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


Abstract: The titanocene-catalyzed cascade cyclization of epoxypolyprenes, 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(m)-based procedure discovered by Nugent and RajanBabu and the catalytic version subsequently developed by Ganssauer 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 13C 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 [Cp₂TiCl][6] we obtained encouraging results, but excess quantities of [Cp₂TiCl₂] 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 epoxypoly-prene 1 with [Cp₂TiCl] 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)[6] together with lesser amounts of acyclic 4 (23%) and monocyclic 7 (10%); no 14 was detected. Moreover, when D₂O 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]

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 1 (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 1 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 1 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-

Scheme 1. Proposed mechanism for the titanocene(m)-mediated cyclization of 1. a) [Cp₂Ti(Cl)H] elimination under anhydrous conditions; b) acidic quenching after the [Cp₂Ti(Cl)H] elimination.
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 \(2E,6E-10,11\)-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 \([\text{Cp}_2\text{TiCl}_2]\) and the high dilutions required in our preliminary experiments.\[14\] Our starting hypothesis was based on the use of the novel combination \(\text{Me}_3\text{SiCl}/2,4,6\)-collidine,\[10b, \[15\] which is compatible with oxiranes and should be capable of regenerating \([\text{Cp}_2\text{TiCl}_2]\) from both \([\text{Cp}_2\text{Ti}(\text{Cl})\text{H}]\) and oxygen-bonded titanium derivatives such as 10 (Scheme 2). To check this hypothesis we treated epoxypolyprene 1 (prepared from commercially available \(2E,6E\)-farnesol by van Tamelen’s procedure)\[10\] with a substoichiometric quantity of \([\text{Cp}_2\text{TiCl}_2]\) (0.2 equiv), Mn dust, and the mixture of \(\text{Me}_3\text{SiCl}\) and collidine in dry THF (\(10^{-2}\text{ M substrate concentration}\)) (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 \([\text{Cp}_2\text{TiCl}_2]\) 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).
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 epoxy-ketal 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 (9R* and 9S* 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 9R* and 9S* 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 9R 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 9S 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]

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 1H and 13C NMR data in accordance with those of natural iso-
drimenediol excreted by the fungus \textit{Polyporus arcularius}.\textsuperscript{[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\textsuperscript{26} proposed by Fleck \textit{et al.} for the fungal metabolite.\textsuperscript{[23]}

We then addressed the chemical preparation of 3β-hydroxymanool (30), a bicyclic diterpenoid with a labdane skeleton from the fern \textit{Gleichenia japonica}.\textsuperscript{[24]} As starting material we chose commercial farnesylacetone,\textsuperscript{[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),\textsuperscript{[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 13S* 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\textsuperscript{[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.\textsuperscript{[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 (1H 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 13R* relative configuration (derived from the hydride attack by the Si face) to the major product (32) and, consequently, the 13S* 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,\textsuperscript{[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 13S* 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\textsuperscript{[28]} and its challenging chemical structure. Recently Xing and Demuth reported an elegant total synthesis of stypoldione via the tricyclic intermediate \textsuperscript{36}.\textsuperscript{[29]} Because of the biological interest of stypoldione, we selected the isocupalane 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

![Scheme 4. Titanocene-catalyzed synthesis of bicyclic terpenoids](image-url)
available geranylgeraniol by van Tamelen’s procedure. 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.

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

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

<table>
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<th>Carbon</th>
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<th>Synthetic 33</th>
<th>Δδ</th>
<th>Synthetic 32</th>
<th>Δδ</th>
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[a] The most significant data are in bold characters.
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 malabaricase 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-exo cyclization step giving the protomalabaricaine 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 [36]. 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 [36]. Through free-radical chemistry, however, it seems unlikely that the double bond at Δ7 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 malabaricases from 2,3-oxidosqualene (and possibly from squalene also) is intriguing from a biogenetic point of view. The recent discovery of malabaricases 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 C10, C15, C20, and C30 terpenoids, including monocyclic, bicyclic, and tricyclic natural products. The key step of the process is the titanocene-catalyzed cascade cyclization of epoxypolyprenes, 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 [28], 17 [39], 34 [39] and 38 [30] 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 [29], 18 [25], 24 [30], 25 [36], 26 [29], 29 [30], 30 [34], 33 [29], and 36 [29]. Other general experimental details have been reported elsewhere [11, 23].

