Supporting Information

Experimental Procedures and Characterization Data

Synthesis of Cardiopetaline via a Wagner–Meerwein Rearrangement without Preactivation of the Pivotal Hydroxy Groups

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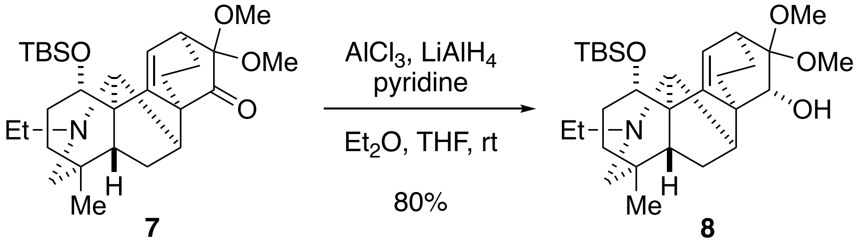
General Remarks

Nuclear magnetic resonance (^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz)) spectra were determined on a JEOL-ECS400 instrument. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfields from tetramethylsilane (δ) as the internal standard and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The reported values of coupling constants are adjusted appropriately from the measured values to account for the resolving power. Chemical shifts for ^{13}C NMR are reported in ppm relative to the center line of a triplet at 77.16 ppm for deuteriochloroform. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrophotometer and are reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-T100LP AccuTOF LC-plus either in positive electrospray ionization (ESI) method, using PEG or sodium trifluoroacetate as the internal standard. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter with a sodium lamp. Analytical thin layer chromatography (TLC) and preparative TLC separations were performed on Merck precoated analytical plates (0.25 mm thick) precoated with silica gel 60 NH_2 unless otherwise noted. Reagents were commercial grades and were used without any purification. Dehydrated tetrahydrofuran and diethyl ether were purchased from Kanto Chemicals Co., Inc., and were purified using a Glass Contour Solvent System. Dehydrated methanol was purchased from Kanto Chemicals Co., Inc. and stored over activated MS3A. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

1α-((*tert*-Butyldimethylsilyl)oxy)-21-ethyl-15α-hydroxy-16,16-dimethoxy-4-methyl-7,20-cyclo-17-noratid-9(11)-ene (8)



To a solution of **7** (42.6 mg, MW = 501.8, 84.9 μmol) and pyridine (41 μL, d = 0.99, MW = 79.10, 0.51 mmol) in tetrahydrofuran (0.85 mL) was added alane solution* (1.0 M in diethyl ether, 0.25 mL, 0.25 mmol) at room temperature. After stirring for 1 h, the reaction mixture was cooled to 0 °C, and then water (3 drops) and aqueous ammonia (3 M, 0.5 mL) were added successively. After stirring for 10 min at room temperature, the reaction mixture was partitioned between diethyl ether and water. The aqueous phase was extracted twice with diethyl ether. The combined organic phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative thin layer chromatography on amino silica gel eluting with 15% ethyl acetate in hexane to give **8** (34.2 mg, MW = 503.8, 67.9 μmol, 80.0%) as a colorless oil. *Alane solution was prepared by addition of aluminum trichloride (0.39 g) to a suspension of lithium aluminum hydride (0.39 g) in diethyl ether (12 mL).

^{1}H NMR: 5.64 (d, *J* = 6.4 Hz, 1H), 4.16 (dd, *J* = 11.0, 6.4 Hz, 1H), 3.48 (dd, *J* = 5.5, 1.8 Hz, 1H), 3.31 (s, 3H), 3.23 (s, 1H), 3.14 (s, 3H), 3.12 (s, 1H), 2.74 (m, 1H), 2.54-2.36 (m, 5H), 2.29 (d, *J* = 5.0 Hz, 1H), 1.81-1.63 (m, 3H), 1.63-1.52 (m, 3H), 1.45 (d, *J* = 7.3 Hz, 1H), 1.26 (m, 1H), 1.05 (m, 1H), 1.01 (t, *J* = 6.9 Hz, 3H), 0.88 (m, 1H), 0.82 (s, 9H), 0.75 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H).

