SÍNTESIS DE (+)-LIPHAGAL Y MEROSESQUITERPENOS RELACIONADOS: BÚSQUEDA DE MOLÉCULAS CON POTENTE ACTIVIDAD ANTITUMORAL

Tesis Doctoral

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Tesis doctoral para aspirar al grado de doctora internacional

presentada por

María José Cano Úbeda

Bajo la dirección de los Doctores

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Granada, 2012

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Memoria presentada por **María José Cano Úbeda** para optar al Grado de Doctora Internacional.

Granada a 26 de Octubre de 2012

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“When life gives you lemons, make lemonade…”

Elbert Hubbard

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ABREVIATURAS/ABBREVIATIONS

ABREVIATURAS

AIBN: 2,2´- Azobisisobutironitrilo.

AMCPB: Ácido *meta*-cloroperbenzoico.

APTS: Ácido p-toluensulfónico.

aq. sol.: Disolución acuosa.

CAN: Nitrato de amonio y cerio.

Conc.: Concentrado.

DBU: Diazabiciclo [5, 4, 0]-undec-7-eno.

DCC: Diciclohexil carbodiimida.

DCM: Diclorometano.

DDQ: 2,3-dicloro-5,6-diciano-p-benzoquinona.

DMAP: 4-dimetilaminopiridina.

DMAD: Dimetilacetilendicarboxilato.

DMF: Dimetilformamida.

DMSO: Dimetilsulfóxido.

dr: Proporción de la mezcla diastereomérica.

ee: Exceso enantiomérico.

equiv.: Equivalente.

HMPA: Hexametilfosforamida.

IBX: Ácido *orto*-iodoxibenzoico.

IGF: Interconversión de grupos funcionales.

LDA: Diisopropilamiduro de litio.

NBS: *N*-bromosuccinimida.

NIS: N-iodosuccinimida.

NP HPLC: Cromatografía de líquidos de alta resolución en fase normal.

PCC: Clorocromato de piridinio.

PDC: Dicromato de piridinio.

PI3K: Fosfoinositol-3-quinasa.

PKC: Fosfoquinasa C.

Py: Piridina.

sat.: Saturado/a.

sem: Semanas.

t.a.: Temperatura ambiente.

TBAF: Fluoruro de tetrabutilamonio.

TBDMS-Cl: Cloruro de *terct*-butildimetilsililo.

TFA: Ácido trifluoroacético.

THF: Tetrahidrofurano.

ABBREVIATIONS

AIBN: 2,2´-Azobisisobutyronitrile.

aq. sol.: Aqueous solution.

CAN: Cerium Ammonium Nitrate.

Conc.: Concentrated.

DBU: Diazabycicle [5, 4, 0]-undec-7-ene.

DCC: Dicyclohexylcarbodiimide.

DCM: Dichlorometane.

DDQ: 2,3-dichloro-5,6-dicyane-p-benzoquinone.

DMAD: Dimethylacetylidenedicarboxylate.

DMAP: 4-dimethyaminopyridine

DMF: Dimethylformamide.

DMSO: Dimethyl sulphoxide.

dr: Diastereomeric ratio.

ee: enantiomeric excess.

equiv.: equivalent.

FGI: Functional groups interconversion.

HMPA: Hexamethylfosforamide.

IBX: *Ortho*-iodoxybenzoic acid.

LDA: Lithium diisopropilamidure.

MCPBA: *Meta*-chloroperbenzoic acid.

NBS: N-bromosuccinimide.

NIS: N-iodosuccinimide

NP HPLC: Normal phase High-performance liquid chromatography.

PCC: Pyridinium chlorochromate.

PDC: Pyridinium dichromate.

PI3K: Phosphoinositide-3-kinase.

PKC: Phosphokinase C.

PTSA: P-toluensulphonic acid.

Py: Pyridine.

rt: Room temperature.

sat.: saturated.

TBAF: Tetrabutylammonium fluoride.

TBS-Cl: *t*ert-butyldimethylsilyl chloride.

TFA: Trifluoroacetic acid.

THF: Tetrahydrofurane.

TMANO: Trimethylamine N-oxide.

TMEDA: Tetramethylenediamine.

wks: weeks.

ABSTRACT

SYNTHESIS OF (+)-LIPHAGAL AND RELATED MEROSESQUITERPENES: SEARCHING FOR MOLECULES WITH POTENT ANTITUMOR ACTIVITY

INTRODUCTION

During the last decades, a wide variety of merosesquiterpenes, characterized by its broad and potent biological activities, have been isolated from different natural sources[1].

Even though they are very valuable natural products, their scarce occurrence in nature, in most of the cases, implies a considerable limitation in order to study their biological properties and therefore, in the search of their potential applications in medicine. This fact has motivated a number of researchers over the years to develop efficient methods to synthesize these marine metabolites.

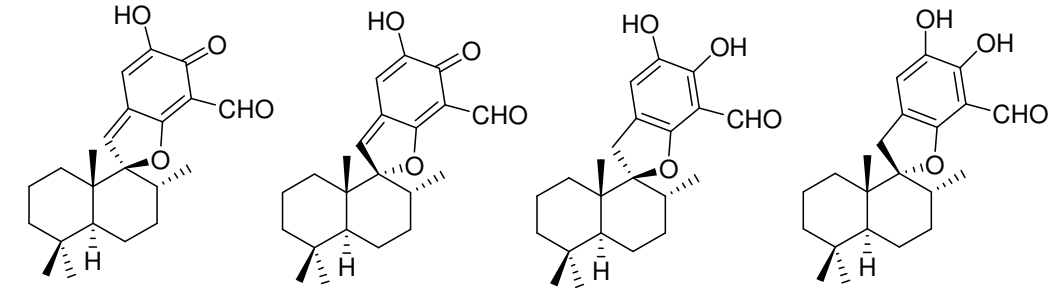
In this thesis, we focused our attention on the synthesis of merosesquiterpenes showing potent antitumor activity. Thus, we chose (+)-liphagal (**21**) and both structurally and biologically related spirodihydrobenzofuran compounds. **1-4**.

Some of the most representative examples of such spiroderivative products are spirosesquiterpene aldehydes corallidictyal A-D (**1-4**), isolated from the marine sponge *Aka coralliphaga*, with protein kinase C inhibitory activity[2]. Other structurally related metabolites are, the widely studied, complement inhibitor K-

[1] For a recent review on marine natural products, see: Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod.Rep.* **2010**, *27*, 165.

[2] (a) Chan, J. A.; Freyer, A. J.; Carte, B. K.; Hemling, M. E.; Hofmann, G. A.; Mattern, M. R.; Mentzer, M. A.; Westley, J. W. *J. Nat. Prod.* **1994**, *57*, 1543. (b) Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Köck, M. *J. Nat. Prod.* **2007**, *70*, 504.

76 (**5**),[3] the antiviral stachybotrydial (**6**)[4] and the myo-Inositol Monophosphatase (IMPase) inhibitor named L-671,776 (**7**).[5] A variety of spirodihydrobenzofuranlactams have been isolated from the cultures of different *Stachybotrys* fungus species. In 1994, Endo et al. reported the isolation of compounds **8-13**, with pancreatic cholesterol esterase inhibitory activity,[6] and therefore considered as potential agents for the treatment and/or prevention of hypercholesterolemia and atherosclerosis[7]. Roggo`s group described two years later the isolation of lactams **14-17**, antagonists of endothelin and inhibitors of HIV-1 protease.[8], that may lead to novel treatments for hypertension, congestive heart failure, asthma or atherosclerosis.



Corallidictyal A (**1**) Corallidictyal B (**2**) Corallidictyal C (**3**) Corallidictyal D (**4**)

FIGURE 1. Bioactive spirodihydrobenzofurans and related metabolites I.

[3] (a) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551. (b) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712. For a recent review concerning K-76 and structurally related compounds see: (c) Larghi, E. L.; Kaufman, T. S. *Arkivoc* **2011** (vii) 49.

[4] (a) Ayer, W. A.; Miao, S. *Can. J. Chem.* **1993**, *71*, 487.. (b) Lin, T.-W.; Chang, W.-W.; Chen, C.-C.; Tsai, Y.-C. *Biochem. Biophys. Res. Commun.* **2005**, *331*, 953.

[5] Lam, Y. K. T.; Wichmann, C. F.; Meinz, M. S.; Guariglia, L.; Giacobbe, R. A.; Mochales, S.; Kong, L.; Honeycutt, S. S.; Zink, D.; Bills, G. F.; Huang, L.; Burg, R. W.; Monaghan, R. L.; Jackson, R.; Reid, G.; Maguire, J. J.; Mcknight, A. T.; Ragan, C. I. *J. Ant.* **1992**, *45*, 1397.

[6] Sakai, K.; Watanabe, K.; Masuda, K.; Tsuji, M.; Hasumi, K.; Endo, A. *J. Antibiot.* **1994**, *48*, 447.

[7] Deng, W.-P-; Zhong, M.; Guo, X.-C.; Kende, A. S. *J. Org. Chem.* **2003**, *68*, 7422.

[8] (a) Roggo, B. E.; Petersen, F.; Sills, M.; Roesel, J. L.; Moerker, T.; Peter, H. H. *J. Antibiot.* **1996**, *49*, 13.. (b) Roggo, B. E.; Hug, P.; Moss, S.; Stampfli, A.; Kriemler, H. P.; Peter, H. H. *J. Antibiot.* **1996**, *49*, 374.

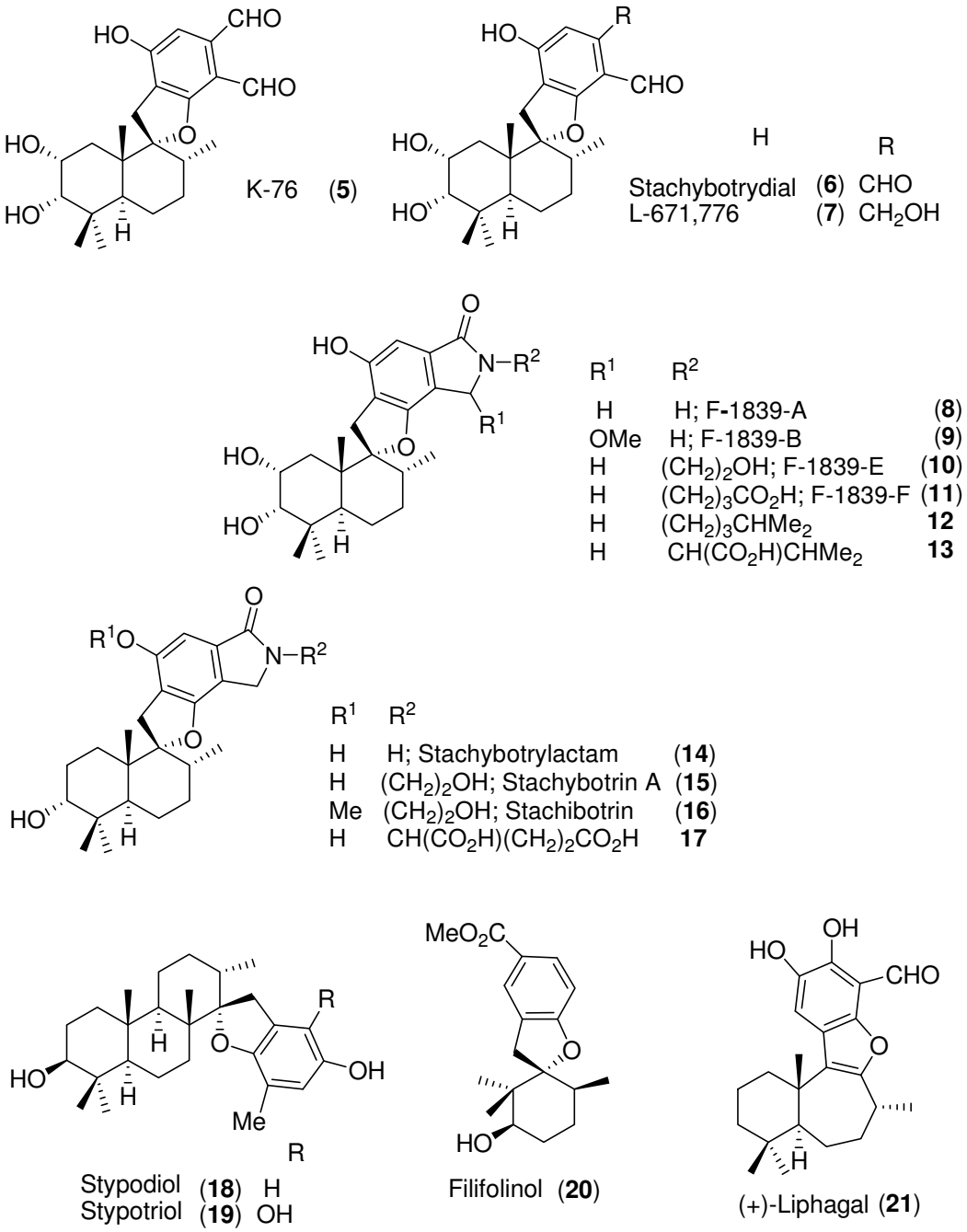
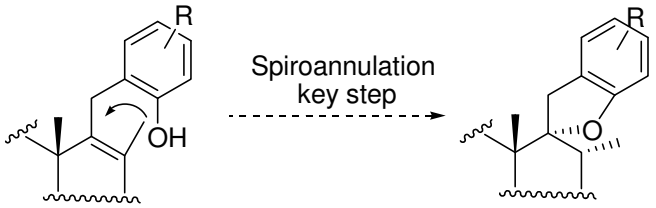


FIGURE 2: Bioactive spirodihydrobenzofurans and related metabolites II.

Among other related compounds, even though showing a variable number of carbon rings in their structures, **18-20** are of outstanding interest due to their biological properties. Pentacyclic stypodiol (**18**) and stypotriol (**19**), isolated from marine algae *Stypopodium zonale*, exhibit relevant narcotic and hyperactive properties. On the other hand, the spiromonoterpene filifolinol (**20**) presents an interesting antioxidant, antiviral, antifungal, antibacterial, anticomplement and cytotoxic activity[9]

Despite the relevant biological activities and the interesting sterically constrained spiro structures of the above mentioned compounds, only a few syntheses have been reported for some of them. In all cases, the key step is the spiroannulation of the suitable drimane (bicyclic sesquiterpene) phenol.



Corey et al. synthesized K-76 (**5**), after cyclization utilizing a THF –ethylene glycol – 2N hydrochloric acid mixture.[2a] Three years later, McMurry et al. described the synthesis of this compound (**5)**, utilizing cationic resin Amberlyst 15 as the cyclizing agent.[2b] More recently, Kende et al. have reported the synthesis of stachybotrylactam (**14**), also utilizing the same cationic resin.[7,10] In all cases a mixture of spirodihydrobenzofuran and benzopyran was obtained, in a (1.7-3.5): 1.0 ratio.

However, it is a remarkable fact that no synthesis of corallidictyals has been reported yet.

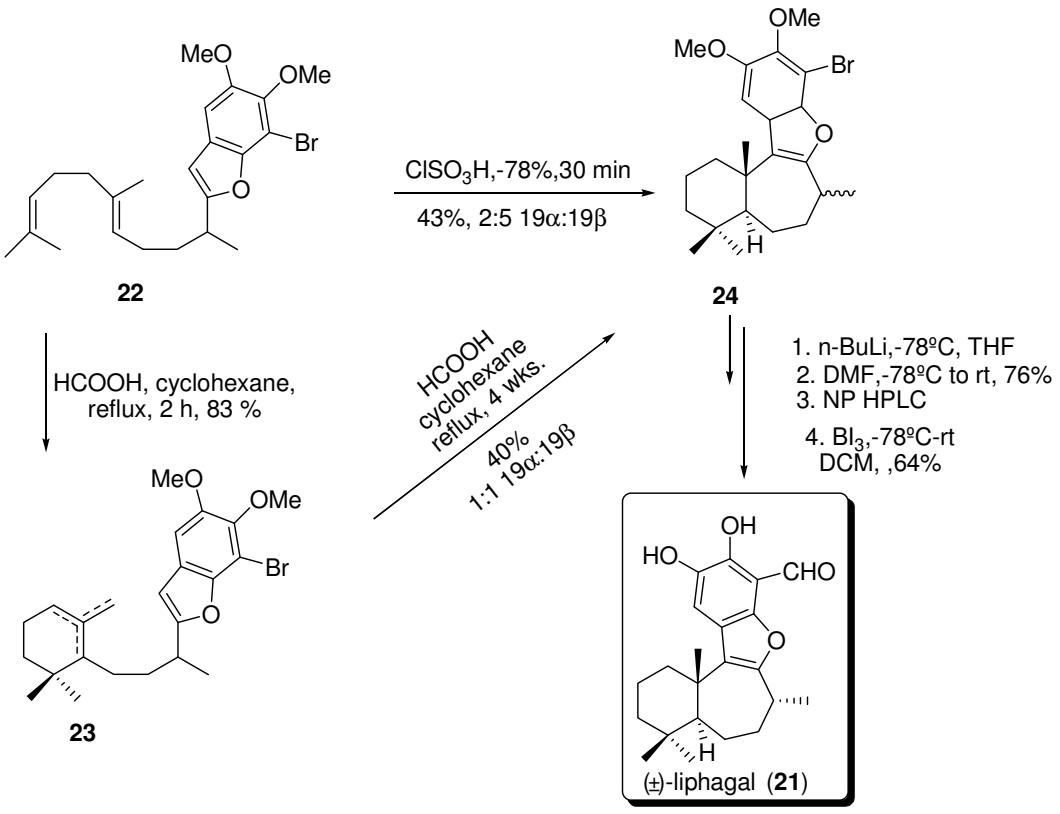
[9] Larghi, E. L.; Operto, M. A.; Torres, R.; Kaufman, T. S. *Bioorganic & Medicinal Chemistry Letters* **2009**, *19*, 6172.
[10] Kende, A. S.; Deng, W.-P-; Zhong, M.; Guo, X.-C. *Org. Lett.* **2003**, *5*, 1785.

Following with the merosesquiterpenes of our interest, liphagal[11] (**21**), a metabolite with selective PI3K inhibitory activity, structurally related with compounds **2** and **4**, was lately isolated from the same natural source as those, the marine sponge *Aka coralliphaga,* and exhibits the novel [7.6.5.6] "liphagane" carbon skeleton. Besides its uncommon structure, liphagal (**21**) presents considerable therapeutic potential, with inhibitory activity against PI3K α (phosphoinositide-3-kinase α). It is more potent than the synthetic LY 294002 and more selective than wortmanin, making it a promising candidate as an agent for the treatment of inflammatory and autoimmune disorders as well as cancer and cardiovascular diseases[12]. In fact, liphagal (**21**) has been observed to be cytotoxic, in secondary in vitro assays, to LoVo (human colon: IC_{50} 0.58 μM), CaCo (human colon: IC_{50} 0.67 μM), and MDA-468 (human breast: IC_{50} 1.58 μM) tumor cell lines.

Two racemic syntheses of liphagal (**21**) have been reported. Andersen et al., after isolating compound **21** from its natural source, developed a synthesis of this bioactive metabolite, which involves a cation-initiated cyclization of a dienyl benzofuran **22** as the key step [10d].

[11] (a) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814. (b) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Cano, M. J.; Haidour, A.; Alvarez-Manzaneda, R. *Org. Lett.* **2010**, *12*, 4450. (c) George, J. H.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 2394. (d) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 321.

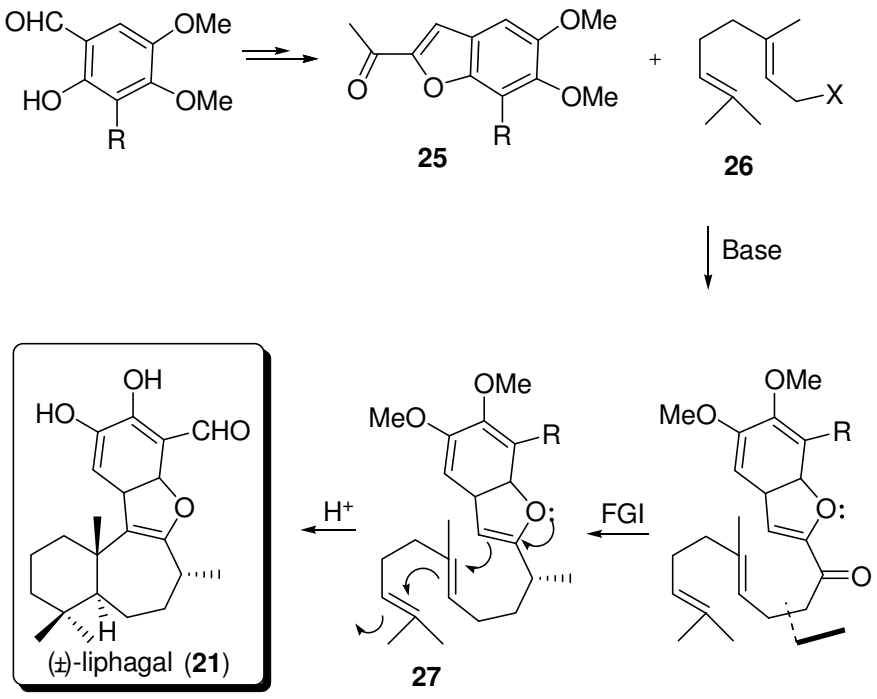
[12] For recent reviews on the therapeutic potential of phosphoinositide-3-kinase inhibitors, see: (a) Ward, S. G.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, P. *Chem. Biol.* **2003**, *10*, 207. (b) Ward, S. G.; Finan, P. *Curr Opin. Pharmacol.* **2003**, *3*, 426.



Scheme 1: Synthesis of liphagal reported by Andersen

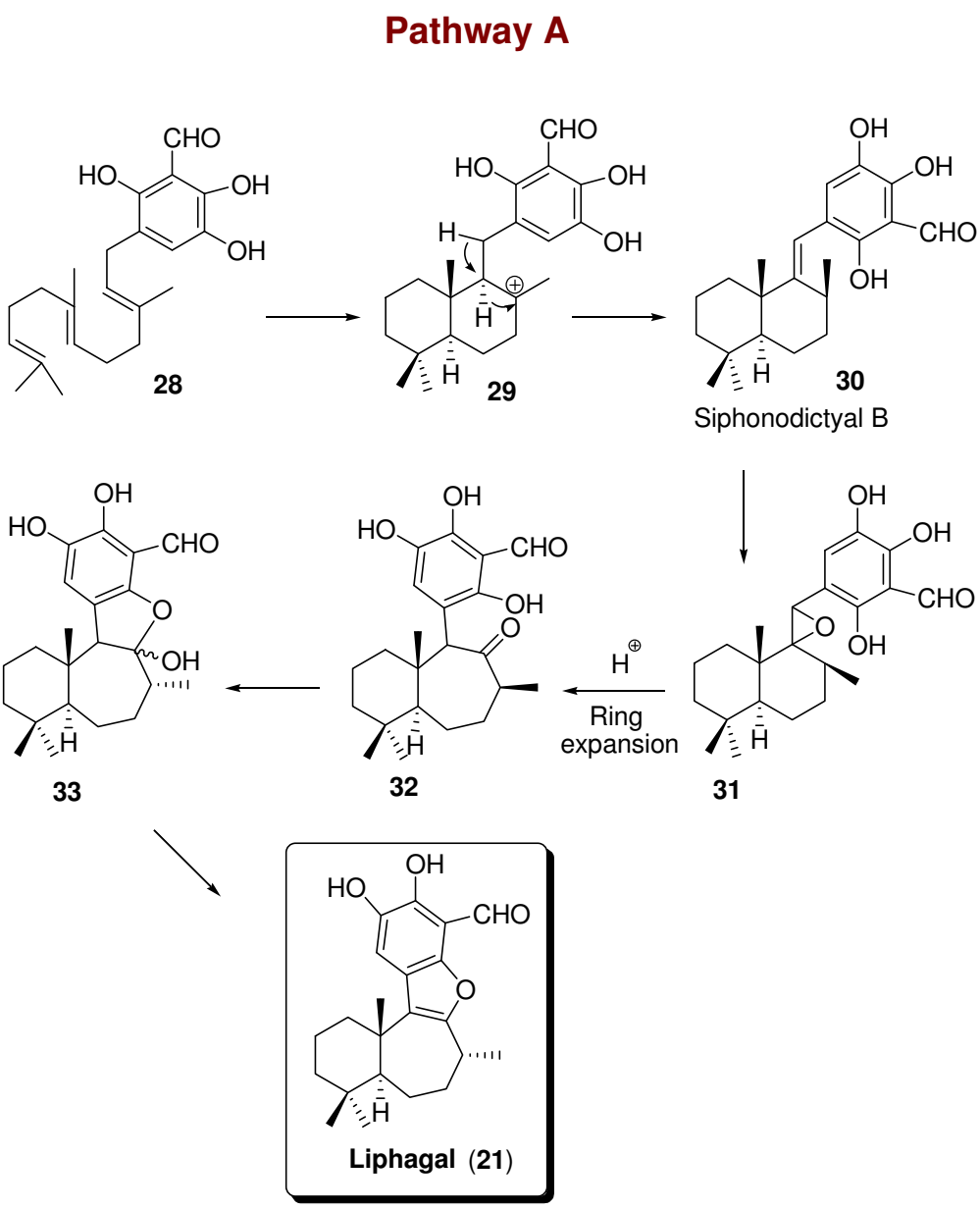
Recently, Mehta et al.[13] described a closely related strategy to synthesize (±)-**21**, based on the acid-promoted cyclization of a cyclohexenyl benzofuran.

[13] Mehta, G.; Likhite, N. S.; Ananda Kumar, C. S. *Tetrahedron Letters* **2009**, *50*, 5260.



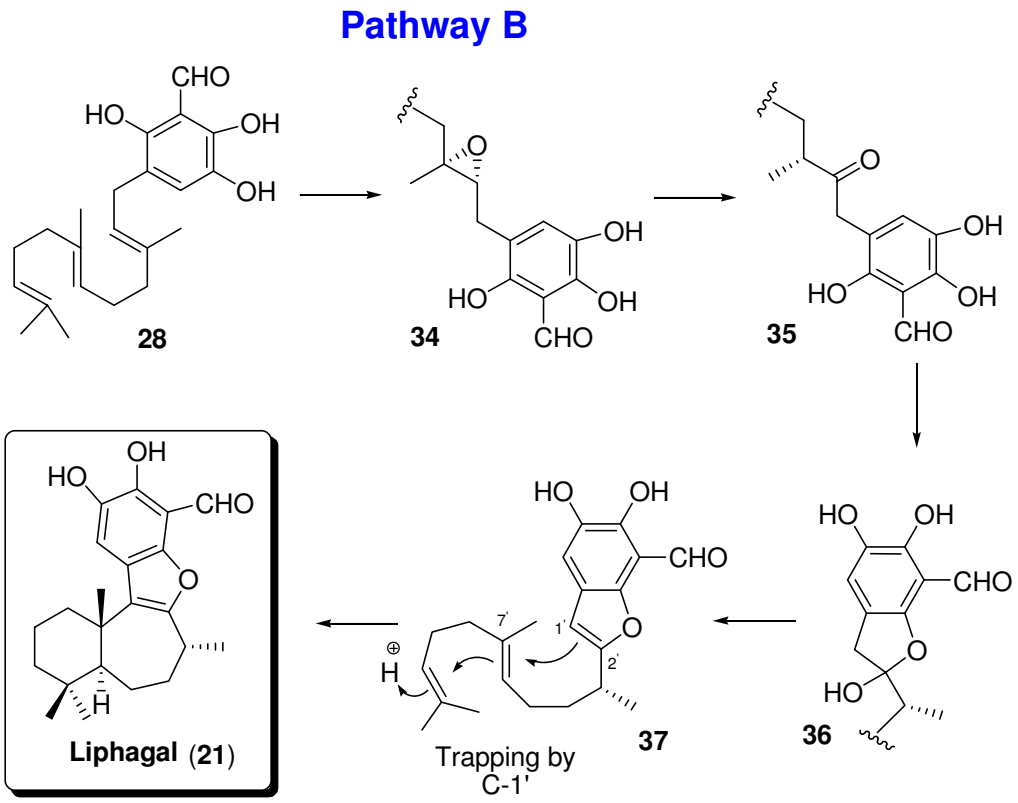
Scheme 2: Synthesis of liphagal reported by Mehta

Andersen's group proposed two possible biogenetic pathways to liphagal (**21**), starting from a farnesyl trihydroxybenzaldehyde[10d]. One of these pathways takes place *via* the bicyclofarnesyl trihydroxybenzaldehyde siphonodictyal B (**30**), (see scheme 3) a metabolite also found in the sponge *Aka coralliphaga*.



Scheme 3: Proposed biosynthetic pathway to liphagal: Pathway A

In the alternative pathway (see scheme 4), the benzofuran system is first formed from an acyclic ketone **35** and the 6,7-ring system is subsequently created, after the acid promoted cyclization of a dienyl benzofuran **37**.



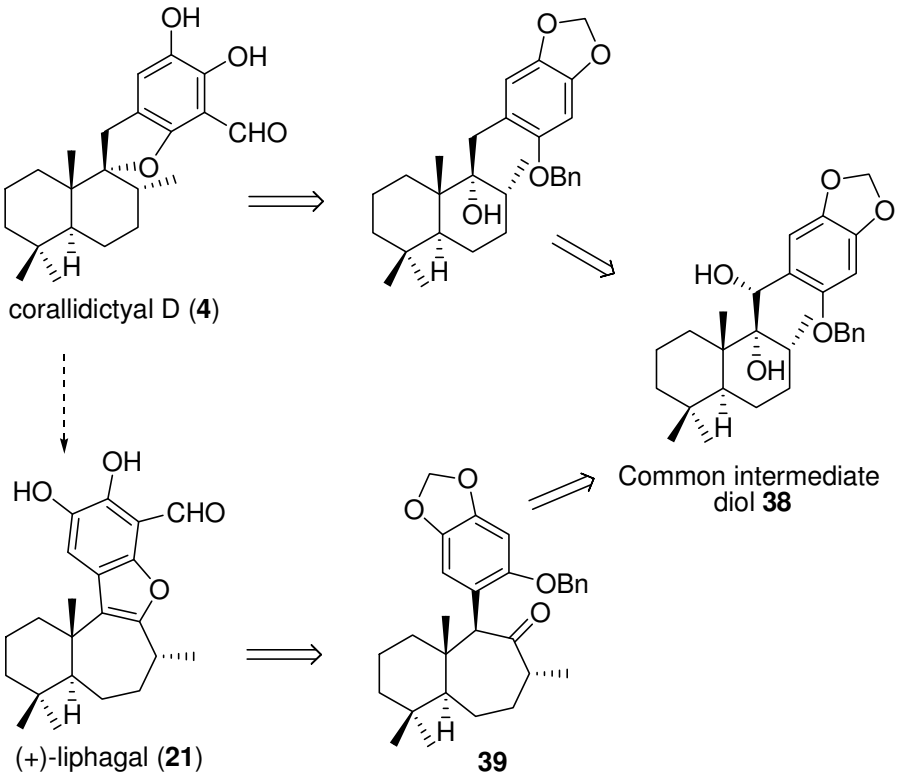
Scheme 4: Proposed biosynthetic pathway to liphagal: Pathway B

RESULTS AND DISCUSSION

As it was pointed out in the introduction, liphagal is a very appealing target for synthetic organic chemists. First of all, it possesses a challenging new "liphagane" skeleton, present in several other molecules with interesting properties as well. Furthermore, no stereoselective synthesis of liphagal existed by the time that our research towards its synthesis started. These reasons, together with the potentially beneficial therapeutic properties of liphagal, made us choose liphagal as our main target.

Besides, we considered tackling the synthesis of corallidictyal D, since it is also an interesting bioactive molecule, structurally related to the latter and no synthesis of it has ever been reported.

At first stage, we proposed a hypothesis that relates both molecules through the existence of a common intermediate **38** between the two molecular families. This idea is supported by the fact that both molecules have been isolated from the same natural source, marine sponge *Aka Coralliphagum*, and both exhibit a structure that may be easily related, since we suggest that corallidictyal´s skeleton might rearrange to liphagane type through a ring expansion process. Therefore, we may speculate on a common biosynthetic origin (see scheme 12).



Scheme 5: Relationship between corallidictyals and liphaganes.

After more than 15 years working on the synthesis of merosesquiterpenes, our research group has achieved, in many cases, the first synthesis of some of these type of substances by using enantiomerically pure synthons from easily accessible abundant natural precursors[14].

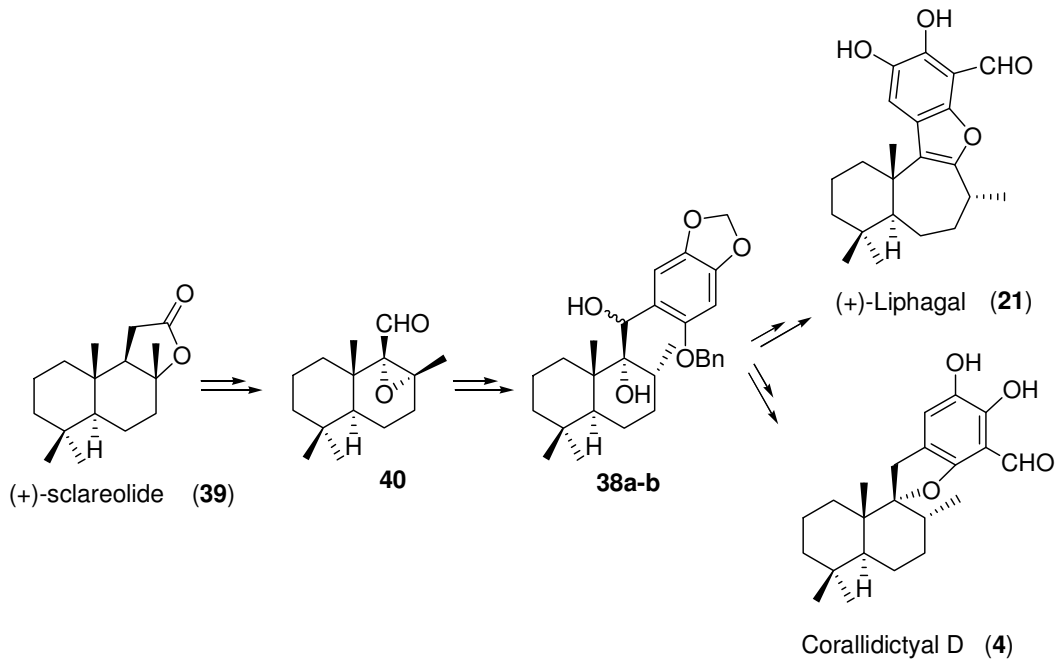
This thesis is enshrined in this field; different synthetic sequences towards the obtention of new bioactive merosesquiterpenes corallidictyal D (**4**) and liphagal (**21**) are described, using commercially available starting materials such as (+)-sclareolide (**39**) and α-ionone (**51**).

Concurrently, the syntheses of meromonoterpenic analogs, structurally related to **4** and **21,** are accomplished. The study of its SAR (structure-activity relationship) is one of our aims as well. These monoterpenes will be of usage in the study of some controversial key step of the syntheses of the target molecules **4** and **21**.

The experimental work is organized in seven sections:

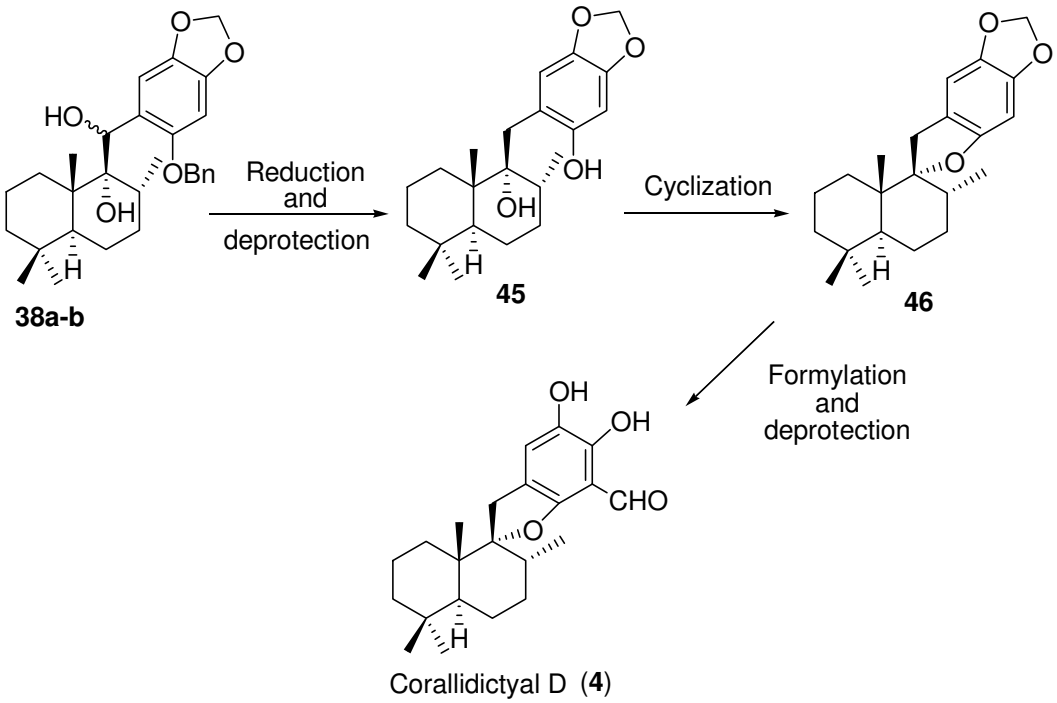
1) In the first part a synthesis of merosesquiterpenic diol **38** *via* the intermediate epoxyaldehyde **40** is tackled. Such merosesquiterpene diol is a plausible key precursor in the synthesis of liphaganes and corallidictyals starting from (+)-sclareolide (**39**).

[14] (a) Alvarez-Manzaneda, E. J.; Chahboun, R.; Barranco Pérez, I.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R. *Organic Letters* **2005**, *7*, 1477 and references cited therein. (b).Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Tapia, R.; Es-Samti, H.; Fernández, A.; Barranco, I. *Eur. J. Org. Chem.* **2009**, 1139 and references cited therein. (c) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Fernández, A.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. M.; Akhaouzana, A. *Chem. Commun.* **2012**, *48*, 606 and references cited therein.



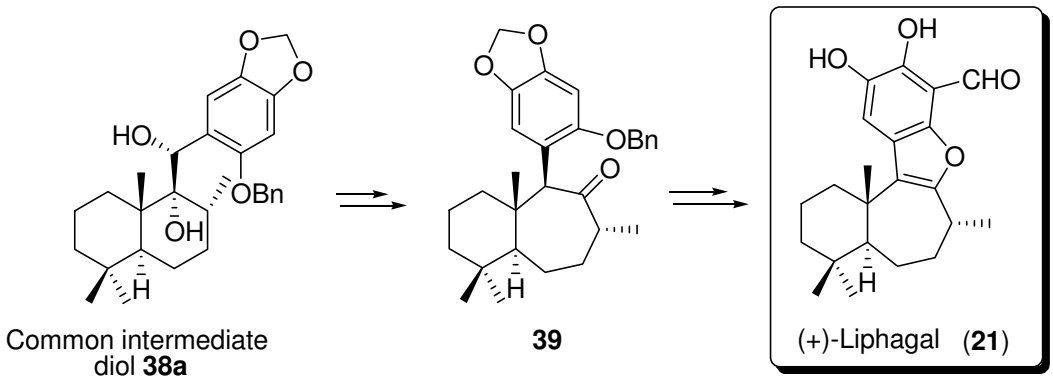
Scheme 6: Merosesquiterpenic diol **38** as a common intermediate: Section I.

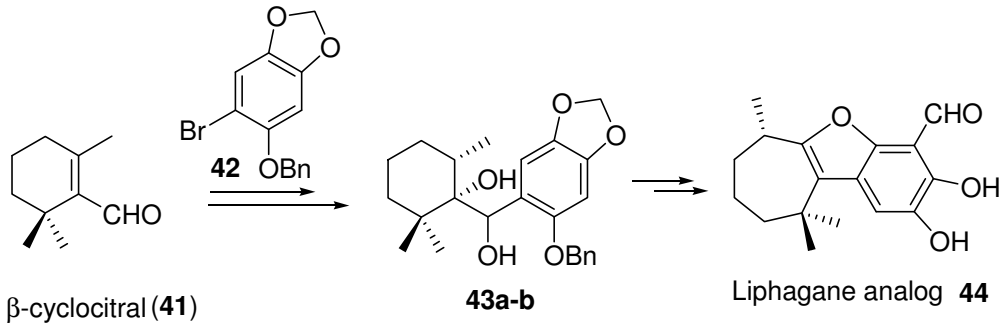
2) In the second section, we describe the study on the reduction of the benzylic hydroxyl group of merosesquiterpene diol **38**, previously synthesized, and the application of the results obtained to the synthetic approach to corallidictyal D (**4**).



Scheme 7: Study of reduction of benzylic alcohol in **38.**

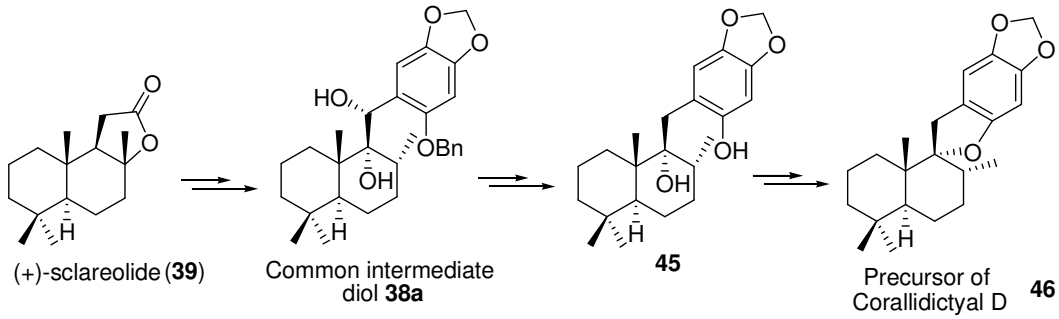
3) Thridly, we carried out the synthesis of (+)-liphagal (**21**) starting from sesquiterpenic diol **38**. The preparation of the monoterpenic analog of liphagal (**44**) starting from β-cyclocitral (**41**) is also depicted.





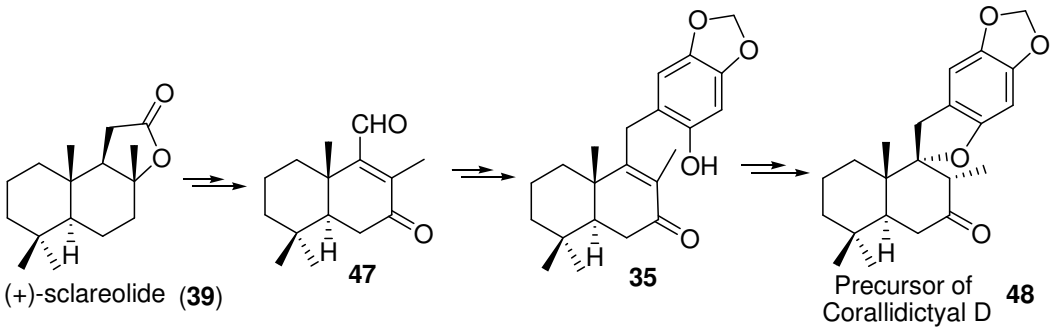
Scheme 8: Sinthesis of (+)-liphagal (**21**) and its monoterpenic analog (**44**).

4) In the fourth part, a synthetic approach towards corallidictyal D (**4**), starting from (+)-sclareolide (**39**), is depicted



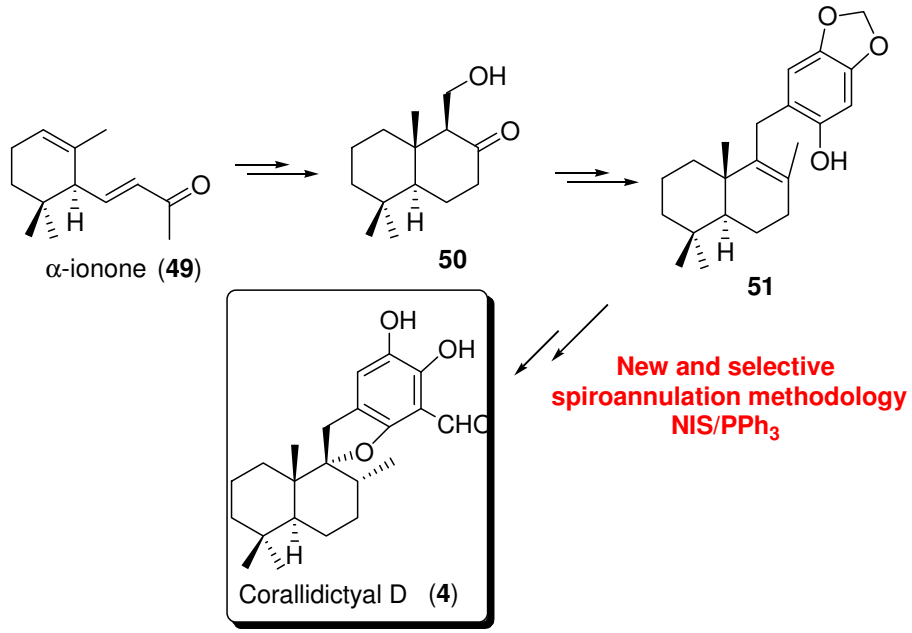
Scheme 9: Synthetic approach towards corallidictyal D starting from (+)-sclareolide.

5) The section five describes a second strategy towards the synthesis of corallidictyal D (**21**) starting from (+)-sclareolide (**39**) *via* the drimanic cetoaldehyde **47**

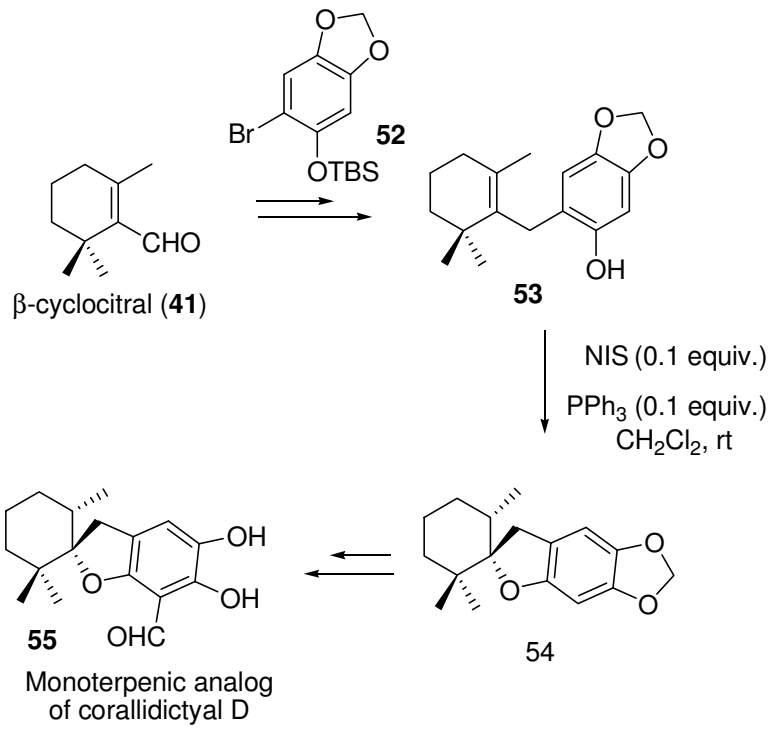


Scheme 10: Second synthetic approach to corallidictyal D starting from (+)-sclareolide.

6) In the sixth place, we describe a third strategy to achieve the total synthesis of corallidictyal D (**4**), starting from α-ionone (**49**), and the synthesis of its monoterpenic analog (**55**). After numerous attempts to access the furane moiety present in corallidictyals, we developed a new and selective methodology for the spiroannulations of *o*-allylphenols by using the system NIS/PPh_3. These mild conditions allow access to spirodihydrobenzofuran core, present in a large number of interesting natural products.



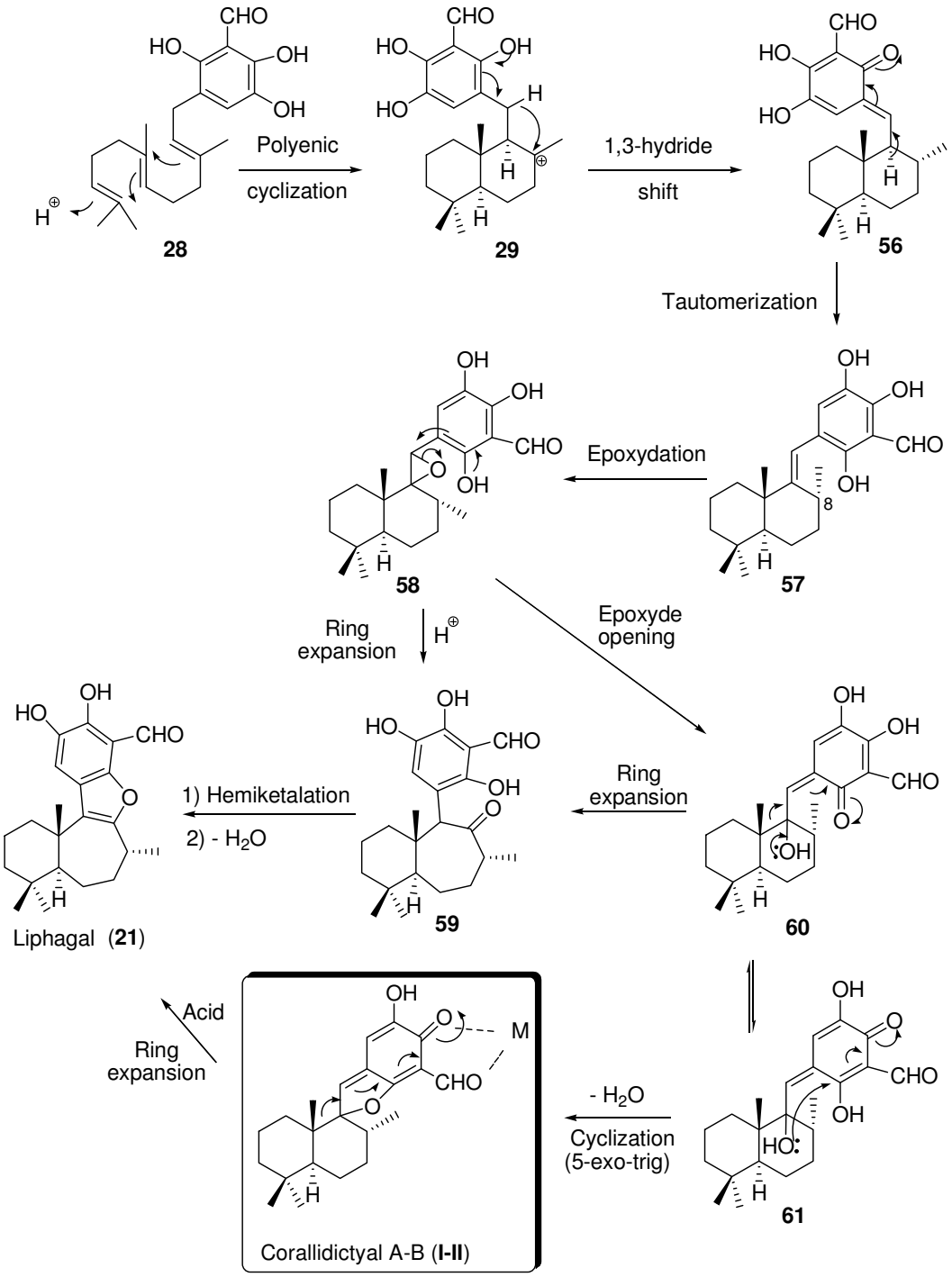
Scheme 11: First total **s**ynthesis of corallidictyal D (**4**) from α-ionone (**49**). Development of new mild and selective methodology for the spiroannulation of *o*-allylphenols.



Scheme 12: Synthesis of monoterpenic analog of corallidictyal D (**55**).

7) Eventually, we propose a new biosynthetic route based on experimental data obtained within this project, that relates both natural products and can explain the natural formation of (+)-liphagal (**21**) and corallidictyal D (**4**) and the conversion of its skeleton into liphagane type, *via* a *o*-quinone methide intermediate.

New biosynthetic proposal



Scheme 12: New biogenetic proposal. Explanation of the possible origin and relationship between the target molecule s

INTRODUCCIÓN

INTRODUCCIÓN

Durante las últimas décadas se han aislado, de diferentes fuentes naturales, una amplia gama de merosesquiterpenos, caracterizados por sus variadas y potentes actividades biológicas.

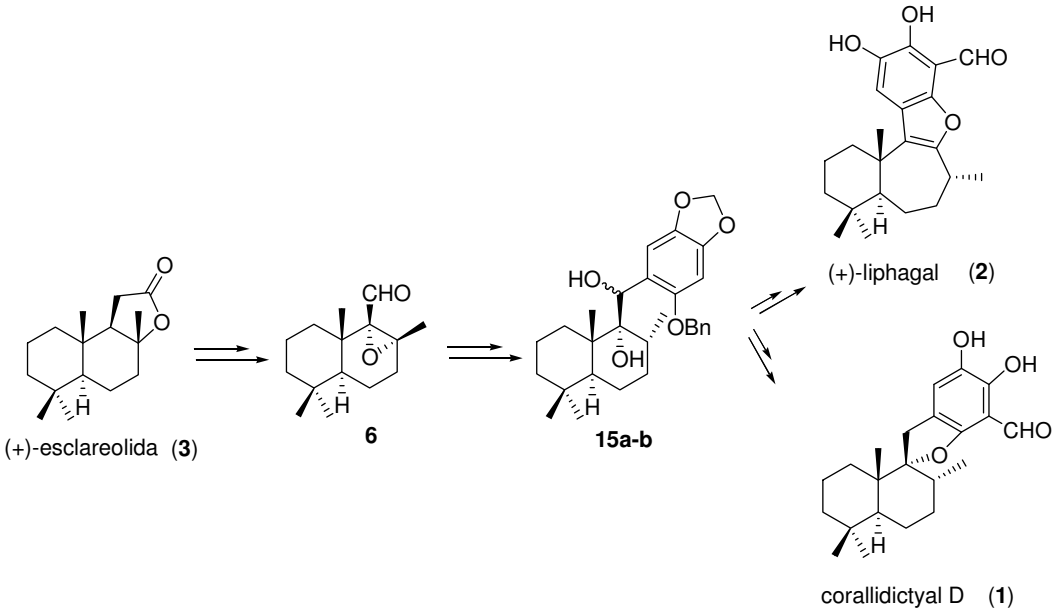
Sin embargo, a pesar de su interés, la escasez, en muchos casos, de estas sustancias bioactivas en la naturaleza, supone una limitación considerable a la hora de completar los estudios de actividad biológica pertinentes, en busca de sus posibles aplicaciones en el campo de la medicina. Este hecho ha motivado a un gran número de investigadores a plantear síntesis de estos productos.

Nuestro grupo de investigación lleva más de 15 años trabajando en síntesis de merosesquiterpenos, logrando en muchos casos la primera síntesis de algunas de estas sustancias, mediante la utilización de sintones enantioméricamente puros, obtenidos de precursores naturales abundantes y, por tanto, fácilmente accesibles,

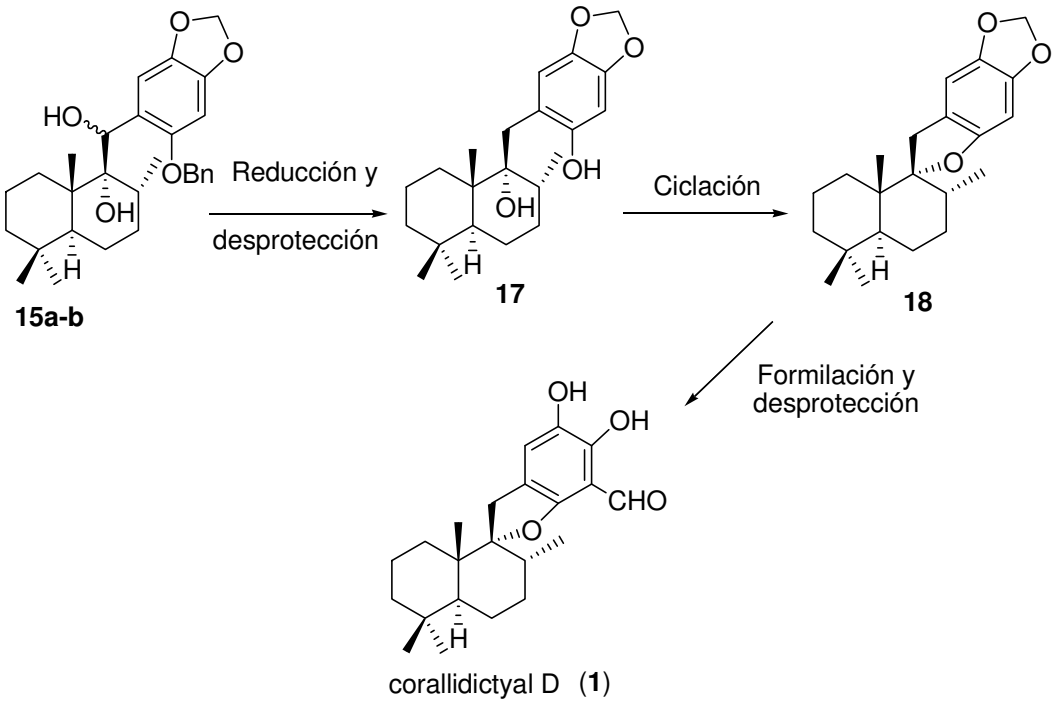
La presente Tesis Doctoral se enmarca dentro de esta línea de investigación. En ella se describen las diferentes secuencias sintéticas desarrolladas hacia la obtención de nuevos merosesquiterpenos bioactivos: corallidictyal D (**1**) y (+)-liphagal (**2**), empleando sustratos de partida comerciales y fácilmente accesibles, como (+)-esclareolida (**3**) y α-ionona (**60**). Paralelamente, se describen las síntesis de análogos meromonoterpénicos **40** y **45**, relacionados estructuralmente con estas sustancias naturales, con objeto de completar el estudio de la relación estructura-actividad (SAR) para estos metabolitos mixtos. Se utilizan en ocasiones los intermedios monoterpénicos para el estudio de algunas etapas claves en las síntesis de las moléculas objetivo.

El trabajo desarrollado se ha estructurado en siete secciones:

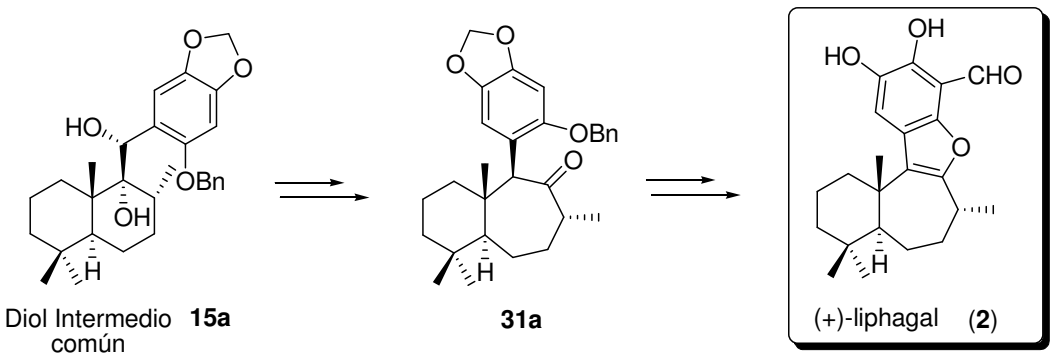
1) Síntesis a partir de (+)-esclareolida (**3**), del diol merosesquiterpénico **15**, posible precursor clave para la síntesis de liphaganos y corallidictyales, *vía* el epoxialdehído drimánico **6**.

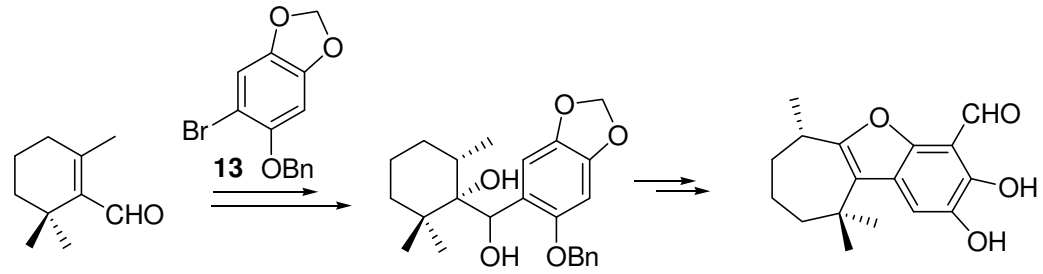


2) Estudio de reducción del grupo hidroxilo bencílico del diol merosesquiterpénico **15**, previamente sintetizado, y aplicación de los resultados obtenidos para llevar a cabo la primera aproximación a la síntesis de corallidictyal D (**1**).



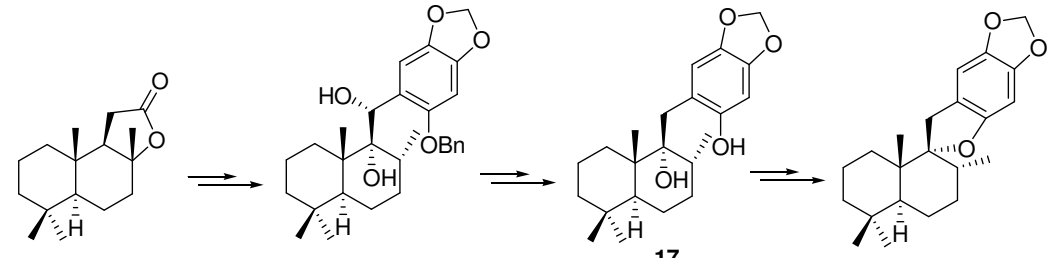
3) Síntesis de (+)-liphagal (**2**) a partir del diol merosesquiterpénico **15**. Se abordará también la síntesis del análogo monoterpénico de liphagal (**40**), a partir de β-ciclocitral (**22**), con objeto de estudiar las etapas controvertidas de la secuencia sintética.





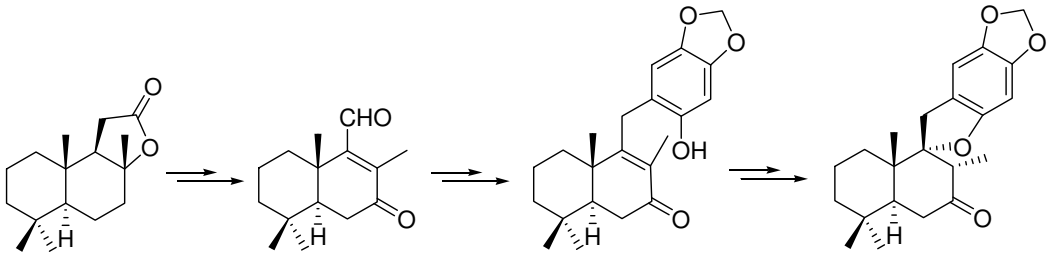
β-ciclocitral (**22**) **26a-b** Análogo liphagano **40**

4) Continuación de la primera estrategia para la aproximación hacia la síntesis de corallidictyal D (**1**), a partir de (+)-esclareolida (**3**).



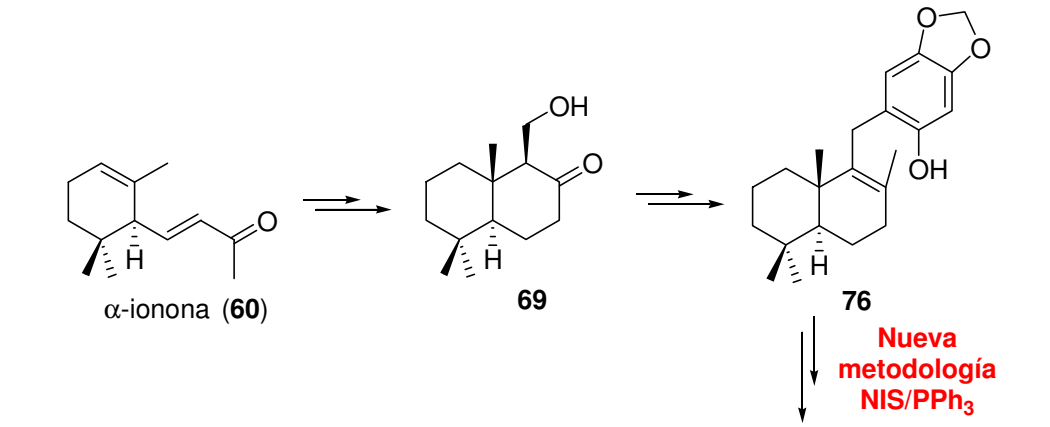
(+)-esclareolida (**3**) Diol Intermedio común **15a** **17** Precursor de corallidictyal D **18**

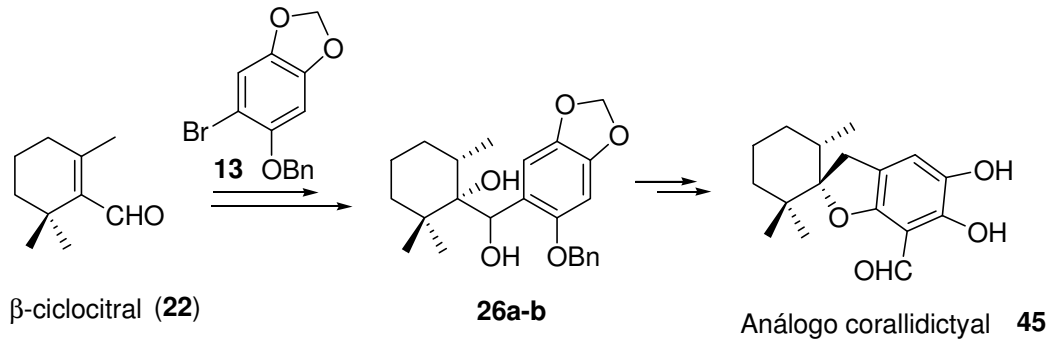
5) Segunda estrategia hacia la síntesis de corallidictyal D (**1**) a partir de (+)-esclareolida (**3**) *via* el cetofenol **58**.



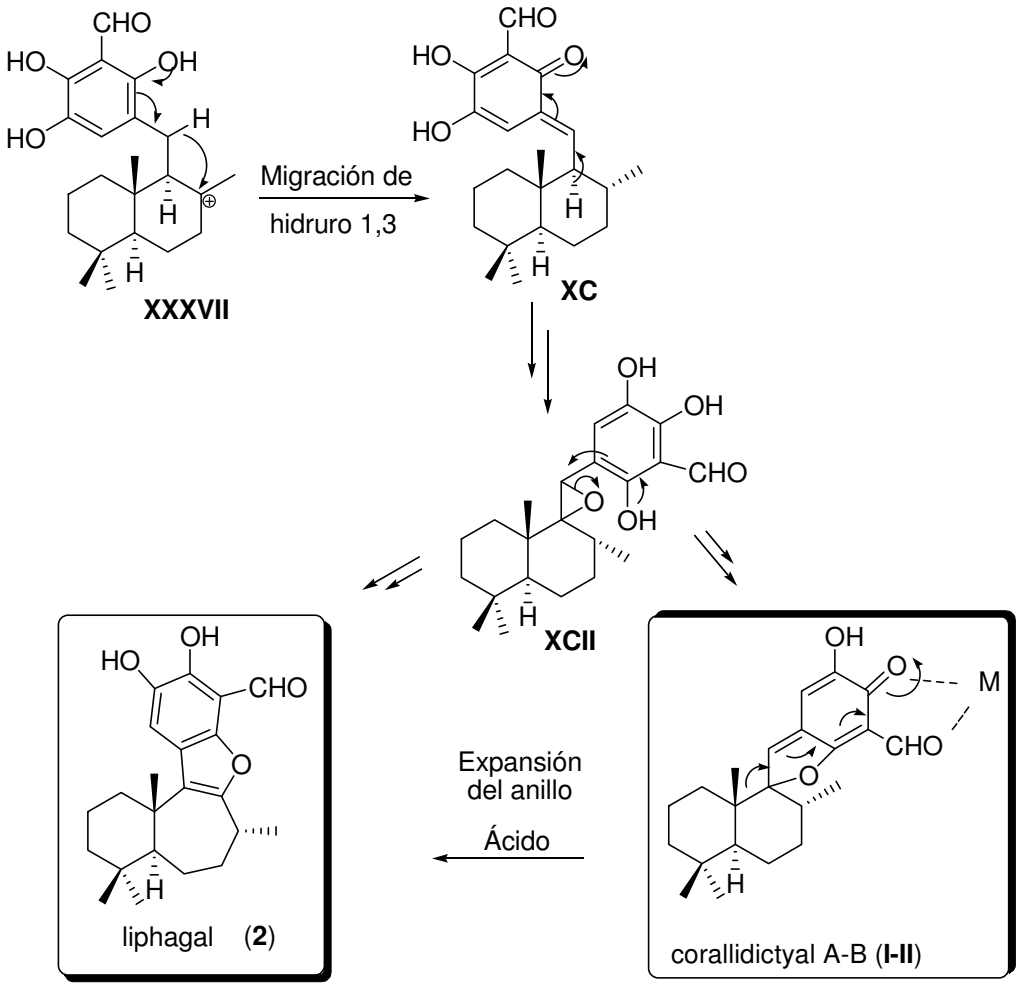
(+)-esclareolida (**3**) **54** **58** Precursor de corallidictyal D **59**

6) Tercera estrategia: Síntesis total de corallidictyal D (**1**), a partir de α-ionona (**60**), y de su análogo monoterpénico (**45**). Desarrollo de una nueva metodología suave y selectiva para la espiroanelación de *o*-alilfenoles, empleando el sistema NIS/PPh_3.





7) Nueva propuesta biosintética para (+)-liphagal y corallidictyales que involucra intermedios tipo *o*-quinometano y, que relaciona además ambas familias mediante un posible proceso de expansión del anillo del esqueleto de corallidictyales, generando así el esqueleto liphagano.



ANTECEDENTES

1.-CORALLIDICTYALES Y COMPUESTOS RELACIONADOS

1.1.-CORALLIDICTYALES

Los corallidictyales **I-IV** son una familia de aldehídos merosesquiterpénicos, con estructura tipo espirodihidrobenzofuránica, que se aislaron de la esponja marina *Aka coralliphaga (Syphonodictyon),*[1,2] del genero *incrustans*[2], que suele crecer a profundidades de entre 20-25 m. El aislamiento de estos meroterpenoides se produjo en dos fases. En 1994, el grupo de Chan[1] publicó el aislamiento de corallidictyales A y B, como una mezcla diastereomérica (3:7), encontrada en los extractos de *Aka coralliphaga* y recogida en la isla de San Salvador. Sin embargo, no fue hasta 2007, cuando Köck y col. aislaron corallidictyales C y D de *Aka coralliphaga* del Caribe como una mezcla de diastereómeros (3:5).

Cabe resaltar el hecho de que las hidroquinonas sesquiterpénicas siphonodictyales A y B (**VIII**)[3], ya fueron aisladas de la misma esponja en 1981 por Sullivan y col.[3] sin detectar, en este caso, la presencia de corallidictyales en los extractos de la misma. La explicación de la dificultad de aislamiento de corallidictyales se debe principalmente a su inestabilidad a pH ácido. Por ello, al aplicar protocolos de extracción y purificación más suaves y libre de ácidos[3,4], se pudieron aislar los cuatro corallidictyales A(**IV**) y B (**III**), C(**II**) y D (**I**); los dos últimos, metabolitos secundarios muy minoritarios en la esponja.

(1) Chan, J., A.;; Freyer, A. J.; Carté, B. K.; Hemling, M. E.; Hofmann, G. A.; Mattern, M. R.; Mentzer, M. A.; Westley, J. W. *J. Nat. Prod.* **1994**, *57*, 1543.
(2) Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Köck, M. *J. Nat. Prod.* **2007**, ***70***, 504.
(3) Sullivan, B.; Djura, P.; McIntyre, D. E.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 979.
(4) Sullivan, B. W.; Faulkner, D. J.; Matsumoto, G. K.; He, C. H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4568.

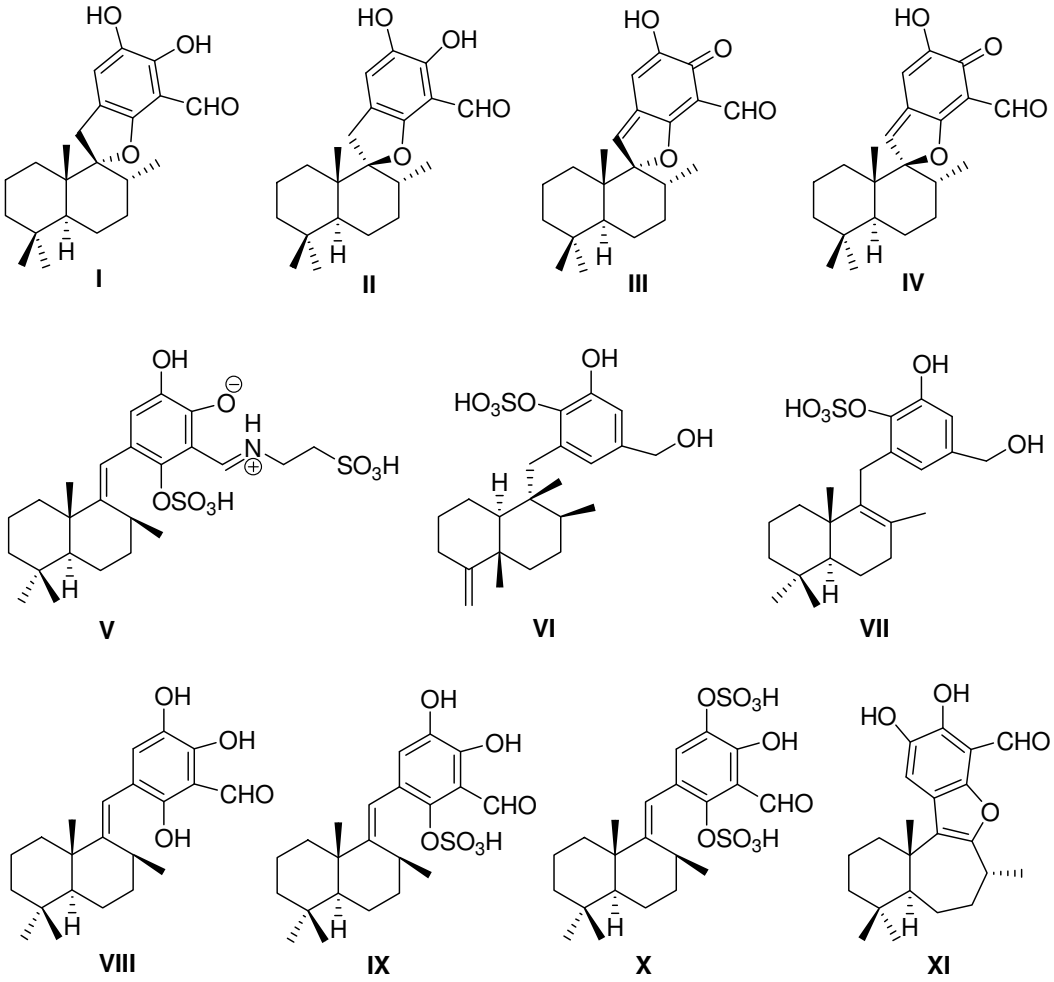


Figura 1: Compuestos aislados de *Aka coralliphagum* tipo *incrunstans*

Los compuestos **V-X** son asimismo metabolitos aislados de la esponja. El análisis de todos estos metabolitos pone de manifiesto la similitud estructural entre ellos, presentando en muchos casos el mismo fragmento sesquiterpénico unido a un fragmento aromático muy parecido en la mayoría de los casos. Las hidroquinonas siphonodictyales B1-B3[5] (**V, IX, X**) presentan una significativa actividad antioxidante y antimicrobiana, mientras que siphonodictyol G[4](**VI**), y su

(4) Sullivan, B. W.; Faulkner, D. J.; Matsumoto, G. K.; He, C. H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4568.
(5) Ragan, M. A. *Can. J. Chem.* **1978**, *56*, 2681.

análogo siphonodictyol H (**VII**), han mostrado una actividad biológica moderada respecto a los demás metabolitos.

Recientemente se ha aislado de esta misma esponja una sustancia directamente relacionada con estos metabolitos: (+)-liphagal (**XI**). Este meroterpenoide natural, de gran interés tanto por su novedosa estructura como por su prometedora actividad terapéutica, fue aislado por vez primera en 2006, por el grupo del Prof. Andersen[6], de la misma esponja marina *Aka coralliphaga* del mar Caribe, en forma de sólido amorfo de color amarillo, al igual que los corallidictyales. Andersen y col. llevaron a cabo numerosos ensayos sobre la esponja con el fin de descubrir nuevos inhibidores de la enzima fosfoinositol kinasa 3 (PI3K)[7]. Los extractos metanólicos de la esponja *Aka coralliphaga*, que contenían (+)-liphagal, resultaron activos frente a la inhibición de la enzima PI3K.

Liphagal presenta un esqueleto carbonado tetracíclico [6-7-5-6], que ha despertado gran interés desde el momento de su aislamiento. El esqueleto "liphagano" contiene un fragmento *trans*-6,7-bicarbocíclico fusionado, con tres centros estereogénicos. La estructura y estereoquímica de liphagal se elucidaron basándose en análisis espectrales de RMN (HMBC, HSQC, NOESY)[6]. (+)-Liphagal está relacionado estructuralmente con varias de las moléculas aisladas de la esponja; poseen el mismo número de carbonos, un fragmento sesquiterpénico y un fragmento aromático similar. Además, presenta numerosas analogías con algunas sustancias, entre ellas los corallidictyales y siphonodyctial B (**VIII**) [4]. En base a la estructura de esta última molécula, propuso Andersen una posible ruta biogenética hacia (+)-liphagal.

---

(4) Sullivan, B. W.; Faulkner, D. J.; Matsumoto, G. K.; He, C. H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4568.

(6) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Organic Letters* **2006**, *8*, 321.

(7) Andersen, R.; Hollander, I.; Roll, D. M.; Kim, S. C.; Mallon, R. G.; Williams, D. E.; Marion, F.; (The University of British Columbia, Can.; Wyeth, John, and Brother Ltd.). Application: WO, 2006, p 64.

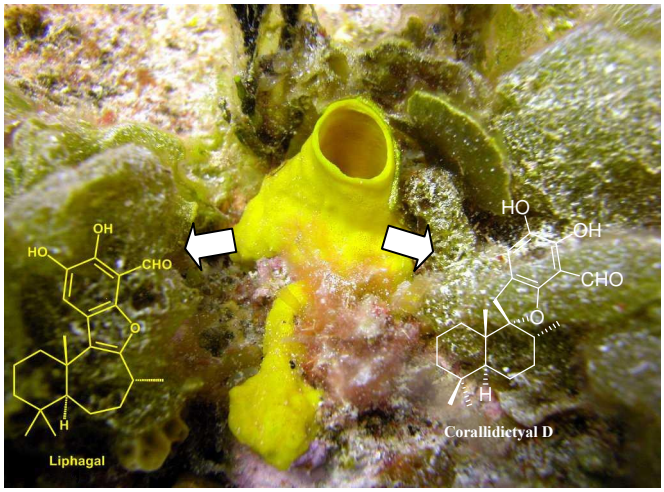


Imagen 1: Fotografía de *Aka coralliphaga*

1.2.-COMPUESTOS RELACIONADOS

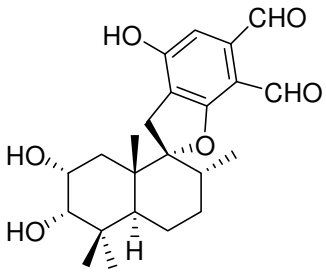
En las últimas décadas se han aislado del hongo *Stachybotrys*[8], y de las esponjas *Siphonodictyon corallyphagum(Aka)*[2] y *Stelospongia conulata*[9], un gran número de compuestos con estructuras espirodihidrobenzofuránicas relacionadas, que muestran una interesante actividad biológica[9] (Figura 2).

Uno de los compuestos de mayor importancia en este grupo es el metabolito fúngico K-76[10,11] (**XII**), que presenta un esqueleto drimánico asociado a un anillo bencénico polisustituido a través de una unidad de espirofurano. Actúa como inhibidor del sistema complemento[12-14], que es uno de los componentes fundamentales responsable de la respuesta inmune innata y la adquirida. Lleva a

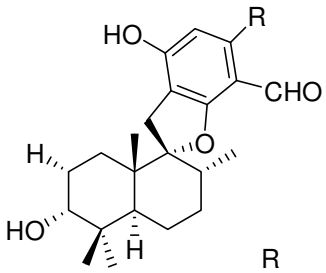
(2) Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Köck, M. *J. Nat. Prod.* **2007**, ***70***, 504.
(8) Roggo, B. E.; Hug, P.; Moss, S.; Stämpfli, A.; Kriemler, H.-P.; Peter, H. H. *J. Antibiot.* **1996**, *49* 374.
(9) Larghi, E. L.; Kaufman, T. S. *ARKIVOC* **2011**, *vii*, 49.
(10) Miyazaki, W.; Tomaoka, H.; Shinohara, M.; Kaise, H.; Izawa, T.; Nakano, Y.; Kinoshita, T.; Hong, K. I.; noue, K. *Microbiol. Immunol.* **1980** *24* 1091.
(11) Kaise, H.; Shinohara, M.; Miyazaki, W.; Izawa, T.; Nakano, Y.; Sugawara, M.; Sugiura, K.; Sasaki, K. *Journal of the Chemical Society, Chemical Communications* **1979**, 726.
(12) Gorbet, M. B.; Sefton, M. V. *Biomaterials* **2004**, *25*, 5681.
(13) Kirschfink, M. *Immunol. Rev.* **2001**, *180*, 177.
(14) Frangogiannis, N. G. *Pharmacol. Res.* **2008**, *58*, 88.

cabo numerosas funciones[15-17], entre las que destacan: la lisis celular, bacteriana o vírica, incluyendo la apoptosis y eliminación de complejos inmunes, además facilita la fagocitosis de antígenos particulados (opsonización), y potencia la respuesta inflamatoria. Como inhibidor de este sistema, K-76 desempeña un papel muy importante en las enfermedades neurológicas, infecciosas, autoinmunes y degenerativas. De ahí su interés para la industria farmacéutica.

Otros miembros de esta familia son L-671,776[18] (X**IV**), inhibidor de la enzima mioinositol monofosfatasa y el antivírico e inhibidor enzimático stachybotrydial (**XIII)**[19,20].

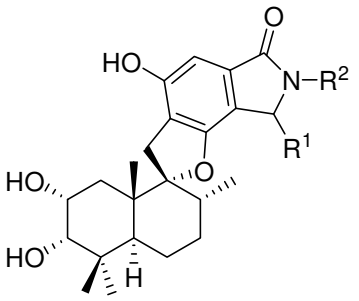


K-76 **XII**



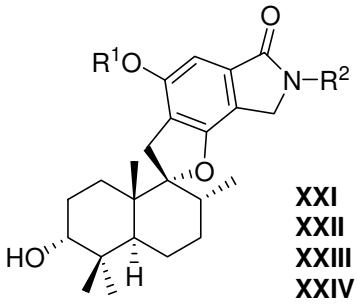
Stachybotrydial **XIII** CHO
L-671,776 **XIV** CH_2OH

(15) Flierman, R.; Daha, M. R. *Immunobiology* **2007**, *212*, 363.
(16) Mollnes, T. E.; Song, W.-C.; Lmbris, J. D. *Trends. Immunol.* **2002**, *23*, 61.
(17) Markiewski, M. M.; De Angelis, R. A.; Benencia, F.; Ricklin; Lichtsteiner, S. K.; Koutoulaki, A.; Gerard, C.; Coukos, G.; Lambris, J. D. *Nature Immunol.* **2008**, *9*, 1225.
(18) Lam, Y. K. T.; Wichmann, C. F.; Meinz, M. S.; Guariglia, L.; Giacobbe, R. A.; Mochales, S.; Kong, L.; Honeycutt, S. S.; Zink, D.; Bills, G. F.; Huang, L.; Burg, R. W.; Monaghan, R. L.; Jackson, R.; Reid, G.; Maguire, J. J.; Mcknight, A. T.; Ragan, C. I. *Journal of Antibiotics* **1992**, *45*, 1397.
(19) Ayer, W. A.; Miao, S. *Can. J. Chem.* **1993**, *71* 487.
(20) Lin, T.-W.; Chang, W.-W.; Chen, C.-C.; Tsai, Y.-C. *Biochem. Biophys. Res. Commun.* **2005**, *331*, 953.



	R^1	R^2
XV	H	H; F-1839-A
XVI	OMe	H; F-1839-B
XVII	H	$(CH_2)_2OH$; F-1839-E
XVIII	H	$(CH_2)_3CO_2H$; F-1839-F
XIX	H	$(CH_2)_3CHMe_2$
XX	H	$CH(CO_2H)CHMe_2$

Espirodihidrobenzofuranlactamas



	R^1	R^2
XXI	H	H; Stachybotrylactama
XXII	H	$(CH_2)_2OH$; Stachybotrin A
XXIII	Me	$(CH_2)_2OH$; Stachibotrin
XXIV	H	$CH(CO_2H)(CH_2)_2CO_2H$

Lactamas y regioisómeros

Figura 2: Corallidictyales y compuestos relacionados I

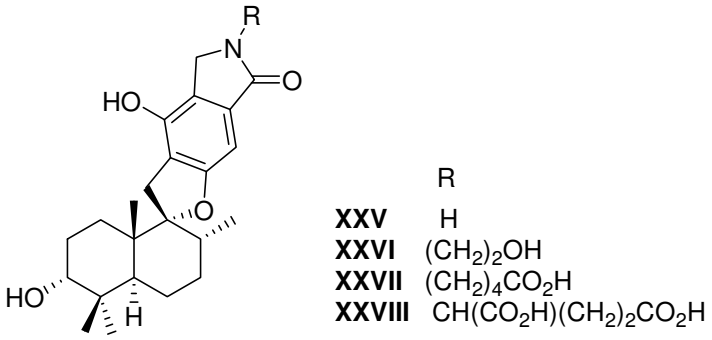
Otro grupo muy amplio de compuestos estructuralmente relacionados son las espirodihidrobenzofuranlactamas **XV-XXXI,** que han sido aisladas de diferentes especies de *Stachybotrys.* Algunas de ellas exhiben actividad inhibidora de la enzima colesterasa pancreática **(XV-XX)**[21] , otras son antagonistas de endotelina y e inhibidoras de la enzima proteasa VIH-1[8] (**XXI-XXVIII**). Las espirodihidrofuranlactamas diméricas stachybocinas A-C (**XXIX-XXXI**)[22] exhiben esta misma actividad.

(8) Roggo, B. E.; Hug, P.; Moss, S.; Stämpfli, A.; Kriemler, H.-P.; Peter, H. H. *J. Antibiot.* **1996**, *49* 374.

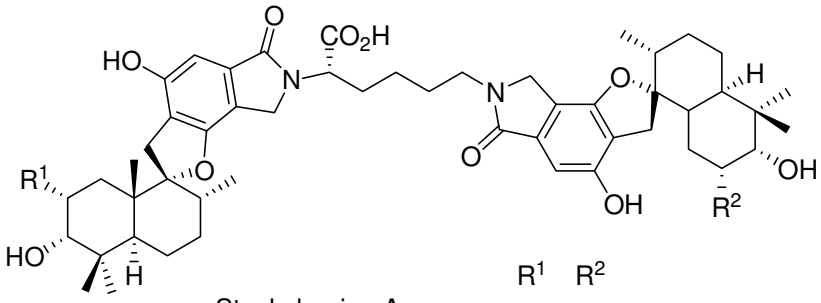
(21) Sakai, K.; Watanabe, K.; Masuda, K.; Tsuji, M.; Hasumi, K.; Endo, A. *Journal of Antibiotics* **1994**, *48*, 447.

(22) Nakamura, M.; Ito, Y.; Ogawa, K.; Michisuj, Y.; Sato, S.-I.; Takada, M.; Hayashi, M.; Yaginuma, S.; Yamamoto, S. *J. Antibiot.* **1995**, *48* 1389.

Otros productos naturales con una estructura espiránica similar son el metabolito ictiotóxico isochromazonarol (**XXXII**) [23], aislado del alga *Dictiopteris Undulata,* que presenta un doble enlace trisustituido $\Delta^{7,8}$ de lo que se intuye una posible diferencia en la formación del sistema espiránico.



	R
XXV	H
XXVI	$(CH_2)_2OH$
XXVII	$(CH_2)_4CO_2H$
XXVIII	$CH(CO_2H)(CH_2)_2CO_2H$



		R^1	R^2
Stachybocina A	**XXIX**	H	H
Stachybocina B	**XXX**	OH	H
Stachybocina C	**XXXI**	H	OH

Figura 3: Corallidictyales y compuestos relacionados II

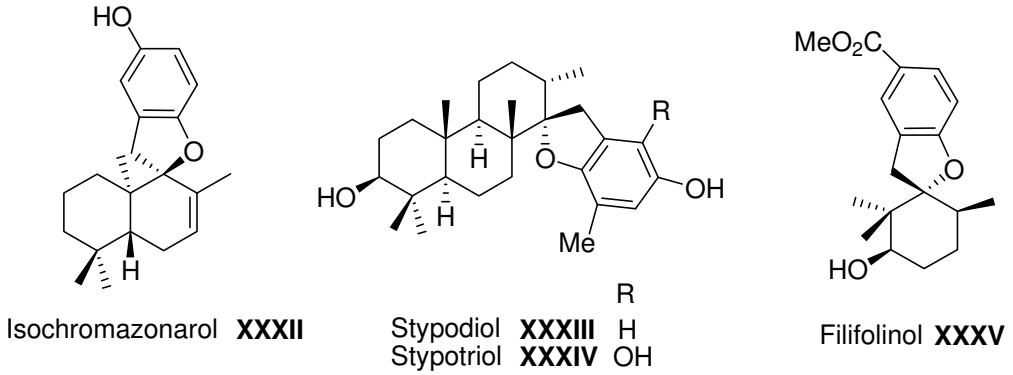
Por último, entre los compuestos relacionados con corallidictyales, a pesar de presentar diferente número de anillos en su esqueleto, destacan los derivados

(7) Andersen, R.; Hollander, I.; Roll, D. M.; Kim, S. C.; Mallon, R. G.; Williams, D. E.; Marion, F.; (The University of British Columbia, Can.; Wyeth, John, and Brother Ltd.). Application: WO, 2006, p 64.

(8) Roggo, B. E.; Hug, P.; Moss, S.; Stämpfli, A.; Kriemler, H.-P.; Peter, H. H. *J. Antibiot.* **1996**, *49* 374.

(23) Dave, M.-N.; Kusumi, T.; Ishitsuka, M.; Iwashita, T.; Kakisawa, H. *Heterocycles* **1984**, *22*, 2301.

pentacíclicos stypodiol y stypotriol (**XXXIIII** y **XXXIV**)[24-27], aislados del alga *Stypopodium zonale,* con potentes propiedades narcóticas y excitantes. Asimismo resalta el monoterpenoide filifolinol (**XXXV**)[28,29] con reconocidas propiedades como antioxidante, antivírico, antifúngico y antibacteriano



Isochromazonarol **XXXII**

R

Stypodiol **XXXIII** H
Stypotriol **XXXIV** OH

Filifolinol **XXXV**

Figura 4: Corallidictyales y compuestos relacionados III

(24) Gerwick, W. H.; Fenical, W.; Fritsch, N.; Clardy, J. *Tetrahedron. Lett.* **1979**, 145.
(25) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *J. Org. Chem.* **1998**, *63* 5100.
(26) Mori, K.; Koga, Y. *Bioorganic & Medicinal Chemistry Letters* **1992**, *2*, 391.
(27) Falck, J. R.; Chandrasekhar, S.; Manna, S.; Chiu, C.-C. *J. Am. Chem. Soc.* **1993**, *115*, 11606.
(28) Torres, R.; Virrarroel, L.; Urzúa, A.; Delle Monache, F.; Delle Monache, G.; Gacs-Baitz, E. *Phytochemistry* **1994**, *36*, 249.
(29) Modak, B.; Salina, M.; Rodilla, J.; Torres, R. *Molecules* **2009**, *14*, 4625.

2.-BIOGÉNESIS

2.1.-BIOGÉNESIS DE LIPHAGAL

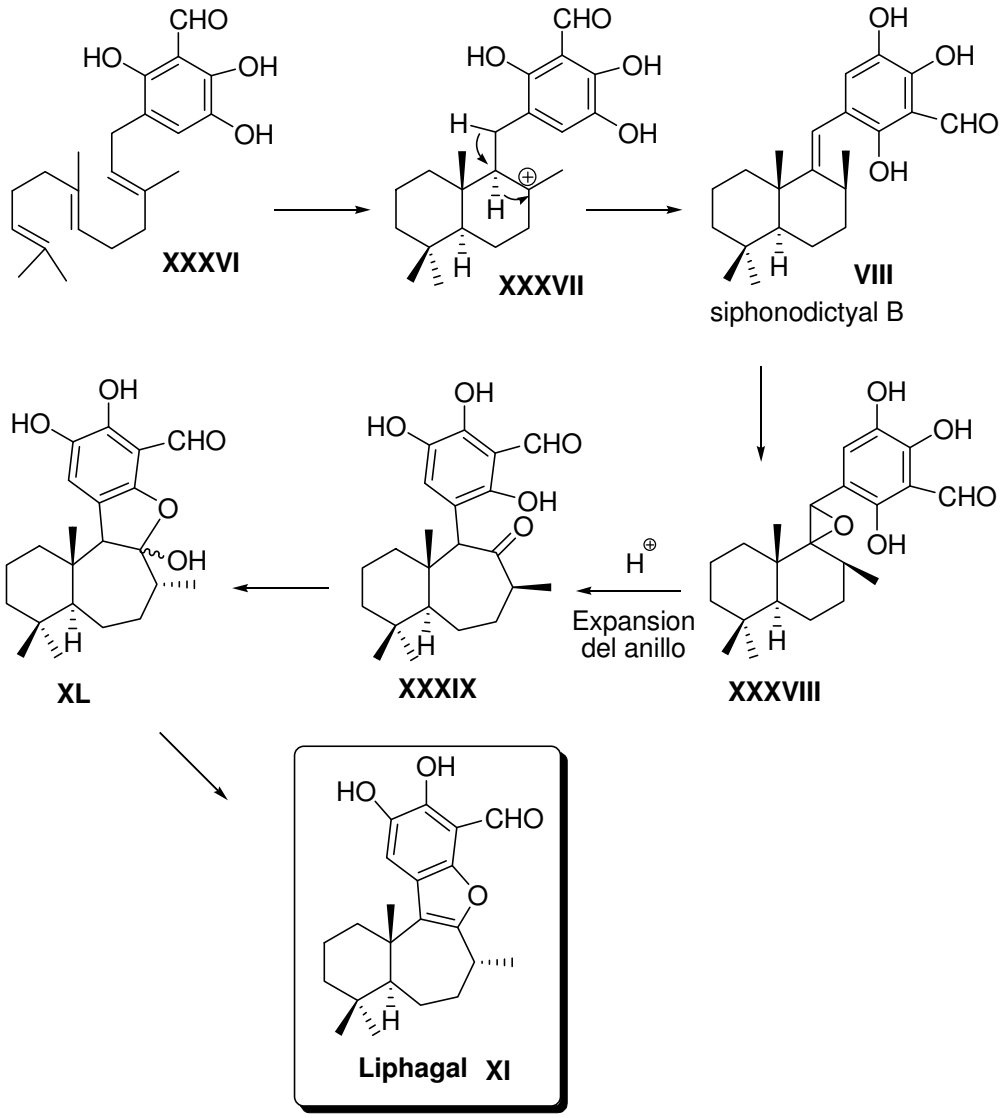
En 2006, el grupo del Prof. Andersen[6] publicó conjuntamente el aislamiento y la síntesis total biomimética de liphagal, con objeto de confirmar su estructura y de algún modo verificar su propuesta biogenética. Esta propuesta se basa en dos rutas alternativas:

*Ruta A: Formación de la decalina y subsecuente expansión del anillo, vía el precursor siphonodictyal B (**VIII**).*

A partir del farnesiltrihidroxibenzaldehído **XXXVI**, mediante una ciclación poliénica catalizada por ácido, en la cual, el C-2' del resto prenílico actúa como centro nucleofílico de la ciclación en cascada, se genera el carbocatión intermedio **XXXVII** que, según estos autores, experimenta desplazamiento 1,2 de hidruro y posterior desprotonación para dar lugar a siphonodictyal B (**VIII**). Este precursor clave, podría transformarse en liphagal (**XI**) vía el epóxido **XXXVIII**, el cuál, tras una expansión del anillo, genera la cetona **XXXIX.** La posterior epimerización del C-8 de dicha cetona permite obtener el metilo en disposición α. La formación del hemicetal correspondiente **XL**, seguida de deshidratación, daría lugar a liphagal.

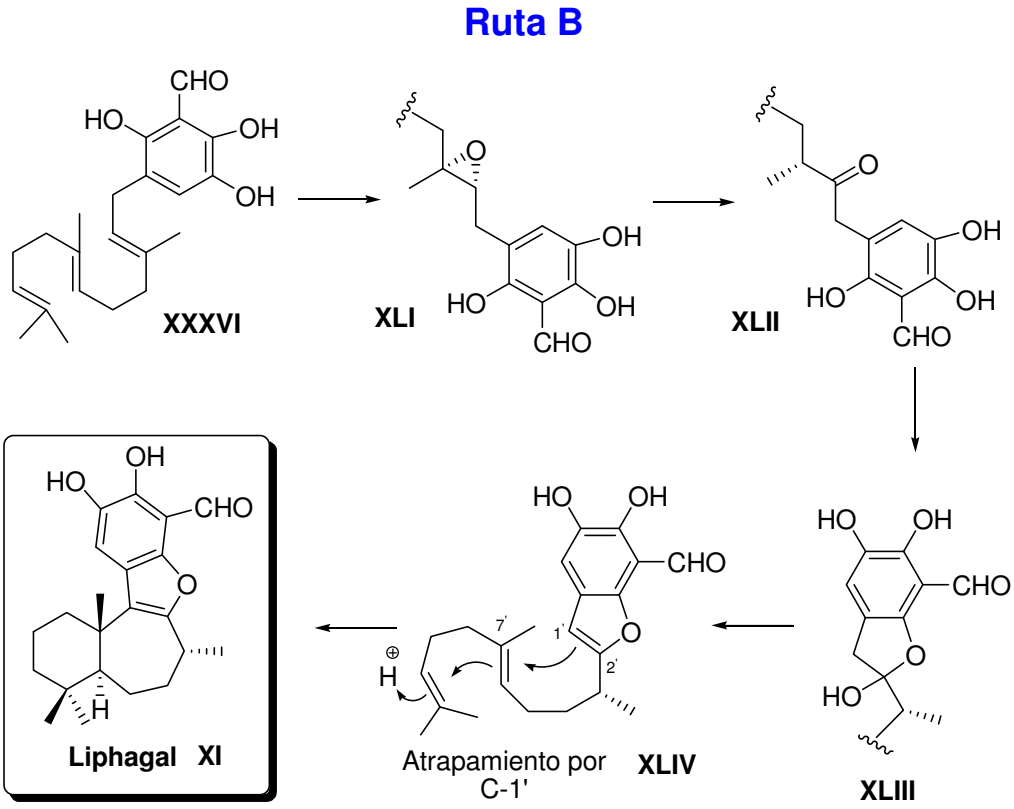
(6) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Organic Letters* **2006**, *8*, 321.

Ruta A



Esquema 1

Ruta B: Formación inicial del furano, seguida de una ciclación catiónica poliénica que da lugar al sistema anular 6-7 directamente.



Esquema 2

Otra ruta más directa comenzaría con la conversión de **XXXVI**, en la cetona **XLII**, a través posiblemente del epóxido **XLI**. Dicha cetona debería formar, espontáneamente, el hemicetal **XLIII**, que tras deshidratación rinde el benzofurano **XLIV**. La ciclación en cascada, catalizada por ácido, conduce directamente a liphagal (**XI**). Esta segunda vía supone la formación del furano, previa a la formación de los anillos 6-7. La preorganización del fragmento furánico genera un aumento de la nucleofília en el C-1' del resto prenil de la cadena lateral, dando así lugar a la ciclación poliénica que rinde de forma directa el sistema anular 6,7.

3.-ACTIVIDAD BIOLÓGICA

Como se ha mostrado anteriormente existe una llamativa diversidad química de sustancias bioactivas procedentes de esponjas marinas[30,31].

3.1.-PROPIEDADES BIOLÓGICAS DE CORALLIDICTYALES

Los corallidictyales son inhibidores de la PKC y, por tanto, juegan un papel fundamental en la regulación de la fisiología celular. Para poder entenderlo mejor, a continuación se hace un breve resumen del papel de PKC y las consecuencias de su inhibición.

a) Papel de las PKC

Las PKCs constituyen una familia de enzimas kinasas, formada por diez isoenzimas, que intervienen en el control del funcionamiento de otras proteínas, mediante la fosforilación de los grupos hidroxilo de serinas y treoninas presentes en dichas proteínas. Estas proteínas diana, tras ser fosforiladas, producirán una respuesta fisiológica específica, de muy distinta naturaleza, dependiendo de la proteína de que se trate. Las PKCs pueden ser activadas por la interacción con una amplia variedad de agonistas de la superficie celular (Ej, DAG, Ca^{2+},…).

Al tratarse de una enzima central en numerosas cascadas de señalización celular, es capaz de actuar sobre proteínas muy diversas, activándolas y, como consecuencia, activando rutas fisiológicas muy variadas. De ahí su importancia en la regulación de las funciones celulares.

(30) Gordaliza, M. *Mar. Drugs* **2010**, *8*, 2849.
(31) Laport, M. S.; Santos, O. C. S.; Muricy, G. *Current Pharmac. Biotech.* **2009**, *10*, 86.

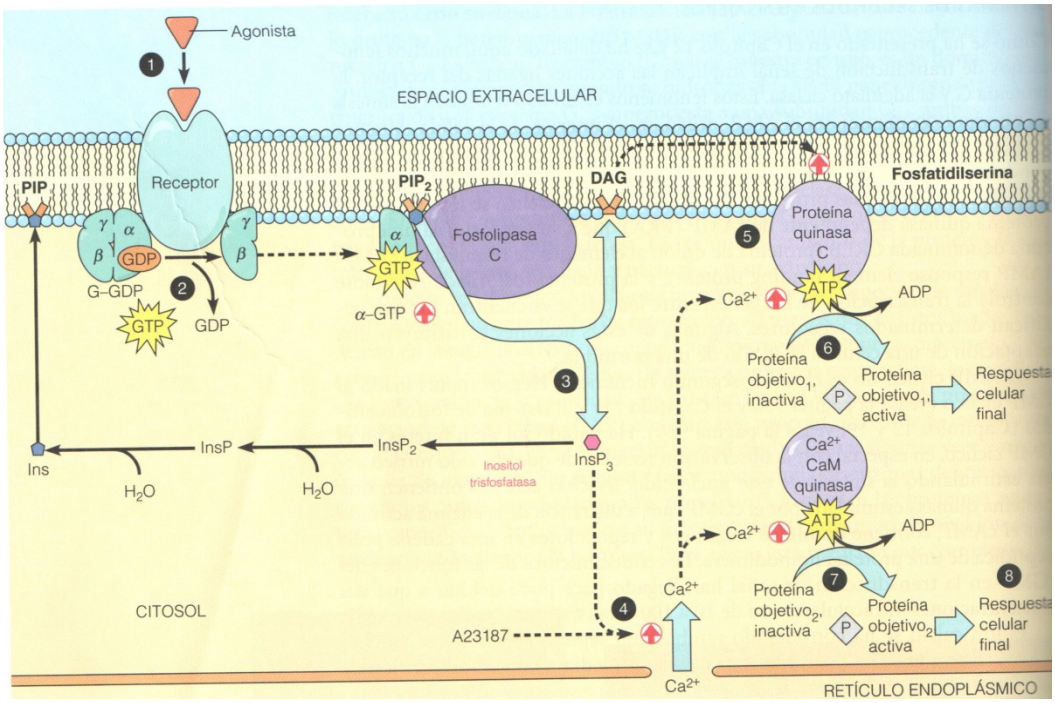


Imagen 2: Papel de la enzima fosfoquinasa C (PKC) en la transducción de señal.

b) Inhibidores de PKCs y potencialidad de corallidictyales

Los corallidictyales actúan inhibiendo de forma selectiva la acción fosforilante de la PKC y han mostrado potencialidad en terapias contra el cáncer[32], tratamiento de enfermedades inflamatorias, cardiovasculares[33] y neurológicas[34]. Presentan, así mismo, actividad antibiótica de amplio espectro y antifúngica[1,2,31,32]

(1) Chan, J., A.;; Freyer, A. J.; Carté, B. K.; Hemling, M. E.; Hofmann, G. A.; Mattern, M. R.; Mentzer, M. A.; Westley, J. W. *J. Nat. Prod.* **1994**, *57*, 1543.
(2) Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Köck, M. *J. Nat. Prod.*
(31) Laport, M. S.; Santos, O. C. S.; Muricy, G. *Current Pharmac. Biotech.* **2009**, *10*, 86.
(32) Monti, M. C.; Casapullo, A.; Santomauro, C.; D'Auria, M. V.; Riccio, R.; Gomez-Paloma, L. *ChemBioChem* **2006**, *7*, 791.
(33) Palaniyandi, S. S.; Sun, L.; Ferreira, J. C. B.; Rosen, D. M. *Cardiovascular Res.* **2009**, *82*, 229.
(34) Mellor, H.; Parker, P. J. *Biochemical Journal* **1998**, *332*, 281.

Su actividad se ha asociado a la presencia de la unidad de catecol,[9,30] así como a la función aldehídica y la presencia de grupos fenólicos libres, ya que los análogos protegidos han resultado inactivos.

Tabla 1: Valores IC_{50} de la mezcla de corallidictyales y para los derivados protegidos para la inhibición de PKC.

INHIBICIÓN PKC	**$IC_{50(A/B)}$**
Mezcla diastereomérica de corallidictyales	28 μM
Metiléteres derivados	Inact.

Además corallidictyales muestran selectividad frente a los diferentes isomorfos de PKC (selectivo para el isomorfo PKCα).

Tabla 2: Valores IC_{50} de corallidictyales frente a los isomorfos de PKC.

$IC_{50(A/B)}$ (μM)	**Isomorfo de PKC**
30	α
89	ϵ
>300	η
>300	ς

3.2.-PROPIEDADES BIOLÓGICAS DE LIPHAGAL

Liphagal actúa como inhibidor de la fosfoinositol 3 kinasa. Las PI3Ks constituyen una familia de enzimas que participan en la regulación de numerosas funciones biológicas y han sido relacionadas de forma directa con la patogénesis

(9) Larghi, E. L.; Kaufman, T. S. *ARKIVOC* **2011**, *vii*, 49.
(30) Gordaliza, M. *Mar. Drugs* **2010**, *8*, 2849.

de la diabetes y del cáncer así como de trastornos inflamatorios, cardiovasculares y enfermedades autoinmunes[35].

a) Papel de PI3K

Las PI3K son miembros de una familia de enzimas lipídicas, claves en el control de una amplia diversidad de funciones celulares[36], incluyendo el crecimiento celular, proliferación, movilidad, adhesión, supervivencia celular y tráfico intracelular. Existen varios isomorfos de PI3K, cada uno de ellos con diferente actividad reguladora, pero todos de interés biológico. Ejercen su regulación mediante la fosforilación de la posición 3 del fosfatidilinositol bifosfato (PIP_2) a fosfatidilinositol trifosfato (PIP_3). La siguiente imagen[37] muestra de forma esquemática y muy gráfica la compleja red de cascadas enzimáticas que son activadas por el proto-oncogen PKB/Akt, que es a su vez activado por la PI3K.

(35) Vijaykumar, D.; Manoj, K. L.; Ramswaroop, M.; Abhijit, R.; Ram, V.; Sanjay, K. *Synth. Comm.* **2011***41* . 177.
(36) Cantley, L. C. *Science* **2002** *296* 1655.
(37) Workman, P.; Clarke, P. A.; Guillard, S.; Raynaud, F. I. *Nat. Biotech.* **2006** *24* 794.

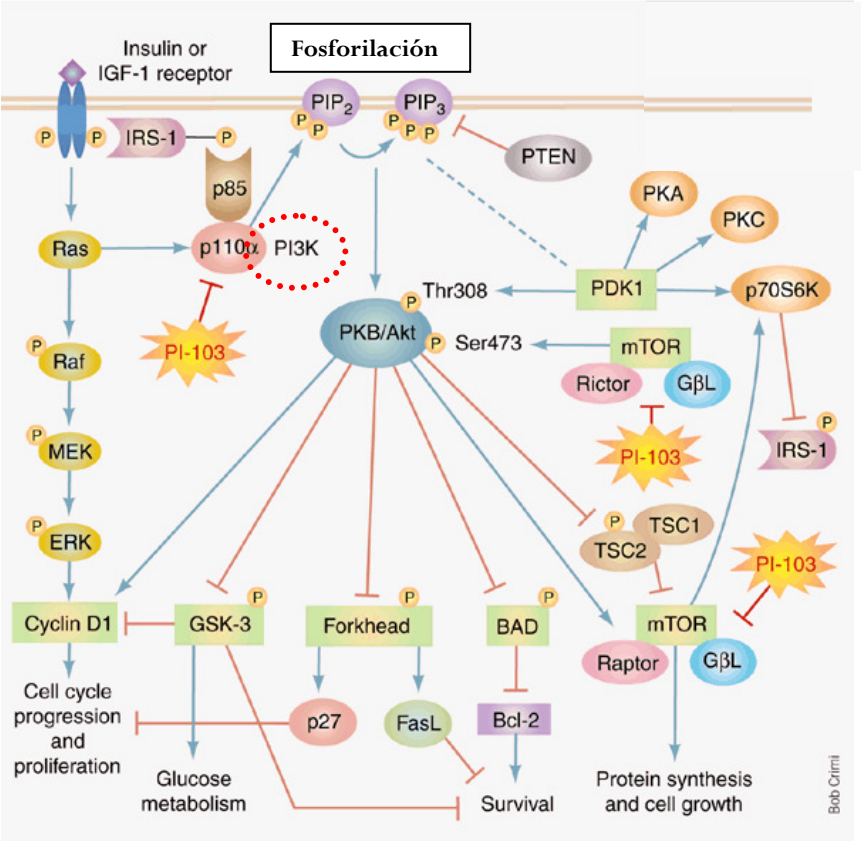


Imagen 3: Papel de la enzima fosfoinositol quinasa 3.

Se ha observado una sobreexpresión de PI3K en numerosos tumores sólidos como los de colon, mama, ovarios o páncreas entre otros[38], lo que hace de liphagal un interesante agente anticancerígeno.

b) Inhibidores de PI3K y potencialidad de liphagal

Se diferencian dos generaciones bien conocidas de inhibidores de PI3K previos a liphagal.

(38) Ward, S.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, P. *Chem. Biol.* **2003** *10* 207.

La primera generación de inhibidores de PI3K[39], wortmannina (**XLV**) y LY294002 (**XLVI**) entre otros, no muestran una selectividad significativa frente a los distintos isomorfos de PI3K y además bloquean las clases II y III de PI3K, así como otras enzimas relacionadas (MTOR) y no relacionadas (CK2, MLCK, PLK)[38,40]. Ante esta falta de selectividad, se desarrolló una segunda generación de inhibidores de PI3K con estructuras de tipo quercetina[41], compuestos arilmorfínicos basados en LY294002, purinas, aminotiazoles, derivados de tiazolidinedionas, quinazolinas, triazinas y derivados de pteridina[7,39].

(7) Andersen, R.; Hollander, I.; Roll, D. M.; Kim, S. C.; Mallon, R. G.; Williams, D. E.; Marion, F.; (The University of British Columbia, Can.; Wyeth, John, and Brother Ltd.). Application: WO, 2006, p 64.
(38) Ward, S.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, P. *Chem. Biol.* **2003** *10* 207.
(39) Pereira, A. R.; Strangman, W. K.; Marion, F.; Feldberg, L.; Roll, D.; Mallon, R.; Hollander, I.; Andersen, R. J. *Journal of Medicinal Chemistry* **2010**, *53*, 8523.
(40) Sundstrom, T. J.; Anderson, A. C.; Wright, D. L. *Biomol. Chem.* **2009** *7* 840.
(41) Patent WO 01/81346, U., 6,403 y US 2003/0236271.

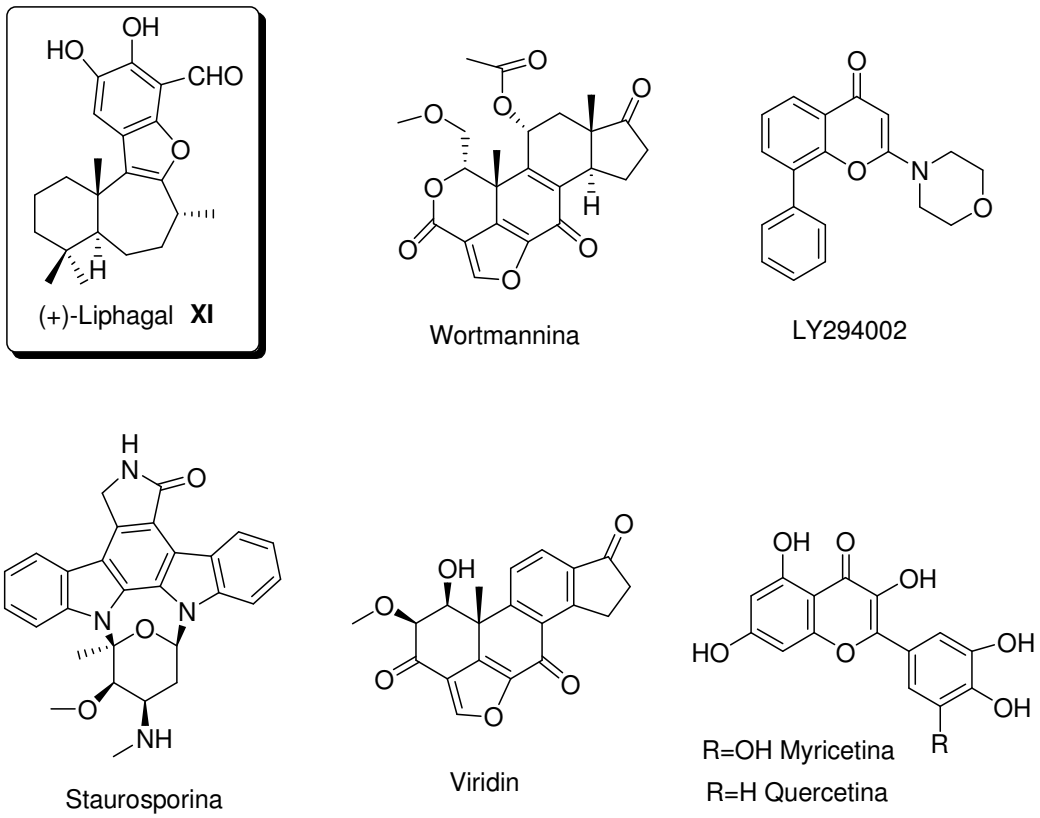


Figura 5: Inhibidores de PI3K**.**

Estos compuestos presentan selectividad por los isomorfos de PI3K, pero resultan ser inhibidores reversibles de menor potencialidad[42].

La actividad inhibidora de (+)-liphagal es llamativa por presentar una alta selectividad para la inhibición de PI3K α, un isomorfo lipídico de la kinasa que soporta un papel central en numerosos tipos de cáncer[43] . El valor de IC_{50} de (+)-liphagal contra PI3K α, es de 100nM, 10veces más potente que para el isomorfo γ de dicha enzima. Además, liphagal presenta actividad citotóxica frente a diferentes líneas tumorales humanas (Tabla 3).

(42) Knight, Z. A.; Shokat, K. M. *Biochem. Soc. Trans.* **2007** *35* 245.
(43) Samuels, Y.; Wang, Z.; Bardelli, A.; Silliman, N.; Ptak, J.; Szabo, S.; Yan, H.; Gazdar, A.; Powell, S. M.; Riggins, G. J.; Willson, J. K. V.; Markowitz, S.; Kinzler, K. W.; Vogelstein, B.; Velculescu, V. E. *Science* **2004** *304* 554

Tabla 3: Valores IC_{50} para varios inhibidores de PI3K, frente a diferentes líneas tumorales humanas.

	Línea tumoral	LoVo (colon)	CaCo (colon)	MDA-468 (mama)	
Inhibidores	Liphagal	**0.58**	**0.67**	**1.58**	**IC_{50} (µM)***
	Wortmannina	0.2	3	4	
	LY294002	3	5	8	

*valores obtenidos en ensayos *in vitro*.

En comparación con otros inhibidores de PI3K, tanto naturales como sintéticos, liphagal exhibe una relación actividad/selectividad superior, que hace de él un candidato prometedor no sólo en la lucha contra el cáncer, sino también como agente en el tratamiento de enfermedades inflamatorias y autoinmunes, así cómo en trastornos cardiovasculares[35,38].

(35) Vijaykumar, D.; Manoj, K. L.; Ramswaroop, M.; Abhijit, R.; Ram, V.; Sanjay, K. *Synth. Comm.* **2011***41* . 177.

(38) Ward, S.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, P. *Chem. Biol.* **2003** *10* 207.

4.- SÍNTESIS

En este apartado se comentan las etapas más relevantes de la síntesis de las moléculas objeto de esta tesis y compuestos relacionados.

4.1. SÍNTESIS DE CORALLIDICTYAL

Hasta la actualidad no se ha descrito ninguna síntesis de corallidictyales, aunque se han desarrollado algunas estrategias para la síntesis de compuestos muy relacionados estructuralmente, como el K-76 y sus derivados. Estos tipos de compuestos difieren de corallidictyales, tanto en el fragmento sesquiterpénico como en el fragmento aromático, aunque poseen un anillo dihidrobenzofuránico, formando un enlace espiro en su posición 2' con el C-9 del biciclo terpénico.

4.2.-SÍNTESIS DE COMPUESTOS RELACIONADOS

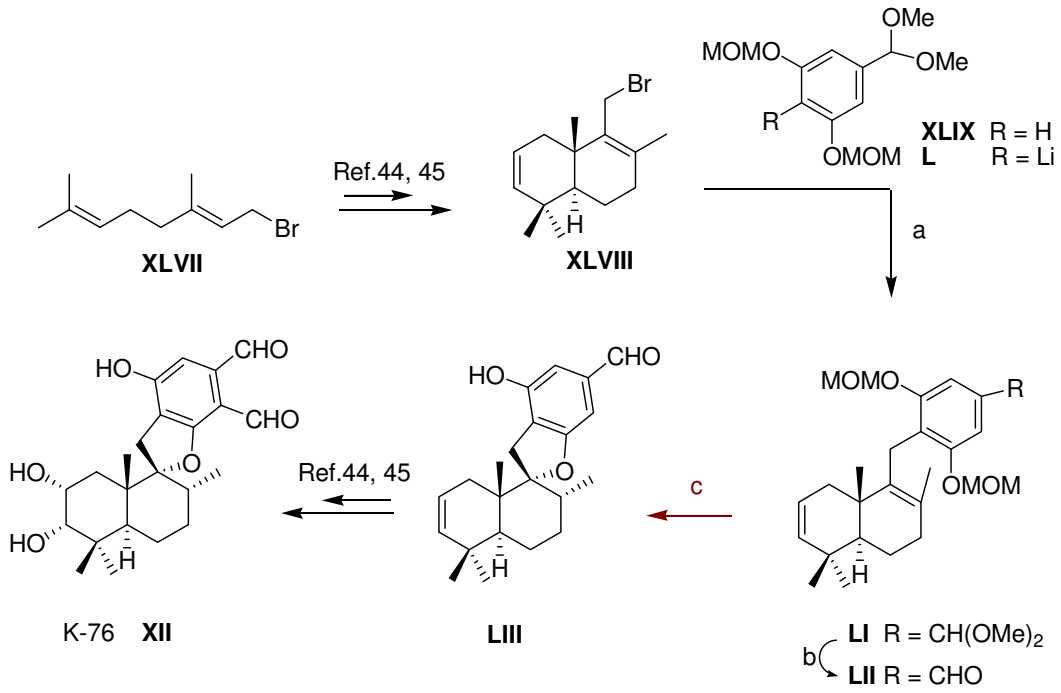
a) Síntesis de K-76

En 1982, el grupo de Corey[44] sintetizó el primero de los espirodihidrobenzofuranos: K-76. Desde entonces, se han publicado tres síntesis más de K-76, como se resume a continuación.

La primera síntesis de K-76 se llevó a cabo mediante la condensación del fragmento drimánico **XLVIII**, preparado a partir de bromuro de geranilo (**XLVII**) [44,45], con el arillitio **L,** generando el acetal tricíclico **LI**. La etapa clave es la ciclación del aldehído **LII**, para formar el derivado espiránico **LIII**, de manera regio y estereoselectiva. Esta etapa se llevó a cabo haciendo reaccionar **LII**

(44) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 7612.
(45) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742.

durante 2 días con ácido clorhídrico 2N en una mezcla de disolventes THF-etilenglicol, que generó el fenol que experimentó la subsecuente ciclación. El deseado espirodihidrobenzofurano se obtuvo en un 50-70% de rendimiento, junto con un 20% del isómero benzopiránico Se trata de una síntesis racémica de (±)-K-76 mediante una ruta que permite el acceso, además, a una amplia variedad de análogos estructurales. El espirocompuesto **LIII** sufrió posteriores transformaciones, que llevaron a la primera síntesis de K-76 (**XII**).



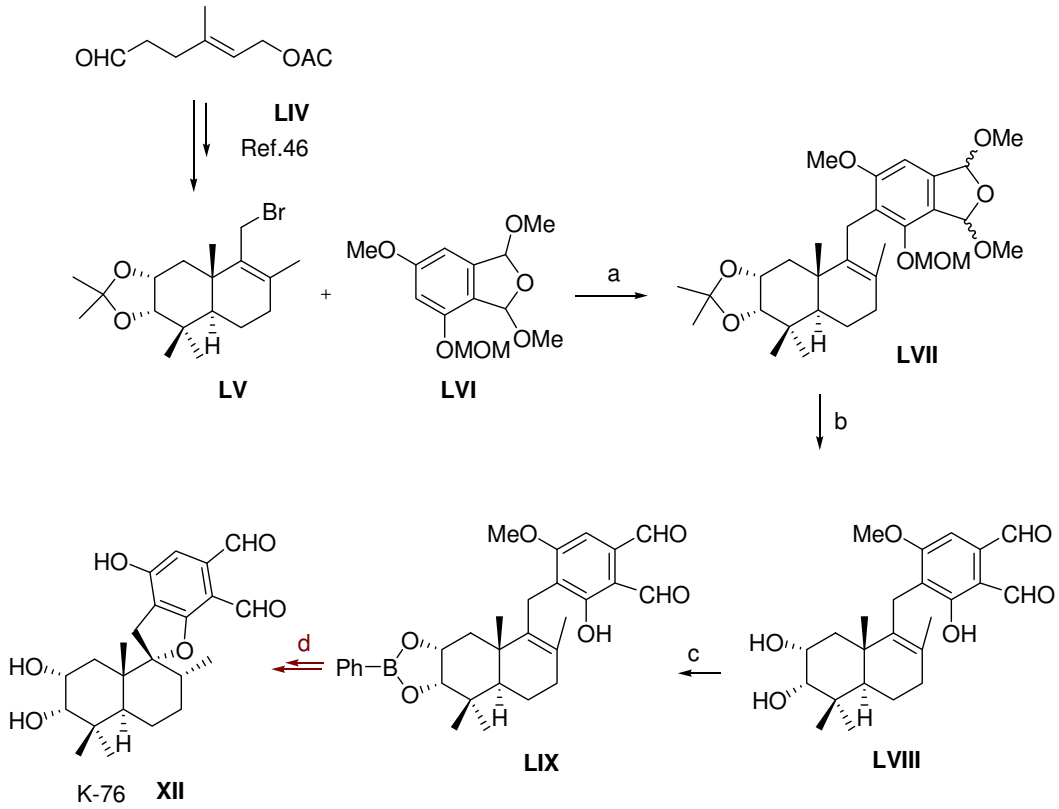
a) **XLIX**, *n*-BuLi, THF-TMEDA, HMPA, -78 ºC-0 ºC, 1h (75%);
b) 1N HCl-THF (1:3), rt, 1h (93%);
c) 2N HCl, $HOCH_2CH_2OH$-THF (2:1:4), rt, 48h (50-70%);

Esquema 3: Síntesis de K-76 por el grupo de Corey.

En 1985, McMurry y Erion[46] llevaron a cabo la síntesis de K-76 a partir del fragmento drimánico **LV** y del aromático **LVI**, siguiendo una estrategia similar a la de Corey. Las modificaciones realizadas respecto a la síntesis de Corey se

(46) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712.

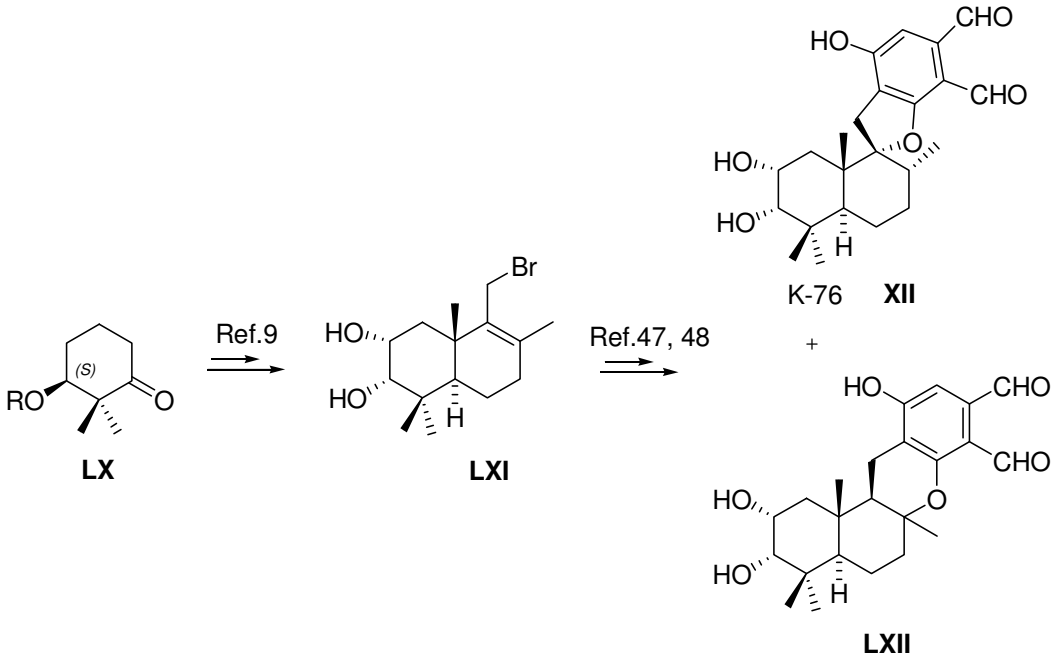
llevaron a cabo principalmente para solventar el problema de la *syn*-dihidroxilación del doble enlace. Esta tiene lugar de forma muy mayoritaria por la cara α frente a la sufrida por la cara β (12:1), utilizando tetróxido de osmio en presencia de N-óxido de trimetilamina. En esta ocasión, el derivado espiránico se formó, junto al isómero benzopiránico, en proporción de 1.7:1 respectivamente, mediante tratamiento del fenol **LIX** con exceso de Amberlyst 15, y con un 72 % de rendimiento total.



a) ^{t}BuLi, TMEDA, THF, CuCN, -78 ºC-(-15ºC), 8 h;
b) 2N HCl, 2-PrOH-THF (10:10:1), 15 h, t.a., (59% global);
c) $PhB(OH)_2$, $MgSO_4$, PhH, t.a., 15 h (100%); d) Amberlyst 15, PhH, t.a., 37 h (45%)

Esquema 4: Síntesis de K-76 por McMurry y Erion.

En 1988 Mori y Komatsu[47] presentan la síntesis de K-76, mediante una nueva metodología para la obtención del sintón drimánico **LXI**[9], a partir de la β-hidroxicetona **LX**[48] y posteriormente, emplean los protocolos descritos por McMurry y Erion para la condensación y subsecuentes transformaciones hasta K-76. En la ciclación se utiliza de nuevo Amberlyst 15, obteniendo la mezcla de isómeros **XII:LXII** con un rendimiento del 16 %.



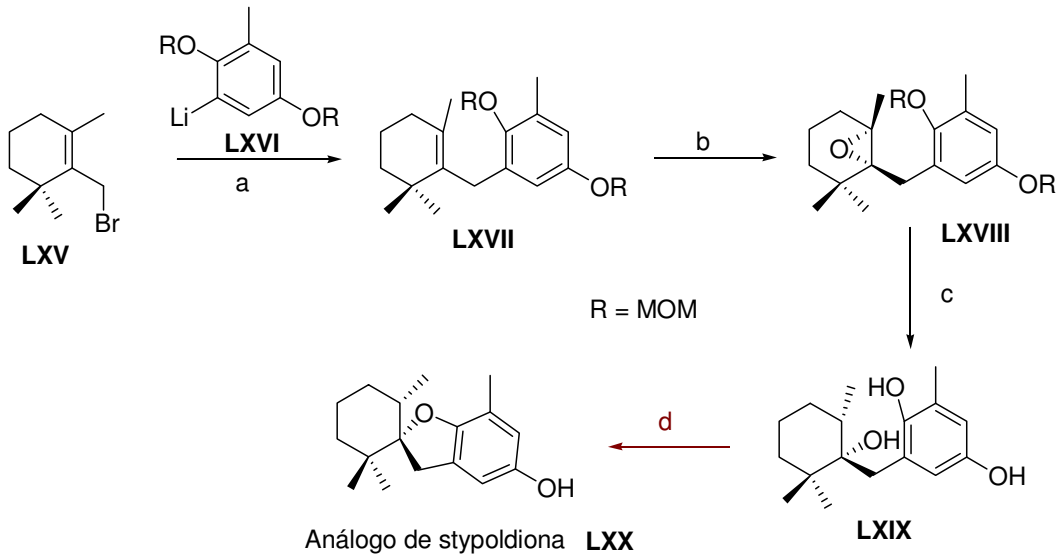
Esquema 5: Síntesis de K-76 por Mori y Komatsu.

b) <u>Síntesis de stypoldiona</u>

En 1990, Pattenden y col.[49] describieron la síntesis de un análogo de stypoldiona **LXX** utilizando la misma estrategia sintética utilizada para la síntesis de K-76. El tratamiento del hidroxiquinol **LXIX** con APTS en cantidades

(9) Larghi, E. L.; Kaufman, T. S. *ARKIVOC* **2011**, *vii*, 49 y referencias citadas.
(47) Mori, K.; Komatsu, M. *Liebigs Annalen der Chemie* **1988**, 107.
(48) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273.
(49) Begley, M. J.; Fish, P. V.; Pattenden, G. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2263.

catalíticas, dió lugar a una ciclación suave que proporcionó el espirodihidrofurano **LXX** exclusivamente, en 90 % de rendimiento.



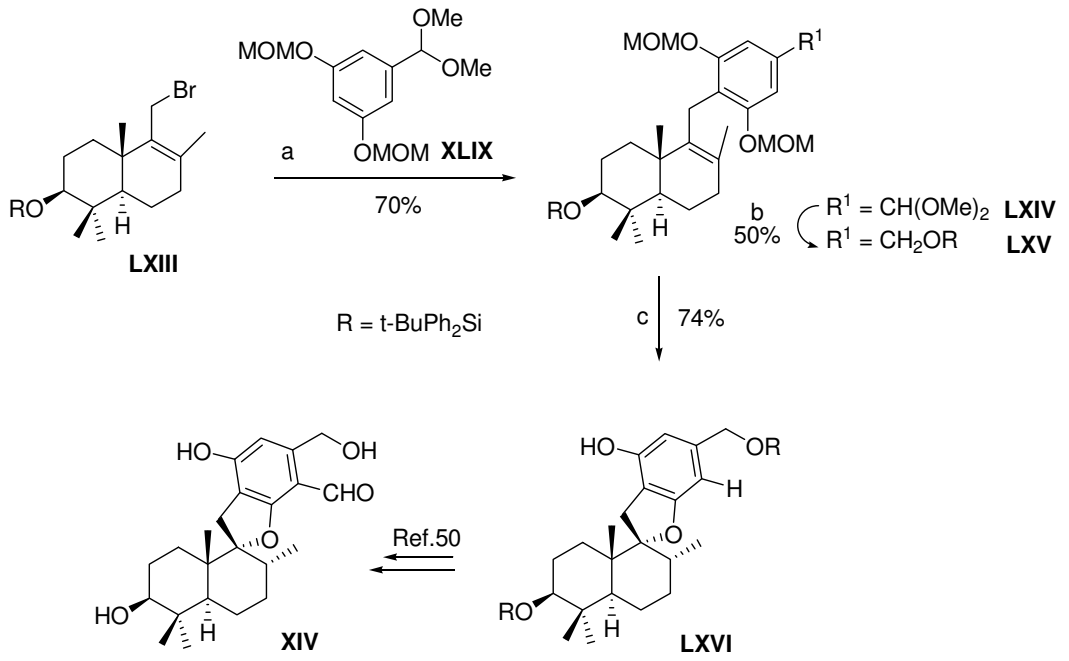
a) 1. CuI, 30 min., -40ºC; 2. **LXV**, -40ºC-t.a., 2.5 h, (64%).
b) AMCPB, DCM, t.a., 16h, (91%). c) AlH_3, Et_2O, 0 ºC, 18 días, (79%).
d) APTS, $CHCl_3$, reflujo, 7 días, (90%).

Esquema 6: Síntesis de stypoldiona por Pattenden.

c) Síntesis de L-671,776

En 1997, Falck y col.[50] sintetizaron L-671,776 empleando de nuevo la estrategia convergente clásica para este tipo de compuestos. Esta vez, la formación del sistema espiránico se logró empleando ioduro de trietoxisilano, generado *in situ,* obteniéndose tan sólo un 5 % del isómero piránico no deseado. El hecho de que esta reacción no haya sido utilizada posteriormente genera cierta incertidumbre acerca de su aplicabilidad y de sus limitaciones.

(50) Falck, J. R.; Reddy, K. K.; Chandrasekhar, S. *Tetrahedron Letters* **1997**, *38*, 5245.



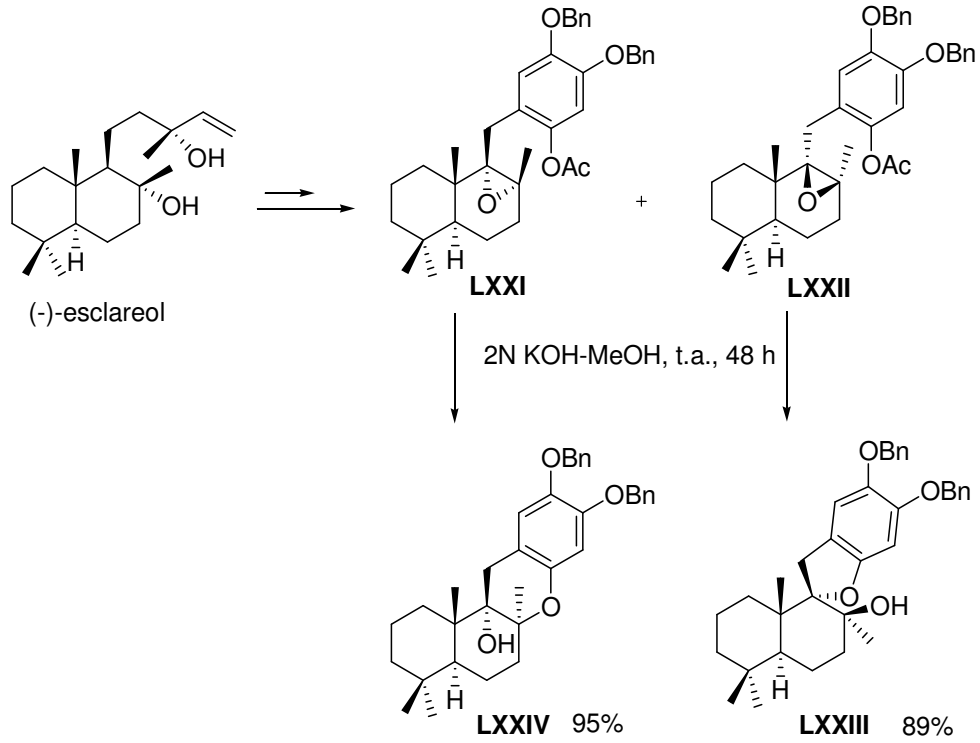
a) **XLIX**, *n*-BuLi, TMEDA, THF, -20 ºC, 40 min; CuCN, -20ºC, 40 min;-78 ºC, 2 h.
b) 1. 1N HCl/THF (1:3), 23 ºC, 1 h; 2. $NaBH_4$, MeOH/THF (10:1), 0 ºC, 15 min. 3. t-$BuPh_2SiCl$, DMAP, py, 23 ºC, 4h. c) $(EtO)_3SiCl/NaI$, CH_3CN/DCM (4:1), -5 ºC, 0.5 h.

Esquema 7: Síntesis de L-671,776 por Falck.

d) Síntesis de análogos de puupehediona

En 1999, durante las aproximaciones hacia la síntesis de puupehediona a partir de (-)-esclareol realizadas en nuestro laboratorio[51], se estudiaron los procesos de ciclación de los epóxidos **LXXI** y **LXXII** en medio básico. El tratamiento del epóxido β (**LXXII**) con disolución 2 N de KOH en MeOH a temperatura ambiente durante 48 h proporcionó de forma totalmente regio- y estereoselectiva el derivado espiránico **LXXIII**, en un 89% de rendimiento. En estas condiciones, el epóxido α (**LXXI**) rindió el derivado benzopiránico **LXXIV**, como único producto.

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.



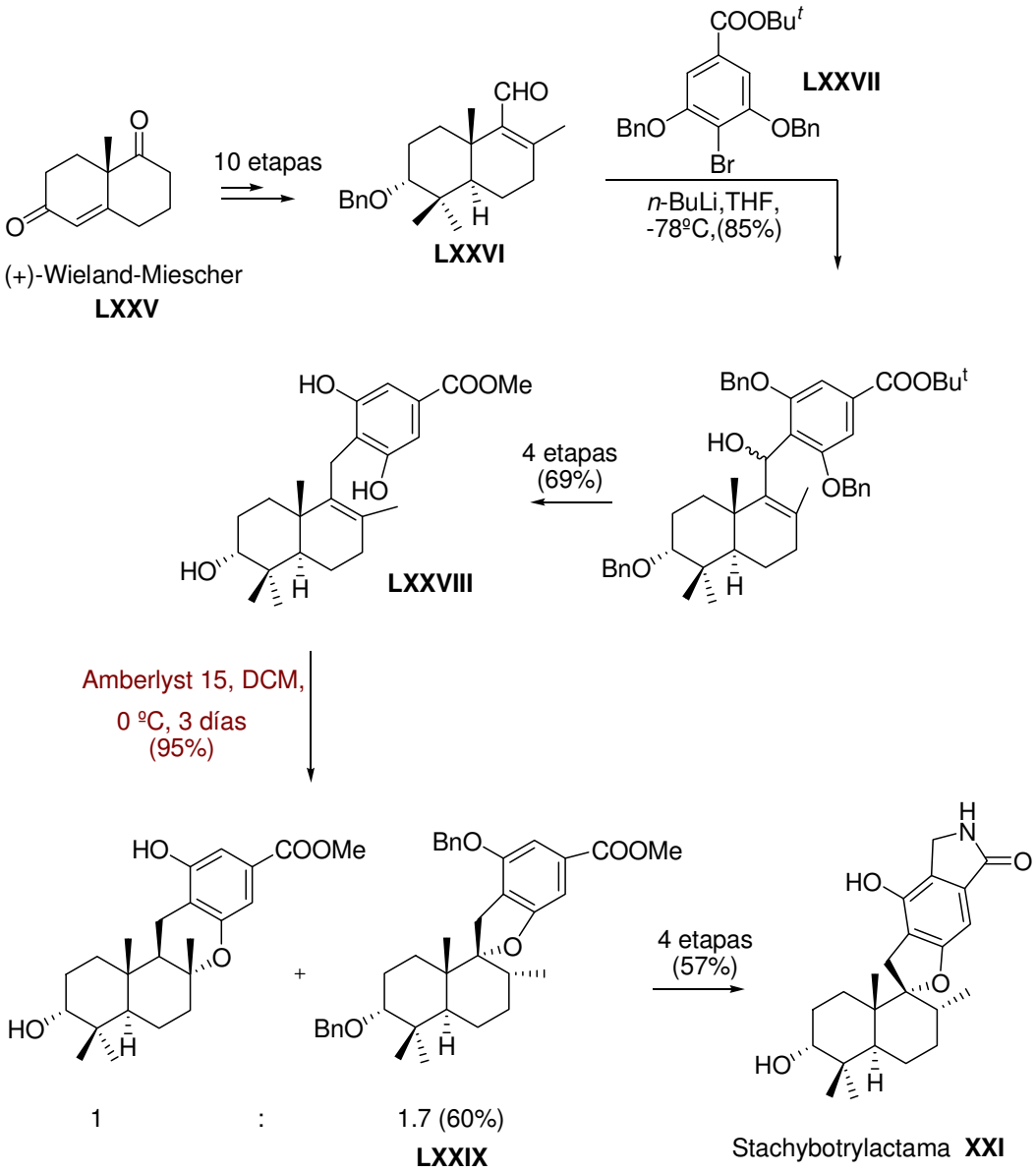
Esquema 8: Ciclaciones selectivas de precursores de puupehediona.

e) Síntesis de espirobenzofuranlactamas

Recientemente Kende y colaboradores,[52,53] han comunicado la primera síntesis de la spirodihydrobenzofuranlactama **XXI** , haciendo uso de la misma estrategia de ciclación empleada por McMurry, 18 años antes, obteniendo también la mezcla isomérica 1.7:1, en el mejor de los casos.

El esquema sintético para la obtención de espirobenzofuranlactamas recuerda bastante a la estrategia empleada para la síntesis de K-76. En este caso, se ha utilizado la cetona de (+)-Wieland-Miescher (**LXXV**) como sustrato de partida.

(52) Kende, A.; Zhong, W.-P. D.; Guo, X.-C. *Organic Letters* **2003**, *5*, 1785.
(53) Kende, A.; Zhong, W.-P. D.; Guo, X.-C. *J. Org. Chem.* **2003**, *68*, 7422.



Esquema 9: Síntesis de espirobenzofuranlactamas por Kende.

En resumen, en todos los casos descritos, se ha utilizado la misma estrategia para acoplar el fragmento drimánico y aromático. Además, en la etapa clave de la síntesis se observa la carencia de una metodología eficaz para formar el esqueleto carbonado de este tipo de compuestos, tal como se recoge en la siguiente tabla.

Tabla 4: Tabla resumen de rendimientos de los procesos de ciclación.

Condiciones	**Ref.**	**Año**	**espiro:pirano**	**Rdto** (%)
HCl 2N, THF-etilenglicol, 2 días	44	1982	2.5-3.5: 1	70-90
Ambelyst 15, PhH, 1.5 días	46	1985	1.7: 1	60?
APTS, $CHCl_3$, 7 días	49	1990	1: 0	90
$(EtO)_3SiI$	50	1997	1: 0.05	74
KOH/MeOH, 2 días	51	1999	1: 0	89
Ácidos variados			0: 1	76-93
Amberlyst 15, 3 días	52, 53	2003	1: 1.7	60

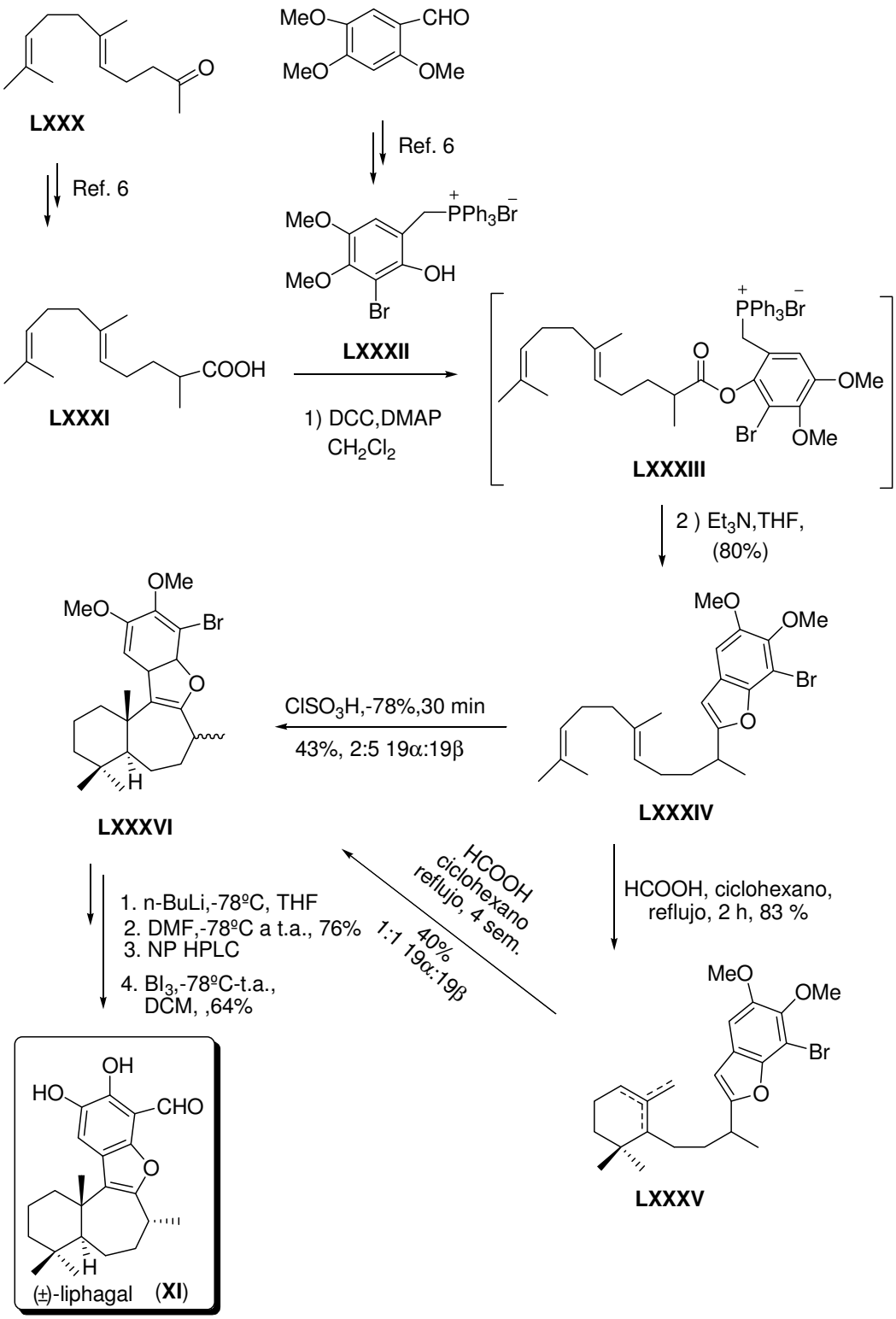
f) Síntesis de liphagal

Andersen et al.[6] llevaron a cabo la primera síntesis de (±) liphagal, utilizando una ciclación biomimética, que se basa en la segunda ruta biogenética propuesta por este mismo grupo de investigación y anteriormente mencionada, en la que la

(6) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Organic Letters* **2006**, *8*, 321.
(44) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 7612.
(46) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712.
(49) Begley, M. J.; Fish, P. V.; Pattenden, G. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2263.
(50) Falck, J. R.; Reddy, K. K.; Chandrasekhar, S. *Tetrahedron Letters* **1997**, *38*, 5245.
(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.
(52) Kende, A.; Zhong, W.-P. D.; Guo, X.-C. *Organic Letters* **2003**, *5*, 1785.
(53) Kende, A.; Zhong, W.-P. D.; Guo, X.-C. *J. Org. Chem.* **2003**, *68*, 7422.

etapa clave es la ciclación poliénica que genera el sistema anular 6-7. La síntesis comienza con la preparación del precursor adecuado **LXXXIV**, para la ciclación.

