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Formal Total Synthesis of (+)-Neopeltolide

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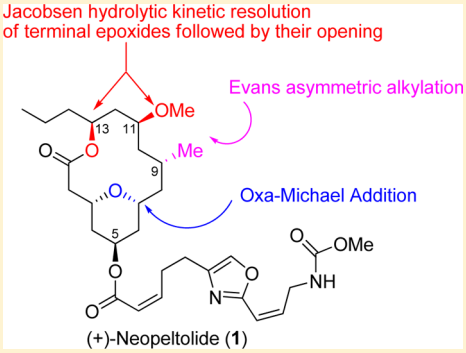
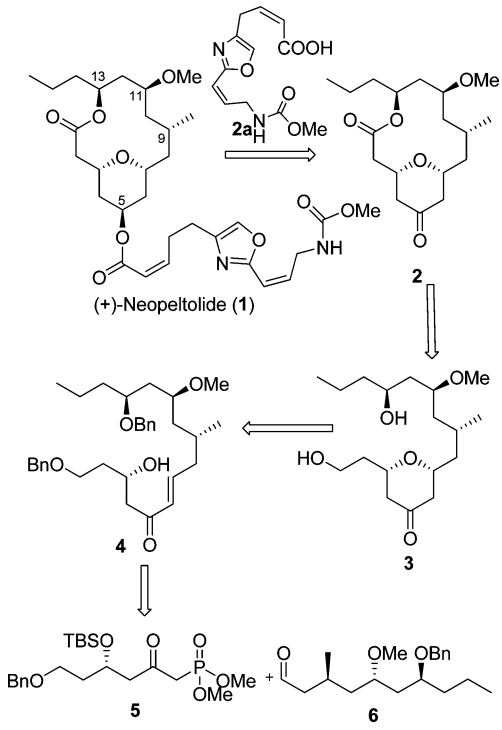
Supporting Information

ABSTRACT: This paper describes the formal total synthesis of (+)-neopeltolide, a cytotoxic macrolide isolated from the marine sponge Neopeltidae. The key features of the synthesis include an asymmetric Evans alkylation to fix the C9-methyl center, Jacobsen hydrolytic kinetic resolution of terminal epoxides followed by their regioselective opening to fix the stereocenters at the C11 and C13 positions, respectively, a Pd-catalyzed oxa-Michael reaction to construct the tetrahydropyran ring, and Yamaguchi macrolactonization to form the macrocyclic core of the molecule.



Secondary metabolites produced by marine sponges are the source of architecturally complex and pharmacologically important compounds. In 2007, Wright and co-workers isolated neopeltolide, a 14-membered macrolide containing a trisubstituted THP ring bearing an O-acylated unsaturated oxazole having a side chain at C5 position from deep-water sponge of the family Neopeltidae.[1] They established the planar structure and its relative stereochemistry with the help of detailed NMR spectroscopic studies. However, in the same year, the correction of the stereocenters and determination of the absolute stereochemistry was reported independently by Panek[2a] and Scheidt[2b] through its first total syntheses. Initial biological studies carried out by Wright and co-workers revealed that it exhibits potent cytotoxic activities against various cell lines with nanomolar IC_{50} values. It also exhibits antifungal activity against *Candida albicans*. Because of its fascinating biological activity and appealing architecture, several total syntheses,[2] formal total syntheses,[3] and syntheses of analogues[4] have been reported in the literature. In this paper, we report the formal total synthesis of (+)-neopeltolide that exploits a Pd-catalyzed oxa-Michael reaction for the construction of a 2,4,6-trisubstituted tetrahydropyran ring in the molecule. The retrosynthetic strategy is depicted in Scheme 1. Retrosynthetically, (+)-neopeltolide could be obtained from the known keto compound **2** via stereoselective reduction followed by attachment of the known side chain. Compound **2** could be obtained from the diol compound **3** through selective oxidation of the primary alcohol followed by Yamaguchi macrolactonization. Compound **4** is a precursor of compound **3**, as the transformation could be achieved through a Pd-catalyzed intramolecular oxa-Michael reaction, a methodology developed by Gouverneur et al.[5] Again, combination of **5** and **6** by means of a Horner−Wadsworth−Emmons (HWE) reaction might provide the desired enone **4**.

Scheme 1. Retrosynthetic Analysis of (+)-Neopeltolide (1)



Accordingly, our synthesis commenced from the known alcohol **7**, which was prepared via an Evans alkylation reaction.[6a,b] TBDPS protection of **7** with TBDPSCl and Et_3N in CH_2Cl_2 provided compound **8**[6c] in quantitative yield. Epoxidation of the olefin **8** with *m*CPBA afforded a

