Enantiocontrolled Construction of Functionalized Tetrahydrofurans: Total Synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-Epoxynonadec-18-ene-7,10-diol, a Marine Natural Product

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An efficient strategy has been developed for the construction of highly functionalized tetrahydrofurans. The key feature involves the use of Sharpless asymmetric dihydroxylation and the choice of a new bis-C_3 building block **5** as the starting material which increased the efficiency. On the basis of this methodology, a marine natural product, (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol (**1**), was successfully synthesized in high enantioselectivity.

Introduction

In recent years, increasing attention has been directed toward biologically active natural products such as acetogenins of Announaceae[1] (to date, more than 230 different compounds have been isolated), macrolides,[2] cytotoxic polyethers,[3] marine toxins,[4] and pheromones,[5] most of which contain one or more functionalized tetrahydrofuran (THF) rings as a chiral core unit. Synthetic routes to enantiomerically pure 2,5-disubstituted tetrahydrofurans are of central interest. Many methodologies[6] have been explored in developing synthetic routes to substituted tetrahydrofurans and the natural products themselves. The recently developed methods involved the use of the Sharpless asymmetric dihydroxylation (AD)[7] or asymmetric epoxidation (AE)[8] reactions, which have gained widespread use in the total syntheses of natural products. However, most methods were concerned with the construction of 2,5-disubstituted tetrahydrofurans,[6,9] while few focused on 2,3,5-trisubstituted tetrahydrofurans.[10] In this paper we describe an efficient approach to 2,3,5-trisubstituted tetrahydrofurans by means of the AD reaction, and we will introduce the general aspects of our methodology by the synthesis of a marine natural product, (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol (**1**).

(6*S*,7*S*,9*R*,10*R*)-6,9-Epoxynonadec-18-ene-7,10-diol (**1**) (our target molecule), which has a characteristic substitution pattern in its tetrahydrofuran ring system, is a novel C_{19} lipid diol isolated from *Notheia anomala*,[11] a member of the Notheiacean family, order Chordaliales, which was found growing as a parasite on brown alga.

The first synthesis of racemic **1** was achieved by NBS oxidation,[12] and three other groups synthesized it in enantiopure form by using diethyl L-tartrate,[13] D-glucose,[14] or (*S*)-glycidol[15] as a chiral source, respectively.

The retrosynthetic route is illustrated in Scheme 1. The desired configuration of C-10 could be achieved by 1,2-addition of 1-nonenylmagnesium bromide onto aldehyde **2**. We envisioned that asymmetric dihydroxylation of **3** would allow us to construct the key tetrahydrofuran **2** having the three required chiral centers. The desired configuration of C-9 would be obtained through the inversion of configuration at the C_3 building block **4**.

To enhance the efficiency of the synthesis, we elected to use a bis-C_3 building block **5** with C_2 symmetry as the starting material, which should allow our synthesis to go bidirectional. It is also noteworthy that the hydroquinone skeleton in **5**, which linked the two identical glycerols **6** (Scheme 2), not only could tolerate even extreme reaction conditions such as strong acid and strong base but also could be readily removed as a protective group with CAN in the end.

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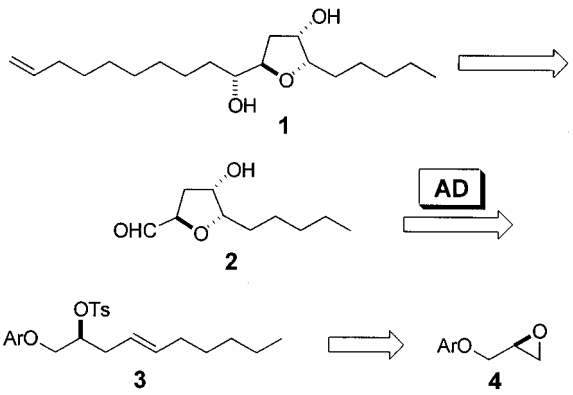
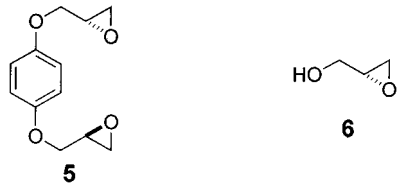
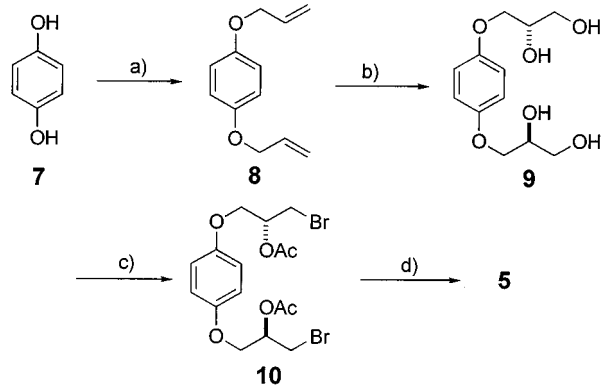
Scheme 1



