Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1539–1549

TETRAHEDRON: *ASYMMETRY*

Synthesis of the C29–C37 segment of spongistatin 1

Ralf Dunkel, Jens Treu † and H. Martin R. Hoffmann *

Department of Organic Chemistry, University of Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

Received 23 March 1999; accepted 19 April 1999

Abstract

Starting from racemic 2α-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one the spongistatin E segment has been prepared in nine steps (2.3 steps per stereogenic center) with umpolung of anomeric reactivity at C37. This 3,5-*syn*-diol sequence completes our methodology to all stereoisomers of 3,5,7-trihydroxy heptanoic ester building blocks functionalized for α-oxyanion chemistry.

1. Introduction

Tetrahydropyrans and their open chain analogs are of enormous interest in polyketide and in natural product chemistry in general.[1] In a previous paper we have described the synthesis of open-chain seven carbon based building blocks of the polyacetate aldol type. Each of the stereogenic centers was built

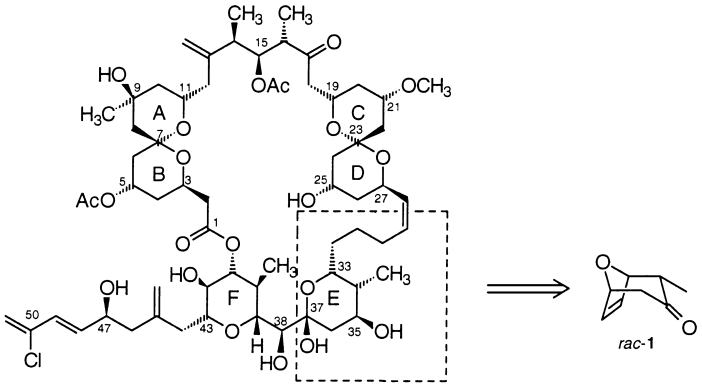
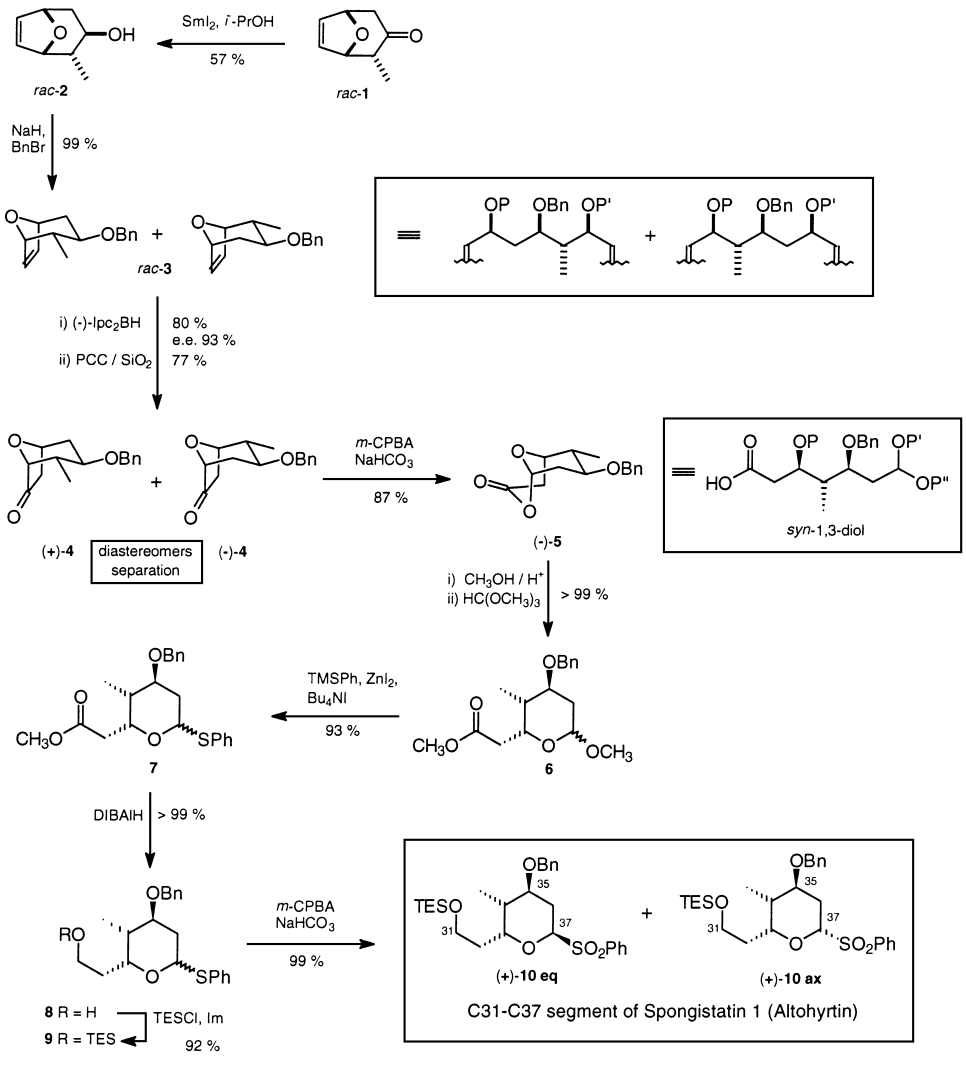


Figure 1.

* Corresponding author. E-mail: hoffmann@mbox.oci.uni-hannover.de

† New address: Product Development cosmed, Cleansing Products, Beiersdorf AG, Unnastr. 48, D-20245 Hamburg, Germany.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00148-2



Scheme 1.

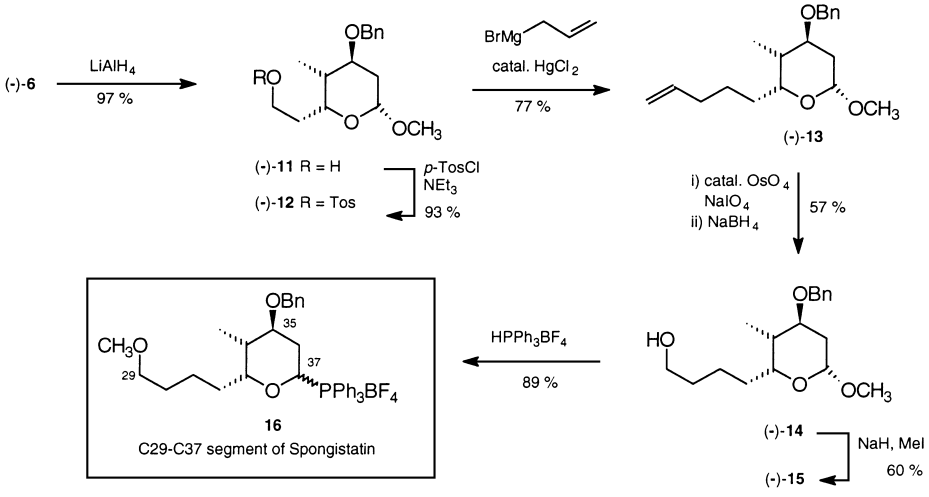
up diastereo- and enantioselectively. The functionalization with carbanion stabilizing π-acceptors at the terminal carbon was described in full detail for one of the 3,5-*anti* diols, yielding the C17–C23 fragment of spongistatin.[2,3] In tackling the synthesis of segment E we now extend our anomeric oxabicyclic lactone concept to methyl substituted bicyclic ketone *rac*-**1**. Our sequence affords the C29–C37 fragment of spongistatin (Fig. 1).

