Supporting Information

Aziridinium from *N,N*-Dibenzylserine Methyl Ester: Synthesis of Enantiomerically Pure β -amino and α,β -diamino Esters

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General information

Mass spectra were obtained either from an AEI MS-50 instrument using electron impact ionization (EI), from an AEI MS-9 using electron spray (ES), or from a MALDI-TOF type of instrument for the high resolution mass spectra (HRMS).

Proton NMR (^1H) spectra were recorded at 300 MHz on a Bruker AC-300 spectrometer. Carbon NMR (^{13}C) spectra were similarly recorded at 75 MHz on a Bruker AC-300 spectrometer, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence.

Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. NMR experiments were carried out in deuteriochloroform (CDCl_3). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, brs: broad singlet for proton spectra. Coupling constants (J) are reported in Hertz (Hz).

Infrared spectra were recorded on a Nicolet 205 FT-IR spectrometer.

Flash chromatography was performed using Kieselgel Si 60, 40-63 μm particle sized silica gel (200-400 mesh). Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with Draggendorf's reagent or potassium permanganate (KMnO_4).

All reagents were obtained from commercial suppliers unless otherwise stated. Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under nitrogen. Other solvents were dried by distillation from the following: tetrahydrofuran (sodium/benzophenone); dichloromethane (calcium hydride). Organic extracts were, in general, dried over anhydrous sodium sulfate (Na_2SO_4).

(R)-methyl 2-(dibenzylamino)-3-hydroxypropanoate (6) To a solution of methyl-D-serine (4.7 g, 30.3 mmol) in a mixture of solvent THF/DMSO (4/1), sodium hydrogenocarbonate (10.1 g, 121.2 mmol, 4 eq) and benzylbromide (10.8 mL, 90.9 mmol, 3 eq) were added at room temperature and the resulting reaction mixture was heated at reflux under an inert atmosphere (Ar) for 15 hours. The resulting slurry was then diluted with water and EtOAc was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with Heptane/EtOAc : 5/1 then 4/1) as the eluent gave **4** (8.6 g, 95 %) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.30 (m, 10H), 3.78 (s, 3H), 3.75 (d, 2H, J = 7.9 Hz), 3.90 and 3.68 (ABq, 4H, J = 13.5 Hz), 3.55 (t, 1H, J = 7.5 Hz), 2.60 (brs, 1H) ; ¹³C NMR (300 MHz, CDCl₃) δ 172.3, 138.7, 129.0, 128.5, 127.4, 61.8, 59.4, 54.8, 51.5 ; IR (cm⁻¹, CHCl₃) 3500, 2851, 1729, 1602, 1496, 1210, 1131, 1044 ; [α]_D²⁵ = + 135 (c = 0.35, CHCl₃); IE (MS) *m/z* calcd for C₁₈H₂₁NO₃ (M⁺) 299, found 299 (M⁺), 240 (M-CO₂Me) Anal. calcd for C₁₈H₂₁NO₃: C, 72.21; H, 7.07; O, 4.68, found C, 72.12; H, 7.21; O, 4.31.

(R)-2-(methoxycarbonyl)-2-(dibenzylamino)ethyl methanesulfonate (4). To a solution of alcohol **6** (2.0 g, 6.69 mmol) in dry CH₂Cl₂ (7 mL) at 0 °C was added dry Et₃N (1.41 mL, 1.5 eq.) and MsCl (0.78 mL, 1.5 eq.). The reaction mixture was stirred for 4 hours at room temperature until all starting material was consumed (TLC monitoring). Water (20 mL) was added and the aqueous layer was extracted three time with CH₂Cl₂ (10 mL). The organic

extracts were unified, dried (Na₂SO₄) and evaporated in vacuo at 20°C. The residue was purified using flash chromatography (Heptane:EtOAc 8/2) to yield **4** as a colorless oil (2.01 g, 80% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.20 (m, 10H), 4.40 (dd, 1H, J = 7.0, 9.0 Hz), 4.25 (dd, 1H, J = 6.2, 9.0 Hz), 3.78 (d, 2H, J = 13.7 Hz), 3.75 (s, 3H), 3.66 (t, 1H, J = 6.5 Hz), 3.57 (d, 2H, J = 13.7 Hz), 2.82 (s, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 170.3, 138.4, 128.4, 127.8, 127.4, 67.4, 59.8, 55.3, 51.8, 37.1; IR (CHCl₃, cm⁻¹) 3036, 2956, 2849, 1732, 1454, 1363, 1175, 964; [α]_D²⁵ = +74.7 (c 0.5, CHCl₃); ESI (MS) *m/z* calcd for C₁₉H₂₄NO₅S (M+H) 378.1, found 378.0.

