SUPPORTING INFORMATION FOR

Asymmetric Synthesis of the Tetrahydropyran Ring, C32-C38 Fragment, of Phorboxazoles

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Experimental Procedures

General: Melting points were obtained in open capillary tubes and are uncorrected. ^1H - and ^{13}C -NMR spectra were recorded in CDCl_3 at 200 and 75 MHz, respectively. All reactions were monitored by thin layer chromatography that was performed on precoated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230-400 mesh) of Merck. Eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was dried by flaming in a stream of dry argon. CH_2Cl_2 was predried using CaCl_2 and distilled over P_2O_5 . CH_3CN was dried over 4Å molecular sieves. All other reagent quality solvents were used without purification. For routine workup, hydrolysis was carried out with a saturated aqueous solution of NH_4Cl , extractions with CH_2Cl_2 , and solvent drying with MgSO_4 . Compounds **4**,¹ **12**,² **13**,¹ **14**,^{3a} **15**^{3b,c} and **16**^{3b} were prepared according to previously reported procedures.

(SS)-5-Oxo-6-(*p*-tolylsulfinyl)hexanoic acid (5**)**

(1) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173-175.

(2) Batelaan, J. G. *Synth. Commun.* **1976**, 6, 81-83.

(3) (a) Solladié, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995**, 60, 7774-7777. (b) Solladié, G.; Colobert, F.; Denni, D. *Tetrahedron : Asymmetry* **1998**, 9, 3081-3094. (c) Solladié, G.; Wilb, N.; Bauder, C. *Eur. J. Org. Chem.* **1999**, 3021-3026.

To a solution of diisopropylamine (4.27 mL, 30 mmol, 2.2 equiv) in THF (12 mL), *n*-butyllithium (11 mL of a 2.5 M solution in hexane, 27.5 mmol, 2 equiv) was added dropwise at $-78\text{ }^{\circ}\text{C}$ under argon. After stirring for 30 minutes at the same temperature, a solution of (SS)-methyl *p*-tolyl sulfoxide¹ (2.1 g, 13.8 mmol, 1 equiv) in THF (18 mL) was added dropwise. The reaction mixture was stirred for 1 hour at $-78\text{ }^{\circ}\text{C}$ before slowly adding a solution of glutaric anhydride (1.57 g, 13.8 mmol, 1 equiv) in THF (9 mL). After stirring at $-78\text{ }^{\circ}\text{C}$ for 3 hours, a saturated solution of NH_4Cl (30 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 50 mL) to recover the remaining methyl *p*-tolyl sulfoxide (490 mg). The aqueous layer was acidified to pH = 4 with a 1 M HCl solution and re-extracted with ethyl acetate (3 x 70 mL). After washing the organic layers with brine (70 mL) and workup, compound **5**⁴ was obtained as a white solid, in 84% yield: R_f (hexane/ethyl acetate/isopropanol 5:5:1) = 0.2; mp $71\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} = -180$ (c 1.1, CHCl_3); ^1H NMR δ 7.53 and 7.34 (AA'BB' system, 4H), 3.93 and 3.78 (AB system, 2H, $J = 13.0$ Hz); 2.62 (m, 2H); 2.42 (s, 3H), 2.35 (t, 2H, $J = 7.0$ Hz), 1.88 (quint, 2H, $J = 7.0$ Hz); ^{13}C NMR δ 200.9, 177.3, 142.4, 139.1, 130.2 (2C), 124.2 (2C), 67.6, 43.8, 32.4, 21.5, 18.0; MS (EI): m/z (%) 268 (M^+ , 5), 140 (27), 139 (100), 137 (20), 124 (39), 123 (17), 91 (60), 86 (28), 84 (30), 77 (16), 65 (18), 55 (24); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4\text{S}$ (M^+) 268.07693, found 268.07626.

(SS)-*N*-Methoxy-*N*-methyl-5-oxo-6-(*p*-tolylsulfinyl)hexanamide (6).

To a cooled solution ($0\text{ }^{\circ}\text{C}$) of compound **5** (1.6 g, 5.97 mmol, 1 equiv) in dry CH_2Cl_2 (38 mL), *N*-ethyl-diisopropylamine (1.22 mL, 7.16 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine chlorhydrate (0.71 g, 7.16 mmol, 1.2 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.22 g, 6.27 mmol, 1.05 equiv) and a catalytic amount of DMAP were added under argon. The reaction mixture was stirred at room temperature for 24 h, diluted with water (20 mL) and acidified with a 0.5 M solution of HCl to pH = 4. After several extractions with CH_2Cl_2 , washing with saturated solutions

(1) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173-175.

(4) (SR) enantiomer: Solladié, G.; Maestro, M. C.; Rubio, A.; Pedregal, C.; Carreno, M. C.; García Ruano, J. L. *J. Org. Chem.* **1991**, 56, 2317-2322.

of NaHCO₃ and NaCl, and workup, compound **6** was obtained as a colourless oil, in 98% yield and used in the next step without further purification: R_f (EtOAc/MeOH 90:10) = 0.48; $[\alpha]_D^{20} = -243$ (c 1.5, CHCl₃); ¹H NMR δ 7.52 and 7.32 (AA'BB' system, 4H), 3.84 and 3.74 (AB system, 2H, J = 13.4 Hz), 3.65 (s, 3H), 3.14 (s, 3H), 2.58 (td, 2H, J = 7.0 and 1.6 Hz), 2.41 (m, 2H), 2.40 (s, 3H), 1.86 (quint, 2H, J = 7.0 Hz); ¹³C NMR δ 201.0, 173.3, 141.8, 139.5, 129.8 (2C), 123.7 (2C), 67.8, 60.9, 43.6, 31.8, 30.2, 21.1, 17.7; MS (FAB): m/z (%) 312 ($[M+1]^+$, 100), 251 (9), 172 (8), 139 (46); HRMS (FAB) calcd for C₁₅H₂₂NO₄S ($M+1$)⁺ 312.12696, found 312.12728. Anal. calcd. for C₁₅H₂₁NO₄S: C, 57.86; H, 6.80; N, 4.50; S, 10.30; found: C, 57.85; H, 7.15; N, 4.42; S, 9.90.