2. Results

Starting from 2α-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one *rac*-**1**, SmI_2 mediated reduction[4] gave the equatorial alcohol *rac*-**2**. *exo*-Orientation of the hydroxy group provided the equivalent of the *syn*-3,5-diol enantiomeric pair. Protection yielded benzyl ether *rac*-**3** quantitatively. Asymmetric hydroboration[5] and oxidation of the corresponding regioisomeric alcohols allowed separation of the almost enantiopure (ee 93%) ketones (−)-**4** and (+)-**4** by simple column chromatography. Baeyer–Villiger oxidation of (−)-**4** furnished anomeric oxabicyclic lactone (−)-**5**, which was opened to monocyclic anomers **6** by acidic methanolysis.

Preparation of the desired sulfone **10** (Scheme 1) required the introduction of thiophenol to afford the anomeric sulfides **7**. However, thiophenol introduction via boron trifluoride etherate at the acetalic center led to deprotection of the benzyl ether. Instead of changing the sequence to (i) ester reduction followed by (ii) protection of the corresponding alcohol, we used milder conditions for the acetal functionalization. Reaction of the acetals **6** with (phenylthio)trimethylsilane Me_3SiSPh in the presence of zinc iodide and tetrabutylammonium iodide[6] afforded anomeric sulfides **7**. Diisobutylaluminum hydride reduction and silylation of the resulting alcohol (**8** → **9**) was straightforward and furnished anomeric sulfides **9**. Oxidation with *m*-chloroperoxybenzoic acid yielded the sulfones (+)-**10 eq** and (+)-**10 ax** which could easily be separated by column chromatography. A building block equivalent to **10** has already been coupled in Evans' total synthesis of spongistatin.[3a]

The synthesis of the triphenylphosphonium tetrafluoroborate **16** (Scheme 2) started again from methyl acetal (−)-**6**.[7] Reduction of the ester function and tosylation afforded (−)-**12** in very good yield. Elongation via allyl group introduction by Grignard reaction, subsequent dihydroxylation and sodium periodate cleavage resulted, after reduction, in the C_2-elongated acetal (−)-**14**. Protection of the alcohol and reaction with triphenylphosphonium tetrafluoroborate furnished **16** as an alternative building block of the spongistatin C29–C37 segment.



Scheme 2.

In summary, three stereogenic centers and one anomeric center have been installed de novo in nine steps from racemic 2α-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one. Asymmetric hydroboration gave single enantiomers. The anomeric center was subjected to umpolung with different π-acceptors. Our methodology provides enantiopure *anti*-1,3-aldols[8] and *syn*-1,3-aldols with chemodifferentiated 1,7-functionality (Scheme 1) and 1,9-functionality (Scheme 2).

3. Experimental

3.1. General

Infrared spectra were recorded on a Perkin–Elmer 1710 infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer in deuterated chloroform unless otherwise stated, with tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan MAT 312 (70 eV) or a VG Autospec spectrometer at room temperature unless otherwise stated. Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30–60 μm). Analytical

TLC was carried out on aluminum-backed 0.2 mm silica gel 60 F_{254} plates (E. Merck). Diethyl ether (E) and THF were distilled over sodium and benzophenone before use. CH_2Cl_2 (DCM) was distilled over CaH_2 before use. DMF was dried over BaO and distilled over CaH_2 before use. Methyl *t*-butyl ether (MTBE), ethyl acetate (EA), cyclohexane (CH) and light petroleum (PE, bp 40–60°C) were distilled before use. For the preparation of compounds *rac*-**1** and *rac*-**2** see Treu and Hoffmann. [4]

3.2. 2α-Methyl-3β-benzyloxy-8-oxabicyclo[3.2.1]oct-6-ene rac-***3***

To a solution of alcohol *rac*-**2** (3.96 g, 28.3 mmol) in THF (40 ml) was added NaH (1.70 g, 56.5 mmol, 80% in mineral oil) under N_2. The mixture was heated to reflux for 45 min. To the resulting mixture was added benzyl bromide (6.70 ml, 56.5 mmol) and Bu_4NI (30 mg, 0.07 mmol) in THF (5 ml) at room temperature. The mixture was heated to reflux for 3 h and then stirred at room temperature overnight. Water was added and the aqueous layer was extracted with E. The combined organic layer was dried ($MgSO_4$), the solvent removed and the crude product was purified by chromatography (E/PE) to afford *rac*-**3** (6.45 g, 99%) as yellow crystals, mp 35°C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.39–7.22 (m, 5H, Ph), 6.14 (s, 2H, H-7, H-6), 4.81 (d, *J*=3 Hz, 1H, H-5), 4.57 (d, *J*=12 Hz, 1H, C*H*HPh), 4.55 (d, *J*=5 Hz, 1H, H-1), 4.35 (d, *J*=12 Hz, 1H, CH*H*Ph), 3.20 (ddd, *J*=9 Hz, *J*=9 Hz, *J*=6 Hz, 1H, H-3), 1.98 (m, 1H, H-4_{eq}), 1.99 (m, 1H, H-4_{ax}), 1.66 (m, 1H, H-2), 0.92 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.83 (C, C_{Ph}), 132.26 (CH, C-7), 129.64 (CH, C-6), 128.34 (CH, *o*-C_{Ph}), 127.71 (CH, *m*-C_{Ph}), 127.54 (CH, *p*-C_{Ph}), 82.30 (CH, C-5), 78.44 (CH, C-1), 77.95 (CH, C-3), 70.74 (CH_2, *C*H_2Ph), 38.58 (CH, C-2), 31.62 (CH_2, C-4), 14.56 (CH_3, CH_3); ν_{max} ($CHCl_3$)/cm^{-1} 3000, 2956, 2872, 1496, 1356, 1252, 1116, 1088, 1072; MS: 230 (M^+, 1), 175 (4), 124 (30), 92 (11), 91 (100), 81 (17), 65 (6). Anal. calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.20; H, 7.86.

*3.3. (1*S*,3*R*,4*S*,5*R*)-3-Benzyloxy-4-methyl-8-oxabicyclo[3.2.1]octan-6-one (+)-**4** and diastereomeric (1*R*,2*R*,3*S*,5*R*)-3-benzyloxy-4-methyl-8-oxabicyclo[3.2.1]octan-6-one (−)-**4**

