

Supporting Information 1

L-Proline-Catalyzed Direct Intermolecular Asymmetric Aldol Reaction of 1-Phenylthio Cycloalkyl Carboxaldehydes with Ketones. Easy Access to Spiro- and Fused- Cyclobutyl Tetrahydrofuran and Cyclopentanones

Angela M. Bernard, Angelo Frongia,* Régis Guillot, Pier Paolo Piras,* Francesco Secci, Marco Spiga.

Dipartimento di Scienze Chimiche, Università di Cagliari, Complesso Universitario di Monserrato, S.S. 554, Bivio per Sestu, I-09042 Monserrato (Cagliari), Italy.

General information:

¹H NMR spectra were recorded on 300 MHz VARIAN spectrometer at ambient temperature with CDCl₃ as solvent and TMS as internal standard. ¹³C NMR were recorded at 75 MHz at ambient temperature with CDCl₃ as solvent unless otherwise stated. Chemical shifts are reported as follows: chemical shifts, integration, multiplicity and coupling constants.

Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer.

Mass spectra analysis were recorded on Agilent 5973N (Cpsil 32m), (E.I. 70eV).

The enantiomeric excesses of the products were determined by HPLC (HITACHI L7100, UV detector L-7400 HITACHI) using a Diacel Chiralcac OD-H analytical column with *i*-PrOH/hexane as eluent in comparison to the corresponding racemic samples (prepared by using racemic proline as catalyst). Absolute configuration of **1a**, **2a** was assigned by X-ray analysis. Absolute configuration of all the other aldols was assigned analogously to **1a**, **2a**.

The optical rotation values were measured at 25°C with a Perkin-Elmer 241 and PolAAr 32.

Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 70-200 mesh Merck silica gel. Yields refer to chromatography and spectroscopically pure materials, unless otherwise stated.

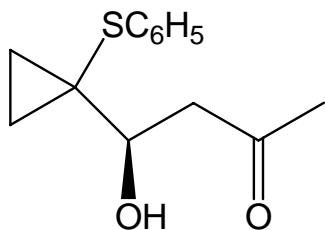
The ketones, (DL)-proline and (L)-proline are all commercially available from Aldrich or Lancaster.

Aldehydes **1**,¹ **2**,² **3**,³ **13b**,⁴ **13c**⁵ were prepared by the literature procedures. Aldehyde **13a** is commercial available.

Experimental Section

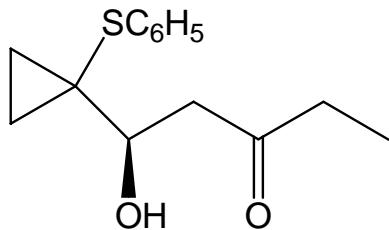
General procedure for the preparation of aldol products **1a-d; 2a,b; 3a,b.**

To a mixture of anhydrous DMSO (20mL) and ketone donor (5mL) was added the corresponding aldehyde **1-3** (4.4 mmol) followed by L-proline (0.1g, 0.88 mmol) and the resulting mixture was stirred at room temperature for 16-48h. The reaction mixture was poured into saturated ammonium chloride solution, the layers were separated and the aqueous phase was extracted several times with diethyl ether. The combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated to afford the crude aldol adducts. The residue was purified by flash chromatography (silica gel, light petroleum-diethyl ether 1:1). The enantiomeric excesses of products were determined after work-up and purification.

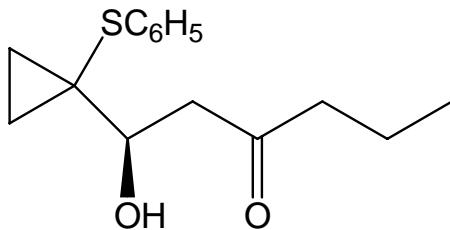


(R)-4-hydroxy-4-(phenylthio)cyclopropylbutan-2-one (1a)(CIF 501). Reaction time 16h. Yield 86%. White solid, mp 61-62°C. $[\alpha]_D^{20} = -8.8$ (*c* 1.36, CHCl_3). IR (neat): 3460, 1700 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.92-0.97 (m, 1H), 0.99-1.04 (m, 1H), 1.06-1.10 (m, 1H), 1.25-1.30 (m, 1H), 2.17 (s, 3H), 2.21 (br.s, 1H), 2.76 (dd, 1H, *J* = 13.2 Hz, *J* = 6.9 Hz) 3.02 (dd, 1H, *J* = 13.2 Hz, *J* = 1.8 Hz), 3.97 (dd, 1H, *J* = 6.9 Hz, *J* = 1.8 Hz), 7.15-7.45 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 12.25, 14.00, 29.20, 30.77, 48.12, 70.44, 125.85, 128.39, 128.78, 136.15, 209.83. HPLC (Daicel chiralpak OD-H column, hexane/*i*-PrOH = 98:2, flow rate 1mL/min, λ = 254 nm) t_R (major) = 19.55 min, t_R (minor) = 17.7 min. MS *m/z*: 236 (M^+ (19)), 218 (7), 178 (100), 160 (14), 149 (56), 134 (51), 115 (48), 109 (42), 105 (30), 91 (34), 77 (18). Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$: C, 66.07; H, 6.82; S, 13.57. Found: C, 66.18; H, 6.72; S, 13.48.

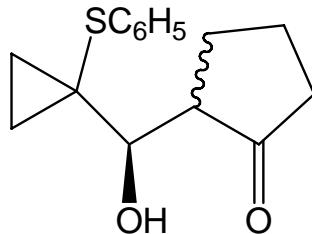
The absolute R-configuration at C-4 was determined by X-ray analysis.



