Supplementary information for

Large scale conversion of trilobolide into the payload of Mipsagargin: 8-*O*-(12-aminododecanoyl)-8-*O*-debutanoylthapsigargin

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Product **1** (3-oxo-3-desangeloyl trilobolide)

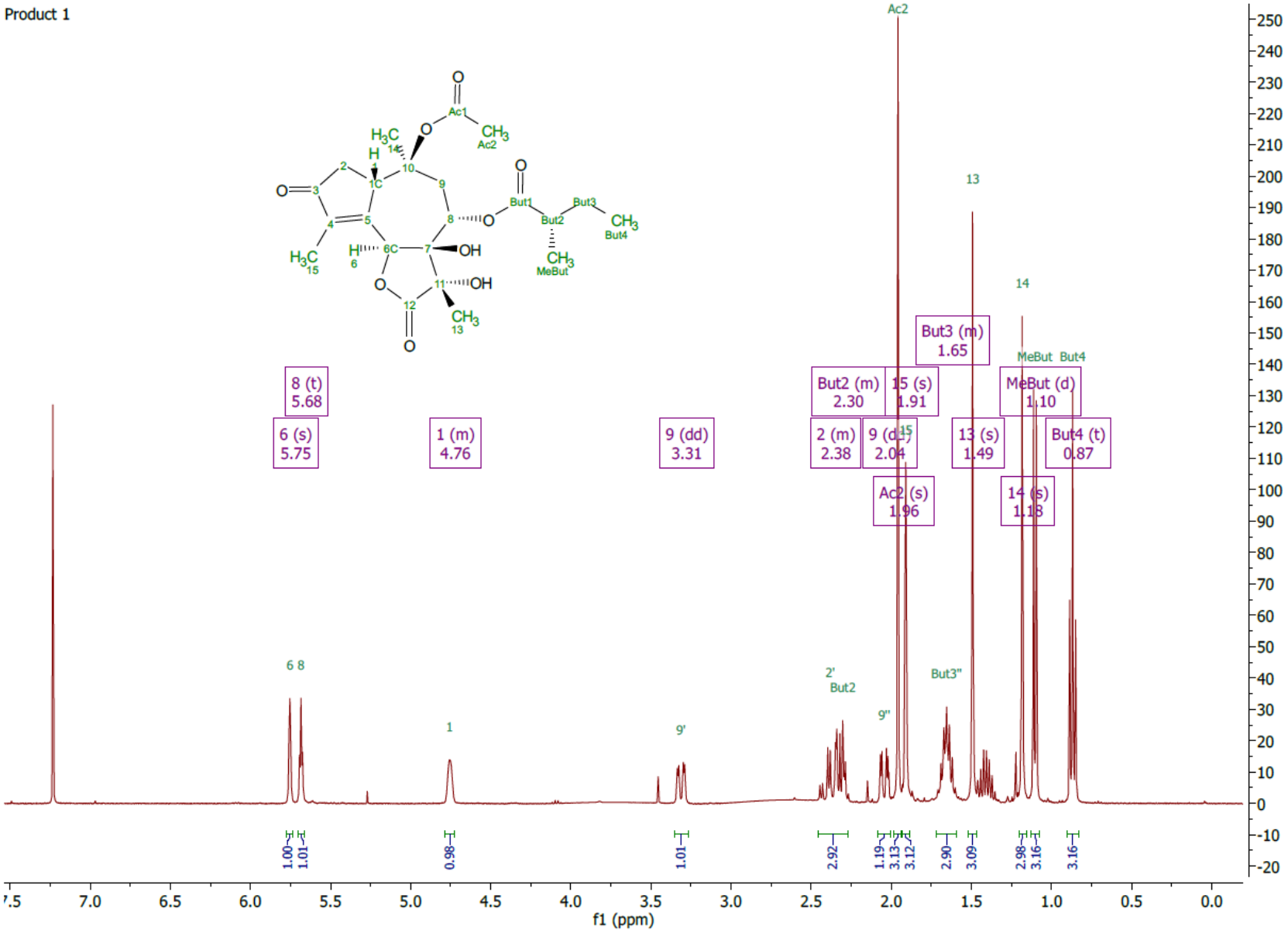


Figure S1A – ^{1}H NMR of product **1** (400 MHz, $CDCl_3$)

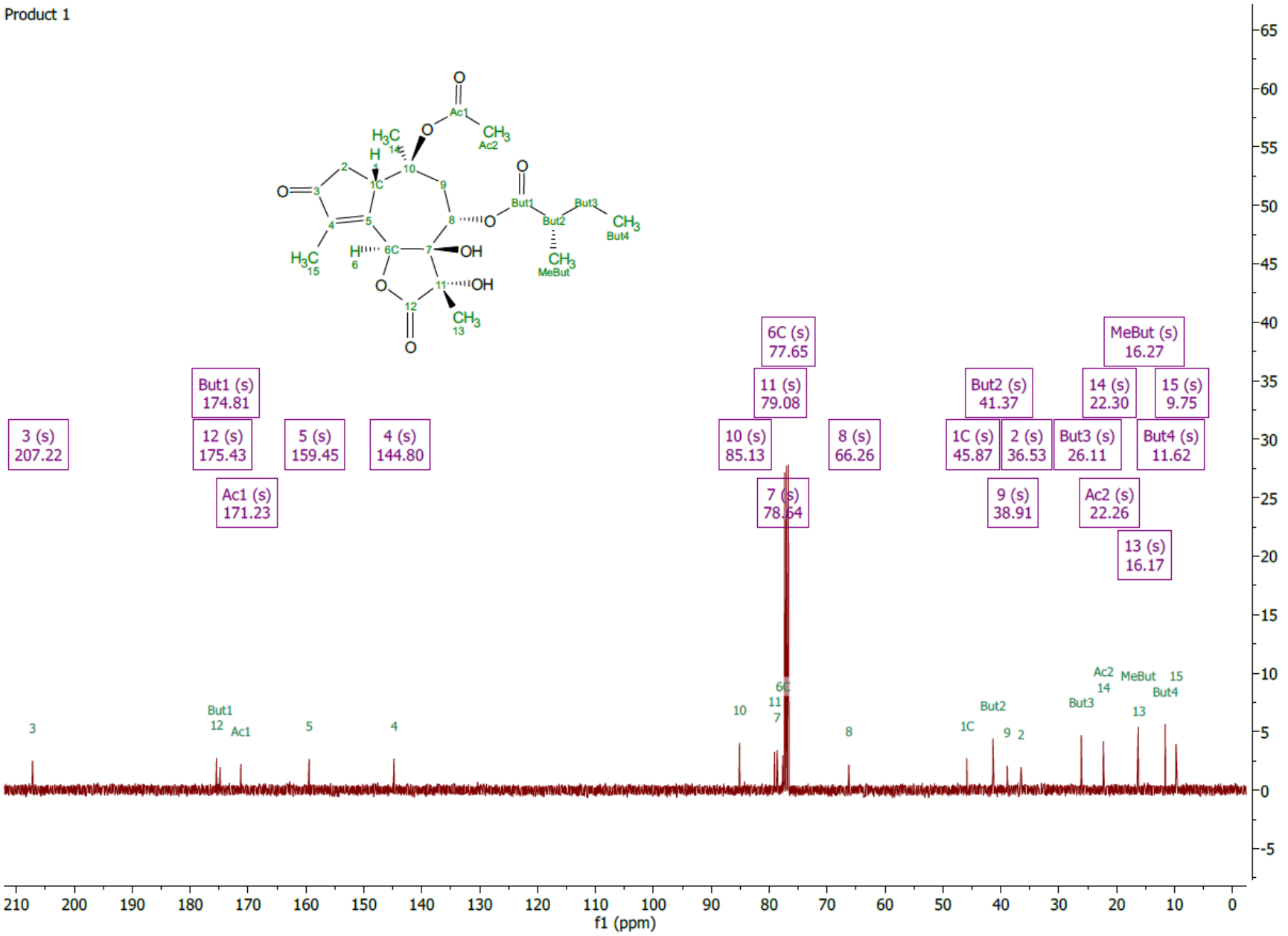


Figure S1B – ^{13}C NMR of product **1** (100 MHz, $CDCl_3$)

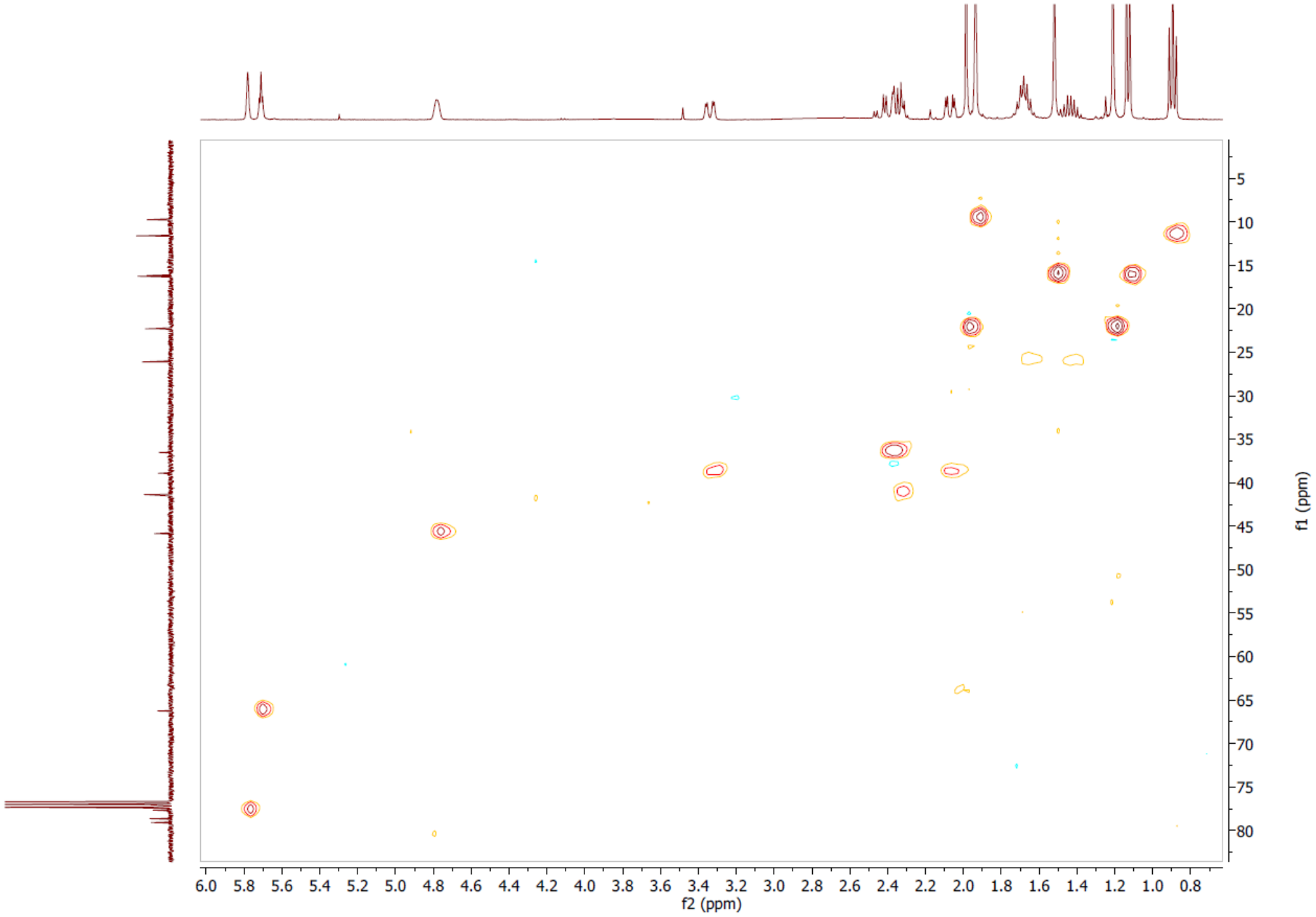


Figure S1C - HMQC of product **1**

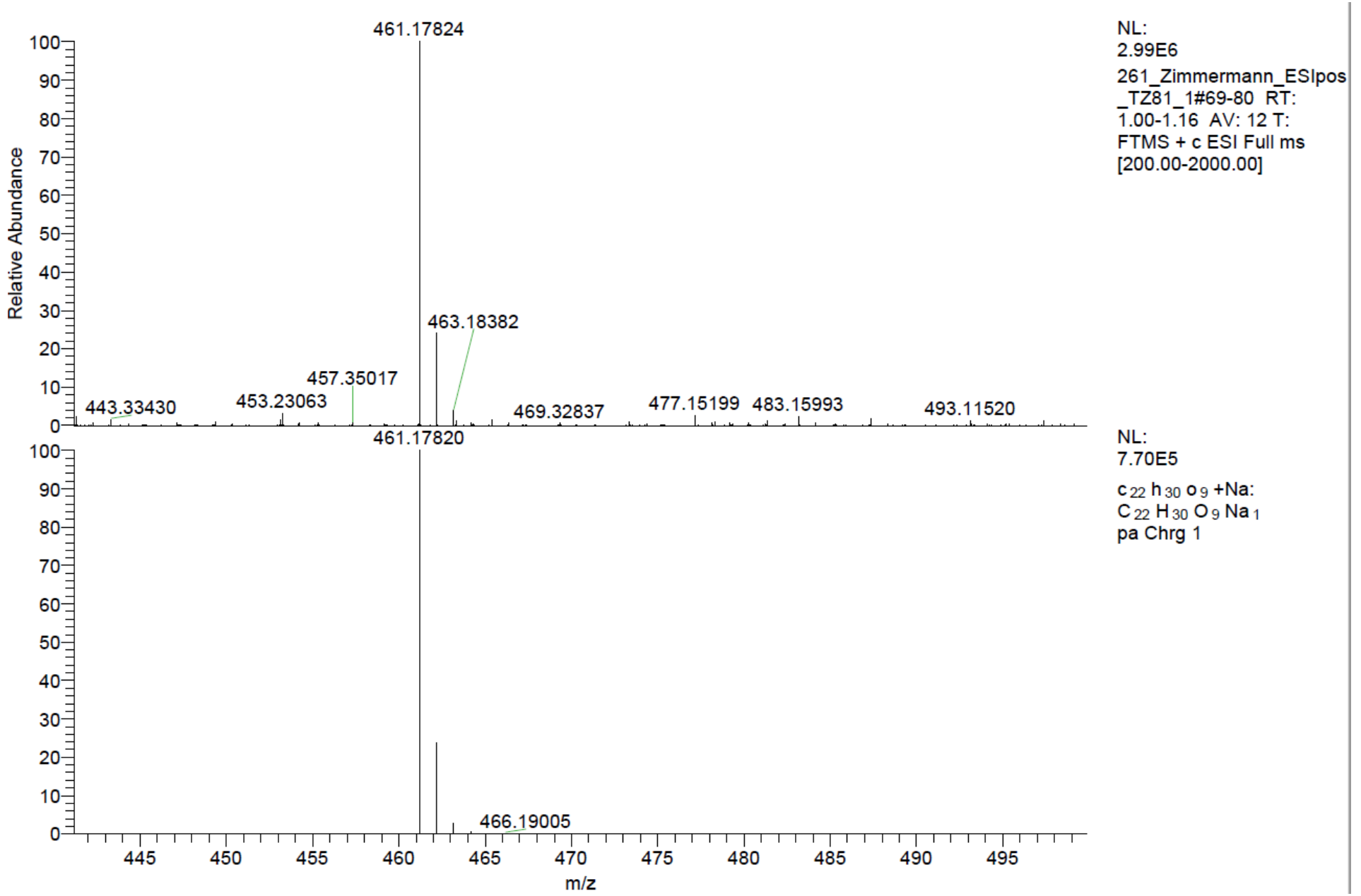


Figure S1D - HRMS of product **1** - $[C_{22}H_{30}O_9+Na]^+$ = 461.17824

Product **2** (2-octanoyl-3-oxo-3-desangeloyl trilobolide)

