Enantiocontrolled Synthesis of α -Methyl Amino Acids via $\text{Bn}_2\text{N-}\alpha$ -Methylserine- β -Lactone

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SUPPORTING INFORMATION

General

All reagents were commercially obtained (Aldrich, Acros) at the highest commercial quality and used without further purification. Air and moisture sensitive reagents were transferred via syringe or cannula. All moisture sensitive reactions were carried out in oven-dried glassware under an atmosphere of argon with freshly distilled solvents. The reactions were monitored by thin-layer chromatography carried out on 0.25mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent. The NMR spectra were obtained on a Varian HG-400 (400 MHz) or a Bruker AMX 500 (500 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet; d=doublet, t=triplet, q=quartet, dd=doublet of doublets, m=multiplet, b=broad. Mass spectroscopic analyses were carried out at the facility at The Scripps Research Institute, La Jolla, CA, University of California, San Diego, La Jolla, CA, or University of California, Riverside, Riverside, CA. IR spectra were recorded on a Nicolet 550 Magna FT-IR and values are reported in cm^{-1} units. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: $[\alpha]^{25}_{\text{D}}$ (c: g/100ml, solvent).

$\text{Bn}_2\text{N-}\alpha$ -Me-Ser-OMe (2)

The starting material, $\text{HCl}\cdot\text{H}_2\text{N-}\alpha$ -Me-Ser-OMe (2.96g, 17.5 mmol), was dissolved in a THF:DMSO (80mL:20mL) solution and NaHCO_3 (8.82g, 105 mmol) and BnBr (8.36mL, 70.3 mmol) were added. The solution was refluxed overnight and H_2O (50mL) was added and extracted with EtOAc (100mL). The organic layer was dried over MgSO_4 and the solvent was removed under reduced pressure. The crude mixture was purified via flash chromatography (9:1, Hexanes:EtOAc to 6:4, Hexanes:EtOAc) to give $\text{Bn}_2\text{N-}\alpha$ -Me-Ser-OMe (4.35g, 11.2 mmol) in 64% yield. ^1H NMR (CDCl_3) δ 1.41 (s, 3H), 3.72-3.80 (m, 2H), 3.75 (s, 3H), 3.88 (d, 2H, $J=14.4\text{Hz}$), 7.15-7.24 (m, 10H). ^{13}C (CDCl_3) δ 20.95, 31.15, 51.75, 55.19, 65.48, 68.41, 127.3, 128.5, 140.9, 175.1. IR (NaCl) 3455, 2952, 1728, 1454. MS (ESI) 314 ($\text{M}+\text{H}^+$), 336 ($\text{M}+\text{Na}^+$). $[\alpha]^{25}_{\text{D}} = -34.3$ (c 1.17, CHCl_3).

Bn₂N- α -Me-Ser- β -lactone (4)

The Bn₂N- α -Me-Ser-OH (30mg, 0.1 mmol) was dissolved in dry CH₂Cl₂ (1.5mL) and cooled to 0°C then distilled TEA (56 μ L, 0.4 mmol) and HBTU (57mg, 0.15 mmol) added. The reaction was allowed to warm slowly to room temperature and stirred overnight under argon. The mixture was diluted with CH₂Cl₂ (5 mL) and washed with brine (5 mL). The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The crude mixture was purified via flash chromatography (7:3, CH₂Cl₂:Hexanes) to give Bn₂N- α -Me-Ser- β -lactone (23 mg, 0.082 mmol) in 82% yield. ¹H NMR (CDCl₃) δ 1.70 (s, 3H), 3.82 (d, 2H, J=14.4 Hz, AB), 7.22-7.28 (m, 10H). ¹³C (CDCl₃) δ 16.45, 30.09, 53.90, 72.40, 76.60, 127.5, 128.5, 128.9, 138.5, 171.5. IR (KBr) 2919, 1811. MS (ESI) 282 (M+H⁺). [α ²⁵_D]= 40.52 (c 1.00, CHCl₃). X-Ray data attached and ORTEP diagram are attached.

General Procedure for the opening of Bn₂N- α -Me-Ser- β -lactone (4) with Grignard derived organocuprates

The Bn₂N- α -Me-Ser- β -lactone (30mg, 0.1 mmol) and CuBr•SMe₂ (5mg, 0.02 mmol) were dissolved in dry THF (300 μ L) and SMe₂ (5 μ L) was added. The solution was purged with argon and cooled to -23°C. The Grignard reagent (0.56 mmol) was then added dropwise. The reaction was allowed to stir at -23°C and monitored by TLC. Upon disappearance of Bn₂N- α -Me-Ser- β -lactone the solvent was removed under reduced pressure and redissolved in EtOAc (15 mL). The solution was acidified with saturated NH₄Cl and the organic layer was dried with MgSO₄ and the crude product was purified via flash chromatography (CH₂Cl₂ to 7:3, CH₂Cl₂:Acetone and flushed with MeOH if necessary).