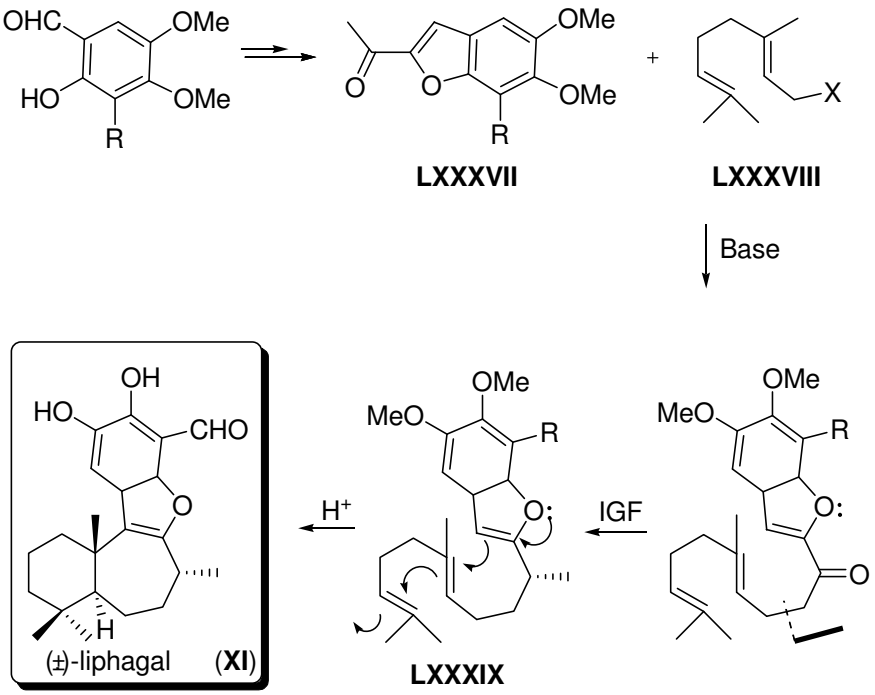
Se sintetizó el fragmento isoprenoide **LXXXI,** a partir de geranilacetona (**LXXX**), en una secuencia de 3 etapas. Se hizo reaccionar **LXXXI** con el sintón aromático (sal de fosfonio) **LXXXII**, mediante una reacción de acoplamiento ácido-fenol. El éster intermedio **LXXXIII**, en medio básico, sufrió una reacción de Wittig intramolecular dando lugar a la formación del deseado benzofurano **LXXXIV**. La etapa clave de ciclación se consiguió sometiendo **LXXXIV** a reflujo en ciclohexano en presencia de ácido fórmico, durante un mes. Con objeto de acortar el tiempo requerido para la ciclación poliénica, se trató **LXXXIV** con ácido clorosulfónico a -78 ºC, en nitropropano durante 30 min, obteniéndose así una mezcla de epímeros **LXXXVI** (proporción 2:5), con un rendimiento del 43%.



Esquema 10: Síntesis de liphagal por Andersen.

Para finalizar, se introdujo el grupo aldehído y se procedió a la ruptura de los grupos metiléter.

Tres años después, Mehta[54] publicó una síntesis formal y racémica de liphagal, que toma igualmente como base la segunda ruta biogenética propuesta por Andersen y se desarrolla de forma lineal en 9 etapas, muy similares a las publicadas previamente por el anterior.



Esquema 11: Síntesis de liphagal por Mehta.

En este caso se trata de la reacción entre el acetilbenzofurano precursor **LXXXVII** y el monoterpenoide **LXXXVIII**, dando lugar a la formación de un enlace C-C crucial, que genera **LXXXIX**, el cual tras sufrir una ciclación catiónica poliénica, como en la propuesta por Andersen, rinde el compuesto objetivo **XI***.

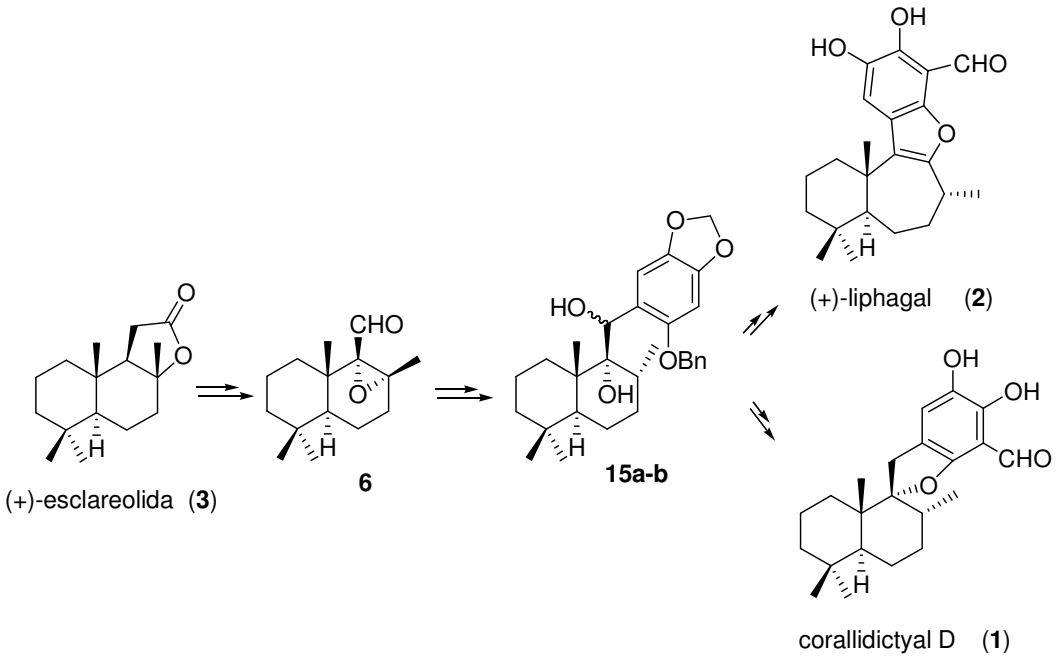
(54) Mehta, G.; Likhite, N. S.; Ananda Kumar, C. S. *Tetrahedron Letters* **2009**, *50*, 5260.
**Trabajos simultáneos y posteriores en la síntesis de (+)-liphagal se referencian en el capítulo de resultados y discusión.*

RESULTADOS Y DISCUSIÓN

1. PREPARACIÓN DEL DIOL SESQUITEPÉNICO 15, PROPUESTO COMO INTERMEDIO CLAVE PARA LA SÍNTESIS DE LIPHAGANOS Y CORALLIDICTYALES, A PARTIR DE (+)-ESCLAREOLIDA

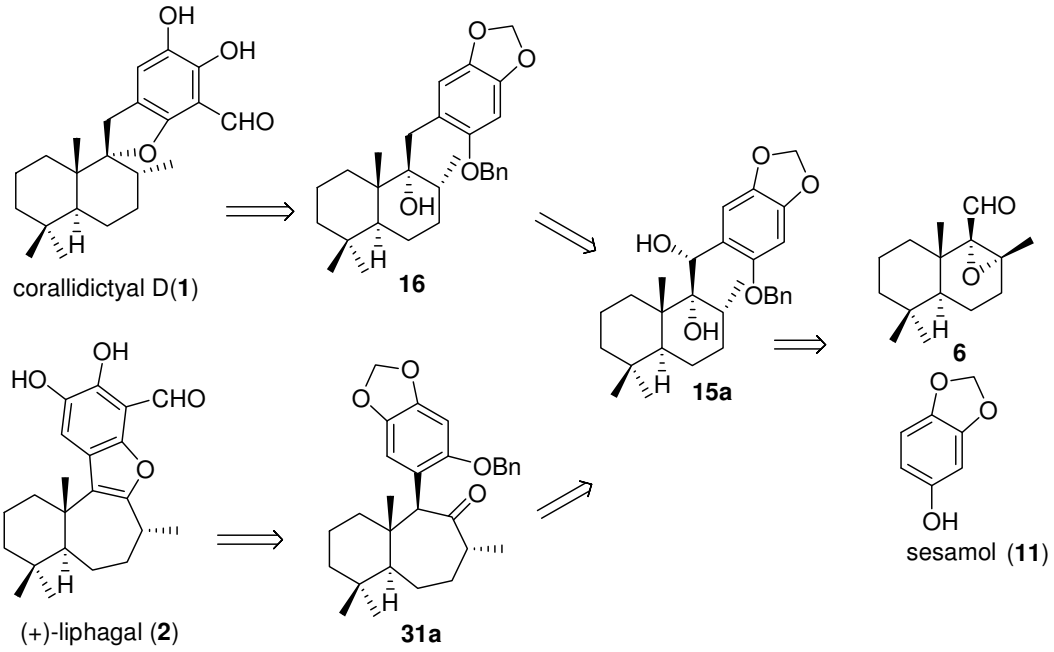
El primer objetivo de esta memoria trata la preparación del diol merosesquiterpénico **15**, postulado como un posible precursor de los meroterpenoides corallidictyal D (**1**) y (+)-liphagal (**2**), a partir de una materia prima barata y comercialmente accesible: (+)-esclareolida (**3**) (Esquema 1).

El epoxialdehído drimánico **6** es un intermedio clave para la síntesis de dicho diol merosesquiterpénico **15**.



Esquema 1

Consecuentemente, la estrategia retrosintética planteada, se basa en la preparación del diol merosesquiterpénico **15**, a partir del epoxialdehído drimánico **6**, que a su vez debe ser fácilmente sintetizado, empleando (+)-esclareolida (**3**) como materia prima (Esquema 2)



Esquema 2

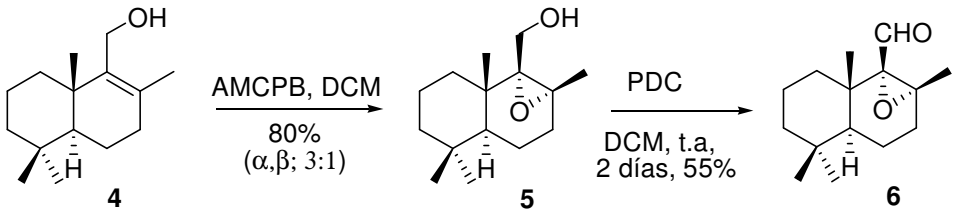
1.1. SÍNTESIS DEL EPOXIALDEHÍDO DRIMÁNICO 6

Se han utilizado dos procedimientos alternativos para la preparación del epoxialdehído drimánico **6**.

*Método 1: Síntesis del epoxialdehido drimánico **6** vía epoxialcohol **5**.*

En primer lugar se preparó el epoxialdehído **6** vía el epoxialcohol **5**

ampliamente descrito en bibliografía[55-64] (Esquema 3). La reacción de epoxidación del alcohol drimánico **4**, se llevó a cabo mediante tratamiento con AMCPB en DCM a 0ºC. Tras 1 h de reacción a 0ºC se obtuvo una mezcla de los α y β epoxialcoholes en proporción 3:1. La posterior oxidación del α–epoxialcohol **5**, empleando PDC, proporcionó el epoxialdehído drimánico **6** con un rendimiento moderado del 55%.



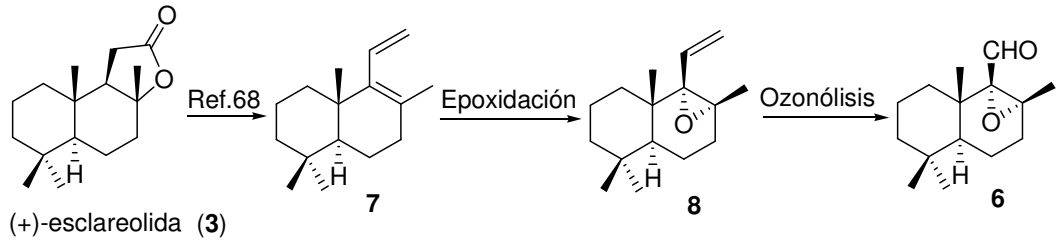
Esquema 3

La baja estereoselectividad del proceso de epoxidación[65,66], junto a la cierta dificultad de separación cromatográfica de los correspondientes estereoisómeros, nos empujó a desarrollar un procedimiento alternativo más selectivo, que conduzca al epoxialdehído **6** bajo condiciones experimentales más adecuadas.

(55) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Letters* **1997**, *38*, 8101.
(56) Tsujimori, H.; Bando, M.; Mori, K. *Eur. J. Org. Chem.* **2000**, 297.
(57) Tsangarakis, C.; Stratakis, M. *Adv. Synth. Catal.* **2005**, *347*, 1280.
(58) Mori, K.; Koga, Y. *Liebigs Ann. Chem.* **1991**, 769.
(59) Arima, Y.; Kinoshita, M.; Akita, H. *Tetrahedron: Asymmetry* **2007**, *18*, 1701.
(60) Okamura, W. H.; Peter, R.; Reischl, N. *J. Am. Chem. Soc.* **1985**, *107*, 1034.
(61) Akita, H.; Amano, H.; Kato, K.; Kinoshita, M. *Tetrahedron: Asymmetry* **2004**, *15*, 725.
(62) Kuchkova, K. I.; Aryku, A. N.; Barba, A. N.; Vlad, P. F. *Chem. Nat. Prod.* **2007**, *43*, 412.
(63) Polovinka, M. P.; Korchagina, D. V.; Gatilov, Y. V.; Bagrianskaya, I. Y.; Barkhash, V. A.; Perutskii, V. B.; Ungur, N. D.; Vlad, P. F.; Shcherbukhin, V. V.; Zefirov, N. S. *J. Org. Chem.* **1994**, *59*, 1509.
(64) Schmidt, C.; Chisti, N. H.; Breining, T. *Synthesis* **1982**, 391.
(65) Dominguez, G.; Hueso-Rodriguez, J. A.; de la Torre, M. C.; Rodriguez, B. *Tetrahedron Letters* **1991**, *32*, 4765.
(66) Kulcitki, V.; Ungur, N.; Gavagnin, M.; Carbone, M.; Cimino, G. *Eur. J. Org. Chem.* **2005**, *9*, 1816.

*Método 2: Nuevo procedimiento para la síntesis del epoxialdehído **6.***

El esquema 4 recoge el planteamiento sintético para la preparación del epoxialdehído drimánico **6** a partir de (+)-esclareolida (**3**). El proceso implicaría la transformación de la materia prima en el dieno **7**, que mediante una epoxidación regio y estereoselectiva del doble enlace tetrasustituido, y posterior degradación del grupo vinilo conduciría al epoxialdehído **6**.

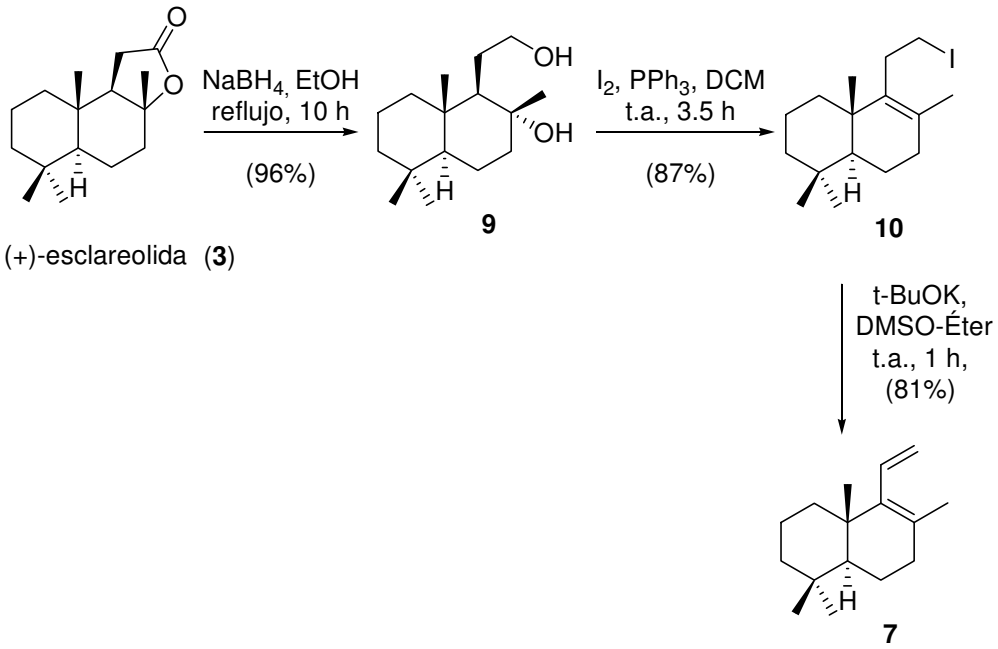


Esquema 4

El dieno **7** se prepara eficientemente a partir de (+)-esclareolida (**3**) mediante una secuencia de 3 etapas con un rendimiento global del 65%, de acuerdo con el procedimiento publicado por nuestro grupo de investigación[67]. Dicha secuencia implica la reducción inicial de **3** con $NaBH_4$, seguida de un tratamiento con I_2/PPh_3[68], que provoca la simultánea deshidratación del alcohol terciario y la formación del ioduro homoalílico **10**. Mediante deshidrohalogenación en medio básico de éste, se obtiene el dieno deseado **7** con buen rendimiento (Esquema 5).

(67) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmammouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592.

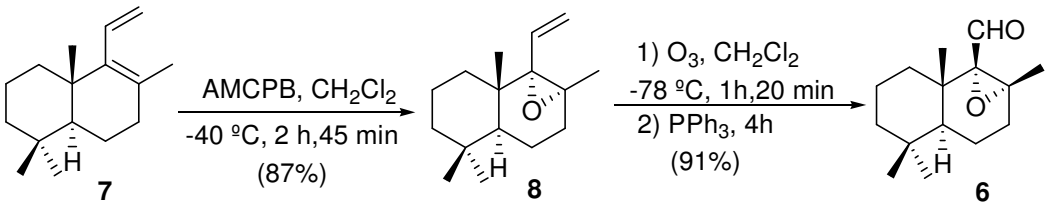
(68) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. M. *Tetrahedron Lett.* **2005**, *46*, 1075.



Esquema 5

La epoxidación regio y estereoselectiva del dieno **7** se llevó a cabo mediante tratamiento con AMCPB a -40ºC. El epoxialqueno obtenido se identificó en base a sus datos espectroscópicos, tanto de RMN-^{1}H como de ^{13}C. La estereoquímica del anillo de oxirano se estableció mediante experiencias de NOE diferencial.

Tras ozonólisis reductiva del epoxialqueno **8** se obtuvo el epoxialdehído **6** con un excelente rendimiento (91%) (Esquema 6)



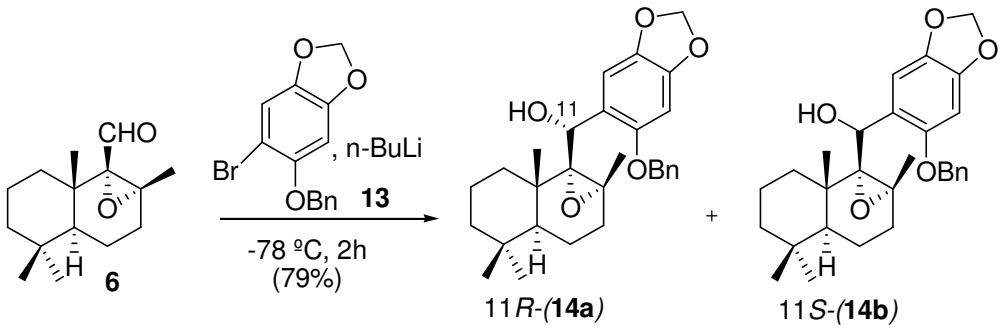
Esquema 6

La estructura de **6** fue corroborada mediante sus datos espectroscópicos, tanto de IR como RMN ^{1}H y de ^{13}C. En el espectro de IR se observa la banda a 1726 cm^{-1} característica del grupo carbonilo. Asimismo, las señales a 9.69 ppm y 201.8

ppm en los espectros de RMN ^{1}H y de ^{13}C respectivamente, confirman la transformación del grupo vinilo en aldehído.

1.2. PREPARACIÓN DEL DIOL SESQUITERPÉNICO 15

Siguiendo un procedimiento análogo al descrito por nuestro grupo de investigación[69] se hizo reaccionar el epoxialdehído **6** con la sal de litio derivada del bromuro **13**[70], preparada mediante tratamiento de una disolución de éste en THF con *n*-BuLi a -78 ºC. Después de 2 h de reacción a esta misma temperatura se obtuvo una mezcla de epoxialcoholes **14a** y **14b** en proporción 1:1, con un rendimiento de 79% (Esquema 7).



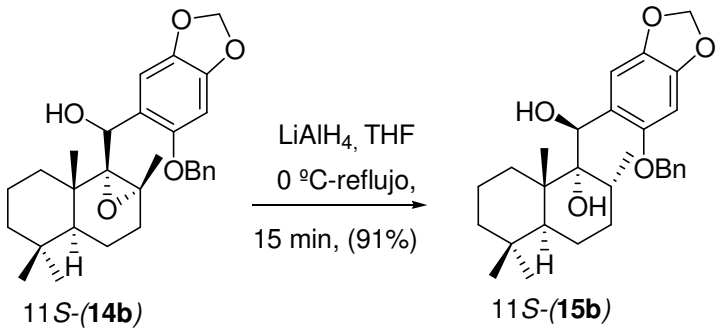
Esquema 7

Los epoxialcoholes se separaron mediante cromatografía en columna de gel de sílice y se caracterizaron en base a sus datos espectroscópicos de RMN-^{1}H y de ^{13}C. Se aprecian las señales a 5.14 ppm y 5.59 ppm, que integran cada una por un protón, correspondientes al grupo metino bencílico de ambos epoxialcoholes **14a** y **14b,** respectivamente. **14a** cristalizó en forma de sólido blanco, mientras que **14b** permaneció como sirupo.

(69) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Meneses, R.; Es-Samti, H.; Fernández, A. *J. Org. Chem.* **2009**, *74*, 3384.

(70) Hitotsuyanagi, Y.; Ichihara, Y.; Takeya, K.; Itokawa, H. *Tetrahedron Letters* **1994**, *35*, 9401.

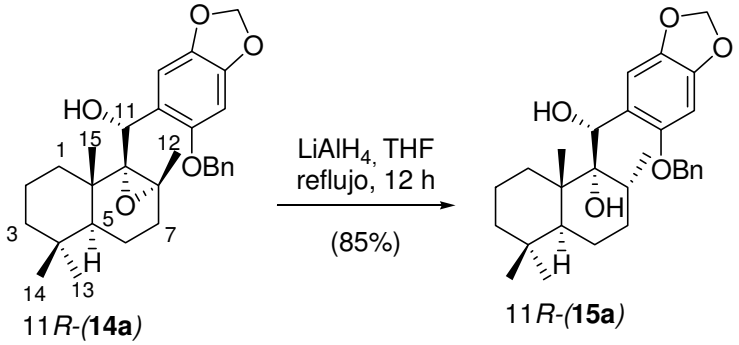
A continuación, se sometieron los dos epoxialcoholes isómeros a condiciones de apertura reductiva del anillo oxiránico, empleando $LiAlH_4$ (Esquema 8).



11*S*-(**14b**) 11*S*-(**15b**)

Esquema 8

El epoxialcohol **14b** sufrió una rápida apertura del anillo oxiránico con completa regio- y estereoselectividad, proporcionando el correspondiente diol **15b**, tras ser tratado con $LiAlH_4$ a reflujo en THF durante 15 min. En cambio, y bajo las mismas condiciones de reacción, el epoxialcohol **14a** tardó 12 horas en transformarse en el diol merosesquiterpénico **15a** (Esquema 9).



11*R*-(**14a**) 11*R*-(**15a**)

Esquema 9

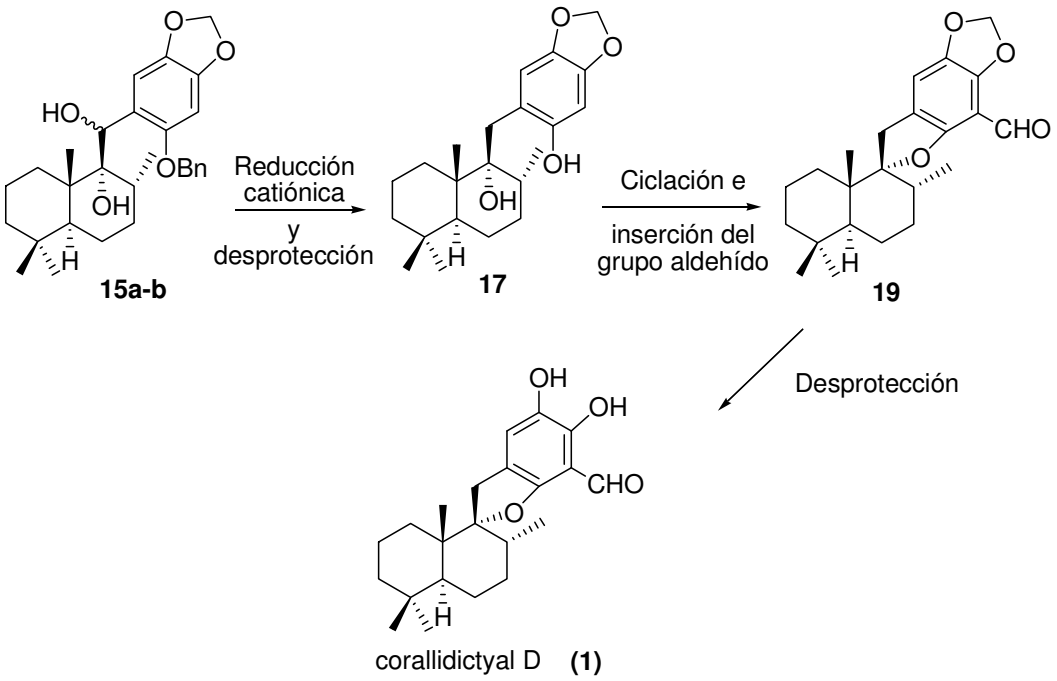
La explicación de este comportamiento tan dispar se puede atribuir al impedimento estérico que ejercen los metilos C-15 y C-12 del fragmento drimánico, que dificultarían la asociación del hidruro de aluminio y litio con el grupo hidroxilo, necesaria para provocar la apertura del anillo oxiránico. La

regioselectividad observada en la apertura de estos epóxidos viene determinada por la tendencia del hidruro a efectuar el ataque axial preferentemente, frente al ataque ecuatorial, asi como por el impedimento estérico ejercido por el metilo axial C-15 anteriormente mencionado.

Se caracterizaron ambos productos en base a sus datos espectroscópicos. En el espectro de RMN-^{1}H, se observa la variación en el desplazamiento químico de un isómero respecto del otro, especialmente para el metilo C-12, que aparece a 0.78 ppm en el isómero 11*R* y a 0.91 ppm en el 11*S*. Ese mismo efecto se observa en los protones bencílicos de los metinos C-11, con diferente configuración en ambos compuestos, apareciendo dichos protones a 3.13 y 3.23 ppm y los carbonos correspondientes a 94.8 y 96.4 ppm, para los isómeros 11*R* y 11*S* respectivamente.

2. ESTUDIO DE REDUCCIÓN DEL GRUPO HIDROXILO BENCÍLICO: APROXIMACIÓN A LA SÍNTESIS DE CORALLIDICTYAL D (1)

Una vez preparados sendos dioles merosesquiterpénicos **15a** y **15b**, se planteó, en primer lugar, la reducción catiónica del grupo hidroxilo secundario y bencílico para aproximarse a la síntesis de corallidictyal D (**1**). La secuencia sintética implicaría entonces, ciclación, introducción regioselectiva del grupo formilo y ruptura de la agrupación metilendioxi (Esquema 10).

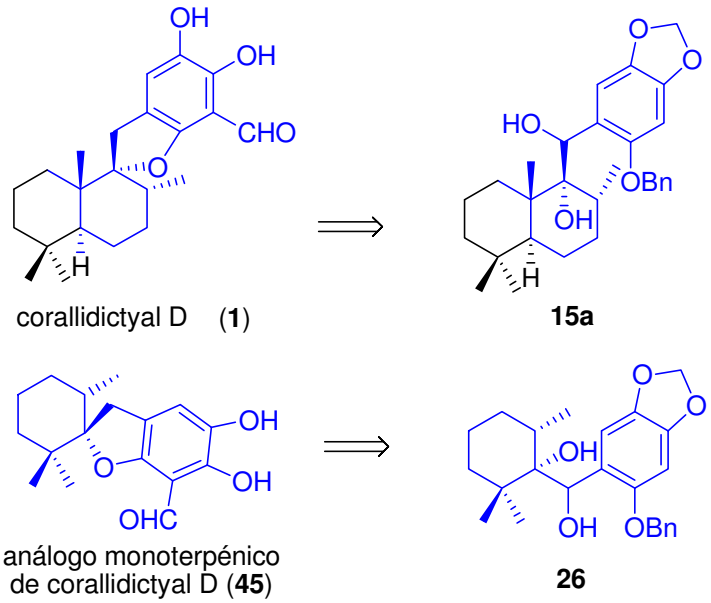


Esquema 10

Antes de ensayar la reacción de reducción catiónica sobre los dioles merosesquiterpénicos **15a-b**, clave para la síntesis de corallidictyales, se planteó el estudió del proceso sobre los análogos monoterpénicos de estos dioles, ya que la posible existencia de enlaces de hidrógeno entre los dos grupos hidroxilo, junto

a la disposición del hidroxilo terciario en C-9, muy inestable en condiciones ácidas[71,72], hace difícil pronosticar el resultado final de esta reducción.

Se llevó a cabo la preparación de los dioles monoterpénicos **26a-b**, análogos de los dioles sesquiterpénicos **15a-b**, con el objeto de facilitar el estudio de la reacción de reducción catiónica, que se considera clave para la síntesis de corallidictyal D (**1**), y a la vez aproximarnos así a la síntesis del análogo monoterpénico de corallidictyal D (**45**). Consideramos interesante el estudio de la relación estructura–actividad (SAR) de **45**, por su parecido con el producto natural **1**, por lo que constituye también uno de los objetivos de esta Tesis doctoral (Esquema 11).



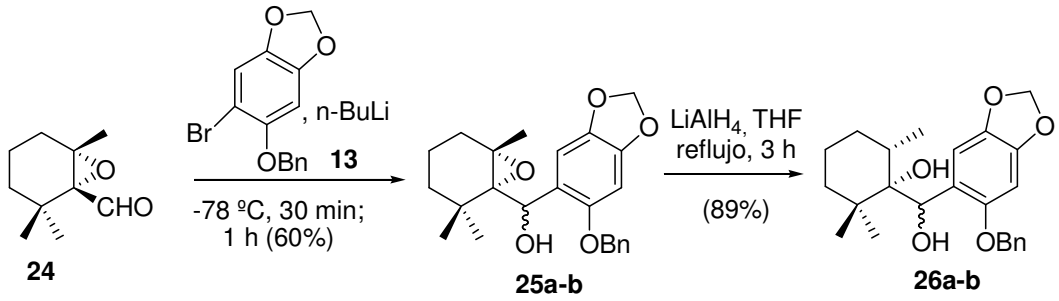
Esquema 11

(71) Takao, K.; Sasaki, K.; Kozaki, T.; Yanagisawa, Y.; Tadano, K.; Kawashima, A.; Shinonaga, H. *Organic Letters* **2001**, *3*, 4291.

(72) Kuan, K. K. W.; Pepper, H. P.; Bloch, W. M.; George, J. H. *Organic Letters* **2012**, *14*, 4710.

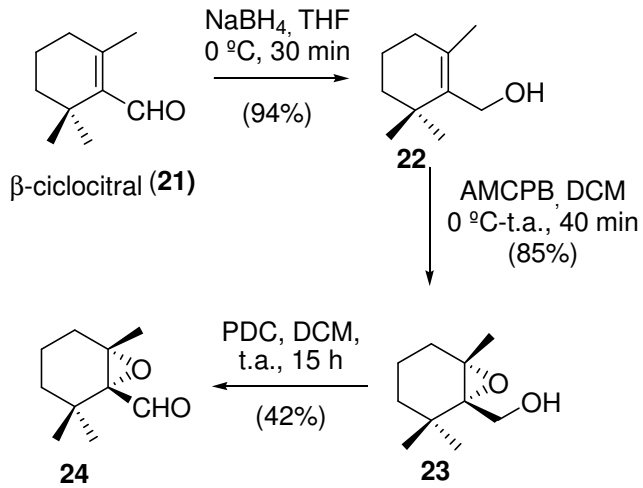
2.1. PREPARACIÓN DEL DIOL MONOTERPÉNICO 26

Siguiendo la misma estrategia utilizada para la preparación del diol sesquiterpénico **15** y utilizando en este caso el epoxialdehído **24**, se obtuvo sin ninguna dificultad el correspondiente diol monoterpénico **26a-b** como mezcla diastereomérica (2:1), con un rendimiento global del 53%. (Esquema 12).



Esquema 12

El esquema 13 recoge la secuencia sintética para la preparación del aldehído monoterpénico **24**[73,74]**,** a partir de β-ciclocitral comercial (**21**).



Esquema 13

(73) Srikrishna, A.; Nagamani, S. A.; Jagadeesh, S. G. *Tetrahedron: Asymmetry* **2005**, *16*, 1569.

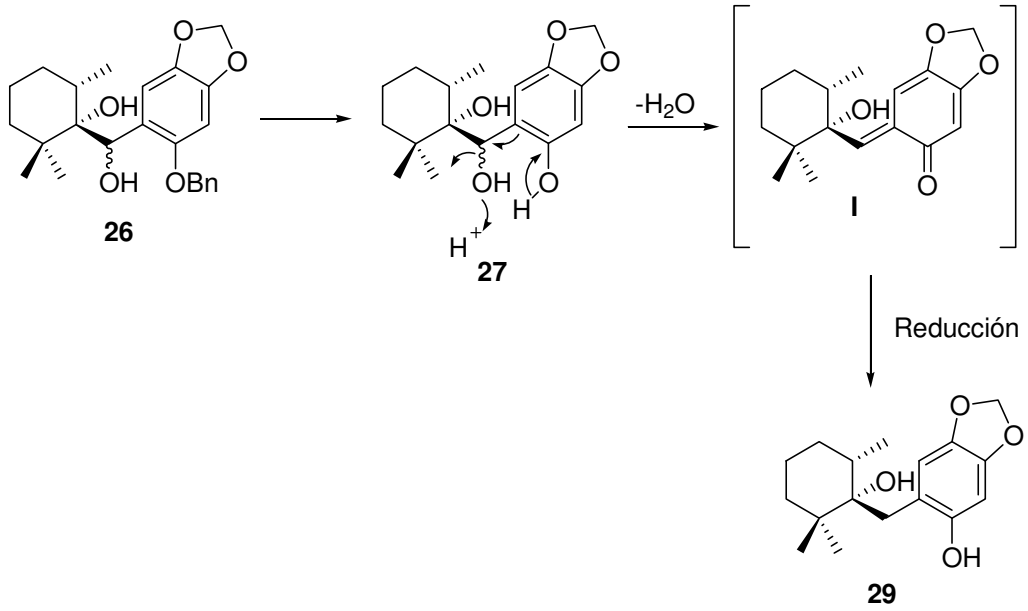
(74) Olpp, T.; Brückner, R. *Angew Chem Int Ed* **2005**, *44*, 1553.

*a) Reducción del hidroxilo bencílico de **26***

Una vez obtenidos los dioles monoterpénicos **26a-b**, se llevó a cabo el estudio de la etapa de reducción del grupo hidroxilo bencílico. En primer lugar, se ensayaron diferentes condiciones para la reducción catalítica con hidrógeno y posteriormente, se investigaron también reducciones catiónicas.

1) Ensayos de reducción catalítica con hidrógeno [75,76].

Se pensó que en condiciones clásicas de hidrogenación, se podría conseguir la simultánea desprotección del hidroxilo fenólico y reducción del hidroxilo bencílico, vía la enona **I**, procedente del dihidroxifenol **27**, que se reduciría muy fácilmente originando el hidroxifenol deseado **29** (Esquema 14).

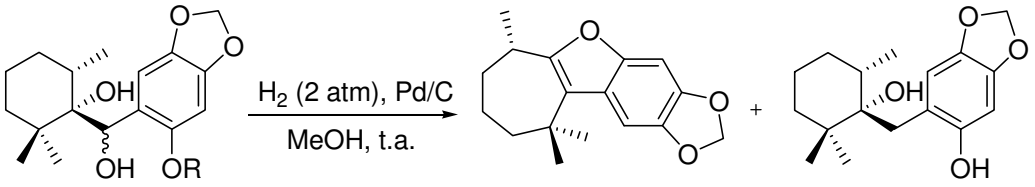


Esquema 14

(75) Quideau, S.; Lebon, M.; Lamidey, A.-M. *Organic Letters* **2002**, *4*, 3975.
(76) Yang, L.; Williams, D. E.; Mui, A.; Ong, C.; Krystal, G.; van Soest, R.; Andersen, R. J. *Organic Letters* **2005**, *7*, 1073.

En la tabla 1 se resumen los resultados obtenidos bajo diferentes condiciones de hidrogenación.

Tabla 1: Ensayos de hidrogenación de los compuestos 26a-b y 27a-b.



R = Bn, **26a-b**
R = H, **27a-b**

28 **29**

Ensayos	t (h)	Producto de partida	Productos de reacción	Rdto(%)
1	0.8	**26a-b**	**27a-b**	84
2	2	**26a-b**	**27a-b**	83
3	4	**26a-b**	**26a-b : 27a-b: 28** (1:1:0.5)[a]	60
4	13	**26a-b**	**27a-b : 28** (1:4)[a]	91.5
5[b]	14	**26a-b**	**28 : 29** (2:1)[a]	60
6[c]	3	**27a-b**	**27a-b**	98
7	15	**27a-b**	**27a-b : 28 : 29** (1:3:2)[a]	65

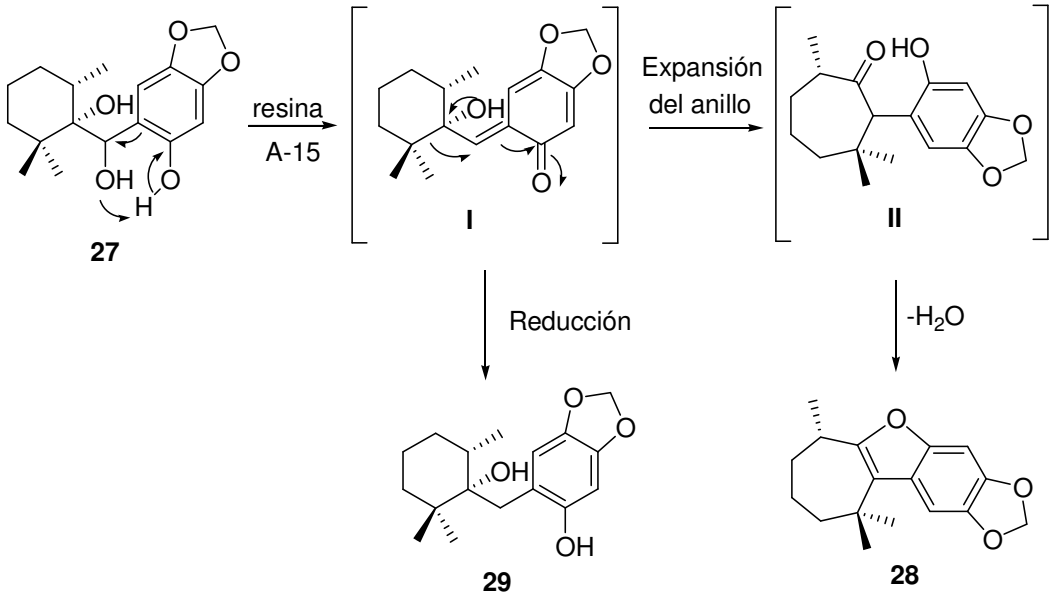
MC: Mezcla compleja de productos no identificados.
[a] Proporciones estimadas en base a espectros de RMN.
[b] Se agregó Amberlita 15 al medio de reacción.
[c] Se agregó AcOH (cat.) al medio de reacción.

En todos los casos se obtuvo el producto de desprotección del hidroxilo fenólico. Los ensayos 3, 4, 5 y 7 muestran la formación del producto de reordenamiento **28**. Cabe resaltar la formación del hidroxifenol **29** deseado, que se obtuvo como producto minoritario en el ensayo 5, en presencia de Amberlita 15, condiciones sin precedentes en bibliografía. También se observa la formación de **29** cuando se efectúa la reacción directamente sobre el dihidroxialcohol **27a-b** (ensayo 7).

El mecanismo de la formación del producto de reducción **29** podría transcurrir vía la enona **I** tal como se ha postulado anteriormente (ver esquema 14).

La caracterización de **27a-b**, **28** y **29** se llevó a cabo mediante técnicas espectroscópicas usuales. En el caso de **27a-b** se obtuvo una mezcla diastereomérica en proporción 6:1, en cuyo espectro de RMN-^{1}H destaca la ausencia del grupo bencilo y se observa un singlete ancho a 9 ppm, atribuible al hidroxilo fenólico. El resto del espectro es muy parecido al del diol precursor, diferenciándose de este último sin lugar a duda en CCF, por ser mucho más polar. En cuanto al derivado benzofuránico **28**, se analizaron detalladamente los espectros de RMN, tanto de ^{13}C como de ^{1}H. Se observa la aparición de dos nuevas señales correspondientes a los carbonos olefínicos generados, a 156 y 123 ppm, y de un multiplete, que integra por un protón, a 3.19 ppm, correspondiente al hidrógeno metínico geminal a grupo metilo. Las señales de los grupos metilo resuenan a campos más bajos que los del producto de partida. Del espectro IR se deduce que no existen hidroxilos libres en la molécula. La caracterización de **29** fue facilitada por los dos dobletes presentes en el espectro de RMN-^{1}H, que integran por un protón cada uno y acoplados entre sí con J = 15.2 Hz,. a δ 3.05 y 2.63 ppm, asignables al metileno bencílico. Se observa asimismo en el espectro de RMN-^{13}C, en conjunción con el DEPT, la aparición de un nuevo metileno a 39.6 ppm, atribuible al correspondiente carbono bencílico.

A la vista de estos resultados, se propone un mecanismo plausible para la formación, tanto del hidroxifenol **29** como del derivado benzofuránico **28**, promovida por la resina catiónica (Esquema 15). El intermedio **I** es clave para la formación tanto del hidroxifenol **29** como para la formación de **28**. Mediante redución de **I** se obtiene el hidroxifenol monoterpénico **29**, mientras que la formación de **28** ocurre vía el intermedio **II** provocado por la expansión del anillo de ciclohexano.

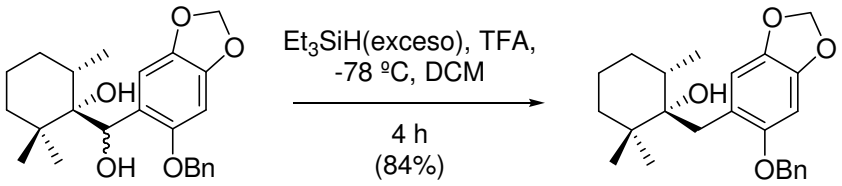


Esquema 15

Desafortunadamente, el rendimiento para la obtención del hidroxifenol **29** no superó el 20% en el mejor de los casos, lo que hace dificil su aplicación en la ruta hacia la síntesis de corallidictyal D (**1**).

b) Ensayos de reducción catiónica

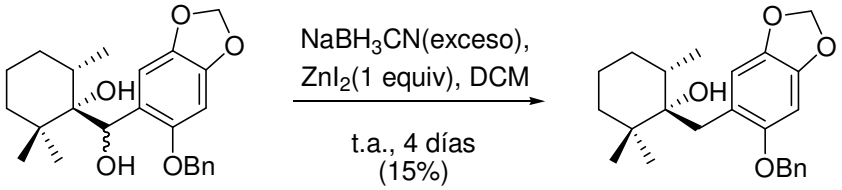
Con el propósito de mejorar el rendimiento en esta etapa, se ensayaron condiciones de reducción catiónica. Inicialmente, se probaron condiciones convencionales de reducción catiónica como Et_3SiH/TFA, obteniéndose de forma selectiva el producto de la reducción deseado **30**, con un buen rendimiento (84%). (Esquema16).



26a-b **30**

Esquema 16

También se ensayó otro método alternativo utilizado en nuestro laboratorio para la síntesis de Wiedendiol A y B[77], consistente en el tratamiento de los dioles monoterpénicos **26a-b** con exceso de $NaBH_3CN$ y ZnI_2 estequiométrico, en DCM. Tras 4 días, se obtuvo una mezcla compleja de productos, entre los que se aisló el alcohol deseado **30** con un rendimiento bajo (15%) (Esquema 17).



26a-b **30**

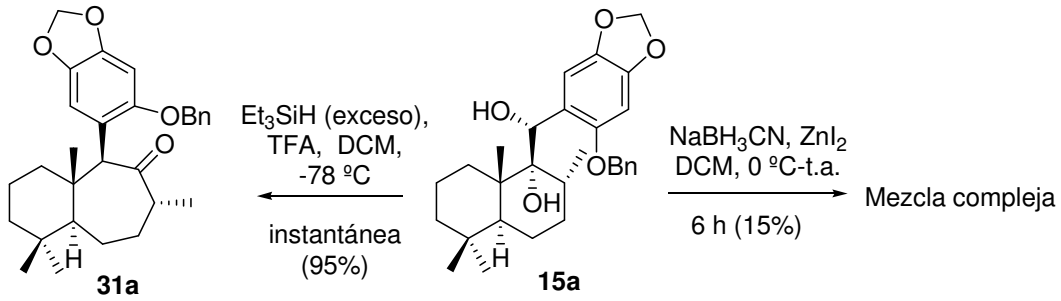
Esquema 17

2.2. PREPARACIÓN DEL HIDROXIFENOL MEROSESQUITERPÉNICO 17

A la vista de estos resultados, se intentó obtener el fenol **17** a partir del diol merosesquiterpénico **15a**, utilizando condiciones de reducción catiónica, más favorables para la preparación de **17** tal como se ha descrito con anterioridad (ver esquema 16). Sin embargo, el transcurso de la reacción de reducción catiónica fue diferente, obteniéndose el producto de reordenamiento **31a** en muy buen

(77) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron* **1998**, *54*, 5635.

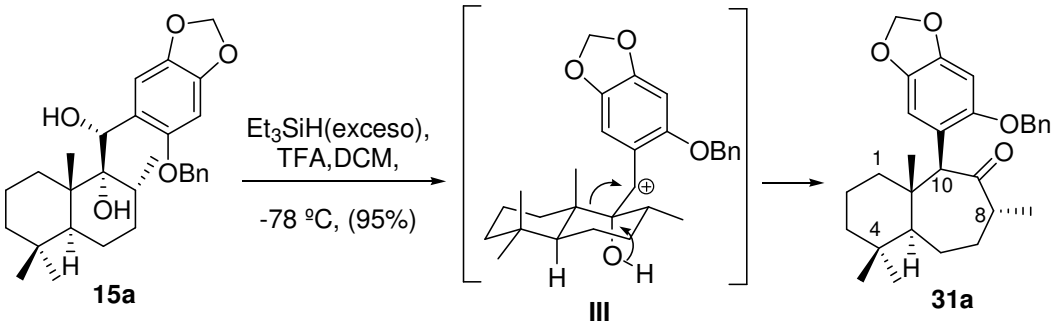
rendimiento, en lugar del alcohol **16** esperado. El uso del sistema $NaBH_3CN/ZnI_2$ en DCM proporcionó una mezcla compleja de productos (Esquema 18).



Esquema 18

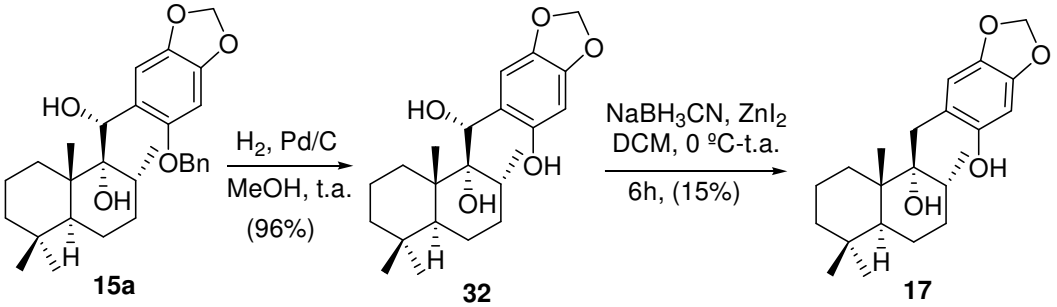
La cetona **31a** se identificó en base a sus datos espectroscópicos de RMN y de IR. Llama la atención el cambio en el desplazamiento, hacia campos más bajos, de uno de los protones aromáticos, que aparece ahora a 7.46 ppm, atribuible al desapantallamiento anisotrópico del grupo carbonilo. Se corrobora la existencia de un grupo carbonílico, mediante el espectro de IR que muestra una banda intensa a 1706 cm^{-1}. El espectro de RMN-^{13}C muestra una señal de un carbono cuaternario a 215.4 ppm que confirma la presencia del grupo carbonílo. Además se identificaron dos multipletes, que integran cada uno por un protón, a 2.41 y 2.05 ppm, atribuíbles a los hidrógenos en posición α de cetona. La configuración relativa del carbono C-10 se estableció en base a los experimentos NOE, y sirvieron de referencia para confirmar la estereoquímica propuesta para el diol precursor **15a**.

En cuanto al mecanismo de la formación de la cetona **31a**, en principio debe transcurrir mediante un reordenamiento pinacólico del diol **15a,** posiblemente vía el carbocatión bencílico **III** altamente estabilizado, como se muestra a continuación (Esquema 19).



Esquema 19

Como alternativa para la preparación del hidroxifenol **17**, precursor de corallidictyales, se procedió a la desprotección del grupo hidroxilo fenólico del compuesto **15a** para obtener el fenol **32** mediante hidrogenación catalítica en metanol. Este compuesto podría ser un precursor adecuado para la preparación del hidroxifenol **17**, vía la enona intermedia análoga a la postulada en el mecanismo de obtención del hidroxifenol monoterpénico (ver esquema 15). Desafortunadamente, el tratamiento del fenol **32** mediante el sistema $NaBH_3CN/ZnI_2$ en DCM condujo a una mezcla de productos en la que se pudo identificar el hidroxifenol **17** con un rendimiento del 15%, en el mejor de los casos (Esquema 20).



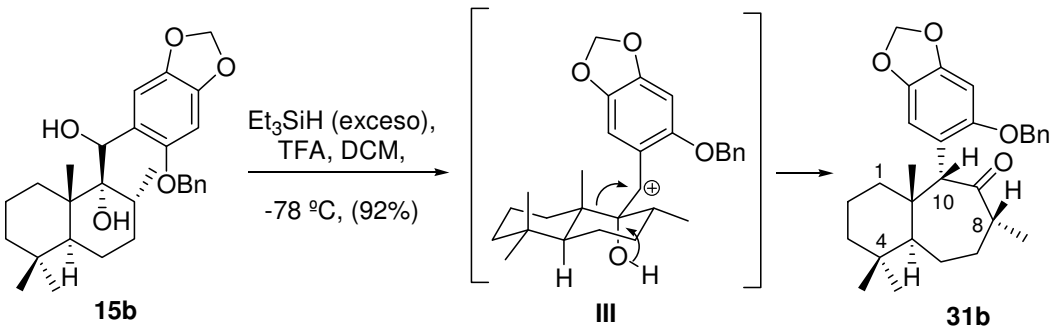
Esquema 20

Se caracterizó **32** mediante análisis de sus espectros de RMN de ^{1}H , ^{13}C y por comparación con el diol precursor **15a**. No se observan las señales correspondientes al benciléter ni en el espectro de RMN-^{1}H ni en el de RMN-^{13}C.

Se aprecia en el espectro de RMN-^{1}H un desplazamiento a campos más altos de los protones aromáticos atribuible al efecto del grupo hidroxilo fenólico. Destaca, además, la variación en el desplazamiento de la señal correspondiente a los protones del metilo doblete C-8, que pasa de 0.78 ppm a 0.85 ppm. El espectro de masas es consistente con la estructura propuesta.

Asimismo, se caracterizó **17** en base a sus datos espectroscópicos. Se observan en el espectro de RMN-^{1}H los dos dobletes correspondientes a los protones bencílicos, a 2.95 ppm y 2.78 ppm (J = 15 Hz), y en el ^{13}C-RMN la señal del nuevo metileno bencílico a 41.6 ppm. Además destaca un singlete ancho a 8.86 ppm, atribuible al hidroxilo fenólico, cuya presencia está corroborada por la existencia de una banda ancha en el espectro IR a 3422 cm^{-1}.

Con objeto de estudiar el comportamiento del otro isómero del diol merosesquiterpénico **15a** frente a condiciones de reducción catiónica, se procedió a realizar el ensayo de reducción sobre el isómero **15b**. Asímismo, el tratamiento de **15b** con Et_3SiH/TFA, rindió la correspondiente cetona **31b** (Esquema 21).

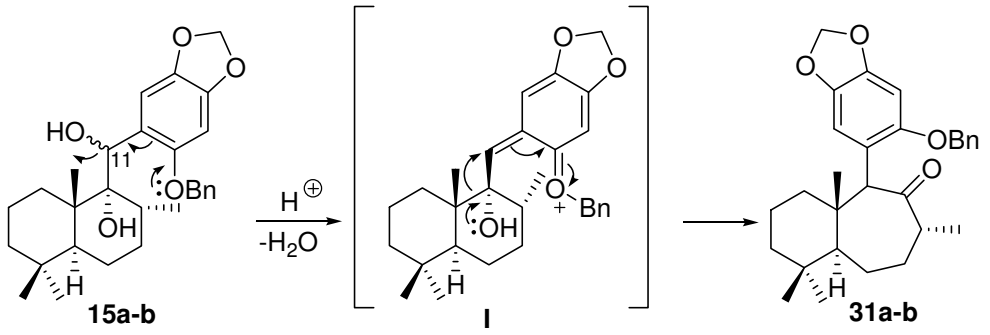


Esquema 21

La cetona **31b** ha sido identificada mediante sus datos espectroscópicos, entre los que destacan las señales correspondientes al metilo en α de carbonilo y al metilo angular. La primera como doblete a 0.89 ppm, con una J = 7.0 Hz y la segunda como un singlete a 0.92 ppm. La configuración del carbono C-10, se estableció en base a las experiencias NOE, como en el caso del isómero **31a**. Los

metinos C-10, con configuración opuesta en ambos isómeros, registran valores en el RMN de ^{13}C apreciablemente diferentes: 56.0 ppm para el isómero **31a** y 62.5 ppm para el epímero **31b.**

La estereoselectividad observada en el proceso de expansión del anillo B, que conduce de los dioles **15a** y **15b** a las cetonas **31a** y **31b**, respectivamente, hace pensar que el mismo tenga lugar a través de un quinometano intermedio **I** (similar al intermedio **I** en el esquema 15), en vez de a través de un carbocatión bencílico como se indicó en los esquemas 19 y 21. Es importante señalar que se ha descrito la formación de quinometanos similares a **I** mediante tratamiento ácido de alcoholes bencílicos del mismo tipo que **13**[78] (Esquema 22).



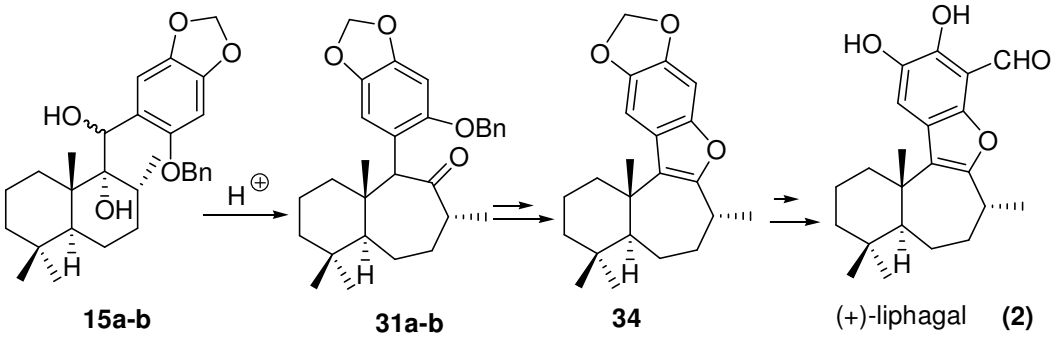
Esquema 22

La configuración del doble enlace exocíclico de **I**, que está determinado por la configuración en C-11 del diol **15**, definirá la configuración en C-10 de la cetona **31.**

(78) Arjona, O.; Garranzo, M.; Mahugo, J.; Maroto, E.; Plumet, J.; Sáez, B. *Tetrahedron Letters* **1997**, *38*, 7249.

3. SÍNTESIS DE (+)-LIPHAGAL (2)

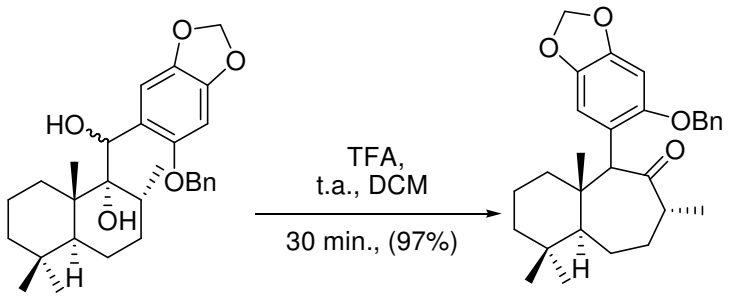
Tras el análisis de los resultados obtenidos con anterioridad, se deduce que la estrategia planteada es más adecuada para la síntesis del (+)-liphagal (**2**), que para la de corallidictyales. Por ello, se procedió a continuación a desarrollar la síntesis de (+)-liphagal (**2**) (Esquema 23).



Esquema 23

3.1. PREPARACIÓN DEL COMPUESTO BENZOFURÁNICO 34

Teniendo en cuenta la diferencia de polaridad entre las cetonas **31a** y **31b**, se optó por continuar el desarrollo de este objetivo, utilizando la mezcla de dioles **15a-b** (1:1) para la obtención de (+)-liphagal (**2**). Así pues, se llevó a cabo la etapa de expansión del anillo sobre la mezcla, obteniendo la correspondiente mezcla de cetonas **31a-b** (1:1). (Esquema 24).



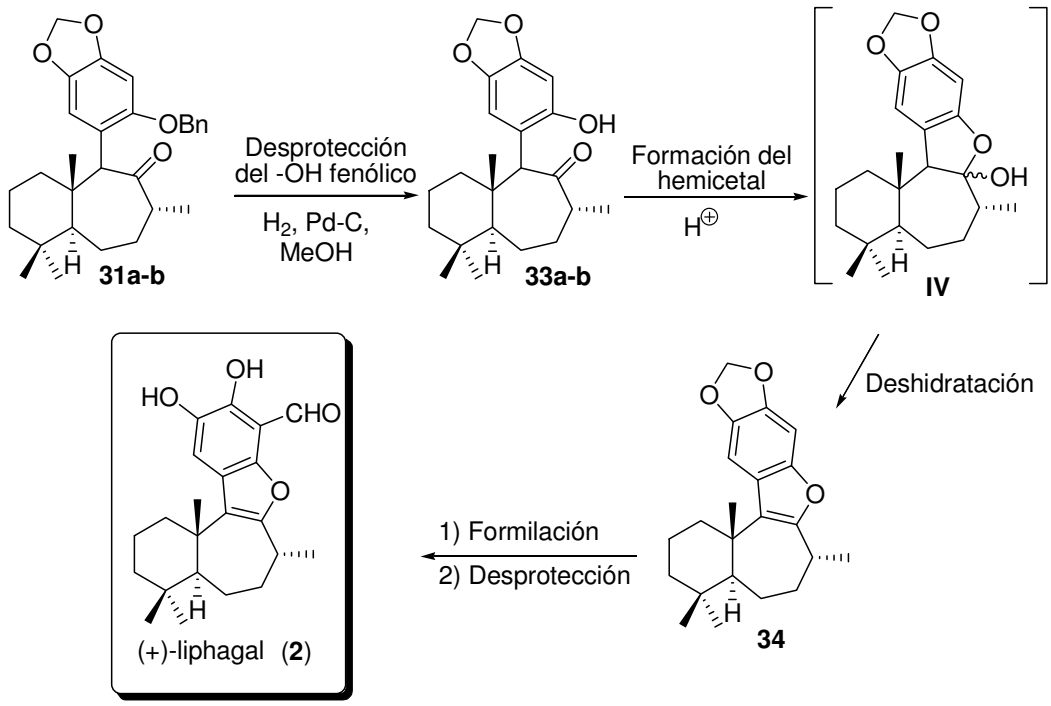
15a-b
(1:1)

31a-b
(1:1)

Esquema 24

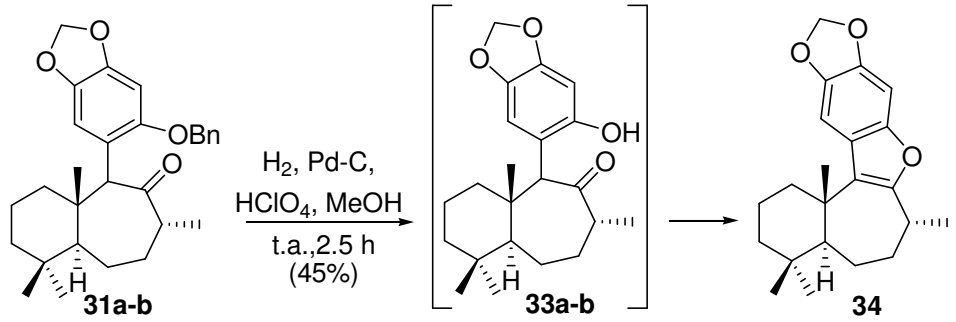
Una vez obtenidas las cetonas **31a-b**, se procedió a la formación del anillo benzofuránico presente en (+)-liphagal (**2**), mediante una secuencia de desprotección del grupo bencilo y ciclación para formar el compuesto benzofuránico **34**; la posterior introducción del grupo formilo en el anillo aromático de **34,** y ruptura del grupo metilendioxi proporcionaría el (+)-liphagal (**2**).

En el esquema 25 se recoge la secuencia sintética planteada para la obtención de (+)-liphagal (**2**) a partir de las cetonas **31a-b**.



Esquema 25

Al someter **31a-b** a las condiciones de ruptura del benciléter[79] en medio ácido, se obtuvo directamente el derivado benzofuránico **34**, sorprendentemente con bajo rendimiento (45%).(Esquema 26).



Esquema 26

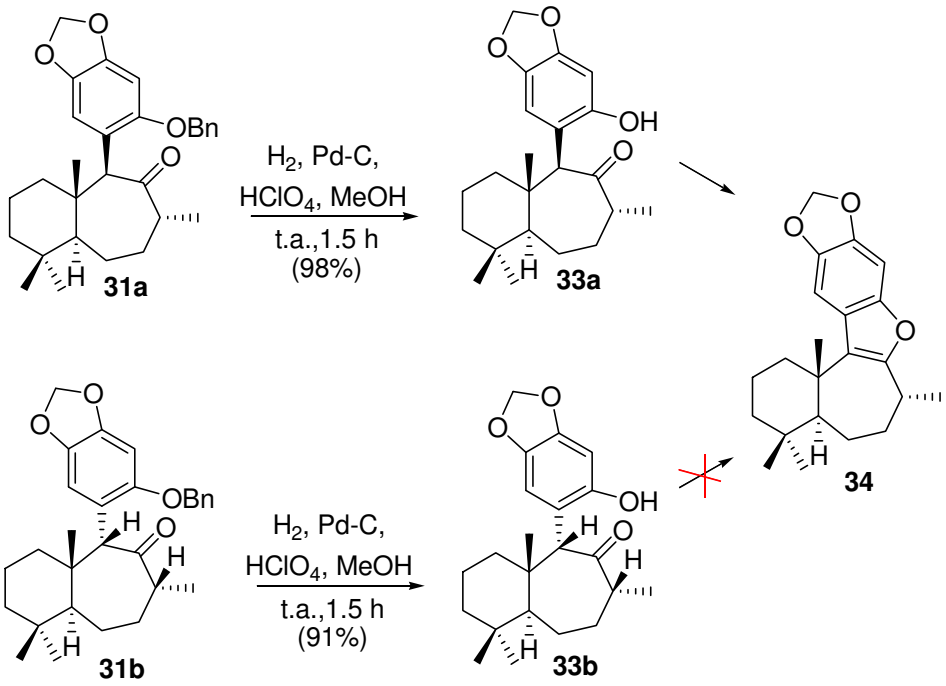
(79) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Tapia, R.; Es-Samti, H.; Fernández, A.; Barranco, I. *Eur. J. Org. Chem.* **2009**, 1139.

El espectro de RMN-^{13}C del compuesto **34** muestra sendas señales de carbonos sp^2 a 156.2 y 125.7 ppm, atribuibles al anillo furánico generado.

La formación de dicho derivado benzofuránico se explica vía el hemicetal **IV**, resultante del ataque nucleofílico del hidroxilo fenólico a la cetona en **33**, y la posterior deshidratación de dicho hemicetal

Con el propósito de encontrar la explicación para el bajo rendimiento obtenido, se procedió a realizar la ciclación de las cetonas **31a-b**, por separado**.**

El proceso sobre **31a**, proporcionó el benzofurano **34** con un excelente rendimiento (98%), mientras, bajo condiciones similares la cetona **31b**, condujo a una mezcla compleja de al menos cuatro productos, muy difícil de separar en columna cromatográfica, entre los que se encuentra el derivado benzofuránico **34** en muy baja proporción (Esquema 27).



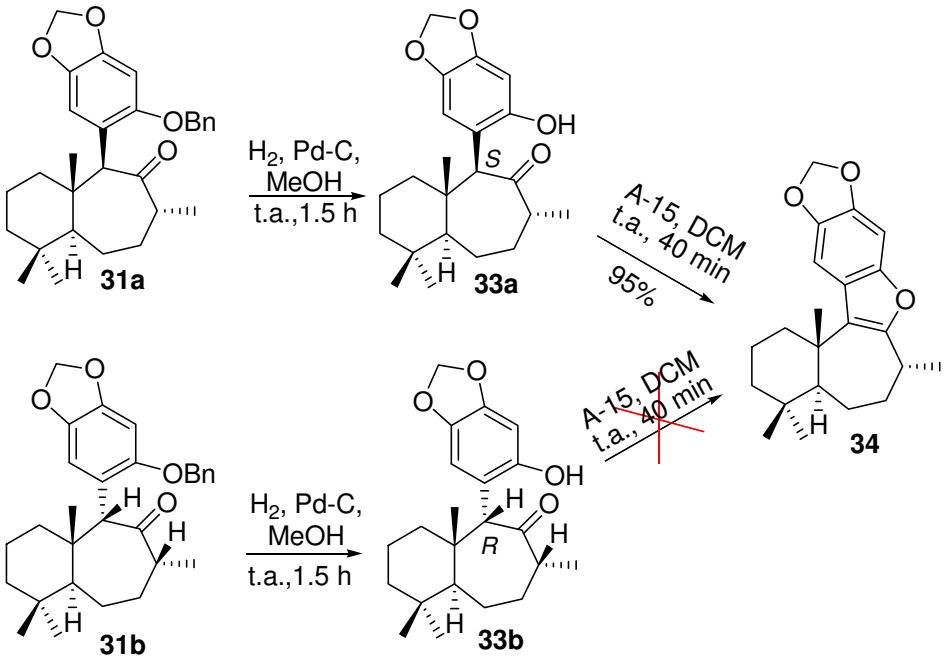
Esquema 27

Los resultados de esta reacción, no concuerdan con los descritos por el grupo del profesor Baldwin[80] , que fueron publicados de forma simultánea a los nuestros. En dicho trabajo, se describe el tratamiento de la mezcla de dihidroxifenoles epímeros en C-11, similares a **15a-b**, con TFA en DCM desde -78 ºC hasta temperatura ambiente, tras el cual obtiene como único producto, el correspondiente benzofurano **34** con un 74% rendimiento.

Con objeto de superar este inconveniente, se plantearon varias alternativas que permitieran aumentar la proporción de la cetona **31a** y obtener así el derivado benzofuránico **34** con mayor rendimiento.

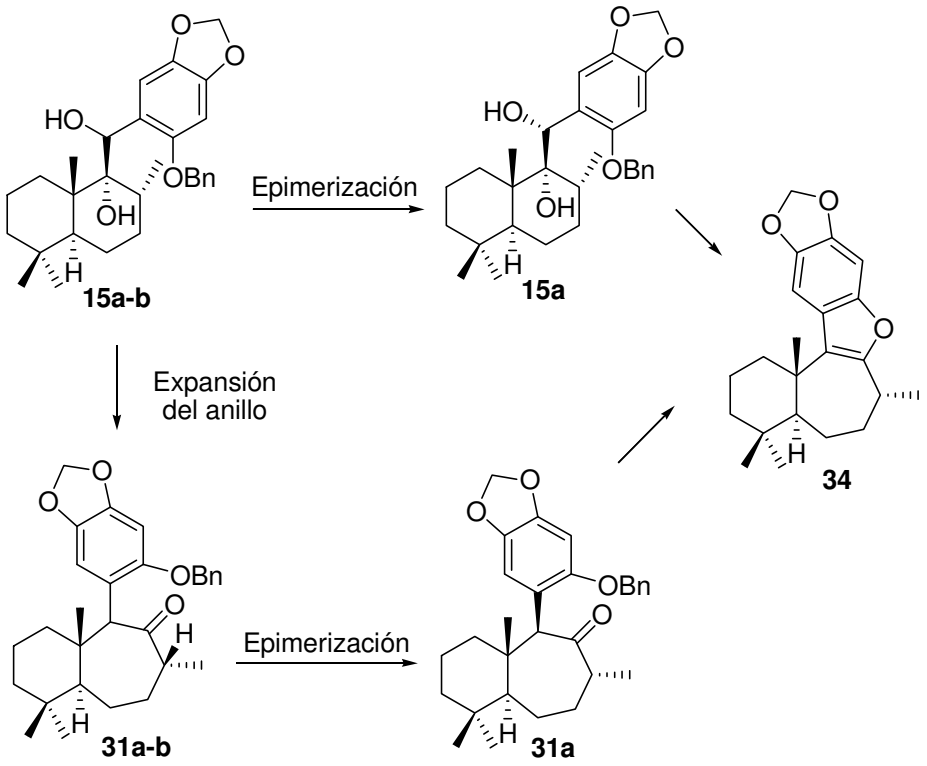
Antes de abordar las nuevas alternativas para la obtención de este derivado benzofuránico en mayor proporción, se prepararon los correspondientes fenoles para verificar que el proceso de ciclación de los derivados cetofenólicos es el responsable del bajo rendimiento de obtención del derivado benzofuránico **34**. Para ello, se preparó el derivado cetofenólico **33b** con buen rendimiento mediante hidrogenación catalítica convencional, y se sometió a reacción de cíclación con resina catiónica Amberlyst 15, obteniéndose la misma mezcla de 4 productos ya descrita con anterioridad. Por otra parte, el derivado cetofenólico **33a** rindió el derivado benzofuránico deseado **34** con un rendimiento prácticamente cuantitativo (95 %), tras 40 minutos de reacción en presencia de la resina catiónica (Esquema 28).

(80) George, J. H.; Baldwin, J. E.; Adlington, R. M. *Organic Letters* **2010**, *12*, 2394.



Esquema 28

Se debe concluir, por tanto, que es la disposición del grupo fenólico en la estructura lo que dificulta la ciclación del isómero **33b**. Por ello, a fin de mejorar el rendimiento en la obtención del precursor benzofuránico **34** se hace imprescindible la epimerización del C-10 del derivado cetofenólico **33b** o la obtención selectiva del diol merosesquiterpénico **15a**. (Esquema 29).

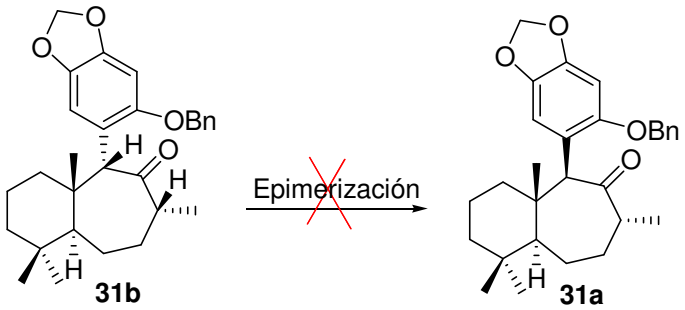


Esquema 29

*a) Epimerización de la cetona **31***

En primer lugar, se trató de epimerizar la cetona **31b** hacia **31a** (Esquema 30), bajo diferentes condiciones ácidas, como CF_3COOH, HCl conc. a reflujo en dioxano y H_2SO_4 conc. a reflujo en dioxano. En el mejor de los casos se logró la epimerización del 10% de la cetona **31b**. Bajo condiciones básicas, como DBU a reflujo en tolueno o KOH a reflujo en diglime, no se observó epimerización alguna[81]

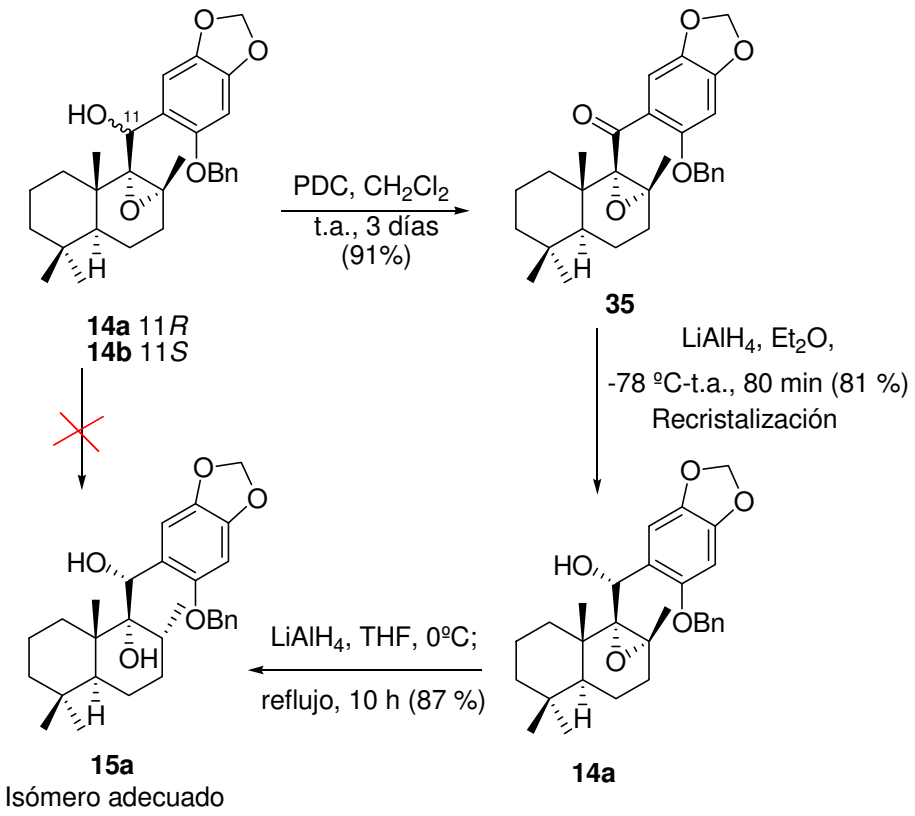
(81) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angewandte Chemie, International Edition* **2011**, *50*, 6814.



Esquema 30

*b) Epimerización del diol **15***

Tras el resultado adverso del ensayo de epimerización de la cetona **31b**, se investigó la preparación selectiva del epímero **15a** (11*R*) precursor de la α-arilcetona **33a** deseada, a partir de la mezcla de epoxialcoholes **14a-b**. Ello se logró mediante un proceso de oxidación y reducción de la mezcla equimolar de epoxialcoholes **14a-b**, utilizando PDC y $LiAlH_4$ respectivamente (Esquema 31).



Esquema 31

La oxidación de la mezcla 1:1 de epoxialcoholes **14a-b** con PDC en DCM, proporcionó después de 4 días de reacción la epoxicetona **35**, que tras tratamiento con hidruro de aluminio y litio ($LiAlH_4$) en éter enfriado a -78 ºC y dejando la reacción evolucionar a temperatura ambiente durante 80 minutos, condujo a una mezcla de epoxialcoholes **14a-b** en una proporción 5:1. Tras un meticuloso proceso de recristalización en hexano:éter 9:1, se aisló con un 81 % de rendimiento el estereoisómero **14a** puro, que fue sometido a una segunda reducción con el mismo reactivo $LiAlH_4$; tras 10 horas a reflujo, se obtuvo el diol **15a,** en un 87% de rendimiento (64 % de rendimiento global tras las cuatro etapas). Como ya se indicó, el proceso de apertura de este epoxialcohol **14a** es más lento que el de su isómero **14b**, por motivos estéricos y por ello requiere de periodos de reacción más prolongados.

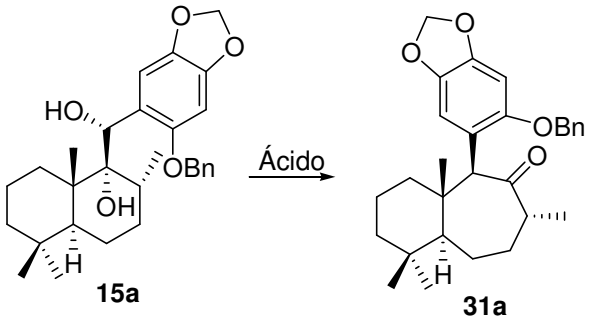
La epoxicetona **35** fue caracterizada en base a sus datos espectroscópicos de RMN-^{1}H y ^{13}C, así como su espectro IR. El grupo carbonílico se confirmó mediante la presencia de la señal a 197.6 ppm en el espectro de RMN-^{13}C y la banda a 1672 cm^{-1} en el espectro de IR.

Solventado el problema de la epimerización, se dispone ahora únicamente del isómero adecuado **15a**, precursor del derivado benzofuránico **34,** que conduce a (+)-liphagal (**2**).

En este punto, dirigimos nuestros esfuerzos a la optimización y acortamiento de la secuencia sintética, intentando encontrar las mejores condiciones para este fin.

3.2. ESTUDIO DEL REORDENAMIENTO DEL DIOL SESQUITERPÉNICO 15

Se ensayó la etapa de reordenamiento del diol **15a** empleando diferentes ácidos.



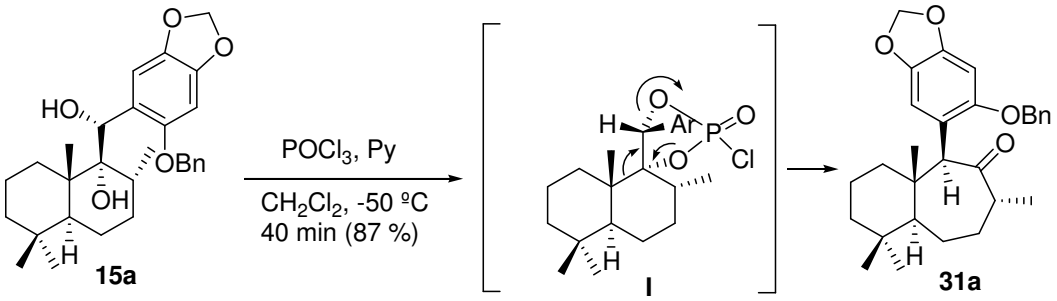
15a **31a**

Tabla 2: Ensayos de reordenamiento del diol sesquiterpénico 15a.

Ensayos	Condiciones	Rdto(%)
1	TFA, DCM, -40ºC	97
2	$HClO_4$, MeOH, t.a.	45
3	APTS, benceno, t.a	85
4	$BF_3.OEt_2$, DCM, -20ºC	84
5	$POCl_3$, Py, DCM, -50ºC	87

Entre los distintos ensayos merece ser destacado el realizado con oxicloruro de fósforo, que transcurre a baja temperatura y en condiciones neutras. Además se obtiene el producto de expansión con elevado rendimiento y completa estereoselectividad.

El tratamiento del diol 11*R* (**15a**) con $POCl_3$ y piridina en DCM a -50 ºC durante 40 minutos proporcionó la correspondiente cetona **31a**, con un 87 % de rendimiento (Esquema 32).



Esquema 32

En este caso, la expansión del anillo B tiene lugar mediante un proceso concertado, a través del intermedio cíclico **I.**

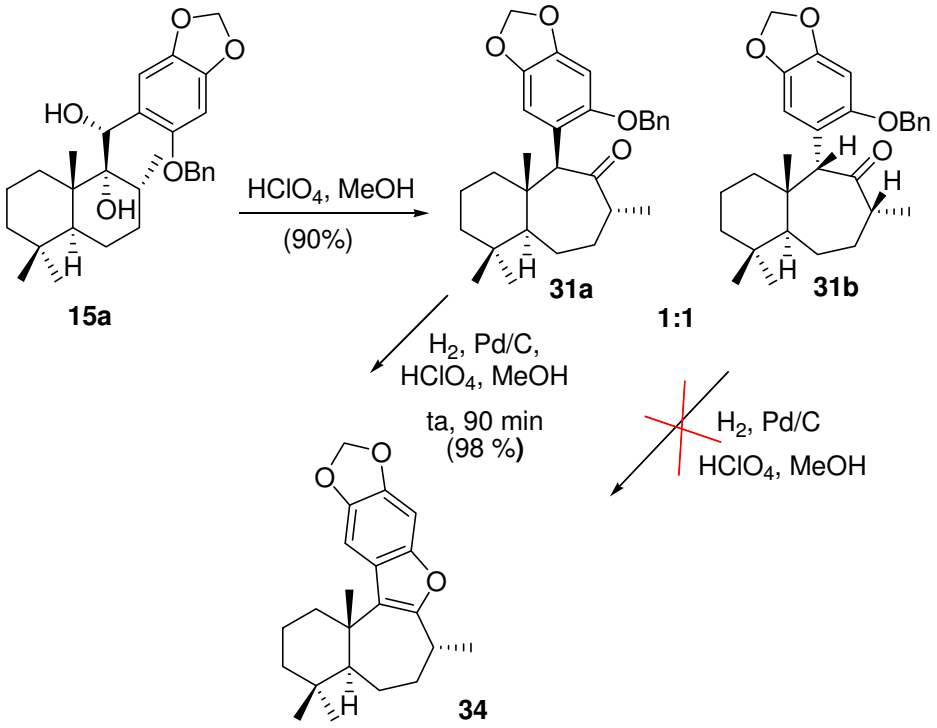
Como era de esperar, el epímero **15b** conduce bajo las mismas condiciones a la α-aril cetona **31b**, como único producto.

3.3. ACORTAMIENTO DE LA SECUENCIA SINTÉTICA

Una vez optimizada la etapa de expansión del anillo, nos centramos en el acortamiento de la secuencia sintética, intentando aunar las etapas de desprotección, expansión del anillo B y ciclación.

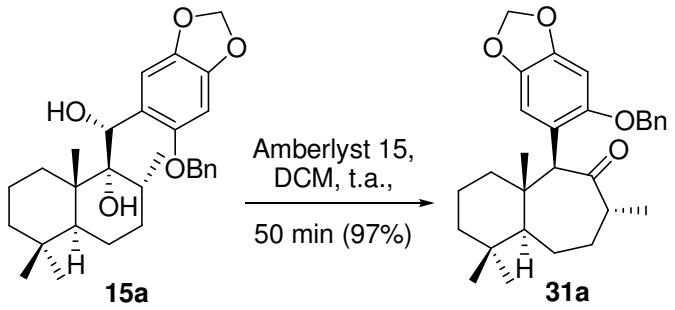
Alentados por los resultados observados en la desprotección de **31a** en medio ácido, que permitió obtener el derivado benzofuránico **34** de forma directa (ver esquema 27), se pensó que el reordenamiento bajo las mismas condiciones (H_2, Pd/C, $HClO_4$, MeOH), permitiría conseguir en una sola etapa la transformación

del diol **15a** en el compuesto **34**. Desafortunadamente, el tratamiento de **15a** con este ácido, realizado como paso previo a la hidrogenación catalítica ácida, proporcionó una mezcla 1:1 de epímeros **31a-b,** que condujo a un bajo rendimiento del derivado benzofuránico **34**, tras la hidrogenación, como se indicó en la tabla 2.



Esquema 33

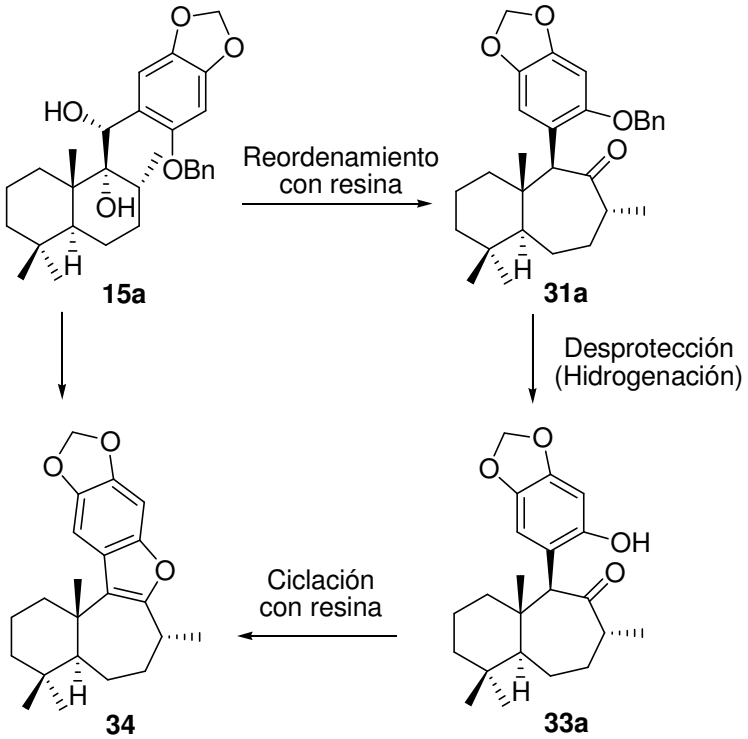
Alternativamente, y aprovechando los resultados de las hidrogenaciones realizadas sobre el análogo monoterpénico, en la etapa de reducción bencílica (Tabla 1), en que se observó también la obtención del derivado benzofuránico monoterpénico **28** directamente a partir del diol **27a-b,** mediante el uso de la resina catiónica A-15 en DCM, se investigó el uso de ésta sobre el diol **15a**, obteniéndose la cetona **31a** tras 50 min de reacción a temperatura ambiente, con completa estereoselectividad del proceso de expansión y excelente rendimiento (97%) (Esquema 34).



Esquema 34

La falta de estereoselectividad observada durante la expansión del anillo promovida por ácido perclórico, puede atribuirse a la formación de un catión bencílico intermedio, que no se genera en el caso de la resina.

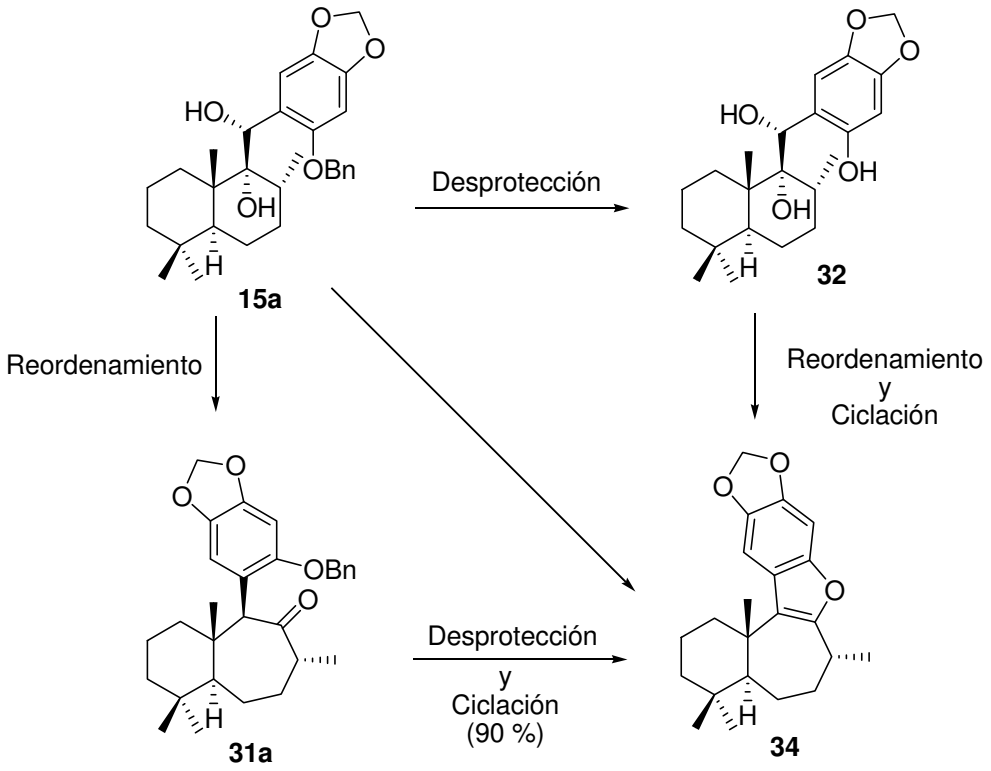
Este resultado nos permite plantear unas condiciones en las que se pudieran realizar en una única etapa, los tres procesos (reordenamiento, desprotección del hidroxilo fenólico y ciclación), utilizando la resina catiónica Amberlyst 15 en el proceso de hidrogenación del diol **15a** (Esquema 35).



Esquema 35

Para ello, primero se comprobó que el resultado de la hidrogenación catalítica en presencia de Amberlyst 15, obtenido sobre el modelo diol monoterpénico **27a-b** (ver tabla 1, ensayo 5), era reproducible en caso de utilizar el diol merosesquiterpénico **15a**. Así, se sometió en primer lugar **31a** a condiciones de hidrogenación catalítica en presencia de Amberlyst 15, según se planteó en el esquema 35, obteniéndose el derivado benzofuránico **34** con un excelente rendimiento (93%) (Esquema 36).

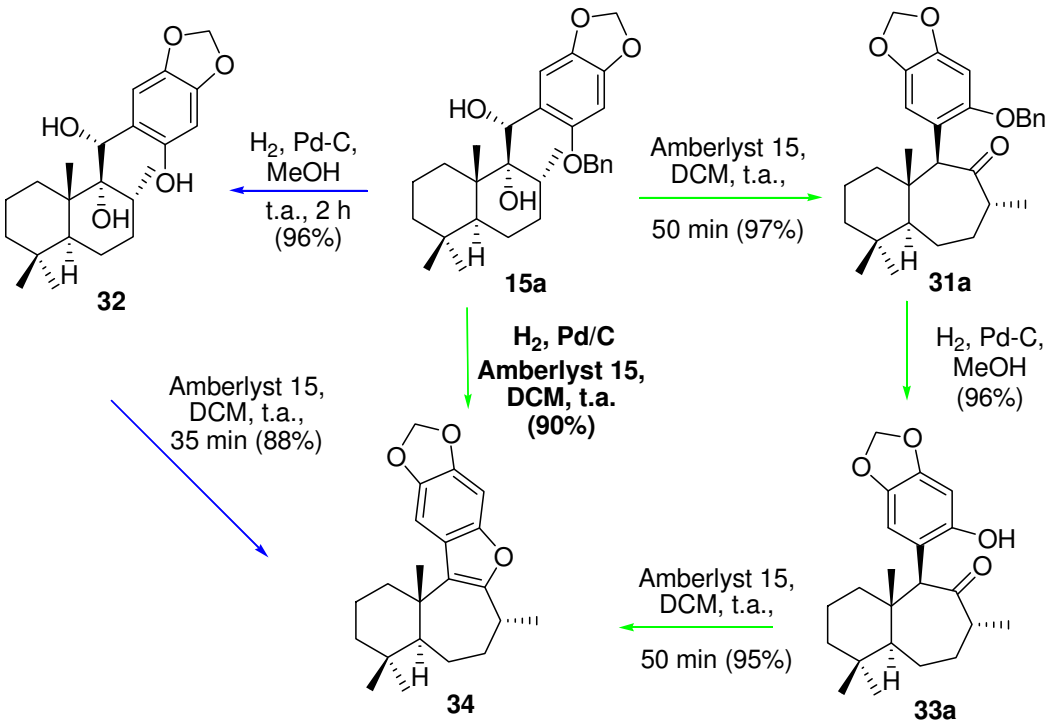
Alternativamente, se planteó la secuencia invirtiendo el orden de estas últimas etapas, de modo que en lugar de reordenar el diol y posteriormente desproteger y ciclar la cetona, se planteó efectuar la desprotección del grupo bencilo del diol merosesquiterpénico **15a**, para obtener el correspondiente derivado dihidroxifenol **32**, que se sometería con posterioridad a reordenamiento y ciclación (Esquema 36).



Esquema 36

De este modo, se desprotegió el diol **15a**, mediante hidrogenación catalítica, aislándose el dihidroxifenol **32** con alto rendimiento. Posteriormente, se trató dicho dihidroxifenol **32** con Amberlyst 15**,** obteniéndose el esperado derivado benzofuránico **34,** con un 88% de rendimiento (Esquema 37).

Comparando las dos vías desarrolladas para la obtención del compuesto **34,** puede proponerse la realización de todos los procesos en una etapa, como se pretendía, de manera que se accedería al derivado benzofuránico **34** directamente empleando las mismas condiciones en presencia de Amberlyst 15. Así, se sometió **15a** a las condiciones de hidrogenación en presencia de Amberlyst 15, descritas previamente, obteniéndose el derivado benzofuránico **34** con un 90% de rendimiento (Esquema 37).

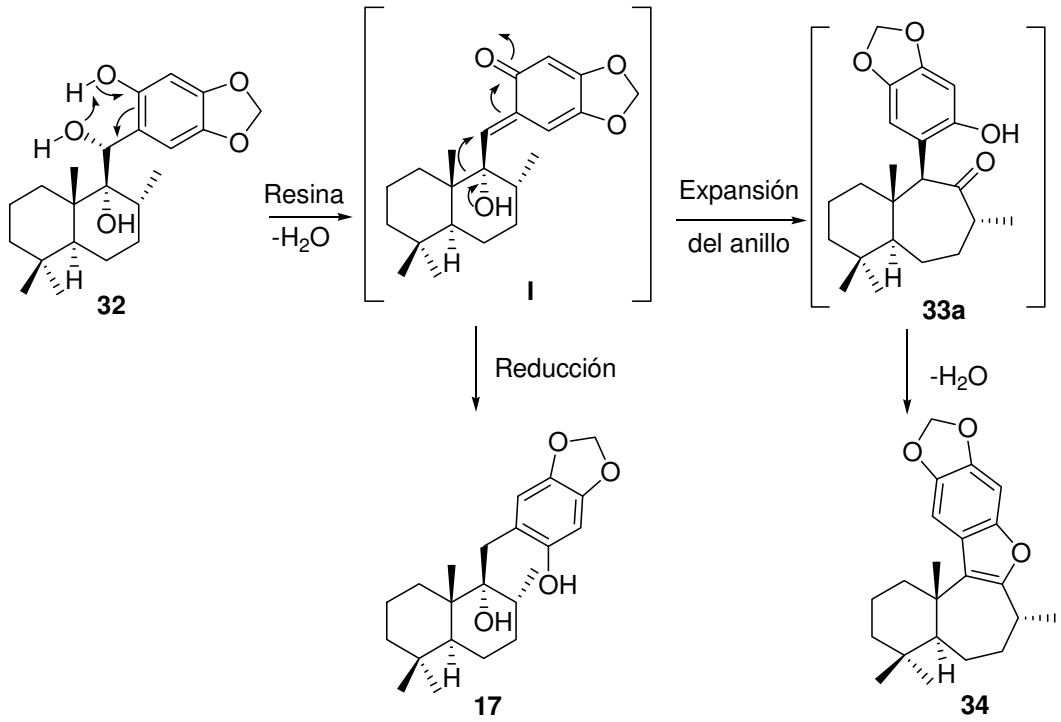


Esquema 37

Al encontrarse presente la resina catiónica en el medio de reducción, a la vez que ocurre la desprotección del fenol por acción del hidrógeno, se produce el

reordenamiento, provocado por la resina ácida y el producto reordenado y desprotegido, cicla inmediatamente en el medio ácido de reacción.

También se observa que, al incrementar la presión de hidrógeno, y disminuir la proporción de resina catiónica, se obtiene, además del benzofurano **34**, una pequeña cantidad del hidroxifenol **17**. Un posible mecanismo de formación directa del derivado benzofuránico **34** y del hidroxifenol **17** a partir del diol **15a** se describe a continuación (Esquema 38)

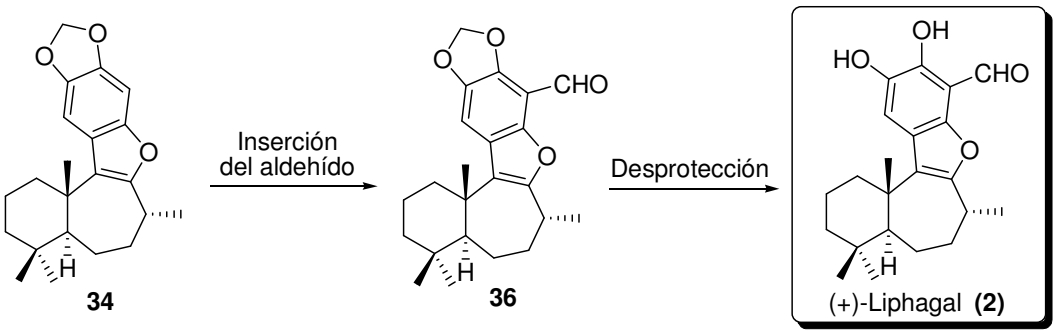


Esquema 38

La hidroxicetona **33a** puede generarse a través del reordenamiento del *o*-quinometano **I**; tras posterior hemicetalación y deshidratación conduciría al intermedio benzofuránico liphagano **34**. Por otra parte, el hidroxifenol **17** se formaría mediante la reducción del intermedio **I**, que se produciría previamente al proceso de reordenamiento del *o*-quinometano **I**.

3.4. FUNCIONALIZACIÓN DEL ANILLO AROMÁTICO

Una vez sintetizado el esqueleto de liphagano [6.7.5.6], se procedió a la adecuada funcionalización del anillo aromático. Para ello, se plantea, en primer lugar, la introducción del grupo aldehído y después la ruptura del grupo metilendioxi para obtener el (+)-liphagal (**2**) (Esquema 39).



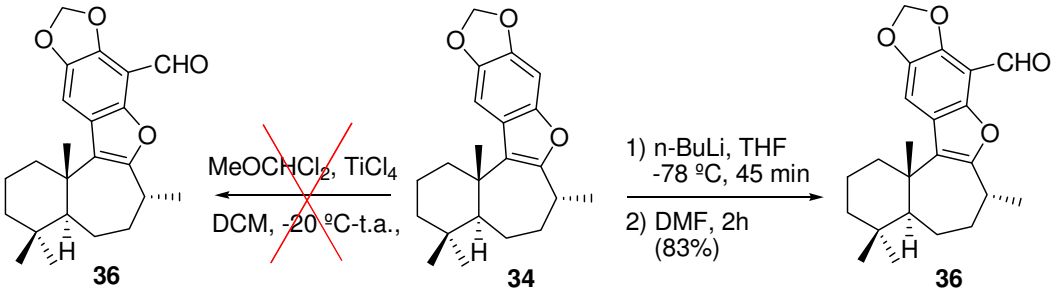
Esquema 39

La introducción del grupo formilo se ensayó, inicialmente, utilizando como electrófilo el reactivo de Rieche[82] , diclorometilmetiléter y $TiCl_4$, más reactivo y de menor tamaño que los correspondientes usados por Vilsmeier[83]. Se comenzó la reacción a -20 ºC en DCM y al no observar cambio tras dos horas, se incrementó la temperatura progresivamente hasta temperatura ambiente, con adiciones sucesivas de reactivo. Tras varias horas de reacción no se observó formación ninguna del aldehído liphagano **36**.

A continuación se optó por introducir el grupo formilo, *vía* orto-metalación regioselectiva de **34**, seguida de adición de DMF anhidra como electrófilo. Así el

(82) March, J. *Advanced Organic Chemistry, 4th edn;Wiley-Interscience* **1992**, 542.
(83) Meth-Cohn, O.; Ashton, M. *Tetrahedron Letters* **2000**, *41* 2749.

tratamiento de **34** con *n*- BuLi en THF anhidro a -78 ºC, seguida de adición de DMF[84,85] proporcionó ell aldehído **36** con un 83% de rendimiento (Esquema 40).



Esquema 40

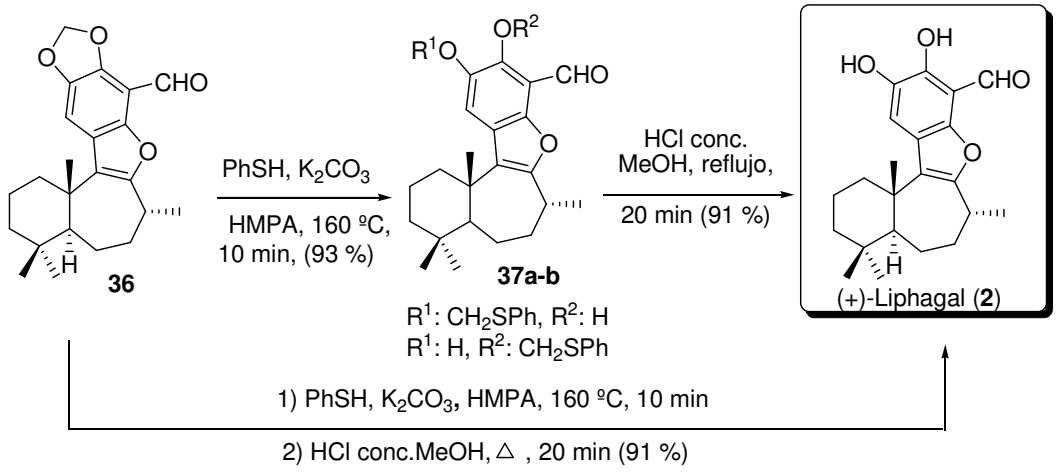
El aldehído **36** ha sido identificado mediante sus datos espectroscópicos. En el espectro RMN-^{1}H se observa la presencia de un singlete a δ 10.47 ppm, correspondiente al aldehído aromático y un único singlete en la zona de los protones aromáticos a 7.36 ppm. Se corrobora la existencia del carbonilo a partir de los datos extraídos de los espectros de RMN-^{13}C e IR. El primero muestra una señal a 185.9 ppm, correspondiente a un carbono cuaternario, y el IR muestra una banda a 1694 cm^{-1}.

3.5. ETAPA FINAL: RUPTURA DE LA AGRUPACIÓN METILENDIOXI

Se han descrito gran variedad de métodos para la ruptura del grupo metilendioxi[86,87]: bien sea en medio ácido[88,89,90] o mediante

(84) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc.* **2004** *126* 11966.
(85) Tietze, L. F.; Spiegl, D. A.; Stecker, F.; Major, J.; Raith, C.; Große, C. *Chem. Eur. J.* **2008** *14*, 8956.
(86) Greene, T. W.; Wuts, P. G. M. **2007**, *4th ed.*
(87) Koeienski, P. J. *Creorg Thieme verlag* **1994**.
(88) Bose, D. S.; Thurston, D. E. *Tetrahedron Letters* **1993**, *34* 1377.
(89) Oh, K.-B.; Lee, J. H.; Lee, J. W.; Yoon, K.-M.; Chung, S.-C.; Jeon, H. B.; Shin, J.; Lee, H.-S. *Bioorganic & Medicinal Chemistry Letters* **2009** *19* 945
(90) Alvarez-Manzaneda, E.; Chahboun, R.; Bentaleb, F.; Alvarez, E.; Escobar, M. A.; Sad-Diki, S.; Cano, M. J.; Messouri, I. *Tetrahedron* **2007** *63* 11204.

nucleofílos[91,92], también mediante condiciones reductoras, oxidantes y procedimientos mixtos[93]. Sin embargo, estos métodos no siempre proporcionan resultados satisfactorios, sobre todo cuando se aplican sobre moléculas con grupos funcionales muy sensibles a estas diferentes condiciones. De entre estas variedad de metodologías descritas en bibliografía, se logró el resultado satisfactorio mediante ruptura nucleofílica, utilizando el tiofenóxido potásico como nucleófilo; éste se genera *in-situ* mediante tiofenol y K_2CO_3[94, 95]. La reacción se llevó a cabo en HMPA a reflujo dando lugar, después de 10 minutos, a una mezcla 6:1 de los tiofenilmetoxifenoles derivados **37a** y **37b** con un 93% de rendimiento. Por último, mediante hidrólisis ácida de los tiofenilmetoxifenoles derivados **37a** y **37b**, se obtuvo (+)-liphagal (**2**) con un rendimiento del 91%. (Esquema 41)



Esquema 41

(91) Newman, M. S.; Sankaran, V.; Olson, D. R. *J. Am. Chem. Soc.* **1976**, *98*, 3227.
(92) Maezawa, N.; Furuichi, N.; Tsuchikawa, H.; Katsumura, S. *Tetrahedron Letters* **2007**, *48* 4865.
(93) Xu, D.-F.; Zhao, L.-M.; Mao, Z.-Q.; Li, S. *Organic Preparations and Procedures International* **2008** *40* 93.
(94) Imakura, Y.; Konishi, T.; Uchida, K.; Sakurai, H.; Kobayashi, S.; Haruno, A.; Tajima, K.; Yamashita, S. *Chem. Pharm. Bull.* **1994**, *42*, 500.
(95) Rao, K. V.; Chattopadhyay, S. K. *J. Org. Chem.* **1990**, *55*, 1427.

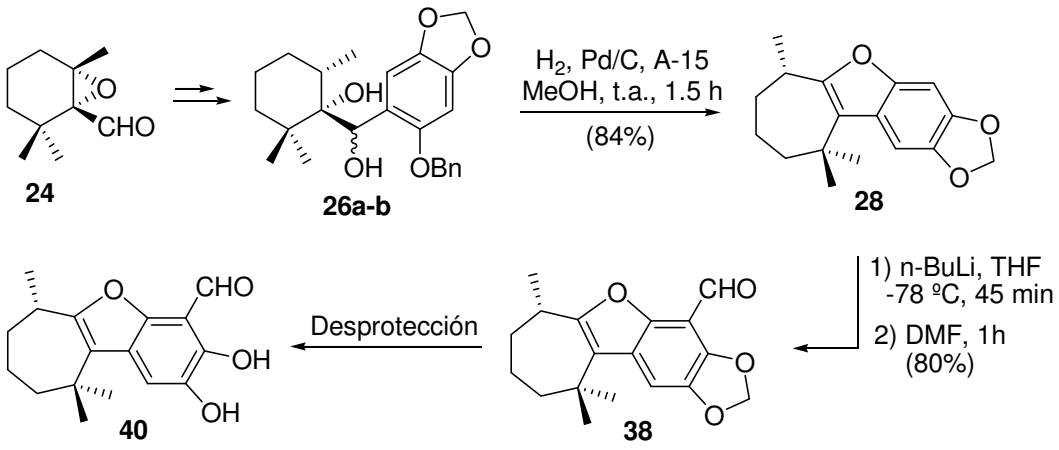
Las estructuras de los compuestos **37a** y **2** se han establecido mediante sus datos de RMN. En el espectro de RMN-^{1}H de la mezcla **37a-b** se observa la desaparición de las señales correspondientes a los protones del grupo metilendioxi y, en su lugar, aparece un singlete que integra por dos protones a 5.63 ppm, correspondiente a los protones del metileno oxiazufrado. Además se observan las señales de los protones aromáticos del resto feniltioeter. El espectro de IR muestra ahora una banda intensa provocada por el hidroxilo fenólico libre a 3059 cm^{-1}. El espectro de masas confirma el valor de la masa esperada para **37a**.

Por último, los datos de (+)-liphagal (**2**) obtenido se compararon con los publicados en la literatura, observándose coincidencia entre ellos. El compuesto exhibe las mismas propiedades espectroscópicas que las previamente publicadas. El $[\alpha]_D$ +17.9 , (lit[6] : $[\alpha]_D$ +12) publicado confirma la estereoquímica absoluta del compuesto final, de acuerdo con lo esperado.

3.6. SÍNTESIS DEL ANÁLOGO MONOTERPÉNICO DE (+) LIPHAGAL (40)

A continuación, se sintetizó el análogo monoterpénico de liphagal, siguiendo para ello, la misma secuencia llevada a cabo para la síntesis de (+)-liphagal (**2**). La mezcla de los dioles monoterpénicos **26a-b**, cuya síntesis a partir de β-ciclocitral (**21**) se describió con anterioridad (ver esquema 12), se sometió a hidrogenación catalítica en presencia de resina catiónica, proporcionado el esperado derivado bezofuránico monoterpénico **28** (Esquema 42).

(6) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Organic Letters* **2006**, *8*, 321.

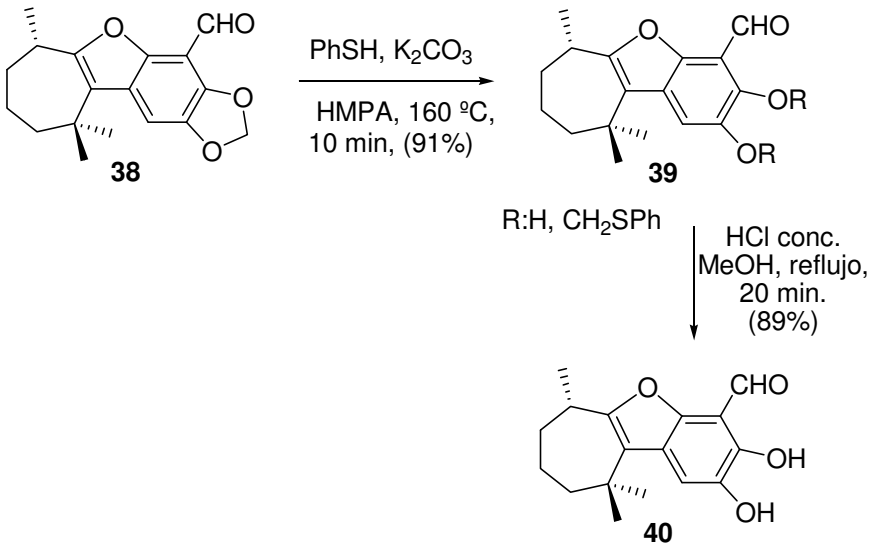


Esquema 42

La formilación de **28,** se llevo a cabo utilizando las mismas condiciones empleadas para la formilación del derivado benzofuránico con esqueleto liphagano **34**. En este caso se obtuvo el aldehído **38** con un 80% de rendimiento**.**

Este derivado se caracterizó en base a sus datos espectroscópicos. El espectro de RMN-^{1}H muestra una señal a 10.43 ppm, característica del grupo aldehído aromático. Esta señal viene confirmada por el espectro de RMN de ^{13}C, que presenta una señal a 186.0 ppm. Por su parte el espectro de IR de esta sustancia, exhibe una banda a 1684 cm^{-1} característica de un aldehído aromático. Además se puede asignar el singlete a 7.34 ppm en el espectro de RMN-^{1}H al protón aromático.

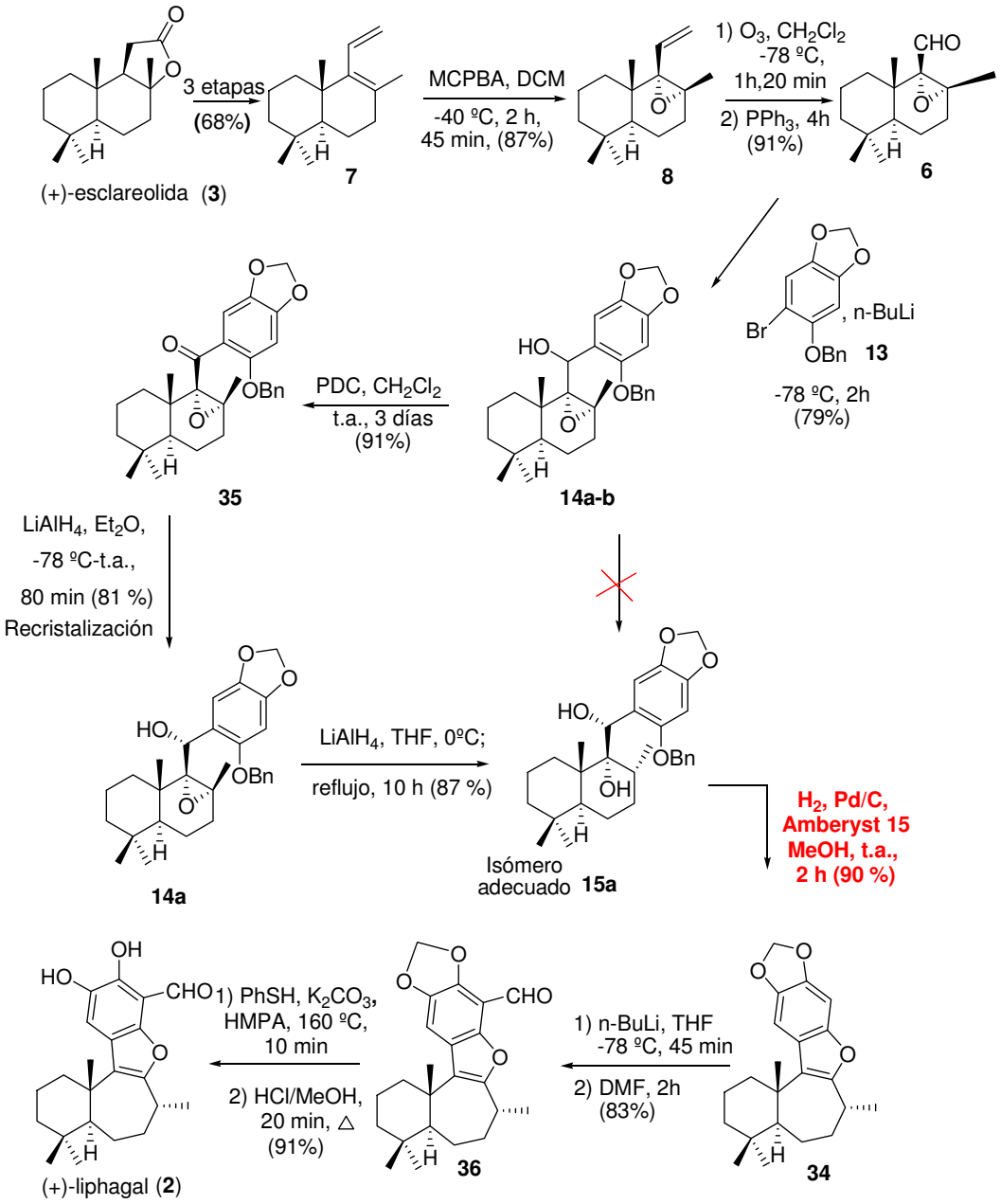
Una vez obtenido **38,** se aplicaron las condiciones de ruptura del grupo metilendioxi, de acuerdo con las condiciones aplicadas a la síntesis de (+)-liphagal (**2**), obteniédose su análogo monoterpénico **40** con un 91% de rendimiento (Esquema 43).



Esquema 43

Los compuestos **39** y **40** se identificaron en base a sus datos espectroscópicos. El grupo metileno oxisulfurado de **39** da lugar a un singlete ancho característico, a 5.63 ppm, que integra por dos protones. Además, se aprecia la aparición de un multiplete a δ 7.58-7.50 ppm que integran por cinco protones, correspondientes al grupo feniltioéter, y la ausencia del doblete a 6.02 ppm, a que daba lugar el grupo metilendioxi del producto de partida. En el espectro de RMN-^{1}H del compuesto **40** destaca la ausencia de las señales correspondientes al grupo fenilsulfuro El espectro de IR de **40** muestra asimismo una banda característica de los hidroxilos fenólicos a 3470 cm^{-1}.

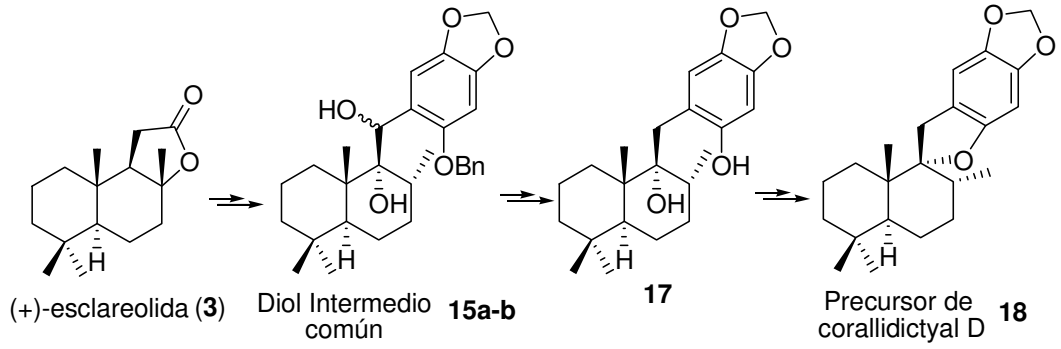
ESQUEMA GENERAL DE SÍNTESIS DE LIPHAGAL



Esquema 44

4. APROXIMACIÓN A LA SÍNTESIS DE CORALLIDICTYAL D (1) A PARTIR DE (+)-ESCLAREOLIDA (3)

Inicialmente, la estrategia sintética planteada para la síntesis de corallidictyal D (**1**), a partir de (+)-esclareolida (**3**), implicaba la obtención del hidroxifenol **17**, a partir de los 9,11-dihidroxifenil derivados **15a-b**, mediante reducción selectiva del grupo hidroxilo bencílico. El hidroxifenol **17** se postuló como un precursor adecuado para la formación del anillo espiránico presente en corallidictyales (ver esquema 10).

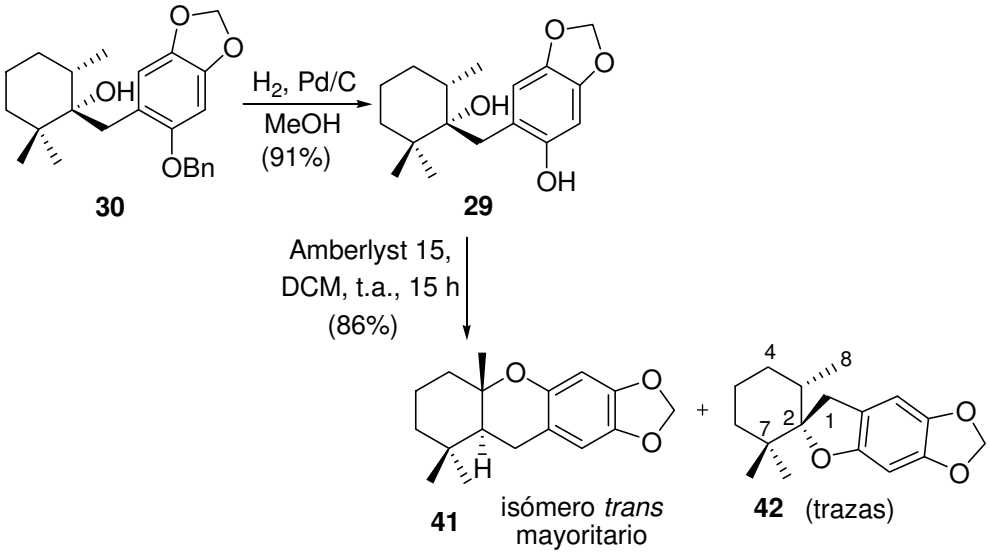


Esquema 45

Antes de proseguir nuestra investigación hacia la aproximación a la síntesis de corallidictyal D (**1**), se realizaron ensayos de ciclación sobre el hidroxifenol monoterpénico **29**, a fin de comprobar la eficacia de la ruta hacia el objetivo marcado en este apartado. Este hidroxifenol monoterpénico **29** se prepara fácilmente mediante hidrogenación catalítica del alcohol **30**, ya obtenido con anterioridad (ver esquema 16).

Todos los ensayos de ciclación realizados en medio ácido proporcionaron mezcla del producto espiránico deseado **42** como producto minoritario junto al

derivado xanténico **41** como mayoritario. Tomamos como ejemplo el caso de la ciclación con resina catiónica Amberlyst 15 (Esquema 46).



Esquema 46

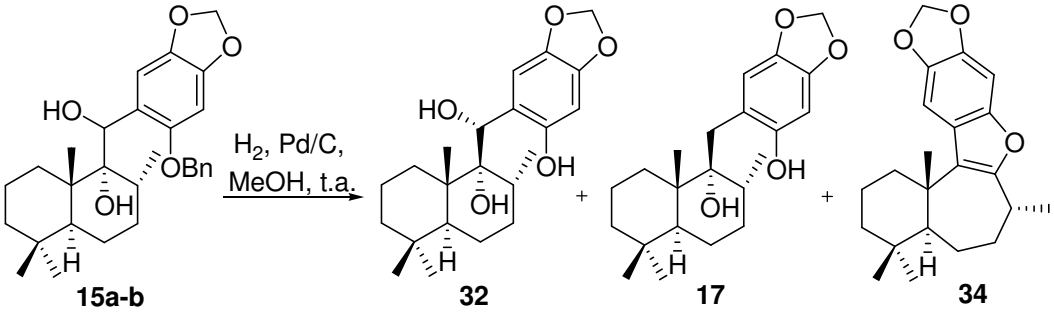
A pesar de que los resultados obtenidos en la ciclación del análogo monoterpénico **29** no animan a proseguir con el plantamiento inicial (recogido en el esquema 45), decidimos preparar el hidroxifenol **17** con el fin de estudiar el proceso de ciclación catiónica que genera el esqueleto espirodihidrobenzofuránico de corallidictyales, confiando en que la diferente reactividad de ambos hidroxifenoles **17** y **29** pudiera proporcionar resultados distintos.

Los ensayos de reducción catiónica del grupo hidroxilo bencílico realizados sobre el diol sesquiterpénico **15a-b** para acceder al hidroxifenol sesquiterpénico **17** no resultaron favorables (ver esquema 18). El medio ácido necesario para dicha reducción provoca preferentemente la expansión del anillo en lugar del producto de reducción deseado **17** (ver esquema 19). Aunque los resultados de reducción del grupo hidroxilo bencílico del análogo monoterpénico **29** con H_2/Pd-C no proporcionaron rendimientos buenos (ver tabla 1), decidimos estudiar esta etapa de hidrogenación catalítica sobre los dioles merosesquiterpénicos **15a-b**, a fin de esclarecer las dudas acerca de la posibilidad de obtención de **17**, *vía* **15a-b**.

4.1. ENSAYOS DE HIDROGENACIÓN CATALÍTICA DEL DIOL SESQUITERPÉNICO 15

Los resultados obtenidos de los ensayos de hidrogenación catalítica de los dioles sesquiterpénicos **15a-b** se resumen en la tabla 3.

Tabla 3: Ensayos de hidrogenación catalítica de 15a-b

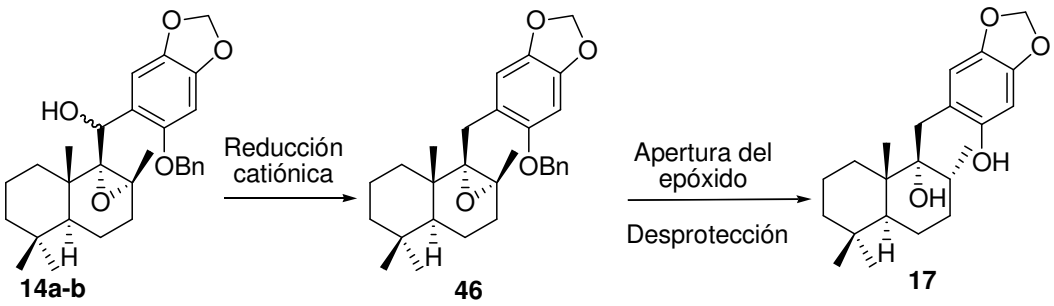


Ensayo	t.(h)	Condiciones	Productos	Rdto(%)
1	1.5	H_2/Pd-C	**32**	85
2	96	H_2/Pd-C	**32**	83
3	2.5	H_2/Pd-C y AcOH	**32**	88
4	3	H_2/Pd-C -Amberlyst 15	**17 : 34**; (1:4)	86

Estos resultados son muy similares a los observados en la reducción de los análogos monoterpénicos **26a-b** y **27a-b** (ver tabla 1). La presencia de resina catiónica Amberlyst 15 favorece la formación del hidroxifenol **17**, aunque su rendimiento sigue siendo muy bajo. (Ensayo 4).

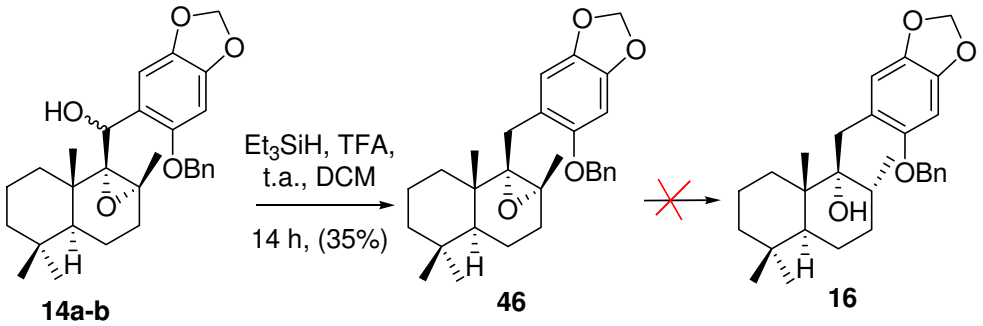
4.2. ENSAYOS DE OBTENCIÓN DE 17 MEDIANTE REDUCCIÓN CATIÓNICA DE 14 Y POSTERIOR APERTURA DEL ANILLO OXIRÁNICO

Ante la dificultad demostrada en la conversión del dihidroxiderivado **15a-b** en el hidroxifenol **17**, se planteó la posibilidad de obtener dicho hidroxifenol, a partir de los epoxialcoholes **14a-b,** invirtiendo el orden de las etapas realizadas anteriormente**.** Es decir, llevando a cabo en primer lugar la reducción catiónica del grupo hidroxilo de los epoxialcoholes **14a-b**, y continuar efectuando la reducción regio- y estereoselectiva del anillo de oxirano (Esquema 47).



Esquema 47

Así pues, se sometieron los epoxialcoholes **14a-b** a reducción catiónica, empleando el sistema Et_3SiH/TFA, que dió lugar al producto de reducción **46** con bajo rendimiento 35%. (Esquema 48).



Esquema 48

Todos los intentos de reducción del epoxiderivado **46**, en diferentes condiciones y con distintos tipos de hidruros; resultaron infructuosos (Tabla 4), con la transformación parcial del producto de partida en una mezcla compleja de productos. Estos resultados corroboran el mecanismo propuesto para la reducción de **14a-b,** (ver explicación esquema 9) que señala la importancia del hidroxilo adyacente en C-11 en el proceso de reducción.

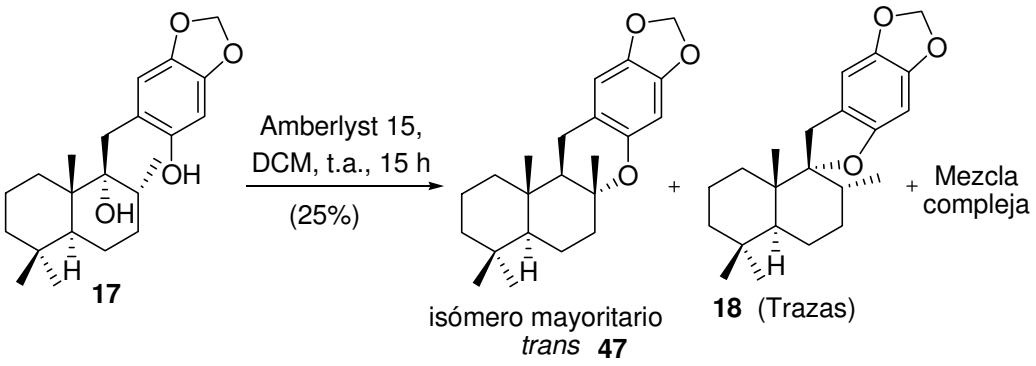
Tabla 4: Ensayos de reducción del epóxido **46**

Ensayo	t (días)	Condiciones
1	4	$LiAlH_4$/THF/Reflujo
2	4	$LiAlH_4$/$MeO(CH_2)_2OMe$/Reflujo
3	3	DIBAL-H/Tolueno/Reflujo
4	4	Red-Al/THF//Reflujo
5	5	$LiEt_3BH$/THF/Reflujo

4.3. CICLACIÓN CON RESINA CATIÓNICA

Por último, y a pesar del bajo rendimiento en la obtención del hidroxifenol **17**, se realizó la reacción de ciclación con resina catiónica, obteniéndose una mezcla compleja de productos, entre los que se identificó como producto mayoritario el isómero piránico **47** junto con trazas del espirocompuesto **18**, que fue identificado mediante el espectro de RMN -^{1}H, pero no pudo aislarse (Esquema 49). El derivado piránico **47** se identificó mediante comparación de sus datos espectroscópicos de RMN con los previamente publicados por nosotros[51].

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.



Esquema 49

Es preciso comentar que este ensayo de ciclación catiónica del hidroxifenol **17**, tiene enorme importancia para el objetivo de la investigación llevada a cabo, ya que de él se concluye que no resulta favorable el acceso al esqueleto de corallidictyales a través de un proceso que implique la formación de un carbocatión en el C-9 de estos precursores merosesquiterpénicos. A pesar de tratarse de un carbocatión terciario, tiende a provocarse la migración del metilo C-15[72] generándose así otro carbocatión más estable que conduce a la formación de una familia de productos estructuralmente muy diferentes a corallidictyales, como puede ser el aureol.

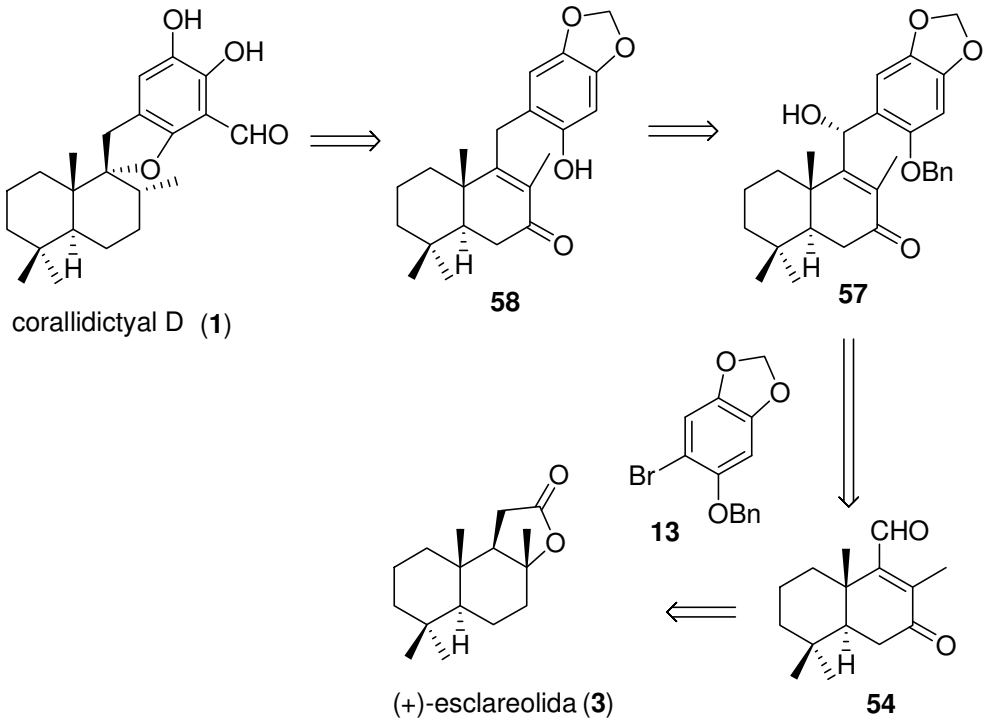
(72) Kuan, K. K. W.; Pepper, H. P.; Bloch, W. M.; George, J. H. *Organic Letters* **2012**, *14*, 4710.

5. SEGUNDA ESTRATEGIA HACIA LA SÍNTESIS DE CORALLIDICTYAL D (1) A PARTIR DE (+)-ESCLAREOLIDA

En base a los resultados obtenidos con anterioridad, concluimos que se precisa de un nuevo planteamiento para la obtención del esqueleto de corallidictyales. En este caso, proponemos la utilización de un proceso de ciclación basado en un mecanismo de adición electrofílica concertado. De este modo, se evitaría la formación de mezclas relativamente complejas de productos, ya puestas de manifiesto anteriormente. La nueva estrategia, implicaría la formación del esqueleto espirodihidrobenzofuránico, presente en la moléculas objetivo, mediante una adición intramolecular 1,4 del hidroxilo fenólico sobre la enona α,β-insaturada en **58**. El grupo carbonilo permitiría la orientación del metilo en C-8 hacia la cara α.

Posteriormente, se procedería a la reducción de dicha cetona, para finalmente completar la síntesis de corallidictyal D, con la adecuada funcionalización del anillo aromático y ruptura de la agrupación metilendioxi, como se realizó en el primer objetivo de esta memoria.

La cetona α,β-insaturada **57** se obtendrá a partir del cetoaldehído **54,** que debe ser fácilmente preparado a partir de (+)-esclareolida (**3**) (Esquema 50).

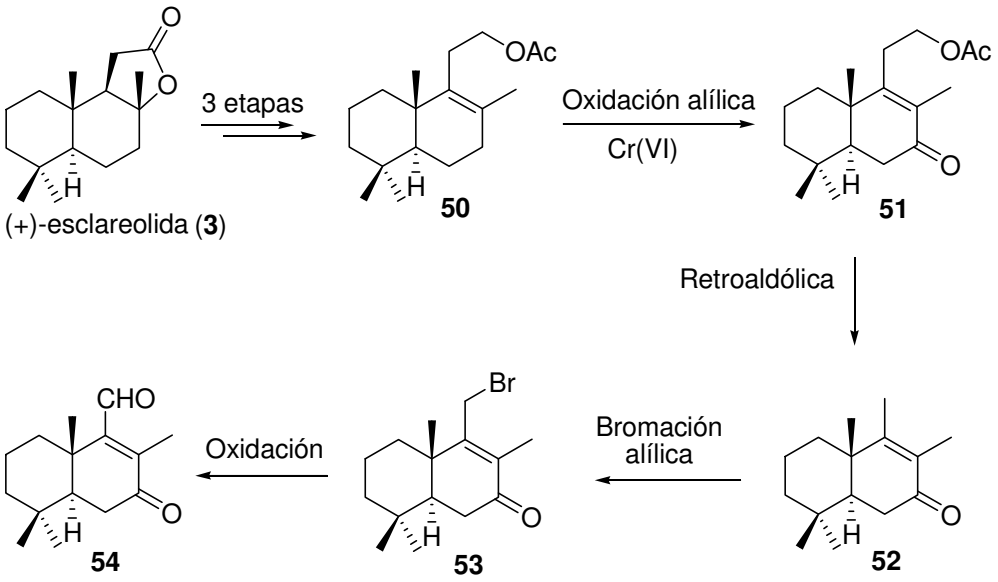


Esquema 50

5.1. PREPARACIÓN DEL CETOALDEHÍDO 54

El esquema 51 recoge el planteamiento sintético para la preparación del cetoaldehído **54** a partir de (+)-esclareolida (**3**). Dicho proceso implicaría la transformación de la materia prima en el acetil derivado **50,** según el procedimiento llevado a cabo por nuestro grupo de investigación[67] , que tras la oxidación alílica del C-7 y posterior reacción retroaldólica, proporcionaría la enona **52**. La bromación alílica regioselectiva de esta cetona y oxidación de la consiguiente bromocetona **53,** conduciría al cetoaldehído objetivo **54** (Esquema 51)

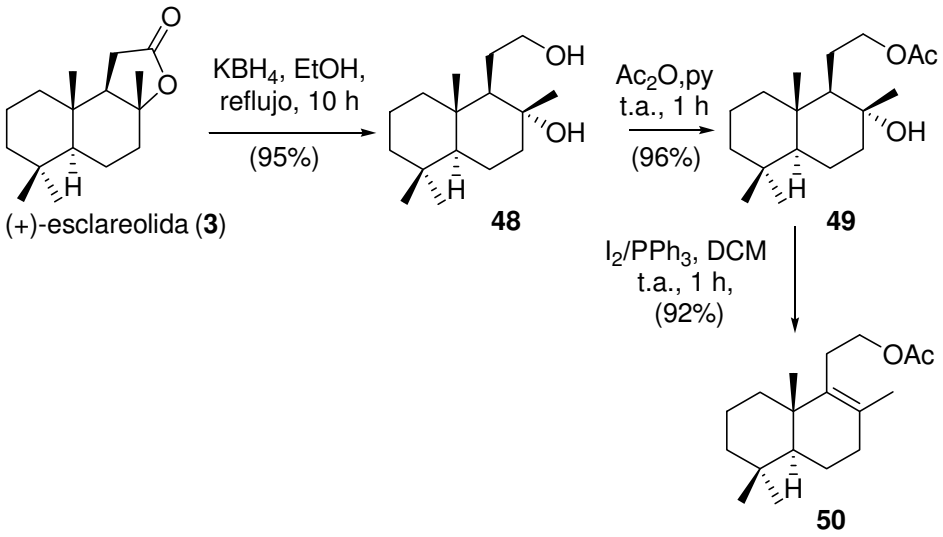
(67) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmammouchi, M.; Es-Samti, H. *Chem. Commun*. **2009**, 592.



Esquema 51

El acetato homodrimánico **50** se obtiene en tres etapas a partir de (+)-esclareolida (**3**) con un 81% de rendimiento global[96]: reducción con $NaBH_4$, acetilación selectiva del grupo hidroxilo primario y deshidratación regioselectiva del alcohol terciario (Esquema 52).

(96) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Arteaga, A. F. *Synth. Comm.* **2004**, *34*, 3631.



Esquema 52

Los productos de estas etapas iniciales se identificaron por comparación de sus datos espectroscópicos con los previamente publicados por nuestro grupo[67] .

Se ensayaron diferentes condiciones para introducir el grupo carbonilo en C-7 del compuesto **50**[97-100]. El mejor resultado se obtuvo mediante el uso del sistema Na_2CrO_4 / AcONa ya empleado en nuestro laboratorio en oxidaciones similares[101]; la reacción tiene lugar en benceno a 70ºC durante 3.5 h y proporciona la enona α,β-insaturada **51** con un 91% de rendimiento. (Esquema 53). La estructura de **51** fue confirmada mediante comparación con los datos bibliográficos descritos[102].

(67) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmammouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592.

(97) Daubenm, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *94*, 3587.

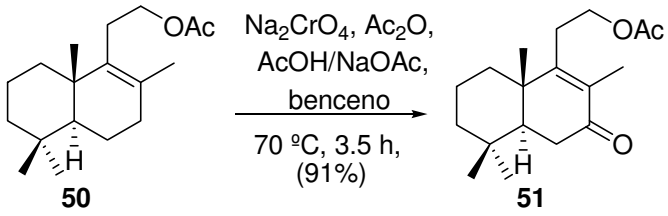
(98) Kim, G.; Jeon, S. Y. *Bull. Korean Chem. Soc.* **2001**, *22*, 1156.

(99) Cui, Y.-M.; Yasutomi, E.; Otani, Y.; Ido, K.; Yoshinaga, T.; Sawada, K.; Ohwada, T. *Bioorg. Med. Chem.* **2010**, *18*, 8642.

(100) Matsushita, Y.-I.; Iwakiri, Y.; Yoshida, S.; Sugamoto, K.; Matsui, T. *Tetrahedron Letters* **2005**, *46*, 3629.

(101) Barrero, A. F.; Cortés, M.; Manzaneda, E. A.; Cabrera, E.; Chahboun, R.; Lara, M.; Rivas, A. R. *J. Nat. Prod.* **1999**, *62*, 1488.

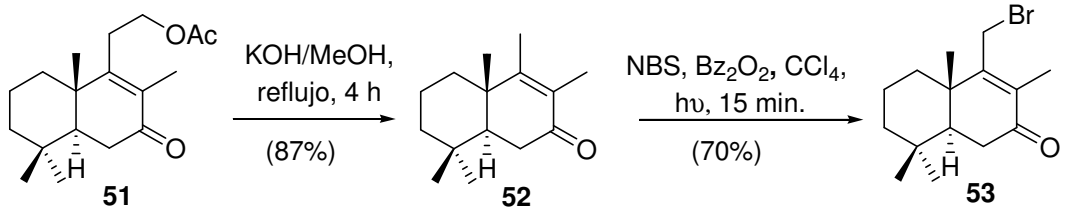
(102) Vlad, P. F.; Edu, K. G.; Koltsa, M. N.; Chokyrlan, A. G.; Nikolescu, A.; Delyanu, K. *Chemistry of Natural Compounds* **2011**, *47*, 574.



50 **51**

Esquema 53

El tratamiento en medio básico (KOH/MeOH) de **51**, conduce a la cetona **52**, vía el alcohol derivado, con un rendimiento del 87%. La identificación de la cetona obtenida se realizó en base a sus datos espectroscópicos de RMN-^{1}H y RMN-^{13}C. En el espectro de RMN-^{1}H se observa la desaparición del grupo metileno oxigenado y la aparición de una nueva señal singlete a 1.82 ppm atribuida a los protones del grupo metilo C-11 y una nueva señal a 15 ppm en el espectro de RMN-^{13}C debida al C-11.

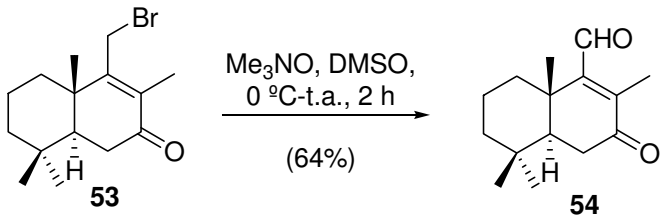


51 **52** **53**

Esquema 54

La reacción de bromación alílica, utilizando el sistema NBS/Bz_2O_2, condujo de manera totalmente regioselectiva al bromo derivado **53** (Esquema 54). La identificación de éste se realizó fundamentalmente en base a sus datos espectroscópicos de RMN-^{1}H, donde se observa la aparición de dos dobletes que integran por un protón cada uno, a 4.01 y 4.07 ppm, con J = 9.9 Hz, atribuidos a los dos protones geminales al bromo.

Por último, la oxidación de la bromocetona derivada **53**, utilizando óxido de trimetilamina en DMSO[103] a 0ºC, dió lugar al aldehído **54** con un 64 % de rendimiento (Esquema 55).



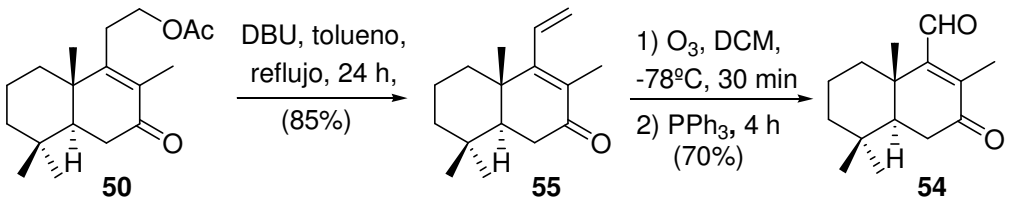
Esquema 55

La estructura de **54** se corrobora mediante el espectro de RMN de ^{1}H, que muestra una señal singlete a 10.27 ppm y el espectro de RMN-^{13}C, que muestra dos señales a 199 y 194 ppm, atribuibles a los dos carbonos carbonílicos. Se observan además dos bandas muy intensas en el espectro de absorción de IR a 1739 y 1674 cm^{-1}.

5.2. PREPARACIÓN DEL CETOALDEHÍDO 54 VÍA EL DIENO 55

Alternativamente, se preparó el cetoaldehído **54**, a partir del acetilderivado **50**, en dos etapas. La eliminación de ácido acético mediante tratamiento con DBU en tolueno proporcionó el cetodieno **55** con 85% de rendimiento. La posterior degradación selectiva del doble enlace terminal de **55**, utilizando ozono y un medio reductor como PPh_3, dió lugar al correspondiente cetoaldehído objetivo **54**, con un rendimiento de 70 % (Esquema 56).

(103) Boulin, B.; Arreguy-San Miguel, B.; Delmond, B. *Tetrahedron* **1998**, *54*, 2753.



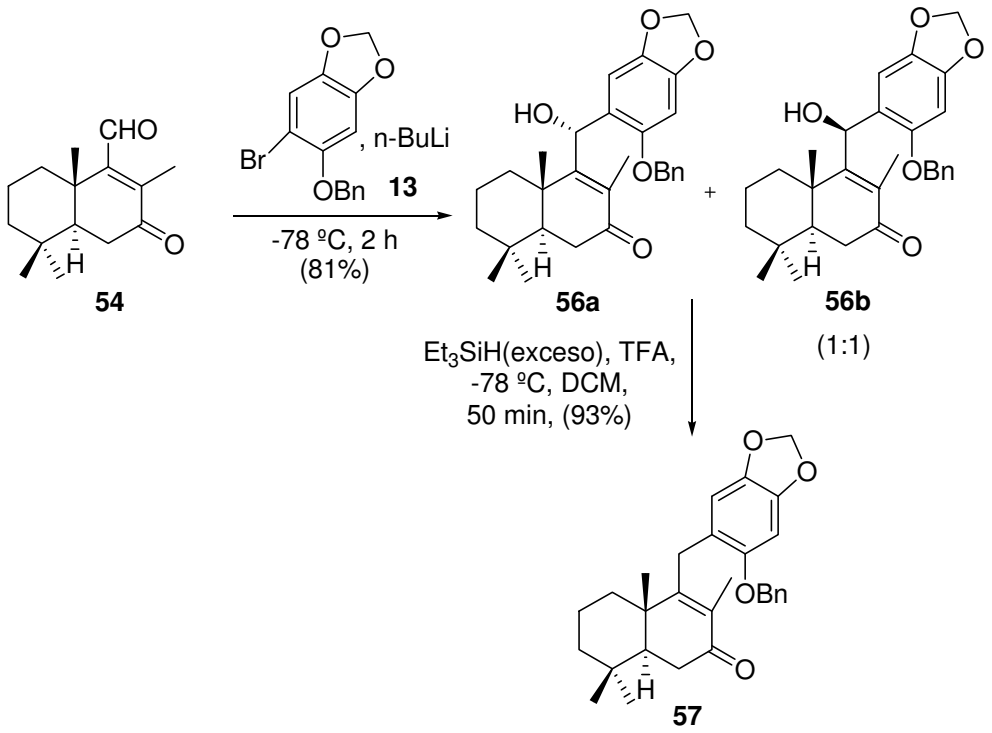
Esquema 56

La identificación de la dienona **55** se realizó en base a sus datos espectroscópicos y por comparación con los datos bibliográficos disponibles[104]. Se observan las tres señales del sistema vinílico que resuenan a 6.29 ppm, como doble doblete con J = 11.8, 7.7 Hz, a 5.47 ppm como doble doblete con J =11.8, 2.1 Hz, y a 5.11 ppm, como doble doblete con J = 17.7, 2.1 Hz. El espectro de RMN-^{13}C muestra los dos carbonos del nuevo doble enlace a 165.4 y 133.2 ppm.

5.3. PREPARACIÓN DEL FENOL 58

Una vez obtenido el precursor terpénico **54**, se efectuó la condensación de éste con la sal de litio derivada de **13**, obteniéndose la mezcla de alcoholes bencílicos **56a-b** en proporción 1:1. Estos alcoholes se identificaron en base a sus datos espectroscópicos. Resaltan las señales del protón metínico del C-11 que resuenan a 5.76 ppm (**56a**) y 5.97 ppm (**56b**). A continuación, se sometió, sin purificación, la mezcla de alcoholes **56a-b** a reducción catiónica con el sistema Et_3SiH/TFA a -30ºC, obteniéndose así el derivado **57** con un rendimiento del 93%. (Esquema 57).

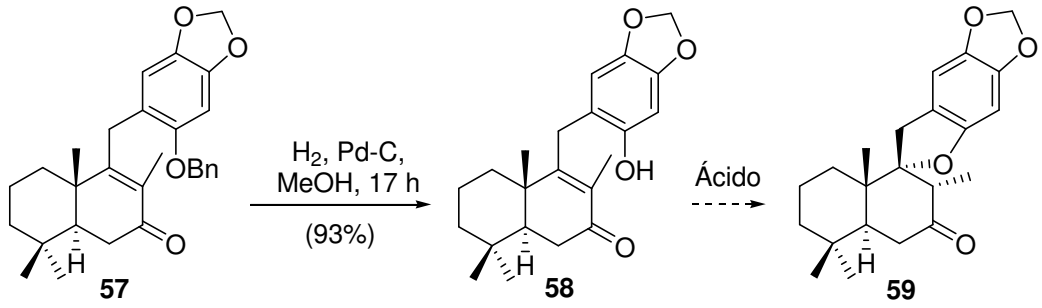
(104) Abad, A.; Agullo, C.; Cunat, A. C.; Garcia, A. B.; Gimenez-Saiz, C. *Tetrahedron* **2003**, *59*, 9523.



Esquema 57

La estructura de **57** se confirmó en base a los datos espectroscópicos de RMN-^{1}H, que muestra sendos dobletes a 3.64 y 3.41 ppm, con J = 16.3 Hz, atribuibles a los protones del grupo metileno generado en C-11.

