Supporting Information for:

Antidiabetic effect of dihydrobetulonic acid derivatives as PPARα/γ agonists

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Experimental data

Chemistry.

The ^{1}H and ^{13}C NMR spectra for compounds were recorded on a Bruker AV-400 spectrometer (Bruker Corporation, Billerica, MA, USA) at 400.13 and 100.61 MHz, respectively in $CDCl_3$ solution. The signals of the solvent were used as the reference (δH 7.27, δC 77.0 for $CDCl_3$). Chemical shifts were given in ppm and the coupling constants (J) were given in hertz (Hz). The structure of the products was determined by means of 1H and 13C NMR spectra (Figures S4–S29). The mass spectra (15–500 m/z, 70 eV) were recorded on a DFS Thermo Scientific high-resolution mass spectrometer (Waltham, MA, USA). Merck silica gel (63–200 μm, Macherey-Nagel, Düren, Germany) was used for the column chromatography. Thin-layer chromatography was performed on TLC Silica gel 60F254 Merck (Darmstadt, Germany).

All reagents were used as described unless otherwise noted. Reagent-grade solvents were redistilled prior to use. Synthetic starting materials, reagents, and solvents were purchased from Sigma-Aldrich, Acros Organics (China) and Alfa Aesar (Germany). Dihydrobetulonic acid, the reference compound TEZ and ethyl (S)-2-ethoxy-3-(4-hydroxyphenyl) propanoate moiety were synthesized according to the methods in the literature [17,18].

To meet the purity requirements for samples sent for biological testing, the compounds were purified by column chromatography. The purity was monitored by HPLC and NMR and was at least 95%.

Synthesis of 2-(4-(benzyloxy)-phenyl) ethanol, 9

12 mmol of tyrosol 8 were dissolved in 100 mL acetone, then 19 mmol of previously ground in a mortar calcined potassium carbonate was added and left to stir for 30 minutes. Then 13 mmol of benzyl bromide were added dropwise and left to heated to reflux for 24 hours. The reaction was monitored by TLC (hexane:EtOAc – 6:1 system). After the reaction was completed, the reaction mixture was cooled and poured into 700 mL of water and left to stir for 30 minutes. The precipitate was filtered off and left to dry. The purification was carried out by precipitation from a mixture of hexane and ethyl acetate.

Material obtained: white powder. Yield 95%. The spectral data agree with the literature [19].

(S)-ethyl 3-(4-(4-(benzyloxy)phenethoxy)phenyl)-2-ethoxypropanoate, 10

In a 250 mL round bottom flask, 22 mmol of 9, 23 mmol of (S)-ethyl-2-ethoxy-3-(4-hydroxyphenyl)-propanoate and 24 mmol of PPh_3 were mixed and dissolved in 70 mL THF. The reaction mixture was cooled in an ice bath, 23 mmol DIAD was then added and left to stir for 24 hours in argon atmosphere. The solvent was evaporated and purification was carried out by column chromatography in the hexane:EtOAc – 5:1 system.

Material obtained: yellow oil. Yield 88%. The spectral data agree with the literature [19].

(S)-ethyl 2-ethoxy-3-(4-(4-hydroxyphenethoxy)phenyl)propanoate, 11

20 mmol of 10 was dissolved in 25 mL EtOAc, the solution was degassed, purged with hydrogen, further spiked with 2 mmol of 10% Pd/C, degassed, purged with hydrogen and left stirring for 24 hours. The reaction was monitored by TLC ($CHCl_3$:MeOH – 20:1 system). The catalyst was filtered off and the solvent was evaporated. The product was used without further purification.

Material obtained: white powder. Yield 91%. The spectral data agree with the literature [19].

Synthesis of (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(2-hydroxyalkyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, 13a-e

In 250 mL round bottom flask 22 mmol of dihydrobetulonic acid was dissolved in 120 mL of dry methylene chloride. To the cooled reaction mixture 40 mmol oxalyl chloride was added dropwise. Then catalytic amounts of DMF were added and left to stir at room temperature for 8 hours. The reaction mixture was further evaporated on a rotary evaporator to remove oxalyl chloride excess. The reaction product is unstable and was used immediately.

4 mmol of resulting dihydrobetulonic acid chloride was dissolved in 20 mL dry CH_2Cl_2 and cooled. Then 24 mmol of NEt_3 was added dropwise. After 10 minutes, 12 mmol of the corresponding amino alcohol was added dropwise. After addition, the reaction mixture was left to stir for 8 hours at room temperature. After the reaction was completed, 20 mL of water was added and acid-base extraction was carried out. The organic layer was dried over $MgSO_4$. The solvent was evaporated and the reaction mixture was purified by column chromatography on silica gel in the $CHCl_3$:MeOH - 100:1 system.

(1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(2-hydroxyethyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, 13a

Material obtained: yellow powder. Yield 87%. ^{1}H-NMR: 0.69 (d, J = 6.7 3 H), 0.74 - 0.83 (m, 3 H), 0.85 - 0.99 (m, 9 H), 1.00 - 1.05 (m, 3 H), 1.07 - 1.13 (m, 3 H), 1.15 - 1.22 (m, 5 H), 1.23 - 1.56 (m, 12 H), 1.57 - 1.79 (m, 7 H), 1.80 - 2.07 (m, 2 H), 2.87 (m, 1 H), 3.25 - 3.48 (m, 2 H), 3.56 - 3.73 (m, 2 H), 5.67 (t, J = 5.3, 1 H). ^{13}C-NMR: 14.7, 14.8, 16.1, 16.2, 19.3, 21.3, 21.4, 23.1, 23.2, 25.8, 29.6, 32.8 (2 C), 33.7, 34.3, 36.7, 37.8, 38.0, 39.1, 39.2, 39.8, 41.0, 42.8, 44.4, 47.5, 49.6, 49.9, 55.1, 56.2, 62.9, 176.4, 218.5. $C_{32}H_{53}NO_3$. m/z (calculated): 499,4025. m/z (found): 499,4023.

(1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(2-hydroxypropyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, 13b

Material obtained: yellow powder. Yield 81%. ^{1}H-NMR: 0.73 (d, J = 6.6, 3 H), 0.79 - 0.88 (m, 3 H), 0.88 - 1.02 (m, 12 H), 1.02 - 1.08 (m, 3 H), 1.09 - 1.17 (m, 2 H), 1.27 - 1.61 (m, 18 H), 1.61 - 1.71 (m, 4 H), 1.86 - 2.00 (m, 2 H), 2.29 (t, J = 10.4, 1 H), 2.33 - 2.43 (m, 1 H), 2.43 - 2.55 (m, 2 H), 3.43 (m, 2 H), 3.63 (t, J = 6.4, 2 H), 3.71 (s, 1 H), 5.95 (t, J = 5.6, 1 H). ^{13}C-NMR: 14.7, 14.8, 16.1, 16.2, 19.3, 21.3, 21.3, 23.1, 23.2 (2C), 25.8, 29.6, 32.8 (2 C), 33.7, 34.3, 36.7, 37.8, 38.0, 39.1, 39.2, 39.8, 41.0, 42.8, 44.4, 47.5, 49.6, 49.9, 55.1, 56.2, 62.9, 176.4, 218.5. $C_{33}H_{55}NO_3$. m/z (calculated): 513,4182. m/z (found): 513,4180.

(1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(2-hydroxybutyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, 13c

Material obtained: yellow powder. Yield 76%. ^{1}H-NMR: 0.66 - 0.74 (m, 3 H), 0.77 - 0.84 (m, 3 H), 0.87 - 0.95 (m, 9 H), 0.98 (s, 3 H), 1.01 - 1.07 (m, 3 H), 1.07 - 1.24 (m, 5 H), 1.24 - 1.48 (m, 13 H), 1.51 - 1.60 (m, 4 H), 1.63 (m, 2 H), 1.70 - 1.80 (m, 1 H), 1.83 - 1.95 (m, 2 H), 2.13 (br. s., 1 H), 2.26 (t, J = 10.3, 1 H), 2.31 - 2.40 (m, 1 H), 2.41 - 2.52 (m, 2 H), 3.15 - 3.35 (m, 2 H), 3.65 (br. s., 2 H), 5.78 (t, J = 5.6, 1 H). ^{13}C-NMR: 14.4, 14.6, 15.9, 16.0, 19.6, 21.0, 21.1, 23.0 (2C), 26.5, 26.9 (2 C), 29.5, 29.7 (2 C), 29.9, 33.6 (2 C), 34.1, 36.8, 37.6, 38.8, 39.6, 40.3, 42.6, 44.1, 47.3, 49.4, 49.7, 54.9, 56.0, 62.4, 176.5, 218.3. $C_{34}H_{57}NO_3$. m/z (calculated): 527,4338. m/z (found): 527,4340.

(1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(2-hydroxypentyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, 13d

Material obtained: yellow powder. Yield 85%. ^{1}H-NMR: 0.73 (d, J = 6.7, 3 H), 0.85 (d, J = 6.8, 3 H), 0.90 - 0.98 (m, 8 H), 0.98 - 1.03 (m, 3 H), 1.03 - 1.09 (m, 3 H), 1.09 - 1.27 (m, 5 H), 1.27 - 1.71 (m, 21 H), 1.77 (qd, J = 6.6, 4.3, 2 H), 1.86 - 1.98 (m, 2 H), 2.25 - 2.35 (m, 1

H), 2.35 - 2.55 (m, 3 H), 3.13 - 3.34 (m, 2 H), 3.64 (t, J = 6.4, 2 H), 5.66 (t, J = 5.7, 1 H). ^{13}C-NMR: 15.2, 15.3, 16.6, 20.3, 20.4, 21.7, 22.1, 23.7 (2 C), 24.2, 27.2, 27.7, 28.5, 30.3, 30.4 (3 C), 30.6, 34.3, 34.8, 37.6, 38.4, 39.5, 40.3, 41.4, 43.1, 44.8, 48.0, 50.1, 50.4, 55.7, 56.7, 63.1, 177.2, 219.0. $C_{35}H_{59}NO_3$. m/z (calculated): 541,4495. m/z (found): 541,4497.

(1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(2-hydroxyhexyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, 13e

Material obtained: yellow powder. Yield 88%. ^{1}H-NMR: 0.75 (d, J = 6.7, 3 H), 0.81 (d, J = 6.8, 3 H), 0.88 - 0.95 (m, 8 H), 1.00 (s, 3 H), 1.05 (s, 3 H), 1.09 - 1.27 (m, 4 H), 1.27 - 1.71 (m, 22 H), 1.77 (m, 2 H), 1.86 - 1.98 (m, 4 H), 2.25 - 2.35 (m, 1 H), 2.35 - 2.55 (m, 3 H), 3.13 - 3.34 (m, 2 H), 3.64 (t, J = 6.4, 2 H), 5.66 (t, J = 5.7, 1 H). ^{13}C-NMR: 14.4, 14.5, 15.9, 19.5, 20.9, 21.4, 21.8 (2 C), 22.9, 25.6, 26.5, 26.9, 29.1, 29.3, 29.7, 29.8, 30.0, 33.6, 33.7, 34.0, 36.1, 36.8, 37.5, 39.0, 40.6, 42.6, 44.1, 47.2, 49.3, 49.6, 54.9, 55.9, 115.3, 132.6, 176.0, 218.0. $C_{36}H_{61}NO_3$. m/z (calculated): 555,4651. m/z (found): 555,4653.

Synthesis of ethers 14a-e

In a 250 mL round bottom flask, 23 mmol amido alcohol 13a-e, 23 mmol (S)-ethyl-2-ethoxy-3-(4-(4-hydroxyphenethoxy)-phenyl) propanoate 11 and 24 mmol PPh_3 were mixed and dissolved in 70 mL THF. The reaction mixture was cooled in an ice bath, added 23 mmol DIAD in an argon current and left to stir for 24 hours. After the reaction the solvent was evaporated and purification was carried out by column chromatography in the system hexane:ethyl acetate - 5:1.

Ethyl (2S)-2-ethoxy-3-[4-(2-{4-[(2-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0^{2},^{10}.0^{5},^{9}.0^{14},^{19}] henicosan-5-yl]formamido}ethyl)oxy]phenyl}ethoxy)phenyl]propanoate, 14a

Material obtained: yellow oil. Yield 81%. Spectral data agree with the literature [20].

Ethyl (2S)-2-ethoxy-3-[4-(2-{4-[(3-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0^{2},^{10}.0^{5},^{9}.0^{14},^{19}] henicosan-5-yl]formamido}propyl)oxy]phenyl}ethoxy)phenyl]propanoate, 14b

Material obtained: yellow oil. Yield 75%. ^{1}H-NMR: 0.85 (m, 3 H), 0.95 (m, 3 H), 1.02 - 1.16 (m, 15 H), 1.22 - 1.71 (m, 26 H), 1.75 – 2.08 (m, 7 H), 2.97 - 3.16 (m, 4 H), 3.25 – 3.49 (m, 3 H), 3.68 (m, 1 H), 4.07 (m, 2 H), 4.02 - 4.31 (m, 6 H), 5.71 (br.s., 1 H), 6.88 (m, 4 H), 7.25 (m, 4 H). ^{13}C-NMR: 14.1, 14.2, 14.5, 14.9, 15.8, 15.9, 19.5, 20.9, 21.8 (2 C), 22.9, 23.0,

26.5, 26.9, 29.2, 29.5, 29.8, 33.4, 34.0, 34.7, 36.8, 37.1, 37.6, 38.3, 40.6, 42.5, 44.0, 47.2, 49.3, 49.6, 54.8, 55.9, 60.7, 66.0, 66.5, 68.7, 69.9, 80.2, 114.2 (2 C), 114.3 (2 C), 115.3, 129.2, 129.9 (2 C), 130.3 (2 C), 130.6, 155.1, 157.2, 172.5, 176.4, 218.4. $C_{54}H_{79}NO_7$. m/z (calculated): 853,5857. m/z (found): 853,5860.

Ethyl (2S)-2-ethoxy-3-[4-(2-{4-[(4-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0²,¹⁰.0⁵,⁹.0¹⁴,¹⁹] henicosan-5-yl]formamido}butyl)oxy]phenyl}ethoxy)phenyl]propanoate, 14c

Material obtained: yellow oil. Yield 83%. ^{1}H-NMR: 0.73 (m, 3 H), 0.83 - 1.16 (m, 12 H), 1.22 - 1.34 (m, 24 H), 1.35 – 1.58 (m, 10 H), 1.61 – 1.98 (m, 5 H), 2.25 – 2.58 (m, 3 H), 2.91 - 3.08 (m, 4 H), 3.13 – 3.41 (m, 3 H), 3.62 (m, 1 H), 3.89 – 4.01 (m, 2 H), 4.07 - 4.22 (m, 5 H), 5.54 (br.s., 1 H), 6.75 – 6.91 (m, 4 H), 7.17 (m, 4 H). ^{13}C-NMR: 14.1 (2 C), 15.0 (2 C), 15.8, 19.5, 20.6, 21.0, 21.8, 22.9, 26.5, 26.7, 29.3, 29.6, 33.7, 34.1, 34.8, 36.8, 37.4, 38.4 (2 C), 38.8, 39.5, 40.4, 42.5, 44.1, 47.6, 49.3, 49.6, 54.9, 56.0, 60.4, 60.8, 66.1, 66.8, 68.9, 80.3, 114.2 (4 C), 115.3 (3 C), 129.1, 130.0 (2 C), 130.3 (2 C), 154.7, 157.5, 171.3, 172.6, 176.6, 218.6. $C_{55}H_{81}NO_7$. m/z (calculated): 867,6013. m/z (found): 867,6015.

Ethyl (2S)-2-ethoxy-3-[4-(2-{4-[(5-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0²,¹⁰.0⁵,⁹.0¹⁴,¹⁹] henicosan-5-yl]formamido}pentyl)oxy]phenyl}ethoxy)phenyl]propanoate, 14d

Material obtained: colorless oil. Yield 85%. ^{1}H-NMR: 0.75 (d, J = 6.7, 3 H), 0.83 - 1.07 (m, 13 H), 1.09 – 1.29 (m, 20 H), 1.30 – 1.64 (m, 13 H), 1.65 – 1.81 (m, 4 H), 1.90 (m, 1 H), 2.28 – 2.59 (m, 3 H), 2.92 (m, 2 H), 2.99 (m, 2 H), 3.13 - 3.37 (m, 3 H), 3.55 - 3.63 (m, 1 H), 3.91 (m, 2 H), 4.12 (m, 7 H), 5.63 (br.s., 1 H), 6.83 (m, 4 H), 7.15 (m, 4 H). ^{13}C-NMR: 14.1, 14.3, 15.0, 15.9, 16.0, 19.4, 19.6, 21.1, 21.9 (2 C), 22.9, 23.1, 26.5, 26.7, 28.9, 29.2, 29.6, 29.8, 33.7, 34.1, 34.8, 36.8, 37.3, 38.4, 39.0, 39.5, 40.7, 42.6, 44.2, 47.3, 49.7, 54.9, 56.0, 60.8, 66.2, 67.3, 68.9, 70.0, 80.4, 114.2 (3 C), 114.4 (2 C), 115.3, 129.2, 129.9 (2 C), 130.3 (3 C), 154.7, 157.5, 172.6, 176.3, 218.3. $C_{56}H_{83}NO_7$. m/z (calculated): 881,6170. m/z (found): 881,6172.