General Procedure for the opening of Bn₂N- α -Me-Ser- β -lactone (4) with Grignard derived organocuprates in the presence of TMSCl

The Bn₂N- α -Me-Ser- β -lactone (30mg, 0.1 mmol) and CuBr•SMe₂ (5mg, 0.02 mmol) were dissolved in dry THF (300 μ L) and SMe₂ (5 μ L) and TMSCl (20 μ L, 0.16 mmol) was added. The solution was purged with argon and cooled to -23°C. The Grignard reagent (0.56 mmol) was then added dropwise. The reaction was allowed to stir at -23°C and monitored by TLC. Upon disappearance of Bn₂N- α -Me-Ser- β -lactone the solvent was removed under reduced pressure and redissolved in EtOAc (15 mL). The solution was acidified with saturated NH₄Cl and the organic layer was dried with MgSO₄ and the crude product was purified via flash chromatography (CH₂Cl₂ to 7:3, CH₂Cl₂:Acetone and flushed with MeOH if necessary).

(S)-2-(dibenzylamino)-2-methylhexanoic acid (5a)

¹H NMR (CD₃OD) δ 0.78 (t, 3H, J=7.2 Hz), 1.13-1.28 (m, 4H), 1.58 (s, 3H), 1.73-1.80 (m, 2H), 4.29 (d, 4H, J=13.8 Hz, AB), 7.27-7.30 (m, 10H). ¹³C (CD₃OD) δ 13.10, 15.84, 22.89, 27.14, 37.11, 55.56, 128.8, 128.9, 133.9, 173.9. IR (NaCl) 2955, 2930, 1698, 1613, 1452. HRMS (EM) [M + H]⁺ calcd for C₂₁H₂₈NO₂ 326.2120, found 326.2115. [α ²⁵_D]= -1.99 (c 1.36, CHCl₃).

(S)-2-(dibenzylamino)-2,5-dimethylhexanoic acid (6a)

¹H NMR (CD₃OD) δ 0.73 (d, 3H, J=6.6 Hz), 0.81 (d, 3H, J=6.6 Hz), 0.97-1.11 (m, 1H), 1.20-1.41 (m, 3H), 1.58 (s, 3H), 1.63-1.88 (m, 1H), 4.31 (d, 4H, J=14.1 Hz, AB), 7.29-7.32 (m, 10H). ¹³C (CD₃OD) δ 15.42, 21.46, 21.57, 55.44, 128.9, 128.9, 129.2, 134.1, 173.9. IR (NaCl) 2947, 1698, 1613, 1452. HRMS (EM) [M + H]⁺ calcd for C₂₂H₃₀NO₂ 340.2277, found 340.2282. [α _D²⁵] = 0.7224 (c 1.94, CHCl₃).

(S)-2-(dibenzylamino)-2,4-dimethylpentanoic acid (7a)

¹H NMR (CD₃OD) δ 0.86 (d, 3H, J=6.3 Hz), 0.98 (d, 3H, J=6.3 Hz), 1.59 (s, 3H), 1.66-1.85 (m, 3H), 4.26 (d, 4H, J=14.1 Hz, AB), 7.24-7.43 (m, 10H). ¹³C (CD₃OD) δ 23.33, 23.92, 24.85, 46.28, 55.37, 69.45, 128.7, 128.8, 129.3, 134.0, 174.2. IR (NaCl) 2955, 1698, 1639, 1460. HRMS (ESI-TOF) [M + H]⁺ calcd for C₂₁H₂₇NO₂ 326.2114, found 326.2119. [α _D²⁵] = 2.688 (c 0.86, CHCl₃).

(S)-2-(dibenzylamino)-5-(1,3-dioxan-2-yl)-2-methylpentanoic acid (8a)

¹H NMR (CD₃OD) δ 1.24-1.52 (m, 6H), 1.54 (s, 3H), 1.72-1.96 (m, 2H), 3.67-3.73 (m, 2H), 3.96-4.0 (m, 2H), 4.25 (d, 4H, J=14 Hz, AB), 7.25 (s, 10H). ¹³C (CD₃OD) δ 16.02, 19.37, 25.75, 34.86, 36.92, 55.44, 66.65, 75.63, 101.8, 128.7, 128.8, 129.3, 134.4, 174.1. IR (KBr) 2964, 2853, 1698, 1639, 1460, 1150. HRMS (ESI-TOF) [M + H]⁺ calcd for C₂₄H₃₁NO₄ 398.2326, found 398.2328. [α _D²⁵] = 1.712 (c 0.93, CHCl₃).