A continuación se efectuó la ruptura del grupo benciléter mediante hidrogenación catalítica, generando el fenol **58,** que se sometió más adelante a distintas condiciones de ciclación, empleando diferentes ácidos. (Esquema 58).



Esquema 58

5.4. ENSAYOS DE CICLACIÓN DEL FENOL 58

El tratamiento del fenol **58** con diferentes ácidos, en distintas condiciones, proporcionó los resultados resumidos en la tabla siguiente.

Tabla 5: Ensayos de ciclación del fenol 58.

Ensayo	Condiciones	Productos	Rdto(%)
1	APTS, benceno, t.a.--reflujo	Mezcla Compleja	---
2	TFA, DCM, t.a.—refujo	Mezcla Compleja	----
3	$BF_3.OEt_2$, DCM, -20 ºC—t.a.	Mezcla Compleja	----
4	Amberlyst 15, DCM, t.a.--reflujo	Mezcla Compleja	---
5	$SnCl_4$, DCM, -40 ºC	**59**	20
6	I_2/PPh_3, DCM, t.a.	Mezcla Compleja	---

Como se observa, todos los ensayos realizados resultaron infructuosos, debido a que la reacción de adición del grupo hidroxilo fenólico sobre el doble enlace α,β-insaturado de **58** no está favorecida y las condiciones ácidas acaban transformando, mayoritariamente, la cetona conjugada en una mezcla compleja de productos. Tan sólo utilizando $SnCl_4$, se obtuvo el producto de ciclación **59**, con un rendimiento muy bajo (20%), junto a otros productos cuya identificación no fue posible. El derivado espirocetónico **59** se identificó en base a sus datos espectroscópicos. El espectro de RMN-^{1}H muestra dos señales dobletes a 2.87 y 3.32 ppm y (J = 16.2 Hz), atribuibles a los dos protones del anillo tetrahidrofuránico. Además aparece una nueva señal de metilo doblete (J = 6.6 Hz), a 0.96 ppm, correspondiente al metilo C-12.

El análisis general de esta reacción de ciclación, apunta otra vez a un proceso, probablemente *vía* formación del carbocatión en el C-9, lo que conduce a mezcla de productos de reacción tal como se ha comentado anteriormente (ver apartado 4.3).

Ante la enorme dificultad que presenta la ciclación del fenol **58** y el bajo rendimiento de obtención de **59**, se abandonó esta segunda estrategia de aproximación a la síntesis de corallidictyal D.

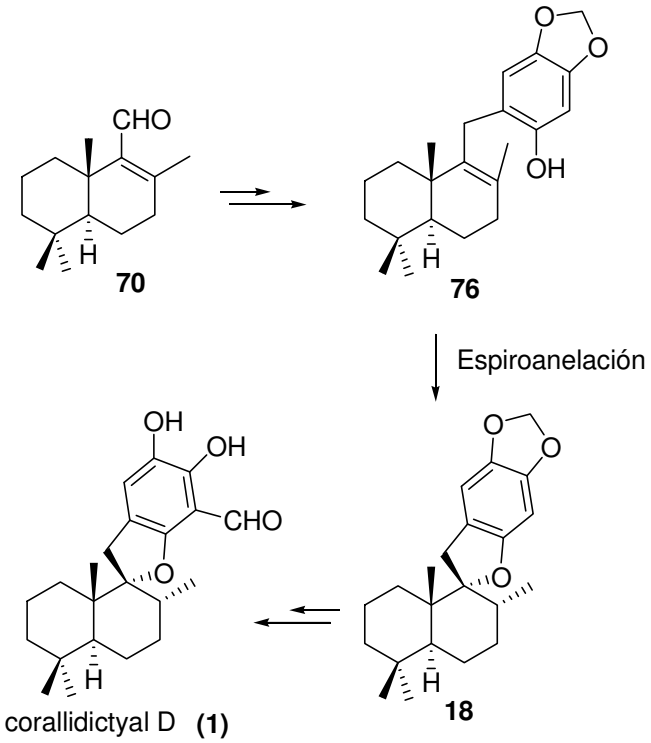
6. TERCERA ESTRATEGIA: SÍNTESIS TOTAL DE CORALLIDICTYAL D A PARTIR DE α-IONONA (60). DESARROLLO DE UNA NUEVA METODOLOGÍA PARA LA ESPIROANELACIÓN DE O-ALILFENOLES

En el desarrollo de las anteriores estrategias se ha puesto de manifiesto que la etapa de espiroanelación resulta clave en la síntesis de corallidictyal D, y se ha hecho evidente la dificultad de la misma.

Se han descrito en bibliografía escasas condiciones para la síntesis de sustancias similares a corallidictyales, tales como K-76[9,48,105] y su derivado espirodihidrobenzofuranolactama stachybotrylactama[52,53] . Estos trabajos revelan la dificultad de la etapa de ciclación, además muestran la efectividad del uso de resina catiónica Amberlyst 15 para generar el anillo espiránico presente en dichas moléculas, aunque con rendimiento moderado. Los antecedentes bibliográficos recogidos en esta memoria dejan patente la carencia de un protocolo general, que pueda ser aplicado con garantías, para esta etapa clave de la síntesis.

Así pues, en base a nuestros resultados anteriores y a los antecedentes bibliográficos, se planteó una tercera estrategia sintética hacia la síntesis de corallidictyales que implica la ciclación del fenol **76** bajo estas condiciones o similares, para la etapa clave de construcción del anillo espirofuránico. Este fenol **76** puede prepararse fácilmente partiendo del aldehído drimánico **70** (Esquema 59).

(9) Larghi, E. L.; Kaufman, T. S. *ARKIVOC* **2011**, *vii*, 49.
(48) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273.
(52) Kende, A.; Zhong, W.-P. D.; Guo, X.-C. *Organic Letters* **2003**, *5*, 1785.
(53) Kende, A.; Zhong, W.-P. D.; Guo, X.-C. *J. Org. Chem.* **2003**, *68*, 7422.
(105) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5552.



Esquema 59

6.1. NUEVA VÍA DE ACCESO AL FENOL SESQUITERPÉNICO 76

Los intermedios drimánicos similares a **70** han sido clave en la síntesis de numerosos meroterpenos[51,67,106,107]. En la mayoría de los casos, los procedimientos utilizados implican la condensación de un fragmento drimánico tal como el aldehído **70** o el bromuro alílico derivado de éste[108,109] y un fragmento

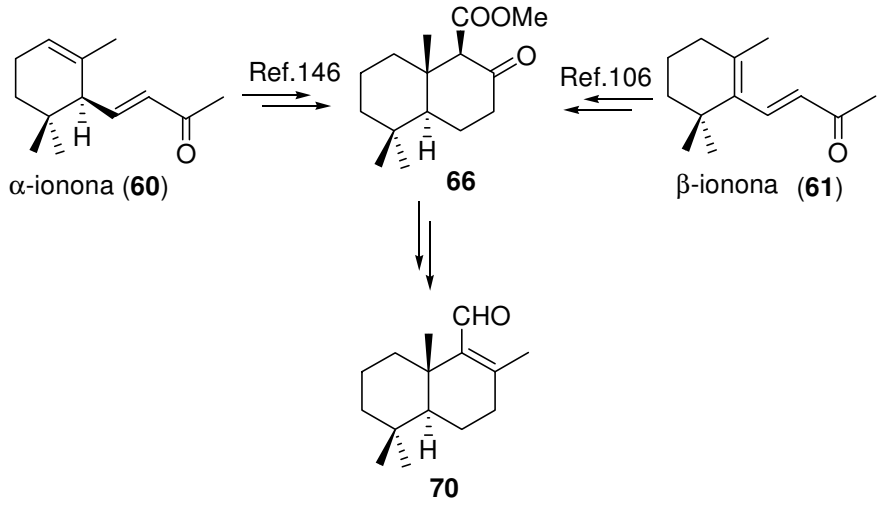
(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.
(67) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmammouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592.
(106) Schroeder, J.; Magg, C.; Seifert, K. *Tet. Lett.* **2000**, *41*, 5469.
(107) Alvarez-Manzaneda, E. J.; Chahboun, R.; Barranco Pérez, I.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R. *Organic Letters* **2005**, *7*, 1477.
(108) Barrero, A. F.; Herrador, M. M.; Quilez del Moral, J., F.; Arteaga, P.; Arteaga, J. F.; Dieguez, H. R.; Sanchez, E. M. *J. Org. Chem.* **2007**, *72*, 2988.
(109) Arima, Y.; Kinoshita, M.; Akita, H. *Tetrahedron: Asymmetry* **2007**, *18*, 1701.

aromático adecuado, tal como se ha descrito en la síntesis de **76**[51] . Debido a la amplia utilización de dichos precursores drimánicos, se han descrito varias vías para su obtención, tanto de forma total o a través de semisíntesis, utilizando materias primas de origen natural como (-)-esclareol o (+)-esclareolida.

*a) Utilización de α-ionona **60** para la síntesis del fenol sesquiterpénico **76***

Con objeto de encontrar nuevas rutas para la síntesis del fragmento drimánico, más eficientes que las descritas en bibliografía, ya sea lasrealizadas en grupo laboratorio[55,77], o las desarrolladas por otros grupos[62,110,111], se investigó la síntesis total del fenol **76** a partir de α-ionona (**60**), una materia prima muy económica, y poco utilizada. Una ventaja del uso de esta materia prima radica en que todos sus carbonos son aprovechables para la preparación del esqueleto carbonado del fenol **76**. Además, ofrece la posibilidad de sintetizar corallidictyales de forma enantioespecífica, mediante el empleo de α-ionona enantioméricamente pura como producto de partida.

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.
(55) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Letters* **1997**, *38*, 8101.
(62) Kuchkova, K. I.; Aryku, A. N.; Barba, A. N.; Vlad, P. F. *Chem. Nat. Prod.* **2007**, *43*, 412.
(77) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron* **1998**, *54*, 5635.
(110) Chackalamannil, S.; Wang, Y.; Xia, Y.; Czarniecki, M. *Tet. Lett.* **1995**, *36*, 5315.
(111) Margaros, I.; Montagnon, T.; Tofi, M.; Pavlakos, E.; Vassilikogiannakis, G. *Tetrahedron* **2006**, *62*, 5308.



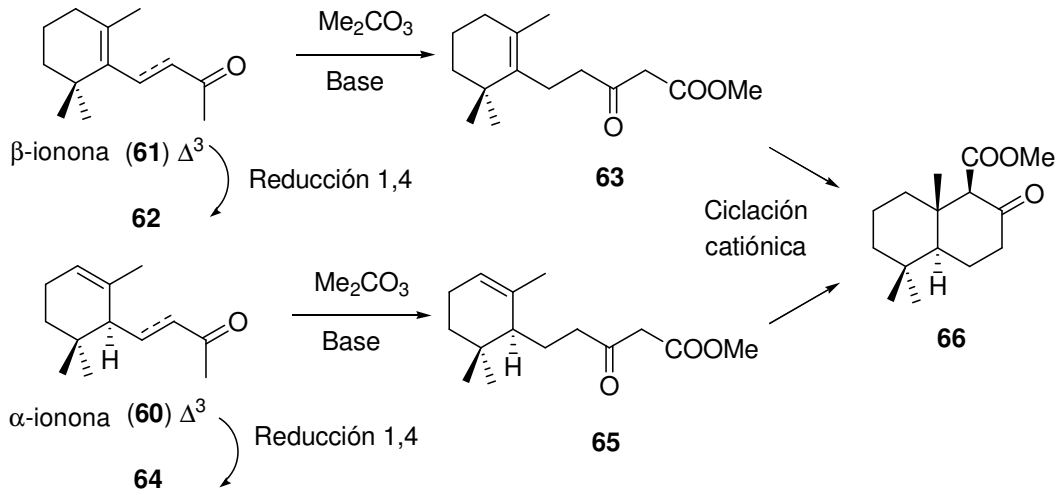
Esquema 60

La β-ionona (**61**) es una de las materias primas monocíclicas más utilizadas para la preparación de derivados bicíclicos como el aldehído **70**[106]**,** y a pesar de ser estructuralmente muy similar a α-ionona, la presencia de un centro estereogénico en ésta última, ausente en la β-ionona, marca una notable diferencia entre ambas. Además, el sistema diénico presente en β-ionona está conjugado con el grupo carbonilo, mientras que en el caso de α-ionona, sólo uno de los dos dobles enlaces lo está. Estos aspectos estructurales hacen que la reactividad de ambas sustancias sea bien distinta, como se pone de manifiesto en la reacción de reducción selectiva del doble enlace Δ^3 presente en sendos compuestos. Mientras para la reducción selectiva de β-ionona (**61**) sólo existen dos procedimiento eficaces descritos en bibliografía, uno de los cuales implica el uso de hidruro de tributil estaño en presencia de AIBN[112] y el otro consiste en la utilización de fuentes de hidruro con catalizadores muy específicos[106,113], la correspondiente reducción 1,4 de α-ionona (**60**) se puede realizar utilizando procedimientos mucho

(106) Schroeder, J.; Magg, C.; Seifert, K. *Tet. Lett.* **2000**, *41*, 5469.
(112) Tesis doctoral. Salido, S. Universidad de Granada, **1994**.
(113) Kojima, S.; Maki, S.; Hirano, T.; Ohmiya, Y.; Niwa, H. *Tet. Lett.* **2000**, *41*.
(146) Escher, S.; Giersch, W.; Niclass, Y.; Bernardinelli, G.; Ohloff, G. *Helv. Chim. Acta* **1990**, *73*, 1935.

más simples y variados[114-118] como el empleo de ditionito sódico[115] o Niquel Raney[119] . Este último protocolo de reducción ha sido desarrollado en nuestro laboratiorio y ofrece la posibilidad de llevar a cabo dicha reacción a escala de gramos. Cabe recordar que al aplicar este procedimiento sobre β-ionona (**61**) se obtiene exclusivamente el producto de reducción de ambos dobles enlaces[119].

Sin embargo, no todo son ventajas para el uso de α-ionona como materia prima. Deben existir evidencias que justifiquen el poco uso de ésta en la elaboración de estructuras bicíclicas y/o tricíclicas. La revisión bibliográfica sobre este tema revela que la ciclación del β-cetoéster **65**, derivado de α-ionona, no resulta diastereoselectiva y proporciona un rendimiento muy bajo del correspondiente compuesto bicíclico **66**[146] (Esquema 61).

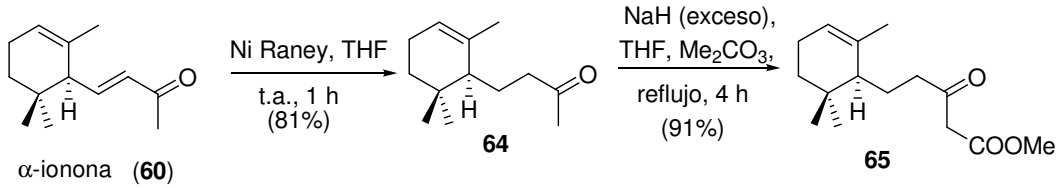


Esquema 61

*b) Preparación del derivado bicíclico **66***

(114) Yamashita, M.; Tanaka, Y.; Arita, A.; Nishida, M. *J. Org. Chem.* **1994**, *59*, 3500.
(115) Dhillon, R. S.; Singh, R. P.; Kaur, D. *Tet. Lett.* **1995**, *36*, 1107.
(116) Baker, B. A.; Boskovic, Z. V.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 289.
(117) Larpent, C.; Dabard, R.; Patin, H.; *Tet. Lett.* **1987**, *28*, 2507.
(118) Snowden, R. L.; Eichenberger, J. C.; Linder, S. M.; Sonnay, P.; Vial, C.; Schulte-Elte, K. H. *J. Org. Chem.* **1992**, *57*, 955.
(119) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Meneses, R. *Synlett* **1999**, 1663.

Consecuentemente, propusimos investigar esta etapa de ciclación de **65**, que resulta clave para el empleo de esta interesante materia prima. Con este fin, preparamos dicho β-cetoéster **65** a partir de α-ionona en dos etapas: Una primera consistente en la reducción de ésta con Niquel Raney, obteniéndose la dihidro-α-ionona (**64**), seguida de un posterior tratamiento con exceso de hidruro sódico y carbonato de dimetilo (Esquema 62).

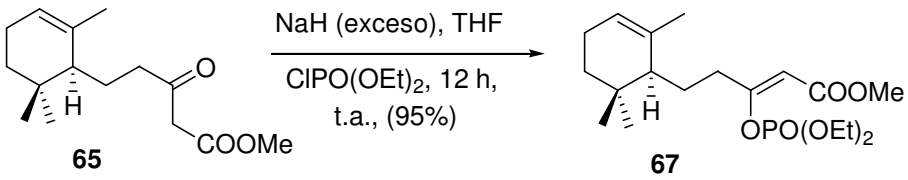


α-ionona (**60**) **64** **65**

Esquema 62

A continuación se realizó una serie de ensayos de ciclación en CH_2Cl_2 utilizando para ello distintos ácidos[120-122] : $SnCl_4$, $BF_3.OEt_2$, CF_3SO_3H y TsOH a diferentes temperaturas. Todos los ensayos realizados dieron lugar a mezclas de varios productos, entre ellos, trazas del derivado bicíclico **66**. Tan solo con $SnCl_4$ se obtuvo un rendimiento máximo del 25% de **66** junto a su epímero en C-5 en proporción 3:1. Aunque no nos planteamos la identificación de los productos de ciclación, observamos en los espectros de los crudos de reacción diferentes productos bicíclicos muy distintos a **66**, resultantes del ataque del doble enlace al grupo carbonílo cetónico. Para evitar este inconveniente, se preparó el fosfato de enol derivado **67** a partir del β-cetoéster **65**, empleando hidruro sódico y clorofosfato de dietilo en THF anhidro, de manera que se obtuvo el estereoisómero *trans* en proporción 8:1 respecto al *cis* (Esquema 63).

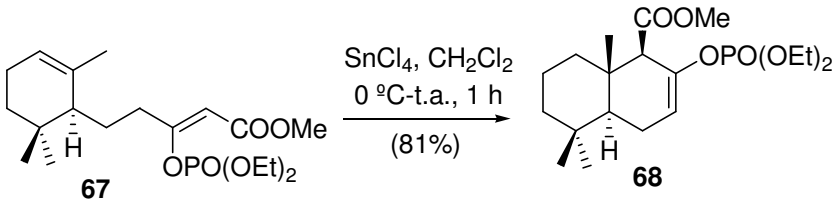
(120) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939.
(121) Buechi, G.; Wueest, H. *Helv. Chim. Acta* **1989**, *72*, 996.
(122) Herlem, D.; Kervagoret, J.; Yu, D.; Khuong-Huu, F.; Kende, A. S. *Tetrahedron* **1993**, *49*, 607.



Esquema 63

La estructura del producto **67** se ha confirmado mediante sus espectros de RMN. En el espectro de RMN-^{1}H destaca un singlete a 5.35 ppm, que integra por un protón, correspondiente al protón olefínico en posición α al éster metílico. El espectro de RMN de ^{13}C confirma la formación del doble enlace del fosfato de enol mediante la aparición de dos señales vinílicas a 164.6 y 104.7 ppm.

A continuación se ensayó de nuevo la ciclación del fosfoenol derivado **67**, empleando las condiciones más favorables del caso anterior: $SnCl_4$ en CH_2Cl_2 a temperatura ambiente. Tras una hora de reacción, se obtuvo un 81% del derivado bicíclico **68** con completa regio- y diastereoselectividad. (Esquema 64).



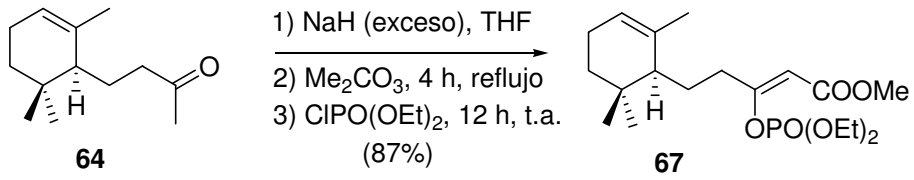
Esquema 64

La estructura del compuesto **68** ha sido confirmada mediante los espectros de RMN. En el espectro de RMN-^{1}H se observa la desaparición del metilo sobre doble enlace a 1.67 ppm y la aparición, en su lugar, de un singlete a 0.96 ppm, originado por el metilo angular. En el espectro de RMN-^{13}C, este metilo origina

una señal a 15.3 ppm. La unión *trans*-decalínica fue confirmada en base a las experiencias NOE.

Cabe señalar la enorme importancia de este resultado, ya que la presencia del grupo carbonilo protegido en forma de fosfato de enol, presente en el producto de ciclación obtenido **68**, permitiría la posterior reducción selectiva del grupo éster, dejando el otro grupo carbonilo inalterado.

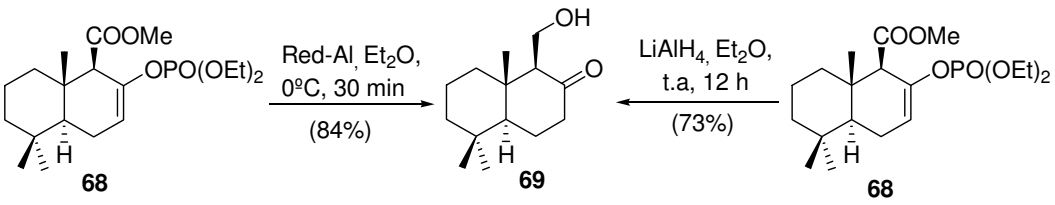
Antes de abordar la siguiente etapa de la síntesis, se planteó la obtención del fosfato de enol **67,** en un solo paso, a partir de dihidro-α-ionona (**64**). Dicho propósito se logró mediante el tratamiento sucesivo de **64** en THF y en presencia de exceso de hidruro sódico, con carbonato de dimetilo y clorofosfato de dietilo, rindiendo así el fosfato de enol **67** deseado con un rendimiento del 87% (53% rendimiento global a partir de α-ionona) (Esquema 65).



Esquema 65

*c) Preparación de la hidroxicetona **69***

A continuación se ensayó la reducción selectiva del fosfato de enol bicíclico **68** con diferentes hidruros metálicos, tales como DIBAL-H, $LiAlH_4$ y bis(2-metoxietoxi)hidruro de aluminio y sodio (Red-Al). Los mejores resultados se alcanzaron mediante el uso de $LiAlH_4$ en éter etílico, a temperatura ambiente, (73%) y el empleo de Red-Al en el mismo disolvente a 0ºC, obteniéndose en este segundo caso hasta 84% de rendimiento de la hidroxicetona **69** (Esquema 66).



Esquema 66

El espectro de ^{1}H-RMN de este compuesto muestra un doble doblete a 3.93 (J = 11.2, 9.4 Hz) y un doblete ancho a 3.57 ppm (J = 9.0 Hz), originados por los protones en C-11. El correspondiente metileno oxigenado aparece a 57.7 ppm en el espectro de RMN-^{13}C. También destaca la existencia de protones en α de carbonilo, que originan señales a 2.44 y 2.33 ppm. La presencia de la cetona viene corroborada por la señal a 215 ppm en el espectro de RMN-^{13}C y por la banda a 1700 cm^{-1} en el espectro de IR. Se observa además, en este último espectro, una banda ancha a 3262 cm^{-1} atribuible al grupo hidroxilo.

Conviene indicar que la hidroxicetona **69** ha sido obtenida en forma enantioméricamente pura mediante procesos quimioenzimáticos[147] o utilizando auxiliares quirales[123].

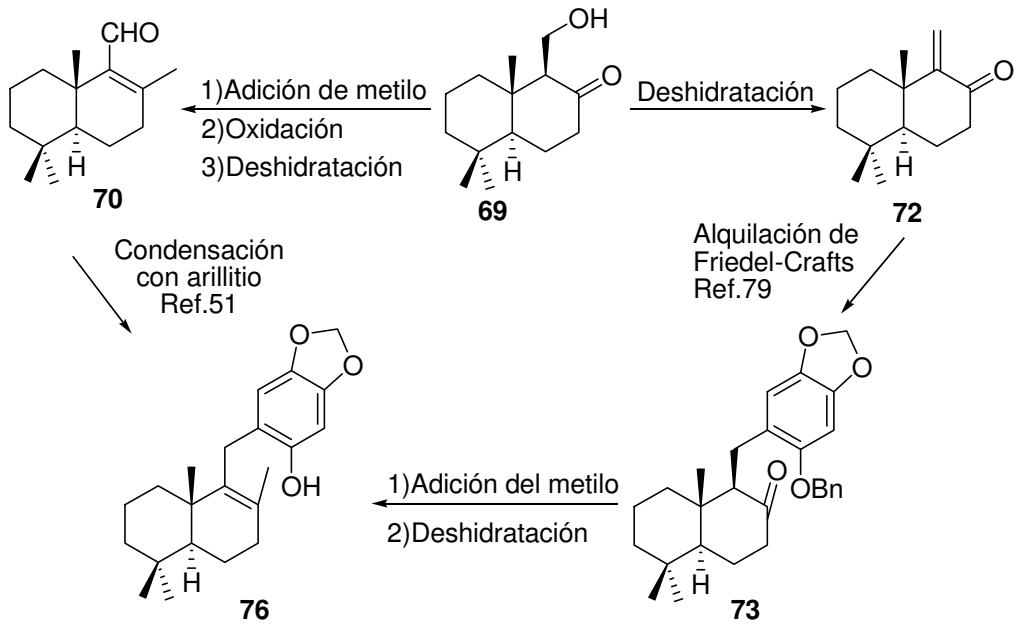
6.2.OBTENCIÓN DEL FENOL 76 VÍA LA ENONA 72

El esquema 67 recoge el planteamiento sintético para la preparación del fenol sesquiterpénico **76** a partir de la *β*-hidroxicetona **69**. El proceso implica la transformación inicial de **69**, bien en el aldehído α,β-insaturado **70** de acuerdo con el planteamiento inicial, o en la enona α,β-insaturada **72**. A partir de cualquiera de estos dos precursores bicíclicos se puede acceder al fenol sesquiterpénico **76**, bien sea mediante una reacción de alquilación de Friedel-Crafts de la α,β-enona **72** o a

(123) Furuichi, N.; Hata, T.; Soetjipto, H.; Kato, M.; Katsumura, S. *Tetrahedron* **2001**, *57*, 8425.
(147) Anilkumar, A. T., Sudhir, U.; Joly, S.; Nair, M. S. *Tetrahedron* **2000**, 56, 1899.

través de la condensación de un arillitio adecuado con el aldehído **70** y posterior reducción catiónica del grupo hidroxilo resultante. Ambos procedimientos han sido desarrollados previamente en nuestro laboratorio[79,124] .

El aldehído α,β-insaturado **70** se prepararía a partir de **69** en tres etapas: adición del metilo, oxidación del grupo hidroxilo primario hasta aldehído y deshidratación regioselectiva del alcohol terciario; mientras la cetona conjugada **72** se prepararía en solo dos etapas: acetilación del grupo hidroxilo primario y elimiación del grupo acetato generado.



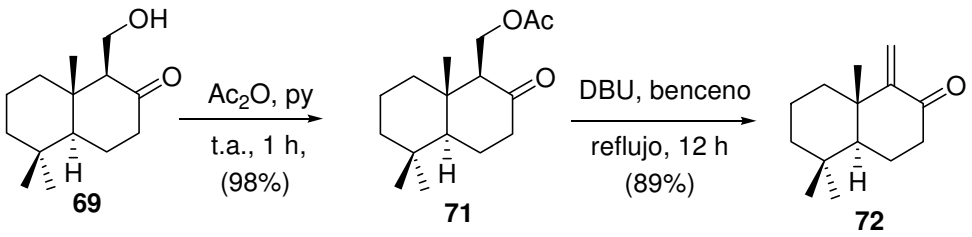
Esquema 67

Optamos por realizar la segunda vía, más corta y novedosa.

(79) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Tapia, R.; Es-Samti, H.; Fernández, A.; Barranco, I. *Eur. J. Org. Chem.* **2009**, 1139.

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.;Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

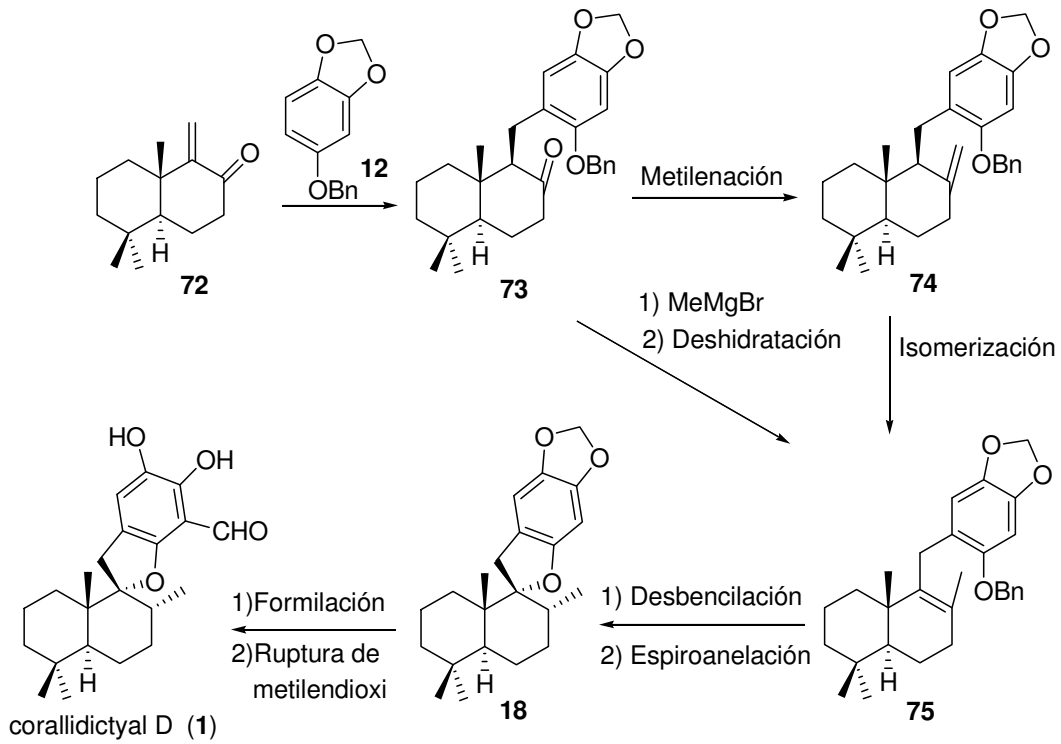
La α,β-enona **72** se obtiene fácilmente a partir de la β-hidroxicetona **69** en dos etapas como se ha comentado. La acetilación inicial generó el acetil derivado **71** de forma casi cuatitativa y la subsecuente eliminación del grupo acetato con DBU en benceno a reflujo dio lugar a la α,β-enona **72** con 89% de rendimiento (Esquema 68).



Esquema 68

a) Preparación de la β-arilcetona 73

De acuerdo con el planteamiento sintético, las siguientes etapas hacia corallidictyal D (**1**), implican la transformación de la α,β-enona **72** en la β-aril cetona **73**, y la conversión de ésta en el derivado merosesquiterpénico **75**. Este último proceso puede realizarse mediante formación del correspondiente alcohol terciario y su subsiguiente deshidratación regioselectiva, o mediante reacción de Wittig y posterior isomerización del doble enlace exocíclico (Esquema 69). El derivado tetrasustituído **75** se transformaría en el compuesto final mediante desprotección del grupo bencilo, subsecuente espiroanelación, funcionalización del anillo aromático y final ruptura de la agrupación metilendioxi.

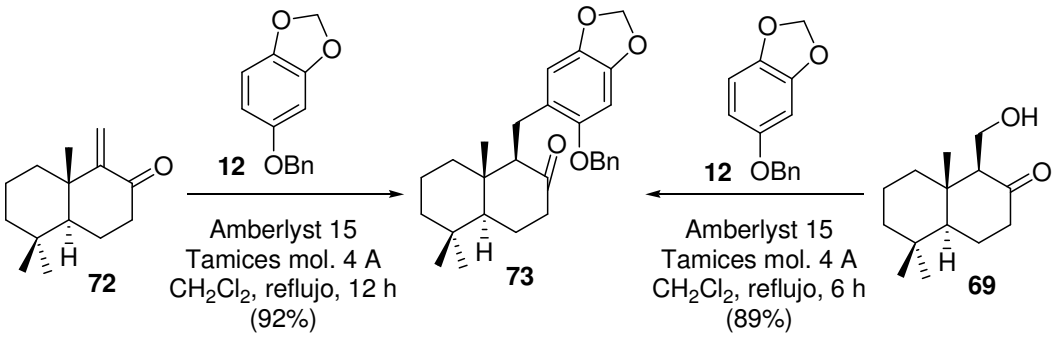


Esquema 69

En una primera aproximación, se procedió a la preparación de la β-aril cetona **73** a partir de la α,β-enona **72**, mediante una alquilación de Friedel-Crafts del *O*-bencil derivado de sesamol **12**, promovida por resina catiónica, utilizando una metodología desarrollada por nuestro grupo[79]. El calentamiento a reflujo de una disolución de la cetona **72** con un equivalente del compuesto **12** en DCM, en presencia de resina catiónica Amberlyst 15 y tamices moleculares de 4Å, durante 12 h, proporcionó la arilcetona **73**, con un rendimiento del 92%. Cuando la reacción se ensayó a mayor escala, se observó que parte del derivado aromático **12** queda sin reaccionar tras la consumición de la enona de partida. Esto hace pensar que parte de dicha cetona conjugada se degrada, dado que la reacción de alquilación se realiza mol a mol respecto al producto de partida

(79) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Tapia, R.; Es-Samti, H.; Fernández, A.; Barranco, I. *Eur. J. Org. Chem.* **2009**, 1139.

Este inconveniente se solventó mediante un proceso alternativo, de menor número de etapas, consistente en la condensación directa de la β-hidroxicetona **69** con el sintón aromático **12**, en presencia de resina catiónica (Esquema 70). De este modo, se obtuvo la arilcetona **73** directamente, a partir de la β-hidroxicetona **69**, con un 89 % de rendimiento en tan sólo 6 horas.



Esquema 70

La asignación estructural de **73** se realizó de modo inequívoco en base a sus espectros de IR, RMN ^{1}H y ^{13}C y por comparación con los datos publicados por nuestro grupo para el análogo con diferentes grupos protectores[79] . El espectro de IR muestra una banda intensa a 1705 cm^{-1}, típica del grupo carbonilo, mientras que no se observa ninguna señal en la zona correspondiente a los hidroxilos. Se aprecia la aparición de las señales características del grupo benciléter, tanto en el espectro de RMN-^{1}H como en el de ^{13}C. En el espectro de RMN de ^{1}H se observan además, sendos dobles dobletes atribuibles a los protones bencílicos, del fragmento sesquiterpénico, a 2.72 ppm y 2.63 ppm, integrando cada uno de ellos por un protón y acoplados entre sí con una J = 13.2 Hz y con H-9 con una J_{cis} = 1.9 Hz y una J_{trans} = 9.6 Hz. El espectro de RMN de ^{13}C presenta una señal a 42.9

(79) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Tapia, R.; Es-Samti, H.; Fernández, A.; Barranco, I. *Eur. J. Org. Chem.* **2009**, 1139.

ppm, debida al correspondiente carbono C-11. La estereoquímica relativa de C-9 y C-15 se determinó mediante experiencia de NOE diferencial.

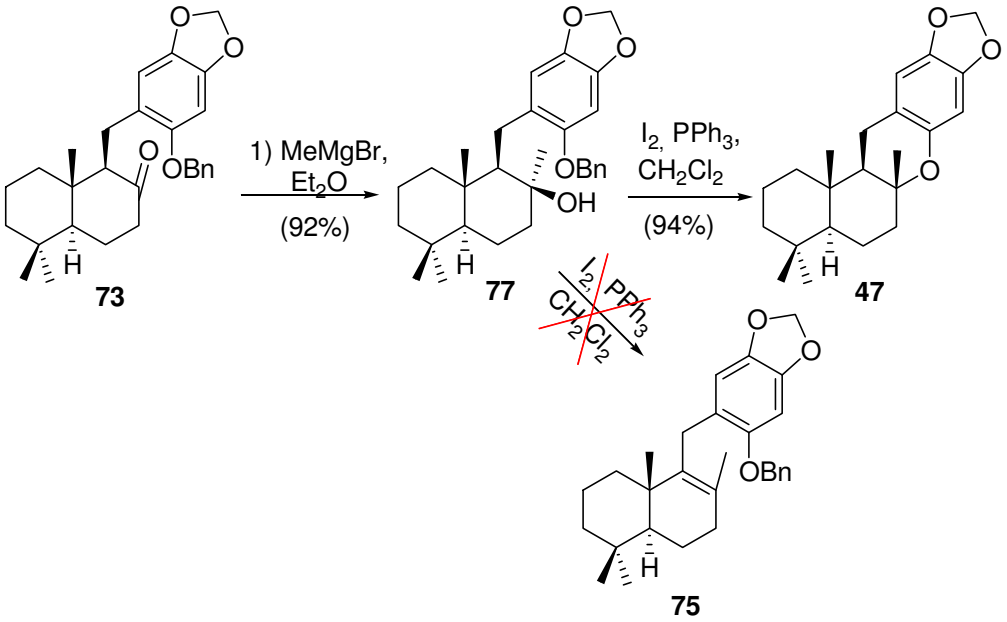
*b) Obtención del fenol sesquiterpénico **76***

De acuerdo con el planteamiento sintético, recogido en el esquema 69, a continuación se abordó la transformación de la β-arilcetona **73** en el merosesquiterpeno tetrasustituído **75**.

Inicialmente, se planteó dicha transformación vía el alcohol terciario **77**, obtenido tras la correspondiente reacción de **73** con bromuro de metilmagnesio (92%). Sin embargo, cuando se intentó efectuar la deshidratación de dicho alcohol mediante tratamiento con el sistema I_2/PPh_3, siguiendo el procedimiento desarrollado previamente por nuestro grupo[125], se obtuvo de forma sorprendente el derivado benzopiránico **47** exclusivamente. La síntesis de **47** ha sido realizada en nuestro laboratorio hace ya algunos años[51].

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

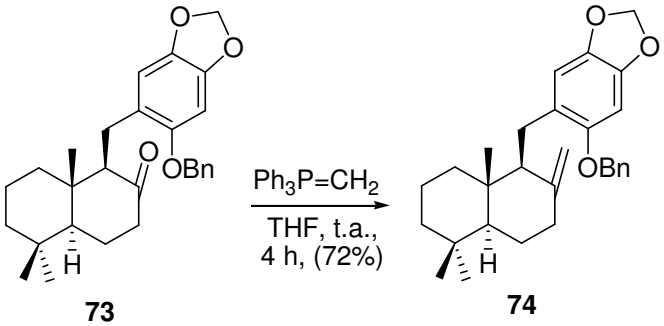
(124) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. M. *Tetrahedron Letters* **2004**, *45*, 4453.



Esquema 71

Ante este resultado adverso, se optó por desarrollar el proceso alternativo, que implica la metilenación de la cetona **73**, y la posterior isomerización del alqueno exocíclico resultante **74**.

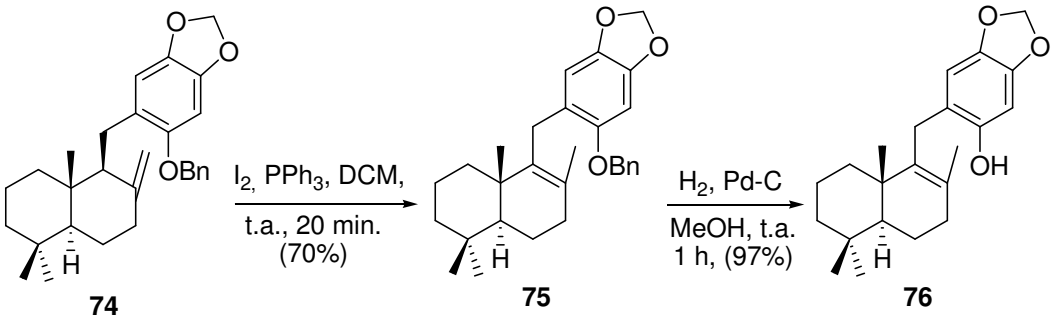
Se accedió al compuesto **74,** a través de una reacción de Wittig de la cetona **73** con el iluro de fósforo adecuado. Como muestra el esquema 72, tras 4 h de reacción a temperatura ambiente se aisló el alqueno **74** con un 72% de rendimiento.



Esquema 72

En el espectro de RMN-^{1}H de **74** se observan las señales correspondientes al doble enlace exocíclico, como singletes anchos a 4.69 ppm y 4.57 ppm. Los correspondientes carbonos aparecen a 141.2 y 107.7 ppm en el espectro de RMN-^{13}C.

La isomerización de **74** al sesquiterpeno con doble enlace tetrasustituido, más estable, mediante el empleo del sistema I_2/PPh_3, proporcionó el derivado **75** con un 70% de rendimiento, recuperándose entre un 20-25% de producto de partida. Finalmente, se desprotegió el fenol mediante el procedimiento convencional de hidrogenación catalítica (H_2/Pd-C), proporcionando **76** con rendimiento prácticamente cuantitativo (Esquema 73).



Esquema 73

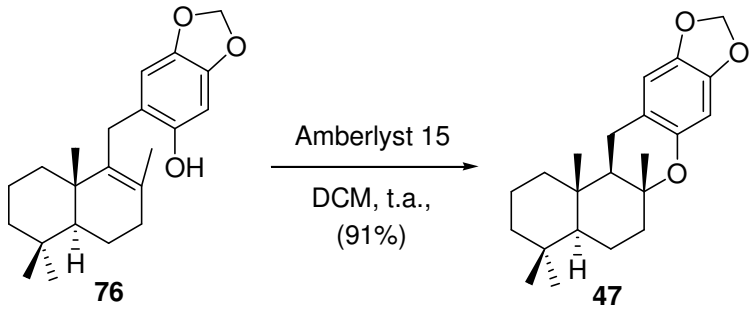
La estructura del compuesto **75** ha sido confirmada mediante sus datos espectroscópicos. El espectro de RMN de ^{1}H muestra la aparición de una señal singlete que integra por tres protones a 1.48 ppm, correspondiente al metilo sobre doble enlace. Además se aprecia la desaparición del doble doblete correspondiente al H-9 y la de los singletes de los protones del doble enlace exocíclico (4.69 ppm y 4.57 ppm).

El compuesto **76** ha sido previamente sintetizado en nuestro laboratorio, por lo que su identificación fue sencilla, basada en la comparación con dichos datos[51]

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

6.3. ESTUDIO DE ESPIROANELACIÓN

De acuerdo con el planteamiento sintético propuesto hacia corallidictyal D (**1**), la etapa siguiente del proceso implicaría la construcción del sistema espirodihidrobenzofuránico de la molécula objetivo mediante espiroanelación del drimenilfenol **76**. Con objeto de confirmar la estereoquímica absoluta de corallidictyal D (**1**), el resto de la secuencia sintética hasta el compuesto **1** se ha desarrollado utilizando intermedios enantioméricamente puros. Así, el proceso de espiroanelación se realizó sobre el drimenilfenol **76**, obtenido a partir del diterpeno comercial (-)-esclareol, siguiendo un procedimiento desarrollado hace algunos años en nuestro laboratorio[51] En un primer ensayo de espiroanelación se trató dicho fenol sesquiterpénico **76** con resina catiónica Amberlyst 15, bajo las mismas condiciones descritas para la síntesis de K-76[9,105] y stachybotrylactama[52,53] . De estos ensayos se obtuvo el derivado piránico **47**, casi exclusivamente, acompañado de trazas del espirodihidrobenzofurano **18** deseado (Esquema 74).



Esquema 74

(9) Larghi, E. L.; Kaufman, T. S. *ARKIVOC* **2011**, *vii*, 49.
(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.
(52) Kende, A.; Zhong, W.-P. D.; Guo, X.-C. *Organic Letters* **2003**, *5*, 1785.
(53) Kende, A.; Zhong, W.-P. D.; Guo, X.-C. *J. Org. Chem.* **2003**, *68*, 7422.
(105) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5552.

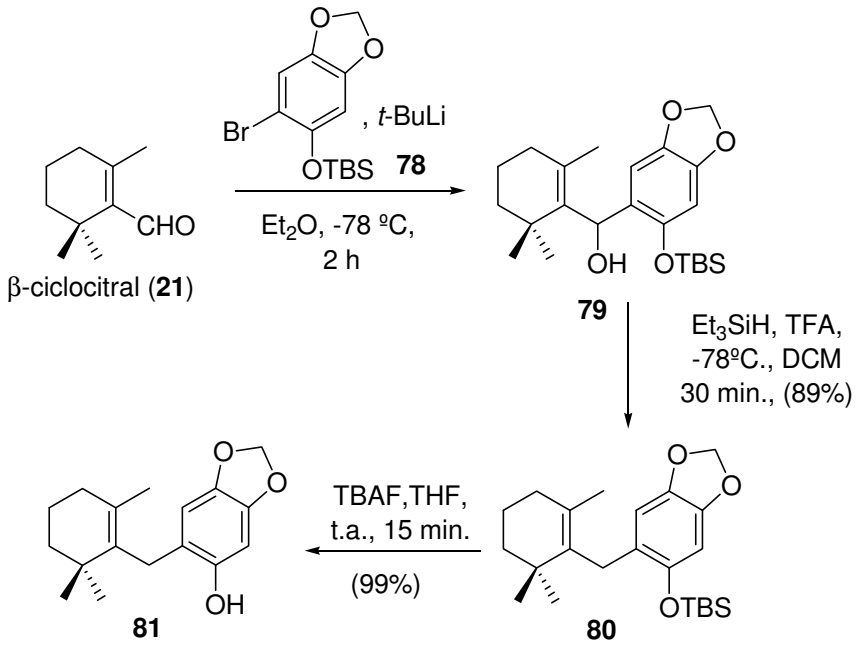
Cuando se emplearon las mismas condiciones descritas por Corey (HCl, THF-etilenglicol)[105], después de 3 días de reacción se recuperó el material de partida inalterado.

*a) Preparación del fenol monoterpénico **81***

Ante este inesperado resultado y con el fin de profundizar en el estudio de la espiroanelación del fenol sesquiterpénico **76**, se preparó su análogo monocíclico, en gran cantidad, de forma rápida y sencilla, posibilitando así un estudio más completo de esta etapa, utilizando resina catiónica Amberlyst 15 bajo diferentes condiciones de temperatura y disolventes.

El esquema 75 muestra la preparación del fenol monocíclico **81.** en 3 etapas a partir de β-ciclocitral comercial (**21**), siguiendo el procedimiento desarrollado hace algunos años en nuestro laboratorio[126]. La condensación del arillitio derivado de **78** con β–ciclocitral, condujo al alcohol **79**, que mediante reducción catiónica, utilizando el sistema Et_3SiH/TFA, en DCM a -78ºC, proporcionó el compuesto **80**. Éste, tras la ruptura del grupo sililéter, mediante el procedimiento usual, condujo al fenol monoterpénico objetivo **81** (65% de rendimiento global).

(126) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Valdivia, M. V.; Chahboun, R. *Tet. Lett.* **1998**, *39*, 2425.



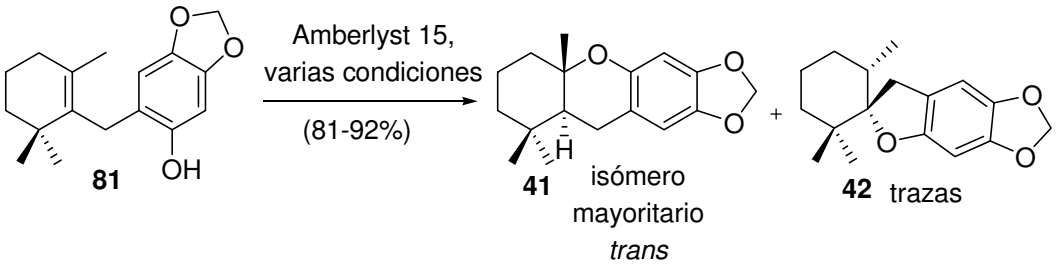
Esquema 75

*b) Ensayos de ciclación sobre el fenol monoterpénico **81**, utilizando las condiciones de Mc Murry y de Corey*

En primer lugar se ha investigado el comportamiento del análogo monocíclico del fenol **76** bajo las condiciones descritas previamente por McMurry[46] y Corey[105] en la espiroanelación de los correspondientes drimenilfenoles para la síntesis de K-76.

(46) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712.
(105) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5552.

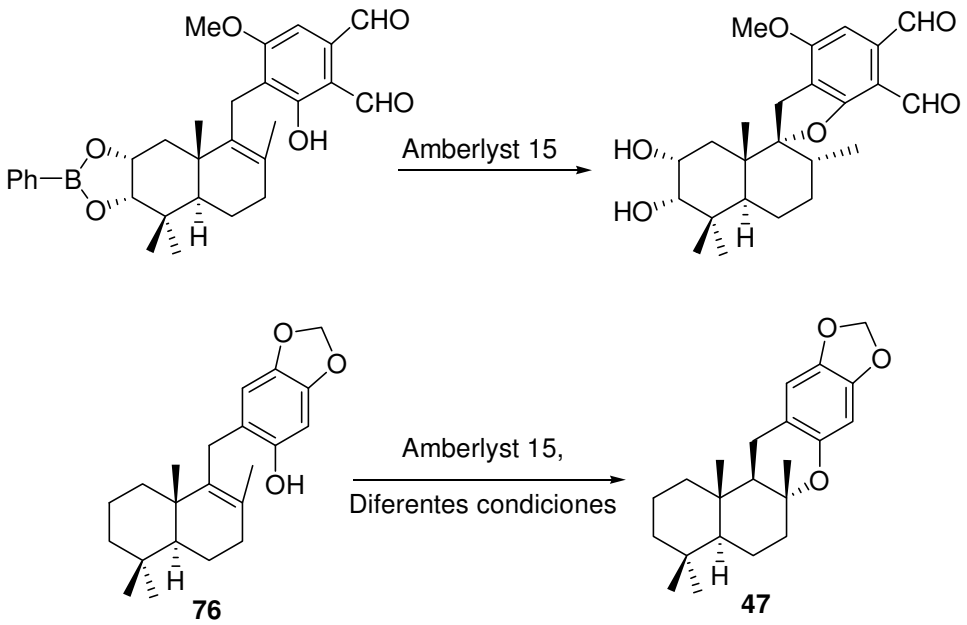
Tabla 6: Ensayos de cicalción del fenol monoterpénico **81** con Amberlyst 15.



Ensayo	mmol	t	Condiciones	Productos	Rdto
1	0.20	1.5 h	DCM, 0ºC	**41** (y trazas de **42**)	82%
2	0.73	2 h	DCM, 0ºC	**41** (y trazas de **42**)	81%
3	0.68	69 h	DCM, 0-10 ºC.	**41** (y trazas de **42**)	87%
4	0.19	19 min	DCM, t.a.	**41** (y trazas de **42**)	92%
5	0.73	2 h	DCM, t.a.	**41** (y trazas de **42**)	92%
6	0.20	15 min	DCM, reflujo	**41** (y trazas de **42**)	89%
7	0.19	2 h	DCM, reflujo	**41** (y trazas de **42**)	87%
8	0.22	24 h	Benceno, t.a	**41** (y trazas de **42**)	86%
9	0.18	4 h	Benceno, reflujo	**41** (y trazas de **42**)	88%

En todos los ensayos se obtuvo el derivado piránico casi exclusivamente, junto a trazas del derivado espiránico. El fenol monoterpénico **81** se recuperó inalterado tras ser sometido a las condiciones de ciclación descritas por Corey.[105.] Estos resultados dejaron patente que las condiciones utilizadas por McMurry y Corey no tienen aplicabilidad cuando se modifica el fragmento aromático (Esquema 76).

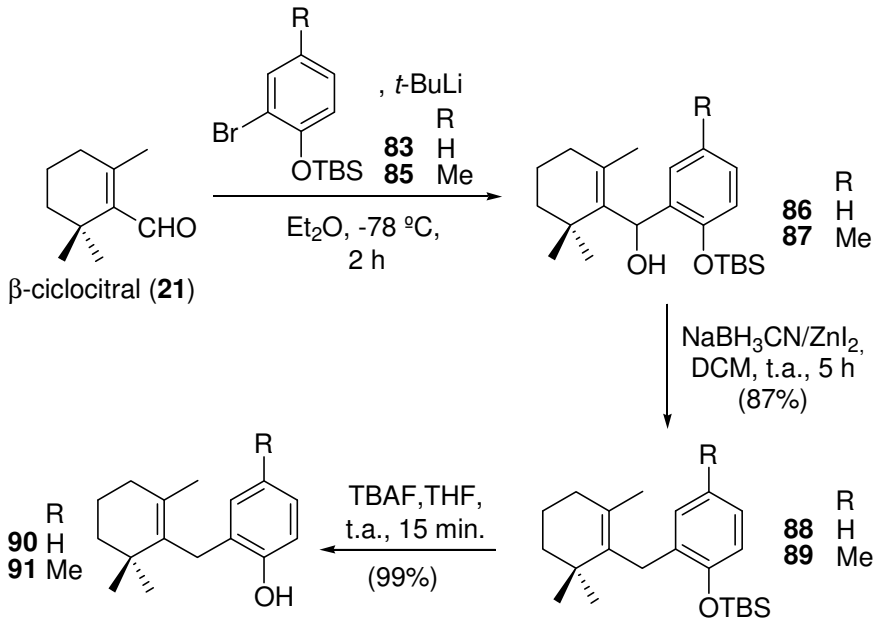
(105) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5552.



Esquema 76

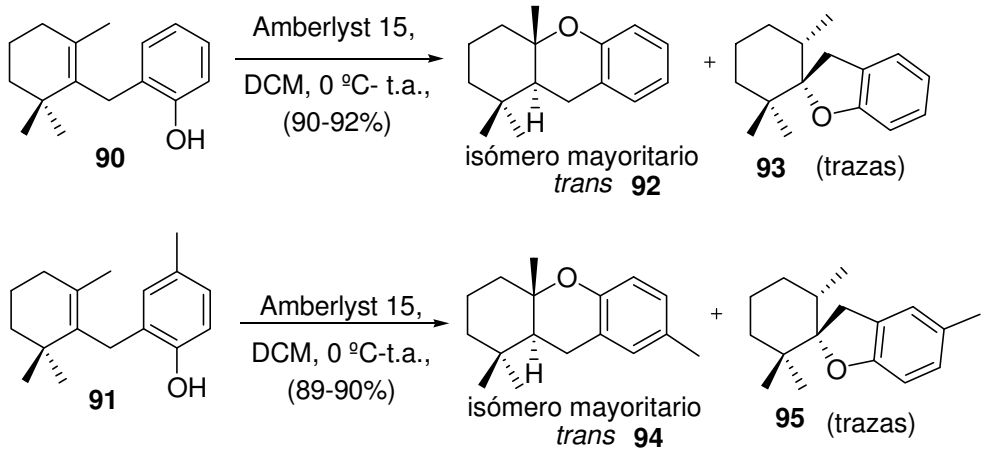
*c) Preparación de otros fenoles análogos monoterpénicos **90** y **91** y ensayos de su ciclación con Amberlyst 15*

En vista de esta conclusión, se planteó el estudio de la reacción cambiando el fragmento aromático, para verificar si existe una variación en el comportamiento de la ciclación al modificar dicho fragmento. Para ello, se prepararon los fenoles monoterpénicos **90** y **91**, similares a **81,** siguiendo la misma metodología empleada para la obtención de éste último, a excepción de la etapa de reducción catiónica del grupo hidroxilo bencílico resultante de la reacción de condensación, que se efectuó de manera eficiente mediante la utilización del sistema $NaCNBH_3/ZnI_2$, en lugar del anterior Et_3SiH/TFA, como se muestra en el esquema 77.



Esquema 77

Todos los ensayos de ciclación con resina catiónica Amberlyst 15 realizados sobre los fenoles **90** y **91** dieron lugar a los correspondientes derivados benzopiránicos **92** y **94** junto a trazas de los derivados espirodihidrobenzofuránicos, **93** y **95**, respectivamente (Esquema 78).

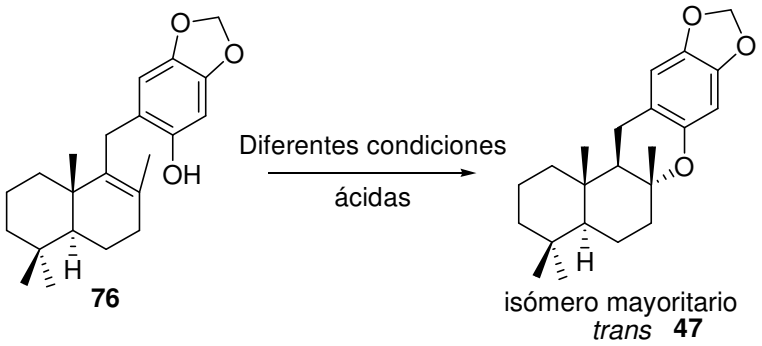


Esquema 78

Como se ha indicado con anterioridad, la reacción de ciclación bajo condiciones ácidas utilizando diferentes fenoles, conlleva al mismo resultado, es decir, proporciona casi exclusivamente los derivados benzopiránicos con configuración *trans:* **41**, **92** y **94**, junto a trazas de los correspondientes derivados espiránicos deseados **42**, **93** y **95**.

En la tabla siguiente se muestran los resultados de todas las ciclaciones del fenol sesquiterpénico **76,** llevadas a cabo tanto en esta memoria como descritas en bibliografía, utilizando diferentes condiciones ácidas.

Tabla 7: Resumen de ciclaciones del fenol sesquiterpénico **76**.



76

isómero mayoritario
trans **47**

Ensayo	Condiciones	Productos	Rdto
1	Resina catiónica A-15, DCM, (0ºC-reflujo), 20 min-69 h	**47** (y trazas del isómero espirodihidrobenzofurano)	92%
2	$BF_3.OEt_2$, DCM, 0ºC	**47** (y su epímero en C-8) (9:1)	85%[51]
3	Ácido β-naftalensulfónico, DCM, reflujo	**47** (y su epímero en C-8) (9:1)	92%[51]

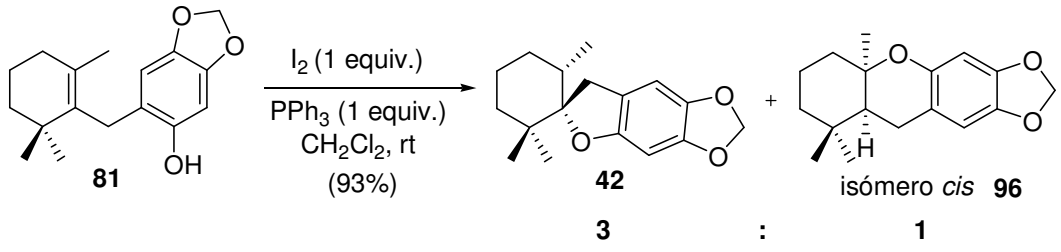
(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.
(68) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. M. *Tetrahedron Lett.* **2005**, *46*, 1075.
(124) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. M. *Tetrahedron Letters* **2004**, *45*, 4453.
(126) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Letters* **2005**, *46*, 3755.
(127) Alvarez-Manzaneda *et al. Resultados no publicados.*

4	Ácido *p*-toluensulfónico, benceno, reflujo, 70 min	**47** (y su epímero en C-8) (4:1)	88%[51]
5	Ácido sulfúrico conc. nitropropano, (-78ºC-0ºC), 1 h	**47** (y trazas del epímero en C-8)	87%[51]
6	HCl, etilenglicol-THF, t.a	**76** inalterado	---
7	HCl, , etilenglicol-THF, 60 ºC	**47** (y su epímero en C-8) (5:1)	83%
8	I_2, DCM, t.a.	**47**	89%

d) Ensayos de ciclación con el sistema I_2/PPh_3 sobre los distintos fenoles

Recientemente, continuando nuestros estudios con el sistema I_2/PPh_3[68,125,127] hemos observado que algunos ácidos carboxílicos insaturados, en presencia de estos reactivos, experimentan un proceso de ciclación que da lugar a las correspondientes espirolactonas[128]. Estos resultados nos animaron a investigar el uso de este sistema en la ciclación de alquenilfenoles.

Comenzamos ensayando estas condiciones sobre el fenol monocíclico **81** y obtuvimos satisfactoriamente el espirodihidrobenzofurano **42** con buen rendimiento (Esquema 79).



Esquema 79

Se procedió a la caracterización de **42**, que se reconoce por los dos dobletes característicos generados por los protones metilénicos del sistema espiránico a 3.12 y 2.77 ppm (J = 15.9 Hz), junto a la correspondiente señal en RMN-^{13}C del C-1* a 36.3 ppm.

Ante este alentador resultado, se realizó la reacción de ciclación de todos los fenoles anteriormente preparados (*o*-β-ciclogeranilfenoles y *o*-drimenilfenoles), con este sistema, añadiendo un ejemplo más; el fenol sesquiterpénico **100**, similar a **76**, pero que presenta diferentes grupos protectores en el fragmento aromático.

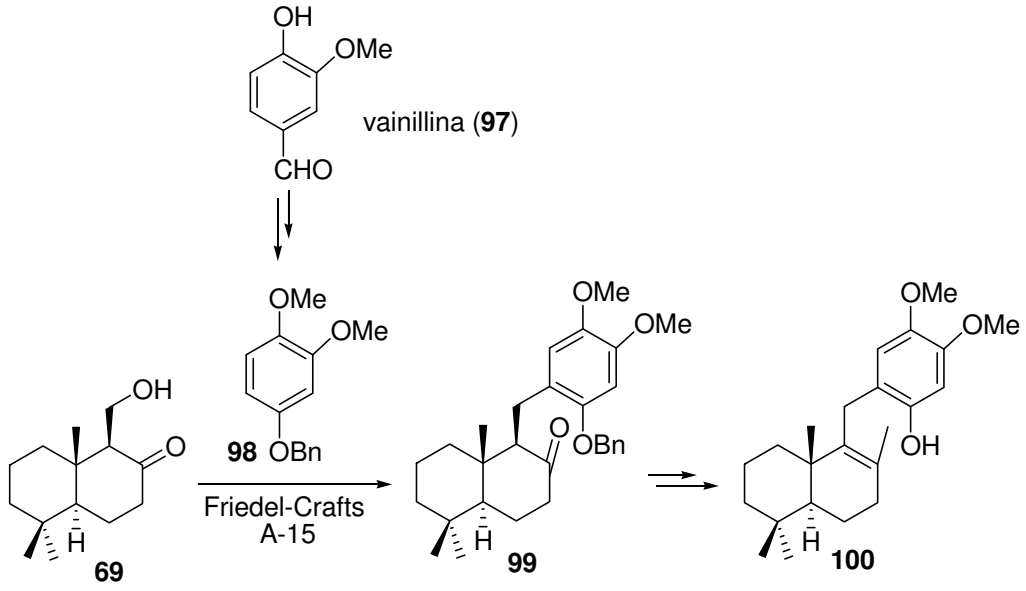
*-Preparación del fenol sesquiterpénico **100***

Se preparó el fenol sesquiterpénico **100**, análogo a **76,** siguiendo el procedimiento previamente descrito para la preparación de **76** (ver esquema 67), empleando en este caso **98**[129] como sintón aromático, sintetizado a partir de vainillina (**97**) (Esquema 80).

* Nota: La numeración se ha realizado en base a la asignada por Chan para corallidictyal

(1) Chan, J., A.;; Freyer, A. J.; Carté, B. K.; Hemling, M. E.; Hofmann, G. A.; Mattern, M. R.; Mentzer, M. A.; Westley, J. W. *J. Nat. Prod.* **1994**, *57*, 1543.

(128) Kupchan, S. M.; Liepa, A. J.; Kameswaran, V.; Sempuku, K. *J . Am. Chem. Soc.* **1973**, *95*, 9.



Esquema 80

Una vez disponemos de los cinco fenoles modelo, llevamos a cabo los ensayos de ciclación de los mismos mediante el sistema I_2/PPh_3, obteniéndose los resultados que se recogen en la tabla 8.

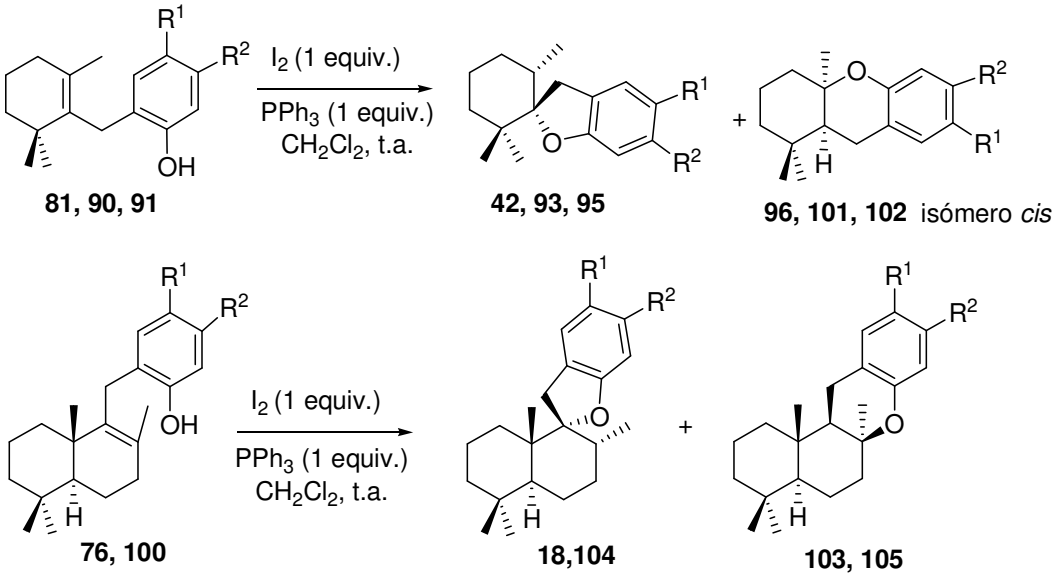


Tabla 8: Ensayos de ciclación de los distintos fenoles con el sistema I_2/PPh_3.

Ensayo	*o*-alilfenol	R^1	R^2	t	Productos	Rdto
1	**81**	-OCH_2O-		15 min	**42+96** (3:1)	93%
2	**90**	H	H	30 min	**93+101** (3:1)	80%
3	**91**	Me	H	10 min	**95+102** (3.5:1)	89%
4	**76**	-OCH_2O-		5 h	**18+103** (4.5:1)	90%
5	**76**	-OCH_2O-		5 h	**18+103** (10:1) *	90%
6	**100**	OMe	OMe	4 h	**104+105** (4:1)	87%

*Se cicló 1g de compuesto **76**; la formación del reactivo se prolongó por 1h.

En todos los casos, predomina la formación del derivado espirodihidrobenzofuránico frente al isómero benzopiránico. Cuando la reacción se realiza con cantidades significativas, se obtiene el derivado espirodihidrobenzofuránico casi exclusivamente (ensayo 5). Analizando los resultados, se observa que los dos productos obtenidos se han formado con completa diastereoselectividad, lo que hace suponer que la reacción de ciclación pudiera transcurrir *vía* un posible mecanismo concertado, puesto que los procesos que transcurren a través de carbocatión proporcionan generalmente mezclas de más de dos productos, o en todo caso, mezclas de epímeros en C-8 del derivado benzopiránico.

Además, durante el transcurso de esta investigación, se observó que la presencia de exceso de iodo altera los resultados de la reacción, propiciando la formación del derivado benzopiránico, resultado concordante con el ensayo 8 de la tabla 7.

e) Ensayos de ciclación con el sistema NIS/PPh_3

Con el fin de optimizar la metodología de ciclación, propusimos el empleo de cantidades catalíticas de reactivo, así como la utilización de un sistema similar al I_2/PPh_3, el sistema NIS /PPh_3, que resulta muy ventajoso frente al anterior, por ser:

-más suave

-menos tóxico y

-menos oxidante

Asimismo el uso del sistema NIS/PPh_3 ayudaría a establecer un posible mecanismo para dicha reacción.

Se realizaron los diferentes ensayos de ciclación utilizando los fenoles disponibles. Los resultados obtenidos (tabla 9) muestran la misma tendencia que para el sistema I_2/PPh_3, mejorando incluso en ocasiones dichos resultados. En el peor de los casos (ensayo 1), se obtuvo la mezcla de isómeros espirodihidrobenzofurano y pirano en proporción 3.5:1, mientras que el fenol sesquiterpénico **76** dió lugar al producto espirodihidrobenzofuránico **18** en proporción mucho mayor que el caso anterior (6: 1) utilizando tan sólo 100 mg de sustrato en este caso.

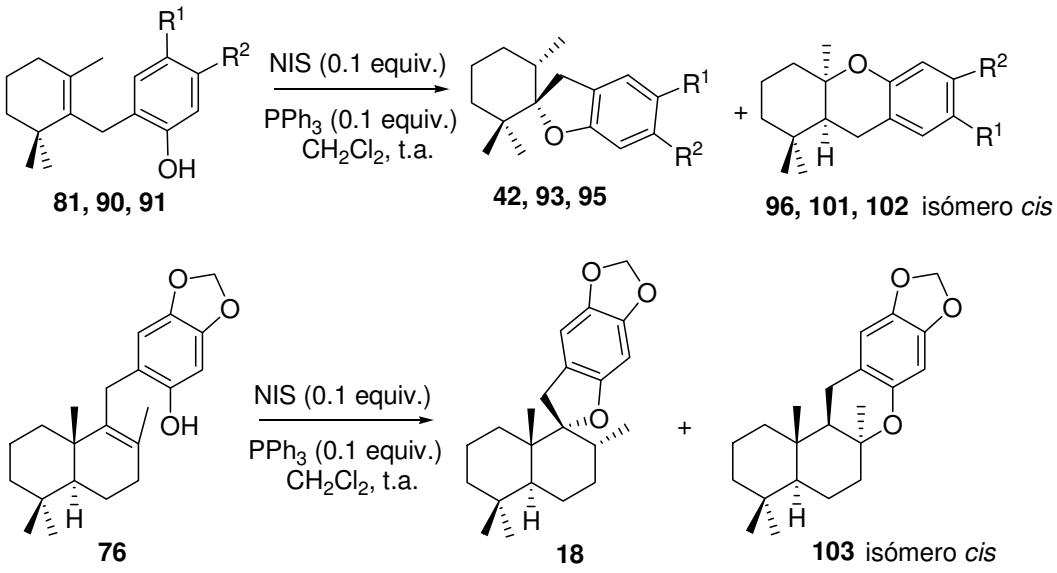


Tabla 9: Ensayos de ciclación de los diferentes fenoles con el sistema NIS/PPh_3.

Ensayo	*o*-alilfenol	R^1	R^2	t	Productos	Rdto
1	**81**	-OCH_2O-		14 h	**42:96** (3.5:1)	86%
2	**90**	H	H	15 h	**93:101** (4:1)	87%
3	**91**	Me	H	12 h	**95:102** (4:1)	89%
4	**76**	-OCH_2O-		10 h	**18:103** (6:1)	90%

Un hecho a considerar antes de postular un mecanismo plausible, acorde a los resultados obtenidos, es la completa estereoselectividad *anti* del proceso, sin precedentes para este tipo de transformaciones.

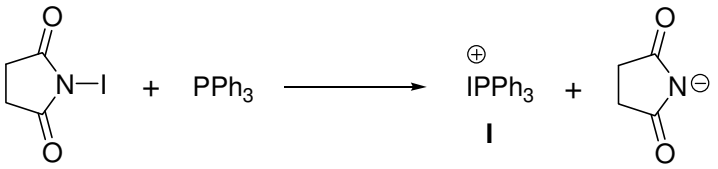
Revisando los mecanismos propuestos en bibliografía para las adiciones catalizadas por ácido, se propone que dichas adiciones pueden proceder, bien *vía* el carbocatión o, en su lugar, de forma concertada, dependiendo de la estructura de la olefina sustrato. Los estudios teóricos llevados a cabo sobre adiciones concertadas catalizadas por ácido, muestran que el estado de transición para la adición *syn* es más estable que el correspondiente para la *anti*; esto se atribuye a la

formación de fuertes interacciones por enlaces de hidrógeno entre el hidroxilo fenólico y uno de los oxígenos del ácido catalizador[130] .

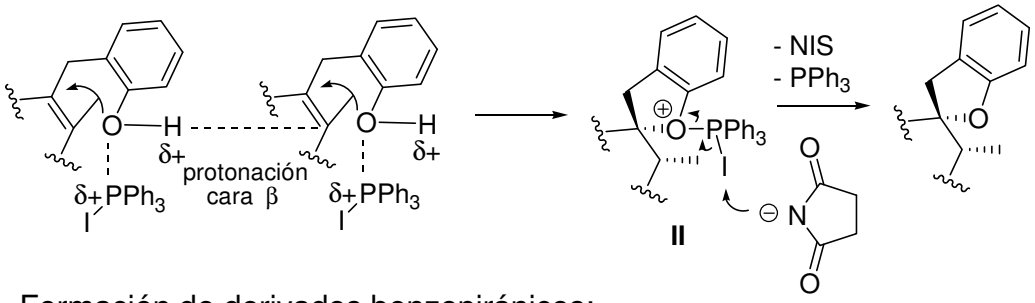
En cambio, a la vista de los productos obtenidos, cuando se emplea el sistema NIS/PPh_3 ocurre un proceso concertado de adición *anti*. Un mecanismo posible sería aquel en el que el fenol actuara simultáneamente como nucleófilo y dador de protones. El grupo hidroxilo, al ser activado por el ión fosfonio **I**, podría tranferir su protón por la cara β del enlace olefínico de la molécula adyacente, la cual podría sufrir simultáneamente un ataque *O*-nucleofílico en el C-9, dando lugar al intermedio **II**, precursor del compuesto espiránico. Alternativamente, cuando el protón es transferido por la cara α del doble enlace, el ataque *O*-nucleofílico ocurriría en el C-8, generando el intermedio **III**, precursor del derivado benzopiránico (Esquema 81).

(129) Kovacs, G.; Lledós, A.; Ujaque, G. *Organometallics* **2010**, *29*, 5919.

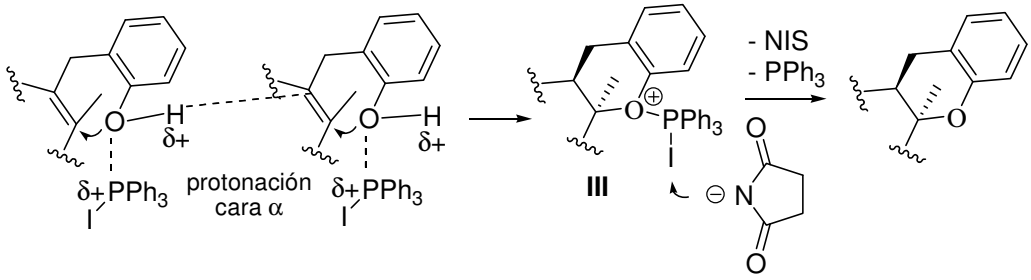
Formación del ión fosfonio **I** :



Formación de derivados espirodihidrobenzofuranos :



Formación de derivados benzopiránicos:



Esquema 81

Se ha observado un comportamiento similar en las ciclaciones de 8,9-epoxiderivados de alquenilfenoles, similares a **76**, catalizadas por base. En esos casos el 8β,9β-epoxiderivado sufrió el ataque nucleofílico en el C-9, rindiendo el correspondiente espirocompuesto, mientras que el isómero 8α,9α sufrió dicho ataque en el C-8, generándose así el derivado benzopiránico[51] (ver antecedentes).

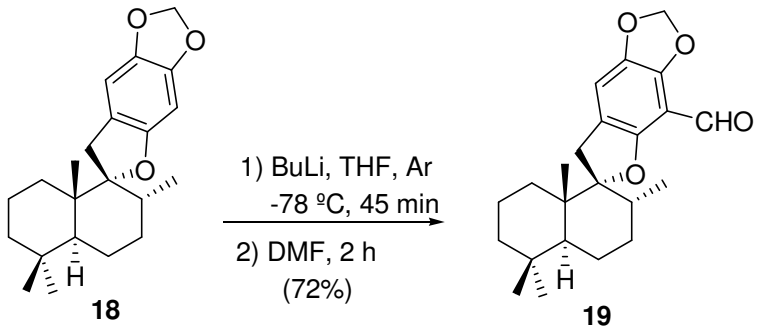
(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

6.4. FUNCIONALIZACIÓN Y DESPROTECCIÓN DEL ANILLO AROMÁTICO: SÍNTESIS DE CORALLIDICTYAL D (1)

Una vez elaborado el sistema espirodihidrobenzofuránico, únicamente restan las etapas finales de formilación y ruptura del grupo metilendioxi, para concluir la síntesis de corallidictyal D (**1**).

a) Formilación del anillo aromático

En primer lugar se introdujo el aldehído aromático, aplicando las condiciones descritas para la síntesis de liphagal (**2**)[84], con *n*-BuLi en presencia de DMF (Esquema 82), obteniéndose el producto de formilación con un 72% de rendimiento.



Esquema 82

La estructura del aldehído **19** ha sido confirmada mediante sus datos espectroscópicos. El espectro de RMN de ^{1}H muestra la aparición de una señal singlete que integra por un protón a 10.26 ppm, correspondiente al protón del aldehído, lo que se confirma en el espectro de RMN de ^{13}C, que muestra una señal

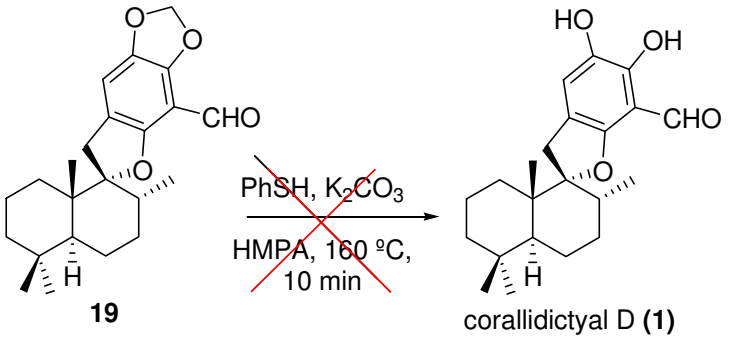
(84) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc.* **2004** *126* 11966.

a 186.7 ppm. En el espectro de IR se observa asimismo una banda intensa a 1689 cm^{-1} correspondiente al grupo carbonilo.

b) Ensayos de ruptura de la agrupación metilendioxi

Por último, para obtener corallidictyal D (**1**), se desprotegió el grupo metilendioxi, obteniendo el catecol **1** deseado. Sin embargo, esta etapa no fue trivial y presentó numerosas dificultades.

Se comenzó aplicando las condiciones óptimas de desprotección encontradas para el caso de liphagal[40,42]. El tratamiento básico, en presencia de tiofenol y carbonato potásico a reflujo en HMPA, desafortunadamente no condujo al catecol **1,** rindiendo, en su lugar, una mezcla compleja de productos no identificados (Esquema 83).

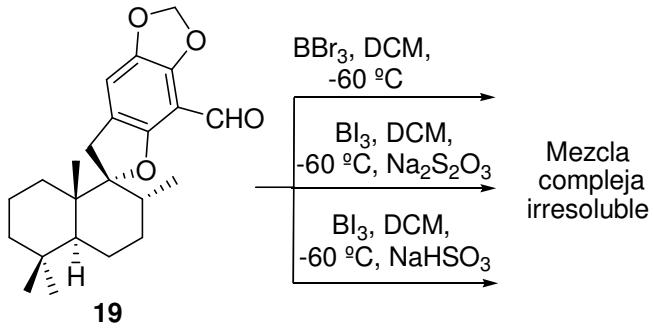


Esquema 83

A la vista de estos resultados, ensayamos la desprotección en medio ácido, comenzando por el método clásico empleado en nuestro grupo para desprotección de arilalquiléteres[89,90]. Ni utilizando tribromuro de boro a baja temperatura, ni

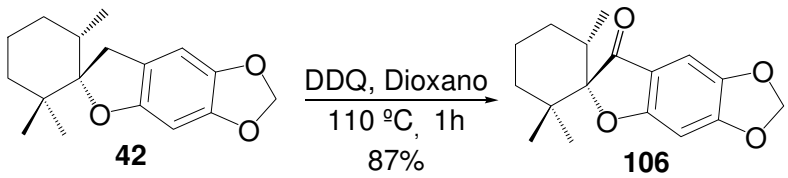
(40) Sundstrom, T. J.; Anderson, A. C.; Wright, D. L. *Biomol. Chem.* **2009** *7* 840.
(42) Knight, Z. A.; Shokat, K. M. *Biochem. Soc. Trans.* **2007** *35* 245.
(89) Oh, K.-B.; Lee, J. H.; Lee, J. W.; Yoon, K.-M.; Chung, S.-C.; Jeon, H. B.; Shin, J.; Lee, H.-S. *Bioorganic & Medicinal Chemistry Letters* **2009** *19* 945
(90) Alvarez-Manzaneda, E.; Chahboun, R.; Bentaleb, F.; Alvarez, E.; Escobar, M. A.; Sad-Diki, S.; Cano, M. J.; Messouri, I. *Tetrahedron* **2007** *63* 11204.

empleando el análogo iodado[6] junto a un agente reductor, se obtuvo el producto deseado **1**. Tras la desaparición del producto de partida **19**, se obtuvo en ambos casos una mezcla compleja de productos no identificados, probablemente derivados de la fragmentación de la molécula.



Esquema 84

Ensayamos alternativamente la desprotección oxidativa[51] sobre el análogo monoterpénico **42**, que permite generar el sistema orto-quinónico, calentando a reflujo una disolución de **42** con DDQ en dioxano (Esquema 85). Sorprendemente tras 1 hora de reacción, se obtuvo la cetona **106** con un rendimiento del 87%.

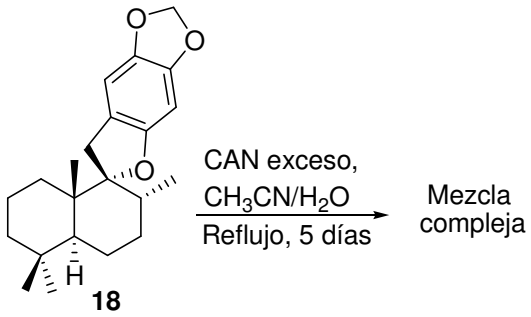


Esquema 85

(6) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Organic Letters* **2006**, *8*, 321.

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

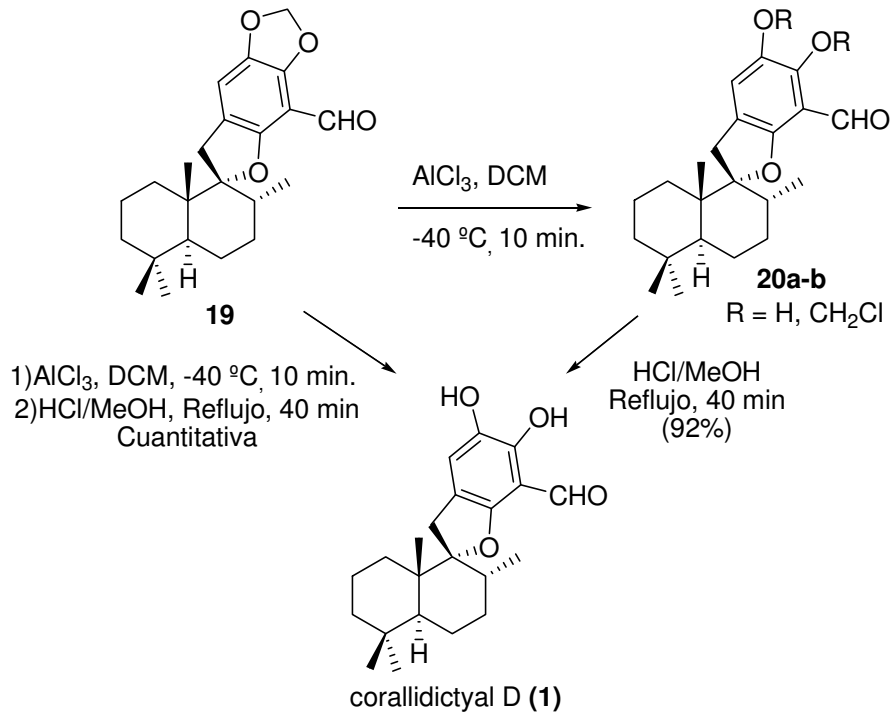
Se prosiguió el estudio de desprotección, empleando la estrategia de Banerjee[131] , usando CAN en cantidades catalíticas sobre una solución de **18** en una mezcla de agua-acetonitrilo (1:1) a reflujo. En este caso se empleó como sustrato de la reacción el producto sin formilar **18**, ya que el grupo aldehído de **19** sería susceptible de oxidación, en presencia de CAN. Tras 5 días de reacción y adiciones sucesivas de reactivo, la cromatografía en capa fina mostró la desaparición del producto de partida y la aparición de numerosas manchas difusas. El ^{1}H-RMN de la mezcla no muestra trazas del producto deseado **1** (Esquema 86).



Esquema 86

Ante las dificultades experimentadas, se desarrolló un método en condiciones más suaves, que permitiera generar el sistema orto-quinónico, modificando el procedimiento descrito por Goodman[132]. El tratamiento de **19** con $AlCl_3$[133,134] a baja temperatura, seguido de la correspondiente hidrólisis ácida a reflujo (HCl en MeOH) rindió el difenol deseado **1** casi cuantitativamente (Esquema 87).

(130) Banerjee, B.; Mandal, S. K.; Roy, S. C. *Chemistry Lett.* **2006**, *35*, 16.
(131) Reitz, A.; Avery, M. A.; Verlander, M. S.; Goodman, M. *J. Org. Chem.* **1981**, *46* 4859.
(132) Li, T.; Wul, Y. L. *J . Am. Chem. Soc.* **1981**, *103*, 7007.
(133) Murphy, B. P. *J. Org. Chem.* **1985** *50* 5875.



Esquema 87

La reacción transcurre a través del intermedio clorometoxifenol **20a-b**, que experimenta una posterior hidrólisis ácida. Se postula la formación de ambos isómeros de posición **20a-b**, basándonos en las manchas observadas en cromatografía de capa fina y en los datos previos recogidos por Goodman. Con objeto de agilizar el proceso, se realizó la desprotección en una sola etapa, de manera que tras la rápida formación del intermedio **20**, se acidificó la mezcla en el mismo matraz de reacción. Esta desprotección final permitió acceder a la molécula objetivo corallidictyal D (**1**) con un excelente rendimiento.

Los datos espectroscópicos de **1** son consistentes con la estructura propuesta, presentando en el espectro RMN-^{1}H a 3.14 y 2.77 ppm los dobletes atribuidos a los protones del anillo furánico (J =16.0 Hz) y a 0.73 ppm la señal de los protones del metilo C-15 que aparece como doblete (J = 6.5 Hz). Se observan asimismo singletes anchos a 11.09 y 5.09 ppm, generados por los hidroxilos fenólicos. La presencia de éstos se corrobora por las bandas anchas presentes en el espectro de

IR a 3565 y 3419 cm^{-1}. Se determinó el valor de la rotación óptica del compuesto **1**, $[\alpha]_D^{25}$ = - 21.8 (c 14.8, $CHCl_3$). Es importante resaltar que este dato no ha sido aportado previamente, ya que durante el aislamiento de corallidictyal D (**1**) de su fuente natural, la esponja *Aka coralliphagum*, se obtuvo una mezcla de este merosesquiterpeno y su epímero en C-9 (corallidictyal C).

Se obtuvieron también los datos espectroscópicos en DMSO, para realizar la comparación con los datos aportados en bibliografía y se encontró correspondencia entre ambos

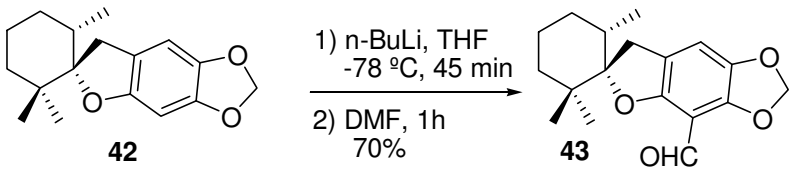
6.5. SÍNTESIS DEL ANÁLOGO MONOTERPÉNICO DE CORALLIDICTYAL D (45): ETAPA FINAL

a) Formilación del anillo aromático

Tras la obtención del isómero monoterpénico **42** con buen rendimiento, mediante ciclación con NIS/PPh_3, éste se aisló y se procedió a completar la adecuada sustitución del anillo aromático.

La formilación se llevó a cabo de forma análoga a lo decrito para la síntesis de corallidictyal (Ver esquema 42).

La introducción del aldehído aromático mediante tratamiento con n-BuLi y DMF proporcionó **43** con un 70% de rendimiento (Esquema 88).

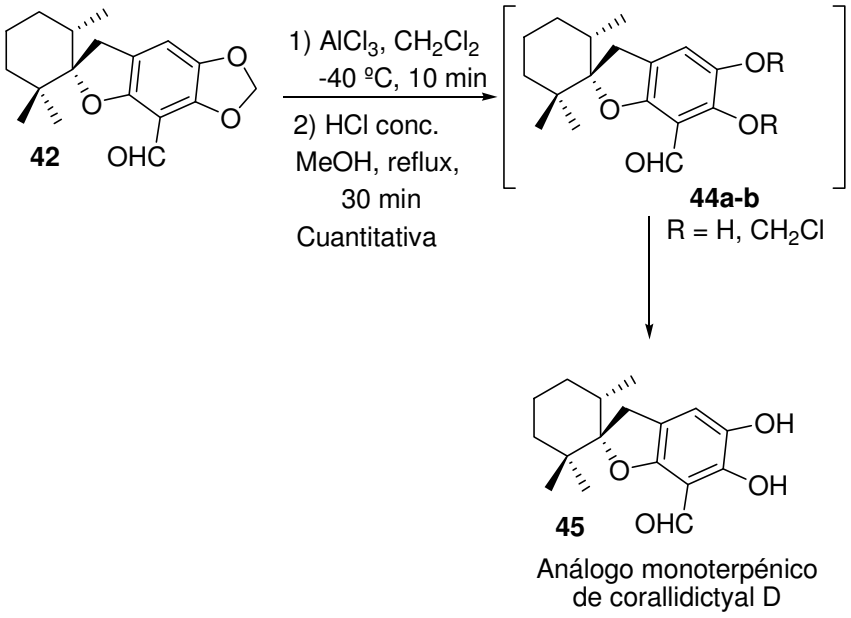


42 **43**

Esquema 88

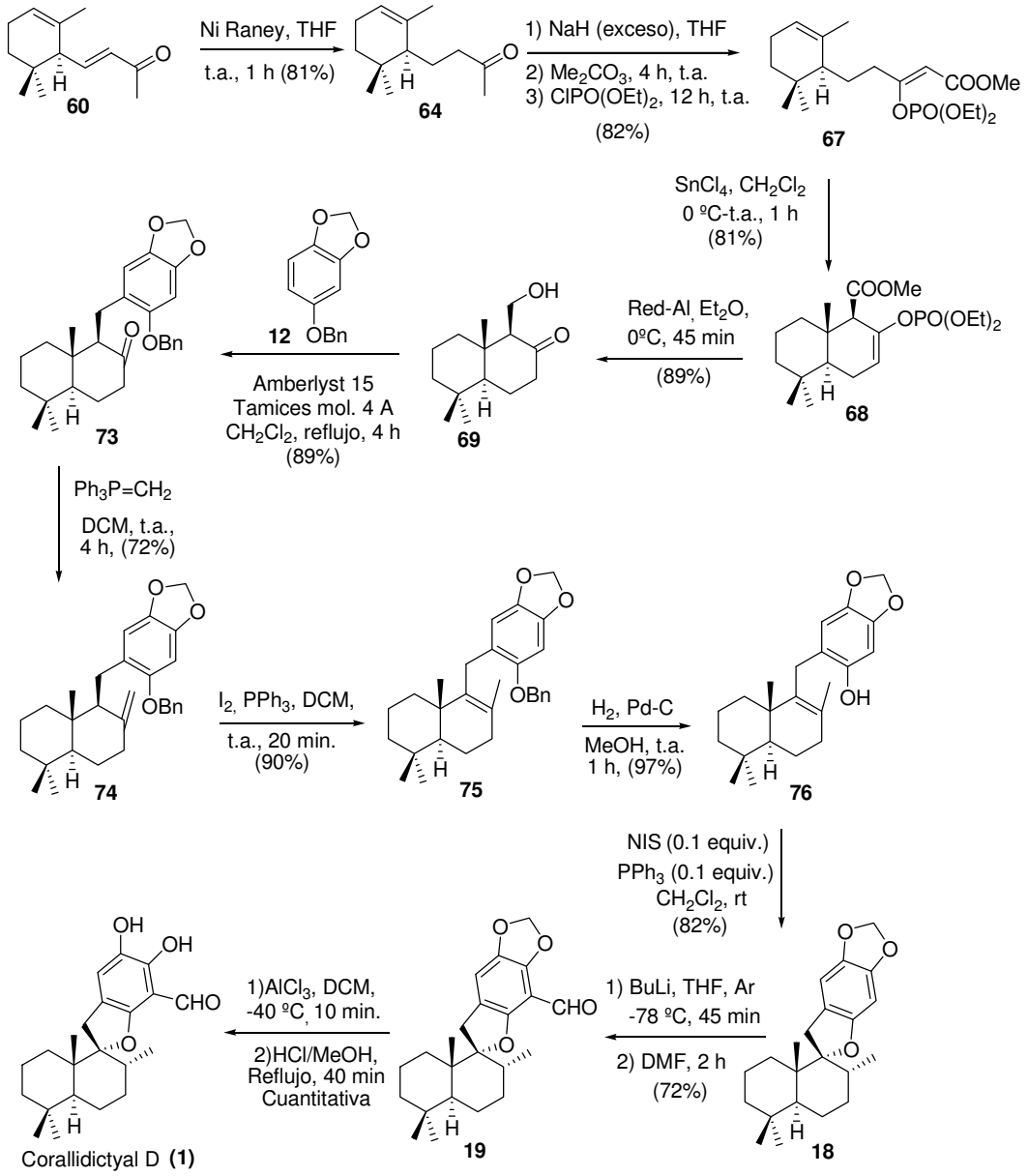
*b) Ruptura de la agrupación metilendioxi: Síntesis del análogo de corallidictyal D (**45**)*

Por último, con objeto de obtener el análogo monoterpénico de corallidictyal D (**45**), se llevó a cabo la desprotección del catecol, según el procedimiento empleado para la síntesis de corallidictyal D, rindiendo **45** en una sola etapa, con un excelente rendimiento, después de 10 min a -40ºC y posterior hidrólisis ácida del grupo clorometiloxi intermedio de la reacción (Esquema 89).



Esquema 89

ESQUEMA GENERAL DE SÍNTESIS DE CORALLIDICTYAL D (1) A PARTIR DE α-IONONA (60)



Esquema 90

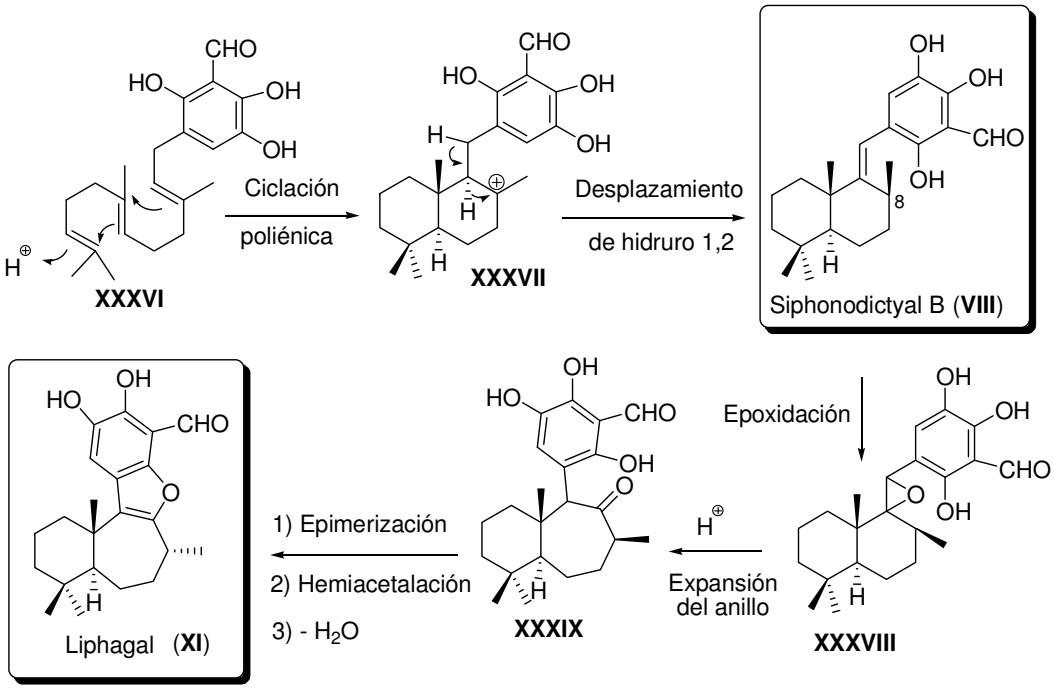
7. PROPUESTA BIOSINTÉTICA HACIA LIPHAGAL Y CORALLIDICTYALES

Como se ha indicado en los antecedentes, Andersen et al[6] han propuesto sendas posibles rutas biosintéticas hacia (+)-liphagal (**2**), a partir del farnesiltrihidroxibenzaldehído **XXXVI**. En una de ellas, ruta A, (Esquema 91), tiene lugar una ciclación poliénica que origina el carbocatión terciario **XXXVII**, con esqueleto de tipo drimaniltrihidroxibenzaldehído, que experimenta un desplazamiento de hidruro 1,2, proporcionando siphonodictyal B (**VIII**), metabolito aislado en el alga *Aka Coralliphaga* junto a (+)-liphagal (**2**). En la otra ruta propuesta por el grupo de Andersen, ruta B, (ver esquema 2 de antecedentes) se postula la formación previa del sistema benzofuránico caraterístico de (+)-liphagal (**2**), y la posterior ciclación poliénica, que proporciona directamente el sistema anular 6-7 del esqueleto liphagano.

Aunque la síntesis de (±)-liphagal desarrollada por Andersen utiliza la secuencia planteada en la ruta B, este proceso biosintético no permite explicar la formación de siphonodictyal B (**VIII**), ni tampoco la de otros metabolitos relacionados estructuralmente, como corallidictyales A-D (**I-IV**), que también se encuentran en la misma fuente natural. Sin embargo, la ruta biosintética A sí proporciona una explicación para la formación de todos estos metabolitos.

(6) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Organic Letters* **2006**, *8*, 321.

Propuesta biogenética de Andersen: Ruta A

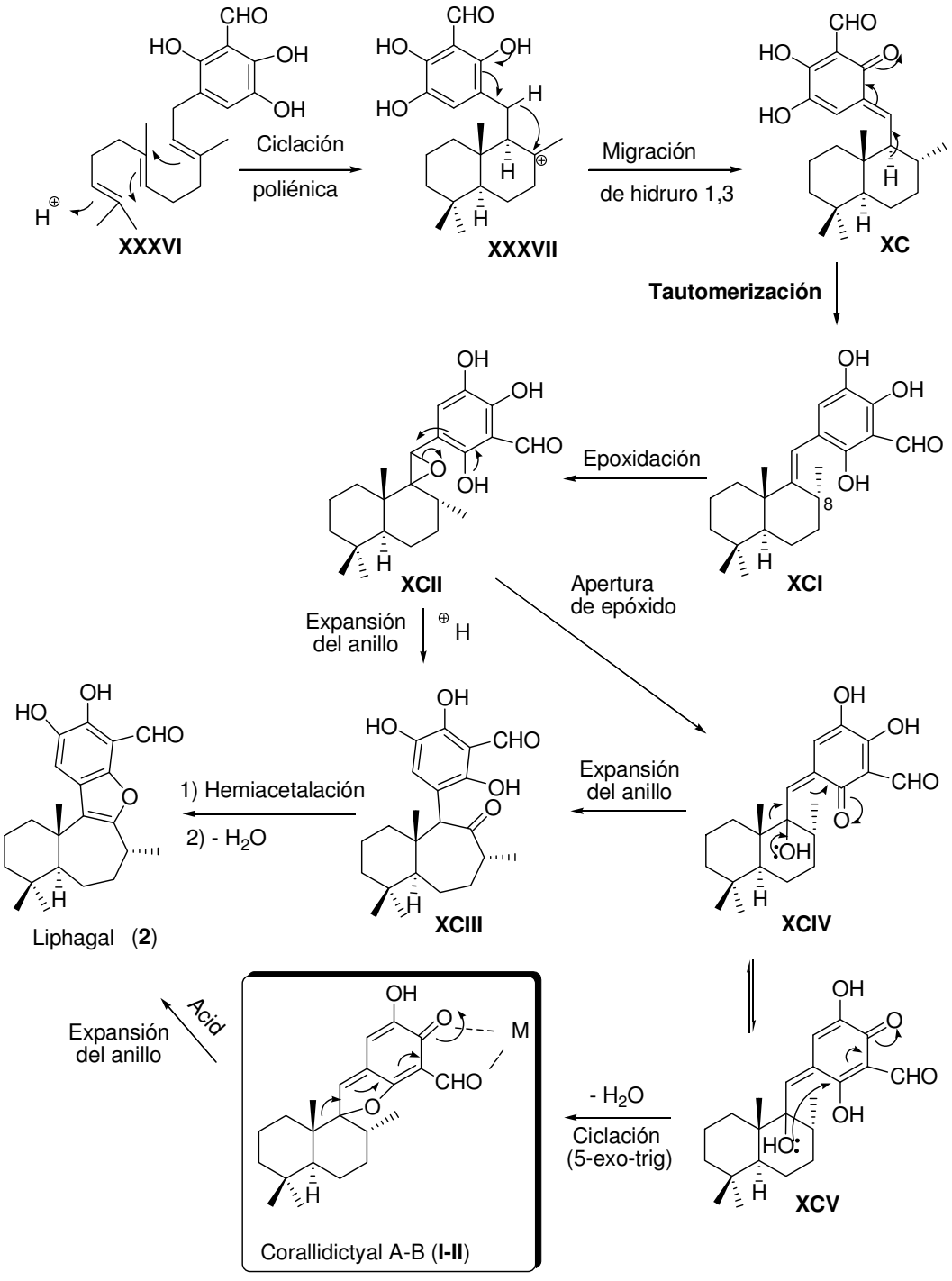


Esquema 91

De acuerdo con la propuesta biosintética de Andersen, mostrada en el esquema 91, el producto de epoxidación **XXXVIII** de siphonodictyal B debe experimentar expansión del anillo, mediante un proceso de tipo pinacólico, que conduzca a la cetona **XXXIX**, que se propone como precursora del esqueleto de liphagano. Sin embargo, esta transformación directa de **XXXVIII** en **XXXIX** no explica la formación de corallidictyales (**I-IV**) y supone un proceso de epimerización de la cetona **XXXIX** anterior a la etapa de hemicetalación y ciclación, generalmente más rápida y favorecida.

En el esquema 92 se recoge una nueva propuesta biogenética, formulada durante el transcurso de nuestras investigaciones, que explica la biosíntesis de todos los antes citados metabolitos (**I-IV**, **VIII** y **XI**) a partir del farnesiltrihidroxibenzaldehído **XXXVI**.

Nueva ruta biosintética propuesta



Esquema 92

En esta nueva propuesta, tras la ciclación poliénica de **XXXVI**, se supone una migración 1,3 de hidruro en **XXXVII**, posiblemente provocada por un proceso de oxidación, que generaría la enona **XC**, que se tautomeriza hacia **XCI**, epímero en C-8 de siphonodictyal B (**VIII**). El intermedio **XCI** presenta la configuración adecuada para la síntesis tanto de liphagal como de corallidictyales, sin necesidad de experimentar un proceso posterior de epimerización.

El epóxido derivado **XCII**, de **XCI**, podría sufrir un reordenamieto pinacólico que conlleva la expansión del anillo, bien de forma directa o *vía* un intermedio de tipo *o*-quinometano **XCIV.**

Aunque el reordenamiento de este tipo de especies *vía* desplazamiento de grupos alquilo, como sería el presente caso, no ha sido descrito aún, su participación en rutas biosintéticas y su utilización como intermedios en síntesis biomiméticas ha sido ampliamente documentado[135] .

En nuestro laboratorio se vienen sintetizando *o*-quinometanos unidos a fragmentos drimánicos, similares al compuesto **XCIV**, desde hace bastantes años[51,107,136]. Este *o*-quinometano **XCIV** podría sufrir también expansión de anillo, mediante un desplazamiento de grupo alquilo, a través de un proceso similar al reordenamiento de α-hidroxialdehídos, transformándose en el precursor de liphagano **XCIII,** ahora sí, con la configuración adecuada para generar liphagal. Alternativamente, el *o*-quinometano **XCIV** puede isomerizarse para dar un *p*-quinometano **XCV,** que podría experimentar espirociclación, con simultánea deshidratación, mediante un proceso 5-exo-trig, que conducirá a corallidictyales A-B (**I-II**) y a los correspondientes productos de reducción corallidictyales C-D (**III-1**), sin necesidad, de nuevo, de epimerización.

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.
(107) Alvarez-Manzaneda, E. J.; Chahboun, R.; Barranco Pérez, I.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R. *Organic Letters* **2005**, *7*, 1477.
(134) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.
(135) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron. Lett.* **1997**, *38*, 2325.

Esta nueva propuesta incluye otra posible vía de formación de liphagal (**2**), que implicaría la expansión del anillo de corallidictyal A-B (**I-II**), favorecida por la deficiencia electrónica del doble enlace conjugado con sendos grupos carbonilo.

Algunos de los resultados obtenidos en nuestro laboratorio, y comentados anteriormente en esta memoria, parecen apoyar la participación de quinometanos como **XCIV** y **XCV** en la biosíntesis de los metabolitos **I-III, 1** y **2.** Especies de este tipo ya han sido postuladas por nosotros[124] para explicar la estereoselectividad observada en la expansión de anillo que sufren los dioles, tanto monoterpénicos (**26a-b**) como sesquiterpénicos (**15a-b**), en medio ácido (ver esquemas 15 y 22), como alternativa a la expansión *via* un catión bencílico. La reducción de intermedios de tipo quinometano explica la formación de productos como el hidroxifenol monoterpénico **29** (esquema 14) o el análogo sesquiterpénico **17** (ver esquema 38) cuando se lleva a cabo la expansión de los correspondientes dioles en atmósfera de hidrógeno.

La posible transformación de corallidictyales en liphagal es una propuesta tentativa, que ha de ser objeto de posteriores estudios.

(123) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Cano, M. J.; Haidour, A.; Alvarez-Manzaneda, R. *Organic Letters* **2010**, *12*, 4450.

EXPERIMENTAL SECTION

1. MATERIALS AND METHODS

Unless stated otherwise, reactions were performed in oven-dried glassware under an argon atmosphere using dry solvents. Solvents were dried as follows: THF and Et_2O over Na – benzophenone, toluene and benzene over Na, DCM and MeOH over CaH_2. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were dried over 4Å molecular sieves.

Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching and phosphomolybdic acid solution staining.

Flash chromatography was performed on silica gel (Merck Kieselgel 60, 230-400 mesh) Chromatography separations were carried out by conventional column on silica gel 60 (230-400 Mesh), using Hexanes-MeO^{t}Bu (H-E) mixtures of increasing polarity.

^{1}H and ^{13}C NMR spectra were recorded on a Varian instrument (at 500 MHz and 125 MHz, respectively). $CDCl_3$ was treated with K_2CO_3. Chemical shifts (δ_H) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak and tetramethylsilane.

Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), with the abbreviations s, br s, d, br d, t, q, and m denoting singlet, broad singlet, doublet, broad doublet, triplet, and multiplet respectively. *J* = coupling constant in Hertz (Hz)

Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0) and the signals were assigned utilizing DEPT experiments and on the basis of heteronuclear correlations.

Infrared spectra (IR) were recorded as thin films or as solids on a Mattson model Satellite FTIR spectrophotometer with samples between sodium chloride

plates or as potassium bromide pellets and are reported in frequency of absorption (cm^{-1}). Only selected absorbancies (ν_{max}) are reported.

($[\alpha]^D$) mesurements were carried out in a PERKIN-ELMER 341 polarimeter; utilizing a 1dm length cell and $CHCl_3$ as a solvent. Concentration is expressed in mg/mL.

Mass spectra: HRMS were recorded on a AutoSpecQ VG-Analytical (Fisons) spectrometer, using FAB Wwith thioglicerol or glycerol matrix doped in NaI 1%.

Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected.

Ozonation reactions were carried out with a mixture of ozone-oxygen provided by an oxygen-feed Fischer apparatus (8.3 mmol of 03 in 10 litres of O_2/h).

2. GENERAL PROCEDURES

℘ General procedure for acidic rearrangement of sesquiterpenic diol 15a*

Acid (0.25 mmol) is added to a solution of diol **15a** (1 mmol) in dry solvent (10 mL) at the specified temperature (-50 ºC-rt) and the reaction mixture is stirred until TLC shows no **15a**. (1 min - 1.5 h). The reaction mixture is then poured into ice and extracted with ether (2 x 20 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (8 % ether/hexanes) giving access to ketone **31a** (45-97%) yield, as a colourless syrup.

*Parameter values may vary within the limits stated in the different experiences (see section of results and discussion table 2).

General cyclization procedure with ion exchange Amberlyst 15*

To a solution of phenol (1 mmol), in DCM (6 mL), exchange-ion acidic resin Amberlyst 15 (1.29 g/mmol) is added. The reaction is stirred at between 0 ºC and room temperature for a variable period of time (from 15 min to 69 hours) until TLC shows no starting material remaining. The cationic resin is filtered and the solvent is removed under reduced pressure to generally furnish piranic isomer together with traces of the corresponding spiroderivative in (81-92) % yield.

General cyclization procedure with I_2/PPh_3 system**

Iodine (1 mmol) was added to a solution of triphenylphosphine (1.65 mmol) in dry CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature for, at least, 15 min. A solution of phenol **81**, **90**, **91**, **76**, **100** (1 mmol) in CH_2Cl_2 (5 mL) was then added at 0 ºC. The reaction mixture is stirred at room temperature for the specified time, until TLC shows no remaining phenol. After removal of most of the solvent under reduced pressure, the reaction mixture was filtered over silica gel and concentrated to give a crude product which was purified by flash chromatography column on silica gel (ether/hexanes)) to afford pure spirobenzofuran derivative **42**, **93**, **95**, **18**, **104** respectively.

General cyclization procedure with NIS/PPh_3 system

N-iodosuccinimide (0.1 mmol) was added to a solution of triphenylphosphine (0.1 mmol) in dry CH_2Cl_2 (4 mL) and the mixture was stirred at room temperature for, at least, 15 min. A solution of phenol **81**, **90**, **91**, **76**, **100** (1 mmol) in CH_2Cl_2 (4

* Parameter values may vary within the limits stated in the different experiences.

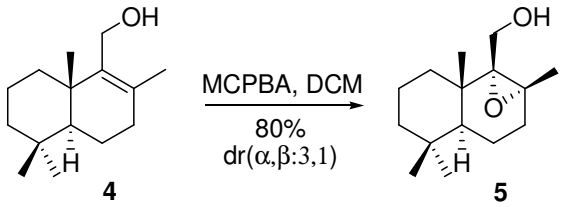
**Note that when the reaction is performed in small scale, corresponding benzopirane is also obtained in low yield.

mL) was then added at 0 ºC and the reaction mixture was stirred at room temperature for the specified time, until TLC shows no remaining phenol. The solvent was removed under vacuum and the crude product was directly purified by flash chromatography column on silica gel (ether/hexanes mixture) to give the desired spirobenzofuran derivative **42**, **93**, **95**, **18**, **104** respectively.

3. EXPERIMENTAL PROCEDURES

3.1 PREPARATION OF MEROSESQUITERPENIC DIOL 15 STARTING FROM (+)-SCLAREOLIDE (3)

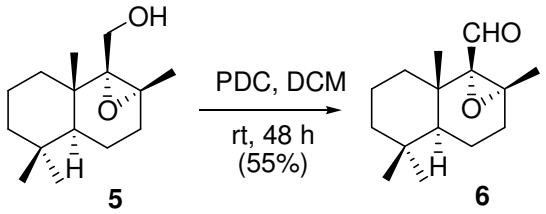
1.-Epoxydation of hydroxyalkene 4



A solution of *m*-Chloroperoxybenzoic acid (75%; 1.91 g, 11.1 mmol) in CH_2Cl_2 (15 mL), was added at -40 ºC to a stirred solution of **4** (1.54 g, 6.9 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred for 45 min, at which time TLC indicated no starting material remaining. Then, the reaction mixture was quenched with saturated aqueous sodium sulfite (sat. aq Na_2SO_3) (5 mL) and stirred at room temperature for an additional 15 min. The solvent was removed under vacuum and ether (40 mL) was added, the phases were shaken and separated; and the organic phase was washed with saturated aqueous sodium bicarbonate solution (sat. aq $NaHCO_3$) (6 x 15 mL) and brine (1 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude product containing the two isomers (α,β-epoxides- 3:1) which, after flash chromatography column on silica gel (2% ether/hexanes), afforded 0.99 g of the epoxyde **5** (60%) as a colourless syrup.

All spectral data for ***(1R,2R,4aS,8aS)-1,2-epoxy-1-(hydroxymethyl)-2,5,5,8a-tetramethyldeca- hydronaphthalene (5)*** match those previously reported[137].

2.-Oxidation of drimanic epoxyalcohol 5 to epoxyaldehyde 6



5 **6**

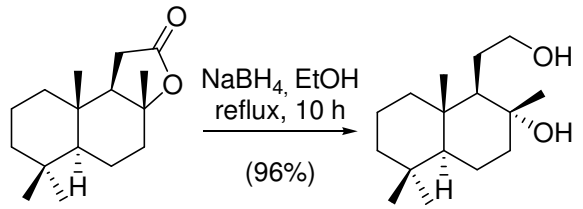
PDC (Piridinum dichromate) (2.26 g, 6 mmol) was added to a solution of epoxyalcohol **5** (715 mg, 3.0 mmol) in anhydrous CH_2Cl_2 (15 mL) and the resulting reaction mixture was stirred at room temperature for 48 h, then it was filtrated over silica, washed with DCM and the solvent was removed from the filtrate under reduced pressure. The residue was diluted in ether (20 mL), washed with 2N-HCl.(3 x 10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution (10 mL) and brine (10 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography column on silica gel (hexanes/EtOAc, 30:1 as eluent) to give **6** (390 mg, 55%)**.**

(1aR,7aS,7bS)-1a,4,4,7a-tetramethyl-decahydronaphtho[2,1-b]oxirene-7b-carbaldehyde (6): $[\alpha]_D^{25}$ = -7.6 (c 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.69 (s, 1H), 1.98 (dt, *J* = 15.7, 9.6 Hz, 1H), 1.85 (ddd, *J* = 15.7, 8.6, 1.6 Hz, 1H), 1.64 (m, 1H), 1.59-1.30 (m, 7H), 1.37 (s, 3H), 1.24 (s, 3H), 1.18 (dd, *J* = 13.4, 13.4, 3.8 Hz, 1H), 0.84 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 201.8 (CHO), 75.4 (C), 64.4 (C), 42.1 (CH), 41.4 (CH_2), 36.7 (C), 35.4 (CH_2), 33.5(CH_3), 32.9 (C), 28.7 (CH_2), 21.5 (CH_3), 21.4 (CH_3), 18.3 (CH_2), 17.2 (CH_3), 16.9 (CH_2).

(136) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez , E.; Alvarez-Manzaneda, R.; Muñoz, P. E.; Jimenez, F.; Bouanou, H. *Tetrahedron* **2011**, *67*, 8910.

IR (film): 1726, 1460, 1381, 1074, 1050, 886, 830 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{15}H_{24}O_2Na$ ($M+Na^+$) 259.1674, found: 259.1670.

3.-Reduction of (+)-sclareolide (3) to diol 9



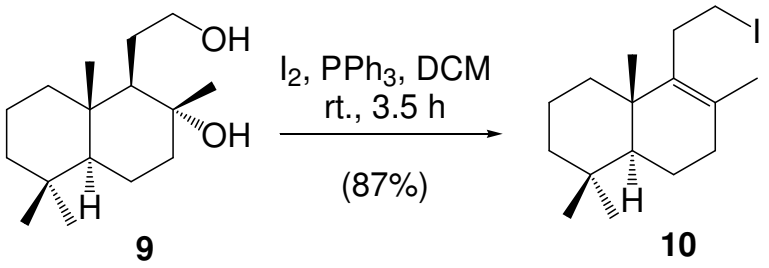
(+)-sclareolide (**3**)

$NaBH_4$ (0.56 g) was added in portions to a solution of (+)-sclareolide (**3)** (1.0 g, 4.0 mmol) in EtOH (20 mL) and the mixture was stirred under reflux for 10 h, at which time TLC showed no starting material. Then, the reaction mixture was allowed to cool to room temperature and water (5 mL) was carefully added. The solvent was evaporated and the mixture was fractionated into H_2O (30 mL)- *t*-BuOMe (30 mL) and extracted with t-BuOMe (3 × 30 mL). The combined organic phases were washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated to give **9** (0.98 g, 96%) as a white solid.

(1R,2R,4aS,8aS)-1-(2-hydroxyethyl)-2,5,5,8a-tetramethyl-decahydronaphthalen-2-ol. (9) [96]: Mp 129–131°C. $[\alpha]_D^{25}$ = -15 (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.78 (dt, *J* = 9.7, 4.7 Hz, 1H), 3.46 (m, 1H), 3.30 (br s, -OH), 1.89 (dt, *J* = 12.0, 3.3 Hz, 1H), 1.70-1.52 (m, 5H), 1.50-1.35 (m, 4H), 1.29-1.22 (m, 3H), 1.19 (s, 3H), 0.94 (m, 1H), 0.87 (s, 3H), 0.79 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 73.2 (C), 64.2 (CH_2), 59.3 (CH), 56.1 (CH), 44.4 (CH_2), 42.0 (CH_2), 39.5(CH_2), 39.1 (C), 33.5 (CH_3), 33.4 (C), 28.0 (CH_2), 24.7 (CH_3), 21.6 (CH_3), 20.6 (CH_2), 18.5 (CH_2), 15.4 (CH_3). IR (film): 3250, 1054 cm^{-1}.

(96) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Arteaga, A. F. *Synth. Comm.* **2004**, *34*, 3631.

4.-Treatment of diol 9 with I_2/PPh_3 system



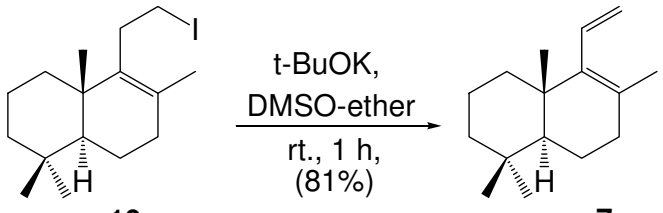
9 **10**

Iodine (5.3 g, 20.88 mmol) was added to a solution of triphenylphosphine (PPh_3) (5.3 g, 20.2 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred at room temperature for 10 min. A solution of diol **9** (5 g, 19.68 mmol) in CH_2Cl_2 (20 mL)was then added and the resulting mixture was further stirred at room temperature for 3h 30 min, at which time TLC showed no **9**. Then aqueous 5% $NaHSO_3$ solution (10 mL) was added and the mixture was vigorously stirred for an additional 5 min and then, the solvent was removed in vacuum. Ether (80 mL) was added and the phases were shaken and separated, the organic phase was washed with water (3 x 20 mL) and brine (2 x 20 mL). After drying over anhydrous Na_2SO_4, the solvent was removed in vacuum and the crude product was purified by flash chromatography column on silica gel (5% ether/hexanes) to give 5.65 g, of **10** (83%) as a colourless oil.

All spectral data for ***(4aS,8aS)-5-(2-iodoethyl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (10)*** match those previously reported[138].

(137) Lian, Y.; Davies, H. M. L.; Miller, L. C.; Born, S.; Sarpong, R. *J . Am. Chem. Soc.* **2010**, *132*, 12422.

5.-Hydrogen iodide elimination to obtain diene 7

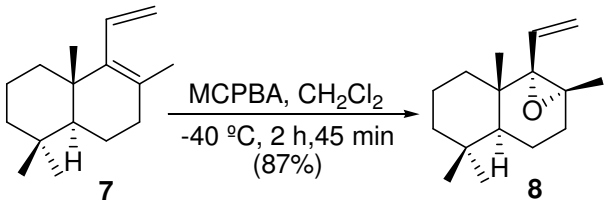


10 **7**

Potassium tert-butoxide (5.8 g, 51.69 mmol) was added to a stirred solution of **10** (6 g, 17.3 mmol) in a DMSO/ether mixture (65:15 mL), and the reaction mixture was stirred at room temperature for 1 h, at which time TLC showed no starting material remaining. Then the reaction was extracted with ether (2 x 60 mL). The combined organic extracts were washed with water (4 x 25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to yield pure **7** (3.06 g, 81%).

(4aS,8aS)-1,1,4a,6-tetramethyl-5-vinyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (7): $[\alpha]_D^{25}$ = + 75.76 (c 3.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.12 (br dd, *J* = 17.6, 11.1 Hz, 1H), 5.23 (dd, *J* = 11.1, 2.8 Hz, 1H), 4.90 (dd, *J* = 17.6, 2.8 Hz, 1H), 2.07 (m, 1H) , 1.65 (s, 3H), 1.71-1.37 (m, 7H), 1.20-1.05 (m, 4H), 1.00 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 142.1 (C), 135.3 (CH), 126.9 (C), 118.3 (CH_2), 51.4 (CH), 41.9 (CH_2), 38.2 (CH_2), 37.7 (C), 33.6 (CH_2), 33.4 (C), 33.3 (CH_3), 21.7 (CH_3), 21.2 (CH_3), 20.1 (CH_3), 19.1 (CH_2), 19.0 (CH_2). IR (film): 3077, 1834, 1621, 1458, 1374, 1006, 915 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{26}Na$ ($M+Na^+$) 241.1932, found: 241.1938.

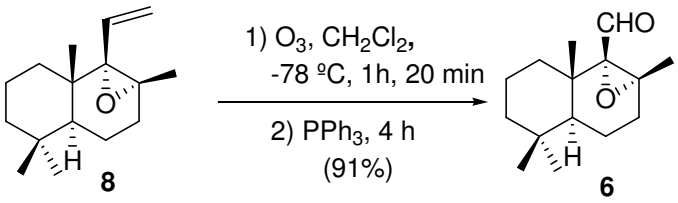
6.-Epoxydation of diene 7



A solution of *m*-Chloroperoxybenzoic acid (75%; 3.81 g, 22.1 mmol) in CH_2Cl_2 (20 mL), was added at -40 ºC to a stirred solution of **7** (3 g, 13.8 mmol) in CH_2Cl_2 (30 mL), and the reaction mixture was stirred for 2 h, 45 min, at which time TLC indicated no starting material remaining. Then, the reaction mixture was quenched with saturated aqueous sodium sulfite (sat. aq Na_2SO_3) (5 mL) and stirred at room temperature for an additional 15 min. The solvent was removed in vacuum and ether (80 mL) was added, the phases were shaken and separated; and the organic phase was washed with saturated aqueous sodium bicarbonate solution (sat. aq $NaHCO_3$) (10 x 15 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated to give a crude product which, after flash chromatography column on silica gel (2% ether/hexanes), afforded 2.81 g of the epoxyde **8** (87%).

(1aR,7aS,7bS)-1a,4,4,7a-tetramethyl-7b-vinyl-decahydronaphtho[2,1-b] oxirane (8): $[\alpha]_D^{25}$ = + 3.0 (c 4.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.96 (dd, *J* = 17.1, 10.9 Hz, 1H), 5.19 (dd, *J* = 10.9, 2.5 Hz, 1H), 5.13 (dd *J* = 17.1, 2.5 Hz, 1H), 1.89 (ddd, *J* = 15.7, 10.4, 9.2 Hz, 1H), 1.77 (ddd, *J* = 15.7, 8.4, 1.4 Hz, 1H), 1.58-1.04 (m, 9H), 1.05 (s, 6H), 0.77 (s, 3H), 0.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 132.7 (CH), 118.1 (CH_2), 74.0 (C), 63.9 (C), 42.4 (CH), 41.6 (CH_2), 36.8 (C), 36.2 (CH_2), 33.6 (CH_3), 33.1 (C), 28.9 (CH_2), 21.5 (CH_3), 21.1 (CH_3), 18.6 (CH_2), 17.9 (CH_3), 17.2 (CH_2). IR (film): 1636, 1459, 1378, 1073, 1041, 990, 925, 841 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{26}ONa$ ($M+Na^+$) 257.1881, found: 257.1885.

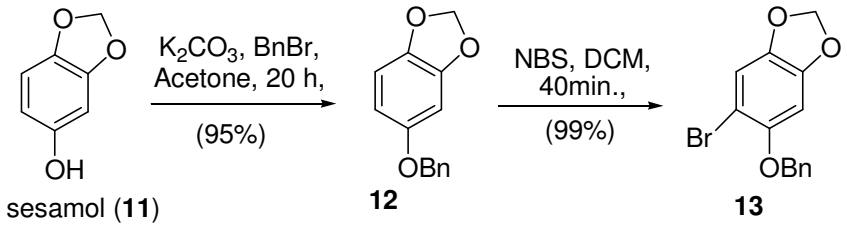
7.-Reductive ozonolysis of epoxyalkene 8



A stirred solution of **8** (2.5 g, 10.68 mmol) in CH_2Cl_2 (20 mL) was slowly bubbled with an O_3/O_2 mixture at -78 ºC, and the course of the reaction was monitored by TLC. When the starting material was consumed (1 h, 20 min), the solution was flushed with argon, and triphenylphosphine (4.2 g, 16 mmol) was added. The mixture was further stirred for 4h at room temperature and the solvent was removed. Flash chromatography column on silica gel (5 % ether/hexanes) gave the epoxyaldehyde **6** (2.30 g, 91%).

(1aR,3As,7aS,7bS)-1a,4,4,7a-tetramethyl-decahydronaphtho[2,1-b]oxirene-7b-carbaldehyde (6): $[\alpha]_D^{25}$ = -7.6 (c 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.69 (s, 1H), 1.98 (dt, *J* = 15.7, 9.6 Hz, 1H), 1.85 (ddd, *J* = 15.7, 8.6, 1.6 Hz, 1H), 1.64 (m, 1H), 1.59-1.30 (m, 7H), 1.37 (s, 3H), 1.24 (s, 3H), 1.18 (dd, *J* = 13.4, 13.4, 3.8 Hz, 1H), 0.84 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 201.8 (CHO), 75.4 (C), 64.4 (C), 42.1 (CH), 41.4 (CH_2), 36.7 (C), 35.4 (CH_2), 33.5(CH_3), 32.9 (C), 28.7 (CH_2), 21.5 (CH_3), 21.4 (CH_3), 18.3 (CH_2), 17.2 (CH_3), 16.9 (CH_2). IR (film): 1726, 1460, 1381, 1074, 1050, 886, 830 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{15}H_{24}O_2Na$ ($M+Na^+$) 259.1674, found: 259.1670.

8.-Preparation of bromide derivative 13 from sesamol (11)



sesamol (**11**) **12** **13**

To a suspension of sesamol (**11**), (3.34 g, 24.2 mmol) in 40 mL of acetone containing anhydrous potassium carbonate (10.0 g, 72.6 mmol) benzyl bromide (2.9 mL, 24.2 mmol) was added and the mixture was stirred at reflux for 20 h, when the TLC analysis permitted us to evidence the total consumption of the starting material. Next, the solvent was removed under vacuum and ether - water (100 : 30 mL) was added, and the phases were shaken and separated. The organic layer was dried, evaporated to give a crude product which was purified by column chromatography (10% ether/hexanes) to furnish 5.25 g (95%) of the desired benzylated sesamol **12**, as a beige crystalline solid[138] .

Finally, to a solution of **12** (4.56 g, 20 mmol) in DCM (30 mL), cooled to 0 ºC, a solution of N-bromosuccinimide (3.8 g, 21 mmol) in DCM (30 mL).was added with stirring and the resulting solution was stirred for 40 min at room temperature. Then, the solvent was evaporated, yielding a crude product which after chromatography column on silica gel (5% ether/hexanes) afforded 6.04 g (99%) of **13** as white crystals[139].

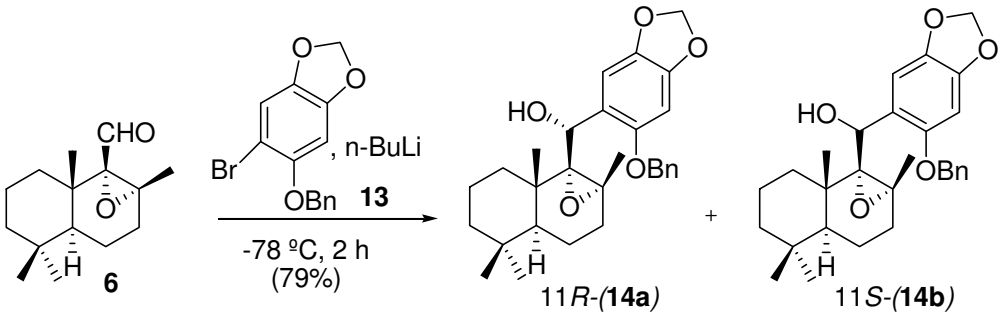
5-(benzyloxy)-6-bromobenzo[d][1,3]dioxole (13): Mp.61-62 ºC. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.47 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J*

(138) Bezerra-Netto, H. J. C.; Lacerda, D. I.; Miranda, A. L. P.; Alves, H. M.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem.* **2006**, *14*, 7924.

(139) Witiak, D. T.; Kim, S. K.; Tehim, A. K.; Sternitzke, K. D.; McCreery, I. R. L.; Kim, S. U.; Feller, D. R.; Romstedt, K. J.; Kamanna, V. S.; Newman, H. A. I. *Journal of Medicinal Chemistry* **1998**, *31*, 144.

= 7.3 Hz, 1H), 7.01 (s, 1H), 6.58 (s, 1H), 5.93 (s, 2H), 5.06 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 150.5 (C), 147.8 (C), 142.7 (CH), 136.8 (C), 128.7 (2 x CH), 128.1 (CH), 127.4 (2 x CH), 112.8 (CH), 103.3 (C), 101.9 (CH_2), 98.7 (CH), 72.7 (CH_2).

9.- Preparation of epoxyalcohols 14a-b by arillithium addition



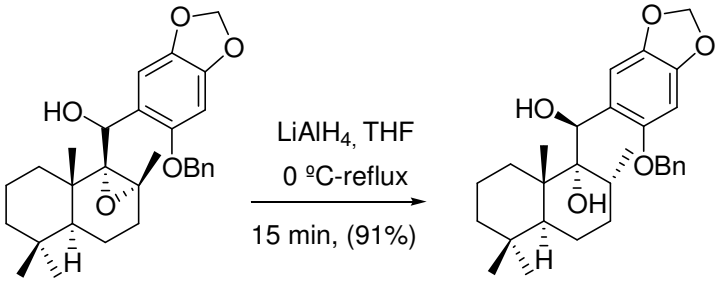
To a solution of bromobenzene derivative **13** (3.12 g, 10.16 mmol) in dry THF (20 mL) was carefully added *n*-butyllithium (10.2 mmol) at -78 ºC under an argon atmosphere, and the reaction mixture was stirred at this temperature for 30 min. Then a precooled solution of epoxyaldehyde **6** (2.0 g, 8.47 mmol) in dry THF (15 mL) was syringed to the first solution and the reaction mixture was stirred for a further 1 h at which time TLC showed no starting material. The reaction was quenched with water (5 mL), the solvent was removed under vacuum, and the mixture was extracted with ether (2 x 20 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield a crude product which was directly purified by chromatography column (20% ether/hexanes) to furnish pure epoxyalcohol **14a** as a white solid (1.65 g, 42%) after a further purification by crystallisation utilizing a mixture of hexanes/ether (9:1) and pure epoxyalcohol **14b** as a colourless syrup (1.53 g, 39%).

Data for (R)-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)((1aR,3aS,7aS,7bR)-1a,4,4,7a-tetramethyl-decahydronaphtho[2,1-b]oxiren-7b-yl)methanol (14a): Mp 180.7 ºC, $[\alpha]_D^{25}$ = + 2.0 (c 6.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.40-7.34 (m, 5H), 7.21 (s, 1H), 6.50 (s, 1H), 5.92 (d, *J* = 1.3 Hz, 1H), 5.90 (d, *J* = 1.3 Hz, 1H), 5.14 (d, *J* = 2.2 Hz, 1H), 5.00 (d, *J* = 11.2 Hz, 1H), 4.96 (d, *J* = 11.2 Hz, 1H), 2.61 (d, *J* = 2.2 Hz, 1H), 1.91 (m, 1H), 1.78 (ddd, *J* = 15.6, 10.6, 9.2 Hz, 1H), 1.77 (dd, *J* = 15.6, 7.8 Hz, 1H), 1.63 (m, 1H), 1.47 (dd, *J* = 12.8, 2.5 Hz, 1H), 1.41-1.12 (m, 7H), 1.11 (s, 3H), 0.89 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.2 (C), 146.8 (C), 141.1 (C), 136.6 (C), 128.8 (2 CH), 128.5 (2 CH), 128.4 (CH), 122.2 (C), 108.5 (CH), 101.2 (CH_2), 94.7 (CH), 74.3 (C), 71.3 (CH_2), 69.7 (CH), 66.7 (C), 43.3 (CH), 41.4 (CH_2), 39.5 (C), 35.2 (C H_2), 34.1 (CH_3), 33.1 (C), 30.3 (CH_2), 22.6 (CH_3), 21.7 (CH_3), 18.6 (CH_2), 17.6 (CH_2), 16.8 (CH_3). IR (film): 3449, 1625, 1504, 1485, 1431, 1394, 1261, 1232, 1157, 1155, 1042, 939, 916, 813, 750 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{36}O_5Na$ ($M+Na^+$) 487.2460, found: 487.2467.

Data for (S)-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)((1aR,3aS,7aS,7bR)-1a,4,4,7a-tetramethyl-decahydronaphtho[2,1-b]oxiren-7b-yl)methanol (14b): $[\alpha]_D^{25}$ = - 3.4 (c 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.42 (brd, *J* = 7.2 Hz, 2H), 7.37 (brt, *J* = 7.4 Hz, 2H), 7.32 (brd, J = 6.7 Hz, 1H), 6.85 (s, 1H), 6.57 (s, 1H), 5.91 (dd, *J* = 1.4 Hz, 1H), 5.89 (dd, *J* = 1.4 Hz, 1H), 5.59 (d, *J* = 2.2 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 2.75 (d, *J* = 2.2 Hz, 1H), 2.02-1.90 (m, 2H), 1.83 (br d, *J* = 12.1 Hz, 1H), 1.53 (dd, *J* = 12.8, 2.3 Hz, 1H), 184 (s, 3H), 1.47-1.40 (m, 3H), 1.38-1.22 (m, 2H), 1.15 (ddd, *J*= 12.7, 12.7, 5.0 Hz, 1H), 0.84 (s, 3H), 0.77 (s, 3H), 0.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 152.1 (C), 147.4 (C), 141.2 (C), 137.0 (C), 128.6 (2 CH), 127.9 (CH), 127.5 (2 CH), 122.9 (C), 108.6 (CH), 101.2 (CH_2), 96.8 (CH), 73.9 (C), 71.9 (CH_2), 65.9 (C), 63.9 (CH), 43.6 (CH), 41.1 (CH_2), 38.9 (C), 34.9 (CH_2), 33.8 (CH_3), 33.1 (C), 31.4 (CH_2), 23.7 (CH_3), 21.6 (CH_3), 18.6 (CH_2), 18.0 (CH_3), 17.5 (CH_2).

IR (film): 3477, 1628, 1504, 1485, 1434, 1389, 1235, 1173, 1041, 936 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{36}O_5Na$ ($M+Na^+$) 487.2460, found: 487.2464.

10.-Reduction of epoxyalcohol 14b



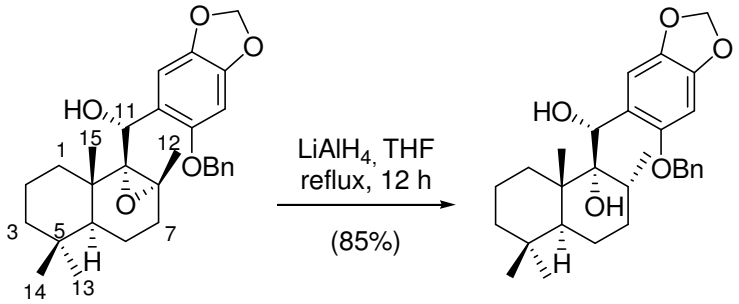
11*S*-(**14b**) 11*S*-(**15b**)

$LiAlH_4$ (100 mg, 2.62 mmol) was added to a stirred solution of epoxyalcohol **14b** (300 mg, 0.65 mmol) in dry THF (15 mL) cooled at 0 ºC and the cooling bath was removed. The reaction mixture was stirred at reflux for 15 min, at which time TLC showed no epoxyalcohol **14b**. Then, the reaction mixture was warmed to room temperature and quenched with acetone (0.2 mL). The solvent was removed under vacuum, and the mixture was extracted with ether (2 x 20 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to yield 276 mg, of **15b** (91%) was obtained.

(1R,2S,4aS,8aS)-1-((S)-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)(hydroxy)methyl)-2,5,5,8a-tetramethyl-decahydronaphthalen-1-ol (15b): $[\alpha]_D^{25}$ = + 3.6 (c 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.41-7.31 (m, 5H), 7.04 (s, 1H), 6.55 (s, 1H), 5.92 (s, 2H), 5.21 (br s, 1H), 5.03 (d, *J* = 11.5 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 3.23 (br s, 1H), 2.43 (br s, 1H), 2.15 (m, 1H), 1.55-1.19 (m, 10H), 1.17-1.05 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.84 (s, 3H), 0.83 (s, 3H), 0.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 150.6 (C), 147.2 (C), 142.1 (C), 136.2 (C), 128.6 (2 CH), 128.3 (CH), 128.0 (2 CH), 125.2 (C), 108.6 (CH), 101.3 (CH_2), 96.4 (CH),

81.4 (C), 72.4 (CH_2), 70.7 (CH), 46.3 (CH), 43.4 (C), 41.4 (CH_2), 34.0 (CH_3), 33.4 (C), 33.2 (CH_2), 32.8 (CH_2), 32.3 (CH), 22.2 (CH_3), 21.7 (CH_2), 18.8 (CH_2), 18.6 (CH_3), 16.3 (CH_3). IR (film): 3503, 1869, 1702, 1627, 1504, 1439, 1434, 1388, 1260, 1172, 1040, 937, 873, 803 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{38}O_5Na$ ($M+Na^+$) 489.2617, found: 485.2623.

11.- Reduction to sesquiterpenic diol 15a



11*R*-(**14a**) 11*R*-(**15a**)

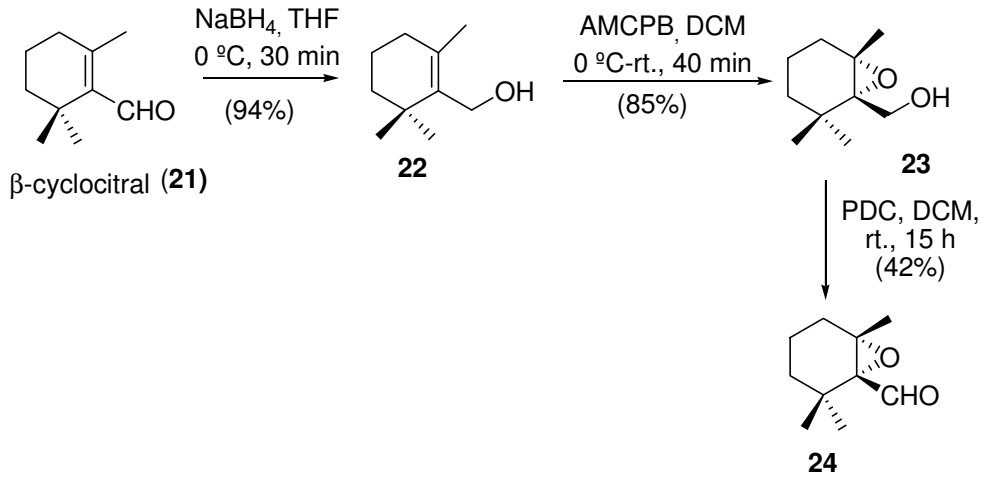
$LiAlH_4$ (150 mg, 3.94 mmol) was added to a stirred solution of epoxyalcohol **14a** (0.5 g, 1.08 mmol) in dry THF (12 mL) cooled at 0 ºC and the cooling bath was removed. The reaction mixture was stirred at reflux for 12 h, at which time TLC showed no compound **14a**. Then, the reaction mixture was warmed at room temperature and quenched with acetone (0.2 mL). Following the same work-up used for **15b**, 438 mg, of diol **15a** (87%) was obtained as a white solid.

(1R,2S,4aS,8aS)-1-((R)-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)(hydroxy)-methyl)-2,5,5,8a-tetramethyl-decahydronaphthalen-1-ol (15a): Mp. 168.5 ºC; $[\alpha]_D^{25}$ = - 19.9 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.34-7.26 (m, 5H), 7.10 (s, 1H), 6.47 (s, 1H), 5.84 (d, *J* = 1.4 Hz, 1H), 5.82 (d, *J* = 1.4 Hz, 1H), 5.21 (d, *J* = 4.9 Hz, 1H), 5.07 (d, *J* = 10.5 Hz, 1H), 4.81 (d, *J* = 10.5 Hz, 1H), 3.13 (br s, 1H), 2.19 (m, 1H), 1.99 (d, *J* = 4.9 Hz, 1H), 1.48-1.14 (m,10H), 0.99 (s, 3H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.74 (s, 3H), 0.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 150.6 (C), 146.7 (C), 141.6 (C), 135.6 (C), 128.9 (2 CH), 128.8 (2 CH),

128.7 (CH), 125.1 (C), 109.3 (CH), 101.3 (CH_2), 94.8 (CH), 81.2 (C), 72.0 (CH_2), 70.7 (CH), 46.4 (CH), 44.3 (C), 41.7 (CH_2), 34.1 (CH_3), 33.5 (C),33.3 (CH_2), 32.9 (CH_2), 32.2 (CH), 22.4 (CH_3), 22.2 (CH_2), 18.9 (CH_2), 18.4 (CH_3), 16.3 (CH_3); IR (film): 3479, 1627, 150, 1485, 1428, 1387, 1257, 1168, 1042, 982, 939, 814 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{38}O_5Na$ ($M+Na^+$) 489.2617, found: 485.2612.

3.2. REDUCTION STUDIES OF BENZYLIC HYDROXYL GROUP: SYNTHETIC APPROACH TO CORALLIDICTYAL D (1)

1.-Synthesis of epoxyaldehyde 24 from β-cyclocitral (21)



$NaBH_4$ (1.5 g, 39.4 mmol) was added to a solution of **21** (3.0 g, 19.7 mmol) in THF (20 mL) at 0 ºC, and the mixture was stirred at room temperature for 30 min. Then, H_2O (15 mL) was added to quench the excess of reagent and the organic solvent was removed under low pressure. The mixture was diluted and extracted

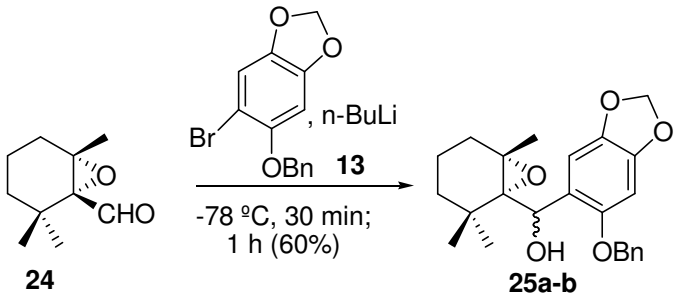
with ether (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to yield 2.85 g (94%) of **22**.

A solution of *m*-chloroperoxybenzoic acid (75%, 3.3 g, 14.3 mmol) in CH_2Cl_2 (20 mL), was added at 0 ºC to a stirred solution of **22** (2 g, 13.0 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred at room temperature for 140 min., at which time TLC indicated no starting material remaining. Then, the reaction mixture was quenched with saturated aqueous sodium sulfite (5 mL) and stirred at room temperature for an additional 15 min. The solvent was removed in vacuum and ether (40 mL) was added. The phases were shaken and separated, and the organic phase was washed with saturated aqueous sodium bicarbonate solution (4 x 15 mL) and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude mixture of epoxyalcohols **23** in 85 % yield (1.88 g).

Finally, to obtain **24,** to a stirred solution of **23** (1.75 g, 10.3 mmol) in dichloromethane (70 mL), PCC (3.5g, 16.2 mmol) was added and the mixture was stirred at room temperature under argon atmosphere for 15 h. Then it was filtered through a short silica gel column (eluted with ether) and the solvent was evaporated under reduced pressure affording 728 mg of epoxyaldehyde **24** (42%) as a colourless oil. This product was used immediately in the next reaction. All spectral data for the products of this sequence match those previously reported[140] .

(140) Vaz, B.; Dominguez, M.; Alvarez, R.; Lera, A. R. *Chemistry--A European Journal,* **2007**, *13*, 1273.

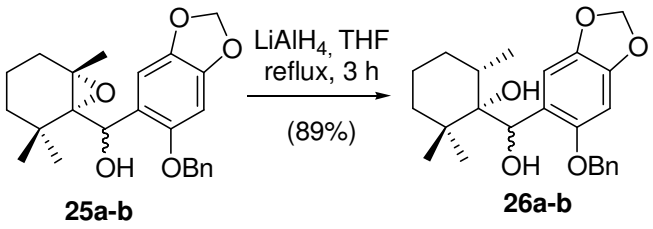
2.-Preparation of monoterpenic epoxyalcohols 25a-b by arillithium addition



Compounds **25a-b** were prepared from **24** (1.11 g, 6.61 mmol) and **13** (2.64 g, 8.6 mmol) according to the same manner as (**14a-b**). **25a-b** was obtained in 60% yield (1.57 g) as a mixture of isomers. The resultant mixture was purified by chromatography column on silica gel (20% ether/hexanes) and the mayor isomer characterized as follows.

(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)(2,2,6-trimethyl-7-oxa-bicyclo[4.1.0] heptan-1-yl)methanol (25a-b): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.46 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.72 (s, 1H), 6.60 (s, 1H), 5.93 (d, *J* = 1.4 Hz, 1H), 5.90 (d, *J* = 1.4 Hz, 1H), 5.48 (s, 1H), 5.19 (d, *J* = 12.2 Hz, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 2.86 (br s, -OH), 2.02 (dt, *J* = 10.4, 4.9 Hz, 1H), 1.84 (m, 1H), 1.58 (s, 3H), 1.55-1.44 (m, 2H);), 1.39-1.29 (m, 2H); 1.06 (s, 3H); 0.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 153.0 (C), 147.8 (C), 141.2 (C), 137.4 (C), 128.7 (2 x CH), 128.0 (CH), 127.4 (2 x CH), 122.2 (C), 108.3 (CH), 101.3 (CH_2), 97.5 (CH), 72.1 (CH_2), 70.6 (C), 65.8 (C), 64.7 (CH), 38.8 (CH_2), 33.9 (CH_2), 31.0 (CH), 27.2 (CH_3), 25.2 (CH_3), 22.3 (CH_3), 17.3 (CH_2).; IR (film): 3482, 1624, 1485, 1235, 1174 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{24}H_{28}O_5Na$ ($M+Na^+$) 419.1834, found: 419.1829.

3.- Preparation of monoterpenic diols 26a-b



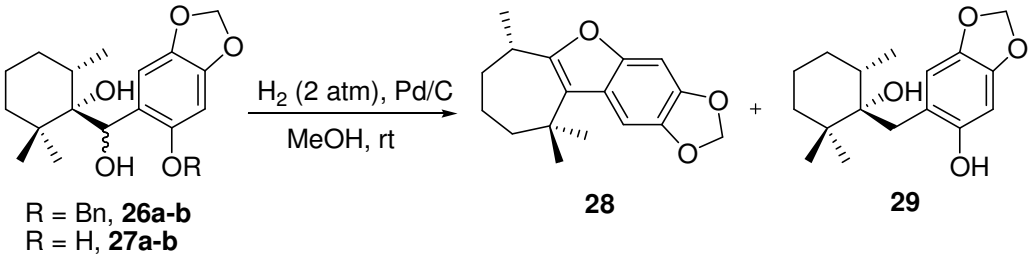
25a-b **26a-b**

Following the same procedure used in the preparation of sesquiterpene diol **15b**, **26a-b** was obtained as a mixture of isomers (1.7 :1) in 89% yield, starting from monoterpenic epoxyalcohols **25a-b** (1.5 g, 3.78 mmol).

