A New Strategy for the Synthesis of Cyclic Terpenoids Based on the Radical Opening of Acyclic Epoxypolyenes

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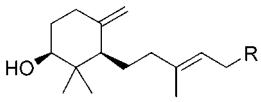
Introduction

The cationic cyclization of polyenes has proved to be a useful tool in the synthesis of natural terpenic products.[1] During recent years biomimetic approaches using radical chemistry have also been described.[2,3] One of the most efficient is based on Mn(III) chemistry, which in the presence of Cu(II) resolves one of the main problems involved in radical reactions, the loss of funcionality.[4,5] Another method is that of using Ti(III)[6] complexes to promote the homolytic opening of epoxides and the addition of the resulting radical to an alkene, forming five-membered rings.[7,8] In this case the reaction normally ends in the protonolysis of the organometallic intermediate, although the use of other electrophiles leads to more functionalized final products.[7a]

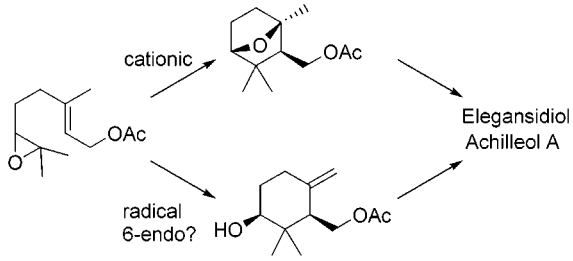
Our recent research has been into the synthesis of terpenes with functionalized cyclohexane skeletons (Figure 1) via the electrophilic opening of acyclic epoxypolyenes.[9] This approach leads to oxabicyclic compounds, which can be further elaborated (Scheme 1). Our intention in this note is to describe a more efficient approach to obtain this kind of terpene skeleton and if possible to generalize to other types of skeleton under mild reaction conditions, since direct policyclizations of epoxides of natural polyenes usually give complex mixtures of products and low yields (less than 10%) of polycyclic compunds.[10] To this end we decided to apply a technique involving the homolytic opening of epoxides with Ti(III) complexes to acyclic epoxypolyenes under reaction conditions that give rise to an oxidative termination step.[11]



Elegansidiol, R = OH
Achilleol A, R = farnesyl

Figure 1. Selected cyclohexanic natural products.

Scheme 1. Strategies for Arriving at Funcionalized Cyclohexanes



Results and Discussion

When 6,7-epoxygeranyl acetate **1** was made to react with stoichiometric quantities of Cp_2TiCl, a cyclization product mixture, **2**−**4**, was obtained (71%)[12] (Table 1), in which the predominant products derive from a 6-endo-trig cyclization mode (63%) since the 5-exo-trig process (8%) is sterically unfavorable.[13]

The *cis*/*trans* stereoselection in the six-membered carbocycles comes from a chairlike (*cis*) or boatlike (*trans*) transition state of the cyclization (Scheme 2). An isomerization process of $\Delta^{2,3}$ double bonding under the reaction conditions in question can be ruled out because when the cyclization reaction is carried out with the isomeric substrate, 6,7-epoxyneryl acetate **5**, no cyclization products are obtained, only the acyclic products **6** and **7**[14]

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(1) For a review see: Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 341.

(2) (a) Mn complexes: Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3661. Snider, B. B.; Mohan, R.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841. Zoretic, P. A.; Fang, H.; Ribeiro, A. A. *J. Org. Chem.* **1998**, *63*, 7213. Zoretic, P. A.; Zhang, Y.; Fang, H. *J. Org. Chem.* **1998**, *63*, 1162. Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Cheung, K.-K. *J. Am. Chem. Soc.* **2000**, *122*, 1658. (b) Acyl radicals: Pattenden, G.; Roberts, L.; Blake, A. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 863. Handa, S.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 843.

(3) For the preparation of terpene skeletons via cation radicals see: Warzecha, K.-D.; Xing, X.; Demuth, M. *Pure Appl. Chem.* **1997**, *69*, 109. Warzecha, K.-D.; Xing, X.; Demuth, M.; Goddard, R.; Kessler, M.; Krüger, C. *Helv. Chim. Acta* **1995**, 2065. Hoffmann, U.; Gao, Y.; Pandey, B.; Klinge, S.; Warzecha, K.-D.; Krüger, C.; Roth, H. D.; Demuth, M. *J. Am. Chem. Soc.* **1993**, *115*, 10358.

