Titanocene-Catalyzed Cascade Cyclization of Epoxypolyprenes: Straightforward Synthesis of Terpenoids by Free-Radical Chemistry

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Abstract: The titanocene-catalyzed cascade cyclization of epoxypolyenes, which are easily prepared from commercially available polyprenoids, has proven to be a useful procedure for the synthesis of C_{10}, C_{15}, C_{20}, and C_{30} terpenoids, including monocyclic, bicyclic, and tricyclic natural products. Both theoretical and experimental evidence suggests that this cyclization takes place in a nonconcerted fashion via discrete carbon-centered radicals. Nevertheless, the termination step of the process seems to be subjected to a kind of water-dependent control, which is unusual in free-radical chemistry. The catalytic cycle is based on the use of the novel combination Me_3SiCl/2,4,6-collidine to regenerate the titanocene catalyst. In practice this procedure has several advantages: it takes place at room temperature under mild conditions compatible with different functional groups, uses inexpensive reagents, and its end step can easily be controlled to give exocyclic double bonds by simply excluding water from the medium.

Keywords: cyclization · domino reactions · homogeneous catalysis · radical reactions · titanium

Introduction

The increasing demand for selectivity and atom- and step-economy in organic synthesis will presumably have a decisive influence on the strategies employed by chemists in coming years.[1] The biosynthesis of lanosterol from squalene fits these requirements admirably, taking place as it does in only two steps: the enantioselective epoxidation of squalene followed by the stereoselective cascade cyclization of 2,3-oxidosqualene. Only one proton is lost during this process, to form the double bond at Δ^8. The enzyme-catalyzed cyclization of (*S*)-2,3-oxidosqualene into lanosterol has received considerable attention in recent years[2] and there is now solid theoretical and experimental evidence to support its carbocationic nature.[3] Mimicking this natural transformation, Goldsmith, van Tamelen, and Corey, among others, have exploited the acid-induced cascade cyclization of epoxypolyprenes as a very useful procedure in the building of polycyclic terpenoids through carbocationic chemistry.[4] This method involves certain drawbacks, however, such as the need to attach extra groups to the polyene substrate to stabilize carbocationic intermediates and control the termination steps. An alternative concept, radical cascade cyclization, introduced by Breslow and Julia[5] more than thirty years ago, has also proven to be an excellent method for the stereoselective synthesis of polycyclic compounds from different acyclic precursors.[6] To the best of our knowledge, however, this concept was never applied to the cyclization of epoxypolyprenes during the last century, probably owing to the lack of a suitable protocol for the radical opening of epoxides. Nevertheless, the titanocene(III)-based procedure discovered by Nugent and RajanBabu and the catalytic version subsequently developed by Gansäuer and co-workers has filled this gap,[7] thus opening up the possibility of mimicking lanosterol synthase with free-radical chemistry. The aim of our work here has been to take advantage of such a method to develop a straightforward procedure for the synthesis of terpenoids with a wide range of carbocyclic skeletons.

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Spectroscopic data of some minor products and copies of selected ^1H and ^{13}C NMR spectra.

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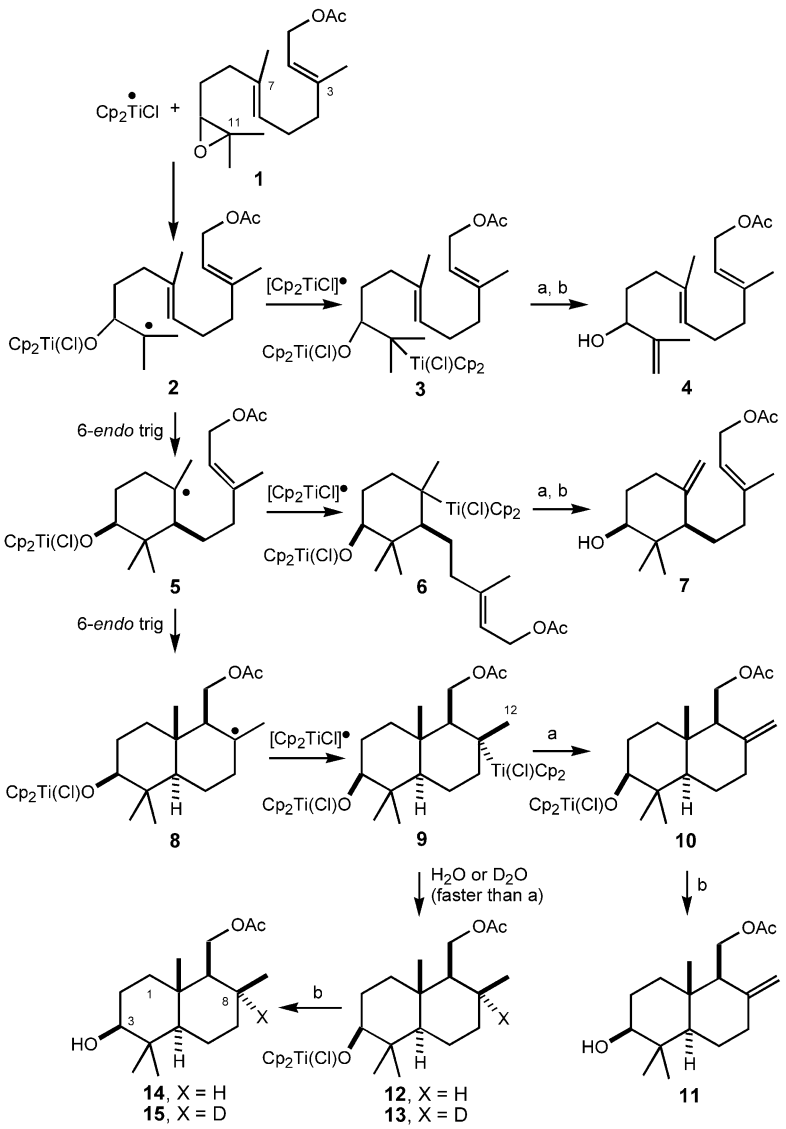
Results and Discussion

The effects of water upon titanocene-promoted radical cyclizations of epoxypolyprenes: In preliminary experiments employing stoichiometric proportions of [Cp_2TiCl][8] we obtained encouraging results, but excess quantities of [Cp_2TiCl_2] were required[9] and varying amounts of reduction products such as **14** were formed, disturbing the chromatographic isolation of the main compounds and endangering the reproducibility of the results. As collateral observations suggested that these products might derive from adventitious water[10] we treated epoxypolyprene **1** with [Cp_2TiCl] under strictly anhydrous conditions. In this manner we obtained a substantially increased yield of bicyclic alkene **11** (40% isolated product versus roughly 25% in our preliminary experiments),[8] together with lesser amounts of acyclic **4** (23%) and monocyclic **7** (10%); no **14** was detected. Moreover, when D_2O was added to the medium, deuterated isotopomer **15**[11] was obtained instead of **14**. These results pointed to a cascade cyclization via discrete carbon-centered radicals (Scheme 1), and confirmed that the termination step of the process can be easily controlled to give either alkenes (as **11**) or reduction products (as **14**) by simply excluding or adding water to the medium. The discovery of this water-dependent phenomenon, which is unusual in free-radical chemistry, guaranteed further reproducible results.[12]



Scheme 1. Proposed mechanism for the titanocene(III)-mediated cyclization of **1**. a) [$Cp_2Ti(Cl)H$] elimination under anhydrous conditions; b) acidic quenching after the [$Cp_2Ti(Cl)H$] elimination.