Ethyl (2S)-2-ethoxy-3-[4-(2-{4-[(6-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0²,¹⁰.0⁵,⁹.0¹⁴,¹⁹] henicosan-5-yl]formamido}hexyl)oxy]phenyl}ethoxy)phenyl]propanoate, 14e

Material obtained: colorless oil. Yield 79%. ^{1}H-NMR: 0.72 (d, J = 6.6, 3 H), 0.78 - 1.15 (m, 15 H), 1.17 – 1.33 (m, 22 H), 1.35 – 1.62 (13 H), 1.65 – 1.82 (m, 4 H), 1.92 (m, 1 H), 2.28 – 2.59 (m, 3 H), 2.96 (m, 2 H), 2.99 (m, 2 H), 3.11 - 3.37 (m, 3 H), 3.56 - 3.63 (m, 1 H), 3.91

(m, 2 H), 4.07 - 4.18 (m, 5 H), 5.62 (br.s., 1 H), 6.81 (m, 4 H), 7.11 - 7.2 (m, 4 H). ^{13}C-NMR: 14.1, 14.3 (2 C), 15.0, 15.9, 19.6, 21.0, 21.1, 21.9 (3 C), 22.9, 25.9, 26.5, 26.7, 26.9, 29.2, 29.3, 29.8, 33.7, 34.1, 34.9, 34.9, 35.8, 38.4, 39.0, 39.3, 40.8, 42.3, 44.2, 47.3, 49.4, 49.7, 54.9, 56.0, 60.8, 66.1, 66.8, 68.9, 70.0, 80.4, 114.2 (2 C), 114.4 (2 C), 115.3, 129.2, 129.8 (2 C), 130.3 (2 C), 157.5, 157.7, 172.5, 176.2, 218.3. $C_{57}H_{85}NO_7$. m/z (calculated): 895,6326. m/z (found): 895,6325.

Hydrolysis of terpene derivatives ethyl esters 14a-g

Hydrolysis of the ester group of the compounds obtained was performed according to the procedure described in our previous work [20].

(2S)-2-ethoxy-3-[4-(2-{4-[(2-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0^{2,10}.0^{5,9}.0^{14,19}] henicosan-5-yl]formamido}ethyl)oxy]phenyl}ethoxy)phenyl]propanoic acid, 15a

Material obtained: yellow oil. Yield: 85%. Spectral data coincide with the literature [20].

(2S)-2-ethoxy-3-[4-(2-{4-[(3-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0^{2,10}.0^{5,9}.0^{14,19}] henicosan-5-yl]formamido}propyl)oxy]phenyl}ethoxy)phenyl]propanoic acid, 15b

Material obtained: white powder. Yield 91%. ^{1}H-NMR: 0.68 - 0.74 (m, 3 H), 0.78 - 0.84 (m, 3 H), 0.89 - 0.95 (m, 3 H), 0.97 - 1.06 (m, 6 H), 1.08 - 1.27 (m, 16 H), 1.27 - 1.47 (m, 8 H), 1.55 - 1.71 m, (6 H), 1.81 - 2.02 (m, 4 H), 2.25 – 2.53 (m, 3 H), 2.85 – 3.03 (m, 4 H), 3.15 - 3.40 (m, 3 H), 3.55 - 3.62 (m, 1 H), 3.93 (t, J = 6.6, 1 H) , 4.01 (t, J = 5.6, 1 H), 4.03 - 4.17 (m, 4 H), 5.66 – 5.78 (m, 1 H), 6.82 (m, 4 H), 7.09 - 7.19 (m, 4 H). ^{13}C-NMR: 14.4, 14.9 (2 C), 15.7, 19.4, 20.9, 21.3, 22.9 (2 C), 26.4, 26.8, 29.0, 29.9, 30.1, 33.3, 34.0, 34.8, 36.7, 37.7, 37.8, 38.3, 38.4, 38.5, 39.7, 40.5, 42.6, 44.4, 47.1, 49.0, 49.5, 54.1, 56.3, 66.0, 66.9, 68.7, 79.7, 114.2 (3 C), 114.3 (3 C), 128.9, 129.9 (2 C), 130.4 (2 C), 130.7, 157.1, 157.5, 176.6, 218.8. $C_{52}H_{75}NO_7$. m/z (calculated): 825,5544. m/z (found): 825,5545.

(2S)-2-ethoxy-3-[4-(2-{4-[(4-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0^{2,10}.0^{5,9}.0^{14,19}] henicosan-5-yl]formamido}butyl)oxy]phenyl}ethoxy)phenyl]propanoic acid, 15c

Material obtained: white powder. Yield 89%. ^{1}H-NMR: 0.72 (d, J = 6.7, 3 H), 0.76 - 0.98 (m, 8 H), 1.00 - 1.19 (m, 8 H), 1.21 - 1.28 (m, 15 H), 1.28 - 1.58 (m, 12 H), 1.65 (m, 3 H), 1.70 - 1.82 (m, 2 H), 1.82 - 1.98 (m, 1 H), 2.21 – 2.56 (m, 3 H), 2.83 - 3.06 (m, 4 H), 3.15 – 3.39 (m,

3 H), 3.54 - 3.66 (m, 1 H), 3.93 (t, J = 6.0, 3 H), 4.01 - 4.14 (m, 3 H), 5.87 (t, J = 5.7, 1 H), 6.73 - 6.86 (m, 4 H), 7.05 - 7.18 (m, 4 H). ^{13}C-NMR: 14.1, 14.2, 14.4, 14.5, 14.9 (3 C), 15.8, 19.5, 20.9, 22.9, 26.4, 26.5, 26.7, 29.3, 29.6, 29.8, 33.4, 33.5, 34.8, 36.7, 37.7, 37.8, 38.6, 40.6, 42.6, 44.1, 47.3, 49.6, 54.8, 56.1, 60.5, 66.5, 67.3, 68.8, 79.8, 114.34 (3 C), 115.4 (2 C), 128.7, 129.5, 129.9 (2 C), 130.3 (3 C), 154.8, 157.6, 176.0, 176.9, 219.4. $C_{53}H_{77}NO_7$. m/z (calculated): 839,5700. m/z (found): 839,5704.

(2S)-2-ethoxy-3-[4-(2-{4-[(5-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0^{2,10}.0^{5,9}.0^{14,19}] henicosan-5-yl]formamido}pentyl)oxy]phenyl}ethoxy)phenyl]propanoic acid, 15d

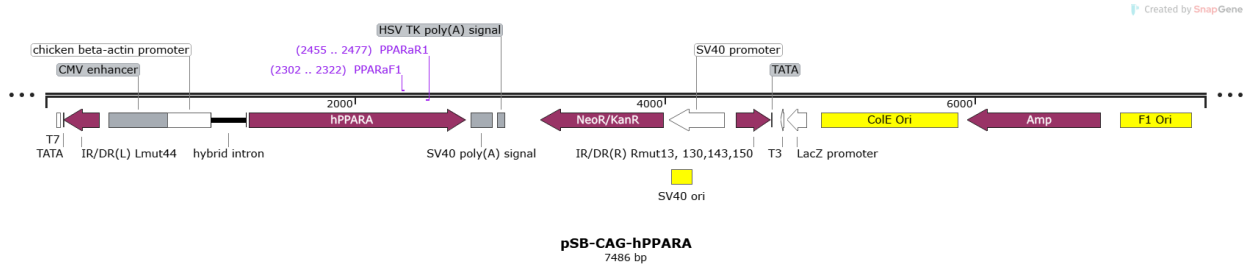
Material obtained: colorless oil. Yield 88%. ^{1}H-NMR: 0.73 (d, J = 6.6, 3 H), 0.76 - 0.96 (m, 9 H), 0.96 - 1.07 (m, 3 H), 1.08 - 1.12 (m, 8 H), 1.13 - 1.20 (m, 5 H), 1.26 - 1.59 (m, 20 H), 1.58 - 1.69 (m, 2 H), 1.69 - 1.82 (m, 2 H), 1.83 - 2.02 (m, 2 H), 2.32 - 2.51 (2 H, m), 2.99 (m, 4 H), 3.16 - 3.41 (m, 3 H), 3.53 - 3.66 (m, 1 H), 3.86 - 3.94 (m, 1 H), 3.94 - 4.01 (m, 1 H), 4.01 - 4.15 (m, 4 H), 5.61 - 5.71 (br.s., 1 H), 6.73 - 6.85 (m, 4 H), 7.12 (m, 4 H). ^{13}C-NMR: 14.3, 14.5, 14.9, 15.7, 15.8, 19.5, 20.9, 21.0, 21.8 (2 C), 22.9, 26.5, 26.7, 28.8, 29.4, 29.72, 33.4, 33.6, 34.71, 36.7, 37.5, 37.9, 38.6, 39.3, 40.5, 42.6, 44.0, 47.2, 49.20, 49.6, 54.8, 56.0, 66.4, 67.5, 68.7, 70.0, 79.7, 114.2 (2 C), 114.3 (2C), 115.3, 128.9, 129.0, 129.8 (2C), 130.3 (2C), 155.1, 156.7, 157.5, 175.2, 176.6, 218.9. $C_{54}H_{79}NO_7$. m/z (calculated): 853,5857. m/z (found): 853,5859.

(2S)-2-ethoxy-3-[4-(2-{4-[(6-{[(1R,2R,5S,8S,9R,10R,13R,14R,19R)-1,2,14,18,18-pentamethyl-17-oxo-8-(propan-2-yl)pentacyclo[11.8.0.0^{2,10}.0^{5,9}.0^{14,19}] henicosan-5-yl]formamido}hexyl)oxy]phenyl}ethoxy)phenyl]propanoic acid, 15e

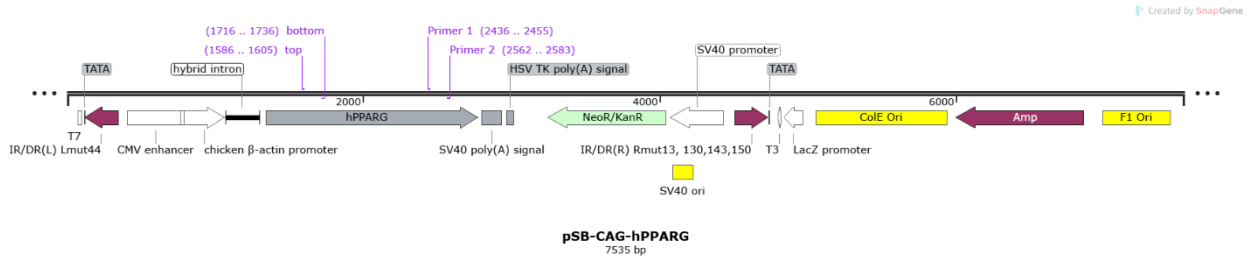
Material obtained: colorless oil. Yield 85%. ^{1}H-NMR: 0.75 (m, 3 H), 0.81 (m, 3 H), 0.87 – 1.00 (m, 11 H), 1.02 – 1.15 (m, 6 H), 1.17 - 1.28 (m, 6 H), 1.30 – 1.58 (m, 18 H), 1.61 – 2.01 (m, 6 H), 2.18 – 2.40 (m, 2 H), 2.43 – 2.51 (m, 3 H), 2.96 - 2.99 (m, 4 H), 3.25 - 3.37 (m, 2 H), 3.56 - 3.59 (m, 1 H), 3.66 (d, J = 4.7, 2 H), 3.96 (t, J = 6.5, 1 H), 4.07 - 4.18 (m, 4 H), 5.61 (br.s., 1 H), 6.71 (m, 4 H), 7.07 - 7.18 (m, 4 H). ^{13}C-NMR: 14.6, 15.0, 15.9, 19.6, 21.0, 21.1, 23.0, 26.2, 26.6, 27.0, 29.7, 29.8, 29.9, 32.0, 33.7, 33.8, 34.1, 34.9, 36.5, 36.7, 37.1, 37.6, 38.7, 39.6, 40.7, 44.1, 44.2, 47.3, 49.2, 49.4, 49.7, 51.2, 54.5, 56.0, 66.8, 67.8, 68.9, 69.0, 79.8, 114.4 (2C), 114.7 (2C), 115.4, 128.6, 129.9 (2C), 130.5 (2C), 154.6, 157.7, 174.4, 176.3, 218.4. $C_{55}H_{81}NO_7$. m/z (calculated): 867,6013. m/z (calculated): 867,6015.

In vitro studies

A



B



C

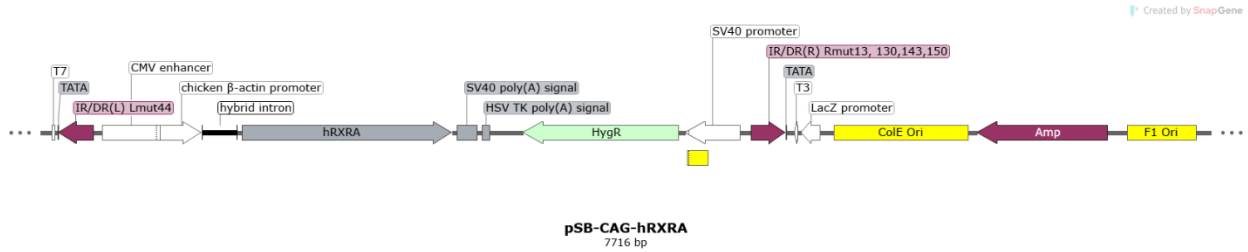


Figure S1. Maps of the plasmids with SB transposons pSB-CAG-hPPARa-neo (A); pSB-CAG-hPPARg-neo (B); pSB-CAG-hRXRa-higro.

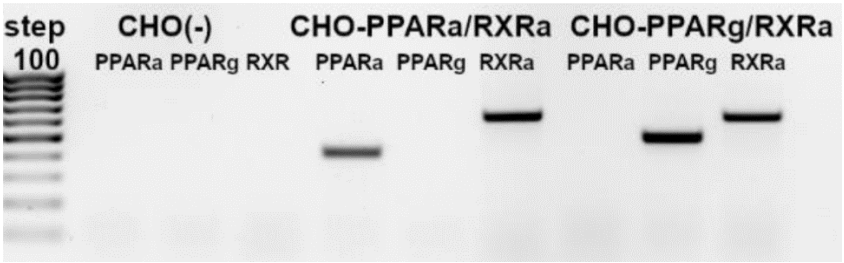
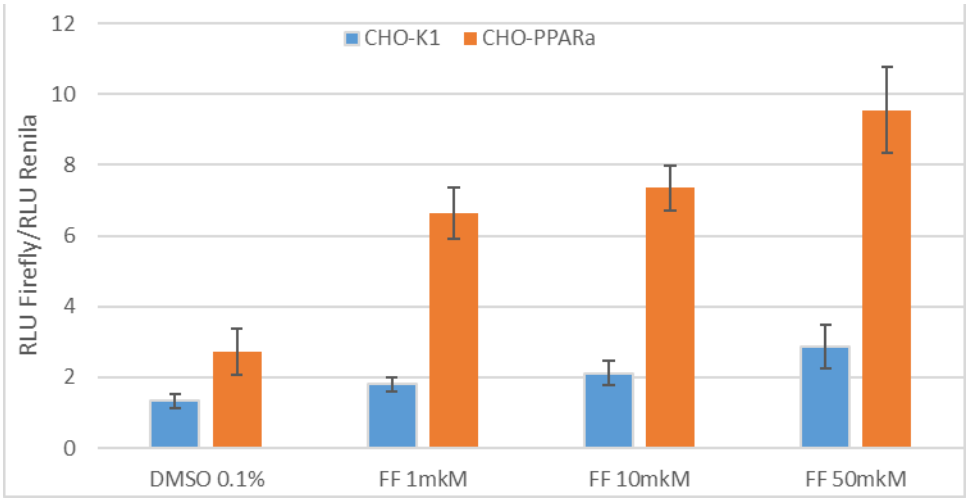


Figure S2. Transgenes *hPPARA, hRXRa* and *hPPARG hRXRa* are expressing in CHO-PPARa и CHO-PPARg cells respectively, but not in CHO-K1. OT-PCR analysis, DNA marker Step100 (100–1000 bp) (Biolabmix).

