Systematic Study of the Synthesis of Macrocyclic Dipeptide β -Turn Mimics Possessing 8-, 9- and 10- Membered Rings by Ring Closing Metathesis

Ramesh Kaul, Simon Surprenant, and William D. Lubell*

Département de chimie, Université de Montréal

C.P. 6128, Succursale Centre Ville, Montréal, Québec, Canada H3C 3J7

lubell@chimie.umontreal.ca

Supporting Information

Table of contents

General experimental section	S5
Spectral data for 18b	S6
Spectral data for 19a	S6
Spectral data for 19b	S7
General procedure for TBTU coupling	S7
Spectral data for 21a	S7
Spectral data for 22a	S7
Spectral data for 21b	S8
Spectral data for 22b	S8
Spectral data for 22c	S8

Spectral data for 23b	S9
General procedure for symmetric anhydride coupling	S9
Spectral data for 22d	S9
Spectral data for 23c	S10
Spectral data for 25b	S10
Spectral data for 26b	S10
Spectral data for 26c	S11
Spectral data for 27b	S11
Spectral data for 27c	S11
Spectral data for 29	S12
Spectral data for 31	S12
Proton NMR spectrum for 12	S13
Carbon NMR spectrum for 12	S14
Proton NMR spectrum for 13b	S15
Carbon NMR spectrum for 13b	S16
Proton NMR spectrum for 14	S17
Carbon NMR spectrum for 14	S18
Proton NMR spectrum for 16a	S19
Carbon NMR spectrum for 16a	S20
Proton NMR spectrum for 18a	S21
Carbon NMR spectrum for 18a	S22

Proton NMR spectrum for 18b	S23
Carbon NMR spectrum for 18b	S24
Proton NMR spectrum for 19a	S25
Carbon NMR spectrum for 19a	S26
Proton NMR spectrum for 19b	S27
Proton NMR spectrum for 21a	S28
Carbon NMR spectrum for 21a	S29
Proton NMR spectrum for 21b	S30
Carbon NMR spectrum for 21b	S31
Proton NMR spectrum for 21c	S32
Carbon NMR spectrum for 21c	S33
Proton NMR spectrum for 22a	S34
Carbon NMR spectrum for 22a	S35
Proton NMR spectrum for 22b	S36
Carbon NMR spectrum for 22b	S37
Proton NMR spectrum for 22c	S38
Carbon NMR spectrum for 22c	S39
Proton NMR spectrum for 22d	S40
Carbon NMR spectrum for 22d	S41
Proton NMR spectrum for 23b	S42
Carbon NMR spectrum for 23b	S43

Proton NMR spectrum for 23c	S44
Proton NMR spectrum for 25b	S45
Carbon NMR spectrum for 25b	S46
Proton NMR spectrum for 25c	S47
Carbon NMR spectrum for 25c	S48
Proton NMR spectrum for 26b	S49
Carbon NMR spectrum for 26b	S50
Proton NMR spectrum for 26c	S51
Carbon NMR spectrum for 26c	S52
Proton NMR spectrum for 27b	S53
Carbon NMR spectrum for 27b	S54
Proton NMR spectrum for 27c	S55
Proton NMR spectrum for 28	S56
Carbon NMR spectrum for 28	S57
Proton NMR spectrum for 29	S58
Carbon NMR spectrum for 29	S59
Proton NMR spectrum for 30	S60
Carbon NMR spectrum for 30	S61
COSY NMR spectrum for 30	S62
NOESY NMR spectrum (400 ms mixing time) for 30	S63
NOESY NMR spectrum (800 ms mixing time) for 30	S64

Proton NMR spectrum for 31	S65
Carbon NMR spectrum for 31	S66
COSY NMR spectrum for 31	S67
NOESY NMR spectrum (500 ms mixing time) for 31	S68
HPLC profile of 30	S69
HPLC profile of 31	S70
Decoupling experiment for 25c	S71
Decoupling experiment for 31	S72

General Experimental Section. Unless otherwise noted, all reactions were performed under argon atmosphere and distilled solvents were transferred by syringe. Anhydrous CH₂Cl₂ (DCM), THF and diethyl ether were obtained from a solvent filtration system. Final reaction mixture solutions were dried over anhydrous MgSO₄ or Na₂SO₄, filtered and rotary-evaporated under reduced pressure. Melting points are uncorrected. Mass spectral data, HRMS/LRMS (EI and FAB), were obtained by the Université de Montréal Mass Spectrometry facility. Unless otherwise noted, ¹H NMR (300/400 MHz) and ¹³C NMR (75/100 MHz) spectra were recorded in CDCl₃. Chemical shifts are reported in ppm (δ units) downfield from internal tetramethylsilane ((CH₃)₄Si), residual CHCl₃ (δ 7.27 and 77.2), residual MeOH (δ 3.31 and 49.0) or residual DMSO (δ 2.50 and 39.5); coupling constant *J*-values are reported in hertz (Hz). Two dimensional NMR experiments COSY and NOESY for **30** and **31** were performed at 500 MHz with mixing times of 400 ms and 800 ms. Analytical thin-layer chromatography (TLC) was performed by using aluminum-backed silica gel plates coated with a 0.2 mm thickness of silica gel. Compounds were purified by column chromatography using 230-400 mesh silica gel.

