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Total Synthesis of the Nonenolide Xyolide Using a Regioselective Nucleophilic Epoxide Opening Approach

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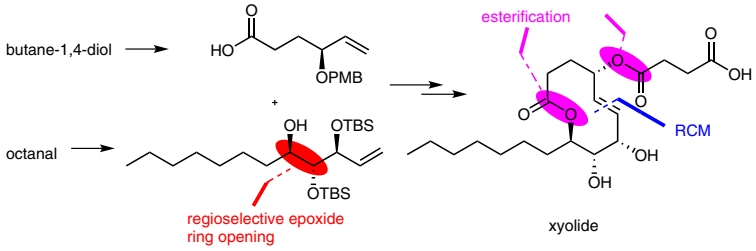

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Abstract The total synthesis of the nonenolide xyolide is described as a convergent synthesis in 16 steps from the commercially available starting material butane-1,4-diol. The key reactions involved are: Sharpless asymmetric epoxidation, Pinnick oxidation, acid-mediated nucleophilic regioselective epoxide ring opening, Steglich esterification, and ring-closing metathesis.

Key words natural product, xyolide, Sharpless epoxidation, regioselective ring opening, ring-closing metathesis

Ten-membered lactones (Figure 1) are abundant and represent the core of many natural products and display a wide range of pharmacological properties, such as antibacterial, antifungal, antiviral, and anticancer activity.[1] Microcarpalide[2] and achaetolide[3] shows antimicrofillament activity, phomol shows antibacterial and antifungal activity,[4] and stagonolide A and herbarumins inhibit the growth of invasive weeds.[5] Xyolide is a newly identified 10-membered-ring lactone isolated as a secondary fungal metabolite from the Amazonian endophytic fungus *Xylaria fejeensis* and it shows good inhibitory activity against the growth of *Pythium ultimum*, an oomcyete plant pathogen with MIC = 425 μM.[6] The structural fascination and biological activity of xyolide has attracted synthetic chemists and led to its synthesis by different routes.[7]

As part of our regular research program on the synthesis of biologically active natural and synthetic compounds,[8] herein we wish to report, our synthetic strategy for the stereoselective total synthesis of the nonenolide xyolide utilizing regioselective 2,3-epoxy ring opening, Steglich esterification, and ring-closing metathesis methods as shown in Scheme 1.

As shown in the retrosynthetic analysis, our synthetic strategy started from commercially available butane-1,4-diol for the acid fragment **10** (Scheme 2) and octanal for the hydroxyalkene fragment **18** (Scheme 3). Butane-1,4-diol was selectively monoprotected using *tert*-butyl(chloro)di-

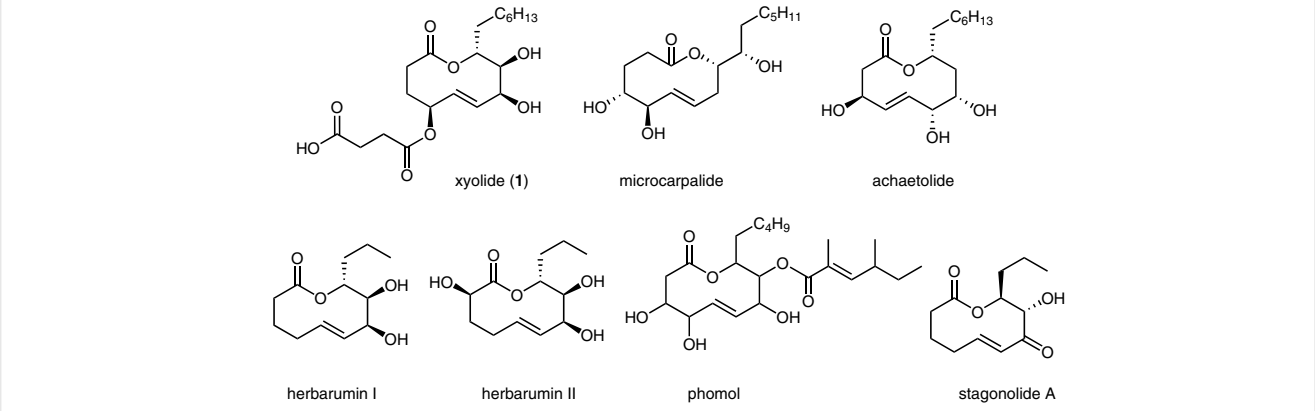
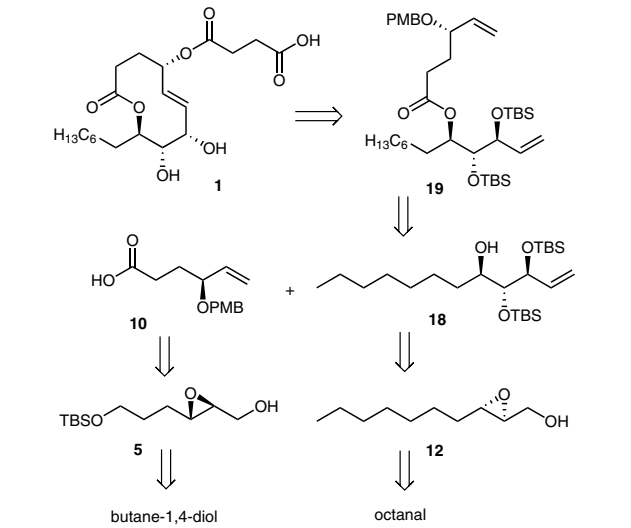


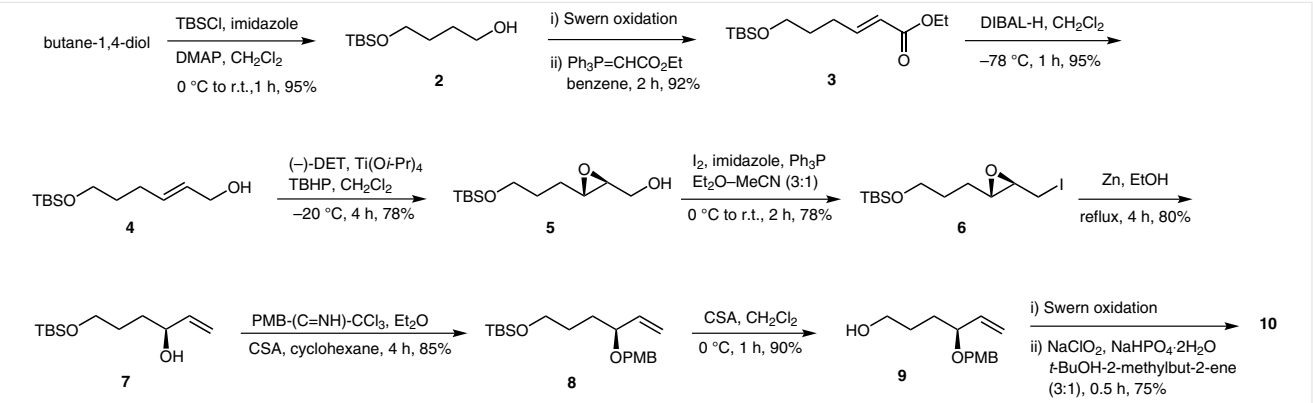
Figure 1 Naturally occurring nonenolides



