A practical method for the synthesis of small peptides using DCC and HOBt as activators in H_2O-THF while avoiding the use of protecting groups.

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1. Characterisation data

Boc-Pro-Phe-OH 6[1]

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.85 (1H, brs), 7.44 (3H, m), 7.23 (2H, m), 6.61 (1H, br s), 4.82 (1H, m), 4.21 (1H, m), 3.29 (2H, m), 3.27 (1H, dd, *J* = 13.8, 6.4 Hz), 3.06 (1H, dd, *J* = 13.8, 4.3 Hz), 1.98 (2H, m), 1.58 (2H, m), 1.38 (9H, s). **^{13}C NMR** ($CDCl_3$, 300MHz): δ 174.0, 173.2, 171.5, 155.4, 136.1, 129.3, 128.2, 127.1, 81.7, 61.2, 60.4, 52.8, 46.9, 37.6, 30.9, 28.3, 23.8.

Boc-Pro-Phe-OMe 8[1]

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.24 (3H, m), 7.09 (2H, m), 6.46 (1H, brs), 4.86 (1H, m), 4.23 (1H, m), 3.72 (3H, s), 3.28 (2H, m), 3.19 (1H, dd, *J* = 14.1, 5.7 Hz), 3.00 (1H, dd, *J* = 14.1, 6.9 Hz), 1.92 (2H, m), 1.62 (2H, m), 1.42 (9H, s). **^{13}C NMR** ($CDCl_3$, 300MHz): δ 171.9, 171.7, 136.0, 129.2, 128.5, 127.0, 80.7, 60.4, 52.9, 52.2, 46.9, 38.2, 30.3, 28.3, 23.9.

Boc-Pro-Gly-OH 9[2]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.30 (1H, brs), 7.71 (1H, brs), 7.36 (1H, brs), 4.29 (1H, m), 4.08 (2H, dd, *J* =18.1, 5.1 Hz), 3.44 (2H, m), 2.36-1.75 (4H, m), 1.40 (9H, s). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 174.54, 156.57, 139.28, 128.57, 127.19, 126.53, 116.37, 111.89, 81.55, 60.18, 59.28, 59.10, 47.13, 41.57, 31.15, 30.91, 28.46, 28.38, 24.38, 23.72.

Boc-Pro-Pro-OH 10[3]

^{1}H NMR (CDCl3, 300 MHz): δ 12.8 (1H, brs), 7.72 (2H brs), 7.36 (2H, brs), 4.66-4.15 (2H, m), 3.82-3.25 (4H, m), 2.36-1.65 (8H, m), 1.37 (9H, brs). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.8, 173.5, 173.0, 172.8, 154.8, 153.9, 138.9, 128.5, 127.0, 127.0, 126.3, 116.0, 111.7, 80.1, 59.4, 59.0, 57.8, 46.9, 29.8, 29.0, 28.3, 28.2, 24.8, 24.0, 23.5.

Boc-Pro-Thr-OH 11

^{1}H NMR (CDCl3, 300 MHz): δ 9.73 (1H, brs), 7.76 (2H, brs), 7.39 (2H, brs), 4.55 (1H, d, *J* = 8.29 Hz), 4.38 (2H, m), 3.58-3.30 (2H, m), 2.32-1.76 (4H, m), 1.42 (9H, s), 1.19 (3H, d, *J* = 6.4 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.7, 172.8, 155.4, 139.1, 128.5, 127.0, 126.4, 116.2, 111.7, 81.1, 67.6, 60.2, 57.4, 47.0, 29.5, 28.2, 24.1, 19.4.

Boc-Pro-Leu-OH 12[4]

^{1}H NMR (CDCl3, 300 MHz): δ 12.35 (brs), 7.75 (1H, s), 7.38 (1H, m), 4.54 (1H, brs), 4.31 (1H, brs), 3.41 (2H, m), 2.16 (2H, m), 1.85 (2H, m), 1.64 (3H, m), 1.41 (9H, s), 0.90 (6H, d, *J* = 4.8 Hz). **^{13}C NMR** (75

MHz, $CDCl_3$) δ 175.5, 172.8, 155.4, 139.3, 128.5, 126.8, 126.4, 116.3, 111.6, 80.9, 60.3, 58.9, 50.8, 46.9, 41.0, 28.1, 24.8, 24.0, 22.7, 21.6.

Boc-Pro-Trp-OH 13

^{1}H NMR (CDCl3, 300 MHz): δ 10.23 (1H brs), 8.73 (1H, s), 7.72 (1H, dd, *J* = 7.2, 0.2 Hz), 7.53 (1, d, *J* = 7.3, 0.3 Hz), 7.37 (1H, brs), 7.28 (1, ddd, *J* = 7.0, 1.4, 0.2 Hz), 7.09 (1, ddd, *J* = 7.0, 1.2. 0.3 Hz), 7.05-6.98) (3H, brs), 4.87 (1H, ddd, *J* = 5.8, 5.2, 0.4 Hz), 4.19 (1H, m), 3.38 (1, dd, *J* = 14.8, 5.2 Hz), 3.28 (1, dd, *J* = 14.8, 5.8 Hz), 3.24 (2H, m), 1.95 (2H, m), 1.63 (2H, m), 1.45 (2H, m), 1.30 (9H, s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.9, 155.3, 138.6, 136.2, 128.6, 127.7, 127.5, 126.5, 123.4, 121.9, 119.4, 118.2, 115.8, 111.9, 111.4, 109.4, 81.2, 60.4, 59.1, 53.2, 46.9, 28.3, 28.1, 27.1.

Boc-Pro-Phe-Gly-OH 14

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (1H, brs), 7.48 (3H, m), 7.31 (2H, m), 6.89 (1H, brs), 4.82 (1H, dd, *J* = 14.4, 7.4 Hz), 4.17 (1H, m), 4.12 (1H, d, *J* = 7.2 Hz), 4.02 (1H, d, *J* = 7.2 Hz), 3.90 (1H, brs), 3.28 (2H, m), 3.25 (1H, dd, *J* = 13.9, 6.4 Hz), 3.16 (1H, dd, *J* = 13.9, 4.5 Hz), 1.92 (2H, m), 1.78 (2H, m), 1.38 (9H, s).

Boc-Pro-Phe-Gly-Pro-OH 15.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (1H, brs), 7.49 (3H, m), 7.28 (2H, m), 6.86 (1H, brs), 4.80 (1H, dd, *J* = 14.5, 7.3 Hz), 4.51 (1H, dd, *J* = 13.8, 6.9 Hz), 4.18 (1H, m), 4.15 (1H, d, *J* = 7.2 Hz), 4.08 (1H, d, *J* = 7.2 Hz), 4.03 (1H, m), 3.57 (2H, m), 3.27 (2H, m), 2.98 (2H, m), 2.25 (2H, m), 2.10 (2H, m), 1.91 (2H, m), 1.72 (2H, m), 1.38 (9H, s).

O-Leu-Val-OH-18

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25 (1H, d, *J* = 8.8 Hz), 6.12 (2H, s), 4.44 (1H, dd, *J* = 8.5, 4.5), 4.19 (1H, dd *J* = 9.1, 3.8 Hz), 2.23 (1H, hectd, *J* = 6.8, 4.7Hz), 1.82 (1H, nan, *J* = 6.5), 1.61 (1H, ddd *J* = 13.9, 9.5, 6.8 Hz), 1.56 (1H, ddd, *J* = 13.8, 6.6, 3.9 Hz), 0.98 (6H, d, *J* = 6.9 Hz), 0.95 (6H, d, *J* = 6.9 Hz).

