

Access to optically active 3-azido- and 3-aminopiperidine derivatives by enantioselective ring expansion of prolinols

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Table of Contents

| | |
|---|-----------|
| GENERAL EXPERIMENTAL METHODS | 1 |
| PREPARATION OF SUBSTRATES | 2 |
| REARRANGEMENT OF PROLINOLS | 17 |
| STAUDINGER REDUCTION | 28 |

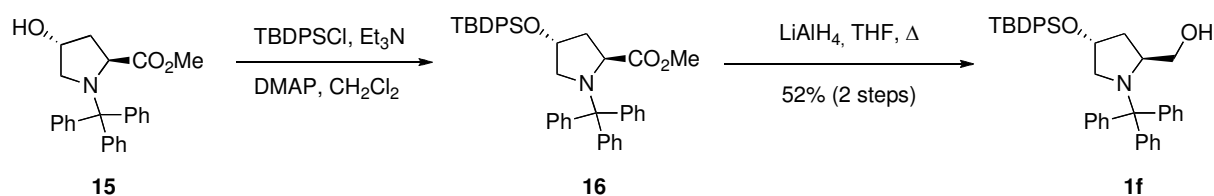
General experimental methods

¹H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane as internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, integration). ¹³C NMR spectra were recorded on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as internal standard (CDCl₃, δ 77.0 ppm or DMSO-d₆, δ 40.4 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH₂, q = CH₃). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column) - 5971 MS (70 eV). Infrared (IR) spectra were recorded on a Bruker TENSOR™ 27 (IRFT), wave-numbers

are indicated in cm^{-1} . THF was distilled from sodium-benzophenone. Et_3N , *N,N*-dimethylformamide (DMF) were distilled from CaH_2 . Reagents obtained from commercial suppliers were used as received. TLC was performed on Merck 60F₂₅₄ silica gel plates and visualized with a UV lamp (254 nm), or by using solutions of $\text{KMnO}_4/\text{K}_2\text{CO}_3/\text{NaOH}$ in water or of *p*-anisaldehyde-sulfuric acid-acetic acid in EtOH followed by heating. Column chromatography was performed with Merck Geduran Si 60 silica gel (40–63 μm). High resolution mass spectra (HRMS) were performed by the centre regional de microanalyse (universite Pierre et Marie Curie Paris VI). Elemental analyses were performed by the Service de Microanalyse of ICSN (Gif sur Yvette, France).

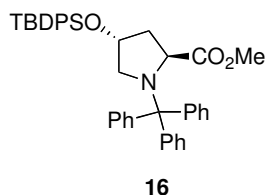
Preparation of substrates

Preparation of compound 1f



(2*S*,4*R*)-methyl 4-(*tert*-butyldiphenylsilyloxy)-*N*,1-tritylpyrrolidine-2-carboxylate (**16**)

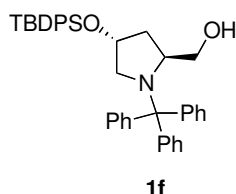
DMAP (0.025 g, 0.21 mmol, 0.1 equiv), Et_3N (0.57 mL, 4.14 mmol, 2 equiv) and TBDPSCl (0.53 mL, 2.48 mmol, 1.2 equiv) were added to a solution of compound **15**ⁱ (800 mg, 2.07 mmol, 1 equiv) in CH_2Cl_2 (15 mL). After 12 h at rt, the reaction mixture was quenched with a saturated aqueous Na_2CO_3 solution until pH=10. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over MgSO_4 and filtered. The solvent was removed in vacuo to afford an oil, which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 90/10 + 0.5% Et_3N) to give **16** (1.30 g, 2.07 mmol, quantitative) as a colorless oil.



$[\alpha]_{\text{D}}^{20} = +5$ (c 2, CHCl_3). IR (neat): 1742, 1448, 1428, 1195, 1191, 909, 821, 736, 699, 611 cm^{-1} . ^1H NMR: δ 7.77–7.13 (m, 25H), 4.49 (m, 1H), 3.81 (m, 1H), 3.49 (m, 1H), 3.43 (s, 3H), 2.67 (ddd, $J = 10.2, 4.9$ and 4.9 Hz, 1H), 1.52 (m, 1H), 1.03–0.91 (m, 10H). ^{13}C NMR: δ 176.1 (s, 1C), 143.8 (s, 3C), 135.6 (d, 4C), 134.0 (s, 1C), 133.8 (s, 1C), 129.7 (d, 2C), 129.6 (d, 1C), 129.4 (d, 5C), 127.8 (d, 1C), 127.7 (d, 5C), 127.6 (d, 2C), 127.5 (d, 2C), 126.3 (d, 3C), 76.9 (s, 1C), 71.9 (d, 1C), 61.0 (d, 1C), 58.0 (t, 1C), 51.5 (q, 1C), 39.2 (t, 1C), 26.8 (q, 3C), 19.0 (s, 1C). HRMS Calcd for $\text{C}_{41}\text{H}_{43}\text{O}_3\text{NNaSi}$ ($\text{M}+\text{Na}^+$): 648.2904; Found: 648.2901.

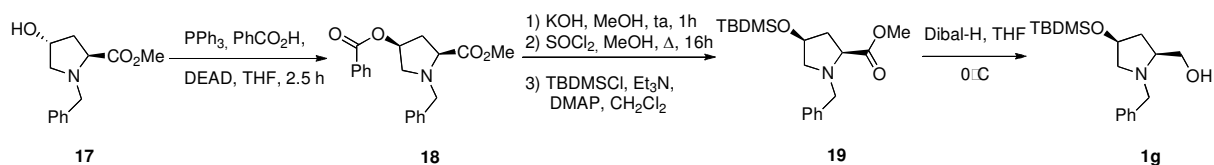
((2*S*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)-*N*,1-tritylpyrrolidin-2-yl)methanol (1f**)**

To a suspension of LiAlH₄ (0.294 g; 7.7 mmol, 3.7 equiv) in THF (15 mL) at 0 °C, a solution of **16** (1.295 g, 2.07 mmol, 1.0 equiv) in THF (15 mL) was added dropwise. After stirring at 0 °C for 10 min, the reaction mixture was stirred for 2 h at rt and then cooled to 0 °C. Water (0.17 mL), an aqueous 3.75 M NaOH solution (0.17 mL), and water (0.38 mL) were successively added. The obtained precipitate was collected on a Celite pad and washed with THF. The organic solvent was removed in vacuo to give **1f** (637 mg, 1.07 mmol, 52%) as a colorless oil.



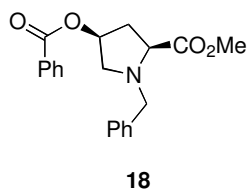
$[\alpha]_D^{20} = +41$ (c 2, CHCl₃). IR (neat): 3397, 1447, 1427, 1110, 1030, 908, 733, 699, 612 cm⁻¹. ¹H NMR: δ 7.75–7.13 (m, 25H), 4.44 (dddd, $J = 7.3, 7.3, 7.3$ and 7.3 Hz, 1H), 3.39 (dd, $J = 11.2$ and 7.5 Hz, 1H), 3.35–3.27 (m, 2H), 3.16 (m, 1H), 2.58 (dd, $J = 11.1$ and 6.8 Hz, 1H), 1.70 (br s, 1H), 1.54 (ddd, $J = 12.3, 7.3$ and 2.3 Hz, 1H), 0.96–0.80 (m, 10H). ¹³C NMR: δ 144.0 (s, 3C), 135.7 (d, 3C), 135.6 (d, 3C), 134.9 (d, 1C), 134.2 (s, 2C), 129.6 (d, 4C), 129.6 (d, 2C), 127.7 (d, 1C), 127.6 (d, 5C), 127.5 (d, 3C), 126.3 (d, 3C), 77.3 (s, 1C), 72.1 (d, 1C), 65.8 (t, 1C), 60.3 (d, 1C), 57.7 (t, 1C), 38.2 (t, 1C), 26.8 (q, 3C), 19.0 (s, 1C). HRMS Calcd for C₄₀H₄₃O₂NNaSi (M+Na⁺): 620.2969; Found: 620.2955.

Preparation of compound 1g



(2*S*,4*S*)-methyl *N*,1-benzyl-4-(phenylcarbonyloxy)pyrrolidine-2-carboxylate (18**)**

To a solution of **17**ⁱⁱ (753 mg, 3.20 mmol, 1 equiv) in THF (20 mL) was added PPh₃ (1.048 g, 4.0 mmol, 1.25 equiv), PhCO₂H (489 mg, 4.0 mmol, 1.25 equiv) and DEAD (2.3 M in toluene, 1.81 mL, 4.17 mmol, 1.3 equiv) at 0 °C. After, 2.5 h at rt, the solvent is removed under reduced pressure. After purification by flash column chromatography on silica gel (petroleum ether/EtOAc: 90/10) **18** (800 mg, 2.36 mmol, 74%) is isolated as a yellow oil.

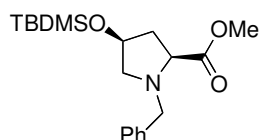


$[\alpha]_D^{20} = -17$ (c 1, CHCl₃). IR (neat): 1713, 1451, 1315, 1274, 1202, 1174, 1111, 710 cm⁻¹. ¹H NMR: δ 8.08–7.98 (m, 2H), 7.59–7.21 (m, 8H), 5.40 (dddd, $J = 7.7, 6.2, 3.6$ and 2.3 Hz, 1H), 4.04 (d, $J = 13.4$ Hz, 1H), 3.70 (s, 3H), 3.64 (d, $J = 13.2$ Hz, 1H), 3.41 (dd, $J = 8.4$ and 6.8 Hz, 1H), 3.22 (dd, $J = 11.0$ and 2.2

Hz, 1H), 2.88 (dd, $J = 11.1$ and 6.3 Hz, 1H), 2.67 (ddd, $J = 14.1$, 8.0 and 8.0 Hz, 1H), 2.27 (dddd, $J = 14.1$, 6.9 and 3.5 Hz, 1H). ^{13}C NMR: δ 173.3 (s, 1C), 166.4 (s, 1C), 137.5 (s, 2C), 133.0 (d, 1C), 129.7 (d, 2C), 129.1 (d, 2C), 128.3 (d, 4C), 127.3 (d, 1C), 73.0 (d, 1C), 63.8 (d, 1C), 58.4 (t, 1C), 57.6 (t, 1C), 51.9 (q, 1C), 36.6 (t, 1C). MS-EI m/z (%): 340 (M^+ , 0.1), 217 (14), 158 (63), 105 (15), 91 (100), 77 (12), 65 (9). HRMS Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{N}$ ($\text{M}+\text{H}^+$): 340.1543; Found: 340.1539.

(2S,4S)-methyl N,1-benzyl-4-(tert-butyldimethylsilyloxy)pyrrolidine-2-carboxylate (19)

To a solution of **18** (800 mg, 2.36 mmol, 1 equiv) in MeOH (10 mL) was added KOH (264 mg, 4.72 mmol, 2 equiv). After 30 min at rt, SOCl_2 (2 mL, 27.5 mmol, 11.7 equiv) is added to the mixture. After being stirred for 16 h under reflux, the solvent is removed under reduced pressure. The residue is dissolved in EtOAc, washed with a saturated solution of NaHCO_3 . The organic layer is dried over MgSO_4 , filtered and evaporated under reduced pressure. DMAP (6 mg, 0.05 mmol, 0.1 equiv), Et_3N (0.14 mL, 0.98 mmol, 2 equiv) and TBDMSCl (89 mg, 0.59 mmol, 1.2 equiv) were added to a solution of the crude (115 mg, 0.49 mmol, 1 equiv) in CH_2Cl_2 (5 mL). After 12 h at rt, the reaction mixture was quenched with a saturated aqueous Na_2CO_3 solution until pH=10. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over MgSO_4 and filtered. The solvent was removed *in vacuo* to afford an oil, which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 95/5 to 90/10) to give **19** (123 mg, 0.35 mmol, 30%, 3 steps) as a yellow oil.

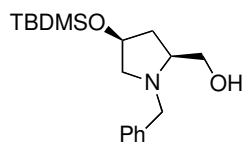


19

$[\alpha]_{\text{D}}^{20} = -40$ (c 0.5, CHCl_3). IR (neat): 2952, 2929, 1743, 1472, 1455, 1386, 1362, 1254, 1199, 1152, 1100, 1029, 836, 776, 700 cm^{-1} . ^1H NMR: δ 7.36–7.21 (m, 5H), 4.34 (dddd, $J = 6.9$, 6.9 , 4.8 and 3.6 Hz, 1H), 3.96 (d, $J = 13.3$ Hz, 1H), 3.69 (s, 3H), 3.63 (d, $J = 13.3$ Hz, 1H), 3.36 (dd, $J = 7.6$ and 7.6 Hz, 1H), 2.94 (dd, $J = 9.9$ and 3.6 Hz, 1H), 2.70 (dd, $J = 9.9$ and 6.6 Hz, 1H), 2.4 (ddd, $J = 13.0$, 7.5 and 7.5 Hz, 1H), 1.99 (ddd, $J = 12.9$, 7.4 and 4.8 Hz, 1H), 0.85 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR: δ 174.0 (s, 1C), 138.2 (s, 1C), 129.0 (d, 2C), 128.2 (d, 2C), 127.0 (d, 1C), 70.4 (d, 1C), 64.0 (d, 1C), 60.9 (t, 1C), 57.8 (t, 1C), 51.7 (q, 1C), 40.1 (t, 1C), 25.8 (q, 3C), 18.1 (s, 1C), -4.8 (q, 2C). MS-EI m/z (%): 349 (M^+ , 0.3), 291 (14), 290 (57), 158 (25), 91 (100), 75 (13), 65 (6). HRMS Calcd for $\text{C}_{19}\text{H}_{32}\text{O}_3\text{NSi}$ ($\text{M}+\text{H}^+$): 350.2146; Found: 350.2136.

((2S,4S)-1-benzyl-4-(tert-butyldimethylsilyloxy)pyrrolidin-2-yl)methanol (1g)

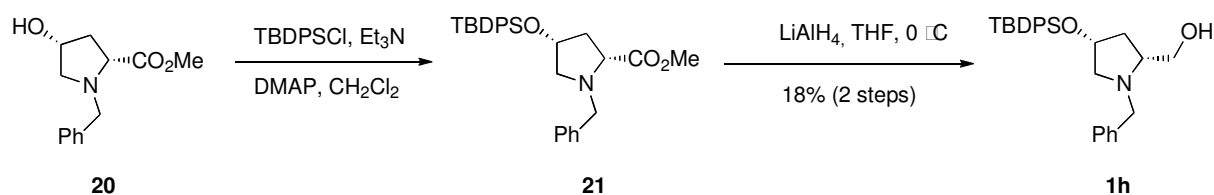
Dibal-H (1M in CH_2Cl_2 , 1.16 mL, 1.16 mmol, 3.3 equiv) was added to a solution of **19** (123 mg, 0.35 mmol, 1 equiv) in THF (5 mL) at $0\text{ }^\circ\text{C}$. After 1h at $0\text{ }^\circ\text{C}$, a saturated solution of potassium sodium tartrate (10 mL) and EtOAc (10 mL) were added to the reaction mixture. After being stirred for 1h at rt, the solution was extracted with EtOAc, dried over MgSO_4 , filtered and concentrated under reduced pressure to give **1g** (79 mg, 0.25 mmol, 70%) as a colorless oil.



