Design, Synthesis, and Biological Activity of Second-Generation Synthetic Oleanane Triterpenoids

Liangfeng Fu,[†] Qi-xian Lin,[†] Evans O. Onyango,[†] Karen T. Liby,*[‡] Michael B. Sporn,*[‡] and Gordon W. Gribble*,[†]

[†]Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States

[‡]Department of Pharmacology and Toxicology, Geisel School of Medicine, Hanover, New Hampshire 03755, United States

SUPPORTING INFORMATION

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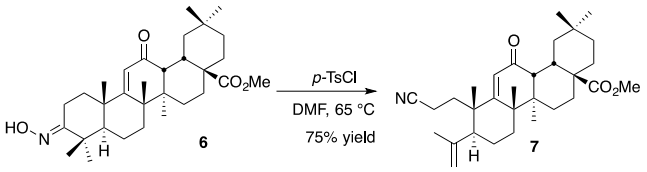
Experimental Section

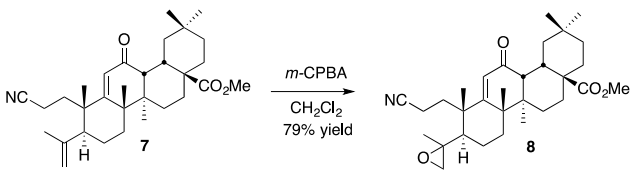
General Experimental Methods

All reactions were performed in the appropriate oven–dried glass apparatus under a balloon of nitrogen gas (N_2). Solvents were reagent grade and in most cases rigorously dried before use. Methylene chloride, DMF, toluene, and THF were dried and stored over molecular sieves. All reagents were obtained commercially as reagent grade and, unless otherwise noted, used without further purification. Reactions were monitored by TLC silica gel plates (0.25 mm) and visualized by UV light or p–anisaldehyde. Column chromatography was performed using silica gel (60, particle size 40–60 mm). Additionally, flash column chromatography was performed on Biotage® Automated Liquid Chromatography System Isolera One® using Biotage® SNAP Ultra 25 um HP-Sphere 10 g silica gel cartridges. The organic extracts were dried over anhydrous Na_2SO_4 or $MgSO_4$. Proton (^1H), carbon (^{13}C), and fluorine (^{19}F) nuclear magnetic resonance spectra were recorded at 500 or 600, 150, or 565 MHz, respectively. Chemical shifts are reported in parts per million (ppm, δ) with the residual deuterated solvent as an internal standard (7.26 ppm for chloroform). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High–resolution mass spectra (HRMS) were obtained employing electron ionization (EI) or electrospray (ES), with TOF as the mass analyzer.

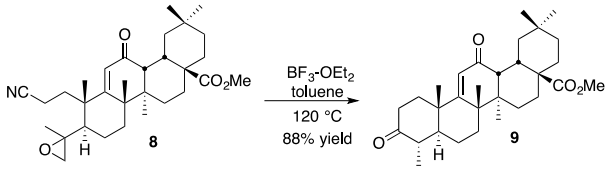
Procedures:



Methyl (1*S*,2*S*,4a*S*,4b*R*,6a*S*,10a*S*,10b*R*)-1-(2-cyanoethyl)-1,4a,4b,9,9-pentamethyl-11-oxo-2-(prop-1-en-2-yl)-1,3,4,4a,4b,5,6,7,8,9,10,10a,10b,11-tetradecahydrochrysene-6a(2*H*)-carboxylate (7). To a stirred solution of oxime **6** (497 mg, 1.0 mmol, 1.0 equiv) in anhydrous dimethyl formamide (5 mL) was added tosyl chloride (380 mg, 2.0 mmol, 2.0 equiv), and the resulting mixture was heated to 65 °C for 24 hours. After completion of the reaction, it was quenched with water, the two layers separated, and the aqueous layer was then extracted with methylene chloride. The combined organic extracts were washed with water, rinsed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (10:1 to 4:1 hexanes/ethyl acetate) afforded **7** as a white solid (360 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (s, 1H), 4.99 (s, 1H), 4.75 (s, 1H), 3.67 (s, 3H), 3.03 (m, 1H), 2.91 (d, 1H, *J* = 4.6 Hz), 2.27 (m, 2H), 1.76-2.12 (m, 5H), 1.78 (s, 3H), 1.46-1.74 (m, 7H), 1.14-1.39 (m, 5H), 1.24 (s, 3H), 1.16 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.5, 178.4, 172.8, 145.6, 125.8, 119.7, 115.9, 52.1, 50.0, 47.4, 47.0, 45.5, 43.5, 42.6, 36.2, 34.7, 34.4, 33.5, 33.0, 31.7, 30.9, 30.5, 28.8, 28.3, 23.9, 23.4, 23.3, 22.9, 22.8, 22.0, 12.2. HRMS (ES) calcd for $C_{34}H_{46}NO_3$ 480.3478, $[M+1]^+$ found 480.3466.

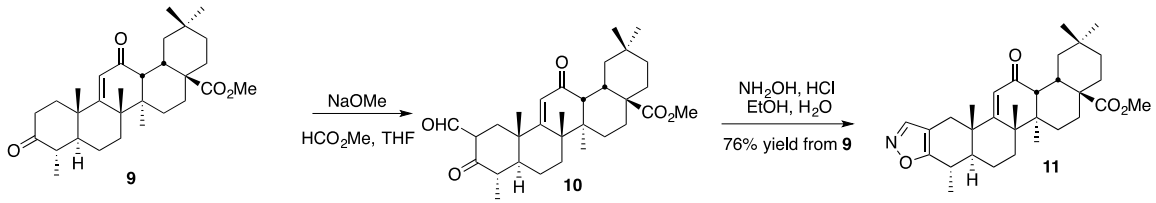


Methyl (1*S*,2*R*,4a*S*,4b*R*,6a*S*,10a*S*,10b*R*)-1-(2-cyanoethyl)-1,4a,4b,9,9-pentamethyl-2-(2-methyloxiran-2-yl)-11-oxo-1,3,4,4a,4b,5,6,7,8,9,10,10a,10b,11-tetradecahydrochrysene-6a(2*H*)-carboxylate (8). To a stirred solution of nitrile **7** (370 mg, 0.77 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added *m*-CPBA (224 mg, 1.00 mmol, 1.3 equiv), and the resulting mixture was stirred at room temperature until the disappearance of starting materials. After the completion of reaction, it was quenched with 20% aqueous sodium thiosulfate (20 mL) and 10% aqueous potassium carbonate (20 mL), and then stirred at room temperature for 1 hour. The two layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (3:1 to 2:1 hexanes/ethyl acetate) afforded **8** as a white solid (300 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (s, 1H), 3.67 (s, 3H), 3.02 (d, 1H, J = 13.2 Hz), 2.91 (d, 1H, J = 3.7 Hz), 2.74 (m, 2H), 1.97-2.50 (m, 5H), 1.09-1.96 (m, 14H), 1.33 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 178.2, 172.5, 125.6, 119.5, 115.7, 51.9, 49.8, 47.2, 46.8, 45.2, 43.3, 42.4, 36.0, 34.5, 34.2, 33.3, 32.8, 31.5, 30.7, 30.3, 28.6, 28.1, 23.7, 23.2, 23.1, 22.7, 21.9, 21.6, 20.3, 12.0. HRMS (ES) calcd for $C_{31}H_{46}NO_4$ 496.3427, $[M+1]^+$ found 496.3418.