Methyl (2S)-2-[(2-Hydroxy-6-nitrobenzyl)amino]pent-4-enoate (18b). Using General Procedure A, followed by chromatography of the product from **14** (1 mmol) using 50:50 EtOAc/hexanes as eluant gave **18b** as a brown gum (52% yield): ¹H NMR δ 7.28 (m, 2H), 7.03 (m, 1H), 5.65 (m, 1H), 5.15 (m, 2H), 4.22-4.0 (q, 2H, *J* = 15.0), 3.77 (s, 3H), 3.45 (m, 1H), 2.5-2.41 (m, 2H); ¹³C NMR δ 173.0 159.5, 150.2, 131.9, 128.6, 121.2, 119.5, 115.8, 114.8, 59.0, 52.2, 45.5, 36.9. MS (ESI, *m/z*) 281.1 (MH)⁺.

Methyl (2S)-2-[(2,4-Dimethoxybenzyl)amino]hex-5-enoate (19a). Using General Procedure A, followed by chromatography of the product from **17** (20 mmol) using 30:70 EtOAc/hexanes as eluant gave **19a** as a yellow oil (70% yield); ^1H NMR δ 7.14 (d, 1H, $J = 8.6$), 6.43 (m, 2H), 5.77 (m, 1H), 5.00 (m, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.73-3.64 (m, 5H), 3.28 (t, 1H, $J = 6.9$), 2.11 (m, 3H), 1.73 (m, 2H); ^{13}C NMR δ 175.6, 159.9, 158.4, 137.5, 130.1, 120.3, 114.9, 103.5, 98.2, 60.0, 55.1, 55.0, 51.3, 46.9, 32.5, 29.7. MS (ESI, m/z) 293.9 (MH) $^+$.

Methyl (2S)-2-[(2-Hydroxy-4-methoxybenzyl)amino]hex-5-enoate (19b). Using General Procedure A, followed by chromatography of the product from **17** (3.0 mmol) using 20:80 EtOAc/hexanes as eluant gave **19b** (79% yield) as a yellow oil: ^1H NMR δ 8.23 (s, 1H), 6.85 (d, 1H, $J = 8.2$), 6.45 (m, 1H), 6.36 (m, 1H), 5.76 (m, 1H), 5.30-4.99 (m, 2H), 4.00 (d, 1H, $J = 13.6$), 3.82 (m, 1H), 3.78-3.76 (m, 6H), 3.69 (d, 1H, $J = 13.6$), 3.38 (t, 1H, $J = 6.6$), 2.12 (m, 2H), 1.80 (m, 2H). MS (ESI, m/z) 279.2 (MH) $^+$.

General Procedure F: Peptide Coupling using TBTU. The selected *N*-protected amino acid (1.0 eq) and amino ester (1.0 eq) were dissolved in CH_2Cl_2 (0.1 M), treated with DIEA (1.5 eq), stirred for 10 min, treated with TBTU (1.5 eq), stirred for 24h and diluted with water. The aqueous layer was separated and extracted with CH_2Cl_2 (3 $\times$). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated to a residue that was purified by chromatography.

***N*-(Boc)-L-Allylglyciny-L-homoallylglycine Methyl Ester (21a).** Using General Procedure F, followed by chromatography of the product from **13a** (1.15 mmol) and **17** (1.15 mmol) using 20:80 EtOAc/hexanes as eluant gave **21a** (86% yield) as a white solid: mp 105.3-106.7 $^\circ\text{C}$; $[\alpha]_D^{20}$ -6.8° (c 1.34, CHCl_3); ^1H NMR δ 6.68 (d, 1H, $J = 7.8$), 5.74 (m, 2H), 5.05 (m, 5H), 4.60 (m, 1H), 4.17 (m, 1H), 3.73 (s, 3H), 2.50 (m, 2H), 2.06 (m, 2H), 1.95 (m, 1H), 1.78 (m, 1H), 1.44 (s, 9H); ^{13}C NMR δ 172.2, 171.0, 155.3, 136.6, 132.8, 118.8, 115.6, 80.0, 53.5, 52.1, 51.5, 36.3, 31.6, 29.1, 28.0. HRMS calcd for $\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}_5 \text{Na}$ 363.18904, found 363.18950.

***N*-(Boc)-L-Homoallylglycinyl-L-allylglycine Methyl Ester (22a).** Using General Procedure **F**, followed by chromatography of the product from **16a** (1.15 mmol) and **14** (1.15 mmol) using 20:80 EtOAc/hexanes as eluant gave **22a** (85% yield) as an oil: $[\alpha]_D^{20} -6.8^\circ$ (*c* 1.3, CHCl₃); ¹H NMR δ 6.48 (d, 1H, *J* = 7.57), 5.85 (m, 1H), 5.65 (m, 1H), 5.05 (m, 5H), 4.66 (m, 1H), 4.10 (m, 1H), 3.75 (s, 3H), 2.55 (m, 2H), 2.15 (q, 2H, *J* = 7.1), 1.95 (m, 1H), 1.70 (m, 1H), 1.45 (s, 9H); ¹³C NMR δ 172.2, 172.1, 155.8, 137.6, 132.4, 119.6, 116.0, 80.3, 54.2, 52.7, 52.0, 36.7, 31.9, 30.0, 28.7. HRMS calcd for C₁₇H₂₈N₂O₅ Na: 363.18904, found 363.18886.

