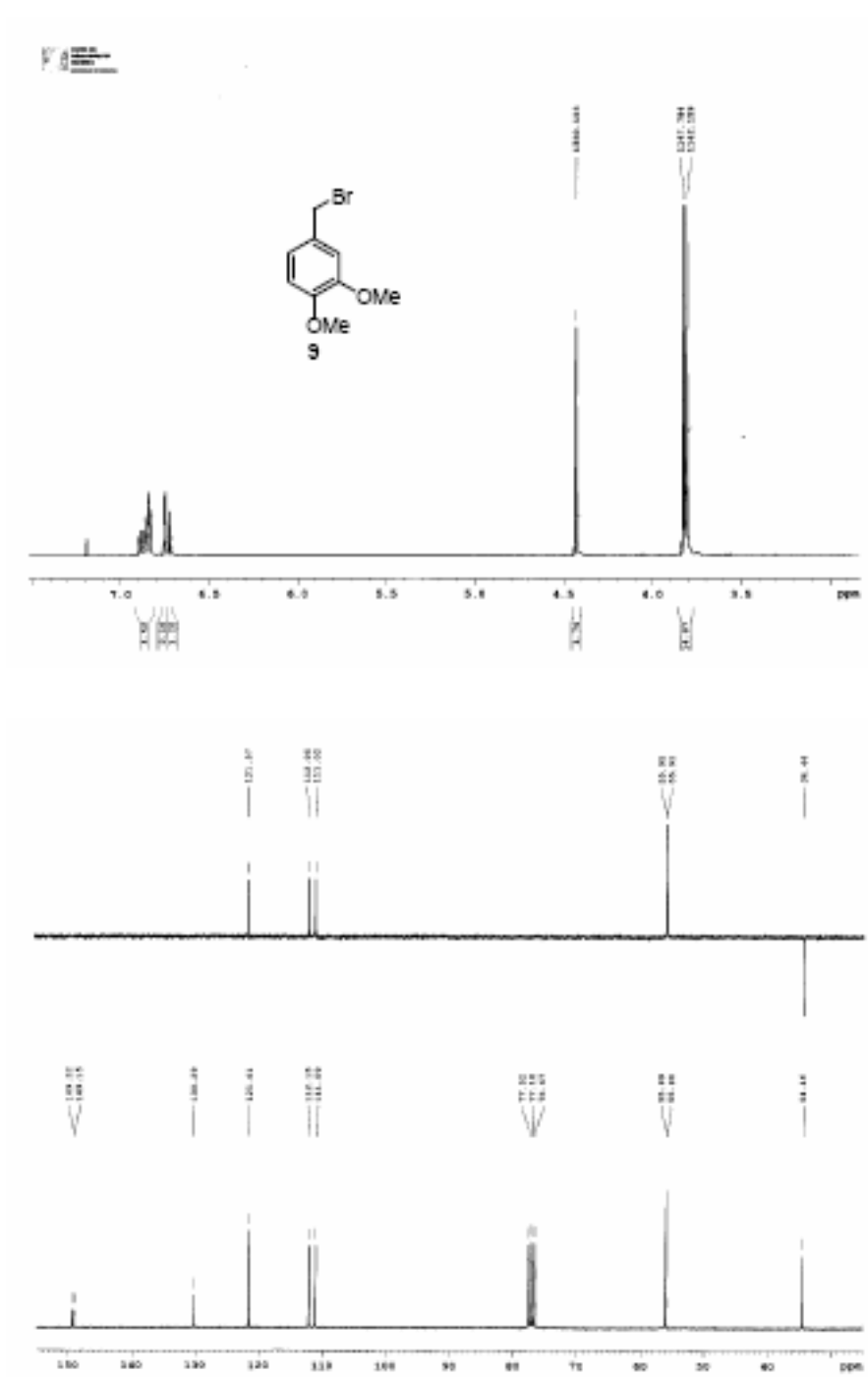


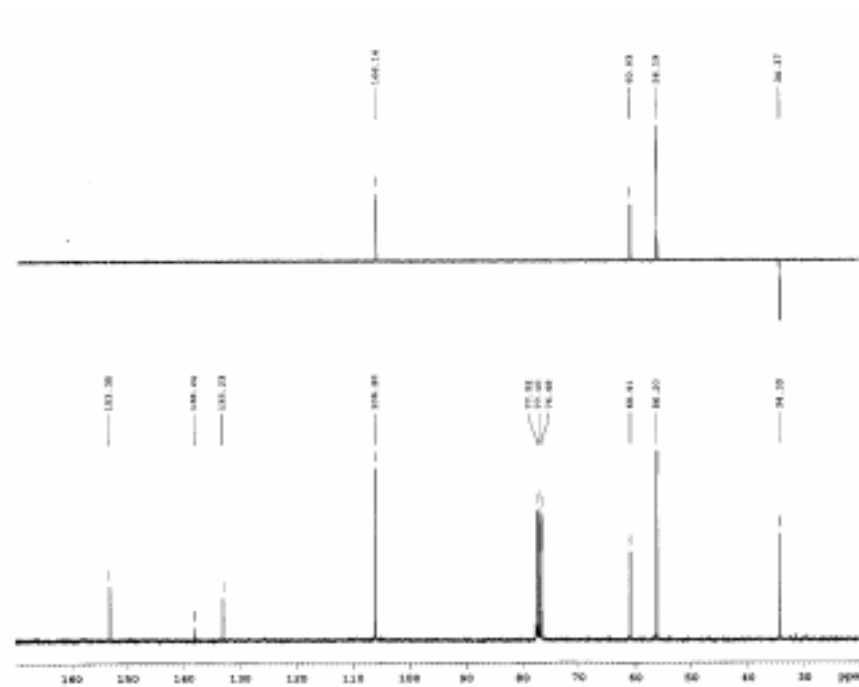
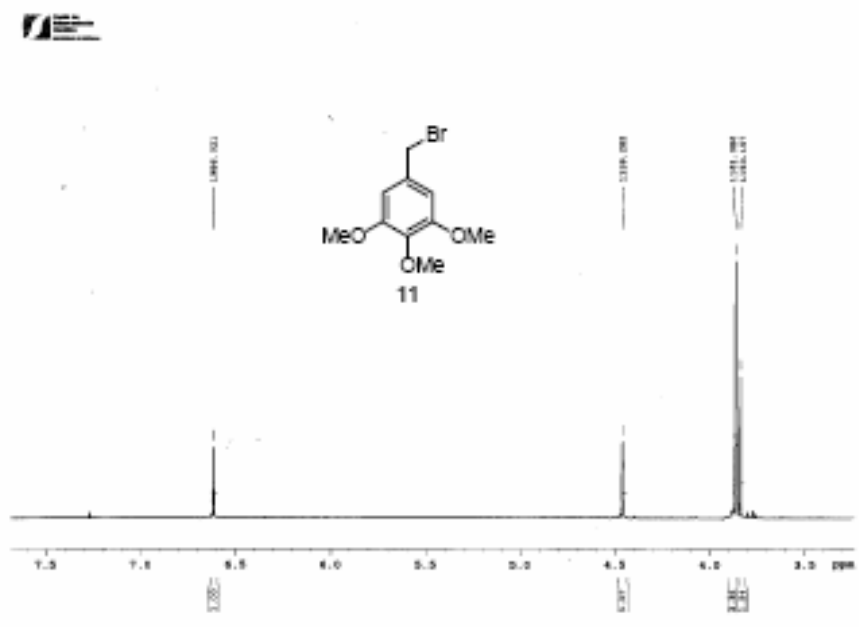
3,3',5,5'-tetramethoxystilbene (21): According to the general procedure described for the homocoupling of benzylic *gem*-dihalides, the resulting crude was purified by column chromatography using hexane as eluent on silica gel to afford 72% of **21**¹⁴ as a colorless solid. Mp 129 - 130 °C, lit.¹⁴ 130 - 132 °C; ^1H NMR (300 MHz; CDCl_3) δ 3.75 (12H, s), 6.33 (2H, t, $J = 2.3$ Hz), 6.60 (4H, d, $J = 2.3$ Hz), 6.94 (2H, s); ^{13}C NMR (75 MHz; CDCl_3) δ 55.5, 100.3, 104.8, 129.3, 139.3, 161.1.

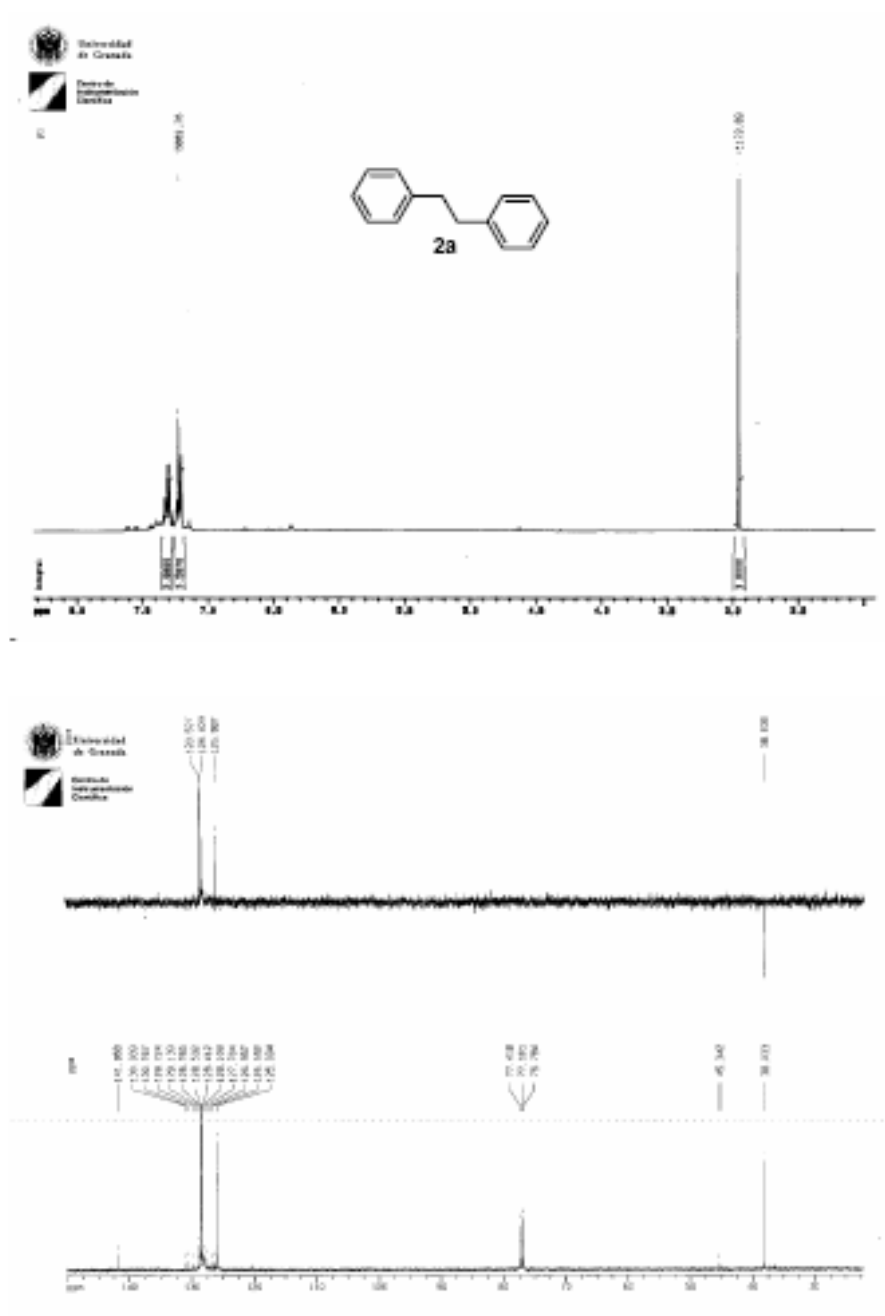


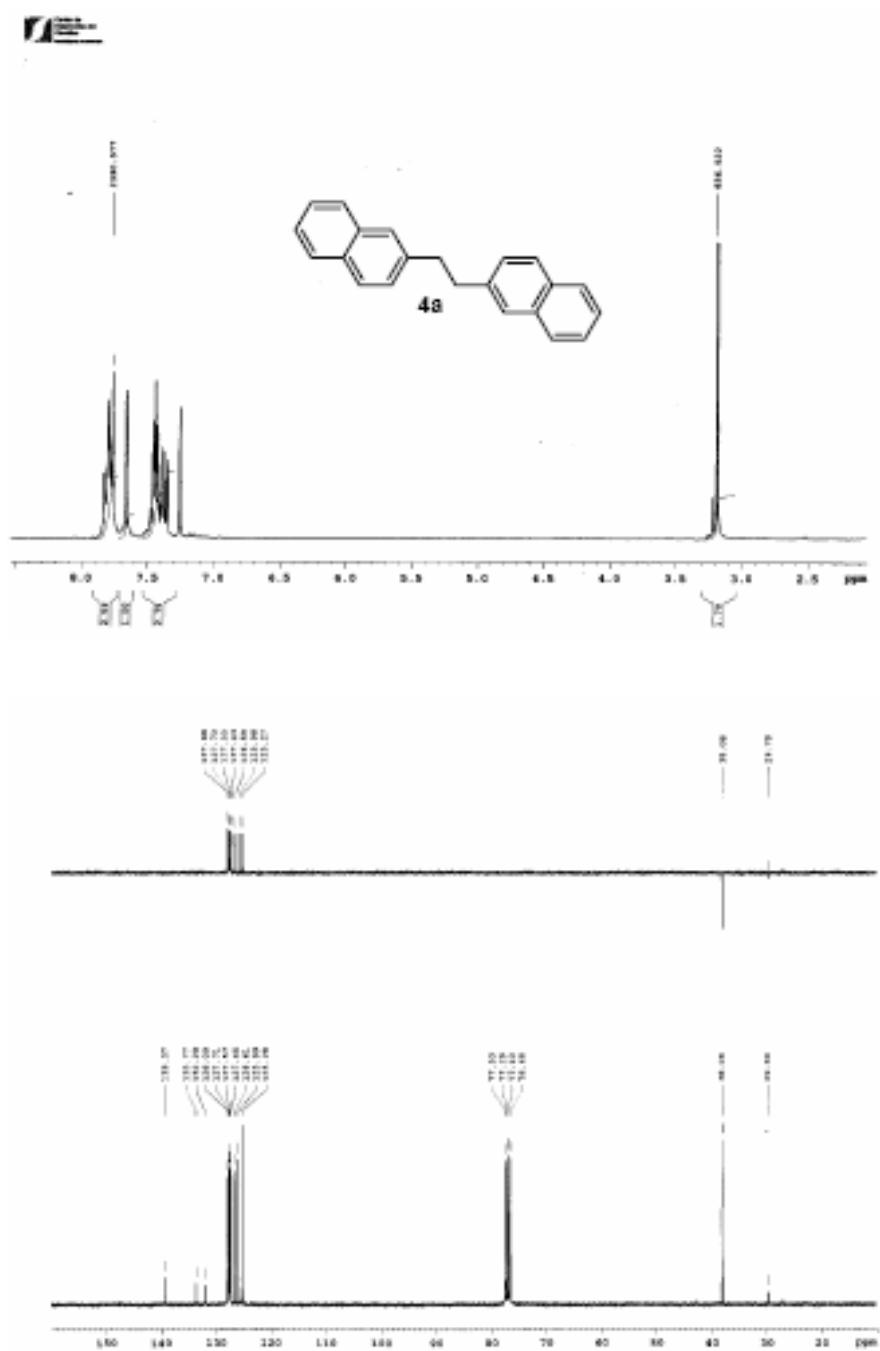
¹⁴ Murias, M.; Handler, N.; Erker, T.; Pleban, K.; Ecker, G.; Saiko, P.; Szekeres, T.; Jäger, W. *Bioorg. Med. Chem.* **2004**, *12*, 5371-5378.

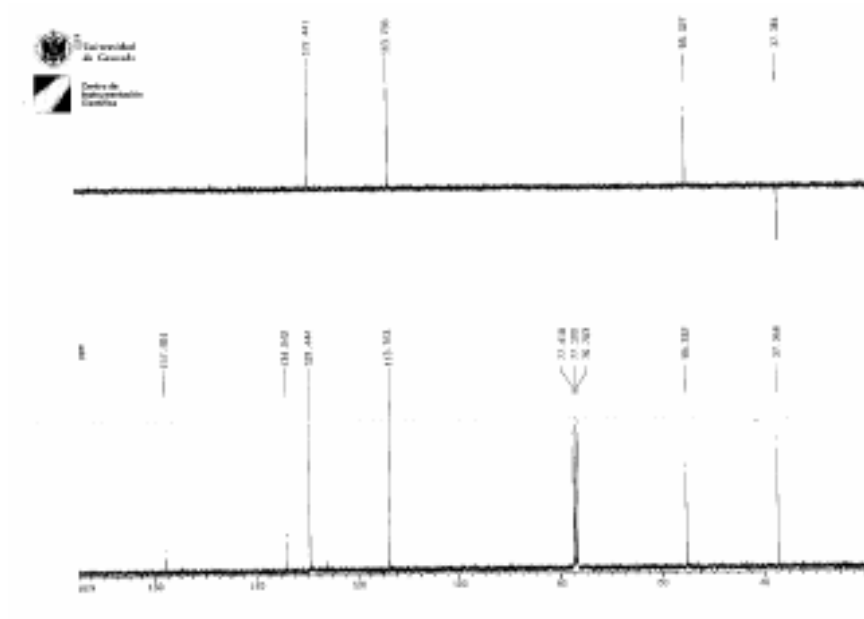
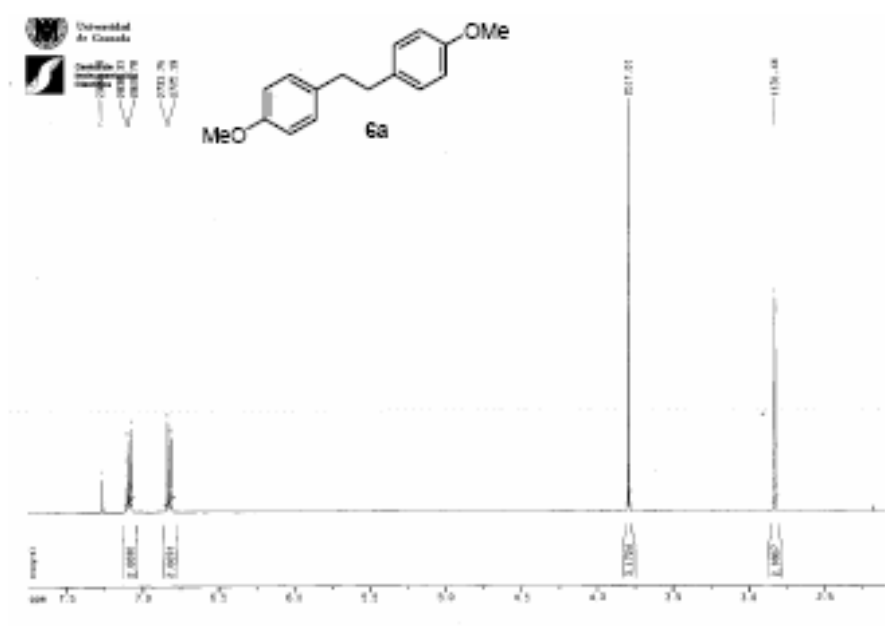


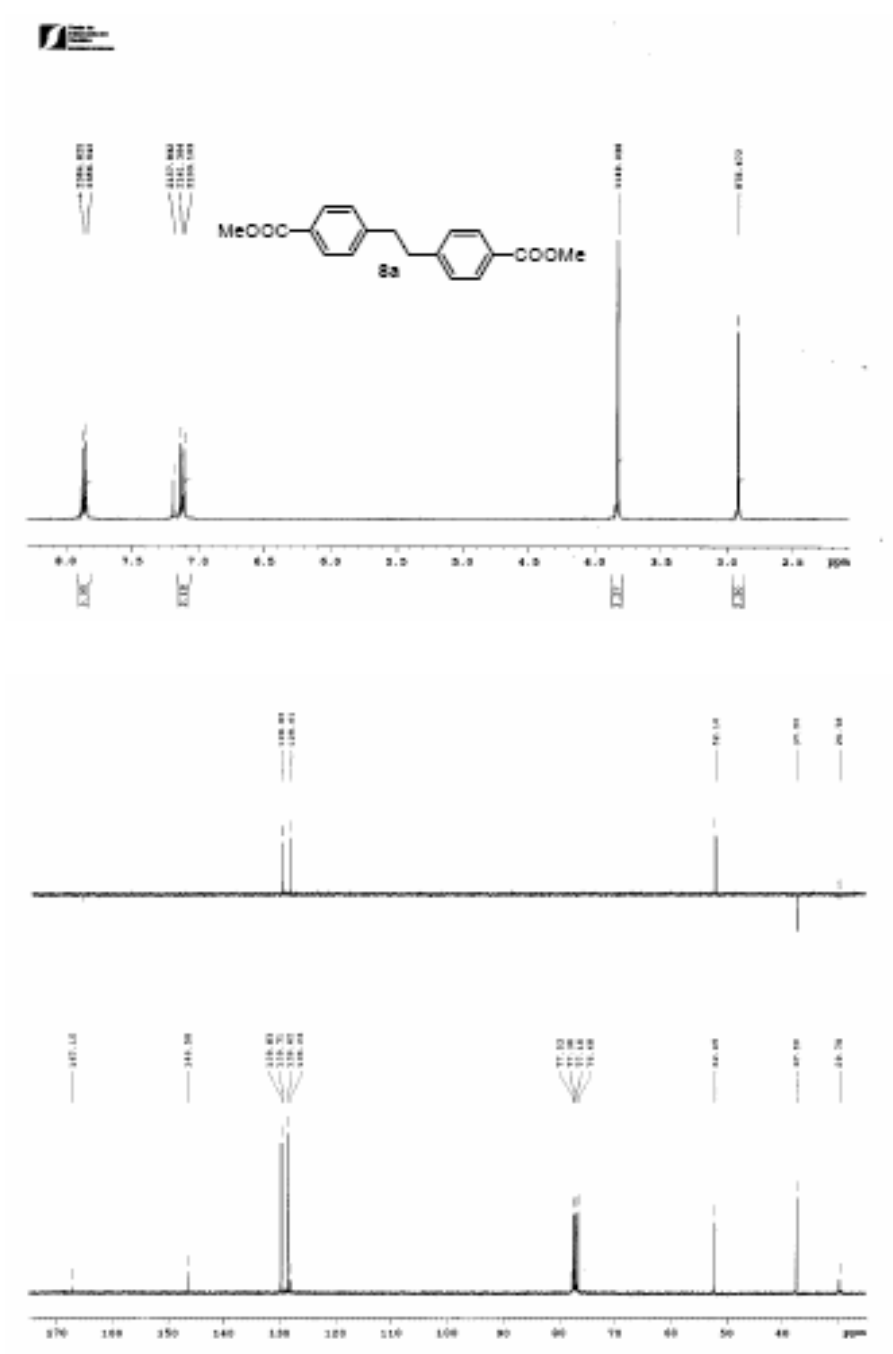


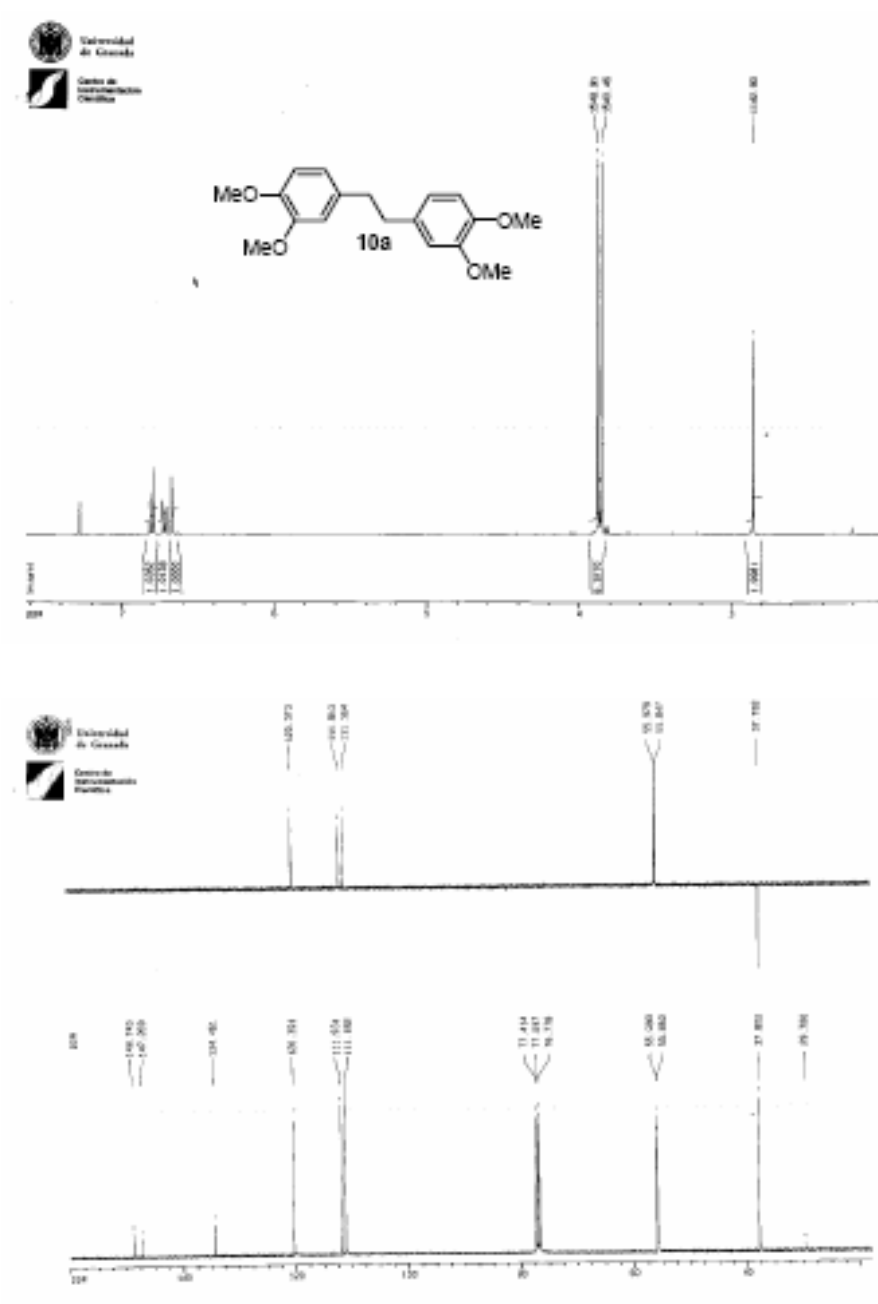


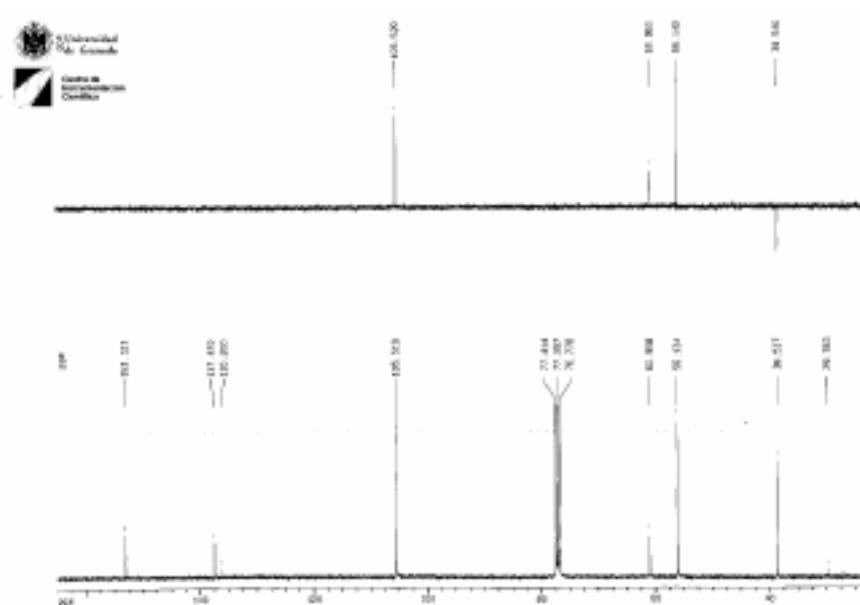
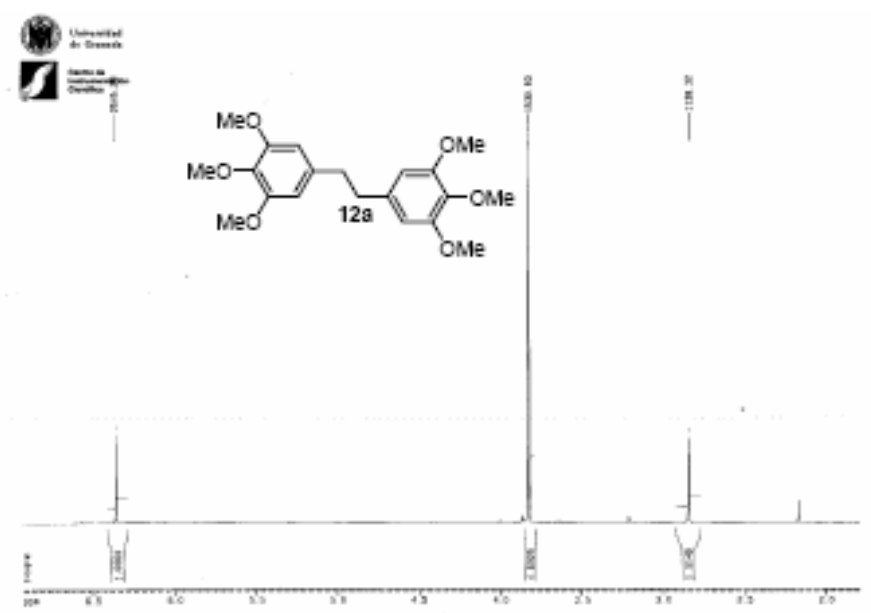