(5*S*,*SS*)-*N*-Methoxy-*N*-methyl-5-hydroxy-6-(*p*-tolylsulfinyl)hexanamide (7) and (5*R*,*SS*)-*N*-methoxy-*N*-methyl-5-hydroxy-6-(*p*-tolylsulfinyl)hexanamide (8).

To a solution of compound **6** (1.61 g, 5.18 mmol, 1 equiv) in THF (64 mL), DIBALH (5.18 mL of a 1 M solution in THF, 5.18 mmol, 1 equiv) was added dropwise at -78 °C under argon. After 30 minutes the reaction was stopped by adding MeOH (10 mL). The solution was allowed to warm to room temperature and the solvent was evaporated. The residue was dissolved in EtOAc, treated with a saturated Na/K tartrate solution and the mixture was stirred until the layers were well separated. After acidification to pH = 4 with HCl 1M, extraction with ethyl acetate (3 x 50 mL) and workup a 7:93 mixture of epimeric alcohols **7** and **8** were obtained, together with starting material and secondary products. Separation by flash chromatography (eluent EtOAc/MeOH 95:5) provided non reacted starting material **6** (43%), impure compound **7** as a yellow oil, in 11% yield (based on recovered **6**), and compound **8** as a colourless oil, in 75% yield (based on recovered **6**).

Compound **7**: R_f (EtOAc/MeOH 90:10) = 0.6; ¹H NMR (500 MHz) δ 7.53 and 7.32 (AA'BB' system, 4H), 4.10 (m, 1H), 3.56 (s, 3H), 2.93 (dd, 1H, J = 10.5 and 13.2 Hz), 2.82 (dd, 1H, J = 2.4 and 13.2 Hz), 2.79 (s, 3H), 2.42 (m, 2H), 2.41 (s, 3H), 1.64-1.28 (m, 4H); ¹³C NMR (125 MHz) δ 174.2, 141.6, 141.3, 130.0 (2C), 123.9 (2C), 64.8, 62.6, 61.4, 31.9, 30.6, 27.9, 21.4, 17.2.

Compound **8**: R_f (EtOAc/MeOH 90:10) = 0.34; $[\alpha]_D^{20} = -197$ (c 1.3, CHCl_3); ^1H NMR δ 7.50 and 7.32 (AA'BB' system, 4H), 4.3 (broad s, 1H), 4.11 (m, 1H), 3.64 (s, 3H), 3.15 (s, 3H), 3.02 (dd, 1H, $J = 9.5$ and 13.3 Hz), 2.67 (dd, 1H, $J = 2.0$ and 13.4 Hz), 2.43 (m, 2H), 2.41 (s, 3H), 1.78-1.45 (m, 4H); ^{13}C NMR δ 174.3, 141.4, 139.9, 130.0 (2C), 123.9 (2C), 65.8, 62.2, 61.1, 36.6, 32.2, 31.1, 21.3, 19.7; MS (EI): m/z (%) 313 (M^+ , 5), 253 (22), 174 (22), 140 (28), 139 (100), 113 (40), 92 (20), 91 (23), 85 (28), 62 (27), 55 (23); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_4\text{S}$ (M^+) 313.13478, found 313.13422.

(6*R*,*SS*)-6-Hydroxy-7-(*p*-tolylsulfinyl)heptan-2-one (9).

To a cooled solution (0 °C) of compound **8** (357 mg, 1.14 mmol, 1 equiv) in dry THF (11 mL), methyl magnesium bromide (1.14 mL of a 3 M solution in ether, 3.42 mmol, 3 equiv) was added dropwise under argon. The mixture was stirred for 45 minutes at room temperature and hydrolyzed with saturated solution of NH_4Cl (10 mL). After workup, compound **9** was obtained as a white solid, in 83% yield and used in the next step without further purification: R_f (EtOAc/MeOH 90:10) = 0.58; mp 56 °C; $[\alpha]_D^{20} = -260$ (c 0.58, CHCl_3); ^1H NMR (300 MHz) δ 7.47 and 7.28 (AA'BB' system, 4H), 4.54 (broad s, 1H), 4.12 (m, 1H), 3.04 (dd, 1H, $J = 9.7$ and 13.7 Hz), 2.63 (dd, 1H, $J = 1.8$ and 13.7 Hz), 2.38 (m, 2H), 2.37 (s, 3H), 2.06 (s, 3H), 1.77-1.45 (m, 4H); ^{13}C NMR δ 208.7, 141.6, 139.4, 130.1 (2C), 124.0 (2C), 66.3, 60.9, 43.0, 36.3, 29.9, 21.4, 19.0; MS (EI): m/z (%) 268 (M^+ , 4), 233 (36), 140 (100), 139 (88), 111 (66), 109 (46), 95 (27), 92 (60), 91 (47), 84 (29), 71 (30), 67 (31), 65 (27), 55 (30); HRMS (EI) calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3\text{S}$ (M^+) 268.11332, found 268.11258.

