Concise enantioselective construction of bridged azatricyclic framework via domino semipinacol-Schmidt reaction

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**General Considerations:** All the solvents were distilled prior to use. Dry solvents were prepared according to the standard procedures. Reactions requiring inert atmosphere were carried out under argon atmosphere. Infrared (IR) spectra were recorded on a Shimadzu IR 470 spectrometer (or) THERMO NICOLET 6700 FT-IR spectrometer. $^1$H NMR spectra were measured on Bruker ADVANCE 400 MHz spectrometers. Chemical shifts were reported in ppm using tetramethylsilane as an internal standard. $^{13}$C NMR spectra were recorded on Bruker 100 MHz spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. The high-resolution mass spectra (HRMS) were performed on Micromass Q-TOF micro mass spectrometer equipped with a Harvard apparatus syringe pump. X-ray crystallographic data were recorded using Bruker-AXS Kappa CCD-Diffractometer with graphite-monochromator Cu K$_{α}$ radiation ($λ$=1.5418 Å). The structures were solved by direct methods (SHELXS-97) and refined by full-matrix least squares techniques against $F^2$ (SHELXL-97). Hydrogen atoms were inserted from geometry consideration using the HFIX option of the program. For thin layer chromatography (TLC) analysis throughout this work, E-merck precoated TLC plates (silica gel 60 F254 grade, 0.25 mm) were used. Acme (India) silica gel (100-200 mesh) was used for column chromatography. The enantiomeric excess was determined by chiral HPLC analyses using DAICEL’s CHIRALPAK ASH column with hexanes/isopropyl alcohol mixtures as an eluent.

(S)-dimethyl 2-(3-oxocyclohexyl)malonate (−)−9a: To a stirred solution of (S)-ALB complex (in dry THF 0.1 M, 5 mL, 0.5 mmol) and molecular sieves 4 Å (1 g) in dry THF (5 mL) at 0 °C, dimethylmalonate (5.9 mL, 52.08 mmol) and cyclohexenone (5.02 mL, 52.08 mmol) were added successively. The resultant suspension was allowed to warm to room temperature and stirred for 72 h. The reaction mixture was diluted with EtOAc (100 mL), filtered over Celite pad to remove the molecular sieves and the filtrate was washed with 1 N HCl (2 × 25 mL). The organic layer was washed with saturated NaHCO$_3$ solution (2 × 50 mL) water (2 × 50 mL) brine solution (2 × 50 mL) dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography over silicagel using 10-20% EtOAc in hexane as solvent gradient to afford optically active pure keto-diester (−)−9a (11.28 g, 95% yield) as a light yellow oil; {99% ee; $[α]_{D}^{25}−3.4$ (c 0.10, CHCl$_3$); lit.$^1$ for $(R)$ enantiomer (+)−9a $[α]_{D}^{24}+3.99$ (c 2.10, CHCl$_3$)};

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The ee was determined by CHIRALPAK ASH (eluent: hexanes/2-propanol 95:5, flow: 0.5 mL/min, retention times [min]: t_{minor} = 46.2, t_{major} = 48.0); the spectral data and analytical data of (−)-9a were found to be in the complete agreement with the literature values; IR (neat) 2954, 1731, 1711, 1435, 1262, cm⁻¹; 

1H NMR (400 MHz, CDCl₃) δ 3.72 (s, 3 H), 3.71 (s, 3 H), 3.31 (d, J = 8.0 Hz, 1 H), 2.56–2.45 (m, 1 H), 2.42–2.35 (m, 2 H), 2.26–2.19 (m, 2 H), 2.09–2.02 (m, 1 H), 1.92–1.89 (m, 1 H), 1.65 (ddt, J = 12.8, 12.8, 3.6 Hz, 1 H), 1.47 (dddd, J = 12.8, 12.8, 12.8, 3.6 Hz, 1 H); 13C NMR (100 MHz, CDCl₃) δ 209.5, 168.3, 168.2, 56.6, 52.6, 45.1, 40.9, 38.1, 28.8, 24.5; HRMS (ESI) m/z calcd for C₁₁H₁₆O₅Na (M⁺ + Na) 251.0895 found 251.0890.

Conditions:

Column: CHIRALPAK ASH, Eluent: Hex/IPA = 95/5; Flow rate: 0.5 ml/min; Wavelength: 214 nm
**Dimethyl 2-(3-oxocyclopentyl)malonate (±)-9b:** Under similar reaction conditions pure keto-diester (±)-9b was obtained (7.2 g, 92% yield) as a light yellow oil from cyclopentenone on 36.5 mmol scale; the spectral data and analytical information of compound (±)-9b were found to be in the complete agreement with the literature values\(^1\); IR (neat) 2956, 1728, 1435, 1265 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.76 (s, 3 H), 3.73 (s, 3 H), 3.37 (d, \(J = 9.4\) Hz, 1 H), 2.86–2.84 (m, 1 H), 2.50 (dd, \(J = 18.4, 7.5\) Hz, 1 H), 2.34–2.30 (m, 1 H), 2.25–2.19 (m, 2 H), 2.00 (dd, \(J = 18.0, 10.8\) Hz, 1 H), 1.69–1.61 (m, 1 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 217.7, 168.6, 168.5, 56.2, 52.8, 42.9, 38.3, 36.5, 27.5; HRMS (ESI) \(m/z\) calcld for C\(_{10}\)H\(_{15}\)O\(_5\) (M\(^+\) + H) 215.0919 found 215.0915.

