Mimicry of Annonaceous Acetogenins: Enantioselective Synthesis of a (4*R*)-Hydroxy Analogue Having Potent Antitumor Activity

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The (4*R*)-hydroxylated analogues of annonaceous acetogenin mimicking compound **2** were designed and synthesized structurally on the basis of the naturally occurring annonaceous acetogenin bullatacin, which was discovered as a typical member of the novel family of polyketides with potent cytotoxicity, antitumoral, and other biological activities. The preliminary screenings show that the IC_{50} values of **2** were 1.6×10^{-3} and 8×10^{-2} μg/mL against HT-29 and HCT-8, respectively. A remarkable enhancement effect was observed by the activity comparison of **1c** and its (4*R*)-hydroxylated analogue **2**.

Introduction

Annonaceous acetogenins, isolated from the *Annonaceae* plants, have been attracting worldwide attention in recent years due to their biological activities, especially as growth inhibitors of certain tumor cells.[1] They have been shown to function by blocking complex I in mitochondria[2] as well as ubiquinone-linked NADPH oxidase in the cells of specific tumor cell lines, including some multidrug-resistant ones.[3] These features make these acetogenins excellent leads for the new antitumor agents. In a previous work by us, the compounds **1a**−**1d** (Figure 1), which rely on structure simplification while maintaining all essential functionalities of the acetogenins, were in vitro tested against several human solid tumor cell lines and showed interesting cell line selectivity. All four analogues show remarkable activity against the HCT-8 and HT-29 cell lines, while compound **1c** was found to be the best.[4] To investigate the effect of the 4-hydroxyl group, which was commonly observed in many of these naturally occurring acetogenins, we designed compound **2** as the target for investigation (Figure 1). Structurally, it combines both the advantages of bullatacin, one of the most potent naturally occurring acetogenins, and our previous results[4] on the study of annonaceous acetogenin mimicry.

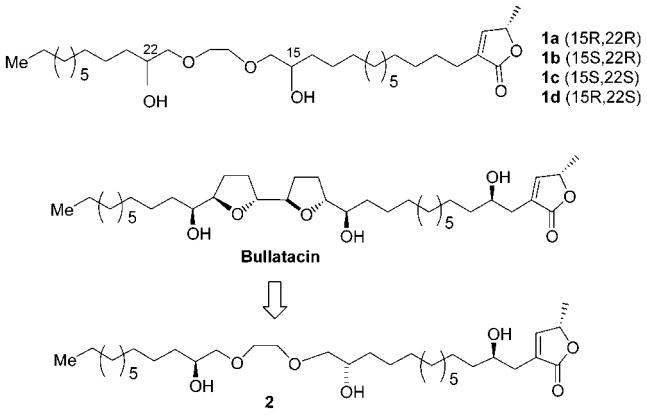

Figure 1.

Chemical Synthesis

The retrosynthetic strategy of **2** is illustrated in Figure 2. A two-directional *C*-alkylation of 1,7-octadiyne **4** with epoxides **3** and **5** was designed as the key step to construct the molecule skeleton.

The synthesis of the key intermediate **3** is shown in Scheme 1. It starts from the readily available chiral aldehyde **9**, which was easily prepared from D-mannitol on a large scale.[5] The extension of the hydrocarbon chain was achieved by Witting reaction of **9** to give **16** in 90% yield,[6] which was further hydrogenated over 10% Pd−C and afforded **17** in 95% yield. Acid-catalyzed deprotection of **17** was achieved in 93% yield with 10% HCl. The resultant diol **8** was regioselectively *O*-alkylated with 2-benzyloxyethyl iodide through a cyclic stannate and gave **18** in 81% yield.[7] The remaining hydroxyl group was masked as the MOM ether **19** (96% yield) first, and then the terminal benzyl protecting group was removed by

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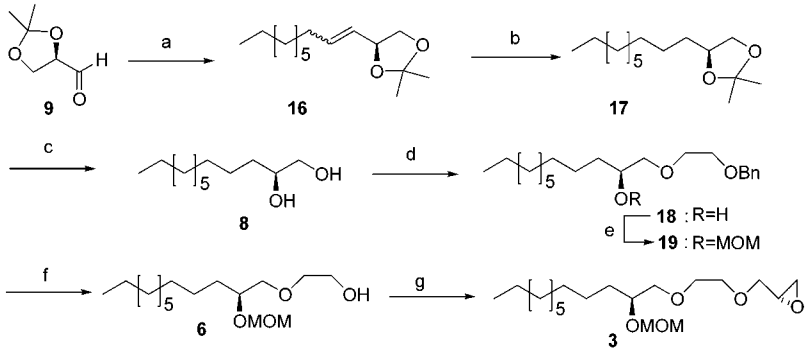
Scheme 1[a]



