

Supplementary Materials to Diversity-oriented synthesis catalyzed by diethylaminosulfur-trifluoride – preparation of new antitumorecdysteroid derivatives

Máté Vágvölgyi ^{1,a}, Endre Kocsis ^{1,a}, Márta Nové ², Nikoletta Szemerédi ², Gabriella Spengler ², Zoltán Kele ³, Róbert Berkecz ⁴, Tamás Gáti ⁵, Gábor Tóth ^{6,*}, and Attila Hunyadi ^{1,7,*}

¹ Institute of Pharmacognosy, Interdisciplinary Excellence Centre, University of Szeged, H-6720 Szeged, Hungary; vagvolgyi.mate@pharmacognosy.hu (M.V.); endrukocsi@gmail.com (E.K.)

² Department of Medical Microbiology and Immunobiology, University of Szeged, H-6720 Szeged, Hungary; nove.marta@gmail.com (M.N.); szemeredi.nikoletta@med.u-szeged.hu (N.S.); spengler.gabriella@med.u-szeged.hu (G.S.)

³ Department of Medical Chemistry, University of Szeged, H-6720, Szeged, Hungary; kele.zoltan@med.u-szeged.hu

⁴ Institute of Pharmaceutical Analysis, University of Szeged, H- 6720 Szeged, Hungary; berkecz.robert@szte.hu

⁵ Servier Research Institute of Medicinal Chemistry (SRIMC), H-1031 Budapest, Hungary; tamas.gati@hu.netgrs.com

⁶ Department of Inorganic and Analytical Chemistry, NMR Group, Budapest University of Technology and Economics, H-1111 Budapest, Hungary

⁷ Interdisciplinary Centre of Natural Products, University of Szeged, H-6720 Szeged, Hungary

^a shared first authorship by M.V. and E.K.

* Correspondence: hunyadi.a@pharmacognosy.hu (A.H.); and drtothgabor@t-online.hu (G.T.)

Table of contents

Figure S1. Compound **4**, ¹H NMR CDCl₃ 600 MHz and selTOCSY on H-5, H-12 and H-7.

Figure S2. Compound **4**, steric proximities detected by selNOESY on signals αMe, H₃-19 and H₃-18.

Figure S3. Compound **4**, DEPTQ 150 MHz.

Figure S4. Compound **4**, edHSQC and edHSQC CH₂ section.

Figure S5. Compound **4**, HMBC and HMBC CH₃ section.

Figure S6. Compound **5**, ¹H NMR CDCl₃ 600 MHz and selTOCSY on H-17.

Figure S7. Compound **5**, Steric proximities detected by selNOESY on signals αMe, H₃-19 and H₃-18.

Figure S8. Compound **5**, DEPTQ 150 MHz.

Figure S9. Compound **5**, edHSQC and edHSQC CH₂ section.

Figure S10. Compound **5**, HMBC and HMBC CH₃ section.

Figure S11. Compound **6**, ¹H NMR CDCl₃ 600 MHz.

Figure S12. Compound **6**, steric proximities detected by selNOESY on signals αMe, H₃-19 and H₃-18.

Figure S13. Compound **6**, DEPTQ 150 MHz.

Figure S14. Compound **6**, edHSQC and edHSQC CH₂ section.

Figure S15. Compound **6**, HMBC and HMBC CH₃ section.

Figure S16. Compound **7**, ¹H NMR CDCl₃ 500 MHz and steric proximities detected by selROESY on signals H₃-19 and H₃-18.

Figure S17. Compound **7**, DEPTQ 125 MHz.

Figure S18. Compound **7**, edHSQC and edHSQC CH₂ section.

Figure S19. Compound **7**, HMBC and HMBC CH₃ section.

Figure S20. Compound **10**, ¹H NMR CDCl₃ 600 MHz and selTOCSY on H-15 and H α -1.

Figure S21. Compound **10**, steric proximities detected by selNOESY on signals β Me, H₃-19 and H₃-18.

Figure S22. Compound **10**, DEPTQ 150 MHz.

Figure S23. Compound **10**, edHSQC.

Figure S24. Compound **10**, HMBC.

Figure S25. Compound **10**, edHSQC CH₂ section and HMBC CH₃ section.

Figure S26. Compound **11**, ¹H NMR CDCl₃ 600 MHz.

Figure S27. Compound **11**, steric proximities detected by selNOESY on signals β Me, H₃-19 and H₃-18.

Figure S28. Compound **11**, DEPTQ 150 MHz.

Figure S29. Compound **11**, edHSQC.

Figure S30. Compound **11**, HMBC.

Figure S31. Compound **11**, edHSQC CH₂ section and HMBC CH₃ section.

Figure S32. Compound **13**, ¹H NMR CDCl₃ 600 MHz and selTOCSY on H-17 and H-3.

Figure S33. Compound **13**, steric proximities detected by selROESY on signals H₃-19 and H₃-18.

Figure S34. Compound **13**, DEPTQ 150 MHz.

Figure S35. Compound **13**, edHSQC.

Figure S36. Compound **13**, HMBC.

Figure S37. Compound **13**, edHSQC CH₂ section and HMBC CH₃ section.

Figure S38. Compound **14**, ¹H CDCl₃ 600 MHz.

Figure S39. Compound **14**, Identification of spin-systems of **A**, **C** and **D** rings by selTOCSY on H-3, H-9 and H-17.

Figure S40. Compound **14**, steric proximities detected by selNOE on CH₃-19, CH₃-18 and NH signals.

Figure S41. Compound **14**, DEPTQ 150 MHz.

Figure S42. Compound **14**, edHSQC.

Figure S43. Compound **14**, edHSQC section with inserted selTOCSY on H-17.

Figure S44. Compound **14**, HMBC.

Figure S45. Compound **17**, ¹H DMSO-d₆ 600 MHz.

Figure S46. Compound **17**, Steric proximities detected by selNOE on CH₃-19 and CH₃-18 and selTOCSY on H-2 signals.

Figure S47. Compound **17**, DEPTQ 150 MHz.

Figure S48. Compound **17**, HSQC.

Figure S49. Compound **17**, HMBC and HMBC CH₃ section.

Figure S50. Compound **19**, ¹H CDCl₃ 500 MHz.

Figure S51. Compound **19**, ¹H,¹H-COSY and selROE on H_α-3.

Figure S52. Compound **19**, APT 125 MHz.

Figure S53. Compound **19**, HSQC section with inserted band-selective HSQC measurements of 37–36 and 40–39 ppm.

Figure S54. Compound **19**, edHSQC section with inserted selROE on H₃-18.

Figure S55. Compound **19**, HMBC and HMBC CH₃ section.

Figure S56. Compound **4**, HR-MS spectra.

Figure S57. Compound **5**, HR-MS spectra.

Figure S58. Compound **6**, HR-MS spectra.

Figure S59. Compound **7**, HR-MS spectra.

Figure S60. Compound **10**, HR-MS spectra.

Figure S61. Compound **11**, HR-MS spectra.

Figure S62. Compound **13**, HR-MS spectrum.

Figure S63. Compound **14**, HR-MS spectrum.

Figure S64. Compound **17**, HR-MS spectrum.

Figure S65. Compound **3**, HPLC chromatogram at its UV absorbance maximum ($\lambda=242.6$ nm). Purity: 95.1 %.

Figure S66. Compound **4**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 97.5 %.

Figure S67. Compound **5**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 97.5 %.

Figure S68. Compound **6**, HPLC chromatogram at its UV absorbance maximum ($\lambda=327.5$ nm). Purity: 95.2 %.

Figure S69. Compound **7**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 95.4 %.

Figure S70. Compound **9**, HPLC chromatogram at its UV absorbance maximum ($\lambda=242.6$ nm). Purity: 98.0 %.

Figure S70. Compound **10**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 99.5 %.

Figure S72. Compound **11**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 99.3 %.

Figure S73. Compound **13**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 98.4 %.

Figure S74. Compound **14**, HPLC chromatogram at its UV absorbance maximum ($\lambda=240$ nm). Purity: 97.7 %.

Figure S75. Compound **16**, HPLC chromatogram at its UV absorbance maximum ($\lambda=220.8$ nm). Purity: 98.4 %.

Figure S76. Compound **17**, HPLC chromatogram at its UV absorbance maximum ($\lambda=358.5$ nm). Purity: 98.1 %.

Figure S1. Compound 4, ^1H NMR CDCl_3 600 MHz and selTOCSY on H-5, H-12 and H-7.

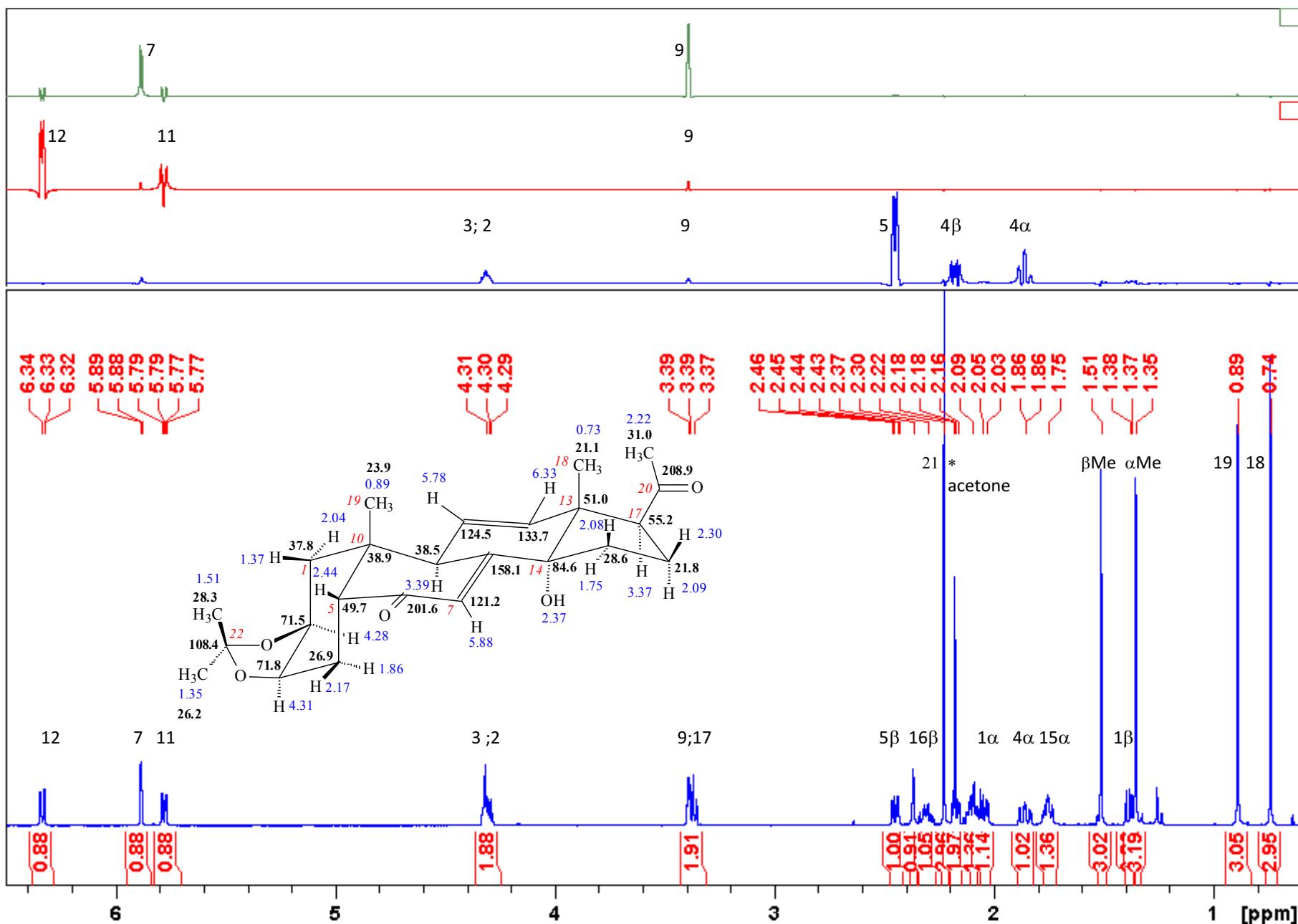


Figure S2. Compound 4, steric proximities detected by selNOESY on signals α Me, H₃-19 and H₃-18.

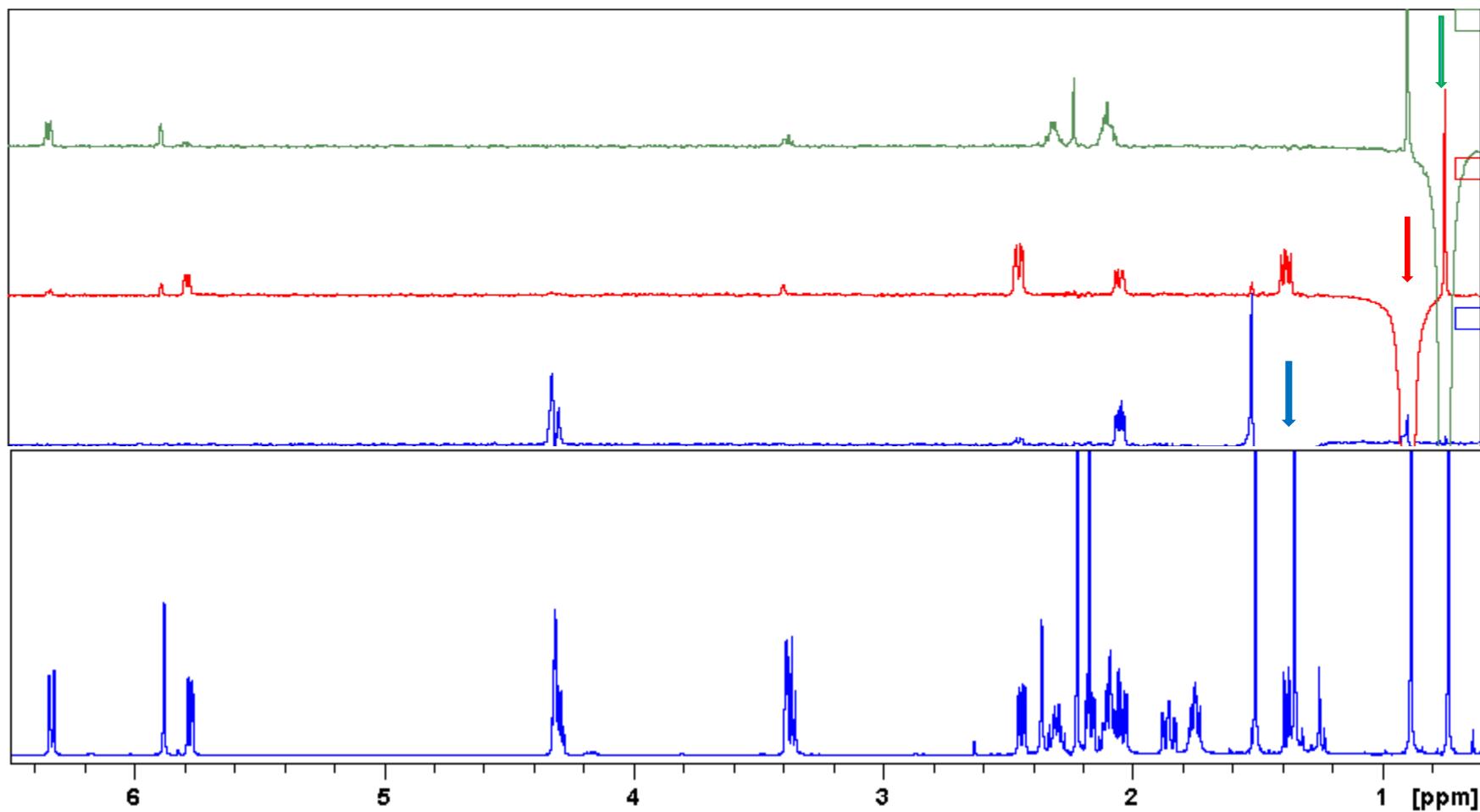
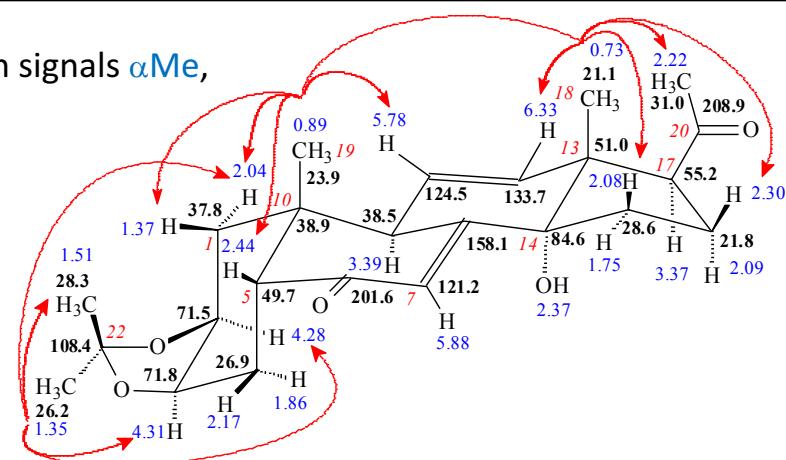


Figure S3. Compound 4, DEPTQ 150 MHz.

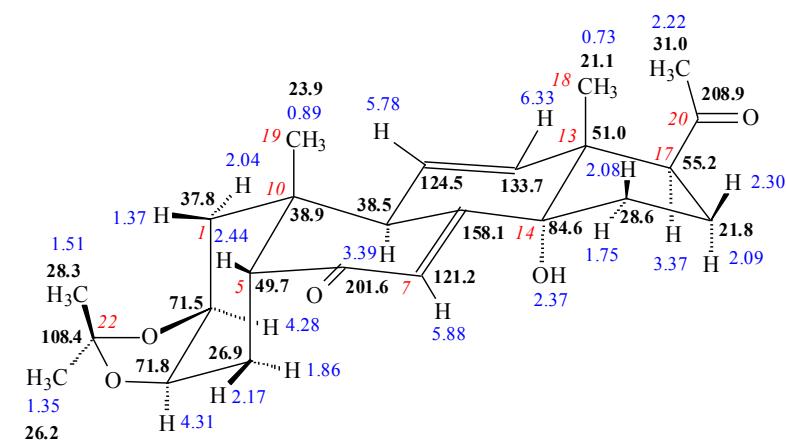


Figure S4. Compound 4, edHSQC and edHSQC CH_2 section.

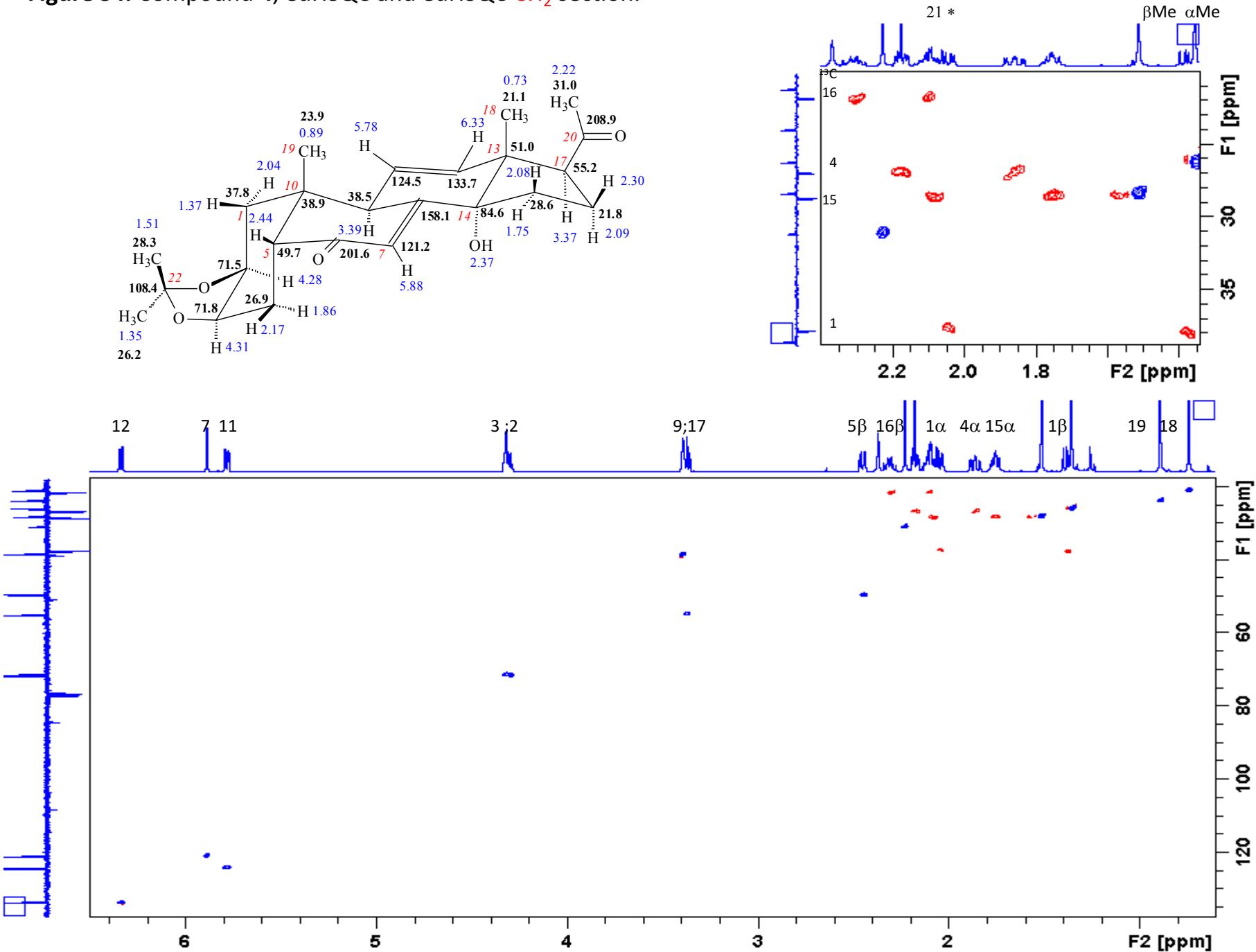


Figure S5. Compound 4, HMBC and HMBC CH₃ section.

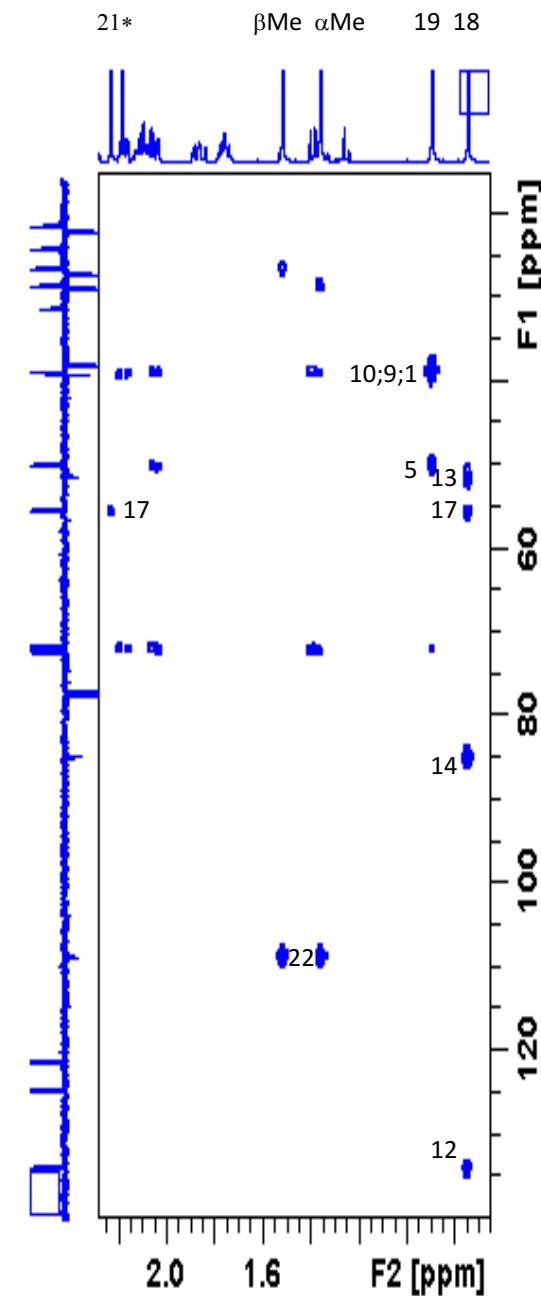
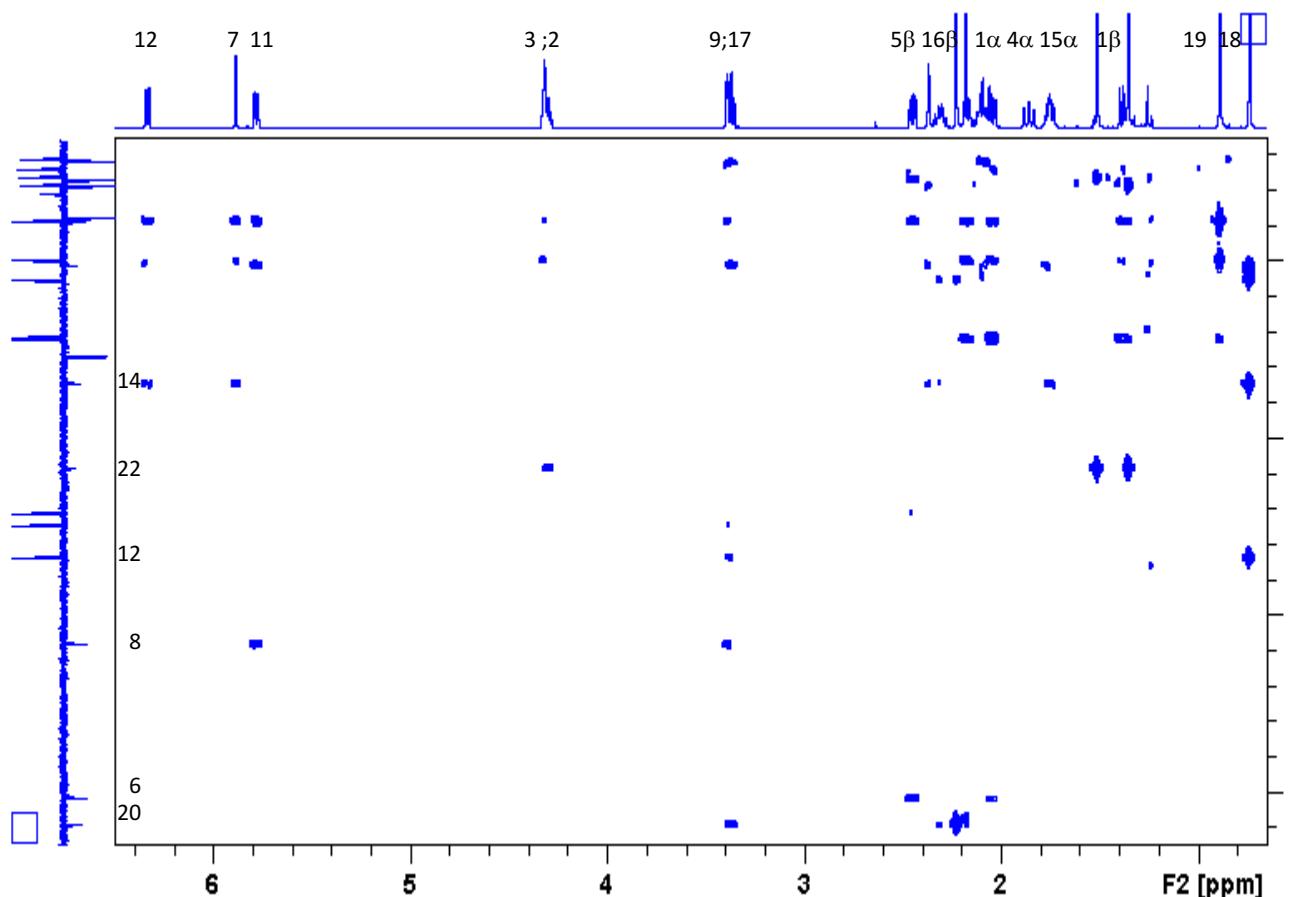
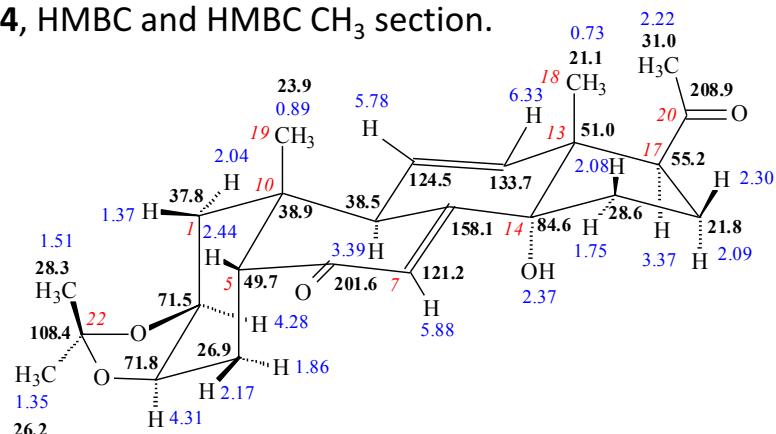


Figure S6. Compound 5, ^1H NMR CDCl_3 600 MHz and selTOCSY on H-17.

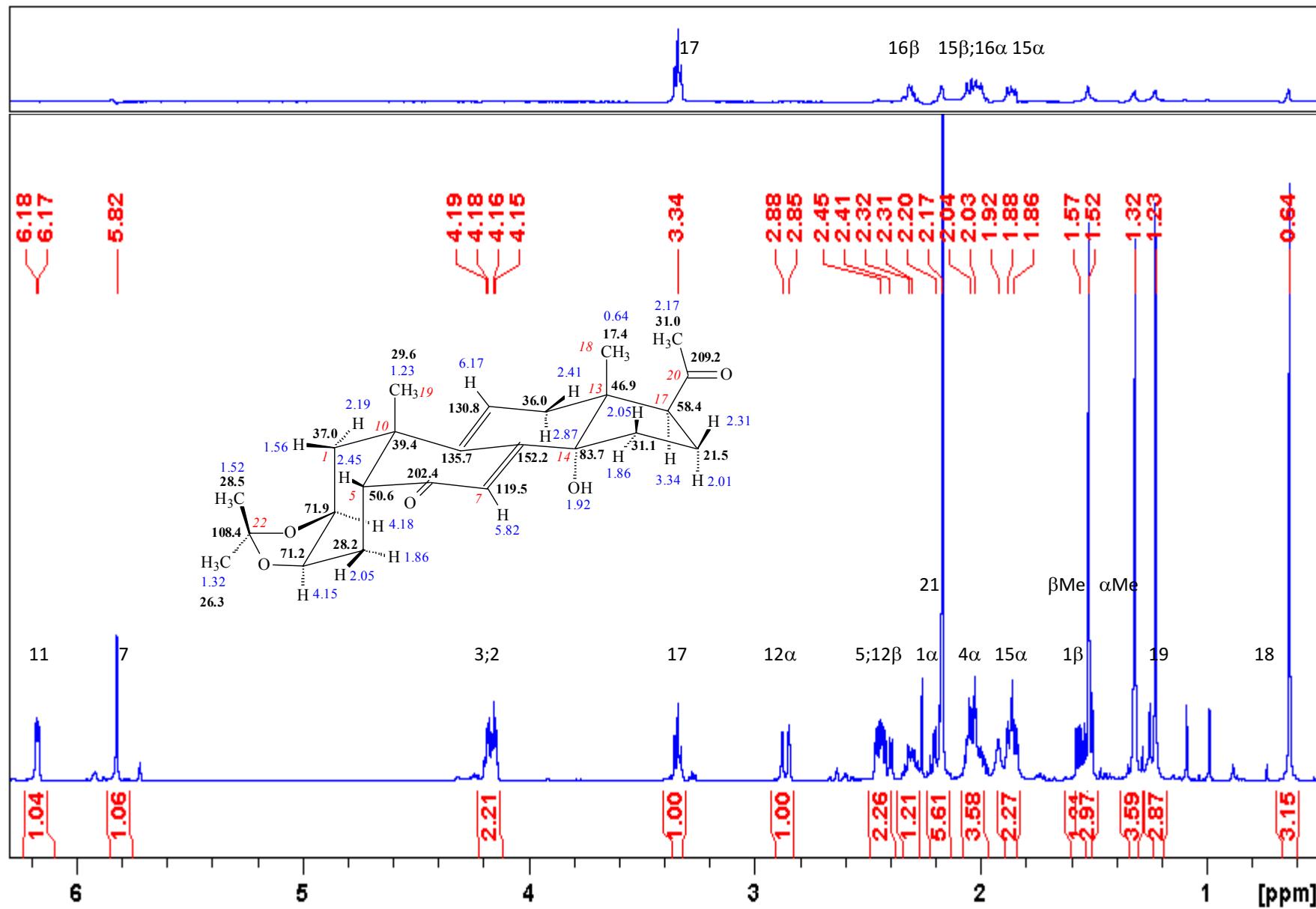


Figure S7. Compound 5, steric proximities detected by selNOESY on signals

α Me, H₃-19 and H₃-18.

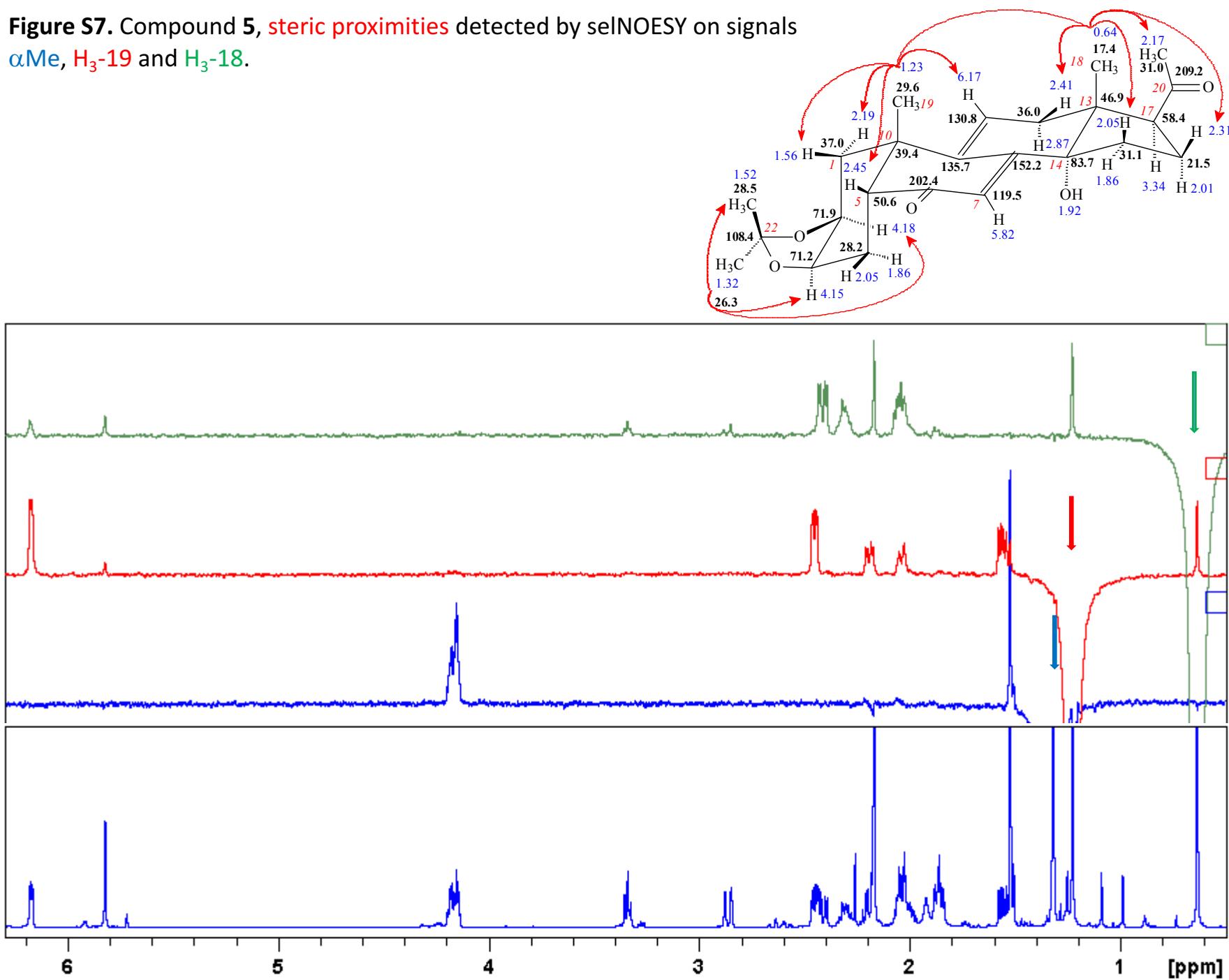


Figure S8. Compound 5, DEPTQ 150 MHz.

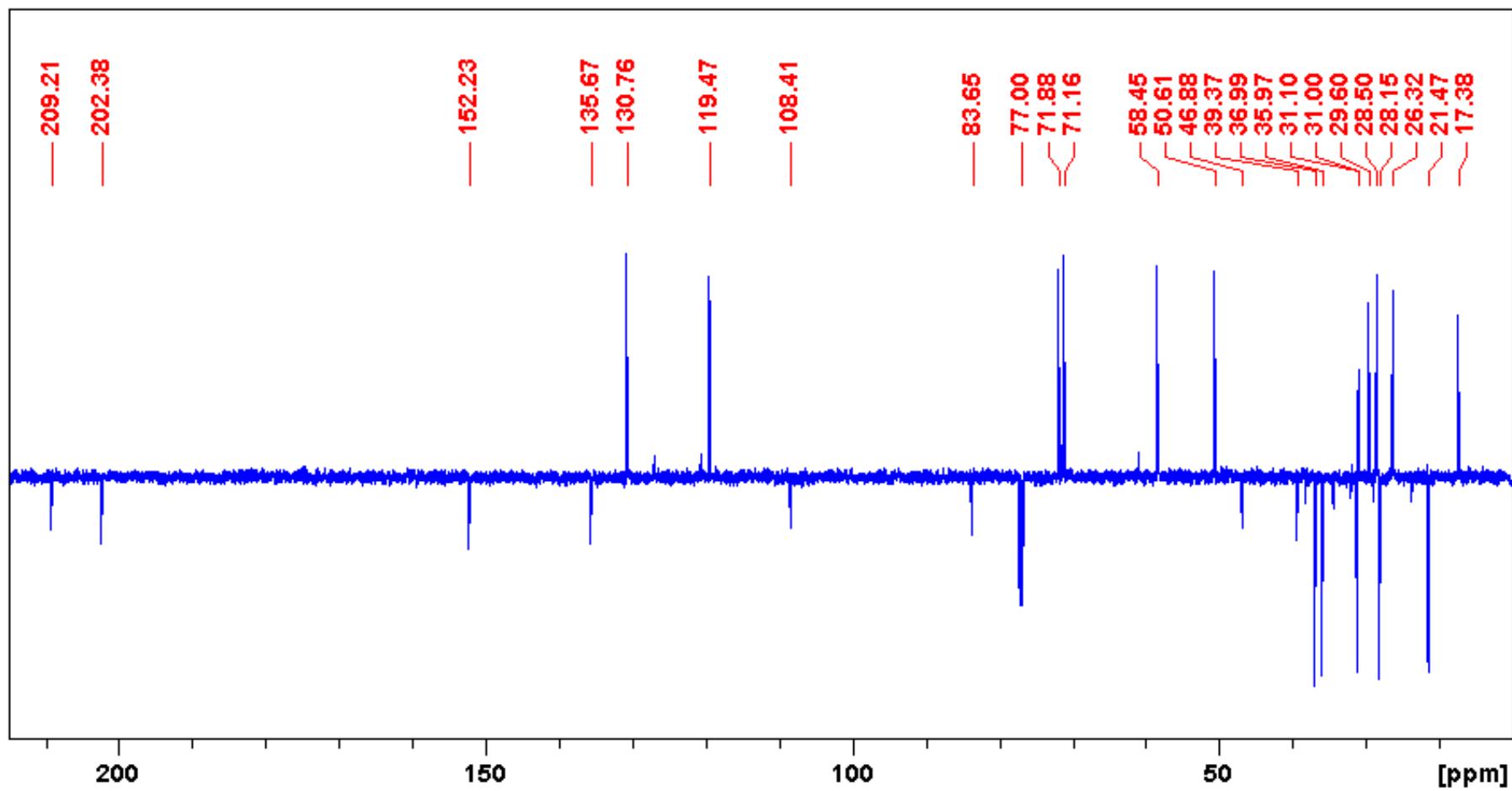
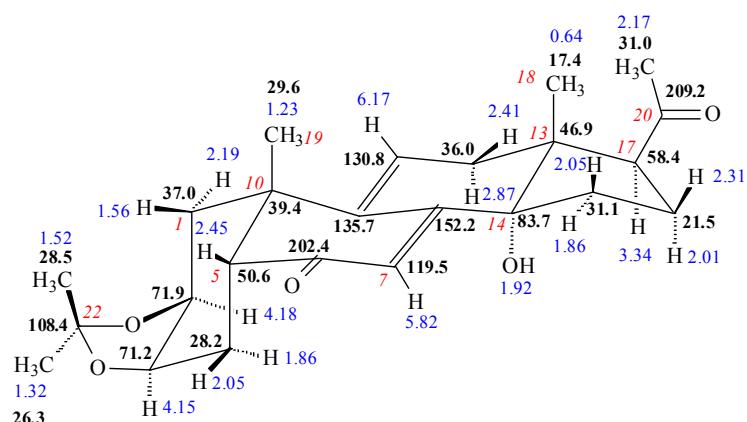


Figure S9. Compound 5, edHSQC and edHSQC CH_2 section.