O-Leu-Val-Leu-OH-20

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 (1H, d, *J* = 9.2 Hz), 7.28 (1H, d, *J* = 7.6 Hz), 4.46 (1H, ddd, *J* = 9.1, 3.2, 7.8, 5.1 Hz), 4.34 (1H, dd, *J* = 8.9. 6.1 Hz), 4.10 (1H, dd, *J* = 9.8, 3.4 Hz), 2.2 (1H, oct, *J* = 6.2 Hz), 1.86 (1H, nan, *J* = 6.8 Hz), 1.72-1.43 (5H, m), 0.95 (3H, d, *J* = 6.7 Hz), 0.94 (3H, d, *J* = 6.6 Hz), 0.94 (6H, d, *J* = 6.4 Hz), 0.93 (3H, d, *J* = 6.5 Hz), 0.9 (3H, d, *J* = 6.9 Hz).

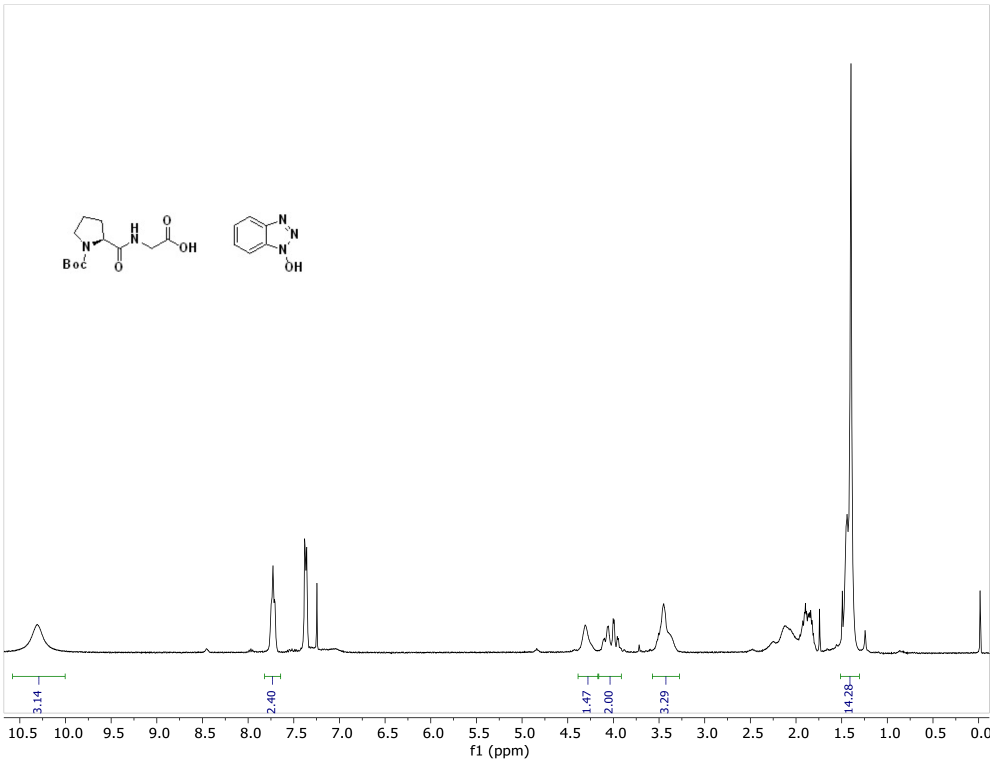
O-Leu-Val-Leu-Phe-OH 21

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 (1H, d, *J*= 8.5 Hz), 7.32 (1H, d, *J* = 9.7 Hz), 7.28-7.17 (5H, m), 7.08 (1H, d, *J* = 7.7 Hz), 5.68 (2H, s, br), 4.73 (1H, ddd, *J* = 7.4, 6.5, 5.3 Hz), 4.39 (1H, td, *J* = 8.5, 5.6 Hz), 4.32 (1H, dd, *J* = 9.2, 6.1 Hz), 4.10 (1H, dd, *J* = 9.6, 3.4 Hz), 3.18 (1H, dd, *J* = 14.2, 5.6 Hz), 3.05 (1H, dd, *J* = 14.2, 6.4 Hz), 2.16 (1H, oct, *J* = 6.3 Hz), 1.6-1.5 (5H, m), 1.86 (1H, hectt, 1H, *J* = 6.6, 2.3 Hz), 0.92 (3H, d, *J* = 6.6 Hz), 0.91 (6H, d, *J* = 6.6 Hz), 0.90 (6H, d, *J* = 6.3 Hz), 0.85 (3H, d, *J* = 6.6 Hz).