Data for 1-((6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)(hydroxy)methyl)-2,2,6-trimethylcyclohexanol (26a): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.58 (dd, *J* = 15.7, 7.2 Hz, 5H), 7.32 (s, 1H), 6.77 (s, 1H), 6.00 (s, 1H), 5.98 (s, 1H), 5.43 (d, *J* = 5.5 Hz, 1H), 5.28 (d, *J* = 11.4 Hz, 1H), 5.26 (d, *J* = 11.4 Hz, 1H), 4.13 (d, *J* = 5.4 Hz, 1H), 3.32 (s, 1H), 2.41 (dt, *J* = 11.5, 6.0 Hz, 1H), 1.81-1.70 (m, 2H), 1.35-1.27 (m, 2H), 1.17 (s, 3H), 1.05-0.93 (m, 2H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.81 (s, 3H). IR (film): 3472, 3390, 1626, 1503, 1484, 1170, 1040, 936 cm^{-1} (Minor isomer).

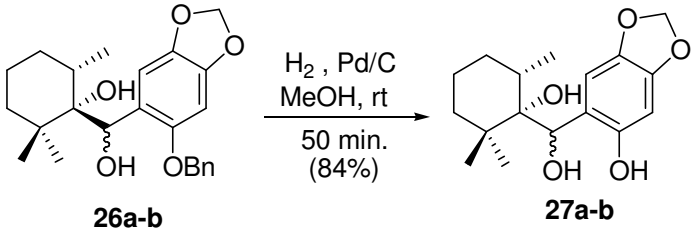
Data for 1-((6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)(hydroxy)methyl)-2,2,6-trimethylcyclohexanol (26b): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.47 (ddd, *J* = 22.9, 13.5, 7.3 Hz, 5H), 7.29 (s, 1H), 6.85 (s, 1H), 6.05 (s, 1H), 6.03 (s, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.16 (d, *J* = 11.6 Hz, 1H), 4.31 (d, *J* = 4.8 Hz, 1H), 3.85 (s, 1H), 2.32 (m, 1H), 1.59-1.45 (m, H), 1.44-1.35 (m, 3H), 1.10 (s, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.71 (s, 3H). (Major isomer). HRMS (FAB) *m/z*: calcd for $C_{24}H_{30}O_5Na$ ($M+Na^+$) 421.1991, found: 421.2002.

4.-Catalytic hydrogenation assays of monoterpenic diols 26a-b and dihydroxyphenols 27a-b



R = Bn, **26a-b**
R = H, **27a-b**

a) Catalytic hydrogenation of monoterpenic diol 26a-b. Preparation of 27a-b. (Assay 1)

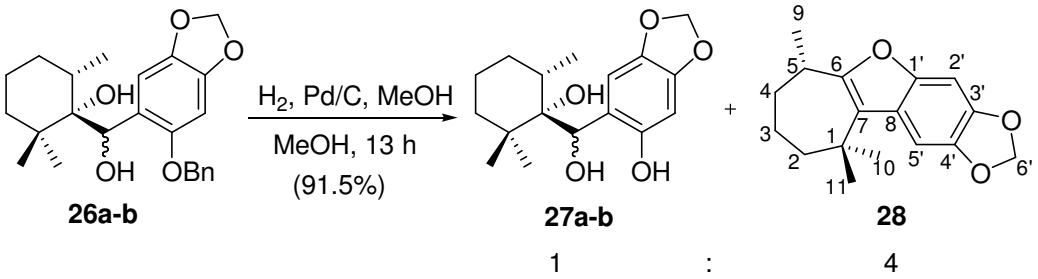


26a-b **27a-b**

To a solution of **26a-b** (500 mg, 1.25 mmol) in dry methanol (8 mL) was added 10 % Pd/C (100 mg) and the reaction mixture was stirred at room temperature under hydrogen atmosphere (2 atm.) for 50 min. Filtration and concentration gave 328 mg of **27a-b**, (84 %) as a colourless syrup.

6-(hydroxy(1-hydroxy-2,2,6-trimethylcyclohexyl)methyl)benzo[d][1,3]dioxol-5-ol (27): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.81 (br s, -OH), 6.92 (s, 1H), 6.33 (s, 1H), 5.80 (d, *J* = 4.5 Hz, 2H), 4.97 (s, 1H) , 3.75 (d, *J* = 4.0 Hz, 1H), 2.7 (m, 1H), 2.45 (m, 1H), 1.56-1.23 (m, 2H), 1.18 (s, 3H), 1.07 (s, 6H), 0.95 (d, *J* = 6 Hz, 3H). IR (film): 3433, 1635, 1479, 1376, 1040 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{24}O_5Na$ (M+Na$^+$) 331.1521, found: 331.1516.

b) Catalytic hydrogenation of monoterpenic diol 26a-b. Obtention of 28. (Assay 4)



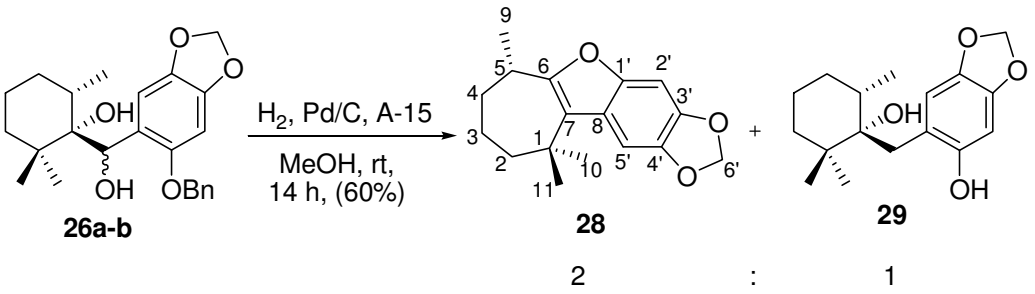
26a-b **27a-b** : **28**

1 : 4

To a solution of **26a-b** (250 mg, 0.63 mmol) in dry methanol (8 mL) was added 10 % Pd/C (67 mg) and the reaction mixture was stirred at room temperature under hydrogen atmosphere (2 atm) for 13 h. Filtration and concentration gave a mixture of **27a-b** and **28** (1:4). The crude product was purified on silica gel column (10% ether/ hexanes) affording 120 mg of **28** (70 %).

1,1,5-trimethyl-6,7-cyclohepta-3',4'-methylendioxy-benzofuran (28): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (s, 1H), 6.89 (s, 1H), 5.94 (d, *J* = 1.5 Hz, 2H), 3.19 (m, 1H) , 1.93-1.82 (m, 3H), 1.80-1.60 (m, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.36 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 156.6 (C), 148.7 (C), 144.6 (C), 143.4 (C), 122.3 (C), 122.1 (C), 101.2 (CH_2), 100.4(CH), 93.1 (CH), 43.2 (CH_2), 34.7 (CH_2), 34.5 (C), 32.9 (CH), 29.8 (CH_3), 28.9 (CH_3), 21.8 (CH_2), 19.4 (CH_3). IR (film): 1869, 1734, 1699, 1652, 1559, 1507, 1457, 1390, 1170, 1092, 1040, 840, 810 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{20}O_3Na$ ($M+Na^+$) 295.1310, found: 295.1305.

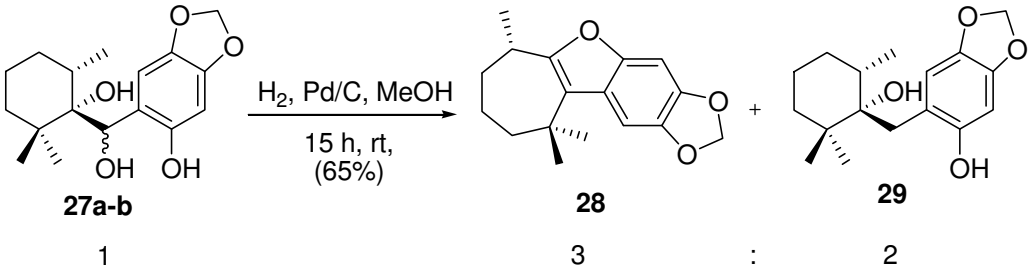
c) Catalytic hydrogenation of monoterpenic diol 26a-b in the presence of ion exchange Amberlyst 15. Obtention of 29. (Assay 5)



To a solution of **26a-b** (100 mg, 0.25 mmol) in dry methanol (5 mL) were added ion-exchange cationic resin Amberlyst 15 and 10 % Pd-C (30 mg) and the reaction mixture was stirred at room temperature under hydrogen atmosphere (2 atm) for 14 h. Filtration and concentration gave a mixture of **28** and **29** (2:1). The crude product was purified by chromatography column on silica gel, eluting with hexanes/ether (9:1) and affording **28** (27 mg, 40 %) and **29** (15 mg, 20%).

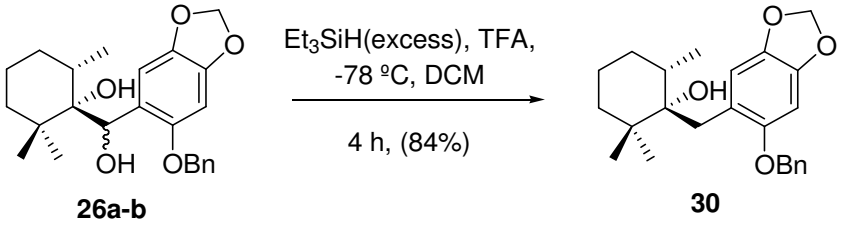
Data for 6-((-1-hydroxy-2,2,6-trimethylcyclohexyl)methyl)benzo[d] [1,3]dioxol-5-ol (29): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.0 (br s, -OH), 6.53 (s, 1H), 6.42 (s, 1H), 5.85 (s, 2H), 3.05 (d, *J* = 15.2 Hz, 1H), 2.63 (d, *J* = 15.2 Hz, 1H), 1.93 (m, 1H) , 1.65 (m, 1H), 1.54-1.39 (m, 4H), 1.34 (m, 1H), 1.10 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.2 (C), 147.2 (C), 140.9 (C), 118.1 (C), 111.3 (CH), 101.0 (CH_2), 99.5 (CH), 81.6 (C), 39.6 (CH_2), 39.2 (C), 38.9 (CH_2), 36.8 (CH), 31.8 (CH_2), 25.6 (CH_3), 23.5 (CH_3), 21.2 (CH_2), 16.6 (CH_3). IR (film): 3430, 1623, 1459, 1364, 1040 cm^{-1}.

d) Catalytic hydrogenation of monoterpenic dihydroxyphenol 27a-b (Assay 7)



Following the same procedure described for the catalytic hydrogenation of **26a-b** (Assay 1), changing the reaction time to 15 h; **27a-b** (200 mg, 0.65 mmol) resulted in a mixture of **28** and **29** (3:2), together with some starting material remaining. The crude was purified by column chromatography (10 % ether/hexanes) to yield 40 mg of **28** (22 %), 63 mg of **29** (33 %) and 18mg of starting material were recovered (9%).

5.-Cationic reduction of monoterpenic diol 26a-b with Et_3SiH/TFA system

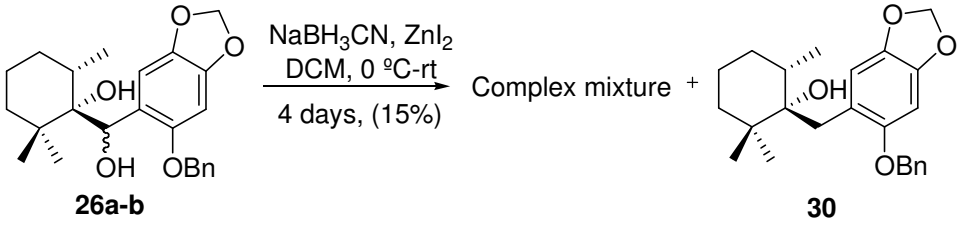


To a solution of **26a-b** (170 mg, 0.43 mmol) in DCM (8 mL) at -78 ºC triethylsilane (0.2 mL, 1.25 mmol) and trifluoroacetic acid (0.05 mL, 0.65 mmol) were added and the mixture was stirred at this temperature for 4 h, at which time. TLC showed no starting material. Then, sat. $NaHCO_3$ solution (1 mL) was slowly added to quench the reaction, it was allowed to warm to room temperature and the solvent was removed in vacuum. Ether (20 mL) was added to the crude product

and the organic phase was washed with sat. $NaHCO_3$ solution (3 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). It was then filtrated, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Purification by flash chromatography column on silica gel (10% ether/hexanes) gave 138 mg of **30** (84 %).

1-((6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)methyl)-2,2,6-trimethyl cyclohexanol (30): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.44 (br d, *J* = 7.1 Hz, 2H), 7.39-7.35 (m, 2H), 7.32 (m, 1H) , 6.80 (s, 1H), 6.55 (s, 1H), 5.89 (s, 2H), 4.99 (s, 2H), 3.47 (d, *J* = 14.3 Hz, 1H), 2.58 (d, *J* = 14.3 Hz, 1H), 2.18 (m, 1H), 1.75 (dt, *J* = 12.5, 4.6 Hz, 1H), 1.55-1.32 (s, 5H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.6 (C), 146.0 (C), 141.5 (C), 137.2, (C), 128.6 (2 x CH), 128.0 (CH), 127.8 (2 X CH), 121.6 (C), 109.6 (CH), 101.1 (CH_2), 96.5 (CH), 85.0 (C), 72.0 (CH_2), 40.1 (C), 39.4 (CH_2), 33.3 (CH), 32.7 (CH_2), 31.5 (CH_2), 26.7 (CH_3), 24.0 (CH_3), 21.7 (CH_2), 18.2 (CH_3). IR (film): 3450, 1631, 1782, 1346, 1175, 1037 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{24}H_{30}O_4Na$ ($M+Na^+$) 405.2042, found: 405.2051.

6.-Cationic reduction of monoterpenic diol 26a-b with $NaBH_3CN/ZnI_2$ system

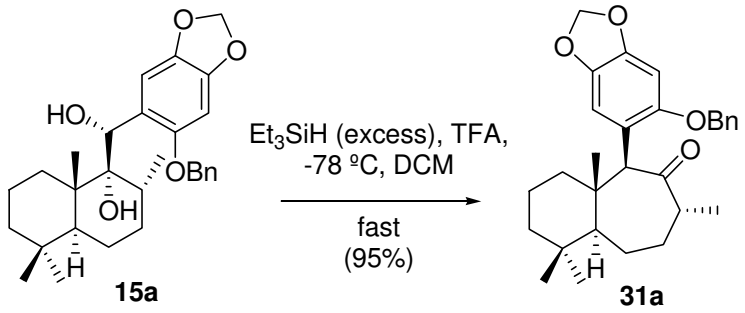


26a-b **30**

ZnI_2 (118 mg, 0.36 mmol) was added at 0°C to a solution of **26a-b** (112 mg, 0.28 mmol) and $NaBH_3CN$ (222 mg, 3.36 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 96 h at room temperature. It was then filtered through silica gel column and washed with ether (15 mL). The combined filtrate was evaporated to afford a complex mixture of at least four products. The crude was purified by flash

chromatography column on silica gel (20% ether/hexane) to give 16 mg (15%) of **30**.

7.-Pinacol rearrangement of sesquiterpenic diol 15a by treatment with Et_3SiH/TFA system

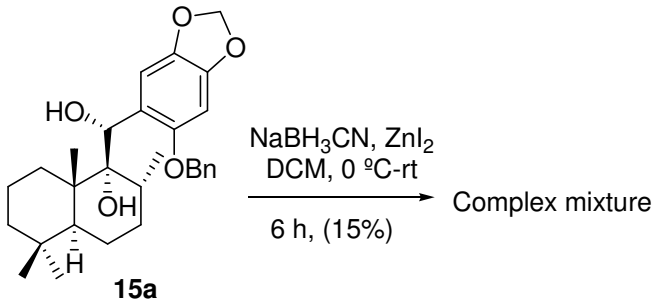


The same procedure described for the reduction of **26a-b** with this system was followed. Starting from **15a** (75 mg, 0.16 mmol) and adding Et_3SiH (0.1 mL, 0.64 equiv) and TFA. (30 μL, 0.40 mmol). Instantaneously after the addition, the reaction mixture abruptly changed colour to dark orange. TLC showed no starting material remaining. Purification by flash chromatography column on silica gel (10% ether/hexanes) afforded **31a** (50 mg, 70 %).

(4aS,5S,7R,9aS)-5-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)-1,1,4a,7-tetramethyl-decahydrobenzo[7]annulen-6-one (31a): $[\alpha]_D^{25}$ = + 2.0 (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.46 (s, 1H), 7.34-7.24 (m, 5H), 6.49 (s, 1H), 5.84 (d, *J* = 1.4 Hz, 1H), 5.80 (d, *J* = 1.4 Hz, 1H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.73 (s, 1H), 2.41 (m, 1H), 2.05 (m, 1H), 1.68 – 0.86 (m, 6H), 1.28 (br d, *J* = 13.1 Hz, 1H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.80 (s, 3H), 0.78 (s, 3H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 215.4 (C), 152.3 (C), 146.6 (C), 141.0 (C), 137.4 (C), 128.7 (2 CH), 128.0 (CH), 127.2 (2 CH), 116.6 (C), 112.6 (CH), 101.1 (CH_2), 95.9 (CH), 72.1 (CH_2), 56.0 (CH), 54.6 (CH), 49.4 (CH), 41.3 (C), 41.1 (CH_2), 37.7 (CH_2), 35.2 (C), 33.8 (CH_2), 32.9 (CH_3), 22.5 (CH_2), 21.7 (CH_3), 20.1 (CH_3),

19.0 (CH_2), 16.1 (CH_3). IR (film): 1706, 1625, 1505, 1482, 1428, 1374, 1327, 1241, 1173, 1040, 938, 882, 818, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{36}O_4Na$ ($M+Na^+$) 471.2511, found: 471.2517.

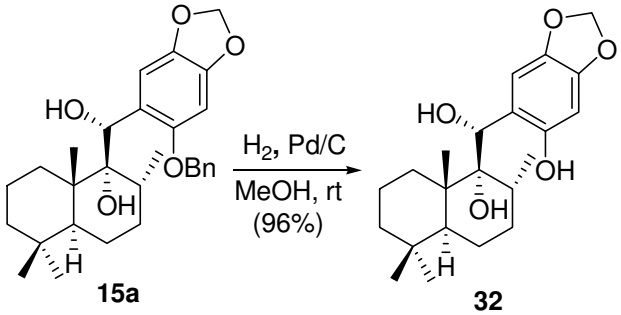
8.-Treatment of sesquiterpenic diol 15a with $NaBH_3CN/ZnI_2$ system



15a

The same procedure described for the reduction of **26a-b** with this system was followed. Starting from 70 mg of **15a** (0.15 mmol) a complex unresolvable mixture was afforded.

9.-Catalytic hydrogenation of sesquiterpenic diol 15a

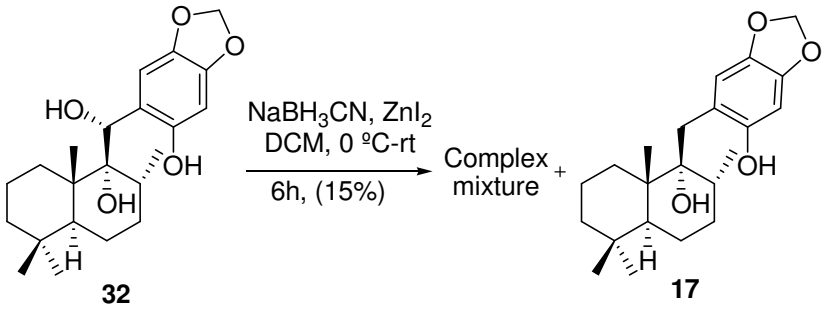


15a **32**

To a solution of **15a** (173 mg, 0.37 mmol) in dry methanol (8 mL) was added 10 % Pd/C (30 mg) and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 3 h. Filtration and concentration gave 134 mg of **32**, (96 %) as a colourless syrup.

6-((R)-hydroxy((1R,2R,8aS)-1-hydroxy-2,5,5,8a-tetramethyl-decahydronaphthalen-1-yl)methyl)benzo[d][1,3]dioxol-5-ol (32): $[\alpha]_D^{25}$ = - 6.9 (c 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.83 (s, 1H), 6.37 (s, 1H), 5.87 (br s, 2H), 5.23 (s, 1H), 3.47 (br s, 1H), 2.42 (m, 1H), 1.79-1.13 (m, 10H), 0.88 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H), 0.85 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 150.1 (C), 147.2 (C), 141.2 (C), 120.8 (C),107.8 (CH), 101.1 (CH_2), 99.9 (CH), 82.1 (C), 72.8 (CH), 47.2 (CH), 44.0 (C), 41.7 (CH_2), 34.2 (CH_3), 33.6 (C), 33.0 (CH_2), 32.7 (CH_2), 31.9 (CH), 22.4 (CH_3), 21.9 (CH_2), 18.8 (CH_2), 17.7 (CH_3), 16.1 (CH_3). IR (film): 3405, 1698, 1635, 1503, 1485, 1389, 1263, 1236, 1167, 1041, 984, 940, 798 cm-^{1}. HRMS (FAB) m/z: calcd for $C_{22}H_{32}O_5Na$ (M^+Na^+) 399.2147, found: 399.2153.

10.-Reduction of sesquiterpenic dihydroxyphenol 32 with $NaBH_3CN/ZnI_2$ system



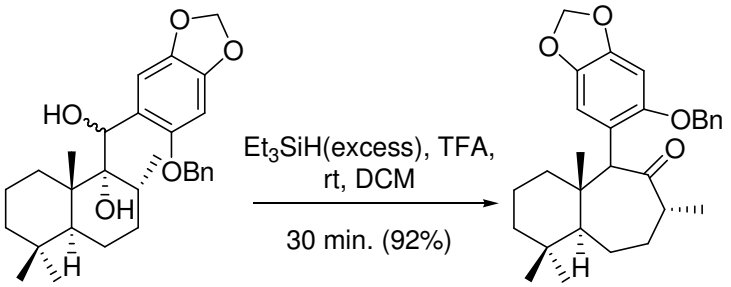
32 **17**

The same procedure described for the preparation of **30** using this system was followed. Starting from **32** (310 mg, 0.79 mmol), a complex mixture was afforded. After purification of the crude on silica gel column, **17** was isolated (43 mg, 15%).

6-(((1R,2R,4aS,8aS)-1-hydroxy-2,5,5,8a-tetramethyl-decahydronaphthalen-1-yl)methyl)benzo[d][1,3]dioxol-5-ol (17): $[\alpha]_D^{25}$ = + 9.8 (c 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.86 (br s, 1H), 6.50 (s, 1H), 6.42 (br s, 1H), 5.88 (br s, 1H), 5.86 (s, 1H), 2.95 (d, *J* = 15 Hz, 1H), 2.78 (d, *J* = 15 Hz, 1H), 2.38 (brs, 1H), 2.18

(m, 1H), 2.00 (m, 1H), 1.68-1.15 (m, 10H), 1.13 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 3H), 0.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.2 (C), 147.1 (C), 140.8 (C), 118.4 (C), 111.3 (CH) , 100.9 (CH_2), 99.4 (CH), 82.8 (C), 47.9 (CH), 44.3 (C), 41.6 (CH_2), 34.1 (CH_3), 33.8 (C), 33.0 (CH_2), 32.5 (CH_2), 29.8 (CH_2), 22.1 (CH_3), 21.7 (CH_2), 18.8 (CH_2), 17.0 (CH_3), 16.8 (CH_3). IR (film): 3422, 1655, 1627, 1481, 1455, 1384, 1261, 1183, 1093, 1040, 939, 835, 802 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{32}O_4Na$ ($M+Na^+$) 383.2198, found: 383.2192.

11.-Pinacol rearrangement of sesquiterpenic diol 15b with Et_3SiH/TFA system



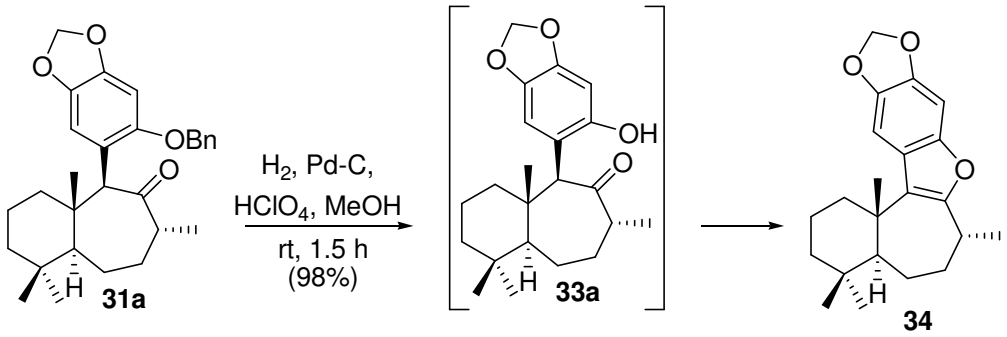
The same procedure described for the reduction of **26a-b** with this system was followed. Starting from 75 mg of **15b** (0.16 mmol) and adding Et_3SiH (0.1 mL, 0.64 equiv) and TFA (30 μL, 0.40 mmol). 30 minutes after the addition, TLC showed no starting material remaining. Purification by flash chromatography column on silica gel (10% ether/hexanes) afforded **31b** (66 mg, 92 %).

(4aS,5R,7R)-5-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)-1,1,4a,7-tetramethyl-decahydrobenzo[7]annulen-6-one (31b): $[\alpha]_D^{25}$ = - 84.0 (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.39 (br d, *J* = 7.5 Hz, 2H), 7.34 (dd, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.19 (s, 1H), 6.48 (s, 1H), 5.84 (d, *J* = 1.0 Hz, 1H), 5.81 (d, *J* = 1.0 Hz, 1H), 4.93 (br s, 2H), 4.74 (br s, 1H), 2.34 (m, 1H), 1.96-1.82 (m, 2H), 1.51-1.01 (m, 9H), 0.92 (s, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 3H), 0.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 216.1 (C), 151.5 (C), 146.2 (C), 141.2 (C),

137.5 (C), 128.6 (2 CH), 128.0 (CH), 127.2 (2 CH), 119.7 (C), 111.4 (CH), 101.1 (CH_2), 95.5 (CH), 71.8 (CH_2), 62.5 (CH), 53.3 (CH), 49.8 (CH), 42.2 (CH_2), 41.3 (C), 38.3 (CH_2), 35.3 (C), 34.2 (CH), 34.2 (CH), 34.0 (CH_2), 24.6 (CH_2), 21.8 (CH_3), 19.6 (CH_3), 19.2 (CH_2), 17.5 (CH_3). IR (film): 1702, 1623, 1505, 1482, 1430, 1388, 1328, 1236, 1172, 1040, 938, 736 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{36}O_4Na$ ($M+Na^+$) 471.2511, found: 471.2519.

3.3. SYNTHESIS OF (+)-LIPHAGAL STARTING FROM SESQUITERPENIC DIOL 15

1.-Acidic hydrogenation of ketone 31a

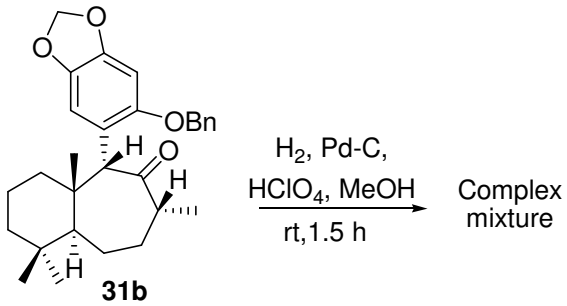


To a solution of **31a** (190 mg, 0.42 mmol) in dry methanol (10 mL), perchloric acid (0.2 mL) and 10 % Pd/C (60 mg) were added and the reaction mixture was stirred at room temperature under hydrogen atmosphere (2 atm) for 90 min, at which time TLC showed no remaining starting material. Then the solvent was removed under vacuum, and ether/water (35/10 mL) was added to the resulting crude product. The phases were shaken and separated, and the organic phase was

then washed with water (3 x 10 mL) and (2 x10 mL) brine dried. Finally, it was filtrated and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded 140 mg of **34** (98 %) as a colourless syrup.

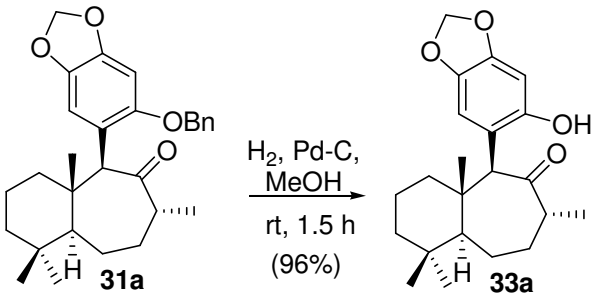
18-nor-15,16-di-O-methylenliphagal (34): $[\alpha]_D^{25}$ = + 4.3 (c 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13 (s, 1H), 6.85 (s, 1H), 5.93 (s, 2H), 3.18 (m, 1H), 2.56 (br d, *J* = 14.1 Hz, 1H), 2.15 (m, 1H), 1.82 (m, 1H), 1.71 (qt, *J* = 13.7, 3.5 Hz, 1H), 1.69 (m, 1H), 1.64 - 1.41 (m, 8H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.36 (s, 3H), 1.25 (ddd, *J* = 13.3, 13.3, 3.5 Hz, 1H), 0.99 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.2 (C), 148.8 (C), 144.5 (C), 143.2 (C), 125.7 (C), 121.5 (C), 101.4 (CH), 101.0 (CH_2), 92.9 (CH), 53.7 (CH), 42.1 (CH_2), 40.2 (CH_2), 39.6 (C), 35.2 (CH_2), 34.9 (C), 33.7 (CH), 33.4 (CH_3), 24.2 (CH_2), 22.13 (CH_3), 22.08 (CH_3), 20.1 (CH_3), 19.0 (CH_3). IR (film): 1716, 1463, 1380, 1312, 1161, 1040, 947 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{28}O_3Na$ ($M+Na^+$) 363.1936, found: 363.1931.

2.-Acidic hydrogenation of ketone 31b



The procedure previously depicted for **31a** was followed over **31b** (290 mg, 0.65 mmol). A complex unresolvable mixture was afforded, together with trace amount of compound **34**.

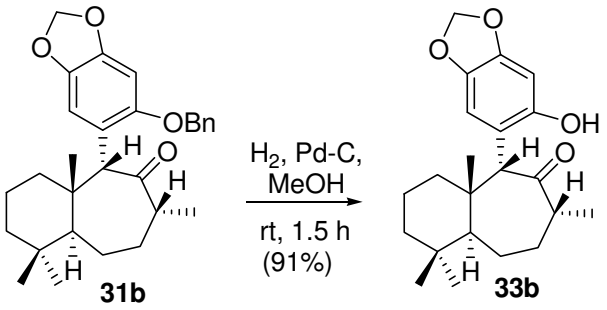
3.-Catalytic hydrogenation of ketone 31a



The standard procedure for hydrogenation followed for **15a** (see section 3.2-9 of experimental section) was followed. Starting from **31a** (138 mg, 0.31 mmol), 102 mg of **33a**, (96 %) was afforded as a colourless syrup.

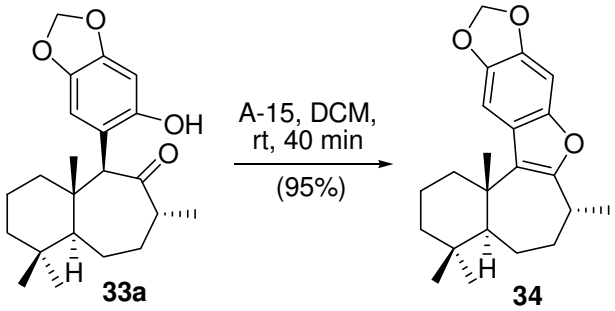
(4aS,5S,7R,9aS)-5-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-1,1,4a,7-tetramethyl-decahydrobenzo[7]annulen-6-one (33a): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.39 (br s, -OH), 6.46 (s, 1H), 6.37 (br s, 1H), 5.88 (d, *J* = 1.3 Hz, 1H), 5.87 (d, *J* = 1.3 Hz, 1H), 3.82 (br s, 1H), 2.81 (m, 1H), 2.24 (m, 1H), 1.76 (m, 1H), 1.72-1.62 (m, 2H), 1.47-1.43 (m, 2H), 1.39 (m, 1H), 1.37-1.33 (m, 2H), 1.16-1.09 (m, 2H), 1.04 (*J* = 6.3 Hz, 3H), 0.96 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 222.2 (C), 152.8 (C), 148.1 (C), 140.5 (C), 113.3 (CH), 101.3 (CH_2), 100.4 (C), 55.3 (CH), 49.7 (CH), 49.3 (CH), 43.3 (C), 41.4 (CH_2), 37.5 (CH_2), 35.4 (C), 33.7 (CH_2), 33.1 (CH), 27.1 (CH_3), 22.5 (CH_2), 22.1 (CH_3), 19.6 (CH_3), 19.1 (CH_2), 16.2 (CH_3). IR (film): 3406, 3183, 1687, 1504, 1484, 1173, 1040 cm^{-1}

4.-Catalytic hydrogenation of ketone 31b



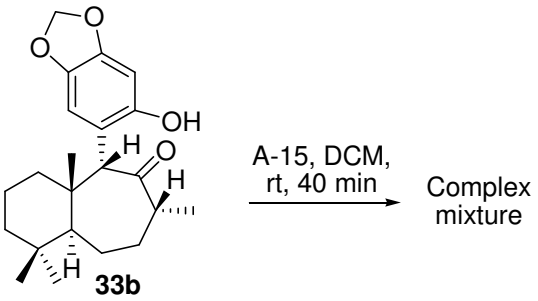
The same procedure followed for **31a** starting from 290 mg of **31b** (0.65 mmol), afforded ***(4aS,5R,7R,9aS)-5-(6-hydroxybenzo[d][1,3]dioxol-5-yl)-1,1,4a,7-tetra methyl-decahydrobenzo[7]annulen-6-one (33b)*** (201 mg, 91 %).

5.-Treatment of phenol 33a with Amberlyst 15: Synthesis of 34



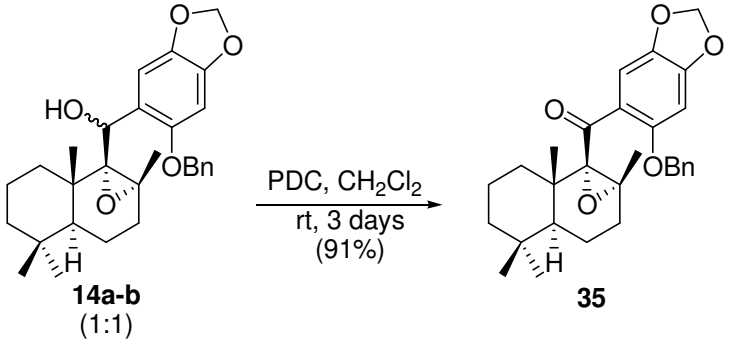
To a solution of phenol **33a** (190 mg, 0.53 mmol) in CH_2Cl_2 (10 mL) was added Amberlyst 15 ion-exchange (0.4g), and the reaction mixture was stirred for 40 min, at which time TLC showed no starting material. Then the mixture was filtered and the solvent was removed under vacuum to yield 171 mg of benzofuran **34** (95%) as a colourless syrup.

6.-Treatment of phenol 33b with Amberlyst 15



Following the procedure described above for **33a** and starting from **33b** (210 mg, 0.59 mmol), a complex mixture was afforded. No **34** was observed.

7.-Oxidation of sesquiterpenic epoxyalcohols 14a-b

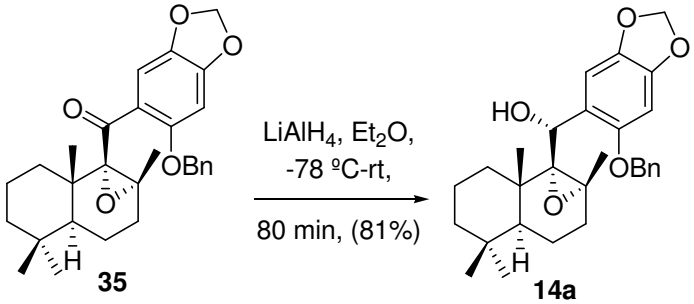


Pyridinium dichromate (PDC; 2.4 g, 6.47 mmol) was added to a stirred solution of epoxyalcohols **14a-b** (2 g, 4.31 mmol) in dry CH_2Cl_2 (80 mL), and the mixture was stirred at room temperature under argon atmosphere for 3 days, at which time TLC showed no remaining starting material. Then the reaction was worked up by the addition of ether (40 mL), and the resulting mixture was filtered through a silica gel pad and washed with ether (2 x 20 mL). The filtrate was washed with 2N HCl (2 x 10 mL), water and brine, dried over anhydrous Na_2SO_4, filtrated and the solvent was evaporated to give a

crude product which was chromatographed on silica gel column (15% ether/hexanes) to give 1.81 g of pure epoxyketone **35** (91%) as a colourless syrup.

6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)((1aR,7aS,7bS)-1a,4,4,7a-tetramethyl-decahydronaphtho[2,1-b]oxiren-7b-yl) methanone (35): $[\alpha]_D^{25}$ = + 34.9 (c 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.38 (br d, *J* = 7.5 Hz, 2H), 7.35 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 6.49 (s, 1H), 5.90 (d, *J* = 1.3 Hz, 1H), 5.88 (d, *J* = 1.3 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 1.83 (dt, *J* =15.7, 9.4 Hz, 1H), 1.85 (br dd, *J* = 15.7, 8.2 Hz, 1H), 1.53 (dd, *J* = 12.6, 3.5 Hz, 1H), 1.50 - 1.23 (m, 7H), 1.25 (s, 3H), 1.09 (s, 3H), (ddd, *J* = 13.1, 13.1, 3.1 Hz, 1H), 0.766 (s, 3H), 0.762 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 197.6 (C), 155.0 (C), 151.4 (C), 141.0 (C), 136.7 (C), 128.7 (2 CH), 128.0 (CH), 127.4 (2 CH), 121.8 (C), 110.9 (CH), 102.0 (CH_2), 96.8 (CH), 71.9 (CH_2), 63.5 (C), 42.0 (CH), 41.5 (CH_2), 37.9 (C), 36.7 (CH_2), 33.9 (CH_3), 33.1 (C), 28.3 (CH_2), 27.1 (C), 22.8 (CH_3), 21.7 (CH_3), 18.5 (CH_2), 17.6 (CH_3), 17.2 (CH_2). IR (film): 1672, 1616, 1505, 1483, 1425, 1389, 1353, 1244, 1174, 1041, 936, 826, 750 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{34}O_5Na$ ($M+Na^+$) 485.2304, found: 485.2300.

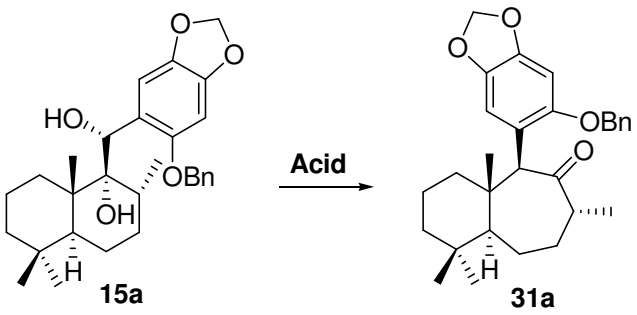
8.-Synthesis of sesquiterpenic epoxyalcohol 14a from epoxyketone 35



$LiAlH_4$ (200 mg, 5.26 mmol) was added to a stirred solution of epoxyketone **35** (1.5 g, 3.25 mmol) in dry Et_2O (20 mL) cooled at -78 ºC and the reaction mixture

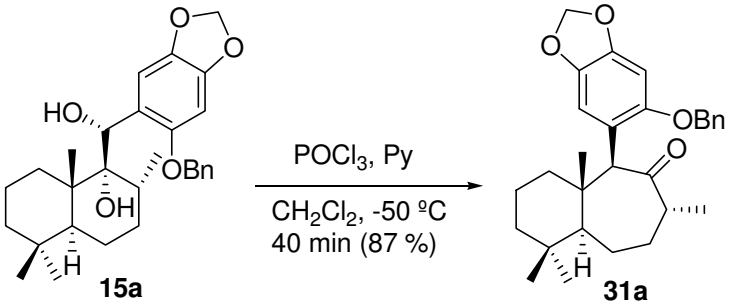
was slowly warmed at room temperature and was further stirred for 80 min, at which time TLC showed no starting material. Then, acetone (0.5 mL) was slowly added at 0ºC and Et_2O (30 mL) was added, and the organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 1.22 g of the epoxyalcohols **14a-b** (81%) (ratio 5:1, based on ^{1}H NMR spectrum data). Crystallisation gave pure alcohol **14a**.

9.-Acidic rearrangement of sesquiterpenic diol 15a



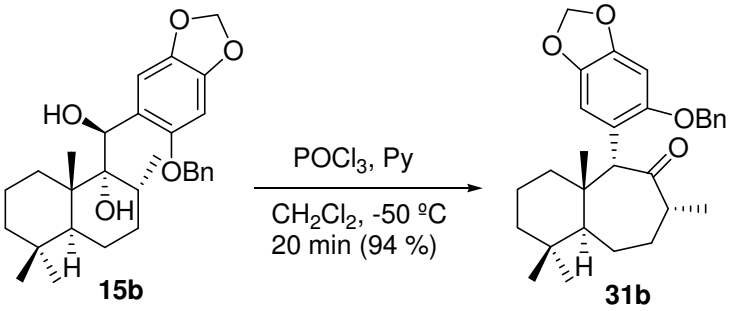
Sesquiterpenic diol **15a** was subjected to acidic rearrangement following the general procedure (see section of general procedures). Ketone **31a** was obtained. Specific variables are depicted in table 2 (results and discussion).

10.-Pinacol rearrangement of sesquiterpenic diol 15a with $POCl_3$



Dry phosphorus oxychloride (0.3 mL, 3.22 mmol) was added to a solution of diol **15a** (630 mg, 1.35 mmol) and freshly distilled pyridine (3 mL), in dry CH_2Cl_2 (15 mL) at -50 ºC and the reaction mixture was stirred at this temperature for 40 min, at which time TLC showed no **15a**. The reaction mixture was poured into ice and extracted with ether (2 x 20 mL). The combined organic phases were washed with 2N HCl (3 x 10 mL), water and brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated to give a crude product which was purified by flash chromatography column on silica gel (8 % ether/hexanes) furnishing 527 mg of ketone **31a** (87%) as a colourless syrup.

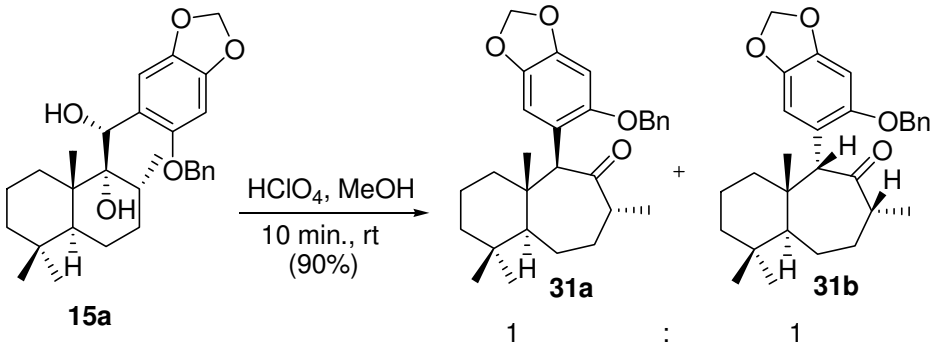
11.-Pinacol rearrangement of sesquiterpenic diol 15b with $POCl_3$



Dry phosphorus oxychloride (0.2 mL, 2.14 mmol) was added to a solution of diol **15b** (210 mg, 0.45 mmol) and freshly distilled pyridine (3 mL), in dry CH_2Cl_2 (15

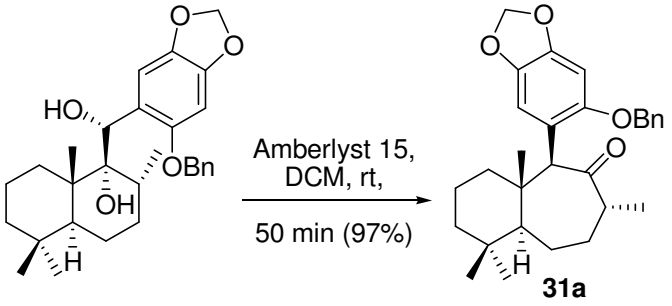
mL) at -50 ºC and the reaction mixture was stirred at this temperature for 20 min, at which time TLC showed no **15b**. Following the same work-up used for **31a**, 190 mg, of **31b** (94%) was obtained as a colourless syrup.

12.-Treatment of sesquiterpenic diol 15a with perchloric acid



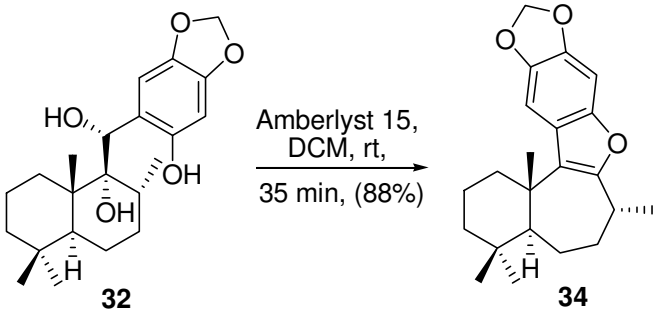
To a solution of diol **15a** (60 mg, 0.13 mmol) in methanol (3 mL), perchloric acid (1M, 0.2 mL) was added. The reaction mixture was stirred for 10 min. at room temperature and the reaction was monitored by TLC. Then, the solvent was removed under reduced pressure and ether/water (30/10 mL) were added to the resulting crude product. The phases were shaken and separated and the organic layer was washed with water (2 x 15 mL) and brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent afforded an isomeric mixture of ketones **31a-31b** (1:1), (53 mg, 90 %).

13.-Pinacol rearrangement of sesquiterpenic diol 15a with Amberlyst 15



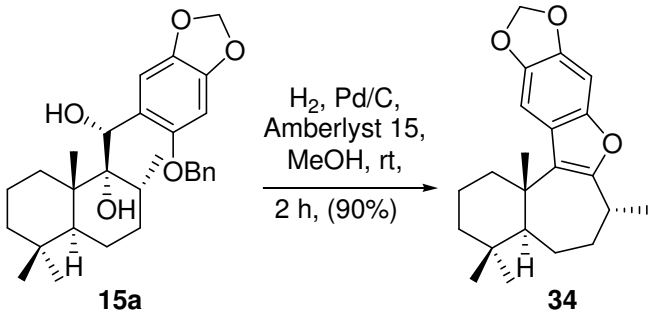
To a solution of diol **15a** (130 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) was added Amberlyst 15 ion-exchange resin (0.4g), and the reaction mixture was stirred at room temperature for 50 min, at which time TLC showed no starting material. Then, the mixture was filtered and the solvent was removed under vacuum to yield 122 mg of ketone **31a** (97%) as a colourless syrup.

14.-Treatment of sesquiterpenic dihydroxyphenol 32 with Amberlyst 15: Pinacol rearrangement and cyclization towards 34



The same procedure described above for sesquiterpenic diol **15a** was applied to **32** (80 mg, 0.21 mmol) After 35 min. the reaction yielded 63 mg of benzofuran **34** (88%) as a colourless syrup.

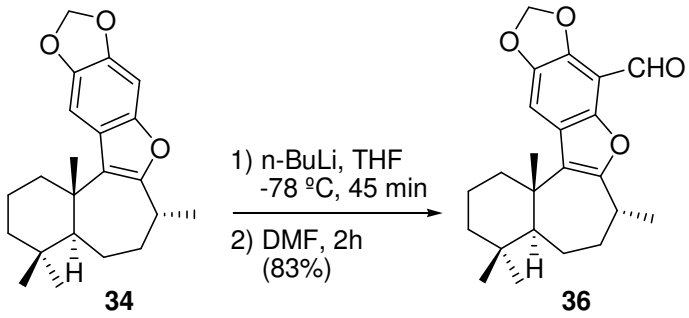
15.-Catalytic hydrogenation of sesquiterpenic diol 15a in the presence of Amberlyst 15



15a **34**

To a solution of **15a** (210 mg, 0.468 mmol) in dry methanol (10 mL) were added Amberlyst 15 ion-exchange (0.3 g) and 10 % Pd/C (70 mg) and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 2 h. Filtration and concentration gave 143 mg of **34**, (90 %) as a yellow oil.

16.-Formylation of benzofuran 34 with DMF



34 **36**

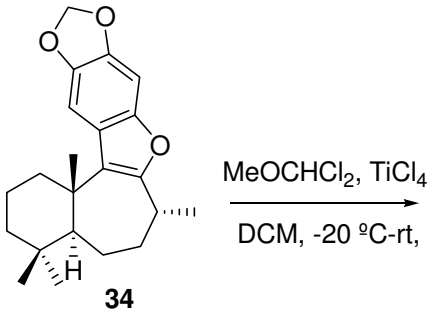
To a solution of **34** (430 mg, 1.26 mmol) in THF (25 mL) were added *n*-butyllithium (2.4 M, 1.5 mL, 3.6 mmol) at -78 ºC under an argon atmosphere, and the reaction mixture was stirred at this temperature for 45 min. Freshly distilled DMF (0.25 mL, 3.87 mmol) was then added and the mixture was stirred for a further 2 h, at which time TLC showed no starting material. Then the mixture was

quenched with water (0.3 mL) and the solvent was removed, and ether – water (40 - 10 mL) were added to the crude product. The phases were shaken and separated, and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product was directly purified by flash chromatography column (20% ether /hexanes) to give 375 g of aldehyde **36** (83 %) as a white solid.

15,16-Di-O-methyleneliphagal (36): $[\alpha]_D^{25}$ = + 6.0 (c 0.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 10.47 (s, 1H), 7.36 (s, 1H), 6.11 (s, 2H), 3.26 (m, 1H), 2.50 (br d, *J* = 11.6 Hz, 1H), 2.18 (m, 1H), 1.85 (m, 1H), 1.70 (m, 1H), 1.64-1.45 (m, 5H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.35 (s, 3H), 1.27 (m, 1H), 0.98 (s, 3H), 0.95 (s, 3H), 0.86 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 185.9 (CHO), 157.6 (C), 148.1 (C), 145.0 (C), 144.1 (C), 125.6 (C), 122.2 (C), 107.5 (CH), 106.1 (C), 102.9 (CH_2), 53.7 (CH), 42.0 (CH_2), 40.3 (CH_2), 39.6 (C), 35.1 (CH_2), 34.9 (C), 33.8 (CH_3)*, 33.4 (CH)*, 24.2 (CH_2), 22.1 (CH_3), 20.3 (CH_3), 18.9 (CH_3). IR (film): 1694, 1626, 1464, 1366, 1318, 1292, 1194, 1102, 1058, 927, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{28}O_4Na$ ($M+Na^+$) 391.1885, found: 391.1891.

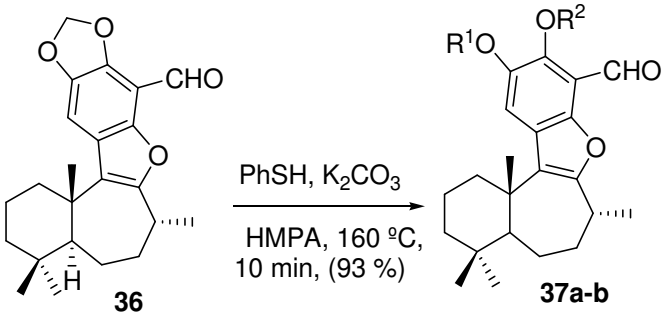
* interchangeable signals

17.-Rieche formylation of 34



To a solution of **34** (80 mg, 0.24 mmol) and dichloromethyl methyl ether (0.2 mL, 2.17 mmol) in dry DCM (15 mL) at -20°C was added $TiCl_4$ (0.2 mL, 1.83 mmol) dropwise with stirring. After an additional 1 h at this temperature, no reaction was observed. Thus, temperature was gently allowed to increase to room temperature. After 4 hours at room temperature the starting material was still inaltered.

18.-Methylenedioxy group basic cleavage*: Formation of 37a-b



To a solution of **36** (0.31 g, 0.84 mmol) in hexamethylphosphoramide (10 mL) was added potassium carbonate (140 mg, 1.01 mmol) and thiophenol (112 mg, 1.01 mmol) and the reaction mixture was heated at 160 ºC for 10 min, at which

* Optimization of this transformation: steps 18 and 19 can be carried out in a single reaction.

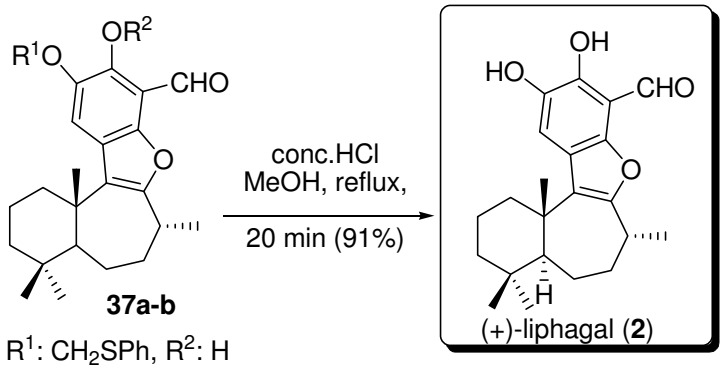
time TLC indicated no **36** remaining. The reaction mixture was allowed to warm to room temperature and then extracted with ether (2 x 20 mL), the organic phase was washed with water (5 x 10 mL) and brine, dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography column (5% ether/hexanes) to yield a mixture of **37a-b** ratio (6:1)** (457 mg, 93%) as a yellow oil.

16-O-phenylthiomethylliphagal (37a): $[\alpha]_D^{25}$ = + 61.9 (c 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.30 (s, 1H), 10.44 (s, 1H), 7.53 (s, 1H), 7.51 (br d, *J* = 8.0 Hz, 2H), 7.30 (br t, *J* = 7.5 Hz, 2H), 7.24 (br d, *J* = 7.5 Hz, 1H), 5.63 (s, 2H), 3.21 (m, 1H), 2.39 (br d, *J* = 11.8 Hz, 1H), 2.18 (m, 1H), 1.91-1.20 (m, 9H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.31 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 192.4 (CHO), 156.8 (C), 151.0 (C), 150.7 (C), 139.0 (C), 135.1 (C), 130.2 (2 CH), 129.0 (2 CH), 126.4 (CH),125.6 (C), 123.9 (CH), 120.1 (C), 107.1 (C), 76.2 (CH_2), 53.9 (CH), 42.0 (CH_2), 40.4 (CH_2), 39.5 (C), 35.3 (C), 34.9 (CH_2), 33.8 (CH) #, 33.4 (CH_3)#, 24.3 (CH_2), 22.1 (CH_3), 21.7 (CH_3), 20.5 (CH_3), 18.9 (CH_2). IR (film): 3059, 1665, 1584, 1447, 1390, 1300, 1205, 1117, 1028, 962, 924 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{34}O_4SNa$ ($M+Na^+$) 501.2075, found: 501.2081.

** Based in ^{1}H NMR data.

interchangeable signals

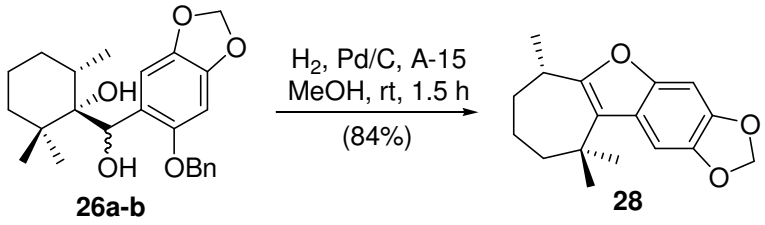
19.-Acidic hydrolysis. Synthesis of (+)-liphagal (2)



Conc. hydrochloric acid (2mL) was added to a stirred solution of **37a-b** (230 mg, 0.48 mmol) in MeOH (8 mL), and the yellow reaction mixture was heated at 80 ºC for 20 min, at which time TLC showed no starting material remaining. Then, the solvent was removed in vaccum and ether -water (30: 10 mL) was added. The phases were shaken and separated and the organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography column (7 % ether/hexanes) to yield 155 mg of (+)-liphagal (**2**) (91%) as a yellow oil.

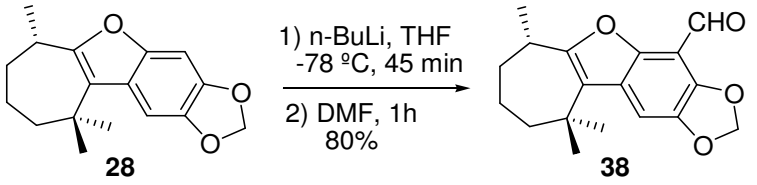
(+)-liphagal (2): $[\alpha]_D^{25}$ = + 33.6 (c 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.23 (s, 1H), 10.45 (s, 1H), 7.55 (s, 1H), 3.22 (m, 1H), 2.54 (m, 1H), 2.17 (m, 1H), 1.87 (m, 1H), 1.72 (m, 1H), 1.65-1.44 (m, 6H), 1.43 (d, *J* = 7 Hz, 3H), 1.35 (s, 3H), 1.27 (m, 1H), 0.99 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 192.5 (CHO), 156.6 (C), 148.1 (C), 145.4 (C), 139.6 (C), 125.6 (C), 120.4 (C), 116.1 (CH), 106.4 (C), 53.9 (CH), 42.0 (CH_2), 40.4 (CH_2), 39.6 (C), 35.3 (C), 34.9 (CH_2), 33.6 (CH_3), 33.4 (CH_3), 24.3 (CH_2), 22.1 (CH_3), 21.7 (CH_3), 20.3 (CH_3), 18.9 (CH_2). IR (film): 3559, 3452, 1654, 1456, 1391, 1329, 1301, 1193, 1094, 1038, 946 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{28}O_4Na$ ($M+Na^+$) 379.1885, found: 379.1889.

20.-Catalytic hydrogenation of monoterpenic diol 26a-b in the presence of Amberlyst 15



The same procedure described for the catalytic hydrogenation of sesquiterpenic diol **15a** in the presence of Amberlyst 15 (see entry 13 of this section) was followed. Starting from **26a-b** (700 mg, 1.76 mmol), **28** (403 mg, 84%) was obtained.

21.-Formylation of benzofuran derivative 28 with DMF

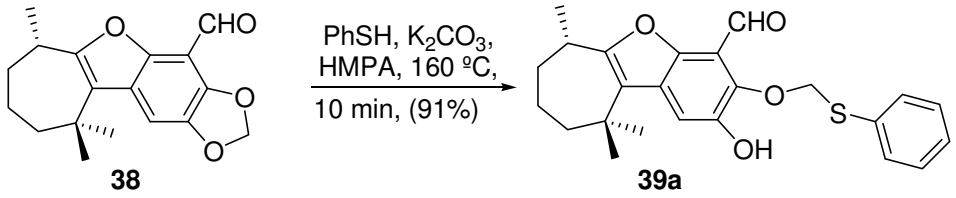


The same procedure described for the formylation of **34** with DMF was followed (see entry 16 of thissection). Starting from 260 mg of **28** (0.96 mmol), the reaction yielded **34** (230 mg, 80%).

2'-formyl-1,1,5-trimethyl-6,7-cyclohepta-3',4'-methylendioxy-benzofuran (38): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.47 (s, 1H, -CHO), 7.34 (s, 1H), 6.13 (s, 1H), 6.12 (s, 1H), 3.25 (m, 1H), 1.93-1.85 (m, 2H), 1.84-1.71 (m, 2H), 1.70-1.60 (m, 2H), 1.34 (s, 3H), 1.32 (s, 3H), 1.32 (d, J = 97 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 186.0 (C), 158.0 (C), 148.0 (C), 145.2 (C), 144.4 (C), 123.0 (C), 122.2

(C), 106.6 (CH), 106.2 (C), 102.9 (CH_2), 43.3 (CH_2), 34.7 (CH_2), 34.5 (C), 33.1 (CH), 29.9 (CH_3), 29.1 (CH_3), 21.9 (CH_2), 19.5 (CH_3).

22.-Methylenedioxy group basic cleavage: Formation of 39a-b

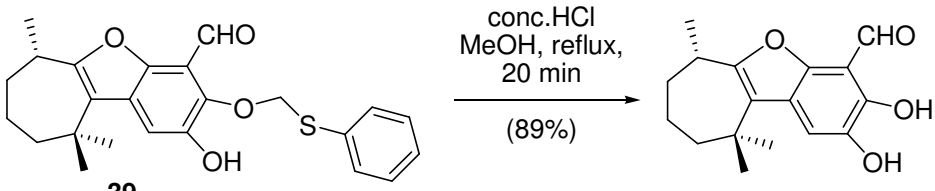


38 **39a**

Following the procedure described for the deprotection of **36**, starting from **38** (50 mg, 0.17 mmol), **39** was obtained (63 mg, 91 %) as a mixture of the two phenylthiometoxy derivatives as yellow oils.

2'-formyl-4'-hydroxy-1,1,5-trimethyl-6,7-cyclohepta-,3'-phenylthiometiloxy-benzofuran (39a): ^{1}H NMR ($CDCl_3$, 500 MHz) δ11.25 (s, -OH), 10.44 (s, -CHO), 7.54 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.28 (m, 3H), 5.63 (s, 2H), 3.24 (m, 1H), 1.89-1.79 (m, 3H), 1.73-1.60 (m, 3H), 1.36 (d, *J* = 6.5 Hz, 3H), 1.26 (br s, 6H). IR (film): 2855, 1654, 1462, 1203 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{24}H_{26}O_4SNa$ ($M+Na^+$) 433.1449, found: 433.1442.

23.- Acidic hydrolisis.Synthesis of monoterpenic analog of liphagal 40



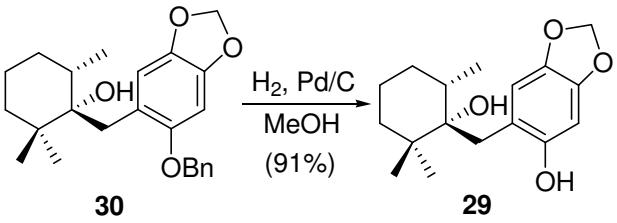
39 **40**

Compound **40** was prepared from **39** (50 mg, 0.12 mmol) according to the same manner as target molecule (+)-liphagal (**1**) 31 mg of **40** was obtained in 89 % yield as a yellow oil.

2'-formyl-3',4'-dihydroxy-1,1,5-trimethyl-6,7-cyclohepta-benzofuran (40): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.25 (br s, -OH), 10.46 (s, -CHO), 7.54 (s, 1H), 5.33 (br s, -OH) , 3.23 (m, 1H), 1.94-1.84 (m, 2H), 1.82-1.72 (m, 2H), 1.64-1.60 (s, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.38 (d, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 192.6 (CHO), 156.9 (C), 148.1 (C), 145.5 (C), 143.2 (C), 139.9 (CH), 122.1 (C), 115.0 (C), 106.5 (CH), 43.4 (CH_2), 34.7 (CH_2), 34.5 (C), 33.1 (CH), 29.8 (CH_3), 29.1 (CH_3), 21.8 (CH_2), 19.5 (CH_3). IR (film): 1654, 1454, 1296, 1235, 1047 cm^{-1}.

3.4. SYNTHETIC APPROACH TOWARDS CORALLIDICTYAL D (1) STARTING FROM (+)-SCLAREOLIDE (3)

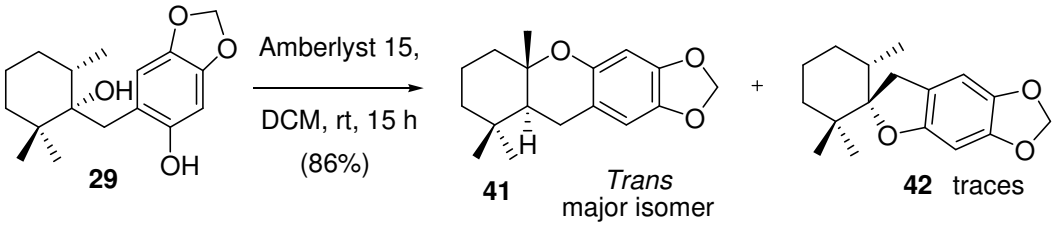
1.-Benzyl ether cleavage: Obtention of 29



30 **29**

Conventional catalytic hydrogenation procedure was followed, starting from **30** (300 mg, 0.78 mmol), **29** was obtained in 91% yield (207 mg).

2.-Cyclization of monoterpenic hydroxyphenol 29 with Amberlyst 15

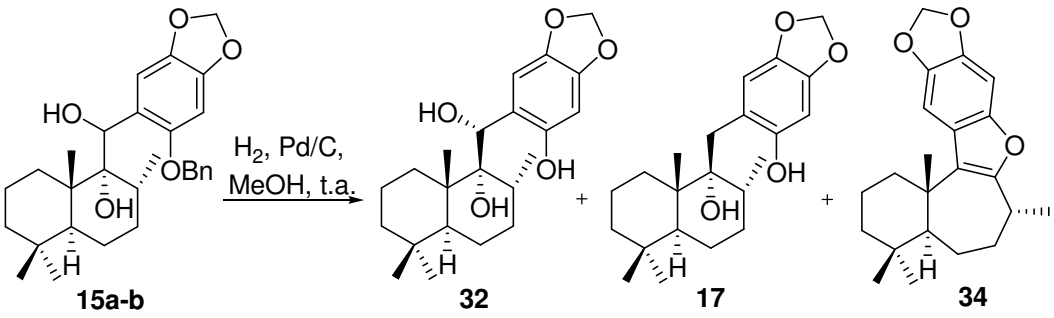


29 **41** *Trans* major isomer **42** traces

To a solution of monoterpenic hydroxyphenol **29** (50 mg, 0.17 mmol), in DCM (3 mL), exchange-ion acidic resin Amberlyst 15 (0.2 g) was added. The reaction mixture was stirred at room temperature for 15 hours at which time TLC showed no starting material remaining. The cationic resin was filtered and the solvent was removed under reduced pressure to furnish **41** together with traces of **42**, (8:1) in 86% yield.

Spectral data for ***5a,9,9-trimethyl-6,7,8,9,9a,10-hexahydro-5aH-[1,3]dioxolo[4,5-b]xanthene (41)*** match those previously reported[141].

3.-Catalytic hydrogenation assays of sesquiterpenic diols 15a-b



a) Catalytic hydrogenation of sesquiterpenic diols 15a-b. Preparation of 32. (Assay 1 and 2)

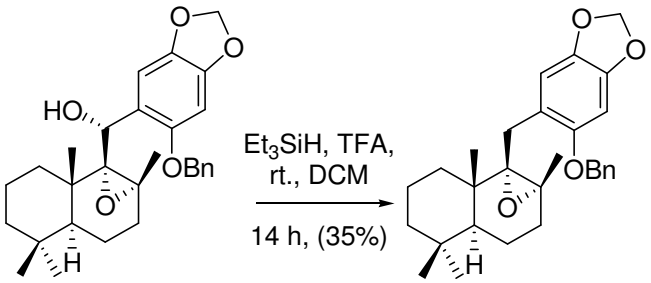
Following the same procedure described for the catalytic hydrogenation of monoterpenic diols **26a-b** (See 2.4 of Experimental Section III), starting from sesquiterpenic diols **15a-b** a series of assays were performed varying the reaction times. Sesquiterpenic dihydroxyphenol **32** was obtained in a (83-85)% yield.

b) Catalytic hydrogenation of sesquiterpenic diols 15a-b in the presence of ion exchange Amberlyst 15. (Assay 4)

The catalytic hydrogenation procedure of monoterpenic diol **26a-b** in the presence of Amberlyst A.15 previously described (See 2.4 of Experimental Section III) was followed. Starting from sesquiterpenic diols **15a-b** , after 3 hours of reaction, a mixture 1:4 of sesquiterpenic hydroxyphenol **17** and benzofuran derivative **34** was obtained in 86% yield.

(141) Sakakura, A.; Sakuma, M.; Ishihara, K.; *Heterocycles* **2011**, *82*, 249.

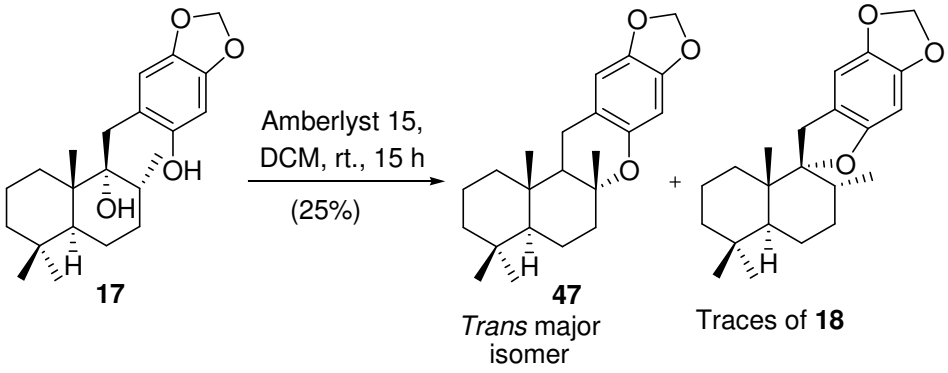
4.-Reduction of sesquiterpenic epoxyalcohol 14a with Et_3SiH/TFA system



(11*R*)-**14a** **46**

To a solution of **14a** (70 mg, 0.15 mmol) and triethylsilane (0.25 mL, 1.6 mmol) in DCM (3 mL) at room temperature, trifluoroacetic acid (0.1 mL, 1.3 mmol) was added and the reaction mixture was stirred at this temperature for 14 h, at which time. TLC showed no starting material. Then, sat. $NaHCO_3$ solution (1 mL) was slowly added to quench the reaction and the solvent was removed under reduced pressure. Ether (10 mL) was added to the crude residue and the organic phase was washed with sat. $NaHCO_3$ solution (3 x 5 mL), water (1 x 5 mL) and brine (1 x 5 mL). The organic extract was then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Purification by flash chromatography column on silica gel (10% ether/hexanes) gave 24 mg of **46** (35 %) as a colorless syrup.

5.-Cyclization of sesquiterpenic hydroxyphenol 17 with Amberlyst 15

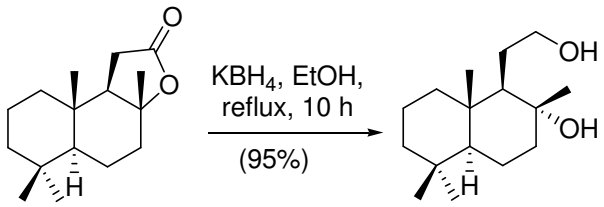


Following the general procedure described for cyclization with Amberlyst 15, starting from sesquiterpenic hydroxyphenol **17** compound **47** was obtained in 25% yield, together with trace amounts of its isomer **18**, that was identified by its characteristic NMR signals. Both appeared as overlapped spots according to TLC. Spectral data for **47** match those previously reported[51] .

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

3.5. SECOND SYNTHETIC APPROACH TOWARDS CORALLIDICTYAL D (1) STARTING FROM (+)-SCLAREOLIDE

1.-Reduction of (+) sclareolide (3). Preparation of 13,14,15,16-Tetra-nor-8α,12-labdanediol (48)

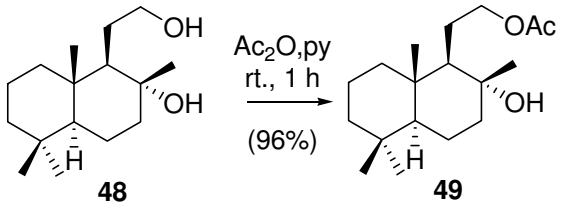


(+)-sclareolide (**3**) **48**

KBH_4 (2 g) was added to a solution of **3** (4.0 g, 16.0 mmol) in EtOH (50 mL) and the mixture was stirred under reflux for 12 h. The solvent was evaporated and the mixture was fractionated into H_2O/ether (30/50 mL) and extracted with ether (3 × 30 mL). The combined organic phases were washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to give the corresponding diol **48** (3.87 g, 95%) as white crystals. All spectral data match those previously reported[96].

(96) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Arteaga, A. F. *Synth. Comm.* **2004**, *34*, 3631.

2.-Selective acetylation of primary alcohol. Synthesis of acetoxy derivative (49)

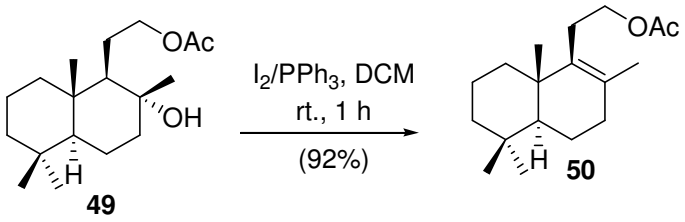


A solution of diol **48** (3.5 g, 13.78 mmol) in Py (8 mL) was treated with Ac_2O (4 mL, 21 mmol) and stirred for 1 h at room temperature (TLC monitoring). The reaction was quenched by careful addition of water (20 mL) and extracted with ether (150 mL), washed with HCl 2N (3 x 30 mL), H_2O (30 mL) and saturated $NaHCO_3$ solution (3 × 30 mL). The organic layer was then dried over anhydrous Na_2SO_4; filtered and the solvent was finally distilled off. The syrupy residue was chromatographed over a silica gel column (20% ether/hexanes) to afford ***2-((1R,2R,4aS,8aS)-2-hydroxy-2,5,5,8a-tetramethyl-decahydronaphthalen-1-yl)ethyl acetate (49)***, (3.92 g, 96%).

Spectral data of **49** were identical to those published[102] .

(102) Vlad, P. F.; Edu, K. G.; Koltsa, M. N.; Chokyrlan, A. G.; Nikolescu, A.; Delyanu, K. *Chemistry of Natural Compounds* **2011**, *47*, 574.

3.-Dehydration of acetoxy derivative 49

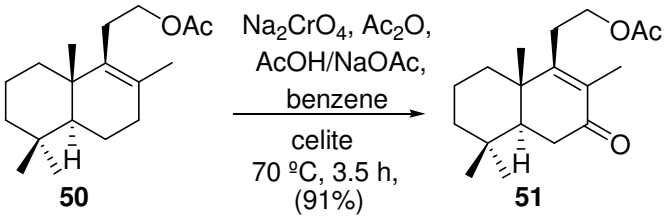


A solution of triphenylphosphine (4 g, 15.4 mmol) in CH_2Cl_2 (35 mL) was stirred at room temperature, treated with iodine (4 g, 15.7 mmol) and stirred for another 15 min. Then a solution of monoacetate **49** (3.8 g, 12.8 mmol) in CH_2Cl_2 (20 mL) was added and the reaction mixture stirred at room temperature for 1 h at which time TLC showed no starting material.Then, the reaction mixture was treated with Na_2SO_3 solution (5% aq, 25 mL), stirred for an additional 10 min, and then extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was washed with H_2O (2 × 30 mL) and brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under vacuum. The residue was chromatographed over a silica gel column (10% ether/hexanes) to yield **50** (3.27 g, 92%) as a colorless syrup.

All spectral data obtained match with those previously reported[102] .

(102) Vlad, P. F.; Edu, K. G.; Koltsa, M. N.; Chokyrlan, A. G.; Nikolescu, A.; Delyanu, K. *Chemistry of Natural Compounds* **2011**, *47*, 574.

4.- Allylic oxidation of unsaturated acetate 50



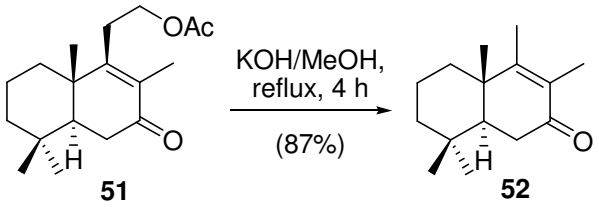
50 **51**

To a solution of **50** (3.2 g, 11.5 mmol) in benzene (50 mL), celite (0.4 g), sodium chromate (5.61 g, 34.5 mmol), sodium acetate (7.53 g, 91.8 mmol), acetic anhydride (30 mL), and glacial acetic acid (18 mL) were added and the mixture was stirred at 70ºC for 3.5 h. at which time TLC showed no **50**. Then, the reaction mixture was allowed to cool to room temperature and poured into ice. Benzene was evaporated under vacuum and the reaction mixture was extracted with ether (3 × 50 mL). The combined organic phases were washed with sat. $NaHCO_3$ (3 × 30 mL) and brine (2 × 30 mL). The ethereal phase was dried over anhydrous $NaSO_4$, filtered and evaporated to give a crude residue which after chromatography column on silica gel (20% ether/hexane) to yield ***2-((4aS,8aS)-2,5,5,8a-tetramethyl-3-oxo-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl acetate (51)*** (3.06 g, 91%) as a colorless syrup.

All spectral data match to those previously reported[101] .

(101) Barrero, A. F.; Cortés, M.; Manzaneda, E. A.; Cabrera, E.; Chahboun, R.; Lara, M.; Rivas, A. R. *J. Nat. Prod.* **1999**, *62*, 1488.

5.-Retroaldol reaction of 51

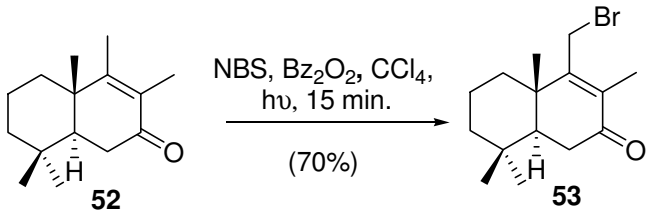


51 **52**

To a stirred solution of **51** (316 mg, 1.1 mmol) in MeOH (2 mL), 2N KOH/MeOH (4 mL) was added. The reaction mixture was refluxed for 4 h (TLC control). Methanol was removed *in vacuo,* and the residue was diluted with water (10 mL) and extracted with ether (3 x 20 mL). The ethereal extract was then washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. Solvent removal furnished 211 mg (87%) of the enone **52** as a colorless oil.

(4aS,8aS)-3,4,4a,8,8-pentamethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (52): $[\alpha]_D^{25}$ = + 82.9, (c 11.4; CH_3Cl) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (dd, *J* = 17.5, 3.7 Hz, 1H), 2.33 (dd, *J* = 17.5, 14.3 Hz, 1H), 1.86 (brdt, *J* = 12.4, 2.7 Hz, 1H) 1.82(s, 3H), 1.72 (s, 3H), 1.68 (dd, *J* = 14.3, 3.6 Hz, 2H), 1.56 (dquint, *J* = 14.2, 3.6 Hz, 1H), 1.45 (dtd, *J* = 13.3, 3.1, 1.4 Hz, 1H), 1.28 – 1.10 (m, 2H), 1.07 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9 (C), 165.3 (C), 129.5 (C), 50.3 (CH), 41.4 (CH_2), 40.6 (C), 36.5 (CH_2), 35.3 (CH_2), 33.1 (C), 32.6 (CH_3), 21.4 (CH_3), 18.8 (CH_2), 17.6 (CH_3), 15.0 (CH_3), 11.7 (CH_3). IR (film): 1662, 1612, 1460, 1373, 1322, 1203, 1139, 1077, 980 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{15}H_{22}O_2Na$ (M+Na$^+$) 257.1517, found: 257.1524.

6.- Regioselective allylic bromination of enone 52

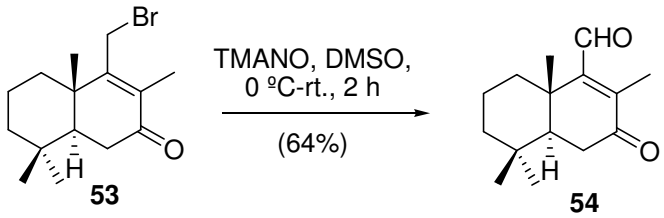


52 53

NBS (267 mg, 1.5 mmol) and benzoil peroxide (4 mg) were added to a solution of enone **52** (300 mg, 1.36 mmol) in 4 mL of anhydrous CCl_4. The mixture was heated for 15-20 min with irradiation by an incandescent lamp (200W) and was monitored by TLC. When no starting material remained, (15 min), it was cooled to room temperature and the solvent was removed under vaccum. After flash chromatography of the resulting crude product on silica gel column (20% ether/hexanes), **53** was obtained **(**285 mg, 70%) as a colorless syrup.

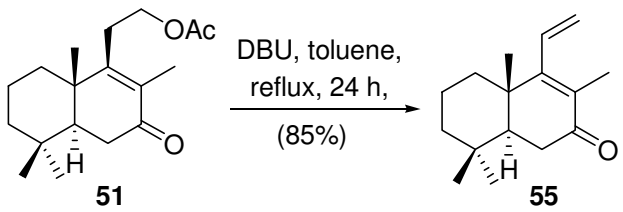
(4aS,8aS)-4-(bromomethyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydro-naphthalen-2(1H)-one (53): $[\alpha]_D^{25}$ = + 146.7,(c 15.9; CH_3Cl). ^1H NMR (500 MHz, $CDCl_3$) δ 4.07 (dd, *J* = 9.9 Hz, 1H), 4.01 (dd, *J* = 9.9 Hz, 1H), 2.48 (dd, *J* = 17.7, 3.7 Hz, 1H), 2.34 (dd, *J* = 17.5, 14.4 Hz, 1H), 1.88 (br dd, *J* = 9.9, 3.3 Hz, 1H), 1.81 (s, 3H), 1.72 (dd, *J* = 14.4, 3.7 Hz, 1H), 1.69-1.54 (m, 3H), 1.45 (br d, *J* = 13.1 Hz, 1H), 1.21 (m, 1H), 1.11 (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H).^{13}C NMR (125 MHz, CDCl3) δ 199.7 (C), 160.4 (C), 134.4 (C), 50.2 (CH), 41.1 (CH_2), 40.6 (C), 35.6 (CH_2), 35.3 (CH_2), 33.2 (C), 32.5 (CH_3), 26.5 (CH_2), 21.3 (CH_3), 19.0 (CH_3), 18.6 (CH_2), 11.4 (CH_3). IR (film): 1661, 1604, 1468, 1377, 1332, 1220, 1009, 912, 714, 683 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{15}H_{23}BrONa$ ($M+Na^+$) 321.0830, found: 321.0828.

7.-Oxidation of allylic bromide 53



To a solution of 122 mg (0.41 mmol) of **53** in a solvent mixture of DMSO/DCM (4/4) mL at 0 ºC, trimethylamine oxide (250 mg, 2.25 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, time after which TLC showed no **53** remaining. It was then hydrolyzed by addition of water (5 mL) and subsequently extracted with ether (3 x 15 mL). The organic phase was washed with water (2 x 5 mL) and brine (2 x 5 mL), dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent, 62 mg of **54** were afforded (64%) as a yelow oil.

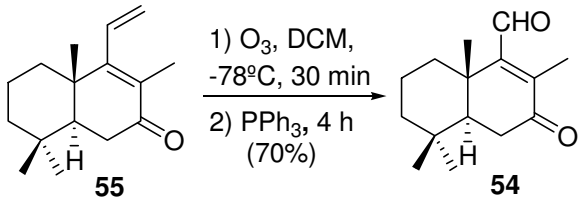
8.- Acetate elimination with DBU



To a stirred solution of acetate **51** (1.93 g, 6.6 mmol) in toluene (16 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), (8 mL, 53 mmol) was added. The reaction stirred under reflux for 24 h, at which time TLC showed no **55**. It was then allowed to cool to room temperature and the solvent was removed under vacuum. The resulting crude product was purified by flach chromatography column (10% ether/hexanes, providing 1.3 g of dienone **55** (85%) as a colorless oil.

Spectral data for ***(4aS,8aS)-3,4a,8,8-tetramethyl-4-vinyl-4a,5,6,7,8,8a-hexahydro- naphthalen-2(1H)-one (52)*** match to those previously reported[104].

9.- Terminal alkene reductive ozonolysis. Preparation of aldehyde 54

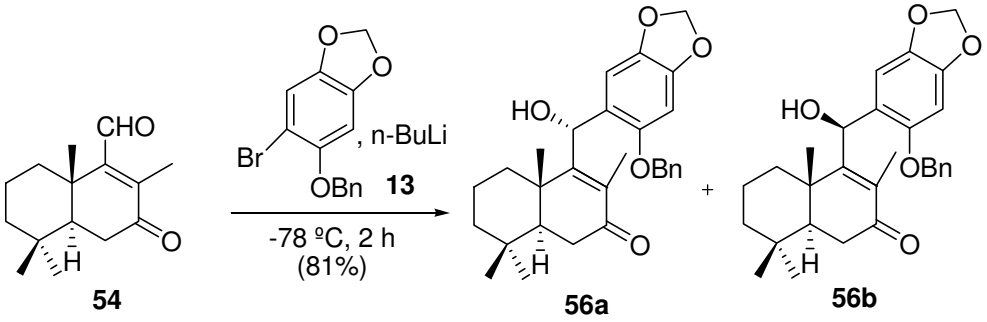


55 **54**

A stirred solution of **55** (510 g, 2.19 mmol) in CH_2Cl_2 (15 mL) was slowly bubbled with an O_3/O_2 mixture at -78 ºC, and the course of the reaction was monitored by TLC. When the starting material was consumed (30 min), the solution was flushed with argon, and triphenylphosphine (862 mg, 3.3 mmol) was added. The mixture was further stirred for 4h while gradually increasing the temperature to room temperature and the solvent was removed. Flash chromatography column on silica gel (5 %ether/hexanes) allowed access to unsaturated aldehyde **54** (359 mg, 70%) as a yelow oil..

(104) Abad, A.; Agullo, C.; Cunat, A. C.; Garcia, A. B.; Gimenez-Saiz, C. *Tetrahedron.*

10.-Aryl addition reaction. Preparation of benzylic alcohols 56a-b



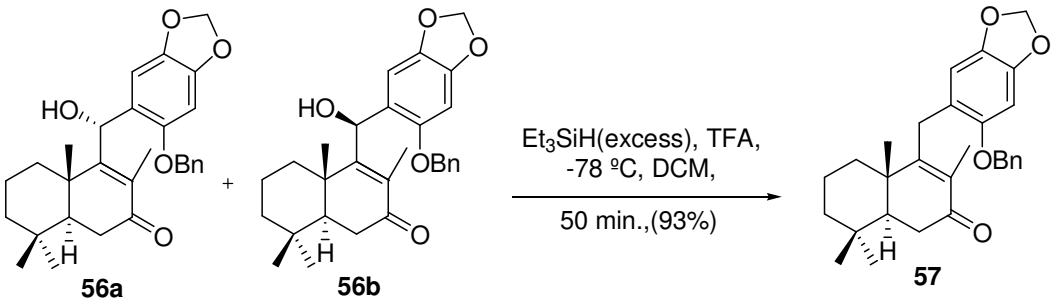
A solution n-BuLi (1.4 M in hexanes, 1.9 mL, 2.6 mmol, 1.2 equiv) was syringed dropwise into a solution of **13** (854 mg, 2.78 mmol, 1.3 equiv) in THF (15 mL) at -78ºC and the reaction mixture was stirred for 25 min. Then, a solution of aldehyde **54** (500 mg, 2.14 mmol, 1.0 equiv) in THF (5 mL) was was added at -78ºC. After stirring for 40 min at this temperature, the reaction mixture was quenched by water (5 mL) and THF was removed under reduced pressure. The residue was diluted with ether – water (60 : 10 mL) and the phases were shaken, separated and the organic phase was washed with water (2 x 10 mL), brine (2 x 10 mL), dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography column on silica gel (15 % ether/hexanes) to yield 0.8 g (81%) of a mixture of separable benzylic alcohol diastereomers

Data for (4aS,8aS)-4-((S)-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)(hydroxy)methyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (56a): $[\alpha]_D^{25}$ = + 53.2, (c 4.23 ; CH_3Cl). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.31 (m, 5H), 6.67 (s, 1H), 6.59 (s, 1H), 5.95 (d, *J* = 1.3 Hz, 1H), 5.93 (d, *J* = 1.3 Hz, 1H), 5.76 (s, 1H), 5.16 (d, *J* = 11.7 Hz, 1H), 5.10 (d, *J* = 11.7 Hz, 1H), 3.16 (br s, 1H, -OH), 2.56 (dd, *J* = 17.3, 3.4 Hz, 1H), 2.45 (dd, *J* = 17.5, 14.5 Hz, 1H), 1.90 (s, 3H), 1.76 (dd, *J* = 14.5, 3.4 Hz, 1H), 1.65-1.51 (m, 2H), 1.47-1.33 (m, 3H), 1.25 (s, 3H), 1.15 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (125

MHz, $CDCl_3$) δ 200.8 (C), 163.4 (C), 152.0 (C), 147.9 (C), 141.3 (C), 136.2 (C), 134.2 (C), 128.9 (2 CH), 128.4 (CH), 127.6 (2 CH), 121.9 (C), 108.5 (CH), 101.4 (CH_2), 96.6 (CH), 71.7 (CH_2), 67.3 (CH), 50.2 (CH), 41.0 (CH_2), 40.8 (C), 35.2 (CH_2), 34.6 (CH_2), 32.9 (C), 32.5 (CH_3), 21.2 (CH_3), 18.4 (CH_2), 17.3 (CH_3), 14.6 (CH_3). IR (film): 3478, 1741, 1650, 1483, 1456, 1377, 1244, 1164, 1067, 1017, 961, 912, 854, 752, 628 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{34}O_5Na$ ($M+Na^+$) 485.2304, found: 485.2304.

Data for ***(4aS,8aS)-4-((R)-(6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)(hydroxy)methyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (56b):*** $[\alpha]_D^{25}$ = - 20.23, (c 15.77; CH_3Cl). ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.32 (m, 5H), 6.63 (s, 1H), 6.52 (s, 1H), 5.97 (s,1H), 5.91 (s, 2H), 5.11 (d, J = 11.5 Hz, 1H), 5.10 (d, J = 11.5 Hz, 1H), 3.61 (brs, 1H, -OH), 2.55 (dd, J = 17.5, 3.8 Hz, 1H), 2.47 (dd, J = 18.2, 13.5 Hz, 1H), 2.26 (br d , J = 12.6 Hz, 1H), 1.87 (dd J = 13.0, 3.8 Hz, 1H), 1.69 (s, 3H), 1.60 (m, 1H), 1.54-1.34 (m, 4H), 1.16 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9 (C), 163.2 (C), 151.9 (C), 147.5 (C), 141.3 (C), 136.0 (C), 133.3 (C), 128.9 (2 CH), 128.5 (CH), 127.6 (2 CH), 122.5 (C), 108.0 (CH), 101.4 (CH_2), 96.3 (CH), 71.7 (CH_2), 67.3 (CH), 50.6 (CH), 41.3 (C), 41.0 (CH_2), 35.8 (C), 33.3 (CH_2), 32.7 (CH_2), 30.9 (CH_3), 21.4 (CH_3), 18.8 (CH_3), 18.6 (CH_2), 13.3 (CH_3). IR (film): 3524, 1748, 1659, 1483, 1390, 1330, 1240, 1171, 1040, 935, 867, 805, 753, 698 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{34}O_5Na$ ($M+Na^+$) 485.2304, found: 485.2298.

11.-Cationic reduction of benzylic alcohols 56a-b

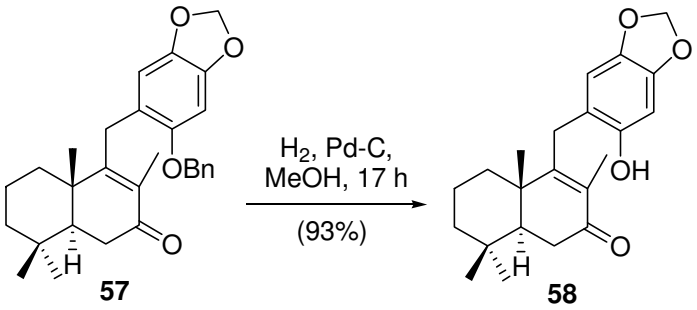


TFA (0.4 mL, 5.4 mmol, 5.0 equiv) was added dropwise to a solution of the mixture of benzylic alcohols (500 mg, 1.08 mmol, 1.0 equiv) and Et_3SiH (1.6 mL, 10 mmol, 10 equiv) in CH_2Cl_2 (3×5 mL) at -78 ºC. After stirring for 50 min at the same temperature, the reaction mixture was quenched by the careful addition of saturated aqueous $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water and dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography column on silica gel (10% ether/hexanes) afforded **57** in 93% yield (423 mg) as a colorless amorphous solid.

(4aS,8aS)-4-((6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)methyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (57): $[\alpha]_D^{25}$ = + 76.53, (c 12.27; CH_3Cl). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.32 (m, 5H), 6.60 (s, 1H), 6.42 (s, 1H), 5.90 (d, *J* = 1.3 Hz, 1H), 5.89 (d, *J* = 1.3 Hz, 1H), 5.07 (d, *J* = 12 Hz, 1H), 5.04 (d, *J* = 12 Hz, 1H), 3.64 (d, *J* = 16.3 Hz, 1H), 3.41 (d, *J* = 16.3 Hz, 1H), 2.57 (dd, *J* = 17.6, 3.7 Hz, 1H), 2.44 (dd, *J* = 17.6, 14.3 Hz, 1H), 1.80 (dd, *J* = 14.3, 3.7 Hz, 1H), 1.69 (s, 3H), 1.67-1.54 (m, 3H), 1.43-1.35 (m, 2H), 1.17 (m, 1H), 1.12 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 200.2 (C), 165.8 (C), 150.9 (C), 146.3 (C), 141.6 (C), 137.2 (C), 132.7 (C), 128.8 (2 CH), 128.2 (CH), 127.5 (2 CH), 119.4 (C), 108.2 (CH), 101.2 (CH_2), 96.6 (CH), 71.5 (CH_2), 50.6 (CH), 41.3 (CH_2), 41.2 (C), 35.6 (CH_2), 35.1 (CH_2), 33.3 (C), 32.6 (CH_3), 28.7 (CH_2), 21.5 (CH_3), 18.6 (CH_2), 18.6 (CH_3),

12.2 (CH_3).IR (film): 1746, 1662, 1504, 1483, 1376, 1330, 1216, 1176, 1039, 936, 871, 749, 697 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{34}O_4Na$ ($M+Na^+$) 469.2355, found: 469.2356.

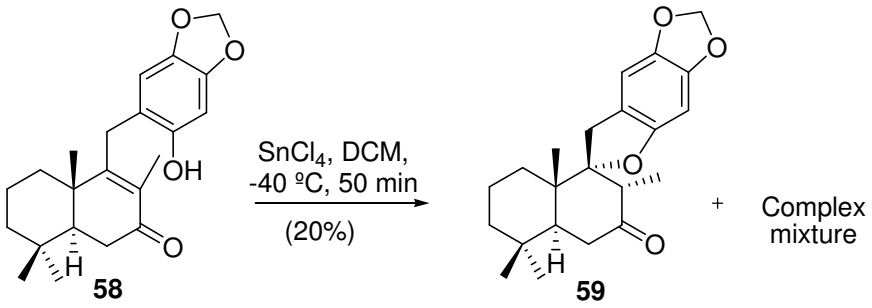
12.-Benzyl ether cleavage. Obtention of phenol 58



To a solution of **57** (250 mg, 0.56 mmol) in dry methanol (8 mL) was added 10 % Pd/C (60 mg) and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 17 h. Filtration and concentration yielded 191 mg of **58**, (93 %) as a colourless syrup.

(4aS,8aS)-4-((6-hydroxybenzo[d][1,3]dioxol-5-yl)methyl)-3,4a,8,8-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (58): $[\alpha]_D^{25}$ = + 70.42,(c 9.23 CH_3Cl). ^1H NMR (500 MHz, $CDCl_3$) δ 6.43 (s, 1H), 6.37 (s, 1H), 5.89 (s, 1H), 5.88 (s, 1H), 5.25 (br s, 1H, -OH), 3.59 (d, *J* = 15.9 Hz, 1H), 3.40 (d, *J* = 15.9 Hz, 1H), 2.59 (dd, *J* = 17.7, 3.5 Hz, 1H), 2.46 (dd, *J* = 17.7, 14.4 Hz, 1H), 1.81 (dd, *J* = 14.4, 3.5 Hz, 1H), 1.72 (s, 3H), 1.68-1.54 (m, 2H), 1.20 (m, 1H), 1.14 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.4 (C), 165.6 (C), 147.5 (C), 146.0 (C), 141.5 (C), 132.6 (C), 116.2 (C), 107.8 (CH), 101.0 (CH_2), 98.2 (CH), 50.4 (CH), 41.1 (CH_2), 41.0 (C), 35.4 (CH_2), 34.9 (CH_2), 33.1 (C), 32.4 (CH_3), 28.2 (CH_2), 21.3 (CH_3), 18.4 (CH_3), 18.4 (CH_2), 12.1 (CH_3). IR (film): 3330, 1642, 1504, 1482, 1441, 1378, 1335, 1260, 1172, 1039, 938, 797, 754, 618 cm^{-1}.

13.- Acidic cyclization of phenol 58



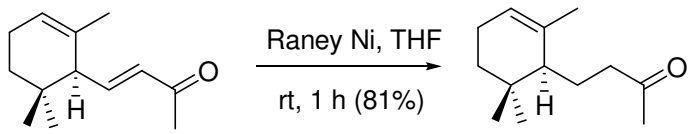
To a solution of phenol **58** (120 mg, 0.32 mmol) in DCM (5 mL) cooled at -40 ºC, tin tetrachloride (0.06 mL, 0.5 mmol) was carefully added and the reaction mixture reacted for 50 min at that temperature,.at which time TLC showed no **58** remaining. Then, the reaction was quenched by water addition (3 mL) and it was allowed to warm to room temperature. The solvent was removed under vacuum and the crude was fractionated in water-ether (10-20 mL), extracted with ether (2 x 20 mL), and washed with water (2 x 10 mL), satd aqueous $NaHCO_3$ (2 x 10 mL), water (10 mL) and brine (10 mL). The dried organic layers were evaporated and the residue was directly purified by flash chromatography column (hexanes/ether mixture) to afford **58** (23 mg, 20%) together with a complex mixture of unidentified products.

[1'(2)R,2'R,4'aR,8'aS]-3'-oxo-5,6-methylenedioxy-3',4',4'a,5',6',7',8',8'a-octahydro-2',5',5',8'a-tetramethyl-spiro[benzofuran-2(3H),1'(2'H)-naphtalene] (59): $[\alpha]_D^{25}$ = - 20.77 , (c 7.08 ; CH_3Cl). ^1H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 6.30 (s, 1H), 5.86 (d, *J* = 1.4 Hz, 1H), 5.85 (d, *J* = 1.4 Hz, 1H), 3.32 (d, *J* = 16.2 Hz, 1H), 2.87 (d, *J* = 16.2 Hz, 1H), 2.61 (q, *J* = 6.6 Hz, 1H), 2.52 (dd, *J* = 14.4, 3.5 Hz, 1H), 2.35 (dd, *J* = 14.3, 14.3 Hz, 1H), 2.06 (dd, *J* = 14.3, 3.5 Hz, 1H), 1.65-1.53 (m, 2H), 1.51-1.39 (m, 2H), 1.34 (m, 1H), 1.24 (m, 1H), 1.17 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.1 (C), 165.3 (C), 155.2 (C), 147.5 (C), 116.8 (C), 104.3 (CH), 101.2 (CH_2), 99.1 (CH), 92.3 (CH), 51.4 (CH), 46.4 (CH), 42.8 (C), 41.5 (CH_2), 39.2

(CH_2), 34.9 (CH_2), 33.7 (C), 32.8 (CH_3), 31.3 (CH_2), 21.5 (CH_3), 18.3 (CH_2), 16.4 (CH_3), 7.7 (CH_3). IR (film): 1713, 1618, 1480, 1457, 1390, 1304, 1265, 1189, 1151, 1040, 937, 850, 754 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{28}O_4Na$ ($M+Na^+$) 379.1885, found: 379.1879.

3.6. THIRD APPROACH: TOTAL SYNTHESIS OF CORALLIDICTYAL D STARTING FROM α-IONONE (60). DEVELOPMENT OF A NEW METHODOLOGY FOR SELECTIVE SPIROANNULATION OF *O*-ALLYL PHENOLS

1.-Selective reduction of α-ionone (60)



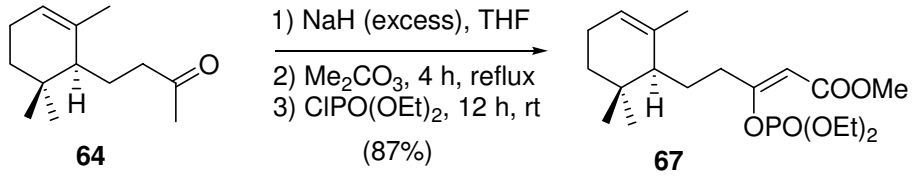
60 **64**

To a solution of α-ionone (**60**) (2 g, 10.4 mmol) in THF (25 mL), Ni Raney solution was added (50% in water, 3 mL) and the reaction was stirred for 1h at room temperature, at which time TLC showed no starting material. Then, the reaction mixture filtered through a mixture of silica gel –Na_2SO_4 (100 g), washed with acetone (10 mL) and the solvent was removed under vacuum to give **64** (1.64 g, 81%) as a colorless oil.

All spectral data for dihydro-α-ionone (**64)** match those previously reported [116,142].

(116) Baker, B. A.; Boskovic, Z. V.; Lipshutz, B. H. *Org. Lett* **2008**, *10*, 289.

2.- Synthesis of β-phosphoenol ester 59



64 **67**

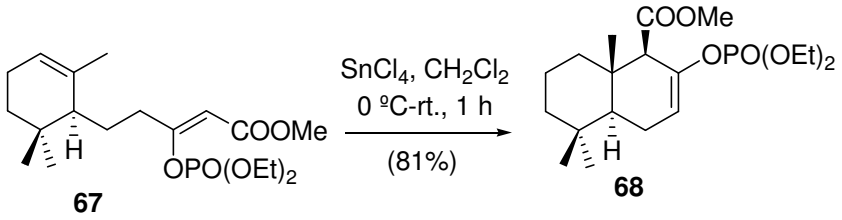
Sodium hydride (1.65 g, 41.2 mmol, 60 % dispersion in mineral oil) was carefully added, in portions, to a precooled solution (0ºC) of **64** (2 g, 10.3 mmol) in dry THF (20 mL), under argon atmosphere. After the reaction mixture was stirred at this temperature for 10 min., dimethylcarbonate (103 mmol, 8.66 mL) was added and the reaction mixture was stirred at reflux for an additional 4 h, at which time, TLC showed the disappearance of the starting material. Diethyl chlorophosphonate (3.1 mL, 20.6 mmol), was then added dropwise and the mixture was stirred for another 12 h at room temperature. After this time, it was poured into ice (50 g) and extracted with ether (2 x 50 mL). The combined organic layers were washed with water (2 x 30 mL), brine (1 x 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow oil crude product that was purified by chromatography column on silica gel (30% ether/hexanes) affording pure β-ketoester (2.28 g, 87%) as a yelow oil.

(S,Z)-methyl 3-(diethoxyphosphoryloxy)-5-(2,6,6-trimethylcyclohex-2-enyl)pent-2-enoate (67): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (br s , 1H), 5.32 (t; *J* = 4.1 Hz, 1H), 4.25 (dq, *J* = 7.3, 1.8 Hz, 2H), 4.23 (dq, *J* = 7.3, 1.8 Hz, 2H), 3.68 (s, 3H), 2.46 (m, 1H), 1.98-1.88 (m, 2H), 1.75-1.68 (m, 2H), 1.67 (br s, 3H), 1.60 (m, 1H), 1.48 (m, 1H), 1.41 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 6H), 1.14 (m, 1H), 0.92 (s, 3H), 0.86 (s, 3H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.34 (C), 164.32 (C), 162.6 (C), 121.1. (CH), 104.8 (CH), 64.8 (CH_2), 64.7 (CH_2), 51.1 (CH_3); 48.7 (CH), 35.6 (CH_2), 32.6 (C), 31.5 (CH_2), 28.0 (CH_2), 27.6 (CH_3), 27.5 (CH_3), 23.5 (CH_3), 23.0 (CH_2), 16.2 (CH_3), 16.1 (CH_3). IR (film): 3449, 1732, 1665, 1440, 1276,

(142) Tang, Y.-X.; Suga, T.; *Phytochemistry* **1994**, *37*, 737.

1207, 1164, 1032, 986 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{33}O_6PNa$ ($M+Na^+$) 411.1912, found: 411.1904.

3.-Acidic esteroselective cyclization with $SnCl_4$

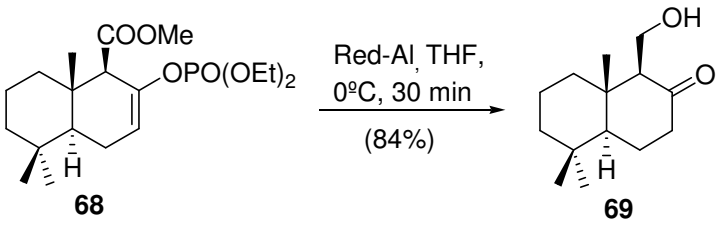


To a solution of **67** (2 g, 5.15 mmol) in dry CH_2Cl_2 (15 mL) was added tin tetrachloride (1.21 mL, 10.30 mmoles) at 0 °C. After being stirred at the same temperature for 10 min., the cooling bath was removed and the reaction mixture was allowed to warm to room temperature for 1h, at which time TLC showed no starting material. It was then cooled to 0 ºC and water was added to quench the reaction. The solvent was removed under vacuum and the crude product was fractionated in water-ether (30 : 100 mL), and the phases were shaken and separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 25 mL), water (25 mL) and brine (25 mL). The dried organic layers were filtered and evaporated, and the residue was directly purified by flash chromatography column (30% ether/hexanes) to yield **68** (1.6 g; 81%) as a colorless syrup.

(1R,4aS,8aS)-methyl 2-(diethoxyphosphoryloxy)-5,5,8a-trimethyl-1,4,4a,5,6,7, 8,8a-octahydronaphthalene-1-carboxylate (68): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (m, 1H). 4.17-4.04 (m, 4H) 3.66 (s, 3H), 3.21 (br s, 1H), 2.14 (m, 1H), 1.99 (m, 1H), 1.70 (m, 1H), 1.52 (m, 1H), 1.47-1.39 (m, 3H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.30 (t, *J* = 7.4 Hz, 3H), 1.24 (dd, *J* = 12.0, 4.2 Hz, 1H), 1.18 (m, 1H), 0.96 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (C). 142.9 (C), 112.0 (CH), 64.4 (CH_2), 64.2 (CH_2), 60.5 (CH), 51.3 (CH_3), 48.9 (CH), 42.0

(CH_2), 40.4 (CH_2), 37.5 (C), 33.4 (CH_3), 33.1 (C), 22.2 (CH_3), 22.0 (CH_2), 18.6 (CH_2), 16.13 (CH_3), 16.07 (CH_3), 15.35 (CH_3). IR (film):3455, 1739, 1686, 1442, 1273, 1165, 1036, 970 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{33}O_6PNa$ ($M+Na^+$) 411.1912, found: 411.1923.

4.-Reduction of the phosphoenol ester 68 with Red-Al

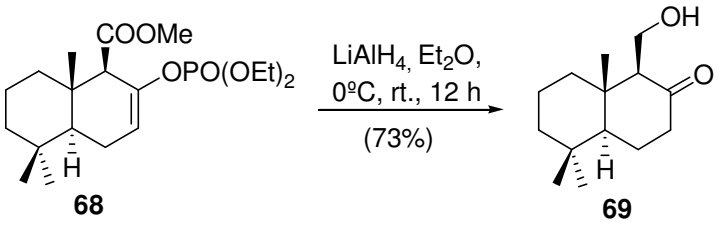


Phosphoenol ester **68** (1.5 g, 3.86 mmol) in dry THF (200 mL) was added dropwise to a solution of sodium aluminium bis(2-methoxy)hydride in toluene (d:1.02 g/ml) (1 mL, 5.0 mmol) at 0 °C under argon atmosphere. After stirring at the same temperature for 30 min, the solution was quenched with 0.1 M HCl (53 mL) and was then concentrated under reduced pressure, diluted with ether - water (80 : 20 mL) and the phases were shaken and separated. The organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel chromatography column (35% ether/hexanes) to afford 727 mg of **69** (84%) as a colorless oil.

All spectral data for ***(1S,4aS,8aS)-1-(hydroxymethyl)-5,5,8a-trimethyl-octahydronaphthalen-2(1H)-one (69)*** match those previously reported[143] .

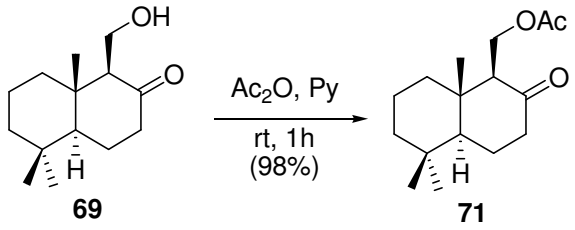
(143) Furuichi, N.; Hata, T.; Soetjipto, H.; Kato, M.; Katsumura, S. *Tetrahedron* **2001**, *57*, 8425.

5.-Reduction of the phosphoenol ester 68 with $LiAlH_4$



$LiAlH_4$ (49 mg, 1.29 mmol) was added at 0°C to a stirred solution of **68** (1 g, 2.57 mmol) in dry Et_2O (15 mL) and the reaction mixture was stirred at room temperature under argon atmosphere for 12 h, at which time TLC showed no **68** remaining. The reaction quenching was carried out by careful addition of H_2O (1 mL) at 0 °C and the reaction mixture was then extracted with ether (2 x 40 mL). The organic layers were combined and washed with brine (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude product wich was purified by flash chromatography column (35% ether/hexanes) to afford 421 mg of **69** (73%) as a colorless oil.

6.-Acetylation of β-hydroxy ketone 69

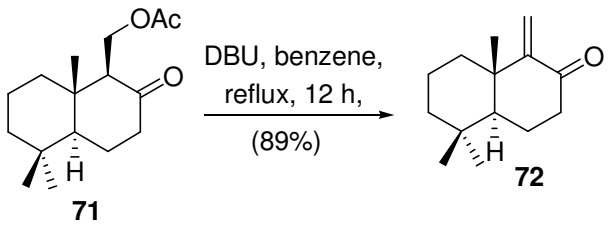


To a solution of β-hydroxy ketone **69** (500 mg, 2.24 mmol) in pyridine (4 mL) was added Ac_2O (1.5 mL) and the mixture was stirred at room temperature for 1 h (TLC monitoring). The reaction was quenched with H_2O (5 mL) and the mixture was stirred for an additional 10 min. Then, it was diluted with t-BuOMe (50 mL), washed with H_2O (20 mL), 2 N HCl (5 × 20 mL), saturated aqueous $NaHCO_3$ (5 x

20 mL) and brine (2 × 20 mL), dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent under vacuum afforded acetoxy ketone **71** (585 mg, 98%).

All spectral data for ***((1S,4aS,8aS)-5,5,8a-trimethyl-2-oxo-decahydronaphthalen-1-yl)methyl acetate (71)*** match those previously reported[144].

7.- Acetate elimination with DBU. Obtention of α,β-enone (72)



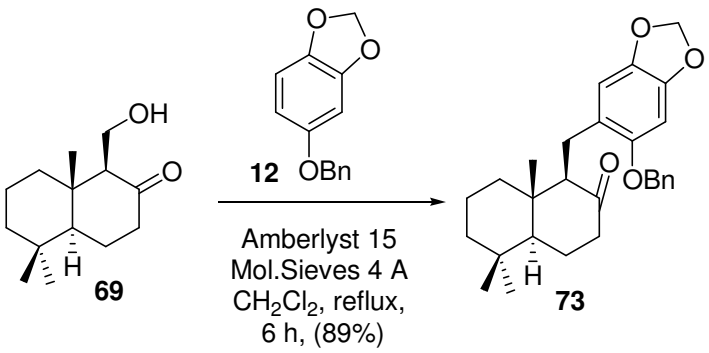
To a stirred solution of acetoxy ketone **71** (700 mg, 2.79 mmol) in benzene (10 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), (4 mL, 27 mmol) was added. The reaction stirred for 1 h. under reflux and was monitored by TLC. It was then allowed to cool to room temperature and the solvent was removed under vacuum. The resulting crude product was purified by flash chromatography column providing α,β-enone 512 mg of **72** (89%).

Spectral data for ***(4aS,8aS)-5,5,8a-trimethyl-1-methylene-octahydronaphthalen-2(1H)-one (72)*** match to those previously reported[79]

(144) Nair, M. S.; Anilkumar, A. T. *Tetrahedron: Asymmetry* **1996**, *7*, 511.

(79) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Tapia, R.; Es-Samti, H.; Fernández, A.; Barranco, I. *Eur. J. Org. Chem.* **2009**, 1139.

8.- Cationic-resin-promoted Friedel Crafts alkylation of 69

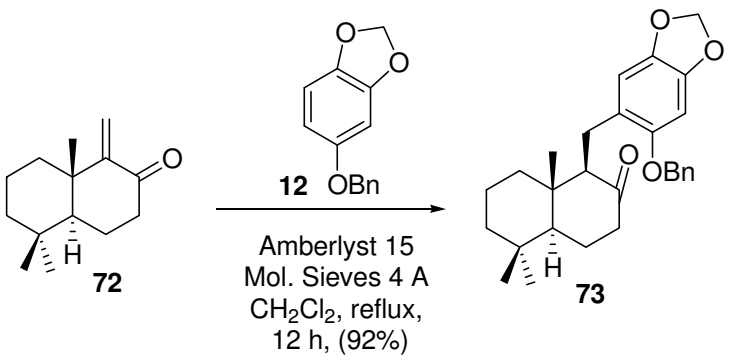


Amberlyst 15 ion-exchange resin (Aldrich) (0.5 g) and molecular sieves 4 Å (1 g) were added to a solution of β-hydroxyketone **69** (800 mg, 3.57 mmol) and **12** (913 mg, 4 mmol) in dry DCM (20 mL) and the mixture was stirred at reflux for 6 h, at which time TLC showed no **69**. Then, it was filtered and the solvent was removed under vacuum to give a crude product which was purified by flash chromatography column on silica gel (25% ether/hexanes) to give **73** (1.1 g, 89 %) as a colorless syrup.

(1R,4aS,8aS)-1-((6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)methyl)-5,5,8a-trimethyl-octahydronaphthalen-2(1H)-one (73): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.42-7.32 (m, 5H), 6.89 (s, 1H), 6.52 (s, 1H), 5.86 (d, *J* = 1.5 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.93 (d, *J* = 11.2 Hz, 1H), 2.72 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.63 (dd, *J* = 13.2, 1.9 Hz, 1H), 2.42 (br d, *J* = 9.6 Hz, 1H), 2.31 (ddd, *J* = 12.9, 4.7, 2.0 Hz, 1H), 2.16 (m, 1H), 1.98 (m, 1H), 1.65 (br d, *J* = 13.5 Hz, 1H), 1.60 (ddd, *J* = 26.4, 13.2, 4.7 Hz, 1H), 1.42 (ddt, *J* = 27.4, 13.6, 3.3 Hz, 1H), 1.34 (dd, *J* = 12.7, 3.0 Hz, 1H), 1.33 (dd, *J* = 13.2, 1.3 Hz, 1H), 1.22 (m, 1H), 1.06-0.92 (m, 2H), 0.91 (s, 3H), 0.80 (s, 3H), 0.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 211.9 (C), 151.4 (C), 146.0 (C), 140.9 (C), 137.1 (C), 128.6 (2 CH), 128.5 (2 CH), 128.3 (CH), 123.1 (C), 112.3 (CH), 101.0 (CH_2), 95.5 (CH), 71.6 (CH_2), 64.5 (CH), 54.4 (CH), 43.3 (C), 42.9 (CH_2), 42.0 (CH_2), 38.8 (CH_2), 33.8

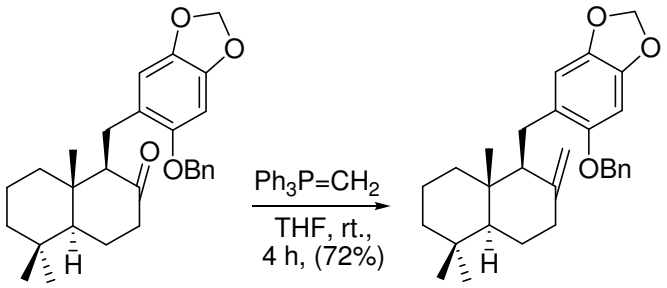
(C), 33.7 (CH_3), 24.4 (CH_2), 23.2 (CH_2), 21.8 (CH_3), 19.1 (CH_2), 14.7 (CH_3). IR (film): 1709, 1622, 1505, 1484, 1389, 1170, 1041, 939, 896, 751, 698 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{28}H_{34}O_4Na$ ($M+Na^+$) 457.2355, found: 457.2353.

9- Cationic-resin-promoted Friedel Crafts alkylation of 72



The same procedure described for alkylation of **69** was followed. Starting in this case from unsaturated ketone **72** (220 mg, 1.07 mmol), **12** (272 mg, 1.11 mmol), Amberlyst 15 ion-exchange resin (0.3 g) and molecular sieves 4 Å (0.4 g), The mixture was stirred at reflux for 12 h, at which time TLC showed no **72**. Then, it was filtered and the solvent was removed under vacuum to yield a crude product which was purified by flash chromatography column on silica gel (25% ether/hexanes) to give**73** (432 mg, 92%).

10-Methenylation of sesquiterpenic ketone 73



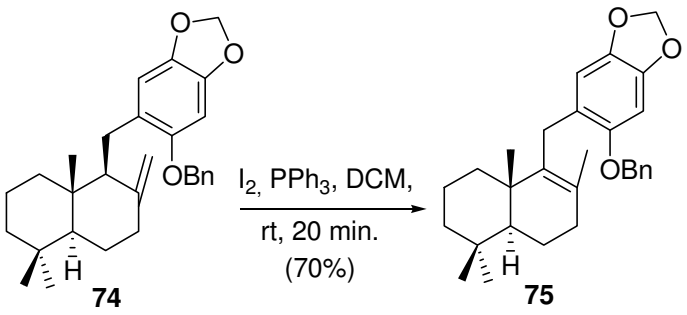
73 **74**

A 2 M solution of *n*-butyllithium in hexanes (0.7 mL, 1.4 mmol) was added dropwise under argon atmosphere, to a stirred suspension of methyltriphenylphosphonium bromide (400 mg, 1.12 mmol) in dry THF (10 mL) at 0 ºC and the reaction mixture was allowed to warm to room temperature after stirring for 15 min. Then, a solution of **73** (250 mg, 0.58 mmol) in dry THF (10 mL) was added dropwise at 0 ºC, and the reaction mixture was further stirred at room temperature for an additional 4 h. Then, water (1 mL) was added to quench the reaction and the solvent was removed under vacuum. The crude product was extracted with ether (2 x 30 mL). The dried organic layers were evaporated and the residue was directly purified by flash chromatography column on silica gel (10% ether/hexanes) to yield **74** (181 mg, 72%) as a colourless syrup and 30 mg (12%) of starting material.

5-(benzyloxy)-6-(((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylene-decahydro naphthalen-1-yl)methyl)benzo[d][1,3]dioxole (74): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.30 (m, 5H), 6.59 (s, 1H), 6.46 (s, 1H), 5.78 (s, 2H), 4.92 (s, 2H), 4.69 (s, 1H), 4.57 (s, 1H), 2.68 (br d, *J* = 15.4 Hz, 1H), 2.59 (dd, *J* = 15.1, 10.5 Hz, 1H), 2.27 (br d, *J* = 12.8 Hz, 1H), 2.09 (br d, *J* = 10.0 Hz, 1H), 1.90 (ddd, *J* = 13.0, 13.0, 5.0 Hz, 1H), 1.71-1.60 (m, 2H), 1.46 (dd, *J* = 27.7, 13.9 Hz, 1H), 1.34-1.18 (m, 3H), 1.08-0.98 (m, 2H), 0.95 (ddd, *J* = 18.7, 16.7, 3.8 Hz, 1H), 0.80 (s, 3H), 0.74 (s, 3H), 0.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.3 (C), 148.9 (C), 145.7 (C),

141.2 (C), 137.4 (C), 128.9 (CH), 128.7 (2 CH), 128.0 (CH), 127.8 (CH), 123.8 (C), 109.8 (CH), 107.7 (CH_2), 101.1 (CH_2), 96.3 (CH), 71.7 (CH_2), 56.3 (CH), 55.8 (CH), 42.3 (CH_2), 40.1 (C), 39.1 (CH_2), 38.5 (CH_2), 33.8 (CH_3), 33.7 (C), 24.6 (CH_2), 23.9 (CH_2), 21.9 (CH_3), 19.6 (CH_2), 14.7 (CH_3). IR (film): 1644, 1585, 1504, 1483, 1434, 1388, 1167, 1040, 1000, 938, 867, 743, 696 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{36}O_3Na$ ($M+Na^+$) 455.2562, found: 455.2554.

11-Isomerization to tetrasubstituted alkene 75

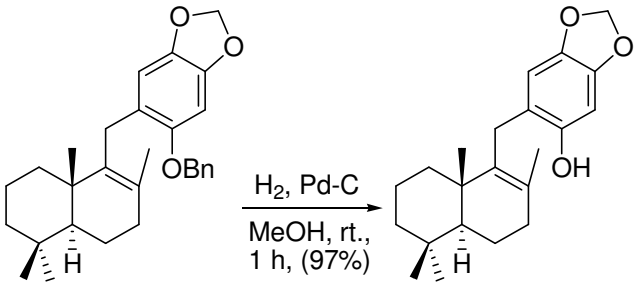


Iodine (66 mg, 0.25 mmol) was added to a solution of triphenylphosphine (78 mg, 0.31 mmol) in dry CH_2Cl_2 (6 mL) and the mixture was stirred at room temperature for 10 min. A solution of alkene **74** (110 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was then added at room temperature. The reaction mixture was stirred at room temperature for 20 min, at which time an aliquot was checked by NMR, showing no starting material. After removal of most of the solvent under reduced pressure, the crude product was purified by flash chromatography column on silica gel (10% ether/hexanes) to yield **75** (75 mg, 70 %) as a colourless syrup.

5-(benzyloxy)-6-(((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a octahydronaphthalen-1-yl)methyl)benzo[d][1,3]dioxole (75): $[\alpha]_D^{25}$ = + 0.47 (c 6.4, $CHCl_3$. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.44 (br d, *J* = 7.4 Hz, 2H), 7.38 (br t, *J* = 7.4 Hz, 2H), 7.32 (br t, *J* = 7.3 Hz, 1H), 6.60 (s, 1H), 6.56 (s,1H), 5.89 (d, *J* = 1.5 Hz, 1H), 5.88 (d, *J* = 1.5 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.0

Hz, 1H), 3.38 (d, *J* = 17.4 Hz, 1H), 3.22 (d, *J* = 17.4 Hz, 1H), 2.17 (m, 1H), 2.06 (dd, *J* = 17.8, 6.3 Hz, 1H), 1.72 (m, 1H), 1.60-1.50 (m, 2H), 1.48 (s, 3H), 1.45-1.20 (m, 5H), 1.09 (m, 1H), 0.98 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H).). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 150.8 (C), 145.4 (C), 141.3 (C), 137.7 (C), 137.6 (C), 129.1 (C), 128.7 (2 CH), 128.0 (CH), 127.4 (2 CH), 123.3 (C), 109.0 (CH), 100.9 (CH_2), 96.4 (CH), 71.4 (CH_2), 52.1 (CH), 41.9 (CH_2), 39.1 (C), 36.2 (CH_2), 33.7 (CH_2), 33.5 (C), 33.4 (CH_3), 27.0 (CH_2), 21.9 (CH_3), 20.5 (CH_3), 20.3 (CH_3), 19.3 (CH_2), 19.1 (CH_2). IR (film): 1729, 1626, 1505, 1481, 1387, 1382, 1316, 1174, 1041, 939, 870, 739, 696 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{36}O_3Na$ ($M+Na^+$) 455.2562, found: 455.2562.

12-Cleavage of benzyl ether 75



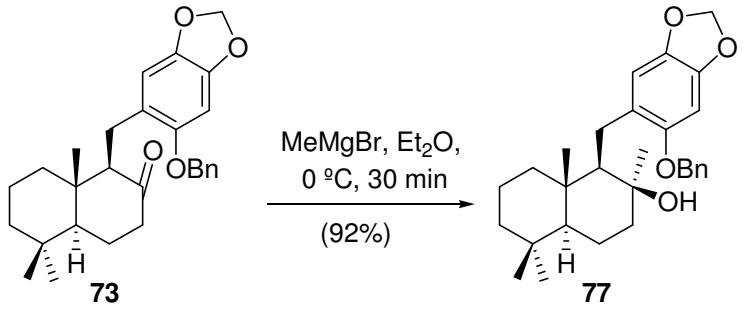
75 **76**

To a solution of **75** (2.1 g, 4.86 mmol) in dry methanol (20 mL) was added 10 % Pd/C (500 mg, 10 % mmol) and the reaction mixture was stirred at room temperature under hydrogen atmosphere (1.5 atm) for 1 h. Filtration and concentration yielded 1.62 g of **76** (97 %) as a colourless syrup.

Spectroscopic data for *6-(((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)benzo[d][1,3]dioxol-5-ol (**76**)* correspond to those previously reported[51].

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

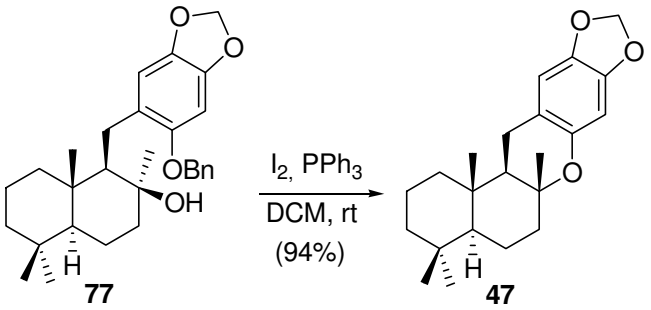
13.-Grignard reaction of 73



To a solution of **73** (687 mg, 1.58 mmol) in 18 mL of anhydrous Et_2O was added dropwise a solution of methylmagnesium bromide (1.8 mL of a 1.4 M solution in Toluene/THF, 2.52 mmol) at 0 ºC. The mixture was stirred under argon atmosphere for 30 min, at which time TLC showed no starting material. Then, water (1 mL) was added slowly at 0 ºC to quench the reaction and then extracted with ether (2 x 20 ml).The combined organic layers was washed with water (3 x 10 mL), brine (3 x 10 mL), and dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum. Purification by flash chromatography column on silica gel (25% ether/hexanes) gave 655 mg of **77** (92%).

(1R,4aS,8aS)-1-((6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)methyl)-2,5,5,8a-tetramethyl-decahydronaphthalen-2-ol (77): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.44 (br d, *J* = 7.4 Hz, 2H), 7.38 (br t, *J* = 7.4 Hz, 2H), 7.32 (br t, *J* = 7.3 Hz, 1H), 6.73 (s, 1H), 6.53 (s,1H), 5.02 (d, *J* = 12.0 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 2.91 (dd, *J* = 15.9, 7.1 Hz, 1H), 2.54 (d, *J* = 15.9, 2.8 Hz, 1H), 2.17 (m, 1H), 1.75 (m, 1H), 1.60-1.05 (m, 11H), 1.03 (s, 3H), 0.95 (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 150.8 (C), 145.7 (C), 141.9 (C), 137.6 (C), 137.6 (C),, 129.0 (2 CH), 128.3 (CH), 127.9 (2 CH), 126.3 (C), 109.4 (CH), 101.3 (CH_2), 96.5 (CH), 73.6 (C), 72.2 (CH_2), 59.6 (CH), 59.5 (CH), 43.2 (CH_2), 42.4 (CH_2), 40.3 (CH_2), 39.4 (C), 33.4 (CH_3), 33.8 (C), 31.8 (CH_3), 23.5 (CH_2), 22.3 (CH_3), 20.3 (CH_3), 18.8 (CH_2), 15.2 (CH_3).

14.-Ciclyzation of alcohol 77 with I_2/PPh_3 system

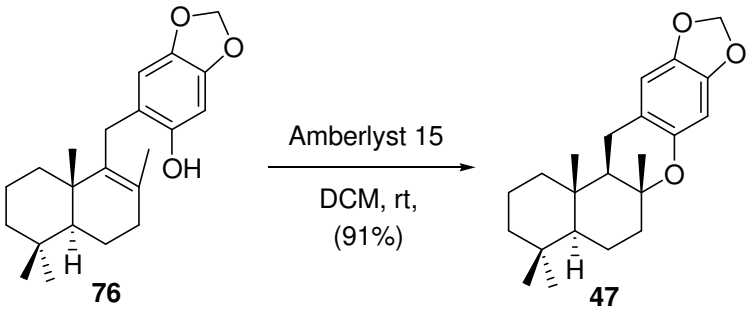


Iodine (254 mg, 1 mmol) was added to a solution of triphenylphosphine (262 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature for 10 min. A solution of alcohol **77** (450 mg, 1 mmol) in CH_2Cl_2 (5 mL) was then added at room temperature and the reaction mixture was stirred for 30 min, at which time TLC showed no starting material remaining. After removal of most of the solvent under reduced pressure, to give a crude product which was purified by flash chromatography column on silica gel (5% ether/hexanes) affording **47** (239 mg, 94%) as a colourless syrup.

All spectral data for ***(1R,4aS,8aS)-1-((6-(benzyloxy)benzo[d][1,3]dioxol-5-yl)methyl)-2,5,5,8a-tetramethyl-decahydronaphthalen-2-ol (47)*** match those previously reported[51].

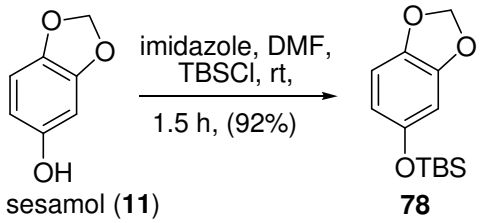
(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

15.- Cyclization of sesquiterpenic phenol 76 with Amberlyst 15



General procedure described for the cyclization witn cationic ion-exchange resin Amberlyst 15 was followed. Starting from **76** (100 mg, 0.29 mmol) benzopiranic derivative **47** was obtained in 91% yield (91 mg).

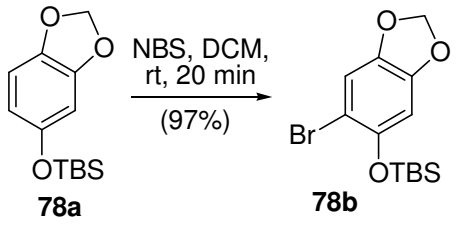
16.- Silylation of sesamol (11)



Tert-butyldimethylsilyl chloride (2.6 g, 17.38 mmol) and imidazole (1.5 g, 21.7 rnmol) were added to solution of commercially available sesamol (**11**) (2 g, 14.49 mmol) in anhydrous dimethylformamide (8 mL) and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with Et_2O (30 mL), and washed with water (2 x 20 mL) and brine (2 x 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to give a crude product, which after chromatography column on silica gel (5% ether/hexanes) afforded 3.4 g of **78** (92%) as a colourless oil.

All spectral data for ***1,2-methylenedioxy-4-tert-butyldimethylsiloxybenzene from sesamol (78)*** correspond to those previously reported[125].

17.- Bromination of silylated sesamol 78a



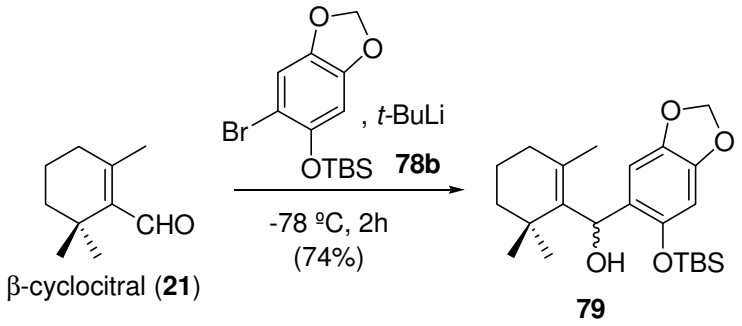
N-Bromosuccinimide (1.2 g, 6.74 mmol) was added to a solution of **78a** (1.65 g, 6.54 mmol) in DCM and the mixture was stirred at room temperature for 20 min. Then, the solvent was evaporated, yielding a crude product which after chromatography column on silica gel (5% ether/hexanes) afforded 2.09 g of **78b** (96%) as a white solid.

All spectral data for ***2-bromo-1-tert-butyldimethylsililoxy-4,5-methylenedioxybenzene (78b)*** match those previously reported[51].

(125) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Valdivia, M. V.; Chahboun, R. *Tet. Lett.* **1998**, *39*, 2425.

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

18.-Preparation of alcohol 79 from β-cyclocitral. Aryllithium addition.



A 1.7 M solution of tert-butyllithium (3.2 mL, 5.5 mmol) was added at -78°C to a solution of **78b** (1.5 g, 4.5 mmol) in Et_2O (25 mL), under argon atmosphere. After stirring for 25 min, **21** (1.0 g, 5.4 mmol) was added and the mixture was further stirred for 40 min at -78°C, at which time TLC showed no starting material remaining. Then, H_2O (10 mL) was added and the mixture was allowed to warm to room temperature. Then it was extracted with Et_2O (2 x 30 mL). The combined organic phases were dried, filtered and concentrated to give a crude product impure**79** which was used in the next step without further purification.

All spectral data for ***(6-(tert-butyldimethylsilyloxy)benzo[d][1,3]dioxol-5-yl)(2,6,6-trimethylcyclohex-1-enyl)methanol (79) match those previously reported***[51]

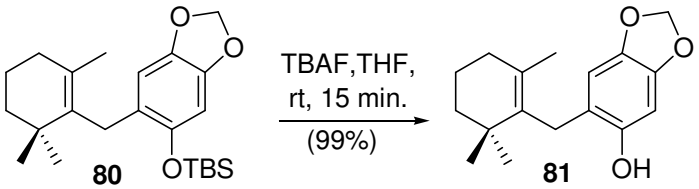
(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

19.-Cationic reduction of benzylic alcohol 79 with Et_3SiH/TFA system

The procedure described for the cationic reduction of **26a-b** with this system was followed (see section 2.5 of Experimental Section III). Starting from **79** (1.5 g, 3.7 mmol), tetrasubstituted alkene **80** was obtained in 89% yield (1.28 g) after 30 minutes.

All spectral data for ***tert-butyldimethyl(6-((2,6,6-trimethylcyclohex-1-enyl)methyl)benzo[d][1,3]dioxol-5-yloxy)silane (80)*** match those previously reported[125].

20.-Tertbutylsilyl ether cleavage of 80



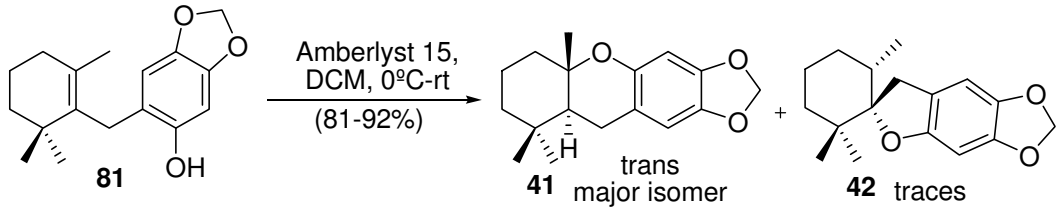
A solution of **80** (1 g, 2.57 mmol) in THF (10 mL) and tetrabutylammonium fluoride (0.9 g, 2.85 mmol) was added. After stirring for 15 min at room temperature, H_2O (10 mL) was added and the organic solvent was evaporated. The mixture was diluted with ether and extracted with ether (3 x 20 mL). The organic layer was dried and the solvent was evaporated to afford a crude, which

(125) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Valdivia, M. V.; Chahboun, R. *Tet. Lett.* **1998**, *39*, 2425.

was chromatographed on silica gel (25% ether/hexanes) to furnish phenol **81** (698 mg, 99%).

6-((2,6,6-trimethylcyclohex-1-enyl)methyl)benzo[d][1,3]dioxol-5-ol (81): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.55 (s, 1H), 6.38 (s, 1H), 5.86 (s, 2H), 5.11 (s, 1H), 3.30 (s, 2H), 2.05 (t, *J* = 6.3 Hz, 2H), 1.75-1.58 (m, 2H), 1.56 (s, 3H), 1.52-1.46 (m, 2H), 0.94 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.2 (C), 145.5 (C), 141.2 (C), 134.1 (C), 131.2 (C), 118.6 (C), 108.5 (CH), 100.7 (CH_2), 98.0 (CH), 39.8 (CH_2), 35.0 (C), 32.8 (CH_2), 28.4 (CH_3), 28.4 (CH_3), 28.3 (CH_2), 20.4 (CH_3), 19.3 (CH_2). IR (film): 3446, 1631, 1504, 1477, 1439, 1361, 1295, 1222, 1164, 1040, 937, 860, 761 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{22}O_3Na$ ($M+Na^+$) 297.1467, found: 297.1471

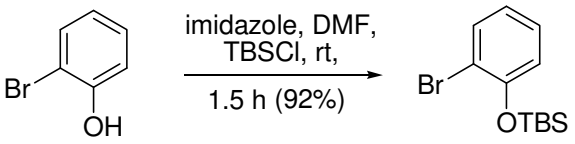
21.- Phenol cyclization with ion-exchange resin Amberlyst 15



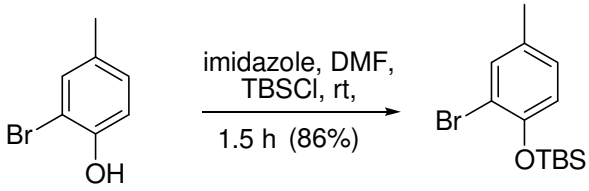
Over a solution of phenol **81** general cyclization procedure wirh Amberlyst 15 was applied. A series of assays were performed varying the reaction conditions according to what is showed in table 6 (see results and discussion). The reaction yielded benzopiranic derivative **41** together with traces of **42** in high yield (81-92) %*

*Parameter values may vary within the limits showed in the different experiences.

22.-Preparation of aromatic fragments



82 **83**



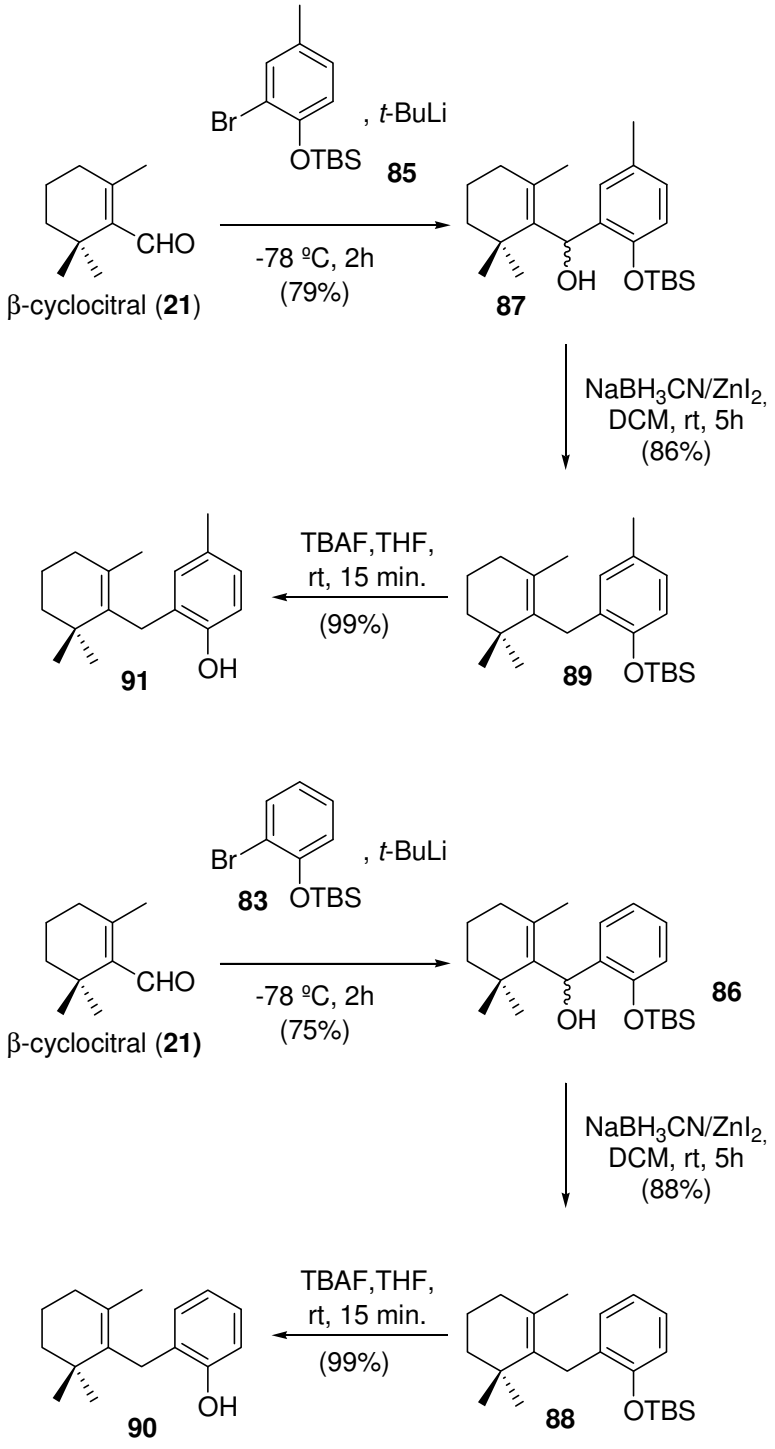
84 **85**

Following the procedure described for the silylation of sesamol, aromatic synthons **83** (3.06 g, 92 %) and **85** (2.77 g, 86 %) starting from commercially available phenols **82** (2.0 g, 11.56 mmol) and **84** (2.0 g, 10.64 mmol).

All spectral data for (***2-bromophenoxy)(tert-butyl)dimethylsilane (83)*** and ***(2-bromo-4-methylphenoxy)(tert-butyl)dimethylsilane (85)*** correspond to those previously reported[145].

(145) Pena, D.; Cobas, A.; Perez, D.; Guitian, E. *Synthesis* **2002**, *10*, 1454.

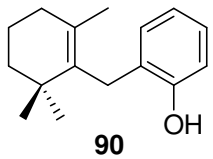
23.-Preparation of monoterpenic phenols 90 and 91



Firstly an arillithium addition reaction was carried out following the procedure described for the preparation of monoterpenic phenol **79** (see section 18 of Experimental Procedures VI). Starting from aromatic fragment **83** (1 g, 3.48 mmol) and **85** (1 g, 3.31 mmol), both corresponding benzylic alcohols **86** and **87** were obtained and subjected to subsequent reduction step without purification.

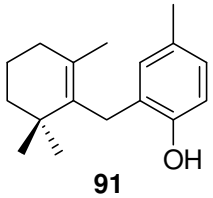
Procedure of cationic reduction with the $NaBH_3CN/ZnI_2$ system, described for the obtention of **29** was followed and the corresponding reduced product furnished and subsequently deprotected following the deprotection procedure described for **80** (see section 20 of Experimental Procedures VI).

Both phenols were purified on silica gel chromatography column and characterized; **90** (520 mg, 65% global yield) and **91** (544 mg, 67% global yield).



90

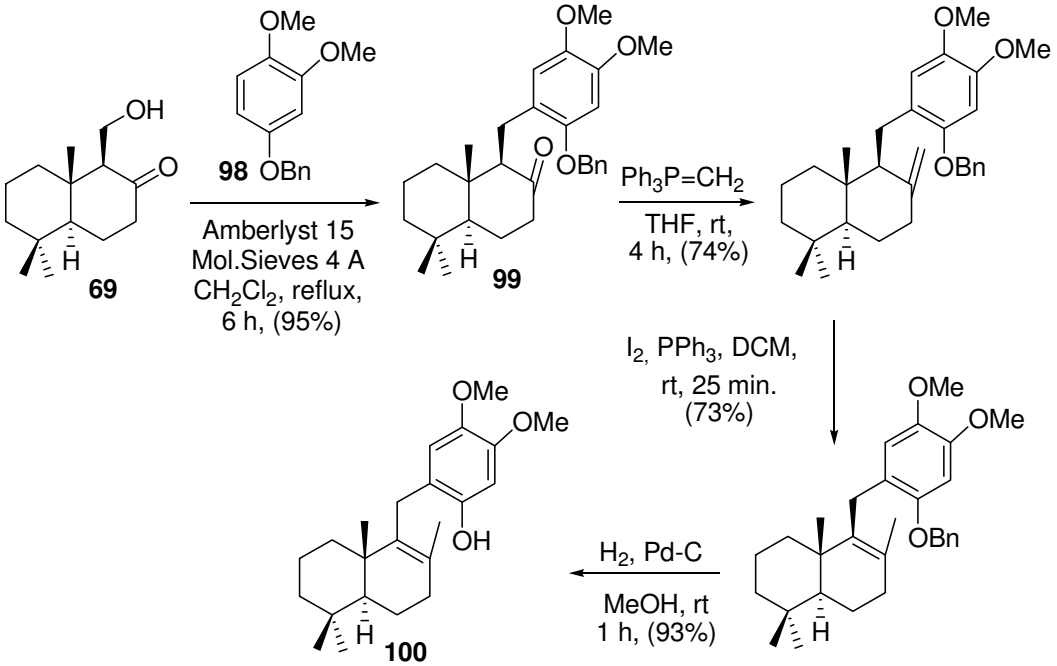
Data for 2-((2,6,6-trimethylcyclohex-1-enyl)methyl)phenol (90): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.04 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.82 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.49 (s, 1H), 3.41 (s, 2H), 2.07 (t, *J* = 6.3 Hz, 2H), 1.75-1.61 (m, 2H), 1.56 (s, 3H), 1.53-1.46 (m, 2H), 0.94 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 154.3 (C), 134.1 (C), 130.9 (C), 129.1 (CH), 126.8 (C), 126.6 (CH), 120.1 (CH), 115.2 (CH), 39.8 (CH_2), 35.1 (C), 32.8 (CH_2), 28.5 (CH_2), 28.4 (2 X CH_3), 27.0 (CH), 20.5 (CH_3), 19.4 (CH_2). IR (film): 3470, 3434, 1589, 1499, 1454, 1336, 1273, 1206, 1087, 1040, 843, 756 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{22}ONa$ ($M+Na^+$) 253.1568, found: 253.1570.



91

Data for 4-methyl-2-((2,6,6-trimethylcyclohex-1-enyl)methyl)phenol (91): ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.86 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 1H), 3.40 (s, 2H), 2.25 (s, 3H), 2.08 (t, *J* = 6.3 Hz, 2H), 1.76-1.64 (m, 2H), 1.60 (s, 3H), 1.54-1.45 (m, 2H), 0.96 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.9 (C), 134.4 (C), 131.2 (C), 129.8 (CH), 129.4 (C), 127.0 (CH), 126.2 (C), 115.0 (CH), 39.9 (CH_2), 35.1 (C), 32.8 (CH_2), 29.0 (CH_2), 28.4 (2 CH_3), 20.7 (CH_3), 20.5 (CH_3), 19.3 (CH_2). IR (film): 3410, 1705, 1611, 1505, 1469, 1361, 1259, 1204, 1092, 1041, 929, 807, 759 cm^{-1}.

24.-Preparation of sesquiterpenic phenol 100



Following the same procedure described for the preparation of sesquiterpenic phenol **76** (see sections 8, 10, 11, and 12 of Experimental procedures VI), sesquiterpenic phenol **100** was obtained[79]. Starting from β-hydroxy ketone (**69**)[143] (900 mg, 4.0 mmol) and aromatic fragment **98**[128] (1.17 g, 4.8 mmol), Friedel-Crafts reaction proceded in 95% yield, furnishing ketone **99** (1.71 g). Wittig reaction of resulting ketone **99** (1.7g, 3.8 mmol) provided corresponding alkene in 74% yield (1.23 g). Isomerization step according to that previously described furnished tetrasubstituted alkene in 73% yield (876 mg) starting from 1.2 g of previous exocyclic alkene (2.7 mmol). Final catalytic hydrogenation of tetrasubstituted alkene (800 mg, 1.83mmol) gave access to sesquiterpenic phenol **100** in high yield (610 mg, 93%).