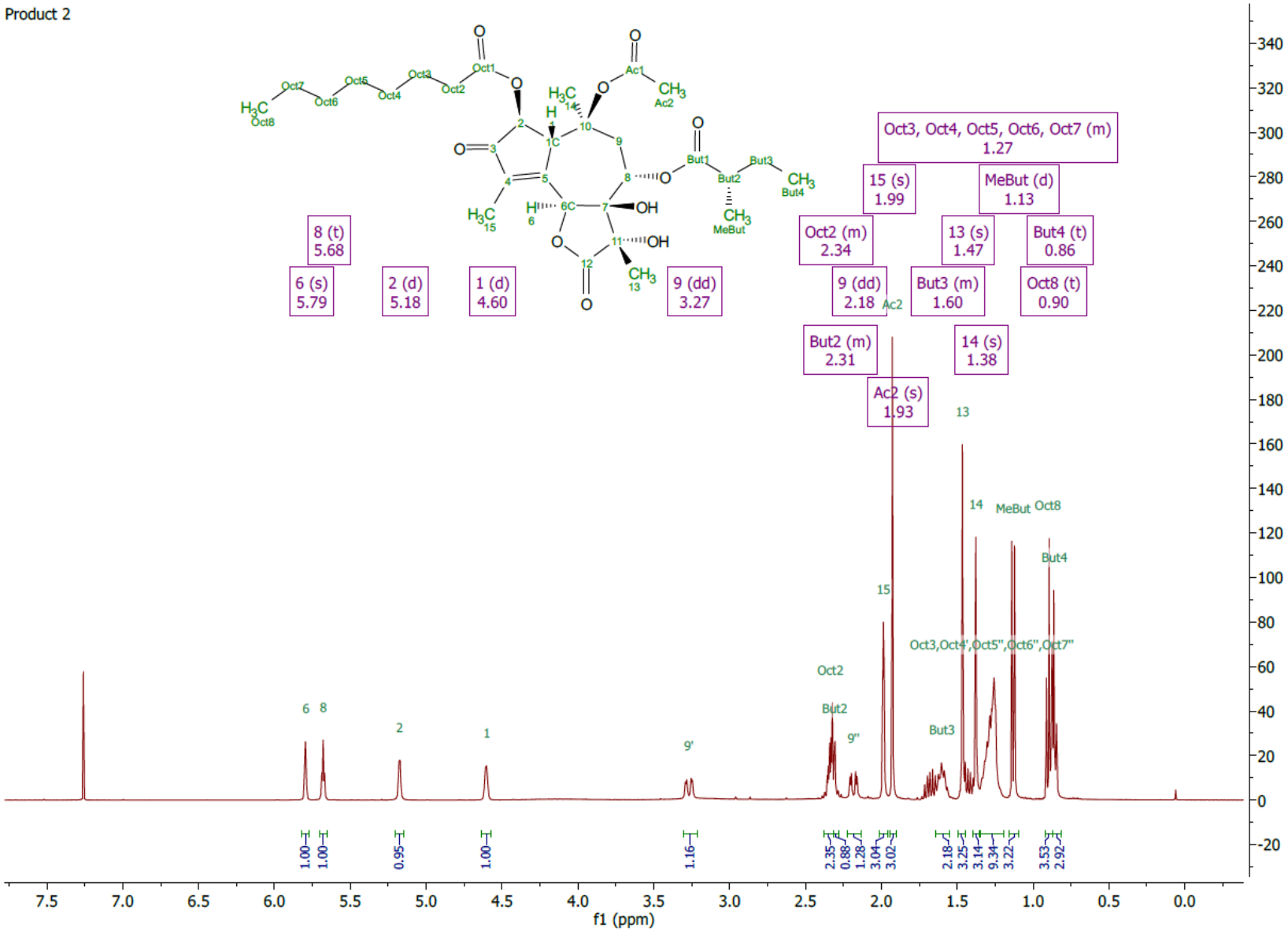


Figure S2A ^{1}H NMR of product **2** (400 MHz, $CDCl_3$)

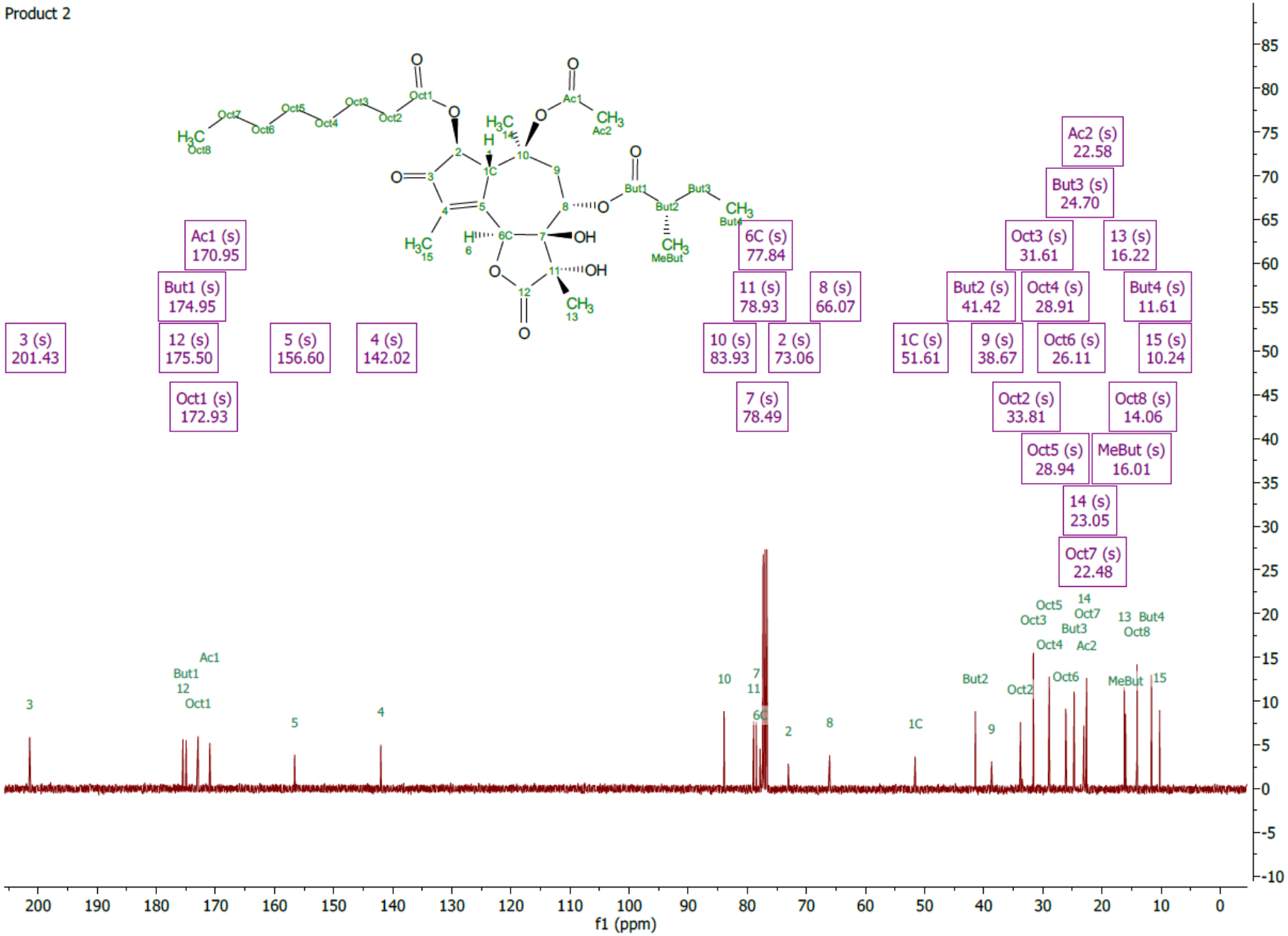


Figure S2B ^{13}C NMR of product **2** (100 MHz, $CDCl_3$)

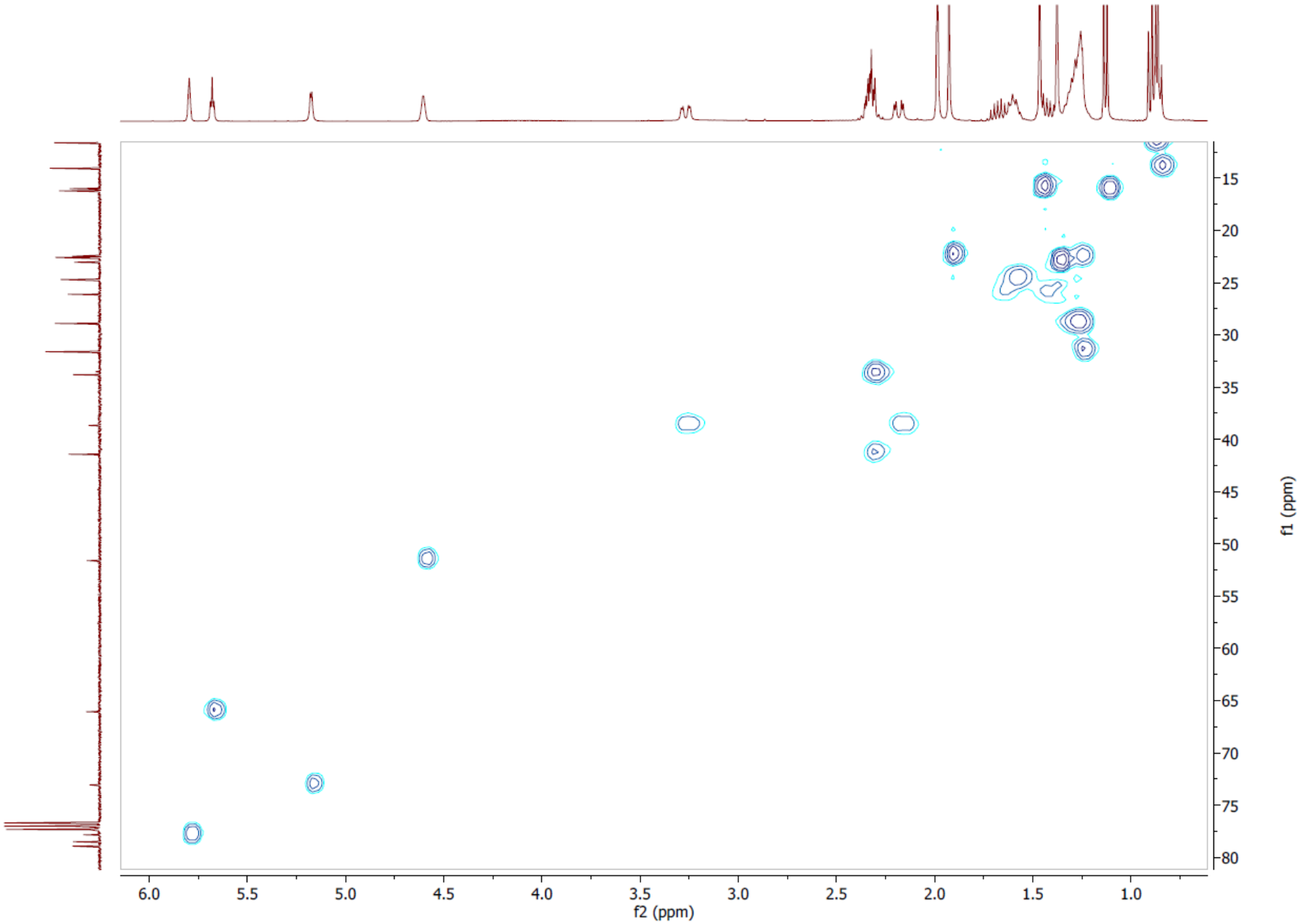


Figure S2C HMQC of product **2**

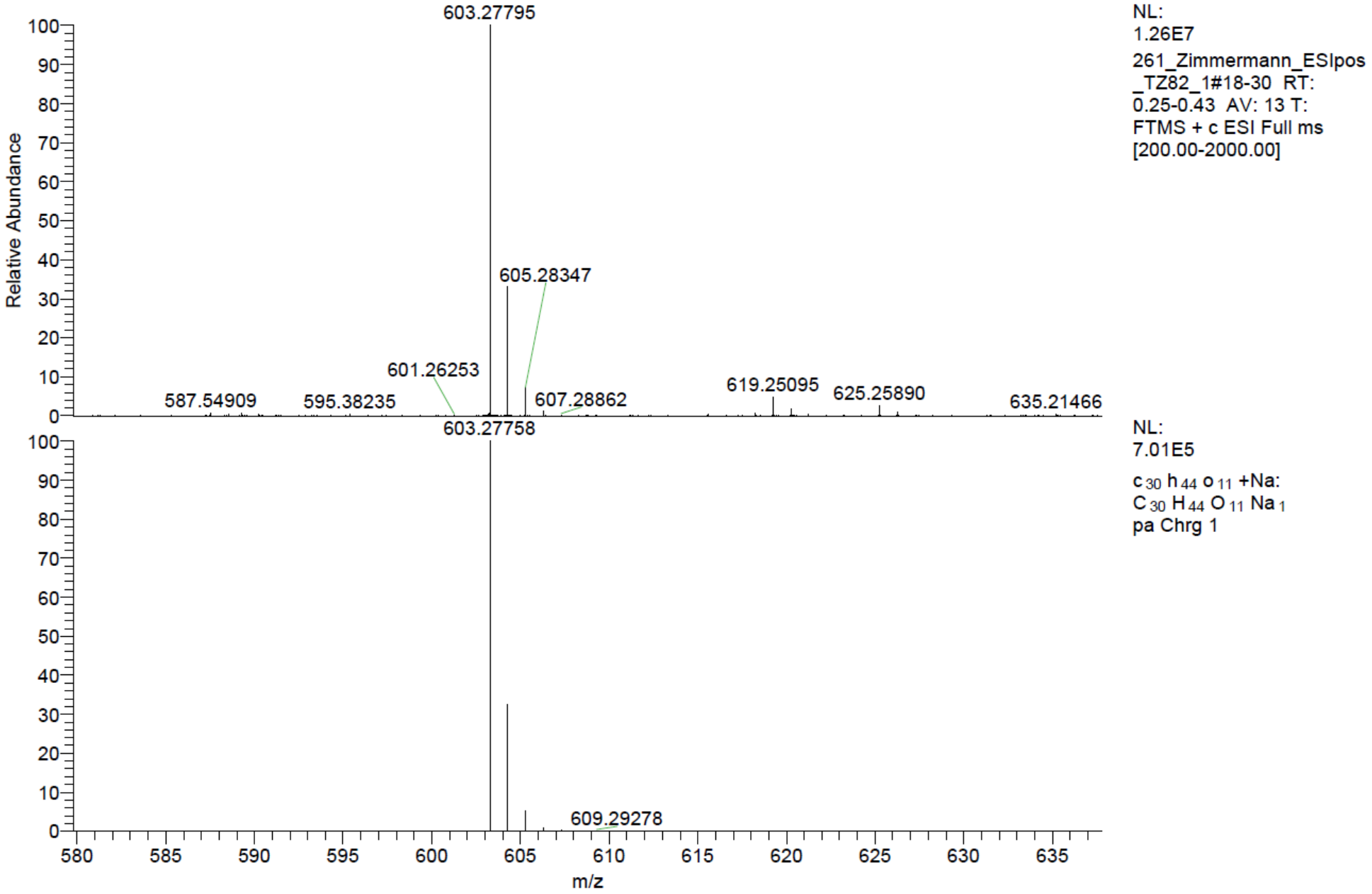


Figure S2D LCMS of product **2 -** $[C_{30}H_{44}O_{11}+Na]^+$ = 603.27795

Product **3** ((3*S*)-hydroxy-2-octanoyl-3-desangeloyl trilobolide)

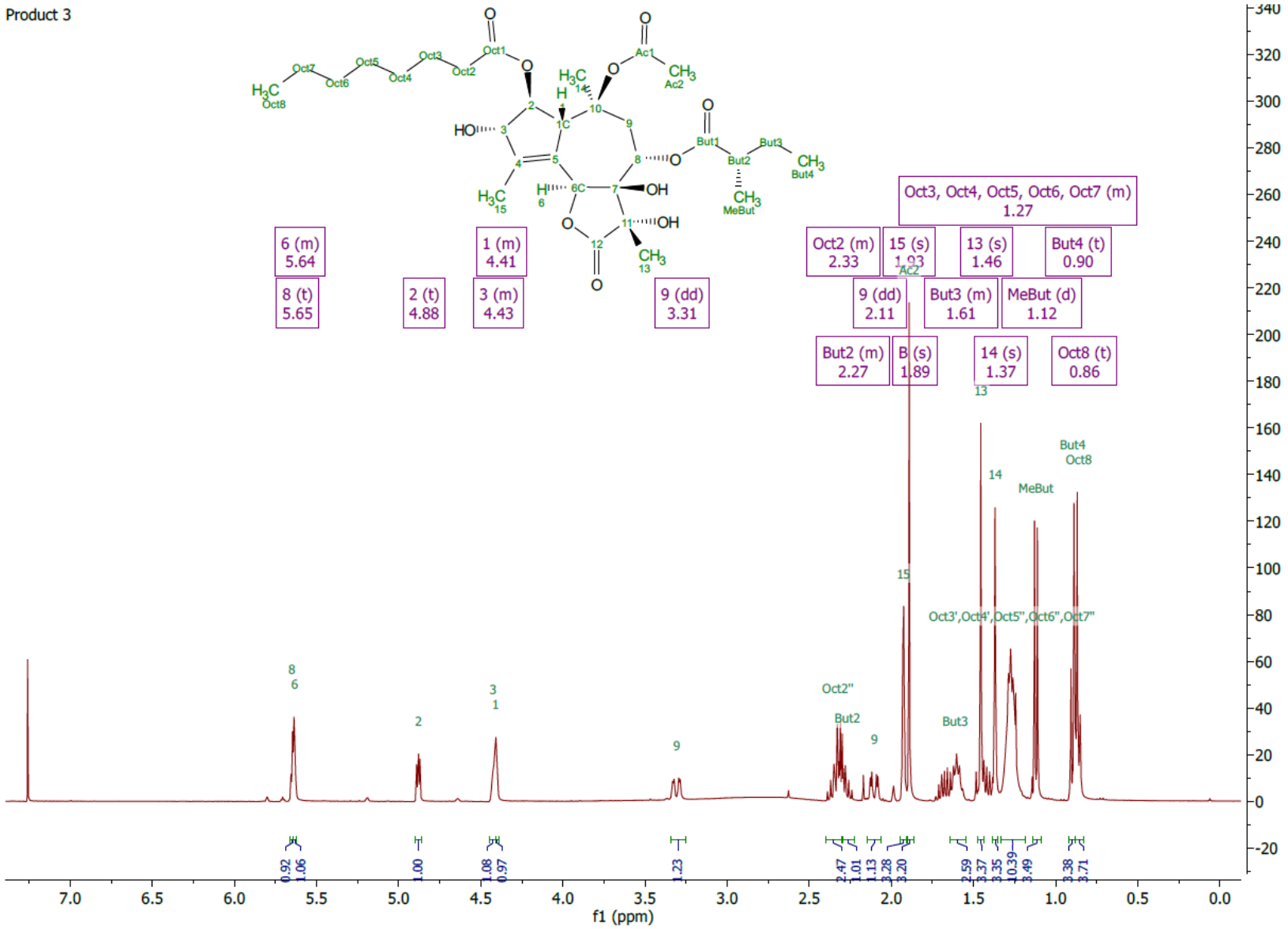


Figure S3A ^{1}H NMR of product **3** (400 MHz, $CDCl_3$)