[a] Reagents and conditions: (a) $C_8H_{17}CH{=}PPh_3$, 90%; (b)10% Pd−C, H_2, CH_3OH, 95%; (c) 10% HCl, CH_3OH, 93%; (d) (i) Bu_2SnO, CH_3OH/$CHCl_3$ (1:10); (ii) CsF, DMF, ICH_2CH_2OBn, 25 °C, two steps, 81%; (e) *i*-Pr_2NEt, MOMCl, CH_2Cl_2, 96%; (f) Na, NH_3(l), 92%; (g) NaOH, H_2O, Bu_4NHSO_4, (*R*)-epichlorohydrin, 88%.

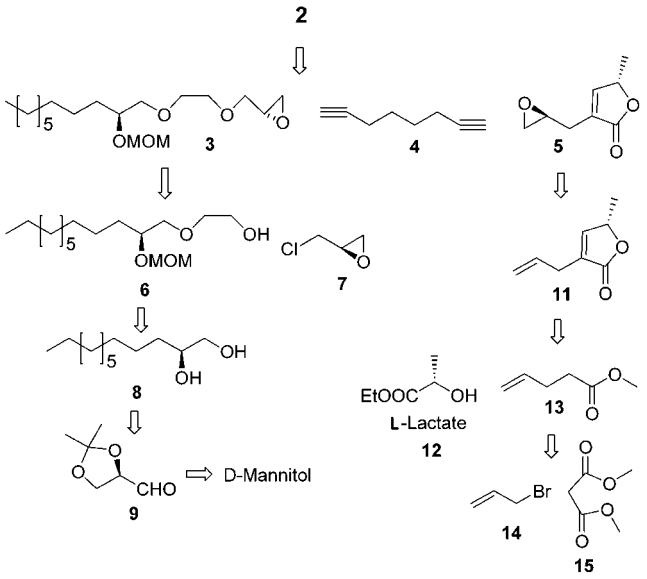
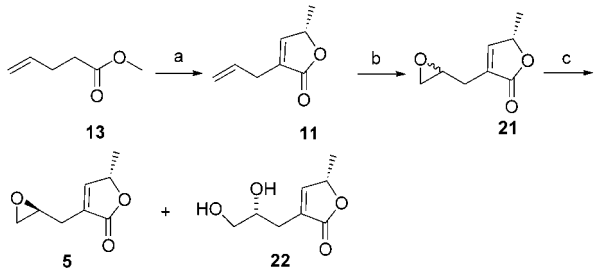


Figure 2.

reductive cleavage to afford **6** in 92% yield. The coupling reaction of the alcohol **6** with (*R*)-(−)-epichlorohydrin **7** furnished the key intermediate **3** in 88% yield in the presence of a phase-transfer catalyst.[8]

The other key intermediate (**5**) was synthesized as in Scheme 2. Compound **13** can be easily prepared from malonate and allyl bromide.[9] Subsequent introduction of the butenolide unit to **11** involved a three-step sequence: (i) aldol reaction of **13** with (*S*)-*O*-tetrahydropyranyl lactal, (ii) acid-catalyzed THP cleavage and in situ lactonization, and (iii) *β*-elimination of hydroxyl in the presence of $(CF_3CO)_2O$ and Et_3N.[10] Regioselective epoxidation of **11** was achieved by treatment with MCPBA to give **21** in 86% yield. To resolve the terminal epoxides, Jacobsen's hydrolytic kinetic resolution[11] was

Scheme 2[a]



[a] Reagents and conditions: (a) (i) LDA, THF−HMPA, (*S*)-*O*-tetrahydropyranyl lactal, −78 °C; (ii) 10% H_2SO_4, THF, rt; (iii) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 60%; (b) *m*-CPBA, CH_2Cl_2, 0 °C, 86% yield based on 31% recovery of **11**; (c) (*S*,*S*)-Salen-Co(OAc), H_2O, 43%.

applied. The reaction was performed in the presence of (*S*,*S*)-Salen-Co(OAc) complex (0.5 mol %) and H_2O (0.55 equiv) to yield **5** (43%) and diol **22** (50%, 70% de) at 4 °C. The de value (>99%) of **5** was measured by HPLC using **21** as the reference.