(4) Transition-metal radical chemistry has the advantage of final functionalizing reaction steps. For a review see: Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771.

(5) (a) Mn review: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Recent references: Cole, B. M.; Han, L.; Snider, B. B. *J. Org. Chem.* **1996**, *61*, 7832. O'Neil, S. V.; Quickley, C. A.; Snider, B. B. *J. Org. Chem.* **1997**, *62*, 1970. Garcia-Ruano, J. L.; Rumbero, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4427. Pettus, T. R. R.; Inoue, M.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6160.

(6) For a recent review of Cp_2TiCl chemistry see: Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103.

(7) (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986 and references therein. (b) Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 9855. For the Ti catalytic version see: (c) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849.

(8) The reaction has hardly been used in natural product synthesis: Clive, D. J. L.; Magnuson, S. R.; Manning, H. W.; Mayhew, D. L. *J. Org. Chem.* **1996**, *61*, 2095. Mandal, P. K.; Maiti, G.; Roy, S. C. *J. Org. Chem.* **1998**, *63*, 2829.

(9) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Rodriguez, A.; Linares, P. *Tetrahedron* **2000**, *56*, 6099.

(10) Van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152.

(11) For a precedent see: Chakraborty, T. K.; Dutta, S. *Tetrahedron Lett.* **1998**, *39*, 101.

(12) . The stereochemical assigments for all new compounds were established on the basis of NOE diff experiments.

(13) For a regio- and stereochemical study of radical cyclizations see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH Publishers: New York, 1996. (b) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059. (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(14) Similar products with *E* configuration in $\Delta^{2,3}$ double bond were obtained in the cyclization of **1**. See Supporting Information.

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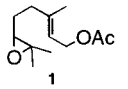
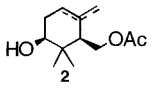
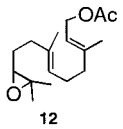
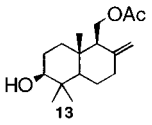
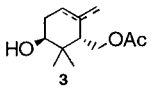
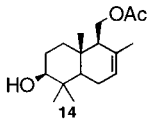
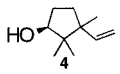
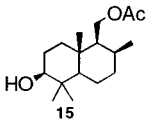
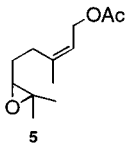
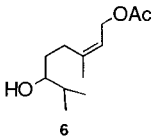
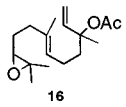
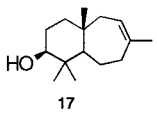
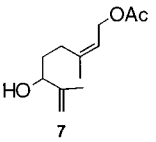
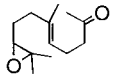
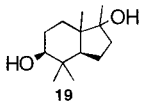
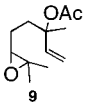
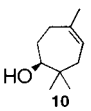
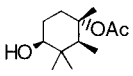
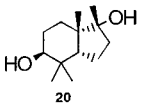
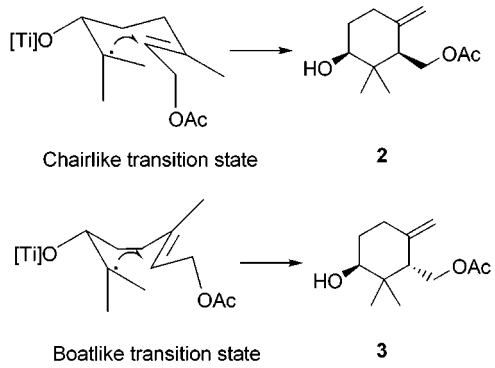
Table 1. Cyclization Reactions

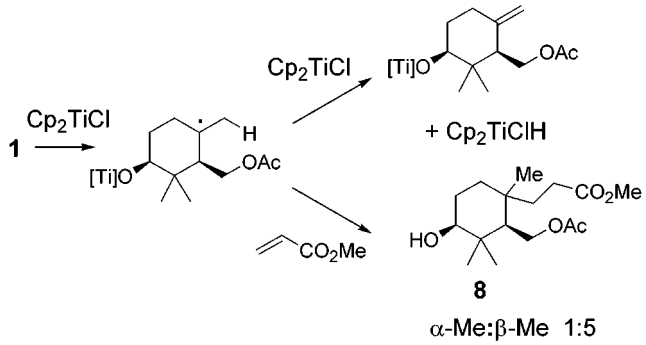
Epoxide	Product	Yield (%)	Epoxide	Product	Yield (%)
 1	 2	54.5[a]	 12	 13	25
	 3	8.5[b]		 14	5
	 4	8[c]		 15	25
 5	 6	74[d]	 16	 17	44
	 7		 18	 19	41[e]
 9	 10	55			
	 11	22.5		 20	6

[a] Product **2** presents an exo:endo ratio of 6.3:1. [b] Product **3** presents an exo:endo ratio of 7.3:1. [c] 1:1 mixture of diastereoisomers. [d] The **6**:**7** ratio was 10:1. [e] Product **19** is a mixture of three diastereoisomers at a ratio of 1:1:1.