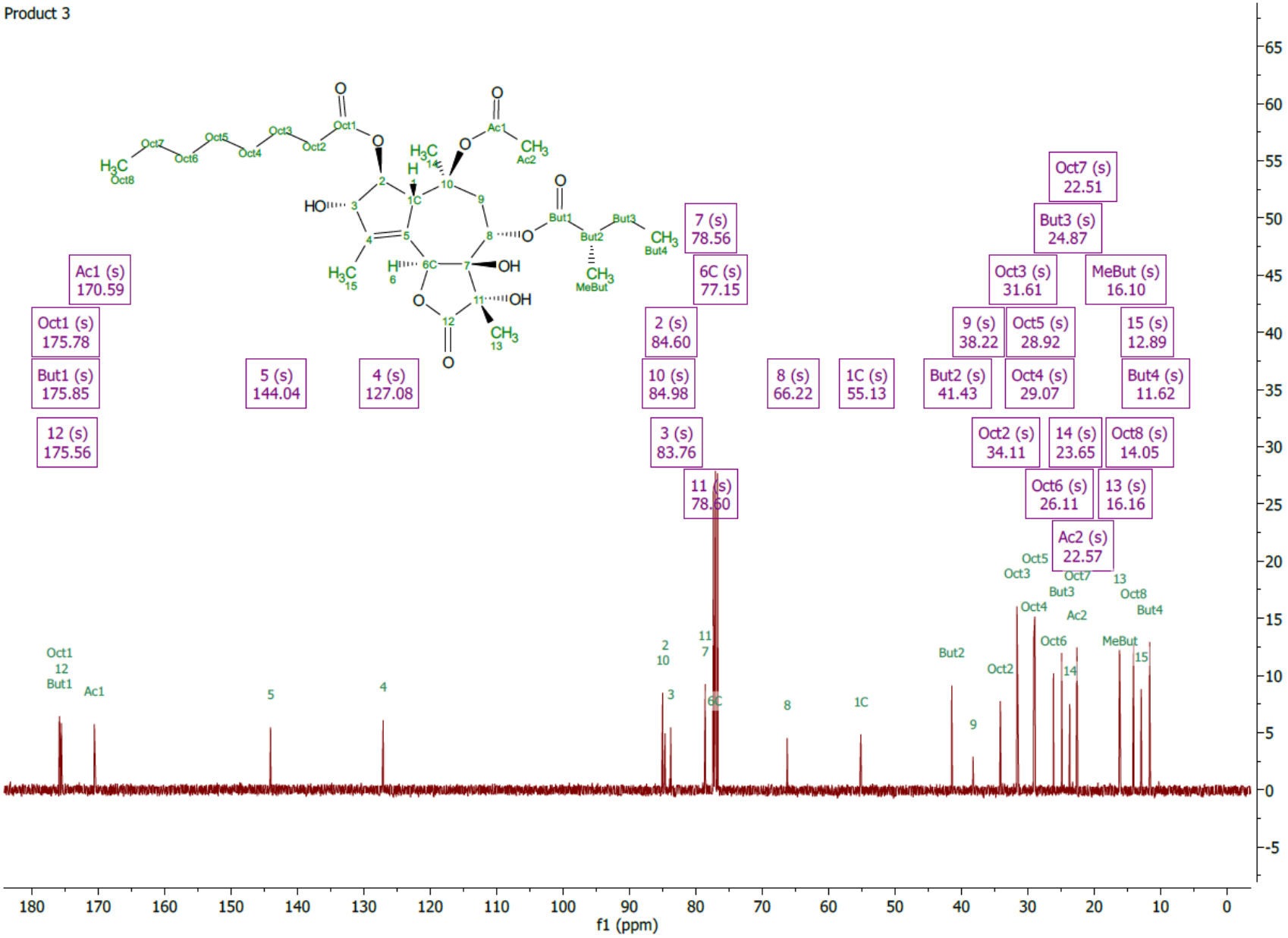


Figure S3B ^{13}C NMR of product **3** (100 MHz, $CDCl_3$)

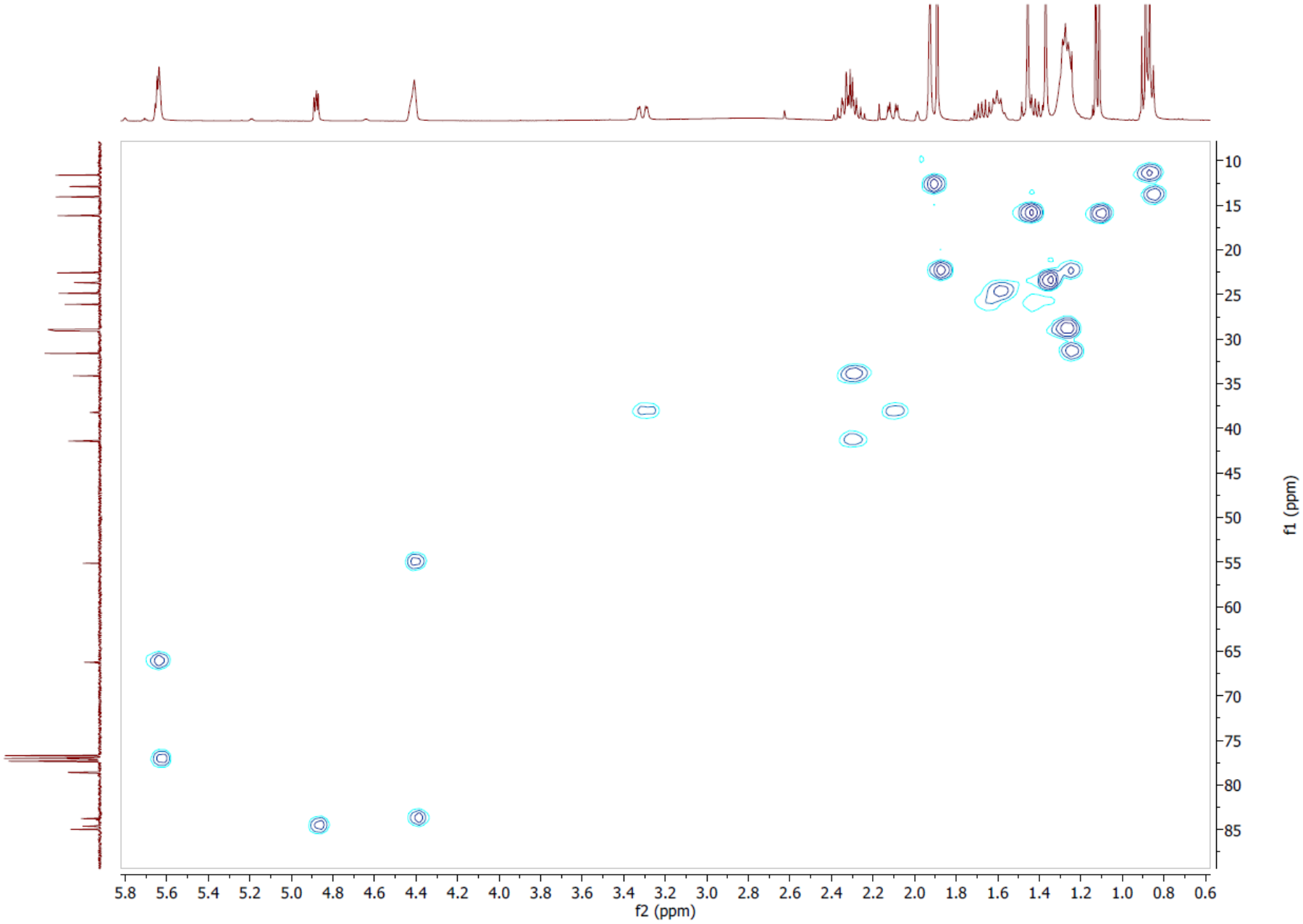


Figure S3C HMQC of product **3**

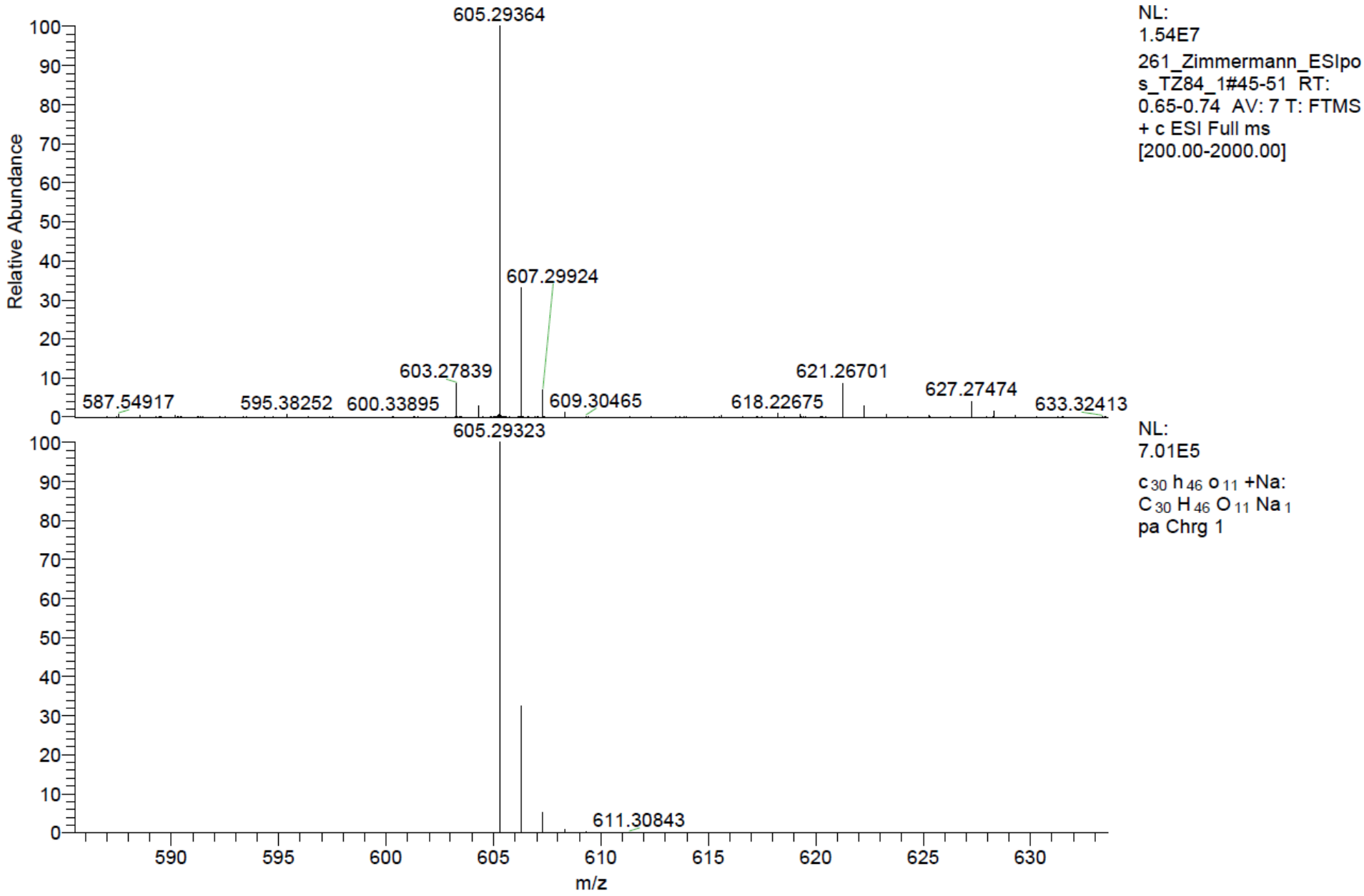


Figure S3D HRMS of product **3 -** $[C_{30}H_{46}O_{11}+Na]^+$ = 605.29364

Product **4** (8-*O*-((2*S*)-Methylbutanoyl)-8-*O*-debutanoyl thapsigargin)

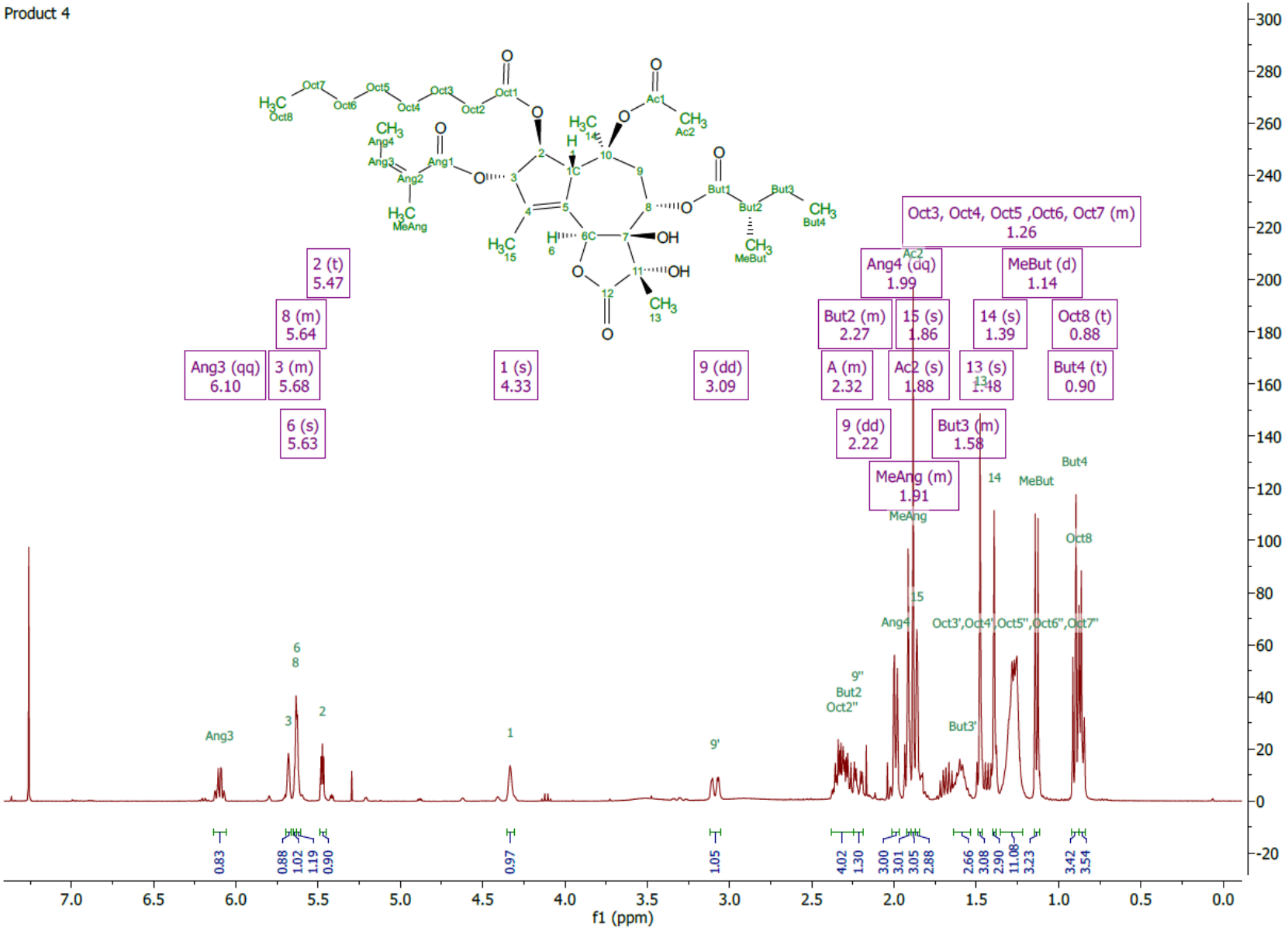


Figure S4A ^{1}H NMR of product **4** (400 MHz, $CDCl_3$)