(S)-methyl 2-(dibenzylamino)-5-(1,3-dioxan-2-yl)-2-methylpentanoate

The (S)-2-(dibenzylamino)-5-(1,3-dioxan-2-yl)-2-methylpentanoic acid (0.36 g, 0.91 mmol) was dissolved in DMF (10 mL) and K₂CO₃ (0.63 g, 4.53 mmol) was added. This solution was allowed to stir for five minutes then CH₃I (170 μ L, 2.72 mmol) was added dropwise. The reaction was allowed to stir overnight and the DMF was removed under reduced pressure. The crude mixture was diluted with H₂O (20 mL) and extracted with CH₂Cl₂ (3X, 40 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (1.5:8.5, acetone:CH₂Cl₂) to give (S)-methyl 2-(dibenzylamino)-5-(1,3-dioxan-2-yl)-2-methylpentanoate (0.34 g, 0.83 mmol) in 92% yield. ¹H NMR (CDCl₃) δ 1.27-1.31 (m, 2H), 1.33 (s, 3H), 1.44-1.56 (m, 3H), 1.74-1.79 (m, 2H), 1.98-2.10 (m, 1H), 3.66 (s, 3H), 3.67-3.74 (m, 2H), 3.80 (s, 4H), 4.04-4.09 (m, 2H), 4.43 (t, 1H, J=4.8 Hz), 7.09-7.27 (m, 10H). ¹³C (CDCl₃) δ 18.87, 21.34, 26.06, 35.56, 37.64, 67.08, 67.4, 102.2, 126.6, 128.1, 128.7, 141.6, 175.9. IR (NaCl) 2951, 2847, 1728, 1466, 1151, 706. MS (ESI) 412.10 (M+H⁺). [α _D²⁵] = 12.37 (c 0.87, CHCl₃).

(S)-methyl 2-(dibenzylamino)-2-methyl-6-oxohexanoate (8c)

The (S)-methyl 2-(dibenzylamino)-5-(1,3-dioxan-2-yl)-2-methylpentanoate (0.21 g, 0.51 mmol) was dissolved in an acetic acid/H₂O mixture (8mL:2 mL) and heated to 100°C for five hours. The mixture was diluted with EtOAc (60 mL) and saturated NaHCO₃ was added until basic. The aqueous layer was extracted three times with EtOAc (60 mL) dried over MgSO₄. The crude product was purified via flash chromatography (CH₂Cl₂) to yield (S)-methyl 2-(dibenzylamino)-2-methyl-6-oxohexanoate (**8c**) (0.15 g, 0.42 mmol) in an 83% yield. ¹H NMR (CDCl₃) δ 1.38 (s, 3H), 1.51-1.79 (m, 4H), 2.11-2.27 (m, 2H), 3.69 (s, 3H), 3.81 (d, 4H, J=14.8 Hz, AB), 7.11-7.28 (m, 10H), 9.64 (s, 1H). ¹³C (CDCl₃) δ 14.44, 21.71, 37.03, 44.13, 51.66, 55.17, 67.23, 126.8, 128.2, 128.7, 141.4, 175.7, 202.4. IR (NaCl) 2960, 1728, 1457, 1204, 1125, 706. MS (ESI) 354.09 (M+H⁺). [α ²⁵_D]= 10.46 (c 1.05, CHCl₃).

(S)-methyl 2-(dibenzylamino)-6-hydroxy-2-methylhexanoate (8d)

The (S)-methyl 2-(dibenzylamino)-2-methyl-6-oxohexanoate (17.0 mg, 0.048 mmol) was dissolved in EtOH (1 mL) and NaBH₄ (2 mg, 0.053 mmol) was added. The reaction was allowed to stir for one and a half hours and the reaction was quenched with H₂O (3 mL) and extracted with CH₂Cl₂ (3X, 10 mL). The organic layer was dried over sodium sulfate and concentrated to give pure (S)-methyl 2-(dibenzylamino)-6-hydroxy-2-methylhexanoate (**8d**) (16 mg, 0.0456 mmol) in a 95% yield. ¹H NMR (CDCl₃) δ 1.26-1.45 (m, 2H), 1.35 (s, 3H), 1.68-1.85 (m, 4H), 3.55 (t, 2H, J=6 Hz), 3.67 (s, 3H), 3.81 (s, 4H), 7.10-7.26 (m, 10H). ¹³C (CDCl₃) δ 20.68, 21.48, 33.27, 37.65, 51.63, 55.24, 62.92, 67.56, 126.8, 128.2, 128.8, 141.5, 175.9. IR(NaCl) 3415, 2951, 1737, 1457, 1117. HRMS (ESI-TOF) [M + H]⁺ calcd for C₂₂H₂₉NO₃ 356.222, found 356.2226. [α ²⁵_D]= 11.66 (c 2.71, CHCl₃).