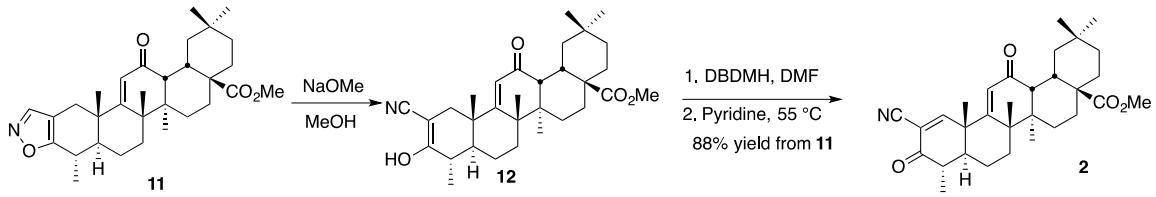
Methyl (4a*S*,6a*R*,6b*S*,8a*S*,9*S*,12a*S*,14a*R*,14b*S*)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-octadecahydropicene-4a(2*H*)-carboxylate (9). To a stirred solution of epoxynitrile **8** (1 g, 2.02 mmol, 1.0 equiv) in

toluene (10 mL) was slowly added $BF_3.OEt_2$ (2 mL, 16.16 mmol, 8.0 equiv). The reaction was stirred under nitrogen at 120 °C overnight. The reaction was allowed to cool to room temperature and then diluted with Et_2O. The two layers were separated and the ether layer was washed with 3N HCl, 5% $NaHCO_3$, washed with water, rinsed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes/ethyl acetate) afforded **9** as a white solid (832 mg, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.63 (s, 3H), 2.97 (dd, 1H, J_1 = 10.4 Hz, J_2 = 3.3 Hz), 2.84 (d, 1H, J = 4.4 Hz), 2.48 (m, 1H), 2.26-2.40 (m, 2H), 2.20 (m, 1H), 1.40-1.90 (m, 10H), 1.10-1.40 (m, 6H), 1.32 (s, 3H), 1.24 (s, 3H), 1.00 (d, 3H, J = 6.3 Hz), 0.93 (s, 3H), 0.83 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.9, 200.2, 178.4, 175.0,124.6, 52.0, 49.7, 49.6, 47.4, 45.2, 44.7, 42.1, 39.4, 37.8, 37.7, 36.0, 34.6, 33.5, 33.0, 31.7, 31.7, 30.8, 28.2, 24.2, 23.3, 22.9, 21.9, 21.6, 21.4, 11.9. HRMS (ES) calcd for $C_{30}H_{45}O_4$ 469.3318, $[M+1]^+$ found 469.3296.



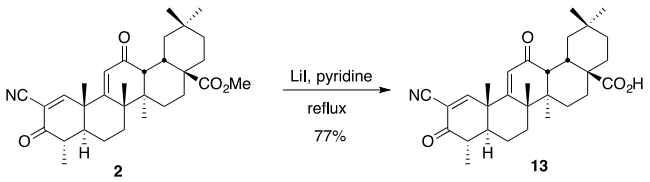
Methyl (4a*S*,6a*R*,6b*S*,8a*S*,9*S*,13a*S*,15a*R*,15b*S*)-2,2,6a,6b,9,13a-hexamethyl-15-oxo-1,3,4,5,6,6a,6b,7,8,8a,9,13,13a,15,15a,15b-hexadecahydropiceno[2,3-*d*]isoxazole-4a(2*H*)-carboxylate (11). To a stirred solution of sodium methoxide (0.70 g, 13.0 mmol, 20.0 equiv) in anhydrous THF (20 mL) was added a solution of ketone **9** (312 mg, 0.67 mmol, 1.0 equiv) in anhydrous THF (5 mL), and the resulting mixture was stirred at 0 °C for 10 min. Methyl formate (0.80 mL, 13.0 mmol, 20.0 equiv) was then added, and the mixture was allowed to stir at room temperature for 3 hours. The reaction was then

quenched with water (100 mL), the two layers were separated and the aqueous layer was then extracted with methylene chloride. The combined organic extracts were washed with 1 N aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvent was removed to give crude product **10**, which was used for the next step without further purifications. To a stirred solution of **10** obtained above in ethanol (20 mL) and water (2 mL) was added hydroxylamine hydrochloride (70 mg, 1.0 mmol, 1.3 equiv), and the resulting mixture was heated to 55 °C for 3.5 hours. After the completion of reaction, it was cooled to room temperature, diluted with water (80 mL), and then extracted with methylene chloride. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), rinsed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (2:1 hexanes/ethyl acetate) afforded **11** as a white solid (250 mg, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (s, 1H), 5.95 (s, 1H), 3.72 (s, 3H), 3.02 (m, 1H), 3.00 (d, 1H, J = 4.6 Hz), 2.72 (d, 1H, J = 15.2 Hz), 2.65 (m, 1H), 2.40 (d, 1H, J = 15.2 Hz), 1.93-1.98 (m, 3H), 1.40-1.74 (m, 8H), 1.35 (d, 3H, J = 6.8 Hz), 1.14-1.32 (m, 4H), 1.25 (s, 3H), 1.03 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.1, 178.4, 175.2, 168.9, 150.4, 125.0, 110.1, 52.1, 49.8, 47.5, 47.3, 45.6, 42.1, 40.3, 36.1, 34.7, 33.5, 33.4, 33.0, 31.7, 31.4, 30.9, 30.7, 28.4, 23.4, 23.3, 22.9, 22.5, 21.8, 20.9, 15.7. HRMS (ES) calcd for $C_{31}H_{44}NO_4$ 494.3270, $[M+1]^+$ found 494.3273.

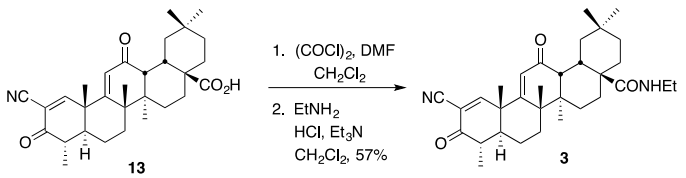


Methyl (4a*S*,6a*R*,6b*S*,8a*S*,9*S*,12a*R*,14a*R*,14b*S*)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2*H*)-carboxylate (2). To a stirred solution of isooxazole **11** (183 mg, 0.37 mmol, 1.0 equiv) in methanol (10 mL) was added a solution of NaOMe (0.37 mL, 1.0 M in methanol, 0.37 mmol, 1.0 equiv), and the resulting mixture was heated to 55 ^{o}C for 3.5 hours. After completion of reaction, it was cooled to room temperature, quenched with water (100 mL), and extracted with methylene chloride. The combined organic extracts were washed with 1 N aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvent was removed to give crude product **12**, which was used for the next step without further purifications. To a stirred solution of nitrile **12**, in anhydrous DMF (5 mL) was added a solution of DBDMH (106 mg, 0.37 mmol, 1.0 equiv) in DMF (5 mL), and the resulting mixture was stirred at 0 ^{o}C for 1 hour. Pyridine (0.13 mL, 1.5 mmol, 4.0 equiv) was added, and the reaction mixture was heated to 55 ^{o}C for 3.5 hours. The reaction was cooled to room temperature, quenched with water (50 mL), and extracted with ethyl acetate. The combined organic extracts were washed with water, 20% aqueous sodium thiosulfate, rinsed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (2:1 hexanes/ethyl acetate) afforded **2** as an off yellow solid (161 mg, 88%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.01 (s, 1H), 3.69 (s, 3H), 3.04 (m, 1H), 2.95 (d, 1H, J = 4.6 Hz), 2.47 (m, 1H), 1.80-1.94 (m, 3H), 1.62-1.79 (m, 5H), 1.44-1.60 (m, 2H), 1.44 (s, 3H), 1.32 (s, 3H), 1.16-1.30 (m, 4H), 1.24 (d, 3H, J = 6.6 Hz), 1.01 (s, 3H), 0.99 (s, 3H), 0.80-0.90 (m, 1H), 0.89 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.7, 193.2, 178.2, 166.9, 165.5, 124.7, 115.3, 114.1, 51.9, 49.8, 47.2, 45.9,

45.4, 42.2, 41.9, 35.8, 34.4, 33.3, 32.7, 31.5, 30.8, 28.2, 24.8, 23.6, 23.1, 22.6, 21.6, 20.3, 12.1. HRMS (ES) calcd for $C_{31}H_{42}NO_4$ 492.3114, $[M+1]^+$ found 492.3128.

