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An alternative stereoselective synthesis of (-)-1-tetrahydropyrenophorol

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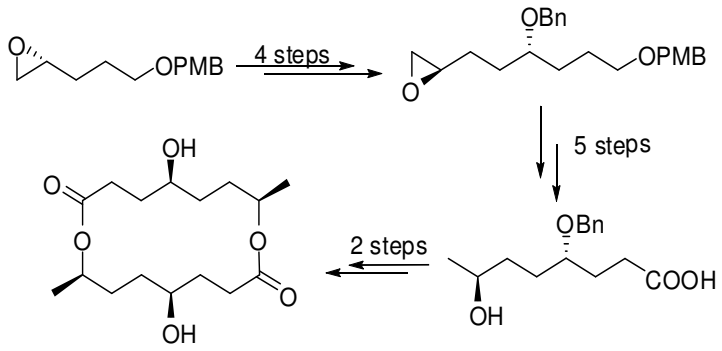
Abstract

Macrodiolides have become highly attractive target molecules because of their interesting structural features and biological properties, including antibacterial, antifungal, cytotoxic, and phytotoxic activity. A simple and efficient synthesis of the macrocyclic dilactone, (-)-1-tetrahydropyrenophorol, has been accomplished from commercially available compounds. The synthesis utilizes regioselective ring opening of a chiral epoxide, followed by asymmetric dihydroxylation and a Mitsunobu reaction for the construction of the macrolactone.



(-)-**1**-Tetrahydropyrenophorol

Keywords: (-)-1-Tetrahydropyrenophorol, macrodiolide, asymmetric dihydroxylation, cyclodimerisation, Mitsunobu reaction

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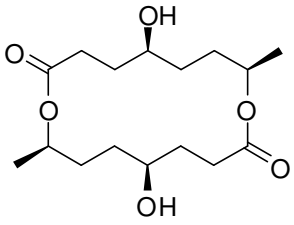
Introduction

Macrodiolides have become highly attractive target molecules to synthetic chemists in recent years because of their biological properties and interesting structural features. In nature, macrodiolides are found as both homodimers[1-4], consisting of two identical units and showing C_2 symmetry, and heterodimers[5], consisting of two different units. Many of these macrodiolides (both homo and hetero) exhibit potent biological activities, such as antibacterial, antifungal, cytotoxic, and phytotoxic activity.[6,9]

(-)-1-Tetrahydropyrenophorol (Fig. 1) is an example of a C_2-symmetric macrodiolide. It was isolated from the ethyl-acetate extract of a culture of an endophytic *Phoma* sp. isolated from the plant *Fagonia cretica*. It exhibits good herbicidal and algicidal and moderate fungicidal activities. The relative configuration of (-)-1-tetrahydropyrenophorol (**1**) was confirmed by X-ray single-crystal analysis. Its absolute configuration was determined by solid-state time-dependent density-functional theory (TDDFT) CD methodology.[2] Recently, a synthesis of (-)-1-tetrahydropyrenophorol was reported by Prataparedy *et al*.,[10] while Trost and Quintard[11] reported the total synthesis of (+)-tetrahydropyrenophorol.



(-)-1-Tetrahydropyrenophorol

Figure 1

Results and Discussion

In continuation of our work on the synthesis of biologically-active natural products,[12] we report herein an efficient straightforward and concise total synthesis of (-)-1-tetrahydropyrenophorol starting from commercially available starting materials.

As depicted in Scheme 1, retrosynthetic analysis of (**1)** envisioned that it could be obtained from the hydroxy-acid (**2)** *via* cyclodimerisation under Mitsunobu reaction conditions, followed by deprotection of the benzyl ether. The hydroxy-acid (**2)** could easily be prepared from the diol (**3)**, which in turn could be prepared from the known chiral epoxide (**4)**, all by simple chemical transformations.