(S)-5-(dibenzylamino)-6-methoxy-5-methyl-6-oxohexanoic acid (8e)

The (S)-methyl 2-(dibenzylamino)-2-methyl-6-oxohexanoate (18.0 mg, 0.051 mmol) was dissolved in acetone (732 μ l) and cooled to 0°C then Jones reagent, CrO₃ (26.0 mg, 0.254 mmol), H₂O (183 μ l, 10.2 mmol), H₂SO₄ (14 μ l, 0.254 mmol), was added dropwise. The reaction was allowed to warm to room temperature and stir for one hour. The reaction was diluted with water (15 mL) and extracted with EtOAc (3X, 20 mL). The combined organic layers were washed with sodium thiosulfate (20 mL) and brine (20 mL) then dried over MgSO₄ and concentrated under reduced pressure to give (S)-5-(dibenzylamino)-6-methoxy-5-methyl-6-oxohexanoic acid (**8e**) (18mg, 0.049 mmol) in an 96% yield. ¹H NMR (CD₃OD) δ 1.33 (s, 3H), 1.48-1.52 (m, 1H), 1.74-1.85 (m, 3H), 2.08-2.15 (m, 2H), 3.65 (s, 3H), 3.79 (d, 4H, J= 14.8 Hz, AB). ¹³C (CD₃OD) δ 19.57, 20.35, 33.73, 36.81, 50.70, 54.60, 67.10, 126.3, 127.7, 128.4, 141.43, 175.9, 176.1. IR (KBr) 3432, 2951, 1711, 1457, 1209, 1125. HRMS (ESI-TOF) [M + H]⁺ calcd for C₂₂H₂₇NO₄ 370.2013, found 370.2018. [α ²⁵_D]= 6.54 (c 3.03, C CHCl₃).

(S)-2-(dibenzylamino)-2-methyl-6-(1H-pyrrol-1-yl)hexanoic acid (9a)

^1H NMR (CD_3OD) δ 1.09-1.80 (m, 6H), 1.49 (s, 3H), 3.69-3.77 (m, 2H), 4.19 (d, 4H, $J=14$ Hz, AB), 6.00 (t, 2H, $J=2$ Hz), 6.59 (t, 2H, $J=2$ Hz), 7.24-7.26 (m, 10H). ^{13}C (CD_3OD) δ 16.53, 22.05, 31.67, 36.62, 48.77, 55.44, 75.05, 107.5, 120.2, 128.5, 128.8, 129.2, 135.0, 174.6. IR (KBr) 2943, 1702, 1641, 1457, 1290, 723. HRMS (ESI-TOF) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2$ 391.238, found 391.2379. $[\alpha]_{\text{D}}^{25} = -3.11$ (c 2.49, CHCl_3).

(S)-3-allyl-2-(dibenzylamino)-2-methylhex-5-ene-1,3-diol (10b)

^1H NMR (CDCl_3) δ 1.19 (s, 3H), 2.50 (d, 2H, $J=7.2$ Hz), 2.64 (d, 2H, $J=7.2$ Hz), 3.64 (d, 1H, $J=11.4$ Hz), 3.79 (d, 1H, $J=10.5$ Hz), 4.21 (d, 4H, $J=15$ Hz, AB), 5.17-5.26 (m, 4H), 5.88-6.08 (m, 2H), 7.10-7.26 (m, 10H). ^{13}C (CDCl_3) δ 1.25, 20.08, 42.26, 42.42, 55.42, 55.57, 56.27, 64.84, 113.9, 114.4, 119.3, 119.4, 126.8, 127.9, 128.5, 128.6, 128.7, 128.8, 128.9, 134.7. IR (NaCl) 3414, 2930, 1639, 1460, 1027, 925. HRMS (EM) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{32}\text{NO}_2$ 366.2433, found 366.2437. $[\alpha]_{\text{D}}^{25} = -2.62$ (c 1.73, CHCl_3).

(S)-2-(dibenzylamino)-2-methylpent-4-enoic acid (11a)

^1H NMR (CD_3OD) δ 1.47 (s, 3H), 2.62 (d, 2H, 6.9 Hz), 4.19 (d, 4H, $J=14.1$ Hz, AB), 5.11-5.17 (m, 2H), 5.79-5.93 (m, 1H), 7.18-7.25 (m, 10H). ^{13}C (CD_3OD) δ 17.81, 41.20, 55.44, 118.4, 128.1, 128.5, 129.0, 132.9, 135.9, 174.7. IR (NaCl) 3023, 2921, 1698, 1639, 1494, 1460, 917. HRMS (ESI-TOF) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_2$ 310.1801, found 310.1805. $[\alpha]_{\text{D}}^{25} = -3.07$ (c 1.1, CHCl_3).