(R)-1-hydroxy-1-(phenylthio)cyclopropylpentan-3-one (1b). Reaction time 24h. Yield 51%. Yellow oil. $[\alpha]_D^{20} = -1.21$ (*c* 0.826, CHCl_3). IR (neat): 3460, 1700 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.92-1.10 (m, 3H), 1.03 (t, 3H, *J* = 7.5 Hz), 1.24-1.29 (m, 1H), 2.44 (q, 2H, *J* = 7.5 Hz), 2.71 (dd, 1H, *J* = 17.4 Hz, *J* = 9.3 Hz) 2.98 (dd, 1H, *J* = 17.4 Hz, *J* = 2.7 Hz), 3.25 (d, 1H, *J* = 3.9 Hz), 3.94-4.00 (m, 1H), 7.15-7.44 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 7.43, 12.17, 13.96, 29.26, 36.77, 46.74, 70.52, 125.77, 128.36, 128.72, 136.16, 212.51. HPLC (Daicel chiralpak OD-H column, hexane/*i*-PrOH = 98:2, flow rate 1mL/min, λ = 254 nm) t_R (major) = 13.40 min, t_R (minor) = 10.95 min. MS *m/z*: 232 ($\text{M}^+ - 18(1)$), 218 (67), 203 (4), 189 (9), 175 (100), 160 (6), 136 (33), 109 (22), 91 (18), 65 (25), 51 (11). Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2\text{S}$: C, 67.17; H, 7.25; S, 12.81. Found: C, 67.28; H, 7.31; S, 12.74.

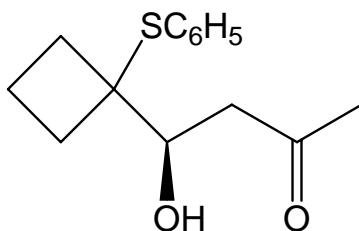


(R)-1-hydroxy-1-(phenylthio)cyclopropylhexan-3-one (1c). Reaction time 48h. Yield 21%. Yellow oil. $[\alpha]_D^{20} = +1.41$ (*c* 1.42, CHCl_3). IR (neat): 3460, 1700 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.90 (t, 3H, *J* = 7.5 Hz), 0.91-1.11 (m, 3H), 1.24-1.30 (m, 1H), 1.52-1.65 (m, 2H), 2.40 (t, 2H, *J* = 7.5 Hz), 2.71 (dd, 1H, *J* = 17.4 Hz, *J* = 9.3 Hz), 2.98 (dd, 1H, *J* = 17.4 Hz, *J* = 2.7 Hz), 3.19 (d, 1H, *J* = 3.9 Hz), 3.94-4.00 (m, 1H), 7.13-7.45 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 12.30, 13.64, 14.04, 16.99, 29.29, 45.62, 47.10, 70.62, 125.86, 128.44, 128.81, 136.22, 212.39. HPLC (Daicel chiralpak OD-H, hexane/*i*-PrOH = 98:2, flow rate 1mL/min, λ = 254 nm) t_R (major) = 10.7 min, t_R (minor) = 8.7 min. MS *m/z*: 264 ($\text{M}^+ - 18(3)$), 218 (8), 189 (14), 175 (100), 160 (8), 136 (35), 123 (28), 109 (41), 91 (24), 65 (42), 51 (22). Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_2\text{S}$: C, 68.15; H, 7.62; S, 12.13. Found: C, 68.28; H, 7.51; S, 12.24.



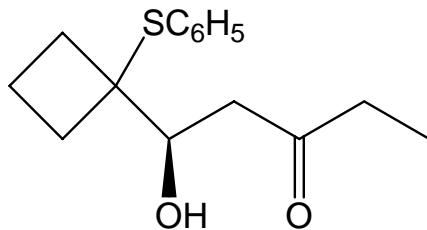
(R)-2-(hydroxyl(1-(phenylthio)cyclopropyl)methyl)cyclopentanone (1d). Reaction time 16h. Yield 80%. Yellow oil. Mixture (36:64) of two *syn* (e.e.> 99%) and *anti* (e.e. 89%) inseparable diastereoisomers. (The assignment of the *syn* and *anti* stereochemistry of aldols **1d** has been made

analogously with the results reported in the reaction of cyclopentanone with isovaleraldehyde^{6a} or benzaldehyde^{6b}) IR (neat): 3440, 1700 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.88-1.24 (m, 8H), 1.52-2.44 (m, 12H), 2.67-2.77 (m 1H), 2.84-2.91 (m, 1H), 3.20 (br s, 1H), 3.24 (br s, 1H), 4.27 (dd, 1H, J = 2.7 Hz, J = 5.7 Hz), 4.60 (d, 1H, J = 0.9 Hz), 7.12-7.58 (m, 10H). HPLC (Daicel chiralpak OD-H, hexane/*i*-PrOH = 98:2, flow rate 1mL/min, λ = 254 nm) t_R (major) = 7.83 min (major isomer) and 10.94 min (minor isomer); t_R (minor) = 9.47 min (major isomer) and 14.83 min (minor isomer). MS m/z (minor isomer): 244 (M^+ -18 (42)), 229 (8), 211 (17), 188 (27), 173 (14), 153 (27), 135 (100), 121 (50), 91 (84), 77 (88), 51 (33). MS m/z (major isomer): 244 (M^+ -18 (21)), 229 (14), 188 (27), 173 (9), 135 (69), 121 (26), 109 (54), 91 (46), 77 (100), 65 (51), 51 (45).



