Synthesis of (–)-Pseudotabersonine, (–)-Pseudovincadifformine, and (+)-Coronaridine Enabled by Photoredox Catalysis in Flow

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Supporting Information

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General Information:

Chemicals were either used as received or purified according to *Purification of Common Laboratory Chemicals*. Catharanthine was obtained as a tartrate salt from both Ontario Chemicals, Inc. and Arking Pharma Scientific, Inc. and was free-based within two hours prior to use through workup with ethyl acetate and saturated sodium bicarbonate. All reactions were performed using common dry, inert atmosphere techniques. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with an ethanolic solution of potassium permanganate or p-anisaldehyde. Column flash chromatography was performed using 230-400 mesh silica gel. NMR spectra were recorded on Varian Unity Plus 400, Varian MR400, Varian vnmrs 500, Varian Inova 500, Varian Mercury 500, and Varian vnmrs 700 spectrometers. Chemical shifts for ^{1}H NMR were reported as δ, parts per million, relative to the signal of $CHCl_3$ at 7.26 ppm. Chemical shifts for ^{13}C NMR were reported as δ, parts per million, relative to the center line signal of the CDCl3 triplet at 77.0 ppm. The abbreviations s, br. s, d, dd, br. d, ddd, t, q, br. q, qi, m, and br. m stand for the resonance multiplicity singlet, broad singlet, doublet, doublet of doublets, broad doublet, doublet of doublet of doublets, triplet, quartet, broad quartet, quintet, multiplet and broad multiplet, respectively. IR spectra were recorded either on an Avatar 360 FT-IR or Perkin-Elmer Spectrum BX FT-IR spectrometer. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry if the University of Michigan in Ann Arbor, MI on an Agilent Q-TOF HPLC-MS with ESI high resolution mass spectrometer. The enantiomeric purity of relevant samples was determined by chiral HPLC analysis performed on a Shimadzu system using a CHIRALPAK AD-H column from Daicel Chemical Ind., Ltd. with iPrOH/hexane as the eluent. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg).

Batch Reaction Apparatus:

Photoredox catalyzed reactions were carried out under visible light irradiation by a commercially available 2W blue LED strip in a circle around and approximately 4 cm from the reaction flask.

Flow Reaction Apparatus:

A photograph of the assembled photoreactor is shown in Figure S-1. The LED assembly (5.88 W) consists of 7 prearranged Luxeon Rebel high power LEDs (royal blue color, λ_{max} = 447.5 nm) (http://www.luxeonstar.com/Royal-Blue-447-5nm-7-LED-40mm-Round-Assembly-p/sr-02-r0425.htm). This is mounted to a heat sink to dissipate heat generated by the LEDs (http://www.luxeonstar.com/60mm-Round-Alpha-Heat-Sink-p/cn60-45b.htm) and powered by a 24V power supply (http://www.ledsupply.com/24vdc17a.php). To support the tubing, three flint glass test tubes were supported at both ends by small pieces of cardboard. The PFA Tubing (IDEX Health and Science, Part # 1514L) is wrapped around and between the tubes so that a total volume of 1.34 mL is placed on the test tubes. This is done so that the total length of the coils does not exceed the size of the LED apparatus (4.0 cm). The tubing is secured in place by a small piece of tape. The coiled tubing is then suspended approximately 2 cm above the LED apparatus. The temperature can be varied by placing the reactor closer or further away from the light. Compressed air can be passed over the reactor to further control temperature.

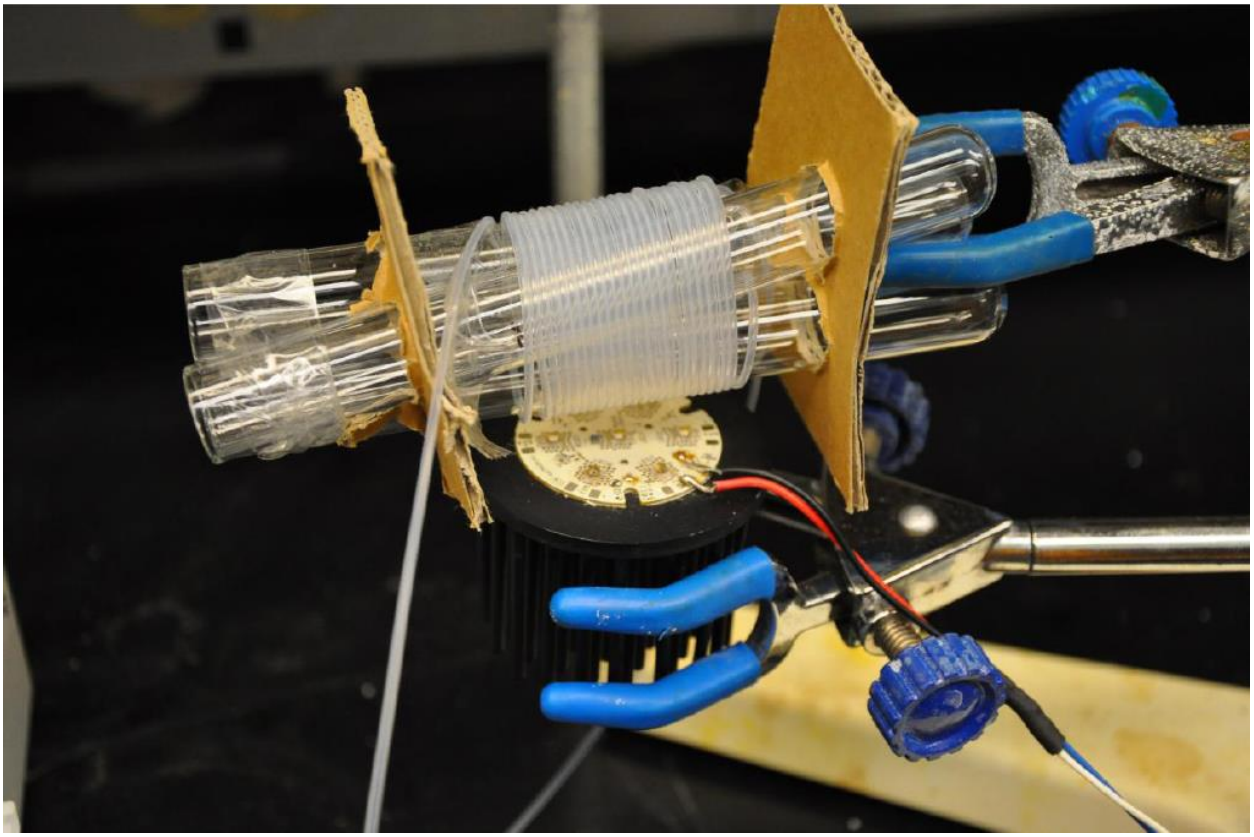


Figure S-1: Close up of photoreactor

The photoreactor tubing is then connected to the peristaltic pump tubing (IDEX Health and Science, Part # SC0717) by means of a conical adapter (IDEX Health and Science, Part # P-797) which contains the appropriate female nut, ferrule and washer. Likewise another short piece of PFA tubing, for delivery of the reaction mixture, was connected to the other end of the peristaltic pump tubing and fitted with a 20 gauge needle to pierce the septum of the reaction flask. Figure S-2 depicts the assembled reactor. During the operation of the flow reactor a sheet of aluminum foil is placed in front of the reaction apparatus due to the brightness of the LEDs.

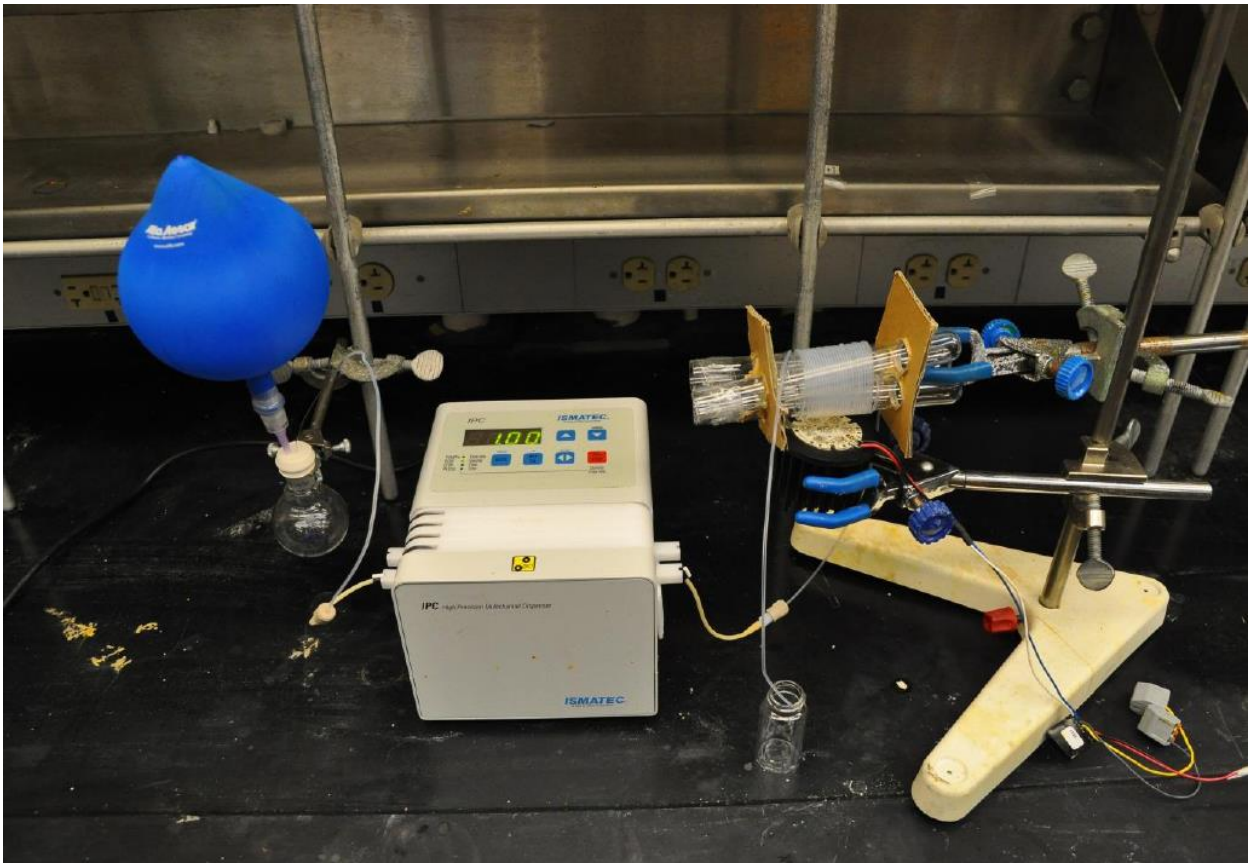
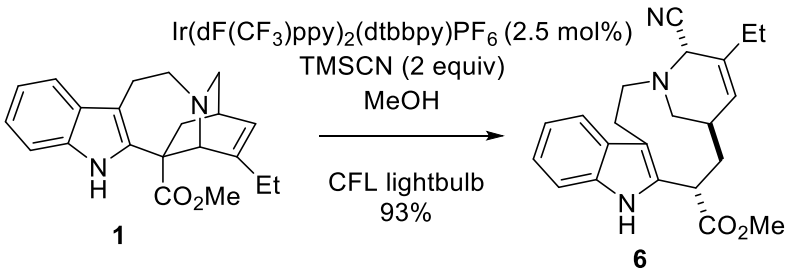


Figure S-2: Assembled photochemical reactor

Batch Fragmentation Procedure:



A flame dried 5 ml round bottom flask was charged with freshly free-based catharanthine (0.1 mmol, 33.6 mg, 1 equiv), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ **5** (0.0025 mmol, 2.8 mg, 2.5 mol%), and methanol (1 ml, 0.1 M). The resulting solution was degassed *via* the freeze pump-thaw method (3 cycles) and the flask was back-filled with argon. Trimethylsilylcyanide (0.2 mmol, 25 µl, 2 equiv) was then added *via* micro syringe. The flask was then irradiated by a 2W blue LED strip under an atmosphere of nitrogen and stirred for three hours. Upon consumption of starting material by TLC, the reaction was removed from the light source and quenched with sat. $NaHCO_3$ (5 ml). The layers were separated and the aqueous layer was extracted with EtOAC (x3). The combined organic layers were washed with brine and dried (Na_2SO_4) before concentrating. Internal standard solution was prepared by mixing 216 µl (2 mmol) of 2,5-dimethylfuran in $CDCl_3$ prepared in a 10 ml volumetric flask. The crude residue was dissolved in 500 µl (0.1 mmol) of internal standard solution and diluted to a final volume of 1 ml for ^{1}HNMR analysis. The reaction yields a pale yellow amorphous solid (93% yield vs. internal standard), which can be further purified through rinsing with ice cold methanol to yield the pure product as a white crystalline solid.

(4S,7R,9S)-methyl 4-cyano-5-ethyl-2,4,7,8,9,10-hexahydro-1H-3,7-methano[1]azacycloundecino[5,4-b]indole-9-carboxylate[1]

IR (neat): 3377, 2924, 1723, 1460, 1434, 1248m 1163, 844, 737 cm^{-1};

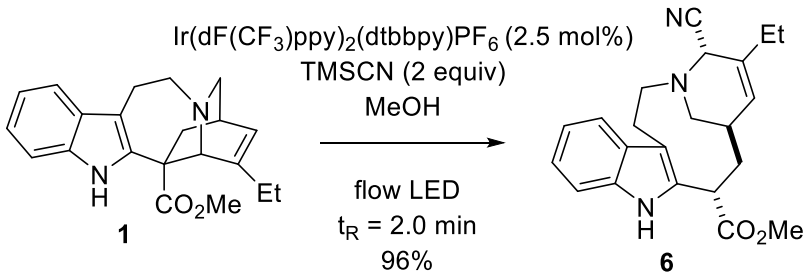
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.61 (br. s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.18 (dd, *J* = 7.6, 7.4 Hz, 1H) 7.11 (dd, *J* = 7.6, 7.4 Hz, 1H), 5.54 (d, *J* = 4.1 Hz, 1H), 4.78 (d, *J* = 10.3 Hz, 1H), 4.13 (s, 1H), 3.67 (s, 3H), 2.99-2.93 (m, overlap, 2H), 2.89-2.83 (m, 1H), 2.75 (dd, *J* = 12.6, 3.5 Hz, 1H), 2.53 (m, 1H), 2.42-2.34 (m, overlap, 2H), 2.29-2.16 (m, overlap, 3H), 2.10 (d, *J* = 14.4 Hz, 1H), 1.17 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR ($CDCl_3$, 175 MHz): δ 175.0, 136.0, 135.8, 133.9, 127.6, 126.4, 122.0, 119.3, 118.2, 117.8, 110.9, 110.7, 55.7, 52.3, 51.8, 49.4, 38.3, 37.4, 33.7, 26.2, 25.8, 12.0

HRMS (ESI) *m/z* calculated for $C_{21}H_{25}N_2O_2^+$ ($[M\text{-}CN]^+$) 337.1911, found 337.1916

$[\alpha]_D^{26}$ = -43 (c 1.0, $CHCl_3$)

Flow Fragmentation Procedure:

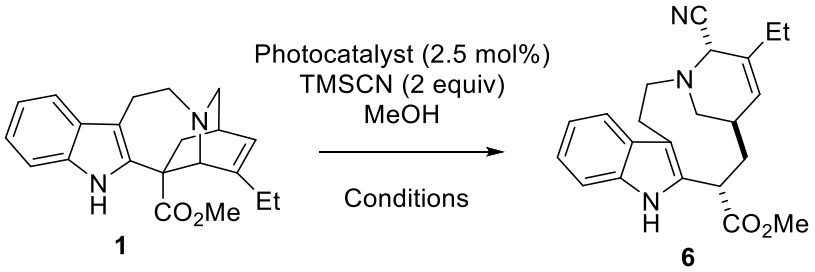


To a flame dried 5 ml round bottom flask equipped with a rubber septum and magnetic stir bar was added catharanthine (0.25 mmol, 1.0 equiv, 84 mg), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ **5** (0.006 mmol, 0.025 equiv, 7.0 mg) and methanol (2.5 ml). The resultant mixture was degassed *via* the freeze pump-thaw method (3 cycles) and the flask back-filled with argon. TMSCN (0.5 mmol, 2.0 equiv, 63 μl) was subsequently added to the degassed solution. The reaction mixture was then pumped through the photoreactor at a flow rate of 670 μl/min to achieve a residence time of 2.0 minutes and collected in a 25 ml round bottom flask. After 3.0 minutes the needle was taken out of the feeder solution, resulting in an overall reaction scale of 0.20 mmol. The reaction mixture was poured into a separatory funnel containing saturated $NaHCO_3$. The resulting solution was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to provide a yellow amorphous solid. Yield (96% by NMR) was determined as outlined in the batch procedure.