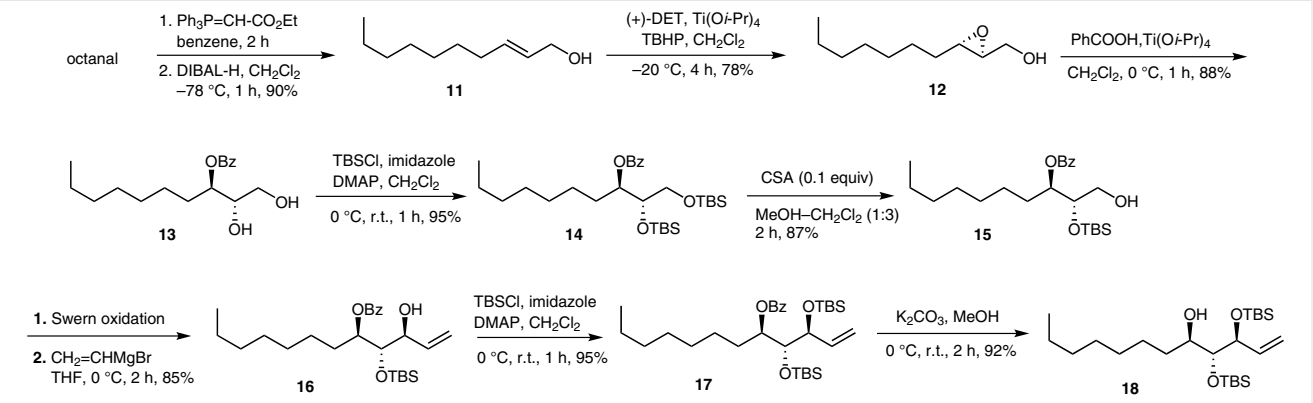
Scheme 1 Retrosynthesis of xyolide

methylsilane in the presence of imidazole in dichloromethane to give 4-(*tert*-butyldimethylsiloxy)butan-1-ol (**2**)[9] in 95% yield. Swern oxidation[10] of compound **2** followed by C2 Wittig[11] olefination in benzene at room temperature afforded ethyl (*E*)-6-(*tert*-butyldimethylsiloxy)hex-2-enoate (**3**) in 92% (two steps). Reduction of the obtained ester **3** was carried out using diisobutylaluminum hydride[12] to give (*E*)-6-(*tert*-butyldimethylsiloxy)hex-2-en-1-ol (**4**) in 95% yield, which was subjected to Sharpless asymmetric epoxidation[13] with (–)-diethyl tartrate, titanium(IV) isopropoxide, and *tert*-butyl hydroperoxide to give enantiopure epoxide **5** in 78% yield. Conversion of the free alcohol into the iodo group was achieved using molecular iodine, imidazole, and triphenylphosphine in diethyl ether–acetonitrile (3:1) at 0 °C to obtain *tert*-butyl{3-[(2*S*,3*R*)-3-(iodomethyl)oxiran-2-yl]propoxy}dimethylsilane (**6**) in 78%. Compound **6** was converted into secondary allylic alcohol **7** (80% yield) using activated zinc in ethanol at reflux for four hours.[14] Protection of the hydroxy group in compound **7** with a 4-methoxybenzyl imidate[15] produced the PMB-protected compound **8** in 85% yield.

Desilylation of compound **8** with 10-camphorsulfonic acid in dichloromethane produced primary alcohol **9** in 90% yield, which was subjected to Swern oxidation followed by Pinnick oxidation[16] using sodium chlorite under buffer conditions to afford (*S*)-4-(4-methoxybenzyloxy)hex-5-enoic acid (**10**) in 75% yield (after two steps).[17]



Scheme 2 Synthesis of fragment **10**



Scheme 3 Synthesis of fragment **18**

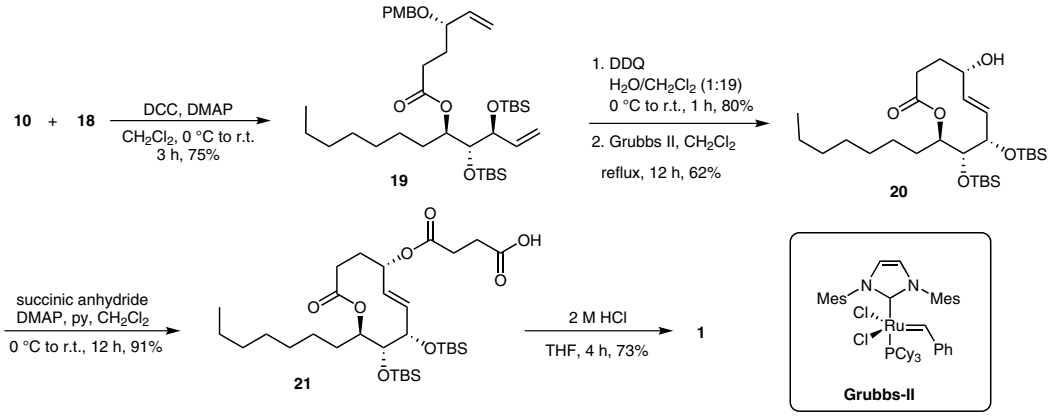
Synthesis of segment **18** began from commercially available octanal, which was subjected to C2 Wittig followed by reduction with diisobutylaluminum hydride to afford (*E*)-dec-2-en-1-ol (**11**) in 95% yield. Sharpless asymmetric epoxidation of allylic alcohol **11** was performed using (+)-diethyl tartrate, titanium(IV) isopropoxide, and *tert*-butyl hydroperoxide in dichloromethane to give enantiopure [(2*R*,3*R*)-3-heptyloxiran-2-yl]methanol (**12**) in 78% yield with 95% ee. The treatment of chiral epoxide **12** with acid-mediated nucleophilic regioselective 2,3-ring opening in presence of benzoic acid and titanium(IV) isopropoxide gave (2*S*,3*R*)-3-(benzoyloxy)decane-1,2-diol (**13**) in 88% yield as a single isomer,[18] which was confirmed by ^{1}H NMR spectroscopy. This regioselective ring-opening protocol serve as the key synthetic intermediate in this approach. Thus, obtained diol benzoate **13** was subjected to protection with *tert*-butyl(chloro)dimethylsilane in the presence of imidazole in dichloromethane to give, (2*S*,3*R*)-1,2-bis(*tert*-butyldimethylsiloxy)decan-3-yl benzoate (**14**) in 95% yield.