Synthesis of (-)-1-tetrahydropyrenophorol (**1)** (Scheme 2) began with the reported chiral *p*-methoxybenzyloxy-epoxide (**4).**[13] Regioselective ring-opening of (**4)** by allyl magnesium chloride in the presence of CuI yielded the alcohol (**5)** in 87% yield, which, on subsequent benzylation with NaH and benzyl bromide at 0 °C, gave (**6)** in 91% yield. The terminal olefin group in (**6)** was subjected to asymmetric dihydroxylation with AD-mix-β in *t*-BuOH/H_2O to afford diol (**3)** in 79% yield (d.r. 9:1).[14] Selective monotosylation of the diol (**3)** using TsCl and Et_3N in CH_2Cl_2, followed by cyclization of the resulting monotosylate (**3a)** in the presence of K_2CO_3 in MeOH, afforded the chiral epoxide (**7)** in 77% yield.

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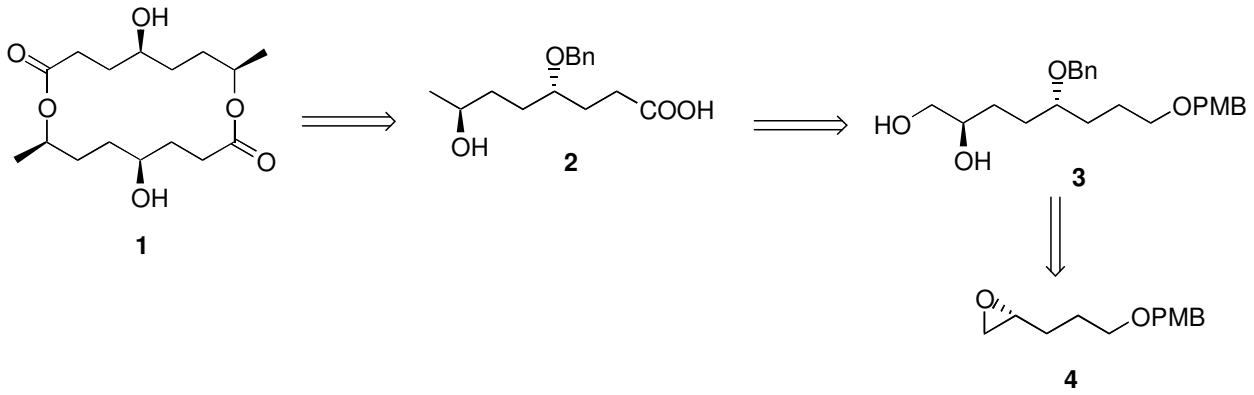
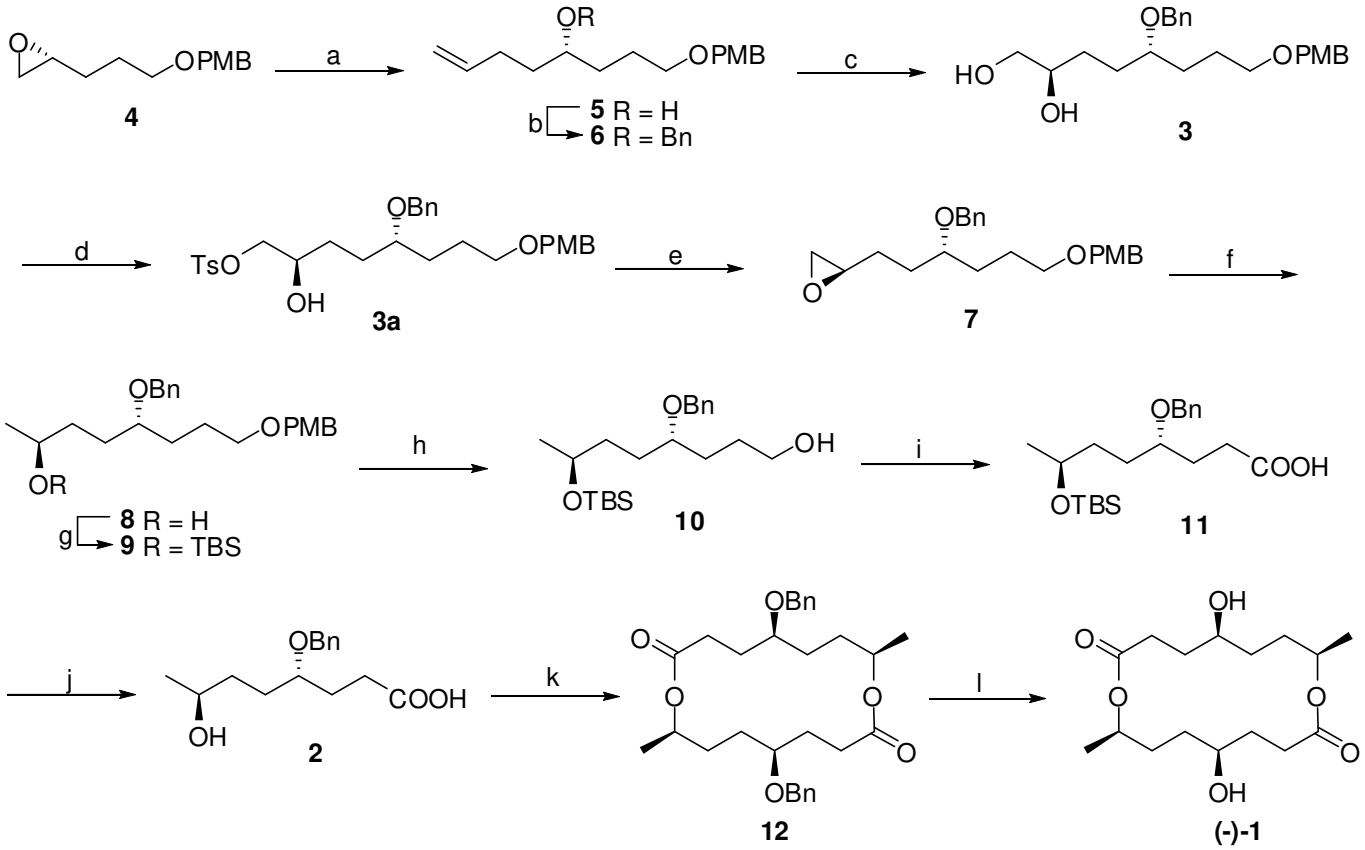