Theoretical calculations supporting the nonconcerted nature of the radical cascade cyclization: Because some controversy remains as to whether radical cascade cyclizations take place in a concerted or stepwise fashion,[13] we made computational studies on the cyclization of the model radical **I** (closely related to **2**) to gain more information about the nature of our process. Both concerted and stepwise mechanisms were considered and the pathways were carried out at DFT level. After careful inspection of the potential energy surface, no transition state for a concerted reaction from **I** to **III** could be found. The theoretical calculations pointed instead to a reaction following a two-step mechanism, in accordance with the experimental evidence. An energy profile of the reaction is shown in Figure 1. Both the first (**I**→**II**) and the second (**II**→**III**) 6-*endo* cyclizations are exothermic, with reaction energies of -7.5 kcal mol^{-1} and -8.9 kcal mol^{-1} respectively, and both steps have moderate activation energies (11.3 and 10.6 kcal mol^{-1} respectively). These energies are considerably higher than those calculated for cationic cyclizations in model systems.[3e] In these systems the second cyclization has been calculated to proceed with activation energies of about 1 kcal mol^{-1}, suggesting a concerted mechanism for the acid-catalyzed formation of A and B rings from 2,3-oxidosqualene. In turn, the concerted process of oxirane opening and ring A formation from the protonated epoxide takes place with even lower barriers (about 0.6 kcal mol^{-1}).[3h] In our case, however, the values of the activation energy barriers suggest a two step mechanism. Interestingly, there exists an energy minimum for radical **I** with the appropriate conformation to give the first cyclization product. This type of structure was also detected at the AM1 semiempirical level. Nevertheless, no interaction be-

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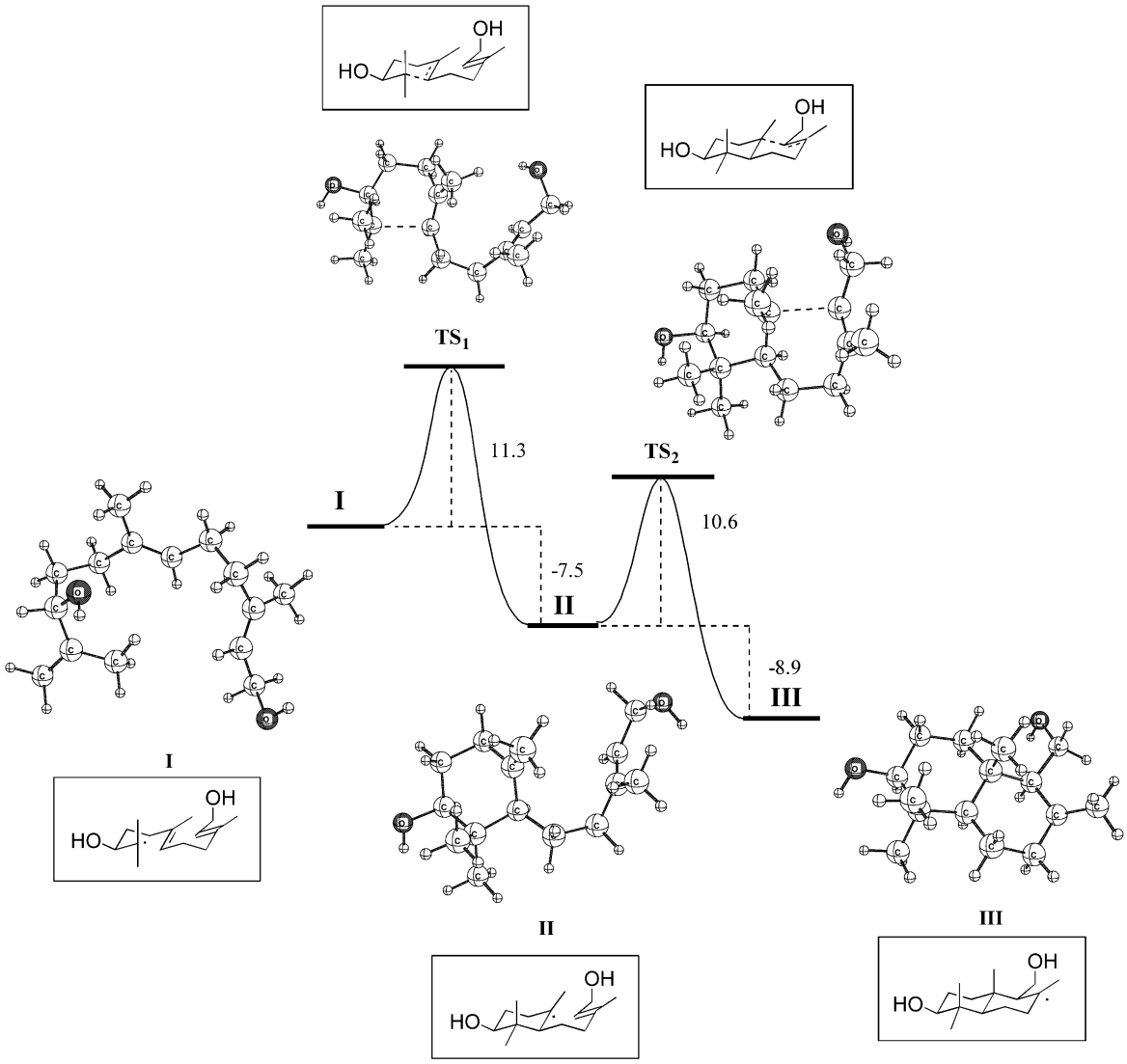

Figure 1. An energy profile of the cyclization reaction of the model radical **I**.

tween the carbon-centered radical and the double bond exists at this stage because the distance is too large. On the other hand, a similar conformer for 2*E*,6*E*-10,11- epoxyfarnesol could not be located. Radical **II** exhibited an even better pre-organization towards cyclization, which may account for the lower activation energy of the second step. All these theoretical results strongly support the stepwise mechanism depicted in Scheme 1. Assuming the nonconcerted nature of our radical cyclizations, the stereoselectivity observed can be explained in terms of Beckwith–Houk rules described elsewhere.[13]

Development of the titanocene-catalyzed version: With valuable mechanistic data available to us, we envisaged the development of a catalytic version to reduce the considerable proportions of $[Cp_2TiCl_2]$ and the high dilutions required in our preliminary experiments.[14] Our starting hypothesis was based on the use of the novel combination Me_3SiCl/2,4,6-collidine,[10b], [15] which is compatible with oxiranes and should be capable of regenerating $[Cp_2TiCl_2]$ from both $[Cp_2Ti(Cl)H]$ and oxygen-bonded titanium derivatives such as **10** (Scheme 2). To check this hypothesis we treated epoxypolyprene **1** (prepared from commercially available 2*E*,6*E*-farnesol by van Tamelen's procedure)[16] with a substoichiometric quantity of $[Cp_2TiCl_2]$ (0.2 equiv), Mn dust, and the mixture of Me_3SiCl and collidine in dry THF (10^{-1} M substrate concentration) (Scheme 2). In this way we obtained the expected exocyclic alkene[17] **11** (after fluoride workup) at the same yield (40%) as that under stoichiometric conditions but employing lower $[Cp_2TiCl_2]$ proportions and dilution levels by one and two orders of magnitude respectively. This result supported the main features of the catalytic cycle depicted in Scheme 2.

Synthesis of terpenoids with various carbocyclic skeletons: Once we were confident about the viability of the titanocene-catalyzed cyclization and the experimental conditions required to control the end step of the process, we decided that with a judicious choice of starting material this method might be a useful tool for the synthesis of terpenoids with different carbon skeletons, including monocyclic compounds such as **18**, **24**, and **25**, bicyclic sesquiterpenoids (such as **26**)