**(+)-9c:** To a stirred solution of (S)-ALB complex (in dry THF 0.1M, 5.7 mL, 0.5 mmol) and molecular sieves 4 Å (1 g) in dry THF (5.7 mL) at 0 °C dimethylmalonate (5.2 mL, 45.4 mmol) and cycloheptenone (5.0 mL, 45.4 mmol) were added successively. The resultant suspension was allowed to warm to room temperature and stirred for 72 h. The reaction mixture was diluted with EtOAc (100 mL) filtered over Celite pad to remove the molecular sieves and the filtrate was washed with 1 N HCl (2 × 25 mL). The organic layer was washed with saturated NaHCO\(_3\) solution (2 × 50 mL) water (2 × 50 mL) brine solution (50 mL) dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using 10-20% EtOAc in hexane as solvent gradient to afford optically active pure keto-diester (–)-9c (10.5 g, 95% yield) as a light yellow oil; \(\{99\%\) ee; \([\alpha]^{25}_D -41.0\) (c 1.0, CHCl\(_3\)); lit.\(^1\) for (R) enantiomer (+)-9c \([\alpha]^{21}_D +49.7\) (c 1.76, CHCl\(_3\)); \(\{\) ee was determined by CHIRALPAK ASH (eluent: hexanes/2-propanol 95:5, flow: 0.5 mL/min, retention times [min]: \(t_{\text{minor}} = 29.4, t_{\text{major}} = 33.1\); the spectral data and analytical data of (–)-9c were found to be in the complete agreement with the literature values\(^1\); IR (neat) 2931, 2858, 1730, 1697, 1434 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.72 (s, 6 H), 3.33 (d, \(J = 6.8\) Hz, 1 H), 2.57–2.45 (m, 5 H), 1.94–1.82 (m, 3 H), 1.58–1.46 (m, 2 H), 1.44–1.38 (m, 1 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 212.5, 168.7, 168.6, 57.26, 52.67, 47.3, 43.7, 35.8, 34.2, 28.8, 24.4; HRMS (ESI) \(m/z\) calcld for C\(_{12}\)H\(_{19}\)O\(_5\) (M\(^+\) + H) 243.1232, found 243.1227.
Conditions:

Column: CHIRALPAK ASH, Eluent: Hex/IPA = 95/5; Flow rate: 0.5ml/min; Wavelength: 214 nm
(S)-dimethyl 2-(1,4-dioxaspiro[4.5]decan-7-yl)malonate ((–)-7a.1): To a stirred solution of keto diester (–)-9a (5 g, 21.92 mmol) in toluene (70 mL) at room temperature was added ethylene glycol (3.67 mL, 65.78 mmol) and para-toluenesulphonic acid (431 mg, 2.26 mmol). The resulting mixture was refluxed with a Dean Stark apparatus for 18 h, cooled the reaction mixture to the room temperature and was concentrated under reduced pressure, diluted the resultant residue with EtOAc (70 mL) and water (70 mL). Layers were separated and the reaction mixture was extracted with EtOAc (2 × 50 mL). Combined organic layer was washed with saturated NaHCO₃ solution (2 × 50 mL) water (2 × 50 mL) and brine solution (1 × 50 mL) dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography over silicagel using 10-20% EtOAc in hexane as solvent gradient to afford optically active pure ketal diester (–)-7a.1 (5.9 g, 99% yield) as a colorless liquid; [α]D₂₅ –2.85 (c 0.14, CHCl₃); lit.² for (R) enantiomer (+)-7a.1 [α]D₂₀ +2.80 (c 0.14, CHCl₃); the spectral data and analytical information of compound (–)-7a.1 were found to be in the complete agreement with the literature values²; IR (neat) 2949, 2886, 1731, 1434, 1251, 1145, 1071 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.95–3.89 (m, 4 H), 3.71 (s, 6 H), 3.25 (d, J = 8.0 Hz, 1 H), 2.43–2.38 (m, 1 H), 1.80–1.65 (m, 4 H), 1.61–1.50 (m, 1 H), 1.42 (dt, J = 13.2, 4.8 Hz, 1 H), 1.31 (t, J = 12.4 Hz, 1 H), 1.04 (dq, J = 12.8, 3.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) 169.0, 168.9, 108.7, 64.4, 64.3, 57.2, 52.4, 38.8, 35.8, 34.8, 29.2, 22.8; HRMS (ESI) m/z calcd for C₁₃H₂₀O₆Na (M⁺ + Na) 295.1158, found 295.1151.

Dimethyl 2-(1,4-dioxaspiro[4.4]nonan-7-yl)malonate ((±)-7b.1): Under similar reaction conditions pure ketal-diester (±)-7b.1 (5.9 g, 98% yield) was obtained as a colorless oil, from keto-diester (±)-9b on 23.5 mmol scale; IR (neat) 2956, 1731, 1434, 1251, 1145, 1071 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.89–3.86 (m, 4 H), 3.73 (s, 6 H), 3.30 (d, J = 10.1 Hz, 1 H), 2.71–2.65 (m, 1 H), 2.09–2.04 (m, 1 H), 1.95–1.87 (m 2 H), 1.81–1.79 (m, 1 H), 1.65 (bs, 1 H), 1.59–1.53 (m, 1 H), 1.44–1.38 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) 169.0, 169.1, 108.7, 64.4, 64.3, 57.2, 52.4, 38.8, 35.8, 34.8, 29.2, 22.8; HRMS (ESI) m/z calcd for C₁₂H₁₈O₆Na (M⁺ + Na) 281.1001, found 281.1007.