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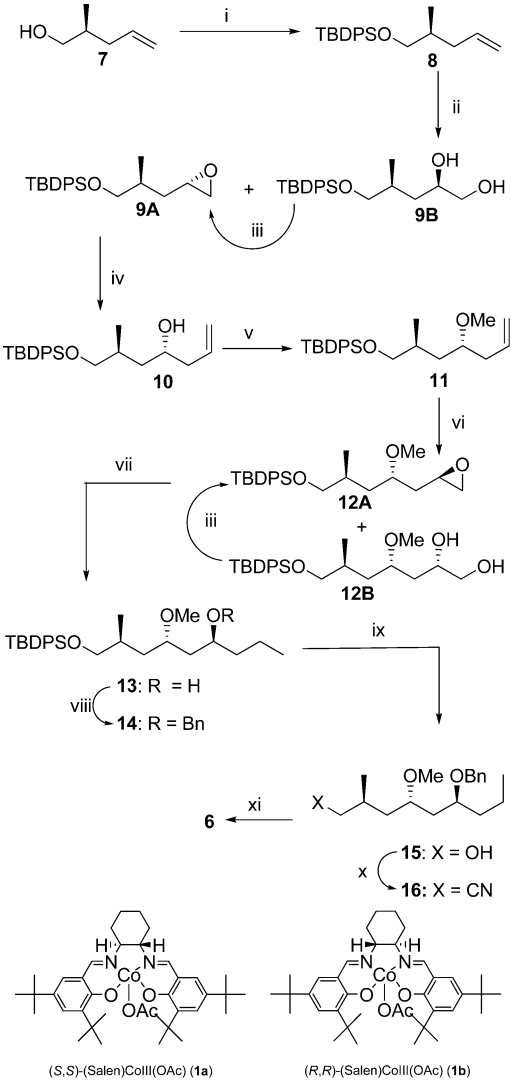
diastereomeric mixture of terminal epoxides, which on Jacobsen hydrolytic kinetic resolution with (*S*,*S*)-**1a** furnished diastereomerically pure terminal epoxide **9A** (de >98%, 44%) and the diol compound **9B** (de >95%, 45%).[7] However, the diol **9B** was converted back to the required epoxide **9A** by following a three-step reaction sequence, as shown in Scheme 2.[8] The terminal epoxide was then opened with vinylmagnesium bromide to give the homoallylic alcohol **10** in 90% yield. Methylation of the secondary hydroxyl group furnished the O-methylated compound **11**,[9] which on epoxidation followed by Jacobsen hydrolytic kinetic resolution with (*R*,*R*)-**1b** afforded diastereomerically pure terminal epoxide **12A** (de >98%, 43%) and the diol compound **12B** (45%).[7] Again the diol **12B** was converted back to the required epoxide following the same sort of reactions as used earlier for the transformation of **9A** from **9B**.[8] Opening of the terminal epoxide with ethylmagnesium bromide[10] at −40 °C led to the formation of the secondary alcohol **13**, which on benzylation provided the fully protected compound **14**.[11] TBDPS deprotection of **14** with TBAF in THF gave the primary alcohol **15**,[12a] which on tosylation followed by tosyl displacement with cyanide generated the cyano compound **16** in 84% over three steps. Finally, partial reduction of the cyano group with DIBAL-H, followed by hydrolysis of the intermediate imine, afforded the aldehyde **6**.[12]

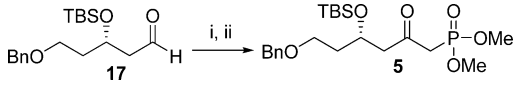
The ketophosphonate **5** was synthesized from the known compound **17**[13] in two steps. Addition of the anion generated from $CH_3PO(OMe)_2$ to the aldehyde **17** afforded a secondary alcohol, which on oxidation with DMP provided the ketophosphonate **5** in 80% yield over two steps (Scheme 3).

Scheme 2. Synthesis of Aldehyde 6[a]



[a]Reagents and conditions: (i) TBDPS-Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temperature, 12 h, quantitative; (ii) (a) *m*CPBA, CH_2Cl_2, 0 °C to room temperature, 10 h, 96%, (b) (*S*,*S*)-**1a**, H_2O, 24 h, 44% (**9A**), 45% (**9B**); (iii) (a) AcCl, 2,4,6-collidine, CH_2Cl_2, −78 °C, 10 h, (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, (c) K_2CO_3, MeOH, 0 °C, 1 h, 66% over three steps; (iv) vinylmagnesium bromide, CuI, THF, −40 to 0 °C, 1 h, 90%; (v) KH, MeI, THF; 0 °C to room temperature, 30 min, 91%; (vi) (*R*,*R*)-**1b**, H_2O, 24 h, 43% (**12A**), 45% (**12B**); (vii) EtMgBr, CuI, THF, −40 °C to room temperature, 1 h, 88%; (viii) benzyl trichloroacetimidate, CF_3SO_3H, cyclohexane/CH_2Cl_2 (2/1), 0 °C to room temperature, 2 h, 88%; (ix) TBAF, THF, 0 °C to room temperature, 3 h, 99%; (x) (a) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to room temperature, 3 h, (b) NaCN, NaI, DMSO, 90 °C, 1 h, 84% over two steps; (xi) DIBAL-H, CH_2Cl_2, −78 to 0 °C, 1 h, then 3 N NaOH, 0 °C, 89%.

Scheme 3. Synthesis of Ketophosphonate 5[a]



[a]Reagents and conditions: (i) *n*-BuLi, $MePO(OMe)_2$, THF, −78 °C to room temperature, 1 h; (ii) DMP, CH_2Cl_2, 0 °C to room temperature, 1 h, 80%, over two steps.

After synthesizing the two key fragments, we turned our attention to coupling them together. Accordingly, a Horner−Wadsworth−Emmons (HWE) reaction between **5** and **6** was performed with DIPEA and LiCl in CH_3CN to furnish compound **18** (Scheme 4) in 77% yield.[14] TBS deprotection of **18** with HF-Py in CH_3CN provided the crucial intermediate **4** for an oxa-Michael reaction. To perform the oxa-Michael reaction, compound **4** was subjected to different Pd catalysts (Table 1); however, the best result was obtained with $Pd(CH_3CN)_4BF_4$ in CH_2Cl_2 and provided chromatographically separated compound **19A** in 48% yield along with the unrequired isomer **19B** in 12% yield.[5] The required isomer **19A** was subjected to benzyl deprotection to give diol compound **3** in 95% yield. Selective oxidation of the primary alcohol with TEMPO provided an aldehyde, which on further oxidation under Pinnick conditions[15] followed by Yamaguchi macrolactonization[16] of the resulting *seco* acid provided the known macrocyclic ketone **2**, whose analytical and spectral data were in good agreement with the literature report.[2c,d]

In conclusion, a formal total synthesis of (+)-neopeltolide has been achieved by using Evans asymmetric alkylation, Jacobsen hydrolytic kinetic resolution, a Horner−Wadsworth−Emmons (HWE) reaction, a Pd-catalyzed intramolecular oxa-Michael reaction, and Yamaguchi macrolactonization as key steps. The known keto compound **2** was synthesized in 27 steps (longest linear sequence) from compound **8** with an overall yield of 3.49%.