***N*-(Boc)-Allylglycinyl-*N*-(2,4-dimethoxybenzyl)homoallylglycine Methyl Ester (21b).** Using General Procedure **B**, followed by chromatography of the product from **13a** (1.5 mmol) and **19a** (1.0 mmol) using 30:70 EtOAc/hexanes as eluant gave **21b** (86% yield) as an oil; $[\alpha]_D^{20} -42.6^\circ$ (*c* 1.12, CHCl₃); ¹H NMR δ 7.10 (d, 1H, *J* = 7.4), 6.42 (m, 2H), 5.87- 5.60 (m, 2H), 5.40 (d, 1H, *J* = 8.5), 5.08-5.16 (m, 2H), 4.99 (m, 2H), 4.64 (d, 1H, *J* = 15.7), 4.36 (d, 1H, *J* = 15.7), 4.11 (dd, 1H, *J* = 6.0, 9.0), 3.80 (s, 6H), 3.57 (s, 3H), 2.55 (m, 1H), 2.45 (m, 1H), 2.15-1.95 (m, 3H), 1.85-1.75 (m, 2H), 1.4(s, 9H); ¹³C NMR δ 172.2, 171.0, 160.8, 158.7, 154.9, 137.4, 132.7, 130.3, 118.2, 115.9, 115.2, 103.5, 98.3, 79.1, 57.5, 55.1, 54.9, 51.7, 50.2, 47.1, 37.8, 30.4, 29.4, 28.1. HRMS calcd for C₂₆H₃₉N₂O₇ (MH)⁺ 491.27518, found 491.27280.

***N*-(Boc)-L-Homoallylglycinyl-*N*-(2,4-dimethoxybenzyl)-L-allylglycine Methyl Ester (22b).** Using General Procedure **B**, followed by chromatography of the product from **16b** (1.0 mmol) and **18a** (0.5 mmol) using 30:70 EtOAc/hexanes as eluant gave **22b** (81% yield) as a colorless oil: $[\alpha]_D^{20} -38.4^\circ$ (*c* 1.05, CHCl₃); ¹H NMR δ 7.10 (d, 1H, *J* = 7.9), 6.41 (m, 2H), 5.85- 5.63 (m, 2H), 5.41 (d, 1H, *J* = 8.7), 5.06-4.92 (m, 5H), 4.63 (d, 1H, *J* = 15.5), 4.30 (d, 1H, *J* = 15.5), 4.01 (dd, 1H, *J* = 5.5, 9.0), 3.79 (s, 6H), 3.56 (s, 3H), 2.70 (m, 1H), 2.58 (m, 1H), 2.13 (m, 2H), 1.83 (m, 1H), 1.66 (m, 1H), 1.44 (s, 9H); ¹³C NMR δ 172.4, 170.5, 160.9, 158.8, 155.0, 137.4, 134.3, 130.6, 117.5, 115.7, 115.0, 103.4, 98.2, 79.0, 58.1, 55.1, 54.9, 51.7, 50.0, 47.7, 33.2, 33.1, 29.1, 28.1; MS (ESI, *m/z*) 513.2 (MNa)⁺.

***N*-(Fmoc)-L-homoallylglycinyll-*N*-(2,4-dimethoxybenzyl)-L-allylglycine Methyl Ester (22c).** Using General Procedure **B**, followed by chromatography of the product from **16b** (1.5 mmol) and **18a** (1.0 mmol) using 30:70 EtOAc/hexanes as eluant gave **22c** (82% yield) as a colorless oil: $[\alpha]_D^{20}$ -6.0 (*c* 1.32, CHCl₃); ¹H NMR δ 7.75 (d, 2H, *J* = 7.4), 7.61 (dd, 2H, *J* = 3.2, 3.1), 7.38 (t, 2H, *J* = 7.3), 7.30 (t, 2H, *J* = 7.3), 7.10 (d, 1H, *J* = 8.2), 6.40 (dd, 2H, *J* = 2.1, 2.2), 5.87- 5.66 (m, 3H), 5.12-4.87 (m, 5H), 4.64 (d, 1H, *J* = 15.5), 4.44-4.20 (m, 4H), 4.04 (m, 1H), 3.76 (s, 6H), 3.56 (s, 3H), 2.74 (m, 1H), 2.61 (m, 1H), 2.15 (m, 2H), 1.89 (m, 1H), 1.72 (m, 1H); ¹³C NMR δ 172.0, 170.5, 160.9, 158.8, 155.6, 143.7, 141.1, 137.2, 134.3, 130.5, 127.5, 126.9, 125.0, 119.8, 117.7, 115.6, 115.3, 103.5, 98.3, 66.6, 58.2, 55.1, 55.0, 51.8, 50.7, 47.7, 47.0, 33.3, 32.9, 29.0; HRMS calcd for C₃₆H₄₁N₂O₇ (MH)⁺ 613.29083, found 613.29071.