Scheme 2. Nature of the Stereoselection in the Cyclization of Epoxide 1



Scheme 3. Proposed Mechanism



probably as the result of a decrease of the cyclization rate toward others secondary processes.

The most interesting result is that the cyclic products produced had an alkene function. Cyclopentane **4** shows a double bond that derives from β-acetoxy elimination of the intermediate organotitanium.[15] The formation of cyclohexenes **2** and **3** can in this case be attributed to a β-hydride elimination of hydrogen in the intermediate organotitanium (Scheme 3).[16,17,18] The regiochemistry of the mainly exocyclic elimination of hydrogen is well

(15) The reaction has wide precedents in early transition-metal chemistry: (a) Ti: ref 7a. Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3559. Spencer, R. P.; Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1999**, *64*, 3987. (b) Zr: Takahashi, T.; Kondanov, D. Y.; Xi, Z.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *117*, 5871. (c) Sm: Molander, G. A.; Mckie, J. A. *J. Org. Chem.* **1994**, *59*, 3186.

(16) It is known that the β-hydrid elimination process in d^0 metal complexes is slow: Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; Wiley & Sons: New York, 1994; pp 45−48. Although some examples of this process in Ti(IV) chemistry have been described: Okamoto, S.; Livinghouse, T. *J. Am. Chem. Soc.* **2000**, *122*, 1223. Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976. Moreover this is the final step in some Co-mediated radical cyclizations: Branchaud, B. P.; Meier, M. S.; Choi, Y. *Tetrahedron Lett.* **1988**, *29*, 167. Begley, M. J.; Bhandal, H.; Hutchinson, J. H.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1317.

(17) A cationic pathway can be ruled out because of the regiochemistry of the final double bond.

(18) A mixed radical disproportionation between the cyclic radical and some type of titanium-based radical cannot be ruled out. For a review of radical disproportionation see: Gibian, M. J.; Corley, R. C. *Chem. Rev.* **1973**, *73*, 441.

documented in the literature concerning organometallic transition complexes.[19] An intermediate cyclic radical was detected when a Michael acceptor such as methyl acrylate was added to the reaction mixture, leading to the more functionalized product **8**, which can be used in the synthesis of other kinds of compound.

When the reaction was carried out with 6,7-epoxylinalyl acetate **9**, we expected to obtain a mixture of functionalized cyclohexanes structurally related to some natural products. Instead we obtained good yields (77.5%) of a mixture of seven- (**10**) and six- (**11**) membered carbocycles. It is worth noting that the main product was the seven-membered carbocycle **10** karahanahenol,[20] derived from a 7-endo-trig cyclization, an unfavorable process for nucleophilic radicals.[21−24] This result may be due to the exertion of a Thorpe−Ingold effect of the methyl and acetate group upon C-3 carbon. The double bond is formed once more in a β-acetoxy elimination process. The cyclohexane **11** was obtained via 6-exo-trig cyclization with a consecutive protonolysis of primary alkyltitanium.[25,26]

When the reaction was performed with 10,11-epoxyfarnesyl acetate **12**, we obtained bicyclization products **13**−**15** (55%)[27] with drimane skeletons, derived from two consecutive 6-endo-trig cyclizations.[28,29] Thus the reaction was completely stereospecific, generating only the trans decalin with the acetylcarbinol group being disposed equatorially.[28] The termination process of the bicyclic radical is similar to that described for epoxide **1** showing as well a preferential exocyclic elimination unlike the cationic process. The formation of bicyclic product **15** is probably due to the transfer of a hydrogen atom from the solvent.[30,31]

The reaction made with the 10,11-epoxynerolidyl acetate **16** yields only the interesting bicyclic product **17**,[32] derived from consecutive 6-endo and 7-endo-trig cyclizations, concerning which there are no references in the literature. Once more the reaction ends with a β-acetoxy elimination process.