With both intermediates in hand, a stepwise two-directional *C*-alkylation of 1,7-octadiyne was performed to construct the skeleton of **2**. At first, the mono-lithiated derivative of 1,7-octadiyne was reacted with epoxide **3** in the presence of $BF_3{\cdot}Et_2O$ to afford **23** in 80% yield, and then the produced hydroxyl was protected as the MOM ether **24** in 96% yield. **24** was treated with *n*-BuLi again and then reacted with epoxide **5** as above to give **25** in 69% yield.[12] The triple C−C bonds of **25** were reduced by diimide. Deprotection of the MOM ethers in **25** with $BF_3{\cdot}Et_2O$ in Me_2S afforded the target **2** in 72% yield.[13] (Scheme 3).

Biological Evaluation

The preliminary testing (Table 1) of the compound **2** in vitro against the HT-29 cell line shows that it exhibits better activity than adriamycin and **1c**. It is also found that the activities greatly increase (up to 15 times more potent) by the introduction of the (4*R*)-hydroxyl in **1c**.

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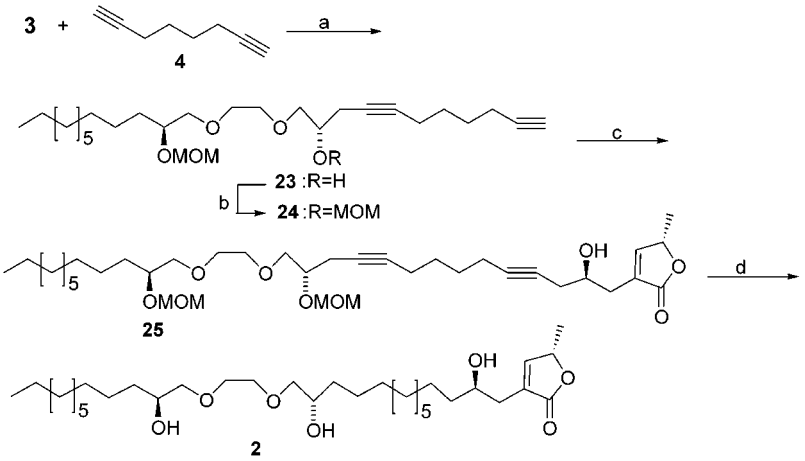
Scheme 3[a]



[a] Reagents and conditions: (a) *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 80%; (b) *i*-Pr_2NEt, MOMCl, CH_2Cl_2, 96%; (c) *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, 5, −78 °C, 69%; (d) (i) $TsNHNH_2$, NaOAc, DME, reflux; (ii) $BF_3{\cdot}Et_2O$, Me_2S, 0 °C, 72%.

Table 1. Cytotoxicity Data of 1c, 2, and Adriamycin

	IC_{50} (μg/mL)			
sample	HT-29	HCT-8	KB	HELF
1c	2.4×10^{-2} (15)			
2	1.6×10^{-3} (1)	8.0×10^{-2}	>10	>10
adriamycin	6.0×10^{-2} (37.5)	3.6×10^{-2}	7.6×10^{-2}	1.92

This obviously indicates that (4*R*)-hydroxyl is an important group that contributes activity against tumor cell lines. Additionally, compound **2** shows better selectivity among the various tumor cells.

Conclusion

In summary, (4*R*)-hydroxylated analogue **2** structurally based on annonaceous acetogenin mimic **1c** was synthesized enantioselectively. The preliminary screenings show that the introduction of the (4*R*)-hydroxyl group greatly enhanced the cytotoxicity against HCT-8 and HT-29 compared with those of **1c**. These results open a potential way to find more active antitumor agents with a simplified structure based on natural annonaceous acetogenins. The described procedure also could be expanded to synthesize the annonaceous acetogenins with a (4*R*)-hydroxylated butenolide unit in high yield and excellent enantiomeric purity. It has the advantages of starting from readily available chemical substrates and inexpensive reagents as well.

Experimental Section

General Methods. Optical rotations were measured at rt. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded at 300, 400, and 600 MHz and are reported in parts per million (δ) downfield relative to TMS as internal standard, and ^{13}C NMR spectra were recorded at 100 and 150 MHz and are reported in parts per million (δ). Flash column chromatography was performed on silica gel (10−40 μm) using a mixture of petroleum ether and ethyl acetate as the eluent.

