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Synthesis of five- to seven-membered polyfunctional terpenic carbocycles via Ti(III)-catalyzed radical cyclizations of epoxypolyprenes

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Abstract—Ring size on Ti(III)-mediated radical cyclization of monoepoxypolyprenoids can be controlled by varying the substitution pattern and/or the electronic distribution of the double bond involved in the ring closure. The feasibility of applying this idea to tandem cyclizations has also been proven. Besides, when a silyloxy function is located in α position to the oxirane ring of the acyclic polyprene, the cyclization leads to carbocyclic terpenoids doubly functionalized in the A ring with acceptable yields. These results widen significantly the scope of this methodology.
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1. Introduction

The bis(cyclopentadienyl)titanium(III) chloride-mediated radical cyclization of suitable unsaturated epoxides, first reported by RajanBabu and Nugent using Ti(III) in equimolecular quantities,[1] and then by Gansauer in its catalytic version,[2] has recently proved to be an efficient tool in the synthesis of natural products. In this context, Barrero et al. developed a new biomimetic strategy for the synthesis of cyclic terpenoids containing six- and seven-membered rings, based on the radical opening of acyclic epoxypolyprenes.[3] This and other cyclization strategies have also been applied to numerous cyclic terpenic structures, either by using stoichiometric or catalytic protocols.[4] Most of the above-mentioned synthetic efforts have led to the formation of terpenic structures with six-membered rings, although Fernández-Mateos et al. have achieved cyclizations leading to rings containing three to seven members.[5] The substrates used by these latter authors were mostly monocyclic terpenic compounds with carbonyls, nitriles, and α,β-unsaturated carbonyls as radical acceptors, although structurally different from the natural acyclic polyprenes.

Considering the synthesis in nature of polycyclic isoprenoids, it is thought that the specific cyclizations occur in a four-step-sequence, the first step being the generation of a carbocation.[6] However, two radical-mediated synthetic strategies, namely, the aforementioned Ti(III)-based opening of epoxypolyprenes, and the photoinduced cascade cyclizations of polyalkenes via radical cationic intermediates,[7] proved to induce a number of impressive biomimetic polycyclizations. Furthermore, these radical protocols permitted not only to improve the results obtained in certain cationic processes, but also to induce some transformations, which could not be achieved via cationic intermediates.[8] Both methods could be considered as illustrations of the 'minimal enzymatic assistance' theory.[9]

2. Results and discussion

We describe here our results using mono- and tandem cyclization processes carried out with acyclic epoxypolyprenes possessing α,β-unsaturated esters as radical traps (Fig. 1a). Previous reports using α,β-unsaturated esters as radical acceptors in intermolecular processes let anticipate good yields in this kind of cyclizations.[10] A point of special interest in this type of cyclizations lies in the regioselectivity of the process: 5-*exo*-trig versus 6-*endo*-trig ring closures.

Furthermore, the likelihood of obtaining polyfunctionalized structures with five- to seven-membered rings prompted us also to test the influence of oxygenated functions in α position to the oxirane ring not only regarding the efficiency of the cyclization process, but concerning the stereochemical

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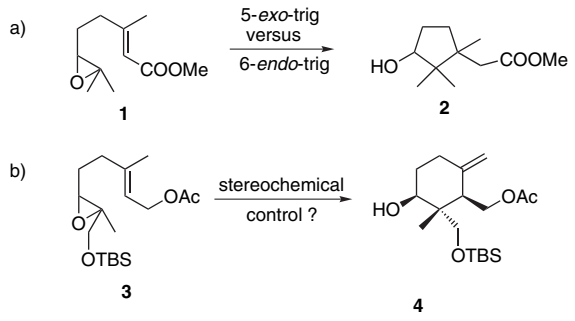
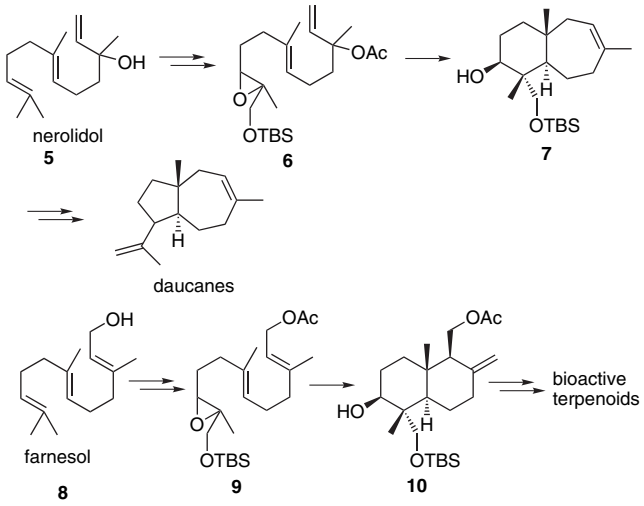


Figure 1.