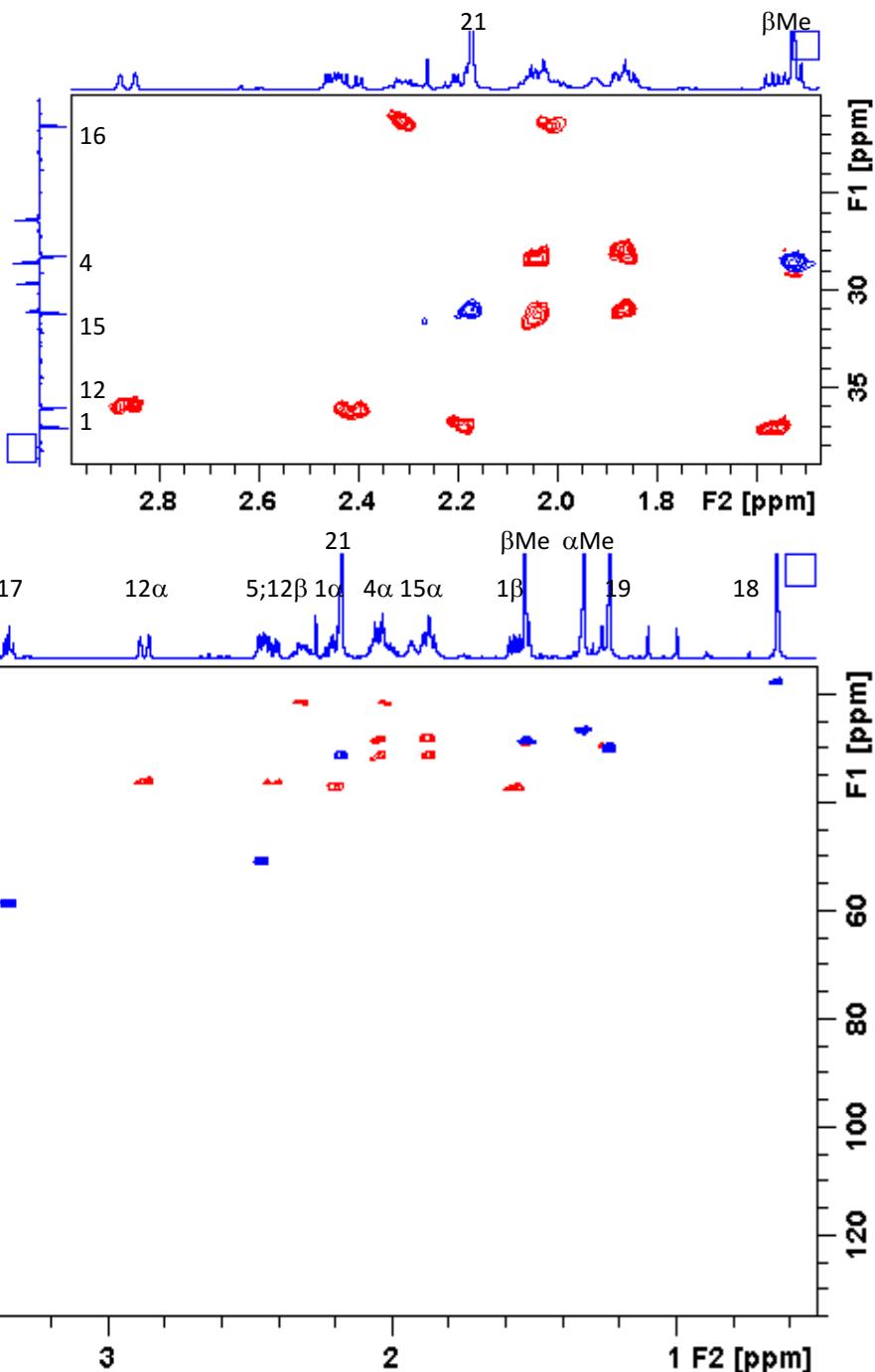
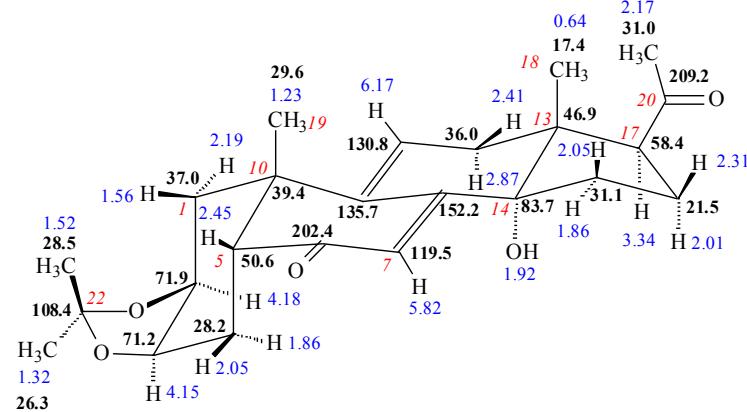


Figure S10. Compound 5, HMBC and HMBC CH₃ section.

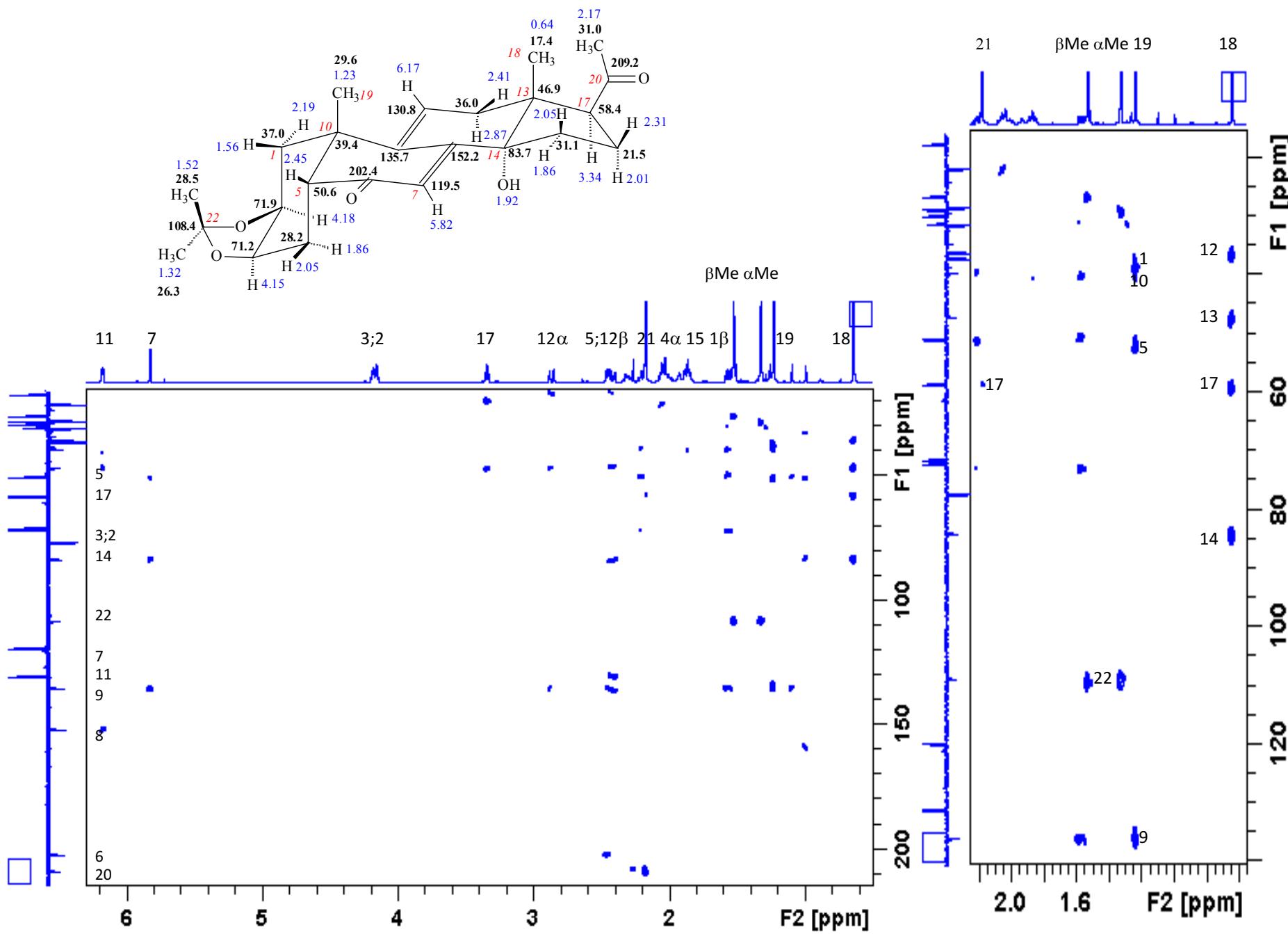


Figure S11. Compound 6, ^1H NMR CDCl_3 600 MHz.

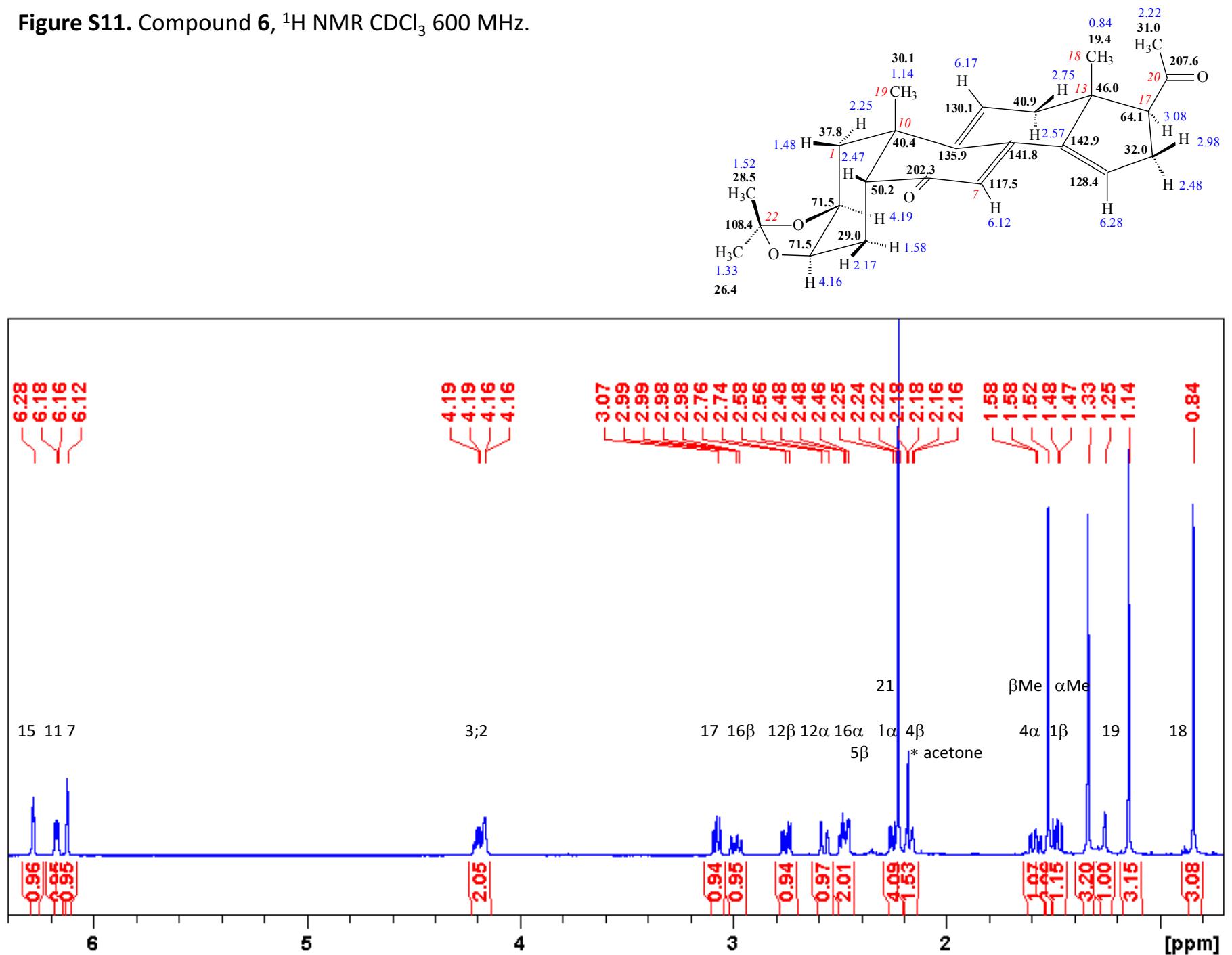


Figure S12. Compound **6**, steric proximities detected by selNOESY on signals αMe , $\text{H}_3\text{-19}$ and $\text{H}_3\text{-18}$.

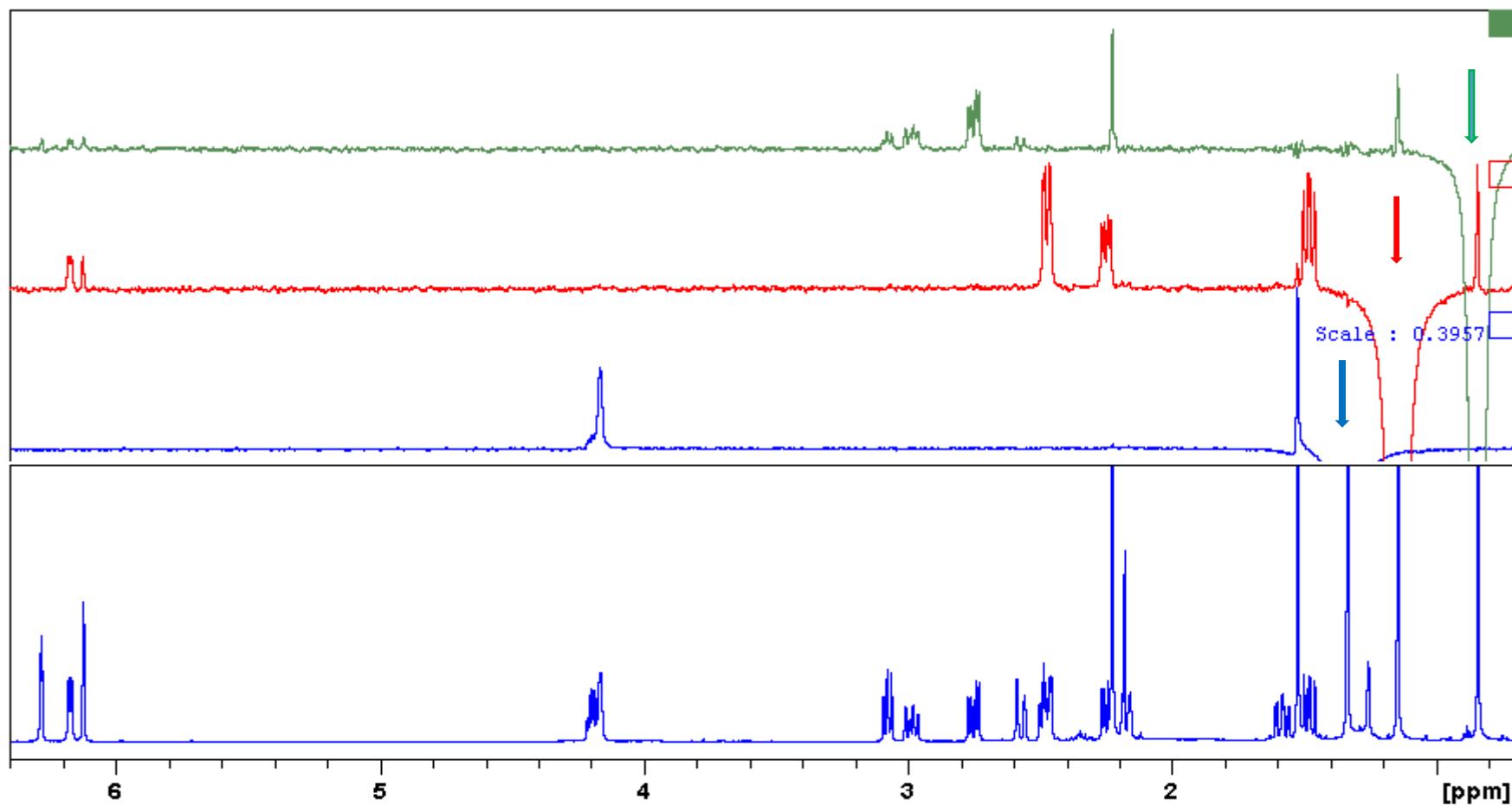
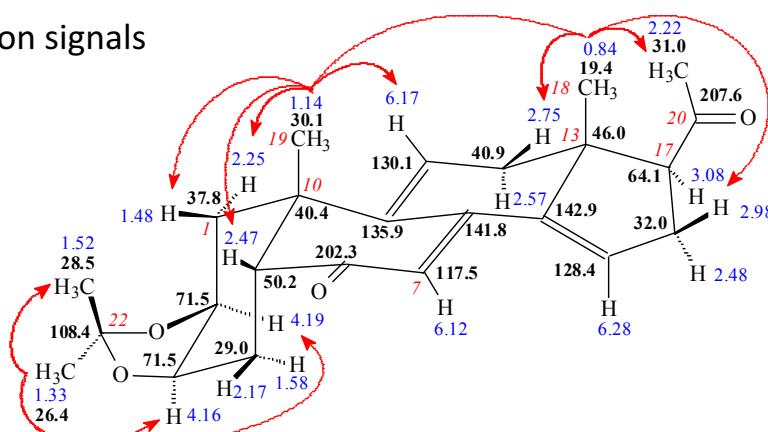


Figure S13. Compound **6**, DEPTQ 150 MHz.

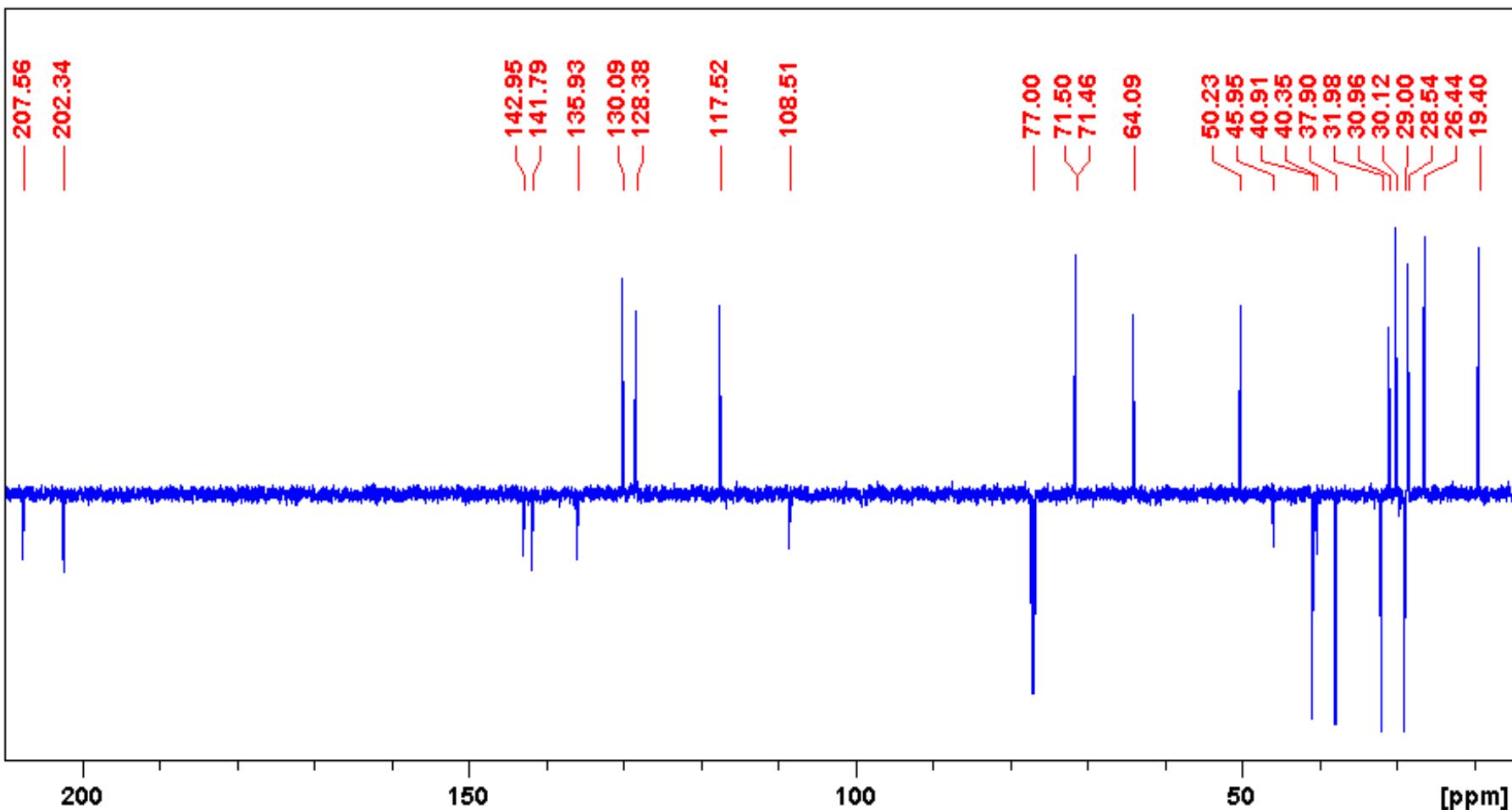
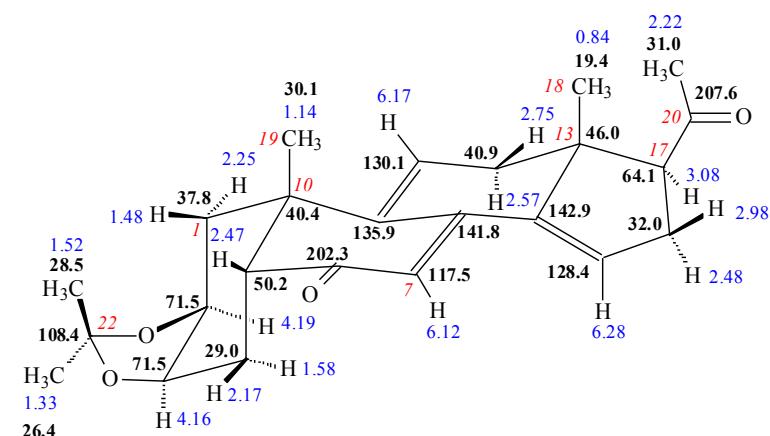


Figure S14. Compound 6, edHSQC and edHSQC CH₂ section.

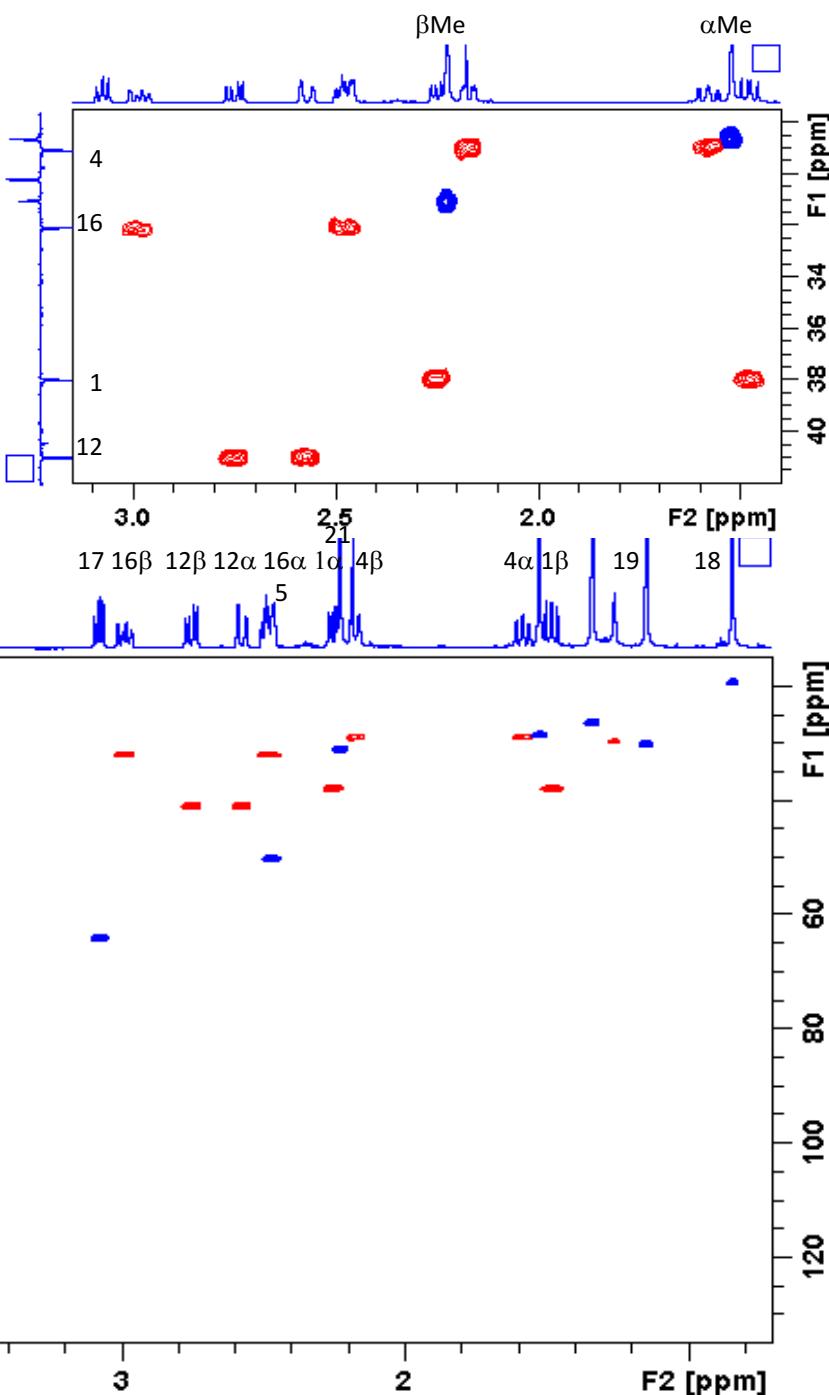
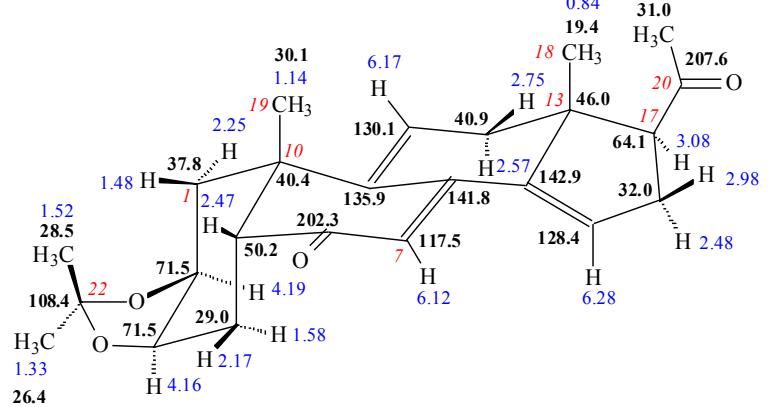


Figure S15. Compound **6**, HMBC and HMBC CH₃ section.

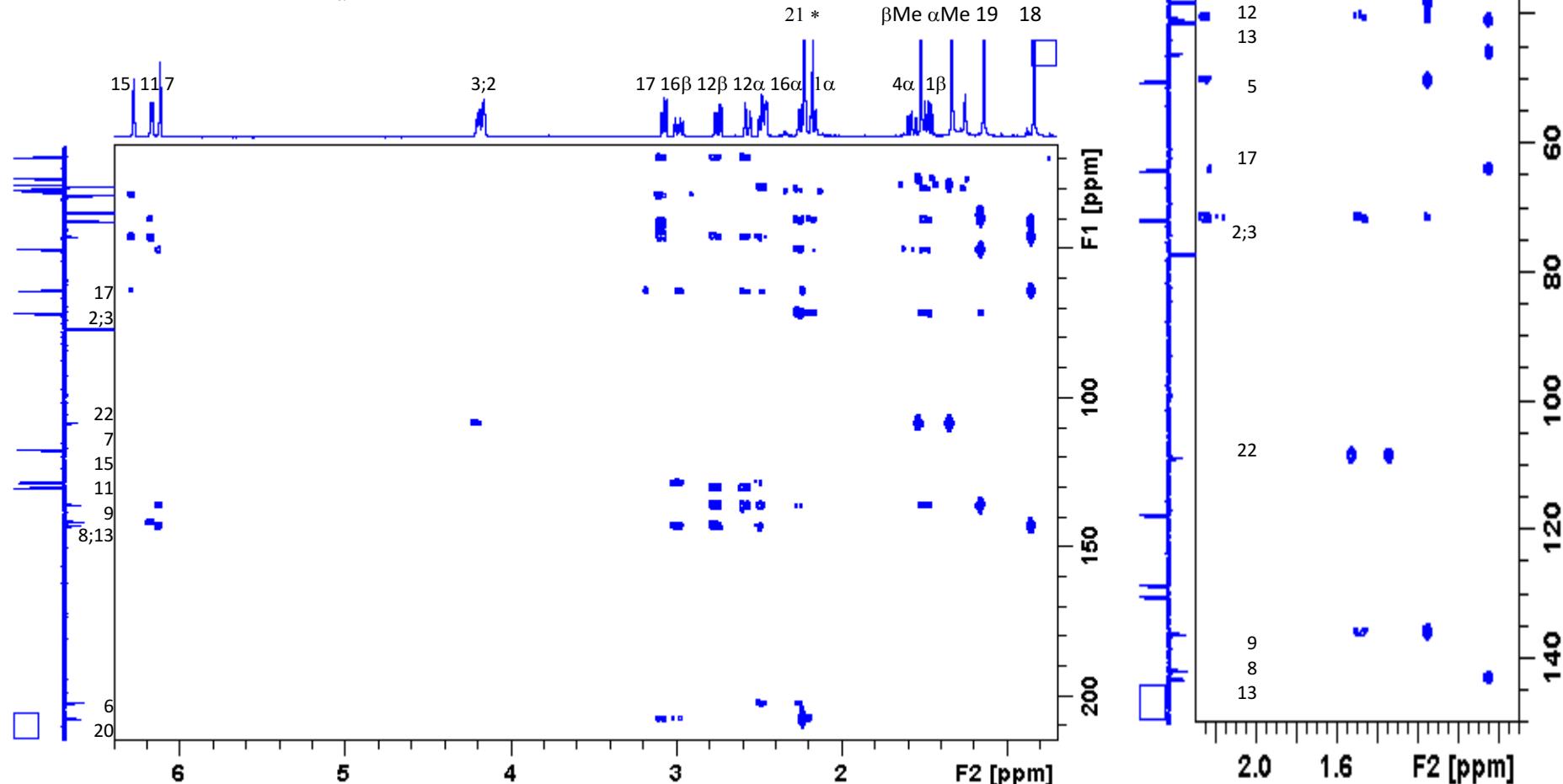
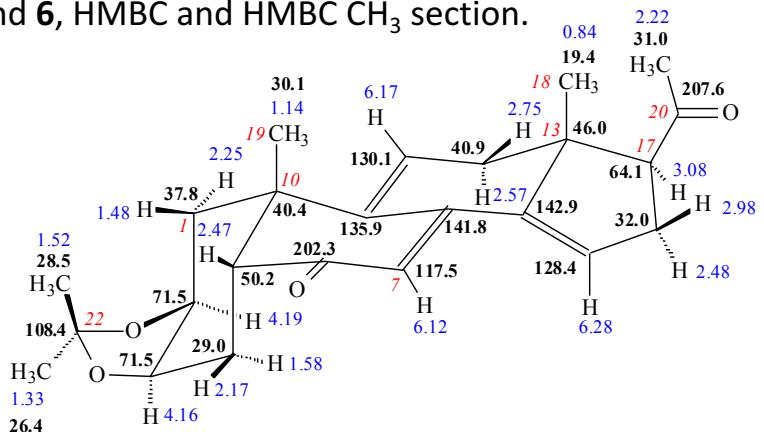


Figure S16. Compound **7**, ^1H NMR CDCl_3 500 MHz and **steric proximities** detected by selROESY on signals $\text{H}_3\text{-19}$ and $\text{H}_3\text{-18}$.

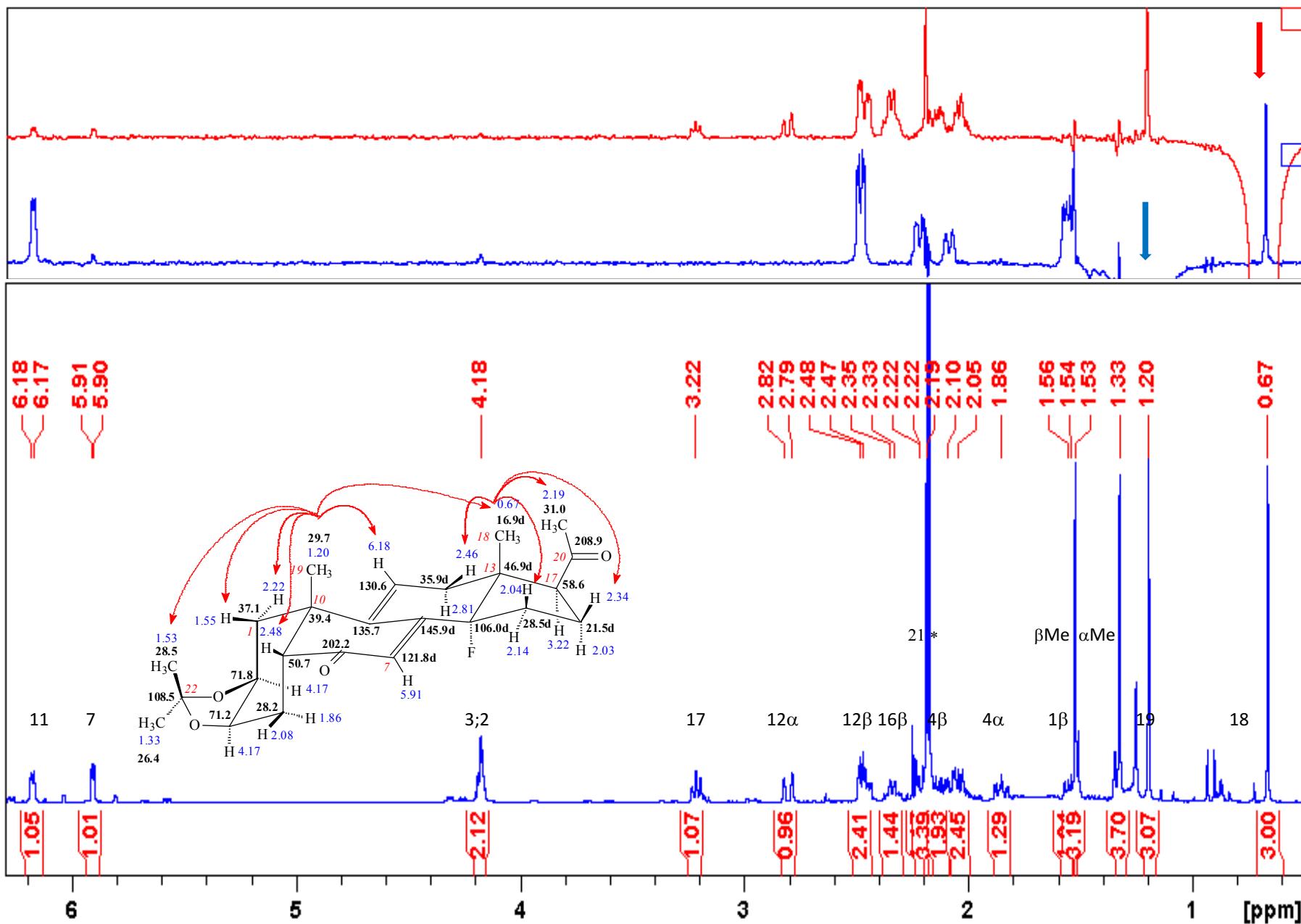


Figure S17. Compound **7**, DEPTQ 125 MHz.

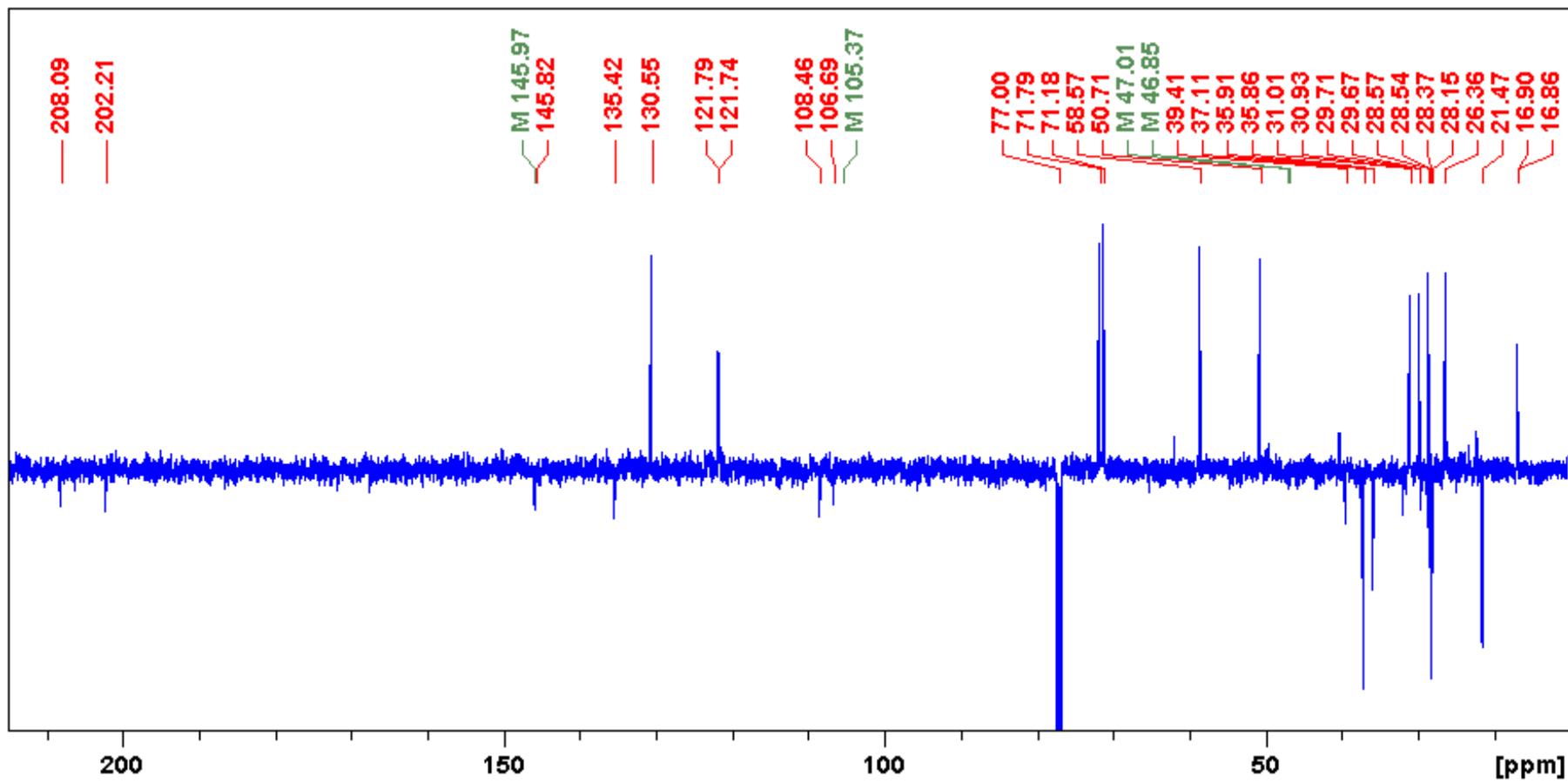
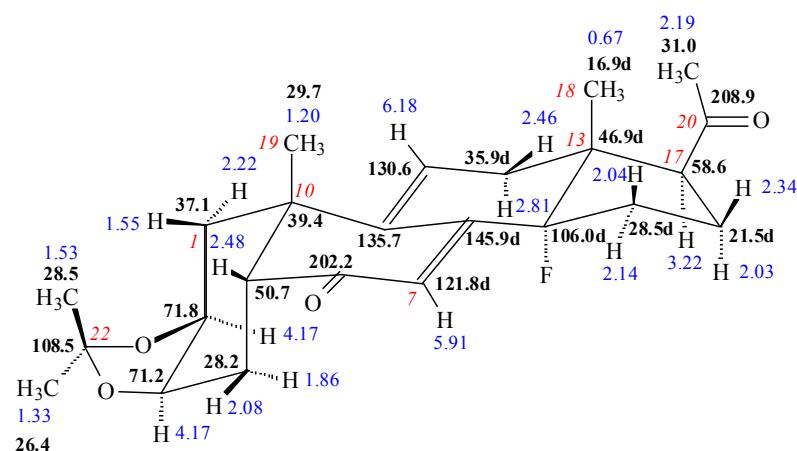


Figure S18. Compound 7, edHSQC and edHSQC CH_2 section.