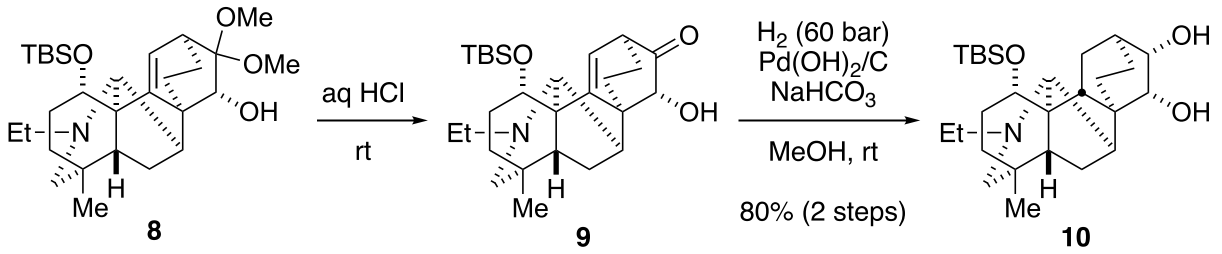
^{13}C NMR: 150.7 (C), 117.2 (CH), 101.4 (C), 71.2 (CH), 69.4 (CH), 66.4 (CH), 57.7 (CH_2), 55.4 (C), 49.9 (CH_2), 49.3 (C), 49.1 (CH_3), 48.4 (CH_3), 47.8 (CH), 39.9 (CH), 38.7 (CH_2), 37.8 (CH), 34.0 (C), 30.1 (CH_2), 26.3 (CH_3), 26.0 (CH_3), 24.0 (CH_2), 23.3 (CH_2), 18.7 (CH_2), 18.2 (C), 13.6 (CH_3), –2.8 (CH_3), –4.4 (CH_3).

IR: 3542, 2953, 2854, 1462, 1360, 1254, 1092, 1061, 880, 837, 772.

HRMS: 504.3509 (Calculated for $C_{29}H_{50}NO_4Si^+$: 504.3504).

$[\alpha]_D^{25} = 18°$ (*c* 0.67, $CHCl_3$).

1α-((*tert*-Butyldimethylsilyl)oxy)-21-ethyl-15α,16α-dihydroxy-4-methyl-7,20-cyclo-17-noratidane (10)



To **8** (24.6 mg, MW = 503.8, 48.8 μmol) was added hydrochloric acid (0.50 M, 0.49 mL) at room temperature. After stirring for 2 min, aqueous sodium bicarbonate was added to the reaction mixture, and the mixture was extracted with dichloromethane. The aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. This material was used for the next step without further purification.

A Parr pressure bomb was charged with the residue, sodium bicarbonate (41 mg, MW = 84.01, 0.49 mmol), 10% palladium(II) hydroxide on carbon (69 mg, MW = 140.4, 0.049 mmol), and methanol (0.33 mL). The bomb was then pressurized with hydrogen gas (60 bar) and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was filtered through a pad of Celite and the filter cake was washed with ethyl acetate. The filtrate was concentrated, and then the residue was purified by preparative thin layer chromatography on amino silica gel eluting with 70% ethyl acetate in hexane to give **10** (18.1 mg, MW = 461.8, 67.9 μmol, 80.3% in two steps) as a colorless oil.

^{1}H NMR: 4.04-3.86 (m, 3H), 3.72 (s, 1H), 2.73 (d, J = 6.4 Hz, 1H), 2.53-2.32 (m, 5H), 2.24 (dd, J = 11.0, 2.3 Hz, 1H), 2.07 (dd, J = 12.4, 12.4 Hz, 1H), 1.97 (d, J = 5.5 Hz, 1H), 1.83 (m, 1H), 1.77-1.61 (m, 3H), 1.61-1.45 (m, 4H), 1.38 (m, 1H), 1.31 (m, 1H), 1.19 (m, 1H), 1.07 (d, J = 7.8 Hz, 1H), 1.02 (t, J = 7.3 Hz, 3H), 0.94 (m, 1H), 0.92 (s, 9H), 0.68 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H).