Selective desilylation of compound **14** was carried out using 10-camphorsulfonic acid in a mixture of methanol–dichloromethane (1:3) solvent to afford (2*S*,3*R*)-3-(benzoyloxy)-2-(*tert*-butyldimethylsiloxy)decan-1-ol (**15**) in 87% yield. The obtained alcohol **15** was oxidized under Swern conditions to give the corresponding aldehyde, which was directly subjected to Grignard reaction with 1 M vinylmagnesium bromide in tetrahydrofuran in anhydrous tetrahydrofuran to produce the secondary allyl alcohol **16** as a mixture of *anti*/*syn* diastereomers (9:1). The major diastereomer was separated by column chromatography to give pure *anti* isomer (3*S*,4*S*,5*R*)-5-(benzoyloxy)-4-(*tert*-butyldimethylsiloxy)dodec-1-en-3-ol (**16**) (85% yield in two steps). The TBS protection of alcohol **16** with *tert*-butyl(chloro)dimethylsilane, imidazole, and a catalytic amount of 4-(dimethylamino)pyridine gave silyl ether **17** in 95% yield. Treatment of compound **17** with potassium carbonate in methanol resulted in deprotection of the benzoyl group to give (3*S*,4*R*,5*R*)-3,4-bis(*tert*-butyldimethylsiloxy)dodec-1-en-5-ol (**18**) in 92% yield.

The coupling of fragments **10** and **18** (Scheme 4) was successfully performed using the Steglich protocol[19] in the presence of *N*,*N*′-dicyclohexyldicarbodiimide and 4-(dimethylamino)pyridine in dichloromethane to give ester **19** in 75% yield. Deprotection of the PMB group was carried out with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in a mixture of water–dichloromethane (1:19) solvent to afford the diene ester in 80% yield; Ring-closing metathesis reaction with this compound using Grubbs' second-generation catalyst[20] (10 mol%) afforded the 10-membered lactone **20** as the sole product (*E*-isomer) in 82% yield. Compound **20** was subjected to esterification with succinic anhydride[21] using pyridine with 4-(dimethylamino)pyridine as the catalyst in dichloromethane to give acid **21** (91%), which on desilylation with 2 M hydrochloric acid gave xyolide (**1**) in 73% yield. The spectroscopic data and optical rotation of synthetic compound **1** are comparable with that in the literature, which is good agreement with the reported xyolide.[1]

In conclusion, the stereoselective total synthesis of xyolide is accomplished in 16 steps from readily available butane-1,4-diol. The main feature of the synthesis includes the construction of a chiral fragment by using Sharpless asymmetric epoxidation, acid-mediated nucleophilic regioselective epoxide opening, and ring-closing metathesis.

All reagents were purchased from commercial sources and were used without additional purification. All reactions were performed under an inert atmosphere unless otherwise noted. THF was freshly distilled over Na/benzophenone ketyl. Petroleum ether refers to the fraction boiling in the 60–80 °C range. Column chromatography was performed on silica gel (Acme grade 60–120 mesh). All reactions were monitored by TLC to completion; TLC plates (Merck precoated silica gel 60 F 254 plates) were made visible with UV light, in an I_2 chamber



Scheme 4 Synthesis of xyolide **1**

or with phosphomolybdic acid spray. Melting points were recorded using a Buchi M-560 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer. ^{1}H NMR spectra were recorded on Bruker-300 MHz, spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Optical rotations were measured on Rudolph Autopol IV polarimeter at 25 °C.

4-(*tert*-Butyldimethylsiloxy)butan-1-ol (2)

To a stirred solution of butane-1,4-diol (3 mL, 33.3 mmol) in anhydrous CH_2Cl_2 (30 mL) was added imidazole (2.73 g, 66.6 mmol) at 0 °C and the mixture was stirred for 30 min. TBSCl (5 g, 33.3 mmol) dissolved in CH_2Cl_2 (20 mL) was added and the mixture was stirred at r.t. for 1 h (TLC monitoring). The mixture was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc–hexane, 2:8) to afford TBS ether **2** as a colorless syrup; yield: 6.4 g (95%).

IR (neat): 3682, 3611, 3339, 3017, 2930, 2858, 1424, 1265, 1219, 1091, 1025, 942, 860, 784 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.72 (t, *J* = 6.5 Hz, 2 H), 3.62 (t, *J* = 6.5 Hz, 2 H), 1.53–1.64 (m, 4 H), 0.90 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.3, 62.8, 30.2, 29.9, 25.9, 25.5, 18.3, –3.5.

MS (ESI): *m*/*z* = 205 [M + H]$^+$.

Ethyl (*E*)-6-(*tert*-Butyldimethylsiloxy)hex-2-enoate (3)

To a stirred solution of oxalyl chloride (5.5 g, 44.1 mmol) in anhydrous CH_2Cl_2 (40 mL) at –78 °C was added DMSO (6.9 g, 88.2 mmol) over 20 min and the mixture was stirred for an additional 15 min. Alcohol **2** (6 g, 29.4 mol) dissolved in CH_2Cl_2 (10 mL) was added and the mixture was stirred for 30 min. Et_3N (20.4 mL, 147 mmol) was added dropwise and the mixture was stirred at r.t. for 1 h (TLC monitoring). The mixture was quenched with water and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the aldehyde which was used in the next step.

The aldehyde was dissolved in benzene (60 mL), the Wittig ylide (12.4 g, 35.2 mmol) was added at r.t. and the mixture was stirred for 2 h (TLC monitoring). The solvent was evaporated and the residue was purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to afford unsaturated ester **3** as a colorless liquid; yield: 7.3 g (92%).

IR (neat): 2929, 2855, 1717, 1653, 1368, 1317, 1268, 1213, 1040, 980, 771 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.9 (dt, *J* = 15.8, 6.9 Hz, 1 H), 5.82 (d, *J* = 15.4 Hz, 1 H), 4.19 (q, *J* = 6.4 Hz, 2 H), 3.62 (t, *J* = 6.5 Hz, 2 H), 2.28 (q, *J* = 6.5 Hz, 2 H), 1.60–1.71 (m, 2 H), 1.28 (t, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 148.3, 121.7, 61.9, 60.2, 30.8, 28.4, 25.8, 25.6, 14.2, –3.6.

MS (ESI): *m*/*z* = 273 [M + H]$^+$.

(*E*)-6-(*tert*-Butyldimethylsiloxy)hex-2-en-1-ol (4)

To a stirred solution of unsaturated ester **3** (7.2 g, 25.7 mmol) in anhydrous CH_2Cl_2 (50 mL) at –78 °C was added 25% DIBAL-H in toluene (29.2 mL, 51.5 mmol) slowly over 15 min. The mixture was stirred at this temperature for 1 h, cooled to 0 °C, and quenched with sat. sodium potassium tartrate and the mixture stirred for 2 h. The mixture was passed through a bed of Celite. The filtrate was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc–hexane 2:8) to obtain allylic alcohol **4** as a colorless liquid; yield: 5.6 g (95%).