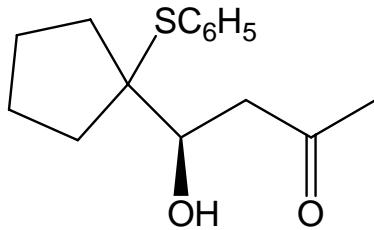
(R)-4-hydroxy-4-(1-(phenylthio)cyclobutyl)butan-2-one (2a) (CIF 503). Reaction time 16h. Yield 88%. White solid, mp = 80-81°C. $[\alpha]_D^{23} = +12.5$ (*c* 0.482, CHCl_3). IR (neat): 3460, 1700 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 1.74-1.87 (m, 1H), 1.90-2.12 (m, 3H), 2.16 (s, 3H), 2.31-2.41 (m, 2H), 2.64 (dd, 1H, J = 17.1 Hz, J = 9.9 Hz), 2.94 (dd, 1H, J = 17.1 Hz, J = 1.8 Hz), 3.42 (d, 1H, J = 3.9 Hz), 4.13-4.18 (m, 1H), 7.26-7.47 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 15.28, 28.53, 29.01, 30.49, 44.85, 56.56, 70.37, 127.69, 128.46, 132.41, 134.36, 209.22. HPLC (Daicel chiralpak OD-H column, hexane/*i*-PrOH = 98:2, flow rate 1mL/min, λ = 254 nm) t_R (major) = 21.53 min, t_R (minor) = 13.16 min. MS m/z: 232 (M^+ -18 (6)), 218 (3), 189 (50), 161 (22), 123 (30), 109 (100), 95 (40), 79 (40), 65 (60), 51 (46). Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2\text{S}$: C, 67.17; H, 7.25; S, 12.81. Found: C, 67.1; H, 7.28; S, 12.85.

The absolute R-configuration at C-4 was determined by X-ray analysis.

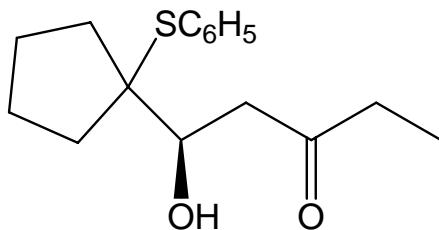


(R)-1-hydroxy-1-(1-(phenylthio)cyclobutyl)pentan-3-one (2b). Reaction time 24h. Yield 44%. Yellow oil. $[\alpha]_D^{22} = +12.82$ (*c* 1.87, CHCl_3). IR (neat): 3480, 1700 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 1.07 (t, 3H, J = 7.5 Hz), 1.78-1.90 (m, 1H), 1.92-2.14 (m, 3H), 2.31-2.43 (m, 2H), 2.49

(q, 2H, J = 7.5 Hz), 2.63 (dd, 1H, J = 17.4 Hz, J = 9.9 Hz), 2.93 (dd, 1H, J = 17.4 Hz, J = 2.4 Hz), 3.20 (d, 1H, J = 3.9 Hz), 4.15-4.21 (m, 1H), 7.26-7.48 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 7.52, 15.55, 28.97, 29.34, 36.88, 43.62, 56.85, 70.86, 128.00, 128.75, 132.65, 134.64, 212.40. HPLC (Daicel chiralpak OD-H column, hexane/*i*-PrOH = 98:2, flow rate 1mL/min, λ = 254 nm) t_R (major) = 23.52 min, t_R (minor) = 10.80 min. MS m/z: 246 (M^+-18 (6)), 189 (100), 161 (30), 136 (48), 109 (100), 79 (44), 57 (41). Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_2\text{S}$: C, 68.15; H, 7.62; S 12.13. Found: C, 68.11; H 7.68; S, 12.11.



(R)-4-hydroxy-4-(1-(phenylthio)cyclopenty)butan-2-one (3a). Reaction time 24h. Yield 56%. White solid, mp 59-60°C. $[\alpha]_D^{21} = +30.30$ (c 1.32, CHCl_3). IR (neat): 3480, 1700 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 1.57-1.94 (m, 8H), 2.21 (s, 3H), 2.73 (dd, 1H, J = 17.1 Hz, J = 9.9 Hz), 3.03 (dd, 1H, J = 17.1 Hz, J = 1.8 Hz), 3.18 (d, 1H, J = 3.6 Hz), 4.06-4.11 (m, 1H), 7.28-7.51 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 24.36, 24.44, 30.79, 33.72, 33.92, 46.34, 65.04, 71.35, 128.63, 128.68, 132.00, 136.48, 209.30. HPLC (Daicel chiralpak OD-H column, hexane/*i*-PrOH = 98:2, flow rate 1mL/min, λ = 254 nm) t_R (major) = 15.7 min, t_R (minor) = 19.3. MS m/z: 246 (M^+-18 (2)), 203 (100), 137 (99), 123 (10), 109 (72), 93 (43), 79 (38), 65 (46), 51 (14). Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_2\text{S}$: C, 68.15; H, 7.62; S, 12.13. Found: C, 68.17; H, 7.59; S, 12.14.

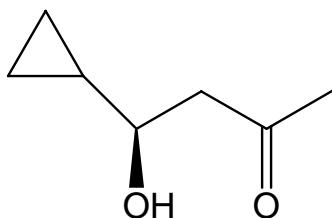


(R)-1-hydroxy-1-(1-(phenylthio)cyclopentyl)pentan-3-one (3b). Reaction time 48h. Yield 21%. Colourless oil. $[\alpha]_D^{20} = -33.93$ (c 1.65, CHCl_3). IR (neat): 3480, 1700 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 1.07 (t, 3H, J = 7.2 Hz), 1.59-1.96 (m, 8H), 2.51 (q, 2H, J = 7.2 Hz), 2.70 (dd, 1H, J = 16.8 Hz, J = 9.9 Hz), 2.98 (dd, 1H, J = 16.8 Hz, J = 2.1 Hz), 3.17 (d, 1H, J = 2.7 Hz), 4.08-4.12 (m, 1H), 7.24-7.53 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 7.59, 24.47, 24.53, 33.87, 34.06, 36.96, 45.05, 65.23, 71.64, 128.70, 128.72, 132.12, 136.58, 212.11. HPLC (Daicel chiralpak OD-H column, hexane/*i*-PrOH = 98:2, flow rate 1mL/min, λ = 254 nm) t_R (major) = 15.8 min, t_R (minor) =

18.5 min. MS m/z: 260 ($M^+ - 18$ (3)), 231 (3), 203 (100), 151 (100), 123 (42), 109 (56), 81 (60), 57 (100). Anal. Calcd. for $C_{16}H_{22}O_2S$: C, 69.03; H, 7.96; S, 11.52. Found: C, 69.06; H, 7.98; S, 11.47.

