SUPPORTING INFORMATION FOR

Short Asymmetric Synthesis of (–)- and (+)-*cis*-Lauthisan

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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 300 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 dried over P_2O_5 . Dry THF was distilled from sodium/benzophenone ketyl. CH_3CN was dried over $4\text{\AA}$ molecular sieves. All other reagent quality solvents were used without purification. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2 , and solvent drying with MgSO_4 .

(*SR*)-Ethyl-*p*-tolylsulfoxide (6)

(*SR*)-6

A solution of ethyl bromide (3.3 mL, 40.8 mmol) in ethyl ether (50 mL) was added at room temperature to magnesium previously flamed (1.00 g, 40.8 mmol). Once the magnesium was consumed (1 h), the ethyl magnesium bromide solution was slowly added at 0 °C to a vigorously stirred solution of (–)-menthyl-(*SS*)-*p*-toluenesulfinate (**5**)¹ (10.0 g, 34.0 mmol) in dry toluene (50 mL). The resulting

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

mixture was stirred at room temperature for 2 h, hydrolyzed with a saturated solution of NH_4Cl and extracted with ethyl ether. After workup and flash chromatography (eluent EtOAc), compound (SR)-**6** was obtained as a colourless oil, in 91% yield: R_f 0.49 (EtOAc); $[\alpha]_D^{20} +194$ (c 1, acetone) [lit.² $[\alpha]_D^{20} +196$ (c 1, acetone)]; ^1H NMR δ 7.51 and 7.33 (4H, AA'BB' system), 2.80 (2H, m), 2.40 (3H, s), 1.17 (3H, t, $J = 7.4$ Hz).

Ethyl (8R,SR)- and (8S,SR)-7-oxo-8-(*p*-tolylsulfinyl)nonanoate (7)

To a solution of LDA (13.0 mmol, 2 equiv) in THF (20 mL), a solution of (SR)-ethyl-*p*-tolylsulfoxide (**6**) (2.0 g, 13.0 mmol, 2 equiv) in THF (10 mL) was added dropwise at -78 °C, under argon. After stirring for 1.5 h, the resulting solution was slowly added at -78 °C to a solution of commercially available diethyl pimelate (1.34 mL, 6.5 mmol) in THF (10 mL). The reaction mixture was stirred at -78 °C for 3 h, warmed to room temperature and hydrolyzed with a saturated NH_4Cl aqueous solution followed by 10% HCl, until pH 2. The aqueous phase was extracted with EtOAc and after workup and flash chromatography (eluent EtOAc/hexane 2:1), compound **7** was obtained as a colorless oil, in 70% yield, as a 50:50 mixture of epimers at C-8: R_f 0.56 (EtOAc/hexane 2:1); ^1H NMR δ 7.49 et 7.32 (4H, AA'BB system), 7.44 et 7.31 (4H, AA'BB system), 4.11 (4H, q, $J = 7$ Hz), 3.72 (2H, m), 2.41 (6H, s), 2.29 (8H, m), 1.8-1.4 (12H, m), 1.37 (3H, d, $J = 7$ Hz), 1.21 (3H, d, $J = 7$ Hz), 1.25 (6H, t, $J = 7.5$ Hz); IR 2936, 1733, 1700, 1048 cm^{-1} ; MS (EI) m/z (%): 338 (M^+ , 0.4), 214 (5), 151 (9), 139 (35), 107 (22), 91 (54).

Ethyl (7R,8R,SR) and (7R,8S,SR)-7-hydroxy-8-(*p*-tolylsulfinyl)nonanoate (8)

² T. Satoh, T. Sato, T. Oohara, K Yamakawa, *J. Org. Chem.* **1989**, 54, 3973-3978.

A solution of β -ketosulfoxide **7** (2.5 g, 7.4 mmol) and dry zinc bromide (4.2 g, 18.5 mmol) in THF (130 mL) was stirred at room temperature for 90 min and cooled to $-78\text{ }^{\circ}\text{C}$. DIBALH (9.0 mL of a 1 M solution in toluene, 9.0 mmol) was added dropwise and the resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 90 min. After addition of MeOH, the solvents were evaporated and the residue was solved in EtOAc and acidified with a HCl 1M solution. The aqueous phase was extracted with EtOAc and after workup and flash chromatography (eluent EtOAc/hexane 1:1), pure alcohol **8** was obtained as a colorless oil, in 88% yield, as a 50:50 mixture of epimers at C-8: R_f 0.50 (EtOAc/hexane 5:1); ^1H NMR δ 7.60 and 7.31 (4H, AA'BB' system), 7.42 and 7.31 (4H, AA'BB' system), 4.27 (2H, m), 4.10 (4H, q, $J = 7\text{ Hz}$), 3.13 (2H, s), 2.88 (1H, m), 2.54 (1H, m), 2.40 (6H, s), 2.27 (4H, m), 1.7-1.3 (16H, m), 1.23 (6H, t, $J = 7.5\text{ Hz}$), 1.01 (3H, d, $J = 7.0\text{ Hz}$), 0.89 (3H, d, $J = 7\text{ Hz}$); IR 3374, 2936, 1733, 1032 cm^{-1} ; MS (EI): m/z (%) 341 (M^+ , 0.2), 201 (27), 155 (60), 140 (100), 109 (82), 92 (50).