(2*S*,6*R*,*SS*)-2-Methoxy-2-methyl-6-[(*p*-tolylsulfinyl)methyl]tetrahydro-2*H*-pyran (10) and (2*R*,6*R*,*SS*)-2-methoxy-2-methyl-6-[(*p*-tolylsulfinyl)methyl]tetrahydro-2*H*-pyran (11).

To a solution of compound **9** (348 mg, 1.3 mmol, 1 equiv) in MeOH (25 mL), PPTS (25 mg, 0.1 mmol, 0.08 equiv) was added under argon. After stirring for 24 hours at room temperature, solid NaHCO₃ (~25 mg) was added. The reaction mixture was filtered over celite and the solvent was evaporated to obtain a 13:87 mixture of diastereoisomers **10** and **11**. Separation by flash chromatography (hexane/ethyl acetate 50:50) provided compound **10** (88:12 mixture of **10** and **11**) as a colourless oil, and diastereoisomer **11** as a white solid, in 77% yield.

Compound **10** (from a 88:12 mixture of **10** and **11**): R_f (hexane/EtOAc 50:50) = 0.38; $[\alpha]_D^{20} = -65$ (c 0.75, CHCl₃); ¹H NMR (300 MHz) δ 7.55 and 7.32 (AA'BB' system, 4H), 3.91 (m, 1H), 3.15 (s, 3H), 3.06 (dd, 1H, J = 6.0 and 13.2 Hz), 2.83 (dd, 1H, J = 6.0 and 13.2 Hz), 2.41 (s, 3H), 1.87-1.37 (m, 6H), 1.25 (s, 3H); ¹³C NMR δ 141.9, 141.8, 129.9 (2C), 124.3 (2C), 98.5, 65.6, 64.0, 48.1, 35.0, 30.2, 23.7, 21.4, 18.6; MS (EI): m/z (%) 251 ($[M - OCH_3]^+$, 22), 233 (27), 139 (93), 111 (79), 85 (100); HRMS (EI) calcd for C₁₄H₁₉O₂S ($M - OCH_3$)⁺ 251.11058, found 251.11015.

Compound **11**: R_f (hexane/EtOAc 50:50) = 0.4; mp 54 °C; $[\alpha]_D^{20} = -270$ (c 1, CHCl₃); ¹H NMR (500 MHz) δ 7.54 and 7.31 (AA'BB' system, 4H), 4.22 (m, 1H), 3.36 (s, 3H), 2.79 (dd, 1H, J = 2.8 and 12.9 Hz), 2.73 (dd, 1H, J = 10.3 and 12.9 Hz), 2.4 (s, 3H), 1.93 (qt, 1H, J = 13.5 and 4 Hz), 1.77 (dtd, 1H, J = 13.5, 4 and 1.3 Hz), 1.58 (m, 2H), 1.46 (td, 1H, J = 13.5 and 4 Hz), 1.36 (s, 3H), 1.24 (qdd, 1H, J = 13.5, 4 and 1.3 Hz); ¹³C NMR δ 141.9, 141.2, 129.9 (2C), 123.7 (2C), 98.3, 65.0, 64.2, 48.2, 35.2, 30.3, 23.8, 21.4, 18.8; MS (EI): m/z (%) 282 (M^+ , 0.6), 251 (12), 139 (100), 111 (69), 85 (40); HRMS (EI) calcd for C₁₅H₂₂O₃S (M^+) 282.12897, found 282.12823. Anal. calcd. for C₁₅H₂₂O₃S: C, 63.80; H, 7.85; S, 11.35; found: C, 63.39; H, 7.97; S, 11.59.

(2R,6R)-6-Methoxy-6-methyltetrahydro-2H-pyran-2-carbaldehyde (2).

To a cooled solution (0 °C) of compound **11** (38 mg, 0.13 mmol, 1 equiv) in dry acetonitrile (1 mL), 2,6-lutidine (50 μ L, 0.43 mmol, 3.2 equiv) and trifluoroacetic anhydride (58 μ L, 0.41 mmol, 3.05 equiv) were added under argon. After 10 minutes at the same temperature, the reaction was quenched with aqueous NaHCO₃ (92 mg in 2 mL H₂O, 1.1 mmol, 8 equiv). The mixture was allowed to warm up

to room temperature, stirred for 2 hours and diluted with water (4 mL) and ethyl acetate (4 mL). After workup and flash chromatography (eluent hexane/ethyl acetate 70:30) on deactivated silica gel (treated with a 1% solution of NEt_3 prior use), compound **2** was obtained as an unstable colourless oil, in 42% yield: R_f (hexane/EtOAc 70:30) = 0.6; $[\alpha]_D^{20} = -40$ (c 0.36, CH_2Cl_2); ^1H NMR (500 MHz) δ 9.63 (s, 1H), 4.03 (dd, 1H, $J = 12.3$ and 2.5 Hz), 3.24 (s, 3H), 1.90 (qt, 1H, $J = 13.0$ and 4.0 Hz), 1.83 (m, 1H), 1.77 (m, 1H), 1.66 (m, 1H), 1.50 (td, 1H, $J = 13.2$ and 4.4 Hz), 1.38 (s, 3H), 1.32 (qd, 1H, $J = 13.0$ and 4.0 Hz); ^{13}C NMR δ 202.0, 98.5, 75.2, 48.0, 35.1, 25.0, 23.6, 18.2.