To expand the possibilities of these cyclizations with regard to their cationic analogues we performed the reaction with epoxide **18**, thus obtaining the bicyclic diols **19** and **20**, which derive from consecutive 6-endo and 5-exo-trig cyclizations.[33,34]

Conclusions

In summary, this work represents a extension of biomimetic radical cyclizations in the context of the synthesis of terpene skeletons to obtain a wide range of structures under controlled conditions, with the added value of using simple, readily available primary materials, thus rendering this approach highly attractive for the synthesis of natural products. Moreover it represents one of few examples of final functionalization in radical reactions. Although the yields in some cases are low and an improvement in reaction conditions might be seen as desirable, we are now working in this direction to develop a titanium catalytic version[35] of the reaction and its application to the synthesis of polycyclic natural products with medium-sized rings.

Experimental Section

Melting points were determined with a Kofler hot stage melting point apparatus. NMR spectra were recorded on Bruker AMX300 (300 MHz) and ARX400 (400 MHz) instruments. Mass spectra were obtained on a Micromass Platform 2 spectrometer. HMRS were obtained on a trisector WG AutoSpecQ spectrometer. Only the most significant molecular ions and/or base peaks in the MS are given. Microanalysis were recorded at the Servicios Técnicos (UGR) with a Perkin-Elmer 2400 apparatus. Chromatography was performed with flash grade silica gel using hexane/MeO*t*Bu mixtures. All reactions were carried out under an atmosphere of argon. Dry THF was obtained by distillation under Ar from sodium/benzophenone ketyl. The epoxides **1**, **5**, **9**, **12**, and **18** were prepared according to known procedures.[36,37] The following known compounds were isolated as pure samples and showed NMR spectra identical with the reported data: **2**,[38] **10**,[39] **14**,[40] and **15**.[3]

General Procedure. A mixture of Cp_2TiCl_2 (2.2 mmol) and Mn dust (8 mmol) in strictly deoxygenated THF (50 mL) was stirred at room temperature until the red solution turned green.

(19) Hegedus, L. S. In *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Sausalito, CA, 1999.

(20) Odorant product related structurally with natural terpene Karahanaenone: Miyazawa, M.; Tsuruno, K.; Kameoka, H. *Tetrahedron: Asymmetry* **1995**, *6*, 2121.

(21) For a review of the preparation of medium-sized rings via radicals see: Yet, L. *Tetrahedron* **1999**, *55*, 9349.

(22) The 7-endo-trig cyclization mode of the 6-heptenyl radical is unfavorable towards the 6-exo-trig cyclization mode. Theoretical study: Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472. Some examples of these cyclizations in low yield: Porter, N. A.; Chang, V. H−T. *J. Am. Chem. Soc.* **1987**, *109*, 4976. Porter, N. A.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 2787.

(23) For precedents with electrophilic radicals see: Snider, B. B.; Merritt, J. E. *Tetrahedron* **1991**, *47*, 8663. Colombo, M. I.; Signorella, S.; Mischne, M. P.; Gonzalez-Sierra, M.; Ruveda, E. A. *Tetrahedron* **1990**, *46*, 4149. White, J. D.; Somers, T. C.; Yager, K. M. *Tetrahedron Lett.* **1990**, *31*, 59. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

(24) There are few reports in cationic cyclization of the formation of seven-membered rings: Armstrong, R. J.; Weiler, L. *Can. J. Chem.* **1986**, *64*, 584.

(25) The stereochemistry of **11** is in accordance with a cyclization via a chairlike transition state.

(26) Other three stereoisomers of **11** (11.5%) can be isolated from the reaction mixture. See Supporting Information.

(27) 5-Exo and 6-endo-trig monocyclic products can also be isolated (14%, 4:1 ratio), the latter being the acetate of elegansidiol, a natural product: Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Alvarez-Manzaneda, R.; Quilez, J.; Chahboun, R.; Linares, P.; Rivas, A. *Tetrahedron Lett.* **1999**, *40*, 8273. See Supporting Information.

(28) . The yields of analogous cationic cyclizations are generally low, and the double bond has an endocyclic regiochemistry: Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *48*, 7005 and references therein.

(29) Related cationic cyclization with loss of stereochemistry: van Tamelen, E. E.; Storni, A.; Hessler, E.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295. The cyclization of a derivative of **12** was described in low yield (9%): Taylor, S. K. *Org. Prep. Proc. Int.* **1992**, *24*, 245

(30) Neither can it be ruled out that this product was obteined via a radical disproportionation process.