Data for ***4,5-dimethoxy-2-(((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydro naphthalen-1-yl)methyl)phenol (100):*** $[\alpha]_D^{25}$ = + 54.3 (c 14.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.57 (s, 1H), 6.39 (s, 1H), 5.37 (br s, 1H, -OH), 3.82 (s, 3H), 3.79 (s, 3H), 3.35 (d, *J* = 16.5 Hz, 1H), 3.30 (d, *J* = 16.5 Hz, 1H), 2.20-2.09 (m, 2H), 1.74 (dd, *J* = 13.0, 6.9 Hz, 1H), 1.62 (s, 3H), 1.58-1.45 (m, 2H), 1.42-1.31 (m, 2H), 1.29-1.16 (m, 2H), 1.13-1.01 (m, 2H), 1.00 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.4 (C), 143.0 (C), 138.4 (C), 135.6 (C), 130.7 (C), 117.0 (C), 114.0 (CH), 101.1 (CH), 57.0 (CH_3), 56.1 (CH_3), 52.2 (CH), 41.9 (CH_2), 39.4 (C), 36.7 (CH_2), 33.8 (C), 33.6 (CH_2), 33.5 (CH_3), 28.4 (CH_2), 22.0 (CH_3), 20.6 (CH_3), 20.5 (CH_3), 19.2 (CH_2), 19.1 (CH_2). IR (film): 3462, 1604, 1521, 1451, 1412, 1366, 1201, 1095, 999, 862, 752 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{34}O_3Na$ ($M+Na^+$) 381.2406, found: 381.2398.

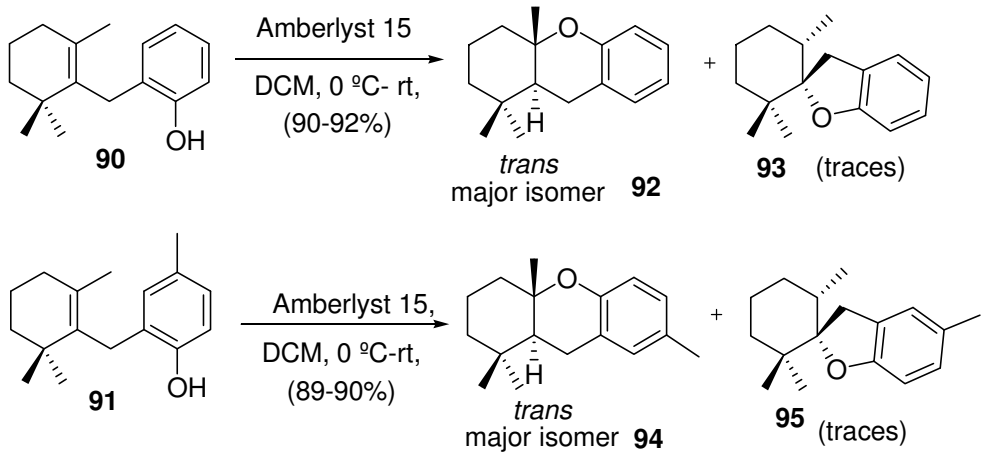
(79) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Tapia, R.; Es-Samti, H.; Fernández, A.; Barranco, I. *Eur. J. Org. Chem.* **2009**, 1139.

(128) Kupchan, S. M.; Liepa, A. J.; Kameswaran, V.; Sempuku, K. *J . Am. Chem. Soc.* **1973**, *95*, 9.

(143) Furuichi, N.; Hata, T.; Soetjipto, H.; Kato, M.; Katsumura, S. *Tetrahedron* **2001**, *57*, 8425.

All spectral data for ***(1R,4aS,8aS)-1-(2-(benzyloxy)-4,5-dimethoxybenzyl)-5,5,8a-trimethyl-octahydronaphthalen-2(1H)-one (99)*** and ***(4aS,5S,8aS)-5-(2-(benzyloxy)-4,5-dimethoxybenzyl)-1,1,4a-trimethyl-6-methylene-decahydro naphthalene*** correspond to those previously reported[79].

25.- Cyclization of monoterpenic phenols 90 and 91 with ion-exchange resin Amberlyst 15



General procedure for cyclization with Amberlyst 15 was followed starting from monoterpenic phenols **90** (53 mg, 0.23 mmol) and **91** (54 mg, 0.23 mmol). Benzopiranic derivatives **92**(48 mg, 90%) and **94** (49 mg, 90%), were obtained in high yield together with trace amounts of corresponding spiroderivatives **93** and **95** respectively.

All spectral data for *trans* piranic isomers ***(4aS,9aS)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (92)*** and (***4aS,9aS)-1,1,4a,5-tetramethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (94)*** match those previously reported[141].

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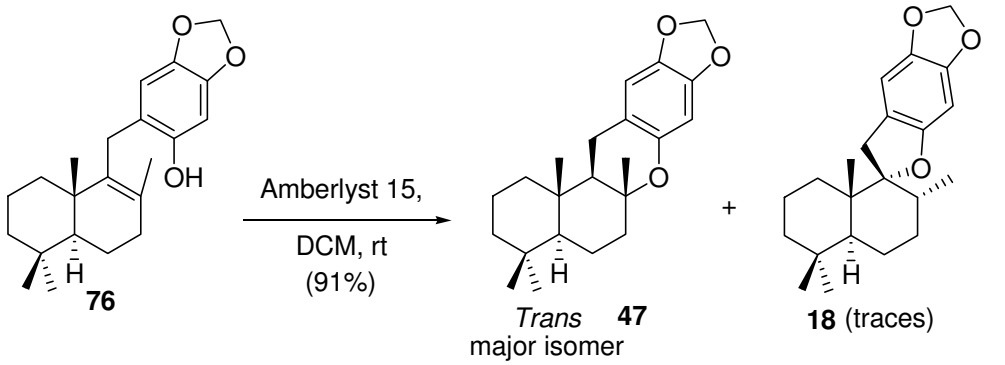
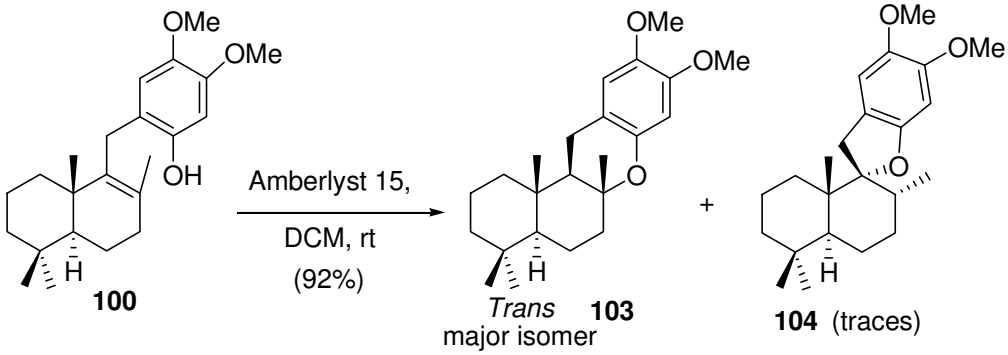
(79) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Tapia, R.; Es-Samti, H.; Fernández, A.; Barranco, I. *Eur. J. Org. Chem.* **2009**, 1139.

(141) Sakakura, A.; Sakuma, M.; Ishihara, K.; *Heterocycles* **2011**, *82*, 249.

26.-Cyclization of sesquiterpenic phenols 76 and 100 with ion exchange resin Amberlyst 15



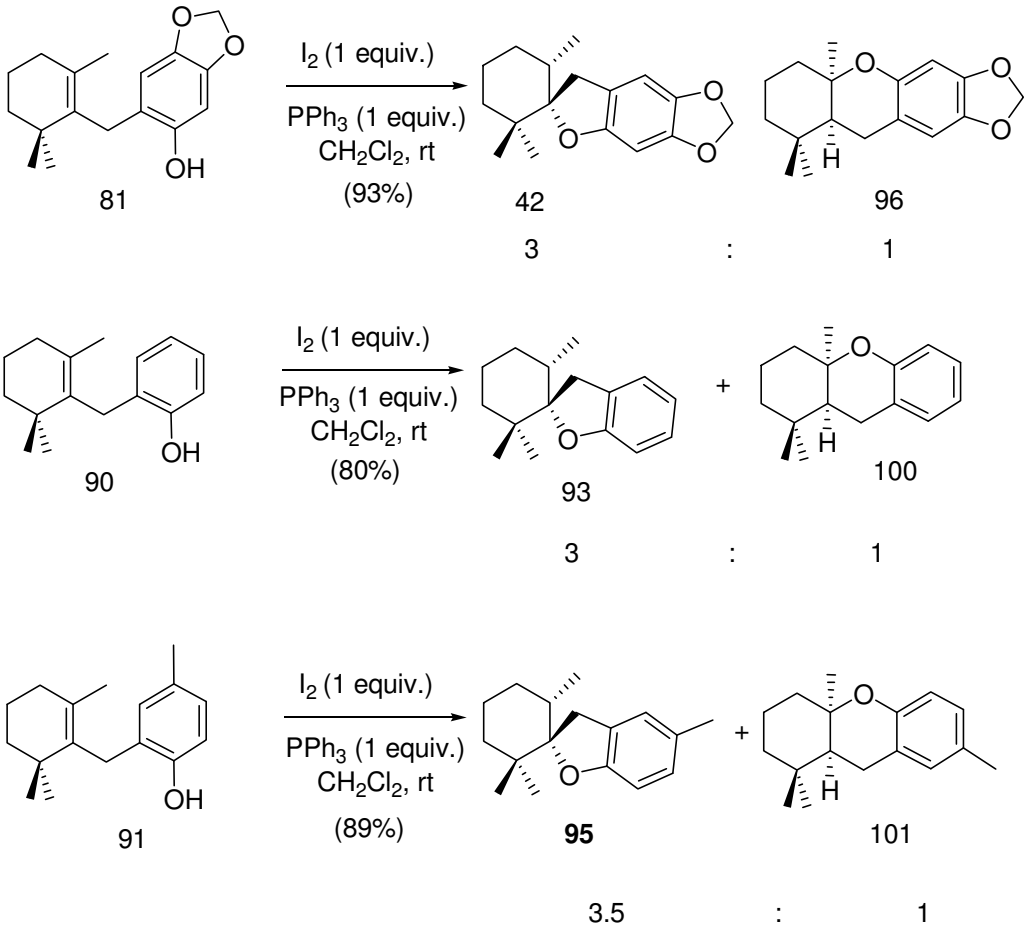


Following the general procedure described for cyclization with ion-exchange resin Amberlyst A-15, both sesquiterpenic phenols **76** (60 mg, 0.18 mmol) and **100** (40 mg, 0.11 mmol) were cyclized as well. The reaction allowed access to piranic compound **47** (55 mg, 91%) together with traces of spiro isomer **18** in the first case and to pirane **103** (37 mg, 92%), together with traces of spiro isomer **104,** respectively in the second cyclization.

All spectral data for *trans* piranic isomers ***19,20-di-O-methylene-8-epi-puupehenol (103)*** and ***19,20-di-O-methoxy-8-epi-puupehenol (47)*** match those previously reported[51].

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

27.-Cyclization of monoterpenic phenols with I_2/PPh_3 system



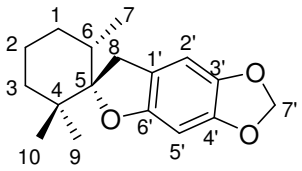
Following the general cyclization procedure with I_2/PPh_3 system monoterpenic phenols **81**, **90** and **91** were cyclized.

Cyclization of **81** (135 mg, 0.5 mmol) yielded a mixture of isomers **42** and **96** in a 3:1 ratio and 86% yield.

Phenol **90** (115 mg, 0.5 mmol) was cyclized in the same manner furnishing the corresponding isomeric mixture of **93** and **100** in a 3:1 ratio and 87% yield.

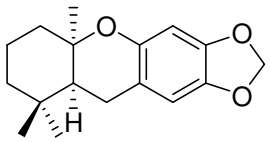
Treatment of **91** (122 mg, 0.5 mmol) following the same procedure provided the corresponding isomeric mixture of **95** and **101** in a 3.5:1 ratio and 89% yield.

After careful separation in silica gel (100%hexanes) both isomers were isolated and characterized in each case.



42

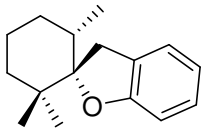
Data for ***3',4'-mehyilenedioxy-4,4,6-trimethyl-spiro[benzofuran-5(8H),5(6H)-cyclohexane] (42)***: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.55 (s, 1H), 6.31 (s,1H), 5.85 (s, 1H), 5.84 (s, 1H), 3.12 (d, *J* = 15.9 Hz, 1H), 2.77 (d, *J* = 15.9 Hz, 1H), 1.86-1.66 (m, 2H), 1.65-1.37 (m, 4H), 1.22 (m, 1H), 0.96 (s, 3H), 0.84 (s, 3H), 0.76 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.7 (C), 147.1 (C), 140.6 (C), 118 (C), 104.4 (CH), 100.9 (CH_2), 95.1 (C), 91.9 (CH), 38.2 (C), 37.3 (CH), 36.3 (CH_2), 35.2 (CH_2), 30.7 (CH_2), 24.8 (CH_3), 22.4 (CH_3), 21.5 (CH_2), 15.7 (CH_3). IR (film): 1875, 1730, 1619, 1501, 1479, 1387, 1305, 1268, 1184, 1150, 1040, 942, 920, 844, 766, 743 cm^{-1}.



96

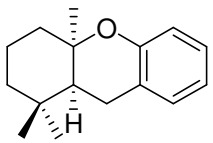
Data for ***(5aR,9aS)-5a,9,9-trimethyl-6,7,8,9,9a,10-hexahydro-5aH-[1,3]dioxolo[4,5-b]xanthene (96):*** ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.49 (s, 1H), 6.30 (s, 1H), 5.84 (d, *J* = 8.0 Hz, 2H), 2.92 (dd, *J* = 17.4, 8.0 Hz, 1H), 2.63 (d, *J* = 17.4 Hz, 1H), 1.97 (ddd, *J* = 15.4, 6.3, 3.5 Hz, 1H), 1.82 (m, 1H), 1.47-1.38 (m, 2H), 1.35 (d, *J* = 8.0 Hz, 1H), 1.25 (dd, *J* = 9.7, 3.5 Hz, 2H), 1.17 (s, 3H), 0.94 (s, 3H), 0.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.9 (C), 146.2 (C), 141.1 (C), 113.3 (C), 107.7 (CH), 100.6 (CH_2), 99.0 (CH), 75.2 (C), 44.4 (CH), 41.8 (CH_2),

39.6 (CH_2), 34.0 (C), 32.4 (CH_3), 26.8 (CH_3), 23.9 (CH_2), 21.4 (CH_3), 18.2 (CH_2). IR (film): 1876, 1731, 1631, 1503, 1479, 1438, 1387, 1366, 1235, 1180, 1148, 1040, 941, 915, 868, 845, 775 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{22}O_3Na$ ($M+Na^+$) 297.1467, found: 297.1472.



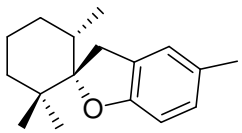
93

Data for ***4,4,6-trimethyl-spiro[benzofuran-5(8H),5(6H)-cyclohexane] (93):*** ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.04 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.82 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.49 (s, 1H), 3.41 (s, 2H), 2.07 (t, *J* = 6.3 Hz, 2H), 1.75-1.61 (m, 2H), 1.56 (s, 3H), 1.53-1.46 (m, 2H), 0.94 (m, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 161.0 (C), 127.7 (CH), 127.4 (C), 124.1 (CH), 119.2 (CH), 108.2 (CH), 94.0 (C), 38.1 (C), 37.1 (CH), 36.3 (CH_2), 34.9 (CH_2), 30.7 (CH_2), 24.8 (CH_3), 22.4 (CH_3), 21.4 (CH_2), 15.6 (CH_3). IR (film): 1729, 1600, 1484, 1462, 1387, 1325, 1267, 1244, 1134, 1017, 945, 919, 871, 747, 707 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{22}ONa$ ($M+Na^+$) 253.1568, found: 253.1572.



101

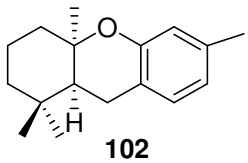
Data for ***(4aR,9aS)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (100):*** ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.05 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.75 (d, *J* = 8 Hz, 1H), 3.04 (dd, *J* = 17.6 Hz, 8.0 Hz, 1H), 2.77 (d, *J* = 17.6 Hz, 1H), 2.04 (brd, *J* = 14.6 Hz, 1H), 1.86 (m, 1H), 1.59-1.36 (m, 4H), 1.27 (t, *J* = 11.9 Hz o dd, *J* = 26.0, 15.5 Hz, 1H), 1.21 (s, 3H), 0.97 (s, 3H), 0.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 154.5 (C), 128.9 (CH), 126.6 (CH), 122.0 (C), 119.8 (CH), 117.1 (CH), 75.2 (C), 44.5 (CH), 41.7 (CH_2), 39.6 (CH_2), 34.0 (C), 32.3 (CH_3), 27.0 (CH_3), 23.6 (CH_2), 21.4 (CH_3), 18.1 (CH_2). IR (film): 1610, 1586, 1489, 1455, 1373, 1312, 1239, 1160, 1107, 1057, 1021, 946, 848, 753, 707 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{22}ONa$ ($M+Na^+$) 253.3351, found: 253.3346.



95

Data for ***3',4,4,6,-tetramethyl-spiro[benzofuran-5(8H),5(6H)-cyclohexane] (95):*** ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.89 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 3.18 (d, *J* = 16.3 Hz, 1H), 2.84 (d, *J* = 16.3 Hz, 1H), 2.26 (s, 3H), 1.85-1.71 (m, 2H), 1.65-1.49 (m, 2H), 1.44 (m, 1H), 1.35-1.19 (m, 2H), 0.99 (s, 3H), 0.84 (s, 3H), 0.75 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 161.7 (C), 130.9 (C), 130.7 (CH), 130.0 (C), 127.4 (CH), 110.3 (CH), 96.6 (C), 40.8 (C), 39.8 (CH), 39.0 (CH_2), 37.6 (CH_2), 33.4 (CH_2), 27.4 (CH_3), 25.1 (CH_3), 24.1 (CH_2), 23.4 (CH_3), 18.3 (CH_3)**.** IR (film): 1730, 1615, 1494, 1469, 1386, 1263,

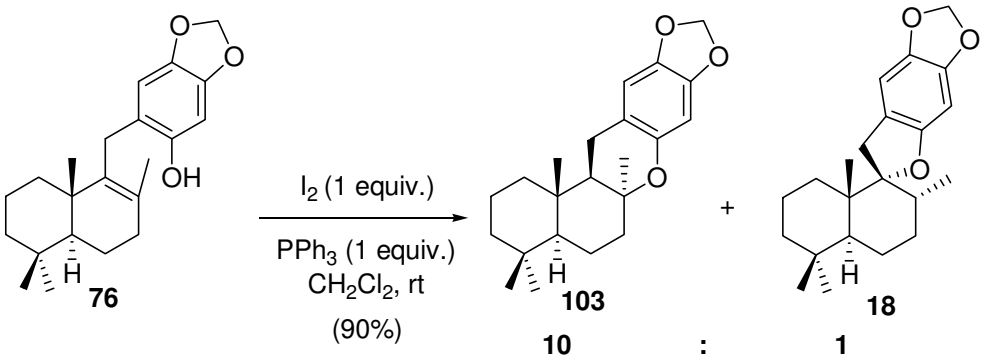
1243, 1224, 1133, 945, 920, 807 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{24}ONa$ ($M+Na^+$) 267.1725, found: 267.1723.



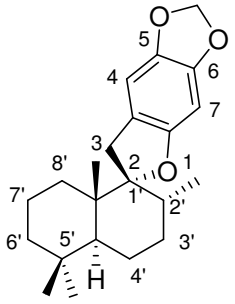
102

Data for (4aR,9aS)-1,1,4a,6-tetramethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene (102): ^1H NMR ($CDCl_3$, 500 MHz) δ: 6.85 (s, 2H), 6.63 (d, *J* = 8.8 Hz, 1H), 2.99 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.72 (d, *J* = 17.6 Hz, 1H), 2.25 (s, 3H), 2.03 (m, 1H), 1.85 (m, 1H), 1.56-1.36 (m, 5H), 1.19 (s, 3H), 0.95 (s, 3H), 0.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 154.9 (C), 131.9 (C), 131.5 (CH), 130.0 (CH), 124.3 (C), 119.4 (CH), 77.7 (C), 47.2 (CH), 44.4 (CH_2), 42.3 (CH_2), 36.6 (C), 34.9 (CH_3), 29.6 (CH_3), 26.2 (CH_2), 24.1 (CH_3), 23.2 (CH_3), 20.8 (CH_2). IR (film): 1730, 1503, 1457, 1372, 1306, 1267, 1237, 1160, 1122, 947, 812 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{24}ONa$ ($M+Na^+$) 267.1725, found: 267.1723.

28.-Cyclization of sesquiterpenic phenol 76 with I_2/PPh_3 system



Sesquiterpenic phenol **76** was cyclized following the general cyclization procedure with the I_2/PPh_3 system. The corresponding isomeric mixture of **18** and **104** was obtained in a 10:1 ratio and 90% yield.

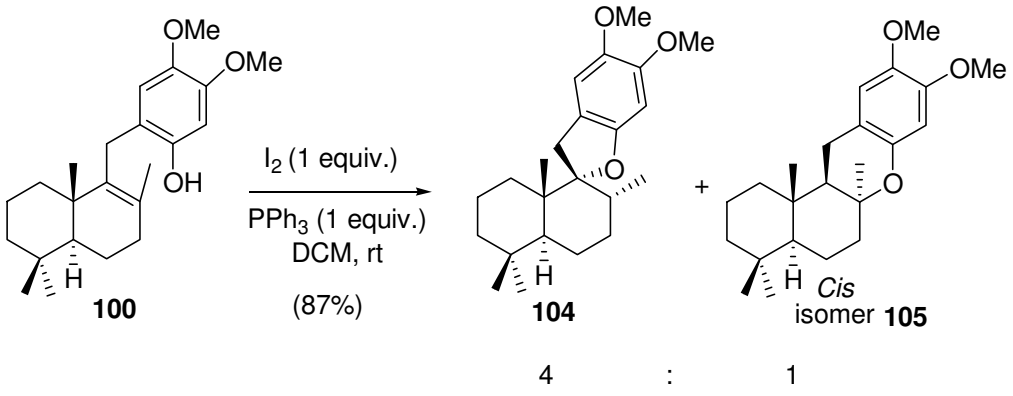


Data for ***[1'(2)R,2'R,4'aR,8'aS]-5,6-methylenedioxy-3',4',4'a,5',6',7',8',8'a-octahydro-2',5',5',8'a-tetramethyl-spiro[benzofuran-2(3H),1'(2'H)-naphtalene] (18):*** $[\alpha]_D^{25}$ = + 2.07 (c 16.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.54 (s, 1H), 6.35 (s, 1H), 5.85 (s,1H), 5.84 (s, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 2.71 (d, *J* = 16.0 Hz, 1H), 1.71 (tt, *J* = 12.0, 6.5 Hz, 1H), 1.65-1.44 (m, 5H), 1.43-1.28 (m, 5H), 1.19 (m, 1H), 0.93 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H), 0.73 (d, *J* = 6.5 Hz, 3H).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.7 (C), 147.0 (C), 140.6 (C), 117.8 (C), 104.3 (CH), 100.9 (CH_2), 96.6 (C), 91.9 (CH), 46.5 (CH), 42.5 (C), 41.8 (CH_2), 37.3 (CH), 34.8 (CH_2), 33.4 (C), 33.3 (CH_3), 31.3 (CH_2), 31.2 (CH_2), 22.1 (CH_3),

1.5 (CH_2), 18.4 (CH_2), 16.2 (CH_3), 15.7 (CH_3). IR (film): 1618, 1501, 1472, 1458, 1386, 1304, 1263, 1211, 1151, 1041, 1006, 940, 843, 797, 751 cm^{-1}.

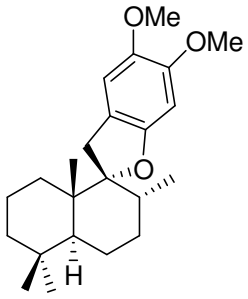
All spectral data for ***19,20-methylenedioxy-8-puupehenol (103)*** match those previously reported[51].

29.-Cyclization of sesquiterpenic phenol 100 with I_2/PPh_3 system



Sesquiterpenic phenol **100** (150 mg, 0.28 mmol) was cyclized following the general cyclization procedure with the I_2/PPh_3 system. The corresponding isomeric mixture of **104** and **105** in a 4:1 ratio and 87% yield.

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.



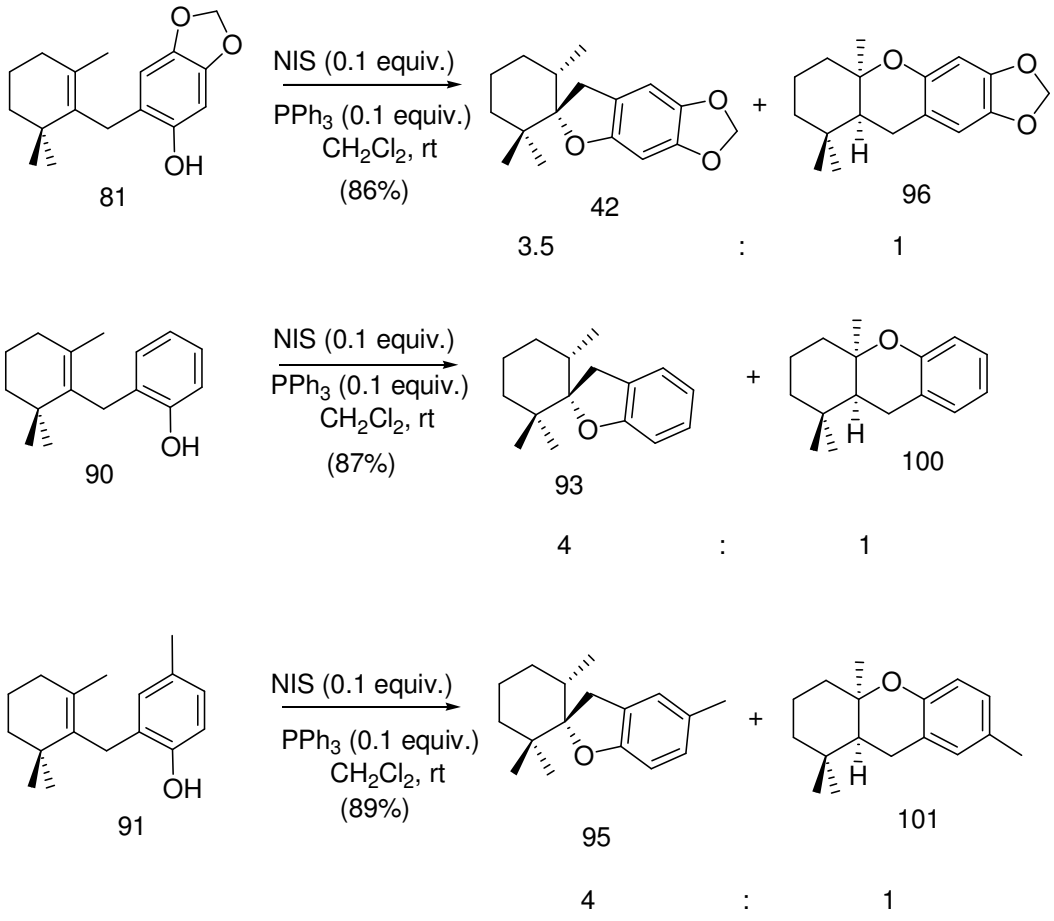
104

Data for ***[1'(2)R,2'R,4'aR,8'aS]-5,6-methoxy-3',4',4'a,5',6',7',8',8'a-octahydro-2',5',5',8'a-tetramethyl-spiro[benzofuran-2(3H),1'(2'H)-naphtalene] (104):*** ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.66 (s, 1H), 6.42 (s, 1H), 3.83 (s,3H), 3.79 (s, 3H), 3.18 (d, *J* = 15.8 Hz, 1H), 2.74 (d, *J* = 15.8 Hz, 1H), 1.73 (m, 1H), 1.68-1.23 (m, 10H), 1.18 (ddd, *J* = 13.6, 3.6 Hz,1H), 0.95 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H), 0.73 (d, *J* = 6.5 Hz, 3H).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.8 (C), 149.2 (C), 142.6 (C), 116.9 (C), 108.70 (CH), 96.6 (C), 93.9 (CH), 57.0 (CH_3), 56.1 (CH_3) 46.7 (CH), 42.6 (C), 41.8 (CH_2), 37.4 (CH), 35.0 (CH_2), 33.3 (C), 33.3 (CH_3), 31.3 (CH_2), 31.3 (CH_2), 22.1 (CH_3), 21.6 (CH_2), 18.4 (CH_2), 16.3 (CH_3), 15.8 (CH_3).

All spectral data for ***19,20-di-O-methyl-8-puupehenol(105)*** match those previously reported[51].

(51) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

30.-Cyclization of phenols with NIS/PPh_3 system

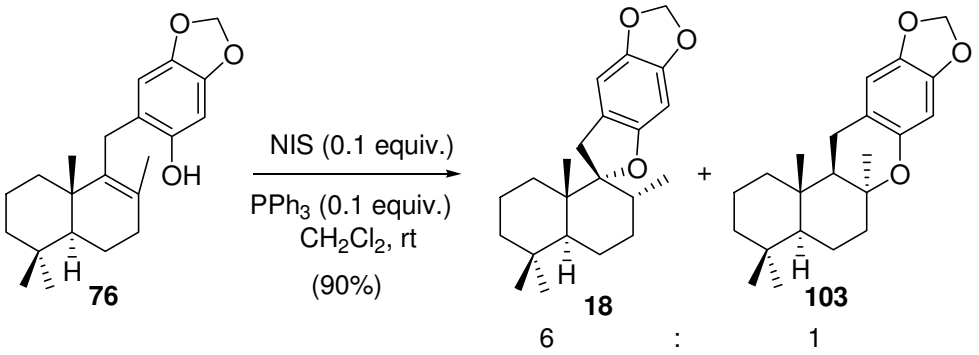


Following the general cyclization procedure with NIS/PPh_3 system monoterpenic phenols **81**, **90** and **91** were cyclized.

Cyclization of **81** (135 mg, 0.5 mmol) yielded a mixture of isomers **42** and **96** in a 3.5:1 ratio and 86% yield.

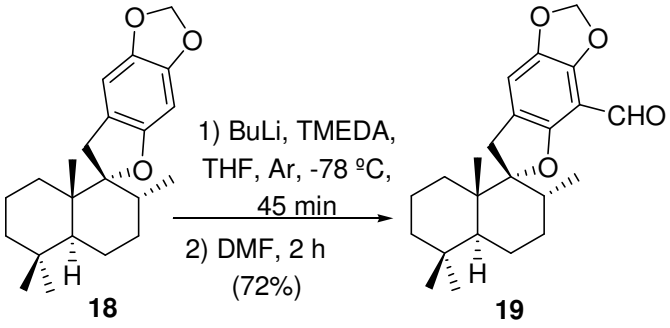
Phenol **90** (115 mg, 0.5 mmol) was cyclized in the same manner furnishing the corresponding isomeric mixture of **93** and **100** in a 4:1 ratio and 87% yield.

Treatment of **91** (122 mg, 0.5 mmol) following the same procedure provided the corresponding isomeric mixture of **95** and **101** in a 4:1 ratio and 89% yield.



Sesquiterpenic phenol **76** (110 mg, 0.32 mmol) was also cyclized in the same manner giving access to the corresponding isomeric mixture of **18** and **103** in a 6:1 ratio and 90% yield[*].

31.-Formylation of espirodihidrobenzofuran derivative 18



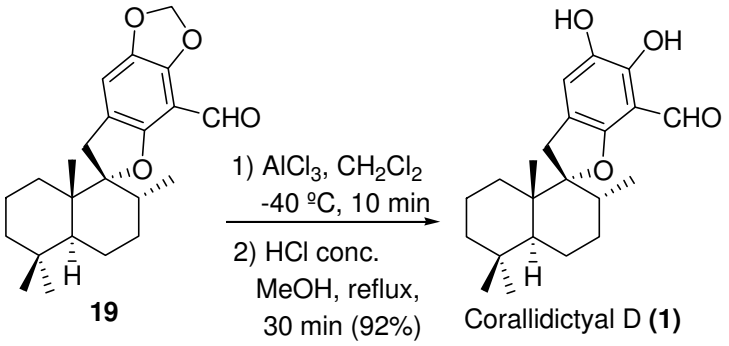
To a solution of **18** (420 mg, 1.22 mmol) in THF (12 mL), *n*-butyllithium (2.2 M in hexanes, 1.70 mL, 3.66 mmol) was added at -78 ºC under an argon atmosphere, and the reaction mixture was stirred at this temperature for 5 min. It was then allowed to warm to 5 ºC and subsequently cooled to -50 ºC. TMEDA (1.13 mL, 0.18 mmol) was added dropwise at -50 ºC and freshly distilled DMF (0.71 mL, 9.18 mmol) was added dropwise to the resultant pale yellow solution. The mixture

[*] Note that this cyclization was performed in a mg scale whlist the one with I_2/PPh_3 system was carried out over 1g of starting material.

was stirred and allowed to warm to -40 ºC over 20 min, at which time TLC showed no starting material. Then, the reaction mixture was quenched with water (3 mL) and the solvent was removed. Et_2O - water (40: 10 mL) were added to the crude product and the phases were shaken and separated. The organic phase was washed with 2N HCl (3 x 10 mL), brine (2 x 10 mL), dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent under reduced pressure afforded a crude product that was directly purified by flash chromatography (10% ether /hexanes) to give 322 mg of aldehyde **19** (72 %) as a yellow syrup.

***[1'(2)R,2'R,4'aR,8'aS]-7-formyl-5,6-methylenedioxy-3',4',4'a,5',6',7',8',8'a-octahydro-2',5',5',8'a-tetramethyl-spiro[benzofuran-2(3H),1'(2'H)-naphtalene] (19)*:** $[\alpha]_D^{25}$ = - 33.5 (c 20.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 10.26 (s, 1H, -CHO), 6.77 (s, 1H), 6.023 (s, 1H), 6.018 (s, 1H), 3.15 (d, *J* = 16.1 Hz, 1H), 2.74 (d, *J* = 16.1 Hz, 1H), 1.77 (tt, *J* = 12.1, 6.5 Hz, 1H), 1.66-1.45 (m, 5H), 1.43-1.24 (m, 5H), 1.14 (ddd, *J* = 13.4, 13.4, 3.7 Hz, 1H), 0.95 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H), 0.75 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 186.7 (-CHO), 157.3 (C), 145.5 (C), 141.4 (C), 118.9 (C), 110.7 (CH), 105.5 (C), 102.6 (CH_2), 99.1 (C), 46.7 (CH), 42.5 (C), 41.6 (CH_2), 37.2 (CH), 33.7 (C), 33.4 (CH_2), 33.2 (CH_3), 31.3 (CH_2), 31.1 (CH_2), 21.9 (CH_3), 21.3 (CH_2), 18.2 (CH_2), 16.1 (CH_3), 15.6 (CH_3). IR (film): 1689, 1637, 1455, 1392, 1310, 1256, 1190, 1091, 1072, 1007, 968, 927, 760, 714, 630 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{30}O_4Na$ ($M+Na^+$) 393.2042, found: 393.2046.

32.-Methylenedioxy cleavage: Synthesis of corallidictyal D (1)



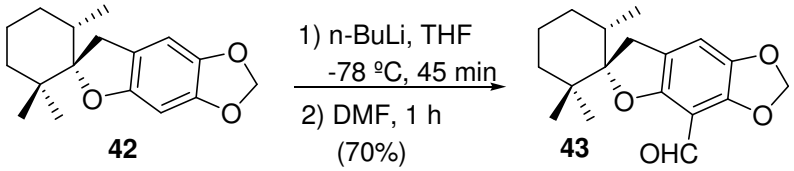
Anhydrous $AlCl_3$, (172 mg, 3 equiv.) was added to a cold (- 40 ºC) solution of **19** (60 mg, 0.43 mmol) in dry dichloromethane (10 mL) under an atmosphere of Argon and the reaction mixture was stirred for 5 min, at which time TLC showed no starting material remaining. Then water (0.5 mL) was added and the organic solvent was removed under vacuum. The resulting crude product was dissolved in methanol (4 mL) and concentrated HCl (1 mL) was added, and the mixture was refluxed for 30 min (until none of the intermediate chloromethyl ether remained). The reaction mixture was allowed to cool to room temperature, the methanol was evaporated and the crude product was diluted with ether (50 mL), washed with water (3 x 20 mL) and brine (2 x 20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the solvent removed to give pure corallidictyal D **(1)** (144 mg, 92 %).

Corallidictyal D (1): $[\alpha]_D^{25}$ = - 21.8 (c 14.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 11.09 (brs, 1H, -OH), 10.20 (s, 1H, -CHO), 6.93 (s, 1H), 5.09 (brs, 1H, -OH), 3.14 (d, *J* = 16.0 Hz, 1H), 2.73 (d, *J* = 16.0 Hz, 1H), 1.78 (tt, *J* = 12.4, 6.5 Hz, 1H), 1.67-1.53 (m, 3H), 1.48 (ddd, *J* = 16.3, 12.7, 3.1 Hz, 1H), 1.42-1.11 (m, 7H), 0.96 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H), 0.73 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 193.0 (-CHO), 157.0 (C), 146.3 (C), 137.0 (C), 119.5 (CH), 117.5 (C), 105.8 (C), 99.5 (C), 47.0 (CH), 42.6 (C), 41.8 (CH_2), 37.3 (CH), 33.7 (CH_2), 33.6 (CH_3), 33.4 (C), 31.5 (CH_2), 31.3 (CH_2), 22.0 (CH_3), 21.5 (CH_2), 18.4

(CH_2), 16.4 (CH_3), 15.8 (CH_3). IR (film): 3565, 3419, 1652, 1634, 1470, 1386, 1332, 1299, 1255, 1236, 1213, 1109, 1069, 1032, 1010, 977, 936, 892, 856, 782, 752, 728, 667, 621 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{30}O_4Na$ ($M+Na^+$) 381.2042, found: 381.2033.

^{1}H NMR (DMSO, 500 MHz) δ: 10.15 (s, 1H, -CHO), 6.91 (s, 1H), 3.08 (d, *J* = 16.2 Hz, 1H), 2.70 (d, *J* = 16.2 Hz, 1H), 1.76 (m, 1H), 1.05-1.60 (m, 11H), 0.92 (s, 3H), 0.87 (s, 3H), 0.81 (s, 3H), 0.66 (d, *J* = 6.5 Hz, 3H).

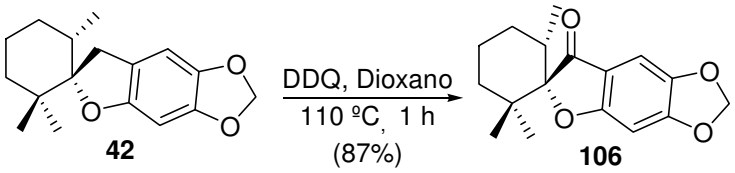
33.-Formylation of 42 with DMF



The same procedure described above for the formylation of **18** with DMF was followed (see section 31 of Experimental Procedures VI). Starting from 275 mg of **42** (1 mmol), the reaction delivered **43** (212 mg, 70%).

7-formyl-5,6-methylendioxy-2',2',6'-trimethyl-spiro[benzofuran-2(3H),1'(6'H)-yiclohexane] (43): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.24 (s, -CHO), 6.79 (s, 1H), 6.03 (s, 2H), 3.12 (d, *J* = 16.0 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H), 1.83-1.75 (m, 2H), 1.58-1.53 (m, 2H), 1.50 (m, 1H), 1.29 (m, 1H), 0.99 (s, 3H), 0.85 (s, 3H), 0.78 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 186.7 (CHO), 157.2 (C), 141.3 (C), 119.1 (C), 110.7 (CH), 105.6 (C), 102.6 (CH_2), 97.6 (C), 38.2 (C), 37.1 (CH), 36.2 (CH_2), 34.0 (CH_2), 30.6 (CH_2), 27.0 (C), 24.7 (CH_3), 22.3 (CH_3), 21.3 (CH_2), 15.6 (CH_3). IR (film): 1692, 1638, 1455, 1391, 1259, 1074, 967 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{18}H_{22}O_4Na$ ($M+Na^+$) 325.1416, found: 325.1423.

34- Treatment of 42 with DDQ

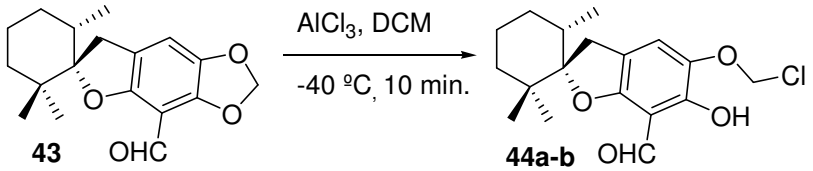


42 **106**

DDQ (140 mg, 0.62 mmol) was added to a solution of **42** (150 mg, 0.547 mmol) in dioxane (8 mL) and the mixture was stirred at reflux for 1 h, at which time TLC showed no **42**. Then, the solvent was removed under vacuum and the crude product was chromatographed on silica gel column (15% ether/hexanes) affording pure ketone **106** (137 mg, 87%) as yellow syrup.

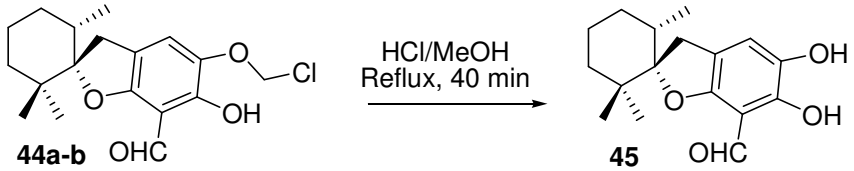
5,6-methylenedioxy-2',2',6'-trimethyl-2-oxa-spiro[benzofuran-2(3H),1'(6'H)-cyclohexane] (106):. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.91 (s, 1H), 6.56 (s, 1H), 6.04 (s, 2H), 2.26 (m, 1H), 1.78-1.62 (m, 2H), 1.61-1.55 (m, 2H), 1.47 (m, 1H), 1.26 (m, 1H), 1.20 (s, 3H), 0.68 (s, 3H), 0.60 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 202.0 (C), 171.3 (C), 156.8 (C), 143.7 (C), 102.5 (CH_2), 100.4 (CH), 97.8 (C), 93.6 (CH), 37.8 (C), 37.1 (CH_2), 33.5 (CH), 30.4 (CH_2), 25.4 (CH_3), 21.3 (CH_2), 20.6 (CH_3), 15.8 (CH_3). IR (film): 1695, 1622, 1463, 1291, 1274, 1196, 1036, 942 cm^{-1}.

35.-Acidic methylendioxy cleavage with aluminium trichloride



To a cooled (-40ºC) solution of methylenedioxy derivative **43** (30 mg, 0.1 mmol) in dry DCM (2 mL), was added anhydrous $AlCl_3$ (30 mg, 0.22 mmol) and the mixture was stirred for 10 minutes at -40 ºC, at which time TLC showed the appearance of **43**. Water (0.5 mL) was added, and the reaction was allowed to warm to room temperature. Then, the organic phase was separated and washed with water (2 x 5 mL) and brine (2 x 5 mL). The resulting organic phase was dried over Na_2SO_4, filtered, and evaporated to give a mixture of the two regioisomers **44a-b** in nearby quantitative yield (33 mg, 97%).

36.-Acidic hydrolysis: synthesis of monoterpenic analog of corallidictyal D (45)



To a solution of **44a-b** (30 mg, 0.09 mmol) in MeOH (1 mL), was added concentrated HCl (0.2 mL) and the reaction was stirred at reflux for 40 minutes, until none of the intermediate chloromethyl ether remained. The reaction mixture was then allowed to cool to room temperature and the methanol was evaporated. The crude product was diluted with ether (30 mL) and washed with water and

brine, dried over Na_2SO_4, filtered and the solvent was finally removed to give 25 mg (96%) of **45.**

7-formyl-5,6-dihydroxy-2',2',6'-trimethyl-spiro[benzofuran-2(3H),1'(6'H)-cyclohexane] (45): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.1 (br s, -OH), 10.17 (s, 1H, -CHO), 6.94 (s, 1H), 3.12 (d, *J* = 15.9 Hz, 1H), 2.79 (d, *J* = 15.9 Hz, 1H),), 1.83-1.20 (m, 7H), 1.00 (s, 3H), 0.84 (s, 3H), 0.76 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 186.7 (CHO), 157.2 (C), 141.3 (C), 119.1 (C), 110.7 (CH), 105.6 (C), 102.6 (CH_2), 97.6 (C), 38.2 (C), 37.1 (C), 36.2 (CH_2), 34.0 (CH_2), 30.6 (CH_2), 27.0 (C), 24.7 (CH_3), 22.3 (CH_3), 21.3 (CH_2), 15.6 (CH_3). IR (film): 3432, 1729, 1691, 1637, 1455, 1261, 1073, 800 cm^{-1}.

CONCLUSIONS

CONCLUSIONS

1.- The enantioselective total synthesis of (+)-liphagal, a selective inhibitor of PI3K α, isolated from the marine sponge *Aka coralliphaga*, has been achieved in 12 steps and 19% global yield. The novel tetracyclic "liphagane" skeleton is formed in one step, after the hydrogenation of a dihydroxydrimane phenol benzyl ether in the presence of cationic resin Amberlyst 15.

2.-The syntheses of monoterpenic analogs of liphagal and the corresponding analog of corallidictyal D have been performed and both their SAR studies are currently ongoing.

3.-Two synthetic approaches towards the protein kinase C inhihitors corallidictyals B and D starting from (+)-sclareolide (**3**) have been developed. Both alternative strategies showed the difficulties in the spiroannulation process that turned out to be the key step in this synthesis.

4.-During the course of our investigations, a synthetic sequence allowing access to drimanic aldehyde **49** starting from (+)-sclareolide (**3**) has been reported.

5.-First total synthesis of protein kinase C inhibitor corallidictyal D (**1**) from α-ionone (**60**) has been achieved in 11 steps and 17% global yield. The benzofuran moiety formation proceeded successfully after treatment of unsaturated phenol **63** with the NIS/PPh_3 system.

6.-A new methodology for the spiroannulation of *o*-allylphenols has been developed. The treatment of *o*-allylphenols with the NIS-PPh_3 system affords the corresponding spirodihydrobenzofuran derivatives in high yield, with high region- and total stereoselectivity, under mild conditions.

7.-A new biogenetic pathway to liphagal and corallidictyal D has been proposed based on the experimental results obtained within this project. It suggests the existence of an *o*-quinone methide intermediate that will allow access to both products enantioselectively and it also provides an explanation to the possible formation of (+)-liphagal through a ring expansion process of corallidictyals' skeleton.

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ANEXO

De forma paralela a la realización del trabajo presentado en esta memoria, la etapa de formación predoctoral en el grupo de "Productos Naturales y Síntesis Orgánica Aplicada", me ha permitido llevar a cabo otras actividades complementarias y ha dado lugar a las siguientes publicaciones y comunicaciones en congresos:

PUBLICACIONES

- **"O_3/Pb(OAc)$_4$: a new and efficient system for the oxidative cleavage of allyl alcohols."**

  Alvarez-Manzaneda, E.; Chahboun, R.; Cano, M. J.; Cabrera, E.; Alvarez, R.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. M. *Tetrahedron Lett.*. **2006**, .47, 6619.

- **"Regioselective routes towards 14-hydroxyabietane diterpenes. A formal synthesis of immupressasnt (-)-triptolide ferom (+)-abietic acid."**

  Alvarez-Manzaneda, E.; Chahboun, R.; Bentaleb, F.; Alvarez, E.; Escobar, M. A.; Sad-Diki, S.; Cano, M. J.; Messouri, I. *Tetrahedron.* **2007**,.63, 11204.

- **"Enantioselective Total Synthesis of the Selective PI3 Kinase Inhibitor liphagal."**

  Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Cano, M, J.; Haidour, A.; Alvarez-Manzaneda, R. *Org. Lett.* **2010**, 20, 4459-4453.

- **"NIS-PPh$_3$: A Selective Reagent for the Spiroannulation of *O*-Allyl Phenols. Total Synthesis of corallidictyal D."**

  Cano, M, J.; Bounanou, H.; Tapia, R.; Chahboun, R.; Alvarez-Manzaneda, E. *Eur. J. Chem.* Submitted.

- **"I_2/PPh_3 mediated spiroannulation of unsaturated β-ketoesters: First enantiospecific synthesis of negundoin A."**

  Tapia, R.; Cano, M. J.; Bounanou, H.; Chahboun, R.; Alvarez, E.; Alvarez-Manzaneda, R.; Alvarez-Manzaneda, E; *J. Org. Chem*. Submitted.

- **"I_2/PPh_3 mediated spiroannulation of unsaturated carboxylic acids. First enantiospecific synthesis of isoambreinolide, vitexifolin D and vitedoin B"**

  Bounanou, H.; Tapia, R.; Cano, M. J.; Alvarez-Manzaneda, E.; Chahboun, R.; Boulifa. E.; Ibn Manssour, A. *J. Org. Chem*. Submitted.

COMUNICACIONES EN CONGRESOS

- **"A New Synthetic Approach To The Protein Kinase C Inhibitors Corallidictyals B And D"**

  M. J. Cano Úbeda; E. Álvarez-Manzaneda, R. Chahboun, E. Alvarez and E. Boulifa.

  CHALLENGES IN ORGANIC CHEMISTRY 2011, Villars Sur Ollon (Switzerland).

- **"New Synthetic Route Towards Bioactive Terpenoids with Perhidroindane Core".**

  M. J. Cano, E. Álvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Álvarez,a R. Álvarez-Manzaneda, I. Barranco, H. Bouanou, I. Herráiz.

  CMERAM 2009, Tetuán (Marocco).

"Synthetic Approaches to the Protein Kinase C Inhibitors Corrallidictyal A and B."

M. J. Cano Úbeda, E. Álvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Álvarez, R. Álvarez-Manzaneda, R. Tapia, S. El Baghouria.

2ND EUCHEMS CHEMISTRY CONGRESS 2008, Turin (Italy).

ESTANCIAS BREVES EN CENTROS DE INVESTIGACIÓN DE PRESTIGIO EN EL EXTRANJERO

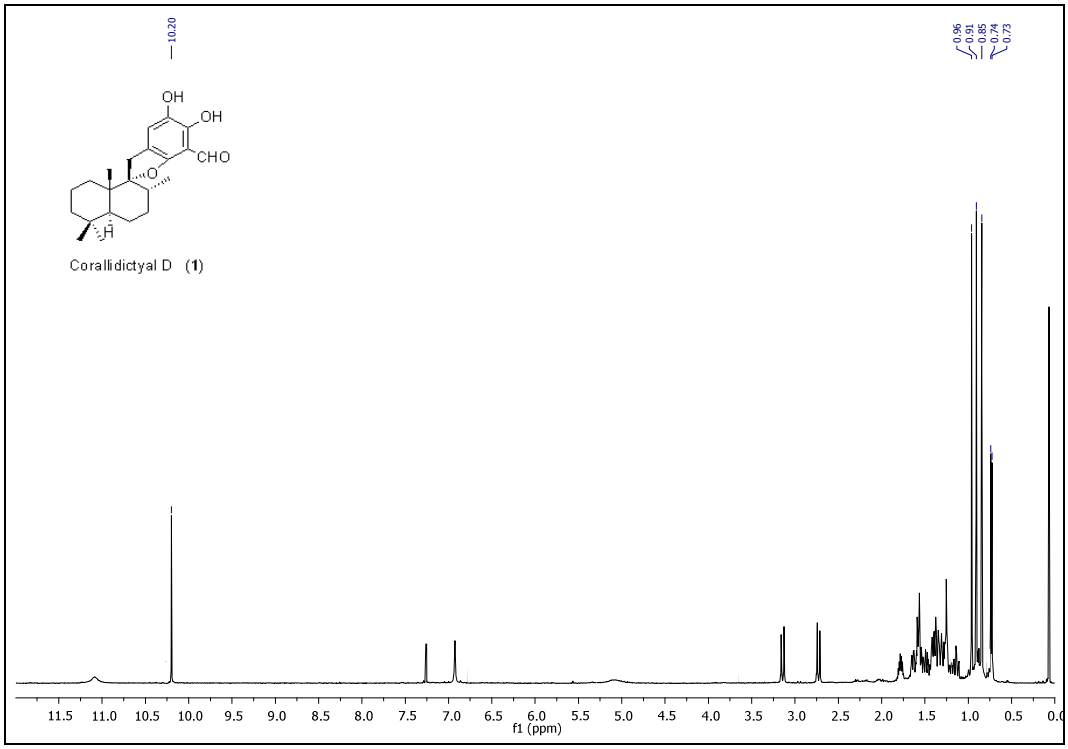
California Institute of Technology: Julio 2010-Noviembre 2010.

Grupo Prof. Brian M. Stoltz.
Proyecto: Progress toward the enantioselective synthesis of new bidentated ligands N-alkene.

University of Oxford: Mayo 2012-Agosto 2012

Grupo Prof. Darren J. Dixon.
Proyecto: Development of new intramolecular nitro Michael cascade cyclisation.

ESPECTROS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0.74
0.73
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CHO
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H
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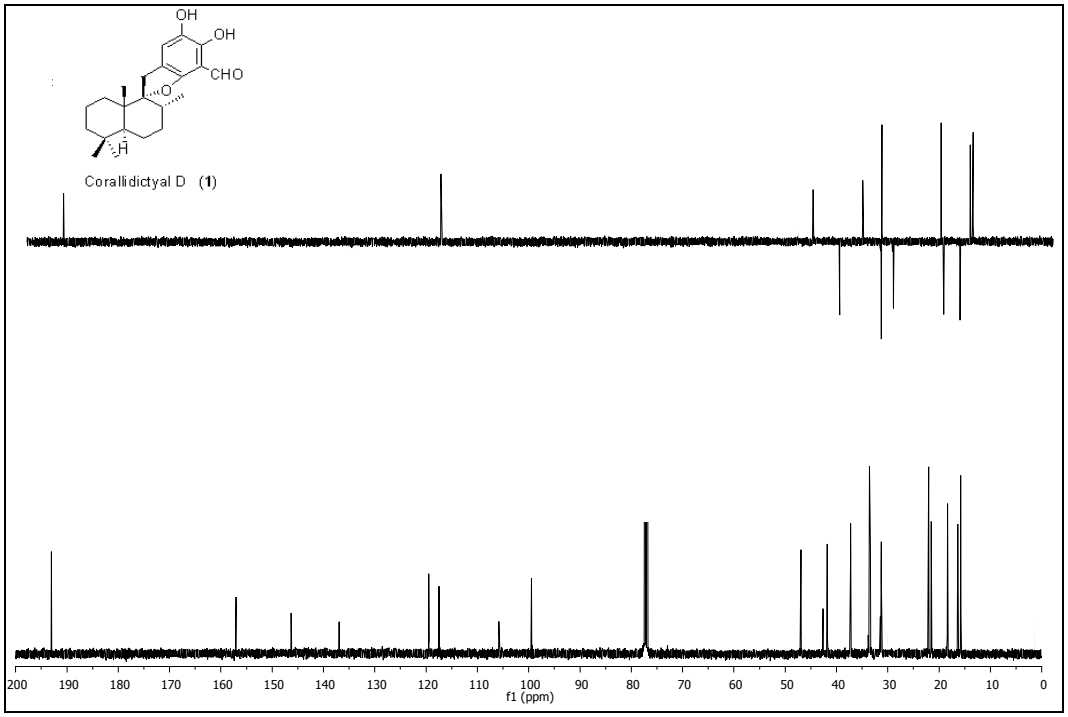
f1 (ppm)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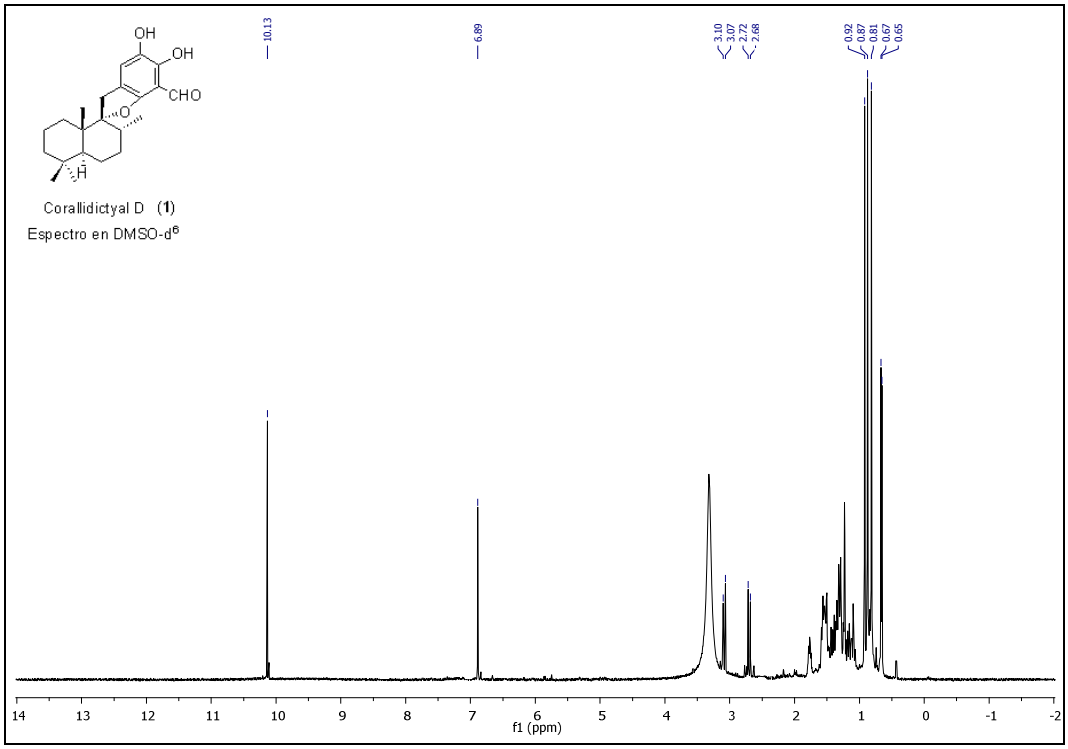
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H
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3.10
3.07
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2.68
0.92
0.87
0.81
0.67
0.65
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9
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3
2
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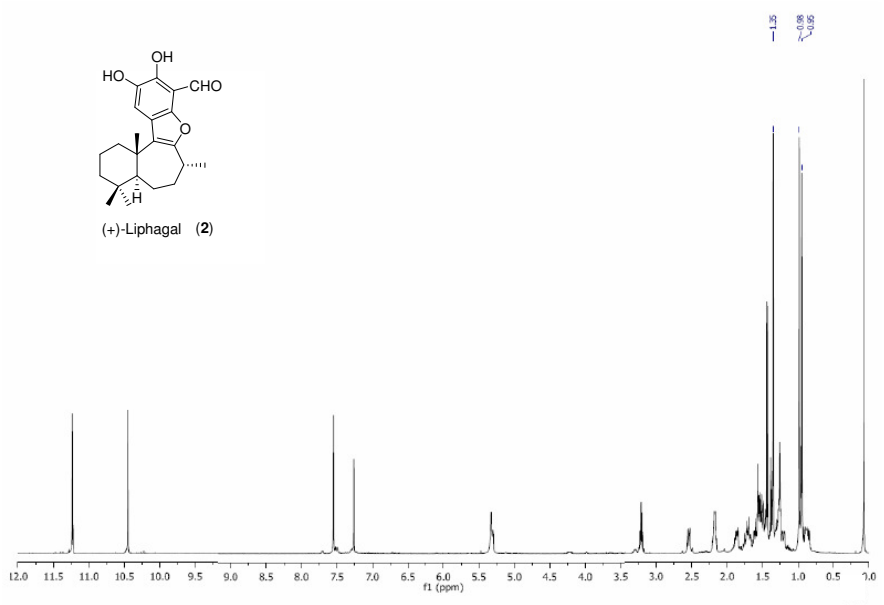
-2
f1 (ppm)



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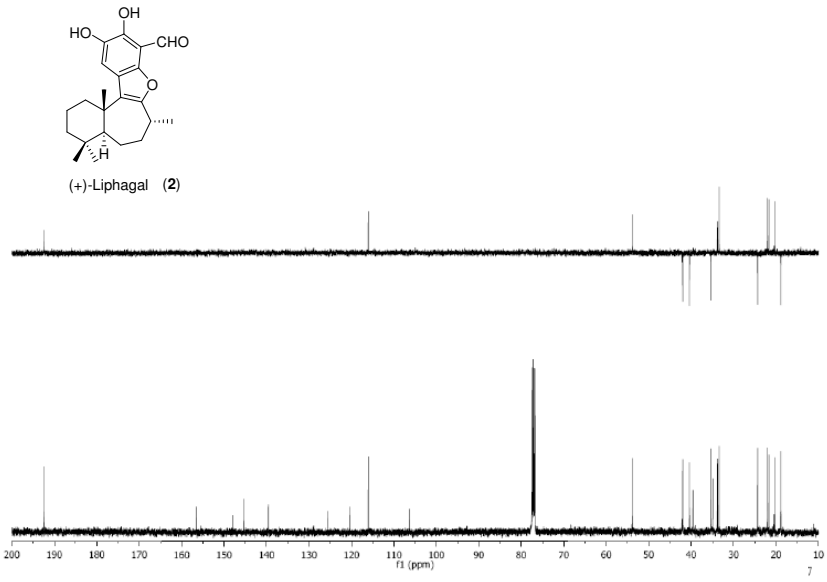
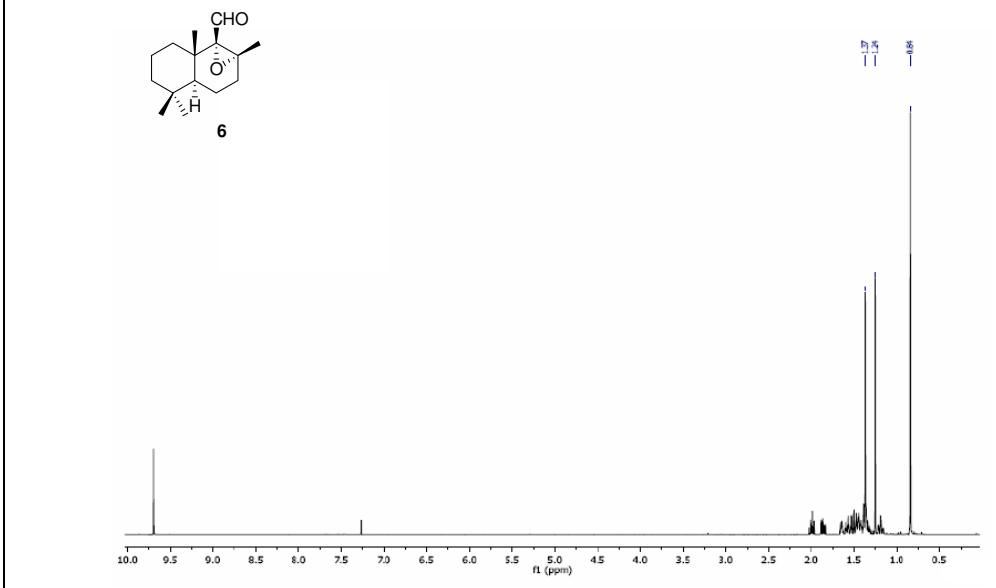


(+)-Liphagal (**2**)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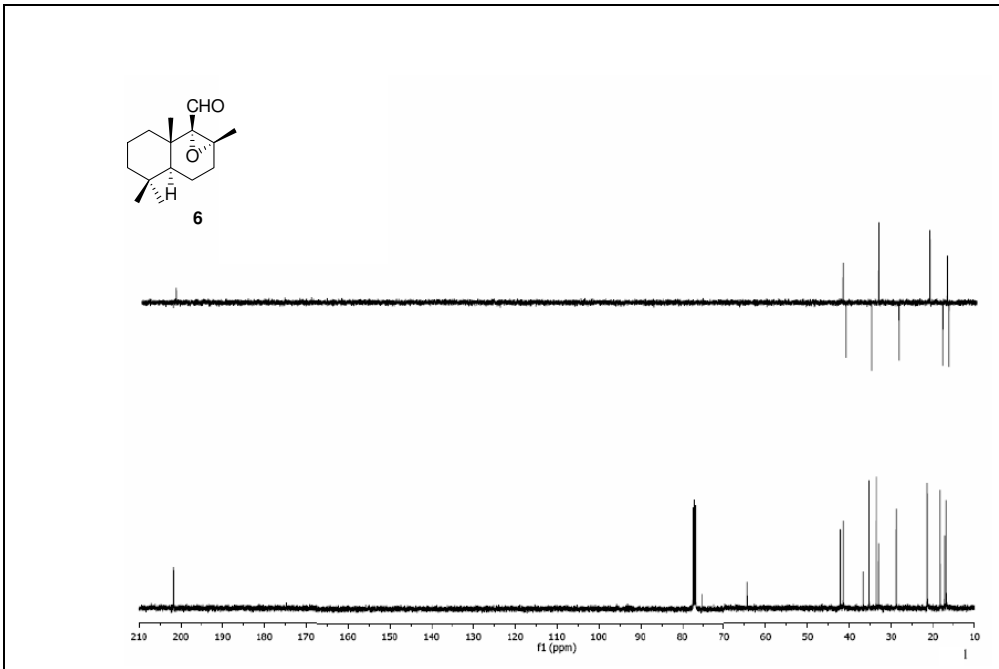
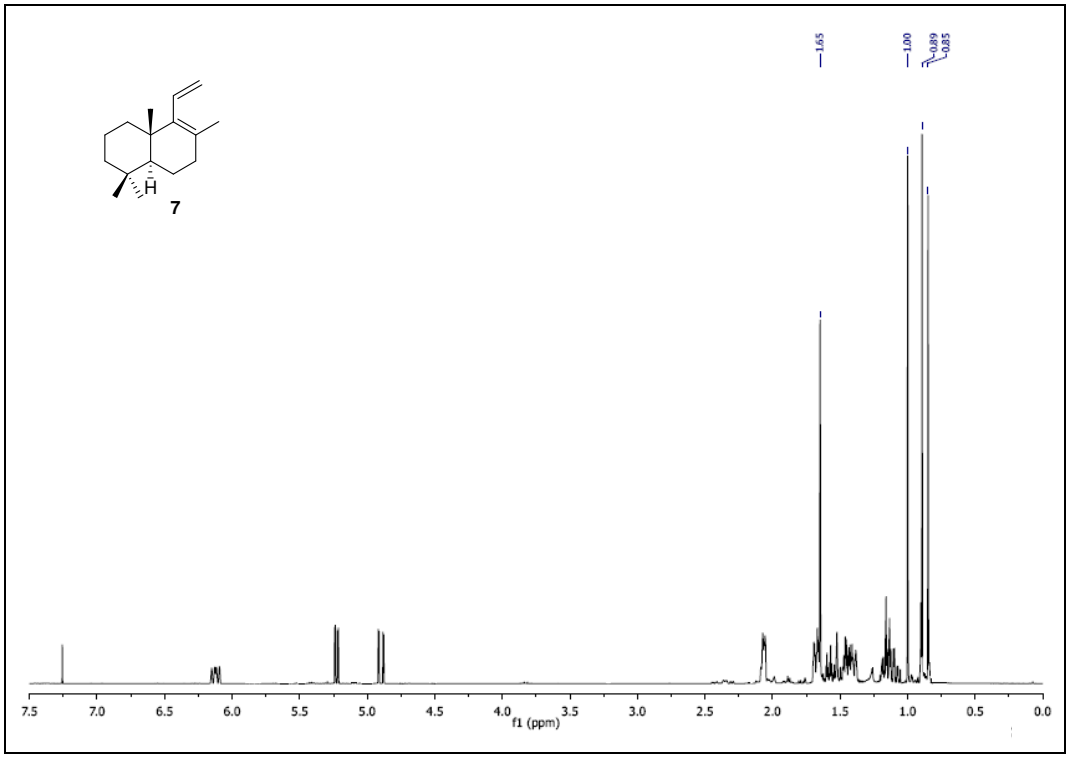
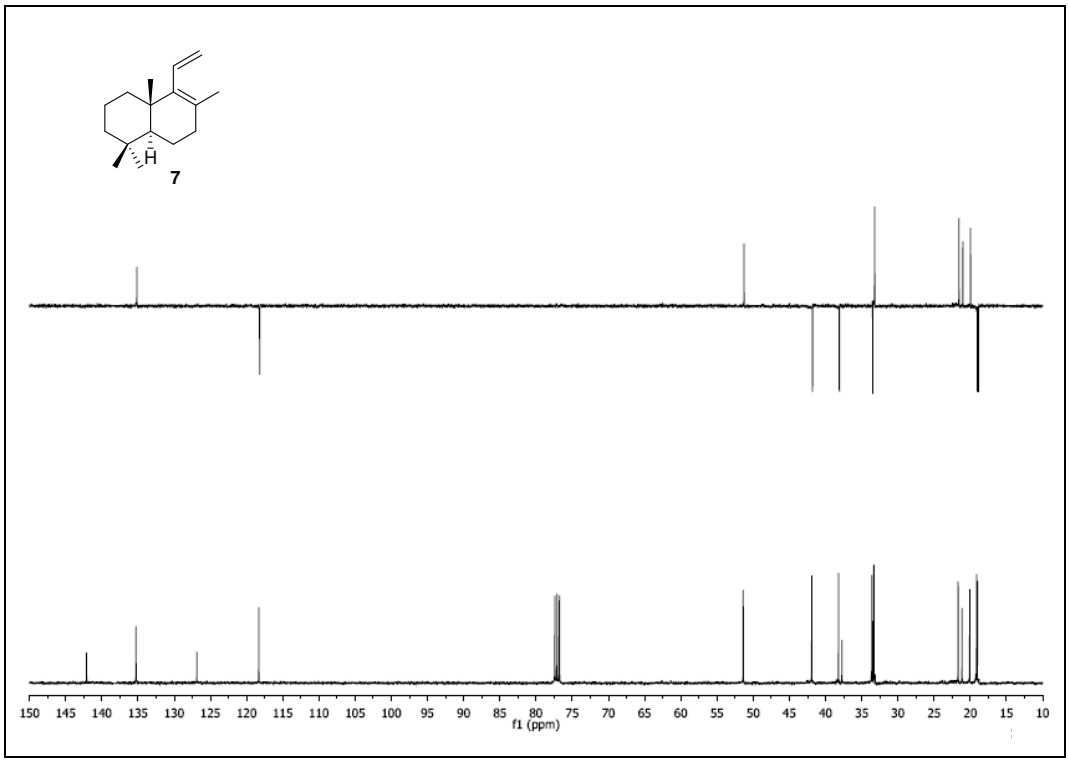
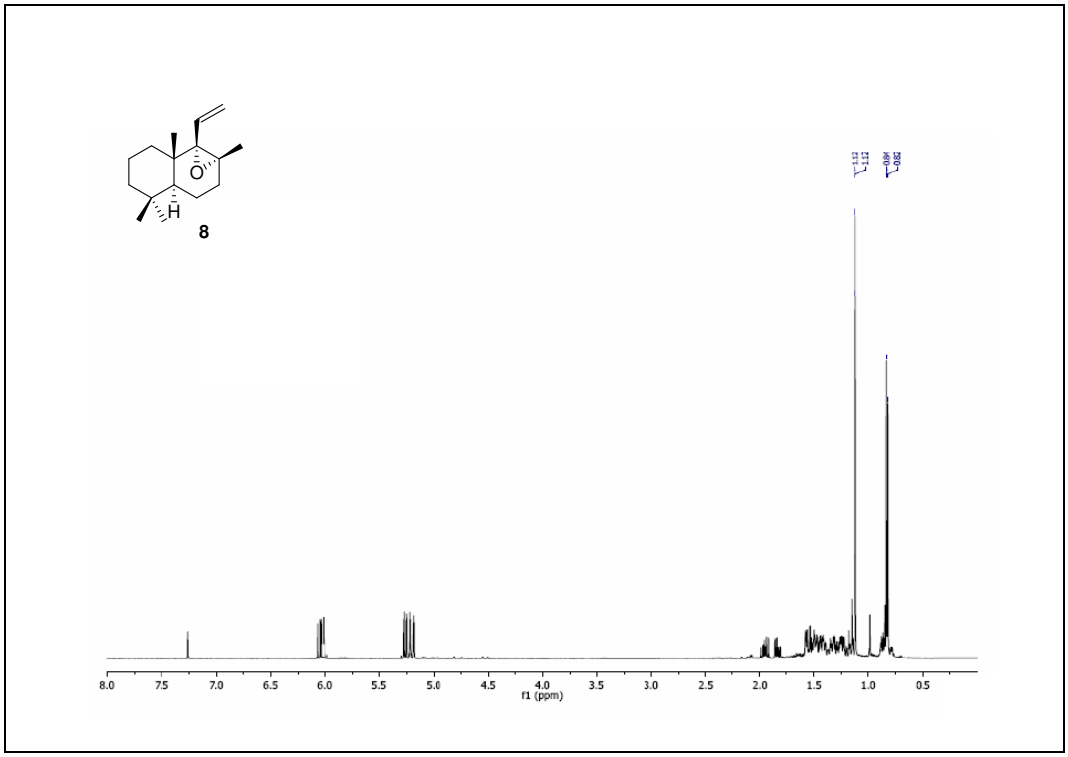
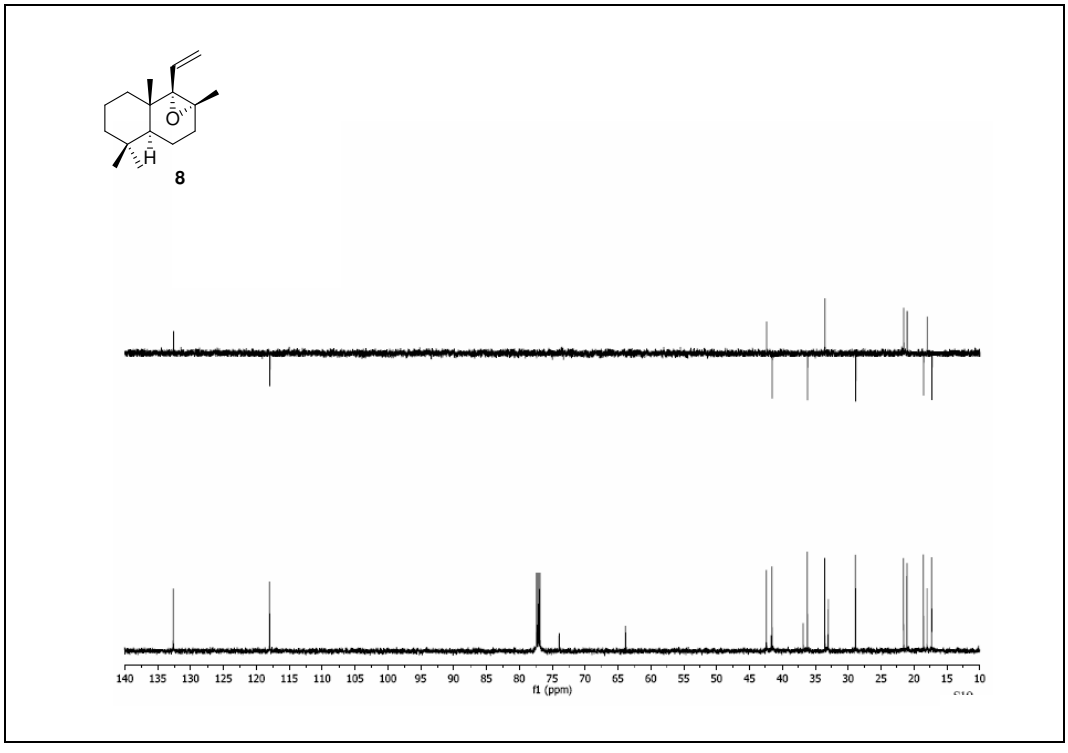
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

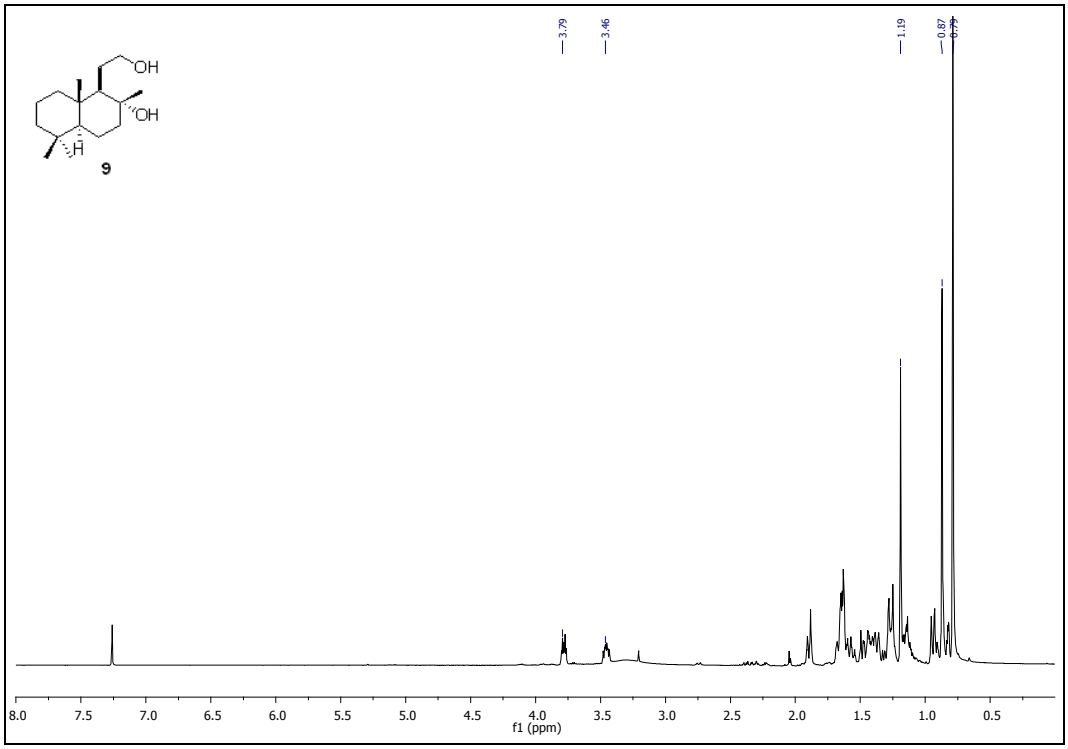

CHO
O
H
6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

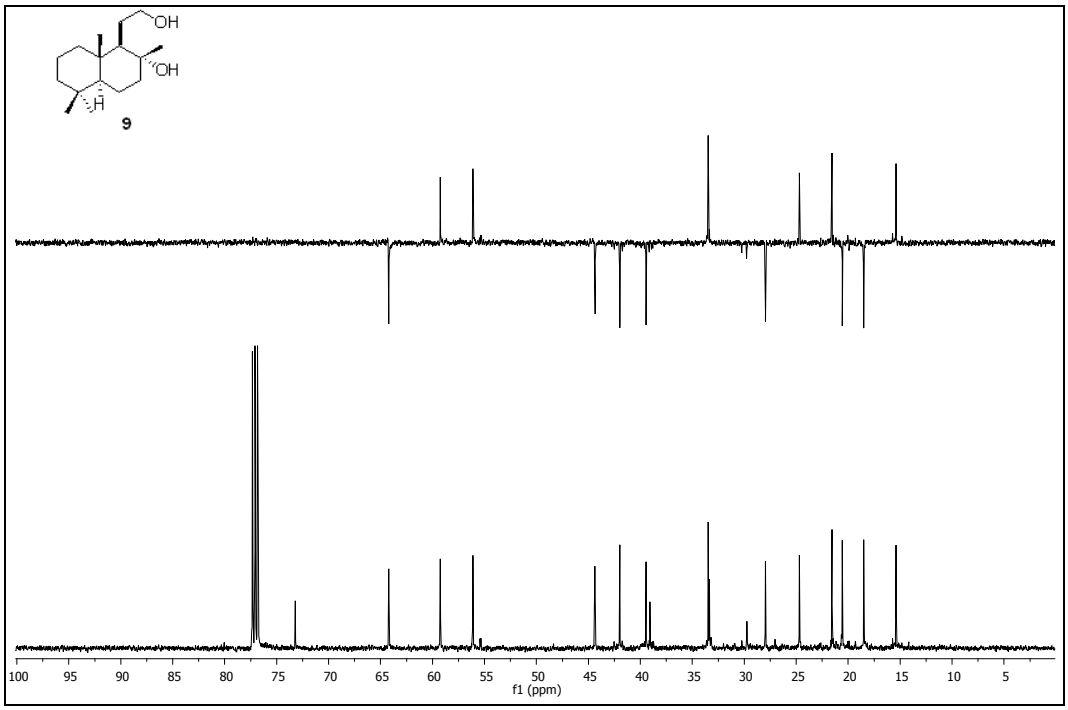

1.65
1.00
0.89
0.85
7
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

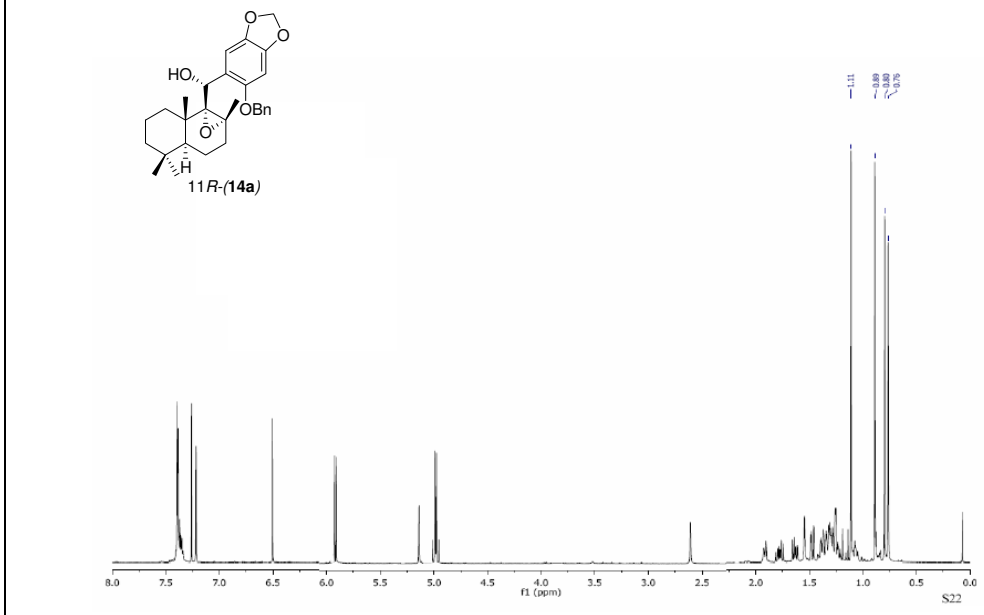

7
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

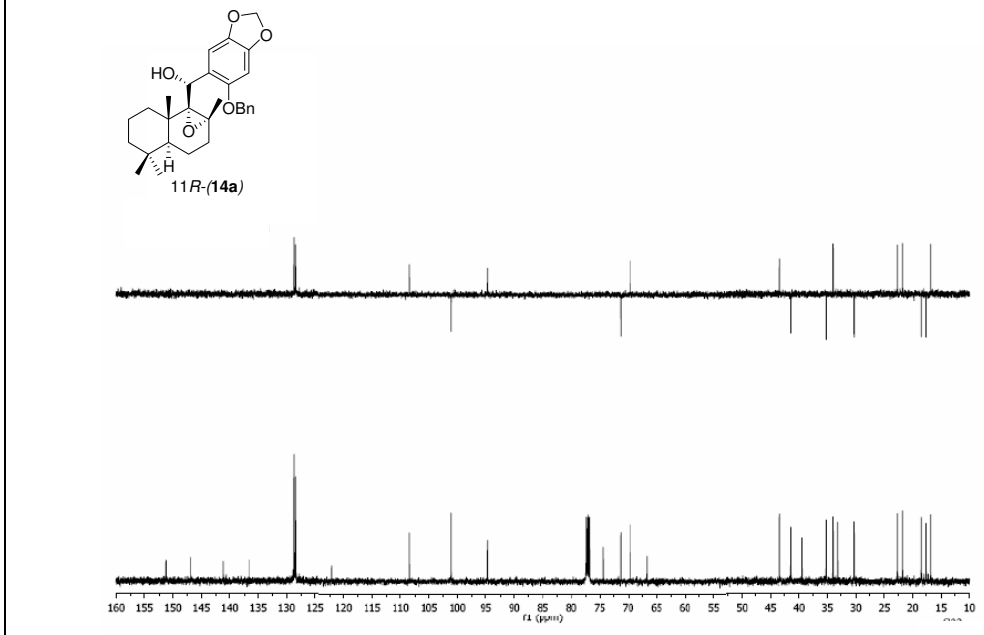

O
H
8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

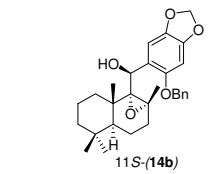

O
H
8
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)


OH
OH
H
9
3.79
3.46
1.19
0.87
0.79
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


OH
OH
H
9
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)

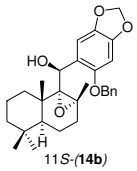

HO
OBn
O
H
11R-(14a)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
S22


HO
OBn
O
H
11R-(14a)
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)

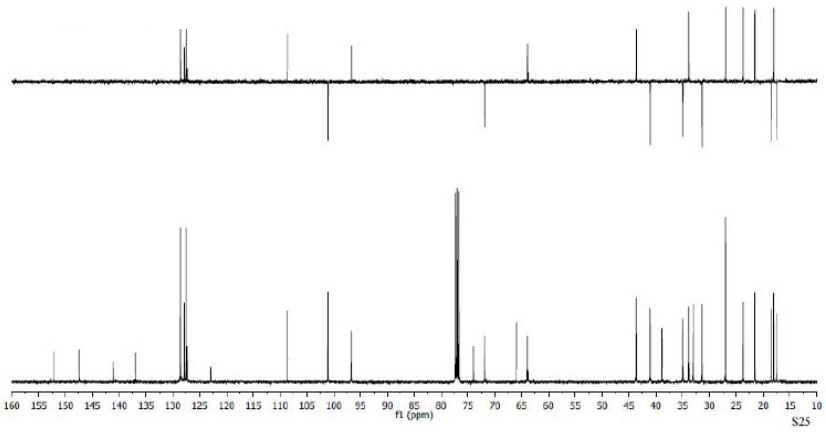


11*S*-(**14b**)

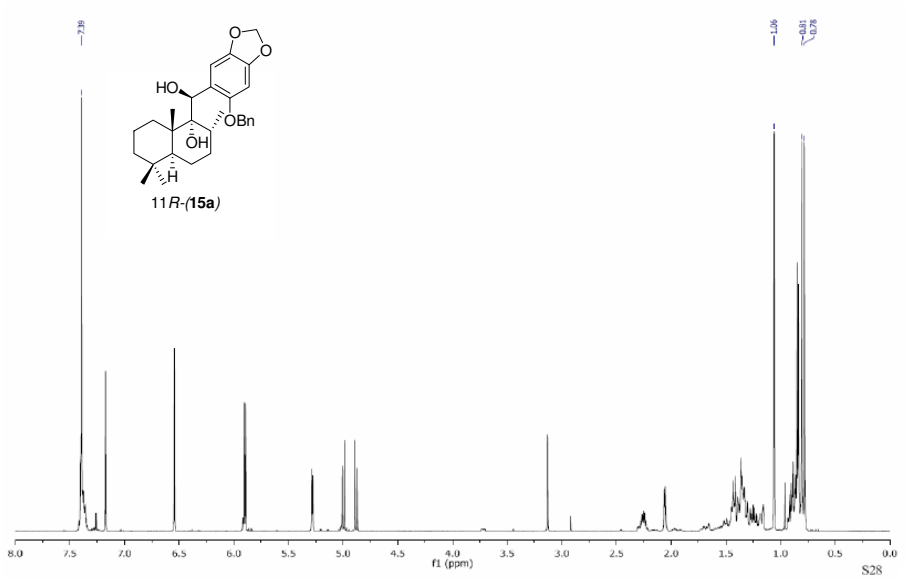
S24

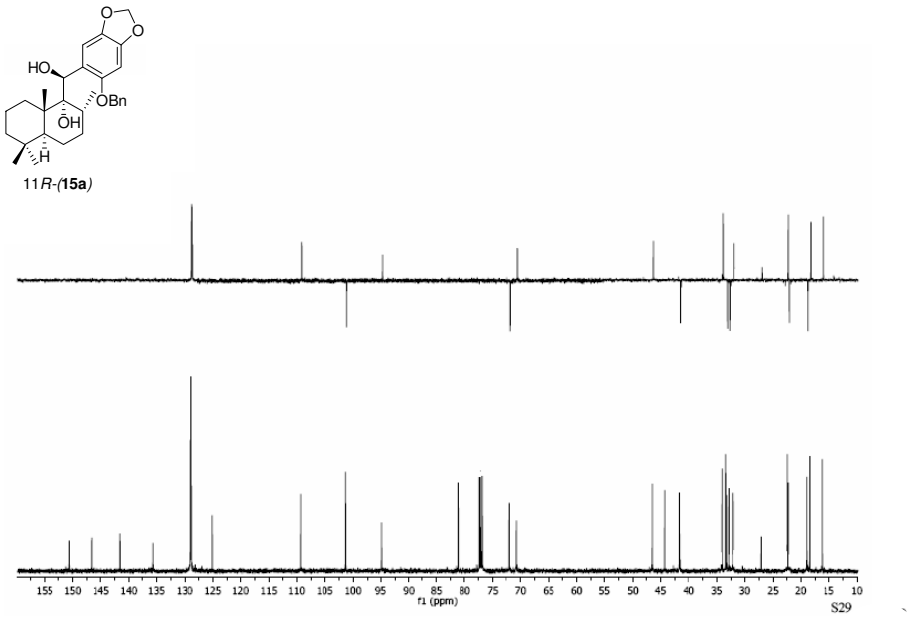


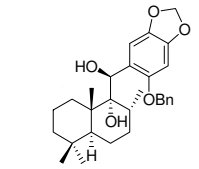
11*S*-(**14b**)



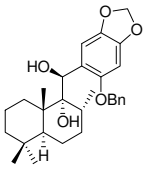
S25


HO
OBn
OH
H
11R-(15a)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
S28

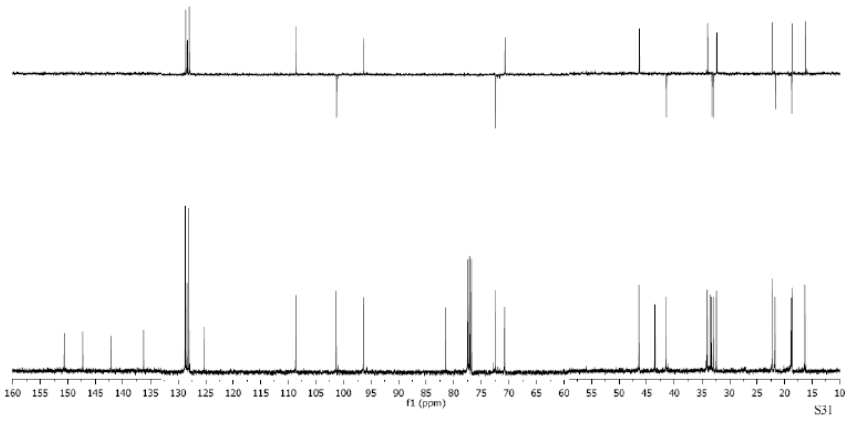

HO
OBn
OH
H
11R-(15a)
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
f1 (ppm)
S29

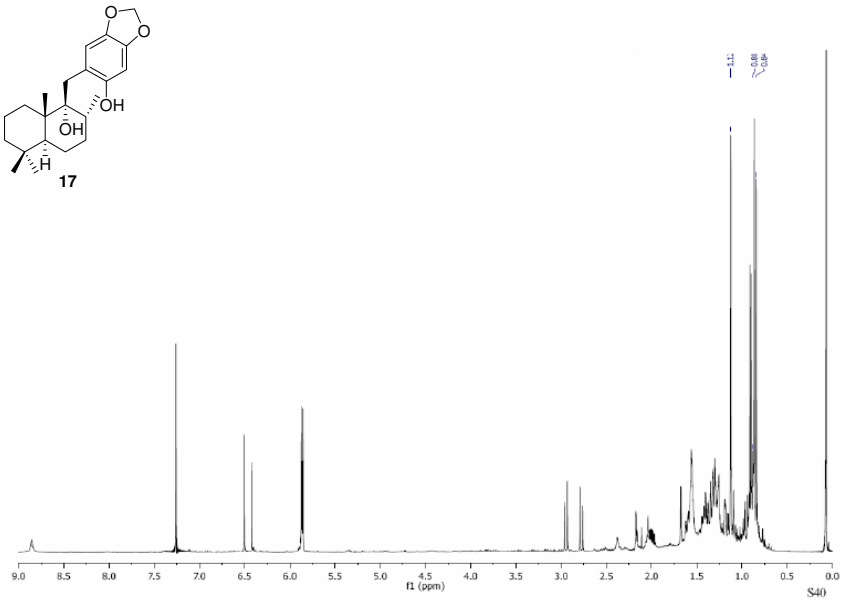


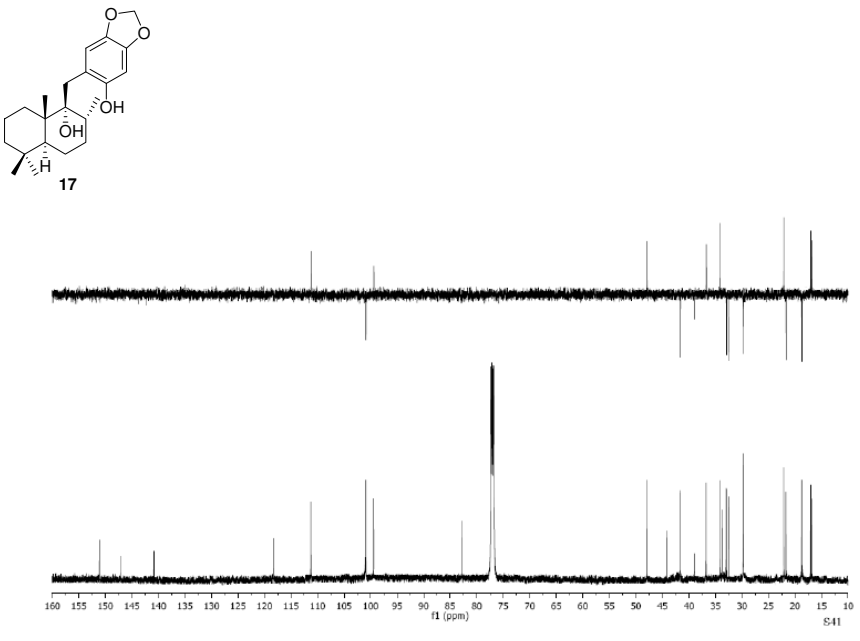
11*S*-(**15b**)

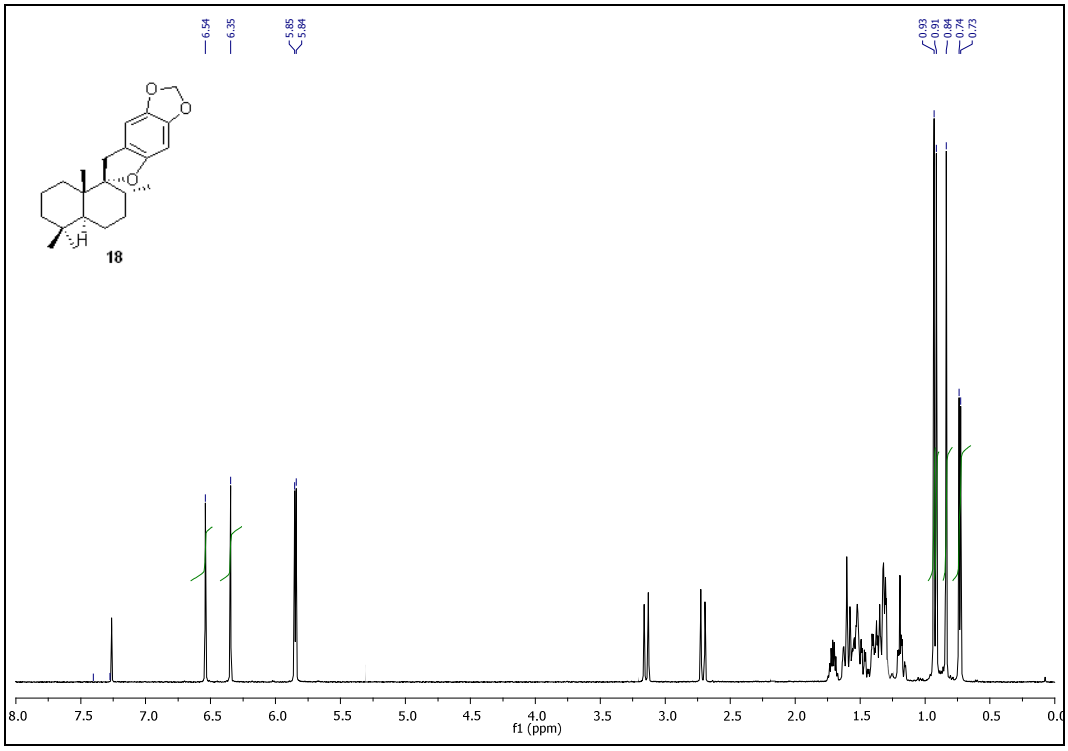


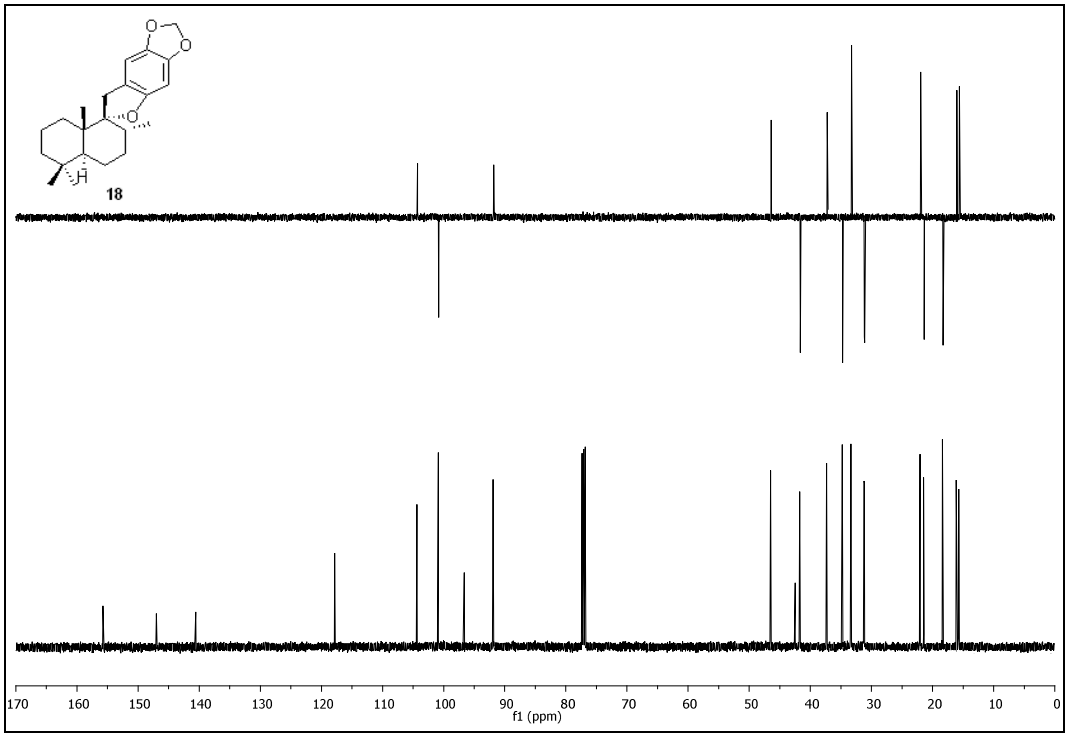
11*S*-(**15b**)

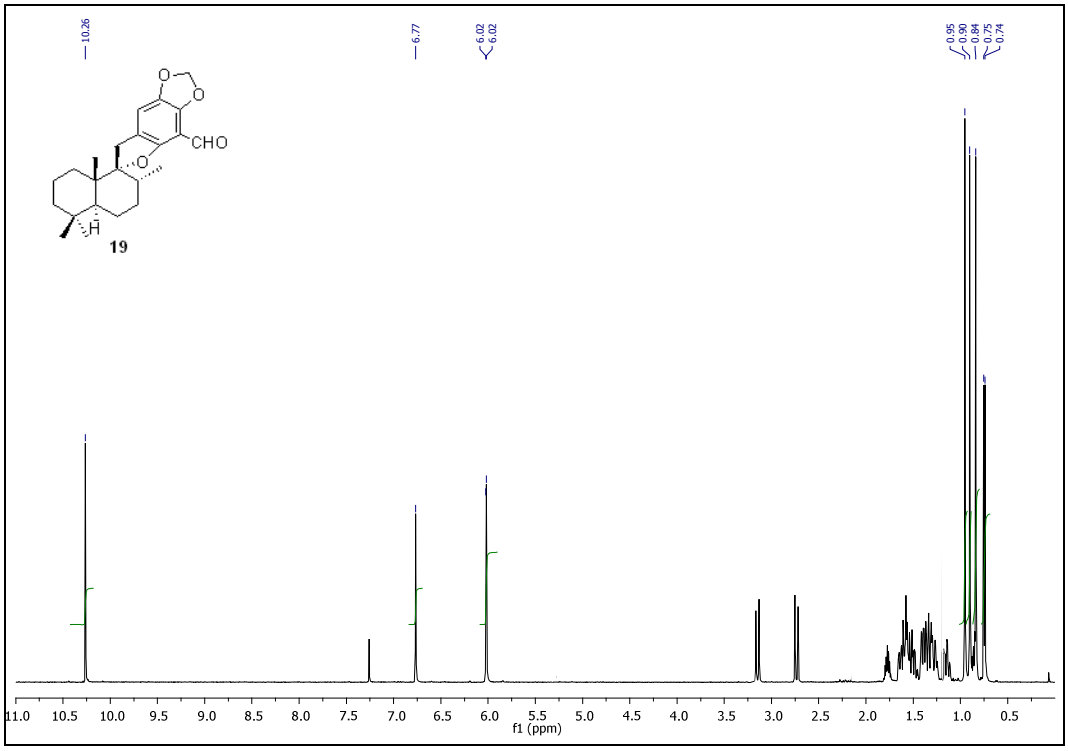


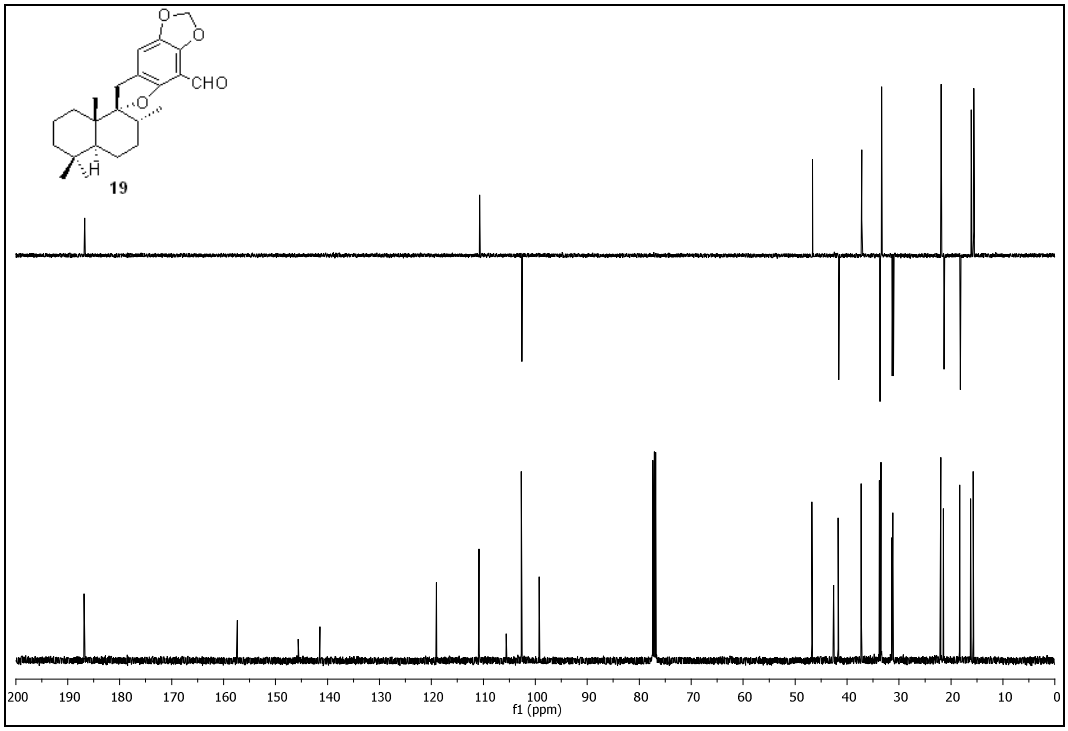

OH
OH
H
17
f1 (ppm)
S40

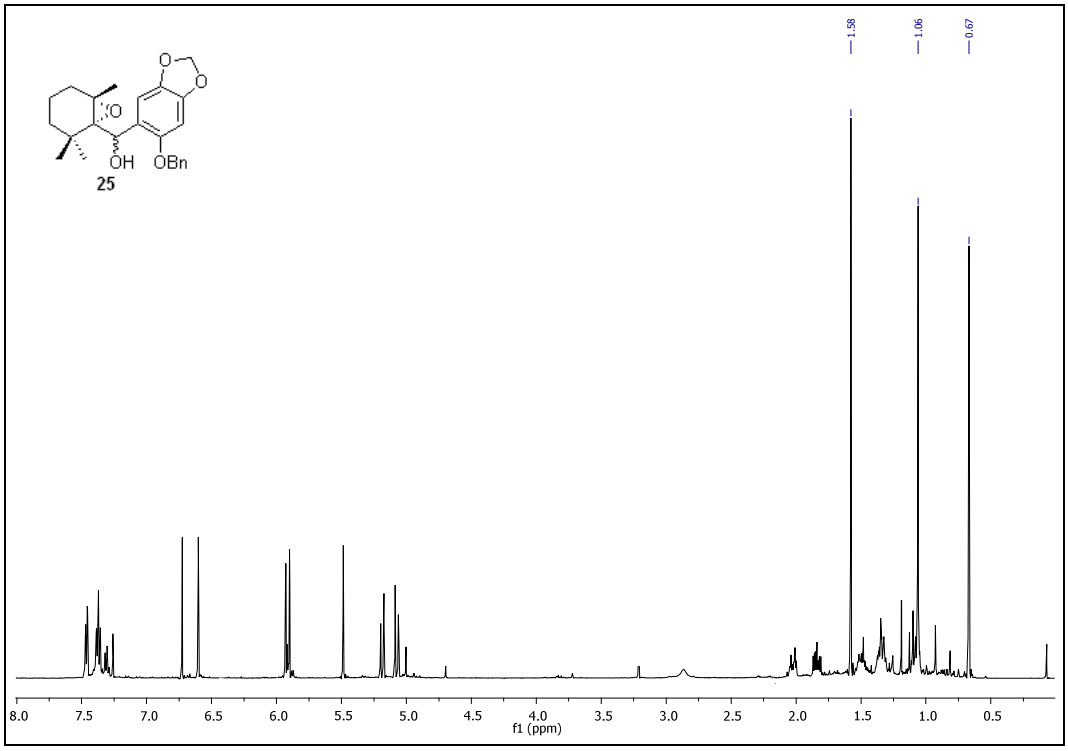

OH
OH
H
17
f1 (ppm)
S41

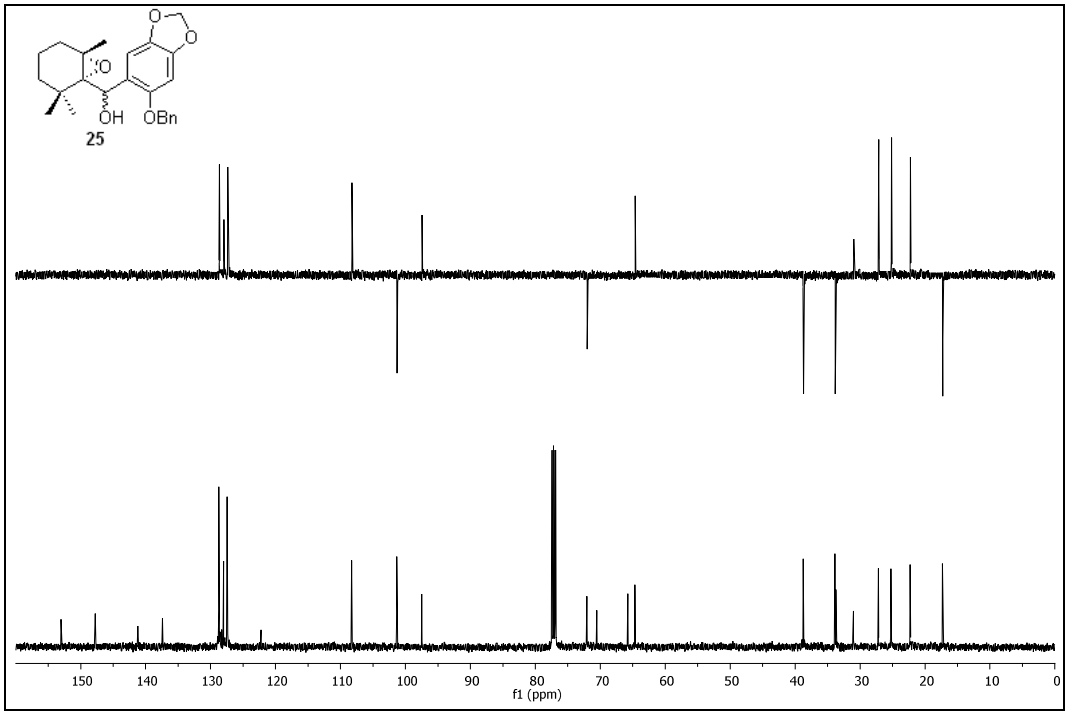

6.54
6.35
5.85
5.84
0.93
0.91
0.84
0.74
0.73
18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

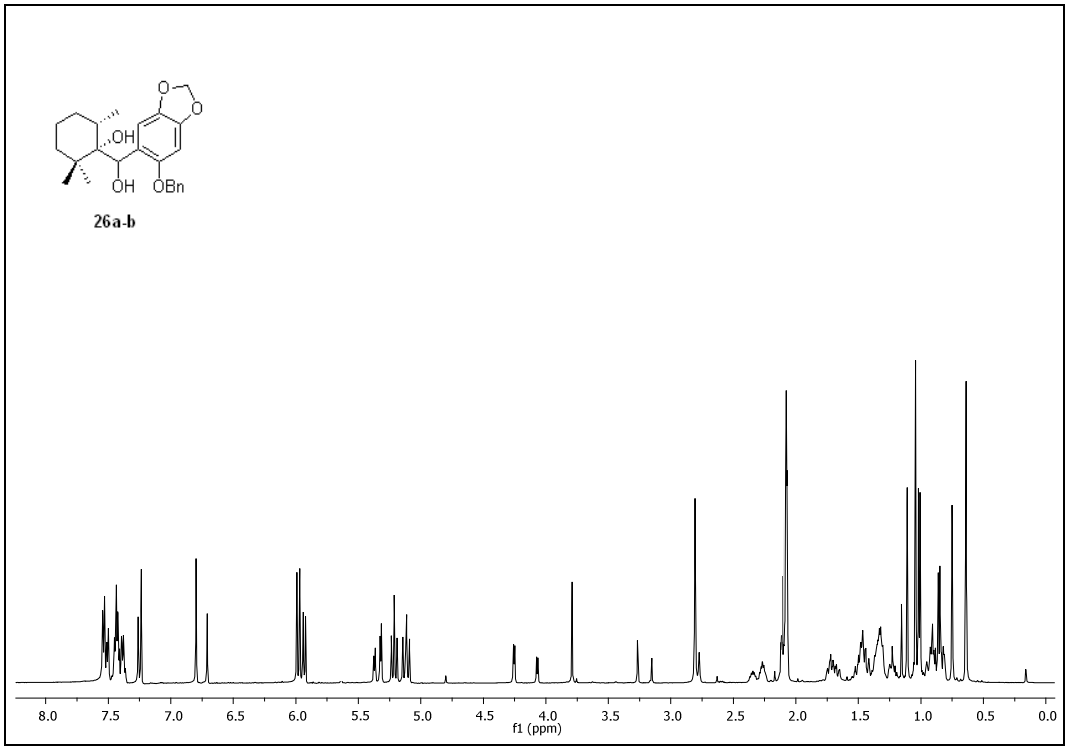

18
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

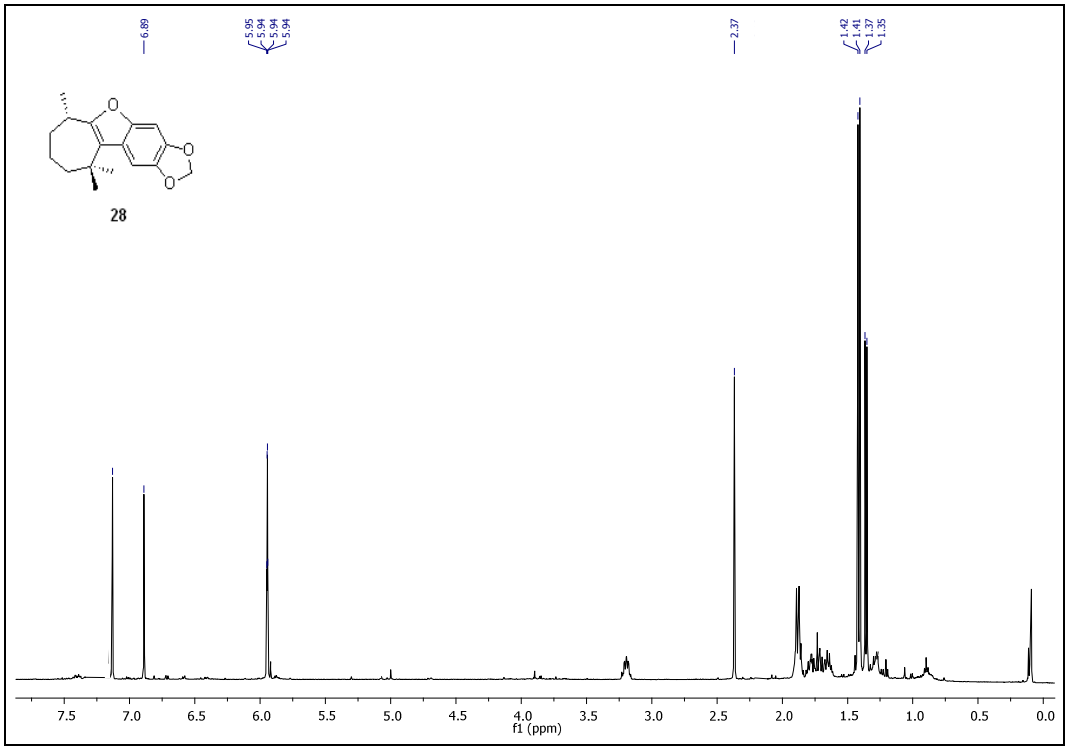

10.26
6.77
6.02
6.02
0.95
0.90
0.84
0.75
0.74
CHO
19
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

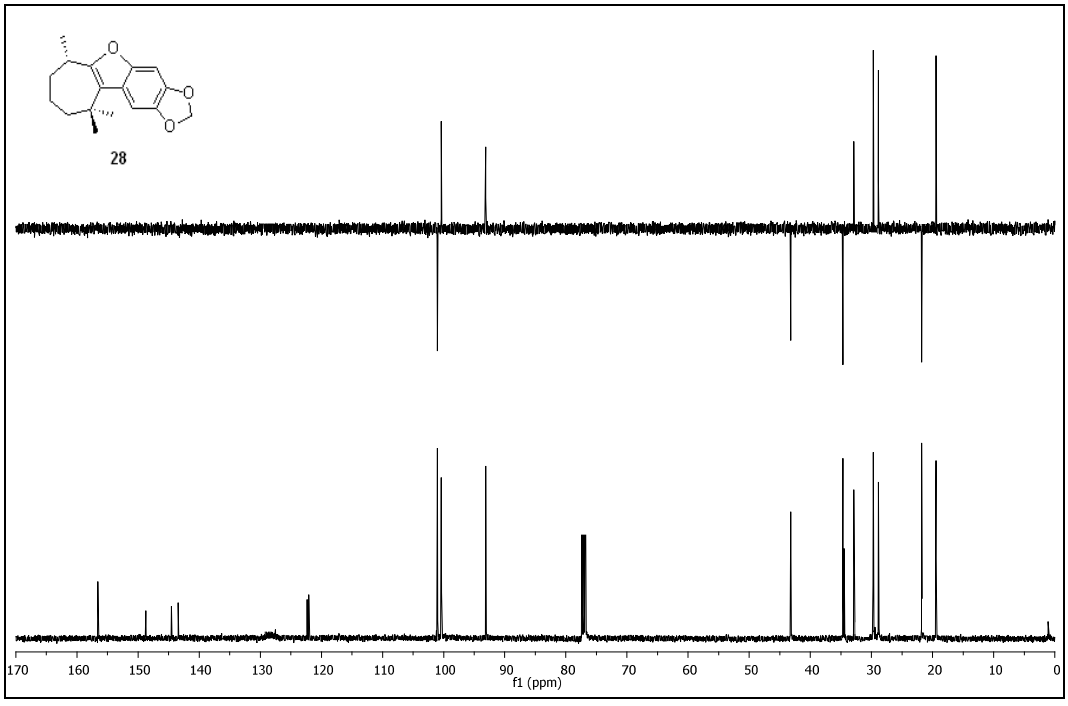

CHO
19
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

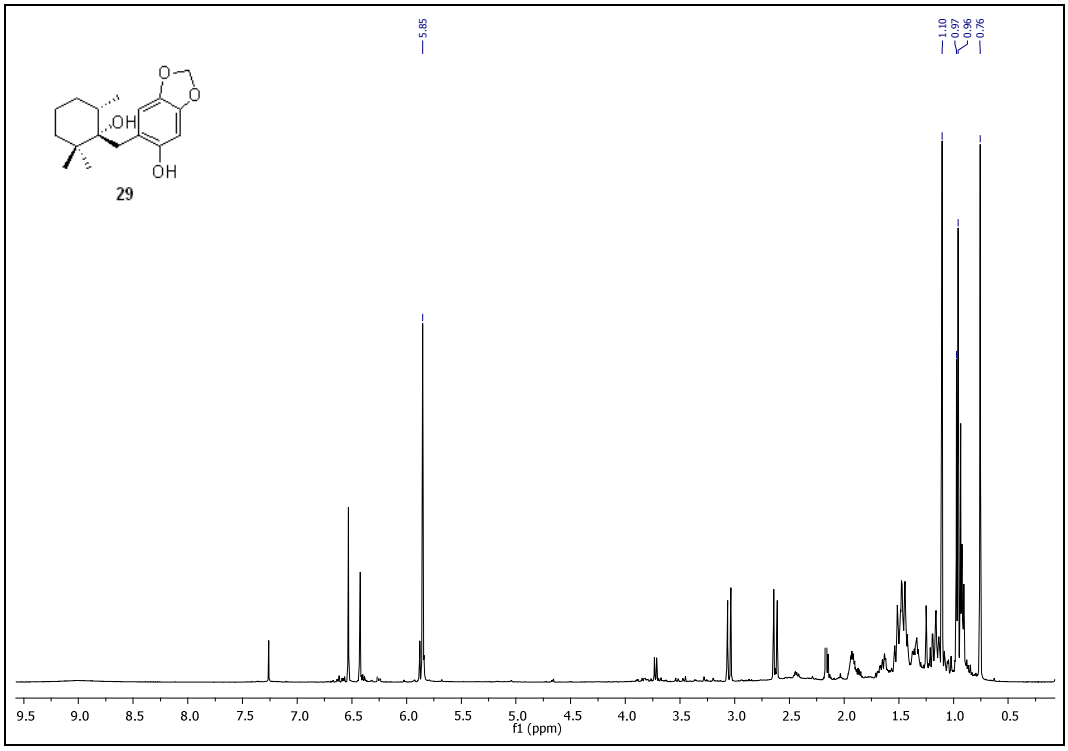

1.58
1.06
0.67
OH
OBn
25
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

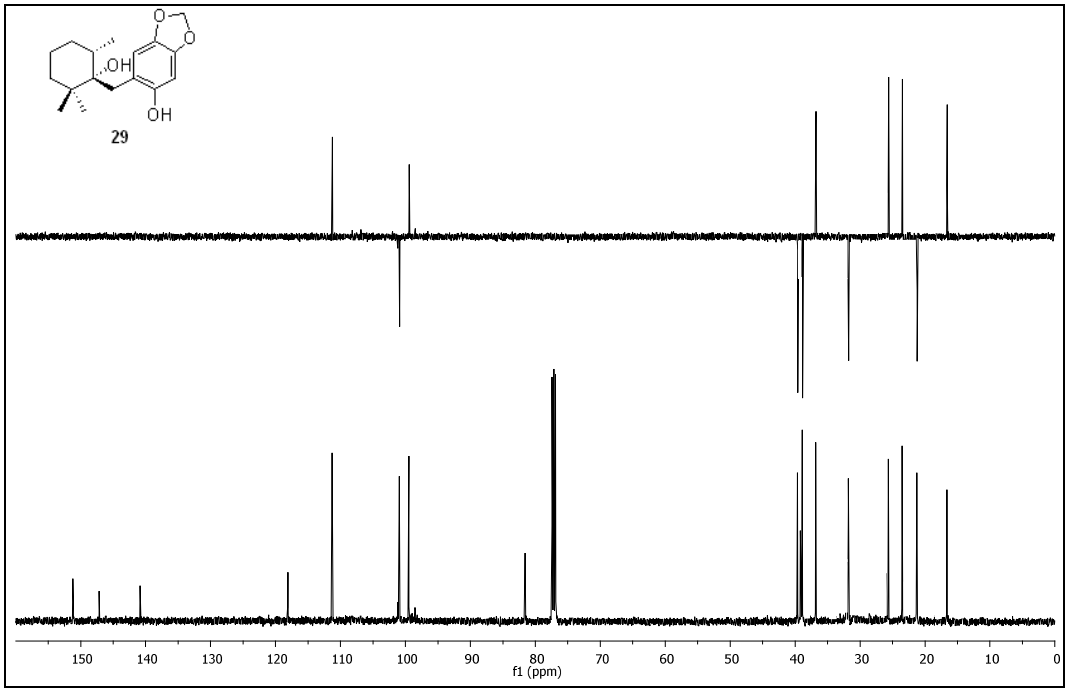

OH
OBn
25
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

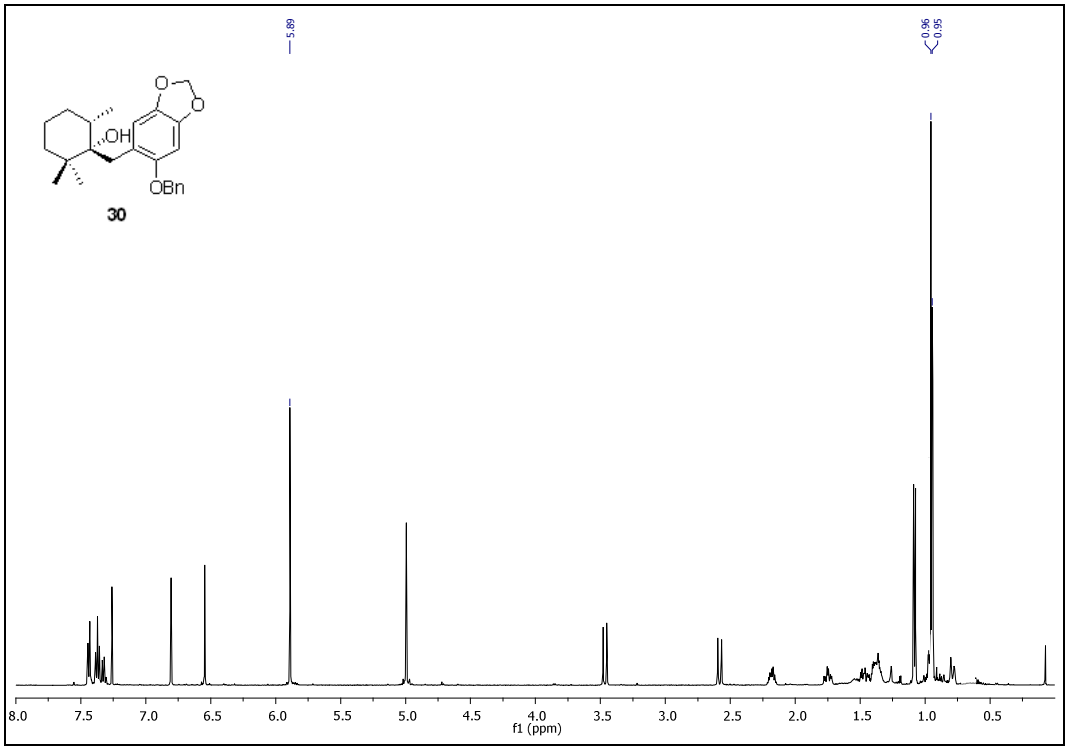

OH
OH
OBn
O
O
26a-b
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

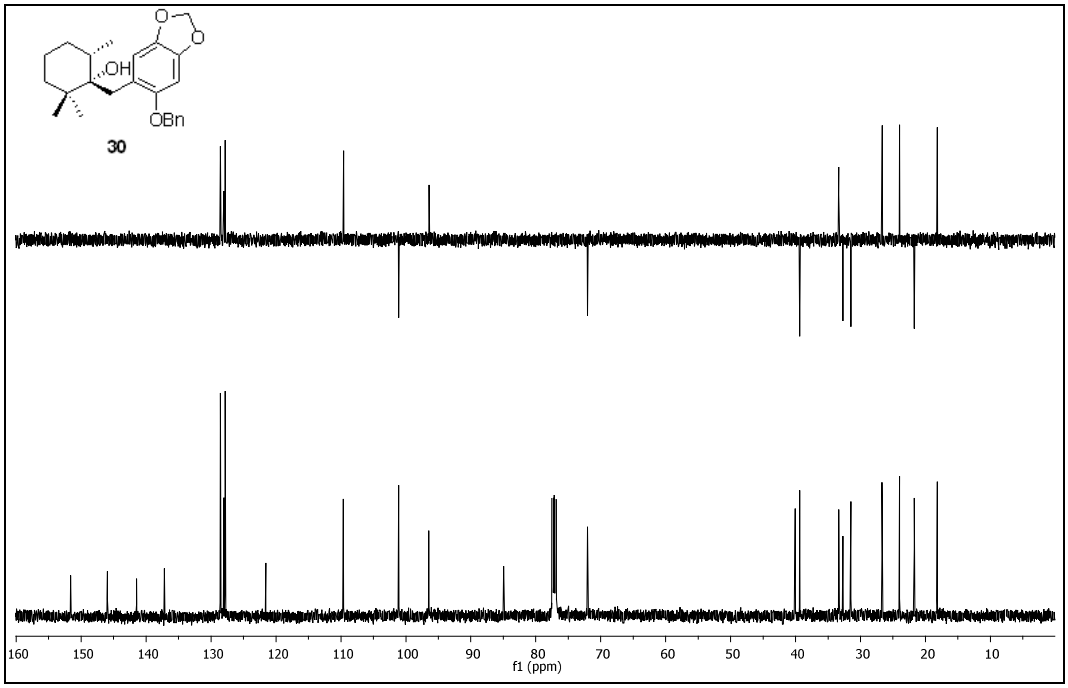

6.89
5.95
5.94
5.94
5.94
2.37
1.42
1.41
1.37
1.35
28
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

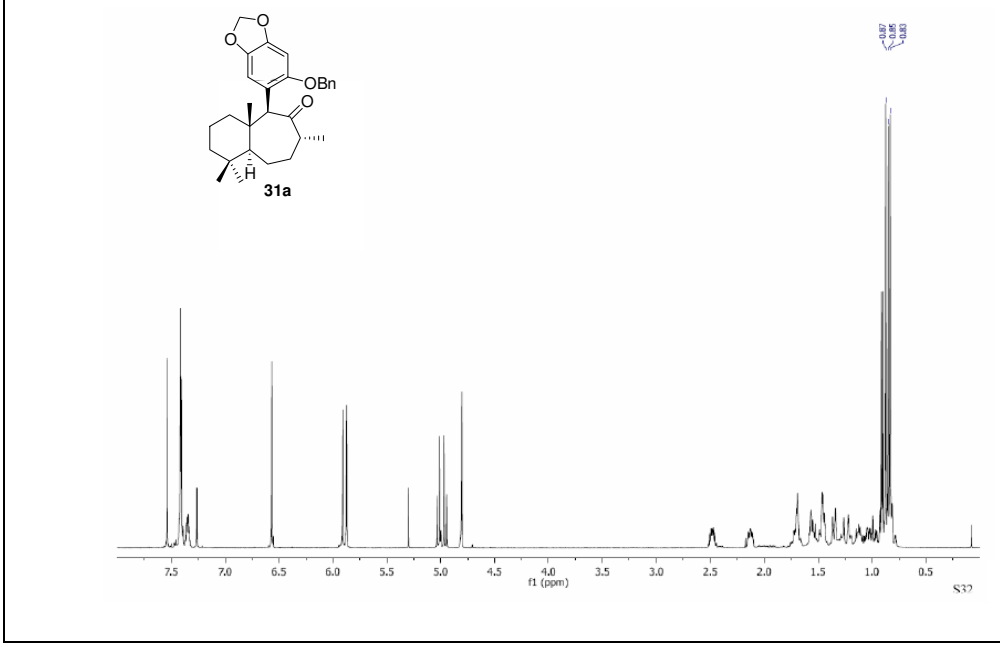

28
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

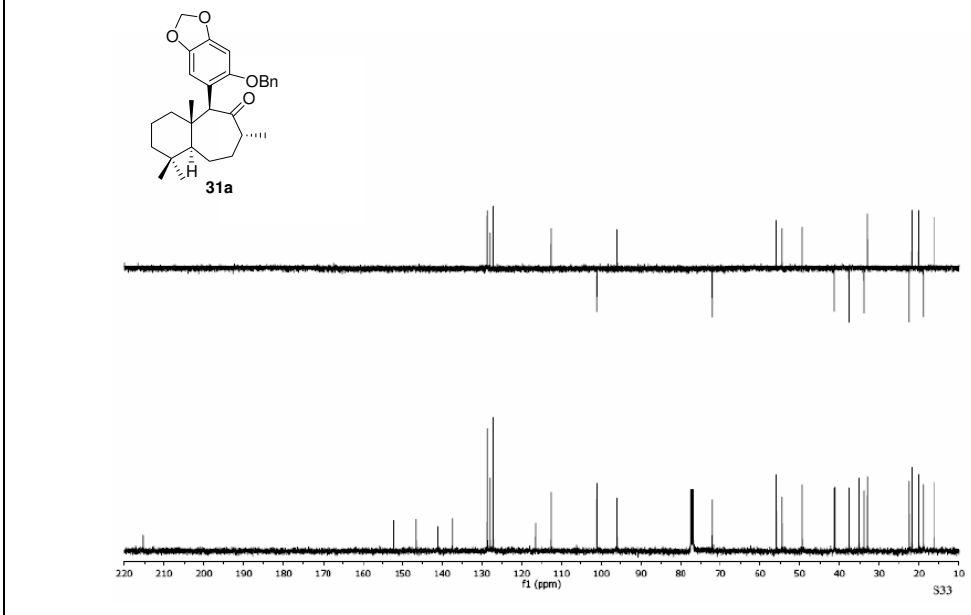

5.85
1.10
0.97
0.96
0.76
OH
OH
29
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

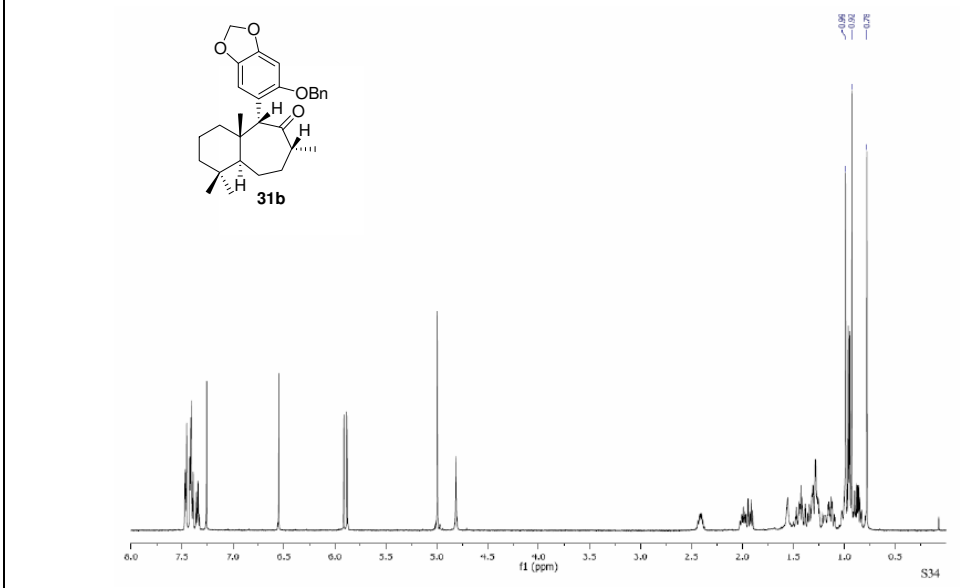

OH
OH
29
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

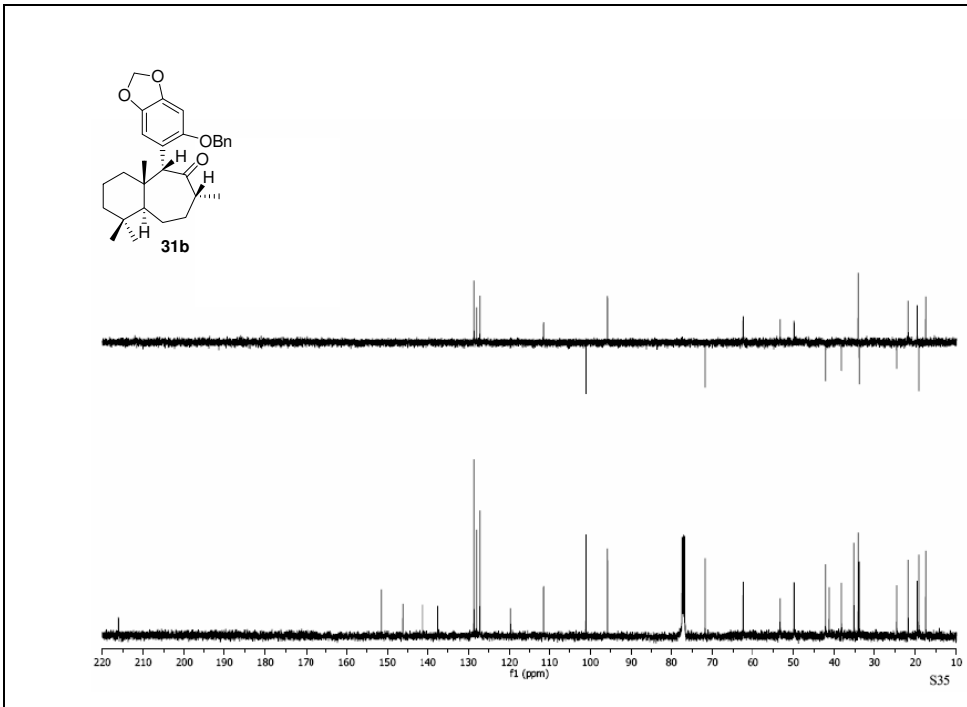

5.89
0.96
0.95
OH
O
O
OBn
30
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

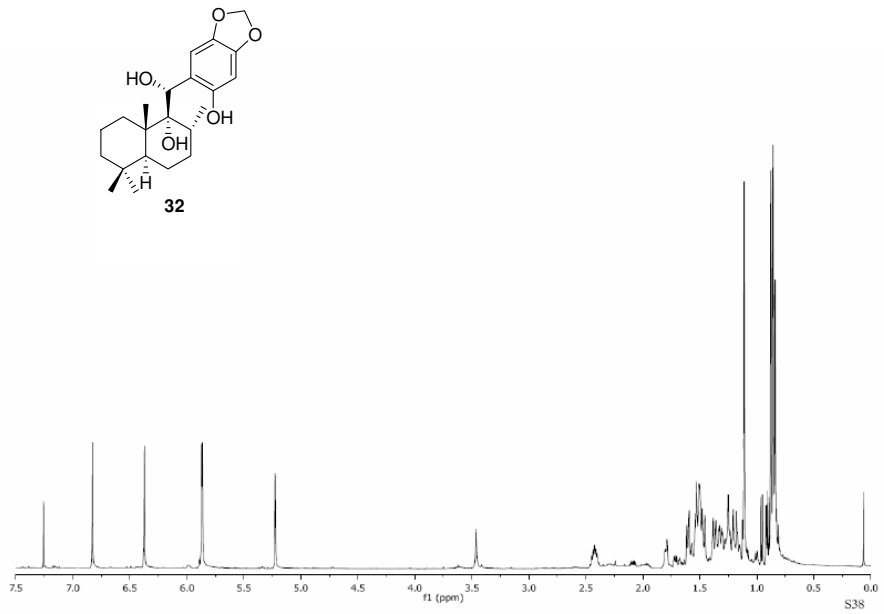

OH
O
O
OBn
30
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

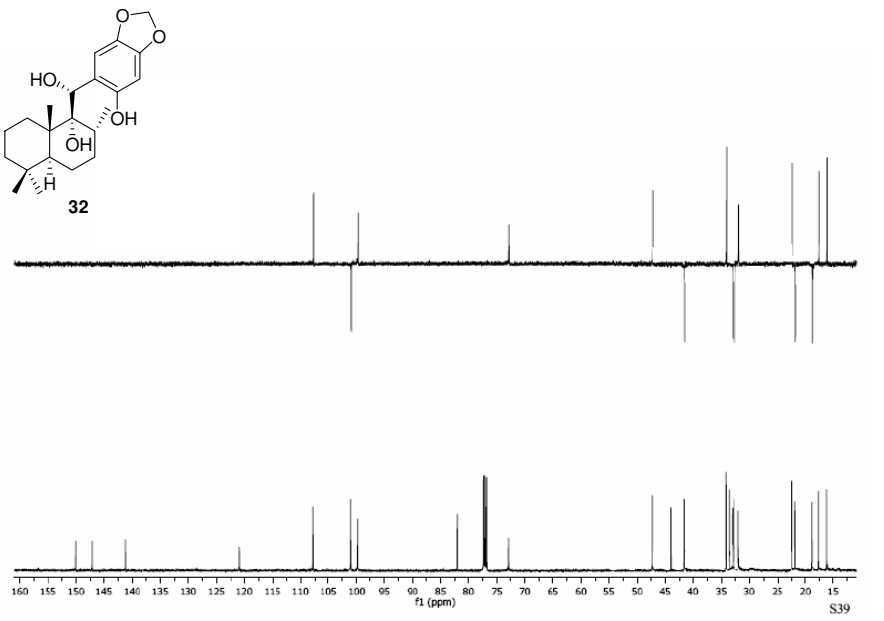

OBn
O
H
31a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

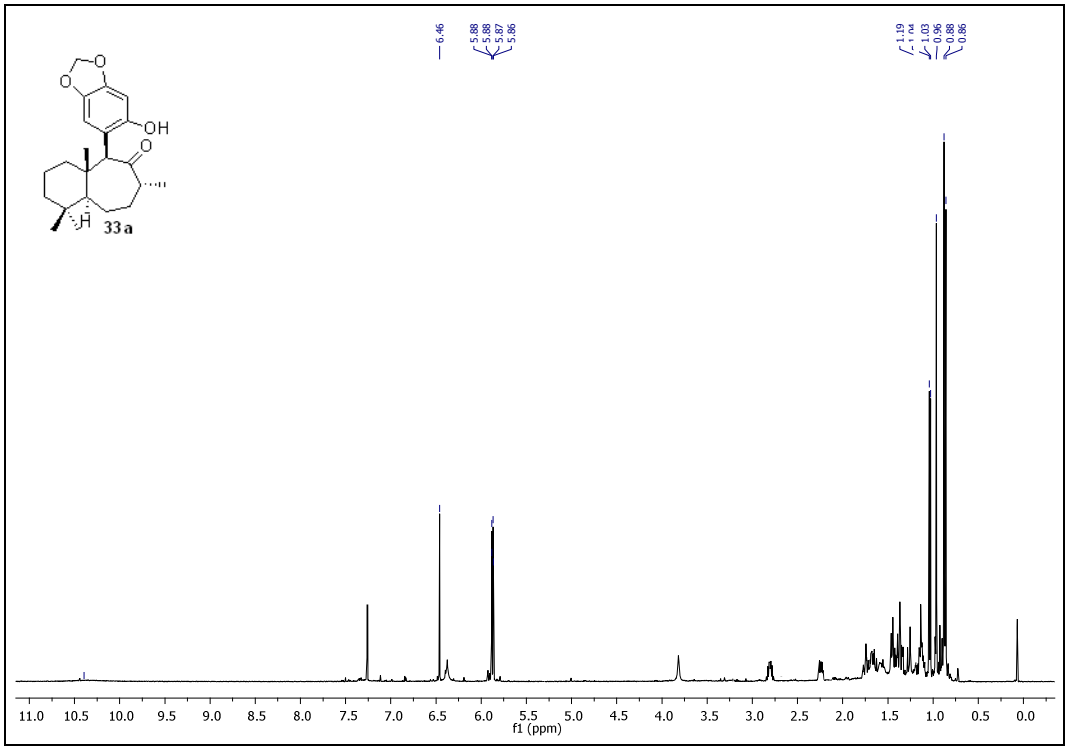

OBn
O
H
31a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

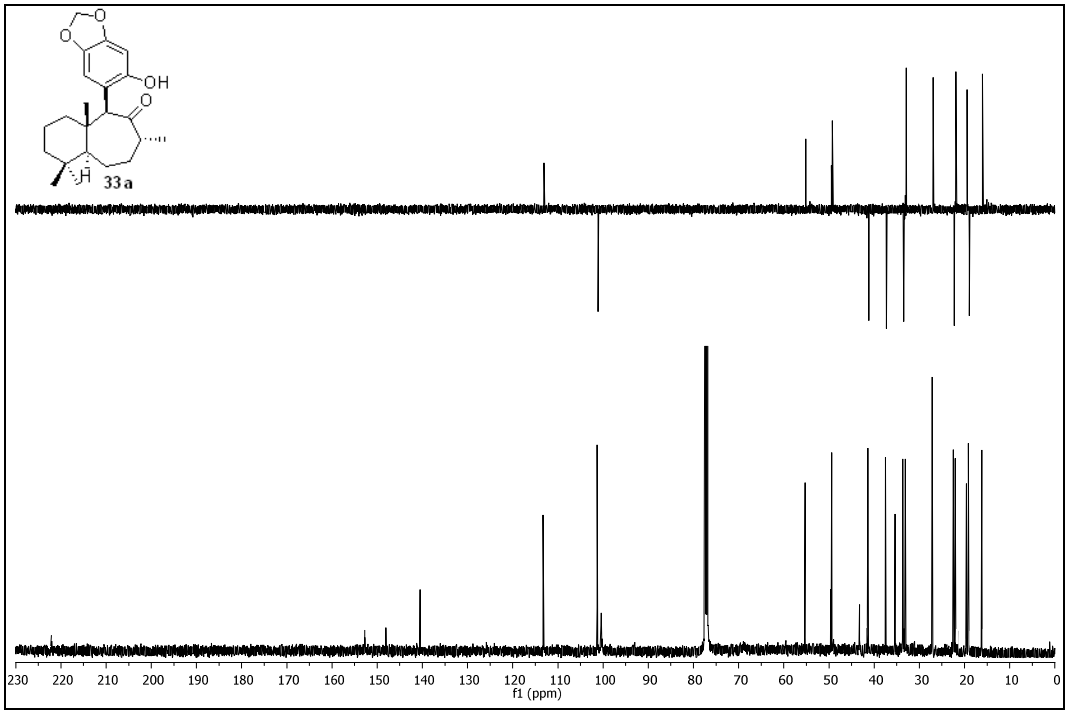

O
O
OBn
H
O
H
H
31b
f1 (ppm)
S34

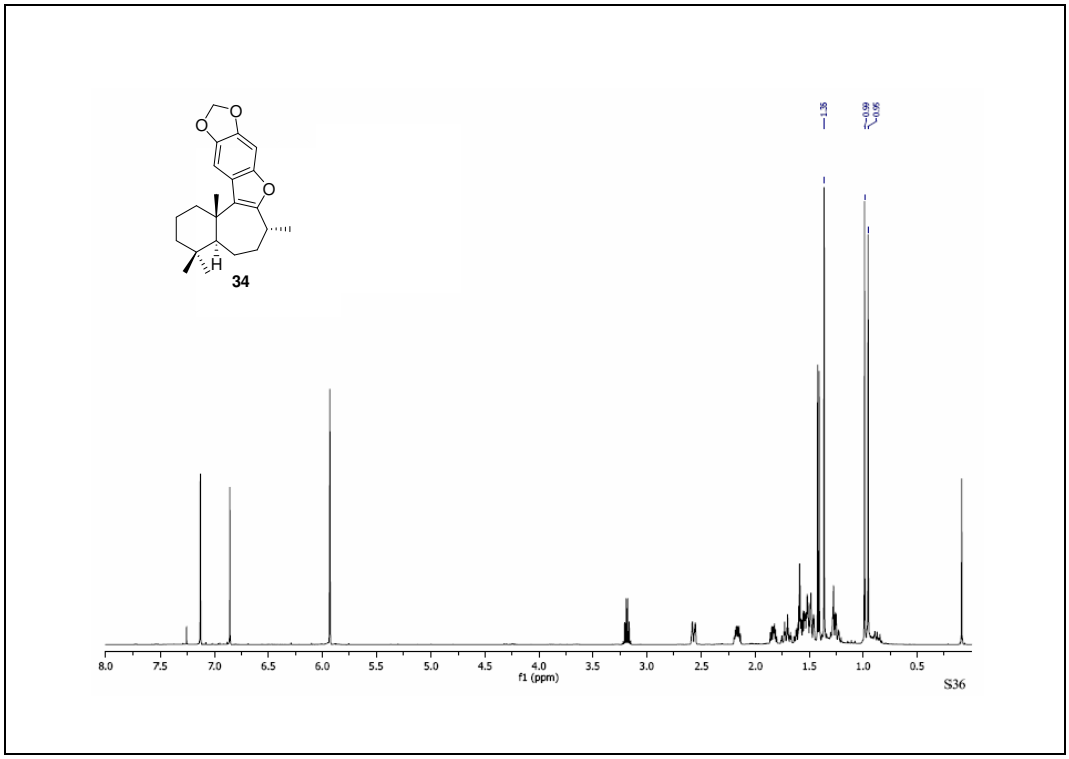

O
O
OBn
H
O
H
H
31b
f1 (ppm)
S35

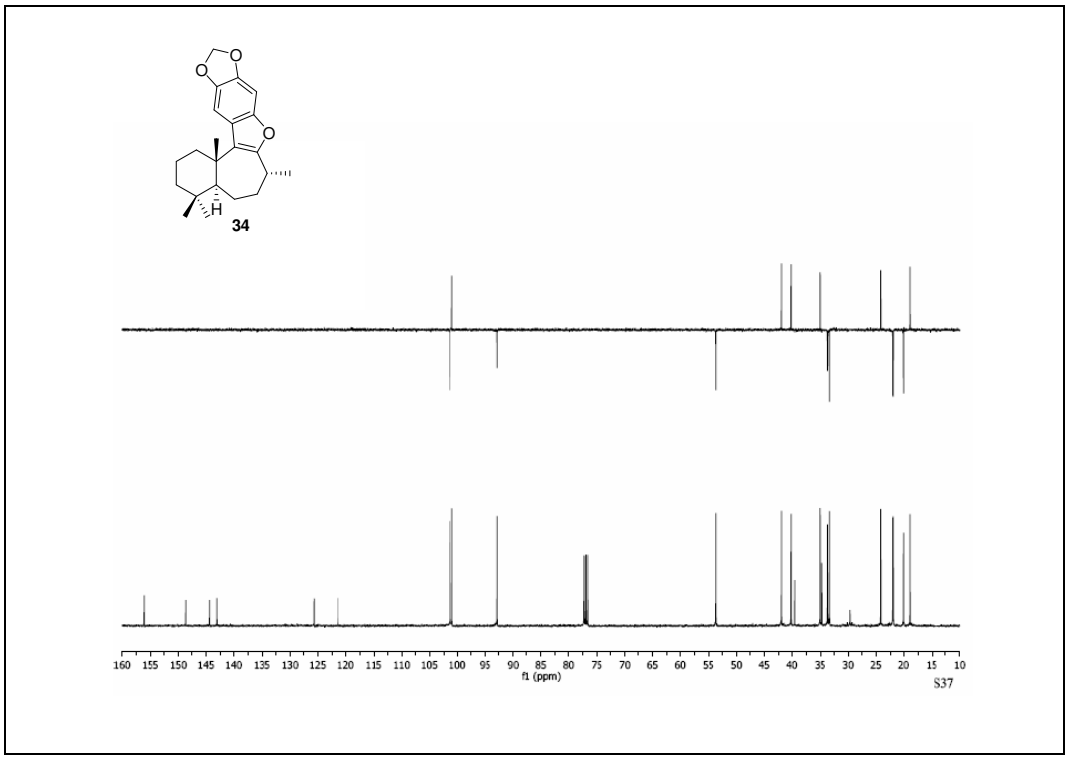

HO
OH
OH
H
O
O
32
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
S38

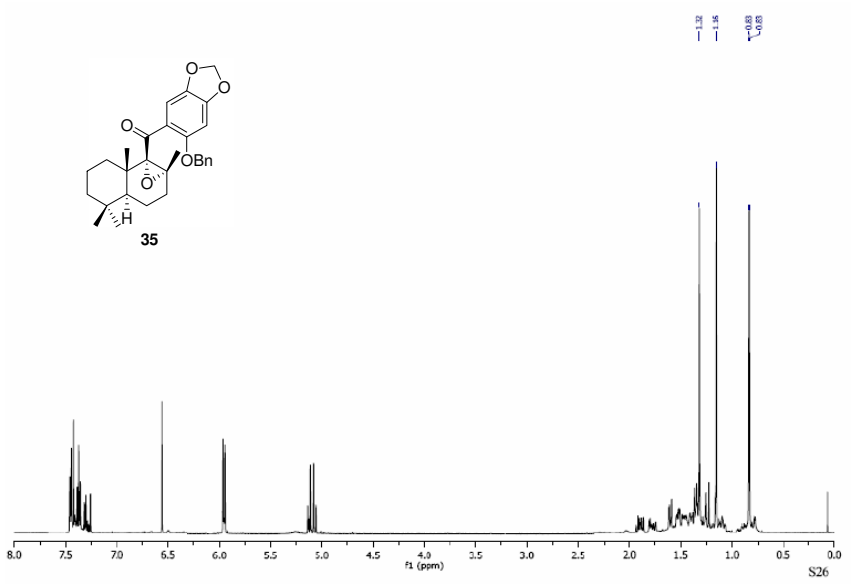

HO
OH
OH
H
O
O
32
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
f1 (ppm)
S39

