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Control of the Regio- and Diastereoselectivity for the Preparation of Highly Functionalized Terpenic Cyclopentanes through Radical Cyclization

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The titanocene-mediated cyclization of suitably functionalized acyclic C10 epoxy-polyprenes leads, with moderate stereoselectivity, to high yields of functionalized terpenic cyclopentanes with three contiguous stereogenic centers. These highly functionalized cyclopentanes are useful intermediates for the synthesis of several natural compounds that include this interesting subunit in their structure. Both the regioselectivity of the process leading to cyclopentanes and the stereoselectivity of the cyclization could be controlled by using malonyl derivatives or α,β-unsaturated nitriles as radical acceptors.

Introduction

Highly functionalized cyclopentanes and cyclohexanes are structural features found in many compounds of biological interest. Five-membered carbocyclic cores bearing stereopentads of comparable molecular complexity are found both in biologically relevant terpenoids, which is a subset of the highly sought-after pyrrole-imidazole family of marine alkaloids, and aminocyclopentitol-based glycosidase inhibitors (Figure 1).[1] Although cylopentanes are common structural motifs in many natural products, the synthesis of these segments is often lengthy and tedious, especially when they are highly functionalized. In short, achieving stereocontrol in the synthesis of these compounds is quite challenging.

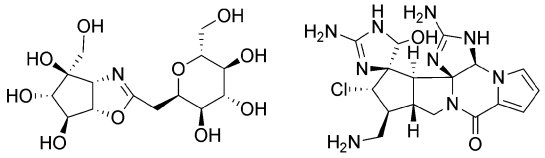

Figure 1. Representative structures of aminocyclopentitol and pyrrole-imidazole marine alkaloid families.

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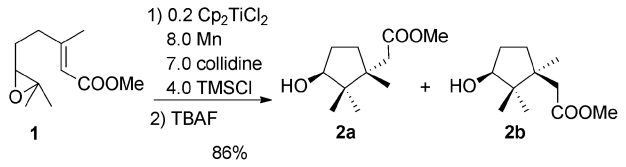
Cyclopentenes and cyclopentanones do not show general conformational preferences, and to reliably introduce or modify functionality synthetic chemists must usually resort to stereoselective methods that include such tactics as using a bulky reagent that approaches from the less-hindered cyclopentane face, a chiral reagent with inherent enantioface selectivity, a coordinating or hydrogen-bonding *syn*-directing group,[2] or a tethered nucleophile.[3] Stereochemically intricate cyclopentanes surrounded by contiguous arrays of heteroatoms at the periphery of the carbocycle and/or fused to heterocyclic ring systems present some of the more daunting challenges for modern synthetic chemistry.

Radical reactions constitute a very useful tool in synthetic organic chemistry;[4] they complement ionic and concerted processes and are able to take part in cascade reactions, making them particularly interesting. An attractive method for the preparation of cyclopentanes is intramolecular radical cyclization, because radical cyclizations can be performed under neutral conditions. Internal radical cyclization of a suitable carbohydrate derivative possessing both a radical donor and a radical acceptor gives rise to cyclic products with all stereocenters preserved, and, ideally, with stereocontrol at the new C–C bond formed during the ring-closing reaction.[4b,4d] Within this context, [$Cp_2Ti^{III}Cl$]-mediated radical cyclization of acyclic monoepoxy-polyprenoids is a powerful synthetic tool that permits the construction of rings of different sizes.[5] In contrast to reported cyclizations involving carbocations,[6] this kind of radical cyclization can be used in cascade processes to create different-sized rings, after suitably modulating the electronic distribution of the double bonds involved. A few years ago, our research group reported that the [$Cp_2Ti^{III}Cl$]-mediated cyclization of methyl 6,7-epoxy-geraniate (**1**) led to the formation of an equimolecular mixture of **2a** and **2b** through

a 5-*exo*-trig process (Scheme 1),[7] thus generating two stereogenic centers, albeit without stereoselectivity at the quaternary center.

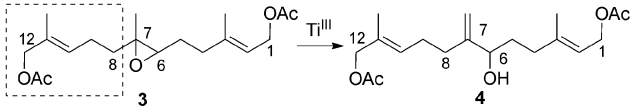


Scheme 1. Synthesis of diastereoisomers **2a** and **2b**.

The stereocontrolled synthesis of highly versatile cyclopentane fragments to generate advanced intermediates for the synthesis of biologically active natural products has been achieved in recent years with jatrophane diterpenes,[8] pactamycin,[9] kansuinine,[10] and viridenomycin.[11] The preparation, in moderate yields, of five-membered carbocycles from 2,3-epoxy alcohols by using Ti^{III} for the oxirane opening has also been reported.[12] We describe here the efficient synthesis of synthons containing highly functionalized terpenic cyclopentane derivatives.

Results and Discussion

We began our study by verifying the reactivity of a range of 6,7-epoxy-farsenyl derivatives with [$Cp_2Ti^{III}Cl$]. At this juncture, we must mention the lack of precedents for radical cyclization of epoxy-polyprenes with the oxirane located in an intermediate position in an acyclic chain, and the possibility of also obtaining the desired highly functionalized cyclopentanes with a functionalized carbon chain attached to them, which adds to their importance as advanced synthetic intermediates. Thus, when compound **3** (obtained from farnesyl acetate by using standard transformations), which possesses two acetate groups located at C1 and C12, was allowed to react with a catalytic amount of [Cp_2Ti^{III}-Cl],[5p] the reaction led almost exclusively to the formation of the opened allylic alcohol **4** (Scheme 2; Table 1, Entry 1). We should point out that all the epoxides used in this study, and therefore the resulting products, were racemic mixtures; for the sake of convenience, a single enantiomer has been drawn for each compound where applicable.



Scheme 2. Epoxide ring opening of **3** with [$Cp_2Ti^{III}Cl$].

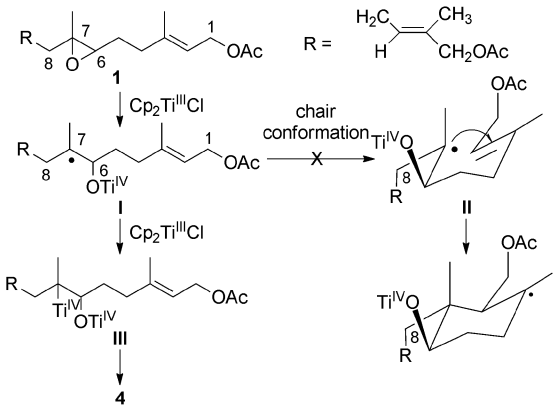
In contrast to the situation with 6,7-epoxy-geranyl acetate, which, after treatment with Ti^{III}, produced the 6-*endo*-trig cyclization product,[13] the isoprenic chain at C8 in **3** prevented the formation of the chair-like transition state **II** needed to complete the cyclization process (Scheme 3).

When the epoxy-farnesyl derivative **5**,[14] which has an isopropenyl group at the end of the acyclic moiety, was allowed to react with a catalytic amount of [$Cp_2Ti^{III}Cl$], the resulting products were again an acyclic allylic alcohol **6** (40% yield), together with a minor amount of the cyclization product **7** (13% yield), resulting from a 6-*endo*-trig process (Scheme 4; Table 1, Entry 2). The formation of this highly functionalized cyclohexane is understandable considering that the radical produced after the homolytic opening of the oxirane adds to the $\Delta^{2,3}$ double bond. In comparison to the results obtained with **3**, the formation here of a significant quantity of the cyclization product seems to suggest a higher degree of conformational freedom in the intermediate radical, which progresses more easily to the chair-like transition state, leading, in turn, to cyclization.

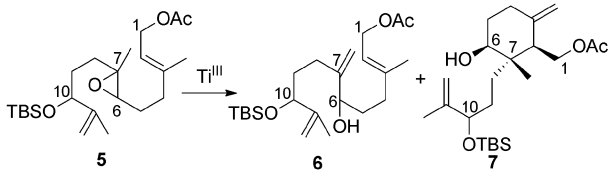
Table 1. Ti^{III}-mediated cyclization of 6,7-epoxy-farnesyl derivatives.

Entry	SM[a]	Product	Time [min]	Yield [%]	Ratio
1	**3**	**4**	70	56	
2	**5**	**6** + **7**	50	53	75:25
3	**8**	**9** + **10**	25	95	53:47
4	**11**	**12** + **13** + **14**	200	90	31:54:15
5	**15**	**16**[b]	120	93	28:29:14:29

[a] SM: Starting material. [b] Mixture of four diastereomers.