1g

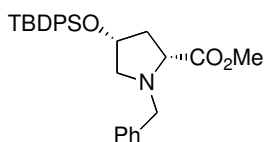
$[\alpha]_D^{20} = -50$ (c 0.5, CHCl_3). IR (neat): 3550–3100, 2953, 2928, 1471, 1463, 1374, 1255, 1099, 1052, 1039, 911, 835, 776, 699 cm^{-1} . ^1H NMR: δ 7.32–7.17 (m, 5H), 4.22 (dddd, $J = 5.9, 4.2, 2.0$ and 2.0 Hz, 1H), 3.98 (d, $J = 13.9$ Hz, 1H), 3.68 (dd, $J = 10.7$ and 2.8 Hz, 1H), 3.42 (dd, $J = 11.0$ and 2.1 Hz, 1H), 3.37 (d, $J = 13.3$ Hz, 1H), 2.89–2.80 (m, 2H), 2.39 (dd, $J = 9.9$ and 4.4 Hz, 1H), 2.17 (ddd, $J = 13.6, 9.5$ and 6.1 Hz, 1H), 1.83 (dddd, $J = 13.7, 5.3, 2.0$ and 2.0 Hz, 1H), 0.83 (s, 9H), 0.0 (s, 3H), -0.04 (s, 3H). ^{13}C NMR: δ 139.2 (s, 1C), 128.5 (d, 2C), 128.3 (d, 2C), 126.9 (d, 1C), 70.7 (d, 1C), 63.2 (d, 1C), 62.1 (t, 1C), 61.4 (t, 1C), 57.7 (t, 1C), 37.8 (t, 1C), 25.8 (q, 3C), 18.0 (s, 1C), -4.85 (q, 2C). MS-EI m/z (%): 290 ($\text{M}^+ - \text{CH}_2\text{OH}$; 39), 158 (21), 91 (100), 75 (14), 65 (6). HRMS Calcd for $\text{C}_{18}\text{H}_{32}\text{O}_2\text{NSi}$ ($\text{M} + \text{H}^+$): 322.2197; Found: 322.2185.

Preparation of compound 1h



(2R,4R)-methyl *N*,1-benzyl-4-(*tert*-butyldiphenylsilyloxy)pyrrolidine-2-carboxylate (**21**)

DMAP (0.016 g, 0.13 mmol, 0.1 equiv), Et_3N (0.37 mL, 2.55 mmol, 2 equiv) and TBDPSCI (0.34 mL, 1.53 mmol, 1.2 equiv) were added to a solution of compound **20**ⁱⁱⁱ (300 mg, 1.28 mmol, 1 equiv) in CH_2Cl_2 (10 mL). After 12 h at rt, the reaction mixture was quenched with a saturated aqueous Na_2CO_3 solution until pH=10. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over MgSO_4 and filtered. The solvent was removed *in vacuo* to afford an oil, which was purified by flash column chromatography on silica gel (petroleum ether/ Et_2O : 80/20) to give **21** (604 mg, 1.28 mmol, quantitative) as a colorless oil.

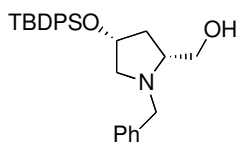


21

^1H NMR: δ 7.74–7.19 (m, 15H), 4.32 (m, 1H), 3.92 (d, $J = 13.4$ Hz, 1H), 3.68 (s, 3H), 3.57 (d, $J = 13.3$ Hz, 1H), 3.28 (dd, $J = 7.6$ and 7.6 Hz, 1H), 3.06 (dd, $J = 10.0$ and 3.5 Hz, 1H), 2.57 (dd, $J = 10.0$ and 6.5 Hz, 1H), 2.24 (ddd, $J = 12.9, 7.5$ and 7.5 Hz, 1H), 2.11 (ddd, $J = 12.9, 7.2$ and 4.7 Hz, 1H), 1.02 (s, 9H). ^{13}C NMR: δ 174.1 (s, 1C), 138.4 (s, 1C), 135.7 (d, 2C), 135.2 (s, 1C), 134.8 (d, 2C), 134.0 (s, 1C), 129.7 (d, 2C), 128.9 (d, 1C), 128.2 (d, 1C), 127.7 (d, 3C), 127.6 (d, 2C), 127.6 (d, 2C), 71.4 (d, 1C), 63.9 (d, 1C), 60.6 (t, 1C), 57.8 (t, 1C), 51.7 (q, 1C), 39.8 (t, 1C), 26.6 (q, 3C), 19.1 (s, 1C).

((2*R*,4*R*)-*N*,1-benzyl-4-(*tert*-butyldiphenylsilyloxy)pyrrolidin-2-yl)methanol (1h**)**

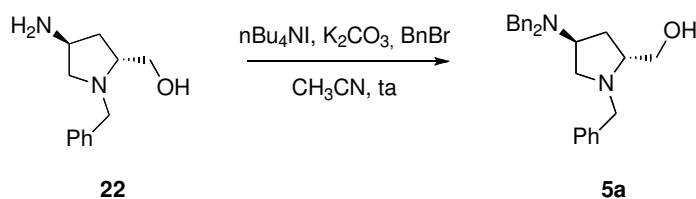
To a suspension of LiAlH₄ (97 mg, 2.55 mmol, 2 equiv) in THF (10 mL) at 0 °C, a solution of **21** (604 mg, 1.28 mmol, 1.0 equiv) in THF (7 mL) was added dropwise. After stirring at 0 °C for 30 min, water (65 μL), an aqueous 3.75 M NaOH solution (65 μL), and water (150 μL) were successively added. The obtained precipitate was collected on a Celite pad and washed with THF. The organic solvent was removed in vacuo to give, after purification by flash column chromatography on silica gel (petroleum ether/Et₂O: 80/20 to 60/40), **1g** (102 mg, 0.23 mmol, 18%) as a colorless oil.



1h

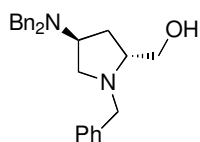
$[\alpha]_D^{20} = +60$ (c 1, CHCl₃). IR (neat): 3550–3100, 2930, 1495, 1472, 1454, 1428, 1111, 1050, 822, 740, 701 cm⁻¹. ¹H NMR: δ 7.68–7.62 (m, 2H), 7.59–7.54 (m, 2H), 7.45–7.22 (m, 11H), 4.22 (dddd, *J* = 5.7, 4.4, 2.0 and 2.0 Hz, 1H), 3.99 (d, *J* = 13.3 Hz, 1H), 3.76 (dd, *J* = 10.7 and 2.8 Hz, 1H), 3.49 (dd, *J* = 11.1 and 2.4 Hz, 1H), 3.30 (d, *J* = 13.4 Hz, 1H), 2.88 (ddd, *J* = 10.3, 1.7 and 1.7 Hz, 1H), 2.81 (dddd, *J* = 9.3, 5.6, 2.5 and 2.5 Hz, 1H), 2.33 (dd, *J* = 10.2 and 4.1 Hz, 1H), 2.11 (ddd, *J* = 13.8, 9.3 and 6.0 Hz, 1H), 2.00 (dddd, *J* = 13.6, 5.7, 2.1 and 1.6 Hz, 1H), 1.04 (s, 9H). ¹³C NMR: δ 139.2 (s, 1C), 135.0 (d, 2C), 135.7 (d, 2C), 133.9 (s, 1C), 133.7 (s, 1C), 129.7 (d, 1C), 129.6 (d, 1C), 128.6 (d, 1C), 128.5 (d, 1C), 128.3 (d, 1C), 127.7 (d, 2C), 127.6 (d, 2C), 127.0 (d, 2C), 71.6 (d, 1C), 63.4 (d, 1C), 61.9 (t, 1C), 61.2 (t, 1C), 57.8 (t, 1C), 37.6 (t, 1C), 26.8 (q, 3C), 19.1 (s, 1C). HRMS Calcd for C₂₈H₃₆O₂NSi (M+H⁺): 446.2510; Found: 446.2503.

Preparation of compound 5a



((2*R*,4*S*)-*N*,1-benzyl-4-(*N,N*-dibenzylamino)pyrrolidin-2-yl)methanol (5a**)**

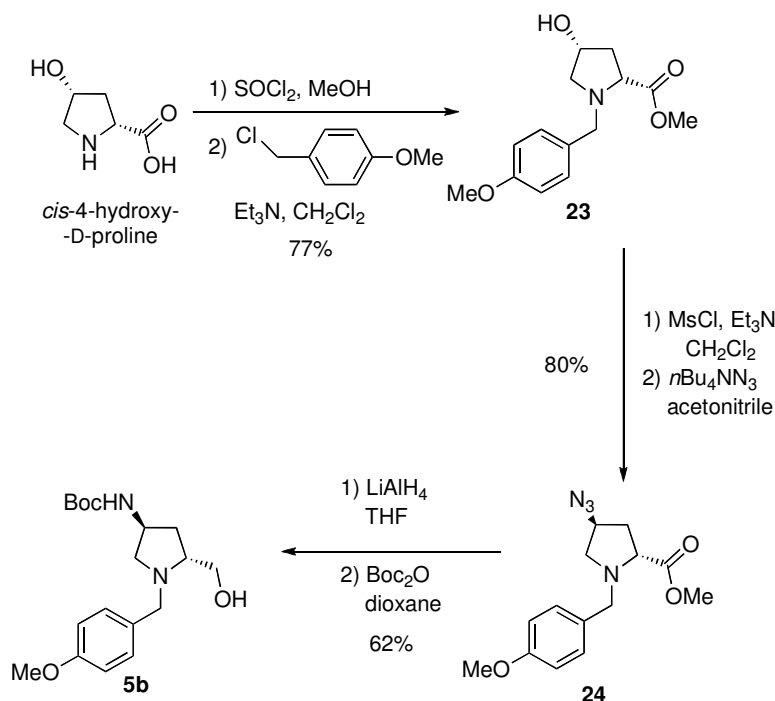
nBu₄NI (97 mg, 0.26 mmol, 0.3 equiv), BnBr (0.22 mL, 1.85 mmol, 2.2 equiv) and K₂CO₃ (362 mg, 2.61 mmol, 3 equiv) were added to a solution of **22**^{iv} (179 mg, 0.87 mmol, 1 equiv) in CH₃CN (9 mL). After 5 h at rt, water (10 mL) was added to the mixture and then it was extracted with EtOAc. The organic layer was then dried over MgSO₄, filtered and then concentrated under reduced pressure. After purification by flash column chromatography on silica gel (petroleum ether/EtOAc: 60/40) **5a** (153 mg, 0.40 mmol, 46%) was isolated as a yellow oil.



5a

$[\alpha]_D^{20} = +50$ (c 1, CHCl_3). IR (neat): 3405, 1493, 1494, 1453, 1050, 1028, 733, 698 cm^{-1} . ^1H NMR: δ 7.33–7.16 (m, 15H), 3.91 (d, $J = 12.9$ Hz, 1H), 3.66 (dd, $J = 10.9$ and 3.2 Hz, 1H), 3.62 (d, $J = 14.3$ Hz, 2H), 3.50 (d, $J = 14.1$ Hz, 2H), 3.39 (dd, $J = 11.0$ and 2.0 Hz, 1H), 3.32 (m, 1H), 3.26 (d, $J = 12.8$ Hz, 1H), 3.01 (dd, $J = 8.9$ and 6.4 Hz, 1H), 2.84 (dddd, $J = 9.5, 6.5, 3.1$ and 1.6 Hz, 1H), 2.28 (dd, $J = 9.2$ and 9.2 Hz, 1H), 2.08–1.95 (m, 2H). ^{13}C NMR: δ 139.8 (s, 2C), 138.7 (s, 1C), 128.8 (d, 2C), 128.7 (d, 4C), 128.4 (d, 2C), 128.2 (d, 4C), 127.2 (d, 1C), 126.8 (d, 2C), 63.8 (d, 1C), 61.4 (t, 1C), 59.3 (d, 1C), 58.2 (t, 1C), 57.6 (t, 1C), 55.8 (t, 2C), 31.2 (t, 1C). HRMS Calcd for $\text{C}_{26}\text{H}_{31}\text{ON}_2$ ($\text{M}+\text{H}^+$): 387.2431; Found: 387.2431.

Preparation of compound 5b

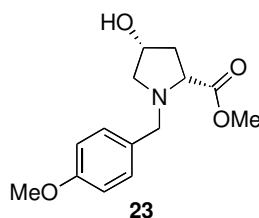


Methyl (2*R*,4*R*)-4-hydroxy-1-*N*(4-methoxybenzyl)pyrrolidine-2-carboxylate (23)

To a suspension of *cis*-4-hydroxy-D-proline (5 g, 38.1 mmol, 1 equiv) in MeOH (250 mL) at 0 °C was added dropwise thionyl chloride (3.32 mL, 45.8 mmol, 1.2 equiv). The reaction mixture was heated at reflux for 23 h. After evaporation of the methanol under reduced pressure, the reaction mixture was taken up in CH_2Cl_2 (3 times) and concentrated under reduced pressure.

To a solution of the hydrochloride prepared above in CH_2Cl_2 under nitrogen atmosphere were added Et_3N (13.19 mL, 95.3 mmol, 2.5 equiv) and *p*-methoxybenzyl chloride (10.34 mL, 76.3 mmol, 2 equiv). The reaction mixture was heated at reflux for 7 h. The resulting suspension was partitioned between chloroform and 1M aqueous sodium hydroxide, the layers were separated, and the organic phase was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The

resulting mixture was purified by flash column chromatography (silica gel, CH₂Cl₂/MeOH: 98/2) to obtain the desired compound **23** (7.75g, 29.2 mmol, 77%) as a yellow oil.

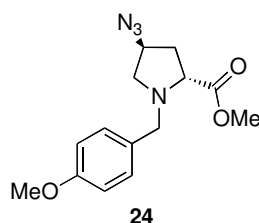


$[\alpha]_D^{20} = +43.7$ (c 0.5, CHCl₃). IR (film): 3411, 2951, 2835, 1731, 1511, 1243, 1174, 1032, 817 cm⁻¹. ¹H NMR: δ 7.23–7.19 (dm, $J = 8.8$ Hz, 2H), 6.86–6.81 (dm, $J = 8.8$ Hz, 2H), 4.23 (br s, 1H), 3.79 (s, 3H), 3.78 (d, $J = 13.0$ Hz, 1H), 3.64 (d, $J = 13.0$ Hz, 1H), 3.63 (s, 3H), 3.30 (dd, $J = 10.2, 3.8$ Hz, 1H), 3.15 (br s, 1H), 2.98 (ddd, $J = 9.9, 2.9, 2.9$ Hz, 1H), 2.60 (dd, $J = 9.7, 4.0$ Hz, 1H), 2.36 (ddd, $J = 15.6, 10.0, 5.7$ Hz, 1H), 1.92 (dm, $J = 14.2$ Hz, 1H). ¹³C NMR: δ 175.7 (s, 1C), 159.0 (s, 1C), 130.3 (d, 2C), 130.0 (s, 1C), 113.7 (d, 2C), 71.0 (d, 1C), 63.2 (d, 1C), 61.8 (t, 1C), 57.5 (t, 1C), 55.4 (q, 1C), 52.2 (q, 1C), 39.4 (t, 1C). MS-EI m/z (%): 265 (M⁺, 0.5), 206 (15), 122 (9), 121 (100), 94 (2), 91 (4), 78 (5), 77 (6). HRMS Calcd for C₁₄H₂₀O₄N (M + H⁺) 266.13868, found 266.13835.

Methyl (2R,4S)-4-azido-N,1-(4-methoxybenzyl)pyrrolidine-2-carboxylate (**24**)

To a solution of compound **23** (3 g, 11.3 mmol, 1 equiv) in CH₂Cl₂ (20 mL) at 0 °C under nitrogen atmosphere, was added Et₃N (6.89 mL, 49.8 mmol, 4.4 equiv) followed by MsCl (1.93 mL, 24.9 mmol, 2.2 equiv). The reaction mixture was stirred for 14 h, during which time the ice bath expired. The reaction mixture was diluted with CH₂Cl₂ and washed with saturated aqueous sodium bicarbonate, water, and brine. The dichloromethane solution was dried over Na₂SO₄ and concentrated under reduced pressure to afford 4.54 g of crude product.