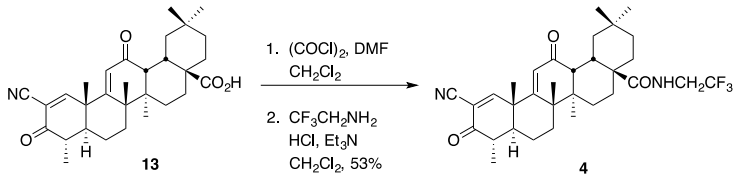


(4a*S*,6a*R*,6b*S*,8a*S*,9*S*,12a*R*,14a*R*,14b*S*)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2*H*)-carboxylic acid (13). To a stirred solution of cyano enone **2** (2.21 g, 4.5 mmol, 1.0 equiv) in pyridine (20 mL) was added lithium iodide (6.0 g, 45 mmol, 10.0 equiv), and the resulting mixture was heated to reflux for 24 hours. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was quenched with 1 N aqueous HCl (100 mL) and extracted with ethyl acetate. The combined organic extracts were washed with water, followed by saturated aqueous $NaHCO_3$ (20 mL), rinsed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes/ethyl acetate) afforded **2** as an off yellow solid (1.7g, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.05 (s, 1H), 3.03 (m, 2H), 2.48 (m, 1H), 1.84-1.98 (m, 3H), 1.10-1.82 (m, 11H), 1.44 (s, 3H), 1.34 (s, 3H), 1.24 (d, 3H, J = 6.6 Hz), 1.02 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H), 0.80-0.90 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.9, 193.5, 183.9, 167.4, 165.8, 125.0, 115.5, 114.3, 50.0, 47.2, 46.0, 45.7, 42.7, 42.4, 42.1, 35.9, 34.6, 33.4, 33.1, 31.6, 31.0, 30.8, 28.1, 25.0, 23.8, 23.2, 22.7, 21.8, 20.5, 12.3. HRMS (ES) calcd for $C_{30}H_{40}NO_4$ 478.2957, $[M+1]^+$ found 478.2972.



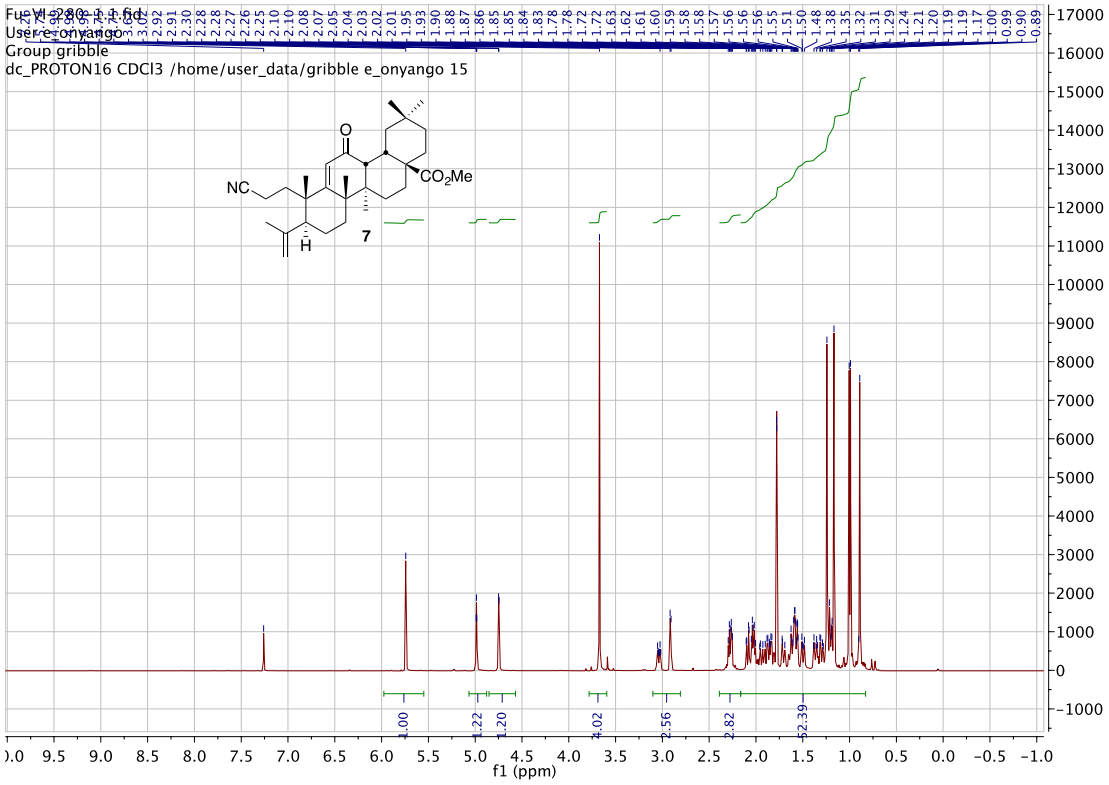
(4a*S*,6a*R*,6b*S*,8a*S*,9*S*,12a*R*,14a*R*,14b*S*)-11-cyano-*N*-ethyl-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2*H*)-carboxamide (3). To a stirred solution of acid **13** (880 mg, 1.84 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added oxalyl chloride (0.50 mL, 5.79 mmol, 3.0 equiv) and anhydrous dimethyl formamide (0.15 μL, 2.8 μmol, catalytic) slowly at 0 °C. The reaction was allowed to warm to room temperature for 2 h. The solvent was removed under reduced pressure, and toluene (10 mL) was added and removed by vacuum. This process was repeated three times to provide the corresponding acyl chloride. To a stirred solution of the resulting acyl chloride obtained above in methylene chloride (15 mL) was added Et_3N (1.16 mL, 8.10 mmol, 4.4 equiv) followed by slow addition of ethylamine hydrochloride (680 mg, 8.1 mmol, 4.4 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature overnight. The solvent was removed and reduced pressure and the residue was then diluted with methylene chloride (80 mL), washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (2:1 to 1:1 hexanes/ethyl acetate) afforded the amide **3** as a yellow solid (530 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 6.08 (s, 1H), 6.00 (brs, 1H), 3.30 (m, 2H), 3.08 (d, 1H, J = 3.9 Hz), 2.87 (d, 1H, J = 13.0 Hz), 2.47 (m, 1H), 1.06-2.04 (m, 14H), 1.44 (s, 3H), 1.33 (s, 3H), 1.22 (d, 3H, J = 6.8 Hz), 1.11 (t, 3H, J = 7.1 Hz), 1.00 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H), 0.80-0.90 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.3, 193.5, 177.1, 167.6, 166.1, 124.9, 115.3, 114.5, 49.8, 46.5, 46.0,

45.8, 42.8, 42.4, 42.1, 36.3, 34.8, 34.7, 34.2, 33.5, 32.1, 31.0, 29.6, 27.9, 25.2, 23.7, 23.3, 23.1, 22.0, 20.5, 15.4, 12.3. HRMS (ES) calcd for $C_{32}H_{45}N_2O_3$ 505.3430, $[M+1]^+$ found 505.3439.



