Stereoselective Synthesis of Stagonolide G from D-Mannitol

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Abstract: A highly convergent, stereoselective total synthesis of a ten-membered lactone, stagonolide G, is described. Epoxide ring-opening with vinyl Grignard, Yamaguchi esterification and ring-closing metathesis are the key steps involved in the present approach. D-Mannitol was used as a chiral pool material for the construction of both of the key fragments – the olefinic acid and the olefinic alcohol moieties.

Key words: chiral pool, Grignard reaction, esterification, ring closure, macrocycles

Macrolides, particularly lactones with medium-sized rings (8–10 membered), have continued to attract the attention of both biologists and chemists during recent years, due to their interesting biological properties[1] and scarce availability. Ten-membered ring lactones nonenolides, stagonolides B–I (**1**–**8**) and modiolide A (**9**) are recent examples (Figure 1) that have been isolated in both liquid and solid cultures of *Stagonospora cirsii* Davis, which is a fungal pathogen isolated from *Cirsium arvense*.[2] In accordance with our continuing synthetic efforts[3] towards molecules with intriguing characteristics and usefulness, recently we reported the synthesis and bioevaluation of stagonolide F.[3c]

Herein, we report a simple and efficient approach to the total synthesis of stagonolide G (**6**), starting from the inexpensive and easily available starting material, D-mannitol. During the course of our study, Yadav et al.[4] reported the first total synthesis of stagonolide G using D-glucose diacetonide and 1,4-butanediol as starting materials.

Our retrosynthetic strategy for stagonolide G is depicted in Scheme 1. The analysis revealed that **6** could be prepared efficiently by a ring-closing metathesis (RCM) protocol from bis-olefin **28**, which, in turn, could be prepared by Yamaguchi esterification of acid **20** and vinyl alcohol **25**. Fragments **20** and **25** were both envisaged to be obtained from cyclohexylidene-D-glyceraldehydes, which could be obtained easily from D-mannitol.

Accordingly, our synthesis began with 2,3-*O*-cyclohexylidene-D-glyceraldehyde (**10**), which was readily obtained from D-mannitol.[5] C_2-Wittig olefination under Masamune–Roush conditions gave unsaturated ester **11**.[6] Hydrogenation of the latter with Pd/C, followed by lithium aluminum hydride mediated reduction, afforded alcohol **13** in high yield.[7] Protection of the alcohol using *p*-methoxybenzyl chloride (PMBCl) and sodium hydride produced the corresponding ether **14**, which, after subsequent cyclohexylidene deprotection with 1 M HCl, gave the diol **15**. Selective tosylation of diol **15** with tosyl chloride[8] using triethylamine and a catalytic amount of dibutyltin oxide (Bu_2SnO) at 0 °C, followed by treatment with potassium carbonate in methanol, provided epoxide **16**.[9] The crucial regioselective ring-opening of the epoxide to allyl alcohol **17** was achieved[10] by treatment of **16** with vinylmagnesium bromide and copper(I) iodide at –20 °C (Scheme 2). Silylation of allylic alcohol **17** with *tert*-butyldimethylsi-

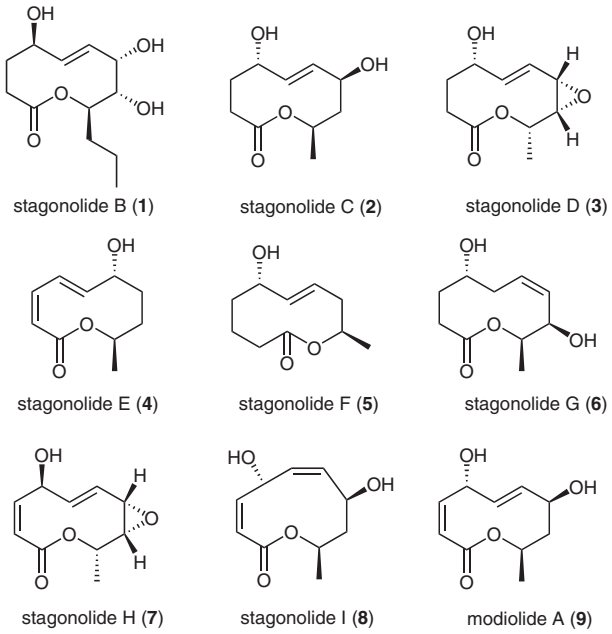
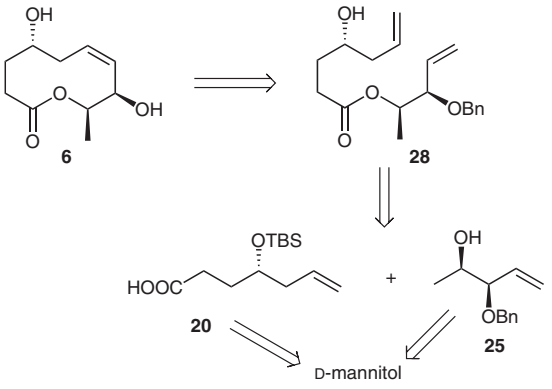


Figure 1 Phytotoxic nonenolides.