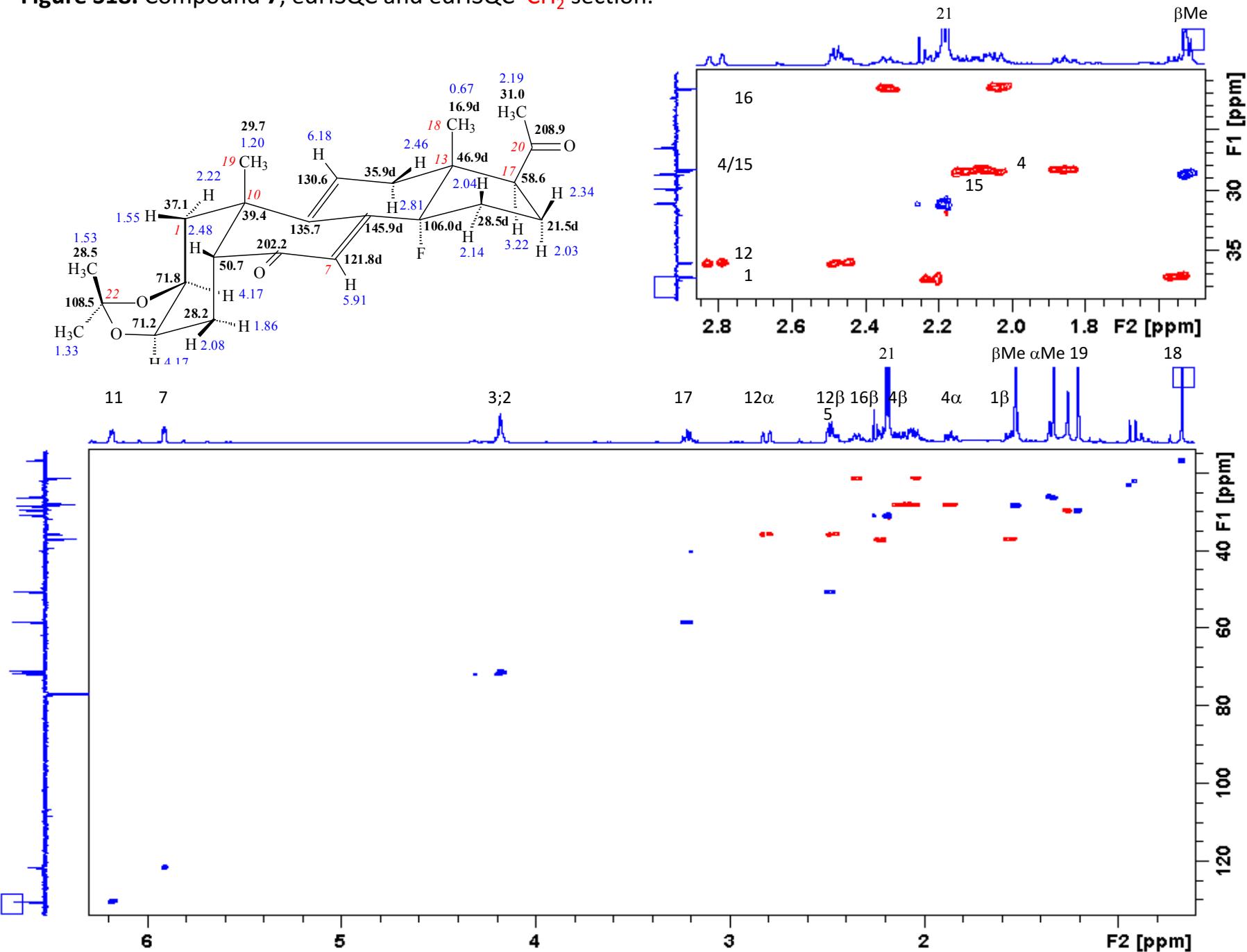


Figure S19. Compound 7, HMBC and HMBC CH₃ section.

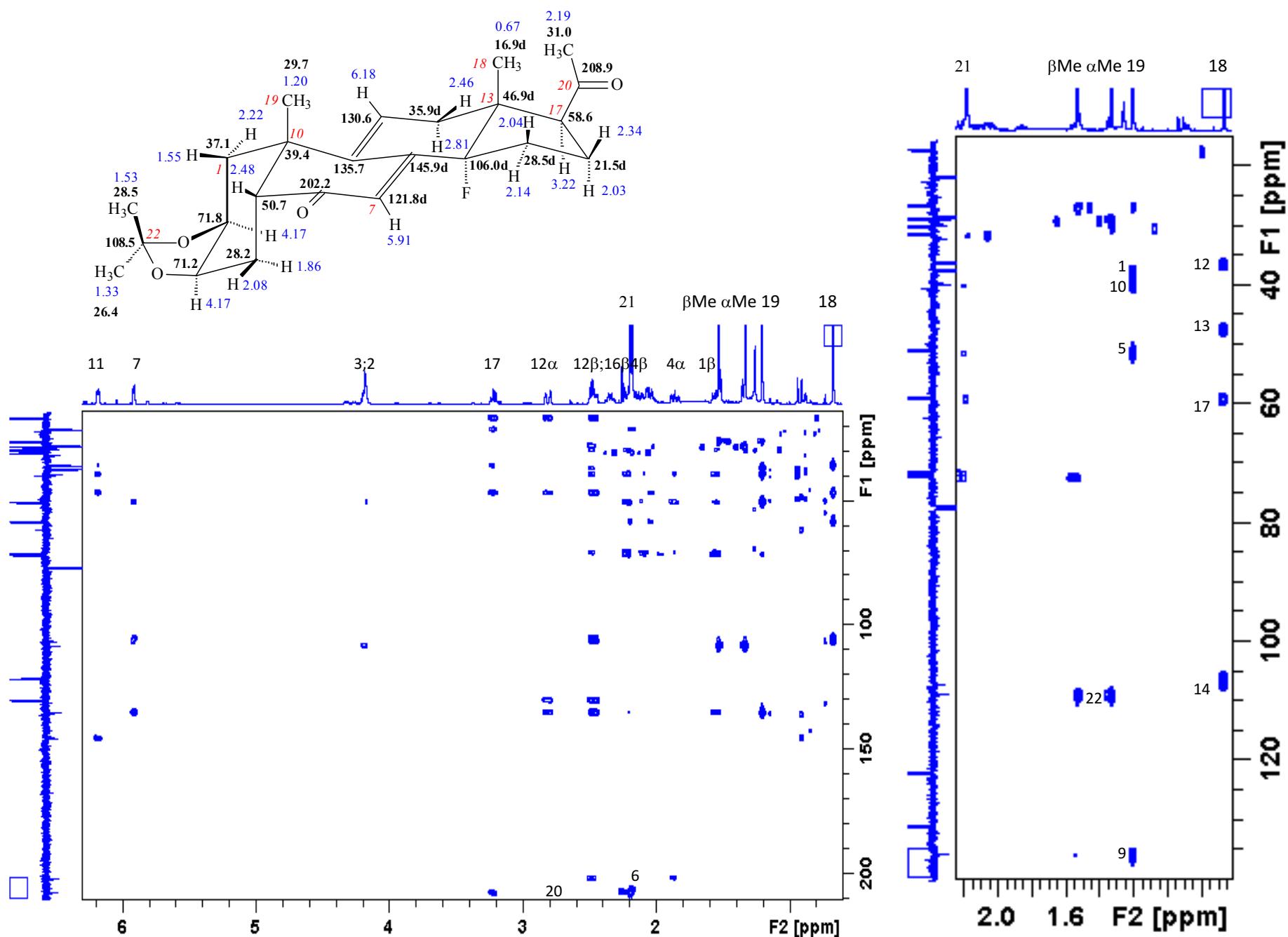


Figure S20. Compound **10**, ^1H NMR CDCl_3 600 MHz and selTOCSY on H-15 and $\text{H}\alpha$ -1.

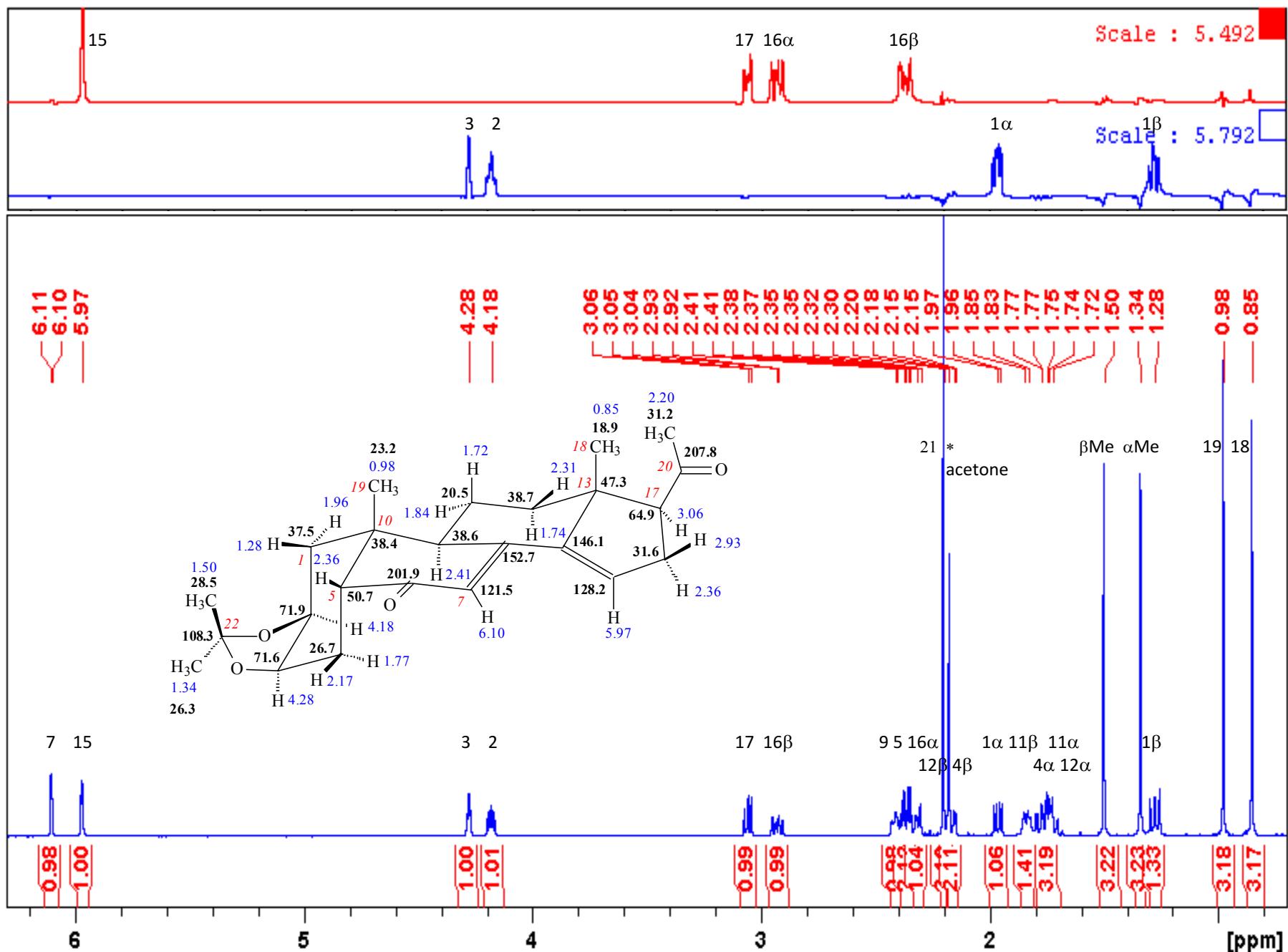


Figure S21. Compound 10, steric proximities detected by selNOESY on signals

β Me, H₃-19 and H₃-18.

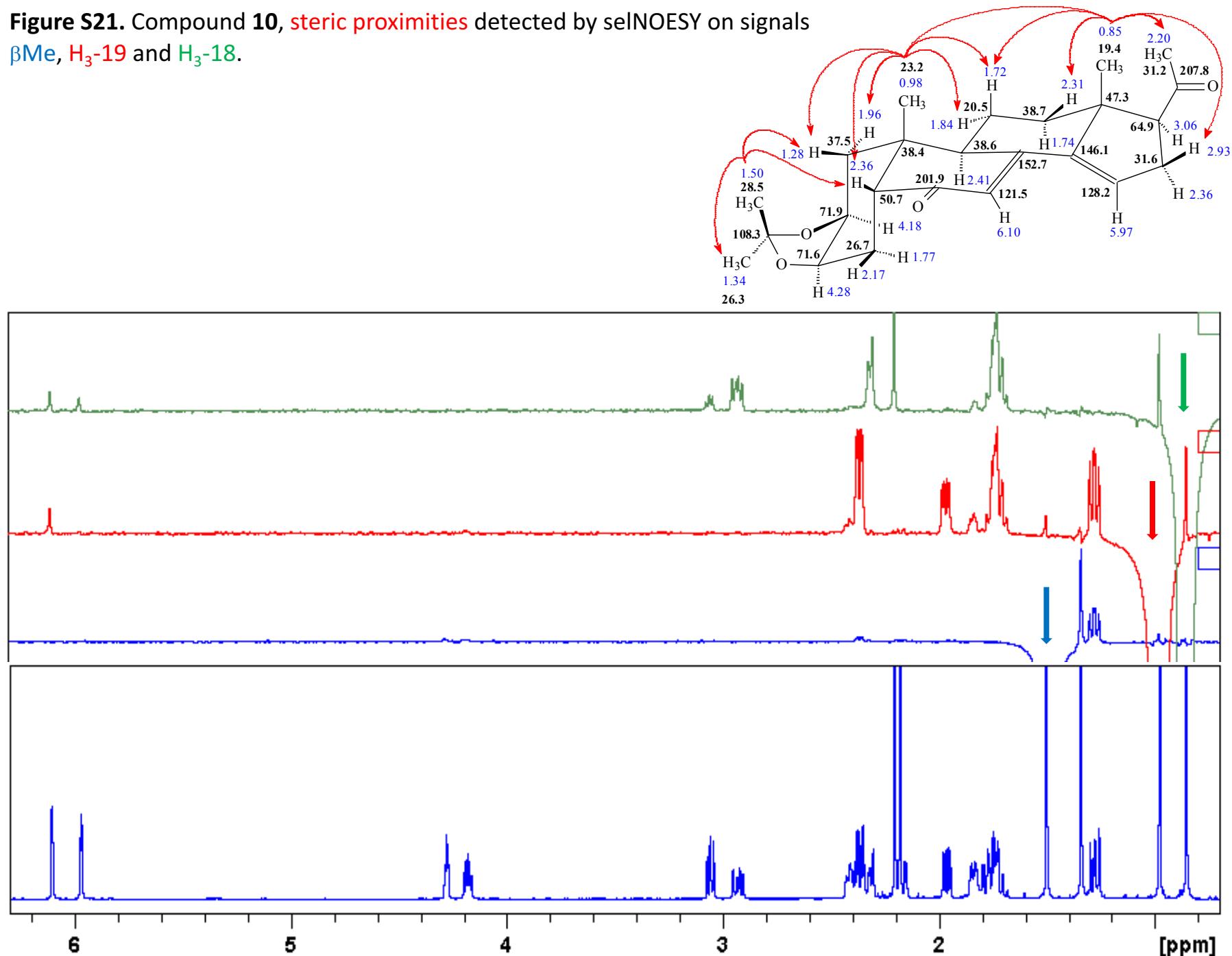


Figure S22. Compound **10**, DEPTQ 150 MHz.

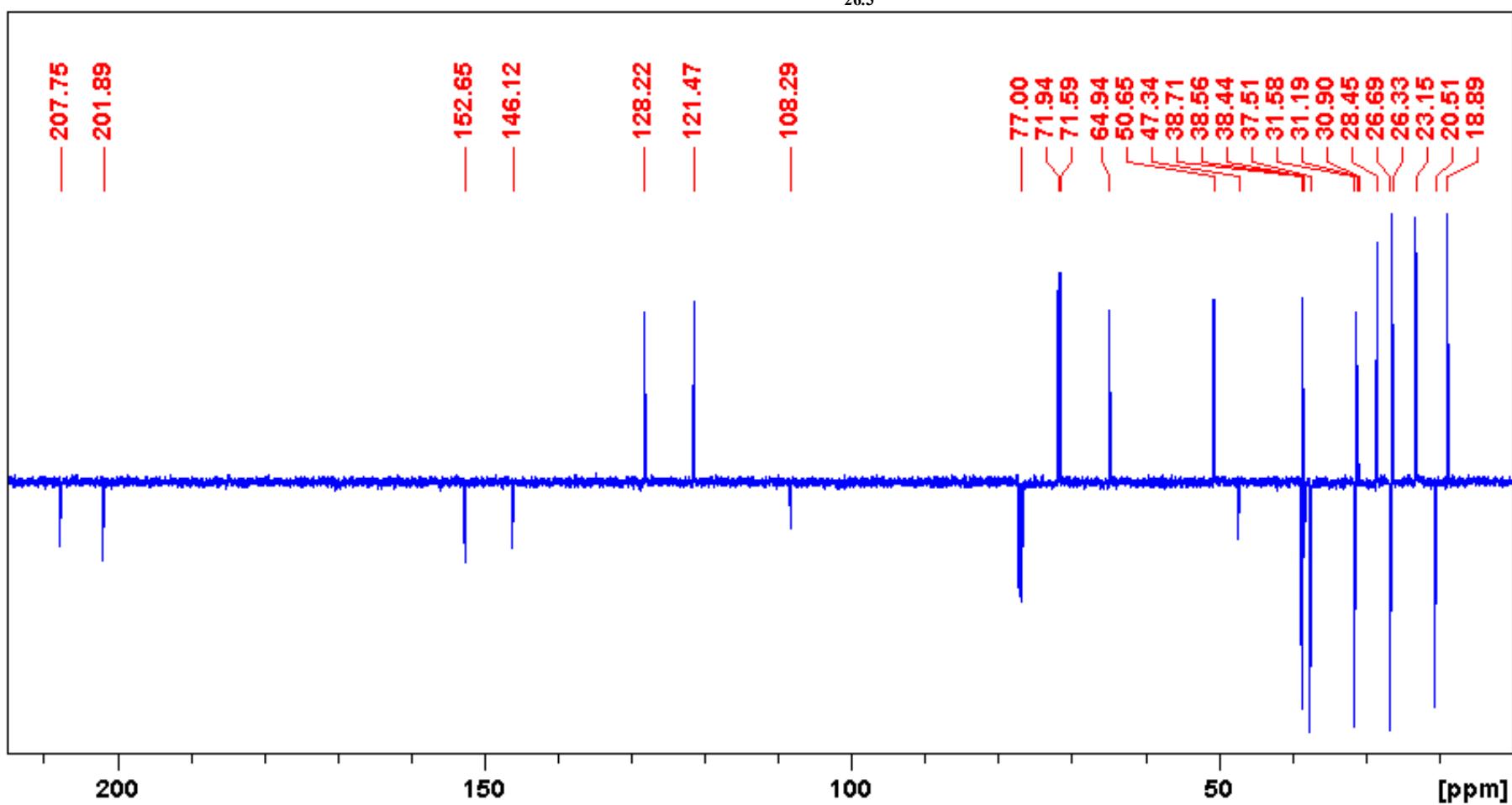
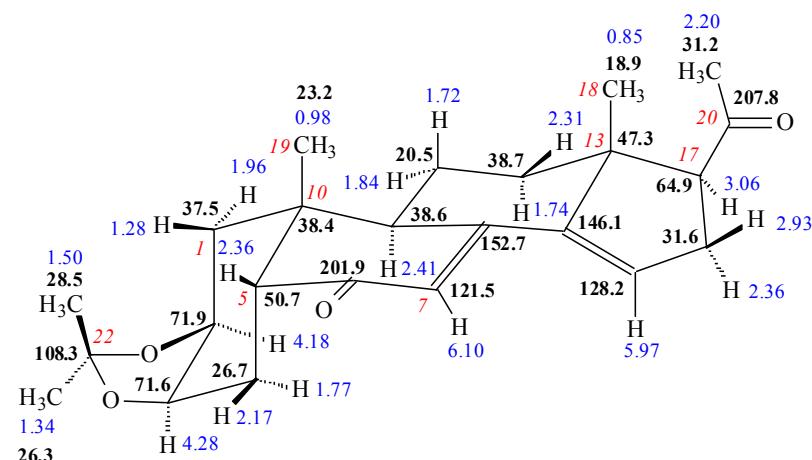


Figure S23. Compound **10**, edHSQC.

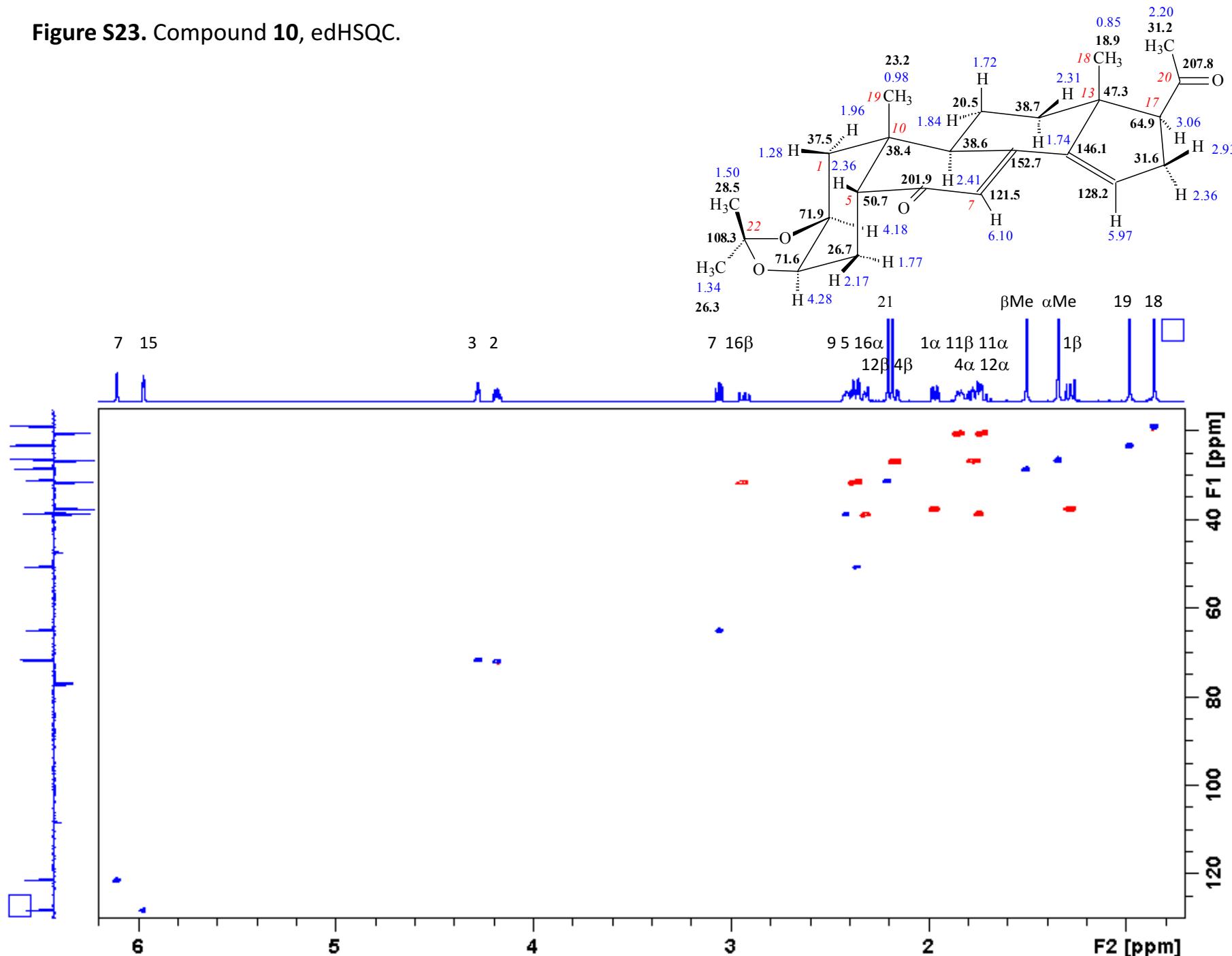


Figure S24. Compound **10**, HMBC.

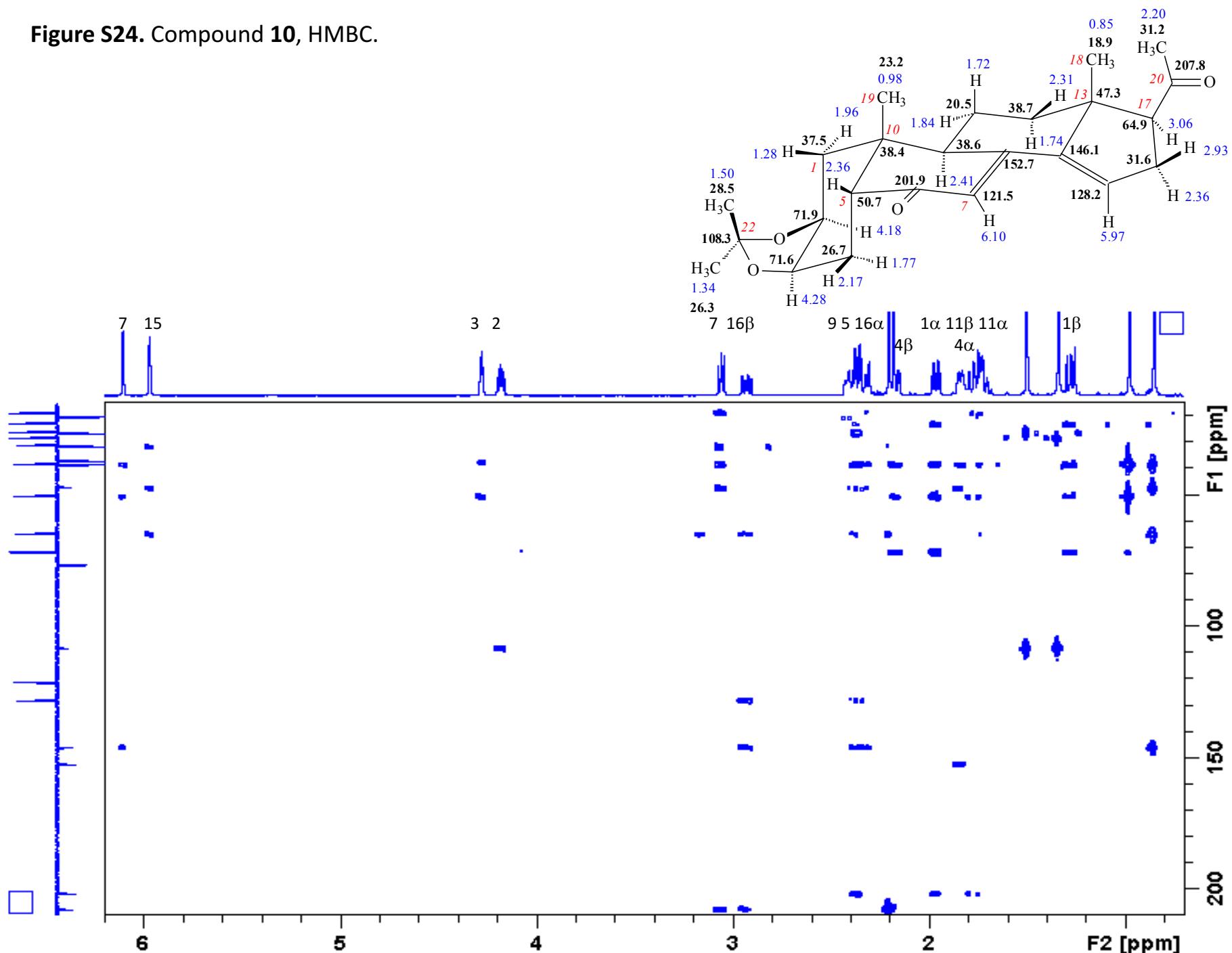


Figure S25. Compound 10, edHSQC CH₂ section and HMBC CH₃ section.

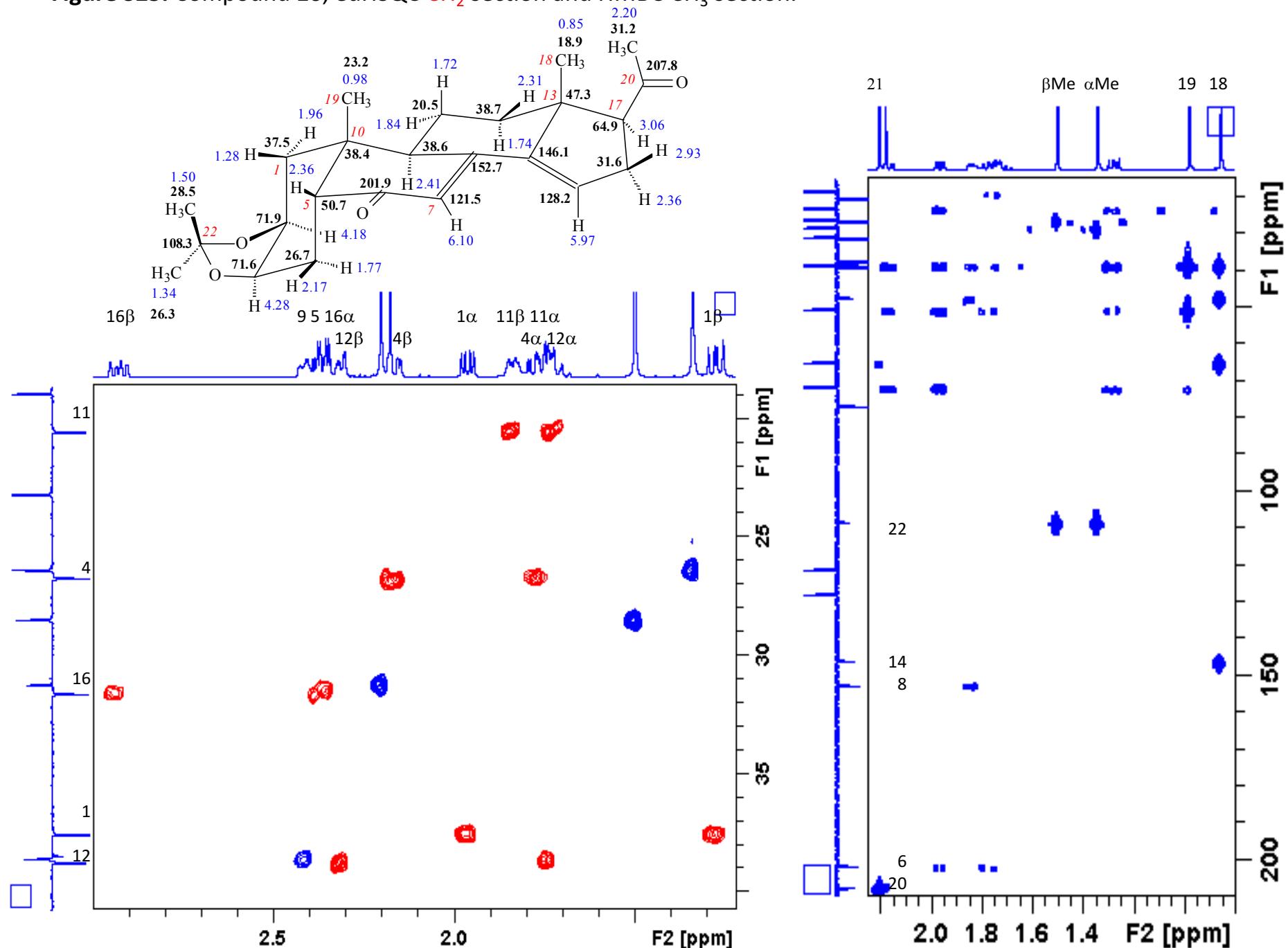


Figure S26. Compound **11**, ^1H NMR CDCl_3 600 MHz.

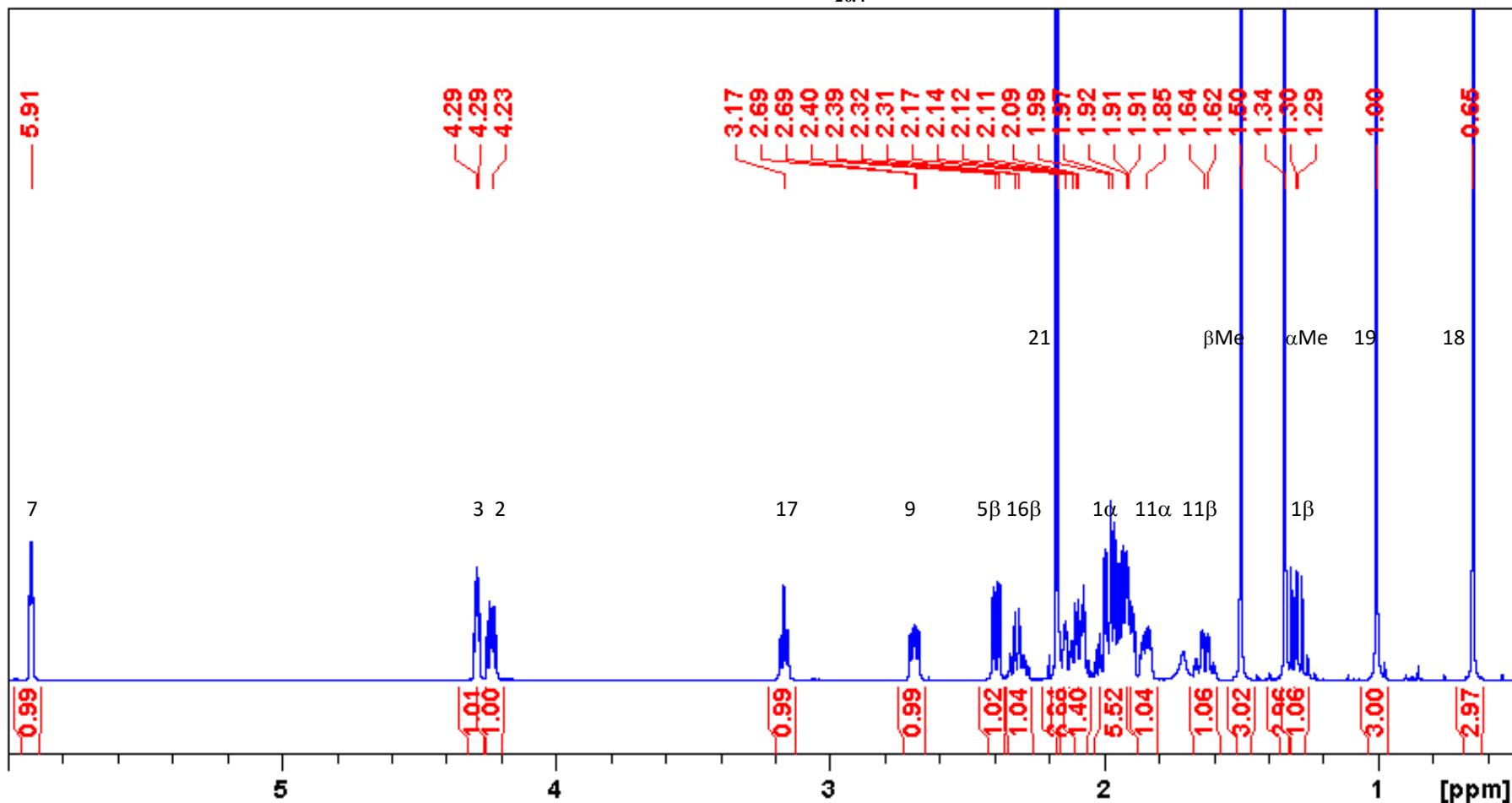
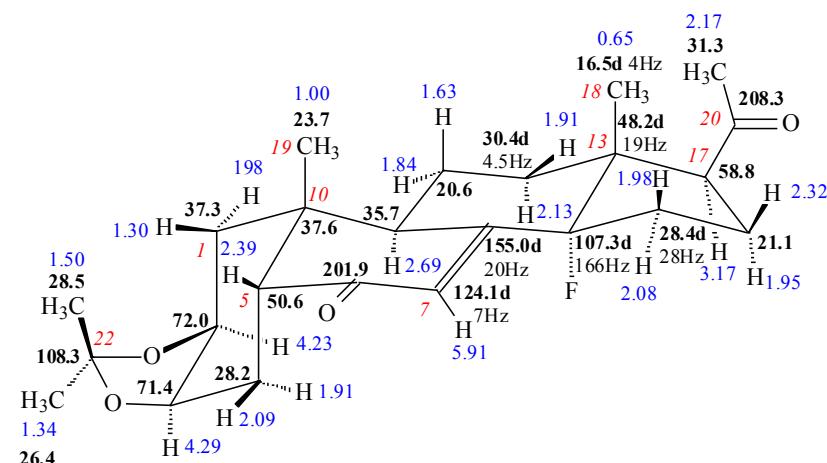


Figure S27. Compound 11, steric proximities detected by selNOESY on signals β Me, H₃-19 and H₃-18.

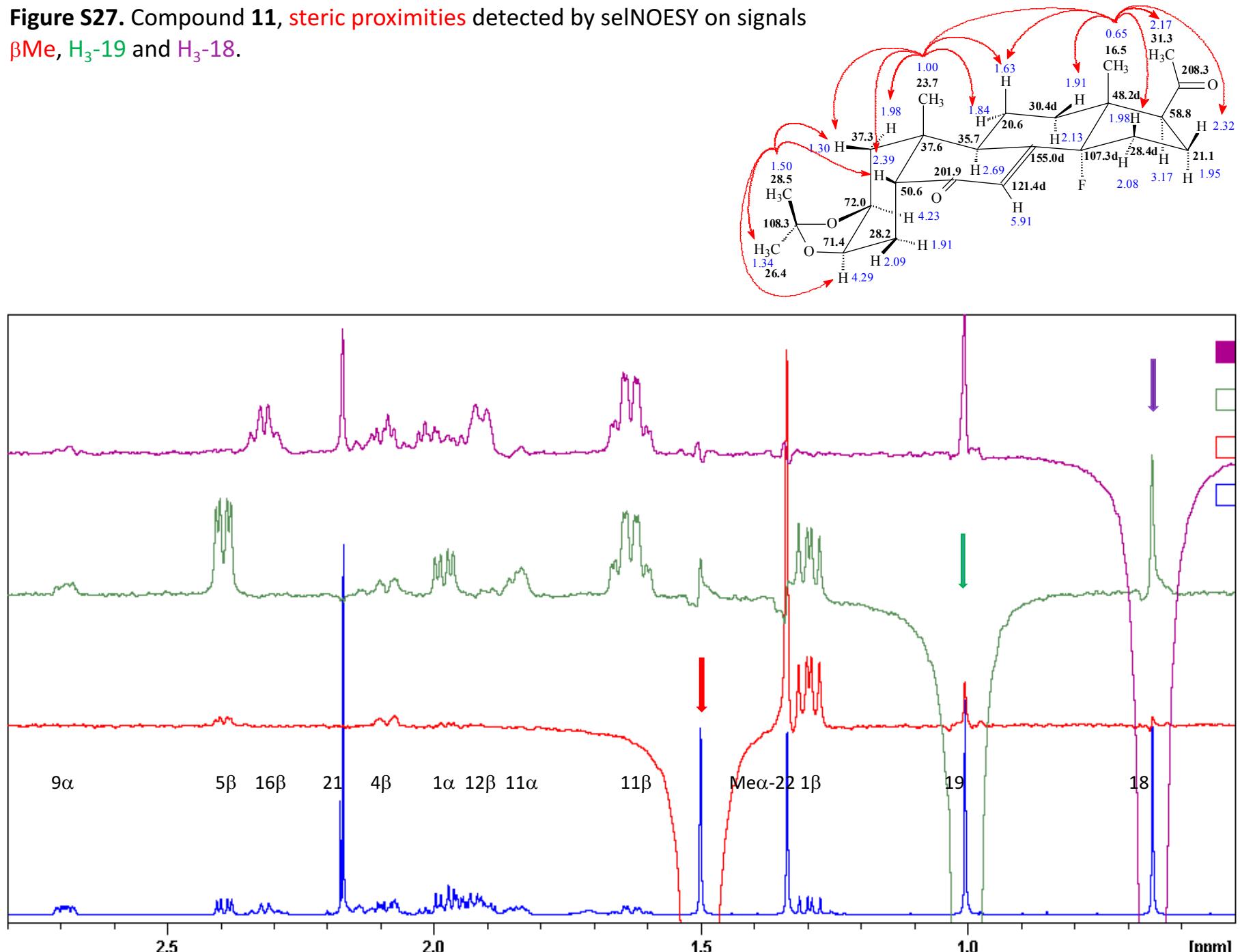


Figure S28. Compound **11**, DEPTQ 150 MHz.

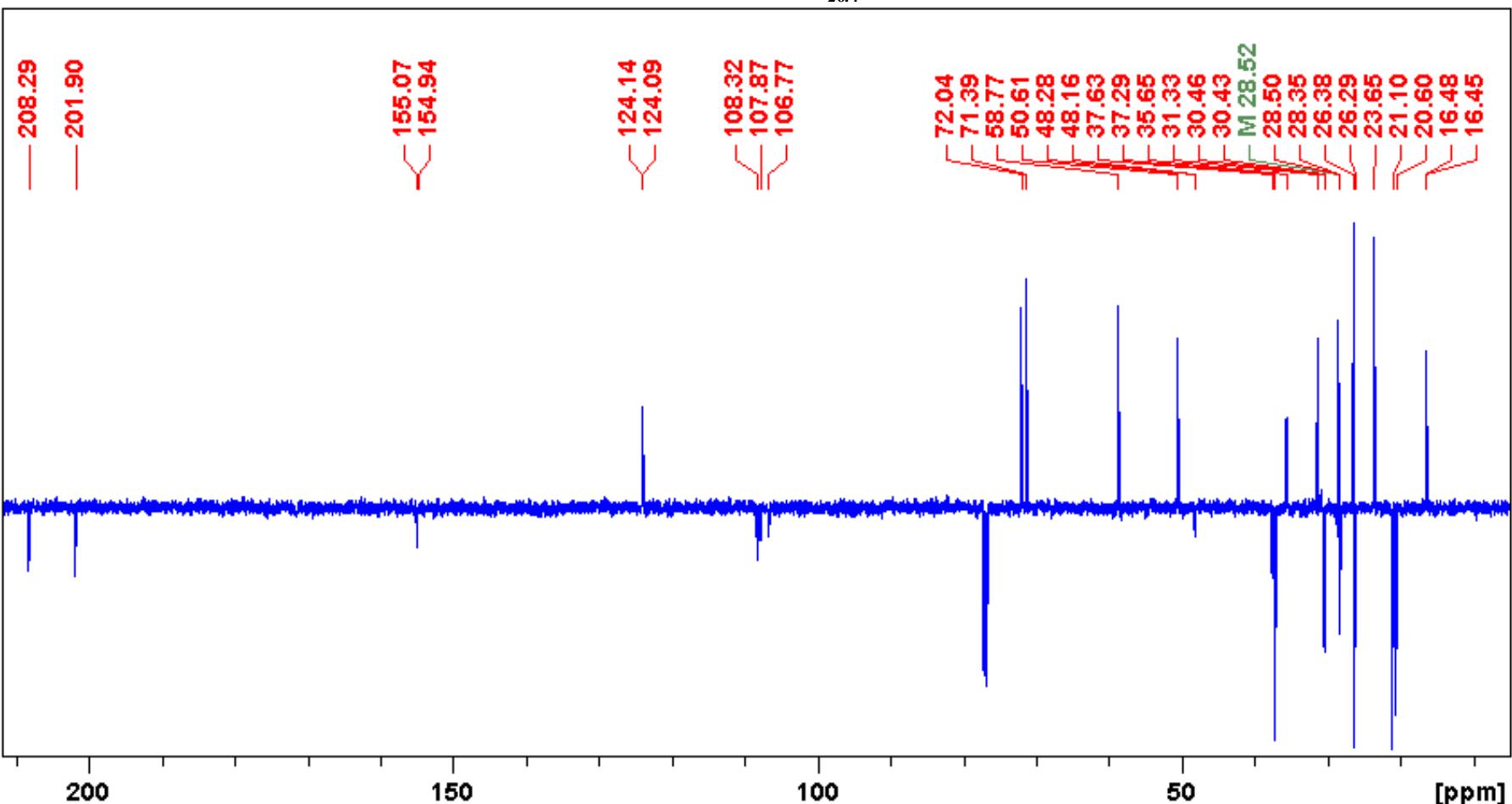
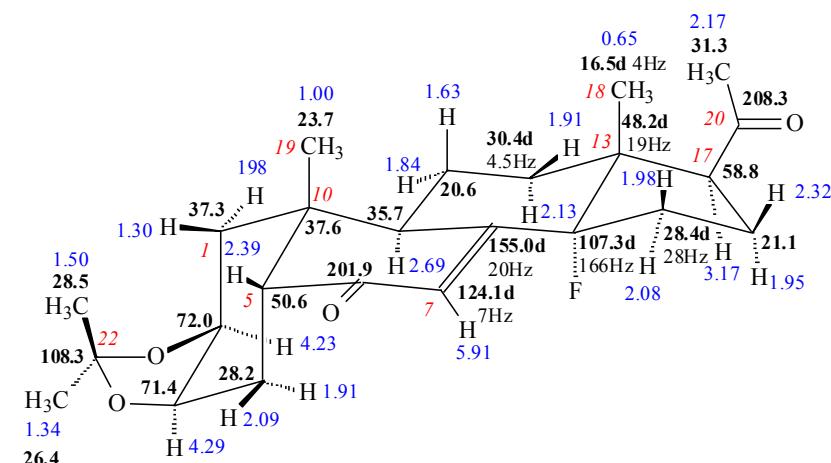


Figure S29. Compound **11**, edHSQC.