Scheme 1. Retrosynthesis model for (-)-1-tetrahydropyrenophorol (**1**) from *p*-methoxybenzyloxy-epoxide (4).



Scheme 2. Preparative route to (-)-1-tetrahydropyrenophorol (**1**). *Reagents and conditions*: (a) allyl chloride, Mg, CuI, dry ether, -40 ºC to rt, 6 h; (b) BnBr, NaH, THF, 0 °C to rt, 6 h; (c) AD-mix-β, *t*-BuOH/H_2O, 0 °C to rt, 48 h; (d) *p*-TsCl, Et_3N, rt, 2 h; (e) K_2CO_3, MeOH, rt, 1 h; (f) LAH, THF, 0 °C to rt, 3h; (g) TBSCl, imidazole, CH_2Cl_2, rt, 4 h; (h) DDQ, CH_2Cl_2:H_2O (19:1), rt, 3 h; (i) TEMPO, [bis(acetoxy)iodo]benzene, aq. CH_2Cl_2, 0 ºC, 1 h; (j) TBAF, THF, 0 °C to rt, 3 h; (k) Ph_3P, DEAD, toluene:THF (10:1) -20 °C, 10 h; (l) $TiCl_4$, CH_2Cl_2, 0 °C to rt, 1 h.

Regioselective opening of the epoxide (**7)** with LAH in dry THF furnished the alcohol (**8)** in 87% yield, which, on subsequent masking with t-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole at 0 °C, afforded (**9)** in 91% yield. Next, selective cleavage of the *p*-methoxybenzyloxy (PMB) ether from compound (**9)**, in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in aq. CH_2Cl_2, gave alcohol (**10)** in 86%

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yield. The alcohol (**10)** was then oxidized following treatment with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and [bis(acetoxy)iodo]benzene in aq. CH_2Cl_2, affording the corresponding carboxylic acid (**11)** in 75% yield, which, on desilylation with tetra-n-butylammonium fluoride (TBAF) in dry THF, gave the hydroxy-acid (**2)** in 86 % yield.