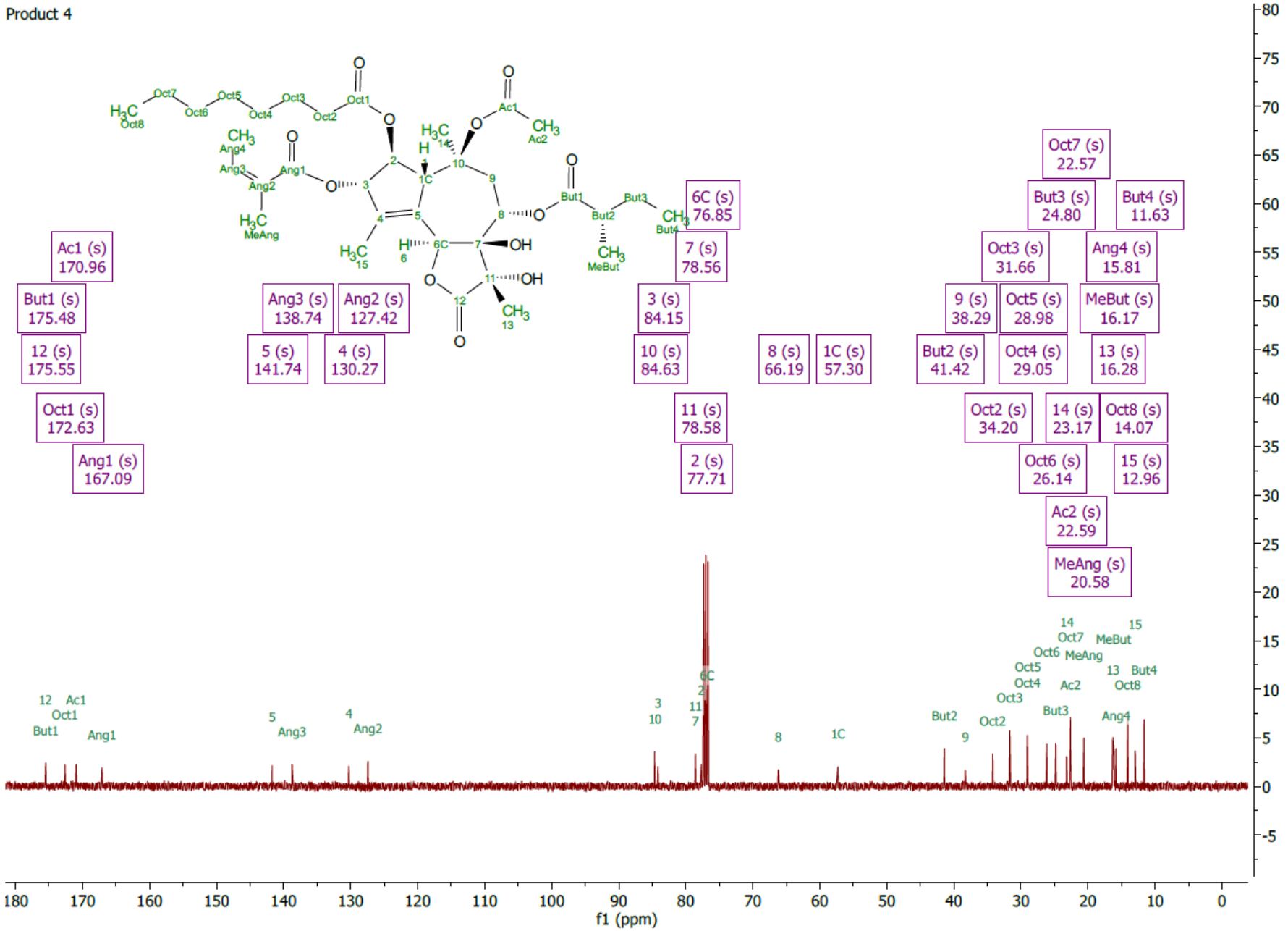


Figure S4B ^{13}C NMR of product **4** (100 MHz, $CDCl_3$)

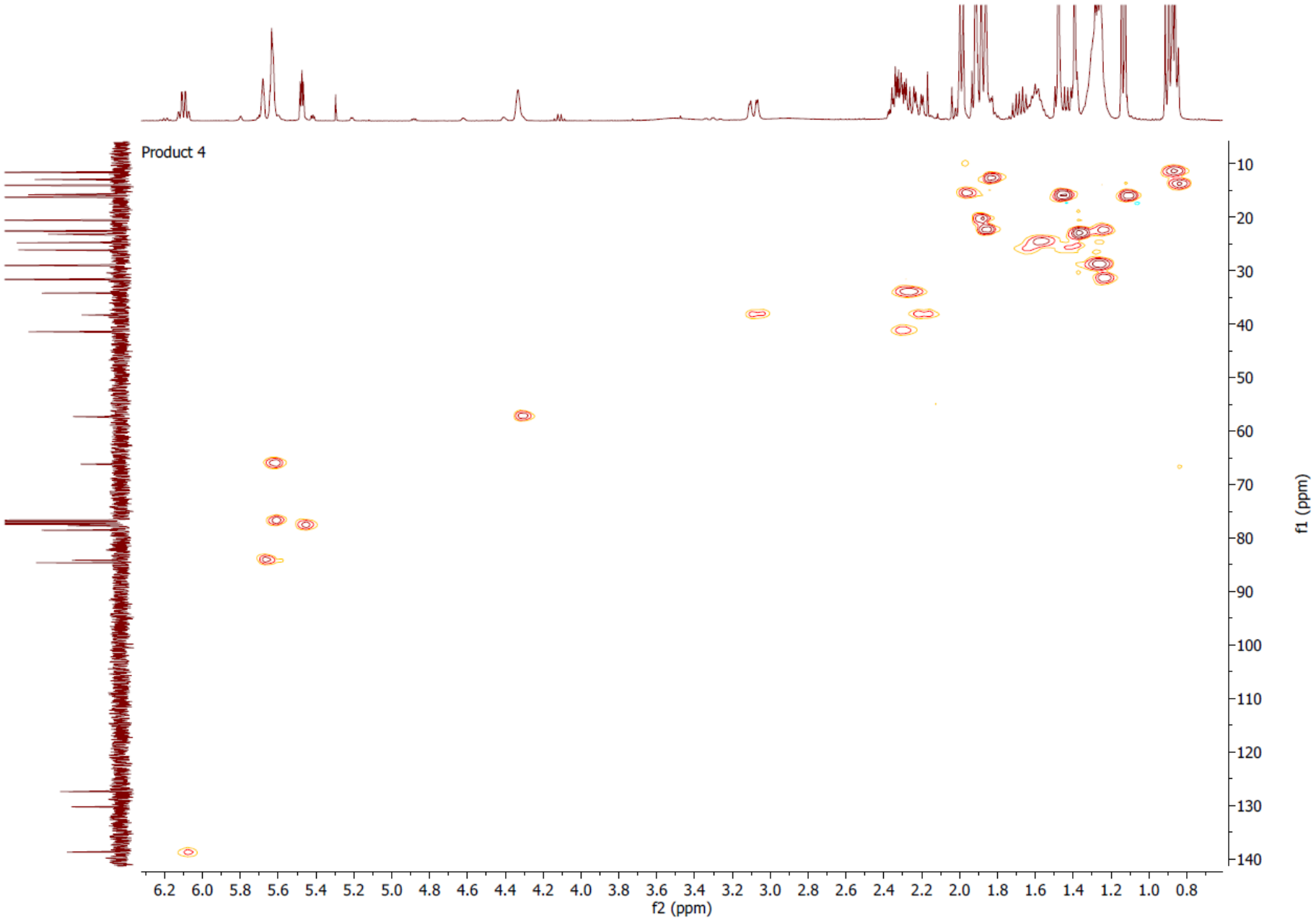


Figure S4C HMQC of product **4**

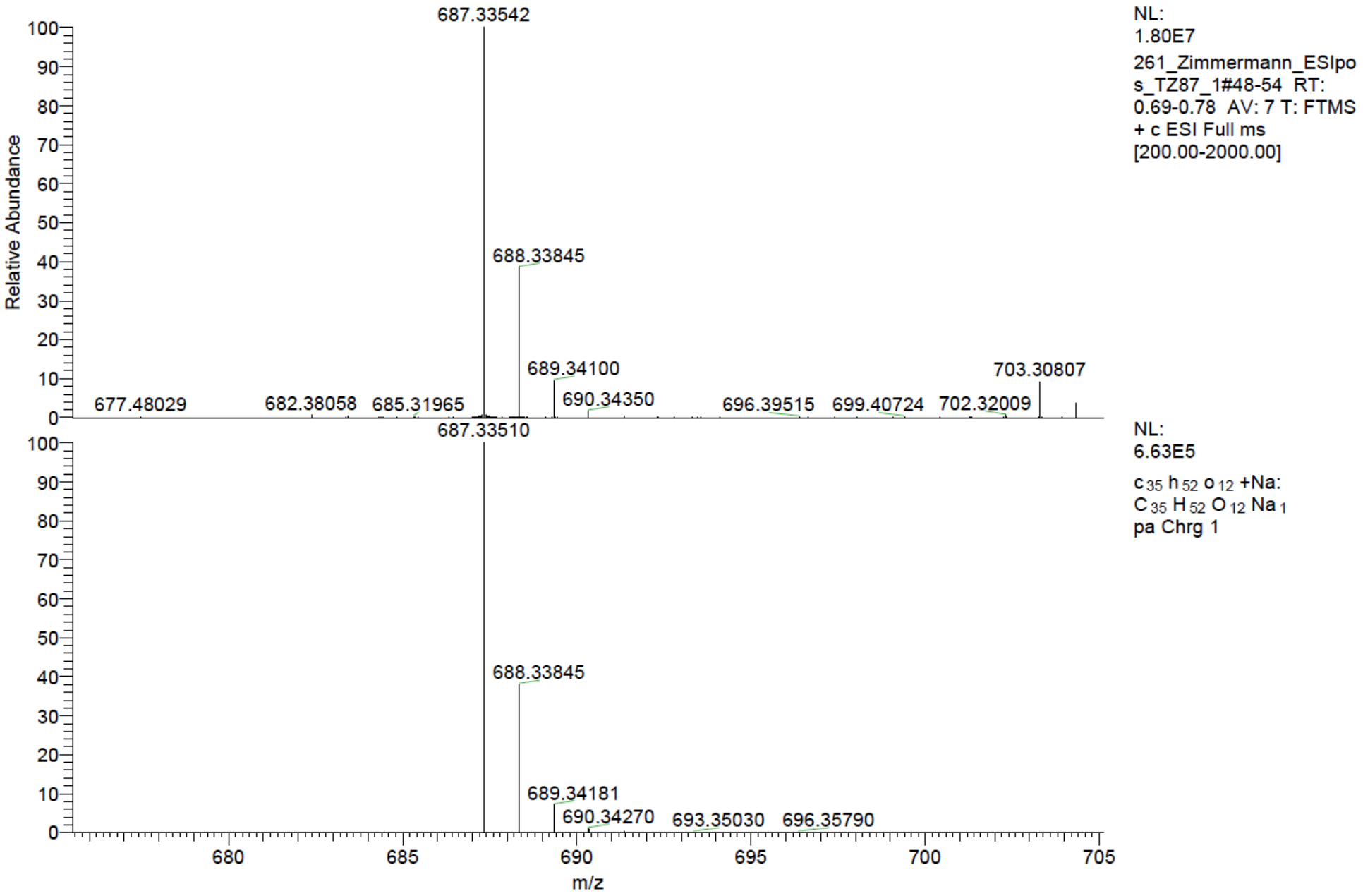


Figure S4D HRMS of product **4 -** $[C_{35}H_{52}O_{12}+Na]^+ = 687.33542$

Product **5** (8-*O*-debutanoyl thapsigargin)

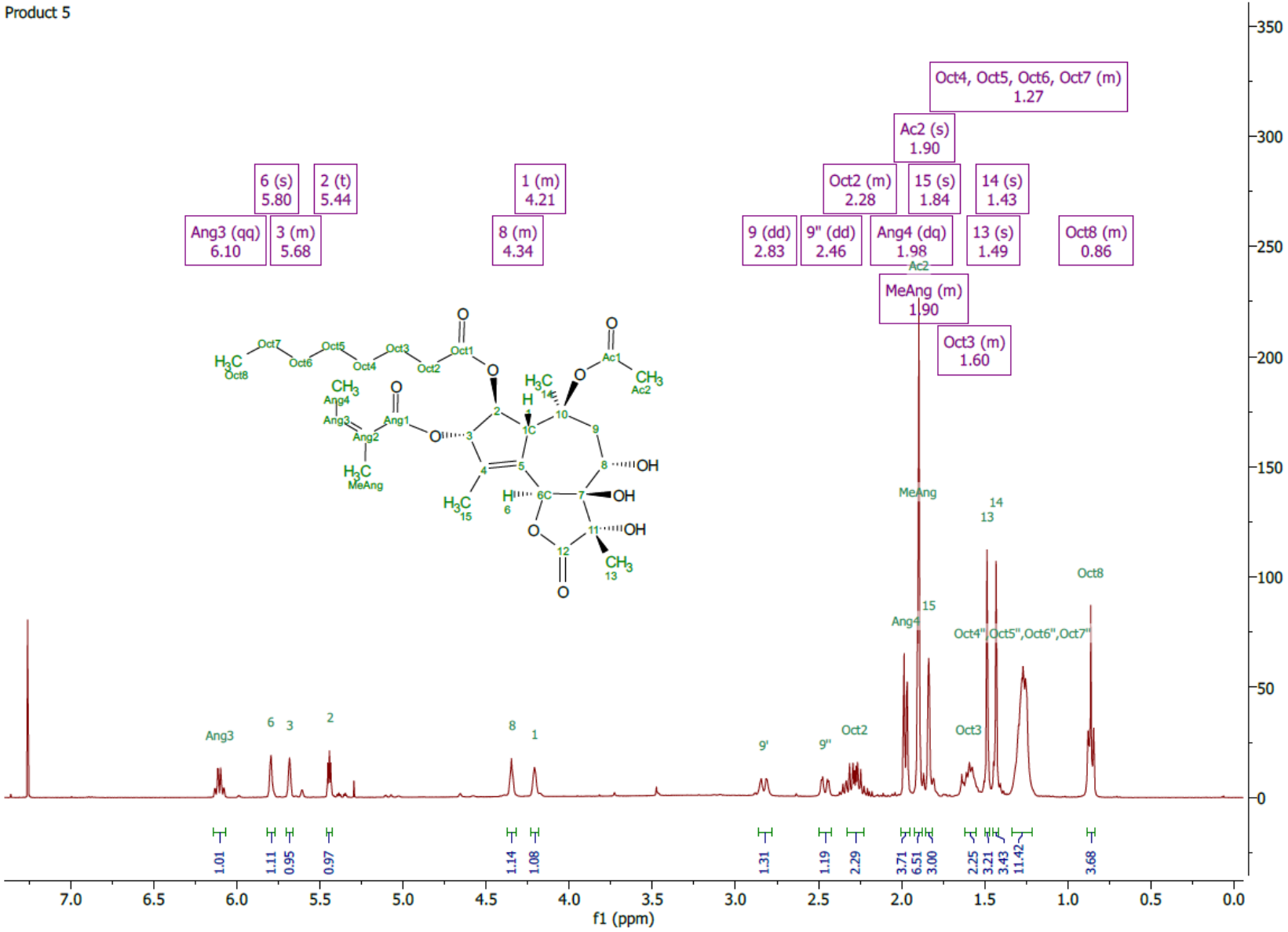


Figure S5A ^{1}H NMR of product **4** (400 MHz, $CDCl_3$)