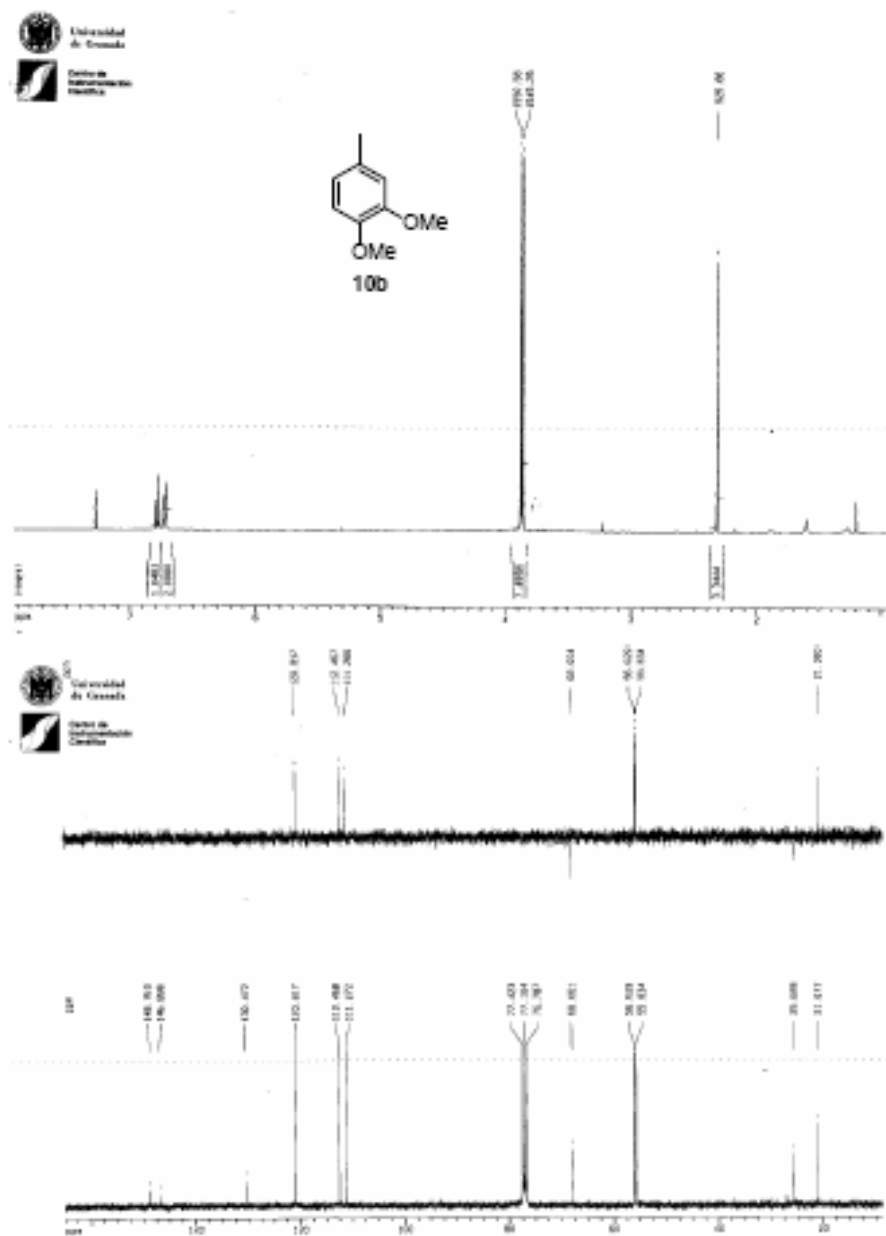


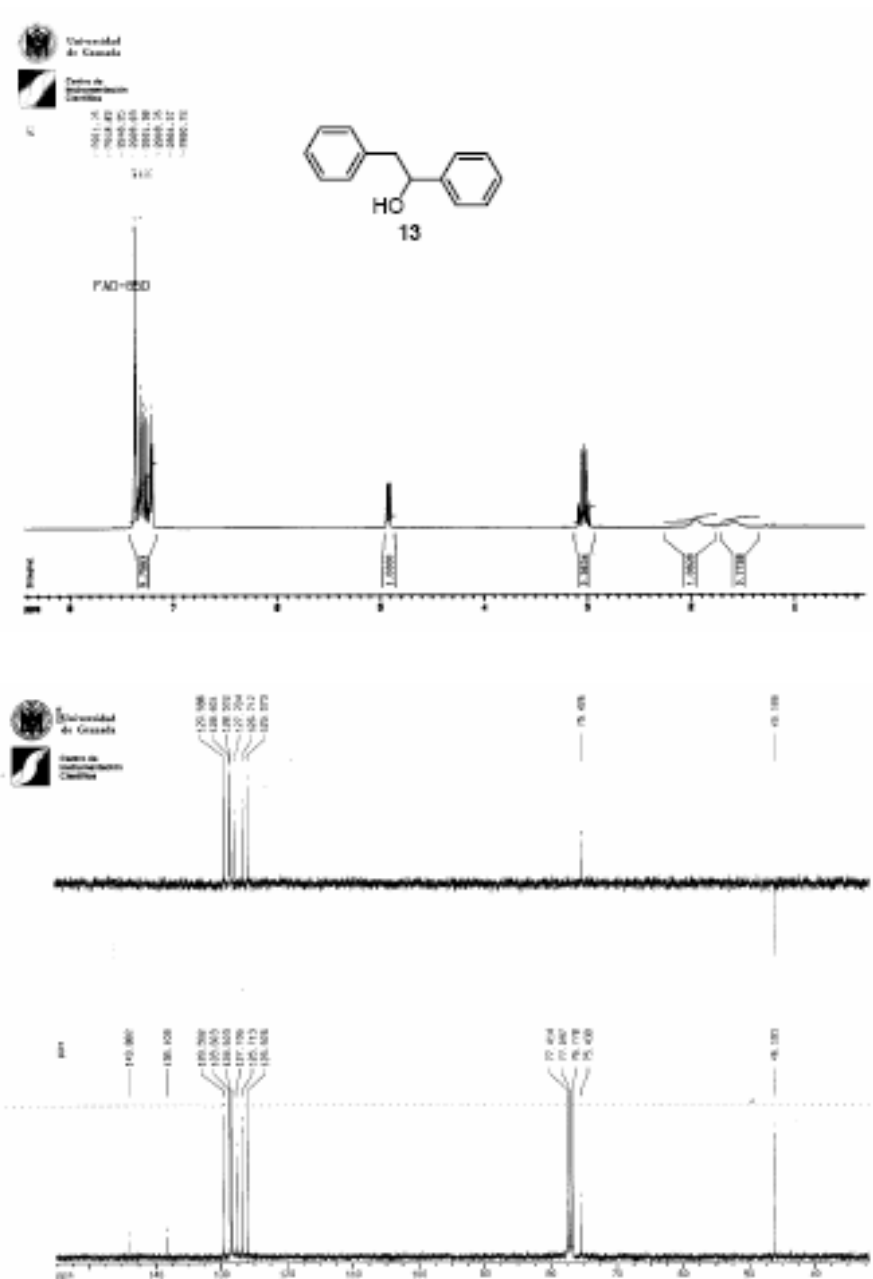


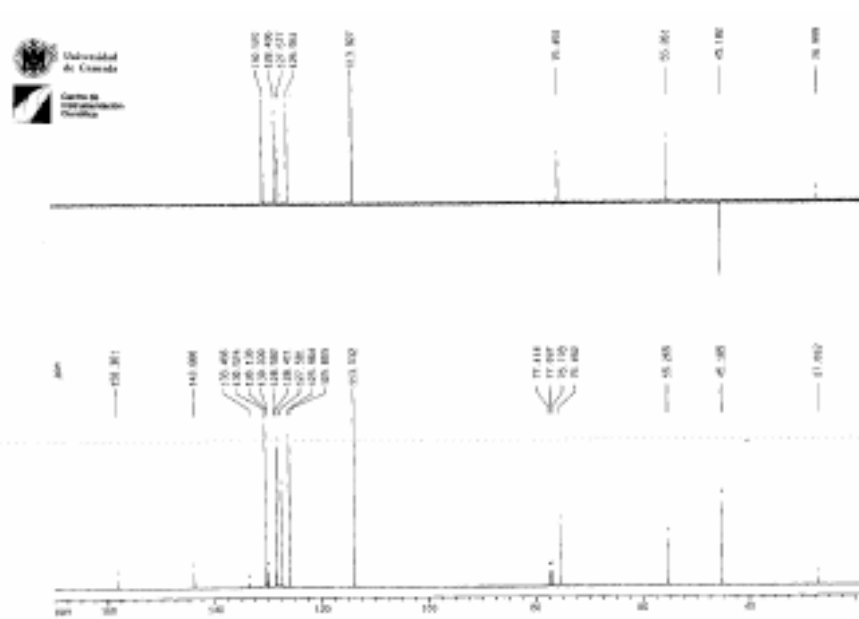
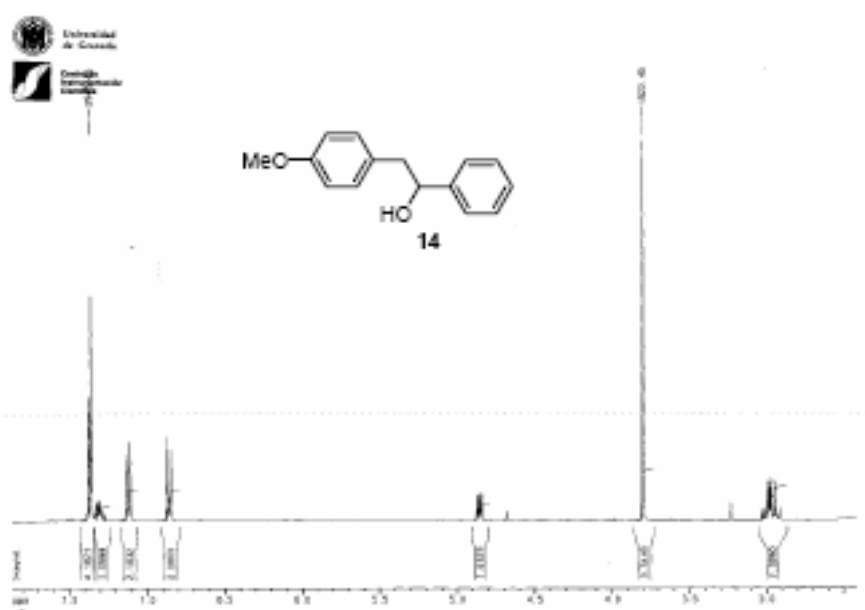


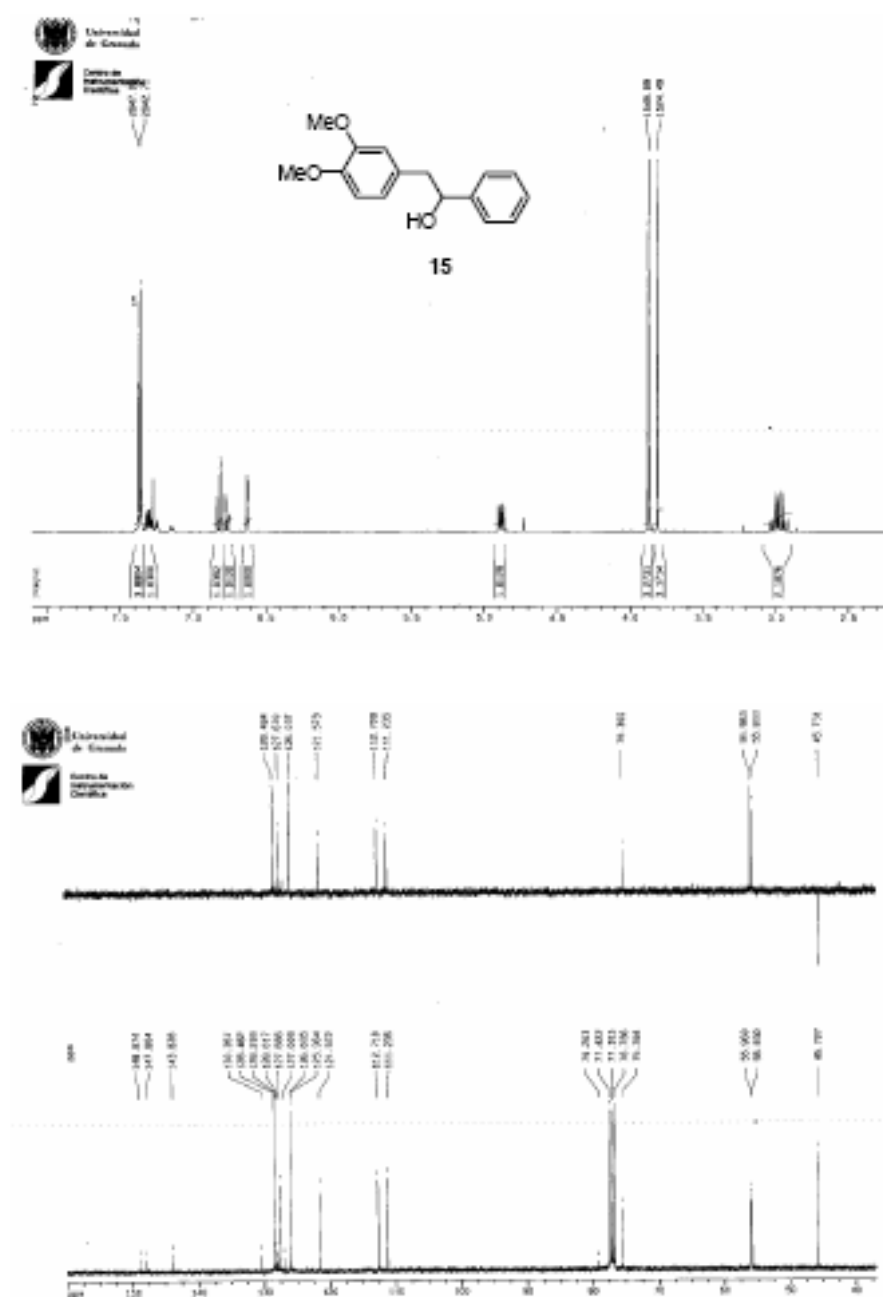


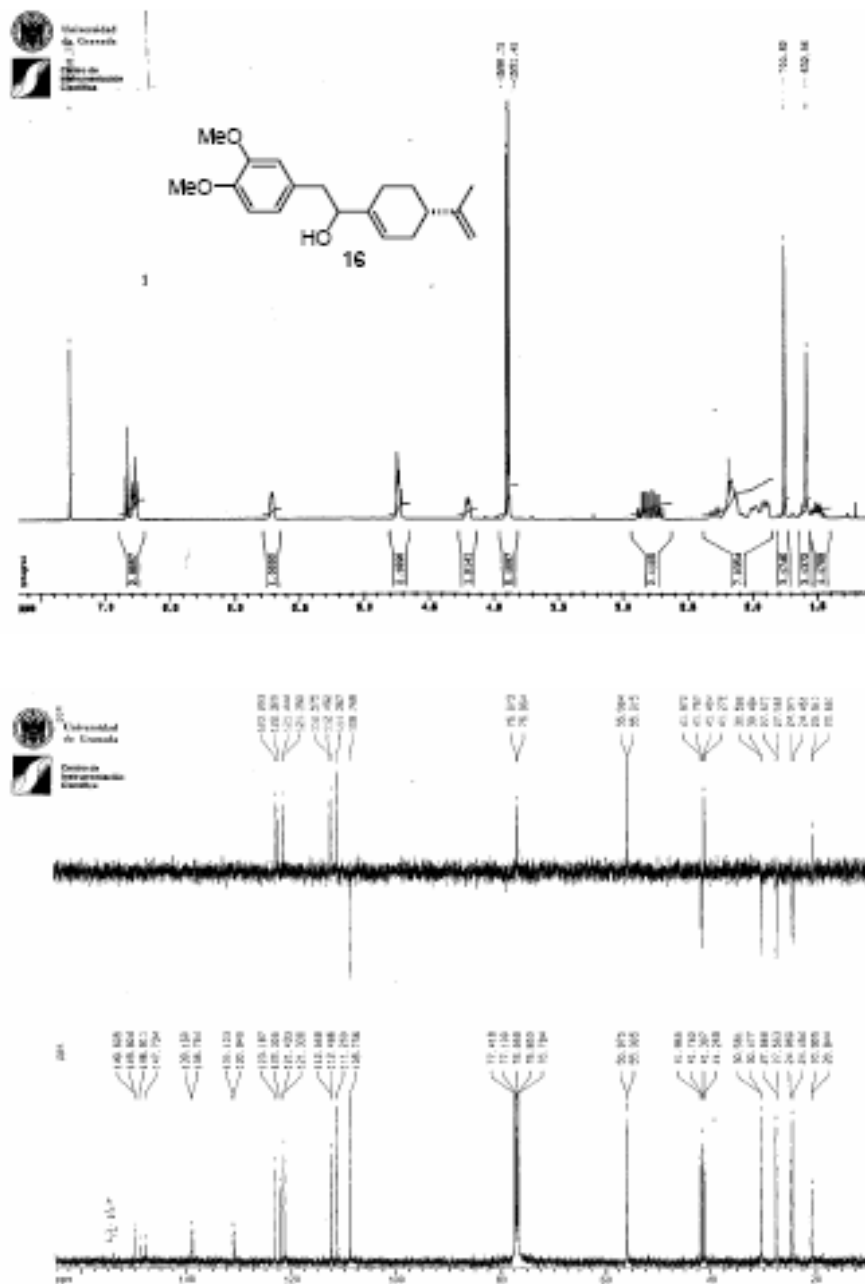


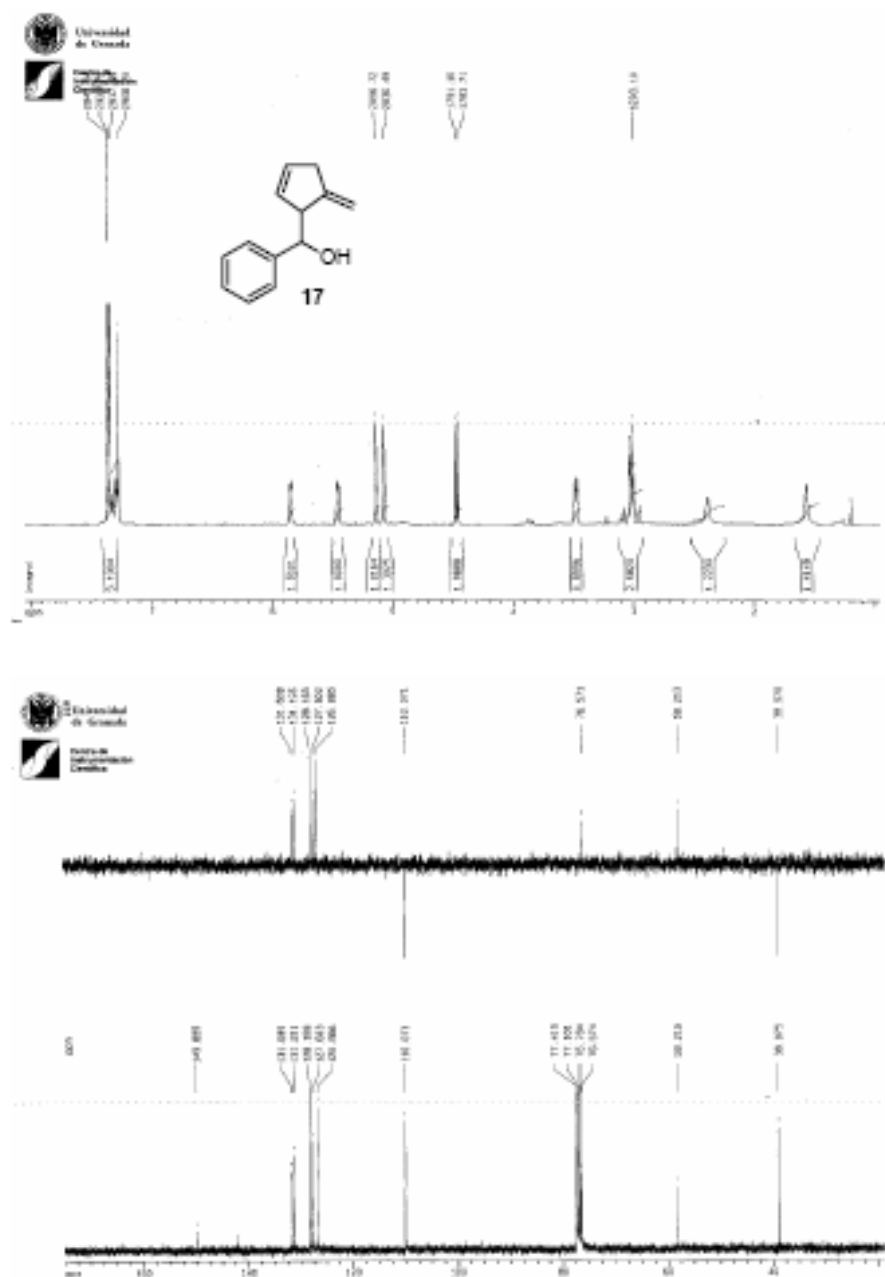


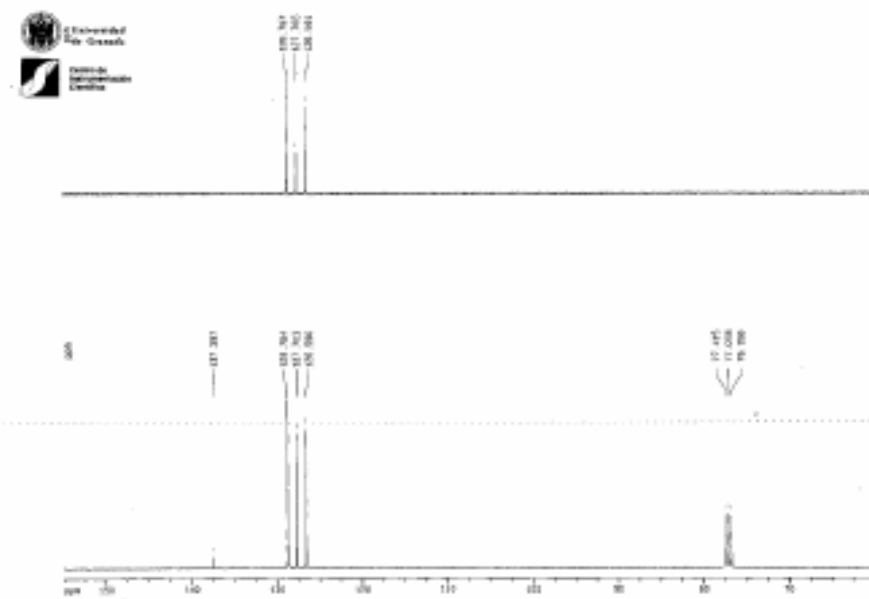
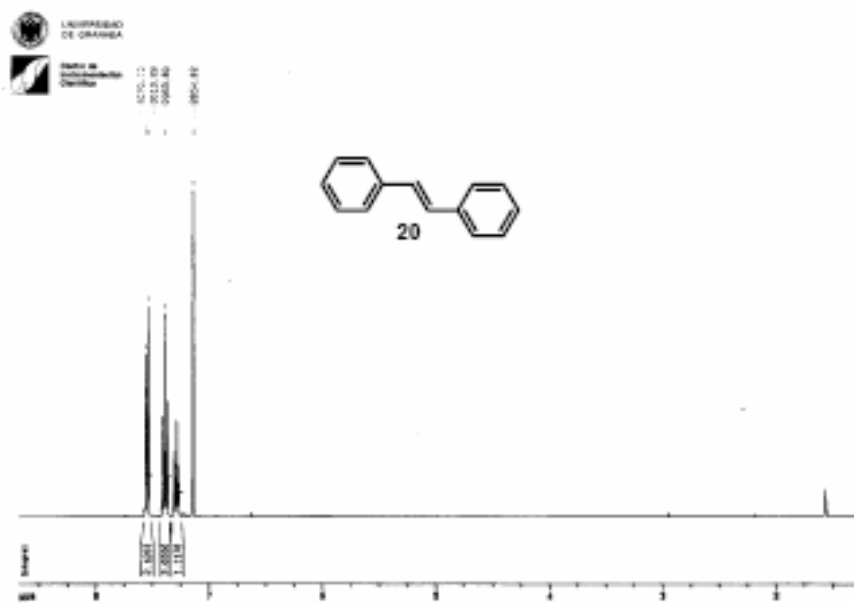