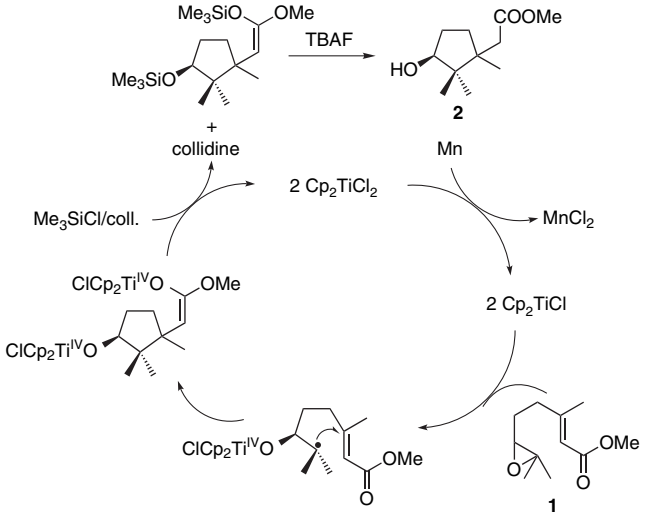
outcome of the process, since three or more stereogenic centers are created (Fig. 1b). These functionalizations can be incorporated using Sharpless asymmetric epoxidation protocol, which increases the interest of this study. Thus, efficient regio- and stereoselectively controlled cyclizations of suitable substrates such as **6** and **9**, easily obtained from commercially available farnesol and natural nerolidol,[11] would facilitate the enantioselective access to polyfunctionalized structures such as **7** and **10** (Scheme 1).



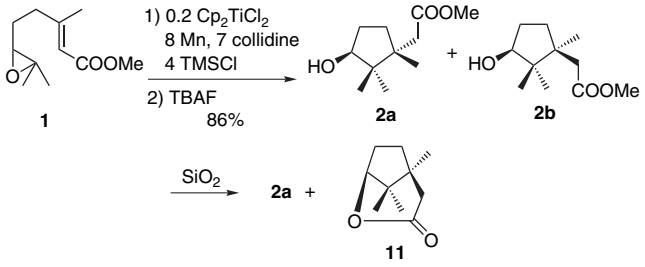
Scheme 1.

These bicyclic compounds might be advanced intermediates in the synthesis of compounds of interest. Thus, **7** could be used as a precursor of daucanes with an isopropenyl group,[12] whilst **10** could lead to functionalized drimanes (whose main skeleton is already contained in **10**) and advanced synthons for the preparation of A and B rings of bioactive terpenoids, including triterpenic structures.[13]

We began by reacting methyl 6,7-epoxygeraniate (prepared from commercial geraniol) with catalytic Cp_2TiCl_2[14] to afford, after 10 min and subsequent trimethylsilylether deprotection, an 86% yield of 5-*exo*-trig cyclization products **2a** and **2b**. The complete catalytic cycle for this transformation is shown in Scheme 2. These compounds could be easily separated since **2b** is quantitatively transformed into **11** by spontaneous lactonization on silica gel or by treatment with *p*TsOH in DCM (Scheme 3). Two features of these reactions are particularly noteworthy: firstly, the regioselectivity of the cyclization towards 5-*exo* products, caused by the substitution pattern and the electronic distribution of the α,β-unsaturated ester, and secondly, the remarkable increase in yield (approx. 25%) as compared to that obtained when a six-membered ring is created.[4i]

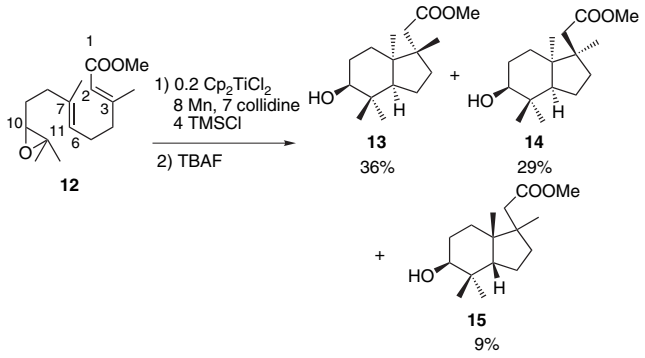


Scheme 2.



Scheme 3.

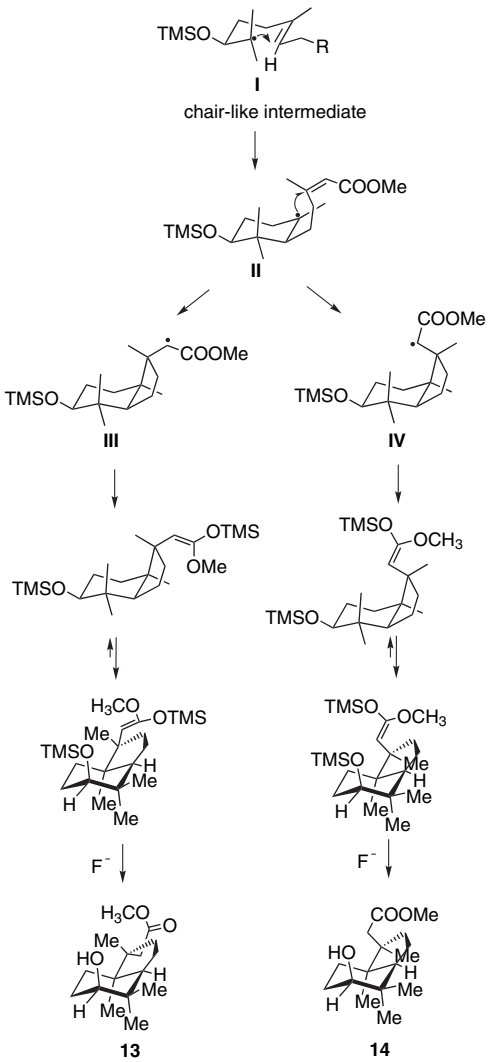
This gratifying result encouraged us to try the corresponding tandem process starting from methyl 10,11-epoxyfarnesoate, **12**, obtained from commercial farnesol. The exposure of **12** to the same experimental conditions used for **1** led to a 75% yield of compounds **13**–**15**, as a result of a tandem 6-*endo*-trig and 5-*exo*-trig cyclization (Scheme 4). As happened with **1**, the presence of an α,β-unsaturated ester caused a change in the regioselectivity on the closing of the second cycle. The yield also increased considerably



Scheme 4.