(S)-dimethyl 2-(1,4-dioxaspiro[4.6]undecan-7-yl)malonate ((+) 7c.1): Under similar reaction conditions pure ketal-diester (+)-7c.1 (2.33 g, 99% yield) was obtained as a colorless oil, from keto-diester (–)-9c on 8.26 mmol scale; [α]D₂₃ +0.8 (c = 1.0, CHCl₃); IR (neat) 2949, 2886, 1731, 1434 cm⁻¹;

(S)-Methyl 2-(1, 4-dioxaspiro[4.5] decan-7-yl) acetate ((–)-7a): To the ketal diester ((–)-7a.1 (5 g, 18.38 mmol) in DMSO (36 mL) was added NaCl (1.61 g, 27.50 mmol) and the reaction mixture was stirred at 145 °C for 3 h. The reaction mixture was cooled to room temperature and poured into ice cold water (150 mL). The resultant mixture was extracted with diethyl ether (3 × 50 mL) the combined organic layer was washed with water (2 × 50 mL) brine solution (2 × 50 mL) dried over anhydrous Na2SO4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silicagel using 10-20% EtOAc in hexane as solvent gradient to afford optically active pure ketal monoester (–)-7a (2.59 g, 66% yield) as a colorless oil; [(α)25D –3.39 (c 0.14, CHCl3); lit.2 for (R) enantiomer (+)-7a [α]20D +3.0 (c 0.14, CHCl3)]; the spectral data and analytical information of compound (–)-7a were found to be in the complete agreement with the literature values2; IR (neat) 2934, 2884, 1732, 1435, 1169, 1093, 1067 cm−1; 1H NMR (400 MHz, CDCl3) δ 3.91–3.89 (m, 4 H), 3.60 (s, 3 H), 2.22 (d, J = 7.0 Hz, 2 H), 2.16–2.04 (m, 1 H), 1.79–1.68 (m, 4 H), 1.56–1.52 (m, 1 H), 1.44–1.38 (m, 1 H), 1.22 (t, J = 12.4 Hz, 1 H), 0.95 (dq, J = 12.4, 2.8 Hz, 1 H); 13C NMR (100 MHz, CDCl3) δ 173.1, 108.9, 64.4, 64.3, 51.5, 41.3, 41.2, 34.8, 32.8, 31.6, 22.9; HRMS (ESI) m/z calcd for C11H18O4Na (M+ + Na) 237.1103, found 237.1109.

Methyl 2-(1,4-dioxaspiro[4.4]nonan-7-yl)acetate ((±)-7b): Under similar reaction conditions pure ketal-monoester ((±)-7b (2.7 g, 63% yield) was obtained as a colorless oil, from Ketal-diester ((±)-7b.1 on 21.4 mmol scale; IR (neat) 2953, 1731, 1437, 1269 cm−1; 1H NMR (400 MHz, CDCl3) δ 3.89–3.81 (m, 4 H), 3.62 (s, 3 H), 2.41–2.32 (m, 3 H), 2.04 (dd, J = 13.6, 7.2 Hz, 1 H), 1.93–1.85 (m, 2 H), 1.80–1.72 (m, 1 H), 1.44 (dd, J = 13.2, 8.4 Hz, 1 H), 1.35–1.28 (m, 1 H); 13C NMR (100 MHz, CDCl3) δ 173.2, 117.6, 64.3, 64.2, 51.5, 42.4, 40.0, 35.9, 34.0, 30.1; HRMS (ESI) m/z calcd for C10H17O4 (M+ + H) 201.1127, found 201.1124.
(S)-methyl 2-(1,4-dioxaspiro[4.6]undecan-7-yl)acetate ((−)-7c): Under similar reaction conditions pure ketal-monoester (−)-7c (0.52 g, 65% yield) was obtained as a colorless oil, from Ketal-diesterm (+)-7c.1 on 3.77 mmol scale; ([α]_{D}^{23} -10.0 (c 1.0, CHCl_3); IR (neat) 2924, 1732, 1436, 1259 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 3.90–3.80 (m, 4 H), 3.64 (s, 3 H), 2.22 (d, J = 7.2, Hz, 2 H), 2.17–2.10 (m, 1 H) 1.84–1.57 (m, 7 H), 1.54–1.41 (m, 2 H), 1.29–1.23 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 173.2, 111.8, 64.2, 64.0, 51.5, 44.0, 42.6, 38.6, 35.6, 31.1, 27.8, 22.5; HRMS (ESI) m/z calcd for C\(_{12}\)H\(_{21}\)O\(_4\) (M\(^{+}\) + H) 229.1440, found 229.1439.

