Total Synthesis of (10*R*)- and (10*S*)-Corossolin: Determination of the Stereochemistry at C-10 of the Natural Corossolin and the Differential Toxicity toward Cancer Cells Caused by the Configuration at C-10

Qian Yu,[†] Zhu-Jun Yao,[†] Xiao-Guang Chen,[‡] and Yu-Lin Wu*,[†]

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China, and Institute of Materia Medica, Chinese Academy of Medical Sciences, 1 Xiannongtan Street, Beijing 100050, China

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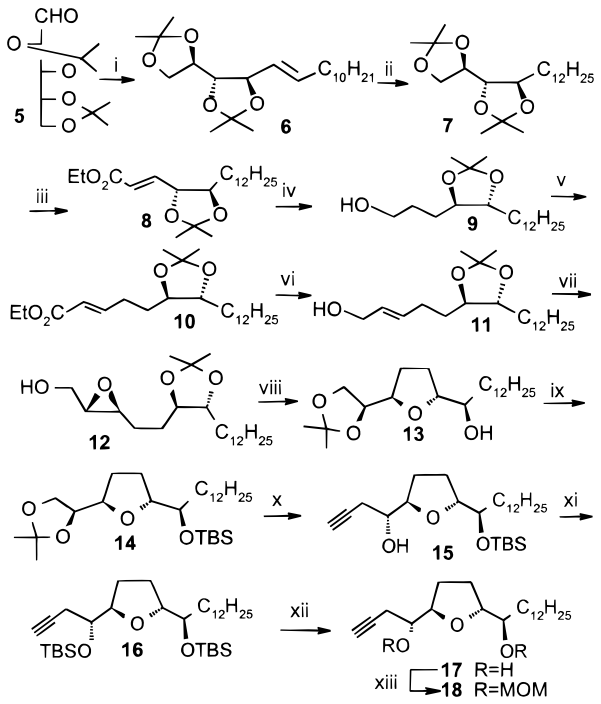
(10*R*) and (10*S*)-corossolin have been synthesized by coupling of the alkyne intermediate **18** with epoxide **27** or **29**, respectively. Comparison of the physical data of both synthetic corossolins with those reported for the natural one shows that the configuration at C-10 of the natural corossolin is highly likely to be *R*. The *R* isomer is found to be 18 times as active as the *S* isomer in the preliminary in vitro tests against the B16BL6 cell line.

Annonaceous acetogenins, isolated from several species of the family of Annonaceae, are waxy substances characterized[1] by a long alkyl chain with a γ-lactone, 1−3 THF rings, and some carbinol chiral centers along it. The broad range of biological activities and the uncertainty of the stereochemistry of these compounds have attracted more and more organic chemists to the syntheses,[2] which may lead to more samples of natural or unnatural configurations for further biological studies. As part of our research in the synthesis[3] of this growing class of natural products, we attempted to obtain both enantiomers of corossolin **1**, which was originally isolated[4a] from the seeds of *Annona muricata* in 1991. To establish the previously undefined[4b] configuration at C-10 of the natural **1**, herein we wish to report the synthesis of (10*R*)- and (10*S*)-corossolin and the preliminary results of in vitro antitumor activities tests against the B16BL6 cell line.

Synthesis of the Alkyne Intermediate 18. As shown in Scheme 1, the synthesis of the alkyne segment starts from the cheap and readily available D-gluconolactone. The aldehyde **5**, easily obtained[5] from D-gluconolactone on large scales, was subjected to Wittig reaction to give compound **6** in 92% yield. Hydrogenation of **6** over 10% Pd−C gave **7** in 97% yield. Selective cleavage/oxidation of the terminal isopropylidene acetal in the compound **7** and subsequent Horner−Emmons reaction with triethyl phosphonoacetate afforded the ester **8** in 83% yield, which was subjected to hydrogenation (10% Pd−C) and reduction with lithium aluminum hydride to give alcohol **9** in 72% yield. The following Swern oxidation of **9** and Horner−Emmons reaction of the resultant

Scheme 1[a]



[a] Reagents and conditions: (i) $C_{11}H_{23}PPh_3^+Br^-$, *n*-BuLi; (ii) H_2, 10% Pd−C; (iii) H_5IO_6, Et_2O; 80% NaH, $(OEt)_2POCH_2CO_2Et$; (iv) H_2, 10% Pd−C; LAH, Et_2O; (v) $(COCl)_2$, DMSO; 80% NaH, $(OEt)_2POCH_2CO_2Et$; (vi) Dibal-H, CH_2Cl_2, −78 °C; (vii) TBHP, Ti(O-*i*-Pr)$_4$, L-(+)-DIPT, 4 Å MS, −20 °C; (viii) CSA, DMOP, CH_2Cl_2; (ix) TBSCl, imidazole, DMF; (x) H_5IO_6, Et_2O; 4 Å MS, allenylboronic acid, D-(−)-DIPT; (xi) TBSCl, imidazole, DMF; (xii) 40% HF, MeCN; (xiii) *i*-Pr_2NEt, MOMCl.

* To whom correspondence should be addressed. E-mail: YLWU@PUB.SIOC.AC.CN.

[†] Shanghai Institute of Organic Chemistry.

[‡] Institute of Materia Medica.

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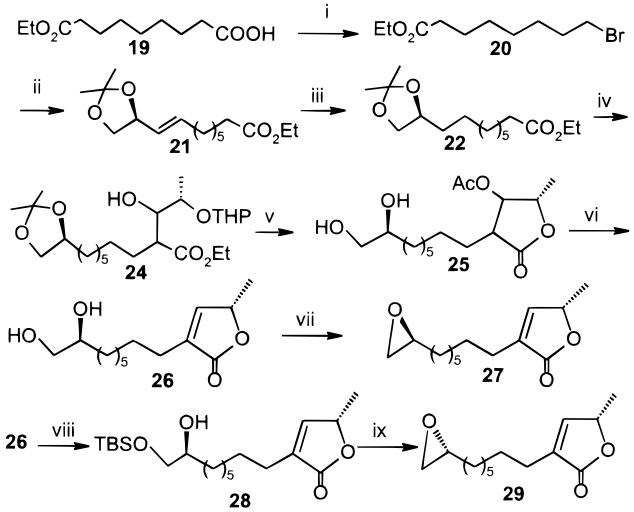
Scheme 2[a]

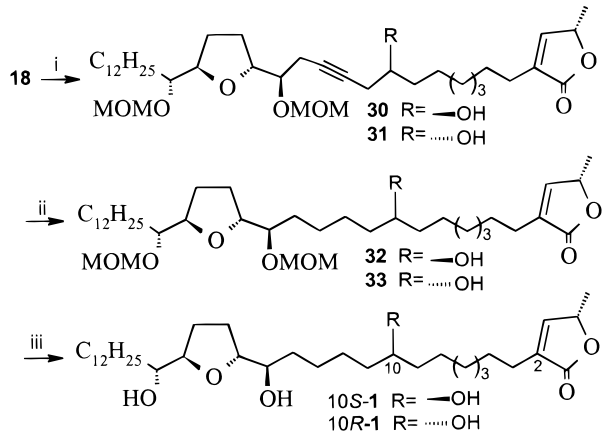


[a] Reagents and conditions: (i) red HgO, Br_2, CCl_4; (ii) PPh_3, 130 °C; *t*-BuOK, (2*R*)-2,3-*O*-isopropylideneglyceral, THF; (iii) H_2, 10% Pd−C; (iv) *i*-Pr_2NH, *n*-BuLi, HMPA, (2*S*)-*O*-tetrahydropyranyl lactal; (v) Ac_2O, pyridine; Amberlyst15 resin, MeOH; (vi) DBU, THF; (vii) trimethyl orthoacetate, PPTs, CH_2Cl_2; AcBr, CH_2Cl_2; K_2CO_3, MeOH; (viii) TBSCl, imidazole, DMAP, CH_2Cl_2; (ix) MsCl, Py, CH_2Cl_2; 40% HF, MeCN; 60% NaH, THF.