Scheme 2



Scheme 3[a]



[a] Reagents and conditions: (a) K_2CO_3, allyl bromide, acetone, reflux (95%); (b) AD-mix-β, *t*-BuOH−H_2O (1:1), 0 °C (80%); (c) 30% HBr/AcOH, 50 °C; (d) K_2CO_3, MeOH (overall yield: 73% from **9**).

Results and Discussion

Preparation of the Bis-C_3 Building Block 5. According to the known procedure,[16] the bis-epoxide **5** was generated from hydroquinone (Scheme 3). Hydroquinone was added to a stirred mixture of allyl bromide and K_2CO_3 in acetone and then refluxed for 5 h. The crude product was recrystallized from hexane at −20 °C to give diallyl ether **8** in 95% yield. Dihydroxylation of **8** with AD-mix-β in *tert*-butyl alcohol−water at 0 °C yielded tetrol **9** in 80% yield and 90% de. The de was increased to 95% in 95% recovery by recrystallization from EtOH−*i*-PrOH, mp 120−123 °C, $[\alpha]_D$ −8.2 (*c* 0.55, EtOH). Tetrol **9** was stirred in 30% HBr in acetic acid at 50 °C for 30 min to give acetoxy bromide **10**. The crude **10** was subjected immediately to treatment with K_2CO_3 in methanol[17] to afford the bis-C_3 building block **5** as solid in 73% yield (95% de), mp 63.5−65 °C, $[\alpha]_D$ +17.5 (*c* 1.10, EtOH).

Construction of Chiral 2,3,5-Trisubstituted THF 17. The bis-C_3 building block **5** was treated with heptynyllithium in the presence of boron trifluoride etherate at −78 °C[18] to give the diol **11** in 75% yield (Scheme 4). Reduction of **11** with $LiAlH_4$ in THF was sluggish.[19] Considering the low reactivity of compound **12**, we decided to replace THF with diglyme[20] which has a higher boiling point. The reduction proceeded perfectly at the elevated temperature, and the *E*-olefin[21] **12** was obtained in 95% yield. Tosylation of **12** with *N*-TsIm[22] and NaH in THF[23] at 0 °C gave **13** in 79% yield. Dihydroxylation of **13** with AD-mix-α in *tert*-butyl alcohol−water at 0 °C afforded **14**, which, without further purification, was subjected to treatment with K_2CO_3 in MeOH followed by subsequent protection of the hydroxyl with TBDMSCl−NaH−THF[24] to produce compound **16** in 90% overall yield. The removal of hydroquinone from **16** by treatment with CAN[25] produced 2 equiv of the desired trisubstituted THF **17** (ds = 94:6).[26]

Although we have not done so, the other isomers of trisubstituted tetrahydrofurans (2*R*,3*R*, 2*S*,3*R*, 2*R*,3*S*) should be available by repeating the aforementioned sequences from **11** by using AD-mix-β or using cis-hydrogenation followed by AD-mix-β or AD-mix-α, alternatively.

Synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-Epoxynonadec-18-ene-7,10-diol (1). The Swern oxidation of the alcohol **17** gave the aldehyde **18** (Scheme 5). 1,2-Addition of 1-nonenylmagnesium bromide[27] on **18** in ether at −78 °C gave **19** as the major product with the desired configuration and a (10*S*)-isomer in 3:1 selectivity.[28] The major product **19** was then deprotected by treatment with *n*-Bu_4NF (1 M in THF) in THF[23] to afford the marine natural product **1**,[29] mp 52−55 °C, $[\alpha]^{20}_D$ +14.0 (*c* 3.5, $CHCl_3$) [lit.[11] mp 54.5−55 °C, $[\alpha]^{20}_D$ +15.0 (*c* 1.00 $CHCl_3$)].

In summary, we have described an effective route which provides a straightforward and overall enantio-

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(21) The ^1H NMR spectrum of **12** shows a large coupling constant (J = 15.3 Hz) between the two olefinic protons attributable to the *E* configuration, which differs from a smaller J value (7−8 Hz) for *Z* configuration.