(R)-2-(1,4-dioxaspiro[4.5]decan-7-yl) ethanol ((−)-6a.1): To a stirred suspension of LiAlH\(_4\) (266 mg, 7.0 mmol) in dry THF (15 mL) at 0 °C was added methyl ester (−)-7a (1.5 g, 7.0 mmol) in dry THF (20 mL) dropwise and the resultant mixture stirred for 4 h at room temperature. The excess LiAlH\(_4\) was quenched with moist Na\(_2\)SO\(_4\) at 0 °C and the white precipitate obtained was filtered through Celite pad, the filter cake was washed with EtOAc (3 × 10 mL), the combined organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by column chromatography over silicagel using 50-60% EtOAc in hexane as solvent gradient to afford optically active pure ketal alcohol (−)-6a.1 (1.2 g, 94%) as a colorless oil; ([α]_{D}^{25} -7.29 (c 0.06, CHCl\(_3\)); lit.\(^{2}\) for (R) enantiomer (+)-6a.1 [α]_{D}^{20} +8.6 (c 0.06, CHCl\(_3\)); the spectral data and analytical information of compound (−)-6a were found to be in the complete agreement with the literature values\(^{2}\); IR (neat) 3450, 2935, 1459, 1074, 1046 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 3.92–3.88 (m, 4 H), 3.65 (t, J = 6.4 Hz, 2 H), 1.76–1.69 (m, 5 H), 1.53–1.35 (m, 4 H), 1.26–1.15 (m, 2 H), 0.92–0.83 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 109.3, 64.4, 64.2, 60.6, 41.7, 39.8, 34.8, 32.3, 31.9, 23.2; HRMS (ESI) m/z calcd for C\(_{10}\)H\(_{18}\)O\(_3\)Na (M\(^{+}\) + Na) 209.1154, found 209.1153.

2-(1,4-Dioxaspiro[4.4]nonan-7-yl)ethanol ((±)-6b.1): Under similar reaction conditions pure ketal-alcohol (±)-6b.1 (0.47 g, 94% yield) was obtained as a colorless oil, from Ketal-monoester 7b on 2.90 mmol scale; IR (neat) 3395, 2930, 1459 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ 3.90–3.84 (m, 4 H), 3.64 (t, J
= 6.8 Hz, 2 H), 2.14–1.99 (m, 2 H), 1.94–1.84 (m, 2 H), 1.80–1.74 (m, 1 H), 1.67–1.60 (m, 3 H), 1.45 (dd, \( J = 22.0, 9.6 \) Hz, 1 H), 1.37–1.27 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 117.9, 64.4, 64.2, 61.9, 42.9, 38.9, 36.1, 34.5, 30.5; HRMS (ESI) \( m/z \) caled for C\(_9\)H\(_{16}\)O\(_3\)Na (M\(^+\) + Na) 195.0997, found 195.0997.

(R)-2-(1,4-dioxaspiro[4.6]undecan-7-yl)ethanol ((–)-6c.1): Under similar reaction conditions pure ketal-alcohol (–)-6c.1 (0.49 g, 92% yield) was obtained as a colorless oil, from Ketal-monoester (–)-7c on 2.67 mmol scale; \([\alpha]^{23}_{D} -12.2 \) (c 1.0, CHCl\(_3\)); IR (neat) 3391, 2937, 1457 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.91–3.79 (m, 4 H), 3.63–3.59 (m, 2 H), 2.33 (bs, 1 H), 1.81–1.69 (m, 6 H), 1.63–1.53 (m, 2 H), 1.50–1.37 (m, 4 H), 1.24–1.19 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 112.3, 64.1, 64.0, 60.5, 44.2, 40.8, 38.6, 36.2, 30.2, 28.4, 22.5; HRMS (ESI) \( m/z \) caled for C\(_{11}\)H\(_{20}\)O\(_3\)Na (M\(^+\) + Na) 223.1310, found 223.1313.

(R)-7-(2-azidoethyl)-1,4-dioxaspiro[4.5]decane ((–)-6a.2): To a stirred solution of ketal alcohol (–)-6a.1 (1 g, 5.37 mmol) in DCM (28 mL) at 0 °C was added triethylamine (1.5 mL, 10.74 mmol) followed by methanesulfonyl chloride (0.5 mL, 6.45 mmol). The reaction mixture was stirred for 30 min, and diluted with DCM (25 mL). Organic layer was washed with water (2 \( \times \) 10 mL) brine solution (10 mL) dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure to afford crude mesylate as pale yellow color liquid. The crude mesylate (1.42 g, 5.37 mmol) was re-dissolved in DMF (16 mL) and treated with NaN\(_3\) (700 mg, 10.75 mmol). The reaction mixture was stirred at 55 °C for 3.5 h, after cooling to room temperature, poured into ice-cold water (30 mL) extracted with diethyl ether (2 \( \times \) 20 mL). Combined organic extracts were washed with water (2 \( \times \) 10 mL) brine solution (10 mL) dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by column chromatography over silicagel using 10-20% EtOAc in hexane as solvent gradient to afford optically active pure ketal azide (–)-6a.2 (0.94 g, 83% yield) as a colorless oil; \([\alpha]^{27}_{D} -14.63 \) (c 0.06, CHCl\(_3\)); IR (neat) 2933, 2089, 1447, 1260, 1155, 1072 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.95–3.92 (m, 4 H), 3.30 (t, \( J = 7.2 \) Hz, 2 H), 1.78–1.68 (m, 5 H), 1.59–1.48 (m, 3 H), 1.45–1.39 (m, 1 H), 1.21 (t, \( J = 12.4 \) Hz, 1 H), 0.95–0.85 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 109.1, 64.4, 64.3, 49.3, 41.5, 35.7, 34.9, 33.2, 31.6, 23.1; HRMS (ESI) \( m/z \) caled for C\(_{10}\)H\(_{18}\)NO\(_2\) (M\(^+\) + H–N\(_2\)) 184.1338, found 184.1337.
7-(2-azidoethyl)-1,4-dioxaspiro[4.4]nonane ((±)-6b.2): Under similar reaction conditions pure ketal-azide (±)-6b.2 (0.32 g, 82% yield) was obtained as a colorless oil, from ketal-alcohol (±)-6b.1 on 2.0 mmol scale; IR (neat) 2927, 2863, 2086, 1459, 1274 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.92–3.86 (m, 4 H), 3.26 (t, J = 7.2 Hz, 2 H), 2.11–2.00 (m, 2 H), 1.95–1.84 (m, 2 H), 1.82–1.74 (m, 1 H), 1.65 (q, J = 7.2 Hz, 2 H), 1.48–1.38 (m, 1 H), 1.36–1.24 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 117.7, 64.4, 64.2, 50.3, 42.6, 36.0, 35.1, 34.8, 30.2; HRMS (ESI) m/z calcld for C₉H₁₅N₃O₂Na (M⁺ + Na) 220.1062, found 220.1064.