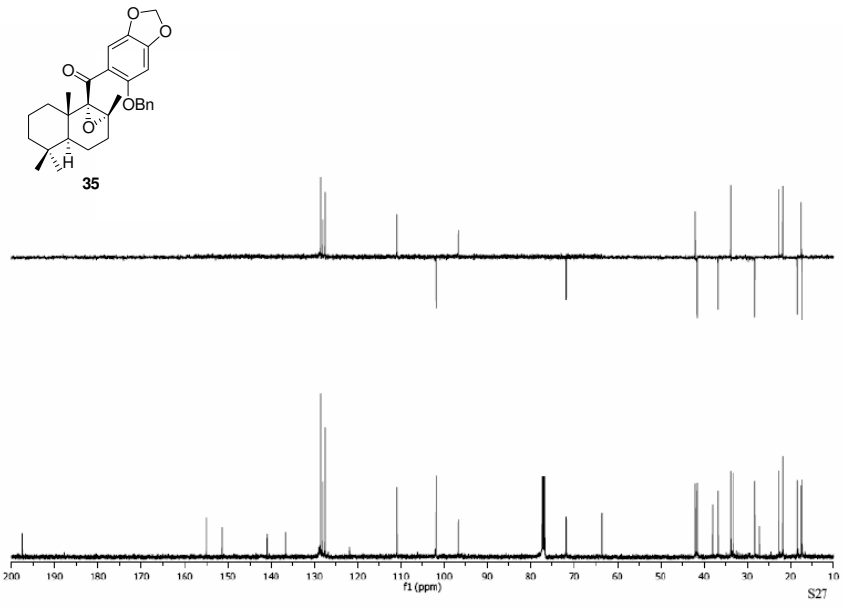

6.46
5.88
5.88
5.87
5.86
1.19
1.14
1.03
0.96
0.88
0.86
OH
O
O
O
H
33a
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

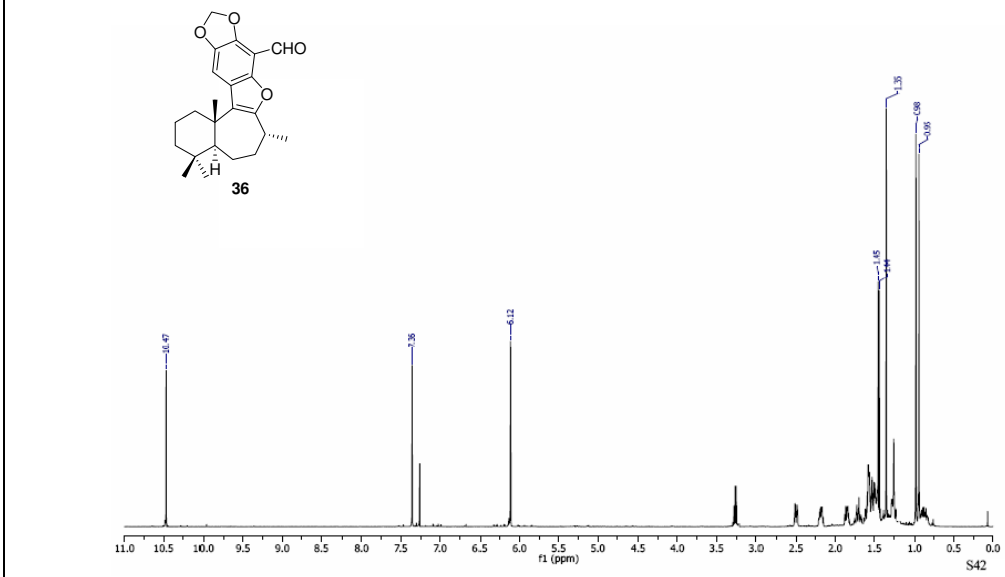

OH
O
O
O
H
33a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

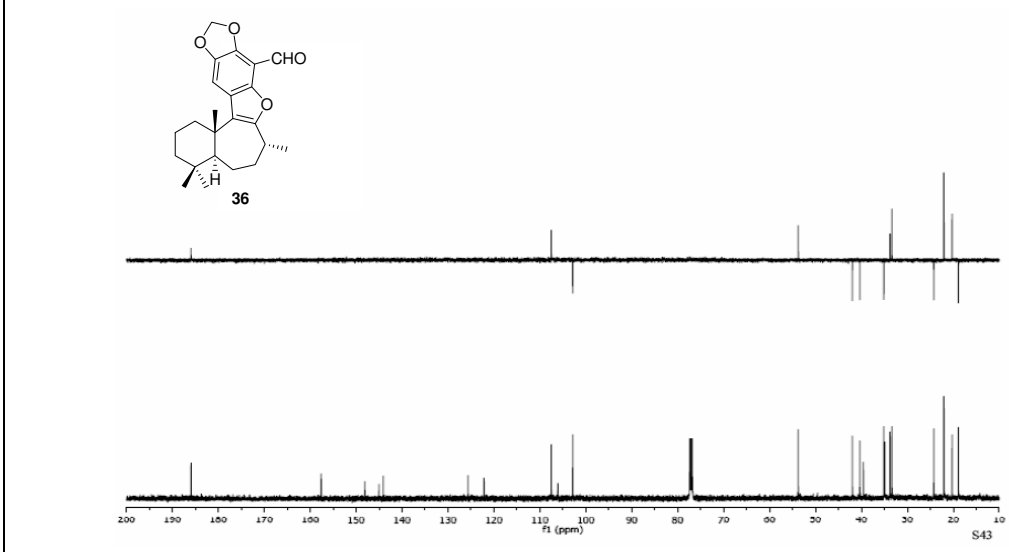

34
1.35
0.99
0.95
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
S36

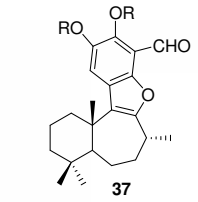

34
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)
S37


OBn
35
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
S26


OBn
35
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)
S27

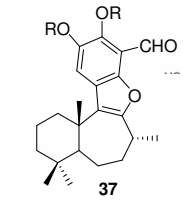

CHO
O
O
O
H
36
10.47
7.35
6.12
1.65
1.44
1.35
0.98
0.95
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
S42


CHO
O
O
O
H
36
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)
S43



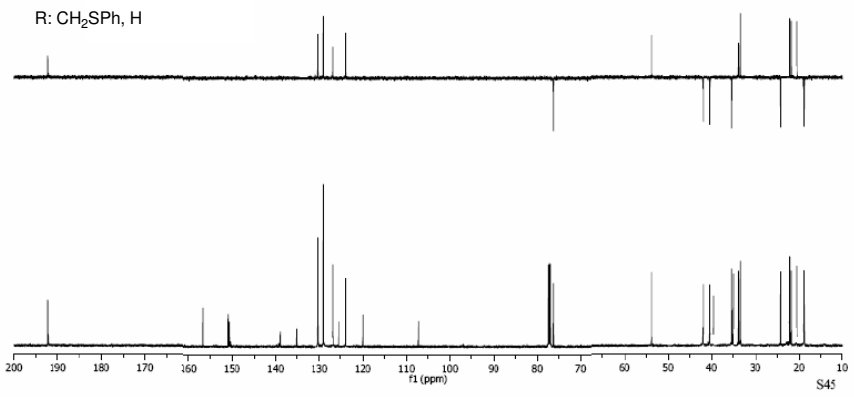
37

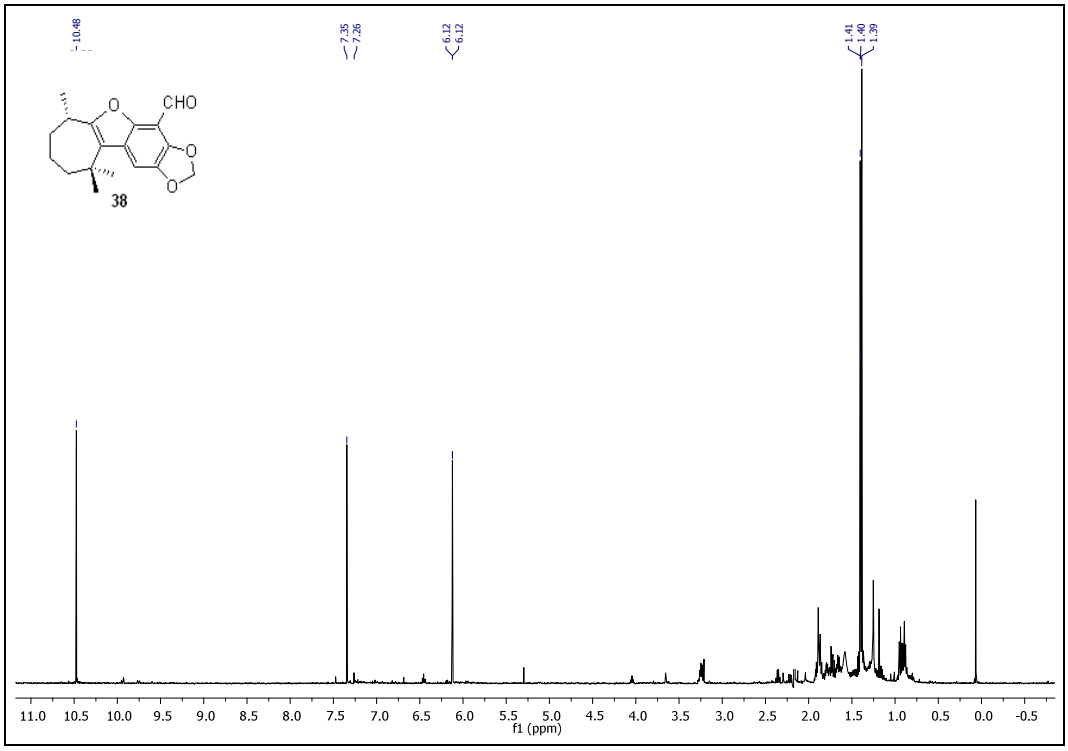
R: CH_2SPh, H

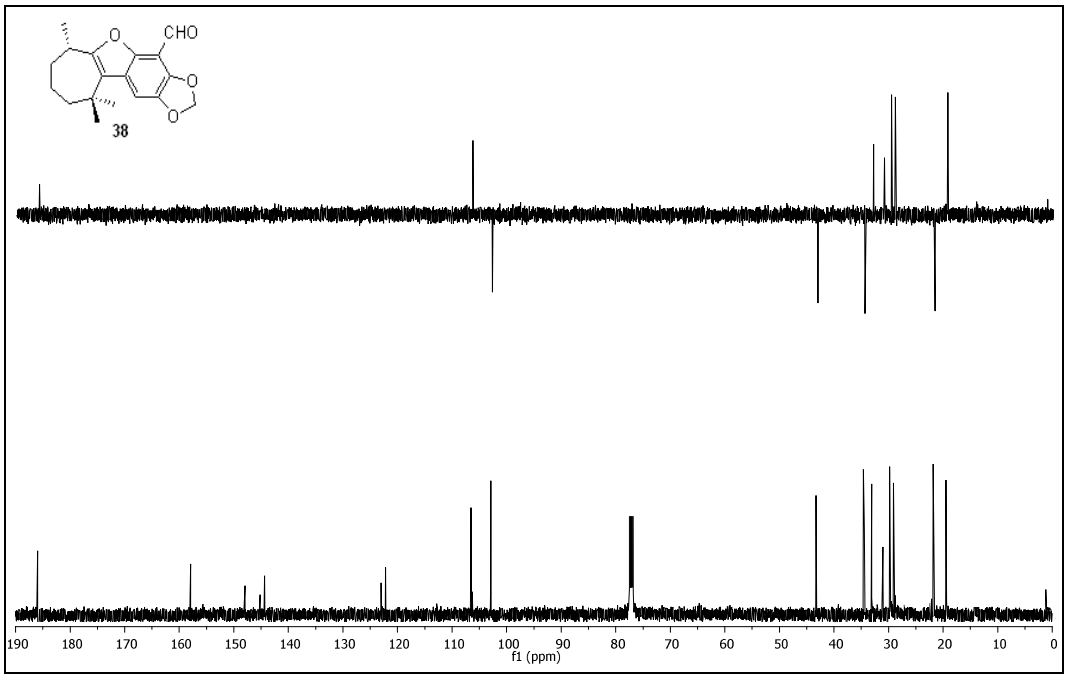


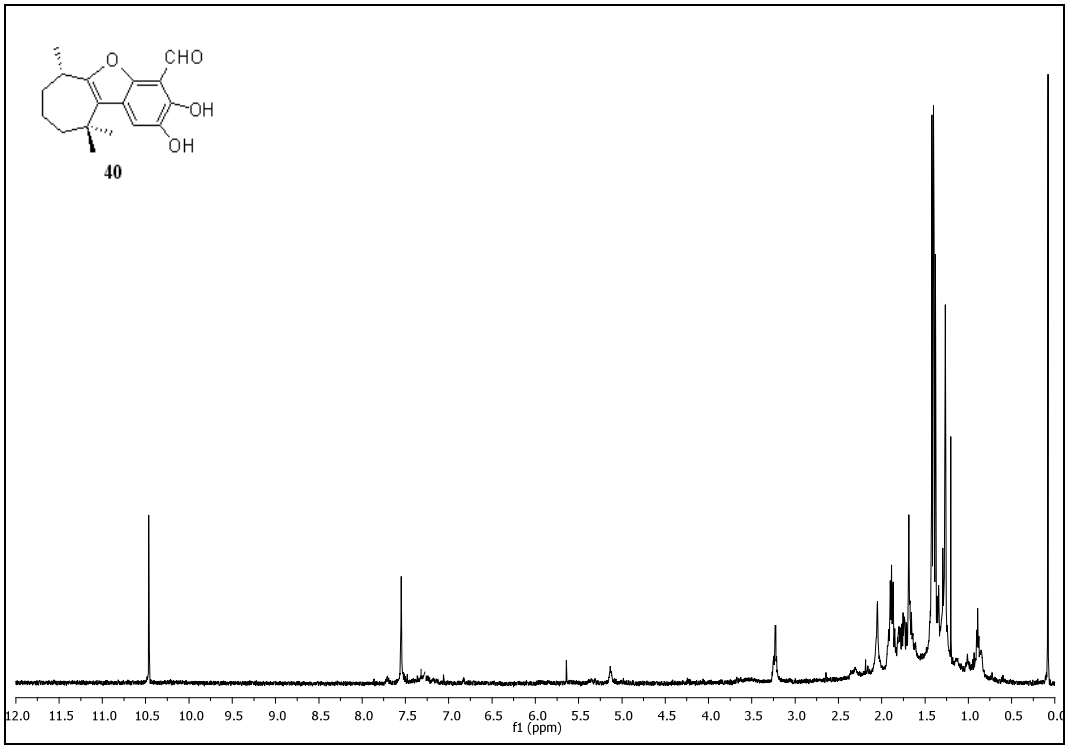
37

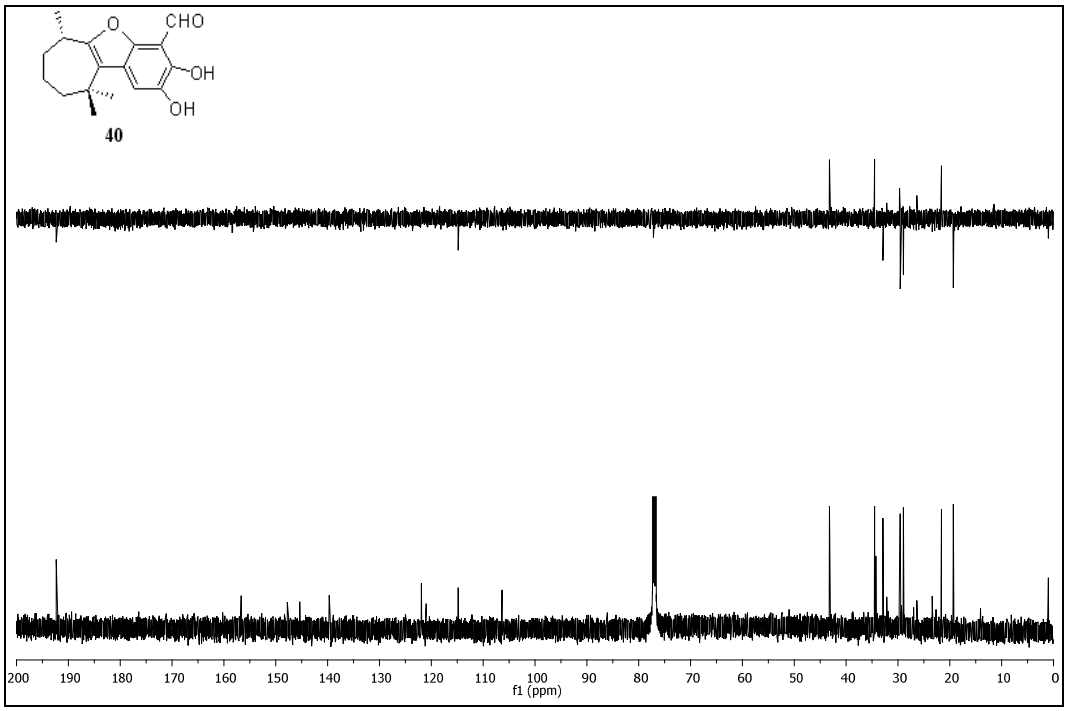
R: CH_2SPh, H

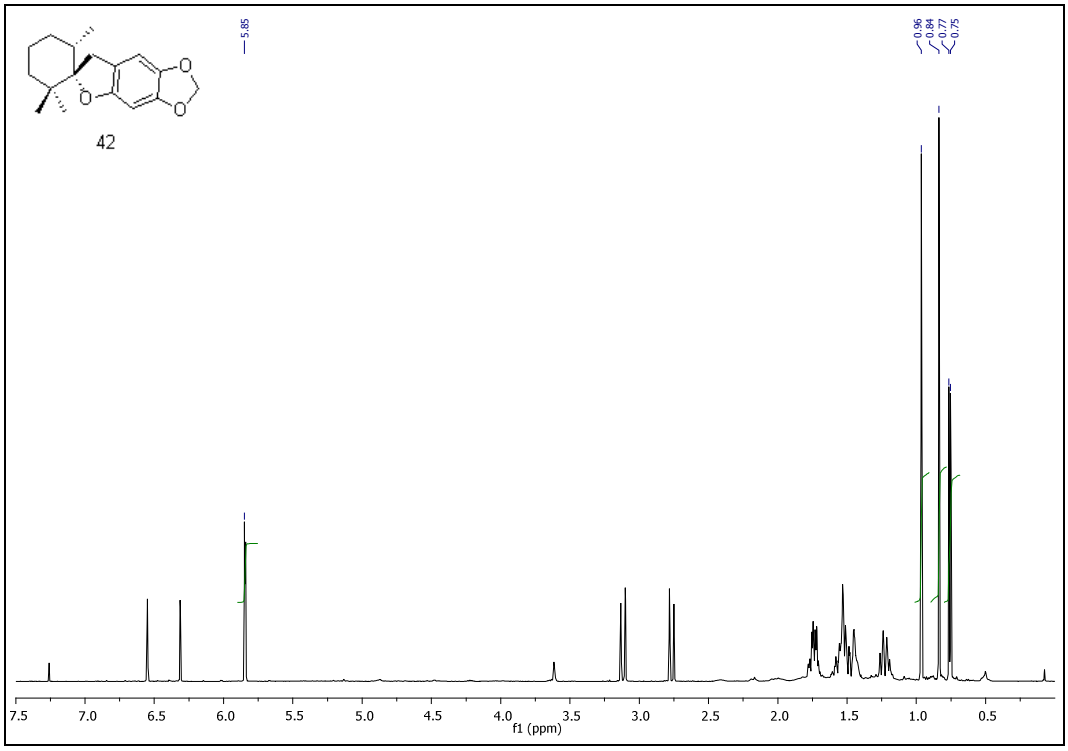


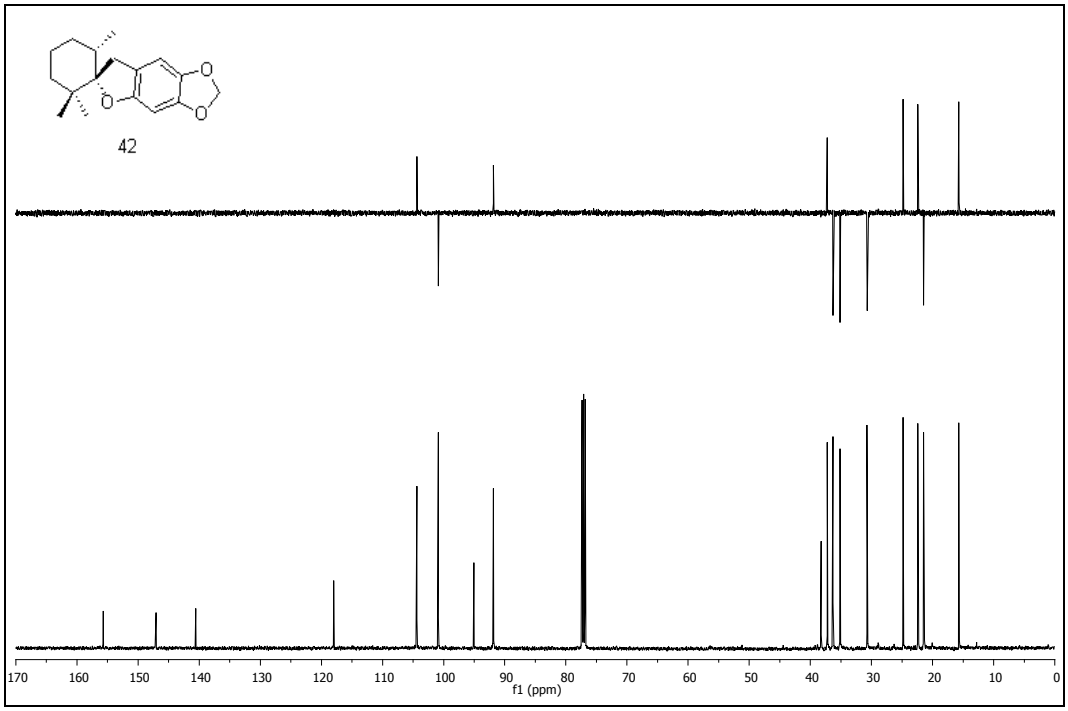

10.48
7.35
7.26
6.12
6.12
1.41
1.40
1.39
CHO
O
O
O
38
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

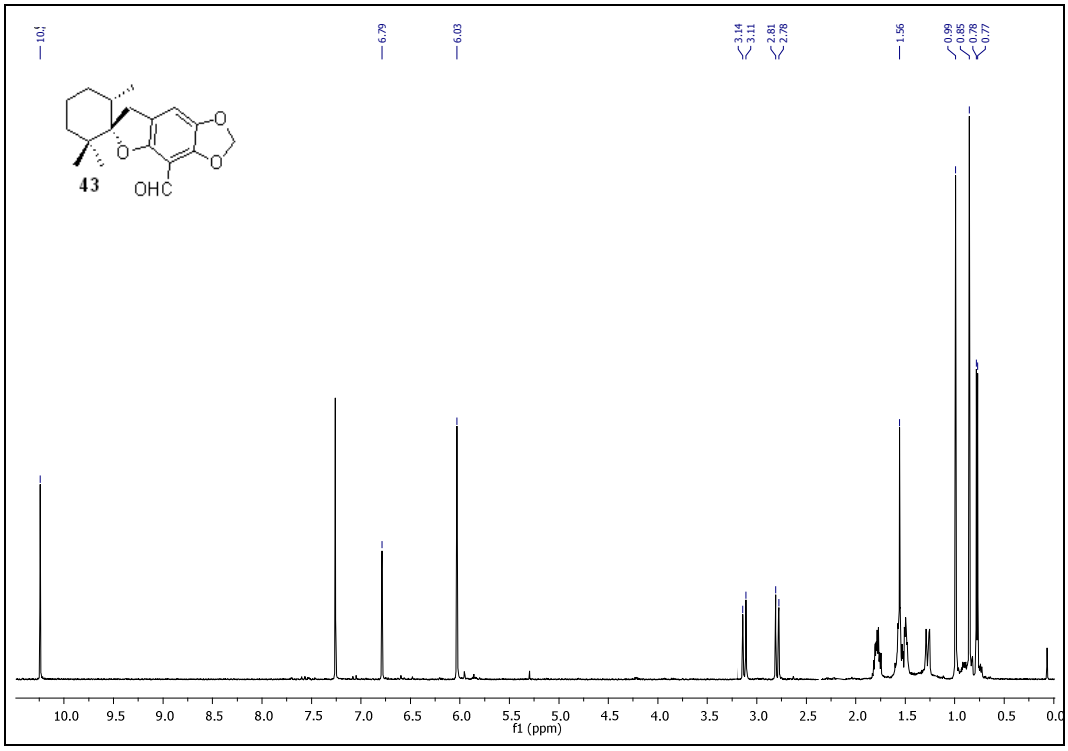

CHO
O
O
O
38
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

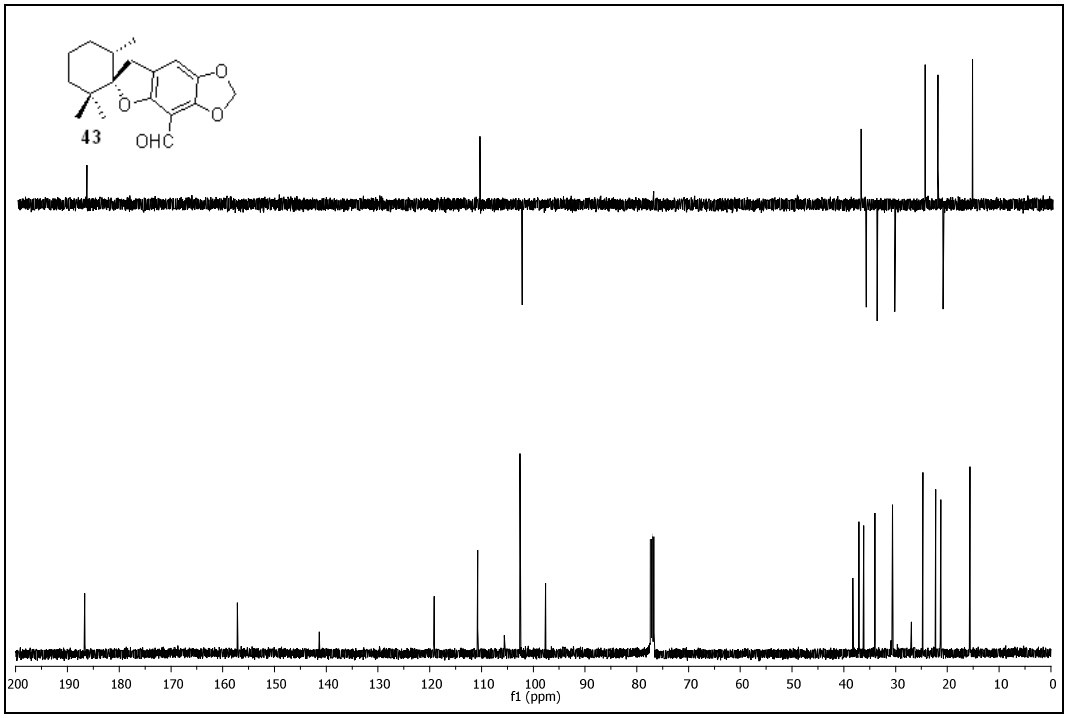

CHO
OH
OH
O
40
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

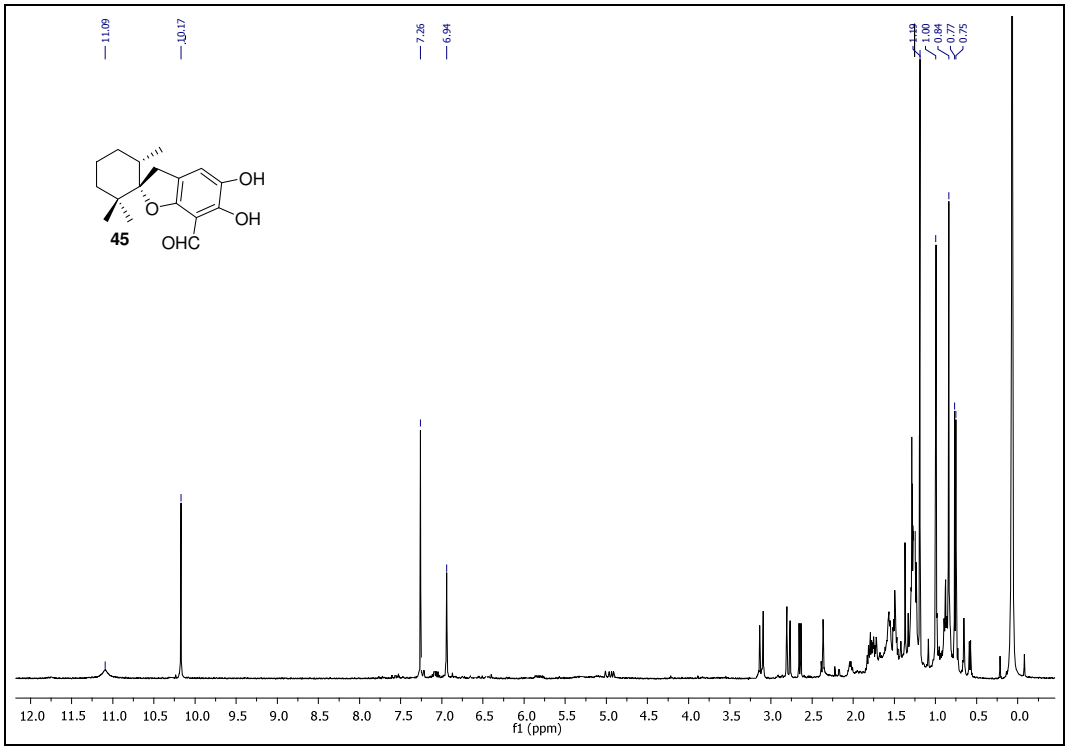

CHO
OH
OH
O
40
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

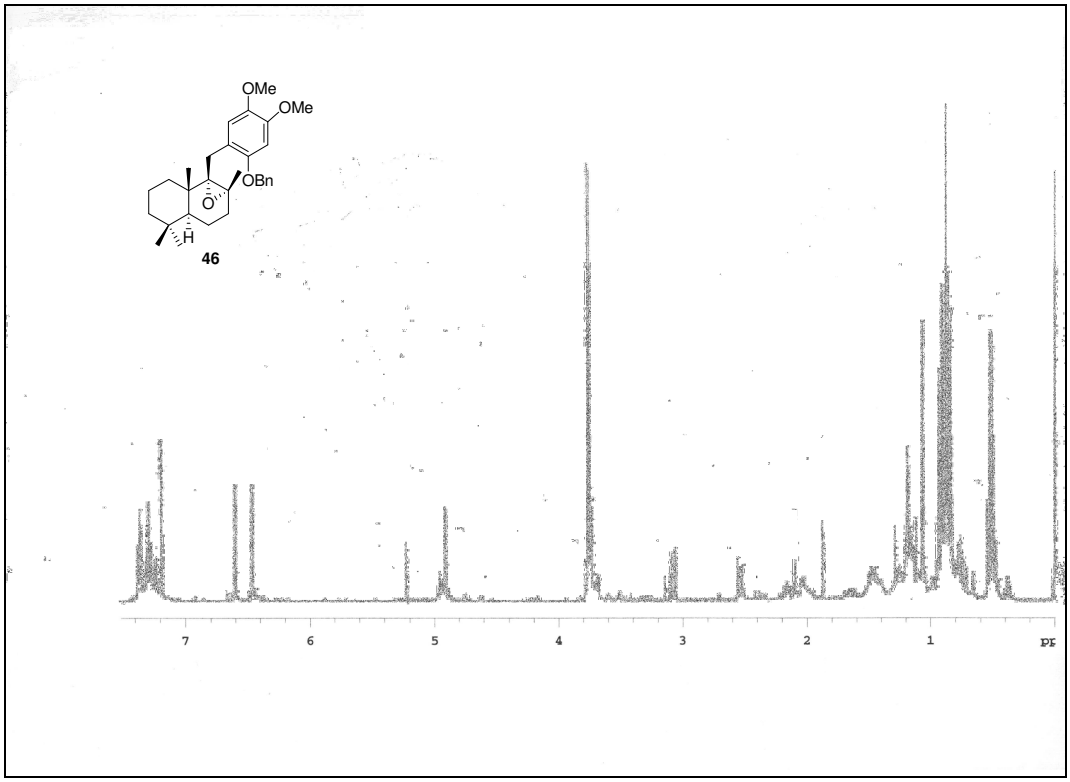

42
5.85
0.96
0.84
0.77
0.75
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

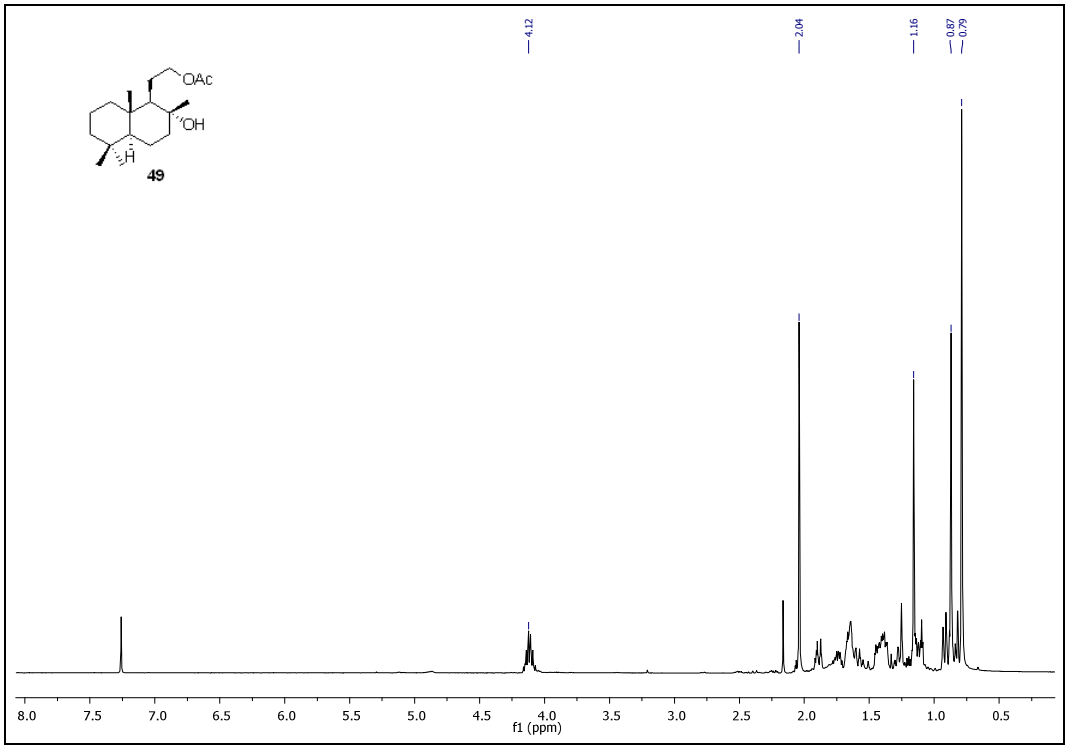

42
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

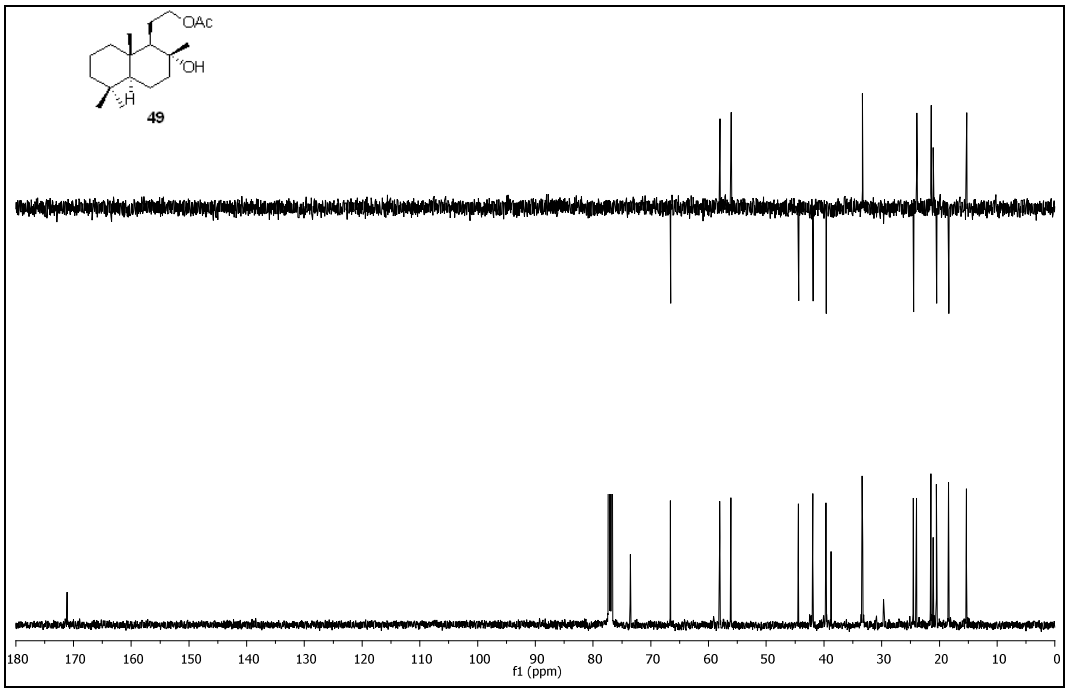

10.1
6.79
6.03
3.14
3.11
2.81
2.78
1.56
0.99
0.85
0.78
0.77
43
OHC
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

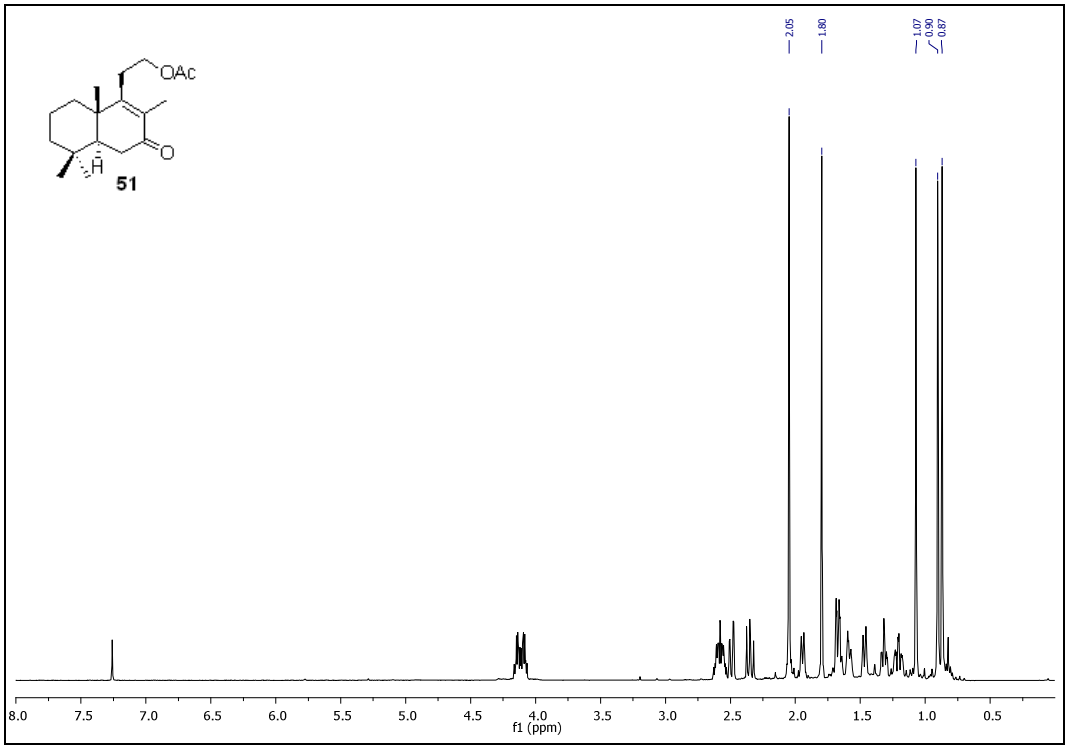

43
OHC
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

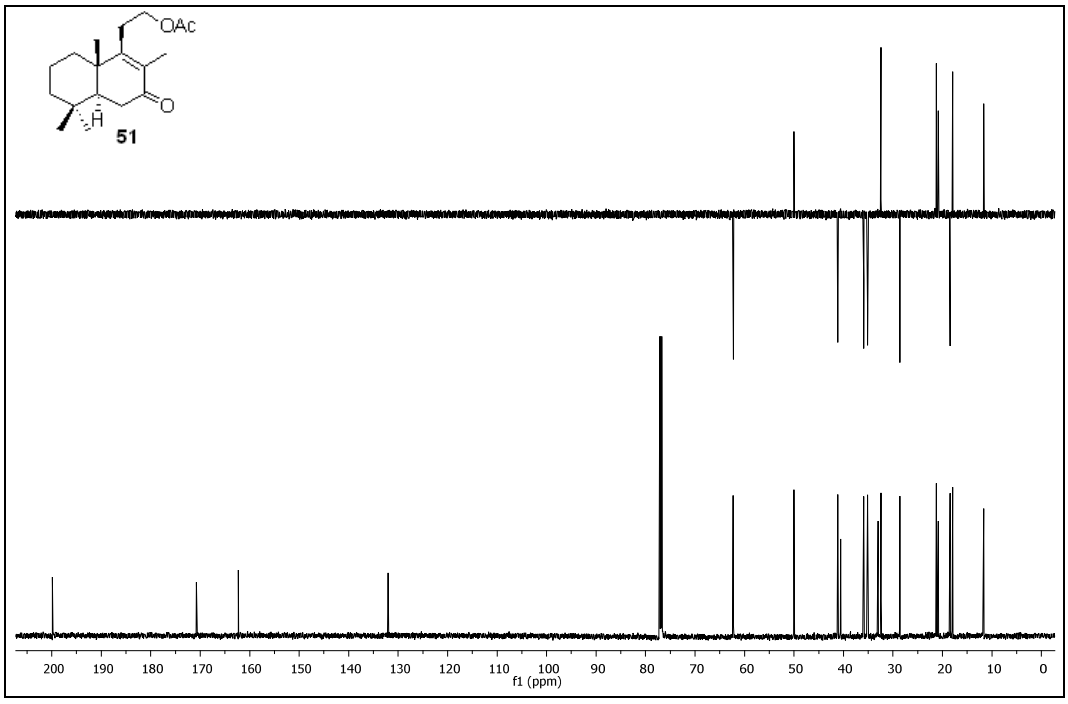

11.09
10.17
7.26
6.94
1.19
1.00
0.84
0.77
0.75
OH
OH
O
OHC
45
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

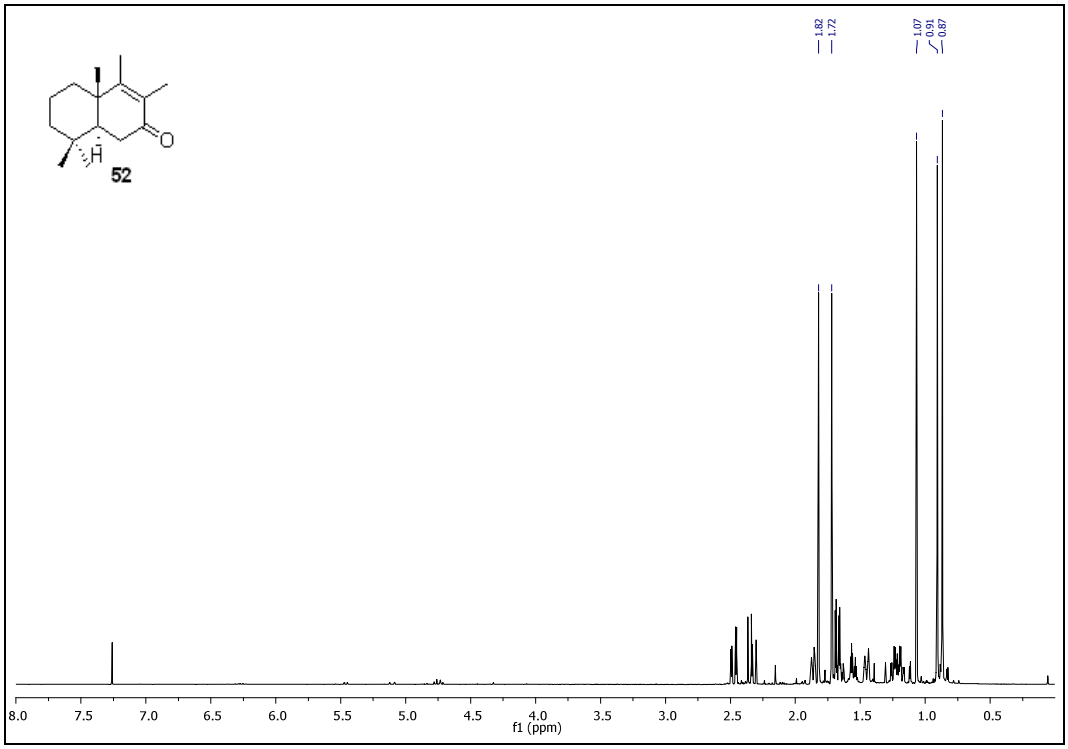

OMe
OMe
OBn
O
H
46
7
6
5
4
3
2
1
ppm

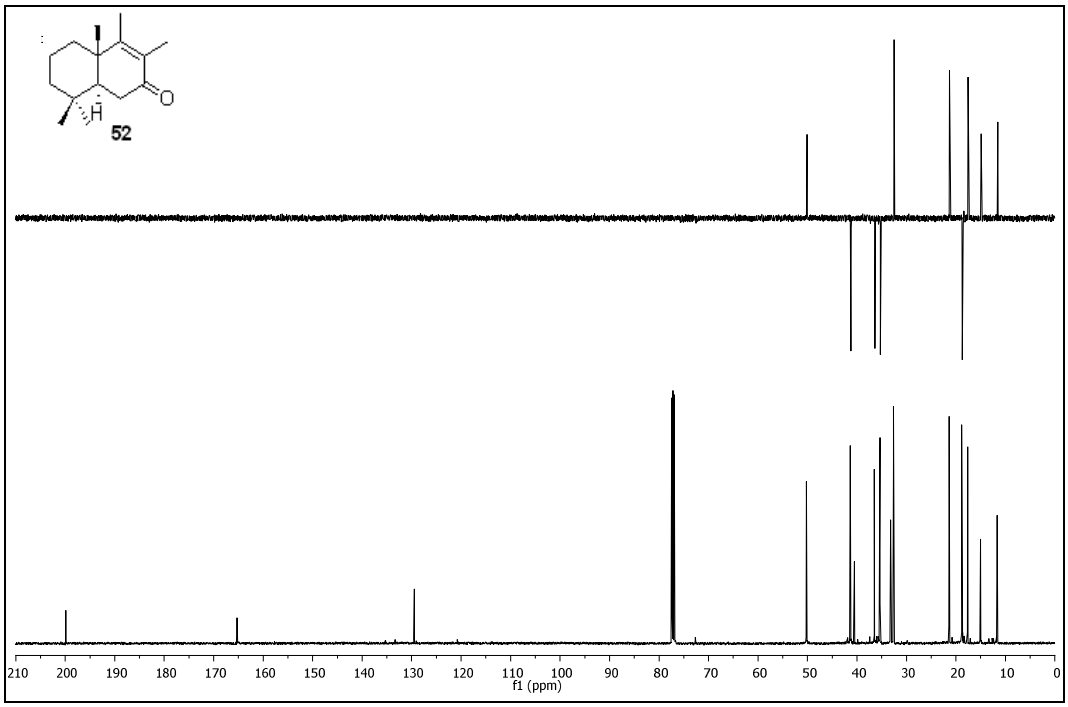

OAc
OH
H
49
4.12
2.04
1.16
0.87
0.79
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

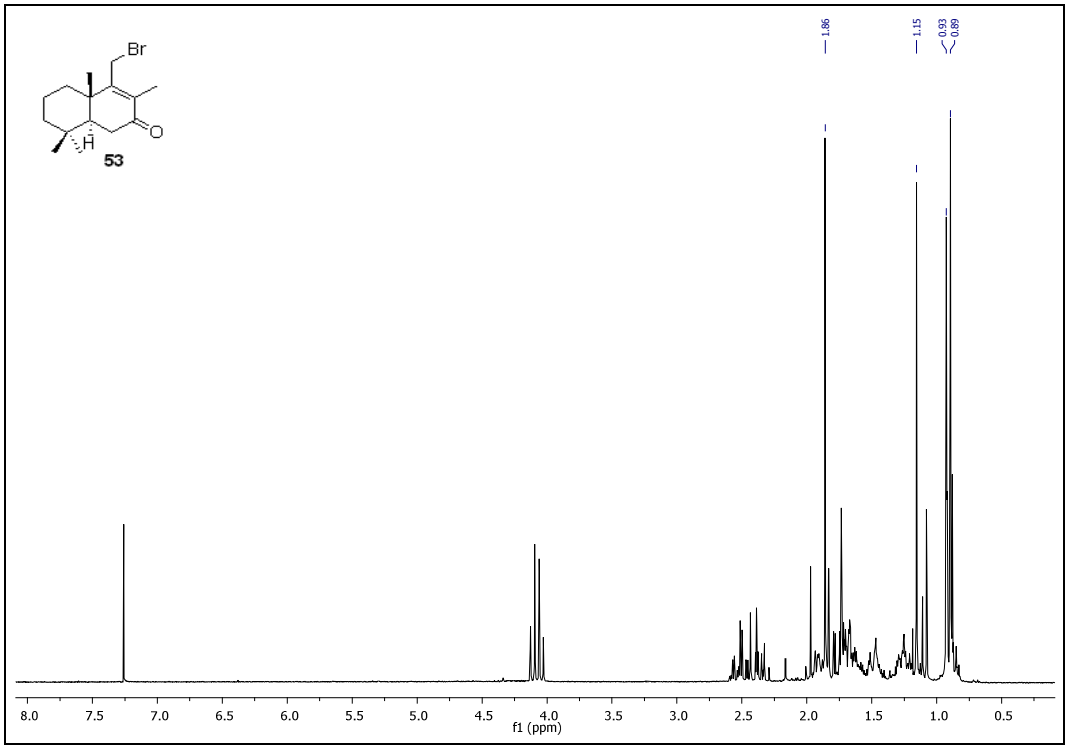

OAc
OH
H
49
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

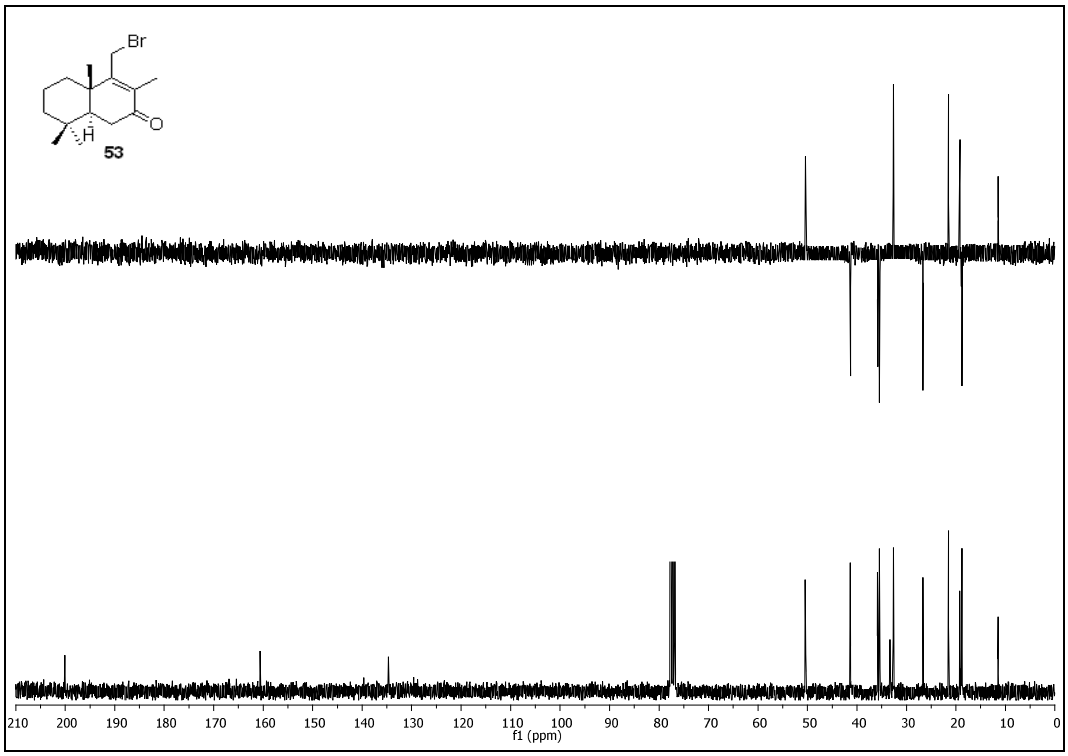

OAc
O
H
51
2.05
1.80
1.07
0.90
0.87
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

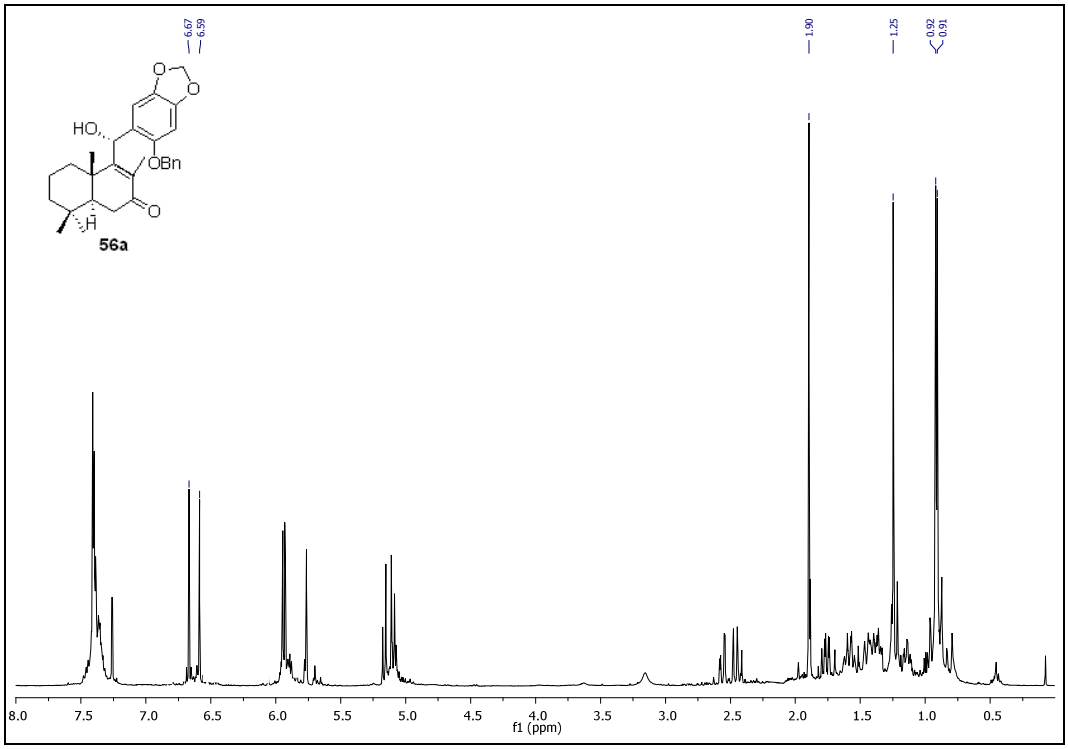

OAc
O
H
51
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

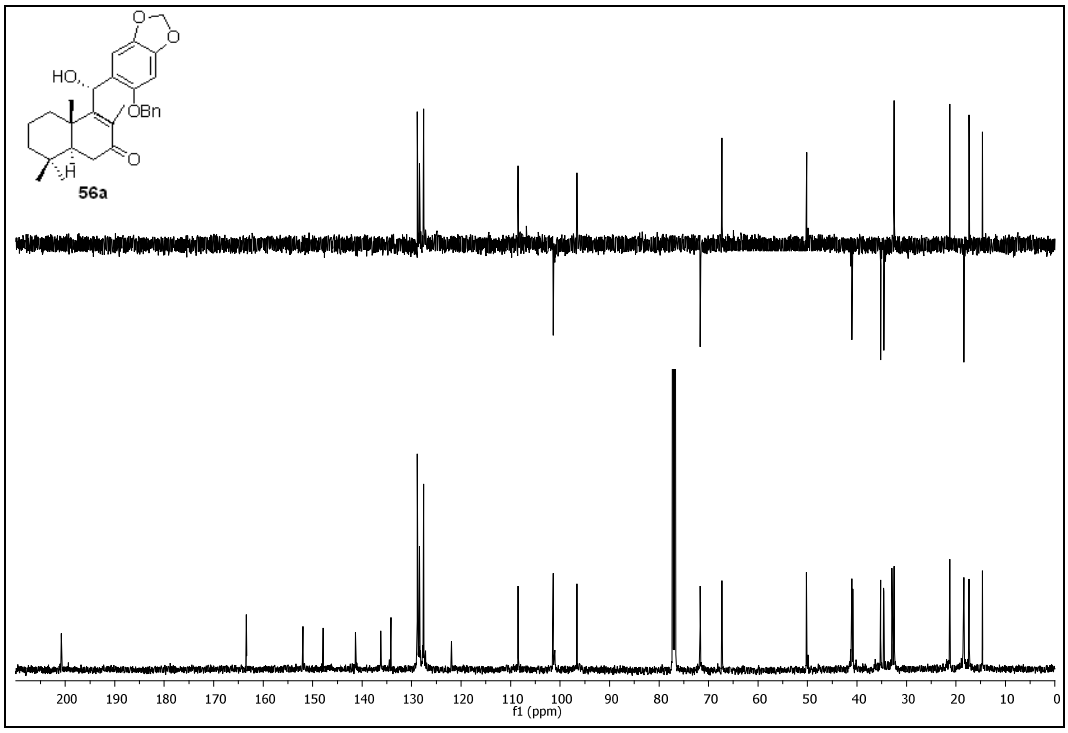

1.82
1.72
1.07
0.91
0.87
O
H
52
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

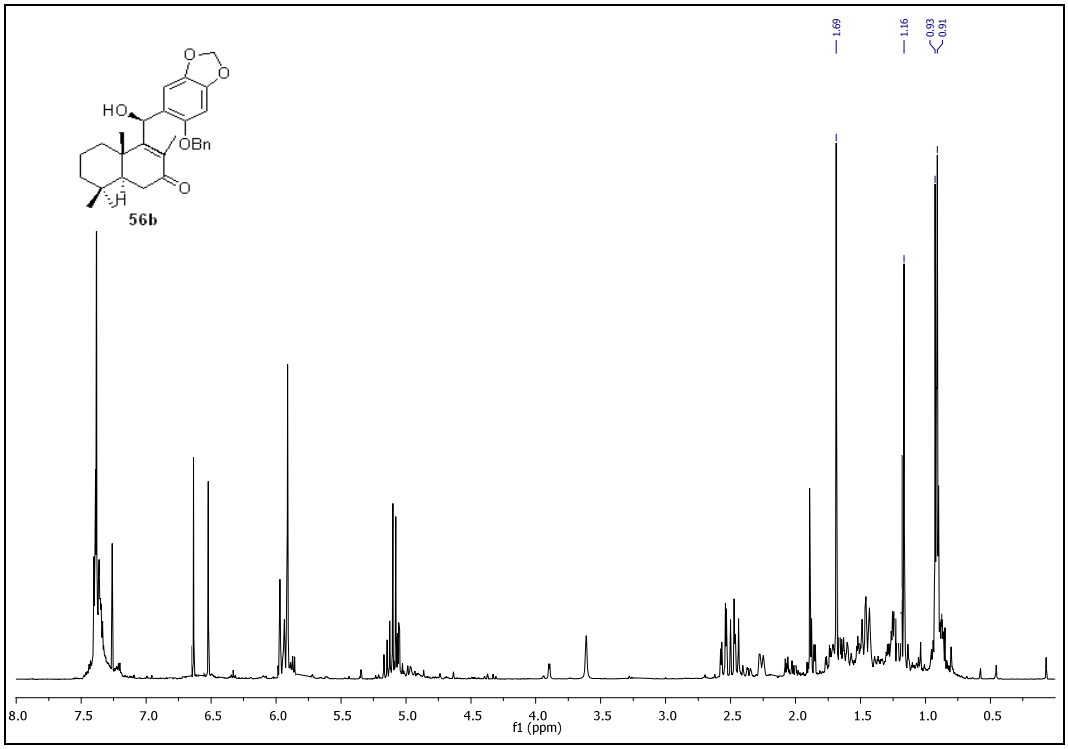

O
H
52
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

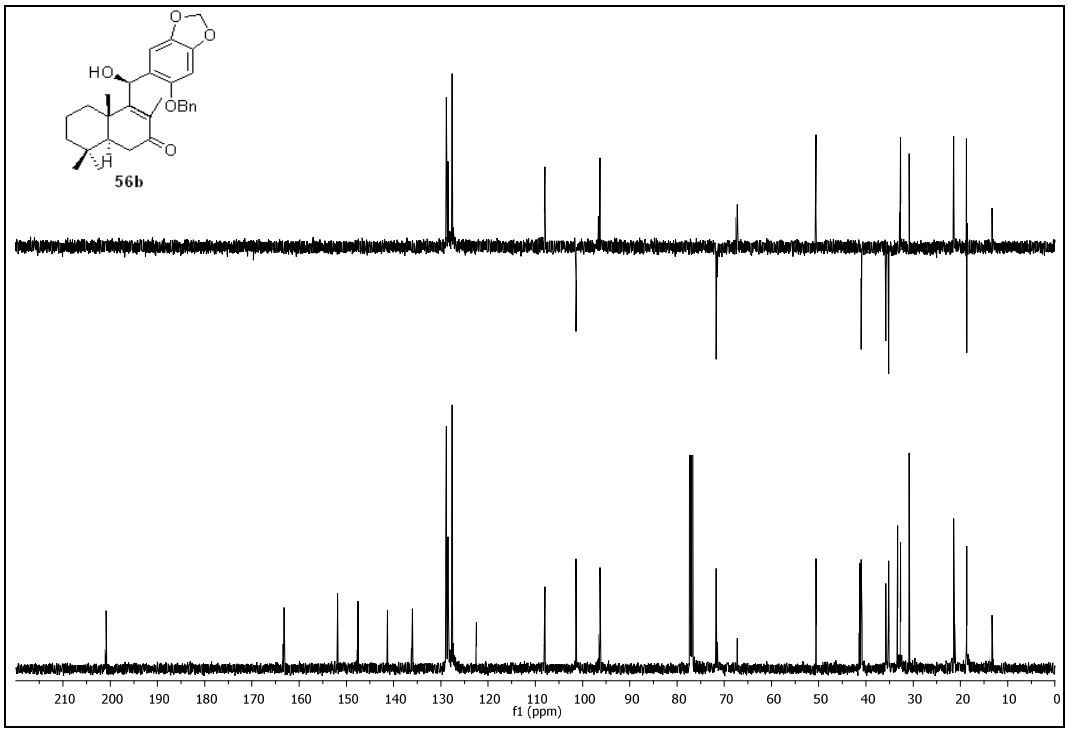

Br
O
H
53
1.86
1.15
0.93
0.89
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

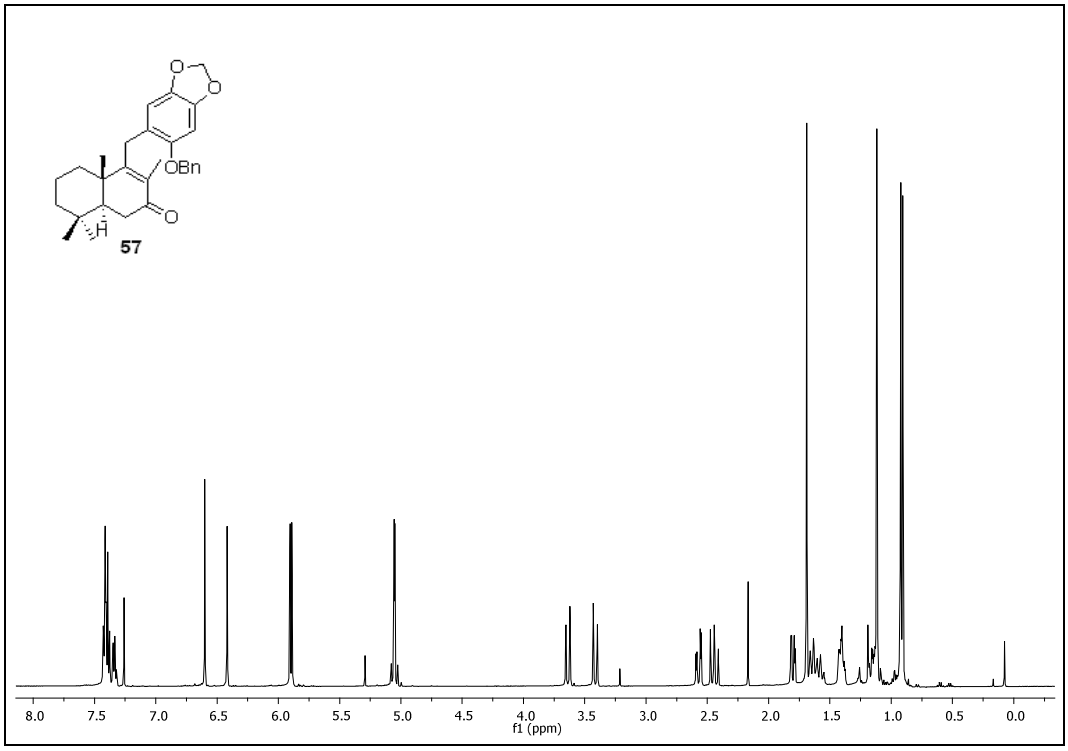

Br
O
H
53
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

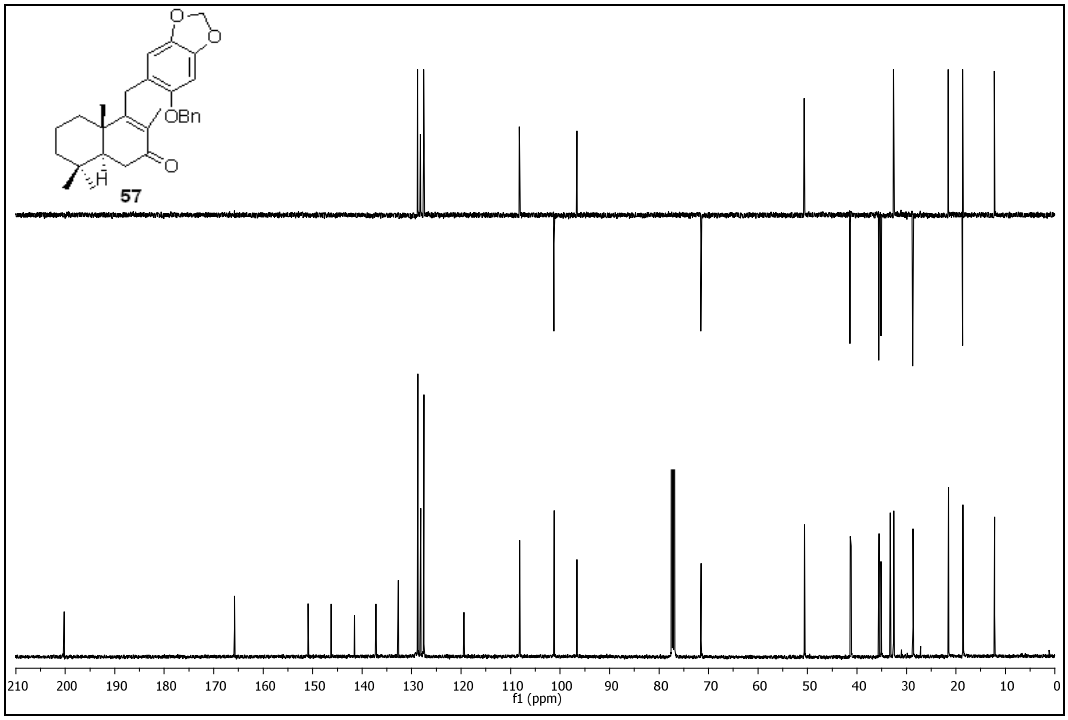

6.67
6.99
1.90
1.25
0.92
0.91
HO
OBn
O
H
56a
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

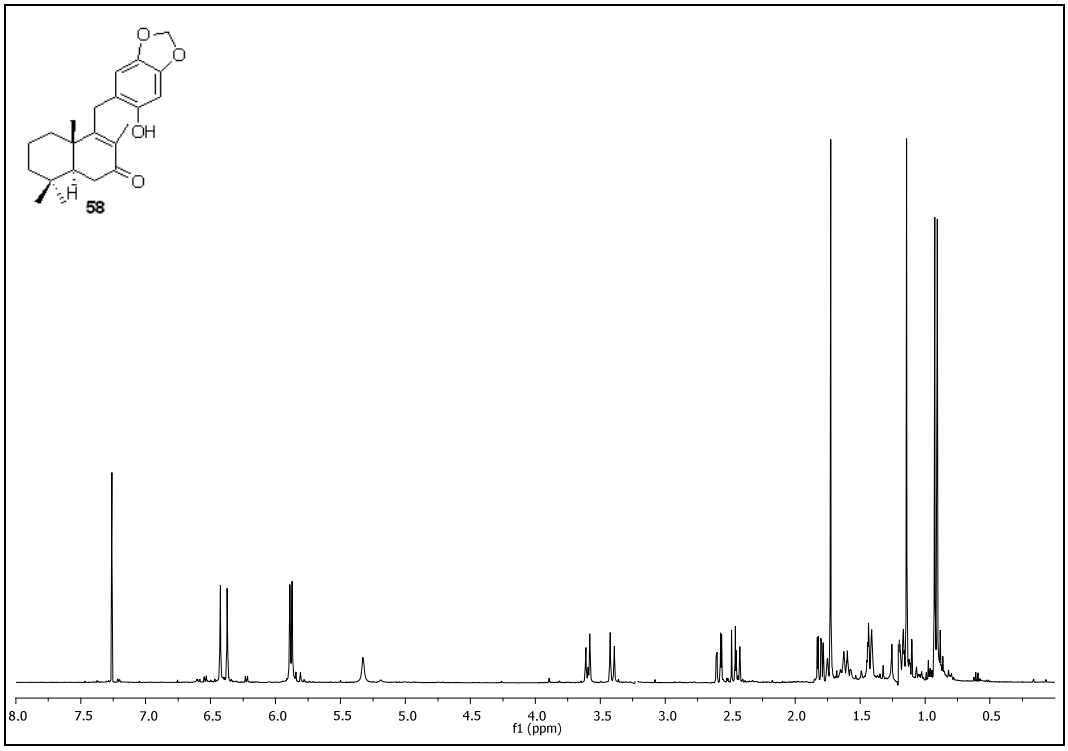

HO
OBn
O
H
56a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

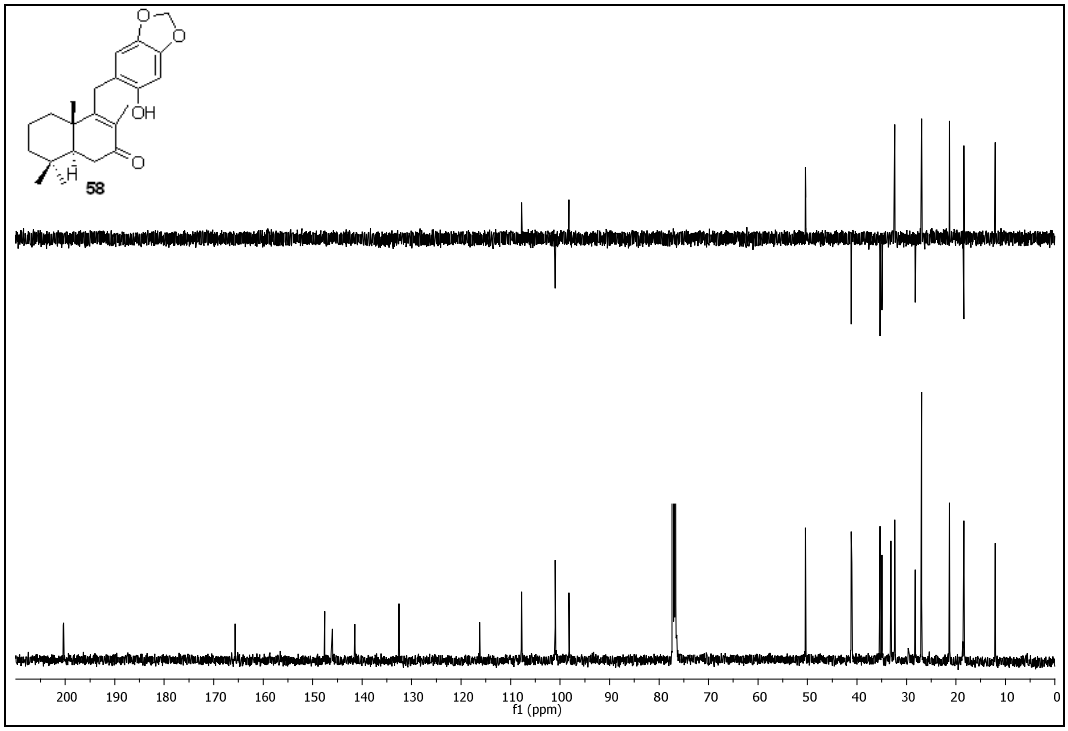

HO
OBn
O
O
O
H
56b
1.69
1.16
0.93
0.91
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

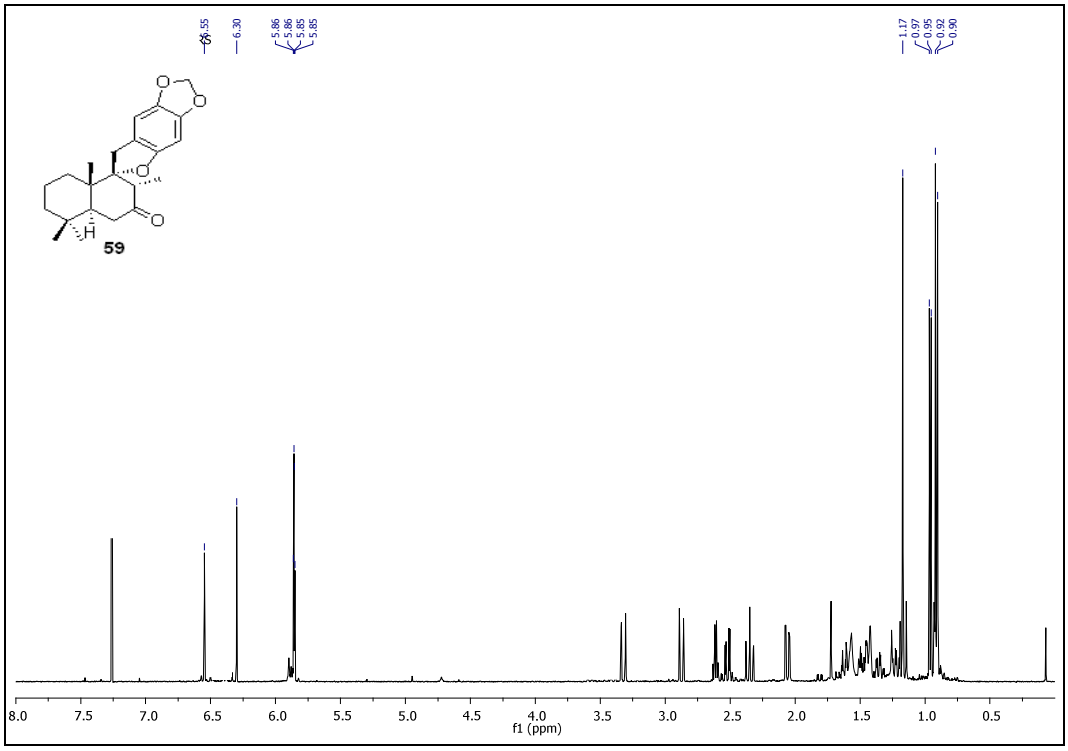

HO
OBn
O
O
O
H
56b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

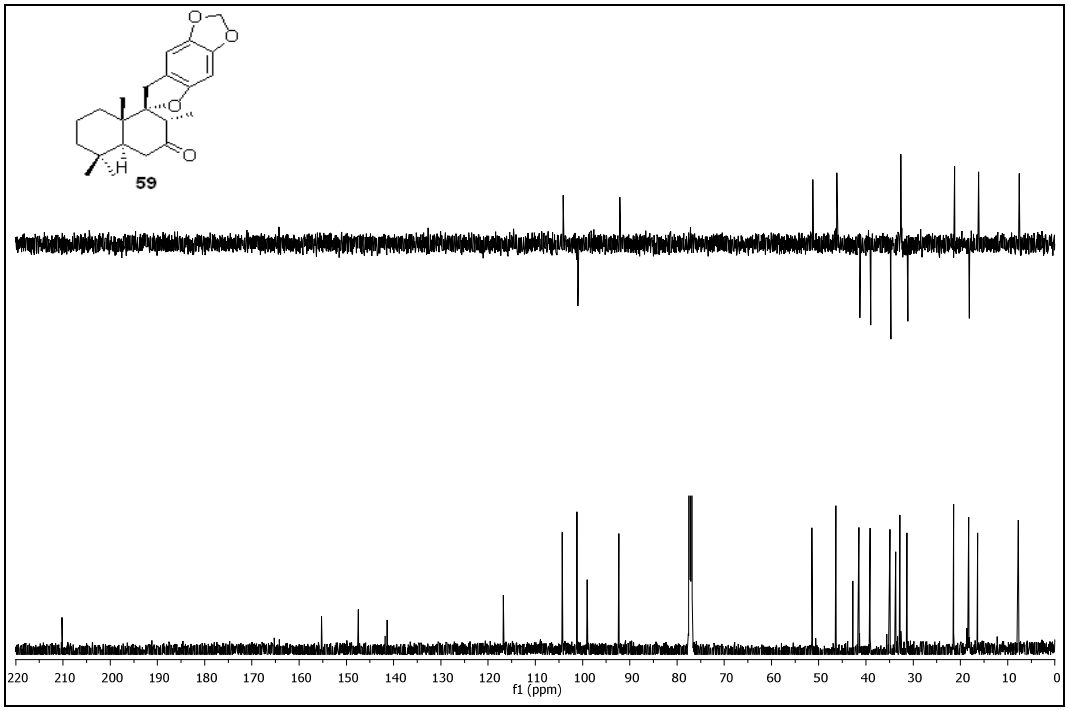

OBn
O
O
O
H
57
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

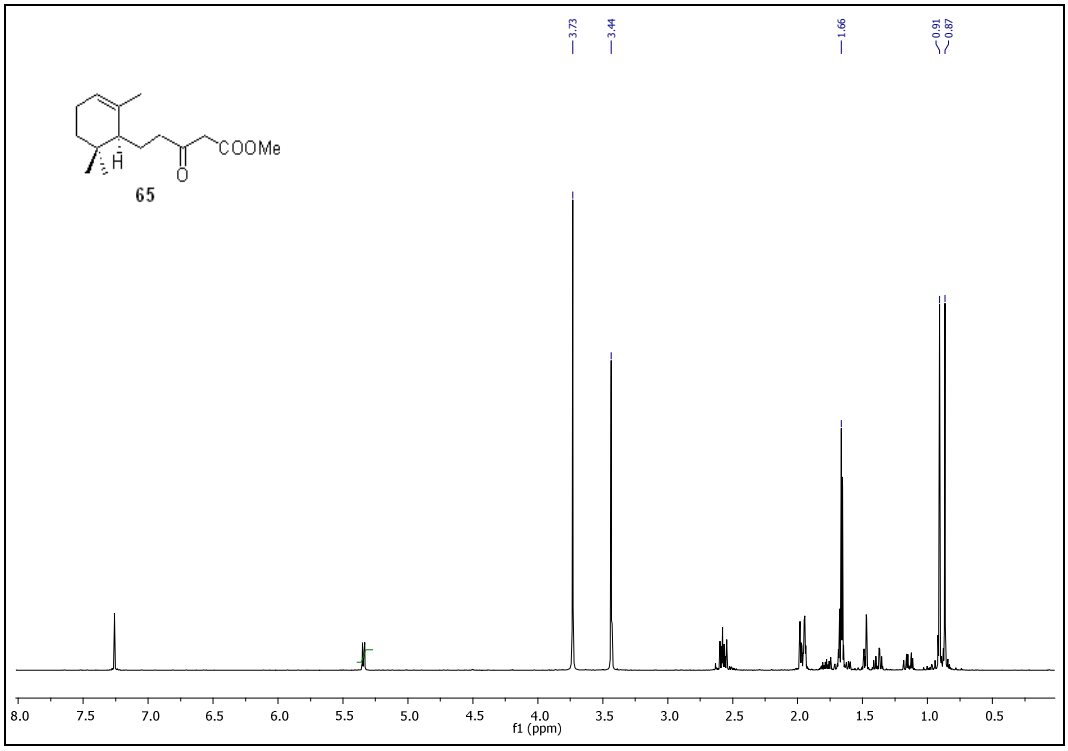

OBn
O
O
O
H
57
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

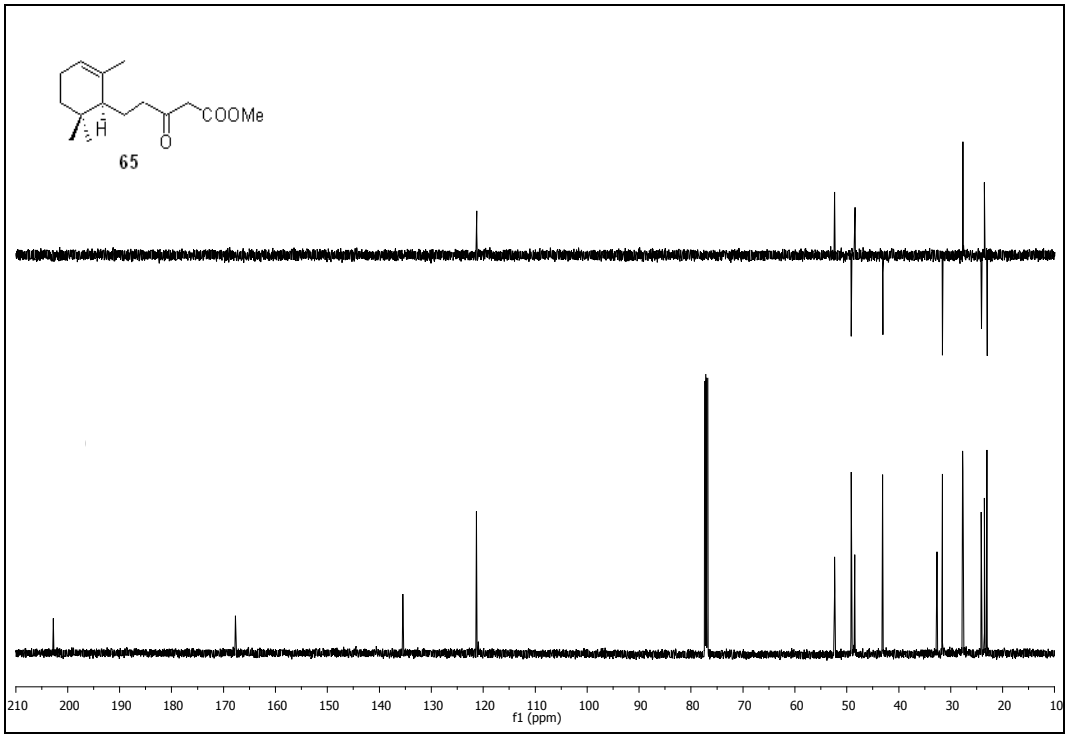

O
O
OH
O
H
58
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

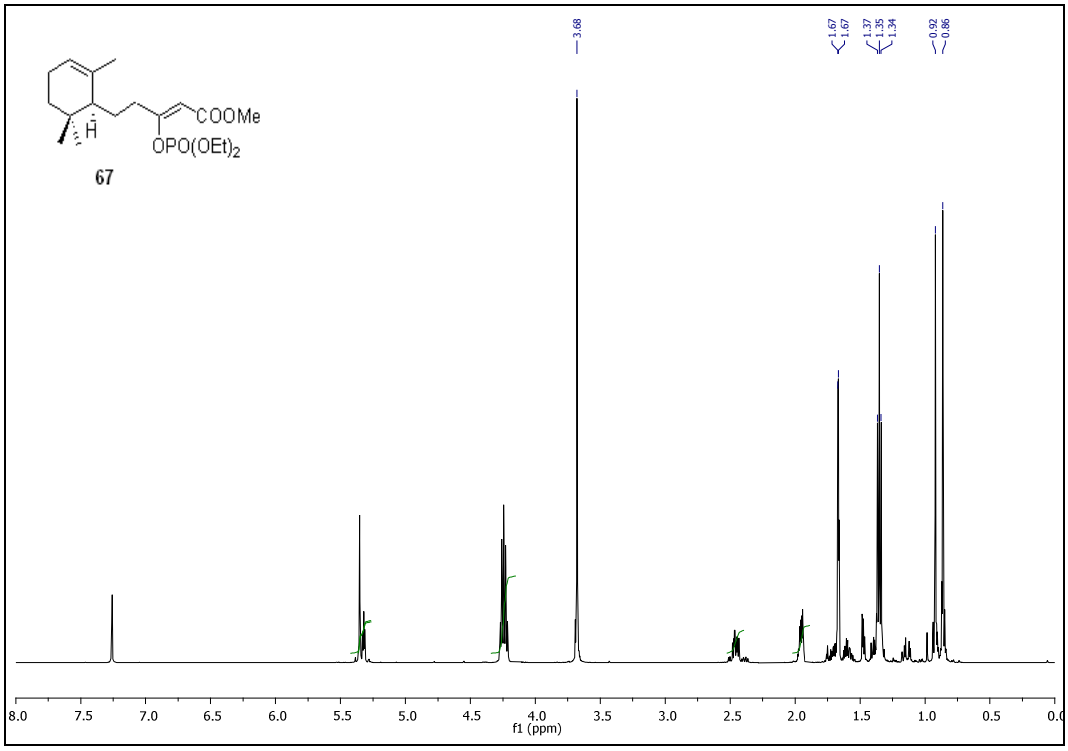

O
O
OH
O
H
58
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

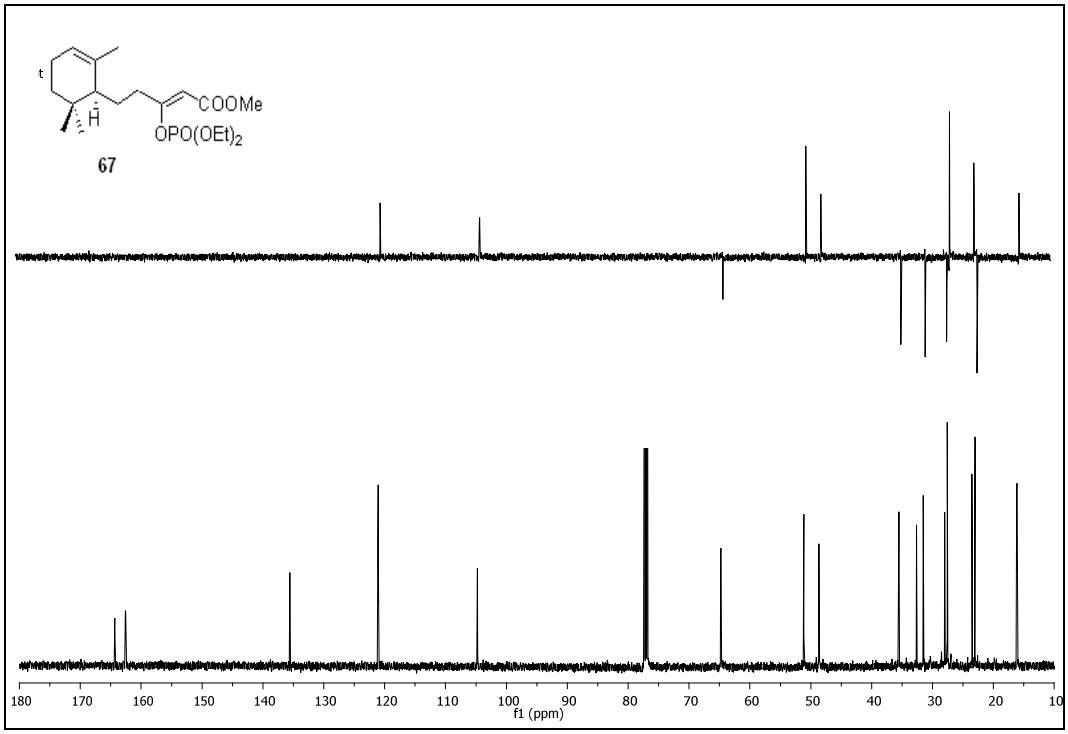

6.55
6.30
5.86
5.86
5.85
5.85
1.17
0.97
0.95
0.92
0.90
59
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

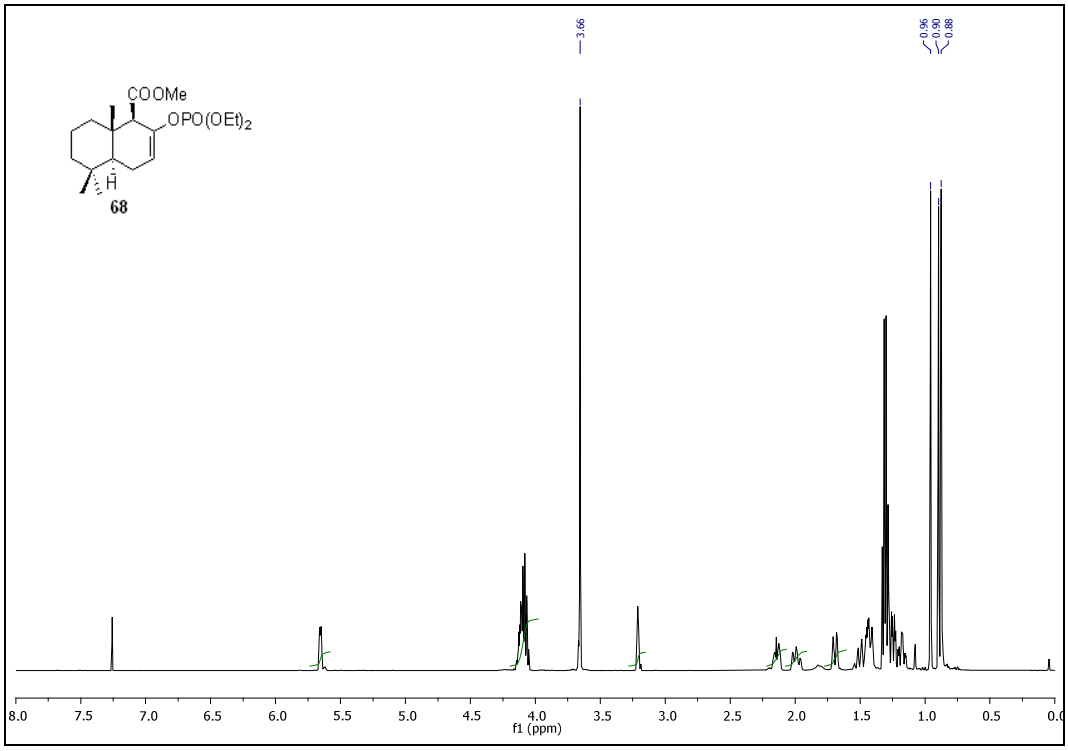

59
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

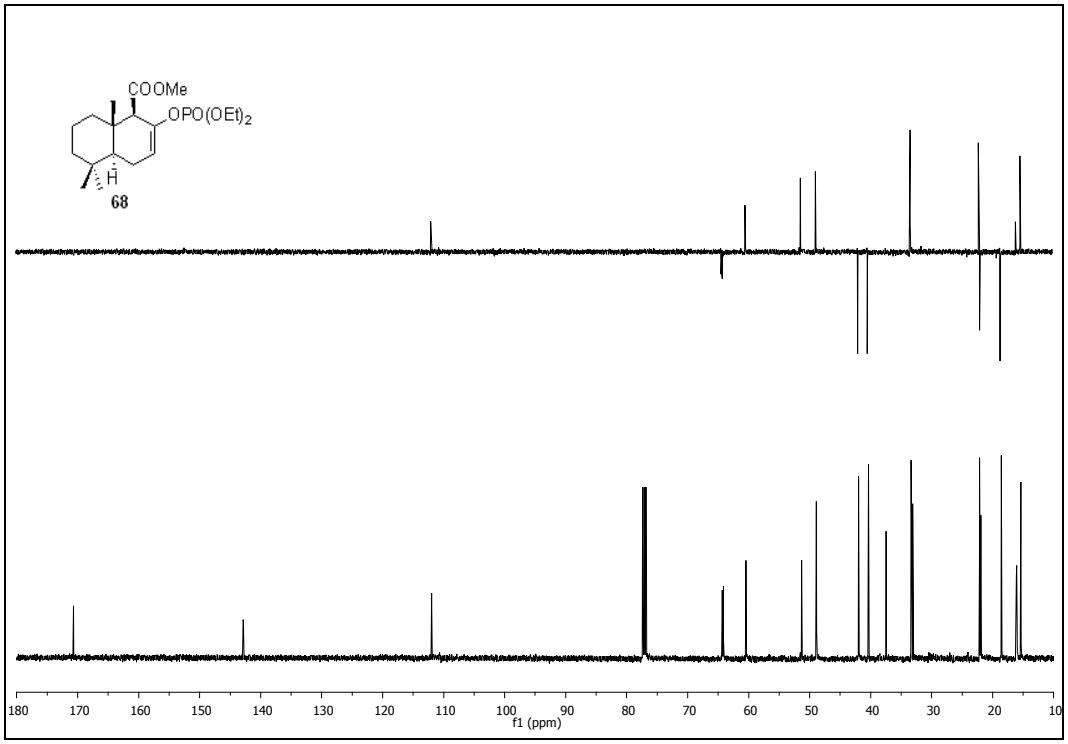

3.73
3.44
1.66
0.91
0.87
COOMe
H
O
65
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

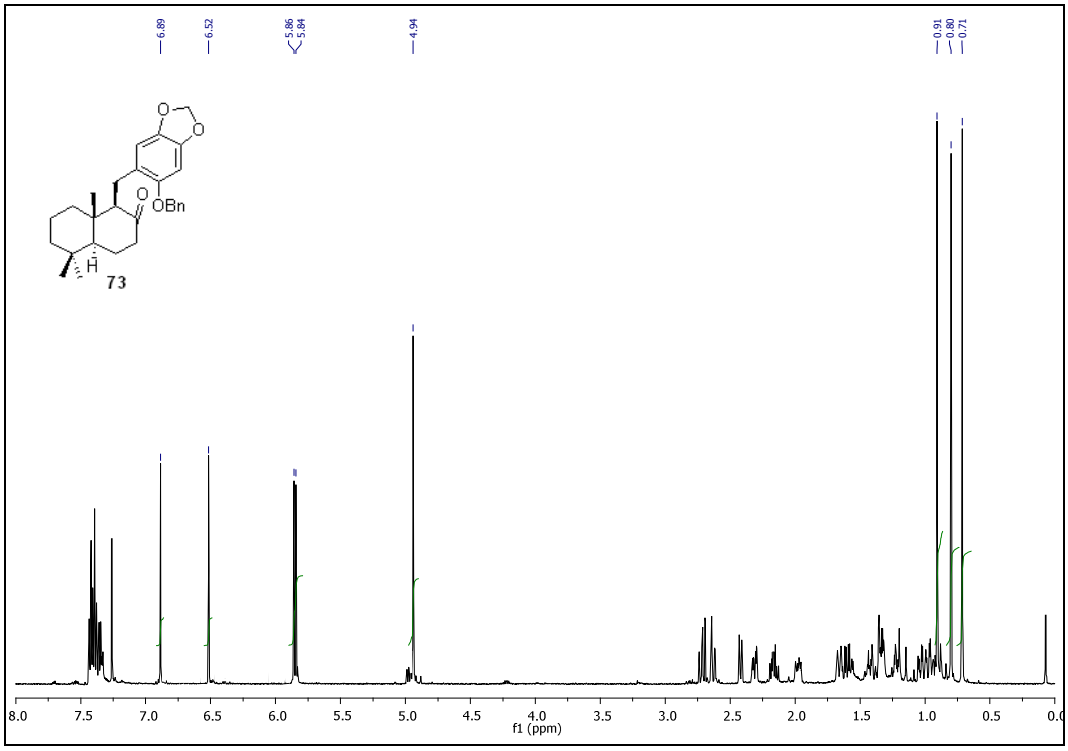

COOMe
H
O
65
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

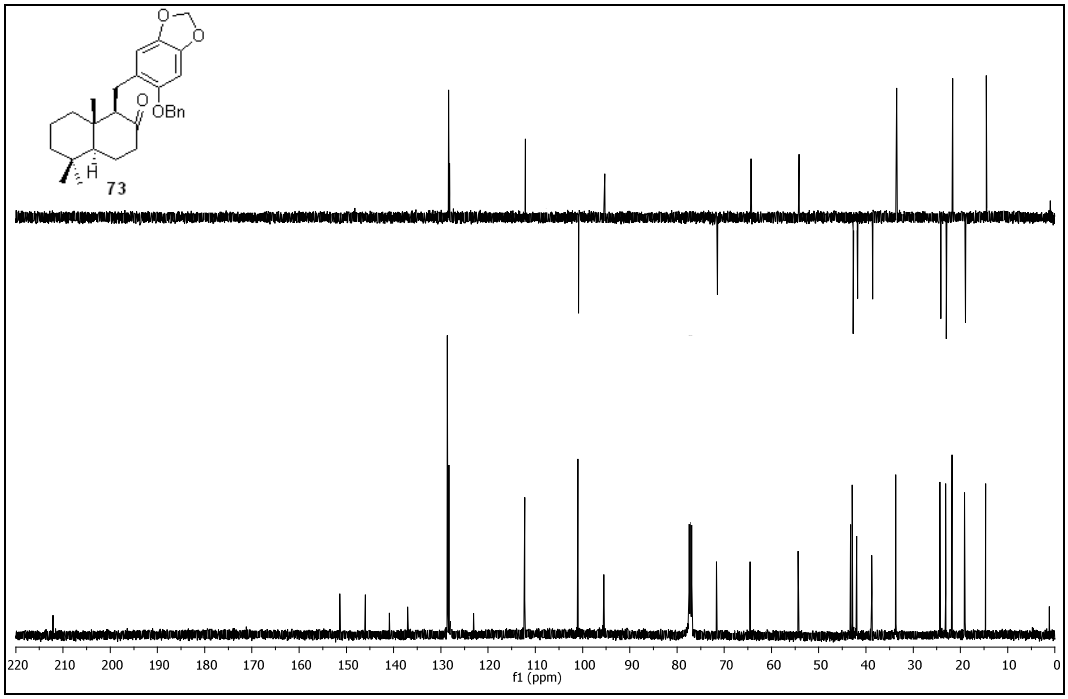

COOMe
OPO(OEt)2
H
67
3.68
1.67
1.67
1.37
1.35
1.34
0.92
0.86
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

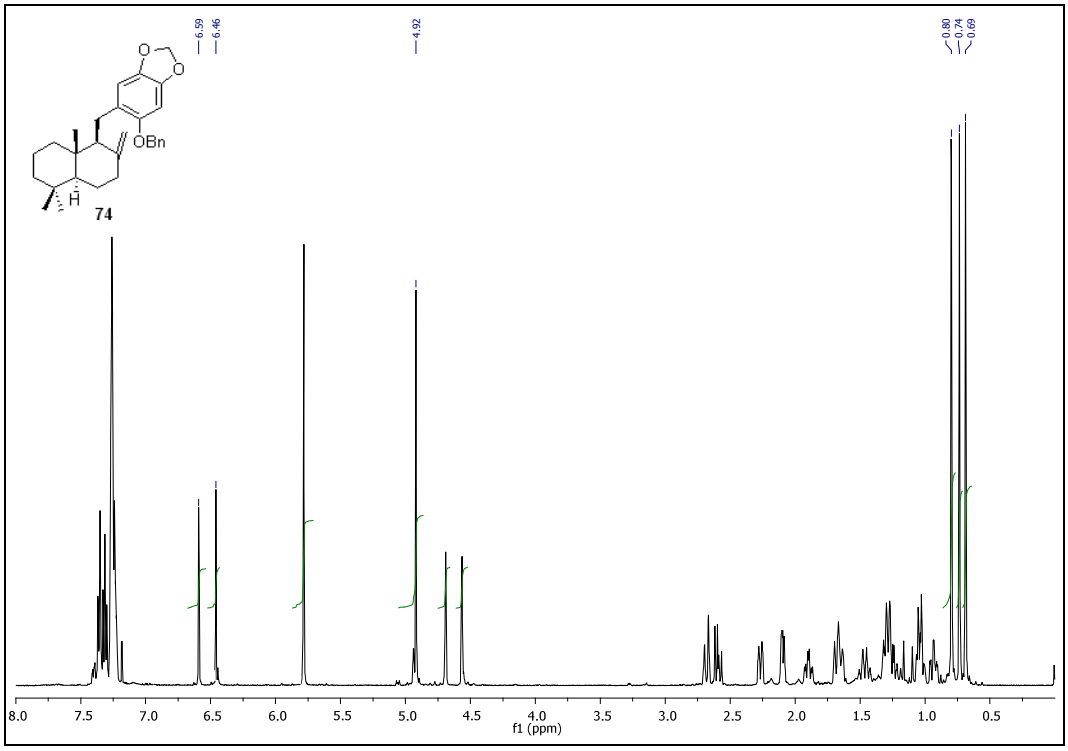

t
COOMe
OPO(OEt)2
H
67
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

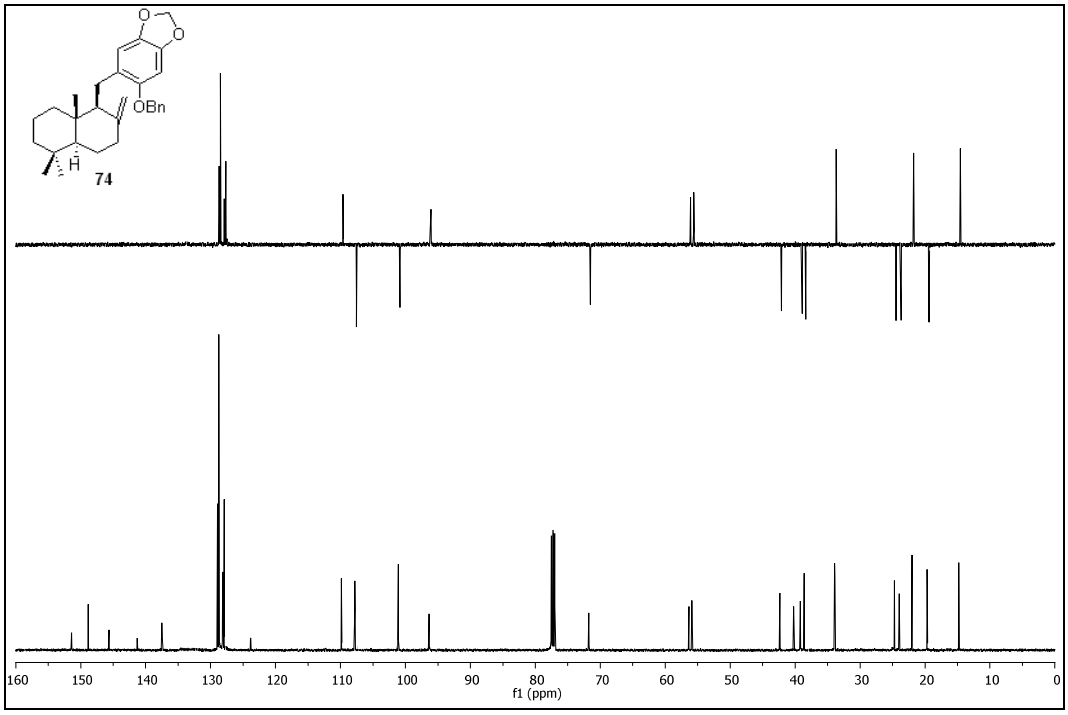

COOMe
OPO(OEt)2
H
68
3.66
0.96
0.90
0.88
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

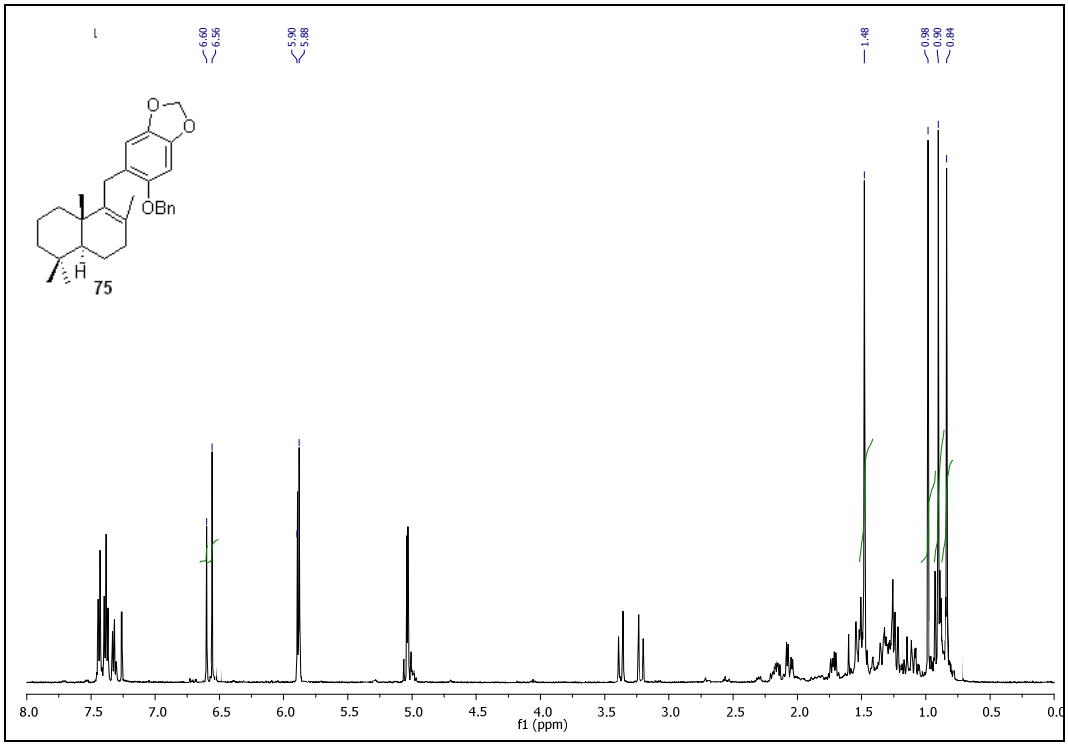

COOMe
OPO(OEt)2
H
68
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

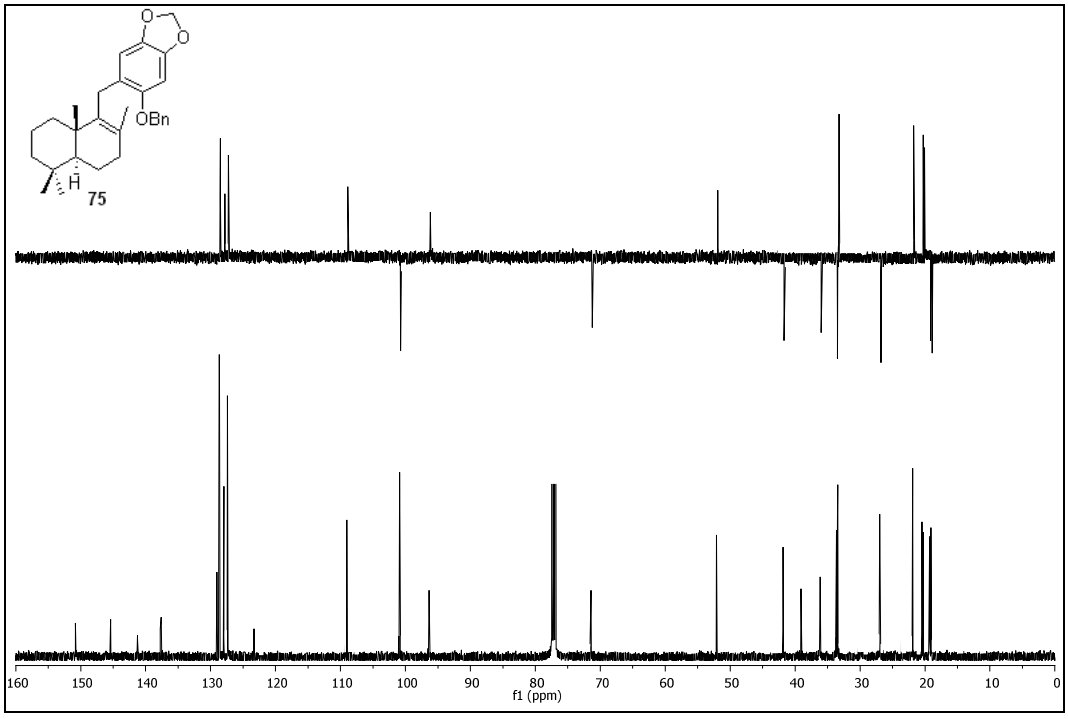

6.89
6.52
5.86
5.84
4.94
0.91
0.80
0.71
O
O
O
OBn
H
73
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

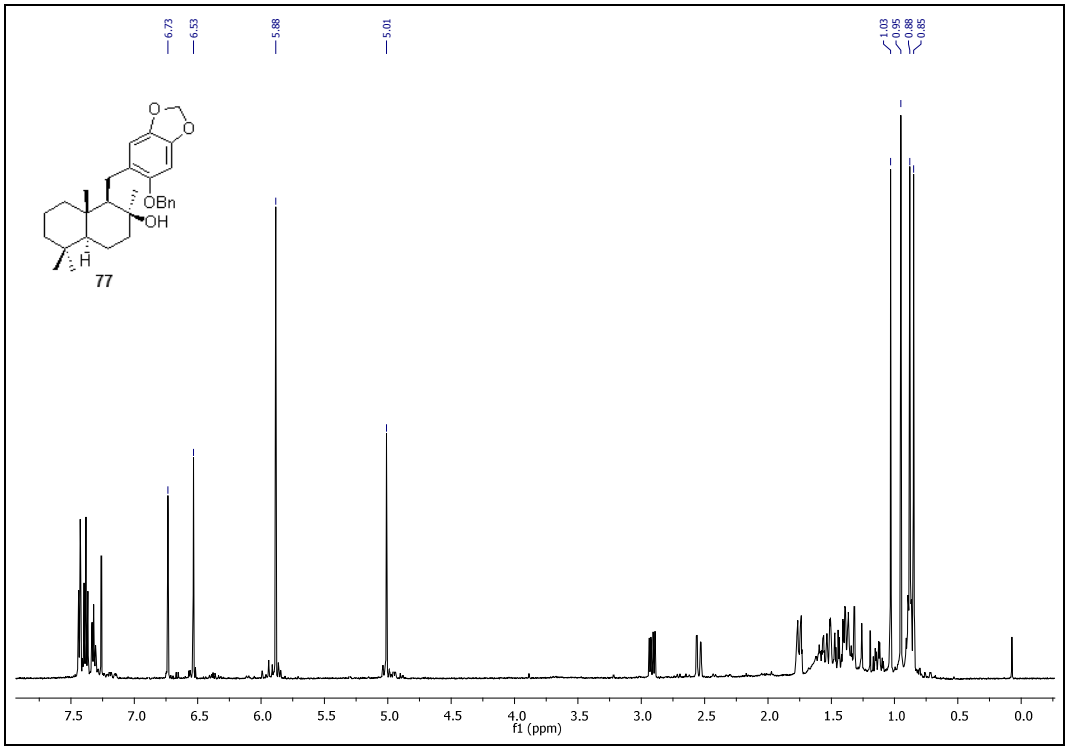

O
O
O
OBn
H
73
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

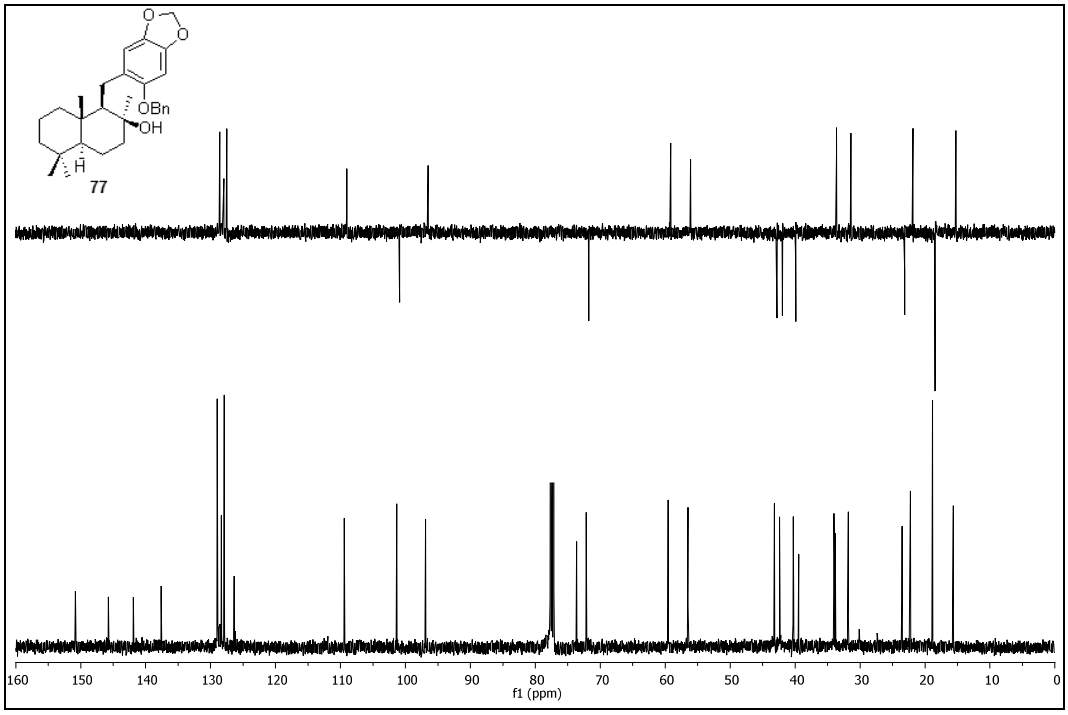

6.59
6.46
4.92
0.80
0.74
0.69
OBn
H
74
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

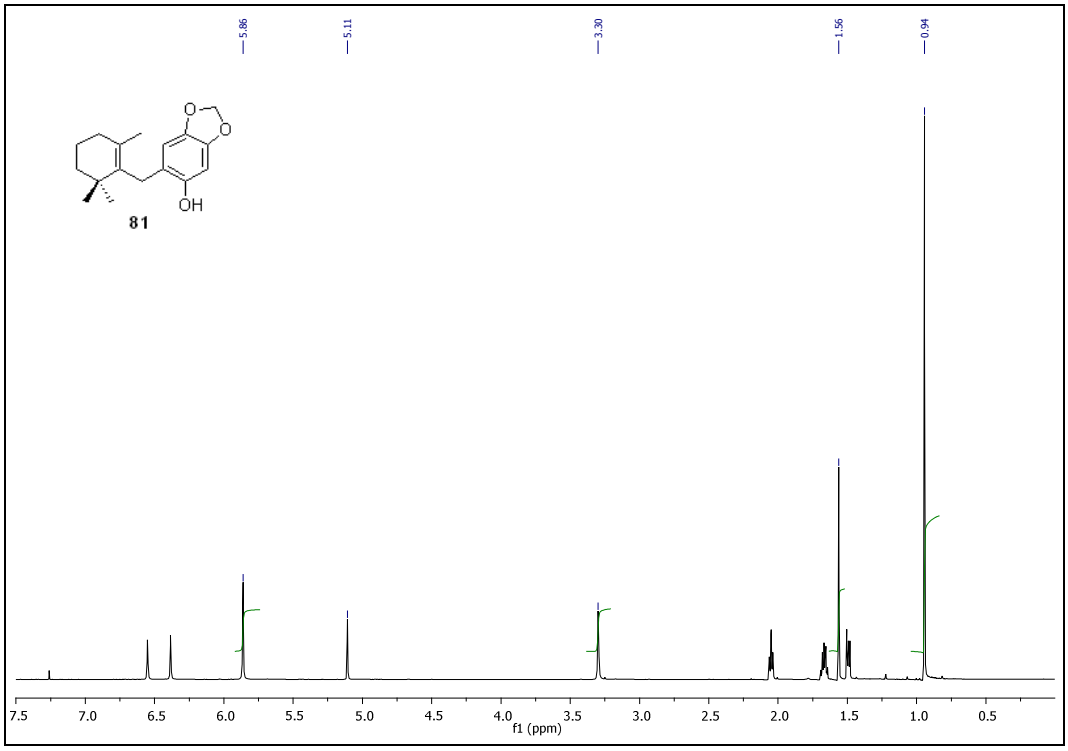

OBn
H
74
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

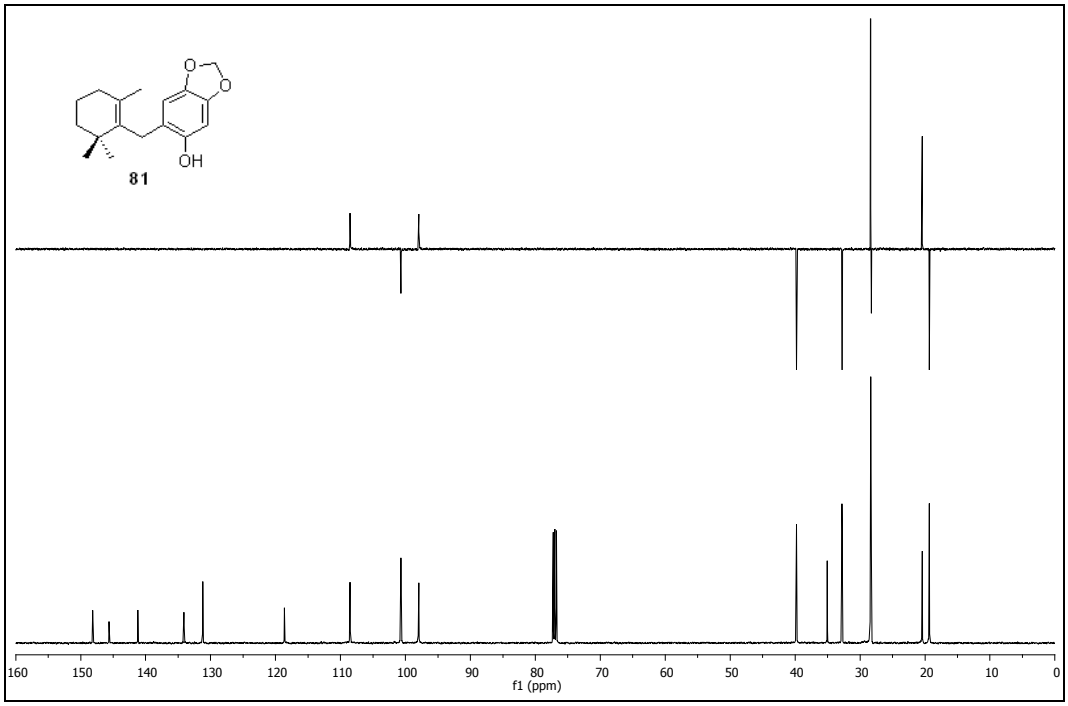

6.60
6.56
5.90
5.88
1.48
0.98
0.90
0.84
OBn
H
75
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

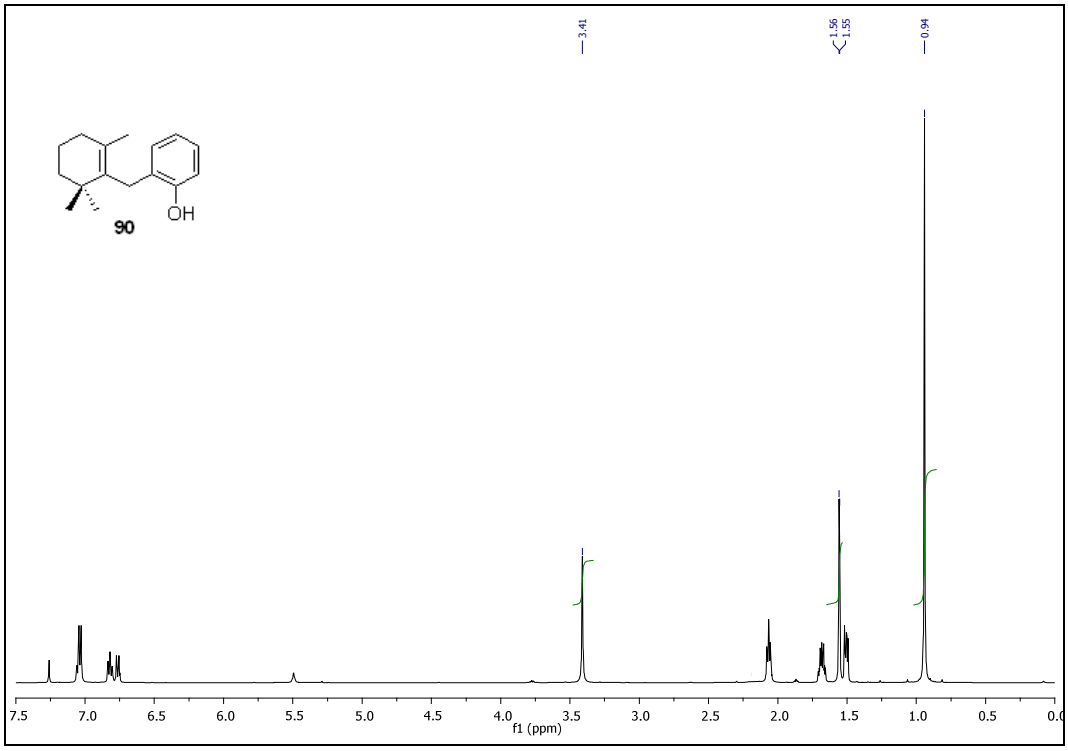

OBn
H
75
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

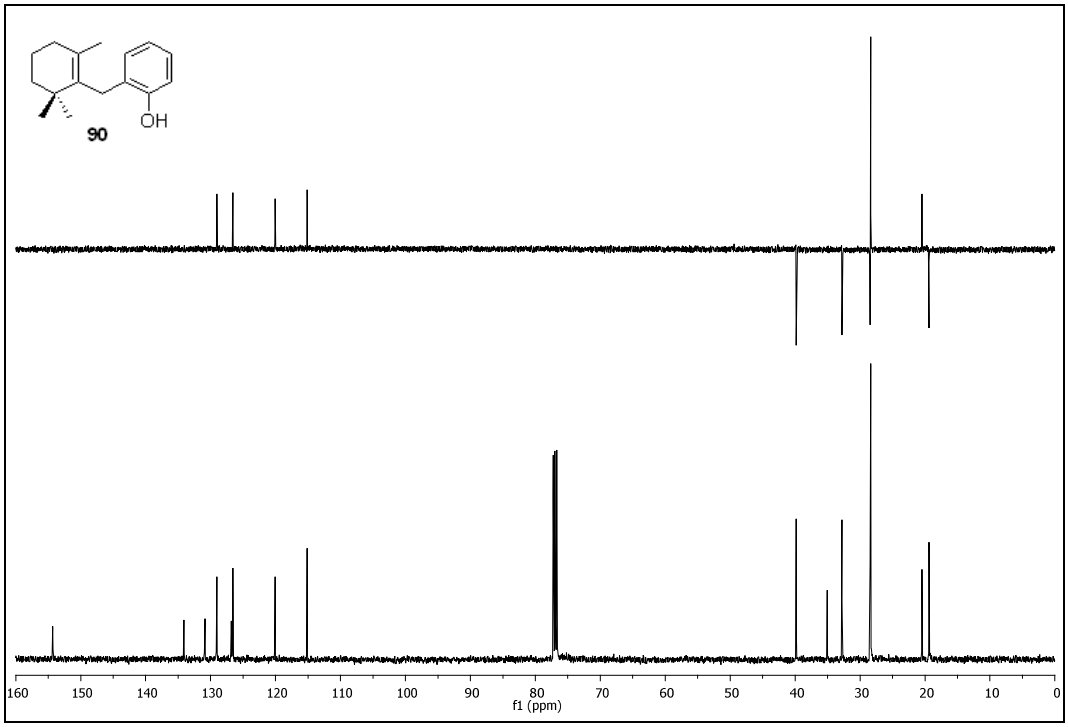

6.73
6.53
5.88
5.01
1.03
0.95
0.88
0.85
O
O
OBn
OH
H
77
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

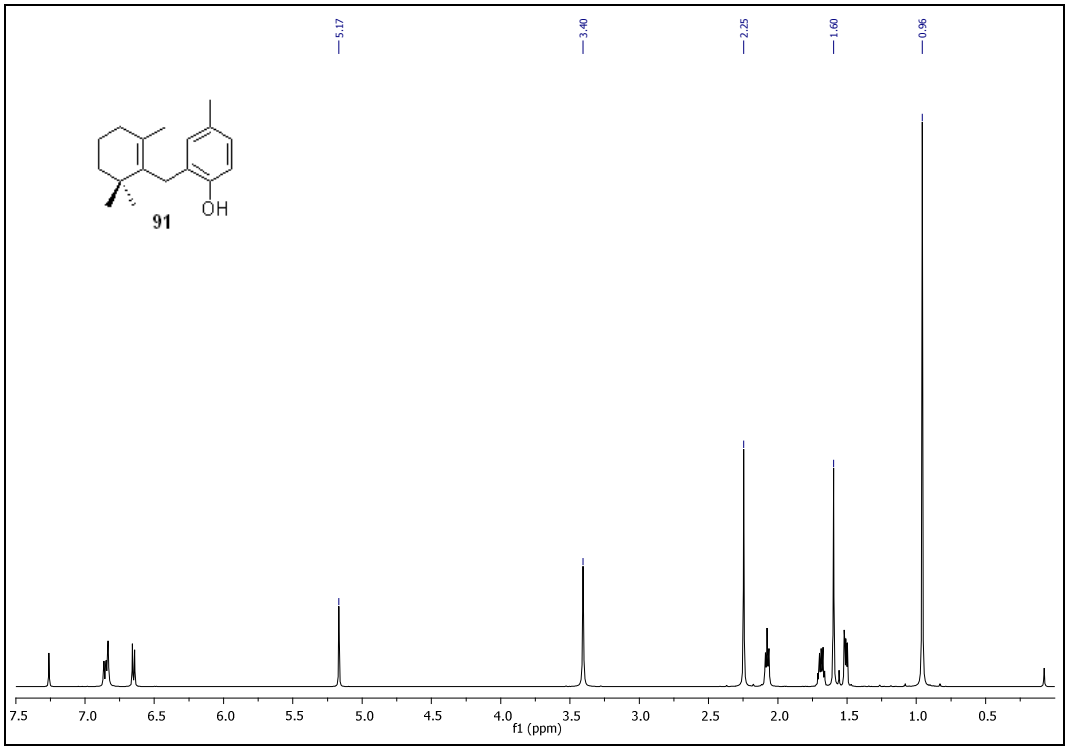

O
O
OBn
OH
H
77
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

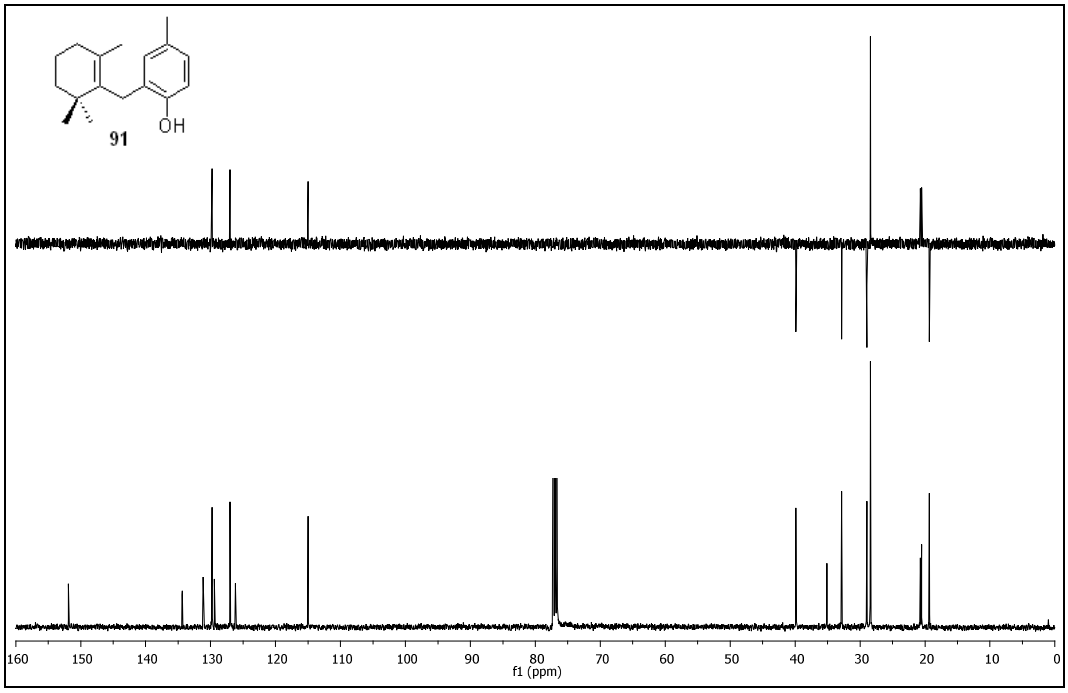

5.86
5.11
3.30
1.56
0.94
O
O
OH
81
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

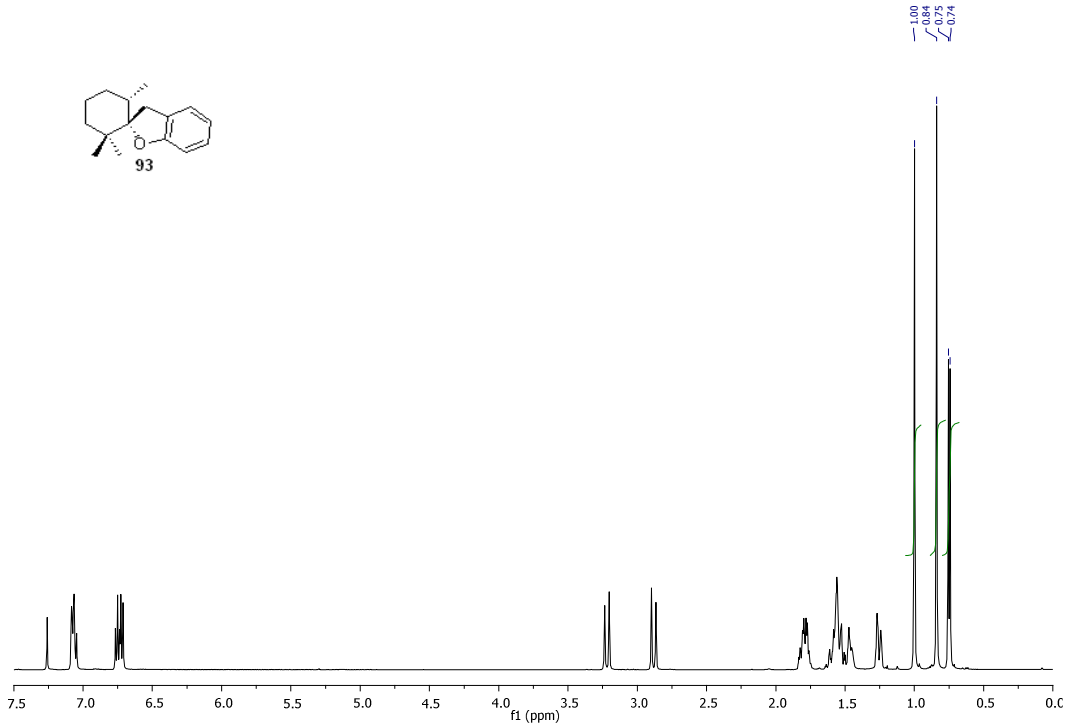

O
O
OH
81
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

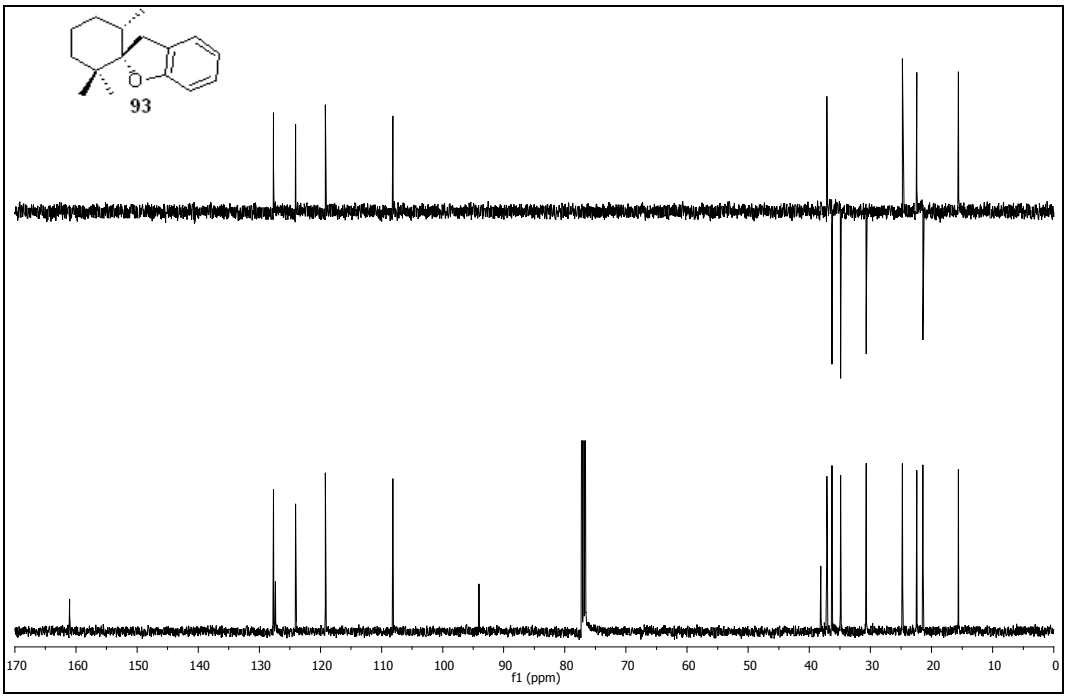

3.41
1.56
1.55
0.94
OH
90
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

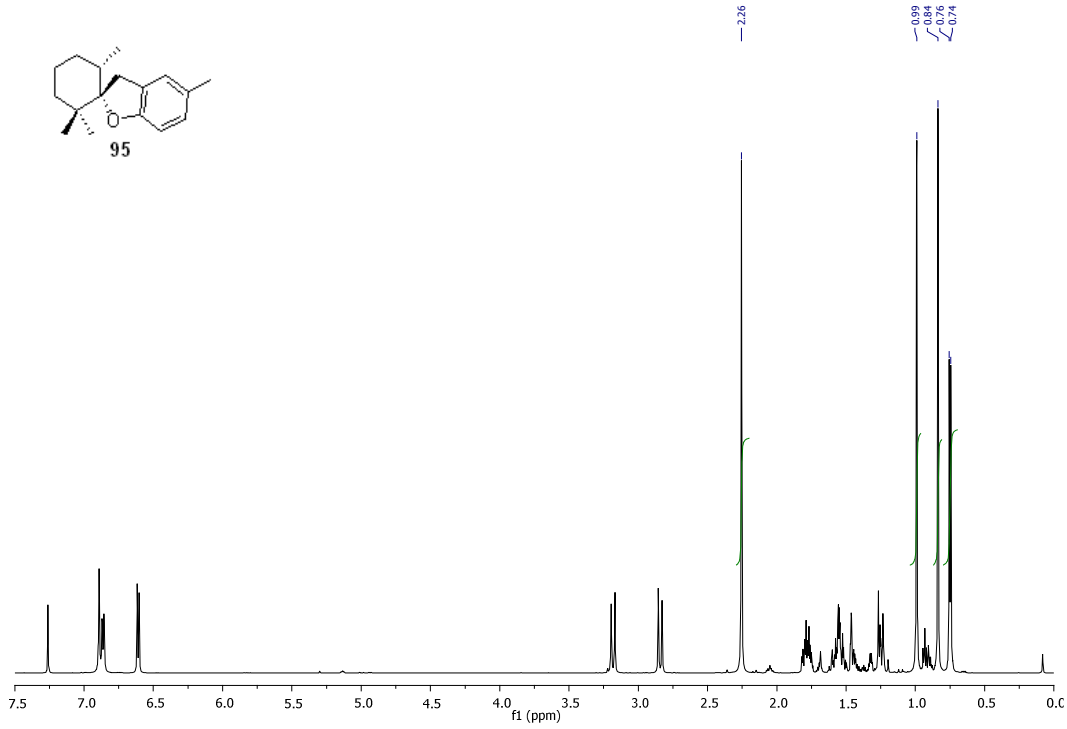

OH
90
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

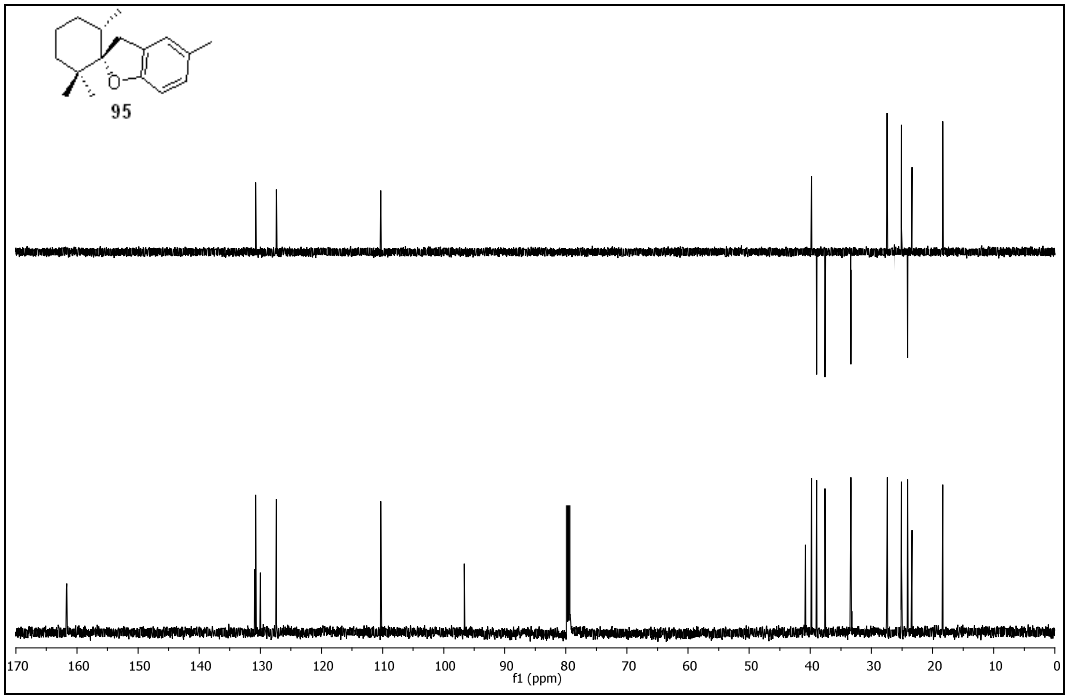

5.17
3.40
2.25
1.60
0.96
OH
91
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

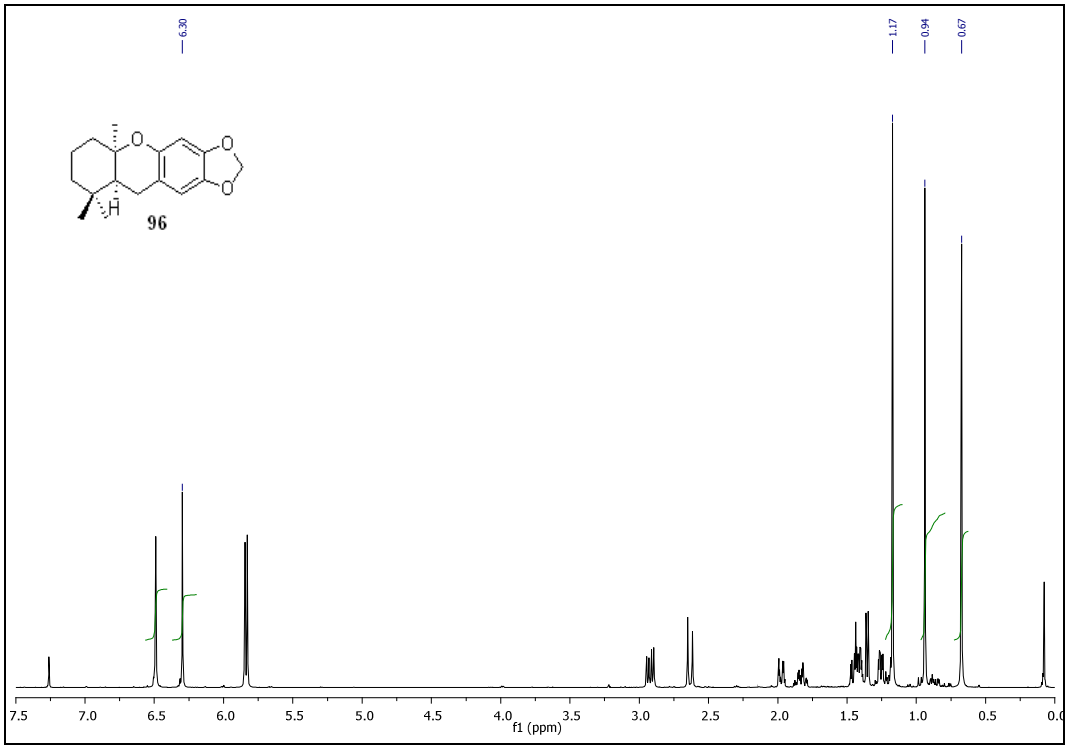

OH
91
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

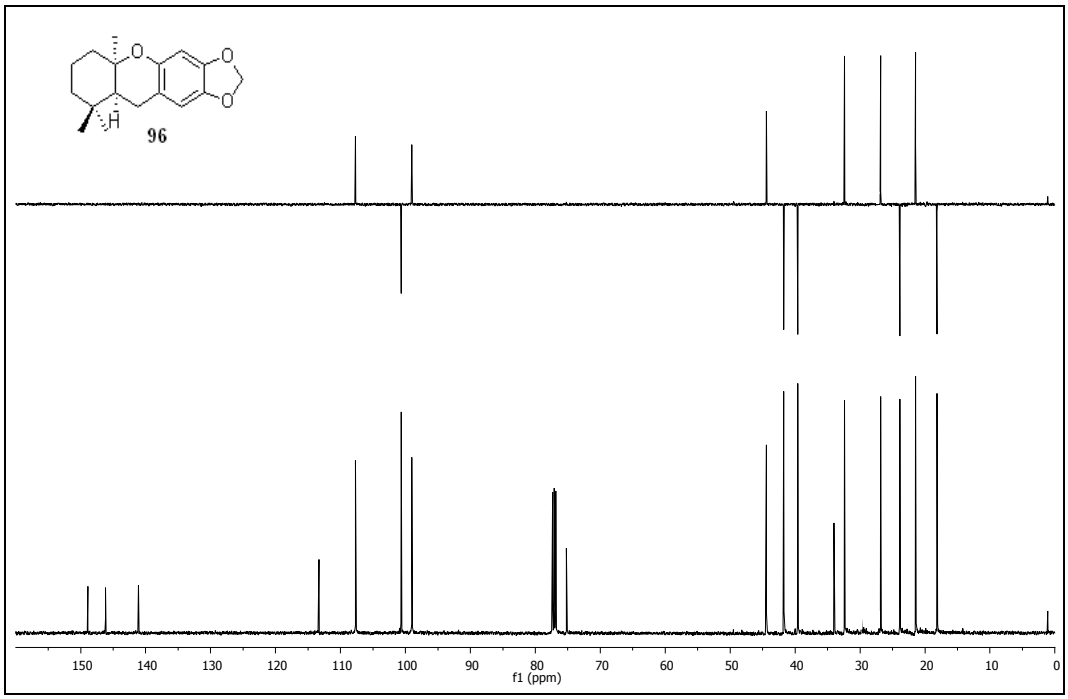

93
1.00
0.84
0.75
0.74
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

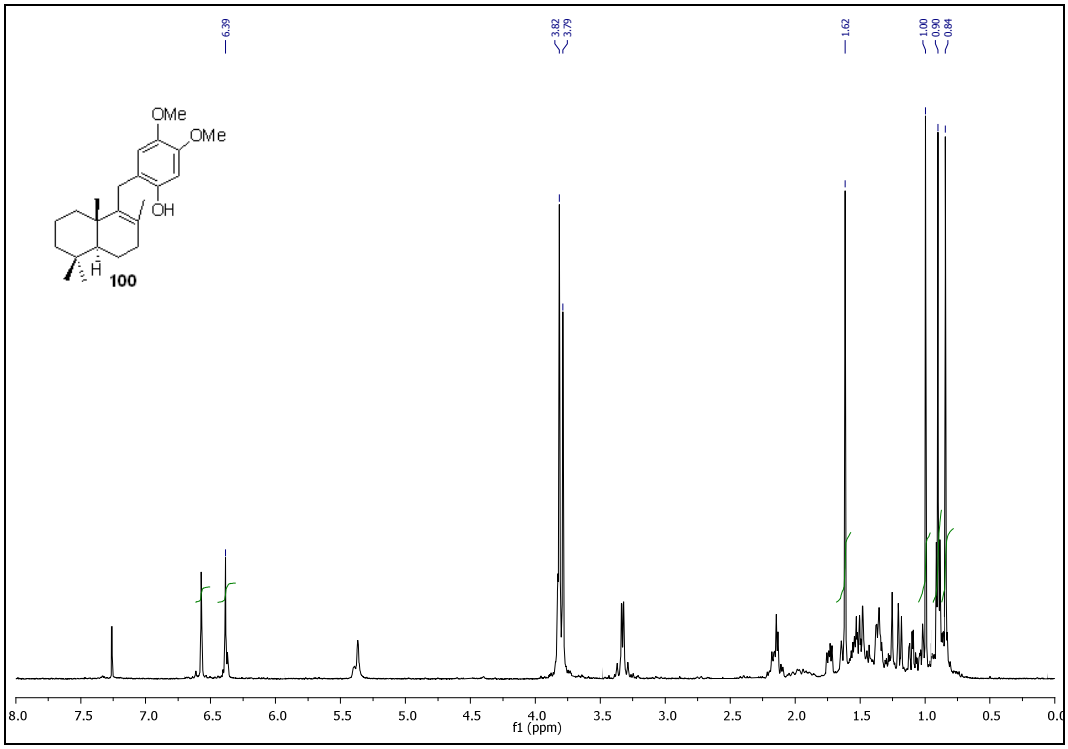

93
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

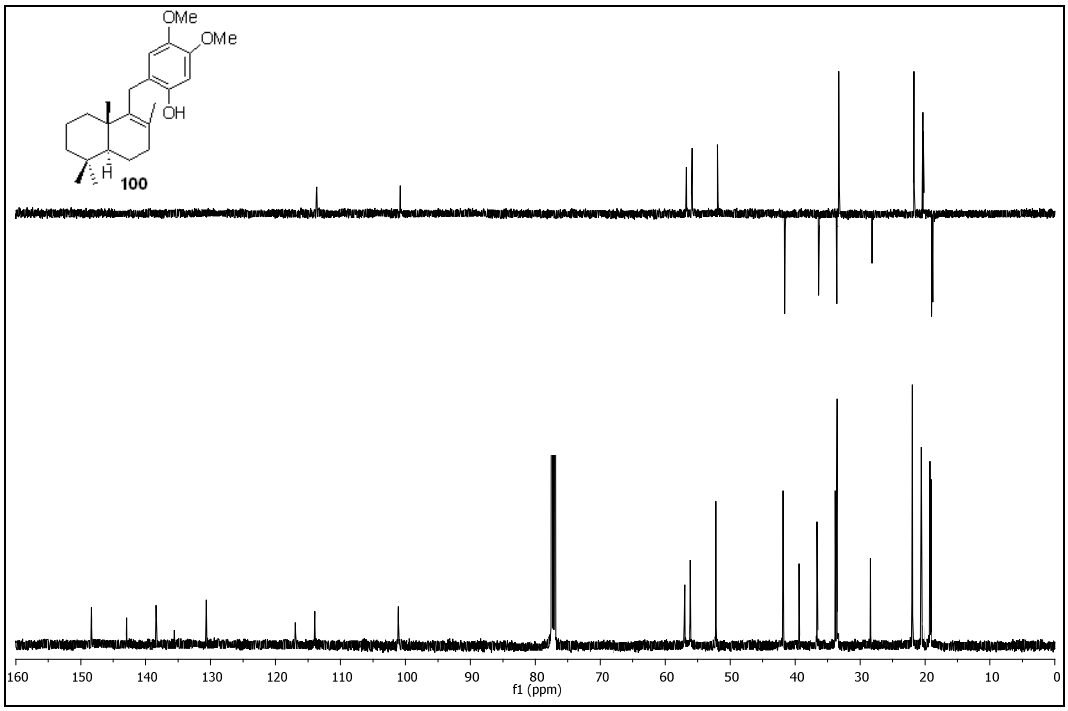

95
2.26
0.99
0.84
0.76
0.74
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