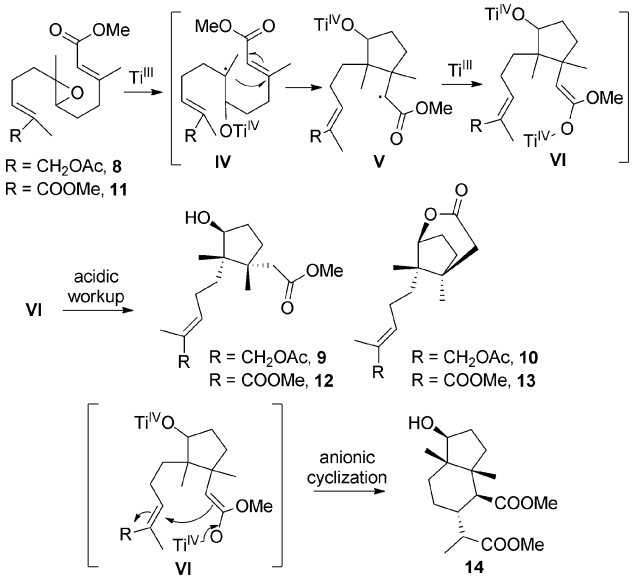


Scheme 3. Cyclization of **3** is prevented by the isoprenic chain at C8.



Scheme 4. Reaction of **5** to give **6** (40%) and **7** (13%).

Reaction of acetoxy ester **8** with [$Cp_2Ti^{III}Cl$] for 25 min, following the catalytic protocol, afforded yields of 51 and 44% of cyclopentanes **9** and **10**, respectively (Scheme 5; Table 1, Entry 3). Compound **10** formed as a result of spontaneous lactonization after the acidic workup of the reaction mixture, which allowed the mixture of epimers to be easily separated, thus optimizing the method for their preparation.



Scheme 5. Reaction of esters **8** and **11** with catalytic [$Cp_2Ti^{III}Cl$].

The treatment of diester **11** with catalytic quantities of [$Cp_2Ti^{III}Cl$] led to 28 and 48% yields of cyclopentanes **12** and **13**, respectively, together with a diastereomeric mixture of hydrindane derivatives (14% yield), from which compound **14** could be isolated. The stereochemistry of **14** was established by NOE difference experiments (Figure 2) and also by the coupling constant value (J = 12.0 Hz) observed between 2-H and 10-H, which suggests an *anti* relationship between these two protons. These hydrindane derivatives were probably generated as a result of a cascade process involving a radical cyclization and a Michael addition (Scheme 5), the second step being brought about via the enolate intermediate **VI** (Scheme 5) produced after the first cyclization.

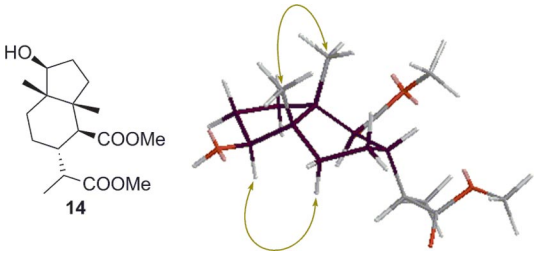
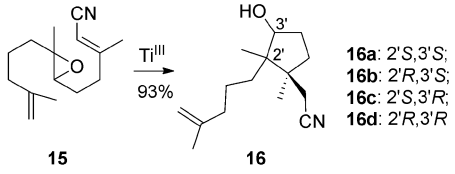


Figure 2. NOE experiments to establish the stereochemistry of **14**.

In the light of previous work published by Fernández-Mateos[15] and Gansäuer[16] on the use of acrylates or acrylonitriles to enforce cyclizations, we also studied the [$Cp_2Ti^{III}Cl$]-mediated cyclization of 6,7-epoxy-farnesylnitrile derivative **15**, which led to an excellent 93% yield of the corresponding five-membered cyclization product **16** (Scheme 6).



Scheme 6. Cyclization of **15** to give **16**.

Compound **16** was obtained with low diastereoselectivity as a mixture of four diastereomers (2′*S*,3′*S*), (2′*R*,3′*S*), (2′*S*,3′*R*), and (2′*R*,3′*R*), which could be separated by column chromatography and HPLC in a ratio of 28:29:14:29 (Scheme 6; Table 1, Entry 5). The stereochemistry of **16a–d** was established by NOE experiments (Figure 3).

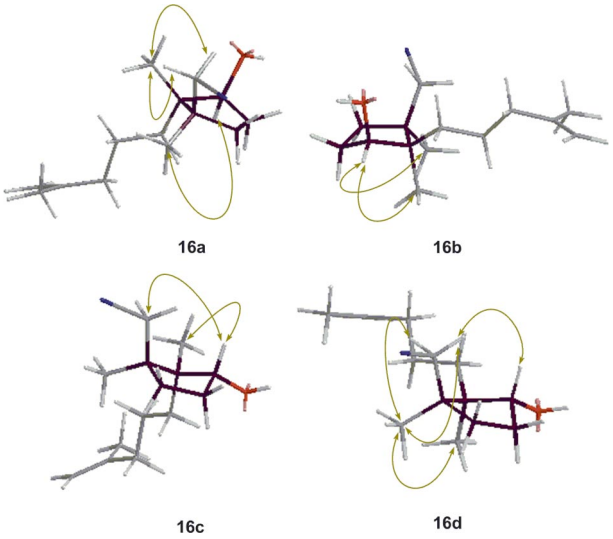


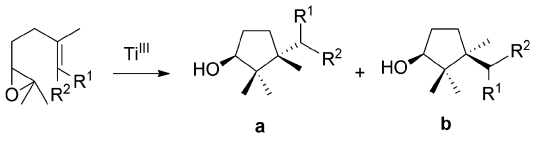
Figure 3. NOE experiments to establish the stereochemistry of **16a–d**.

In the light of the excellent yields obtained for the closure of the cyclopentane ring of these C15 precursors, and because of the absence of stereoselectivity, we focused our efforts on studying the outcome of the radical 5-*exo*-trig cyclization by using C10 epoxy-polyprenes derived from commercial geraniol (**17**–**21**) (Table 2).

At this point it should be mentioned that the menthyl esters **27** and **28**, which are the precursors of epoxides **18** and **19**, could not be prepared by using standard esterification or transesterification transformations,[19] but only by resorting to a convergent method involving the corresponding 2-(diethyl phosphonates) (**24** and **25**) and subsequent Wadsworth–Emmons condensation[20] with commercially available 6-methylhept-5-en-2-one (**26**) (Scheme 7).[21]

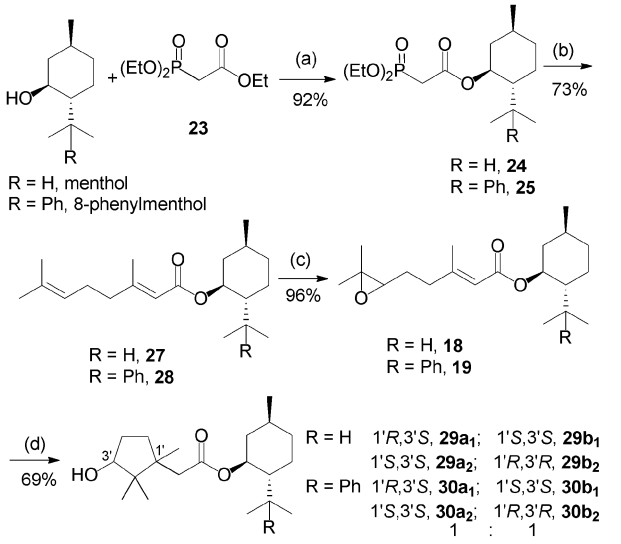
The epoxy derivatives **17**–**19** showed moderate cyclization yields but no diastereoselection in their reaction with [$Cp_2Ti^{III}Cl$] (Table 2, Entries 2–4). Thus, in the reaction of menthyl esters **18** and **19**, two pairs of diastereomers were obtained in each case, which were identified by ^{1}H NMR spectroscopic analysis as **29a** (*trans*)/**29b** (*cis*) and **30a** (*trans*)/**30b** (*cis*), respectively, in 50:50 ratios.

Table 2. Ti^{III}-mediated cyclization of 6,7-epoxy-geranyl derivatives.



Entry	SM[a]	R^1	R^2	RP[b]	Yield [%]	Ratio **a/b**
1	**1**	COOMe	H	**2**	86	50:50
2	**17**[17]	COO*t*Bu	H	**22**	81	50:50
3	**18**	COO-(–)-menthyl	H	**29**	71	50:50
4	**19**	COO-8-phenyl-(–)-menthyl	H	**30**	69	50:50
5	**20**[18]	COOEt	COOEt	**31**	93	67:33
6	**21**[c]	CN	H	**32**	99	80:20

[a] SM: Starting material. [b] RP: Reaction product. [c] Diastereomeric mixture of (*E*) and (*Z*).



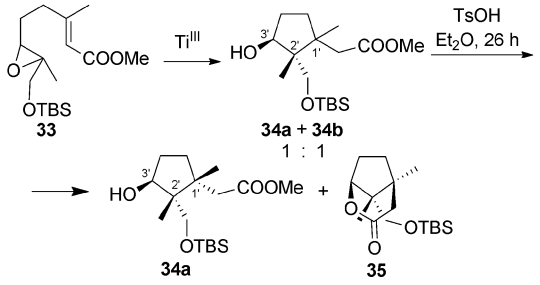
Scheme 7. Cyclization of menthyl ester derivatives. (a) **23**, DMAP, toluene, 120 °C, 140 h; (b) **26**, NaH, THF, 25 °C; (c) *m*-CPBA, DCM, 0 °C, 20 min; (d) 0.2 $Cp_2Ti^{IV}Cl_2$, 8.0 Mn , 7.0 2,4,6-collidine, 4.0 TMSCl, THF, 25 °C, 80 min.