(31) Similar products (6.5%) were obtained in the cyclization of **1**. See Supporting Information.

(32) This bicyclic terpene skeletom is related to widdrol, a natural sesquiterpene.

(33) Fernandez-Mateos, A.; Martin de la Nava, E.; Coca, G. P.; Silva, R. R.; Gonzalez, R. R. *Org. Lett.* **1999**, *1*, 607.

(34) In this case the cationic cyclization usually ends with an O-nucleophile capture: Parker, K. A.; Resnick, L. *J. Org. Chem.* **1995**, *60*, 5726.

(35) The use of previously described reaction conditions did not lead to the results hoped for, probably because the intermediate species were not the same (see ref 7c).

(36) The epoxides **1**, **5**, and **9** were prepared by *m*-CPBA epoxidation: Barrero, A. F.; Alvarez-Manzaneda, E. J.; Palomino, P. L. *Tetrahedron* **1994**, *50*, 13239 and references therein. Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1996**, *61*, 5307 and references therein. **12**: van Tamelen, E. E.; Storni, A.; Hessler, E.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295. **18**: Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005.

(37) The epoxide **9** is a mixture 1:1 of diastereoisomers.

(38) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Rodriguez, A.; Linares, P. *Tetrahedron* **2000**, *56*, 6099.

(39) Wang, D.; Chan, T. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1273.

(40) Synthesis: ref 29. Natural product: Ayer, W. A.; Craw, P. A. *Can. J. Chem.* **1989**, *67*, 1371.

Then the solution of Cp_2TiCl was slowly added to epoxide (1 mmol) in strictly deoxygenated THF (150 mL, 0.005M). The reaction was stirred for 1 h, quenched with 10% aqueous HCl, extracted with MeO*t*Bu, washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (hexane/MeO*t*Bu mixtures, $R_f = 0.3$).

(1*SR*,3*SR*)-3-Acetoxymethyl-2,2-dimethyl-4-methylenecyclohexanol (3-*exo*) and (1*SR*,3*SR*)-3-Acetoxymethyl-2,2,4-trimethyl-4-cyclohexenol (3-*endo*). The compounds **3-*exo*** and **3-*endo*** were obtained as a mixture in a 7.3:1 ratio. **3-*exo***: colorless oil (hexane/MeO*t*Bu 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (bs, 1H), 4.63 (bs, 1H), 4.28−4.18 (m, 2H), 3.58 (dd, J = 8.4, 4.0 Hz, 1H), 2.41 (dd, J = 9.1, 5.1 Hz, 1H), 2.35−2.15 (m, 2H), 2.01 (s, 3H), 1.85−1.75 (m, 1H), 1.61−1.51 (m, 1H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 174.22 (C), 145.80 (C), 111.04 (CH_2), 74.77 (CH), 62.49 (CH_2), 50.78 (CH), 38.74 (C), 31.07 (CH_2), 30.29 (CH_2), 23.53 (CH_3), 22.42 (CH_3), 21.21 (CH_3); HRMS *m*/*z* calcd for $C_{12}H_{20}O_3Na$ 235.1310, found 235.1315. **3-*endo***: ^{1}H NMR (400 MHz, $CDCl_3$) δ (only distinctive signals) 5.36 (bs, 1H), 4.28 (dd, J = 11.8, 4.9 Hz, 1H), 4.09 (dd, J = 11.8, 3.8 Hz, 1H), 3.71 (dd, J = 7.7, 5.6 Hz, 1H), 2.02 (s, 3H), 1.72 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ (only distinctive signals) 121.12 (CH), 72.13 (CH), 63.22 (CH_2), 49.58 (CH), 32.91 (CH_2), 23.11 (CH_3), 21.61 (CH_3).