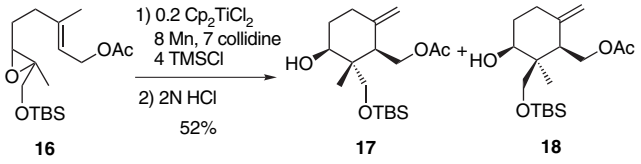
(approx. 20%) compared to that obtained with 10,11-epoxyfarnesyl acetate, which gave a double 6-*endo* tandem cyclization.[4i] Apart from this we also observed a pronounced stereoselectivity towards cis interannular junction anti to the hydroxyl group (7:1).

We postulate the mechanism shown in Scheme 2 to account for the regio- and stereochemical outcome of this reaction. An epoxide reductive opening originates radical **I**, the stable chair-like conformation of this intermediate determining the stereoselectivity of the first 6-*endo* cyclization.[3] The monocyclic radical thus generated is trapped by the conjugated double bond via a 5-*exo*-trig process, the regioselectivity of which is now determined by the electronic distribution of this olefin.[15] With respect to the stereochemistry of the interannular junction, proven to be cis,[16] this must be determined by the size of the new ring created. No stereoselectivity was observed at C-8, on the other hand, since there appears to be no preference for the ensuing attack of the carbon-centered radical against the double bond Δ^2. Finally, a conformational change leads to the most stable conformation, as depicted in Scheme 4. MM2 theoretical calculations confirm the most stable conformation proposed for compounds **13** and **14** (Scheme 5).[17]



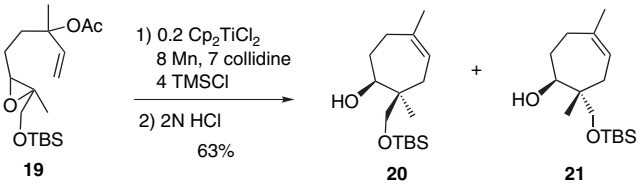
Scheme 5.

To test the influence of an oxygenated function in the α position upon the oxirane ring, which initiates the radical cyclization, epoxide **16** was prepared from geraniol. Thus the Ti(III)-induced homolytic opening of the oxirane ring and subsequent radical cyclization afforded the 6-*endo*-trig products **17** and **18** in relative proportions of 7:1, favoring the isomer possessing the equatorially oriented CH_2OTBS group, together with minor quantities of *endo*-isomers (Scheme 6). This result agrees with those reported previously by Takahashi et al.,[18] who proposed the existence of an association between the CH_2OTBS group and the titanoxy group at C-3 to account for the stereochemical control of the process.



Scheme 6.

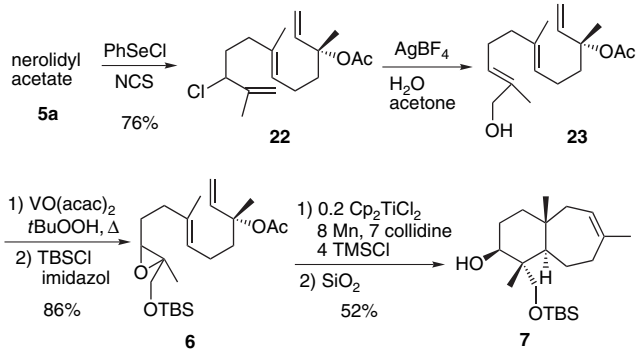
When we carried out this reaction with the corresponding epoxy derivative of linalyl acetate, 7-*endo* cyclization products **20** and **21** were formed in a 63% yield (Scheme 7).[19]



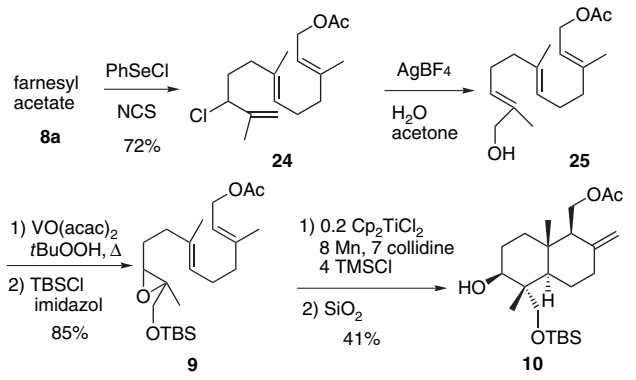
Scheme 7.

Nevertheless, no stereoselectivity was observed in this case, which may be put down to the higher conformational mobility of the seven-membered ring.

Bearing these results in mind, it would be interesting to test the stereochemical outcome of the tandem cyclizations of the α-oxygenated derivatives of farnesol and nerolidol (Schemes 8 and 9).



Scheme 8.



Scheme 9.