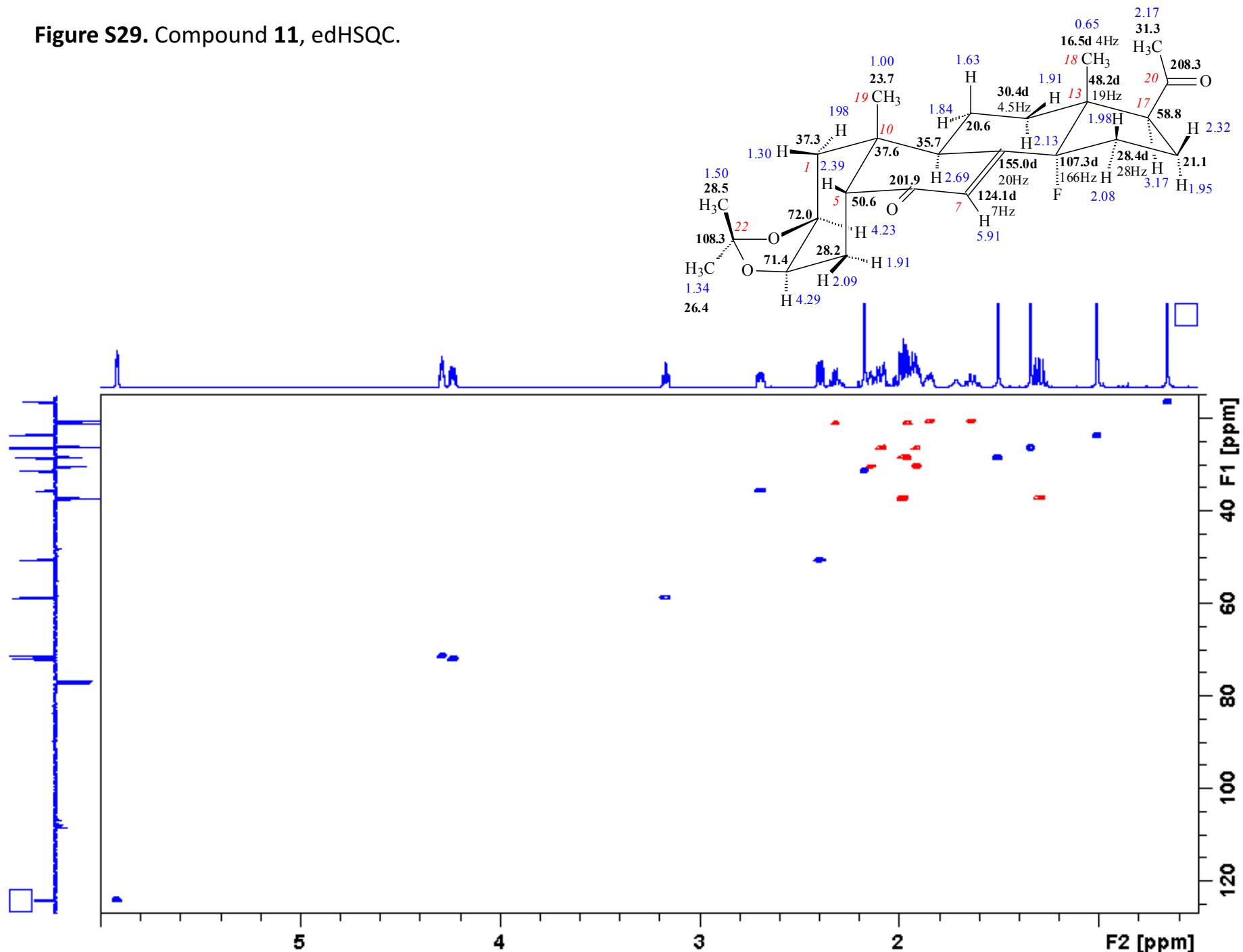


Figure S30. Compound 11, HMBC.

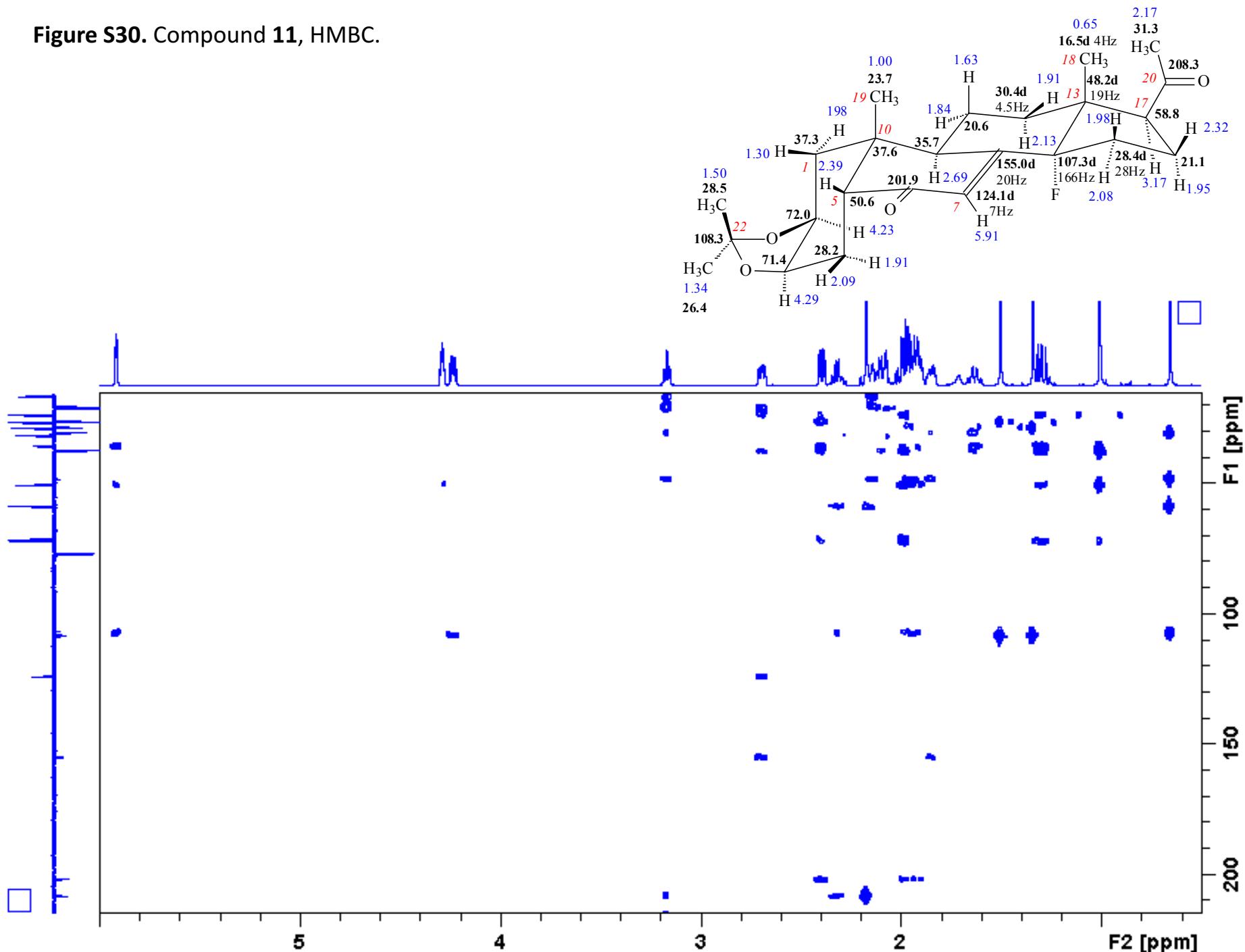


Figure S31. Compound **11**, edHSQC CH_2 section and HMBC CH_3 section.

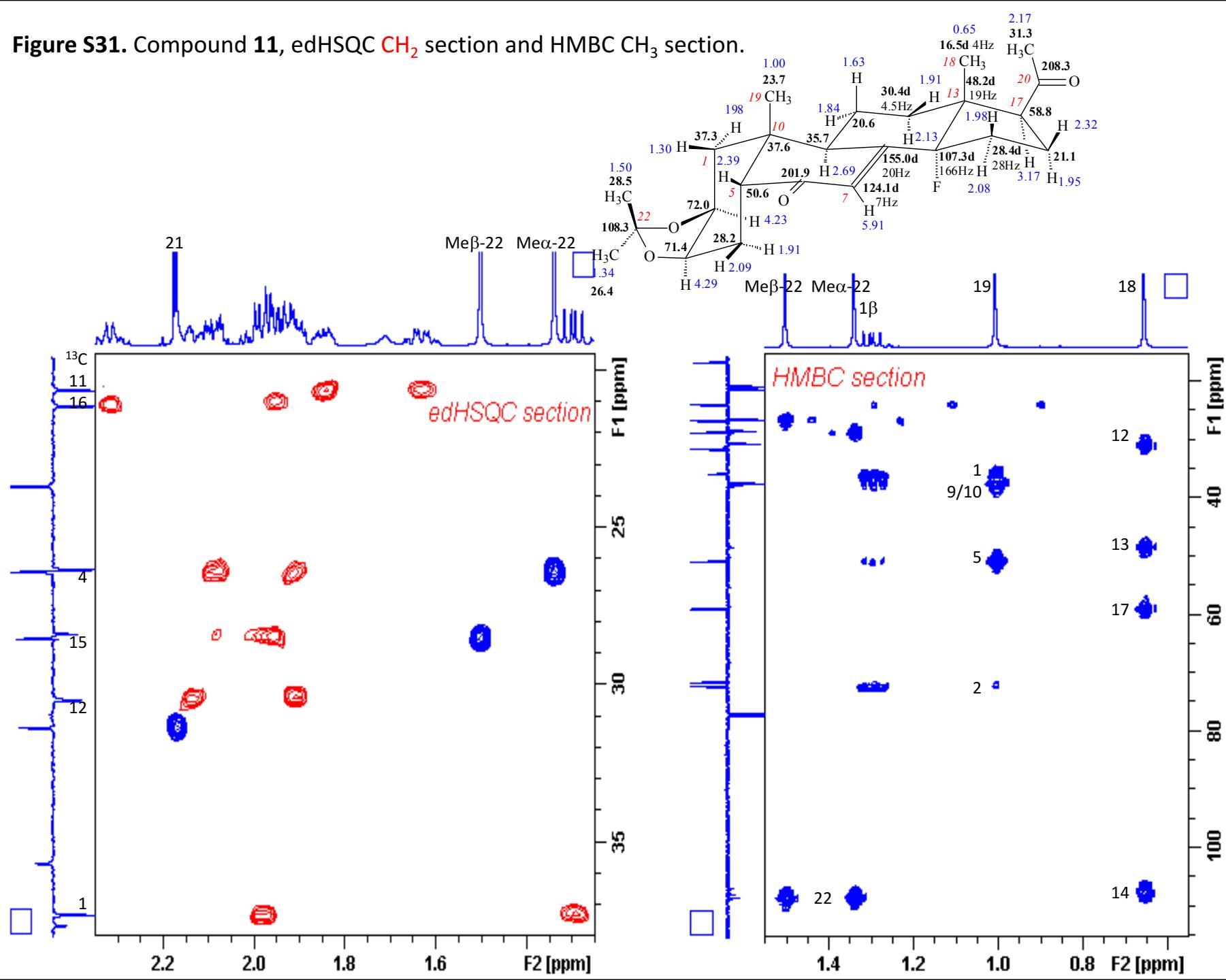
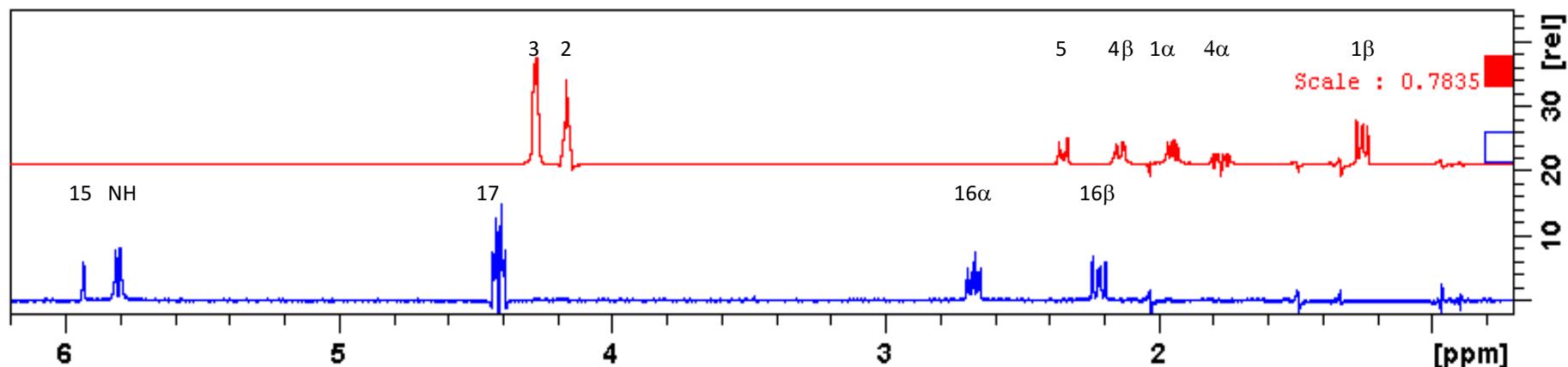


Figure S32. Compound **13**, ^1H NMR CDCl_3 600 MHz and selTOCSY on H-17 and H-3.



POSTAOF2 1H 600 MHz CDCl3

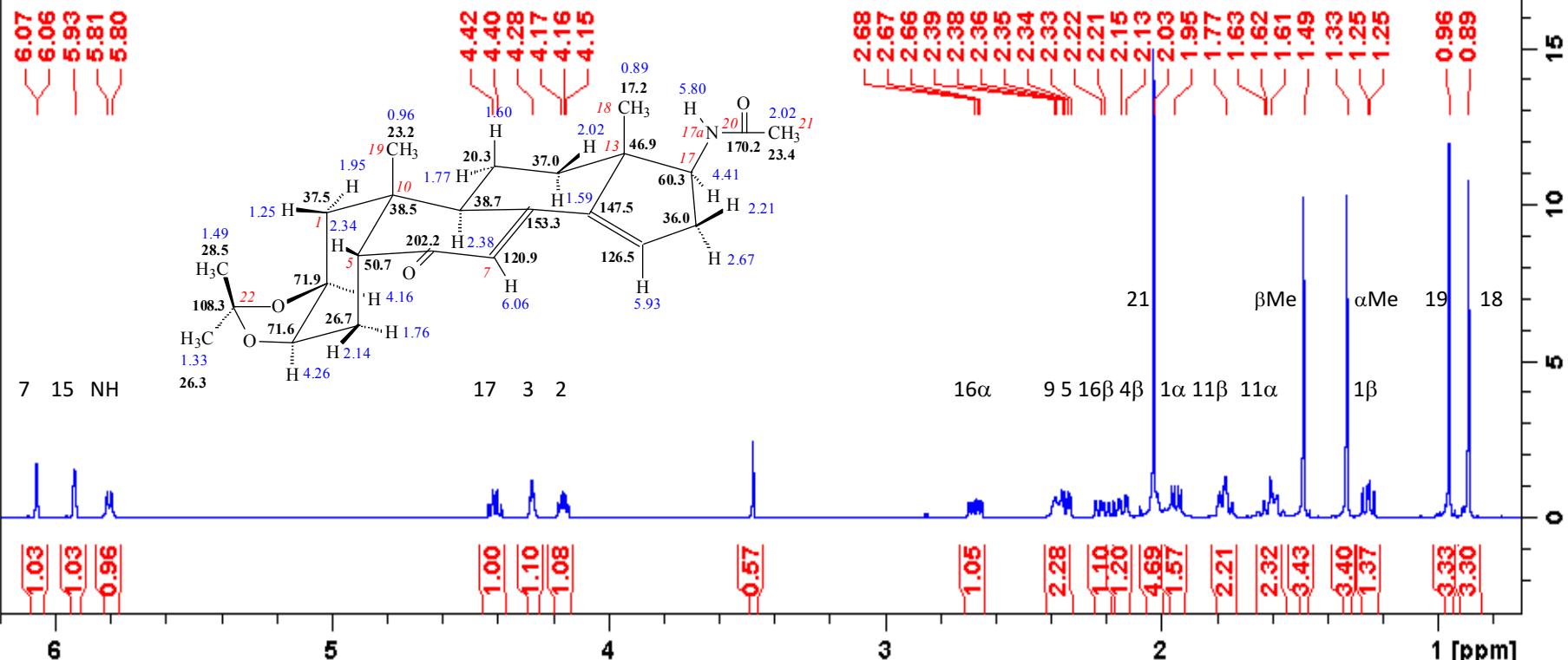


Figure S33. Compound 13, steric proximities detected by selROESY on signals

H₃-19 and **H₃-18.**

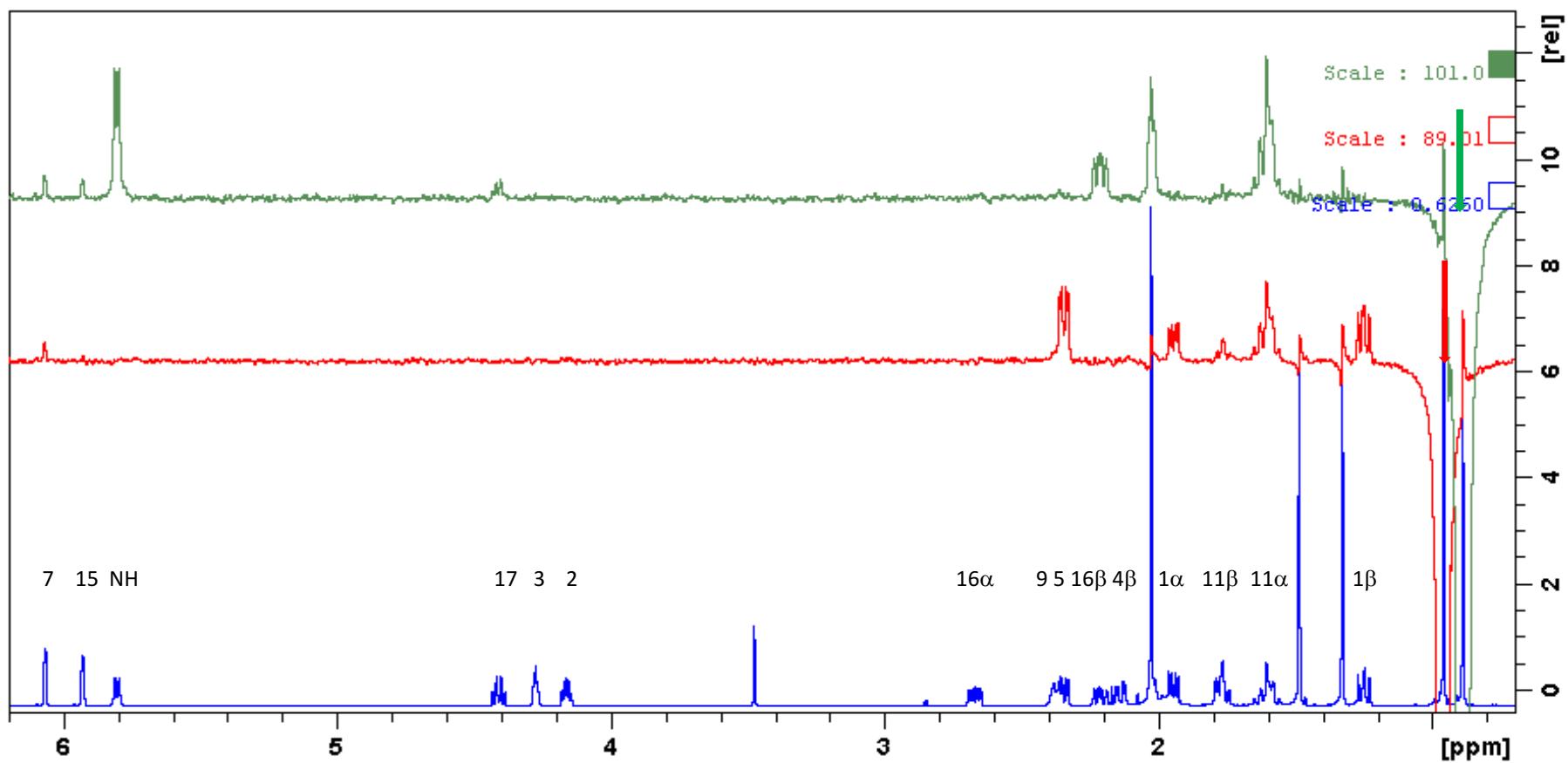
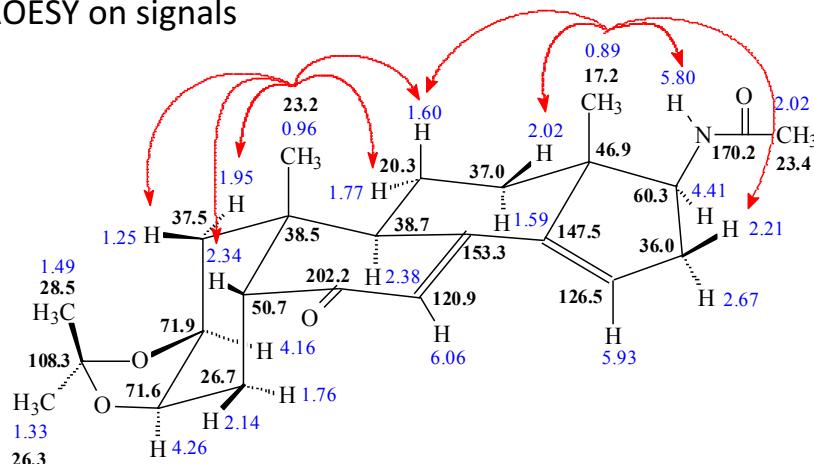


Figure S34. Compound **13**, DEPTQ 150 MHz.

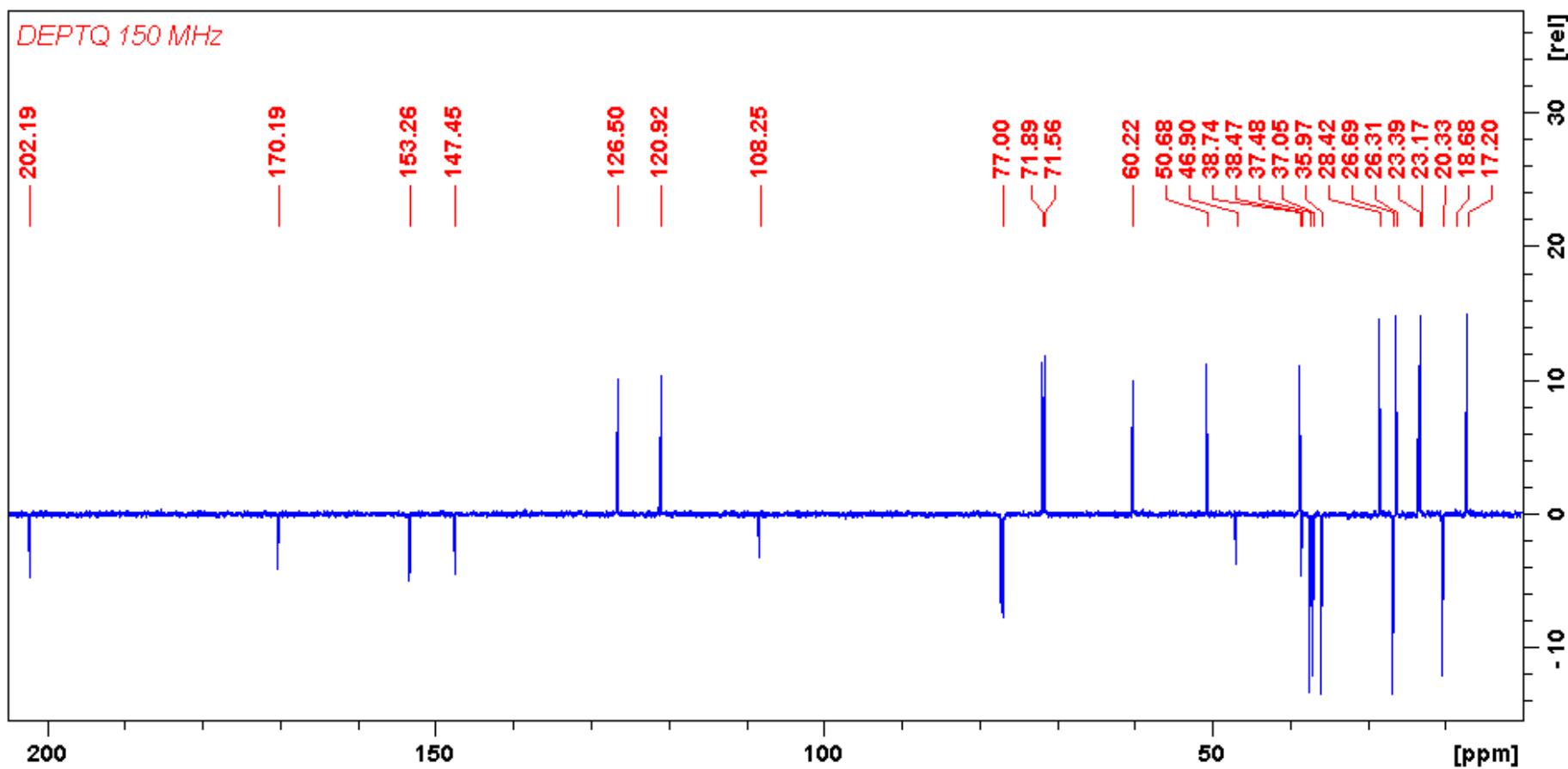
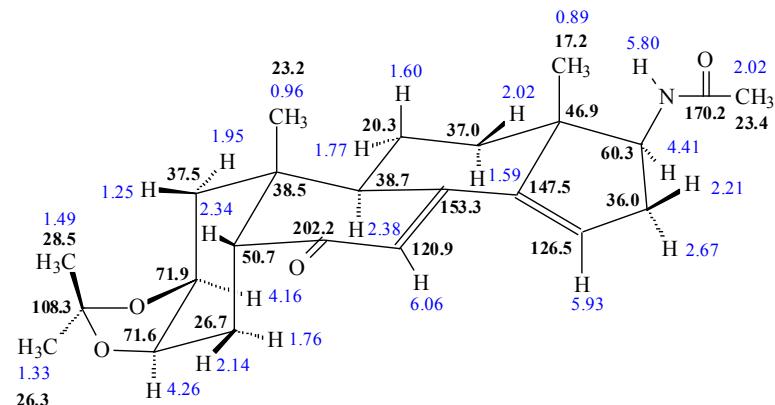


Figure S35. Compound **13**, edHSQC.

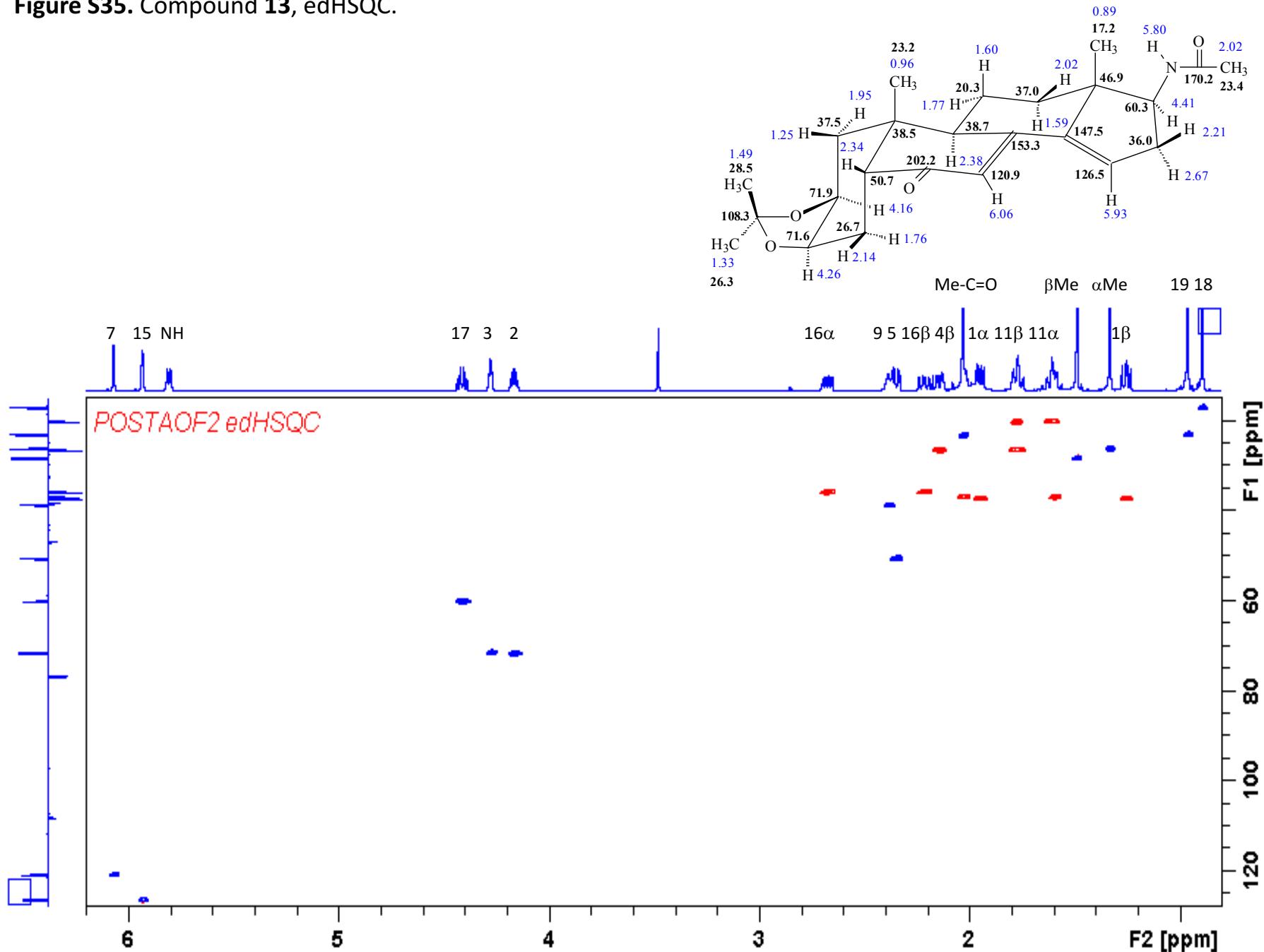


Figure S36. Compound 13, HMBC.

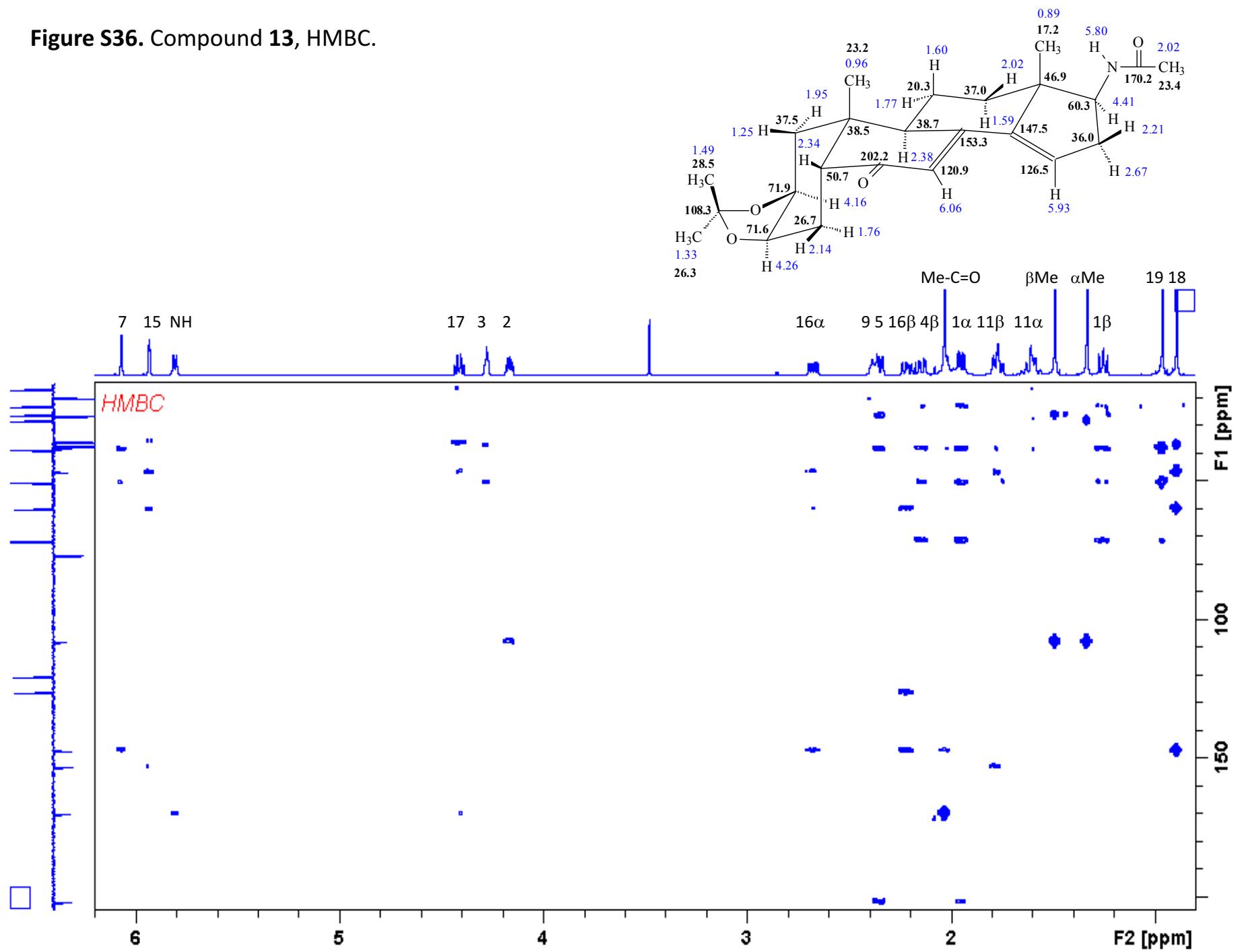


Figure S37. Compound **13**, edHSQC CH_2 section and HMBC CH_3 section.

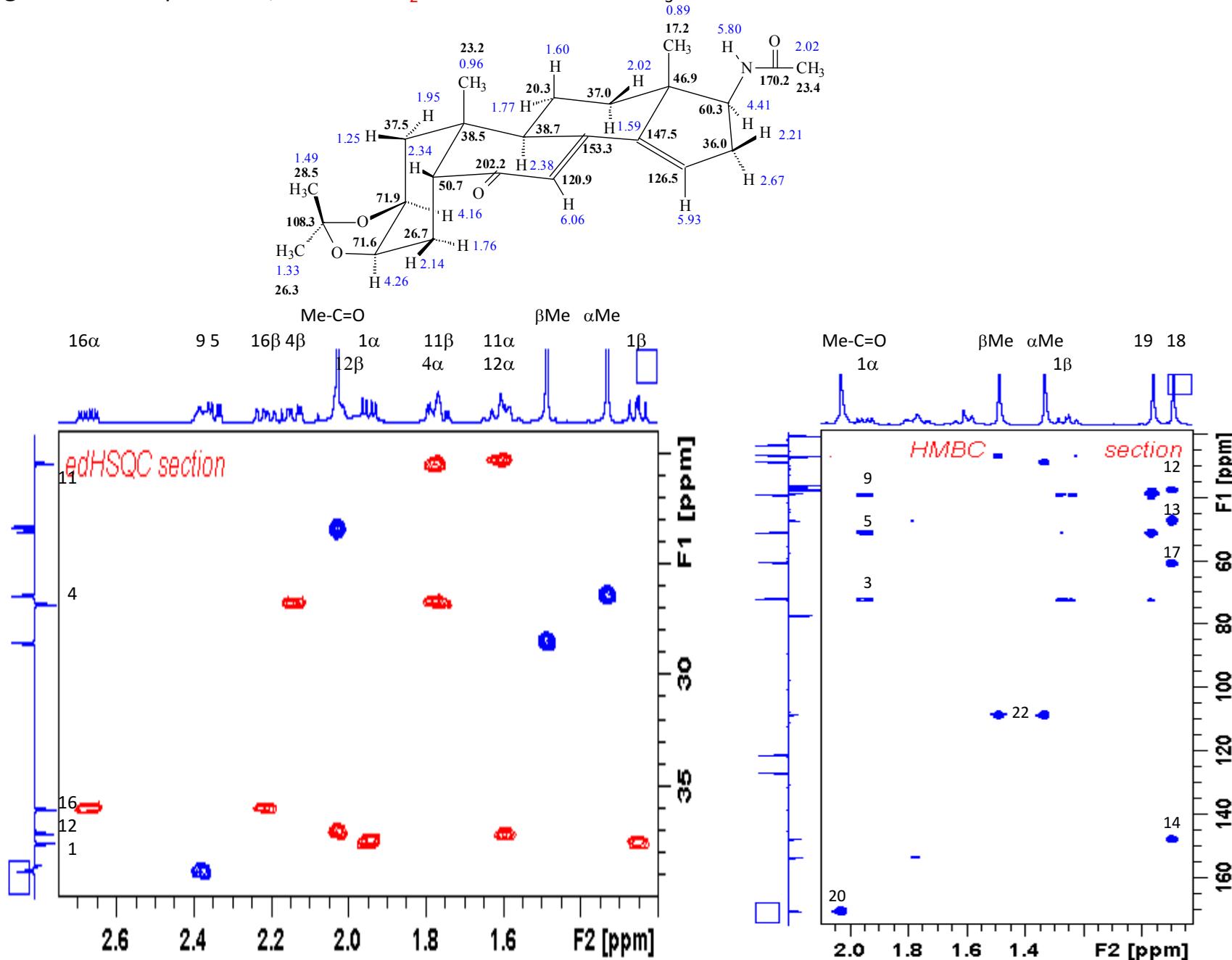


Figure S38. Compound **14**, ^1H CDCl_3 600 MHz.

