Supporting Information

Short Stereoselective Synthesis of α -Substituted γ -Lactams

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Figure 1. X-ray structure of **7a**

Figure 2. X-ray structure of **15a**

General Methods Melting points are uncorrected. THF was freshly distilled over sodium and benzophenone and then used. Spectral data was collected on 300 MHz NMR (75 MHz for ^{13}C NMR). DMF was dried over 4Å Mol. Sieves and CH_2Cl_2 was distilled over CaH_2 wherever necessary. TLCs were performed on silica-gel coated glass plates and the methods of detection were I_2 , ninhydrin, UV and 2,6-dichlorophenol-indophenol.

3-Bromo-1-(4-methoxy-benzyl)-pyrrolidin-2-one (5). Tetramethyl ammonium hydrogen sulfate (0.27 g, 0.79 mmol), NaOH (1.54 g, 38.42 mmol) and 4-methoxybenzylamine (1.9 mL, 14.2 mmol) were added to 20 mL CH_2Cl_2 in a three necked flask equipped with a condenser. A solution of **4** (3 g, 11.3 mmol) in 10 mL CH_2Cl_2 was added to the stirring mixture over a period of 5 min. The reaction mixture began to reflux lightly during the addition of the acid chloride. After the addition, the reaction was refluxed for 4 h. The reaction was then diluted with 50 mL of cold water. The two layers were then separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, washed with saturated NH_4Cl solution, water and brine and then

dried over MgSO₄. After removal of solvent under vacuum, the crude residue was purified on a silica gel column (4.5 × 8.5 cm) using EtOAc/hexanes (1:1) as the eluent to provide 1.2 g (20% yield) of product as a yellow solid. TLC *R_f* 0.45 (hexanes/EtOAc, 1:2); ¹H NMR (CDCl₃, COSY assignment) δ 2.23–2.30 (m, 1H, β-CH₂), 2.47–2.60 (m, 1H, β-CH₂), 3.14–3.21 (m, 1H, γ-CH₂), 3.35–3.43 (m, 1H, γ-CH₂), 3.79 (s, 3H, OCH₃), 4.36 (d, 1H, *J* = 14.7 Hz, CH₂Ph), 4.33–4.51 (m, 1H, α-CH), 4.48 (d, 1H, *J* = 14.1 Hz, CH₂Ph), 6.86 (d, 2H, *J* = 9 Hz, *o*-CH), 7.18, (d, 2H, *J* = 8.4 Hz, *m*-CH); ¹³C NMR (CDCl₃, HMQC assignment) δ 30.5 (β-CH₂), 44.8 (α-CH, γ-CH₂), 46.9 (CH₂Ph), 55.6 (OCH₃), 114.4 (*o*-CH), 127.9 (Ar-C), 129.7 (*m*-CH), 159.4 (Ar-C), 170.7 (C=O); ESI HRMS *m/z* 306.0090 and 308.0086 [M+Na]⁺, (C₁₂H₁₄BrNO₂ + Na⁺) requires 306.0106 and 308.0085.

3-(1-(4-Methoxy-benzyl)-2-oxopyrrolidin-3(*RS*)-yl)-4(*S*)-phenyl-oxazolidin-2-one (2).

To a solution of **6** (500 mg, 3.1 mmol) in 9 mL THF at 0 °C under argon, was added NaH (122 mg, 3.1 mmol) as a 60% dispersion in mineral oil. Evolution of hydrogen was observed and a white precipitate formed. After vigorous stirring for 20 min, a solution of the bromolactam **5** (870 mg, 3.1 mmol) in 4 mL DMF was added dropwise at 0 °C. The reaction turned from white to orange to purple to grey overnight. The next day one equivalent of citric acid was added to the reaction mixture and the color of the reaction immediately changed to brown. The solution was concentrated under vacuum and the residue obtained was partitioned between brine and ethyl acetate (100 mL). The ethyl acetate layer was washed with NaHCO₃ solution, water, brine, dried over MgSO₄ and concentrated under vacuum. The crude residue was loaded on a silica gel column (3.2 × 8.5 cm) and then eluted with EtOAc/hexanes (2:1) to obtain the product as a mixture of diastereoisomers in the ratio 1:1. The diastereoisomers were separable under these chromatographic conditions and they could be crystallized from CH₂Cl₂/ether. The separated diastereoisomers were analyzed by NMR, but in each case traces of the other diastereoisomer was observed by TLC. The yield of the reaction was about 60 %. In the subsequent alkylation reactions, the oxazolidinone was used as a mixture of diastereoisomers.

Diastereoisomer A: TLC *R_f* 0.35 (EtOAc/hexanes, 4:1); ¹H NMR (CDCl₃, COSY assignment) δ 1.42–1.55 (m, 1H, β-CH₂), 2.03–2.16 (m, 1H, β-CH₂), 2.73–2.8 (m, 1H, γ-CH₂), 2.96 (dd, 1H, *J* = 8.3, 17.3 Hz, γ-CH₂), 3.78 (s, 3H, OCH₃), 4.18 (t, 1H, *J* = 7.1 Hz, CH₂CHPh), 4.22 (d, 1H, *J* = 14.1 Hz, CH₂Ph), 4.4 (d, 1H, *J* = 14.4 Hz, CH₂Ph), 4.47 (t, 1H, *J* = 9.3 Hz, α-H), 4.67 (t, 1H, *J* = 8.7 Hz, CH₂CHPh), 5.07 (t, 1H, *J* = 9 Hz, CH₂CHPh), 6.83 (d, 2H, *J* = 8.7 Hz, *o*-CH), 7.08 (d, 2H, *J* = 8.4 Hz, *m*-CH), 7.34 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, HMQC assignment) δ 24.2 (β-CH₂), 43.4 (γ-CH₂), 46.8 (CH₂Ph), 55.1 (α-C), 55.6 (OCH₃), 58.9 (CH₂CHPh), 70.8 (CH₂CHPh), 114.3 (*o*-CH), 127.8, 127.9, 129.3, 129.4, 129.6, 138.9, (*m*-CH, Ar-CH, Ar-C), 158.4, 159.3 (OCON, Ar-C), 169.5 (CCON); ESI HRMS *m/z* 389.1458 [M+Na]⁺, (C₂₁H₂₂N₂O₄ + Na⁺) requires 389.1477.

