10.1071/CH14569_AC

Australian Journal of Chemistry 2015, 68(4), 627-634

Supplementary Material

Synthesis of Dichotomin A: Use of a Penicillamine Derived Pseudoproline to Furnish Native Valine Residues

Michelle S. Y. Wong[A], *Deni Taleski*[A], *Katrina A. Jolliffe*[A,B]

[A]School of Chemistry, The University of Sydney, NSW 2006, Australia.
[B]Corresponding author. Email: kate.jolliffe@sydney.edu.au

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Figures and Tables

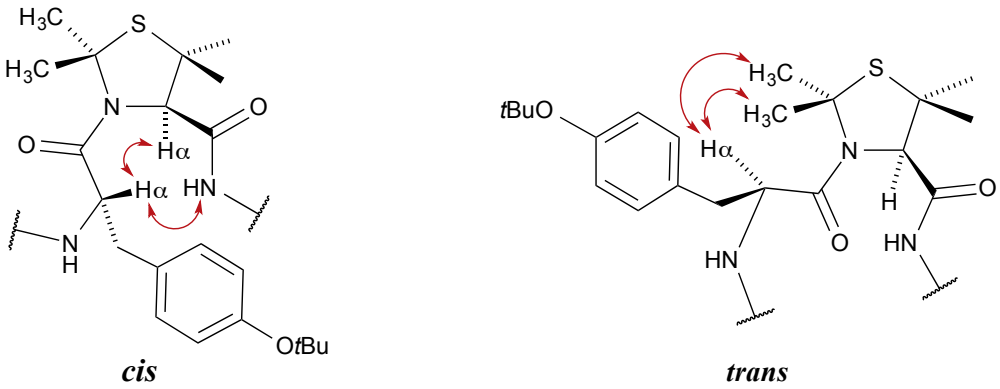


Figure S1. Characteristic NOE interactions indicative of *cis* or *trans* conformation of the Tyr(*t*Bu)-Pen($\Psi^{H,H}$Pro) amide bond.

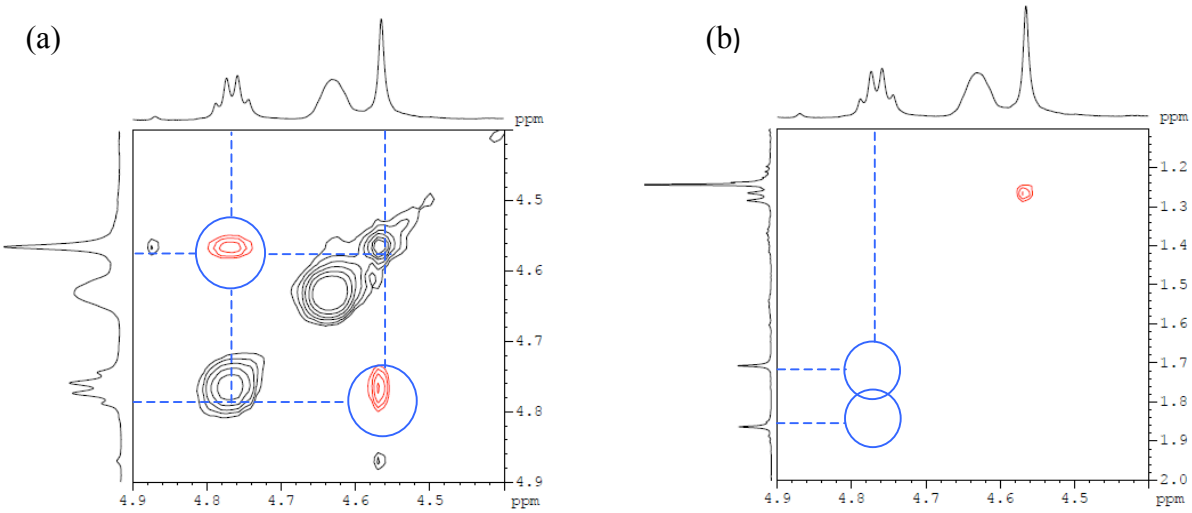


Figure S2. Partial ROESY spectra of dichotomin A linear precursor **2**, collected on a 500 MHz spectrometer in DMSO-d_6. (a) Characteristic cross peaks between the Tyr-α-H and the Pen-α-H signals indicate that the conformation of the Tyr(*t*Bu)-Pen($\Psi^{Me,Me}$Pro) amide bond is *cis*. (b) Cross peaks between the ΨPro-CH_3 and the Tyr-α-H signals, which would indicate the *trans* conformation, are absent.