To a solution of (+)-α-pinene (12.8 ml, 80.5 mmol) in THF (8.6 ml) was added BH_3·DMS (3.20 ml, 32.0 mmol, 10 M solution) at rt. Stirring was stopped after 5 min and after a short time (−)-$(Ipc)_2BH$ crystallized. Crystallization was completed overnight. The mixture was cooled to 0°C and the supernatant liquid was removed with a syringe. The crystals were cooled to −20°C and washed with ice-cold E. The solvent was removed with a syringe and the crystals were dried for 15 min (oil pump vacuum). To the resulting (−)-$(Ipc)_2BH$ was added THF (2 ml) at −20°C followed by *rac*-**3** (5.24 g, 23.0 mmol) in THF (1 ml). The mixture was stored for 8 days at −15°C and 6 days at −3°C, then MeOH (5.2 ml) was added at 0°C, followed by 3 N NaOH (14.3 ml, 43.2 mmol) and 30% H_2O_2 (14.3 ml, 141 mmol). The mixture was stirred for 1.5 h at 0°C and 2 h at rt. The aqueous layer was saturated with NaCl and extracted with EA. The combined organic phase was dried ($MgSO_4$), the solvent evaporated, and the crude product purified by column chromatography to afford a mixture of alcohols (4.59 g, 80%), yellowish oil. To a suspension of PCC on silica gel (18.4 g, 36.8 mmol, ca. 2 mmol/g) in DCM (50 ml) was added a mixture of alcohols (4.52 g, 18.4 mmol) in DCM (25 ml) at 0°C. The mixture was stirred for 2 h at 0°C and overnight at rt and then filtered through silica gel (E). After removal of the solvent, the crude product was purified by column chromatography (E/PE) to afford (+)-**4** and (−)-**4**. Data for (+)-**4**, yield 1.68 g (37%), crystals, mp 73°C, $[\alpha]_D^{20}$=+67.0 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.38–7.23 (m, 5H, Ph), 4.60 (d, *J*=12 Hz, 1H, C*H*HPh), 4.51 (d, *J*=4 Hz, 1H, H-5), 4.36 (d, *J*=12 Hz, 1H, CH*H*Ph), 4.18–4.12 (m, 1H, H-1), 3.25 (ddd, *J*=11 Hz, *J*=10 Hz, *J*=6 Hz, 1H, H-3), 2.53 (dd, *J*=15 Hz, *J*=8 Hz, 1H, H-7_{exo}), 2.30 (d, *J*=15 Hz, 1H, H-7_{endo}), 2.26 (m, 1H, H-2_{eq}), 2.16 (m, 1H, H-4), 1.80 (m, 1H, H-2_{ax}), 0.97 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 215.12 (C, C-6), 138.09 (C, C_{Ph}), 128.44 (CH, *o*-C_{Ph}, *p*-C_{Ph}), 127.71 (CH, *m*-C_{Ph}), 78.12 (CH, C-5), 77.05 (CH, C-1), 75.49 (CH, C-3), 70.9 (CH_2, *C*H_2Ph),

40.11 (CH, C-4), 38.29 (CH_2, C-7), 31.43 (CH_2, C-2), 14.18 (CH_3, CH_3); ν_{max} (KBr)/cm^{-1} 3032, 2980, 2944, 2916, 1752, 1452, 1352, 1176, 1108, 1084, 1024; MS (50°C): 246 (M^+, 3), 218 (5), 163 (25), 155 (33), 140 (100); HR-MS calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256, found 246.1256. Data for (−)-**4**, 1.825 g, (40%), light-yellow oil, $[\alpha]_D^{20}$=−31.4 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.40–7.20 (m, 5H, Ph), 4.82 (m, 1H, H-5), 4.61 (d, *J*=12 Hz, 1H, C*H*HPh), 4.42 (d, *J*=12 Hz, 1H, CH*H*Ph), 3.85 (d, *J*=4 Hz, 1H, H-1), 3.30 (ddd, *J*=11 Hz, *J*=11 Hz, *J*=5 Hz, 1H, H-3), 2.63 (dd, *J*=18 Hz, *J*=8 Hz, 1H, H-7_{exo}), 2.17 (d, *J*=18 Hz, 1H, H-7_{endo}), 2.14 (m, 1H, H-4_{eq}) 2.07 (m, 1H, H-2), 1.91 (m, 1H, H-4_{ax}), 1.08 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 213.53 (C, C-6), 138.02 (C, C_{Ph}), 128.37 (CH, *o*-C_{Ph}, *p*-C_{Ph}), 127.42 (CH, *m*-C_{Ph}), 80.37 (CH, C-5), 75.77 (CH, C-1), 73.86 (CH, C-3), 70.93 (CH_2, *C*H_2Ph), 41.95 (CH_2, C-7), 41.55 (CH, C-2), 35.62 (CH_2, C-4), 12.27 (CH_3, CH_3); ν_{max} (film)/cm^{-1} 3028, 2964, 2896, 2876, 1752, 1496, 1452, 1364, 1112, 1076; MS (50°C): 246 (M^+, 4), 190 (3), 177 (33), 161 (2), 155 (17), 140 (100); HR-MS calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256, found 246.1256.

*3.4. (−)-(1S,5R,6R,7S)-7-Benzyloxy-6-methyl-2,9-dioxabicyclo[3.3.1]nonan-3-one (−)-**5***

To a solution of ketone (−)-**4** (1.6 g, 6.5 mmol) in DCM (40 ml) was added a mixture of $KHCO_3$ (1.3 g, 13 mmol) and *m*-CPBA (3.2 g, 13 mmol, 70%) portionwise at 0°C. The mixture was stirred overnight at rt, then 2 N NaOH was added to dissolve the precipitate. The aqueous layer was extracted with DCM and the combined organic phase dried ($MgSO_4$). After removal of the solvent the residue was purified by column chromatography (E/PE) to afford (−)-**5**, 1.47 g (87%), crystals, mp 81°C, $[\alpha]_D^{20}$=−5.0 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.40–7.24 (m, 5H, Ph), 5.86 (s, 1H, H-1), 4.61 (d, *J*=12 Hz, 1H, C*H*HPh), 4.42 (d, *J*=12 Hz, 1H, CH*H*Ph), 4.28 (dd, *J*=8 Hz, *J*=4 Hz, 1H, H-5), 3.47 (ddd, *J*=11 Hz, *J*=10 Hz, *J*=5 Hz, 1H, H-7), 2.87 (dd, *J*=18, *J*=8 Hz, 1H, H-4_{exo}), 2.62 (d, *J*=18 Hz, 1H, H-4_{endo}), 2.55 (m, 1H, H-8_{eq}), 2.20 (m, 1H, H-6), 1.78 (ddd, *J*=13 Hz, *J*=11 Hz, *J*=3 Hz, 1H, H-8_{ax}), 1.04 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 166.46 (C, C-3), 137.88 (C, C_{Ph}), 128.51 (CH, *o*-C_{Ph}), 127.61 (CH, *p*-C_{Ph}), 127.56 (CH, *m*-C_{Ph}), 99.55 (CH, C-1), 72.48 (CH, C-5), 72.4 (CH, C-7), 71.31 (CH_2, *C*H_2Ph), 40.13 (CH, C-6), 36.78 (CH_2, C-8), 29.88 (CH_2, C-4), 13.74 (CH_3, CH_3); ν_{max} (KBr)/cm^{-1} 2984, 2900, 1740, 1720, 1496, 1376, 1244, 1100, 1068; MS: 190 (1), 172 (2), 171 ($M^+-C_7H_7$, 17), 130 (5), 92 (1), 91 (100), 77 (2), 65 (7); HR-MS calcd for $C_{15}H_{18}O_4$ (M^+) 262.1205, found 262.1201.