Flow Fragmentation Procedure (2 gram scale):

To a flame dried 100 ml round bottom flask equipped with a rubber septum and magnetic stir bar was added catharanthine (6.02 mmol, 1.0 equiv, 2.025 g), $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ **5** (0.150 mmol, 0.025 equiv, 147 mg) and methanol (60.2 ml). The resultant mixture was degassed *via* the freeze pump-thaw method (3 cycles) and the flask back-filled with argon. TMSCN (12.04 mmol, 2.0 equiv, 1.51 ml) was subsequently added to the degassed solution. The reaction mixture was then pumped through the photoreactor at a flow rate of 670 μl/min to achieve a residence time of 2.0 minutes and flowed into a 500 ml Erlenmeyer flask containing 300 ml of ethyl acetate. The reactor tubing was submerged beneath the surface of the solvent in the collection flask to ensure that no crystallization occurred in the tubing due to evaporation of solvent upon elution. Care should be taken to ensure that no crystals form in the collection flask, and if they do the solution should be replaces immediately with fresh ethyl acetate. As the reaction progressed, white crystals began to form in feeder solution. Upon full uptake of the reaction solution, an additional 2 ml of methanol were added to rinse any residue through the reactor, but was insufficient to dissolve all remaining material. The reaction mixture was poured into a separatory funnel containing saturated $NaHCO_3$. The resulting solution was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to provide a yellow amorphous solid. Yield (88% by NMR) was determined vs. 2,5-dimethylfuran as the internal standard.

Table S1. Fragmentation Optimization and Control Experiments:

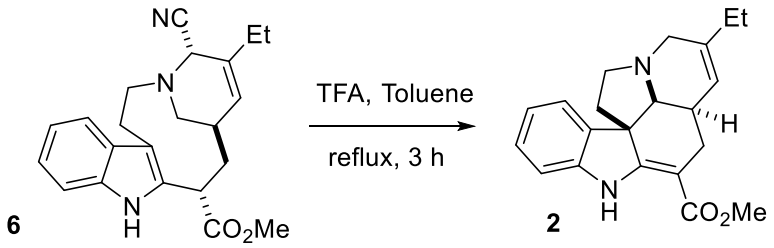


Entry	Photocatalyst	Conditions	Yield
1	$Ru(bpy)_3Cl_2$	batch	83%
2	$Ir(ppy)_2(dtbbpy)PF_6$	batch	80%
3	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	batch	93%
4	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	batch, no light	N.R.
5	none	batch	N.R.
6	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	flow	96%
7	none	flow	N.R.

Reaction optimization reactions (**Table S1**) were conducted using the procedures outlined above. $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ was found to perform superiorly to both $Ru(bpy)_3Cl_2$ and $Ir(ppy)_2(dtbbpy)PF_6$. Thorough exclusion of light (entry 4) resulted in no observable reactivity, and there was no background reaction observed when the reaction was run with light irradiation but without photocatalyst (entry 5). As the flow reaction utilizes a 5.88 W LED as opposed to the 14W CFL used for batch reactions, photocatalyst was also excluded from the flow reaction (entry 7) but again no light-driven background reaction was observed. Yields are NMR yields vs. 2,5-dimethylfuran as the internal standard.

Synthesis of (-)-pseudotabersonine 2:

Procedure for the formation of (-)-pseudotabersonine:



To a flame dried 2-dram vial with a stir bar was added starting material **6** (0.1 mmol, 36.4 mg) and dry toluene (2.0 ml, 0.05M). The solution of starting material was degassed *via* three cycles of freeze pump thaw under a nitrogen atmosphere. Trifluoroacetic acid (0.1 mmol, 8 µl) was added and the reaction was heated to reflux under nitrogen with a stream of air concentrated on the outside of the upper half of the vial to ensure condensation. Reaction progress was monitored by TLC, but the consumption of starting material is difficult to follow due to proposed stoichiometric ionization to the imminium ion. After three hours, the reaction had formed on major spot off the baseline with 20% EtOAc in hexanes as the TLC mobile phase. The reaction was diluted with ethyl acetate and poured into saturated sodium bicarbonate. The organic phase was separated, and the aqueouse phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to provide a crude yellow oil. Purification on SiO_2 with 5% EtOAc in hexanes provided (-)-pseudotabersonine **2** (30.3 mg, 90%) as an amorphous solid.

(-)-pseudotabersonine:[2,3]

R_f (20% EtOAc in hexanes): 0.53;

IR (neat): 3362, 3052, 2960, 2874, 1728, 1672, 1606, 1477, 1464, 1435, 1238, 1201, 1117, 735 cm^{-1};

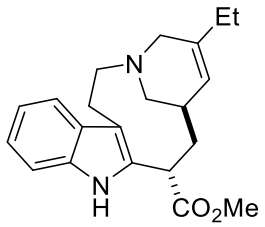
^1H NMR ($CDCl_3$, 500 MHz): δ 8.99 (br. s, 1 H), 7.31 (d, *J* = 7.1 Hz, 1H), 7.16 (dd, *J* = 7.6, 7.5 Hz, 1H), 6.89 (dd, *J* = 7.5, 7.1 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.52 (d, *J* = 4.1 Hz, 1H), 3.78 (s, 3H), 3.37 (d, *J* = 16.5 Hz, 1H), 3.28 (d, *J* = 16.5 Hz, 1H), 3.05-3.02 (m, overlap, 2H), 2.82-2.78 (m, 1H), 2.68 (d, *J* = 14.8, 3.1 Hz, 1H), 2.16 (dd, *J* = 14.8, 11.5 Hz, 1H), 2.10-2.04 (m, overlap, 3H), 1.91 (ddd, *J* = 11.5, 4.9, 1.5 Hz, 1H), 1.77 (br. s, 1H), 1.07 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz): δ 168.7, 165.9, 143.6, 139.3, 138.0, 127.7, 121.8, 121.4, 120.6, 109.1, 95.5, 65.2, 55.5, 53.2, 51.0, 51.0, 44.4, 36.8, 27.8, 26.3, 12.5;

HRMS (ESI) *m/z* calculated for $C_{21}H_{25}N_2O_2^+$ ($[M+H]^+$) 337.1911, found 337.1913

$[\alpha]_D^{26}$ = -171.6 (c 1.0, MeOH) lit.[3] $[\alpha]_D^{26}$ = +320 (MeOH)

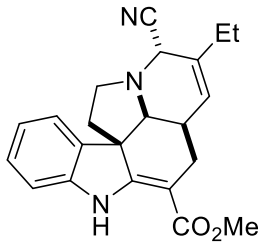
Carbomethoxy cleavamine 8:[1]



8

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.58 (br. s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.16 (dd, *J* = 8.0, 7.7 Hz, 1H), 7.10 (dd, *J* = 7.7, 7.6 Hz, 1H), 5.30 (d, *J* = 5.4 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 3.67 (s, 3H), 3.18 (d, *J* = 15.5 Hz, 1H), 3.09 (d, *J* = 15.5 Hz, 1H), 2.92-2.83 (m, overlap, 2H), 2.74 (ddd, *J* = 13.6, 3.0, 3.0 Hz, 1H), 2.42-2.32 (m, overlap, 4H), 2.19 (br. s, 1H), 2.11-2.05 (m, overlap, 3H), 1.09 (t, *J* = 7.6 Hz, 3H)

21-cyanopseudotabersonine 7:



7

IR (neat): 3367, 2924, 2853, 1731, 1677, 1608, 1465, 1239, 1203, 748 cm^{-1};

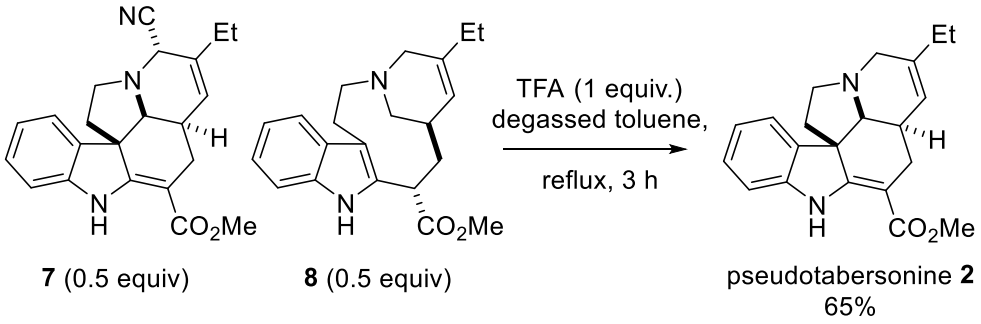
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.92 (br. s, 1H), 7.33 (d, 7.5 Hz, 1H), 7.16 (ddd, *J* = 7.7, 7.6, 1.2 Hz, 1H), 6.90 (ddd, *J* = 7.6, 7.5, 0.9 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 5.71 (dd, *J* = 5.3, 1.5 Hz, 1H), 4.33 (s, 1H), 3.76 (s, 3H), 3.38 (d, *J* = 3.6 Hz, 1H), 3.07-3.01 (m, overlap, 2H), 2.66 (ddd, *J* = 14.9, 3.6, 1.4 Hz, 1H), 2.29-2.24 (m, 1H), 2.16-2.10 (m, overlap, 2H), 2.04 (ddd, *J* = 11.7, 11.5, 6.6 Hz, 1H), 1.90 (dd, *J* = 11.7, 3.7 Hz, 1H), 1.84 (br. m., 1H), 1.12 (t, *J* = 7.4, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz): δ 168.5, 165.4, 143.5, 137.0, 135.0, 128.3, 126.4, 122.2, 121.2, 116.5, 109.5, 95.5, 60.9, 54.7, 53.6, 51.2, 48.4, 43.9, 37.4, 26.4, 24.7, 12.2;

HRMS (ESI) *m/z* calculated for $C_{22}H_{24}N_3O_2^+$ ($[M+H]^+$) 362.1881, found 362.1863

$[\alpha]_D^{26}$ = -25.2 (c 0.19, $CHCl_3$)

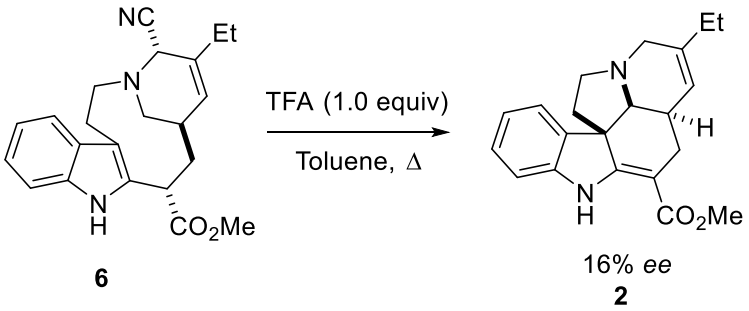
Formation of pseudotabersonine from 7 and 8



7 (0.5 equiv) **8** (0.5 equiv) pseudotabersonine **2** 65%

Cyanated pseudotabersonine **7** (18.1 mg, 0.05 mmol, 0.5 equiv) and reduced fragmentation product **8** (16.9 mg, 0.05 mmol, 0.5 equiv) were combined in a 2 dram vial equipped with a stir bar and a septum screw top. Toluene (2 ml) was added to the vial and the solution was degassed *via* the freeze-pump-thaw method (3 cycles) and the vial was back-filled with nitrogen. TFA (7.6 µl, 0.1 mmol, 1 equiv) was added to the reaction and the vial was placed on a pre-equilibrated heating block set to 120 °C. Upon TFA addition the reaction turned a slightly yellow-brown color, and some precipitate could be observed. A slow stream of air was directed at the top of the sealed vial to facilitate solvent condensation. The reaction was stirred for 3 hours at reflux, after which the reaction mixture was diluted with ethyl acetate and poured into saturated sodium bicarbonate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to provide a crude yellow oil. Purification on SiO_2 with 5% EtOAc in hexanes provided pseudotabersonine **2** (22.0 mg, 65% yield) as an amorphous solid.

Preparation of Near-Racemic pseudotabersonine:

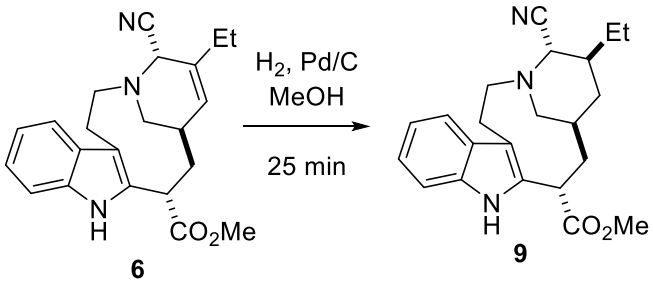


6 16% *ee*
2

Crude, solid α-aminonitrile **6** from the flow fragmentation procedure was placed on filter paper in a Buchner funnel inserted in a side-arm Erlenmeyer flask attached to house vacuum. The solid was washed with ice-cold methanol until the faint-yellow color was removed from the sample. The solution of filtrate was concentrated to a yellow foam constituted by the α-aminonitrile **6** with impurities. This impure material (457 mg, ~1.26 mmol) was suspended in anhydrous toluene (25 ml, 0.05M) in a flame-dried 50 ml round-bottom flask attached to a reflux condenser and degassed *via* the freeze pump-thaw method (3 cycles) and the flask back-filled with nitrogen. To the solution was added trifluoroacetic acid (96 µl, 1.26 mmol, 1.0 equiv) and the reaction was placed on a heating block pre-equilibrated to 135 degrees. The reaction was stirred for 14 hours under nitrogen. Upon completion, the reaction was diluted with ethyl acetate and poured into saturated aqueous sodium bicarbonate solution. The organic phase was removed and the aqueous phase was washed with ethyl acetate (x3). The combined organic phase was washed with brine and dried over sodium sulfate before concentrating. Purification on SiO_2 with 5% EtOAc in hexanes provided pure pseduotabersonine **2** (43.0 mg, 10% yield, 16% *ee*, $[\alpha]_D^{26}$ = -63.1 (c 1.0, MeOH)) along with a number of mixed fractions.

Synthesis of (+)-coronaridine:

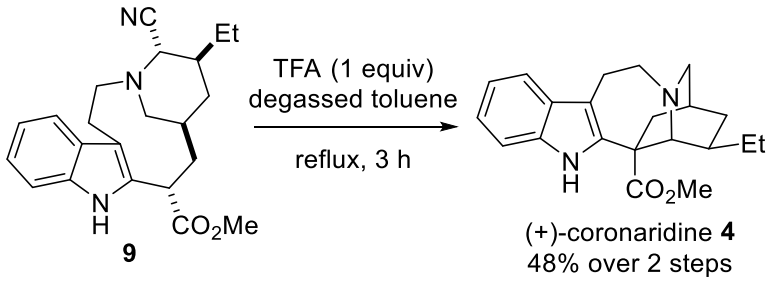
Hydrogenation of 6 to generate 9:



6 **9**

Fragmentation product **6** (50.0 mg, 0.14 mmol) was placed in a 10 ml round-bottom flask with 10% palladium on carbon (20 mg). The flask was evacuated and back-filled with nitrogen three times, after which methanol was added to the flask (2 ml). Hydrogen was bubbled through the reaction from a balloon for 25 minutes, venting the flask with a needle through the septum. After 25 minutes the reaction mixture was promptly filtered through celite with ethyl acetate, and the filtrate was concentrated to yield chromatographically unstable **9** as the major product. Reaction time had been determined previously by taking aliquots for HNMR analysis, as the reaction is unable to be monitored by TLC. Longer reaction times result in de-cyanation of the product, as well as epimerization of the ethyl group. The product was found to be unstable to purification on silica gel, and so the crude material was brought on to the next step without purification.

Conversion of 9 to (+)-coronaridine:



Crude hydrogenation product **9** (0.14 mmol) was placed in a 2 dram vial equipped with a stir bar and a septum screw top. Toluene (2.75 ml) was added to the vial and the solution was degassed *via* the freeze-pump-thaw method (3 cycles) and the vial was back-filled with nitrogen. TFA (10.5 µl, 0.14 mmol, 1 equiv) was added to the reaction and the vial was placed on a pre-equilibrated heating block set to 120 °C. Upon TFA addition the reaction turned a slightly yellow-brown color, and some precipitate could be observed. A slow stream of air was directed at the top of the sealed vial to facilitate solvent condensation. The reaction was stirred for 3 hours at reflux, after which the reaction mixture was diluted with ethyl acetate and poured into saturated sodium bicarbonate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated to provide a crude yellow oil. Purification of the crude material on SiO_2 with 5% EtOAc in hexanes provided (+)-coronaridine **4** (22.0 mg, 48% yield) as an amorphous solid. Treatment with ethereal HCl provided the hydrochloride salt.