Following the successful synthesis of the hydroxyacid (**2)**, it was subjected to cyclodimerisation under Mitsunobu reaction conditions [Ph_3P and diethyl azodicarboxylate (DEAD)][15] at -20 ^oC for 10 h to furnish (**12)** in 59% yield. Finally, debenzylation of (**12)** with $TiCl_4$ in CH_2Cl_2 for 3 h afforded (-)-1-tetrahydropyrenophorol (**1**) in 77% yield. The spectroscopic data (^1H and ^{13}C NMR) and specific optical rotation ($[\alpha]_D^{25}$ −70.3 (*c* 0.54, $CHCl_3$)) of (**1)** were in good agreement with the reported values ($[\alpha]_D^{25}$ −68 (*c* 0.14, $CHCl_3$)).[10]

Conclusions

A concise stereoselective total synthesis of the macrodiolide, (-)-1-tetrahydropyrenophorol, was accomplished using an efficient combination of regioselective opening of a known chiral epoxide, subsequent asymmetric dihydroxylation, and Mitsunobu reaction.

Experimental Section

General. Solvents were dried over standard drying agents or freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (60-120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 ^oC in *vacuo*. ^1H NMR spectra were acquired at 300 MHz, 500 MHz and 600 MHz while ^{13}C NMR spectra were acquired at 75 MHz and 125 MHz, both with TMS as internal standard for solutions in $CDCl_3$. *J* values are given in Hz. The following abbreviations are used in reporting NMR data: s, singlet; brs, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet; and t, triplet. IR spectra were recorded on an FT IR spectrophotometer with NaCl optics. Optical rotations were measured on a digital polarimeter at 25 ^oC. Mass spectra were recorded with a direct inlet system or LC by MSD trap SL. The HRMS data were obtained using Q-TOF mass spectrometry.

(*S*)-1-(4-Methoxybenzyloxy)oct-7-en-4-ol (**5**). To a stirred solution of epoxide (4) (4.6 g, 20.72 mmol) in dry diethyl ether (100 mL), copper(I) iodide (1.96 g, 10.35 mmol) was added and the mixture was cooled to -40 ^oC. A solution of allylmagnesium chloride in ether [generated from Mg (1.49 g, 62.16 mmol) and allyl chloride (2.13 mL, 24.86 mmol in 50 mL ether)] was added. After the addition was complete, the mixture was stirred for 6 h and then quenched with aq. NH_4Cl solution (30 mL) dropwise. The residue was filtered using through celite and the filtrate was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 60-120 mesh, 12% EtOAc in pet. ether) to furnish (5) (4.75 g, 87%) as a yellow liquid. $[\alpha]_D^{25}$ +11.3 (*c* 1.5, $CHCl_3$); IR (neat): 3457, 3077, 2988, 2929, 1622, 1375, 1213, 854 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.19 (d, 2H, *J* 8.0 Hz), 6.89 (d, 2H, *J* 8.0 Hz), 5.83 (m, 1H), 4.99 (m, 2H), 4.47 (s, 2H), 3.79 (s, 3H), 3.68-3.57 (m, 1H), 3.49 (t, 2H, *J* 8.0 Hz), 2.81 (brs, 1H, -OH), 2.16-2.08 (m, 2H), 1.71-1.59 (m, 2H), 1.41-1.30 (m, 4H); ^{13}C NMR ($CDCl_3$,

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75 MHz): δ 159.3, 134.5, 130.3, 129.6, 114.6, 113.3, 76.1, 69.3, 68.3, 56.2, 37.2, 35.2, 31.2, 30.9; ESIMS: 287 $(M+ Na)^+$ HRMS (ESI): *m/z* calcd for $C_{16}H_{24}O_3Na$: 287.1626; found: 287.1631 $[M+Na]^+$.