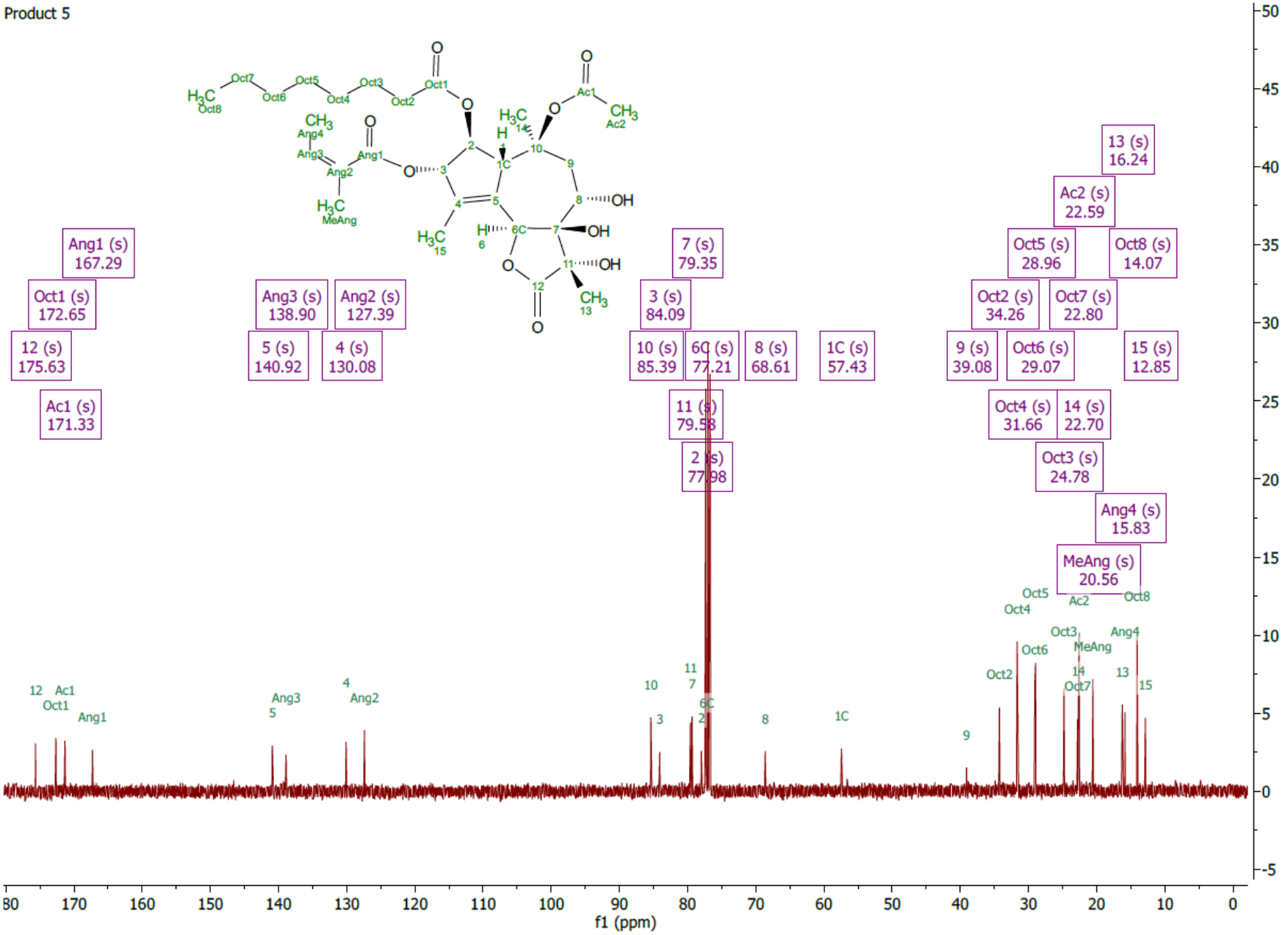


Figure S5B ^{13}C NMR of product **5** (100 MHz, $CDCl_3$)

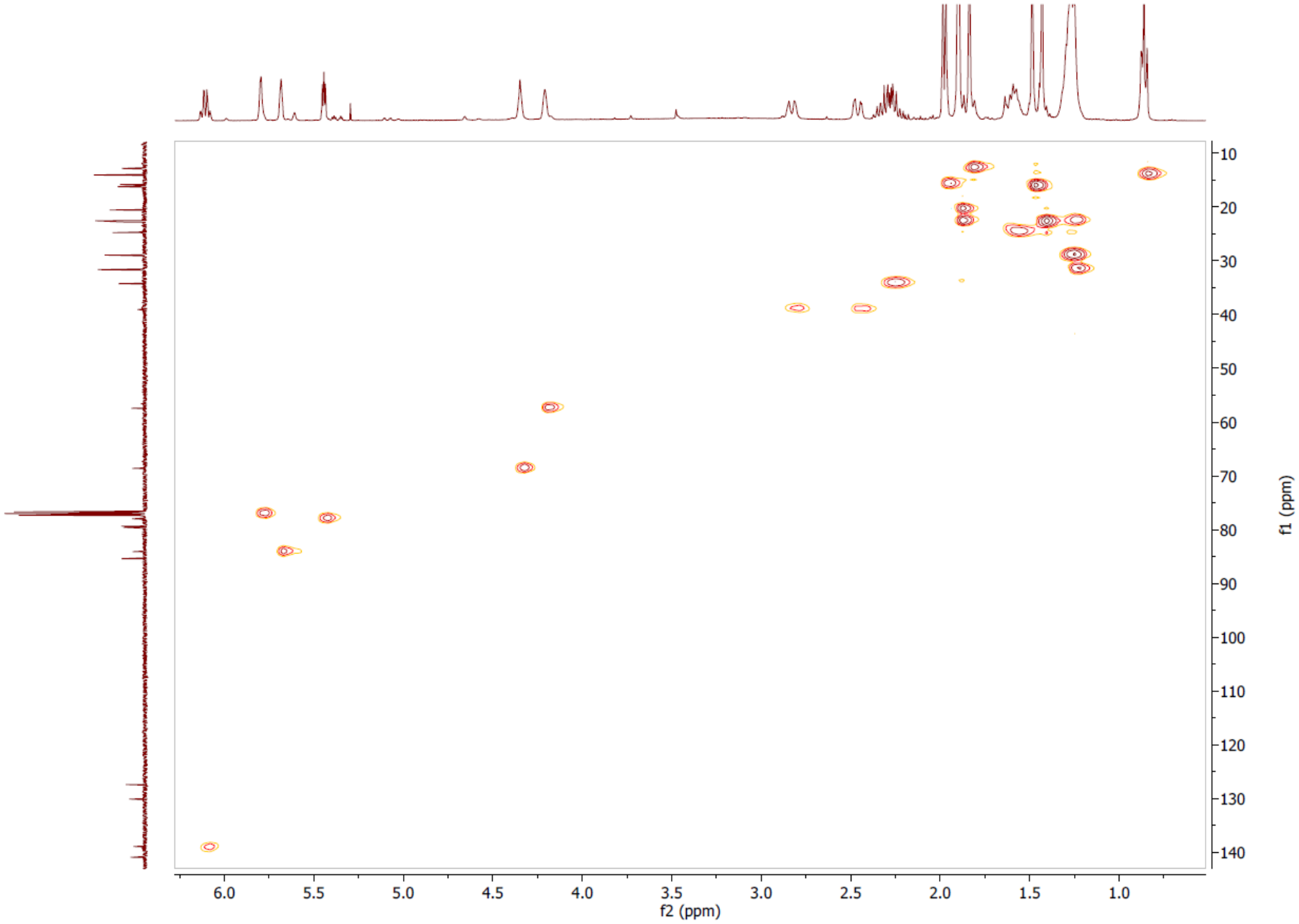


Figure S5C HMQC of product **5**

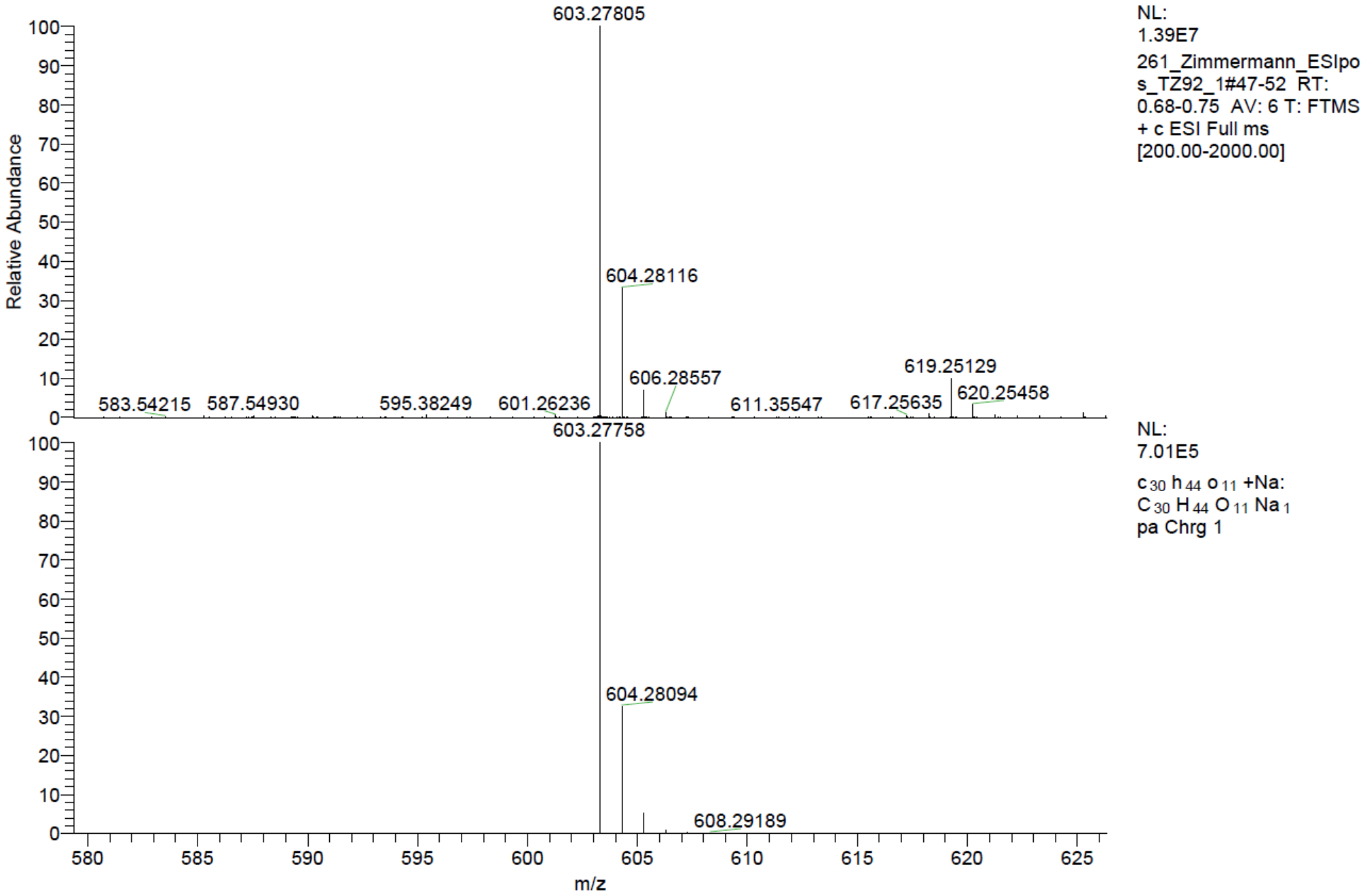


Figure S5D HRMS of product **5 -** $[C_{30}H_{44}O_{11}+Na]^+$ = 603.27805

Product **6** (8-*O*-(Boc-12-aminododecanoyl)-8-*O*-debutanoyl thapsigargin)

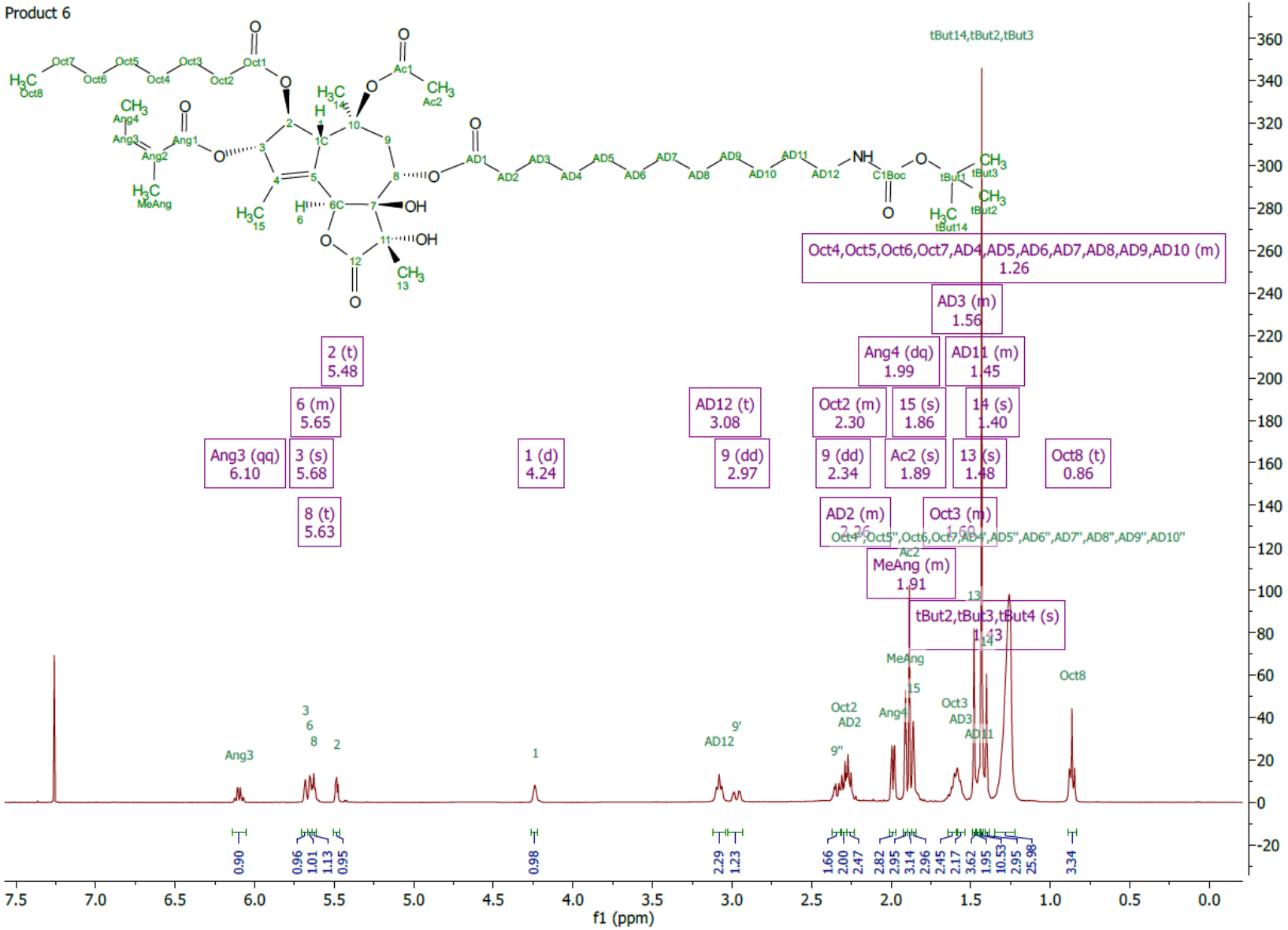


Figure S6A ^{1}H NMR of product **6** (400 MHz, $CDCl_3$)

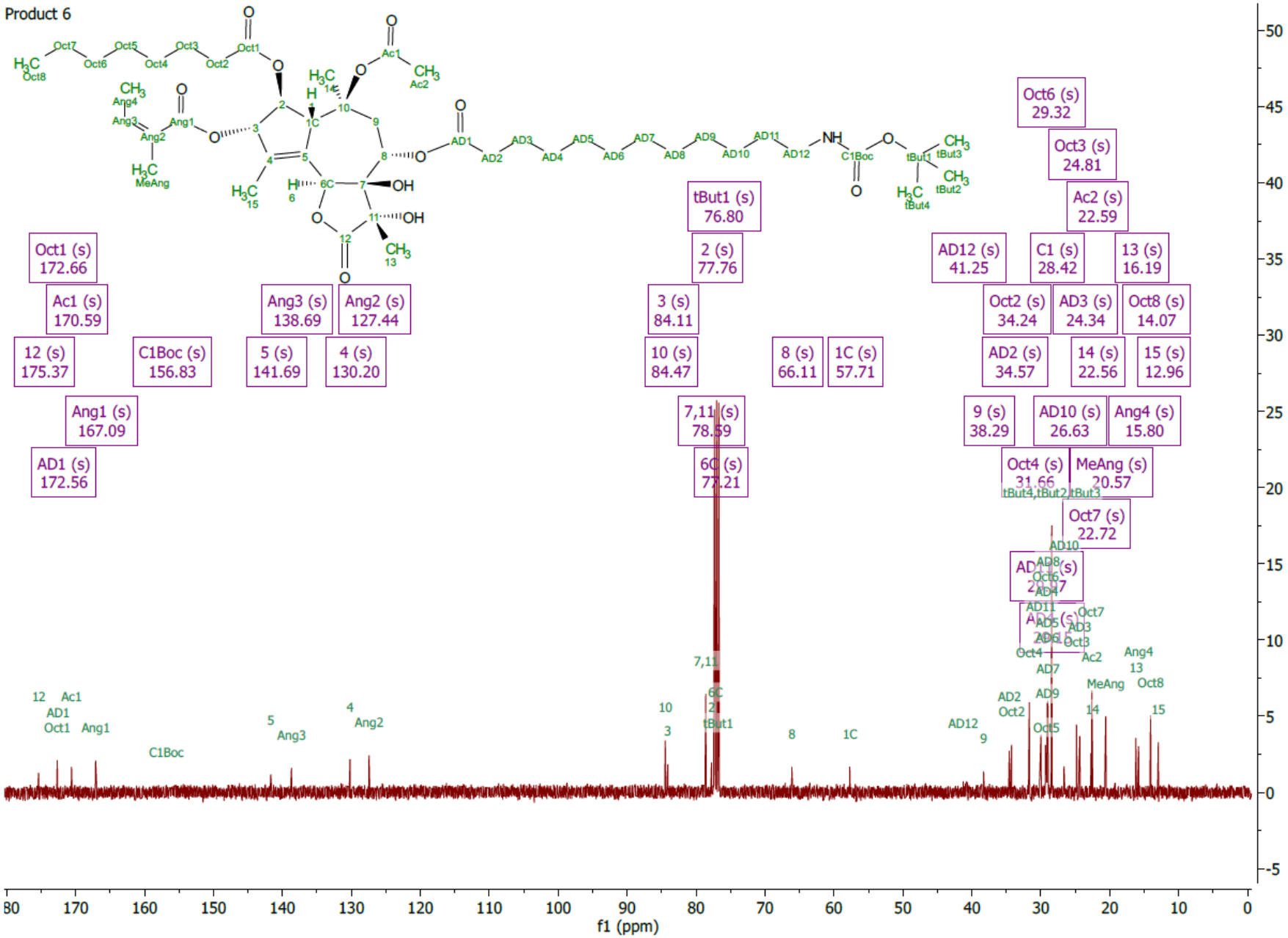


Figure S6B ^{13}C NMR of product **6** (100 MHz, $CDCl_3$)

