

Supporting Information

Total Synthesis of Talarolide A and *atrop*-Talarolide A: Hydroxamate H-Bond Bridge Stabilization of Cyclic Peptide Conformers Invokes Non-Canonical Atropisomerism.

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1. Spectroscopic characterisation of *atrop*-talarolide A (**8**)

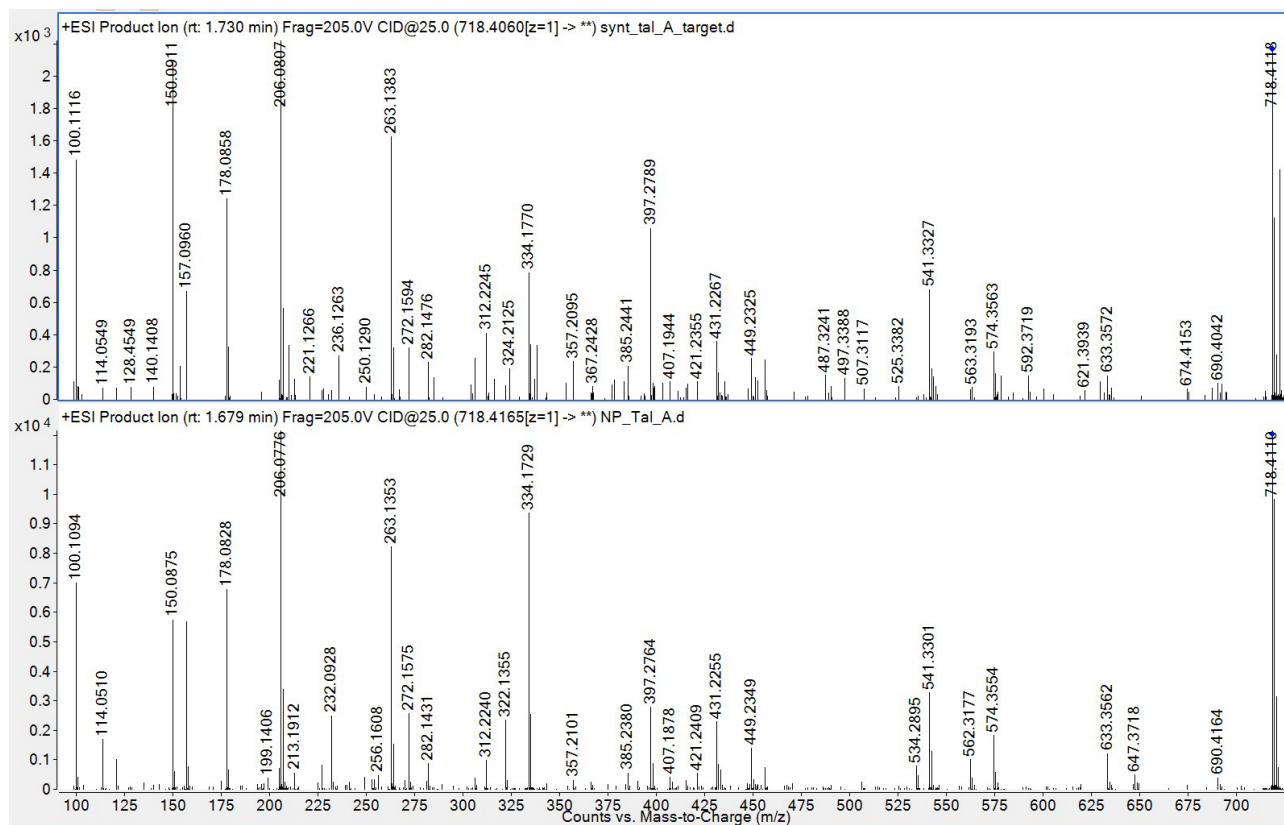


Figure S1. MSMS chromatograms of *atrop*-talarolide A (**8**) (top) and natural talarolide A (**1**) (bottom)

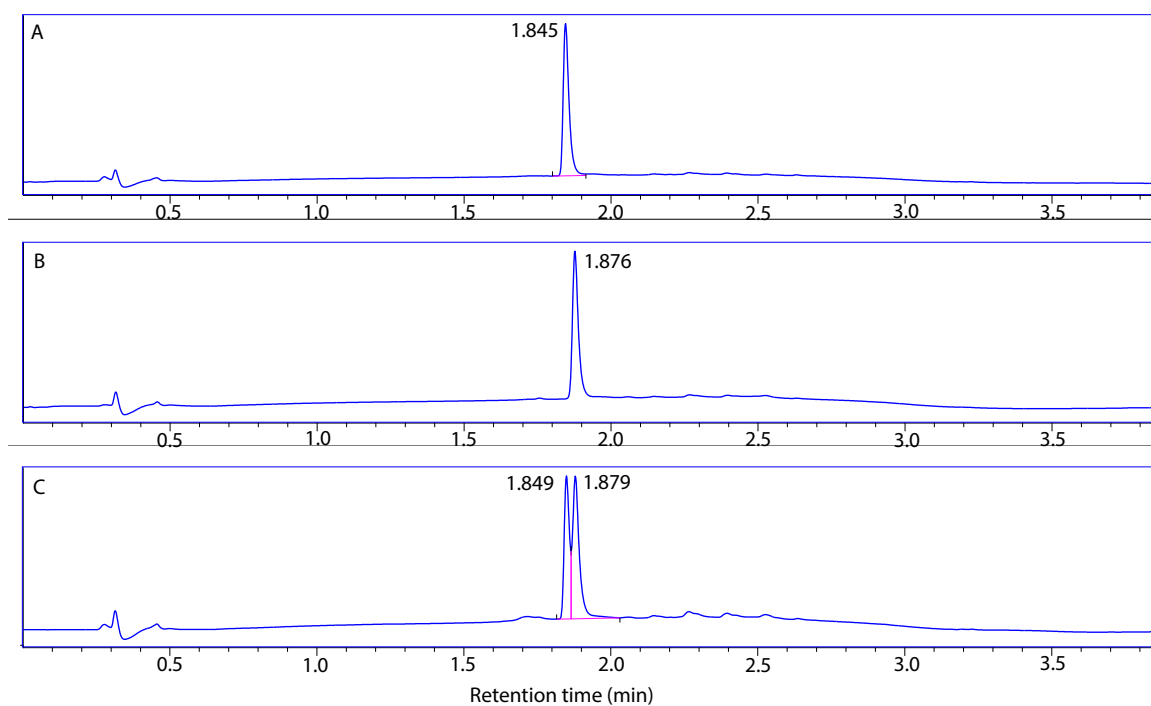


Figure S2. UPLC-DAD (210 nm) chromatograms of (A) natural talarolide A (**1**), (B) *atrop*-talarolide A (**8**), and (C) co-injection of **1** and **8**.