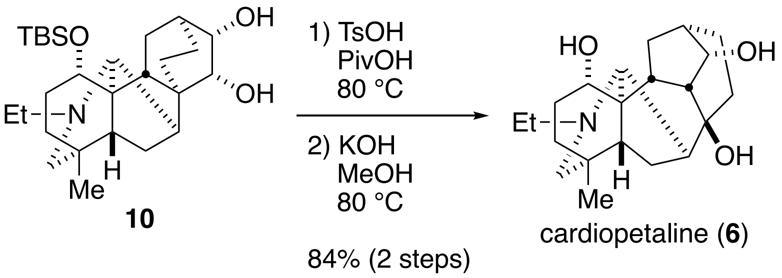
^{13}C NMR: 71.9 (CH), 68.8 (CH), 67.8 (CH), 65.6 (CH), 57.2 (CH_2), 53.1 (CH), 50.6 (C), 50.3 (CH_2), 44.8 (CH), 42.7 (C), 39.4 (CH), 38.8 (CH_2), 34.6 (CH), 33.3 (C), 31.1 (CH_2), 26.3 (CH_3), 26.1 (CH_3), 25.3 (CH_2), 23.5 (CH_2), 20.2 (CH_2), 20.2 (CH_2), 18.4 (C), 13.7 (CH_3), –1.9 (CH_3), –3.9 (CH_3).

IR: 3366, 2930, 1460, 1359, 1254, 1170, 1075, 862, 835, 772.

HRMS: 462.3412 (Calculated for $C_{27}H_{48}NO_3Si^{+}$: 462.3398).

$[\alpha]_D^{25}$ = –58° (c 0.90, $CHCl_3$).

20-Ethyl-4-methylaconitane-1α,8,14α-triol (cardiopetaline, 6)



To a solution of **10** (9.5 mg, MW = 461.8, 21 μmol) in pivalic acid (0.51 mL) was added *p*-toluenesulfonic acid (98 mg, MW = 190.2, 0.52 mmol). After heating at 80 °C for 150 min, aqueous sodium hydroxide (1 M) was added to the reaction mixture, and the mixture was extracted with dichloromethane. The aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. This material was used for the next step without further purification.

The residue was dissolved in potassium hydroxide solution (1.0 M in methanol, 0.51 mL) and the resulting solution was heated at 80 °C for 4 h in a sealed tube. After cooling to room temperature, water was added to the reaction mixture, and the mixture was extracted with dichloromethane. The aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative thin layer chromatography on amino silica gel eluting with ethyl acetate to give **6** (cardiopetaline, 6.0 mg, MW = 347.5, 17 μmol, 84% in two steps) as a white solid.