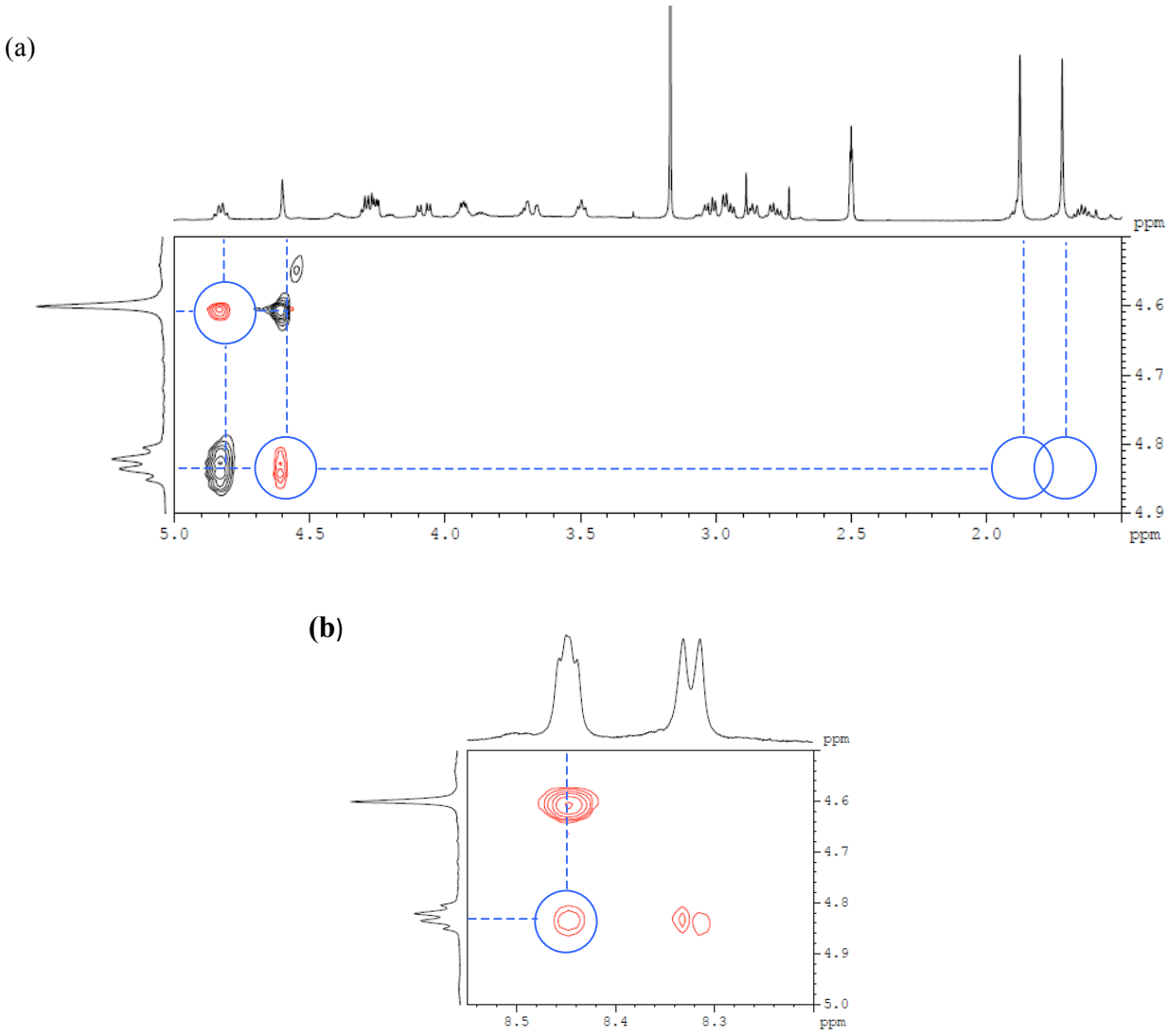
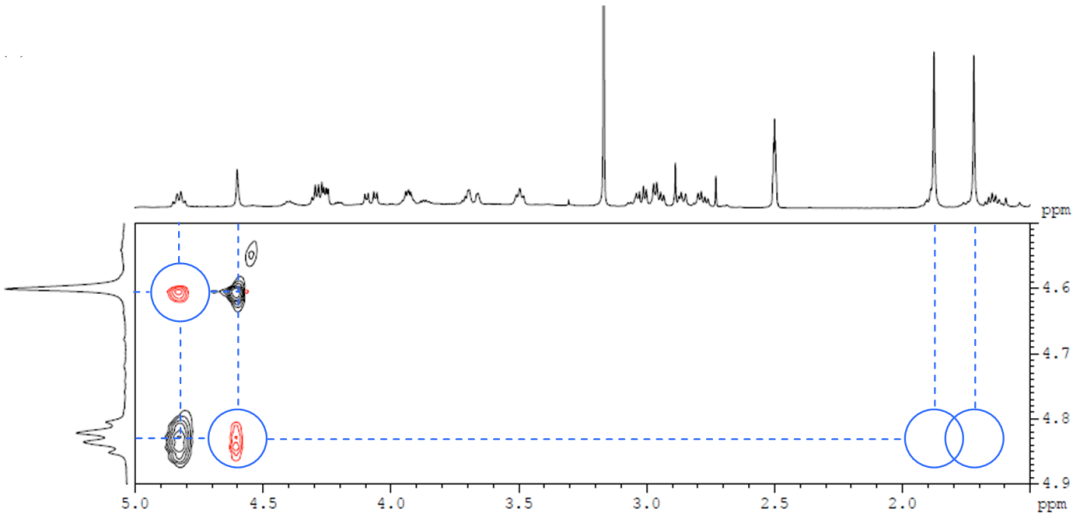


Figure S3. Partial ROESY spectra of dichotomin A linear precursor **3**, collected on a 500 MHz spectrometer in DMSO-d_6. (a) The presence of a characteristic cross peak between the Tyr-α-H and the Pen-α-H signals indicating that the Tyr(*t*Bu)-Pen($\Psi^{Me,Me}$Pro) amide bond is in the *cis* conformation, and the absence of ΨPro-CH_3–Tyr-α-H cross peaks which would be evidence of the *trans* form. (b) NOE interaction between the Tyr-α-H and Gly-NH signals, providing further evidence of a *cis* amide bond.