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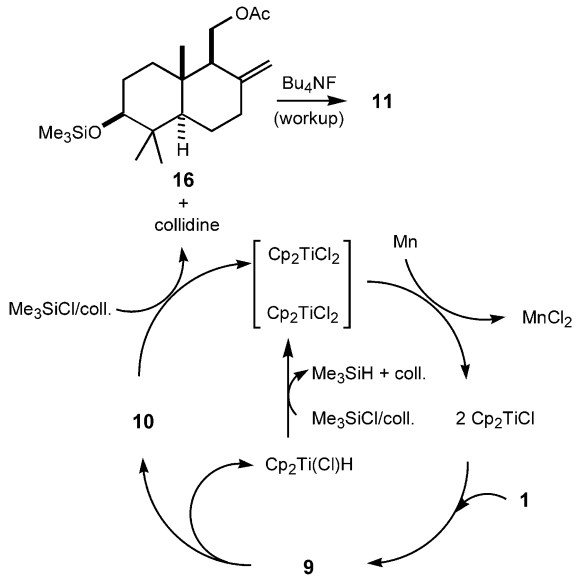
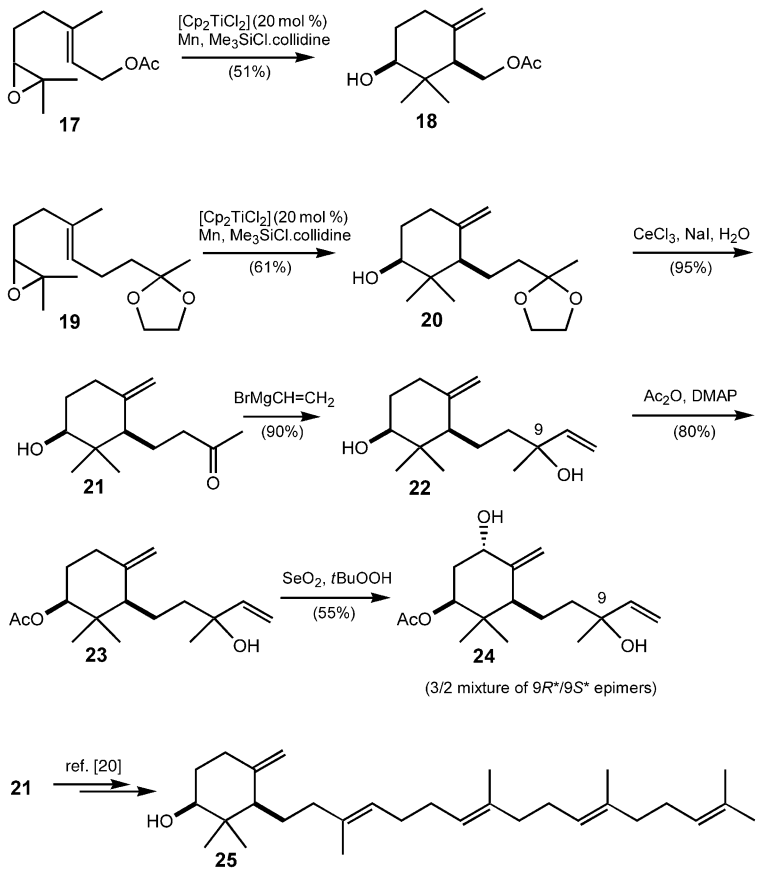


Scheme 2. Hypothetical catalytic cycle for the Ti^{III} mediated cyclization of **1** to **11**.

and diterpenoids (such as **30**), as well as tricyclic products as the isocopalane diterpenoid **36**.

As we expected, the titanocene-catalyzed cyclization of 6,7-epoxygeranyl acetate[8] (**17**) under anhydrous conditions selectively gave 1,3-*cis*-disubstituted monoterpenoid **18** with an exocyclic double bond (Scheme 3). The initial results obtained in the synthesis of **18** encouraged us to extend our method to the preparation of more complex monocyclic terpenoids. Cyclofarnesane sesquiterpenoid **24** was discovered by Marco et al.[18] in the plant *Artemisia chamaemelifolia* together with other polyoxygenated metabolites. We started its synthesis (Scheme 3) with commercial geranylacetone, which was easily transformed into epoxyketal **19** by conventional chemistry (see Experimental Section). Unlike ketones, the ketal group of **19** proved to be inert toward free-radical chemistry (at least under our conditions) and remained unchanged after titanocene-catalyzed cyclization of **19** to **20** (61% yield). The deprotection of the carbonyl group with cerium(III) chloride[19] avoided extensive isomerization of the exocyclic double bond of **20** (promoted by other acids), and an excellent 95% yield of ketone **21** was obtained. Subsequent treatment of **21** with vinylmagnesium bromide provided tertiary alcohol **22** as a mixture (9*R** and 9*S** epimers) in a 3:2 isomeric ratio. Selective esterification of the secondary alcohol of **22**, followed by allylic hydroxylation of **23** afforded a 3:2 mixture of the 9*R** and 9*S** epimers **24**.

Originally Marco and co-workers did not establish the C-9 stereochemistry of the metabolite found in *A. chamaemelifolia*.[18] Recently, however, Uttaro et al. have demonstrated the 9*R* stereochemistry of the natural product by means of chemical synthesis and X-ray crystallographic analysis.[20] In our epimeric mixture (**24**) the NMR signals corresponding to the major component matched those of the natural metabolite,[18] whereas the signals of the minor one agreed closely with those of the 9*S* isomer.[20] Therefore we completed the total synthesis of the natural product in seven steps in 23% overall yield, confirming the usefulness of our method for the preparation of cyclofarnesane-type monocyclic sesquiterpenoids. Ketone **21** also proved to be a valuable intermediate for the total synthesis of the monocyclic triterpenoid achilleol A (**25**) (Scheme 3) following the convergent strategy recently developed in our laboratory.[21]



Scheme 3. Titanocene-catalyzed synthesis of monocyclic terpenoids. DMAP = 4-(dimethylamino)pyridine.

Drimanes constitute a family of bicyclic sesquiterpenoids with interesting biological properties.[22] The simple saponification of **11** (obtained from commercial farnesol as described above) gave synthetic drimane **26** (Scheme 4), with ^{1}H and ^{13}C NMR data in accordance with those of natural iso-

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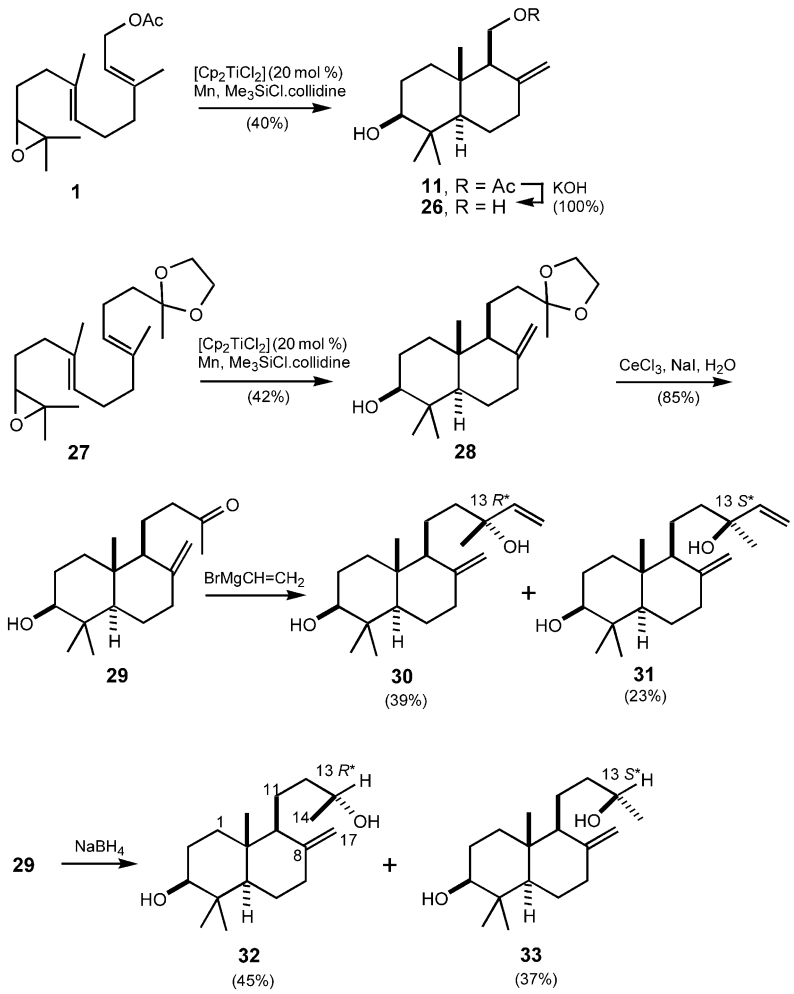
drimenediol excreted by the fungus *Polyporus arcularius*.[23] We thus achieved the total synthesis of isodrimenediol in just four steps, high regio- and stereoselectivity degrees, and in a considerable overall yield of 21%. To the best of our knowledge this is the first total synthesis reported for isodrimenediol and confirms the structure **26** proposed by Fleck et al. for the fungal metabolite.[23]