Diastereoisomer B: TLC *R_f* 0.25 (EtOAc/hexanes, 4:1); ¹H NMR (CDCl₃, COSY assignment) δ 1.95–2.05 (m, 1H, β-CH₂), 2.46–2.60 (m, 1H, β-CH₂), 3.04 (dd, 1H, *J* = 8.1, 17.4 Hz, γ-CH₂), 3.27 (dt, 1H, *J* = 1.95, 9.45 Hz, γ-CH₂), 3.67–3.73 (m, 1H, α-H), 3.76 (s, 3H, OCH₃), 4.1 (t, 1H, *J* = 9 Hz, CH₂CHPh), 4.30 (d, 1H, *J* = 14.7 Hz, CH₂Ph), 4.42 (d, 1H, *J* = 14.7 Hz, CH₂Ph), 4.68 (t, 1H, *J* = 8.7 Hz, CH₂CHPh), 5.20 (t, 1H, *J* = 9

Hz, CH₂CHPh), 6.82 (d, 2H, *J* = 8.7 Hz, *o*-CH), 7.13 (d, 2H, *J* = 8.4 Hz, *m*-CH), 7.38–7.41 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, HMQC assignment) δ 22.7 (β-CH₂), 43.6 (γ-CH₂), 46.7 (CH₂Ph), 54.9 (α-C), 55.5 (OCH₃), 63.0 (CH₂CHPh), 70.7 (CH₂CHPh), 114.2 (*o*-CH), 127.8, 127.6, 128.0, 129.4, 129.5, 137.6 (*m*-CH, Ar-CH, Ar-C), 157.7, 159.2 (OCON, Ar-C), 170.6 (CCON); ESI HRMS *m/z* 389.1465 [M+Na]⁺, (C₂₁H₂₂N₂O₄ + Na⁺) requires 389.1477.

3-[3(*RS*)-Benzyl-1-(4-methoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-4(*S*)-phenyl-oxazolidin-2-one (7a and 8a). To a solution of diisopropylamine (0.16 mL, 1.14 mmol) in 2 mL THF at –78 °C under argon was added *n*-BuLi (2.56 M solution in hexanes, 0.4 mL, 0.98 mmol). The reaction was stirred for 5 min at –78 °C and then warmed to 0 °C. After 15 min, the reaction mixture was cooled back to –78 °C. γ-Lactam **2** (300 mg, 0.82 mmol) was dissolved in 3 mL THF and this solution was cooled to –78 °C and then added dropwise to the solution containing LDA. The solution turned from pale yellow to dark green. The reaction was stirred at –78 °C for 1 h before the addition of benzyl bromide (0.17 mL, 2 mmol). The reaction was stirred for 4 h at –78 °C, then warmed to room temperature. During the course of the reaction, the solution became turbid and a white solid precipitated out. After a total of 4.5 h, the reaction was quenched with 1 mL of saturated NH₄Cl solution. The mixture was concentrated under vacuum and the residue that was obtained was partitioned between water and CH₂Cl₂ (25 mL). The aqueous layer was extracted again with CH₂Cl₂ (25 mL). The organic layers were combined, washed with citric acid solution, water and brine, dried over MgSO₄ and then concentrated under vacuum to give an oily residue. The diastereoisomers **7a** and **8a** were isolated on a silica gel column (2 × 4.6 cm) eluting with EtOAc/hexanes (2:1) followed by CH₂Cl₂/MeOH (20:1) in a ratio of 6:1.

For studying the effect of HMPA on diastereoselectivity, one equivalent of HMPA was added to the reaction after formation of the enolate. The reaction mixture was stirred at –78 °C for 20 min before the addition of benzyl bromide. The alkylation in this case proceeded to give the products in the ratio of 3:2.

7a (major isomer, 3*R*-configuration): TLC *R_f* 0.36 (EtOAc/hexanes, 4:1); [α]_D +78.7 (*c* 1.12, CHCl₃); mp >220 °C; ¹H NMR (CDCl₃, COSY assignment) δ 1.56 (dd, 1H, *J* = 8.1, 17.4 Hz, γ-CH₂), 1.83–1.91 (m, 1H, β-CH₂), 2.41–2.52 (m, 1H, β-CH₂), 2.75 (d, 1H, *J* = 12 Hz, CH₂Ph), 2.73–2.84 (m, 1H, γ-CH₂), 3.3 (d, 1H, *J* = 11.7 Hz, CH₂Ph) 3.53 (d, 1H, *J* = 14.7 Hz, CH₂PhOCH₃), 3.75 (s, 3H, OCH₃), 4.17 (dd, 1H, *J* = 3.6, 8.7 Hz, CH₂CHPh), 4.69–4.79 (m, 2H, CH₂PhOCH₃, CH₂CHPh), 5.21 (dd, 1H, *J* = 3.3, 8.55 Hz, CH₂CHPh), 6.78 (d, 2H, *J* = 9 Hz, *o*-CH), 7.02–7.44 (m, 12H, *m*-CH, Ar-CH); ¹³C NMR (CDCl₃, HMQC assignment) δ 29.2 (β-CH₂), 41.8 (CH₂Ph), 43.1 (γ-CH₂), 46.7 (CH₂PhOCH₃), 55.5 (OCH₃), 59.7 (CH₂CHPh), 65.4 (α-C), 70.9 (CH₂CHPh), 114.0, (*o*-CH), 126.5, 127.6, 127.8, 128.3, 129.1, 129.5, 129.6, 130.5, 133.8, 141.7 (*m*-CH, Ar-CH, Ar-C), 157.2, 158.9 (Ar-C, OCON), 171.7 (CCON); ESI HRMS *m/z* 479.1950 [M+Na]⁺, (C₂₈H₂₈N₂O₄ + Na⁺) requires 479.1947.