(4*S*)-Dec-1-enyl-2,2-dimethyl[1,3]dioxolane (16). The stirred mixture of 1-bromononane (10.4 g, 50.2 mmol) and Ph_3P (13.2 g, 50.2 mmol) was heated at 140 °C under N_2. After 3 h, the reaction was cooled, and dry THF (100 mL) was added to dissolve the syrup. A solution of *n*-BuLi in hexanes (1.6 M, 31.4 mL, 50.2 mmol) was then added under a N_2 atmosphere at 0 °C. The reaction was stirred for 15 min at 0 °C, and then (*R*)-glyceraldehyde acetonide (6.53 g, 50.2 mmol) in dry THF (30 mL) was added. The reaction mixture was warmed to rt slowly and stirred overnight. Petroleum ether (200 mL) and aqueous saturated NH_4Cl (20 mL) were added at rt, and the aqueous phase was extracted with petroleum ether. The combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography to give **16** as an oil (10.9 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): 5.63 (1H, m), 5.40 (1H, t, J = 9.8 Hz), 4.84 (1H, q, J = 7.8 Hz), 4.05 (2H, m), 2.06−2.17 (2H, m), 1.40 (3H, s), 1.38 (3H, s), 1.40−1.27 (12H, m), 0.88 (3H, t, J = 6.9 Hz) ppm. MS (EI, *m*/*z*): 240 (M^+). Anal. Calcd for $C_{15}H_{26}O_2$: C, 74.95; H, 11.74. Found: C, 74.96; H, 12.00.

(4*S*)-Decyl-2,2-dimethyl[1,3]dioxolane (17). A mixture of **16** (10.9 g, 45.4 mmol), CH_3OH (100 mL), and Pd−C (10%, 0.2 g) was stirred vigorously under a H_2 atmosphere until hydrogen could not be absorbed. The mixture was filtrated and concentrated. Flash chromatography of the crude product afforded **17** as an oil (10.44 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): 4.04 (2H, m), 3.49 (1H, t, J = 7.0 Hz), 1.40 (3H, s), 1.38 (3H, s), 1.20−2.20 (18H, m), 0.88(3H, t, J = 7.1 Hz) ppm. $[\alpha]_D^{25}$ = +15.2 (*c* 1.18, $CHCl_3$).

(2*S*)-Dodecane-1,2-diol (8). To a stirred solution of compound **17** (10.44 g, 43.1 mmol) in CH_3OH (100 mL) was added 10% HCl (10 mL). The reaction was stirred overnight at rt. Methanol was removed under reduced pressure, and aqueous saturated $NaHCO_3$ was added until a pH of 7 was reached. The mixture was extracted with ethyl acetate (3 × 30 mL), dried over sodium sulfate, and concentrated. Recrytallization of the crude product with ethyl acetate afforded **8** as a white solid (8.10 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): 3.69 (1H, m), 3.65 (1H, t, J = 3.0 Hz), 3.43 (1H, m), 1.26−1.88 (18H, m), 0.88 (3H, t, J = 6.6 Hz) ppm (two protons of hydroxyls were not observed). IR (neat): 3316, 2920, 2851, 1470, 1438 cm^{-1}. MS (EI, *m*/*z*): 206 (M^+). $[\alpha]_D^{25}$ = +9.36 (*c* 1.1, CH_3OH). Anal. Calcd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95. Found: C, 70.97; H, 12.90.

(2*S*)-1-(2-Benzyloxyethoxy)dodecan-2-ol (18). A stirred mixture of compound **8** (1.01 g, 5 mmol), Bu_2SnO (1.25 g, 5 mmol), and $CHCl_3/CH_3OH$ (10:1, 20 mL) was refluxed until the solution turned clear. The solvent was removed under reduced pressure, and the residue was dried in vaccum for 6 h. To the residue were added DMF (30 mL) and CsF (0.911 g, 6 mmol), followed by ICH_2CH_2OBn (1.97 g, 7.50 mmol) in DMF (7 mL). The reaction was stirred for 18 h at 50 °C. The solvent was removed under reduced pressure, and the residue was treated with saturated brine and stirred for 0.5 h. The mixture was extracted with ethyl acetate (3 × 10 mL). The organic phase was washed with saturated NH_4Cl and saturated brine, dried over sodium sulfate, and concentrated. Flash chromatography of the residue afforded **18** as an oil (1.36 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.34 (5H, m), 4.57 (2H, s), 3.79

(1H,m), 3.61−3.72 (4H, m), 3.52 (1H, q, J = 7.2,1.2 Hz), 3.31-(1H, t, J = 8.1 Hz), 2.70 (1H, br s), 1.79 (2H, m), 1.26−1.45 (16H, m,), 0.88 (3H, t, J = 7.2 Hz) ppm. IR (neat): 3426, 3028, 1100, 702 cm^{-1}. MS (EI, m/z): 337 ($M^+ + 1$). $[\alpha]_D^{25} = +4.08$ (c 10.6, $CHCl_3$).