(*S*)-1-((4-(Benzyloxy)oct-7-enyloxy)methyl)-4-methoxybenzene (**6**). To a cooled (0 ^oC) solution of (5) (4.4 g, 16.66 mmol) in dry THF (15 mL), NaH (1.2 g, 49.98 mmol) was added, stirred for 30 min and treated with a solution of benzyl bromide (2.36 mL, 19.92 mmol) in dry THF (10 mL). After stirring at room temperature for 6 h, the reaction mixture was quenched with sat. NH_4Cl solution (15 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layers were washed with water (2 × 30 mL), brine (30 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue purified by column chromatography (60-120 silica gel, 8% EtOAc in pet. ether) to furnish (6) (5.25 g, 91%) as a yellow liquid. $[\alpha]_D^{25}$ +141.7 (*c* 1.2, $CHCl_3$); IR (neat): 3071, 2989, 2935, 1617, 1515, 1248, 1061 cm^{-1} ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41-7.29 (m, 5H), 7.19 (d, 2H, *J* 8.5 Hz), 6.77 (d, 2H, *J* 8.4 Hz), 5.79 (m, 1H), 5.01 (m, 2H), 4.59 (d, 1H, *J* 10.6 Hz), 4.49 (s, 2H), 4.39 (d, 1H, *J* 10.6 Hz), 3.76 (s, 3H), 3.54 (t, 2H, *J* 7.1 Hz), 3.46-3.32 (m, 1H), 2.21-2.11 (m, 2H), 1.63-1.31 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 138.3, 136.6, 129.8, 129.0, 128.4, 128.1, 127.7, 114.7, 113.1, 79.1, 76.0, 73.1, 72.2, 56.1, 33.4, 32.4, 31.8, 29.8; HRMS (ESI): *m/z* calcd for $C_{23}H_{30}O_3Na$: 377.2091; found: 377.2096 $[M+Na]^+$.

(2*R*,5*R*)-5-(Benzyloxy)-8-(4-methoxybenzyloxy)octane-1,2-diol (**3**). A mixture of ADmix-β (11.20 g, 14.40 mmol) in 50 mL of *t*-BuOH/H_2O (1:1 v:v) was stirred at rt for 15 min, and then cooled to 0 ^oC. To this solution was added olefin (6) (5.1 g, 14.40 mmol). The reaction mixture was stirred at 0 ^oC for 48 h and then quenched with Na_2SO_3 (7.5 g) at 0 ^oC within 0.5 h. EtOAc (50 mL) was added to the reaction mixture, and the aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated. The crude product was purified by column chromatography on silica gel (30% EtOAc in pet. ether) to give the corresponding diol (3) (4.41 g, 79%) as a colorless oil: $[\alpha]_D^{25}$-66.8 (*c* 0.5, $CHCl_3$); IR (neat): 3457, 3069, 2952, 2846, 1613, 1518, 1247, 1079, 936, 707 cm^{-1} ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (m, 5H), 7.21 (d, 2H, *J* 8.3 Hz), 6.81 (d, 2H, *J* 8.4 Hz), 4.60 (d, 1H, *J* 11.0 Hz), 4.48 (d, 1H, J 11.0 Hz), 4.38 (s, 2H), 3.78 (s, 3H), 3.69-3.61 (m, 3H), 3.40-3.26 (m, 3H), 3.01 (brs, 1H, -OH), 2.42 (brs, 1H, -OH), 1.63-1.57 (m, 2H), 1.49-1.31 (m, 5H), 1.23-1.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.7, 136.6, 130.1, 129.8, 129.5, 129.3, 128.8, 113.9, 79.1, 76.2, 73.3, 72.4, 68.3, 56.7, 32.2, 31.6, 31.0, 29.8; HRMS (ESI): *m/z* calcd for $C_{23}H_{32}O_5Na$: 411.2148; found: 411.2141 $[M+Na]^+$.

(*R*)-2-[(*R*)-3-(Benzyloxy)-6-(4-methoxybenzyloxy)hexyl]oxirane (**7**). To a mixture of diol (3) (4.26 g, 10.97 mmol) in dry dichloromethane (30 mL) was added *p*-toluenesulfonyl chloride (2.08 g, 10.97 mmol), triethylamine (2.2 mL, 16.45 mmol). The reaction was stirred for 2 h at room temperature under nitrogen and was monitored by TLC. After completion of the reaction, the mixture was quenched by adding water. The solution was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phase washed with water, dried (Na_2SO_4), and concentrated to give (3a) as a yellow liquid which was immediately used for the next step without any purification.