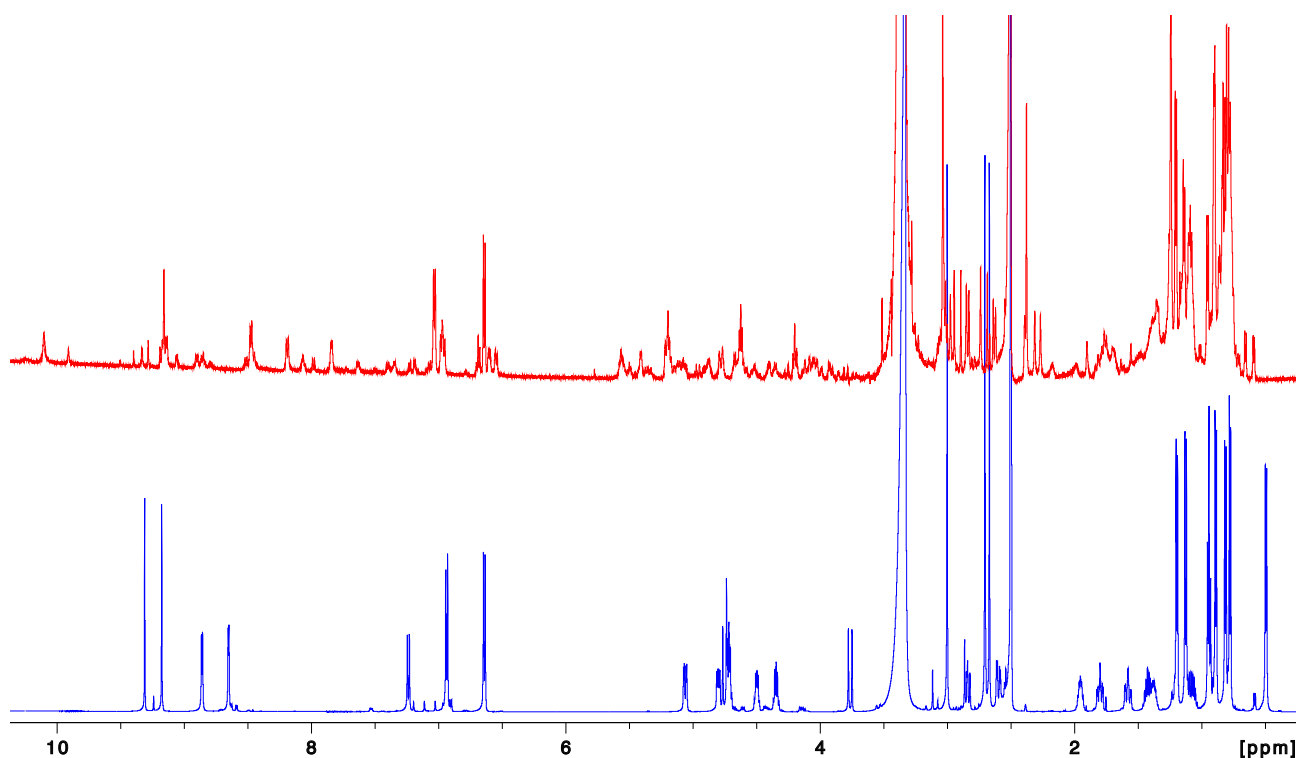


Figure S3. Overlay of ^1H NMR (600 MHz, $\text{DMSO-}d_6$) spectra of *atrop*-talarolide A (**8**) (red) and natural talarolide A (**1**) (blue).

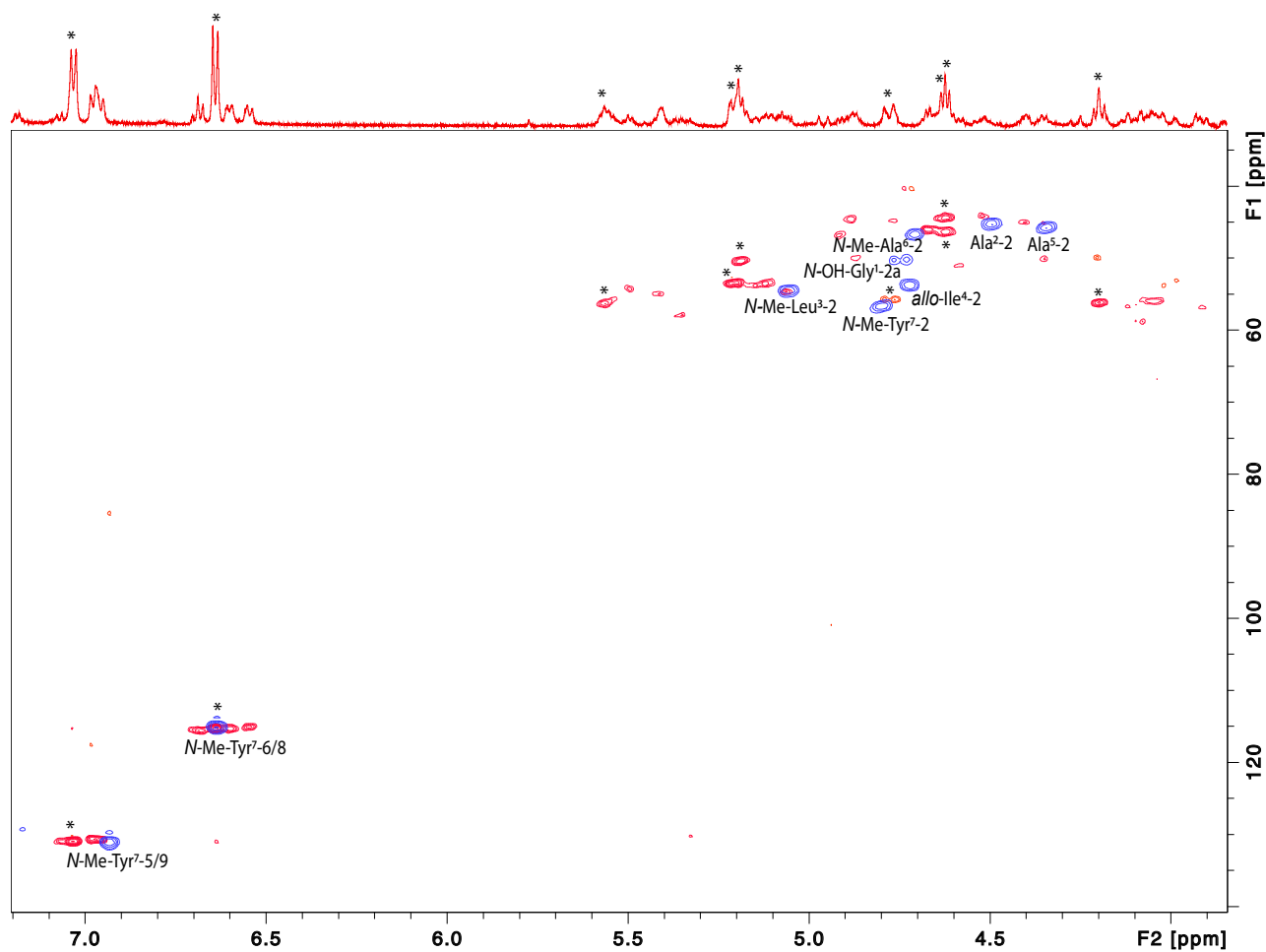


Figure S4. Overlay of HSQC (600 MHz, $\text{DMSO-}d_6$) spectra of *atrop*-talarolide A (**8**) (red) and natural talarolide A (**1**) (blue) - annotated, * indicates signals from the major conformer of *atrop*-talarolide A (**8**).

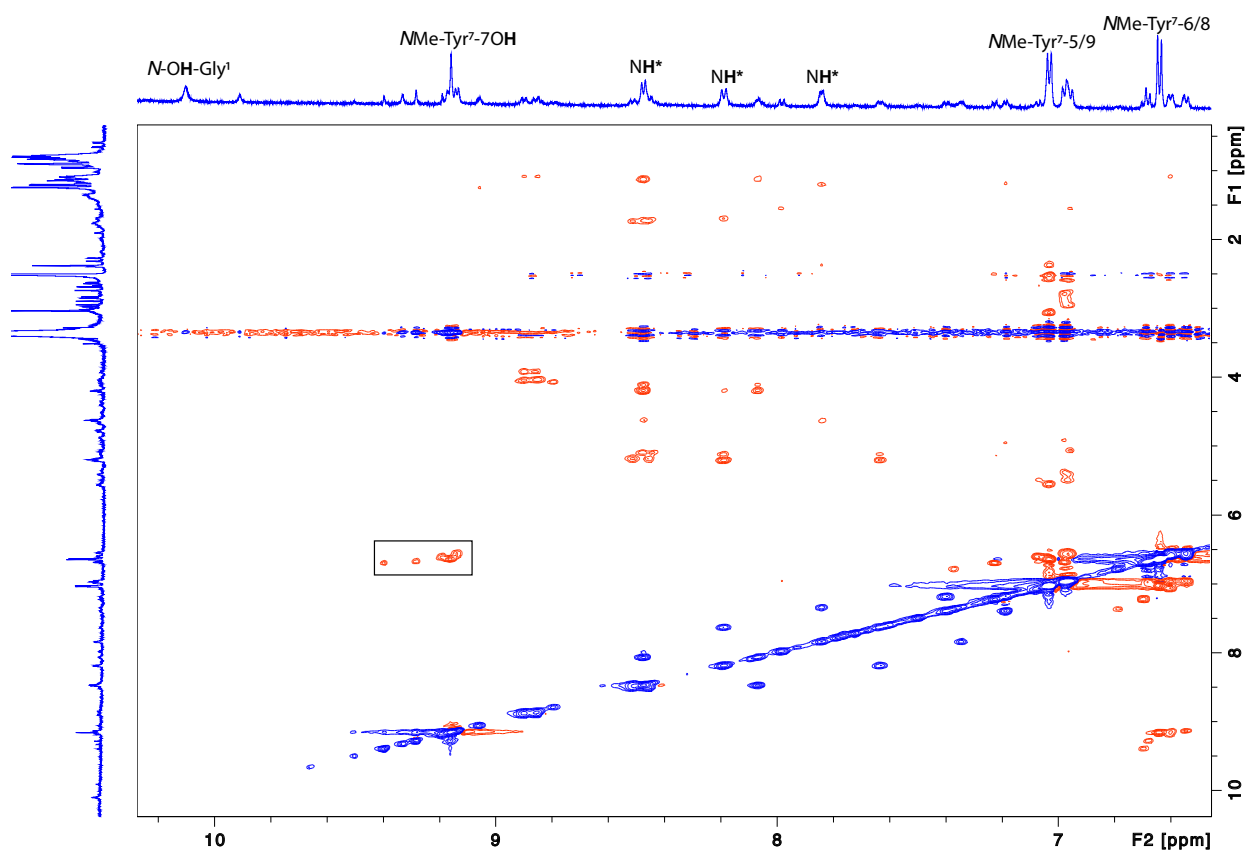


Figure S5. ROESY NMR (600 MHz, DMSO- d_6) spectrum of *atrop*-talarolide A (**8**). There were no observable ROESY correlations from *N*-OH-Gly. Black box highlighted ROESY correlations between *N*Me-Tyr⁷-7OH and *N*Me-Tyr⁷-6/8. *NH are not assigned to a particular amino acid residue.