(4a*S*,6a*R*,6b*S*,8a*S*,9*S*,12a*R*,14a*R*,14b*S*)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-*N*-(2,2,2-trifluoroethyl)-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2*H*)-carboxamide (4). To a stirred solution of acid **13** (680 mg, 1.42 mmol, 1.0 equiv) in methylene chloride (15 mL) was added oxalyl chloride (0.35 mL, 4.05 mmol, 3.0 equiv) and anhydrous dimethyl formamide (0.11 μL, 2.0 μmol, catalytic) slowly at 0 °C. The reaction was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure, and then toluene (10 mL) was added and also removed under reduced pressure. This process was repeated three times to provide the corresponding acyl chloride. To a stirred solution of the resulting acyl chloride obtained above in methylene chloride (10 mL) was added triethylamine (0.58 mL, 4.05 mmol, 3.0 equiv) followed by slow addition of trifluoroethylamine hydrochloride (600 mg, 4.05 mmol, 3.0 equiv) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred overnight. After the completion of the reaction, the solvent was removed reduce pressure and the residue was diluted with methylene chloride (80 mL), washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), rinsed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (2:1 to 1:1 hexanes/ethyl acetate) afforded the amide **4** as a yellow solid (421 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ

8.15 (s, 1H), 6.38 (brs, 1H), 6.14 (s, 1H), 3.98 (m, 2H), 3.07 (d, 1H, *J* = 4.4 Hz), 2.96 (d, 1H, *J* = 12.9 Hz), 2.48 (m, 1H), 2.03 (m, 1H), 1.06-1.92 (m, 13H), 1.46 (s, 3H), 1.32 (s, 3H), 1.25 (d, 3H, *J* = 6.6 Hz), 1.03 (s, 3H), 0.98 (s, 3H), 0.90 (s, 3H), 0.82-0.90 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.2, 193.5, 177.7, 168.0, 166.2, 124.9 124.5 (q), 115.4, 114.5, 49.8, 47.1, 46.1, 45.8, 42.8, 42.4, 42.1, 36.2, 34.7, 34.0, 33.4, 32.1, 31.1, 29.7, 27.8, 25.0, 23.8, 23.3, 23.2, 22.0, 20.5, 12. HRMS (ES) calcd for $C_{32}H_{42}N_2O_3F_3$ 559.3148, $[M+1]^+$ found 559.3140.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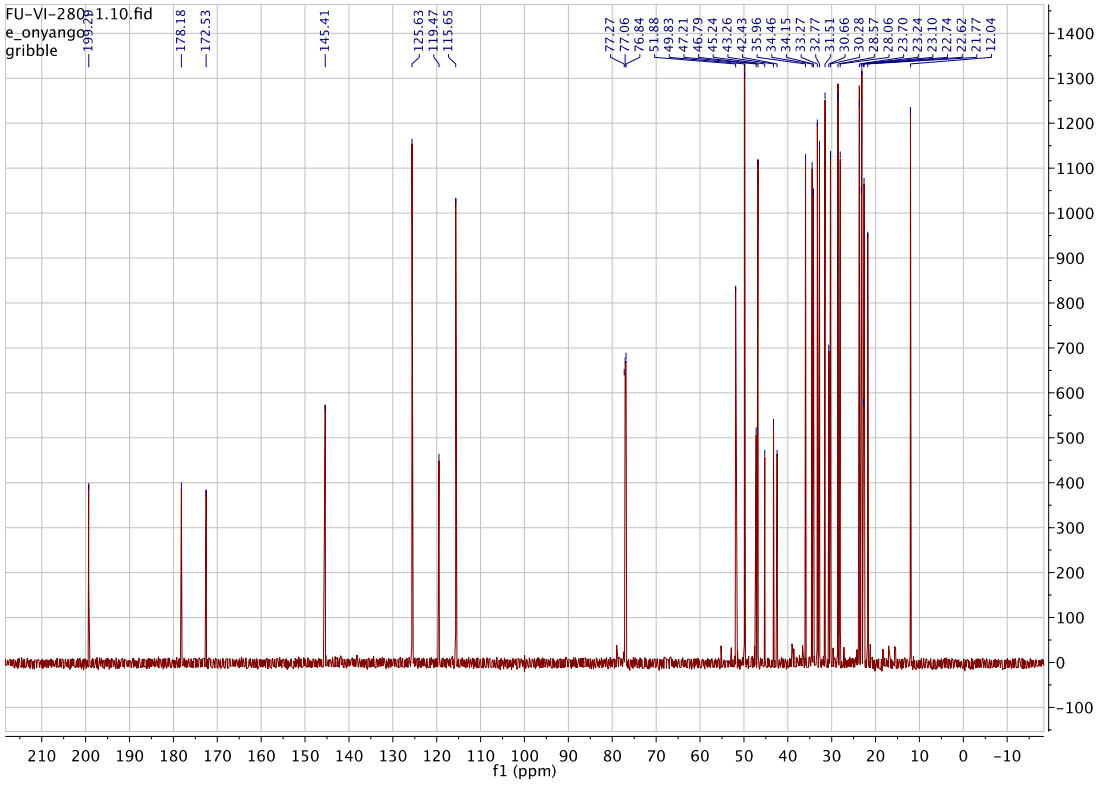
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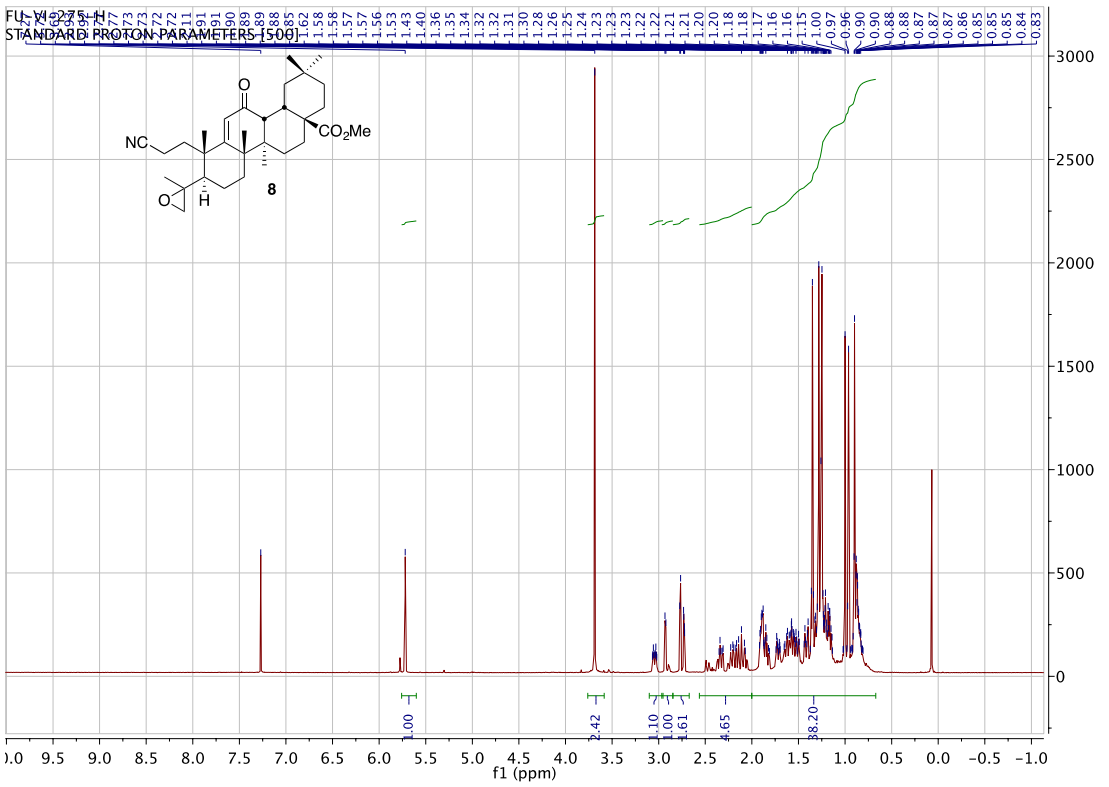
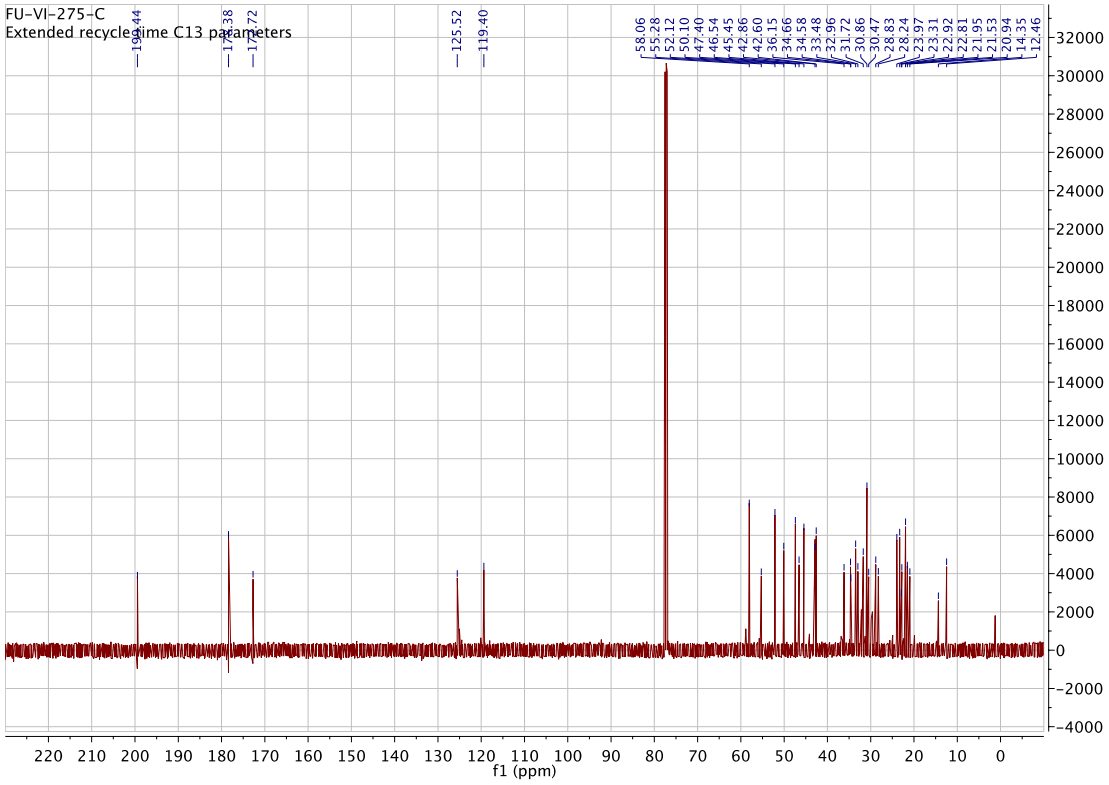
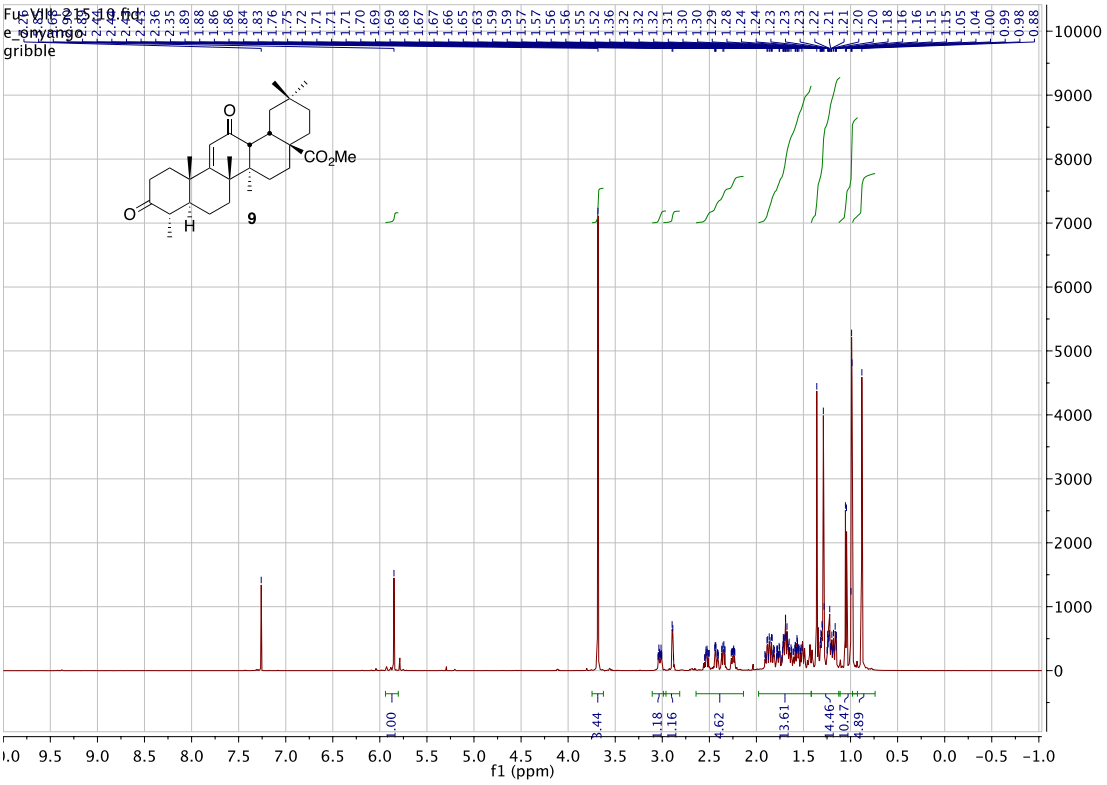
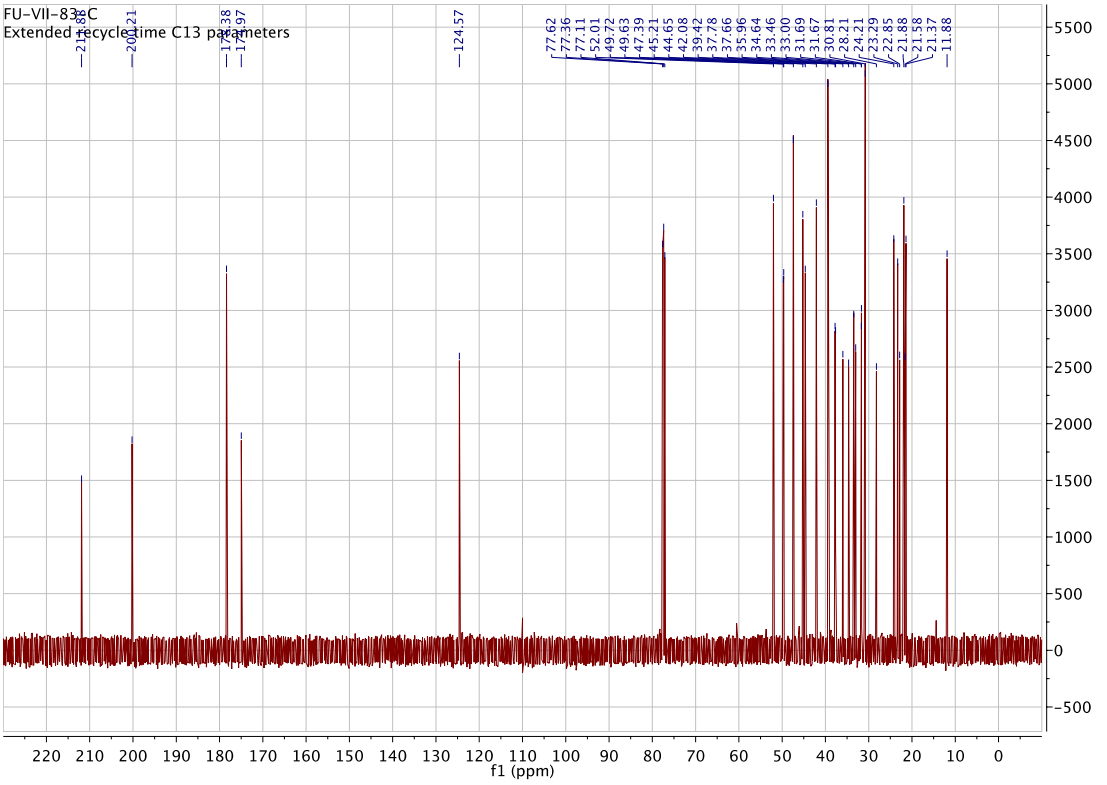
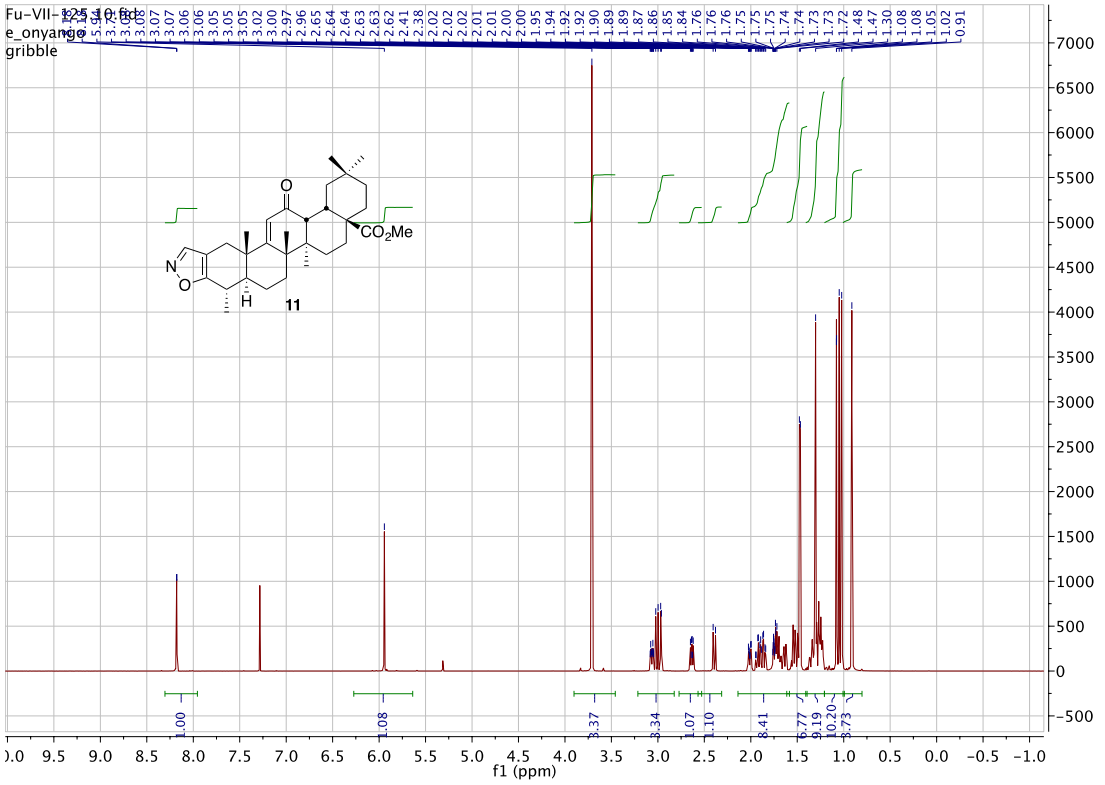
23.24
23.10
22.74
22.62
21.77
12.04
f1 (ppm)