*3.5. (−)-(2R,3R,4S,6R)-4-Benzyloxy-6-methoxy-3-methyl-tetrahydropyran-2-acetic acid methyl ester [(−)-**6**]*

To a solution of lactone (−)-**5** (1.33 g, 5.09 mmol) in MeOH was added concentrated HCl (a few drops) and the mixture was stirred overnight at rt, then DCM was added. The mixture was neutralized with sat. aqueous $NaHCO_3$ solution. The aqueous layer was extracted with DCM, the combined organic phase dried ($MgSO_4$), and the solvent evaporated. Purification by column chromatography afforded (−)-**6** (93% ee, ^{1}H NMR shift experiment with (+)-Eu(hfc)$_3$), 1.36 g (86%), as a colorless oil, $[\alpha]_D^{20}$=−17.4 (c=1, $CHCl_3$). Alternatively, methanolysis in the presence of trimethyl orthoformate (1 equiv.) and catalytic H_2SO_4 gave **6** (99% yield) as an anomeric mixture, ax:eq=1:3. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.40–7.30 (m, 5H, Ph), 4.71 (dd, *J*=10 Hz, *J*=3 Hz, 1H, H-6), 4.58 (d, *J*=12 Hz, 1H, C*H*HPh), 4.52 (d, *J*=12 Hz, 1H, CH*H*Ph), 4.45 (m, 1H, H-2), 3.68 (s, 3H, OCH_3), 3.63 (dd, *J*=10 Hz, *J*=3 Hz, 1H, H-4), 3.46 (s, 3H, OCH_3), 2.66 (dd, *J*=15 Hz, *J*=9 Hz, 1H, H-7a), 2.39 (dd, *J*=15 Hz, *J*=5 Hz, 1H, H-7b), 1.90 (m, 2H, H-5_{eq}, H-3), 1.64 (ddd, *J*=13 Hz, *J*=10 Hz, *J*=3 Hz, 1H, H-5_{ax}), 0.95 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 171.8 (C, C-8), 138.54 (C, C_{Ph}), 128.42 (CH, *o*-C_{Ph}), 127.58 (CH, *p*-C_{Ph}), 127.4 (CH, *m*-C_{Ph}), 100.4 (CH, C-6), 78.38 (CH, C-2), 70.44 (CH_2, *C*H_2Ph), 69.6 (CH, C-4), 56.24 (CH_3, OCH_3), 51.63 (CH_3, OCH_3), 37.52 (CH_2, C-7), 34.35 (CH, C-3), 31.38 (CH_2, C-5), 10.94

(CH_3, CH_3); ν_{max} (film)/cm^{-1} 3028, 2956, 2936, 1740, 1496, 1436, 1300, 1192, 1144, 1040; MS: 308 (M^+, 5), 230 (1), 185 (4), 170 (5), 91 (100), 77 (2), 65 (6); HR-MS calcd for $C_{17}H_{24}O_5$ (M^+) 308.1624, found 308.1613.

*3.6. (2*R,*3*R,*4*S*)-(4-Benzyloxy-3-methyl-6-phenylsulfanyl-tetrahydro-pyran-2-yl)-acetic acid methyl ester **7***

A suspension of 198.0 mg (0.6 mmol) of acetal **6**, 382.5 mg (1.2 mmol) of zinc iodide, 255.3 mg (0.7 mmol) of tetra-*n*-butylammonium iodide and 220.0 μl (1.2 mmol) of (phenylthio)trimethylsilane in 3 ml of abs. 1,2-dichloroethane was heated to 60°C for 5 h. The reaction mixture was poured into sodium hydrogen carbonate solution, extracted with DCM, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (CH:EA=1:0 to 10:1) afforded 231.2 mg (0.6 mmol, 93%) of **7** as anomeric mixture (ax:eq=1:3). Spectroscopic data for the major anomer were determined from the anomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.47–7.16 (10H, Ph, SPh), 5.26 (dd, *J*=12.2 Hz, *J*=2.3 Hz, 1H, H-6), 4.55 (ddd, *J*=9.5 Hz, *J*=4.3 Hz, *J*=2.4 Hz, 1H, H-2), 4.54 (2H, C*H*$_2$Ph), 3.64 (s, 3H, OCH_3), 3.60 (1H, H-4), 2.66 (dd, *J*=15.4 Hz, *J*=9.5 Hz, 1H, H-7a), 3.24 (dd, *J*=15.4 Hz, *J*=4.3 Hz, 1H, H-7b), 2.02 (dm, *J*=14.4 Hz, H-5$_{ax}$), 1.90 (2H, H-5$_{eq}$, H-3), 0.96 (d, *J*=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 171.69 (C, C-8), 138.36 (C, C_{SPh}), 135.02 (C, C_{Ph}), 129.98 (CH, *m*-C_{Ph}), 128.67 (CH, *o*-C_{Ph}), 128.40 (CH, *o*-CSPh), 127.60 (CH, *p*-C_{Ph}), 127.38 (CH, *m*-C_{SPh}), 126.57 (CH, *p*-C_{SPh}), 83.91 (CH, C-6), 80.79 (CH, C-2), 72.19 (CH, C-4), 70.41 (CH_2, *C*H_2Ph), 51.67 (CH_3, OCH_3), 37.93 (CH_2, C-7), 34.35 (CH, C-3), 30.81 (CH_2, C-5), 10.89 (CH_3, CH_3); ν_{max} ($CHCl_3$)/cm^{-1} 3000, 2956, 2928, 2872, 1732, 1600, 1480, 1452, 1436, 1384, 1352, 1292, 1276, 1192, 1176, 1140, 1092, 1072, 1040, 988, 944; MS (100°C): 386 (M^+, 0.68), 361 (0.5), 355 (1.0), 321 (0.8), 308 (7.5), 278 (9.5), 169 (48.7), 167 (18.0), 149 (48.5), 115 (8.3), 111 (9.5), 95 (13.1), 91 (100.0), 85 (5.4), 83 (5.2), 71 (10.6); HR-MS calcd for $C_{22}H_{26}O_4S$ (M^+) 386.1552, found 386.1552.

*3.7. (2*R,*3*R,*4*S*)-2-(4-Benzyloxy-3-methyl-6-phenylsulfanyl-tetrahydro-pyran-2-yl)-ethanol **8***

At −78°C 2.4 ml (2.4 mmol) of a 1 M diisobutylaluminum hydride solution in hexane were added to a solution of 195.0 mg (0.5 mmol) of ester **7** in abs. THF (3 ml). The reaction mixture was allowed to warm up to rt over 5 h. After an additional hour at rt 6 ml of a 2 M potassium sodium tartrate solution was added and stirred overnight. The aqueous layer was extracted with MTBE, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (CH:EA=2:1) yielded 165.2 mg (0.5 mmol, >99%) of alcohol **8**. Spectroscopic data for the major anomer were determined from the anomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.46 (m, 2H, *o*-Ar), 7.36–7.20 (m, 8H, Ph, *m*-Ar, *p*-Ar), 5.21 (dd, *J*=12.0 Hz, *J*=2.3 Hz, 1H, H-6), 4.54 (d, *J*=12.0 Hz, 1H, C*H*HPh), 4.52 (d, *J*=12.0 Hz, 1H, CH*H*Ph), 4.16 (ddd, *J*=10.4 Hz, *J*=2.5 Hz, *J*=2.4 Hz, 1H, H-4), 3.71 (ddd, *J*=15.7 Hz, *J*=10.3 Hz, *J*=7.5 Hz, 1H, H-8a), 3.69 (ddd, *J*=15.7 Hz, *J*=11.0 Hz, *J*=8.1 Hz, 1H, H-8b), 3.58 (dd, *J*=5.7 Hz, *J*=2.8 Hz, 1H, H-2), 2.03 (m, 1H, H-7a), 2.00 (m, 1H, H-7b), 1.91 (m, 1H, H-5$_{eq}$), 1.87 (ddd, *J*=14.8 Hz, *J*=12.0 Hz, *J*=2.5 Hz, 1H, H-5$_{ax}$), 1.79 (m, 1H, H-3), 0.93 (d, *J*=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.40 (C, C_{Ar}), 133.63 (C, C_{Ph}), 131.65 (CH, *m*-C_{Ph}), 128.89 (CH, *o*-C_{Ph}), 128.45 (CH, *o*-C_{Ar}), 127.64 (CH, *p*-C_{Ph}), 127.38 (CH, *m*-C_{Ar}), 125.37 (CH, *p*-C_{Ar}), 80.77 (CH, C-6), 77.78 (CH, C-2), 75.56 (CH, C-4), 70.44 (CH_2, *C*H_2Ph), 61.53 (CH_2, C-8), 35.29 (CH, C-3), 34.95 (CH_2, C-7), 11.07 (CH_3, CH_3); ν_{max} ($CHCl_3$)/cm^{-1} 3452, 3000, 2968, 2928, 2880, 1600, 1480, 1452, 1440, 1384, 1352, 1304, 1236, 1092, 1072, 1040, 1004, 960, 900, 868, 836; FAB: 381 (M^++23 (Na), 30), 359 (20), 249 (100), 177 (28); HR-MS calcd for $C_{21}H_{26}O_3S$ (M^+) 358.1603, found 358.1606.