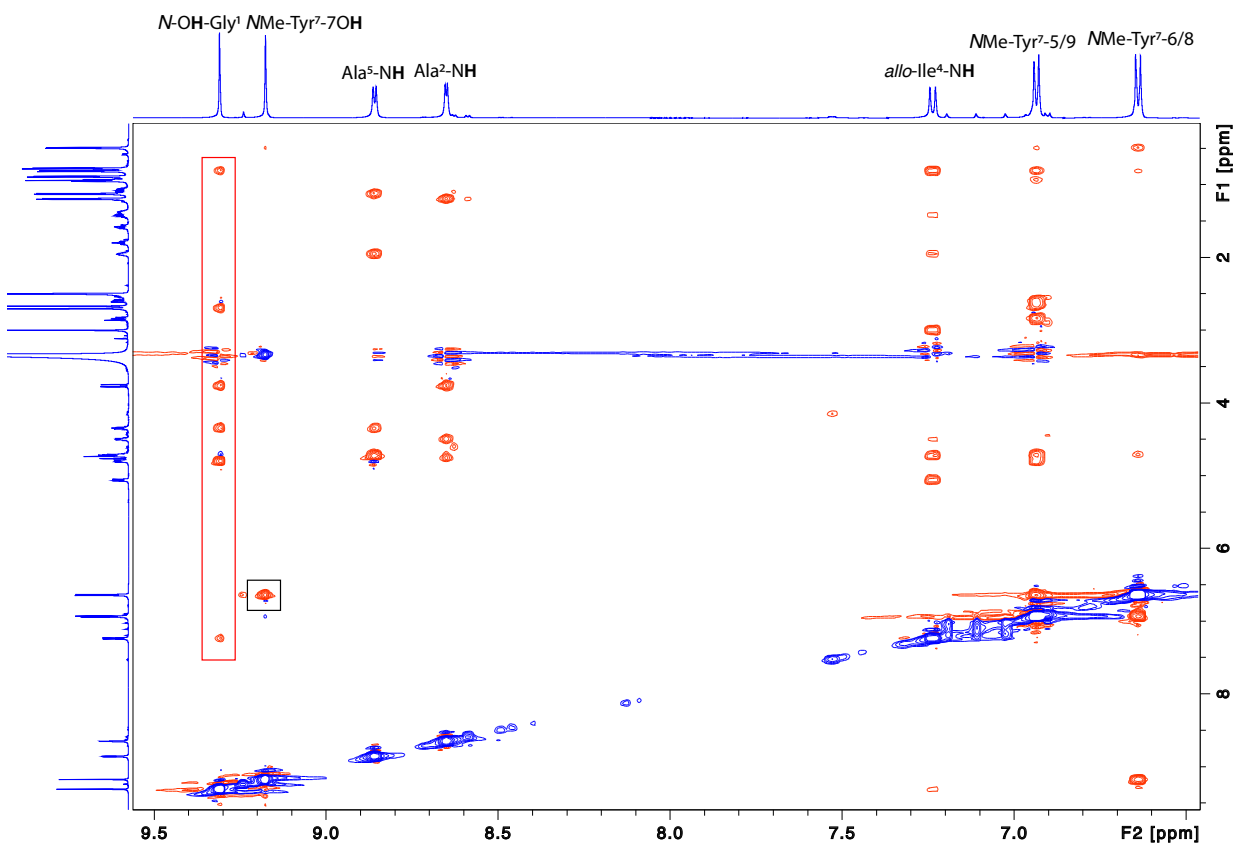


Figure S6. ROESY NMR (600 MHz, DMSO- d_6) spectrum of natural talarolide A (**1**). Red box highlighted ROESY correlations between *N*-OH-Gly to protons of other amino acid residues in close proximity. Black box highlighted ROESY correlations between *N*Me-Tyr⁷-7OH and *N*Me-Tyr⁷-6/8.

Mass Spectrum Molecular Formula Report

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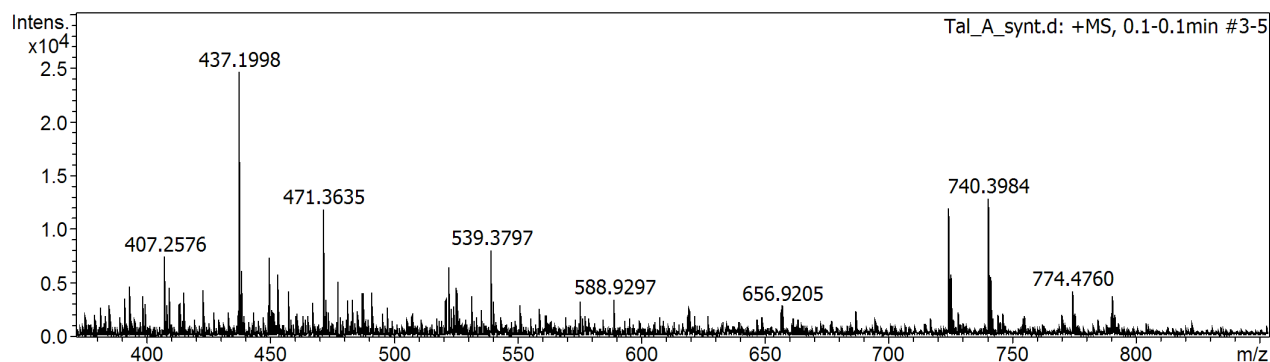
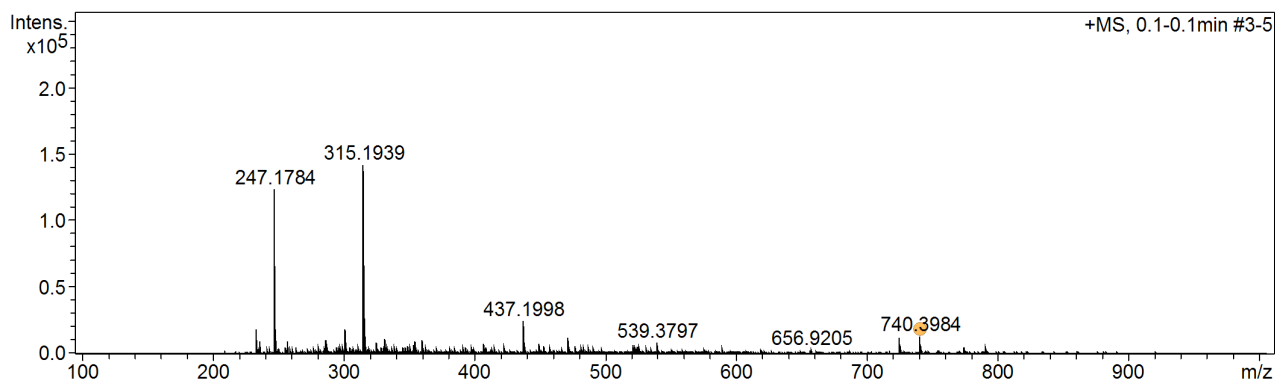
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Instrument / Ser# microTOF 213750.00
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Estimate Carbon		



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Figure S7. HRMS measurement for *atrop*-talarolide A (**8**) obtained from Scheme 2.