Our next step was to test an epoxy derivative with a *gem*-diester at the terminus of the chain, such as compound **20** (Table 2, Entry 5). This substrate offers the possibility of introducing an additional alkoxy-carbonyl group at C2, that is, at the position adjacent to the closure of the ring. Thus, treatment of diester **20** with [$Cp_2Ti^{III}Cl$], following the catalytic protocol, afforded an excellent 93% yield (Table 2, Entry 5) of cyclization products (**31**), with moderate stereoselectivity towards product **31a** (67:33 ratio).

When we studied the [$Cp_2Ti^{III}Cl$]-mediated cyclization of the 6,7-epoxy derivative of geranylnitrile (**21**), we found that the yield was almost quantitative, giving the mixture of cyclopentanes **32** (Table 2, Entry 6) with a better diastereoselectivity of 80:20 in favor of **32a**; the coordination of the Ti^{III} species to the nitrile moiety, thus increasing its steric requirements, is probably responsible for this selectivity.

At this point, the influence of oxygenated functions on the methyl groups located at the α-position adjacent to the oxirane ring was assessed to find out how this new functionalization affects the stereochemical outcome of the process. We also bore in mind the fact that the presence of this functional group in the chain attached to the resulting five-membered ring is necessary to extend the chain farther and thus facilitate the synthesis of several natural products.

Thus, the cyclization of **33** (Scheme 8) by using a catalytic quantity of [$Cp_2Ti^{III}Cl$] led to the formation of a mixture of diastereomers **34**, which could be resolved after lactonization of **34b** in an acidic medium to give **35**. Diastereomers **34** were produced in a 50:50 ratio, which proved that, although formation of the new stereogenic center at C2′ proceeded with total stereochemical control (Figure 4), no diastereoselectivity was observed in the formation of C1′. Coordination between –$OTi^{IV}Cp_2$, resulting from the opening of the oxirane, and an oxygen atom from the –OTBS group via a six-membered intermediate (**I**), possibly determines the α stereochemistry of the –CH_2OTBS chain in the new stereogenic center created at C2′ (Figure 4).



Scheme 8. Cyclization of **33**.

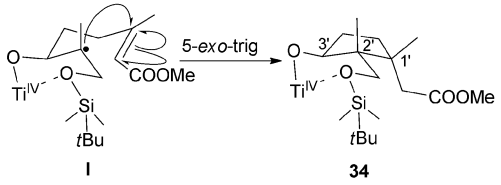
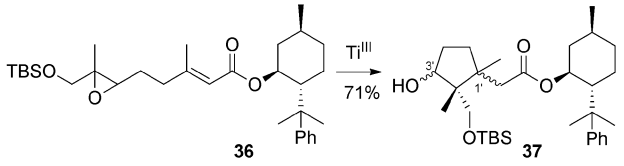


Figure 4. Coordination between –$OTi^{IV}Cp_2$ from the oxirane opening and an oxygen atom from the –OTBS group via a six-membered intermediate.

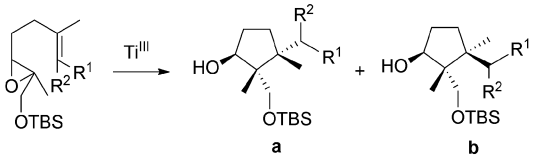
Continuing with this study, cyclization of the phenylmenthyl epoxide **36** by using [$Cp_2Ti^{III}Cl$] led to a 71% yield of the cyclopentane derivatives **37** (Scheme 9; Table 3, Entry 2) as a mixture of four diastereomers, which were distinguished by ^{1}H NMR spectroscopic analysis as two couples: **37a** [*trans*; (1′*R*,2′*R*,3′*S*) and (1′*S*,2′*S*,3′*R*)] and **37b** [*cis*; (1′*S*,2′*R*,3′*S*) and (1′*R*,2′*S*,3′*R*)] in a ratio of 57:43 (Scheme 9).

Subsequently, the behavior of the epoxy derivative **38**, which has an additional ester at C2, was examined. Thus, the reaction of **38** with [$Cp_2Ti^{III}Cl$] resulted in the formation of cyclization product **39** (92% yield), showing a stereoselectivity of 71:29 in favor of compound **39a** (Table 3, Entry 3). Finally, the cyclization of **40**, which is an



Scheme 9. Cyclization of **36**.

Table 3. Cyclization of C8-hydroxylated 6,7-epoxy-geranyl derivatives.

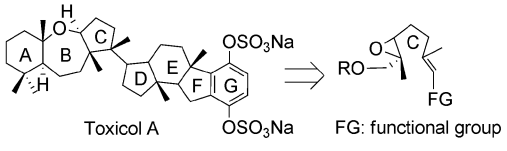


Entry	SM[a]	R^1	R^2	RP[b]	Yield [%]	Ratio **a/b**
1	**33**	COOMe	H	**34**	76	50:50
2	**36**	COO-8-phenyl-(–)-menthyl	H	**37**	71	57:43
3	**38**	COOEt	COOEt	**39**	92	71:29
4	**40**[c]	H	CN	**41**	95	80:20

[a] SM: Starting material. [b] RP: Reaction product. [c] Mixture of diastereomers (*E*) and (*Z*).

oxirane derivative with an unsaturated nitrile group, led to a nearly quantitative yield of cyclopentanes **41**. The diastereoselectivity of the closure of the ring was then acceptable, because the 76% yield of the (1′*R*,2′*R*,3′*S*) isomer **41a** was four times higher than that of isomer **41b**, with (1′*S*,2′*R*,3′*S*) stereochemistry (Table 3, Entry 4).

These results may open the possibility of using these synthons as chiral building blocks that could help in the synthesis of complex structures such as toxicol A,[22] a hexaprenoid hydroquinone sulfate isolated from the Red Sea sponge *Toxiclona toxius*, which has been reported to inhibit the reverse transcriptase of human immune deficiency virus (HIV) and to be active against *Candida albicans*. This compound contains a five-membered ring (Cycle C) that might be obtained with suitable functionalization from commercially available sources by using this Ti^{III}-mediated radical cyclization process (Scheme 10).



Scheme 10. Possible application of the Ti^{III}-mediated radical cyclization process.

Conclusions

We have shown that in radical cyclizations of terpenic epoxy-polyprenes mediated by $[Cp_2Ti^{III}Cl]$ it is possible to control both the regioselectivity of the process leading to cyclopentanes, and the stereoselectivity of the cyclization, by using malonyl derivatives or α,β-unsaturated nitriles as radical acceptors. Thus, the use of suitably functionalized epoxy-polyprenes induces 5-*exo*-trig ring closures with excellent yields and acceptable stereochemical control of the three stereogenic centers created. This process permits easy access to highly functionalized cyclopentanes, which, in turn, are useful in the synthesis of biologically active natural products.

Experimental Section

General: NMR spectra were recorded with Varian Direct-Drive 600 (^{1}H 600 MHz/^{13}C 150 MHz), 500 (^{1}H 500 MHz/^{13}C 125 MHz), Bruker ARX 400 (^{1}H 400 MHz/^{13}C 100 MHz), or Varian Inova Unity 300 (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. 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 an FAB (LSIMS) source. The instrument was operated at 8 kV accelerating voltage, and Cs^+ was used as primary ion. Optical rotations were measured with a Perkin–Elmer 141 polarimeter by using $CHCl_3$ as the solvent. 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) by using UV light as the visualizing agent and a solution of phosphomolybdic acid in ethanol and heat as developing agent. All air- and water-sensitive reactions were performed in flasks that were flame-dried under a positive flow of argon and conducted under argon. Solvents were purified according to standard literature techniques and stored under argon. THF and toluene were 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. Preparation of all varieties of epoxy-polyprenes used in cyclization reactions involving known procedures are described in the Supporting Information.

General Procedure for Catalytic Cyclization of Epoxy-Polyprenes Mediated by Ti^{III}: A mixture of $[Cp_2TiCl_2]$ (70.7 mg, 0.275 mmol) and Mn dust (778.7 mg, 7.34 mmol) in strictly deoxygenated THF (5 mL) under argon, was stirred at room temp. until the red solution became green. A solution of the corresponding epoxide (0.918 mmol), 2,4,6-collidine (0.85 mL, 6.12 mmol), and TMSCl (0.46 mL, 3.67 mmol) in strictly deoxygenated THF (2.0 mL) was then added, and the mixture was stirred until disappearance of the starting material (25–200 min) was observed. The reaction was quenched with HCl (2 N, dropwise addition of 20 mL), extracted with *t*BuOMe (3 × 40 mL), washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was diluted with THF (40.0 mL) and stirred at room temp.. TBAF (1 M in THF, 5.7 mmol) was added and the mixture was stirred for 1 h.[23] The mixture was concentrated under reduced pressure, diluted in H_2O, extracted with EtOAc (4 × 10 mL), washed with brine, and concentrated under reduced pressure. Final purification and isolation of the resulting compounds were carried out by SiO_2 column chromatography eluting with hexane/*t*BuOMe mixtures.