(+)-coronaridine-:[4,5]

R_f (freebase, 25% EtOAc in hexanes): 0.50;

IR (freebase, neat): 3375, 2951, 2926, 2856, 1709, 1459, 1434, 1250, 739 cm^{-1};

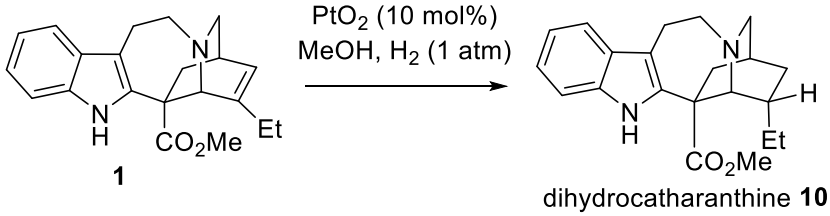
^{1}H NMR (HCl, CD_3OD, 700 MHz): 7.48 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.12 (ddd, *J* = 8.0, 8.0, 0.9 Hz, 1H), 7.05 (ddd, *J* = 8.0, 8.0, 0.7 Hz, 1H), 4.58 (s, 1H), 4.05 (ddd, *J* = 12.9, 5.3, 3.8 Hz, 1H), 3.76 (s, 3H), 3.52 (ddd, *J* = 16.5, 11.5, 5.3 Hz, 1H) 3.47 (ddd, *J* = 11.5, 4.2, 2.4 Hz, 1H), 3.41 (ddd, *J* = 12.9, 12.8, 4.6 Hz, 1H), 3.24 (ddd, *J* = 16.5, 4.3, 4.2 Hz, 1H), 3.89 (br. d, *J* = 11.6 Hz, 1H), 2.73 (ddd, *J* = 14.0, 1.7, 1.7 Hz, 1H), 2.39 (ddd, *J* = 14.0, 4.6, 2.0 Hz, 1H), 2.21 (br. d, *J* = 3.8 Hz, 1H), 2.09 (m, 1H), 1.81-1.67 (m, overlap, 3H), 1.37 (dd, *J* = 13.9, 8.4 Hz, 1H), 1.03 (t, *J* = 7.2 Hz);

^{13}C NMR (free base, $CDCl_3$, 175 MHz): δ 175.7, 136.6, 135.4, 128.8, 121.9, 119.2, 118.4, 110.31, 110.30, 57.5, 55.1, 53.1, 52.6, 51.5, 39.1, 36.5, 32.0, 27.4, 26.7, 22.1, 11.6;

HRMS (ESI) *m/z* calculated for $C_{21}H_{27}N_2O_2^+$ ($[M+H]^+$) 339.2067, found 339.2068

$[\alpha]_D^{26}$ = +6.0 (HCl salt c 1.0 MeOH) lit.[4] $[\alpha]_D^{26}$ = -8.5 (HCl salt c 1.0 $CHCl_3$)

Synthesis of dihydrocatharanthine 10:[6]



Freshly free-based catharanthine **1** (42.8 mg, 0.13 mmol, 1.0 equiv) was placed in a 10 ml round-bottom flask and PtO_2 (2.9 mg, 0.013 mmol, 0.1 equiv) was added. The flask was evacuated and backfilled three times with nitrogen gas before methanol (2.5 ml) was added. The solution was sparged for 5 minutes from a hydrogen balooon. During this time, the suspended PtO_2 turned from brown to black. The reaction was complete by TLC after 24 hours. The reaction mixture was filtered through celite with ethyl acetate and concentrated to yield pure dihydrocatharanthine **10** as a white foam (40.2 mg, 93% yield)

R_f (40% EtOAc in hexanes, 5 drops Et_3N/10 ml): 0.61;

IR (neat): 3372, 2928, 2857, 1706, 1460, 1433, 1250, 1172, 740 cm^{-1};

^1H NMR ($CDCl_3$, 500 MHz): δ 7.76 (br. s, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.16 (dd, *J* = 7.7, 7.4, 1H), 7.11 (dd, *J* = 7.5, 7.4 Hz, 1H), 3.82 (br. s, 1H), 3.67 (s, 3H), 3.60-3.56 (m, 1H), 3.18-3.12 (m, overlap, 2H), 3.10-3.05 (m, overlap, 2H), 2.83 (d, *J* = 8.9 Hz, 1H), 2.65 (d, *J* = 13.1 Hz, 1H), 2.11 (br. s, 1H), 1.99-1.93 (m, overlap, 3H), 1.37 (ddd, *J* = 12.9, 7.1, 5.2 Hz, 1H), 1.18 (d, *J* = 11.2 Hz, 1H), 1.05 (ddd, *J* = 12.9, 10.7, 7.1 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H);

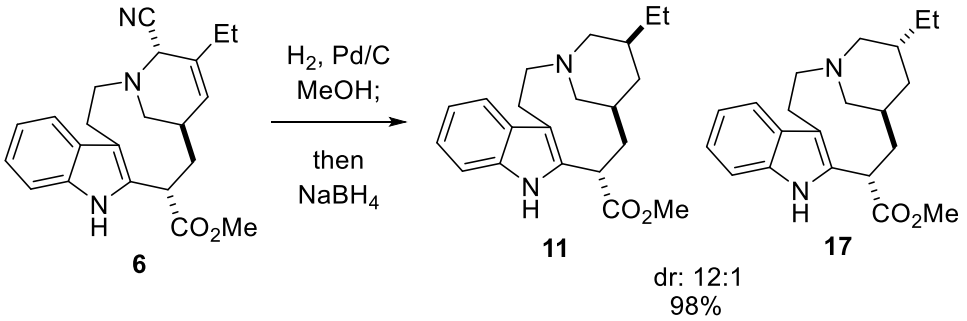
^{13}C NMR ($CDCl_3$, 175 MHz): δ 175.6, 137.1, 135.3, 128.5, 121.9, 119.2, 118.4, 110.40, 110.35, 56.3, 53.1, 52.4, 52.2, 51.3, 43.9, 37.1, 31.5, 27.34, 27.30, 21.7, 12.6;

HRMS (ESI) *m/z* calculated for $C_{21}H_{27}N_2O_2^+$ ($[M+H]^+$) 339.2067, found 339.2056

$[\alpha]_D^{26}$ = +37 (c 1.0 $CHCl_3$) lit.[6] $[\alpha]_D^{26}$ = +33 (c 1.0 $CHCl_3$)

Synthesis of pseudovincadifformine 3:

Hydrogenation of 6 to generate 11:[7 7]



Fragmentation product **6** (430 mg, 1.16 mmol) was placed in a 25 ml pear-shaped flask with 10% palladium on carbon (252 mg, 20 mol%). The flask was evacuated and back-filled with nitrogen three times, after which methanol was added to the flask (16 ml). Hydrogen was bubbled through the reaction from a balloon for 25 minutes, venting the flask with a needle through the septum. After 25 minutes the reaction mixture was cooled to zero degrees and $NaBH_4$ (179 mg, 4.0 equiv) was added in one portion. The reaction was allowed to stir for ten minutes at zero degrees before it was run through a column of celite, washed through with ethyl acetate, and concentrated to form a light yellow amorphous solid. This material was pure by HNMR (395 mg, 98% yield). Purification on silica gel (5% EtOAc in hexanes to 30% EtOAc in hexanes to 100% EtOAc) resulted in decolorization of the material with a significant loss in yield (126 mg recovered, 31% yield) possibly due to oxidative decomposition.

IR (neat): 3381, 2917, 1723, 1461, 1433, 1251, 1158, 738 cm^{-1};

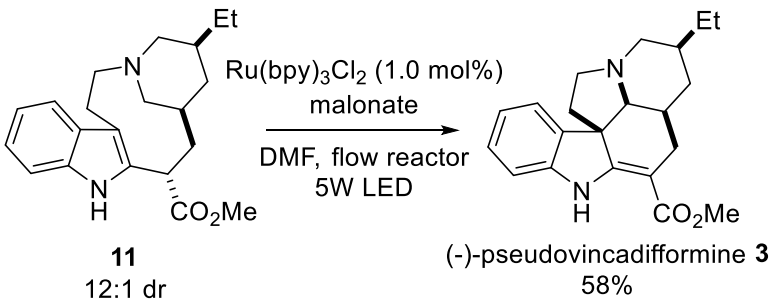
^1H NMR ($CDCl_3$, 500 MHz, mixture of diastereomers): 8.64 (br. s, 1H), 8.59 (br. s, 0.14H), 7.50 (app. d, overlap, 1.2H), 7.35 (app. d, overlap, 1.2H), 7.16 (app. t, overlap, 1.3H), 7.09 (app. t, overlap, 1.2H), 5.55 (d, 11.7 Hz, 0.08 H), 5.09 (d, *J* = 10.3 Hz, 1H), 3.72 (s, overlap, 3.6), 2.92-2.87 (m, overlap, 2.5H), 2.68 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.54-2.47 (m, overlap, 2.2H), 2.35-2.26 (m, overlap, 2.5H), 2.26-2.11 (m, overlap, 1.34H), 2.07 (app. d, overlap, 1.2H), 1.87-1.81 (m, overlap, 1.87-1.80, 2.5H), 1.55-1.48 (m, overlap, 2.2H), 1.37-1.28 (m, overlap, 4H), 0.91 (app. t, overlap, 3.4 H);

^{13}C NMR ($CDCl_3$, 175 MHz): δ 175.5, 135.9, 133.9, 127.7, 121.5, 119.0, 118.2, 111.9, 110.6, 59.0, 52.1, 51.8, 51.2, 38.6, 37.6, 34.8, 32.1, 31.0, 28.7, 26.5, 11.7;

HRMS (ESI) *m/z* calculated for $C_{21}H_{27}N_2O_2^+$ ($[M+H]^+$) 341.2224, found 341.2225

$[\alpha]_D^{26}$ = -84.46 (c 1.0, $CHCl_3$)

Conversion of 11 to (-)-pseudovincadifformine:



Tertiary amine **11** (34 mg, 0.1 mmol) and $Ru(bpy)_3Cl_2$ (0.6 mg, 1 mol%) were placed in a 2-dram vial equipped with a septum and dissolved in dry DMF (1.0 ml). This solution was degassed *via* the freeze-pump-thaw method (x3) and backfilled with nitrogen. Diethyl 2-bromo-2-methylmalonate (57.3 µl, 75.9 mg, 0.3 mmol, 3 equiv) was added to the solution. A flow photoreactor with a 670 µl internal volume was placed ~1 cm from the LED light source and allowed to warm to 50-55 ˚C. The reaction mixture was then flowed through the reactor at a rate of 134 µl/min (5 minute residence time). Upon complete uptake of the reaction mixture by the pump (nitrogen is beginning to be pumped through the reactor tubing), an additional 0.5 ml of DMF was added to the reactor input flask to minimize transfer loss. Upon complete elution of all solvent, the reaction was diluted with ethyl acetate and partitioned with water. 2 ml of triethylamine were added to the separatory funnel, and the mixture was extracted with ethyl acetate (x3). The combined organic phases were washed with brine before drying over sodium sulfate and concentrating. Purification on SiO_2 under nitrogen with nitrogen-sparged solvent (5% EtOAc in hexanes) provided (-)-pseudovincadifformine (19.5 mg, 58% yield) as an amorphous solid.

IR (neat): 3367, 2927, 2779, 1675, 1608, 1465, 1436, 1241, 1199, 1119, 743 cm^{-1};

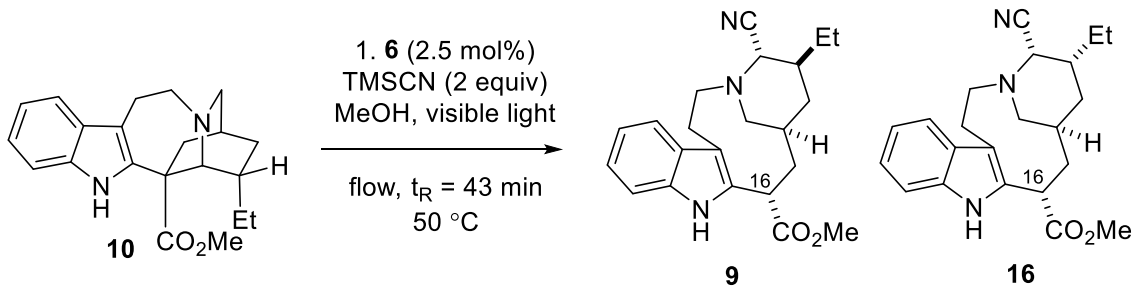
^1H NMR ($CDCl_3$, 500 MHz): δ 8.94 (br. s), 7.24 (d, *J* = 7.3 Hz, 1H), 7.15 (ddd, *J* = 7.7, 7.5, 1.0 Hz, 1H), 6.88 (dd, *J* = 7.5, 7.3 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 3.77 (s, 3H), 3.00 (d, *J* = 4.1 Hz, 1H), 2.92 (dd, *J* = 8.4, 6.2 Hz, 1H), 2.84 (d, *J* = 5.8 Hz, 2H), 2.69 (ddd, *J* = 11.4, 8.5, 4.3 Hz, 1H), 2.54 (dd, *J* = 14.6, 2.9 Hz, 1H), 2.30 (dd, *J* = 14.6, 11.7 Hz, 1H), 2.02 (ddd, *J* = 11.5, 11.5, 6.2 Hz, 1H), 1.81-1.76 (m, overlap, 2H), 1.66-1.62 (br. m, 1H), 1.54-1.45 (m, overlap, 2H), 1.43-1.38 (m, overlap, 2H), 0.93 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 175 MHz): δ 168.6, 165.8, 143.5, 137.9, 127.6, 121.8, 120.4, 109.1, 96.1, 66.0, 55.2, 54.9, 51.4, 50.9, 44.2, 36.2, 35.5, 32.5, 28.7, 26.5, 12.4;

HRMS (ESI) *m/z* calculated for $C_{21}H_{27}N_2O_2^+$ ($[M+H]^+$) 339.2067, found 339.2076

$[\alpha]_D^{26}$ = -460 (c 0.24, EtOH) lit.[8] $[\alpha]_D^{26}$ = -506 (c 0.62 EtOH)

Fragmentation of dihydrocatharanthine 10:

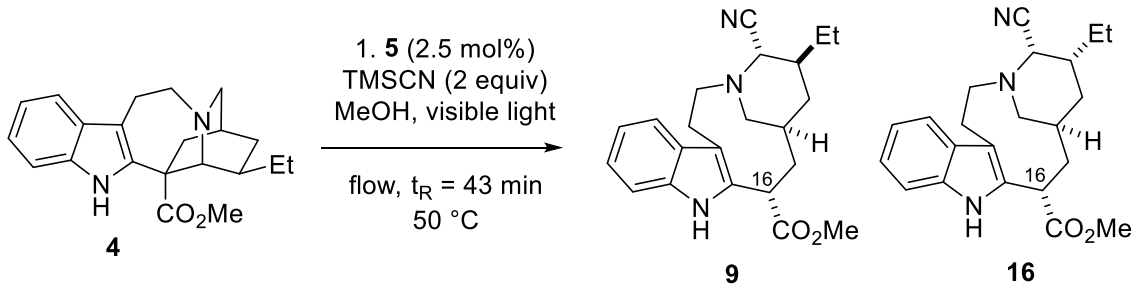


The flow reaction apparatus was set up with the reactor ~1.0 cm away from the LED puck. A thermometer was placed inside one of the test tubes to accurately measure the internal reaction temperature, and the temperature was regulated to 50 °C using a slow stream of air directed at the reactor. Dihydrocatharanthine **10** (33.9 mg, 0.1 mmol, 1.0 equiv) was placed in a 5ml round-bottom flask. $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ **5** (2.8 mg, 2.5 mol%) was then added to the flask before the addition of methanol (1.0 ml). The resulting solution was degassed *via* the freeze-pump-thaw method (3 cycles) and the flask was backfilled with nitrogen. TMSCN (25 µl, 0.2 mmol, 2.0 equiv) was added to the solution. The reaction mixture was then pumped through the photoreactor at a flow rate of 32.2 µl/min (t_R = 43 minutes) and collected in a 25 ml round bottom flask. Upon complete uptake of the reaction solution an additional 0.5 ml of methanol was added to the reaction flask to rinse any residue through the reactor. Upon elution the reaction mixture was poured into a separatory funnel containing a mixture of saturated $NaHCO_3$ and water. The resulting solution was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Crude ^{1}HNMR analysis in $CDCl_3$ revealed two distinct doublets (δ 4.77 and δ 5.20, **9** and **16** respectively) corresponding to the C16 benzylic methine (see above) present in the ring opened products. Yields were determined for each residence time by ^{1}HNMR with diethyl phenylmalonate as an internal standard.

t_R = 42 minutes 8.3:1 dr **9**:**16**, 37% yield

All attempts to isolate α-aminonitrile **9** or **16** through column chromatography on both SiO_2 and neutral Al_2O_3 were met with decomposition. Further confirmation of the structure of **9** was obtained through further reductive decyanation of the product to compound **11** with sodium borohydride in a manner identical to the procedure described for the coronaridine fragmentation products (page S18).