Ethyl (7*S*,8*R*,*SR*) and (7*S*,8*S*,*SR*)-7-hydroxy-8-(*p*-tolylsulfinyl)nonanoate (15**)**

DIBALH (9.8 mL of a 1 M solution in heptane, 9.8 mmol) was added dropwise to a solution of β -ketosulfoxide **7** (2.2 g, 6.5 mmol) in THF (100 mL), at $-78\text{ }^{\circ}\text{C}$. The solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h and hydrolyzed with a saturated aqueous solution of sodium tartrate. After extraction with EtOAc, workup and flash chromatography (eluent EtOAc/hexane 1:1), compound **15** was obtained as a colorless oil, in 83% yield, as a 50:50 mixture of epimers at C-8: R_f 0.51 (EtOAc/hexane 5:1); ^1H NMR δ 7.52 and 7.32 (4H, AA'BB' system), 7.45 and 7.31 (4H, AA'BB' system), 4.10 (4H, q, $J = 7.0\text{ Hz}$), 3.87 (2H, m), 2.75 (1H, m), 2.53 (1H, m), 2.41 (6H, s), 2.28 (4H, m), 1.7-1.3 (16H, m), 1.23 (6H, t, $J = 7.5\text{ Hz}$), 1.02 (3H, d, $J = 7.0\text{ Hz}$), 0.90 (3H, d, $J = 7.0\text{ Hz}$).

(13*R*,14*R*,*SR*)- and (13*R*,14*S*,*SR*)-13-Hydroxy-14-(*p*-tolylsulfinyl)pentadecan-7-one (10)

A solution of AlMe_3 (5.1 mL of a 2 M solution in toluene, 10.2 mmol) was added dropwise at rt to a solution of *N,O*-dimethylhydroxylamine hydrochloride (1.0 g, 10.0 mmol) in CH_2Cl_2 (25 mL). After stirring for 30 min, a solution of ketosulfinyl ester **8** (1.14 g, 3.3 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was refluxed overnight, cooled and quenched with 0.5 M HCl. After workup and flash chromatography (eluent EtOAc, then EtOAc/EtOH 4:1), pure amide **9** was obtained in 70% yield, as a 50:50 mixture of epimers at C-8.

A solution of hexyl bromide (361 μL , 2.5 mmol) in ethyl ether (3 mL) was added to magnesium (60 mg, 2.4 mmol) at rt, under argon. After 1 h, the Grignard reagent was added to a solution of amide **9** (280 mg, 0.8 mmol) in THF (5 mL) at rt. The reaction mixture was stirred at 50 $^\circ\text{C}$ for 3 h, cooled and quenched with saturated NH_4Cl . After workup and flash chromatography (eluent EtOAc/EtOH 9:1), pure ketone **10** was obtained as a colorless oil, in 90% yield, as a 50:50 mixture of epimers at C-14: R_f 0.58 (EtOAc); ^1H NMR δ 7.59 and 7.38 (4H, AA'BB' system), 7.42 and 7.26 (4H, AA'BB' system), 4.21 (2H, m), 3.32 (2H, broad s), 2.89 (1H, m), 2.53 (1H, m), 2.37 (6H, s), 2.34 (8H, m), 1.7-1.2 (32H, m), 1.00 (3H, d, $J = 7.0$ Hz), 0.87 (3H, d, $J = 7.0$ Hz), 0.83 (6H, t, $J = 7.5$ Hz).

Ethyl (*S*)-7-hydroxynonanoate (12)

Freshly activated Nickel Raney (10 mg) was added to a vigorously stirred solution of sulfoxide **8** (100 mg, 0.29 mmol) in EtOH (3 mL) at room temperature. After 1h, the reaction mixture was filtered over Celite, washed with EtOH and the solvent evaporated to give compound (*S*)-**12** as a colourless oil, in 94% yield: R_f 0.47 (EtOAc/hexane 1:2); $[\alpha]_D^{20} +5.0$ (c 1, CHCl_3); ^1H NMR δ 4.11 (2H, q, $J = 7.0$ Hz), 3.51 (1H, m), 2.29 (2H, m), 1.7-1.2 (10H, m), 1.25 (3H, t, $J = 7.5$ Hz), 0.93 (3H, t, $J = 7.0$ Hz, CH_3); ^{13}C NMR δ 173.7, 73.2, 60.1 36.6, 34.3, 30.2, 29.1, 25.3, 24.8, 14.1, 9.8; IR 3433, 2934, 1737 cm^{-1} ; MS (EI): m/z (%) 184 ($[\text{M} - 18]^+$, 1), 173 (17), 144 (29), 127 (100), 101 (92), 81 (79), 69 (40).