Procedure for the preparation of (R)-4-cyclopropyl-4-hydroxybutan-2-one

A solution of aldol **1a** (0.5g, 2.1 mmol), in dry EtOH (10mL), was added at 0°C to a suspension of Raney Nickel in EtOH (10mL) under hydrogen atmosphere. After 6h the mixture was filtered over Celite and the solvent evaporated to afford the crude aldol product. This was taken up in diethyl ether (20mL), washed with brine, dried and evaporated to give an oil which was purified by flash chromatography (silica gel, light petroleum-diethyl ether 1:1).

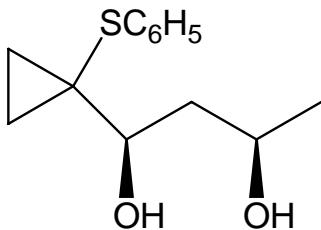


Reaction time 6h. Yellow oil. Yield 80%. $[\alpha]_D^{25} = -13$ (c 0.074, $CHCl_3$). IR (neat): 3440, 1700 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$) δ : 0.14-0.22 (m, 1H), 0.34-0.42 (m, 1H), 0.45-0.60 (m, 2H), 0.85-0.98 (m, 1H), 2.19 (s, 3H), 2.74 (d, 1H, $J = 4.5$ Hz), 2.75 (br.s, 1H), 2.84 (d, 1H, $J = 3.3$ Hz), 3.28-3.36 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ : 2.10, 3.22, 16.73, 30.78, 49.90, 72.37, 209.51. MS m/z: 128 ($M^+ + 4$), 127 (8), 111 (100), 100 (13), 95 (15), 83 (24), 71 (89), 53 (67). Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.44. Found: C, 65.54; H, 9.5.

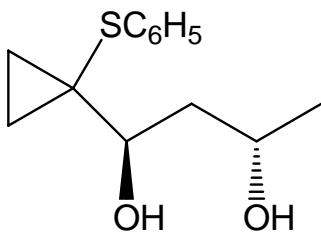
General procedure for the preparation of 1-(1-(phenylthio)cyclopropyl)butane-1,3-diol: (1*R*,3*R*)-(syn)-4 and (1*R*,3*S*)-(anti)-4.

To a stirred solution of the aldol **1a** (0.4g, 1.7 mmol) in dry THF (10mL) and MeOH (10mL), at -70°C was added Et_2BOMe (1M in THF, 3.2mL, 3.3 mmol). After 30min, $NaBH_4$ (0.16g, 4.25 mmol) was added and the mixture was stirred for 1h at -70°C. The reaction mixture was quenched by the addition of pH 7 phosphate buffer (1mL) and MeOH (3.2mL), then at 0°C, was added 2:1 MeOH/30% aqueous H_2O_2 (3mL) carefully. The mixture was stirred at same temperature for 1.5h and then, at room temperature for 30'. The reaction mixture was extracted with CH_2Cl_2 and the combined extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography (silica gel, light petroleum-diethyl ether 1:1) to afford the diols *syn*-4 and *anti*-4 in the ratio 99:1. (Overall yield, 70%).

The same alcohols were obtained in the ratio 60:40 (*syn:anti*) and 90% yield by reduction of **1a** with $NaBH_4$ in the absence of the chelating Lewis acid Et_2BOMe at r.t.



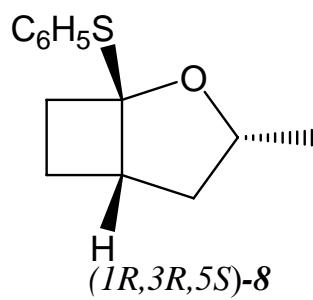
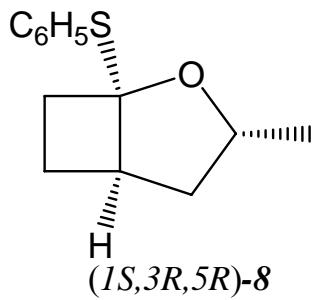
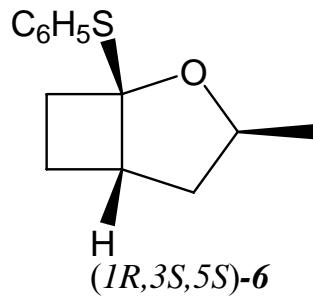
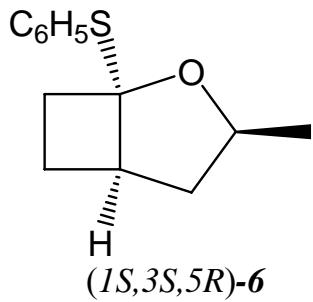
(IR,3R)-(syn)-4. Major diastereomer: Colourless oil. $[\alpha]_D^{18} = +162.2$ (*c* 1.196, CHCl_3). IR (neat): 3460 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.94-1.26 (m, 4H), 1.19 (d, 3H, *J* = 6.0 Hz), 1.58 (dt, 1H, *J* = 14.4 Hz, *J* = 10.2 Hz), 1.87 (dt, 1H, *J* = 14.4 Hz, *J* = 2.4 Hz), 2.83 (br.s, 2H), 3.74-3.78 (m, 1H), 3.95-4.02 (m, 1H), 7.14-7.45 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 12.86, 13.28, 24.18, 30.70, 42.11, 68.66, 75.54, 125.96, 127.69, 128.79, 128.86, 136.23. MS *m/z*: 238 (M^+ (29)), 220 (11), 194 (14), 176 (84), 161 (38), 150 (100), 143 (24), 135 (64), 117 (92), 110 (90), 105 (52), 91 (64), 77 (38). Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_2\text{S}$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.59; H, 7.54; S, 13.44.