■ EXPERIMENTAL SECTION

***tert*-Butyl((*S*)-2-methyl-3-((*S*)-oxiran-2-yl)propoxy)-diphenylsilane (9A) and (2*R*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methylpentane-1,2-diol (9B).** To a stirred solution of olefin **8** (6

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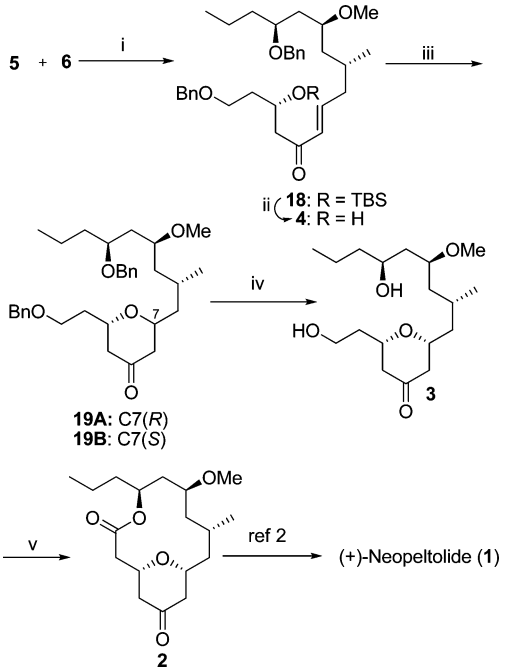
Scheme 4. Coupling of Compounds 5 and 6 and Completion of the Synthesis[a]



[a]Reagents and conditions: (i) LiCl, DIPEA, CH_3CN, room temperature, 30 min, then **6**, 12 h, 77%; (ii) HF-Py, CH_3CN, 0 °C to room temperature, 12 h, 80%; (iii) $Pd(CH_3CN)_4BF_4$, CH_2Cl_2, room temperature, 12 h, **19A** (48%) and **19B** (12%); (iv) (a) separation, (b) **19A**, H_2, Pd/C, EtOAc, rtoom temperature, 2 h, 95%; (v) (a) TEMPO, BAIB, CH_2Cl_2, 0 °C to room temperature, 5 h; (b) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, $^tBuOH/H_2O$ (2/1), 0 °C to room temperature, 1 h, 77% over two steps; (c) $Cl_3C_6H_2COCl$, Et_3N, THF, room temperature, 1 h, then it was added to a solution of DMAP in toluene at 80 °C, 16 h, 83%.

Table 1

entry	cat. (10 mol %)	conditions	19A:19B	combined yield, %
1	$PdCl_2$	CH_2Cl_2, room temp, 12 h		
2	$Pd(OAc)_2$	CH_2Cl_2, room temp, 12 h		
3	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2, room temp, 12 h		
4	$Pd(dppf)Cl_2$	CH_2Cl_2, room temp, 24 h	n.d.	10
5	$Pd(CH_3CN)_2Cl_2$	CH_2Cl_2, room temp, 12 h	3:2	45
6	$Pd(CH_3CN)_4BF_4$	CH_2Cl_2, room temp, 12 h	4:1	60

g, 17.7 mmol) in CH_2Cl_2 (53 mL) at 0 °C was added *m*CPBA (70%, 5.24 g, 21.2 mmol). The reaction mixture was stirred at room temperature for 10 h and then quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 2% EtOAc in PE) to yield a diastereomeric mixture of epoxides (6 g, 96%) as a colorless oil.

A mixture of Co(II) (*S*,*S*)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino precatalyst (49 mg, 0.08 mmol) in toluene (1 mL) and AcOH (9.4 μL, 0.08 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed by a rotary evaporator under reduced pressure, and the brown residue was dried under vacuum. The epoxide prepared above (5.8 g, 16.3 mmol) was added in one portion, and the stirred mixture was cooled in an ice–water bath. Water (162 μL, 9 mmol) was added slowly to the reaction mixture, and the reaction mixture was stirred for 24 h at room temperature. The crude products were purified by column chromatography (SiO_2, 2% EtOAc in hexane for **9A** and 40% EtOAc in hexane for **9B**) to give compound **9A** as a colorless oil (2.52 g, 44%) and **9B** (2.36 g, 45%).

Analytical data of compound ***9A****:* R_f = 0.4 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{24}$ = −2.97° (*c* 5.35, $CHCl_3$); IR ν_{max} 3418, 1627, 1108, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66–7.59 (m, 4H), 7.42–7.31 (m, 6H), 3.51 (dq, *J* = 10.0, 6.0 Hz, 2H), 2.86 (m, 1H), 2.69 (m, 1H), 2.38 (dd, *J* = 5.0, 2.0 Hz, 1H), 1.90 (m, 1H), 1.66 (m, 1H), 1.35 (m, 1H), 1.05 (s, 9H), 1.0 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 133.7, 129.5, 127.6, 68.7, 50.9, 47.5, 36.2, 33.7, 26.8, 19.2, 16.6; MS (ESI) *m*/*z* 377 $[M + Na]^+$; HRMS (ESI, TOF) calcd for $C_{22}H_{30}O_2SiNa$ $[M + Na]^+$ 377.1912, found 377.1897.