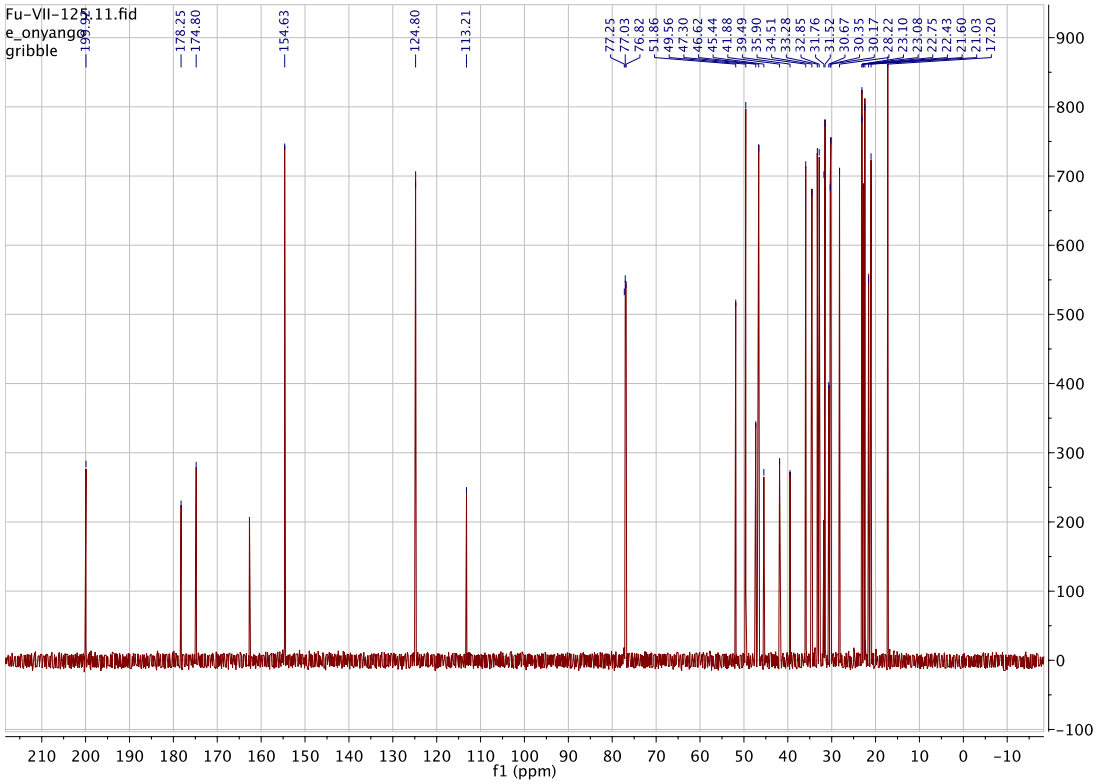

FU-VI-275-H
STANDARD PROTON PARAMETERS [500]
O
NC
CO2Me
O
H
8
1.00
2.42
1.10
1.00
1.61
4.65
38.20
f1 (ppm)