***N*-(Boc)-L-Homoallylglycinyll-*N*-(2,4-dimethoxybenzyl)-L-homoallylglycine Methyl Ester (23b).** Using General Procedure **B**, followed by chromatography of the product from **16a** (0.8 mmol) and **19a** (0.4 mmol) using 30:70 EtOAc/hexanes as eluant gave **23b** (74% yield) as a gum: ¹H NMR δ 7.05 (d, 1H, *J* = 8.0), 6.39 (m, 2H), 5.79 (m, 1H), 5.66 (m, 1H), 5.43 (d, 1H, *J* = 8.6), 5.04-4.86 (m, 4H), 4.60 (d, 1H, *J* = 15.5), 4.34 (d, 1H, *J* = 15.5), 4.01 (dd, 1H, *J* = 6.1, 7.7), 3.76 (s, 6H), 3.54 (s, 3H), 2.15-1.95 (m, 5H), 1.85-1.71 (m, 2H), 1.70-1.55 (m, 2H), 1.41 (s, 9H); ¹³C NMR δ 172.8, 171.1, 160.8, 158.7, 155.1, 137.3, 130.3, 116.0, 115.2, 115.1, 103.5, 98.3, 79.1, 57.4, 55.1, 54.9, 51.7, 50.1, 46.9, 33.0, 30.4, 29.5, 29.1, 28.1, 28.0. MS (ESI, *m/z*) 527.3 (MNa⁺).

General Procedure G: Peptide Coupling using Symmetrical Anhydrides. The *N*-Boc protected amino acid **16a** (3.0 eq) and DCC (1.5 eq) were dissolved in CH₂Cl₂ (0.2 M) and stirred for 2h. The mixture was filtered and *N*-(2-hydroxybenzyl) amino ester **18b** or **19b** (1.0 eq) was added to the filtrate which was then stirred overnight at rt. The mixture was diluted with CH₂Cl₂, washed with sat. NaHCO₃, 10% HCl and with brine, dried over MgSO₄, filtered and concentrated to a residue that was purified by chromatography.

***N*-(Boc)-L-Homoallylglycyl-*N*-(2-hydroxy-6-nitrobenzyl)-L-allylglycine Methyl Ester (22d).** Using General Procedure G, followed by chromatography of the product from **16a** (0.69 mmol) and **18b** (0.23 mmol) using 30:70 EtOAc/hexanes as eluant gave **22d** (87% yield) as a greenish oil in 4.6:1 mixture of isomers: ¹H NMR (major isomer) 9.31 (s, 1H), 7.33 (m, 3H), 5.82 (m, 2H), 5.47 (m, 1H), 5.22 (m, 1H), 5.04 (m, 4H), 4.77 (m, 2H), 3.77 (m, 1H), 3.58 (s, 3H), 2.80 (m, 2H), 2.10 (m, 2H), 1.82 (m, 2H), 1.48 (s, 9H); ¹³C NMR δ 172.5, 170.9, 158.7, 156.6, 151.2, 137.6, 134.7, 130.2, 122.6, 121.1, 118.9, 116.3, 115.9, 80.9, 58.7, 52.4, 51.0, 44.0, 33.8, 33.6, 29.6, 28.8.

***N*-(Boc)-L-Homoallylglycyl-*N*-(2-hydroxy-4-methoxybenzyl)-L-homoallylglycine Methyl Ester (23c).** Using General Procedure G, followed by chromatography of the product from **16a** (1.08 mmol) and **19b** (0.36 mmol) using 30:70 EtOAc/hexanes as eluant gave **23c** (86% yield) as an oil: ¹H NMR δ 9.51 (s, 1H), 6.92 (d, 1H, *J* = 8.4 Hz), 6.43 (d, 1H, *J* = 2.51), 6.31 (dd, 1H, *J* = 8.4, 2.5 Hz), 5.76 (m, 2H), 5.21 (d, 1H, *J* = 9.2 Hz), 5.00 (m, 4H), 4.62 (m, 2H), 4.45 (m, 1H), 4.35 (m, 1H), 3.73 (s, 3H), 3.43 (s, 3H), 2.04 (m, 6H), 1.71 (m, 2H), 1.40 (s, 9H).

Methyl (*E*, 3*S*, 9*S*)-3-*N*-(Boc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7,8,9-hexahydro-1*H*-azonine-9-carboxylate (25b). Using General Procedure C, followed by chromatography of the product from **21b** (0.6 mmol) using 20:80 EtOAc/hexanes eluant gave **25b** (80% yield) as a brown gum: $[\alpha]_D^{20} -38.5^\circ$ (*c* 2.53, CHCl₃); ¹H NMR δ 7.21 (d, 1H, *J* = 8.3), 6.41 (m, 2H), 6.17 (d, 1H, *J* = 6.6), 6.09 (q, 1H, *J* = 9.4), 5.58 (q, 1H, *J* = 9.2), 4.62-4.49 (m, 4H), 3.78 (s, 3H), 3.77 (s, 3H), 3.45 (s, 3H), 2.61 (m, 1H), 2.28-2.17 (m, 2H), 1.91-1.87 (m, 2H), 1.70 (m, 1H), 1.47 (s, 9H); ¹³C NMR δ 173.6, 170.5, 159.7, 157.4, 154.7, 130.6, 129.9, 129.2, 117.6, 104.0, 97.8, 79.3, 60.1, 56.8, 55.1, 51.9, 51.3, 39.8, 34.9, 28.2, 27.9, 22.0; HRMS calcd for C₂₄H₃₄N₂O₇Na 485.22582, found 485.22543.