Scheme 1 Retrosynthesis of stagonolide G

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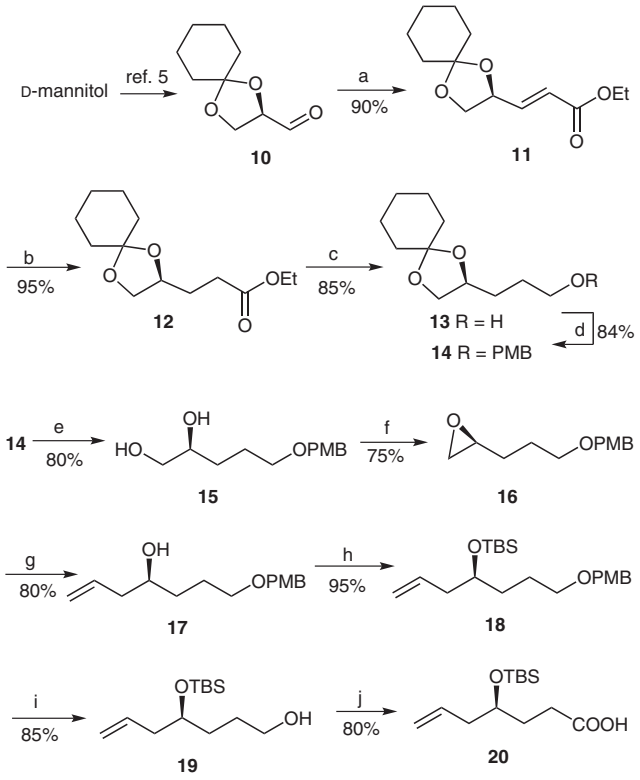
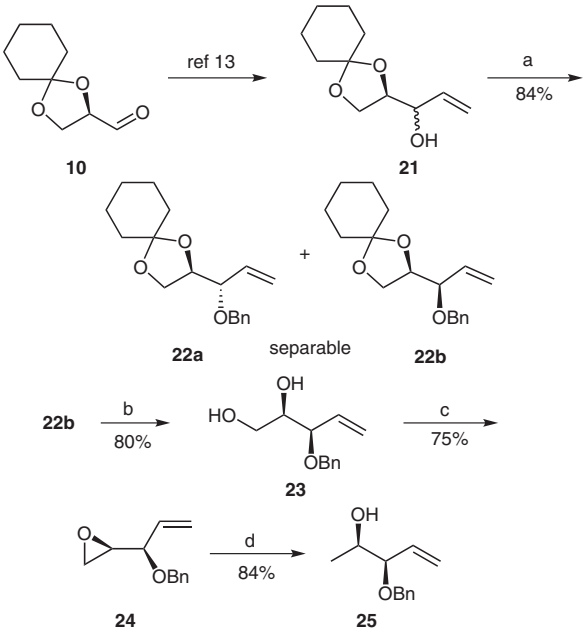
lyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine afforded the corresponding ether **18**, which was subjected to selective PMB deprotection with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dichloromethane/water to give **19**. Finally, oxidation of alcohol **19** either with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/bis(acetoxy)iodobenzene (BAIB)[11] or with pyridinium dichromate (PDC)/*N*,*N*-dimethylformamide[12] provided the desired acid fragment **20** in 80% yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) $(OEt)_2P(O)CH_2COOEt$, LiCl, DIPEA, MeCN, r.t.; (b) Pd/C, H_2, EtOAc, r.t.; (c) LAH, THF, 0 °C→r.t.; (d) NaH, PMBCl, anhyd DMF, 0 °C→r.t.; (e) 1 M HCl, MeCN, r.t.; (f) (i) TsCl, Et_3N, nBu_2SnO, CH_2Cl_2, 0 °C→r.t.; (ii) K_2CO_3, MeOH, 0 °C→r.t.; (g) CH_2=CH-MgBr, CuI, anhyd THF, –20 °C; (h) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (i) DDQ, CH_2Cl_2/H_2O (10:1), 0 °C→r.t.; (j) TEMPO, BAIB, MeCN–H_2O (1:1), r.t. or PDC, DMF, r.t.

The synthesis of alcohol fragment **25** is summarized in Scheme 3. In this regard, 2,3-*O*-cyclohexylidene-D-glyceraldehyde was treated with vinylmagnesium bromide to give **21** as an almost inseparable 1:1 diastereomeric mixture[13] (from GC-MS analysis); the free hydroxy group in the mixture of **21** was protected as the corresponding ethers by treatment with benzyl bromide to give compounds **22a** and **22b**, which were separated by silica gel column chromatography.[14] For the assignment of *syn* and *anti* configurations, a small amount of the two compounds **22a/22b** were subjected to cyclohexylidene deprotection separately and the resulting *syn* and *anti* alcohols were compared with the reported spectral and rotation values {optical rotation of the *syn* compound, observed: $[\alpha]_D^{25}$ –34.4 (*c* 1,$CHCl_3$), reported: $[\alpha]_D^{25}$ –40.6 (*c* 0.47, $CHCl_3$); for the *anti* compound, observed: $[\alpha]_D^{25}$ +39.6 (*c* 0.6, $CHCl_3$), reported: $[\alpha]_D^{25}$ +46.6 (*c* 0.81, $CHCl_3$)}.[14] The *anti* isomer was subjected to debenzylation, followed by Mitsunobu reaction, to furnish the desired *syn* product. Cyclohexylidene cleavage of the *syn* compound **22b** led to the formation of diol **23**. Subsequent selective tosylation of the primary hydroxy group **23** with tosyl chloride, triethylamine and a catalytic amount of Bu_2SnO produced the corresponding tosylate, which, on treatment with potassium carbonate in methanol, gave epoxide **24**.[9c] Finally, epoxide ring-opening with lithium aluminum hydride in anhydrous tetrahydrofuran afforded alcohol fragment **25** in 84% yield.[15]

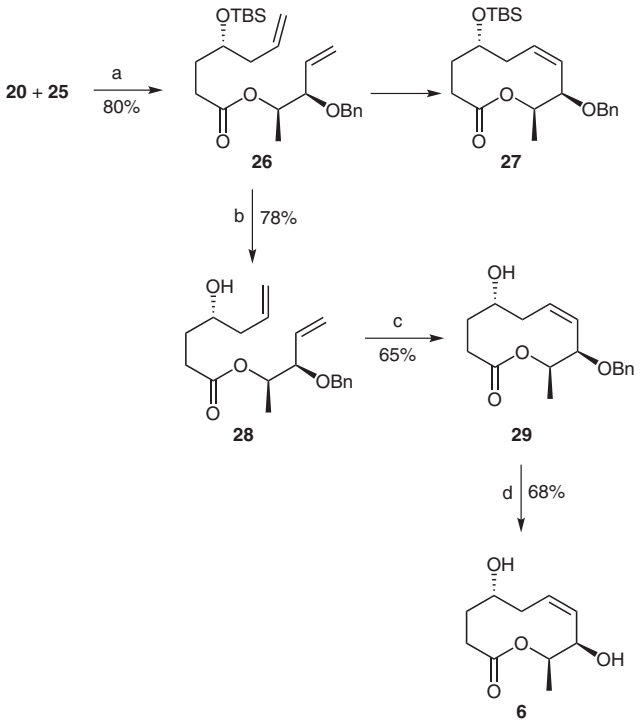
Condensation of fragments **20** and **25** was achieved under Yamaguchi conditions[16] to furnish bis-olefinic ester **26** in 80% yield (Scheme 4). Initial attempts at ring-closing metathesis of **26** under typical conditions were problematic.



Scheme 3 *Reagents and conditions*: (a) NaH, BnBr, anhyd THF, 0 °C→r.t.; (b) 1 M HCl, MeCN, r.t.; (c) (i) TsCl, Et_3N, nBu_2SnO, CH_2Cl_2, 0 °C→r.t.; (ii) K_2CO_3, MeOH, 0 °C→r.t.; (d) $LiAlH_4$, anhyd THF, 0 °C→r.t.