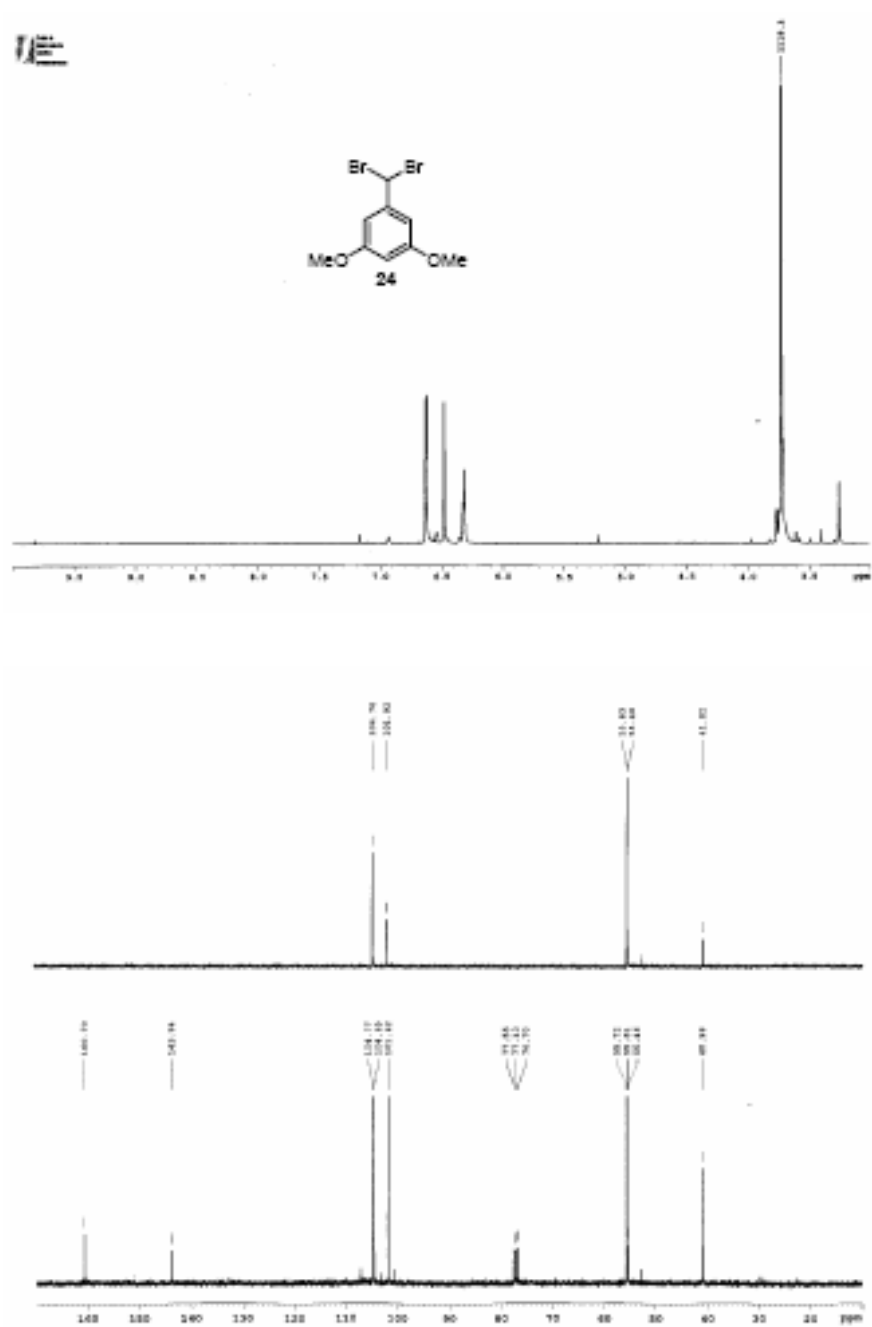


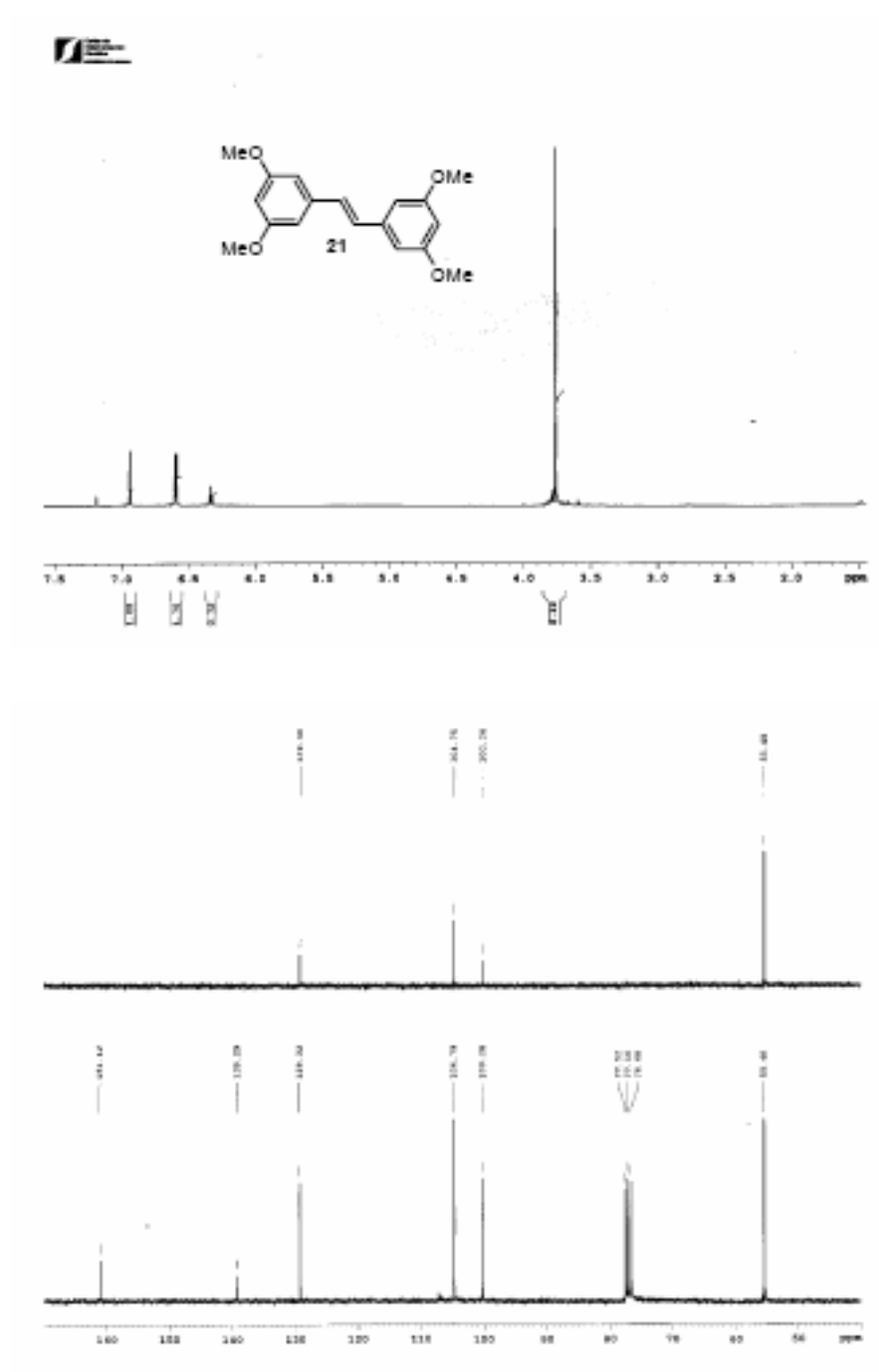












ANEXO 3

Supporting Information Artículo 3

Supporting information
For
**Control of the regio- and diastereoselectivity on the
radical cyclization of acyclic epoxy-polyprenoids to
cyclopentane derivatives**

Jesús F. Arteaga*, Horacio R. Diéguez, José A. G. Delgado, José F. Quílez del Moral,
and Alejandro F. Barrero*

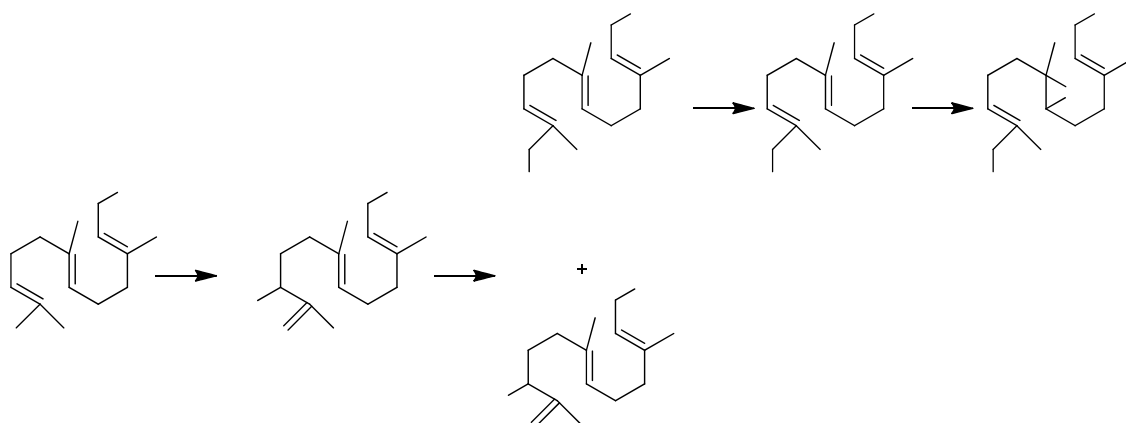
Experimental

General details. All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an argon atmosphere. The solvents used were purified according to standard literature techniques and stored under argon. Tetrahydrofuran (THF) was freshly distilled immediately prior to use from sodium/benzophenone.

EXPERIMENTAL PROCEDURES

Synthesis of precursors, epoxy-polyprenes derivatives.

1. Synthesis of 3.



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1.1 Allylic Chlorination of Farnesyl Acetate (I).¹⁸¹ Phenyl-selenenyl chloride (209 mg, 1.09 mmol) was dissolved in DCM (35 mL). To this solution was added **I** (2890 mg, 10.95 mmol) and *N*-chlorosuccinimide (1602 mg, 12.04 mmol), and stirred at rt (TLC monitoring). The solution was concentrated after 70 min and then suspended with diethyl ether (15 mL). The organic layer was decanted from the solid, washed with H₂O and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (Hexane/*t*-BuOMe, 5:1) on silica gel to afford 2382 mg of **II** (7.99 mmol, 73%).

II, ¹H NMR (CDCl₃, 400 MHz): δ 5.34 (1H, t, *J*=7.1 Hz), 5.13 (1H, t, *J*=7.0 Hz), 4.99 (1H, bs), 4.90 (1H, t, *J*=1.4 Hz), 4.59 (2H, d, *J*=7.1 Hz), 4.34 (1H, t, *J*=7.1 Hz), 2.06 (3H, s), 2.15-1.83 (8H, m), 1.81 (3H, s), 1.71 (3H, s), 1.60 (3H, s) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 171.2, 144.4, 142.1, 133.9, 124.9, 118.5, 114.2, 66.3, 61.4, 39.4, 36.6, 34.8, 26.2, 21.1, 17.0, 16.5, 16.0 ppm.

1.2. Hydrolysis of II.¹⁸² **II** was first dissolved in acetone (160 mL) and subsequently H₂O (80 mL), 2,4,6-collidine (3.96 mL, 30.04 mmol), and AgBF₄ (3827 mg, 22.53 mmol) were added, and the resulting mixture refluxed at 60-70 °C for 1 h (TLC monitoring). Acetone was then removed under reduced pressure and the residue extracted with EtOAc (3x20 mL). The organic layer was washed with HCl 2 N and brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting crude was purified by column chromatography (Hexane/*t*-BuOMe, 6:1) on silica gel to afford 843 mg of **III** (3.00 mmol, 40%) and 947 mg of **IV** (3.38 mmol, 45%).

III, ¹H NMR (CDCl₃, 400 MHz): δ 5.38 (1H, t, *J*=7.0 Hz), 5.34 (1H, t, *J*=7.1 Hz), 5.10 (1H, t, *J*=6.7 Hz), 4.60 (2H, d, *J*=7.1 Hz), 3.99 (2H, bs), 2.05 (3H, s), 2.25-1.95 (9H, m), 1.70 (3H, s), 1.66 (3H, s), 1.60 (3H, s) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 171.0, 141.9, 134.9, 134.7, 125.4, 123.7, 118.2, 68.4, 61.2, 39.3, 39.1, 26.1, 26.0, 20.8, 16.2, 15.8, 13.4 ppm; FABHRMS: calcd for C₁₇H₂₈O₃Na [M+Na]⁺ 303.1936, found: 303.1903.

IV, ¹H NMR (CDCl₃, 300 MHz): δ 5.28 (1H, tq, *J*=7.0, 7.0, 1.2 Hz), 5.07 (1H, dt, *J*=6.8, 1.2, 1.2 Hz), 4.86 (1H, t, *J*=0.9 Hz), 4.76 (1H, q, *J*=1.5 Hz), 4.51 (2H, d, *J*=7.1 Hz), 3.96 (1H, t, *J*=6.5 Hz), 1.98 (3H, s), 2.12-1.85 (6H, m), 1.68-1.55 (2H, m), 1.66 (3H, s),

¹⁸¹ *J. Org. Chem.* **2006**, *71*, 5811-5814

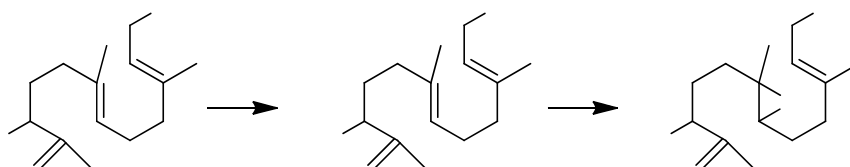
¹⁸² *J. Org. Chem.* **2006**, *71*, 5811-5814

1.63 (3H, s), 1.54 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 171.2, 147.6, 142.1, 135.2, 124.2, 118.5, 111.0, 75.6, 61.5, 39.5, 35.7, 33.2, 26.1, 21.1, 17.7, 16.5, 16.0 ppm; FABHRMS: calcd for $\text{C}_{17}\text{H}_{28}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 303.1936, found: 303.1904.

1.3-1.4. Acetylation of III and subsequent selective epoxidation of V. Acetic anhydride (3.52 mL) was added to a stirred mixture of **III** (246 mg, 0.88 mmol) and cat. DMAP in pyridine (5.3 ml) at 0 °C under argon atmosphere. After 1.5 h (TLC monitoring), the mixture was diluted with DCM and washed with HCl, saturated aqueous sodium bicarbonate, water, brine and dried over anhydrous Na_2SO_4 . The solvent was then evaporated under reduced pressure affording a crude corresponding to di-acetylated product (**V**).^{183,184} To a solution of **V** (470 mg, 1.67 mmol) in DCM (12.2 mL) at 0 °C under argon atmosphere, was dropwisely added *m*-CPBA (444 mg, 1.81 mmol) in DCM (12.2 mL) and the mixture stirred until the disappearance of starting material. Then the mixture was diluted with DCM, washed with NaOH 2 N and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (Hexane/*t*-BuOMe, 4:1) on silica gel affording 452 mg (1.34 mmol, 80%) of **3**.

3, ^1H NMR (CDCl_3 , 500 MHz): δ 5.43 (1H, t, $J=6.8$ Hz), 5.38 (1H, t, $J=7.1$ Hz), 4.59 (2H, d, $J=7.0$ Hz), 4.44 (2H, s), 2.70 (1H, t, $J=6.2$ Hz), 2.21 (1H, m), 2.14 (2H, m), 2.07 (3H, s), 2.05 (3H, s), 1.72 (3H, s), 1.66 (3H, s), 1.75-1.50 (5H, m), 1.26 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ 171.1, 171.1, 141.3, 130.7, 128.7, 119.0, 70.1, 63.1, 61.3, 60.7, 38.2, 36.3, 27.0, 23.5, 21.1, 21.1, 16.7, 16.5, 14.0 ppm; FABHRMS calcd for $\text{C}_{19}\text{H}_{30}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 361.1985, found: 361.1983.

2. Synthesis of 5.



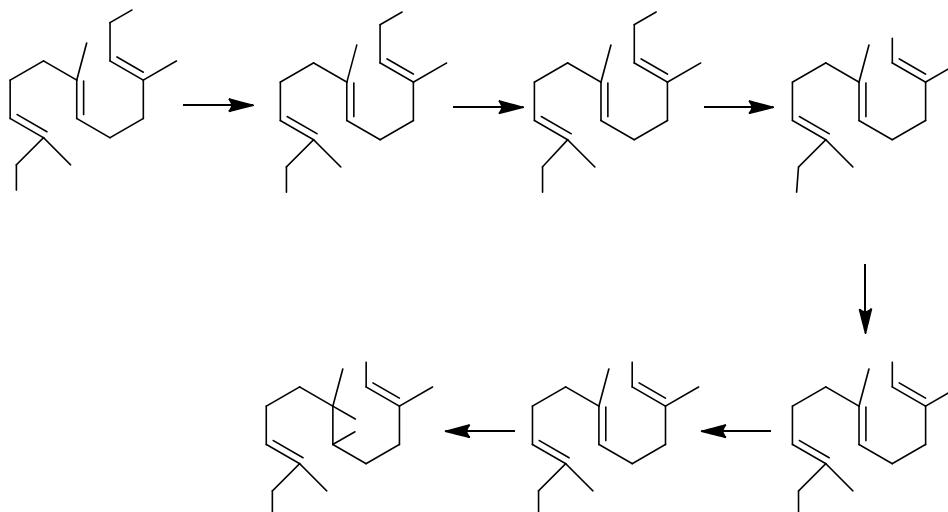
¹⁸³ Takabe, K.; Mase, N.; Hisano, T.; Yoda, H. *Tetrahedron Lett.* **2003**, *44*, 3267-3269.

¹⁸⁴ Masake, Y.; Hashimoto, K.; Kaji, K. *Tetrahedron Lett.* **1978**, *51*, 5123-5126.

2.1-2.2. TBS-Protection of IV and subsequent selective epoxidation of VI. *tert*-Butyldimethylsilyl chloride (4268 mg, 9.19 mmol) was added to a solution of imidazole (1932 mg, 9.19 mmol) and IV (600 mg, 2.14 mmol) in DCM (21 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 15 min (TLC monitoring). After cooling at 0 °C, extraction with DCM, washings with HCl 1 N, saturated aqueous NaHCO₃ and drying over anhydrous Na₂SO₄, the residue was concentrated under reduced pressure. The resulting crude was purified by column chromatography (Hexane/*t*-BuOMe, 4.5:1) on silica gel to afford 702 mg of 5 (1.71 mmol, 80% overall yield in two steps).

5, ¹H NMR (CDCl₃, 500 MHz): δ 5.38 (1H, t, *J*=6.9 Hz), 4.85 (1H, s), 4.76 (1H, s), 4.58 (2H, d, *J*=7.0 Hz), 3.99 (1H, dd, *J*=13.7, 7.0 Hz), 2.68 (1H, ddd, *J*=9.9, 6.2, 3.6 Hz), 2.19 (2H, m), 2.05 (3H, s), 1.72 (3H, s), 1.66 (3H, d, *J*=4.2 Hz), 1.75-1.50 (6H, m), 1.24 (3H, d, *J*=2.2 Hz), 0.89 (9H, s), 0.03 (3H, d, *J*=2.2 Hz), 0.00 (3H, d, *J*=2.2 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 171.1, 171.1, 147.3, 141.4, 119.0, 111.1, 76.5, 63.1, 61.3, 61.0, 36.3, 34.5, 31.7, 27.1, 25.9, 21.1, 18.3, 17.3, 16.9, 16.8, -4.7, -5.0 ppm; FABHRMS calcd for C₂₃H₄₂O₄SiNa [M+Na]⁺ 433.2750, found: 433.2745.

3. Synthesis of 8.



3.1-3.4 Synthesis of X from III. According to experimental procedure 2.5, alcohol III led to VII (1140 mg, 2.83 mmol) employed without further purification in the next step. To a solution of VII (1100 mg, 2.78 mmol) in MeOH (13.0 mL) at rt was added K₂CO₃

(164.5 mg, 2.93 mmol) and the mixture stirred for 20 min. Then MeOH was removed under reduced pressure and the resulting residue diluted with H₂O and extracted with *t*-BuOMe. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to yield 95% of alcohol **VIII** (628 mg, 2.64 mmol).¹⁸⁵ To a solution of **VIII** (1040 mg, 2.94 mmol) in DCM (6.5 mL) at rt, under argon atmosphere, was added PDC (1692 mg, 4.41 mmol) and the mixture stirred for 1 h (TLC monitoring). The reaction was then quenched with *t*-BuOMe (40 mL) and filtered through silica gel (*t*-BuOMe, 200 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford a crude containing aldehyde **IX**¹⁸⁶ as major component as showed its ¹H-NMR spectrum. Over a solution of this crude (**IX**, 950 mg) and 2-methyl-2-butene (19.21 mL) in *t*-BuOH (51.2 mL), at rt, was added dropwise (20 min) a mixture of NaClO₂ (1941 mg, 21.56 mmol), NaH₂PO₄·H₂O (2227 mg, 16.14 mmol) and H₂O (20 mL). After 3 h solvent was removed under reduced pressure, diluted with H₂O and extracted with *t*-BuOMe. Organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford **X**.

X: ¹H NMR (CDCl₃, 300 MHz): δ 5.65 (1H, s), 5.31 (1H, t, *J*=7.1 Hz), 5.06 (1H, m), 3.92 (2H, s), 2.14 (3H, s), 2.10-1.92 (8H, m), 1.56 (3H, d, *J*=0.7 Hz), 1.53 (3H, s), 0.86 (9H, s) y 0.0 (6H, s) ppm.

3.5-3.8 Synthesis of 8. TMSCHN₂ (2.01 mL, 3.99 mmol) 2.0 M in Et₂O was slowly added to a solution of **X** (1125 mg) in anhydrous benzene (26.5 mL) and anhydrous MeOH (6.5 mL) under argon atmosphere and stirred for 1 h (TLC monitoring). The mixture was concentrated under reduced pressure and the resulting crude purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel affording 882 mg of **XI** (2.32 mmol, 79% overall yield over three steps). To a solution of **XI** (882 mg, 2.32 mmol) in anhydrous THF (24 mL) at 0 °C, was added TBAF 1.0 M in THF (9.5 mL, 9.57 mmol) and the mixture stirred for 15 min at the same temperature and then at rt for 1 h. Solvent was then removed under reduced pressure and the crude extracted with EtOAc. Organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel yielding 85% of **XII** (537 mg,

¹⁸⁵ Marshall, J. A.; Robinson, E. D.; Lebreton, J. *Tetrahedron Lett.* **1988**, 29, 3547-3550.

¹⁸⁶ Marshall, J. A.; Robinson, E. D.; Lebreton, J. *J. Org. Chem.* **1990**, 55, 227-239.

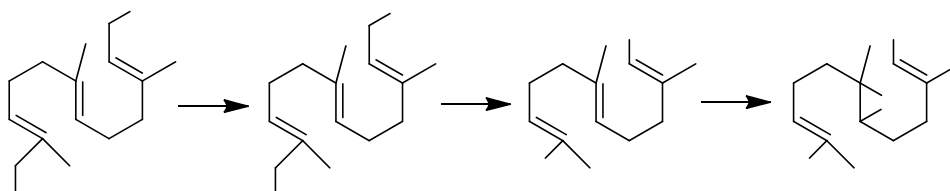
2.02 mmol).¹⁸⁷ According to general acetylation procedure, **XII** (537 mg, 2.02 mmol) led after column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel purification to **XIII** in 87% yield (541 mg, 1.76 mmol).

XIII, ¹H NMR (CDCl₃, 300 MHz): δ 5.66 (1H, s), 5.26 (1H, dt, *J*=7.1, 1.0 Hz), 5.06 (1H, dd, *J*=6.7, 5.8 Hz), 4.52 (2H, s), 3.66 (3H, s), 2.15-1.94 (8H, m), 2.11 (3H, s), 1.76 (3H, d, *J*=0.7 Hz), 1.54 (3H, s) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 171.1, 168.7, 142.2, 142.1, 134.4, 127.6, 124.6, 118.5, 61.4, 51.7, 39.5, 38.2, 27.3, 26.2, 21.1, 16.5, 16.0, 12.4 ppm; FABHRMS: calcd for C₁₈H₂₈O₄Na [M+Na]⁺ 331.1885, found: 331.1880.

XIII (700 mg, 2.27 mmol) was then subjected to epoxidation general procedure affording **8** in 78% yield (574 mg, 1.77 mmol) after column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel purification.

8, ¹H NMR (CDCl₃, 300 MHz): δ 5.71 (1H, s), 5.36 (1H, dt, *J*=7.1, 1.3 Hz), 4.57 (2H, d, *J*=7.0 Hz), 3.71 (3H, s), 2.69 (1H, t, *J*=6.2 Hz), 2.31-2.05 (4H, m), 2.09 (3H, s), 1.70 (3H, s), 1.70-1.52 (4H, m), 1.25 (3H, s) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 171.1, 168.5, 141.3, 141.1, 128.1, 119.1, 63.0, 61.3, 60.4, 51.8, 37.3, 36.2, 26.9, 24.4, 21.1, 16.6, 16.5, 12.4 ppm; HRFABMS: calcd for C₁₈H₂₈O₅Na [M+Na]⁺ 347.1834, found: 347.1830.

4. Synthesis of 11.



4.1-4.5 Synthesis of 11.^{27e} According to experimental procedure 3.2, **III** (300 mg, 1.11 mmol) led after column chromatography (hexane/*t*-BuOMe, 1:2) on silica gel purification to 290 mg of **XIV** (1.11 mmol, 99%).¹⁸⁸

XIV, ¹H NMR (CDCl₃, 300 MHz): δ 5.32 (2H, m), 5.04 (1H, td, *J*=6.8, 6.8, 1.2 Hz), 4.07 (2H, d, *J*=6.9 Hz), 3.91 (2H, s), 2.06 (4H, q, *J*=6.2 Hz), 1.97 (4H, q, *J*=6.8 Hz),

¹⁸⁷ Stritzke, K.; Schulz, S.; Boppre, M. *Eur. J. Org. Chem.* **2003**, 1337-1342.

¹⁸⁸ Sato, A.; Nakajima, K.; Kuwana, N.; Takahara, Y.; Kijima, S.; Abe, S.; Yamada, K. Br. Pat. GB 2068370, **1981**.

1.68 (2H, m), 1.60 (3H, s), 1.59 (3H, s), 1.53 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 139.4, 134.9, 134.8, 125.8, 124.2, 123.6, 68.8, 59.4, 39.5, 39.3, 26.2, 26.0, 16.3, 16.0, 13.8 ppm.

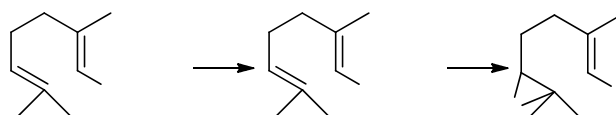
Proceeding as experimental procedure 3.3, **XIV** (2200 mg, 9.22 mmol) afforded a crude whose major component was di-aldehyde **XV**,¹⁸⁹ as showed its ^1H -NMR spectrum. According to experimental procedure 3.4, **XV** (1650 mg, 6.97 mmol) led to a crude possessing di-acid **XVI**¹⁹⁰ as major component. **XVI** (1800 mg, 6.65 mmol) led by esterification and column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel purification to **XVII**¹⁹¹ in 72% yield (2137 mg, 6.64 mmol) (overall yield in last three steps).

XVII, ^1H NMR (CDCl_3 , 400 MHz): δ 6.72 (1H, dt, $J=7.3$, 1.2 Hz), 5.67 (1H, s), 5.12 (1H, m), 3.73 (3H, s), 3.68 (3H, s), 2.27 (2H, dd, $J=15.3$, 7.3 Hz), 2.25-2.05 (6H, m), 2.16 (3H, s), 1.83 (3H, s), 1.61 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 168.7, 167.3, 160.0, 142.1, 135.1, 123.8, 115.9, 115.3, 51.7, 50.9, 40.8, 38.2, 27.3, 25.9, 18.9, 16.0, 12.4 ppm; FABHRMS: calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 317.1729, found: 317.1732.

According to general epoxidation procedure, **XVII** (480 mg, 1.61 mmol) led after column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel purification to **11** in 83% yield (433 mg, 1.34 mmol).

11, ^1H NMR (CDCl_3 , 400 MHz): δ 6.73 (1H, t, $J=7.3$ Hz), 5.72 (1H, s), 3.74 (3H, s), 3.69 (3H, s), 2.72 (1H, t, $J=6.2$ Hz), 2.38-2.22 (4H, m), 2.19 (3H, s), 1.85 (3H, s), 1.76-1.53 (4H, m), 1.28 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 168.5, 167.1, 158.8, 141.2, 128.1, 115.8, 62.7, 60.5, 51.9, 51.0, 37.6, 37.3, 36.2, 26.7, 24.4, 18.8, 16.6, 12.5 ppm; FABHRMS: calcd for $\text{C}_{17}\text{H}_{26}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 333.1678, found: 333.1678.

5. Synthesis of 15.



¹⁸⁹ Cox, N. J. G.; Mills, S. D.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 11, 1313-21.

¹⁹⁰ Gonzalez-Pacanowska, D.; Arisong, B.; Havell, C. M.; Watsonll, J. A. *J. Biol. Chem* **1988**, 263, 1301-1306.

¹⁹¹ Moro, J. C.; Fernandes, J. B.; Vieira, P. C.; Yoshida, M.; Gottlieb, O. R.; Gottlieb, H. E. *Phytochemistry* **1987**, 26, 269-272.

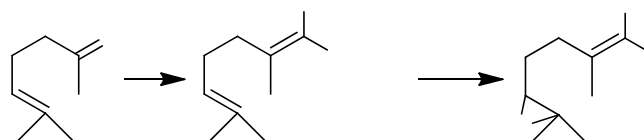
5.1. Esterification of XVIII. A solution of **XVIII** (540 mg, 3.21 mmol) in anhydrous Et₂O (27 mL) under argon atmosphere was added dropwise over a mixture of KO^t-Bu (1324 mg, 10.29 mmol) in anhydrous Et₂O (50 mL) and stirred for 4 h. At this point the mixture was filtered through silica gel (hexane), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford a crude mostly composed for **XIX**¹⁹² as ¹H-NMR showed.

XIX, ¹H NMR (CDCl₃, 400 MHz): δ 5.57 (1H, s), 5.06 (1H, bt), 2.16-2.06 (4H, m), 2.10 (3H, s), 1.67 (3H, s), 1.58 (3H, s), 1.45 (9H, s) ppm.

5.2. Epoxidation of XIX. After subjecting **XIX** (587 mg, 2.62 mmol) to general epoxidation procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 9:1) on silica gel to afford 578 mg (2.41 mmol, 92%) of **15**.¹⁹³

15, ¹H NMR (CDCl₃, 300 MHz): δ 5.60 (1H, d, *J*=1.2 Hz), 2.69 (1H, t, *J*=6.2 Hz), 2.35-2.14 (2H, m), 2.12 (3H, d, *J*=1.2 Hz), 1.68 (2H, m), 1.46 (9H, s), 1.29 (3H, s), 1.24 (3H, s) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ 166.3, 156.8, 117.9, 79.7, 63.7, 58.5, 37.6, 28.3, 27.1, 24.9, 18.8, 18.6 ppm; FABHRMS: calcd for C₁₄H₂₄O₃Na [M+Na]⁺ 263.1623, found: 263.1621.