A



B

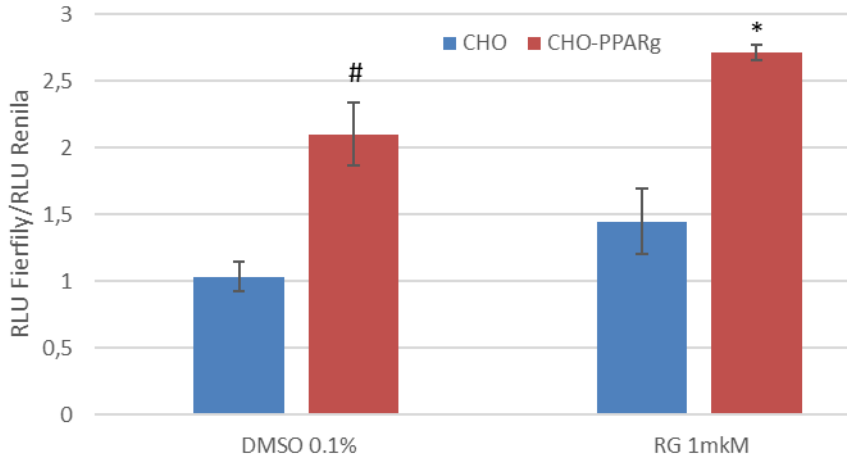


Figure S3. Effect of Fenofibrat (FF, agonists PPARa) on the activity of the dual luciferase assay system (DLA) in parental CHO-K1 and transgenic CHO-PPARa (A); effect of Rosiglitasone (RG, agonist PPARg) in CHO-K1 and CHO-PPARg, (#) $p<0,05$ with CHO; (*) $p<0,05$ with CHO-PPARg DMSO 0.1% (B). Dual-Luciferase reporter Assay, relative units.

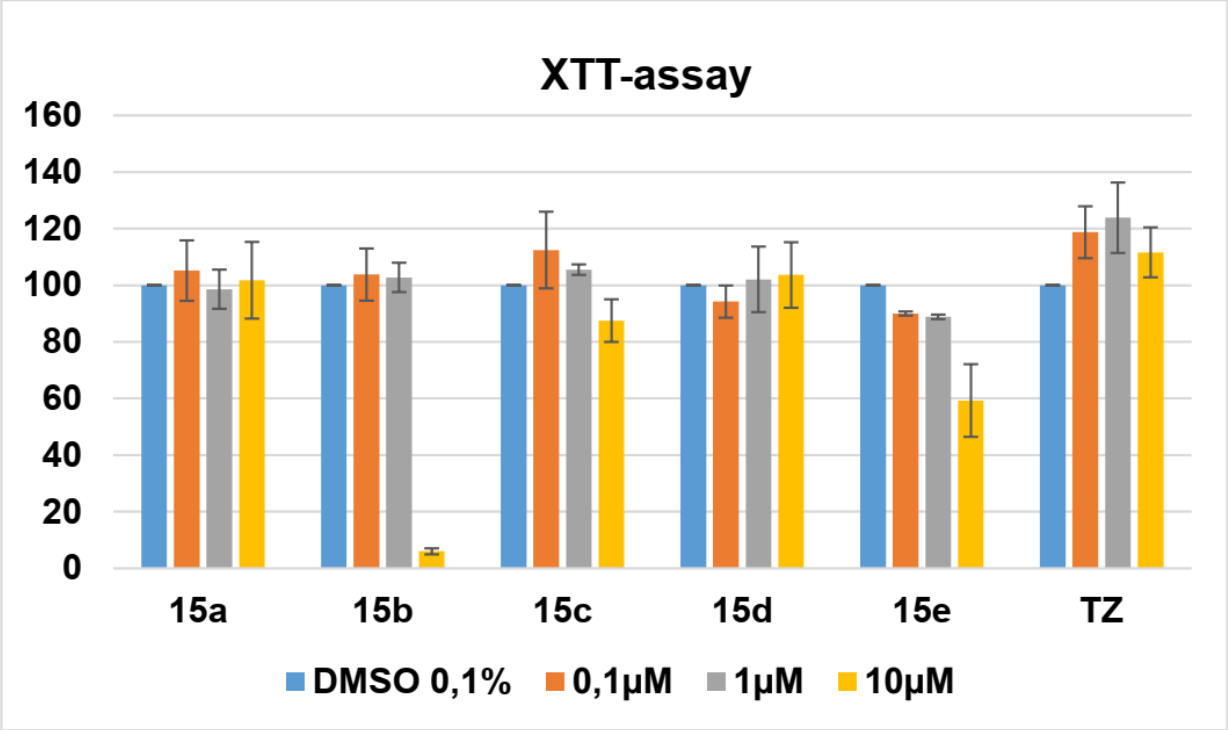


Figure S4. Viability of CHO-K1 after treatment with experimental compound in 0,1 µM, 1µM, 10 µM (0,1% DMSO, HBSS) determined by XTT-assay. Data are normalized to 0,1%DMSO sample and presented as the mean ± S.D.

Figure S5. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(4-hydroxybutyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13a** ^{1}H NMR spectrum.

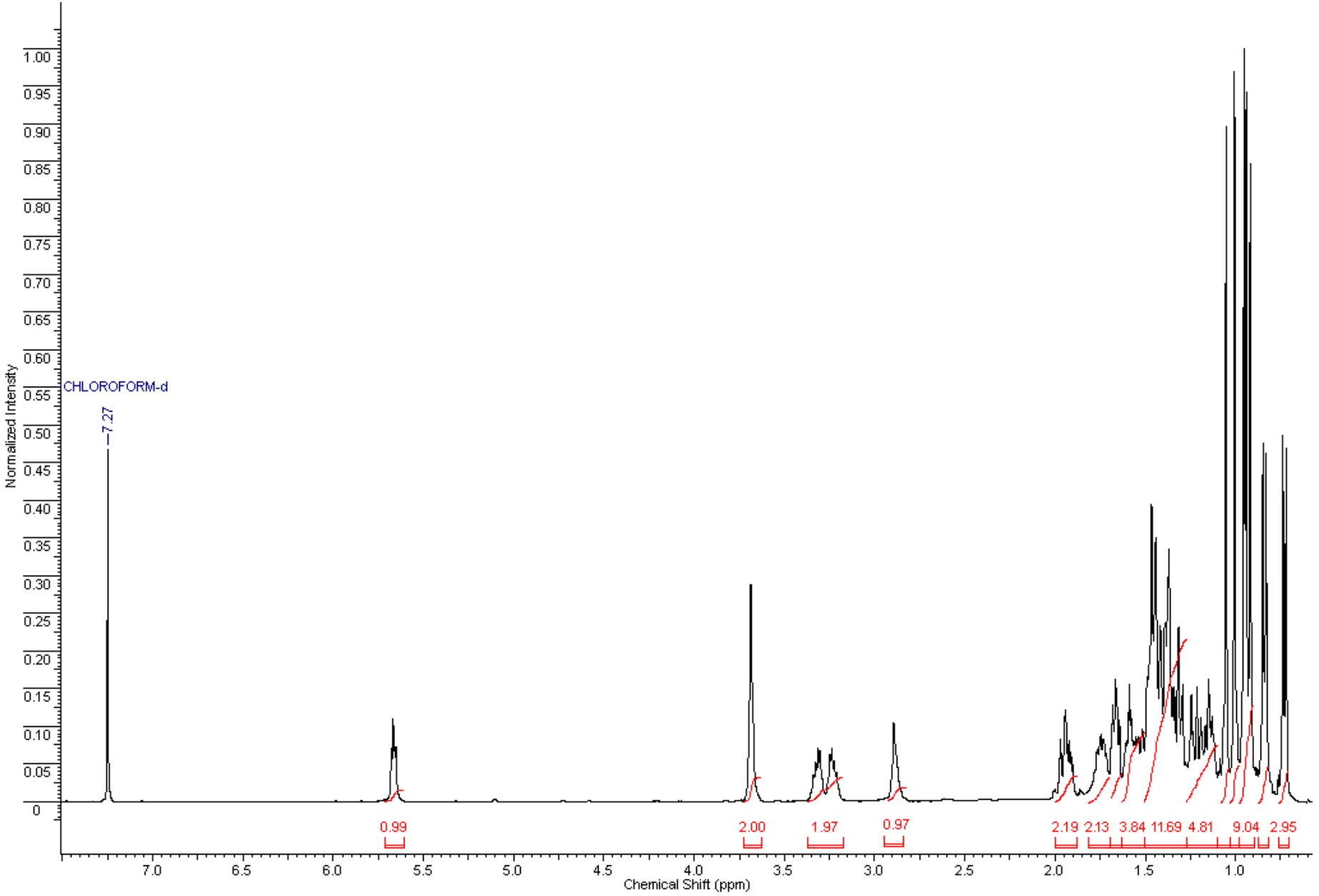


Figure S6. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(4-hydroxybutyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13a** ^{13}C NMR spectrum.

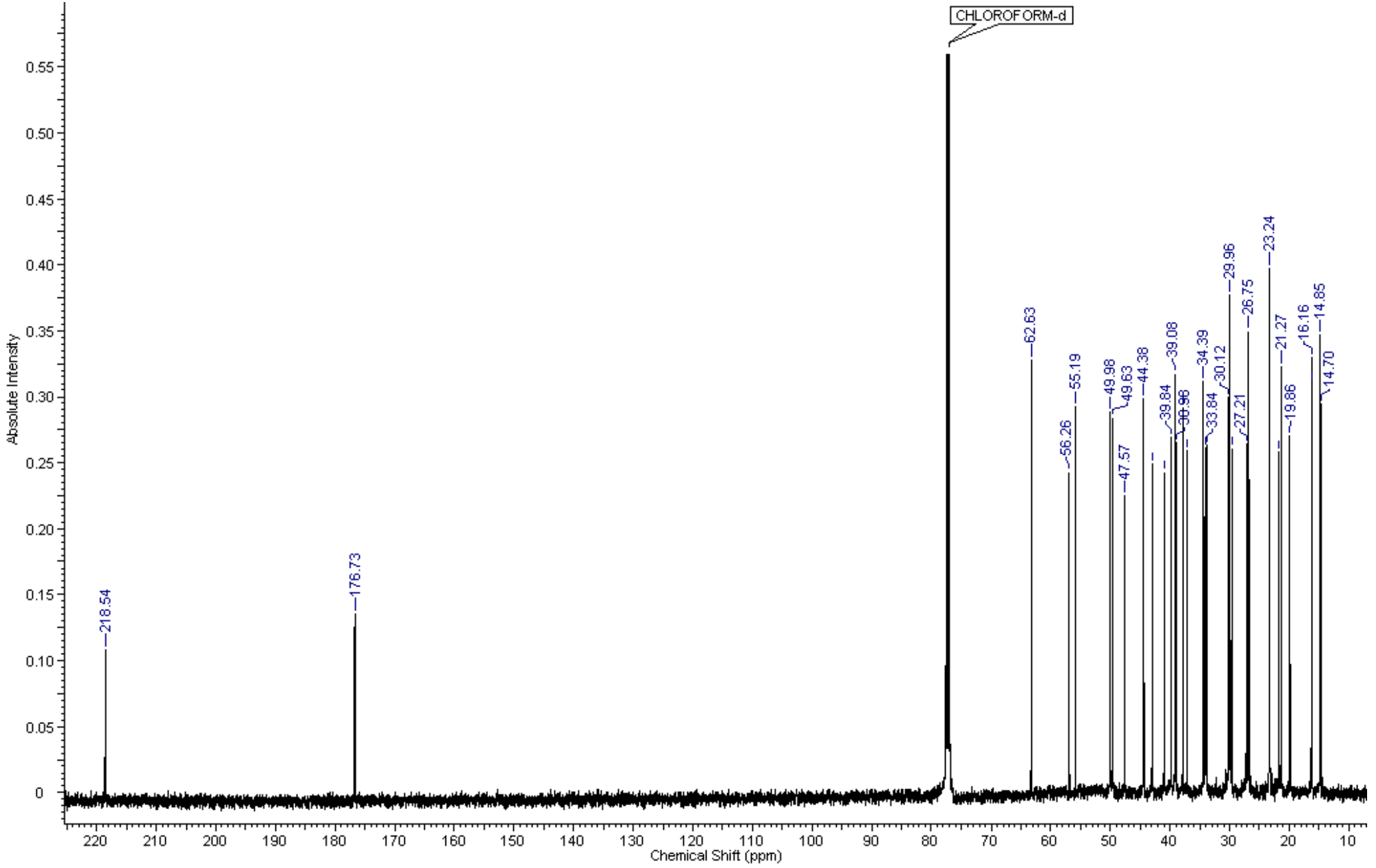


Figure S7. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(3-hydroxypropyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13b** ^{1}H NMR spectrum.

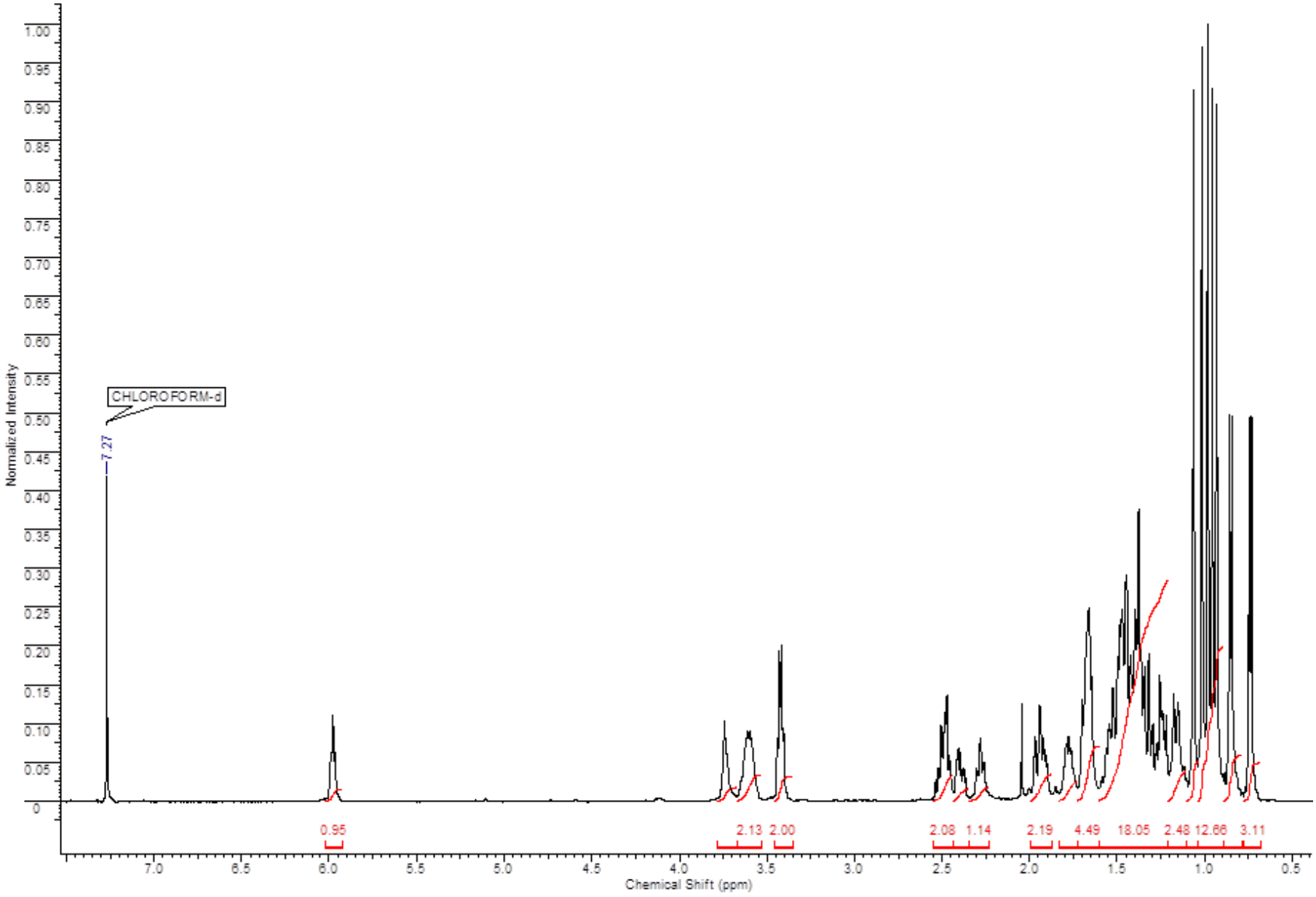


Figure S8. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(3-hydroxypropyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13b** ^{13}C NMR spectrum.