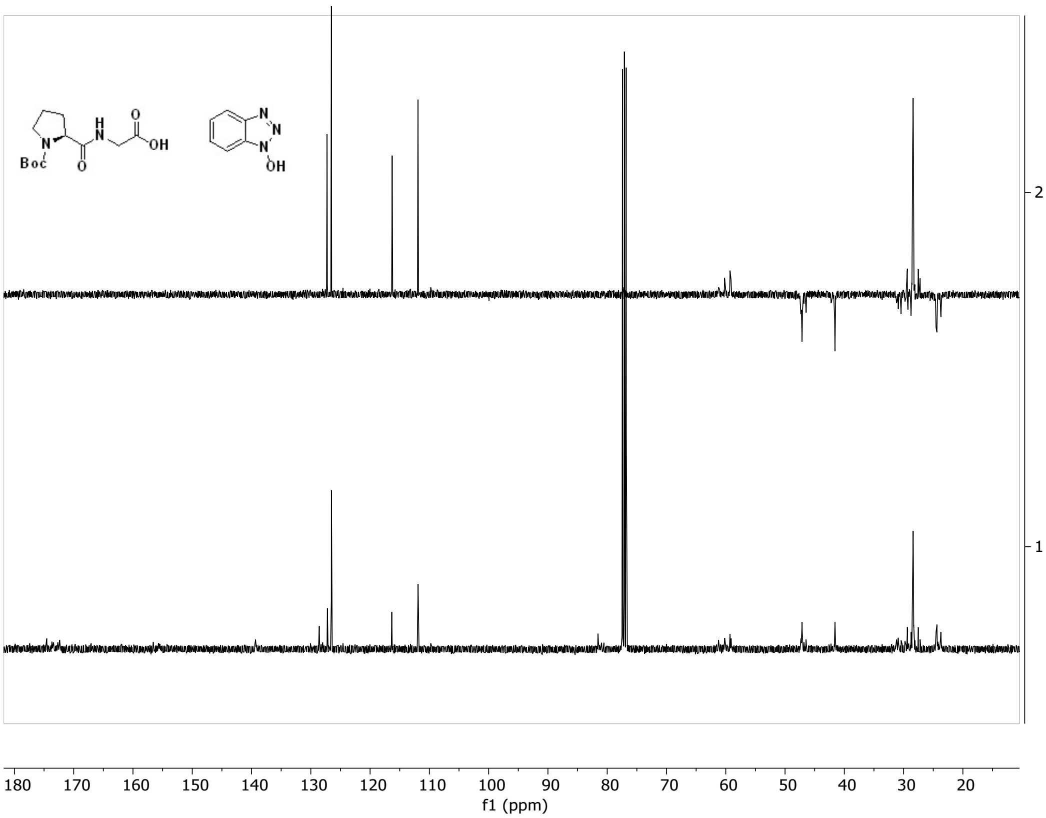
O-Leu-Va-lLeu-Phe-Leu-OH 22

^{1}H NMR (CD_3OD, 300 MHz): δ 8.13 (1H d, *J* = 8.4 Hz), 8.01 (1H, d, *J* = 7.6 Hz), 7.8 (1H, d, *J* = 8.1 Hz), 7.5 (1H, d, *J* = 9.1 Hz), 7.24-7.13 (5H, m), 4.58 (1H, td, *J* = 8.5, 4.6 Hz), 4.25 (ddd, 1H, *J* = 7.8, 6.8, 6.5 Hz), 4.25 (1H, ddd, *J* = 7.6, 6.8, 6.5 Hz), 4.17 (1H, dd, *J* = 8.9, 2.6 Hz), 3.84 (1H, td, *J* = 8.8, 4.3 Hz), 3.03 (1H, dd, *J* = 14.2, 4.8 Hz), 2.78 (1H, dd, *J* = 14.1, 8.6 Hz), 1.87 (1H, nan, *J* = 6.6 Hz), 1.72 (1H, oct, *J* = 6.6 Hz), 1.58 (3H, oct, *J* = 6.5 Hz), 1.52-1.34 (5H, m), 0.84 (6H, d, *J* = 6.6 Hz), 0.83 (6H, d, *J* = 6.6 Hz), 0.82 (3H, d, *J*= 6.6 Hz), 0.78 (3H, d, *J* = 6.6 Hz), 0.75 (3H, d, *J* = 6.6 Hz), 0.70 (3H, d, *J* = 6.6 Hz).