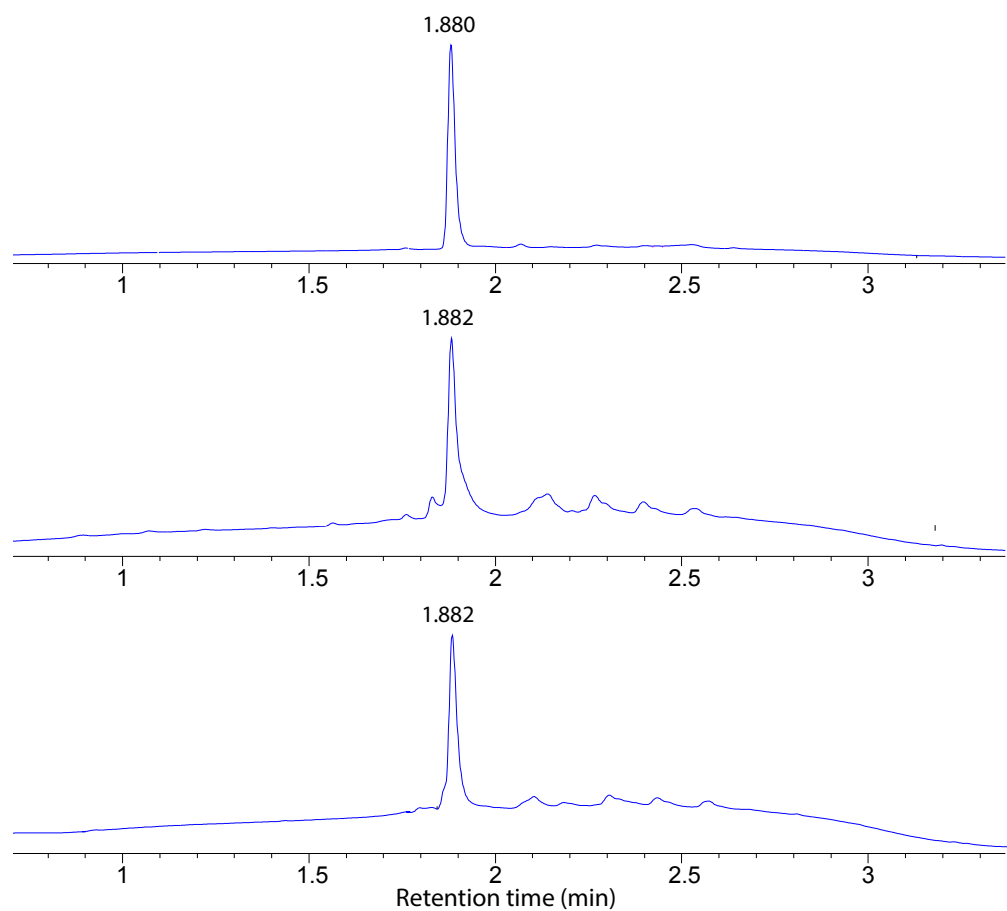


Figure S8. UPLC-DAD (210 nm) chromatograms of *atrop*-talarolide A (**8**) obtained from (A) Scheme 2 and (B) Scheme 3 and (C) co-injection of both.

Mass Spectrum Molecular Formula Report

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 Sample Name
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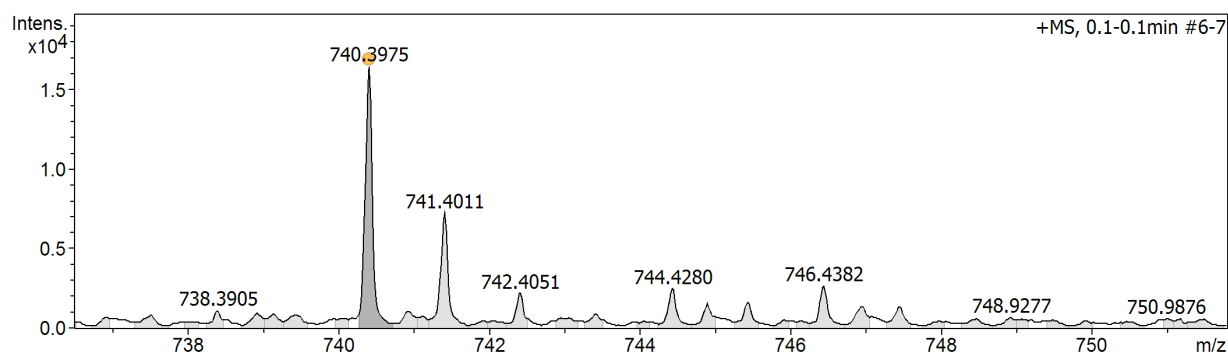
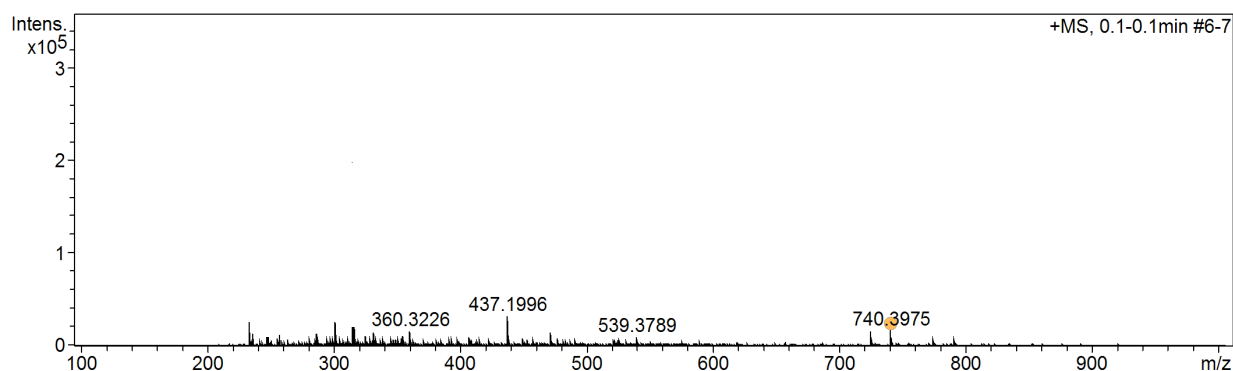
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Generate Molecular Formula Parameter

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Formula, max.		Minimum		Maximum	
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Nitrogen Rule					
Filter H/C Ratio					
Estimate Carbon					



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# Sigma	Score	rdb	e ⁻ Conf	N-Rule
740.3975	1	C35H55N7NaO9	740.3953	-2.9	27.4	1	100.00	11.5	even	ok

Figure S9. HRMS measurement for *atrop*-talarolide A (**8**) obtained from Scheme 3

2. Spectroscopic characterisation of synthetic talarolide A (1)

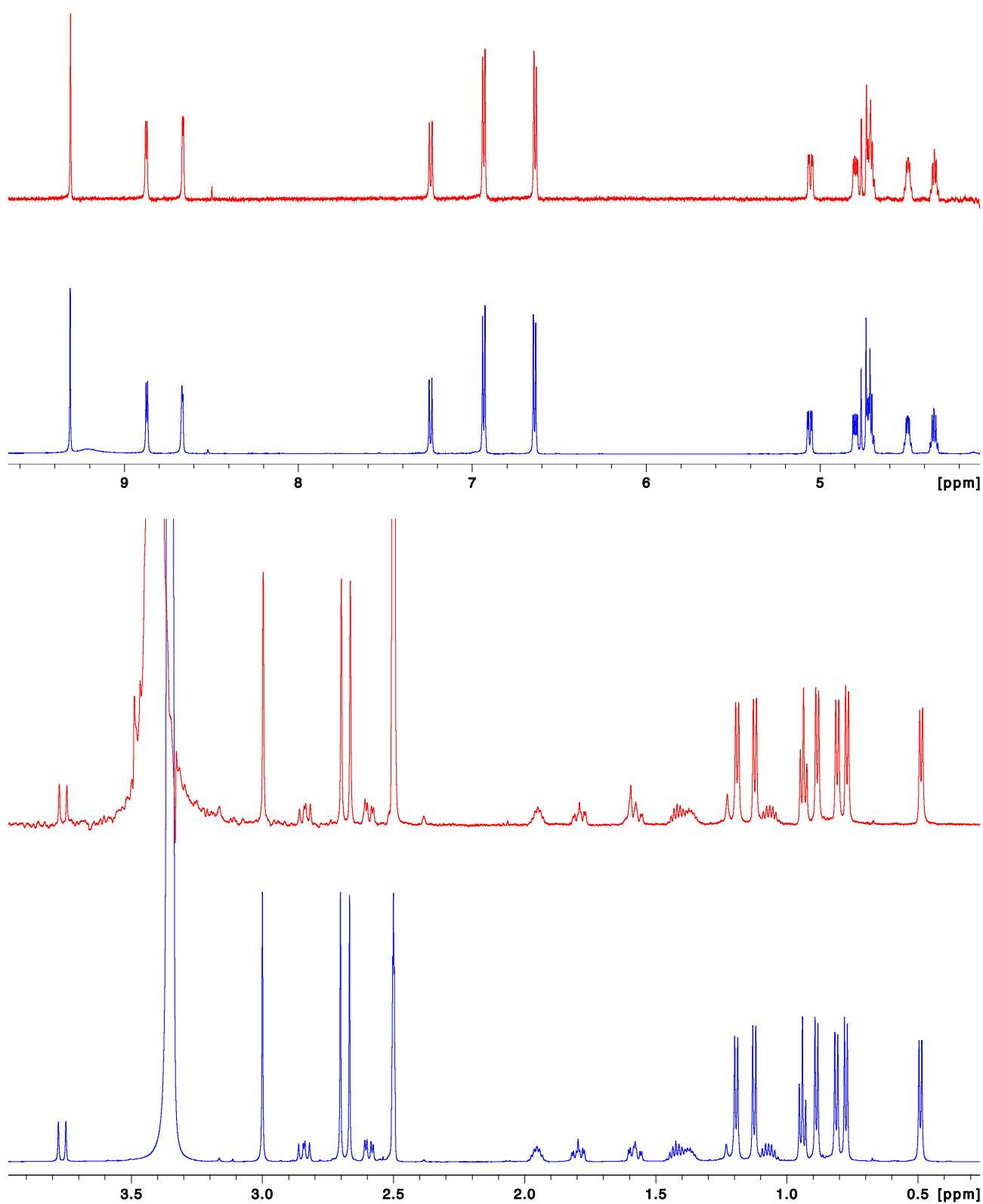


Figure S10. Overlay of ^1H NMR (600 MHz, $\text{DMSO}-d_6$) spectra of synthetic (red) and natural (blue) talarolide A.