8a (minor isomer, 3*S*-configuration): TLC *R_f* 0.64 (EtOAc/hexanes, 4:1); [α]_D +69.5 (*c* 0.89, CHCl₃); ¹H NMR (CDCl₃, COSY assignment) δ 1.85–1.94 (m, 1H, γ-CH₂), 2.21–2.42 (m, 3H, β-CH₂, γ-CH₂), 3.26 (d, 1H, *J* = 12.9 Hz, CH₂Ph) 3.5 (apparent doublet, 2H, *J* = 13.2 Hz, CH₂PhOCH₃, CH₂Ph) 3.67 (s, 3H, OCH₃), 3.72 (d, 1H, *J* = 15

Hz, $\text{CH}_2\text{PhOCH}_3$), 4.08 (dd, 1H, $J = 2.7, 8.4$ Hz, CH_2CHPh), 4.54 (t, 1H, $J = 8.7$ Hz, CH_2CHPh), 5.34 (dd, 1H, $J = 3.15, 9.15$ Hz, CH_2CHPh), 6.42 (d, 2H, $J = 8.4$ Hz, $o\text{-CH}$), 6.56 (d, 2H, $J = 8.4$ Hz, $m\text{-CH}$), 7.15–7.28 (m, 10H, Ar-H); ^{13}C NMR (CDCl_3 , HMQC assignment) δ 29.4 ($\beta\text{-CH}_2$), 41.1 (CH_2Ph), 43.1 ($\gamma\text{-CH}_2$), 46.1 ($\text{CH}_2\text{PhOCH}_3$), 55.5 (OCH_3), 58.7 (CH_2CHPh), 65 ($\alpha\text{-C}$), 71.1 (CH_2CHPh), 114 ($o\text{-CH}$) 127.2, 127.2, 127.3, 128.3, 128.7, 129.1, 129.2, 131 ($m\text{-CH}$, Ar-CH, Ar-C), 141.4 (Ar-C), 157.7, 159 (Ar-C, OCON), 170.3 (CCON); ESI HRMS m/z 457.1964 $[\text{M}+\text{Na}]^+$, ($\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_4 + \text{Na}^+$) requires 479.1947.

3-[3(RS)-Methyl-1-(4-methoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-4(S)-phenyl-oxazolidin-2-one (7b and 8b). The reaction was carried out with methyl iodide in the same manner as that described above for **7a** and **8a** to give **7b** and **8b** in a ratio of 6:1.

7b (major isomer, 3*R*-configuration): TLC R_f 0.18 (EtOAc/hexanes, 4:1); $[\alpha]_D +36.41$ (c 0.95, CHCl_3); mp 145–146 °C; ^1H NMR (CDCl_3 , COSY assignment) δ 1.24 (s, 3H, CH_3), 1.55 (dq, 1H, $J = 1.2, 8.1$ Hz, $\beta\text{-CH}_2$), 2.57–2.68 (m, 1H, $\beta\text{-CH}_2$), 2.92–3.0 (m, 1H, $\gamma\text{-CH}_2$), 3.22 (dt, 1H, $J = 1.8, 9.6$ Hz, $\gamma\text{-CH}_2$), 3.77 (s, 3H, OCH_3), 4.09 (dd, $J = 3.7, 9$ Hz, CH_2CHPh), 4.31 (d, 1H, $J = 14.4$ Hz, CH_2Ph), 4.52 (d, 1H, $J = 14.7$ Hz, CH_2Ph), 4.73 (t, 1H, $J = 9$ Hz, CH_2CHPh), 5.09 (dd, 1H, $J = 3.3, 9$ Hz, CH_2CHPh), 6.85 (d, 2H, $J = 8.7$ Hz, $o\text{-CH}$), 7.2–7.4 (m, 7H, $m\text{-CH}$, Ar-H); ^{13}C NMR (CDCl_3 , HMQC assignment) δ 24.2 (CH_3), 31.7 ($\beta\text{-CH}_2$), 42.5 ($\gamma\text{-CH}_2$), 46.8 (CH_2Ph), 55.5 (OCH_3), 59.8 (CH_2CHPh), 61.3 ($\alpha\text{-C}$), 70.8 (CH_2CHPh), 114.3, ($o\text{-CH}$) 126.3, 128.3, 128.9, 129.5 ($m\text{-CH}$, Ar-CH, Ar-C), 141.8 (Ar-C), 157.2, 159.1 (Ar-C, OCON), 173.4 (CCON); ESI HRMS m/z 403.1611 $[\text{M}+\text{Na}]^+$, ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4 + \text{Na}^+$) requires 403.1634.

8b (minor isomer, 3*S*-configuration): TLC R_f 0.43 (EtOAc/hexanes, 4:1); $[\alpha]_D +147.5$ (c 0.92, CHCl_3); mp 135–136 °C; ^1H NMR (CDCl_3 , COSY assignment) δ 1.54 (s, 3H, CH_3), 2.05–2.14 (m, 1H, $\beta\text{-CH}_2$), 2.36–2.45 (m, 1H, $\beta\text{-CH}_2$), 2.64–2.72 (m, 1H, $\gamma\text{-CH}_2$), 2.82–2.9 (m, 1H, $\gamma\text{-CH}_2$), 3.61 (d, 1H, $J = 14.4$ Hz, CH_2Ph), 3.76 (s, 3H, OCH_3), 4.12 (dd, $J = 3.45, 8.25$ Hz, CH_2CHPh), 4.23 (d, 1H, $J = 15$ Hz, CH_2Ph), 4.61 (t, 1H, $J = 8.7$ Hz, CH_2CHPh), 5.27 (dd, 1H, $J = 3.45, 8.85$ Hz, CH_2CHPh), 6.76 (d, 2H, $J = 8.7$ Hz, $o\text{-CH}$), 6.88 (d, 2H, $J = 8.7$ Hz, $m\text{-CH}$), 7.36–7.38 (m, 5H, Ar-H); ^{13}C NMR (CDCl_3 , HMQC assignment) δ 22.5 (CH_3), 32.3 ($\beta\text{-CH}_2$), 42.8 ($\gamma\text{-CH}_2$), 46.3 (CH_2Ph), 55.6 (OCH_3), 58.6 (CH_2CHPh), 61.4 ($\alpha\text{-C}$), 71.1 (CH_2CHPh), 114.2 ($o\text{-CH}$), 127.2, 127.8, 128.8, 129.1, 129.5 ($m\text{-CH}$, Ar-CH, Ar-C), 141.2 (Ar-C), 157.6, 159.2 (Ar-C, OCON), 172.1 (CCON); ESI HRMS m/z 403.1631 $[\text{M}+\text{Na}]^+$, ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4 + \text{Na}^+$) requires 403.1634.