(SS)-Methyl 3,5-dioxo-6-(*p*-tolylsulfinyl)hexanoate (14**).**

To a suspension of NaH (2.2 g, 91 mmol, 1.4 equiv) in THF (250 mL), a solution of methyl 3,5-dioxohexanoate (**12**)² (12.1 g, 74.5 mmol, 1 equiv) in THF (25 mL) was added dropwise at 0 °C under argon. The resulting thick white suspension was stirred at the same temperature for 15 minutes before quickly adding *tert*-butyllithium (100 mL of a 1.5 M solution in pentane, 150 mmol, 2.04 equiv) via cannula. The solution turned yellow, orange and finally deeply red as the addition progressed. Then, (*SR*)-(+)-menthyl-*p*-toluenesulfinate (**13**)¹ (11.3 g, 37.1 mmol, 1 equiv) in THF (35 mL) was slowly added. The resulting reaction mixture was stirred for about 50 minutes, quenched with saturated aqueous solution of NH_4Cl (10 mL), diluted with AcOEt (250 mL), and acidified to pH = 1 with a 1 M HCl solution (~ 170 mL), followed by concentrated H_2SO_4 (~ 2 mL). After extraction of the aqueous layer with EtOAc (3 x 150 mL), workup and flash chromatography on metal-free silica gel (eluent hexane, hexane/ CH_2Cl_2 2:1, then CH_2Cl_2), an orange oil was obtained which, after crystallization (CH_2Cl_2 /diethyl ether), afforded pure compound **14**^{3a} as pale yellow prisms, in 68% yield: R_f (CH_2Cl_2 /EtOAc 50:50) = 0.35; mp 58 °C; $[\alpha]_D^{20} = -268$ (c 0.89, CHCl_3); ^1H NMR δ 14.51 (broad s, 1H), 7.51 and 7.32 (AA'BB' system, 4H), 5.65 (s, 1H), 3.72 (s, 3H), 3.70 and 3.60 (AB system, 2H, $J = 14$ Hz), 3.35 (s, 2H), 2.4 (s, 3H); ^{13}C NMR δ 188.9, 179.6, 167.4, 142.4, 139.6, 130.2 (2C), 124.1 (2C), 102.8, 64.9, 52.6, 45.3, 21.6. Anal. calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_5\text{S}$: C, 56.74; H, 5.44; found: C, 56.67; H, 5.53.

(1) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173-175.

(2) Batelaan, J. G. *Synth. Commun.* **1976**, 6, 81-83.

(3a) Solladié, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995**, 60, 7774-7777.

(5*R*,*SS*)-Methyl 5-hydroxy-3-oxo-6-(*p*-tolylsulfinyl)hexanoate (15).

To a solution of compound **14** (5.67 g, 19.1 mmol, 1 equiv) in THF (340 mL), DIBALH (25.5 mL of a 1.5 M solution in toluene, 38.2 mmol, 2 equiv) was added dropwise at $-78\text{ }^{\circ}\text{C}$ under argon. After 30 minutes, the reaction was quenched with MeOH (80 mL) at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was stirred for 1 more hour at $-78\text{ }^{\circ}\text{C}$ before being allowed to warm to room temperature. After 30 minutes, the solvent was evaporated to afford a fine orange powder which was dissolved in EtOAc (300 mL) and treated with a saturated Na/K tartrate solution (200 mL). The resulting mixture was stirred overnight and then acidified to pH = 4 with concentrated HCl. The aqueous layer was extracted with EtOAc (2 x 150 mL) before being saturated with solid NaCl and re-extracted with EtOAc (150 mL). After washing the combined organic layers with brine (150 mL) and workup, the resulting orange solid was washed several times with cold ether and crystallized ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$) to afford compound **15**^{3b,c} as a pale yellow solid, in 42% yield: R_f (EtOAc) = 0.36; mp $123\text{ }^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} = -206$ (c 0.82, CHCl_3); ^1H NMR δ 7.52 and 7.35 (AA'BB' system, 4H), 4.62 (m, 1H), 4.21 (d, 1H), 3.71 (s, 3H), 3.47 (s, 2H), 3.08 (dd, 1H, $J = 9.4$ and 13.4 Hz), 2.79 (d, 2H, $J = 6.0$ Hz), 2.74 (dd, 1H, $J = 2.4$ and 13.4 Hz), 2.42 (s, 3H); ^{13}C NMR δ 201.5, 167.2, 141.8, 139.2, 130.2 (2C), 124.0 (2C), 63.5, 60.4, 52.5, 49.6, 49.0, 21.6. Anal. calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_5\text{S}$: C, 56.36; H, 6.08; found: C, 56.3; H, 6.21.

(3*R*,5*R*,*SS*)-Methyl 3,5-dihydroxy-6-(*p*-tolylsulfinyl)hexanoate (16).

To a cooled solution ($0\text{ }^{\circ}\text{C}$) of tetramethylammonium triacetoxyborohydride (15.5 g, 59 mmol, 8 equiv) in anhydrous acetic acid (109 mL), a solution of compound **15** (2.2 g, 7.32 mmol, 1 equiv) in

(3) (b) Solladié, G.; Colobert, F.; Denni, D. *Tetrahedron : Asymmetry* **1998**, 9, 3081-3094. (c) Solladié, G.; Wilb, N.; Bauder, C. *Eur. J. Org. Chem.* **1999**, 3021-3026.