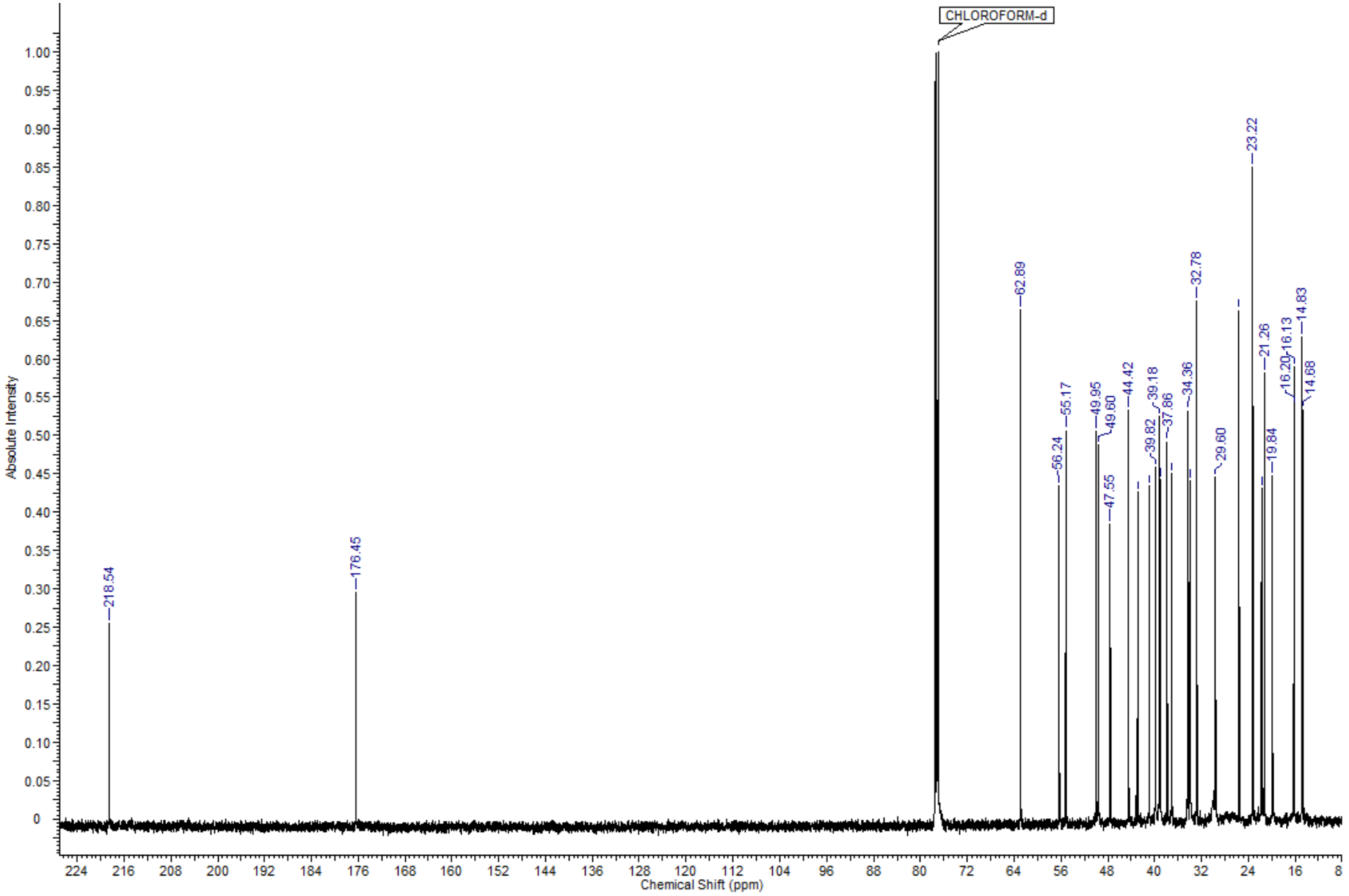


Figure S9. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(4-hydroxybutyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13c** ^{1}H NMR spectrum.

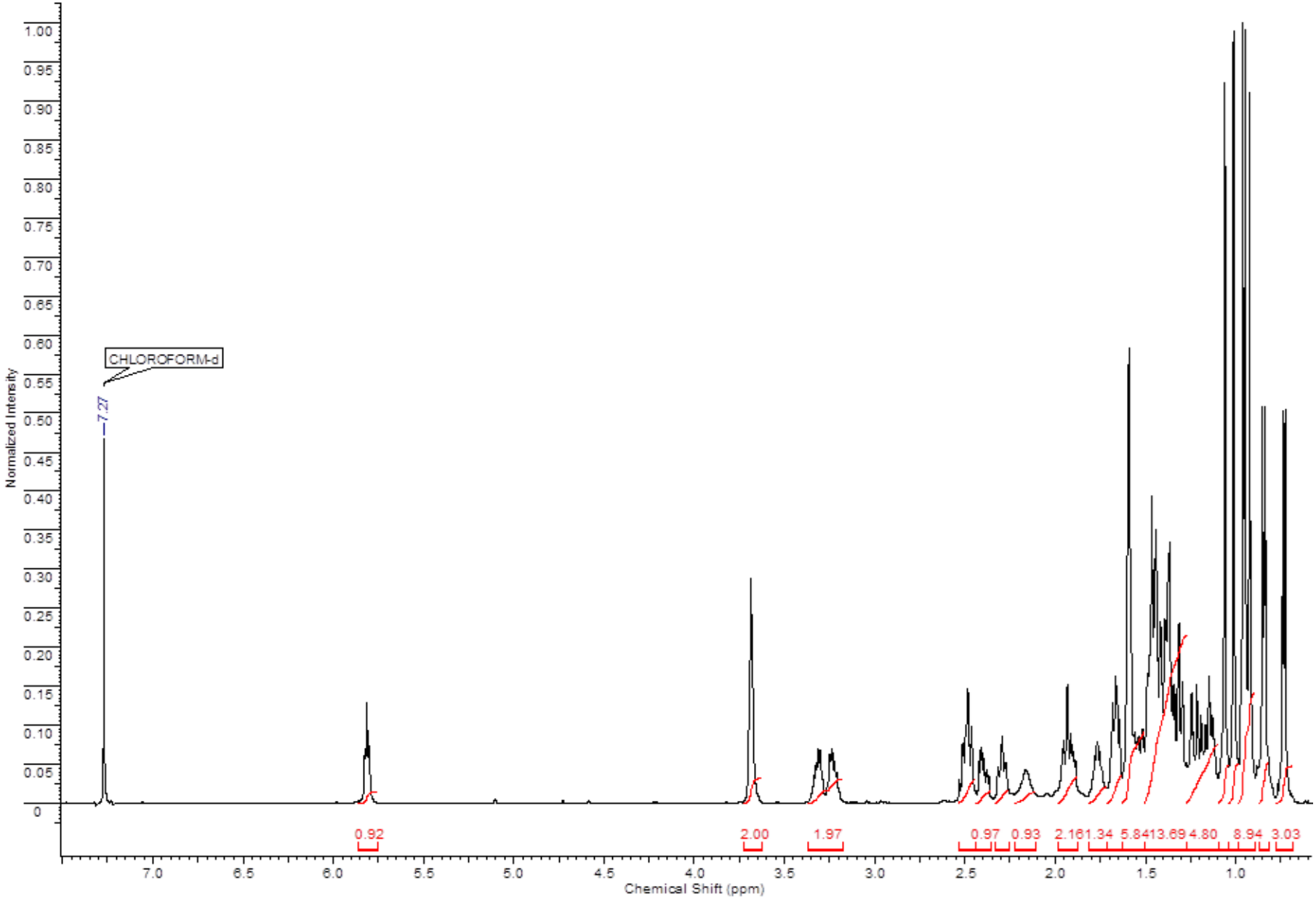


Figure S10. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(4-hydroxybutyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13c** ^{1}H NMR spectrum.

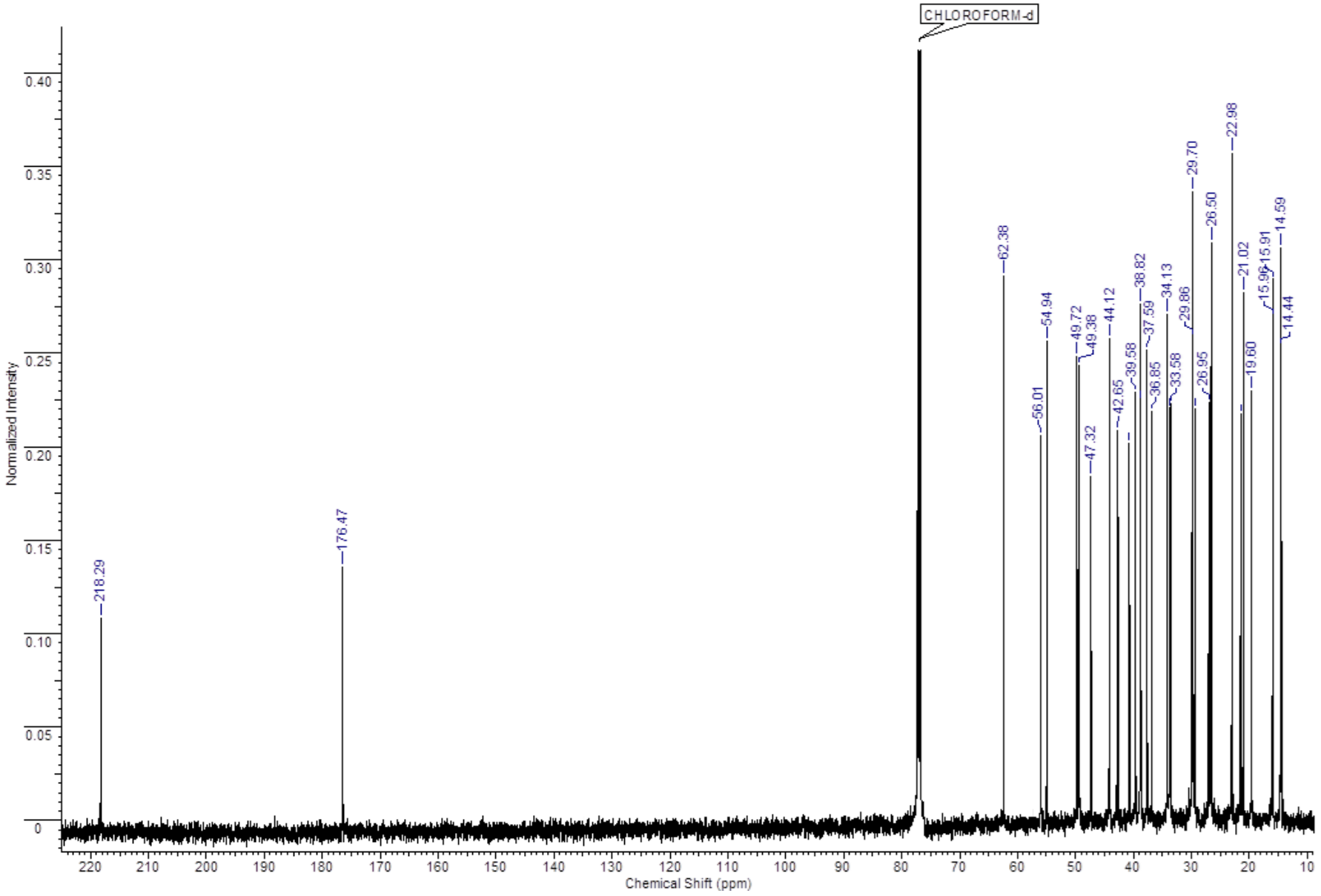


Figure S11. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(5-hydroxypentyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13d** ^{1}H NMR spectrum.

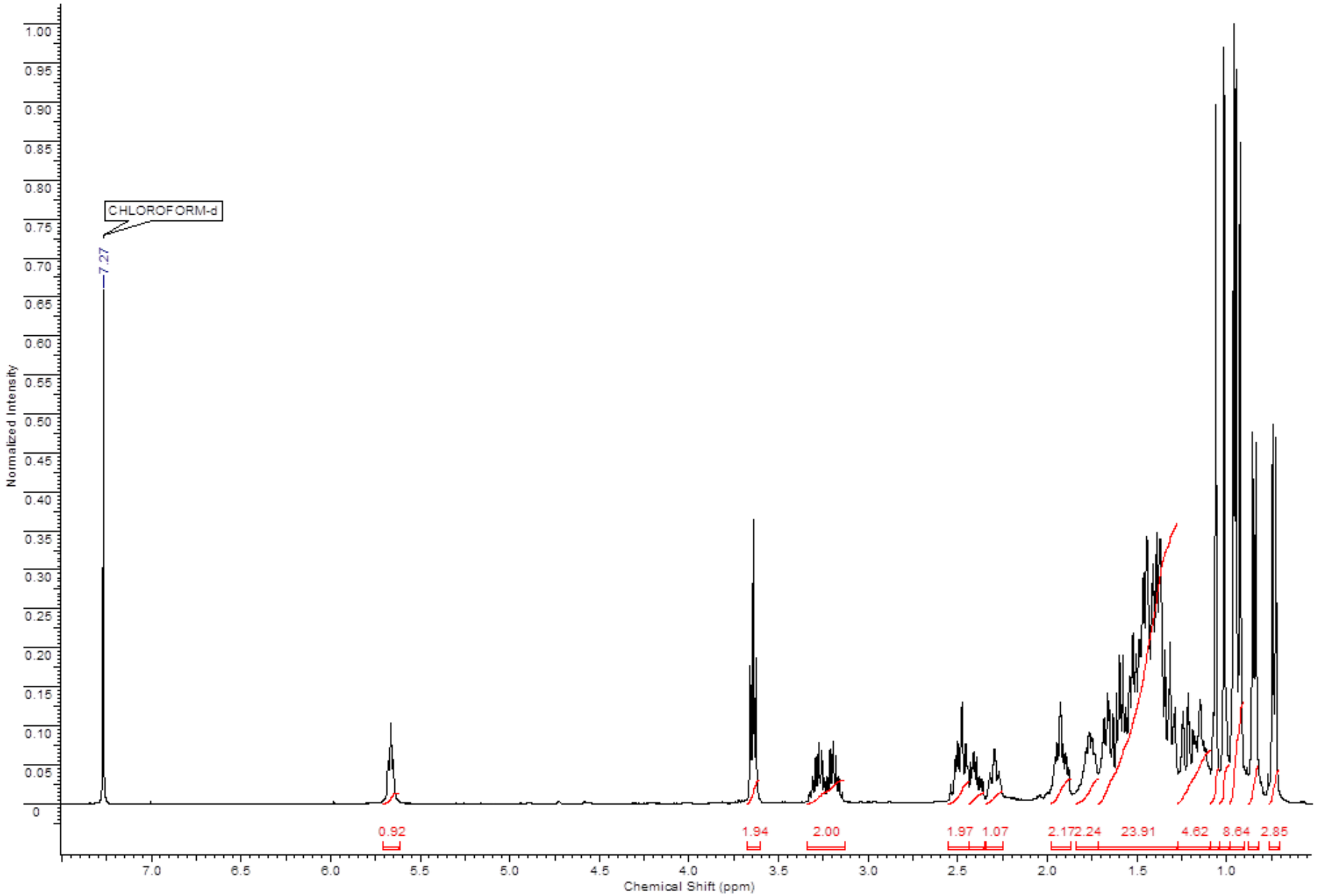


Figure S12. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(5-hydroxypentyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13d** ^{13}C NMR spectrum.

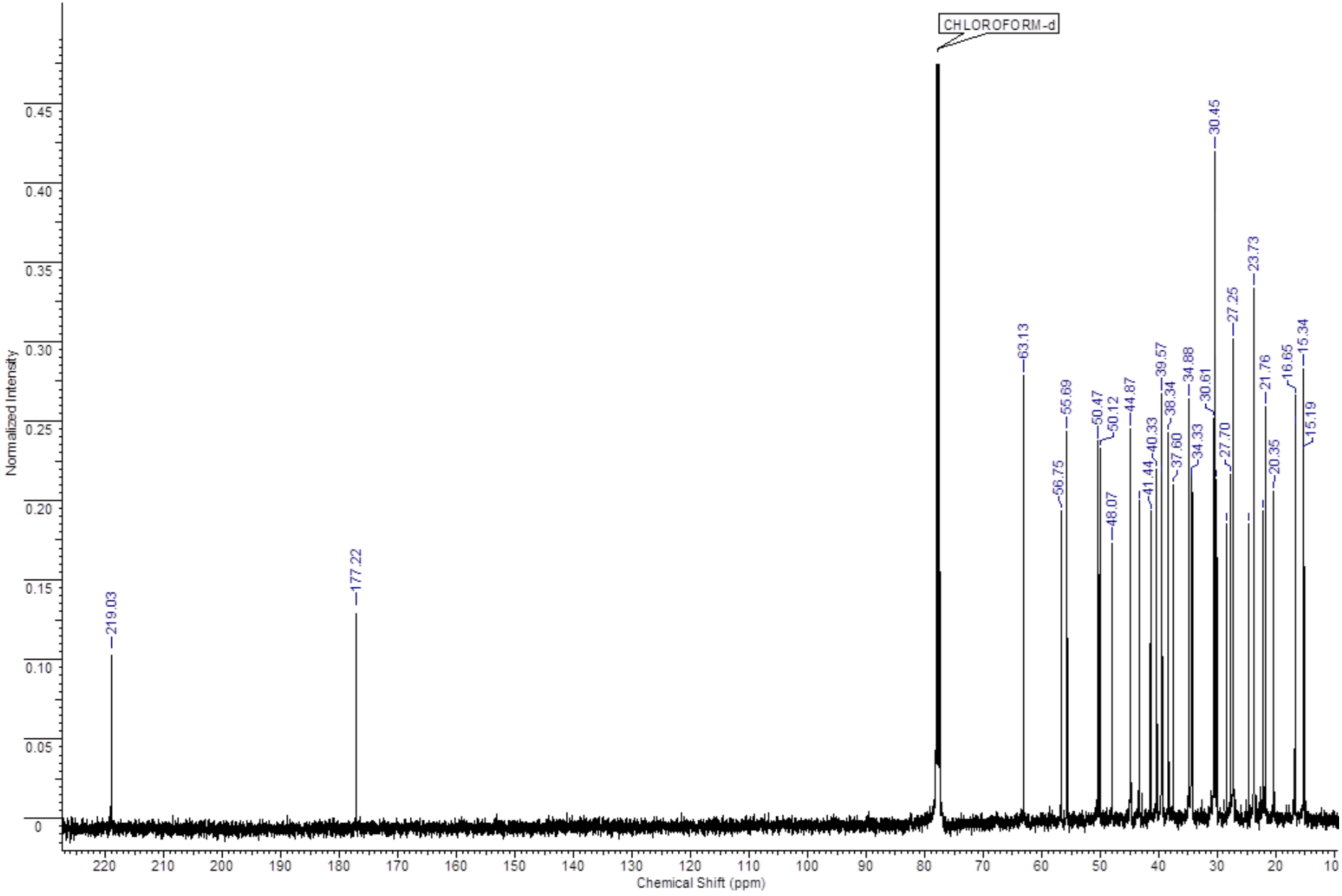


Figure S13. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(6-hydroxyhexyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13e** ^{1}H NMR spectrum.