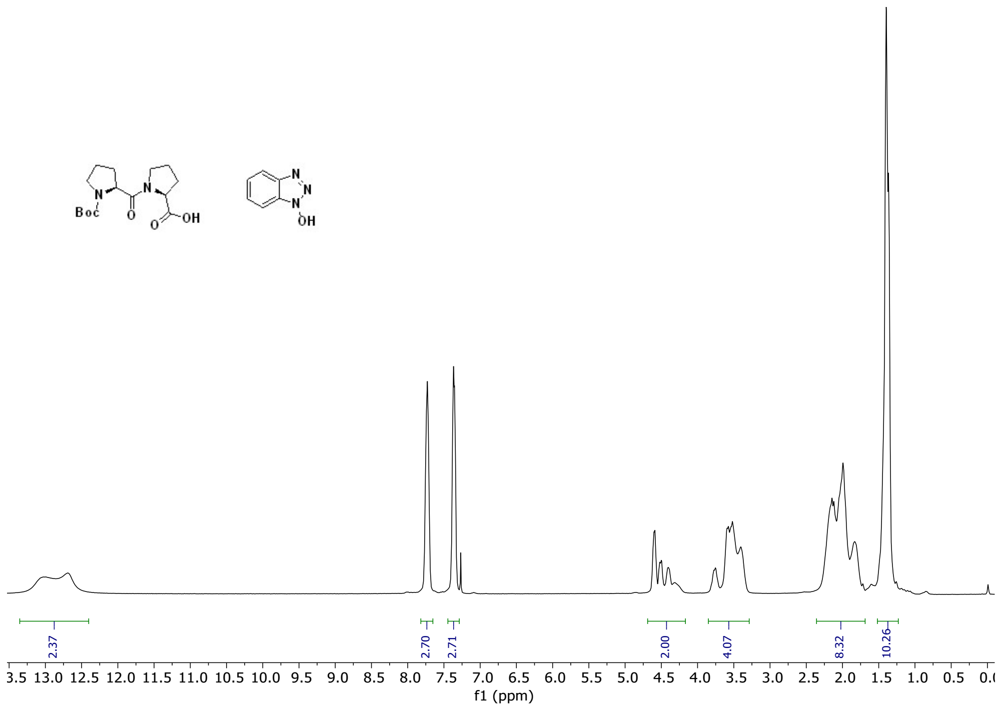
2. NMR spectrum of compounds 9-13



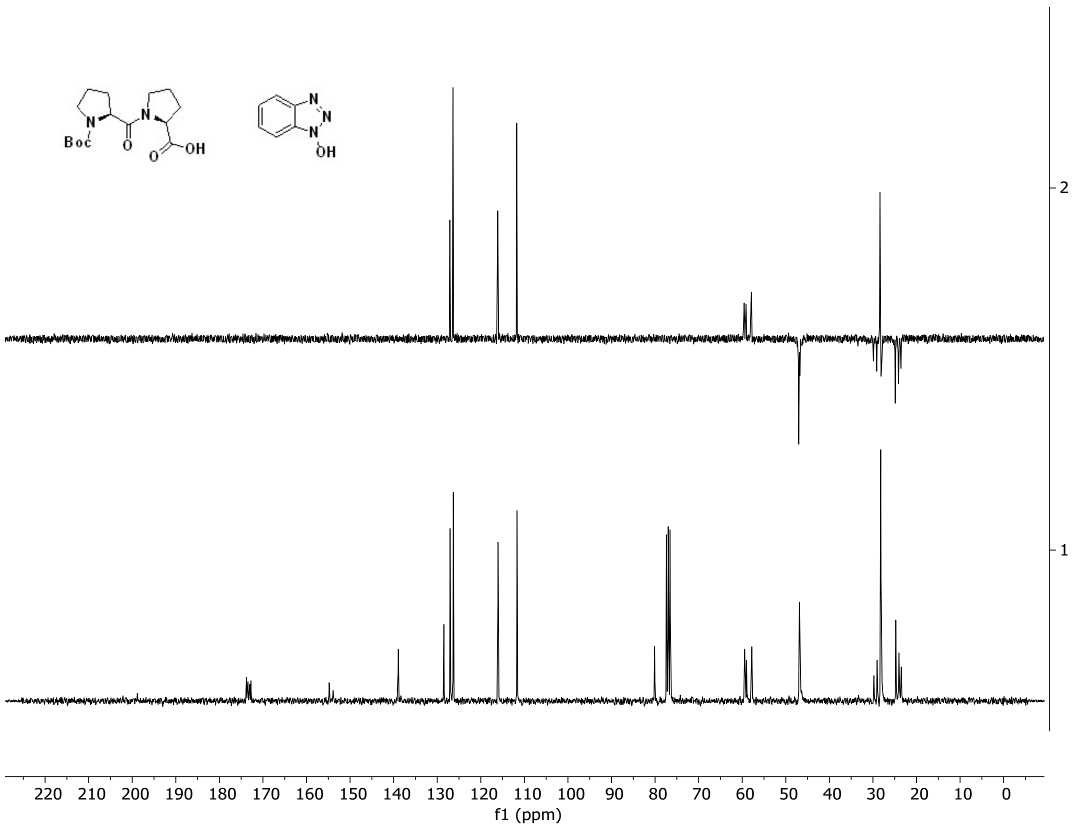
^{1}H NMR of 9 + HOBt



^{13}C and DEPT NMR of 9 + HOBt