Allylic oxidation at the C-12 position of nerolidyl acetate was achieved via allylic chlorination with catalytic PhSeCl,[20] and a noteworthy yield of 75% of the desired chloro derivative **22** was obtained, which was then transformed into the primary alcohol **23** (40%) by treatment with $AgBF_4$.[21] Hydroxyl-directed epoxidation using Sharpless conditions[22] and protection with TBSCl let us to obtain the key intermediate **6** in 86% yield. Exposure of **6** to catalytic Ti(III) led, after silica gel separation, to the isolation of a noticeable 65% yield of bicyclic compound **7**. Regarding the stereochemical outcome of the reaction, it is worth mentioning that only one stereoisomer could be detected in this radical process where up to four contiguous stereogenic centers are created.

Following a synthetic route parallel to that used with nerolidyl acetate farnesyl acetate was converted to the desired 6+6 bicyclic sesquiterpenoid **10**. Again the reaction took place with high diastereoselectivity, and only isomer **10** could be isolated in a 41% yield, although in this case the formation of minor quantities of other stereoisomers was detected.

In conclusion, with the present work we have shown that, in radical cyclizations of epoxypolyprenes catalyzed by Cp_2TiCl, the employment of α,β-unsaturated methyl esters as radical acceptors provokes 5-*exo*-trig ring closures. A significant increase of the reaction yield (20–25%) was also observed in these cyclizations, as compared to the yield obtained when a six-membered ring is created. Furthermore, in the cases where a silyloxy function is located in the α position to the oxirane ring, the cyclizations lead to carbocyclic terpenoids doubly functionalized in the A ring with acceptable yields. Besides, a good stereoselectivity is observed in most cases, the major stereoisomers presenting the CH_2OTBS group disposed equatorially. Thus, this methodology permits an easy access to advanced intermediates in the synthesis of both polyfunctionalized terpenoids and terpenoids possessing unusual skeletons.

3. Experimental

3.1. General methods

All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an atmosphere of argon. Tetrahydrofuran (THF) was freshly distilled immediately prior to use from sodium/benzophenone and strictly deoxygenated for 30 min under argon for each of the Cp_2TiCl_2/Mn reactions. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated. Silica gel SDS 60 (35–70 μm) was used for flash column chromatography. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and a solution of phosphomolybdic acid in ethanol and heat as developing agent. IR spectra were recorded with a Matson model Satellite FTIR instrument as NaCl plates (films). NMR studies were performed with a Bruker ARX 400 (^{1}H 400 MHz/^{13}C 100 MHz) spectrometer. The accurate mass determination was carried out with an AutoSpec-Q mass spectrometer arranged in an EBE geometry (Micromass Instrument, Manchester, UK) and equipped with a FAB (LSIMS) source.

3.1.1. General procedure for catalytic Ti(III)-mediated cyclization of epoxides. A mixture of Cp_2TiCl_2 (62 mg, 0.24 mmol) and Mn dust (532 mg, 9.68 mmol) in strictly deoxygenated THF (7 mL) was stirred at room temperature until the red solution turned green. Then, a solution of the corresponding oxirane (1.20 mmol), 2,4,6-collidine (1.1 mL, 8.33 mmol), and TMSCl (0.6 mL, 4.76 mmol) in strictly deoxygenated THF (3 mL) was added to the solution of Cp_2TiCl. The reaction mixture was stirred until dispartition of the starting material (20 min–3 h), quenched with 2 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure.

3.2. Cylization of epoxypolyprenes possessing α,β-unsaturated methyl esters as radical acceptors

3.2.1. Cyclization of 1. After subjecting commercially available **1** (150 mg, 0.76 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford 130 mg (86%) of an equimolecular mixture of **2a** and **2b**. A solution of this mixture (100 mg, 0.59 mmol) in Et_2O was treated with an excess of *p*TsOH for 26 h at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/*t*-BuOMe, 3:1) to give 16 mg of **11**, 25 mg of **2a**, and 52 mg of a mixture of these two compounds. Compound **2a**, colorless oil. IR (film) ν: 3464, 2957, 2878, 1735, 1462, 1438, 1326, 1205, 1014 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 0.87 (s, 3H), 1.05 (s, 3H), 1.45–2.25 (m, 4H), 2.19 (s, 3H), 3.64 (s, 3H), 3.88 (dd, J=8.2, 5.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 21.7, 22.7, 31.0, 34.3, 42.3, 44.8, 47.3, 51.3, 81.4, 173.6 ppm. HRFABMS calcd for $C_{11}HO_3Na$ [M+Na]$^+$ 223.1310, found 223.1317. Compound **11**, colorless oil. IR (film) ν: 2960, 2878, 1736, 1468, 1370, 1211, 1040 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H), 0.86 (s, 3H), 0.95 (s, 3H), 1.63–1.88 (m, 2H), 1.89–2.11 (m, 2H), 2.30 (d, J=18.8 Hz, 1H), 2.48 (dd, J=18.8, 3.2 Hz, 1H), 4.16 (d, J=4.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 19.2, 20.5, 29.7, 36.1, 41.9,

43.6, 44.9, 89.1, 171.5 ppm. HRFABMS calcd for $C_{10}H_{16}O_2Na$ $[M+Na]^+$ 191.1048, found 191.1060.

