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Formal synthesis of herbarumin III

Priti Gupta and Pradeep Kumar*

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411 008, India

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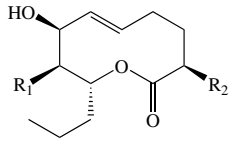
Abstract—An enantioselective synthesis of herbarumin III is described employing Jacobsen's hydrolytic kinetic resolution and Sharpless asymmetric dihydroxylation as the key steps.

1. Introduction

During the search for a potential herbicidal agent from Mexican biodiversity, Mata et al. isolated a phytotoxic lactone herbarumin III along with two other known lactones, herbarumin I, and herbarumin II (Fig. 1).[1a] Herbarumin III showed a relevant phytotoxic effect when tested against seedlings of *Amaranthus hypochondriacus*.[1b] It inhibited radical growth with higher potency than 2,4-dichlorophenoxy acetic acid, used as positive control. Compounds **1**–**3** interacted with bovine-brain calmodulin and inhibited the activation of the calmodulin-dependent enzyme camp phosphodiesterase.



1 R_1 = OH, R_2 = H; Herbarumin I
2 R_1 = R_2 = OH; Herbarumin II
3 R_1 = R_2 = H; Herbarumin III

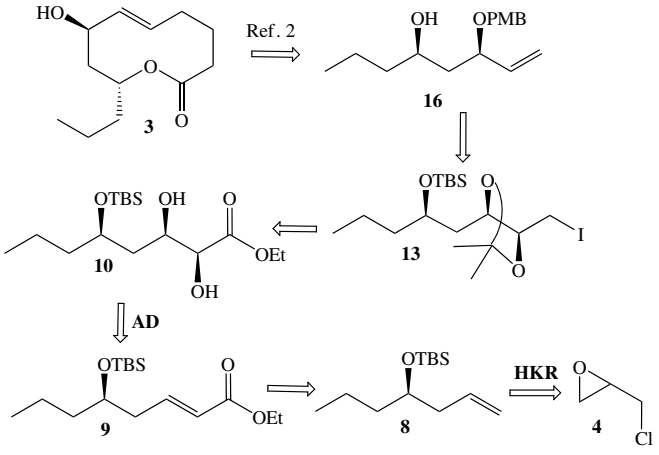
Figure 1.

In the literature various synthetic approaches have been reported for herbarumin III. The syntheses described so far for **3** derive the asymmetry either from chiral pool materials such as glucose[2] and glyceraldehyde,[3] by a chemoenzymatic method[4] or by the Sharpless asymmetric epoxidation.[5]

As part of our ongoing research program aimed at developing the enantioselective syntheses of naturally occurring lactones[6] and amino alcohols,[7] we herein report an enantioselective synthesis of herbarumin III using hydrolytic kinetic resolution and Sharpless asymmetric dihydroxylation as the key steps.

2. Results and discussion

Our synthetic strategy for the synthesis of herbarumin III **3** is outlined in Scheme 1. The main fragment, alcohol **16** could be derived from the base induced reductive elimination of **13**, which in turn would be prepared from diol **10**. Diol **10** was obtained by the Sharpless asymmetric dihydroxylation of olefin **9**, which in turn could be prepared from epichlorohydrin **4**.



Scheme 1. Retrosynthetic analysis of herbarumin III.

* Corresponding author. Tel.: +91 20 25902050; fax: +91 20 25902629; e-mail: pk.tripathi@ncl.res.in

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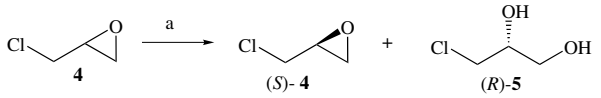
In designing a route to **3**, we chose racemic epichlorohydrin as an appropriate starting material. Thus, racemic epichlorohydrin **4** was subjected to Jacobsen's HKR by using (*R*,*R*)-salen-Co-OAc catalyst to give (*S*)-epichlorohydrin (*S*)-**4** as a single isomer, which was easily isolated from the more polar diol (*R*)-**5** by distillation[8] (Scheme 2).