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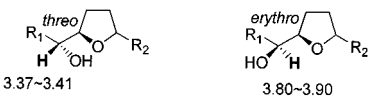
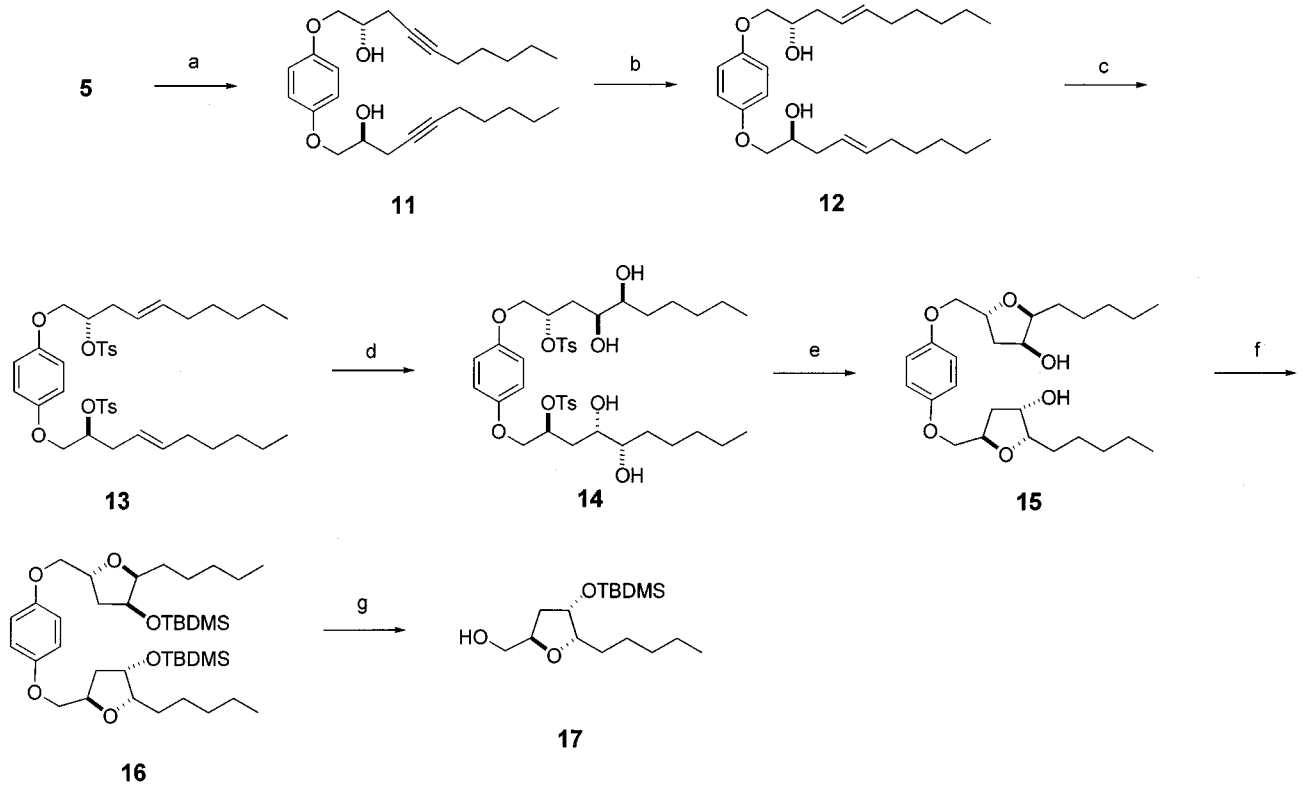
(27) 9-Bromo-1-nonene was prepared from commercially available 1,6-hexadiol via mono-tosylation, allylation with allylmagnesium bromide (Derguini-Boumechal, F.; Lorne, R.; Linstrumelle, R. *Tetrahedron Lett.* **1977**, *13*, 1181), and bromination with PPh_3−CBr_4.

(28) The two isomers were separated by chromatography on silica gel column. Their ratio was then determined by their weights.

(29) Comparison of the data of ^1H and ^{13}C NMR of our synthetic sample to those in refs 11 and 12 verified that the major isomer we obtained was the 10*R* natural product. The diagnostic NMR chemical shift of different THF subunits with various relative configurations in Annonaceous acetogenins showed that when the relative configuration of the THF ring and adjacent OH group was threo, the range of the chemical shift of the proton on the carbon with adjacent OH group was 3.34−3.41 ppm, and for the erythro isomer, the range of chemical shift was 3.80−3.90 ppm. For our synthetic sample, the chemical shift was 3.37 ppm, which was in accordance with the threo configuration. This observation further confirmed our identification.