anhydrous acetic acid (109 mL) was added dropwise under argon. The resulting reaction mixture was stirred for 2 hours at room temperature, quenched with water (250 mL) and diluted with CH₂Cl₂ (150 mL). The aqueous layer was extracted with several portions of CH₂Cl₂ (3 x 250 mL) and the combined organic layers were washed with saturated solution of NaHCO₃ (3 x 100 mL) and brine (100 mL). After workup, compound **16**^{3b} was obtained as a white solid, in 80% yield: *R_f* (EtOAc) = 0.18; *R_f* (EtOAc/MeOH 80:20) = 0.68; mp 137 °C; $[\alpha]_D^{20} = -172$ (*c* 1, CHCl₃); ¹H NMR δ 7.52 and 7.35 (AA'BB'system, 4H), 4.52 (m, 1H); 4.35 (d, 1H, *J* = 3.4 Hz), 4.33 (m, 1H), 3.69 (s, 3H), 3.45 (d, 1H, *J* = 3.5 Hz), 3.17 (dd, 1H, *J* = 9.5 and 13.4 Hz), 2.70 (dd, 1H, *J* = 2.0 and 13.4 Hz), 2.50 (m, 2H, *J* = 5.7 Hz), 2.42 (s, 3H), 1.67 (m, 2H); ¹³C NMR δ 172.7, 147.8, 139.3, 130.2 (2C), 124.0 (2C), 64.9, 64.0, 61.9, 51.8, 42.4, 41.3, 21.4. Anal. calcd. for C₁₄H₂₀NO₅S: C, 55.98; H, 6.71; found: C, 55.92; H, 6.70.

(3*R*,5*R*,SS)-N-Methoxy-N-methyl-3,5-dihydroxy-6-(*p*-tolylsulfinyl)hexanamide (17).

To a solution of *N,O*-dimethylhydroxylamine chlorhydrate (66.3 mg, 0.67 mmol, 2 equiv) in dry CH₂Cl₂ (3.6 mL), trimethyl aluminium (330 µl of a 2M solution in toluene, 0.66 mmol, 1.98 equiv) was slowly added under argon. The resulting solution was stirred for 30 minutes and cooled to 0 °C. A solution of diol **16** (100 mg, 0.33 mmol, 1 equiv) in dry CH₂Cl₂ (3 mL) was added dropwise and the reaction mixture was allowed to warm up to room temperature and then was refluxed for 26 hours. The solution was slowly cooled down to 0 °C and hydrolyzed with a 0.5 M solution of HCl (7 mL). After workup and flash chromatography (eluent EtOAc/MeOH 90:10), compound **17** was obtained as a colourless oil, in 82% yield: *R_f* (EtOAc/MeOH 90:10) = 0.3; $[\alpha]_D^{20} = -200$ (*c* 1, CHCl₃); ¹H NMR δ 7.52 and 7.33 (AA'BB'system, 4H), 4.57 (m, 2H), 4.27 (m, 2H), 3.67 (s, 3H), 3.17 (s, 3H), 3.05 (dd, 1H, *J* = 9.4 and 13.4 Hz), 2.80 (dd, 1H, *J* = 2.0 and 13.4 Hz), 2.59 (m, 2H), 2.41 (s, 3H), 1.70 (m, 2H); ¹³C NMR δ 173.1, 141.3, 140.0, 129.9 (2C), 124.0 (2C), 65.0, 63.9, 63.5, 61.2, 42.7, 38.4, 31.8, 21.2. Anal. calcd. for C₁₅H₂₃NO₅S: C, 54.69; H, 7.04; N, 4.25; found: C, 50.03; H, 6.70; N, 3.52.

(3b) Solladié, G.; Colobert, F.; Denni, D. *Tetrahedron : Asymmetry* **1998**, 9, 3081-3094.

(3*R*,5*R*,*SS*)-*N*-Methoxy-*N*-methyl-3,5-isopropylidenedioxy-6-(*p*-tolylsulfinyl)hexanamide (18).

To a solution of compound **17** (937 mg, 2.8 mmol, 1 equiv) in acetone (42 mL), 2,2-dimethoxypropane (4.2 mL, 34.2 mmol, 12 equiv) and camphorsulfonic acid (42 mg, 0.1 equiv) were added under argon. The reaction mixture was stirred for 24 hours and neutralized with NEt₃ (3 drops). After evaporation of the solvent and flash chromatography (EtOAc/hexane 90:10) on silica gel treated with a 1% solution of NEt₃ prior use, acetone **18** was obtained as a colourless oil in 84% yield: R_f (EtOAc/hexane 90:10) = 0.23; $[\alpha]_D^{20} = -128$ (c 2.2, CHCl₃); ¹H NMR δ 7.49 and 7.27 (AA'BB' system, 4H), 4.38 (m, 2H), 3.64 (s, 3H), 3.12 (s, 3H), 2.79 (d, 2H, $J = 6.0$ Hz), 2.80 (m, 1H), 2.43 (m, 1H), 2.36 (s, 3H), 1.74 (m, 2H), 1.41 (s, 3H), 1.39 (s, 3H); ¹³C NMR δ 171.4, 141.5, 141.4, 130.1 (2C), 123.8 (2C), 101.3, 64.1, 63.5, 61.3, 61.1, 38.1, 37.5, 32.1, 24.9, 24.6, 21.4. Anal. calcd. for C₁₈H₂₇NO₅S: C, 58.51; H, 7.37; N, 3.79; found: C, 58.14; H, 7.37; N, 3.23.

(3*R*,5*R*,*SS*)-3,5-Isopropylidenedioxy-7-(*p*-tolylsulfinyl)heptan-2-one (19).