aldehyde gave ester **10** in 85% yield, which on reduction with diisobutylaluminum hydride led to (*E*)-allylic alcohol **11** in 95% yield. Asymmetric epoxidation[6] of **11** directed by L-(+)-diisopropyl tartrate gave epoxy alcohol **12** in 83% yield, which showed >95% de by ^1H NMR analysis of the corresponding Mosher ester[7] derivative. Acid-catalyzed one-pot transformation of **12** to **13** was achieved with camphorsulfonic acid (90% yield). The secondary hydroxyl moiety of **13** was protected as a TBS ether to afford **14** in 85% yield. After cleavage of the isopropyliene acetal of **14**, the resultant aldehyde was treated with chiral allenylboronic ester prepared according to Yamamoto's procedure[8] to afford **15** in 81% yield (threo/erythro 18.8:1, total yield 85.3%). Up to this point, all four asymmetric centers were established with the desired threo-trans-threo configuration. Protection of the hydroxyl in **15** with *tert*-butyldimethylchlorosilane gave **16** in 91% yield. Due to the difficulty confronted in the further step, the TBS group was transferred to MOM by successive treatment with 40% HF, MOMCl, and *i*-Pr_2NEt to give alkyne **18** in 86% yield.

Syntheses of (10*R*)-Corossolin and (10*S*)-Corossolin. The terminal epoxide **27** and **29** were prepared from the same synthon **26**, which was constructed via a multistep process (Scheme 2) starting from azelic acid monoethyl ester **19**. Ethyl ω-bromooctanoate **20** was obtained by Hünsdiecker reaction[9] of **19** using red mercury(II) oxide and bromine in 72% yield. The subsequent Wittig reaction with 2.3-*O*-isopropylidene-D-glyceraldehyde gave **21** in 61% yield. Hydrogenation over 10% Pd−C afforded **22** in 94% yield. Treatment with LDA and (2*S*)-*O*-tetrahydropyranyl lactal[3] gave the aldol-type product **24** in 80% yield. Protection of the hydroxyl by

Scheme 3[a]



[a] Reagents and conditions: (i) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF and **27** (leading to **30**) or **29** (leading to **31**); (ii) H_2, $RhCl(PPh)_3$, Ph; (iii) $BF_3{\cdot}OEt_2$, DMS, 0 °C.

an acetyl group, acid-catalyzed lactone closure, and hydrolysis of the acetonide in one pot gave **25** in 85% overall yield. After β-elimination of the acetate ester with DBU, the intermediate **26** was obtained in 92% yield. The preparation of (10*S*)-epoxide **27** was achieved in one pot by treatment of **26** with trimethyl orthoacetate, acetyl bromide, and K_2CO_3/MeOH in 82% yield.[10] Transformation of **26** into (10*R*)-epoxide **29** was carried out as follows:[11] Selective primary hydroxyl protection with *tert*-butyldimethylchlorosilane afforded **28** (80%). Methyl sulfonation of the secondary hydroxyl with MsCl, desilylation with 40% HF, and ring closure with NaH gave **29** in 65% yield.

In our original attempt, coupling reaction between the lithium salt of **16** and **27** in the presence of boron trifluoride etherate followed by selective catalytic hydrogenation of the triple bond with Wilkinson's catalyst to the saturated compound failed to afford the desired product. We thought that this might be caused by the steric hindrance associated with the TBS group. Therefore, alkyne **16** was then transformed to the MOM ether **18** (vide ante). Coupling of **18** with **27** (or **29**) in the same manner as described gave **30** (63%, or 76% on the recovery of **18**) or **31** (85%, or 92% on the recovery of **18**). The following hydrogenation using Wilkinson's catalyst led to **32** (71%) or **33** (58%). Removal of the MOM protecting group with the dimethyl sulfide−boron trifluoride etherate system gave (10*S*)-**1** in 86% and (10*R*)-**1** in 62% yield, respectively,

During our work, Tanaka[11] reported the total syntheses of (10*R*)- and (10*S*)-**1**. The IR and NMR spectra of their synthetic corossolin were consistent with those reported for natural **1** by the French group.[4a] However, both (10*S*)-**1** and (10*R*)-**1** showed an optical rotation (+22.2 and +21.0, respectively) close to that for natural **1** (+19). This made an unambiguous assignment very difficult. Our samples gave different results; the rotation of (10*R*)-**1** (+19.1) was closer to that of natural **1** than that of (10*S*)-**1** (+24.6). And, the ^{13}C NMR (600 MHz) data of the THF fragment for (10*R*)-**1** was close to that of natural **1** and both were "symmetrical" (i.e., C-15 had the same shift as C-20) (Table 1). On the basis of these results, we

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Table 1. Comparison of Optical Rotation and ^{13}C Chemical Shift Data of Our Synthetic 1 and the Natural 1

compd	$[\alpha]_D$ (deg)	δ_c C-15	C-16	C-19	C-20	C-10
natural **1**[a]	+19.0	73.9	82.6	82.6	73.9	71.6
(10*R*)-**1**[b]	+19.1	74.099	82.616	82.616	74.099	71.897
(10*S*)-**1**	+24.6	74.022[c]	82.678[d]	82.612[d]	73.854[c]	71.739

[a] ^{13}C NMR ($CDCl_3$, 50 MHz). [b] ^{13}C NMR ($CDCl_3$, 150 MHz). [c,d] The shifts with same superscript may be interchanged.

Table 2. In Vitro Activity of (10*R*)- and (10*S*)-1 against the B16BL6 Cell Line

compd	GI_{50} (μg/mL)	LC_{50} (μg/mL)
(10*R*)-**1**	0.042	~7
(10*S*)-**1**	0.77	>10

[a] GI_{50} and LC_{50} stand for the concentrations required for 50% growth inhibition and 50% lethality, respectively.

assign with a relatively high degree of certainty the absolute configuration of natural-**1** at C-10 to *R*, the configuration observed for all known acetogenins to the best of our knowledge.

The (10*S*)-**1** and (10*R*)-**1** synthesized in this work were then tested in vitro against the B16BL6 cell line. Then the cells were visualized with sulforhodamine (SRB),[12] a pink water-soluble dye that can combine with basic amino acids in biomacromolecules and the optical density at 515 nm has good linear relationship with the number of cells present. The preliminary results are very interesting. Contrary to what most people would expect, the (10*R*)-**1** is not of equal activity, but instead, is about 18 times as active as the (10*S*)-**1** (Table 2) and both compounds affect the tumor cells mainly through suppression of the proliferation of the tumor cell, although there could also be some cellulicidal effect. It should be noted that since natural **1** exists only as one of the two C-10 isomers, the differential activity associated with the C-10 configuration could never be revealed without a synthetic sample of the nonnatural **1**.