Scheme 2. Reagents and conditions: (a) (*R*,*R*)-salen-Co-III-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 °C, 19 h, 46% for (*S*)-**4**, 45% for (*R*)-**5**.

Thus, epichlorohydrin (*S*)-**4** was opened with vinylmagnesium bromide, followed by base treatment to give epoxide **6** in 90% yield. Epoxide **6** was opened with propylmagnesium bromide[9] to afford homoallylic alcohol **7** in 78% yield, which was protected as TBS ether to furnish **8** in 94% yield. Olefin **8** was oxidized to the aldehyde in the presence of OsO_4 and $NaIO_4$ followed by reaction with (ethoxycarbonylmethylene)-triphenylphosphorane in benzene under reflux conditions to furnish *trans*-olefin **9** in 89% yield. The dihydroxylation of **9** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQD)_2PHAL$ ligand under the AD conditions[10] gave diol **10** in 95% yield and >96% de.[11] Treatment of diol **10** with 2,2-dimethoxypropane in the presence of *p*-TSA gave compound **11** in 91% yield, which upon reduction with DIBAL-H furnished alcohol **12** in 88% yield. The alcohol **12** was converted into an *O*-tosyl derivative which on treatment with sodium iodide furnished iodide **13** in 85% yield. Iodide **13**, on reductive fragmentation using Zn powder in refluxing ethanol furnished allylic alcohol **14** in 92% yield, which was protected as PMB ether followed by subsequent TBS deprotection to give alcohol **16** in 87% yield. As the synthesis of **3** from **16** has already been reported,[2b] the formal synthesis of herbarumin III was completed (Scheme 3).

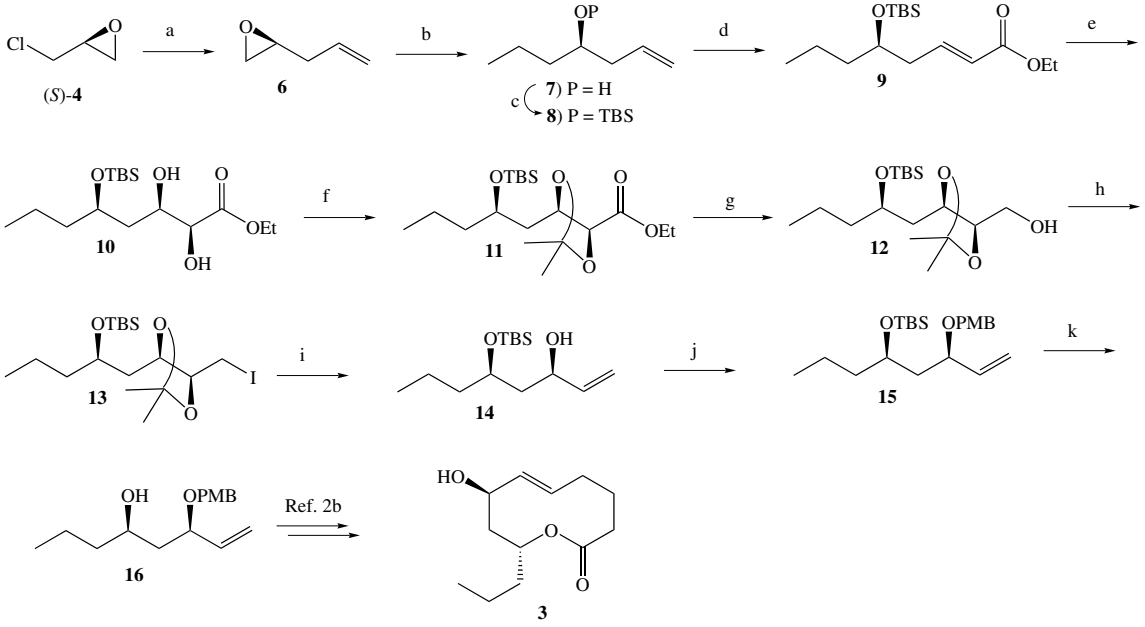
3. Conclusion

In conclusion, a formal synthesis of herbarumin III with high enantioselectivity has been accomplished in which the stereocenters were established by Jacobsen's hydrolytic kinetic resolution and Sharpless asymmetric dihydroxylation. Further application of this methodology to the syntheses of all the isomers of herbarumin and other biologically active compounds for structure–activity relationship studies is currently underway in our laboratory.