Fragmentation of coronaridine 10:

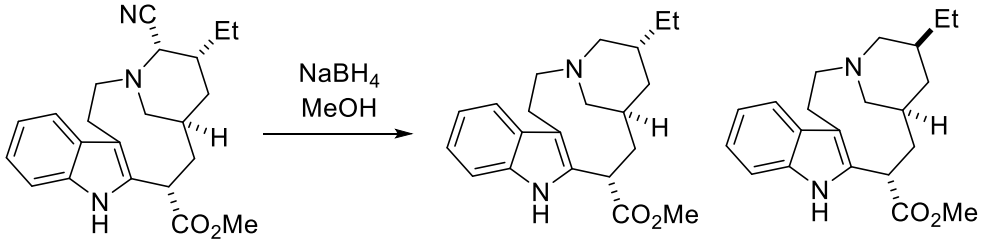


4 **9** **16**

The flow reaction apparatus was set up with the reactor ~1.0 cm away from the LED puck. A thermometer was placed inside one of the test tubes to accurately measure the internal reaction temperature, and the temperature was regulated to 50 °C using a slow stream of air directed at the reactor. Coronaridine **4** (33.9 mg, 0.1 mmol, 1.0 equiv) was placed in a 5ml round-bottom flask. $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ **5** (2.8 mg, 2.5 mol%) was then added to the flask before the addition of methanol (1.0 ml). The resulting solution was degassed *via* the freeze-pump-thaw method (3 cycles) and the flask was backfilled with nitrogen. TMSCN (25 µl, 0.2 mmol, 2.0 equiv) was added to the solution. The reaction mixture was then pumped through the photoreactor at a flow rate of 32.2 µl/min (t_R = 43 minutes) and collected in a 25 ml round bottom flask. Upon complete uptake of the reaction solution an additional 0.5 ml of methanol was added to the reaction flask to rinse any residue through the reactor. Upon elution the reaction mixture was poured into a separatory funnel containing a mixture of saturated $NaHCO_3$ and water. The resulting solution was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Crude ^{1}HNMR analysis in $CDCl_3$ revealed two distinct doublets (δ 4.77 and δ 5.20, **9** and **16** respectively) characteristic of the C16 benzylic methine (see above) present in the ring opened products. Yields were determined for each residence time by ^{1}HNMR with diethylphenyl malonate as an internal standard.

t_R = 42 minutes 1:12 dr **9**:**16**, 25% yield

Further confirmation of the structure of **16** was obtained through further reduction of the product to the known compound **17**.



16 **17** **11**

The above fragmentation protocol was repeated on a 0.25 mmol scale without the final addition of the diethyl phenyl malonate as an internal standard. The crude reaction mixture was dissolved

in 2.5 ml of methanol and cooled to zero degrees in an ice bath. Sodium borohydride (37.7 mg, 1.0 mmol, 4.0 equiv) was added in one portion and the reaction was allowed to stir for 20 minutes at zero degrees, at which point the reaction was removed from the ice bath and stirred for an additional 20 minutes. The reaction mixture was poured into saturated sodium bicarbonate, and the resulting solution was extracted with ethyl acetate (x3). The organic phases were combined and washed with brine before drying over sodium sulfate and concentrating.

The crude reaction mixture was purified on silica gel with a gradient of 100% hexanes to 20% ethyl acetate 80% hexanes to yield known compound **17** (16.1 mg, 19% yield, 6:1 dr **17**:**11**, 2 steps).[7]

IR (neat): 3381, 2917, 1716, 1460, 1433, 1335, 1258, 1154, 909, 739 cm^{-1};

^{1}H NMR ($CDCl_3$, 700 MHz, 6:1 mixture of diastereomers with integrals normalized for the major isomer): δ 8.64 (br. s, 0.17H), 8.59 (br. s, 1H), 7.51 (app d, overlap, *J* = 8.0 Hz, 1.09H), 7.34 (app ddd, overlap, *J* = 8.0, 0.8, 0.8 Hz, 1.03H), 7.15 (app ddd, overlap, *J* = 8.1, 7.0, 1.1 Hz, 1.08H), 7.09 (app ddd, overlap, *J* = 7.9, 6.9, 1.0 Hz, 1.08H), 5.55 (dd, *J* = 12.1, 1.7 Hz, 1H), 5.09 (d, *J* = 10.8 Hz, 0.16H), 3.72 (s, 0.34 H), 3.71 (s, 3H), 3.05 (dd, *J* = 10.6, 4.4 Hz, 1H), 2.92-2.90 (m, overlap, 0.35H), 2.89-2.86 (m, overlap, 1.93H), 2.67 (dd, *J* = 8.9, 8.9 Hz, 0.18H), 2.64-2.61 (m, overlap, 1.03H), 2.57-2.47 (m, overlap, 1.41H), 2.31 (app ddd, overlap, *J* = 13.5, 9.4, 5.1 Hz, 1.26H), 2.26 (app dd, overlap, *J* = 11.8, 1.9 Hz, 1.05H), 2.18 (dd, *J* = 12.8, 6.1 Hz, 0.2H), 2.14-2.06 (m, overlap, 2.29H), 1.98 (d, *J* = 14.6 Hz, 1H), 1.88-1.79 (m, overlap, 2.34H), 1.66 (ddd, *J* = 12.9, 4.3, 1.9 Hz, 1H), 1.53 (m, overlap, 0.34H), 1.36-1.33 (m, overlap, 0.41H), 1.22-1.15 (m, overlap, 2H), 1.07 (app ddd, overlap, *J* = 12.9, 12.9, 4.9 Hz, 1.11H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 0.54H);

^{13}C NMR ($CDCl_3$, 175 MHz): δ 175.7, 135.8, 133.9, 127.8, 121.4, 118.9, 118.2, 111.6, 110.6, 60.7, 55.9, 54.1, 52.1, 42.0, 40.4, 39.2, 36.1, 31.1, 27.8, 26.5, 11.4;

HRMS (ESI) *m/z* calculated for $C_{21}H_{28}N_2O_2^+$ ($[M+H]^+$) 341.2224, found 341.2232

$[\alpha]_D^{26}$ = -6.5 (c 0.81, $CHCl_3$)

Computational Studies

The Gaussian 09 program was used to optimize structures at the (B3LYP/6-31G*) level of theory. Structures were minimized with no symmetry restrictions, and vibrational modes were generated simultaneously to ensure the absence of imaginary frequencies corresponding to unstable structures or transition states.

Homodesmotic Reactions

The homodesmotic reactions used to evaluate ring strain for this work are listed below and were balanced in accordance with the standardized definition of homodesmotic reactions (RC4) proposed by Wheeler *et al*.[9]

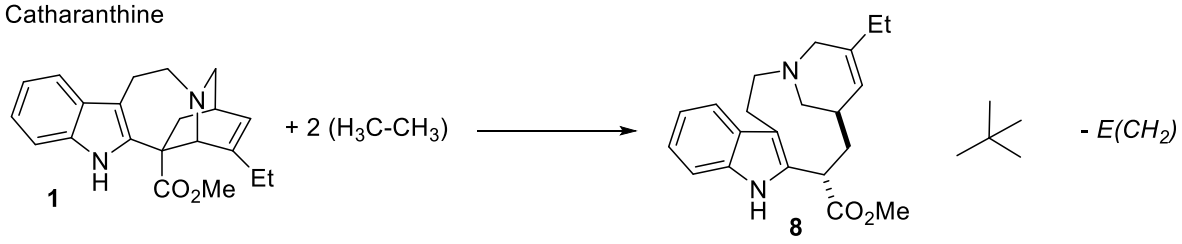
To ensure minimal energy distortion due to steric clashing around the ring-opening sites, hydrogen atoms were added across each broken carbon-carbon bond. All methyl, methine, and quaternary carbon substituents balance out on each side of the reaction and are incorporated in "strain-free" reference molecules in accordance with the guidelines put forth by Schleyer and coworkers.[10] To balance the number of methylenes on both sides of each reaction, a methylene correction term, as reported by Khoury and coworkers,[11] was incorporated. This term is abbreviated $E(CH_2)$ and is the (B3LYP/6-31G*) optimized energy difference between n-pentane and n-butane.

Complete Reference 26:

Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

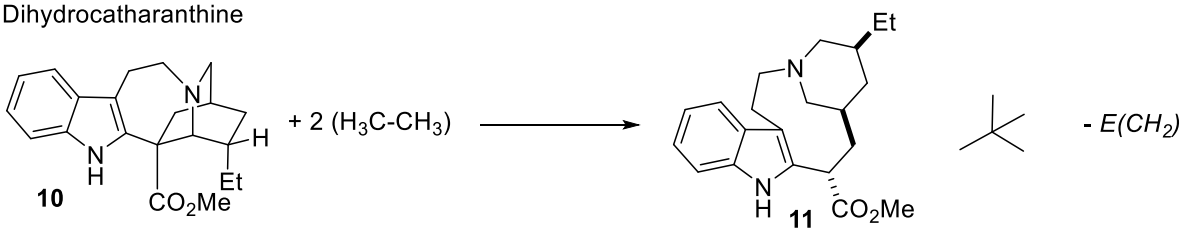
Scheme S1. Homodesmotic Reactions of selected bicyclic compounds

A. Catharanthine



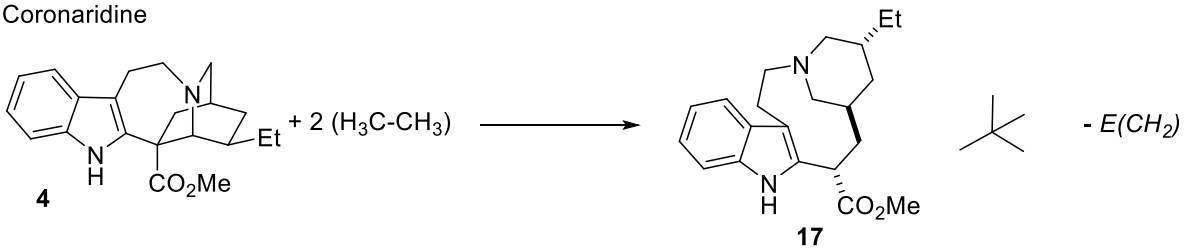
1 **8**

B. Dihydrocatharanthine



10 **11**

C. Coronaridine



4 **17**

Table S2. Total energies of all reference compounds (B3LYP/6-31G*)

Structure	Total Energy (Hartrees) B3LYP/6-31G*
Ethane	-79.83041744
isobutane	-158.4588127
n-butane	-158.4580421
n-pentane	-197.7717819
neopentane	-197.7729563
E(CH2)	-39.31373986

Table S3. Total energies of all bicyclic compounds (B3LYP/6-31G*)

Structure	Total Energy (Hartrees) B3LYP/6-31G*
1	-1074.622737
8	-1075.833776
10	-1075.846281
11	-1077.052450
4	-1075.854670
17	-1077.057331

Table S4. Strain release energies (kcal/mol) of structures **1**, **10**, and **4** in accordance with their homodesmotic reactions reported in Scheme S1

Structure	Strain Release Energy (kcal/mol)
1	-4.23
10	-0.00
4	+0.08

Structure 1

catharanthine

OPT FREQ B3LYP/6-31G(d) temperature=300.0 geom=(connectivity)

C	0.60834400	0.35105900	0.53573900
C	1.60148600	-0.45423600	-0.38893200
C	2.07364000	-1.12167400	2.00481600
C	0.90941000	-0.09878800	2.01339000
H	1.16215900	0.77198300	2.62289500
H	0.01546900	-0.55772700	2.44852700
H	2.30403900	-1.43977400	3.02640800
H	1.42035100	-0.20062200	-1.43447900
C	1.62068200	-2.34171800	1.16181800
H	2.36711300	-3.14879700	1.21231100
H	0.68660100	-2.73447100	1.59403400
N	1.43816700	-1.90099000	-0.22653700
C	3.02711900	-0.12327800	0.04533400
C	3.25754900	-0.48369100	1.31443300
H	4.21818700	-0.36536600	1.81124100
C	4.03725800	0.43895000	-0.91673100
H	3.63596600	1.34686600	-1.38604300
H	4.93480100	0.73810200	-0.35998800
C	4.43306100	-0.55790100	-2.02244100
H	5.15196100	-0.10338900	-2.71393200
H	4.88916600	-1.45576800	-1.59227700
H	3.56214100	-0.87690200	-2.60563500
C	0.83837900	1.86382700	0.38513600

O	0.64285500	2.68614800	1.26024100
O	1.20069400	2.20978900	-0.86578400
C	1.33578600	3.62219100	-1.10653900
H	1.64702500	3.71054500	-2.14745400
H	0.37975100	4.12764100	-0.94742700
H	2.08480700	4.05516100	-0.43933100
C	-0.85690800	0.10938300	0.19125600
C	-1.54078100	-1.00434000	-0.26015400
N	-1.77218200	1.13334800	0.42996800
C	-2.93858900	-0.64095900	-0.29803800
C	-3.04750900	0.70152700	0.14775200
H	-1.53088100	2.00494400	0.87996600
C	-1.05174000	-2.40220200	-0.53219200
H	-1.19461500	-3.01485400	0.37179600
H	-1.69537400	-2.86669800	-1.29215700
C	0.40183700	-2.54346700	-1.01625900
H	0.63794900	-3.61531800	-1.08264800
H	0.48049300	-2.14363600	-2.03537200
C	-4.10943300	-1.32975800	-0.66038200
C	-5.33290600	-0.67652400	-0.57210300
H	-6.24344200	-1.20112000	-0.84915000
C	-5.41515300	0.65841800	-0.12614900
H	-6.38587900	1.14305700	-0.06570200
C	-4.27479100	1.36610200	0.23770200
H	-4.33602500	2.39528100	0.58215400
H	-4.06249800	-2.36066700	-1.00214400

Structure 8

ring-opened catharanthine

OPT FREQ B3LYP/6-31G(d) temperature=300.0 geom=(connectivity)

C	0.29229000	0.82985200	0.27552900
C	2.69182800	-1.99387000	-0.51004700
C	1.71758300	-0.65283800	1.93078100
C	0.80423400	0.59120000	1.74909000
H	1.36429500	1.46971900	2.09458200
H	-0.06801100	0.50605300	2.40710800
H	1.80857900	-0.80213100	3.01761300
H	2.77329200	-1.76774900	-1.58237000
C	1.12198800	-1.93250000	1.31989200
H	1.61103000	-2.82274800	1.76194100
H	0.05830100	-1.99583300	1.55700900
N	1.30395600	-1.86336200	-0.12226900
C	3.57698900	-1.04882200	0.27923200
C	3.10586800	-0.43616800	1.37333700
H	3.74884300	0.26139600	1.91198500
C	4.97833000	-0.82519400	-0.24153200
H	5.58693400	-0.36924200	0.54873500
H	5.44530400	-1.79422200	-0.47312400
C	5.03157400	0.06751300	-1.49599400
H	6.06787300	0.23013000	-1.81363000
H	4.49455100	-0.38192100	-2.33890200
H	4.57435400	1.04221400	-1.29353000
C	0.46780400	2.30906600	-0.04079800

O	-0.28599800	3.21879800	0.26287600
O	1.64177700	2.52882900	-0.66498600
C	1.95290900	3.90702000	-0.93758200
H	2.92181900	3.89231900	-1.43705200
H	1.19201600	4.35030500	-1.58478200
H	2.00683000	4.47970900	-0.00797100
C	-1.12707200	0.34102300	0.05787200
C	-1.67209300	-0.87964200	-0.32608800
N	-2.16093700	1.22729700	0.33609300
C	-3.10878400	-0.70169700	-0.29520800
C	-3.37504100	0.63148600	0.10742700
H	-1.98073500	2.20960300	0.50543800
C	-4.19421300	-1.55297400	-0.57069200
C	-5.48838100	-1.05844500	-0.45813200
H	-6.33264500	-1.70851000	-0.67237800
C	-5.72642200	0.27578300	-0.06951900
H	-6.74888700	0.63585600	0.00812500
C	-4.67456700	1.13802200	0.21834200
H	-4.85452600	2.16602100	0.52215200
H	-4.02984700	-2.58501300	-0.87034200
H	3.07293100	-3.03393300	-0.39247200
H	0.95344600	0.27781800	-0.38707400
C	-1.12372600	-2.26440300	-0.61185700
H	-1.71525500	-2.69023200	-1.43384200
H	-1.35966400	-2.90894300	0.24914400
C	0.34180300	-2.49515300	-1.00209100

H	0.51815900	-2.09157300	-2.00923500
H	0.48624200	-3.59320900	-1.07878800

Structure 10

dihydrocatharanthine

OPT FREQ B3LYP/6-31G(d) temperature=300.0 geom=(connectivity)

C	0.65860300	0.21571300	0.34169200
C	1.53066500	-0.63038800	-0.64890000
C	1.87219600	-1.56318600	1.69352100
C	1.03454400	-0.27154300	1.78745000
H	1.59797400	0.50924000	2.30799600
H	0.12351700	-0.44866500	2.36768800
H	1.98580800	-1.99719500	2.69402400
H	1.36572400	-0.27940800	-1.66961100
C	1.15681200	-2.57522800	0.78046700
H	1.66536400	-3.55141700	0.80957600
H	0.13356100	-2.73488500	1.15982800
N	1.16777300	-2.04619000	-0.58985500
C	3.05203700	-0.58438400	-0.31405300
C	3.24764900	-1.22043000	1.09844400
H	3.87009100	-2.12097600	1.04053900
C	3.76183800	0.77257200	-0.47288600
H	3.45940100	1.23051500	-1.42292900
H	3.45487800	1.46520700	0.32227800
C	5.29080400	0.64169300	-0.44901400
H	5.77214900	1.61924000	-0.56629200
H	5.64738500	0.20996700	0.49334100