(S)-methyl 2-azido-3-(dibenzylamino)propanoate (5a) To a mixture of mesylate **4** (103 mg, 0.27 mmol.) in dry CH₃CN (2 mL) and dry DMF (0.5 mL), sodium azide (0.82 mmol, 3 eq.) was added at room temperature and the mixture was heated at 60 °C under an inert atmosphere (Ar) for 6 hours. The resulting slurry was then diluted with EtOAc (10 mL) and water (10 mL) was added. The layers were separated and the aqueous layer was extracted twice with EtOAc (10 mL). The organic layers were combined, washed with brine (10 mL), dried (Na₂SO₄) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with Heptane-EtOAc (10:1) as the eluent gave **5a** (80 mg, 90% yield) as a colorless oil : ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.20 (m, 10H), 3.88 (t, 1H, J = 6.5 Hz), 3.66 (d, 2H, J = 13.5 Hz), 3.65 (s, 3H), 3.54 (d, 2H, J = 13.5 Hz), 2.88 (m, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 169.9, 138.5, 128.7, 128.4, 127.3, 60.9, 58.8, 55.0, 52.5; IR (CHCl₃, cm⁻¹) 3033, 3011, 2108, 1745, 1232, 1199; [α]_D²⁵ = -14.5 (c 0.4, CHCl₃); HMRS (ESI) *m/z* calcd for C₁₈H₂₁N₄O₂ (M+H) 325.1665 found 325.1666.

(S)-methyl 3-(dibenzylamino)-2-aminopropanoate (9) To a mixture of compound **5a** (193 mg, 0.59 mmol.) in dry THF (4 mL) was added under inert atmosphere triphenylphosphine (234 mg, 0.88 mmol, 1.5 eq) and water (107 μ L, 10 eq). The mixture was stirred at room temperature for 2 hours. The resulting mixture was then diluted with EtOAc and water was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried (Na_2SO_4) and evaporated. Purification by flash column chromatography on silica with Heptane-EtOAc (1:1) as the eluent gave **9** (145 mg, 82%) as a yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.37 (m, 10H), 3.68 (s, 3H), 3.67 (d, 2H, $J = 13.2$ Hz), 3.64 (dd, 1H, $J = 5.3, 8.3$ Hz), 3.55 (d, 2H, $J = 13.2$ Hz), 2.79 (dd, 1H, $J = 5.3, 12.8$ Hz), 2.64 (dd, 1H, $J = 8.3, 12.8$ Hz), 1.60 (bs, 2H); ^{13}C NMR (300 MHz, CDCl_3) δ 175.0, 139.0, 129.1, 128.5, 127.3, 58.9, 58.4, 53.4, 52.1; IR (cm^{-1} , CHCl_3) 3372, 2948, 2801, 1736, 1677, 1494, 1451, 1119, 1027; $[\alpha]_D^{25} = -3.8$ (c 1.0, CHCl_3); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) 321.1578, found 325.1666.

tert-butyl (S)-1-(methoxycarbonyl)-2-(dibenzylamino)ethylcarbamate (10) To a mixture of compound **9** (135 mg, 0.45 mmol.) in dry CH_3CN (4 mL) was added under inert atmosphere Boc_2O (222 mg, 1.05 mmol, 2.2 eq) and triethylamine (96 μ L). The mixture was stirred at room temperature for 15 hours. The resulting mixture was then diluted with EtOAc and water was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried (Na_2SO_4) and

evaporated. Purification by flash column chromatography on silica with Heptane-EtOAc (10:1) as the eluent gave **10** (80 mg, 90%) as a yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.42 (m, 10 H), 4.99 (bd, 1H), 4.41 (bq, 1H), 3.63 (s, 3H), 3.59 (d, 2H, $J = 13.5$ Hz), 3.48 (d, 2H, $J = 13.5$ Hz), 2.75 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (300 MHz, CDCl_3) δ 172.4, 138.8, 129.1, 128.4, 127.2, 80.5, 58.5, 55.0, 52.5, 28.4; IR (cm^{-1} , CHCl_3) 3417, 2977, 2803, 1748, 1716, 1495, 1452, 1366, 1248, 1164, 1058, 1027; $[\alpha]_D^{25} = -5.9$ (c 0.7, MeOH); HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) 421.2103, found 421.2092.