(R)-7-(2-azidoethyl)-1,4-dioxaspiro[4.6]undecane ((–)-6c.2): Under similar reaction conditions pure ketal-azide (–)-6c.2 (0.49 g, 84% yield) was obtained as a colorless oil, from ketal-alcohol (–)-6c.1 on 2.6 mmol scale; [α]₂₃D –10.0 (c 1.0, CHCl₃); IR (neat) 2928, 2879, 2888, 1451, 1259 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.92–3.80 (m, 4 H), 3.26 (t, J = 7.2 Hz, 2 H), 1.82–1.69 (m, 7 H), 1.62–1.54 (m, 1 H), 1.53–1.43 (m, 4 H), 1.25–1.18 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 111.9, 64.2, 64.0, 49.5, 44.3, 38.6, 36.9, 35.5, 31.3, 28.0, 22.5; HRMS (ESI) m/z calcld for C₁₁H₂₀NO₂ (M⁺ + H – N₂) 198.1494, found 198.1495.

(R)-3-(2-azidoethyl)cyclohexanone ((–)-6a): To a stirred solution of ketal-azide (–)-6a.2 (1.38 g, 6.5 mmol) in acetone-H₂O (18 mL, 3:1) at room temperature was added pyridinium para-toluenesulphonic acid (88 mg, 0.327 mmol) and the reaction mixture was refluxed for 17 h. The resultant mixture was cooled to room temperature, acetone was removed under reduced pressure and the mixture was extracted with EtOAc (2 × 15 mL), washed with water (2 × 15 mL) brine solution (15 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography over silicagel using 20-30% EtOAc in hexane as solvent gradient to afford optically active pure azido-ketone (–)-6a (0.69 g, 64% yield) as a colorless oil; [α]₂₈D –29.93 (c 0.06, CHCl₃); IR (neat) 2929, 2091, 1708, 1447, 1226, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.32 (t, J = 6.8 Hz, 2 H), 2.45–2.35 (m, 2 H), 2.30–2.21 (m, 1 H), 2.08–2.01 (m, 2 H), 1.96–1.90 (m, 2 H), 1.69–1.56 (m, 3 H), 1.41–1.35 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 210.9, 48.9, 47.8, 41.4, 36.4, 35.3, 31.1, 25.1; HRMS (ESI) m/z calcld for C₈H₁₃N₃ONa (M⁺ + Na) 190.0956, found 190.0961.
3-(2-azidoethyl)cyclopentanone ((±)-6b): Under similar reaction conditions pure azido-ketone (±)-6b (0.13 g, 62% yield) was obtained as a colorless oil, from ketal-azide (±)-6b on 1.4 mmol scale; IR (neat) 2955, 2093, 1735, 1229 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.29 (dt, J = 6.8, 1.6 Hz, 2 H), 2.35 (dd, J = 10.4, 7.6 Hz, 1 H), 2.30–2.10 (m, 4 H), 1.80–1.61 (m, 3 H), 1.53–1.42 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 218.5, 49.9, 44.8, 38.4, 34.7, 34.6, 29.4; HRMS (ESI) m/z calcd for C₇H₁₂NO (M⁺ + H – N₂) 126.0919, found 126.0912.

(R)-3-(2-azidoethyl)cycloheptanone ((–)-6c): Under similar reaction conditions pure azido-ketone (–)-6c (0.25 g, 64% yield) was obtained as a colorless oil, from ketal-azide (–)-6c on 2.17 mmol scale; [α]²³D – 37.7 (c 1.0, CHCl₃); IR (neat) 2926, 2859, 2094, 1696, 1264 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.32 (dt, J = 6.8, 2.4 Hz, 2 H), 2.51–2.46 (m, 3 H), 2.42–2.36 (m, 1 H), 1.90–1.83 (m, 4 H), 1.64–1.54 (m, 3 H), 1.50–1.43 (m, 1 H), 1.35–1.25 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 213.6, 49.4, 49.1, 43.9, 36.5, 35.7, 33.2, 28.3, 24.3; HRMS (ESI) m/z calcd for C₉H₁₆N₃O (M⁺ + H) 182.1293, found 182.1293.