General Procedure for Stoichiometric Cyclization of Epoxy-Polyprenes Mediated by Ti^{III}: A mixture of $[Cp_2TiCl_2]$ (707.0 mg, 2.75 mmol) and Mn dust (778.7 mg, 7.34 mmol) in strictly deoxy-

genated THF (5.0 mL) under argon was stirred at room temp. until the red solution became green. A solution of the corresponding epoxide (0.918 mmol) in strictly deoxygenated THF (2.0 mL) was added, and the mixture was stirred until disappearance of the starting material (25–200 min) was observed. The reaction was quenched with HCl (2 N, dropwise addition of 20 mL), extracted with *t*BuOMe (3 × 40 mL), washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Final purification and isolation of the resulting compounds were carried out by SiO_2 column chromatography eluting with hexane/*t*BuOMe mixtures.

Radical Cyclization of 3. (2*E*,10*E*)-6-Hydroxy-3,11-dimethyl-7-methylenedodeca-2,10-diene-1,12-diyl Diacetate (4): After subjecting **3** (320 mg, 0.918 mmol) to the catalytic procedure, the resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 4:1 to 2:1) on silica gel to afford non-cyclized **4** (173 mg, 0.514 mmol, 56% yield). Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 5.49 (t, J = 7.4 Hz, 1 H), 5.38 (t, J = 7.3 Hz, 1 H), 5.07 (s, 1 H), 4.88 (s, 1 H), 4.60 (d, J = 7.2 Hz, 2 H), 4.45 (s, 2 H), 4.07 (m, 1 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 1.72 (s, 3 H), 1.69 (s, 3 H) ppm. HRMS (FAB): calcd. for $C_{19}H_{30}O_5Na$ [M + Na]$^+$ 361.1985; found 361.1983.

Radical Cyclization of 5: After subjecting **5** (220 mg, 0.536 mmol) to the catalytic procedure, the resulting crude material was treated with TBAF in THF (3.3 mmol) for 3 h. The corresponding diol derivatives of **6** and **7**, that is **6a** and **7a**, were purified by column chromatography (hexane/*t*BuOMe, 4:1 to 2:1) on silica gel to afford **6a** (88 mg, 40% yield) and **7a** (29 mg, 13% yield).

(*E*)-6,10-Dihydroxy-3,11-dimethyl-7-methylenedodeca-2,11-dienyl Acetate (6a): Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 5.37 (t, J = 7.4 Hz, 1 H), 5.05 (s, 1 H), 4.96 (s, 1 H), 4.90 (s, 1 H), 4.85 (s, 1 H), 4.58 (d, J = 7.0 Hz, 2 H), 4.10 (m, 2 H), 2.19–2.05 (m, 5 H), 2.05 (s, 3 H), 1.74 (s, 3 H), 1.71 (s, 3 H), 1.70–1.40 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 173.6, 150.1, 144.2, 135.3, 120.7, 113.7, 113.2, 77.9, 77.8, 63.9, 38.2, 36.0, 35.9, 29.6, 23.7, 20.2, 19.4 ppm. HRMS (FAB): calcd. for $C_{17}H_{28}O_4Na$ [M + Na]$^+$ 319.1880; found 319.1882.

[(1*R*,2*S*,3*S*)-3-Hydroxy-2-(3-hydroxy-4-methylpent-4-enyl)-2-methyl-6-methylenecyclohexyl]methyl Acetate (7a): Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 4.98 (m, 1 H), 4.85 (s, 1 H), 4.84 (s, 1 H), 4.64 (s, 1 H), 4.57 (dd, J = 13.2, 7.0 Hz, 1 H), 4.35 (dd, J = 11.2, 3.9 Hz, 1 H), 4.07 (m, 1 H), 3.61 (s, 1 H), 2.54 (dt, J = 13.3, 4.0 Hz, 1 H), 2.18 (dd, J = 10.6, 3.8 Hz, 1 H), 2.00 (s, 3 H), 1.83 (m, 1 H), 1.74 (s, 3 H), 1.65–1.15 (m, 6 H), 0.88 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 174.0, 150.1, 145.0, 114.6, 113.9, 79.2, 74.8, 65.8, 54.6, 33.2, 33.0, 30.7, 30.4, 23.7, 20.4, 16.0 ppm. HRMS (FAB): calcd. for $C_{17}H_{28}O_4Na$ [M + Na]$^+$ 319.1880; found 319.1862.

Radical Cyclization of 8: After subjecting **8** (350 mg, 1.08 mmol) to the catalytic procedure, the resulting crude material (332 mg, 95% yield) was purified by column chromatography (hexane/*t*BuOMe, 4:1) on silica gel to afford **9** (169 mg, 51% yield) and **10** (133 mg, 44% yield).

Methyl {(1*R*,2*S*,3*S*)-2-[(*E*)-5-Acetoxy-4-methylpent-3-enyl]-3-hydroxy-1,2-dimethylcyclopentyl}acetate (9): Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 5.45 (t, J = 7.2 Hz, 1 H), 4.39 (s, 2 H), 3.83 (dd, J = 7.2, 2.2 Hz, 1 H), 3.58 (s, 3 H), 2.16 (dd, J = 17.0, 13.0 Hz, 2 H), 2.05–1.10 (m, 8 H), 2.00 (s, 3 H), 1.60 (m, 3 H), 1.06 (s, 3 H), 0.75 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 173.8, 171.2, 130.4, 130.2, 81.1, 76.9, 70.35, 51.4, 50.6, 45.8, 43.1, 36.7, 32.3, 30.2, 23.7, 22.3, 20.9, 14.1 ppm. HRMS (FAB): calcd. for $C_{18}H_{30}O_5Na$ [M + Na]$^+$ 349.1985; found 349.1977.

(*E*)-2-Methyl-5-{(1*S*,5*S*,8*S*)-5,8-dimethyl-3-oxo-2-oxabicyclo-[3.2.1]oct-8-yl}pent-2-enyl Acetate (10): Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 5.35 (t, J = 7.2 Hz, 1 H), 4.38 (s, 1 H), 4.37 (t, J = 4.2 Hz, 2 H), 2.48 (dd, J = 18.9, 3.4 Hz, 1 H), 2.26 (d, J = 18.9 Hz, 1 H), 2.11–1.85 (m, 4 H), 2.01 (s, 3 H), 1.66 (m, 1 H), 1.60 (m, 3 H), 1.33–1.15 (m, 3 H), 1.00 (s, 3 H), 0.87 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 171.5, 171.1, 131.1, 128.8, 86.7, 70.1, 46.3, 45.5, 43.2, 36.3, 33.1, 29.8, 22.4, 21.2, 19.1, 14.2, 13.5 ppm. HRMS (FAB): calcd. for $C_{17}H_{26}O_4Na$ [M + Na]$^+$ 317.1723; found 317.1727.

Radical Cyclization of 11: After subjecting **11** (297 mg, 0.92 mmol) to the stoichiometric procedure conditions, the resulting crude material (280 mg, 90%) was purified by column chromatography (hexane/*t*BuOMe, 4:1) on silica gel to afford **12** (79 mg, 28% yield), **13** (125 mg, 48% yield), and **14** (40 mg, 14% yield).

Methyl (*E*)-5-{(1*S*,2*R*,5*S*)-5-Hydroxy-2-[(methoxycarbonyl)methyl]-1,2-dimethylcyclopentyl}-2-methylpent-2-enoate (12): Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.80 (dt, J = 7.4, 1.4 Hz, 1 H), 3.91 (dd, J = 7.3, 1.3 Hz, 1 H), 3.72 (s, 3 H), 3.67 (m, 1 H), 3.63 (s, 3 H), 2.27–2.13 (m, 3 H), 1.85–1.10 (m, 6 H), 1.84 (s, 3 H), 1.11 (s, 3 H), 0.81 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 173.6, 168.8, 143.0, 127.5, 80.8, 51.8, 51.3, 50.4, 45.7, 43.0, 36.6, 32.5, 29.4, 24.6, 22.2, 20.8, 12.4 ppm. HRMS (FAB): calcd. for $C_{17}H_{28}O_5Na$ [M + Na]$^+$ 335.1829; found 335.1834.