(IR,3S)-(anti)-4. Minor diastereomer: Colourless oil. $[\alpha]_D^{18} = +9.7$ (*c* 0.218, CHCl_3). IR (neat): 3460 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 1.00-1.03 (m, 2H), 1.08-1.14 (m, 2H), 1.22 (d, 3H, *J* = 6.3 Hz), 1.66-1.75 (m, 1H), 1.79-1.91 (m, 2H), 2.58 (d, 1H, *J* = 6.3 Hz), 3.75-3.80 (m, 1H), 4.11-4.22 (m, 1H), 7.15-7.47 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 13.32, 13.64, 23.61, 30.77, 42.10, 65.60, 72.35, 126.05, 128.79, 129.00, 136.24. MS *m/z*: 238 (M^+ (36)), 176 (74), 161 (36), 150 (100), 143 (26), 135 (58), 117 (95), 110 (84), 105 (62), 91 (69), 77 (44). Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_2\text{S}$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.58; H, 7.55; S, 13.44.

Procedure for the synthesis of 3-methyl-1-(phenylthio)-2-oxa-biciclo[3.2.0]heptane: (1*S*,3*S*,5*R*)-6, (1*R*,3*S*,5*S*)-6 and (1*S*,3*R*,5*R*)-8, (1*R*,3*R*,5*S*)-8.

To a solution of (1*R*,3*S*)-(anti)-4 (228mg, 0.96 mmol) in CH_2Cl_2 (10mL) at room temperature was added anhydrous stannic chloride (1M in CH_2Cl_2 , 0.96mL, 0.96 mmol). After stirring for 16 h, water (20mL) was added followed by diethyl ether. The organic layer was washed with saturated aqueous NaHCO_3 solution, dried (Na_2SO_4), and the solvents removed in vacuo. The residue was purified by flash chromatography (silica gel, light petroleum-diethyl ether 10:1) to give the corresponding tetrahydrofurans (1*S*,3*S*,5*R*)-6 and (1*R*,3*S*,5*S*)-6.



Spectral data worked out from a 86:14 mixture of two inseparable diastereoisomers $(1S,3S,5R)\text{-6}$ and $(1R,3S,5S)\text{-6}$. Yield 72%. Colourless oil. Major isomer $(1S,3S,5R)\text{-6}$: ^1H NMR (300 MHz, CDCl_3): 1.03-1.13 (m, 1H), 1.25 (d, 3H, $J = 6.0$ Hz), 1.45-1.57 (m, 1H), 1.64 (dd, 1H, $J = 12.6$ Hz, $J = 5.4$ Hz), 2.14-2.49 (m, 3H), 2.94-3.02 (m, 1H), 4.35-4.42 (m, 1H), 7.20-7.54 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 19.53, 19.91, 34.72, 39.70, 46.91, 76.63, 93.41, 127.58, 128.34, 132.79, 133.77. MS m/z: 220 (M^+ (2)), 192 (22), 178 (1), 135 (6), 121 (3), 109 (100), 91 (7), 83 (30), 77 (18), 65 (52), 55 (54), 41 (70). Minor isomer $(1R,3S,5S)\text{-6}$: ^1H NMR (300 MHz, CDCl_3): 1.35 (d, 3H, $J = 6.3$ Hz), 1.41-1.67 (m, 2H), 2.16-2.44 (m, 4H), 2.86-2.92 (m, 1H), 4.09-4.18 (m, 1H), 7.20-7.54 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3) δ : 20.46, 22.90, 34.51, 42.42, 45.87, 78.66, 94.87, 126.95, 128.58, 132.34, 133.77. MS m/z: 220 (M^+ (2)), 192 (22), 178 (1), 135 (6), 121 (3), 109 (100), 91 (7), 83 (30), 77 (18), 65 (52), 55 (54), 41 (62).

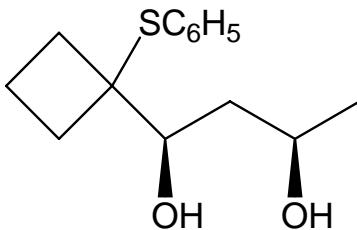
The acid catalysed rearrangement of $(1R,3R)$ -(*syn*)-4 gave a mixture of $(1S,3R,5R)\text{-8}$ and $(1R,3R,5S)\text{-8}$ in 60:40 ratio and 66% of yield.

The relative stereochemistry of *cis*-fused cyclobutyl tetrahydrofurans: $(1S,3S,5R)\text{-6}$; $(1R,3S,5S)\text{-6}$ and $(1S,3R,5R)\text{-8}$; $(1R,3R,5S)\text{-8}$ was assigned on the basis of X-ray crystal structure analysis of sulfones $(1S^*3R^*5R^*)\text{-16}$ and $(1R^*3R^*5S^*)\text{-16}$ obtained analytically pures after oxidation of compounds $(1S^*3R^*5R^*)\text{-8}$ and $(1R^*3R^*5S^*)\text{-8}$ ⁷ with m-CPBA (2 equiv.) followed by chromatography on silica gel.