Experimental Section

The melting points were uncorrected. Microanalyses were carried out in the Microanalytic Laboratory of the Institute. Flash column chromatography was performed on silica gel H (10−40 μm).

(2*R*,3*R*,4*R*)-1,2:3,4-Di-*O*-isopropylidene-5-ene-1,2,3,4-hexadecanetetraol (6). A mixture of $C_{11}H_{23}Br$ (44.18 g, 18.78 mmol) and Ph_3P (49.27 g, 18.78 mmol) was heated in an oil bath (120 °C) for 9 h. After being cooled to room temperature, 90 mL of dry ether was added. After the mixture had stood at −10 °C for 5 days, a white solid was formed, which was filtered and washed with ether. The filter cake was dried in vacuo to give a white powder (88.77 g, 95%). To a solution of the obtained powder (53.0 g, 106.5 mmol) in THF (500 mL) was added *n*-BuLi (2.3 N, 46.3 mL, 106.5 mmol) at −70 °C. After being stirred for 20 min, a solution of **5** (19.2 g, 83.4 mmol) in anhydrous THF (60 mL) was added dropwise. The reaction mixture was stirred at −70 °C for 1 h, at 0 °C for 2 h, and at last at room temperature overnight. NH_4Cl (200 mL) was added to quench the reaction. The separated aqueous phase was extracted with petroleum ether−Et_2O (1:1,3 × 100 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and then concentrated to give the residue, which was shaken with petroleum ether. Ph_3PO was filtered off. The filtrate was purified by silica gel column chromatography to give **6** (28.39 g, 92%) as a colorless oil: $[\alpha]^{20}_D$ −10.3 (*c* 0.72, $CHCl_3$); IR (film) 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H), 1.26 (m, 16H), 1.34 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.42 (s, 3H), 2.16 (m, 2H), 3.72 (m, 1H), 3.92 (dd, J = 8.0, 5.3 Hz, 1H), 4.06 (m, 1H), 4.14 (m, 1H), 4.67 (dd, J = 8.2, 7.2 Hz, 1H,), 5.40 (ddt, J = 10.2, 1.6 Hz, 1H,), 5.66 (dt, J = 10.3, 7.2 Hz, 1H,); EIMS *m*/*z* 369 (M + 1), 353 (M − CH_3), 237, 131. Anal. Calcd for $C_{22}H_{40}O_4$: C, 71.70; H, 10.94. Found: C, 71.49; H, 10.81.

(2*R*,3*S*,4*R*)-1,2:3,4-Di-*O*-isopropylidene-1,2,3,4-hexadecanetetraol (7). In the presence of 10% Pd−C (1 g, 50 wt %), a solution of **6** (14 g, 38.04 mmol) in 95% EtOH (200 mL) was hydrogenated under 1 atm of hydrogen for 5 h. The Pd−C was filtered off, and the filtrate was concentrated in vacuo to afford **7** as a white solid (13.6 g, 97%): $[\alpha]^{20}_D$ +13.3 (*c* 0.85, $CHCl_3$); IR (film) 1460 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 0.88 (t, 3H), 1.26 (m, 20H), 1.34 (s, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 1.85 (m, 2H), 3.56 (t, J = 7.5 Hz, 1H), 3.93 (m, 2H), 4.03 (m, 1H), 4.12 (dd, J = 7.7, 5.7 Hz, 1H); EIMS *m*/*z* 370 (M^+, 0.74), 355 (M − CH_3, 70.86), 297 (12.47), 269 (100). Anal. Calcd for $C_{22}H_{42}O_4$: C, 71.31; H, 11.42. Found: C, 71.35; H, 11.14.

Ethyl (4*R*,5*R*)-4,5-Diol-4,5-*O*-isopropylidene-2-heptadecenoate (8). H_5IO_6 (10.6 g, 46.4 mmol) was suspended in dry ether (250 mL). After being stirred for 10 min, a solution of **7** (13.2 g, 35.7 mmol) in dry ether (50 mL) was added to the suspension at room temperature. The reaction mixture was stirred overnight and then filtered. The filtrate was washed, in turn, with brine, saturated $NaHCO_3$, 10% $Na_2S_2O_3$, and brine. Drying ($MgSO_4$) and evaporation gave the crude aldehyde. NaH (80%, 1.17 g, 39 mmol) was suspended in anhydrous THF (80 mL). A solution of $(EtO)_2POCH_2CO_2Et$ (8.0 g, 35.7 mmol) in anhydrous THF (20 mL) was added dropwise to the chilled mixture (0 °C) with stirring. After the mixture was stirred for 20 min, a solution of the obtained crude aldehyde in THF (30 mL) was added slowly. After the mixture had been refluxed for 4 h, it was cooled, diluted with ether (150 mL), washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography to give **8** (10.85 g, 83%) as a colorless oil: $[\alpha]^{20}_D$ +12.5 (*c* 0.75, $CHCl_3$); IR (film) 1720, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3H), 1.26 (m, 20H), 1.30 (t, J = 7.0 Hz, 3H,), 1.41 (s, 3H), 1.44 (s, 3H), 1.59 (m, 2H), 3.73 (m, 1H), 4.01 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H,), 6.12 (dd, J = 15.5, 1.3 Hz, 1H), 6.87 (dd, J = 15.5, 5.8 Hz, 1H); EIMS *m*/*z* 369 (M + 1, trace), 353 (M − CH_3, 48.73), 311 (14.91), 269 (22.60), 112 (100); HREIMS calcd for $C_{21}H_{37}O_4$ (M − CH_3) 353.2692, found 353.2719.

(4*R*,5*R*)-4,5-*O*-Isopropylidene-1,4,5-heptadecanetriol (9). To a solution of **8** (9.7 g, 26.4 mmol) in 95% EtOH (120 mL) was added 10% Pd−C (400 mg) at room temperature, and the suspension was vigorously stirred under 1 atm of hydrogen. After being stirred for 4 h, the mixture was filtered and concentrated in vacuo to afford an oil. LAH (1.0 g, 26.3 mmol) was suspended in dry ether (80 mL) at 0 °C. Then a solution of the above oil in THF was added dropwise. After that, the reaction mixture was refluxed for 2 h, cooled to 0 °C, and then quenched with water (3.8 mL). After the color of the mixture turned to white, it was filtered and the solid was washed with ether. The filtrate was dried, concentrated to give crude **9**, and then chromatographed to afford **9** (6.22 g, 72%) as a colorless oil: $[\alpha]^{20}_D$ +22.9 (*c* 1.17, $CHCl_3$); IR (film) 3400, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.26 (m, 20H), 1.39 (s, 6H), 1.51 (m, 2H), 1.73 (m, 4H), 2.17 (brm, 1H), 3.61 (m, 2H), 3.69 (m, 2H); EIMS *m*/*z* 313 (M − CH_3, 15.18), 269 (2.39), 253 (100.00); HREIMS calcd for $C_{19}H_{37}O_3$ (M − CH_3) 313.2743, found 313.2724.