IR (neat): 3355, 2928, 2856, 1468, 1254, 1219, 1100, 968, 836, 773 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.70 (q, *J* = 5.4 Hz, 2 H), 4.10 (d, *J* = 5.4 Hz, 2 H), 3.62 (t, *J* = 6.4 Hz, 2 H), 2.05–2.15 (m, 2 H), 1.55–1.68 (m, 2 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.8, 129.0, 63.7, 62.4, 32.1, 30.8, 28.4, 25.8, –5.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{27}O_2Si$: 231.1774; found: 231.1785.

{(2*S*,3*S*)-3-[3-(*tert*-Butyldimethylsiloxy)propyl]oxiran-2-yl}methanol (5)

To a stirred mixture of molecular sieves powder (4 Å, 5.5 g) and Ti(O*i*-Pr)$_4$ (0.85 mL, 2.8 mmol) in CH_2Cl_2 (15 mL) at –20 °C was added (–)-DET (0.6 mL, 3.5 mmol) dissolved in CH_2Cl_2 (2 mL) and the mixture was stirred for 15 min. Then 3 M TBHP in toluene (15.9 mL, 47.8 mmol) was added. After 30 min, a solution of allylic alcohol **4** (5.5 g, 23.9 mmol) dissolved in CH_2Cl_2 (8 mL) was added. The resulting mixture was stirred at –20 °C for 4 h and then quenched with H_2O (17 mL) followed by 20% NaOH solution (5.7 mL). The mixture was stirred at r.t. for 45 min, and it was filtered and the filtrate was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residual oil was purified by column chromatography (hexanes–EtOAc, 1.5: 8.5) to give chiral epoxy alcohol **5** as a colorless liquid; yield: 4.5 g (78%).

$[\alpha]_D^{25}$ +0.2 (*c* 0.5, $CHCl_3$).

IR (neat): 3441, 2927, 2856, 1692, 1467, 1253, 1219, 1096, 835, 773 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87–3.92 (m, 1 H), 3.60–3.71 (m, 3 H), 2.90–3.10 (m, 2 H), 1.60–1.72 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.5, 61.6, 58.4, 55.8, 29.0, 28.1, 25.9, 18.3, –5.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{27}O_3Si$: 247.1724; found: 247.1737.

***tert*-Butyl{3-[(2*S*,3*R*)-3-(iodomethyl)oxiran-2-yl]propoxy}dimethylsilane (6)**

To a solution of epoxy alcohol **5** (4.5 g, 18.2 mmol) in Et_2O–MeCN (3:1, 40 mL) was added Ph_3P (4.8 g, 18.2 mmol) followed by imidazole (1.5 g, 21.9 mmol) at 0 °C and the mixture was stirred for 10 min. Then I_2 (4.6 g, 18.2 mmol) was added at 0 °C and the mixture was stirred for 2 h at r.t. (TLC monitoring). The mixture was quenched with sat. $Na_2S_2O_3$ (15 mL) and extracted with EtOAc (3 × 20 mL). The organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated and residue was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:9.5) to afford epoxy iodo **6** as a colorless liquid; yield: 5 g (78%).

$[\alpha]_D^{25}$ +3.2 (*c* 0.5, $CHCl_3$).

IR (neat): 2928, 2856, 1692, 1467, 1253, 1219, 1096, 835, 773 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62–3.72 (m, 2 H), 3.20–3.30 (m, 1 H), 2.95–3.10 (m, 2 H), 2.70–2.80 (m, 1 H), 1.60–1.72 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.3, 58.3, 28.9, 28.2, 25.8, 18.2, 4.9, –5.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{26}O_2ISi$: 357.0741; found: 357.0761.

(*S*)-6-(*tert*-Butyldimethylsiloxy)hex-1-en-3-ol (7)

To a stirred solution of epoxy iodo **6** (5 g, 14 mmol) in EtOH (20 mL) was added activated Zn dust (9.1 g, 140 mmol) and the mixture was stirred at reflux for 4 h. After complete consumption of the starting material, the mixture was passed through a Celite bed. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, EtOAc–hexane, 2:8) to afford allylic alcohol **7** as a colorless liquid; yield: 2.7 g (80%).

$[\alpha]_D^{25}$ +1.4 (*c* 0.5, $CHCl_3$).

IR (neat): 3392, 2926, 2855, 1467, 1387, 1361, 1253, 1099, 991, 920, 834 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.84–5.91 (m, 1 H), 5.24 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.10 (dd, *J* = 17.2, 1.3 Hz, 1 H), 4.10–4.18 (m, 1 H), 3.67 (t, *J* = 7.0 Hz, 2 H), 2.75 (br. s, 1 H), 1.52–1.56 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 114.2, 72.6, 63.3, 34.4, 28.7, 25.9, 25.6, –5.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{27}O_2Si$: 231.1774; found: 231.1785.

***tert*-Butyl{[(*S*)-4-(4-methoxybenzyloxy)hex-5-en-1-yl]oxy}dimethylsilane (8)**

To a stirred solution of 4-methoxybenzyl alcohol (3.5 g, 25.3 mmol) in Et_2O (20 mL) was added a suspension of NaH (0.2 g, 60%, 5 mmol) dissolved in Et_2O (20 mL) at r.t. The resulting mixture was stirred for 30 min and cooled to 0 °C, to this was added trichloroacetonitrile (1.93 mL, 1.2 mmol) slowly and stirring was continued at r.t. for 6 h. The solvent was evaporated to give an orange syrup, which was dissolved in anhyd hexane (50 mL) containing a few drops of MeOH. This suspension was shaken vigorously and filtered on Celite bed; filtrate was concentrated to afford the imidate.

The above imidate (6.1 g, 21.7 mmol) was taken up in cyclohexane (30 mL) and added to a solution of alcohol **7** (2.5 g, 10.8 mmol) dissolved in CH_2Cl_2 (15 mL). The resulting mixture was cooled to 0 °C and CSA (0.25 g, 2.17 mmol) was added and the mixture was stirred at r.t. for 4 h to give a white precipitate of trichloroacetamide. The solution was filtered off, and washed with CH_2Cl_2. The filtrate was washed with sat. $NaHCO_3$ and brine. The solvent was evaporated and the residue was purified by column chromatography (silica gel, EtOAc–hexane, 1: 9) to give PMB ether **8** as a pale yellow liquid; yield: 3.2 g (85%).

$[\alpha]_D^{25}$ –19.3 (*c* 0.45, $CHCl_3$).

IR (neat): 2952, 2925, 2854, 1626, 1512, 1464, 1247, 1173, 1093, 833, 773 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 7.0 Hz, 2 H), 6.88 (d, *J* = 7.0 Hz, 2 H), 5.69–5.77 (m, 1 H), 5.23–5.29 (m, 2 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 4.28 (d, *J* = 11.2 Hz, 1 H), 3.79 (s, 3 H), 3.74–3.78 (m, 1 H), 3.59–3.63 (m, 2 H), 1.18–1.96 (m, 4 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 139.1, 130.8, 129.3, 116.9, 113.6, 80.0, 69.8, 63.0, 55.2, 31.7, 28.6, 25.9, –5.3.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{35}O_3Si$: 351.2350; found: 351.2370.