2,2,3-Trimethyl-3-vinylcyclopentanol (4). Colorless volatile oil (hexane/MeO*t*Bu 4:1), 1:1 mixture of two isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (dd, J = 17.5, 10.9 Hz, 1H, one isomer), 5.84 (dd, J = 17.4, 10.9 Hz, 1H, one isomer), 5.03−4.87 (m, 2H), 4.00 (dd, J = 8.5, 6.4 Hz, 1H, one isomer), 3.90 (dd, J = 8.5, 6.4 Hz, 1H, one isomer), 2.30−1.2 (m, 4H), 1.01 (s, 3H, one isomer), 0.94 (s, 3H, one isomer), 0.87 (s, 3H, one isomer), 0.85 (s, 3H, one isomer), 0.82 (s, 3H, one isomer), 0.79 (s, 3H, one isomer); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 145.72 (CH), 145.67 (CH), 111.58 (CH_2), 111.03 (CH_2), 80.99 (CH), 80.75 (CH), 48.32 (C), 46.63 (C), 46.37 (C), 33.16 (CH_2), 33.00 (CH_2), 30.48 (CH_2), 22.72 (CH_3), 22.68 (CH_3), 21.62 (CH_3), 21.58 (CH_3), 17.71 (CH_3), 17.06 (CH_3), (two carbon signals were not observed); MS *m*/*z* 139 (3), 136 (4, $M^+ - H_2O$), 84 (43).

(*Z*)-6-Hydroxy-3,7-dimethyl-2-octenyl Acetate (6) and (*Z*)-6-Hydroxy-3,7-dimethyl-2,7-octadienyl Acetate (7). The compounds **6** and **7** were obtained as an inseparable mixture in a 10:1 ratio. Compound **6**: colorless oil (hexane/MeO*t*Bu 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (t, J = 7.2 Hz, 1H), 4.65 (dd, J = 12.3, 7.2 Hz, 1H), 4.59 (dd, J = 12.3, 7.2 Hz, 1H), 3.32 (ddd, J = 9.0, 5.2, 3.0 Hz, 1H), 2.45−2.15 (m, 2H), 2.06 (s, 3H), 1.78 (s, 3H), 1.71−1.40 (m, 3H), 0.93 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 170.64 (C), 142.68 (C), 119.53 (CH), 75.90 (CH), 61.12 (CH_2), 33.72 (CH), 32.19 (CH_2), 28.51 (CH_2), 23.36 (CH_3), 21.09 (CH_3), 18.84 (CH_3), 17.34 (CH_3); HRMS *m*/*z* calcd for $C_{12}H_{22}O_3Na$ 237.1466, found 237.1469. Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (only distinctive signals) 4.97 (bs, 1H), 4.86 (bs, 1H), 4.12 (dd, J = 7.0, 4.8 Hz, 1H).

(1*SR*,3*RS*,4*SR*)-3-Acetoxymethyl-4-(2-(methoxycarbonyl)ethyl)))-2,2,4-trimethylcyclohexanol (8a) and (1*SR*,3*RS*,4*RS*)-3-Acetiloxymethyl-4-(2-(methoxycarbonyl)ethyl)))-2,2,4-trimethylcyclohexanol (8b). The compounds **8a** and **8b** were obtained as a mixture in a 5:1 ratio. Compound **8a**: vitreous solid (hexane/MeO*t*Bu 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (dd, J = 12.2, 3.6 Hz, 1H), 4.11 (dd, J = 12.2, 4.9 Hz, 1H), 3.65 (s, 3H), 3.22 (dd, J = 10.8, 4.9 Hz, 1H), 2.30−2.20 (m, 2H), 2.03 (s, 3H), 1.75−1.25 (m, 7H), 1.07 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 174.61 (C), 171.17 (C), 78.42 (CH), 63.05 (CH_2), 51.70 (CH_3), 50.54 (CH), 39.40 (C), 38.37 (CH_2), 35.92 (C), 35.32 (CH_2), 28.46 (CH_2), 28.40 (CH_3), 27.23 (CH_2), 21.17 (CH_3), 20.96 (CH_3), 16.09 (CH_3); HRMS *m*/*z* calcd for $C_{16}H_{28}O_5Na$ 323.1834, found 323.1839. Anal. calcd for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40. Found: C, 63.81; H 9.66. Compound **8b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (only distinctive signals) 4.19 (dd, J = 12.0, 4.3 Hz, 1H), 4.12 (dd, J = 12.0, 5.3 Hz, 1H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ (only distinctive signals) 75.91 (CH), 63.21 (CH_2), 44.48 (CH), 38.76 (CH_2), 30.02 (CH_2), 25.17 (CH_2), 21.36 (CH_3).