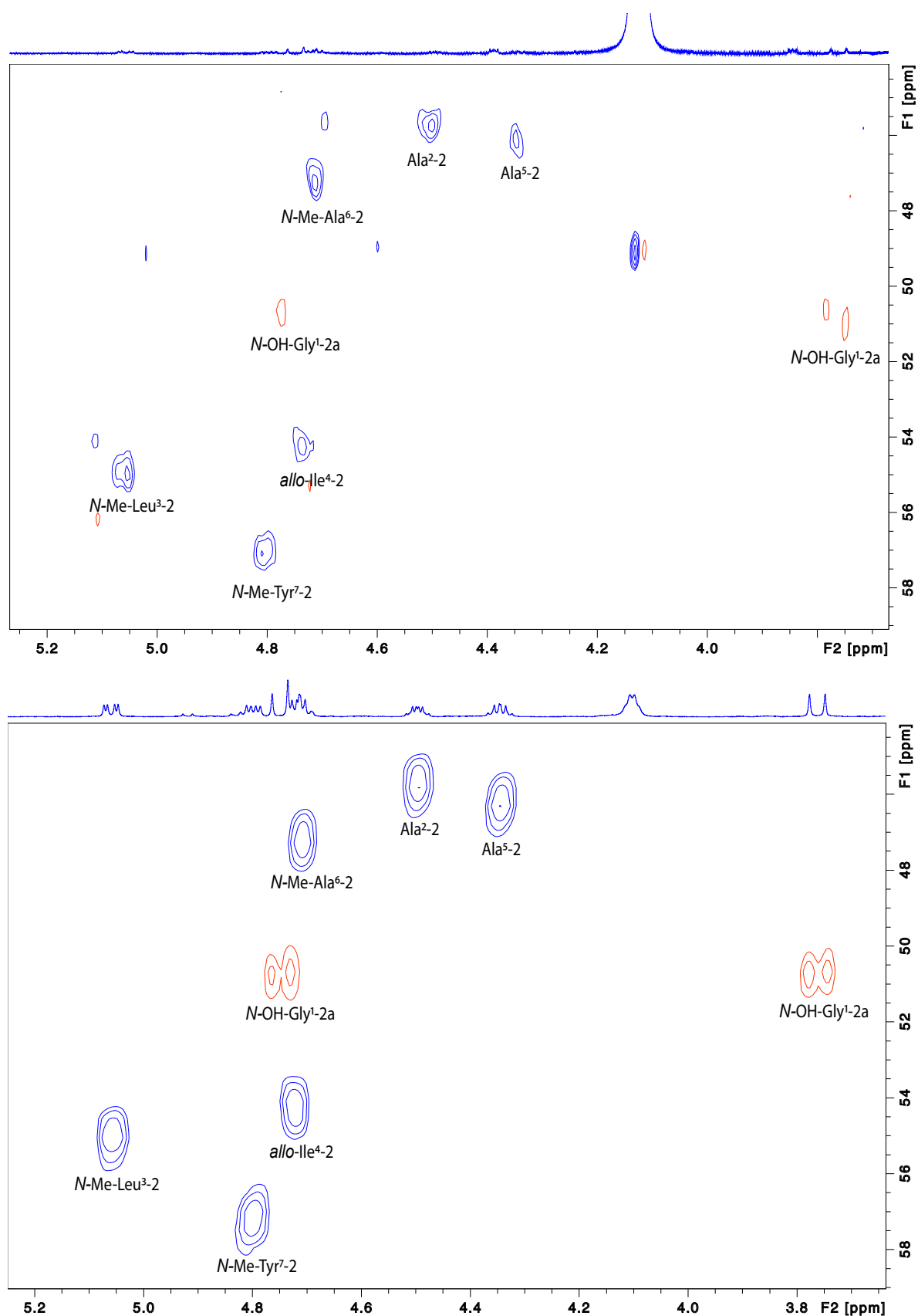


Figure S11. Expanded HSQC (600 MHz, DMSO- d_6) spectra of synthetic (top) and natural (bottom) talarolide A showing the α protons region.

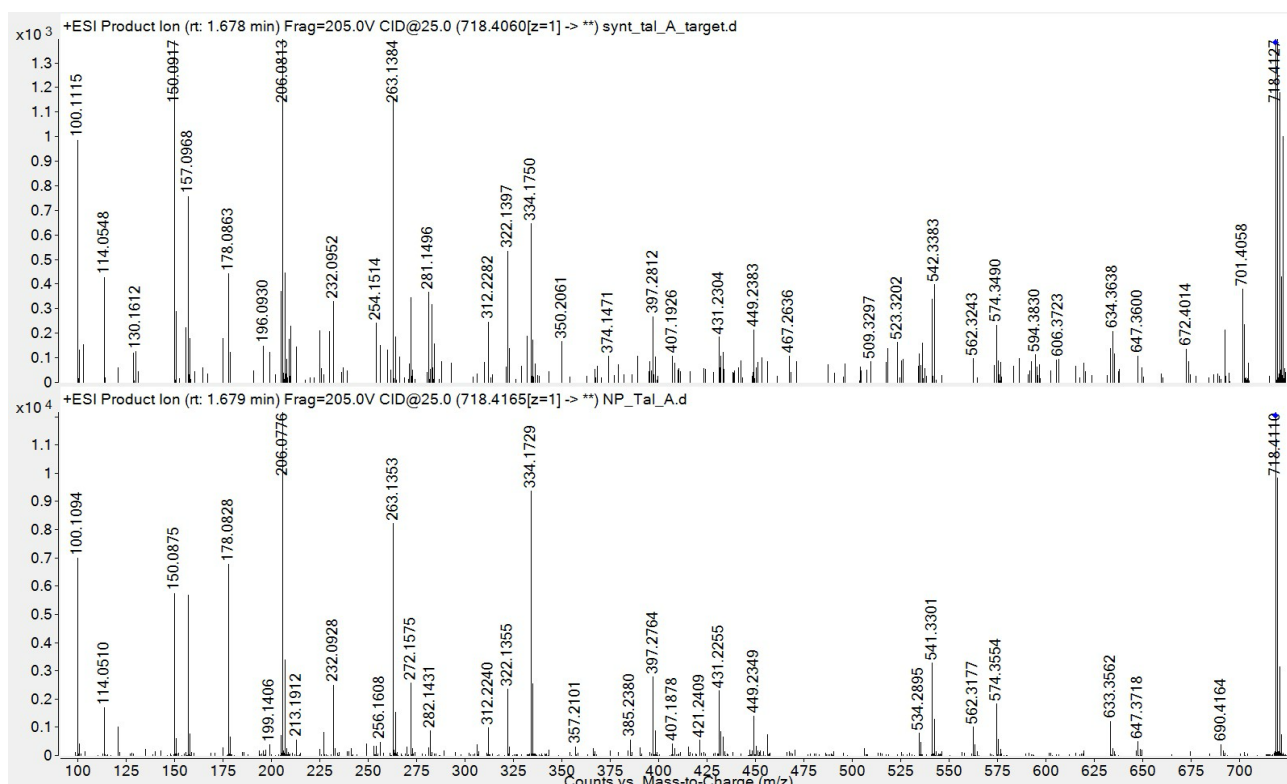


Figure S12. MSMS chromatograms of synthetic (top) and natural (bottom) talarolide A (1)