(*S*)-4-(4-Methoxybenzyloxy)hex-5-en-1-ol (9)

To a stirred solution of **8** (3 g, 8.5 mmol) in anhydrous CH_2Cl_2 (25 mL) was added CSA (0.55 g, 1.7 mmol) and the mixture was stirred at 0 °C for 1 h (TLC monitoring). The mixture was quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The crude alcohol was purified by column chromatography (silica gel, EtOAc–hexane, 2:8) to afford primary alcohol **9** as a colorless liquid; yield: 1.8 g (90%).

$[\alpha]_D^{25}$ –22.4 (*c* 0.4, $CHCl_3$).

IR (neat): 3393, 2923, 2854, 1611, 1512, 1462, 1300, 1246, 1174, 1055, 772 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 7.0 Hz, 2 H), 6.88 (d, *J* = 7.0 Hz, 2 H), 5.72–5.82 (m, 1 H), 5.20–5.30 (m, 2 H), 4.53 (d, *J* = 11.2 Hz, 1 H), 4.28 (d, *J* = 11.2 Hz, 1 H), 3.80 (s, 3 H), 3.74–3.78 (m, 1 H), 3.59 (t, *J* = 6.5 Hz, 2 H), 1.18–1.96 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 138.7, 130.4, 129.4, 117.6, 113.7, 80.0, 69.8, 62.8, 55.2, 32.2, 28.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}O_3Na$: 259.1304; found: 259.1317.

(*S*)-4-(4-Methoxybenzyloxy)hex-5-enoic Acid (10)

To a stirred solution of oxalyl chloride (1 mL, 10.8 mmol) in anhydrous CH_2Cl_2 (40 mL) at –78 °C was added DMSO (1.6 mL, 21.6 mmol) over 20 min. The resulting mixture was stirred for an additional 15 min. Alcohol **9** (1.7 g, 7.2 mmol) dissolved in CH_2Cl_2 (10 mL) was added slowly and the mixture was stirred for 30 min. To this mixture was added Et_3N (5 mL, 136 mmol) and the mixture was stirred at r.t. for 1 h (TLC monitoring). The mixture was quenched with water and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), and concentrated in vacuo to give the aldehyde.

To a stirred mixture of the aldehyde (1.6 g, 4.9 mmol) in *t*-BuOH–2-methylbut-2-ene (3:1, 20 mL) at 0 °C was added a solution of $NaClO_2$ (1.2 g, 9.9 mmol) and NaH_2PO_4 (2.1 g, 9.9 mmol) dissolved in the minimum quantity of water. Stirring was continued for 30 min at r.t. (TLC monitoring). The mixture was diluted with H_2O (20 mL) and *t*-BuOH was removed under reduced pressure; the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give the crude acid, which was purified by column chromatography (hexane–EtOAc, 7:3) to afford acid **10** as a colorless liquid; yield: 1.3 g (75%).

$[\alpha]_D^{25}$ –22.0 (*c* 0.5, $CHCl_3$) [Lit.[17a] $[\alpha]_D^{25}$ –27.4 (*c* 0.1, $CHCl_3$)].

IR (neat): 3459, 3074, 2954, 2854, 1706, 1611, 1512, 1421, 1246, 1174, 1034, 929, 851, 736 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 7.5 Hz, 2 H), 6.89 (d, *J* = 7.5 Hz, 2 H), 5.68–5.80 (m, 1 H), 5.25–5.32 (m, 2 H), 4.53 (d, *J* = 11.2 Hz, 1 H), 4.28 (d, *J* = 11.2 Hz, 1 H), 3.79 (s, 3 H), 3.76–3.78 (m, 1 H), 2.5 (t, *J* = 7.2 Hz, 2 H), 1.18–1.96 (m 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 159.1, 138.1, 130.4, 129.3, 117.6, 113.7, 78.8, 69.8, 55.2, 30.1, 30.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}O_4Na$: 273.1097; found: 273.1110.

(*E*)-Dec-2-en-1-ol (11)

To a stirred mixture of octanal (2 g, 15.6 mmol) in benzene (60 mL) was added the Wittig ylide (10.9 g, 31.2 mmol) at r.t. and the mixture was stirred for 1 h (TLC monitoring). The solvent was evaporated and the residue was purified by column chromatography (silica gel, EtOAc–hexane, 1:9) to afford the unsaturated ester as white solid. Thus obtained ester (2.8 g, 14.14 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) at –78 °C and to this was added 25% DIBAL-H in toluene (16 mL, 28.28 mmol) slowly over 15 min. The mixture was stirred

at this temperature for 2 h, cooled to 0 °C, quenched with sat. sodium potassium tartrate (15 mL), and stirred for 2 h. The mixture was passed through bed of Celite and the filtrate was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc–hexane 2:8) to give allylic alcohol **11** as a as colorless liquid; yield: 2.2 g (90%, 2 steps).

IR (neat): 3355, 2928, 2856, 1696, 1552, 1219, 1100, 968, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.60–5.73 (m, 2 H), 4.09 (d, *J* = 6.2 Hz, 2 H), 2.01–2.07 (m, 2 H), 1.22–1.41 (m, 10 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.6, 128.7, 63.8, 32.2, 31.8, 29.1, 22.6, 14.0.

MS (ESI): *m*/*z* = 157 $[M + H]^+$.

[(2*S*,3*S*)-3-Heptyloxiran-2-yl]methanol (12)

To a stirred mixture of molecular sieves powder (4 Å, 2 g) and Ti(O*i*-Pr)$_4$ (0.43 mL, 1.5 mmol) in CH_2Cl_2 (15 mL) at –20 °C was added (+)-DET (0.4 mL, 1.9 mmol) dissolved in CH_2Cl_2 (2 mL) and the mixture was stirred for 15 min. Then 3 M TBHP in toluene (9.2 mL, 25.6 mmol) was added and the mixture was stirred for 30 min. To this mixture, allylic alcohol **11** (2 g, 12.8 mmol) dissolved in CH_2Cl_2 (10 mL) was added slowly. The resulting mixture was stirred at –20 °C for 4 h and then quenched with H_2O (8.7 mL) followed by the addition of 20% NaOH solution (3 mL). The mixture was stirred at r.t. for 45 min, then it was filtered and the filtrate was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (EtOAc–hexanes, 1:9) to give chiral epoxy alcohol **12** as a colorless liquid; yield: 1.72 g (78%); 95% ee [Chiral HPLC (Gilson, Chiralpak IC column, 250 × 4.6 mm, hexane–*i*-PrOH, 95:5, flow rate 1.5 mL/min, 25 °C, λ_{max} = 210 nm)].