After numerous conditions were tried with Grubbs I and Grubbs II catalysts in a range of traditional solvents for metathesis (CH_2Cl_2, benzene, or toluene), the final outcome was the same in all cases. Either inseparable mixtures of various compounds (along with a small amount of product **27**) were obtained or the starting material decomposed during the course of the reaction. Gratifyingly, after desilylation of **26** under neutral conditions with HF·pyridine and subsequent olefin metathesis using Grubbs II catalyst (20 mol%) in refluxing anhydrous dichloromethane under high dilution conditions,[17] the desired lactone **29** was furnished exclusively in the *Z* form.[18] The ^1H NMR shift values at $\delta = 5.4–5.7$ ppm in the crude spectrum with a coupling constant $J_{H\text{-}6,H\text{-}7} = 11.3$ Hz, allowed the *Z*-ste-

reochemistry to be assigned for **29**. Finally, deprotection of the benzyl moiety with sodium and liquid ammonia under Birch conditions[19] afforded the target molecule **6** (Scheme 4). The physical and spectral data of **6** were identical to those reported in the literature.[2b,4]



Scheme 4 *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, anhyd THF, r.t., 2 h, DMAP, toluene, r.t.; (b) HF·pyridine, anhyd THF, 0 °C→r.t.; (c) Grubbs II catalyst, anhyd CH_2Cl_2, reflux; (d) Na, liq NH_3, anhyd THF, –78 °C.

In conclusion, we have developed a simple, convenient and economic route for the stereoselective synthesis of stagonolide G by employing D-mannitol as a chiral template. This protocol involves the use of a Grignard reaction and ring-closing metathesis as key steps. The syntheses of other related compounds of this family are underway in our laboratory.

All reactions were carried out under an inert atmosphere unless mentioned otherwise, and standard syringe–septa techniques were followed. Solvents were freshly dried and purified by conventional methods prior to use. The progress of all the reactions were monitored by TLC, using TLC aluminum-backed sheets precoated with silica gel 60 F_{254} to a thickness of 0.25 mm (Merck). Column chromatography was performed on silica gel (60–120 mesh and 100–200 mesh), and Et_2O, EtOAc, and hexane were used as eluents. Optical rotation values were measured with a Perkin–Elmer P241 polarimeter and a JASCO DIP-360 digital polarimeter, and IR spectra were recorded with a Perkin–Elmer FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with Varian Gemini 200 MHz, Bruker Avance 300 MHz, Varian Unity 400 MHz, or Varian Inova 500 MHz spectrometers; TMS was used as an internal standard in $CDCl_3$. Mass spectra were recorded with a VG Micromass 7070 H (EI), QSTAR XL high-resolution mass spectrometer, a Thermo Finnigan ESI ion trap Mass Spectrometer and a GC-MS system on an Agilent 6890 series (column: Varian CP-Sil 8 CB, 5% phenyl, 95% PDMS, 30.0 m × 250 μm × 0.30 μm nominal).

(*S*,*E*)-Ethyl 3-(1,4-Dioxaspiro[4.5]decan-2-yl)acrylate (11)[7]

To a well-stirred solution of anhydrous LiCl (0.98 g, 23.3 mmol) in anhydrous MeCN (15 mL) under nitrogen were sequentially added triethyl phosphonoacetate (5.21 g, 23.3 mmol), DIPEA (3.01 g, 23.3 mmol) and freshly prepared aldehyde **10** (3.3 g, 19.4 mmol) at r.t., and the mixture was stirred for 24 h at the same temperature. The reaction was diluted with H_2O (15 mL), extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give an oily residue that was subjected to silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:49) to give separable *E*-isomer (4.01 g, 86.4%) and *Z*-isomer (0.16 g, 3.5%) as a colorless oils.

***E*-Isomer**

R_f = 0.8 (silica gel; EtOAc–hexane, 2:8); $[\alpha]_D^{25}$ +32.1 (*c* 1.4, MeOH).

IR (neat): 2937, 2861, 1722, 1660, 1302, 1267 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.41–1.63 (m, 10 H, Cy-H), 3.65 (t, *J* = 7.5 Hz, 1 H, OCH_2), 4.08–4.22 (m, 3 H, CH_2CO_2, OCH_2), 4.65 (dd, *J* = 6.7, 1.5 Hz, 1 H, OCH), 6.08 (d, *J* = 16.6 Hz, 1 H, =CH), 6.87 (dd, *J* = 6.0, 15.8 Hz, 1 H, =CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1 (CH_3), 23.7 (Cy), 23.8 (Cy), 24.9 (Cy), 35.1 (Cy), 35.9 (Cy), 60.4 (OCH_2CH_3), 68.3 (CH_2O), 74.5 (CH), 110.6 (C), 122.1 (=CH), 144.8 (=CH), 165.8 (CO).

MS (ESI): *m*/*z* = 263 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{20}O_4Na$: 263.1259; found: 263.1262.

(*S*)-Ethyl 3-(1,4-Dioxaspiro[4.5]decan-2-yl)propanoate (12)[7]

A solution of the unsaturated ester **11** (1.0 g, 3.33 mmol) in EtOAc (8 mL) was stirred magnetically in the presence of 10% Pd/C as catalyst in an atmosphere of hydrogen for 6 h. The catalyst was filtered off and the solvent was removed under reduced pressure to afford the ester **12**.

Yield: 0.95 g (95%); colorless liquid; R_f = 0.7 (silica gel; EtOAc–hexane, 2:8); $[\alpha]_D^{25}$ –3.1 (*c* 1.1, $CHCl_3$).

IR (neat): 2936, 2861, 1735, 1447, 1368, 1105, 1037, 930 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 6.0 Hz, 3 H, CH_3), 1.43–1.63 (m, 10 H, Cy-H), 1.70–1.93 (m, 2 H, CH_2), 2.28–2.47 (m, 2 H, $COCH_2$), 3.49 (t, *J* = 7.5 Hz, 1 H, OCH), 3.87–4.17 (m, 4 H, 2 × OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_3), 23.6 (Cy), 23.8 (Cy), 24.9 (Cy), 28.7 (CH_2), 30.3 (CH_2CO), 34.9 (Cy), 36.4 (Cy), 60.2 (OCH_2CH_3), 68.5 (CH_2O), 74.3 (CH), 109.3 (C), 173.0 (CO).

MS (ESI): *m*/*z* = 243 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{23}O_4$: 243.1490; found: 243.1484.

(*S*)-3-(1,4-Dioxaspiro[4.5]decan-2-yl)propan-1-ol (13)[7]

To a suspension of LAH (0.45 g, 12.39 mmol) in anhydrous THF (20 mL) was added ester **12** (3.0 g, 12.39 mmol) in anhydrous THF (10 mL) at 0 °C under a nitrogen atmosphere and the mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with sat. aq NH_4Cl (10 mL), filtered, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 2:8) to afford **13**.