Ethyl (6*R*,7*R*)-6,7-diol-6,7-*O*-isopropylidene-2-nonadecenoate (10). To a solution of $(COCl)_2$ (1.07 mL, 12.3 mmol) in anhydrous CH_2Cl_2 (30 mL) was added a solution of DMSO

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(1.92 g, 24.6 mmol) in CH_2Cl_2 (5 mL) at −70 °C, and then the mixture was stirred for 20 min followed by addition of a solution of **9** (3.1 g, 9.45 mmol) in dry CH_2Cl_2 (10 mL). After the reaction mixture had been stirred for 2 h, Et_3N (7 mL) was added, and the mixture was stirred for 0.5 h and warmed to room temperature. The mixture was washed, in order, with saturated NaCl, saturated NH_4Cl, and saturated NaCl. Drying and evaporation of the solvent gave crude aldehyde. NaH (80%, 340 mg, 11.33 mmol) was suspended in anhydrous THF (30 mL). To the suspension was added a solution of $(EtO)_2P{=}OCH_2CO_2Et$ (2.12 g, 9.45 mmol) in anhydrous THF (10 mL), and then the mixture was stirred for 0.5 h, followed by addition of the mixture of the above crude aldehyde in THF (10 mL). After the reaction mixture had been refluxed for 1.5 h, it was cooled, diluted with ether, and washed with water and brine. Drying and evaporation of the solvent gave crude product, which was purified by chromatography to afford **10** (3.19 g, 85%): $[\alpha]^{20}_D$ +26.3 (*c* 0.31, $CHCl_3$); IR (film) 1730, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3H), 1.26 (m, 20H), 1.29 (t, J = 7.2 Hz, 3H), 1.38 (s, 6H), 1.50 (m, 2H), 1.59 (m, 2H), 2.37 (ddt, J = 1.5, 7.5, 6.5 Hz, 2H), 3.60 (m, 2H), 4.19 (q, J = 7.2 Hz, 2H), 5.86 (dt, J = 1.5, 15.6 Hz, 1H), 6.99 (dt, J = 6.8, 15.5 Hz, 1H); EIMS *m*/*z* 396 (M^+, 2.21), 381 (M − CH_3, 100); HREIMS calcd for $C_{23}H_{41}O_4$ (M − CH_3) 381.3005, found 381.3000.

(6*R*,7*R*)-6,7-*O*-Isopropylidene-2-nonadecene-1,6,7-triol (11). To a solution of **10** (2.96 g, 7.47 mmol) in CH_2Cl_2 (30 mL) was added DIBAL (1.1 M in toluene, 30.0 mL, 33 mmol) dropwise with stirring at −70 °C. The mixture was stirred for 3 h, quenched by addition of saturated NH_4Cl (20 mL), warmed to room temperature, and extracted with EtOAc. The solid was filtered and washed with EtOAc. After drying and concentration of the combined filtrate, the residue was purified by silica gel column chromatography to afford **11** (2.51 g, 95%): $[\alpha]^{20}_D$ +24.4 (*c* 0.59, $CHCl_3$); IR (film) 3400, 1475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26 (m, 20H), 1.38 (s, 6H), 1.62 (m, 4H), 2.17 (m, 2H), 3.61 (m, 2H), 4.09 (m, 2H), 5.71 (m, 2H); EIMS *m*/*z* 354 (M^+, 4.02), 339 (M − CH_3, 47.56), 337 (M + 1 − H_2O, 2.43); HREIMS calcd for $C_{22}H_{42}O_3$ (M^+) 354.3134, found 354.3126.

(2*S*,3*S*,6*R*,7*R*)-2,3-Epoxy-6,7-*O*-isopropylidene-1,6,7-nonadecanetriol (12). Smashed 4 Å MS (350 mg) were suspended in 50 mL of anhydrous CH_2Cl_2 under the N_2 atmosphere and cooled to −30 °C, and then a solution of L-(+)-DIPT (50 mg, 0.213 mmol) in 3 mL of CH_2Cl_2 followed by $Ti(OPr^i)_4$ (50 μL, 0.176 mmol) was added to it. After the mixture was stirred, TBHP (9.0 M, 0.78 mL, 7.06 mmol) was added dropwise, and the mixture was stirred for another 30 min. Then, a solution of **11** (1.25 g, 3.53 mmol) in 10 mL of anhydrous CH_2Cl_2 was dropped in slowly and stirred for a further 30 min. The mixture was stored in a refrigerator (−20 °C) overnight. Then, a solution of $FeSO_4$ (2 g, 7.27 mmol) and citric acid (670 mg, 3.64 mmol) in distilled water (10 mL) was added and stirred for 20 min until the two phases separated. The mixture was filtered through Celite and washed with CH_2Cl_2. The aqueous phase was separated and extracted with CH_2Cl_2. The combined organic phase was washed with 5% $NaHCO_3$ (60 mL) and brine (60 mL). After drying and concentration in vacuo, the residue was purified by silica gel column chromatography to afford **12** (1.08 g, 83%, de >95%). The de value was determined by ^{1}HNMR analysis of the corresponding Mosher ester derivative: $[\alpha]^{20}_D$ +13.2 (*c* 0.23, $CHCl_3$); IR (film) 3450, 1470 cm^{-1}; ^1H NMR (**12** was transformed to **13** in $CDCl_3$); EIMS *m*/*z* 355 (M − CH_3, 63.39), 313 (M − C_4H_9, 46.42), 311 (28.30), 295 (36.68); HREIMS calcd for $C_{21}H_{39}O_3$ (M − CH_3) 355.2847, found 355.2878.

(2*R*,5*R*,1′*S*,1″*R*)-2-[1′,2′-(1-methylehtylidene)dioxy]-5-(1″-hydroxytridecyl)tetrahydrofuran (13). To an ice-cooled solution of **12** (1.07 g, 2.89 mmol) in anhydrous CH_2Cl_2 (10 mL) was added CSA (60 mg), and the mixture was stirred for a few minutes. Then, DMOP (500 μL) was added and the mixture stirred at room temperature for 2 h. Concentration in vacuo and purification by chromatography to afford **13** (958 mg, 90%) as a colorless oil: $[\alpha]^{20}_D$ +3.5 (*c* 0.49, $CHCl_3$); IR (film) 3455, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26 (m, 20H), 1.36 (s, 3H), 1.42 (s, 3H), 1.60 (m, 2H), 1.60−1.90 (m, 2H), 2.02 (m, 1H), 2.12 (m, 1H), 3.38 (dt, J = 7.2, 6.5 Hz, 1H), 3.81 (dd, J = 13.4, 6.8 Hz, 1H), 3.87 (dd, J = 13.2, 6.9 Hz, 1H), 3.90 (dd, J = 6.9, 6.5 Hz, 1H), 4.02 (ddd, J = 6.7, 5.5, 1.0 Hz, 1H), 4.09 (ddd, J = 7.8, 6.3, 1.6 Hz, 1H); EIMS *m*/*z* 371 (M + 1, 14.26), 355 (M − CH_3, 17.08), 313 (M − C_4H_9, 22.44); HREIMS calcd for $C_{21}H_{39}O_4$ (M − CH_3) 355.2848, found 355.2806.