To a solution of the methanesulfonate ester (4.54 g, 11.3 mmol, 1 equiv) previously synthesized in acetonitrile (20 mL) under nitrogen atmosphere, was added tetra-*n*-butylammonium azide (8.05 g, 28.3 mmol, 2.5 equiv). This stirring solution was heated at 65 °C for 1 h 40, diluted with EtOAc, and washed with water and brine. The combined aqueous washings were extracted with EtOAc, the combined organic fractions were dried over Na₂SO₄, and the solvent was removed under reduced pressure to afford 7.06 g of crude material. The crude material was purified by flash column chromatography (silica gel, EP/EtOAc from 90/10 to 80/20) to obtain the desired compound **24** (2.62 g, 9.0 mmol, 80 %).



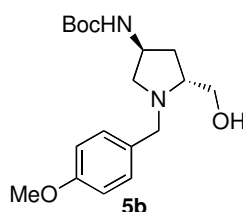
$[\alpha]_D^{20} = +18.0$ (c 0.4, CHCl₃). IR (film): 2952, 2836, 2098, 1732, 1511, 1244, 1172, 1033, 819 cm⁻¹. ¹H NMR: δ 7.24–7.19 (dm, $J = 8.9$ Hz, 2H), 6.87–6.82 (dm, $J = 8.7$ Hz, 2H), 4.09 (m, 1H), 3.83 (d, $J = 12.8$ Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.59 (d, $J = 12.8$ Hz, 1H), 3.52 (dd, $J = 6.6, 8.2$ Hz, 1H), 3.29 (dd, $J = 6.5, 10.0$ Hz, 1H), 2.51 (dd, $J = 5.2, 10.1$ Hz, 1H), 2.32 (ddd, $J = 13.6, 7.8, 6.6$ Hz, 1H), 2.15 (ddd, $J =$

13.5, 8.5, 4.6 Hz, 1H). ^{13}C NMR: δ 172.6 (s, 1C), 158.1 (s, 1C), 129.3 (d, 2C), 128.9 (s, 1C), 112.8 (d, 2C), 62.6 (d, 1C), 58.1 (d, 1C), 56.8 (t, 1C), 56.3 (t, 1C), 54.4 (q, 1C), 51.0 (q, 1C), 35.0 (t, 1C). MS-EI m/z (%): 290 (M^+ , 0.2), 232 (1), 231 (9), 203 (6), 162 (1), 136 (1), 129 (1), 122 (9), 121 (100), 91 (5), 90 (1), 89 (2), 78 (6), 79 (7), 65 (1), 55 (3), 52 (1), 51 (2). HRMS Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_3\text{N}_4$ ($\text{M} + \text{H}^+$) 291.14517, found 291.14457.

***tert*-Butyl (3*S*,5*R*)-5-(hydroxymethyl)-*N*,1-(4-methoxybenzyl)pyrrolidin-3-ylcarbamate (5b)**

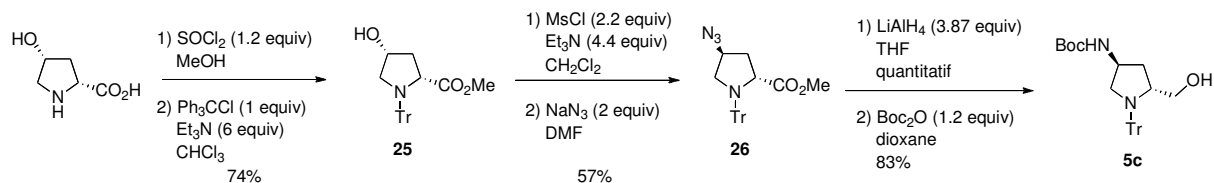
To a stirring suspension of LiAlH_4 (1.33 g, 34.9 mmol, 3.87 equiv) in THF (150 mL) at 0 °C under nitrogen atmosphere, was added dropwise a solution of compound **24** (2.62 g, 9.0 mmol, 1 equiv) in THF (50 mL). The reaction mixture was stirred at 0 °C for 0.5 h and then 3 h at rt. The system was cooled at 0 °C and water (1.32 mL, 73.3 mmol, 8.13 equiv) was added dropwise. After 5 min of stirring, an aqueous solution of NaOH (1.32 mL, 3.75 M) was added. After 5 min of stirring, water (3.3 mL) was added and the mixture was stirred at rt for 1 h. The white granular precipitate was removed by suction filtration through a pad of Celite, and the filtrate was concentrated under reduced pressure to afford 2.02 g of reduction product.

To a stirring solution of reduction product (2.02 g, 8.52 mmol, 1 equiv) previously synthesized in dioxane (50 mL) under nitrogen atmosphere, was added Boc_2O (2.23 g, 10.21 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 20 h. The mixture was taken up in Et_2O and washed with water, dried with Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, from EtOAc to EtOAc/MeOH: 98/2) to obtain the desired compound **5b** (1.87 g, 5.56 mmol, 62%).



Mp = 110 °C. $[\alpha]_{\text{D}}^{20} = +46.4$ (c 1, CHCl_3). IR (neat): 3360, 2934, 2809, 1681, 1513, 1249, 1170, 1035, 618 cm^{-1} . ^1H NMR: δ 7.17–7.11 (dm, $J = 8.8$ Hz, 2H), 6.84–6.78 (dm, $J = 8.6$ Hz, 2H), 4.62 (br s, $J = 7.4$ Hz, 1H), 4.01 (m, 1H), 3.86 (d, $J = 13.0$ Hz, 1H), 3.76 (s, 3H), 3.60 (dd, $J = 11.0, 3.5$ Hz, 1H), 3.37 (dd, $J = 11.0, 2.0$ Hz, 1H), 3.31 (d, $J = 13.2$ Hz, 1H), 3.24 (dd, $J = 7.6, 7.6$ Hz, 1H), 2.83 (m, 1H), 2.72 (br s, 1H), 2.19 (ddd, $J = 13.3, 8.4, 6.1$ Hz, 1H), 2.10 (dd, $J = 8.7, 8.7$ Hz, 1H), 1.67 (ddd, $J = 13.1, 9.2, 7.2$ Hz, 1H), 1.38 (s, 9H). ^{13}C NMR: δ 157.8 (s, 1C), 154.4 (s, 1C), 129.5 (s, 1C), 128.9 (d, 2C), 112.8 (d, 2C), 78.3 (s, 1C), 61.8 (d, 1C), 60.6 (t, 1C), 58.9 (t, 1C), 56.4 (t, 1C), 54.3 (q, 1C), 47.8 (d, 1C), 34.1 (t, 1C), 27.4 (q, 1C). SM (IE) m/z (%): 305 ($\text{M}^+ - \text{CH}_2\text{OH}^+$, 8), 188 (3), 122 (9), 121 (100), 91 (3), 78 (3), 77 (4), 57 (7). HRMS Calcd for $\text{C}_{18}\text{H}_{29}\text{O}_4\text{N}_2$ ($\text{M} + \text{H}^+$) 337.21218, found 337.21240.

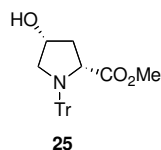
Preparation of compound 5c



(2R,4R)-Methyl 4-hydroxy-1-tritylpyrrolidine-2-carboxylate (**25**)

To a stirring suspension of *trans*-4-hydroxy-D-proline (232 mg, 1.77 mmol, 1 equiv) in MeOH (50 mL) at 0 °C was added dropwise SOCl₂ (0.15 mL, 2.12 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature 60 h and heated at reflux for 17 h. The solvent was removed under reduced pressure and the reaction residue was taken up in dichloromethane (3 times).

To a solution of the ester previously formed in CHCl₃ (4.5 mL) at 0 °C under argon atmosphere was added Et₃N (1.47 mL, 10.62 mmol, 6 equiv) and trityl chloride (493 mg, 1.77 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 27 h. Then a mixture (2:1) of a saturated solution of NH₄Cl and NH₃ (28% in water) was added to the crude mixture. After separation of the phases, the aqueous phase was extracted with dichloromethane (3 times). The organic phases were gathered, dried over MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, PE/EtOAc: 7/3 + 0.25% of Et₃N) to obtain the desired product **25** (505 mg, 1.30 mmol, 74%).



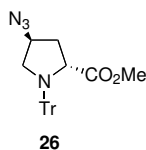
Mp = 132 °C. $[\alpha]_D^{20} = +19.1$ ($c = 0.87$, CHCl₃). IR (film): 3444, 1750, 1713, 1448, 1206, 1080, 748, 710, 700 cm⁻¹. ¹H NMR: δ 7.50–7.44 (m, 6H), 7.23–7.16 (m, 6H), 7.13–7.07 (m, 3H), 3.84–3.75 (m, 2H), 3.58 (s, 3H), 3.39 (ddd, $J = 11.4, 1.5$ and 1.5 Hz, 1H), 2.74 (dd, $J = 11.5$ and 4.5 Hz, 1H), 1.55 (dd, $J = 13.8$ and 1.6 Hz, 1H), 1.49 (br s, 1H), 1.12 (m, 1H). ¹³C NMR: δ 179.3 (s, 1C), 143.5 (s, 3C), 129.4 (d, 6C), 127.7 (d, 6C), 126.4 (d, 3C), 72.0 (d, 1C), 60.4 (d, 1C), 58.6 (t, 1C), 52.1 (q, 1C), 39.2 (t, 1C).

(2R,4S)-Methyl 4-azido-1-tritylpyrrolidine-2-carboxylate (**26**)

To a solution of (2R,4R)-methyl 4-hydroxy-1-tritylpyrrolidine-2-carboxylate **25** (479 mg, 1.24 mmol, 1 equiv) in CH₂Cl₂ (10 mL) at 0 °C under argon atmosphere, was added Et₃N (0.75 mL, 5.45 mmol, 4.4 equiv) followed by MsCl (0.21 mL, 2.72 mmol, 2.2 equiv). The reaction mixture was stirred for 15h, during which time the ice bath expired. The reaction mixture was diluted with CH₂Cl₂ and washed with saturated aqueous sodium bicarbonate, water, and brine. The dichloromethane solution was dried over Na₂SO₄ and concentrated under reduced pressure to afford 530 mg of crude product.

To a solution of the methanesulfonate ester (479 mg, 1.03 mmol, 1 equiv) previously synthesized in DMF (8 mL), under argon atmosphere was added sodium azide (134 mg, 2.06 mmol, 2 equiv). This stirring solution was heated at 80 °C for 20 h, concentrated under reduced pressure and partitioned between H₂O and EtOAc (1:2, 15 mL). The aqueous phase was extracted with EtOAc (4

times). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. The crude material was purified by flash column chromatography (silica gel, EP/EtOAc: 8/2 + 0.5% Et_3N) to obtain the desired compound **26** (264 mg, 0.64 mmol, 57%).

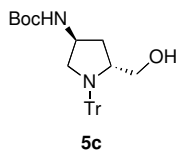


Mp = 113 °C. $[\alpha]_{\text{D}}^{20} = -31.6$ ($c = 1$, CHCl_3). IR (film): 2924, 2102, 1744, 1196, 746, 713, 626 cm^{-1} . ^1H NMR: δ 7.51–7.43 (m, 6H), 7.25–7.15 (m, 6H), 7.15–7.06 (m, 3H), 4.06 (m, 1H), 3.83 (d, $J = 9.1$ Hz, 1H), 3.65 (ddd, $J = 10.3, 7.5$ and 2.5 Hz, 1H), 3.55 (s, 3H), 2.56 (ddd, $J = 10.4, 7.7$ and 2.4 Hz, 1H), 1.75 (ddd, $J = 12.4, 6.7$ and 1.6 Hz, 1H), 0.81 (m, 1H). ^{13}C NMR: δ 175.9 (s, 1C), 143.4 (s, 3C), 129.2 (d, 6C), 127.9 (d, 6C), 126.6 (d, 3C), 61.4 (d, 1C), 59.0 (d, 1C), 53.3 (t, 1C), 51.9 (q, 1C), 36.0 (t, 1C).

tert-Butyl (3S,5R)-5-(hydroxymethyl)-1-tritylpyrrolidin-3-ylcarbamate (**5c**)

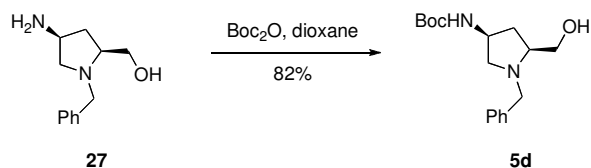
To a solution of (2R,4S)-methyl 4-azido-1-tritylpyrrolidine-2-carboxylate **26** (264 mg, 0.64 mmol, 1 equiv) in THF (2 mL) at 0 °C was added a solution of LiAlH_4 (94 mg, 2.48 mmol, 3.87 equiv) in THF (2 mL). The resulting mixture was stirred at 0 °C for 30 min and 3 h at rt. The system was cooled at 0 °C and water (0.1 mL, 5.55 mmol, 8.7 equiv) was added dropwise. After 5 min of stirring, an aqueous solution of NaOH (0.1 mL, 3.75 M) was added. After 5 min of stirring, water (0.25 mL) was added and the mixture was stirred at rt for 1 h. The white granular precipitate was removed by suction filtration through a pad of Celite, and the filtrate was concentrated under reduced pressure to afford 293 mg of reduction product.

To a stirring solution of reduction product (50 mg, 0.14 mmol, 1 equiv), previously synthesized, in dioxane (2 mL) under argon atmosphere, was added Boc_2O (37 mg, 0.17 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 14 h. The mixture was taken up in Et_2O and washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, EP/EtOAc: 7/3) to obtain the desired compound **5c** (53 mg, 0.12 mmol, 83%).



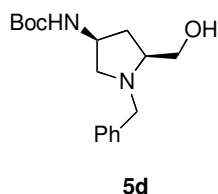
Mp = 71 °C. $[\alpha]_{\text{D}}^{20} = -102.3$ ($c = 0.5$, CHCl_3). IR (film): 3411, 2974, 1689, 1167, 1033, 709, 628 cm^{-1} . ^1H NMR: δ 7.54–7.46 (m, 6H), 7.23–7.16 (m, 6H), 7.14–7.06 (m, 3H), 4.14 (m, 1H), 3.71–3.55 (m, 2H), 3.47 (dd, $J = 10.8$ and 7.8 Hz, 1H), 3.39 (br s, 1H), 3.30 (m, 1H), 2.47 (dd, $J = 12.5$ and 6 Hz, 1H), 1.79 (dd, $J = 12.6$ and 8.8 Hz, 1H), 1.28 (s, 9H), 0.40 (ddd, $J = 12.8, 9.1$ and 7.8 Hz, 1H). ^{13}C NMR: δ 155.3 (s, 1C), 144.6 (s, 3C), 129.6 (d, 6C), 127.7 (d, 6C), 126.5 (d, 3C), 79.1 (s, 1C), 65.2 (t, 1C), 61.0 (d, 1C), 59.4 (t, 1C), 50.2 (d, 1C), 35.2 (t, 1C), 28.4 (q, 3C). HRMS Calcd for $\text{C}_{29}\text{H}_{34}\text{O}_3\text{N}_2\text{Na}$ ($\text{M} + \text{Na}^+$) 481.24616; Found 481.24509.

Preparation of compound 5d



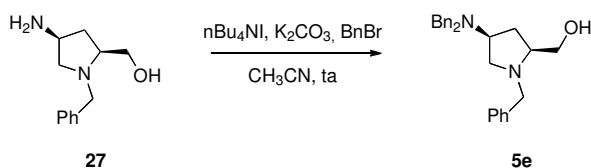
tert-Butyl (3*S*,5*S*)-*N*,1-benzyl-5-(hydroxymethyl)pyrrolidin-3-ylcarbamate (5d)

Di-*tert*-butyl dicarbonate (152 mg, 0.70 mmol, 1.2 equiv) was added to a solution of **27**^{iv} (120 mg, 0.58 mmol, 1 equiv) in dioxane (8 mL). After 1h at rt, water (10 mL) was added to the reaction mixture, and then the solution was extracted with Et₂O. The organic layer was dried over Na₂SO₄, filtered and then concentrated under reduced pressure. After purification by flash column chromatography on silica gel (CH₂Cl₂ to CH₂Cl₂/MeOH: 90/10) **5d** (146 mg, 0.48 mmol, 82%) was isolated as a yellow oil.