Yield: 2.1 g (85%); colorless liquid; R_f = 0.3 (silica gel; EtOAc–hexane, 3:7); $[\alpha]_D^{25}$ +6.6 (*c* 0.95, $CHCl_3$).

IR (neat): 3423, 2935, 2861, 1637, 1446, 1103, 930 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.35–1.43 (m, 2 H, CH_2), 1.53–1.71 (m, 12 H, Cy-H, CH_2), 2.25 (br s, 1 H, OH), 3.47 (t, *J* = 7.5 Hz, 1 H, OCH), 3.59–3.68 (m, 2 H, C*H*$_2$OH), 3.98–4.03 (m, 1 H, OCH), 4.04–4.12 (m, 1 H, OCH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8 (Cy), 23.9 (Cy), 25.0 (Cy), 29.2 (CH_2), 30.4 (CH_2), 35.1 (Cy), 36.4 (Cy), 62.5 (CH_2OH), 69.1 (CH_2O), 75.5 (CH), 109.5 (C).

MS (ESI): *m*/*z* = 201 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{21}O_3$: 201.1490; found: 201.1484.

(*S*)-2-[3-(4-Methoxybenzyloxy)propyl]-1,4-dioxaspiro[4.5]decane (14)

To a suspension of NaH (0.72 g, 30.0 mmol) in anhydrous DMF (10 mL) was added alcohol **13** (3.0 g, 15.0 mmol) in DMF (10 mL) at 0 °C and the mixture was stirred for 30 min. *p*-Methoxybenzyl chloride (PMBCl; 2.2 mL, 16.5 mmol) was added and the mixture was stirred for 8 h. The reaction was quenched with cold H_2O (10 mL) and then extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:24) to afford **14**.

Yield: 4.0 g (84%); colorless liquid; R_f = 0.8 (silica gel; EtOAc–hexane, 2:8); $[\alpha]_D^{25}$ +4.5 (*c* 1, $CHCl_3$).

IR (neat): 2935, 2857, 1613, 1512, 1246, 1097, 1035, 931, 819 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33–1.45 (m, 4 H, 2 × CH_2), 1.49–1.68 (m, 10 H, Cy-H), 3.37–3.50 (m, 3 H, OCH_2, OCH), 3.78 (s, 3 H, OCH_3), 3.94–4.07 (m, 2 H, OCH_2), 4.38 (s, 2 H, C*H*$_2$Ar), 6.81 (d, *J* = 8.6 Hz, 2 H, ArH), 7.18 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (Cy), 24.0 (Cy), 25.3 (CH_2), 26.1 (Cy), 30.5 (CH_2), 35.3 (Cy), 36.7 (Cy), 55.0 (OCH_3), 69.0 (CH_2O), 69.6 (CH_2O), 72.5 (CH), 75.3 (*C*H_2Ar), 109.1 (C), 113.7 (2 × C_{Ar}), 129.1 (2 × C_{Ar}), 130.5 (C_{Ar}), 159.1 (C_{Ar}).

MS (ESI): *m*/*z* = 321 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{28}O_4Na$: 343.1885; found: 343.1898.

(*S*)-5-(4-Methoxybenzyloxy)pentane-1,2-diol (15)

To a solution of **14** (3.0 g, 12.5 mmol) in MeCN (45 mL) was added HCl (1 M, 36 mL) and the mixture was stirred at r.t. for 3 h. After completion of the reaction, the contents were neutralized with solid $NaHCO_3$ and the solvent was removed. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to obtain the crude product, which was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:1) to afford **15**.

Yield: 1.8 g (80%); colorless oil; R_f = 0.2 (silica gel; EtOAc–hexane, 1:1); $[\alpha]_D^{25}$ –2.0 (*c* 1.1, $CHCl_3$).

IR (neat): 3402, 2934, 2862, 1612, 1512, 1246, 1080, 1033, 819 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.63 (m, 2 H, CH_2), 1.67–1.78 (m, 2 H, CH_2), 3.34–3.69 (m, 5 H, 2 × OCH_2, OCH), 3.79 (s, 3 H, OCH_3), 4.42 (s, 2 H, C*H*$_2$Ar), 6.82 (d, *J* = 8.4 Hz, 2 H, ArH), 7.18 (d, *J* = 8.6 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1 (CH_2), 30.7 (CH_2), 55.2 (OCH_3), 66.7 (CH_2OH), 70.1 (CHOH), 71.9 (CH_2O), 72.7 (CH_2Ar), 113.8 (2 × C_{Ar}), 129.3 (2 × C_{Ar}), 129.8 (C_{Ar}), 159.2 (C_{Ar}).

MS (ESI): *m*/*z* = 241 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{20}O_4Na$: 263.1259; found: 263.1254.

(*S*)-2-[3-(4-Methoxybenzyloxy)propyl]oxirane (16)

To an ice-cold solution of diol **15** (2.5 g, 10.4 mmol), a catalytic amount of dibutyl tin oxide (0.5 g, 2 mmol) and Et_3N (1.6 mL, 12.0 mmol) in anhydrous CH_2Cl_2 (30 mL) were added. After 15 min at r.t., the reaction mixture was cooled to 0 °C then TsCl (2.3 g, 12.0 mmol) was added portion-wise and the reaction was stirred at r.t. for 4 h. After completion of reaction, the mixture was diluted with H_2O (5 mL) and extracted into CH_2Cl_2 (3 × 50 mL). The organic layer was washed with brine (2 × 25 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude residue. This residue was dissolved in MeOH (10 mL) and anhydrous K_2CO_3 (1.68 g, 12.1 mmol) was added at 0 °C. The mixture was stirred at r.t. for 3 h. After dilution with EtOAc (20 mL), the organic layer was washed with H_2O (2 × 10 mL) and brine (25 mL). Drying, followed by evaporation and purification by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:24) afforded **16**.

Yield: 75%; colorless oil; R_f = 0.7 (silica gel; EtOAc–hexane, 3:7); $[\alpha]_D^{25}$ –4.5 (*c* 0.88, $CHCl_3$).

IR (neat): 2933, 2856, 1612, 1512, 1246, 1094, 1033, 821 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.47–1.81 (m, 4 H, 2 × CH_2), 2.38 (dd, *J* = 2.6, 5.1 Hz, 1 H, oxirane-H), 2.68 (t, *J* = 4.9 Hz, 1 H, oxirane-H), 2.83–2.89 (m, 1 H, oxirane-H), 3.38–3.49 (m, 2 H, OCH_2), 3.78 (s, 3 H, OCH_3), 4.39 (s, 2 H, CH_2Ar), 6.81 (d, *J* = 8.4 Hz, 2 H, ArH), 7.18 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1 (CH_2), 29.2 (CH_2), 46.9 (oxirane-CH_2), 51.9 (oxirane-CH), 55.1 (OCH_3), 69.3 (CH_2O), 72.4 (*C*H_2Ar), 113.6 (2 × C_{Ar}), 129.1 (2 × C_{Ar}), 130.4 (C_{Ar}), 159.0 (C_{Ar}).