(1*SR*,3*SR*,4*SR*)-4-Acetoxy-2,2,3,4-tetramethylcyclohexanol (11). White solid (hexane/MeO*t*Bu 7:3): mp 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (dd, J = 11.4, 4.4 Hz, 1H), 2.84 (dt, J = 14.7, 3.3 Hz, 1H), 1.98 (s, 3H), 1.75−1.50 (m, 3H), 1.46 (s, 3H), 1.33 (td, J = 14.3, 4.1 Hz, 1H), 1.01 (d, J = 4.6 Hz, 3H), 1.00 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 170.25 (C), 83.20 (C), 78.27 (CH), 49.79 (CH), 39.51 (C), 33.16 (CH_2), 27.66 (CH_3), 27.04 (CH_2), 25.45 (CH_3), 22.54 (CH_3), 14.04 (CH_3), 8.35 (CH_3); MS *m*/*z* 154 (18), 72 (100). Anal. calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.14; H 10.58.

(2*SR*,4a*SR*,5*SR*,8a*RS*,)-5-Acetoximethyl-2-hydroxy-1,1,4a-trimethyl-6-methylene-decahydronaphthalene (13). White solid (hexane/MeO*t*Bu 7:3): mp 77−79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (bs, 1H), 4.47 (bs, 1H), 4.25 (dd, J = 11.3, 3.9 Hz, 1H), 4.12 (dd, J = 11.3, 8.6 Hz, 1H), 3.21 (dd, J = 11.5, 4.4 Hz, 1H), 2.35 (ddd, J = 13.0, 4.0, 2.3 Hz, 1H), 2.00−1.00 (m, 6H), 1.95 (s, 3H), 1.39 (dd, J = 12.7, 4.3 Hz, 1H), 1.30 (dd, J = 12.7, 4.1 Hz, 1H), 1.06 (dd, J = 12.4, 2.6 Hz, 1H), 0.94 (s, 3H), 0.72 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 171.40 (C), 146.30 (C), 107.64 (CH_2), 78.66 (CH), 61.54 (CH_2), 54.59 (CH), 54.39 (CH), 39.23 (C), 38.78 (C), 37.51 (CH_2), 37.06 (CH_2), 28.40 (CH_3), 27.81 (CH_2), 23.57 (CH_2), 21.17 (CH_3), 15.53 (C), 15.18 (C); MS *m*/*z* 220 (22, $M^+ - HOAc$), 202 (35), 135 (89). The compound **13** was chemically correlated with its diol derivative, a previously known natural product, showing identical spectroscopic data.[41]

Preparation of 10,11-Epoxy-3,7,11-trimethyl-1,6-dodecadien-3-yl Acetate (16). To a solution of nerolidyl acetate (674 mg, 2.55 mmol) in a mixture of DME/water (20 mL, 1:1) at 0 °C was slowly added NBS (500 mg, 2.80 mmol). The reaction was stirred for 30 min, diluted with MeO*t*Bu, washed with water, dried (Na_2SO_4), and evaporated. The residue was chromatographed (9:1 hexane/MeO*t*Bu) to give **16** (330 mg, 46%) 2.5:1 mixture of two stereoisomers as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (dd, J = 17.4, 10.9 Hz, 1H, minor isomer), 5.94 (dd, J = 17.4, 10.9 Hz, 1H, major isomer), 5.16−5.09 (m, 2H), 2.68 (t, J = 6.3 Hz, 1H, major isomer), 2.67 (t, J = 6.3 Hz, 1H, minor isomer), 1.99 (s, 3H), 1.67 (s, 3H, major isomer), 1.59 (s, 3H, minor isomer), 1.52 (s, 3H), 1.29 (s, 3H, major isomer), 1.28 (s, 3H, minor isomer), 1.25 (s, 3H, major isomer), 1.23 (s, 3H, minor isomer); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 169.99 (C), 141.82 (CH), 134.63 (C), 125.21 (CH), 124.34 (CH), 113.23 (CH_2), 82.89 (C), 82.84 (C), 64.20 (CH), 64.11 (CH), 58.38 (C), 39.97 (CH_2), 39.72 (CH_2), 36.34 (CH_2), 28.50 (CH_2), 27.44 (CH_2), 24.98 (CH_3), 24.95 (CH_3), 23.69 (CH_3), 23.66 (CH_3), 23.38 (CH_3), 22.32 (CH_3), 22.25 (CH_2), 22.19 (CH_2), 18.81 (CH_3), 18.77 (CH_3), 15.97 (CH_3), (some carbon signals were not observed); MS *m*/*z* 221 (7), 119 (88), 80 (100); HRMS *m*/*z* calcd for $C_{17}H_{28}O_3Na$ 303.1936, found 303.1933.