6. Epoxide 18.



6.1. Synthesis of 18.¹⁹⁴ A mixture of TiCl₄ (100 mmol, 11 ml), CCl₄ (25 ml) and dry THF (200 ml) was stirred at 0 °C under argon atmosphere until appearance of a yellow solid. Then, 6-methylhept-5-en-2-one (6305 mg, 50 mmol) and diethyl malonate (8008 mg, 50 mmol) were added, and finally pyridine (16 ml) in THF (35 ml) was added dropwise (50 min) and the resulting mixture stirred until the starting material disappeared (TLC monitoring). The reaction was quenched by addition of H₂O (100 ml) and extracted with *t*-BuOMe. Organic extracts were washed with NaHCO₃ and brine,

¹⁹² Vasin, V. A.; Razin, V. V. *Synlett* **2001**, 5, 658-660.

¹⁹³ Couladouros, E. A.; Vidali, V. P. *Chem. Eur. J.* **2004**, 10, 3822-3835.

¹⁹⁴ Lehnert, W. *Tetrahedron.* **1973**, 29, 635-638.

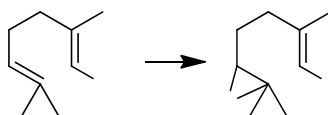
dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to yield 78% of **XX**.¹⁹⁵

XX, ^1H NMR (CDCl_3 , 400 MHz): δ 5.16 (1H, t, $J=7.2$ Hz), 4.22 (4H, q, $J=7.4$ Hz), 2.38 (2H, $J=7.0$ Hz), 2.17 (2H, q, $J=7.2$ Hz), 2.06 (3H, s), 1.55 (3H, s), 1.50 (3H, s), 1.25 (6H, t, $J=7.4$ Hz) ppm.

After subjecting **XX** (1265 mg, 4.72 mmol) to general epoxidation procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 1100 mg (4.11 mmol, 87%) of **18**.

18, ^1H NMR (400 MHz, CDCl_3): 4.23 (2H, q, $J=7.0$ Hz), 4.22 (2H, q, $J=7.0$ Hz), 2.75 (1H, t, $J=6.3$ Hz), 2.63-2.56 (1H, m), 2.52-2.45 (1H, m), 2.06 (3H, s), 1.77-1.74 (2H, m), 1.30 (3H, s), 1.27 (3H, s) ppm; ^{13}C NMR (100 MHz, CDCl_3): 165.6, 165.2, 157.1, 125.2, 63.6, 60.9, 58.6, 33.2, 27.5, 27.0, 24.8, 21.1, 18.6, 14.1 ppm. FABHRMS: calcd for $\text{C}_{15}\text{H}_{24}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 307.1521, found: 307.1526.

7. Epoxide 19.



7.1. Epoxidation of geranyl-nitrile. After subjecting commercial geranyl-nitrile¹⁹⁶ (1490 mg, 10.0 mmol) to general epoxidation procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 1495 mg (9.02 mmol, 90%) of **19**.¹⁹⁷

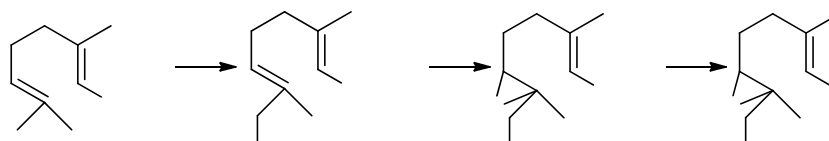
19, ^1H NMR (CDCl_3 , 400 MHz): δ 5.17 (2H, s), 2.72 (1H, dt, $J=15.7, 6.3$ Hz), 2.56 (1H, t, $J=7.7$ Hz), 2.36 (2H, m), 2.09 (3H, 1s), 1.95 (3H, s), 1.85-1.58 (6H, m), 1.33 (3H, s), 1.32 (3H, s), 1.29 (3H, s), 1.27 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 164.3, 164.1, 117.0, 116.8, 95.5, 95.9, 63.3, 63.2, 58.6, 58.5, 35.6, 33.3, 27.2, 26.8, 24.8, 23.0, 21.1, 18.8 ppm; FABHRMS: calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 237.1103, found: 237.1099.

¹⁹⁵ Weyerstahl, P.; Schneider, K. *Lieb. Ann. Chem.* **1992**, *10*, 1049-53.

¹⁹⁶ Diastereomeric mixture of *E* and *Z*.

¹⁹⁷ Diastereomeric mixture of *E* and *Z*.

8. Synthesis of 31.



8.1. Allylic oxidation of methyl geraniate (1). A mixture of SeO_2 (110.0 mg, 1.00 mmol), *t*-BuOOH 5.0-6.0 M in decane (0.36 mL, 2.00 mmol) and DCM (22 mL) was stirred at 0 °C for 20 min, then **1** (364 mg, 2.00 mmol) was added and the complete mixture stirred at the same temperature (TLC monitoring). The reaction was quenched by addition of DCM, washed with H_2O , dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 1:1) on silica gel to yield 75% (based on recovered starting material) of **XXI**.¹⁹⁸

XXI, ^1H NMR (CDCl_3 , 300 MHz): δ 5.63 (1H, s), 5.33 (1H, t, $J=7.2$ Hz), 3.95 (2H, s), 3.64 (3H, s), 2.23-2.14 (4H, m), 2.12 (3H, s), 1.93 (1H, s), 1.61 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 167.2, 159.6, 135.9, 124.2, 115.4, 68.6, 50.8, 40.5, 25.5, 18.8, 13.7 ppm; FABHRMS: calcd for $\text{C}_{11}\text{H}_{18}\text{O}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 221.1154, found: 221.1151.

8.2. Epoxidation of XXI. After subjecting **XXI** (1073 mg, 2.58 mmol) to general epoxidation procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 1:1) on silica gel to afford 513 mg (2.40 mmol, 93%) of **XXII**.

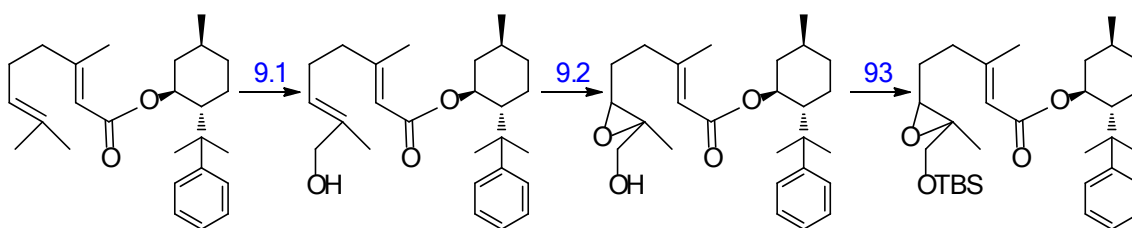
XXII, ^1H NMR (CDCl_3 , 300 MHz): δ 5.70 (1H, s), 3.66 (3H, s), 3.64 (1H, d, $J=9.1$ Hz), 3.55 (1H, d, $J=9.1$ Hz), 3.01 (1H, t, $J=6.7$ Hz), 2.35-2.21 (2H, m), 2.16 (3H, s), 1.99 (1H, bs), 1.77-1.71 (2H, m), 1.26 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 167.1, 162.4, 158.6, 115.9, 65.3, 59.3, 50.9, 37.6, 26.3, 18.9, 14.3 ppm; FABHRMS: calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 237.1103, found: 237.1099.

8.3. TBS-protection of XXII. According to experimental procedure 2.5, **XXII** (507 mg, 2.37 mmol) led after purification by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to 738 mg (2.25 mmol, 95%) of **31**.

¹⁹⁸ Barrero, A. F.; Quílez del Moral, J. F.; Herrador, M. M.; Sánchez, E. M.; Arteaga, J. F. *J. Mex. Chem. Soc.* **2006**, *50*, 149-156.

31, ^1H NMR (CDCl_3 , 300 MHz): δ 5.69 (1H, q, $J=1.2$ Hz), 3.67 (3H, s), 3.56 (2H, s), 2.84 (1H, t, $J=6.2$ Hz), 2.39-2.16 (2H, m), 2.17 (3H, d, $J=1.2$ Hz), 1.72 (2H, m), 1.25 (3H, s), 0.87 (9H, s), 0.04 (3H, s), 0.03 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 167.1, 158.8, 115.8, 67.7, 61.2, 60.1, 50.9, 37.7, 26.6, 25.9, 18.9, 18.4, 14.2, -5.3 ppm; FABHRMS: calcd for $\text{C}_{17}\text{H}_{32}\text{O}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 351.1968, found: 351.1975.

9. Synthesis of 34.



9.1. Allylic oxidation of 26. According to experimental procedure 8.1, **26** (975 mg, 2.54 mmol) led after purification by column chromatography (hexane/*t*-BuOMe, 1:1) on silica gel to 336 mg (0.88 mmol, 35%) of starting material and 504 mg (1.27 mmol, 50%, 76% based on recovered starting material) of **XXIII**.

XXIII, ^1H NMR (CDCl_3 , 300 MHz): δ 7.24 (4H, m), 7.11 (1H, m), 5.42 † (0.16H, t), 5.35 (0.84H, t, $J=6.8$ Hz), 4.97 (1H, d, $J=1.2$ Hz), 4.78 (1H, td, $J=10.7, 10.7, 4.41$ Hz), 3.99 (2H, s), 2.07 (3H, s), 2.19-0.75 (13H, m), 1.66 (3H, s), 1.30 (3H, s), 1.21 (3H, s), 0.85 (3H, d, $J=6.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 166.0, 158.3, 151.7, 135.8, 127.9, 125.5, 124.9, 124.6, 116.3, 73.5, 68.8, 50.7, 42.0, 40.4, 39.8, 34.7, 31.4, 27.4, 26.7, 25.6, 25.5, 21.9, 18.7, 13.7 ppm; FABHRMS: calcd for $\text{C}_{26}\text{H}_{38}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 421.2719; found: 421.2719.

[† : signal corresponding to minor diastereomer, (2*Z*,6*E*)]

9.2. Epoxidation of XXIII. After subjecting **XXIII** (488 mg, 1.22 mmol) to general epoxidation procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 1:1) on silica gel to afford 459 mg (1.11 mmol, 91%) of **XXIV**.

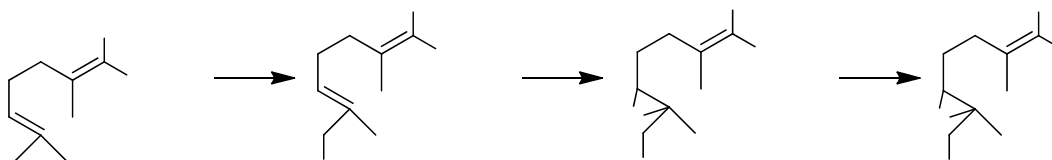
XXIV, ^1H NMR (CDCl_3 , 300 MHz): δ 7.23 (4H, m), 7.08 (1H, m), 4.97 (1H, m), 4.78 (1H, td, $J=10.7, 10.7, 4.2$ Hz), 3.66 (1H, d, $J=12.2$ Hz), 3.55 (1H, m), 2.99 (1H, td, $J=6.2, 6.2, 1.7$ Hz), 2.29-2.10 (2H, m), 2.08 (3H, s), 2.00 (2H, td, $J=11.1, 11.1, 3.3$ Hz), 1.95-0.85 (9H, m), 1.29 (3H, s), 1.27 (3H, s), 1.20 (3H, s), 0.85 (3H, d, $J=6.5$ Hz) ppm;

^{13}C NMR (CDCl_3 , 75 MHz): δ 165.8, 157.3, 151.8, 127.9, 125.5, 124.9, 116.7, 73.5, 65.3, 61.1, 59.4, 50.7, 42.0, 39.8, 37.3, 34.7, 31.4, 27.6, 26.7, 26.3, 25.4, 21.9, 18.8, 14.3 ppm; FABHRMS: calcd for $\text{C}_{26}\text{H}_{38}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 437.2668; found: 437.2671.

9.3. TBS-protection of XXIV. According to experimental procedure 2.5, **XXIV** (381 mg, 0.92 mmol) led after purification by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to 454 mg (0.86 mmol, 94%) of **34**.

34, ^1H NMR (CDCl_3 , 400 MHz): δ 7.27 (4H, m), 7.11 (1H, m), 4.99 (1H, d, $J=7.8$ Hz), 4.78 (1H, td, $J=10.7, 10.7, 4.3$ Hz), 3.59 (2H, s), 2.84 (1H, t, $J=6.2$ Hz), 2.29-2.10 (2H, m), 2.10 (3H, s), 2.01 (2H, td, $J=10.4, 10.4, 1.3$ Hz), 1.92 (1H, bd, $J=12.1$ Hz), 1.64 (4H, m), 1.31 (3H, s), 1.29 (3H, d, $J=5.3$ Hz), 1.22 (3H, s), 0.91 (9H, s), 0.87 (3H, d, $J=6.5$ Hz), 0.07 (3H, s), 0.06 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 165.9, 157.6, 151.8, 127.9, 125.5, 124.9, 116.5, 73.4, 67.7, 61.2, 60.2, 50.7, 42.0, 39.8, 37.4, 34.7, 31.4, 27.7, 27.5, 26.7, 26.7, 25.9, 25.4, 25.2, 21.9, 18.7, 18.4, 14.2, -5.3 ppm; FABHRMS: calcd for $\text{C}_{32}\text{H}_{52}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 551.3733; found: 551.3730.

10. Synthesis of 36.



10.1. Allylic oxidation of XX. According to experimental procedure 8.1, **XX** (268 mg, 1.00 mmol) led after purification by column chromatography (hexane/*t*-BuOMe, 1:1) on silica gel to 216 mg (0.76 mmol, 50%, 76% based on recovered starting material) of **XXIV**.

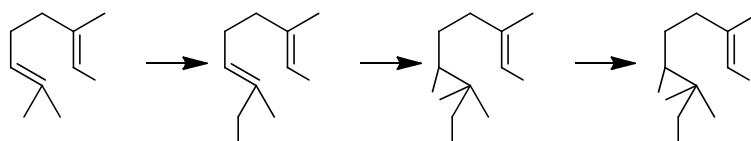
XXIV, ^1H NMR (CDCl_3 , 400 MHz): δ 5.39 (1H, t, $J=7.1$ Hz), 4.23 (4H, q, $J=7.4$ Hz), 4.19 (2H, d, $J=6.5$ Hz), 2.52 (2H, m), 2.17 (2H, q, $J=7.2$ Hz), 2.08 (3H, s), 1.67 (3H, m), 1.26 (6H, t, $J=7.4$ Hz) ppm.

10.2. Epoxidation of XXIV. After subjecting **XXIV** (1253 mg, 3.14 mmol) to general epoxidation procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 1079 mg (2.31 mmol, 83%) of **XXV**.

XXV, ^1H NMR (CDCl_3 , 400 MHz): δ 4.22 (4H, ddd, $J=14.2$, 7.1, 1.3 Hz), 3.58 (2H, d, $J=6.3$ Hz), 3.00 (1H, t, $J=6.3$ Hz), 2.51 (2H, m), 2.06 (3H, s), 1.85 (1H, m), 1.72 (1H, m), 1.27 (6H, t, $J=7.4$ Hz), 1.17 (3H, s) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 165.6, 165.4, 156.7, 125.5, 65.9, 61.2, 61.0, 59.8, 33.2, 27.0, 26.6, 20.9, 14.2, 14.1, 14.1 ppm; FABHRMS: calcd for $\text{C}_{15}\text{H}_{24}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 323.1465 found: 323.1461.

10.3. TBS-protection of XXV. According to experimental procedure 2.5, **XXV** (925 mg, 4.40 mmol) led after purification by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to 1679 mg (4.22 mmol, 94%) of **36**, ^1H NMR (CDCl_3 , 400 MHz): δ 4.22 (4H, ddd, $J=14.2$, 7.1, 1.3 Hz), 3.57 (2H, d, $J=6.2$ Hz), 2.82 (1H, t, $J=6.1$ Hz), 2.51 (2H, m), 2.02 (3H, s), 1.74 (2H, m), 1.27 (6H, t, $J=7.4$ Hz), 1.24 (3H, s), 0.82 (9H, s), 0.00 (6H, s) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 165.6, 165.3, 157.0, 125.4, 67.7, 61.3, 61.0, 60.9, 60.1, 33.4, 27.1, 25.9, 21.1, 18.4, 14.1, -5.3 ppm; FABHRMS: calcd for $\text{C}_{21}\text{H}_{38}\text{O}_6\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 437.2335 found: 437.2339.

11. Synthesis of 38.



According to experimental procedure 8.1, geranyl-nitrile (746 mg, 5.00 mmol) led to alcohol **XXVI** employed without further purification in the next step. This crude (700 mg, 3.93 mmol) was subjected to general epoxidation procedure with *m*-CPBA and TBS-protection and purified by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to afford 885 mg (3.01 mmol, 75%) of **38**.¹⁹⁹

38, ^1H NMR (CDCl_3 , 400 MHz): δ 5.10 (1H, bs), 3.51 (2H, dt, $J=18.0$, 10.2 Hz), 2.80 (1H, m), 2.49 (1H, t, $J=7.5$ Hz), 2.29 (1H, m), 2.02-1.90 (3H, 2s),²⁰⁰ 1.75-1.58 (2H, m), 1.22 (3H, 2s),²¹ 0.82 (9H, s), 0.00 (6H, s) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.5, 169.2, 122.3, 122.1, 101.9, 101.3, 72.8, 72.7, 66.5, 66.4, 65.0, 64.9, 40.9, 38.5, 36.3, 32.1, 31.6, 31.2, 31.0, 28.3, 26.4, 23.7, 19.6, 19.5, 1.8, 0.0 ppm; FABHRMS: calcd for $\text{C}_{16}\text{H}_{29}\text{NO}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 318.1865 found: 318.1825.

¹⁹⁹ Diastereomeric mixture of *E* and *Z*.

²⁰⁰ Signal corresponding to diastereomeric mixture of *E* and *Z*.

ANEXO 4

Supporting Information Artículo 4

Weakening C-O Bonds: Ti(III), a New Reagent for Alcohol Deoxygenation and Carbonyl Coupling Olefination

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Supporting Information

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General Details

IR spectra were recorded on a Mattson Satellite FTIR spectrometer. NMR spectra were performed with a Varian Direct-Drive 600 (^1H 600 MHz/ ^{13}C 150 MHz), 500 (^1H 500 MHz/ ^{13}C 125 MHz), Bruker ARX 400 (^1H 400 MHz/ ^{13}C 100 MHz) and Varian Inova Unity 300 (^1H 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 a solution of phosphomolybdic acid in ethanol and heat as developing agent. GC-MS analyses were carried out in a Hewlett Packard 6890 chromatograph connected to a Hewlett-Packard 5988A mass spectrometer using an ionization voltage of 70 eV. The GC conditions were: HP-1 methylsilicone capillary column (25 m x 0.2 mm); He 1.9 mL/min; the injection and detector heater temperature was 250°C; temperature program from 50°-300°C at 10°C/min. Quantitative chromatographic analysis were carried out on Hewlett Packard 6890 chromatograph equipped with a flame ionization detector (FID) and coupled to an integrator HP-3390A. The column and experimental conditions were the same as those described above, except that the detector heater temperature was 300°C and the inlet head was 20 psi. The percentage compositions were computed from the GC peak areas without correction factors. 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 Serie 1100 instrument. 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. All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an argon atmosphere. The solvents used were purified according to standard

literature techniques and stored under argon. 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 $\text{Cp}_2\text{TiCl}_2/\text{Mn}$ or Zn reactions. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated.

General procedure for stoichiometric deoxygenation-reduction reactions (Procedure A): toluene, 8, 10, 12, 14, 16, 18, 20, 23, 25, 27, 29, 31, 33, 35, 37, 38.

A mixture of Cp_2TiCl_2 (998 mg, 3.88 mmol) and Mn dust (154 mg, 2.77 mmol) in strictly deoxygenated THF (7 mL) was heated at reflux under stirring until the red solution turned green. Then, to this mixture was added a solution of the corresponding alcohol (1.85 mmol) in strictly deoxygenated THF (4 mL). The reaction mixture was heated at reflux under stirring until starting material disappearance (TLC monitoring), quenched with 1N HCl and extracted with *t*-BuOMe. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo yielding a crude which was analyzed by CG-MS, purified by column chromatography over silica gel column and/or subjected to HPLC.

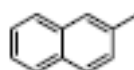
General procedure for catalytic deoxygenation- homocoupling carbonyl reactions (Procedure B): 20, 27, 31.

A mixture of Cp_2TiCl_2 (160 mg, 0.639 mmol) and Mn dust (935 mg, 17.04 mmol) in thoroughly deoxygenated THF (8 mL) and under Ar atmosphere was stirred until the red solution turned green. This mixture was then heated at reflux and the corresponding TMSCl (1.07 mL, 8.52 mmol) was added, finally the allylic aldehyde (1.92 mmol) in strictly deoxygenated THF (2 mL) was then added. The reaction mixture was stirred until starting material disappearance (TLC monitoring). It was then quenched with *t*-BuOMe, washed with 1 N HCl, brine, dried over anhydrous Na_2SO_4 and concentrated

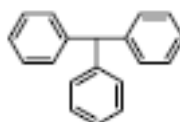
under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products.



Toluene: According to the procedure A, the mixture containing benzyl alcohol (**1**) was heated for 45 min. The resulting crude was analyzed by GC-MS. **Toluene** (93 %, $R_t = 4.42$ min) was identified by the standard use.

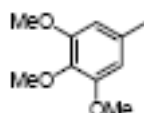


2-Methylnaphthalene (8): According to the procedure A described for deoxygenation-reduction, the mixture containing 2-naphthylmethanol (**7**) was heated for 60 min. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 6:1) on silica gel to afford **8** (79%). $^1\text{H NMR}$ (CD_3Cl , 300 MHz): δ 2.56 (s, 3H), 7.37 (d, $J = 8.5$ Hz, 1H), 7.47 (quintet, $J = 6.4$ Hz, 2H), 7.66 (bs, 1H), 7.78-7.86 (m, 3H); $^{13}\text{C NMR}$ (CD_3Cl , 75 MHz): δ 21.8, 125.0, 125.9, 126.9, 127.3, 127.7, 127.8, 128.2, 131.8, 133.7, 135.5. $^1\text{H NMR}$ spectroscopic data of this compound were identical to that of a standard.

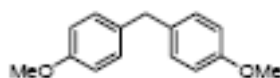


Triphenylmethane (10): According to the procedure A described for deoxygenation-reduction, the mixture containing triphenylmethanol (**9**) was heated for 60 min. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 6:1) on silica gel to afford **10** (91%). $^1\text{H NMR}$ (CD_3Cl , 300

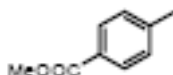
MHz): δ 7.38 (br s, 15H); ^{13}C NMR (CD_3Cl , 75 MHz): δ 82.1, 127.3, 128.0, 146.9. ^1H NMR spectroscopic data of this compound were identical to that of a standard.



1,2,3-Trimethoxy-5-methylbenzene (12): According to the procedure A described for deoxygenation-reduction, the mixture containing (3,4,5-trimethoxyphenyl)methanol (**11**) was heated for 50 min. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford **12** (90%). ^1H NMR (CD_3Cl , 300 MHz): δ 2.32 (s, 3H), 3.83 (s, 3H), 3.85 (s, 6H), 6.41 (s, 2H); ^{13}C NMR (CD_3Cl , 300 MHz): δ 21.7, 55.9, 60.8, 105.9, 133.5, 135.7, 152.9. ^1H NMR spectroscopic data of this compound were identical to that of a standard.



Bis(4-methoxyphenyl)methane (14): According to the procedure A described for deoxygenation-reduction, the mixture containing bis(4-methoxyphenyl)methanol (**13**) was heated for 90 min. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 6:1) on silica gel to afford **14** (60%). ^1H NMR (CD_3Cl , 300 MHz): δ 3.82 (s, 6H), 3.90 (s, 2H), 6.86 (d, J = 8.5 Hz, 4H), 7.12 (d, J = 8.5 Hz, 4H); ^{13}C NMR (CD_3Cl , 75 MHz): δ 40.2, 55.3, 113.9, 129.8, 133.8, 158.0. ^1H NMR spectroscopic data of this compound were identical to that of a standard.

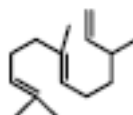


Methyl *p*-toluate (16): According to the procedure A described for the deoxygenation-reduction, the mixture containing methyl 4-formolbenzoate **15** was heated at reflux for 55 min. The resulting crude

was purified by column chromatography using hexane as eluent on silica gel to afford **16** (83 %) as brown prisms. IR (film): 2952, 2925, 2855, 1725, 1614, 1435, 1310, 1108, 1021, 840, 754, 691 cm^{-1} . ^1H NMR (400 MHz; CDCl_3) δ 2.31 (s, 3H), 3.81 (s, 3H), 7.14 (d, $J = 7.8$ Hz, 2H), 7.85 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (100 MHz; CDCl_3) δ 21.6, 51.9, 127.5, 129.1 (2C), 129.6 (2C), 143.5, 167.1. HREIMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_9\text{H}_{10}\text{O}_2$ 150.0681 found 150.0675.



1-Dodecene (18): According to the procedure A described for deoxygenation-reduction, the mixture containing (*E*)-2-dodecen-1-ol (**17**) was heated for 50 min. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 9:1) on silica gel to afford **18** (91%). ^1H NMR (CD_3Cl , 500 MHz): δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.21-1.41 (m, 16H), 2.04 (q, $J = 6.8$ Hz, 2H), 4.92 (br d, $J = 10.0$ Hz, 1H), 4.99 (br d, $J = 17.0$ Hz, 1H), 5.81 (ddt, $J = 6.8$ Hz, 10.0 Hz, 17.0 Hz, 1H); ^{13}C NMR (CD_3Cl , 125 MHz): δ 14.1, 22.6, 28.9, 29.1, 29.3, 29.4, 29.6, 31.9, 33.8, 114.0, 139.2. ^1H NMR spectroscopic data of this compound were identical to that of a standard.



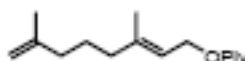
(E)-3,7,11-Trimethyldodeca-1,6,10-triene (20): According to the procedure A described for deoxygenation-reduction, the mixture containing *trans-trans*-farnesol (**19**) was heated for 60 min. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 8:1) on silica gel to afford a mixture of **20**² (30%).

According to the procedure B described for catalytic deoxygenation-reduction, the mixture containing *trans-trans*-farnesol (**19**) was heated for 55 min. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 8:1) on silica gel to afford a mixture of **20**² (92%). ^1H NMR (CD_3Cl , 500 MHz): δ 0.99 (d, $J = 7.0$ Hz, 3H), 1.30-1.36 (m, 2H), 1.59 (s, 3H), 1.61 (s, 3H), 1.69 (s,

3H), 1.96-2.01 (m, 2H), 2.05-2.10 (m, 4H), 2.13 (sept, $J = 7.2$ Hz, 1H), 4.92 (br d, $J = 10.0$ Hz, 1H), 4.96 (br d, $J = 17.4$ Hz, 1H), 5.08-5.14 (m, 2H), 5.70 (ddd, $J = 7.2$ Hz, 10.0 Hz, 17.4 Hz, 1H); ^{13}C NMR (CD_3Cl , 125 MHz): δ 15.9, 17.6, 20.1, 25.6, 25.7, 26.6, 36.7, 37.3, 39.7, 112.4, 124.4, 124.5, 131.2, 134.8, 144.7.



3-Methyl-3-butenyl benzoate (23): According to the procedure A described for deoxygenation-reduction, the mixture containing (*E*)-4-hydroxy-3-methyl-2-butenyl benzoate (22) was heated for 60 min. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 23¹ (70%). ^1H NMR (CD_3Cl , 500 MHz): δ 1.82 (s, 3H), 2.49 (t, $J = 6.8$ Hz, 2H), 4.44 (t, $J = 6.8$ Hz, 2H), 4.81 (br s, 1H), 4.84 (br s, 1H), 7.43 (br t, $J = 7.9$ Hz, 2H), 7.55 (tt, $J = 1.1$ Hz, 7.9 Hz, 1H), 8.03 (dd, $J = 1.1$ Hz, 7.9 Hz, 1H); ^{13}C NMR (CD_3Cl , 300 MHz): δ 14.1, 29.6, 63.1, 112.4, 128.3, 129.5, 132.8, 141.7, 166.5.

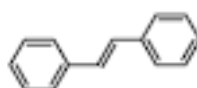


(2*E*)-3,7-Dimethylocta-2,7-dienyl pivalate (25): According to the procedure A described for the deoxygenation-reduction, the mixture containing (3*E*,7*E*)-8-hydroxy-3,7-dimethylocta-2,6-dienyl pivalate 24 was heated at reflux for 2 h. The resulting crude was purified by column chromatography using hexane as eluent on silica gel to afford 25 as colorless oil. IR (film): 2971, 2935, 1729, 1480, 1459, 1397, 1282, 1151, 1032, 955, 887 cm^{-1} . ^1H NMR (400 MHz; CDCl_3) δ 5.32 (t, $J = 7.0$ Hz, 1H), 4.70 (s, 1H), 4.66 (s, 1H), 4.56 (d, $J = 7.0$ Hz, 2H), 2.01 (m, 4H), 1.71 (s, 3H), 1.69 (s, 3H), 1.55 (qt, $J = 8.0$ Hz, 2H), 1.18 (s, 9H). ^{13}C NMR (100 MHz; CDCl_3) δ 16.3, 22.3, 25.4, 27.2 (3C), 37.2, 38.8, 38.9, 61.3, 109.9, 118.8, 141.7, 145.7, 178.5. HRCIMS (m/z): $[\text{M}-\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_2$ 238.1933 found 237.1859.