4. Experimental

4.1. General experimental

Solvents were purified and dried by standard procedures prior to use; petroleum ether of boiling range 60–80 °C was used. Optical rotations were measured using a sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on Perkin–Elmer FT-IR spectrometer. The enantiomeric excess was measured using either the chiral HPLC or by comparison with the specific rotation.



Scheme 3. Reagents and conditions: (a) (i) vinylmagnesium bromide, ether, CuI, −73 to −40 °C, 19 h, 72%; (ii) KOH, 90%; (b) C_3H_7MgBr, THF, CuI, −20 °C, 4 h, 78%; (c) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 2.5 h, 94%; (d) (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1), 0 °C; (ii) $Ph_3P=CHCO_2Et$, benzene, reflux, 6 h, 84% from two steps; (e) $(DHQD)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1 M in toluene), *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 95%; (f) *p*-TSA, 2,2-DMP, CH_2Cl_2, 1.5 h, 91%; (g) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h, 88%; (h) (i) TsCl, Et_3N, CH_2Cl_2, 2 h; (ii) NaI, 2-butanone, reflux, 6 h, 85% for both the steps; (i) Zn, EtOH, reflux, 3 h, 92%; (j) PMBBr, NaH, THF, 90%; (k) TBAF, THF, 8 h, 87%.

Elemental analyses were carried out with a Carlo Erba CHNS–O analyzer.

4.2. Synthesis of (*S*)-epichlorohydrin (*S*)-4

The racemic epichlorohydrin **4** was resolved to (*S*)-epichlorohydrin (*S*)-**4** in high enantiomeric excess by the HKR method following a literature procedure.[8d] $[\alpha]_D^{25} = +30.6$ (*c* 1.2, MeOH); lit.[8d] for (*R*)-epichlorohydrin $[\alpha]_D^{26} = -32.8$ (*c* 1.27, MeOH).

4.3. Synthesis of (*S*)-2-allyloxirane 6

A round bottomed flask was charged with copper(I) iodide (0.103 g, 0.54 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, after which dry diethyl ether (30 mL) was added. This suspension was cooled into −20 °C and vigorously stirred, after which vinylmagnesium bromide (1 M in THF, 108 mL, 108.08 mmol) was injected to it. A solution of epichlorohydrin (*S*)-**4** (5 g, 54.04 mmol) in diethyl ether (10 mL) was added slowly to the above reagent, and the mixture stirred at −73 °C to −40 °C for 19 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford the crude homoallylic alcohol, which on vacuum distillation provided homoallylic alcohol (*S*)-1-chloropent-4-en-2-ol as a colorless liquid (4.7 g, 72%). Bp 66–69 °C/21 mm of Hg; $[\alpha]_D^{25} = +5.2$ (*c* 1.4, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914; ^1H NMR ($CDCl_3$, 400 MHz): 5.74–5.87 (m, 1H), 5.08–5.19 (m, 2H), 3.85–3.90 (m, 1H), 3.54 (d, $J = 8.1$ Hz, 2H), 2.34 (t, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 133.2, 118.1, 70.4, 48.9, 38.4.