3.8. (2R,3R,4S)-4-Benzyloxy-2-(2-triethylsilyloxy-ethyl)-3-methyl-6-phenylsulfanyl-tetrahydro-pyran **9**

At 0°C a solution of 126.0 mg (0.4 mmol) of alcohol **8** in abs. DMF (0.5 ml) was added to a solution of 78.0 mg (1.2 mmol) of imidazole and 200.0 μl (1.2 mmol) of triethylsilyl chloride in abs. DMF (0.3 ml). After 10 min the reaction mixture was warmed to rt and stirred for 3 h. The solution was poured into sodium hydrogen carbonate solution, extracted with MTBE, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (CH:MTBE=5:1) afforded 167.1 mg (0.4 mmol, 92%) of **9**. Spectroscopic data for the major anomer was determined from the anomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.49 (m, 2H, *o*-SPh), 7.33–7.20 (m, 8H, *m*-SPh, *p*-SPh, Ph), 5.18 (dd, *J*=12.0 Hz, *J*=2.5 Hz, 1H, H-6), 4.54 (s, 3H, OCH_3), 4.14 (ddd, *J*=9.2 Hz, *J*=3.0 Hz, *J*=2.5 Hz, 1H, H-4), 3.72 (ddd, *J*=14.8 Hz, *J*=10.0 Hz, *J*=5.3 Hz, 1H, H-8a), 3.65 (m, 1H, H-8b), 3.59 (dd, *J*=5.7 Hz, *J*=2.8 Hz, 1H, H-2), 2.01 (dm, *J*=13.3 Hz, 1H, H-7a), 1.85 (m, 4H, H-7b, H-5_{eq}, H-5_{ax}, H-3), 0.94 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.93 (d, *J*=7.2 Hz, 3H, CH_3), 0.57 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.62 (C, C_{SPh}), 134.81 (C, C_{Ph}), 130.97 (CH, *m*-C_{Ph}), 128.61 (CH, *o*-C_{Ph}), 128.33 (CH, *o*-C_{SPh}), 127.51 (CH, *p*-C_{Ph}), 127.39 (*m*-C_{SPh}), 126.86 (CH, *p*-C_{SPh}), 80.85 (CH, C-6), 78.05 (CH, C-2), 72.35 (CH, C-4), 70.31 (CH_2, CH_2Ph), 59.88 (CH_2, C-8), 36.20 (CH_2, C-5), 35.03 (CH, C-3), 31.31 (CH_2, C-7), 10.98 (CH_3, CH_3), 6.81 (CH_3, $Si(CH_2CH_3)_3$), 4.40 (CH_2, $Si(CH_2CH_3)_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3064, 3000, 2956, 2912, 2876, 1584, 1480, 1456, 1440, 1416, 1384, 1352, 1308, 1288, 1236, 1188, 1096, 1060, 1040, 964, 880; MS (130°C): 364 (M^+−108, 0.6), 363 (1.9), 333 (1.8), 257 (12.2), 256 (56.1), 225 (4.7), 199 (2.2), 171 (5.0), 159 (15.9), 145 (2.4), 123 (13.7), 117 (17.8), 115 (9.7), 105 (4.8), 97 (12.7), 91 (100.0), 87 (8.6), 69 (4.8); HR-MS calcd for $C_{21}H_{35}O_3Si$ (M^+−109 (SPh)) 363.2355, found 363.2354.

3.9. (2R,3R,4S,6R)-6-Benzenesulfonyl-4-benzyloxy-2-(2-triethylsilyloxy-ethyl)-3-methyl-tetrahydro-pyran (+)-**10 eq**

At 0°C 165.0 mg (2.0 mmol) of sodium hydrogen carbonate and 207.0 mg (0.8 mmol) of *m*-chloroperoxybenzoic acid (70%) were added successively to a solution of 99.0 mg (0.2 mmol) of **9** in 7 ml of abs. DCM. After 15 min the reaction was quenched with sodium hydrogen carbonate solution. The organic layer was washed with ice cooled 2 N sodium hydroxide. The combined aqueous layers were extracted with DCM, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (CH:EA=5:1) allowed separation of the anomeric sulfones (99.0 mg, 0.2 mmol, >99%, eq:ax=4:1). $[\alpha]_D^{20}$=+63.7 (c=1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.93 (dd, *J*=7.9 Hz, *J*=1.4 Hz, 2H, *o*-Ar), 7.65 (ddd, *J*=7.5 Hz, *J*=1.6 Hz, *J*=1.4 Hz, 1H, *p*-Ar), 7.54 (ddd, *J*=7.9 Hz, *J*=7.5 Hz, *J*=1.6 Hz, 2H, *m*-Ar), 7.36–7.29 (m, 5H, Ph), 4.72 (dd, *J*=12.0 Hz, *J*=2.5 Hz, 1H, H-6), 4.57 (d, *J*=11.9 Hz, 1H, C*H*HPh), 4.52 (d, *J*=11.9 Hz, 1H, CH*H*Ph), 4.00 (ddd, *J*=9.8 Hz, *J*=2.8 Hz, *J*=2.5 Hz, 1H, H-4), 3.72 (dd, *J*=5.8 Hz, *J*=2.9 Hz, 1H, H-2), 3.46 (ddd, *J*=8.0 Hz, *J*=6.9 Hz, *J*=4.5 Hz, 1H, H-8a), 3.30 (ddd, *J*=9.9 Hz, *J*=8.4 Hz, *J*=5.8 Hz, 1H, H-8b), 2.24 (ddd, *J*=13.8 Hz, *J*=2.5 Hz, *J*=2.2 Hz, 1H, H-5_{eq}), 2.03 (ddd, *J*=13.8 Hz, *J*=12.0 Hz, *J*=2.8 Hz, 1H, H-5_{ax}), 1.80 (m, 1H, H-3), 1.71 (ddd, *J*=14.1 Hz, *J*=5.8 Hz, *J*=4.5 Hz, 1H, H-7a), 1.45 (dddd, *J*=14.1 Hz, *J*=8.4 Hz, *J*=6.9 Hz, *J*=2.9 Hz, 1H, H-7b), 0.88 (d, *J*=7.2 Hz, 3H, CH_3), 0.86 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.42 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.20 (C, C_{Ar}), 136.71 (C, C_{Ph}), 133.71 (CH, *p*-C_{Ar}), 129.61 (CH, *m*-C_{Ar}), 128.66 (CH, *m*-C_{Ph}), 128.41 (CH, *o*-C_{Ar}), 127.66 (CH, *p*-C_{Ph}), 127.35 (CH, *o*-C_{Ph}), 88.04 (CH, C-6), 76.52 (CH, C-4), 72.52 (CH, C-2), 70.45 (CH_2, CH_2Ph), 59.07 (CH_2, C-8), 35.74 (CH_2, C-7), 35.25 (CH, C-3), 22.92 (CH_2, C-5), 10.67 (CH_3, CH_3), 6.74 (CH_3, $Si(CH_2CH_3)_3$), 4.16 (CH_2, $Si(CH_2CH_3)_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2956, 2912, 2876, 1496, 1448, 1412, 1384, 1320, 1288, 1152, 1068, 1016, 968, 884, 588, 548; FAB: 505 (M^++1, 9), 367 (8), 255 (100), 225 (29), 197 (6), 171 (6), 154 (12), 137 (16).