95
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


6.30
1.17
0.94
0.67
96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


96
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


6.39
3.82
3.79
1.62
1.00
0.90
0.84
OMe
OMe
OH
H
100
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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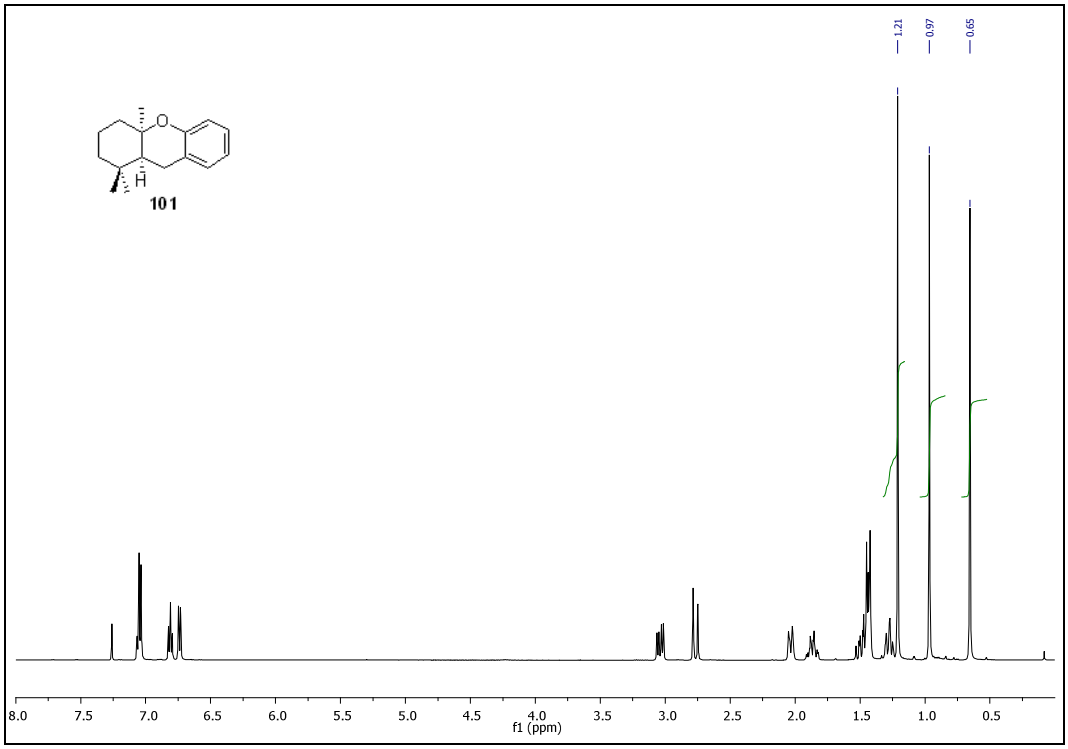
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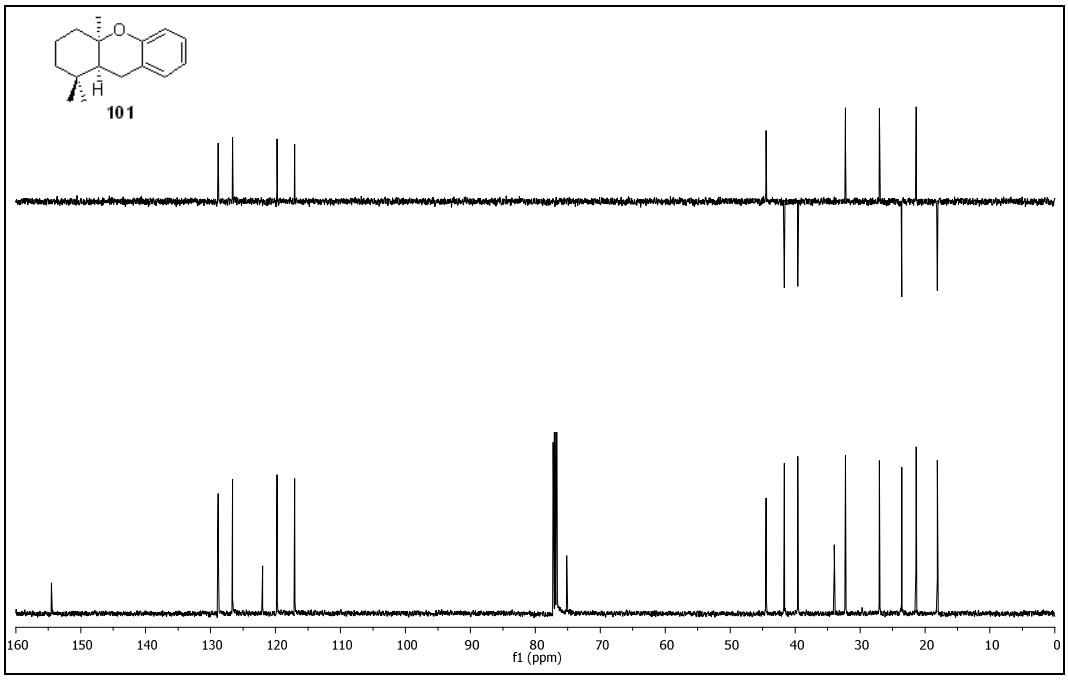
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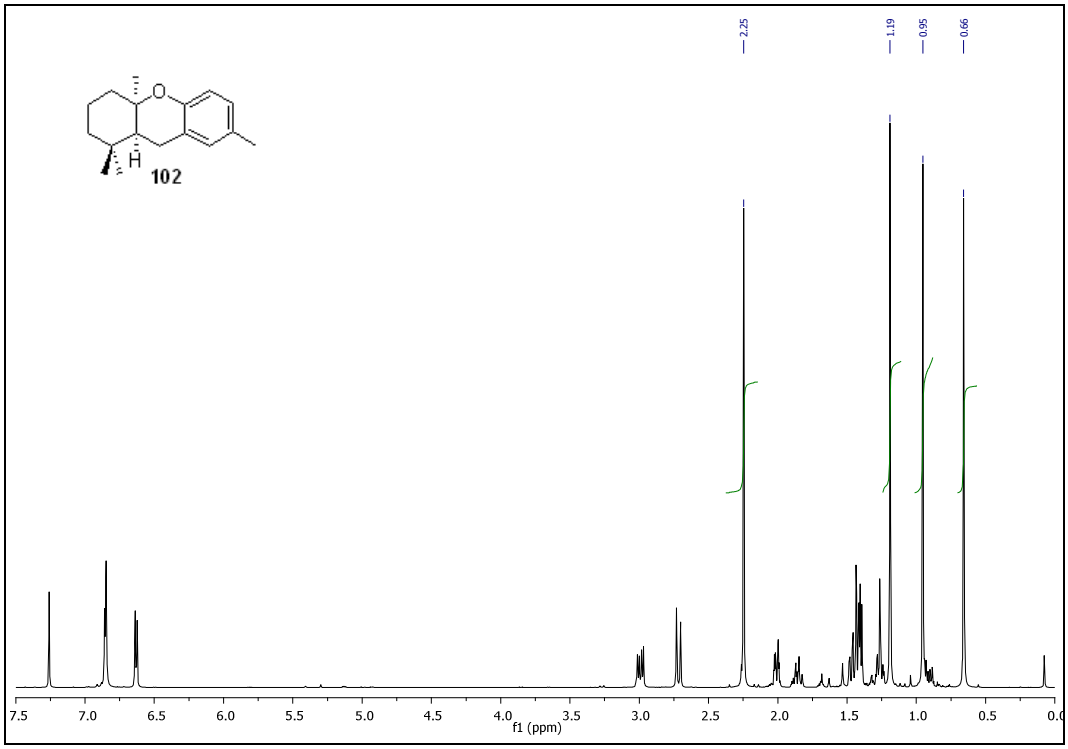
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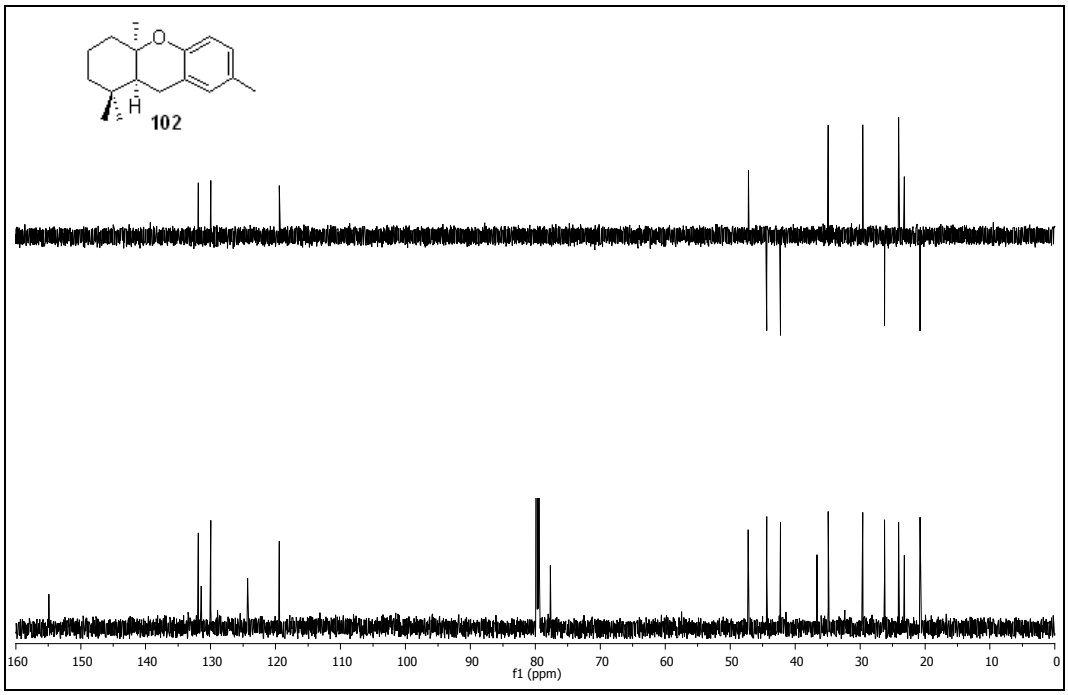
f1 (ppm)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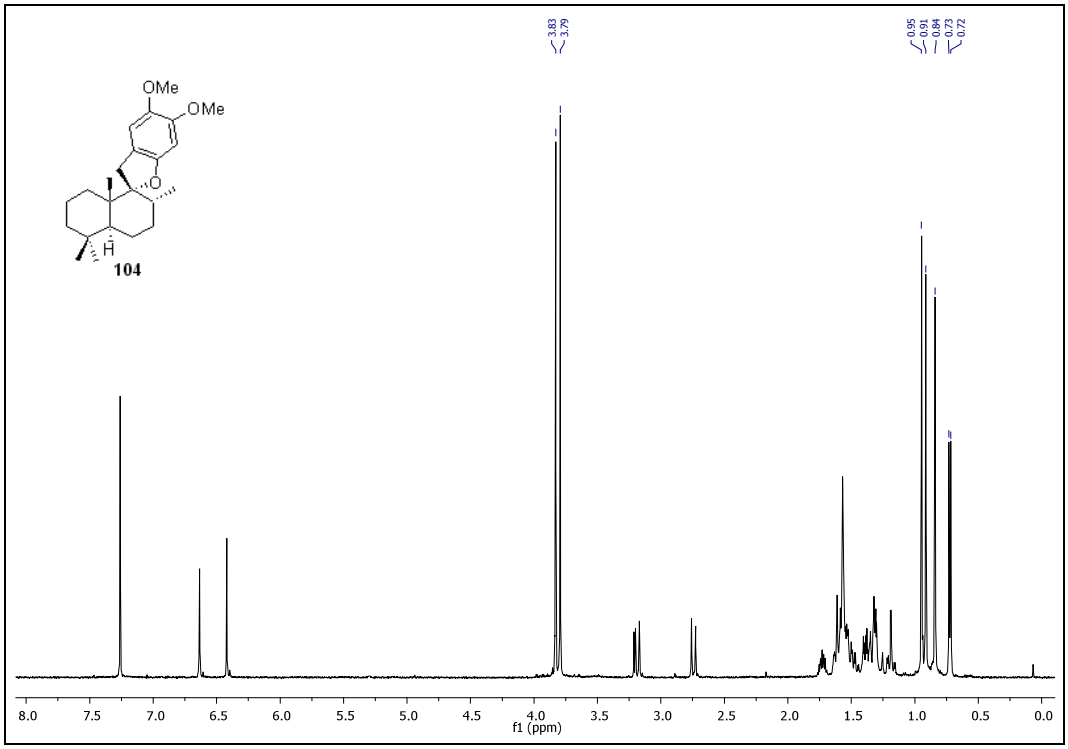
f1 (ppm)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0.72
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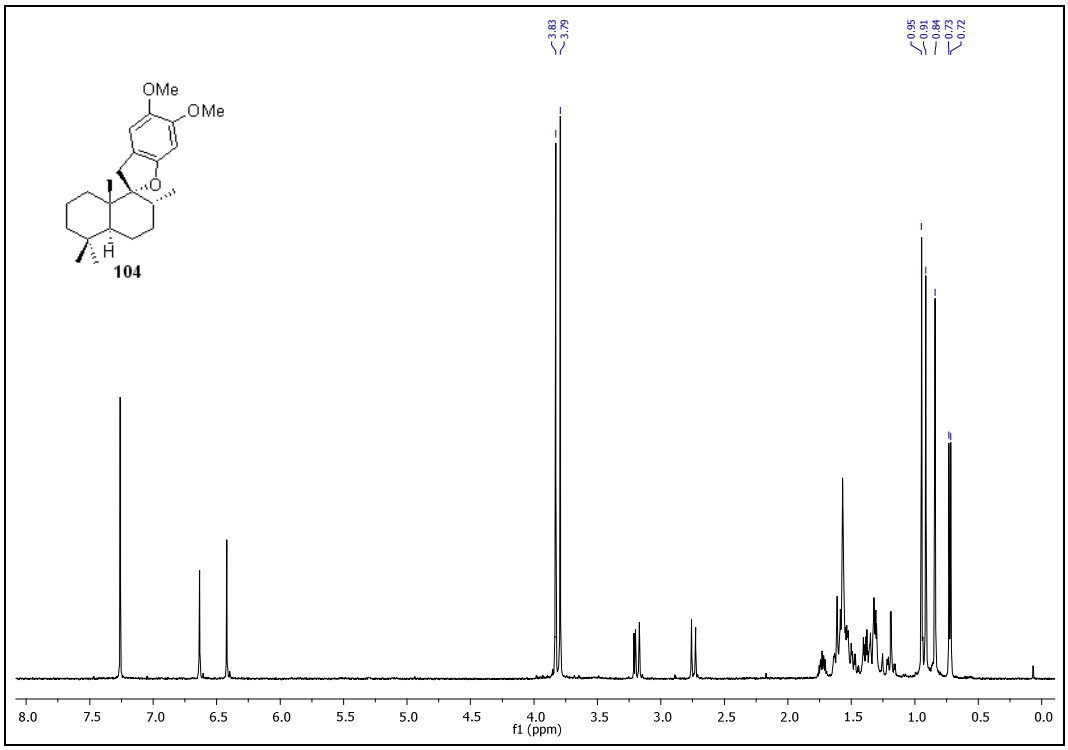
f1 (ppm)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H
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0.72
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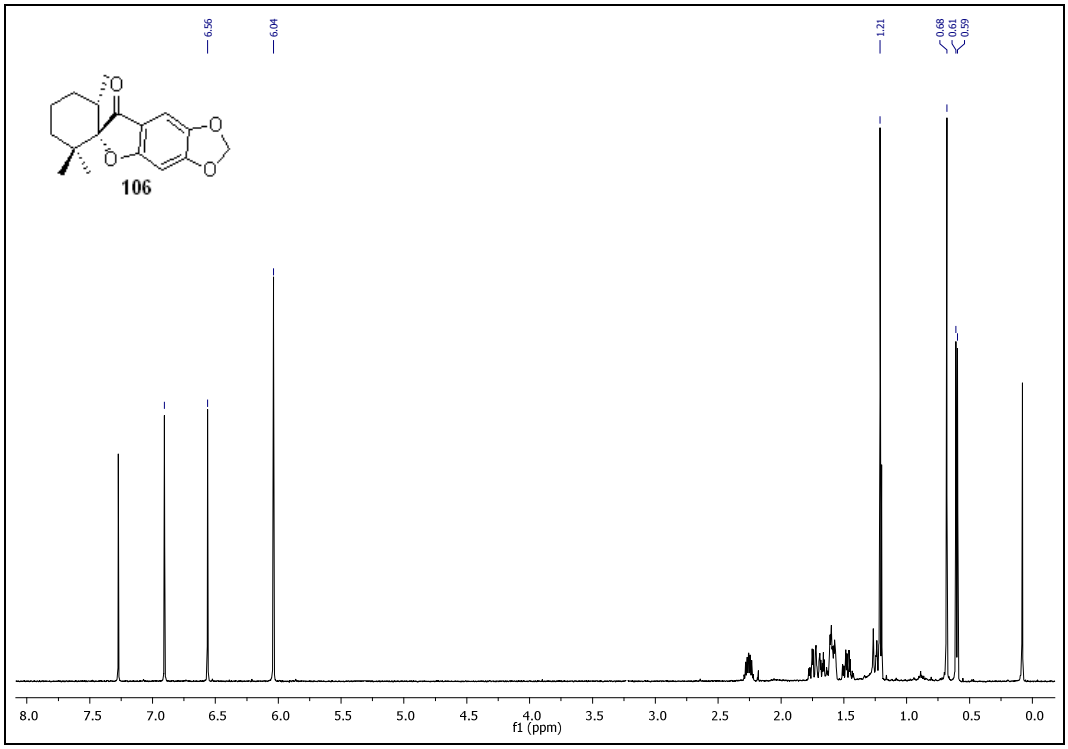
f1 (ppm)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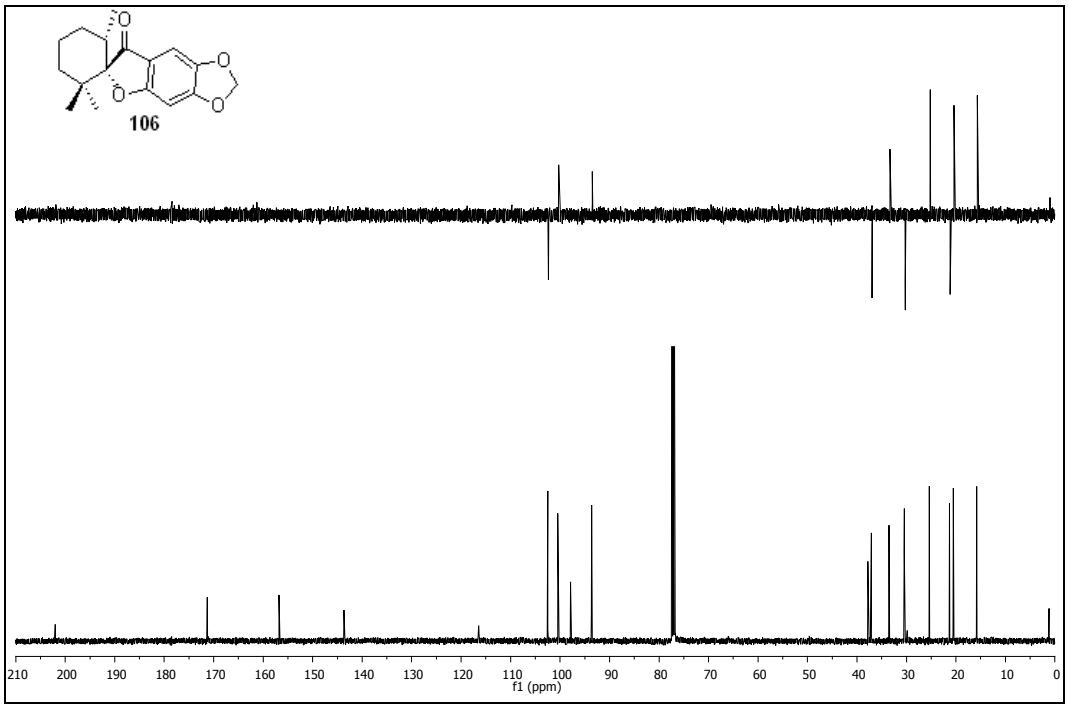
f1 (ppm)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f1 (ppm)

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Tetrahedron Letters 47 (2006) 6619–6622

$O_3/Pb(OAc)_4$: a new and efficient system for the oxidative cleavage of allyl alcohols

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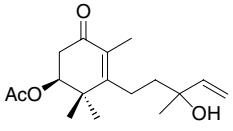
Abstract—Allyl alcohols undergo oxidative cleavage, affording the corresponding carbonyl compounds in good yields, when treated with ozone–lead(IV) acetate under mild conditions.

1. Introduction

The oxidation of tertiary alcohols is a reaction seldom utilized for synthetic purposes because of the structural requirements of the substrate for achieving good selectivities and yields. These reactions consist of one or two-electron oxidation processes leading to rearrangement, cyclization or fragmentation products.[1]

Among this type of alcohols, vinyl derivatives are of particular interest because they form part of the structure of natural compounds, such as sesquiterpenes **1** or **2**, or diterpenes manool (**3**), larixol (**4**) or cupressic acid (**5**).



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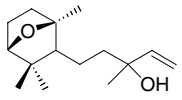

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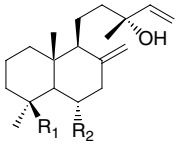
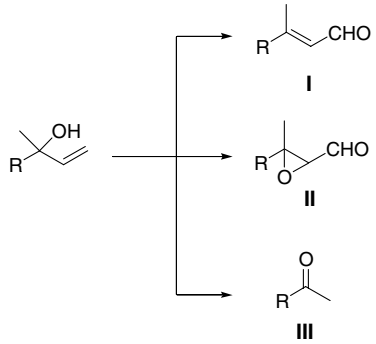


3 R_1: Me; R_2: H
4 R_1: Me; R_2: OH
5 R_1: COOH; R_2: H

Three reaction modes have been reported for this methyl vinyl carbinol moiety under oxidative conditions (Scheme 1). PCC oxidation affords transposed 3-methyl α,β-unsaturated aldehydes **I**.[2] The use of Collins reagent results in oxidative rearrangement to α-epoxyaldehydes **II**.[3] The third reaction mode, which involves C2–C3 fragmentation leading to methylketones **III**, takes place by utilizing potassium permanganate or chromium trioxide–acetic acid; however, in all cases the resulting ketone **III** is obtained in low to moderate yields, mainly due to work-up difficulties.[4,5] The obtention of small amounts of the oxidative cleavage type-**III** methylketones has been described when some manool (**3**) or



Scheme 1.

Keywords: Allyl alcohols; Oxidative cleavage; Ozonolysis; Lead(IV) acetate.
* Corresponding author. Tel./fax: +34 958 24 80 89; e-mail: eamr@ugr.es

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Table 1. Oxidative cleavage of some allyl alcohols with the $O_3/Pb(OAc)_4$ system

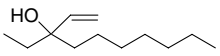
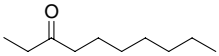
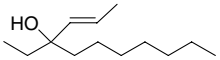
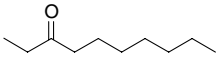
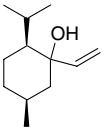
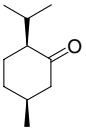
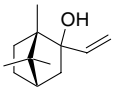
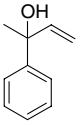
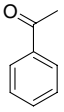
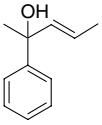
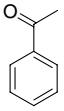
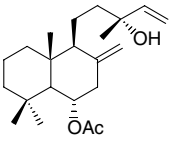
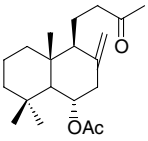
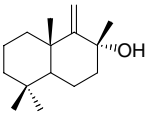
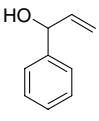
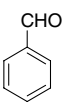
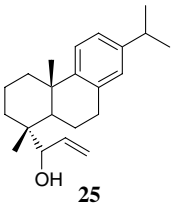
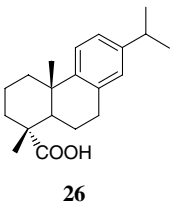
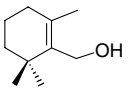
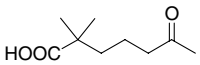
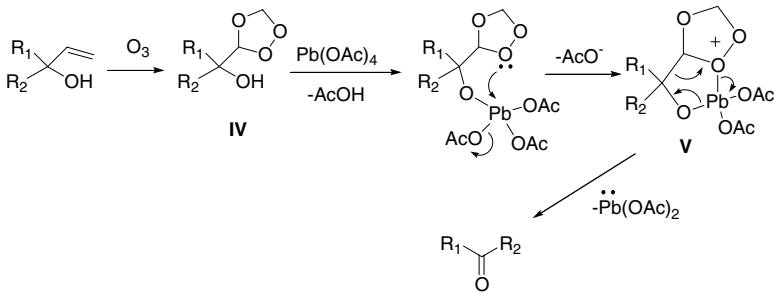
Entry	Substrate	Time (min)	Product	Procedure (%)
1	 **6**	60	 **7**	A (86)
2	 **8**	60	 **7**	A (90)
3	 **9**	90	 **10**	A (82)
4	 **11**	60	 **12**	A (89)
5	 **13**	90	 **14**	A (91) B (85)
6	 **15**	90	 **16**	A (94)
7	 **17**	60	 **18**	A (91) B (87)
8	 **19**	60	 **18**	A (87)
9	 **20**	75	 **21**	A (81)
10	 **22**	75	—[a]	
11	 **23**	60	 **24**	A (92) B (87)

Table 1 (*continued*)

Entry	Substrate	Time (min)	Product	Procedure (%)
12	 **25**	75	 **26**	A (78)
13	 **27**	75	 **28**	A (75)

[a] A complex mixture of compounds was obtained.



Scheme 2.

larixol (**4**) derivatives were ozonyzed in MeOH;[6] however, the procedure is not useful for synthetic purposes, because a mixture of compounds in low yield is usually obtained. The protic solvent seems to play an important role in this 'anomalous' ozonyzation, because it is known that ozonolysis of allyl alcohols, utilizing CH_2Cl_2 as solvent, affords the corresponding α-hydroxycarbonyl compounds in good yields.[7] Our studies on some of compounds cited here are in agreement with the literature data.

We have centred our attention on the latter oxidative cleavage, which can be utilized to prepare a variety of synthons starting from natural terpenoids.[8–10] In order to avoid the drawbacks involved in the use of potassium permanganate or chromium trioxide, we investigated alternative reagents. The ozone–lead(IV) acetate system was found to be a suitable oxidant to achieve this purpose. When an ozone–oxygen stream is bubbled through a solution of allyl alcohol in dichloromethane containing lead(IV) acetate (1.5 equiv), the carbonyl derivative resulting from the oxidative cleavage is obtained in good yields (Table 1).

Secondary and primary allyl alcohols (entries 11–13) also undergo oxidative cleavage. The benzylic alcohol **23** was transformed into benzaldehyde (**24**), whereas compound **25** afforded the carboxylic acid **26**, probably resulting from the overoxidation of the corresponding aldehyde. On the other hand, the primary cyclic alcohol **27** gave the ketoacid **28**.

A tentative mechanism is depicted in Scheme 2. The carbon–carbon bond cleavage takes place via the cyclic intermediate **V** derived from the hydroxyozonide **IV**. This supposition is supported by the fact that the same results were observed when lead(IV) acetate was added after completion of ozonolysis of allylic alcohol (experimental procedure B) and by the failure observed for compound **22**, which does not possess a suitable geometry to form the intermediate **V**.

2. Experimental procedure

Procedure A[†]: A stirred mixture of alcohol (1 mmol) and $Pb(OAc)_4$ (1.5 equiv) in CH_2Cl_2 (15 mL) was

[†] The utilization of both procedures gave similar results (entries 5, 7 and 11 in Table 1). Oxidation of compound **20** was carried out at −78 °C, utilizing the procedure A, and monitorizing the reaction by TLC; when the ozonyzation was carried out at 0 °C, partial oxidation of exocyclic carbon–carbon double bond was observed. In the work-up for entries 12 and 13, washing with satd $NaHCO_3$ solution was eluded. $NaHSO_3$ was not added after oxidation of alcohol **23**.

slowly bubbled with an O_3/O_2 mixture at 0 °C for the specified time. The solution was flushed with argon, and $NaHSO_3$ (2 equiv) was added. The mixture was filtered and the filtrate diluted with ether (25 mL), and washed successively with sat. $NaHCO_3$ solution (2×10 mL) and brine (2×10 mL). The organic phase was dried over anhyd Na_2SO_4 and evaporated to yield the product.

Procedure B[†]: A stirred solution of alcohol (1 mmol) in CH_2Cl_2 (15 mL) was slowly bubbled with an O_3/O_2 mixture at −78 °C, and the course of the reaction was monitored by TLC. When the starting material was consumed, the solution was flushed with argon, and $Pb(OAc)_4$ (1.5 equiv) was added. The mixture was further stirred for 45 min at room temperature and $NaHSO_3$ (2 equiv) was added. After working-up, as described above, the product was obtained.

Acknowledgements

The authors thank Junta de Andalucia for financial support.

References and notes

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Regioselective routes towards 14-hydroxyabietane diterpenes. A formal synthesis of immunosuppressant (−)-triptolide from (+)-abietic acid

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Abstract—Two procedures to introduce an oxygenated function into the C-14 of abietane diterpenes with complete regioselectivity have been developed. Utilizing these, the synthesis of the antileishmanial quinone (−)-12-deoxyroyleanone (**1**) and a formal synthesis of antitumour and immunosuppressant (−)-triptonide (**7**) and (−)-triptolide (**8**) from (+)-abietic acid (**13**) have been carried out.

1. Introduction

Natural abietane phenols and quinones, as well as other variously oxidized related compounds, constitute an interesting group of diterpene metabolites, due to the significant biological activities exhibited by some of them such as (−)-12-deoxyroyleanone (**1**), an antileishmanial agent,[1] and cryptoquinone (**2**) with antifungal and cytotoxic activities against mouse lymphoid neoplasm (P388) cells.[2] Other significant compounds are the antifungal (−)-deoxybuddlejone (**3**),[3] and a group of A ring modified terpenoids such as (+)-triptoquinone A (**4**), which is under study with respect to the treatment of rheumatoid arthritis,[4] the leukotriene D_4 antagonists (+)-triptinine A (**5**) and B (**6**),[5] and the lactones (−)-triptonide (**7**) and (−)-triptolide (**8**), which exhibit a variety of features, including antitumour,[6] anti-inflammatory,[7] immunosuppressive[7b,8] and antifertile activities (Fig. 1).[7b,9]

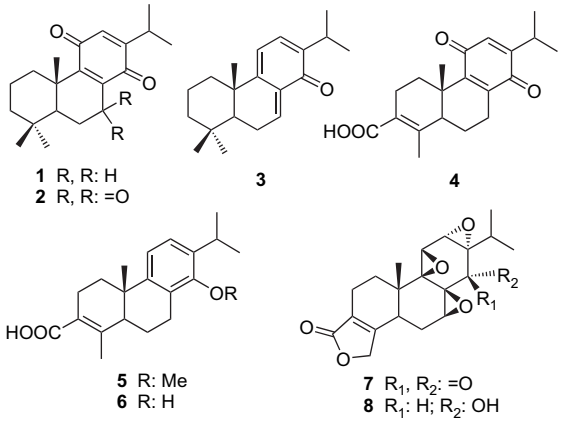

Figure 1. 12-Deoxyroyleanone (**1**) and other bioactive oxidized abietane terpenoids.

Despite the interest in these metabolites, few syntheses have been reported, and most of these have been total syntheses involving Diels–Alder cycloaddition,[10] Robinson annulation,[4] radical cyclizations[11] and electrophilic cyclizations.[12] A synthesis of lactones **7** and **8** from dehydroabietic acid has been reported by van Tamelen,[13] utilizing 14-hydroxydehydroabietic acid, prepared by electrophilic substitution,[14] as a key intermediate.

Our group recently communicated the first synthesis of quinone **1** from abietic acid, utilizing a novel methodology for introducing an oxygenated function into C-14.[15,16] Subsequently, Matsushita et al. described the synthesis of quinones **1** and **2** from dehydroabietic acid, utilizing an electrophilic substitution strategy.[17] Very recently, Yajima et al. reported an asymmetric synthesis of quinones **1** and **2**, utilizing a *B*-alkyl Suzuki–Miyaura coupling and subsequent electrophilic cyclization.[18] These authors pay special attention to the ^{13}C NMR chemical shift of aromatic carbons, which they assign incorrectly, of the phenol precursor of quinone **1**. Yajima et al. criticize our previous results on the basis of a small discrepancy with our spectroscopic data for this intermediate and their inability to reproduce our described oxidation of this phenol to quinone **1**, utilizing Fremy's salt.

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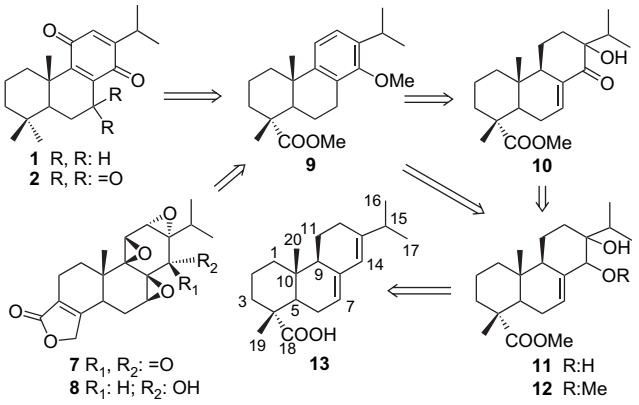
In this paper we report our studies on the synthesis towards 14-hydroxyabietic acid derivatives, including a very efficient alternative route to that we had previously communicated, which reaffirms our first synthesis of (−)-12-deoxyroyleanone (**1**), and a formal synthesis of (−)-triptonide (**7**) and (−)-triptolide (**8**). Moreover, we aim to end the controversy provoked by Yajima's article and correct the erroneous ^{13}C NMR assignments made in the latter.

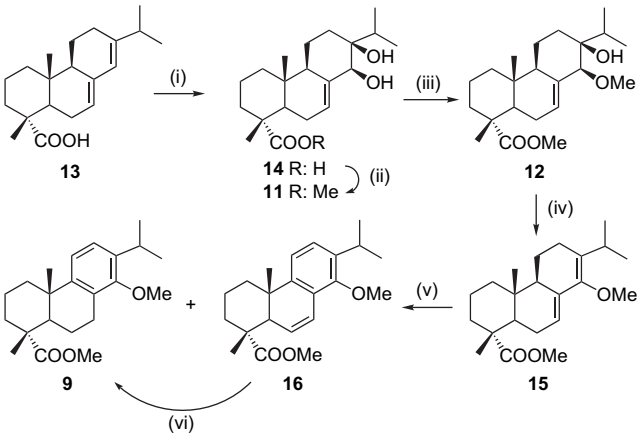
2. Results and discussion

During our research in the synthesis of bioactive compounds starting from natural diterpenes, we focused on the synthesis of this type of oxygenated terpenoids from the very accessible abietic acid (**13**). The key intermediate should be 14-hydroxydehydroabietic acid or related compounds such as **9**. The procedure based on the electrophilic substitution in dehydroabietic acid derivatives, involving nitration of the aromatic ring and the further transformation of the nitro into the hydroxyl group, could raise some problems of regio- and/or chemoselectivity. Thus, we planned an alternative method to prepare methoxy ester **9** directly from acid **13**, as depicted in the retrosynthetic Scheme 1. Compound **9** is obtained after aromatization of dienol ether resulting from the dehydration of β-methoxy alcohol **12**. Alternatively, ester **9** could be prepared from the phenol synthesized by dehydration and subsequent aromatization of hydroxy ketone **10**, resulting from the oxidation of 13,14-diol **11**, which can be synthesized by regioselective dihydroxylation of abietic acid (**13**).[19]



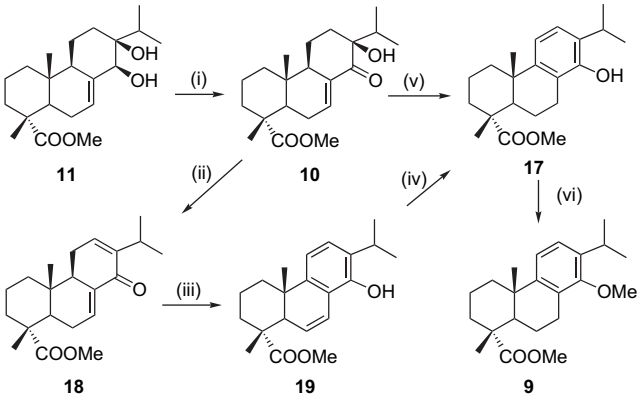
Scheme 1. Retrosynthetic analysis of 12-deoxyroyleanone (**1**) and other related terpenoids from abietic acid (**13**).

Scheme 2 shows the synthesis of ester **9** from acid **13** via the β-methoxy alcohol **12**. Abietic acid (**13**) was efficiently converted into diol **14**, utilizing a modification of the method reported in the literature.[19] Compound **12**, which is obtained after methylation of dihydroxy ester **11**, underwent regioselective dehydration by treating with $SOCl_2$ and Et_3N to give the dienol ether **15**. This compound was then transformed into the corresponding dehydroabietic acid derivative by treating with Br_2 in CCl_4 under reflux. It should be noted that the desired compound **9** resulted when 1 equiv of Br_2 was utilized; however, the use of Br_2 in excess afforded a mixture of ester **9** and the Δ^6 derivative **16**, which can easily be converted into **9** after hydrogenation or by treating with Et_3SiH and CF_3COOH.



Scheme 2. Synthesis of ester **9** from acid **13** via methoxyalcohol **12**. Reagents, conditions and yields: (i) OsO_4, Me_3NO, pyridine, *t*-BuOH, reflux, seven days; (ii) MeI, K_2CO_3, acetone, reflux, 24 h; (iii) NaH, THF, MeI, rt, 2 h (96%); (iv) $SOCl_2$, Et_3N, CH_2Cl_2, −78 °C, 20 min (74%); (v) Br_2, CCl_4, $CaCO_3$, reflux, 12 h (70%); (vi) H_2, Pd–C, MeOH, 24 h (94%) or Et_3SiH, CF_3COOH, CH_2Cl_2, −40 °C, 16 h (93%).

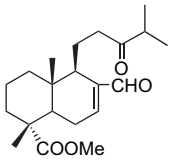
The alternative sequence from acid **13** to key intermediate **9**, via hydroxy ketone **10**, is depicted in Scheme 3. After esterification of carboxylic acid **14**, oxidation of the secondary hydroxyl group was undertaken. The transformation of diol **11** into ketone **10** was assayed under different oxidizing conditions, as shown in Table 1.



Scheme 3. Synthesis of ester **9** via hydroxy ketone **10**. Reagents, conditions and yields: (i) PhSeSePh, *t*-BuOOH, CCl_4, reflux, 2 h (92%); (ii) TsOH, benzene, reflux, 36 h (78%); (iii) K_2CO_3, MeOH, reflux, three days (70%); (iv) H_2, Pd–C; MeOH, 24 h (96%); (v) TsOH, toluene, reflux, 10 h (91%); (vi) MeI, K_2CO_3, acetone, reflux, 15 h (91%).

Diol **11** remained unaltered after treatment with MnO_2 at room temperature; however, keto aldehyde **20** was obtained in good yield when the mixture was refluxed for 16 h. Small quantities of this compound, together with aromatic esters **21** and **22** resulted when Jones reagent was utilized. Diol **11** was recovered unaltered after treatment with IBX in DMSO at room temperature; nevertheless, keto aldehyde **20**[20] resulted when the reaction was carried out in THF under reflux.[21] Treatment with PCC in CH_2Cl_2 gave the desired hydroxy ketone **10**, together with the keto aldehyde **20**. Utilization of Swern reagent gave compounds **10** and **18** in low yields. Oxidation with DDQ and TsOH in benzene gave similar results. Treatment with PDC and *t*-BuOOH in benzene gave only hydroxy ketone **10**, but in low yield. A successful

Table 1. Reaction of diol **11** under different oxidizing conditions



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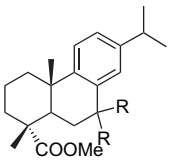


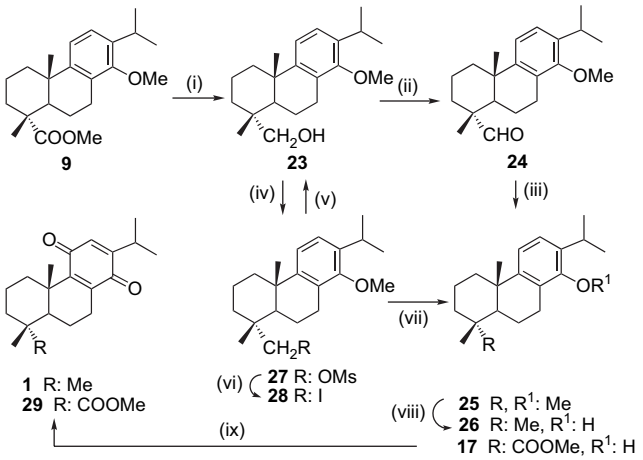
21 R, R: H
22 R, R: =O

Entry	Conditions	Product(s) (%)
1	MnO_2, benzene, rt, 24 h	No reaction
	MnO_2, benzene, reflux, 16 h	**20** (75)
2	Jones reagent, acetone, rt, 20 h	**20** (5), **21** (20), **22** (11)
3	IBX, DMSO, rt, 16 h	No reaction
4	IBX, THF, reflux, 48 h	**20** (72)
5	PCC, CH_2Cl_2, 4 Å molecular sieves, 0 °C, 30 min	**20** (37), **10** (30)
6	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, rt, 24 h	**10** (15), **18** (5)
7	DDQ, TsOH, benzene, rt, 48 h	**10** (18), **18** (12)
8	PDC, *t*-BuOOH, benzene, rt, 3 h	**10** (36)
9	PhSeSePh, *t*-BuOOH, CCl_4, reflux, 2 h	**10** (92)

oxidation of diol **11** was attained after reaction with PhSeSePh and *t*-BuOOH in CCl_4 under reflux:[22] the desired compound **10** was obtained in 92% yield (entry 9). This ketone was converted into enone **18** by refluxing with TsOH in benzene; this compound could be a suitable intermediate for synthesizing compounds such as deoxybuddlejone (**3**). Treatment of enone **18** with K_2CO_3 in MeOH under reflux led to phenol **19**,[23] which was then hydrogenated to give phenol **17**. This compound was directly obtained in high yield when the enone **10** was refluxed with TsOH in toluene. Finally, this phenol was transformed into the desired methoxy ester **9**. Compound **17**, which has also been synthesized by Matsushita et al.,[17] had the same spectroscopic properties as those reported by these authors.

Ester **9**, which as indicated is a suitable precursor of bioactive metabolites such as **1**,**2** and **4**–**8**, was then transformed into 12-deoxyroyleanone (**1**) (Scheme 4). First, the methyl ester was converted into methyl group. Treatment of **9** with $LiAlH_4$ gave alcohol **23**, which was oxidized to aldehyde **24** and this transformed into compound **25** under the Wolff–Kishner conditions. Alternative transformations of **23** into **25**, via mesyl derivative **27**, were investigated. The treatment of **27** with $LiAlH_4$ regenerated alcohol **23**; nevertheless, compound **25** was obtained after treating mesylate **27** with Zn and NaI.[24] It should be noted that the yield of this reaction depends upon the quantity of mesylate; a more suitable procedure applicable to large amounts of compound **27** involves its conversion into iodide **28**, by treating with NaI in HMPA under reflux, and further reduction with $LiAlH_4$. Deprotection of methyl ether with BBr_3 led to phenol **26**.

Even though the structure of this phenol is quite evident, given that a simple inspection of the ^1H NMR spectrum reveals two doublets (J=8.2 Hz) at 6.85 and 7.01 ppm, characteristic of the H-11 and H-12 *ortho* protons, Yajima et al.[18] pay special attention to the ^{13}C NMR signals for the aromatic carbons of this compound. In their article, these authors announce a good agreement between the aromatic ^{13}C NMR chemical shifts for the phenol they synthesized and those

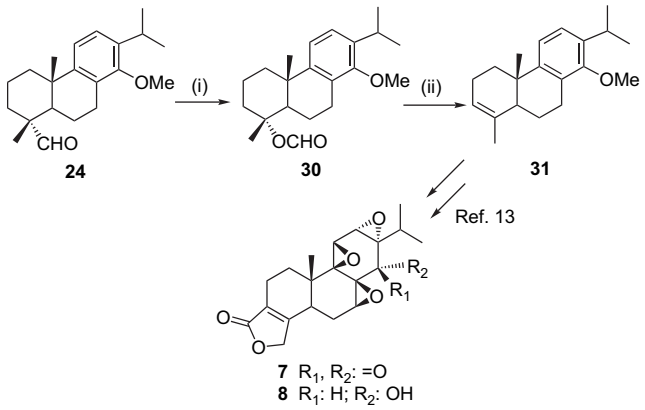


Scheme 4. Synthesis of 12-deoxyroyleanone (**1**) from ester **9**. Reagents, conditions and yields: (i) $LiAlH_4$, THF, rt, 3 h (95%); (ii) PCC, CH_2Cl_2, rt, 1 h (70%); (iii) N_2H_4, KOH, ethyleneglycol–ethyleneglycol dimethylether (3:2), 180 °C, three days (70%); (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C–rt, 4 h (93%); (v) $LiAlH_4$, THF, reflux, 24 h (95%); (vi) NaI, HMPA, reflux, three days (90%); (vii) Zn, NaI, HMPA, 110 °C, three days (75%) for **27**, or $LiAlH_4$, THF, reflux, 24 h (96%) for **28**; (viii) BBr_3, CH_2Cl_2, −10 °C, 30 min (95%); (ix) Fremy's salt, MeOH–H_2O, rt (91% for **26** and 83% for **17**).

reported by Matsushita et al.,[17] and emphasize a small discrepancy with our previously reported data.[15] However, Yajima et al. make a wrong assignment, which they also attribute unfoundedly to Matsushita et al. The signal at 123.24 ppm, assigned to C-8 by Yajima et al. is due to a methine carbon, as the DEPT experiment revealed, and therefore it would be attributed to C-12. On the other hand, the signal at 120.62 ppm, which they assigned to C-12, and which as the DEPT indicated is a quaternary carbon, would be attributed to C-8. Then, a tentative assignation for the aromatic ring carbons, in accordance with the chemical shift pattern observed in similar structures, is δ 116.5 (C-11), 120.7 (C-8), 123.3 (C-12), 130.1 (C-13), 149.1 (C-9), 150.3 (C-14). This assignation agrees with that of Yajima et al., but interchanging the assignations for C-8 and C-12.

Finally, phenol **26** was transformed into 12-deoxyroyleanone (**1**) by treating with potassium nitrosodisulfonate. It should be noted that Yajima et al. indicate that they also assayed this oxidation unsuccessfully. However, we insist on the total reproducibility of this reaction. In fact, before synthesizing compound **1**, we assayed this oxidation over the less elaborated phenol **17**, which under the same reaction conditions afforded quinone **29**, which had also been prepared by Matsushita et al.;[17] our spectroscopic data and those reported by these authors were identical.

As we initially postulated, ester **9** is a suitable precursor of the A ring functionalized bioactive compounds **4**–**8**. Thus, aldehyde **24** was efficiently transformed into alkene **31**, utilizing novel procedures developed by our group (Scheme 5). The treatment of compound **24** with MCPBA gave in good yield formate **30**,[25] which was converted with complete regioselectivity into the trisubstituted alkene **31** by treating with I_2 and PPh_3.[26] Compound **31** has previously been transformed into (−)-triptonide (**7**) and (−)-triptolide (**8**),[13] and therefore the sequence reported herein involves a formal synthesis of these bioactive compounds from (+)-abietic acid (**13**).



Scheme 5. Synthesis of alkene **31**, precursor of bioactive compounds **7** and **8**, from aldehyde **24**. Reagents, conditions and yields: (i) MCPBA, $NaHCO_3$, CH_2Cl_2, reflux, 3 h (93%); (ii) I_2, PPh_3, CH_2Cl_2, rt, 12 h (91%).

3. Conclusion

In summary, two efficient procedures to prepare 14-hydroxyabietic acid and related compounds, from abietic acid (**13**) are reported. Utilizing these, the synthesis of the antileishmanial 12-deoxyroyleanone (**1**) and a formal synthesis of antitumour and immunosuppressant (−)-triptonide (**7**) and (−)-triptolide (**8**) from this diterpenic acid are described.

4. Experimental

4.1. General

Dichloromethane (DCM) was dried over calcium hydride, while toluene, tetrahydrofuran (THF) and benzene were dried over sodium-benzophenone. Methanol was distilled from magnesium at 760 Torr. Dimethylformamide (DMF) and ethanol were dried over 4 Å molecular sieves. Chromatography separations were carried out by conventional column on silica gel 60 (230–400 mesh) using hexane–MeO*t*-Bu (H–E) mixtures of increasing polarity. Infrared (IR) spectra were obtained using Perkin Elmer Spectrum Models 782 and 983G spectrophotometers with samples between sodium chloride plates or as potassium bromide pellets. Data are presented as the frequency of absorption (cm^{-1}). Proton and carbon-13 nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded on Varian 300 and 400 spectrometers, chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane. Data are presented as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, br d=broad doublet, t=triplet, m=multiplet), *J*=coupling constant in hertz (Hz). The signals of the ^{13}C NMR were assigned utilizing DEPT experiments and on the basis of literature data. HRMS were obtained on a trisector WG AutoSpecQ spectrometer. FAB spectra acquisition was performed with a 10,000 resolution and a relative error of 5 ppm.

4.1.1. 13β,14β-Dihydroxyabieta-7-en-18-oic acid (14). To a solution of abietic acid (**13**) (10.01 g, 33.11 mmol) in *t*-BuOH (50 mL) were added trimethylamine-*N*-oxide dihydrate (4.42 g, 39.8 mmol) and pyridine (0.3 mL) under argon atmosphere. After stirring for 5 min at room temperature, a 2% aqueous solution of OsO_4 (14 mL) was added and the reaction mixture was further stirred under an atmosphere of argon at reflux for seven days. $NaHSO_3$ (10 mL) was added and the solvent was evaporated, then AcOEt (100 mL) was added and the mixture was washed with 5% HCl (2×20 mL), water (3×20 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 3:7) to give pure **14** (6.5 g, 58%) as a colourless solid. Mp 156–157 °C [lit.:[19a] 154–155 °C]; $[\alpha]_D^{25}$ −3.75 (*c* 0.8, $CHCl_3$); IR (KBr) ν 3441, 2924, 1693, 1462, 1262, 1023, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.83 (3H, s), 0.87 (3H, d, *J*=6.9 Hz), 0.93 (3H, d, *J*=6.9 Hz), 1.32 (3H, s), 1.43 (1H, dd, *J*=11.6, 2.9 Hz), 1.91 (1H, m), 2.17 (1H, h, *J*=6.9 Hz), 3.68 (3H, s, COOMe), 4.02 (1H, br s), 5.88 (1H, d, *J*=4.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.8 (C-1), 19.2 (C-2), 39.1 (C-3), 46.2 (C-4), 51.2 (C-5), 26.5 (C-6), 119.9 (C-7), 137.8 (C-8), 44.5 (C-9), 35.2 (C-10), 19.2 (C-11), 24.9 (C-12), 76.4 (C-13), 73.1 (C-14), 33.12 (C-15), 17.8 (C-16), 18.0 (C-17), 183.9 (C-18), 15.1 (C-19), 19.2 (C-20); HRMS (FAB) *m/z* calcd for $C_{20}H_{32}O_4Na$, 359.2198; found, 359.2202.

4.1.2. Methyl 13β,14β-dihydroxyabieta-7-en-18-oate (11).

4.1.2.1. Synthesis of diol 11 from 14. K_2CO_3 (5.7 g, 41.97 mmol) was added to a solution of **14** (5.59 g, 16.79 mmol) in acetone (75 mL) and the reaction mixture was kept stirring at room temperature for 15 min. Then, iodomethane (3.1 mL, 51 mmol) was added and the reaction mixture was stirred at reflux for 24 h. The solvent was evaporated and the crude reaction mixture was poured into ether–water (60:10 mL) and it was extracted with ether (2× 30 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **11** (5 g, 94%) as a colourless solid. Mp 107–107.1 °C; $[\alpha]_D^{25}$ −0.57 (*c* 0.7, $CHCl_3$). The MS, IR, ^1H and ^{13}C NMR data agreed with the literature data.[27]

4.1.2.2. Synthesis of diol 11 from 13. To a solution of abietic acid (**13**) (5.00 g, 16.55 mmol) in *t*-BuOH (25 mL) were added trimethylamine-*N*-oxide dihydrate (2.21 g, 19.9 mmol) and pyridine (0.1 mL) under argon atmosphere. After stirring for 5 min at room temperature, a 2% aqueous solution of OsO_4 (7 mL) was added and the reaction mixture was further stirred under an atmosphere of argon at reflux for seven days. Following the same workup described for **14**, 5.54 g of the crude product was obtained. This was dissolved in acetone (75 mL) and K_2CO_3 (5.4 g, 39.76 mmol) was added; after stirring for 10 min at room temperature, iodomethane was added (3.5 mL, 57.59 mmol) and the reaction mixture was stirred at reflux for 24 h. Following the same workup described above, a crude product (5.3 g) was obtained. The chromatography of this crude on silica gel (H–E, 7:3) gave pure **11** (5.2 g, 90%) as a colourless oil.

4.1.3. Methyl 13β-hydroxy-14β-methoxyabieta-7-en-18-oate (12). NaH (60% dispersion in mineral oil) (170 mg, 4.26 mmol) was carefully added to a cold (0 °C) solution of **11** (0.5 mg, 1.43 mmol) in dry THF (10 mL) under argon atmosphere and the mixture was stirred at this temperature for 5 min. MeI (0.6 mL) was added and the resulting reaction

mixture was stirred at room temperature for 2 h, at which time TLC showed the disappearance of starting material. The reaction mixture was poured into ice-water and it was extracted with ether (2×20 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give a crude product, which was purified by column chromatography on silica gel (H–E, 85:15) affording pure **12** (0.51 g, 96%) as a colourless oil. $[\alpha]_D^{25}$ +5.13 (*c* 0.91, $CHCl_3$); IR (film) *ν* 3519, 2944, 1726, 1460, 1371, 1242, 1146 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{22}H_{36}O_4Na$, 387.2511; found, 387.2507. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.4. Methyl 14-methoxyabieta-7,13-dien-18-oate (15). $SOCl_2$ (1 mL, 13.7 mmol) was added slowly to a solution of **12** (1.7 mg, 4.67 mmol) and triethylamine (5 mL) in dry CH_2Cl_2 (50 mL) at −78 °C. The reaction mixture was stirred at this temperature under argon atmosphere for 20 min, at which time TLC showed no starting material. The reaction mixture was quenched with satd aq $NaHCO_3$ (6 mL) and the cooling bath was removed. The mixture was poured into ether–water (60:20 mL) and it was extracted with ether (2×30 mL). The organic phase was washed with 2 N HCl (3×20 mL), brine (3×20 mL), dried over Na_2SO_4 and the solvent evaporated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 95:5) affording pure **15** (1.2 g, 74%) as a colourless oil. $[\alpha]_D^{25}$ −11.0 (*c* 0.85, $CHCl_3$); IR (film) *ν* 2836, 1726, 1624, 1385, 738 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{22}H_{34}O_3Na$, 369.2405; found, 369.2412. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.5. Methyl 14-methoxyabieta-6,8,11,13-tetraen-18-oate (16). A solution of bromine (0.18 mL, 3.51 mmol) in CCl_4 (15 mL) was added to a suspension of **15** (0.96 g, 2.90 mmol) and $CaCO_3$ (0.79 g, 7.89 mmol) in CCl_4 (20 mL), and the reaction mixture was stirred at reflux for 12 h, at which time TLC showed no **15**. Then the precipitated solid was filtered, the filtrate was washed with ether (10 mL) and the solvent was evaporated to give a crude product, which was purified by flash chromatography to give pure **16** (0.69 g, 70%) as a colourless oil. $[\alpha]_D^{25}$ +22.2 (*c* 1.0, $CHCl_3$); IR (film) *ν* 2947, 1726, 1447, 1245, 816 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{22}H_{30}O_3Na$, 395.2092; found, 365.2094. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.6. Methyl 14-methoxyabieta-8,11,13-trien-18-oate (9).

4.1.6.1. Treatment of 16 with H_2/Pd–C. To a solution of **16** (0.50 g, 1.46 mmol) in methanol (30 mL), 10% Pd–C (100 mg) was added and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 24 h. Filtration and concentration gave **9** (472 mg, 94%) as a colourless solid. Mp 97 °C; $[\alpha]_D^{25}$ +38.2 (*c* 0.71, $CHCl_3$); IR (KBr) *ν* 2956, 1726, 1620, 1448, 1246, 817 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{22}H_{32}O_3Na$, 367.2249; found, 367.2254. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.6.2. Treatment of 16 with Et_3SiH/CF_3COOH. To a solution of **16** (0.87 g, 2.56 mmol) in dichloromethane (20 mL), triethylsilane (0.6 mL) and trifluoroacetic acid (0.4 mL) were successively added at −40 °C, and the resulting mixture was stirred for 16 h. Then, the mixture was diluted with ether (50 mL) and washed with satd aq $NaHCO_3$ (2×10 mL), water (2×10 mL) and brine (2×10 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated to give **9** (819 mg, 93%).

4.1.7. Oxidation of diol 11.

4.1.7.1. Treatment of 11 with MnO_2. To a stirred solution of **11** (100 mg, 0.285 mmol) in dry benzene (10 mL) was added MnO_2 (0.49 g, 5.71 mmol). After stirring at reflux for 48 h, TLC showed no **11**, then the reaction was worked up by the addition of ether (10 mL), and the resulting mixture was filtered through a silica gel pad and washed with ether (10 mL). The solvent was evaporated to yield **20** (74 mg, 75%) as a colourless oil.

*Methyl 13,14-dioxo-13-secoabieta-7,13-dien-18-oate (**20**).* IR (film) *ν* 3500, 2951, 1714, 1652, 1631, 1462, 1386, 1246, 1187 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 0.78 (3H, s), 1.03 (3H, d, *J*=6.9 Hz), 1.05 (3H, d, *J*=6.9 Hz), 1.21 (3H, s), 2.21 (1H, m), 2.40 (1H, m), 2.57 (1H, h, *J*=6.9 Hz), 3.05 (1H, m), 3.6 (3H, s, COOMe), 6.7 (1H, q, *J*=2.7 Hz, H-7), 9.3 (1H, s, H-CHO); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 42.4 (C-1), 20.7 (C-2), 37.7 (C-3), 46.9 (C-4), 49.9 (C-5), 26.7 (C-6), 152.2 (C-7), 144.2 (C-8), 44.1 (C-9), 36.3 (C-10), 18.3 (C-11), 37.0 (C-12), 215.2 (C-13), 194.7 (C-14), 40.6 (C-15), 17.4 (C-16), 17.6 (C-17), 178.4 (C-18), 14.1 (C-19), 18.2 (C-20), 52.0 (C-COOMe); HRMS (FAB) *m/z* calcd for $C_{21}H_{32}O_4Na$, 371.2198; found, 371.2191.

4.1.7.2. Treatment of 11 with *Jones reagent*. To a stirred solution of **11** (0.32 g, 0.91 mmol) in acetone (15 mL) was added at 0 °C *Jones reagent*[28] (0.5 mL) and the reaction mixture was stirred for 30 min, at which time TLC showed no **11**. Then the solvent was evaporated and the crude product was diluted with ether (30 mL), washed with water (6×10 mL), brine, dried over anhyd Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 9:1) to give **20** (15 mg, 5%), **21** (58 g, 20%) and **22** (32 mg, 11%).

*Methyl 7-oxoabieta-8,11,13-trien-18-oate (**22**).* IR (film) *ν* 2952, 1726, 1682, 1460, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 1.11 (3H, s), 1.16 (3H, d, *J*=6.9 Hz), 1.18 (3H, d, *J*=6.9 Hz), 1.27 (3H, s), 2.65 (1H, dd, *J*=6.9, 3.5 Hz), 2.85 (1H, h), 3.56 (3H, s, COOMe), 7.21 (1H, d, *J*= 8.2 Hz), 7.34 (1H, dd, *J*=8.2, 2.1 Hz), 7.79 (1H, d, *J*= 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 16.4 (CH_3), 18.2 (CH_2), 23.8 (CH_3), 23.9 (CH_3), 24.0 (CH), 33.5 (CH_3), 36.6 (CH_2), 37.2 (CH_2), 37.4 (C), 37.9 (CH_2), 43.8 (CH), 52.2 (CH_3), 123.5 (CH), 125.1 (CH), 132.6 (CH), 146.9 (C), 153.0 (C), 177.8 (C), 198.6 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{28}O_3Na$, 351.1936; found, 351.1928.

4.1.7.3. Treatment of 11 with IBX in DMSO. IBX (0.3 g, 1.07 mmol) was added to a solution of diol **11** (0.20 g, 0.57 mmol) in DMSO (6 mL) and the reaction mixture was stirred at room temperature for 16 h. Then the reaction mixture was diluted with ether (20 mL), washed with satd aq Na_2CO_3 (2×6 mL), dried over Na_2SO_4 and the solvent evaporated to give the unaltered **11** (194 mg).

4.1.7.4. Treatment of 11 with IBX in THF. IBX (0.3 g, 1.07 mmol) was added to a solution of diol **11** (0.20 g,

0.57 mmol) in dry THF (10 mL) and the reaction mixture was stirred at reflux for 48 h. Then the solvent was evaporated and the residue was extracted with ether (2×15 mL), the organic phase was washed with satd aq Na_2CO_3 (2×10 mL), dried over Na_2SO_4 and the solvent evaporated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 7:3), affording **20** (143 mg, 72%) as a colourless oil.

4.1.7.5. Treatment of 11 with PCC. Pyridinium chlorochromate (PCC) (1.28 g, 5.49 mmol) and molecular sieves 3 Å (3.75 g) were added to a stirred solution of **11** (0.50 g, 1.43 mmol) in dry CH_2Cl_2 (20 mL) and the mixture was kept stirring at room temperature under argon atmosphere for 30 min, at which time TLC showed no remaining starting material. Then, the reaction was worked up by the addition of CH_2Cl_2 (10 mL) and the resulting mixture was filtered through a silica gel pad and washed with a mixture of ether–CH_2Cl_2 (20:30 mL). The solvent was evaporated to yield a crude product, which was chromatographed on silica gel (H–E, 7:3) to yield **10** (150 mg, 30%) and **20** (184 mg, 37%).

4.1.7.6. Swern oxidation of 11. To a stirred solution of $(COCl)_2$ (1.79 mL, 20.57 mmol) in dry dichloromethane (17 mL) was added DMSO (2.5 mL) at −78 °C, the reaction mixture was stirred for 2 min and the cooling bath was removed for 5 min. Then a solution of **11** (3.0 g, 8.57 mmol) in dichloromethane (35 mL) was added at −78 °C and the reaction mixture was stirred at this temperature for an additional 15 min. Then, triethylamine (5 mL) was added and the cooling bath was removed. After stirring for 15 min, the reaction mixture was diluted with ether (80 mL) and washed with 2 N HCl (3×20 mL), water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product (2.9 g), which was purified by column chromatography on silica gel (H–E, 3:2), to give **10** (447 mg, 15%) and **18** (142 mg, 5%).

4.1.7.7. Treatment of 11 with DDQ. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 113 mg, 0.49 mmol) and *p*-toluenesulfonic acid (15 mg, 0.079 mmol) were added to a stirred solution of **14** (95 mg, 0.271 mmol) in dry benzene (6 mL) and the reaction mixture was stirred at room temperature for 48 h, at which time TLC showed no **14**. Then it was diluted with ether (25 mL), washed with water, satd aq $NaHCO_3$ and brine to give a crude product, which was purified by column chromatography on silica gel (H–E, 9:1), to give **10** (17 mg, 18%) and **18** (11 mg, 12%).

4.1.7.8. Treatment of 11 with PDC. Pyridinium dichromate (PDC; 13.9 g, 36.25 mmol) and 6 M *t*-BuOOH in decane (7.32 mL, 43.92 mmol) were added to a stirred solution of **11** (3.14 g, 8.97 mmol) and Celite (10.78 g) in dry benzene (114 mL). The reaction mixture was stirred at room temperature under argon atmosphere for 3 h 15 min, at which time TLC showed no **11**. The resulting mixture was filtered through a silica gel pad and washed with a 1:1 mixture of hexane–ether (50 mL) and the solvent was evaporated to give a crude product (3.5 g). The chromatography of this crude on silica gel (H–E, 7:3) gave **10** (1.13 g, 36%) as a colourless oil.

*Methyl 13β-hydroxy-14-oxoabieta-7-en-18-oate (**10**).* $[\alpha]_D^{25}$ +16.85 (*c* 0.94, $CHCl_3$); IR (film) *ν* 3500, 2951, 1714, 1652, 1631, 1462, 1386, 1246, 1187 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{21}H_{32}O_4Na$, 371.2198; found, 371.2192. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.7.9. Treatment of 11 with PhSeSePh/*t*-BuOOH. Diphenyl diselenide (0.60 g, 1.92 mmol) and 6 M *t*-BuOOH in decane (0.65 mL, 3.9 mmol) were added to a stirred solution of **11** (0.50 g, 1.43 mmol) in dry CCl_4 (20 mL) and the mixture was kept stirring at reflux under argon atmosphere for 2 h, at which time TLC showed no remaining starting material. Then, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (H–E, 7:3) affording **10** (457 mg, 92%) as a colourless oil.

4.1.8. Methyl 7-oxoabieta-7,12-dien-18-oate (18). Hydroxy ketone **10** (0.30 g, 0.862 mmol) and *p*-toluenesulfonic acid (140 mg, 0.736 mmol) in dry benzene (15 mL) were heated at reflux for 36 h, at which time TLC showed the disappearance of starting material. Then the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 7:3) affording **18** (0.22 g, 78%) as a colourless oil. $[\alpha]_D^{25}$ −0.66 (*c* 0.91, $CHCl_3$); IR (film) *ν* 2870, 1724, 1667, 1612, 1460, 1424, 1385, 1302, 1005, 911, 827, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 0.86 (3H, s), 0.97 (3H, d, *J*=6.9 Hz), 1.03 (3H, d, *J*=6.9 Hz), 1.24 (3H, s), 2.90 (1H, h, *J*=6.9 Hz), 3.63 (3H, s, COOMe), 6.69 (1H, d, *J*=8.3 Hz), 7.00 (1H, q, *J*=2.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 36.9 (C-1), 18.2 (C-2), 38.1 (C-3), 46.1 (C-4), 43.6 (C-5), 26.0 (C-6), 135.7 (C-7), 135.0 (C-8), 49.6 (C-9), 37.0 (C-10), 23.1 (C-11), 140.6 (C-12), 145.7 (C-13), 186.3 (C-14), 26.7 (C-15), 22.3 (C-16), 23.1 (C-17), 178.5 (C-18), 14.9 (C-19), 16.9 (C-20), 52.0 (C-COO*Me*); HRMS (FAB) *m/z* calcd for $C_{21}H_{30}O_3Na$, 353.2092; found, 353.2091.

4.1.9. Methyl 7-hydroxyabieta-8,11,13-trien-18-oate (17). Ketone **10** (0.2 mg, 0.575 mmol) and *p*-toluenesulfonic acid (0.1 mg, 0.526 mmol) in dry toluene (10 mL) were heated at reflux for 10 h. Then the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 85:15) affording **17** (172 mg, 91%) as a colourless oil. $[\alpha]_D^{25}$ +7.7 (*c* 1.0, $CHCl_3$) [lit.:[17] +51.7 (*c* 0.5, $CHCl_3$)]. The MS, IR, ^1H and ^{13}C NMR data agreed with the literature data.[17]

4.1.10. Methyl 14-hydroxyabieta-6,8,11,13-tetraen-18-oate (19). K_2CO_3 (0.39 g, 2.85 mmol) was added to a solution of **18** (92 mg, 0.28 mmol) in MeOH (6 mL), and the reaction mixture was kept stirring at reflux for three days, at which time TLC showed the disappearance of compound **18**. The reaction was quenched with 2 N HCl (1 mL). The mixture was poured into ether–water (20:5 mL) and it was extracted with ether (2×15 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **19** (70 mg, 70%) as a colourless oil. IR (film) *ν* 3583, 2948, 2923, 2869, 1724, 1627, 1566, 1433, 1386, 1123, 1002, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 1.05 (3H, s), 1.21 (3H, d, *J*=6.9 Hz), 1.24 (3H, d, *J*=6.9 Hz), 1.38 (3H, s), 2.16 (1H, m), 2.86 (1H, t, *J*=3.0 Hz), 3.10 (1H, h, *J*=6.9 Hz), 3.65 (3H, s, COOMe), 5.77 (1H, dd, *J*=9.8, 2.9 Hz), 6.73 (1H, d, *J*=8.3 Hz), 6.77 (1H, dd, *J*=9.8,

3.1 Hz), 7.03 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.5 (C-1), 18.4 (C-2), 35.6 (C-3), 46.3 (C-4), 46.2 (C-5), 129.6 (C-6), 125.2 (C-7), 119.8 (C-8), 146.6 (C-9), 37.6 (C-10), 114.2 (C-11), 121.0 (C-12), 131.8 (C-13), 148.4 (C-14), 26.9 (C-15), 22.5 (C-16), 22.8 (C-17), 17.9 (C-19), 20.5 (C-20), 52.0 (C-COO*Me*); HRMS (FAB) *m/z* calcd for $C_{21}H_{28}O_3Na$, 351.1936; found, 351.1929.

4.1.11. Treatment of 19 with H_2/Pd–C. To a solution of **19** (0.5 g, 1.52 mmol) in methanol (30 mL), 10% Pd–C (100 mg) was added and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 24 h. Filtration and concentration gave **17** (0.48 g, 96%) as a colourless oil.

4.1.12. Methylation of 17. K_2CO_3 (0.60 g, 4.35 mmol) was added to a solution of **17** (575 mg, 1.74 mmol) in acetone (15 mL) and the reaction mixture was kept stirring at room temperature for 15 min. Then iodomethane (0.54 mL, 8.71 mmol) was added and the reaction mixture was stirred at reflux for 15 h. The solvent was evaporated and the crude reaction mixture was poured into ether–water (30:10 mL) and it was extracted with ether (2×10 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **9** (545 mg, 91%) as a colourless oil.

4.1.13. 14-Methoxyabieta-8,11,13-trien-18-ol (23). $LiAlH_4$ (0.5 g, 13.16 mmol) was added to a stirred solution of **9** (1.0 g, 3.01 mmol) in dry THF (10 mL) cooled to 0 °C, and the reaction mixture was kept stirring at room temperature under argon atmosphere for 3 h, at which time TLC showed the disappearance of starting material. Then, 2 N HCl (0.5 mL) was added slowly at 0 °C and the mixture was extracted with ether (2×25 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **23** (0.9 g, 95%) as a colourless solid. Mp 102 °C; $[\alpha]_D^{25}$ +5.7 (*c* 0.04, $CHCl_3$); IR (KBr) ν 3401, 1484, 1410, 1329, 1263, 1212, 1031, 817 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, s), 1.18 (3H, d, J=6.9 Hz), 1.20 (3H, d, J=6.9 Hz), 1.22–1.95 (8H, m), 2.25 (1H, br d, J=12.7 Hz), 2.74 (1H, ddd, J=17.6, 11.3, 6.2 Hz), 2.98 (1H, dd, J=17.6, 6.2 Hz), 3.23 (1H, d, J=10.8 Hz), 3.27 (1H, h, J=6.9 Hz), 3.48 (1H, d, J=10.8 Hz), 3.70 (3H, s), 7.01 (1H, d, J=8.1 Hz), 7.04 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.4 (CH_3), 18.4 (CH_2), 18.7 (CH_2), 23.9 (CH_3), 24.0 (CH_3), 24.6 (CH_2), 25.3 (CH_3), 26.1 (CH), 35.0 (CH_2), 37.6 (C), 37.9 (C), 38.6 (CH_2), 43.6 (CH), 60.5 (CH_3), 72.2 (CH_2), 120.3 (CH), 123.6 (CH), 128.6 (C), 137.9 (C), 149.1 (C), 154.8 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{32}O_2Na$, 339.2300; found, 339.2304.

4.1.14. 14-Methoxyabieta-8,11,13-trien-18-al (24). Pyridinium chlorochromate (PCC) (0.50 g, 2.32 mmol) was added to a stirred solution of **22** (0.50 g, 1.58 mmol) in dry CH_2Cl_2 (25 mL) and the mixture was kept stirring at room temperature under argon atmosphere for 1 h, at which time TLC showed no remaining starting material. Then, the reaction was worked up by the addition of CH_2Cl_2 (20 mL) and the resulting mixture was filtered through a silica gel pad and washed with a mixture of ether–CH_2Cl_2 (15:30 mL). The solvent was evaporated to yield **23** (0.35 g, 70%), as a colourless oil. $[\alpha]_D^{25}$ +7.13 (*c* 1.1, $CHCl_3$); IR (film) ν 1725, 1449, 1410, 1330, 1219, 1152, 1029, 872, 818, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (3H, s), 1.18 (6H, d, J=6.9 Hz), 1.21 (3H, s), 1.31–1.90 (8H, m), 2.31 (1H, br d, J=12.7 Hz), 2.73 (1H, ddd, J=17.6, 11.3, 6.2 Hz), 2.96 (1H, dd, J=17.6, 6.2 Hz), 3.27 (1H, h, J=6.9 Hz), 3.69 (3H, s), 7.01 (1H, d, J=8.1 Hz), 7.06 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (CH_3), 17.8 (CH_2), 20.9 (CH_2), 23.9 (CH_3), 24.0 (CH_3), 24.3 (CH_2), 25.2 (CH), 26.1 (CH), 32.0 (CH_2), 36.5 (C), 38.0 (CH_2), 42.5 (CH), 49.8 (C), 60.5 (CH), 120.2 (CH), 123.9 (CH), 128.3 (C), 138.4 (C), 147.9 (C), 155.0 (C), 206.2 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{30}O_2Na$, 337.2143; found, 337.2138.

4.1.15. 14-Methoxyabieta-8,11,13-triene (25). Hydrazine hydrate (0.5 mL) and KOH (0.20 g) were added to a solution of aldehyde **24** (0.40 g, 1.27 mmol) in ethyleneglycol–ethylenglycol dimethylether (3:2, 15 mL) and the reaction mixture was heated at 180 °C for three days, at which time TLC showed no **24**. The reaction mixture was allowed to cool to room temperature and was diluted with water (5 mL) and extracted with ether (2×20 mL). The combined organic phases were washed with water and brine, dried over Na_2SO_4 and the solvent evaporated to give a crude product, which was purified by column chromatography on silica gel (H–E, 95:5), affording **25** (267 mg, 70%) as a colourless syrup. $[\alpha]_D^{25}$ +15.1 (*c* 1.0, $CHCl_3$); IR (film) ν 2963, 2945, 1605, 1452, 1378, 1050, 1018, 980 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (3H, s), 0.96 (3H, s), 1.18 (3H, s), 1.21 (3H, d, J=6.8 Hz), 1.20 (3H, d, J=6.8 Hz), 1.32 (1H, dd, J=12.5, 2.1 Hz), 1.39 (1H, ddd, J=13.1, 13.1, 3.6 Hz), 1.48 (1H, br d, J=13.1 Hz), 1.55–1.85 (8H, m), 1.93 (1H, dd, J=13.2, 7.8 Hz), 2.26 (1H, br d, J=12.7 Hz), 2.73 (ddd, J=17.7, 11.4, 7.7 Hz), 3.01 (1H, dd, J=17.6, 7.7 Hz), 3.28 (1H, h, J=6.9 Hz), 3.72 (3H, s), 7.02 (1H, d, J=8.4 Hz), 7.05 (1H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.7 (CH_2), 19.4 (CH_2), 21.7 (CH_3), 23.4 (CH_3), 24.0 (CH_3), 25.0 (CH_3), 29.5 (CH_2), 26.1 (CH), 33.4 (CH_3), 33.4 (C), 37.8 (C), 39.0 (CH_2), 41.7 (CH_2), 50.2 (CH), 60.5 (CH_3), 120.4 (CH), 123.7 (CH), 128.7 (C), 137.8 (C), 149.4 (C), 154.0 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{32}ONa$, 323.2351; found, 323.2347.

4.1.16. 14-Methoxy-18-mesyloxyabieta-8,11,13-triene (27). Mesyl chloride (0.7 mL) was added to a solution of **23** (0.40 g, 1.26 mmol) and triethylamine (1 mL) in dichloromethane (15 mL) at 0 °C and the reaction mixture was stirred at room temperature for 4 h, at which time TLC showed no **23**. The reaction mixture was quenched with water (1 mL) and it was diluted with ether (40 mL) and washed with 2 M aq HCl, water and brine. The organic phase was dried over anhyd Na_2SO_4 and concentrated under vacuum to yield **27** (461 mg, 93%) as a colourless oil. $[\alpha]_D^{25}$ +13.5 (*c* 1.06, $CHCl_3$); IR (film) ν 1495, 1355, 1175, 1028, 956, 847, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95 (3H, s), 1.16 (3H, s), 1.18 (3H, d, J=6.9 Hz), 1.21 (6H, d, J=6.9 Hz), 1.45–1.90 (8H, m), 2.26 (1H, br d, J=12.7 Hz), 2.70 (1H, ddd, J=16.5, 11.5, 6.2 Hz), 2.96 (3H, s), 3.00 (1H, dd, J=16.5, 6.2 Hz), 3.27 (1H, h, J=6.9 Hz), 3.69 (3H, s), 3.79 (1H, d, J=9.4 Hz), 4.05 (1H, d, J=9.4 Hz), 6.99 (1H, d, J=8.1 Hz), 7.01 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.1 (CH_3), 18.4 (CH_2), 18.5 (CH_2), 23.9 (CH_3), 24.0 (CH_3), 24.4 (CH_2), 25.3 (CH_3), 26.1 (CH), 35.1 (CH_2), 37.2 (CH_3), 37.2 (C), 37.6 (C), 38.2

(CH_2), 43.4 (CH), 60.5 (CH_3), 77.1 (CH_2), 120.3 (CH), 123.8 (CH), 128.3 (C), 138.1 (C), 148.4 (C), 154.8 (C); HRMS (FAB) *m/z* calcd for $C_{22}H_{34}O_4SNa$, 417.2075; found, 417.2081.

4.1.17. Treatment of 27 with NaI/Zn. NaI (160 mg, 0.81 mmol) and zinc (105 mg, 1.59 mmol) were added to a solution of **27** (120 mg, 0.30 mmol) in HMPA (5 mL) and the reaction mixture was stirred at 110 °C for three days, at which time TLC showed no **27**. The reaction mixture was quenched with water (2 mL), diluted with ether (30 mL) and washed with water (6×10 mL) and brine. The organic phase was dried over anhyd Na_2SO_4 and concentrated under vacuum to yield **25** (68 mg, 75%).

4.1.18. 14-Methoxy-18-iodoabieta-8,11,13-triene (28). NaI (560 mg, 2.83 mmol) was added to a solution of **27** (420 mg, 1.06 mmol) in HMPA (8 mL) and the reaction mixture was stirred at reflux for three days, at which time TLC showed no **27**. The reaction mixture was quenched with water (2 mL), diluted with ether (30 mL) and washed with water (6×10 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to yield **28** (407 mg, 90%) as a yellow oil. $[\alpha]_D^{25}$ −7.6 (*c* 1.1, $CHCl_3$); IR (film) *ν* 1456, 1381, 1260, 1212, 1030, 979, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 1.10 (3H, s), 1.20 (3H, s), 1.21 (3H, d, *J*=6.9 Hz), 1.21 (3H, d, *J*=6.9 Hz), 1.30–1.82 (7H, m), 2.24 (1H, ddd, *J*=12.8, 12.8, 3.1 Hz), 2.79 (1H, ddd, *J*=17.7, 11.0, 7.5 Hz), 3.01 (1H, ddd, *J*=17.7, 6.2, 1.4 Hz), 3.25 (1H, d, *J*=10.0 Hz), 3.29 (1H, h, *J*=6.9 Hz), 3.38 (1H, d, *J*=10.0 Hz), 3.72 (3H, s), 7.02 (1H, d, *J*=8.4 Hz), 7.06 (1H, d, *J*=8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 18.5 (CH_2), 18.8 (CH_3), 19.2 (CH_2), 24.1 (CH_3), 24.1 (CH_3), 24.8 (CH_2), 24.9 (CH_3), 26.3 (CH), 38.3 (CH_2), 35.9 (C), 38.1 (C), 38.7 (CH_2), 47.2 (CH), 60.7 (CH_3), 120.7 (CH), 124.0 (CH), 128.7 (C), 138.2 (C), 148.9 (C), 155.0 (C).

4.1.19. Treatment of 28 with $LiAlH_4$. $LiAlH_4$ (0.3 g, 7.9 mmol) was added to a stirred solution of **28** (0.75 g, 1.76 mmol) in dry THF (15 mL) cooled to 0 °C, and the reaction mixture was kept stirring under argon atmosphere at reflux for 24 h, at which time TLC showed the disappearance of starting material. Then, 2 N HCl (0.5 mL) was added slowly and the mixture was extracted with ether (3×20 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **25** (507 mg, 96%) as a colourless oil.

4.1.20. Abieta-8,11,13-trien-14-ol (26). BBr_3 (0.25 mL, 2.6 mmol) was added to a solution of **25** (250 mg, 0.83 mmol) in dichloromethane (15 mL) at −10 °C and the reaction mixture was stirred for 30 min, at which time TLC showed no **25**. The reaction mixture was poured into ice-water and it was diluted with ether (30 mL) and washed with water (5×10 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to yield **26** (225 mg, 95%) as a yellow oil. $[\alpha]_D^{25}$ +15.1 (*c* 1.0, $CHCl_3$) [lit.:[17] +52.9 (*c* 0.5, $CHCl_3$); lit.:[18] +27.9 (*c* 0.96, $CHCl_3$)]. IR (film) *ν* 3500, 1569, 1491, 1420, 1381, 1216, 1177, 1103, 995, 809 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*: 0.88 (3H, s), 1.17 (3H, s), 1.19 (3H, s), 1.22 (3H, d, *J*=6.8 Hz), 1.23 (3H, d, *J*=6.8 Hz), 1.41 (1H, dd, *J*=12.3, 1.8 Hz), 2.26 (1H, dt, *J*=12.7, 3.2 Hz), 2.59 (1H, ddd, *J*=16.5, 11.3, 6.8 Hz), 2.78 (1H, dd, *J*=16.5, 6.3 Hz), 3.12 (1H, h, *J*=6.8 Hz), 4.61 (1H, s), 6.84 (1H, d, *J*=8.2 Hz), 7.00 (1H, d, *J*=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 18.3 (CH_2), 19.3 (CH_2), 21.7 (CH_3), 22.6 (CH_3), 22.8 (CH_3), 22.9 (CH_3), 24.4 (CH_3), 24.9 (CH_3), 27.1 (CH), 33.4 (CH_3), 33.4 (C), 38.8 (C), 39.0 (CH_2), 41.7 (CH_2), 49.8 (CH), 116.5 (CH), 120.7 (C), 123.3 (CH), 130.1 (C), 149.1 (C), 150.3 (C); HRMS (FAB) *m/z* calcd for $C_{20}H_{30}ONa$, 309.2194; found, 309.2187.

4.1.21. Oxidation of 17 with $(KSO_3)_2NO$. Potassium nitrosodisulfonate (0.60 g, 2.23 mmol) was added to a stirred solution of **17** (200 mg, 0.606 mmol) in methanol (60 mL) and water (6 mL). After stirring for 10 h, TLC showed no starting material. Then, the solvent was evaporated and the crude product was extracted with ether (2×20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 3:2) to give **29** (173 mg, 83%) as a yellow oil. The MS, IR, ^1H and ^{13}C NMR data agreed with the literature data.[17]

4.1.22. Oxidation of 26 with $(KSO_3)_2NO$. Potassium nitrosodisulfonate (0.80 g, 2.98 mmol) was added to a stirred solution of **26** (150 mg, 0.524 mmol) in methanol (50 mL) and water (5 mL). After stirring for 4 h, TLC showed no starting material. Following the same workup described for **17**, 143 mg (91%) of 12-deoxyroyleanone (**1**) was obtained as a yellow oil.

4.1.23. 4-Formyloxy-14-methoxy-18-norabieta-8,11,13-triene (30). To a stirred solution of **24** (1.0 g, 3.18 mmol) and $NaHCO_3$ (0.6 g) in CH_2Cl_2 (50 mL), *m*-chloroperbenzoic acid (MCPBA) (1.1 g, 4.78 mmol) was added at room temperature. After stirring at reflux for 3 h, TLC indicated that no starting aldehyde **24** remained. The reaction mixture was quenched with 10% aq Na_2SO_3 (5 mL) and the mixture was stirred for an additional 45 min. Then, it was poured into ether–water (80:20 mL), and the organic phase washed with satd aq $NaHCO_3$ (8×20 mL), brine and dried over Na_2SO_4. After evaporating the solvent in vacuo, **30** (0.98 g, 93%) was obtained as a colourless oil. $[\alpha]_D^{25}$ +13.2 (*c* 0.52, $CHCl_3$); IR (film) *ν* 1719, 1567, 1584, 1385, 1330, 1198, 1102, 1029, 861, 820, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ*: 1.20 (3H, s), 1.21 (3H, d, *J*=6.9 Hz), 1.22 (3H, d, *J*=6.9 Hz), 1.59 (3H, s), 1.98 (1H, dd, *J*=12.3, 1.8 Hz), 2.12 (1H, dd, *J*=12.9, 7.6 Hz), 2.24 (1H, d, *J*=12.5 Hz), 2.64 (1H, m), 2.75 (1H, ddd, *J*=17.6, 12.9, 7.6 Hz), 3.06 (1H, dd, *J*=17.6, 5.5 Hz), 3.14 (1H, h, *J*=6.9 Hz), 3.72 (3H, s), 7.02 (1H, d, *J*=8.2 Hz), 7.07 (1H, d, *J*=8.2 Hz), 8.08 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 16.9 (CH_2), 18.9 (CH_3), 19.0 (CH_2), 22.9 (CH_3), 23.7 (CH_3), 25.1 (CH), 36.6 (CH_2), 36.9 (CH_2), 37.6 (C), 48.4 (CH), 59.4 (OCH_3), 119.5 (CH), 122.9 (CH), 127.4 (C), 137.3 (C), 146.6 (C), 153.9 (C), 159.5 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{30}O_3Na$, 353.2093; found, 353.2100.

4.1.24. 14-Methoxy-18-norabieta-3,8,11,13-tetraene (31).[13] Iodine (1.0 g, 3.94 mmol) was added to a solution of Ph_3P (1 g, 3.8 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 5 min. A solution of **30** (1 g, 3.03 mmol) in CH_2Cl_2 (10 mL) was then added and the

reaction mixture was stirred at room temperature for 12 h, at which time TLC showed no **30**. The reaction mixture was quenched with 5% aq $NaHSO_3$ (3 mL) and the mixture was stirred for an additional 15 min. Then, it was diluted with ether (30 mL) and the organic phase was washed successively with satd aq $NaHCO_3$ (2×10 mL), brine, dried over anhyd Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (H–E, 9:1) to give **31** (783 mg, 91%) as a colourless oil. $[\alpha]_D^{25}$ +38.4 (*c* 0.7, $CHCl_3$); IR (film) ν 1647, 1561, 1447, 1329, 1260, 1203, 1032, 820, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.21 (3H, d, *J*=6.9 Hz), 1.22 (3H, d, *J*=6.9 Hz), 1.26 (3H, s), 150–1.60 (2H, m), 1.76 (3H, s), 1.87 (1H, br d, *J*=10.7 Hz), 2.06 (1H, m), 2.61 (1H, ddd, *J*=16.8, 10.4, 5.0 Hz), 2.89 (1H, dd, *J*=16.8, 4.7 Hz), 3.30 (1H, h, *J*=6.9 Hz), 3.71 (3H, s), 5.42 (1H, br s), 7.06 (1H, d, *J*=6.8 Hz), 7.08 (1H, d, *J*=6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.6 (CH_3), 23.3 (CH_2), 23.9 (CH_2), 24.1 (CH_3), 24.1 (CH_3), 26.4 (CH), 27.4 (CH_3), 33.8 (CH_2), 36.6 (C), 46.8 (CH), 60.7 (OCH_3), 121.6 (CH), 123.2 (CH), 123.9 (CH), 130.1 (C), 135.5 (C), 137.8 (C), 145.1 (C), 154.5 (C); HRMS (FAB) *m/z* calcd for $C_{20}H_{28}ONa$, 307.2038; found, 307.2042.

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Supplementary data

Copies of ^1H NMR, ^{13}C NMR and DEPT spectra for compounds **1**, **9**, **10**, **12**, **15**–**19**, **23**–**28**, **30** and **31** are included as supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.088.

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16. The present authors regret making some errors in Ref. 15. The ^{13}C NMR chemical shifts for the aromatic carbons in compound **17** should be δ 116.5 (CH), 120.7 (C), 123.3 (CH), 130.1 (C), 149.1 (C), 150.3 (C). Compounds **8**, **9** and **11** are 13β,14β-disubstituted derivatives.
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Enantioselective Total Synthesis of the Selective PI3 Kinase Inhibitor Liphagal

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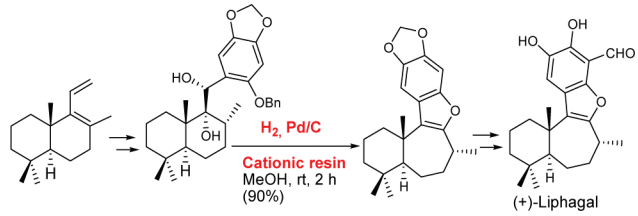
ABSTRACT



The enantioselective total synthesis of liphagal, a selective inhibitor of PI3K α isolated from the marine sponge *Aka coralliphaga*, has been achieved. The novel tetracyclic "liphagane" skeleton is formed in one step, after the hydrogenation of a dihydroxydrimane phenol benzyl ether in the presence of cationic resin.

In recent decades, marine organisms appear to have become an almost inexhaustible source of natural products, showing very different structural patterns and a wide variety of interesting biological activities.[1] A paradigmatic example of this type of metabolites is liphagal (**1**, Figure 1), a meroterpenoid recently isolated from the marine sponge *Aka coralliphaga*,[2] which exhibits the novel "liphagane" carbon skeleton. Besides its uncommon structure, liphagal (**1**) presents considerable therapeutic potential, with inhibitory activity against PI3K α (phosphoinositide-3-kinase α). It is more potent than the synthetic LY 294002 and more selective than wortmanin, making it a promising candidate as an agent for the treatment of inflammatory and autoimmune disorders as well as cancer and cardiovascular diseases.[3] In fact, liphagal (**1**) has been observed to be cytotoxic, in secondary in vitro assays, to LoVo (human colon: IC_{50} 0.58 μM), CaCo (human colon: IC_{50} 0.67 μM), and MDA-468 (human breast: IC_{50} 1.58 μM) tumor cell lines. The protein kinase C inhibitors corallidictyals, such as corallidictyal B (**2**) and D (**3**), are spirosesquiterpene aldehydes closely related to compound **1** and isolated from the same natural source.[4]

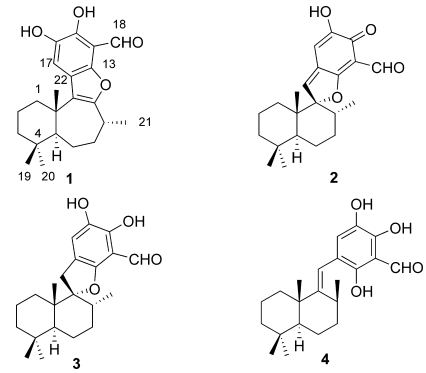


Figure 1. Metabolites from *Aka coralliphaga*.

[†] Universidad de Almería.

(1) For a recent review on marine natural products, see: Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2010**, *27*, 165.

(2) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Soest, R. W.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 321.

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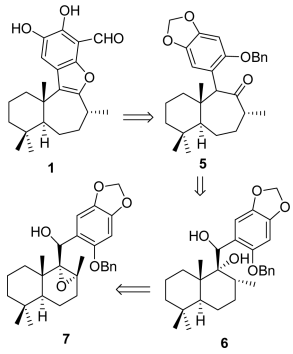
Two racemic syntheses of liphagal (**1**) have been reported. Andersen et al., after isolating compound **1** from its natural source, developed a synthesis of this bioactive metabolite, which involves as the key step the cation-initiated cyclization of a dienyl benzofuran.[2] Recently, Mehta et al. described a closely related strategy to synthesize (±)-**1**, based on the acid-promoted cyclization of a cyclohexenyl benzofuran.[5]

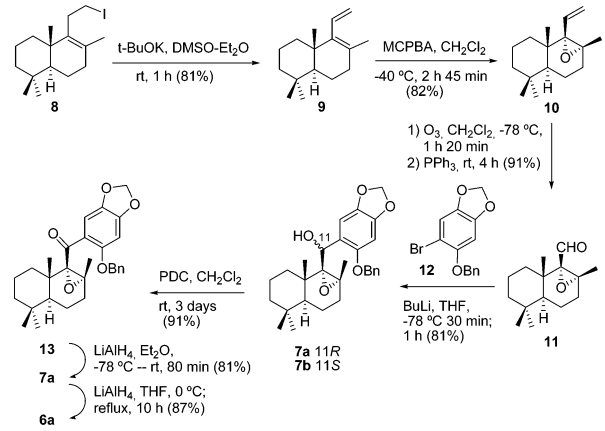
Andersen's group proposed two possible biogenic pathways to liphagal (**1**), starting from a farnesyl trihydroxybenzaldehyde. One of these pathways takes place via the bicyclofarnesyl trihydroxybenzaldehyde siphonodictyal B (**4**),[6] a metabolite also found in the sponge *Aka coralliphaga*. In the alternative pathway, the benzofuran system is first formed from an acyclic ketone and the 6,7-ring system is subsequently created, after the acid promoted cyclization of a dienyl benzofuran.[2]

Scheme 1. Retrosynthesis of Liphagal (**1**)



During our research into the synthesis of bioactive natural products, we were interested in developing an enantioselective synthesis of liphagal (**1**), making it possible to establish its absolute stereochemistry. Scheme 1 shows the retrosynthesis planned for compound **1**. The furan ring will be formed by dehydration of the hemiketal resulting from the hydroxy ketone derived from compound **5**. This will result from the pinacol rearrangement of diol **6**, resulting from the regioselective reduction of epoxy alcohol **7**. This will be obtained after the addition of an aryllithium to an epoxy aldehyde. Scheme 2 shows the synthesis of epoxy alcohols **7a**,**b** via epoxy aldehyde **11**. The synthesis of compound **11** is not a trivial task. Different synthetic procedures have been reported for the construction of the (2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methylene skeleton of this compound, including total syntheses,[7] biomimetic cyclizations,[8] or hemisyntheses starting from polycyclic natural products.[9]

Scheme 2. Synthesis of Epoxy Alcohols **7a**,**b**



However, the stereoselective introduction of the epoxide function involves certain difficulties.

It is well-known that the epoxidation of the allyl alcohol precursor of aldehyde **11** is not stereoselective, leading to a 2.5:1 mixture of the corresponding α- and *β*-epoxy derivatives, respectively.[10] In order to improve the efficiency of synthetic sequence, the utilization of this allyl alcohol as an intermediate was ruled out, and the diene **9** was investigated as an alternative precursor; this compound underwent chemo- and stereoselective epoxidation at low temperatures, affording the epoxy alkene **10** in high yield. Diene **9** has been easily synthesized from various starting materials, such as a (*S*)-(+)-Wieland−Miescher ketone analogue[11] or the natural monoterpene (*R*)-(−)-carvone;[12] compound **9** has also been obtained after dehydrohalogenation of allyl iodide **8**, synthesized after the lipase-catalyzed kinetic resolution following the acid cyclization of homofarnesyl acetate[13] or from commercial sclareolide, the latter being the most efficient procedure for synthesizing diene **9** (three steps, 65% overall yield).[14] Ozonolysis of epoxy alkene **10**, whose relative stereochemistry was established on the basis of NOE experiments, gave aldehyde **11** in good yield.

(3) For recent reviews on the therapeutic potential of phosphoinositide-3-kinase inhibitors, see: (a) Ward, S. G.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, P. *Chem. Biol.* **2003**, *10*, 207. (b) Ward, S. G.; Finan, P. *Curr. Opin. Pharmacol.* **2003**, *3*, 426.

(4) Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Köck, M. *J. Nat. Prod.* **2007**, *70*, 504.

(5) Mehta, G.; Likhite, N. S.; Kumar, C. S. A. *Tetrahedron Lett.* **2009**, *50*, 5260.

(6) Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Köck, M. *J. Nat. Prod* **2007**, *70*, 504.

(7) (a) Tsujimori, H.; Bando, M.; Mori, K. *Eur. J. Org. Chem.* **2000**, 297. (b) Okamura, W. H.; Peter, R.; Reischl, N. *J. Am. Chem. Soc.* **1985**, *107*, 1034. (c) Schmidt, C.; Chisti, N. H.; Breining, T. *Synthesis* **1982**, 391. (d) Arima, Y.; Kinoshita, M.; Akita, H. *Tetrahedro: Asymmetry* **2007**, *18*, 1701. (e) Akita, H.; Amano, H.; Kato, K.; Kinoshita, M. *Tetrahedron: Asymmetry* **2004**, *15*, 725.

(8) (a) Tsangarakis, C.; Stratakis, M. *Adv. Synth. Catal.* **2005**, *347*, 1280. (b) Polovinka, M. P.; Korchagina, D. V.; Gatilov, Y. V.; Bagrianskaya, I. Y.; Barkhash, V. A.; Perutskii, V. B.; Ungur, N. D.; Vlad, P. F.; Shcherbukhin, V. V.; Zefirov, N. S. *J. Org. Chem.* **1994**, *59*, 1509.

(9) (a) Kuchkova, K. I.; Aryku, A. N.; Barba, A. N.; Vlad, P. F. *Chem. Nat. Prod.* **2007**, *43*, 412. (b) Barrero, A. F.; Alvarez-Manzaneda, E.; Chahboun, R. *Tetrahedron* **1998**, *54*, 5635.

(10) (a) Kulcitki, V.; Ungur, N.; Gavagnin, M.; Carbone, M.; Cimino, G. *Eur. J. Org. Chem.* **2005**, 1816. (b) Dominguez, G.; Hueso-Rodriguez, J. A.; de la Torre, M. C.; Rodriguez, B. *Tetrahedron Lett.* **1991**, *32*, 4765.

(11) Hagiwara, H.; Takeuchi, F.; Nozawa, M.; Hoshi, T.; Suzuki, T. *Tetrahedron* **2004**, *60*, 1983.

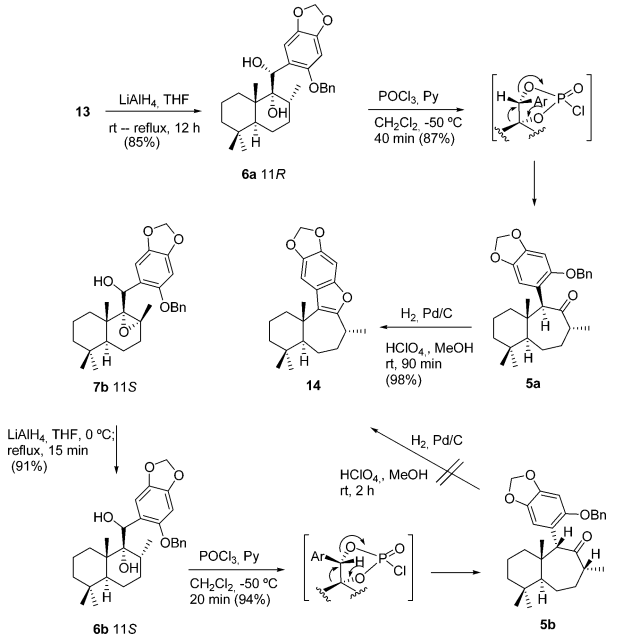
(12) Abad, A.; Agulló, C.; Castelblanque, L.; Cuñat, A. C.; Navarro, I.; Ramirez de Arellano, M. C. *J. Org. Chem.* **2000**, *65*, 4189.

(13) Tanimoto, H.; Oritani, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1695.

(14) Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J. M.; Alvarez-Manzaneda, R.; Hmammouchi, M.; Es-Samti, H. *Chem. Commun.* **2009**, 592.

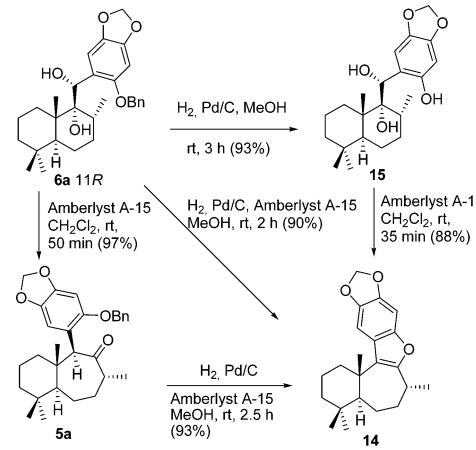
Treatment of this with the aryllithium derived from bromide **12**, which is straightforwardly prepared from the very accessible sesamol,[15] gave epoxy alcohols **7a**,**b** as a 1:1 mixture, which was resolved after combined column chromatography and crystallization. Oxidation of the mixture of epoxy alcohols **7a**,**b** with PDC gave ketone **13**, which after treatment with $LiAlH_4$ in Et_2O cooled at −78 °C and further stirring at room temperature for 80 min gave compounds **7a**,**b** in a 5:1 ratio; further recrystallization afforded pure stereoisomer **7a**. The configuration on the C-11 of compounds **7a** and **7b** was established on the basis of chemical evidence and by chemical correlation with compounds **5a** and **5b**. Epoxy alcohol **7b** underwent fast epoxide ring-opening with complete regio- and stereoselectivity to give the corresponding 11*S* diol **6b** by refluxing with $LiAlH_4$ in THF; under the same reaction conditions, epoxy alcohol **7a** was slowly converted into the corresponding 11*R* diol **6a**. This could be attributed to the steric hindrance of angular methyl and the aromatic ring arising in the alkoxyaluminium intermediate generated during the reduction of compound **7a**.

Scheme 3. Construction of the "Liphagane" Skeleton



The next step was to address the construction of the liphagane skeleton (scheme 3). The elaboration of the fused 6,7-ring system was achieved after the pinacol rearrangement of diols **6a**,**b**. Treatment of the 11*R* diol **6a** with $POCl_3$ and pyridine in dichloromethane at −50 °C for 40 min gave in 87% yield the corresponding cycloheptanone **5a**; the 11*S* diol **6b** under these reaction conditions led to the epimeric ketone **5b**. The C-10 configurations for compounds **5a** and **5b** were established on the basis of NOE experiments. Hydrogenation of compound **5a** in the presence of perchloric acid afforded in excellent yield benzofuran **14**, which possesses the tetracyclic liphagane skeleton. Under the same reaction conditions, the isomer **5b** gave compound **14** in trace amounts, together with an unresolvable mixture of compounds. All attempts at converting compound **5b** into its epimer **5a**, under different acid (e.g., concd HCl or concd H_2SO_4 in refluxing dioxane) or basic conditions (e.g., DBU in refluxing toluene or KOH in diglyme under reflux), were unsuccessful.

Scheme 4. Direct Synthesis of Liphagane Precursor **14**

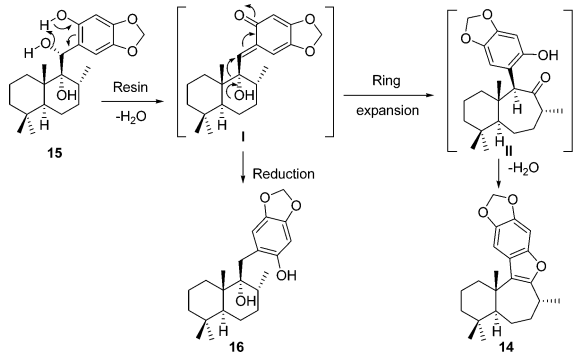


Once the liphagane precursor **14** was achieved, our efforts were directed toward shortening the synthetic sequence, and so one-step benzyl ether deprotection and B ring expansion were investigated. With this purpose in mind, the rearrangement of diol **6a** promoted by perchloric acid was studied. Unfortunately, the treatment of compound **6a** with this acid afforded a 1:1 mixture of epimers **5a**,**b**. After perchloric acid was ruled out, the utilization of mild acid conditions was investigated. Diol **6a** was transformed into ketone **5a** in good yield with complete stereospecificity by treatment with Amberlyst A-15 in methanol. Interestingly, the dihydroxyphenol **15** underwent simultaneous rearrangement and formation of the furan ring, directly affording the liphagane intermediate **14**, after cationic resin treatment (Scheme 4). Next, hydrogenation in the presence of cationic resin was investigated. The treatment of a mixture of ketone **5a**, palladium on carbon, and Amberlyst in methanol, under a hydrogen atmosphere, gave in good yield the liphagane precursor **14**. Finally, the simultaneous rearrangement, benzyl ether deprotection, and furan ring formation were tackled. When a methanolic solution of diol **6a** was treated with palladium on carbon and cationic resin, under a hydrogen atmosphere, the liphagane compound **14** was obtained (Scheme 4); the hydroxyl phenol **16** was also obtained as a minor constituent when the hydrogen pressure was increased and the proportion of cationic resin reduced.

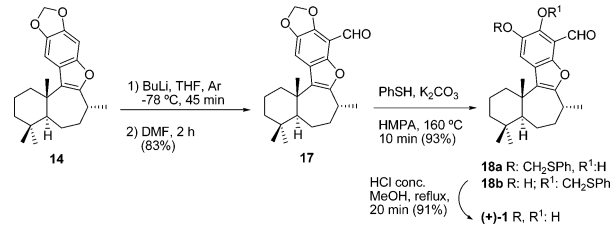
A possible mechanism for the direct formation of the liphagane precursor **14** from diol **6a**, via dihydroxy phenol

(15) Hitotsuyanagi, Y.; Ichihara, Y.; Takeya, K.; Itokawa, H. *Tetrahedron Lett.* **1994**, *35*, 9401.

Scheme 5. Mechanism for the Formation of **14** and **16**



Scheme 6. Synthesis of Liphagal (**1**) from Benzofuran **14**



15, promoted by cationic resin, is depicted in Scheme 5. The cycloheptanone derivative **II** could be generated after the rearrangement of the hydroxy trienone **I**; further hemiketalization and dehydration would lead to the liphagane intermediate **14**. The hydroxyl phenol **16** would be formed by reduction of the intermediate **I**, prior to the rearrangement process. The lack of stereospecificity observed during the perchloric acid promoted ring expansion can be attributed to the formation of an intermediate benzyl cation.

Finally, compound **14** was transformed into liphagal (**1**) (Scheme 6). Treatment of this with BuLi in THF at −78 °C followed by the addition of DMF and further reaction for 2 h gave aldehyde **17**. Deprotection of the methylenedioxy group was achieved utilizing a modification of the Imakura procedure.[16] A 6:1 mixture of phenylsulfides **18a** and **18b** resulted when compound **17** was heated with PhSH and K_2CO_3 in HMPA at 160 °C for 10 min. Refluxing a methanolic solution of sulfides **18a**,**b** in the presence of catalytic concd HCl led to liphagal (**1**). This compound had the same spectroscopic properties as reported in the literature. The $[\alpha]_D$ +17.9 [lit.[2] +12.0] confirms the absolute stereochemistry.

In summary, the first enantioselective synthesis of the selective inhibitor of PI3 kinase α liphagal (**1**) is reported; this allows us to establish absolute stereochemistry for this marine metabolite. Key steps of the synthetic sequence are the chemo- and stereoselective epoxidation of a homodrimane diene and the one-step transformation of a dihydroxydrimane phenol benzyl ether into the tetracyclic "liphagane" precursor, which involves a stereospecific pinacol rearrangement, the benzyl ether deprotection, the formation of a hemiketal, and its subsequent dehydration.[17]

Acknowledgment. We thank the Spanish Ministry of Science and Innovation (Project No. CTQ2009-09932).

Note Added after ASAP Publication. Reference 17 was added to the version reposted on June 17, 2010.

Supporting Information Available: Experimental details and ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **5a**,**b**, **6a**,**b**, **7a**,**b**, **9**−**11**, and **13**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101173W

(16) Imakura, Y.; Konishi, T.; Uchida, K.; Sakurai, H.; Kobayashi, S.; Haruno, A.; Tajima, K.; Yamashita, S. *Chem. Pharm. Bull.* **1994**, *42*, 500.

(17) While this manuscript was in preparation, a similar approach to liphagal was published, see: George, J. H.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 2394.

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NIS-PPh_3: A Selective Reagent for the Spiroannulation of *o*-Allyl Phenols. Total Synthesis of Corallidictyal D

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Dedication ((optional))

During the last decades a variety of spirodihydrobenzofuran derivatives and related compounds, characterized by its wide and potent biological activities have been isolated from different natural sources. Representative examples are corallidictyal B (**1**) and D (**2**), two spirosesquiterpene aldehydes isolated from the marine sponge *Aka coralliphaga*, with protein kinase C inhibitory activity,[1] the complement inhibitor K-76 (**4**),[2] the antiviral stachybotrydial (**5**)[3] and the myo-Inositol Monophosphatase (IMPase) inhibitor named L-671,776 (**6**).[4] A variety of spirodihydrobenzofuranlactams have been isolated from the cultures of different *Stachybotrys* species, such as compounds **7-11**, with pancreatic cholesterol esterase inhibitor activity,[5] and lactams **12-15**, antagonists of endothelin and inhibitors of HIV-1 protease.[6] More recently, liphagal (**3**), a metabolite with selective PI3K kinase inhibitory activity, structurally related with compounds **1** and **2**, have also been reported.[7]

Despite the relevant biological activities and the interesting sterically constrained spiro structure of the above mentioned compounds only a few syntheses have been reported for some of these compounds; in all cases, the key step is the spiroannulation of the suitable drimane (bicyclic sesquiterpene) phenol. Corey et al. synthesized K-76 (**4**), after cyclization utilizing a THF –ethylene glycol – 2N hydrochloric acid mixture.[2a] Three years later, McMurry et al. described the synthesis of compound **4**, utilizing cationic resin as the cyclizing agent.[2b] More recently, Kende et al. have reported the synthesis of stachybotrylactam (**12**), also utilizing cationic resin. [8] In all cases a mixture of spirodihydrobenzofuran and benzopyran in a 1.7-3.5:1.0 ratio was obtained.

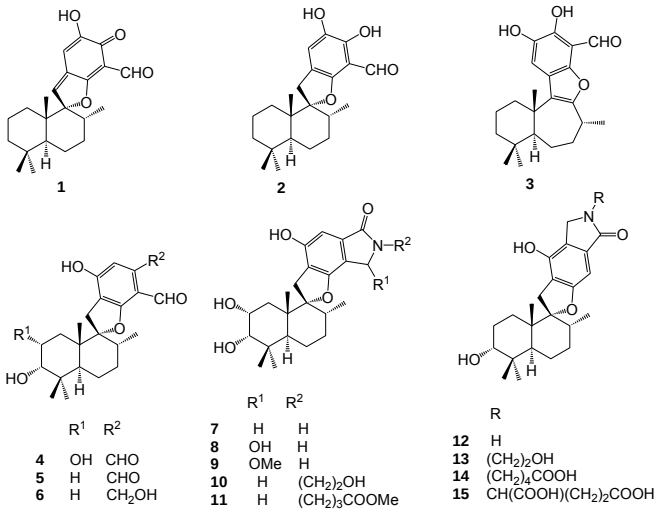

Figure 1. Bioactive spirodihydrobenzofurans and related metabolites.

The interest of the above mentioned metabolites encouraged us to develop the first synthetic access to some of them. After synthesizing liphagal (**3**),[7b] we undertook the synthesis of corallidictyal D (**2**), a potential agent suitable in cancer therapies and in treatment of inflammatory and cardiovascular diseases. At a first sight, diol **16**, an intermediate in our synthesis of liphagal (**3**), could also be a suitable precursor of corallidictyal D (**2**). The related spirocompound **18** would be obtained after removal of the benzylic hydroxyl group, debenzylation and subsequent acid cyclization of the resulting hydroxyphenol **17** (Scheme 1). However, all attempts of removing the benzylic hydroxyl group were unsuccessfull; in all cases the cycloheptanone derivative resulting from the pinacol rearrangement was obtained as the main product together with a little amount of hydroxyphenol **17**. The treatment of the latter under

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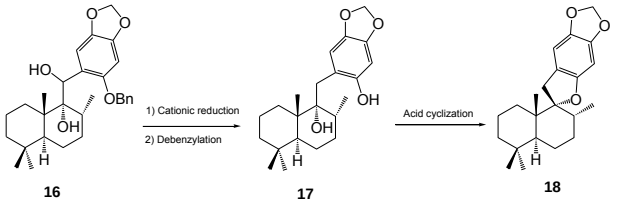
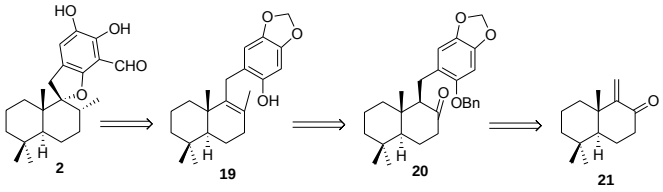
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

acidic conditions gave the benzopyran derivative together with a little quantity of spirocompound **18**.



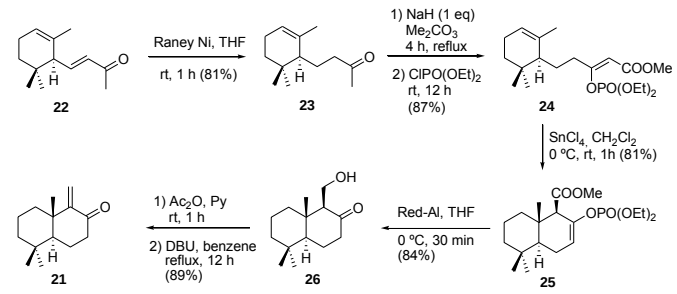
Scheme 1. A first synthetic approach to corallidictyal D (**2**) from diol **16**.

This failure led us to plan an alternative synthesis of the spirodihydrobenzofuran skeleton, utilizing a suitable spiroannulation proccess of the sesquiterpene phenol **19** as the key step. This will be synthesized from ketone **20**, obtained after the Friedel-Crafts alkylation of the suitable sesamol (3,4-methylenedioxyphenol) derivative with the α,β-enone **21** (Scheme 2).



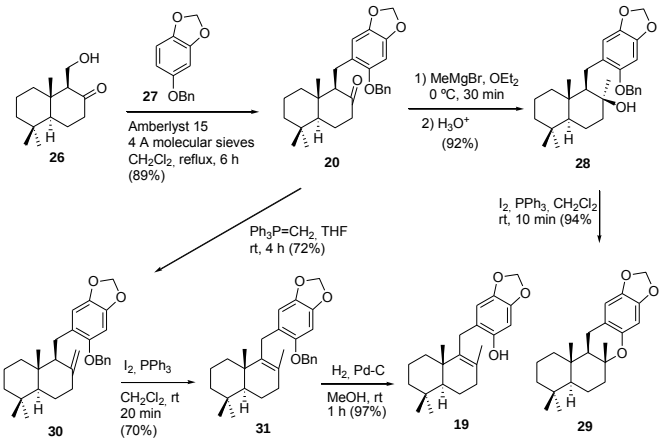
Scheme 2. Retrosynthesis of corallidictyal D (**2**).

(±)-α,β-Enone **21** has been synthesized from the corresponding bicyclic β-ketoester (4 steps, 60% global yield), [9] prepared from β-ionone through a three-step sequence involving Bu_3SnH regioselective 1,4-reduction to dihydro-β-ionone, [10] followed by methoxycarbonylation and stereoselective $SnCl_4$ catalysed cyclization (60% global yield from β-ionone to bicyclic β-ketoester). [11] The alternative synthesis of bicyclic β-ketoester starting from α-ionone (**22**) has also been reported, but has serious drawbacks. Even though the regioselective conjugated reduction to dihydro-α-ionone (**23**) can be carried out in a more convenient way,[12] the $SnCl_4$ mediated cyclization of the corresponding monocyclic β-ketoester is not stereoselective, affording a mixture of the desired A/B *trans*-fused β-ketoester and its *cis*-fused stereoisomer, among other compounds. [13]



Scheme 3. Synthesis of α,β−enone **21** from α-ionone (**22**).

In spite of this considerable disadvantage, the possibility of using enantiomerically pure α-ionone (**22**) [14] as starting material, which makes feasible the enantiospecific synthesis of the target compound **2**, as well as the easy 1,4-reduction of enone **22**, realizable in the gram scale utilizing Nickel Raney,[12c] prompted us to investigate a synthetic sequence from α-ionone (**22**) to α,β-enone (**21**), which circumvents the problem of the lack of stereoselectivity during the obtention of the *trans*-decalone skeleton starting from α-ionone (**22**). Scheme 3 shows the alternative sequence we have developed to achieve this goal. The key step is the $SnCl_4$ catalyzed cyclization of enol phosphate **24** which takes place with complete regio and stereoselectivity to give the bicyclic derivative **25**. [15] The selective 1,4-reduction of dienone **22** has been achieved by treating with Raney Ni.[12c] The enol phosphate **24** was obtained in one-pot reaction after treating the methyl ketone **23** with one equivalent of NaH and successively with Me_2CO_3 and $ClPO(OEt)_2$. Treatment of compound **24** with $SnCl_4$ in dichloromethane at 0 ºC gave with complete regio- and stereoselectivity the bicyclic enol phosphate **25**, which was transformed into the hydroxy ketone **26** by treating with red-Al at 0 ºC. Finally, the α,β-enone **21** was obtained after acetylation of compound **26** and further treatment with DBU. All the sequence steps from dienone **22** to enone **21**, including the cyclization from **24** to **25**, proceed satisfactorily in the gram-scale.



Scheme 4. Synthesis of sesquiterpene phenol **19**.

Then, the preparation of intermediate sesquiterpene phenol **19**[16] was tackled. The merosesquiterpene skeleton of this type of compounds has been most frequently created utilizing a two-synthon strategy, involving in most cases the reaction of a drimane (bicyclic sesquiterpene) electrophile with a nucleophilic phenol derivative, usually an aryllthium compound.[17] However, this procedure has some drawbacks, such as a greater difficulty in handling which make less feasible a larger scale synthesis. For this reason we have chosen an alternative method developed in recent years in our laboratory, which involves the cationic-resin-promoted Friedel-Crafts alkylation of the suitable phenol derivative with the *nor*-drimane α,β-enone **21**.[17] Although aryl ketone **20** can be obtained efficiently after the treatment of α,β-enone **21** with benzyl ether **27**, easily prepared from commercial sesamol, in the presence of the cationic resin Amberlyst A-15, this proccess has been shortened utilizing the hydroxy ketone **26** instead of the unsaturated compound **21**. Treatment of ketone **20** with MeMgI gave the expected tertiary

alcohol **28**, which, interestingly, when was reacted with I_2 and PPh_3 gave the benzopyrane **29**,[16] instead of the expected dehydrated derivative **31**. This was obtained in an alternative way, after the olefination of ketone **20** and the further isomerization to the most stable tetrasubstituted compound **31**, by treating with I_2 and PPh_3. The alkenyl phenol **19** was finally obtained after hydrogenation (Scheme 4).

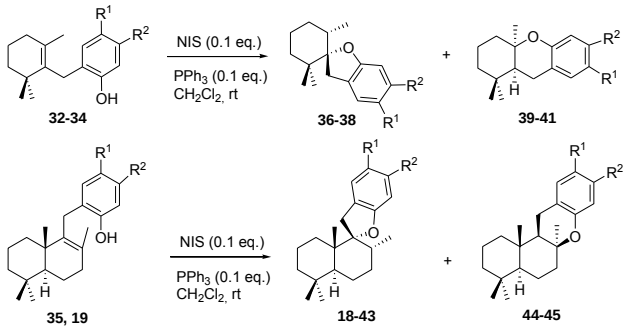


Table 1. treatment of some *o*-allyl phenols with NIS_PPh3

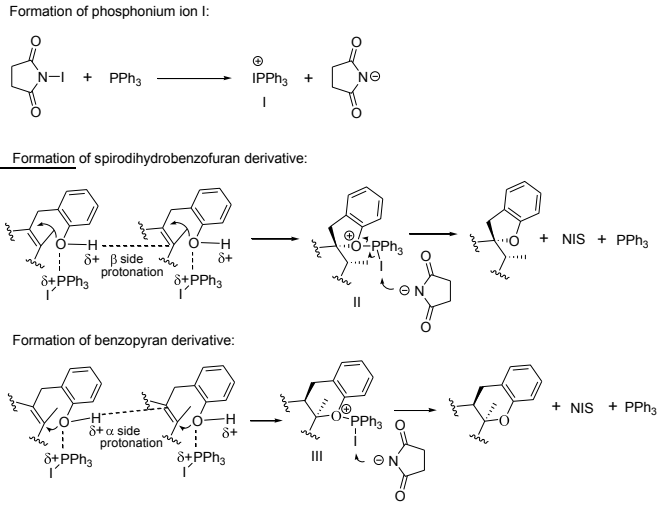
Entry	o-Allyl phenol	R1	R2	Time	Products
1	**32**	H	H	15 h	**36**+**39** (4.0:1) (87%)
2	**33**	Me	H	12 h	**37**+**40** (4.0:1) (89%)
3	**34**	-OCH_2O-	-	14 h	**38**+**41** (3.5:1) (86%)
4	**35**	OMe	OMe	12 h	**42**+**44** (5.0:1) (85%)
5	**19**	-OCH_2O-	-	10 h	**18**+**45** (6.0:1) (90%)
6	**19**	-OCH_2O-	-	14 h	**18**+**45** (10.0:1) (85%)[a]

[a] 1 g of compound **19** was cyclized.

Next, the spiro annulation of C and D ring of target compound was undertaken. Hydroalkoxylation of unactivated olefins have been commonly achieved through nucleophilic additions catalyzed by transition-metal complex, such as platinum,[18] ruthenium,[19] palladium[20] and gold,[21] catalyzed by Lewis acids, such as Et_2AlCl[22] and $BF_3.OEt_2$[23] and catalyzed by Bronsted acids, including 2-naphthalenesulfonic, p-toluenesulfonic and sulfuric acid[23a] and trifluoromethanesulfonic acid. [24] Most of these procedures involve harsh conditions. The intramolecular hydroalkoxylation of alkenylphenols similar to compound **19**, catalyzed by Lewis[22,23a] and by Bronsted acids,[23a] have been previously reported. In all cases, the corresponding benzopyran derivatives, as a mixture of 8-epimers was obtained, being the C8β-Me isomer, similar to compound **29**, the major constituent. As indicated above, McMurry[2b] and Corey,[2a] reported the obtention of the corresponding spirodihydrobenzofurans, when the cyclization was accomplished with hydrochloric acid and cationic resin, respectively; however, the desired product was obtained together with a considerable amount of the corresponding benzopyran derivative. Recently, continuing our studies on the use of PPh_3 and iodine derivatives,[25] we have found that some alkenyl phenols after treatment with NIS and PPh_3 undergo cyclization providing the corresponding spirodihydrobenzofuran derivatives. In table 1 the reaction of several *o*-(β-cyclogeranyl)phenols and *o*-drimenylphenols with catalytic NIS-PPh_3 in dichloromethane at room temperature is shown. As it can be seen, in the worst case a 3 : 1 mixture of spirodihydrobenzofuran and benzopyran derivative results. The treatment of compounds **32-34** with cationic resin gave almost exclusively the benzopyran compounds, as a mixture of *cis* and *trans* isomers, while the drimenyl phenols **35** and **19** provided a mixture of spirodihydrobenzofurans and benzopyrans, as the C8β-Me epimer, in an 1 : 7 aproximate proportion. These alkenyl phenols remained unaltered after treatment under the Corey's conditions.

A first fact that must be considered in rationalizing the results obtained with the NIS-PPh_3 system is the complete *anti* stereoselectivity of the addition process, which is unprecedented in this type of reactions. Under the conditions previously described in the literature, the hydroalkoxylation process is not stereoselective, obtaining the products resulting from the *syn* and *anti* addition. Depending upon the structure of the olefin, the acid-catalyzed addition can proceed in a stepwise manner, involving an intermediate carbocation, or through a concerted proccess. Theoretical studies carried out in concerted acid-catalyzed additions show that the transition state for the *syn* addition is more stable to that for the *anti* addition; this fact is attributed to the formation of strong hydrogen bonding between the OH group of phenol and one of the oxygens of the acid.[21d]

When the NIS-PPh_3 system is utilized an *anti* concerted process, precluding the formation of an intermediate carbocation, must take place. A possible mechanism, in which the phenol acts simultaneously as a nucleophile and a proton donor, is depicted in scheme 5.

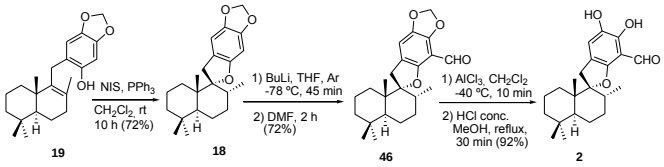


Scheme 5. A possible mechanism for the NIS-PPh_3 mediated cyclization of *o*-allyl phenols.

The OH group, activated by the fosfonium ion **I**, can transfer the proton by the β side of the olefinic bond of the adjacent molecule, which at the same time undergoes the *O*-nucleophilic attack on the C-9, affording the intermediate **II**, precursor of the spiro compound. Alternatively, when the proton is transferred by the double bond α side, the *O*-nucleophilic attack occurs on the C-8, leading to the intermediate **III**, precursor of the benzopyran derivative. A similar

behaviour has been previously found in the base-mediated cyclization of the 8,9-epoxyderivatives of alkenyl phenols similar to compound **19**: the 8β,9β-epoxyderivative underwent the nucleophilic attack on the C-9, providing the corresponding spiro compound, whereas the 8α,9α-epoxyderivative underwent the C-8 attack, affording the benzopyran derivative.[23a]

In order to confirm the absolute configuration of natural corallidictyal D (**2**), enantiopure drimenyl phenol **19**, easily prepared from the commercial diterpene (-)-sclareol,[16] was utilized to obtain the spirodihydrobenzofuran compound **18**, which was finally transformed into corallidictyal D (**2**) (Scheme 6). Treatment of compund **18** with BuLi in THF at -78 ºC followed by the addition of DMF and further reaction for 2 h gave aldehyde **46** (72% after column chromatography). The Imakura method, which had been successfully utilized by us for the methylenedioxy group deprotection in our synthesis of liphagal (**3**),[7b] failed with aldehyde **46**. This purpose was achieved utilizing the Goodman method. Treatment of aldehyde **46** with $AlCl_3$ in dichloromethane at -40 ºC for 10 min and the subsequent refluxing of a methanolic solution of the crude product in the presence of catalytic conc. HCl led to corallidictyal D (**2**). The spectroscopic properties of synthetic corallidictyal D (**2**) were identical to those previously reported for the natural product; the optical rotation ($[\alpha]_D^{25}$ = - 21.8 (c 14.8, $CHCl_3$) had not been previously reported, because corallidictyal D was isolated together with its unresolvable 9-epimer (corallidictyal C) from their natural source. [1]



Scheme 6. Synthesis of corallidictyal D (**2**).

In summary, a very efficient procedure for achieving the spiroannulation of *o*-allyl phenols is reported. Treatment of these with catalytic NIS and PPh_3 affords the corresponding spirodihydrobenzofuran derivatives in high yield, with high stereoselectivity and complete regioselectivity. This spiroannulation process seems to be the most suitable procedure reported until now to achieve the great variety of spirodihydrobenzofuran derivatives, such as compounds **1-2** and **4-15**, which exhibit relevant biological activities. Utilizing this new methodology, and a Lewis acid catalysed cyclization of a β-ketoester enol phosphate, the first total synthesis of the protein kinase C inhibitor corallidictyal D (**2**) starting from α-ionone is reported.

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Keywords: natural products • terpenes • total synthesis • annulation • spiro compounds

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I_2-PPh_3 Mediated Spiroannulation of Unsaturated β-Ketoesters: First Enantiospecific Synthesis of Negundoin A

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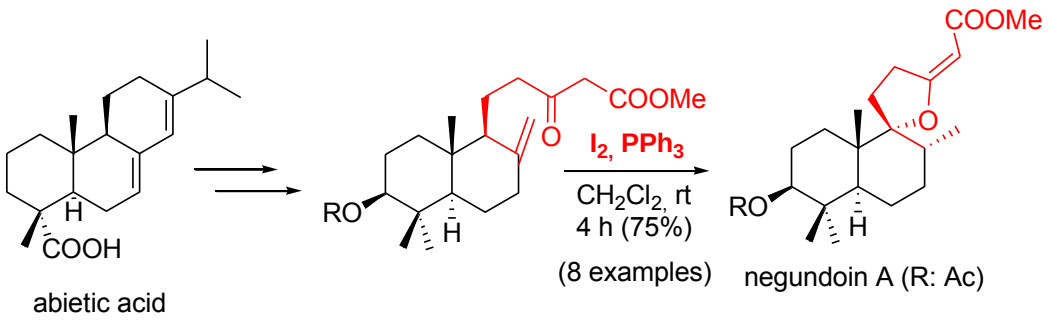
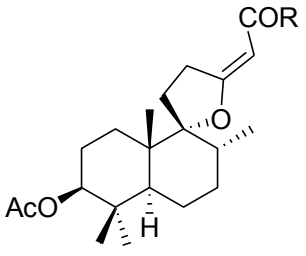


Unsaturated β-ketoesters undergo cyclization by reaction with the I_2-PPh_3 system, affording the corresponding spiroenol ether derivatives, with complete regio- and stereoselectivity. Utilizing this new methodology, the first enantiospecific synthesis of the anti-inflammatory diterpene negundoin A, starting from commercial abietic acid, and of a naturally occurring tripanocydal aldehyde is reported. A very efficient synthesis of a key intermediate in the preparation of 3-hydroxy terpenoids and related compounds is also described.

Introduction

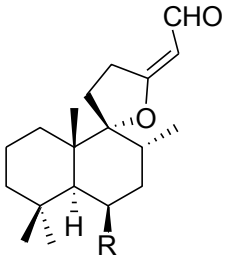
Recently, a serie of *nor*-diterpene aldehydes, carboxylic acids or esters, with relevant biological activities have been isolated from different species of genus *Vitex*, widely used in folk medicine in some Asian countries. These compounds have a characteristic tricyclic structure with a α,β-unsaturated aldehyde, acid or ester, containing a spiro enol ether group. Representative examples are negundoin C (**1**), a potent anti-inflammatory aldehyde isolated from *V. Negundo*, together with acid **2**, named negundoin B, and ester **3** (negundoin A),[1] and the tripanocydal aldehydes **4** and **5**, found in *V. trifolia*.[2]



1 R: H

2 R: OH

3 R: OMe



4 R: H

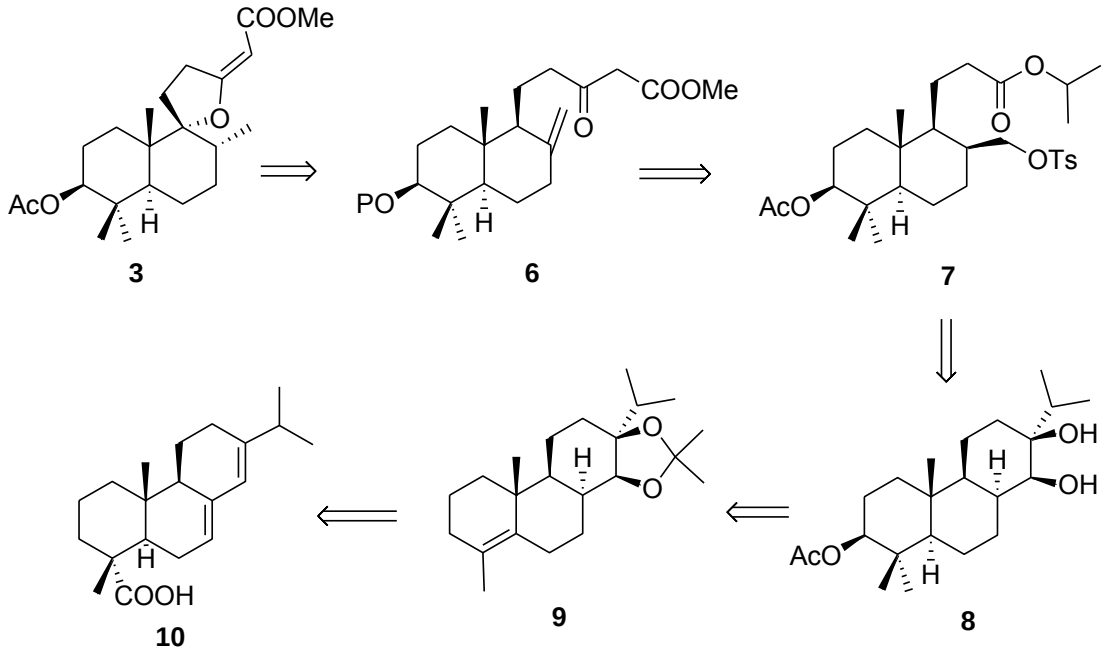
5 R: OAc

FIGURE 1. Negundoin A-C and related *nor*-diterpenes

Results and Discussion

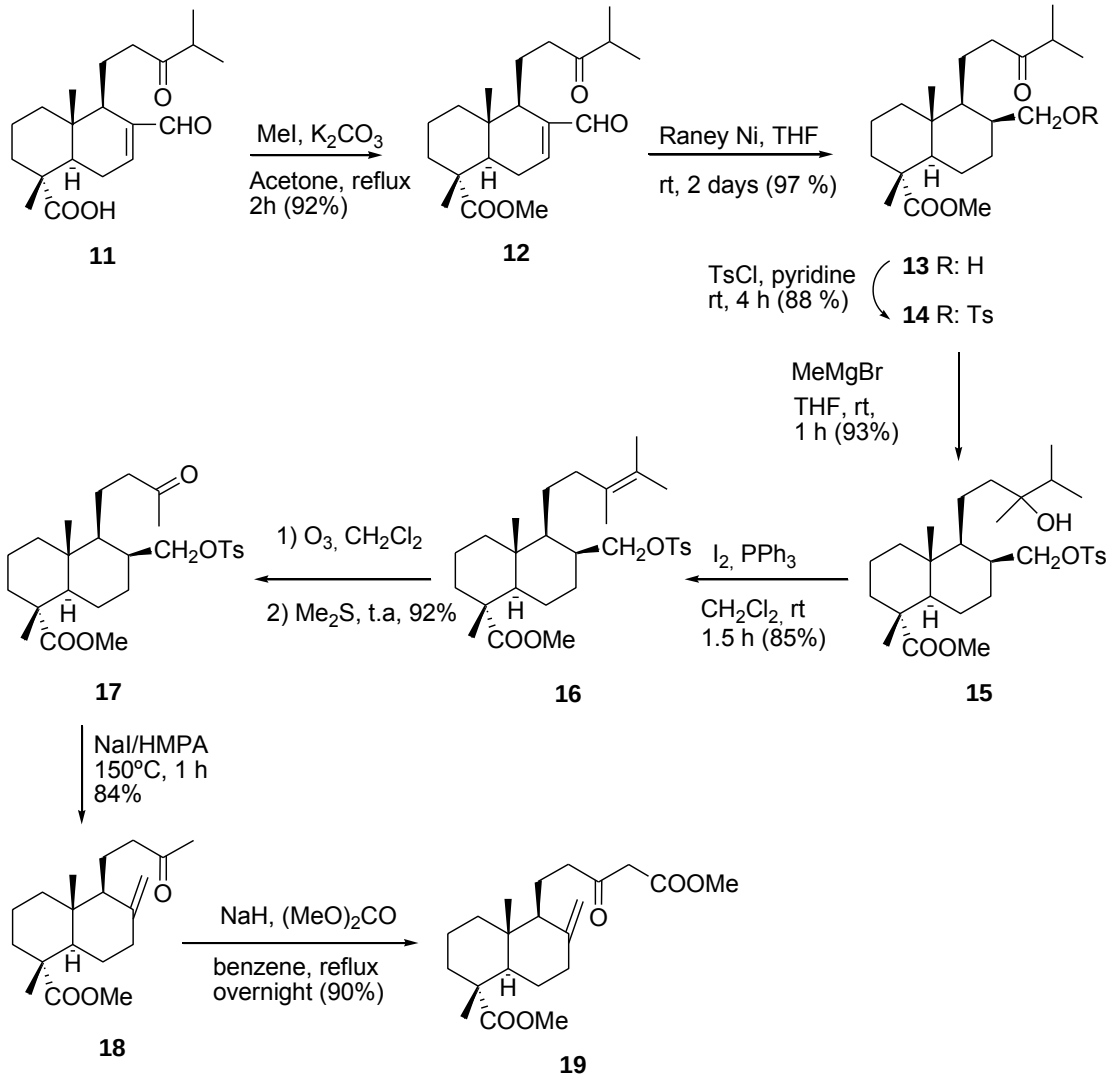
The unique tricyclic structural skeleton and the impressive biological activity of some of these compounds, such as negundoin C (**1**), which is among the most potent inhibitors on nitric oxide production by LPS-stimulated RAW 264.7 macrophages, with a IC_{50} value of 0.12 μM, attracted us to develop a synthetic strategy that could be used to access structural analogues in addition to the larger quantities of natural products required for further biological studies. Scheme 1 shows the synthetic strategy we planned to achieve this goal, starting from the very cheap commercial diterpene abietic acid (**10**). The spirocyclic enol ether framework of target compound will be formed by spiro annulation of the enol derived from β-ketoester **6**, easily obtainable from ester **7**. This will be obtained after the Baeyer-Villiger oxidation of isopropylketone resulting from the oxidative rupture of the appropriate 13,14-dihydroxyderivative. The oxigenated function on the C-3 of target compound will be introduced through allylic oxidation of tetrasubstituted alkene **9**, which results after removing the carboxylic group of the starting abietic acid (**10**).

SCHEME 1. Retrosynthesis of negundoin A (**3**)



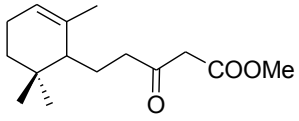
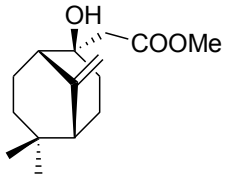
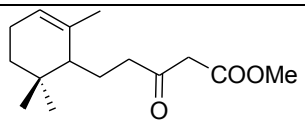
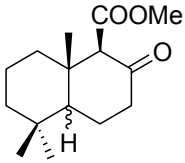
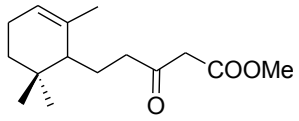
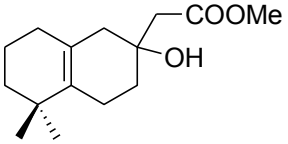
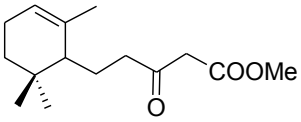
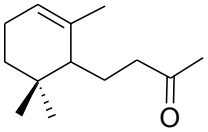
Before undertaking the construction of the oxygenated A ring of target compound, the elaboration of the β-ketoester moiety of the precursor of spiro enol ether framework was studied. Scheme 2 shows the transformation of dihydroxy ester **11**,[3] easily prepared from abietic acid (**10**) into ketoester **19**. The ketoaldehyde **12**, resulting from the oxidative cleavage of *cis* diol group, underwent chemoselective reduction to give ketoalcohol **13**, after treating with Raney nickel, utilizing a procedure developed in our laboratory.[4] The treatment of ketone **14** with methylmagnesium bromide gave tertiary alcohol **15**, which after treating with I_2 and PPh_3[5] gave alkene **16**. Ozonolysis of the later led to methylketone **17**, wich after refluxing with DBU in toluene was transformed into ketone **18**. Ketoester **19** was finally obtained by treating methylketone **18** with dimethyl carbonate in the presence of sodium hydride.

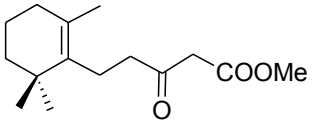
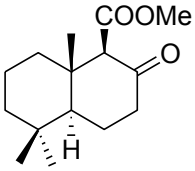
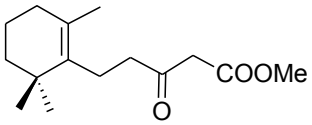
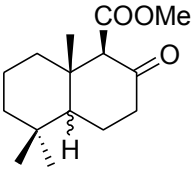
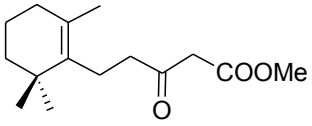
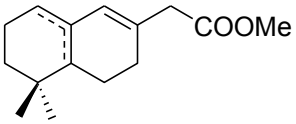
SCHEME 2. Synthesis of β-ketoester **19**.



Next, the construction of the spiro enol ether framework of target compound was investigated. This goal could be achieved after spiro annulation of the enol derived from the corresponding unsaturated β-ketoester under suitable reaction conditions. In order to explore this transformation, the behavior of unsaturated β-ketoesters **20** and **21** under different cyclization conditions was studied (Table 1).

Table 1. Treatment of β-ketoesters **20** and **21** with some cyclizig reagents.

Entry	β-Ketoester	Reaction conditions	Product
1	 **20**	BF_3, CH_2Cl_2, -30 ºC, 2.5 h	 **22** (42%)
2	 **20**	$SnCl_4$, CH_2Cl_2, rt, 45 min	 **23** (α-H) **24** (β-H) (1:1) (54%)[6]
3	 **20**	TsOH, benzene, 60 ºC, 12 h	 **25** (40%)
4	 **20**	$Pd(OAc)_2$, DMF, 100 ºC, 2 h	 **26** (82%)

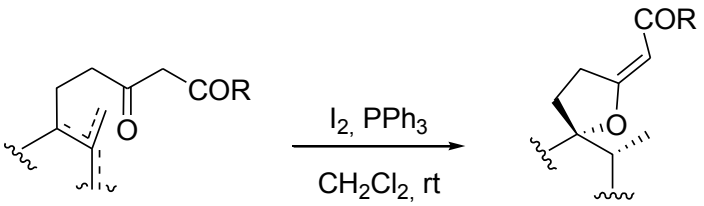
5	 **21**	$SnCl_4$, CH_2Cl_2, 30 ºC, 2 h	 **23** (71%)[8]
6	 **21**	I_2, CH_2Cl_2, rt, 7 h	 **23** (α-H) **24** (β-H) (1:1) (71%)
7	 **21**	Amberlyst A-15, CH_2Cl_2, reflux, 27 h	 **27a, 27b** (1:1) (55%)

The β-ketoester **20** after treatment with boron trifluoride etherate in dichloromethane at -30 ºC for 2.5 h gave the bicyclic hydroxyester **22**, with recovering the unaltered starting material in approximately 50%; a complex mixture resulted when the reaction time was prolongued or the temperature was increased. The treatment of compound **20** with $SnCl_4$ in dichloromethane at room temperature for 45 min afforded a 1:1 mixture of *trans*- and *cis*-fused bicyclic ketoesters, **23** and **24,** respectively.[6] When compound **20** was treated with p-toluenesulphonic acid, in benzene at room temperature, no reaction was observed after 12h; hydroxy ester **25** was obtained in moderate yield when the reaction was carried out at 60 ºC. The treatment of ketoester **20** with $Pd(OAc)_2$ in dimethylformamide at 100 ºC led to methylketone **26** together with small amounts of the corresponding α,β-unsaturated ketone;

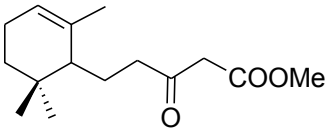
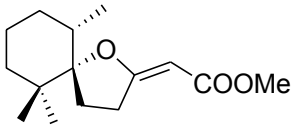
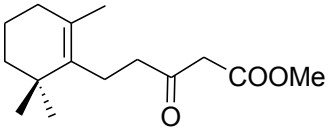
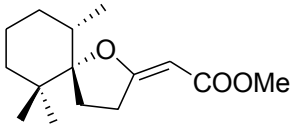
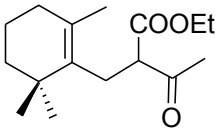
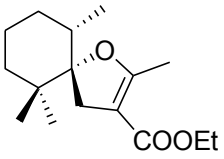
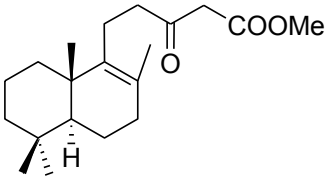
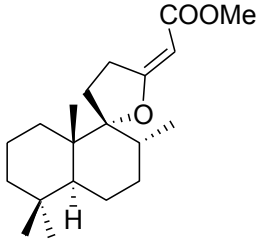
no reaction took place at room temperature, after 12h.[7] On the other hand, β-ketoester **21** was transformed into the bicyclic ketoester **23** by treating with $SnCl_4$ in dichloromethane at 30 ºC.[8] A mixture of diastereomeric ketoesters **23** and **24** resulted after treatment with iodine in dichloromethane at room temperature. Bicyclic regioisomer esters **27a-b** were obtained when compound **21** was treated with cationic resin in dichloromethane under reflux. Under the above acid conditions, ketoester **19** leds always to unresolvable mixtures of compounds.