To the above crude mixture in MeOH at 0 ^oC was added K_2CO_3 (2.2 g, 16.45 mmol). The resultant mixture was stirred for 1 h at the same temperature. After completion of the reaction (as indicated by TLC), the reaction was quenched by the addition of pieces of ice, and the methanol was evaporated off. The concentrated reaction mixture was then extracted with ethyl acetate (3 × 20 mL), the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography of the crude product using 10% EtOAc in pet. ether gave the epoxide (**7)** (3.12 g, 77%) as a colorless liquid. $[\alpha]_D^{25}$-74.8 (*c* 0.9, $CHCl_3$); ^{1}HNMR (300 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 7.14 (d, 2H, *J* 8.6 Hz), 6.80 (d, 2H, *J* 8.6 Hz), 4.52 (d, 1H, *J* 10.9 Hz), 4.41 (s, 2H), 4.32 (d, 1H, *J* 10.9 Hz), 3.68 (s, 3H), 3.51 (t, 2H, *J* 6.8 Hz), 3.42-3.31 (m, 1H), 2.91-2.86 (m, 1H), 2.67 (dd, 1H, *J* 5.1, 3.2 Hz), 2.44 (dd, 1H, J 5.1, 3.0 Hz), 1.69-1.58 (m, 2H), 1.41-1.21 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 138.2,

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130.1, 128.6, 128.4, 128.0, 127.8, 114.1, 78.9, 76.6, 73.4, 72.0, 56.1, 54.7, 45.1, 31.3, 30.8, 30.2, 29.8; ESIMS: 393 (M+ Na)$^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{30}O_4Na$: 393.2042; found: 393.2047 [M+Na]$^+$.

(2*S*,5*R*)-5-(Benzyloxy)-8-(4-methoxybenzyloxy)octan-2-ol (**8**)**.** To a stirred suspension of LAH (0.46 g, 12.16 mmol) in dry THF (5 mL), a solution of (7) (3.0 g, 8.10 mmol) in dry THF (10 mL) was added dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was cooled to 0 °C, treated with saturated aq. Na_2SO_4 solution, filtered, and the filtrate was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (60-120 Silica gel, 18% EtOAc in pet. ether) to give (8) (2.62 g, 87%) as a colorless syrup. $[\alpha]_D^{25}$+28.1 (*c* 0.49, $CHCl_3$); IR (neat): 3448, 2932, 1611, 1513, 1455, 1374, 1093, 928 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 7.19 (d, 2H, J 8.7 Hz), 6.82 (d, 2H, J 8.7 Hz), 4.56 (d, 1H, J 11.1 Hz), 4.48 (d, 1H, J 11.1 Hz), 4.41 (s, 2H), 3.80-3.69 (m, 1H), 3.67 (s, 3H), 3.55 (t, 2H, J 6.6 Hz), 3.48-3.32 (m, 1H), 2.41 (brs, 1H, -OH), 1.69-1.58 (m, 2H), 1.47-1.33 (m, 3H), 1.28-1.13 (m, 3H), 1.06 (d, 3H, J 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.7, 138.2, 129.8, 129.5, 129.1, 128.7, 128.4, 113.9, 79.2, 75.9, 73.2, 72.7, 69.3, 54.9, 37.3, 32.1, 31.3, 30.7, 25.4; ESIMS: 373 (M+ H)$^+$. HRMS (ESI): *m/z* calcd for $C_{23}H_{32}O_4Na$: 395.2195; found: 395.2211 [M+Na]$^+$.

[(2*S*,5*R*)-5-(Benzyloxy)-8-(4-methoxybenzyloxy)octan-2-yloxy](*tert*-butyl)dimethylsilane (**9**)**.** A mixture of the alcohol (8) (2.5 g, 6.72 mmol) and imidazole (1.37 g, 20.16 mmol) in dry CH_2Cl_2 (20 mL) was treated with TBSCl (1.20 g, 8.06 mmol) at 0 ^{o}C under nitrogen atmosphere and stirred at room temperature for 4 h. The reaction mixture was quenched with aq. NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (60-120 silica gel, 12% EtOAc in pet. ether) to furnish (9) (2.97 g, 91%) as a colorless liquid, $[\alpha]_D^{25}$-57.4 (*c* 0.76, $CHCl_3$); IR (neat): 3069, 2931, 2858, 1613, 1512, 1247, 1105, 1083, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.22 (m, 5H), 7.19 (d, 2H, *J* 8.4 Hz), 6.79 (d, 2H, *J* 8.4 Hz), 4.53 (d, 1H, *J* 10.6 Hz), 4.43-4.27 (m, 3H), 3.68 (s, 3H), 3.59-3.42 (m, 1H), 3.40-3.27 (m, 3H), 1.70-1.50 (m, 4H), 1.49-1.31 (m, 3H), 1.22 (d, 3H, *J* 6.6 Hz), 1.18-1.05 (m, 1H), 0.81 (s, 9H), 0.16 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 137.2, 129.8, 128.8, 128.3, 127.9, 127.7, 113.8, 78.7, 75.9, 73.2, 71.6, 67.1, 55.9, 36.2, 33.3, 32.8, 31.6, 26.3, 24.1, 17.3, -4.1; ESIMS: 487 (M+ H)$^+$. HRMS (ESI): *m/z* calcd for $C_{29}H_{46}O_4SiNa$: 509.3064; found: 509.3055 [M+Na]+.