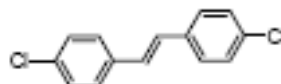


(5E,9E)-6,10,14-Trimethylpentadeca-5,9,14-trien-2-one (27): According to the procedure A described for the deoxygenation-reduction, (5E,9E,13Z)-15-hydroxy-6,10,14-trimethylpentadeca-5,9,13-trien-2-one **26** was heated at reflux for 2 h. The resulting crude was purified by column chromatography using (4:1) hexanes: *t*-BuOMe as eluent on silica gel to afford **27**(38 %) as a colorless oil.

According to the procedure B described for the catalytic deoxygenation-reduction, the compound **26** was heated at reflux for 4 h. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe 4:1) as eluent on silica gel to afford **27**(85 %). IR (film): 3073, 2933, 1719, 1649, 1441, 1358, 1158, 885 cm^{-1} . ^1H NMR (400 MHz; CDCl_3) δ 1.39 (quintuplet, $J = 7.4$ Hz, 2H), 1.47 (s, 3H), 1.49 (s, 3H), 1.59 (s, 3H), 1.85 (m, 6H), 1.95 (t, $J = 7.4$ Hz, 2H), 2.01 (s, 3H), 2.15 (t, $J = 7.4$ Hz, 2H), 2.33 (t, $J = 7.4$ Hz, 2H), 4.54 (s, 1H), 4.58 (s, 1H), 4.96 (m, 2H). ^{13}C NMR (100 MHz; CDCl_3) δ 15.8, 15.9, 22.3, 22.4, 25.9, 26.4, 29.8, 37.3, 39.2, 39.6, 43.7, 109.7, 122.5, 124.1, 134.9, 136.2, 145.9, 208.7. HRFABMS (m/z): $[\text{M} + \text{Na}]^+$ calcd. for $\text{C}_{18}\text{H}_{30}\text{O}\text{Na}$ 285.2194 found 285.2197.

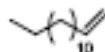


trans-Stilbene (29): According to the procedure A described for deoxygenation-reduction, the mixture containing 1,2-diphenylethane-1,2-diol (**28**) was heated for 65 min, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 6:1) on silica gel to afford **29**³ (94 %). ^1H NMR (CD_3Cl , 300 MHz): δ 7.22 (s, 2H), 7.37 (t, $J = 7.3$ Hz, 2H), 7.47 (t, $J = 7.3$ Hz, 4H), 7.62 (d, $J = 7.3$ Hz, 4H); ^{13}C NMR (CD_3Cl , 75 MHz): δ 126.6, 127.7, 128.7, 128.8, 137.4.



(E)-4,4'-Dichlorostilbene (31): According to the procedure A described for the deoxygenation-reduction, the mixture containing 1,2-bis(4-chlorophenyl)ethane-1,2-diol **30** was heated at reflux for 1 h. The resulting crude was purified by column chromatography using (hexane/*t*-BuOMe 1:1) as eluent on silica gel to afford **31** (79 %) as a white powder.

According to the procedure B described for the catalytic deoxygenation-reduction, the mixture containing 1,2-bis(4-chlorophenyl)ethane-1,2-diol **30** was heated at reflux for 1.5 h. The resulting crude was purified by column chromatography using (hexane/*t*-BuOMe 1:1) as eluent on silica gel to afford **31** (86 %). IR (film): 3040, 3010, 2938, 1701, 1600, 1497, 1405, 1102 cm^{-1} . ^1H NMR (400 MHz; CDCl_3) δ 7.02 (s, 2H), 7.33 (d, $J = 8.2$ Hz, 4H), 7.43 (d, $J = 8.2$ Hz, 4H). ^{13}C NMR (100 MHz; CDCl_3) δ 135.5, 133.4, 128.9, 127.9, 127.6. HREIMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{14}\text{H}_{10}\text{Cl}_2$ 248.0160 found 248.0150.



1-Tetradecene (33): According to the procedure A described for deoxygenation-reduction, the mixture containing tetradecane-1,2-diol (**32**) was heated for 90 min. The resulting crude was purified by column chromatography on silica gel to afford **33** (68 %). ^1H NMR (CD_3Cl , 500 MHz): δ 0.88 (t, $J = 6.8$ Hz, 3H), 1.22-1.42 (m, 20H), 2.04 (q, $J = 6.8$ Hz, 2H), 4.93 (br d, $J = 10.2$ Hz, 1H), 4.99 (br d, $J = 17.1$ Hz, 1H), 5.81 (ddt, $J = 6.8$ Hz, 10.2 Hz, 17.1 Hz, 1H); ^{13}C NMR (CD_3Cl , 125 MHz): δ 14.2, 22.8, 29.0, 29.3, 29.4, 29.6, 29.7, 29.8, 32.0, 33.9, 114.1, 139.3. ^1H NMR spectroscopic data of this compound were identical to that of a standard.



S9

β -Pinene (35): According to the procedure A described for deoxygenation-reduction, the mixture containing pinane-2 α ,10-diol (34) was heated for 90 min. The resulting crude was analyzed by GC-MS. **35** (92%, RT = 6.32 min) was identified by the standard use.



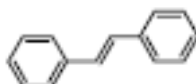
Octadecane (37) and 1-octadecene (38): A mixture of Cp_2TiCl_2 (200 mg, 0.77 mmol) and Zn dust (36.72 mg, 0.55 mmol) in strictly deoxygenated toluene (2 mL) was heated at reflux under stirring until the red solution turned green. Then, to this mixture was added a solution of octadecan-1-ol (36) (100 mg, 0.37 mmol) in strictly deoxygenated toluene (1 mL). The reaction mixture was heated at reflux under stirring for 120 min. It was then quenched with 1N HCl and extracted with *t*-BuOMe. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo yielding a crude was purified by column chromatography (hexane/*t*-BuOMe, 9:1) on silica gel to afford a mixture (90%) that was analyzed by GC-MS. This mixture was constituted for **37** (RT = 17.21 min) and **38** (RT = 17.10 min) at a ratio 1:1. These compounds were identified by the standard use.

When the procedure A described for deoxygenation-reduction was followed, starting compound **36** was recovered.

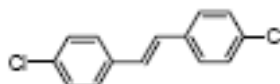
General procedure for stoichiometric homocoupling carbonyl reactions (Procedure C): 29, 31, 41, 43, 45, 48, 50, 52, 54, 56, 58.

A mixture of Cp_2TiCl_2 (392 mg, 1.57 mmol) and Mn dust (172 mg, 3.15 mmol) or Zn dust (206 mg, 3.15 mmol) in thoroughly deoxygenated THF (6.5 mL) and under Ar atmosphere was stirred until the red solution turned green. This mixture was then heated at reflux and the corresponding allylic aldehyde (1.31 mmol) in strictly deoxygenated THF (2 mL) was then added. The reaction mixture was stirred until starting material disappearance (TLC monitoring). It was then quenched with *t*-BuOMe, washed

with 1 N HCl, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products.

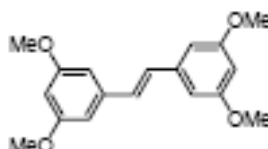


trans-Stilbene (29): According to the procedure C described for the carbonyl homocoupling, the mixture containing benzaldehyde (39) was heated at reflux for 1 h. The resulting crude was purified by column chromatography (hexane) on silica gel to afford 29 (93%).



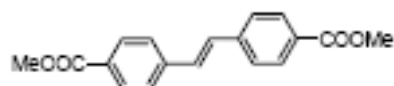
(E)-4,4'-Dichlorostilbene (31): According to the procedure C described for the carbonyl homocoupling, the mixture containing 4-chlorobenzaldehyde 46 was heated at reflux for 1.5 h. The resulting crude was purified by column chromatography using (hexane/*t*-BuOMe 1:1) as eluent on silica gel to afford 31 (74 %) as a white powder.

According to the procedure B described for the catalytic carbonyl homocoupling, the mixture containing 4-chlorobenzaldehyde 46 was heated at reflux for 2 h. The resulting crude was purified by column chromatography using (hexane/*t*-BuOMe 1:1) as eluent on silica gel to afford 31 (95 %).

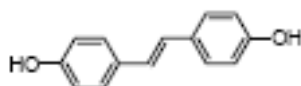


(E)-3,3',5,5'-Tetramethoxystilbene (41): According to the procedure C described for the carbonyl homocoupling, the mixture containing 3,5-dimethoxybenzaldehyde (40) was heated at reflux for 1 h.

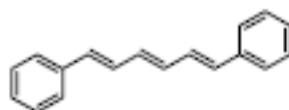
The resulting crude was purified by column chromatography (hexane) on silica gel to afford **41**⁴ (87%).
¹H NMR (300 MHz; CDCl₃): δ 3.75 (s, 12H), 6.33 (t, *J* = 2.3 Hz, 2H), 6.60 (d, *J* = 2.3 Hz, 4H), 6.94 (s, 2H); ¹³C NMR (75 MHz; CDCl₃): δ 55.5, 100.3, 104.8, 129.3, 139.3, 161.1.



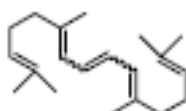
Dimethyl (*E*)-4,4'-stilbenedicarboxylate (43): According to the procedure C described for the carbonyl homocoupling, the mixture containing methyl 4-formylbenzoate **42** was heated at reflux for 2 h. The resulting crude was purified by column chromatography using EtOAc as eluent on silica gel to afford **43** (94%) as a white powder. IR (film): 1721, 1284, 1108, 965, 858, 774 cm⁻¹. ¹H NMR (400 MHz; CDCl₃) δ 3.93 (s, 6H), 7.25 (s, 2H), 7.59 (d, *J* = 8.6 Hz, 4H), 8.04(d, *J* = 8.6 Hz, 4H). ¹³C NMR (100 MHz; CDCl₃) δ 26.9, 52.1, 86.6, 126.6, 130.1, 141.2, 166.7. HREIMS (*m/z*): [M]⁺ calcd. for C₁₈H₁₆O₄ 296.1049 found 296.1048.



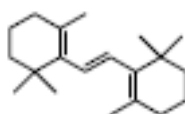
(*E*)-4,4'-Dihydroxystilbene(45): According to the procedure C described for the carbonyl homocoupling, the mixture containing 4-Hydroxybenzaldehyde **44** was heated at reflux for 4 h. The resulting crude was purified by column chromatography using *t*-BuOMe as eluent on silica gel to afford **45** (93 %) as a white powder. IR (film): 3333, 2926, 1510, 1439, 1270, 825 cm⁻¹. ¹H NMR (500 MHz; CDCl₃) δ 6.82 (d, *J* = 8.7 Hz, 4H), 6.96 (s, 2H), 7.39 (d, *J* = 8.7 Hz, 4H), 8.37 (s, 2H). ¹³C NMR (125 MHz; CDCl₃) δ 116.3, 126.5 128.3, 130.5, 157.7 ppm. HREIMS (*m/z*): [M]⁺ calcd. for C₁₄H₁₂O₂ 212.0837 found 212.0841.



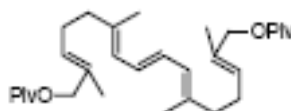
(1E,3E,5E)-1,6-Diphenylhexa-1,3,5-triene (48): According to the procedure C described for the carbonyl homocoupling, the mixture including *E*-cinnamaldehyde (47) was heated at reflux for 2 h. The resulting crude was purified by column chromatography (hexane) on silica gel to afford 48⁵ (65%). ¹H NMR (CDCl₃, 500 MHz): δ 6.53 (dd, *J* = 7.0, 2.9 Hz, 2H), 6.61 (d, *J* = 15.5 Hz, 2H), 6.90 (ddd, *J* = 15.5, 7.0, 3.0 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 4H), 7.43 (d, *J* = 7.5 Hz, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 126.4, 127.5, 128.6, 129.1, 132.7, 133.6, 137.4.



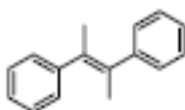
(6E,8E,10E)- and (6E,8Z,10E)-2,6,11,15-Tetramethylhexadeca-2,6,8,10,14-pentaene (50): According to the procedure C described for the carbonyl homocoupling, the mixture including citral (49) was heated at reflux for 1 h. The resulting crude was purified by column chromatography (hexane) on silica gel to afford 50⁶ (76%) as a mixture of (6E,8E,10E) and (6E,8Z,10E) isomers at a 6:1 ratio. (6E,8E,10E) isomer: ¹H NMR (CDCl₃, 500 MHz): δ 1.59 (s, 6H), 1.67 (s, 6H), 1.76 (s, 6H), 2.07 (m, 8H), 5.09 (bt, *J* = 6.7 Hz, 2H), 5.90 (bd, *J* = 7.5 Hz, 1H), 6.33 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 16.7, 17.7, 25.7, 26.7, 40.1, 124.1, 125.4, 127.2, 131.6, 138.1. (6E,8Z,10E) isomer: ¹H NMR (CDCl₃, 500 MHz): δ 1.59 (s, 3H), 1.67 (s, 3H), 1.76 (s, 3H), 2.07 (m, 4H), 5.09 (bt, *J* = 6.7 Hz, 1H), 6.10 (m, 1H), 6.33 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 16.5, 17.7, 25.7, 26.7, 40.4, 120.3, 123.4, 124.0, 131.6, 139.3.



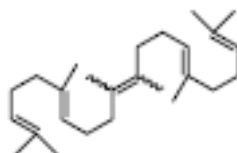
Mini-3- β -carotene (52): According to the procedure C described for the carbonyl homocoupling, the mixture including β -cyclocitral (**51**) was heated at reflux for 2 h 30 min. The resulting crude was purified by column chromatography (hexane) on silica gel to afford **52** (74%). IR (film) 2960, 2923, 2849, 2823, 1652, 1452, 1378, 1357, 1032, 971, 740 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz): δ 1.03 (s, 12H), 1.45-1.48 (m, 4H), 1.59-1.64 (m, 4H), 1.76 (s, 6H), 2.01 (t, $J = 6.3$ Hz, 4H), 5.81 (s, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 19.5, 22.0, 29.0, 29.9, 33.0, 34.4, 39.7, 128.4, 132.3, 139.3; HRFABMS (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{32}\text{Na}$ 295.2402, found 295.2403.



(2E,6E,10E)-2,6,11,15-Tetramethylhexadeca-2,6,8,10,14-pentaene-1,16-pivaloate (54): According to the procedure C described for the carbonyl homocoupling, the mixture containing the corresponding aldehyde **53** was heated at reflux for 1.15 h. The resulting crude was purified by column chromatography using hexane as eluent on silica gel to afford **54** (73 %) as a colorless oil. IR (film): 2969, 2931, 2872, 1726, 1281, 1151, 955 cm^{-1} . ^1H NMR (600 MHz; CDCl_3) δ 1.19 (s, 18H), 1.71 (s, 6H), 1.76 (s, 6H), 2.10 (t, $J = 7.7$ Hz, 4H), 2.28 (q, $J = 7.1$ Hz, 4H), 4.57 (d, $J = 6.9$ Hz, 4H), 5.33 (d, $J = 6.9$, 2H), 5.34 (d, $J = 6.9$ Hz, 2H), 5.45 (t, $J = 7.2$ Hz, 2H). ^{13}C NMR (150 MHz; CDCl_3) δ 12.4, 16.4, 26.6, 27.2 (3C), 38.7, 39.2, 61.2, 119.1, 130.9, 131.2, 134.2, 141.2, 178.6 ppm. HRFABMS (m/z): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{30}\text{H}_{48}\text{O}_4\text{Na}$ 495.3450 found 495.3448.

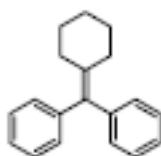


(E)- α,β -Dimethylstilbene (56): According to the procedure C described for the carbonyl homocoupling, the mixture including acetophenone (**55**) was heated at reflux for 4 h. The resulting crude was purified by column chromatography (hexane) on silica gel to afford **56**⁷ (71%). ¹H NMR (CDCl₃, 500 MHz): δ 1.89 (s, 6H), 7.27 (m, 6H), 7.37 (t, $J = 7.6$ Hz, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 22.5, 126.3, 128.2, 128.3, 133.1, 144.6.

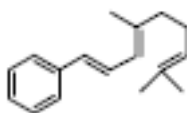


(6E,14E)-2,6,10,11,15,19-hexamethylcosa-2,6,10,14,18-pentaene (58): According to the procedure C described for the carbonyl homocoupling, the mixture including geranylacetone (**57**) was heated at reflux for 4 h. The resulting crude was purified by column chromatography (hexane) on silica gel to afford **58** (62%). IR (film) 2964, 2923, 2855, 1705, 1630, 1448, 1375, 1260, 1105, 1079, 979, 894, 746 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 1.60 (bs, 15H), 1.68 (bs, 9H), 1.91-2.08 (m, 16H), 5.02-5.08 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 16.1, 17.8, 25.8, 26.8, 27.1, 39.8, 124.5, 124.6, 124.7, 131.4, 135.1, 135.2. HRFABMS (m/z): [M + Na]⁺ calcd for C₂₆H₄₆Na 379.3341, found 379.3358.

General procedure for heterocoupling carbonyl reactions: 61, 62.



Diphenylmethylenecyclohexane (61). A mixture of Cp_2TiCl_2 (845 mg, 3.29 mmol) and Mn dust (487 mg, 8.78 mmol) or Zn dust (573 mg, 8.78 mmol) in thoroughly deoxygenated THF (4 mL) and under Ar atmosphere was stirred until the red solution turned green. This mixture was then heated at reflux and the corresponding mixture of benzophenone (60) (200 mg, 1.10 mmol) and cyclohexanone (59) (431 mg, 4.40 mmol) in strictly deoxygenated THF (2 mL) were then added. The reaction mixture was stirred until starting material disappearance (TLC monitoring). It was then quenched with *t*-BuOMe, washed twice with 1N HCl, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane) on silica gel to afford **61⁸** (65%). ^1H NMR (CDCl_3 , 500 MHz): δ 1.56–1.60 (m, 6H), 2.23–2.25 (m, 4H), 7.10–7.29 (m, 10H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 26.8, 28.7, 32.4, 126.0, 127.8, 129.8, 134.5, 139.1, 143.1.



(1E,3E)-4,8-Dimethyl-1-phenyl-1,3,7-nonatriene (62). A mixture of Cp_2TiCl_2 (2.45 g, 9.85 mmol) and Mn dust (1.44 g, 26.28 mmol) or Zn dust (1.71 g, 26.28 mmol) in thoroughly deoxygenated THF (140 mL) and under Ar atmosphere was stirred until the red solution turned green. This mixture was then heated at reflux and the corresponding mixture of citral (49) (500 mg, 3.28 mmol) and benzaldehyde (39) (1.743 g, 16.42 mmol) in strictly deoxygenated THF (23 mL) were then added. The reaction mixture was stirred until starting material disappearance (TLC monitoring). It was then quenched with *t*-BuOMe, washed twice with 1N HCl, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified, by column chromatography (hexane) on silica gel to afford **62⁹** (77%). ^1H NMR (CDCl_3 , 500 MHz): δ 1.62 (s, 3 H) , 1.69 (s, 3 H) ,

1.85 (s, 3 H) , 2.13 (m, 4 H) , 5.12 (bs, 1 H) , 6.00 (d, $J = 11.0$ Hz, 1 H) , 6.44 (d, $J = 15.4$ Hz, 1 H) , 7.02 (dd, $J = 15.4, 11.0$ Hz, 1 H), 7.18 (t, $J = 7.3$ Hz, 1H), 7.29 (t, $J = 7.3$ Hz, 2H), 7.39 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 16.9, 17.7, 25.7, 26.6, 40.1, 123.9, 125.1, 125.7, 126.1, 126.9, 128.5, 129.9, 131.8, 138.1, 140.2.

Computational Details

Calculations based on density functional theory (DFT) were performed with Gaussian 03 package. We have used the M05 functional from the Truhlar group together with the "Ahlichs VDZ" basis set, for the geometry optimization and for the calculation of the Gibbs free energy of activation and free energy of reactions. The local stability of all structures was checked through the eigenvalues of the matrix of second derivatives (Hessian); all energetic minima presented no imaginary frequencies, while transition states (TS) presented a single imaginary frequency. Unrestricted calculations (UM05) were carried out for all the structures, being the electronic state doublet for the reactives, TS's and products and singlet for the Cp_2TiClOH compound.

DFT energies (a.u.), first frequency value (cm^{-1}) in parentheses, zero point vibrational energy (ZPVE a.u.), and cartesian coordinates (Å) of the optimized structures discussed:

1prod. E(UM05/Ahlichs-VDZ) = -117.036600505 a.u. / (441 cm^{-1}) / ZPVE = 0.066701 a.u.



C	1.238023000	-0.196776000	0.000000000
C	0.000000000	0.443327000	0.000000000
C	-1.238021000	-0.196742000	0.000000000

S17

H	0.000013000	1.540943000	0.000000000
H	-2.173762000	0.371126000	0.000000000
H	-1.311224000	-1.290980000	0.000000000
H	2.173772000	0.371073000	0.000000000
H	1.311191000	-1.291017000	0.000000000

Ireact. E(UM05/Ahlrichs-VDZ) = -1888.72168194 a.u. / (11 cm⁻¹) / ZPVE = 0.259089 a.u.



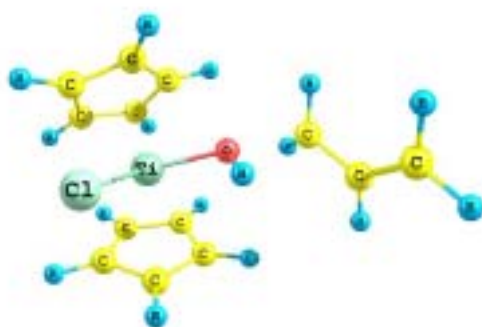
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C	-2.606385000	-0.321118000	-0.829773000
H	-1.721399000	-0.148357000	1.056265000
H	-2.235934000	0.009241000	-1.814073000
H	-2.790019000	-1.410291000	-0.880053000
C	1.347401000	1.688622000	-1.554236000
C	0.146336000	2.137068000	-0.945021000

S18

C	0.391322000	2.290983000	0.450018000
C	1.762330000	1.970245000	0.700226000
C	2.349126000	1.596113000	-0.538045000
H	1.485575000	1.471105000	-2.611491000
H	-0.803823000	2.302853000	-1.449659000
H	-0.335461000	2.576748000	1.205277000
H	2.249034000	1.984474000	1.672562000
H	3.381826000	1.288591000	-0.689086000
C	1.915240000	-1.305879000	-1.464273000
C	0.566725000	-1.764998000	-1.483537000
C	0.285927000	-2.313635000	-0.191042000
C	1.454383000	-2.201556000	0.608282000
C	2.455414000	-1.555596000	-0.164401000
H	2.448547000	-0.856169000	-2.298168000
H	-0.106550000	-1.744084000	-2.339026000
H	-0.659966000	-2.739524000	0.137015000
H	1.535134000	-2.483347000	1.654469000
H	3.463455000	-1.317286000	0.169116000
C	-3.847971000	0.421694000	-0.444087000

C	-5.038598000	-0.155831000	-0.218035000
H	-3.735597000	1.509349000	-0.349071000
H	-5.920273000	0.435192000	0.050917000
H	-5.179041000	-1.241456000	-0.297532000

Its. E(UM05/Ahlrichs-VDZ) = -1888.6706425 a.u. / (731i cm⁻¹) / ZPVE = 0.254425 a.u.



Ti	0.557818000	0.015559000	0.039625000
Cl	0.608967000	0.136312000	2.487180000
O	-1.315720000	-0.442073000	0.268712000
C	-2.815941000	-0.757425000	-0.965625000
H	-1.803878000	-0.070736000	1.031429000
H	-2.278676000	-0.457593000	-1.869539000
H	-2.839945000	-1.832977000	-0.764384000
C	0.437997000	1.594576000	-1.719198000
C	-0.499495000	2.067211000	-0.753010000

C	0.204883000	2.377971000	0.430601000
C	1.599881000	2.151483000	0.192365000
C	1.745326000	1.709067000	-1.146316000
H	0.210277000	1.291298000	-2.739527000
H	-1.578924000	2.106607000	-0.880237000
H	-0.224890000	2.692699000	1.377071000
H	2.394130000	2.295705000	0.921034000
H	2.681305000	1.476840000	-1.647528000
C	1.662729000	-1.292814000	-1.635938000
C	0.552692000	-2.033889000	-1.146205000
C	0.791459000	-2.328295000	0.227608000
C	2.062078000	-1.789070000	0.579361000
C	2.596893000	-1.141038000	-0.564939000
H	1.787398000	-0.921996000	-2.651064000
H	-0.336237000	-2.305807000	-1.711667000
H	0.106586000	-2.830331000	0.904837000
H	2.508847000	-1.816649000	1.568916000
H	3.554184000	-0.626756000	-0.614631000
C	-3.893259000	0.058268000	-0.493665000

C	-4.779008000	-0.321162000	0.480043000
H	-3.970660000	1.073368000	-0.903040000
H	-5.559338000	0.357513000	0.838984000
H	-4.746242000	-1.323498000	0.925338000

2prod. E(UM05/Ahlrichs-VDZ) = -309.667408309 a.u. / (49 cm⁻¹) / ZPVE = 0.144905 a.u.

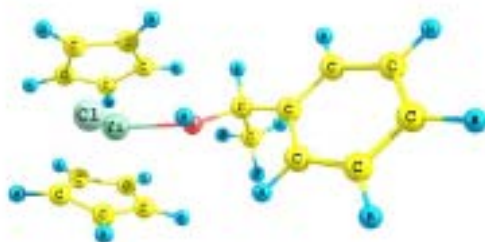


C	-0.465164000	-0.297813000	-0.000146000
C	0.540858000	-1.315242000	-0.000025000
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C	1.896422000	-0.994940000	0.000070000
H	2.642376000	-1.793865000	0.000158000
C	2.310573000	0.350757000	0.000078000
C	1.342390000	1.371242000	0.000004000
H	1.656972000	2.418164000	0.000048000
C	-0.017373000	1.060673000	-0.000122000
H	-0.752066000	1.869145000	-0.000040000
C	-1.842702000	-0.646714000	-0.000351000

S22

C	-2.969845000	0.333075000	0.000111000
H	-2.085270000	-1.715757000	0.000777000
H	3.374329000	0.599908000	0.000147000
H	-2.940947000	1.002399000	-0.882677000
H	-2.947691000	0.993555000	0.889873000
H	-3.945995000	-0.176632000	-0.005985000

2react. E(UM05/Ahlrichs-VDZ) = -2081.3576433 a.u. / (16 cm⁻¹) / ZPVE = 0.337207 a.u.

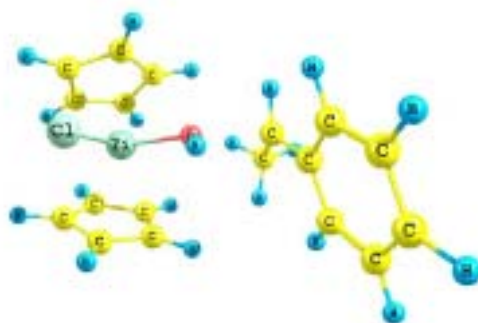


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C	1.609737000	0.660749000	-0.857276000
H	0.818779000	-0.192731000	0.868349000
H	1.463969000	1.747428000	-0.717014000
C	-2.299964000	-1.207148000	-1.852766000
C	-1.243570000	-1.975486000	-1.290715000

C	-1.638711000	-2.398238000	0.003576000
C	-2.967059000	-1.921922000	0.243903000
C	-3.379333000	-1.203539000	-0.914054000
H	-2.305253000	-0.745551000	-2.838802000
H	-0.273248000	-2.154927000	-1.746985000
H	-1.030762000	-2.951869000	0.713142000
H	-3.550770000	-2.094944000	1.145455000
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C	-2.381361000	1.846308000	1.408066000
C	-3.400016000	1.550392000	0.467563000
H	-3.409655000	1.637243000	-1.778937000
H	-0.847232000	2.443292000	-1.529291000
H	-0.251671000	2.465307000	1.133724000
H	-2.450947000	1.742884000	2.487471000
H	-4.411672000	1.227056000	0.704626000
C	2.986927000	0.290931000	-0.344486000

C	3.286863000	-1.030727000	0.032295000
C	3.999151000	1.263354000	-0.280216000
C	4.574446000	-1.370064000	0.466317000
H	2.505105000	-1.794173000	-0.000358000
C	5.289685000	0.923144000	0.145692000
H	3.775690000	2.297516000	-0.559615000
C	5.580145000	-0.395335000	0.520724000
H	4.791350000	-2.398490000	0.764746000
H	6.065847000	1.690706000	0.193273000
H	6.584035000	-0.660917000	0.860341000
C	1.416997000	0.318157000	-2.328884000
H	0.388816000	0.550638000	-2.652346000
H	2.120110000	0.901336000	-2.945715000
H	1.608010000	-0.752441000	-2.507696000

2ts. E(UM05/Ahlrichs-VDZ) = -2081.30718572 a.u. / (623i cm⁻¹) / ZPVE = 0.332613 a.u.