(2*SR*,4a*RS*,9a*RS*)-2-Hydroxy-1,1,4a,7-tetramethyl-2,3,4,4a,5,8,9,9a-octahydro-1*H*-benzocycloheptene (17). Vitreous solid (hexane/MeO*t*Bu 4:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (m, 1H), 3.21 (dd, J = 9.2, 6.8 Hz, 1H), 2.09 (bd, J = 14.5 Hz, 1H), 2.10 (bdd, J = 14.5, 6.4 Hz, 1H), 1.85 (bd, J = 14.0 Hz, 1H), 1.72 (bs, 3H), 1.67−1.57 (m, 4H), 1.14 (bs, OH), 1.35 (dt, J = 13.4, 3.7 Hz, 1H), 1.31−1.12 (m, 2H), 1.02−0.98 (m, 1H), 0.99, (s, 3H), 0.82 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 141.31 (C), 122.45 (CH), 79.01 (CH), 59.29 (CH), 45.91 (CH_2), 40.71 (CH_2), 40.14 (C), 35.58 (C), 34.83 (CH_2), 28.13 (CH_3), 27.98 (CH_2), 25.54 (CH_3), 21.53 (CH_2), 19.37 (CH_3), 15.17 (CH_3); MS *m*/*z* 222 (8), 135 (39).

1,5-Dihydroxy-1,4,4,7a-tetramethyl-octahydroindene (19). White solid (hexane/MeO*t*Bu 1:1), mixture of three isomers in a 1:1:1 ratio: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (t, J = 3.1 Hz, 1H, one isomer), 3.23 (dd, J = 10.6, 5.0 Hz, 1H, one isomer), 3.16 (dd, J = 10.5, 5.5 Hz, 1H, one isomer), 2.10−1.00 (m, 9H), 1.14 (s, 3H, one isomer), 1.08 (s, 3H, one isomer), 1.05 (s, 3H, one isomer), 0.92 (s, 3H, one isomer), 0.90 (s, 3H), 0.86 (s, 3H, one isomer), 0.85 (s, 3H, one isomer), 0.80 (s, 3H, one isomer), 0.79 (s, 3H, one isomer), 0.74 (s, 3H, one isomer); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 83.07 (C), 81.87 (C), 80.99 (C), 80.02 (CH), 79.82 (CH), 75.15 (CH), 51.86 (CH), 51.15 (CH), 50.82 (CH), 47.14 (C), 45.79 (C), 44.54 (C), 38.82 (CH_2), 38.64 (C), 38.28 (CH_2), 37.95 (C), 36.88 (CH_2), 36.25 (C), 30.07 (CH_2), 29.41 (CH_3), 29.03 (CH_3), 28.80 (CH_3), 28.53 (CH_2), 28.32 (CH_2), 26.38 (CH_3), 26.29 (CH_2), 25.34 (CH_3), 24.62 (CH_3), 23.07 (CH_3), 22.87 (CH_2), 22.22 (CH_2), 21.97 (CH_3), 19.70 (CH_2), 19.03 (CH_2), 16.97 (CH_3), 15.52

(41) Fleck, W. F.; Schlegel, B.; Hoffmann, P.; Ritzau, M.; Heinze, S.; Gräfe, U. *J. Nat. Prod.* **1996**, *59*, 780.

(CH_3), 15.41 (CH_3), 14.52 (CH_3), (one carbon signal was not observed); HRMS *m*/*z* calcd for $C_{13}H_{24}O_2Na$ 235.1674, found 235.1678.

(1*RS*,3a*SR*,5*SR*,7a*RS*)-1,5-Dihydroxy-1,4,4,7a-tetramethyloctahydroindene (20). White solid (hexane/MeO*t*Bu 2:3): mp 78−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (dd, J = 10.5, 5.0 Hz, 1H), 1.80−1.25 (m, 9H), 1.08 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT) δ 82.93 (C), 74.32 (CH), 54.10 (CH), 44.85 (C), 37.05 (C), 36.36 (CH_2), 28.81 (CH_2), 27.81 (CH_2), 26.53 (CH_3), 25.49 (CH_3), 22.09 (CH_3), 21.79 (CH_2), 20.82 (CH_3); MS *m*/*z* 194 (10, $M^+ - H_2O$), 176 (12, $M^+ - 2H_2O$).

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for all new compounds and spectroscopic data for some minor products. This material is available free of charge via the Internet at http://pubs.acs.org.

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