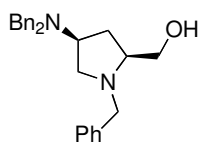
Mp = 105 °C. $[\alpha]_D^{20} = -38$ (c 1, CHCl₃). IR (neat): 1694, 1498, 1366, 1250, 1167, 906, 726, 647 cm⁻¹. ¹H NMR: δ 7.37–7.23 (m, 5H), 5.15 (br s, 1H), 4.08 (m, 1H), 3.92 (d, *J* = 13.1 Hz, 1H), 3.63 (dd, *J* = 11.1 and 3.0 Hz, 1H), 3.44–3.34 (m, 2H), 2.90 (d, *J* = 10.0 Hz, 1H), 2.75 (m, 1H), 2.53 (dd, *J* = 9.6 and 5.6 Hz, 1H), 2.37 (m, 1H), 1.66 (dd, *J* = 14.1 and 5.7 Hz, 1H), 1.41 (s, 9H). ¹³C NMR: δ 155.4 (s, 1C), 138.4 (s, 1C), 128.8 (d, 2C), 128.5 (d, 2C), 127.3 (d, 1C), 79.2 (s, 1C), 63.3 (d, 1C), 61.2 (t, 2C), 58.0 (t, 1C), 48.7 (d, 1C), 35.7 (t, 1C), 28.4 (q, 3C). HRMS Calcd for C₁₇H₂₇O₃N₂ (M+H⁺): 307.2016; Found: 307.2006.

Preparation of compound 5e



((2*S*,4*S*)-*N*,1-benzyl-*N,N*-4-(dibenzylamino)pyrrolidin-2-yl)methanol (5e)

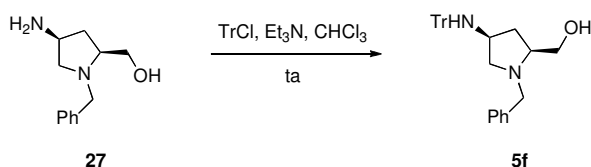
*n*Bu₄NI (123 mg, 0.33 mmol, 0.3 equiv), BnBr (0.29 mL, 2.44 mmol, 2.2 equiv) and K₂CO₃ (462 mg, 3.33, 3 equiv) were added to a solution of **27** (229 mg, 1.11 mmol, 1 equiv) in CH₃CN (11 mL). After 4 h at rt, water (10 mL) was added to the mixture and then it was extracted with EtOAc. The organic layer was then dried over MgSO₄, filtered and then concentrated under reduced pressure. After purification by flash column chromatography on silica gel (petroleum ether/EtOAc: 80/20) **5e** (300 mg, 0.78 mmol, 70%) was isolated as a yellow oil.



5e

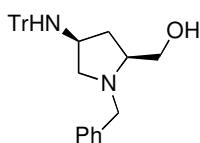
$[\alpha]_D^{20} = -47$ (c 2, CHCl_3). IR (neat): 3408, 1493, 1452, 1365, 1125, 1047, 1027, 733, 696 cm^{-1} . ^1H NMR: δ 7.36–7.16 (m, 15H), 3.99 (d, $J = 13.6$ Hz, 1H), 3.80 (dd, $J = 11.0$ and 4.2 Hz, 1H), 3.65–3.51 (m, 5H), 3.38 (m, 1H), 3.16 (d, $J = 13.1$ Hz, 1H), 3.08 (dd, $J = 10.5$ and 3.4 Hz, 1H), 2.61 (m, 1H), 2.40 (dd, $J = 10.5$ and 8.9 Hz, 1H), 2.13 (ddd, $J = 16.5$, 9.7 and 7.1 Hz, 1H), 1.95 (ddd, $J = 15.0$, 8.4 and 7.1 Hz, 1H). ^{13}C NMR: δ 140.0 (s, 2C), 139.0 (s, 1C), 128.8 (d, 4C), 128.5 (d, 2C), 128.4 (d, 2C), 128.2 (d, 4C), 127.2 (d, 1C), 126.8 (d, 2C), 64.6 (d, 1C), 60.6 (t, 1C), 58.2 (t, 1C), 57.0 (t, 1C), 56.3 (d, 1C), 54.5 (t, 2C), 29.2 (t, 1C). HRMS Calcd for $\text{C}_{26}\text{H}_{31}\text{ON}_2$ ($\text{M}+\text{H}^+$): 387.2431; Found: 387.2429.

Preparation of compound 5f



((2S,4S)-N,1-benzyl-4-(tritylamino)pyrrolidin-2-yl)methanol (5f)

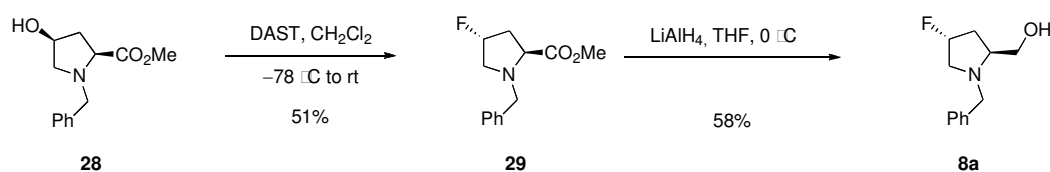
TrCl (160 mg, 0.57 mmol, 1 equiv) and Et_3N (0.48 mL, 3.42 mmol, 6 equiv) were added to a solution of **27** (118 mg, 0.57 mmol, 1 equiv) in CHCl_3 (4 mL). After 24 h at rt, a saturated solution of NaHCO_3 was added to the mixture that was then extracted with CH_2Cl_2 . The organic layer was then dried over Na_2SO_4 , filtered and then concentrated under reduced pressure. After purification by flash column chromatography on silica gel (petroleum ether/EtOAc: 60/40 + 0.5 % Et_3N) **5f** (101 mg, 0.23mmol, 39%) was isolated as a white solid.



5f

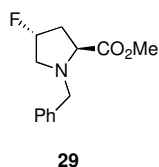
$[\alpha]_D^{20} = -19$ (c 1, CHCl_3). IR (neat): 1491, 1449, 1208, 1151, 1030, 907, 729, 698 cm^{-1} . ^1H NMR: δ 7.50–7.44 (m, 6H), 7.31–7.10 (m, 14H), 3.78 (d, $J = 13.1$ Hz, 1H), 3.60 (dd, $J = 10.9$ and 3.4 Hz, 1H), 3.33 (dd, $J = 10.9$ and 2.1 Hz, 1H), 3.14–3.05 (m, 2H), 2.51 (dddd, $J = 7.7$, 7.7, 3.3 and 2.2 Hz, 1H), 2.1 (dd, $J = 10.3$ and 3.7 Hz, 1H), 2.00 (dd, $J = 10.1$ and 6.8 Hz, 1H), 1.82 (ddd, $J = 13.3$, 7.9 and 7.9 Hz, 1H), 1.44 (ddd, $J = 13.1$, 7.8 and 5.3 Hz, 1H). ^{13}C NMR: δ 146.8 (s, 3C), 139.0 (s, 1C), 128.7 (d, 6C), 128.3 (d, 3C), 127.9 (d, 6C), 127.0 (d, 1C), 126.3 (d, 4C), 71.5 (s, 1C), 63.6 (d, 1C), 61.0 (t, 1C), 60.9 (t, 1C), 58.3 (t, 1C), 51.8 (d, 1C), 37.5 (t, 1C). HRMS Calcd for $\text{C}_{31}\text{H}_{33}\text{ON}_2$ ($\text{M}+\text{H}^+$): 449.2587; Found: 449.2575.

Preparation of compound 8a



(2S,4R)-methyl N,1-benzyl-4-fluoropyrrolidine-2-carboxylate (29)

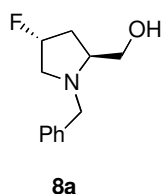
DAST (0.56 mL, 4.25 mmol, 2.5 equiv) was added to a solution of **28** (400 mg, 1.70 mmol, 1 equiv) in CH_2Cl_2 (12 mL) at $-78\text{ }^{\circ}\text{C}$. After 30 min at $-78\text{ }^{\circ}\text{C}$, the temperature was slowly raised to rt. After 2 h, a saturated solution of Na_2CO_3 was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2 . The organic phase was dried over MgSO_4 , filtered and then evaporated *in vacuo*. A purification by flash column chromatography on silica gel (petroleum ether/ Et_2O : 70/30) give **29** (204 mg, 0.86 mmol, 51%) as a colorless oil.



$[\alpha]_{\text{D}}^{20} = -46$ (c 1, CHCl_3). IR (neat): 2953, 1737, 1454, 1437, 1375, 1328, 1204, 1176, 1080, 1029, 754, 701 cm^{-1} . $^1\text{H NMR}$: δ 7.37–7.21 (m, 5H), 5.19 (dm, $J = 55.2\text{ Hz}$, 1H), 3.94 (d, $J = 13.0\text{ Hz}$, 1H), 3.71–3.62 (m, 5H), 3.38 (ddd, $J = 29.8, 11.9$ and 5.0 Hz , 1H), 2.77 (dddd, $J = 30.7, 11.9, 2.0$ and 1.4 Hz , 1H), 2.46–2.15 (m, 2H). $^{13}\text{C NMR}$: δ 173.5 (s, 1C), 138.0 (s, 1C), 129.0 (d, 2C), 128.3 (d, 2C), 127.3 (d, 1C), 92.5 (dd, $J = 175.4\text{ Hz}$, 1C), 63.9 (d, 1C), 59.1 (dt, $J = 23.2\text{ Hz}$, 1C), 58.4 (t, 1C), 51.9 (q, 1C), 37.7 (dt, $J = 22.0\text{ Hz}$, 1C). MS-EI m/z (%): 237 (M^+ , 0.6), 178 (29), 91 (100), 65 (12). HRMS Calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{NF}$ ($\text{M}+\text{H}^+$): 238.1238; Found: 238.1229.

((2S,4R)-N,1-benzyl-4-fluoropyrrolidin-2-yl)methanol (8a)

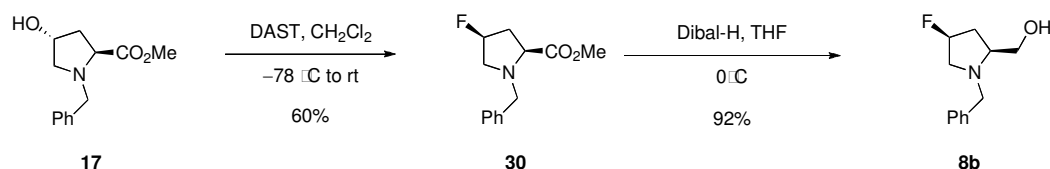
To a suspension of LiAlH_4 (49 mg, 1.29 mmol, 1.5 equiv) in THF (5 mL) at $0\text{ }^{\circ}\text{C}$, a solution of **29** (204 mg, 0.86 mmol, 1.0 equiv) in THF (5 mL) was added dropwise. After stirring at $0\text{ }^{\circ}\text{C}$ for 30 min, water (32 μL), an aqueous 3.75 M NaOH solution (32 μL), and water (73 μL) were successively added at $0\text{ }^{\circ}\text{C}$. The obtained precipitate was collected on a Celite pad and washed with THF. The organic solvent was removed *in vacuo* to give **8a** (104 mg, 0.50 mmol, 58%) as a colorless oil.



$[\alpha]_{\text{D}}^{20} = -42$ (c 1, CHCl_3). IR (neat): 3403, 2926, 2871, 2803, 1496, 1454, 1374, 1342, 1306, 1271, 1243, 1129, 1093, 1070, 1028, 956, 741, 701 cm^{-1} . $^1\text{H NMR}$: δ 7.36–7.23 (m, 5H), 5.09 (dm, $J = 55.2\text{ Hz}$, 1H), 4.03 (d, $J = 13.2\text{ Hz}$, 1H), 3.71 (dd, $J = 11.4$ and 3.7 Hz , 1H), 3.52 (d, $J = 13.2\text{ Hz}$, 1H), 3.46 (dd, $J = 11.2$ and 2.0 Hz , 1H), 3.30 (ddd, $J = 30.5, 12.4$ and 4.9 Hz , 1H), 3.14 (m, 1H), 2.72 (dm, $J = 30.9\text{ Hz}$, 1H), 2.58 (br s, 1H), 2.17–1.99 (m, 2H). $^{13}\text{C NMR}$: δ 138.9 (s, 1C), 128.5 (d, 2C), 128.5 (d, 2C), 127.3 (d,

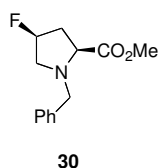
1C), 93.0 (dd, $J = 174.2$ Hz, 1C), 63.2 (d, 1C), 60.2 (t, 1C), 60.2 (dt, $J = 22.4$ Hz, 1C), 58.7 (t, 1C), 35.3 (dt, $J = 21.2$ Hz, 1C). MS-EI m/z (%): 209 (M^+ , 0.1), 178 (23), 91 (100), 65 (11). HRMS Calcd for $C_{12}H_{17}ONF$ ($M+H^+$): 210.1289; Found: 210.1285.

Preparation of compound 8b



(2S,4S)-Methyl N,1-benzyl-4-fluoropyrrolidine-2-carboxylate (30)

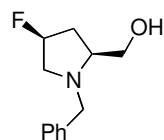
DAST (1.4 mL, 10.65 mmol, 2.5 equiv) was added to a solution of **17** (1.0 g, 4.26 mmol, 1 equiv) in CH_2Cl_2 (25 mL) at -78 °C. The temperature was slowly raised to rt. After 12 h, a saturated solution of Na_2CO_3 was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2 . The organic phase was dried over Na_2SO_4 , filtered and then evaporated *in vacuo*. A purification by flash column chromatography on silica gel (petroleum ether/ Et_2O : 80/20) gave **30** (598 mg, 2.52 mmol, 60%) as a colorless oil.



$[\alpha]_D^{20} = -74$ (c 1, $CHCl_3$). IR (neat): 2954, 1747, 1496, 1454, 1437, 1376, 1280, 1204, 1175, 1073, 1055, 961, 752, 702 cm^{-1} . 1H NMR: δ 7.39–7.22 (m, 5H), 5.1 (dm, $J = 54.9$ Hz, 1H), 4.03 (d, $J = 13.1$ Hz, 1H), 3.70 (s, 3H), 3.60 (d, $J = 13.1$ Hz, 1H), 3.33–3.22 (m, 2H), 2.65–2.43 (m, 2H), 2.29 (dm, $J = 29.9$ Hz, 1H). ^{13}C NMR: δ 173.2 (s, 1C), 137.3 (s, 1C), 129.2 (d, 2C), 128.3 (d, 2C), 127.3 (d, 1C), 91.5 (dd, $J = 178.6$, 1C), 63.7 (d, 1C), 59.2 (dt, $J = 22.4$ Hz, 1C), 57.7 (t, 1C), 52.0 (q, 1C), 37.2 (dt, $J = 23.2$ Hz, 1C). MS-EI m/z (%): 237 (M^+ , 0.5), 18 (28), 91 (100), 65 (12). HRMS Calcd for $C_{13}H_{17}O_2NF$ ($M+H^+$): 238.1238; Found: 238.1229.