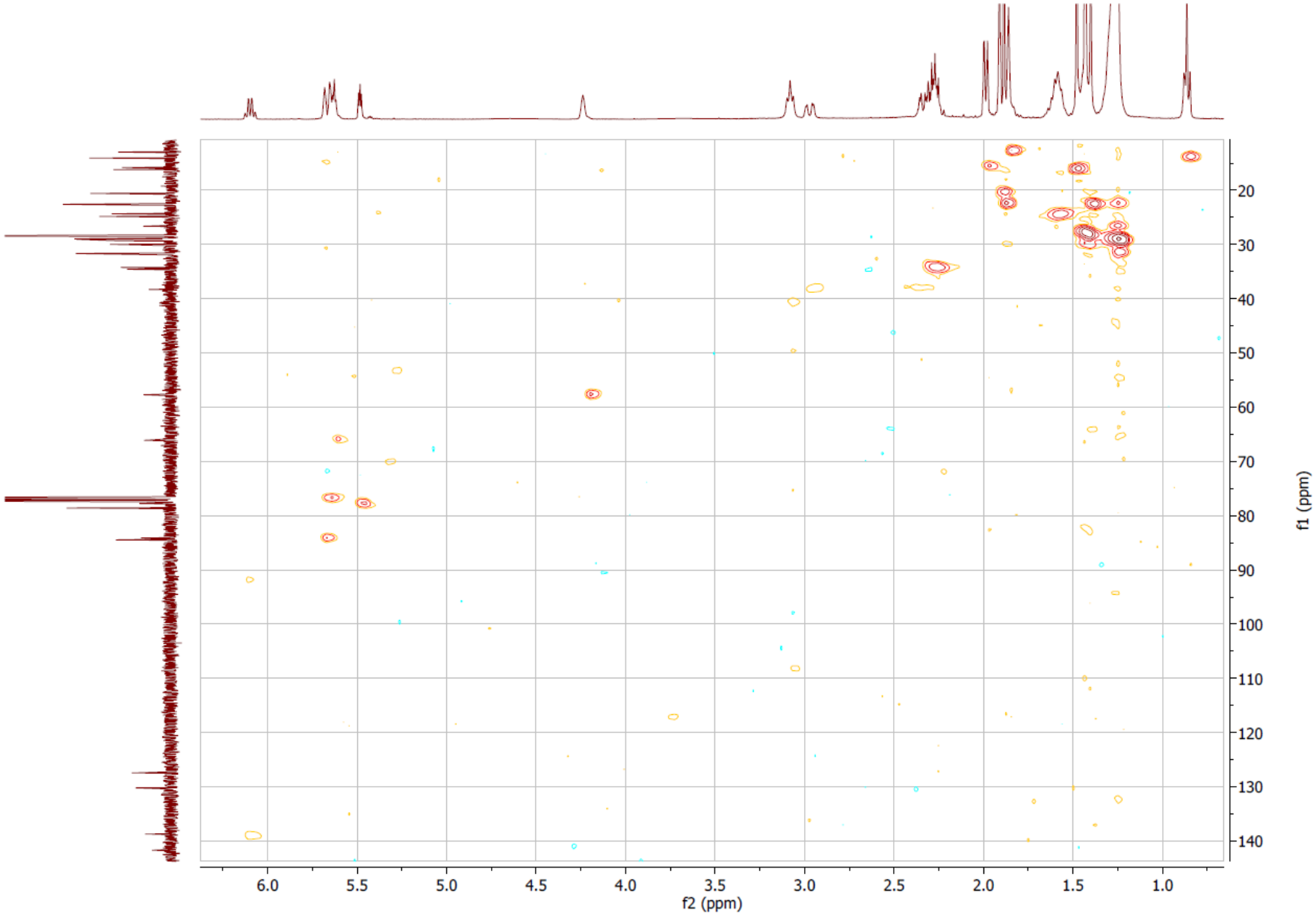


Figure S6C HMQC of product **6**

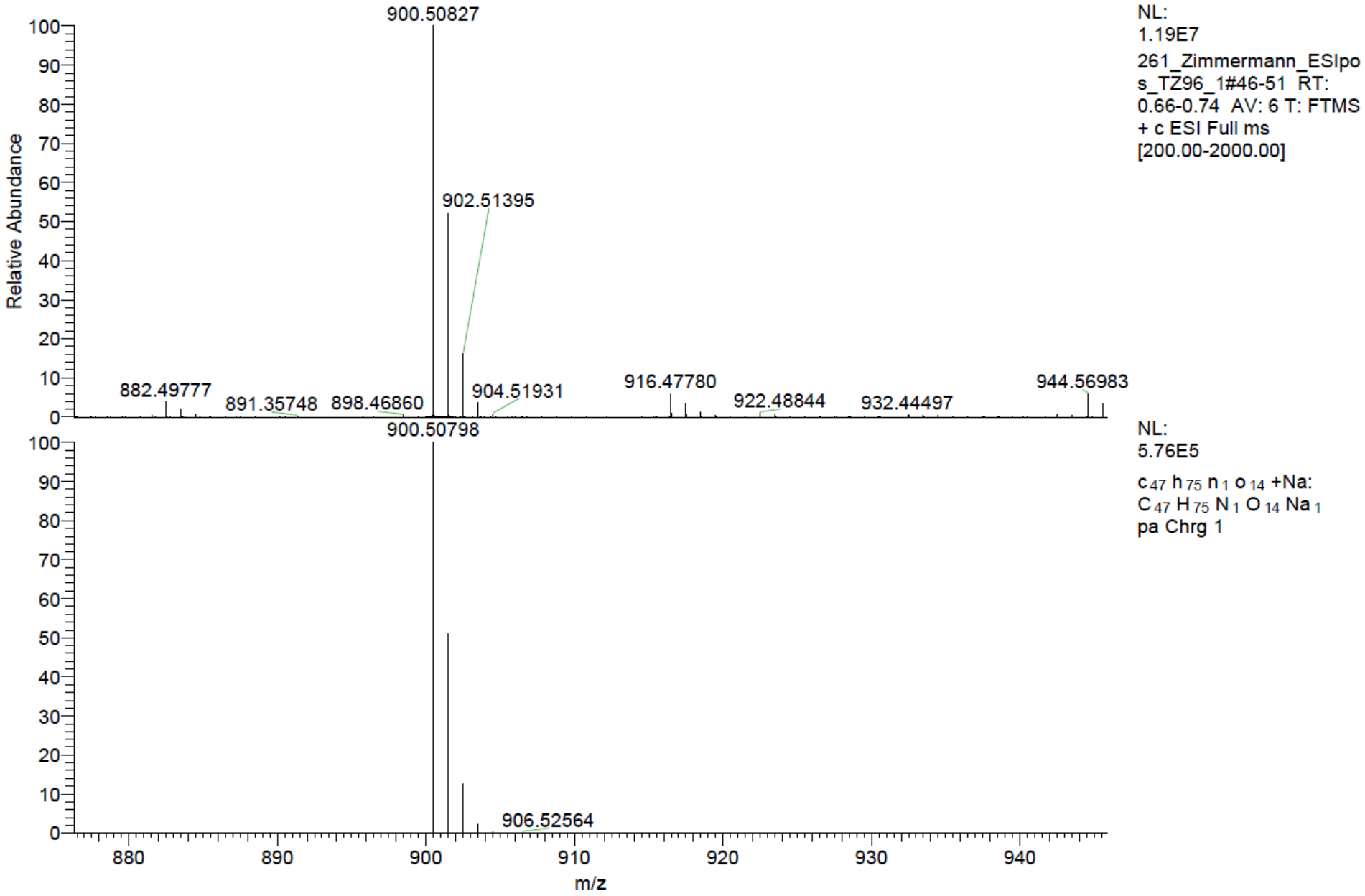


Figure S6D HRMS of product **6** - $[C_{47}H_{75}NO_{14}+Na]^+$ = 900.50827

Product **7** (8-*O*-(12-Aminododecanoyl)-8-*O*-debutanoyl thapsigargin)

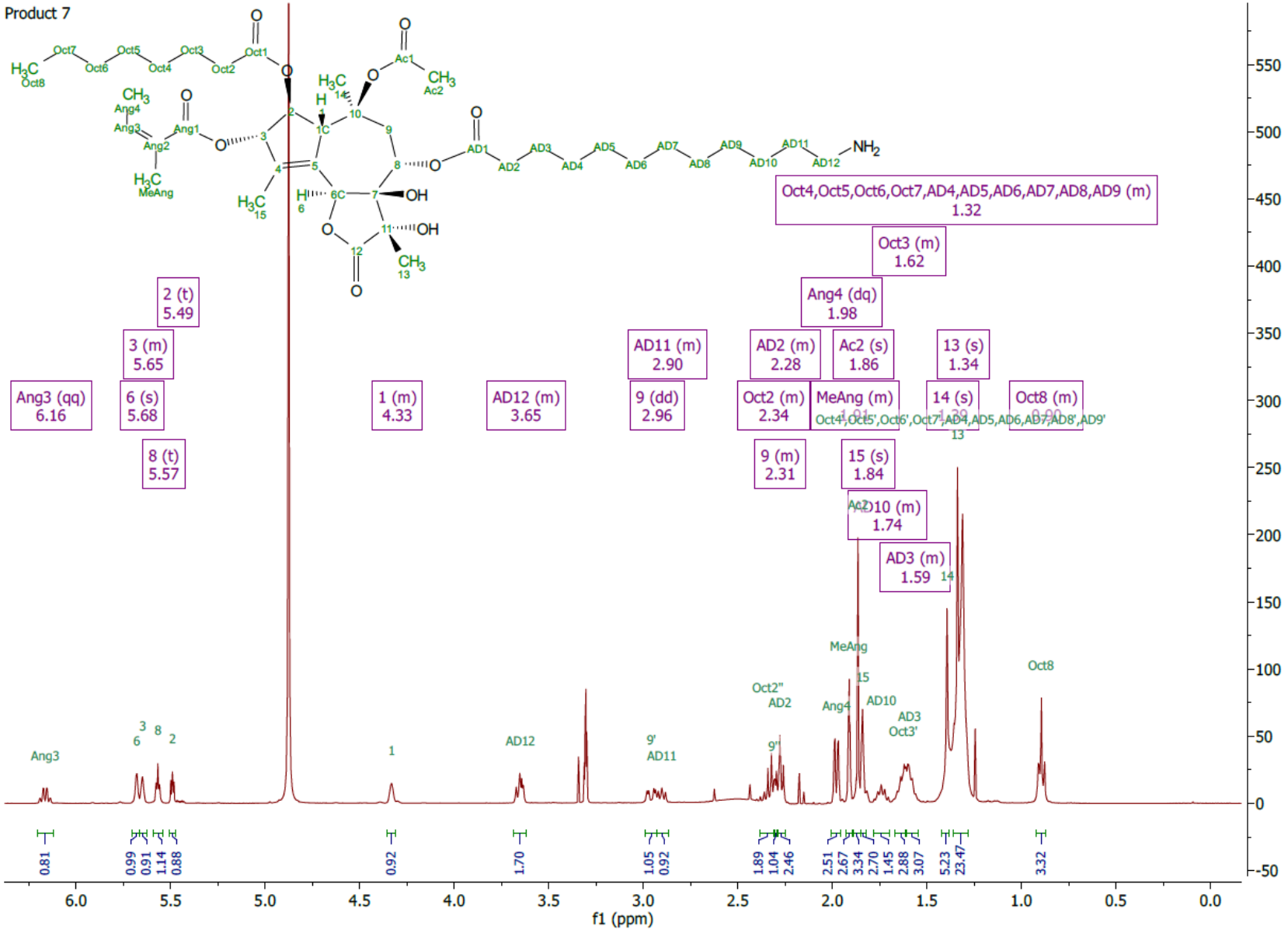


Figure S7A ^{1}H NMR of product **7** (400 MHz, CD_3OD)

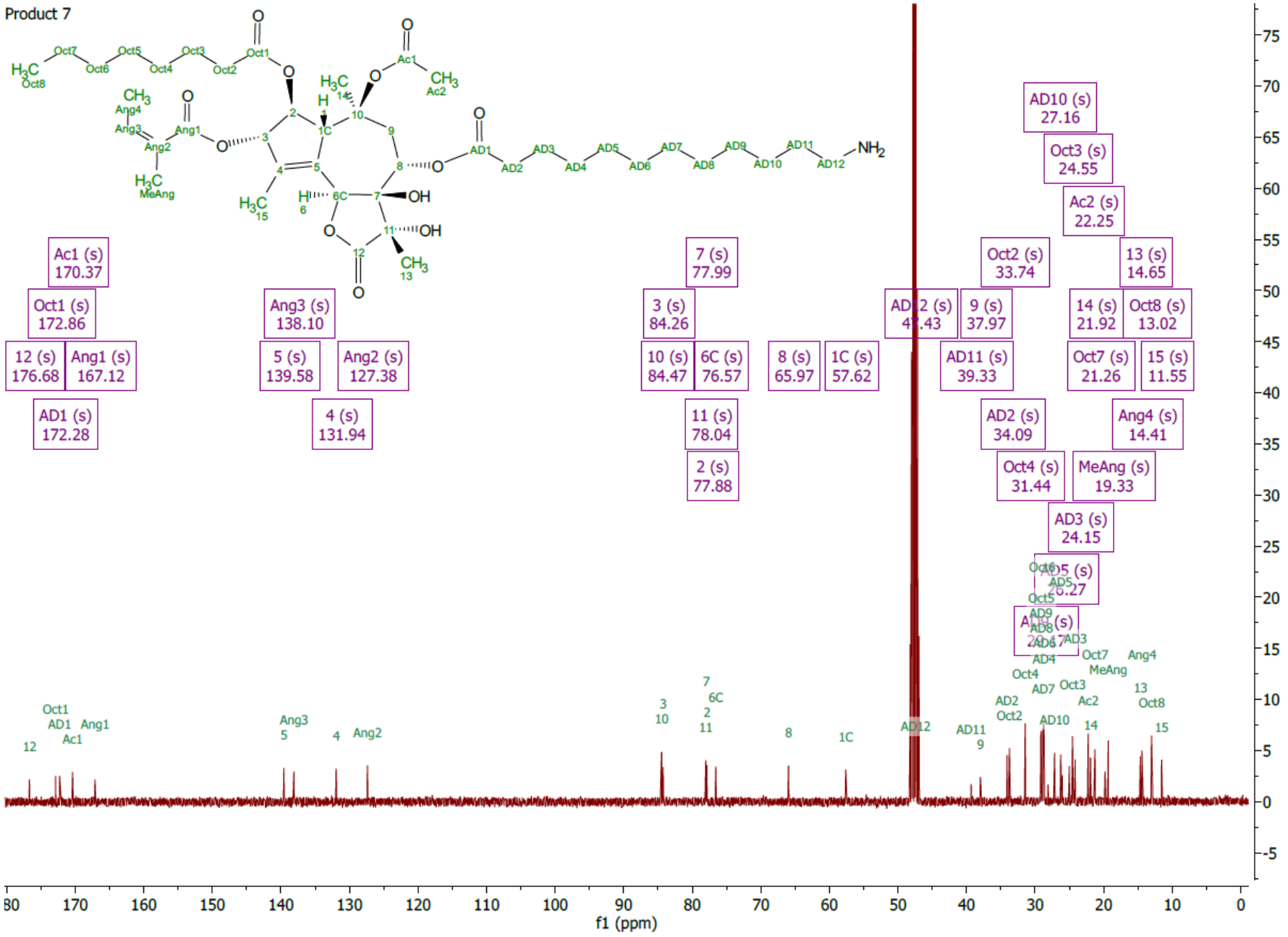


Figure S7B ^{13}C NMR of product **7** (100 MHz, CD_3OD)