Ethyl (*R*)-7-hydroxynonanoate (**12**) was prepared in a similar way from sulfoxide **15**, in 86% yield, after flash chromatography (eluent EtOAc/hexane 1:2): $[\alpha]_D^{20} -5.0$ (c 1, CHCl_3).

***N*-Methoxy-*N*-methyl (*S*)-7-hydroxynonanamide (**13**)**

A solution of AlMe_3 (14.1 mL of a 2 M solution in toluene, 28.2 mmol) was added dropwise at rt to a solution of *N,O*-dimethylhydroxylamine hydrochloride (2.8 g, 26.7 mmol) in CH_2Cl_2 (100 mL). After stirring for 30 min, a solution of ester (*S*)-**12** (1.8 g, 8.9 mmol) in CH_2Cl_2 (100 mL) was added. The mixture was refluxed overnight, cooled and quenched with 0.5 M HCl. After workup and flash chromatography (eluent EtOAc), pure amide (*S*)-**13** was obtained as colourless oil, in 85% yield: R_f 0.12 (EtOAc/hexane 1:1); $[\alpha]_D^{20} +6.0$ (c 1, CHCl_3); ^1H NMR δ 3.66 (3H, s), 3.51 (1H, m), 3.16 (3H, s), 2.40 (2H, t, $J = 7.0$ Hz), 1.7-1.2 (10H, m), 0.91 (3H, t, $J = 7.0$ Hz); ^{13}C NMR δ 174.7, 73.2, 61.2, 32.2, 36.7, 31.8, 30.2, 29.7, 25.4, 24.6, 9.9; IR 3435, 2934, 1648 cm^{-1} .

N-Methoxy-*N*-methyl (*R*)-7-hydroxynonanamide (**13**) was prepared in a similar way from ester (*R*)-**12**, in 75% yield: $[\alpha]_D^{20} -6.0$ (c 1, CHCl_3).

(S)-13-Hydroxypentadecan-7-one (14)

A solution of hexyl bromide (2.2 mL, 14.7 mmol) in ethyl ether (8 mL) was added to magnesium (347 mg, 14.3 mmol) at rt, under argon. After 1 h, the Grignard reagent was added to a solution of the amide (*S*)-**13** (1.0 g, 4.6 mmol) in THF (35 mL) at rt. The reaction mixture was stirred at 50 °C for 3 h, cooled and quenched with saturated NH₄Cl. After workup, pure ketone (*S*)-**14** was obtained as a colorless oil, in 100% yield: *R_f* 0.55 (EtOAc/hexane 1:2); $[\alpha]_D^{20} +6.0$ (*c* 1, CHCl₃); ¹H NMR δ 3.41 (1H, m), 2.29 (4H, m), 1.5-1.2 (18H, m), 0.87 (3H, t, *J* = 7.2 Hz), 0.82 (3H, t, *J* = 7.0 Hz); ¹³C NMR δ 211.5, 72.8, 42.6, 42.4, 36.5, 31.4, 30.0, 29.4, 29.1, 28.7, 25.2, 23.6, 22.4, 13.8, 9.7; IR 3271, 2929, 1706 cm⁻¹. Anal. calcd. for C₁₅H₃₀O₂: C, 74.33; H, 12.47. Found: C, 74.11; H, 12.42.

(*R*)-13-Hydroxypentadecan-7-one (**14**) was prepared in a similar way from amide (*R*)-**13**, in 83% yield: $[\alpha]_D^{20} -6.0$ (*c* 1, CHCl₃).

(2*R*,8*S*)-8-Ethyl-2-hexyloxocane (3) [(*-*)-*cis*-Lauthisan]

To a solution of the hydroxy ketone (*S*)-**14** (500 mg, 2.06 mmol) in CH₂Cl₂ (40 mL), TMSOTf (373 μL, 2.06 mmol), followed by Et₃SiH (659 μL, 4.13 mmol) were added dropwise at 0 °C. The mixture

was stirred for 2 h at 0 °C and quenched with a saturated aqueous solution of NH₄Cl. After workup and flash chromatography (eluent EtOAc/hexane 1:40), pure (–)-*cis*-Lauthisan (**3**) was obtained as a colourless oil, in 40% yield: R_f 0.78 (EtOAc/hexane 1:19); [α]²⁰_D –4.0 (c 0.15, CHCl₃); ¹H NMR δ 3.43 (1H, m), 3.35 (1H, m), 1.8–1.2 (22H, m), 0.93 (6H, t, *J* = 7.5 Hz, CH₃), 0.88 (6H, t, *J* = 7.5 Hz, CH₃); ¹³C NMR δ 81.1, 79.6, 37.1, 33.7, 33.5, 32.0, 30.0, 29.6, 27.2, 26.4, 24.2, 22.7, 14.2, 10.9; IR 2910, 2860, 1460, 1090 cm^{–1}.

(2*R*,8*S*)-8-Ethyl-2-hexyloxocane (**3**) [(+)-*cis*-Lauthisan] was prepared in a similar way from hydroxy ketone (*R*)-**14**, in 39% yield: [α]²⁰_D +4.0 (c 0.15, CHCl₃).