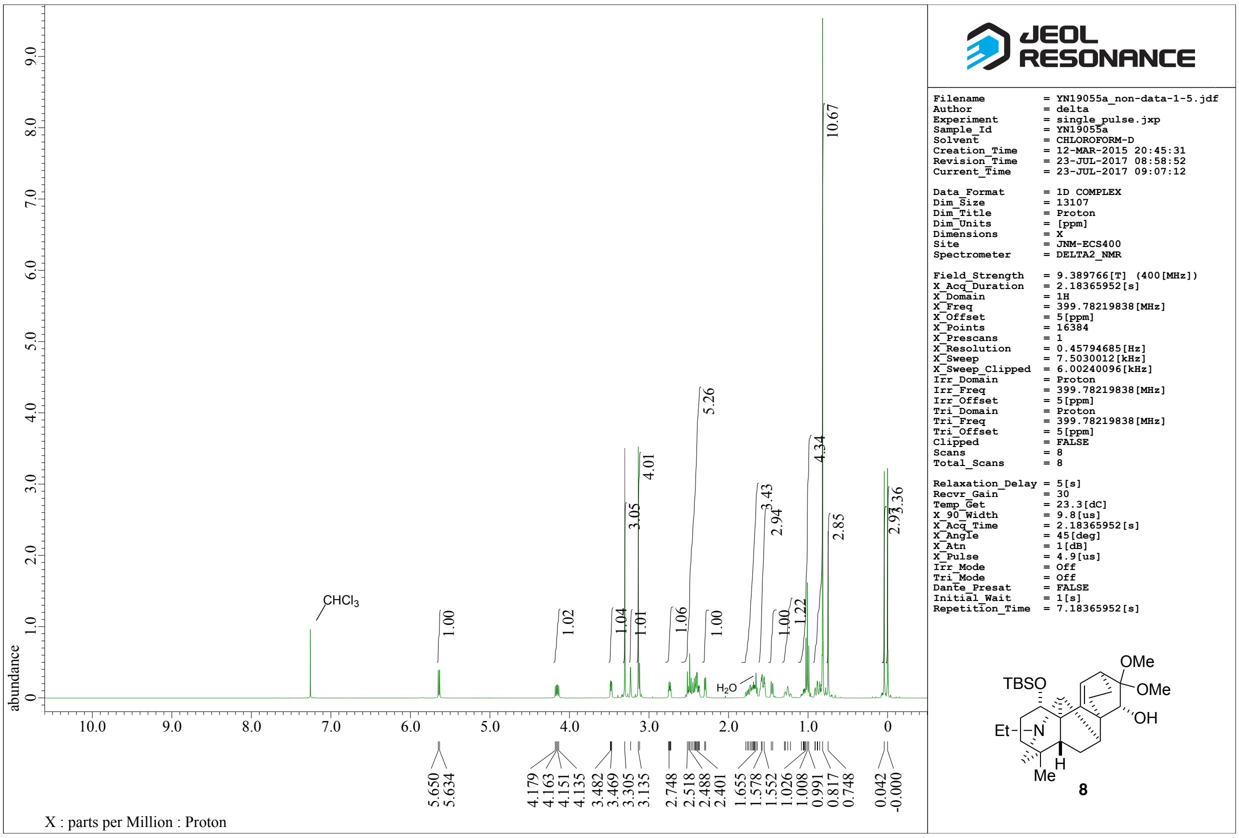
^{1}H NMR: 7.14 (m, 1H), 4.15 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.75 (m, 1H), 3.06 (s, 1H), 2.53 (m, 1H), 2.42 (m, 1H), 2.23 (m, 1H), 2.16 (m, 1H), 2.12 (m, 1H), 2.08-1.92 (m, 4H), 1.90-1.69 (m, 5H), 1.69-1.52 (m, 5H), 1.48 (m, 1H), 1.41 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 3H).

^{13}C NMR: 77.2 (C)*, 76.2 (CH), 72.4 (CH), 63.1 (CH), 60.5 (CH_2), 49.1 (C), 48.4 (CH_2), 47.1 (CH), 46.8 (CH), 46.4 (CH), 44.2 (CH), 35.0 (CH), 33.0 (C), 32.7 (CH_2), 32.7 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 27.8 (CH_3), 25.7 (CH_2), 25.3 (CH_2), 13.2 (CH_3). *This peak was overlapped with a peak of $CDCl_3$.

IR: 3357, 2929, 2869, 1492, 1457, 1376, 1196, 1144, 1094, 1045, 1012, 974, 930.

HRMS: 348.2542 (Calculated for $C_{21}H_{34}NO_3{}^+$: 348.2539).

$[\alpha]_D^{25} = -5.9°$ (*c* 0.29, EtOH).