MS (ESI): *m*/*z* = 240 $[M + NH_4]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{18}O_3Na$: 245.1153; found: 245.1147.

(*S*)-7-(4-Methoxybenzyloxy)hept-1-en-4-ol (17)

A solution of vinylmagnesium bromide (1 M in THF, 18 mL, 18 mmol; Aldrich) in THF (10 mL) was quickly added to a solution of epoxide **16** (1.0 g, 4.5 mmol) in anhydrous THF (10 mL) and freshly flame-dried CuI (0.85 g, 4.5 mmol) at –20 °C. The progress of the reaction was monitored by TLC. After completion (1 h), sat. aq NH_4Cl (5 mL) was added, the organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:9) to afford **17**.

Yield: 0.9 g (80%); colorless oil; R_f = 0.3 (silica gel; EtOAc–hexane, 2:8); $[\alpha]_D^{25}$ –9.1 (*c* 0.92, $CHCl_3$).

IR (neat): 3422, 3072, 2927, 2856, 1612, 1512, 1246, 1090, 1033, 819 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.49 (m, 1 H, CH_2), 1.58–1.66 (m, 1 H, CH_2), 1.67–1.76 (m, 2 H, CH_2), 2.11–2.26 (m, 2 H, CH_2C=), 2.33 (br s, 1 H, OH), 3.44 (t, *J* = 5.7 Hz, 2 H, OCH_2), 3.56–3.63 (m, 1 H, C*H*OH), 3.78 (s, 3 H, OCH_3), 4.41 (s, 2 H, CH_2Ar), 5.06 (s, 1 H, =CH), 5.09 (d, *J* = 4.8 Hz, 1 H, =CH), 5.75–5.84 (m, 1 H, =CH), 6.81 (d, *J* = 8.6 Hz, 2 H, ArH), 7.19 (d, *J* = 8.6 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1 (CH_2), 33.9 (CH_2), 41.8 (CH_2), 55.1 (OCH_3), 70.0 (CH), 70.5 (CH_2O), 72.5 (CH_2O), 113.7 (2 × C_{Ar}), 117.5 (=CH_2), 129.2 (2 × C_{Ar}), 130.1 (C_{Ar}), 135.0 (=CH), 159.1 (C_{Ar}).

MS (ESI): *m*/*z* = 251 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{22}O_3Na$: 273.1466; found: 273.1455.

[(*S*)-7-(4-Methoxybenzyloxy)hept-1-en-4-yloxy](*tert*-butyl)dimethylsilane (18)

To a stirred solution of alcohol **17** (1.0 g, 4.0 mmol) in CH_2Cl_2 (10 mL), 2,6-lutidine (1.39 mL, 12 mmol) and TBSOTf (1.37 mL, 6 mmol) were added sequentially at 0 °C, under a nitrogen atmosphere. The reaction mixture was stirred from 0 °C to r.t. for 15 min and then quenched by addition of sat. aq $NaHCO_3$ (5 mL). The resulting mixture was extracted with EtOAc (2 × 15 mL) and the organic extracts were washed with sat. aq $CuSO_4$ (2 × 5 mL), H_2O (10 mL), and brine (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:24) furnished compound **18**.

Yield: 1.3 g (95%); colorless liquid; R_f = 0.9 (silica gel; EtOAc–hexane, 1:9); $[\alpha]_D^{25}$ –10.8 (*c* 1, $CHCl_3$).

IR (neat): 3073, 2932, 2856, 1612, 1513, 1249, 1094, 1040, 833, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, $Si(CH_3)_2$], 0.87 [s, 9 H, $C(CH_3)_3$], 1.39–1.69 (m, 4 H, 2 × CH_2), 2.18 (t, *J* = 6.2 Hz, 2 H, CH_2C=), 3.37 (t, *J* = 6.2 Hz, 2 H, OCH_2), 3.63–3.73 (m, 1 H, OCH), 3.78 (s, 3 H, OCH_3), 4.38 (s, 2 H, CH_2Ar), 4.97 (s, 1 H, =CH), 4.99–5.04 (m, 1 H, =CH), 5.67–5.84 (m, 1 H, =CH), 6.80 (d, *J* = 8.3 Hz, 2 H, ArH), 7.18 (d, *J* = 8.3 Hz, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.5 ($SiCH_3$), –4.3 ($SiCH_3$), 18.1 [*C*$(CH_3)_3$], 25.6 (3 × CH_3), 25.8 (CH_2), 33.2 (CH_2), 41.9 (CH_2), 55.2 (OCH_3), 70.2 (CH_2O), 71.7 (CH), 72.4 (CH_2O), 113.6 (2 × C_{Ar}), 116.6 (=CH_2), 129.1 (2 × C_{Ar}), 130.6 (C_{Ar}), 135.2 (=CH), 159.0 (C_{Ar}).

MS (ESI): *m*/*z* = 365 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{36}O_3NaSi$: 387.2331; found: 387.2331.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)hept-6-en-1-ol (19)

To a stirred solution of **18** (0.5 g, 1.37 mmol) in CH_2Cl_2–H_2O (10:1, 15 mL), DDQ (0.37 g, 1.6 mmol) was added at 0 °C and the mixture was stirred at r.t. for 2 h. Sat. aq $NaHCO_3$ (5 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:49) to afford **19**.

Yield: 0.28 g (85%); colorless syrup; R_f = 0.5 (silica gel; EtOAc–hexane, 1:9); $[\alpha]_D^{25}$ –5.6 (*c* 0.8, $CHCl_3$).

IR (neat): 3358, 3077, 2932, 2859, 1640, 1435, 1253, 1054, 834, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 [s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $C(CH_3)_3$], 1.46–1.67 (m, 4 H, 2 × CH_2), 2.23 (t, *J* = 6.7 Hz, 2 H, CH_2C=), 3.54–3.65 (m, 2 H, C*H*$_2$OH), 3.69–3.80 (m, 1 H, OCH), 4.99 (s, 1 H, =CH), 5.03 (d, *J* = 5.8 Hz, 1 H, =CH), 5.67–5.82 (m, 1 H, =CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.5 ($SiCH_3$), –4.4 ($SiCH_3$), 18.1 [*C*$(CH_3)_3$], 25.8 (3 × CH_3), 28.2 (CH_2), 33.0 (CH_2), 41.4 (CH_2), 63.1 (CH_2OH), 71.7 (CH), 116.9 (=CH_2), 135.0 (=CH).