Oxaspiropentane-azide ((±)-5a): To a stirred solution of azido-ketone (±)-6a (170 mg, 1.017 mmol) and diphenycyclopropyl sulphoniumtetrafluoroborate (431 mg, 1.372 mmol) in dry DMSO (5mL) at 0 °C, dry powdered KOH (114 mg, 2.034 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, diluted the reaction mixture with hexane (15 mL). Layers were separated and the DMSO layer was extracted with hexane (3 × 15 mL), combined hexane layer was washed with saturated NaHCO₃ solution (2 × 10 mL) followed by water (5 mL) and brine solution (5 mL) dried the organic layer over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude oxaspiropentane-azide (±)-5a (396 mg) as a single diastereomer (by NMR) as a light yellow oil; IR (neat) 2932, 2099, 1580, 1476, 1264, 1074, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.05 (q, J = 7.2 Hz, 4 H), 3.95–3.91 (m, 3 H), 3.74–3.68 (m, 3 H), 2.35–2.32 (m, 2 H), 2.18–2.14 (m, 2 H), 1.16 (t, J = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 65.6, 63.6, 49.3, 38.9, 35.6, 33.0, 32.4, 31.9, 23.1, 2.35, 2.27; HRMS (ESI) m/z calcd for C₁₁H₁₇N₃ONa (M⁺ + Na) 230.1269, found 230.1269.
Oxaspiropentane-azide ((±)-5b): Under similar reaction conditions crude oxaspiropentane-azide (±)-5b (422 mg) was obtained as a mixture of two diastereomers (syn- & anti- 1:1 by $^{13}$C NMR) as a light yellow oil, from azido-ketone (±)-6b on 1.11 mmol scale; IR (neat) 2927, 2094, 1579, 1474, 1438, 1067 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.28 (q, $J$ = 6.6 Hz, 2 H), 2.07–1.90 (m, 6 H), 1.74–1.54 (m, 5 H), 1.30–1.20 (m, 1 H), 1.06–1.04 (m, 3 H), 0.89–0.80 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 72.0, 61.9, 50.4, 39.1, 38.1, 36.8, 36.5, 34.48, 34.42, 31.8, 31.6, 31.3, 31.2, 8.6, 3.5, 3.3, 3.1; HRMS (ESI) m/z calcd for C$_{10}$H$_{15}$N$_3$O (M$^+$) 193.1215, found 193.1219.

Oxaspiropentane-azide ((±)-5c): Under similar reaction conditions crude oxaspiropentane-azide (±)-5c (410 mg) was obtained as a mixture of two diastereomers (syn- & anti- 5:1 by $^{13}$C NMR) as a light yellow oil, from azido-ketone (±)-6c on 1.0 mmol scale; IR (neat) 2928, 2093, 1579, 1474, 1438 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.22 (t, $J$ = 7.2 Hz, 2 H), 1.90–1.89 (m, 2 H), 1.88–1.60 (m, 4 H), 1.51–1.45 (m, 2 H), 1.44–1.18 (m, 4 H), 1.14–1.05 (m, 1 H), 0.96–0.89 (m, 2 H), 0.87–0.81 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 66.2, 65.4, 49.5, 41.7, 41.2, 36.7, 35.5, 35.4, 35.2, 35.0, 33.6, 33.1, 27.9, 27.5, 24.6, 24.2, 3.4, 3.2, 3.0, 2.6; HRMS (ESI) m/z calcd for C$_{12}$H$_{22}$NO (M$^+$ + NH$_3$ – N$_2$) 196.1699, found 196.1699.

Azatricyclic lactam ((–)4a): To a stirred solution of the crude oxaspiropentane-azide 5a {((396 mg, obtained from spiroannelation of azido-ketone (–)6a (1.01 mmol scale)) in dry CH$_2$Cl$_2$ (10 mL), at −78 °C, was added TiCl$_4$ (1.0 M solution in CH$_2$Cl$_2$, 0.28 mL, 2.53 mmol). The resultant mixture was stirred for 1 h at −78 °C and allowed to warm to room temperature, stirred for 4 h at room temperature, diluted the reaction mixture with saturated aqueous NH$_4$Cl (5 mL) extracted with CH$_2$Cl$_2$ (2 × 15 mL). The combined organic layer was washed with saturated NaHCO$_3$ solution (2 × 5 mL) water (1 × 5 mL) brine solution (1 × 5 mL) dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to give crude compound. The crude product was purified by column chromatography over silicagel using 80-90% EtOAc in hexane as solvent gradient to afford optically active pure azatricyclic lactam (–)4a (142 mg, 78%) as a colorless
oil; [99%ee, $\alpha^{26}_D$ -38.0 ($c$ 1.0, CHCl$_3$); the ee was determined by HPLC on corresponding thiolactam derivative, using CHIRALPAK ASH (eluent: hexanes/2- propanol 95:5, flow: 0.5 mL/min, retention times [min]: $t_{\text{minor}}$ = 38.9, $t_{\text{major}}$ = 40.9); IR (neat) 2920, 2849, 1659, 1488, 1407, 1223, 1118 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.89 (dd, $J$ = 14.0, 8.0 Hz, 1 H), 3.28 (dt, $J$ = 12.8, 6.4 Hz, 1 H), 2.42–2.32 (m, 1 H), 2.25–2.17 (m, 1 H), 2.10 (t, $J$ = 2.4 Hz, 1 H), 1.85–1.77 (m, 1 H), 1.76–1.64 (m, 9 H), 1.48–1.40 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.8, 58.6, 41.5, 39.2, 37.2, 33.9, 29.6, 29.1, 28.6, 28.2, 22.2; HRMS (ESI) $m/z$ calcd for C$_{11}$H$_{18}$NO (M$^+$ + H) 180.1388, found 180.1388.