To a cooled solution (0 °C) of compound **18** (850 mg, 2.3 mmol, 1 equiv) in THF (22 mL), methyl magnesium bromide (1.76 mL of a 3M solution in ether, 5.29 mmol, 2.3 equiv) was added under argon. The reaction mixture was stirred for 45 minutes at the same temperature, diluted with EtOAc (80 mL) and hydrolyzed with a saturated solution of NH₄Cl (60 mL). After workup and flash chromatography (eluent EtOAc/hexane 3:2) on silica gel previously treated with a 1% solution of NEt₃, compound **19** was obtained as a colourless oil, in 75% yield: R_f (EtOAc) = 0.36; $[\alpha]_D^{20} = -142$ (c 1.1, CHCl₃); ¹H NMR δ 7.52 and 7.30 (AA'BB' system, 4H), 4.44 (m, 1H), 4.29 (m, 1H), 2.78 (d, 2H, $J = 6.0$ Hz), 2.73 (dd, 1H, $J = 8.0$ and 16.3 Hz), 2.46 (dd, 1H, $J = 5.2$ and 16.4 Hz), 2.39 (s, 3H), 2.15 (s, 3H), 1.68 (m,

2H), 1.42 (s, 3H), 1.39 (s, 3H); ^{13}C NMR δ 206.5, 141.5, 141.4, 130.1 (2C), 123.8 (2C), 101.4, 64.1, 63.0, 61.0, 49.3, 37.4, 31.0, 24.8, 24.5, 21.4; Anal. calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_4\text{S}$: C, 61.51; H, 7.74; found: C, 62.14; H, 7.51.

(2*R*,4*R*,6*R*,*SS*)-2-Methoxy-2-methyl-6-[(*p*-tolylsulfinyl)methyl]-tetrahydro-2*H*-pyran-4-ol (20).

To a solution of **19** (541 mg, 1.73 mmol, 1 equiv) in MeOH (25 mL), PPTS (33 mg, 0.13 mmol, 0.08 equiv) was added under argon. After stirring for 24 hours, solid NaHCO_3 (~33 mg) was added and the reaction mixture was filtered over celite. After evaporation of the solvent and flash chromatography (eluent EtOAc) on silica gel previously treated with a 1% solution of NEt_3 , compound **20** was obtained as white crystals in 93% yield: R_f (EtOAc) = 0.29; mp 95 °C; $[\alpha]_D^{20} = -213$ (c 2.4, CHCl_3); ^1H NMR (400 MHz) δ 7.51 and 7.30 (AA'BB' system, 4H), 4.17 (m, 1H), 4.09 (m, 1H), 3.28 (s, 3H), 2.77 (m, 2H), 2.61 (broad s, 1H), 2.38 (s, 3H), 2.12 (ddd, 1H, J = 12.5, 4.5 and 1.5 Hz), 1.87 (dtd, 1H, J = 12.1, 5.0 and 1.5 Hz), 1.38 (s, 3H), 1.35 (dd, 1H, J = 12.6 and 11.0 Hz), 1.18 (q, 1H, J = 12.0 Hz); ^{13}C NMR δ 141.6, 141.3, 130.2 (2C), 123.9 (2C), 100.1, 64.4, 64.1, 63.1, 48.3, 44.7, 39.7, 23.5, 21.5. Anal. calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_4\text{S}$: C, 60.38; H, 7.43; found: C, 60.26; H, 7.46.

(2*R*,4*R*,6*R*,*SS*)-2,4-Dimethoxy-2-methyl-6-[(*p*-tolylsulfinyl) methyl]tetrahydro-2*H*-pyran (21).

To a suspension of NaH (42.2 mg, 60% in oil, 1.06 mmol, 3.35 equiv) in THF (1 mL), a solution of compound **20** (94 mg, 0.32 mmol, 1 equiv) in THF (1 mL) was added at 0 °C under argon. After stirring for 30 minutes at the same temperature, CH_3I (66 μL , 1.06 mmol, 3.35 equiv) was added and the reaction mixture was stirred for 10 hours at the same temperature before being quenched with a saturated solution of NaHCO_3 (2 mL). Layers were separated and the aqueous one was extracted with

EtOAc (3 x 10 mL). The combined organic layers were washed with a saturated solution of NaHSO₃ (10 mL) and then with brine (10 mL). After workup and flash chromatography (eluent EtOAc) on silica gel previously treated with a 1% solution of NEt₃, compound **21** was obtained as a colourless oil in 59% yield (based on recovered starting material): R_f (EtOAc) = 0.4; $[\alpha]_D^{20} = -320$ (c 0.46, CHCl₃); ¹H NMR (300 MHz) δ 7.55 and 7.33 (AA'BB' system, 4H), 4.22 (m, 1H), 3.71 (tt, 1H, J = 11.3 and 4.5 Hz); 3.33 (s, 6H), 2.80 (m, 2H), 2.41 (s, 3H), 2.25 (ddd, 1H, J = 12.5, 4.4 and 2.0 Hz), 1.98 (dtd, 1H, J = 11.7, 4.4 and 2.0 Hz), 1.42 (s, 3H), 1.30 (dd, 1H, J = 12.3 and 11.7 Hz), 1.14 (q, 1H, J = 11.7 Hz); ¹³C NMR δ 141.7, 141.3, 130.0 (2C), 123.7 (2C), 100.0, 73.0, 64.6, 63.1, 55.6, 48.2, 41.5, 36.6, 23.5, 21.4; MS (EI): m/z (%) 312 (M⁺, 8), 141 (49), 140 (62), 139 (100), 137 (21), 124 (26), 123 (25), 109 (58), 108 (99), 95 (52), 91 (94); HRMS (EI) calcd for C₁₆H₂₄O₄S (M⁺) 312.13953, found 312.13885.

(2*R*,4*R*,6*R*)-4, 6-Dimethoxy-6-methyl-tetrahydro-2*H*-pyran-2-carbaldehyde (1).