Scheme 4. Titanocene-catalyzed synthesis of bicyclic terpenoids

We then addressed the chemical preparation of 3β-hydroxymanool (**30**), a bicyclic diterpenoid with a labdane skeleton from the fern *Gleichenia japonic*a.[24] As starting material we chose commercial farnesylacetone,[25] which was successively transformed into epoxyketal **27**, cyclic derivative **28**, and ketone **29** (Scheme 4), in the same way that geranylacetone was transformed into ketone **21** (see Scheme 3). Interestingly, the NMR data of synthetic ketone **29** matched those of one of the components of copaiba oil (a commercial mixture of natural oleoresins used both for cosmetics and medicinal purposes),[26] confirming the chemical structure of this natural product. The treatment of ketone **29** with vinylmagnesium bromide provided **30** (39% isolated yield) together with a lesser quantity of its 13*S** epimer **31** (23% yield). Fortunately both isomers could be easily isolated by flash chromatography and analyzed by spectroscopic techniques. Apart from optical rotation, synthetic **30** had the same physical properties as natural (+)-3β-hydroxymanool[24] and thus the first total synthesis of this terpenoid was achieved in five steps in an overall yield of 6%. It should be noted that the relative proportions of products **30** and **31** obtained from the reaction with vinylmagnesium bromide revealed that the nucleophilic attack by the *Si* face of ketone **29** was faster than that by the *Re* face.

Dinor-labdane **33** was recently isolated from copaiba oil and its structure elucidated by NMR spectroscopy, but the relative stereochemistry at C-13 had not so far been determined.[27] We attempted its synthesis by reducing ketone **29** with $NaBH_4$ (Scheme 4). We thus obtained a mixture of two epimeric alcohols, **32** and **33**, in relative proportions of 6:5 respectively (^{1}H NMR analysis). When L-Selectride was used instead of $NaBH_4$ the stereoselectivity of the reduction increased, and the product ratio was **32**:**33** = 3:1. Since the *Si* face of ketone **29** proved to be more reactive than the opposite face against nucleophilic reagents (see above) we tentatively assigned the 13*R** relative configuration (derived from the hydride attack by the *Si* face) to the major product (**32**) and, consequently, the 13*S** to the minor one (**33**). Both diastereomers **32** and **33** were isolated (45% and 37% yields respectively) and their NMR spectra were compared with those of the copaiba oil component. The ^{13}C NMR spectrum of the minor isomer **33** virtually matched that reported for the natural compound,[27] whereas in the spectrum of **32** slight but significant differences were observed in the chemical shifts of carbons C-8, C-9, C-11 to C-14, and C-17 (see Table 1). Therefore, we propose the relative stereochemistry 13*S** depicted in **33** for the bicyclic terpenoid isolated from copaiba oil.

The marine metabolite stypoldione (**37**) has attracted the attention of chemists owing both to its pharmacological properties[28] and its challenging chemical structure. Recently Xing and Demuth reported an elegant total synthesis of stypoldione via the tricyclic intermediate **36**.[29] Because of the biological interest of stypoldione, we selected the isocopalane diterpenoid **36** as a target to prove the efficiency of our method for the synthesis of tricyclic terpenoids from epoxypolyene **34**, previously prepared from commercially

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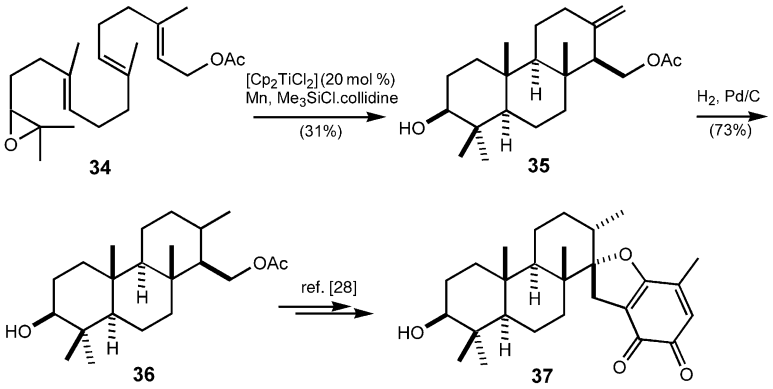
Table 1. ^{13}C NMR data[a] for a natural dinor-labdane terpenoid (**33**) isolated from copaiba oil and the synthetic compounds **32** and **33**.

Carbon	Natural	Synthetic **33**	$\Delta\delta$	Synthetic **32**	$\Delta\delta$
1	37.16	37.22	0.06	37.24	0.08
2	27.98	28.04	0.06	28.05	0.07
3	78.94	78.96	0.02	78.98	0.04
4	39.18	39.22	0.04	39.23	0.05
5	54.69	54.76	0.07	54.79	0.10
6	24.06	24.10	0.04	24.08	0.02
7	38.23	38.27	0.04	38.26	0.03
8	**148.19**	**148.23**	**0.04**	**148.02**	**0.17**
9	**56.80**	**56.88**	**0.08**	**56.59**	**0.21**
10	39.52	39.57	0.05	39.50	0.02
11	**20.05**	**20.09**	**0.04**	**19.72**	**0.33**
12	**38.54**	**38.60**	**0.06**	**38.38**	**0.16**
13	**68.90**	**68.91**	**0.01**	**68.47**	**0.43**
14	**23.60**	**23.62**	**0.02**	**23.79**	**0.19**
17	**106.78**	**106.79**	**0.01**	**107.00**	**0.22**
18	14.47	14.49	0.02	14.50	0.03
19	15.46	15.47	0.01	15.46	0.00
20	28.37	28.39	0.03	28.40	0.04

[a] The most significant data are in bold characters.

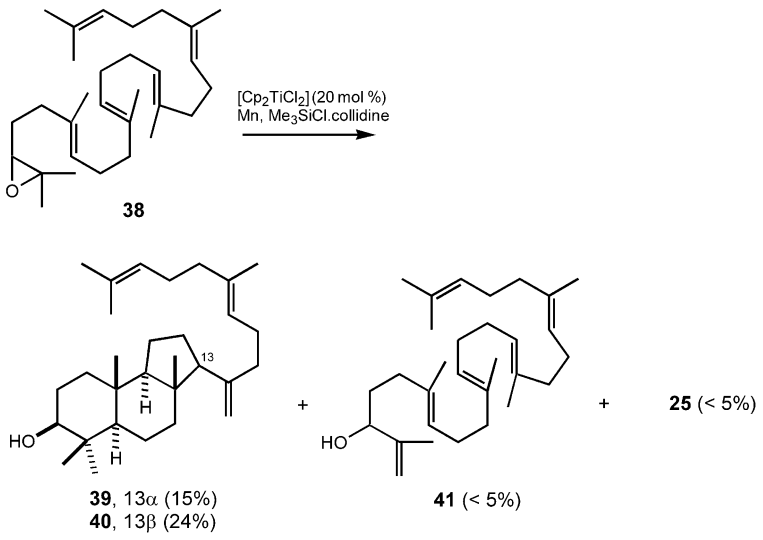
available geranylgeraniol by van Tamelen's procedure.[30] Titanocene-catalyzed cyclization of **34** gave tricyclic alkene **35** in a moderate 31% yield (Scheme 5). This yield can be regarded as satisfactory, however, if we bear in mind that the synthesis of **35** selectively afforded a product containing three fused (*trans*/*anti*/*trans*) six-membered rings, an exocyclic double bond, and six stereogenic centers, among 192 potential regio- and stereoisomers. Catalytic hydrogenation of **35** gave **36** (73% yield) and thus the formal synthesis of stypoldione was completed.