(2*R*,5*R*,1′*S*,1″*R*)-2-[1′,2′-(1-methylethylidene)dioxy]-5-[1″-(*tert*-butyldimethylsilyl)oxytridecyl]tetrahydrofuran (14). A mixture of **13** (262 mg, 0.707 mmol), TBSCl (140 mg, 0.93 mmol), and imidazole (144 mg, 2.12 mmol) with a catalytic amount of DMAP in anhydrous DMF (10 mL) was stirred at room temperature for 2 days, diluted with Et_2O (20 mL), and washed with saturated NH_4Cl (10 mL) and brine (2 × 10 mL). Drying over Na_2SO_4, concentration in vacuo, and chromatography over silica gel afforded **14** (264 mg, 77% or 91% on the recovery of **13**) and recovered **13** (41 mg): $[\alpha]^{20}_D$ +9.1 (*c* 0.15, $CHCl_3$); IR (film) 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.063 (s, 3H), 0.072 (s, 3H), 0.90 (m, 12H), 1.26 (m, 20H), 1.36 (s, 3H), 1.42 (s, 3H), 1.60−1.80 (m, 4H), 2.10 (m, 1H), 3.55 (m, 1H), 3.90 (m, 3H), 3.95 (m, 1H), 4.11 (ddd, J = 7.9, 6.1 Hz, 1H); EIMS *m*/*z* 469 (M − CH_3, 3.85), 427 (M − C_4H_9,17.67); HREIMS calcd for $C_{27}H_{53}O_4Si$ (M − CH_3) 469.3713, found 469.3709.

(2*R*,5*R*,1′*R*,1″*R*)-2-(1′-Hydroxy-3′-butynyl-5-[1″-(*tert*-butyldimethylsilyl)oxytridecyl)tetrahydrofuran (15). To a suspension of H_5IO_6 (318 mg, 1.39 mmol) in dry Et_2O (10 mL) was added a solution of **14** (450 mg, 0.928 mmol) in dry Et_2O (2 mL). After the mixture had been stirred for 1 day, it was filtered. The filtrate was washed with 5% $NaHCO_3$ and brine, dried, and concentrated to give the crude aldehyde. A solution of allenylboronic acid (165 mg, 2.11 mmol) prepared according Yamamoto's procedure[8] in dry toluene (6 mL) was placed in a 25 mL round-bottomed flask under N_2 atmosphere. D-(−)-DIPT (500 mg, 2.14 mmol) and freshly dried 4 Å MS (600 mg) were added. The mixture was allowed to stand for 24 h. Then, a solution of the obtained aldehyde in dry toluene (3 mL) was added dropwise at −78 °C. After the mixture was stirred at −78 °C for 1 day, 1 N HCl (3 mL, 3 mmol) was added. The mixture was stirred for 2 min, poured into brine (25 mL), and separated. The resulting aqueous phase was extracted with ether. The combined organic phases were washed with brine, dried, concentrated, and chromatographed to afford **15** (340 mg, 81%) and its isomer (18 mg, 4.3%, threo:erytheo = 18.8:1): $[\alpha]^{20}_D$ −10.3 (*c* 0.25, $CHCl_3$); IR (film) 3450, 3300, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.88 (t, J = 6.8 Hz, 3H), 0.90 (s, 9H), 1.26 (m, 20H), 1.60−1.98 (m, 6H), 2.01(t, J = 2.7 Hz, 1H), 2.41 (dd, J = 6.2, 2.7 Hz, 2H), 3.56 (m, 1H), 3.60 (dt, J = 6.2, 4.9 Hz, 1H), 3.90 (ddd, J = 6.1, 8.2 Hz, 1H), 3.99 (ddd, J = 5.8, 7.8 Hz, 1H); EIMS *m*/*z* 437 (M − CH_3), 413 (M − $CH_2C{\equiv}CH$), 395 (M − $C_4H_9{}^t$).

(2*R*,5*R*,1′*R*,1″*R*)-2-[1′-(*tert*-Butyldimethylsilyl)oxy-3′-butynyl]-5-[1″-(1″-(*tert*-butyldimethylsilyl)oxytridecyl]-tetrahydofuran (16). To a solution of **15** (480 mg, 1.06 mmol) in anhydrous DMF (2 mL) were added TBSCl (208 mg, 1.38 mmol) and imidazole (217 mg, 3.19 mmol) and the mixture stirred for 1 day at room temperature. The mixture was diluted with ether and then washed with brine, saturated NH_4Cl, and brine in order. Drying and evaporation of the solvent gave the crude product, which was chromatographed over silica gel to afford **16** (549 mg, 91%): $[\alpha]^{20}_D$ +4.73 (*c* 0.28, $CHCl_3$); IR (film) 3300, 2920, 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.12 (s, 3H), 0.89 (t, 3H), 0.90 (s, 6H), 0.91 (s, 6H), 0.92 (s, 6H), 1.28 (m, 20H), 1.60−1.95 (m, 6H), 1.95 (t, J = 2.6 Hz, 1H), 2.29 (ddd, J = 2.6, 6.2, 16.4 Hz, 1H), 2.56 (ddd, J = 2.6, 6.4, 16.4 Hz, 1H), 3.60 (m, 1H), 3.78 (m, 1H), 3.93 (m, 1H), 4.11 (m, 1H); EIMS *m*/*z* 479 (M − $2CH_3$ − Bu^t).

(2*R*,5*R*,1′*R*,1″*R*)-2-(1′-Hydroxy-3′-butynyl)-5-(1″-hydroxytridecyl)tetrahydofuran (17). To a mixture of **16** (110 mg, 0.194 mmol) in THF (1.3 mL) and MeCN (2.2 mL) was added 40% HF (160 μL). After the reaction mixture had been stirred for 10 h at room temperature, CH_2Cl_2 (6 mL) and brine (6 mL) were added. The separated aqueous phase was extracted with

CH_2Cl_2 (4 × 6 mL), and the combined organic phase was washed with brine, dried, concentrated. The residue was chromatographed to afford **17** (61 mg, 93%) as white needles: mp 83 °C; $[\alpha]^{21}_D$ 6.4 (*c* 0.84, $CHCl_3$); IR (film) 3420, 3310, 1467 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.25 (m, 22H), 1,74 (m, 2H), 2.01 (m, 2H), 2.44 (dd, J = 6.2, 2.1 Hz, 2H), 2.51 (s, 1H), 3.42 (m, 1H), 3.63 (dd, J = 5.9, 5.7 Hz, 1H), 3.83 (dd, J = 7.9, 6.5 Hz, 1H), 4.00 (m, 1H); EIMS *m*/*z* 339 (M + 1, 1.41), 321 (M + 1 − H_2O, 100.00), 303 (M + 1 − 2H_2O, 14.87).