H	5.64248500	-0.00427000	-1.26294200
C	0.91192300	1.72442300	0.18113800
O	0.98463900	2.52405100	1.09579800
O	0.95168500	2.09223700	-1.11385400
C	1.08693900	3.50256500	-1.35845900
H	1.10063200	3.60893200	-2.44323500
H	0.24138300	4.04655200	-0.92962200
H	2.01472100	3.88006200	-0.92116400
C	-0.84508900	0.06123900	0.11210600
C	-1.65503500	-0.91159900	-0.44532800
N	-1.65860500	1.06836300	0.63847500
C	-3.01931900	-0.47195100	-0.25456800
C	-2.98383000	0.76909000	0.42945800
H	-1.30872300	1.86166500	1.15652000
C	-1.33340100	-2.26353300	-1.02250200
H	-1.60371000	-3.03031700	-0.28004000
H	-1.99223100	-2.46009300	-1.88025000
C	0.11510000	-2.49330100	-1.48458200
H	0.24795900	-3.56930000	-1.67117200
H	0.27617600	-1.98995800	-2.44550000
C	-4.26695600	-1.02224300	-0.59497400
C	-5.42498300	-0.33175600	-0.25636400
H	-6.39468900	-0.74814200	-0.51567000
C	-5.36367000	0.90299800	0.42084800
H	-6.28525300	1.42033600	0.67369200
C	-4.14377900	1.47112900	0.77226600

H	-4.09512200	2.42232400	1.29613700
H	-4.32883400	-1.97476300	-1.11510900
H	3.49169400	-1.25993900	-1.05741800
H	3.76461200	-0.52151500	1.76888600

Structure 11

ring-opened dihydrocatharanthine

OPT FREQ B3LYP/6-31G(d) temperature=300.0 geom=(connectivity)

C	-0.15908100	1.37225700	-0.00241800
C	3.17650100	-1.92279900	-0.13029400
C	1.70938700	0.17302900	1.45452900
C	0.61862500	1.26365200	1.35404200
H	1.10739400	2.22774200	1.55389000
H	-0.12191400	1.12332100	2.14998200
H	2.03166000	0.20709300	2.50639900
H	3.47649500	-2.00233500	-1.18203300
C	1.24729500	-1.29725300	1.17889700
H	1.66110700	-1.93729800	1.96998000
H	0.16281300	-1.39094200	1.24662000
C	3.90645200	-0.70970700	0.52793700
C	2.95585700	0.49593400	0.60365100
H	3.47898600	1.36129200	1.03254300
C	5.22420400	-0.36457000	-0.18570400
H	5.00395900	-0.08534700	-1.22693500
H	5.65718800	0.53007800	0.28387700
C	6.26610000	-1.49010100	-0.16654400
H	7.19391100	-1.17599400	-0.65795500

H	6.51570900	-1.77854000	0.86218200
H	5.90792000	-2.38755700	-0.68373700
C	-0.61315300	2.82149200	-0.14305500
O	-1.55176000	3.33413500	0.44031100
O	0.20440800	3.51238400	-0.95875100
C	-0.09333200	4.91430800	-1.09923300
H	0.66185700	5.30393100	-1.78190400
H	-1.09549700	5.05139500	-1.51269700
H	-0.03465100	5.41643200	-0.13019700
C	-1.31872000	0.40714100	-0.09686200
C	-1.42060900	-0.85894000	-0.64216700
N	-2.51270900	0.73370600	0.53575900
C	-2.76234100	-1.31314600	-0.35647200
C	-3.42042100	-0.28427700	0.36821700
H	-2.69801900	1.67115300	0.86922400
C	-0.43809700	-1.71131300	-1.41258900
H	-0.58846400	-2.75851300	-1.11788300
H	-0.70201400	-1.66611900	-2.48084200
C	1.07326200	-1.43989300	-1.32915800
H	1.53361900	-2.04064900	-2.12290100
H	1.28069700	-0.39073200	-1.60686600
C	-3.46826600	-2.49329200	-0.65037100
C	-4.78758000	-2.61342100	-0.23109200
H	-5.34243400	-3.52075300	-0.45469000
C	-5.42321800	-1.57395000	0.47903700
H	-6.45703500	-1.69493200	0.79150600

C	-4.75006900	-0.39756700	0.78856000
H	-5.23767200	0.40347800	1.33809600
H	-2.99269500	-3.30014900	-1.20219500
H	4.15893100	-0.98569800	1.56441700
H	2.66903700	0.79120600	-0.41471600
H	0.53083200	1.18839100	-0.82457500
H	3.50895700	-2.84990900	0.35997300
N	1.70862000	-1.86909300	-0.08354700

Structure 4

Coronaridine

OPT FREQ B3LYP/6-31G(d) temperature=300.0 geom=(connectivity)

C	0.55199700	0.43848300	0.43166700
C	1.54692900	-0.35860900	-0.47352400
C	1.90886100	-1.10805600	1.92919800
C	0.91792300	0.07371400	1.92077800
H	1.35368100	0.94344700	2.42251500
H	0.00909400	-0.18878000	2.47130500
H	2.04079200	-1.46856200	2.95621600
H	1.38135300	-0.09060200	-1.51864000
C	1.34333100	-2.24491900	1.06017600
H	1.94553200	-3.15906800	1.17424500
H	0.32303900	-2.48433000	1.40357500
N	1.37187400	-1.80302600	-0.34114600
C	3.00240000	-0.01406600	-0.05982500
C	3.25541700	-0.66067600	1.33464500
H	3.91567700	-1.53225600	1.23755000
C	0.69155000	1.95421500	0.20565200

O	0.51262700	2.80109300	1.06161300
O	0.96160400	2.26281500	-1.07679700
C	1.01538300	3.66761200	-1.38273000
H	1.24821300	3.72412200	-2.44610200
H	0.05207400	4.13993500	-1.17394700
H	1.79070900	4.15931400	-0.79001400
C	-0.91172200	0.12275300	0.14272100
C	-1.57578200	-0.96736800	-0.39127300
N	-1.85597100	1.06534500	0.55226600
C	-2.98799200	-0.66904900	-0.30618400
C	-3.12607400	0.60955400	0.29147000
H	-1.61823500	1.92825500	1.02062400
C	-1.07638100	-2.31166000	-0.85248400
H	-1.29950600	-3.05052400	-0.06730400
H	-1.66739500	-2.63912200	-1.71955300
C	0.40960600	-2.41900700	-1.24048700
H	0.65879800	-3.48554200	-1.34038500
H	0.56312800	-1.97044300	-2.22917300
C	-4.14754300	-1.37296300	-0.67475900
C	-5.39049000	-0.79351700	-0.44787500
H	-6.29306700	-1.32920300	-0.72960100
C	-5.50178100	0.48088000	0.14455200
H	-6.48678300	0.90875400	0.31069500
C	-4.37289500	1.20049900	0.52082200
H	-4.45727700	2.18251000	0.97916300
H	-4.07646500	-2.35743900	-1.13022700
H	3.75670300	0.04356800	2.00909600
H	3.08087000	1.07806500	0.03563400

C	4.01593400	-0.45220300	-1.12754400
H	3.72924500	-0.00545400	-2.09023300
H	3.93870100	-1.53926800	-1.25485200
C	5.46239500	-0.05773800	-0.80856800
H	6.14181600	-0.37788100	-1.60678900
H	5.56413700	1.02994700	-0.70284100
H	5.81360400	-0.51421800	0.12411200

Structure 17

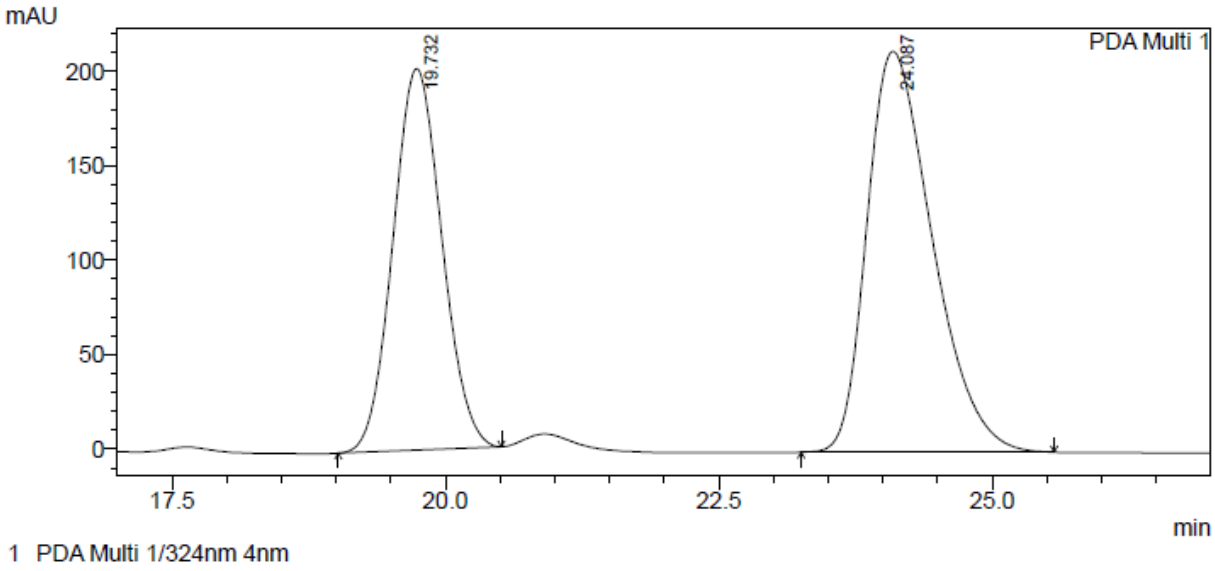
ring-opened coronaridine

C	0.20510200	0.90967600	0.18429000
C	2.73666700	-1.77842400	-0.45784400
C	1.59880300	-0.55143600	1.96121500
C	0.77870700	0.73194000	1.64626100
H	1.41597100	1.59338500	1.88645800
H	-0.07440200	0.78920100	2.33161000
H	1.50993000	-0.69512500	3.04753800
H	2.85244600	-1.76948200	-1.54754400
C	1.04846200	-1.81338300	1.27636100
H	1.51422600	-2.71341500	1.72848900
H	-0.02676500	-1.88838900	1.44726200
N	1.31834200	-1.71524700	-0.14996600
C	3.47858800	-0.57716500	0.16325200
C	3.11087000	-0.45061800	1.65436500
H	3.51932100	0.48548700	2.05976300
C	5.00464900	-0.66920400	-0.01584600
H	5.46848100	0.15554600	0.54310000
H	5.36638000	-1.59453700	0.45652100
C	5.48589200	-0.61515400	-1.47113000

H	6.58062300	-0.61992600	-1.52207400
H	5.12871000	-1.47152100	-2.05410200
H	5.13397900	0.29621100	-1.97046300
C	0.28592600	2.39478800	-0.14258100
O	-0.50827100	3.26252700	0.17767100
O	1.43078000	2.67522400	-0.79885100
C	1.66237800	4.06709800	-1.08280600
H	2.61686700	4.10105000	-1.60834000
H	0.86192300	4.46691500	-1.71011600
H	1.71129600	4.64494200	-0.15613900
C	-1.19164100	0.34530200	0.01472400
C	-1.68081900	-0.88916500	-0.39569600
N	-2.26225100	1.16106700	0.36515100
C	-3.12291400	-0.79550400	-0.30879600
C	-3.44878000	0.50482200	0.15280100
H	-2.13401700	2.15171300	0.53309200
C	-4.16667900	-1.69830100	-0.57983900
C	-5.48202800	-1.28385100	-0.40569700
H	-6.29535300	-1.97331900	-0.61635000
C	-5.78101400	0.01971300	0.04041300
H	-6.81882100	0.31719700	0.16517300
C	-4.77016400	0.93067900	0.32601500
H	-4.99750600	1.93485800	0.67442600
H	-3.95365400	-2.70701700	-0.92477300
H	3.19495300	-2.72439100	-0.09526200
H	0.86456900	0.38909600	-0.50116500
C	-1.06365900	-2.22678900	-0.75598400
H	-1.60220000	-2.62048200	-1.62940200

H	-1.30829700	-2.93410900	0.05142900
C	0.42790700	-2.37224600	-1.08768800
H	0.62610400	-1.93498000	-2.07635300
H	0.62967100	-3.45907900	-1.18458500
H	3.61256300	-1.26566600	2.19922800
H	3.13278700	0.32642300	-0.35902100

Chiral HPLC traces of (-)-pseudotabersonine: near-racemic sample



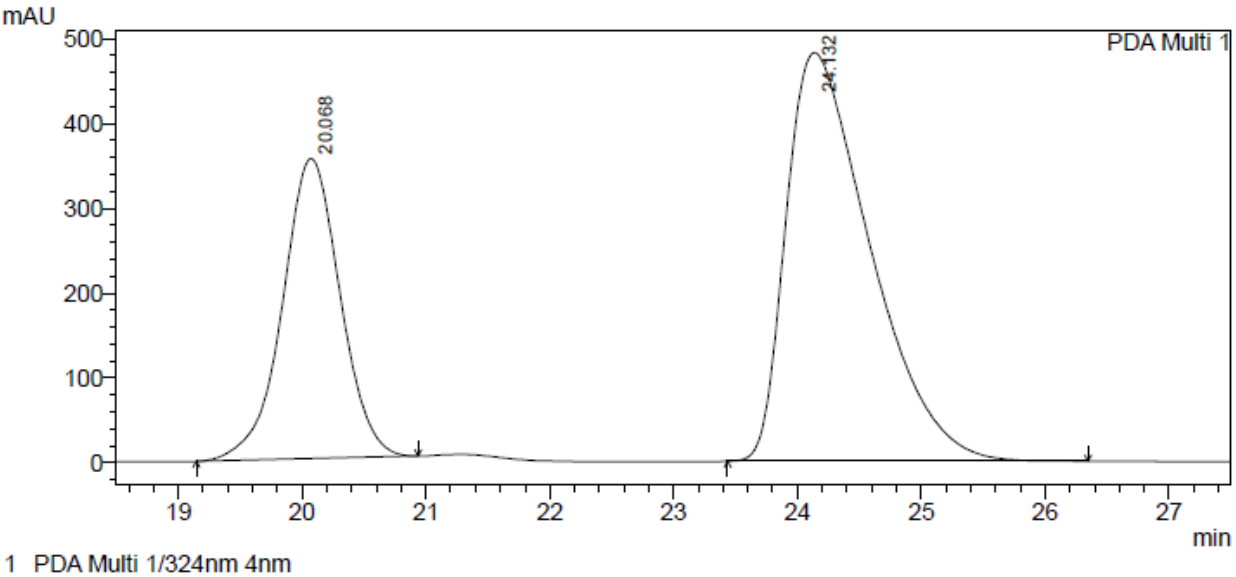
1 PDA Multi 1/324nm 4nm

PeakTable

PDA Ch1 324nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.732	6294034	201956	41.623	48.759
2	24.087	8827423	212235	58.377	51.241
Total		15121457	414191	100.000	100.000

Sample from rearrangement at reflux:



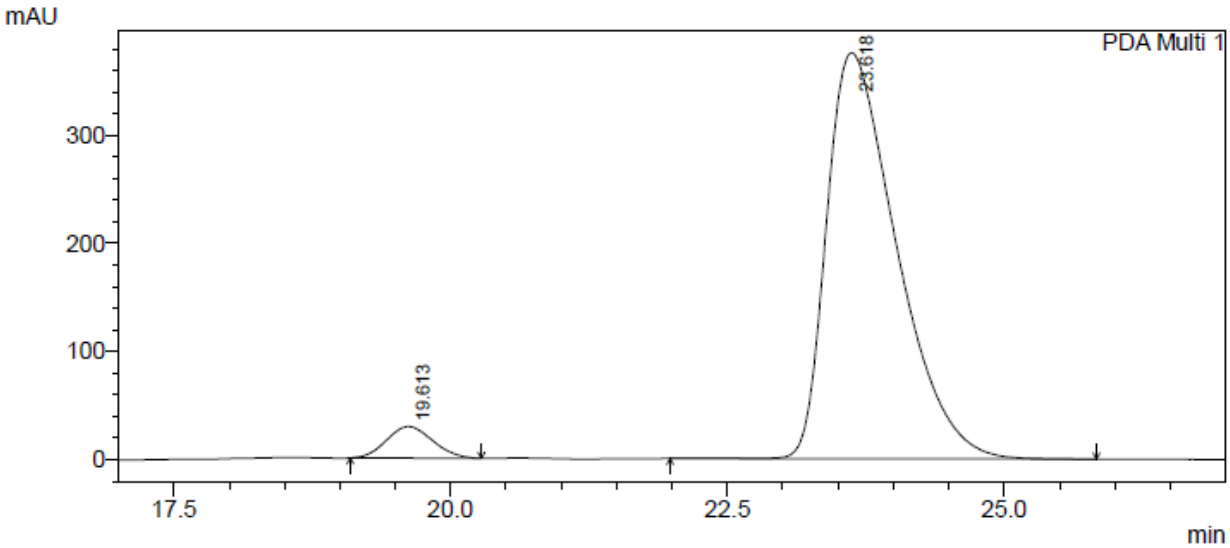
1 PDA Multi 1/324nm 4nm

PeakTable

PDA Ch1 324nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	20.068	11461227	353915	33.549	42.358
2	24.132	22701577	481610	66.451	57.642
Total		34162804	835525	100.000	