*3.10. (2R,3R,4S,6S)-6-Benzenesulfonyl-4-benzyloxy-2-(2-triethylsilyloxy-ethyl)-3-methyl-tetrahydro-pyran (+)-**10 ax***

$[\alpha]_D^{20}$=+63.2 (c=0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.92 (m, 2H, *o*-Ar), 7.65 (m, 1H, *p*-Ar), 7.55 (m, 2H, *m*-Ar), 7.36–7.29 (m, 5H, Bn), 4.72 (d, *J*=11.5 Hz, 1H, C*H*HPh), 4.55 (dd, *J*=10.5 Hz, *J*=3.7 Hz, 1H, H-6), 4.45 (d, *J*=11.5 Hz, 1H, CH*H*Ph), 4.28 (ddd, *J*=11.3 Hz, *J*=4.5 Hz, *J*=4.2 Hz, 1H, H-4), 3.41 (ddd, *J*=9.3 Hz, *J*=9.2 Hz, *J*=4.4 Hz, 1H, H-2), 3.30 (m, 2H, H-8), 2.59 (ddd, *J* =13.1 Hz, *J*=4.2 Hz, *J*=4.0 Hz, 1H, H-5_{eq}), 1.94 (m, 1H, H-3), 1.58 (m, 3H, H-5_{ax}, H-7), 0.92 (d, *J*=6.7 Hz, 3H, CH_3), 0.90 (t, *J*=8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.50 (q, *J*=8.0 Hz, 6H, $Si(CH_2CH_3)_3$).

*3.11. (−)-(2R,3R,4S,6R)-2-(4-Benzyloxy-6-methoxy-3-methyl-tetrahydro-pyran-2-yl)-ethanol (−)-**11***

To a suspension of $LiAlH_4$ (114 mg, 3 mmol) in E (10 ml) was added dropwise a solution of ester (−)-**6** (842 mg, 2.73 mmol) in E (5 ml) at rt and the mixture was stirred for 2 h. Water was added and the precipitate was dissolved by addition of 2 N HCl. The aqueous layer was saturated with NaCl and extracted with EA. The combined organic phase was dried ($MgSO_4$) evaporated and purified by column chromatography (E/PE) to afford (−)-**11**, 740 mg (97%), as a colorless oil, $[\alpha]_D^{20}$=−7.9 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.40–7.23 (m, 5H, Ph), 4.52 (dd, *J*=10 Hz, *J*=2 Hz, 1H, H-6), 4.54 (s, 2H, CH_2Ph), 4.17 (ddd, *J*=10 Hz, *J*=3 Hz, *J*=2 Hz, 1H, H-4), 3.80 (m, 2H, H-8), 3.62 (dd, *J*=6 Hz, *J*=3 Hz, 1H, H-2), 3.48 (s, 3H, OCH_3), 2.4 (br. s, 1H, OH), 1.95 (m, 2H, H-7), 1.79 (m, 1H, H-3), 1.66 (ddd, *J*=13 Hz, *J*=10 Hz, *J*=3 Hz, 1H, H-5_{ax}), 1.59–1.50 (m, 1H, H-5_{eq}), 0.98 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.55 (C, C_{Ph}), 128.43 (CH, *o*-C_{Ph}), 127.61 (C, *p*-C_{Ph}), 127.36 (CH, *m*-C_{Ph}), 100.49 (CH, C-6), 78.53 (CH, C-2), 72.75 (CH, C-4), 70.49 (CH_2, CH_2Ph), 61.66 (CH_2, C-8), 56.38 (CH_3, OCH_3), 35.42 (CH, C-3), 34.69 (CH_2, C-7), 31.27 (CH_2, C-5), 11.09 (CH_3, CH_3); ν_{max} (film)/cm^{-1} 3420, 3028, 2960, 2936, 1496, 1388, 1192, 1144, 1092, 1044; MS: 280 (M^+, 1), 177 (4), 148 (13), 119 (7), 91 (100), 81 (3), 65 (5); HR-MS calcd for $C_{16}H_{24}O_4$ (M^+) 280.1675, found 280.1686.

*3.12. (−)-(2R,3R,4S,6R)-2-(4-Benzyloxy-6-methoxy-3-methyl-tetrahydropyran-2-yl)-ethyl-4′ toluene-sulfonic ester (−)-**12***

To a solution of alcohol (−)-**11** (612 mg, 2.18 mmol) in DCM (6.5 ml) was added NEt_3 (0.33 ml, 2.4 mmol) at rt and the mixture was stirred for 10 min. Then tosyl chloride (873 mg, 4.60 mmol) was added in portions under a stream of N_2. The reaction mixture was stirred overnight and then diluted with H_2O and acidified (dilute H_2SO_4). The aqueous layer was extracted with DCM, the combined organic phase dried ($MgSO_4$) and the solvent removed. The crude product was purified by column chromatography (E/PE) to give (−)-**12** (877 mg, 93%), crystals, mp 69°C, $[\alpha]_D^{20}$=−6.67 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.79 (d, *J*=5 Hz, 2H, Ar), 7.42–7.21 (m, 7H, Ar), 4.51 (m, 3H, CH_2Ph, H-6), 4.27–4.09 (m, 2H, H-8), 4.01 (dd, *J*=11 Hz, *J*=2 Hz, 1H, H-2), 3.59 (dd, *J*=6 Hz, *J*=3 Hz, 1H, H-4), 3.34 (s, 3H, OCH_3), 2.42 (s, 3H, Ar–CH_3), 1.88 (m, 2H, H-7), 1.72 (m, 2H, H-5), 1.58 (m, 1H, H-3), 0.89 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 144.67 (C, C_{Ar}), 138.55 (C, C_{Ph}), 133.15 (C, *p*-C_{Ar}), 129.83 (CH, *o*-C_{Ar}), 128.45 (CH, *m*-C_{Ar}), 127.93 (CH, *o*-C_{Ph}), 127.63 (CH, *p*-C_{Ph}), 127.40 (CH, *m*-C_{Ph}), 100.27 (CH, C-6), 78.42 (CH, C-2), 70.47 (CH_2, CH_2Ph), 68.44 (CH, C-4), 67.58 (CH_2, C-8), 56.2 (CH_3, OCH_3), 34.87 (CH, C-3), 32.00 (CH_2, C-7), 31.43 (CH_2, C-5), 21.60 (CH_3, Ar–CH_3), 10.81 (CH_3, CH_3); ν_{max} (film)/cm^{-1} 2960, 2900, 1496, 1464, 1388, 1356, 1176, 1148, 1096, 1048; MS (140°C): 434 (M^+, 2), 325 (1), 296 (3), 171 (5), 124 (7), 91 (100), 65 (6); HR-MS calcd for $C_{23}H_{30}O_6S$ (M^+) 434.1763, found 434.1767.