To a cooled solution (0 °C) of compound **21** (28 mg, 0.09 mmol, 1 equiv) in dry acetonitrile (0.7 mL), 2,6-lutidine (33 μ L, 0.29 mmol, 3.2 equiv) and trifluoroacetic anhydride (39 μ L, 0.27 mmol, 3.05 equiv) were added under argon. After 10 minutes at the same temperature, the reaction was quenched with aqueous NaHCO₃ (62 mg in 1.5 mL H₂O, 0.72 mmol, 8 equiv). The mixture was allowed to warm up to room temperature, stirred for 2 hours and diluted with water (2 mL) and ethyl acetate (2 mL). After workup and flash chromatography (eluent hexane/ethyl acetate 80:20) on silica gel previously treated with a 1% solution of NEt₃, compound **1** was obtained as an unstable colourless oil, in 49% yield: R_f (hexane/EtOAc 80:20) = 0.6; $[\alpha]_D^{20} = -66.4$ (c 0.28, CH₂Cl₂); ¹H NMR (500 MHz) δ 9.67 (d, 1H, J = 0.8 Hz), 3.99 (ddd, 1H, J = 12.5, 2.5 and 0.8 Hz), 3.70 (tt, 1H, J = 11.0 and 4.4 Hz), 3.36, (s, 3H), 3.21 (s, 3H), 2.29 (m, 1H), 2.21 (ddd, 1H, J = 12.5, 4.6 and 2.0 Hz), 1.43 (s, 1H), 1.34 (dd, 1H, J = 12.5 and 11.2 Hz), 1.18 (dt, 1H, J = 12.3 and 11.3 Hz); ¹³C NMR δ 200.9, 100.4, 74.3, 72.6, 55.6, 48.0, 41.7, 31.3, 23.3; MS (EI): m/z (%) 159 ([M – CHO]⁺, 63), 157 (22), 127 (33), 123 (36), 92 (21), 87 (64), 75 (24), 59 (100), 55 (29).

X-Ray ORTEP for compound (2*R*,4*R*,6*R*,*SS*)-**20**.

Table 1 : X-ray experimental data

Formula	: C ₁₅ H ₂₂ O ₄ S
Molecular weight	: 298.40
Crystal system	: monoclinic
Space group	: P 1 2 ₁ 1
a(Å)	: 9.1861(4)
b(Å)	: 7.6778(3)
c(Å)	: 11.8759(7)
β(deg)	: 107.682(5)
V(Å ³)	: 798.02(7)
Z	: 2
Color	: colorless
Crystal dim(mm)	: 0.20*0.10*0.03
D _{calc} (gcm ⁻³)	: 1.24
F ₀₀₀	: 320
μ(mm ⁻¹)	: 0.213
Temperature(K)	: 173
Wavelength(Å)	: 0.71073
Radiation	: MoKα graphite monochromated
Diffractometer	: KappaCCD
Scan mode	: 'phi scans'
hkl limits	: -12,12/-9,10/-16,16
Theta limits(deg)	: 2.5/30.07
Number of data meas.	: 4125
Number of data with	: 2928
I > 3 σ(I)	
Number of variables	: 180
R	: 0.042
R _w	: 0.057
GOF	: 1.050
Largest peak in final	: 0.472
difference (eÅ ⁻³)	

Table of Positional Parameters and Their E.S.D.

Atom ----	x --	y --	z --	Ueqv ----	
C1	0.0701(2)	0.9050	0.7441(2)	0.026(1)	
C2	0.1648(2)	0.9752(3)	0.6710(2)	0.025(1)	
C3	0.1121(2)	1.1581(3)	0.6255(2)	0.028(1)	
C4	0.2177(3)	1.2325(3)	0.5605(2)	0.029(1)	
O1	0.1772(2)	1.4081(2)	0.5229(1)	0.0347(8)	
C5	0.3814(2)	1.2221(3)	0.6399(2)	0.031(1)	
C6	0.4251(3)	1.0378(3)	0.6845(2)	0.033(1)	
C7	0.5817(3)	1.0272(4)	0.7748(2)	0.044(1)	
O2	0.4111(2)	0.9356(2)	0.5822(1)	0.0426(8)	
C8	0.4449(3)	0.7533(4)	0.6039(3)	0.058(1)	
O3	0.3207(2)	0.9767(2)	0.7450(1)	0.0277(7)	
S	0.14575(6)	0.7047(1)	0.81907(5)	0.0327(2)	
O4	0.1537(2)	0.5762(2)	0.7279(2)	0.0541(9)	
C9	-0.0219(2)	0.6517(3)	0.8600(2)	0.028(1)	
C10	-0.0436(3)	0.7286(3)	0.9594(2)	0.032(1)	
C11	-0.1760(2)	0.6955(4)	0.9880(2)	0.034(1)	
C12	-0.2867(3)	0.5840(3)	0.9196(2)	0.032(1)	
C13	-0.4331(3)	0.5501(4)	0.9490(2)	0.051(1)	
C14	-0.2603(3)	0.5044(3)	0.8212(2)	0.032(1)	
C15	-0.1296(3)	0.5385(3)	0.7911(2)	0.029(1)	
H01	0.1633	1.4749	0.5891	0.0469	*

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as one third of the trace of the orthogonalized U_{ij} tensor. Starred atoms were refined isotropically.