^{1}H NMR of 10 + HOBt



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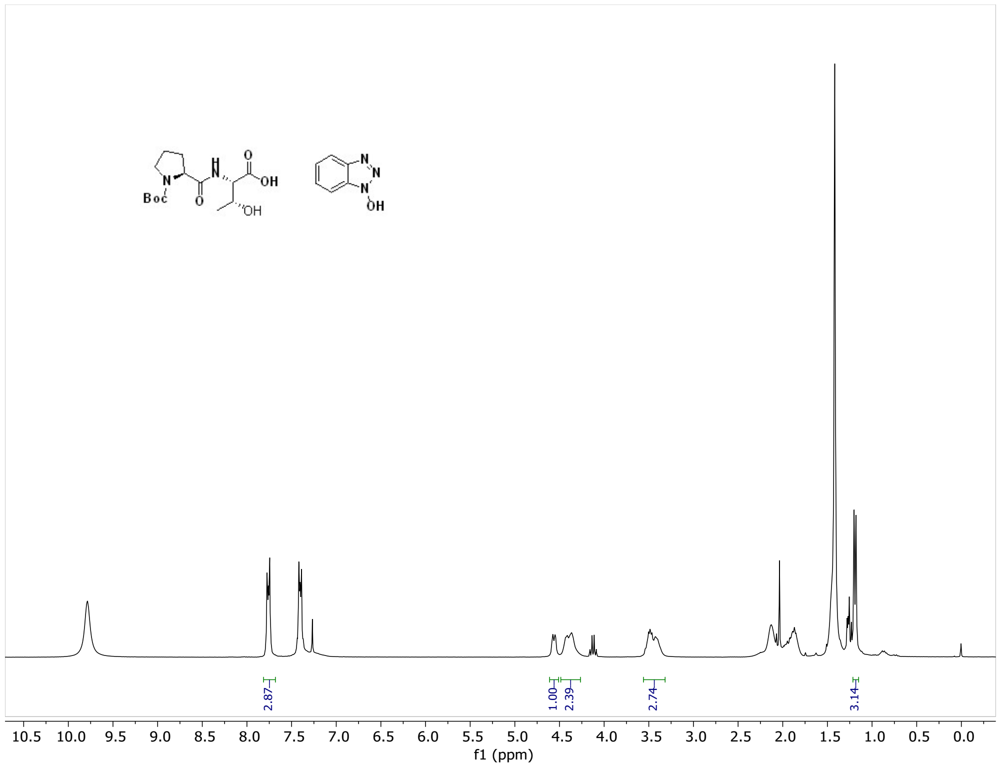
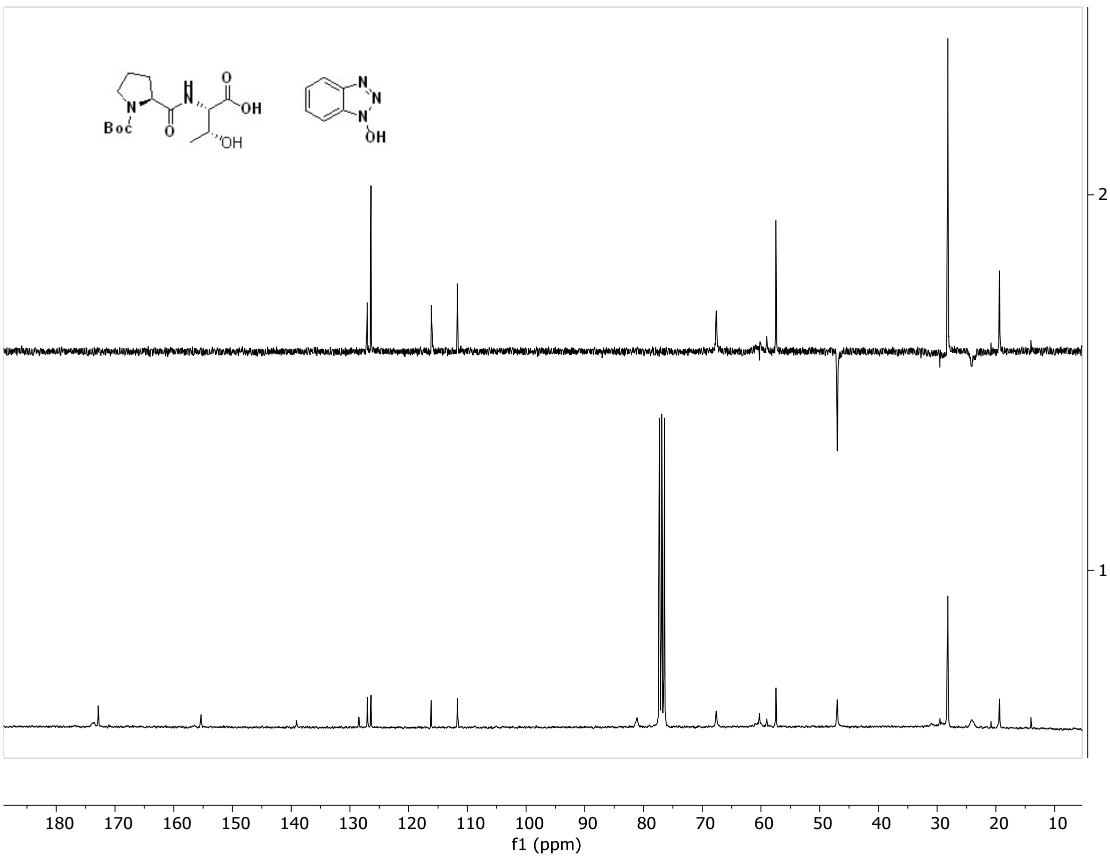
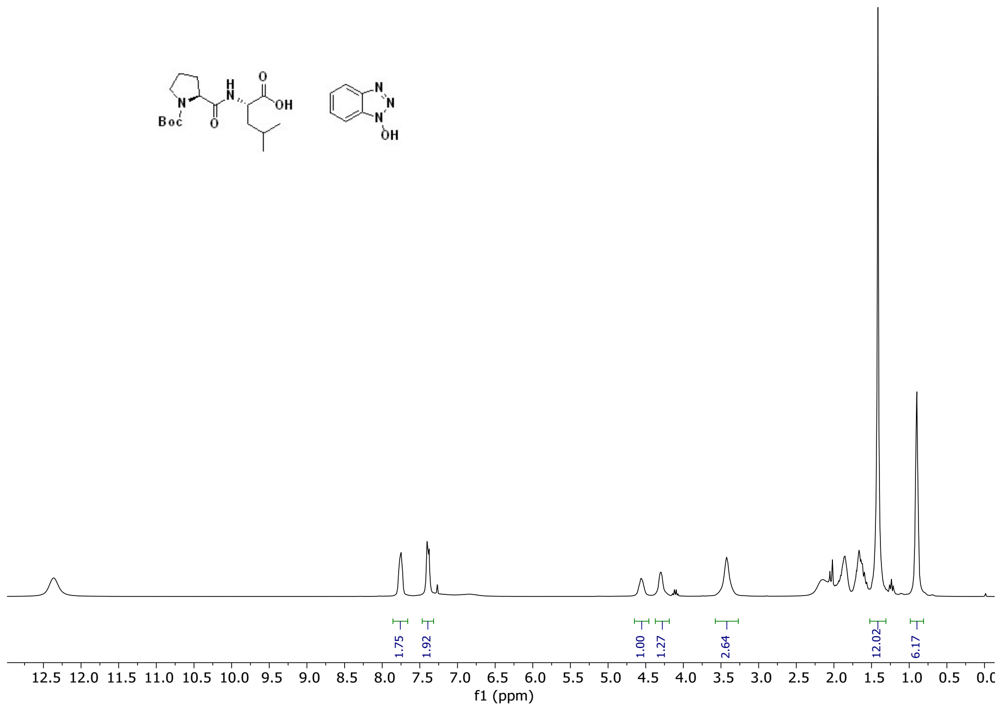