KOH (2.8 g, 49.76 mmol) was added to the homoallylic alcohol (5 g, 41.47 mmol) in a flask fitted with a distillation head. The mixture was heated and epoxide **6** distilled over as a colorless liquid (3.14 g, 90%). Bp 80–82 °C; $[\alpha]_D^{27} = -16.2$ (neat); IR ($CHCl_3$, cm^{-1}): 2995, 1647, 1410, 920; ^1H NMR ($CDCl_3$, 200 MHz): 5.68–5.92 (m, 1H), 5.03–5.22 (m, 2H), 2.91–3.03 (m, 1H), 2.73 (dd, $J = 5.0$, 4.0 Hz, 1H), 2.48 (dd, $J = 5.0$, 2.6 Hz), 2.23–2.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): 133.0, 117.5, 51.1, 46.4, 36.4.

4.4. Synthesis of (*R*)-hept-1-en-4-ol 7

A round bottomed flask was charged with copper(I)-iodide (0.91 g, 0.48 mmol), gently heated under vaccum and slowly cooled with a flow of argon after which THF (20 mL) was added. This suspension was cooled to −30 °C, stirred, and ethylmagnesium bromide [prepared from Mg (2.31 g, 95.10 mmol) and ethyl bromide (10.36 g, 95.10 mmol) in THF] added to it. A solution of epoxide **6** (4.0 g, 47.55 mmol) in THF (10 mL) was added to the above reagent and the mixture was stirred at −20 °C for 4 h. After consumption of starting material, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The water layer was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Silica gel column chromatography of the crude product using Pet ether/EtOAc (9:1) as eluent provided alcohol **7** as a colorless liquid (4.24 g, 78%). $[\alpha]_D^{25} = -17.4$ (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3425, 3019, 2927, 2106, 1601, 1493, 1455, 1251, 1123, 863, 758; ^1H NMR ($CDCl_3$, 500 MHz): 5.74–5.79 (m, 1H), 5.02–5.11 (m, 2H), 3.54–3.59 (m, 1H), 2.34 (br s, 1H), 2.02–2.11 (m, 2H), 1.30–1.54 (m, 4H), 0.91 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 135.5, 117.2, 71.1, 42.2, 38.9, 19.2, 14.1.

4.5. Synthesis of (*R*)-*tert*-butyl(hept-1-en-4-yloxy)dimethylsilane 8

To a stirred solution of alcohol **7** (4.0 g, 35.03 mmol) in CH_2Cl_2 (25 mL), imidazole (3.58 g, 52.54 mmol) was added. To this solution *t*-butylchlorodimethylsilane (5.81 g, 38.53 mmol) was added at 0 °C and reaction stirred at room temperature for 2.5 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine, dried over Na_2SO_4, and concentrated. Silica gel column chromatography of the crude product using Pet ether/EtOAc (49:1) as eluent provided **8** (7.52 g, 94%) as a light yellow liquid. $[\alpha]_D^{25} = -21.2$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 3086, 2972, 2921, 2892, 1640, 1493, 1453, 1359, 1248, 1075, 1002, 916, 872; ^1H NMR ($CDCl_3$, 400 MHz): 5.75–5.86 (m, 1H), 5.02–5.12 (m, 2H), 3.74–3.82 (m, 1H), 2.22–2.36 (m, 2H), 2.05–2.18 (m, 1H), 1.62–1.71 (m, 1H), 1.32–1.59 (m, 2H), 0.92 (t, $J = 6.6$ Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 135.2, 116.8, 70.9, 41.1, 40.8, 25.6, 18.2, 17.8, 14.3, −4.5; Anal. Calcd for $C_{13}H_{28}OSi$ (228.45): C, 68.35; H, 12.35. Found: C, 68.24; H, 12.38.

4.6. Synthesis of (*R*,*E*)-ethyl 5-(*tert*-butyldimethylsilyloxy)oct-2-enoate 9

To a solution of compound **8** (4 g, 17.51 mmol) in dioxane–water (3:1, 40 mL) were added 2,6-lutidine (4.1 mL, 35.02 mmol), OsO_4 (0.1 M solution in toluene, 3.5 mL, 0.35 mmol), and $NaIO_4$ (14.98 g, 70.04 mmol). The reaction was stirred at 25 °C for 3 h. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine and dried over Na_2SO_4 to give the crude aldehyde, which was used as such for the next step without further purification.