(a)



(b)

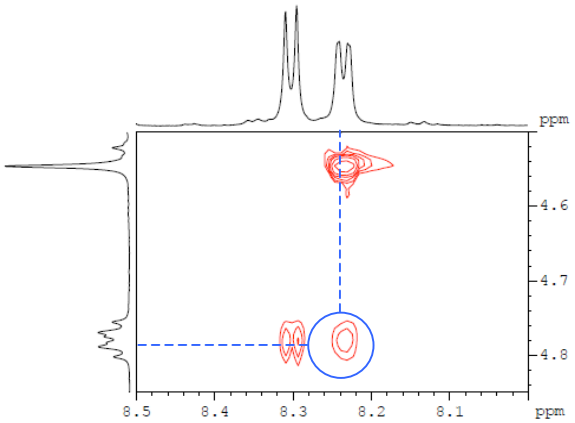


Figure S4. Excerpts from the ROESY spectrum of Pen($\Psi^{Me,Me}$Pro)-containing cyclic hexapeptide **8**, collected on a 500 MHz in DMSO-d_6. (a) The Tyr(*t*Bu)-Pen($\Psi^{Me,Me}$Pro) amide bond is in the *cis* conformation, as indicated by cross peaks between the Tyr-α-H and Pen-α-H signals, and the absence of characteristic *trans* cross peaks between the ΨPro-CH_3 and Tyr-α-H signals. (b) A cross peak between the Tyr-α-H and Gly-NH signals also indicates the *cis* conformation.

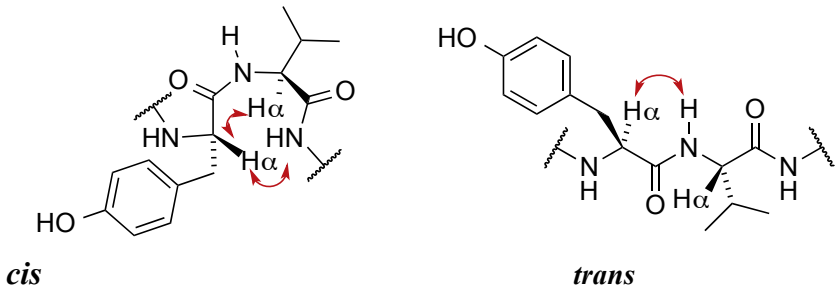


Figure S5. Characteristic NOE interactions indicative of *cis* or *trans* conformation in the Tyr-Val amide bond.

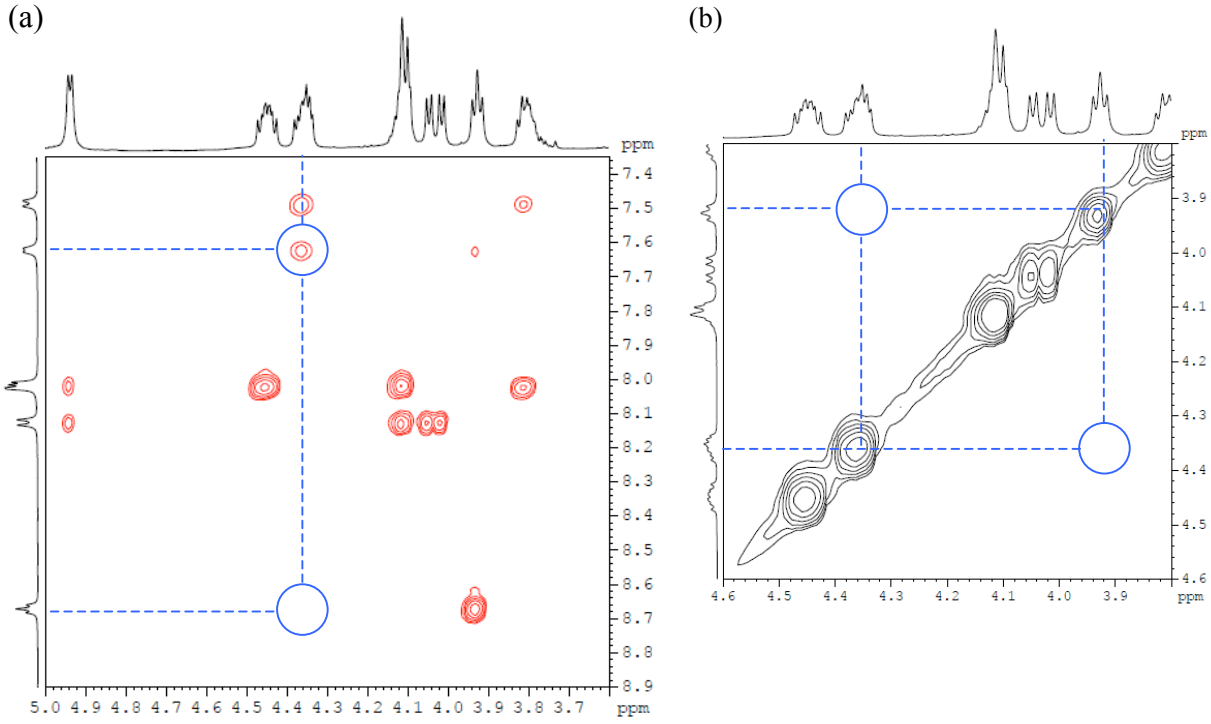


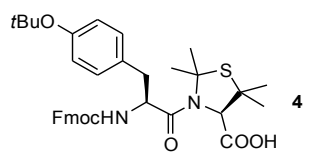
Figure S6. Partial ROESY spectrum of dichotomin A **1**, collected on a 500 MHz spectrometer in DMSO-d_6. (a) The presence of a cross peak between the Val-NH and Tyr-α-H signals, and the absence of a cross peak between the Tyr-α-H and Gly-NH signals indicates that the Tyr-Val amide bond is in the *trans* conformation in the natural product. (b) The absence of NOE interactions between the Tyr-α-H and Val-α-H peaks provides further evidence of the *trans* conformation.