$[\alpha]_D^{25}$ –31.4 (*c* 0.5, $CHCl_3$) [Lit.[13b,22] $[\alpha]_D^{20}$ –36.5 (*c* 2.8, $CHCl_3$).

IR (neat): 3392, 2923, 2854, 1512, 1463, 1377, 1214, 1079, 1032, 880, 732 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.91 (dd, *J* = 12.5, 2.4 Hz, 1 H), 3.62 (dd, *J* = 12.5, 4.2 Hz, 1 H), 2.90–2.97 (m, 2 H), 1.54–1.61 (m, 2 H), 1.38–1.52 (m, 2 H), 1.23–1.37 (m, 8 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.7, 58.4, 56.0, 31.7, 31.5, 29.3, 29.1, 25.9, 22.6, 14.0.

MS (ESI): *m*/*z* = 195 $[M + Na]^+$.

(2*S*,3*R*)-3-(Benzoyloxy)decane-1,2-diol (13)

To a stirred solution of epoxy alcohol **12** (1.6 g, 9.3 mmol) in anhydrous CH_2Cl_2 (20 mL) was added Ti(O*i*-Pr)$_4$ (2.75 mL, 13.9 mmol) under N_2 at 0 °C. The mixture was stirred for 15 min, then benzoic acid (1.7 mg, 13.9 mmol) was added and the stirring was continued for a further 1 h at 0 °C (TLC monitoring). Aq 15% tartaric acid solution (25 mL) was added and stirring was continued until the distinct phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic phases were washed with sat. $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (hexanes–EtOAc, 6:4) to yield diol **13** as a colorless oil; yield: 2.48 g (88%).

$[\alpha]_D^{25}$ +22.3 (*c* 0.5, $CHCl_3$).

IR (neat): 3457, 2923, 2854, 1738, 1512, 1454, 1244, 1108, 1079, 1032, 880, 731 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.12 (m, 2 H), 7.52–7.62 (m, 1 H), 7.41–7.48 (m, 2 H), 5.05–5.14 (m, 1 H), 3.69–3.78 (m, 2 H), 3.60–3.66 (m, 1 H), 1.75–1.93 (m, 2 H), 1.18–1.39 (m, 10 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 133.3, 129.7, 128.4, 74.9, 73.0, 62.4, 31.7, 30.7, 29.3, 29.0, 25.4, 22.5, 14.1.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{27}O_4$: 295.1903; found: 295.1896.

(2*S*,3*R*)-1,2-Bis(*tert*-butyldimethylsiloxy)decan-3-yl Benzoate (14)

To a stirred solution of diol **13** (2 g, 6.8 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C was added imidazole (1 g, 14.9 mmol) and the mixture was stirred for 15 min. TBSCl (2 g, 13.6 mmol) dissolved in anhydrous CH_2Cl_2 (5 mL) was added followed by DMAP (cat.) and the mixture was stirred for 1 h at r.t. (TLC monitoring). Water was added to the mixture and it was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine and dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:9.5) to afford TBS ether **14** as a colorless liquid; yield: 3.37 g (95%).

$[\alpha]_D^{25}$ +5.7 (*c* 0.5, $CHCl_3$).

IR (neat): 2953, 2856, 2311, 1720, 1467, 1271, 1253, 1108, 834, 774, 709 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.12 (m, 2 H), 7.52–7.62 (m, 1 H), 7.41–7.48 (m, 2 H), 5.26–5.29 (m, 1 H), 3.95–3.99 (m, 1 H), 3.55–3.66 (m, 2 H), 1.77–1.87 (m, 1 H), 1.63–1.70 (m, 1 H), 1.18–1.42 (m, 10 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.06 (s, 6 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 132.6, 129.6, 128.2, 75.8, 74.3, 64.8, 31.7, 29.5, 29.1, 28.3, 25.9, 25.7, 25.5, 22.6, 14.0, –4.8, –4.4, –5.5, –5.4.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{55}O_4Si_2$: 523.3633; found: 523.3604.

(2*S*,3*R*)-3-(Benzoyloxy)-2-(*tert*-butyldimethylsiloxy)decan-1-ol (15)

To a stirred solution of **14** (3 g, 5.7 mmol) in MeOH–CH_2Cl_2 (1:3, 24 mL) was added CSA (0.13 g, 0.57 mmol) and the mixture was stirred for 2 h. When the reaction was complete, water was added and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The residue was purified by using column chromatography (silica gel, EtOAc–hexane, 2:8) to afford alcohol **15** as a colorless liquid; yield: 2 g (87%).

$[\alpha]_D^{25}$ +3.5 (*c* 0.5, $CHCl_3$).

IR (neat): 3450, 2927, 2856, 1717, 1465, 1274, 1108, 1050, 834, 775 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.12 (m, 2 H), 7.52–7.62 (m, 1 H), 7.41–7.48 (m, 2 H), 5.26–5.29 (m, 1 H), 3.95–3.99 (m, 1 H), 3.55–3.66 (m, 2 H), 2.02–2.05 (m, 1 H), 1.70–1.80 (m, 2 H), 1.25–1.35 (m, 10 H), 0.93 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.10 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 132.9, 129.6, 128.3, 75.1, 74.0, 63.3, 31.7, 29.9, 29.4, 29.1, 25.8, 25.5, 22.6, 14.0, –4.5, –4.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{41}O_4Si$: 409.2768; found: 409.2757.

(3*S*,4*S*,5*R*)-5-(Benzoyloxy)-4-(*tert*-butyldimethylsiloxy)dodec-1-en-3-ol (16)

To a stirred solution of oxalyl chloride (0.7 mL, 7.3 mmol) in CH_2Cl_2 (40 mL) at –78 °C was added DMSO (1.14 mL, 14.7 mmol) over 20 min. The resulting mixture was stirred for an additional 15 min and

then alcohol **15** (2 g, 4.9 mmol) dissolved in CH_2Cl_2 (10 mL) was added. The mixture was stirred for 30 min, and Et_3N (3.4 mL, 24.5 mmol) was added dropwise. The mixture was allowed to reach r.t. and stirred for 3 h. When the reaction was complete, the mixture was quenched with water and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), and concentrated in vacuo to obtained the aldehyde.

To a stirred solution of the aldehyde (2 g, 4.9 mmol) in anhydrous THF (20 mL) was added slowly 1 M vinylmagnesium bromide in THF (9.85 mL, 9.8 mmol) at 0 °C and the mixture was stirred for 2 h (TLC monitoring). The mixture was quenched with sat. NH_4Cl and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 8:2) to give chiral allyl alcohol **16** as a colorless liquid; yield: 1.75 g (85%).

$[\alpha]_D^{25}$ +5.5 (*c* 0.5, $CHCl_3$).