Conditions:

Column: CHIRALPAK ASH, Eluent: Hex/IPA = 95/5; Flow rate: 0.5ml/min; Wavelength: 214 nm

Azatricyclic lactam ((±)-4b): Under similar cyclization reaction conditions pure lactam (±)-4b (73 mg, 40% yield (80% based on syn- oxaspiropentane-azide intermediate) was obtained as a single diastereomer as a light yellow oil from (±)-5b (422 mg, obtained as a mixture of two diastereomers (syn- & anti- 1:1 by $^{13}$C NMR) from spiroannelation of azido-ketone 6b) on 1.11 mmol scale; IR (neat) 2931,1645, 1415, 1261 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.90 (dd, $J$ = 13.6, 6.4 Hz, 1 H), 2.83 (dt, $J$ = 12.4, 5.6 Hz, 1 H),
2.42–2.38 (m, 1 H), 2.35–2.27 (m, 2 H), 1.94–1.80 (m, 2 H), 1.74–1.62 (m, 1 H), 1.56–1.53 (m, 2 H), 1.52–1.34 (m, 5 H). 13C NMR (100 MHz, CDCl3) δ 172.3, 68.1, 43.9, 35.9, 35.2, 34.5, 30.5, 29.7, 27.1, 26.9; HRMS (ESI) m/z calcd for C10H16NO (M+ + H) 166.1232, found 166.1236.

Azatricyclic lactam (–)-4c: Under similar cyclization reaction conditions, pure lactam (–)-4c (127 mg, 66% yield, (80% based on syn-oxaspiropentane-azide intermediate) was obtained as a single diastereomer as a light yellow oil from 5c (410 mg, obtained as a mixture of two diastereomers (syn- & anti-) 5:1 by 13C NMR) from spiroannelation of azido-ketone (–)-6c on 1.0 mmol scale; [99%ee, [α]23D −32.0 (c 1.0, CHCl3); the ee was determined by HPLC on corresponding thiolactam derivative, using CHIRALPAK ASH (eluent: hexanes/2-propanol 95:5, flow: 0.5 mL/min, retention times [min]: t_major = 33.6, t_minor = 39.8); IR (neat) 2915, 2856, 1663, 1461, 1265 cm−1; 1H NMR (400 MHz, CDCl3) δ 3.94 (ddd, j = 14.0, 5.6, 1.2 Hz, 1 H), 2.98 (ddt, J = 14.8, 3.6, 1.6 Hz, 1 H), 2.39–2.30 (m, 1 H), 2.20–2.12 (m, 2 H), 2.01–1.93 (m, 2 H), 1.84–1.79 (m, 2 H), 1.72–1.61 (m, 3 H), 1.52–1.30 (m, 7 H); 13C NMR (100 MHz, CDCl3) δ 173.4, 61.8, 41.4, 39.6, 38.0, 35.4, 32.0, 31.3, 29.6, 27.7, 26.7, 26.2; HRMS (ESI) m/z calcd for C12H20NO (M+ + H) 194.1545, found 194.1541.
Azatricyclic thiolactam ((±)-10b): To a stirred solution of the azatricyclic lactam (±)-4b (30 mg, 0.18 mmol) in toluene (5 mL) at room temperature was added Lawesson’s reagent (88 mg, 0.2 mmol) and the resultant mixture was refluxed for 30 min. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to give crude product. Purification of the crude compound by column chromatography over silica gel using 10% EtOAc in hexane as an eluent afforded pure thiolactam (±)-10b (31 mg, 94% yield) as a white solid. This compound upon recrystallization from dichloromethane - n-hexane (20:80) gave colorless crystals. m. p. = 127–128 °C; IR (neat) 2927, 1467, 1275 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.67 (dd, J = 14.4, 6.8 Hz, 1 H), 3.15–3.05 (m, 1 H), 3.01–2.97 (m, 2 H), 2.42 (bs, 1 H), 2.05 (t, J = 8.0 Hz, 2 H), 2.00–1.90 (m, 2 H ), 1.87–1.75 (m, 2 H), 1.70–1.62 (m, 2 H), 1.59–1.56 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 196.7, 43.7, 43.2, 40.7, 35.7, 34.2, 29.9, 28.6, 27.3, 1.15; HRMS (ESI) m/z calcd for C₁₀H₁₆NS (M⁺ + H) 182.1003, found 182.1000.

ORTEP diagram of 10b with thermal ellipsoid drawn at 30% probability

Note: The asymmetric unit of this racemic (±) 10b compound has two independent molecules, for the sake of simplicity one of the crystal structures has been omitted in the manuscript.

Crystal data and structure refinement for thiolactam (±)-10b, ellipsoids percentage probability is found to be 30%.