Scheme 5. Titanocene-catalyzed synthesis of tricyclic terpenoids.

All the above results confirm the value of our procedure for synthesizing terpenoids with different carbon skeletons, including monocyclic, bicyclic, and tricyclic products. Our free-radical-based method constitutes an especially convenient alternative to conventional carbocationic chemistry when the synthetic targets are cyclic terpenoids bearing exocyclic double bonds.[17]

Titanocene-catalyzed cyclization of 2,3-oxidosqualene, mimicking the enzyme lanosterol synthase by free-radical chemistry: Finally, the possibility of achieving the first radical cyclization of 2,3-oxidosqualene (**38**) encouraged us to prepare this epoxide from commercially available squalene[31] and treat it with a catalytic quantity of titanocene (Scheme 6). In this manner we obtained malabaricane **39**[32] and its 13β-epimer



Scheme 6. Titanocene-catalyzed cyclization of 2,3-oxidosqualene.

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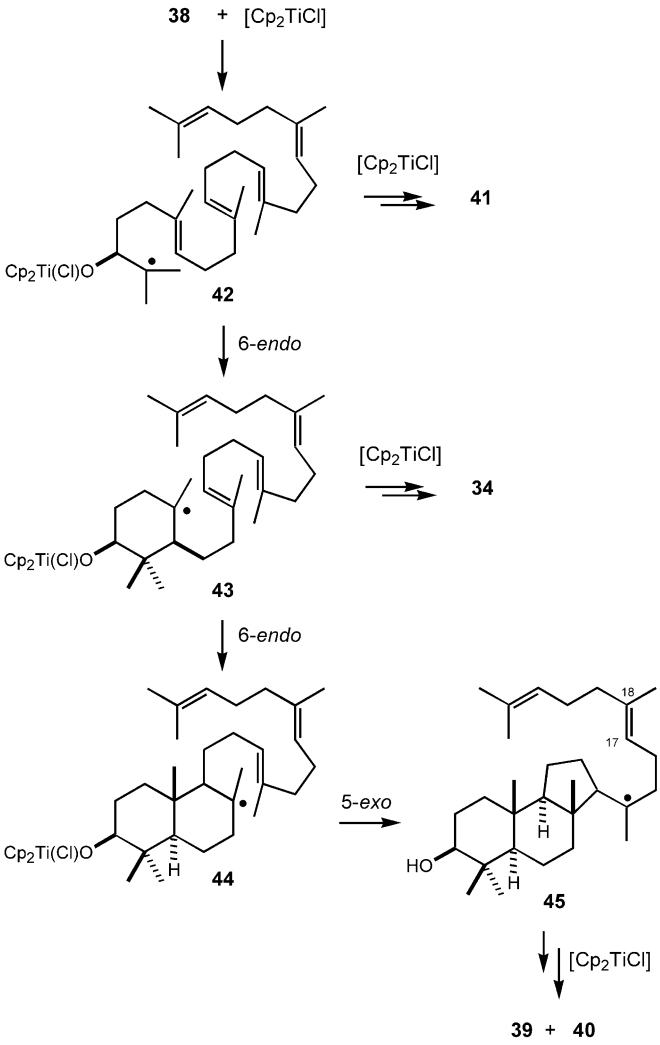
40, together with minor amounts of the acyclic alcohol **41** and achilleol A (**25**). Bicyclic compounds or Wagner–Meerwein rearrangement products, as described for the acid-induced cyclization of **38**,[31] were not detected.

Apart from the preparative interest (total synthesis of malabaricanes in only two steps), the above results also have mechanistic relevance and merit some further comment. As in the acid-induced rearrangement of **38**,[31] the main products (**39** and **40**) derive from a 6-*endo*/6-*endo*/5-*exo* cyclization process[33] (Scheme 7), but under our conditions the 5-



Scheme 7. Proposed mechanism for the titanocene-catalyzed cyclization of 2,3-oxidosqualene.

exo cyclization step giving the protomalabaricane radical **45** seems to be specially fast, thus avoiding the generation of bicyclic byproducts (see ref. [30b]). It is generally accepted nowadays that the biosynthesis of lanosterol takes place via a carbocation intermediate with a tricyclic skeleton containing a five-membered C-ring closely related to **45**.[2b] In this context, recent theoretical calculations suggest that this intermediate undergoes a C-ring expansion and concomitant D-ring formation through a transition structure involving the double bond between C-17 and C-18 (malabaricane numbering), which is similar to a nonclassical carbocation.[3f] Through free-radical chemistry, however, it seems unlikely that the double bond at Δ^{17} could give anchimeric assistance to facilitate ring-C expansion and D-ring formation from **45**. Therefore, this radical has no option but to evolve towards malabaricatrienes (**39** and **40**). This intrinsic tendency of free-radical chemistry to give malabaricanes from 2,3-oxidosqualene (and possibly from squalene also) is intriguing from a biogenetic point of view. The recent discovery of malabaricanes in marine sediments,[34] for example, is especially relevant because it is believed that they are synthesized by organisms living under anoxic conditions similar to those provided by the strictly deoxygenated solvents required for free-radical chemistry.

Conclusion

We have developed a novel procedure for the straightforward total synthesis of terpenoids with different carbon skeletons by means of free-radical chemistry. This method has proven to be useful for synthesizing C_{10}, C_{15}, C_{20}, and C_{30} terpenoids, including monocyclic, bicyclic, and tricyclic natural products. The key step of the process is the titanocene-catalyzed cascade cyclization of epoxypolyenes, easily prepared from commercially available polyprenoids. The cyclization proceeds with high regio- and stereoselectivity and provides yields which can generally be regarded as satisfactory. Mechanistically the reaction is likely to occur via discrete carbon-centered radicals, but the termination step of the process seems to be subject to a type of water-dependent control that is unusual in free-radical chemistry. In practice the method has many advantages: it proceeds at room temperature under mild conditions compatible with several functional groups, uses inexpensive reagents, and the termination step can easily be controlled to give exocyclic alkenes. Moreover, as epoxypolyprenes can be enantioselectively obtained by asymmetric catalysis, an enantioselective version of our method seems plausible. We are currently working on this task and the application of our procedure to the synthesis of marine terpenoids containing seven-membered rings.

Experimental Section

General: For the reactions employing titanocene all solvents and additives were thoroughly deoxygenated prior to use. The numbering used in the NMR assignments corresponds to the cyclofarnesane, drimane, labdane, and isocopalane systems and not the IUPAC nomenclature. Epoxides **1**,[16] **17**,[8] **34**,[30] and **38**[31] were prepared according to known procedures. The following known compounds were isolated as pure samples and showed identical NMR spectra to the reported compounds: **11**,[8] **14**,[6c] **18**,[35] **24**,[18] **25**,[36] **26**,[23] **29**,[26] **30**,[24] **33**,[27] and **36**.[29] Other general experimental details have been reported elsewhere.[8],[10a]

General procedure for the titanocene-catalyzed cyclization of epoxypolyprenes: Strictly deoxygenated THF (20 mL) was added to a mixture of $[Cp_2TiCl_2]$ (0.5 mmol) and Mn dust (20 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of epoxide (2.5 mmol) and 2,4,6-collidine (20 mmol) in THF (2 mL), and Me_3SiCl (10 mmol) were

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added and the solution was stirred for 8 h. The reaction was then quenched with 2 N HCl and extracted with *t*BuOMe. The organic layer was washed with brine, dried (anhydrous Na_2SO_4), and the solvent removed. The residue was dissolved in THF (20 mL) and stirred with Bu_4NF (10 mmol) for 2 h. The mixture was then diluted with *t*BuOMe, washed with brine, dried (anhydrous Na_2SO_4), and the solvent removed. Products obtained were isolated by column chromatography of the residue on silica gel (hexane/*t*BuOMe) and characterized by spectroscopic techniques. The main polycyclic compounds were isolated in the following yields: **11** (40%), **18** (51%), **20** (61%), **28** (42%), **35** (31%), and **39**–**40** (39%).