MS (ESI): *m*/*z* = 245 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{28}O_2NaSi$: 267.1756; found: 267.1756.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)hept-6-enoic Acid (20)

Method 1: BAIB (1.9 g, 6 mmol) was added to a solution of alcohol **19** (0.5 g, 2 mmol) and TEMPO (95 mg, 0.3 mmol) in MeCN–H_2O (1:1, 10 mL). The reaction mixture was stirred for 2 h at r.t., and then diluted with CH_2Cl_2 (10 mL). The mixture was washed with sat. aq $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with aq $NaHCO_3$ (5 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography over silica gel (60–120 mesh; EtOAc–hexane, 1:5) afforded pure acid **20** (0.42 g, 80%) as a colorless liquid.

Method 2: To a stirred solution of **19** (0.5 g, 2.0 mmol) in DMF (20 mL) was added PDC (3.76 g, 10 mmol) at r.t. After 10 h, the mixture was quenched with cold H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with $KHSO_4$ (15 mL, 1 mol/L), H_2O (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue over silica gel afforded **20** as a colorless liquid (0.39 g, 75%).

R_f = 0.2 (silica gel; EtOAc–hexane, 3:7); $[\alpha]_D^{25}$ –28.2 (*c* 0.75, $CHCl_3$).

IR (neat): 3076, 2932, 2858, 1710, 1254, 1087, 836, 775 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 [s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $C(CH_3)_3$], 1.65–1.88 (m, 2 H, CH_2), 2.19–2.26 (m, 2 H, CH_2C=), 2.37–2.45 (m, 2 H, CH_2CO_2), 3.72–3.82 (m, 1 H, OCH), 5.0–5.11 (m, 2 H, 2 × =CH), 5.69–5.86 (m, 1 H, =CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.7 ($SiCH_3$), –4.3 ($SiCH_3$), 18.0 [*C*$(CH_3)_3$], 25.8 (3 × CH_3), 29.8 (CH_2), 31.1 (CH_2), 41.7 (CH_2), 70.6 (CH), 117.2 (=CH_2), 134.5 (=CH), 180.1 (COOH).

MS (ESI): *m*/*z* = 259 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{26}O_3NaSi$: 281.1548; found: 281.1552.

(*R*)-2-[(*R*)-1-(Benzyloxy)allyl]-1,4-dioxaspiro[4.5]decane (22)[14]

Anhydrous THF (10 mL) was added to a 60% dispersion of NaH in mineral oil (0.9 g, 37.8 mmol). The flask was cooled in an ice bath, **21** (3.0 g, 15.1 mmol) dissolved in anhydrous THF (20 mL) was added dropwise and the mixture was stirred for 30 min. Benzyl bromide (2.1 mL, 18.1 mmol) was added and the reaction mixture was stirred overnight and quenched by the careful addition of a few milliliters of cold H_2O. The solvent was then evaporated under reduced pressure to yield two separable diastereomers (84% yields), which were separated by silica gel chromatography (100–200 mesh; EtOAc–hexane, 1:99) to give **22a** and **22b**.

Data for 22b

R_f = 0.9 (silica gel; EtOAc–hexane, 1:9), $[\alpha]_D^{25}$ –12.4 (*c* 0.7, $CHCl_3$).

IR (neat): 2934, 2859, 1632, 1447, 1103, 928, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (m, 2 H, Cy-H), 1.50–1.63 (m, 8 H, Cy-H), 3.70 (q, *J* = 6.0 Hz, 1 H, OCH), 3.80 (t, *J* = 6.8 Hz, 1 H, OCH), 3.88 (q, *J* = 6.0 Hz, 1 H, OCH), 4.15 (q, *J* = 6.8 Hz, 1 H, OCH), 4.44 (d, *J* = 12.8 Hz, 1 H, C*H*$_2$Ar), 4.66 (d, *J* = 12.8 Hz, 1 H, C*H*$_2$Ar), 5.27–5.35 (m, 2 H, 2 × =CH), 5.65–5.79 (m, 1 H, =CH), 7.21–7.34 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7 (Cy), 23.8 (Cy), 25.0 (Cy), 34.7 (Cy), 36.0 (Cy), 65.2 (CH_2O), 70.1 (*C*H_2Ar), 76.9 (CH), 80.9 (CH), 110.1 (C), 119.8 (=CH_2), 127.3 (2 × C_{Ar}), 127.6 (C_{Ar}), 128.1 (2 × C_{Ar}), 134.1 (=CH), 138.2 (C_{Ar}).

MS (ESI): *m*/*z* = 306 $[M + NH_4]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{24}O_3Na$: 311.1623; found: 311.1621.

(2*R*,3*R*)-3-(Benzyloxy)pent-4-ene-1,2-diol (23)[14]

To a solution of **22b** (2.0 g, 6.9 mmol) in MeCN (30 mL) was added HCl (1 M, 24 mL) and the mixture was stirred at r.t. for 3 h. After completion of the reaction, the contents were neutralized with solid $NaHCO_3$ and the solvent was removed. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 50 mL). The com-

bined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to obtain the crude product, which was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:1) to afford **23**. The spectral characteristic data of **23** (^{1}H NMR, ^{13}C NMR and specific rotation) were in perfect agreement with the literature values.[14]

Yield: 1.15 g (80%); colorless oil; R_f = 0.2 (silica gel; EtOAc–hexane, 1:1); $[\alpha]_D^{25}$ –34.4 (*c* 1, $CHCl_3$).

IR (neat): 3424, 2923, 1716, 1633, 1275, 1069, 770, 711 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (br s, 2 H, 2 × OH), 3.54 (dd, *J* = 4.8, 11.7 Hz, 1 H, OCH), 3.54–3.64 (m, 1 H, C*H*OH), 3.67 (dd, *J* = 2.9, 10.7 Hz, 1 H, CH_2OH), 3.84 (t, *J* = 7.8 Hz, 1 H, CH_2OH), 4.34 (d, *J* = 11.7 Hz, 1 H, CH_2Ar), 4.64 (d, *J* = 11.7 Hz, 1 H, CH_2Ar), 5.34–5.42 (m, 2 H, 2 × =CH), 5.73–5.82 (m, 1 H, =CH), 7.23–7.38 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.1 (CH_2OH), 70.7 (*C*H_2Ar), 73.0 (CHOH), 82.2 (CH), 120.2 (=CH_2), 127.8 (2 × C_{Ar}), 128.4 (C_{Ar}), 129.7 (2 × C_{Ar}), 134.8 (=CH), 137.7 (C_{Ar}).

MS (ESI): *m*/*z* = 231 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}O_3Na$: 231.0997; found: 231.1004.