Analytical data of compound ***9B****:* R_f = 0.4 (SiO_2, 60% EtOAc in hexane); $[\alpha]_D^{22}$ = −1.13° (*c* 4.05, $CHCl_3$); IR ν_{max} 3347, 2931, 1465, 1426, 1107, 1066, 821, 739, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.62 (m, 4H), 7.49–7.34 (m, 6H), 3.84 (m, 1H), 3.65–3.38 (m, 4H), 2.88 (br s, 1H), 2.03 (br s, 1H), 1.91 (m, 1H), 1.52–1.43 (m, 2H), 1.06 (s, 9H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 135.5, 133.3, 129.7, 127.7, 69.9, 68.7, 66.9, 37.5, 32.2, 26.8, 19.2, 17.5; MS (ESI) *m*/*z* 395 $[M + Na]^+$; HRMS (ESI, TOF) calcd for $C_{22}H_{32}O_3SiNa$ $[M + Na]^+$ 395.2018, found 395.2023.

Experimental Procedure for the Conversion of 9B to 9A. To a solution of compound **9B** (2 g, 5.36 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C was added 2,4,6-collidine (1.4 mL, 10.7 mmol). After 10 min, acetyl chloride (0.4 mL, 5.9 mmol) was added to the reaction mixture and stirring was continued for another 10 h at the same temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with saturated $CuSO_4$ solution, water, and brine, dried (Na_2SO_4), and concentrated in vacuo. The monoacetyl compound (R_f = 0.5, 40% EtOAc in hexane) thus obtained was used for the next reaction.

To a solution of crude monoacetyl compound (1.96 g, 4.7 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added Et_3N (1.3 mL, 9.4 mmol). After 10 min of stirring, MsCl (0.5 mL, 7.1 mmol) and then DMAP (58 mg, 0.47 mmol) were added to the reaction mixture, the temperature was raised to room temperature, and stirring was continued for another 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc. The organic layer was separated and washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The mesylate (R_f = 0.5, 20% EtOAc in hexane) thus obtained was used directly in the next reaction.

To a solution of mesylate (2.09 g, 4.2 mmol) in anhydrous methanol (15 mL) at room temperature was added anhydrous K_2CO_3 (2.93 g, 21.2 mmol) under a nitrogen atmosphere, and stirring was continued for 1 h. The reaction mixture was diluted with water, and methanol was evaporated under reduced pressure. Then the reaction mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 2% EtOAc in hexane) gave pure compound **9A** (1.38 g, 66%, over three steps) as a colorless oil.

(4*R*,6*S*)-7-(*tert*-Butyldiphenylsilyloxy)-6-methylhept-1-en-4-ol (10). To a cold (−20 °C) suspension of CuI (268 mg, 1.4 mmol) in THF (10 mL) was added a solution of vinylmagnesium bromide (1 M in THF, 21 mL, 21 mmol) via a syringe under an argon atmosphere. The resulting mixture was stirred for 5 min and then cooled to −40 °C before adding a solution of epoxide **9A** (2.5 g, 7.0 mmol) in THF (10 mL). The reaction mixture was warmed to −20 °C and stirred for 1 h at this temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The product was purified by silica gel column chromatography (SiO_2, 3% EtOAc in hexane) to yield alcohol **10** (2.42 g (90%) as a clear liquid:

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R_f = 0.4 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{24}$ = −5.93° (*c* 4.30, $CHCl_3$); IR ν_{max} 3396, 2363, 1641, 1107, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.62 (m, 4H), 7.47−7.33 (m, 6H), 5.83 (m, 1H), 5.16−5.06 (m, 2H), 3.75 (m, 1H), 3.50 (d, *J* = 6.0 Hz, 2H), 2.45 (bs, 1H), 2.31−2.12 (m, 2H), 1.89 (dd, *J* = 12.8, 6.8 Hz, 1H), 1.51 (m, 1H), 1.35 (m, 1H), 1.06 (s, 9H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 135.0, 133.5, 129.6, 127.6, 117.6, 69.7, 69.0, 42.6, 41.6, 33.2, 26.8, 19.20, 17.2; MS (ESI) *m*/*z* 405 $[M + Na]^+$; HRMS (ESI, TOF) calcd for $C_{24}H_{34}O_2SiNa$ $[M + Na]^+$ 405.2225, found 405.2228.

***tert*-Butyl((2*S*,4*R*)-4-methoxy-2-methylhept-6-enyloxy)-diphenylsilane (11).** Alcahol **10** was converted to O-methylated compound **11** according to the reported procedure:[9] R_f = 0.5 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{24}$ = −12.02° (*c* 3.60, $CHCl_3$); IR ν_{max} 1638, 1104, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.63 (m, 4H), 7.45−7.34 (m, 6H), 5.78 (m, 1H), 5.05 (t, *J* = 9.0 Hz, 2H), 3.53 (m, 1H), 3.43 (m, 1H), 3.34−3.27 (m, 4H), 2.33−2.16 (m, 2H), 1.88 (m, 1H), 1.60 (m, 1H), 1.21 (m, 1H), 1.05 (s, 9H), 0.96 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 135.6, 134.7, 133.9, 129.4, 127.5, 116.9, 78.1, 69.2, 56.2, 38.0, 37.5, 32.3, 26.8, 19.3, 16.9; MS (ESI) *m*/*z* 397 $[M + H]^+$; HRMS (ESI, Orbitrap) calcd for $C_{25}H_{37}O_2Si$ $[M + H]^+$ 397.25573, found 397.25617.

***tert*-Butyl((2*S*,4*S*)-4-methoxy-2-methyl-5-((*R*)-oxiran-2-yl)-pentyloxy)diphenylsilane (12A) and (2*S*,4*S*,6*S*)-7-(*tert*-Butyldiphenylsilyloxy)-4-methoxy-6-methylheptane-1,2-diol (12B).** Epoxide **12A** and the diol **12B** were prepared by following the same procedure as used above for the synthesis of **9A** and **9B**.