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (7.85 g, 22.57 mmol) in dry benzene (150 mL) was added a solution of the above aldehyde in dry benzene (100 mL). The reaction mixture was refluxed for 6 h. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to afford the α,β-unsaturated ester **9** (4.42 g, 84%) as a pale yellow liquid. $[\alpha]_D^{25} = -23.1$ (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 3056, 3019, 2962, 2916, 1712, 1661, 1472, 1463, 1372, 1269, 1182, 1094 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.89–7.05 (m, 1H), 5.80 (dt, $J = 15.7$, 14.3, 1.4 Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.72–3.83 (m, 1H), 2.30–2.40 (m, 2H), 1.39–1.50 (m, 4H), 1.29 (t, $J = 7.1$ Hz, 3H), 0.92 (t, $J = 6.6$ Hz, 3H), 0.89 (s,

9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.3, 145.9, 123.1, 71.0, 59.9, 40.1, 39.4, 25.7, 18.4, 17.9, 14.1, −4.7; Anal. Calcd for $C_{16}H_{32}O_3Si$ (300.51): C, 63.95; H, 10.73. Found C, 63.88; H, 10.81.

4.7. Synthesis of (2*S*,3*R*,5*R*)-ethyl 5-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxyoctanoate 10

To a mixture of $K_3Fe(CN)_6$ (6.57 g, 19.97 mmol), K_2CO_3 (2.76 g, 19.97 mmol), and $(DHQD)_2PHAL$ (52 mg, 1 mol %), in *t*-BuOH/H_2O (1:1, 35 mL) cooled at 0 °C was added OsO_4 (0.27 mL, 0.1 M sol in toluene, 0.4 mol %) followed by methanesulfonamide (0.63 g, 6.66 mmol). After stirring for 5 min at 0 °C, olefin **9** (2.0 g, 6.66 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (10 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave diol **10** (2.12 g, 95%) as a colorless syrupy liquid. $[\alpha]_D^{25} = -11.2$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3446, 3018, 2958, 2898, 2412, 1733, 1665, 1465, 1261, 1092 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.28 (q, $J = 7.1$ Hz, 2H), 4.02–4.12 (m, 2H), 3.96 (d, $J = 4.2$ Hz, 1H), 3.09 (br s, 2H), 1.63–1.82 (m, 2H), 1.49–1.56 (m, 2H), 1.32 (t, $J = 7.1$ Hz, 3H), 0.95 (t, $J = 6.6$ Hz, 3H), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.2, 74.1, 71.2, 69.4, 61.7, 39.9, 38.7, 25.8, 17.9, 17.9, 14.2, 14.1, −4.6; Anal. Calcd for $C_{16}H_{34}O_5Si$ (334.52): C, 57.45; H, 10.24. Found C, 57.36; H, 10.21.

4.8. Synthesis of (4*S*,5*R*)-ethyl 5-((*R*)-2-(*tert*-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate 11

To a solution of diol **10** (2.0 g, 5.98 mmol), *p*-TSA (50 mg) in CH_2Cl_2 (50 mL) was added 2,2-dimethoxypropane (0.93 g, 1.1 mL, 8.97 mmol) and the mixture stirred for 1.5 h. Solid $NaHCO_3$ was added and stirred. The reaction was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) gave **11** (2.04 g, 91%) as a colorless liquid. $[\alpha]_D^{25} = -24.1$ (*c* 0.8, $CHCl_3$); IR (neat): ν_{max} 3021, 2952, 2946, 1742, 1664, 1471, 1375, 1216, 1135, 1078, 964, 856 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.22 (q, $J = 7.1$ Hz, 2H), 4.03–4.14 (m, 2H), 3.85–3.94 (m, 1H), 1.80–1.94 (m, 2H), 1.61–1.74 (m, 2H), 1.46 (s, 3H), 1.44 (s, 3H), 1.36–1.39 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 3H), 0.92 (t, $J = 6.6$ Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 110.7, 79.2, 76.1, 69.3, 61.2, 41.1, 40.4, 38.7, 27.2, 25.8, 18.4, 17.9, 14.3, 14.1, −4.53; Anal. Calcd for $C_{19}H_{38}O_5Si$ (374.59): C, 60.92; H, 10.23. Found C, 61.04; H, 10.18.