tert-butyl (S)-1-(methoxycarbonyl)-2-aminoethylcarbamate (11) To a solution of compound **10** (71 mg, 0.178 mmol.) in dry MeOH (3 mL) was added under inert atmosphere Pd/C (catalytic amount). The mixture was stirred under hydrogen atmosphere ($P = 1$ atm) at room temperature for 5 hours. The resulting mixture was then filtered and the solution was concentrated under pressure to give **11** (33 mg, 85%) as a yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 5.39 (bs, 1H), 4.32 (bs, 1H), 3.79 (s, 3H), 3.07 (d, 2H, $J = 4.9$ Hz), 1.48 (s, 9H); ^{13}C NMR (300 MHz, CDCl_3) δ 171.5, 155.8, 80.4, 54.3, 52.8, 42.8, 28.4; IR (cm^{-1} , CHCl_3) 3348, 2978, 2932, 1700, 1521, 1393, 1367, 1252, 1167; $[\alpha]_D^{25} = -25.0$ (c 1.0, MeOH); MS (ESI) m/z calcd for $\text{C}_9\text{H}_{19}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) 219.1, found 219.1.

(S)-methyl 3-(dibenzylamino)-2-((S)-2-methoxy-2-phenylacetamido)-propanoate (12) To a solution of compound **9** (34 mg, 0.156 mmol.) in dry CH₂Cl₂ (1 mL) was added under inert atmosphere the methyl ether of (S)-mandelic acid (30 mg, 0.18 mmol, 1.15 eq) and EDCI (37 mg, 0.2 mmol, 1.25 eq). The mixture was stirred at room temperature for 8 hours. The resulting mixture was then filtered and the solution was concentrated under reduced pressure to give **13** (45 mg, 82%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.20 (m, 15H), 4.69 (s, 1H), 4.59 (q, J = 6.6 Hz, 1H), 3.71 (s, 3H), 3.63 (d, J = 13.5 Hz, 2H), 3.44 (s, 3H), 3.42 (d, J = 13.5 Hz, 2H), 2.83 (d, J = 6.6 Hz, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 171.0, 170.8, 138.7, 137.0, 129.1, 128.5, 128.6, 127.3, 127.0, 83.7, 58.4, 57.6, 54.0, 52.5, 50.8.

(S)-methyl 3-(dibenzylamino)-2-((R)-2-methoxy-2-phenylacetamido)-propanoate (13)

To a solution of compound **9** (34 mg, 0.156 mmol.) in dry CH₂Cl₂ (1 mL) was added under inert atmosphere (R)-mandelic acid (30 mg, 0.18 mmol, 1.15 eq) and EDCI (37 mg, 0.2 mmol, 1.25 eq). The mixture was stirred at room temperature for 8 hours. The resulting mixture was then filtered and the filtrate was concentrated under pressure to give **13** (45 mg, 82%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.51-7.24 (m, 15H), 4.65 (q, J = 6.7 Hz, 1H), 4.64 (s, 1H), 3.65 (d, J = 13.5 Hz, 2H), 3.61 (s, 3H), 3.58 (d, J = 13.5 Hz, 2H), 3.40 (s, 3H), 2.92 (m, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 171.6, 170.5, 138.6, 136.8, 129.1, 128.6, 128.5, 127.6, 127.4, 83.9, 58.4, 57.1, 54.1, 52.3, 50.8.

General procedure for nucleophilic addition of amine on mesylate 4.

To a mixture of mesylate **4** in dry CH₃CN, amine (2 or 3 eq.) was added at room temperature and the mixture was heated at 60 °C under an inert atmosphere (Ar) for 2-3 hours. The

resulting mixture was then diluted with EtOAc and water was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried (Na₂SO₄) and evaporated. Purification by flash column chromatography on silica with Heptane-EtOAc (9:1) as the eluent gave the corresponding diamine.