General procedure for the titanocene-catalyzed cyclization of epoxypolyprenes: Strictly deoxygenated THF (20 mL) was added to a mixture of [Cp2TiCl2] (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 Me3SiCl (10 mmol) were added to the mixture over 1 h. After the reaction was complete (checked by TLC), the reaction mixture was quenched with 0.1 M HCl (15 mL) and extracted with Et2O (3 x 20 mL). After drying of the combined organic layers over MgSO4, the filtrate was evaporated to dryness and the crude mixture was purified by column chromatography on silica gel.
added and the solution was stirred for 8 h. The reaction was then quenched with 2 N HCl and extracted with BuOMe. The organic layer was washed with water, dried (anhydrous Na2SO4), and the solvent removed. The residue was dissolved in THF (20 mL) and stirred with BuNF (10 mmol) for 2 h. The mixture was then diluted with BuOMe, washed with brine, dried (anhydrous Na2SO4), and the solvent removed. Products obtained were isolated by column chromatography of the residue on silica gel (hexane/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 [CP2TiCl2] (703 mg, 1.95 mmol) and NaI (57 mg, 0.38 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 D2O (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 NaH2PO4 and extracted with H2O.

Preparation of acetate 23: A mixture of 22 (35 mg, 0.15 mmol), Ac2O (17 mg, 0.16 mmol), and DMAP (20 mg, 0.16 mmol) in CH2Cl2 (5 mL) was stirred at room temperature for 1 h. The reaction was then quenched with ice-water, extracted with BuOMe, dried (anhydrous Na2SO4), and the solvent removed. Flash chromatography (hexane/BuOMe 3:2) of the residue gave a mixture of the 9R* and 9S* epimeric acetates 23 (33 mm, 80%) in a 3:2 ratio. 1H NMR (300 MHz, CDCl3); δ = 5.90 (dd, J = 17.3, 10.7 Hz, 1H; 9R* isomer), 5.89 (dd, J = 17.3, 10.7 Hz, 1H; 9S* isomer), 5.04 (d, J = 10.7 Hz, 1H; 9S* isomer), 4.85 (s, 1H; 9R* isomer), 4.55 (s, 1H; 9R* 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; 9R* isomer), 0.72 (s, 3H; 9R* isomer), 0.71 ppm (s, 3H; 9S* isomer). 13C NMR (75 MHz, CDCl3, DEPT): δ = 147.40 (C), 147.34 (C), 145.36 (CH), 145.34 (CH), 111.79 (CH), 108.73 (CH), 108.64 (CH), 77.32 (CH), 73.63 (CH), 73.51 (C), 52.26 (CH), 52.15 (CH), 46.72 (CH), 41.56 (CH), 40.83 (C), 34.52 (CH), 32.94 (CH), 28.16 (CH), 27.78 (CH), 26.49 (CH), 19.76 (CH), 15.76 ppm (CH3), (some signals were not observed); HRMS (FAB): calcd for C15H26O2NaH2O2: 261.1830, found 261.1835.

Synthesis of monocyclic diol 22: Vinylmagnesium bromide (1 mmol 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 BuOMe, dried (anhydrous Na2SO4), and the solvent removed. Flash chromatography (hexane/BuOMe 3:2) of the residue gave a mixture of the 9R* and 9S* epimeric alcohols 22 (14 mg, 90%) in a 3:2 ratio. 1H NMR (300 MHz, CDCl3); δ = 5.90 (dd, J = 17.3, 10.7 Hz, 1H, 9R* isomer), 5.89 (dd, J = 17.3, 10.7 Hz, 1H, 9S* isomer), 5.04 (d, J = 10.7 Hz, 1H, 9S* isomer), 4.85 (s, 1H, 9R* isomer), 4.55 (s, 1H, 9R* 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; 9R* isomer), 0.72 (s, 3H; 9R* isomer), 0.71 ppm (s, 3H; 9S* isomer). 13C NMR (75 MHz, CDCl3, DEPT): δ = 147.40 (C), 147.34 (C), 145.36 (CH), 145.34 (CH), 111.79 (CH), 108.73 (CH), 108.64 (CH), 77.32 (CH), 73.63 (CH), 73.51 (C), 52.26 (CH), 52.15 (CH), 46.72 (CH), 41.56 (CH), 40.83 (C), 34.52 (CH), 32.94 (CH), 28.16 (CH), 27.78 (CH), 26.49 (CH), 19.76 (CH), 15.76 ppm (CH3), (some signals were not observed); HRMS (FAB): calcd for C15H26NaO2: 261.1830, found 261.1835.
The bonding characteristics of the local minima were analyzed by means of the Natural Bond Orbital (NBO) analysis of Weinhold et al.[12]
Despite of the free-radical nature of Ti(III) mediated epoxide openings, GC-MS analysis indicated a 77% deuterium incorporation.

In initial experiments using an excess of titanocene (ref. [8]), dilutions levels of the order of 10−6 were needed to avoid increased proportions of byproducts such as 4 and 7 derived from the premature trapping of intermediate radicals such as 2 and 5.


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