Methyl (*E*)-2-Methyl-5-[(1*S*,5*S*,8*S*)-5,8-dimethyl-3-oxo-2-oxabicyclo[3.2.1]oct-8-yl]pent-2-enoate (13): Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 6.72 (t, J = 7.4 Hz, 1 H), 4.43 (d, J = 4.1 Hz, 1 H), 3.74 (s, 3 H), 2.59 (dd, J = 14.5, 1.4 Hz, 1 H), 2.36 (d, J = 14.5 Hz, 1 H), 2.35–1.13 (m, 8 H), 1.83 (s, 3 H), 1.04 (s, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 171.3, 168.1, 141.4, 128.7, 86.7, 51.8, 46.6, 45.7, 43.4, 36.6, 33.1, 29.8, 28.3, 19.8, 14.6, 12.5 ppm. HRMS (FAB): calcd. for $C_{16}H_{24}O_4Na$ [M + Na]$^+$ 303.1719; found 303.1716.

Methyl (1*S*,3a*R*,4*S*,5*S*,7a*S*)-5-[(1-Methoxycarbonyl)ethyl]octahydro-1-hydroxy-3a,7a-dimethyl-1*H*-indene-4-carboxylate (14): Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 4.36 (dd, J = 9.1, 7.2 Hz, 1 H), 3.67 (s, 3 H), 3.64 (s, 3 H), 2.50 (dq, J = 7.1, 2.3 Hz, 1 H), 2.48 (d, J = 12.0 Hz, 1 H), 2.19–1.23 (m, 8 H), 1.90 (m, 1 H), 1.13 (d, J = 7.1 Hz, 3 H), 0.91 (s, 3 H), 0.79 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 178.3, 177.1, 77.5, 54.6, 54.5, 54.4, 47.9, 48.2, 43.1, 41.9, 35.3, 32.6, 32.3, 24.5, 20.6, 20.1, 18.2 ppm. HRMS (FAB): calcd. for $C_{17}H_{28}O_5Na$ [M + Na]$^+$ 335.1834; found 335.1812.

Radical Cyclization of 15: After subjecting **15** (200 mg, 0.86 mmol) to the catalytic procedure conditions, the resulting crude material (194 mg, 96%) corresponding to a mixture of four diastereomers [**a**: (2′*S*,3′*S*); **b**: (2′*R*,3′*S*); **c**: (2′*S*,3′*R*), and **d**: (2′*R*,3′*R*)] of the five-membered cyclization product **16** was purified by column chromatography (hexane/*t*BuOMe, 88:12 to 87:13) on silica gel to afford **16a** (57 mg, 0.24 mmol, 28% yield), **16b** (59 mg, 0.25 mmol, 28% yield), **16c** (28 mg, 0.12 mmol, 14% yield), and **16d** (59 mg, 0.25 mmol, 29% yield).

2-[(1*S*,2*S*,3*S*)-3-Hydroxy-1,2-dimethyl-2-(4-methylpent-4-enyl)cyclopentyl]acetonitrile (16a): Colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C): δ = 4.69 (d, J = 24.0 Hz, 2 H), 4.10 (t, J = 7.9 Hz, 1 H), 2.62 (d, J = 16.6 Hz, 1 H), 2.32 (d, J = 6.6 Hz, 1 H), 2.21–2.14 (m, 2 H), 1.99 (t, J = 7.4 Hz, 2 H), 1.71 (s, 3 H), 1.64–1.60 (m, 2 H), 1.48–1.43 (m, 2 H), 1.33–1.29 (m, 2 H), 1.10 (s, 3 H), 0.88 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz, 25 °C): δ = 145.4, 119.2, 110.1,

79.2, 48.6, 45.0, 38.7, 35.4, 34.7, 30.5, 27.1, 22.5, 22.3, 22.2, 13.6 ppm. HRMS (FAB): calcd. for $C_{15}H_{25}NONa$ [M + Na]$^+$ 258.1834; found 258.1841. 1D-NOESY: δ = 4.69 (d, J = 24.0 Hz, 2 H), 1.48–1.43 (m, 2 H), 1.10 (s, 3 H) ppm.

2-[(1*S*,2*R*,3*S*)-3-Hydroxy-1,2-dimethyl-2-(4-methylpent-4-enyl)-cyclopentyl]acetonitrile (16b): ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C): δ = 4.71 (d, J = 23.6 Hz, 2 H), 3.95 (s, J = 7.4 Hz, 1 H), 3.09 (d, J = 16.7 Hz, 1 H), 2.31 (d, J = 15.2 Hz, 1 H), 2.19 (m, 2 H), 2.03 (t, J = 6.5 Hz, 2 H), 1.72 (s, 3 H), 1.57 (m, 4 H), 1.30 (m, 2 H), 1.10 (s, 3 H), 0.82 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz, 25 °C): δ = 148.4, 122.8, 112.8, 83.4, 52.7, 48.2, 41.2, 38.0, 34.1, 32.3, 29.7, 29.3, 25.5, 25.1, 24.3 ppm. HRMS (FAB): calcd. for $C_{15}H_{25}NONa$ [M + Na]$^+$ 258.1834; found 258.1828. 1D-NOESY: δ = 4.71 (d, J = 23.6 Hz, 2 H), 2.19 (m, 2 H), 1.57 (m, 4 H), 0.82 (s, 3 H) ppm; 0.82 (s, 3 H), 1.10 (s, 3 H), 1.57 (m, 4 H), 1.72 (s, 3 H), 4.71 (d, 2 H, J = 23.6 Hz) ppm.

2-[(1*S*,2*S*,3*R*)-3-Hydroxy-1,2-dimethyl-2-(4-methylpent-4-enyl)-cyclopentyl]acetonitrile (16c): ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C): δ = 4.71 (d, J = 20.7 Hz, 2 H), 3.94 (d, J = 5.5 Hz, 1 H), 2.27 (s, 2 H), 2.18 (m, 2 H), 2.04 (t, J = 7.1 Hz, 2 H), 1.76 (m, 2 H), 1.73 (s, 3 H), 1.66 (m, 2 H), 1.38 (m, 2 H), 1.30 (s, 3 H), 0.84 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz, 25 °C): δ = 148.4, 121.8, 112.7, 83.9, 52.4, 47.5, 41.2, 39.4, 33.9, 32.9, 29.6, 26.0, 25.8, 25.1, 23.4 ppm. HRMS (FAB): calcd. for $C_{15}H_{25}NONa$ [M + Na]$^+$ 258.1834; found 258.1829. 1D-NOESY: δ = 4.71 (d, J = 20.7 Hz, 2 H), 2.27 (s, 2 H), 1.66 (m, 2 H), 0.84 (s, 3 H) ppm.

2-[(1*S*,2*R*,3*R*)-3-Hydroxy-1,2-dimethyl-2-(4-methylpent-4-enyl)-cyclopentyl]acetonitrile (16d): ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C): δ = 4.69 (d, J = 24.5 Hz, 2 H), 4.03 (t, J = 7.8 Hz, 1 H), 2.27 (s, 2 H), 2.19–2.11 (m, 1 H), 1.99 (t, J = 7.5 Hz, 2 H), 1.74 (t, J = 7.9 Hz, 3 H), 1.71 (s, 3 H), 1.55–1.52 (m, 2 H), 1.36 (br. s, 1 H), 1.25–1.22 (m, 2 H), 1.17 (s, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz, 25 °C): δ = 145.3, 119.1, 110.2, 79.5, 48.3, 45.6, 38.7, 35.5, 34.3, 30.5, 26.7, 22.9, 22.4, 22.3, 14.1 ppm. HRMS (FAB): calcd. for $C_{15}H_{25}NONa$ [M + Na]$^+$ 258.1834; found 258.1832. 1D-NOESY: δ = 4.69 (d, J = 24.5 Hz, 2 H), 2.27 (s, 2 H), 2.19–2.11 (m, 1 H), 1.55–1.52 (m, 2 H), 1.25–1.22 (m, 2 H) ppm; 1.17 (s, 3 H), 0.93 (s, 3 H) ppm.

Radical Cyclization of 17: After subjecting **17** (571 mg, 2.38 mmol) to the catalytic procedure conditions, the resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 2:1) on silica gel, yielding an equimolecular mixture of **22a** and **22b** (455 mg, 1.93 mmol, 81% yield). A solution of this mixture (61 mg, 0.25 mmol) in Et_2O was treated with an excess of TsOH at room temp. for 26 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 25 mL) and brine (30 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 4:1) on silica gel to afford the lactone of **22b** (21 mg, 0.12 mmol) and **22a** (30 mg, 0.12 mmol).

***tert*-Butyl 2-[(1*R*,3*S*)-3-Hydroxy-1,2,2-trimethylcyclopentyl]acetate (22a):** Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 3.86 (dd, J = 8.4, 5.2 Hz, 1 H), 2.21–2.08 (m, 1 H), 2.07 (s, 2 H), 1.90–1.79 (m, 1 H), 1.68–1.48 (m, 2 H), 1.45 (s, 9 H), 1.04 (s, 3 H), 0.85 (s, 3 H), 0.80 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 172.6, 81.4, 80.2, 47.3, 44.8, 43.7, 34.2, 31.0, 28.2, 22.8, 21.6, 17.4 ppm.