((2S,4S)-N,1-benzyl-4-fluoropyrrolidin-2-yl)methanol (8b)

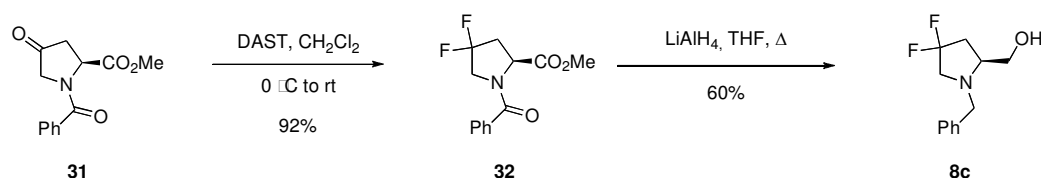
Dibal-H (1M in CH_2Cl_2 , 3.8 mL, 3.8 mmol, 3.0 equiv) was added to a solution of **30** (300 mg, 1.27 mmol, 1.0 equiv) in THF (15 mL) at 0 °C. After 30 min at 0 °C, a saturated solution of potassium sodium tartrate (10 mL) and EtOAc (10 mL) were added to the reaction mixture. After being stirred for 1 h at rt, the solution was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **8b** (245 mg, 1.18 mmol, 92%) as a colorless oil.



8b

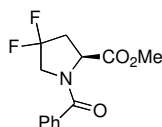
$[\alpha]_D^{20} = -52$ (c 1, CHCl_3). IR (neat): 3403, 2926, 2871, 2803, 1496, 1454, 1374, 1342, 1306, 1271, 1243, 1129, 1093, 1070, 1028, 956, 741, 701 cm^{-1} . $^1\text{H NMR}$: δ 7.37–7.23 (m, 5H), 5.05 (dm, $J = 54.5$ Hz, 1H), 4.04 (d, $J = 13.3$ Hz, 1H), 3.77 (dd, $J = 11.2$ and 3.2 Hz, 1H), 3.49 (dd, $J = 11.1$ and 2.1 Hz, 1H), 3.33 (d, $J = 13.1$ Hz, 1H), 3.23 (ddd, $J = 18.5$, 11.6 and 2.2 Hz, 1H), 2.79 (m, 1H), 2.49–2.25 (m, 2H), 2.18 (dm, $J = 31.2$ Hz, 1H). $^{13}\text{C NMR}$: δ 138.2 (s, 1C), 128.6 (d, 2C), 128.5 (d, 2C), 127.3 (d, 1C), 91.8 (dd, $J = 176.6$ Hz, 1C), 63.2 (d, 1C), 60.6 (t, 1C), 60.4 (t, 1C), 57.5 (t, 1C), 35.3 (dt, $J = 22.8$ Hz, 1C). MS-EI m/z (%): 209 (M^+ , 0.1), 178 (24), 91 (100), 65 (10). HRMS Calcd for $\text{C}_{12}\text{H}_{17}\text{ONF}$ ($\text{M}+\text{H}^+$): 210.1289; Found: 210.1289.

Preparation of compound 8c



(S)-Methyl 4,4-difluoro-1-(phenylcarbonyl)pyrrolidine-2-carboxylate (32)

DAST (1.4 mL, 10.65 mmol, 5 equiv) was added to a solution of **31**^y (526 mg, 2.13 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at $0\text{ }^\circ\text{C}$. The temperature was slowly raised to rt. After 12 h, a saturated solution of Na_2CO_3 was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2 . The organic phase was dried over MgSO_4 , filtered and then evaporated *in vacuo*. A purification by flash column chromatography on silica gel (petroleum ether/EtOAc: 80/20) gave **32** (529 mg, 1.97 mmol, 92%) as a colorless oil.

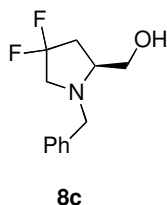


32

$[\alpha]_D^{20} = -116$ (c 1, CHCl_3). IR (neat): 1749, 1646, 1405, 1365, 1288, 1268, 1202, 1179, 1148, 1130, 1100, 1027, 931, 791, 726, 701, 665 cm^{-1} . $^1\text{H NMR}$ (DMSO- d_6 at $120\text{ }^\circ\text{C}$): δ 7.56–7.44 (m, 5H), 4.87 (dd, $J = 9.6$ and 4.7 Hz, 1H), 4.00 (d, $J = 12.9$ Hz, 1H), 3.97 (d, $J = 12.9$ Hz, 1H), 3.69 (s, 3H), 2.96 (ddd, $J = 29.5$, 14.8 and 9.8 Hz, 1H), 2.57 (ddd, $J = 27.6$, 13.2 and 4.6 Hz, 1H). $^{13}\text{C NMR}$ (DMSO- d_6): δ 170.3 (s, 1C), 168.5 (s, 1C), 134.5 (s, 1C), 130.8 (d, 1C), 128.5 (d, 2C), 127.2 (d, 2C), 56.3 (d, 1C), 54.9 (ddt, $J = 32.0$ and 32.0 Hz, 1H), 52.4 (q, 1C), 36.0 (ddt, $J = 23.0$ and 23.0 Hz, 1C). MS-EI m/z (%): 269 (M^+ , 0.3), 249 (5), 210 (11), 105 (100), 77 (40). HRMS Calcd for $\text{C}_{13}\text{H}_{12}\text{O}_3\text{NF}_2\text{Na}$ ($\text{M}+\text{Na}^+$): 292.0756; Found: 292.0756.

(S)-(1-benzyl-4,4-difluoropyrrolidin-2-yl)methanol (**8c**)

To a suspension of LiAlH₄ (140 mg, 2.55 mmol, 3.3 equiv) in THF (5 mL) at 0 °C, a solution of **32** (300 mg, 1.12 mmol, 1.0 equiv) in THF (5 mL) was added dropwise. After stirring at reflux for 1 h, water (90 μL), an aqueous 3.75 M NaOH solution (90 μL), and water (212 μL) were successively added at 0 °C. The obtained precipitate was collected on a Celite pad and washed with THF. The organic solvent was removed in vacuo to give **8c** (152 mg, 0.67 mmol, 60%) as a colorless oil.



$[\alpha]_D^{20} = -58$ (c 1, CHCl₃). IR (neat): 3400, 2930, 2820, 1454, 1375, 1294, 1261, 1222, 1170, 1097, 1029, 960, 940, 827, 743, 700 cm⁻¹. ¹H NMR: δ 7.38–7.25 (m, 5H), 4.04 (d, *J* = 13.5 Hz, 1H), 3.80 (dd, *J* = 11.4 and 2.6 Hz, 1H), 3.48 (dd, *J* = 11.5 and 2.2 Hz, 1H), 3.37 (d, *J* = 13.2 Hz, 1H), 3.27 (ddd, *J* = 11.7, 11.7 and 8.3 Hz, 1H), 3.04 (dddd, *J* = 8.4, 8.4, 2.1 and 2.1 Hz, 1H), 2.72 (ddd, *J* = 16.0, 16.0 and 11.3 Hz, 1H), 2.53–2.2 (m, 3H). ¹³C NMR: δ 137.5 (s, 1C), 128.6 (d, 2C), 128.5 (d, 2C), 127.8 (dds, *J* = 249.3 and 245.7 Hz, 1C), 127.6 (d, 1C), 63.0 (d, 1C), 61.2 (ddt, *J* = 28.8 and 28.8 Hz, 1C), 59.8 (t, 1C), 57.5 (t, 1C), 37.3 (ddt, *J* = 24.4 and 24.4 Hz, 1C). MS-EI *m/z* (%): 227 (M⁺, 0.1), 196 (18), 91 (100), 65 (10). HRMS Calcd for C₁₂H₁₆ONF₂ (M+H⁺): 228.1195; Found: 228.1196.

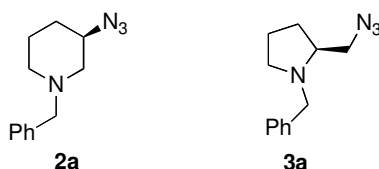
Rearrangement of prolinols

General procedure for rearrangement of prolinols induced by XtalFluor E

To a solution of prolinols in CH₂Cl₂ (0.06 M) was added *n*Bu₄NN₃ (1.1 equiv) and XtalFluor E (1.1 equiv) at 0 °C or –78 °C. The mixture was stirred for 15 min to 4 h at 0 °C or –78 °C. After addition of NaOH (3.75 M), the mixture was extracted with CH₂Cl₂ (x2), dried over MgSO₄, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel afforded 3-azidopiperidine derivatives.

(R)-3-Azido-1-benzylpiperidine (**2a**) and (S)-2-(azidomethyl)-1-benzylpyrrolidine (**3a**)

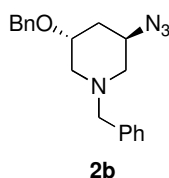
Following the general procedure with *n*Bu₄NN₃ (1.1 equiv, 0 °C, 2 h) and XtalFluor E (1.1 equiv), the transformation of **1a**^{vi} (100 mg, 0.52 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/Et₂O: 80/20) to give a mixture of **2a** and **3a** (78 mg, 0.36 mmol, 69%, **2a/3a** = 50/50).



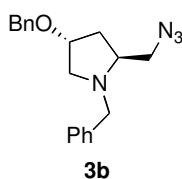
IR (neat): 2091, 1453, 1267, 737, 698 cm^{-1} . ^1H NMR: mixture **2a** + **3a**: δ 7.36–7.21 (m, 5H₂ and 5H₃), 3.99 (d, J = 12.8 Hz, 1H₃), 3.52 (s, 2H₂), 3.47 (dddd, J = 9.0, 9.0, 5.1 and 5.1 Hz, 1H₂), 3.42 (d, J = 12.8 Hz, 1H₃), 3.27 (dd, J = 12.4 and 5.8 Hz, 1H₃), 3.16 (dd, J = 12.4 and 3.9 Hz, 1H₃), 2.96 (ddd, J = 9.4, 7.3 and 2.7 Hz, 1H₃), 2.82 (dd, J = 10.8 and 2.8 Hz, 1H₂), 2.75 (m, 1H₃), 2.60 (ddd, J = 10.1, 4.4 and 4.4 Hz, 1H₂), 2.23 (m, 1H₃), 2.15–2.05 (m, 2H₂), 2.0–1.86 (m, 1H₂ and 1H₃), 1.83–1.66 (m, 1H₂ and 3H₃), 1.56 (m, 1H₂), 1.38 (m, 1H₂). ^{13}C NMR: mixture **2a** + **3a**: δ 139.4 (s, 1C₂ or 1C₃), 137.9 (s, 1C₂ or 1C₃), 129.1 (d, 2C₂ or 2C₃), 128.8 (d, 2C₂ or 2C₃), 128.3 (d, 2C₂ or 2C₃), 128.2 (d, 2C₂ or 2C₃), 127.2 (d, 1C₂ or 1C₃), 127.0 (d, 1C₂ or 1C₃), 63.2 (d, 1C₃), 63.0 (t, 1C₂), 59.4 (t, 1C₃), 57.5 (t, 1C₂), 57.3 (d, 1C₂), 54.6 (t, 1C₃), 54.5 (t, 1C₃), 53.0 (t, 1C₂), 29.6 (t, 1C₂), 28.9 (t, 1C₃), 23.3 (t, 1C₂), 23.1 (t, 1C₃). MS-EI m/z (%): **2a**: 216 (M^+ , 0.2), 174 (.5), 160 (17), 91 (100); **3a**: 174 (0.1), 160 ($\text{M}^+ - \text{CH}_2\text{N}_3$, 19), 91 (100).

(3R,5R)-3-Azido-1-benzyl-5-(benzyloxy)piperidine (2b) and (2S,4R)-2-(azidomethyl)-1-benzyl-4-(benzyloxy)pyrrolidine (3b)

Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, -78°C , 4.5 h) and XtalFluor E (1.1 equiv), the transformation of **1b**^{vii} (100 mg, 0.34 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/Et₂O: 90/10 to 80/20) to give a mixture of **2b** (61 mg, 0.19 mmol, 56%) and **3b** (4 mg, 0.01 mmol, 4%).



$[\alpha]_{\text{D}}^{20} = -62$ (c 1, CHCl_3). IR (neat): 2096, 1495, 1454, 1271, 1153, 1093, 1028, 734, 698 cm^{-1} . ^1H NMR: δ 7.41–7.22 (m, 10H), 4.51 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 3.64 (d, J = 13.2 Hz, 1H), 3.54 (d, J = 13.3 Hz, 1H), 2.65–2.55 (m, 2H), 2.50–2.40 (m, 2H), 1.89–1.77 (m, 2H). ^{13}C NMR: δ 138.5 (s, 1C), 137.4 (s, 1C), 129.1 (d, 2C), 128.4 (d, 2C), 128.3 (d, 2C), 127.6 (d, 2C), 127.3 (d, 2C), 71.6 (d, 1C), 70.6 (t, 1C), 62.5 (t, 1C), 56.4 (t, 1C), 56.2 (t, 1C), 55.3 (d, 1C), 34.8 (t, 1C). HRMS Calcd for $\text{C}_{19}\text{H}_{23}\text{ON}_4$ ($\text{M} + \text{H}^+$): 323.1866; Found: 323.1868.

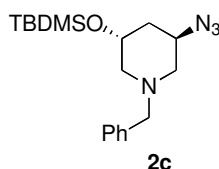


$[\alpha]_{\text{D}}^{20} = -13$ (c 0.3, CHCl_3). IR (neat): 2098, 1495, 1454, 1366, 1334, 1274, 1106, 1067, 736, 698 cm^{-1} . ^1H NMR: δ 7.37–7.22 (m, 10H), 4.67 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.10 (m, 1H), 4.04 (d,

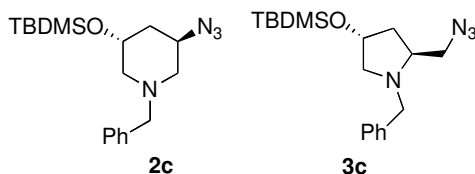
$J = 12.9$ Hz, 1H), 3.47 (d, $J = 12.9$ Hz, 1H), 3.37 (dd, $J = 12.6$ and 5.1 Hz, 1H), 3.26 (dd, $J = 10.3$ and 5.6 Hz, 1H), 3.18 (dd, $J = 12.1$ and 3.8 Hz, 1H), 3.09–3.00 (m, 1H), 2.42 (dd, $J = 10.3$ and 5. Hz, 1H), 2.11–1.94 (m, 2H). ^{13}C NMR: δ 138.9 (s, 1C), 138.2 (s, 1C), 129.1 (d, 2C), 128.4 (d, 2C), 128.4 (d, 2C), 127.6 (d, 3C), 127.1 (d, 1C), 76.7 (d, 1C), 71.3 (t, 1C), 62.3 (d, 1C), 59.7 (t, 1C), 59.3 (t, 1C), 53.6 (t, 1C), 35.9 (t, 1C). HRMS Calcd for $\text{C}_{19}\text{H}_{23}\text{ON}_4$ ($\text{M}+\text{H}^+$): 323.1866; Found : 323.1867.

(3*R*,5*R*)-3-Azido-1-benzyl-5-(*tert*-butyldimethylsilyloxy)piperidine (2c**) and (2*S*,4*R*)-2-(azidomethyl)-1-benzyl-4-(*tert*-butyldimethylsilyloxy)pyrrolidine (**3c**)**

Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, -78 °C, 4.5 h) and XtalFluor E (1.1 equiv), the transformation of **1c**^{viii} (300 mg, 0.93 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (CH_2Cl_2 then $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98/2) to give **2c** (213 mg, 0.62 mmol, 66%) and a mixture of **2c** and **3c** (25 mg, 0.07 mmol, 8%, **2c/3c** = 77/23), **2c/3c** = 98/2.