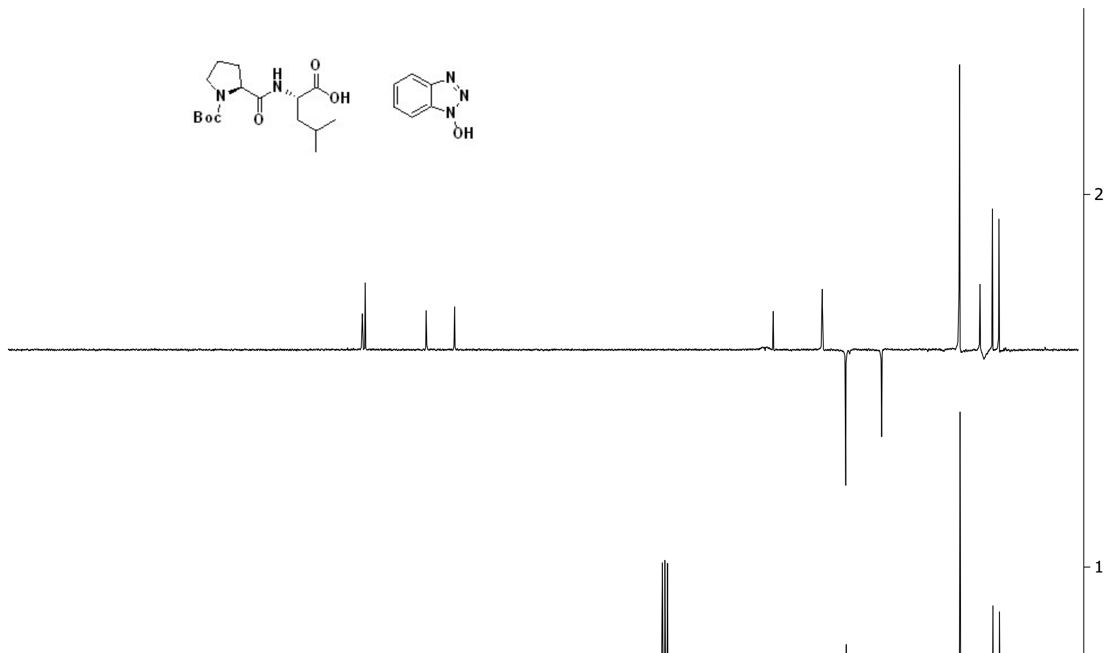
[1]H NMR of 11 + HOBt



[13]C and DEPT NMR of 11 + HOBt



^{1}H NMR of 12 + HOBt



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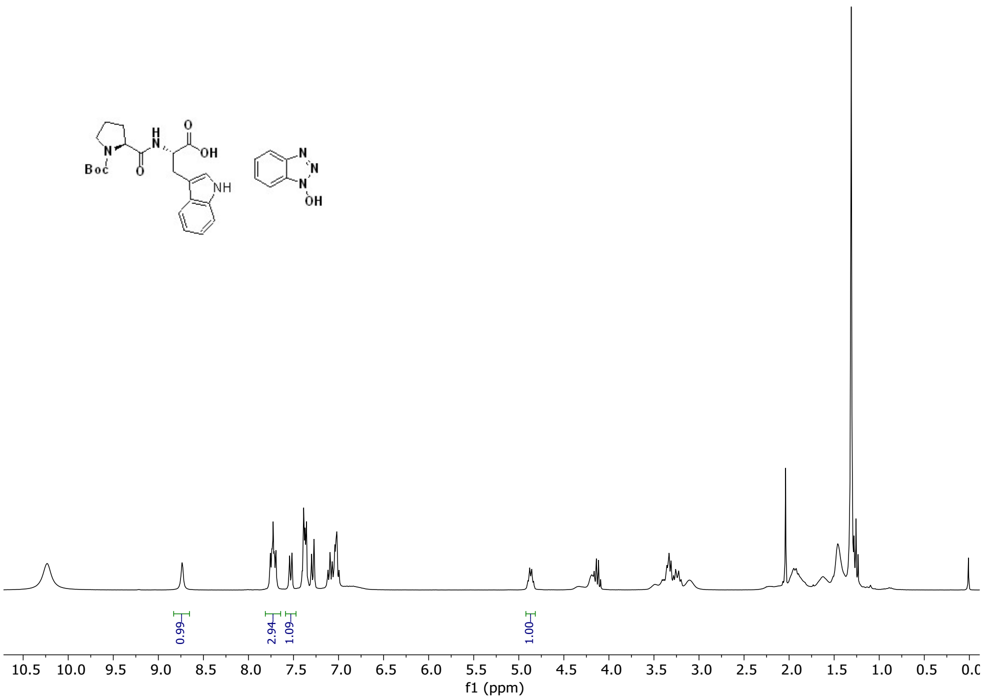
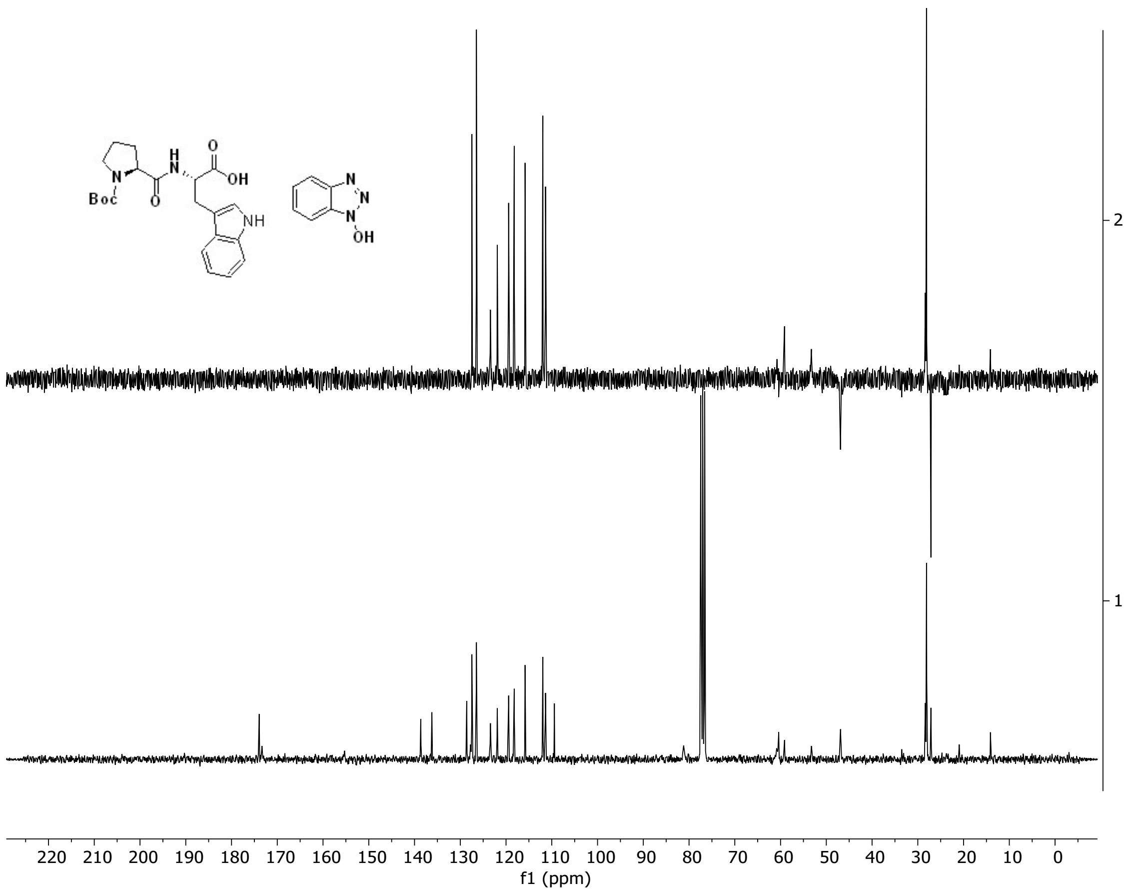
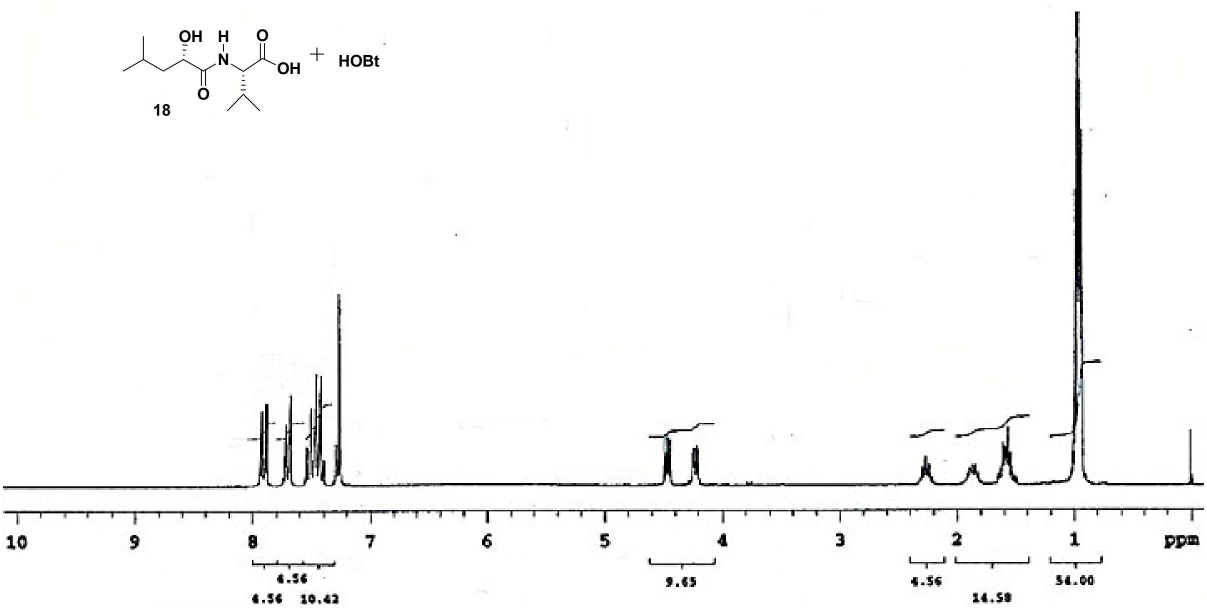