*Analytical data for **12A**:* R_f = 0.6 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{24}$ = +2.54° (*c* 2.75, $CHCl_3$); IR ν_{max} 3047, 2931, 2859, 1736, 1465, 1427, 1189, 1103, 821, 741, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.62 (m, 4H), 7.47−7.32 (m, 6H), 3.57−3.41 (m, 3H), 3.35 (s, 3H), 3.02 (m, 1H), 2.79 (m, 1H), 2.47 (m, 1H), 1.86 (m, 1H), 1.79−1.65 (m, 2H), 1.61 (m, 1H), 1.2 (m, 1H), 1.05 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 135.8, 134.1, 129.7, 127.7, 77.1, 69.3, 57.0, 49.8, 47.7, 38.4, 37.8, 32.5, 27.0, 19.5, 17.2; MS (ESI) *m*/*z* 413 $[M + H]^+$; HRMS (ESI, TOF) calcd for $C_{25}H_{36}O_3SiNa$ $[M + Na]^+$ 435.2331, found 435.2335.

*Analytical data for compound **12B**:* R_f = 0.4 (SiO_2, 60% EtOAc in hexane); $[\alpha]_D^{24}$ = +5.95° (*c* 4.45, $CHCl_3$); IR ν_{max} 3393, 2930, 2859, 2362, 1464, 1427, 1103, 1081, 819, 740, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.61 (m, 4H), 7.48−7.33 (m, 6H), 3.84 (m, 1H), 3.72 (br s, 1H), 3.65−3.52 (m, 2H), 3.51−3.38 (m, 3H), 3.33 (s, 3H), 2.20 (br s, 1H), 1.91−1.69 (m, 2H), 1.69−1.48 (m, 2H), 1.25 (m, 1H), 1.06 (s, 9H), 0.96 (d, *J* = 6.42 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 133.8, 133.7, 129.6, 127.6, 79.6, 71.5, 68.7, 66.7, 55.7, 37.2, 37.1, 32.3, 26.8, 19.2, 17.6; MS (ESI) *m*/*z* 453 $[M + Na]^+$; HRMS (ESI, TOF) calcd for $C_{25}H_{38}O_4SiNa$ $[M + Na]^+$ 453.243, found 453.2444.

(4*S*,6*S*,8*S*)-9-(*tert*-Butyldiphenylsilyloxy)-6-methoxy-8-methylnonan-4-ol (13). Alcohol **13** was synthesized from the epoxide **12A** in 88% yield by following the same procedure as used above for the synthesis of compound **10**: R_f = 0.4 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{24}$ = +4.75° (*c* 4.50, $CHCl_3$); IR ν_{max} 3449, 2954, 2930, 2861, 1463, 1427, 1384, 1104, 1085, 819, 704, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.62 (m, 4H), 7.48−7.33 (m, 6H), 3.88 (m, 1H), 3.62−3.41 (m, 3H), 3.32 (s, 3H), 2.97 (br s, 1H), 1.91−1.57 (m, 4H), 1.56−1.15 (m, 5H), 1.06 (s, 9H), 1.01−0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.8, 129.5, 127.9, 127.6, 77.6, 68.8, 68.4, 56.5, 39.8, 39.2, 36.9, 32.5, 26.8, 19.2, 18.8, 17.3, 14.1; MS (ESI) *m*/*z* 443 $[M + H]^+$; HRMS (ESI, TOF) calcd for $C_{27}H_{42}O_3SiNa$ $[M + Na]^+$ 465.2800, found 465.2805.

((2*S*,4*S*,6*S*)-6-(Benzyloxy)-4-methoxy-2-methylnonyloxy)-(*tert*-butyl)diphenylsilane (14). To a solution of compound **13** (600 mg, 1.45 mmol) in cyclohexane and CH_2Cl_2 (2/1, 6 mL) were added benzyl trichloroacetimidate (30 mg, 2.9 mmol) and trifluoromethanesulfonic acid (0.5 mL, 0.14 mmol) at 0 °C, and stirring was continued at room temperature for 2 h. The reaction mixture was then diluted with CH_2Cl_2 and passed through a short pad of silica gel and washed with cyclohexane and DCM (2/1, 10 mL). The combined filtrates were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude benzyl ether was purified by column chromatography (SiO_2, 2% EtOAc in hexane) afforded compound **14** as a colorless oil (632 mg, 88%): R_f = 0.5 (SiO_2, 2.5% EtOAc in hexane); $[\alpha]_D^{24}$ = +14.11° (*c* 1.76, $CHCl_3$); IR ν_{max} 3030, 2927, 2859, 1459, 1369, 1091, 836, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.63 (m, 4H), 7.45−7.29 (m, 11H), 4.51 (ABq, *J* = 11.3 Hz, 2H), 3.63−3.41 (m, 4H), 3.24 (s, 3H), 1.78 (m, 1H), 1.64−1.31 (m, 7H), 1.16 (m, 1H), 1.05 (s, 9H), 0.99−0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 135.6, 133.9, 129.5, 128.3, 127.8, 127.5, 127.4, 75.8, 75.7, 71.0, 69.0, 56.0, 40.2, 37.8, 36.6, 32.4, 26.9, 19.3, 18.3, 17.2, 14.3; MS (ESI) *m*/*z* 533 $[M + H]^+$; HRMS (ESI, TOF) calcd for $C_{34}H_{48}O_3SiNa$ 555.3270 $[M + Na]^+$, found 555.3254.