4.9. Synthesis of ((4*R*,5*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 12

To a solution of ester **11** (1.9 g, 5.07 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added dropwise DIBAL-H (5.58 mL, 5.58 mmol, 1 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, then re-cooled to 0 °C and treated with a saturated solution of sodium potassium tartrate. The solid material was filtered through a pad of Celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (17:3) as eluent gave alcohol **12** (1.48 g, 88%) as a colorless liquid. $[\alpha]_D^{25} = -16.2$ (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 3459, 3021, 2958, 2946, 1720, 1469, 1374, 1265, 1221, 1164, 1047, 963, 942 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.14–3.97 (m, 2H), 3.81 (d, $J = 7.2$ Hz, 2H), 3.78–3.63 (m, 1H), 1.73–1.62 (m, 2H), 1.60–1.44 (m, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.40–1.38 (m, 2H), 0.94 (t, $J = 6.6$ Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 108.6, 81.7, 73.6, 69.6, 61.9, 40.9, 38.6, 26.9, 25.8, 18.6, 17.7, 14.3, −4.36; Anal. Calcd for $C_{17}H_{36}O_4Si$ (332.55): C, 61.40; H, 10.91. Found C, 61.52; H, 10.89.

4.10. Synthesis of ((*R*)-1-((4*R*,5*S*)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-yloxy)(*tert*-butyl)dimethylsilane 13

To a stirred solution of alcohol **12** (1.4 g, 4.21 mmol) in CH_2Cl_2 (40 mL) at 0 °C under nitrogen was added triethyl-amine (1.65 mL, 11.82 mmol), followed by tosyl chloride (0.90 g, 4.73 mmol). After being stirred for 2 h at room temperature, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the tosylate as a pale yellow oil, which was used as such for the next step, without further purification.

The tosylate (2.05 g, 4.21 mmol) was dissolved under argon in dry 2-butanone (20 mL) and treated with NaI (1.89 g, 12.65 mmol). The reaction mixture was refluxed for 6 h. After cooling to room temperature the volatiles were removed under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent gave iodo compound **13** (1.58 g, 85%) as a light yellow liquid. $[\alpha]_D^{25} = -64.7$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3020, 2965, 2932, 2856, 1522, 1468, 1384, 1298, 1211, 1028, 968 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.95–3.83 (m, 2H), 3.65–3.53 (m, 1H), 3.35–3.19 (m, 2H), 1.84–1.64 (m, 2H), 1.62–1.41 (m, 4H), 1.44 (s, 3H), 1.41 (s, 3H), 0.95 (t, $J = 6.6$ Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 108.9, 80.1, 78.2, 69.5, 40.6, 38.5, 27.3, 27.2, 25.9, 18.6, 18.0, 14.4, 5.41, −4.29, −4.60; Anal. Calcd for $C_{17}H_{35}IO_3Si$ (442.45): C, 46.15; H, 7.97. Found C, 46.22; H, 7.90.

4.11. Synthesis of (3*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)oct-1-en-3-ol 14

A mixture of **13** (1.5 g, 3.39 mmol), zinc (0.44 g, 6.78 mmol) in refluxing ethanol (15 mL) under nitrogen was stirred for 3 h. The zinc was filtered and filtrate concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **14** (0.81 g, 92%) as a light yellow liquid. $[\alpha]_D^{25} = -32.1$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3445, 3082, 3958, 2932, 2858,