^{1}H NMR of 13 + HOBt



^{13}C and DEPT NMR of 13 + HOBt

3. NMR spectrum of intermediates 18, 20, 21 and 22



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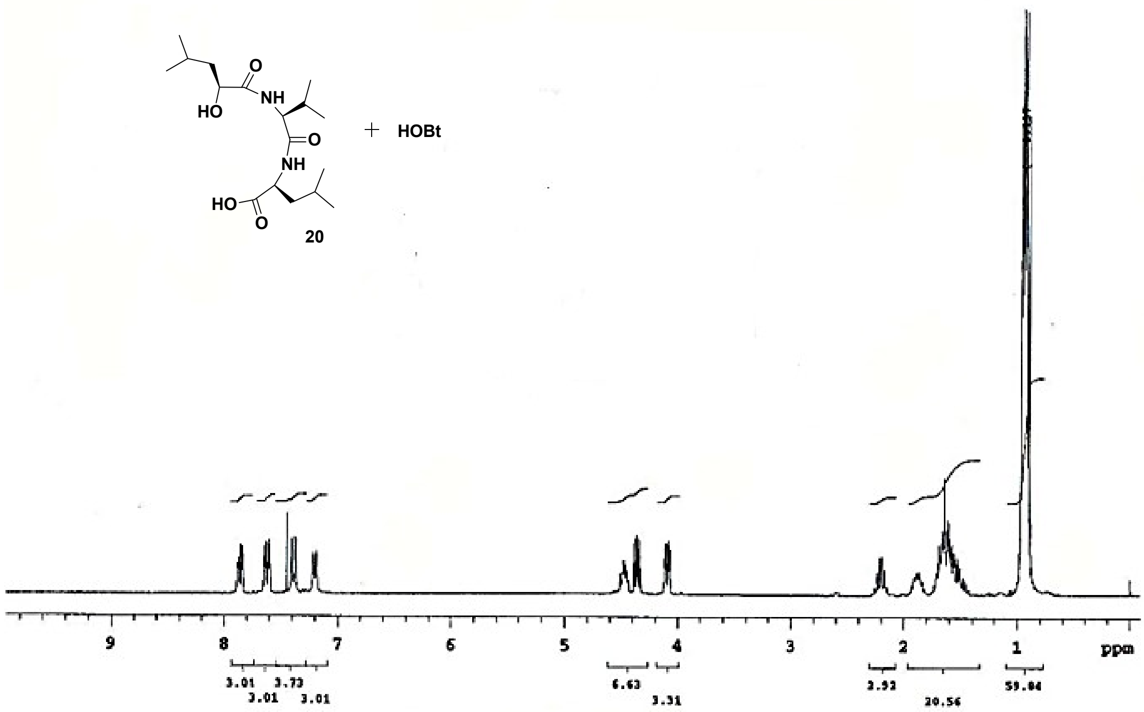
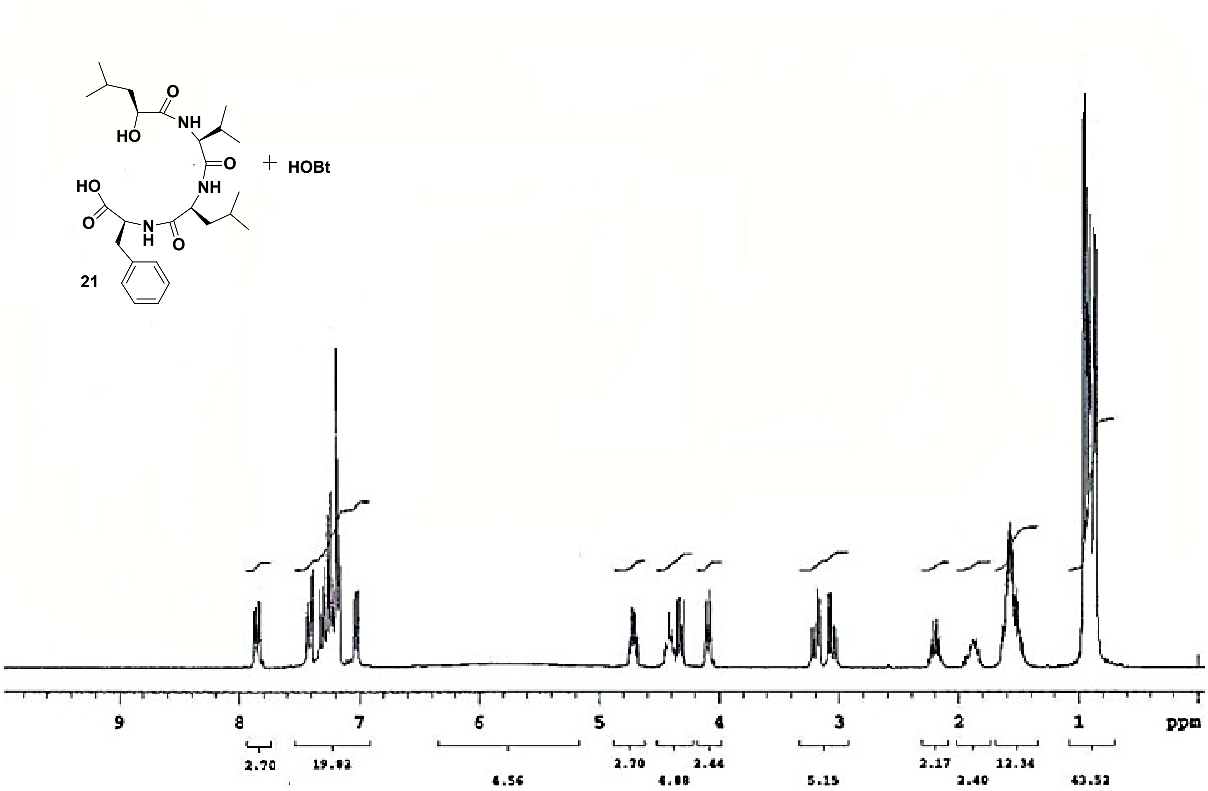
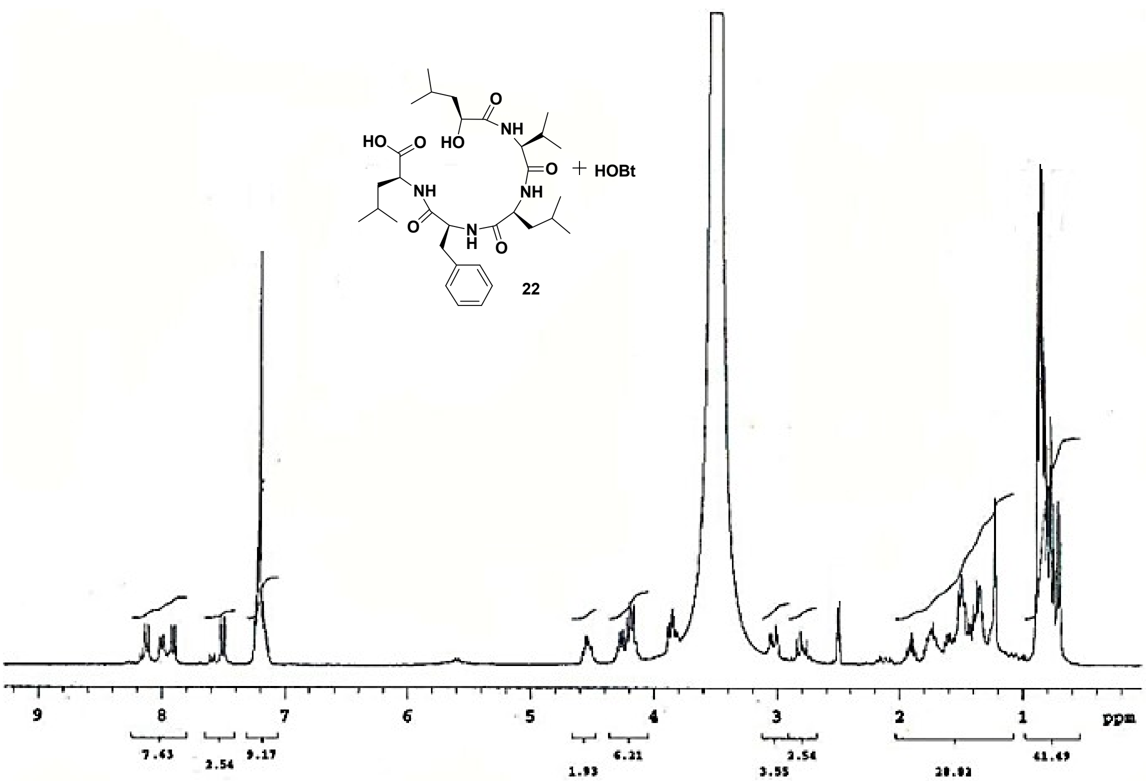