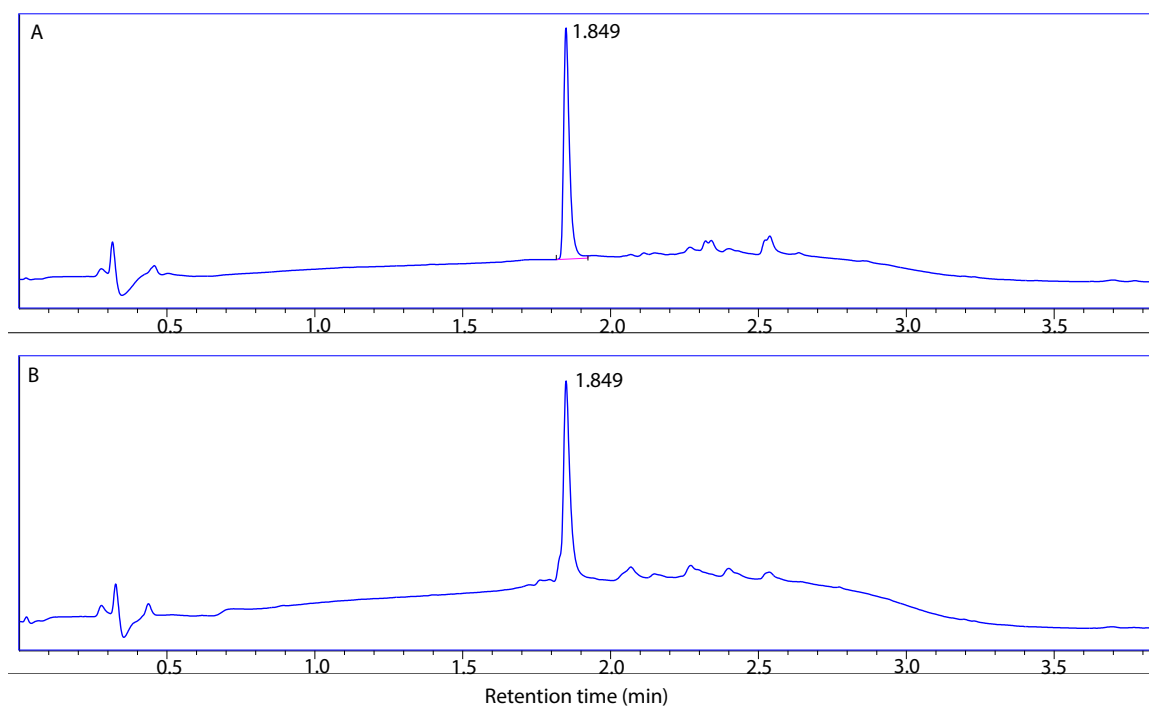


Figure S13. UPLC-DAD (210 nm) chromatograms of (A) natural and (B) synthetic talarolide A.

Mass Spectrum Molecular Formula Report

Analysis Info

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Sample Name
Comment

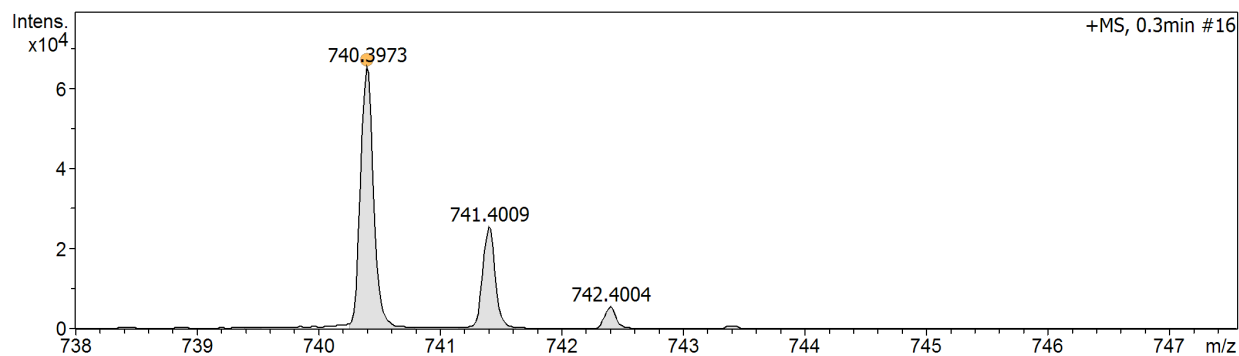
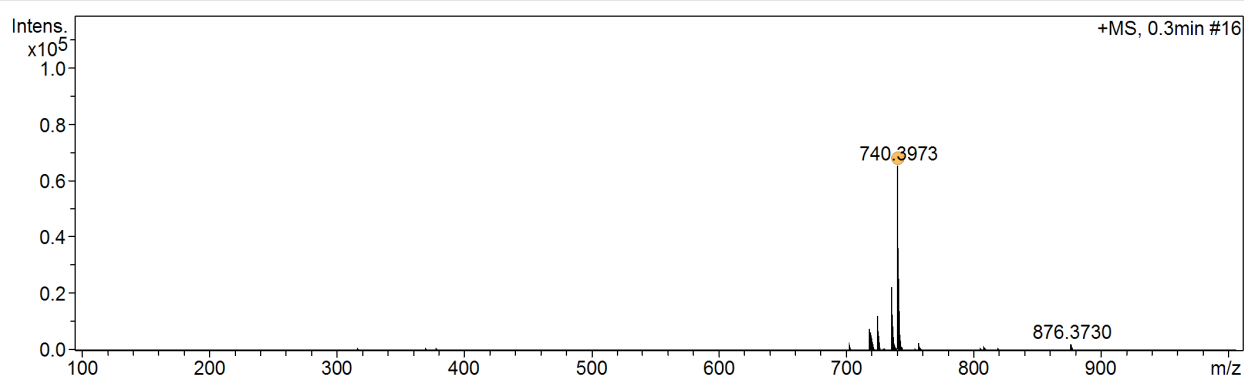
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Scan End	1000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Source

Generate Molecular Formula Parameter

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Estimate Carbon		



Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# Sigma	Score	rdb	e ⁻ Conf	N-Rule
740.3973	1	C35H55N7NaO9	740.3953	-2.6	14.3	1	100.00	11.5	even	ok

Figure S14. HRMS measurement for synthetic talarolide A (1)

3. Characterisation of synthetic intermediates

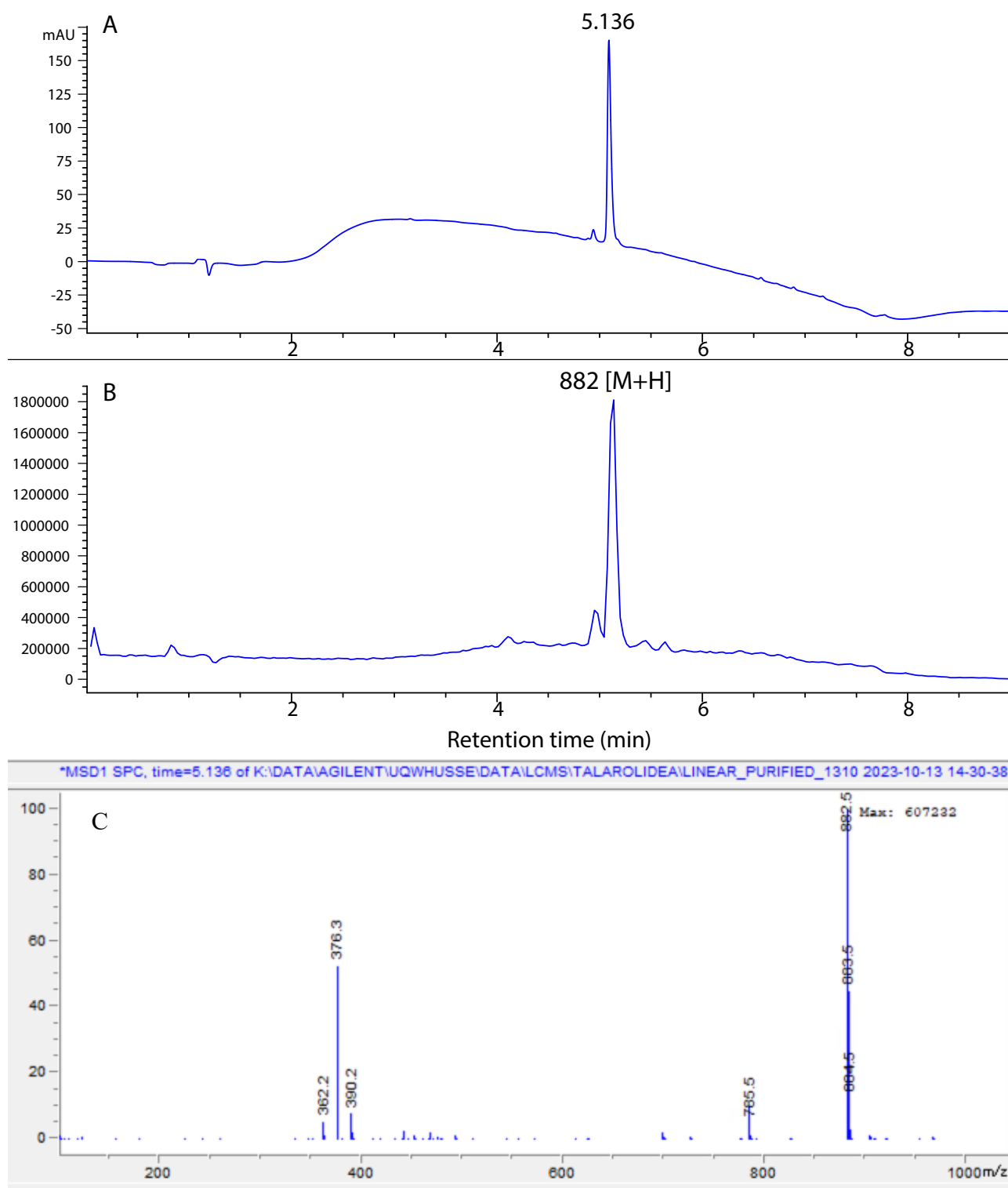


Figure S15. HPLC-DAD-MS chromatograms of protected linear peptide 5. (A) DAD chromatogram at 210 nm, (B) MS(+) total ion chromatogram, (C) MS spectrum at 5.14 min.