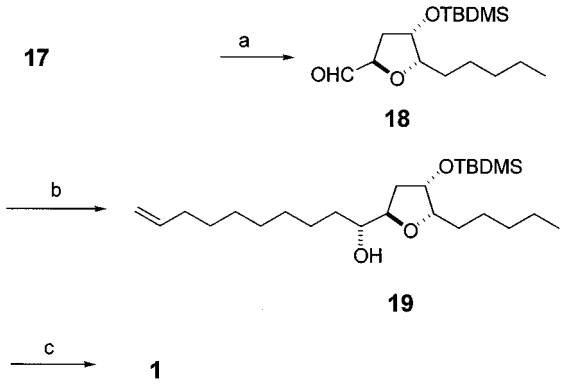


Scheme 4[a]



[a] Reagents and conditions: (a) 1-heptyne, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C (75%); (b) $LiAlH_4$, THF, diglyme, reflux (95%); (c) *N*-Ts*T*m, THF, 0 °C (79%); (d) K_2CO_3, $K_3Fe(CN)_6$, $NAHCO_3$, $K_2OSO_2(OH)_4$, $(DHQ)_2PHAL$, H_2O/*t*/BuOH = 1:1, rt; (e) K_2CO_3, CH_3OH, rt; (f) TBDMSCl, imidazole, THF, rt (the yield for three steps is 90%); (g) CAN, CH_3CN/H_2O = 2:1, 0 °C, 0.5 h (68%).

Scheme 5[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 20 °C; (b) $H_2C{=}CH(CH_2)_6CH_2MgBr$, Et_2O, −78 °C (3:1, 80%); (c) *n*-Bu_4NF (1 M in THF), THF (100%).

controlled construction of 2,3,5-trisubstituted tetrahydrofurans. The construction of the chiral centers of the THF is realized through the AD reaction, with high enantioselectivity. With **5** as the starting material, the bidirectional feature of our strategy is remarkable as shown also by ref 16b. As exemplified with the concise synthesis of the marine natural product **1,** our approach should be applicable to the syntheses of a number of bioactive products, which contain highly functionalized tetrahydrofurans.

Experimental Section

1,4-Bis(allyloxy)benzene (8). To a stirred mixture of allyl bromide (40 g) and potassium carbonate (34.5 g) in 200 mL of acetone was added hydroquinone (11 g). The reaction mixture was refluxed for 5 h. After filtration, the filtrate was concentrated and the crude product was recrystallized from hexane at −20 °C to give 36.1 g of 1,4-bis(allyloxy)benzene in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52−6.40 (m, 4H), 5.84 (dd, J = 1.6, 1.5 Hz, 1H), 5.78 (dd, J = 1.6, 1.5 Hz, 1H), 5.70 (dd, J = 1.5, 0.9 Hz, 1H), 5.67 (dd, J = 1.6, 1.4 Hz, 1H), 4.90 (dd, J = 1.5, 1.5 Hz, 2H), 4.89 (dd, J = 1.5, 1.5 Hz, 2H) ppm.

1,4-Bis((2*S*)-2,3-dihydroxy-1-propoxy)benzene (9). To a well-stirred solution of $(DHQD)_2$−PHAL (624 mg, 1 mol %), potassium osmate (58.9 mg, 0.2 mol %), potassium ferricyanide (79.04 g), and potassium carbonate (33.2 g) in 1:1 *t*-BuOH−water (800 mL) at 0 °C was added the allyl ether **8** (7.6 g, 40 mmol). The mixture was stirred at 0 °C until the reaction finished (about 15 h), and then 120 g of sodium sulfite was added to quench the reaction. The resulting mixture was stirred at room temperature for 4 h and filtered. The solid was dried under vacuum and boiled in ethanol (500 mL) for 30 min, and the insoluble material was quickly filtered off. After evaporation of the filtrate, 8.3 g of tetrol was given in 80% yield and 90% de. The de was increased to 95% in 90% recovery by recrystallization from EtOH−*i*-PrOH: mp 123−125 °C; $[\alpha]_D$ +6.60 (*c* 2.38, EtOH); IR (neat) 3354, 1608, 1457 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 6.84 (s, 4H), 4.94 (dd, J = 7.0, 3.2 Hz, 2H), 4.71−4.68 (m, 2H), 3.90−3.88 (m, 2H); 3.78−3.73 (m, 4H), 3.42−3.39 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.75, 115.27, 115.20, 70.05, 62.78 ppm; EIMS (*m*/*z*) 258 (M^+, 9.8), 209 (0.6), 184 (9.4), 161 (0.6), 152 (1.6), 135 (1.8), 110 (100).