3-[3(S)-Hydroxymethyl-1-(4-methoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-4(S)-phenyl-oxazolidin-2-one (7c). The reaction was carried out with either paraformaldehyde or formaldehyde in the same manner as that described above for **7a** and **8a**.

Paraformaldehyde (20 equiv) was added as a suspension in THF after the formation of the enolate. Formaldehyde was freshly distilled from a suspension of paraformaldehyde and p-toluenesulfonic acid monohydrate in THF (for every 1g of paraformaldehyde, 35 mL THF was used). TLC R_f 0.64 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 10:1); $[\alpha]_D +21.2$ (c 1.1, CHCl_3); mp 187–188 °C; ^1H NMR (CDCl_3 , COSY assignment) δ 1.35–1.57 (m, 1H, $\beta\text{-CH}_2$), 2.21–2.31 (m, 1H, $\beta\text{-CH}_2$), 2.94–3.02 (m, 1H, $\gamma\text{-CH}_2$), 3.32 (dt, 1H, $J = 3.6, 9.75$ Hz, $\gamma\text{-CH}_2$), 3.47 (d, 1H, $J = 10.5$ Hz, CH_2OH), 3.61–3.72 (m, 2H, CH_2OH), 3.79 (s, 3H,

OCH₃), 4.20 (dd, 1H, *J* = 3, 8.7 Hz, CH₂CHPh), 4.38 (d, 1H, *J* = 14.4 Hz, CH₂Ph), 4.53 (d, 1H, *J* = 15 Hz, CH₂Ph), 4.77 (t, 1H, *J* = 9 Hz, CH₂CHPh), 5.40 (dd, 1H, *J* = 2.9, 8.55 Hz, CH₂CHPh), 6.87 (d, 2H, *J* = 8.4 Hz, *o*-CH), 7.2 (d, 2H, *J* = 8.4 Hz, *m*-CH), 7.34–7.38 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, HMQC assignment) δ 27.8 (β-CH₂), 43.6 (γ-CH₂), 46.9 (CH₂Ph), 55.5 (OCH₃), 59.1 (CH₂CHPh), 63 (α-C), 64.6 (CH₂OH), 71.4 (CH₂CHPh), 114.3 (*o*-CH), 126.6, 127.7, 129.1, 129.5, 129.6 (Ar-CH, Ar-C, *m*-CH), 141.5 (Ar-C), 157.7, 159.3 (Ar-C, OCON), 172.4 (CCON); ESI HRMS *m/z* 419.1579 [M+Na]⁺, (C₂₂H₂₄N₂O₅ + Na⁺) requires 419.1583.

3-[3(*RS*)-Allyl-1-(4-methoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-4(*S*)-phenyl-oxazolidin-2-one (7d and 8d). The reaction was carried out with allyl bromide in the same manner as that described above for **7a** and **8a** to give **7d** and **8d** in a ratio of 6:1. In a separate experiment, the following modifications were made. When the starting material was added in one portion to LDA, the reaction was stirred for 15 min. The reaction was warmed to –40 °C and the color of the reaction turned to bright yellow over a period of 30 min. After stirring at –78 °C for a further 20 min, allyl bromide was added. The workup was as mentioned above. In this case the diastereoselectivity did not change. For experiments to study the effect of LiCl on the alkylation, around 10 eq of LiCl was added to the flask prior to formation of the LDA. There was no observable change in diastereoselectivity in this case.

7d (major isomer, 3*R*-configuration): TLC *R_f* 0.33 (EtOAc/hexanes, 4:1); [α]_D +64.23 (*c* 1.0, CHCl₃); mp 131–132 °C; ¹H NMR (CDCl₃, COSY assignment) δ 1.68 (apparent dq, 1H, *J* = 2.1, 8.1 Hz, β-CH₂), 2.16 (dd, 1H, *J* = 7.8, 12.6 Hz, CH₂CH=CH₂), 2.4–2.5 (m, 1H, β-CH₂), 2.63 (q, 1H, *J* = 6.6 Hz, CH₂CH=CH₂), 2.80–2.89 (m, 1H, γ-CH₂), 3.18 (dt, 1H, *J* = 2.1, 9.6 Hz, γ-CH₂), 3.74 (s, 3H, OCH₃), 4.07 (dd, 1H, *J* = 3.7, 8.4 Hz, CH₂CHPh), 4.28 (d, 1H, *J* = 15 Hz, CH₂Ph), 4.49 (d, 1H, *J* = 14.4 Hz, CH₂Ph), 4.67 (t, 1H, *J* = 8.6 Hz, CH₂CHPh), 4.97–5.03 (m, 2H, CH₂CH=CH₂), 5.07 (dd, 1H, *J* = 3.15, 8.85 Hz, CH₂CHPh), 5.49–5.62 (m, 1H, CH₂CH=CH₂), 6.81 (d, 2H, *J* = 9 Hz, *o*-CH), 7.18–7.37 (m, 7H, Ar-H, *m*-CH); ¹³C NMR (CDCl₃, HMQC assignment) δ 29.8 (β-CH₂), 40.6 (CH₂CH=CH₂), 43.5 (γ-CH₂), 46.9 (CH₂Ph), 55.5 (OCH₃), 59.3 (CH-Ph), 63.9 (α-C), 70.9 (CH₂CHPh), 114.1 (*o*-CH), 120.4 (CH₂CH=CH₂), 126.4, 128.1, 129.0, 129.5, 129.8 (Ar-CH, Ar-C, *m*-CH), 131.1 (CH₂CH=CH₂), 141.5 (Ar-C), 157.2, 159.1 (Ar-C, OCON), 171.7 (CCON); ESI HRMS *m/z* 429.1805 [M+Na]⁺, (C₂₄H₂₆N₂O₄ + Na⁺) requires 429.1790.