[2-(2*S*)-Methoxymethoxydodecyloxy)ethoxymethyl]-benzene (19). To a solution of compound **18** (3.50 g, 10.4 mmol) in CH_2Cl_2 (60 mL) were added *i*-Pr_2NEt (6.68 mL, 38.3 mmol) and MOMCl (2.9 mL, 38.3 mmol) at 0 °C. The reaction was stirred overnight at rt and quenched with aqueous NH_4-Cl (20 mL). The mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over sodium sulfate, and concentrated. Flash chromatography of the crude product afforded **19** as a yellow liquid (3.80 g, yield 96%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.32 (5H, m), 4.70 (2H, dd, J = 6.8 Hz), 4.55 (2H, s), 3.69 (1H,m), 3.62−3.75 (4H, m), 3.66 (3H, s), 3.50 (2H, d, J = 5.0 Hz), 1.22−1.52 (18H, m,), 0.87 (3H, t, J = 7.1 Hz) ppm. IR (neat): 2922, 1448, 1108, 1042 cm^{-1}. MS (EI, m/z): 350 ($MH^+ - OCH_3$). $[\alpha]_D^{25} = -13.7$ (c 6.06, $CHCl_3$).

2-[(2*S*)-Methoxymethoxydodecyloxy]ethanol (6). To liquid ammonia (100 mL) was added Na (0.60 g, 26.1 mmol) slowly at −78 °C. The mixture was stirred until the disappearance of Na metal. Compound **19** (1.57 g, 4.13 mmol) in THF (40 mL) was then added, and the reaction was stirred for 3 h. The reaction was quenched by slow addition of aqueous NH_4Cl (20 mL) and warmed to rt. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After concentration and flash chromatography, compound **6** was obtained as a yellow liquid (1.10 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): 4.72 (2H, dd, J = 6.8 Hz), 3.72 (3H, m), 3.58 (2H, q, J = 5.0, 3.5 Hz), 3.51(2H, d, J = 4.9 Hz), 3.39 (3H, s), 2.21 (1H, br s), 1.50 (2H, t, J = 6.6 Hz), 1.25 (16H, m,), 0.87 (3H, t, J = 6.6 Hz) ppm. IR (neat): 3453, 2926, 2856, 1467, 1215, 1042, 919 cm^{-1}. MS (EI, m/z): 273 ($MH^+ - H_2O$). $[\alpha]_D^{25} = +9.8$ (c 6.3, $CHCl_3$). Anal. Calcd for $C_{16}H_{34}O_4$: C, 66.04; H, 11.80. Found: C, 66.02; H, 11.93.

(2*S*)-[2-((2*S*)-Methoxymethoxydodecyloxy)ethoxymethyl]oxirane (3). To (*R*)-(−)-epichlorohydrin (0.36 g, 3.89 mmol) were added compound **6** (0.67 g, 2.31 mmol), 50% NaOH aqueous solution (2 mL), and tetrabutylammonium hydrogen sulfate (0.067 g) successively at rt. The resulting suspension was stirred for 24 h at rt. The solution was diluted with 20 mL of ether, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (3 × 15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue afforded **3** as a colorless liquid (0.70 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.77 (1H, d, J = 6.7 Hz), 4.67 (1H, d, J = 6.7 Hz), 3.40−3.83 (9H, m), 3.39 (3H, s), 3.17 (1H, m), 2.80 (1H, m), 2.62 (1H, m), 1.51 (2H, t, J = 6.3 Hz), 1.26 (16H, br s), 0.88 (3H, t, J = 6.6 Hz) ppm. IR (film): 2926, 2856, 1467, 1143, 1108, 1041, 918 cm^{-1}. MS (ESI, m/z): 364 ($M^+ + H_2O$). Anal. Calcd for $C_{19}H_{38}O_5$: C, 65.90; H, 10.98. Found: C, 66.18; H, 10.50. $[\alpha]_D^{25} = -8.1$ (c 1.14, $CHCl_3$).

Pent-4-enoic Acid Methyl Ester (13). This compound was prepared as in the literature.[9] ^{1}H NMR (90 MHz, CCl_4): 5.80 (1H, m), 5.03 (2H, m), 3.75 (3H, s), 2.26−2.42 (4H, m) ppm. IR (film): 2950, 1750, 1650, 1440, 1170 cm^{-1}.