Sample from rearrangement at 60 °C:

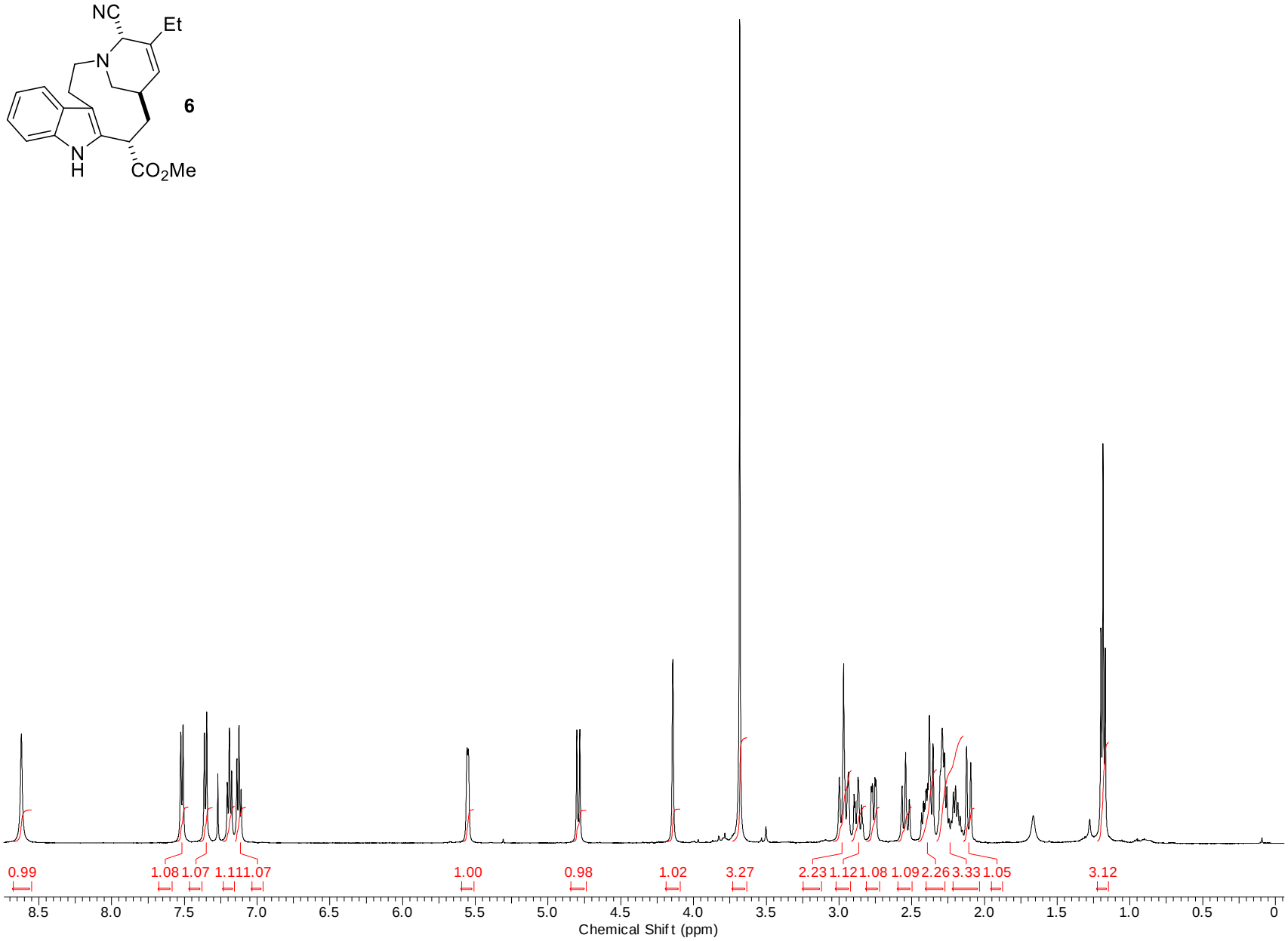


1 PDA Multi 1/324nm 4nm

PeakTable

PDA Ch1 324nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	19.613	842630	29134	4.867	7.200
2	23.618	16470181	375490	95.133	92.800
Total		17312812	404624	100.000	100.000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Et
N
6
N
H
CO2Me
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1.08
1.07
1.11
1.07
1.00
0.98
1.02
3.27
2.23
1.12
1.08
1.09
2.26
3.33
1.05
3.12
8.5
8.0
7.5
7.0
6.5
6.0
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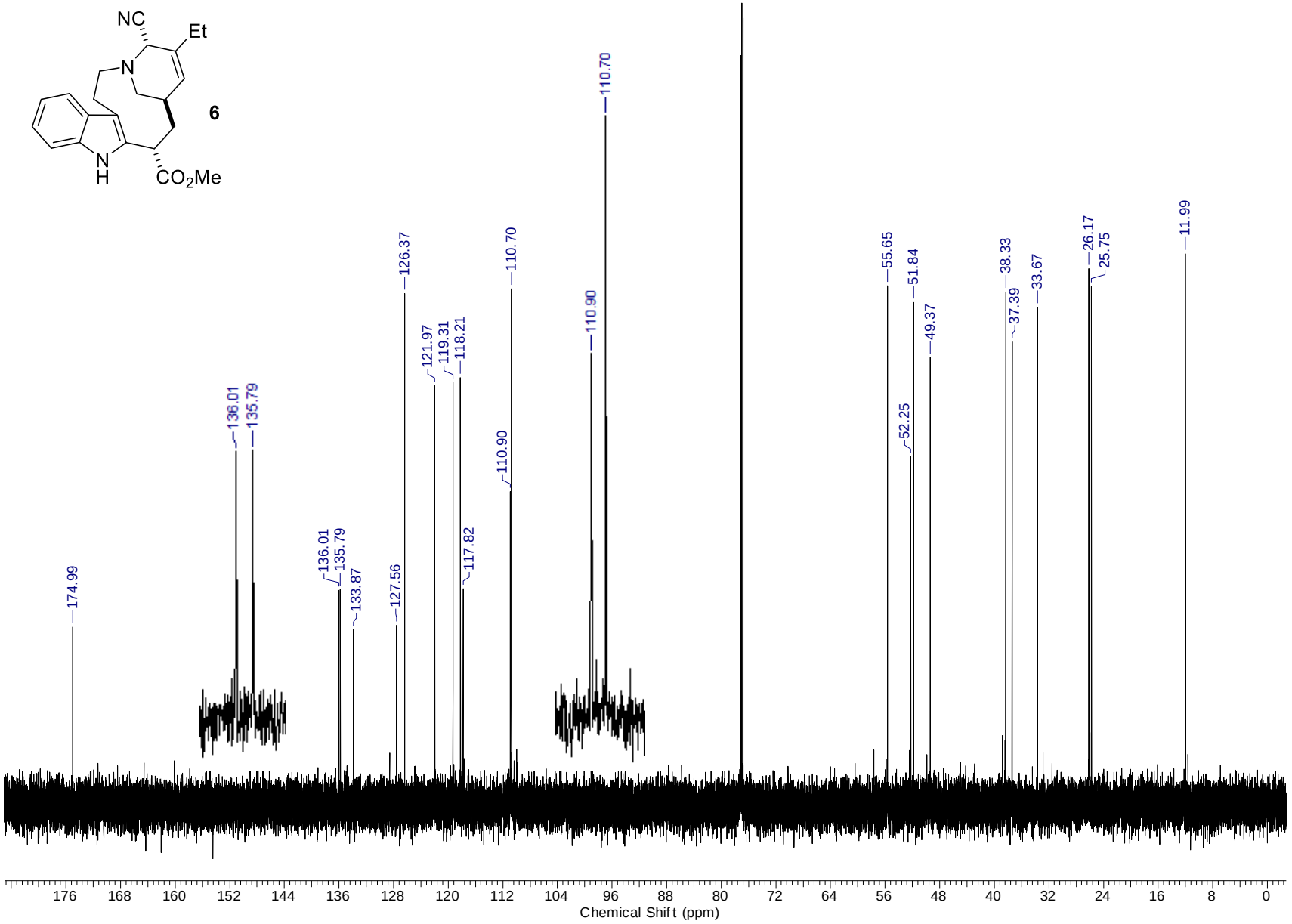
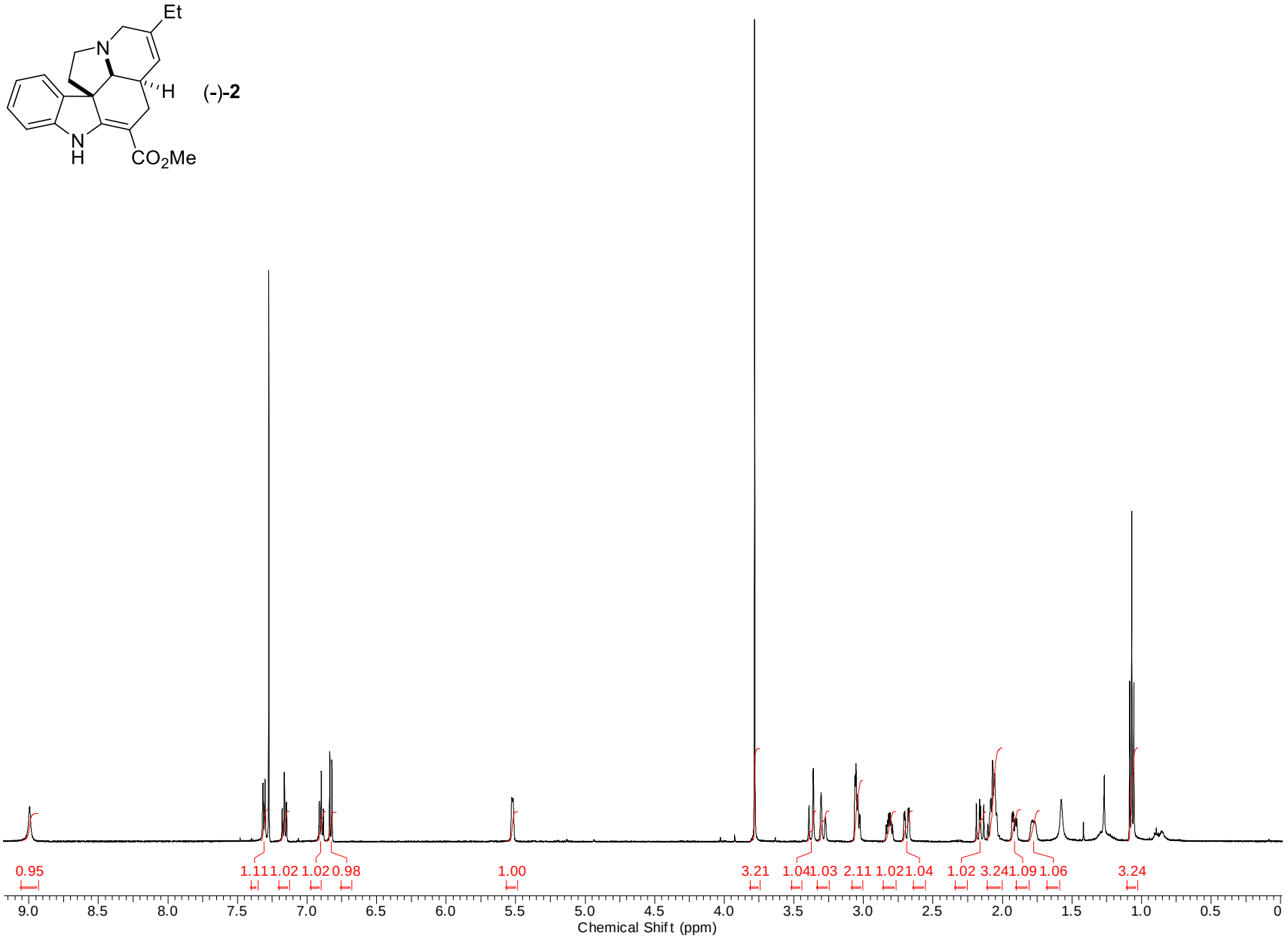
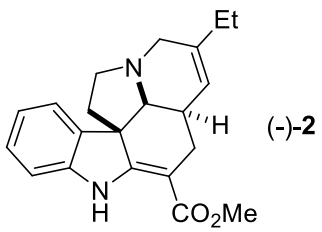
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

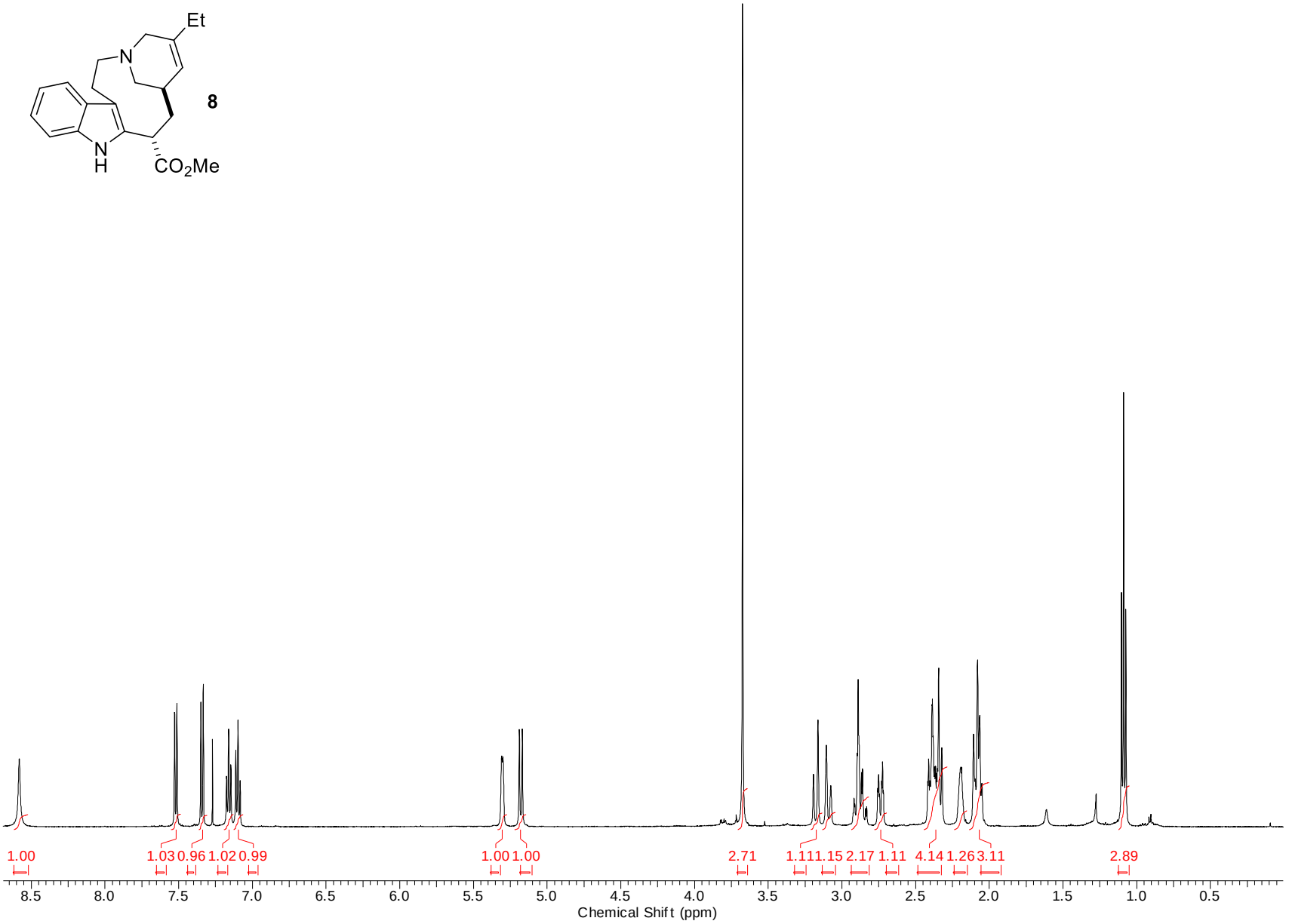

NC
Et
N
6
N
H
CO2Me
174.99
136.01
135.79
133.87
136.01
135.79
127.56
126.37
121.97
119.31
118.21
117.82
110.90
110.70
110.90
110.70
55.65
52.25
51.84
49.37
38.33
37.39
33.67
26.17
25.75
11.99
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