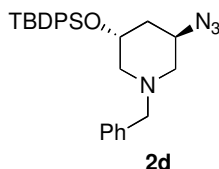
$[\alpha]_{\text{D}}^{20} = +56$ (c 2, CHCl_3). IR (neat): 2095, 1253, 835, 774, 697 cm^{-1} . ^1H NMR: δ 7.30–7.16 (m, 5H), 3.99 (dddd, $J = 7.8, 7.8, 4.1$ and 4.1 Hz, 1H), 3.76 (dddd, $J = 5.4, 5.4, 3.8$ and 3.8 Hz, 1H), 3.60 (d, $J = 13.4$ Hz, 1H), 3.46 (d, $J = 13.5$ Hz, 1H), 2.63 (d, $J = 12.8$ Hz, 1H), 2.55 (dd, $J = 11.7$ and 5.4 Hz, 1H), 2.37 (d, $J = 10.1$ Hz, 1H), 2.12 (dd, $J = 11.3$ and 8.2 Hz, 1H), 1.82 (ddd, $J = 13.2, 4.3$ and 4.3 Hz, 1H), 1.57 (ddd, $J = 12.8, 8.5$ and 3.9 Hz, 1H), 0.83 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H). ^{13}C NMR: δ 137.6 (s, 1C), 128.9 (d, 2C), 128.3 (d, 2C), 127.2 (d, 1C), 65.3 (d, 1C), 62.3 (t, 1C), 60.1 (t, 1C), 55.9 (t, 1C), 55.7 (d, 1C), 37.9 (t, 1C), 25.8 (q, 3C), 18.1 (s, 1C), -4.7 (q, 1C), -4.8 (q, 1C). MS-EI m/z (%): 347 (M^+ , 0.1), 132 (23), 91 (100), 75 (40). HRMS Calcd for $\text{C}_{18}\text{H}_{31}\text{ON}_4\text{Si}$ ($\text{M}+\text{H}^+$): 347.2262; Found : 347.2254.



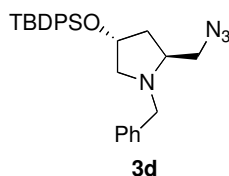
^1H NMR: mixture **2c** + **3c** : δ 7.30–7.19 (m, 5H₂ and 5H₃), 4.28 (dddd, $J = 10.5, 10.5, 10.5$ and 5.5 Hz, 1H₃), 3.99 (dddd, $J = 7.8, 7.8, 4.1$ and 4.1 Hz, 1H₂), 3.97 (d, $J = 12.9$ Hz, 1H₃), 3.76 (dddd, $J = 5.4, 5.4, 3.8$ and 3.8 Hz, 1H₂), 3.60 (d, $J = 13.4$ Hz, 1H₂), 3.46 (d, $J = 13.2$ Hz, 1H₂), 3.46 (d, $J = 13.2$ Hz, 1H₃), 3.28 (dd, $J = 12.8$ and 5.4 Hz, 1H₃), 3.13–3.07 (m, 2H₃), 3.03 (dddd, $J = 12.0, 4.7, 3.8$ and 3.8 Hz, 1H₃), 2.63 (d, $J = 12.8$ Hz, 1H₂), 2.55 (dd, $J = 11.7$ and 5.4 Hz, 1H₂), 2.37 (d, $J = 10.1$ Hz, 1H₂), 2.26 (dd, $J = 10.1$ and 5.6 Hz, 1H₃), 2.12 (dd, $J = 11.3$ and 8.2 Hz, 1H₂), 1.93–1.80 (m, 2H₃ and 1H₂), 1.57 (ddd, $J = 12.8, 8.5$ and 3.9 Hz, 1H₂), 0.84 (s, 9H₂), 0.83 (s, 9H₃), 0.00 (s, 3H₂), 0.00 (s, 3H₃), -0.01 (s, 3H₂), -0.02 (s, 3H₃).

(3*R*,5*R*)-3-Azido-1-benzyl-5-(*tert*-butyldiphenylsilyloxy)piperidine (2d) and (2*S*,4*R*)-2-(azidomethyl)-1-benzyl-4-(*tert*-butyldiphenylsilyloxy)pyrrolidine (3d)

Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, $-78\text{ }^\circ\text{C}$, 4.5 h) and XtalFluor E (1.1 equiv), the transformation of **1dⁱⁱ** (72 mg, 0.16 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/ Et_2O : 95/5) to give **2d** (55 mg, 0.12 mmol, 72%) and **3d** (2 mg, 0.004 mmol, 2%).



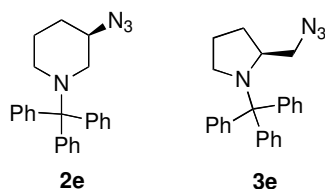
$[\alpha]_{\text{D}}^{20} = +42$ (c 1, CHCl_3). IR (neat): 2093, 1463, 1427, 1258, 1106, 1036, 1028, 821, 738, 698, 610 cm^{-1} . ^1H NMR: δ 7.65–7.60 (m, 4H), 7.44–7.22 (m, 11H), 4.07 (dddd, $J = 7.1, 7.1, 3.9$ and 3.9 Hz, 1H), 3.83 (dddd, $J = 7.3, 7.3, 3.6$ and 3.6 Hz, 1H), 3.51 (d, $J = 13.5$ Hz, 1H), 3.46 (d, $J = 13.2$ Hz, 1H), 2.61 (d, $J = 11.4$ Hz, 1H), 2.51–2.20 (m, 3H), 1.78 (dddd, $J = 7.1, 7.1, 4.1$ and 4.1 Hz, 1H), 1.64 (dddd, $J = 8.0, 8.0, 4.1$ and 4.1 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR: δ 137.8 (s, 1C), 135.7 (d, 1C), 135.7 (d, 1C), 134.1 (s, 1C), 133.9 (s, 1C), 129.8 (d, 2C), 129.7 (d, 2C), 128.9 (d, 2C), 128.3 (d, 2C), 127.7 (d, 2C), 127.6 (d, 2C), 127.1 (d, 1C), 66.4 (d, 1C), 62.3 (t, 1C), 59.4 (t, 1C), 56.4 (t, 1C), 55.4 (d, 1C), 37.5 (t, 1C), 27.0 (q, 3C), 19.2 (s, 1C). HRMS Calcd for $\text{C}_{28}\text{H}_{35}\text{ON}_4\text{Si}$ ($\text{M}+\text{H}^+$): 471.2575; Found : 471.2573.



$[\alpha]_{\text{D}}^{20} = +10$ (c 0.8, CHCl_3). IR (neat): 2096, 1427, 1273, 1105, 910, 822, 738, 698, 611 cm^{-1} . ^1H NMR: δ 7.66–7.57 (m, 5H), 7.44–7.20 (m, 10H), 4.34 (dddd, $J = 6.6, 5.1, 5.1$ and 4.1 Hz, 1H), 4.0 (d, $J = 13.8$ Hz, 1H), 3.57 (d, $J = 13.1$ Hz, 1H), 3.21 (dd, $J = 11.9$ and 4.9 Hz, 1H), 3.15–3.03 (m, 3H), 2.44 (dddd, $J = 5.6, 5.0, 0.6$ and 0.6 Hz, 1H), 1.93 (m, 1H), 1.74 (dddd, $J = 7.0, 7.0, 7.0$ and 7.0 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR: δ 139.3 (s, 1C), 135.7 (d, 2C), 135.7 (d, 2C), 134.0 (s, 1C), 133.9 (s, 1C), 129.7 (d, 1C), 129.7 (d, 1C), 128.7 (d, 2C), 128.3 (d, 2C), 127.7 (d, 2C), 127.7 (d, 2C), 127.0 (d, 1C), 71.6 (d, 1C), 62.4 (d, 1C), 62.2 (t, 1C), 59.8 (t, 1C), 54.0 (t, 1C), 39.0 (t, 1C), 26.7 (q, 3C), 19.1 (s, 1C). HRMS Calcd for $\text{C}_{28}\text{H}_{35}\text{ON}_4\text{Si}$ ($\text{M}+\text{H}^+$): 471.2575; Found : 471.2572.

(*R*)-3-Azido-1-tritylpiperidine (2e) and (*S*)-2-(azidomethyl)-1-tritylpyrrolidine (3e)

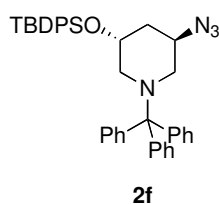
Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, $-78\text{ }^\circ\text{C}$, 30 min) and XtalFluor E (1.1 equiv), the transformation of **1e^{ix}** (100 mg, 0.29 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/ EtOAc 99/1 +0.5% Et_3N) to give a mixture of **2e** and **3e** (72 mg, 0.20 mmol, 67%, **2e/3e** = 88/12).



^1H NMR (DMSO- d_6 at 120 °C, 400 MHz): mixture **2e** + **3e**: δ 7.67–6.95 (m, 15H₃ and 15H₂), 3.83 (dddd, J = 8.3, 8.3, 3.9 and 3.9 Hz, 1H₂), 3.50–3.42 (m, 2H₃), 3.34 (m, 1H₃), 3.25 (m, 1H₃), 2.98–2.70 (m, 2H₂), 1.94–1.68 (m, 5H₂), 1.53–1.41 (m, 2H₃), 1.31 (m, 1H₂), 1.03–0.70 (m, 4H₃).

(3*R*,5*R*)-3-Azido-5-(*tert*-butyldiphenylsilyloxy)-1-tritylpiperidine (**2f**)

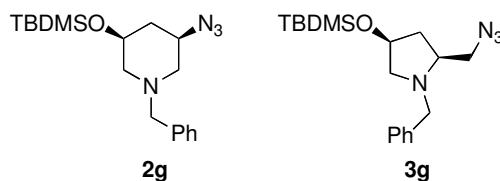
Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, 0 °C, 30 min) and XtalFluor E (1.1 equiv), the transformation of **1f** (100 mg, 0.17 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/Et₂O: 98/2 + 0.5% Et₃N) to give **2f** (68 mg, 0.11 mmol, 65%).



$[\alpha]_{\text{D}}^{20} = +24$ (c 0.7, CHCl₃). IR (neat): 2098, 1448, 1428, 1110, 740, 698 cm⁻¹. ^1H NMR (DMSO- d_6 at 120 °C, 400 MHz): δ 7.72–7.13 (m, 25H), 4.39 (dddd, J = 6.8, 6.8, 2.7 and 2.7 Hz, 1H), 3.96 (dddd, J = 4.8, 4.8, 2.7 and 2.7 Hz, 1H), 2.69 (d, J = 11.5 Hz, 1H), 2.53 (m, 1H), 2.07 (d, J = 11.5 Hz, 1H), 1.97–1.76 (m, 2H), 1.52 (dddd, J = 8.6, 8.6, 4.3 and 4.3 Hz, 1H), 1.07 (s, 9H). HRMS Calcd for C₄₀H₄₂ON₄NaSi (M+Na⁺): 645.3020; Found : 645.3025.

(3*R*,5*S*)-3-Azido-1-benzyl-5-(*tert*-butyldimethylsilyloxy)piperidine (**2g**) and (2*S*,4*S*)-2-(azidomethyl)-1-benzyl-4-(*tert*-butyldimethylsilyloxy)pyrrolidine (**3g**)

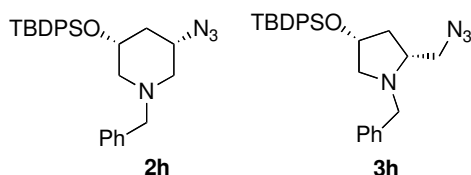
Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, 0 °C, 2.5 h) and XtalFluor E (1.1 equiv), the transformation of **1g** (79 mg, 0.25 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 95/5) to give a mixture of **2g** and **3g** (76 mg, 0.22 mmol, 88%, **2g/3g** = 60/40).



IR (neat): 2952, 2929, 2856, 2094, 1470, 1253, 1100, 835, 775, 738, 698 cm^{-1} . ^1H NMR : δ 7.37–7.18 (m, 5H₂ and 5H₃), 4.27 (dddd, $J = 5.8, 5.8, 3.1$ and 3.1 Hz, 1H₃), 3.99 (d, $J = 13.5$ Hz, 1H₃), 3.74 (dddd, $J = 9.5, 9.5, 4.7$ and 4.7 Hz, 1H₂), 3.59 (d, $J = 13.4$ Hz, 1H₂), 3.48 (d, $J = 13.4$ Hz, 1H₂), 3.45 (d, $J = 13.4$ Hz, 1H₃), 3.41–3.25 (m, 2H₂ and 1H₃), 2.94–2.80 (m, 2H₂ and 2H₃), 2.45 (dd, $J = 10.3$ and 5.4 Hz, 1H₃), 2.27–2.12 (m, 2H₃), 1.87–1.75 (m, 2H₂), 1.69 (ddd, $J = 14.0, 5.7$ and 4.0 Hz, 1H₂), 1.51 (m, 1H₃), 0.85 (s, 9H₃), 0.84 (s, 9H₂), 0.02 (s, 3H₂), 0.00 (s, 3H₂ and 3H₃), -0.025 (s, 3H₃). ^{13}C NMR : δ 139.3 (s, 1C₃), 137.6 (s, 1C₂), 128.9 (d, 2C₂), 128.5 (d, 2C₃), 128.3 (d, 2C₂), 128.3 (d, 2C₃), 127.3 (d, 1C₂), 126.9 (d, 1C₃), 71.0 (d, 1C₃), 66.9 (d, 1C₂), 62.7 (d, 1C₃), 62.4 (t, 1C₃), 62.2 (t, 1C₂), 60.5 (t, 1C₃), 59.3 (t, 1C₃), 56.6 (t, 1C₂), 55.7 (d, 1C₂), 54.9 (t, 1C₂), 39.6 (t, 1C₂), 39.3 (t, 1C₃), 25.9 (q, 3C₃), 25.8 (q, 3C₂), 19.2 (s, 1C₃), 18.1 (s, 1C₂), -4.7 (q, 2C₂), -4.8 (q, 2C₃). MS-EI m/z (%): **2g** : 304 ($\text{M}^+ - \text{N}_3$; 0.4), 290 (1), 157 (1), 133 (19), 132 (20), 91 (100), 75 (50), 73 (19); **3g** : 290 ($\text{M}^+ - \text{CH}_2\text{N}_3$; 9), 157 (19), 91 (100), 75 (87).

(3S,5R)-3-Azido-1-benzyl-5-(tert-butyldiphenylsilyloxy)piperidine (2h) and (2R,4R)-2-(azidomethyl)-1-benzyl-4-(tert-butyldiphenylsilyloxy)pyrrolidine (3h)

Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, -78 °C, 4.5 h) and XtalFluor E (1.1 equiv), the transformation of **1h** (67 mg, 0.15 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 90/10 to 80/20) to give a mixture of **2h** and **3h** (47 mg, 0.10 mmol, 67%, **2h/3h** = 60/40).

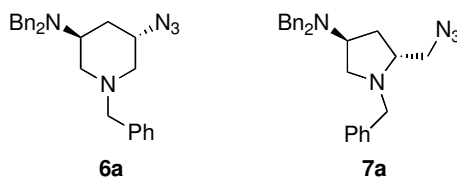


IR (neat): 2095, 1471, 1454, 1427, 1272, 1172, 1105, 909, 822, 736, 699, 611 cm^{-1} . ^1H NMR: δ 7.66–7.57 (m, 4H₂ and 4H₃), 7.46–7.22 (m, 10H₂ and 10H₃), 7.17–7.12 (m, 1H₂ and 1H₃), 4.28 (dddd, $J = 5.3, 5.3, 2.6$ and 2.6 Hz, 1H₃), 4.01 (d, $J = 13.4$ Hz, 1H₃), 3.75 (dddd, $J = 9.5, 9.5, 4.5$ and 4.5 Hz, 1H₂), 3.46 (s, 2H₂), 3.45–3.30 (m, 3H₃), 3.22 (dddd, $J = 10.8, 10.8, 4.4$ and 4.4 Hz, 1H₂), 2.96 (ddd, $J = 10.5, 1.8$ and 1.8 Hz, 1H₃), 2.90–2.78 (m, 2H₂ and 1H₃), 2.30 (dd, $J = 10.3$ and 5.1 Hz, 1H₃), 2.16 (m, 1H₂), 2.09 (m, 1H₃), 1.90 (dd, $J = 10.1$ and 10.1 Hz, 1H₂), 1.83 (dd, $J = 10.4$ and 10.4 Hz, 1H₃), 1.43–1.27 (m, 2H₂), 1.04 (s, 9H₃), 1.03 (s, 9H₂). ^{13}C NMR: δ 139.3 (s, 1C₃), 137.5 (s, 1C₂), 135.8 (d), 135.7 (d), 135.7 (d), 134.9 (s, 2C₃), 133.9 (s, 2C₂), 129.8 (d), 129.8 (d), 129.7 (d), 129.6 (d), 128.9 (d), 128.5 (d), 128.3 (d), 127.7 (d), 127.6 (d), 127.6 (d), 127.2 (d), 127.0 (d), 72.0 (d, 1C₃), 67.5 (d, 1C₂), 62.8 (d, 1C₃), 62.2 (t, 1C₃), 62.1 (t, 1C₂), 60.0 (t, 1C₂), 59.3 (t, 1C₃), 55.7 (t, 1C₂), 55.6 (d, 1C₂), 55.0 (t, 1C₃), 39.2 (t, 1C₂), 38.9 (t, 1C₃), 26.9 (q, 3C₂), 26.9 (q, 3C₃), 19.12 (s, 1C₂ and 1C₃).