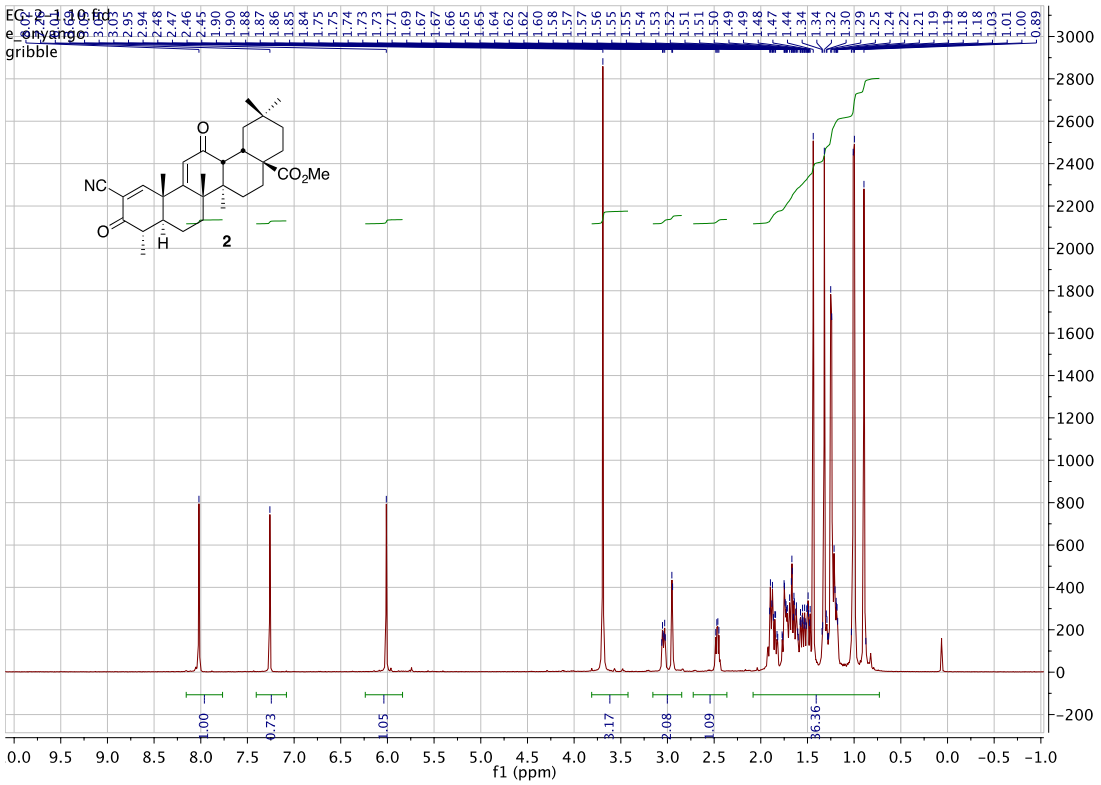

FU-VI-275-C
Extended recycle time C13 parameters
f1 (ppm)

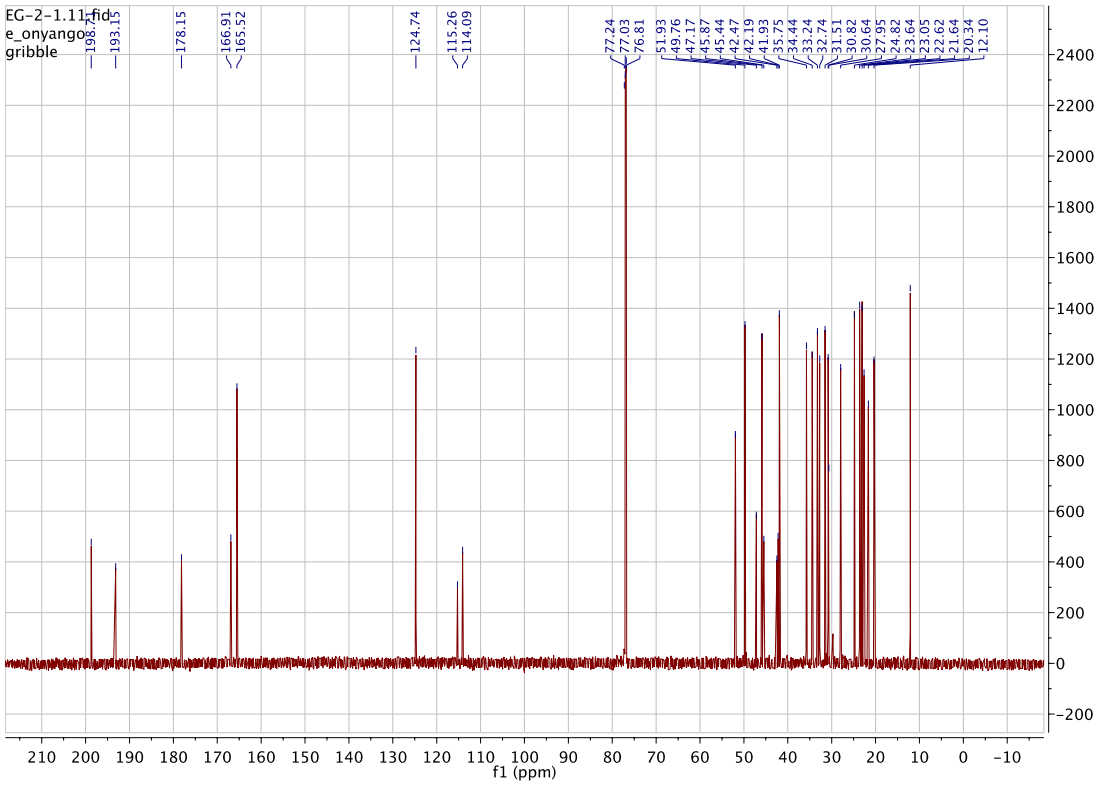

Fu-VII-215-10.fid
e_cmyang
gribble
O
O
H
CO2Me
9
f1 (ppm)

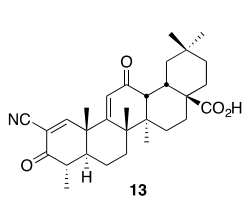

FU-VII-83-C
Extended recycle time C13 parameters
f1 (ppm)


Fu-VII-125.10.fid
e_onyango
gribble
O
CO2Me
N
O
H
11
f1 (ppm)


Fu-VII-125.11.fid
e_onyango
gribble
178.25
174.80
154.63
124.80
113.21
77.25
77.03
76.82
f1 (ppm)


EG-2-1.10.fid
e_onyango
gribble
NC
O
O
H
CO2Me
2
1.00
0.73
1.05
3.17
2.08
1.09
16.36
f1 (ppm)


EG-2-1.11.fid
e_onyango
gribble
198.71
193.15
178.15
166.91
165.52
124.74
115.26
114.09
77.24
77.03
76.81
51.93
49.76
47.17
45.87
45.44
42.47
42.19
41.93
35.75
34.44
33.24
32.74
31.51
30.82
30.64
27.95
24.82
23.64
23.05
22.62
21.64
20.34
12.10
f1 (ppm)