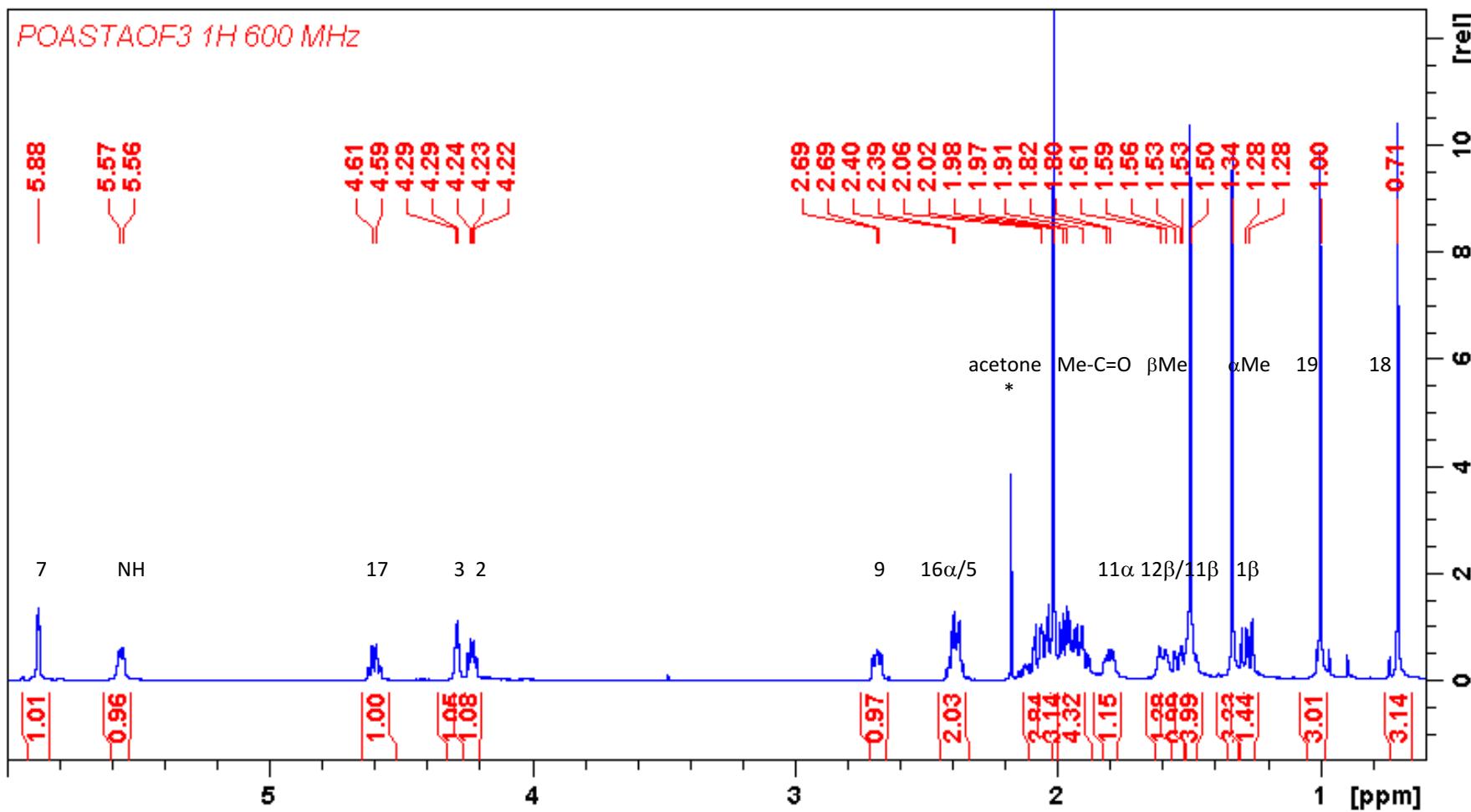
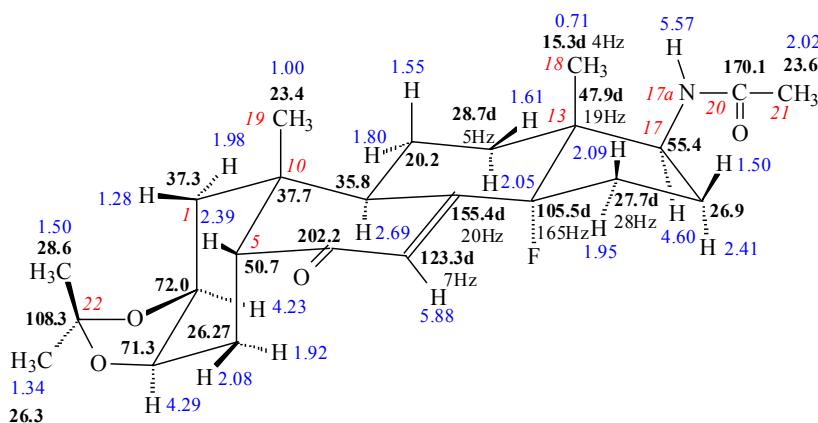


Figure S39. Compound **14**, identification of spin-systems of **A**, **C** and **D** rings by selTOCSY on H-3, H-9 and H-17.

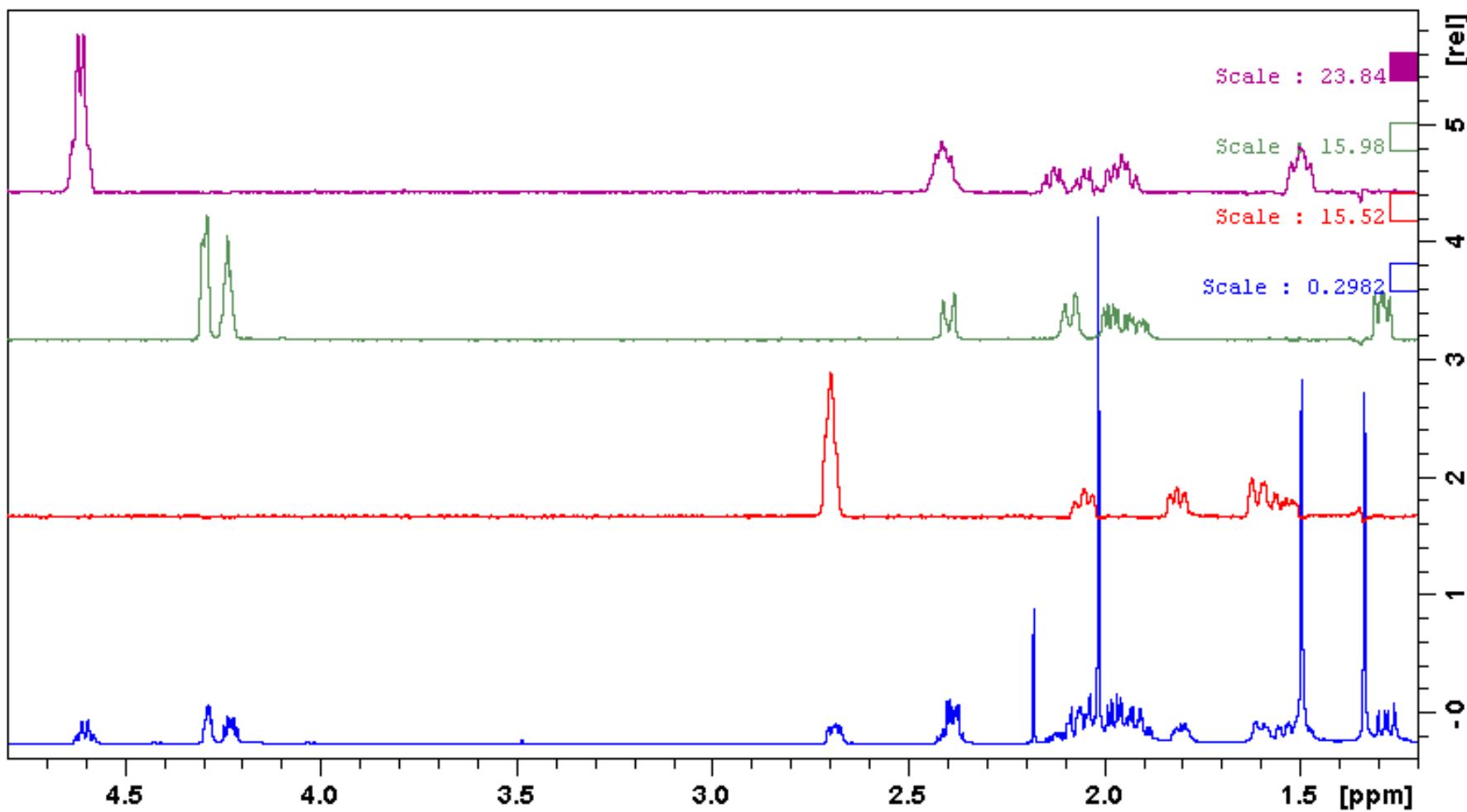
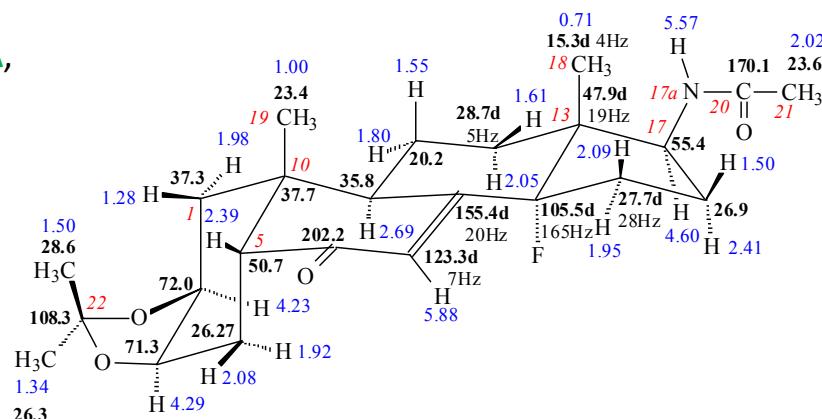


Figure S40. Compound **14**, steric proximities detected by selNOE on CH₃-19, CH₃-18 and NH signals.

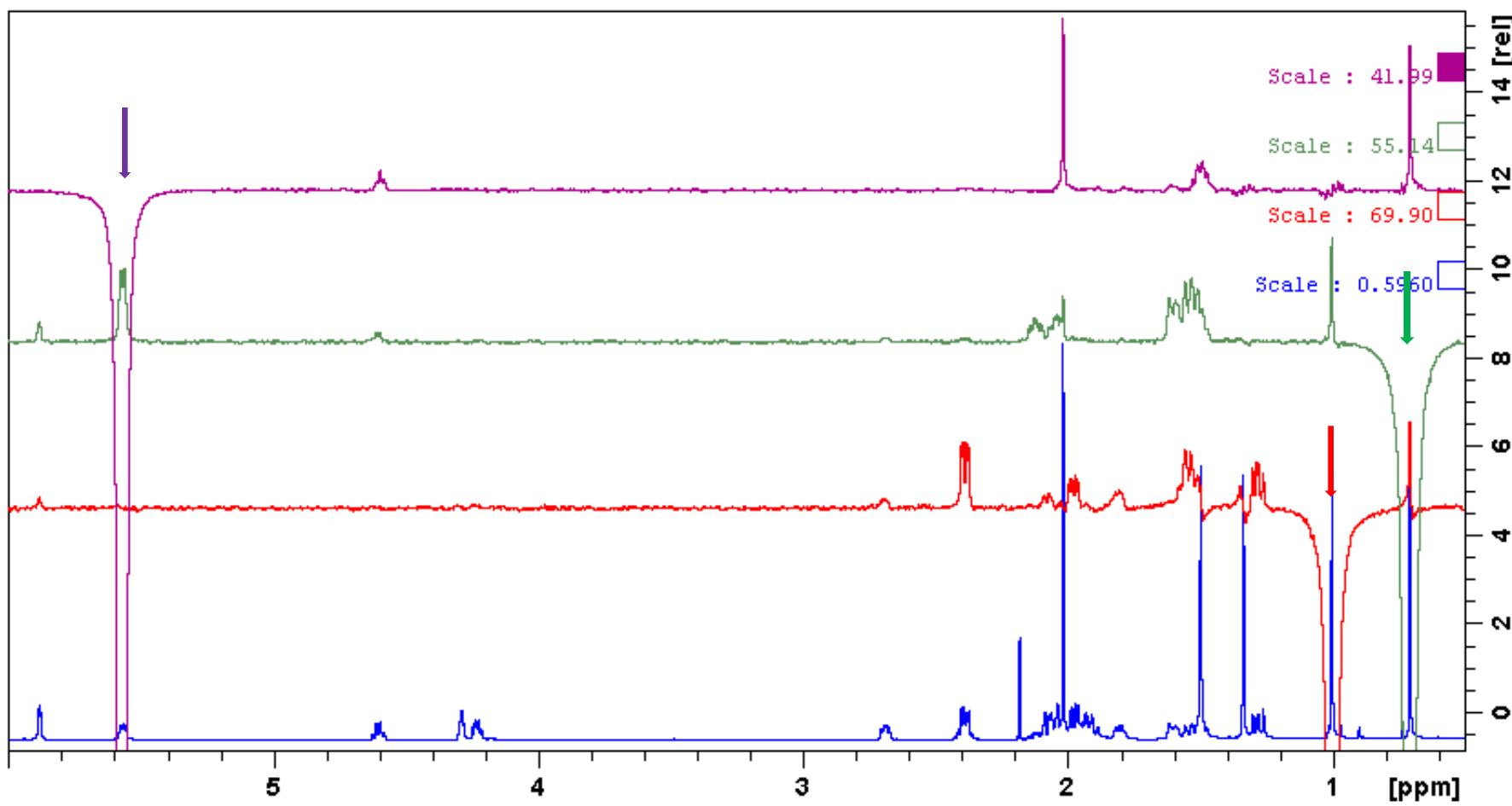
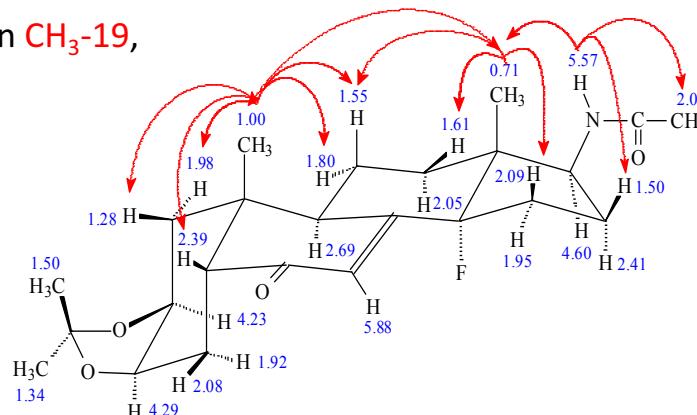


Figure 41. Compound 14, DEPTQ 150 MHz.

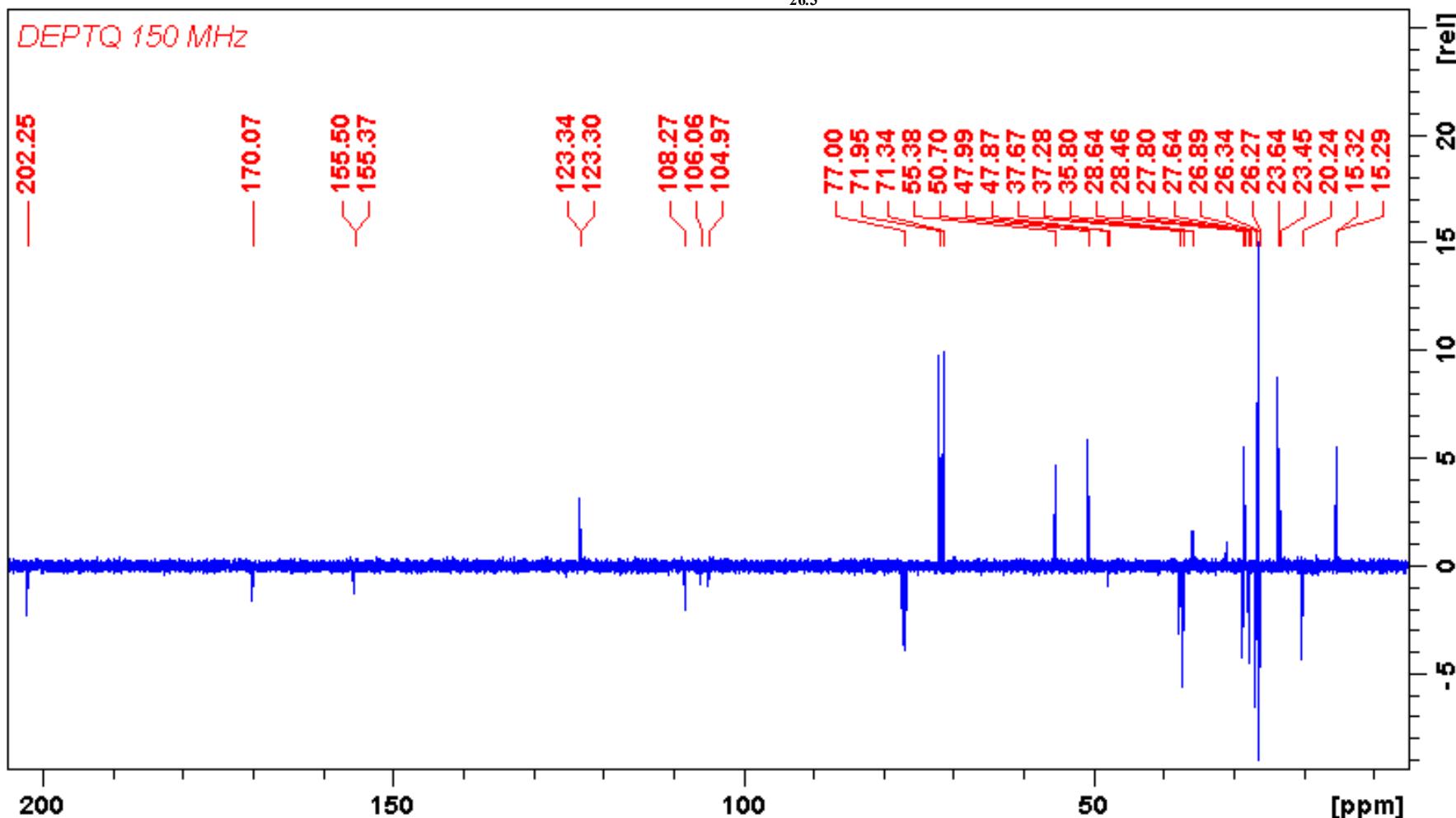
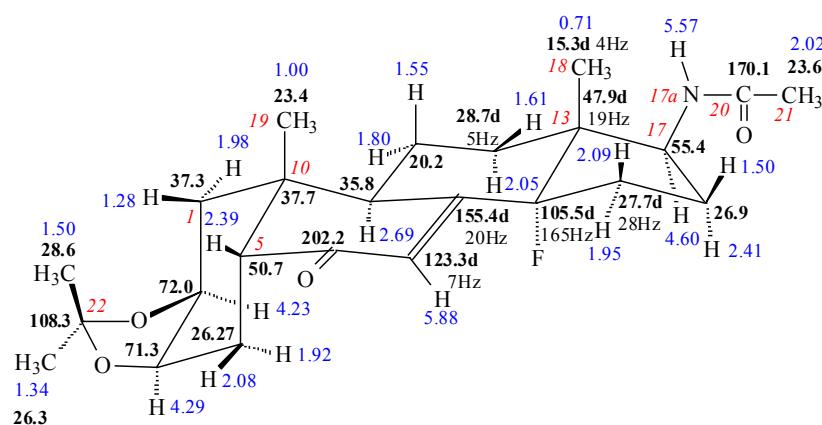


Figure S42. Compound **14**, edHSQC.

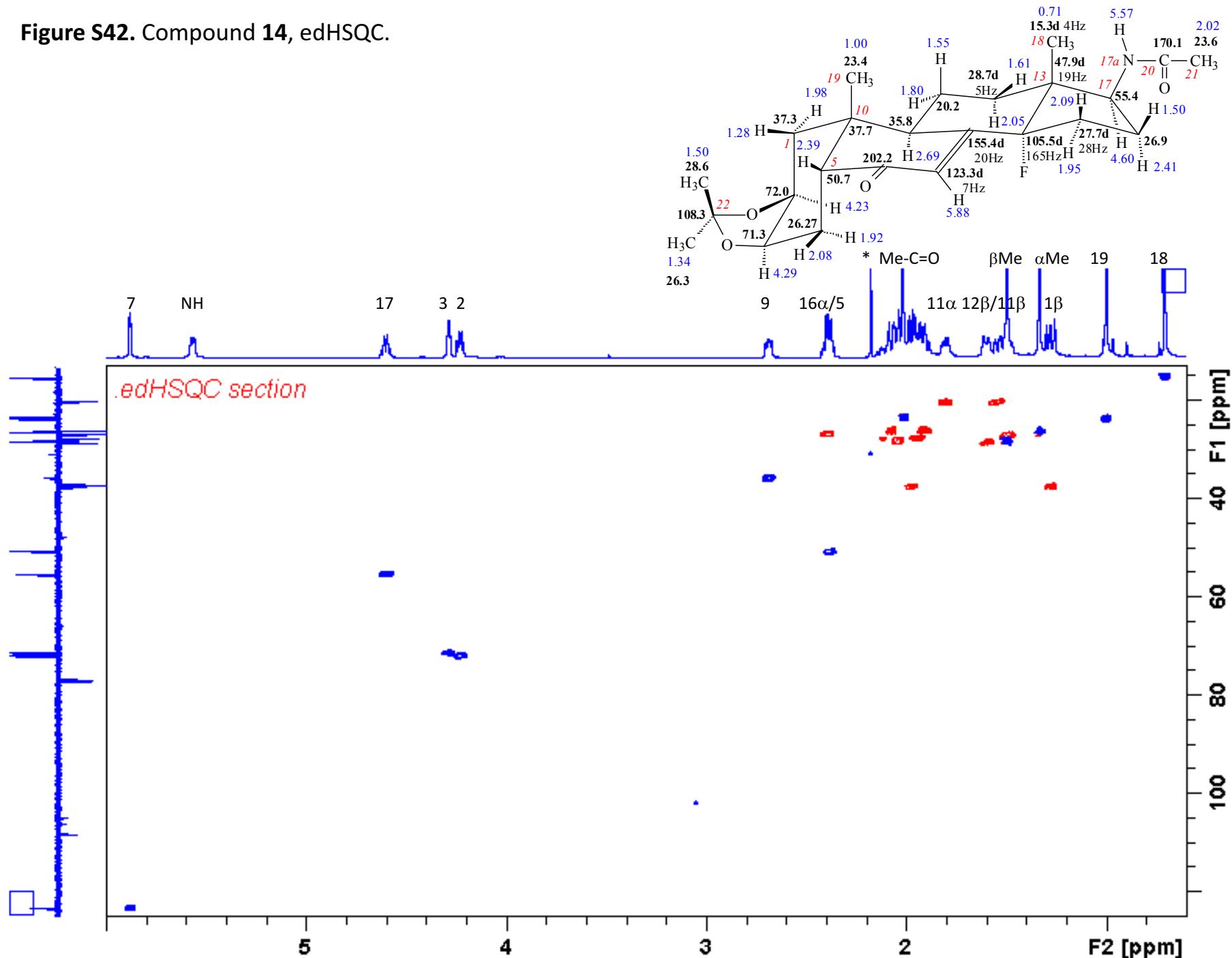


Figure S43. Compound **14**, edHSQC section with inserted selTOCSY on H-17.

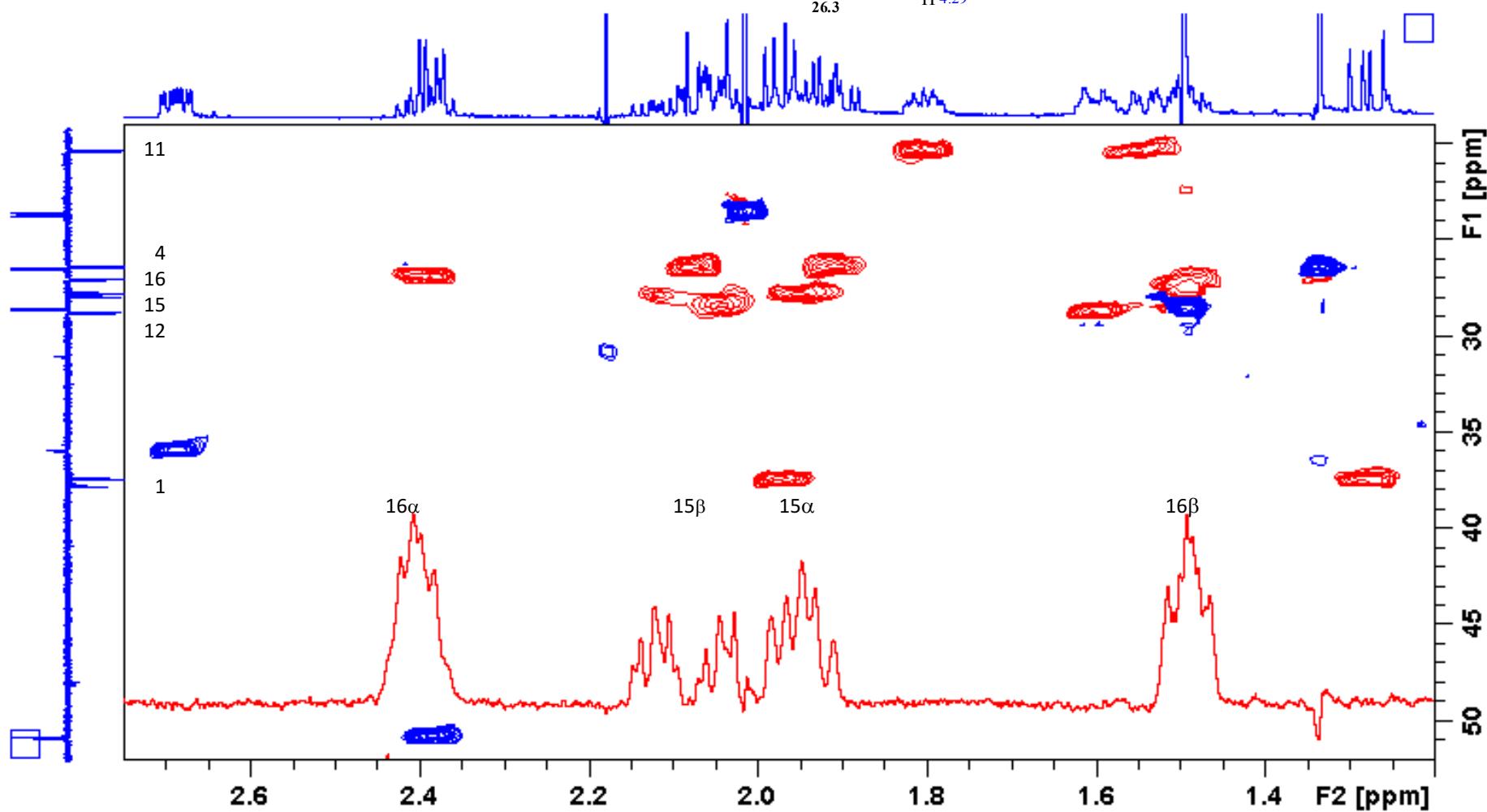
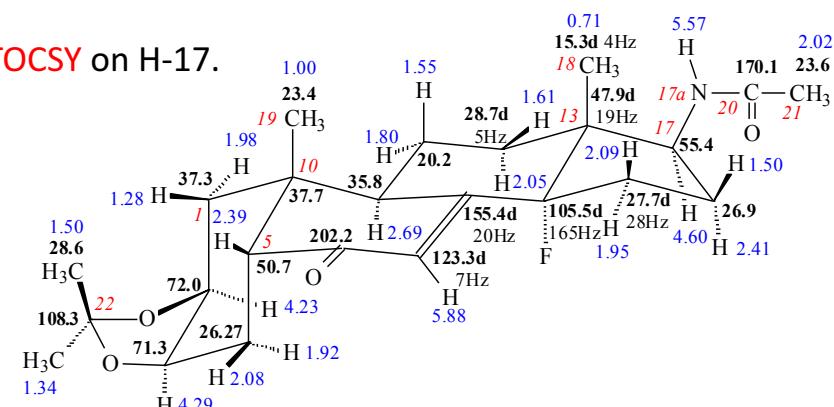


Figure S44. Compound 14, HMBC.

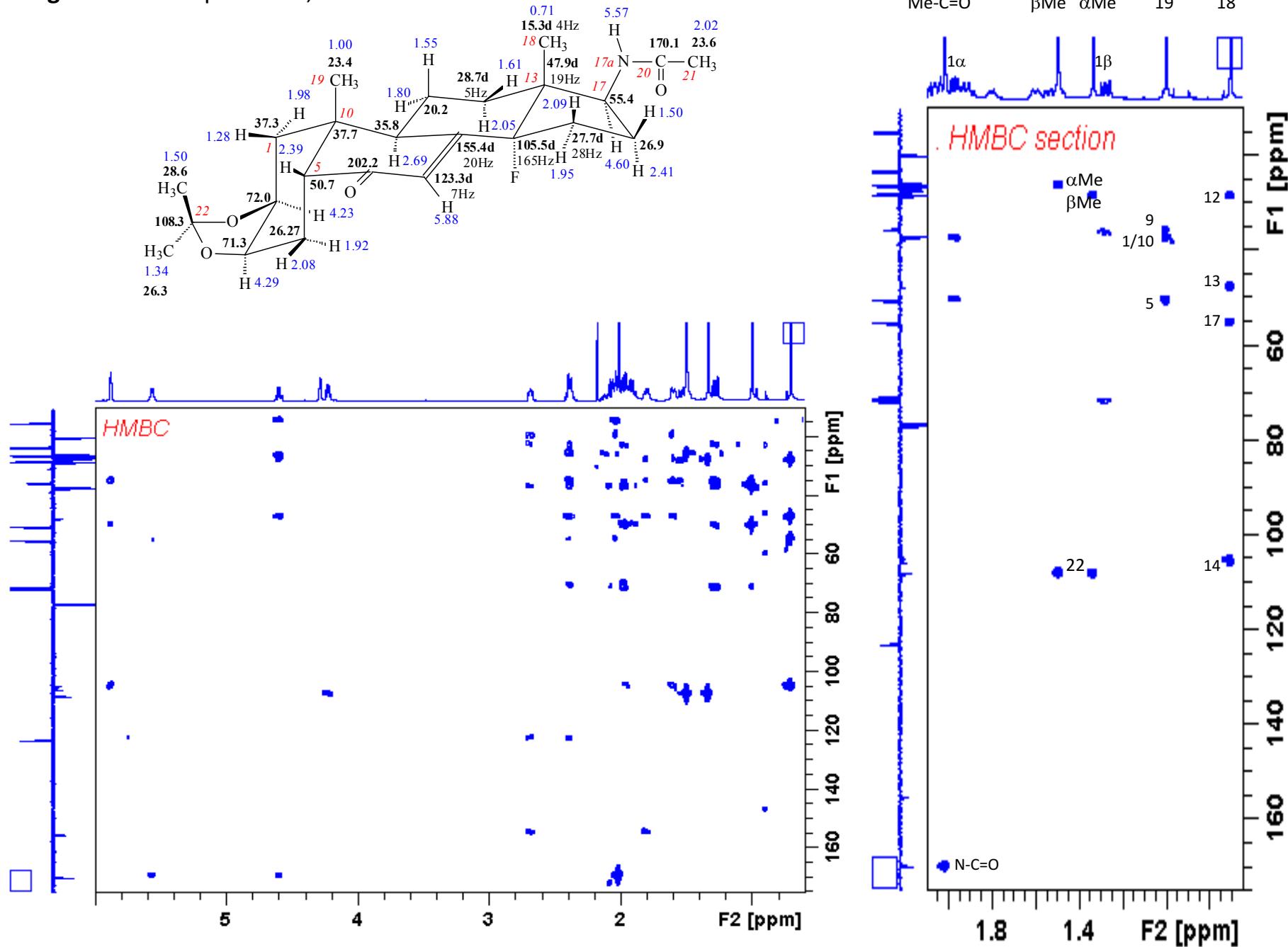


Figure S45. Compound **17**, ^1H DMSO-d₆ 600 MHz.

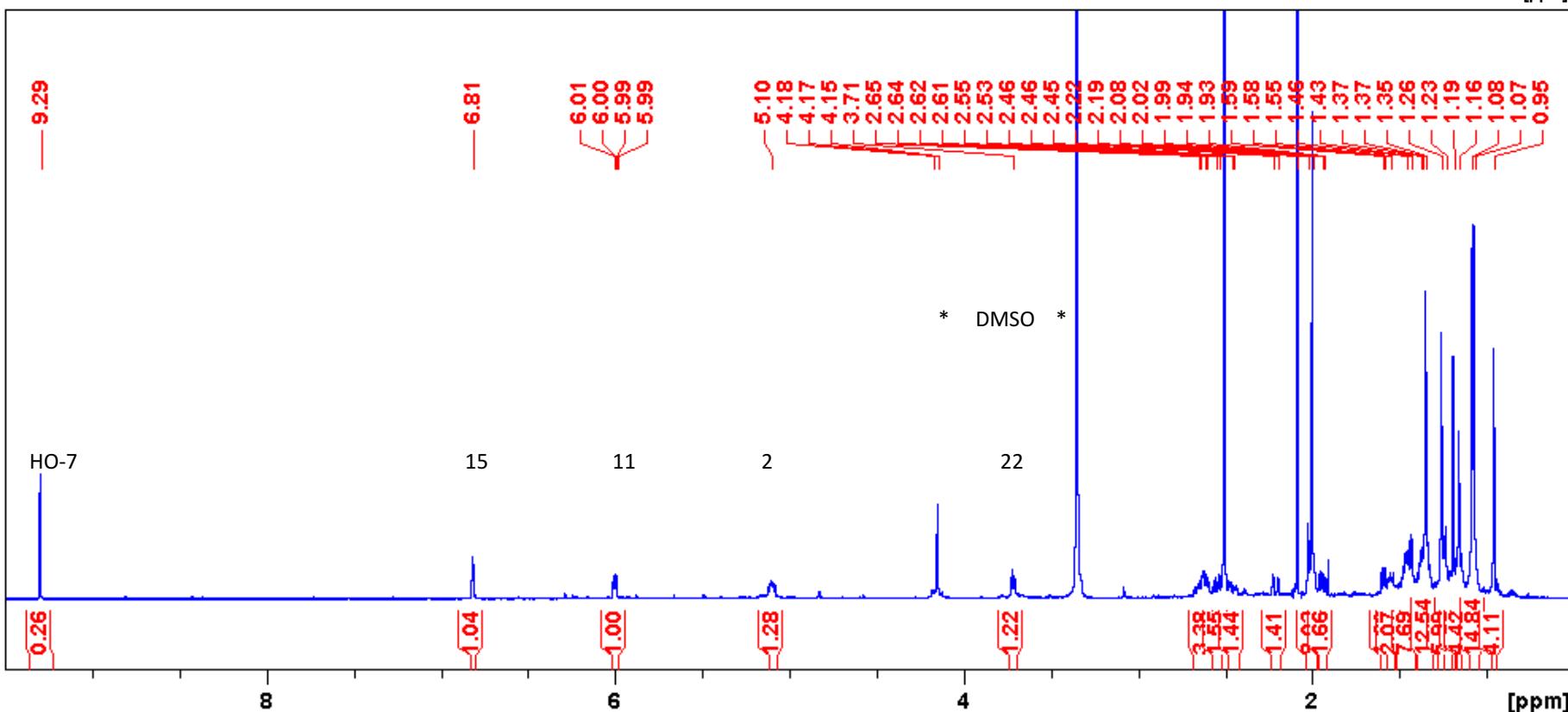
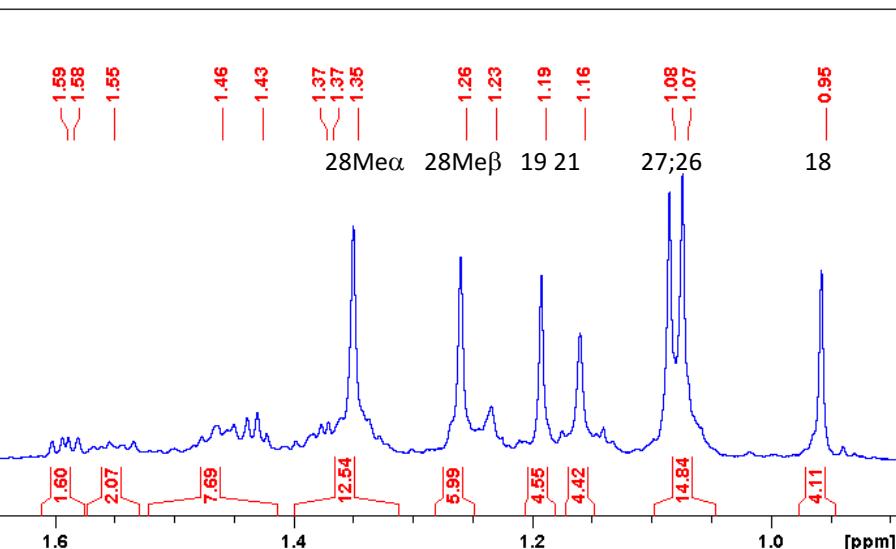
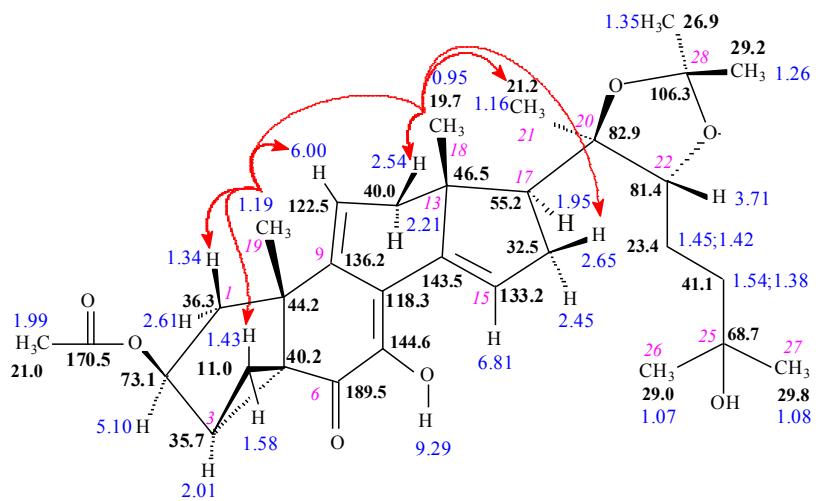


Figure S46. Compound 17, steric proximities detected by selNOE on CH_3 -19 and CH_3 -18 signals and selTOCSY on H-2.

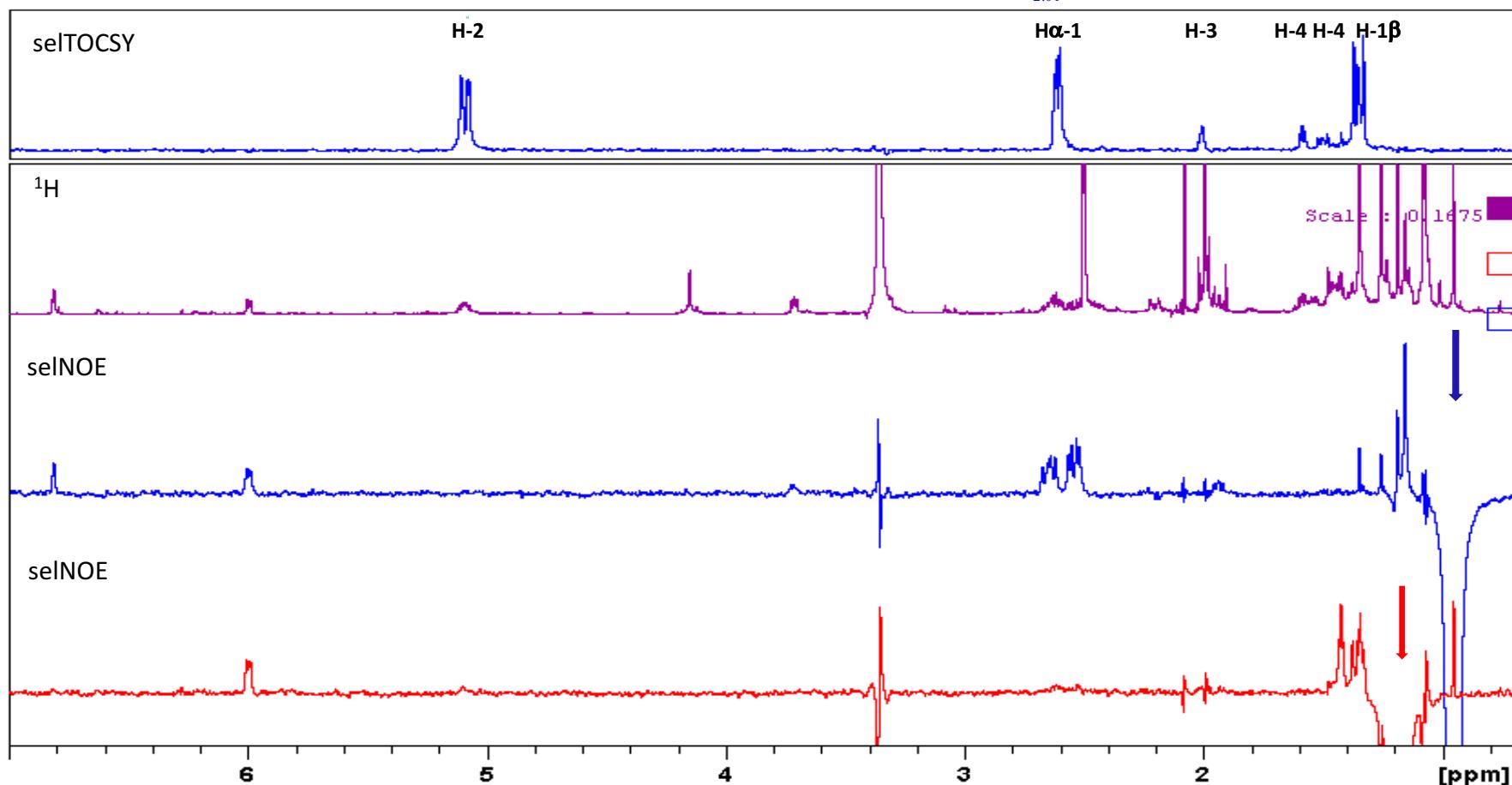
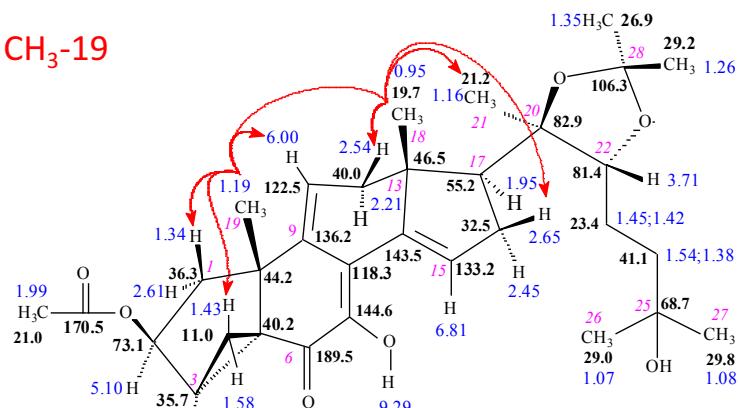


Figure S47. Compound 17, DEPTQ 150 MHz.