(3S,5S)-5-azido-N,N,3-dibenzylamine-N,1-benzylpiperidine (6a) and (3S,5R)-5-(azidomethyl)-N,N,3-dibenzylamine-N,1-benzylpyrrolidine (7a)

Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, 0 °C, 4.5 h) and XtalFluor E (1.1 equiv), the transformation of **5a** (40 mg, 0.10 mmol, 1 equiv) afforded on oil which was purified by flash column

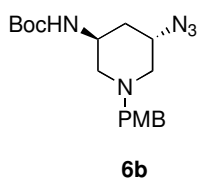
chromatography on silica gel (petroleum ether/Et₂O: 70/30) to give a mixture of **6a** and **7a** (23 mg, 0.06 mmol, 56%, **6a/7a** : 50/50).



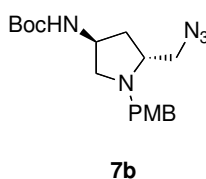
IR (neat): 2096, 1493, 1453, 1364, 1275, 1153, 1072, 1050, 1028, 967, 735, 696 cm⁻¹. ¹H NMR: δ 7.34–7.17 (m, 15H₆ and 15H₇), 3.94 (d, *J* = 12.9 Hz, 1H₇), 3.80 (dddd, *J* = 3.2, 3.2, 3.2 and 3.2 Hz, 1H₇), 3.69–3.46 (m, 6H₆ and 4H₇), 3.45–3.33 (m, 1H₆ and 1H₇), 3.25 (dd, *J* = 12.4 and 5.6 Hz, 1H₇), 3.20 (m, 1H₆), 3.14 (dd, *J* = 12.7 and 4.0 Hz, 1H₇), 3.05–2.97 (m, 2H₆), 2.90–2.77 (m, 1H₆ and 1H₇), 2.26 (dd, *J* = 9.1 and 9.1 Hz, 1H₆), 2.14 (dd, *J* = 11.9 and 2.3 Hz, 1H₇), 2.08 (dd, *J* = 10.5 and 10.5 Hz, 1H₇), 2.05–1.96 (m, 1H₆ and 1H₇), 1.87 (ddd, *J* = 13.1, 8.8 and 5.6 Hz, 1H₆), 1.61 (ddd, *J* = 13.5, 11.6 and 3.8 Hz, 1H₇). ¹³C NMR: δ 140.2 (s, 2C), 139.7 (s, 2C), 138.8 (s, 1C), 137.5 (s, 1C), 129.0 (d, 1C), 128.8 (d, 1C), 128.7 (d, 2C), 128.4 (d, 2C), 128.4 (d, 1C), 128.3 (d, 3C), 128.2 (d, 2C), 127.1 (d, 1C), 126.9 (d, 2C), 62.7 (t, 1C₆), 62.2 (d, 1C₆), 59.1 (t, 1C₆), 58.7 (d, 1C₇), 57.4 (t, 1C₆), 56.4 (d, 1C₇), 55.8 (t, 2C₆ and 4C₇), 54.4 (t, 1C₇), 51.7 (d, 1C₆), 32.2 (t, 1C₆), 30.5 (t, 1C₇).

***tert*-Butyl (3*S*,5*S*)-5-azido-1-(4-methoxybenzyl)piperidin-3-ylcarbamate (**6b**) and *tert*-butyl (3*S*,5*R*)-5-(azidomethyl)-1-(4-methoxybenzyl)pyrrolidin-3-ylcarbamate (**7b**)**

Following the general procedure with *n*Bu₄NN₃ (1.1 equiv, 0 °C, 4.5 h) and XtalFluor E (1.1 equiv), the transformation of **5b** (50 mg, 0.15 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 70/30 to 60/40) to give **6b** (17 mg, 0.05 mmol, 31%) as a yellow solid and **7b** (13 mg, 0.04 mmol, 24%) as a yellow solid.



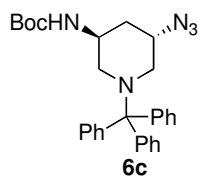
Mp = 83 °C. [α]_D²⁰ = +1 (c 1, CHCl₃). IR (neat): 3351, 2928, 2099, 1710, 1512, 1366, 1300, 1249, 1172, 821 cm⁻¹. ¹H NMR: δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.05 (br s, 1H), 3.96 (m, 1H), 3.81 (s, 3H), 3.62 (m, 1H), 3.50 (d, *J* = 13.3 Hz, 1H), 3.45 (d, *J* = 12.8 Hz, 1H), 2.88 (m, 1H), 2.57 (m, 1H), 2.30 (m, 1H), 2.17–1.91 (m, 2H), 1.50–1.44 (m, 10H). ¹³C NMR: δ 159.0 (s, 1C), 155.0 (s, 1C), 130.2 (d, 2C), 129.2 (s, 1C), 113.8 (d, 2C), 79.5 (s, 1C), 61.8 (t, 1C), 57.1 (t, 1C), 57.0 (t, 1C), 55.3 (d, 1C), 54.6 (q, 1C), 45.3 (d, 1C), 34.7 (t, 1C), 28.5 (q, 3C). HRMS Calcd for C₁₈H₂₈O₃N₅ (M+H⁺) : 362.2187; Found : 362.2179.



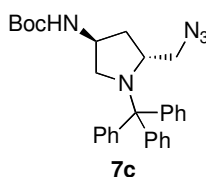
Mp = 66–70 °C. $[\alpha]_D^{20} = +15$ (c 1, CHCl₃). IR (neat) : 3339, 2927, 2099, 1698, 1513, 1366, 1298, 1249, 1172, 1037 cm⁻¹. ¹H NMR : δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.42 (br s, 1H), 4.14 (m, 1H), 3.92 (d, *J* = 13.1 Hz, 1H), 3.80 (s, 3H), 3.41 (d, *J* = 13.0 Hz, 1H), 3.32–3.21 (m, 2H), 3.15 (dd, *J* = 12.7 and 3.8 Hz, 1H), 2.91 (m, 1H), 2.18–2.04 (m, 2H), 1.74 (ddd, *J* = 12.5, 8.3 and 8.3 Hz, 1H), 1.42 (s, 9H). ¹³C NMR : δ 158.8 (s, 1C), 155.3 (s, 1C), 130.5 (s, 1C), 129.8 (d, 2C), 113.8 (d, 2C), 79.5 (s, 1C), 61.6 (d, 1C), 59.8 (t, 1C), 58.0 (t, 1C), 55.3 (q, 1C), 54.0 (t, 1C), 48.5 (d, 1C), 36.3 (t, 1C), 28.4 (q, 3C). HRMS Calcd for C₁₈H₂₈O₃N₅ (M+H⁺) : 362.2187; Found : 362.2178.

***tert*-Butyl (3*S*,5*S*)-5-azido-1-tritylpiperidin-3-ylcarbamate (6c) and *tert*-butyl (3*S*,5*S*)-5-azido-1-tritylpiperidin-3-ylcarbamate (7c)**

Following the general procedure with *n*Bu₄NN₃ (1.1 equiv, 0 °C, 2.5 h) and XtalFluor E (1.1 equiv), the transformation of **5c** (100 mg, 0.22 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 90/10 to 80/20) to give **6c** (79 mg, 0.16 mmol, 74%) as a white solid and **7c** (18 mg, 0.04 mmol, 17%) as a colorless oil.



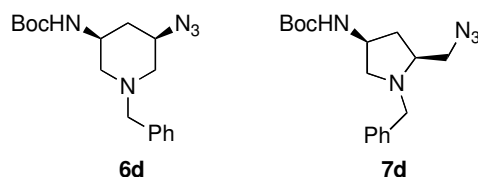
Mp = 100 °C. $[\alpha]_D^{20} = -50$ (c 2, CHCl₃). IR (neat): 2099, 1695, 1491, 1448, 1391, 1366, 1250, 1164, 1045, 1028, 747, 709, 630 cm⁻¹. ¹H NMR (DMSO-d₆ at 120 °C, 400 MHz): δ 7.50–7.44 (m, 5H), 7.33–7.25 (m, 7H), 7.22–7.14 (m, 3H), 6.49 (br s, 1H), 4.09 (m, 1H), 3.95 (dddd, *J* = 11.8, 7.9, 7.9 and 3.7 Hz, 1H), 2.48–2.17 (m, 3H), 1.94 (m, 1H), 1.76 (m, 1H), 1.60 (dddd, *J* = 12.5, 7.8 and 4.9 Hz, 1H), 1.43 (s, 9H). HRMS Calcd for (M+Na⁺) : 506.2527; Found : 506.2519.



IR (neat): 2099, 1695, 1491, 1448, 1391, 1366, 1250, 1164, 1045, 1028, 747, 709, 630 cm⁻¹. ¹H NMR (DMSO-d₆ at 120 °C, 400 MHz): δ 7.56–7.48 (m, 6H), 7.35–7.25 (m, 6H), 7.25–7.15 (m, 3H), 5.21 (br s, 1H), 4.04 (m, 1H), 3.78–3.40 (m, 3H), 3.27 (m, 1H), 2.66 (dd, *J* = 7.2 and 7.2 Hz, 1H), 2.37 (m, 1H), 1.95–1.77 (m, 1H), 1.35 (s, 9H).

***tert*-Butyl (3*S*,5*R*)-5-azido-1-benzylpiperidin-3-ylcarbamate (6d) and *tert*-butyl (3*S*,5*S*)-5-(azidomethyl)-1-benzylpyrrolidin-3-ylcarbamate (7d)**

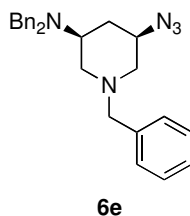
Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, 0 °C, 15 min) and XtalFluor E (1.1 equiv), the transformation of **5d** (100 mg, 0.33 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$: 98/2) to give a mixture of **6d** and **7d** (68 mg, 0.21 mmol, 63%, **6d/7d** = 90/10).



IR (neat): 2095, 1693, 1496, 1365, 1250, 1165, 1070, 742, 699 cm^{-1} . ^1H NMR (DMSO- d_6 at 120 °C, 400 MHz): δ 7.37–7.21 (m, 5H₆), 6.17 (br s, 1H₆), 3.67–3.49 (m, 4H₆), 2.91 (dd, J = 10.9 and 4.2 Hz, 1H₆), 2.84 (dd, J = 10.7 and 4.1 Hz, 1H₆), 2.09 (dd, J = 10.8 and 10.8 Hz, 1H₆), 1.97 (dd, J = 10.8 and 10.8 Hz, 1H₆), 1.90 (dd, J = 10.8 and 10.8 Hz, 1H₆), 1.40 (s, 9H₆), 1.31 (ddd, J = 12.0, 12.0 and 12.0 Hz, 1H₆). ^{13}C NMR: δ 155.1 (s, 1C₆), 137.4 (s, 1C₆), 128.9 (d, 2C₆), 128.4 (d, 2C₆), 127.3 (d, 1C₆), 79.5 (s, 1C₆), 62.3 (t, 1C₆), 57.9 (t, 1C₆), 56.3 (t, 1C₆), 56.1 (d, 1C₆), 45.6 (d, 1C₆), 35.1 (t, 1C₆), 28.4 (q, 3C₆).

(3S,5R)-5-Azido-*N,N*,3-dibenzylamine-*N*,1-benzylpiperidine (**6e**)

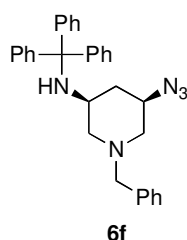
Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, 0 °C, 4.5 h) and XtalFluor E (1.1 equiv), the transformation of **5e** (116 mg, 0.30 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 95/5) to give **6e** (70 mg, 0.17 mmol, 57%).



$[\alpha]_{\text{D}}^{20}$ = +4 (c 2, CHCl_3). IR (neat): 2091, 1494, 1453, 1254, 1065, 734, 696 cm^{-1} . ^1H NMR: δ 7.34–7.18 (m, 15H), 3.72 (d, J = 14.0 Hz, 2H), 3.61 (d, J = 14.0 Hz, 2H), 3.58 (d, J = 13.1 Hz, 1H), 3.49 (d, J = 13.1 Hz, 1H), 3.36 (dddd, J = 13.4, 9.0, 9.0 and 4.2 Hz, 1H), 3.0 (ddd, J = 10.4, 2.1 and 21 Hz, 1H), 2.93 (ddd, J = 12.3, 2.9 and 2.9 Hz, 1H), 2.86 (m, 1H), 2.25 (m, 1H), 1.98 (dd, J = 10.4 and 10.4 Hz, 1H), 1.77 (dd, J = 10.7 and 10.7 Hz, 1H), 1.41 (ddd, J = 11.7, 11.7 and 11.7 Hz, 1H). ^{13}C NMR: δ 140.10 (s, 2C), 137.7 (s, 1C), 128.7 (d, 2C), 128.4 (d, 4C), 128.3 (d, 2C), 128.3 (d, 4C), 127.2 (d, 1C), 126.9 (d, 2C), 62.5 (t, 1C), 57.5 (d, 1C), 57.0 (t, 1C), 54.7 (t, 1C), 54.4 (t, 2C), 54.0 (d, 1C), 32.0 (t, 1C). HRMS Calcd for $\text{C}_{20}\text{H}_{30}\text{N}_5$ ($\text{M}+\text{H}^+$): 412.2496; Found : 412.2497.

(3S,5R)-5-Azido-*N*,1-benzylpiperidin-*N*,3-tritylamine (**6f**)

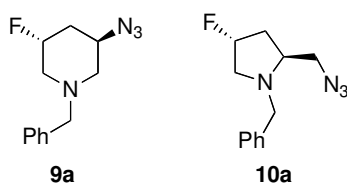
Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, 0 °C, 4.5 h) and XtalFluor E (1.1 equiv), the transformation of **5f** (43 mg, 0.10 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 60/40 + 0.5% Et₃N) to give **6f** (38 mg, 0.08 mmol, 84%).



$[\alpha]_D^{20} = +12$ (c 1.75, CHCl₃). IR (neat): 2093, 1490, 1448, 1069, 1028, 902, 733, 697 cm⁻¹. ¹H NMR: δ 7.58–7.07 (m, 20H), 3.35 (d, $J = 13.2$ Hz, 1H), 3.30 (d, $J = 13.2$ Hz, 1H), 3.18 (dddd, $J = 10.3, 10.3, 4.5$ and 4.5 Hz, 1H), 2.74 (dd, $J = 10.9$ and 4.3 Hz, 1H), 2.64 (dddd, $J = 10.4, 7.8, 7.8$ and 3.9 Hz, 1H), 2.22 (dd, $J = 11.0$ and 3.8 Hz, 1H), 1.79 (dd, $J = 10.2$ and 10.2 Hz, 1H), 1.55 (br s, 1H), 1.42 (m, 1H), 0.95 (ddd, $J = 11.3, 11.3$ and 11.3 Hz, 1H). ¹³C NMR: δ 146.9 (s, 3C), 137.6 (s, 1C), 129.0 (d, 2C), 128.6 (d, 6C), 128.3 (d, 2C), 127.9 (d, 6C), 127.1 (d, 1C), 126.4 (d, 3C), 71.3 (s, 1C), 62.3 (t, 1C), 60.0 (t, 1C), 57.0 (t, 1C), 56.4 (d, 1C), 48.9 (d, 1C), 38.3 (t, 1C). HRMS Calcd for C₃₁H₃₂N₅ (M+H⁺): 474.2652; Found: 474.2646.