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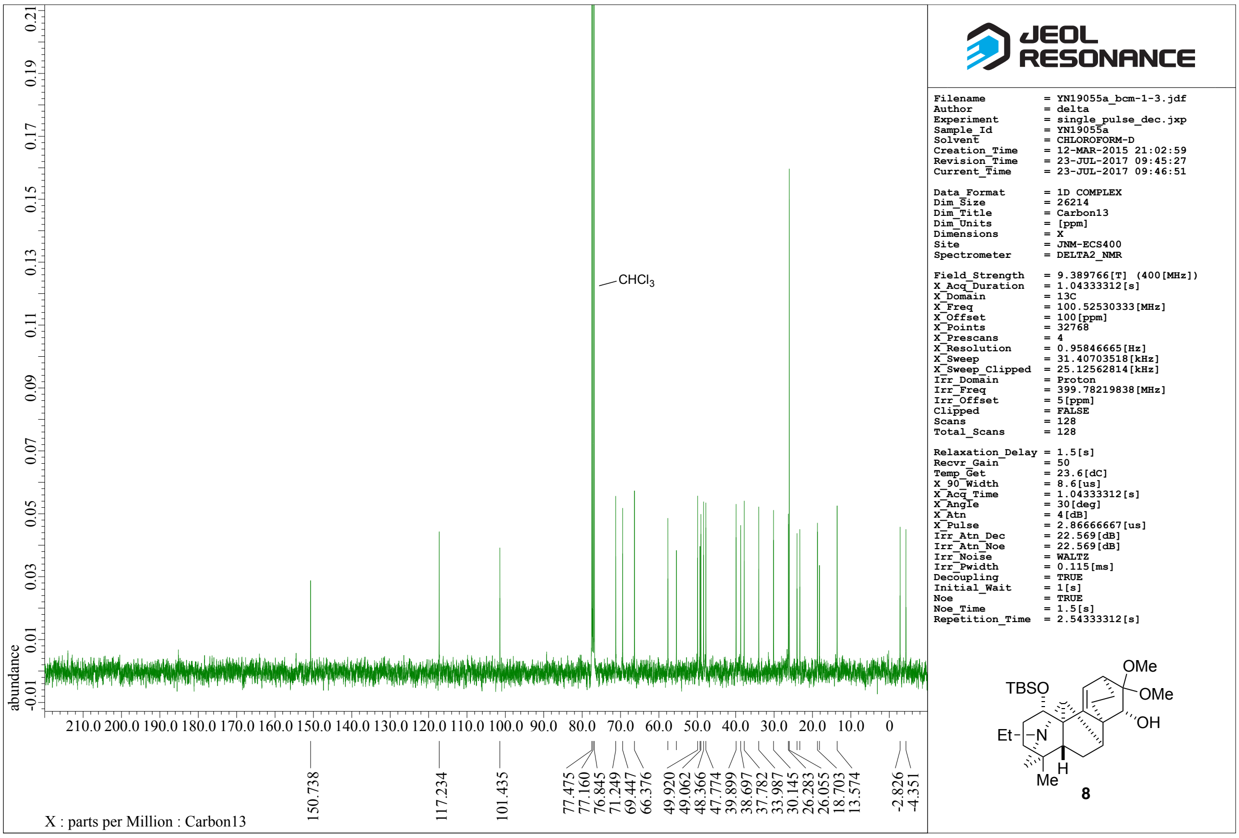

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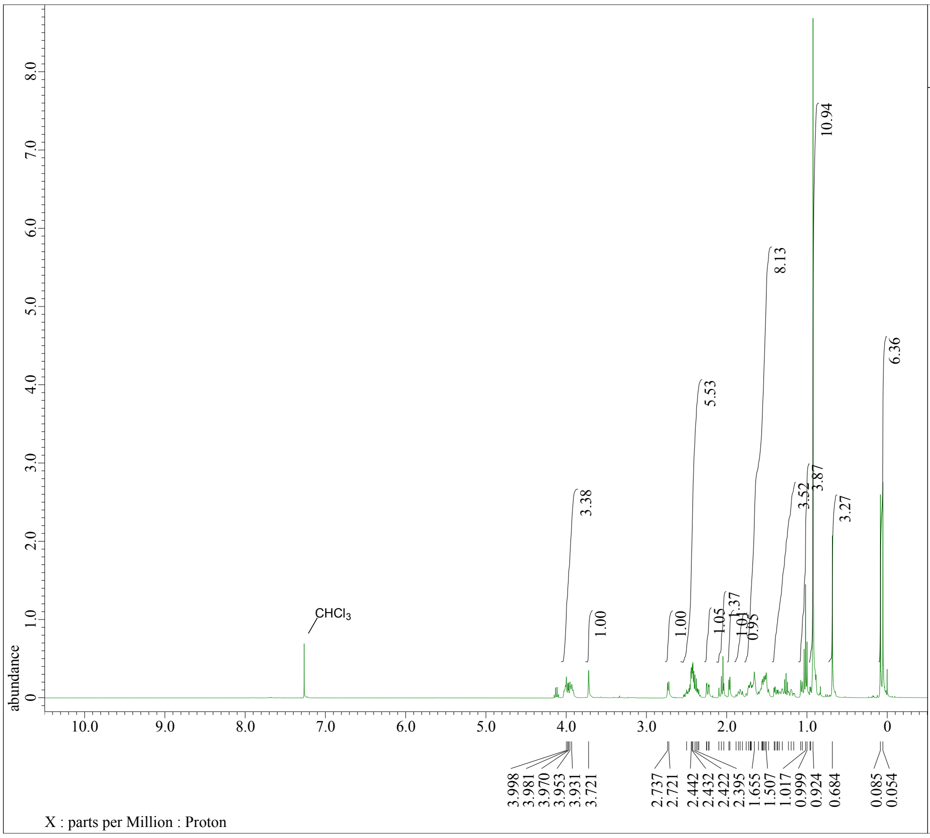