IR (neat): 3450, 2927, 2856, 1717, 1568, 1453, 1320, 1274, 1106, 1053, 835, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.01–8.10 (m, 2 H), 7.52–7.62 (m, 1 H), 7.41–7.48 (m, 2 H), 5.90–6.05 (m, 1 H), 5.45 (d, *J* = 11.0 Hz, 1 H), 5.22–5.27 (m, 1 H), 5.20 (d, *J* = 11.0 Hz, 1 H), 4.08–4.12 (m, 1 H), 3.95–4.02 (m, 1 H), 2.23 (br s, 1 H), 1.38–1.48 (m, 2 H), 1.10–1.40 (m, 10 H), 0.89 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 136.4, 132.9, 129.6, 128.3, 116.5, 76.2, 75.5, 74.4, 31.7, 29.6, 29.2, 25.9, 25.5, 22.6, 14.0, –4.4.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{43}O_4Si$: 435.2925; found: 435.2910.

(3*S*,4*R*,5*R*)-3,4-Bis(*tert*-butyldimethylsiloxy)dodec-1-en-5-yl Benzoate (17)

To a stirred solution of allyl alcohol **16** (1.5 g, 3.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added imidazole (0.36 g, 5.3 mmol) at 0 °C followed by TBSCl (0.64 g, 4.2 mmol) dissolved in anhydrous CH_2Cl_2 (5 mL) and DMAP (cat.) and the mixture was stirred at r.t. for 1 h. After complete consumption of the starting material (TLC monitoring), water was added to the mixture and it was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:9.5) to afford TBS ether **17** as a colorless liquid; yield: 1.85 g (95%).

$[\alpha]_D^{25}$ +4.2 (*c* 0.5, $CHCl_3$).

IR (neat): 2954, 2856, 1720, 1571, 1465, 1271, 1251, 1103, 1070, 925, 831, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.04–8.10 (m, 2 H), 7.50–7.60 (m, 1 H), 7.41–7.48 (m, 2 H), 5.85–5.92 (m, 1 H), 5.30–5.36 (m, 1 H), 5.20 (d, *J* = 11.0 Hz, 1 H), 5.17 (d, *J* = 11.0 Hz, 1 H), 4.08–1.12 (m, 1 H), 3.85–3.90 (m, 1 H), 1.76–1.88 (m, 2 H), 1.20–1.40 (m, 10 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.06 (s, 6 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 138.4, 132.7, 130.5, 129.6, 128.2, 116.9, 77.8, 76.2, 75.8, 31.7, 29.6, 29.1, 28.9, 26.0, 25.9, 25.5, 22.6, 18.3, 18.2, 14.0, 3.8, –4.0, –4.5, –4.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{31}H_{57}O_4Si_2$: 549.3789; found: 549.3773.

(3*S*,4*R*,5*R*)-3,4-Bis(*tert*-butyldimethylsiloxy)dodec-1-en-5-ol (18)

To a stirred solution of benzoate **17** (1.7 g, 3.1 mmol) in MeOH (20 mL) was added K_2CO_3 (0.85 g, 6.2 mmol) at 0 °C, and the mixture was stirred for 2 h at r.t. (TLC monitoring). The mixture quenched by with H_2O (15 mL), and then MeOH was removed in vacuo and the residue was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine and dried (Na_2SO_4) and the solvent was evaporated in vacuo. Residue was purified by column chromatography (EtOAc–hexane, 1:9) to obtain the pure secondary alcohol **18** as a colorless liquid; yield: 1.26 g (92%).

$[\alpha]_D^{25}$ –2.5 (*c* 0.5, $CHCl_3$).

IR (neat): 3350, 2955, 2856, 1601, 1467, 1275, 1253, 1107, 1071, 926, 833, 749 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.84–5.93 (m, 1 H), 5.22 (dd, *J* = 17.2, 1.3 Hz, 1 H), 5.13 (dd, *J* = 10.3, 1.2 Hz, 1 H), 4.19–4.25 (m, 1 H), 3.65 (m, 1 H), 3.50–3.55 (m, 1 H), 1.50–1.55 (m, 2 H), 1.25–1.35 (m, 10 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.06 (s, 6 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.1, 115.9, 79.3, 76.7, 73.5, 32.6, 31.8, 29.6, 29.2, 26.0, 25.9, 22.6, 18.2, 18.1, 14.0, –3.7, –4.1, –4.5, –4.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{53}O_3Si_2$: 445.3527; found: 445.3513.

(3*S*,4*R*,5*R*)-3,4-Bis(*tert*-butyldimethylsiloxy)dodec-1-en-5-yl (*S*)-4-(4-Methoxybenzyloxy)hex-5-enoate (19)

To a stirred solution of acid **10** (0.33 g, 1.35 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added DCC (0.35 g, 1.6 mmol) in portions followed by DMAP (cat.). The mixture was stirred for 15 min and then alcohol **18** (0.5 g, 1.1 mmol) dissolved in CH_2Cl_2 (10 mL) was added. The cooling bath was removed and stirring was continued for 3 h (TLC monitoring). The mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc–hexane, 0.5:9.5) to give ester **19** as a colorless liquid; yield: 0.66 g (75%).

$[\alpha]_D^{25}$ +50.7 (*c* 0.5, $CHCl_3$).

IR (neat): 3074, 2954, 2854, 1706, 1611, 1512, 1421, 1246, 1174, 1034, 929, 770 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.30 (m, 2 H), 6.85–6.90 (m, 2 H), 5.68–5.85 (m, 2 H), 5.10–5.30 (m, 4 H), 4.51–4.53 (m, 2 H), 4.25–4.30 (m, 1 H), 3.95–4.0 (m, 1 H), 3.81 (s, 3 H), 3.75–3.80 (m, 1 H), 3.61–3.63 (m, 1 H), 2.31–2.48 (m, 2 H), 1.82–1.95 (m, 2 H), 1.57–1.62 (m, 2 H), 1.15–1.35 (m, 10 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.05 (s, 6 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 159.0, 140.4, 138.7, 130.6, 130.1, 116.9, 115.0, 80.2, 78.0, 75.9, 72.2, 72.1, 56.5, 31.7, 31.5, 30.4, 29.6, 29.2, 28.7, 26.0, 25.9, 25.5, 22.6, 14.0, –3.8, –3.9, –4.4.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{38}H_{68}O_6NaSi_2$: 699.4452; found: 699.4484.

(3*S*,4*R*,5*R*)-3,4-Bis(*tert*-butyldimethylsiloxy)dodec-1-en-5-yl (*S*)-4-Hydroxyhex-5-enoate

To a stirred solution of ester **19** (0.6 g, 0.88 mmol) in CH_2Cl_2–H_2O (19:1, 20 mL) was added DDQ (0.3 g, 1.32 mmol) at 0 °C and the mixture was stirred at r.t. for 1 h (TLC monitoring). The mixture was filtered and the filtrate was washed with 5% $NaHCO_3$ solution and then extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 3:7) to afford the pure alcohol as a pale yellow syrup; yield: 0.39 g (80%).