3.2.2. Cyclization of 12. After subjecting **12**[23] (300 mg, 1.13 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford 109 mg (36%) of **13**, 88 mg (29%) of **14**, and 27 mg (9%) of **15**. Compound **13**, colorless oil. IR (film) ν: 3515, 2950, 2879, 1731, 1470, 1439, 1212, 1124, 1013 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.92 (s, 3H), 0.93 (s, 3H), 1.00 (s, 3H), 1.50–1.98 (m, 10H), 2.11 (d, J=12.8 Hz, 1H), 2.22 (d, J=12.9 Hz, 1H), 3.46 (t, J=2.8 Hz, 1H), 3.61 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) ™18.8, 20.8, 23.4, 24.9, 26.3, 26.5, 29.6, 31.8, 36.3, 40.7, 45.2, 49.1, 51.3, 51.8, 75.1, 174.1 ppm. HRFABMS calcd for $C_{16}H_{28}O_3Na$ $[M+Na]^+$ 291.1936, found 291.1943. Compound **14**, colorless oil. IR (film) ν: 3514, 2949, 2879, 1731, 1471, 1439, 1212, 1001 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.91 (s, 3H), 0.94 (s, 3H), 1.01 (s, 3H), 1.35–2.18 (m, 10H), 2.16 (d, J=12.8 Hz, 1H), 2.22 (d, J=12.8 Hz, 1H), 3.47 (t, J=2.8 Hz, 1H), 3.62 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.6, 23.2, 25.0, 26.4, 26.6, 29.7, 34.5, 36.2, 40.9, 45.0, 47.9, 51.3, 51.4, 75.1, 174.2 ppm. HRFABMS calcd for $C_{16}H_{28}O_3Na$ $[M+Na]^+$ 291.1936, found 291.1935. Compound **15**, colorless oil. IR (film) ν: 3515, 2949, 2878, 1731, 1471, 1438, 1321, 1212, 1124, 1001 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.93 (s, 3H), 0.95 (s, 3H), 0.98 (s, 3H), 1.15–1.90 (m, 10H), 2.13 (d, J=13.0 Hz, 1H), 2.16 (d, J=13.0 Hz, 1H), 3.58 (dd, J=5.7, 10.5 Hz, 1H), 3.61 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 22.2, 22.3, 24.0, 27.3, 28.0, 29.9, 34.2, 37.1, 40.8, 45.2, 47.8, 51.3, 54.6, 74.1, 174.0 ppm. HRFABMS calcd for $C_{16}H_{28}O_3Na$ $[M+Na]^+$ 291.1936, found 291.1937.

3.3. Monocyclizations of epoxypolyprenes possessing a CH_2OTBS group in the α position to the oxirane ring

3.3.1. Synthesis of 16. To a solution of 229 mg (1.03 mmol) of the primary alcohol in DCM (7 mL) resulting from subjecting geranyl acetate to the SeO_2/*t*-BuOOH system at 0 °C was added *m*CPBA (557 mg, 2.26 mmol) in 7 mL of DCM. The reaction mixture was stirred under argon at this temperature for 1 h 15 min. Then, the mixture was diluted with DCM, washed with 1 N NaOH, and brine. The solvent was removed to afford a crude product, which was used in the next reaction. To a solution of the above crude in 33 mL of DCM at 0 °C and under argon was added imidazole (334 mg, 4.91 mmol) and TBSCl (570 mg, 3.78 mmol). The reaction was stirred at room temperature for 1 h and then diluted with *t*-BuOMe and washed with H_2O, 2 N HCl, saturated $NaHCO_3$, and brine and worked up as usual. The product obtained was purified by chromatography on silica gel (hexane/*t*-BuOMe, 4:1) to give 239 mg (68% overall yield) of **16** as a colorless oil. IR (film) ν: 2955, 2930, 2857, 1741, 1472, 1366, 1233, 1097, 838, 778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.27 (s, 3H), 1.69 (q, J=7.6 Hz, 2H), 1.73 (s, 3H), 2.06 (s, 3H), 2.19 (m, 2H), 2.86 (t, J=6.2 Hz, 1H), 3.58 (s, 2H), 4.59 (d, J=7.1 Hz, 2H), 5.40 (t, J=7.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 14.2, 16.5, 18.3, 21.0, 25.9, 26.6, 36.2, 60.4, 61.0, 61.2, 67.7, 118.9, 141.2, 171.1 ppm. HRFABMS calcd for $C_{18}H_{34}O_4SiNa$ $[M+Na]^+$ 365.2124, found 365.2105.

3.3.2. Cyclization of 16. After subjecting **16** (260 mg, 0.76 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (4:1) afforded **17** and **18**, 135 mg (52%) in a 7:1 ratio. This mixture was re-subjected to column chromatography on $AgNO_3$ (20%)–silica gel to isolate **17** in a pure state as colorless oil. IR (film) ν: 3491, 2954, 2929, 2857, 1741, 1463, 1252, 1091, 838 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.19 (s, 3H), 1.70 (q, J=7.6 Hz, 2H), 2.05 (s, 3H), 2.20 (br s, 1H), 3.53 (d, J=9.9 Hz, 1H), 3.71 (d, J=9.9 Hz, 1H), 3.83 (dd, J=8.5, 5.6 Hz, 1H), 4.15 (dd, J=11.9, 4.3 Hz, 1H), 4.29 (dd, J=11.9, 4.3 Hz, 1H), 5.41 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 12.1, 18.3, 21.2, 22.0, 25.8, 30.8, 41.4, 43.1, 62.9, 69.4, 71.6, 121.3, 132.3, 170.9 ppm. HRFABMS calcd for $C_{18}H_{34}O_4SiNa$ $[M+Na]^+$ 365.2124, found 365.2101. Compound **18** was characterized from a mixture of this compound with **17**. ^1H NMR (400 MHz, $CDCl_3$) δ (only distinctive signals) 1.02 (s, 3H), 4.41 (s, 1H), 4.85 (s, 1H) ppm.