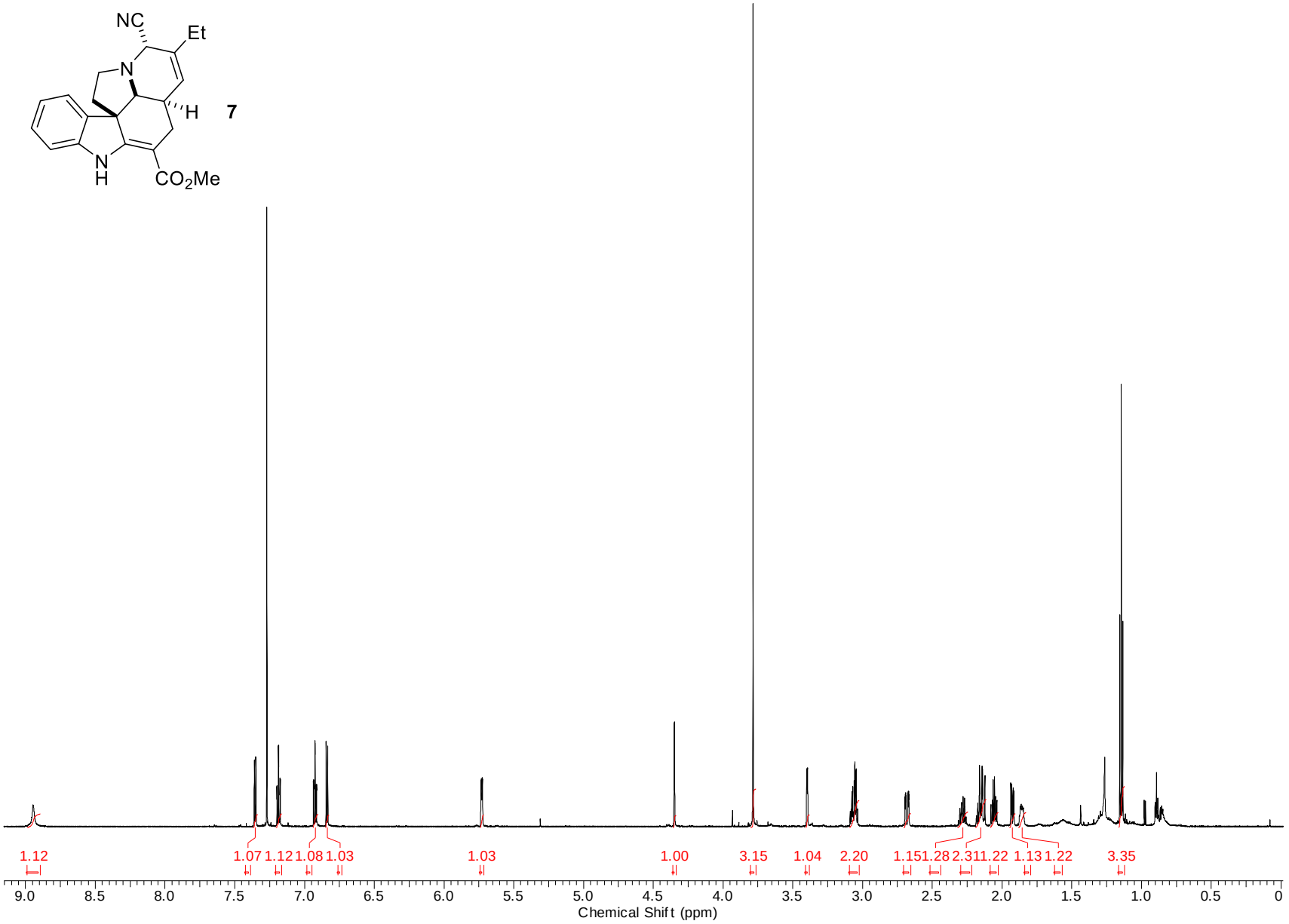

Et
N
H
H
N
H
CO2Me
(-)-2
0.95
1.11
1.02
1.02
0.98
1.00
3.21
1.04
1.03
2.11
1.02
1.04
1.02
3.24
1.09
1.06
3.24
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

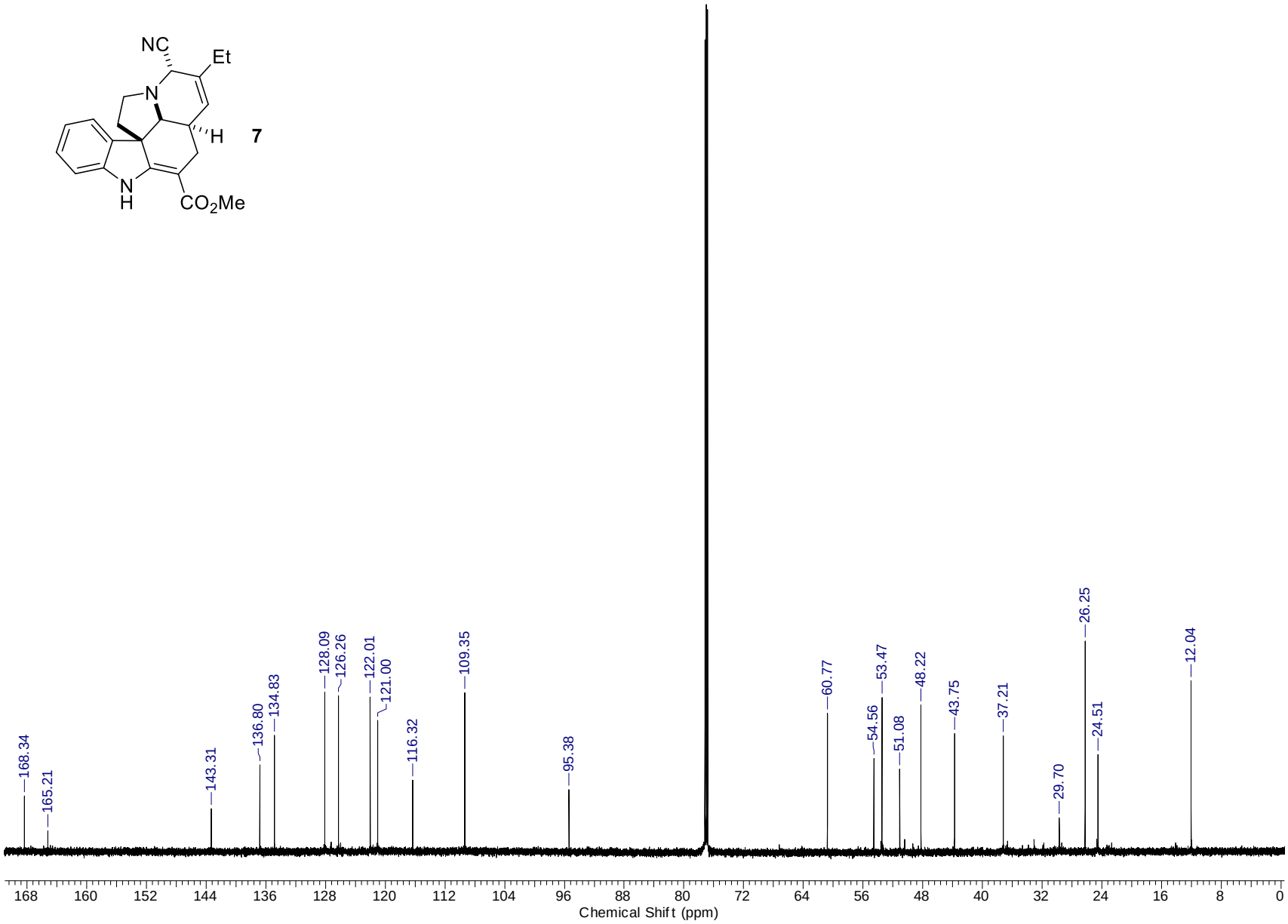

Et
N
H
N
H
CO2Me

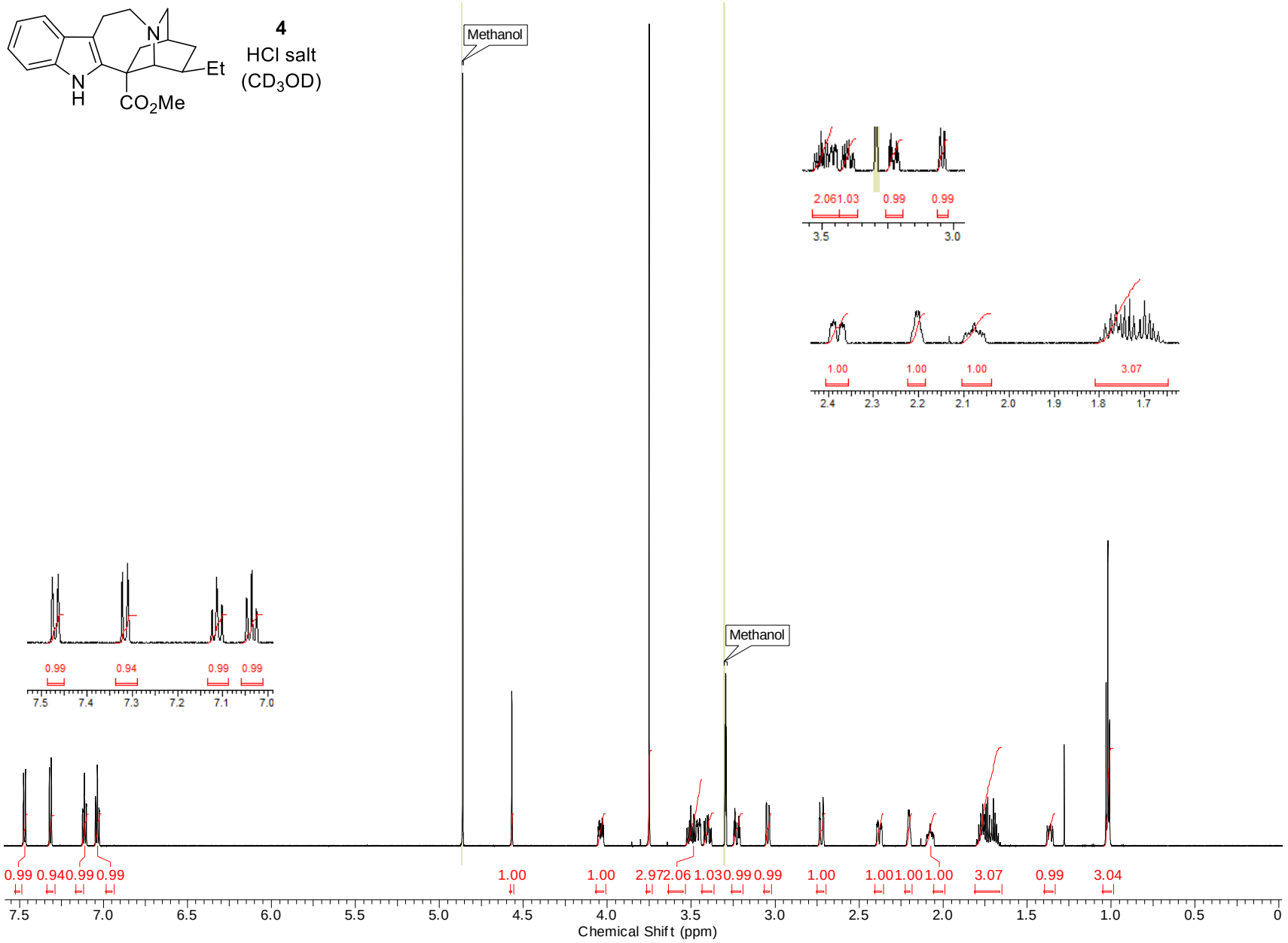
(-)-**2**

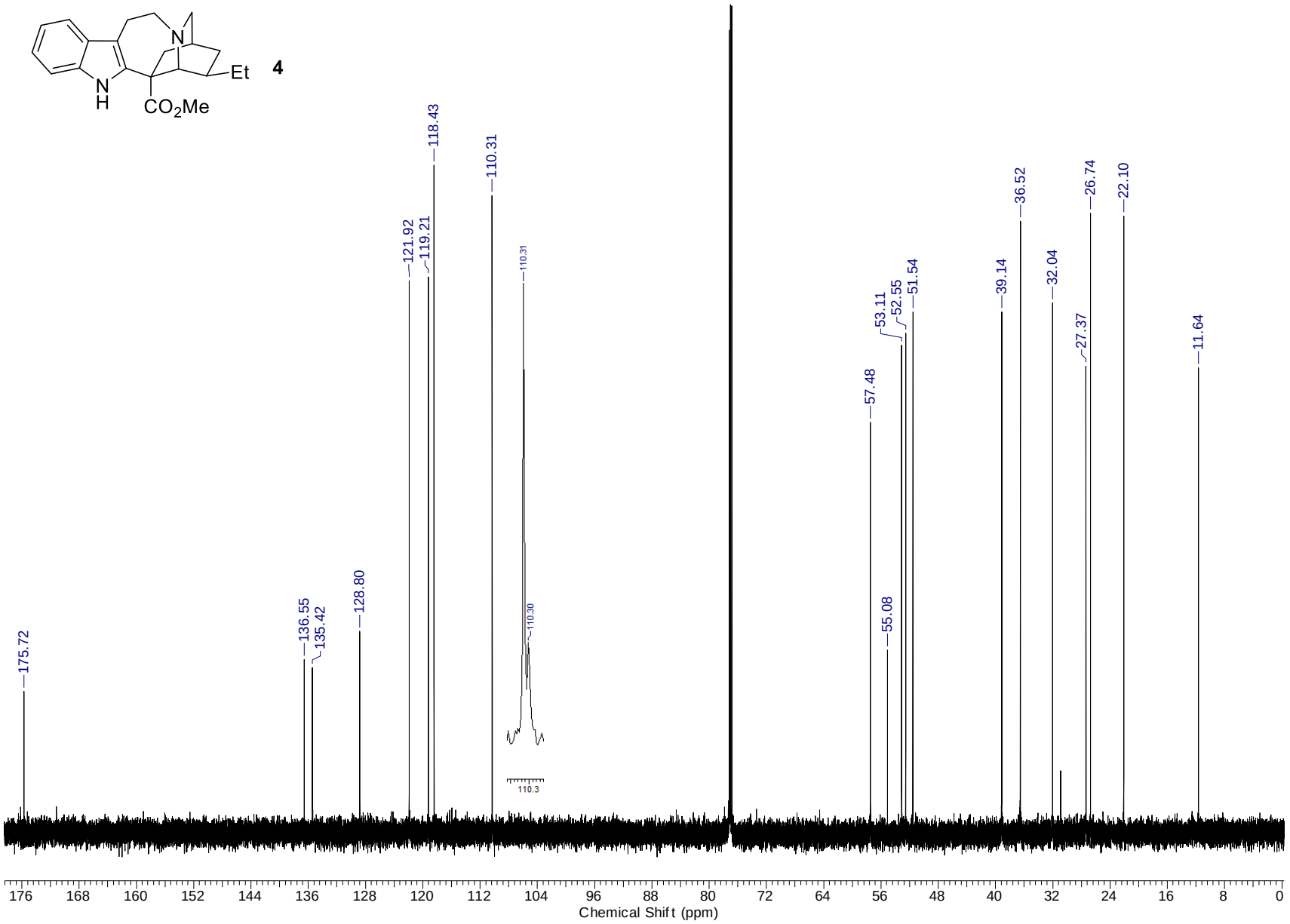
168.68
165.90
143.55
139.30
138.00
127.66
121.84
121.37
120.57
109.13
95.45
65.18
55.45
53.23
50.97
44.41
36.83
27.81
26.34
12.45
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

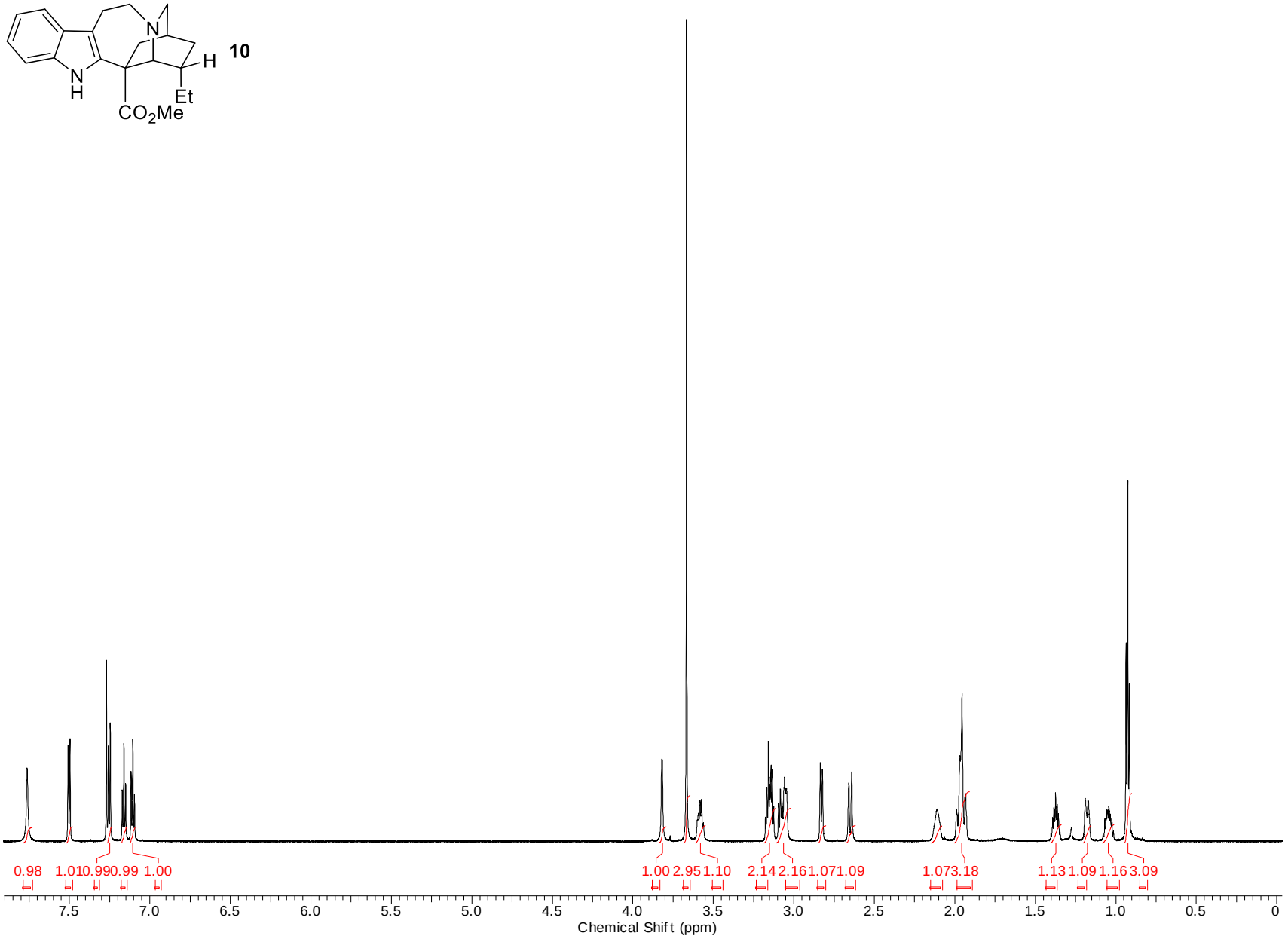

Et
N
8
N
H
CO2Me
1.00
1.03
0.96
1.02
0.99
1.00
1.00
2.71
1.11
1.15
2.17
1.11
4.14
1.26
3.11
2.89
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