(S)-2-(dibenzylamino)-1-hydroxy-2-methylhept-6-en-3-one (11d)

^1H NMR (CDCl_3) δ 1.27 (s, 3H), 2.33 (q, $J=6.9$ Hz, $J=7.8$ Hz), 2.92 (t, 2H, 7.2 Hz), 3.77 (dd, 2H, $J=11.7$ Hz, $J=87.6$ Hz), 3.79 (d, $J=14.7$ Hz, AB), 4.72-5.10 (m, 2H), 5.76-5.90 (m, 1H), 7.17-7.32 (m, 10H). ^{13}C (CDCl_3) δ 18.18, 28.08, 36.98, 54.99, 55.12, 65.23, 72.71, 115.6, 127.2, 128.6, 128.9, 137.6, 140.6. IR (NaCl) 3448, 2921, 1706, 1494, 1454, 1030, 917. HRMS (ESI-TOF) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_2$ 338.2114, found 338.2118.

(S)-2-(dibenzylamino)-2-methyl-3-phenylpropanoic acid (12a)

^1H NMR (CD_3OD) δ 1.42 (s, 3H), 3.12 (d, 2H, $J=12.4$ Hz), 4.22 (d, 4H, $J=14$ Hz, AB), 7.20-7.26 (m, 10H). ^{13}C (CD_3OD) δ 16.56, 42.86, 55.40, 126.8, 127.9, 128.5, 128.9, 130.6, 135.9, 174.3. IR (KBr) 3032, 2930, 1707, 1622, 1494, 1460, 1214, 747, 705. HRMS (EM) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{26}\text{NO}_2$ 360.1964, found 360.1960. $[\alpha]_{\text{D}}^{25} = 15.56$ (c 0.97, CHCl_3).

(S)-2-(dibenzylamino)-2-methyl-1,1-diphenylpropane-1,3-diol (12b)

^1H NMR (CD_3OD) δ 1.14 (s, 3H), 6.67 (m, 2H), 3.92 (d, 4H, $J=14.8$ Hz, AB), 7.05-7.33 (m, 20H). ^{13}C (CD_3OD) δ 19.54, 20.19, 43.87, 54.98, 59.28, 60.31, 126.2, 126.4, 127.3, 127.6, 127.8, 128.2, 128.3, 128.4, 129.2, 130.9, 156.0. IR (KBr) 3414, 3023, 1494, 1452, 749, 700. HRMS (EM) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{32}\text{NO}_2$ 438.2433, found 438.2444. $[\alpha]_{\text{D}}^{25} = -2.67$ (c 0.39, CHCl_3).

(S)-methyl 2-(dibenzylamino)-2-methyl-3-phenylpropanoate (12c)

The 2-(dibenzylamino)-2-methyl-3-phenylpropanoic acid (27.8 mg, 0.77 mmol) was dissolved in DMF (1 mL) and K_2CO_3 (54 mg, 0.386 mmol) was added and allowed to stir for 5 min. Next, MeI (15 μ L, 0.232 mmol) was added dropwise. The reaction was allowed to stir for four hours then the DMF was concentrated under reduced pressure. The crude mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3X, 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified via flash chromatography (9:1, CH_2Cl_2 :Acetone) to give (S)-methyl 2-(dibenzylamino)-2-methyl-3-phenylpropanoate (26.0 mg, 0.70 mmol) in a 90% yield. ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 2.82 (d, 1H, $J=12.8$ Hz), 3.35 (d, 1H, $J=12.8$ Hz), 3.68 (s, 3H), 3.91 (d, 4H, $J=15.2$ Hz, AB), 7.11-7.31 (m, 15 H). ^{13}C ($CDCl_3$) δ 20.58, 44.36, 51.54, 55.20, 68.91, 126.7, 126.8, 128.2, 128.6, 130.8, 141.5, 175.0. IR (NaCl) 3039, 2943, 1737, 1501, 1449, 1204, 1117, 750, 706. MS (ESI) 374.07 ($M+H^+$). HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{25}H_{27}NO_2$ 374.2114, found 374.2118. $[\alpha]_D^{25} = 41.8$ (c 0.65, $CHCl_3$).