(1*S*,5*S*)-5,8,8-Trimethyl-2-oxabicyclo[3.2.1]octan-3-one (Lactone Derived from 22b): Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 4.16 (d, J = 4.5 Hz, 1 H), 2.48 (dd, J = 18.8, 3.2 Hz, 1 H), 2.30 (d, J = 18.8 Hz, 1 H), 2.11–1.89 (m, 2 H), 1.88–1.63 (m, 2 H), 0.95 (s, 3 H), 0.86 (s, 3 H), 0.82 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 171.5, 89.1, 44.9, 43.6, 41.9, 36.1, 29.7, 20.5, 19.2, 16.8 ppm. HRMS (FAB): calcd. for $C_{10}H_{16}O_2Na$ [M + Na]$^+$ 191.1048; found 191.1060.

(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl 2-(Diethoxyphosphoryl)-acetate (24): A solution of (–)-menthol (600 mg, 3.84 mmol) in anhydrous toluene (10.0 mL), DMAP (142 mg, 1.15 mmol), and $(EtO)_2P(O)CH_2CO_2Et$ (**23**; 2.34 mL, 11.54 mmol), was heated at reflux under argon. After 27 h, the solvent was removed under reduced pressure, and the crude material was filtered through silica gel eluting with hexane (100 mL) and *t*BuOMe (200 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (hexane/*t*BuOMe, 3:1) on silica gel afforded **24** as a colorless oil (1243 mg, 3.72 mmol, 97% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 4.68 (td, J = 10.9, 10.9, 4.4 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 4 H), 2.91 (d, J = 21.7 Hz, 2 H), 2.00–1.88 (m, 2 H), 1.67–1.60 (m, 2 H), 1.48–1.35 (m, 2 H), 1.30 (t, J = 7.1 Hz, 6 H), 1.06–0.92 (m, 2 H), 0.90–0.80 (m, 1 H), 0.87 (d, J = 2.7 Hz, 3 H), 0.85 (d, J = 3.2 Hz, 3 H), 0.71 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 165.4, 75.6, 62.6, 62.5, 46.9, 40.6, 35.2, 34.1, 33.9, 31.4, 25.8, 23.1, 22.0, 20.8, 16.3, 16.0 ppm.

(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl (*E*)-3,7-Dimethylocta-2,6-dienoate (27): A mixture of NaH (163 mg, 4.07 mmol) and anhydrous THF (15.0 mL) was stirred and cooled to 0 °C under argon. Compound **24** (1236 mg, 3.70 mmol) in anhydrous THF (3.0 mL) was added, and the mixture was stirred for 7 min. Commercial **26** (0.6 mL, 4.07 mmol) was added, and the solution was stirred at room temp. for 4 h. The reaction was diluted with *t*BuOMe (50 mL), saturated aqueous NH_4Cl was added dropwise, and finally H_2O (60 mL) was added. The aqueous layer was extracted with *t*BuOMe (3 × 80 mL), and the resulting organic mixture was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (hexane/*t*BuOMe, 10:1) on silica gel afforded condensation product **27** as a colorless oil (780 mg, 2.70 mmol, 73% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 5.62 (s, 1 H), 5.07 (m, 1 H), 4.68 (td, J = 10.8, 10.8, 4.4 Hz, 1 H), 2.62 (td, J = 7.8, 7.8, 1.6 Hz, 1 H), 2.14 (s, 3 H), 2.00 (d, J = 11.7 Hz, 1 H), 1.92–0.75 (m, 12 H), 1.86 (s, 3 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 0.89 (d, J = 2.2 Hz, 3 H), 0.87 (d, J = 2.6 Hz, 3 H), 0.75 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.6, 166.0*, 159.7*, 159.4, 132.5, 132.0*, 123.8*, 123.2, 116.8*, 116.1, 73.2, 47.2, 41.3, 41.1, 34.4, 33.5, 31.5, 29.8, 26.9, 26.4, 26.2, 25.7, 25.4, 23.7, 22.1, 20.8, 18.9, 17.7, 16.5 ppm. *Signals corresponding to minor diastereomer (2*Z*). HRMS (FAB): calcd. for $C_{20}H_{34}O_2Na$ [M + Na]$^+$ 329.2456; found 329.2461.

(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl (*E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-enoate (18): To a solution of **27** (400 mg, 1.31 mmol) in dichloromethane (7.0 mL) at 0 °C under argon, was added dropwise *m*CPBA (271 mg, 1.57 mmol) in dichloromethane (7 mL), and the mixture was stirred until disappearance of starting material was observed. The mixture was diluted with dichloromethane (25 mL), washed with NaOH (2 N, 3 × 40 mL) and brine (2 × 40 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 5:1) on silica gel to afford **18** as a colorless oil (409 mg, 1.27 mmol, 97% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 5.66 (s, 1 H), 4.68 (td, J = 10.8, 10.8, 4.4 Hz, 1 H), 2.69 (t, J = 6.2 Hz, 1 H), 2.28 (m, 2 H), 2.16 (d, J = 1.2 Hz, 3 H), 1.98 (d, J = 11.7 Hz, 1 H), 1.92–0.75 (m, 10 H), 1.28 (s, 3 H), 1.24 (s, 3 H), 0.89 (d, J = 2.2 Hz, 3 H), 0.87 (d,

J = 2.6 Hz, 3 H), 0.75 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.3, 158.2, 116.6, 73.3, 63.7, 58.6, 47.2, 41.2, 37.6, 34.4, 31.5, 27.0, 26.3, 24.8, 23.6, 22.1, 20.8, 18.9, 18.8, 16.5 ppm. HRMS (FAB): calcd. for $C_{20}H_{34}O_3Na$ [M + Na]$^+$ 345.2406; found 345.2407.

Radical Cyclization of 18: After subjecting **18** (322 mg, 1.00 mmol) to the catalytic procedure conditions, the resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 4:1 then 1:1) on silica gel to afford a diasteromeric mixture [(1′*R*,3′*S*), (1′*S*,3′*S*), (1′*S*,3′*R*), and (1′*R*,3′*R*)] (230 mg, 71% yield) showing two representative groups of signals in the ^{1}H NMR spectra corresponding to **29a** (*trans*) and **29b** (*cis*) in an equimolecular ratio. Compounds **29a$_1$** + **29a$_2$** + **29b$_1$** + **29b$_2$**. Pale-yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 4.63 (tdd, J = 10.8, 10.8, 4.3, 1.4 Hz, 2 H), 3.96 (ddd, J = 9.1, 7.4, 2.3 Hz, 1 H), 3.85* (ddd, J = 8.1, 5.3, 1.9 Hz, 1 H), 2.33 (dd, J = 13.1, 4.5 Hz, 1 H), 2.20–1.75 (m, 31 H), 1.03* (s, 3 H), 0.92 (d, J = 2.1 Hz, 3 H), 0.87 (s, 6 H), 0.84 (s, 12 H), 0.78 (dd, J = 4.4, 1.7 Hz, 6 H), 0.71 (d, J = 7.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 172.8, 172.7, 81.3, 81.2, 74.1, 74.0, 49.4, 47.3, 47.2, 47.0, 46.5, 46.5, 44.8, 44.7, 44.2, 44.1, 42.8, 42.7, 42.7, 42.6, 41.0, 34.3, 34.3, 34.2, 34.0, 31.4, 31.0, 30.9, 30.0, 30.0, 27.0, 26.2, 23.3, 23.3, 22.8 ppm. *Signals corresponding to diastereomeric couple **29a**.

(1*S*,2*R*,5*S*)-5-Methyl-2-(2-phenylprop-2-yl)cyclohexyl (Diethoxyphosphoryl)acetate (25): A solution of (–)-8-phenylmenthol (1000 mg, 4.30 mmol) in anhydrous toluene (10.0 mL), DMAP (158 mg, 1.29 mmol), and $(EtO)_2P(O)CH_2CO_2Et$ (**23**; 2.61 mL, 12.91 mmol) was heated to reflux under argon. After 140 h, the solvent was removed under reduced pressure, and the crude material was filtered through silica gel eluting with hexane (100 mL) and *t*BuOMe (200 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography (hexane/*t*BuOMe, 2:1) on silica gel afforded **25** (1720 mg, 4.17 mmol, 97% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.23 (m, 4 H), 7.07 (m, 1 H), 4.79 (td, J = 10.8, 10.8, 4.4 Hz, 1 H), 4.08–3.91 (m, 4 H), 2.35 (dd, J = 21.3, 14.3 Hz, 1 H), 2.03 (dd, J = 21.3, 14.4 Hz, 1 H), 2.00 (m, 1 H), 1.79 (tq, J = 13.4, 13.4, 3.4 Hz, 2 H), 1.63 (dt, J = 12.9, 2.8, 2.8 Hz, 1 H), 1.40 (m, 1 H), 1.30–0.80 (m, 3 H), 1.25 (m, 9 H), 1.15 (s, 3 H), 0.83 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.0, 151.7, 127.9 (2 C), 125.3, 125.0, 75.1, 62.4, 62.3, 50.2, 41.3, 39.4, 34.7, 34.4, 33.0, 31.2, 29.1, 26.2, 23.2, 21.7, 16.3, 16.2 ppm.