Methyl (*E*, 3*S*, 9*S*)-3-*N*-(Boc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-azonine-9-carboxylate (26b). Using General Procedure C, followed by chromatography of the product from **22b** (0.5 mmol) using 30:70 EtOAc/hexanes as eluant gave **26b** (81% yield) as

gum; $[\alpha]_D^{20}$ -27.3° (c 1.21, CHCl_3); ^1H NMR δ 7.13 (d, 1H, $J = 8.1$), 6.41 (m, 2H), 5.77-5.50 (m, 2H), 4.90 (t, 1H, $J = 7.8$), 4.72 (t, 1H, $J = 8.5$), 4.62 (d, 1H, $J = 15.5$), 4.16 (d, 1H, $J = 15.5$), 3.78 (s, 3H), 3.76 (s, 3H), 3.42 (q, 1H), 3.38 (s, 3H), 2.65 (m, 2H), 2.06 (m, 3H), 1.70 (m, 1H), 1.45 (s, 9H); ^{13}C NMR δ 174.0, 169.9, 159.7, 157.6, 154.8, 133.4, 129.8, 124.7, 116.9, 103.8, 97.6, 79.3, 58.3, 55.1, 55.0, 52.0, 50.5, 40.0, 34.6, 28.2, 26.5, 25.2; HRMS calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_7$ (MH) $^+$ 463.24388, found 463.24259.

Methyl (*E*, 3*S*, 9*S*)-3-*N*-(Fmoc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-azonine-9-carboxylate (26c). Using General Procedure C, followed by chromatography of the product from **22c** (0.4 mmol) using 30:70 EtOAc/hexanes as eluant gave **26c** (71% yield) as an oil; $[\alpha]_D^{20}$ -24.3° (c 0.90, CHCl_3); ^1H NMR δ 7.76 (d, 2H, $J = 7.4$), 7.61 (d, 2H, $J = 7.5$), 7.40 (t, 2H, $J = 7.3$), 7.31 (t, 2H, $J = 7.2$), 7.13 (d, 1H, $J = 8.0$), 5.95 (d, 1H, $J = 7.5$), 5.63 (q, 1H, $J = 8.7$), 5.53 (m, 1H), 4.90 (t, 1H, $J = 7.7$), 4.81 (m, 1H), 4.67 (d, 1H, $J = 15.3$), 4.36-4.32 (m, 2H), 4.30-4.10 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.54 (q, 1H, $J = 35.0$), 3.39 (s, 3H), 2.65 (m, 1H), 2.16 (m, 3H), 1.79 (m, 1H); ^{13}C NMR δ 173.5, 169.8, 159.8, 157.6, 155.2, 143.8, 141.1, 133.4, 129.8, 127.5, 126.9, 125.04, 119.8, 116.7, 103.8, 97.7, 66.8, 58.1, 55.1, 55.0, 52.1, 51.1, 47.0, 40.3, 34.7, 29.5, 26.2, 25.2; HRMS calcd for $\text{C}_{34}\text{H}_{37}\text{N}_2\text{O}_7$ (MH) $^+$ 585.25953, found 585.25807.

Methyl (*E*, 3*S*, 10*S*)-3-*N*-(Boc)Amino-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,5,8,9,10-octa-hydro-1*H*-azocine-10-carboxylate (27b). Using General Procedure C, followed by chromatography of the product from **23b** (0.3 mmol) using 30:70 EtOAc/hexanes as eluant gave **27b** (87% yield) as an oil; ^1H NMR δ 7.40 (d, 1H, $J = 8.4$), 6.41 (m, 2H), 5.58 (dt, 1H, $J = 4.1, 11.4$), 5.40 (dt, 1H, $J = 4.2, 10.6$), 5.29 (d, 1H, $J = 9.2$), 4.81 (m, 2H), 4.57 (q, 2H, $J = 15.1$), 3.77 (s, 3H), 3.76 (s, 3H), 3.40 (s, 3H), 2.26 (m, 1H), 2.20-1.79 (m, 7H), 1.43 (s, 9H); ^{13}C NMR δ 175.1, 171.0, 159.8, 157.5, 154.7, 131.6, 131.2, 128.9, 118.0, 104.2, 97.6, 79.2, 57.6, 55.1, 55.0, 51.8, 47.6, 38.5, 33.8, 28.1, 26.5, 23.3, 21.8; MS (ESI, m/z) 499.2 (MNa) $^+$.

Methyl (*E*, 3*S*, 10*S*)-3-*N*-(Boc)Amino-1-(2-hydroxy-4-methoxybenzyl)-2-oxo-1,2,3,4,5,8,9,10-octa-hydro-1*H*-azocine-10-carboxylate (27c).

Using General Procedure C, followed by chromatography of the product from **23c** (0.09 mmol) using 30:70 EtOAc/hexanes as eluant gave **27c** (86% yield) as an oil; ^1H NMR δ 9.77 (s, 1H), 6.92 (d, 1H, J = 8.4 Hz), 6.43 (d, 1H, J = 2.6 Hz), 6.33 (dd, 1H, J = 8.4, 2.6 Hz), 5.56 (m, 1H), 5.43 (m, 1H), 5.23 (d, 1H, J = 9.6 Hz), 4.87 (m, 2H), 4.43 (m, 2H), 3.75 (s, 3H), 3.37 (s, 3H), 2.35 (m, 1H), 1.96 (m, 7H), 1.40 (s, 9H). MS (ESI, m/z) 463.0 (MH) $^+$.