Table S2. Comparison of ^{1}H and ^{13}C NMR signals of isolated and synthesised samples of dichotomin A **1**. $\Delta\delta_H$ of labile NH groups are highlighted in blue. Spectral data for the both samples were collected in pyridine-d_5. Spectral data for the isolated sample were collected on a 500 MHz spectrometer, and data for the synthetic sample were collected on a 400 MHz.

Assignment	δ_H (J in Hz)		$\Delta\delta_H$	δ_C		$\Delta\delta_c$
	Natural	Synthetic		Natural	Synthetic	
Thr						
NH	9.21 (d, 7.9)	9.22 (d, 8.0)	–0.01			
α	4.99 (dd, 3.2, 7.9)	4.99 (m)	0.00	59.5	59.3	0.2
β	4.91 (dq, 3.2, 6.4)	4.90 (m)	0.01	67.0	67.1	–0.1
γ	1.49 (d, 6.4)	1.48 (d, 6.4)	0.01	20.2	20.1	0.1
CO				171.3	171.2	0.1
Phe						
NH	8.79 (d, 7.5)	8.81 (d, 7.6)	–0.02			
α	5.19 (m)	5.20 (m)	–0.01	56.3	56.4	–0.1
β	3.57 (dd, 8.2, 13.9)	3.57 (dd, 6.0, 14.0)	0.00	38.1	38.0	0.1
	3.37 (dd, 8.6, 13.9)	3.40 (dd, 8.8, 14.0)	–0.03			
γ				138.2	138.2	0.0
δ	7.20 (d, 7.4)	7.23 (m)	–0.03	128.7	128.7	0.0
ε	7.35 (t, 7.4)	7.37 (d, 7.2)	–0.02	129.6	129.5	0.1
ζ	7.17 (m)	7.19 (m)	–0.02	126.8	126.8	0.0
CO				172.7	172.7	0.0
Leu						
NH	9.07 (d, 7.5)	9.01 (d, 7.2)	0.06			
α	4.40 (dt, 7.5)	4.46 (m)	–0.06	55.1	54.9	0.2
β	1.97 (t, 7.5)	1.95 (t, 7.4)	0.02	40.0	40.3	–0.3
γ	1.51 (m)	1.53 (m)	–0.02	24.9	24.9	0.0
δ	0.78 (d, 6.5)	0.79 (d, 6.0)	–0.01	23.1	23.1	0.0
	0.78 (d, 6.6)	0.78 (d, 6.4)	0.00	21.5	21.5	0.0
CO				172.4	172.4	0.0
Tyr						

NH	8.60 (d, 6.9)	8.52 (d, 7.2)	0.08			
α	4.82 (m)	4.83 (m)	–0.01	56.3	56.0	0.3
β	3.56 (dd, 6.7, 14.0)	3.53 (app d, 7.2)	0.005	37.1	37.2	–0.1
	3.51 (dd, 6.8, 14.0)					
γ				128.6	128.5	0.1
δ	7.42 (d, 8.4)	7.42 (d, 8.4)	0.00	131.2	131.2	0.0
ε	7.14 (d, 8.4)	7.14 (d, 8.4)	0.00	116.3	116.2	0.1
ζ				157.7	157.7	0.0
CO				172.3	172.3	0.0
Val						
NH	8.35 (d, 6.0)	8.44 (d, 5.2)	–0.09			
α	4.53 (t, 6.0)	4.48 (m)	0.05	61.3	61.4	–0.1
β	2.46 (m)	2.43 (m)	0.03	30.2	30.1	0.1
γ	1.13 (d, 6.7)	1.12 (d, 6.4)	0.01	19.4	19.4	0.0
	1.09 (d, 6.8)	1.08 (d, 6.8)	0.01	19.2	19.2	0.0
CO				172.7	172.7	0.0
Gly						
NH	9.97 (t, 5.5)	9.94 (t, 5.6)	0.03			
α	4.83 (dd, 5.5, 15.6)	4.84 (m)*	–0.01	44.2	44.1	0.1
	3.88 (dd, 5.5, 15.6)	3.87 (dd, 4.6, 15.8)	0.01			
CO				170.7	170.6	0.1

Fmoc-Tyr(OtBu)-Pen(Ψ^{Me,Me}Pro)-OH (4)