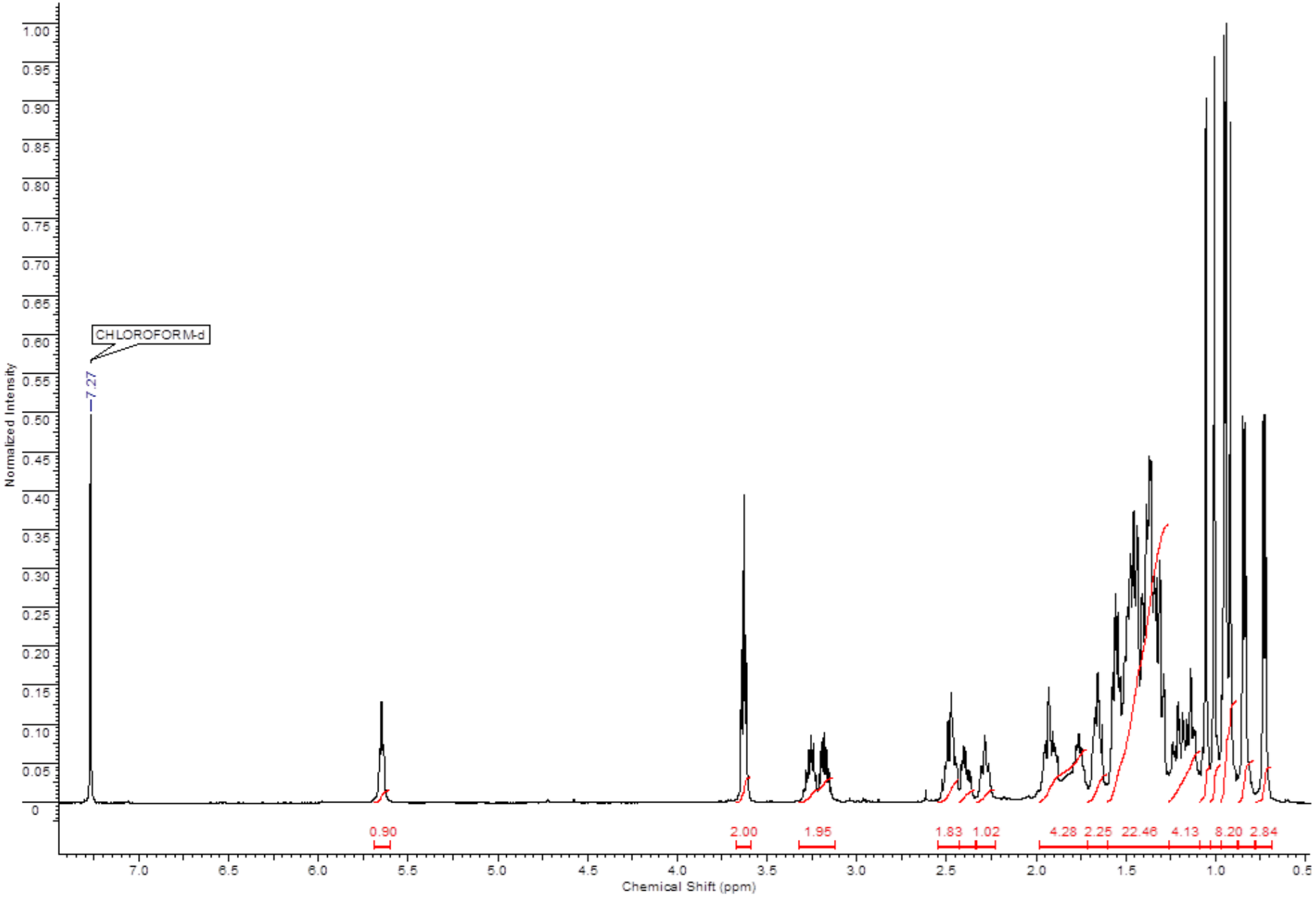


Figure S14. (1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-N-(6-hydroxyhexyl)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamide, **13e** ^{13}C NMR spectrum.

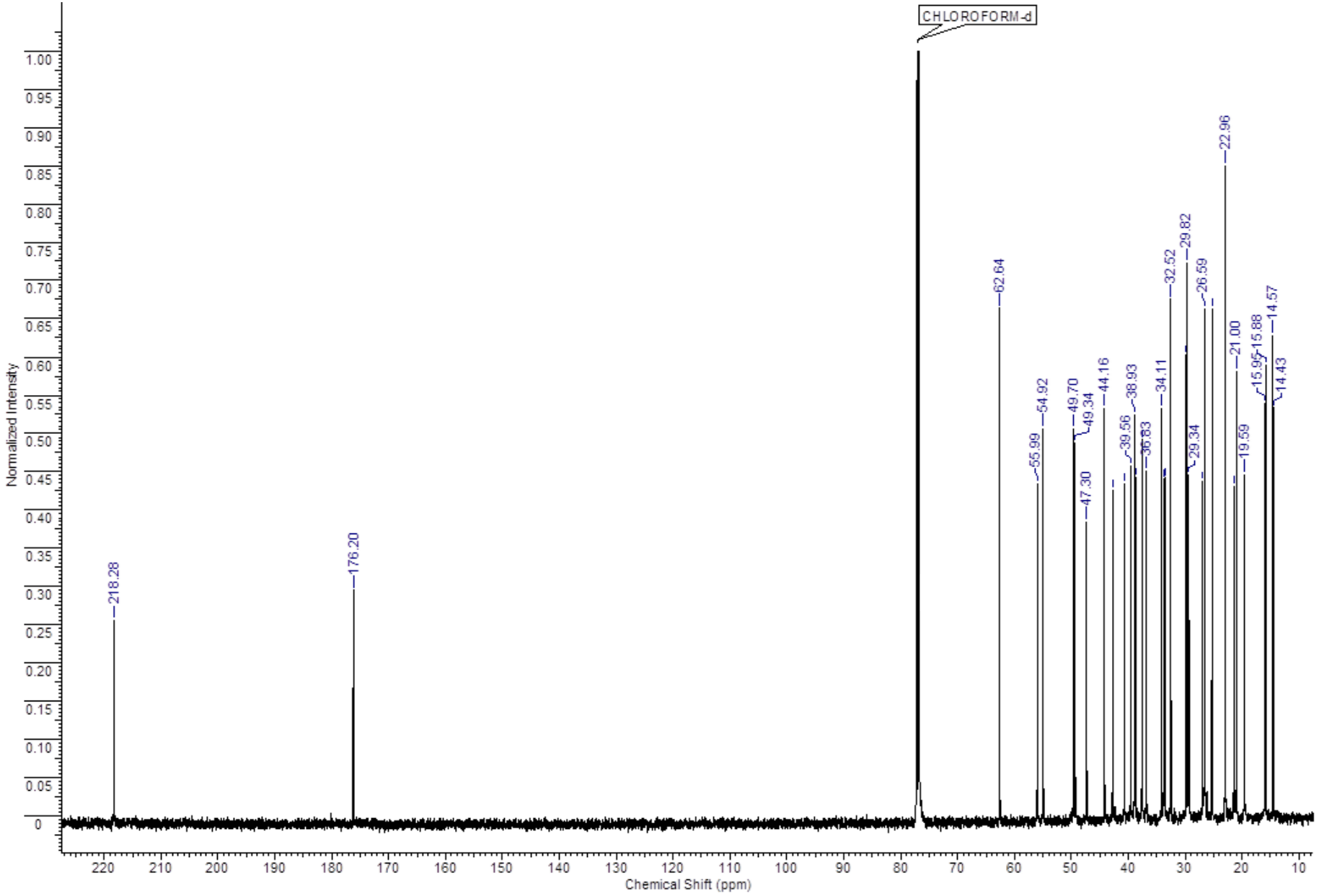


Figure S15. *(S)*-ethyl 2-ethoxy-3-(4-(4-(3-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)propoxy)phenethoxy)phenyl)propanoate**, 14b** ^{1}H NMR spectrum

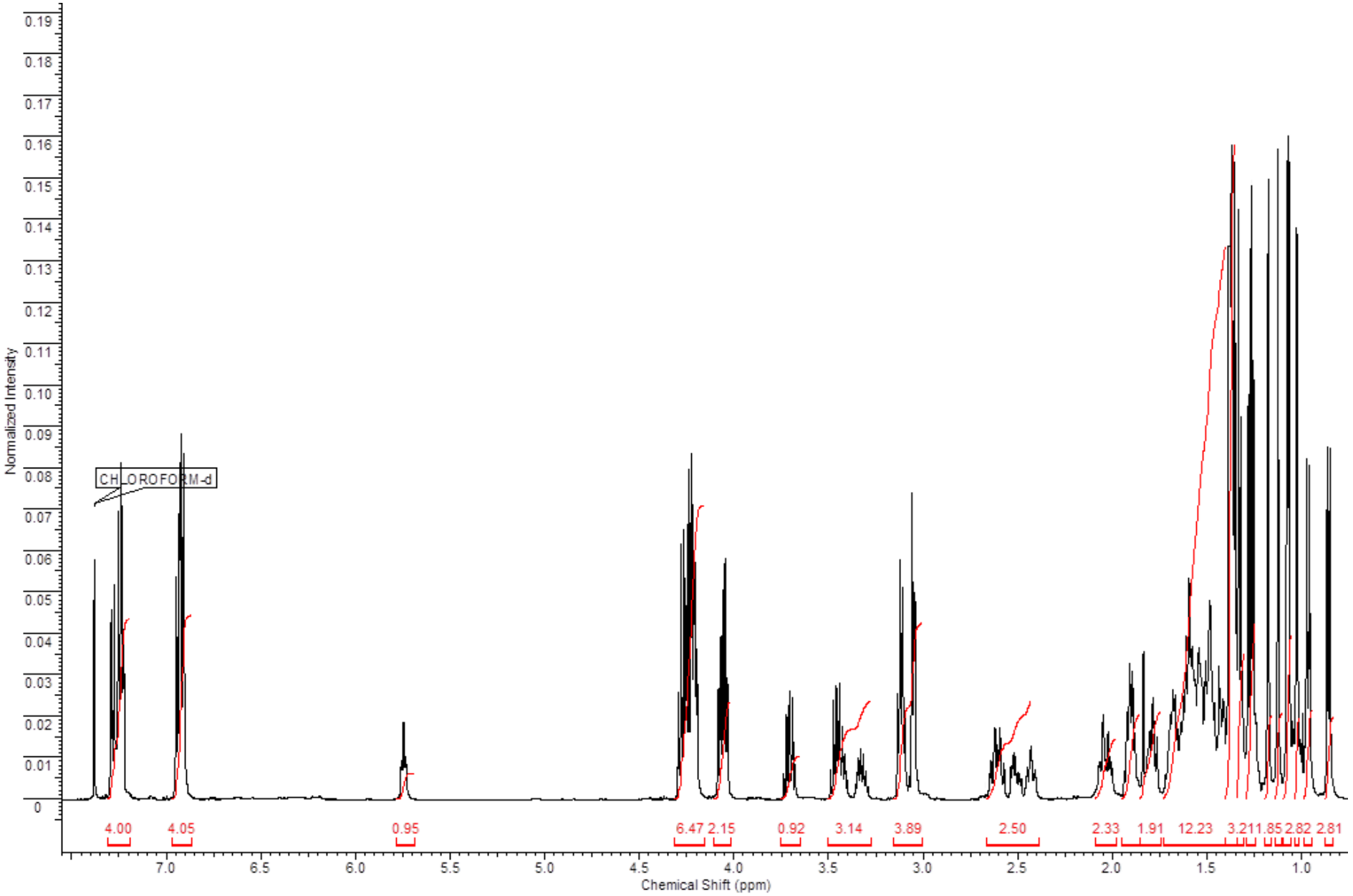


Figure S16. *(S)*-ethyl 2-ethoxy-3-(4-(4-(3-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)propoxy)phenethoxy)phenyl)propanoate**, 14b** ^{13}C NMR spectrum.

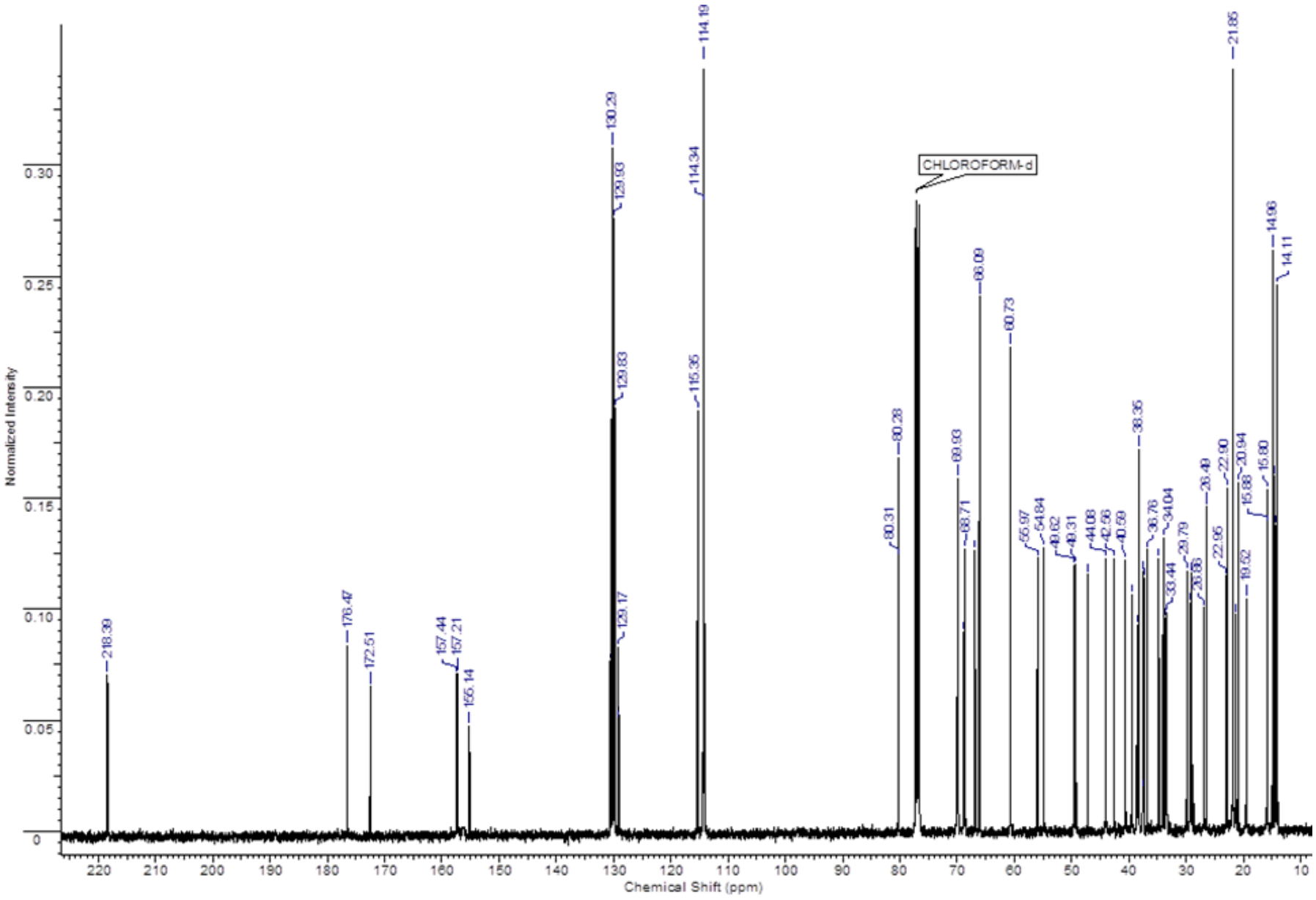


Figure S17. *(S)*-ethyl 2-ethoxy-3-(4-(4-(4-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido) butoxy)phenethoxy)phenyl)propanoate**, 14c** ^{1}H NMR spectrum.