Synthesis of deuterium-labeled drimane 15: A mixture of $[Cp_2TiCl_2]$ (703 mg, 2.85 mmol) and Mn dust (412 mg, 7.56 mmol) in THF (25 mL) was stirred at room temperature until the red solution turned green. Subsequently, the green solution was slowly added to a mixture of **1** (100 mg, 0.36 mmol) and D_2O (128 mg, 7.14 mmol) in THF (20 mL), and was stirred at room temperature for 24 h. The reaction was then quenched with 5% aqueous NaH_2PO_4 and extracted with *t*BuOMe. The organic layer was washed with brine, dried (anhydrous Na_2SO_4), and the solvent removed. The residue was chromatographed (hexane/*t*BuOMe 7:3) affording **15** (36 mg, 36% yield). ^{1}H and ^{13}C NMR spectra of **15** matched those of the isotopomer **14**,[6c] except for the following significant signals: δ = 0.92 (brs; H_3–12), 28.97 ppm (small t, $^1J(^{13}C,D)$ = 20.1 Hz; C-8); MS (70 eV, EI): *m*/*z* (%): 265 (3), 222 (10), 121 (100); HRMS (FAB): calcd for $C_{17}H_{29}DO_3Na$: (M^+) 306.2155, found 306.2160. Minor amounts of a C-8 epimer could also be detected. ^{1}H and ^{13}C NMR signals of this minor isomer agreed closely with a related structure described elsewhere.[6c],[37]

Preparation of epoxide 19: Powdered NBS (1.73 g, 9.75 mmol) was gradually added to a solution of geranylacetone ethylene ketal[38] (1.50 g, 6.34 mmol) in a mixture of DME/water (100 mL, 3:2) at 0°C. The reaction was stirred for 30 min, diluted with *t*BuOMe, washed with water, dried (anhydrous Na_2SO_4), and the solvent removed. The residue was dissolved in 0.5 M methanolic K_2CO_3 (20 mL) and stirred for 10 min. The methanolic solution was then diluted with *t*BuOMe, washed with water, dried (anhydrous Na_2SO_4), and concentrated to dryness, giving a residue which was submitted to flash chromatography (hexane/*t*BuOMe 4:1) to give **19** (1.15 g, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.18 (t, J = 5.1 Hz, 1H), 3.94 (m, 4H), 2.71 (t, J = 6.3 Hz, 1H), 2.21–2.04 (m, 5H), 1.63 (s, 3H), 1.73–1.55 (m, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.26 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 134.36 (C), 124.68 (CH), 109.94 (C), 64.71 (CH_2), 64.21 (CH), 58.35 (C), 39.11 (CH_2), 36.34 (CH_2), 27.49 (CH_2), 24.95 (CH_3), 23.86 (CH_3), 22.73 (CH_2), 18.81 (CH_3), 15.99 ppm (CH_3); HRMS (FAB): calcd for $C_{15}H_{26}O_2Na$ [M^+] 277.1779, found 277.1773.

Data for the cyclic alcohol 20: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.85 (brs, 1H), 4.60 (brs, 1H), 3.91 (m, 4H), 3.39 (dd, J = 9.7, 4.3 Hz, 1H), 2.30 (dt, J = 13.0, 4.6 Hz, 1H), 2.20–0.75 (m, 8H), 1.30 (s, 3H), 1.03 (s, 3H), 0.69 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 147.26 (C), 110.40 (C), 108.66 (CH_2), 77.35 (CH), 64.67 (CH_2), 51.85 (CH), 40.76 (C), 38.23 (CH_2), 33.14 (CH_2), 32.30 (CH_2), 25.98 (CH_3), 23.92 (CH_3), 19.80 (CH_2), 15.47 ppm (CH_3); MS: *m*/*z* (%): 254 (1) [M^+], 239 (1) [M^+–CH_3], 221 (1) [M^+–CH_3–H_2O, 159 (12), 87 (100). Minor signals (13:1 relationship) for an endocyclic regioisomer could be observed in the ^{1}H NMR spectrum (300 MHz, $CDCl_3$): (only distinctive signals) δ = 5.26 (brs, 1H), 3.43 ppm (dd, J = 7.7, 5.6 Hz, 1H).

Obtention of ketone 21: A solution of **20** (160 mg, 0.69 mmol), [$CeCl_3$·$7H_2O$] (726 mg, 1.95 mmol), and NaI (57 mg, 0.38 mmol) in MeCN (50 mL) was stirred at room temperature for 16 h. The mixture was diluted with *t*BuOMe, washed with brine, dried (anhydrous Na_2SO_4), and the solvent removed. Flash chromatography (hexane/*t*BuOMe 1:1) of the residue afforded **21** (125 mg, 95%) as a white solid. M.p. 38–40°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84 (brs, 1H), 4.50 (brs, 1H), 3.38 (dd, J = 8.9, 4.1 Hz, 1H), 2.51 (ddd, J = 14.3, 9.1, 5.0 Hz, 1H), 2.35–2.23 (m, 2H), 2.08 (s, 3H), 2.00–1.40 (m, 6H), 1.01 (s, 3H), 0.74 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 209.27 (C), 147.23 (C), 108.78 (CH_2), 76.94 (CH), 51.38 (CH), 42.95 (CH_2), 40.55 (C), 32.24 (CH_2), 32.05 (CH_2), 30.05 (CH_3), 26.11 (CH_3), 19.69 (CH_2), 16.25 ppm (CH_3); HRMS (FAB): calcd for $C_{13}H_{22}O_2Na$ 233.1517, found 233.1519.

Synthesis of monocyclic diol 22: Vinylmagnesium bromide (1 M in THF, 0.22 mL, 0.22 mmol) was added to a solution of **21** (14 mg, 0.07 mmol) in THF (3 mL) at 0°C. The reaction was stirred for 2 h and then quenched with ice-water, extracted with *t*BuOMe, dried (anhydrous Na_2SO_4), and the solvent removed. Flash chromatography (hexane/*t*BuOMe 3:2) of the residue gave a mixture of the 9*R** and 9*S** epimeric alcohols **22** (14 mg, 90%) in a 3:2 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (dd, J = 17.3, 10.7 Hz, 1H; 9*R** isomer), 5.89 (dd, J = 17.3, 10.7 Hz, 1H; 9*S** isomer), 5.20 (d, J = 17.3 Hz, 1H), 5.05 (d, J = 10.7 Hz, 1H; 9*S** isomer), 5.04 (d, J = 10.7 Hz, 1H; 9*R** isomer), 4.85 (s, 1H), 4.58 (s, 1H; 9*R** isomer), 4.55 (s, 1H; 9*S** isomer), 3.39 (dd, J = 9.7, 4.3 Hz, 1H), 2.30 (dt, J = 12.9, 5.0 Hz, 1H), 2.00–0.80 (m, 8H), 1.26 (s, 3H), 1.03 (s, 3H; 9*S** isomer), 1.02 (s, 3H; 9*R** isomer), 0.71 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 147.40 (C), 147.34 (C), 145.36 (CH), 145.19 (CH), 111.79 (CH_2), 111.69 (CH_2), 108.73 (CH_2), 108.64 (CH_2), 77.32, (CH), 73.63 (C), 73.51 (C), 52.26 (CH), 52.15 (CH), 41.62 (CH_2), 41.56 (CH_2), 40.83 (C), 34.52 (CH_2), 32.94 (CH_2), 28.16 (CH_3), 27.78 (CH_3), 26.49 (CH_3), 19.76 (CH_2), 15.76 ppm (CH_3), (some signals were not observed); HRMS (FAB): calcd for $C_{15}H_{26}O_2Na$ 261.1830, found 261.1835.