(S)-methyl 2-amino-2-methyl-3-phenylpropanoate (12d)

The (S)-methyl 2-(dibenzylamino)-2-methyl-3-phenylpropanoate (13.0 mg, 0.035 mmol) was dissolved in MeOH (2mL) and Pd/C (5 mg) was added. The reaction was allowed to stir overnight under an atmosphere of H_2 . The reaction was filtered and the MeOH was concentrated under reduced pressure to give (S)-methyl 2-amino-2-methyl-3-phenylpropanoate (6.8 mg, 0.035 mmol) in a quantitative yield. ^1H NMR (CD_3OD) δ 1.56 (s, 3H), 3.04 (d, 1H, $J=14$ Hz), 3.24 (d, 1H, $J=14$ Hz), 3.79 (s, 3H), 7.16-7.35 (m, 5H). ^{13}C (CD_3OD) δ 21.95, 43.61, 52.60, 60.47, 127.8, 128.7, 129.9, 133.5, 174.8. IR (KBr) 3353, 2803, 1728, 1605, 1518, 1264, 749, 714. HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{11}H_{15}NO_2$ 194.1175, found 194.1177.

(S)-2-(dibenzylamino)-3-(4-methoxyphenyl)-2-methylpropanoic acid (13a)

^1H NMR (CD_3OD) δ 1.44 (s, 3H), 3.06 (dd, 2H, $J=12.9$ Hz, $J=22.5$ Hz), 3.74 (s, 3H), 4.25 (d, 4H, $J=14.1$ Hz, AB), 6.81 (d, 2H, $J=8.7$ Hz), 7.16 (d, 2H, $J=8.7$ Hz), 7.25 (m, 10H). ^{13}C (CD_3OD) δ 16.11, 42.09, 54.51, 55.54, 113.4, 127.4, 128.2, 129.0, 129.1, 131.5, 135.4, 158.9, 173.9. IR (KBr) 2938, 1698, 1613, 1511, 1452, 1257, 1180. HRMS (EM) $[M + H]^+$ calcd for $C_{25}H_{28}NO_3$ 390.2069, found 390.2081. $[\alpha]_D^{25} = 24.55$ (c 1.95, $CHCl_3$).

(S)-2-(dibenzylamino)-1,1-bis(4-methoxyphenyl)-2-methylpropane-1,3-diol (13b)

^1H NMR (CD_3OD) δ 1.12 (s, 3H), 3.72 (s, 3H), 3.74 (s, 3H), 3.85 (d, 4H, $J=14.4$ Hz, AB), 4.22 (d, 1H, $J=11.6$ Hz), 4.46 (d, 1H, $J=11.6$ Hz), 6.78-6.83 (m, 4H), 7.13-7.21 (m, 10H), 7.73 (d, 2H, $J=8.8$ Hz), 7.81 (d, 2H, $J=8.8$ Hz). ^{13}C (CD_3OD) δ 20.10, 54.41, 55.07, 65.06, 112.5, 112.8, 126.4, 127.9, 128.6, 128.6, 138.9, 141.7, 158.3. IR (NaCl) 3388, 2964, 1605, 1511, 1257, 1036, 832. HRMS (EM) $[M + H]^+$ calcd for $C_{32}H_{36}NO_4$ 498.2644, found 498.2652. $[\alpha]_D^{25} = 8.31$ (c 0.51, $CHCl_3$).

(S)-2-(dibenzylamino)-3-(1H-indol-3-yl)-2-methylpropanoic acid (14a)

¹H NMR (CD₃OD) δ 1.65 (s, 3H), 3.36 (d, 2H, J=13.6 Hz), 3.85 (d, 2H, J=13.6 Hz), 3.85 (d, 4H, J=13.2 Hz, AB), 7.19-7.49 (m, 14H). ¹³C (CD₃OD) δ 23.91, 57.49, 58.81, 87.39, 111.8, 116.7, 119.0, 119.6, 121.6, 123.3, 124.8, 128.9, 130.0, 132.3, 136.8, 137.8, 145.5, 169.9. IR (KBr) 3414, 3065, 2925, 1710, 1632, 1465, 1107, 749, 705. HRMS (ESI-TOF) [M + H]⁺ calcd for C₂₆H₂₆N₂O₂ 399.2067, found 399.2064. [α ²⁵_D] = -30.3 (c 0.85, CHCl₃).

(S)-3-cyano-2-(dibenzylamino)-2-methylpropanoic acid (15a)

¹H NMR (CD₃OD) δ 1.45 (s, 3H), 3.01 (dd, 2H, J=17.2 Hz, J=70.8 Hz), 3.88 (d, 4H, J=15 Hz, AB), 7.10-7.35 (m, 10H). ¹³C (CD₃OD) δ 23.23, 26.35, 54.91, 118.4, 126.5, 127.8, 128.3, 140.9, 176.4. IR (KBr) 3405, 2930, 2242, 1715, 1673, 1460, 1367, 1231, 747, 705. HRMS (ESI-TOF) [M - H]⁻ calcd for C₁₉H₂₀N₂O₂ 307.1452, found 307.1458. [α ²⁵_D] = -31.63 (c 0.37, CHCl₃).