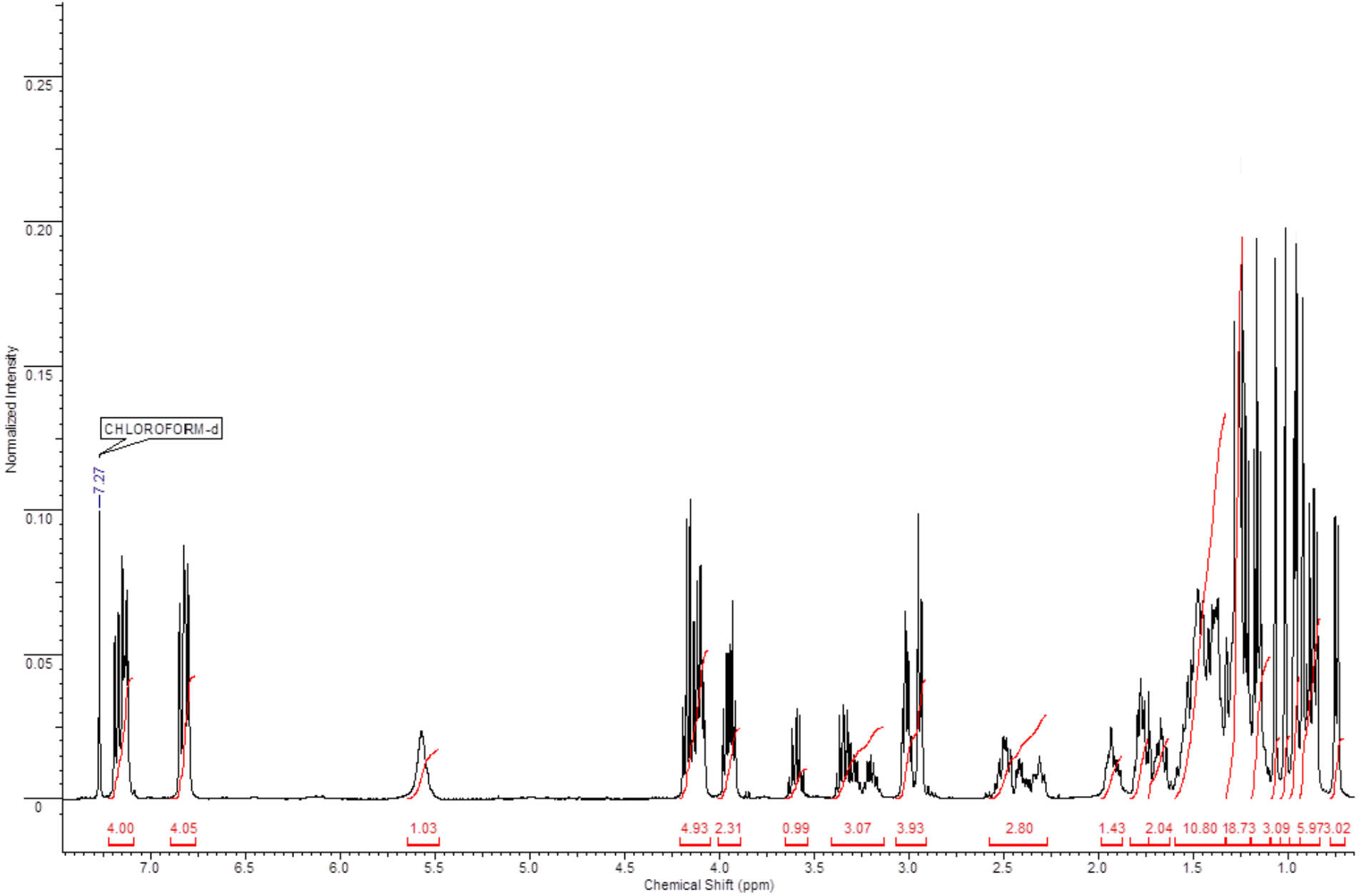


Figure S18. *(S)*-ethyl 2-ethoxy-3-(4-(4-(4-(((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)butoxy)phenethoxy)phenyl)propanoate**, 14c** ^{13}C NMR spectrum.

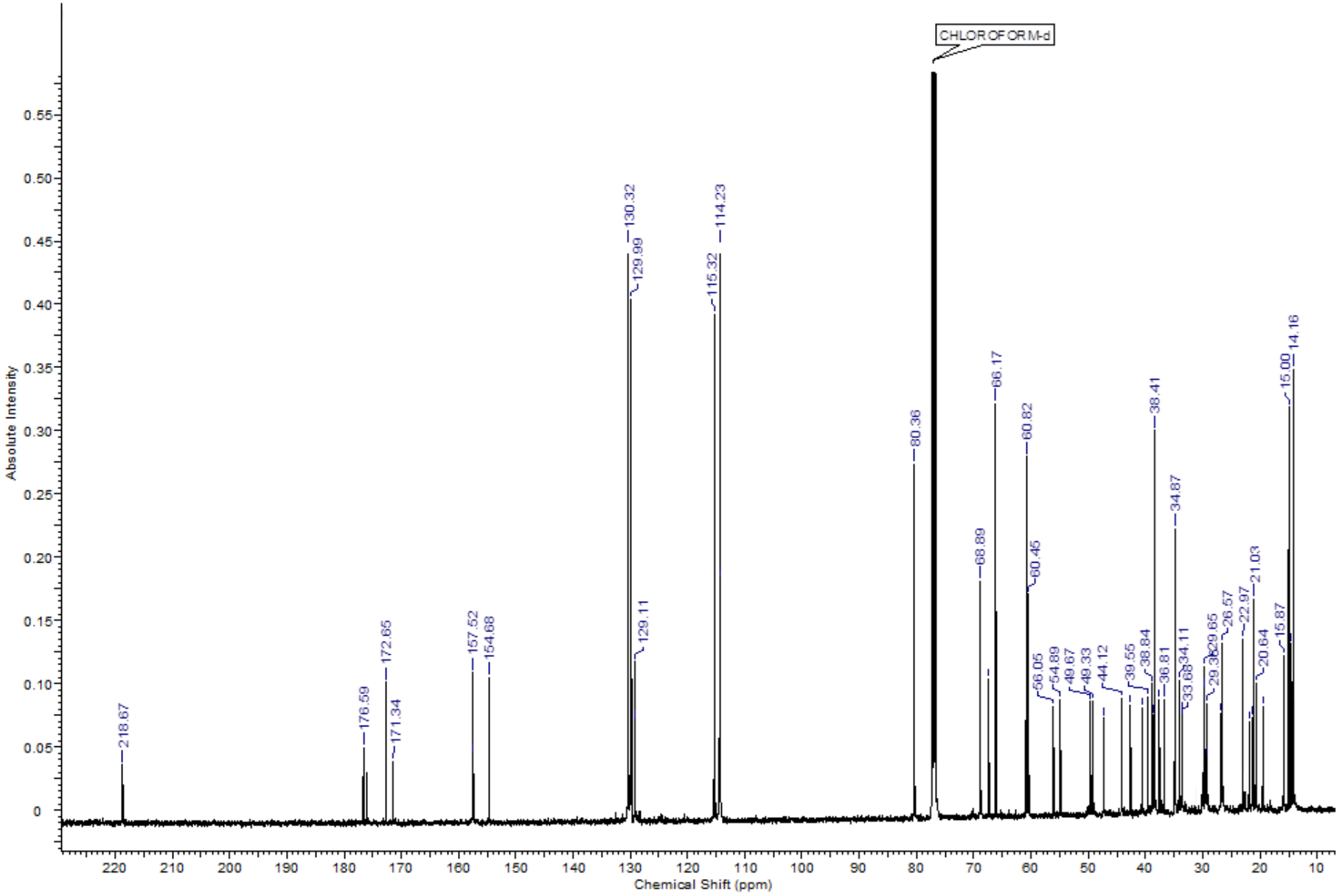


Figure S19. *(S)*-ethyl 2-ethoxy-3-(4-(4-(5-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)pentoxy)phenethoxy)phenyl)propanoate**, 14d** ^{1}H NMR spectrum.

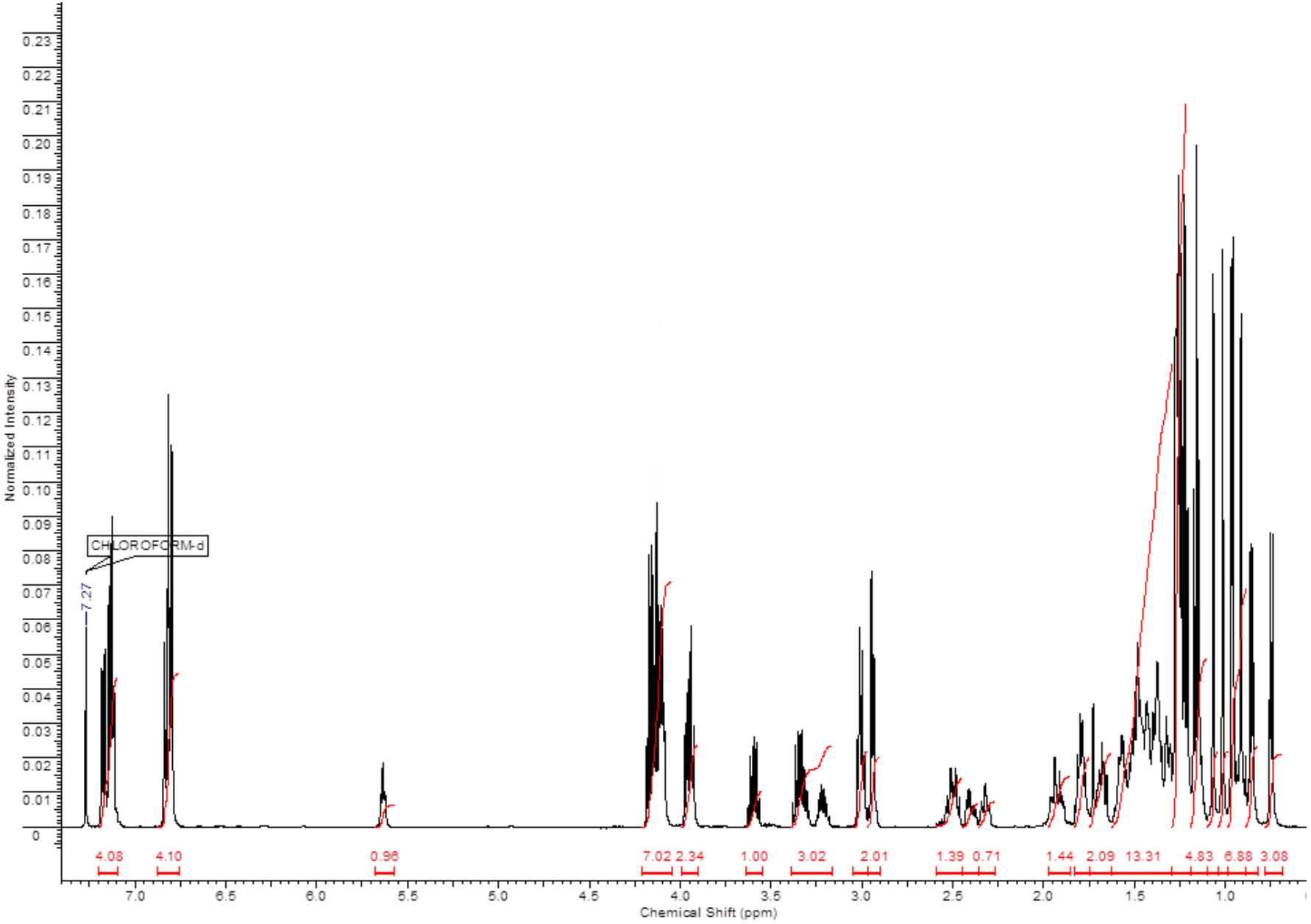


Figure S20. *(S)*-ethyl 2-ethoxy-3-(4-(4-(5-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)pentoxy)phenethoxy)phenyl)propanoate**, 14d** ^{13}C NMR spectrum.

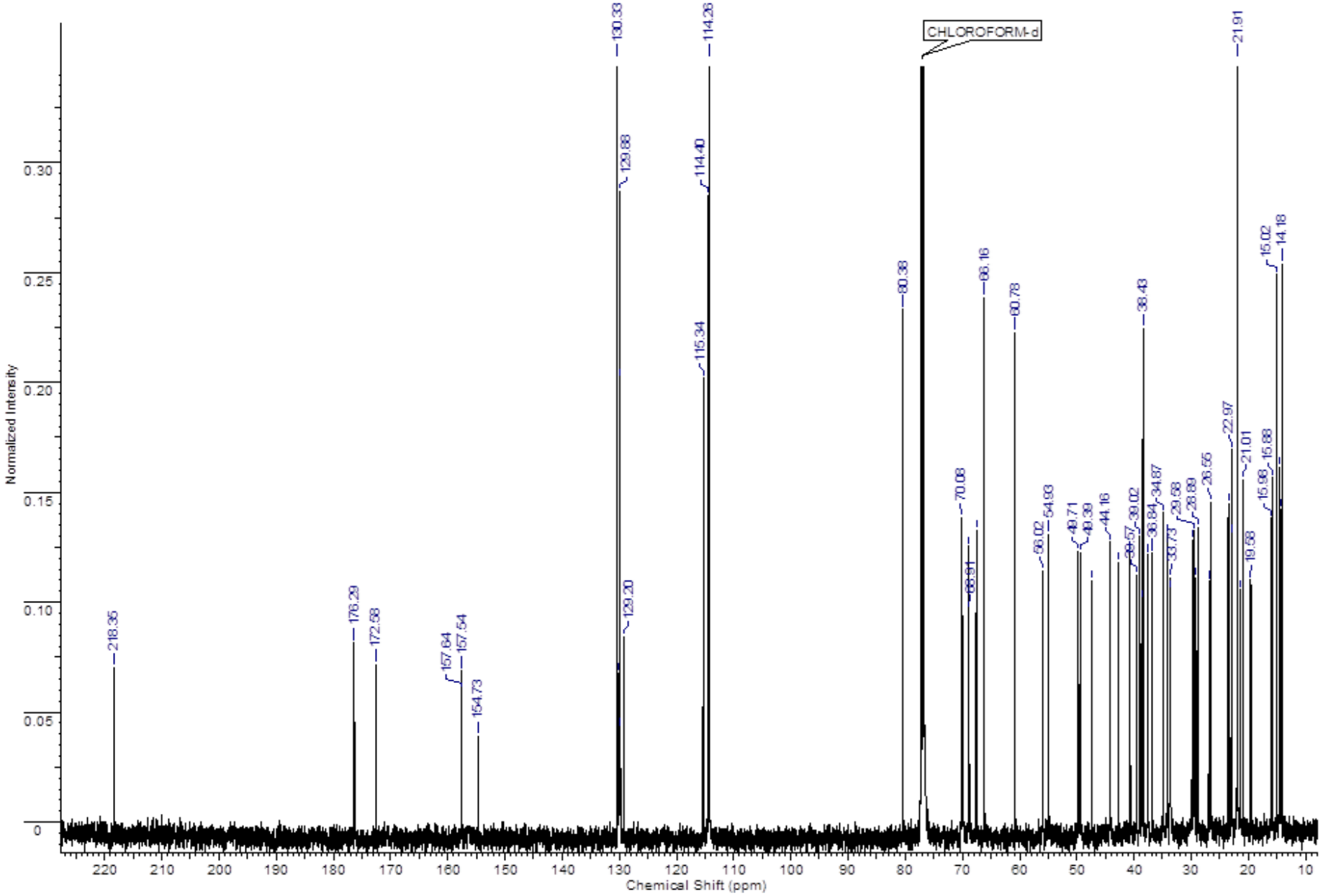


Figure S21. *(S)*-ethyl 2-ethoxy-3-(4-(4-(6-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)hexoxy)phenethoxy)phenyl)propanoate**, 14e** ^{1}H NMR spectrum.