Preparation of acetate 23: A mixture of **22** (35 mg, 0.15 mmol), Ac_2O (17 mg, 0.16 mmol), and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1 h. The mixture was then diluted with *t*BuOMe and washed with 2 N HCl, saturated $NaHCO_3$, and brine. The organic layer was dried (anhydrous Na_2SO_4) and the solvent removed. Flash chromatography (hexane/*t*BuOMe 4:1) of the residue gave a mixture of the 9*R** and 9*S** epimeric acetates **23** (33 mg, 80%) in a 3:2 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (dd, J = 17.3, 10.7 Hz, 1H; 9*R** isomer), 5.89 (dd, J = 17.3, 10.7 Hz, 1H; 9*S** isomer), 5.19 (d, J = 17.3 Hz, 1H), 5.01 (d, J = 10.7 Hz, 1H), 4.85 (s, 1H), 4.64 (dd, J = 9.5, 4.1 Hz, 1H), 4.60 (s, 1H; 9*R** isomer), 4.57 (s, 1H; 9*S** isomer), 2.30–0.80 (m, 9H), 2.02 (s, 3H), 1.25 (s, 3H), 0.91 (s, 3H), 0.76 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 170.68 (C), 146.86 (C), 145.38 (CH), 145.34 (CH), 111.65 (CH_2), 111.61 (CH_2), 109.54 (CH_2), 109.52 (CH_2), 78.60 (CH), 78.51 (CH), 73.51 (C), 73.39 (C), 53.46 (CH_2), 52.63 (CH), 41.40 (CH_2), 41.32 (CH_2), 39.44 (C), 28.66 (CH_2), 28.31 (CH_3), 27.88 (CH_3), 26.30 (CH_3), 26.22 (CH_3), 21.31 (CH_3), 19.98 (CH_2), 17.97 ppm (CH_3), (some signals were not observed); MS (70 eV, EI): *m*/*z* (%): 262 (1), 205 (28), 96 (100); HRMS (EI): calcd for $C_{17}H_{28}O_3Na$ 303.1936, found 303.1929.

Synthesis of monocyclic sesquiterpene 24: SeO_2 (4 mg, 0.012 mmol) and *t*butyl hydroperoxide (70 wt% in water, 0.056 mL, 0.35 mmol) were added to a solution of **23** (33 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at room temperature for 48 h. It was then diluted with *t*BuOMe and washed with 10% KOH and brine. The organic layer was dried (anhydrous Na_2SO_4) and the solvent removed. Flash chromatography (hexane/*t*BuOMe 3:2) of the residue gave a mixture of the 9*R** and 9*S** epimeric sesquiterpenes **24** (19 mg, 55%) in a 3:2 ratio.

Synthesis of isodrimenediol 26: A sample of acetate **11** (440 mg, 1.60 mmol) was dissolved in 0.5 M methanolic K_2CO_3 (50 mL) and stirred at room temperature for 15 h. Then *t*BuOMe was added and the mixture was washed with aqueous 2 N HCl and brine, dried (anhydrous Na_2SO_4), and the solvent removed. Flash chromatography (hexane/*t*BuOMe 1:1) of the residue gave **26** (374 mg, quantitative yield).

Preparation of epoxide 27: Powdered NBS (324 g, 1.82 mmol) was gradually added to a solution of farnesylacetone ethylene ketal[39] (500 mg, 1.65 mmol) in a mixture of DME/water (100 mL, 3:2) at 0°C. The reaction was stirred for 30 min, diluted with *t*BuOMe, washed with water, dried (anhydrous Na_2SO_4), and the solvent removed. The residue was dissolved in 0.5 M methanolic K_2CO_3 (20 mL) and stirred for 40 min. The methanolic solution was then diluted with *t*BuOMe, washed with water, dried (anhydrous Na_2SO_4), and concentrated to dryness. The residue was submitted to flash chromatography (hexane/*t*BuOMe 4:1) affording colorless oil **27** as a mixture of four stereoisomers (220 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.20–5.00 (m, 2H), 3.90–3.80 (m, 4H), 2.70–2.60 (m, 1H), 1.62 (s, 3H), 1.57 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.20 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 135.80 (C), 135.01 (C), 134.67 (C), 134.92 (C), 125.71 (CH), 125.04 (CH), 124.90 (CH), 124.81 (CH), 124.20 (CH), 124.12 (CH), 109.93 (C), 64.65 (CH_2), 64.16 (CH), 64.08 (CH), 58.64 (C), 39.86 (CH_2), 39.60 (CH_2), 39.42 (CH_2), 39.14 (CH_2), 36.34 (CH_2), 32.02 (CH_2), 31.81 (CH_2), 28.56 (CH_2), 28.52 (CH_2),

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27.51 (CH_2), 27.49 (CH_2), 26.60 (CH_2), 26.53 (CH_2), 26.49 (CH_2), 26.30 (CH_2), 24.90 (CH_3), 23.83 (CH_3), 23.40 (CH_3), 22.68 (CH_2), 22.59 (CH_2), 18.77 (CH_3), 18.74 (CH_3), 15.97 ppm (CH_3); HRMS (FAB): calcd for $C_{20}H_{34}ONa$ 345.2405, found 345.2408.

Data for cyclic alcohol 28: White solid; m.p. 95–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.81 (brs, 1H), 4.55 (brs, 1H), 3.95–3.85 (m, 4H), 3.22 (dd, J = 11.5, 4.1 Hz, 1H), 2.37 (ddd, J = 12.7, 4.0, 2.5 Hz, 1H), 2.05–0.80 (m, 13H), 1.28 (s, 3H), 0.96 (s, 3H), 0.75 (s, 3H), 0.66 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$; DEPT): δ = 148.01 (C), 110.45 (C), 106.95 (CH_2), 78.94 (CH), 64.71 (CH_2), 64.69 (CH_2), 56.71 (CH), 54.72 (CH), 39.50 (C), 39.21 (C), 38.23 (CH_2), 37.99 (CH_2), 37.18 (CH_2), 28.39 (CH_3), 28.02 (CH_2), 24.06 (CH_2), 23.88 (CH_3), 18.04 (CH_2), 15.49 (CH_3), 14.47 ppm (CH_3); MS (70 eV, EI): m/z (%): 322 (1) $[M]^+$, 289 (1), 260 (8), 135 (15); HRMS (FAB): calcd for $C_{20}H_{34}O_3N$: 345.2405, found 345.2399.

Preparation of bicyclic ketone 29: A solution of **28** (66 mg, 0.20 mmol), [$CeCl_3$·$7H_2O$] (273 mg, 0.73 mmol), and NaI (22 mg, 0.14 mmol) in MeCN (10 mL) was stirred at room temperature for 16 h. The mixture was diluted with *t*BuOMe, washed with brine, dried (anhydrous Na_2SO_4), and the solvent removed. Flash chromatography (hexane/*t*BuOMe 7:3) of the residue afforded **29** (49 mg, 85%).

Synthesis of 3β-hydroxymanool (30): Vinylmagnesium bromide (1 M in THF, 0.5 mL, 0.5 mmol) was added to a solution of **29** (22 mg, 0.08 mmol) in THF (5 mL) at 0 °C and stirred for 30 min. The reaction was quenched with ice water, extracted with *t*BuOMe, dried (anhydrous Na_2SO_4), and the solvent removed. Flash chromatography (hexane/*t*BuOMe 1:1) of the residue gave epimeric alcohols **30**[24] (9.5 mg, 39%) and **31** (5.5 mg, 23%). Data for **31**: vitreous solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.89 (dd, J = 17.3, 10.7 Hz, 1H), 5.20 (d, J = 17.3, 1H), 5.05 (d, J = 10.7 Hz, 1H), 4.81 (brs, 1H), 4.48 (brs, 1H), 3.23 (dd, J = 11.6, 4.6 Hz, 1H), 2.38 (ddd, J = 12.8, 6.7, 2.6 Hz, 1H) 2.00–0.80 (m, 13H), 1.26 (s, 3H), 0.98 (s, 3H), 0.76 (s, 3H), 0.67 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 148.21 (C), 145.19 (CH), 111.78 (CH_2), 106.86 (CH_2), 78.98 (CH), 73.71 (C), 57.05 (CH), 54.77 (CH), 41.36 (CH_2), 38.67 (C), 38.33 (C), 38.28 (CH_2), 37.18 (CH_2), 28.39 (CH_3), 28.21 (CH_2), 28.04 (CH_3), 24.10 (CH_2), 17.92 (CH_2), 15.47 (CH_3), 14.55 ppm (CH_3); MS (70 eV, EI): m/z (%): 273 (6), 255 (8), 135 (100); HRMS (EI): calcd for $C_{20}H_{34}O_2$ 306.2558, found 306.2563.