8d (minor isomer, 3*S*-configuration): yellow oil; TLC *R_f* 0.61 (EtOAc/hexanes, 4:1); [α]_D +125.9 (*c* 1.05, CHCl₃); ¹H NMR (CDCl₃, COSY assignment) δ 2.19–2.29 (m, 1H β-CH₂), 2.39–2.56 (m, 2H, γ-CH₂, β-CH₂), 2.74–2.85 (m, 3H, γ-CH₂, CH₂CH=CH₂), 3.32 (d, 1H, *J* = 14.4 Hz, CH₂Ph), 3.75 (s, 3H, OCH₃), 4.12 (dd, *J* = 3.15, 8.85 Hz, CH₂CHPh), 4.23 (d, 1H, *J* = 14.4 Hz, CH₂Ph), 4.60 (t, 1H, *J* = 8.7 Hz, CH₂CHPh), 5.08–5.22 (m, 2H, CH₂CH=CH₂), 5.3 (dd, 1H, *J* = 3, 8.7 Hz, CH₂CHPh), 5.71–5.82 (m, 1H, CH₂CH=CH₂), 6.71–6.81 (m, 4H, *o*-CH, *m*-CH), 7.25–7.36 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, HMQC assignment) δ 29.8 (β-CH₂), 40.0 (CH₂CH=CH₂), 43.2 (γ-CH₂), 46.1 (CH₂Ph), 55.5 (OCH₃), 58.8 (CH₂CHPh), 63.7 (α-C), 71 (CH₂CHPh), 114.1 (*o*-CH), 120.3 (CH₂CH=CH₂), 127.1, 127.6, 128.7, 129.1, 129.5 (Ar-CH, Ar-C, *m*-CH), 132.4

(CH₂CH=CH₂), 141.3 (Ar-C), 157.6, 159.2 (Ar-C, OCON), 170.4 (CCON); ESI HRMS m/z 429.1793 [M+Na]⁺, (C₂₄H₂₆N₂O₄ + Na⁺) requires 429.1790.

3-Methyloxetane-3-methyl Ester of N-Carbobenzyloxy Glycine (11). To a solution of 3-methyloxetane-3-methanol (**10**, 7 mL, 71.7 mmol) in 40 mL dry CH₂Cl₂ under argon, was added DCC (2.95 g, 14.3 mmol) and 4-DMAP (87 mg, 0.72 mmol). Then N-carbobenzyloxyglycine (**9**, 3 g, 14.3 mmol) was added in small portions to the stirring reaction mixture. The reaction was stirred overnight. As the reaction proceeded, a dense white precipitate formed. The next day, 50 mL CH₂Cl₂ was added to the reaction mixture. After filtration, the organic layer was extracted with saturated NaHCO₃ solution, water and brine and then dried over MgSO₄. A mixture of ethyl acetate/ether was added to the residue and this mixture was cooled to precipitate the dicyclohexyl urea, which was then removed by filtration. The filtrate was concentrated and the product was purified by column chromatography (6 × 4.2 cm) using hexanes/EtOAc (1:1) to give 3.4 g of a colorless oil (81% yield). TLC R_f 0.31 (hexanes/EtOAc, 1:1); ¹H NMR (CDCl₃, COSY assignment) δ 1.32 (s, 3H, CH₃), 4.02 (d, 2H, J = 5.7 Hz, NHCH₂), 4.25 (s, 2H, OCH₂), 4.37 (d, 2H, J = 5.7 Hz, CH₂OCH₂), 4.48 (d, 2H, J = 6.3 Hz, CH₂OCH₂), 5.13 (s, 2H, C₆H₅CH₂), 5.32 (br s, NH), 7.34–7.36 (m, 5H, Ar-CH); ¹³C NMR (CDCl₃, HMQC assignment) δ 21.3 (CH₃), 39.3 (CH₃C), 42.9 (NHCH₂), 67.7 (C₆H₅CH₂), 69.7 (COOCH₂), 79.6 (CH₂OCH₂), 128.3, 128.4, 128.7 and 136.4 (Ar-C), 156.6 (NHCO), 170.4 (OCO); ESI HRMS m/z 316.1155 [M+Na]⁺; (C₁₅H₁₉NO₅ + Na⁺) requires 316.1161.

4-Methyl-2,6,7-trioxa-bicyclo[2.2.2.]oct-1-yl Ester of N-Carbobenzyloxyglycine (12)

The ester **11** (3.4 g, 11.6 mmol) was dissolved in dry dichloromethane under argon. BF₃·Et₂O (0.15 mL, 1.16 mmol) was added and the reaction mixture was stirred overnight. Then triethylamine (1.62 mL, 11.6 mmol) was added, the reaction was stirred for 5 min, and then concentrated under vacuum. The residue was loaded on a silica gel column that had been neutralized with triethylamine and then eluted with 1:1 hexanes/EtOAc. The pure product was obtained in 80% yield. TLC R_f 0.46 (hexanes/EtOAc, 1:1); mp 106 °C; ¹H NMR (CDCl₃, COSY assignment) δ 0.81 (s, 3H, CH₃), 3.41 (d, 2H, J = 6 Hz, NHCH₂), 3.90 (s, 6H, C(OCH₂)₃), 5.00 (br s, NH), 5.11 (s, 2H, C₆H₅CH₂), 7.32–7.36 (m, 5 H, C₆H₅). ¹³C NMR (CDCl₃, HMQC assignment) δ 14.7 (CH₃), 30.95 (CH₃C), 45.8 (NHCH₂), 67.1 (C₆H₅CH₂), 72.9 (C(OCH₂)₃), 107.2 (C(OCH₂)₃), 128.2, 128.3, 128.6 (Ar-CH), 136.7 (Ar-C), 156.6 (NHCO); ESI HRMS m/z 316.1164 [M+Na]⁺, (C₁₅H₁₉NO₅ + Na⁺) requires 316.1161

Glycine 4-Methyl-2,6,7-trioxa-bicyclo[2.2.2.]oct-1-yl Ester (13).