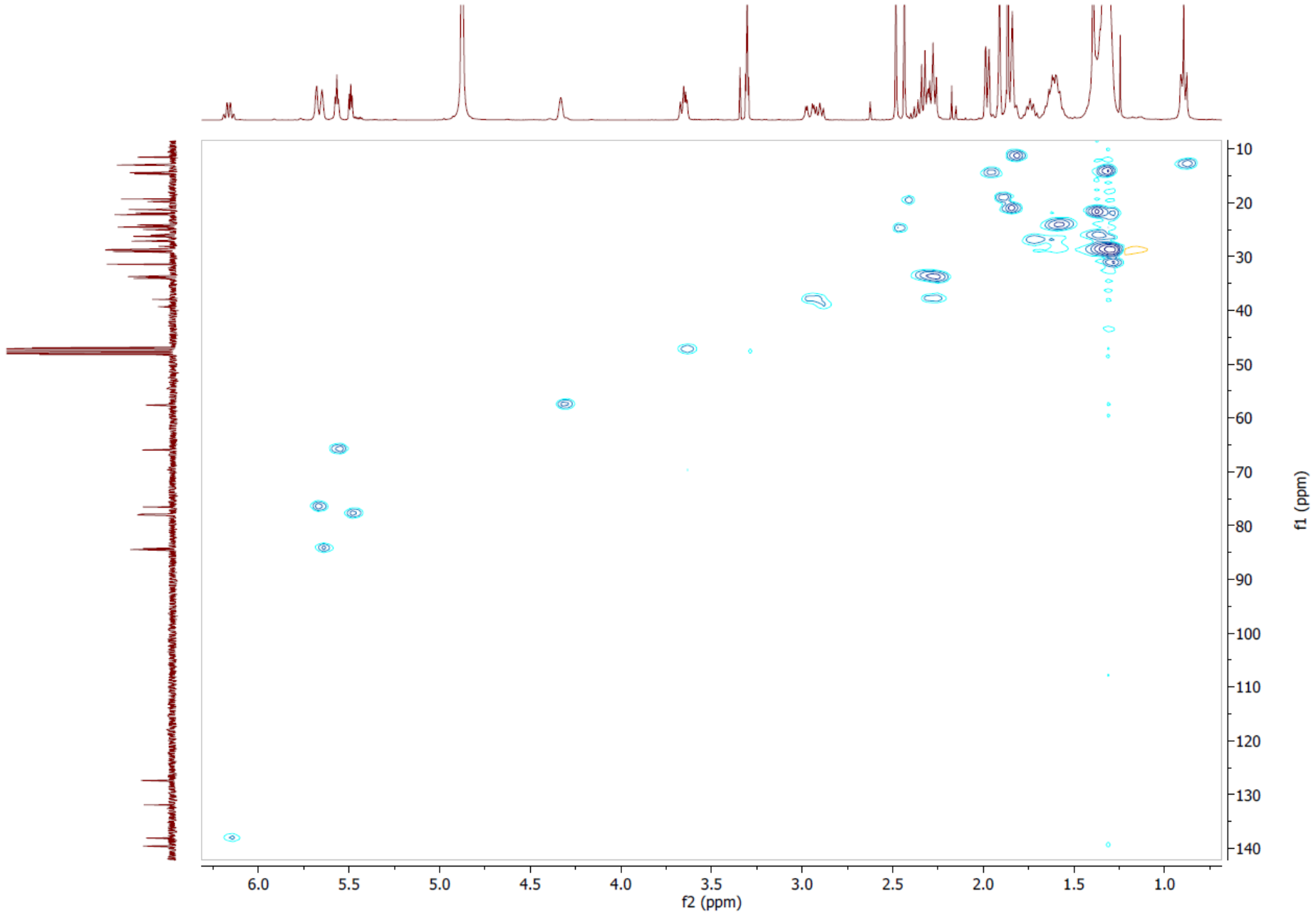


Figure S7C HMQC of product **7**

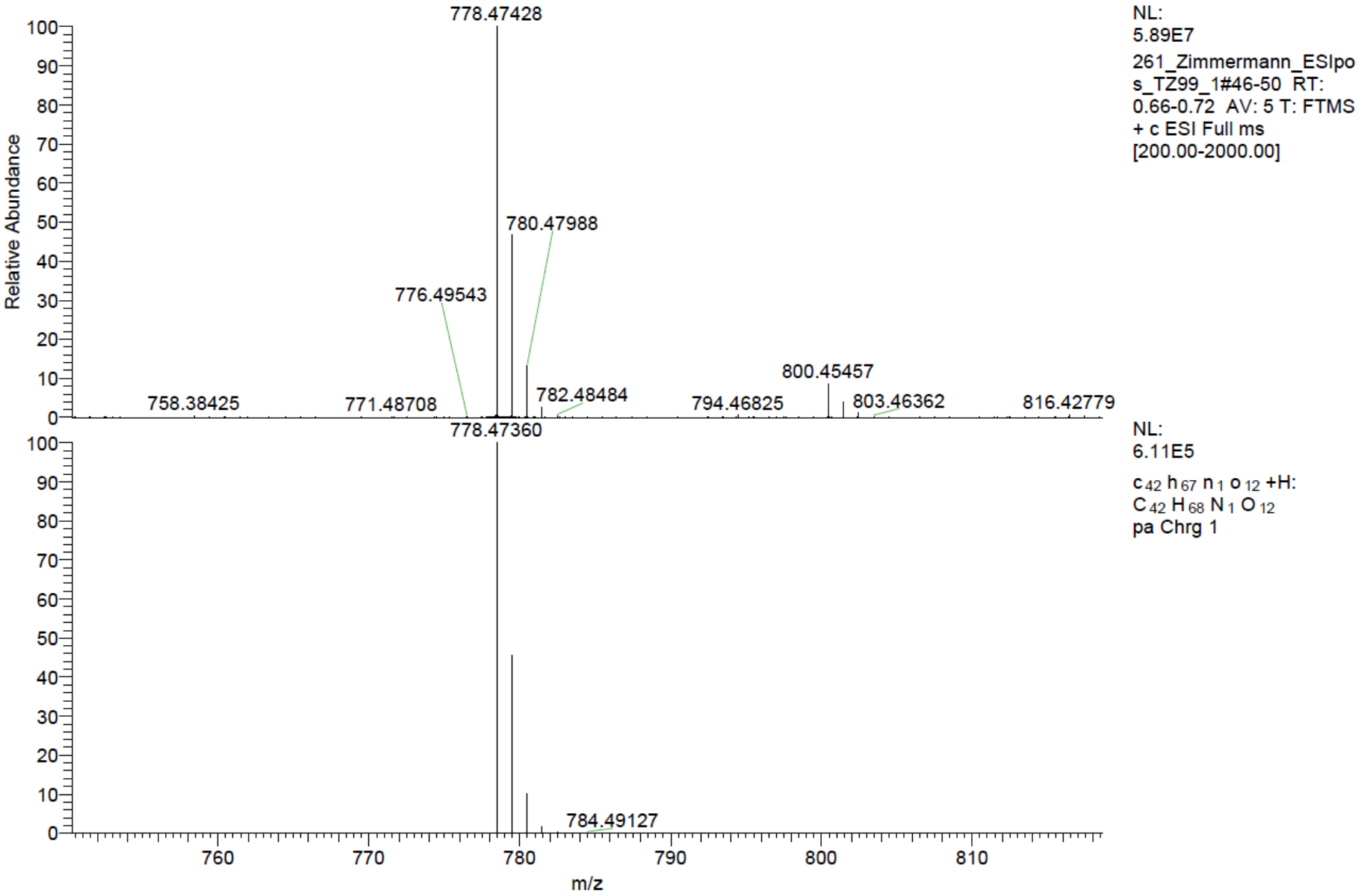


Figure S7D HRMS of product **7 -** $[C_{42}H_{67}NO_{12}+H]^+$ =778.47428

2,4,6-trichlorobenzoic (Z)-2-methylbut-2-enoic anhydride (**8**)

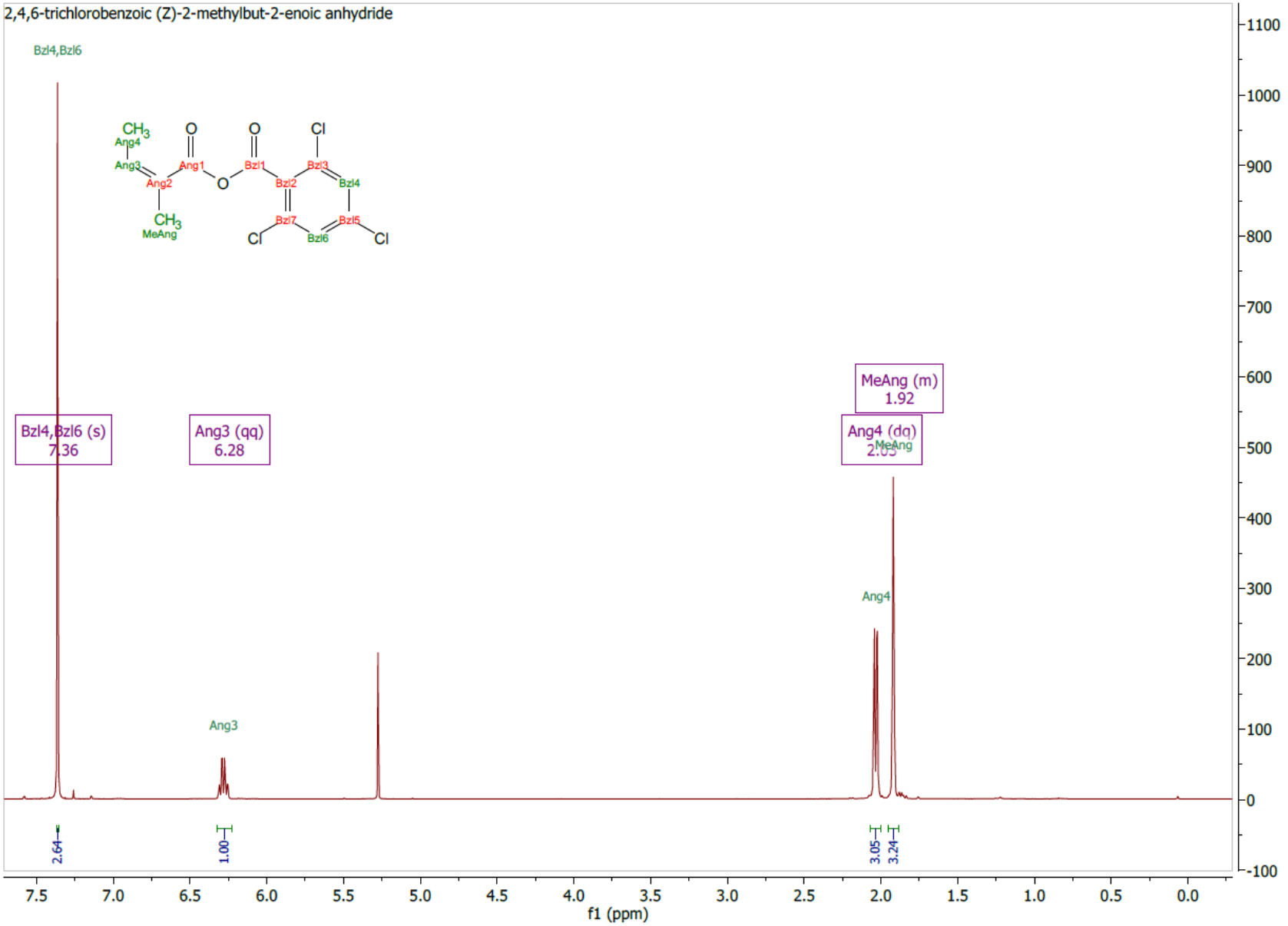


Figure S8A ^{1}H NMR of product **8** (400 MHz, CD_3Cl)

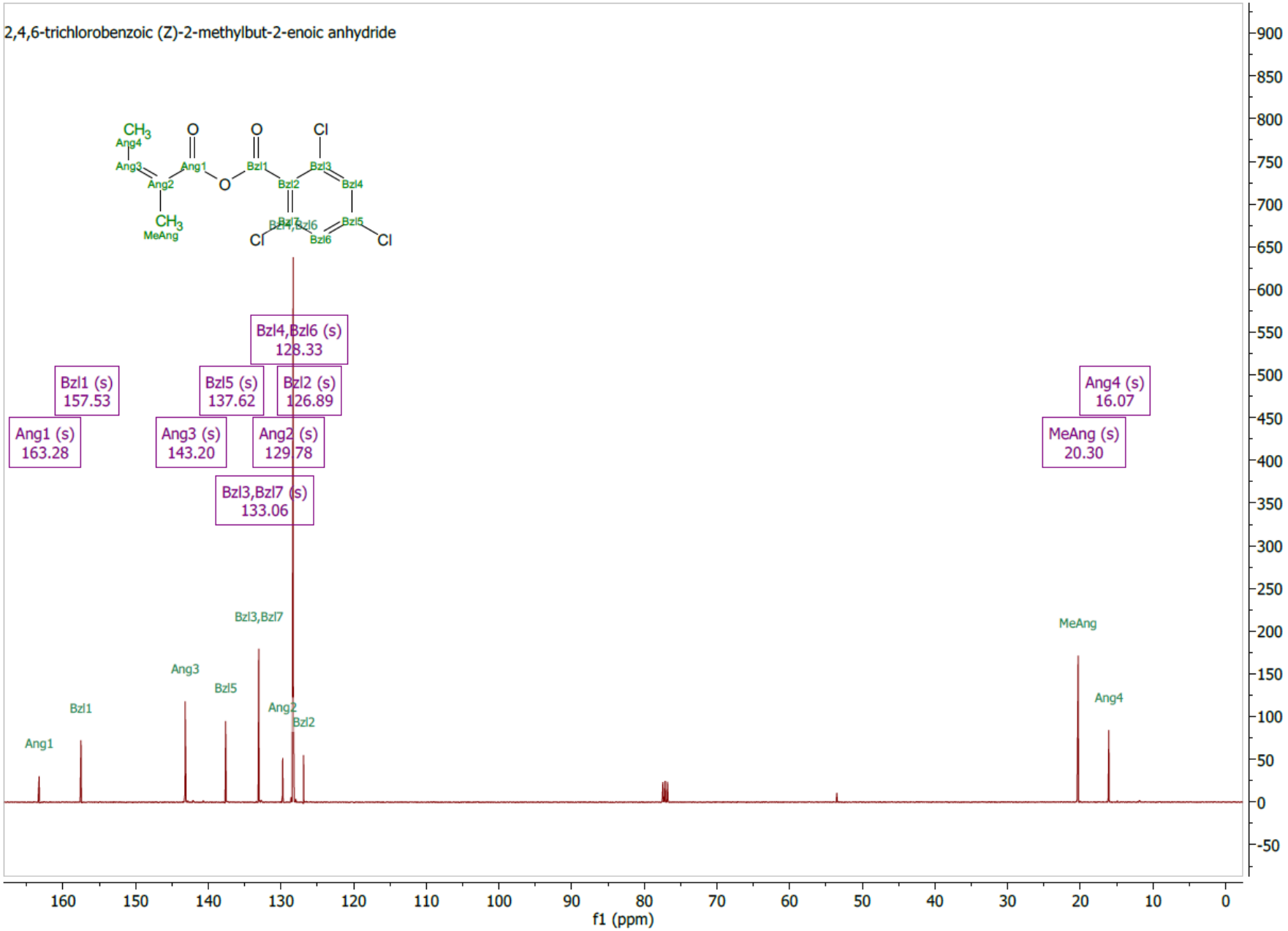


Figure S8B ^{13}C NMR of product **8** (100 MHz, CD_3Cl)

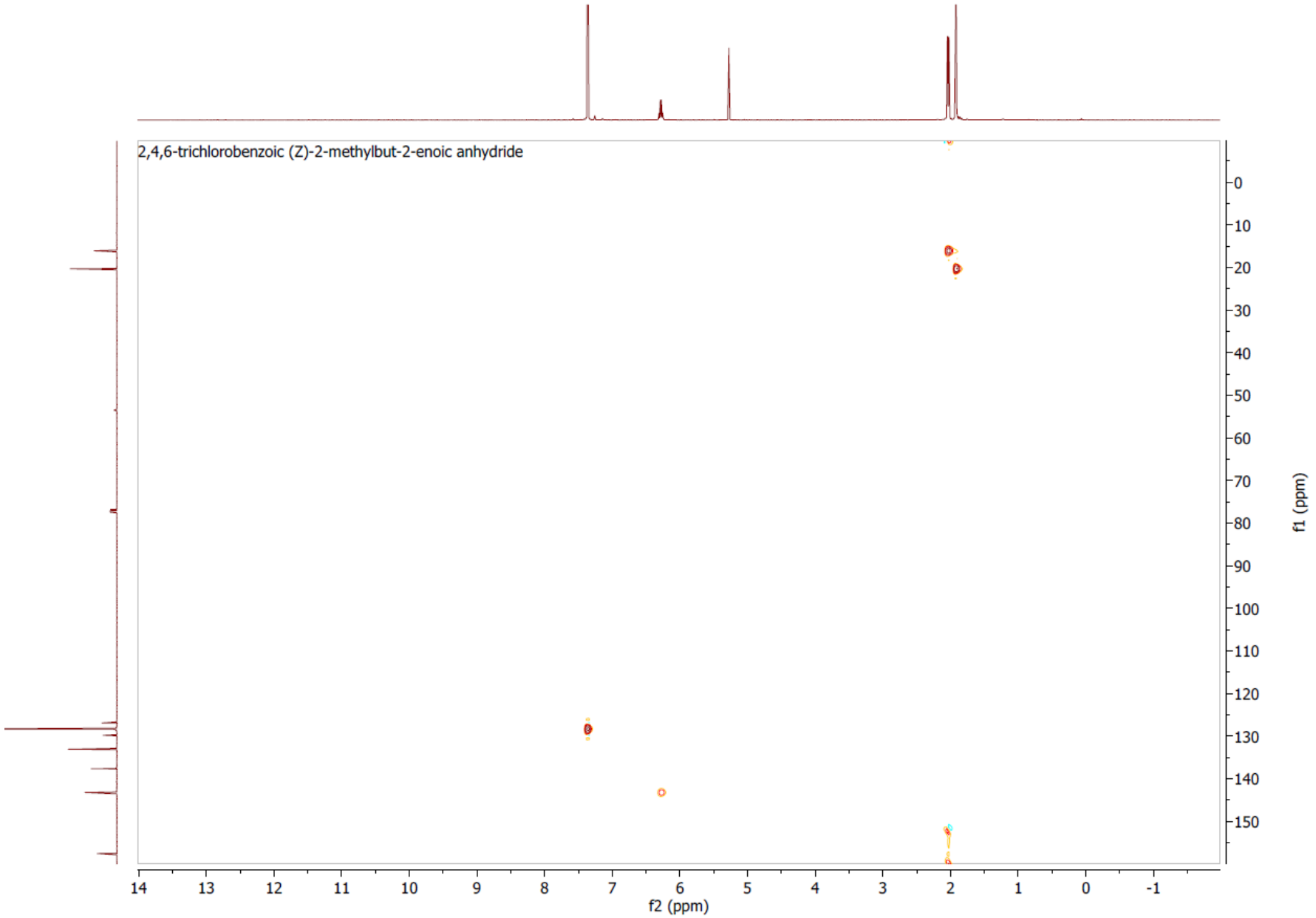


Figure S8C HMQC of product **8**

Boc-*N*-12-aminododecanoic acid (**9**)