ORTEP Diagram for Bn₂N- α -Me-Ser- β -lactone (4)

Table 1. Crystal data and structure refinement for Bn₂N- α -Me-Ser- β -lactone (4)

Identification code	goodml	
Empirical formula	C ₁₈ H ₁₉ N O ₂	
Formula weight	281.34	
Temperature	213(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.2738(10) Å	$\alpha = 90^\circ$.
	b = 10.6398(16) Å	$\beta = 90^\circ$.
	c = 20.230(3) Å	$\gamma = 90^\circ$.
Volume	1565.6(4) Å ³	
Z	4	
Density (calculated)	1.194 Mg/m ³	
Absorption coefficient	0.078 mm ⁻¹	
F(000)	600	
Crystal size	0.30 x 0.30 x 0.30 mm ³	
Theta range for data collection	2.01 to 26.00°.	
Index ranges	-8 ≤ h ≤ 8, -13 ≤ k ≤ 12, -24 ≤ l ≤ 22	
Reflections collected	9045	
Independent reflections	3061 [R(int) = 0.0252]	
Completeness to theta = 26.00°	99.8 %	
Absorption correction	None	
Max. and min. transmission	0.9771 and 0.9471	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3061 / 0 / 190	
Goodness-of-fit on F ²	1.037	
Final R indices [I > 2σ(I)]	R1 = 0.0452, wR2 = 0.1138	
R indices (all data)	R1 = 0.0550, wR2 = 0.1195	
Absolute structure parameter	0.9(17)	
Largest diff. peak and hole	0.179 and -0.135 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for $\text{Bn}_2\text{N-}\alpha\text{-Me-Ser-}\beta\text{-lactone}$ (4). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	7903(2)	5412(2)	8815(1)	45(1)
O(1)	10030(2)	3044(2)	8252(1)	64(1)
O(2)	11339(2)	3657(2)	9208(1)	76(1)
C(1)	8060(3)	4047(2)	8822(1)	48(1)
C(2)	10069(3)	3616(2)	8845(1)	55(1)
C(3)	8127(3)	3451(2)	8133(1)	54(1)
C(4)	6895(3)	3335(2)	9325(1)	63(1)
C(5)	6044(3)	5866(2)	8660(1)	54(1)
C(6)	5514(3)	5705(2)	7950(1)	47(1)
C(7)	4086(3)	4925(2)	7757(1)	63(1)
C(8)	3635(3)	4788(2)	7101(1)	73(1)
C(9)	4591(4)	5437(2)	6626(1)	67(1)
C(10)	5985(3)	6230(2)	6807(1)	56(1)
C(11)	6448(3)	6357(2)	7461(1)	50(1)
C(12)	8555(3)	5993(2)	9432(1)	51(1)
C(13)	9110(3)	7330(2)	9315(1)	46(1)
C(14)	10406(3)	7623(2)	8839(1)	53(1)
C(15)	10943(4)	8851(2)	8741(1)	61(1)
C(16)	10195(3)	9801(2)	9113(1)	62(1)
C(17)	8916(3)	9530(2)	9583(1)	57(1)
C(18)	8377(3)	8303(2)	9685(1)	52(1)

Table 3. Bond lengths [Å] and angles [°] for Bn₂N- α -Me-Ser- β -lactone (4)