(2*S*,4*S*,6*S*)-6-(Benzyloxy)-4-methoxy-2-methylnonan-1-ol (15). Compound **14** (600 mg, 1.1 mmol) was converted to alcohol **15** according to the procedure reported earlier.[12a] Purification by column chromatography (SiO_2, 15−20% EtOAc in hexane) afforded compound **15** as a colorless liquid (328 mg, 99%): R_f = 0.2 (SiO_2, 20% EtOAc in hexane); $[\alpha]_D^{29}$ = +12.57° (*c* 1.79, $CHCl_3$); IR ν_{max} 3424, 2927, 2870, 1457, 1373, 1200, 1085, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5H), 4.58 and 4.46 (ABq, *J* = 11.3 Hz, 2H), 3.57 (m, 1H), 3.50−3.39 (m, 3H), 3.29 (s, 3H), 2.18 (br s, 1H), 1.78 (dq, *J* = 12.9, 6.5 Hz, 1H), 1.72−1.55 (m, 4H), 1.50 (m, 1H), 1.45−1.35 (m, 2H), 1.30 (m, 1H), 0.96−0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 128.3, 127.8, 127.5, 76.0, 70.9, 68.4, 56.3, 39.8, 39.1, 36.4, 33.4, 18.2, 17.8, 14.3; MS (ESI) *m*/*z* 317 $[M + Na]^+$; HRMS (ESI, TOF) calcd for $C_{18}H_{30}O_3Na$ $[M + Na]^+$ 317.2092, found 317.2088.

(3*R*,5*S*,7*S*)-7-(Benzyloxy)-5-methoxy-3-methyldecanenitrile (16). Compound **15** (200 mg, 1.0 mmol) was converted to cyano compound **16** by following the same procedure as described in earlier published work.[12a] Purification by column chromatography (SiO_2, 5% EtOAc in hexane) afforded compound **16** as a colorless liquid (259 mg, 84%): R_f = 0.2 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{24}$ = +38.02° (*c* 3.60, $CHCl_3$); IR ν_{max} 3031, 2927, 2362, 1516, 1367, 1089, 835, 776, 738, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 4.60 and 4.43 (ABq, *J* = 11.3 Hz, 2H), 3.58 (m, 1H), 3.42 (m, 1H), 3.26 (s, 3H), 2.39−2.19 (m, 2H), 2.02 (m, 1H), 1.70−1.30 (m, 8H), 1.09 (t, *J* = 6.8 Hz, 3H), 0.99−0.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 128.3, 127.8, 127.5, 118.6, 75.8, 75.7, 71.0, 56.4, 40.5, 39.8, 36.3, 27.3, 24.8, 19.7, 18.1, 14.3; MS (ESI) *m*/*z* 326 $[M + Na]^+$; HRMS (ESI, TOF) calcd for $C_{19}H_{29}NO_2Na$ $[M + Na]^+$ 326.2096, found 326.2090.

(*S*)-Dimethyl 6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-2-oxohexylphosphonate (5). To a solution of freshly distilled dimethyl methylphosphonate (2 mL, 18 mmol) in anhydrous THF (37 mL) was added *n*-BuLi (1.6 M solution in hexane, 9 mL, 15 mmol) in a dropwise manner at −78 °C and stirred at the same temperature for 1 h. Compound **17** (2 g, 6.2 mmol) was added to the reaction mixture as a THF solution (12 mL) slowly over a period of 10 min. The resulting mixture was stirred for 1 h at the same temperature and then warmed to ambient temperature before quenching with saturated aqueous NH_4Cl solution at 0 °C. The product was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The hydroxyl compound (R_f = 0.4, 70% EtOAc in hexane) thus obtained was directly used after silica gel column chromatography for the next reaction.

To a solution of the alcohol prepared above (2.5 g, 5.5 mmol) in CH_2Cl_2 (16 mL) was added $NaHCO_3$ (1.4 g, 16.5 mmol) at room temperature. Dess−Martin periodinane (DMP; 4.7g, 11 mmol) was added to the reaction mixture and stirred for 1 h at room temperature under a nitrogen atmosphere. Saturated $Na_2S_2O_3$ and $NaHCO_3$ were then added, and the biphasic mixture was stirred for 15 min and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 20% EtOAc in hexane) provided pure compound **5** as a colorless oil (2.2 g, 80%): R_f = 0.5 (SiO_2, 60% EtOAc in hexane); $[\alpha]_D^{24}$ = +9.61° (*c* 2.85, $CHCl_3$); IR ν_{max} 3421, 2953, 2929, 2856, 1714, 1460, 1367, 1254, 1031, 836, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m,

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5H), 4.47 (ABq, J = 11.3 Hz, 2H), 4.33 (dd, J = 11.3, 6.1 Hz, 1H), 3.76 (d, J = 1.5 Hz, 3H), 3.74 (d, J = 1.5 Hz, 3H), 3.53 (td, J = 6.1,1.5 Hz, 2H), 3.12 (s, 1H), 3.05 (s, 1H), 2.79 (d, J = 6.0 Hz, 2H), 1.84−1.66 (m, 2H), 0.85 (s, 9H), 0.04 (d, J = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 138.2, 128.2, 127.5, 127.4, 72.8, 66.3, 66.2, 52.9, 52.8, 51.3, 43.2, 41.5, 37.0, 25.7, 17.8; MS (ESI) m/z 445 $[M + H]^+$; HRMS (ESI, TOF) calcd for $C_{21}H_{37}O_6PSiNa$ $[M + Na]^+$ 467.1994, found 467.1974.

(3*S*,9*R*,11*S*,13*S*,*E*)-1,13-Bis(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-11-methoxy-9-methylhexadec-6-en-5-one (18). To a solution of **16** (200 mg, 0.66 mmol) in CH_2Cl_2 (4 mL) was added DIBAL-H (1 M, 1.4 mL, 1.4 mmol) at −78 °C, and the mixture was stirred for 1 h at the same temperature. Then it was quenched with 3 N aqueous NaOH solution (1.45 mL) and stirred for an additional 1 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 (6 mL), washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. The aldehyde **6** (R_f = 0.3; SiO_2, 10% EtOAc in hexane) thus obtained was directly used after flash chromatography for the next reaction.