3.13. (−)-(2R,3R,4S,6R)-4-Benzyloxy-6-methoxy-3-methyl-2-pent-4-enyl-tetrahydropyran (−)-13

To a solution of tosylate (−)-**12** (808 mg, 1.86 mmol) and a catalytic amount of $HgCl_2$ in E (15 ml) was added allylmagnesium bromide (7.44 ml, 7.44 mmol, 1 M solution in E) at −5°C. The mixture was stirred for 1 h at the same temperature and then allowed to reach 5°C. After complete reaction the mixture was hydrolyzed by the addition of dilute HCl. The aqueous layer was extracted with E and the combined organic phase dried ($MgSO_4$). After removal of the solvent the crude product was purified by column chromatography (E/PE) to afford (−)-**13**, 437 mg (77%), as a colorless liquid, $[\alpha]_D^{20}$=−10.6 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.38–7.23 (m, 5H, Ph), 5.81 (m, 1H, H-10), 4.98 (m, 1H, H-11), 4.65 (dd, *J*=7 Hz, *J*=1 Hz, 1H, H-6), 4.55 (s, 2H, C*H*$_2$Ph), 3.88 (m, 1H, H-2), 3.60 (dd, *J*=6 Hz, *J*=3 Hz, 1H, H-4), 3.49 (s, 3H, OCH_3), 2.08 (m, 2H, H-9), 1.92 (d, *J*=12 Hz, 1H, H-5$_{ax}$), 1.78 (m, 1H, H-3), 1.61 (m, 3H, H-7, H-5$_{eq}$), 1.39 (m, 2H, H-8), 0.92 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.86 (CH, C-10), 138.74 (C, C_{Ph}), 128.41 (CH, *m*-C_{Ph}), 127.54 (CH, *p*-C_{Ph}), 127.32 (CH, *m*-C_{Ph}), 114.49 (CH_2, C-11), 100.38 (CH, C-6), 78.92 (CH, C-2), 72.79 (CH, C-4), 70.41 (CH_2, *C*H_2Ph), 56.25 (CH_3, OCH_3), 34.98 (CH, C-3), 33.78 (CH_2, C-9), 31.82 (CH_2, C-7), 31.58 (CH_2, C-5), 25.53 (CH_2, C-8), 10.9 (CH_3, CH_3); ν_{max} ($CHCl_3$)/cm^{-1} 3064, 3028, 2936, 2860, 1640, 1496, 1452, 1344, 1192, 1096; MS: 304 (M^+, 3), 196 (3), 177 (2), 148 (12), 91 (100), 81 (5), 65 (5); HR-MS calcd for $C_{19}H_{28}O_3$ (M^+) 304.2038, found 304.2038.

3.14. (−)-(2R,3R,4S,6R)-4-Benzyloxy-6-methoxy-3-methyl-tetrahydropyran-2-yl)-butan-1-ol (−)-14

To a solution of (−)-**13** (420 mg, 1.38 mg) in THF:H_2O (12 ml, 3:1) were added a few drops of OsO_4 (2.5% in *t*-BuOH), and the mixture was stirred for 1 h. Then $NaIO_4$ (650 mg, 3.04 mmol) was added in portions and the resulting mixture was stirred overnight. Water was added and the aqueous layer was extracted with E. The combined organic phase was dried ($MgSO_4$), and the solvent was removed. The crude aldehyde was dissolved in E. To this solution was added a solution of $NaBH_4$ (57.4 mg, 1.52 mmol) in EtOH (3 ml) at −78°C. After 1 h at the same temperature water was added carefully. The aqueous layer was extracted with EA, the combined organic phase dried ($MgSO_4$) and the solvent evaporated. The crude product was purified by column chromatography (E/PE) to afford (−)-**14** (242 mg, 57%), as a colorless oil, $[\alpha]_D^{20}$=−11.9 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.42–7.23 (m, 5H, Ph), 4.65 (dd, *J*=9 Hz, *J*=2 Hz, 1H, H-6), 4.53 (s, 2H, C*H*$_2$Ph), 3.89 (m, 1H, H-4), 3.65 (m, 2H, H-10), 3.61 (dd, *J*=6 Hz, *J*=3 Hz, 1H, H-2), 3.50 (s, 3H, OCH_3),1.92 (d, *J*=12 Hz, 1H, H-5$_{ax}$), 1.78 (q, *J*=7 Hz, 1H, H-3), 1.75–1.51 (m, 6H, H-9, H-7, H-5$_{eq}$, O*H*), 1.40 (m, 2H, H-8), 0.93 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.72 (C, C_{Ph}), 128.41 (CH, *o*-C_{Ph}), 127.55 (CH, *p*-C_{Ph}), 127.33 (CH, *m*-C_{Ph}), 100.42 (CH, C-6), 78.88 (CH, C-2), 72.9 (CH, C-4), 70.42 (CH_2, *C*H_2Ph), 62.84 (CH_2, C-10), 56.30 (CH_2, C-11), 35.01 (CH, C-3), 32.72 (CH_2, C-7), 32.06 (CH_2, C-9), 31.55 (CH_2, C-5), 22.43 (CH_2, C-8), 10.9 (CH_3, CH_3); ν_{max} (film)/cm^{-1} 3420, 2936, 2864, 1452, 1388, 1192, 1144, 1092, 1048; MS (60°C): 217 (M^+−C_7H_7, 2), 199 (2), 184 (2), 148 (11), 119 (5), 91 (100), 85 (7), 77 (2), 71 (6), 65 (5); HR-MS calcd for $C_{18}H_{28}O_4$ (M^+) 308.1988, found 308.1983.

3.15. (−)-(2R,3R,4S,6R)-4-Benzyloxy-6-methoxy-2-(4-methoxy-butyl)-3-methyl-tetrahydropyran (−)-15

To a solution of alcohol (−)-**14** (200 mg, 0.65 mmol) in THF (1 ml) was added NaH (58.4 mg, 1.95 mmol, 80% in mineral oil) portionwise under a stream of N_2. After 5 min MeI (0.81 ml, 13 mmol) was added. The mixture was stirred overnight and then diluted with E. The organic phase was washed with an $NaHCO_3$ solution (twice). The combined aqueous layer was extracted with DCM, and the combined organic phase dried ($MgSO_4$). After removal of the solvent the crude product was purified

by column chromatography (E/PE) to afford (−)-**15** (127 mg, 60%), as a colorless liquid, $[\alpha]_D^{20}$=−13.0 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.43–7.23 (m, 5H, Ph), 4.65 (dd, *J*=10 Hz, *J*=2 Hz, 1H, H-6), 4.55 (s, 2H, C*H*$_2$Ph), 3.89 (m, 1H, H-2), 3.61 (dd, *J*=6 Hz, *J*=3 Hz, 1H, H-4), 3.50 (s, 3H, OCH_3), 3.38 (m, 2H, H-10), 3.33 (s, 3H, OCH_3), 1.92 (d, *J*=10 Hz, 1H, H-5$_{ax}$), 1.80 (q, *J*=7 Hz, 1H, H-3), 1.70–1.48 (m, 5H, H-9, H-7, H-5$_{eq}$), 1.39 (m, 2H, H-8), 0.93 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.74 (C, C_{Ph}), 128.4 (CH, *o*-C_{Ph}), 127.52 (CH, *p*-C_{Ph}), 127.32 (CH, *m*-C_{Ph}), 100.38 (CH, C-6), 78.88 (CH, C-2), 72.86 (CH, C-4), 72.77 (CH_2, C-10), 70.39 (CH_2, *C*H_2Ph), 58.52 (CH_3, OCH_3), 56.27 (CH_3, OCH_3), 34.91 (CH, C-3), 32.16 (CH_2, C-7), 31.58 (CH_2, C-5), 29.62 (CH_2 C-9), 22.75 (CH_2, C-8), 10.88 (CH_3, CH_3); ν_{max} (film)/cm^{-1} 2936, 2864, 2756, 1496, 1452, 1388, 1192, 1144, 1116, 1096, 1048; MS: 322 (M^+, 1), 263 (1), 182 (6), 148 (13), 119 (7), 91 (100), 79 (5), 77 (3), 72 (12), 65 (5); HR-MS calcd for $C_{19}H_{30}O_4$ (M^+) 322.2144, found 322.2146.

