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 Tetrahydrofurans and Cyclopentanones

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General information:

$^1$H NMR spectra were recorded on 300 MHz VARIAN spectrometer at ambient temperature with CDCl$_3$ as solvent and TMS as internal standard. $^{13}$C NMR were recorded at 75 MHz at ambient temperature with CDCl$_3$ 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 Chiralpac 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 $\text{1a, 2a}$ was assigned by X-ray analysis. Absolute configuration of all the other aldols was assigned analogously to $\text{1a, 2a}$.

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 Merk 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 $\text{1, 1}^\text{, 2, 2}^\text{, 3, 3}^\text{, 13b, 4}^\text{, 13c}^\text{5}$ were prepared by the literature procedures. Aldehyde $\text{13a}$ 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 (20 mL) and ketone donor (5 mL) was added the corresponding aldehyde 1-3 (4.4 mmol) followed by L-proline (0.1 g, 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 Na₂SO₄ 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-(1-(phenylthio)cyclopropyl)butan-2-one (1a) (CIF 501). Reaction time 16h. Yield 86%. White solid, mp 61-62°C. \([\alpha]_{D}^{20} = -8.8 \) (c 1.36, CHCl₃). IR (neat): 3460, 1700 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) 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_¹(minor) = 19.55 min, _t_²(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 C₁₃H₁₆O₂S: 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-(1-(phenylthio)cyclopropyl)pentan-3-one (1b). Reaction time 24h. Yield 51%. Yellow oil. \([\alpha]_D^{20} = -1.21\ (c\ 0.826, \text{CHCl}_3)\). IR (neat): 3460, 1700 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta: 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\(_3\)) \(\delta: 7.43, 12.17, 13.96, 29.26, 36.77, 46.74, 70.52, 125.77, 128.36, 128.72, 136.16, 212.51.\)

HPLC (Daicel chiralpak OD-H column, hexane/i-PrOH = 98:2, flow rate 1mL/min, \(\lambda = 254\ nm\)) \(t_R\) (major) = 13.40 min, \(t_R\) (minor) = 10.95 min. MS m/z: 232 (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 C\(_{14}\)H\(_{18}\)O\(_2\)S: C, 67.17; H, 7.25; S, 12.81. Found: C, 67.28; H, 7.31; S, 12.74.

(R)-1-hydroxy-1-(1-(phenylthio)cyclopropyl)hexan-3-one (1c). Reaction time 48h. Yield 21%. Yellow oil. \([\alpha]_D^{20} = +1.41\ (c\ 1.42, \text{CHCl}_3)\). IR (neat): 3460, 1700 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta: 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\(_3\)) \(\delta: 12.30, 13.64, 14.04, 16.99, 29.29, 45.62, 47.10, 70.62, 125.86, 128.44, 128.81, 136.22, 212.39.\)

HPLC (Daicel chiralpak OD-H, hexane/i-PrOH = 98:2, flow rate 1mL/min, \(\lambda = 254\ nm\)) \(t_R\) (major) = 10.7 min, \(t_R\) (minor) = 8.7 min. MS m/z: 264 (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 C\(_{15}\)H\(_{20}\)O\(_2\)S: C, 68.15; H, 7.62; S, 12.13. Found: C, 68.28; H, 7.51; S, 12.24.

(R)-2-(hydroxy(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\textsuperscript{6a} or benzaldehyde\textsuperscript{6b}) IR (neat): 3440, 1700 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 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, \(J = 2.7\;\text{Hz}\), \(J = 5.7\;\text{Hz}\)), 4.60 (d, 1H, \(J = 0.9\;\text{Hz}\)), 7.12-7.58 (m, 10H).

HPLC (Daicel chiralpak OD-H, hexane/i-PrOH = 98:2, flow rate 1mL/min, \(\lambda = 254\;\text{nm}\)) \(t_{R}\)(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\textsuperscript{+}-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\textsuperscript{+}-18 (21)), 229 (14), 188 (27), 173 (9), 135 (69), 121 (26), 109 (54), 91 (46), 77 (100), 65 (51), 51 (45).