To compound **5** (340 mg, 0.76 mmol) in anhydrous CH_3CN (6 mL) were added LiCl (33 mg, 0.76 mmol) and DIPEA (1.3 mL, 7.6 mmol) sequentially at room temperature, and the reaction mixture was stirred for 30 min. Aldehyde **6** (179 mg, 0.58 mmol) was transferred to the reaction mixture as a solution of CH_3CN under a nitrogen atmosphere, and the resulting mixture was stirred at the same temperature for 12 h. CH_3CN was evaporated on a rotary evaporator, and the residue was dissolved in EtOAc, washed with a saturated aqueous solution of NH_4Cl, water, and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 5% EtOAc in hexane) afforded pure compound **18** as a colorless oil (271.6 mg, 77%): R_f = 0.6 (SiO_2, 10% EtOAc in hexane); $[\alpha]_D^{24}$ = +21.20° (c 2.90, $CHCl_3$); IR ν_{max} 3030, 2953, 2927, 2859, 1669,1627, 1459, 1369, 1252, 1091, 836, 777, 738, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.26 (m, 10H), 6.76 (m, 1H), 6.08 (d, J = 15.9 Hz, 1H), 4.59 (d, J = 10.9 Hz, 1H), 4.52−4.43 (m, 2H), 4.38 (dt, J = 11.9, 5.9 Hz, 1H), 3.62−3.51 (m, 4H), 3.45 (m, 1H), 3.25 (s, 3H), 2.77 (dd, J = 6.9, 5.9 Hz, 1H), 2.62 (dd, J = 5.9, 4.9 Hz, 1H), 2.21 (m, 1H), 2.03 (m, 1H), 1.88−1.75 (m, 3H), 1.67−1.45 (m, 5H), 1.44−1.35 (m, 2H), 1.20 (m, 1H), 0.98−0.90 (m, 6H), 0.85 (s, 9H), 0.03 (d, J = 20.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 146.1, 138.8, 138.4, 132.6, 128.3, 127.8, 127.5, 127.4, 75.7, 75.6, 72.8, 70.9, 66.8, 66.5, 56.4, 47.8, 41.6, 40.2, 40.1, 37.5, 36.4, 29.6, 29.1, 25.7, 19.7, 18.2, 17.9, 14.3; MS (ESI) m/z 648 $[M + Na]^+$; HRMS (ESI, TOF) calcd for $C_{38}H_{60}O_5SiNa$ $[M + Na]^+$ 647.4107, found 647.4107.

(3*S*,9*R*,11*S*,13*S*,*E*)-1,13-Bis(benzyloxy)-3-hydroxy-11-methoxy-9-methylhexadec-6-en-5-one (4). To a solution of compound **18** (150 mg, 0.24 mmol) in anhydrous CH_3CN (1 mL) was added HF-py complex (40%, 0.1 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was cautiously poured into aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 16% EtOAc in hexane) afforded compound **4**(104 mg, 80%) as a colorless oil: R_f = 0.4 (30%, EtOAc in hexane); $[\alpha]_D^{24}$ = +22.73° (c 4.35, $CHCl_3$); IR ν_{max} 3441, 2926, 2869, 2363, 1659, 1456, 1367, 1090, 739, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.18 (m, 10H), 6.75 (m, 1H), 6.03 (d, J = 15.82 Hz, 1H), 4.56 and 4.40 (ABq, J = 11.86 Hz, 2H), 4.48 (s, 2H), 4.21 (m, 1H), 3.63 (m, 2H), 3.54 (m, 1H), 3.43−3.28 (m, 2H), 3.20 (s, 3H), 2.65 (d, J = 5.93 Hz, 2H), 2.20 (m, 1H), 2.03 (m, 1H), 1.84−1.69 (m, 3H), 1.62−1.32 (m, 7H), 1.17 (m, 1H), 0.97−0.89 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 147.0, 139.0, 138.0, 132.0, 128.3, 128.2, 127.7, 127.6, 127.4, 75.7, 75.8, 73.1, 71.0, 67.8, 66.4, 56.4, 46.2, 41.6, 40.2, 40.1, 36.3, 36.1, 29.0, 19.8, 18.1, 14.2; MS (ESI) m/z 511 $[M + H]^+$; HRMS (ESI, TOF) calcd for $C_{32}H_{46}O_5Na$ $[M + Na]^+$ 533.3242, found 533.3240.

(2*R*,6*S*)-2-((2*S*,4*S*,6*S*)-6-(Benzyloxy)-4-methoxy-2-methylnonyl)-6-(2-(benzyloxy)ethyl)dihydro-2*H*-pyran-4(3*H*)-one (19A) and (2*S*,6*S*)-2-((2*S*,4*S*,6*S*)-6-(Benzyloxy)-4-methoxy-2-methylnonyl)-6-(2-(benzyloxy)ethyl)dihydro-2*H*-pyran-4(3*H*)-one (19B). To a stirred solution of compound **4** (66 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (3 mL) was added $Pd(CH_3CN)_4BF_4$ (6 mg, 10 mol %) at room temperature under an argon atmosphere, and the mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with Et_2O and filtered through a short pad of silica gel. The solvent was removed in vacuo to give the crude products, which were further purified by column chromatography (SiO_2, 8% EtOAc in hexane) to afford compound **19A** as a colorless oil (32 mg, 48%) and (SiO_2, 9% EtOAc in hexane) **19B** (8 mg, 12%).