The OBO ester **12** (7 g, 23.9 mmol) was dissolved in 60 mL of MeOH. This solution was placed in a Parr bottle and the vessel was flushed with argon. Pd/C (400 mg of 10% wt) was added and the reaction vessel left on the Parr shaker for hydrogenation at 50 psi for 4 h. The next day the catalyst was filtered off and the filtrate passed through a 45 μm Acrodisc® to remove the fine impurities. The solvent was removed in vacuum to give a white solid in quantitative yield. TLC R_f 0.82 (EtOH/NH₄OH, 5:1); ¹H NMR (CDCl₃, COSY assignment) δ 0.81 (s, 3H, CH₃), 1.86 (br s, 2H, NH₂), 2.75 (s, 2H, NHCH₂), 3.90 (s, 6H, C(OCH₂)₃). ¹³C NMR (CDCl₃, HMQC assignment) δ 14.8 (CH₃), 30.97 (CH₃C), 47.4

(NHCH₂), 73.0 (C(OCH₂)₃), 108.1 (C(OCH₂)₃); HRMS *m/z* 160.0959 [M+H]⁺, [C₇H₁₃NO₃ + H⁺] requires 160.0974.

3-[3(*R*)-Benzyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-2-oxo-pyrrolidin-3-yl]-4(*S*)-phenyl-oxazolidin-2-one (15a). This material was prepared in the same manner as that described for **15c** and **16c** with benzyl bromide as the alkylating agent. TLC *R_f* 0.33 (EtOAc/hexanes, 4:1); [α]_D +82.05 (*c* 1, CH₃OH); mp 174–176 °C; ¹H NMR (CDCl₃, COSY assignment) δ 0.70 (s, 3H, O₃CCH₃), 1.88–1.97 (m, 2H, γ-CH₂, β-CH₂), 2.5–2.56 (m, 1H, β-CH₂), 2.73 (d, 1H, *J* = 12.3 Hz, CH₂Ph), 2.81 (d, 1H, *J* = 14.1 Hz, NCH₂CO₃), 3.00 (d, 1H, *J* = 12.3 Hz, CH₂Ph), 3.22 (t, 1H, *J* = 7.95 Hz, γ-CH₂), 3.59 (d, 1H, *J* = 14.7 Hz, NCH₂CO₃), 3.75 (s, 6H, C(OCH₂)₃), 4.08 (dd, 1H, *J* = 2.1, 8.4 Hz, CH₂CHPh), 4.57 (t, 1H, *J* = 8.55 Hz, CH₂CHPh), 5.13 (dd, 1H, *J* = 2.55, 8.25 Hz, CH₂CHPh), 6.92–6.95 (m, 2H, Ar-H), 7.07–7.09 (m, 3H, Ar-H), 7.31–7.36 (m, 5H, Ar-H); ¹³C NMR (CDCl₃, HMQC assignment) δ 14.8 (O₃CCH₃), 29.3 (β-CH₂), 30.9 (CCH₃), 41.5 (CH₂Ph), 45.5 (γ-CH₂), 47.9 (NCH₂CO₃), 59.8 (OCH₂CH), 65.3 (α-C), 71.0 (OCH₂CH), 72.7 ((CH₂)₃), 107.4 (CH₂CO₃), 126.8, 127.1, 128.2, 128.8, 129.3, 130.6 (Ar-C, Ph-CH), 141.9 (Ar-C), 157.1 (OCON), 172.3 (CCON); ESI HRMS *m/z* 501.2017 [M+Na]⁺, (C₂₇H₃₀N₂O₆ + Na⁺) requires 501.2002.

3-[3(*RS*)-Methyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-2-oxo-pyrrolidin-3-yl]-4(*S*)-phenyl-oxazolidin-2-one (15b and 16b). This material was prepared in the same manner as that described for **15c** and **16c** except methyl iodide was used as the alkylating agent. For experiments to study the effect of LiCl on alkylation, around 10 eq of LiCl was added in the flask prior to formation of LDA. There was no observable change in diastereoselectivity in this case.

15b (major isomer, 3*R*-configuration): TLC *R_f* 0.1 (EtOAc/hexanes, 4:1); [α]_D +26.2 (*c* 1.25, CH₃OH); mp > 220 °C; ¹H NMR (CD₃OD, COSY assignment) δ 0.77 (s, 3H, O₃CCH₃), 1.25 (s, 3H, NCCH₃), 1.55 (dq, 1H, *J* = 1.8, 6.9 Hz, β-CH₂), 2.50–2.61 (m, 1H, β-CH₂), 3.05 (d, 1H, *J* = 14.1 Hz, NCH₂CO₃), 3.29–3.39 (m, 1H, γ-CH₂), 3.45–3.54 (m, 1H, γ-CH₂), 3.83 (d, 1H, *J* = 14.7 Hz, NCH₂CO₃), 3.86 (s, 6H, C(OCH₂)₃), 4.09 (dd, 1H, *J* = 3.3, 8.7 Hz, CH₂CHPh), 4.75 (t, 1H, *J* = 9 Hz, CH₂CHPh), 5.16 (dd, 1H, *J* = 3, 9 Hz, CH₂CHPh), 7.34–7.43 (m, 5H, Ar-H); ¹³C NMR (CD₃OD, HMQC assignment) δ 13.2 (O₃CCH₃), 20.1 (NCCH₃), 30.5 (CCH₃), 31.6 (β-CH₂), 44.6 (γ-CH₂), 47.5 (NCH₂CO₃), 59.4 (CH₂CHPh), 61.2 (α-C), 71.2 (CH₂CHPh), 72.4 ((CH₂)₃), 107.1 (CH₂CO₃), 126.1, 128.6, 129.2 (Ar-CH), 141.7 (Ar-C), 157.8 (OCON), 175.2 (CCON); ESI HRMS *m/z* 403.1863 [M+H]⁺ (C₂₁H₂₆N₂O₆ + H⁺) requires 403.1869.