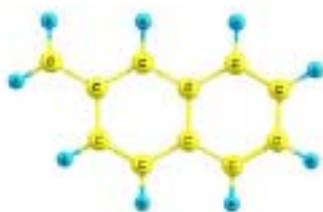


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Cl	1.122356000	-0.855594000	2.419190000
O	-0.381142000	-0.508028000	-0.109648000
C	-1.832388000	-0.528648000	-1.540603000
H	-0.952869000	-0.549463000	0.683153000
H	-1.595297000	-1.576470000	-1.745273000
C	1.366863000	2.165856000	-0.830590000
C	0.386261000	2.199253000	0.209252000
C	1.046718000	2.025641000	1.443339000
C	2.451559000	1.911268000	1.187106000
C	2.649873000	2.053034000	-0.211274000
H	1.180782000	2.296874000	-1.894681000
H	-0.690574000	2.265873000	0.071602000
H	0.577150000	1.929574000	2.417559000

H	3.220229000	1.761617000	1.942290000
H	3.605581000	2.054588000	-0.728327000
C	2.820925000	-0.598103000	-1.746688000
C	1.776577000	-1.558116000	-1.639462000
C	1.934428000	-2.245935000	-0.406381000
C	3.110824000	-1.745841000	0.230723000
C	3.659587000	-0.734023000	-0.595206000
H	2.978724000	0.088633000	-2.576236000
H	0.968494000	-1.709847000	-2.351348000
H	1.259676000	-2.989821000	0.007336000
H	3.481594000	-2.056285000	1.203492000
H	4.557205000	-0.157883000	-0.382731000
C	-3.009788000	-0.314935000	-0.723739000
C	-3.664826000	0.940555000	-0.617666000
C	-3.508549000	-1.389574000	0.062240000
C	-4.767244000	1.104989000	0.224307000
H	-3.316170000	1.791457000	-1.206888000
C	-4.606764000	-1.218012000	0.906793000
H	-3.018085000	-2.365328000	-0.000281000

C	-5.244297000	0.030270000	0.992240000
H	-5.259801000	2.078614000	0.284543000
H	-4.970076000	-2.059509000	1.501459000
H	-6.104889000	0.164673000	1.651447000
C	-1.332766000	0.449123000	-2.547760000
H	-0.267804000	0.269515000	-2.766595000
H	-1.886884000	0.340208000	-3.500958000
H	-1.434600000	1.494851000	-2.220358000

3prod. E(UM05/Ahlrichs-VDZ) = -423.800904062 a.u. / (116 cm⁻¹) / ZPVE = 0.164236 a.u.



C	2.184542000	-0.231630000	-0.000088000
C	1.067675000	-1.108160000	-0.000383000
C	-0.266904000	-0.629665000	-0.000325000
C	-0.504838000	0.789604000	-0.000238000
C	0.626798000	1.672435000	-0.000458000
C	1.911242000	1.190226000	-0.000325000
H	2.757567000	1.882287000	-0.000312000

S28

H	1.240244000	-2.188371000	-0.000473000
C	3.505235000	-0.714562000	0.000581000
H	4.357649000	-0.027765000	0.001011000
H	3.714063000	-1.789138000	0.000698000
H	0.445021000	2.750711000	-0.000599000
C	-1.389785000	-1.510688000	-0.000161000
C	-1.839766000	1.266087000	0.000166000
C	-2.913484000	0.383839000	0.000558000
C	-2.683990000	-1.015273000	0.000354000
H	-1.210882000	-2.589425000	-0.000336000
H	-2.014259000	2.345645000	0.000267000
H	-3.936981000	0.766207000	0.001024000
H	-3.532778000	-1.703438000	0.000632000

3react. E(UM05/Ahlrichs-VDZ) = -2195.49075667 a.u. / (6 cm⁻¹) / ZPVE = 0.356129 a.u.



Ti	2.519859000	0.015508000	0.050504000
Cl	1.809173000	-0.036722000	2.464242000

S29

C	3.136049000	1.645417000	-1.614825000
C	1.807474000	1.911612000	-1.191089000
C	1.849704000	2.238315000	0.197786000
C	3.213262000	2.206351000	0.622410000
C	4.004578000	1.829936000	-0.493994000
H	3.439980000	1.362785000	-2.620646000
H	0.915840000	1.860702000	-1.814038000
H	0.998249000	2.453530000	0.838282000
H	3.564051000	2.388769000	1.635238000
H	5.085146000	1.699434000	-0.496484000
C	4.099301000	-1.174862000	-1.214087000
C	2.830928000	-1.805801000	-1.381789000
C	2.465864000	-2.365082000	-0.115746000
C	3.493488000	-2.077718000	0.817541000
C	4.493882000	-1.316089000	0.152578000
H	4.677506000	-0.686474000	-1.994100000
H	2.275949000	-1.895873000	-2.314326000
H	1.550296000	-2.909978000	0.105555000
H	3.475818000	-2.322070000	1.875912000

H	5.412739000	-0.941577000	0.599713000
C	-4.403407000	-0.661644000	-0.207080000
C	-3.092544000	-1.161116000	-0.459916000
C	-1.998082000	-0.316043000	-0.545506000
C	-2.186480000	1.085929000	-0.357617000
C	-3.441728000	1.600294000	-0.103227000
C	-4.584026000	0.749965000	-0.025111000
C	-5.539367000	-1.518237000	-0.125326000
C	-5.893123000	1.251578000	0.228272000
C	-6.798972000	-1.001787000	0.120797000
C	-6.977745000	0.395959000	0.298439000
H	-2.963101000	-2.240242000	-0.589304000
H	-1.321190000	1.752233000	-0.407175000
H	-3.575551000	2.675430000	0.041856000
C	-0.625528000	-0.852941000	-0.853444000
H	-0.629453000	-1.957589000	-0.849976000
H	-0.282965000	-0.518897000	-1.846664000
O	0.371321000	-0.357883000	0.065789000
H	0.157993000	-0.416268000	1.034969000

H	-5.399508000	-2.594014000	-0.261505000
H	-6.026823000	2.327732000	0.366674000
H	-7.662408000	-1.668428000	0.179976000
H	-7.977146000	0.792745000	0.492128000

3ts. E(UM05/Ahlrichs-VDZ) = -2195.43925331 a.u. / (697i cm⁻¹) / ZPVE = 0.351863 a.u.

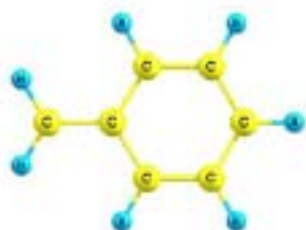


Ti	2.314759000	-0.020170000	0.152395000
Cl	1.992751000	-1.104928000	2.320626000
C	2.060915000	2.179737000	-0.642052000
C	1.033979000	2.045774000	0.343178000
C	1.649029000	1.829227000	1.594214000
C	3.068536000	1.861229000	1.406693000
C	3.319391000	2.130348000	0.035969000
H	1.912975000	2.376305000	-1.702806000
H	-0.036669000	2.039763000	0.151494000
H	1.145205000	1.616868000	2.532422000

H	3.811234000	1.717442000	2.188483000
H	4.295541000	2.256101000	-0.424670000
C	3.808273000	-0.289260000	-1.703191000
C	2.804767000	-1.290944000	-1.797351000
C	2.930328000	-2.148872000	-0.668114000
C	4.039966000	-1.698324000	0.106195000
C	4.577789000	-0.547831000	-0.525456000
H	3.977008000	0.516425000	-2.414743000
H	2.047368000	-1.366192000	-2.574272000
H	2.271845000	-2.973624000	-0.411041000
H	4.369720000	-2.128254000	1.047464000
H	5.428077000	0.032213000	-0.173296000
C	-4.079015000	-0.685915000	-0.212419000
C	-2.831570000	-1.054981000	-0.779235000
C	-1.956907000	-0.103237000	-1.334361000
C	-2.359784000	1.277963000	-1.313386000
C	-3.566375000	1.660243000	-0.774103000
C	-4.462706000	0.700284000	-0.205281000
C	-4.970993000	-1.647005000	0.351231000

C	-5.712421000	1.068329000	0.360198000
C	-6.182148000	-1.257174000	0.895751000
C	-6.557885000	0.111433000	0.901278000
H	-2.550178000	-2.112578000	-0.784650000
H	-1.695031000	2.028247000	-1.751286000
H	-3.860636000	2.713217000	-0.776395000
C	-0.673917000	-0.490667000	-1.846080000
H	-0.510866000	-1.533288000	-2.128402000
H	-0.075855000	0.250951000	-2.383722000
O	0.528184000	-0.657715000	-0.271249000
H	-0.142898000	-0.673433000	0.440997000
H	-4.679615000	-2.700760000	0.347248000
H	-5.999319000	2.123439000	0.362942000
H	-6.854277000	-2.004061000	1.324848000
H	-7.516093000	0.408325000	1.333974000

4prod. E(UM05/Ahlrichs-VDZ) = -270.423582107 a.u. / (205 cm⁻¹) / ZPVE = 0.116375 a.u.



C	2.411443000	-0.000001000	0.000132000
H	2.975914000	0.938025000	0.000313000
H	2.975900000	-0.938029000	0.000026000
C	1.000402000	0.000003000	-0.000130000
C	0.253896000	1.222665000	-0.000364000
C	0.253902000	-1.222659000	-0.000049000
C	-1.138960000	1.216910000	-0.000200000
H	0.797780000	2.171325000	-0.000641000
C	-1.138955000	-1.216912000	0.000272000
H	0.797789000	-2.171317000	-0.000134000
C	-1.847926000	-0.000004000	0.000284000
H	-1.684881000	2.163754000	-0.000369000
H	-1.684869000	-2.163761000	0.000537000
H	-2.940443000	-0.000009000	0.000595000

4react. E(UM05/Ahlrichs-VDZ) = -2042.11502756 a.u. / (4 cm⁻¹) / ZPVE = 0.308330 a.u.

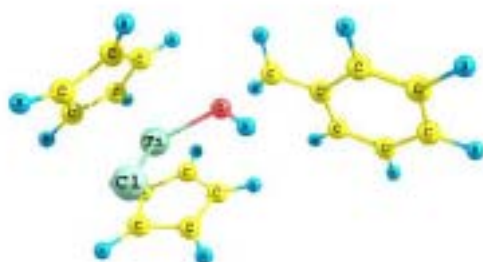


Ti	1.524408000	0.044127000	0.022064000
Cl	0.902565000	0.173228000	2.460574000
C	1.902816000	1.540333000	-1.830023000
C	0.654859000	1.881699000	-1.246120000
C	0.895002000	2.290738000	0.096897000
C	2.304158000	2.237400000	0.335149000
C	2.923246000	1.772285000	-0.855642000
H	2.056793000	1.182750000	-2.846199000
H	-0.318255000	1.810571000	-1.729030000
H	0.145810000	2.573940000	0.831210000
H	2.798138000	2.482278000	1.272331000
H	3.989759000	1.615013000	-1.001806000
C	3.001748000	-1.259253000	-1.274281000
C	1.751154000	-1.936888000	-1.194820000
C	1.559525000	-2.315880000	0.172509000

C	2.686326000	-1.884775000	0.920932000
C	3.567688000	-1.207089000	0.037551000
H	3.455990000	-0.862513000	-2.178791000
H	1.089905000	-2.164479000	-2.029308000
H	0.698328000	-2.839956000	0.581540000
H	2.806358000	-1.981865000	1.996268000
H	4.518334000	-0.752849000	0.309497000
C	-5.405947000	-0.888141000	-0.252159000
C	-4.104477000	-1.342909000	-0.501186000
C	-3.006518000	-0.474387000	-0.375663000
C	-3.232698000	0.857443000	0.016041000
C	-4.532533000	1.310612000	0.273446000
C	-5.622931000	0.440533000	0.136357000
H	-3.941231000	-2.385180000	-0.791425000
H	-2.384463000	1.537254000	0.131655000
H	-4.693563000	2.346033000	0.582686000
C	-1.615404000	-0.962603000	-0.694122000
H	-1.566197000	-2.064638000	-0.621559000
H	-1.324949000	-0.683201000	-1.721274000

O	-0.612124000	-0.366796000	0.149491000
H	-0.784162000	-0.368686000	1.128546000
H	-6.249595000	-1.575184000	-0.352451000
H	-6.636660000	0.794706000	0.337825000

4ts. E(UM05/Ahlrichs-VDZ) = -2042.0624215 a.u. / (683i cm⁻¹) / ZPVE = 0.304015 a.u.

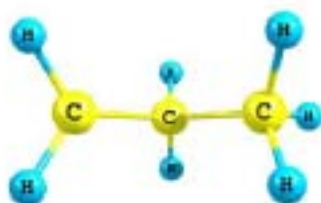


Ti	1.415291000	0.036074000	0.069476000
Cl	1.379701000	-0.321414000	2.492030000
C	1.055606000	1.888979000	-1.341623000
C	0.097586000	2.055179000	-0.295301000
C	0.795859000	2.226797000	0.918848000
C	2.199765000	2.212963000	0.633414000
C	2.356199000	2.053222000	-0.767202000
H	0.835733000	1.753831000	-2.399355000
H	-0.982533000	1.983867000	-0.401981000
H	0.358983000	2.304153000	1.909953000

H	2.993552000	2.314682000	1.370172000
H	3.297661000	2.036901000	-1.309765000
C	2.721257000	-0.779320000	-1.770400000
C	1.726589000	-1.747503000	-1.465468000
C	1.982973000	-2.245575000	-0.155685000
C	3.157777000	-1.605965000	0.336530000
C	3.609618000	-0.695045000	-0.653226000
H	2.804010000	-0.217029000	-2.698169000
H	0.895648000	-2.034248000	-2.106212000
H	1.367552000	-2.950961000	0.395157000
H	3.588639000	-1.748031000	1.323309000
H	4.481814000	-0.049848000	-0.572690000
C	-4.883968000	-0.970815000	0.815067000
C	-3.712922000	-1.406236000	0.192384000
C	-3.015695000	-0.567474000	-0.720696000
C	-3.549134000	0.726211000	-0.975970000
C	-4.723449000	1.153271000	-0.354230000
C	-5.396637000	0.309627000	0.546406000
H	-3.320594000	-2.405037000	0.404210000

H	-3.036586000	1.385561000	-1.682834000
H	-5.121162000	2.147784000	-0.570724000
C	-1.777344000	-1.000479000	-1.309198000
H	-1.558598000	-2.069886000	-1.350710000
H	-1.321720000	-0.385283000	-2.090963000
O	-0.382223000	-0.696604000	0.086536000
H	-0.961754000	-0.486600000	0.846772000
H	-5.404468000	-1.630953000	1.513108000
H	-6.314205000	0.647313000	1.033551000

5prod. E(UM05/Ahlrichs-VDZ) = -118.235153895 a.u. / (38 cm⁻¹) / ZPVE = 0.089354 a.u.



C	-1.323463000	-0.240423000	0.002960000
H	-1.807268000	-0.515427000	0.948273000
H	-1.715466000	-0.693438000	-0.916433000
C	-0.069045000	0.566698000	-0.017570000
C	1.220016000	-0.283783000	0.012727000
H	-0.051446000	1.259068000	0.844248000

S40

H	-0.043343000	1.199431000	-0.925339000
H	2.116048000	0.361794000	-0.010481000
H	1.268299000	-0.901783000	0.926309000
H	1.268124000	-0.964595000	-0.855275000

$\epsilon_{\text{reac.}}$ E(UM05/Ahlrichs-VDZ) = -1889.95058967 a.u. / (4 cm⁻¹) / ZPVE = 0.283029 a.u.

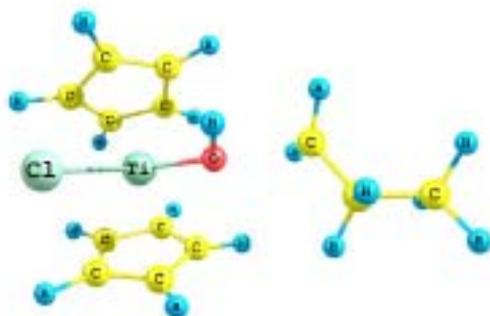


Ti	0.706423000	0.029978000	0.007984000
Cl	0.422952000	-0.073488000	2.514848000
O	-1.378467000	-0.424808000	0.384636000
C	-2.584877000	-0.702903000	-0.352364000
H	-1.425035000	-0.470891000	1.375556000
H	-2.352808000	-0.462338000	-1.402043000
H	-2.810385000	-1.785196000	-0.294772000
C	-0.048765000	1.806322000	-1.308730000
C	-0.179025000	2.211570000	0.057861000

C	1.122025000	2.334328000	0.615938000
C	2.064028000	1.976967000	-0.384247000
C	1.343084000	1.667971000	-1.579123000
H	-0.859423000	1.668442000	-2.023019000
H	-1.110374000	2.381584000	0.593074000
H	1.346087000	2.578291000	1.650915000
H	3.145512000	1.960784000	-0.264682000
H	1.784193000	1.390611000	-2.533525000
C	1.509149000	-1.384307000	-1.774516000
C	0.568151000	-2.133924000	-1.020664000
C	1.068392000	-2.261301000	0.306588000
C	2.344390000	-1.617811000	0.366283000
C	2.613578000	-1.077442000	-0.919393000
H	1.416214000	-1.111815000	-2.823733000
H	-0.382177000	-2.518737000	-1.386954000
H	0.568178000	-2.741541000	1.143480000
H	2.971990000	-1.537347000	1.250634000
H	3.504265000	-0.522630000	-1.206027000
C	-3.762377000	0.122228000	0.147792000

C	-5.045479000	-0.152960000	-0.634292000
H	-3.497920000	1.192817000	0.084301000
H	-3.923454000	-0.096643000	1.220086000
H	-5.882038000	0.451025000	-0.245286000
H	-4.927403000	0.094032000	-1.704398000
H	-5.342829000	-1.214630000	-0.565559000

5ts. E(UM05/Ahlrichs-VDZ) = -1889.88014427 a.u. / (505i cm⁻¹) / ZPVE = 0.277385 a.u.



Ti	0.665763000	0.032436000	0.028526000
Cl	1.374527000	0.157879000	2.368671000
O	-1.095468000	-0.358852000	0.696472000
C	-2.896194000	-0.912696000	-0.247038000
H	-1.171352000	-0.951849000	1.469610000
H	-2.554217000	-0.721005000	-1.270981000
H	-2.925319000	-1.972786000	0.041940000

C	-0.542806000	1.767949000	-1.047883000
C	-0.140663000	2.246786000	0.231825000
C	1.280002000	2.354335000	0.234801000
C	1.756963000	1.916605000	-1.028576000
C	0.627551000	1.551435000	-1.825095000
H	-1.565373000	1.569142000	-1.360223000
H	-0.794325000	2.444261000	1.076495000
H	1.890110000	2.656572000	1.080835000
H	2.800053000	1.875569000	-1.334393000
H	0.657875000	1.191675000	-2.851328000
C	0.875208000	-1.565542000	-1.700653000
C	0.489455000	-2.325632000	-0.556407000
C	1.505650000	-2.204735000	0.416492000
C	2.561555000	-1.409170000	-0.137887000
C	2.189618000	-1.052086000	-1.457228000
H	0.310215000	-1.470604000	-2.625990000
H	-0.458772000	-2.843733000	-0.432390000
H	1.489813000	-2.604404000	1.426490000
H	3.476956000	-1.131208000	0.379092000

H	2.784278000	-0.470621000	-2.156896000
C	-3.859044000	0.032755000	0.389794000
C	-5.309413000	-0.148813000	-0.095010000
H	-3.534013000	1.070271000	0.195503000
H	-3.826676000	-0.095598000	1.487252000
H	-5.979548000	0.570702000	0.407299000
H	-5.394039000	0.014879000	-1.183752000
H	-5.682952000	-1.165127000	0.121887000

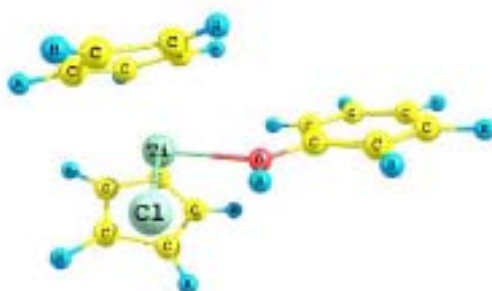
$\epsilon_{\text{prod.}}$ E(UM05/Ahlrichs-VDZ) = -231.141931752 a.u. / (408 cm^{-1}) / ZPVE = 0.088812 a.u.



C	0.000000000	0.000000000	1.410155000
C	0.000000000	1.231036000	0.774398000
C	0.000000000	-1.231036000	0.774398000
C	0.000000000	1.219876000	-0.635751000
H	0.000000000	2.174527000	1.327045000

C	0.000000000	-1.219876000	-0.635751000
H	0.000000000	-2.174527000	1.327045000
C	0.000000000	0.000000000	-1.330905000
H	0.000000000	2.165569000	-1.184873000
H	0.000000000	-2.165569000	-1.184873000
H	0.000000000	0.000000000	-2.423611000

6reac. E(UM05/Ahlrichs-VDZ) = -2002.8814114 a.u. / (6 cm⁻¹) / ZPVE = 0.279397 a.u.



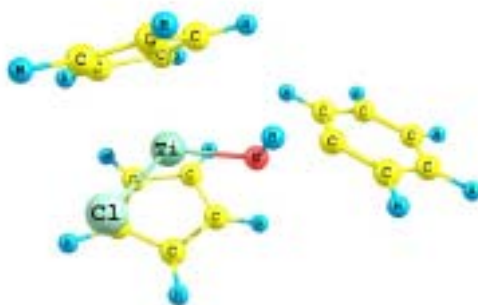
Ti	-1.155932000	-0.006428000	0.010506000
Cl	-1.161216000	-2.034510000	-1.520662000
C	-2.666498000	-0.590432000	1.772375000
C	-1.793914000	0.443884000	2.236173000
C	-0.463419000	-0.062940000	2.239558000
C	-0.521586000	-1.417095000	1.778803000
C	-1.880181000	-1.744679000	1.518717000
H	-2.098827000	1.440191000	2.547745000

S46

H	0.429342000	0.465246000	2.568707000
H	0.325755000	-2.086882000	1.649621000
H	-2.237562000	-2.687363000	1.113388000
H	-3.745624000	-0.515457000	1.653513000
C	-2.640071000	0.914855000	-1.548111000
C	-2.750893000	1.711530000	-0.376837000
C	-1.496469000	2.363231000	-0.157952000
C	-0.620096000	1.987546000	-1.209967000
C	-1.312200000	1.076066000	-2.055648000
H	-3.636331000	1.810840000	0.247112000
H	-1.262981000	3.044782000	0.657741000
H	0.412591000	2.309026000	-1.330264000
H	-0.906207000	0.570285000	-2.927029000
H	-3.409731000	0.277278000	-1.976500000
C	4.933482000	0.460054000	0.340197000
C	4.624103000	-0.697951000	-0.386517000
C	3.294340000	-1.010374000	-0.694399000
C	2.269852000	-0.152174000	-0.269936000
C	2.564146000	1.010076000	0.454917000

C	3.898595000	1.308820000	0.757253000
H	5.971809000	0.699000000	0.578825000
H	4.128632000	2.214990000	1.322573000
H	1.754983000	1.667960000	0.773654000
H	3.051421000	-1.913635000	-1.259876000
H	5.420945000	-1.367672000	-0.717982000
O	0.946672000	-0.444015000	-0.567448000
H	0.764422000	-1.250889000	-1.133293000

6ts. E(UM05/Ahlrichs-VDZ) = -2002.79311832 a.u. / (437i cm⁻¹) / ZPVE = 0.274919 a.u.



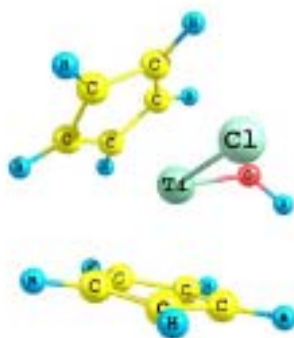
Ti	1.142442000	-0.036634000	-0.024518000
Cl	2.352271000	-0.997982000	-1.908009000
C	2.493317000	1.744780000	0.854463000
C	1.115190000	2.090850000	1.049310000
C	0.530624000	2.285067000	-0.231184000
C	1.512860000	1.985057000	-1.212529000

S48

C	2.736377000	1.682094000	-0.537548000
H	0.623990000	2.239245000	2.008633000
H	-0.508766000	2.543374000	-0.423410000
H	1.381363000	1.995012000	-2.291897000
H	3.667437000	1.397678000	-1.018667000
H	3.229059000	1.578165000	1.636441000
C	2.212627000	-1.801239000	1.153131000
C	1.786541000	-0.853314000	2.118411000
C	0.356392000	-0.795910000	2.078580000
C	-0.092139000	-1.777064000	1.148321000
C	1.043750000	-2.368481000	0.550030000
H	2.428361000	-0.274268000	2.776433000
H	-0.278712000	-0.178417000	2.710442000
H	-1.125325000	-1.959445000	0.865847000
H	1.040873000	-3.089135000	-0.262391000
H	3.239398000	-2.048826000	0.894466000
C	-5.100767000	0.135662000	0.213219000
C	-4.712412000	-0.582277000	-0.929831000
C	-3.357023000	-0.627618000	-1.308204000

C	-2.449804000	0.066622000	-0.521884000
C	-2.785891000	0.775696000	0.620871000
C	-4.145074000	0.810581000	0.989318000
H	-6.153513000	0.164289000	0.503935000
H	-4.454358000	1.363680000	1.880815000
H	-2.027819000	1.290070000	1.219832000
H	-3.032745000	-1.196174000	-2.184441000
H	-5.461514000	-1.111657000	-1.525286000
O	-0.500856000	-0.219808000	-1.015240000
H	-0.550608000	0.193494000	-1.900111000

(TiCp₂ClOH). E(UM05/Ahlrichs-VDZ) = -1771.6588927 a.u. / (38 cm⁻¹) / ZPVE = 0.185620 a.u.