1,4-Bis((2*S*)-2-acetoxy-3-bromo-1-propoxy)benzene (10). Tetrol **9** (7.0 g) was placed in a 50 mL one-neck round-bottomed flask followed by addition of 30 mL of 30% HBr in acetic acid, and the reaction mixture was stirred at 50 °C for 30 min. After evaporation of HBr and acetic acid, the crude product was recrystallized from hexane−acetone at 0 °C to give 12.1 g (95% yield) of colorless crystals: mp 74−76 °C; $[\alpha]_D$ −14.89 (*c* 4.42, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (s,

4H), 5.31−5.26 (m, 2H), 4.17−4.09 (m, 4H), 3.72−3.68 (m, 2H), 3.64−3.60 (m, 2H), 2.14 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.13, 152.94, 115.78, 70.78, 67.54, 30.37, 20.91 ppm.

1,4-Bis((2*S*)-2,3-epoxy-1-propoxy) benzene (5). K_2CO_3 (8.28 g, 60 mmol) was added to a stirred solution of the bromide acetate (9.4 g) in methanol (30 mL). The mixture was stirred at room temperature for 2 days and filtered. After evaporation of the filtrate, the residue was dissolved in ethyl acetate (200 mL) and water (20 mL), washed with water and brine, and dried over Mg_2SO_4. The solvent was evaporation and the crude product was recrystallized from hexanes−ethyl acetate to give 4.0 g of compound **5** in 90% yield: mp 69−71 °C; $[\alpha]_D$ +9.14 (*c* 0.7, $CHCl_3$); IR (neat) 3073, 1590, 1464 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 4H), 4.17 (dd, J = 8.4, 2.4 Hz, 2H), 3.90 (dd, J = 8.4, 4.2 Hz, 2H), 3.35−3.33 (m, 2H), 2.90 (dd, J = 3.6, 3.0 Hz, 2H), 2.75 (dd, J = 3.6, 2.1 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.06, 115.64, 69.43, 50.25, 44.76 ppm; EIMS (*m*/*z*) 222 (M^+, 100), 205 (3.0), 192 (9.2), 179 (15); HRMS calcd for $C_{12}H_{14}O_4$ 222.0892, found 222.0900.

1,4-Bis((2*S*)-2-hydroxy-4-decyn-1-yloxy)benzene (11). A solution of heptyne (3.89 g, 40.5 mmol) in tetrahydrofuran (100 mL) at −78 °C was treated with *n*-butyllithium (2.5 M in hexane, 16.2 mL), and the resultant mixture was stirred for 15 min. Diepoxide **5** (3 g, 13.5 mmol) and boron trifluoride etherate (5 mL) were successively added dropwise. After an additional 2 h at −78 °C, the cold bath was removed. Saturated aqueous $NaHCO_3$ (50 mL) was then added. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (petroleum ether/ethyl acetate = 10/1) furnished the alcohol **11** (4.2 g, 75% yield) as a white solid: mp 56−59 °C; $[\alpha]_D$ +272.6 (*c* 0.08, $CHCl_3$); IR (neat) 3368, 2240, 1508, 1458 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 4H), 4.13−4.08 (m, 2H), 4.05 (dd, J = 9.2, 3.9 Hz, 2H), 3.93 (dd, J = 9.2, 6.4 Hz, 2H), 2.57−2.52 (m, 6H), 2.19−2.13 (m, 4H), 1.51−1.44 (m, 4H), 1.37−1.26 (m, 8H), 0.89 (t, J = 7.1 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 153.12, 115.64, 83.50, 75.04, 71.44, 68.86, 31.11, 28.63, 23.98, 22.21, 18.73, 13.98 ppm; EIMS (*m*/*z*) 414 (M^+, 57), 304 (2.9), 263 (3.9), 262 (20), 219 (0.6), 152 (11), 110 (100); HRMS calcd for $C_{26}H_{38}O_4$ 414.2770, found 414.2805.

1,4-Bis((*E*)-(2*S*)-2-hydroxy-4-decen-1-yloxy)benzene (12). THF (5 mL) and diglyme (50 mL) were added to a flask with $LiAlH_4$ (2 g). The solution was heated until THF was distilled out, and then the solution was allowed to cool to rt. A solution of alkyne **11** (2.1 g, 5.1 mmol) in diglyme (5 mL) was then added. The reaction mixture was refluxed for 24 h. The oil bath was replaced with a salt−ice bath. Water was slowly added dropwise until the solid turned gray. After filtration, the solid was washed with ethyl acetate and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate = 3/1) to afford **12** (2.02 g, 95% yield) as a white solid: mp 70−75 °C; $[\alpha]_D$ +13.5 (*c* 1.02, $CHCl_3$); IR (neat) 3416, 1601, 1454 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 4H), 5.58 (dt, J = 15.3, 6.4 Hz, 2H), 5.45 (dt, J = 15.3, 6.8 Hz, 2H), 4.00 (m, 2H), 3.93 (dd, J = 9.3, 3.4 Hz, 2H), 3.82 (dd, J = 9.3, 7.1 Hz, 2H), 2.35−2.29 (m, 4H), 2.09−1.99 (m, 4H), 1.20−1.40 (m, 14H), 0.88 (t, J = 7.0 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 153.20, 134.90, 124.82, 115.65, 72.27, 69.82, 36.80, 32.68, 31.47, 29.14, 22.60, 14.14 ppm; EIMS (*m*/*z*) 418 (M^+, 43), 313 (1.4), 264 (14), 199 (1.7), 165 (2.4), 151 (13), 135 (7.9), 110 (100); HRMS calcd for $C_{26}H_{42}O_4$ 418.3083, found 418.3075.