Methyl (3*S*, 9*S*)-3-*N*-(Fmoc)Amino-2-oxo-2, 3, 4, 5, 8, 9-hexahydro-1*H*-azonine-9-carboxylate (29). Using General Procedure D, followed by chromatography of the product from **26c** (0.5 mmol) using EtOAc as eluant gave **29** (90% yield) as a brown gum: ^1H NMR δ 7.74 (d, 2H, J = 7.4), 7.57 (d, 2H, J = 6.8), 7.38 (t, 2H, J = 7.0), 7.27 (t, 2H, J = 7.3), 6.71 (d, 1H, J = 7.7), 5.87 (q, 1H, J = 9.1), 5.80 (m, 1H), 5.7 (d, 1H, J = 8.1), 5.52 (m, 1H), 4.48 (m, 1H), 4.32 (m, 2H), 4.17 (m, 1H), 3.8 (s, 3H), 2.51 (m, 2H), 2.28 (m, 1H), 2.15 (m, 1H), 2.0 (m, 1H), 1.87 (m, 1H); ^{13}C NMR 173.7, 171.4, 155.5, 143.6, 143.5, 141.1, 133.1, 127.5, 126.9, 126.5, 124.9, 119.8, 66.9, 54.6, 52.9, 49.5, 46.9, 33.9, 24.1; HRMS calcd for $\text{C}_{25}\text{H}_{27}\text{N}_2\text{O}_5$ (MH) $^+$ 435.19145, found 435.19201.

(*E*, 3*S*, 9*S*)-3-*N*-(Fmoc)Amino-2-oxo-2,3,4,5,8,9-hexahydro-1*H*-azonine-9-carboxylic Acid (31). Using General Procedure E, hydrolysis of **29** (0.15 mmol) gave **31** (99% yield) as a white solid: mp 170-171°C; $[\alpha]_D^{20}$ -12.6° (c 0.42, CH_3OH); ^1H NMR δ 8.85 (d, 1H, J = 7.0), 7.73 (d, 2H, J = 7.5), 7.54 (t, 2H, J = 6.9), 7.36 (t, 2H, J = 7.4), 7.28 (d, 1H, J = 7.4), 5.95 (q, 1H, J = 9.3), 5.80 (q, 1H, J = 9.0), 5.45 (d, 1H, J = 8.7), 4.51 (m, 1H), 4.35 (m, 3H), 4.18 (t, 1H, J = 7.0), 2.72-2.62 (m, 2H), 2.18-2.15 (m, 2H), 1.84 (m, 1H), 1.29 (bs, 1H); ^{13}C NMR δ 177.0, 175.3, 156.3, 144.4, 144.3, 141.9, 133.4, 128.3, 127.7, 125.8, 125.6, 120.6, 67.8, 55.8, 50.6, 47.7, 34.5, 30.3; HRMS calcd for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_5$ (MH) $^+$ 421.17580, found 421.17591.

ppm

ppm

172.879
171.153

160.856
158.708
155.121

137.392
130.312

116.021
115.279
115.143

103.508
98.317

79.145
77.204
76.886
76.568

57.458
55.178
54.934
51.744
50.194
46.965

33.037
30.432
29.511
29.138
28.151
28.083
22.505
13.935

ppm

172.766
172.032

155.244

143.746
143.610
141.132

130.146
128.788
127.560
126.915
124.971
119.829

77.249
76.932
76.614

66.818

52.559
52.161
51.732
47.001

34.172
33.868

22.559

```

Current Data Parameters
NAME          tan
EXPNO         1
PROCNO        1

F2 - Acquisition Parameters
Date_         20041205
Time          14.23
INSTRUM       av500
PROBHD        5 mm TBI 1H/13
PULPROG       zgpg30
TD            65536
SOLVENT       CDCl3
NS            16
DS            1
SWH           6127.451 Hz
FIDRES        2.991920 Hz
AQ            0.1672484 sec
RG            512
DM            81.600 usec
DE            6.00 usec
TE            293.2 K
d0            0.00000000 sec
d1            2.00000000 sec
d13           0.00004400 sec
d16           0.00005000 sec
IM0           0.00016320 sec
MCREST        0.00000000 sec
MCMK          2.00000000 sec

----- CHANNEL f1 -----
NUC1           1H
P0             3.00 usec
P1             5.80 usec
PL1            0.00 dB
SFO1          500.1326132 MHz

----- GRADIENT CHANNEL -----
GPMAN1        SINE.100
GPMAN2        SINE.100
GPX1           0.00 %
GPX2           0.00 %
GPY1           0.00 %
GPY2           0.00 %
GPZ1          10.00 %
GPZ2          10.00 %
P16           1000.00 usec

F1 - Acquisition parameters
ND0            1
TD            512
SFO1          500.1326 MHz
FIDRES        11.967678 Hz
SW            12.252 ppm
FHM000        GF

F2 - Processing parameters
SI            2048
SF            500.1300000 MHz
WDW           SINE
SSB           0
LB            0.00 Hz
GB            0
PC            1.00

F1 - Processing parameters
SI            16384
NC2           GF
SF            500.1300000 MHz
WDW           SINE
SSB           0
LB            0.00 Hz
GB            0

2D NMR plot parameters
CX2           15.00 cm
CX1           15.00 cm
F2P0         11.951 ppm
F2L0         5976.91 Hz
F2PH1        -0.301 ppm
F2H1         -150.54 Hz
F1P0         11.951 ppm
F1L0         5976.91 Hz
F1PH1        -0.301 ppm
F1H1         -150.54 Hz
F2PPMCH      0.81678 ppm/cm
F2HZCH       408.49673 Hz/cm
F1PPMCH      0.81678 ppm/cm
F1HZCH       408.49673 Hz/cm