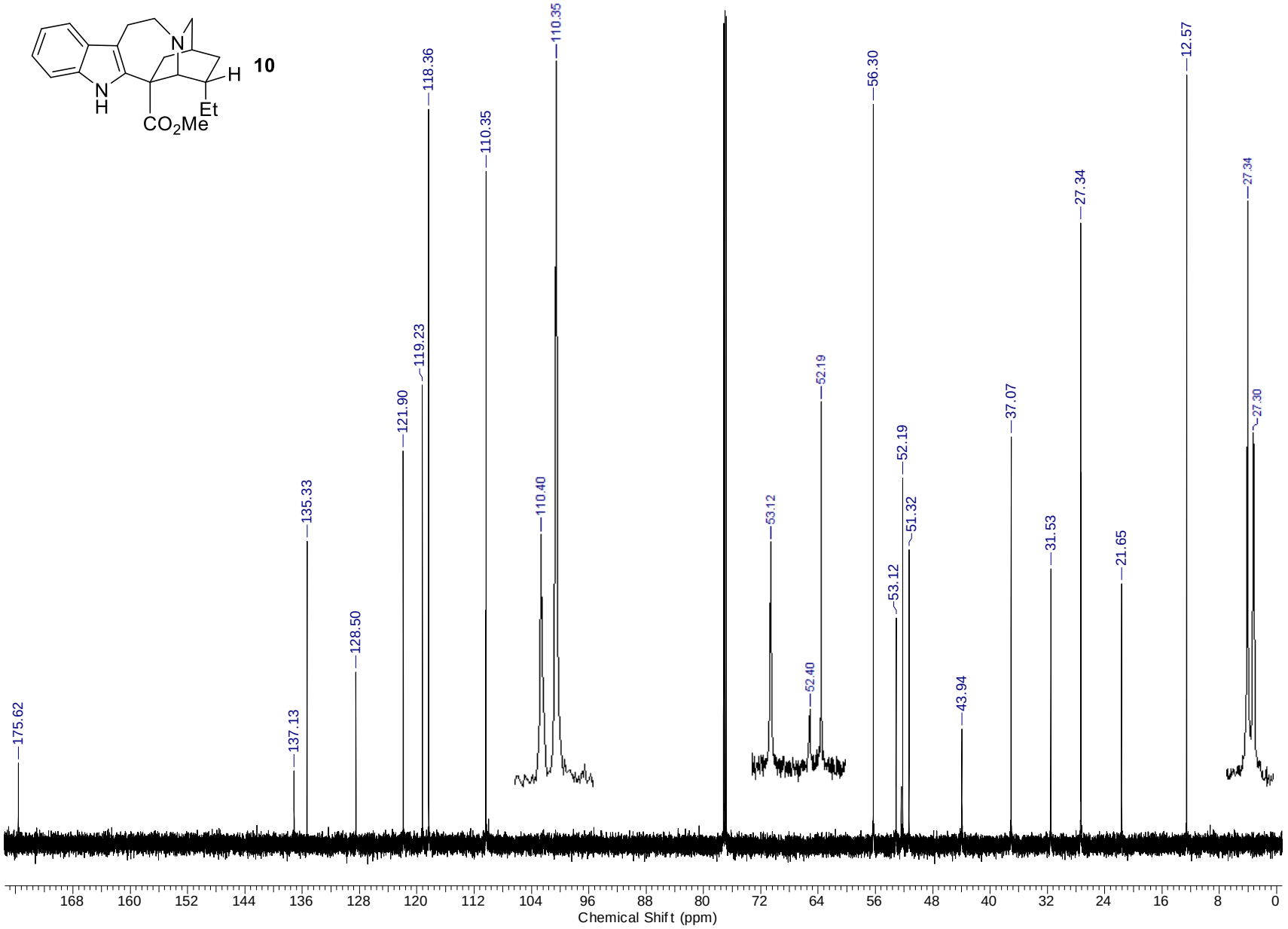

NC
Et
N
H
7
N
H
CO2Me
1.12
1.07
1.12
1.08
1.03
1.03
1.00
3.15
1.04
2.20
1.15
1.28
2.31
1.22
1.13
1.22
3.35
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

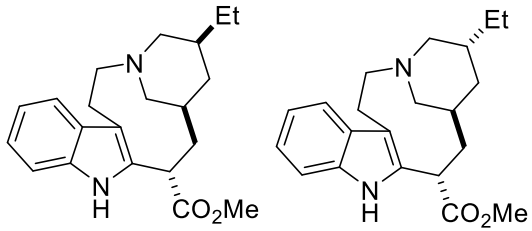

NC
Et
N
H
H
7
N
H
CO2Me
168.34
165.21
143.31
136.80
134.83
128.09
126.26
122.01
121.00
116.32
109.35
95.38
60.77
54.56
53.47
51.08
48.22
43.75
37.21
29.70
26.25
24.51
12.04
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


4
HCl salt
(CD3OD)
Et
N
H
CO2Me
Methanol
Methanol
2.06 1.03
0.99
0.99
1.00
1.00
1.00
3.07
0.99
0.94
0.99
0.99
0.99 0.94 0.99 0.99
1.00
1.00
2.97 2.06 1.03 0.99 0.99
1.00
1.00 1.00 1.00
3.07
0.99
3.04
Chemical Shift (ppm)


N
Et
4
N
H
CO2Me
175.72
136.55
135.42
128.80
121.92
119.21
118.43
110.31
110.31
110.30
110.3
57.48
55.08
53.11
52.55
51.54
39.14
36.52
32.04
27.37
26.74
22.10
11.64
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

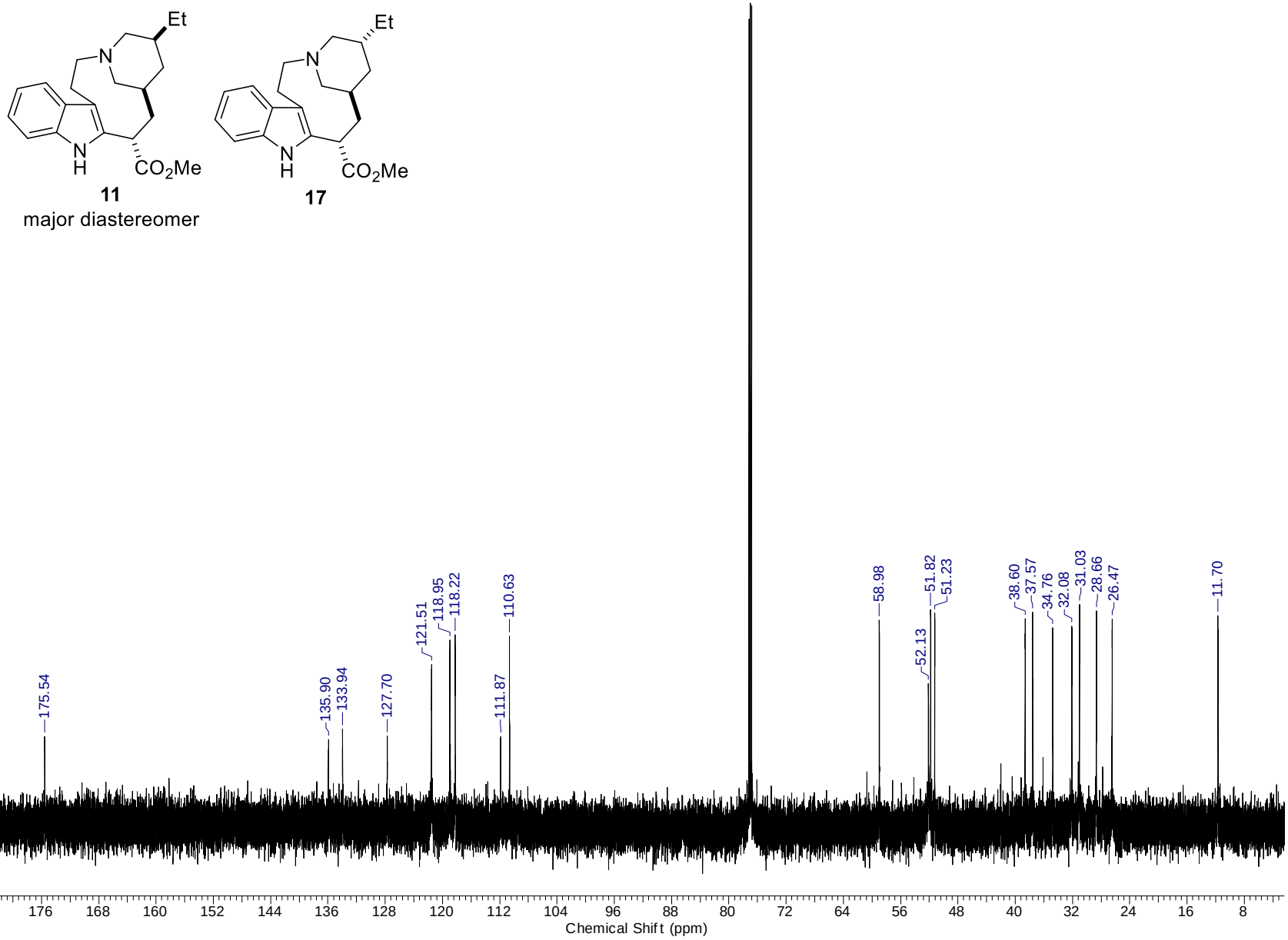

10
N
H
N
H
Et
CO2Me
0.98
1.01
0.99
0.99
1.00
1.00
2.95
1.10
2.14
2.16
1.07
1.09
1.07
3.18
1.13
1.09
1.16
3.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

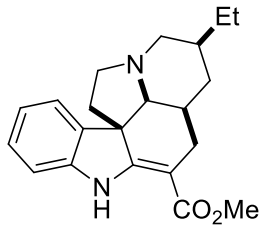

10
N
H
H
Et
CO2Me
175.62
137.13
135.33
128.50
121.90
119.23
118.36
110.35
110.40
110.35
53.12
52.40
52.19
56.30
53.12
52.19
51.32
43.94
37.07
31.53
27.34
21.65
12.57
27.34
27.30
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)



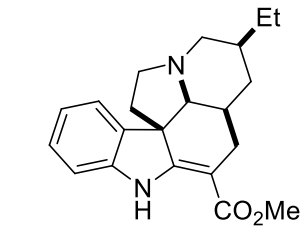
11
major diastereomer

17

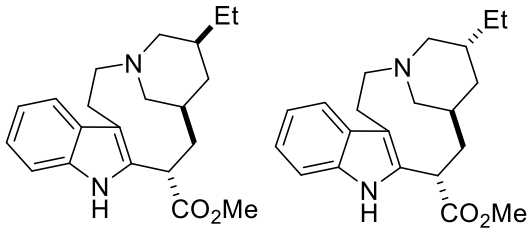

Et
N
H
CO2Me
11
major diastereomer
Et
N
H
CO2Me
17
175.54
135.90
133.94
127.70
121.51
118.95
118.22
111.87
110.63
58.98
52.13
51.82
51.23
38.60
37.57
34.76
32.08
31.03
28.66
26.47
11.70
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)



(-)-pseudovincadifformine **3**



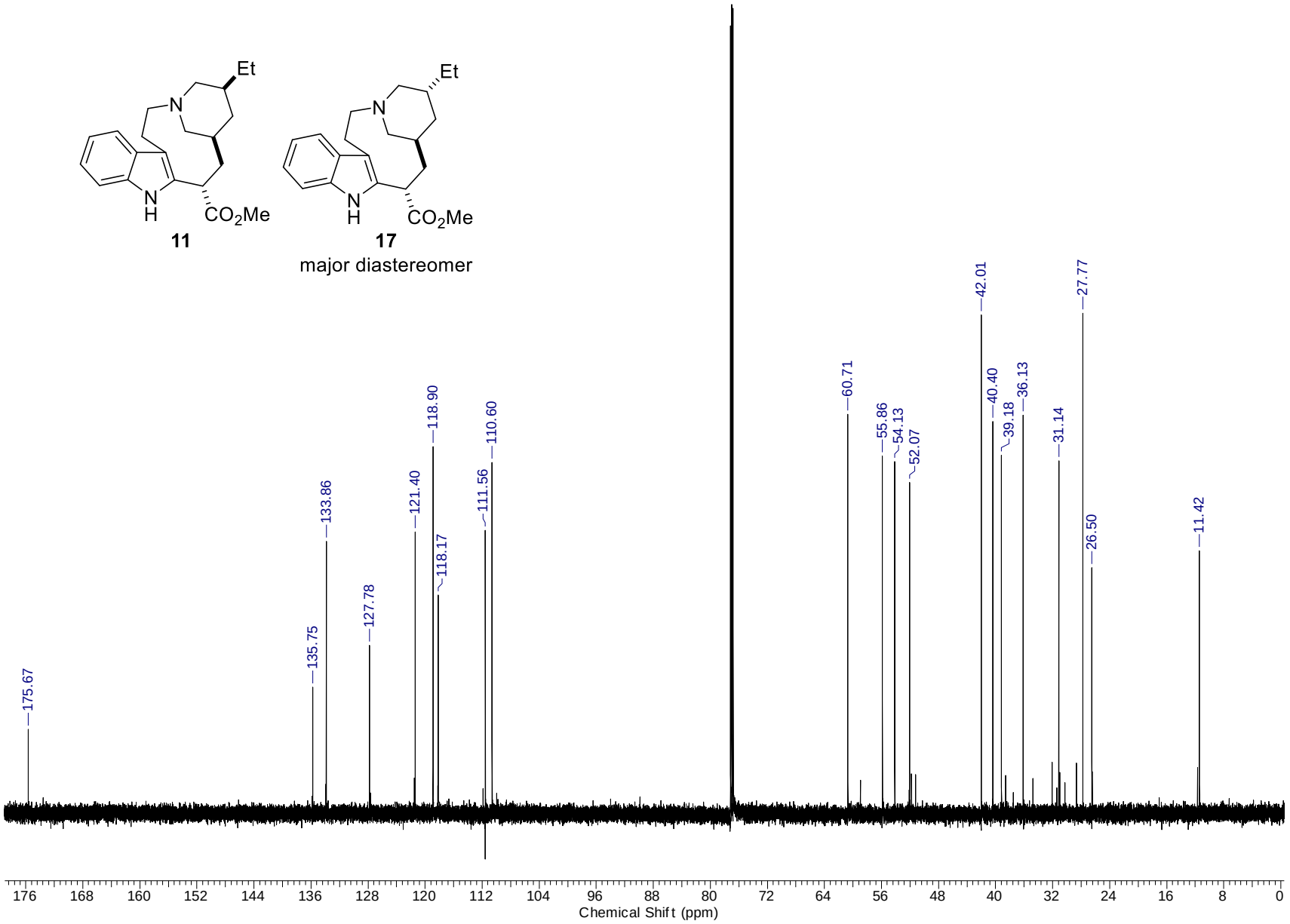
(-)-pseudovincadifformine **3**



11

17

major diastereomer


Et
N
N
H
CO2Me
11
Et
N
N
H
CO2Me
17
major diastereomer
175.67
135.75
133.86
127.78
121.40
118.90
118.17
111.56
110.60
60.71
55.86
54.13
52.07
42.01
40.40
39.18
36.13
31.14
27.77
26.50
11.42
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

References:

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