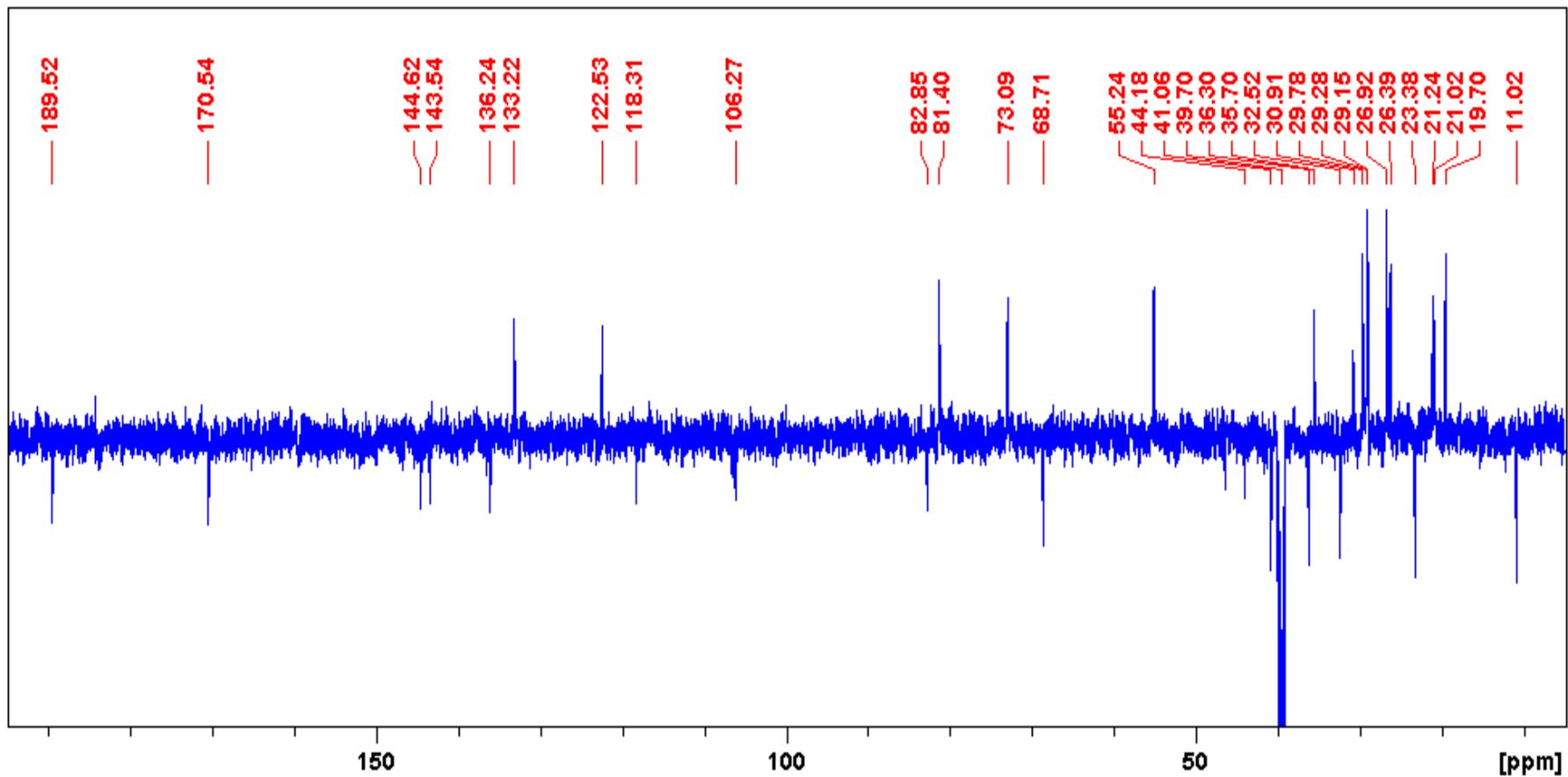
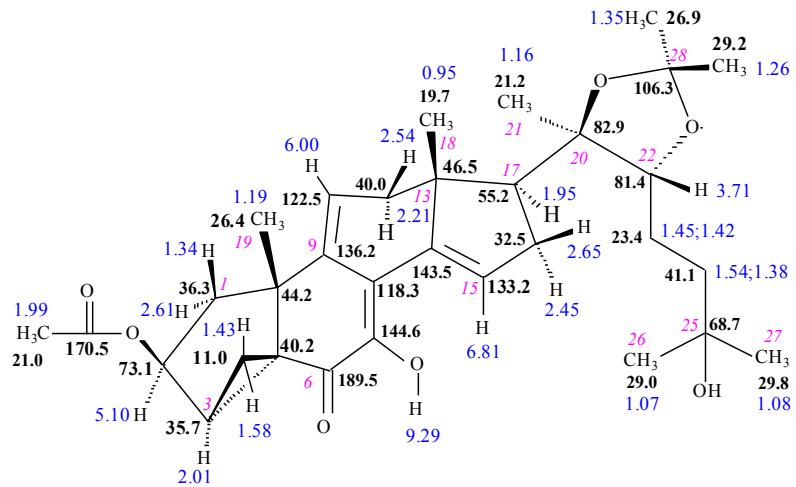


Figure S48. Compound 17, HSQC.

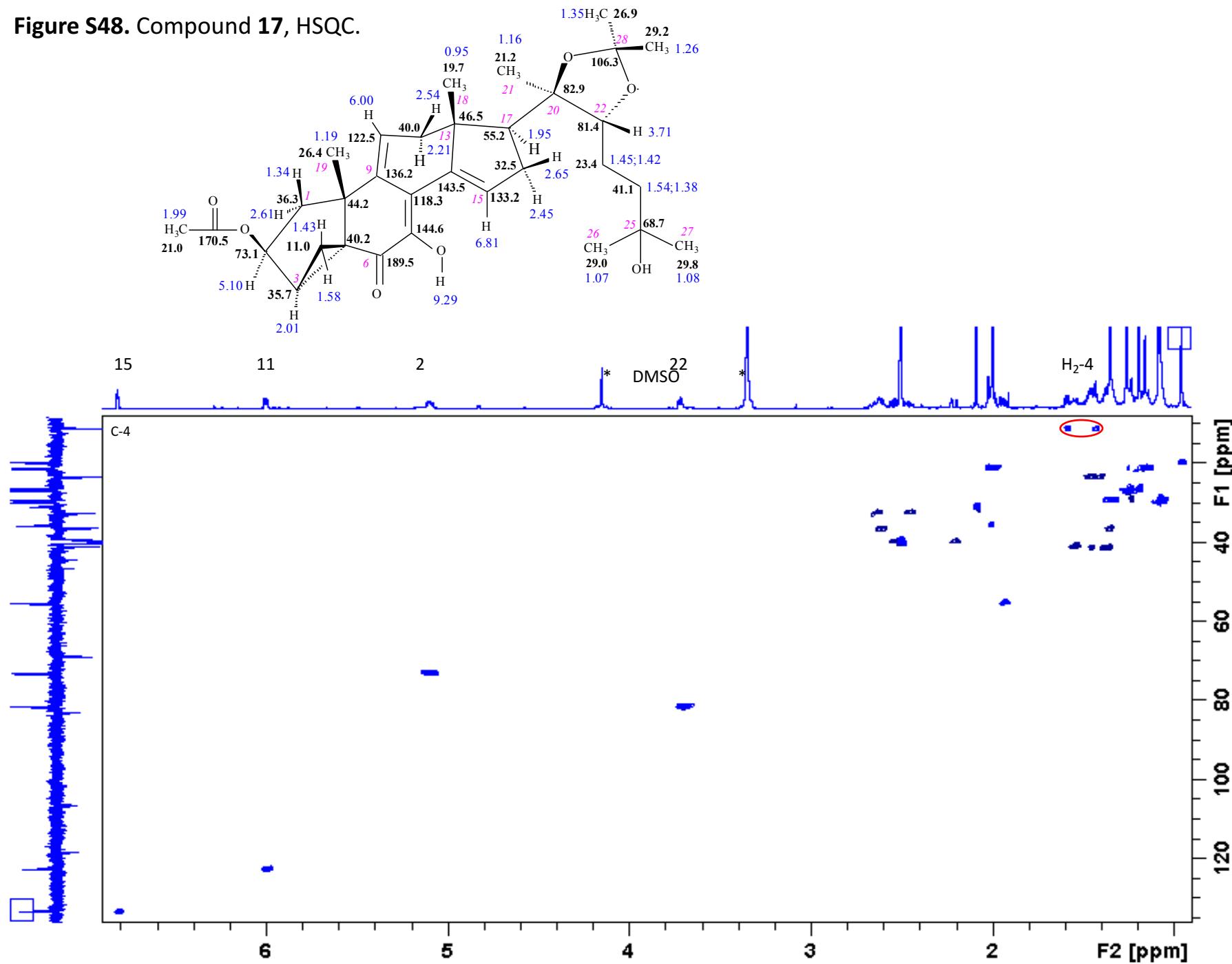


Figure S49. Compound 17, HMBC and HMBC CH₃ section. Black arrows show CH₃/C responses.

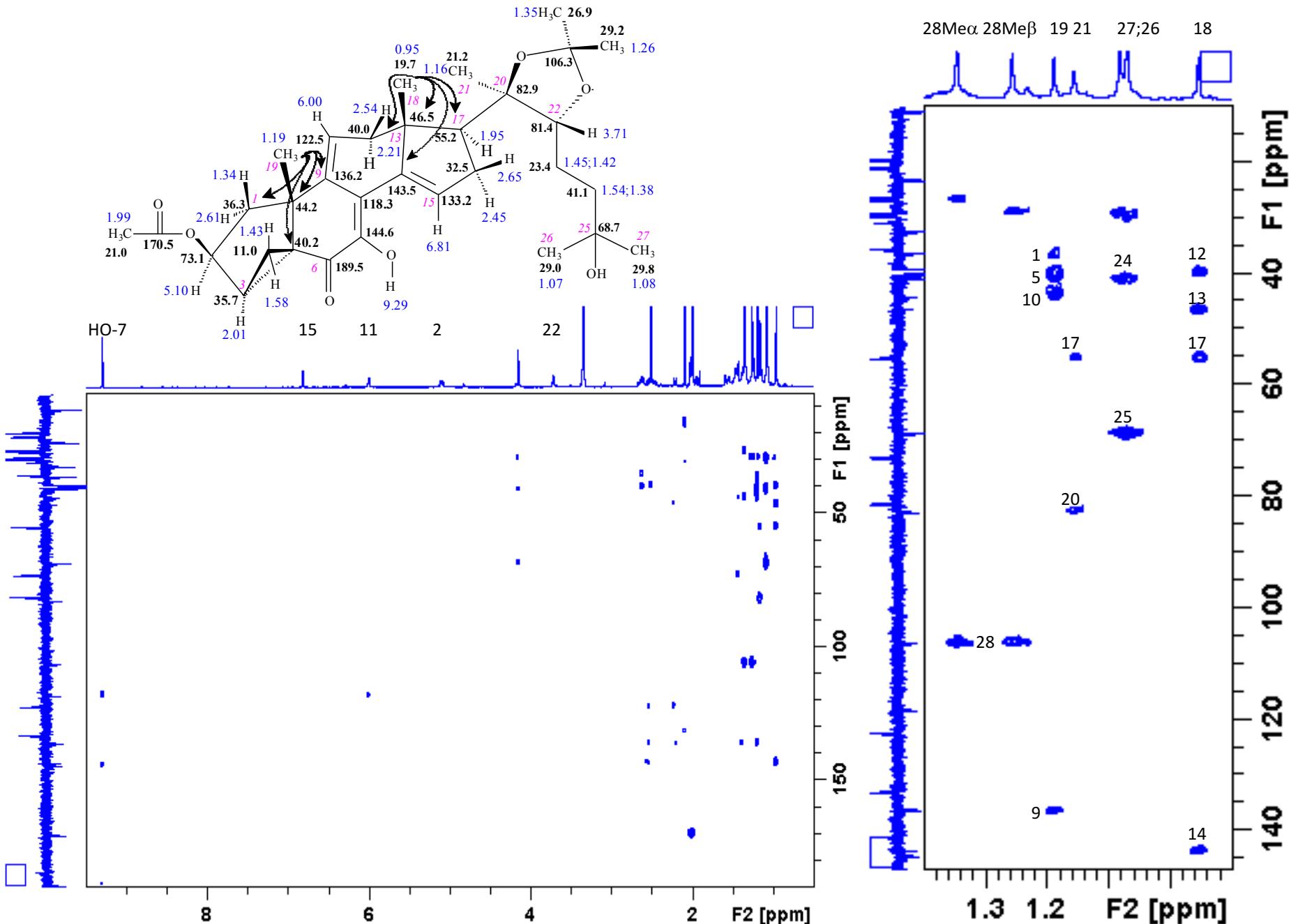


Figure S50. Compound **19**, ^1H CDCl_3 500 MHz.

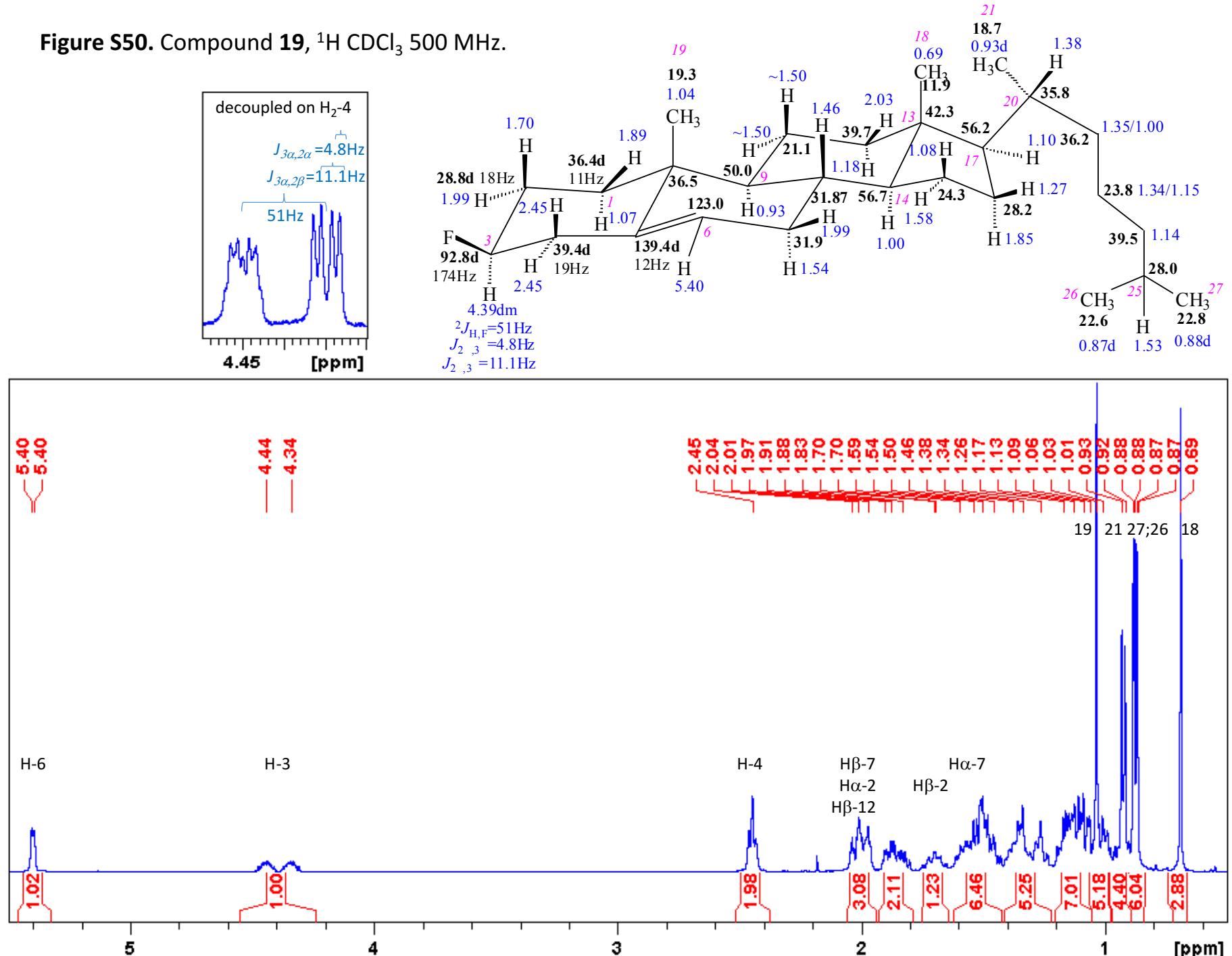


Figure S51. Compound **19**, ^1H , ^1H -COSY and selROE on $\text{H}\alpha$ -3.

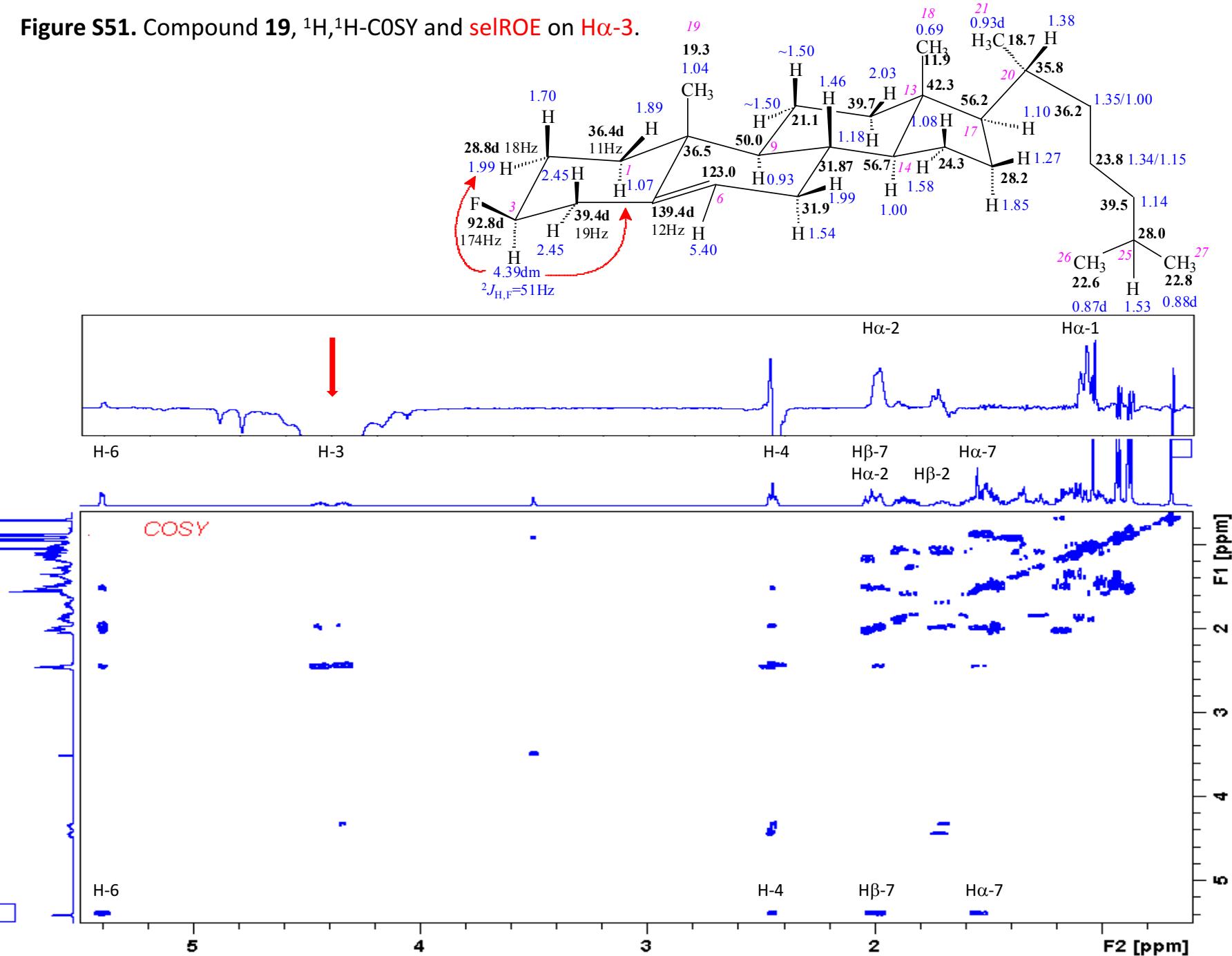


Figure S52. Compound **19**, APT 125 MHz.

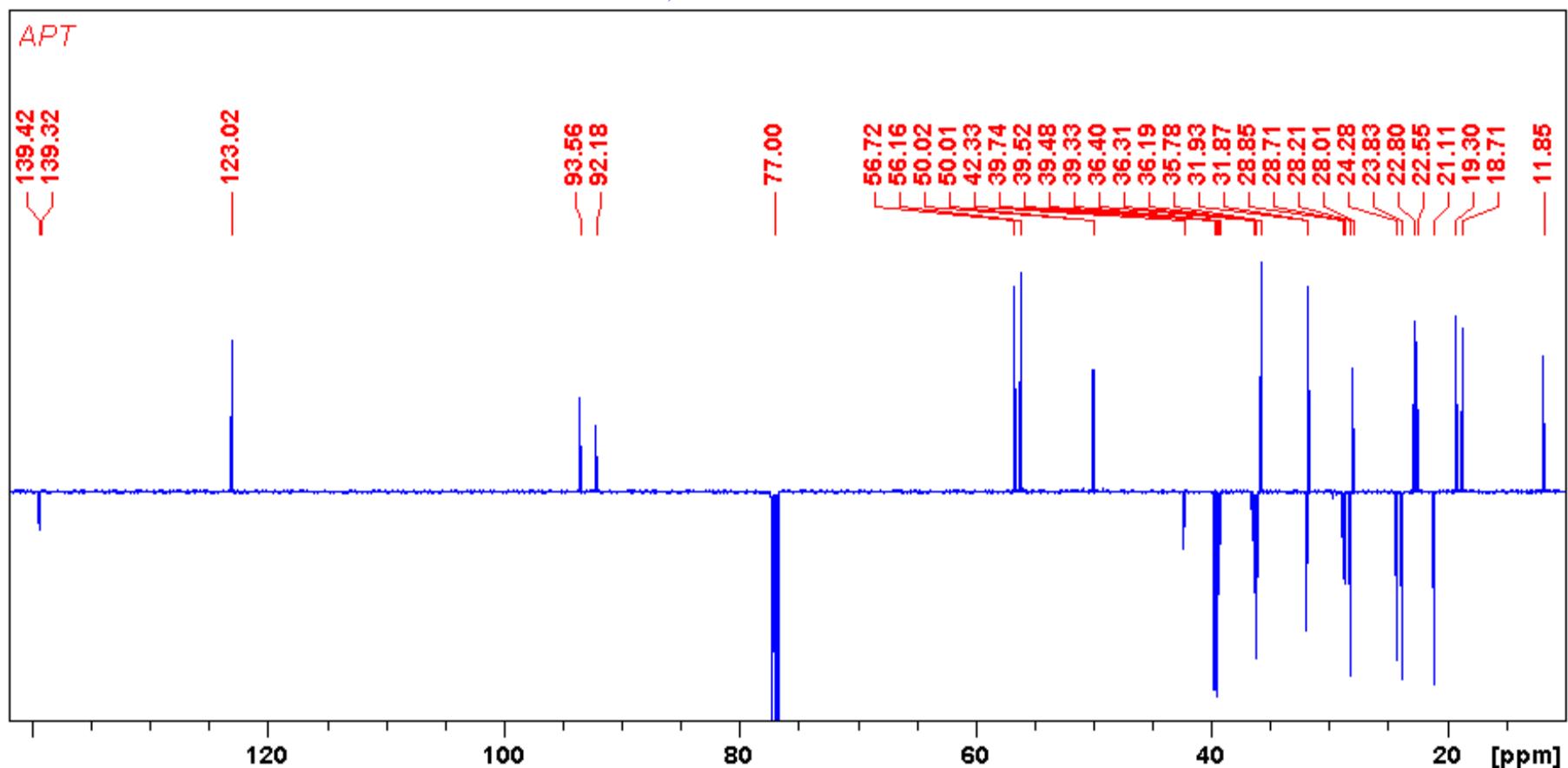
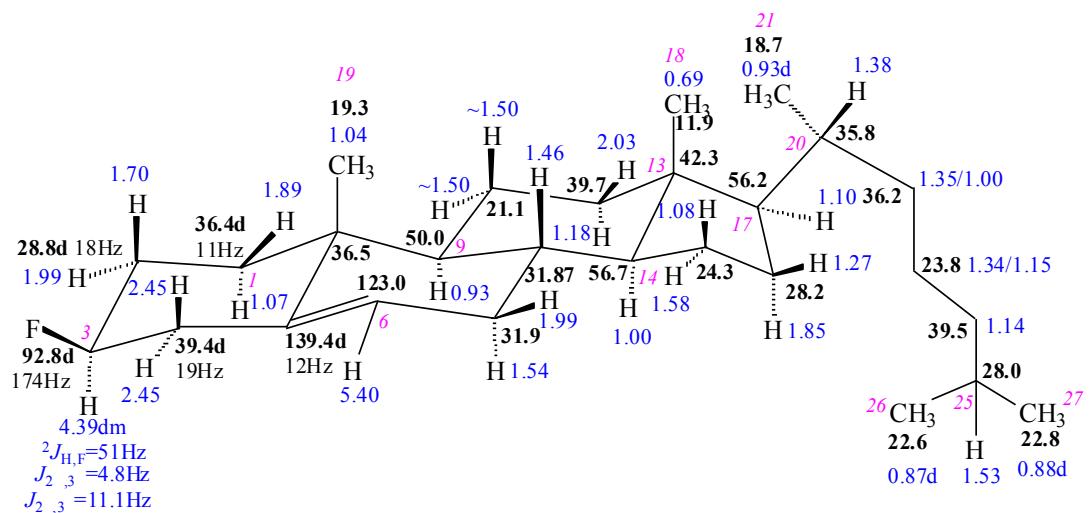


Figure S53. Compound **19**, HSQC section with inserted band-selective HSQC measurements of 37–36 and 40–39 ppm. *19*

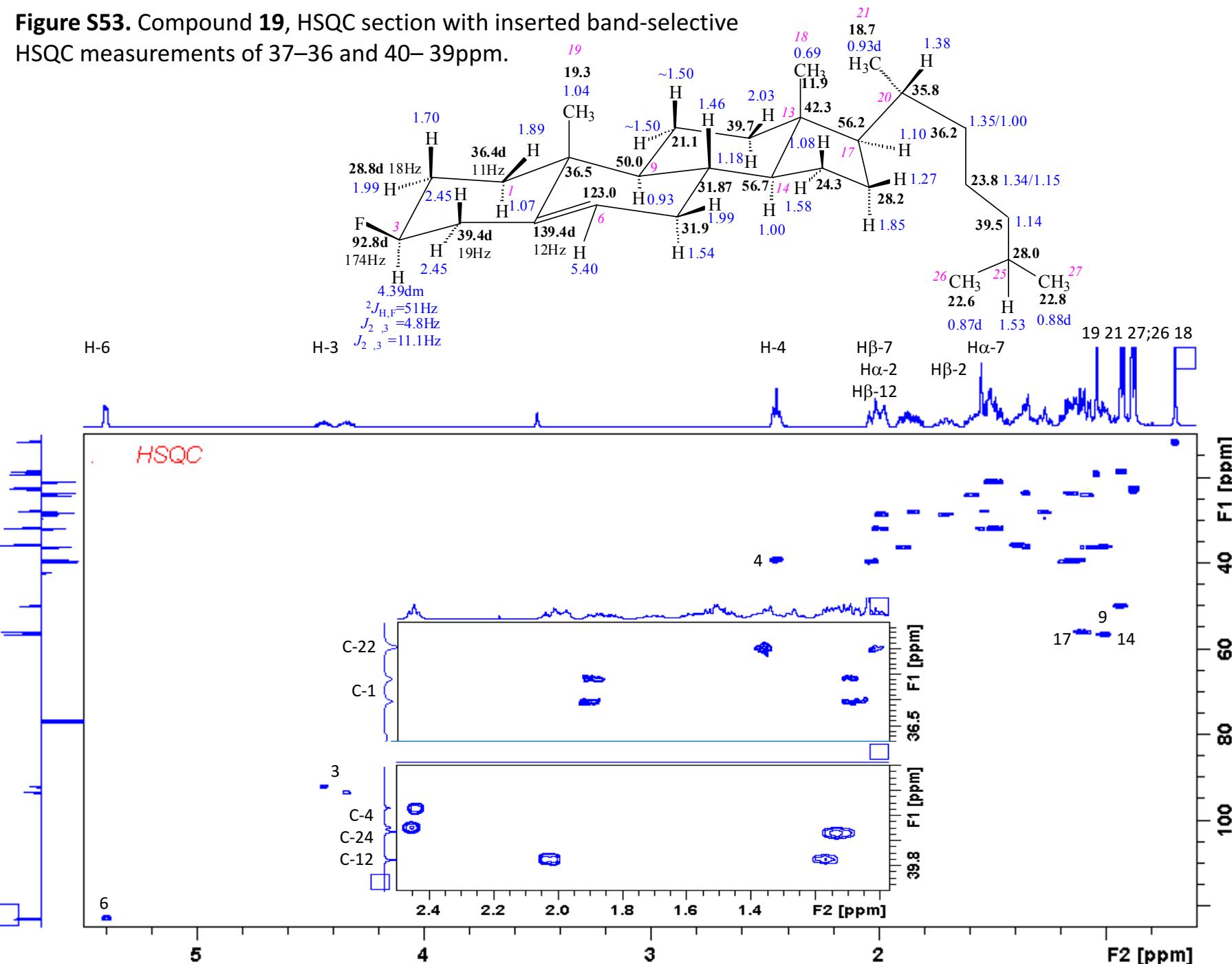


Figure S54. Compound **19**, edHSQC section with inserted selROE on $\text{H}_3\text{-}18$.

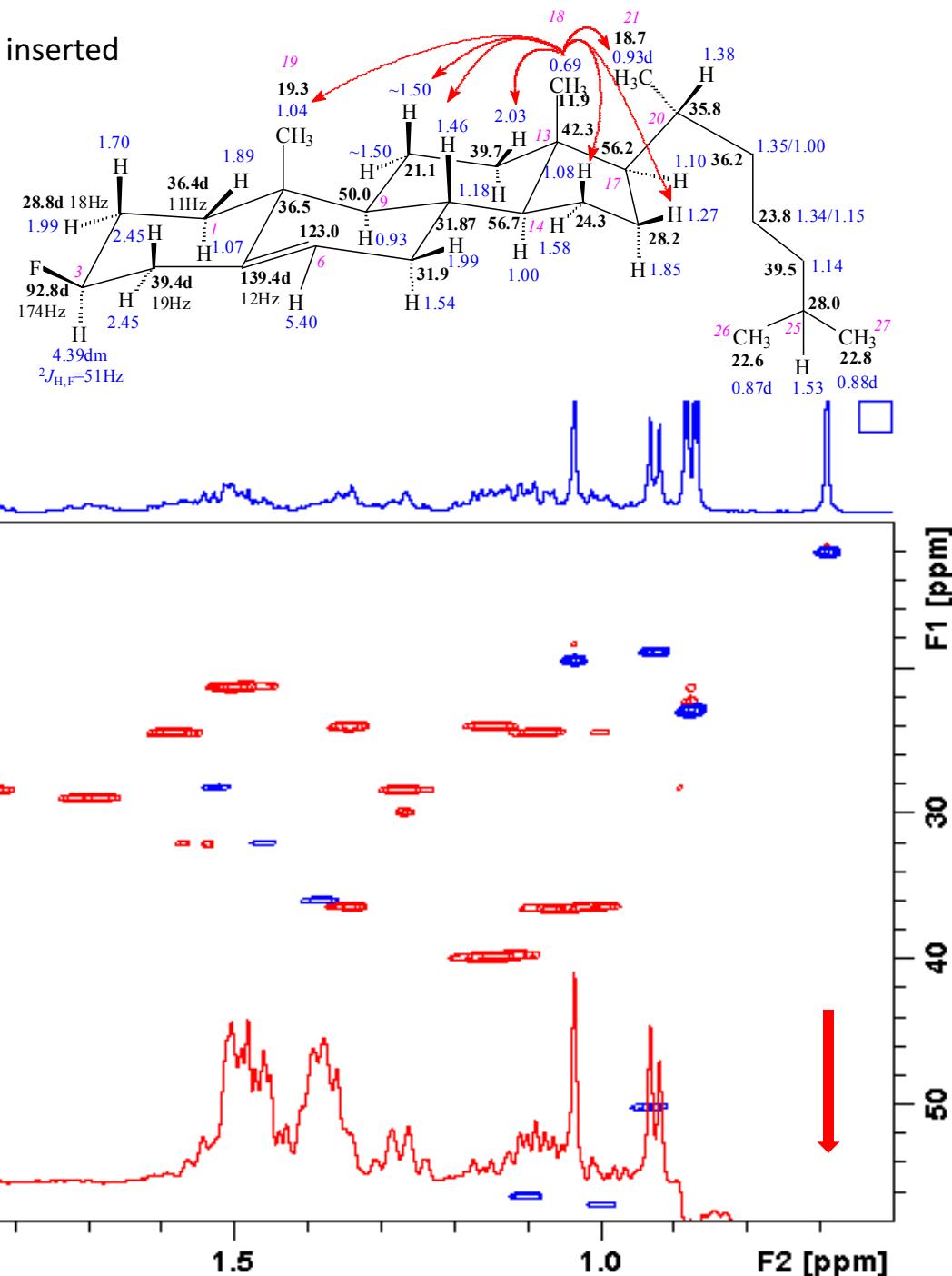


Figure S55. Compound **19**, HMBC and HMBC CH₃ section.

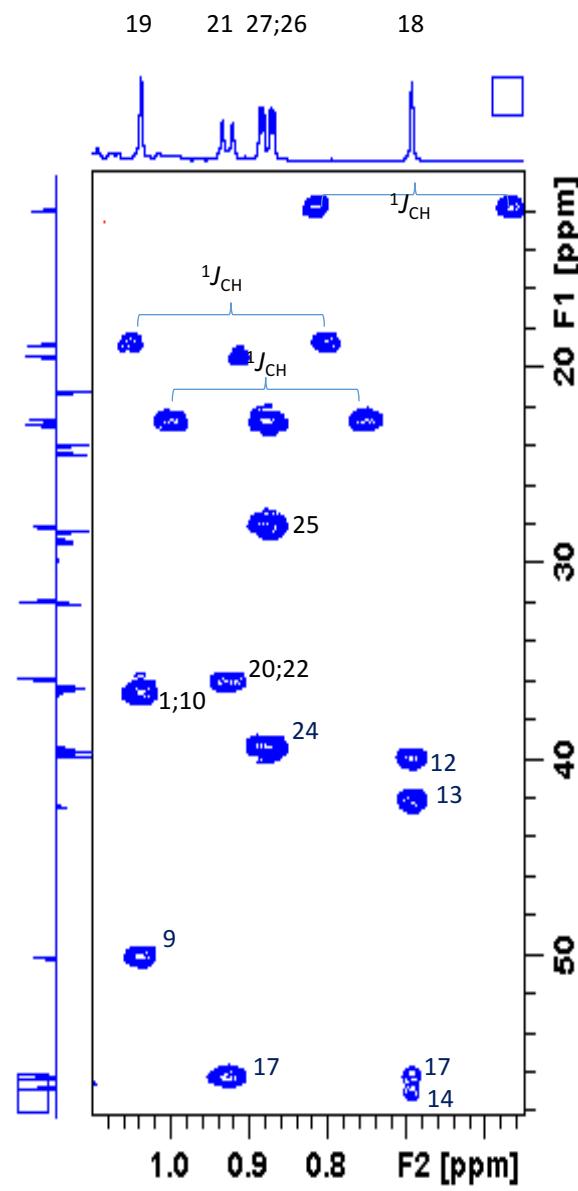
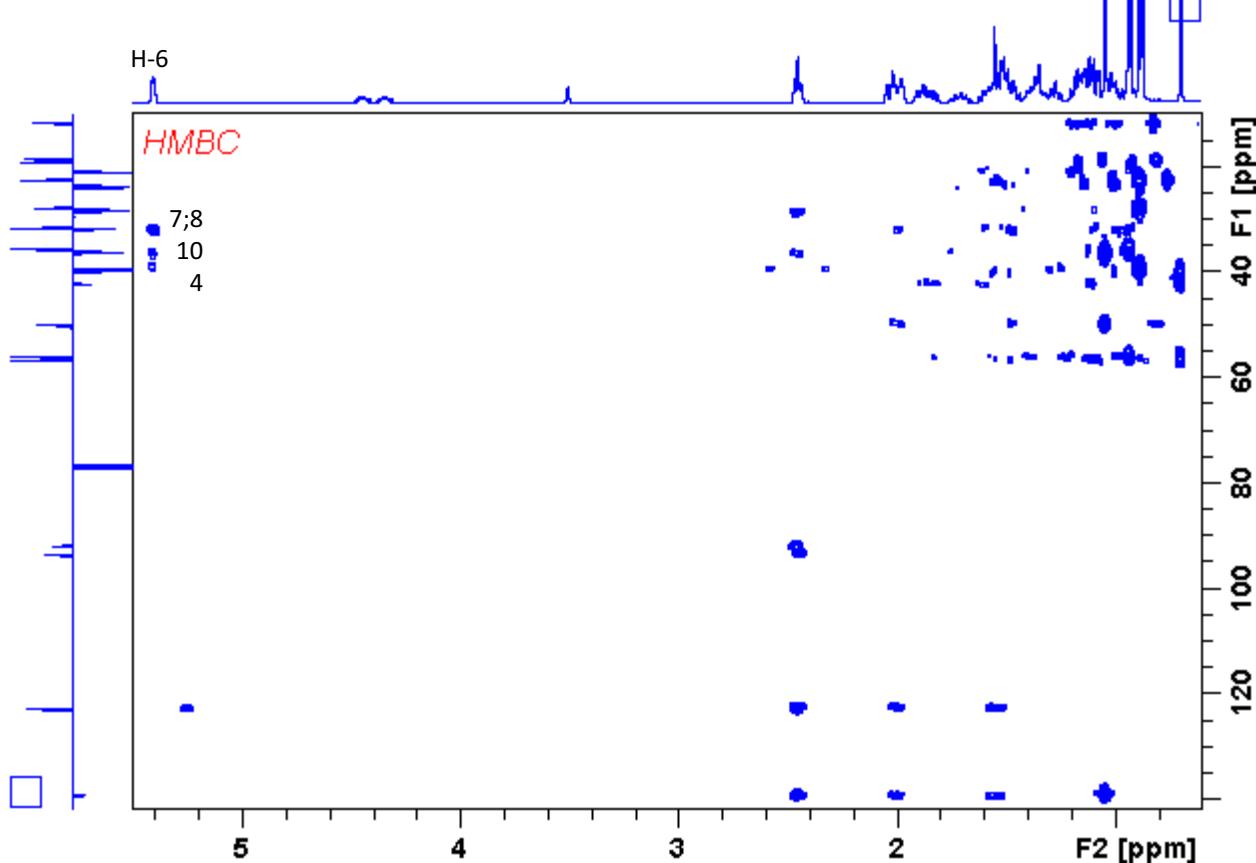
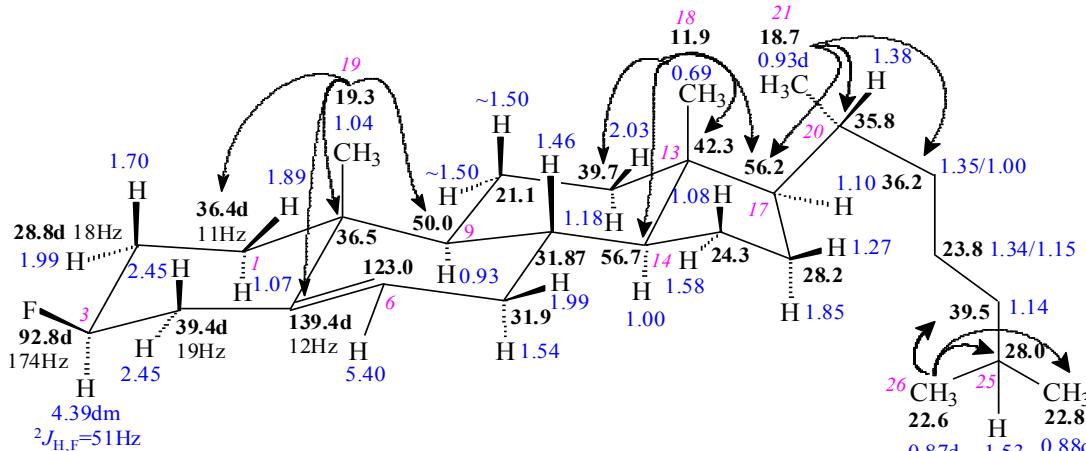


Figure S56. Compound 4, HR-MS spectra.