```

NOESY

```

Current Data Parameters
NAME          ExpNO
EXPNO         4
PROCNO        1

F2 - Acquisition Parameters
Date_         20041208
Time          16.14
INSTRUM       spect
PROBHD        5 mm TBI 1H/13
PULPROG       zgpg30
TD            65536
SOLVENT       CDCl3
NS            16
DS            4
SWH           6127.451 Hz
FIDRES        2.991920 Hz
AQ            0.1672484 sec
RG            101.6
DM            81.600 usec
DE            6.00 usec
TE            293.2 K
DQ            0.00007423 sec
O1            2.20000005 sec
O2            0.40000001 sec
O3            0.00000000 sec
IND           0.00016320 sec
NOEPRST       0.00000000 sec
NOEPRG        1.10000002 sec
STOCH         256
TAU           0.19692001 sec

----- CHANNEL f1 -----
NUC1          1H
P1            5.80 usec
P2            11.50 usec
PL1           0.00 dB
SFO1          500.1326132 MHz

----- GRADIENT CHANNEL -----
GPMAX1        SINE.100
GPMAX2        SINE.100
GPX1          0.00 %
GPX2          0.00 %
GPY1          0.00 %
GPY2          0.00 %
GPT1          40.00 %
GPT2          -40.00 %
PI6           1000.00 usec

F1 - Acquisition parameters
NO          1
TD          512
SFO1        500.1326132 MHz
FIDRES      11.967678 Hz
SW          12.252 ppm
FHM000      States-TPPI

F2 - Processing parameters
SI          32768
SF          500.1300000 MHz
WDW          SINE
SSB          2
LB           0.00 Hz
GB           0
PC           1.00

F1 - Processing parameters
SI          1024
NC2         States-TPPI
SF          500.1300000 MHz
WDW          SINE
SSB          2
LB           0.00 Hz
GB           0

2D NMR plot parameters
CX2         15.00 cm
CX1         15.00 cm
FAPLO       11.951 ppm
FBL0        5076.91 Hz
FPMH1       -0.301 ppm
F2H1        -150.54 Hz
FPL0        11.951 ppm
FBL0        5076.91 Hz
FPMH1       -0.301 ppm
F1H1        -150.54 Hz
FPMH0H      0.81678 ppm/cm
F2H0H       408.49673 Hz/cm
F1PMH0H     0.81678 ppm/cm
F1H0H       408.49673 Hz/cm

```

NOESY

Current Data Parameters
NAME: lan
EXPNO: 5
PROCNO: 1

F2 - Acquisition Parameters
Date_: 20041208
Time: 22.36
INSTRUM: av500
PROBHD: 5 mm TBI 1H/13
PULPROG: noesygph
TD: 2648
SOLVENT: CDCl3
NS: 16
DS: 16
SWH: 6127.451 Hz
FIDRES: 2.991520 Hz
AQ: 0.1672464 sec
RG: 90.5
DW: 81.600 usec
DE: 6.00 usec
TE: 293.2 K
d0: 0.0007422 sec
d1: 1.7999999 sec
d8: 0.80000001 sec
d16: 0.00050000 sec
INRG: 0.0001320 sec
HOREST: 0.00000000 sec
HOREK: 0.89999998 sec
STICT: 256
TAU: 0.39895001 sec

----- CHANNEL f1 -----
NUC1: 1H
P1: 5.80 usec
P2: 11.50 usec
PL1: 0.00 dB
SF01: 500.1306132 MHz

----- GRADIENT CHANNEL -----
GPMAX1: SINE:100
GPMAX2: SINE:100
GPX1: 0.00 %
GPX2: 0.00 %
GPY1: 0.00 %
GPY2: 0.00 %
GPZ1: 40.00 %
GPZ2: -40.00 %
P16: 1000.00 usec

F1 - Acquisition parameters
ND0: 1
TD: 512
SF01: 500.1329 MHz
FIDRES: 11.967678 Hz
SW: 12.252 ppm
FHM00E: States-TPPI

F2 - Processing parameters
SI: 2648
SF: 500.1300000 MHz
WDW: SINE
SSB: 2
LB: 0.00 Hz
GB: 0
PC: 1.00

F1 - Processing parameters
SI: 1024
HC2: States-TPPI
SF: 500.1300000 MHz
WDW: SINE
SSB: 2
LB: 0.00 Hz
GB: 0

2D NMR plot parameters
CX2: 15.00 cm
CX1: 15.00 cm
FZLO: 11.951 ppm
FZLO: 5976.91 Hz
FZPH1: -0.301 ppm
FZPH1: -150.54 Hz
FZPL0: 11.951 ppm
FZPL0: 5976.91 Hz
FZPH1: -0.301 ppm
FZPH1: -150.54 Hz
FZPH0H: 0.81678 ppm/cm
FZPH0H: 408.49673 Hz/cm
FZPH0H: 0.81678 ppm/cm
FZPH0H: 408.49673 Hz/cm