\((\text{R})\)-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\textsubscript{3}). IR (neat): 3460, 1700 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 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, \(J = 17.1\;\text{Hz}\), \(J = 9.9\;\text{Hz}\)), 2.94 (dd, 1H, \(J = 17.1\;\text{Hz}\), \(J = 1.8\;\text{Hz}\)), 3.42 (d, 1H, \(J = 3.9\;\text{Hz}\)), 4.13-4.18 (m, 1H), 7.26-7.47 (m, 5H). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 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, \(\lambda = 254\;\text{nm}\)) \(t_{R}\)(major) = 21.53 min, \(t_{R}\)(minor) = 13.16 min. MS m/z: 232 (M\textsuperscript{+}-18 (6)), 218 (3), 189 (50), 161 (22), 123 (30), 109 (100), 95 (40), 79 (40), 65 (60), 51 (46). Anal. Calcd. for C\textsubscript{14}H\textsubscript{18}O\textsubscript{2}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.

\((\text{R})\)-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\textsubscript{3}). IR (neat): 3480, 1700 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 1.07 (t, 3H, \(J = 7.5\;\text{Hz}\)), 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$_3$) $\delta$: 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, $\lambda$ = 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 C$_{15}$H$_{20}$O$_2$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$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: 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, $\lambda$ = 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 C$_{15}$H$_{20}$O$_2$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$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: 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, $\lambda$ = 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_{2}S: 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 Nichel in EtOH (10mL) under hydrogen atmosphere. After 6h the mixture was filtered over Celite and the solvent evaporated to afforded 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).

![Chemical Structure](image)

Reaction time 6h. Yellow oil. Yield 80%. [α]_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). 13C 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_{7}H_{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: (1R,3R)-(syn)-4 and (1R,3S)-(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.
(1R,3R)-(syn)-4. Major diastereomer: Colourless oil. [α]D18 = +162.2 (c 1.196, CHCl3). IR (neat): 3460 cm⁻¹. ¹H NMR (300 MHz, CDCl3) 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). ¹³C NMR (75 MHz, CDCl3) 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 C₁₃H₁₈O₂S: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.59; H, 7.54; S, 13.44.

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

To a solution of (1R,3S)-(anti)-4 (228mg, 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. The organic layer was washed with saturated aqueous NaHCO₃ solution, dried (Na₂SO₄), 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 (1S,3S,5R)-6 and (1R,3S,5S)-6.
Spectral data worked out from a 86:14 mixture of two inseparable diastereoisomers \((1S,3S,5R)\)-6 and \((1R,3S,5S)\)-6. Yield 72%. Colourless oil. Major isomer \((1S,3S,5R)\)-6: \(^1\)H 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\(_3\)) \(\delta\): 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 \((1R,3S,5S)\)-6: \(^1\)H 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\(_3\)) \(\delta\): 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 \((1S,3R,5R)\)-8 and \((1R,3R,5S)\)-8 in 60:40 ratio and 66% of yield.

The relative stereochemistry of cis-fused cyclobutyl tetrahydrofurans: \((1S,3S,5R)\)-6; \((1R,3S,5S)\)-6 and \((1S,3R,5R)\)-8; \((1R,3R,5S)\)-8 was assigned on the basis of X-ray crystal structure analysis of sulfones \((1S*3R*5R*)\)-16 and \((1R*3R*5S*)\)-16 obtained analytically purities after oxidation of compounds \((1S*3R*5R*)\)-8 and \((1R*3R*5S*)\)-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: (1R,3S)-(syn)-9 and (1R,3S)-(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.

\[ (1R,3R)-(syn)-9 \]

Major diastereomer: Colourless oil. \([\alpha]_D^{21} = +14.93\) (c 0.402, CHCl₃). IR (neat): 3460 cm⁻¹. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\): 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). \(^13\)C NMR (75 MHz, CDCl₃) \(\delta\): 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.

\[ (1R,3R)-(anti)-9 \]

Minor diastereomer: Colourless oil. \([\alpha]_D^{21} = +43.21\) (c 0.972, CHCl₃). IR (neat): 3460 cm⁻¹. \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\): 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). \(^13\)C NMR (75 MHz, CDCl₃) \(\delta\): 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.