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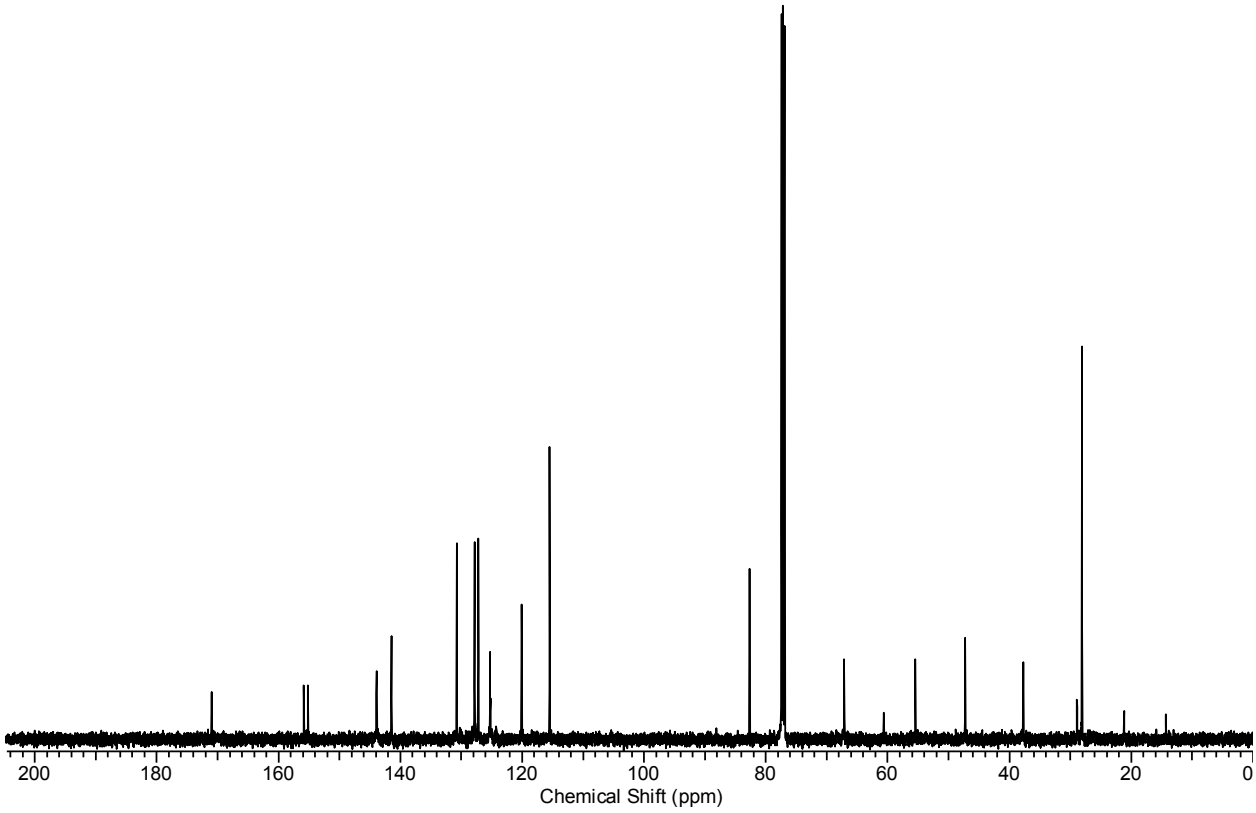
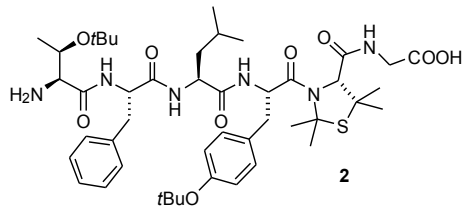


H_2N-Thr(*t*Bu)-Phe-Leu-Tyr(*t*Bu)-Pen($\Psi^{Me,Me}$Pro)-Gly-OH (2)