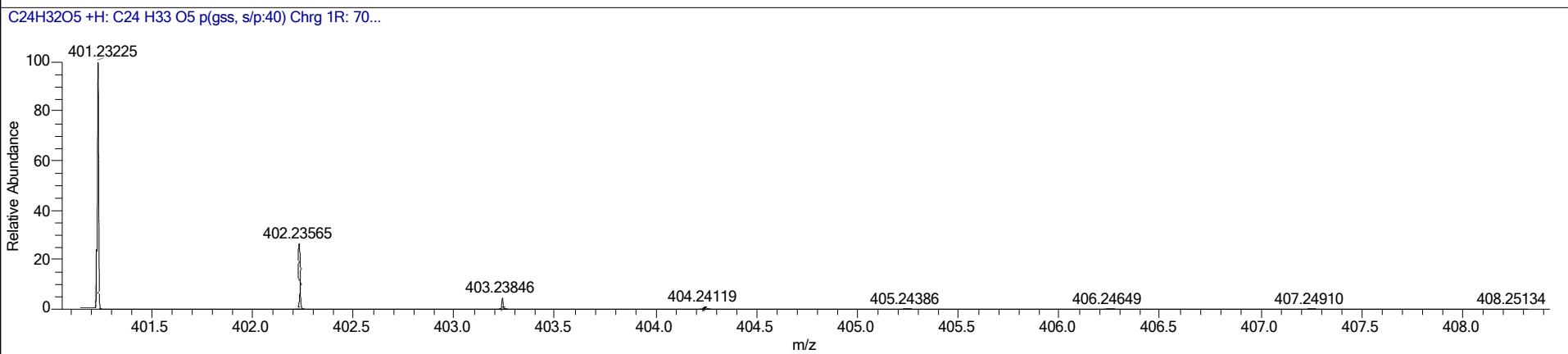
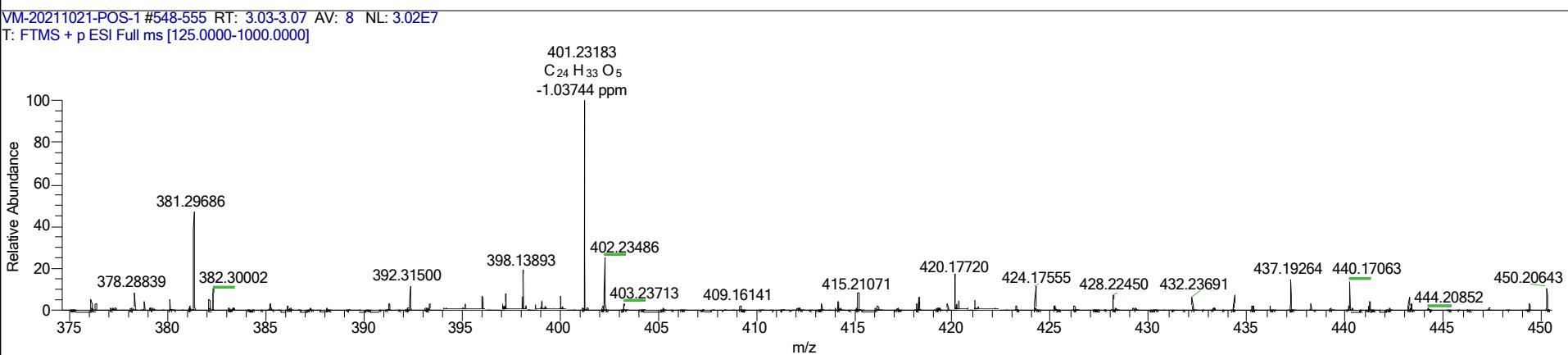
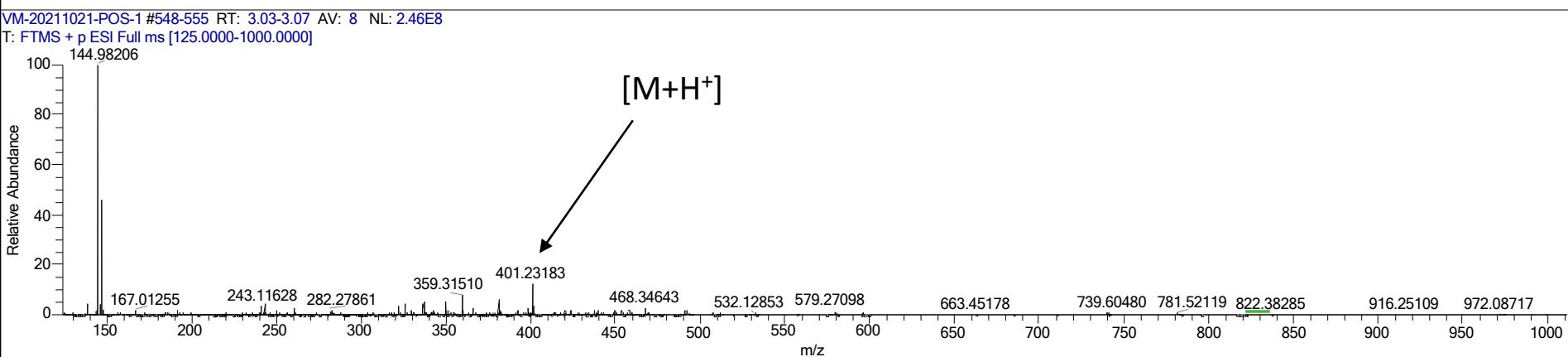
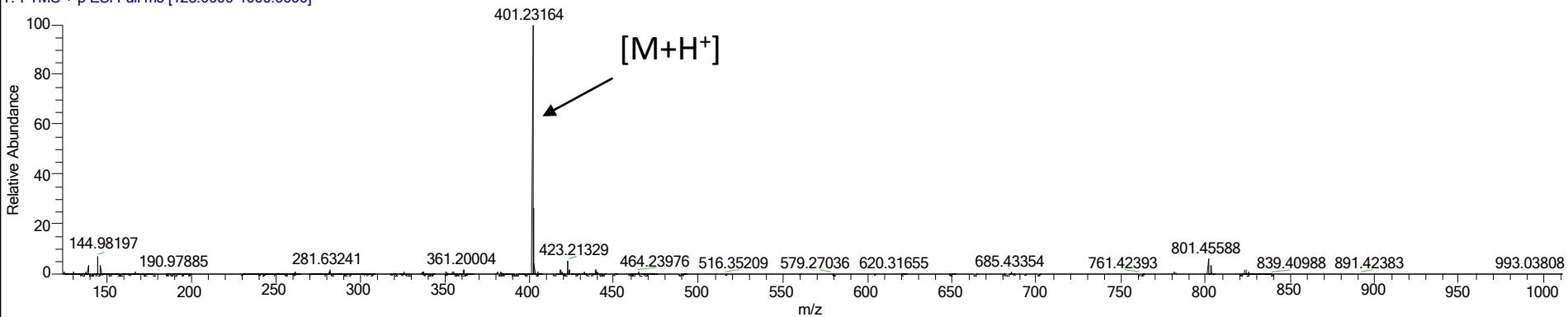
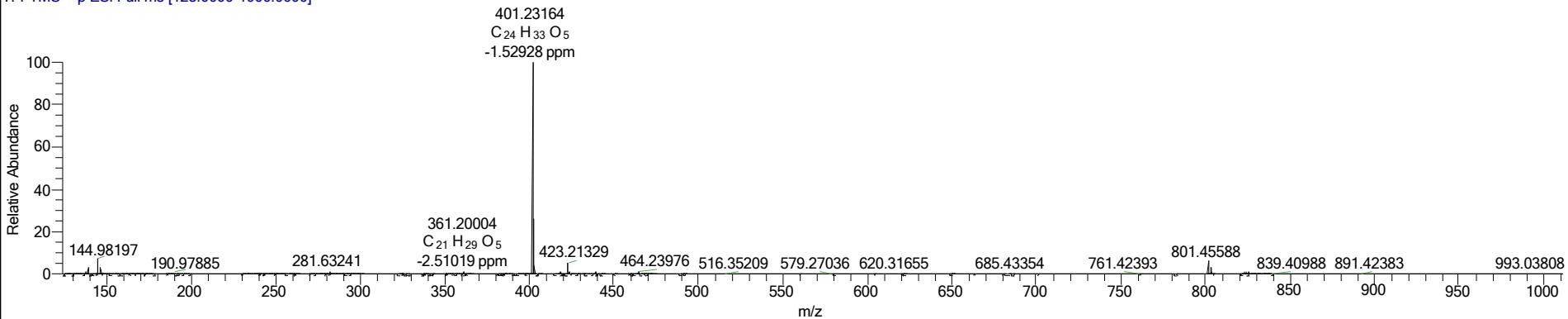


Figure S57. Compound 5, HR-MS spectra.

VM-20211021-POS-1 #743-777 RT: 4.13-4.31 AV: 35 NL: 3.84E8
T: FTMS + p ESI Full ms [125.0000-1000.0000]



VM-20211021-POS-1 #743-777 RT: 4.13-4.31 AV: 35 NL: 3.84E8
T: FTMS + p ESI Full ms [125.0000-1000.0000]



C24H32O5 +H: C24 H33 O5 p(gss, s/p:40) Chrg 1R: 70...

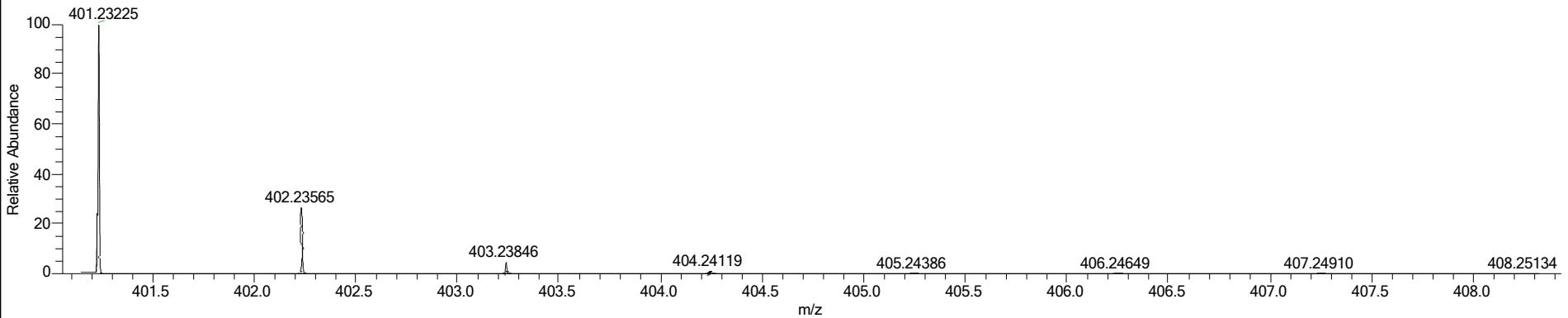


Figure S58. Compound 6, HR-MS spectra.

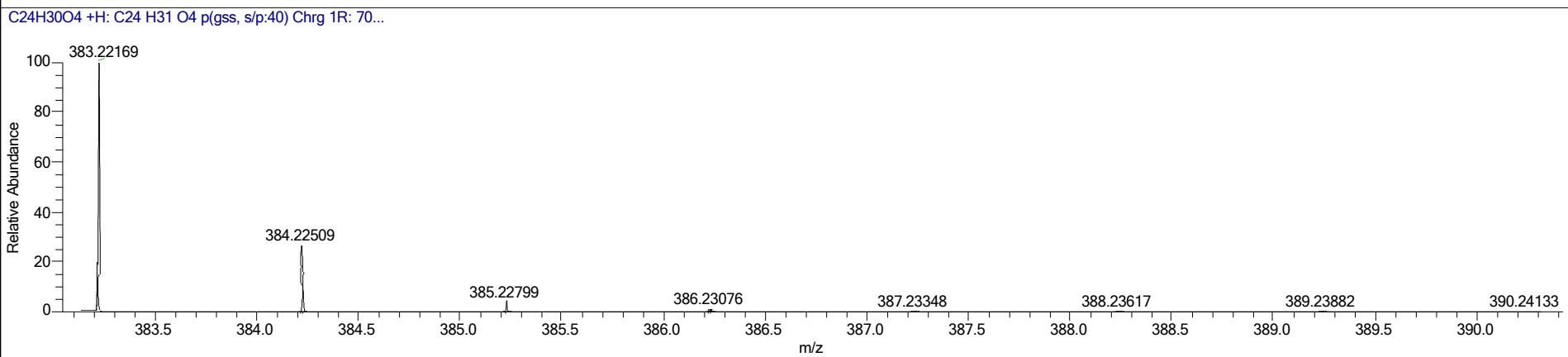
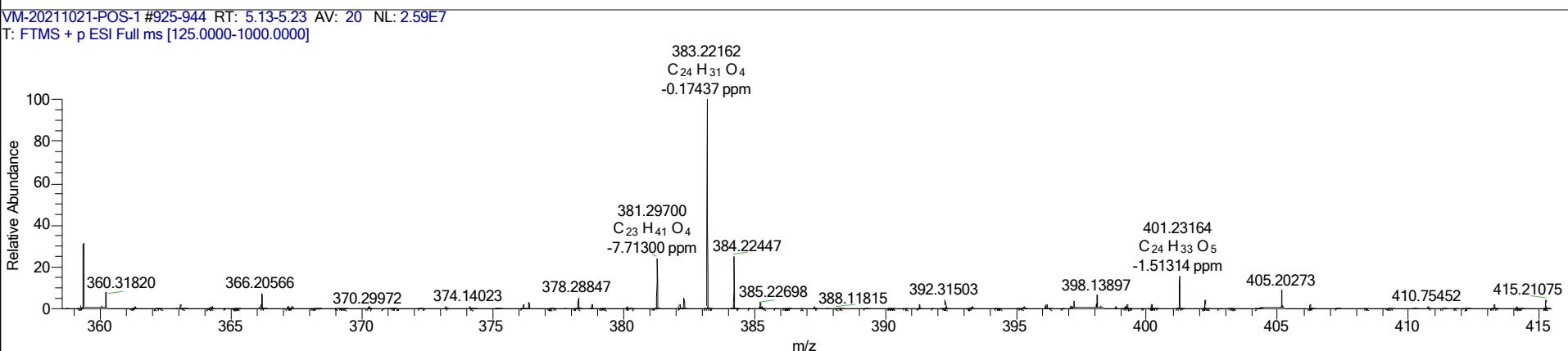
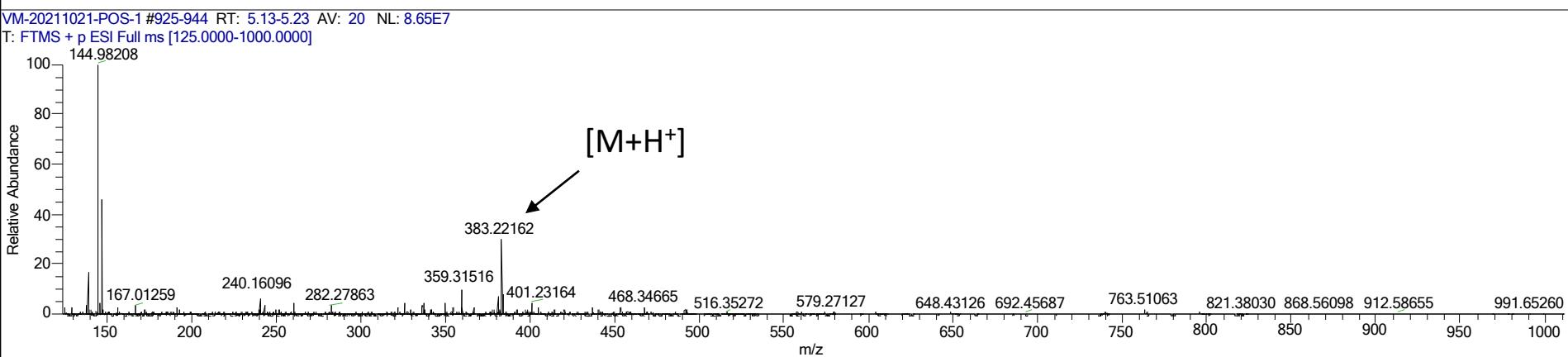
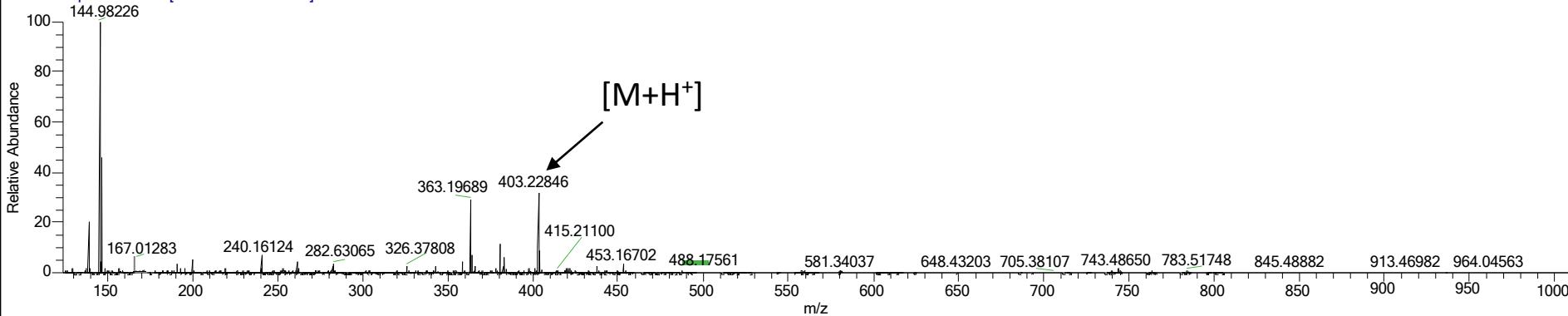
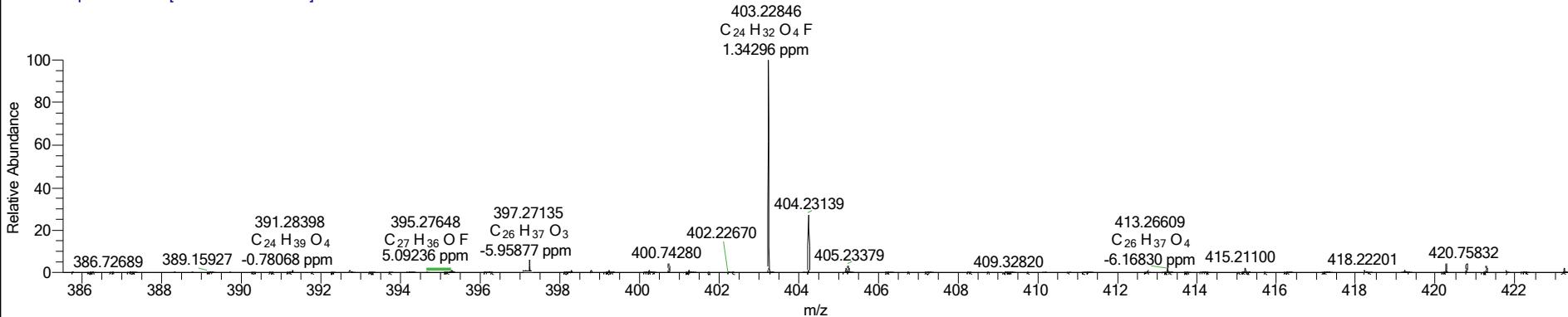


Figure S59. Compound 7, HR-MS spectra.

VM-20211021-POS-2 #171-184 RT: 0.99-1.06 AV: 14 NL: 1.33E8
 T: FTMS + p ESI Full ms [125.0000-1000.0000]



VM-20211021-POS-2 #171-184 RT: 0.99-1.06 AV: 14 NL: 4.29E8
 T: FTMS + p ESI Full ms [125.0000-1000.0000]



C24H31FO4 +H: C24 H32 F1 O4 p(gss, s/p:40) Chrg 1R...

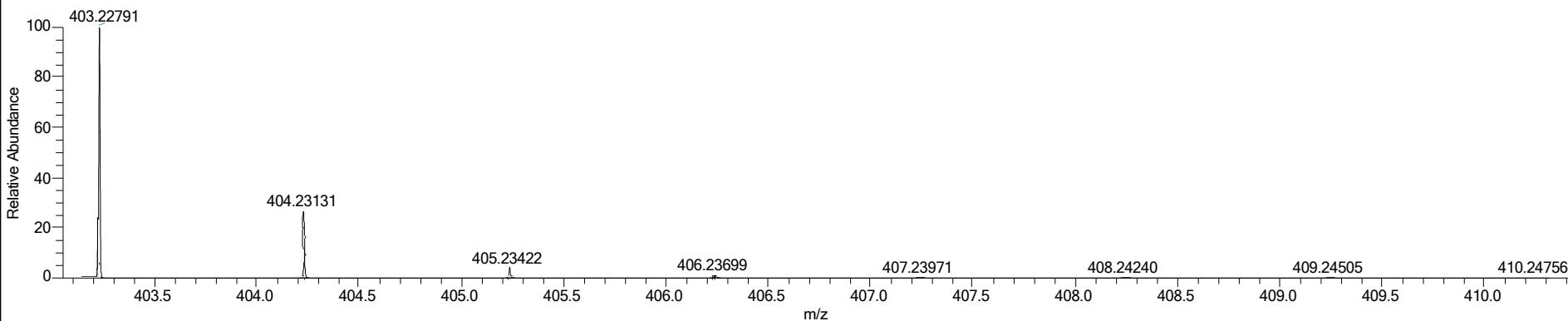
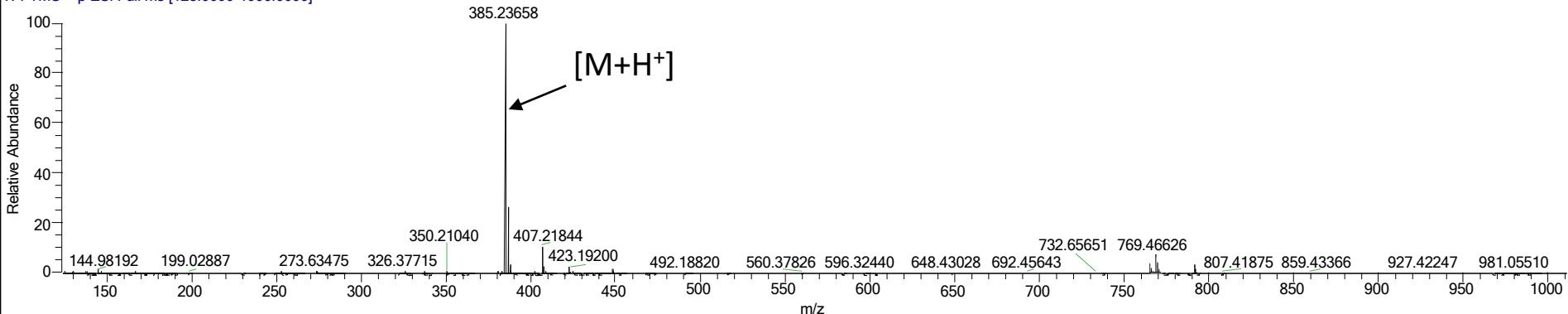
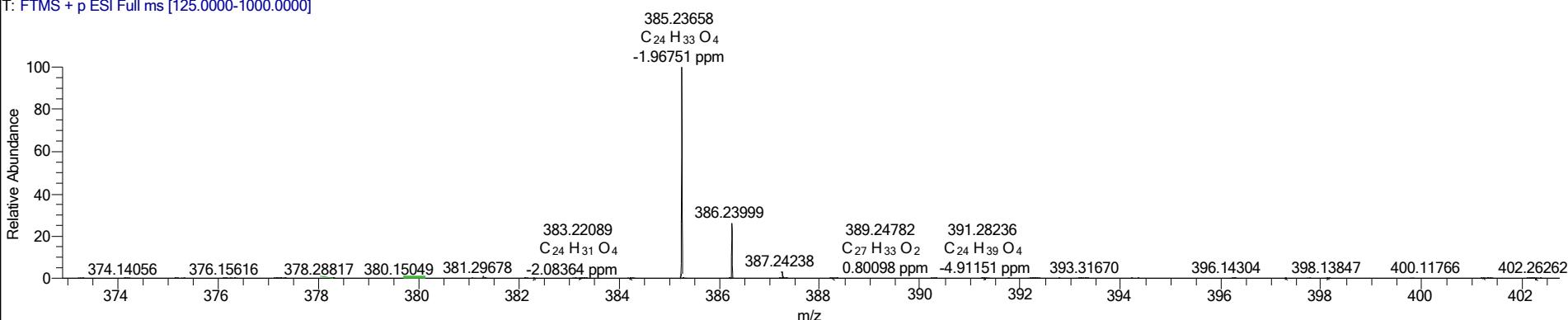


Figure S60. Compound 10, HR-MS spectra.

VM-20211021-POS-1 #1165-1191 RT: 6.49-6.63 AV: 27 NL: 4.24E8
 T: FTMS + p ESI Full ms [125.0000-1000.0000]



VM-20211021-POS-1 #1165-1191 RT: 6.49-6.63 AV: 27 NL: 4.24E8
 T: FTMS + p ESI Full ms [125.0000-1000.0000]



C₂₄H₃₂O₄ +H: C₂₄H₃₃O₄ p(gss, s/p:40) Chrg 1R: 70...

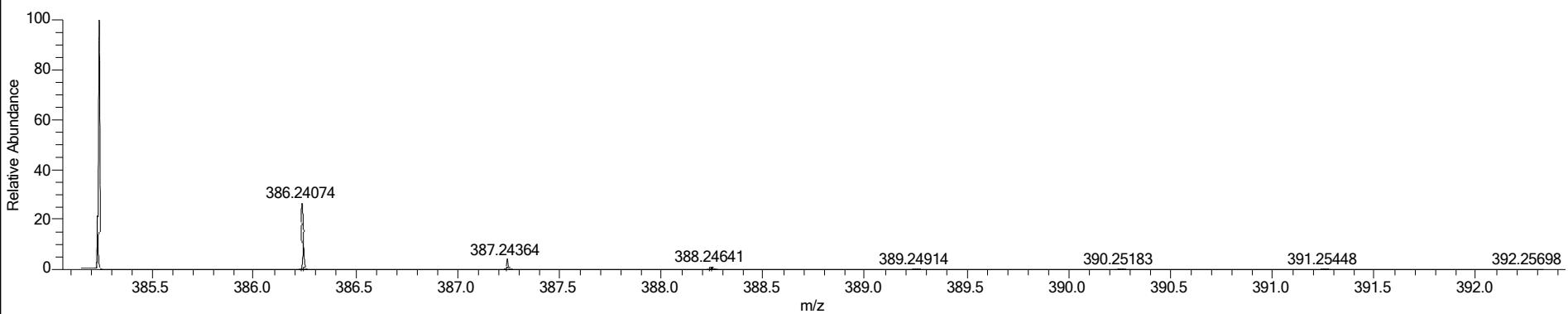
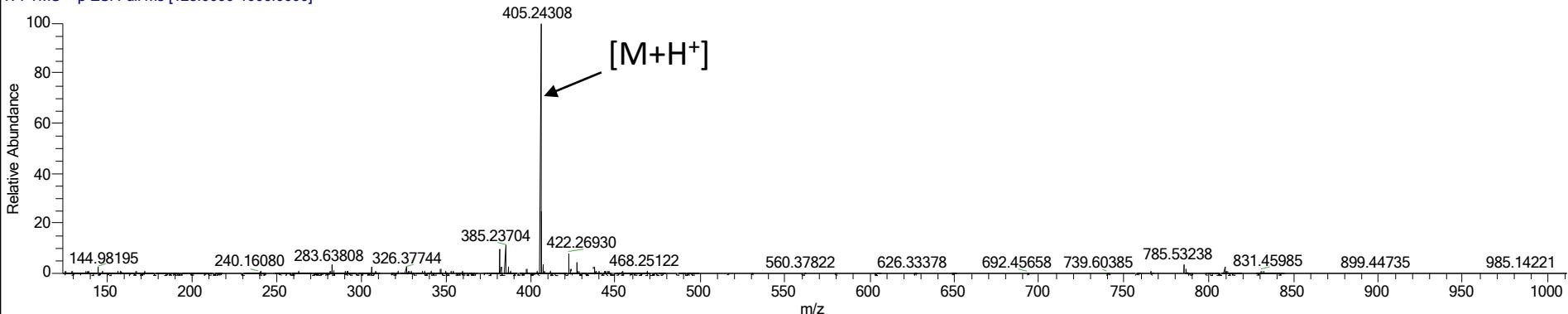
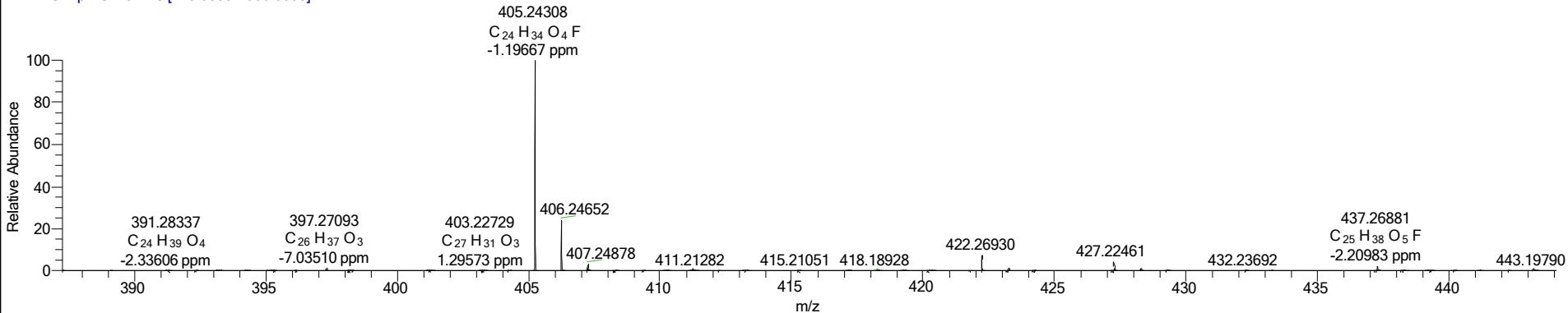


Figure S61. Compound 11, HR-MS spectra.

VM-20211021-POS-1 #1395-1416 RT: 7.79-7.90 AV: 22 NL: 2.59E8
 T: FTMS + p ESI Full ms [125.0000-1000.0000]



VM-20211021-POS-1 #1395-1416 RT: 7.79-7.90 AV: 22 NL: 2.59E8
 T: FTMS + p ESI Full ms [125.0000-1000.0000]



C24H33FO4 +H: C24 H34 F1 O4 p(gss, s/p:40) Chrg 1R...

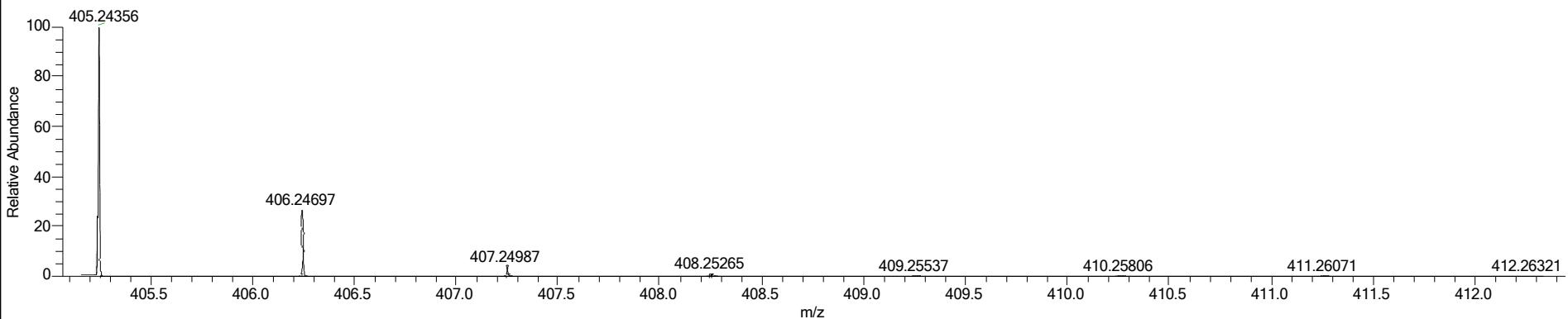


Figure S62. Compound 13, HR-MS spectrum.

postaof2 #68-83 RT: 0.30-0.36 AV: 16 NL: 5.27E8
T: FTMS + p ESI Full ms [50.0000-750.0000]

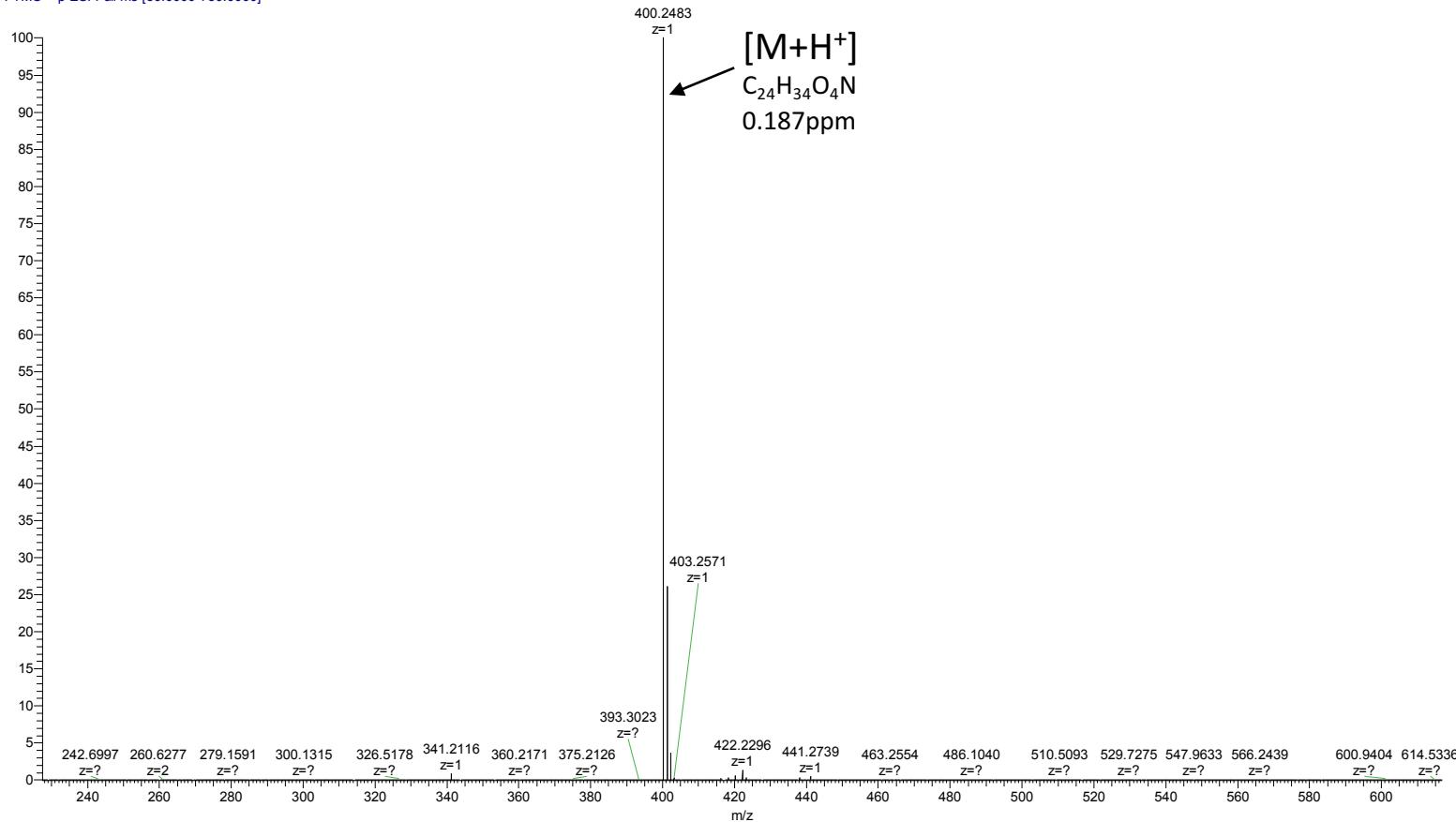


Figure S63. Compound 14, HR-MS spectrum.

postaof3 #127-165 RT: 0.56-0.72 AV: 39 NL: 1.70E8
T: FTMS + p ESI Full ms [50.0000-750.0000]

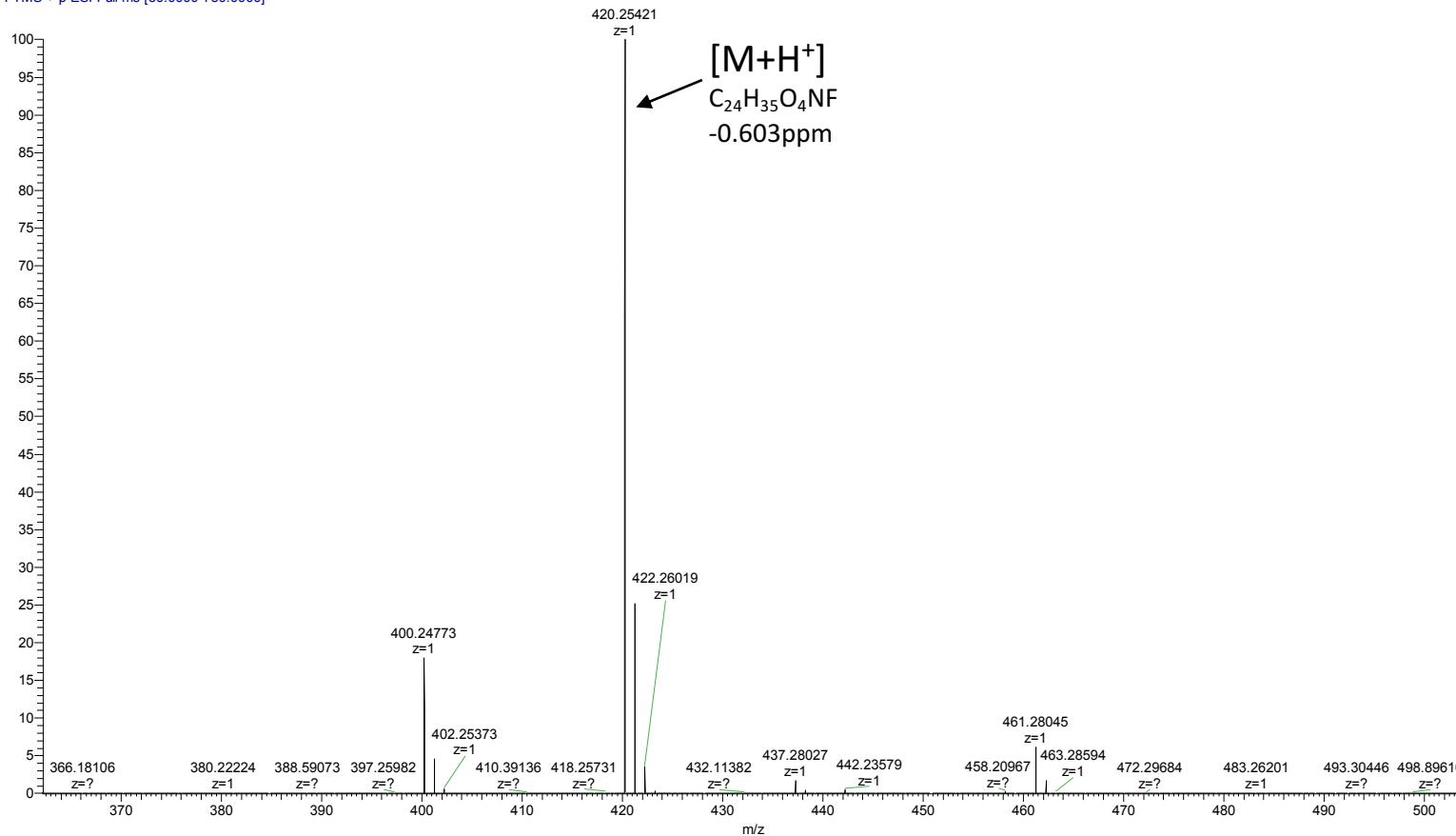


Figure S64. Compound 17, HR-MS spectrum.

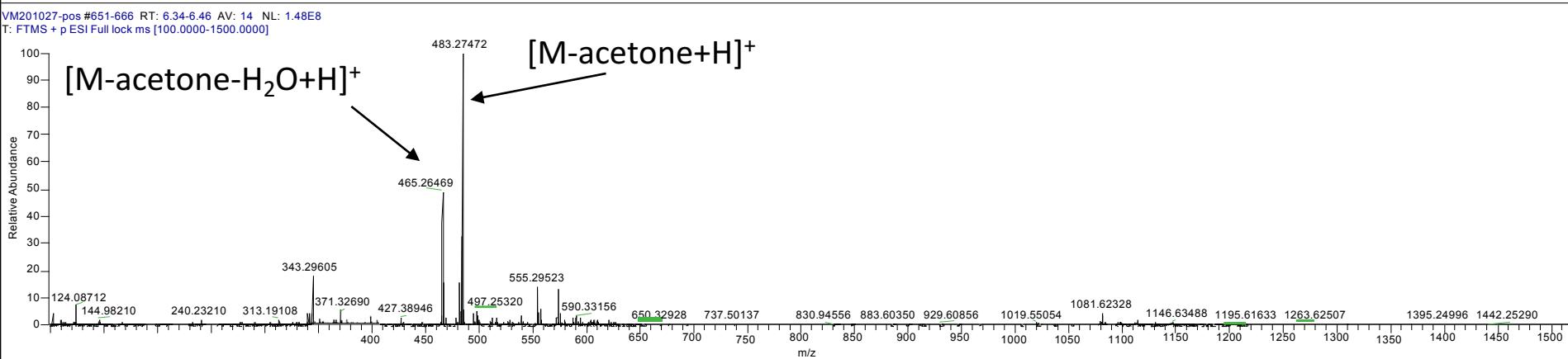


Figure S65. Compound **3**, HPLC chromatogram at its UV absorbance maximum ($\lambda=242.6$ nm). Purity: 95.1 %. Column: Kinetex[®], 5 μ m, XB-C18, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 30 \rightarrow 65% B.