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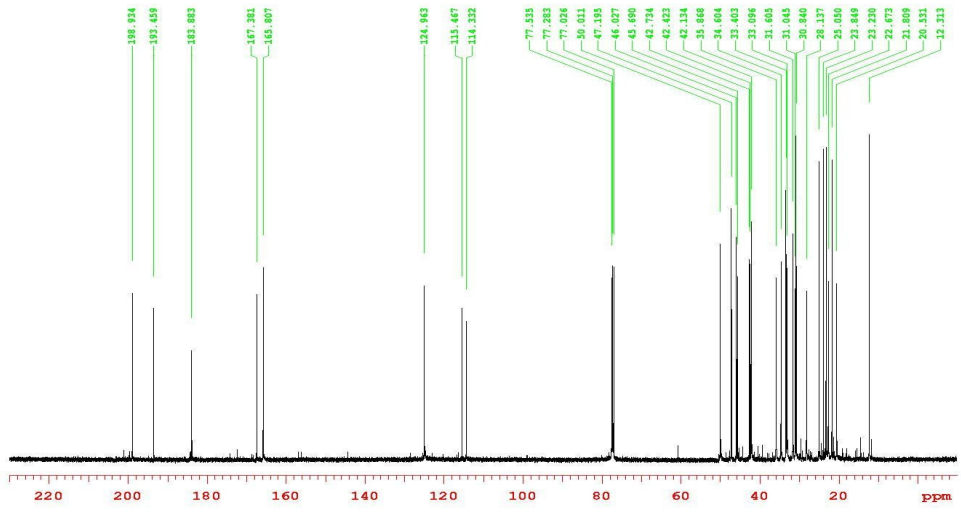
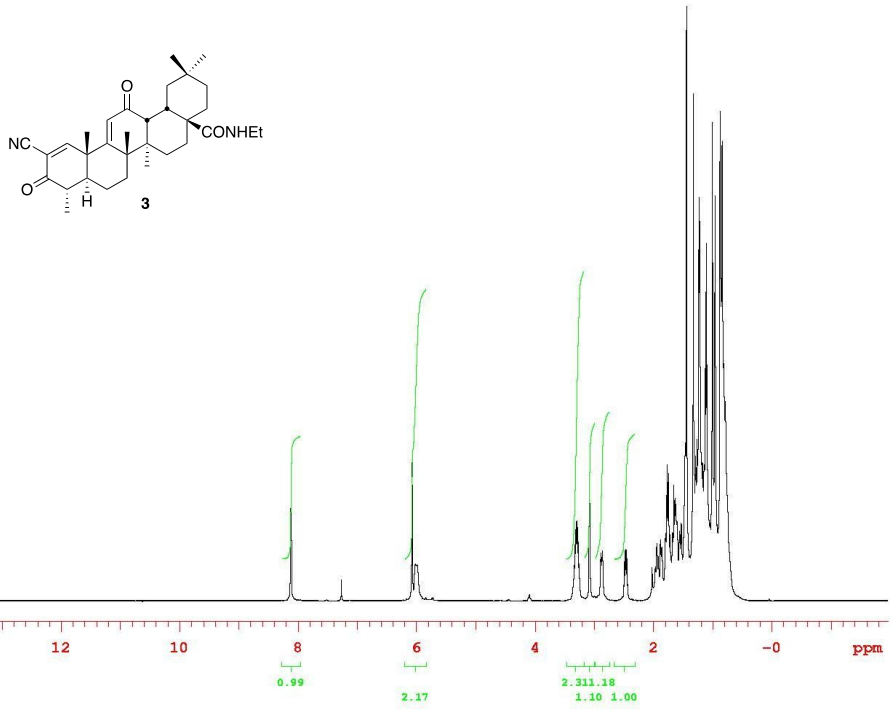
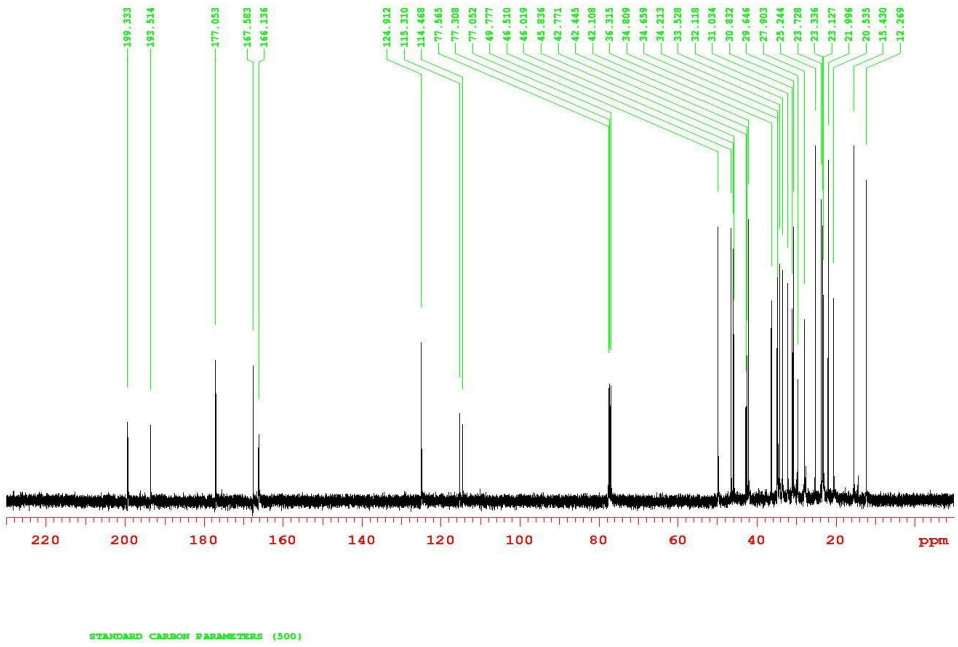
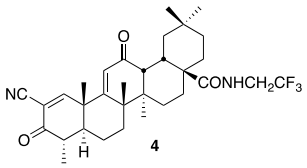
Standard Proton Parameters (500)



STANDARD CARBON PARAMETERS (500)


NC
O
O
H
CONHEt
3
14
12
10
8
6
4
2
−0
ppm
0.99
2.17
2.311.18
1.10 1.00
Standard Proton Parameters (500)


199.333
193.514
177.053
167.583
166.136
124.912
115.310
114.468
77.565
77.308
77.052
49.777
46.510
46.019
45.836
42.771
42.445
42.108
36.315
34.809
34.659
34.213
33.528
32.118
31.034
30.832
29.646
27.903
25.244
23.728
23.336
23.127
21.996
20.535
15.430
12.269
220
200
180
160
140
120
100
80
60
40
20
ppm
STANDARD CARBON PARAMETERS (500)



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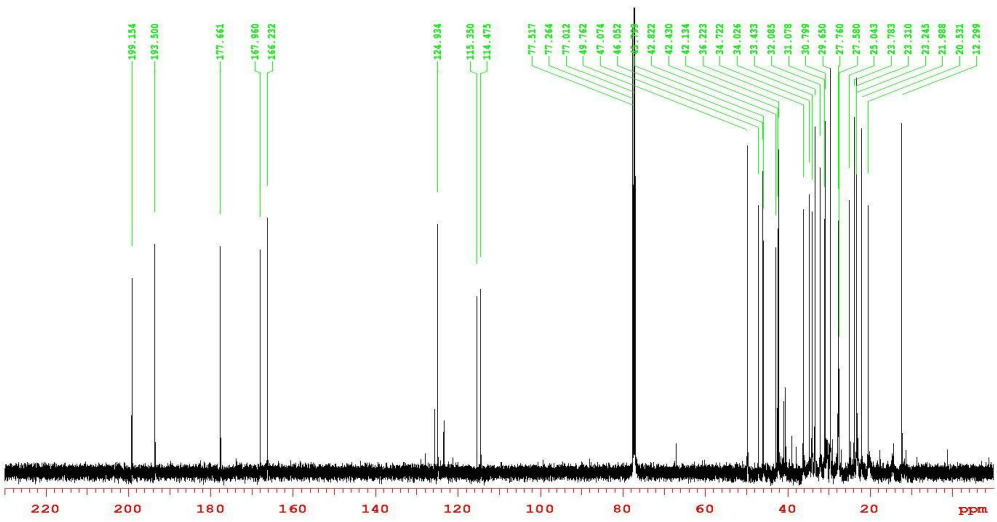
Standard Proton Parameters (500)



STANDARD CARBON PARAMETERS (500)