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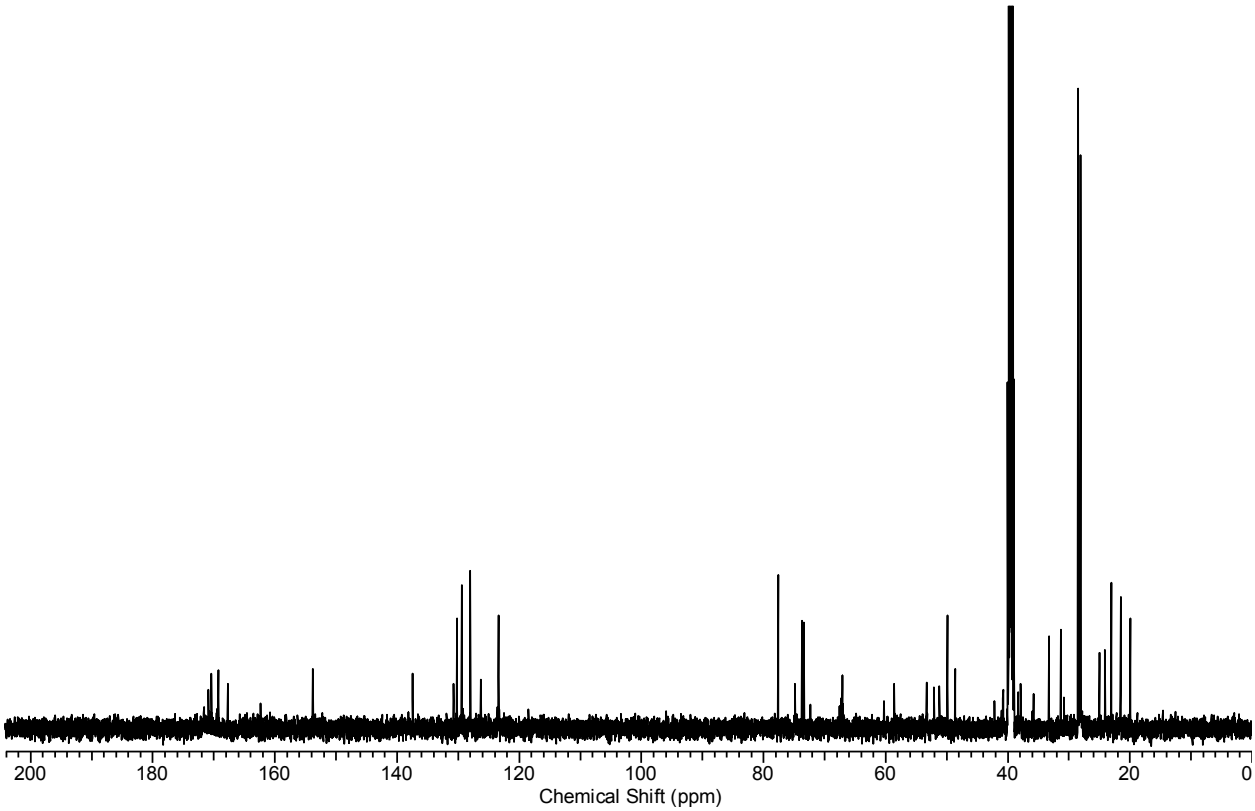
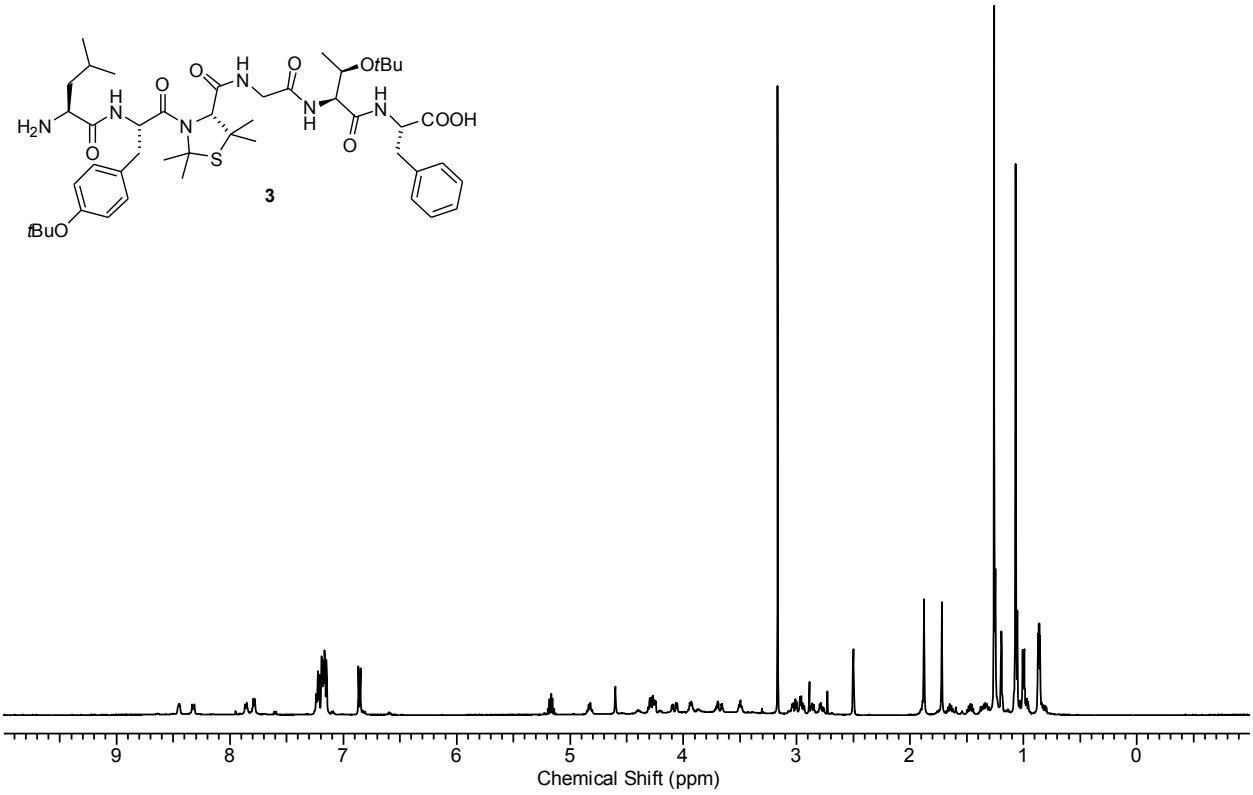
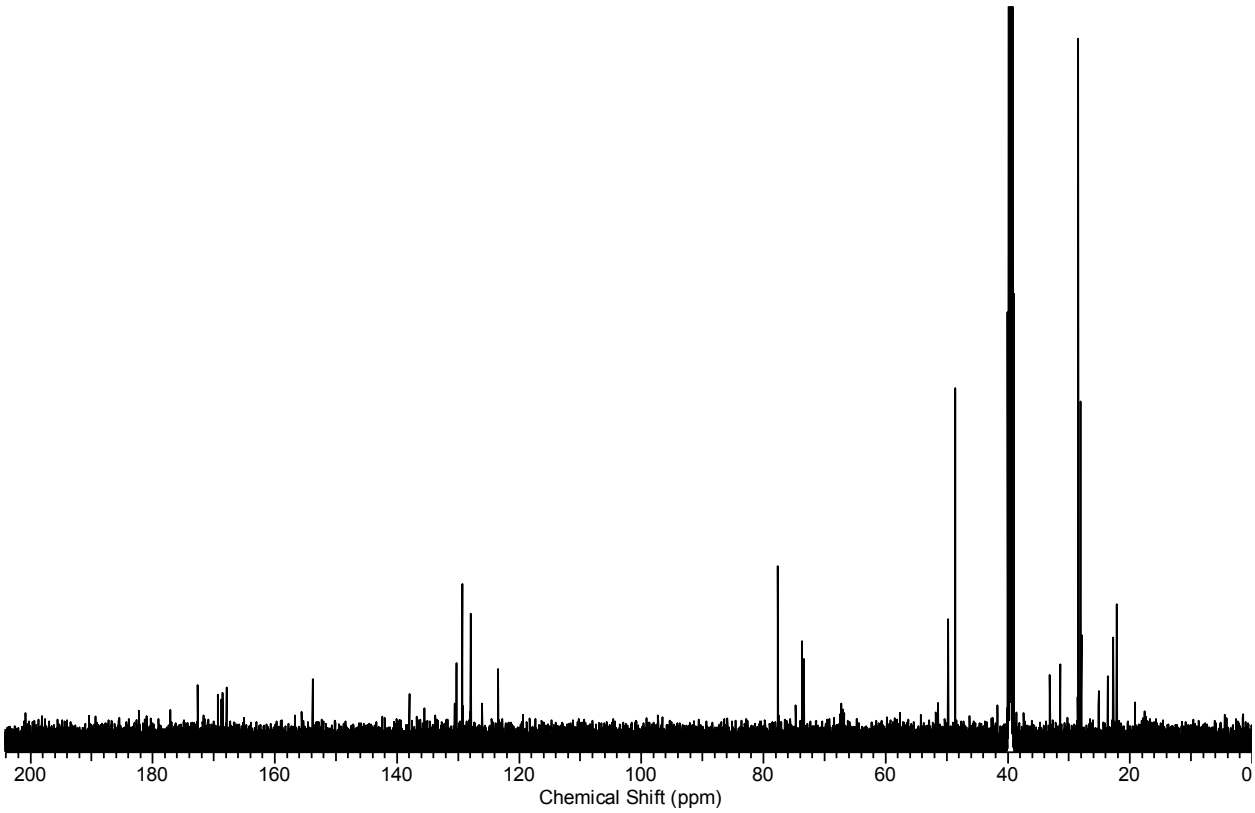
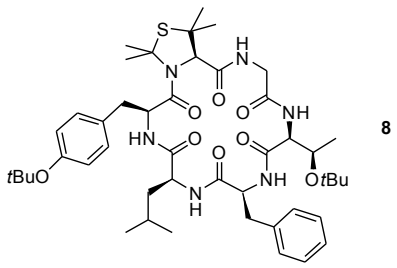