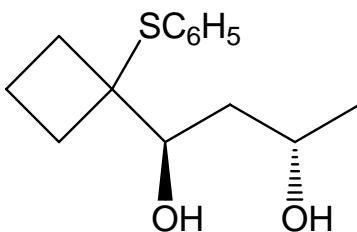
General procedure for the preparation of 1-(1-(phenylthio)cyclobutyl)butane-1,3-diol: (1*R*,3*R*)-(*syn*)-9 and (1*R*,3*S*)-(*anti*)-9.

To a stirred solution of **2a** (0.4g, 1.6 mmol) in MeOH/THF (10mL/10mL) at room temperature, NaBH₄ (60mg, 1.6 mmol) was added. After 2h, the reaction mixture was evaporated and the residue, diluted in diethyl ether, was washed twice with brine. After flash chromatography (silica gel, light petroleum-diethyl ether 1:1), the diols were obtained in 60:40 ratio (*syn:anti*) and 90% of yield.

The *syn* and *anti* stereochemistry of diols **9** was assigned by analogy with the corresponding cyclopropyl derivatives **4**.



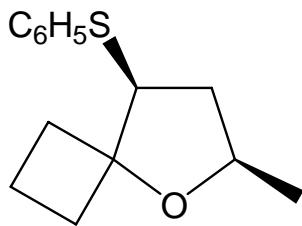
(1*R*,3*R*)-(*syn*)-9. Major diastereomer: Colourless oil. $[\alpha]_D^{21} = +14.93$ (*c* 0.402, CHCl₃). IR (neat): 3460 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 1.22 (d, 3H, *J* = 6.0 Hz), 1.58-1.70 (m, 2H), 1.78-1.91 (m, 2H), 2.05-2.38 (m, 4H), 3.25 (br s, 1H), 3.38 (br s, 1H), 3.81-3.85 (m, 1H), 3.99-4.04 (m, 1H), 7.26-7.49 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ : 15.70, 23.97, 28.96, 29.98, 38.85, 58.42, 68.81, 75.31, 128.36, 128.89, 132.23, 135.03. MS m/z: 252 (M⁺ (21)), 224 (2), 192 (10), 166 (100), 135 (48), 110 (27), 91 (30), 77 (14). Anal. Calcd. for C₁₄H₂₀O₂S: C, 66.63; H, 7.99; S, 12.7. Found: C, 66.58; H, 8.02; S, 13.47.



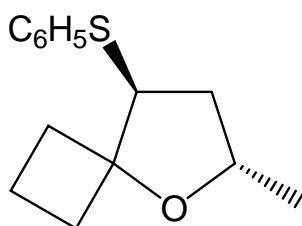
(1*R*,3*R*)-(*anti*)-9. Minor diastereomer: Colourless oil. $[\alpha]_D^{21} = +43.21$ (*c* 0.972, CHCl₃). IR (neat): 3460 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 1.24 (d, 3H, *J* = 6.3 Hz), 1.72-1.85 (m, 3H), 2.01-2.16 (m, 3H), 2.22-2.38 (m, 3H), 2.84 (br s, 1H), 3.94-3.99 (m, 1H), 4.10-4.16 (m, 1H), 7.26-7.51 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ : 15.61, 23.50, 29.47, 30.09, 39.09, 58.59, 65.47, 71.38, 128.24, 128.79, 132.42, 135.14. MS m/z: 252 (M⁺ (21)), 192 (11), 166 (100), 135 (68), 109 (61), 91 (52), 77 (27), 55 (60), 45 (91). Anal. Calcd. for C₁₄H₂₀O₂S: C, 66.63; H, 7.99; S, 12.7. Found: C, 66.6; H, 8.01; S, 12.71.

Procedure for the synthesis of 6-methyl-8-(phenylthio)-5-oxaspiro[3.4]octane: (6*R*,8*S*)-(syn)-10** and (6*S*,8*S*)-(anti)-**10**.**

To a solution of (*1R,3R*)-(syn)-**9** or (*1R,3R*)-(anti)-**9** (242mg, 0.96 mmol) in CH₂Cl₂ (10mL) at room temperature was added anhydrous stannic chloride (1M in CH₂Cl₂, 0.96mL, 0.96 mmol). After stirring for 16 h, water (20mL) was added, followed by diethyl ether (30mL). The organic layer was washed with saturated aqueous NaHCO₃ solution, dried (Na₂SO₄), and the solvent removed in vacuo. The residue was purified by flash chromatography (silica gel, light petroleum-diethyl ether 10:1) to give the corresponding tetrahydrofuran (6*R*,8*S*)-(syn)-**10** or (6*S*,8*S*)-(anti)-**10**.



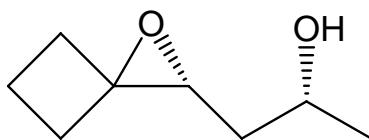
(6*R*,8*S*)-(syn)-**10**. Yield 86%. Colourless oil. $[\alpha]_D^{26} = +4.8$ (*c* 0.416, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ : 1.29 (d, 3H, *J* = 6.3 Hz), 1.58-1.71 (m, 2H), 1.72-1.85 (m, 1H), 2.02-2.10 (m, 1H), 2.19-2.33 (m, 2H), 2.46-2.55 (m, 2H), 3.65 (t, 1H, *J* = 7.2 Hz), 4.04-4.15 (m, 1H), 7.18-7.44 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ : 12.87, 22.06, 31.66, 34.74, 40.42, 53.61, 72.55, 85.92, 126.50, 128.94, 130.56, 136.08. MS m/z: 234 (M⁺ (48)), 206 (76), 173 (100), 145 (18), 131 (20), 109 (42), 91 (34), 77 (18). Anal. Calcd. for C₁₄H₁₈OS: C, 71.75; H, 7.74; S, 13.68. Found: C, 71.71; H, 7.77; S, 13.69.