3.3.3. Synthesis of 19. This compound was prepared by the same procedure used for **16** with an overall yield of 66%. Compound **19**, colorless oil. IR (film) ν: 2955, 2930, 2857, 1740, 1472, 1368, 1251, 1098, 838, 778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.25 (s, 3H), 1.54 (s, 3H), 1.40–1.95 (m, 4H), 1.97 (s, 3H), 2.83 (t, J=6.2 Hz, 1H), 3.56 (s, 2H), 5.08 (d, J=11.0 Hz, 1H), 5.14 (d, J=17.3 Hz, 1H), 5.92 (dd, J=17.3, 11.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 14.1, 16.5, 18.4, 23.0, 23.7, 25.9, 26.4, 36.5, 60.6, 67.8, 82.4, 113.6, 141.6, 170.0 ppm. HRFABMS calcd for $C_{18}H_{34}O_4SiNa$ $[M+Na]^+$ 365.2124, found 365.2111.

3.3.4. Cyclization of 19. After subjecting **19** (213 mg, 0.62 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (6:1) afforded 111 mg (63%) of **20** and **21** in an equimolecular ratio. This mixture was re-subjected to column chromatography on $AgNO_3$ (20%)–silica gel to isolate **21** in a pure state as a colorless oil. IR (film) ν: 3487, 3437, 2956, 2930, 2857, 1471, 1255, 1086, 1068, 836, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.86 (s, 3H), 0.88 (s, 9H), 1.35 (q, J=13.0 Hz, 1H), 1.45 (dd, J=8.5, 14.1 Hz, 1H), 1.66 (m, 1H), 1.71 (s, 3H), 1.76 (m, 1H), 1.89 (dd, J=6.9, 14.7 Hz, 1H), 2.12 (t, J=13.1 Hz, 1H), 3.35 (d, J=9.6 Hz, 1H), 3.55 (d, J=9.6 Hz, 1H), 3.69 (dd, J=3.9, 10.9 Hz, 1H), 4.35 (s, 1H), 5.26 (t, J=5.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, −5.5, 14.0, 18.1, 25.3, 25.9, 29.0, 29.4, 32.4, 40.1, 75.9, 81.8, 120.1, 141.3 ppm. HRFABMS calcd for $C_{16}H_{32}O_2SiNa$ $[M+Na]^+$ 307.2069, found 307.2059. Compound **20** was characterized from a mixture of this compound with **21**. ^1H NMR (400 MHz, $CDCl_3$) δ (only distinctive signals) 0.89 (s, 3H), 0.91 (s, 3H), 1.58 (m, 1H), 1.63 (m, 1H), 1.73 (s, 3H), 1.76 (m, 1H), 1.86 (m, 1H), 2.36 (m, 1H), 3.42 (d, J=9.6 Hz, 1H), 3.57 (m, 1H), 3.67 (d, J=9.6 Hz, 1H), 4.16 (s, 1H) ppm.

3.4. Biscyclizations of epoxypolyprenes possessing a CH_2OTBS group in the α position to the oxirane ring

3.4.1. Synthesis of the 6+7 bicyclic structure 7.

3.4.1.1. Chlorination of nerolidyl acetate. To a stirred solution of PhSeCl (222 mg, 1.14 mmol) in DCM (75 mL) was added under argon and at room temperature 2500 mg of nerolidyl acetate (9.47 mmol). The mixture was further stirred for 5 min and then, NCS (1420 mg, 10.42 mmol) was added. The resulting mixture was stirred for 50 min and then, most of the DCM was evaporated resulting in the formation of a white solid. Et_2O was added to the above mixture and the liquid was separated from the white solid by decantation. This operation was repeated three times. The combined organic extracts were washed with brine. Evaporation of the solvent followed by column chromatography (hexane/*t*-BuOMe, 20:1) afforded 2144 mg of **22** (76%) as a colorless oil. IR (film) *ν*: 3487, 3437, 2956, 2930, 2857, 1471, 1255, 1086, 1068, 836, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.47 (s, 3H), 1.52 (s, 3H), 1.60–2.05 (m, 8H), 1.74 (s, 3H), 1.94 (s, 3H), 4.26 (t, *J*=6.8 Hz, 1H), 4.82 (m, 1H), 4.93 (br s, 1H), 5.05 (d, *J*=10.9 Hz, 1H), 5.08 (d, *J*=17.5 Hz, 1H), 5.08 (m, 1H), 5.90 (dd, *J*=17.5, 10.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 15.9, 17.1, 22.2, 22.3, 23.7, 34.9, 36.6, 39.7, 66.3, 82.9, 113.2, 114.2, 124.9, 133.9, 141.8, 144.4, 169.9 ppm.