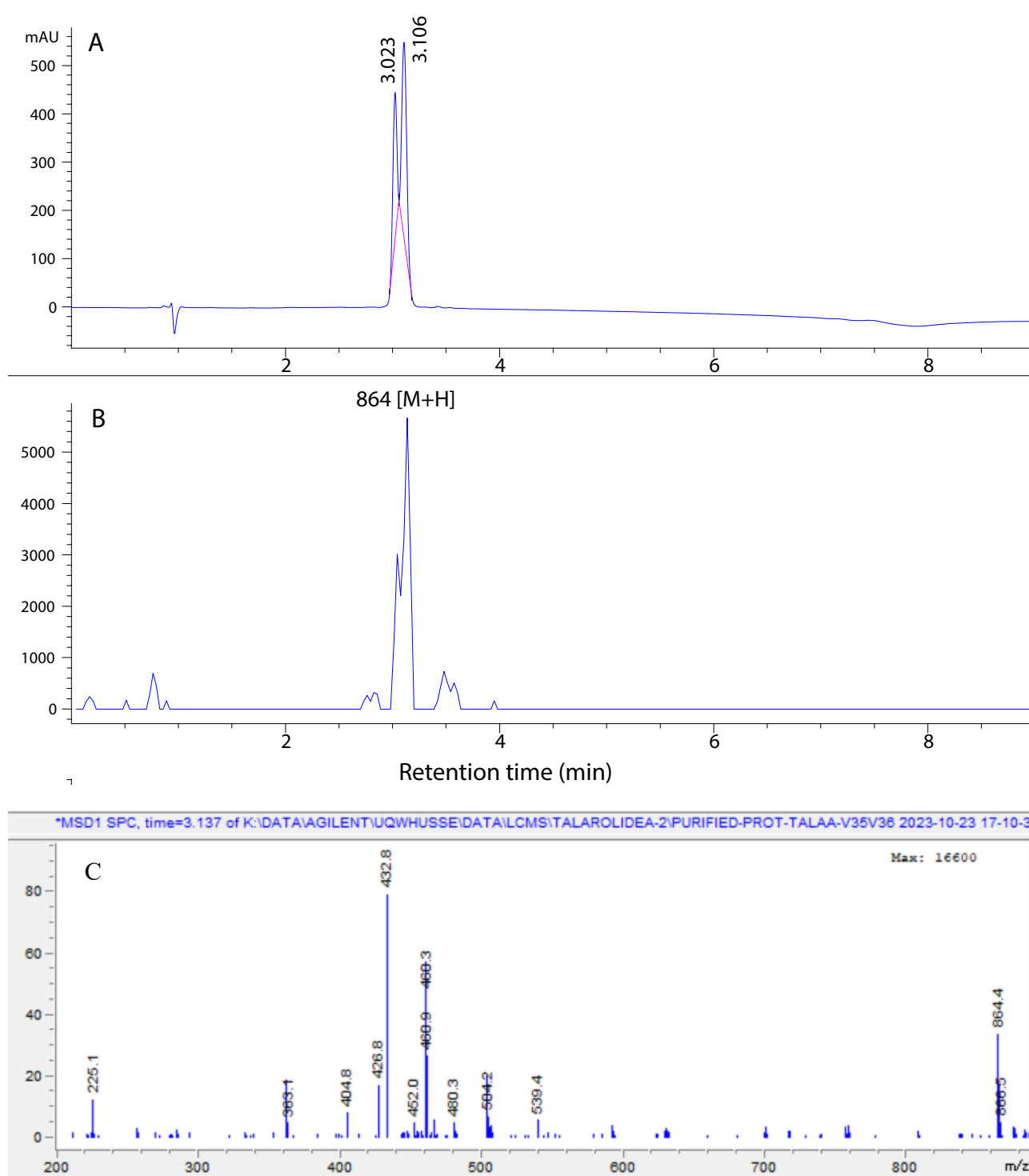


Figure S16. HPLC-DAD-MS chromatograms of protected cyclic peptide **6**. (A) DAD chromatogram at 210 nm, (B) MS(+) extracted ion chromatogram at 864, (C) MS spectrum at 3.13 min.

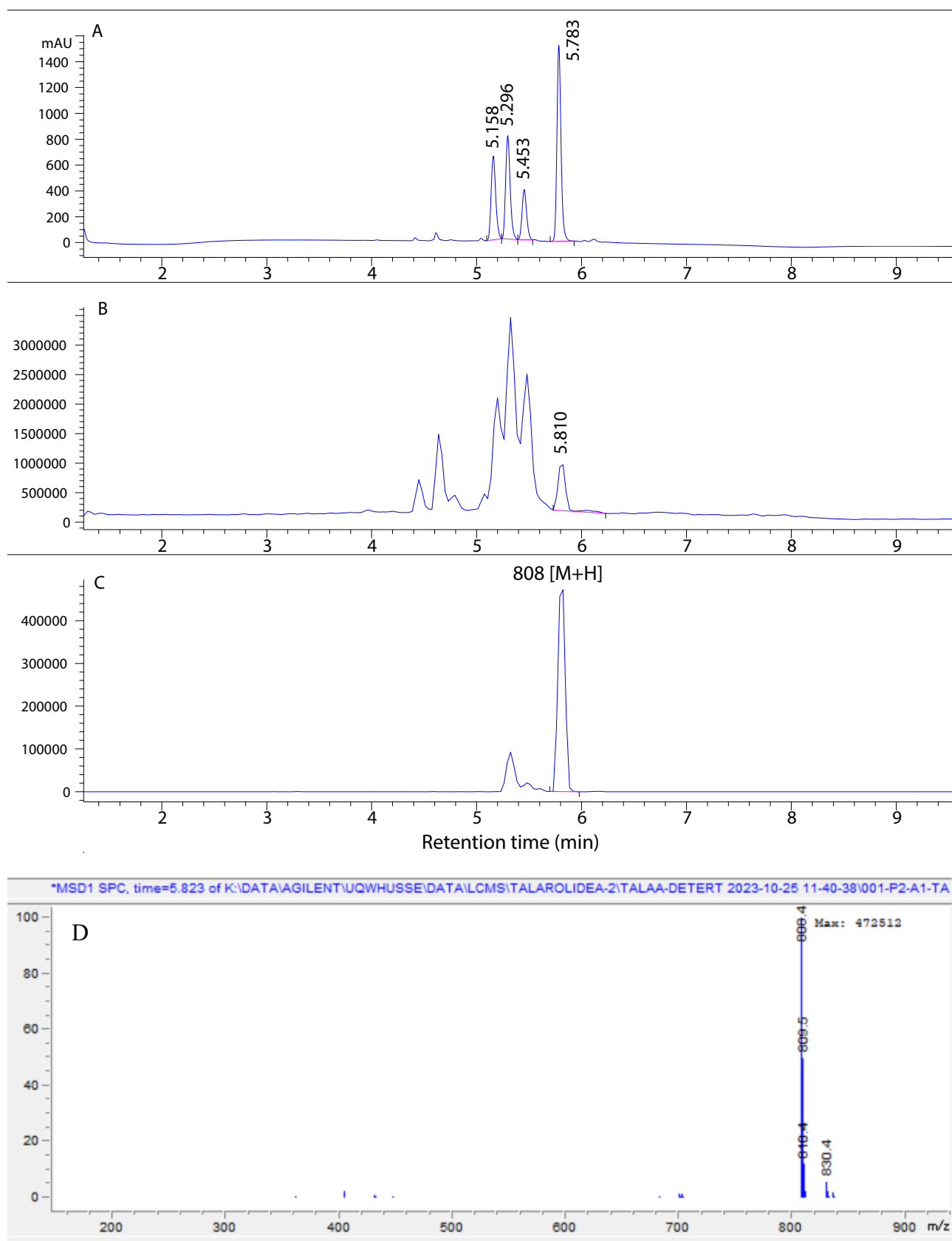


Figure S17. HPLC-DAD-MS chromatograms of crude semi-protected cyclic peptide **7** without *tert* butyl group. (A) DAD chromatogram at 210 nm, (B) MS(+) total ion chromatogram, (C) MS(+) extracted ion chromatogram at 808, (D) MS spectrum at 5.8 min.