(6*S*,8*S*)-(anti)-**10**. Yield 70%. Colourless oil. $[\alpha]_D^{27} = +78$ (*c* 0.474, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ : 1.23 (d, 3H, *J* = 6.0 Hz), 1.56-1.81 (m, 2H), 1.88-1.97 (m, 1H), 2.00-2.14 (m, 2H), 2.15-2.30 (m, 2H), 2.47-2.55 (m, 1H), 3.72 (dd, 1H, *J* = 6.6 Hz, *J* = 3.9 Hz), 4.23-4.30 (m, 1H), 7.19-7.44 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ : 12.75, 22.07, 31.17, 36.82, 39.94, 54.13, 72.86, 85.77, 126.48, 128.94, 130.67, 136.05. MS m/z: 234 (M⁺ (32)), 206 (66), 173 (100), 131 (14), 109 (36), 91 (34), 65 (19), 43 (32). Anal. Calcd. for C₁₄H₁₈OS: C, 71.75; H, 7.74; S, 13.68. Found: C, 71.70; H, 7.78; S, 13.69.

Procedure for the synthesis of (2R)-1-[(2R)-1-oxaspiro[2.3]hex-2-yl]propan-2-ol (11).

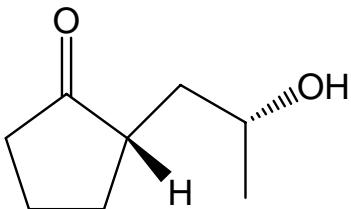
To a solution of *(6R,8S)*-(*syn*)-**10** (0.44g, 1.74 mmol) in 30mL of CH₂Cl₂ at room temperature was added (0.3g, 2 mmol) trimethyloxonium fluoborate. After stirring until all the solid dissolved, 10mL of a 0.5 M aqueous sodium hydroxide solution was added and stirring continued for 15h. The reaction mixture was poured into 20mL of water and extracted with 90mL of diethyl ether. The organic layer was washed with 20mL of brine, dried (Na₂SO₄) and the solvent removed in vacuo. The residue was purified by flash chromatography (silica gel, light petroleum-diethyl ether 1:1) to give the corresponding oxaspirohexane **11**.



Yield 70%. Colourless oil. $[\alpha]_D^{18} = +26.7$ (*c* 0.3, CHCl₃). IR (neat): 3460 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 1.25 (d, 3H, *J* = 6.3 Hz), 1.37-1.47 (m, 1H), 1.68-2.52 (m, 7H), 2.71 (br s, 1H), 3.00 (dd, 1H, *J* = 4.5 Hz, *J* = 8.1 Hz), 4.06-4.12 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ : 12.85, 23.37, 28.48, 30.88, 38.64, 59.86, 63.19, 66.78. MS m/z: 142 (M⁺ (1)), 127 (48), 113 (49), 101 (11), 83 (8), 59 (67), 55 (100), 43 (32), 45 (7), 39 (42). Anal. Calcd. for C₈H₁₄O₂: C, 67.57; H, 9.92. Found: C, 67.56; H, 9.93.

Procedure for the synthesis of (S)-2-((R)-2-hydroxypropyl)cyclopentanone (12).

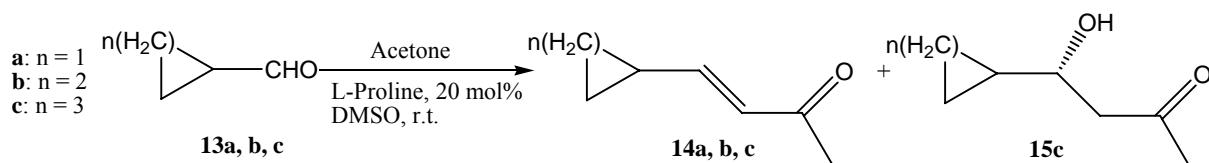
A solution of the oxaspirohexane **11** (0.08g, 0.56 mmol), with a catalytic amount (10%) of LiI in CH₂Cl₂ (10mL) was refluxed for 5h. The solution after cooling and filtration was evaporated under vacuum to give the crude cyclopentanone **12** which was purified by flash chromatography (silica gel, diethyl ether/light petroleum, 1:1).



Yield 87%. Colourless oil. $[\alpha]_D^{29} = +50$ (*c* 0.04, CHCl₃). IR (neat): 3460, 1700 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ : 1.20 (d, 3H, *J* = 6.3 Hz), 1.49-1.91 (m, 4H), 1.95-2.36 (m, 6H), 3.94-4.04 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ : 20.97, 23.45, 30.28, 37.89, 38.60, 46.32, 66.17, 222.00. MS m/z: 142 (M⁺ (1)), 125 (86), 113 (10), 97 (19), 81 (18), 67 (32), 55 (100), 41 (83). Anal. Calcd. for C₈H₁₄O₂: C, 67.57; H, 9.92. Found: C, 67.53; H, 9.96.