1,4-Bis((*E*-(2*S*)-2-(tosyloxy)-4-decen-1-yloxy)benzene (13). Sodium hydride (48 mg, 2 mmol) was added to the solution of **12** (215 mg, 0.51 mmol) in 10 mL of THF at 0 °C. After the solution was stirred for 1 h, *N*-TsIm (334 mg, 1.53 mmol) was added. After an additional 24 h at 0 °C, saturated NH_4Cl (10 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 20 mL). The organic phases were washed with brine, dried (Na_2SO_4), and evaporated. Purification of the crude product by flash chromatography (petroleum ether/ethyl acetate = 20/1 to 5/1) yielded the required compound **13** (295 mg, 79% yield) as white crystals: mp 69−72 °C; $[\alpha]_D$ −6.79 (*c* 0.66, $CHCl_3$); IR (neat) 1596, 1509, 1358, 1239, 1187 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.80 (d, J = 8.4 Hz, 4H), 7.31 (d, J = 8.4 Hz, 4H), 6.61 (s, 4H), 5.51−5.46 (m, 2H), 5.25−5.15 (m, 2H), 4.74−4.71 (m, 2H), 3.95 (dd, J = 5.28, 3.98 Hz, 4H), 2.51−2.44 (m, 10H), 1.90 (dt, J = 6.6, 6.6 Hz, 4H), 1.33−1.19 (m, 12H), 0.87 (t, J = 6.7 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 152.72, 144.57, 135.76, 134.18, 129.66, 127.98, 122.70, 115.45, 80.27, 68.67, 34.88, 32.52, 31.39, 28.87, 22.51, 21.63, 14.04 ppm; EIMS (*m*/*z*) 726 (M^+, 0.4), 418 (8.5), 246 (7.9), 199 (15), 172 (52), 107 (42), 91 (100).

1,4-Bis((2*S*,4*S*,5*S*)-2-(tosyloxy)-4,5-dihydroxydec-1-yloxy)benzene (14). To a stirred solution of AD-mix-α [K_2CO_3 (248 mg, 1.8 mmol), $K_3Fe(CN)_6$ (592 mg, 1.8 mmol), $NaHCO_3$ (151 mg, 1.8 mmol), $K_2OsO_2(OH)_4$ (225 mg), and $(DHQ)_2PHAL$ (23 mg, 0.03 mmol)] in 50% aqueous *t*-BuOH (6 mL) was added *E*-olefin **13** (217.8 mg, 0.3 mmol). The resulting mixture was stirred for 24 h at rt. Sodium sulfite (0.9 g) was added. The mixture was stirred for 3 h and extracted with ethyl acetate. The combined extracts were washed with aqueous HCl and brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue (**14**) without purification.

1,4-Bis((2*R*,4*S*,5*S*)-2,5-epoxy-4-hydroxydec-1-yloxy)benzene (15). To a solution of crude product **14** (250 mg) in MeOH (10 mL) was added K_2CO_3 (250 mg). After 24 h of stirring at rt, most of the MeOH was evaporated under reduced pressure. The residue was dissolved in water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give **15** without purification.

1,4-Bis((2*R*,4*S*,5*S*)-2,5-epoxy-4-((*tert*-butyldimethylsilyl)oxy)dec-1-yloxy)benzene (16). To a stirred solution of **15** in dry THF (10 mL) was added *tert*-butyldimethylsilyl chloride (151 mg, 1 mmol) at rt. The mixture was stirred for 24 h at the same temperature, and water (5 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 20/1) to afford **16** (180 mg, 90% yield for three steps) as a colorless oil: $[\alpha]_D$ +21.08 (*c* 0.3, $CHCl_3$); IR (neat) 1508, 1470, 1255 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (s, 4H), 4.51 (ddd, J = 12.5, 7.8, 4.7 Hz, 2H), 4.28 (dt, J = 2.9, 2.9 Hz, 2H), 3.91 (d, J = 4.8, 4H), 3.85 (dt, J = 6.9, 3.1 Hz, 2H), 2.01−1.98 (m, 4H), 1.61 (m, 4H), 1.31−1.26 (m, 12H), 0.91−0.86 (m, 24H), 0.10−0.04 (m, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 153.44, 115.58, 83.83, 75.47, 73.22, 71.41, 38.61, 32.24, 29.49, 26.08, 25.85, 22.76, 18.15, 14.17 ppm; EIMS (*m*/*z*) 678 (M^+, 15), 319 (6.8), 285 (33), 263 (13), 227 (35), 187 (42), 171 (51), 149 (32), 113 (39); HRMS calcd for $C_{38}H_{70}O_6Si_2$ 678.4711, found 678.4683.