Ti	-0.002442000	0.035201000	0.228339000
Cl	-0.012950000	2.386425000	-0.280607000
O	0.043503000	0.227126000	2.060855000

H	-0.712286000	0.406188000	2.648226000
C	-1.436079000	-1.758281000	-0.370822000
C	-1.974955000	-1.172128000	0.803142000
C	-2.361133000	0.163953000	0.488413000
C	-2.124608000	0.377205000	-0.899343000
C	-1.525781000	-0.792371000	-1.427154000
H	-1.057071000	-2.772916000	-0.463137000
H	-2.024540000	-1.646307000	1.780899000
H	-2.778823000	0.899208000	1.172811000
H	-2.296001000	1.305869000	-1.434527000
H	-1.223771000	-0.940784000	-2.460777000
C	1.579995000	-1.717793000	0.089583000
C	2.216277000	-0.729248000	0.891125000
C	2.370838000	0.435900000	0.107692000
C	1.908494000	0.147111000	-1.219374000
C	1.447963000	-1.189443000	-1.238474000
H	1.323483000	-2.726176000	0.406995000
H	2.403387000	-0.802904000	1.958097000
H	2.739682000	1.398368000	0.450795000

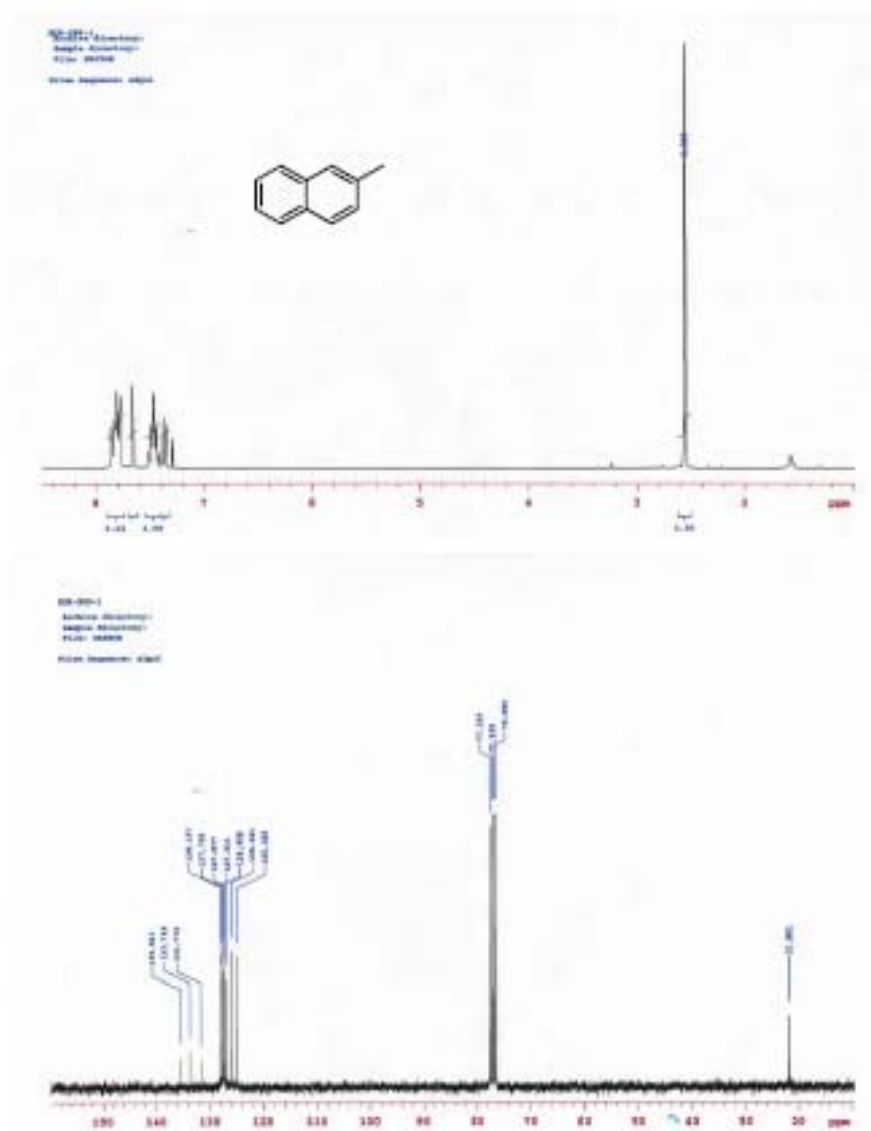
H 1.891142000 0.850965000 -2.047416000

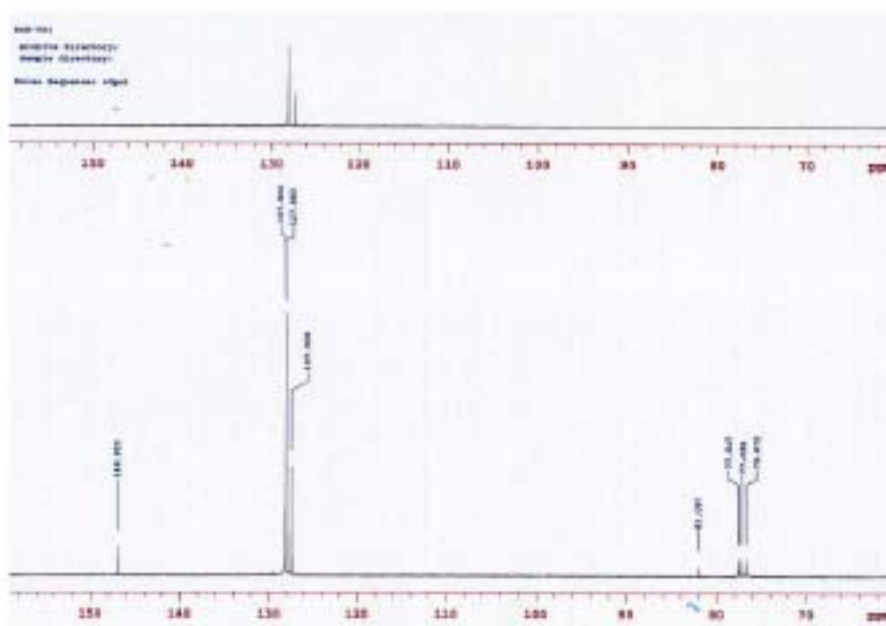
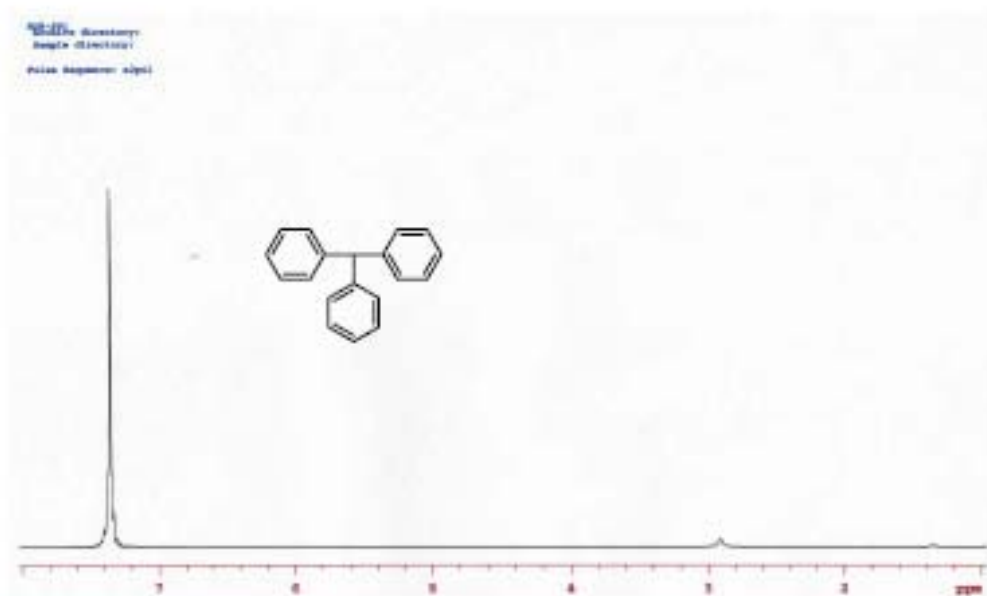
H 1.054606000 -1.721604000 -2.100672000

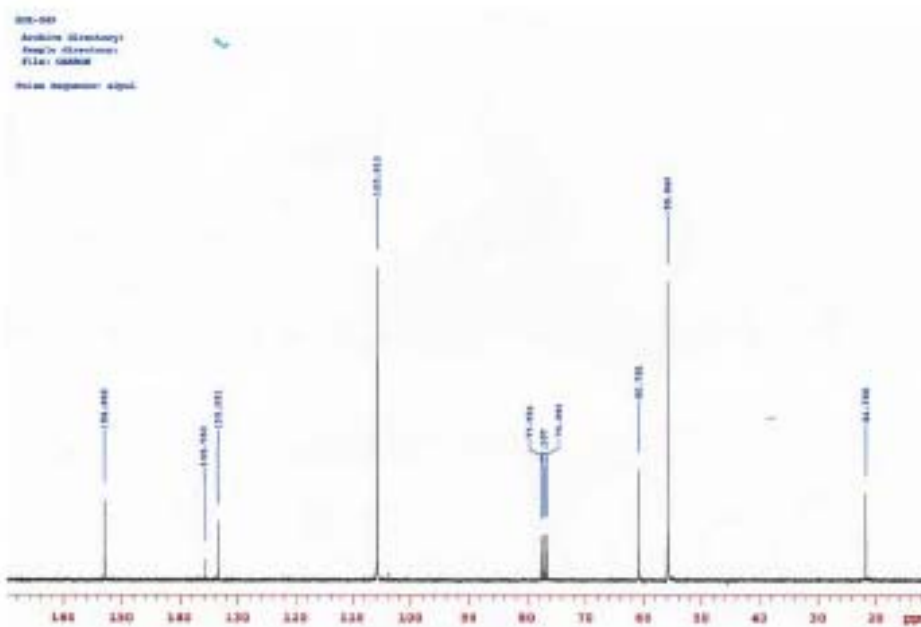
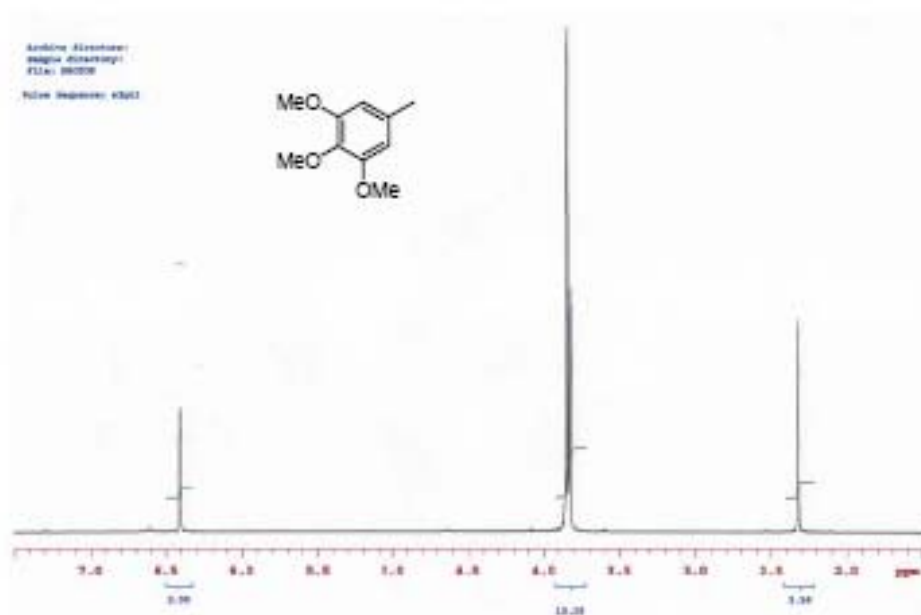
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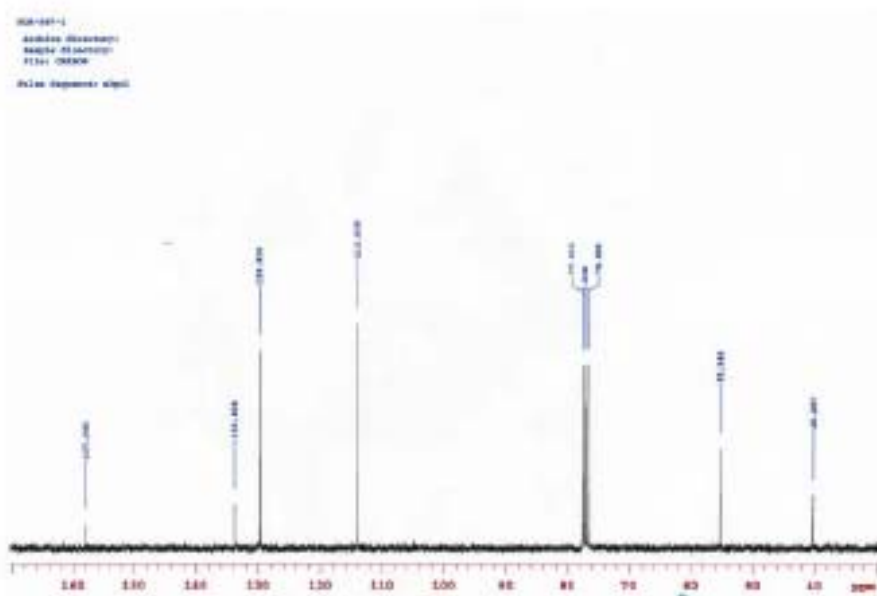
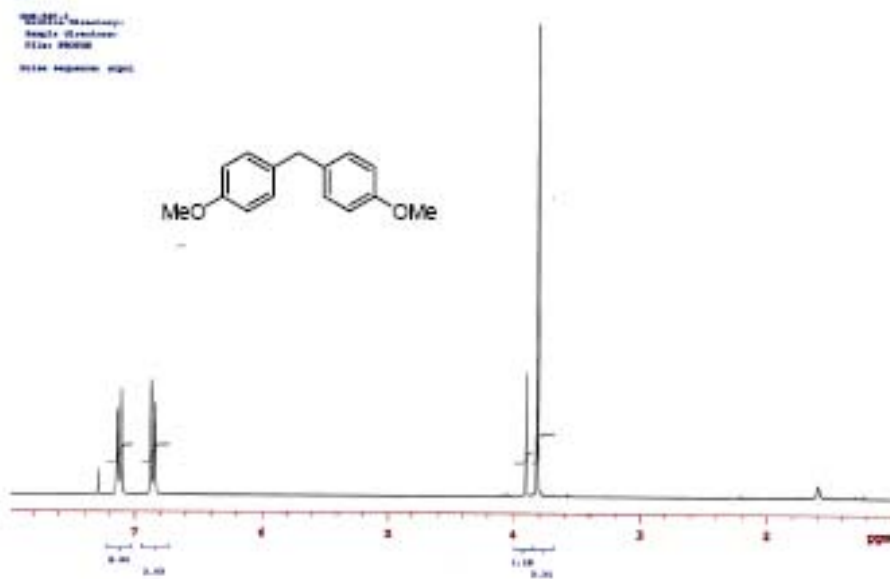
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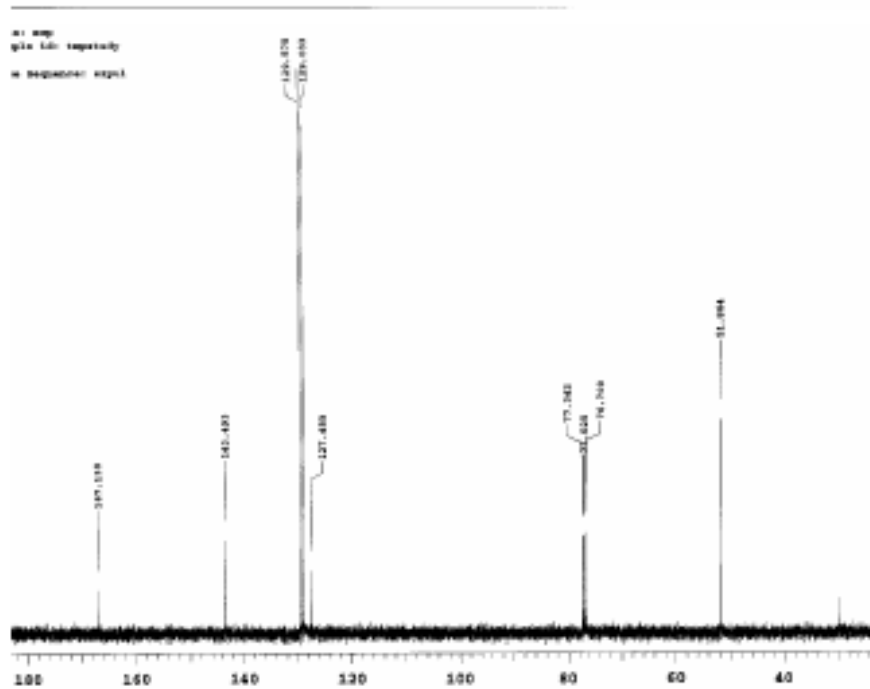
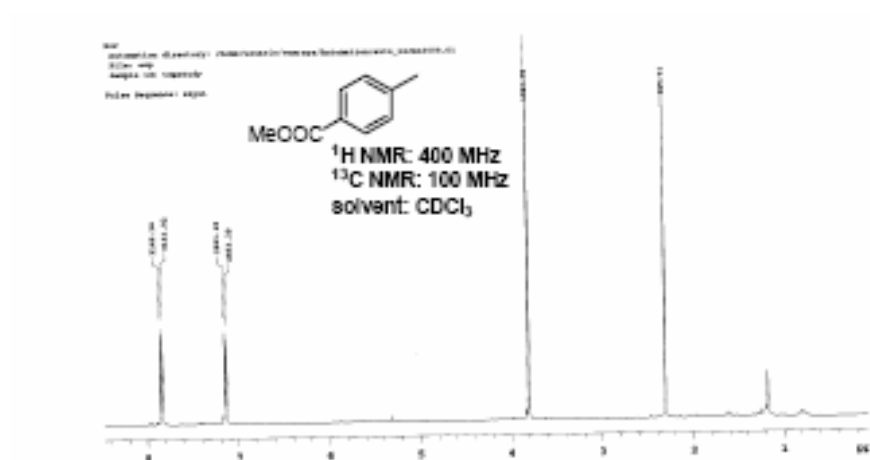
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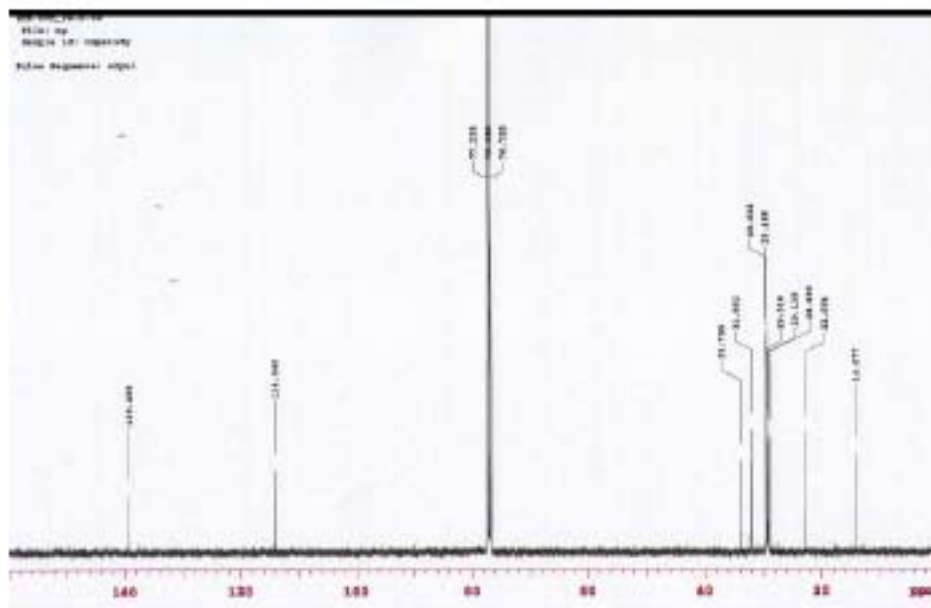
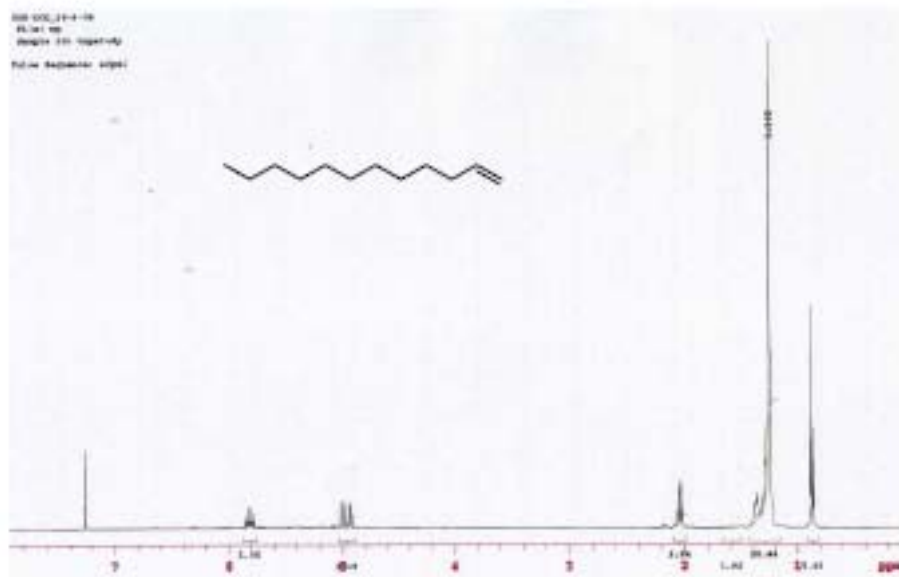


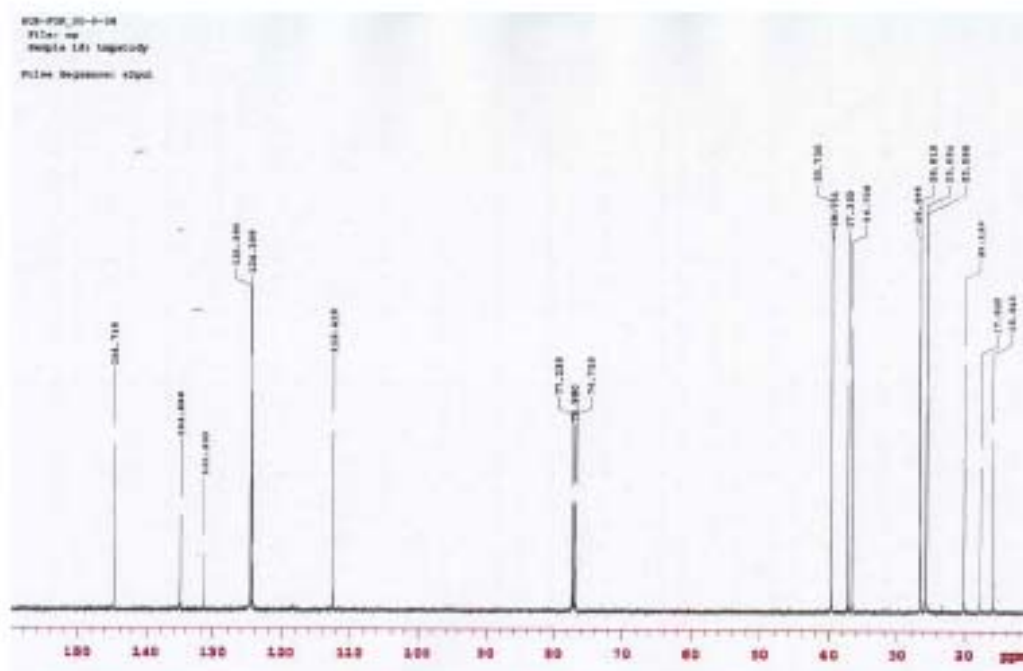
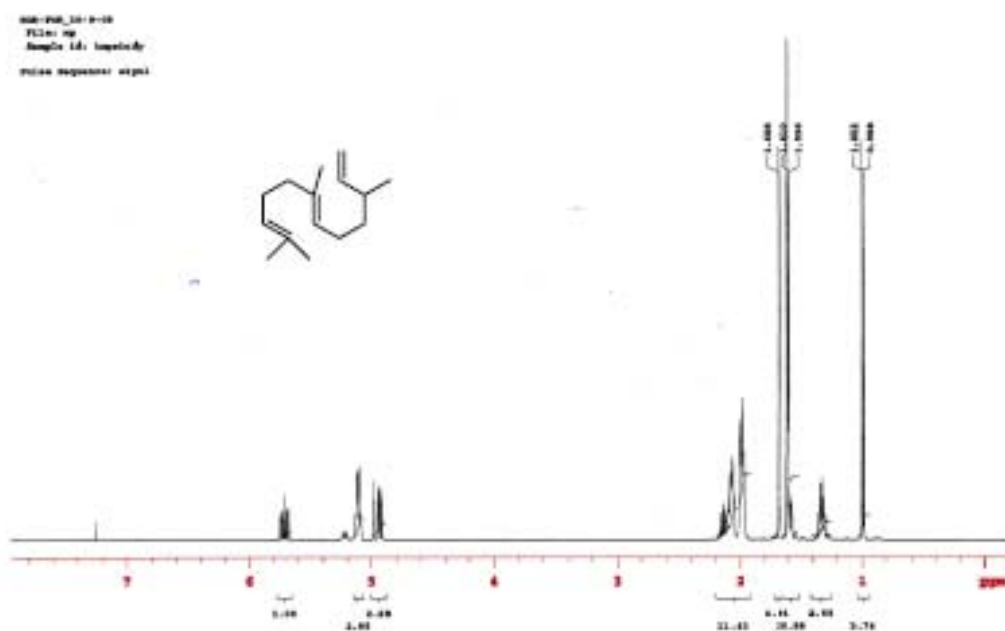


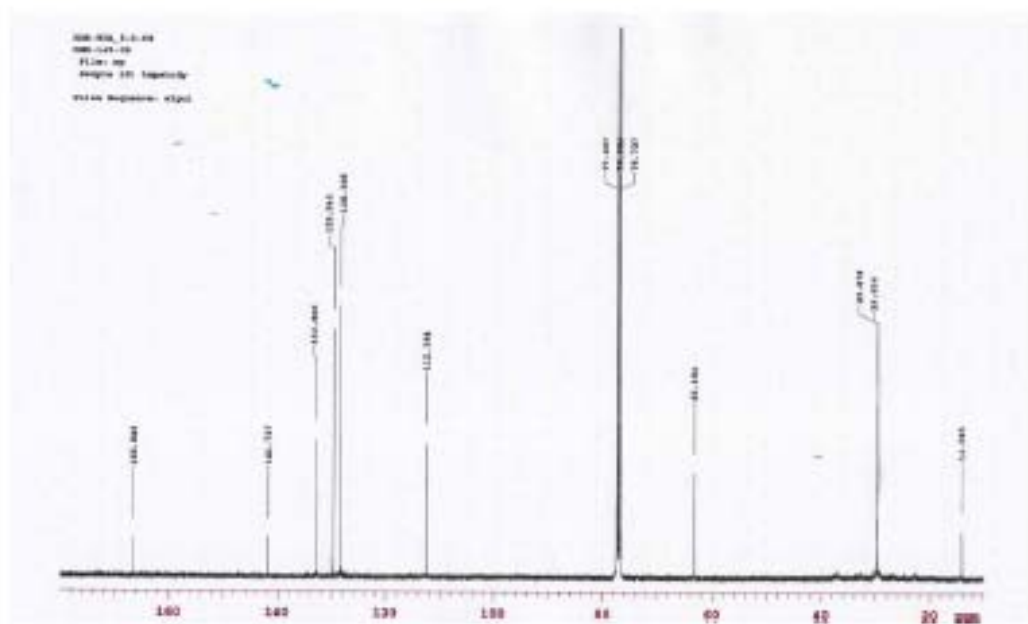
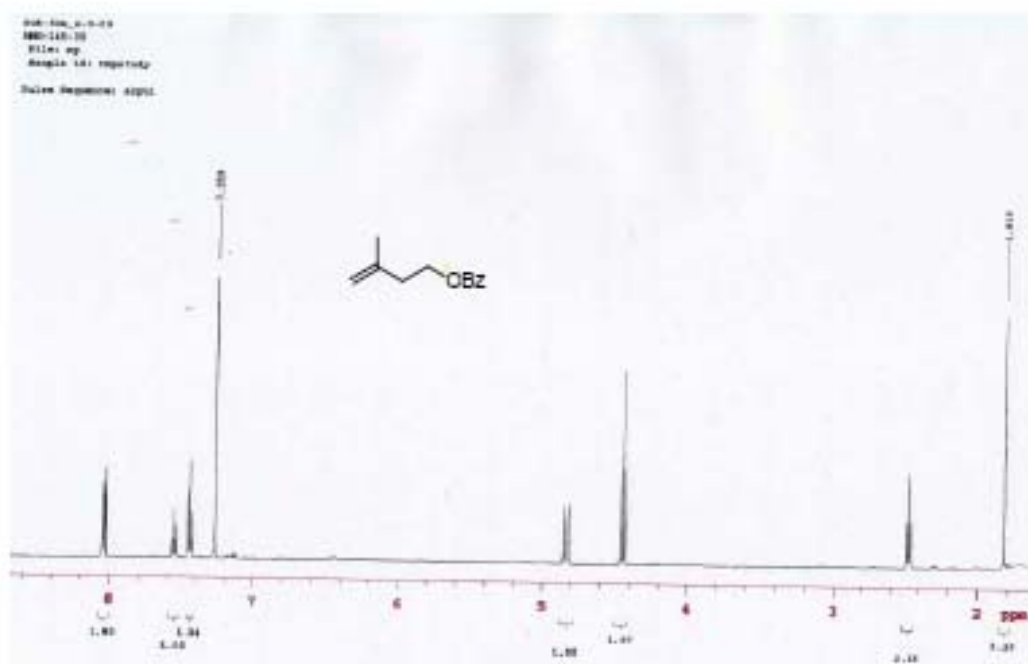