3.4.1.2. Reaction of 22 with $AgBF_4$ in acetone/H_2O. To a solution of **22** (1337 mg, 4.49 mmol) collidine (2.4 mL, 17.95 mmol) in acetone/H_2O (120 mL, 1:1) under argon was added $AgBF_4$ (2623 mg, 13.47 mmol). The mixture was stirred under reflux for 1 h. Then acetone was removed under reduced pressure, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with 1 N HCl and brine and worked up as usual. The residue was purified by column chromatography. Eluting with hexane/*t*-BuOMe, 2:1, afforded 502 mg of **23** (40%). Eluting with hexane/*t*-BuOMe, 4:1, gave 565 mg (45%) of the isomer possessing a secondary alcohol. Compound **23**, colorless oil. IR (film) *ν*: 3425, 2973, 2920, 2859, 1737, 1646, 1449, 1370, 1250, 1018, 923, 842 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.47 (s, 3H), 1.52 (s, 3H), 1.59 (s, 3H), 1.65–2.10 (m, 8H), 1.94 (s, 3H), 3.92 (br s, 2H), 4.93 (br s, 1H), 5.04 (m, 1H), 5.05 (d, *J*=10.9 Hz, 1H), 5.08 (d, *J*=17.5 Hz, 1H), 5.31 (br t, *J*=8.3 Hz, 1H), 5.90 (dd, *J*=17.5, 10.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 13.7, 15.9, 22.2, 22.3, 23.7, 26.2, 39.3, 39.7, 69.0, 83.0, 113.2, 124.0, 126.0, 134.9, 135.1, 141.9, 170.0 ppm. HRFABMS calcd for $C_{17}H_{28}O_3Na$ $[M+Na]^+$ 303.1936, found 303.1901.

3.4.1.3. Synthesis of 6. A mixture of allylic alcohol **23** (350 mg, 1.25 mmol) and $VO(acac)_2$ (10 mg) in benzene (40 mL) was refluxed for 10 min under argon. Addition of *t*-BuOOH in decane (0.3 mL, 2 mmol) followed, and stirring continued at this temperature for 20 min. After cooling, the mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, and brine, worked up as usual, and chromatographed on silica gel (hexane/*t*-BuOMe, 1:1) to give 335 mg of the desired epoxide. To a solution of the above epoxide in 11 mL of DCM at 0 °C and under argon was added imidazole (177 mg, 2.6 mmol) and TBSCl (285 mg, 1.89 mmol). The reaction was stirred at room temperature for 1 h and then diluted with *t*-BuOMe and washed with H_2O, 2 N HCl, saturated $NaHCO_3$, and brine, and worked up as usual. The product obtained was purified by chromatography on silica gel (hexane/*t*-BuOMe, 4:1) to give 440 mg (86% overall yield) of **6** as a colorless oil. IR (film) *ν*: 2956, 2930, 2857, 1739, 1462, 1368, 1250, 1097 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 0.05 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.27 (s, 3H), 1.55 (s, 3H), 1.61 (s, 3H), 1.65–2.20 (m, 8H), 2.01 (s, 3H), 2.84 (t, *J*=6.3 Hz, 1H), 3.57 (s, 2H), 5.13 (d, *J*=10.9 Hz, 1H), 5.15 (t, 1H), 5.15 (d, *J*=17.5 Hz, 1H), 5.97 (dd, *J*=17.5, 10.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *δ* −5.3, 14.2, 15.9, 18.3, 22.3, 23.6, 25.9, 26.9, 28.6, 36.3, 39.7, 60.6, 61.0, 67.8, 82.8, 113.1, 124.3, 134.5, 141.8, 169.9 ppm. HRFABMS calcd for $C_{23}H_{42}O_4SiNa$ $[M+Na]^+$ 433.2750, found 433.2751.

3.4.1.4. Cyclization of 6. After subjecting **6** (244 mg, 0.59 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 8:1) on silica gel to afford 109 mg (52%) of **7** as a colorless oil. IR (film) *ν*: 3450, 2953, 2928, 2857, 1739, 1640, 1462, 1384, 1252, 1093, 837, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) *δ* 0.08 (s, 6H), 0.81 (s, 3H), 0.86 (s, 3H), 0.91 (s, 9H), 1.21–2.10 (m, 11H), 1.73 (s, 3H), 3.36 (d, *J*=9.5 Hz, 1H), 3.47 (br s, 1H), 3.62 (dd, *J*=10.3, 5.8 Hz, 1H), 3.71 (d, *J*=9.5 Hz, 1H), 5.35 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *δ* −5.6, 11.3, 19.6, 21.9, 25.4, 25.9, 26.9, 34.6, 35.3, 40.5, 43.0, 45.9, 53.5, 72.3, 76.3, 113.2, 122.6, 141.0 ppm. HRFABMS calcd for $C_{21}H_{40}O_2SiNa$ $[M+Na]^+$ 375.2695, found 375.2690.

3.4.2. Synthesis of the 6+6 bicyclic structure 10.

3.4.2.1. Chlorination of farnesyl acetate. To a stirred solution of PhSeCl (222 mg, 1.14 mmol) in DCM (75 mL) was added under argon and at room temperature 2500 mg of nerolidyl acetate (9.47 mmol). The mixture was further stirred for 5 min and then, NCS (1420 mg, 10.42 mmol) was added. The resulting mixture was stirred for 50 min and then, most of the DCM was evaporated resulting in the formation of a white solid. Et_2O was added to the above mixture and the liquid was separated from the white solid by decantation. This operation was repeated three times. The combined organic extracts were washed with brine. Evaporation of the solvent followed by column chromatography (hexane/*t*-BuOMe, 20:1) afforded 2032 mg of **24** (72%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) *δ* 1.60 (s, 3H), 1.71 (s, 3H), 1.81 (s, 3H), 1.75–2.20 (m, 8H), 2.06 (s, 3H), 4.34 (t, *J*=6.9 Hz, 1H), 4.59 (d, *J*=7.1 Hz, 2H), 4.90 (s, 1H), 5.0 (s, 1H), 5.14 (t, *J*=6.5 Hz, 1H), 5.35 (t, *J*=7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 16.0, 16.5, 17.1, 21.1, 26.2, 34.8, 36.7, 39.5, 61.4, 66.4, 114.3, 118.5, 124.9, 133.9, 142.1, 144.4, 171.2 ppm.