1645, 1472, 1464, 1379, 1256, 1216, 1127, 1066, 922, 836 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.87 (dq, $J = 17.1$, 11.9, 6.7, 1.0 Hz, 1H), 5.23 (dd, $J = 17.1$, 15.5, 1.6 Hz, 1H), 5.07 (dd, $J = 11.9$, 10.36, 1.51 Hz, 1H), 4.32–4.23 (m, 1H), 4.15–3.92 (m, 1H), 1.68–1.63 (m, 2H), 1.55–1.48 (m, 2H), 1.37–1.23 (m, 2H), 0.94 (t, $J = 6.6$ Hz, 3H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.9, 113.9, 71.8, 69.6, 43.0, 40.1, 25.8, 18.7, 17.8, 14.2, −4.10, −4.73; Anal. Calcd for $C_{14}H_{30}O_2Si$ (258.47): C, 65.06; H, 11.70. Found C, 65.11; H, 11.81.

4.12. Synthesis of *tert*-butyl-((4*R*,6*R*)-6-(4-methoxybenzyloxy)oct-7-en-4-yloxy)dimethylsilane 15

To a solution of **14** (0.50 g, 1.93 mmol) in dry THF (20 mL) was added sodium hydride (50%, 0.11 g, 2.32 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl bromide (0.36 g, 2.13 mmol) and tetra *n*-butylammonium iodide (0.71 g, 0.19 mmol) with further stirring for 1 h at the same temperature. The reaction mixture was quenched with addition of cold water and EtOAc at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3×100 mL). The combined organic layers were washed with water (3×100 mL), brine, dried over Na_2SO_4 and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish **15** (0.66 g, 90%) as a colorless oil. $[\alpha]_D^{25} = -38.3$ (*c* 1.1, $CHCl_3$); IR (neat): ν_{max} 3085, 2951, 2936, 2847, 1641, 1487, 1464, 1378, 1247, 1121, 1055, 913, 839 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, $J = 8.2$ Hz, 2H), 6.88 (d, $J = 8.3$ Hz, 2H), 5.82–5.65 (m, 1H), 5.26–5.19 (m, 2H), 4.32 (s, 2H), 4.04–3.99 (m, 1H), 3.98–3.94 (m, 1H), 3.79 (s, 3H), 1.68–1.61 (m, 2H), 1.48–132 (m, 4H), 0.92 (t, $J = 6.9$ Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1, 139.6, 129.7, 129.5, 116.9, 114.1, 81.7, 72.3, 71.6, 55.3, 43.9, 40.4, 25.9, 18.7, 17.6, 14.3, −4.3, −4.6; Anal. Calcd for $C_{22}H_{38}O_3Si$ (378.62): C, 69.79; H, 10.12. Found C, 69.65; H, 10.16.

4.13. Synthesis of (4*R*,6*R*)-6-(4-methoxybenzyloxy)oct-7-en-4-ol 16

To a solution of **15** (0.65 g, 1.72 mmol) in THF (10 mL) was added TBAF (2.58 mL, 2.58 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 8 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 3:1) to give **16** (0.395 g, 87%) as a colorless oil. $[\alpha]_D^{25} = -9.6$ (*c* 0.80, $CHCl_3$); IR (neat): ν_{max} 3448, 3073, 2985, 2931, 2852, 1634, 1469, 1445, 1257, 1221, 1127, 918, 834 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.21 (d, $J = 8.2$ Hz, 2H), 6.84 (d, $J = 8.3$ Hz, 2H), 5.84–5.66 (m, 1H), 5.29–5.21 (m, 2H), 4.54 (d, $J = 11.1$ Hz, 1H), 4.26 (d, $J = 11.2$ Hz, 2H), 4.06–4.01 (m, 1H), 4.0–3.96 (m, 1H), 3.80 (s, 3H), 3.59 (br s, 1H), 1.69–1.60 (m, 2H), 1.44–1.26 (m, 2H), 0.94 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.3, 138.3, 129.9, 124.5, 117.5, 113.9, 81.2, 71.1, 69.8, 55.2, 42.5, 39.8, 18.6, 14.1; Anal. Calcd for $C_{16}H_{24}O_3$ (264.36): C, 72.62; H, 9.19. Found C, 72.54; H, 9.28.

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