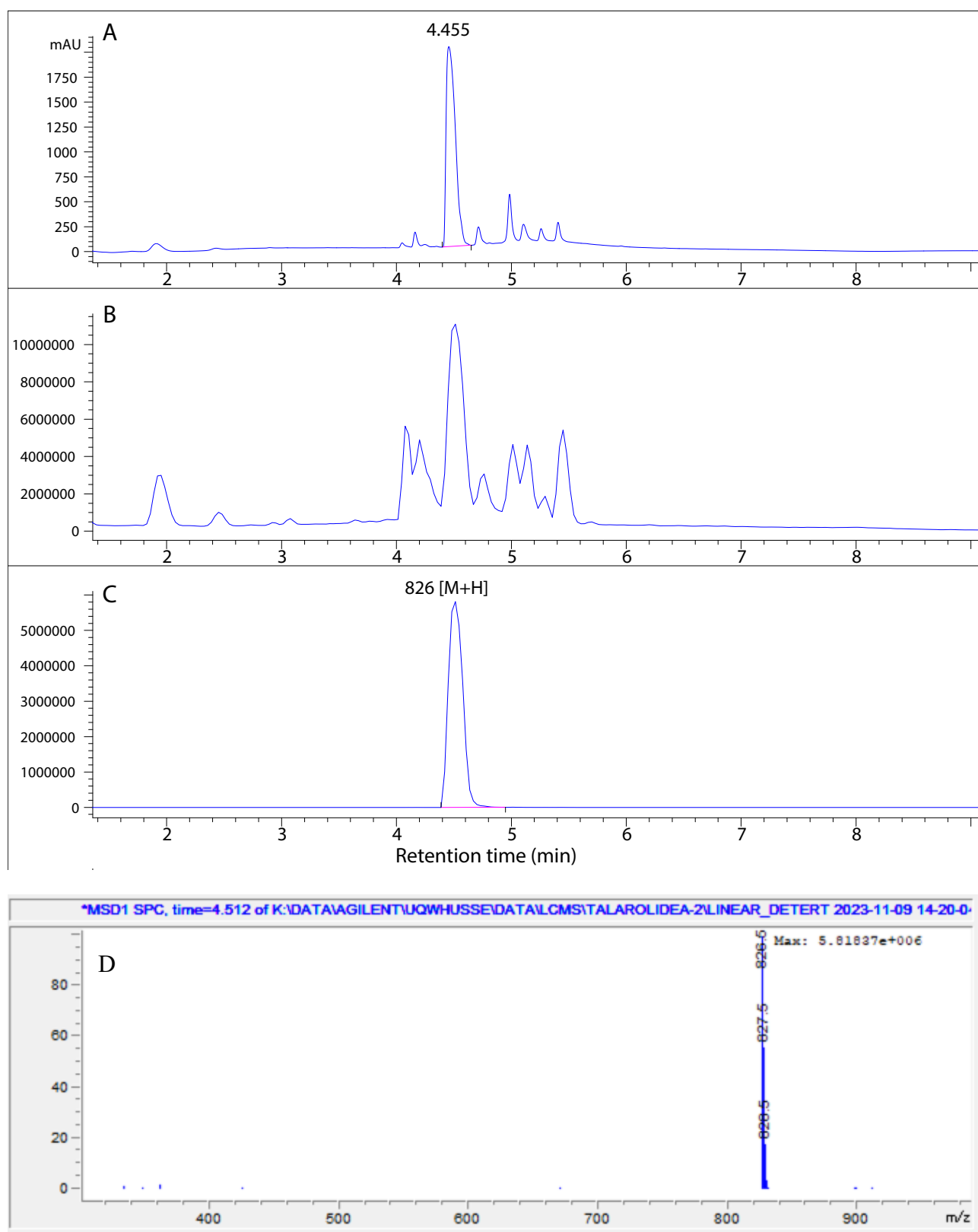


Figure S18. HPLC-DAD-MS chromatograms of crude semi-protected linear peptide **9** without *tert* butyl group. (A) DAD chromatogram at 210 nm, (B) MS(+) total ion chromatogram, (C) MS(+) extracted ion chromatogram at 826, (D) MS spectrum at 4.5 min.

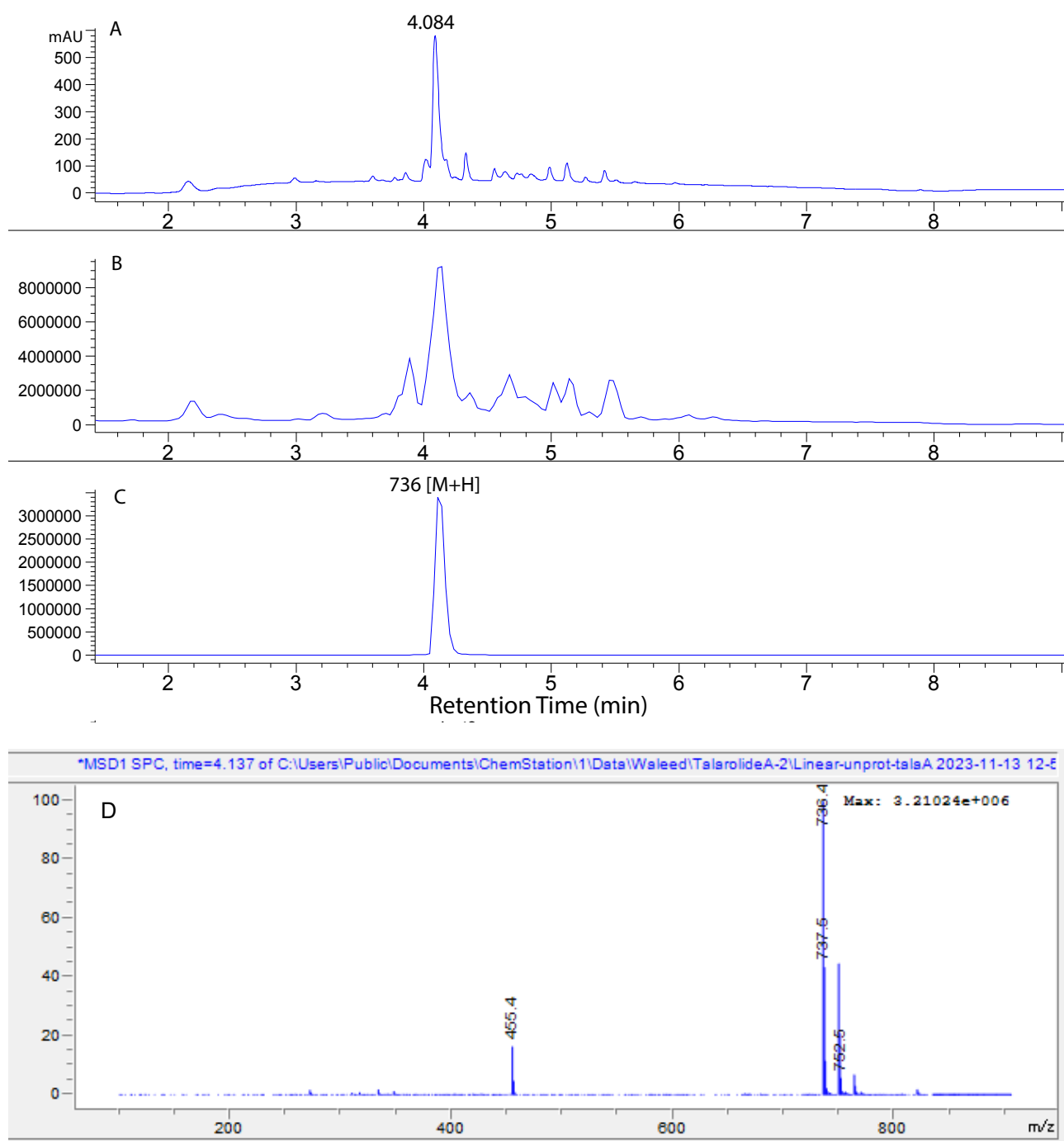


Figure S19. HPLC-DAD-MS chromatograms of unprotected linear peptide **10**. (A) DAD chromatogram at 210 nm, (B) MS(+) total ion chromatogram, (C) MS(+) extracted ion chromatogram at 736, (D) MS spectrum at 4.1 min.