(1*S*,5*S*)-5-Methyl-2-(2-phenylprop-2-yl)cyclohexyl (*E*)-3,7-Dimethylocta-2,6-dienoate (28): A mixture of NaH (172 mg, 4.31 mmol) and anhydrous THF (20.0 mL) was stirred and cooled to 0 °C under argon. Compound **25** (1615 mg, 3.92 mmol) in anhydrous THF (3.0 mL) was added, and the mixture was stirred for 7 min. Commercial **26** (0.64 mL, 4.31 mmol) was added, and the solution was stirred at room temp. for 4 h. The reaction mixture was diluted with *t*BuOMe (50 mL), saturated aqueous NH_4Cl was added dropwise, and finally H_2O (60 mL) was added. The aqueous layer was extracted with *t*BuOMe (3 × 80 mL), and the resulting organic mixture was then dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (hexane/*t*BuOMe, 10:1) on silica gel afforded condensation product **28** (1093 mg, 2.86 mmol, 73% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.23 (m, 4 H), 7.07 (m, 1 H), 5.12* (m, 0.22 H), 5.05 (m, 0.77 H), 4.99 (s, 1 H), 4.78 (td, J = 10.7, 10.7, 4.3 Hz, 1 H), 2.68–2.48 (m, 1 H), 2.07 (s, 3 H), 1.92–0.75 (m, 12 H), 1.78 (s, 1 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.30 (s, 3 H), 1.22 (s, 3 H), 0.85 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 166.1, 159.4*, 159.0*, 151.8, 132.4, 128.0, 125.6, 125.0, 123.9*, 123.3, 116.9*, 116.2, 73.4, 73.3*, 50.8, 42.1, 40.9, 39.9, 34.8, 33.3*, 31.4, 27.3, 26.9, 26.8, 26.3*, 26.1, 25.9, 25.7, 25.2*, 21.9, 18.8, 17.8 ppm. *Signals corresponding to minor diastereoisomer (2*Z*). HRMS (FAB): calcd. for $C_{26}H_{38}O_2Na$ [M + Na]$^+$ 405.2770; found 405.2771.

(1*S*,2*R*,5*S*)-5-Methyl-2-(2-phenylprop-2-yl)cyclohexyl (*E*)-5-(3,3-Dimethyloxiran-2-yl)-3-methylpent-2-enoate (19): To a solution of **28** (1073 mg, 2.81 mmol) in dichloromethane (9.0 mL) at 0 °C under argon, was added dropwise *m*CPBA (582 mg, 3.37 mmol) in dichloromethane (9.0 mL), and the mixture was stirred until disappearance of starting material was observed. The mixture was diluted with dichloromethane (25 mL), washed with NaOH 2 N (3 × 40 mL) and brine (2 × 40 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 5:1) on silica gel to afford **19** (1085 mg, 2.73 mmol, 97% yield) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.23 (m, 4 H), 7.07 (m, 1 H), 5.02–4.96 (m, 1 H), 4.78 (td, J = 10.8, 10.8, 4.2 Hz, 1 H), 2.67 (t, J = 6.2 Hz, 1 H), 2.28–1.93 (m, 2 H), 2.08 (s, 3 H), 1.92 (d, J = 12.3 Hz, 1 H), 1.70–1.56 (m, 5 H), 1.52–1.40 (m, 2 H), 1.29 (m, 6 H), 1.26 (s, 3 H), 1.21 (s, 3 H), 1.16–1.03 (m, 2 H), 0.85 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 165.8, 157.6, 151.8, 127.9, 125.5, 124.9, 116.6, 116.5, 73.5, 63.6, 58.4, 50.7, 42.0, 39.8, 37.4, 34.7, 31.4, 27.7, 27.4, 26.9, 26.7, 25.6, 25.4, 25.1, 24.9, 21.9 ppm. HRMS (FAB): calcd. for $C_{26}H_{38}O_3Na$ [M + Na]$^+$ 421.2719; found 421.2717.

Radical Cyclization of 19. Compounds 30a$_1$ and 30a$_2$: After subjecting **19** (398 mg, 1.00 mmol) to the catalytic procedure conditions, the resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 4:1 to 1:1) on silica gel to afford a diastereomeric mixture (1′*R*,3′*S*), (1′*S*,3′*S*), (1′*S*,3′*R*), and (1′*R*,3′*R*) showing two representative groups of signals in the ^{1}H NMR spectra corresponding to **30a** (*trans*) and **30b** (*cis*) (276 mg, 69% yield), in an equimolecular ratio. The general structure of this mixture was determined after isolation of the *trans* diasteromeric couple (**30a**). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ = 7.28 (m, 4 H), 7.13 (m, 1 H), 4.78 (td, J = 10.7, 10.7, 4.3 Hz, 2 H), 3.71 (dd, J = 8.2, 4.8 Hz, 1 H), 2.11–1.95 (m, 2 H), 1.89–1.78 (m, 2 H), 1.73–1.65 (m, 1 H), 1.62 (d, J = 13.0 Hz, 1 H), 1.57–1.39 (m, 4 H), 1.35–1.15 (m, 3 H), 1.29 (s, 3 H), 1.18 (s, 3 H), 0.98–0.84 (m, 1 H), 0.94 (s, 3 H), 0.87 (d, J = 6.5 Hz, 3 H), 0.80 (s, 3 H), 0.66 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C): δ = 172.4, 152.3, 128.0, 125.4, 124.8, 81.3, 73.9, 50.3, 47.2, 42.3, 41.8, 39.5, 34.7, 34.0, 31.4, 30.9, 29.5, 26.4, 23.2, 22.8, 21.9, 21.5, 17.2 ppm.

Radical Cyclization of 20: After subjecting **20** (260 mg, 0.91 mmol) to the catalytic procedure conditions, the resulting crude was purified by column chromatography on silica gel (hexane/*t*BuOMe, 4:1) to yield a mixture of **31a** and **31b** in a 2:1 ratio (241 mg, 93% yield). A solution of this mixture (241 mg, 0.84 mmol) in Et_2O was treated with an excess of TsOH at room temp. for 26 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 25 mL) and brine (30 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 4:1) on silica gel to afford **31a** (154.6 mg, 0.54 mmol, 63% yield) and the lactone derived from **31b** (61.1 mg, 0.27 mmol, 31% yield).

Diethyl 2-[(1*R*,3*S*)-3-Hydroxy-1,2,2-trimethylcyclopentyl]malonate (31a): Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 4.18 (m, 4 H), 3.76 (dd, J = 3.6, 3.6 Hz, 1 H), 3.46 (s, 1 H), 2.19 (m, 1 H), 1.84 (m, 2 H), 1.61 (m, 1 H), 1.34 (s, 3 H), 1.28 (t, J = 7.0 Hz, 3 H), 1.25 (t, J = 7.0 Hz, 3 H), 0.95 (s, 6 H) ppm. ^{13}C NMR

($CDCl_3$, 125 MHz, 25 °C): δ = 169.0, 168.8, 83.5, 61.2, 61.1, 58.1, 48.6, 48.2, 36.8, 31.1, 24.6, 19.1, 18.6, 14.3, 14.2 ppm. HRMS (FAB): calcd. for $C_{15}H_{26}O_5Na$ $[M + Na]^+$ 309.1672; found 309.1667.

Ethyl (1*S*,4*R*,5*S*)-5,8,8-Trimethyl-3-oxo-2-oxabicyclo[3.2.1]octane-4-carboxylate (Lactone Derived from 31b): Colorless oil. ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 4.26 (m, 1 H), 4.24 (dd, *J* = 7.1, 7.1 Hz, 2 H), 3.48 (d, *J* = 2.2 Hz, 1 H), 2.34 (ddd, *J* = 13.9, 9.2, 4.2 Hz, 1 H), 2.08 (m, 2 H), 1.61 (m, 1 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.06 (s, 3 H), 1.05 (s, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 169.0, 167.8, 89.1, 61.7, 58.3, 46.1, 45.5, 30.3, 29.7, 20.9, 18.0, 17.0, 14.4 ppm. HRMS (FAB): calcd. for $C_{13}H_{20}O_4Na$ $[M + Na]^+$ 263.1254; found 263.1252.

Radical Cyclization of 21: After subjecting **21** (165 mg, 1.00 mmol) to the catalytic procedure conditions, the resulting crude material was purified by column chromatography on silica gel (hexane/*t*BuOMe, 5:1 and 2:1) to afford **32a** (131.2 mg, 79% yield) and **32b** (32.8 mg, 20% yield).

2-[(1*R*,3*S*)-3-Hydroxy-1,2,2-trimethylcyclopentyl]acetonitrile (32a): ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 5.12 (m, 1 H), 3.95 (dd, *J* = 8.2, 6.4 Hz, 1 H), 2.18 (m, 2 H), 1.75 (t, *J* = 7.2 Hz, 1 H), 1.61 (m, 1 H), 1.50 (m, 2 H), 1.18 (s, 3 H), 0.93 (s, 3 H), 0.89 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 119.4, 81.1, 46.6, 44.5, 34.8, 30.4, 27.3, 22.7, 22.4, 17.7 ppm.