*Analytical data for compound **19A**:* R_f = 0.5 (SiO_2, 20% EtOAc in hexane); $[\alpha]_D^{24}$ = +3.47° (c 0.835, $CHCl_3$); IR ν_{max} 2923, 2861, 1718, 1456, 1369, 1092, 738, 629 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.17 (m, 10H), 4.56 and 4.42 (two d, J = 12.0 Hz, 2H), 4.44 (s, 2H), 3.74 (m, 1H), 3.65−3.48 (m, 4H), 3.40 (m, 1H), 3.21 (s, 3H), 2.36−2.23 (m, 2H), 2.21−2.09 (m, 2H), 1.92−1.74 (m, 2H), 1.70−1.22 (m, 10H), 1.17 (m, 1H), 0.97−0.82 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 139.0, 138.3, 128.4, 128.3, 127.7, 127.6, 127.4, 75.8, 75.7, 74.6, 73.8, 70.9, 66.3, 56.4, 48.4, 47.9, 43.9, 42.4, 40.2, 36.6, 36.5, 25.9, 19.7, 18.3, 14.3; MS (ESI) m/z 353 $[M + Na]^+$; HRMS (ESI, TOF) calcd for $C_{32}H_{46}O_5Na$ $[M + Na]^+$ 533.3242, found 533.3229.

*Analytical data for compound **19B**:* R_f = 0.45 (20% EtOAc in hexane); $[\alpha]_D^{24}$ = −6.99° (c 0.30, $CHCl_3$); IR ν_{max} 2923, 2855, 2362, 1718, 1459, 1273, 1027, 709 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.16 (m, 10H), 4.60−4.36 (m, 4H), 4.25 (m, 1H), 4.13 (m, 1H), 3.64−3.45 (m, 3H), 3.41 (m, 1H), 3.21 (s, 3H), 2.52−2.40 (m, 2H), 2.21(dd, J = 14.0, 7.0 Hz, 1H), 2.14 (dd, J = 14.0, 6.0 Hz, 1H), 1.84 (m, 1H), 1.78−1.68 (m, 2H), 1.66−1.22 (m, 9H), 1.08 (m, 1H), 0.98−0.82 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 138.9, 138.3, 129.5, 128.3, 127.8, 127.6, 127.5, 75.9, 75.6, 73.0, 72.2, 70.9, 69.0, 66.2, 47.2, 46.9, 41.7, 40.2, 37.2, 34.6, 25.9, 22.6, 20.4, 18.5, 14.3; MS (ESI) m/z 353 $[M + Na]^+$; HRMS (ESI, Orbitrap) calcd for $C_{32}H_{46}O_5Na$ $[M + Na]^+$ 533.32375, found 533.32605.

(2*R*,6*S*)-2-((2*S*,4*S*,6*S*)-6-Hydroxy-4-methoxy-2-methylnonyl)-6-(2-hydroxyethyl)dihydro-2*H*-pyran-4(3*H*)-one (3). To a solution of **19A** (28 mg, 0.05 mmol) in EtOAc (8 mL) was added Pd−C (10%), and the mixture was hydrogenated using a H_2-filled balloon for 2 h. It was then filtered through a short pad of Celite, and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated in vacuo. Purification by column chromatography (SiO_2, 60% EtOAc in hexane) afforded compound **3** as a colorless oil (17.1 mg, 95%): R_f = 0.5 (100% EtOAc); $[\alpha]^{24}_D$ = +3.38° (c 1.95, $CHCl_3$); IR ν_{max} 3406, 2924, 2286, 1713, 1459, 1373, 1329, 1239, 1136, 1083 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94−3.76 (m, 4H), 3.71 (m, 1H), 3.54 (m, 1H), 3.37 (s, 3H), 2.41−2.21 (m, 4H), 1.92−1.66 (m, 6H), 1.53−1.32 (m, 4H), 1.31−1.18 (m, 3H), 0.94 (dd, J = 13.8, 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 77.5, 75.9, 75.5, 68.5, 60.0, 56.8, 48.3, 47.6, 43.8, 41.2, 40.1, 39.6, 38.2, 26.7, 20.0, 18.7, 14.0; MS (ESI) m/z 331 $[M + H]^+$, 353 $[M + Na]^+$; HRMS (ESI, Orbitrap) calcd for $C_{18}H_{35}O_5$ $[M + H]^+$ 331.24790, found 331.24827.

(1*R*,5*S*,7*S*,9*S*,11*R*)-7-Methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecane-3,13-dione (2). BAIB (12.8 mg, 0.04 mmol) was added to a solution of **3** (12 mg, 0.036 mmol) and TEMPO (0.56 mg, 0.003 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After the reaction mixture was stirred at room temperature for 5 h, the mixture was diluted with CH_2Cl_2 (2 mL), washed with saturated aqueous $Na_2S_2O_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were washed with aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. The crude aldehyde was immediately used for the next reaction.

The conversion of crude aldehyde to *seco* acid followed by its macrolactonization, leading to the formation of compound **2** (7 mg, 64%) from **3**, was carried out according to the reported procedure.[3a,2e,f]

*Analytical data for compound **2**:* R_f = 0.45 (20% EtOAc in hexane); $[\alpha]_D^{24}$ = +17.12° (c 0.80, $CHCl_3$); IR ν_{max} 2923, 1726, 1250, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (m, 1H), 4.04 (tt, J = 10.8, 2.9 Hz, 1H), 3.58 (m, 1H), 3.50 (dt, J = 9.8, 2.9 Hz, 1H), 3.33 (s, 3H), 2.71 (dd, J = 14.8, 3.9 Hz, 1H), 2.51 (dd, J = 14.8, 9.8 Hz, 1H),

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2.43 (m, 1H), 2.36−2.28 (m, 2H), 2.24 (dd, J = 14.8, 11.8 Hz, 1H), 1.85 (m, 1H), 1.73−1.46 (m, 6H), 1.42 (m, 1H), 1.38−1.16 (m, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.92 (t, 7.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 169.9, 79.7, 75.7, 73.4, 73.3, 56.2, 48.7, 46.9, 44.3, 42.5, 41.9, 39.9, 36.9, 31.0, 25.4, 18.9, 13.8; MS (ESI) m/z 349 $[M + Na]^+$; HRMS (ESI, Orbitrap) calcd for $C_{18}H_{30}O_5Na$ $[M + Na]^+$ 349.19885, found 349.19904.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H and ^{13}C NMR spectra for all of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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