(S)-methyl 3-(dibenzylamino)-2-morpholinopropanoate (5b) yellow oil (92%) column chromatography on silica with Heptane-EtOAc (4:1) as the eluent. ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.21 (m, 10H), 3.62-3.40 (m, 7H), 3.45 (d, 2H, J = 13.4 Hz), 3.31 (dd, 1H, J = 5.8, 9.0 Hz), 2.90 (dd, 1H, J = 9.1, 12.7 Hz), 2.66 (dd, 1H, J = 5.7, 12.6 Hz), 2.44 (m, 4H); ¹³C NMR (75.5 MHz, CDCl₃) δ 171.4, 138.9, 128.9, 128.7, 128.1, 126.9, 67.0, 58.7, 53.6, 52.8, 51.0, 50.4; IR (CHCl₃, cm⁻¹): 3032, 2955, 2829, 1732, 1453, 1199, 1116; [α]_D²⁵ = +27.5 (c 0.7, CHCl₃); HRMS (ESI) *m/z* calcd for C₂₂H₂₉N₂O₃ (M+H) 369.2178, found 369.2194.

(S)-methyl 3-amino-2-(4-benzylpiperazin-1-yl)propanoate (5c) yellow oil (77%) column chromatography on silica with Heptane-EtOAc (5:1) as the eluent. ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.22 (m, 15H), 3.74 (d, 2H, J = 13.3 Hz), 3.65 (s, 3H), 3.51 (s, 2H), 3.45 (d, 2H, J = 13.3 Hz), 3.39 (dd, 1H, J = 9.4, 5.4 Hz), 2.99 (dd, 1H, J = 12.8, 9.4 Hz), 2.71 (dd, 1H, J = 12.8, 5.4 Hz), 2.48 (m, 8H); ¹³C NMR (250 MHz, CDCl₃) δ 171.8, 139.2, 138.1, 129.3,

129.1, 128.3, 128.2, 127.1, 127.0, 67.2, 63.2, 63.1, 58.9, 53.5, 53.3, 50.2 ; IR (cm⁻¹, CHCl₃) 3024, 2944, 2810, 1731, 1494, 1453, 1157, 1011 ; [α]_D²⁵ = +22.5 (c 3.2, CHCl₃) ; HRMS (ESI) m/z calcd for C₂₉H₃₆N₃O₂ (M+H) 458.2807, found 458.2796.

(S)-methyl 3-(dibenzylamino)-2-thiomorpholinopropanoate (5d) yellow oil (84%) column chromatography on silica with Heptane-EtOAc (5:1) as the eluent. ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.24 (m, 10H), 3.69 (d, 2H, J = 13.6 Hz), 3.66 (s, 3H), 3.55 (d, 2H, J = 13.6 Hz), 3.38 (dd, 1H, J = 8.3, 6.2 Hz), 2.95 (dd, 1H, J = 12.9, 8.3 Hz), 2.76 (m, 5H), 2.62 (m, 4H) ; ¹³C NMR (250 MHz, CDCl₃) δ 171.7, 139.3, 129.3, 128.2, 127.1, 67.7, 58.9, 53.5, 52.4, 51.2, 28.5; IR (cm⁻¹, CHCl₃) 2949, 2910, 2819, 1731, 1494, 1452, 1281, 1193, 1166, 1133 ; [α]_D²⁵ = +3.3 (c 1.0, CHCl₃) ; HRMS (ESI) m/z calcd for C₂₂H₂₈SNaN₂O₂ (M+Na) 401.1769, found 407.1770.

(S)-methyl 3-(dibenzylamino)-2-(piperidin-1-yl)propanoate (5e) yellow oil (37%) column chromatography on silica with Heptane-EtOAc (5:1) as the eluent. ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.22 (m, 10H), 3.73 (d, 1H, J = 13.7 Hz), 3.63 (s, 3H), 3.43 (d, 2H, J = 13.5 Hz), 3.37 (dd, 1H, J = 5.2, 9.4 Hz), 2.99 (dd, 1H, J = 9.5, 12.5 Hz), 2.68 (dd, 1H, J = 5.3, 12.6 Hz), 2.43 (t, 4H, J = 5.2 Hz), 1.52 (dd, 4H, J = 5.5, 10.9 Hz), 1.40 (dd, 2H, J = 5.5, 11.1 Hz); ¹³C NMR (250 MHz, CDCl₃) δ 172.0, 139.3, 129.0, 128.1, 126.9, 67.8, 58.7, 53.6, 51.6, 51.0,

26.3, 24.5 ; IR (cm⁻¹, CHCl₃) 3011, 2939, 2807, 1728, 1453, 1199; [α]_D²⁵ = +22.6 (c 1.1, CHCl₃); HRMS (ESI) m/z calcd for C₂₃H₃₇N₂O₂ (M+H) 367.2386, found 367.2384.