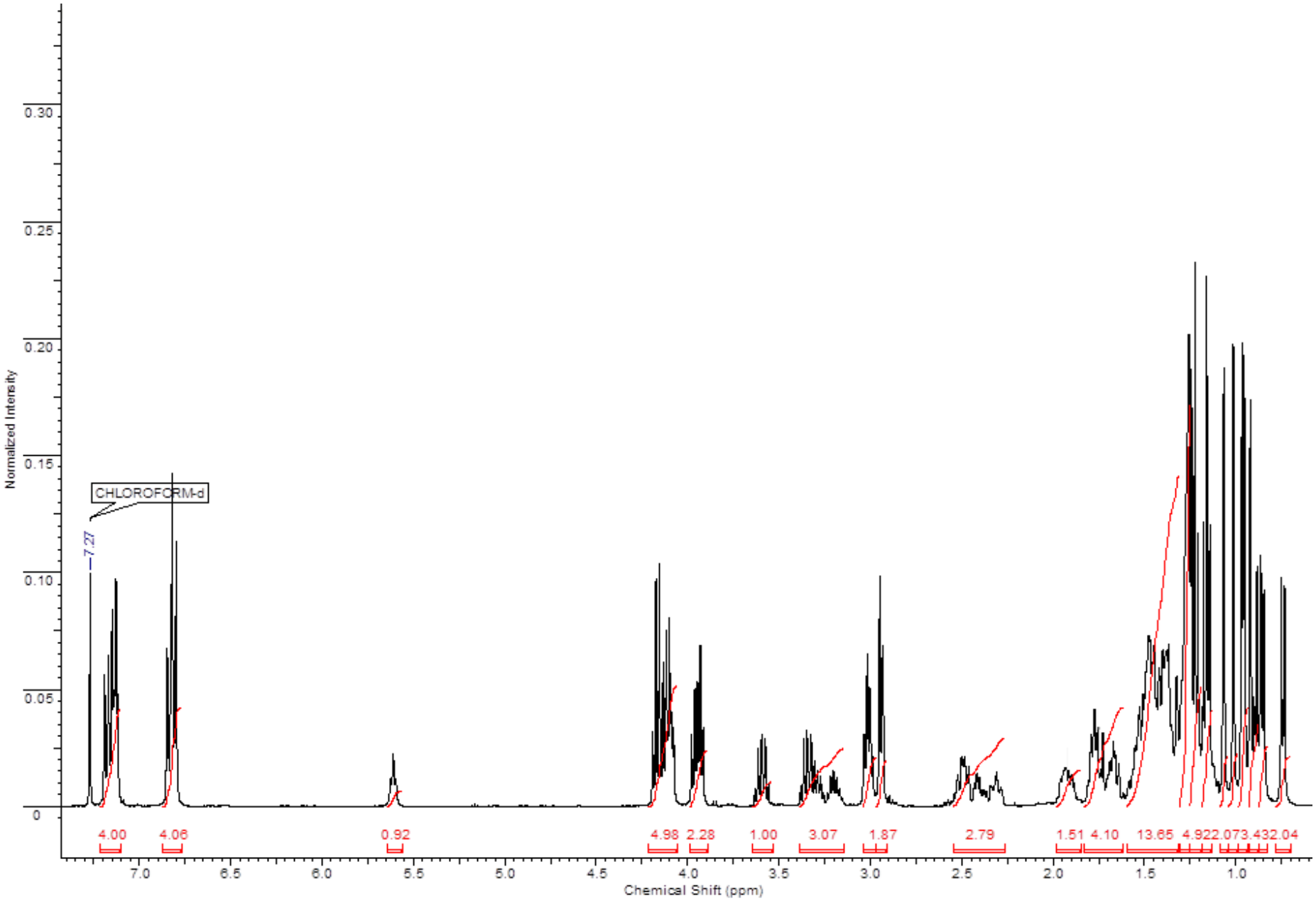


Figure S22. *(S)*-ethyl 2-ethoxy-3-(4-(4-(6-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)hexoxy)phenethoxy)phenyl)propanoate**, 14e** ^{13}C NMR spectrum.

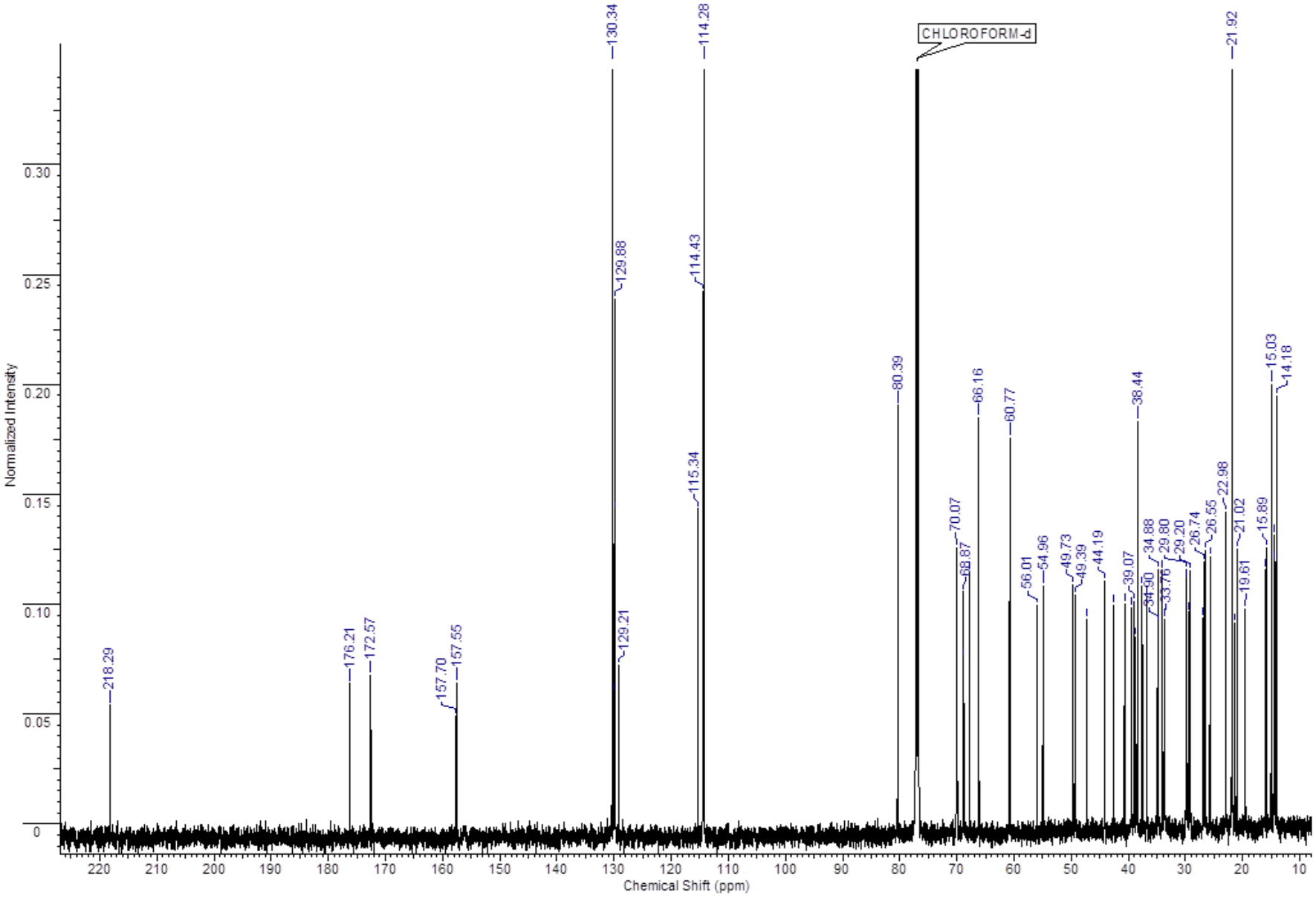


Figure S23. *(S)*-2-ethoxy-3-(4-(4-(3-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)propoxy)phenethoxy)phenyl)propanoic acid, **15b** ^{1}H NMR spectrum.

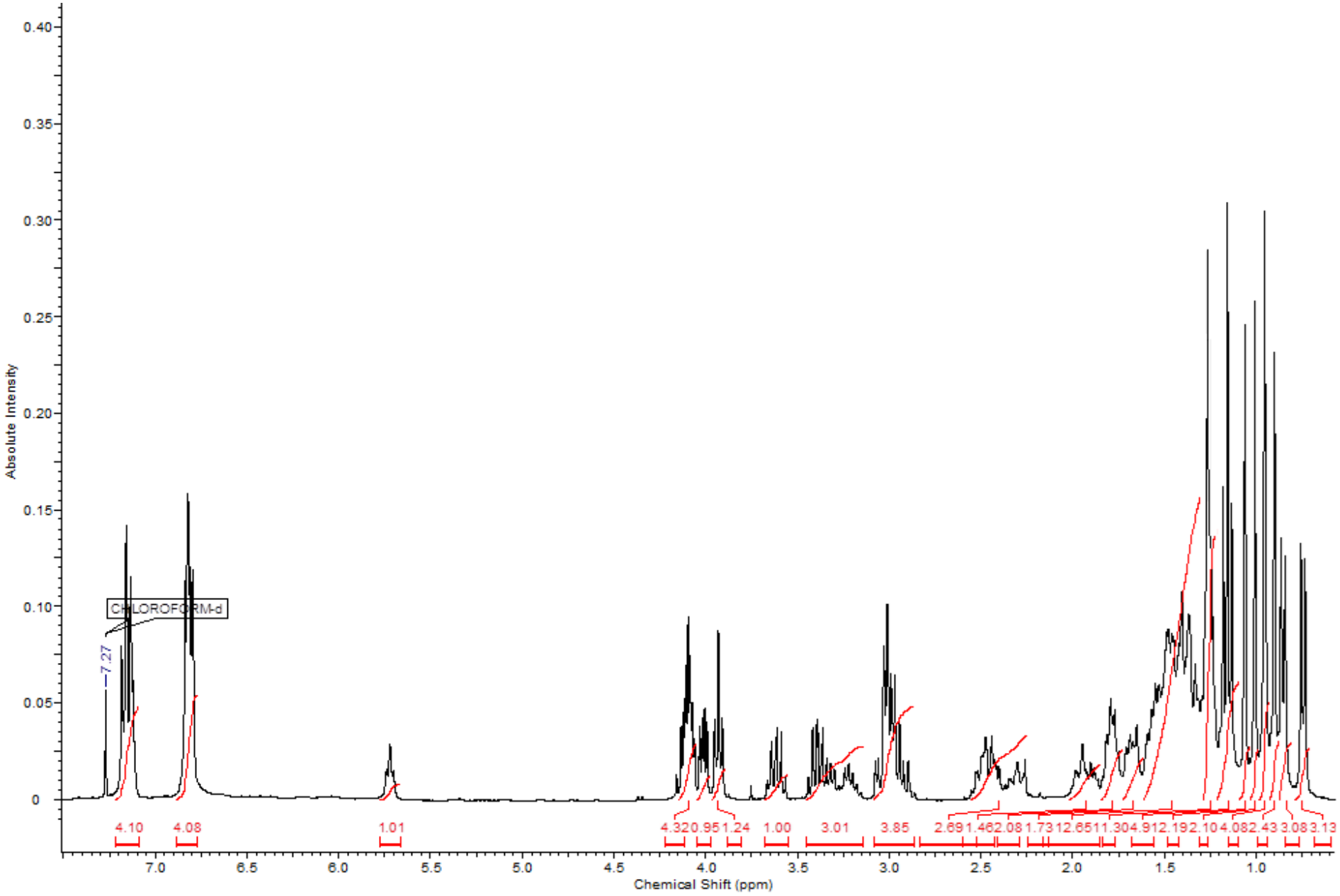


Figure S24. *(S)*-2-ethoxy-3-(4-(4-(3-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)propoxy)phenethoxy)phenyl)propanoic acid, **15b** ^{13}C NMR spectrum.

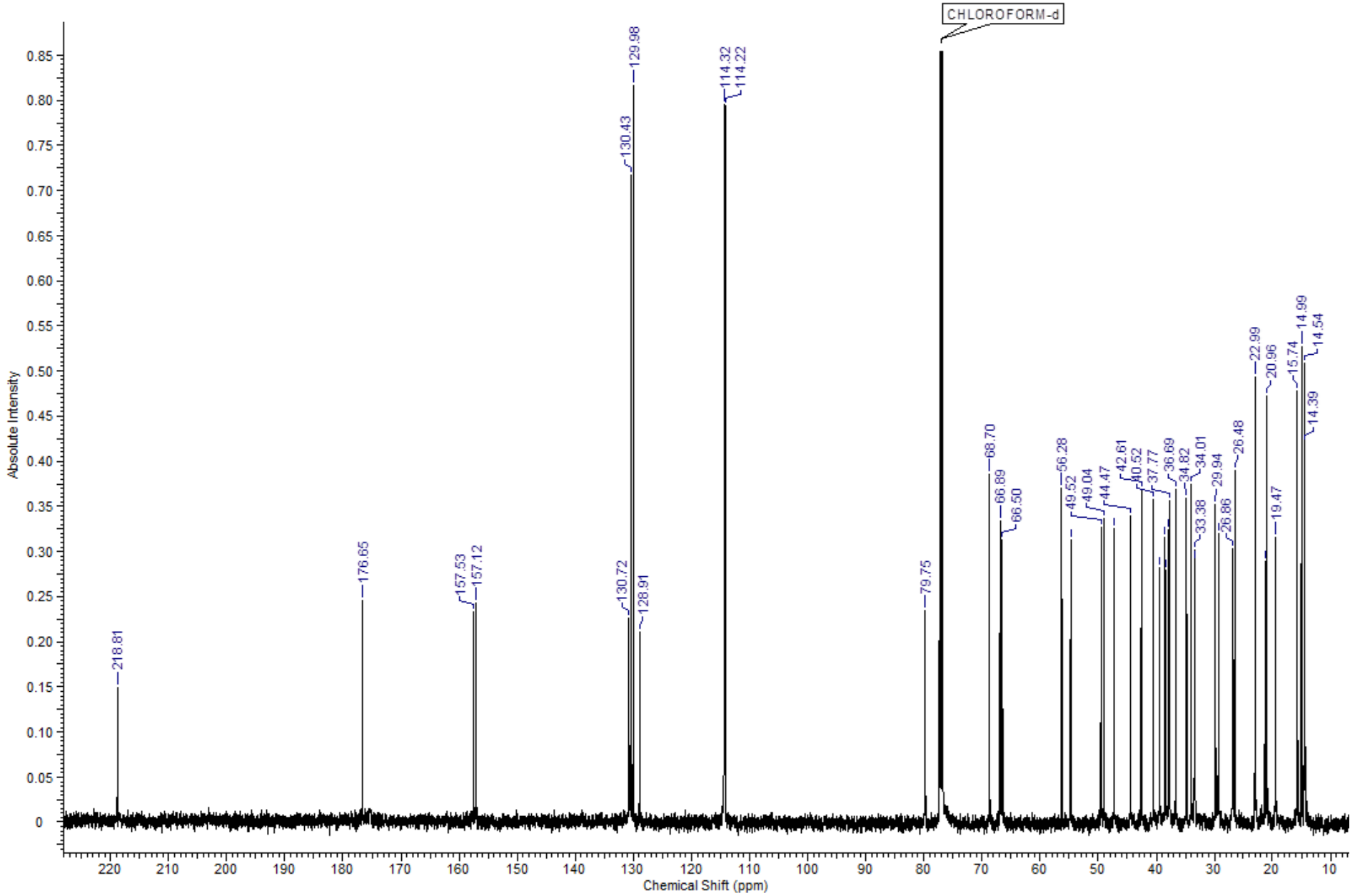


Figure S25. *(S)*-2-ethoxy-3-(4-(4-(4-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)butoxy)phenethoxy)phenyl)propanoic acid, **15c** ^{1}H NMR spectrum.

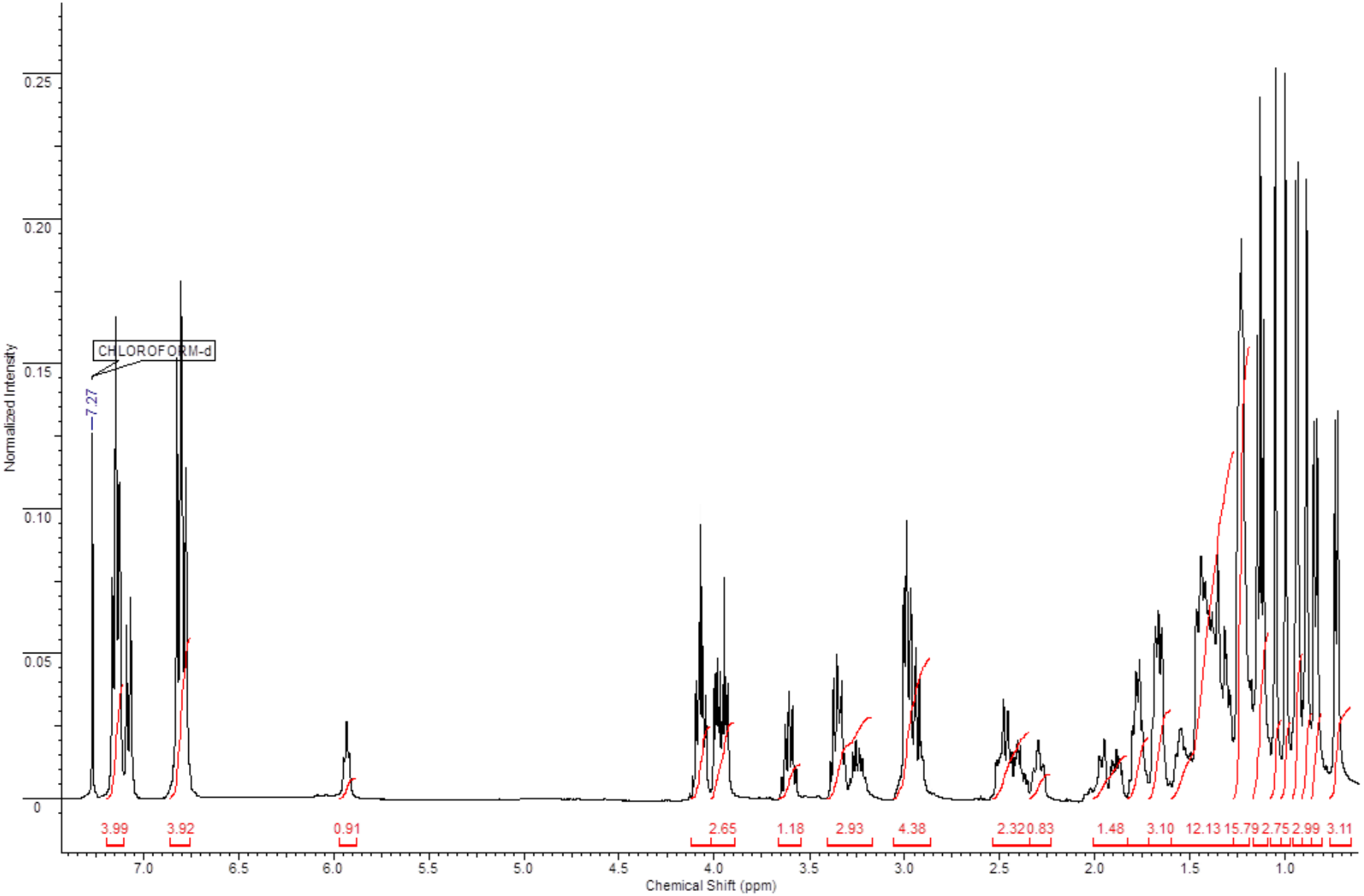


Figure S26. *(S)*-2-ethoxy-3-(4-(4-(4-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)butoxy)phenethoxy)phenyl)propanoic acid, **15c** ^{13}C NMR spectrum.