H_2N-Leu-Tyr(*t*Bu)-Pen($\Psi^{Me,Me}$Pro)-Gly-Thr(*t*Bu)-Phe-OH (3)





***Cyclo*-[Thr(*t*Bu)-Phe-Leu-Tyr(*t*Bu)-Pen($\Psi^{Me,Me}$Pro)-Gly] (8)**



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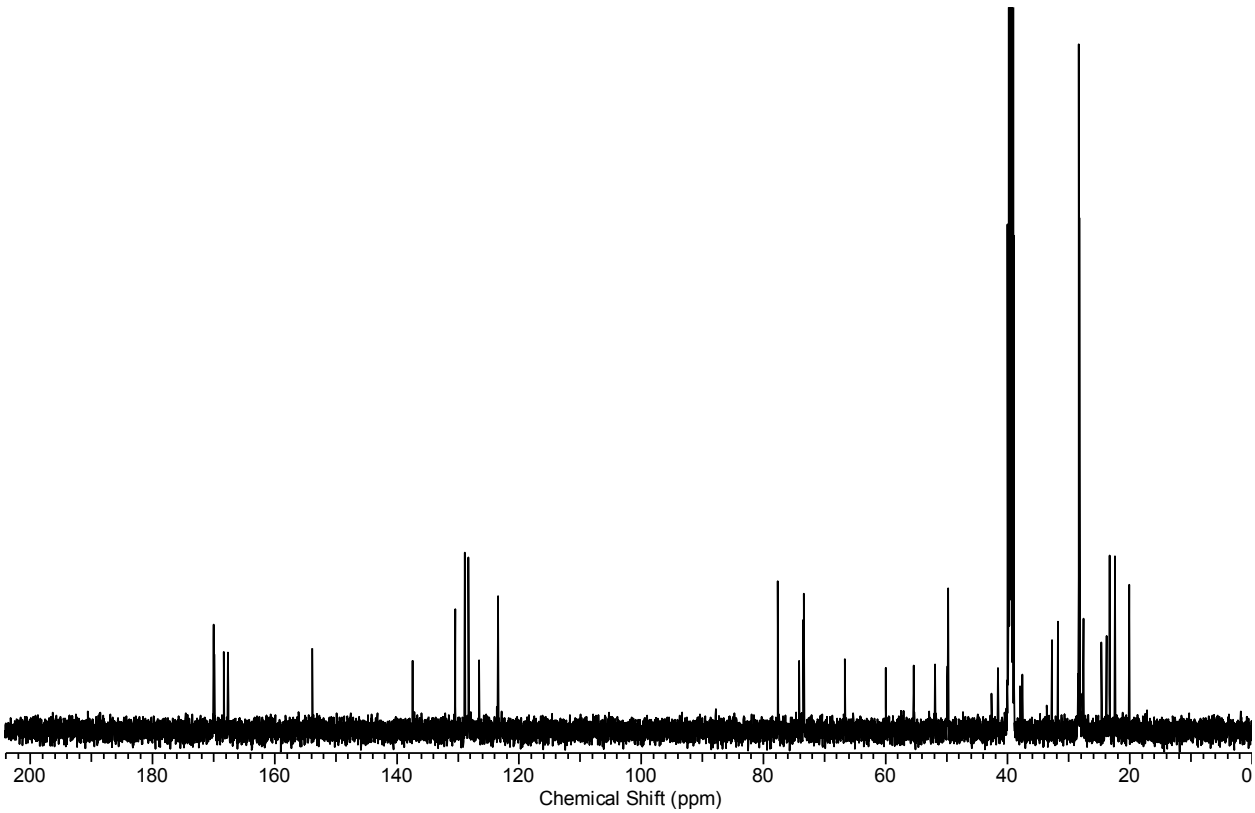
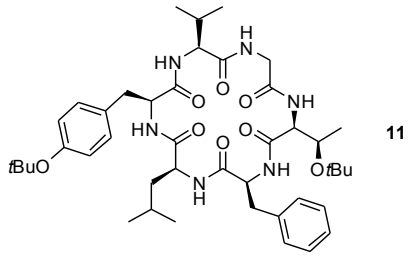