16b (minor isomer, 3*S*-configuration): TLC *R_f* 0.33 (EtOAc/hexanes, 4:1); [α]_D +138.7 (*c* 1, CH₂Cl₂); mp 205–207 °C; ¹H NMR (CD₃OD, COSY assignment) δ 0.75 (s, 3H, O₃CCH₃), 1.34 (s, 3H, NCCH₃), 2.01–2.10 (m, 1H, β-CH₂), 2.35–2.45 (m, 1H, β-CH₂), 2.58 (d, 1H, *J* = 13.8 Hz, NCH₂CO₃), 2.95–3.02 (m, 1H, γ-CH₂), 3.54 (d, 1H, *J* = 13.8 Hz, NCH₂CO₃), 3.42–3.50 (m, 1H, γ-CH₂), 3.82 (s, 6H, C(OCH₂)₃), 4.09 (dd, 1H, *J* = 3.9, 8.7 Hz, CH₂CHPh), 4.65 (t, 1H, *J* = 9 Hz, CH₂CHPh), 5.15 (dd, 1H, *J* = 3.9, 9.15 Hz, CH₂CHPh), 7.37–7.43 (m, 5H, Ar-H); ¹³C NMR (CD₃OD, HMQC assignment) δ 11.6 (O₃CCH₃), 19.5 (NCCH₃), 28.8 (CCH₃), 29.9 (β-CH₂), 42.9 (γ-CH₂), 46.0 (NCH₂CO₃), 57.3 (CH₂CHPh), 60 (α-C), 69.8 (CH₂CHPh), 70.8 ((CH₂)₃), 105.4 (CH₂CO₃), 125.1,

126.8, 127.2 (Ar-CH), 139.8 (Ar-C), 156.9 (OCON), 172.2 (CCON); ESI HRMS m/z 425.1680 $[M+Na]^+$, ($C_{21}H_{26}N_2O_6 + Na^+$) requires 425.1689.

3-[3(*RS*)-Hydroxymethyl-1-(4-methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-ylmethyl)-2-oxo-pyrrolidin-3-yl]-4(*S*)-phenyl-oxazolidin-2-one (15d, 16d) This material was prepared in the same manner as that described below for **15c** and **16c** except formaldehyde was used as the alkylating agent. Formaldehyde was freshly distilled from a suspension of paraformaldehyde and p-toluenesulfonic acid monohydrate in THF (for every 1g of paraformaldehyde, 35 mL THF was used).

15d (3*S*-configuration): TLC R_f 0.33 (EtOAc/MeOH, 20:1); 1H NMR (DMSO- d_6 , COSY assignment) δ 0.73 (s, 3H, CH_3), 1.82–1.90 (m, 1H, β - CH_2), 2.26–2.35 (m, 1H, β - CH_2), 3.14–3.42 (m, 6H, NCH_2CO_3 , CH_2OH , γ - CH_2), 3.80 (s, 6H, $C(OCH_2)_3$), 3.95 (dd, 1H, $J = 2.1, 8.7$ Hz, CH_2CHPh), 4.55 (t, 1H, $J = 8.25$ Hz, CH_2CHPh), 4.84 (t, 1H, $J = 5.25$ Hz, CH_2OH) 5.06 (dd, 1H, $J = 2.25, 8.25$ Hz, CH_2CHPh), 7.23–7.40 (m, 5H, Ar-H); ^{13}C NMR (DMSO- d_6 , HMQC assignment) δ 14.5 (CH_3), 27.4 (CCH_3), 30.8 (β - CH_2), 45.3 (γ - CH_2), 47.9 (NCH_2CO_3), 58.8 (CH_2CHPh), 62.8 (CH_2OH), 65.0 (NCCO), 71.5 (CH_2CHPh), 72.3 ($((CH_2)_3$), 107.2 (CH_2CO_3), 126.6, 128.7, 128.4, 142.8 (Ar-CH and Ar-C), 157 (OCON), 171.5 (CCON); ESI HRMS m/z 419.1823 $[M+H]^+$ ($C_{21}H_{26}N_2O_7 + H^+$) requires 419.1818.

16d (3*R*-configuration): TLC R_f 0.38 (EtOAc/MeOH, 20:1); 1H NMR (CD_3OD , COSY assignment, peaks of the principal component listed) δ 0.78 (s, 3H, CH_3), 2.11–2.21 (m, 1H, β - CH_2), 2.66–2.65 (m, 1H, β - CH_2), 3.23 (d, 1H, $J = 14.1$ Hz, NCH_2CO_3), 3.41–3.47 (m, 1H, γ - CH_2), 3.43 (d, 1H, $J = 13.8$ Hz, NCH_2CO_3), 3.5–3.54 (m, 1H, γ - CH_2), 3.85 (s, 6H, $C(OCH_2)_3$), 3.87–3.91 (m, 1H, CH_2OH), 4.24 (d, 1H, $J = 9$ Hz, CH_2CHPh), 4.55 (d, 1H, $J = 8.7$ Hz, CH_2CHPh), 4.27 (d, 2H, CH_2OH , CH_2CHPh), 7.27–7.43 (m, 5H, Ar-H); ^{13}C NMR (DMSO- d_6 , HMQC assignment) δ 13.15 (CH_3), 29.1 (CCH_3), 30.5 (β - CH_2), 44.9 (γ - CH_2), 47.6 (NCH_2CO_3), 60 (CH_2CHPh), 63.1 (CH_2OH), 67.3 (NCCO), 71.6 (CH_2CHPh), 72.4 ($((CH_2)_3$), 107.1 (CH_2CO_3), 127.6, 128.1, 128.6, 137.2 (Ar-CH and Ar-C), 157.9 (OCON), 172.1 (CCON); ESI HRMS m/z 441.1644 $[M+Na]^+$, ($C_{21}H_{26}N_2O_7 + Na^+$) requires 441.1638.