(3R,5R)-3-Azido-1-benzyl-5-fluoropiperidine (9a) and (2S,4R)-2-(azidomethyl)-1-benzyl-4-fluoropyrrolidine (10a)

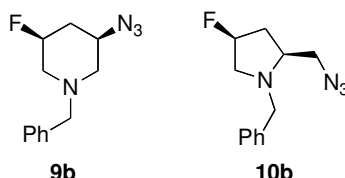
Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, -78 °C, 4 h) and XtalFluor E (1.1 equiv), the transformation of **8a** (103 mg, 0.49 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/Et₂O: 90/10) to give a mixture of **9a** and **10a** (76 mg, 0.32 mmol, 66%, **9a/10a** = 93/7).



IR (neat): 2926, 2097, 1454, 1257, 1152, 1055, 1029, 989, 930, 731, 699 cm⁻¹. ¹H NMR: δ 7.36–7.24 (m, 5H₉), 4.84 (dddd, $J = 47.2, 5.3, 5.3, 3.0$ and 3.0 Hz, 1H₉), 3.84 (dddd, $J = 8.5, 8.5, 4.1$ and 4.1 Hz, 1H₉), 3.61 (s, 2H₉), 2.90–2.77 (m, 2H₉), 2.43 (ddd, $J = 29.2, 12.4$ and 2.1 Hz, 1H₉), 2.28–2.21 (m, 2H₉), 1.68 (dddd, $J = 32.1, 13.2, 9.5$ and 3.1 Hz, 1H₉). ¹³C NMR: δ 137.0 (s, 1C₉), 129.0 (d, 2C₉), 128.4 (d, 2C₉), 127.4 (d, 1C₉), 86.5 (dd, $J = 173.4$ Hz, 1C₉), 62.2 (t, 1C₉), 56.3 (t, 1C₉), 56.0 (dt, $J = 21.2$ Hz, 1C₉), 54.4 (dd, $J = 3.6$ Hz, 1C₉), 34.8 (dt, $J = 21.2$ Hz, 1C₉). MS-EI m/z (%): **9a**: 234 (M⁺, 0.2), 178 (13), 132 (7), 102 (32), 91 (100), 88 (37), 65 (23); **10b**: 178 (M⁺-CH₂N₃, 15), 91 (100), 65 (14).

(3*R*,5*S*)-3-Azido-1-benzyl-5-fluoropiperidine (9b) and (2*S*,4*S*)-2-(azidomethyl)-1-benzyl-4-fluoropyrrolidine (10b)

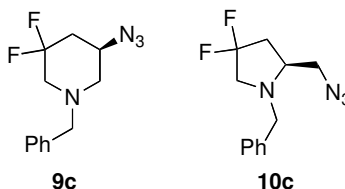
Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, $-78\text{ }^\circ\text{C}$, 4 h) and XtalFluor E (1.1 equiv), the transformation of **8b** (51 mg, 0.24 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/ Et_2O : 80/20) to give a mixture of **9b** and **10b** (33 mg, 0.14 mmol, 58%, **9b/10b** = 50/50).



IR (neat): 2094, 1454, 1273, 1089, 1071, 1028, 736, 699 cm^{-1} . ^1H NMR: δ 7.37–7.22 (m, 5 H_9 and 5 H_{10}), 5.07 (dm, J = 54.2 Hz, 1 H_{10}), 4.61 (dddd, J = 48.1, 9, 9, 4.5 and 4.5 Hz, 1 H_9), 4.08 (d, J = 13.3 Hz, 1 H_{10}), 3.6 (s, 2 H_9), 3.47 (m, 1 H_9), 3.43 (d, J = 13.1 Hz, 1 H_{10}), 3.40–3.18 (m, 3 H_{10}), 3.02 (m, 1 H_9), 2.93–2.79 (m, 1 H_9 and 1 H_{10}), 2.94–1.93 (m, 3 H_9 and 3 H_{10}), 1.56 (m, 1 H_9). ^{13}C NMR: δ 138.3 (s, 1 C_9 or 1 C_{10}), 137.1 (s, 1 C_9 or 1 C_{10}), 129.0 (d, 2 C_9 or 2 C_{10}), 128.7 (d, 2 C_9 or 2 C_{10}), 128.4 (d, 4C), 127.5 (d, 1 C_9 or 1 C_{10}), 127.3 (d, 1 C_9 or 1 C_{10}), 92.1 (dd, J = 177 Hz, 1 C_{10}), 86.3 (dd, J = 174.6 Hz, 1 C_9), 62.3 (t, 1 C_9), 62.1 (d, 1 C_{10}), 60.4 (dt, J = 21.6 Hz, 1 C_{10}), 58.7 (t, 1 C_{10}), 56.2 (dt, J = 21.2 Hz, 1 C_9), 56.5 (t, 1 C_9), 54.9 (dd, J = 11.6 Hz, 1 C_9), 54.2 (t, 1 C_{10}), 36.6 (dt, J = 22.4 Hz, 1 C_{10}), 36.0 (dt, J = 20 Hz, 1 C_9). MS-EI m/z (%): **9b** : 234 (M^+ , 0.1), 178 (12), 102 (30), 91 (100), 88 (35), 65 (24); **10b** : 178 ($\text{M}^+ - \text{CH}_2\text{N}_3$; 20), 91 (100), 65 (13).

(*R*)-5-Azido-1-benzyl-3,3-difluoropiperidine (9c) and (*S*)-2-(azidomethyl)-1-benzyl-4,4-difluoropyrrolidine (10c)

Following the general procedure with $n\text{Bu}_4\text{NN}_3$ (1.1 equiv, $-78\text{ }^\circ\text{C}$, 4 h) and XtalFluor E (1.1 equiv), the transformation of **8c** (115 mg, 0.51 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (petroleum ether/ Et_2O : 90/10) to give a mixture of **9c** and **10c** (85 mg, 0.34 mmol, 66%, **9c/10c** = 91/9).



IR (neat): 2099, 1454, 1281, 1253, 1188, 1103, 1084, 1012, 976, 918, 820, 741, 699, 627 cm^{-1} . ^1H NMR: δ 7.41–7.21 (m, 5 H_9 and 5 H_{10}), 4.08 (d, J = 13.3 Hz, 1 H_{10}), 3.76–3.60 (m, 3 H_9), 3.46 (m, 1 H_{10}), 3.39 (dd, J = 13.2 Hz, 1 H_{10}), 3.31–3.20 (m, 2 H_{10}), 3.05 (m, 1 H_{10}), 3.0–2.88 (m, 2 H_9), 2.73–2.52 (m, 2 H_{10}), 2.47–2.32 (m, 2 H_9), 2.27 (m, 1 H_{10}), 2.17 (dd, J = 10.0 Hz, 1 H_9), 1.76 (m, 1 H_9). ^{13}C NMR: δ 136.5 (s, 1 C_9), 128.9 (d, 2 C_9), 128.6 (d, 2 C_9), 127.7 (d, 1 C_9), 119.5 (dds, J = 243.0 and 243.0 Hz, 1 C_9), 61.5 (t, 1 C_9), 57.4 (ddt, J = 29.2 and 25.6 Hz, 1 C_9), 55.9 (t, 1 C_9), 54.4 (dd, J = 9.2 Hz, 1 C_9), 37.9 (ddt, J = 24.0

and 24.0 Hz, 1C₉). MS-EI *m/z* (%): **9c** : 252 (M⁺, 0.1), 196 (15), 120 (25), 106 (23), 91 (100), 65 (20); **10c** : 196 (M⁺-CH₂N₃⁻, 11), 91 (100), 65 (14).

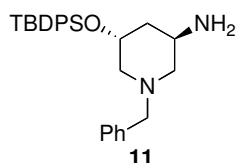
Staudinger reduction

General procedure for the Staudinger reduction of the azido group

To a solution of 3-aminopiperidine derivatives in THF (0.05 M) was added PPh₃ (1.5 equiv) and H₂O (7 equiv) at rt. The mixture was heated under reflux for 5 h. After evaporation of the solvent under reduced pressure, purification of the residue by flash chromatography on silica gel afforded 3-aminopiperidine derivatives of type **A**.

(3*R*,5*R*)-*N*,1-Benzyl-5-(*tert*-butyldiphenylsilyloxy)piperidin-3-amine (**11**)

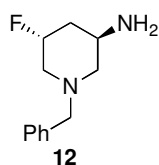
Following the general procedure with PPh₃ (1.5 equiv) and H₂O (7 equiv), the transformation of **2d** (582 mg, 1.24 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (CH₂Cl₂/MeOH: 90/10) to give **11** (500 mg, 1.13 mmol, 91%).



[α]_D²⁰ = +33 (c 1.3, CHCl₃). IR (neat): 2930, 1427, 1109, 822, 737, 699, 609 cm⁻¹. ¹H NMR: δ 7.67–7.59 (m, 4H), 7.43–7.20 (m, 11H), 4.00 (dddd, *J* = 7.2, 7.2, 3.9 and 3.9 Hz, 1H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 13.8 Hz, 1H), 3.26 (m, 1H), 2.52 (d, *J* = 10.7 Hz, 1H), 2.38 (d, *J* = 10.7 Hz, 1H), 2.30–2.12 (m, 2H), 2.04 (br s, 1H), 1.73 (dddd, *J* = 7.8, 7.8, 4.1 and 4.1 Hz, 1H), 1.50 (m, 1H), 1.04 (s, 9H). ¹³C NMR: δ 138.5 (s, 1C), 135.8 (d, 2C), 135.7 (d, 2C), 134.4 (s, 1C), 134.2 (s, 1C), 129.6 (d, 1C), 129.5 (d, 1C), 128.8 (d, 2C), 128.2 (d, 2C), 127.6 (d, 2C), 127.5 (d, 2C), 126.9 (d, 1C), 66.7 (d, 1C), 62.4 (t, 1C), 60.6 (t, 1C), 60.1 (t, 1C), 45.7 (d, 1C), 41.4 (t, 1C), 27.0 (q, 3C), 19.2 (s, 1C). MS-EI *m/z* (%): 188 (M⁺-TBDPSO, 69), 146 (71), 134 (32), 91 (100). HRMS Calcd for C₂₈H₃₇ON₂Si (M+H⁺) : 445.2670; Found : 445.2671.

(3*R*,5*R*)-*N*,1-Benzyl-5-fluoropiperidin-3-amine (**12**)

Following the general procedure with PPh₃ (1.5 equiv) and H₂O (7 equiv), the transformation of the mixture of **9a** and **10a** (56 mg, 0.24 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel (CH₂Cl₂/MeOH: 90/10) to give **12** (41 mg, 0.20 mmol, 82%).

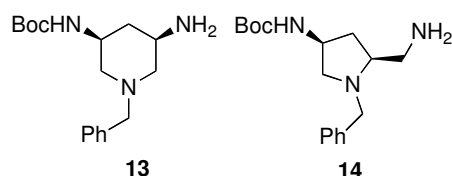


[α]_D²⁰ = + 11 (c 1.95, CHCl₃). IR (neat): 3700–2750, 1600, 1454, 1340, 1306, 1152, 1028, 972, 928, 910, 814, 724, 699, 619 cm⁻¹. ¹H NMR: δ 7.36–7.21 (m, 5H), 4.82 (dddd, *J* = 47.4, 5.3, 5.3, 3.0 and 3.0 Hz,

1H), 3.58 (s, 2H), 3.26 (dddd, $J = 8.3, 8.3, 3.8$ and 3.8 Hz, 1H), 2.87–2.69 (m, 2H), 2.37 (dd, $J = 29.6$ and 12.2 Hz, 1H), 2.16–1.95 (m, 4H), 1.48 (dddd, $J = 23.1, 13.1, 9.5$ and 3.0 Hz, 1H). ^{13}C NMR: δ 137.5 (s, 1C), 129.1 (d, 2C), 128.3 (d, 2C), 127.2 (d, 1C), 87.2 (dd, $J = 172.6$ Hz, 1C), 62.4 (t, 1C), 60.8 (t, 1C), 56.5 (dt, $J = 21.6$ Hz, 1C), 44.8 (dd, $J = 2.8$ Hz, 1C), 38.4 (dt, $J = 20.4$ Hz, 1C). MS-EI m/z (%): 208 (M^+ , 1), 188 ($\text{M}^+ - \text{F}$, 16), 146 (27), 134 (19), 91 (100), 80 (12), 65 (13). HRMS Calcd for $\text{C}_{12}\text{H}_{18}\text{FN}_2$ ($\text{M} + \text{H}^+$): 209.1449; Found: 209.1448.

***tert*-Butyl (3*S*,5*R*)-5-amino-*N*,1-benzylpiperidin-3-ylcarbamate (13) and *tert*-butyl (3*S*,5*S*)-5-(aminomethyl)-*N*,1-benzylpyrrolidin-3-ylcarbamate (14)**

Following the general procedure with PPh_3 (1.5 equiv) and H_2O (7 equiv), the transformation of the mixture of **6d** and **7d** (88 mg, 0.27 mmol, 1 equiv) afforded on oil which was purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$: 80/20) to give a mixture of **13** and **14** (56 mg, 0.18 mmol, 68%, **13/14** = 90/10).



IR (neat): 3376–2805, 1685, 1512, 1365, 1311, 1230, 1164, 1111, 1055, 913, 732, 698 cm^{-1} . ^1H NMR (DMSO- d_6 at 120 $^\circ\text{C}$, 400 MHz): δ 7.39–7.19 (m, 5 H_{13}), 6.17 (br s, 1 H_{13}), 3.54 (d, $J = 13.4$ Hz, 1 H_{13}), 3.50 (d, $J = 13.2$ Hz, 1 H_{13}), 3.46 (m, 1 H_{13}), 2.86–2.75 (m, 3 H_{13}), 2.64 (br s, 2 H_{13}), 1.96 (m, 1 H_{13}), 1.78 (dd, $J = 10.2$ and 10.2 Hz, 1 H_{13}), 1.67 (dd, $J = 11.7$ and 11.7 Hz, 1 H_{13}), 1.39 (s, 9 H_{13}), 1.0 (ddd, $J = 11.2, 11.2$ and 11.2 Hz, 1 H_{13}). ^{13}C NMR: δ 155.2 (s, 1 C_{13}), 138.0 (s, 1 C_{13}), 129.0 (d, 2 C_{13}), 128.3 (d, 2 C_{13}), 127.1 (d, 1 C_{13}), 79.3 (s, 1 C_{13}), 62.3 (t, 1 C_{13}), 60.9 (t, 1 C_{13}), 58.5 (t, 1 C_{13}), 47.1 (d, 1 C_{13}), 46.6 (d, 1 C_{13}), 40.3 (t, 1 C_{13}), 28.4 (q, 3 C_{13}).

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ⁱⁱ a) R. Roudeau, D. Gomez Pardo, J. Cossy *Tetrahedron* **2006**, *62*, 2388–2394; b) T.-X. Métro, D. Gomez Pardo, J. Cossy *J. Org. Chem.* **2007**, *72*, 6556–6561; c) S. Kovačková, M. Dračínský, D. Rejman *Tetrahedron* **2011**, *67*, 1485–1500.

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^{iv} C. Heindl, H. Huebner, P. Gmeiner *Tetrahedron :Asym.* **2003**, *14*, 3141–3152.

^v J. E. Baldwin, S. J. Bamford, A. M. Fryer, M. P. W. Rudolph, M. E. Wood *Tetrahedron* **1997**, *53*, 5233–5254.

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