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 (6R,8S)-(syn)-10 or (6S,8S)-(anti)-10.

\[
\begin{align*}
(6R,8S)-(syn)-10. & \text{ Yield 86%. Colourless oil. } [\alpha]_D^{26} = +4.8 \text{ (c 0.416, CHCl}_3). \text{ } ^1H \text{ NMR (300 MHz, CDCl}_3) \delta: 1.29 \text{ (d, 3H, } J = 6.3 \text{ Hz, 1.58-1.71 (m, 2H), 1.72-1.85 (m, 1H), 2.02-2.10 (m, 1H), 2.19-2.33 (m, 2H), 2.46-2.55 (m, 2H), 3.65 (t, 1H, } J = 7.2 \text{ Hz, 4.04-4.15 (m, 1H), 7.18-7.44 (m, 5H).} \text{ } ^13C \text{ NMR (75 MHz, CDCl}_3) \delta: 12.87, 22.06, 31.66, 34.74, 40.42, 53.61, 72.55, 85.92, 126.50, 128.94, 130.56, 136.08. \text{ MS m}/z: 234 \text{ (M}^+ \text{ (48)), 206 (76), 173 (100), 145 (18), 131 (20), 109 (42), 91 (34), 77 (18).} \text{ Anal. Calcd. for C}_{14}H_{18}OS: \text{ C, 71.75; H, 7.74; S, 13.68. Found: C, 71.71; H, 7.77; S, 13.69.} \\
(6S,8S)-(anti)-10. & \text{ Yield 70%. Colourless oil. } [\alpha]_D^{27} = +78 \text{ (c 0.474, CHCl}_3). \text{ } ^1H \text{ NMR (300 MHz, CDCl}_3) \delta: 1.23 \text{ (d, 3H, } J = 6.0 \text{ Hz, 1.56-1.81 (m, 2H), 1.88-1.97 (m, 1H), 2.00-2.14 (m, 2H), 2.15-2.30 (m, 2H), 2.47-2.55 (m, 1H), 3.72 (dd, 1H, } J = 6.6 \text{ Hz, } J = 3.9 \text{ Hz, 4.23-4.30 (m, 1H), 7.19-7.44 (m, 5H).} \text{ } ^13C \text{ NMR (75 MHz, CDCl}_3) \delta: 12.75, 22.07, 31.17, 36.82, 39.94, 54.13, 72.86, 85.77, 126.48, 128.94, 130.67, 136.05. \text{ MS m}/z: 234 \text{ (M}^+ \text{ (32), 206 (66), 173 (100), 131 (14), 109 (36), 91 (34), 65 (19), 43 (32).} \text{ Anal. Calcd. for C}_{14}H_{18}OS: \text{ C, 71.75; H, 7.74; S, 13.68. Found: C, 71.70; H, 7.78; S, 13.69.}
\end{align*}
\]

To a solution of (6R,8S)-(syn)-10 (0.44g, 1.74 mmol) in 30mL of CH$_2$Cl$_2$ 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 (Na$_2$SO$_4$) 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, CHCl$_3$). IR (neat): 3460 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 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 C$_8$H$_{14}$O$_2$: 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 CH$_2$Cl$_2$ (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, CHCl$_3$). IR (neat): 3460, 1700 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 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 C$_8$H$_{14}$O$_2$: 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$_2$SO$_4$ 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.

\[
\begin{align*}
& a: n = 1 \\
& b: n = 2 \\
& c: n = 3
\end{align*}
\]

\[
\begin{align*}
\text{Acetone} & \\
\text{L-Proline, 20 mol\%} & \\
\text{DMSO, r.t.} & \\
\end{align*}
\]

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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$_2$Cl$_2$, m-chloroperbenzoic acid (96mg, 0.56 mmol) was added portionwise. After stirring for 16 h, the solution was diluted with CH$_2$Cl$_2$ and washed with a saturated NaHCO$_3$ solution. The organic layer was dried over anhydrous Na$_2$SO$_4$ 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. \((IS*3R*5R*)-16\) Major diastereoisomer: White solid, mp 70-71°C. IR (nujol): 1350, 1130 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): 1.06-1.21 (m, 1H), 1.20 (d, 1H), 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 C\(_{13}\)H\(_{16}\)O\(_3\)S: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.81; H, 6.45; S, 12.72.

\((IR*3R*5S*)-16\) Minor diastereoisomer: White solid, mp 68-70°C. IR (nujol): 1350, 1140 cm\(^{-1}\). \(^1\)H 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 C\(_{13}\)H\(_{16}\)O\(_3\)S: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.85; H, 6.45; S, 12.75.

References
7) Compounds \((IS*3R*5R*)-8\) and \((IR*3R*5S*)-8\) were prepared starting from racemic \((IR*3R*)-(\text{syn})-4\) according to the procedure described for the synthesis of \((IS, 3R, 5R)-8\) and \((IR, 3R, 5S)-8\).