(*R*)-2-[(*R*)-1-(Benzyloxy)allyl]oxirane (24)[9c]

To an ice-cold solution of diol **23** (1.5 g, 7.2 mmol), a catalytic amount of dibutyl tin oxide (0.35 g, 1.4 mmol) and Et_3N (1 mL, 8 mmol) in CH_2Cl_2 (15 mL) were added. A solution of TsCl (1.5 g, 8 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the reaction was stirred at r.t. for 4 h. After completion of reaction, the mixture was diluted with H_2O (5 mL) and extracted into CH_2Cl_2 (3 × 20 mL). The organic layer was washed with brine (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude residue. This residue was dissolved in anhydrous MeOH (10 mL), anhydrous K_2CO_3 (1.0 g, 7.6 mmol) was added at 0 °C and the mixture was stirred at r.t. for 3 h. The reaction mixture was treated with sat. aq NH_4Cl (5 mL), H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried with Na_2SO_4 followed by evaporation under reduced pressure and purification by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 5:95) to afford **24**.

Yield: 75%; colorless oil; R_f = 0.7 (silica gel; EtOAc–hexane, 2:8); $[\alpha]_D^{25}$ +0.65 (*c* 1, $CHCl_3$).

IR (neat): 3064, 2994, 2925, 2861, 1636, 1257, 1067, 934, 743, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52 (q, *J* = 3 Hz, 1 H, oxirane-H), 2.72 (t, *J* = 5.2 Hz, 1 H, oxirane-H), 2.99–3.05 (m, 1 H, oxirane-H), 3.53–3.59 (m, 1 H, OCH), 4.61 (q, *J* = 12 Hz, 2 H, CH_2Ar), 5.24–5.38 (m, 2 H, 2 × =CH), 5.79 (m, 1 H, =CH), 7.19–7.35 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.8 (oxirane-CH_2), 53.9 (oxirane-CH), 70.5 (*C*H_2Ar), 81.0 (CH), 119.6 (=CH_2), 127.6 (2 × C_{Ar}), 127.7 (C_{Ar}), 128.3 (2 × C_{Ar}), 134.3 (=CH), 138.0 (C_{Ar}).

MS (ESI): *m*/*z* = 213 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}O_2Na$: 213.0891; found: 213.0892.

(2*R*,3*R*)-3-(Benzyloxy)pent-4-en-2-ol (25)[4]

To a stirred suspension of $LiAlH_4$ (540 mg, 14.2 mmol) in THF (10 mL), was added dropwise a solution of **24** (0.9 g, 4.73 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at r.t. and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by addition of EtOAc (5 mL). The reaction mixture was treated with 20% NaOH (2 mL), the white precipitate formed was filtered off, and the residue was washed with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, the solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography (60–120 mesh; EtOAc–hexane, 1:24) to give the corresponding alcohol **25**.

Yield: 0.76 g (84%); liquid; R_f = 0.6 (silica gel; EtOAc–hexane, 2:8); $[\alpha]_D^{25}$ –43.9 (*c* 1.1, $CHCl_3$).

IR (neat): 3452, 2977, 2870, 1453, 1259, 1068, 993, 930, 741, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.2 Hz, 3 H, CH_3), 2.60 (br s, 1 H, OH), 3.48 (t, *J* = 7.9 Hz, 1 H, OCH), 3.58–3.70 (m, 1 H, C*H*OH), 4.32 (d, *J* = 11.5 Hz, 1 H, CH_2Ar), 4.62 (d, *J* = 11.7 Hz, 1 H, CH_2Ar), 5.27–5.4 (m, 2 H, 2 × =CH), 5.62–5.77 (m, 1 H, =CH), 7.21–7.36 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3 (CH_3), 69.5 (*C*H_2Ar), 70.4 (CHOH), 86.1 (CH), 120.1 (=CH_2), 127.7 (2 × C_{Ar}), 127.9 (C_{Ar}), 128.4 (2 × C_{Ar}), 135.4 (=CH), 138.0 (C_{Ar}).

MS (ESI): *m*/*z* = 215 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}O_2Na$: 215.1047; found: 215.1047.

(*S*)-[(2*R*,3*R*)-3-(Benzyloxy)pent-4-en-2-yl] 4-(*tert*-Butyldimethylsilyloxy)hept-6-enoate (26)

To a stirred solution of acid **20** (0.3 g, 1.16 mmol) in anhydrous THF (4 mL), Et_3N (0.3 mL, 2.32 mmol) was added at r.t. 2,4,6-Trichlorobenzoyl chloride (0.19 mL, 1.27 mmol) was added and the reaction mixture was further stirred at r.t. for 2 h then filtered and the filtrate was evaporated. The residue was dissolved in toluene (4 mL), treated with DMAP (0.35 g, 2.9 mmol) and alcohol **25** (0.22 g, 1.16 mmol) in toluene (3 mL). The mixture was stirred at r.t. for 3 h and then diluted with EtOAc (10 mL), washed with sat. aq $NaHCO_3$ (2 × 5 mL), brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:49) to afford ester **26**.

Yield: 0.4 g (80%); colorless liquid; R_f = 0.9 (silica gel; EtOAc–hexane, 1:9); $[\alpha]_D^{25}$ –13.4 (*c* 0.8, $CHCl_3$).

IR (neat): 3075, 2930, 2857, 1735, 1456, 1364, 1253, 1077, 996, 835, 774 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 [s, 6 H, $Si(CH_3)_2$], 0.87 [s, 9 H, $C(CH_3)_3$], 1.18 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.59–1.86 (m, 2 H, CH_2), 2.18 (t, *J* = 6 Hz, 2 H, CH_2), 2.27–2.36 (m, 2 H, CH_2), 3.69–3.81 (m, 2 H, 2 × OCH), 4.37 (d, *J* = 12.8 Hz, 1 H, CH_2Ar), 4.62 (d, *J* = 12.1 Hz, 1 H, CH_2Ar), 4.94–5.08 (m, 3 H, 2 × =CH, OCH), 5.25–5.35 (m, 2 H, 2 × =CH), 5.66–5.81 (m, 2 H, 2 × =CH), 7.24–7.31 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6 ($SiCH_3$), –4.4 ($SiCH_3$), 15.9 (CH_3), 18.0 [*C*$(CH_3)_3$], 25.8 [C(*C*$H_3)_3$], 30.2 (CH_2), 31.5 (CH_2), 41.7 (CH_2), 70.3 (CH), 70.8 (*C*H_2Ar), 71.3 (CH), 81.3 (CH), 117.0 (=CH_2), 119.5 (=CH_2), 127.5 (2 × C_{Ar}), 127.6 (C_{Ar}), 128.2 (2 × C_{Ar}), 134.3 (=CH), 134.6 (=CH), 138.2 (C_{Ar}), 173.2 (CO).