(5*S*)-3-Allyl-5-methyl-5H-furan-2-one (11). To a solution of diisopropylamine (7.1 mL, 0.051mol) in anhydrous THF (100 mL) was added *n*-BuLi (21.1 mL, 1.6 M in hexane, 0.034 mol) at 0 °C, and the mixture was stirred for 30 min. After the mixture was stirred for an additional 30 min at −78 °C, anhydrous HMPA (11.3 mL, 0.065 mol) was added, and the mixture was stirred for 30 min. A solution of **13** (3.85 g, 0.034 mol) in THF (20 mL) was injected into the above mixture. After 30 min, a solution of *O*-THP-(*S*)-lactal (6.45 g, 0.041 mol) in THF (30 mL) was introduced, and the reaction mixture was stirred for 2 h at −78 °C. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvents afforded a crude oil, which was treated with 10% H_2SO_4 (30 mL) in THF (100 mL) for 18 h at rt. The reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated to give a crude oil. To the mixture of the above oil and Et_3N (18 mL, 0.128 mol) in CH_2Cl_2 (40 mL) at 0 °C was added $(CF_3CO)_2O$ (9 mL, 0.064 mmol). The reaction was stirred at 0 °C for 12 h and at rt for 6 h, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2. After being dried (Na_2SO_4), the extracts were filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford pure **11** (2.80 g, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.06 (1H, dd, J = 3.0, 1.5 Hz), 5.89 (1H, m), 5.19 (1H, ddt, J = 1.4, 2.9, 8 Hz), 5.15 (1H, dd, J = 1.3 Hz), 5.02 (1H, m), 3.04 (2H, ddd, J = 1.5, 3.1, 8.2 Hz), 1.43 (3H, dd, J = 1.6, 6.6 Hz) ppm. IR (neat): 3084, 2983, 2935, 1755, 1643, 1321, 1199, 1118, 1072, 1027, 919, 863, 675 cm^{-1}. MS (EI, m/z): 139 ($M^+ + 1$). $[\alpha]_D^{25} = +47.2$ (c 3.56, $CHCl_3$). HRMS (EI, m/z): calcd for $C_8H_{10}O_2$ [M^+] 138.0681, found 138.0689.

(5*S*)-Methyl-3-oxiranylmethyl-5H-furan-2-one (21). To a 25 mL flask were added **11** (0.26 g, 1.88 mmol), dry CH_2Cl_2 (5 mL), and MCPBA (0.295 g, 1.88 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under a N_2 atmosphere. The reaction mixture was stirred at rt for 12 h. Excess MCPBA was removed by the addition of aqueous sodium thiosulfate. The mixture was transferred to a separating funnel. The organic layer was diluted with CH_2Cl_2 (20 mL), washed successively with saturated $NaHCO_3$ and saturated brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel to give a yellow liquid (**21**) (0.18 g, 86%) along with recovered **11** (0.08 g). ^{1}H NMR (300 MHz, $CDCl_3$): 7.26 (1H, dd, J = 1.5, 3 Hz), 5.05 (1H, dq, J = 1.3, 5.6 Hz), 3.15 (1H, m), 2.82 (1H, dd, J = 4.4 Hz), 2.66 (1H, m), 2.56 (1H, dd, J = 2.6, 4.8 Hz), 2.41 (1H, m), 1.43 (3H, dd, J = 1.7, 6.8 Hz) ppm. IR (neat): 2950, 2861, 1718, 1648, 1199 cm^{-1}. MS (EI, m/z): 155 ($M^+ + 1$). $[\alpha]_D^{25} = +42.6$ (c 0.703, $CHCl_3$). HRMS (EI, m/z): calcd for $C_8H_{10}O_3$ [M^+] 154.0630, found 154.0617.