2-[(1*S*,3*S*)-3-Hydroxy-1,2,2-trimethylcyclopentyl]acetonitrile (32b): ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 5.19 (m, 1 H), 3.93 (dd, *J* = 7.6, 4.6 Hz, 1 H), 2.70 (d, *J* = 16.5 Hz, 1 H), 2.29 (d, *J* = 16.5 Hz, 1 H), 2.18 (m, 1 H), 1.90 (m, 1 H), 1.88–1.50 (m, 2 H), 1.10 (s, 3 H), 0.90 (s, 3 H), 0.89 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 118.4, 80.0, 45.6, 43.1, 33.6, 29.2, 25.7, 21.7, 21.3, 15.9 ppm.

Radical Cyclization of 33: After subjecting **33** (594 mg, 1.81 mmol) to the catalytic procedure conditions, the resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 3:1) on silica gel to afford an equimolecular mixture of **34a** and **34b** (455 mg, 1.38 mmol, 76% yield). A solution of this mixture (53 mg, 0.16 mmol) in Et_2O (5.0 mL) was treated with an excess of TsOH at room temp. for 26 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 5:1) on silica gel to afford lactone **35** (14 mg), **34a** (29 mg), and a mixture of both compounds (7 mg).

Methyl 2-[(1*R*,2*R*,3*S*)-2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-hydroxy-1,2-dimethylcyclopentyl]acetate (34a): ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 4.20 (dd, *J* = 8.6, 6.8 Hz, 1 H), 3.64 (s, 3 H), 3.54 (d, *J* = 9.6 Hz, 1 H), 3.46 (d, *J* = 9.6 Hz, 1 H), 2.25 (q, *J* = 13.2 Hz, 2 H), 2.17–2.05 (m, 1 H), 1.86–1.74 (m, 1 H), 1.65–1.46 (m, 2 H), 1.07 (s, 3 H), 0.92 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 173.3, 78.2, 68.7, 51.4, 50.6, 44.8, 41.5, 34.1, 30.1, 25.9 (3 C), 22.6, 18.2, 13.1, –5.6 (2 C) ppm. HRMS (FAB): calcd. for $C_{17}H_{34}O_4SiNa$ $[M + Na]^+$ 353.2124; found 353.2106.

(1*S*,5*S*,8*R*)-8-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-5,8-dimethyl-2-oxabicyclo[3.2.1]octan-3-one (35): Colorless oil. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 4.51 (d, *J* = 4.5 Hz, 1 H), 3.39 (dd, *J* = 11.9, 10.2 Hz, 2 H), 2.49 (dd, *J* = 18.5, 2.9 Hz, 1 H), 2.24 (d, *J* = 17.7 Hz, 1 H), 1.98 (m, 2 H), 1.75 (m, 2 H), 1.05 (s, 3 H), 0.86 (s, 3 H), 0.84 (s, 9 H), 0.00 (s, 3 H), –0.01 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 171.4, 86.2, 65.5, 49.0, 45.5, 41.5, 36.6, 29.6, 25.9 (3 C), 19.0, 18.3, 12.2, –5.6 (2 C) ppm. HRMS (FAB): calcd. for $C_{16}H_{30}O_3SiNa$ $[M + Na]^+$ 321.1862; found 321.1855.

Radical Cyclization of 36: After subjecting **36** (391 mg, 0.74 mmol) to the catalytic procedure conditions, the resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 3:1) on silica gel to afford a diasteromeric mixture **37** [**37a**, *trans*: (1*R*,2*R*,3*S*) and (1*S*,2*S*,3*R*); **37b**, *cis*: (1*S*,2*R*,3*S*) and (1*R*,2*S*,3*R*)] (278 mg, 0.54 mmol, 71% yield). Compound **37** was saponified by reaction with KOH/MeOH, and the corresponding crude material was treated with $TMSCHN_2$ to obtain a mixture of compounds **34a** and **35** at a 1.3:1 ratio.

Radical Cyclization of 38: After subjecting **38** (216 mg, 0.72 mmol) to the catalytic procedure conditions, the resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 3:1 and 2:1) on silica gel to afford **39a** (145 mg, 0.47 mmol, 66% yield) and **39b** (58 mg, 0.19 mmol, 26% yield).

Diethyl 2-[(1*R*,2*R*,3*S*)-2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-hydroxy-1,2-dimethylcyclopentyl]malonate (39a): Colorless oil. ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 4.16 (m, 4 H), 4.02 (d, *J* = 9.9 Hz, 1 H), 3.96 (dd, *J* = 8.2, 4.2 Hz, 1 H), 3.47 (d, *J* = 9.9 Hz, 1 H), 3.45 (s, 1 H), 2.14 (m, 1 H), 1.78 (m, 2 H), 1.65 (m, 1 H), 1.39 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 0.95 (s, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 174.3, 174.2, 88.0, 71.3, 66.7, 66.5, 63.5, 58.2, 53.0, 44.7, 35.2, 31.4 (3 C), 25.5, 23.6, 23.4, 19.7, 19.6, –5.6 (2 C) ppm. HRMS (FAB): calcd. for $C_{21}H_{40}O_6SiNa$ $[M + Na]^+$ 439.2492; found 439.2517.

Diethyl 2-[(1*S*,2*R*,3*S*)-2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-hydroxy-1,2-dimethylcyclopentyl]malonate (39b): Colorless oil. ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 4.16 (m, 5 H), 3.69 (s, 1 H), 3.59 (d, *J* = 9.9 Hz, 1 H), 3.48 (d, *J* = 9.9 Hz, 1 H), 2.16 (m, 1 H), 1.95 (m, 1 H), 1.63 (ddd, *J* = 15.2, 9.5, 2.6 Hz, 1 H), 1.56 (m, 1 H), 1.32 (s, 3 H), 1.26 (m, 6 H), 0.92 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 174.5, 174.4, 84.4, 74.9, 66.7, 66.6, 62.5, 57.7, 53.4, 42.4, 37.2, 31.6 (3 C), 26.0, 23.9, 23.7, 19.8, 19.7, 0.0 (2 C) ppm. HRMS (FAB): calcd. for $C_{21}H_{40}O_6SiNa$ $[M + Na]^+$ 439.2492; found 439.2517.

Radical Cyclization of 40: After subjecting **40** (502 mg, 1.81 mmol) to the catalytic procedure conditions, the resulting crude material was purified by column chromatography (hexane/*t*BuOMe, 5:1 and 3:1) on silica gel to afford **41a** (381.6 mg, 1.38 mmol, 76% yield) and **41b** (95.4 mg, 0.34 mmol, 19% yield).

2-[(1*R*,2*R*,3*S*)-2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-hydroxy-1,2-dimethylcyclopentyl]acetonitrile (41a): Colorless oil. ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 4.02 (dd, *J* = 7.9, 4.2 Hz, 1 H), 3.73 (d, *J* = 10.1 Hz, 1 H), 3.58 (d, *J* = 10.1 Hz, 1 H), 2.81 (d, *J* = 16.5 Hz, 1 H), 2.41 (d, *J* = 16.5 Hz, 1 H), 2.19 (m, 1 H), 1.98 (m, 1 H), 1.62 (m, 2 H), 1.12 (s, 3 H), 0.93 (m, 3 H), 0.90 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 119.4, 81.4, 65.1, 50.6, 43.9, 36.4, 30.8, 26.5, 25.9 (3 C), 23.2, 19.1, 18.1, –5.6 (2 C) ppm. HRMS (FAB): calcd. for $C_{16}H_{31}NO_2Na$ $[M + Na]^+$ 320.2022; found 320.1974.

2-[(1*S*,2*R*,3*S*)-2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-hydroxy-1,2-dimethylcyclopentyl]acetonitrile (41b): Colorless oil. ^1H NMR ($CDCl_3$, 500 MHz, 25 °C): δ = 4.18 (t, *J* = 8.0 Hz, 1 H), 3.53 (d, *J* = 10.1 Hz, 1 H), 3.48 (d, *J* = 10.1 Hz, 1 H), 2.39 (d, *J* = 1.7 Hz, 2 H), 2.14 (m, 1 H), 1.75 (m, 2 H), 1.59 (m, 1 H), 1.19 (s, 3 H), 0.94 (m, 3 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.06 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, 25 °C): δ = 119.3, 76.8, 68.1, 50.0, 44.3, 35.0, 29.9, 27.1, 25.9 (3 C), 23.5, 18.2, 13.5, –5.6 (2 C) ppm. HRMS

(FAB): calcd. for $C_{16}H_{31}NO_2Na$ $[M + Na]^+$ 320.2022; found 320.1974.

Supporting Information (see footnote on the first page of this article): Preparation and spectroscopic data of epoxy-polyprenes **3**, **5**, **8**, **11**, **15**, **17**, **20**, **21**, **33**, **36**, **38**, and **40**.

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