(2*R*,5*R*,1′*R*,1″*R*)-2-(1′-Methoxymethoxy-3′-butynyl)-5-(1″-methoxymethoxytridecyl)tetrahydofuran (18). To a solution of **17** (40 mg, 0.118 mmol) in anhydrous CH_2Cl_2 (0.5 mL) were added *i*-Pr_2NEt (150 μL, 0.861 mmol) and MOMCl (60 μL, 0.790 mmol). The mixture was stirred at room temperature for 18 h and then concentrated. The residue was purified by silica gel chromatography to give **18** (47 mg, 93%) as a low-melting solid: mp 29−31 °C; $[\alpha]^{21}_D$ 23.0 (*c* 0.5, $CHCl_3$); IR (film) 3310, 2121, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.28 (m, 22H), 1,70 (m, 2H), 1.98 (m, 2H), 2.43 (m, 3H), 3.32 (s, 3H), 3.35 (s, 3H), 3.44 (m, 1H), 3.60 (m, 1H), 3.97 (m, 1H), 4.12 (m, 1H), 4.61 (d, J = 6.6 Hz, 1H), 4.75 (s, 2H), 4.82 (d, J = 6.7 Hz, 1H); EIMS *m*/*z* 365 (M^+ − MOM). Anal. Calcd for $C_{25}H_{46}O_5$: C, 70.38; H, 10.87. Found: C, 70.34; H, 11.09.

Ethyl ω-Bromooctanoate (20). Azelic acid monoethyl ester (80.0 g, 0.37 mol), red HgO (43.0 g, 0.20 mol), and dry CCl_4 (500 mL) were placed in a 1000 mL three-necked flask equipped with a 40 cm-long fractionation column. The mixture was heated to maintain the distillation rate of CCl_4 at 1 drop/s. A solution of anhydrous bromine (60.0 g, 0.38 mol) and CCl_4 (180 mL) was added dropwise over 2 h with stirring. Then, CCl_4 (120 mL) was added over another hour. The reaction mixture was cooled, and the solids were removed by filtration. The organic solution was successively washed with water (100 mL), 5% NaOH (100 mL), and water (100 mL), dried ($MgSO_4$), and concentrated. Fractional distillation afforded a pale-yellow oil **20** (66.5 g, 72%): bp 95−98 °C/100Pa; ^1H NMR (60 MHz, CCl_4) δ 1.32 (t, J = 6.8 Hz, 3H), 1.45 (m, 10H), 2.30 (t, J = 6.0 Hz, 2H), 3.43 (t, J = 6.0 Hz, 2H), 4.13 (q, J = 6.8 Hz, 2H).

Ethyl (10*S*)-10,11-*O*-Isopropylidene-8-undecenoate (21). The mixture of ethyl ω-bromooctanoate **20** (12.0 g, 47.8 mmol) and PPh_3 (12.5 g, 47.7 mmol) was stirred for 5 h at 130 °C. Then the oil bath was cooled to 70 °C, and dry ether (25 mL) was added. The mixture was refluxed for 1 h and cooled to room temperature, and the ether was decanted. After drying under vacuum, the residue (21.4 g) was dissolved in anhydrous THF (120 mL) and cooled to 0 °C. To the mixture was added *t*-BuOK (4.56 g, 40.68 mmol) portionwise under a N_2 atmosphere. The mixture was stirred for 0.5 h and cooled to −65 °C. Then, (2*R*)-2,3-*O*-isopropylideneglyceral (4.45 g, 34.52 mmol) in anhydrous THF (20 mL) was added, and the mixture was stirred for 1 h at −65 °C and 2 h at room temperature. The reaction was quenched with saturated NH_4Cl (70 mL), and the organic phase was separated. The aqueous phase was extracted with petroleum ether (30 mL × 3). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column (PE−EtOAc, 40:1 to 12:1) gave **21** as a colorless oil (5.94 g, 61%): $[\alpha]^{20}_D$ 4.58 (*c* 0.70, $CHCl_3$); IR (film) 3020, 1738, 1460 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.26 (m, 17H), 2.20 (m, 4H), 3.41 (m, 1H), 4.07 (m, 3H), 4.71 (m, 1H), 5.40 (m, 2H); EIMS *m*/*z* 284 (M^+), 269 (M^+ − CH_3, 2.72), 254 (M − 2CH_3). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.58; H, 10.27.

Ethyl (10*S*)-10,11-*O*-isopropylidene undecanoate (22). The mixture of **21** (5.94 g, 20.96 mmol) and 10% Pd−C (600 mg, 50% wet) in 95% EtOH (80 mL) was stirred at room temperature for 5 h under 1 atm of hydrogen. The catalyst was filtered, and the filtrate was concentrated. Chromatography on silica gel afforded **22** as a colorless oil (5.60 g, 94%): $[\alpha]^{20}_D$ 10.9 (*c* 0.14, $CHCl_3$); IR (film) 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 7.1 Hz, 3H), 1.30 (m, 12H), 1.35 (s, 3H), 1.40 (s, 3H), 1.61 (m, 2H), 2.28 (t, J = 7.5 Hz, 2H), 3.49 (t, J = 6.8 Hz, 1H), 4.03 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H); EIMS *m*/*z* 287 (M + 1, 20.86), 286 (M^+, 1.92), 271 (M^+ − CH_3, 100.00); HREIMS calcd for $C_{15}H_{27}O_4$ (M^+ − CH_3) 271.1909, found 271.1919.

Aldol Adduct (24). To a solution of *i*-Pr_2NH (3.1 mL, 22.12 mmol) in anhydrous THF (90 mL) was added *n*-BuLi (2.0M, 11 mL, 22 mmol) at −65 °C under N_2. After the mixture was stirred for 20 min, anhydrous HMPA (13 mL) was added, and the mixture was stirred for an additional 30 min. A solution of **22** (4.87 g, 17.09 mmol) in anhydrous THF (20 mL) was added, and the mixture was stirred for another 20 min. (2*S*)-*O*-Tetrahydropyranyl lactal (3.47 g, 21.96 mmol) in 20 mL of anhydrous THF was added dropwise, and the mixture was stirred for 4 h at −65 °C. Saturated NH_4Cl (130 mL) was added to quench the reaction, and the reaction mixture was warmed to room temperature. The organic phase was separated, and the aqueous phase was extracted with ether (40 mL × 3). The combined organic phases were washed with brine (40 mL × 3) and dried (Na_2SO_4). The solvent was removed, and the residue was purified by chromatography on silica gel to give **24** as a clear oil (mixture of diastereomers, 6.03 g, 80%): IR (film) 3450, 1730, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, only for characteristic peaks) δ 1.15 (t, J = 6.3 Hz, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.41 (d, J = 7.8 Hz, 3H), 2.54 (m, 1H), 3.49 (m, 2H), 3.76 (m, 1H), 3.86 (m, 2H), 4.03 (m, 2H), 4.16 (m, 2H), 4.62−4.67 (m, 1H); EIMS *m*/*z* 445 (M + 1, 1.47), 429 (M^+ − CH_3, 10.56), 411 (M^+ − CH_3 − H_2O, 1.73).