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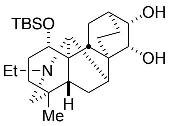

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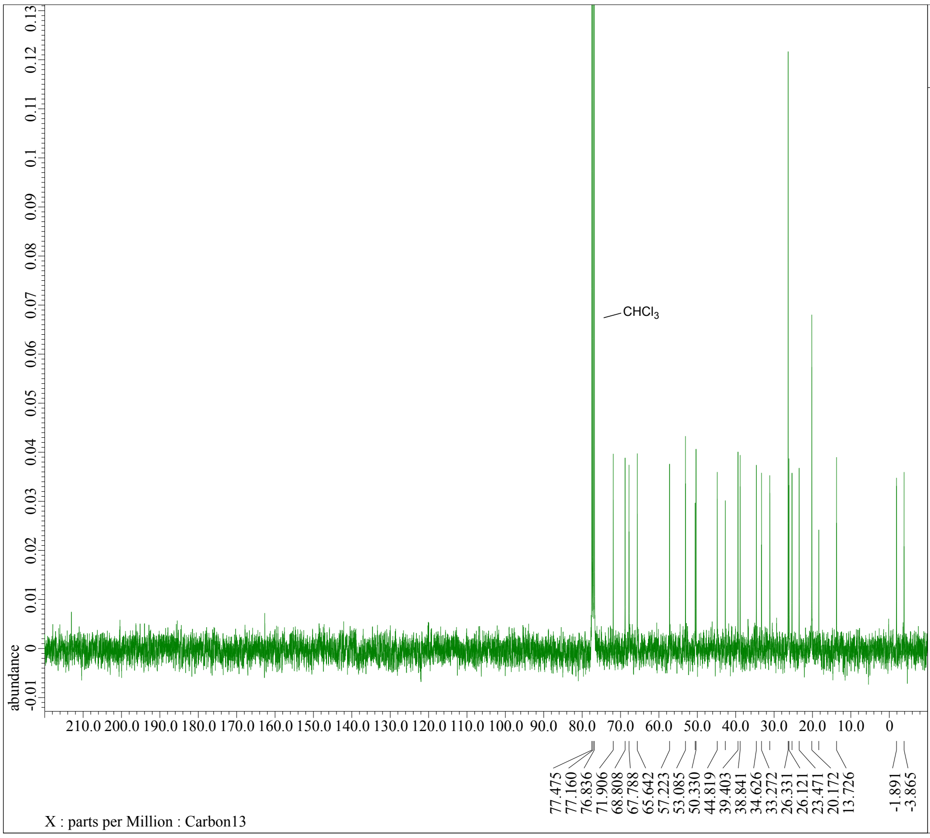

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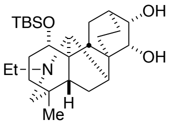