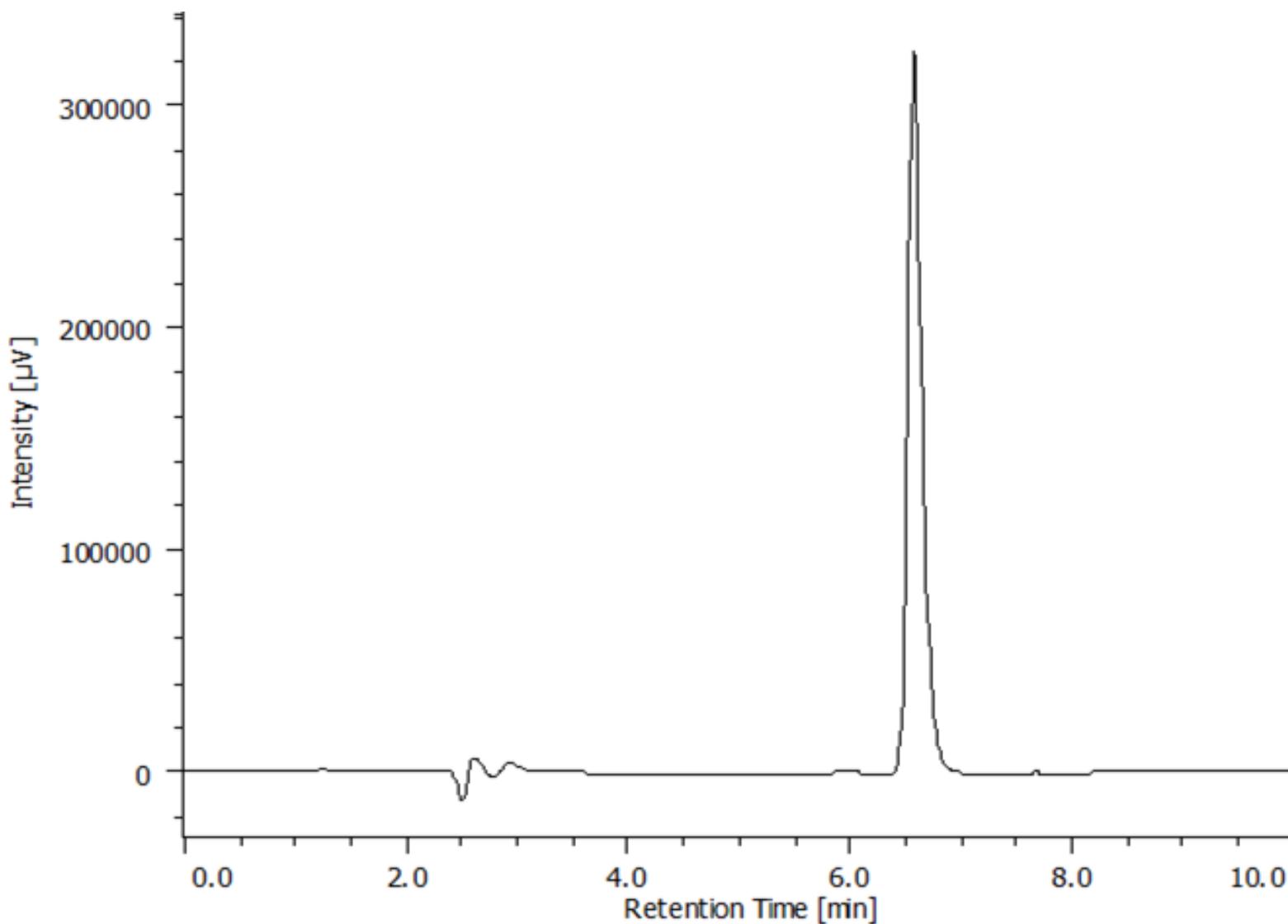


Figure S66. Compound 4, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 97.5 %. Column: Luna® 5 μ m, Phenyl-Hexyl, 100 Å, 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 44% B.

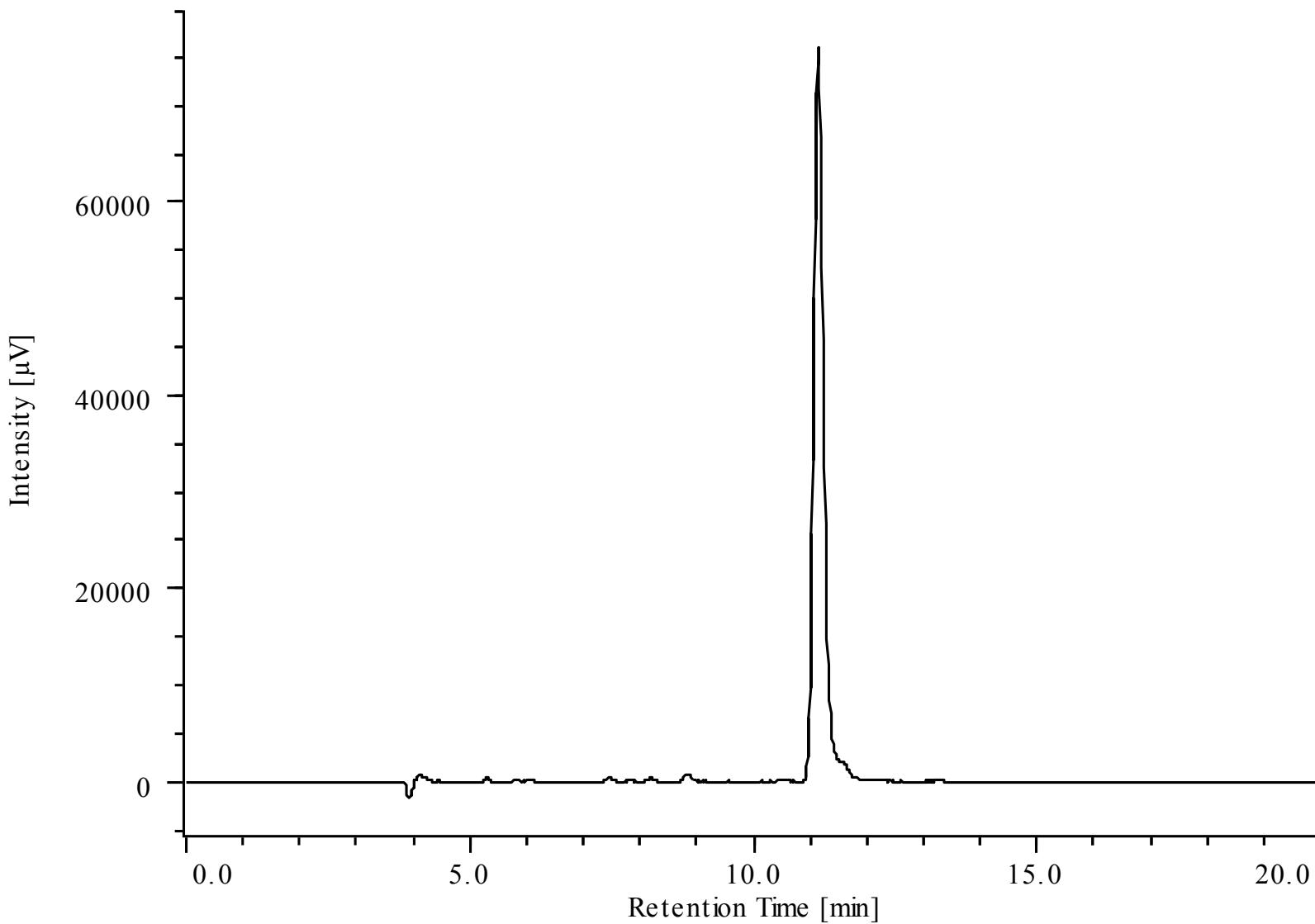


Figure S67. Compound 5, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 97.5 %. Column: Luna® 5 μ m, Phenyl-Hexyl, 100 Å, 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 44% B.

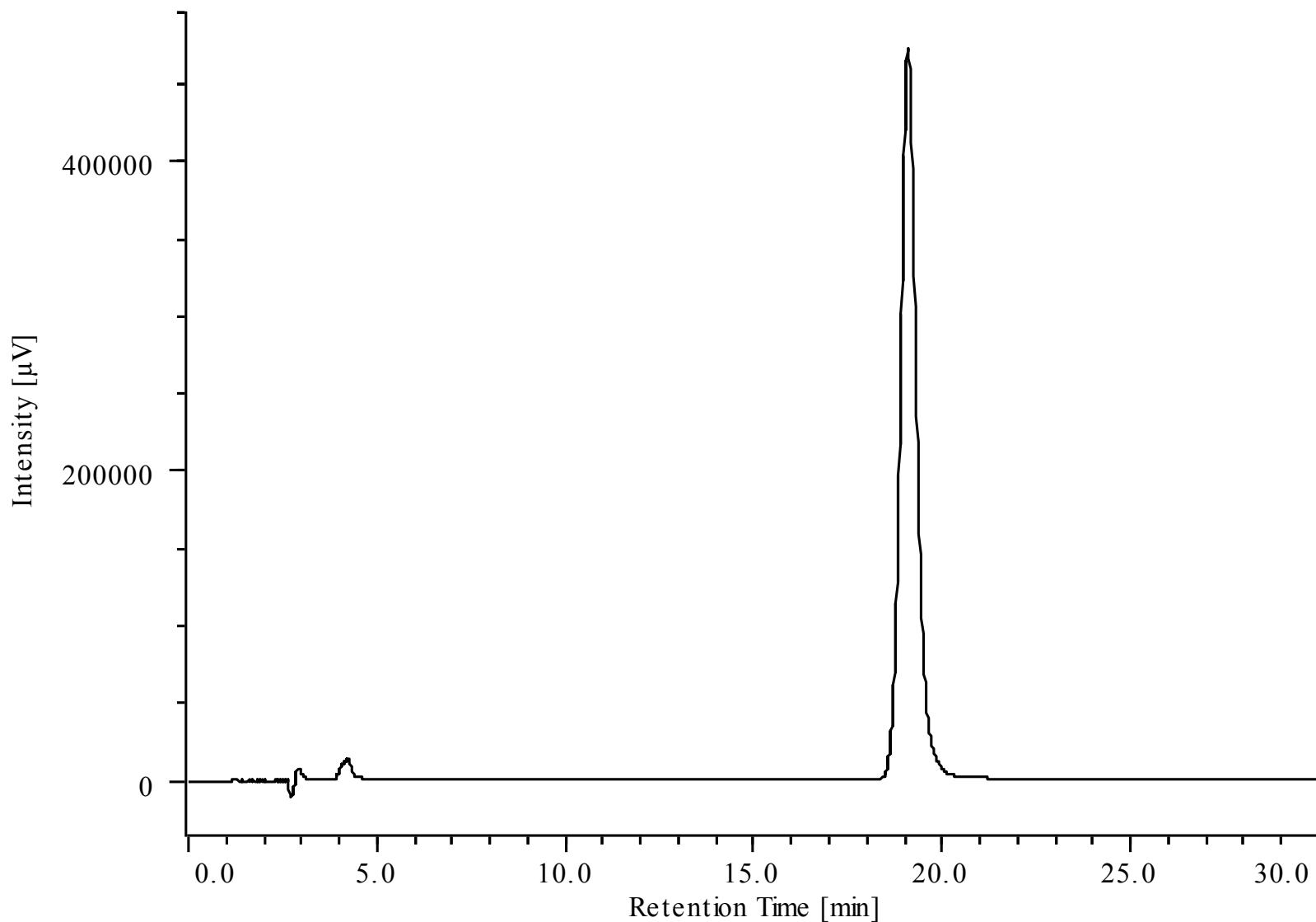


Figure S68. Compound **6**, HPLC chromatogram at its UV absorbance maximum ($\lambda=327.5$ nm). Purity: 95.2 %. Column: Kinetex[®], 5 μ m, Biphenyl, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 40% B.

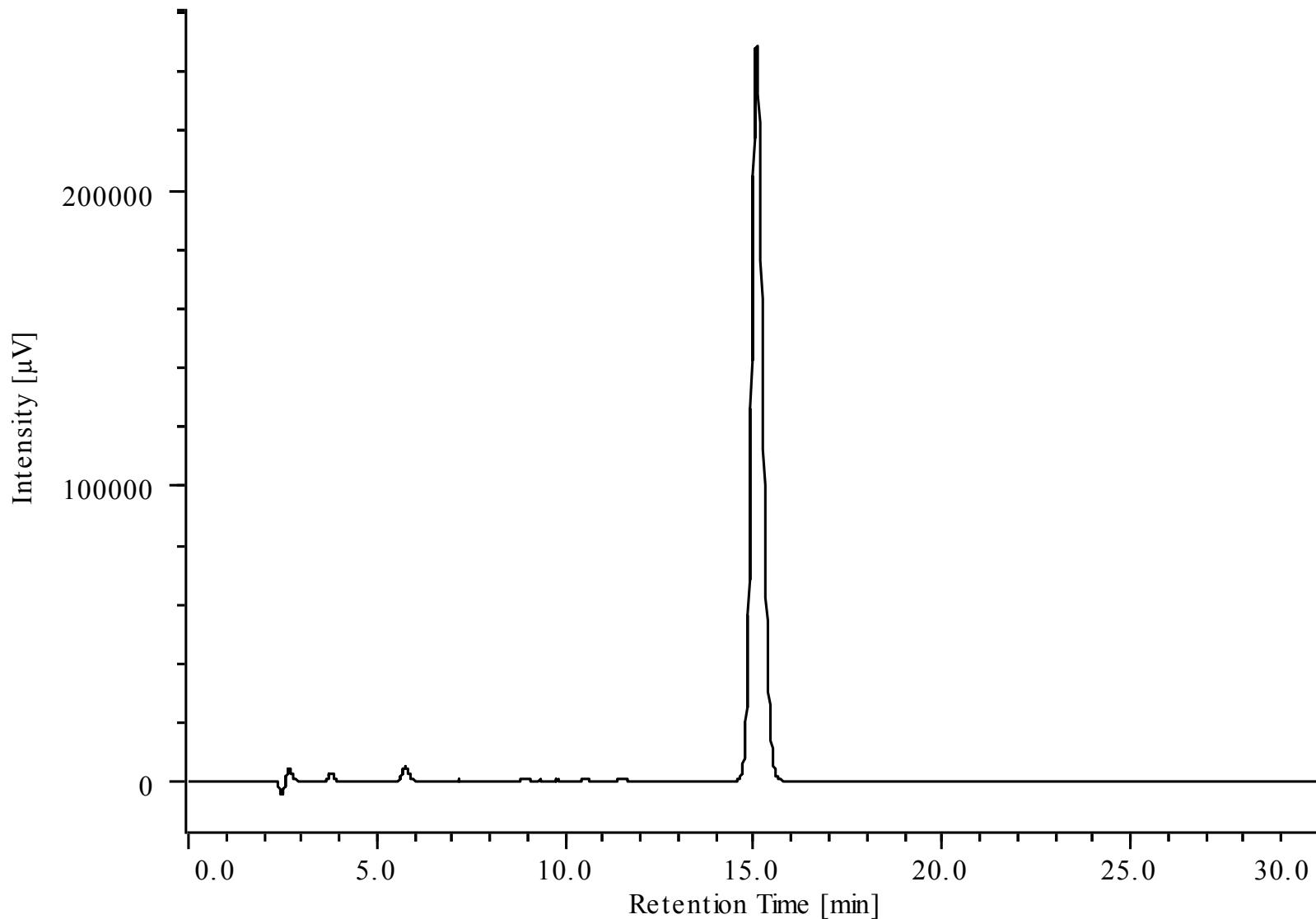


Figure S69. Compound **7**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300$ nm). Purity: 95.4 %. Column: Kinetex[®], 5 μ m, Biphenyl, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 40% B.

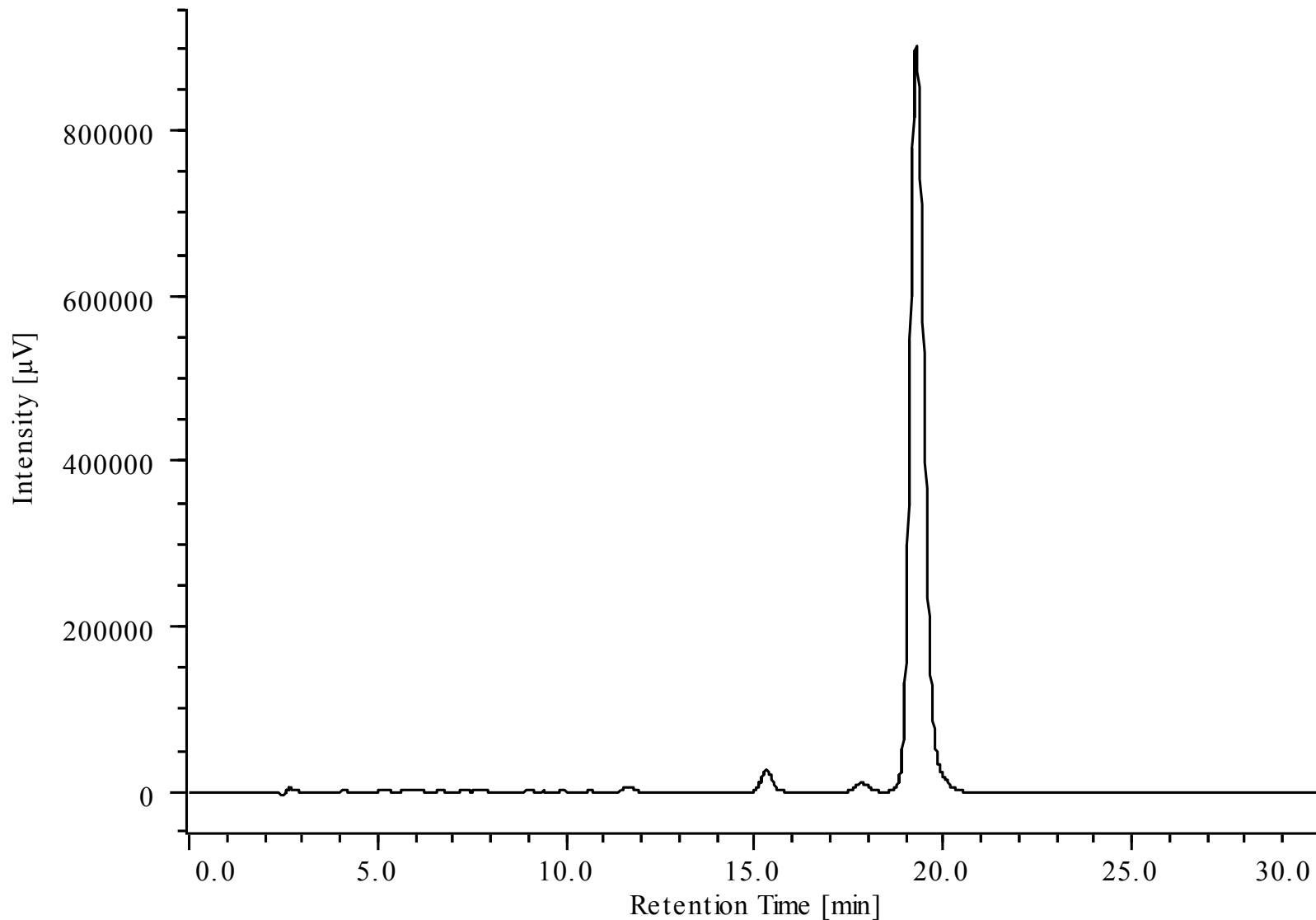


Figure S70. Compound **9**, HPLC chromatogram at its UV absorbance maximum ($\lambda=242.6$ nm). Purity: 98.0 %. Column: Kinetex[®], 5 μ m, XB-C18, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 42% B.

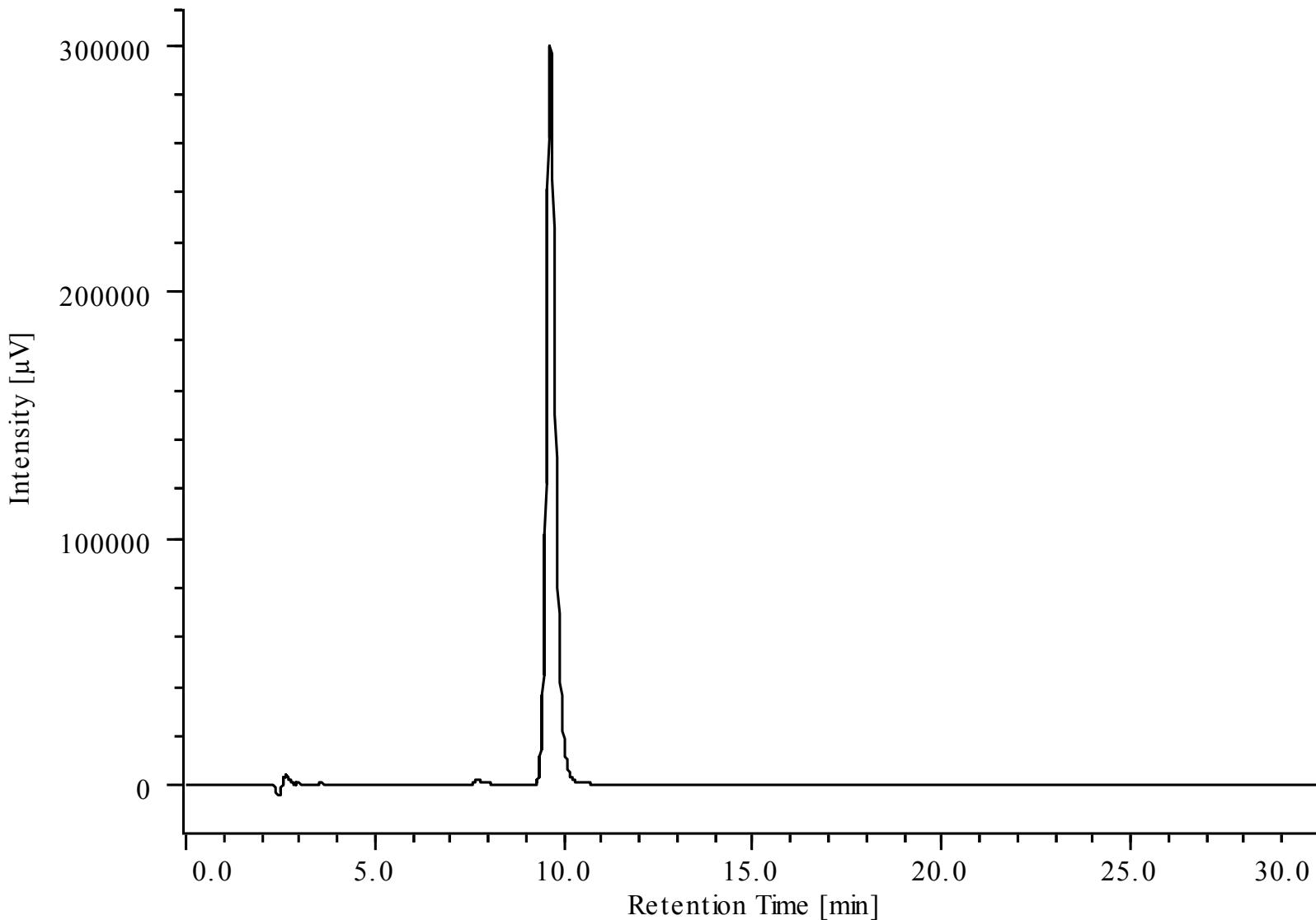


Figure S70. Compound **10**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300\text{ nm}$). Purity: 99.5 %. Column: Kinetex[®], 5 μm , XB-C18, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 42% B.

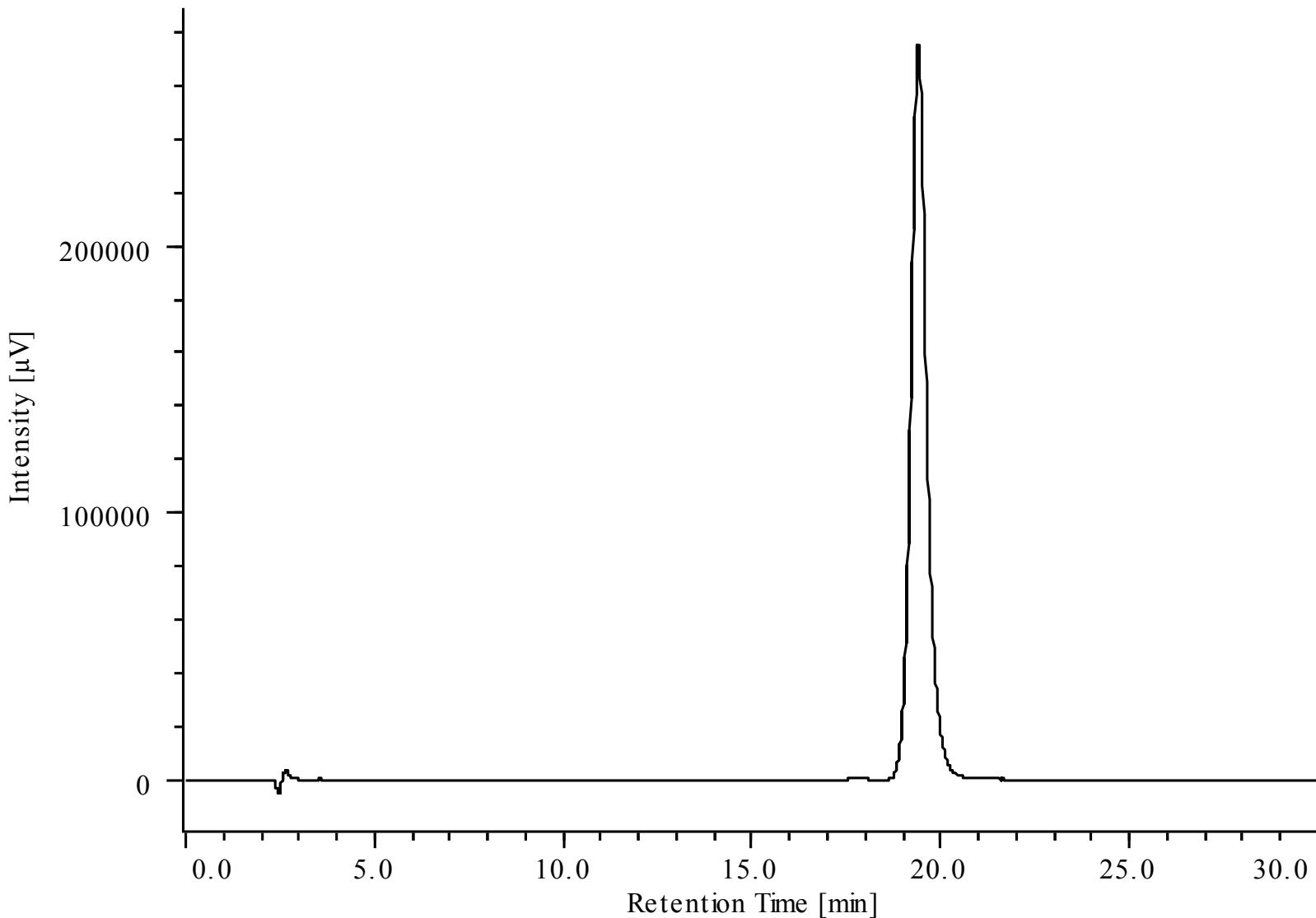


Figure S72. Compound **11**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300\text{ nm}$). Purity: 99.3 %. Column: Kinetex[®], 5 μm , XB-C18, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 42% B.

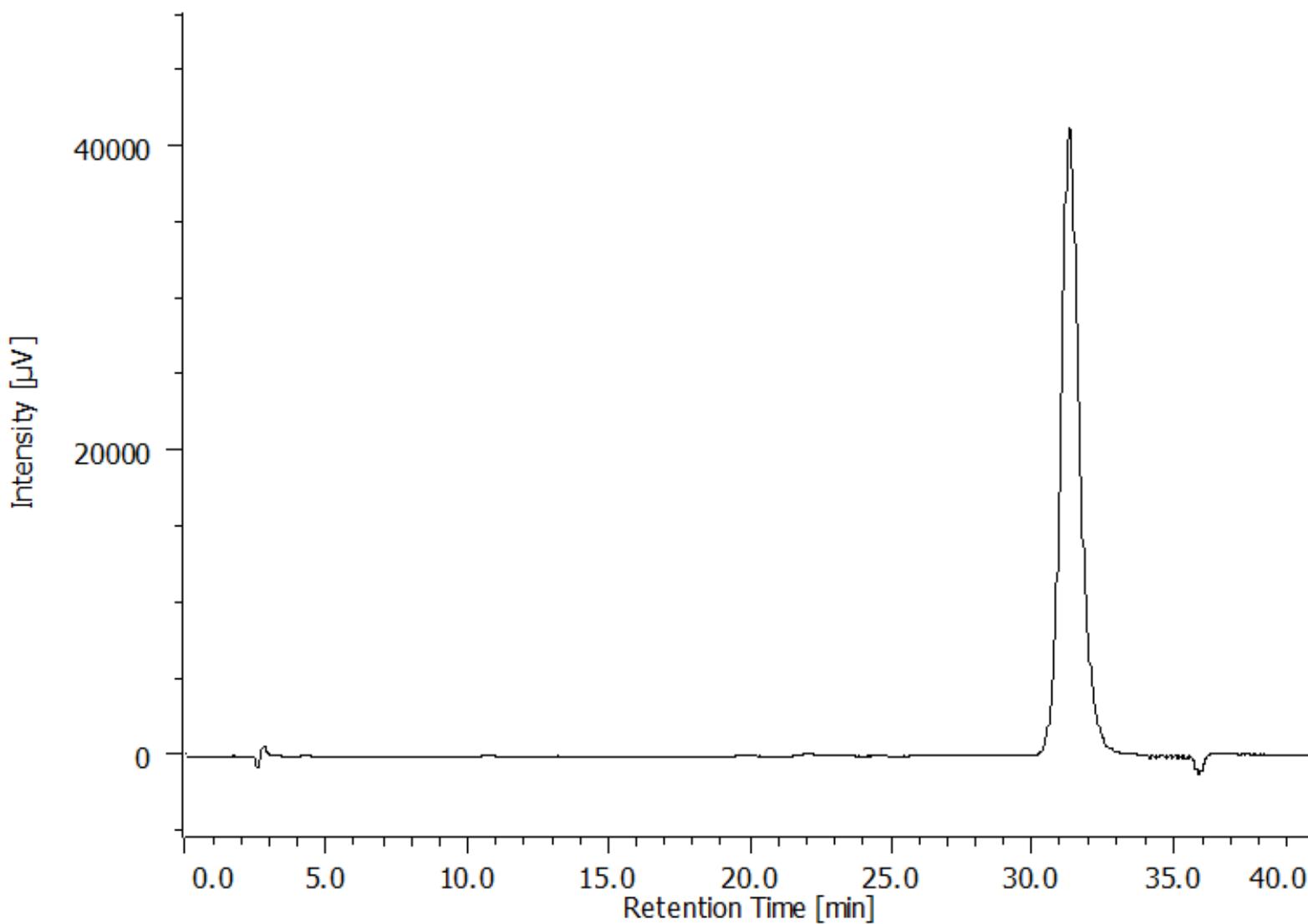


Figure S73. Compound **13**, HPLC chromatogram at its UV absorbance maximum ($\lambda=300\text{ nm}$). Purity: 98.4 %. Column: Kinetex[®], 5 μm , XB-C18, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 35% B.

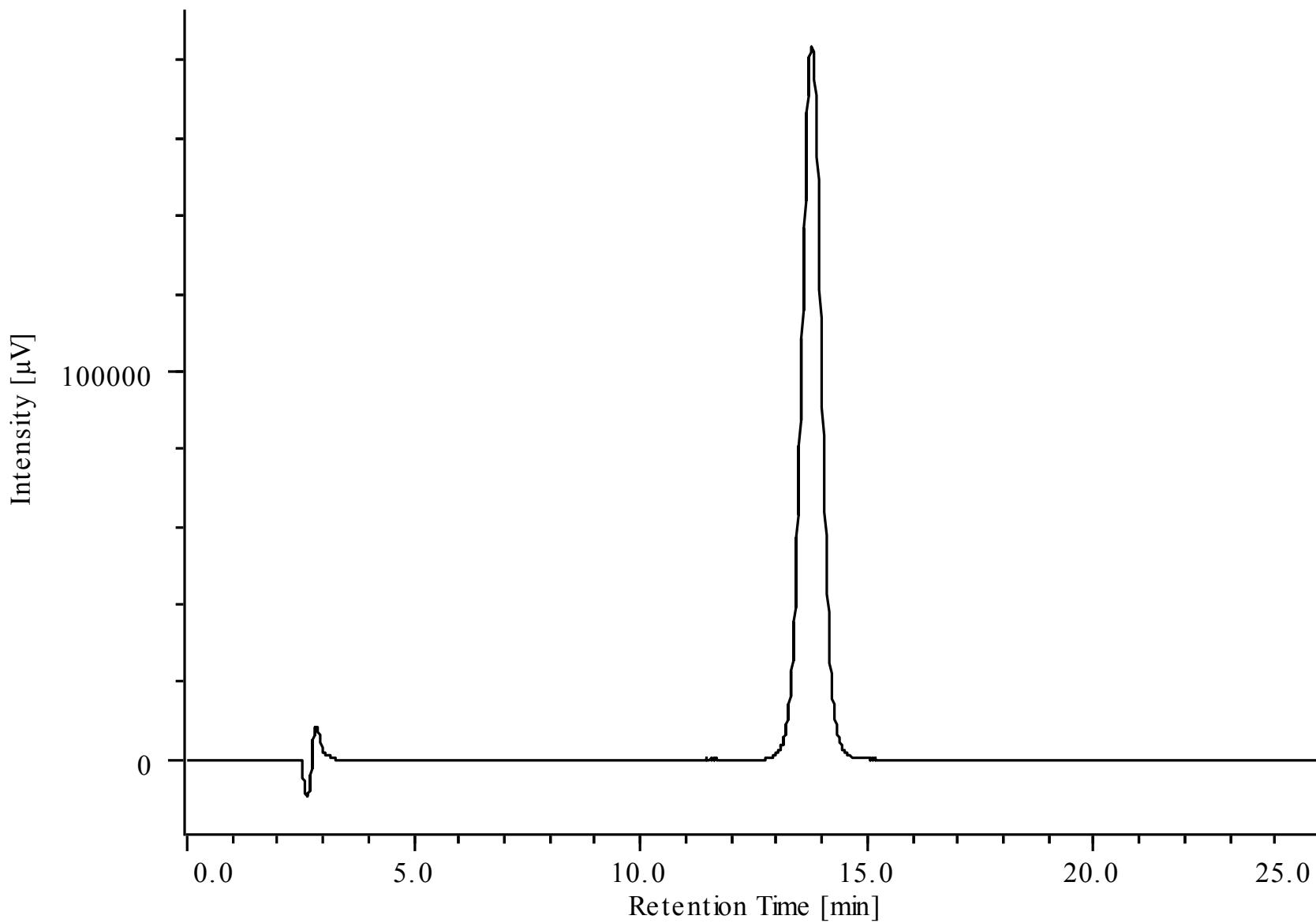


Figure S74. Compound **14**, HPLC chromatogram at its UV absorbance maximum ($\lambda=240\text{ nm}$). Purity: 97.7 %. Column: Kinetex[®], 5 μm , XB-C18, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 35% B.

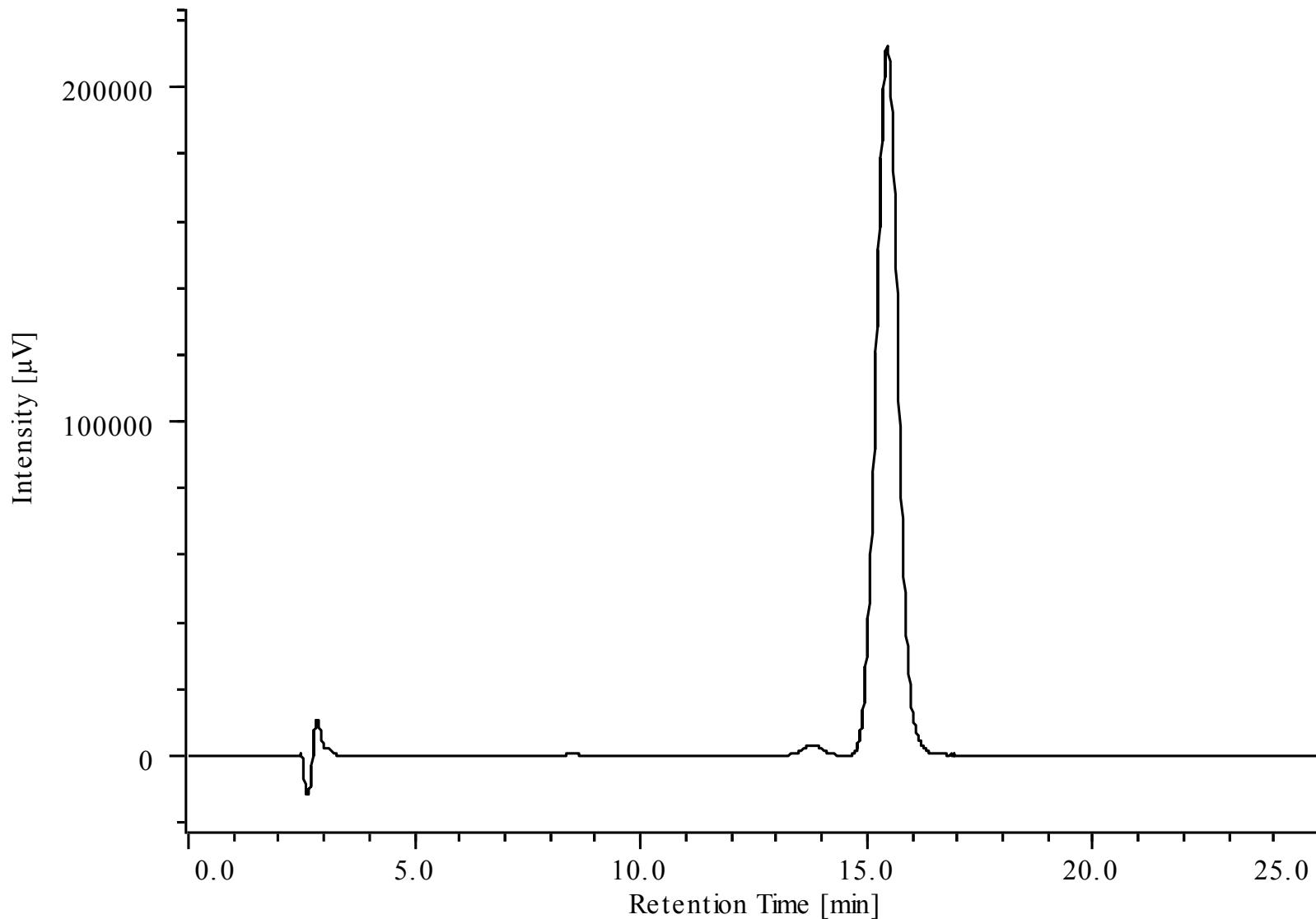


Figure S75. Compound **16**, HPLC chromatogram at its UV absorbance maximum ($\lambda=220.8\text{ nm}$). Purity: 98.4 %. Column: Kinetex[®], 5 μm , XB-C18, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 50% B.

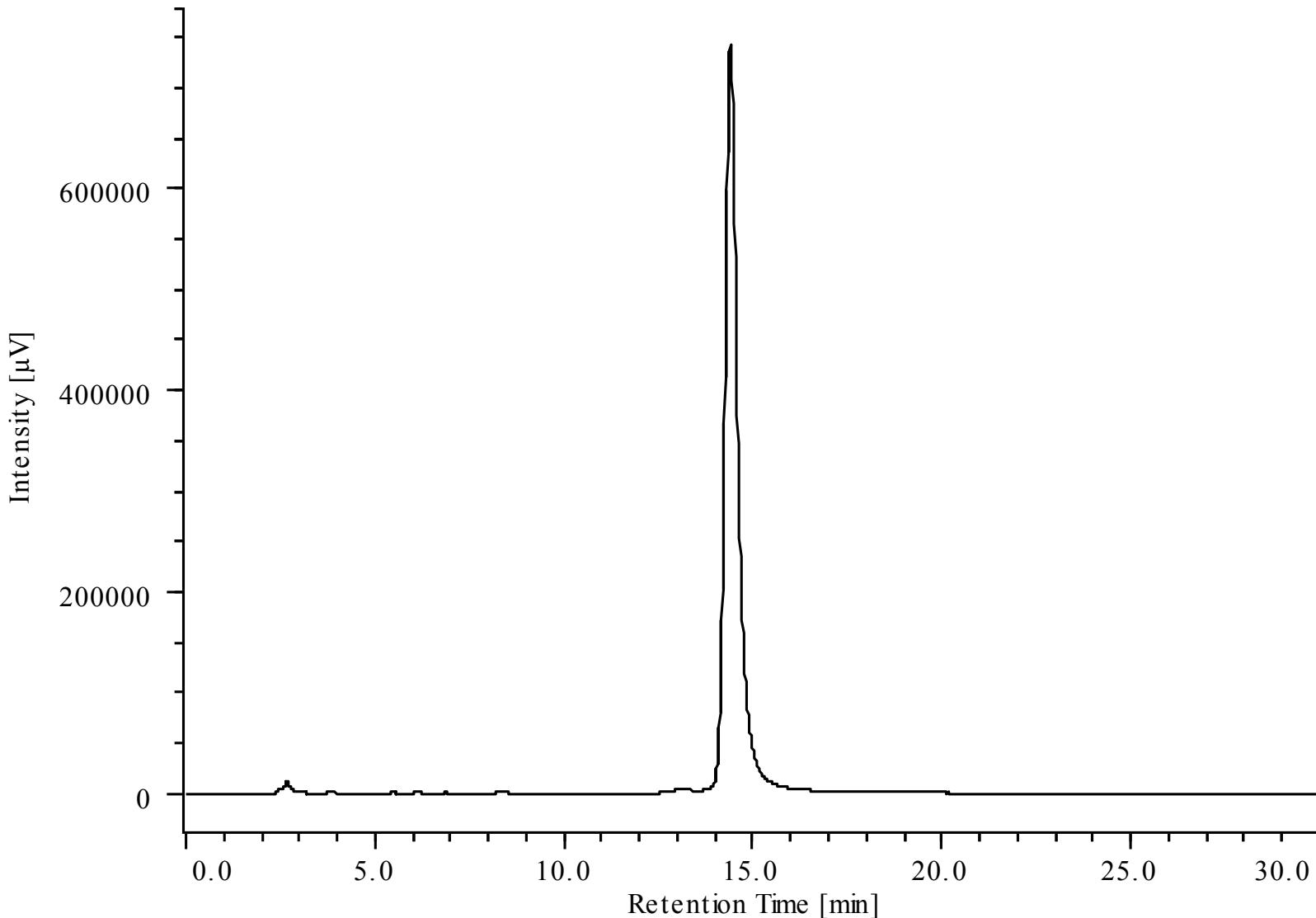


Figure S76. Compound **17**, HPLC chromatogram at its UV absorbance maximum ($\lambda=358.5$ nm). Purity: 98.1 %. Column: Kinetex[®], 5 μ m, XB-C18, 100 \AA , 250 x 4.6 mm (Phenomenex Inc.); Elution: water:CH₃CN (A:B) 71% B.