General procedure for the preparation of products **14a-c; 15c.**

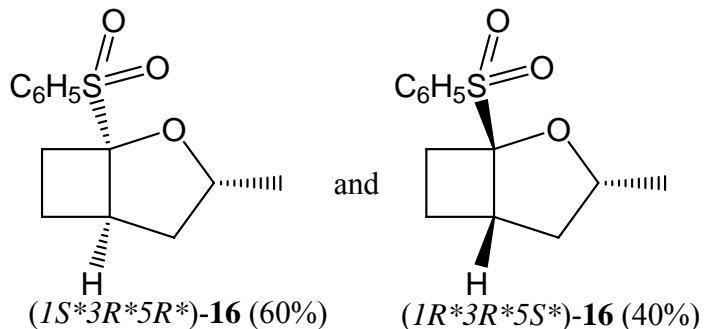
To a mixture of anhydrous DMSO (20mL) and acetone (5mL) was added the corresponding aldehyde **13a-c** (4.4 mmol) followed by L-proline (0.88 mmol) and the resulting mixture was stirred at room temperature for 3-16h. The reaction mixture was poured into saturated ammonium chloride solution, the layers were separated and, the aqueous phase was extracted several times with diethyl ether. The combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated to afford the crude aldol adducts. The residue was purified by flash chromatography (silica gel, light petroleum-diethyl ether 1:1). Spectral data of compounds **14a-c**⁸ and **15c**⁹ has been previously reported in literature.



Entry	Aldehyde	Time (h)	14:15 Ratio (%)	Yield of 14 (%)	Yield of 15 (%)
1	13a	3	100:0	60	0
2	13b	16	100:0	55	0
3	13c	16	80:20	50	20

3-methyl-1-(phenylsulfonyl)-2-oxa-bicyclo[3.2.0]heptane (1S*3R*5R*)-16** (CIF 553) and (**1R*3R*5S*)-16** (CIF 554)**

To an ice-cooled solution containing a mixture of racemic (**1S*3R*5R*)-8** and (**1R*3R*5S*)-8**,⁷ in 60:40 ratio (62mg, 0.28 mmol) in 10 mL of CH_2Cl_2 , m-chloroperbenzoic acid (96mg, 0.56 mmol) was added portionwise. After stirring for 16 h, the solution was diluted with CH_2Cl_2 and washed with a saturated NaHCO_3 solution. The organic layer was dried over anhydrous Na_2SO_4 and after filtration concentrated under reduced pressure. The residue was chromatographed on silica gel using light petroleum-diethyl ether (1:1) as eluent to give the separated purified products.



Yield 90 %. Mixture 60:40 of two diastereoisomers. $(IS^*3R^*5R^*)\text{-16}$ Major diastereoisomer: White solid, mp 70-71°C. IR (nujol): 1350, 1130 cm^{-1} . ^1H NMR (CDCl_3): 1.06-1.21 (m, 1H), 1.20 (d, 3H), 1.58-1.70 (m, 1H), 1.74-1.81 (m, 1H), 2.02-2.07 (m, 1H), 2.15-2.25 (m, 1H), 2.96-3.04 (m, 1H), 3.47-3.53 (m, 1H), 4.53-4.60 (m, 1H), 7.51-7.57 (m, 2H), 7.63-7.65 (m, 1H), 7.90-7.93 (m, 2H). ^{13}C NMR δ : 19.36, 19.99, 27.20, 38.49, 43.07, 80.37, 100.06, 128.69, 129.92, 133.73, 135.53. MS m/z: 224 ($M^+ - 28$ (3)), 141 (3), 125 (14), 111 (100), 97 (4), 83 (58), 69 (45), 55 (71), 41 (51). Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_3\text{S}$: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.81; H, 6.45; S, 12.72. $(IR^*3R^*5S^*)\text{-16}$ Minor diastereoisomer: White solid, mp 68-70°C. IR (nujol): 1350, 1140 cm^{-1} . ^1H NMR (CDCl_3): 1.50-1.57 (m, 1H), 1.63-1.72 (m, 1H), 1.89-1.97 (m, 1H), 2.34-2.46 (m, 2H), 2.68-2.73 (m, 1H), 3.53-3.58 (m, 1H), 4.33-4.43 (m, 1H), 7.52-7.57 (m, 2H), 7.63-7.67 (m, 1H), 7.92-7.94 (m, 2H). ^{13}C NMR δ : 20.94, 22.22, 26.79, 40.55, 42.26, 83.04, 100.60, 128.90, 129.55, 133.69, 135.99. MS m/z: 141 ($M^+ - 111$ (3)), 125 (8), 111 (100), 83 (63), 69 (48), 55 (74), 41 (54). Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_3\text{S}$: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.85; H, 6.45; S, 12.75.

References

- 1) Trost, B.; Jungheim, L. N.; *J. Am. Chem. Soc.* **1980**, *102*, 7910.
- 2) Yamashita, M.; Onozuka, J.; Tsuchihashi, G.; Ogura, K. *Tetrahedron Lett.* **1983**, *24*, 79.
- 3) Aggarwal, V.K.; Coldham, L.; Mc Intyre, S.; Warren, S. *J. Chem. Soc. Perkin Trans. I* **1991**, *2*, 451.
- 4) Wessig, P.; Muehling, O. *Helv. Chim. Acta* **2003**, *86*, 865.
- 5) Tashiro, Y.; Togo, H. *Synlett* **2004**, *11*, 2010.
- 6) (a) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.*, **2001**, *3*, 573. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
- 7) Compounds $(IS^*3R^*5R^*)\text{-8}$ and $(IR^*3R^*5S^*)\text{-8}$ were prepared starting from racemic $(IR^*3R^*)(syn)\text{-4}$ according to the procedure described for the synthesis of $(IS, 3R, 5R)\text{-8}$ and $(IR, 3R, 5S)\text{-8}$.

8) Collins, P. W.; Gasiecki, A. F.; Perkins, W. E.; Gullikson, G. W.; Bianchi, R. G.; Kramer, S. W.; Ng, J. S.; Yonan, E. E.; Swenton, L.; Jones, P. H.; Bauer, R. F. *J. Med. Chem.* **1990**, *33*, 2784.

9) de Botton, M. *Bull. Soc. Chim. Fr.* **1976**, 849.

