

Skeletal Diversity Through Radical Cyclization of Tetrahydropyridine Scaffolds.

Sivaraman Dandapani, Mihai Duduta, James S. Panek, John A. Porco, Jr**

*Department of Chemistry and Center for Chemical Methodology and Library
Development (CMLD-BU), Boston University, 590 Commonwealth Avenue,
Boston, Massachusetts 02215*

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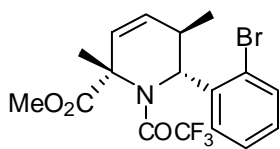
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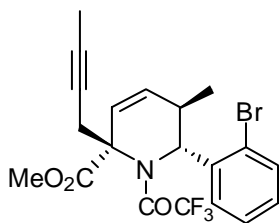
1. General Experimental Information: ^1H NMR and ^{13}C spectra were recorded at 400 MHz and 100.0 MHz respectively at ambient temperature with CDCl_3 as solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to CDCl_3 (^1H , δ 7.26; ^{13}C , δ 77.0) or benzene- d_6 (^1H , δ 7.15; ^{13}C , δ 128.0) or acetonitrile- d_3 (^1H , δ 1.94; ^{13}C , δ 1.24). Data are reported as follows: chemical shift, multiplicity (overlp=overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. All ^{13}C NMR spectra were recorded with complete proton decoupling. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Waters Q-TOF mass spectrometer under chemical ionization. Optical rotations were recorded at 589 nm, and are reported as $[\alpha]_D^{20}$ (concentration in grams/100 mL solvent). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-A plates. Methylene chloride, THF and toluene were purified by passing through two packed columns of neutral alumina.

2. Alkylation of Tetrahydropyridines

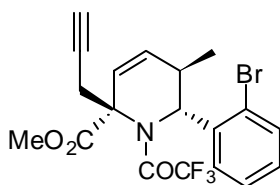
General Procedure 1 – Enolization and Alkylation of Dienolate from 1: A solution of lithium hexamethyldisilazide in THF (1.25 M, 0.16 mL, 0.20 mmol) was slowly added to a solution of (2*S*,5*R*,6*R*)-methyl 6-(2-bromophenyl)-2-(but-2-ynyl)-5-methyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate **1** (38 mg, 0.09 mmol, 1 equiv.) and methyl iodide (29 μL , 0.47 mmol, 5.2 equiv.) in THF (0.6 mL) and hexamethylphosphoramide (0.2 mL, 0.9 mmol, 10 equiv.) at -78°C and slowly warmed to 0°C over 5 h. The reaction was quenched by the addition of saturated brine (2 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated. Silica gel chromatography with ethyl acetate in hexane (from 0% to 20%) gave the desired product (2*S*,5*R*,6*R*)-methyl 6-(2-bromophenyl)-2,5-dimethyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate **15** as colorless oil (33 mg, 85% yield).

(2*S*,5*R*,6*R*)-Methyl 6-(2-bromophenyl)-2,5-dimethyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate **15:** ^1H NMR (400 MHz, CDCl_3) δ 8.15 (dd, $J = 7.90, 1.6$ Hz, 1H), 7.52 (dd, $J = 7.9, 1.2$ Hz, 1H), 7.27-7.23 (m, 1H), 7.09 (app. dt, $J = 7.7, 1.61$ Hz, 1H), 5.97 (d, $J = 10.2$ Hz, 1H), 5.88 (dd, $J = 10.2, 7.2$ Hz, 1H), 5.54 (s, 1H), 3.85 (s, 3H), 2.65 (app. p, $J = 7.3$ Hz, 1H), 1.89 (s, 3H), 1.43 (d, $J = 7.24$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 158.3 (q, $J = 36.5$ Hz), 143.0, 132.6, 129.0, 128.5, 128.3, 127.9, 127.2, 121.8, 116.0 (q, $J = 287.4$ Hz), 61.0 (q, $J = 3.4$ Hz), 63.0, 53.0, 36.0, 26.4, 20.7. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{17}\text{H}_{17}\text{NO}_3\text{F}_3\text{Br}+\text{Na}]$ 442.0242, found 442.0260. IR (thin film) ν_{max} 2956, 1746, 1694, 1266, 1146 cm^{-1} . $[\alpha]_D^{20} +32.7^\circ$ ($c = 1.0$, CHCl_3).

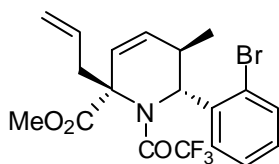


(2S,5R,6R)-Methyl

6-(2-bromophenyl)-2-(but-2-ynyl)-5-methyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 16: This compound was synthesized by general procedure 1 and isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.03 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.54 (dd, $J = 7.9, 1.2$ Hz, 1H), 7.27-7.23 (m, 1H), 7.12-7.08 (m, 1H), 6.04-5.92 (m, 2H), 5.50 (d, $J = 1.9$ Hz, 1H), 3.84 (s, 3H), 3.31 (qd, $J = 16.9, 2.6$ Hz, 1H), 3.20 (qd, $J = 16.9, 2.5$ Hz, 1H), 2.57 (app. dp, $J = 7.2, 1.9$ Hz, 1H), 1.79 (t, $J = 2.6$ Hz, 3H), 1.49 (d, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 159.2 (d, $J = 36.9$ Hz), 143.1, 132.8, 130.0, 128.6, 128.2, 127.4, 126.6, 122.5, 116.0 (q, $J = 286.4$ Hz), 79.9, 74.2, 64.8, 61.3, 61.2, 53.1, 36.7, 29.5, 21.3, 3.6. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{20}\text{H}_{19}\text{NO}_3\text{BrF}_3+\text{Na}]$ 480.0398, found 480.0413. IR (thin film) ν_{max} 1745, 1691, 1205, 1152 cm^{-1} . $[\alpha]_{\text{D}}^{20} +5.5^\circ$ ($c = 0.3$, CHCl_3).