^{1}H NMR of 20 + HOBt

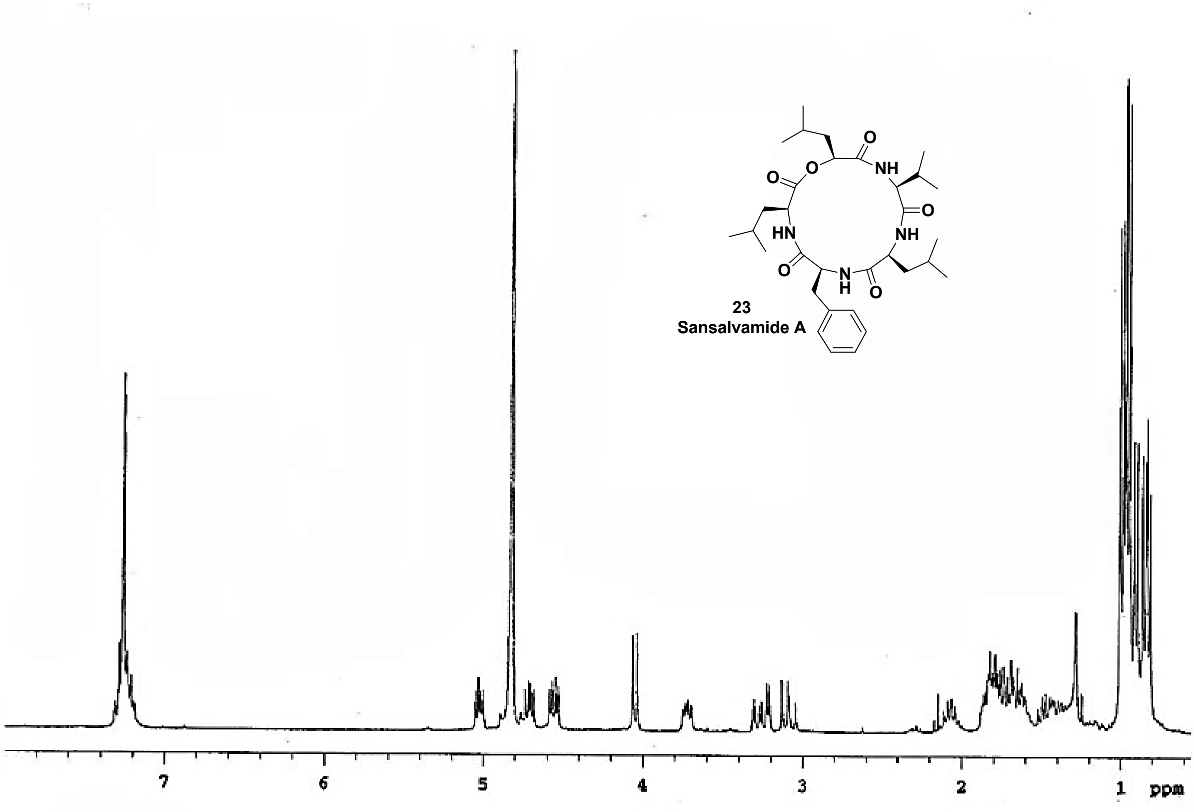


^{1}H NMR of 21 + HOBt

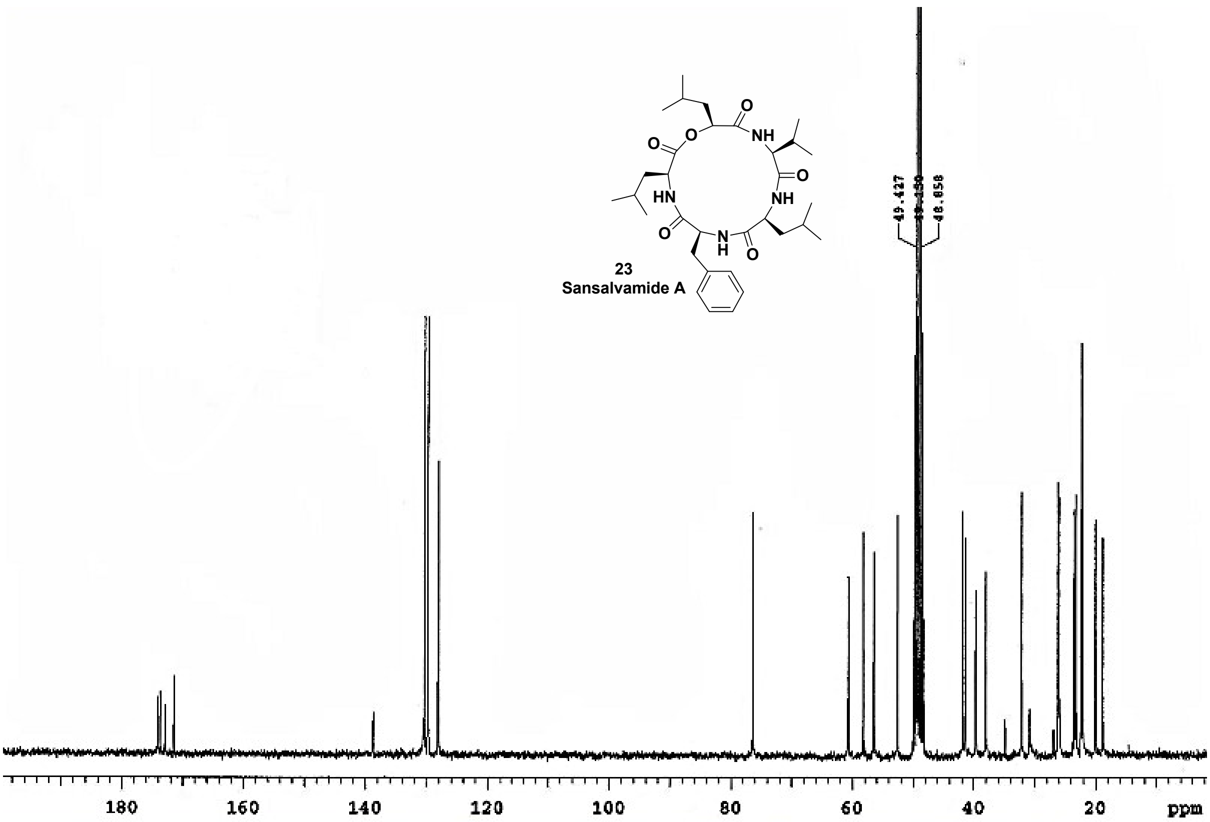


^{1}H NMR of 22 + HOBt

4. NMR Spectrum of Sansalvamide A



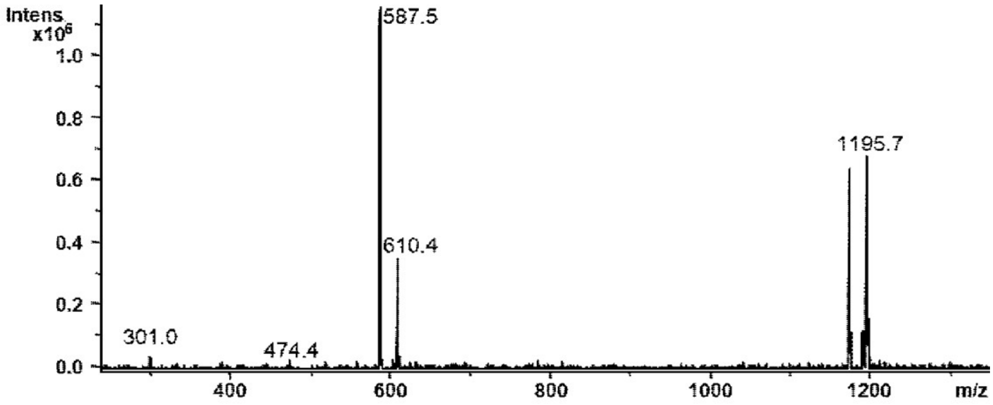
^{1}H NMR of Sansalvamide A in CD_3OD



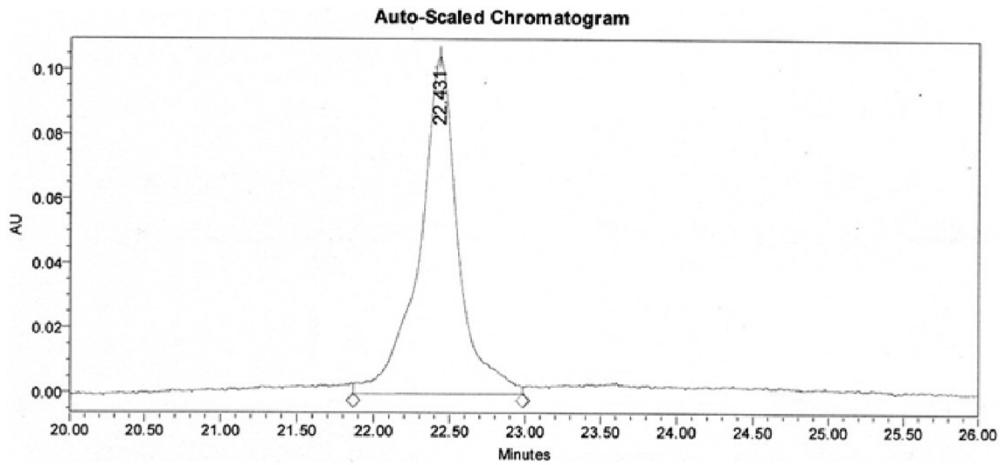
^{13}C NMR of Sansalvamide A in CD_3OD

5. ESI-Mass of Sansalvamide A

Calculated for $C_{32}H_{51}O_6N_4$ 587.3809, found 587.5



6. HPLC of Sansalvamide A



7. References

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[4] M. El Khatib, M. Elagawany, E. Çalışkan, E. F. Davis, H. M. Faidallah, S. A. El-feky and A. R. Katritzky, *Chem. Commun.*, 2013, **49**, 2631–2633.