(2*R*,4*S*,5*S*)-2,5-Epoxy-4-((*tert*-butyldimethylsilyl)oxy)decan-1-ol (17). To a stirred solution of **16** (100 mg, 0.2 mmol) in 2:1 CH_3CN-H_2O (9 mL) was added CAN (345 mg, 0.63 mmol) at 0 °C. The mixture was stirred for an additional 1 h at 0 °C. The product was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water, an aqueous sodium bisulfite solution, and brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography (petroleum ether/ethyl acetate = 10/1) to afford **17** (61 mg, 68% yield) as a colorless oil. The ratio of diastereomers was 94:6 (determined by GC-MS (column: OV-1, 30 m × 0.2 mm)): IR (neat) 3426, 1464, 1285, 1191 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28−4.23 (m, 2H), 3.79−3.69 (m, 1H), 3.72 (dd, J = 11.7, 3.0, 1H), 3.48 (m, 1H), 2.30 (br, 1H), 1.90−1.84 (m, 2H), 1.55 (m, 2H), 1.30−1.22 (m, 6H), 0.87 (m, 12H), 0.07 (s, 3H), 0.06 (s, 3H) ppm; EIMS (*m*/*z*) 303 (M^+ + 1, 7.00), 301 (M^+ − 1, 1.7), 285 (51), 267 (6.9), 245 (48), 227 (65), 187 (39), 171 (100); HRMS calcd for $C_{16}H_{33}O_3Si$ 301.2199, found 301.2182.

(2*R*,4*S*,5*S*)-2,5-Epoxy-4-((*tert*-butyldimethylsilyl)oxy)decan-1-al (18). A solution of the oxalyl chloride (26 mg, 0.2 mmol) in dichloromethane (5 mL) was stirred and cooled to −60 °C. Dimethyl sulfoxide (33 mg, 0.425 mmol) in

dichloromethane (2 mL) was added dropwise. After 10 min, a solution of **17** (50 mg, 0.17 mmol) in dichloromethane (3 mL) was added dropwise at −78 °C. The reaction mixture was allowed to warm to −40 °C for 5 min. After the solution was cooled to −78 °C again, triethylamine (0.1 mL) was added. The resulting suspension was stirred for 1 h at −78 to −20 °C, and then a saturated aqueous solution of sodium dihydrogen phosphate (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a crude aldehyde **18** which was unstable. The aldehyde was used immediately for next reaction without purification.

(6*S*,7*S*,9*R*,10*R*)-6,9-Epoxy-7-((*tert*-butyldimethylsilyl)oxy)nonadec-18-en-10-ol (19) and Its (10*S*)-Isomer. To a stirred solution of **18** in ether (5 mL) was added 1-nonenylmagnesium bromide (0.6 M in ether, 1.5 mL) at −78 °C. After being stirred for 2 h at −78 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 20/1). The first fraction gave **19** (43 mg, 60% yield) as a white solid: mp 40−42 °C; $[\alpha]_D$ +17.10 (*c* 0.65, $CHCl_3$); IR (neat) 3462, 1257, 1051 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.2, 10.2, 6.7 Hz, 1H), 4.99 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.92 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.23 (br, 1H), 4.00 (dt, *J* = 9.2, 6.2 Hz, 1H), 3.74 (dt, *J* = 6.7, 2.8 Hz, 1H), 3.37−3.35 (m, 1H), 2.03 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.88−1.85 (m, 1H), 1.83−1.79 (m, 1H), 1.60−1.20 (m, 21H), 0.90−0.88 (m, 9H), 0.05 (s, 6H) ppm; EIMS (*m*/*z*) 427 (M^+ + 0.5), 369 (13), 351 (36), 271 (17), 241 (27), 187 (69), 113 (100); HRMS calcd for $C_{24}H_{47}O_3Si$ 411.3295, found 411.3261. The second fraction gave the (10*S*)-isomer (14 mg, 20% yield): mp 40−45 °C; $[\alpha]_D$ +18.7 (*c* 0.40, $CHCl_3$); IR (neat) 3443, 1361, 1258, 1155, 1067 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.2, 10.2, 6.7 Hz, 1H), 5.00 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.93 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.25 (br, 1H), 4.13 (ddd, J = 9.9, 5.9, 3.7 Hz, 1H), 3.83−3.86 (m, 1H), 3.79 (dt, *J* = 6.6, 3.1 Hz, 1H), 2.05−2.12 (m, 2H), 1.80−1.70 (m, 2H), 1.60−1.30 (m, 25H), 0.90−0.89 (m, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 139.31, 114.22, 84.26, 80.23, 73.47, 71.82, 34.58, 33.88, 32.35, 32.24, 31.03, 29.75, 29.68, 29.45, 29.13, 28.99, 26.11, 26.06, 25.84, 22.77, 18.14, 14.19 ppm; EIMS (*m*/*z*) 425 (M^+ − 1, 8.0), 409 (8.4), 369 (10), 351 (30), 295 (5.2), 271 (14), 241 (25), 187 (77), 113 (100).