N(1)-C(1)	1.457(3)	C(6)-C(11)	1.386(3)
N(1)-C(5)	1.470(3)	C(7)-C(8)	1.376(4)
N(1)-C(12)	1.472(3)	C(8)-C(9)	1.372(4)
O(1)-C(2)	1.346(3)	C(9)-C(10)	1.370(3)
O(1)-C(3)	1.470(3)	C(10)-C(11)	1.371(3)
O(2)-C(2)	1.181(3)	C(12)-C(13)	1.498(3)
C(1)-C(4)	1.525(3)	C(13)-C(14)	1.383(3)
C(1)-C(3)	1.532(3)	C(13)-C(18)	1.385(3)
C(1)-C(2)	1.532(3)	C(14)-C(15)	1.378(3)
C(2)-C(3)	2.024(3)	C(15)-C(16)	1.372(3)
C(5)-C(6)	1.496(3)	C(16)-C(17)	1.361(3)
C(6)-C(7)	1.386(3)	C(17)-C(18)	1.379(3)
C(1)-N(1)-C(5)	113.70(17)		
C(1)-N(1)-C(12)	112.63(16)		
C(5)-N(1)-C(12)	109.87(17)		
C(2)-O(1)-C(3)	91.83(16)		
N(1)-C(1)-C(4)	117.24(18)		
N(1)-C(1)-C(3)	113.98(17)		
C(4)-C(1)-C(3)	114.76(18)		
N(1)-C(1)-C(2)	111.93(17)		
C(4)-C(1)-C(2)	111.18(19)		
C(3)-C(1)-C(2)	82.72(16)		
O(2)-C(2)-O(1)	126.0(2)		
O(2)-C(2)-C(1)	138.9(2)		
O(1)-C(2)-C(1)	95.08(18)		
O(2)-C(2)-C(3)	172.4(2)		
O(1)-C(2)-C(3)	46.54(12)		
C(1)-C(2)-C(3)	48.63(12)		
O(1)-C(3)-C(1)	90.19(16)		
O(1)-C(3)-C(2)	41.63(11)		
C(1)-C(3)-C(2)	48.65(12)		
N(1)-C(5)-C(6)	113.86(17)		
C(7)-C(6)-C(11)	117.7(2)		
C(7)-C(6)-C(5)	122.2(2)		
C(11)-C(6)-C(5)	120.09(19)		
C(8)-C(7)-C(6)	120.9(2)		
C(9)-C(8)-C(7)	120.1(2)		
C(8)-C(9)-C(10)	119.8(2)		
C(9)-C(10)-C(11)	120.1(2)		
C(10)-C(11)-C(6)	121.3(2)		
N(1)-C(12)-C(13)	110.54(16)		
C(14)-C(13)-C(18)	118.0(2)		
C(14)-C(13)-C(12)	120.59(19)		
C(18)-C(13)-C(12)	121.37(19)		
C(15)-C(14)-C(13)	120.5(2)		
C(16)-C(15)-C(14)	120.5(2)		
C(17)-C(16)-C(15)	119.8(2)		
C(16)-C(17)-C(18)	120.0(2)		
C(17)-C(18)-C(13)	121.1(2)		

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for $\text{Bn}_2\text{N-}\alpha\text{-Me-Ser-}\beta\text{-lactone (4)}$. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	47(1)	42(1)	48(1)	0(1)	0(1)	-3(1)
O(1)	59(1)	63(1)	69(1)	-4(1)	7(1)	10(1)
O(2)	65(1)	77(1)	86(1)	4(1)	-17(1)	9(1)
C(1)	51(1)	43(1)	51(1)	1(1)	4(1)	-6(1)
C(2)	59(1)	44(1)	63(1)	7(1)	1(1)	0(1)
C(3)	53(1)	48(1)	59(1)	-3(1)	5(1)	2(1)
C(4)	76(2)	49(1)	65(1)	-1(1)	19(1)	-12(1)
C(5)	49(1)	49(1)	65(1)	-3(1)	7(1)	-1(1)
C(6)	36(1)	39(1)	66(1)	0(1)	-3(1)	5(1)
C(7)	46(1)	49(1)	92(2)	11(1)	-7(1)	-8(1)
C(8)	65(1)	48(1)	105(2)	3(1)	-38(2)	-8(1)
C(9)	72(1)	54(1)	75(2)	-3(1)	-25(1)	15(1)
C(10)	55(1)	47(1)	66(1)	3(1)	-7(1)	11(1)
C(11)	41(1)	36(1)	72(1)	0(1)	-2(1)	0(1)
C(12)	60(1)	51(1)	44(1)	3(1)	1(1)	-7(1)
C(13)	47(1)	47(1)	43(1)	2(1)	-6(1)	-3(1)
C(14)	59(1)	53(1)	47(1)	-3(1)	2(1)	-7(1)
C(15)	70(1)	64(2)	47(1)	6(1)	0(1)	-21(1)
C(16)	79(2)	46(1)	61(1)	7(1)	-20(1)	-14(1)
C(17)	64(1)	45(1)	63(1)	-6(1)	-14(1)	3(1)
C(18)	49(1)	58(1)	49(1)	-2(1)	0(1)	-2(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for $\text{Bn}_2\text{N-}\alpha\text{-Me-Ser-}\beta\text{-lactone}$ (4).

	x	y	z	U(eq)
H(3A)	7262	2753	8076	64
H(3B)	8007	4061	7773	64
H(4A)	5634	3627	9301	95
H(4B)	7374	3483	9766	95
H(4C)	6938	2443	9228	95
H(5A)	5965	6760	8774	65
H(5B)	5157	5414	8936	65
H(7A)	3417	4482	8079	75
H(8A)	2671	4249	6977	87
H(9A)	4289	5337	6177	80
H(10A)	6626	6688	6484	67
H(11A)	7417	6896	7580	60
H(12A)	9607	5518	9603	62
H(12B)	7575	5964	9765	62
H(14A)	10924	6980	8581	63
H(15A)	11828	9039	8418	73
H(16A)	10566	10637	9043	75
H(17A)	8400	10180	9837	69
H(18A)	7497	8124	10012	62