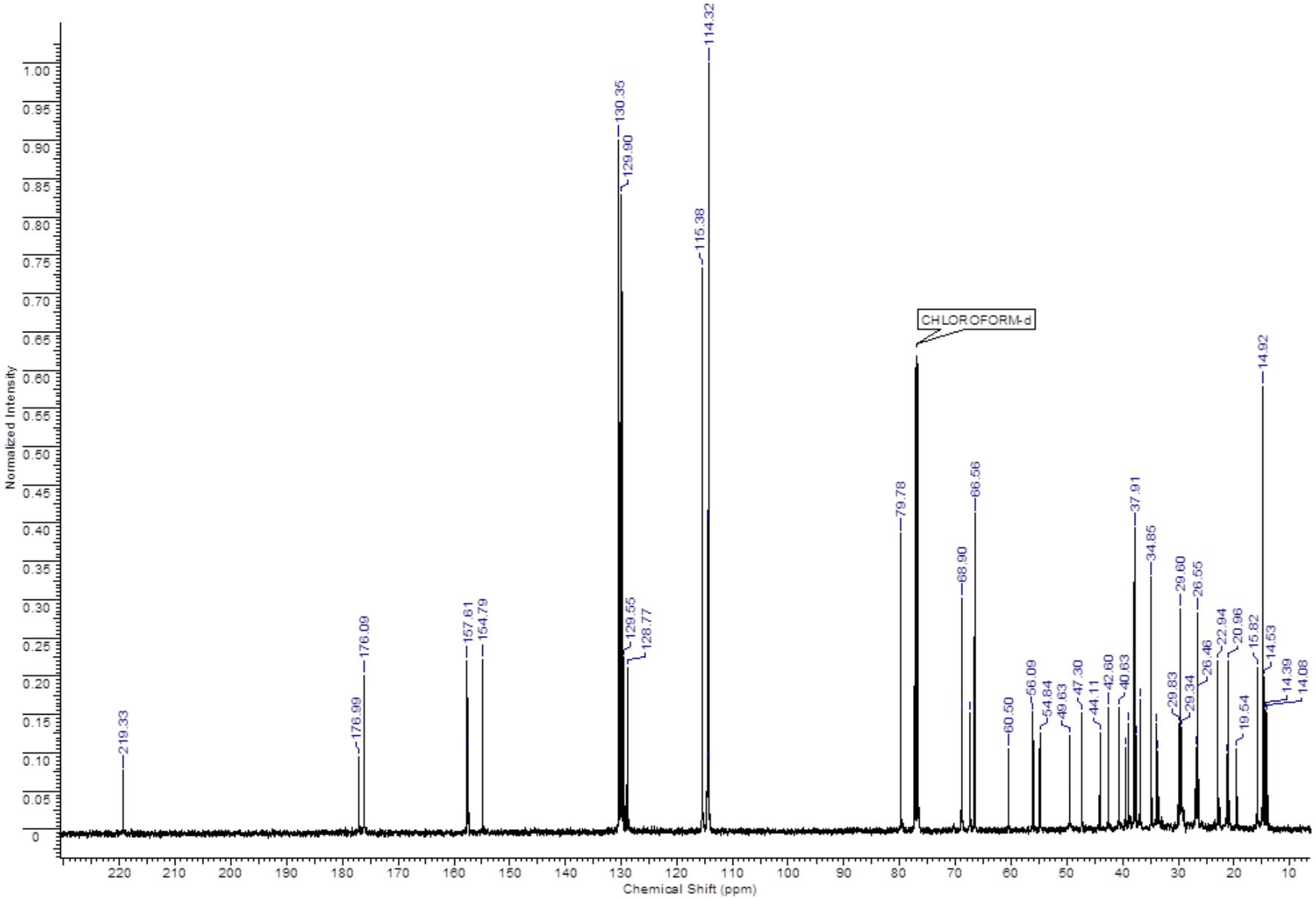


Figure S27. *(S)*-2-ethoxy-3-(4-(4-(5-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)pentoxy)phenethoxy)phenyl)propanoic acid, **15d** ^{1}H NMR spectrum.

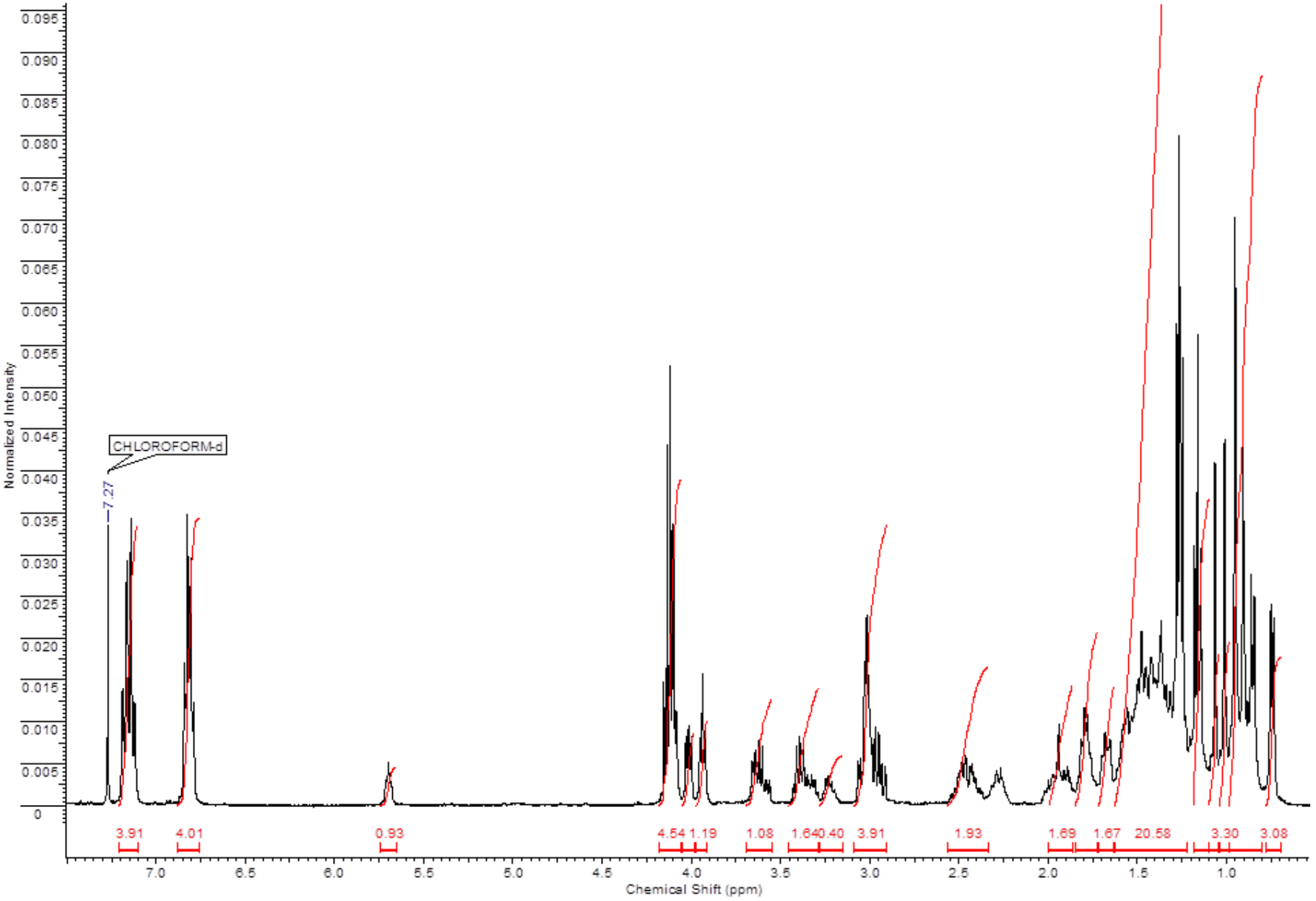


Figure S28. *(S)*-2-ethoxy-3-(4-(4-(5-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)pentoxy)phenethoxy)phenyl)propanoic acid, **15d** ^{13}C NMR spectrum.

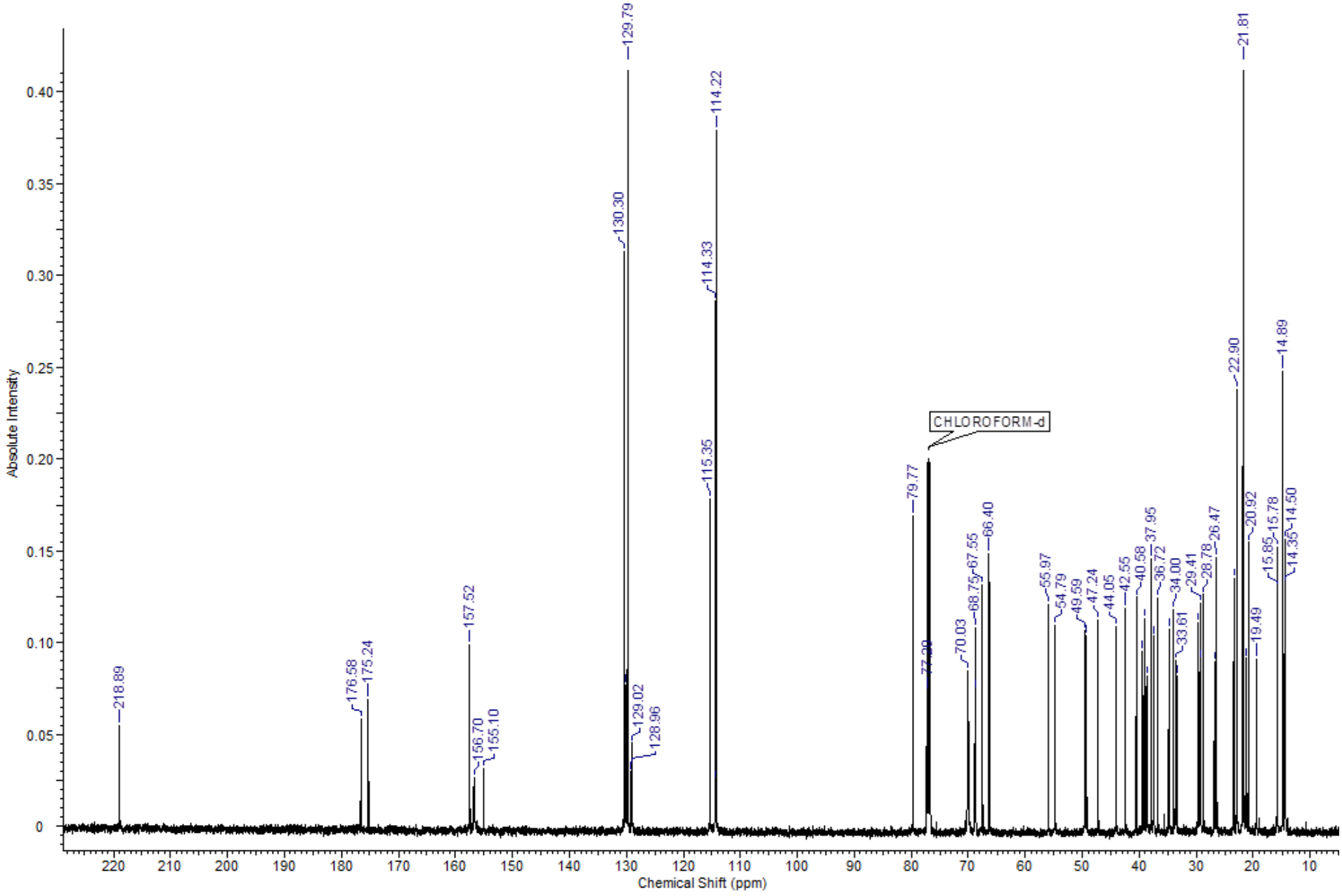


Figure S29. *(S)*-2-ethoxy-3-(4-(4-(6-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)hexoxy)phenethoxy)phenyl)propanoic acid, **15e** ^{1}H NMR spectrum.

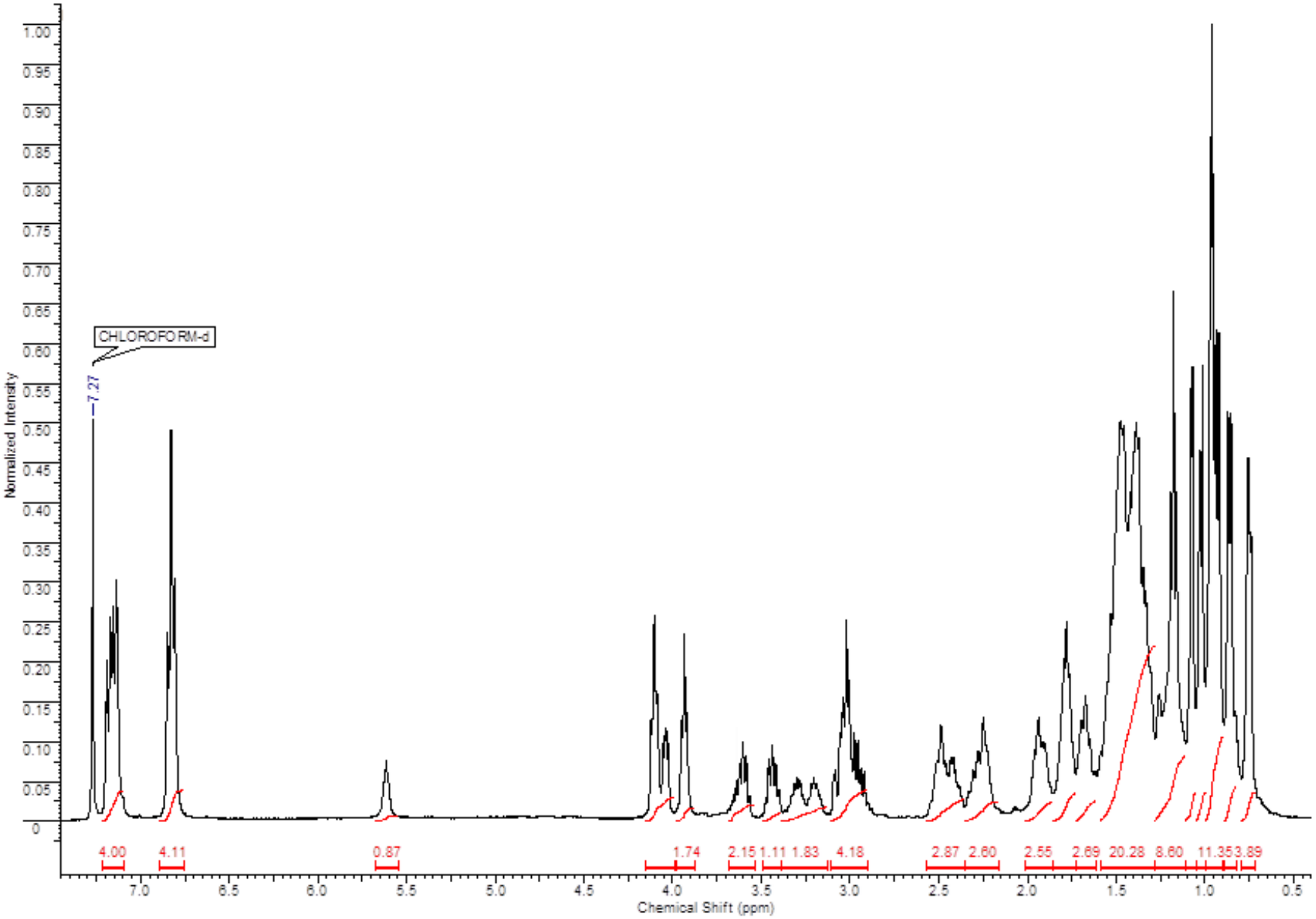


Figure S30. *(S)*-2-ethoxy-3-(4-(4-(6-((1S,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-9-oxoicosahydro-1H-cyclopenta[a]chrysene-3a-carboxamido)hexoxy)phenethoxy)phenyl)propanoic acid, **15e** ^{13}C NMR spectrum.