MS (ESI): *m*/*z* = 433 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{40}O_4NaSi$: 455.2593; found: 455.2582.

(*S*)-[(2*R*,3*R*)-3-(Benzyloxy)pent-4-en-2-yl] 4-Hydroxyhept-6-enoate (28)

Compound **26** (0.2 g, 0.46 mmol) was dissolved in THF (2 mL) in a plastic vial and HF·pyridine (1 mL) was added at 0 °C. The reaction mixture was stirred at r.t. for 8 h then poured into cold sat. aq $NaHCO_3$ (5 mL) and extracted with EtOAc (2 × 10 mL). The organic layers were washed with sat. aq $CuSO_4$ (2 × 5 mL), H_2O (5 mL), brine (2 × 10 mL), dried (Na_2SO_4) and concentrated under reduced

pressure. Silica gel column chromatography (60–120 mesh; EtOAc–hexane, 2:8) gave pure alcohol **28**.

Yield: 0.11 g (78%); colorless liquid; R_f = 0.4 (silica gel; EtOAc–hexane, 2:8); $[\alpha]_D^{25}$ –7.0 (*c* 0.16, $CHCl_3$).

IR (neat): 3450, 3074, 2927, 2862, 1730, 1639, 1168, 1067, 926, 739, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.60–1.88 (m, 2 H, CH_2), 2.07–2.34 (m, 2 H, CH_2), 2.43 (t, *J* = 6.7 Hz, 2 H, CH_2), 3.57–3.68 (m, 1 H, OCH), 3.77 (t, *J* = 6.7 Hz, 1 H, OCH), 4.36 (d, *J* = 12.1 Hz, 1 H, C*H*$_2$Ar), 4.63 (d, *J* = 12.1 Hz, 1 H, C*H*$_2$Ar), 5.01 (t, *J* = 6.7 Hz, 1 H, =CH), 5.05–5.16 (m, 2 H, =CHOCH), 5.27–5.39 (m, 2 H, 2 × =CH), 5.66–5.85 (m, 2 H, 2 × =CH), 7.21–7.36 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (CH_3), 26.9 (CH_2), 28.5 (CH_2), 39.3 (CH_2), 69.1 (CHOH), 70.1 (*C*H_2Ar), 79.6 (CH), 84.1 (CH), 118.8 (=CH_2), 120.2 (=CH_2), 127.5 (2 × C_{Ar}), 127.6 (C_{Ar}), 128.2 (2 × C_{Ar}), 131.8 (=CH), 134.3 (=CH), 138.1 (C_{Ar}), 176.9 (CO).

MS (ESI): *m*/*z* = 319 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{26}O_4Na$: 341.1728; found: 341.1715.

(*Z*,5*S*,9*R*,10*R*)-9-(Benzyloxy)-3,4,5,6,9,10-hexahydro-5-hydroxy-10-methyloxecin-2-one (29)

To a stirred solution of ester **28** (50 mg, 0.16 mmol) in freshly distilled, degassed, anhydrous CH_2Cl_2 (50 mL), Grubbs II catalyst (26 mg, 0.03 mmol) was added and the mixture was heated at reflux for 4 h under a nitrogen atmosphere. Most of the solvent was then distilled off and the concentrated solution was stirred at r.t. for 2 h under air bubbling in order to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:3) to afford **29**.

Yield: 29 mg (65%); colorless syrup; R_f = 0.4 (silica gel; EtOAc–hexane, 1:1); $[\alpha]_D^{25}$ –12.0 (*c* 0.2, $CHCl_3$).

IR (neat): 3448, 2922, 2853, 1728, 1634, 1457, 1177, 1067, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.87–2.04 (m, 2 H, CH_2), 2.18–2.55 (m, 4 H, 2 × CH_2), 3.61–3.73 (m, 1 H, OCH), 3.82 (t, *J* = 7.9, 9 Hz, 1 H, OCH), 4.29 (d, *J* = 11.7 Hz, 1 H, C*H*$_2$Ar), 4.39–4.52 (m, 1 H, OCH), 4.57 (d, *J* = 11.5 Hz, 1 H, C*H*$_2$Ar), 5.42 (td, *J* = 11.3, 9.8 Hz, 1 H, =CH), 5.74 (qt, *J* = 11.3, 7.5 Hz, 1 H, =CH), 7.21–7.33 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3 (CH_3), 28.9 (CH_2), 32.1 (CH_2), 34.3 (CH_2), 69.8 (CHOH), 70.6 (CH_2Ar), 79.7 (CH), 79.9 (CH), 123.6 (=CH), 128.0 (=CH), 128.7 (2 × C_{Ar}), 130.0 (C_{Ar}), 130.6 (2 × C_{Ar}), 135.4 (C_{Ar}), 176.0 (CO).

MS (ESI): *m*/*z* = 291 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}O_4Na$: 313.1415; found: 313.1406.

(*Z*,5*S*,9*R*,10*R*)-3,4,5,6,9,10-Hexahydro-5,9-dihydroxy-10-methyloxecin-2-one (6)[2b,4]

To a solution of THF (2 mL) and liq. NH_3 (5 mL), Na (8 mg, 0.37 mmol) was added and the reaction mixture was stirred for 10 min at –78 °C. Compound **29** (25 mg, 0.09 mmol) in THF (1 mL) was added and the mixture was stirred further for 10 min at the same temperature. The reaction was quenched with solid NH_4Cl, filtered, diluted with EtOAc (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (60–120 mesh; EtOAc–hexane, 1:2) to afford **6**.

Yield: 11 mg (68%); colorless liquid; R_f = 0.3 (silica gel; EtOAc–hexane, 1:1); $[\alpha]_D^{25}$ +6.4 (*c* 0.24, $CHCl_3$).

IR (neat): 3425, 2923, 2853, 1748, 1712, 1640, 1261 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.88–2.08 (m, 1 H, CH), 2.26–2.44 (m, 2 H, CH_2), 2.46–2.68 (m, 3 H, CH_2, CH), 3.66–3.71 (m, 1 H, OCH), 4.07–4.14 (m, 1 H, OCH), 4.51–4.59 (m, 1 H, OCH), 5.55–5.72 (m, 2 H, 2 × =CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6 (CH_3), 27.4 (CH_2), 28.7 (CH_2), 33.7 (CH_2), 70.8 (CHOH), 72.2 (CH), 79.5 (CHOH), 127.8 (=CH), 132.4 (=CH), 177.0 (CO).

MS (ESI): *m*/*z* = 201 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{16}O_4Na$: 223.1335; found: 223.1323.

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