(S)-methyl 1-((S)-1-(methoxycarbonyl)-2-(dibenzylamino)ethyl)pyrrolidine-2-carboxylate (5f) yellow oil (75%) column chromatography on silica with Heptane-EtOAc (10:1) as the eluent. ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.21 (m, 10H), 3.89 (dd, 1H, J = 8.7, 6.0 Hz), 3.73 (d, 2H, J = 13.5 Hz), 3.67 (s, 6H), 3.55 (d, 2H, J = 13.5 Hz), 3.49 (dd, 1H, J = 8.7, 5.6 Hz), 3.04 (dd, 1H, J = 9.0, 12.8), 2.96 (m, 1H), 2.77 (m, 2H), 2.05 (m, 1H), 1.95 (m, 1H), 1.80 (m, 2H) ; ¹³C NMR (300 MHz, CDCl₃) δ 174.5, 172.4, 139.2, 129.0, 128.1, 126.9, 63.0, 61.8, 58.3, 54.4, 51.8, 51.2, 48.0, 29.5, 23.8 ; IR (cm⁻¹, CHCl₃) 2950, 2851, 1734, 1456, 1198, 1171 ; [α]_D²⁵ = - 17.2 (c 1.1, MeOH) ; HRMS (ESI) m/z calcd for C₂₄H₃₁N₂O₄ (M+H) 411.2284, found 411.2274.

(S)-methyl 2,3-bis(dibenzylamino)propanoate (5g) yellow oil (86%) column chromatography on silica with Heptane-EtOAc (5:1) as the eluent. ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.15 (m, 20H), 3.80 (d, 2H, J = 14.0 Hz), 3.69 (s, 3H), 3.67 (dd, 1H, J = 5.3, 8.5 Hz), 3.50 (m, 2H), 3.43 (m, 4H), 3.00 (dd, 1H, J = 8.7, 12.7 Hz), 2.71 (dd, 1H, J = 5.3, 12.7 Hz) ; ¹³C NMR (250 MHz, CDCl₃) δ 172.6, 139.7, 139.6, 129.4, 127.2, 127.0, 126.9, 60.0, 58.3, 58.0, 55.1, 54.3, 51.1 ; IR (cm⁻¹, CHCl₃) 3030, 3013, 1727, 1494, 1453, 1202.

$[\alpha]_D^{25} = -0.6$ (c 0.77, CHCl_3); HRMS (ESI) m/z : calcd for $\text{C}_{32}\text{H}_{35}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) 479.2699, found: 479.2690.

(S)-methyl 3-(dibenzylamino)-2-(N-methyl-N-(prop-2-ynyl)amino)propanoate (5h)

yellow oil (65%) column chromatography on silica with Heptane-EtOAc (10:1) as the eluent.

^1H NMR (300 MHz, CDCl_3) δ 7.45-7.23 (m, 10H), 3.76 (d, 2H, $J = 13.6$ Hz), 3.68 (s, 3H), 3.61 (dd, 1H, $J = 9.4, 5.3$ Hz), 3.46 (d, 2H, $J = 13.6$ Hz), 3.42 (dd, 1H, $J = 2.2, 17.1$ Hz), 3.33 (dd, 1H, $J = 2.2, 17.1$ Hz), 2.94 (dd, 1H, $J = 9.4, 12.5$ Hz, 1H), 2.73 (dd, 1H, $J = 5.3, 12.5$ Hz), 2.32 (s, 3H), 2.24 (t, 1H, $J = 2.2$ Hz); ^{13}C NMR (300 MHz, CDCl_3) δ 172.1, 139.0, 129.2, 128.2, 127.1, 79.0, 73.2, 64.7, 58.8, 53.8, 51.5, 44.0, 39.2; IR (cm^{-1} , CHCl_3) 3290, 2949, 2800, 1733, 1494, 1252, 1366, 1028; $[\alpha]_D^{25} = +37.9$ (c 1.8, CHCl_3); HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) 373.1892, found 373.1888.