Saturated Lactone (25). To an ice-cooled solution of **24** (1.844 g, 4.15 mmol) in dry CH_2Cl_2 (15 mL) were added pyridine (0.7 mL, 8.68 mmol) and Ac_2O (0.8 mL, 8.5 mmol). After completion of the reaction, the mixture was washed successively with 1 N HCl, water, and brine. The separated organic phase was dried and concentrated. Chromatography on silica gel afforded a colorless oil (1.825 g, 90%). To an ice-cooled solution of the obtained acetyl ester (1.454 g, 2.99 mmol) in MeOH (6 mL) was added Amberlyst15 ion-exchange resin (270 mg, 3 mequiv) and the mixture stirred for 24 h at room temperature. The solution was concentrated and purified by flash column chromatography on silica gel to give **25** (0.6 g, 70%). The recovered mixture was treated in the same manner as just described and afforded second crop of **25** (312 mg, 15%, total 85%): IR (film) 3398, 1783, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39−1.61 (m, 17 H), 2.10 (s, 3H), 2.67 (m, 1H), 3.44 (m, 1H), 3.68 (m, 2H), 4.38−4.49 (m, 1H), 4.91 (m, $^2/_3$ H), 5.51 (m, $^1/_3$H); EIMS *m*/*z* 317 (M + 1, 33.22), 299 (M + 1 − H_2O, 75.47), 281 (M + 1 − 2H_2O, 22.90). Anal. Calcd for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92. Found: C, 60.70; H, 9.20.

Unsaturated Lactone (26). To a solution of **25 (**1.46 g, 4.62 mmol) in anhydrous THF (15 mL) was added DBU (0.39 mL, 2.61 mmol). The mixture was stirred at room temperature for 1 h and then neutralized with several drops of HOAc and concentrated. The residue was chromatographed on silica gel to give **26** as a low melting point solid (1.088 g, 92%): mp 47−48 °C; $[\alpha]^{18}_D$ 31.1 (*c* 0.65, $CHCl_3$); IR (film) 3502, 3309, 1737, 1654, 1471 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 1.30−1.55 (m, 15H), 2.20 (m, 2H), 3.39 (m, 1H), 3.54 (m, 2H), 5.04 (m, 1H), 7.29 (m, 1H); EIMS *m*/*z* 257 (M + 1, 5.89), 239 (M + 1 − H_2O, 40.86), 221 (M + 1 − 2H_2O, 16.62); HREIMS calcd for $C_{14}H_{22}O_3$ (M^+ − H_2O) 238.1563, found 238.1598.

(10*S*)-Epoxide (27). To a solution of **26** (210 mg, 0.82 mmol) in CH_2Cl_2 (2 mL) were added PPTs (2 mg, 0.008 mmol) and trimethyl orthoacetate (120 μL, 0.94 mmol). The mixture was stirred for 20 min and then concentrated and dried under high vacuum for 1 min to give an oil, which was dissolved in CH_2Cl_2 (1.5 mL). To the resulting solution was added AcBr (47 μL) and the mixture stirred for 50 min and then concentrated. The residue was dissolved in MeOH (3.0 mL) and treated with K_2CO_3 (148 mg, 1.07 mmol). After being stirred for 2 h, the mixture was quenched with saturated NH_4Cl and then extracted with CH_2Cl_2. The extract was dried ($NaSO_4$), concentrated, and purified by silica gel column chromatography to afford **27** (160 mg, 82%): $[\alpha]_D$ 26.0 (*c* 0.4, $CHCl_3$); IR (film) 1748, 1456 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 1.4 (m, 15H), 2.3 (m, 3H), 2.7 (m, 2H), 4.95 (m, 1H), 6.9 (m, 1H); EIMS *m*/*z* 239 (M + 1, 46.99), 221 (M + 1 − H_2O, 68.83); HREIMS calcd for $C_{14}H_{22}O_3$ 238.1563, found 238.1569.

Selective Protection of the Hydroxyl Group of 26 (28). To a mixture of **26** (200 mg, 0.78 mmol) in CH_2Cl_2 (4 mL), imidazole (160 mg, 2.35 mmol), and DMAP (28 mg) was added TBSCl (130 mg, 0.86 mmol) and the mixture stirred overnight. The mixture was diluted with ether and washed successively with saturated $NaHCO_3$, NH_4Cl, and brine. Drying ($MgSO_4$) and subsequent concentration gave crude **28**, which was purified by silica gel column chromatography to give **28** (230 mg, 80%) and recycled **26** (20 mg): $[\alpha]_D$ +25.8 (*c* 0.83, $CHCl_3$); IR (film) 3450, 1750, 1460 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.33 (m, 13H), 1.51 (m, 2H), 2.20 (t, J = 6.5 Hz, 2H), 3.41 (m, 1H), 3.51 (m, 2H), 5.03 (m, 1H), 7.29 (m, 1H); EIMS *m*/*z* 371 (M + 1, 10.74), 353 (M + 1 − H_2O, 100). Anal. Calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.33. Found: C, 64.67; H, 10.75.

(10*R*)-Epoxide (29). To a mixture of **28** (316 mg, 0.85 mmol) in CH_2Cl_2 (3 mL) and DMAP (20 mg) were added dropwise MsCl (90 μL, 1.16 mmol) and then pyridine (210 μL, 2.09 mmol). After the mixture was stirred for 1 day, brine was added (5 mL) to the mixture. The mixture was extracted with ether and washed with saturated NH_4Cl and brine. Drying ($MgSO_4$) and evaporation of the solvent gave an oil, which was dissolved in MeCN (2 mL) and treated with 40% aqueous HF (80 μL, 1.6 mmol) at 0 °C. After being stirred for 11 h at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with ether. The organic phase was washed with brine and dried over $MgSO_4$ and concentrated to give an oil (294 mg). Part of the oil (100 mg, 0.27 mmol) was dissolved in anhydrous THF and treated with 60% NaH (10 mg, 0.25 mmol). After stirred at room temperature for 10 h, the reaction mixture was extracted with ether and the extract was washed with water and brine. Drying ($MgSO_4$) and concentration gave an oil, which was purified by silica gel column chromatography to afford **29** (46 mg, overall 65%) as a colorless oil. $[\alpha]_D$ 25.3 (*c* 0.8, $CHCl_3$); IR (film) 1748, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32−1.52 (m, 15H), 2.24 (t, J = 7.3 Hz, 2H), 2.45 (dd, J = 5.0, 2.8 Hz, 1H), 2.72 (dd, J = 4.9, 4.0 Hz, 1H), 2.88 (m, 1H), 4.99 (m, 1H), 6.97(m, 1H); EIMS *m*/*z* 239 (M + 1, 62.78), 221(M + 1-H_2O, 100.00). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.25; H, 9.47.

Coupling of 18 with 27 (30). To a solution of **18** (170 mg, 0.389 mmol) in THF (2.5 mL) was added n-BuLi (2.5 M, 160 μL, 0.4 mmol) at −78 °C. After stirring for 20 min., $BF_3.OEt_2$ (50 uL, 0.407 mmol) was added to the mixture and stirred for a further 20 min. Then, a solution of **27** (60 mg, 0.25 mmol) in 1 mL of THF was added to the mixture. After the mixture had been stirred for 2 h, the reaction was quenched with saturated NH_4Cl and allowed to warm to room temperature. The organic layer was extracted with ether (2 × 4 mL), and the extract was washed with brine. Drying over $MgSO_4$ and evaporating the solvent gave an oil, which was chromatographed over silica gel to give **30** (106 mg, 63% or 76% on the recovery of **18**); 80 mg of **18** was recovered: $[\alpha]^{21}_D$ 23.3 (*c* 0.38, $CHCl_3$); IR (film) 3474, 1755, 1647, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 1.34 (m, 37H), 1.65 (m, 2H), 1.95 (m, 2H), 2.25 (t, J = 7.4 Hz, 2H), 2.35−2.49 (m, 4H), 3.38 (s, 3H), 3.40 (s, 3H), 3.45 (m, 1H), 3.62 (m, 2H), 4.00 (m, 1H), 4.12 (m, 1H), 4.65 (d, J = 6.9 Hz, 1H), 4.75 (m, 2H), 4.86 (d, J = 6.8 Hz, 1H), 4.98 (qd, J = 6.7, 1.6 Hz, 1H), 6.97 (d, J = 1.4 Hz, 1H); ESIMS *m*/*z* 688 (M + 1 + Na). Anal. Calcd for $C_{39}H_{68}O_8$: C, 70.44; H, 10.31. Found: C, 70.22; H, 10.51.