(4*R*,7*S*)-4-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)octan-1-ol (**10**)**.** To a solution of the silane (9) (2.76 g, 5.67 mmol) in aq. CH_2Cl_2 (20 mL, 19:1), DDQ (1.54 g, 6.81 mmol) was added and stirred at room temperature for 3 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (10 mL), filtered and washed with CH_2Cl_2 (30 mL). The filtrate was washed with water (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (60-120 Silica gel, 20% EtOAc in pet. ether) to furnish (10) (1.78 g, 86%). $[\alpha]_D^{25}$+46.1 (*c* 0.9, $CHCl_3$); IR (neat): 3470, 2983, 2927, 1612, 1513, 1458, 1374, 1248, 1173, 1090, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.22 (m, 5H), 4.59 (s, 2H), 3.66-3.54 (m, 1H), 3.48 (t, 2H, *J* 6.5 Hz), 3.33 (m, 1H), 2.98 (brs, 1H), 1.68-1.49 (m, 5H), 1.47-1.30 (m, 2H), 1.22 (d, 3H, *J* 6.3 Hz), 1.17-1.09 (m, 1H), 0.83 (s, 9H), 0.12 (s, 3H), 0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 139.3, 129.2, 128.8, 128.3, 79.2, 72.4, 67.6, 61.9, 39.2, 33.4, 33.3, 31.2, 26.8, 23.9, 19.3, -4.2, -3.9; ESIMS: 389 (M+ Na)$^+$. HRMS (ESI): *m/z* calcd for $C_{21}H_{38}O_3SiNa$: 389.2486; found: 389.2488 [M+Na]$^+$.

(4*S*,7*S*)-4-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)octanoic acid (**11**). To a stirred solution of the octanol (**10)** (1.55 g, 4.23 mmol) in CH_2Cl_2:H_2O (1:1, 10 mL), TEMPO (0.19 g, 1.27 mmol) and [bis(acetoxy)iodo]benzene (0.40 g, 1.27 mmol) were added at 0 ^{o}C and stirred for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) to give acid (**11)** (1.2 g, 75%) as a colorless gummy oil. $[\alpha]_D^{25}$ = -105.3 (c 0.25, $CHCl_3$); IR

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(neat): 3435, 2958, 2855, 1727, 1614, 1520, 1369, 1299, 1174, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.36 (m, 5H), 4.54 (d, 1H, *J* 10.8 Hz), 4.46 (d, 1H, *J* 10.8 Hz), 3.61-3.50 (m, 1H), 3.42-3.37 (m, 1H), 2.36 (t, *J* 7.1 Hz, 2H), 1.59-1.33 (m, 6H), 1.21 (d, 3H, *J* 6.8 Hz), 0.91 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): 177.2, 139.8, 129.6, 129.0, 128.7, 79.3, 72.7, 67.6, 38.3, 33.7, 30.3, 29.6, 26.9, 24.4, 19.7, -4.3, -3.9. ESIMS: 403 $(M+ Na)^+$. HRMS (ESI): m/z calcd for $C_{21}H_{36}O_4SiNa$: 403.2283; found: 403.2286 $[M+Na]^+$.