3.4.2.2. Reaction of 24 with $AgBF_4$ in acetone/H_2O. To a solution of **24** (1070 mg, 3.59 mmol) collidine (1.9 mL, 14.36 mmol) in acetone/H_2O (96 mL, 1:1) under argon was added $AgBF_4$ (2098 mg, 10.78 mmol). The mixture was stirred under reflux for 1 h. The acetone was removed under reduced pressure, and the resulting mixture was extracted with EtOAc. The combined organic extracts were washed with 1 N HCl and brine and worked up as usual. The residue was purified by column chromatography. Eluting with hexane/*t*-BuOMe, 2:1, afforded 402 mg of **25**

(40%). Eluting with hexane/*t*-BuOMe, 4:1, gave 452 mg (45%) of the isomer possessing a secondary alcohol. Compound **25**, IR (film) *ν*: 3425, 2973, 2920, 2859, 1737, 1646, 1449, 1370, 1250, 1018, 923, 842 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.66 (s, 3H), 1.70 (s, 3H), 1.95–2.25 (m, 9H), 2.05 (s, 3H), 3.99 (br s, 2H), 4.60 (d, J=7.1 Hz, 2H), 5.10 (t, J=6.7 Hz, 1H), 5.34 (t, J=7.1 Hz, 1H), 5.38 (t, J=7.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 15.8, 16.2, 20.8, 26.0, 26.1, 39.1, 39.3, 61.2, 68.4, 118.2, 123.7, 125.4, 134.7, 134.9, 141.9, 171.0 ppm. HRFABMS calcd for $C_{17}H_{28}O_3Na$ $[M+Na]^+$ 303.1936, found 303.1903.

3.4.2.3. Synthesis of 9. A mixture of allylic alcohol **25** (245 mg, 0.87 mmol), $VO(acac)_2$ (8 mg) in benzene (33 mL) was refluxed for 10 min under argon. Addition of *t*-BuOOH in decane (0.2 mL, 1.40 mmol) followed and stirring continued at this temperature for 20 min. After cooling, the mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, and brine, worked up as usual, and chromatographed on silica gel (hexane/*t*-BuOMe, 1:1) to give 234 mg of the desired epoxide. To a solution of the above epoxide in 8 mL of DCM at 0 °C and under argon was added imidazole (124 mg, 1.82 mmol) and TBSCl (199 mg, 1.32 mmol). The reaction mixture was stirred at room temperature for 1 h and then diluted with *t*-BuOMe and washed with H_2O, 2 N HCl, saturated $NaHCO_3$, and brine, and worked up as usual. The product obtained was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 4:1) to give 303 mg (85% overall yield) of **9** as a colorless oil. IR (film) *ν*: 2955, 2930, 2857, 1741, 1472, 1382, 1232, 1097, 838, 778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ −0.01 (s, 3H), 0.00 (s, 3H), 0.84 (s, 9H), 1.21 (s, 3H), 1.56 (s, 3H), 1.50–1.60 (m, 2H), 1.64 (s, 3H), 1.95–2.15 (m, 6H), 1.99 (s, 3H), 2.78 (t, J=6.3 Hz, 1H), 3.51 (s, 2H), 4.53 (d, J=7.1 Hz, 2H), 5.09 (t, J=6.7 Hz, 1H), 5.27 (t, J=7.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 14.2, 14.2, 16.1, 16.5, 18.4, 21.1, 25.9, 26.2, 27.1, 36.4, 39.5, 60.8, 61.5, 68.0, 118.4, 124.3, 134.5, 142.1, 170.9 ppm. HRFABMS calcd for $C_{23}H_{42}O_4SiNa$ $[M+Na]^+$ 433.2750, found 433.2740.

3.4.2.4. Cyclization of 9. After subjecting **9** (233 mg, 0.57 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 96 mg (41%) of **10** as a colorless oil. IR (film) *ν*: 3493, 2931, 2857, 1740, 1471, 1386, 1366, 1252, 1092, 1036, 853, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.80 (s, 3H), 0.85 (s, 3H), 0.91 (s, 9H), 1.21–1.80 (m, 10H), 2.02 (s, 3H), 2.39 (dt, J=13.1, 3.3 Hz, 1H), 3.35 (d, J=9.6 Hz, 1H), 3.64 (d, J=9.2, 5.8 Hz, 1H), 3.66 (m, 1H), 4.19 (dd, J=11.2, 8.6 Hz, 1H), 4.31 (dd, J=11.2, 3.8 Hz, 1H), 4.54 (br s, 1H), 4.86 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.6, −5.5, 11.8, 15.5, 18.2, 21.2, 23.7, 25.9, 26.7, 36.7, 37.3, 38.7, 42.2, 48.9, 54.6, 61.4, 72.6, 76.0, 107.8, 146.0, 170.2 ppm. HRFABMS calcd for $C_{23}H_{42}O_4Si$ $[M+H]^+$ 411.2931, found 411.2925.

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