$[\alpha]_D^{25}$ +62.3 (*c* 0.8, $CHCl_3$).

IR (neat): 3462, 2927, 2856, 1778, 1741, 1640, 1372, 1242, 1168, 876, 722 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75–5.90 (m, 2 H), 5.25–5.30 (m, 1 H), 5.10–5.20 (m, 4 H), 4.15–4.22 (m, 1 H), 3.95–4.03 (m, 1 H), 3.62–3.70 (m, 2 H), 2.40–2.50 (m, 2 H), 1.80–1.95 (m, 2 H), 1.60–1.70 (m, 2 H), 1.20–1.32 (m, 10 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.05 (s, 6 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 140.3, 138.6, 116.9, 115.0, 77.9, 75.9, 75.1, 72.2, 72.1, 31.8, 31.5, 30.4, 29.6, 29.1, 28.7, 26.0, 25.8, 25.5, 22.6, 18.2, 14.0, –3.9, –4.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{61}O_5Si_2$: 557.3979; found: 557.3992.

(5*S*,8*S*,9*R*,10*R*,*E*)-8,9-Bis(*tert*-butyldimethylsiloxy)-10-heptyl-5-hydroxy-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one (20)

A stirred solution of the diene compound (0.39 g, 0.7 mmol) in anhydrous CH_2Cl_2 (100 mL) was degassed for 20 min by argon bubbling. Then Grubbs' 2nd generation catalyst (0.057 mg, 0.07 mmol) was added and the mixture was degassed for a further 15 min and then refluxed for 12 h (TLC monitoring). The mixture was allowed to cool to r.t. and the solvent was evaporated under reduced pressure. The crude material was adsorbed on silica gel and purified by column chromatography (silica gel, EtOAc–hexane, 9:1) to give lactone **20** as a colorless liquid; yield: 0.23 g (62%).

$[\alpha]_D^{25}$ +48.7 (*c* 1.0, $CHCl_3$).

IR: 3456, 2925, 2851, 1737, 1394, 1247, 1215, 1173, 1096, 930, 830, 770 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83 (dd, *J* = 15.6, 3.1 Hz, 1 H), 5.64 (dd, *J* = 9.2, 1.9 Hz, 1 H), 5.20 (t, *J* = 7.5 Hz, 1 H), 4.15–4.22 (m, 1 H), 4.02 (t, *J* = 7.5 Hz, 1 H), 3.65–3.70 (m, 2 H), 2.30–2.45 (m, 2 H), 1.82–1.95 (m, 2 H), 1.62–1.68 (m, 2 H), 1.20–1.32 (m, 10 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.05 (s, 6 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 134.4, 133.5, 80.5, 78.0, 73.8, 71.9, 34.5, 31.8, 31.5, 29.3, 29.1, 25.9, 22.6, 14.0, –1.9, –3.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{57}O_5Si_2$: 529.3667; found: 529.3657.

4-{[5*S*,8*S*,9*R*,10*R*,*E*)-8,9-Bis(*tert*-butyldimethylsiloxy)-10-heptyl-2-oxo-3,4,5,8,9,10-hexahydro-2*H*-oxecin-5-yl]oxy}-4-oxobutanoic Acid (21)

To a stirred solution of the lactone **20** (0.22 g, 0.41 mmol) in CH_2Cl_2 (2 mL) was added succinic anhydride (0.041 g, 0.41 mmol), pyridine (33 mg, 0.41 mmol) and DMAP (10 mg, 0.08 mmol) at 0 °C and the mixture was stirred at r.t. for 12 h (TLC monitoring). The mixture was poured into CH_2Cl_2 (20 mL) and phosphate buffer (pH 3.6) with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give the crude product, which was purified by chromatography (silica gel, benzene–acetone) to afford acid **21** as a colorless oil; yield: 238 mg (91%).

$[\alpha]_D^{25}$ +35.2 (*c* 0.5, $CHCl_3$).

IR: 3486, 2987, 2923, 2853, 1741, 1692, 1513, 1373, 1246, 1035, 1048, 822, 772 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.30–6.50 (m, 2 H), 4.40–4.50 (m, 1 H), 3.98 (t, *J* = 7.0 Hz, 1 H), 3.80–3.90 (m, 2 H), 2.50–2.60 (m, 2 H), 2.35–2.45 (m, 2 H), 1.85–1.95 (m, 2 H), 1.65–1.75 (m, 1 H), 1.48–1.58 (m, 2 H), 1.20–1.32 (m, 12 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.05 (s, 6 H), 0.03 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 174.0, 172.6, 133.4, 129.7, 79.5, 74.9, 73.0, 62.4, 31.7, 30.7, 29.3, 29.0, 25.4, 22.5, 14.0, –1.4, –1.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{61}O_8Si_2$: 629.3826; found: 629.3818.

4-{[(5*S*,8*S*,9*S*,10*R*,*E*)-10-Heptyl-8,9-dihydroxy-2-oxo-3,4,5,8,9,10-hexahydro-2*H*-oxecin-5-yl]oxy}4-oxobutanoic Acid (1)

To a stirred solution of acid **21** (230 mg, 0.37 mmol) in anhydrous THF (5 ml) was added 2 M HCl (0.5 mL) at r.t. and the mixture was stirred for 4 h (TLC monitoring). Then water and solvent were removed under reduced pressure. The residue was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography (silica gel, EtOAc–hexane, 1:1) to afford the target molecule xyolide **1** as a colorless syrup; yield: 100 mg (73%).

$[\alpha]_D^{25}$ +10.4 (*c* 0.7, $CHCl_3$) [Lit.[7c] $[\alpha]_D^{28}$ +10.1 (*c* 0.8, $CHCl_3$)].

IR (neat): 3395, 2954, 2928, 2856, 1742, 1465, 1368, 1222, 1036, 834, 772 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.86 (dd, *J* = 15.2, 1.7 Hz, 1 H), 5.49 (dd, *J* = 15.8, 1.9 Hz, 1 H), 5.04–5.12 (m, 1 H), 4.98 (m, 1 H), 4.45 (br s, 1 H), 3.50 (dd, *J* = 9.6, 1.9 Hz, 1 H), 2.50–2.62 (m, 4 H), 2.31–2.40 (m, 1 H), 1.95–2.10 (m, 3 H), 1.80–1.90 (m, 1 H), 1.50–1.60 (m, 1 H), 1.33–1.20 (m, 10 H), 0.87 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 174.5, 171.6, 132.8, 123.4, 74.8, 73.6, 72.6, 70.9, 31.8, 31.5, 31.2, 29.5, 29.4, 29.3, 29.1, 28.8, 24.6, 22.6, 14.0.

HRMS (ESI): *m*/*z* [M + NH_4]$^+$ calcd for $C_{20}H_{36}O_8N$: 418.2435; found: 418.2459.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380780.

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