(5*S*)-Methyl-3-[(2*S*)-oxiranylmethyl]-5*H*-furan-2-one (5) and (5*S*)-3-[(2*R*)-2,3-Dihydroxypropyl]-5-methyl-5*H*-furan-2-one (22). The mixture of compound **21** (0.182 g, 1.18 mmol) and (*S*,*S*)-Salen-Co^{III}(OAc) (3.92 mg, 0.0059 mmol, 0.5 mol %) was stirred at 4 °C, and water (11.68 μL, 0.649 mmol, 0.55 equiv) was slowly added by using a syringe over 1 h. After addition, stirring was continued at 4 °C for 24 h. Flash chromatography of the mixture afforded **5** as a yellow oil (78 mg, 43%) and diol **22** (100 mg, 50%). The following are the data for **5**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.26 (1H, dd, J = 1.3, 3 Hz), 5.06 (1H, dq, J = 1.6, 3.5 Hz), 3.17 (1H, m), 2.83 (1H, dd, J = 4.2 Hz), 2.66 (1H, m), 2.57 (1H, dd, J = 2.5, 4.7 Hz), 2.42 (1H, m), 1.44 (3H, dd, J = 1.7, 6.7 Hz) ppm. IR (neat): 2950, 2861, 1718, 1648, 1199, 1151, 737, 698 cm^{-1}. MS (EI, m/z): 155 ($M^+ + 1$). $[\alpha]_D^{25} = -2.1$ (c 1.95, $CHCl_3$). HPLC: >99% de (a Chiracel AS column; UV detector 214 nm; eluent *i*-PrOH/hexane (2:8); flow rate 0.7 mL/min). The following are the data for **22**. ^{1}H NMR (300 MHz, $CDCl_3$): 7.23 (1H, d, J = 1.1 Hz), 5.10 (1H, m), 3.93 (1H, m), 3.66 (1H, dd, J = 11.3, 3.3 Hz), 3.52 (1H, dd, J = 6, 11.3 Hz), 3.20 (1H, br s), 2.51 (2H, m), 1.77(1H, br s), 1.45 (3H, d, J = 6.9 Hz) ppm. IR (neat): 3401, 2983, 2935, 1741, 1323, 1207, 1104, 1085, 1028 cm^{-1}. MS (EI, m/z): 173 ($M^+ + 1$). HRMS (EI, m/z): calcd for $C_8H_{10}O_3$ [$M^+ - H_2O$] 154.0630, found 154.0613.

Compound 23. To a solution of 1,7-octadiyne **4** (1.53 g, 14.43 mmol) in THF (10 mL) was added *n*-butylithium in hexane (2.0 M, 7.2 mL, 14.39 mmol) at −78 °C under a nitrogen atmosphere. After the resulting solution was stirred for 10 min, boron trifluoride etherate (1.824 mL, 14.39 mmol) was added, and stirring was continued for 30 min at −78 °C. Then a solution of **3** (1.66 g, 4.80 mmol) in THF (12 mL) was added, and the resulting solution was stirred for 3 h at −78 °C. The reaction was quenched by addition of aqueous NH_4-Cl. The whole mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography of the residue afforded **23** as a yellow liquid (1.728 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): 4.79 (1H, d, J = 6.9 Hz), 4.67 (1H, d, J = 6.9 Hz), 3.89 (1H, m), 3.40−3.76 (9H, m), 3.33 (3H, s), 2.69 (1H, m),

2.39 (2H, m), 2.21−2.19 (4H, m), 1.96 (1H, m), 1.43−1.83 (22H, m), 0.88 (3H, t, J = 6.6 Hz) ppm. IR (neat): 3462, 3313, 2926, 2856, 1465, 1144, 1106, 1040, 919 cm^{-1}. MS (ESI, *m*/*z*): 470 ($M^+ + H_2O$). $[\alpha]_D^{25} = +6.25$ (*c* 0.52, $CHCl_3$).

Compound 24. To a solution of compound **23** (0.53 g, 1.17 mmol) and *i*-Pr_2NEt (2.35 mL, 13.5 mmol) in dry CH_2Cl_2 (20 mL) was added MOMCl (1.016 mL, 13.5 mmol) slowly at 0 °C. The reaction was stirred overnight at rt and quenched with aqueous saturated NH_4Cl (3 mL). The mixture was extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with saturated brine, dried over sodium sulfate, and concentrated. Flash chromatography of the residue afforded **24** as a yellow liquid (0.56 g, 97%). ^1H NMR (300 MHz, $CDCl_3$): 4.65−4.88 (4H, m), 3.84 (1H, m), 3.56−3.72 (10H, m), 3.50−3.54 (6H, m), 2.45 (2H, m), 2.20 (4H, m), 1.96 (1H, m), 1.26−1.69 (22H, m), 0.88 (3H, t, J = 6.7 Hz) ppm. IR (film): 3316, 2927, 2857, 1466, 1151, 1107, 1041, 919 cm^{-1}. MS (ESI, *m*/*z*): 519 (M^+ + Na). $[\alpha]_D^{25} = -1.8$ (*c* 1.83, $CHCl_3$). Anal. Calcd for $C_{29}H_{52}O_6$: C, 70.12; H, 10.55. Found: C, 70.08; H, 10.52.