Current Data Parameters
NAME rk-111-34
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20041109
Time 9.04
INSTRUM av400
PROBHD 5 mm PABBO BB-
PULPROG csgyqpf
TD 2048
SOLVENT CDCl3
NS 2
DS 16
SWH 4194.631 Hz
FIDRES 2.048160 Hz
AQ 0.2441716 sec
RG 181
DM 119.200 usec
DE 6.00 usec
TE 294.0 K
d0 0.0000300 sec
D1 1.5000000 sec
d13 0.0000400 sec
D16 0.0000500 sec
IN0 0.00023840 sec
MCOREST 0.0000000 sec
MCORR 1.5000000 sec

***** CHANNEL f1 *****
NUC1 1H
P0 4.60 usec
PL1 9.40 usec
PL1 -3.00 dB
SFO1 400.1319005 MHz

***** GRADIENT CHANNEL *****
GPNAM1 sine.100
GPNAM2 sine.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 15.00 %
GPZ2 15.00 %
P16 1000.00 usec

F1 - Acquisition parameters
ND0 1
TD 256
SFO1 400.1319 MHz
FIDRES 16.385277 Hz
SW 10.493 ppm

F2 - Processing parameters
SI 2048
SF 400.1300000 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 1024
MC2 OF
SF 400.1300000 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0

2D NMR plot parameters
CX2 15.00 cm
CX1 15.00 cm
F2PLO 9.992 ppm
F2LO 3997.93 Hz
F2PHI -0.492 ppm
F2H1 -196.70 Hz
F1PLO 9.992 ppm
F1LO 3997.93 Hz
F1PHI -0.492 ppm
F1H1 -196.70 Hz
F2PMCM 0.69888 ppm/cm
F2HZCM 279.64206 Hz/cm
F1PMCM 0.69888 ppm/cm
F1HZCM 279.64206 Hz/cm

```

Current Data Parameters
NAME          ramesh
EXPNO         12
PROCNO        1

F2 - Acquisition Parameters
Date_         20041201
Time          16:57
INSTRUM       av500
PROBHD        5 mm TBI 1H/13
PULPROG       noesypph
TD            2048
SOLVENT       THF
NS            64
DS            16
SWH           5252.101 Hz
FIDRES        2.564502 Hz
AQ            0.1950196 sec
RG            128
DM            95.200 usec
DE            6.00 usec
TE            298.2 K
d0            0.0008785 sec
d1            1.0000000 sec
d8            0.5000000 sec
d16           0.0005000 sec
IN0           0.0019040 sec
MCREST        0.0000000 sec
MCWRR         0.5000000 sec
ST1CNT        200
TAU           0.24895000 sec

----- CHANNEL f1 -----
NUC1          1H
P1            5.80 usec
P2            11.00 usec
PL1           0.00 dB
SF01          500.1323521 MHz

----- GRADIENT CHANNEL -----
GPNAM1        sine.100
GPNAM2        sine.100
GP1X          0.00 %
GP1Z          0.00 %
GPY1          0.00 %
GPY2          0.00 %
GPZ1          40.00 %
GPZ2          -40.00 %
P16           1000.00 usec

F1 - Acquisition parameters
NUC           1
TD            400
SF01          500.1324 MHz
FIDRES        13.130252 Hz
SM            10.501 ppm

F2 - Processing parameters
SI            2048
SF            500.1300186 MHz
WDW           SINE
SSB           2
LB            0.00 Hz
GB            0
PC            1.00

F1 - Processing parameters
SI            1024
MC2           States-TPPI
SF            500.1300000 MHz
WDW           SINE
SSB           2
LB            0.00 Hz
GB            0

2D NMR plot parameters
CX2           15.00 cm
CX1           15.00 cm
FPLD          9.265 ppm
FZLD          4633.82 Hz
F2PHI         -0.057 ppm
F2HI          -28.44 Hz
F1PLD         9.092 ppm
F1LO          4547.31 Hz
F1PHI         -0.004 ppm
F1HI          -2.11 Hz
F2PHI2CM      0.62147 ppm/cm
F2HI2CM       310.81769 Hz/cm
F1PHI2CM      0.60643 ppm/cm
F1HI2CM       303.29517 Hz/cm

```


Data File: COMPD-30
 Current Data Path: C:\Ana LCUV\DATA\
 Acquisition Date: 02/06/05 09:35:59
 Run Time (min): 25
 Comments: 20-80B% Over 10 min , A=H2O/0.01% TFA, B=ACN/0.01% TFA,
 Flow=0.5 ml/mn, Column:C18 150x4.6mm, Wavelength =214
 Injection Volume (μl): 10.00

RT: 0.00 - 25.97 SM: 15G

RT	Peak Area	Peak Height	Area %
12.75	4026071	287947	100.00

Data File: COMPD-31
 Current Data Path: C:\Ana LCUV\DATA\
 Acquisition Date: 02/06/05 09:35:59
 Run Time (min): 25
 Comments: 20-80B% Over 10 min , A=H2O/0.01% TFA, B=ACN/0.01% TFA,
 Flow=0.5 ml/min, Column:C18 150x4.6mm, Wavelength =214
 Injection Volume (μl): 10.00

RT: 0.00 - 25.97 SM: 15G

RT	Peak Area	Peak Height	Area %
13.13	3338732	356785	96.76
15.12	111800	5628	3.24

Protons H_a and H_b were irradiated on a Bruker AV 500