(6*S*,7*S*,9*R*,10*R*)-6,9-Epoxynonadec-18-ene-7,10-diol (1). To a stirred solution of **19** (11 mg, 0.023 mmol) in THF (5 mL) was added tetrabutylammonium fluoride in THF (1 M, 0.03 mL). After 24 h of stirring at rt, water was added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 1/1) to afford the marine natural product **1** (8 mg, 100% yield) as a white solid: mp 52−55 °C; $[\alpha]_D$ +14.0 (*c* 3.5, $CHCl_3$) [lit.[11] mp 54.5−55 °C, $[\alpha]_D$ +15.0 (*c* 1.00, $CHCl_3$)]; IR (neat) 3447, 3372, 1466, 1284, 1111, 1092, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84−5.73 (m, 1H), 4.98 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.92 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.24 (br, 1H), 4.09−3.97 (m, 1H), 3.74 (dt, *J* = 6.9, 2.7 Hz, 1H), 3.42−3.25 (m, 1H), 2.33 (br, 2H), 2.03−1.98 (m, 3H), 1.92−1.80 (m, 2H), 1.75−1.10 (m, 19H), 0.88 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 139.30, 114.20, 82.57, 80.29, 74.18, 73.58, 38.03, 33.87, 33.29, 32.07, 31.02, 29.73, 29.50, 29.16, 28.973, 26.07, 25.68, 22.65, 14.10 ppm; EIMS (*m*/*z*) 313 (M^+ + 1, 1.8), 295 (22), 277 (4.3), 259 (1.9), 239 (0.8), 157 (87), 139 (39), 113 (100); HRMS calcd for $C_{19}H_{36}O_3$ 312.2664, found 312.2657.

(6*S*,7*S*,9*R*,10*S*)-6,9-Epoxynonadec-18-ene-7,10-diol was prepared as above: $[\alpha]_D$ +15.0 (*c* 0.46, $CHCl_3$); IR (neat) 3380, 2927, 2855, 1467, 1277, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86−5.77 (m, 1H), 4.99 (dd, *J* = 18.6, 1.1 Hz, 1H), 4.93 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.30−4.00 (m, 1H), 4.17 (ddd, *J* = 9.1, 5.6, 3.1 Hz, 1H), 3.90−3.81 (m, 2H), 2.17−2.00 (m, 3H), 1.92−1.82 (m, 2H), 1.75−1.10 (m, 21H), 0.90 (t, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 139.29, 114.23, 83.65, 80.10, 73.34, 72.13, 34.26, 33.87, 32.31, 32.11, 29.67, 29.45, 29.30, 29.14, 28.98, 26.09, 26.00, 22.68, 14.12 ppm; EIMS (*m*/*z*) 313 (M^+ + 3.3), 295 (100), 277 (19), 259 (6.7), 223 (6.2), 205 (26), 167 (25), 157 (84), 139 (39), 121 (39), 113 (84); HRMS calcd for $C_{19}H_{36}O_3$ 312.2664, found 312.2708.

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Supporting Information Available: ^1H NMR spectra of compounds **5**, **8**, **9**, **10**, **11**, **12**, **13**, **16**, **17**, **19**, **1** and (10*S*)-**1**, ^{13}C NMR spectra of **5**, **9**, **10**, **11**, **12**, **13**, **16**, (10*S*)-**19**, **1**, and (10*S*)-**1**, and MS spectra of **5**, **9**, **11**, **12**, **13**, **16**, **17**, **19**, **1**, and (10*S*)-**1** (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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