Cyclo-[Thr(tBu)-Phe-Leu-Tyr(tBu)-Val-Gly] (11)



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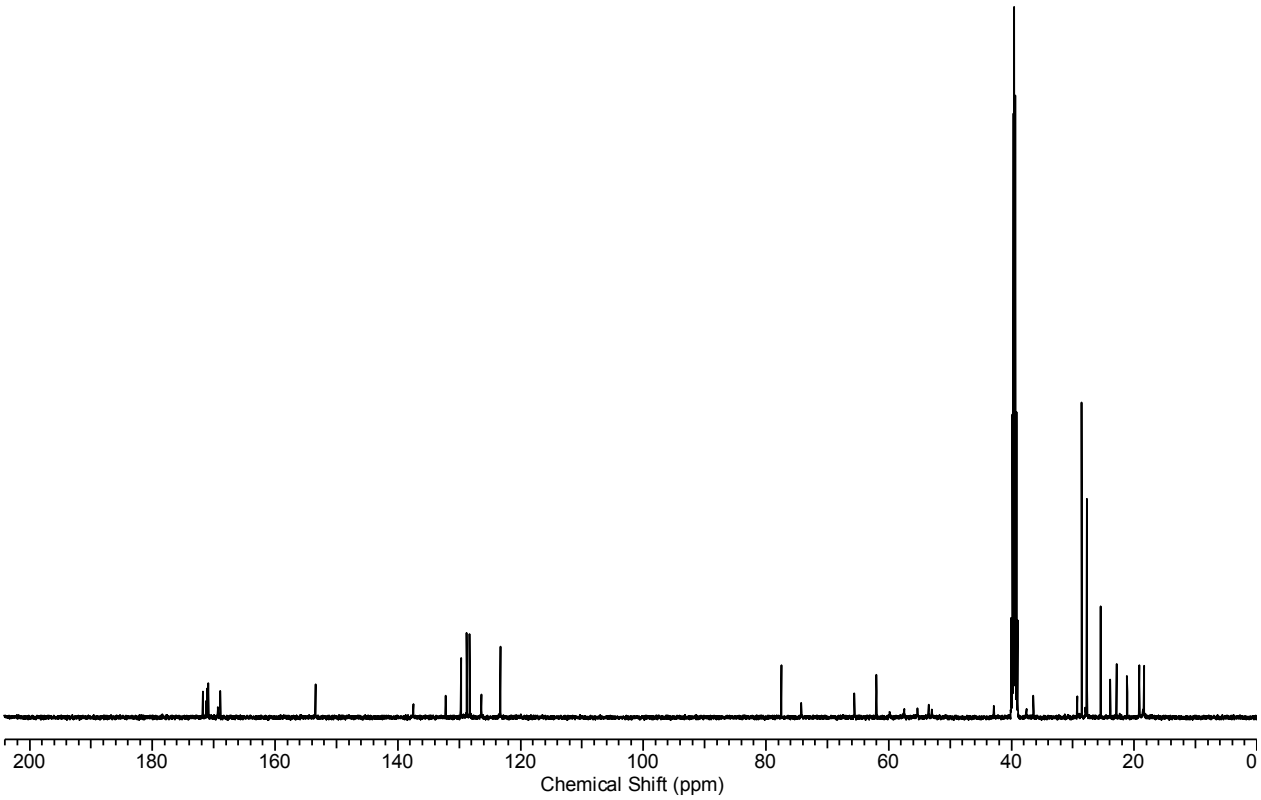

***Cyclo*-[Thr-Phe-Leu-Tyr-Val-Gly] (Dichotomin A) (1)**