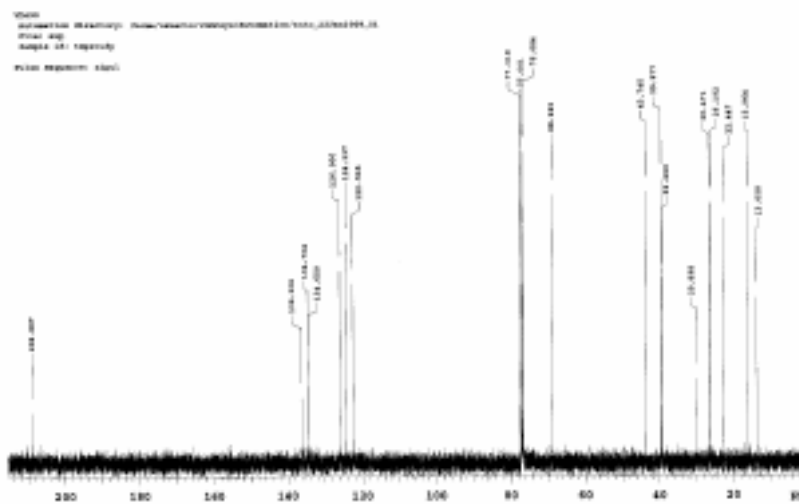
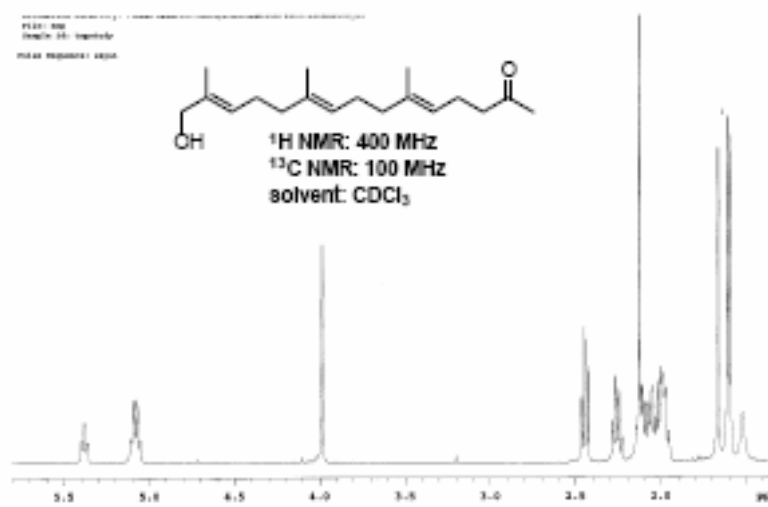


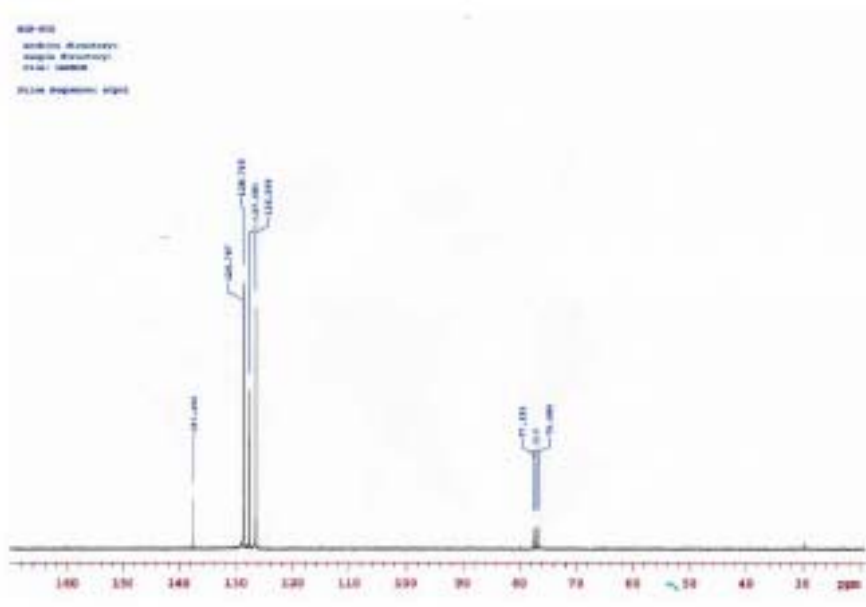
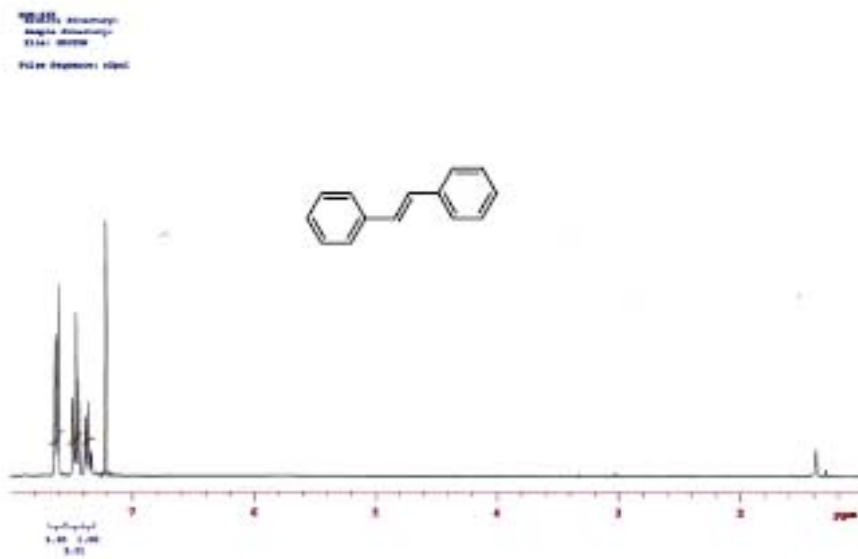


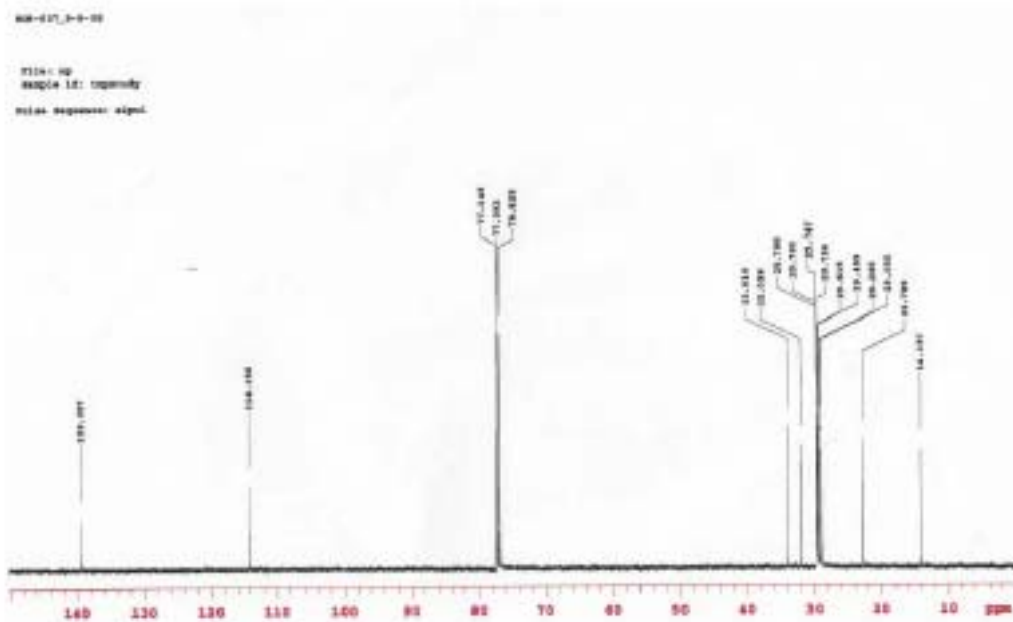
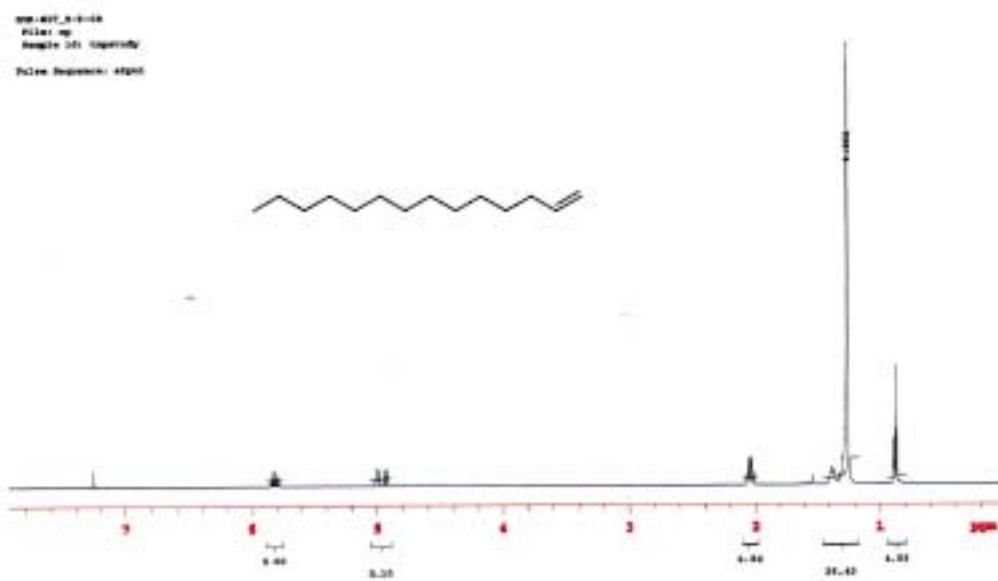


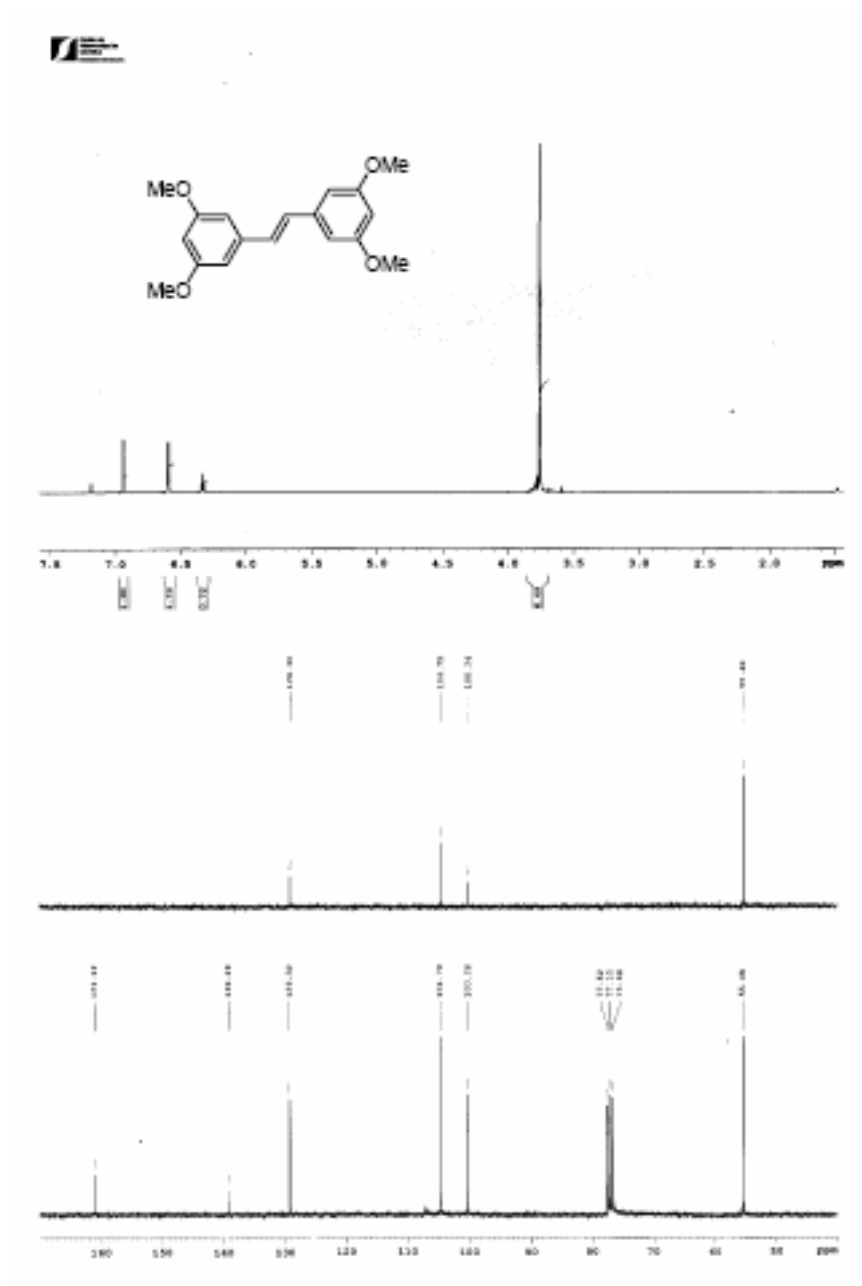


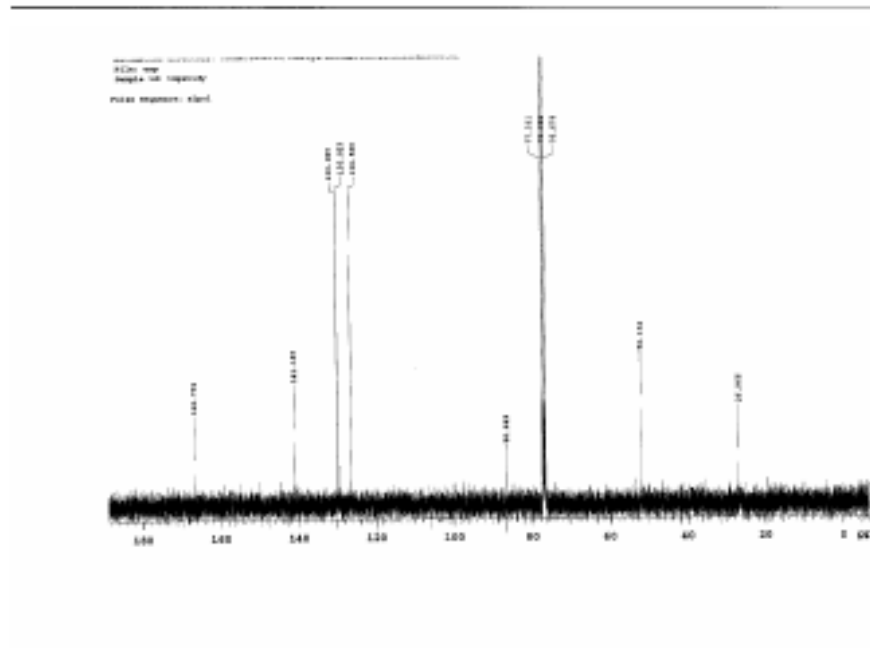
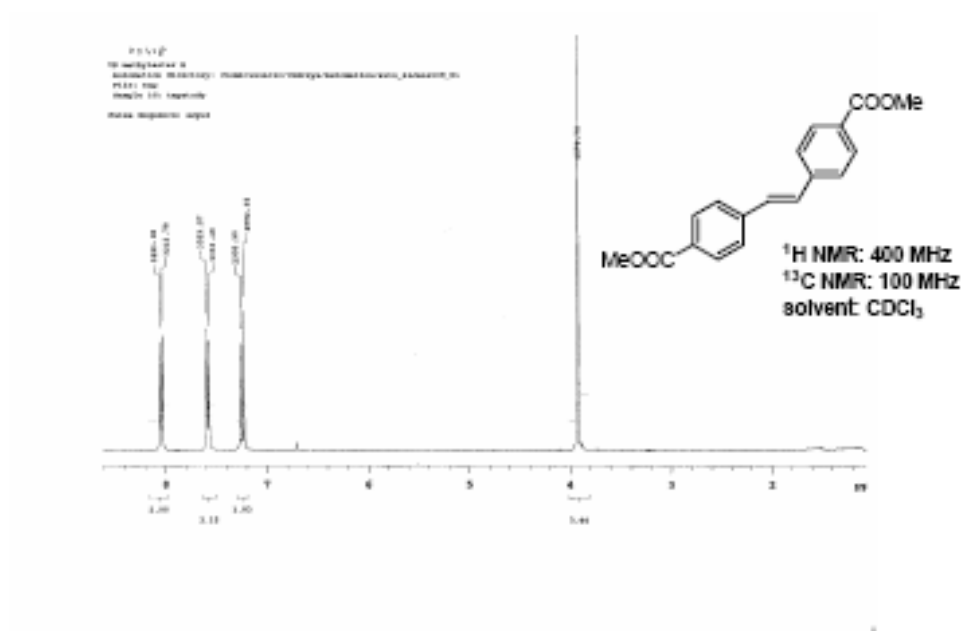


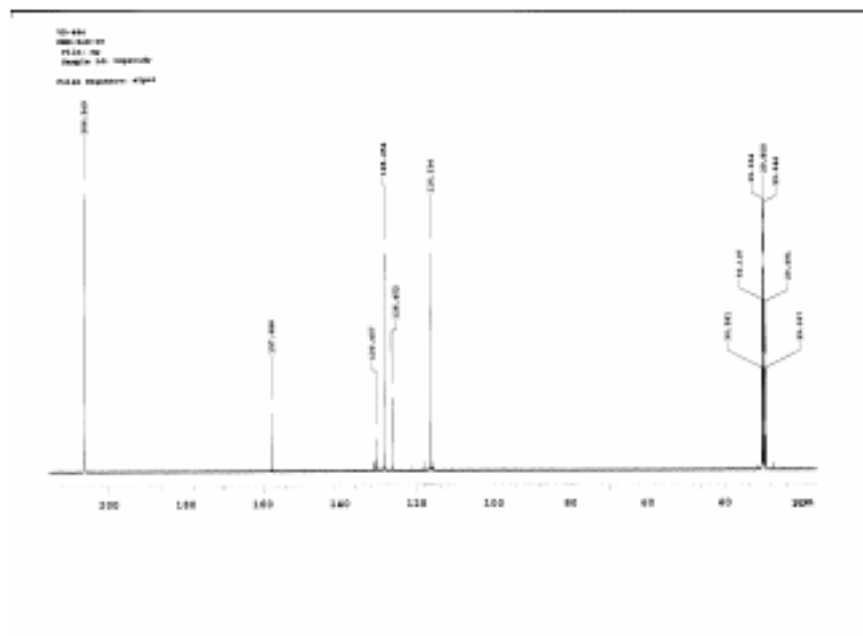
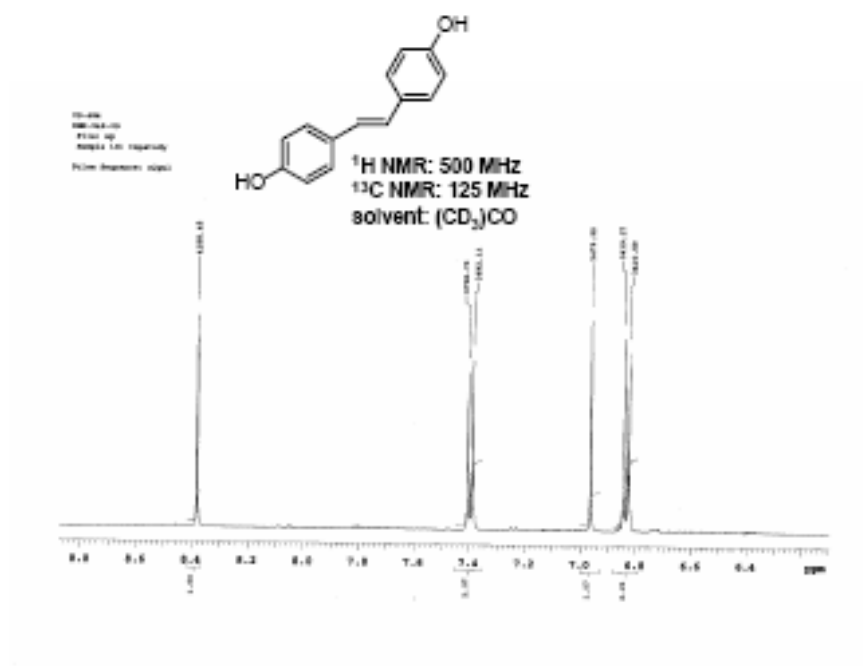


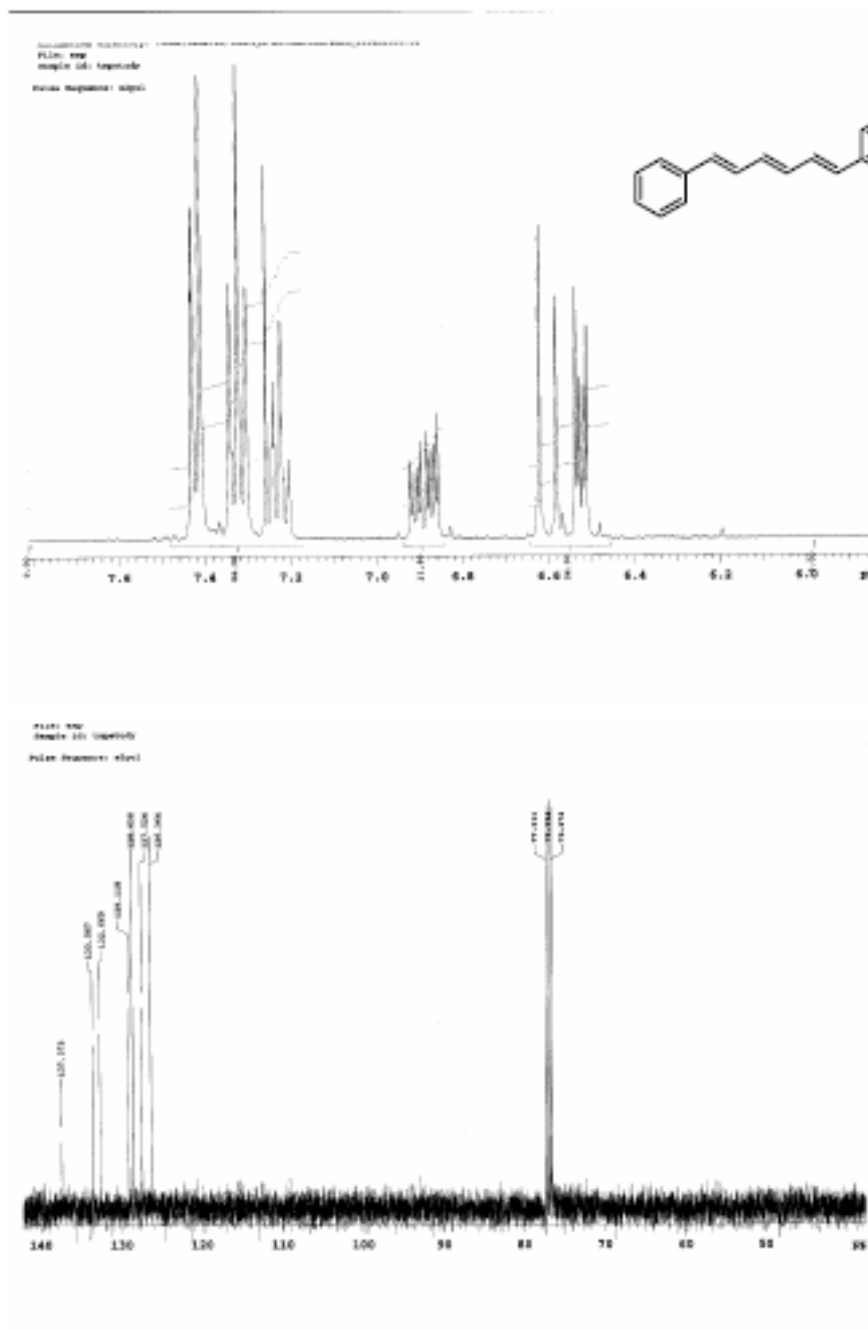


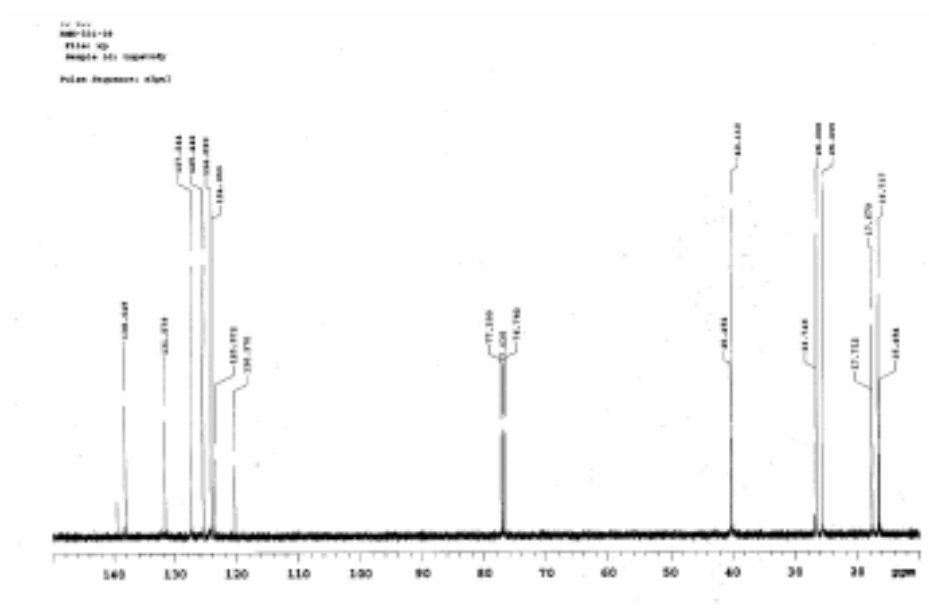
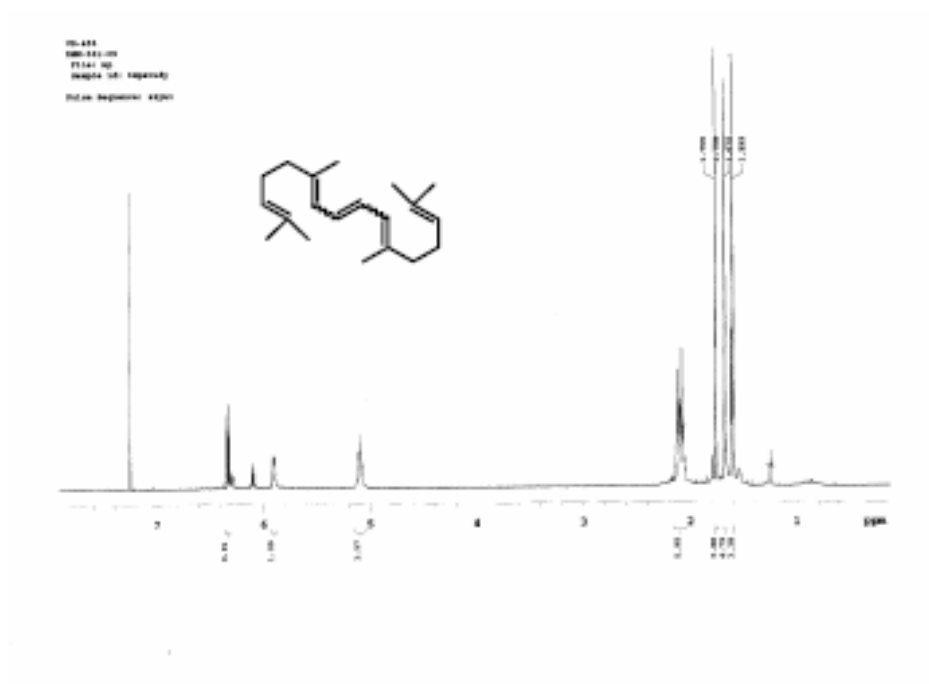


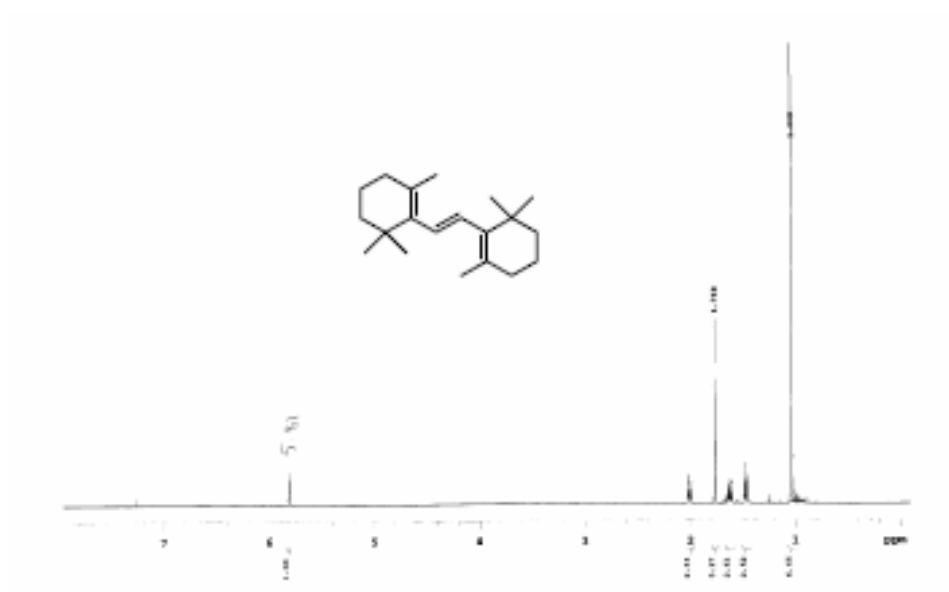












Integración del espectro
Pulse Program: zgpg30