3(*S*)-Methyl-2-oxo-3-(2-oxo-4(*S*)-phenyl-oxazolidin-3-yl)-1-pyrrolidineacetic Acid (17). In a flask containing a solution of **16b** (70 mg, 0.17 mmol) in 5 mL CH_2Cl_2 was added 0.1 mL TFA and 0.1 mL H_2O . The reaction was stirred for 2 h after which it was concentrated under vacuum. To this residue was added 6 mL of 10% Cs_2CO_3 solution in water and 2 mL methanol. The reaction was stirred overnight. The next day the reaction mixture was concentrated under vacuum. Water (2 mL) was added to the residue and the suspension was acidified to a pH 3 with citric acid. The aqueous layer was extracted with CH_2Cl_2 (2 $\times$ 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and then concentrated under vacuum to give product as a white solid in 55 % yield. TLC R_f 0.78 (EtOH/ NH_4OH , 2:1); $[\alpha]_D +103$ (c 0.36, DMSO- d_6); mp 260 $^{\circ}C$ (dec); 1H NMR (DMSO- d_6 , COSY assignment) 1.19 (s, 3H, CH_3), 1.99–2.05 (m, 1H, β - CH_2), 2.27–2.37 (m, 1H, β - CH_2), 3.05 (dt, 1H, $J = 2.7, 9.3$ Hz, γ - CH_2), 3.18–3.27 (m, 1H, γ - CH_2), 3.38 (d, 1H, $J = 17.7$ Hz, NCH_2COOH), 3.87–3.93 (m, 1H, CH_2CHPh), 3.91 (d, 1H, $J = 17.7$ Hz, NCH_2COOH) 4.60 (t, 1H, $J = 8.85$ Hz, CH_2CHPh) 5.15 (dd, 1H, $J = 3.6, 8.7$ Hz, CH_2CHPh), 7.29–7.43 (m, 5H, Ar-CH), 12.7 (s, 1H, COOH); ^{13}C NMR (DMSO-

d₆, HMQC assignment) 21.7 (CH₃), 31.9 (β-CH₂), 43.8 (γ-CH₂), 44.5 (CH₂COOH), 58.1 (CH₂CHPh), 60.9 (α-C), 71.4 (CH₂CHPh), 126.9, 128.6, 129.2, 142.5 (Ar-CH and Ar-C), 157.1 (OCON), 170.3, 173.1 (C=O); ESI HRMS m/z 341.1109 [M+Na]⁺; (C₁₆H₁₈N₂O₅ + Na⁺) requires 341.1113.

3(S)-3-Amino-3-methyl-2-oxo-1-pyrrolidineacetic Acid (18). In a dried 25 mL round bottom flask flushed with argon, approximately 10 mL ammonia was condensed at -78 °C. A small piece of lithium wire was added to the reaction flask under argon. The reaction turned a deep blue color. After 5 min, a solution of γ-lactam acid **17** (18 mg, 0.05 mmol) in 3 mL dry THF/*tert*-butanol (10:1) was added to the reaction. The reaction color lightened and turned white after 5 min. Another piece of lithium wire was added and the blue color reappeared and persisted. After stirring the reaction for 20 min at -78 °C, solid ammonium chloride (600 mg) was added to quench the reaction. The color of the reaction mixture changed from blue to white. The reaction was warmed to room temperature to remove the excess ammonia and then was concentrated under vacuum. The residue was then loaded on a Dowex[®] 50WX8-400 ion-exchange resin pretreated with 2N HCl and eluted with 2% NH₄OH. The fractions containing product were collected and concentrated under vacuum to give a yellow residue. The product crystallized out of methanol as a white solid in a 70% yield. TLC *R_f* 0.62 (NH₄OH/EtOH, 1:5); [α]_D -24.9 (*c* 0.35, H₂O); ¹H NMR (D₂O, COSY assignment) δ 1.33 (s, 3H, CH₃), 2.13–2.18 (m, 2H, β-CH₂), 3.34–3.40 (m, 2H, γ-CH₂), 3.58 (d, 1H, *J* = 17.1 Hz, NCH₂COOH), 3.76 (d, 1H, *J* = 17.1 Hz, NCH₂COOH); ¹³C NMR (D₂O, HMQC assignment) δ 20.4 (CH₃), 30.3 (β-CH₂), 44.7 (γ-CH₂), 46.9 (CH₂COOH), 58.3 (α-C), 172.7, 174.5 (C=O); ESI HRMS m/z 195.0732 [M+Na]⁺, (C₇H₁₂N₂O₃ + Na⁺) requires 195.0746.

Compound 7
 Archive directory: /data/hiocoma/vmr/sys/data
 Sample directory: brfy/rotatorco1_07f602004-11:56:37
 Pulse Sequence: szpu1

Compound 2 dias 1
 Archive directory: /data/biooma/vnmr/sys/data
 Sample directory: P00002017/1_09F02004-16:25:24
 Pulse Sequence: szpu1

Compound 2_dias 2
 Archive directory: /data/bhpcare/ymmsrvc/d488
 Sample directory: phoxazolopyr2_08fa2004-1812740
 Pulse Sequence: szpu1

Compound 8a
 Archive directory: /data/bhogom/ymmsys/data
 Sample directory: benzhyrolf3_12fa2004
 Pulse Sequence: szpu1

Compound 8a
 Archive directory: /data/biochem/vnmr/sys/data
 Sample directory: benzylprol_12760204
 Pulse Sequence: szpu1

Compound 8b
 Archive directory: /data/biomag/ymrcys/data
 Sample directory: methylactam2_02Mar2004
 Pulse Sequence: szpu1

Compound 8c
 Archive directory: /data/biochem/vnmr/sv/data
 Sample directory: /data/biochem/vnmr/sv/data
 Pulse Sequence: zgpg30

Compound 8d
Pulse Sequence: zgpg30

7d

Compound **9d**
Pulse Sequence: zgpg30

Compound 12
 Archive directory: /data/biomag/numsys/data
 Sample directory: 6130E1NME_20041204
 Pulse Sequence: szpu1

Compound 13
 Archive directory: /data/biossma/ymmsys/data
 Sample directory: 000astet_13042004-01:48:55
 Pulse Sequence: szpu1

Compound 14
Pulse Sequence: zgpg30

Compound 15
Pulse Sequence: szpu1

Compound 3 diast.
Pulse Sequence: zgpg30

Compound 3 diast
Pulse Sequence: zgpg30

Compound 17b
Pulse Sequence: szput

Compound 15c
Pulse Sequence: szpu1

Compound 17c
Pulse Sequence: szput

Compound 17d
Pulse Sequence: szpu1

Compound 18
Pulse Sequence: szpu1

Pulse sequence: szpu1