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F(000)       392
Crystal size      0.25 x 0.20 x 0.15 mm
Theta range for data collection   1.94 to 28.30 (°).
Limiting indices     -12<=h<=12, -11<=k<=14, -15<=l<=15
Reflections collected / unique   13277 / 4601 [R(int) = 0.0313]
Completeness to theta = 25.00   98.5 %
Absorption correction    Semi-empirical from equivalents
Max. and min. transmission   0.959 and 0.935
Refinement method     Full-matrix least-squares on F^2
Data / restraints / parameters   4601 / 0 / 217
Goodness-of-fit on F^2    1.041
Final R indices[ I>2sigma(I)]   R1 = 0.0516, wR2 = 0.1482
R indices (all data)    R1 = 0.1030, wR2 = 0.1801
Largest diff. peak and hole 0.271 and -0.231 e.A^-3

Azatricyclic amine ((+)-3a): To a stirred suspension of LiAlH₄ (255 mg, 6.7 mmol) in dry THF (5 mL) at 0 °C was added a solution of azatricyclic lactam (–)-4a (60 mg, 0.33 mmol) in THF (3 mL). The resultant mixture was refluxed for 6 h. The reaction mixture was cooled to room temperature quenched with 15% aqueous NaOH solution at 0 °C. The reaction mixture was then filtered through Celite pad and washed with EtOAc (3 × 5 mL). The combined organic layer was concentrated under reduced pressure to furnish pure compound (+)-3a (52 mg, 94% yield) as a colourless oil; {α}°D +4.2 (c 1.0, CHCl₃); the spectral data was found to be in the complete agreement with the literature values⁵; IR (neat) 2920, 2849, 1488, 1407, 1223, 1118 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.98–2.92 (m, 1 H), 2.89–2.84 (m, 1 H), 2.69–2.56 (m, 2 H), 2.01 (d, J = 2.4 Hz, 1 H), 1.92–1.79 (m, 2 H), 1.68–1.64 (m, 5 H), 1.57–1.31 (m, 7 H), 1.22–1.08 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 57.8, 54.0, 47.7, 40.1, 36.9, 35.5, 31.7, 28.2, 27.2, 21.1, 20.3; HRMS (ESI) m/z calcd for C₁₁H₂₀N (M⁺ + H) 166.1596, found 166.1592.

Azatricyclic amine ((±)-3b): Under similar reaction conditions pure azaquaternary tricyclic amine (±)-3b (50 mg, 92% yield) was obtained as a colourless oil from the azatricyclic lactam (±)-4b on 0.36 mmol scale; IR (neat) 2921, 2851, 1458, 1374 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.90 (dq, J = 11.6, 5.5 Hz, 2 H), 2.26–2.17 (m, 3 H), 1.87–1.78 (m, 1H), 1.77–1.55 (m, 7 H), 1.34–1.30 (m, 3 H), 1.10–1.03 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 68.5, 51.2, 46.1, 43.7, 35.0, 33.4, 31.3, 28.9, 27.8, 20.8; HRMS (ESI) m/z calcd for C₁₀H₁₈N (M⁺ + H) 152.1439, found 152.1437.
Azatricyclic amine ((+)-3c): Under similar reaction conditions pure azaquaternary tricyclic amine (+)-3c (88 mg, 94% yield) was obtained as a colourless oil from the azatricyclic lactam (–)-4c on 0.52 mmol scale; ([α]_23⁰ +6.3 (c 1.0, CHCl₃)); IR (neat) 2922, 2852, 1447, 1263 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.97–2.83 (m, 2 H), 2.78–2.65 (m, 2 H), 2.1 (m, 1 H), 1.94–1.82 (m, 1 H), 1.78–1.40 (m, 14 H), 1.23–1.12 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 61.4, 50.9, 44.4, 43.1, 37.8, 35.1, 34.6, 29.2, 27.6, 27.1, 26.1, 20.8; HRMS (ESI) m/z calcd for C₁₂H₂₂N (M⁺ + H) 180.1752, found 180.1754.

$^{1}$H NMR spectrum of keto-diester (±)-9b
Expanded $^1$H NMR spectrum of keto-diester (±)-9b
13C NMR spectrum of keto-diester (+)9b
Expanded H NMR spectrum of keto-dlister (-)-9c.
$^{13}$C NMR spectrum of keto-diester (−)-9c
Expanded 1H NMR spectrum of ketal-diolster (−)-7a.1
$^{13}$C NMR spectrum of ketal-ester (−)-7a.1
1H NMR spectrum of ketal-diester (±)-7b.1
Expanded $^1$H NMR spectrum of ketal-diester (±)-7b.1
$^{13}$C NMR spectrum of ketal-diester (±)-7b.1
$^1$H NMR spectrum of ketal-diester (+)-7c.1
$^1$H NMR spectrum of ketal-ester (−)-7a
Expanded 1H NMR spectrum of ketol-ester (−)-7a
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$^1$H NMR spectrum of ketal-ester $\pm$-7b
Expanded 1H NMR spectrum of ketol-ester (±)-7b
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Expanded 1H NMR spectrum of ketal-ester (−)-7c
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Expanded $^1$H NMR spectrum of ketal-alcohol $(-)$-6a.1
Expanded 1H NMR spectrum of ketal-alcohol (-)-6b.1
$^{13}$C NMR spectrum of ketal-alcohol (±)-6b.1
$^1$H NMR spectrum of ketal-alcohol (-)-6c.1
Expanded $^1$H NMR spectrum of ketal-alcohol (-)-6c.1
$^13$C NMR spectrum of ketal-alcohol (−)-6c.1
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$^{13}$C NMR spectrum of ketal-azide (±)-6b.2
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Expanded $^1$H NMR spectrum of ketal-azide ($\text{(-)-6c.2}$).
$^{13}$C NMR spectrum of ketal-azole (−)-6c.2
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DEPT spectrum of azatricyclic lactam (-)-4a
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DEPT spectrum of azatricyclic lactam (-)-4c
Expanded $^1$H NMR spectrum of azatricene amine (+) 3c
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$^1$H-$^1$H COSY spectrum of azatricyclic amine (+)-3c