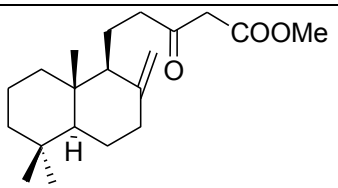
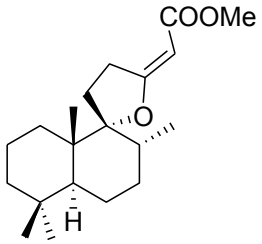
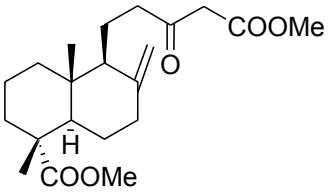
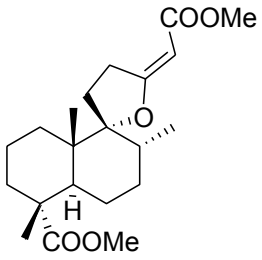
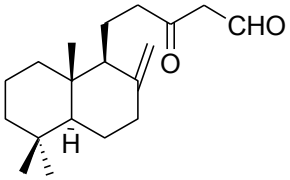
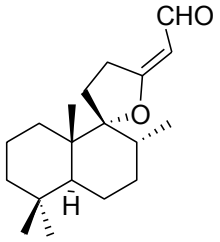
In the course of our research on the use of the I_2-PPh_3 system[5] we found that unsaturated β-ketoesters are efficiently transformed in the presence of this reagent into the corresponding spiro enol ethers. Thus, the β-ketoester **20** was converted with complete regio- and stereoselectivity into the spiro compound **32** by treating with this system in dichloromethane at room temperature for 12 h (Table 2). Ketoester **21** gave the same results under the above reaction conditions. Similarly, compound **19** was transformed in good yield into the spiro compound **35**. In order to optimize the reaction conditions and establish the scope of this reaction some other β-ketoesters were studied. As it can be seen, in all cases the corresponding spiro enol ethers were obtained with complete regio- and stereoselectivity. β-Ketoaldehydes show a similar behaviour; thus, compound **31** was transformed under the same reaction conditions into the spirane **4,** a tripanocydal aldehyde isolated from *V. trifolia*.[2] The optical rotation of synthetic aldehyde **4** ($[\alpha]_D$ +1.2; c 8.6, $CHCl_3$) was similar to that reported for the natural product.

Table 2. I_2-PPh_3 mediated spiroannulation of some β-ketoesters and β-ketoaldehydes.



R: H, OMe

Entry	β-Dicarbonyl compound	t	Product
1	 **20**	8 h	 **32** (58%)
2	 **21**	8h	 **32** (65%)
3	 **28**	5 h	 **33** (81%)
4	 **29**	5 h	 **34** (90%)

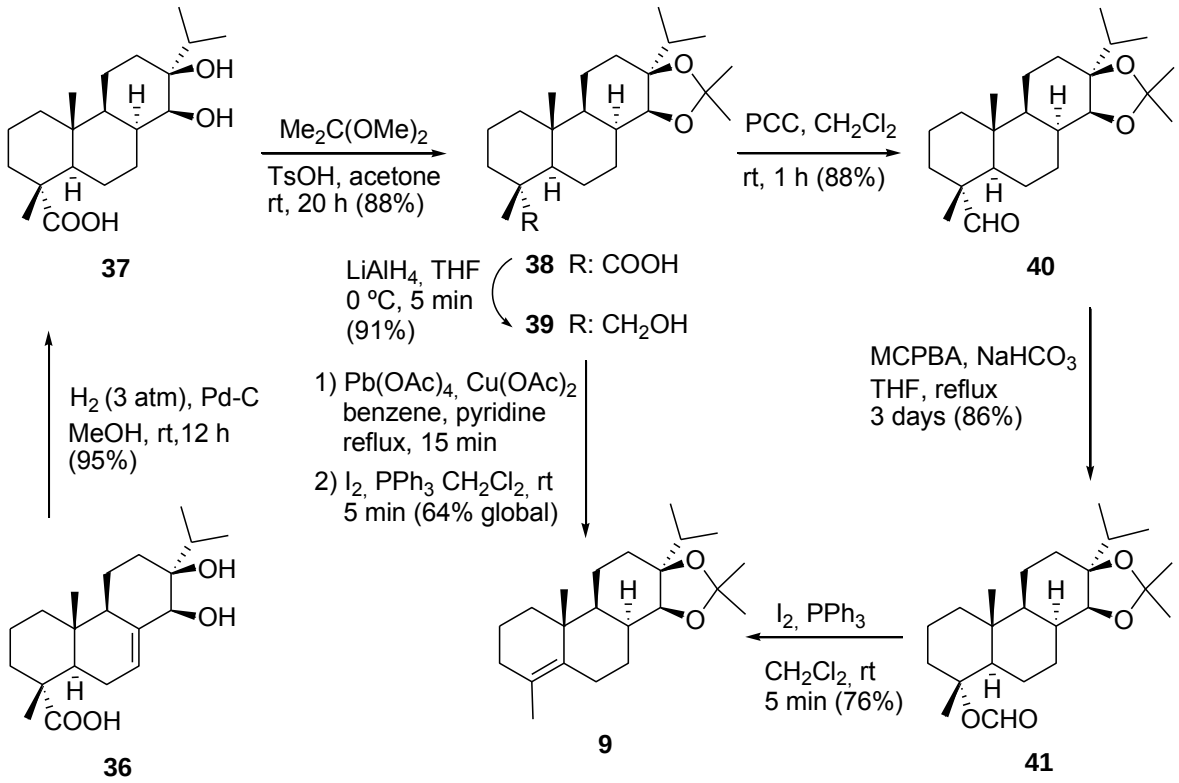
5	 **30**	5 h	 **34** (89%)
6	 **19**	5 h	 **35** (87%)
7	 **31**	5 h	 **4** (82%)

*Compounds **29**, **30** and **31** were synthesized from diterpene (-)-sclareol.[9]

Next, the construction of the oxygenated A ring was undertaken (Scheme 3). The proccess starts with the dihydroxy acid **36**, easily prepared from abietic acid (**10**).[3] After reducing the carbon-carbon double bond and protecting the diol group as isopropylidene derivative, the methyl ester group was converted into aldehyde, affording compound **40**,

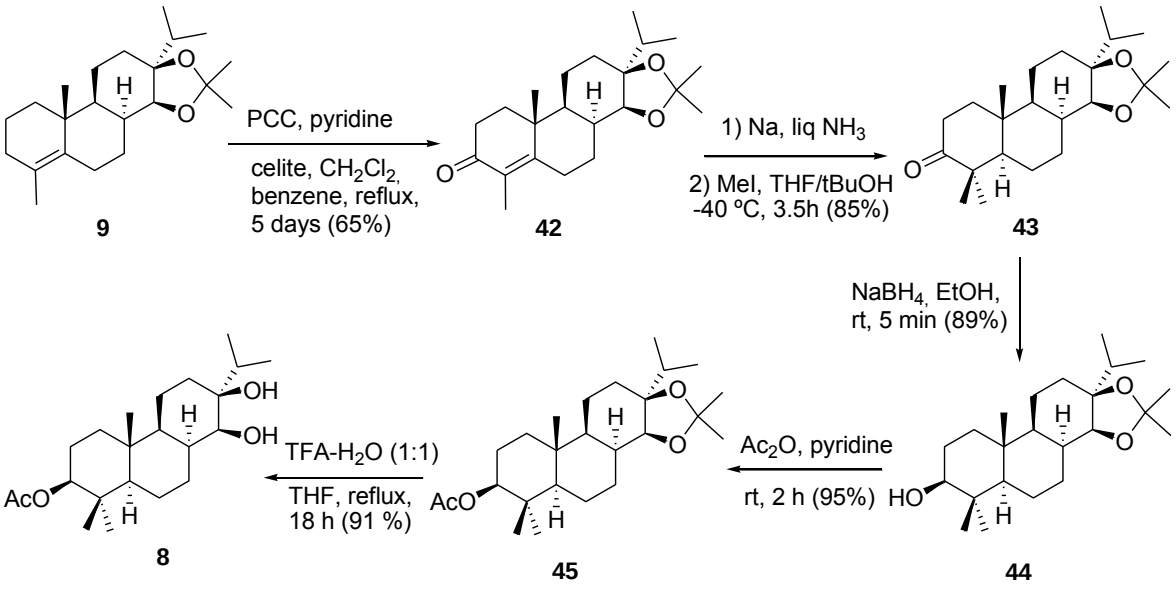
which was then converted into formate **41** by treating with *m*-chloroperbenzoic acid.[10] This was finally transformed into the tetrasubstituted alkene **9**, utilizing a methodolgy developed by our group.[5] An alternative and shorter proccess for converting acid **38** into alkene **9** has been developed. Oxidative decarboxylation of acid **38**, after treatment with $Pb(OAc)_4$ and $Cu(OAc)_2$ in benzene and pyridine under reflux, afforded a mixture of regioisomer alkenes and 4-acetoxy *nor*-abietane derivatives, which was directly converted into the tetrasubstituted alkene **9** by treating with I_2 and PPh_3 in dichloromethane at room temperature.

SCHEME 3. Synthesis of intermediate **9**.



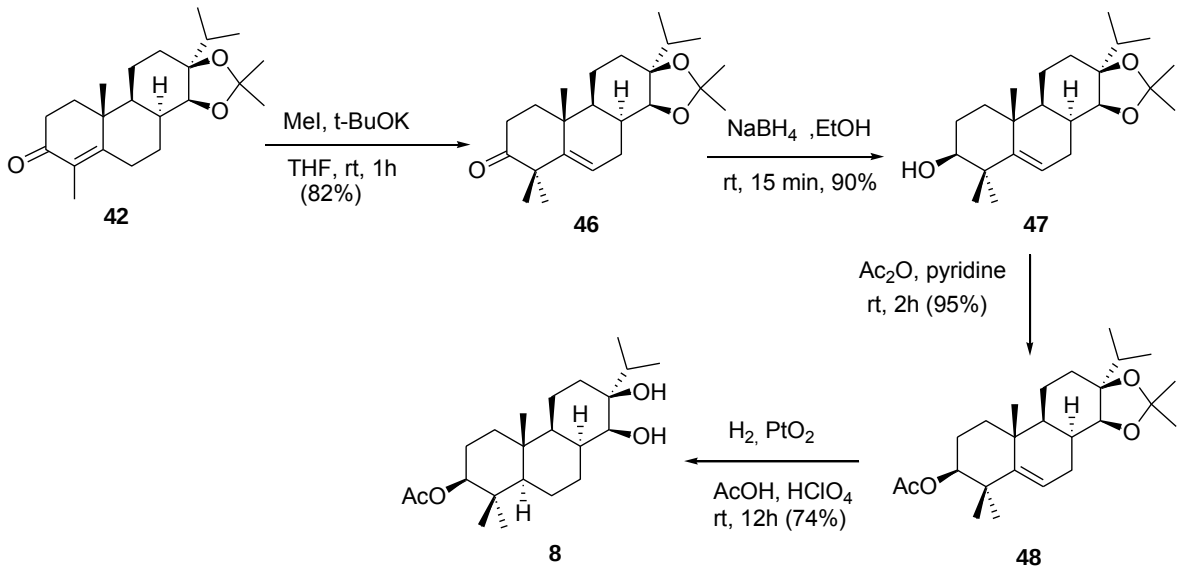
After this, the introduction of the oxygenated function on the A ring was tackled (Scheme 4). The oxidation of compound **9** with pyridinium chlorochromate gave α,β-enone **42**, which after successive treatment with Na in liq NH_3 and MeI led to ketone **43**, possessing the *gem*-dimethyl group of target compound. The reduction of later with sodium boronhydride and subsequent acetylation afforded compound **45**, which was hydrolyzed to give diol **8**.

SCHEME 4. Construction of the oxygenated A ring.



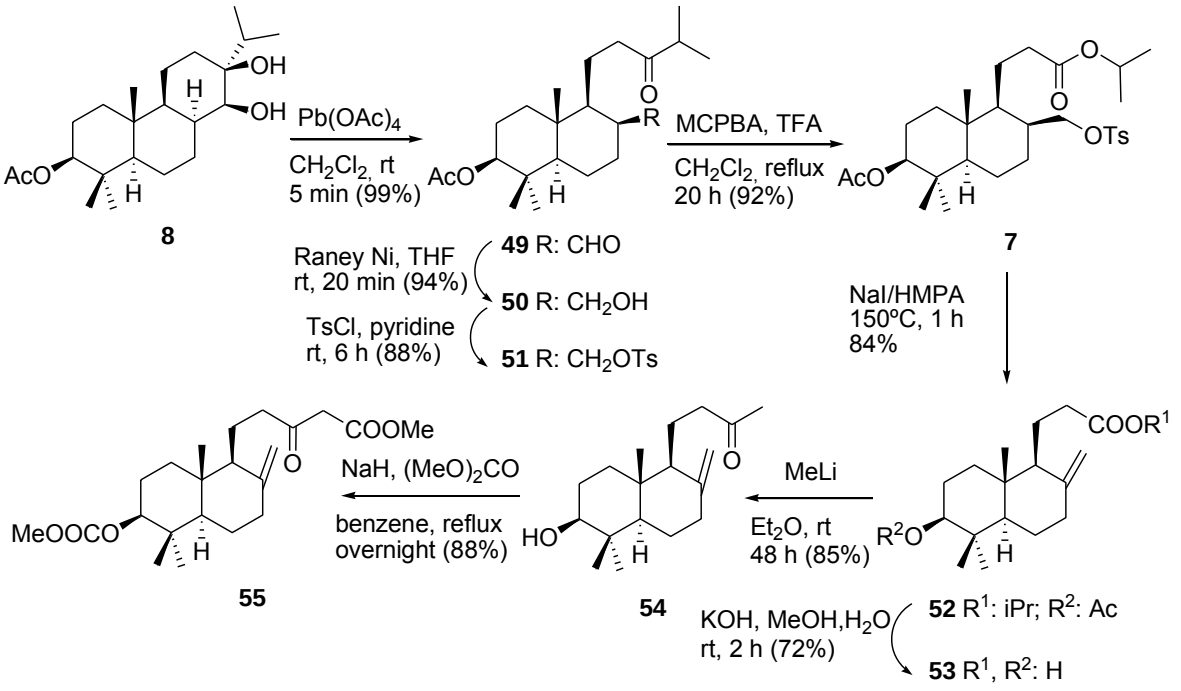
Ketone **42** was transformed into acetoxy diol **8** in an alternative way (Scheme 5). Treatment of of compound **42** with MeI in the presence of *t*-BuOK gave the unsaturated ketone **46**, which was transformed into the acetoxy derivative **48**, which after hydrogenation led directly to diol **8**.

SCHEME 5. Alternative synthesis of acetoxy diol **8**.



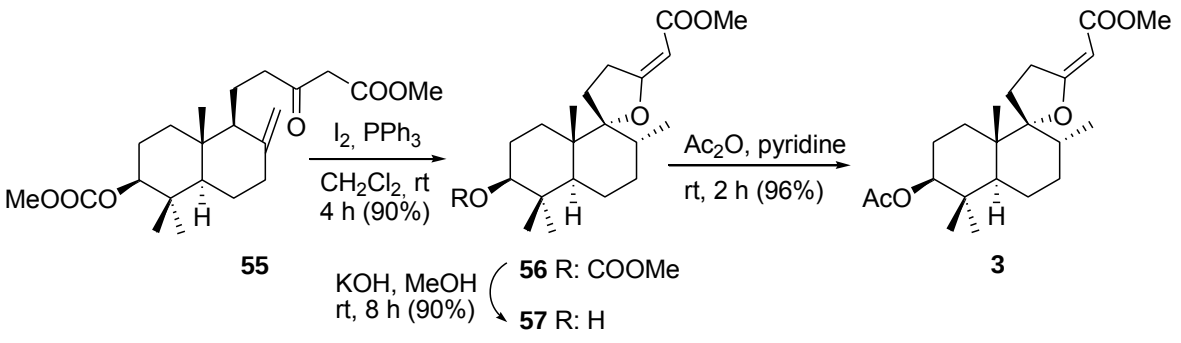
The β-ketoester **55**, precursor of compounds **1-3**, was synthesized starting from diol **8**, as it is shown in Scheme 6. The ketoaldehyde **49**, resulting from the oxidative cleavage of *cis* diol group, was transformed into ketoalcohol **50**, after reduction with Raney nickel. The treatment of ketone **51** with *m*-chloroperbenzoic acid led to ester **7**, which by refluxing with DBU in toluene gave the unsaturated ester **52**, which was further converted into acid **53**. The treatment of this with methyllithium gave ketone **54**, which was finally converted into ketoester **55**.

SCHEME 6. Synthesis of β-ketoester **55**.



Finally, β-ketoester **55** was transformed into negundoin A (**3**) (Scheme 7). Saponification of diester **56** under mild conditions gave hydroxy ester **57**, which was easily converted into negundoin A (**3**). This compound had the same spectroscopic properties as reported in the literature. The optical rotation ($[\alpha]_D$ +12.1; c 3.5, $CHCl_3$) (lit.:[1] +8.9; c 0.2, MeOH) confirms the absolute stereochemistry.

SCHEME 7. Synthesis of negundoin A (**3**).



In summary, the first enantiospecific synthesis of the anti-inflammatory *nor*-diterpene negundoin A (**3**), starting from commercial abietic acid (**10**), and of the tripanocydal aldehyde **4** is reported**.** The characteristic spiro enol ether framework of target compounds is constructed in the key step of synthetic sequence, which involves the spiroannulation of a α,β-unsaturated β-ketoester or β-ketoaldehyde mediated by I_2 and PPh_3. Moreover, ketoaldehyde **49**, a suitable intermediate for synthesizing 3-hydroxy terpenoids and related compounds, has been efficiently prepared starting from commercial abietic acid (**10**).

Acknowledgements

The authors thank the Spanish Ministry of Science and Innovation (Project CTQ2009-09932) and the Regional Government of Andalucia (Project P07-FQM-03101 and assistance for the FQM-348 group) for financial support. R. T. thanks the Spanish Ministry of Science and Innovation for the predoctoral grant provided.

Experimental Section

General procedure for the preparation of spiro enol ether derivatives

To a solution of triphenylphosphine (1 mmol) in dry CH_2Cl_2 (10 mL) was added iodine (1 mmol) and the mixture was stirred at room temperature for 5 min. Then, a solution of compounds **19**, **20**, **21**, **28**, **29**, **30**, **31, 55** (1 mmol) in dry CH_2Cl_2 (5 mL) was added and the resulting mixture was stirred at room temperature for the specified time, and the course of the reaction was monitored by TLC. When the starting material was consumed, the solvent was removed under vacuum and the crude product was directly purified by flash

chromatography on silica gel (ether/hexanes mixture) to give the desired spiro enol ether **35**, **32**, **32**, **33**, **34**, **34**, **4, 56** respectively.

Negundoin A (3):

To a solution of **57** (120 mg, 0.36 mmol) in CH_2Cl_2 (3 ml) at 0 ºC were added pyridine (0.5 mL) and acetic anhydride (0.2 mL), and the reaction mixture was stirred at room temperature for 1 h, at which time TLC showed no starting material. Then, the reaction mixture was cooled at 0 ºC, water (0.5 mL) was added to quench the reaction and the mixture was stirred for an additional 5 min. Then, it was diluted with ether (20 mL) and washed with water (5 mL), 2N HCl (3 x 5 mL), again water (5 mL), sat. aq. $NaHCO_3$ (5 mL) and brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (15 % ether/hexanes) to yield **3** (130 mg, 96%) as a colourless syrup. $[\alpha]_D^{25}$= +12.1 (c = 3.5 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 3H), 0.89 (s, 3H), 0.95 (s, 3H), 1.34 - 1.44 (m, 4H), 1.54 - 1.73 (m, 5H), 1.75 - 1.83 (m, 2H), 2.04 (s, 3H), 2.08 (m, 1H), 3.07 (m, 2H), 3.65 (s, 3H), 4.47 (dd, *J* = 11.7, 4.5 Hz, 1H), 5.29 (t, *J* = 1.8 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.5 (CH_3), 16.6 (CH_3), 16.8 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 23.3 (CH_2), 26.7 (CH_2), 28.0 (CH_3), 29.3 (CH_2), 31.0 (CH_2), 31.6 (CH_2), 36.5 (CH), 37.7 (C), 42.0 (C), 46.2 (CH), 50.5 (CH_3), 80.2 (CH), 87.3 (CH), 97.7 (C), 169.5 (C), 170.8 (C), 178.5 (C). IR (film): 1735, 1707, 1633, 1365, 1244, 1127, 1033, 794, 755 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{34}O_5Na$ ($M+Na^+$) 401.2304, found: 401.2299.

3-desacetoxynegundoin C (4):

(10% ether/hexanes) (82 %) yellow syrup.$[\alpha]_D^{25}$= + 1.2 (c = 8.6 $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.78 (d, *J* = 6.6 Hz, 3H), 0.82 (s, 3H), 0.89 (s, 3H), 0.94 (s, 3H), 1.05 - 1.19

(m, 2H), 1.29 - 1.40 (m, 4H), 1.42 - 1.66 (m, 5H), 1.80 - 1.89 (m, 2H), 2.17 (ddd, *J* = 13.4, 11.5, 7.8 Hz, 1H), 3.00 - 3.15 (m, 2H), 5.60 (d, *J* = 7.8 Hz, 1H), 9.55 (d, *J* = 7.8 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.7 (CH_3), 16.8 (CH_3), 18.2 (CH_2), 21.3 (CH_2), 21.8 (CH_3), 26.0 (CH_2), 30.1 (CH_2), 31.2 (CH_2), 31.3 (CH_2), 33.2 (CH_3), 33.3 (C), 36.6 (CH), 41.4 (CH_2), 42.5 (C), 46.8 (CH), 100.0 (CH), 100.6 (C), 182.6 (C), 190.3 (CH). IR (film): 1656, 1625, 1577, 1354, 1213, 1154, 877 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{30}O_2Na$ ($M+Na^+$) 313.2143, found: 313,2136.

Isopropyl-3-((1S,4aR,6S,8aR)-6-acetoxy-5,5,8a-trimethyl-2-(tosyloxymethyl)-decahydronaphthalen-1-yl)propanoate (7):

m-Chloroperoxybenzoic acid (MCPBA, 70%; 555 mg, 2.25 mmol), and trifluoroacetic acid (256 mg, 2.25 mmol) were added to a stirred solution of **51** (393 mg, 0.75 mmol) in CH_2Cl_2 (20 mL) and the reaction was stirred under reflux for 20 h, at which time TLC indicated no starting material remaining. The reaction was quenched with sat. aq Na_2SO_3 (5 mL) and stirred for an additional 15 min. Then, the organic solvent was removed under vacuum and ether (40 mL) was added. The organic phase was washed with sat. aq. $NaHCO_3$ (5 x 15 mL) and brine, dried over Na_2SO_4 and concentrated to give **7** (505 mg, 90%) as a colorless syrup. $[\alpha]_D^{25}$= - 4.5 (c = 10.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.71 (m, 1H), 0.79 (s, 3H), 0.81 - 0.91 (m, 2H), 0.83 (s, 6H), 1.03 - 1.38 (m, 3H), 1.22 (d, *J* = 6.3 Hz, 6H), 1.50 - 1.86 (m, 8H), 2.03 (s, 3H), 2.04 - 2.22 (m, 2H), 2.45 (s, 3H), 3.88 (dd, *J* = 9.6, 6.1 Hz, 1H), 4.07 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.44 (dd, *J* = 11.7, 4.5 Hz, 1H), 4.96 (h, *J* = 6.3 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.9 (CH_3), 16.5 (CH_3), 20.5 (CH_2), 21.2 (CH_3), 21.6 (CH_3), 21.8 (CH_3), 21.9 (CH_3), 23.5

(CH_2), 23.6 (CH_2), 28.0 (CH_3), 30.3 (CH_2), 35.8 (CH_2), 36.5 (CH_2), 37.7 (C), 37.9 (C), 39.1 (CH), 51.2 (CH), 53.8 (CH), 67.6 (CH), 73.3 (CH_2), 80.6 (CH), 127.9 (CH), 127.9 (CH), 129.8 (CH), 129.8 (CH), 133.1 (C), 144.7 (C), 170.8 (C), 172.6 (C). IR (film): 1731, 1364, 1246, 1177, 1109, 954, 816, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{44}O_7SNa$ ($M+Na^+$) 559.2705, found: 559.2698.

(2S,4aR,4bS,7S,8S,10aR)-7,8-dihydroxy-7-isopropyl-1,1,4a-trimethyl-tetradecahydrophenanthren-2-yl acetate (8):

To a solution of **45** (127 mg, 0.31 mmol) in THF (8 mL) were added trifluoroacetic acid (1mL, 13.5 mmol) and water (1 mL) and the reaction mixture was stirred under reflux for 18 h, at which time TLC showed no starting material. Then, the solvent was removed under vacuum and ether – water (40 : 10 mL) was added. The phases were shaken, separated and the organic phase was washed with brine (3 x 10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (10 % ether/hexanes) to yield **8** (104 mg, 91%) as a colorless syrup. $[\alpha]_D^{25}$= - 15.5 (c = 14.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.66 (ddd, *J* = 11.7, 11.7, 3.4 Hz, 1H), 0.76 - 1.04 (m, 2H), 0.86 (s, 3H), 0.87 (s, 3H), 0.87 (d, *J* = 6.9 Hz, 3H) 0.88 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 1.10 (ddd, *J* = 13.6, 13.6, 4.0 Hz, 1H), 1.17 (ddd, *J* = 13.4, 4.1 Hz, 1H), 1.24 - 1.47 (m, 2H), 1.48 - 1.72 (m, 8H), 1.75 (ddd, *J* = 13.2, 3.5, 3.5 Hz, 1H), 2.04 (s, 3H), 2.05 (m, 1H), 2.22 (ddd, *J* = 12.7, 7.0, 3.7 Hz, 1H), 3.16 (d, *J* = 9.6 Hz, 1H), 4.48 (dd, *J* = 11.7, 4.6 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 16.3 (CH_3), 16.7 (CH_3), 17.7 (CH_3), 18.8 (CH_2), 20.9 (CH_2), 21.3 (CH_3), 23.9 (CH_2), 27.1 (CH_2), 28.2 (CH_3), 31.4 (CH_2), 33.5 (CH), 36.4 (C), 37.0 (CH_2), 37.8 (C), 38.6 (CH), 53.1 (CH), 54.3 (CH), 75.0 (CH), 77.1 (C), 81.0 (CH), 171.0 (C). IR (film): 3475, 1731, 1457,

1368, 1247, 1031, 977 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{38}O_4Na$ ($M+Na^+$) 389.2668, found: 389.2670.

Synthesis of 8 from 48:

To a solution of **48** (650 mg, 1.61 mmol) in dry AcOH (50 mL) was added PtO_2 (80 mg, 0.35 mmol) and $HClO_4$ (1.5 mL, 22.9 mmol) and the mixture was stirred at room temperature under hydrogen atmosphere (3 atm) for 12 h. Then, the mixture was filtered through a silica gel pad and washed with ether (60 mL). The filtrate was washed with water (5 x 15 mL), $NaHCO_3$ (5 x 15 mL), brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (25% ether/hexanes) to yield **8** (418 mg, 71%) as a colourless syrup.

(3aS,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-

3a,3b,4,5,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxole (9):

To a solution of triphenylphosphine (1.61 g, 6.16 mmol) in dry CH_2Cl_2 (30 mL) was added iodine (1.56 g, 6.16 mmol) and the mixture was stirred at room temperature for 5 min. Then, a solution of **41** (2.12 g, 5.60 mmol) in dry CH_2Cl_2 (20 mL) was added and the resulting mixture was stirred at room temperature for 40 min. Then, aq. 5% $NaHSO_3$ (5 mL) was added and the mixture was stirred for 5 min. The solvent was removed under vacuum, and the crude product was diluted with ether – water (90 – 30 mL).The phases were shaken and separated and the organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (5% ether/hexanes) to

give **9** (1.34 g, 72 %) as a colorless syrup. $[\alpha]_D^{25}$= +12.5 (c = 29.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.72 (m, 1H), 0.86 - 1.00 (m, 2H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.96 (s, 3H), 1.19 - 1.30 (m, 2H), 1.44 (s, 3H), 1.45 - 1.60 (m, 2H), 1.52 (s, 3H), 1.61 (s, 3H), 1.68 - 1.78 (m, 2H), 1.80 - 1.90 (m, 4H), 1.95 (m, 1H), 1.99 (h, *J* = 6.9 Hz, 1H), 2.12 (ddd, *J* = 12.6, 6.9, 3.7 Hz, 1H), 2.56 (ddd, *J* = 14.2, 3.4, 3.4 Hz, 1H), 3.55 (d, *J* = 8.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.9 (CH_3), 19.2 (CH_2), 19.3 (CH_3), 19.7 (CH_3), 19.9 (CH_3), 20.7 (CH_2), 25.0 (CH_2), 26.0 (CH_2), 29.7 (CH_3), 30.3 (CH_3), 33.0 (CH_2), 33.2 (CH_2), 33.8 (CH), 37.5 (C), 37.9 (CH_2), 41.0 (CH), 49.3 (CH), 84.9 (CH), 85.6 (C), 108.2 (C), 124.4 (C), 136.0 (C). IR (film): 1457, 1377, 1367, 1236, 1038, 773 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{36}O_2Na$ ($M+Na^+$) 355.2613, found: 355.2621.

Synthesis of 9 from 38:

To a solution of **38** (840 mg, 2.22 mmol) in benzene (25 mL) were added lead (IV) acetate (1.28 mg, 2.89 mmol), cooper (II) acetate (22 mg, 0.11 mmol) and pyridine (668 mg, 8.44 mmol), and the reaction mixture was stirred under reflux for 15 min, at which time TLC showed no **38**. Then, it was diluted with ether (40 mL) and washed with 2N HCl (3 x 10 mL), water (10 mL), sat. aq. $NaHCO_3$ (3 x 10 mL), brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product (837 mg) which was used in the next step without purification.

To a stirred solution of this crude (837 mg) in dry CH_2Cl_2 (15 mL), was added a solution of triphenylphosphine (755 mg, 2.88 mmol) and iodine (731 mg, 2.88 mmol) in dry CH_2Cl_2 (30 mL) and the resulting mixture was stirred at room temperature for 2 h. Following the same work-up used for **9** from **41**, a crude product was obtained which was directly purified

by flash chromatography on silica gel (5% ether/hexanes) to give **9** (472 mg, 64 %) as a colorless syrup.

(1R,4aR,5R,8aR)-6-formyl-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylic acid (11):

To a solution of **10** (1.30 g, 4.30 mmol) in strictly deoxygenated *t*-BuOH (30 mL) were added trimethylamine *N*-oxide dihydrate (0.62 g, 5.16 mmol) and pyridine (0.1 mL) under argon atmosphere. The solution was stirred for 10 min at room temperature and 2 % aq. OsO_4 (2 mL, 0.2%, 0.15 mmol) was added and the reaction mixture was further stirred under argon atmosphere at reflux for 24 h, at which time TLC indicated no remaining starting material. Then $NaIO_4$ (1.20 g, 5.61 mmol) was added, and the mixture was stirred for 1 h at room temperature. After filtering and removing the solvent, the crude was directly purified by flash chromatography on silica gel (20 % ether/hexanes) to yield pure **11** (1.18 g, 82%) as a colorless syrup.[22]

1R,4aR,5R,8aR)-methyl-6-formyl-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (12):

Potassium carbonate (538 mg, 3.89 mmol) and methyl iodide were added to a stirred solution of **11** (1 g, 2.99 mmol) in acetone (30 mL) and the reaction mixture was stirred at reflux for 2h, at which time TLC showed no starting material. The mixture was concentrated in vacuo to give a crude product, which was diluted with ether – water (50 – 20 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (10%

ether/hexanes) affording pure **12** (896 mg, 86%) as colorless syrup. $[\alpha]_D^{25}$= + 9.0 (c = 12.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.83 (s, 3H), 0.88 (m, 1H), 0.83 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 1H), 1.26 (s, 3H), 1.47 - 1.77 (m, 6H), 1.88 (m, 1H), 1.93 - 2.10 (m, 4H), 2.29 (m, 1H), 2.43 (ddd, *J* = 17.0, 10.6, 5.7 Hz, 1H), 2.62 (h, *J* = 6.9 Hz, 1H), 3.11 (ddd, *J* = 17.1, 10.9, 4.7 Hz, 1H), 3.65 (s, 3H), 6.75 (br s, 1H), 9.36 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.0 (CH_3), 16.8 (CH_3), 17.4 (CH_2), 18.0 (CH_3), 18.1 (CH_3), 20.5 (CH_2), 26.5 (CH_2), 36.1 (C), 36.8 (CH_2), 37.5 (CH_2), 40.4 (CH), 42.2 (CH_2), 43.9 (CH), 45.9 (C), 49.6 (CH), 51.8 (CH_3), 144.0 (C), 152.0 (CH), 178.2 (C), 194.5 (CH), 214.9 (C). IR (film): 1724, 1688, 1461, 1245, 1187, 1144, 1008, 727, 671 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{32}O_4Na$ ($M+Na^+$) 371.2198, found: 371.2206.

(1R,4aR,5S,6S,8aR)-methyl-6-(hydroxymethyl)-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-decahydronaphthalene-1-carboxylate (13):

To a solution of **12** (1.00 g, 2.87 mmol) in THF (20 mL) was added 50% aqueous solution of Raney Nickel (4 mL) and the mixture was stirred at room temperature for 20 min, at which time TLC showed no **12**. Then, the reaction mixture was filtered through a silica gel – Na_2SO_4 (15 : 3 g), washed with acetone (20 mL) and concentrated to give pure **13** (0.91 g, 90%) as colorless syrup. $[\alpha]_D^{25}$= + 33.8 (c = 71.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.73 (s, 3H), 0.93 - 1.05 (m, 2H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.13 (s, 3H), 1.29 (m, 1H), 1.39 - 1.62 (m, 7H), 1.67 - 1.85 (m, 5H), 1.96 (m, 1H), 2.40 (ddd, *J* = 17.1, 9.1, 6.1 Hz, 1H), 2.53 (ddd, *J* = 15.2, 10.0, 6.1 Hz, 1H), 2.59 (h, *J* = 6.9 Hz, 1H), 3.54 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.64 (s, 3H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.9 (CH_3), 16.4 (CH_3), 17.8 (CH_2), 18.3 (CH_3), 18.4 (CH_3), 19.2 (CH_2), 20.6 (CH_2), 28.8 (CH_2), 36.8 (CH_2), 37.6 (C), 38.2 (CH_2), 38.9 (CH_2), 39.7 (CH), 41.0 (CH), 47.7 (C), 50.8 (CH), 51.9

(CH_3), 52.7 (CH), 61.3 (CH_2), 179.3 (C), 215.1 (C). IR (film): 3472, 1712, 1459, 1386, 1248, 1141, 1023, 752 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{36}O_4Na$ ($M+Na^+$) 375.2511, found: 375.2504.

(1R,4aR,5S,6S,8aR)-methyl-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-6-(tosyloxymethyl)-decahydronaphthalene-1-carboxylate (14):

To a solution of **13** (1.00 g, 2.84 mmol) in pyridine (15 ml) was added *p*- toluenesulfonyl chloride (0.59 g, 3.12 mmol) and the reaction mixture was stirred at room temperature for 6 h, at which time TLC showed no starting material. Then, it was diluted with ether (50 mL) and washed with 2N HCl (6 x 20 mL), brine and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (15 % ether/hexanes) to yield **14** (1.26 g, 88%) as a colorless syrup. $[\alpha]_D^{25}$= + 20.1 (c = 55.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.64 (s, 3H), 0.85 - 1.02 (m, 2H), 1.04 - 1.44 (m, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 3H), 1.46 - 1.59 (m, 4H), 1.62 - 1.73 (m, 3H), 1.73 - 1.84 (m, 2H), 2.05 (m, 1H), 2.27 (m, 1H), 2.44 (s, 3H), 2.47 (m, 1H), 2.54 (h, *J* = 6.9 Hz, 1H), 3.62 (s, 3H), 3.94 - 4.05 (m, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 16.0 (CH_3), 16.3 (CH_3), 17.7 (CH_2), 18.2 (CH_3), 18.3 (CH_3), 18.9 (CH_2), 20.1 (CH_2), 21.6 (CH_3), 28.3 (CH_2), 35.7 (CH), 36.7 (CH_2), 37.3 (C), 37.9 (CH_2), 38.0 (CH_2), 40.9 (CH), 47.5 (C), 50.4 (CH), 51.86 (CH), 51.90 (CH_3), 69.7 (CH_2), 127.8 (CH), 127.8 (CH), 129.8 (CH), 129.8 (CH), 133.1 (C), 144.8 (C), 179.0 (C), 214.4 (C). IR (film): 1723, 1459, 1362, 1249, 1177,815, 945, 555 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{28}H_{42}O_6SNa$ ($M+Na^+$) 529.2600, found: 529.2612.

(1R,4aR,5S,6S,8aR)-methyl-5-(3-hydroxy-3,4-dimethylpentyl)-1,4a-dimethyl-6-(tosyloxymethyl)-decahydronaphthalene-1-carboxylate (15)

A 1.4 M solution of methylmagnesium bromide in THF (11 mL, 15.39 mmol) was added to a stirred solution of **14** (6 g, 11.84 mmol) in dry THF (30 mL) at 0 °C, under argon atmosphere, and the mixture was warmed to room temperature over night, at which time TLC showed no compound **14**. Then, water (5 mL) was slowly added at 0 °C to quench the reaction, and the solvent was removed under vacuum. The crude product was diluted with ether – water (80 – 25 mL) and the phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (20% ether/hexanes) to give pure **15** (5.01 g, 81%) as a mixture of diastereoisomers. $[\alpha]_D^{25}$= + 23.2 (c = 35.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.66 (s, 6H), 0.82 (d, *J* = 6.1 Hz, 3H), 0.83 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.85 - 0.98 (m, 4H), 0.99 (s, 3H), 1.01 (s, 3H), 1.08 (s, 6H), 1.14 - 1.31 (m, 10H), 1.35 - 1.45 (m, 4H), 1.45 - 1.58 (m, 6H), 1.58 - 1.74 (m, 10H), 1.82 (m, 2H), 2.13 (m, 2H), 2.44 (s, 6H), 3.63 (s, 6H), 3.97 (ddd, *J* = 10.1, 10.1, 6.0 Hz, 2H), 4.08 (dd, *J* = 10.4, 10.4 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 4H), 7.77 (d, *J* = 8.0 Hz, 4H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 16.1 (CH_3), 16.1 (CH_3), 16.3 (CH_3), 16.3 (CH_3), 16.9 (CH_3), 16.9 (CH_3), 17.5 (CH_3), 17.6 (CH_3), 17.7 (CH_2), 17.7 (CH_2), 18.1 (CH_2), 18.2 (CH_2), 20.2 (CH_2), 20.2 (CH_2), 21.6 (CH_3), 21.6 (CH_3), 22.3 (CH_3), 23.0 (CH_3), 28.3 (CH_2), 28.3 (CH_2), 35.6 (CH), 35.7 (CH), 36.5 (CH), 36.7 (CH_2), 36.7 (CH_2), 37.1 (CH), 37.4 (C), 37.4 (C), 37.8 (CH_2), 37.8 (CH_2), 38.0 (CH_2), 38.0 (CH_2), 47.6 (C),

47.6 (C), 50.5 (CH), 50.5 (CH), 51.9 (CH_3), 51.9 (CH_3), 53.3 (CH), 53.3 (CH), 69.9 (CH_2), 70.0 (CH_2), 74.5 (C), 74.6 (C), 127.8 (CH), 127.8 (CH), 127.8 (CH), 127.8 (CH), 129.8 (CH), 129.8 (CH), 129.8 (CH), 129.8 (CH), 129.8 (CH), 133.2 (C), 133.2 (C), 144.7 (C), 144.7 (C), 179.0 (C), 179.0 (C). IR (film): 3544, 1723, 1456, 1361, 1250, 1176, 944, 756, 670, 555 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{46}O_6SNa$ ($M+Na^+$) 545.2913, found: 545.2908.

(1R,4aR,5S,6S,8aR)-methyl-5-(3,4-dimethylpent-3-enyl)-1,4a-dimethyl-6-(tosyloxymethyl)-decahydronaphthalene-1-carboxylate (16):

To a solution of triphenylphosphine (796 mg, 3.03 mmol) in dry CH_2Cl_2 (25 mL) was added successively iodine (769 mg, 3.03 mmol). The mixture was stirred at room temperature for 5 min and a solution of **15** (1.22 g, 2.33 mmol) in dry CH_2Cl_2 (10 mL) was added. The resulting mixture was stirred at room temperature for 1 h, at this time TLC showed no **15**. Following the same work-up used for **9** from **38**, a crude product was obtained, which was directly purified by flash chromatography on silica gel (5% ether/hexanes) to give **16** (931 mg, 79 %) as a colorless syrup. $[\alpha]_D^{25}$= + 21.3 (c = 38.6 $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.65 (s, 3H), 0.83 - 1.00 (m, 2H), 1.08 (s, 3H), 1.10 - 2.00 (m, 14H), 1.53 (s, 3H), 1.55 (s, 3H), 1.61 (s, 3H), 2.11 (br s, 1H), 2.44 (s, 3H), 3.63 (m, 3H), 3.97 - 4.10 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 16.2 (CH_3), 16.3 (CH_3), 17.7 (CH_2), 18.3 (CH_3), 20.0 (CH_3), 20.2 (CH_2), 20.5 (CH_3), 21.6 (CH_3), 23.4 (CH_2), 28.4 (CH_2), 32.8 (CH_2), 35.6 (CH), 36.8 (CH_2), 37.3 (C), 38.0 (CH_2), 47.6 (C), 50.6 (CH), 51.8 (CH_3), 52.8 (CH), 69.8 (CH_2), 124.2 (C), 127.4 (C), 127.8 (CH), 127.8 (CH), 129.8 (CH), 129.8 (CH), 133.2 (C), 144.6 (C), 179.0 (C). IR (film): 1725, 1454, 1364, 1248, 1177, 946, 813, 758, 670, 555 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{44}O_5SNa$ ($M+Na^+$) 527.2807, found: 527.2815.

(1R,4aR,5S,6S,8aR)-methyl-1,4a-dimethyl-5-(3-oxobutyl)-6-(tosyloxymethyl)-decahydronaphthalene-1-carboxylate (17):

A stirred solution of **16** (527 mg, 1.04 mmol) in CH_2Cl_2 – MeOH (45 : 15 mL) was slowly bubbled with an O_3/O_2 mixture at -78 ºC, and the course of the reaction was monitored by TLC. When the starting material was consumed (10 min), the solution was flushed with argon, and methyl sulfide (5 mL) was added. The mixture was further stirred at room temperature under argon atmosphere for 6 h and the solvent was removed. Flash chromatography on silica gel (20 % ether/hexanes) gave **13** (430 mg, 86%) as a colorless syrup. $[\alpha]_D^{25}$= + 30.8 (c = 21.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.65 (s, 3H), 0.85 - 1.00 (m, 2H), 1.08 (s, 3H), 1.18 (ddd, *J* = 26.4, 13.6, 3.2 Hz, 1H), 1.23 - 1.34 (m, 2H), 1.39 (m, 1H), 1.45 - 1.57 (m, 3H), 1.62 - 1.72 (m, 3H), 1.72 - 1.84 (m, 2H), 2.03 (m, 1H), 2.10 (s, 3H), 2.24 (m, 1H), 2.41 (m, 1H), 2.45 (s, 3H), 3.63 (s, 3H), 3.93 - 4.05 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 16.0 (CH_3), 16.3 (CH_3), 17.7 (CH_2), 19.0 (CH_2), 20.2 (CH_2), 21.6 (CH_3), 28.3 (CH_2), 30.0 (CH_3), 35.7 (CH), 36.7 (CH_2), 37.3 (C), 38.0 (CH_2), 41.5 (CH_2), 47.5 (C), 50.4 (CH), 51.9 (CH_3), 51.9 (CH), 69.6 (CH_2), 127.8 (CH), 127.8 (CH), 130.0 (CH), 130.0 (CH), 133.1 (C), 144.8 (C), 179.0 (C), 208.4 (C). IR (film): 1720, 1453, 1360, 1250, 1176, 950, 755, 669, 555 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{26}H_{38}O_6SNa$ ($M+Na^+$) 501.2287, found: 501,2271.

(1R,4aR,5S,8aR)-methyl-1,4a-dimethyl-6-methylene-5-(3-oxobutyl)-decahydronaphthalene-1-carboxylate (18):

To a solution of **17** (367 mg, 0.77 mmol) in hexamethylphosphoramida (HMPA) (5 mL) was added NaI (138 mg, 0.92 mmol) and the reaction mixture was stirred at 150 ºC for 1 h, at which time TLC showed no starting material. Then, ether (40 mL) was added and the organic phase was washed with brine (10 x 10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (10 % ether/hexanes) to yield **18** (202 mg, 86%) as a colorless syrup. $[\alpha]_D^{25}$= + 50.7 (c = 22.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.70 (s, 3H), 1.13 (s, 3H), 1.14 - 1.23 (m, 2H), 1.43 (dq, *J* = 12.9, 4.4 Hz, 1H), 1.49 - 1.62 (m, 4H), 1.65 (br d, *J* = 10.3 Hz, 1H), 1.73 (m, 1H), 1.77 - 1.88 (m, 2H), 1.93 (dd, *J* = 12.6, 2.7 Hz, 1H), 1.99 (ddd, *J* = 13.0, 13.0, 4.8 Hz, 1H), 2.10 (s, 3H), 2.26 - 2.35 (m, 2H), 2.57 (ddd, *J* = 17.7, 9.1, 4.6 Hz, 1H), 3.64 (s, 3H), 4.44 (s, 1H), 4.82 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.5 (CH_3), 16.5 (CH_3), 17.3 (CH_2), 18.4 (CH_2), 26.8 (CH_2), 30.0 (CH_3), 37.0 (CH_2), 37.8 (CH_2), 37.9 (CH_2), 39.1 (C), 42.7 (CH_2), 47.7 (C), 49.8 (CH), 51.8 (CH_3), 56.1 (CH), 106.9 (CH_2), 147.6 (C), 179.2 (C), 209.2 (C). IR (film): 1724, 1446, 1360, 1245, 1172, 983, 892 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{30}O_3Na$ ($M+Na^+$) 329.2093, found: 329.2102.

(1R,4aR,5S,8aR)-methyl-5-(5-methoxy-3,5-dioxopentyl)-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylate (19):

NaH (60% dispersion in mineral oil) (130 mg, 3.25 mmol) and dimethylcarbonate (1.17 g, 13 mmol) were added to a stirred solution of **18** (200 mg, 0.65 mmol) in dry benzene (20 mL) and the mixture was stirred at reflux under argon atmosphere overnight, at which time TLC showed no remaining starting material. Then, the reaction was quenched with water (0.2 mL) at 0 °C and ether –water (40 : 15 mL) was added. The layers were shaken and

separated and the organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (15% ether/hexanes) to give pure **19** (214 mg, 90%) as a colorless syrup. $[\alpha]_D^{25}$= +27.9 (c = 10.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.70 (s, 3H), 1.13 (s, 3H), 1.20 (m, 2H), 1.43 (ddd, *J* = 25.8, 12.9, 4.4 Hz, 1H), 1.49 - 1.78 (m, 4H), 1.62 - 1.77 (m, 2H), 1.80 (br d, *J* = 12.4 Hz, 1H), 1.89 (m, 1H), 1.93 (dd, *J* = 12.6, 2.7 Hz, 1H), 1.99 (ddd, *J* = 13.2, 13.2, 5.3 Hz, 1H), 2.32 (ddd, *J* = 12.7, 4.2, 2.2 Hz, 1H), 2.43 (ddd, *J* = 18.5, 7.5, 7.5 Hz, 1H), 2.68 (ddd, *J* = 18.2, 8.7, 4.7 Hz, 1H), 3.41 (s, 2H), 3.65 (s, 3H), 3.73 (s, 3H), 4.43 (s, 1H), 4.82 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.5 (CH_3), 16.5 (CH_3), 17.0 (CH_2), 18.4 (CH_2), 26.8 (CH_2), 37.0 (CH_2), 37.7 (CH_2), 37.9 (CH_2), 39.1 (C), 42.0 (CH_2), 47.7 (C), 49.1 (CH_2), 49.7 (CH_3), 51.9 (CH_3), 52.3 (CH), 55.9 (CH), 106.9 (CH_2), 147.5 (C), 167.6 (C), 179.2 (C), 202.9 (C). IR (film): 1748, 1723, 1644, 1437, 1245, 1173, 1130, 893 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{32}O_5Na$ ($M+Na^+$) 387.2147, found: 387.2151.

Methyl 3-oxo-5-(2,6,6-trimethylcyclohex-1-enyl)pentanoate (21):

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.96 (s, 6H), 1.40 (m, 2H), 1.55 (s, 3H), 1.55 (m, 2H), 1.89 (t, *J* = 6.3, 6.3 Hz, 2H), 2.28 (m, 2H), 2.60 (m, 2H), 3.44 (s, 2H), 3.73 (s, 3H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 19.3 (CH_2), 19.6 (CH_3), 21.9 (CH_2), 28.28 (CH_3), 28.30 (CH_3), 32.6 (CH_2), 34.9 (C), 39.6 (CH_2), 43.7 (CH_2), 48.9 (CH_2), 52.1 (CH_3),128.0 (C), 135.5 (C), 167.5 (C), 202.4 (C). IR (film): 1750, 1719, 1437, 1321, 1239, 773 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{15}H_{24}O_3Na$ ($M+Na^+$) 275.1623, found: 275.1631.

Methyl-2-((1S,2R,5R)-2-hydroxy-6,6-dimethyl-9-methylenebicyclo[3.3.1]nonan-2-yl)acetate (22):

$BF_3.OEt_2$ (58 mg, 0.85 mmol) was added slowly to a solution of **20** (110 mg, 0.44 mmol) in dry CH_2Cl_2 (8 mL) at -30 ºC and the reaction mixture was stirred at this temperature under argon atmosphere for 2.5 h. Then the reaction was quenched with sat. aq. $NaHCO_3$ (1 mL) and the cooling bath was removed. The mixture was poured into ether-water (40: 10 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product with was directly purified by flash chromatography on silica gel (10% ether/hexanes) to yield **22** (46 mg, 42%) as yellow syrup and recovered starting material (52 mg, 47%). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.92 (s, 3H), 0.99 (s, 3H), 1.23 (dd, *J* = 13.3, 6.6 Hz, 1H), 1.64 - 1.98 (m, 9H), 2.33 (br s, 1H), 2.56 (dd, *J* = 32.1, 14.7 Hz, 2H), 3.71 (s, 3H), 4.80 (dd, *J* = 14.6, 2.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 25.3 (CH_2), 25.4 (CH_2), 28.91 (CH_3), 28.95 (CH_3), 33.96 (CH_2), 33.96 (CH_2), 35.3 (C), 43.9 (CH_2), 49.0 (CH), 49.2 (CH), 51.6 (CH_3), 74.4 (C), 108.4 (CH_2), 150.8 (C), 172.1 (C). IR (film): 3523, 1735, 1483, 1204, 1169, 980, 883 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{15}H_{24}O_3Na$ ($M+Na^+$) 275.1623, found: 275.1615.

(1R,4aS,8aS)-methyl 5,5,8a-trimethyl-2-oxo-decahydronaphthalene-1-carboxylate (23) and (1R,4aR,8aS)-methyl 5,5,8a-trimethyl-2-oxo-decahydronaphthalene-1-carboxylate (24)

To a solution of **21** (85 mg, 0.34 mmol) in dry CH_2Cl_2 (5 mL) was added iodine (104 mg, 0.41 mmol) and the mixture was stirred at room temperature for 7 h, at this time TLC

showed no **21**. Then, aq. 5% $NaHSO_3$ (0.5 ml) was added and the mixture was stirred for an additional 5 min. The reaction mixture was diluted with ether – water (20 – 5 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (10% ether/hexanes) to give a mixture of **23** and **24** (ratio 3:2) (42 mg, 50%). Signals assignables to **23**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.90 (s, 3H), 0.97 (s, 3H), 1.16 (s, 3H), 1.68 (br d, *J* = 7.1 Hz, 1H), 1.75 (ddd, *J* = 26.1, 12.9, 5.3 Hz, 1H), 2.33 (m, 1H), 3.22 (s, 1H), 3.69 (s, 3H). Signals assignables to **24**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.04 (s, 3H), 1.16 (s, 3H), 1.19 (s, 3H), 2.15 (m, 1H), 3.70 (m, 3H), 3.86 (s, 1H). HRMS (FAB) *m/z*: calcd for $C_{15}H_{24}O_3Na$ ($M+Na^+$) 275.1623, found: 275.1634.

Methyl-2-(2-hydroxy-5,5-dimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)acetate (25)

p-Toluenesulfonic acid monohydrate (124 mg, 0.65 mmol) was added to a solution of **20** (127 mg, 0.50 mmol) in benzene (10 mL) and the reaction mixture was stirred at 60ºC for 12 h, at which time TLC showed no **20**. The solvent was removed under vacuum and the crude product was directly purified by flash chromatography on silica gel (20% ether/hexanes) to afford pure **25** (50 mg, 40%) as a colorless syrup. ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.97 (s, 3H), 0.99 (s, 3H), 1.38 - 1.50 (m, 2H), 1.55 - 1.64 (m, 3H), 1.69 - 1.90 (m, 3H), 1.97 (m, 1H), 2.02 (dd, *J* = 39.1, 16.4 Hz, 2H), 2.20 (m, 1H), 2.49 (d, *J* = 2.1 Hz, 2H), 3.71 (s, 3H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 19.2 (CH_2), 21.9 (CH_2), 27.8 (CH_3), 27.9 (CH_3), 31.3 (CH_2), 33.5 (C), 34.2 (CH_2), 39.5 (CH_2), 43.4 (CH_2), 43.7 (CH_2), 51.6 (CH_3),

69.2 (C), 124.5 (C), 133.9 (C), 173.2 (C). IR (film): 3505, 1729, 1450, 1359, 1200, 1166, 1071, 1011 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{15}H_{24}O_3Na$ ($M+Na^+$) 275.1623, found: 275.1622.

Methyl-2-(5,5-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)acetate (27a) and methyl 2-(5,5-dimethyl-3,4,5,6,7,8-hexahydronaphthalen-2-yl)acetate (27b)

To a solution of **21** (97 mg, 0.38 mmol) in dry CH_2Cl_2 (5 mL) was added Amberlyst A-15 (100 mg) and the mixture was stirred under reflux for 27 h, at which time TLC indicated no starting material remaining. Then, the reaction mixture was filtered and the filtrate was evaporated to yield a crude product which was chromatographed on silica gel (5% ether/hexanes) to yield the mixture **27a** and **27b** (ratio 1:1) (49 mg, 55%).

^1H NMR ($CDCl_3$, 500 MHz) δ: 0.76 (s, 3H), 0.99 (s, 9H), 1.40 (m, 2H), 1.48 (m, 2H), 1.55 (m, 1H), 1.64 (m, 2H), 1.84 - 1.94 (m, 4H), 1.97 - 2.28 (m, 4H), 2.53 (dd, *J* = 7.5 Hz, 2H), 2.70 (m, 2H), 2.99 (s, 2H), 3.04 (s, 2H), 3.677 (s, 3H), 3.682 (s, 3H), 5.45 (br s, 1H), 5.62 (br s, 1H), 5.91 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 19.1 (CH_2), 19.4 (CH_3), 23.1 (CH_2), 23.3 (CH_2), 26.3 (CH_2), 27.8 (CH_3), 27.8 (CH_3), 29.3 (CH_3), 29.9 (CH_2), 30.8 (CH_2), 31.1 (C), 33.2 (C), 35.5 (CH_2), 37.8 (CH_2), 39.7 (CH_2), 42.5 (CH_2), 42.9 (CH_2), 44.3 (CH), 51.73(CH_3), 51.75 (CH_3), 123.5 (CH), 123.8 (CH), 124.7 (C), 127.7 (C), 129.2 (CH), 131.2 (C), 131.6 (C), 135.5 (C), 172.0 (C), 172.2 (C). HRMS (FAB) *m/z*: calcd for $C_{15}H_{21}O_2Na$ ($M+Na^+$) 256.1439, found: 256.1445.

Ethyl 3-oxo-2-((2,6,6-trimethylcyclohex-1-enyl)methyl)butanoate (28)

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.938 (s, 3H), 0.942 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.37 - 1.42 (m, 2H), 1.50 (s, 3H), 1.52 - 1.58 (m, 4H), 1.90 (t, *J* = 6.4 Hz, 1H), 2.21 (s, 3H), 2.65 (t, *J* = 6.0 Hz, 1H), 3.55 (t, *J* = 6.0 Hz, 1H), 4.10 - 4.20 (m, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.0 (CH_3), 19.2 (CH_2), 20.5 (CH_3), 26.4 (CH_2), 28.5 (CH_3), 28.7 (CH_3), 29.3 (CH_3), 32.9 (CH_2), 34.8 (C), 40.0 (CH_2), 60.7 (CH), 61.3 (CH_2), 130.1 (C), 134.6 (C), 170.2 (C), 203.0 (C). IR (film): 1739, 1718, 1462, 1360, 1190, 1150, 1051, 1025 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{26}O_3Na$ ($M+Na^+$) 289.1780, found: 289.1772.

Methyl-3-oxo-5-((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)pentanoate (29)

$[\alpha]_D^{25}$= +55.7 (c = 38.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.81 (s, 3H), 0.87 (s, 3H), 0.92 (s, 3H), 1.00 - 1.18 (m, 3H), 1.32 - 1.68 (m, 5H), 1.52 (s, 3H), 1.75 (br d, *J* = 12.3 Hz, 1H), 1.88 - 2.06 (m, 2H), 2.18 (m, 1H), 2.30 (m, 1H), 2.58 (m, 2H), 3.43 (s, 2H), 3.72 (s, 3H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 18.95 (CH_2), 18.97 (CH_2), 19.4 (CH_3), 19.9 (CH_3), 21.3 (CH_2), 21.6 (CH_3), 33.3 (CH_3), 33.3 (C), 33.6 (CH_2), 36.9 (CH_2), 39.0 (C), 41.7 (CH_2), 43.9 (CH_2), 48.9 (CH_2), 51.9 (CH_3), 52.3 (CH), 126.9 (C), 138.8 (C), 167.6 (C), 202.5 (C). IR (film): 1750, 1719, 1654, 1672, 1447, 1319, 1238, 1151 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{32}O_3Na$ ($M+Na^+$) 343.2249, found: 343.2256.

Methyl 3-oxo-5-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)pentanoate (30)

$[\alpha]_D^{25}$= + 18.0 (c = 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.67 (s, 3H), 0.79 (s, 3H), 0.85 (s, 3H), 1.03 - 1.11 (m, 2H), 1.16 (ddd, *J* = 13.4, 13.4, 4.2 Hz, 1H), 1.31 (ddd, *J* = 25.9, 13.0, 4.3 Hz, 1H), 1.38 (br d, *J* = 13.1 Hz, 1H), 1.43 - 1.66 (m, 4H), 1.71 (m, 1H), 1.77 (br d, *J* = 12.7 Hz, 1H), 1.84 - 1.99 (m, 2H), 2.33 - 2.46 (m, 2H), 2.63 - 2.72 (m, 1H), 3.40 (s, 2H), 3.72 (s, 3H), 4.41 (s, 1H), 4.81 (d, *J* = 0.86 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 17.3 (CH_2), 19.4 (CH_2), 21.7 (CH_3), 24.5 (CH_2), 33.63 (C), 33.67 (CH_3), 38.3 (CH_2), 39.0 (CH_2), 39.8 (C), 42.1 (CH_2), 42.2 (CH_2), 49.2 (CH_2), 52.3 (CH_3), 55.5 (CH), 56.1 (CH), 106.3 (CH_2), 148.3 (C), 167.7 (C), 203.1 (C). IR (film): 1749, 1717, 1646, 1457, 1437, 1318, 1236, 889, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{32}O_3Na$ ($M+Na^+$) 343.2249, found: 343.2250.

3-oxo-5-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)pentanal (31):

$[\alpha]_D^{25}$= + 42.6 (c = 17.0, $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.69 (s, 3H), 0.80 (s, 3H), 0.87 (s, 3H), 1.00 - 1.13 (m, 2H), 1.18 (ddd, *J* = 13.2, 13.2, 4.2 Hz, 1H), 1.32 (m, 1H), 1.39 (br d, *J* = 13.0 Hz, 1H), 1.44 - 1.67 (m, 4H), 1.67 - 2.05 (m, 4H), 2.19 (m, 1H), 2.39 (m, 2H), 2.52 (m, 1H), 4.49 (s, 1H), 4.85 (s, 1H), 5.50 (d, *J* = 4.3 Hz, 1H), 7.88 (d, *J* = 4.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 19.1 (CH_2), 19.3 (CH_2), 21.7 (CH_3), 24.4 (CH_2), 33.63 (C), 33.64 (CH_3), 38.2 (CH_2), 38.5 (CH_2), 39.0 (CH_2), 39.8 (C), 42.1 (CH_2), 55.5 (CH), 56.2 (CH), 101.9 (CH), 106.4 (CH_2), 148.1 (C), 175.2 (CH), 196.4 (C). IR

(film): 1639, 1598, 1459, 1387, 1365, 1249, 890 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{30}O_2Na$ ($M+Na^+$) 313.2143, found: 313.2136.

Methyl-(E)-3,4-dihydro-2´,2´,6´-trimethyl-spiro[furan-2,1´-ciclohexane]-2-yliden acetate (32)

(10% ether/hexanes) (65 %) colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (d, *J* = 5.5 Hz, 3H), 0.78 (s, 3H), 0.93 (s, 3H), 1.17 - 1.71 (m, 5H), 1.74 - 1.85 (m, 2H), 2.07 (m, 1H), 2.50 (m, 1H), 3.01 (m, 1H), 3.18 (m, 1H), 3.63 (s, 3H), 5.24 (t, *J* = 1.6 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.7 (CH_3), 21.3 (CH_2), 23.0 (CH_3), 24.7 (CH_3), 27.0 (CH_2), 30.8 (CH_2), 32.1 (CH_2), 32.7 (C), 36.4 (CH_2), 36.7 (CH), 50.4 (CH_3), 86.6 (CH), 96.8 (C), 169.6 (C), 178.9 (C). IR (film): 1750, 1706, 1633, 1436, 1362, 1127, 1106, 1043, 958, 817 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{32}O_3Na$ ($M+Na^+$) 343.2249, found: 343.2254.

4-metoxycarbonil-2´,2´,5,6´-tetramethyl-spiro[furan-2(3H),1´-ciclohexane] (33)

(10% ether/hexanes) (81%) colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.79 (d, *J* = 6.6 Hz, 1H), 0.82 (s, 3H), 0.93 (s, 3H), 1.14 - 1.23 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.32 - 1.44 (m, 3H), 1.45 - 1.56 (m, 2H), 1.56 - 1.72 (m, 2H), 2.18 (s, 3H), 2.50 (d, *J* = 14.9 Hz, 1H), 2.80 (d, *J* = 14.9 Hz, 1H), 4.10 - 4.21 (m, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.8 (CH_3), 14.5 (CH_3), 15.4 (CH_3), 21.3 (CH_2), 21.9 (CH_3), 24.6 (CH_3), 30.4 (CH_2), 34.6 (CH_2), 36.0 (CH_2), 36.7 (CH), 37.8 (C), 59.3 (CH_2), 94.0 (C), 101.9 (C), 166.4 (C), 168.3 (C). IR (film): 1701, 1648, 1384, 1241, 1247, 1074, 770 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{16}H_{26}O_3Na$ ($M+Na^+$) 289.1780, found: 289.1772.

3-desacetoxynegundoin A (34)

(10% ether/hexanes) (90 %) colorless syrup. $[\alpha]_D^{25}$= + 16.0 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.76 (d, *J* = 6.5 Hz, 3H), 0.81 (s, 3H), 0.88 (s, 3H), 0.91 (s, 3H), 1.08 - 1.18 (m, 2H), 1.27 - 1.67 (m, 9H), 1.72 - 1.83 (m, 2H), 2.09 (m, 1H), 2.96 - 3.17 (m, 2H), 3.64 (s, 3H), 5.27 (t, *J* = 1.7 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.7 (CH_3), 16.7 (CH_3), 18.3 (CH_2), 21.4 (CH_2), 21.9 (CH_3), 26.5 (CH_2), 31.3 (2 CH_2), 31.8 (CH_2), 33.28 (CH_3), 33.30 (C), 36.7 (CH), 41.6 (CH_2), 42.4 (C), 46.8 (CH), 50.4 (CH_3), 86.7 (CH), 98.4 (C), 169.6 (C), 179.1 (C). IR (film): 1706, 1635, 1458, 1362, 1129, 1114, 1044, 964 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{32}O_3Na$ ($M+Na^+$) 343.2249, found: 343.2254.

3-desacetoxy-17-metoxycarbonylnegundoin A (35)

(15% ether/hexanes) (87%) colorless syrup. $[\alpha]_D^{25}$= + 56.4 (c = 10.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.76 (d, *J* = 6.6 Hz, 3H), 0.94 (s, 3H), 1.15 (s, 3H), 1.08 - 1.30 (m, 3H), 1.31 - 1.62 (m, 7H), 1.65 - 1.84 (m, 3H), 2.09 (m, 1H), 2.96 - 3.18 (m, 2H), 3.65 (s, 3H), 3.66 (s, 3H), 5.35 (t, *J* = 1.7 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.6 (CH_3), 16.7 (CH_3), 17.0 (CH_3), 17.6 (CH_2), 23.9 (CH_2), 26.5 (CH_2), 30.4 (CH_2), 30.8 (CH_2), 31.6 (CH_2), 33.1 (C), 36.4 (CH_2), 36.7 (CH), 42.0 (CH), 47.5 (C), 50.5 (CH_3), 51.9 (CH_3), 87.1 (CH), 97.9 (C), 169.6 (C), 178.7 (C), 179.0 (C). IR (film): 1725, 1706, 1633, 1434, 1363, 1249, 1125, 957, 772 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{32}O_5Na$ ($M+Na^+$) 387.2147, found: 387.2143.

(1R,4aR,4bS,7S,8S,8aS,10aR)-7,8-dihydroxy-7-isopropyl-1,4a-dimethyl-tetradecahydrophenanthrene-1-carboxylic acid (37)

To a solution of **36** (10 g, 29.72 mmol) in dry AcOH (100 mL) was added 10% Pd/C (1 g) and the mixture was stirred at room temperature under hydrogen atmosphere (3 atm) for 12 h. Then, the mixture was filtered through a silica gel pad and washed with ether (150 mL). The filtrate was washed with water (5 x 30 mL), $NaHCO_3$ (5 x 30 mL) and brine. The solvent was evaporated to yield **37** (9.56 g, 95 %) as a white solid. Mp: 148 ºC. $[\alpha]_D^{25}$ = -9.8 (c = 17.9, MeOH). ^{1}H RMN (CD_3COCD_3, 500 MHz) δ: 0.77 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.93 - 1.04 (m, 2H), 1.16 (s, 3H), 1.17 (m, 1H), 1.22 - 1.30 (m, 2H), 1.35 - 1.44 (m, 2H), 1.48 - 1.69 (m, 4H), 1.70 - 1.83 (m, 4H), 2.07 (m, 1H), 2.23 (m, 1H), 2.84 (br s, 2H), 3.13 (d, *J* = 9.6 Hz, 1H). ^{13}C RMN (CD_3COCD_3, 125 MHz) δ: 15.1 (CH_3), 16.9 (CH_3), 17.4 (CH_3), 18.2 (CH_3), 19.0 (CH_2), 19.6 (CH_2), 24.9 (CH_2), 27.8 (CH_2), 32.3 (CH_2), 34.3 (CH), 37.0 (C), 37.9 (CH_2), 39.4 (CH_2), 39.8 (CH), 47.8 (C), 52.6 (CH), 54.9 (CH), 75.3 (C), 77.4 (CH), 180.1 (C). IR (KBr): 3389, 1695, 1455, 1386, 1261, 692 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{34}O_4Na$ ($M+Na^+$) 361.2355, found: 361.2362.

(3aS,3bS,5aR,6R,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxole-6-carboxylic acid (38)

To a solution of **37** (3.85 g, 11.37 mmol) in dry acetone (40 mL) were added 2,2-dimethoxypropane (2.54 g, 24.4 mmol) and p-toluenesulphonic acid (95 mg, 0.5 mmol) and the reaction mixture was stirred under reflux for 4 h, at which time TLC showed no starting

material. Then, the solvent was removed under vacuum and ether – water (90 : 20 mL) was added. The phases were shaken, separated and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (20 % ether/hexanes) to yield **38** (3.79 g, 88%) as a colorless syrup. $[\alpha]_D^{25}$ = + 34.1 (c = 10.6, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.69 (ddd, *J* = 12.3, 12.3, 3.5 Hz, 1H), 0.87 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.96 - 1.11 (m, 2H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 3H), 1.18 - 1.31 (m, 2H), 1.39 - 1.54 (m, 2H), 1.43 (s, 3H), 1.47 (s, 3H), 1.54 - 1.66 (m, 5H), 1.67-1.84 (m, 4H), 1.98 (h, *J* = 6.8 Hz, 1H), 2.14 (m, 1H), 3.56 (d, *J* = 8.2 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.1 (CH_3), 15.8 (CH_3), 16.5 (CH_3), 17.9 (CH_2), 19.2 (CH_3), 19.3 (CH_2), 24.1 (CH_2), 25.7 (CH_2), 29.5 (CH_3), 30.1 (CH_3), 33.1 (CH_2), 33.7 (CH), 36.3 (C), 37.1 (CH_2), 38.1 (CH_2), 40.3 (CH), 47.2 (C), 48.9 (CH), 51.2 (CH), 85.0 (CH), 85.6 (C), 108.3 (C), 184.8 (C). IR (film): 1695, 1368, 1236, 1215, 1038, 757 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_4Na$ ($M+Na^+$) 401.2668, found: 401.2676.

((3aS,5aR,6R,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxol-6-yl)methanol (39)

$LiAlH_4$ (0.53 g, 14.04 mmol) was added at 0 °C to a stirred solution of **38** (4.43 g, 11.70 mmol) in dry diethyl ether (60 mL) and the mixture was stirred at room temperature under an argon atmosphere for 5 h, at which time TLC showed no compound **38**. Then, acetone (0.5 mL) was slowly added at 0 °C and Et_2O –water (50 : 15 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine,

and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (20% ether/hexanes) to give pure **39** (3.74 g, 88%) as a colorless syrup. $[\alpha]_D^{25}$ = -18.6 (c = 10.8, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.64 (ddd, *J* = 12.4, 12.4, 3.5 Hz, 1H), 0.77 (s, 3H), 0.80 - 1.07 (m, 2H), 0.87 (s, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.10 - 1.35 (m, 4H), 1.36 - 1.67 (m, 7H) 1.43 (s, 3H), 1.48 (s, 3H), 1.74 (br d, *J* = 13.0 Hz, 1H), 1.80 (m, 1H), 1.98 (h, *J* = 6.9 Hz, 1H), 2.17 (m, 1H), 3.09 (d, *J* = 10.8 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 3.54 (d, *J* = 8.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.4 (CH_3), 15.8 (CH_3), 17.8 (CH_3), 18.1 (CH_2), 19.2 (CH_3), 19.5 (CH_2), 21.1 (CH_2), 25.9 (CH_2), 29.5 (CH_3), 30.2 (CH_3), 33.3 (CH_2), 33.7 (CH), 35.4 (CH_2), 36.7 (C), 37.6 (C), 38.7 (CH_2), 40.1 (CH), 47.6 (CH), 51.0 (CH), 71.9 (CH_2), 85.2 (CH), 85.5 (C), 108.2 (C). IR (film): 3453, 1716, 1457, 1381, 1239, 1038, 771 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{40}O_3Na$ ($M+Na^+$) 387.2875, found: 387.2869.

(3aS,5aR,6R,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxole-6-carbaldehyde (40)

Pyridinium chlorochromate (PCC) (5 g, 13.29 mmol) was added to a stirred solution of **39** (3.71 g, 10.18 mmol) in dry CH_2Cl_2 (70 mL) and the mixture was stirred at room temperature under an argon atmosphere for 4 h, at which time TLC showed no remaining starting material. Then, the reaction was worked up by the addition of ether (40 mL) and the resulting mixture was filtered through a silica gel pad and washed with ether (60 mL). The filtrate was washed with 2N HCl (3 x 30 mL) and brine. The solvent was evaporated to

yield a crude product, which was chromatographed on silica gel (10% ether/hexanes) to yield **40** (3.02 g, 82%) as a colorless syrup. $[\alpha]_D^{25}$ = -34.5 (c = 51.6, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.68 (ddd, *J* = 11.6, 11.6, 6.0 Hz, 1H), 0.80 - 1.14 (m, 2H), 0.88 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 3H), 1.17 - 1.28 (m, 2H), 1.33 - 1.54 (m, 6H), 1.42 (s, 3H), 1.46 (s, 3H), 1.55 - 1.68 (m, 3H), 1.76 - 1.86 (m, 2H), 1.98 (h, *J* = 6.9 Hz, 1H), 2.12 (m, 1H), 3.55 (d, *J* = 8.3 Hz, 1H), 9.20 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.2 (CH_3), 14.4 (CH_3), 15.8 (CH_3), 17.1 (CH_2), 19.2 (CH_3), 19.4 (CH_2), 23.9 (CH_2), 25.7 (CH_2), 29.5 (CH_3), 30.2 (CH_3), 32.4 (CH_2), 32.9 (CH_2), 33.7 (CH), 35.8 (C), 38.1(CH_2), 40.3 (CH), 46.8 (CH), 49.6 (C), 50.9 (CH), 84.9 (CH), 85.5 (C), 108.3 (C), 206.5 (CH). IR (film): 1727, 1455, 1235, 1216, 1040, 864, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_3Na$ ($M+Na^+$) 385.2719, found: 385.2723.

(3aS,5aR,6R,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxol-6-yl formate (41)

m-Chloroperoxybenzoic acid (MCPBA, 70%; 7.38 g, 29.94 mmol), and $NaHCO_3$ (2.51 g, 29.94 mmol) were added to a stirred solution of **40** (3.62 g, 9.98 mmol) in CH_2Cl_2 (300 mL) and the reaction was stirred under reflux for 3 h, at which time TLC indicated no starting material remaining. The reaction was quenched with sat. aq. Na_2SO_3 (30 mL) and stirred for an additional 15 min. Then, the organic solvent was removed under vacuum and ether (100 mL) was added. The organic phase was washed with sat. aq. $NaHCO_3$ (8 x 30 mL) and brine, dried over Na_2SO_4 and concentrated to give **41** (3.25 g, 86%) as a colorless syrup. $[\alpha]_D^{25}$ = -52.8 (c = 20.3, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.68 (ddd, *J* = 12.1, 12.1,

3.3 Hz, 1H), 0.84 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.93 - 1.07 (m, 2H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.22 (m, 1H), 1.33 (ddd, *J* =25.6, 12.9, 3.9 Hz, 1H), 1.39 - 1.75 (m, 8H), 1.43 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 1.76 - 1.85 (m, 2H), 1.99 (h, *J* = 6.8 Hz, 1H), 2.20 (ddd, *J* = 12.8, 6.9, 3.7 Hz, 1H), 2.50 (br d, *J* = 12.4 Hz, 1H), 3.55 (d, *J* = 8.3 Hz, 1H), 8.02 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.7 (CH_3), 15.8 (CH_3), 19.2 (CH_3), 19.4 (CH_2), 19.5 (CH_2), 20.3 (CH_3), 20.7 (CH_2), 25.7 (CH_2), 29.5 (CH_3), 30.2 (CH_3), 32.7 (CH_2), 33.7 (CH), 37.7 (CH_2), 37.8 (C), 38.2 (CH_2), 40.1 (CH), 51.0 (CH), 53.1 (CH), 84.9 (CH), 85.5 (C), 87.3 (C), 108.3 (C), 160.5 (CH). IR (film): 1721, 1448, 1385, 1189, 1040, 861, 772 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_4Na$ ($M+Na^+$) 401.2668, found: 401.2677.

(3aS,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-4,5,9,9a,9b,10,11,11a-octahydrophenanthro[2,1-d][1,3]dioxol-7(3aH,3bH,8H)-one (42)

Pyridinium chlorochromate (PCC) (1.55 g, 7.20 mmol), pyridine (0.62 g, 7.80 mmol) and celite (1 g) were added to a stirred solution of **9** (0.4 g, 1.20 mmol) in benzene – CH_2Cl_2 (30 – 15 mL) and the mixture was kept stirring at reflux under argon atmosphere for 4 days, at which time TLC showed no remaining starting material. Following the same work-up used to prepare **40**, a crude product, was obtained which by chromatography on silica gel (30% ether/hexanes) gave **42** (270 mg, 65%) as a colorless syrup. $[\alpha]_D^{25}$= +5.6 (c = 7.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.87 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.08 (m, 1H), 1.13 (s, 3H), 1.34 (m, 1H), 1.46 (s, 3H), 1.52 (m, 2H), 1.53 (s, 3H), 1.68 (ddd, *J* = 13.1, 13.1, 5.5 Hz, 1H), 1.78 (s, 3H), 1.79 - 1.93 (m, 2H), 1.97 - 2.06 (m, 2H), 2.12 (ddd, *J* = 14.3, 14.3, 4.3 Hz, 1H), 2.27 (ddd, *J* = 12.8, 7.0, 2.8 Hz, 1H), 2.35 - 2.47 (m, 2H), 2.77 (ddd, *J* = 14.7, 3.3, 3.3 Hz, 1H), 3.59 (d, *J* = 8.2 Hz, 1H). ^{13}C RMN

($CDCl_3$, 125 MHz) δ: 11.1 (CH_3), 15.7 (CH_3), 17.9 (CH_3), 19.2 (CH_3), 20.1 (CH_2), 25.7 (CH_2), 27.4 (CH_2), 29.6 (CH_3), 30.3 (CH_3), 32.0 (CH_2), 33.6 (CH_2), 33.7 (CH), 34.7 (CH_2), 39.0 (C), 40.4 (CH), 48.8 (CH), 84.1 (CH), 85.4 (C), 108.5 (C), 128.4 (C), 162.4 (C), 198.7 (C). IR (film): 1669, 1376, 1366, 1237, 1214, 1039, 772, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{34}O_3Na$ ($M+Na^+$) 369.2406, found: 369.2411.

(3aS,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-decahydrophenanthro[2,1-d][1,3]dioxol-7(3aH,3bH,8H)-one (43)

A solution of enone **42** (253 mg, 0.73 mmol) in THF - ^tBuOH (5 : 1 mL) was added under argon atmosphere to NH_3 (3 mL) at -78ºC and the mixture was stirred for 5 min. Li (51 mg, 7.3 mmol) was added and the mixture was stirred at -40ºC for 3 h. Then, it was added metil iodide (136 μL, 2.19 mmol), and stirred for an additional 1 h, at which time TLC showed no starting material. Then, the mixture was allowed to warm at room temperature, and ether – water (60 : 20 mL) was added, and the phases were shaken and separated. The organic layer was washed with 2N HCl (20 mL), water, brine, dried over anhidrous Na_2SO_4 and filtered.. Removal of the solvent gave a cruede product which was purified by flash chromatography column on sílica gel (20% ether/hexanes), affording **43** (225 mg, 85%) as a colorles syrup. $[\alpha]_D^{25}$= -39.8 (c = 19.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.63 (ddd, *J* = 12.1, 12.1, 3.4 Hz, 1H), 0.85 - 1.13 (m, 2H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H), 1.03 (s, 3H), 1.06 (s, 3H), 1.20 - 1.34 (m, 3H), 1.34 - 1.54 (m, 2H), 1.43 (s, 3H), 1.48 (s, 3H), 1.55-1.67 (m, 2H), 1.79 (ddd, *J* = 14.3, 4.5, 4.5 Hz, 1H), 1.94 - 2.07 (m, 2H), 2.23 (ddd, *J* = 11.0, 7.0, 3.5 Hz, 1H), 2.32 (ddd, *J* = 15.4, 5.1, 3.6 Hz, 1H), 2.62 (ddd, *J* = 15.3, 13.2, 6.3 Hz, 1H), 3.56 (d, *J* = 8.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125

MHz) δ: 13.5 (CH_3), 15.8 (CH_3), 19.2 (CH_3), 19.9 (CH_2), 21.9 (CH_3), 22.3 (CH_2), 25.7 (CH_2), 25.8 (CH_3), 29.5 (CH_3), 30.2 (CH_3), 33.1 (CH_2), 33.7 (CH), 34.5 (CH_2), 36.5 (C), 37.8 (CH_2), 40.2 (CH), 47.7 (C), 50.3 (CH), 54.6 (CH), 84.8 (CH), 85.6 (C), 108.3 (C), 216.9 (C). IR (film): 1707, 1457, 1366, 1241, 1039, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_3Na$ ($M+Na^+$) 385.2719, found: 385.2724.

(3aS,7S,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxol-7-ol (44):

Sodium borohydride (89 mg, 2.36 mmol) was added to a stirred solution of **43** (345 mg, 0.95 mmol) in EtOH (5 mL) and the reaction mixture was stirred at room temperature for 15 min, at which time TLC showed no **43**. The reaction mixture was quenched with water (1 mL), and the solvent was evaporated. The crude product was diluted with ether – water (30 : 10 mL) and the phases were shaken and separated. The organic phase was washed with water and brine and the organic phase was dried over Na_2SO_4 and concentrated to give **44** (309 mg, 89%) as a colorless syrup. $[\alpha]_D^{25}$= -32.8 (c = 4.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.55 (ddd, *J* = 12.3, 3.7 Hz, 1H), 0.76 - 1.08 (m, 2H), 0.79 (s, 3H), 0.83 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 3H), 1.20 (ddd, *J* = 24.0, 10.8, 3.5 Hz, 1H), 1.34 (ddd, *J* = 25.9, 13.1, 3.7 Hz, 1H), 1.39 - 1.68 (m, 7H), 1.43 (s, 3H), 1.47 (s, 3H), 1.74 - 1.83 (m, 2H), 1.91 (h, *J* = 6.9 Hz, 1H), 2.14 (ddd, *J* = 12.7, 7.1, 3.7 Hz, 1H), 3.14 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.47 (d, *J* = 8.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.9 (CH_3), 15.5 (CH_3), 15.8 (CH_3), 19.2 (CH_3), 19.5 (CH_2), 21.1 (CH_2), 25.8 (CH_2), 27.4 (CH_2), 28.2 (CH_3), 29.5 (CH_3), 30.2 (CH_3), 33.6 (CH_2), 33.7 (CH), 36.7 (C), 37.3

(CH_2), 38.9 (C), 40.0 (CH), 51.0 (CH), 53.9 (CH), 79.0 (CH), 85.1 (CH), 85.5 (C), 108.2 (C). IR (film): 3438, 1637, 1367, 1237, 1037, 756 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{40}O_3Na$ ($M+Na^+$) 387.2875, found: 387.2868.

(3aS,7S,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxol-7-yl acetate (45):

To a solution of **44** (376 mg, 1.03 mmol) in pyridine (5 mL) at 0 ºC was added acetic anhydride (2 mL), and the reaction mixture was stirred at room temperature for 2 h, at which time TLC showed no starting material. Then, the reaction mixture was cooled at 0 ºC, water (5 mL) was added to quench the reaction and the mixture was stirred for an additional 10 min. Then, it was diluted with ether - water (40 : 10 mL) and the phases were shaken and separated. The organic phase was washed with water (10 mL), 2N HCl (4 x 10 mL), again water (10 mL), sat. aq. $NaHCO_3$ (4 x 10 mL), brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (10 % ether/hexanes) gave **45** (385 mg, 92%) as a colorless syrup. $[\alpha]_D^{25}$= 26.7 (c = 4.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.57 (ddd, *J* = 12.1, 12.1, 3.5 Hz, 1H), 0.86 (s, 6H), 0.87 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.40 - 1.41 (m, 4H), 1.43 (s, 3H), 1.48 (s, 3H), 1.40 - 1.70 (m, 7H), 1.73 - 1.85 (m, 2H), 1.98 (h, *J* = 6.9 Hz, 1H), 2.04 (s, 3H), 2.20 (m, 1H), 3.54 (d, *J* = 8.2 Hz, 1H), 4.48 (dd, *J* = 11.6, 4.5 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.0 (CH_3), 15.8 (CH_3), 16.7 (CH_3), 19.2 (CH_3), 19.5 (CH_2), 21.0 (CH_2), 21.3 (CH_3), 23.8 (CH_2), 25.8 (CH_2), 28.2 (CH_3), 29.5 (CH_3), 30.2 (CH_3), 33.5 (CH_2), 33.7 (CH), 36.6 (C), 36.9 (CH_2), 37.8 (C), 40.0 (CH), 50.9 (CH), 54.0 (CH), 80.9 (CH), 85.0 (CH), 85.6 (C), 108.2 (C),

170.9 (C). IR (film): 1734, 1456, 1366, 1240, 1031 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{25}H_{42}O_4Na$ ($M+Na^+$) 429.2981, found: 429.2979.

(3aS,3bS,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-3b,4,9,9a,9b,10,11,11a-octahydrophenanthro[2,1-d][1,3]dioxol-7(3aH,6H,8H)-one (46):

Potassium *tert*-butoxide (155 mg, 1.38 mmol) was added to a stirred solution of **42** (400 mg, 1.15 mmol) in dry THF (20 mL) under an argon atmosphere and the reaction mixture was stirred at room temperature for 20 min. Then, methyl iodide (0.072 mL, 1.38 mmol) was added and the reaction mixture was stirred at room temperature for an additional 1 h, at which time TLC showed no starting material. The mixture was concentrated in vacuo to give a crude product, which was diluted with ether – water (40 : 10 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel

(5% ether/hexanes), affording 340 mg of **46** (82%), as colorless syrup. $[\alpha]_D^{25}$ = -19.9 (c = 22.6, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.81 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.22 (s, 3H), 1.24 (s, 3H), 1.35 - 1.59 (m, 4H), 1.45 (s, 3H), 1.49 (s, 3H), 1.68 (ddd, *J* = 13.5, 11.3, 8.5 Hz, 1H), 1.75 - 1.91 (m, 4H), 1.97 - 2.08 (m, 2H), 2.43 - 2.61 (m, 2H), 3.70 (d, *J* = 7.3 Hz, 1H), 5.60 (dd, *J* = 4.9, 2.0 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.8 (CH_3), 18.8 (CH_3), 19.3 (CH_3), 20.1 (CH_2), 25.5 (CH_2), 27.2 (CH_3), 29.5 (CH_3), 30.07 (CH_3), 30.09 (CH_3), 31.8 (CH_2), 32.6 (CH_2), 33.7(CH_2), 34.1 (CH), 36.3 (CH), 37.4 (C), 44.9 (CH), 48.6 (C), 85.3 (CH), 85.9 (C), 108.7 (C), 119.8 (CH), 149.1 (C),

216.2 (C). IR (film): 2961, 2873, 1710, 1464, 1380, 1238, 1040, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{36}O_3Na$ ($M+Na^+$) 383.2562, found: 383.2555.

(3aS,3bS,7S,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-3a,3b,4,6,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxol-7-ol (47):

Sodium borohydride (84 mg, 2.22 mmol) was added to a stirred solution of **46** (323 mg, 0.90 mmol) in EtOH (5 mL) and the reaction mixture was stirred at room temperature for 15 min, at which time TLC showed no **46**. Following the same work-up used to prepare **44**, **47** (292 mg, 90%) was obtained as a colorless syrup. $[\alpha]_D^{25}$ = -84.0 (c = 20.6, $CHCl_3$). ^1H RMN ($CDCl_3$, 500 MHz) δ: 0.89 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 3H), 1.06 (s, 3H), 1.10 (m, 1H), 1.15 (s, 3H), 1.35 - 1.60 (m, 2H), 1.44 (s, 3H), 1.49 (s, 3H), 1.66 - 1.92 (m, 8H), 1.99 (h, *J* = 6.9 Hz, 1H), 2.54 (m, 1H), 3.23 (dd, *J* = 11.1, 5.0 Hz, 1H), 3.66 (d, *J* = 7.1 Hz, 1H), 5.62 (dd, *J* = 4.4, 2.4 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.8 (CH_3), 19.1 (CH_3), 19.3 (CH_2), 20.8 (CH_3), 23.5 (CH_3), 25.9 (CH_2), 27.22 (CH_2), 27.24 (CH_3), 29.3 (CH_3), 29.9 (CH_3), 33.4 (CH_2), 34.1 (CH), 35.6 (CH), 36.3 (CH_2), 37.2 (C), 41.5 (C), 47.1 (CH), 77.4 (CH), 85.8 (C), 85.9 (CH), 108.5 (C), 120.0 (CH), 149.1 (C). IR (film): 3470, 1467, 1367, 1238, 1040, 866, 756 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_3Na$ ($M+Na^+$) 385.2719, found: 385.2724.

(3aS,3bS,7S,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-3a,3b,4,6,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxol-7-yl acetate (48):

To a solution of **47** (376 mg, 1.04 mmol) in pyridine (5 mL) at 0 ºC was added acetic anhydride (2 mL), and the reaction mixture was stirred at room temperature for 2 h, at which time TLC showed no starting material. Following the same work-up used to prepare **45**, a crude product, was obtained which by chromatography on silica gel. (10 % ether/hexanes) gave **48** (399 mg, 95%) as a colorless syrup. $[\alpha]_D^{25}$ = - 46.6 (c = 32.8, $CHCl_3$). RMN ($CDCl_3$, 500 MHz) δ: 0.89 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H), 1.17 (m, 1H), 1.37 (m, 1H), 1.43 (s, 3H), 1.47 (s, 3H), 1.55 (m, 1H), 1.68 - 1.92 (m, 8H), 1.98 (h, *J* = 6.8 Hz, 1H), 2.05 (s, 3H), 2.53 (m, 1H), 3.66 (d, *J* = 7.2 Hz, 1H), 4.47 (dd, *J* = 11.3, 4.7 Hz, 1H), 5.61 (dd, *J* = 4.5, 2.6 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.9 (CH_3), 19.1 (CH_3), 19.4 (CH_2), 20.9 (CH_3), 21.3 (CH_3), 23.7 (CH_2), 24.8 (CH_3), 25.9 (CH_2), 27.2 (CH_3), 29.4 (CH_3), 30.0 (CH_3), 33.4 (CH_2), 34.1 (CH), 35.7 (CH), 35.9 (CH_2), 37.2 (C), 40.3 (C), 47.0 (CH), 79.4 (CH), 85.9 (CH), 85.9 (C), 108.6 (C), 120.6 (CH), 148.3 (C), 170.7 (C). IR (film): 1736, 1468, 1367, 1241, 1035, 757 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{25}H_{40}O_4Na$ ($M+Na^+$) 427.2824, found: 427.2831.

(2S,4aR,5S,8aR)-6-formyl-1,1,4a-trimethyl-5-(4-methyl-3-oxopentyl)-decahydronaphthalen-2-yl acetate (49):

Lead (IV) acetate (598 mg, 1.35 mmol) was added to a solution of **8** (415 mg, 1.13 mmol) in dry CH_2Cl_2 (15 mL) and the mixture was stirred at room temperature for 5 min, at which time TLC showed no **8**. The reaction was filtered through a silica gel pad and washed with ether (30 mL). The organic phase was then washed with 5% aq. $NaHSO_3$ (10 mL), sat. aq. $NaHCO_3$ (3 x 10 mL) and brine, and dried over Na_2SO_4. Removal of the solvent in vacuum gave a crude product which was directly purified by flash chromatography on silica gel (15 % ether/hexanes) to yield **49** (396 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$= +7.9 (c = 33.1,

$CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.80 - 0.98 (m, 3H), 0.85 (s, 6H), 0.86 (s, 3H), 1.00 - 1.07 (m, 2H), 1.039 (d, *J* = 6.9 Hz, 3H), 1.041 (d, *J* = 6.9 Hz, 3H), 1.08 - 1.47 (m, 3H), 1.53 - 1.87 (m, 4H), 2.03 (s, 3H), 2.25 - 2.39 (m, 2H), 2.45 - 2.57 (m, 2H), 4.47 (dd, *J* = 11.8, 4.5 Hz, 1H), 9.54 (d, *J* = 4.0 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.0 (CH_3), 16.5 (CH_3), 18.1 (CH_3), 18.2 (CH_3), 19.8 (CH_2), 21.2 (CH_3), 22.9 (CH_2), 23.5 (CH_2), 26.8 (CH_2), 28.1 (CH_3), 36.4 (CH_2), 37.6 (C), 37.7 (C), 40.7 (CH), 41.0 (CH_2), 50.0 (CH), 53.5 (CH), 53.8 (CH), 80.4 (CH), 170.8 (C), 204.8 (CH), 213.8 (C). IR (film): 1731, 1711, 1465, 1369, 1246, 1032, 751 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{36}O_4Na$ ($M+Na^+$) 387.2511, found: 387.2508.

(2S,4aR,5S,8aR)-6-(hydroxymethyl)-1,1,4a-trimethyl-5-(4-methyl-3-oxopentyl)-decahydronaphthalen-2-yl acetate (50):

To a solution of **49** (387 mg, 1.06 mmol) in THF (20 mL) was added 50% aqueous solution of Raney Nickel (2 mL) and the mixture was stirred at room temperature for 20 min, at this time TLC showed no **49**. Then, the reaction mixture was filtered through a silica gel – Na_2SO_4 (10 : 2 g), washed with acetone (10 mL) and concentrated to give pure **50** (366 mg, 94 %) as colorless syrup. $[\alpha]_D^{25}$= -0.9 (c = 8.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.65-0.96 (m, 3H), 0.77 (s, 3H), 0.79 (s, 6H), 0.98 - 1.40 (m, 4H), 1.01 (d, *J* = 6.9 Hz, 6H), 1.46 - 1.69 (m, 4H), 1.70 - 1.81 (m, 2H), 1.97 (s, 3H), 2.38 (m, 1H), 2.44 - 2.57 (m, 2H), 3.48 - 3.59 (m, 2H), 4.39 (dd, *J* = 11.7, 2.5 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.1 (CH_3), 16.5 (CH_3), 18.2 (CH_3), 18.3 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 21.8 (CH_2), 23.7 (CH_2), 28.1 (CH_3), 30.5 (CH_2), 37.0 (CH_2), 37.8 (C), 38.1 (C), 40.9 (CH), 41.2 (CH), 41.9 (CH_2), 51.3 (CH), 54.2 (CH), 65.6 (CH_2), 80.5 (CH), 170.9 (C), 215.3 (C). IR (film): 3490,

1733, 1715, 1458, 1367, 1246, 1031 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{38}O_4Na$ ($M+Na^+$) 389.2668, found: 389.2673.

(2S,4aR,5S,8aR)-1,1,4a-trimethyl-5-(4-methyl-3-oxopentyl)-6-(tosyloxymethyl)-decahydronaphthalen-2-yl acetate (51):

To a solution of **50** (320 mg, 0.87 mmol) in pyridine (5 ml) was added *p*- toluenesulfonyl chloride (215 mg, 1.13 mmol) and the reaction mixture was stirred at room temperature for 6 h, at which time TLC showed no starting material. Then, it was diluted with ether (40 mL) and washed with 2N HCl (3 x 20 mL) and brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (15 % ether/hexanes) to yield **50** (391 mg, 86%) as a colorless syrup. $[\alpha]_D^{25}$= -3.5 (c = 10.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.73 - 0.91 (m, 3H), 0.80 (s, 3H), 0.825 (s, 3H), 0.833 (s, 3H), 1.03 - 1.37 (m, 2H), 1.055 (d, *J* = 6.9 Hz, 3H), 1.060 (d, *J* = 6.9Hz, 3H), 1.49 - 1.63 (m, 4H), 1.64 - 1.75 (m, 3H), 1.78 (ddd, *J* = 13.2, 3.5, 3.5 Hz, 1H), 2.03 (s, 3H), 2.34 (m, 1H), 2.44 (m, 1H), 2.45 (s, 3H), 2.51 (h, *J* = 6.9 Hz, 1H), 3.95 (ddd, *J* = 12.5, 9.6, 4.0 Hz, 2H), 4.44 (dd, *J* = 11.8, 4.4 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.8 (CH_3), 16.5 (CH_3), 18.1 (CH_3), 18.2 (CH_3), 20.5 (CH_2), 21.2 (CH_3), 21.6 (CH_3), 22.0 (CH_2), 23.6 (CH_2), 28.0 (CH_3), 30.2 (CH_2), 36.5 (CH_2), 37.7 (C), 38.0 (C), 39.1 (CH), 40.8 (CH), 41.6 (CH_2), 51.0 (CH), 53.8 (CH), 73.2 (CH_2), 80.6 (CH), 127.8 (CH), 127.8 (CH), 129.8 (CH), 129.8 (CH), 133.0 (C), 144.8 (C), 170.8 (C), 214.1 (C). IR (film): 1731, 1713,

1363, 1246, 1177, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{44}O_6$ SNa ($M+Na^+$) 543.2756, found: 543.2757.

Isopropyl-3-((1S,4aR,6S,8aR)-6-acetoxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)propanoate (52):

To a solution of **7** (367 mg, 0.68 mmol) in HMPA (5 mL) were added NaI (123 mg, 0.82 mmol) and the reaction mixture was stirred at 150 ºC for 1 h, at which time TLC showed no starting material. Then, ether (40 mL) was added and the organic phase was washed with brine (8 x 15 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (10 % ether/hexanes) to yield **52** (209 mg, 84%) as a colorless syrup. $[\alpha]_D^{25}$= +22.0 (c = 7.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.71 (s, 3H), 0.84 (s, 3H), 0.86 (s, 3H), 1.13 - 1.45 (m, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.52 - 1.68 (m, 3H), 1.68 - 1.77 (m, 2H), 1.77 - 1.89 (m, 2H), 1.95 (m, 1H), 2.04 (s, 3H), 2.08 (m, 1H), 2.35 - 2.45 (m, 2H), 4.51 (s, 1H), 4.52 (m, 1H), 4.86 (s, 1H), 4.99 (h, *J* = 6.2 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.4 (CH_3), 16.5 (CH_3), 19.2 (CH_2), 21.3 (CH_3), 21.87 (CH_3), 21.91 (CH_3), 23.8 (CH_2), 24.3 (CH_2), 28.2 (CH), 33.4 (CH_2), 36.6 (CH_2), 37.9 (CH_2), 38.0 (C), 39.2 (C), 54.7 (CH), 55.8 (CH), 67.4 (CH), 80.6 (CH), 107.0 (CH_2), 147.2 (C), 170.9 (C), 173.5 (C). IR (film): 1732, 1372, 1243, 1109, 1029, 773, 669 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{36}O_4$ Na ($M+Na^+$) 387.2511, found: 387.2509.

3-((1S,4aR,6S,8aR)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)propanoic acid (53):

2N KOH in MeOH (1 mL) and water (0.1 mL) was added to a solution of **52** (197 mg, 0.54 mmol) in MeOH (5 mL) and the mixture was stirred at room temperature for 2 h, at which time TLC showed no remaining starting material. Then, the solvent was removed in vacuum and ether – water (30 : 10 mL) was added, and the phases were shaken and separated. 2N HCl (2 mL) was added slowly to the aqueous phase and the mixture was diluted with ether (30 mL). The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated to afford pure **53** (109 mg, 72%) as a colourless syrup.

$[\alpha]_D^{25}$= + 26.1 (c = 4.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.70 (s, 3H), 0.77 (s, 3H), 0.99 (s, 3H), 1.09 (dd, *J* = 12.1, 2.3 Hz, 1H), 1.18 - 1.44 (m, 3H), 1.54 - 1.92 (m, 6H), 1.96 (ddd, *J* = 13.0, 13.0, 5.0 Hz, 1H), 2.20 (m, 1H), 2.41 (ddd, *J* = 12.8, 4.1, 2.4 Hz, 1H), 2.52 (ddd, *J* = 16.5, 8.9, 4.4 Hz, 1H), 3.26 (dd, *J* = 11.8, 4.3 Hz, 1H), 4.51 (s, 1H), 4.87 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 15.4 (CH_3), 18.9 (CH_2), 23.9 (CH_2), 27.8 (CH_2), 28.3 (CH_3), 32.7 (CH_2), 36.9 (CH_2), 38.0 (CH_2), 39.1 (C), 39.4 (C), 54.5(CH), 55.8 (CH), 78.8 (CH), 106.9 (CH_2), 147.2 (C), 179.2 (C). IR (film): 3446, 1704, 1652, 1457, 1029, 770, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{28}O_3$ Na ($M+Na^+$) 303.1936, found: 303.1941.

4-((1S,4aR,6S,8aR)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)butan-2-one (54):

MeLi in diethoxymethane (3.0M, 0.5 mL, 1.5 mmol) was added at 0 °C to a stirred solution of **53** (100 mg, 0.36 mmol) in dry diethyl ether (10 mL) and the mixture was stirred at room temperature under an argon atmosphere for 48 h, at which time TLC showed no compound **53**. Then, water (0.5 mL) was slowly added at 0 °C and Et_2O –water

(30 : 15 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (30% ether/hexanes) to give pure **54** (84 mg, 85%) as a colourless syrup. $[\alpha]_D^{25}$= +5.0 (c = 3.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.69 (s, 3H), 0.77 (s, 3H), 0.99 (s, 3H), 1.08 (dd, *J* = 12.5, 2.8 Hz, 1H), 1.15 - 1.34 (m, 3H), 1.39 (ddd, *J* = 25.9, 13.0, 4.4 Hz, 1H), 1.53 - 1.77 (m, 3H), 1.77 - 1.88 (m, 2H), 1.95 (ddd, *J* = 12.9, 12.9, 4.2 Hz, 1H), 2.10 (s, 3H), 2.30 (m, 1H), 2.40 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.58 (m, 1H), 3.25 (m, 1H), 4.45 (s, 1H), 4.84 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 15.4 (CH_3), 17.5 (CH_2), 24.0 (CH_2), 27.9 (CH_2), 28.3 (CH_3), 30.1 (CH_3), 36.9 (CH_2), 38.1 (CH_2), 39.1 (C), 39.5 (C), 42.7 (CH_2), 54.6 (CH), 55.9 (CH), 78.8 (CH), 106.7 (CH_2), 147.7 (C), 209.2 (C). IR (film): 3422, 1712, 1456, 1363, 1163, 889, 670 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{18}H_{30}O_2Na$ ($M+Na^+$) 301.2143, found: 301.2139.

Methyl 5-((1S,4aR,6S,8aR)-6-(methoxycarbonyloxy)-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-3-oxopentanoate (55):

HNa (60%, 112 mg, 2.8 mmol) and dimethylcarbonate (1.01 mg, 11.2 mmol) were added to a stirred solution of **54** (160 mg, 0.56 mmol) in benzene (15 mL) and the mixture was kept stirring at reflux under argon atmosphere overnight, at which time TLC showed no remaining starting material. Then, water (1 mL) was slowly added at 0 °C and ether –water (50 : 20 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (15% ether/hexanes) to give pure **55** (188 mg, 83%) as a

colorless syrup. $[\alpha]_D^{25}$= + 33.7 (c = 8.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.71 (s, 3H), 0.85 (s, 3H), 0.93 (s, 3H), 1.13 - 1.46 (m, 3H), 1.51 - 175 (m, 3H), 1.80 - 2.02 (m, 4H), 2.36 - 2.48 (m, 2H), 2.64 - 2.80 (m, 2H), 3.41 (s, 2H), 3.73 (s, 3H), 3.77 (s, 3H), 4.36 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.45 (brs, 1H), 4.85 (brs, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 16.4 (CH_3), 17.4 (CH_2), 23.7 (CH_2), 24.2 (CH_2), 28.1 (CH_3), 36.5 (CH_2), 37.9 (CH_2), 38.2 (C), 39.3 (C), 42.0 (CH_2), 49.1 (CH_2), 52.3 (CH_3), 54.5 (CH_3), 54.6 (CH), 55.5 (CH), 85.1 (CH), 107.0 (CH_2), 147.2 (C), 155.7 (C), 167.6 (C), 202.8 (C). IR (film): 1745, 1718, 1442, 1271, 974, 793 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{34}O_6Na$ ($M+Na^+$) 417.2253, found: 417.2249.

Synthesis of (56):

(15% ether/hexanes) (90%) colorless syrup. $[\alpha]_D^{25}$= + 23.0 (c = 6.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 1.30 - 1.46 (m, 4H), 1.51 - 1.74 (m, 5H), 1.75 - 1.85 (m, 2H), 2.08 (ddd, *J* = 13.5, 11.8, 7.6 Hz, 1H), 3.02 (m, 1H), 3.13 (m, 1H), 3.65 (s, 3H), 3.77 (s, 3H), 4.31 (dd, *J* = 11.9, 4.5 Hz, 1H), 5.30 (t, *J* = 1.8 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.5 (CH_3), 16.4 (CH_3), 16.8 (CH_3), 20.8 (CH_2), 23.2 (CH_2), 26.7 (CH_2), 27.9 (CH_3), 29.3 (CH_2), 31.0 (CH_2), 31.5 (CH_2), 36.5 (CH), 37.9 (C), 41.9 (C), 46.2 (CH), 50.5 (CH_3), 54.6 (CH_3), 84.6 (CH), 87.3 (CH), 97.7 (C), 155.7 (C), 169.5 (C), 178.4 (C). IR (film): 1746, 1706, 1633, 1441, 1273, 1128, 1108, 968, 956, cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{34}O_6Na$ ($M+Na^+$) 417.2253, found: 417.2253.

3-Hydroxynegundoin A (57):

2N KOH in MeOH (1 mL) was added to a solution of **56** (132 mg, 0.34 mmol) in MeOH (10 mL) and the mixture was stirred at room temperature for 18 h, at which time TLC showed no remaining starting material. Then, the solvent was removed in vacuum and ether – water (50 : 15 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated to afford a crude product which was directly purified by flash chromatography on silica gel (25% ether/hexanes) to give **57** (100 mg, 90 %) as a colorless syrup. $[\alpha]_D^{25}$= +11.5 (c = 6.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (d, *J* = 6.6 Hz, 3H), 0.79 (s, 3H), 0.93 (s, 3H), 1.01 (s, 3H), 1.25 - 1.50 (m, 4H), 1.52 - 1.69 (m, 4H), 1.79 (ddd, *J* = 13.5, 11.3, 4.6 Hz, 1H), 2.09 (ddd, *J* = 13.4, 11.7, 7.5 Hz, 1H), 3.00 (ddd, *J* = 11.4, 7.5, 2.0 Hz, 1H) 3.03 (ddd, *J* = 11.5, 7.6, 2.0 Hz, 1H), 3.11 (ddd, *J* = 11.7, 4.6, 1.7 Hz, 1H), 3.14 (ddd, *J* = 11.8, 4.6, 1.7 Hz, 1H), 3.21 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.65 (s, 3H), 5.28 (t, *J* = 1.8 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.4 (CH_3), 15.5 (CH_3), 16.8 (CH_3), 21.1 (CH_2), 26.6 (CH_2), 26.8 (CH_2), 28.0 (CH_3), 29.5 (CH_2), 31.1 (CH_2), 31.6 (CH_2), 36.5 (CH), 38.8 (C), 42.1 (C), 46.0 (CH), 50.5 (CH_3), 78.3 (CH), 87.0 (CH), 98.0 (C), 169.5 (C), 178.8 (C). IR (film): 1667, 1630, 1364, 1126, 1045, 961, 815, 756 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{32}O_4Na$ ($M+Na^+$) 359.2198, found: 359.2205.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra for compounds **3, 4, 6**, **7**, **8**, **9**, **15**, **16**, **17**, **18**, **19**, **22**, **25**, **31**, **32**, **33**, **34**, **35**, **36**, **38**, **39**, **40**, **41**, **42**, **43**, **44**, **45**, **46**, **47**, **48**, **49**, **50**, **51**, **52**, **53**, **54**, **55**, **56**, **57**. This material is available free of charge via the internet at http://pubs.acs.org.http://pubs.acs.org.

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I_2/PPh_3 Mediated Spiro Annulation of Unsaturated Carboxylic Acids: First Enantiospecific Synthesis of Isoambreinolide, Vitexifolin D and Vitedoin B

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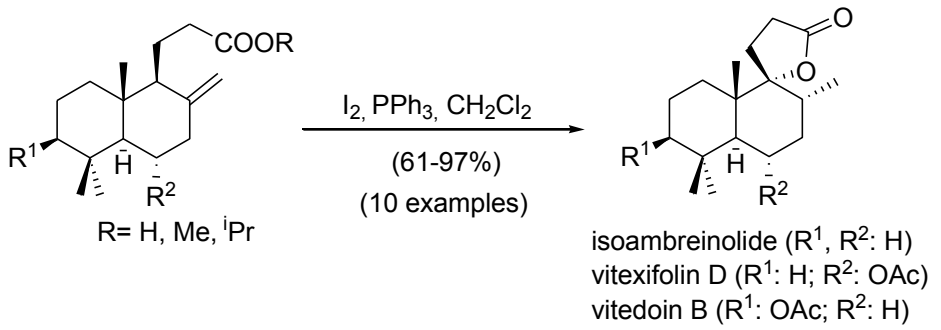


A very efficient method for synthesizing spirolactones is reported. The treatment of δ,ε-unsaturated carboxylic acids with iodine and triphenylphosphine under mild conditions lead to the corresponding γ- orδ-spirolactones in high yield and with complete stereoselectivity. Utilizing this, the first synthesis of terpenespirolactones(+)-isoambreinolide, (-)-vitexifolin D and (+)-vitedoin B has been achieved.

Introduction

Compounds bearing a spiro-carbon are widely found in nature. Among these, spirolactone derivatives are of particular interest, mainly due to the relevant biological properties exhibited by some of them. Aldactone® (**1**) is an antagonist of aldosterone at the receptor level,[1]which has been used for many years as a therapeutic agent for the treatment of edema, congestive heart failure, essential hypertension and cirrhosis of the liver.[2]Drospirenone (**2**) is a synthetic progestin that is a component of certain birth control formulations such as Yasmin 28®,[3] the world's most popular contraceptive pill. More recently, some trinorlabdane type spirolactones, such as isoambreinolide (**3**),[4]vitexifolin D

(**4**)[4]and vitedoin B (**5**),[5] whose biological activities have not yet been investigated, have been isolated from different vegetal species.

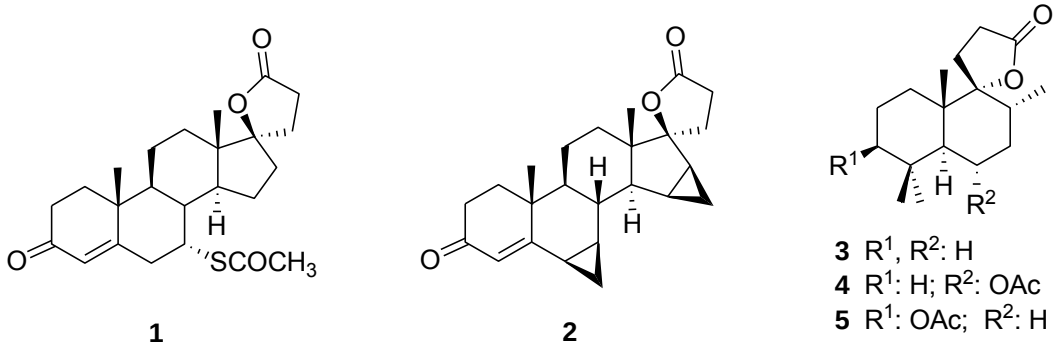


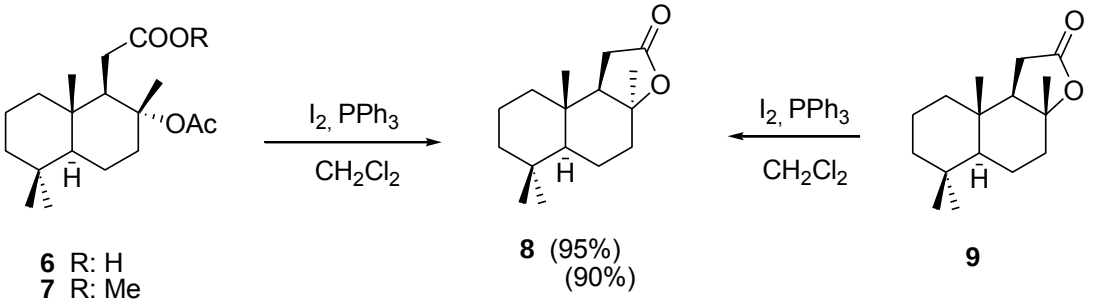
FIGURE 1. Representative bioactive spirolactones.

The biological importance of the above mentioned compounds and the presence of the sterically constrained spiro structure in these substances have motivated to many research groups the investigation on the synthesis of this type of compounds. On the other hand, the stereoselective synthesis of spirocompounds is a challenging task, requiring control in the construction of the quaternary carbon. The most inmediate method to access spirolactones involves an intramolecular esterification reaction,[6] which is favoured for entropic reasons; this strategy requires the prior installation of the tertiary alcohol.[7] Many other strategies involve the creation of the spirolactone concomitant to cyclization with the fused quaternary centre. *p*-Spiroquinones have been synthesized through an iodine (III)-induced dearomatization of phenols to quinones[8] or *via* a cerium (IV)-mediated oxidative coupling of 2,6-dibromophenol derivatives.[9]Spirolactones have also been synthesized *via* radical-based approaches[10] and reductive cross-coupling processes.[11] Other strategies utilized for synthesizing this type of compounds include cationic rearrangements,[12]halolactonization processes[13] and furanyldienolate-based cyclizations.[14]Pericyclic-type reactions, including

electrocyclizations,[15] [2+2] cycloadditions[16] and Diels-Alder reactions[17] have also been employed for this purpose.

During a revision of our research on the use of the I_2/PPh_3system in organic synthesis,[18] some of the previously reported results attracted our attention. The treatment of acetoxy acid **6** or acetoxy ester **7** with this reagent gave 8-epi-sclareolide (**8**) in high yield as the only product, which was an unexpected result, given that it is well-known that lactonization of compounds **6**, **7** or the related hydroxy acid lead exclusively to sclareolide (**9**).[19] This surprising result could be explained considering that the initially formed lactone **9** undergoes the ring-opening and further cyclization to give the most stable 8-epimer **8**, under the reaction conditions. This supposition was confirmed experimentally; the treatment of sclareolide (**9**), obtained from the corresponding hydroxy acid, with I_2/PPh_3gave in high yield lactone **8** as the only isomer (Scheme 1). The transformation of commercial sclareolide (**9**) into its 8-epimer **8** has been utilized as a key step in the synthesis of some relevant natural products.[20]

SCHEME 1.Obtention of 8-epi-Sclareolide (**8**), utilizing the I_2/PPh_3System



6 R: H
7 R: Me

8 (95%)
(90%)

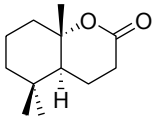
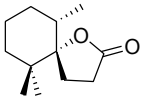
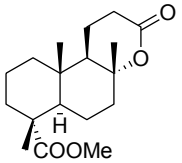
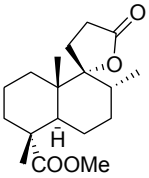
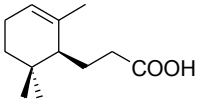
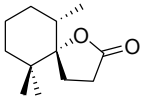
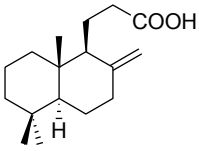
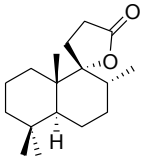
9

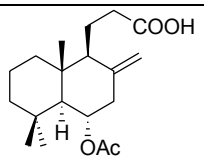
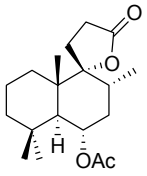
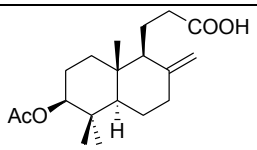
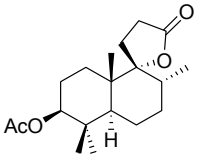
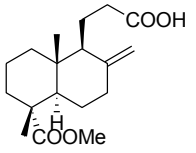
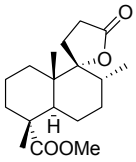
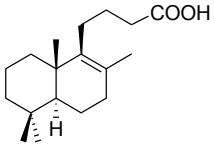
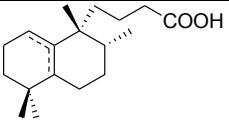
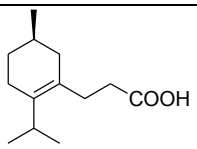
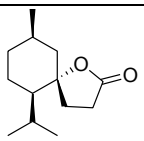
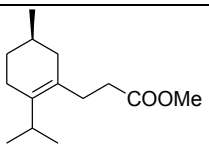
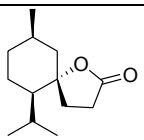
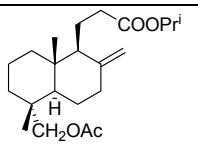
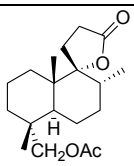
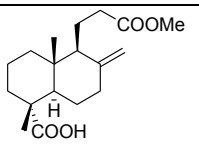
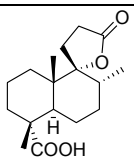
The epimerization of γ-lactone **9** provoked by the I_2/PPh_3system incited us to investigate the behaviour of δ-lactones. Treatment of lactones **10** and **11** under the same reaction conditions led in high yield to γ-spirolactones**22** and **23**, respectively, with complete stereoselectivity (Table 1).[21] On the other hand, the reaction of α-cyclogeranyl acetic acid (**12**), precursor of lactone **10**, under similar conditions for 3 days gave compound **22**; a mixture of lactones **10** and **22** resulted when the reaction time was 12 h. In a similar way, acid **13** was transformed into isoambreinolide (**3**), after 3 days of reaction, and acetoxy acid **14** led to vitexifolin D (**4**), a *nor*-labdanespirolactone, recently isolated from the fruits of *Vitexrotundifolia*[4]and not yet synthesized. Acids **15** and **16** showed a similar behaviour to that observed for compounds **13** and **14**, leading to a mixture of the corresponding δ-lactones andγ-spirolactonesafter 12 h of reaction, and affording γ-lactone as the only product when the reaction time was prolonged; thus, acetoxy acid **15** was transformed into vitedoin B (**5**), a spirolactone recently isolated from the seeds of *Vitexnegundo*[5] and not yet synthesized. The homologue acid **17** gave under the same reaction conditions the mixture of regioisomers acids **24**, resulting from a rearrangement process. On the other hand, the γ,δ-unsaturated acid **19** gave the γ-spirolactone**25**, under the above conditions. Unsaturated esters led under the same reaction conditions to the corresponding γ-spirolactones after prolonged reaction times. Thus, the methyl ester **19** afforded lactone **25** after 24 h, and the isopropyl ester **20** was converted into lactone **26** after 48 h. The treatment of the δ,ε-unsaturated methyl ester **21** with I_2-PPh_3 for 12 h gave the corresponding γ,δ-unsaturated methyl ester; when the reaction was prolonged for 4 days, the corresponding γ-spirolactone**28** was obtained as the only product. The relative stereochemistry of the above spirolactones was established on the basis of NOE

experiments. The structures assigned to compounds **4-5** agree with those reported in the literature for natural compounds.

The results obtained during the treatment of δ,ε-unsaturated acids or lactones with I_2-PPh_3 can be explained considering that the initially formed δ-lactone undergoes the ring opening to give the stable γ,δ-unsaturated acid, which is finally transformed into the termodinamically more stable γ-spirolactone.

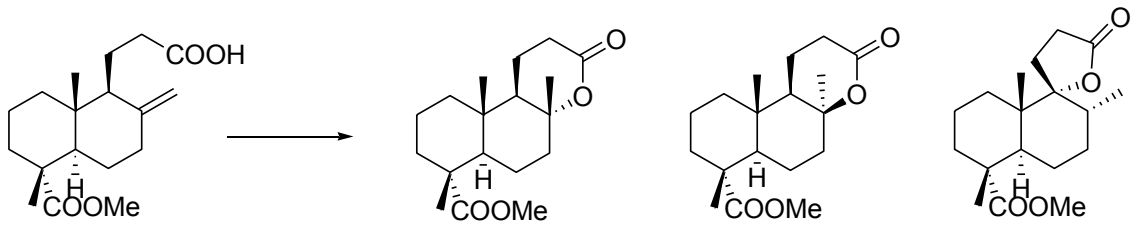
Table 1. Treatment of Unsaturated Carboxylic Acids and Esters, and δ-Lactones with I_2-PPh_3. Synthesis of γ-Spirolactones[a]

Entry	Acid or Lactone	Time	Spirolactone	Yield (%)
1	 **10**[22]	24 h	 **22**[27]	89
2	 **11**[23]	24 h	 **23**[28]	95
3	 **12**[22]	72	 **22**[27]	96
4	 **13**[24]	48 h	 **3**[4]	91

5	 **14**[25]	24 h	 **4**[4]	61
6	 **15**[26]	48 h	 **5**[5]	97
7	 **16**[26]	48 h	 **23**[28]	92
8	 **17**[26]	72 h	 **24**	67
9	 **18**[26]	12 h	 **25**	89
10	 **19**[26]	24 h	 **25**	93
11	 **20**[26]	48 h	 **26**	91
12	 **21**[26]	4 days	 **28**[28]	94

The behaviour of acid **16** under different lactonization conditions have been investigated (Table 2). The treatment with $SnCl_4$ at -30 ºC in dichloromethane for 4 h gave lactone **11** in 94% yield; decomposition was observed when the reaction was carried out at room temperature. The refluxing of acid **16** with *p*-toluenesulphonic acid in benzene for 5 h gave a 1:1 mixture of lactones **11** and **23**, in low yield, together with the unaltered acid **16** (30%). Under the iodolactonization conditions, treatment with I_2 in dichloromethane at room temperature for 3 days, acid **16** was transformed into a mixture of 8α- and 8β-epimers (ratio 1:3) of δ-lactone, compounds **29** and **11**, respectively (55%). Compound **23** (10%), together with decomposition products, resulted after treatment with I_2 in benzene under reflux for 3 ?????. When acid **16** was refluxed with cationic resin (Amberlite A-15) in dichloromethane for 5 h a mixture of 8-epimers **29** and **11** (ratio 1:3) resulted in 60%.

Table 2. Behavior of Acid **16** under Different Lactonization Conditions.



16 **11** **29** **23**

Entry	Reaction conditions	Products
1	$SnCl_4$, CH_2Cl_2, - 30 ºC	**11**
2	$SnCl_4$, CH_2Cl_2, - 30 ºC to rt	Decomposition
3	TsOH, benzene, reflux, 5h	**11 (**10%), **16** (10 %), **23** (10 %)
4	I_2, CH_2Cl_2, rt, 3 d	**11**, **29** (3:1) (55%)

5	I_2, benzene, reflux	**23** (10%) + Decomposition
6	Amberlyst A-15, CH_2Cl_2, reflux, 5 h	**11**, **29** (3:1) (60%)

In summary, a very efficient method for synthesizing γ-spirolactones is reported. The treatment of γ,δ- and δ,ε-unsaturated carboxylic acids and esters with iodine and triphenylphosphine under mild conditions lead to the corresponding γ-spirolactones in high yield and with complete stereoselectivity. Utilizing this new methodology, the first enantiospecific synthesis of terpenespirolactones(+)-isoambreinolide, (-)-vitexifolin D and (+)-vitedoin B has been achieved.

Experimental Section

General procedure for the preparation of lactones from carboxylic acids.

To a solution of triphenylphosphine (1 mmol) in dry CH_2Cl_2 (10 mL) was added iodine (1 mmol). The mixture was stirred at room temperature for 5 min and a solution of starting material (1 mmol) in dry CH_2Cl_2 (10 mL) was added. The resulting mixture was stirred at room temperature for 24h, at this time TLC showed no starting material. The solvent was removed under vacuum and the crude product was diluted with Et_2O – water (90 – 30 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (5% ether/hexanes) to give spirolactone (97 %) as colourless syrup.

(4aS,8aS)-5,5,8a-trimethyl-octahydrochromen-2-one (10)

^{1}H NMR($CDCl_3$, 500 MHz)δ(ppm): 0.78 (s, 3H), 0.82 (s, 3H), 0.88 (s, 3H), 0.91 (s, 3H), 1.23 (ddd, *J*= 13.4, 10.8, 3.5 Hz, 2H), 1.33 - 1.70 (m, 10H), 1.30 (s, 3H), 1.31 (s, 3H), 1.77 - 1.93 (m, 4H), 2.25 (t, *J*= 8.1 Hz, 1H), 2.08 (m, 1H), 2.46 - 2.56 (m, 3H), 2.63 (m, 1H).IR (film) $\nu_{máx}$: 1728, 1461, 1263, 1148, 1097, 1041, 973 cm^{-1}. ^{13}C NMR ($CDCl_3$, 500 MHz) δ(ppm), Signalsasignablestothe major product:16.9 (CH_3), 17.7 CH_2), 20.6 (CH_3), 22.0 (CH_3), 26.1 (CH_2), 31.9 (CH_3), 33.7 (C), 39.2 (CH_2), 40.6 (CH_2), 44.3 (CH_2), 82.2 (CH), 171.7 (C).Signalsasignablestotheminorproduct: 16.5 (CH_3), 19.7 CH_2), 20.6 (CH_3), 22.6 (CH_3), 29.4 (CH_2), 32.1 (CH_3), 33.8 (C), 40.2 (CH_2), 41.1 (CH_2), 49.0 (CH_2), 83.8 (CH), 172.9 (C).

(4aR,6aR,7R,10aS,10bR)-methyl-4a,7,10a-trimethyl-3-oxo-dodecahydro-1H-benzo[f]chromene-7-carboxylate (11)

[□]$_D^{25}$ = + 35.0 (c = 27.6 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.85 (s, 3H), 1.06 (ddd, *J* = 12.6, 3.8, 3.8 Hz, 1H), 1.14 (s, 3H), 1.23 (brd, *J*= 13.8 Hz, 1H), 1.35 (s, 3H), 1.39 (ddd, *J*=26.3, 13.9, 3.3 Hz, 1H), 1.51-1.88 (m, 10H), 1.95 (brd, *J*= 12.7 Hz, 1H), 2.53 (m, 1H), 2.66 (ddd, *J*=18.8, 8.4, 2.5 Hz, 1H), 3.65 (s, 3H).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.3 (CH_3), 15.6 (CH_2), 16.3 (CH_3), 17.4 (CH_2), 22.1 (CH_2), 22.9 (CH_3), 28.9 (CH_2), 36.7(CH_2), 36.7 (C), 38.2 (CH_2), 40.7 (CH_2), 47.2 (C), 50.2 (CH), 52.0 (CH_3), 53.5 (CH), 83.5 (C), 171.2 (C), 178.6 (C). IR (film): 1714, 1460, 1246, 1107, 1067, 987, 957, 771 cm^{-1}.

3-((1S,4S,4aS,8aR)-4-acetoxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)propanoic acid (14)

$[\alpha]_D^{25}$= + 33.5 (c = 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.76 (s, 3H), 0.89 (s, 3H), 1.02 (s, 3H), 1.12 (ddd, *J*= 12.6, 12.4, 4.1 Hz, 1H), 1.20 - 1.77 (m, 9H), 1.92 (dt, *J*= 12.0, 8.1 Hz, 1H), 2.05 (s, 3H), 2.20 (m, 1H), 2.55 (m, 1H), 2.70 (dd, *J*= 12.3, 5.1 Hz, 1H), 4.62 (s, 1H), 4.96 (s, 1H), 5.05 (ddd, J= 11.1, 11.1, 5.09 Hz, 1H), 6.02 (brs, 1H);^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm): 15.9 (CH_3), 18.3 (CH_2), 19.2 (CH_2), 21.9 (CH_3), 22.4 (CH_3), 33.2 (C), 33.5 (CH_2), 39.0 (CH_2), 39.6 (C), 43.3 (CH_2), 44.0 (CH_2), 55.3 (CH), 57.4 (CH), 73.1 (CH), 109.4 (CH_2), 143.6 (C), 170.1 (C), 179.05 (C). IR (film) $\nu_{máx}$: 1735, 1647, 1459, 1377, 1242, 1025, 971, 897, cm^{-1}.

3-((1S,4aR,6S,8aR)-6-acetoxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)propanoic acid (15)

$[\alpha]_D^{25}$ = + 26.5 (c = 6.1 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.72 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 1.26-1.45 (m, 3H), 1.56-1.92 (m, 7H), 1.97 (ddd, *J* = 12.9, 12.9, 5.0 Hz, 1H), 2.05 (s, 3H), 2.20 (m, 1H), 2.40 (ddd,*J* = 13.0, 4.1, 2.5 Hz, 1H), 2.52 (m, 1H), 4.52 (dd, *J* = 11.9, 4.4 Hz, 1H), 4.51 (s, 1H), 4.87 (s, 1H).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.4 (CH_3), 16.5 (CH_3), 19.0 (CH_2), 21.3 (CH_3), 23.8 (CH_2), 24.2 (CH_2), 28.2 (CH_3), 32.7 (CH_2), 36.6 (CH_2), 37.9 (CH_2), 38.0 (C), 39.2 (C), 54.6 (CH), 55.7 (CH), 80.6 (CH), 107.0 (CH_2), 147.0 (C), 171.0 (C), 179.1 (C). IR (film): 1733, 1709, 1369, 1244, 1030, 894, 757 cm^{-1}.

3-((1S,4aR,5R,8aR)-5-(methoxycarbonyl)-5,8a-dimethyl-2-methylene-decahydronaphthalen-1-yl)propanoic acid (16)

$[\alpha]_D^{25}$ = + 25.3 (c = 34.5 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.71 (s, 3H), 1.13 (s, 3H), 1.20 (m, 1H), 1.44 (ddd, *J*= 25.8, 12.9, 4.4 Hz, 1H), 1.52-1.69 (m, 4H), 1.69-1.83 (m, 4H), 1.85-1.97 (m, 2H), 2.01 (ddd, *J*= 12.9, 12.9,5.1 Hz, 1H), 2.20 (m, 1H), 2.33 (ddd, *J*= 12.7, 3.9, 2.1 Hz, 1H), 2.52 (ddd,*J*= 16.4, 9.2, 4.7 Hz, 1H), 3.65 (s, 3H), 4.50 (s, 1H), 4.81 (s, 1H).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.6 (CH_3), 16.5(CH_3), 18.4 (CH_2), 18.6 (CH_2), 26.8 (CH_2), 32.8 (CH_2), 36.9 (CH_2), 37.7 (CH_2), 37.9 (CH_2), 39.0 (C), 47.7 (C), 49.7 (CH), 51.9 (CH_3), 56.0 (CH), 107.1 (CH_2), 147.1 (C), 179.3 (C), 180.1 (C). IR (film): 1726, 1709, 1445, 1245, 1130, 1048, 893 cm^{-1}.

4-((4aS,8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)butanoic acid (17)

$[\alpha]_D^{25}$= + 56.9(c = 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.83 (s, 3H), 0.87 (s, 3H), 0.93 (s, 3H), 1.09 - 1.18 (m, 3H), 1.37 - 1.49 (m, 3H), 1.56 (s, 3H), 1.57 - 1.68 (m, 3H), 1.77 – 2.06 (m, 6H), 2.30 (ddd, *J*= 7.4, 7.3, 1.6 Hz, 2H), 9.02 (brs, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm): 19.0 (CH_2), 19.0 (CH_3),19.5 (CH_3), 20.1 (CH_3),21.6 (CH_3), 25.7 (CH_2),27.6 (CH_2), 33.3 (C),33.3 (CH_3), 33.6 (CH_2),35.0 (CH_2),36.9 (CH_2), 38.8 (C), 41.7 (CH_2),51.8 (CH),126.3 (C), 140.0 (C),179.3 (C).IR (film) $\nu_{máx}$: 1709, 1459, 1374, 1260, 750, cm^{-1}.

(R)-3-(2-isopropyl-5-methylcyclohex-1-enyl)propanoicacid (18)

$[\alpha]_D^{25}$= + 27.7 (c = 0.7, $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm)0.934 (d, *J*= 5.0Hz, 3H), 0.936 (d, J= 6.8, 6H), 1.26 (s a, 1H), 1.56 -1.72 (m, 4H), 1.99 (d, J= 12.7, 1H), 2,15 - 2.40 (m, 5H), 2.84 (h, J= 6.86, 1H), 6.34 (br s, 1H).^{13}C NMR($CDCl_3$, 500 MHz) δ (ppm): 20.62 (CH_3), 21.13 (CH_3), 21.79 (CH_3), 22.97 (CH_2), 28.33 (CH_2), 28.86 (CH), 29.00 (CH), 31.37 (CH_2), 34.4 (CH_2), 38.39 (CH_2), 136.44 (C), 179.15 (C).IR (film) ν_{max}: 3421, 2870, 1708, 1542, 1457, 1260, 1096, 1025, 800cm^{-1}.

(R)-methyl 3-(2-isopropyl-5-methylcyclohex-1-enyl)propanoate (19)

$[\alpha]_D^{25}$ = -31.4 (c = 0.7, $CHCl_3$.^{1}H NMR($CDCl_3$, 500 MHz) δ (ppm)0.934 (d, *J*= 5.0 Hz, 3H), 0.936 (d, *J*= 6.8, 6H), 1.30 (m, 1H), 1.56 - 1.71 (m, 4H), 1.97 - 2.01 (m, 2H), 2,26 - 2.32 (m, 4H), 2.83 (h, *J*= 6.8, 1H), 3.67 (s, 1H).^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm): 20.6 (CH_3), 21.1 (CH_3), 21.7 (CH_3), 22.9 (CH_2), 28.2 (CH_2), 28.8 (CH), 28.9 (CH), 31.3 (CH_2), 33.4 (CH_2), 38.3 (CH_2), 51.4 (CH_3), 136.47 (C), 174.1 (C). IR (film) ν_{max}: 1741, 1639, 1458, 1436, 1363, 1256, 1170 cm^{-1}.

Isopropyl-3-((1S,4aR,5R,8aR)-5-(acetoxymethyl)-5,8a-dimethyl-2-methylene-decahydronaphthalen-1-yl)propanoate (20)

$[\alpha]_D^{25}$ = + 25.6 (c = 16.8 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.72 (s, 3H), 0.81 (s, 3H),1.08 (ddd,*J* = 12.4, 12.4, 4.9 Hz, 1H),1.21 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.34-1.39 (m, 4H), 1.53-1.67 (m, 5H), 1.79 (ddd, *J* = 12.7, 3.2, 3.2 Hz, 1H), 1.84-1.97 (m, 2H), 2.06 (s, 3H), 2.13 (m, 1H), 2.33-2.45 (m, 2H), 3.64 (d, *J* = 10.9 Hz, 1H), 3.84 (d, *J* = 10.9 Hz, 1H), 4.50 (s, 1H), 4.84 (s, 1H), 4.99 (h, *J* = 6.3 Hz, 1H). ^{13}C RMN ($CDCl_3$,

125 MHz) δ: 14.7 (CH_3), 17.5 (CH_3), 18.5 (CH_2), 19.1 (CH_2), 21.0 (CH_3), 21.84 (CH_3), 21.89 (CH_3), 24.3 (CH_2), 33.5 (CH_2), 35.9 (CH_2), 36.8 (C), 37.9 (CH_2), 38.4 (CH_2), 39.5 (C), 49.4 (CH), 56.1 (CH), 67.3 (CH), 72.9 (CH_2), 106.8 (CH_2), 147.4 (C), 171.2 (C), 173.7 (C). IR (film): 1733, 1467, 1379, 1239, 1110, 1038, 891 cm^{-1}.

(1R,4aR,5S,8aR)-5-(3-methoxy-3-oxopropyl)-1,4a-dimethyl-6-methylene-decahydronaphthalene-1-carboxylic acid (21)

$[\alpha]_D^{25}$ = + 7.9 (c = 18.9 $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.75 (s, 3H), 1.14 (m, 1H), 1.23 (s, 3H), 1.33-1.48 (m, 2H), 1.53-1.67 (m, 3H), 1.67-1.81 (m, 4H), 1.87 (m, 1H), 2.08 (ddd, *J* = 12.6, 12.6, 5.7 Hz, 1H), 2.10-2.19 (m, 2H), 2.32 (br d, *J* = 12.7 Hz, 1H), 2.45 (ddd, *J* = 16.0, 9.3, 4.7 Hz, 1H), 3.64 (s, 3H), 4.49 (s, 1H), 4.82 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.8 (CH_3), 18.6 (CH_2), 18.9 (CH_2), 19.0 (CH_3), 27.0 (CH_2), 33.0 (CH_2), 35.8 (CH_2), 37.6 (CH_2), 37.9 (CH_2), 39.4 (C), 46.9 (C), 49.9 (CH), 51.4 (CH_3), 56.4 (CH), 106.7 (CH_2), 147.7 (C), 174.5 (C), 178.4 (C). IR (film): 1737, 1624, 1440, 1357, 1254, 1166, 1042, 891 cm^{-1}.

1-Oxaspiro[4.5]decan-2-one, 6,6,10-trimethyl (1S,6S) (22)

^1H NMR($CDCl_3$, 500 MHz) δ (ppm): 0.86 (d, *J*= 6.7 Hz, 3H), 0.88 (s, 3H), 0.95 (s, 3H), 1.24 (m, 1H), 1.41 - 1.45 (m, 2H), 1.49 - 1.53 (m, 2H), 1.67 (m, 1H), 1.86 (ddd, *J*= 13.6, 11.2, 5.1 Hz, 1H), 2.18 (ddd, *J*= 13.5,11.5, 8.4 Hz, 1H), 2.49 (ddd, *J*= 18.7, 11.3, 5.1 Hz, 1H), 2.56 (ddd, *J*= 18.7, 11.2, 8.4 Hz, 1H).^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm): 15.5 (CH_3), 21.2 (CH_2), 22.0 (CH_3), 24.6 (CH_3), 25.3 (CH_2), 29.7 (CH_2), 30.5 (CH_2), 36.2 (CH_2), 36.8 (CH), 92.6 (C), 177.7 (C). IR (Film) $\nu_{máx}$: 1766, 1481, 1452, 1390, 1369, 1275, 1202, 969 cm^{-1}

Spiro[furan-2(5H),1'(2'H)-naphthalen]-5-one-decahydro-2',5',8'a-trimethyl-5'-(methoxycarbonyl)-(1S,2R,4aR,5R,8aR) (23)

$[\alpha]_D^{25}$= +28.4 (c = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.83 (d, *J*= 6.6 Hz, 3H), 0.92 (s, 3H), 1.14 (s, 3H), 1.10 (m, 1H), 1.35 - 1.49 (m, 6H), 1.71 - 1.78 (m, 2H), 1.83 (ddd, *J*= 13.7, 11.5, 4.9Hz, 1H), 2.17 (m, 1H), 2.31 (m, 1H), 2.46 (ddd, *J*= 18.6, 11.7, 9.0 Hz, 1H), 2.51 (ddd, *J*= 18.7, 11.2, 8.0 Hz, 1H), 3.62 (s, 3H).^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm):15.9 (CH_3), 16.8 (CH_3), 17.6 (CH_2), 23.8 (CH_2), 24.8 (CH_2), 29.5 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 36.1 (CH_2), 36.9 (CH), 41.6 (CH), 41.7 (C), 47.4 (C), 51.8 (CH_3), 93.5 (C), 177.5 (C), 178.6 (C). IR (film) $\nu_{máx}$: 1764, 1720, 1462, 1391, 1243, 1200, 1102, 961, 760, 616 cm^{-1}.

Spiro[furan-2(5*H*),1'(2'*H*)-naphthalen]-5-one-decahydro-2',5',5',8'a-tetramethyl-, (1'*R*,2'*R*,4'a*S*,8'a*S*)

$[\alpha]_D^{25}$= - 4.3 (c = 0.84, $CHCl_3$).^{1}H NMR($CDCl_3$, 500 MHz) δ (ppm): 0.82 (s, 3H), 0.84 (d, *J*= 6.6 Hz, 3H), 0.92 (s, 3H), 1.18 (ddd, *J*= 13.6, 13.2, 4.0 Hz, 1H), 1.25 - 1.64 (m, 10H), 1.76 - 1.85 (m, 2H), 2.19 (ddd, *J*= 13.5, 11.7, 7.8 Hz, 1H), 2.45 (ddd,*J*= 18.6, 11.6, 5.1 Hz, 1H), 2.53 (ddd, *J*= 18.7, 11.3, 7.8 Hz, 1H).^{13}C NMR($CDCl_3$, 500 MHz) δ (ppm): 15.6 (CH_3), 15.7 (CH_3), 18.3 (CH_2), 21.3 (CH_2), 21.9 (CH_3), 24.7 (CH_2), 29.5 (CH_2), 30.9 (CH_2), 31.2 (CH_2), 33.1 (CH_3), 33.3 (C), 36.8 (CH), 41.3 (CH_2), 42.2 (C), 46.6 (CH), 94.0 (C), 177.8 (C). IR (film) $\nu_{máx}$: 1768, 1462, 1388, 1219, 1176, 1116, 971 cm^{-1}.

Spiro[furan-2(5*H*),1'(2'*H*)-naphthalen]-5-one-4'-(acetyloxy)decahydro-2',5',5',8'a-tetramethyl-, (1'*R*,2'*R*,4'*R*,4'a*S*,8'a*S*)

$[\alpha]_D^{25}$= +18.7 (c = 0.33, $CHCl_3$). ^{1}H NMR($CDCl_3$, 500 MHz) δ (ppm): 0.88 (d, *J*= 6.5 Hz, 3H), 0.90 (s, 3H), 1.0 (s, 3H), 1.04 (s, 3H), 1.28-1.66 (m, 6H), 1.81-1.88 (m, 2H), 1.98 (m, 1H), 1.91 (br d, 11.6 Hz, 1H), 2.03 (s, 3H), 2.18 (ddd, *J*= 6.6, 6.6, 1.8 Hz, 1H), 2.48 (ddd, *J*= 19.0, 11.6, 5.6 Hz, 1H), 2.55 (ddd, *J*= 19.0, 11.3, 7.3 Hz, 1H), 5.13 (ddd, *J*= 11.4, 11.4, 4.7 Hz, 1H).^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm): 15.1 (CH_3), 16.9 (CH_3), 18.0 (CH_2), 21.9 (CH_3), 22.6 (CH_3), 24.6 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 33.2 (C), 35.0 (CH), 36.0 (CH_3), 37.0 (CH_2), 42.8 (CH_2), 43.9 (C), 48.9 (CH), 71.5 (CH), 92.6 (C), 170.5 (C), 177.3 (C).IR (film) $\nu_{máx}$: 1771, 1732, 1652, 1457, 1245, 1220, 1097, 1023, 966, 801, 774, 660, 615cm^{-1}.

Spiro[furan-2(5*H*),1'(2'*H*)-naphthalen]-5-one-6'-(acetyloxy)-decahydro-2',5',5',8'a-tetramethyl-, (1'*R*,2'*R*,4'*R*,4'a*S*,6'*S*,8'a*S*)

$[\alpha]_D^{25}$= + 4.7(c = 3.2, $CHCl_3$.^{1}H NMR($CDCl_3$, 500 MHz) δ (ppm)0.85 (d, *J*= 6.6 Hz, 3H), 0.87 (s, 3H), 0.88 (s, 3H), 0.95 (s, 3H), 1.25 (s a, 2H), 1.40-1.47 (m, 2H), 1.50-1.66 (m, 5H), 1.83 (m, 1H), 1.86 (ddd, *J*= 13.7, 11.6, 5.0 Hz, 1H), 2.04 (s, 3H), 2.18 (ddd, *J*= 13.4, 11.8, 8.1 Hz, 1H), 2.46 (ddd, *J*= 18.78, 11.67, 4.97 Hz, 1H), 2.54 (ddd, *J*= 18.7, 11.34, 7.96 Hz, 1H), 4.48 (dd, *J*= 11.53, 4.39 Hz, 1H).^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm): 15.4 (CH_3), 15.8 (CH_3), 16.6 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 23.2 (CH_2), 24.9 (CH_2), 27.8 (CH_3), 29.36 (CH_2), 29.44 (CH_2), 30.7 (CH_2), 36.7 (CH), 37.7 (C), 41.8 (C), 46.1 (CH), 80.0 (CH), 93.3 (C), 170.7 (C), 177.3 (C).). IR (film) $\nu_{máx}$: 1767, 1733, 1462, 1366, 1242, 1199, 1177, 1111, 1281, 1091, 1032, 972, 954, 668 cm^{-1}

4-((1R,2R)-1,2,5,5-tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-1-yl)butanoic acid (24)

$[\alpha]_D^{25}$= - 46.3 (c = 3.7, $CHCl_3$). ^{1}H NMR($CDCl_3$, 500 MHz) δ (ppm): 0.80 (s, 3H), 0.82 (d, *J*= 6.8 Hz, 3H), 0.95 (s, 3H), 0.97 (s, 3H), 1.26 - 1.80 (m, 12H), 1.96 – 1.99 (m, 3H), 2.28 - 2.31 (m, 2H); IR (film) $\nu_{máx}$, 1713, 1456, 1280, 1215, 934 cm^{-1}.^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm): Signalsasignablestothe major product: 16.1 (CH_3), 19.4 (CH_2), 19.9 CH_2), 21.1 (CH_3), 25.1 (CH_2), 25.7 (CH_2), 27.1 (CH_2), 27.7 (CH_3), 31.3 (CH_2) 33.5 (CH_3) 34.4 (C), 34.7 (CH), 35.7 (CH_2), 39.8 (CH_2), 40.5 (C), 132.2 (C), 136.9 (C), 179.8 (C). Signalsasignablestotheminorproduct: 16.3 (CH_3), 19.0 (CH_2), 21.0 (CH_2), 23.24 (CH_2), 27.4 (CH_3), 34.8 (CH), 35.1 (CH_2), 117.0 (C), 145.8 (CH_2).

1 -Oxaspiro[4,5]decan-2-one-6-isopropyl-10-methyl (1S,2R,5R) (25)

$[\alpha]_D^{25}$= -3.6(c = 0.7, $CHCl_3$), ^{1}H NMR($CDCl_3$, 500 MHz) δ (ppm)0.84 (d, *J*= 6.86 Hz, 3H), 0.88 (d, J= 6.26, 3H), 0.96 (d, J= 6.93, 3H), 1.11-1.21 (m, 4H), 1.45-1.65 (m, 2H), 1.75-1.89 (m, 3H), 1.98 (h, J= 6.8, 1H), 2.34 (ddd, *J*= 13.2, 10.7, 7.0 Hz, 1H), 2.5 (ddd, *J*= 18.3, 10.67, 6.9 Hz, 1H), 2.63 (ddd, *J*= 18.37, 10.89, 7.08 Hz, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ (ppm):17.8 (CH_3), 21.7 (CH_2), 22.0 (CH_3), 23.8 (CH_3), 26.3 (CH), 28.6 (CH), 29.0 (CH_2), 31.2 (CH_2), 34.6 (CH_2), 49.3 (CH_2), 49.8 (CH), 89.37 (C), 177.04 (C). IR (film): 2868, 1770, 1465, 1216, 1139, 947, 917 cm^{-1}

Spiro[furan-2(5H),1'(2'H)-naphthalen]-5-one-decahydro-2',5',8'a-trimethyl-5'-(acetoxymethyl)-(1S,2R,4aR,5R,8aR) (26)

$[\alpha]_D^{25}$ = + 15.9 (c = 26.5 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.83 (s, 3H), 0.84 (d, *J* = 6.1 Hz, 3H), 0.94 (s, 3H), 1.22-1.40 (m, 6H), 1.47-1.62 (m, 4H), 1.72-1.80 (m, 2H), 1.83 (ddd, *J* = 13.9, 11.7, 5.2 Hz, 1H), 2.06 (s, 3H), 2.19 (ddd, *J* = 13.7, 11.8, 8.0 Hz, 1H), 2.40-2.58 (m, 2H), 3.68 (d, *J* = 10.9 Hz, 1H), 3.81 (d, *J* = 10.9 Hz, 1H).^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.4 (CH_3), 16.0 (CH_3), 17.4 (CH_2), 17.5 (CH_3), 21.0 (CH_3), 21.3 (CH_2), 24.8 (CH_2), 29.5 (CH_2), 30.58 (CH_2), 30.64 (CH_2), 35.3 (CH_2), 36.6 (CH), 36.6 (C), 41.3 (CH), 42.0 (C), 72.7 (CH_2), 93.7 (C), 171.3 (C), 177.6 (C).IR (film): 1766, 1738, 1464, 1383, 1240, 1038, 967 cm^{-1}.

Spiro[furan-2(5H),1'(2'H)-naphthalen]-5-one-decahydro-2',5',8'a-trimethyl-5'-(carboxylic acid)-(1S,2R,4aR,5R,8aR) (28)

$[\alpha]_D^{25}$ = 17.6 (c 1.0= $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.85 (d, *J* = 6.6 Hz, 3H), 0.95 (s, 3H), 1.17 (s, 3H), 1.25 (s, 3H), 1.23-1.33 (m, 4H), 1.35-1.44 (m, 2H), 1.44-1.55 (m, 2H), 1.55-1.65 (m, 2H), 1.78 (m, 1H), 1.85 (ddd, *J* = 13.7, 11.5, 4.9 Hz, 1H), 2.20 (ddd, *J*

= 13.6, 11.7, 8.1 Hz, 1H), 2.33 (m, 1H), 2.42-2.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.5 (CH_3), 15.9 (CH_3), 16.6 (CH_3), 17.6 (CH_2), 23.8 (CH_2), 24.7 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 30.3 (CH_2), 30.5 (CH_2), 36.2 (CH_2), 36.9 (CH), 41.6 (C), 41.7 (CH), 47.2 (C), 93.6 (C), 177.5 (C), 183.5 (C). IR (film): 1763, 1695, 1464, 1390, 1242, 962, 759 cm^{-1}.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra for compounds **3, 4, 5, 10, 11, 14-26**and **28**. This material is available free of charge via the internet at http://pubs.acs.org..

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