(S)-methyl 3-(dibenzylamino)-2-(tert-butylamino)propanoate (5i) yellow oil (41%)

column chromatography on silica with Heptane-EtOAc (5:1) as the eluent. ^1H NMR (300 MHz, CDCl_3) δ 7.31-7.20 (m, 10H), 3.68 (s, 3H), 3.65 (d, 2H, $J = 13.5$ Hz), 3.58 (t, 1H, $J = 7.4$ Hz), 3.51 (d, 2H, $J = 13.5$ Hz), 2.61 (m, 2H), 1.02 (s, 9H); ^{13}C NMR (250 MHz, CDCl_3) δ 175.2, 137.4, 127.5, 125.6, 57.0, 56.6, 53.4, 50.3, 49.4, 27.9; IR (cm^{-1} , CHCl_3) 3686, 3030, 1733, 1600, 1521, 1232, 1199; $[\alpha]_D^{25} = +8.1$ (c 0.7, CHCl_3); Anal calcd for $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2$: C,

74.54; H, 8.53; N, 7.90 found C, 74.61; H, 8.61; N, 7.71; MS (ESI) m/z calcd for $C_{22}H_{31}N_2O_2$ (M+H) 355.2, found 355.2.

(S)-methyl 3-(dibenzylamino)-2-(1,3-dioxoisindolin-2-yl)propanoate (5k) To a solution of mesylate **4** (187 mg, 0.5 mmol.) in a mixture of dry CH_3CN (4 mL), potassium phthalimide (279 mg, 1.5 mmol, 3 eq.) was added at room temperature and the mixture was heated at $80^\circ C$ under an inert atmosphere (Ar) for 2 hours. The resulting slurry was then diluted with EtOAc (10 mL) and water (10 mL) was added. The layers were separated and the aqueous layer was extracted twice with EtOAc (10 mL). The organic layers were combined, washed with brine (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with Heptane-EtOAc (10:1) as the eluent gave azide **5k** (126 mg, 56% yield) as a colorless oil. 1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.75 (m, 4H), 7.26-7.03 (m, 10H), 5.09 (dd, 1H, $J = 10.9, 3.4$ Hz), 3.86 (d, 2H, $J = 13.2$ Hz), 3.69 (s, 3H), 3.41 (dd, 1H, $J = 13.9, 10.9$ Hz), 3.32 (d, 2H, $J = 13.2$ Hz), 3.19 (dd, 1H, $J = 13.9, 3.4$ Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 168.9, 167.1, 138.8, 134.3, 133.9, 132.0, 129.2, 129.1, 128.1, 127.0, 123.4, 58.4, 52.6, 52.2, 50.5; IR (cm^{-1} , $CHCl_3$) 3029, 2842, 2792, 1774, 1744, 1715, 1494, 1452, 1391, 1217, 1109; $[\alpha]_D^{25} = +18.2$ (c 0.1, MeOH) = + 18.2; HRMS (ESI) m/z calcd for $C_{26}H_{24}NaN_2O_4$ (M+Na) : 451.1634, found 451.1629.

(S)-methyl 3-(dibenzylamino)-2-((methoxycarbonyl)methylthio)-propanoate (5l) yellow oil (42%) column chromatography on silica with Heptane-EtOAc (10:1) as the eluent. ^1H NMR (300 MHz, CDCl_3) δ 7.32 (m, 15H), 3.80 (m, 1H), 3.71 (s, 3H), 3.68 (m, 4H), 3.54 (m, 2H), 3.32 (dAB, 1H, $J = 15.5$ Hz), 3.24 (dAB, 1H, $J = 15.5$ Hz), 3.04 (m, 2H), 2.76 (dd, 1H, $J = 5.7, 13.1$ Hz); ^{13}C NMR (300 MHz, CDCl_3) δ 171.3, 170.3, 169.9, 138.5, 138.3, 128.6, 127.9, 127.8, 126.7, 59.9, 57.9, 54.6, 54.1, 52.4, 52.1, 51.1, 45.9, 33.1; IR (cm^{-1} , CHCl_3) 3013, 2955, 1735, 1454, 1437, 1291; $[\alpha]_D^{25} = +4.5$ (c 0.57, CHCl_3); HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{25}\text{NSO}_4\text{Na}$ ($\text{M}+\text{Na}$) 410.1402, found 410.1400.