(4*S*,7*S*)-4-(Benzyloxy)-7-hydroxyoctanoic acid (**2**). To a cooled (0°C) solution of the octanoic acid (11) (1.1 g, 2.89 mmol) in dry THF (15 mL) under nitrogen atmosphere, TBAF (4.3 mL, 4.34 mmol) was added and stirred for 3 h. After completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with water (2 × 10 mL), brine (10 mL), dried (Na_2SO_4), evaporated, and the residue was purified by column chromatography (60-120 silica gel, 55% EtOAc in pet. ether) to give (2) (0.66 g, 86%) as a white solid which was used for the next step without purification. $[\alpha]_D^{25}$ = -16.8 (c 0.25, $CHCl_3$); IR (neat): 3490, 2976, 2840, 1725, 1619, 1520, 1360, 1268, 1175, 1012 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.47 (s, 2H), 3.77-3.68 (m, 1H), 3.48 (m, 1H), 3.04 (brs, 1H), 2.34 (t, *J* 6.6 Hz, 2H), 1.71-1.64 (m, 1H), 1.57-1.38 (m, 5H), 1.19 (d, 3H, *J* 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): 176.6, 139.3, 129.3, 129.0, 128.6, 80.1, 72.4, 66.6, 36.3, 32.1, 30.4, 29.3, 23.8. ESIMS: 289 $(M+ Na)^+$. HRMS (ESI): m/z calcd for $C_{15}H_{22}O_4Na$: 289.1416; found: 289.1421 $[M+Na]^+$.

(5*S*,8*R*,13*S*,16*R*)-5,13-Bis(benzyloxy)-8,16-dimethyl-1,9-dioxacyclohexadecane-2,10-dione (**12**). To a solution of the hydroxy acid (2) (0.26 g, 0.97 mmol) and Ph_3P (1.28 g, 4.88 mmol) in toluene:THF (10:1, 260 mL), DEAD (2.76 mL, 17.46 mmol) was added at -20 °C and stirred under N_2 atmosphere for 10 h. Solvent was evaporated under reduced pressure, and the residue purified by column chromatography (60-120 silica gel, 15% EtOAc in pet. ether) to afford (12) (0.14 g, 59%) as a colorless oil. $[\alpha]_D^{25}$ +7.9 (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.22 (m, 10H), 5.03-4.91 (m, 2H), 4.51 (s, 4H), 3.58-3.41 (m, 2H), 2.34 (t, 4H, *J* 6.6 Hz), 1.79-1.60 (m, 8H), 1.57-1.41 (m, 2H), 1.37-1.29 (m, 2H), 1.19 (d, *J* 6.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz): 177.9, 139.4, 129.1, 128.7, 128.3, 128.0, 79.4, 73.1, 69.0, 33.2, 32.4, 29.8, 29.4, 23.2; ESIMS: 519 $(M+ Na)^+$. HRMS (ESI): *m/z* calcd for $C_{30}H_{40}O_6Na$: 519.2744; found: 519.2751 $[M+Na]^+$.

(-)-1-Tetrahydropyrenophorol (**1**). To a stirred solution of the dilactone (12) (0.090 g, 0.18 mmol) in dichloromethane (2 mL), $TiCl_4$ (0.04 mL, 0.36 mmol) in dichloromethane was added at 0 °C and stirred for 1 h. Sat. aq. $NaHCO_3$ solution (10 mL) was added and the mixture extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water (15 mL), brine (10 mL), dried (Na_2SO_4) and concentrated. The crude residue was purified by column chromatography (silica gel, 60-120 mesh, 30% EtOAc in pet. ether) to afford the tetrahydropyrenophorol (1) (44 mg) in 77% yield as a white solid. M.p. 126–128 °C; $[\alpha]_D^{25}$ −70.3 (c 0.54, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): *δ* 5.05-4.99 (m, 2H), 3.59-3.51 (m, 2 H), 2.47-2.34 (m, 4 H), 1.91-1.78 (m, 4 H), 1.75-1.63 (m, 4 H), 1.52-1.44 (m, 2 H), 1.38-1.33 (m, 2 H), 1.22 (d, *J* 6.1 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 173.4, 69.8, 68.1, 32.9, 31.0, 30.8, 30.6, 20.1; ESIMS: 317 $(M+ H)^+$. HRMS (ESI): *m/z* calcd for $C_{16}H_{28}O_6Na$: 339.1785; found: 339.1788 $[M+Na]^+$.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra associated with this paper can be found in the online version.

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