Synthesis of dinor-labdane alcohols 32 and 33: A sample of $NaBH_4$ (50 mg, 1.31 mmol) was added to a solution of **29** (12 mg, 0.04 mmol) in EtOH (5 mL), and was stirred at 0 °C for 1 h. The mixture was then diluted with *t*BuOMe, washed with brine, dried (anhydrous Na_2SO_4), and the solvent removed. Flash chromatography (hexane/*t*BuOMe 3:7) of the residue gave epimeric alcohols **32** (5.5 mg, 45%) and **33**[27] (4.5 mg, 37%). Data for **32**: white solid; m.p. 130–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.83 (brs, 1H), 4.54 (brs, 1H), 3.76 (m, 1H), 3.24 (dd, J = 11.6, 4.5 Hz, 1H), 2.39 (ddd, J = 12.8, 4.2, 2.5 Hz, 1H), 1.95 (dt, J = 12.5, 5.0 Hz, 1H), 1.85–0.80 (m, 12H), 1.16 (d, J = 6.1 Hz, 3H), 0.98 (s, 3H), 0.76 (s, 3H), 0.68 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): in Table 1; MS (70 eV, EI): m/z (%): 262 (1), 247 (1), 207 (4), 135 (100); HRMS (EI): calcd for[$C_{18}H_{32}O_2$ 280.2402, found 280.2397.

Data for tricyclic isocopalane 35: White solid; m.p. 132–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.84 (brs, 1H), 4.51 (brs, 1H), 4.34 (dd, J = 11.0, 3.6 Hz, 1H), 4.17 (dd, J = 11.0, 9.4 Hz, 1H), 3.21 (dd, J = 11.4, 4.8 Hz, 1H), 2.39 (brd, J = 12.7 Hz, 1H), 2.10–1.90 (m, 1H), 2.01 (s, 3H), 1.87–1.80 (m, 1H), 1.75–1.25 (m, 12H), 0.98 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H), 0.74 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 171.52, (C), 146.55 (C), 107.13 (CH_2), 78.84 (CH), 61.52 (CH_2), 59.64 (CH), 55.27 (CH), 55.02 (CH), 40.68 (CH_2), 39.14 (C), 38.89 (C), 38.56 (CH_2), 37.57 (C), 37.45 (CH_2), 28.05 (CH_3), 27.33 (CH_2), 22.49 (CH_2), 21.20 (CH_3), 18.70 (CH_2), 16.37 (CH_3), 16.06 (CH_3), 15.37 (CH_3); MS (70 eV, EI): m/z (%): 288 (1), 207 (17), 189 (14), 93 ppm (100); HRMS (FAB): calcd for $C_{22}H_{36}O_3Na$ 371.2562, found 371.2561.

Synthesis of saturated isocopalane 36: A mixture of **35** (11 mg, 0.03 mmol) and 5% Pd/C (5 mg) in MeOH (5 mL) was stirred under H_2 (1 atm) for 6 h. The mixture was filtered and the solvent removed from the filtrate, giving **36** (8 mg, 73%) as a 3:2 mixture of epimers at C-13.

Titanocene-catalyzed cyclization of 2,3-oxidosqualene 38: Strictly deoxygenated THF (20 mL) was added to a mixture of [Cp_2TiCl_2] (58 mg, 0.23 mmol) and Mn dust (512 mg, 9.30 mmol) under an argon atmosphere, and the suspension was stirred at room temperature until it turned lime green (about 15 min). A solution of 2,3-oxidosqualene **38** (500 mg, 1.17 mmol) and 2,4,6-collidine (1.0 mL, 8.19 mmol) in THF (2 mL) and Me_3SiCl (0.60 mL, 4.68 mmol) were then added and the solution was stirred for 4 h. The reaction was then quenched with 2 N HCl and extracted with *t*BuOMe. The organic layer was washed with brine, dried (anhydrous Na_2SO_4), and the solvent removed. The residue was dissolved in THF (20 mL) and stirred with Bu_4NF (1.1 g, 3.51 mmol) for 2 h. The mixture was then diluted with *t*BuOMe, washed with brine, dried (anhydrous Na_2SO_4), and the solvent removed. Column chromatography of the residue on 20% $AgNO_3$/silica gel (hexane/*t*BuOMe 9:1) afforded malabaricanes **39** (75 mg, 15%) and **40** (120 mg, 24%), as well as allylic alcohol **41** (trace) and achilleol A (**25**) (trace).

Data for 39: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.10 (t, J = 6.0 Hz, 1H), 5.08 (t, J = 6.0 Hz, 1H), 4.87 (brs, 1H), 4.58 (brs, 1H), 3.20 (dd, J = 12.0, 5.8 Hz, 1H), 2.10–1.95 (m, 9H), 1.67 (s, 3H), 1.59 (s, 6H), 0.96 (s, 3H), 0.94 (s, 3H), 0.84 (s, 3H), 0.77 ppm (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 154.5 (C), 135.2 (C), 131.3 (C), 124.5 (CH), 124.3 (CH), 108.9 (CH_2), 79.3 (CH), 56.4 (CH), 55.8 (CH), 55.5 (CH), 45.3 (C), 40.3 (C), 39.8 (CH_2), 39.3 (CH_2), 38.8 (CH_2), 37.2 (C), 36.6 (CH_2), 28.1 (CH_3), 27.7 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 25.7 (CH_3), 24.8(CH_3), 20.8 (CH_2), 19.1 (CH_2), 17.7 (CH_3), 16.1 (CH_3), 15.7 (CH_3), 15.4 ppm (CH_3); MS (70 eV, EI): m/z (%): 426 (3), 411 (1), 247 (10), 207 (30), 189 (20), 135 (25), 69 (100).

Data for 40: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.11 (t, J = 6 Hz, 1H), 5.10 (t, J = 6.0 Hz, 1H), 4.89 (brs, 1H), 4.73 (brs, 1H), 3.20 (t, J = 7.8 Hz, 1H), 2.20–1.95 (m, 9H), 1.67 (s, 3H), 1.59 (s, 6H), 0.97 (s, 3H), 0.84 (s, 3H), 0. 78 (s, 3H), 0.65 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.3 (C), 135.0 (C), 131.3 (C), 124.5 (CH), 124.3 (CH), 110.1(CH_2), 79.3 (CH), 63.2 (CH), 57.1 (CH), 56.3 (CH), 43.6 (C), 41.0 (C), 39.8 (CH_2), 38.8 (C), 38.4 (CH_2), 37.6 (CH_2), 36.9 (C), 28.2 (CH_3), 27.3 (CH_2), 27.1 (CH_2), 26.8 (CH_2), 25.7 (CH_3), 25.4 (CH_2), 19.6 (CH_2), 19.3 (CH_2), 17.7 (CH_3), 16.1 (CH_3), 15.5 (CH_3), 15.3 (CH_3), 15.1 ppm (CH_3); MS (70 eV, EI): m/z (%): 426 (3), 411 (1), 247 (10), 207 (30), 189 (20), 135 (25), 69 (100); HRMS (EI): calcd for $C_{30}H_{50}ONa$ 449.3760, found 449.3759.

Computational methods: Calculations were made with the GAUSSIAN 98 series of programs.[40] The geometries of all intermediates were optimized at the DFT level employing the B3LYP hybrid functional,[41] using the standard 6–31G(d) basis set for C, H, and O. Harmonic frequencies were calculated at the same level of theory to characterize the stationary points and to determine the zero-point energies (ZPE). More accurate energies were determined by single-point calculations at the same level using the 6–311+G(d,p) basis set. Final energies include ZPE correction. The bonding characteristics of the local minima were analyzed by means of the Natural Bond Orbital (NBO) analysis of Weinhold et al.[42]

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