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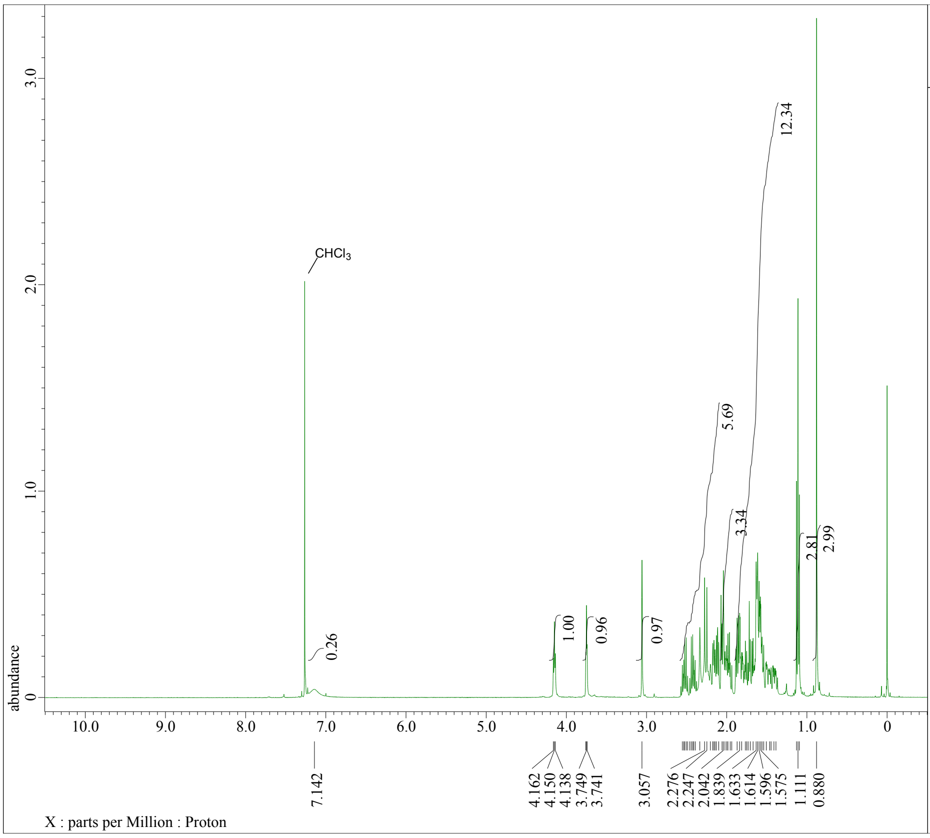

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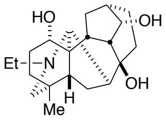
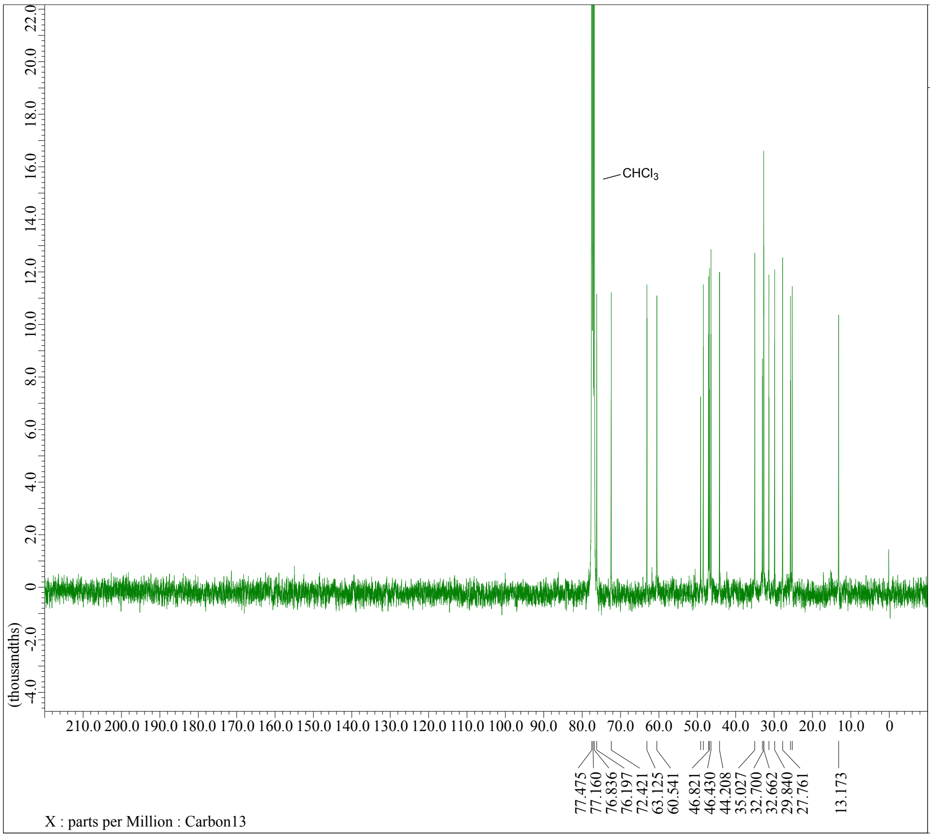


cardiopetaline (**6**)



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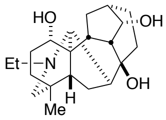

cardiopetaline (**6**)