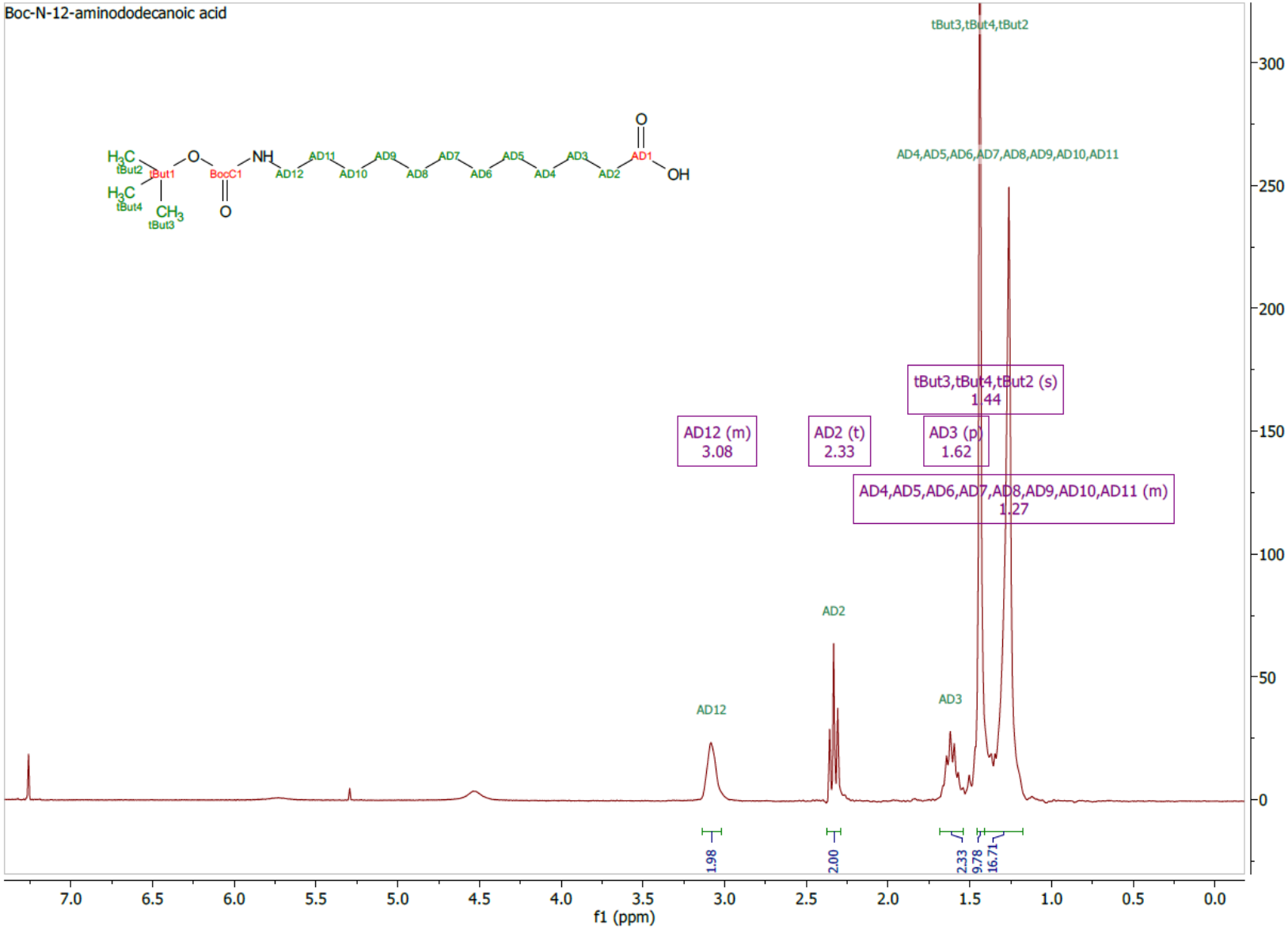


Figure S9A ^{1}H NMR of product **9** (400 MHz, CD_3Cl)

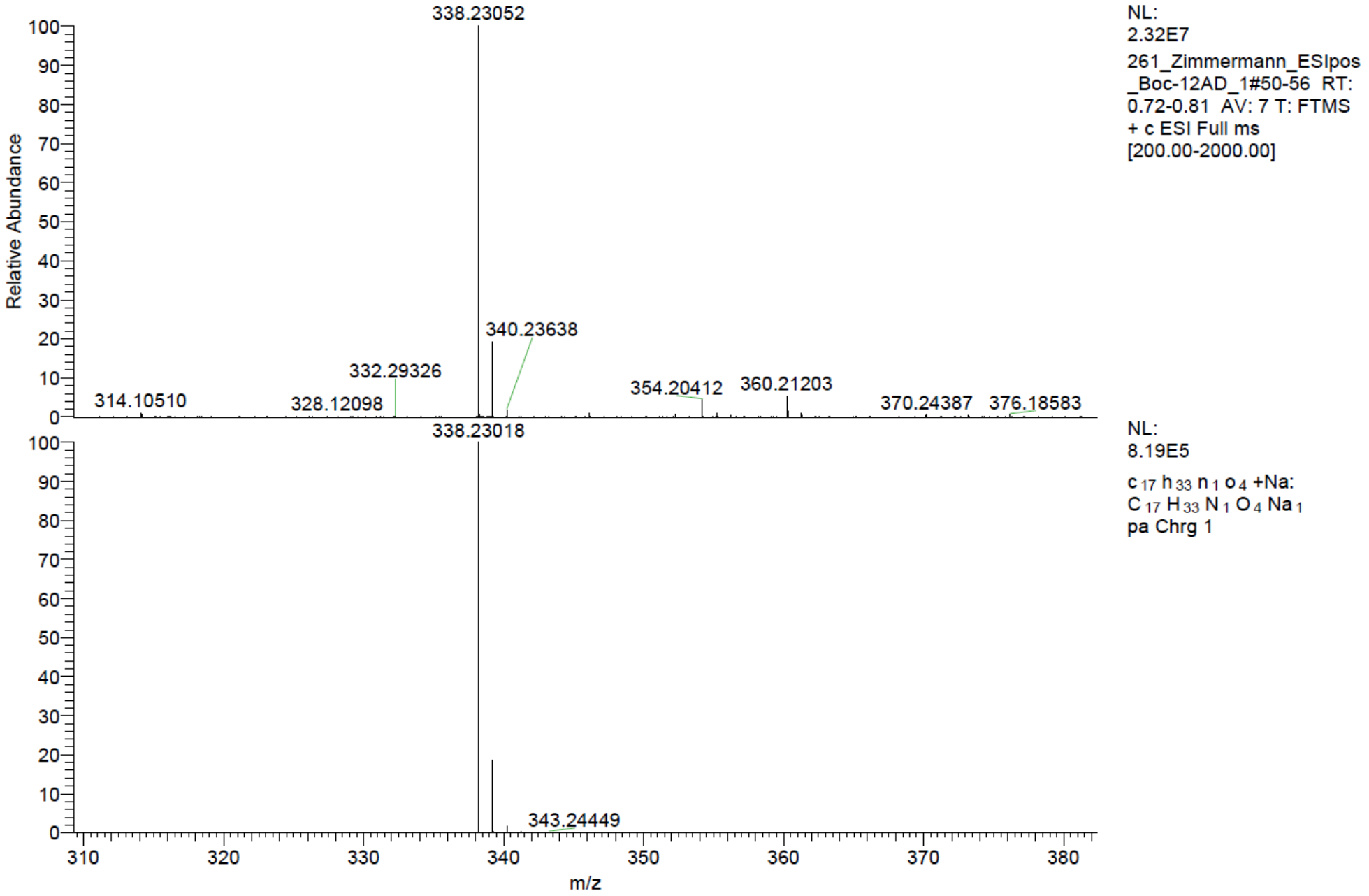
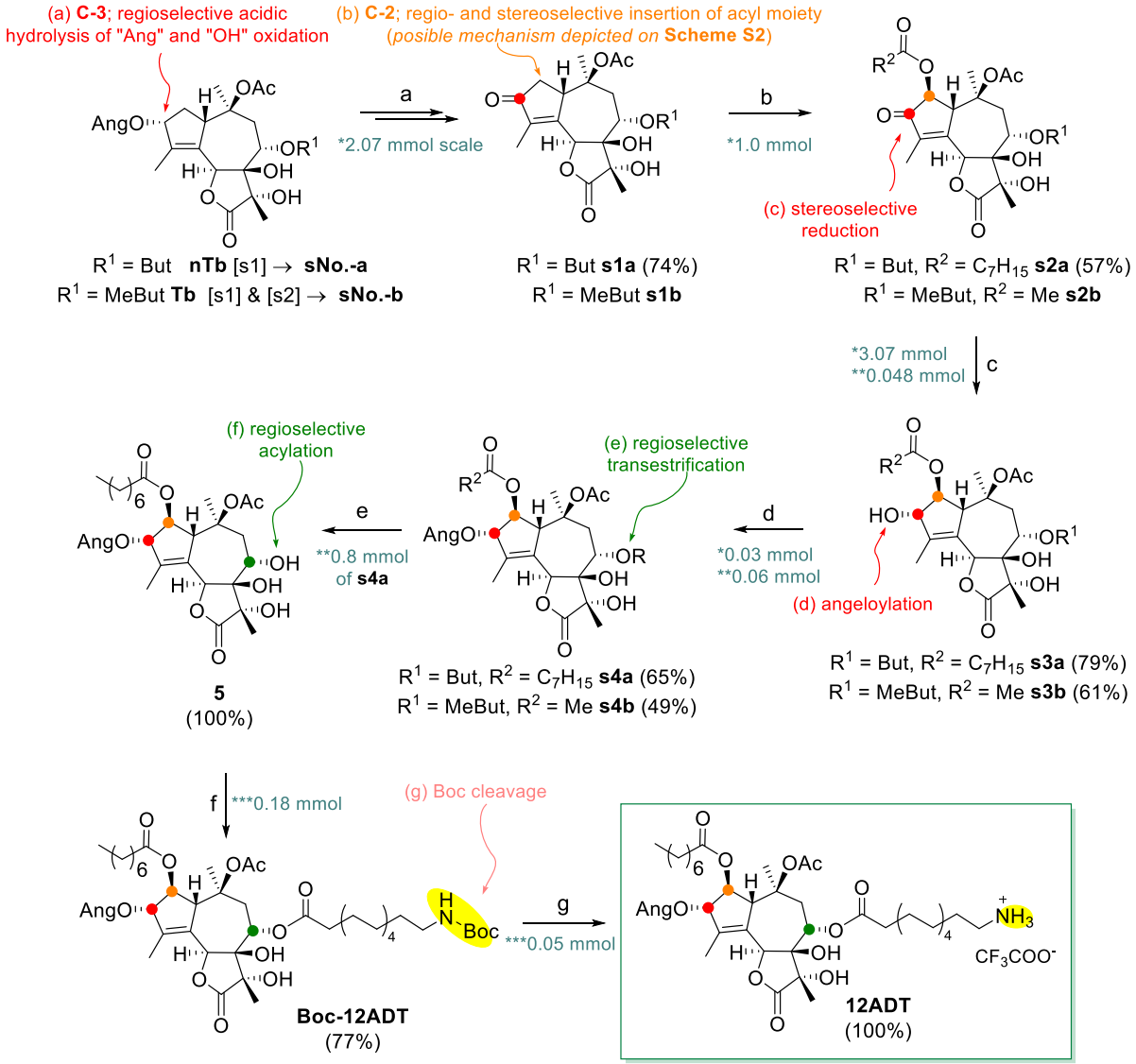
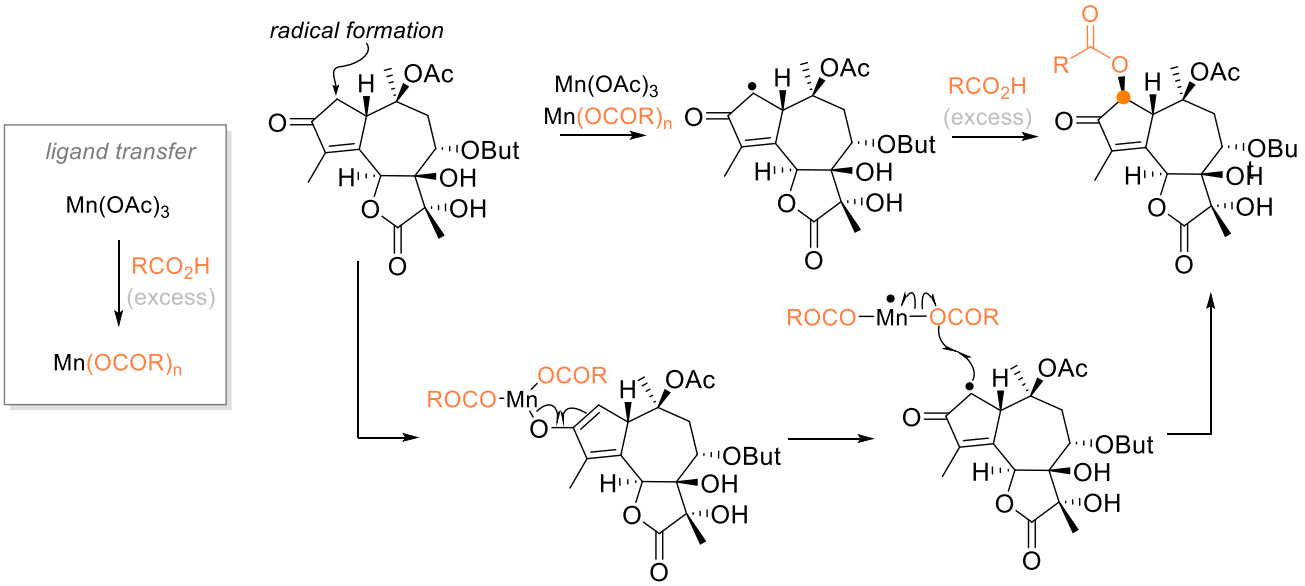


Figure S9B HRMS of product **9 -** $[C_{17}H_{33}NO_4+Na]^+ = 338.23052$



Scheme S1. The reactions addopted from the literature published [s1*, s2**, s3***]. *Reagents and conditions:* a) CrO_3, HF, AcCN, MW-95 °C, 2 h; b) octanoic acid, $Mn(OAc)_3 \cdot 2H_2O$, 120 °C, 6 h; c) $Zn(BH_4)_2$, Et_2O, -20 °C, 3.5 h, then H_2O; d) *in situ preparation of* 2,4,6-trichlorobenzoic (*Z*)-2-methylbut-2-enoic anhydride = acyl chloride, AngOH, TEA, in toluene; 90 °C, 18 h; e) TEA, MeOH, 0 °C→ 20 °C, 21 h; f) Boc-12-aminododecanoic acid, DCC, 4-DMAP, DCM, RT, 0 °C → RT, 6 h; g) TFA, DCM, H_2O, RT, 45 min. Under the arrows, the scale of the starting material is specified in green.



Scheme S2. Proposed mechanism of α-oxylation

References

[s1] Crestey, F.; Toma, M.; Christensen, S. B. Concise synthesis of thapsigargin from nortrilobolide. *Tetrahedron Lett.* **2015**, *56* (43), 5896-5898.
[s2] Doan, N. T. Q.; Crestey, F.; Olsen, C. E.; Christensen, S. B. Chemo- and regioselective functionalization of nortrilobolide: Application for semisynthesis of the natural product 2-acetoxytrilobolide. *J. Nat. Prod.* **2015**, 78 (6), 1406-1414.
[s3] Jakobsen, C. M.; Denmeade, S. R.; Isaacs, J. T.; Gady, A.; Olsen, C. E.; Christensen, S. B. Design, synthesis, and pharmacological evaluation of thapsigargin analogues for targeting apoptosis to prostatic cancer cells. *J. Med. Chem.* **2001**, *44*, 4696-4703.