*3.16. Triphenylphosphonium tetraflouroborate salt **16***

A solution of (−)-**15** (50 mg, 0.16 mmol) and Ph_3PHBF_4 (54.2 mg, 0.16 mmol) in MeCN (1.5 ml) was heated to reflux for 30 min. The mixture was cooled to rt and diluted with E. The solvent was removed and the residue dried (oil pump). The crude product was dissolved in $CHCl_3$ and then crystallized by the addition of E. The white precipitate was washed with E and dried (oil pump) to afford **16** (91 mg, 89%), as a white foam, mp 54°C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.98–7.62 (m, 15H, Ph_3P), 7.39–7.16 (m, 5H, Ph), 5.90 (dd, *J*=10 Hz, *J*=3 Hz, 1H, H-6), 4.62 (d, *J*=12 Hz, 1H, C*H*HPh), 4.33 (d, *J*=12 Hz. 1H, CH*H*Ph), 4.03–3.84 (m, 2H, H-4, H-2), 3.43–3.17 (m, 5H, OCH_3, H-10), 2.25 (m, 1H, H-5), 2.06 (m, 1H, H-5), 1.90 (m, 1H, H-3), 1.71–1.17 (m, 6H, H-9, H-8, H-7), 0.96 (d, *J*=7 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 138.56 (C, C_{Ph}), 138.09 (C, C_{Bu}), 135.18/134.61/134.52/133.84/133.75/130.72/130.69/130.36/130.24/128.53/128.29 (CH, C_{Ph}), 81.98 (CH, C-2), 75.43 (CH, C-6), 74.02 (CH, C-4), 72.44 (CH_2, *C*H_2Ph), 72.20 (CH_2, C-10), 71.98 (CH_2, *C*H_2Ph), 58.42 (CH_3, OCH_3), 40.64 (CH, C-3), 32.41 (CH_2, C-7), 31.32 (CH_2, C-5), 28.85 (CH_2 C-9), 22.98 (CH_2, C-8), 13.74 (CH_3, CH_3); ν_{max} (KBr)/cm^{-1} 2932, 2868, 1440, 1112, 1060; FAB: 553 (M^+-BF_4, 91), 445 (32), 289 (7), 263 (37), 262 (Ph_3P, 34), 183 (16), 133 (100).

Acknowledgements

We thank Deutsche Forschungsgemeinschaft (Graduiertenkolleg Chemische und technische Grundlagen der Naturstofftransformation) for a PhD fellowship (R.D.), the Fonds der chemischen Industrie for financial support and Ulrike Eggert for her help.

References

1. *Comprehensive Natural Products Chemistry*; Barton, D. H. R.; Nakanishi, K.; Meth-Cohn, O., Eds.; Elsevier: Oxford, 1999; vols. 1–9.
2. (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem*. **1993**, *58*, 130; (b) Kobayashi, M.; Aoki, S.; Sakai, H.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett*. **1993**, *34*, 2795; (c) Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc*. **1993**, *113*, 3977; (d) Kobayashi, M.; Aoki, S.; Kitagawa, I. *Tetrahedron Lett*. **1994**, *35*, 1243; (e) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Schmidt, J. M.; Boyd, M. R.; Christie, N. D.; Boettner, F. E. *J. Chem. Soc., Chem. Commun*. **1993**, 1805; (f) Pettit, G. R.; Cichacz, Z. A.; Herald, C. L.; Gao, F.; Boyd, M. R.; Schmidt, J. M.; Hamel, E.; Bai, R. *J. Chem. Soc., Chem. Commun*. **1994**, 1605; (g) Kobayashi, M.; Aoki, S.; Sakai, H.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull*. **1993**, *41*, 989; (h) Pettit, G. R.; Herald, C. L.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Christie, N. D.; Schmidt, J. M. *Nat. Prod. Lett.* **1993**, *3*, 239; (i) Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc*. **1993**, *115*, 3977; (j) Pettit, G. R.; Cichacz, Z. A.; Gao, F.;

Herald, C. L.; Boyd, M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 1166; (k) Bai, R.; Taylor, G. F.; Cichacz, Z. A.; Herald, C. L.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714; (l) Bai, R.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. *Mol. Pharmacol*. **1993**, *44*, 757.

3. Total synthesis: (a) Evans, D. A.; Coleman, P. J.; Diaz, L. C. *Angew. Chem*. **1997**, *109*, 2951; Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem*. **1997**, *109*, 2954; Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Diaz, L. C.; Tyler, A. N. *Angew. Chem*. **1997**, *109*, 2957; (b) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem*. **1998**, *110*, 198; Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem*. **1998**, *110*, 202. Other synthetic efforts and fragment syntheses: (c) Smith III, A. B.; Zhuang, L.; Brook, C. S.; Boldi, A. M.; McBriar, M. D.; Moser, W. H.; Murase, N.; Nakayama, K.; Verhoest, P. R.; Lin, Q. *Tetrahedron Lett.* **1997**, *38*, 8667; (d) Claffey, M. M.; Heathcock, C. H. *J. Org. Chem*. **1996**, *61*, 7646; (e) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett*. **1996**, *37*, 8581; (f) Paquette, L. A.; Zuev, D. *Tetrahedron Lett*. **1997**, *38*, 5115; (g) Paterson, I.; Keown, L. E. *Tetrahedron Lett*. **1997**, *38*, 5727; (h) Hayes, C. J.; Heathcock, C. H. *J. Org. Chem*. **1997**, *62*, 2678; (i) Paterson, I.; Oballa, R. M. *Tetrahedron Lett*. **1997**, *38*, 8241; (j) Dunkel, R.; Mentzel, M.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 14929; (k) Hermitage, S. A.; Roberts, S. M.; Watson, D. J. *Tetrahedron Lett*. **1998**, *39*, 3567; (l) Lemaire-Audoire, S.; Vogel, P. *Tetrahedron Lett*. **1998**, *39*, 134; (m) Zemribo, R.; Mead, K. T. *Tetrahedron Lett*. **1998**, *39*, 3895; (n) Terauchi, T.; Nakata, M. *Tetrahedron Lett.* **1998**, *39*, 3795; (o) Paterson, I.; Wallace, D. J.; Oballa, R. M. *Tetrahedron Lett*. **1998**, *39*, 8545; (p) Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991.
4. Treu, J.; Hoffmann, H. M. R. *J. Org. Chem*. **1997**, *62*, 4650.
5. Brown, H. C.; Joshi, N. N. *J. Org. Chem*. **1988**, *53*, 4059.
6. Hanessian, S.; Guidon, Y. *Carbohydr. Res*. **1980**, *86*, C3.
7. Acetal (−)-**6** is obtained selectively by acidic methanolysis with hydrochloric acid without addition of trimethyl orthoformate, in 86% yield and used for easier spectroscopic analysis in this sequence.
8. Dunkel, R.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, in press.