(S)-methyl 3-(dibenzylamino)-2-(thiométhylcarbonyl)-propanoate (5m) yellow oil (50%) column chromatography on silica with Heptane-EtOAc (6:1) as the eluent. ^1H NMR (300 MHz, CDCl_3) δ 7.43-7.24 (m, 15H, HAr), 3.91 (d, 1H, $J = 13.7$ Hz), 3.82 (s, 3H), 3.58 (d, 2H, $J = 13.7$ Hz), 3.52 (dd, 1H, $J = 6.4, 9.1$ Hz), 3.34 (dd, 1H, $J = 6.3, 13.8$ Hz), 3.22 (dd, 1H, $J = 9.1, 13.8$ Hz), 2.26 (s, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 195.5, 171.5, 138.8, 129.0, 128.2, 127.2, 60.3, 54.6, 51.5, 30.4, 28.8; IR (cm^{-1} , CHCl_3) 3429, 3032, 3011, 2954, 1728, 1686, 1495, 1454, 1248, 1135; $[\alpha]_D^{25} = +107.2$ (c 1.15, CHCl_3); HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{23}\text{NNaSO}_3$ ($\text{M}+\text{Na}$) 380.1296, found 380.1296.

(S)-trimethyl 3-(dibenzylamino)propane-1,1,2-tricarboxylate (5n) To a suspension of NaH (0.053 mmol, 1 eq, 60% in oil) in dry DMF was added under inert atmosphere at 0 °C dimethylmalonate (0.152 g, 1.326 mmol, 1 eq). The solution was stirred for 30 min at room temperature and then a solution of mesylate **4** (500 mg, 1.326 mmol) in dry DMF was added at room temperature and the mixture was heated at 100°C under an inert atmosphere (Ar) for 1 hour. The resulting mixture was then diluted with EtOAc and water was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried (Na₂SO₄) and evaporated. Purification by flash column chromatography on silica with Heptane-EtOAc (8:1) as the eluent gave **5n** (367 mg, 67%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.25 (m, 10H), 3.84 (d, 1H, J = 7.9 Hz), 3.70 (s, 3H), 3.66 (s, 3H), 3.58 (d, 2H, J = 13.5 Hz), 3.57 (s, 3H), 3.49 (d, 2H, J = 13.5 Hz), 3.45 (t, 1H, J = 7.7 Hz), 2.83 (dd, 1H, J = 7.7, 13.1 Hz), 2.58 (dd, 1H, J = 7.4, 13.1 Hz); ¹³C NMR (250 MHz, CDCl₃) δ 172.5, 168.5, 167.9, 138.4, 128.9, 128.1, 126.9, 58.1, 53.0, 52.7, 52.6, 51.8, 51.4, 43.4 ; IR (cm⁻¹, CHCl₃) 3434, 1738, 1261; [α]_D²⁵ = +18.4 (c 0.7, CHCl₃); MS (ESI) *m/z* calcd for C₂₃H₂₇NO₆ (M+H) 414.2, found 414.2; Anal. calcd for C₂₃H₂₇NO₆: C, 66.81; H, 6.58; N, 3.39, found C, 66.73; H, 6.81; O, 3.15.

(3S,4S)-dimethyl 1-benzyl-2-oxopyrrolidine-3,4-dicarboxylate (15) To a solution of compound **5n** (70 mg, 0.17 mmol.) in dry MeOH (3 mL) was added under inert atmosphere Pd(OH)₂ (catalytic amount) The mixture was stirred under hydrogen atmosphere (P = 2.5 bar) at room temperature for 8 hours. The resulting mixture was then filtered and the solution was concentrated under pressure to give **15** (47 mg, 90%) as a yellow oil. ¹H NMR (300

MHz, CDCl₃) δ 7.36-7.21 (m, 5H), 4.47 (s, 2H), 3.85 (s, 3H), 3.72 (d, 1H, J = 8.8 Hz), 3.70 (s, 3H), 3.69 (dd, 1H, J = 8.6, 16.7 Hz), 3.55 (t, 1H, J = 9.7 Hz), 3.39 (dd, 1H, J = 7.2, 9.7 Hz); ¹³C NMR (250 MHz, CDCl₃) δ 171.6, 169.2, 167.5, 135.3, 128.9, 128.2, 128.1, 127.9, 53.1, 52.7, 51.0, 47.0, 46.7, 39.8; IR (cm⁻¹, CHCl₃) 3683, 3032, 3011, 1740, 1697, 1437, 1257, 1233; [α]_D²⁵ = - 26.5 (c 0.5, CHCl₃); MS (ESI) m/z calcd for C₁₅H₁₈NO₅ (M+H) 292.1, found 292.1 ; Anal. calcd for C₁₅H₁₇NO₅ C, 61.85; H, 5.88; N, 4.81, found C, 62.13; H, 5.97; N, 4.57.

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