Table of Positional Parameters

Atom	x	y	z	Ueqv	
----	-	-	-	----	
H1	-0.0304	0.8838	0.6936	0.0345	*
H2	0.0668	0.9897	0.8016	0.0345	*
H3	0.1540	0.9042	0.6035	0.0338	*
H4	0.1141	1.2314	0.6904	0.0388	*
H5	0.0110	1.1525	0.5730	0.0388	*
H6	0.2072	1.1654	0.4913	0.0401	*
H7	0.3931	1.2968	0.7059	0.0395	*
H8	0.4474	1.2593	0.5967	0.0395	*
H9	0.5841	1.0979	0.8409	0.0595	*
H10	0.6029	0.9098	0.7998	0.0595	*
H11	0.6565	1.0670	0.7404	0.0595	*
H12	0.4327	0.6953	0.5309	0.0724	*
H13	0.5473	0.7401	0.6532	0.0724	*
H14	0.3772	0.7042	0.6418	0.0724	*
H15	0.0322	0.8037	1.0076	0.0428	*
H16	-0.1915	0.7499	1.0553	0.0439	*
H17	-0.4322	0.6138	1.0178	0.0651	*
H18	-0.5178	0.5860	0.8847	0.0651	*
H19	-0.4415	0.4292	0.9630	0.0651	*
H20	-0.3339	0.4256	0.7745	0.0438	*
H21	-0.1136	0.4848	0.7237	0.0389	*

Table of General Displacement Parameter Expressions - U's

Name	U(1,1)	U(2,2)	U(3,3)	U(1,2)	U(1,3)	U(2,3)
C1	.029(1)	.0222(9)	.029(1)	-.0008(8)	.0093(8)	.0011(9)
C2	.031(1)	.020(1)	.0258(9)	-.0052(8)	.0076(8)	-.0013(9)
C3	.030(1)	.025(1)	.029(1)	-.0033(8)	.0007(9)	.0014(9)
C4	.040(1)	.024(1)	.0249(9)	-.0047(9)	.0050(8)	.0013(9)
O1	.0497(9)	.0273(8)	.0307(8)	.0004(7)	.0075(7)	.0077(7)
C5	.0345(9)	.030(1)	.0287(9)	-.0033(9)	.0118(7)	.006(1)
C6	.034(1)	.031(1)	.035(1)	-.002(1)	.0148(8)	.007(1)
C7	.031(1)	.048(1)	.060(1)	-.001(1)	.015(1)	.020(1)
O2	.0544(8)	.0311(8)	.0457(8)	.0044(7)	.0309(6)	.0050(8)
C8	.082(2)	.033(1)	.071(1)	.012(1)	.051(1)	.007(1)
O3	.0276(7)	.0295(8)	.0262(7)	-.0016(6)	.0071(5)	.0046(7)
S	.0315(2)	.0272(2)	.0410(2)	.0009(2)	.0166(2)	.0067(3)
O4	.078(1)	.0265(8)	.0763(9)	-.0005(8)	.0563(7)	-.0066(8)
C9	.0296(9)	.026(1)	.0283(9)	.0003(8)	.0103(7)	.0067(9)
C10	.037(1)	.030(1)	.031(1)	-.006(1)	.0078(8)	-.001(1)
C11	.040(1)	.034(1)	.0276(9)	.008(1)	.0117(8)	.005(1)
C12	.030(1)	.036(1)	.032(1)	.0012(9)	.0076(9)	.014(1)
C13	.042(1)	.061(2)	.051(1)	.002(1)	.019(1)	.014(1)
C14	.032(1)	.033(1)	.032(1)	-.0092(9)	.0035(9)	.002(1)
C15	.038(1)	.026(1)	.026(1)	-.0035(9)	.0096(8)	.0005(9)

Table of Bond Distances in Angstroms

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
=====	=====	=====	=====	=====	=====
C1	C2	1.502(3)	O2	C8	1.440(3)
C1	S	1.807(2)	S	O4	1.483(2)
C2	C3	1.530(3)	S	C9	1.796(2)
C2	O3	1.435(3)	C9	C10	1.388(3)
C3	C4	1.522(3)	C9	C15	1.382(4)
C4	O1	1.433(3)	C10	C11	1.382(4)
C4	C5	1.515(4)	C11	C12	1.387(4)
C5	C6	1.521(3)	C12	C13	1.511(4)
C6	C7	1.513(4)	C12	C14	1.404(4)
C6	O2	1.418(3)	C14	C15	1.379(4)
C6	O3	1.441(3)			

Table of Bond Angles in Degrees

At 1 =====	At 2 =====	At 3 =====	Angle =====	At 1 =====	At 2 =====	At 3 =====	Angle =====
C2	C1	S	112.7(2)	C6	O2	C8	115.2(2)
C1	C2	C3	110.9(2)	C2	O3	C6	112.9(2)
C1	C2	O3	107.1(2)	C1	S	O4	107.6(1)
C3	C2	O3	111.0(2)	C1	S	C9	95.4(1)
C2	C3	C4	110.0(2)	O4	S	C9	106.4(1)
C3	C4	O1	111.5(2)	S	C9	C10	119.3(2)
C3	C4	C5	109.2(2)	S	C9	C15	120.0(2)
O1	C4	C5	111.0(2)	C10	C9	C15	120.6(2)
C4	C5	C6	111.9(2)	C9	C10	C11	119.7(2)
C5	C6	C7	113.0(2)	C10	C11	C12	120.9(2)
C5	C6	O2	105.7(2)	C11	C12	C13	121.1(3)
C5	C6	O3	109.4(2)	C11	C12	C14	118.3(2)
C7	C6	O2	113.4(2)	C13	C12	C14	120.6(3)
C7	C6	O3	105.2(2)	C12	C14	C15	121.2(2)
O2	C6	O3	110.2(2)	C9	C15	C14	119.3(2)