Compound 25. To a solution of **24** (374 mg, 0.75 mmol) in THF (3 mL) was added *n*-butyllithium in hexanes (1.6 M, 0.47 mL, 0.75 mmol) at −78 °C under a nitrogen atmosphere, and the resulting solution was stirred for 30 min. Boron trifluoride etherate (0.095 mL, 0.75 mmol) was then added, and stirring was continued for 15 min at −78 °C, after which a solution of **5** (58 mg, 0.38 mmol) in THF (2 mL) was added. After being stirred for 2 h at −78 °C, the reaction was quenched by addition of aqueous NH_4Cl (1.0 mL). The whole mixture was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography of the residue afforded **25** as an oil (168 mg, 69%). ^1H NMR (600 MHz, $CDCl_3$): 7.24 (1H, d, J = 1.4 Hz), 5.06 (1H, q, J = 3.3 Hz), 4.76 (1H, d, J = 7.2 Hz), 4.73 (2H, br s), 4.66 (1H, d,J = 6.6 Hz), 3.98 (1H, m), 3.83 (1H, m), 3.61−3.71 (7H, m) 3.51 (2H, m), 3.36−3.39 (6H, m) 2.60 (1H, m), 2.35−2.53 (5H,m), 2.18−2.20 (4H, m), 1.57−1.60 (4H, m), 1.52 (2H, m), 1.43 (3H, d, J = 6.6 Hz), 1.26−1.41 (16H, m), 0.88 (3H, t, J = 7.2 Hz) ppm. ^{13}C NMR (600 MHz, $CDCl_3$): 174.3, 152.0, 130.7, 96.1, 95.9, 83.2, 81.4, 80.0, 76.6, 76.3, 75.8, 74.9, 74.2, 72.9, 70.9, 70.7, 55.5, 32.1, 31.9, 29.8, 29.6, 29.3, 28.1, 28.0, 27.6, 25.5, 22.7, 22.2, 19.1, 18.3, 14.1 ppm. IR (neat): 3463, 2927, 2856, 1757, 1320, 1151, 1104, 1040, 919 cm^{-1}. MS (ESI, *m*/*z*): 668 ($M^+ + H_2O$), 673 (M^+ + Na). $[\alpha]_D^{25} = +0.1$ (*c* 1.61, $CHCl_3$). Anal. Calcd for $C_{37}H_{62}O_9$: C, 68.28; H, 9.60. Found: C, 68.23; H, 9.41.

3-{(2*R*,13*S*)-2,13-Dihydroxy-14-[2-(2*S*)-hydroxydodecyloxy]ethoxy}tetradecyl}-5-methyl-5*H*-furan-2-one (2). To a stirred solution of **25** (74 mg, 0.114 mmol) and *p*-toluenesulfonyl hydrazide (1.45 g, 7.84 mmol) in dimethoxyethane (15 mL) at reflux was added NaOAc (728 mg, 8.88 mmol) in water (12 mL) over 4 h. The mixture was then cooled to rt, poured into water, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in dimethyl sulfide (9 mL). To this solution at 0 °C was added $BF_3 \cdot Et_2O$ (0.22 mL, 1.71 mmol). The reaction mixture was stirred at rt for 40 min and quenched with saturated aqueous $NaHCO_3$ at 0 °C. The mixture was extracted with ethyl acetate (3 × 15 mL), and the extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford **2** (47 mg, 72%) as a waxy solid. ^1H NMR (400 MHz, $CDCl_3$): 7.18 (1H, d, J = 1.0 Hz), 5.05 (1H, qd, J = 1.3, 6.8 Hz), 3.77−3.81 (4H, m), 3.63−3.71 (5H, m), 3.54 (2H, dd, J = 2.7, 9.8 Hz), 3.32 (3H, m), 2.53 (2H, dt, J = 1.7, 16.0 Hz), 2.40 (2H, dd, J = 8.2, 15.2 Hz), 2.28 (2H, m), 2.04 (1H, m), 1.42 (3H, d, J = 5.9 Hz), 1.26−1.60 (30H, m), 0.88 (3H, t, J = 6.8 Hz) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): 171.2, 151.9, 131.3, 78.1, 75.9, 70.6, 70.3, 70.1, 60.5, 37.5, 33.4, 33.1, 29.8, 29.6, 29.4, 25.6, 22.8, 21.1, 19.2, 14.3, 14.2 ppm. IR (film): 3500, 2919, 2850, 1751, 1470, 1156, 1028, 720 cm^{-1}. MS (ESI, *m*/*z*): 571 (M^+ + 1), 593 (M^+ + Na). $[\alpha]_D^{25} = +6.6$ (*c* 0.63, $CHCl_3$). HRMS (ESI, *m*/*z*): calcd for $C_{33}H_{63}O_7$ [M^+ + H] 571.4562, found 571.4567.

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Supporting Information Available: ^1H NMR spectra for **2**, **3**, **8**, and **25** and ^{13}C NMR spectra for **2** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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