Coupling of 18 with 29 (31). In the same manner as just described, coupling of **18** (203 mg, 0.476 mmol) and **29** (76 mg, 0.319 mmol) afforded **31** (180 mg, 85%, or 92% on the recovery of **18**); 78 mg of **18** was recovered: $[\alpha]^{14}_D$ 17.3 (*c* 0.4, $CHCl_3$). IR (film) 3485, 1758, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.32 (m, 37H), 1.65 (m, 2H), 1.95 (m, 2H), 2.24 (m, 2H), 2.35−2.5 (m, 4H), 3.40 (s, 6H), 3.51 (m, 1H), 3.64 (m, 2H), 3.99 (m, 1H), 4.14 (m, 1H), 4.65 (d, J = 6.9 Hz, 1H), 4.75 (m, 2H), 4.89 (d, J = 6.8 Hz, 1H), 4.99 (qd, J = 6.9, 1.5 Hz, 1H), 6.98 (d, J = 1.4 Hz, 1H); ESIMS *m*/*z* 688 (M + 1 + Na). Anal. Calcd for $C_{39}H_{68}O_8$: C, 70.44; H, 10.31. Found: C, 70.63; H, 10.59.

Hydrogenation of 30 (32). A solution of **30** (84 mg, 0.126 mmol) in dry benzene (1 mL) was hydrogenated over $RhCl(PPh_3)_3$ (31 mg, 0.0335 mmol) for 10 h. Concentration and purification by silica gel chromatography afforded **32** (60 mg, 71%): $[\alpha]^{21}_D$ 52.0 (*c* 0.59, $CHCl_3$); IR (film) 3482, 1755, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.25−1.58 (m, 47H), 1.91 (m, 2H), 2.26 (t, J = 7.7 Hz, 2H), 3.39 (s, 6H), 3.46 (m, 2H), 3.57 (m, 1H), 3.97 (qd, J = 6.0, 1.4 Hz, 2H), 4.66 (d, J = 6.6 Hz, 2H), 4.84 (dd, J = 6.7, 3.3 Hz, 2H), 4.99 (qd, J = 6.8, 1.7 Hz, 1H), 6.98 (d, J = 1.5 Hz, 1H); ESIMS *m*/*z* 692 (M + 1 + Na).

Hydrogenation of 31 (33). In the same manner as just described, **31** (140 mg, 0.21 mmol) was hydrogenated over $RhCl(PPh_3)_3$ (47 mg, 0.051 mmol) to give **33** (81 mg, 58%): $[\alpha]_D$ 45.0 (*c* 0.72, $CHCl_3$); IR (film) 3467, 2928, 2856, 1758, 1652, 1151, 1033 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3) δ 0.87 (t, J = 6.6 Hz, 3H), 1.27 (m, 45H), 1.62 (m, 2H), 1.95 (m, 2H), 2.20 (t, J = 7.6 Hz, 2H), 3.28 (s, 3H), 3.30 (m, 1H), 3.32 (s, 3H), 3.44 (m, 2H), 3.55 (m, 1H), 3.92 (m, 1H), 4.70 (m, 4H), 5.03 (m, 1H), 7.28 (m, 1H); ESIMS *m*/*z* 692 (M + 1 + Na).

(10*S*)-Corossolin ((10*S*)-1). BF_3·OEt_2 (0.25 mL, 2 mmol) was added dropwise to a solution of **32** (35 mg, 0.0523 mmol) in dimethyl sulfide (1.75 mL) at 0 °C. The mixture was stirred for 30 min, quenched with saturated $NaHCO_3$, and then diluted with AcOEt. The mixture was washed with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by silica gel chromatography to afford a wax solid (10*S*)-**1** (26 mg, 86%): mp 56−57 °C; $[\alpha]_D$ 24.6 (*c* 0.26, MeOH); IR (KBr) 3375, 1741, 1469 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 1.26−1.56 (m, 45H), 1.68 (m, 2H), 1.96 (brm, −OH), 1.99 (m, 2H), 2.27 (t, J = 7.3 Hz, 2H), 3.40 (m, 2H), 3.59 (m, 1H), 3.80 (dd, J = 6.6, 6.2 Hz, 2H), 4.99 (qd, J = 6.1, 1.7 Hz, 1H), 6.98 (d, J = 1.3 HZ, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.817, 148.837, 134.298, 82.678, 82.612, 77.359, 74.022, 73.854, 71.739, 37.482, 37.350, 33.523, 33.327, 31.899, 29.696−29.228 (13-C), 29.082, 28.738, 27.384, 25.577, 25.153, 22.658, 19.197, 14.075; EIMS *m*/*z* 581 (M + 1, 4.74), 563 (M + 1 − H_2O, 6.6), 545 (M + 1 − 2H_2O, 25.33), 527 (M + 1 − 3H_2O, 97.90); HREIMS calcd for $C_{35}H_{62}O_5$ (M − H_2O) 562.4581, found 562.4588; ESI MS *m*/*z* 604 (M + 1 + Na), 1185 (2M + 2 + Na).

(10*R*)-Corossolin ((10*R*)-1). In the same manner as just described above, deprotection of **33** (13 mg, 0.019 mmol) afforded (10*R*)-**1** (7 mg, 62%): mp 53−54 °C; $[\alpha]^{21}_D$ 19.1 (*c* 0.35, MeOH); IR (KBr) 3400, 3209, 1757, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.33 (m, 47H), 1.58 (m, 2H), 1.99 (m, 2H), 2.25 (t, J = 7.6 Hz, 2H), 3.40 (m, 2H), 3.60 (m, 1H), 3.79 (m, 2H), 4.99 (qd, J = 6.3, 1.4 Hz, 1H), 6.98 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.852, 148.884, 134.323, 82.616 (2-C), 77.395, 74.099 (2-C), 71.897, 37.486, 37.409, 35.564 (2-C), 31.914, 29.639−29.104 (13-C), 28.834 (2-C), 27.411, 25.603, 25.172, 22.673, 19.227, 14.090; ESIMS *m*/*z* 581 (M + 1), 604 (M + 1+Na); HRFABMS calcd for $C_{35}H_{64}O_6$-Na 603.4595, found 603.4545.

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Supporting Information Available: ^1H NMR spectra of **18**, **29**, (10*S*)-**1** and (10*R*)-**1**. ^{13}C NMR spectra of **18**, **29**, (10*S*)-**1**(**34**), and (10*R*)-**1**(**35**). This material is available free of charge via the Internet at http://pubs.acs.org.

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