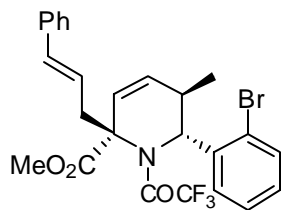
(2S,5R,6R)-Methyl

6-(2-bromophenyl)-5-methyl-2-(prop-2-ynyl)-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 17: This compound was synthesized by general procedure 1 and isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.09 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.28-7.24 (m, 1H), 7.54 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.10 (app. dt, $J = 7.7, 1.6$ Hz, 1H), 6.08-6.01 (m, 2H), 5.50 (d, $J = 1.8$ Hz, 1H), 3.87 (s, 3H), 3.53 (dd, $J = 17.0, 2.6$ Hz, 1H), 3.06 (dd, $J = 17.0, 2.8$ Hz, 1H), 2.67-2.59 (m, 1H), 2.12 (t, $J = 2.7$ Hz, 1H), 1.47 (t, $J = 7.13$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 170.6, 159.3 (q, $J = 37.1$ Hz), 142.8, 132.8, 130.3, 128.7, 128.2, 127.5, 126.3, 122.3, 115.8 (q, $J = 286.3$ Hz), 79.4, 72.0, 64.0, 61.4 (q, $J = 3.2$ Hz), 53.1, 36.5, 29.6, 21.4. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{19}\text{H}_{17}\text{NO}_3\text{BrF}_3+\text{Na}]$ 466.0242, found 466.0247. IR (thin film) ν_{max} 3301, 1747, 1694, 1204, 1154 cm^{-1} . $[\alpha]_{\text{D}}^{20} +6.0^\circ$ ($c = 0.3$, CHCl_3).

(2S,5R,6R)-Methyl

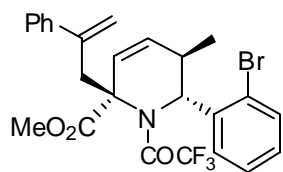
2-allyl-6-(2-bromophenyl)-5-methyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 18: This compound was synthesized by general procedure 1 and isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.07 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.53 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.27-7.23 (m, 1H), 7.11-7.07 (m, 1H), 5.98-5.83 (m, 3H), 5.45 (d, $J = 1.8$ Hz, 1H), 5.14-5.05 (m, 2H), 3.86 (s, 3H), 3.36 (dddd, $J = 14.0, 6.3, 1.3, 1.3$ Hz, 1H), 2.84 (dd, $J = 14.0, 8.62$ Hz, 1H), 2.64-2.57 (m, 1H), 1.42 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 159.0 (q, $J = 36.4$ Hz), 143.0, 133.2, 132.7, 129.1, 128.6, 128.2, 127.4, 127.0, 122.3, 119.2, 115.9 (q, $J = 286.5$ Hz), 65.7, 61.2 (q, $J = 3.2$ Hz), 52.9, 43.3, 36.3, 20.4. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{19}\text{H}_{19}\text{NO}_3\text{F}_3\text{Br}+\text{Na}]$ 468.0398, found 468.0429. IR (thin film) ν_{max} 3076, 1746, 1694, 1207, 1153 cm^{-1} . $[\alpha]_{\text{D}}^{20} +27.8^\circ$ ($c = 1.0$, CHCl_3).

(2S,5R,6R)-Methyl 6-(2-bromophenyl)-2-cinnamyl-5-methyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 19: This compound was synthesized



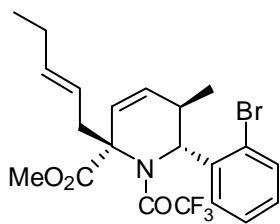
by general procedure 1 and isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.06 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.53 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.37-7.23 (m, 6H), 7.09 (ddd, $J = 7.7, 7.7, 1.6$ Hz, 1H), 6.40 (d, $J = 15.9$ Hz, 1H), 6.30-6.22 (m, 1H), 5.98 (dd, $J = 10.3, 6.6$ Hz, 1H), 5.90 (d, $J = 10.3$ Hz, 1H), 5.48 (d, $J = 1.2$ Hz, 1H), 3.89 (s, 3H), 3.49 (ddd, $J = 13.9, 6.5, 1.2$ Hz, 1H), 3.07 (dd, $J = 14.0, 8.5$ Hz, 1H), 2.60 (app. dp, $J = 7.1, 1.4$ Hz, 1H), 1.40 (d, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 159.0 (q, $J = 36.3$ Hz), 143.0, 137.0, 134.2, 132.7, 129.1, 128.6, 128.5, 128.2, 127.4, 127.3, 127.0, 126.2, 124.7, 122.3, 116.0 (q, $J = 286.5$ Hz), 66.1, 61.1 (q, $J = 3.3$ Hz), 53.0, 42.5, 36.2, 20.4. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{25}\text{H}_{23}\text{NO}_3\text{F}_3\text{Br}+\text{Na}]$ 544.0711, found 544.0735. IR (thin film) ν_{max} 3028, 1746, 1693, 1207, 1152 cm^{-1} . $[\alpha]_{\text{D}}^{20} +57.2^\circ$ ($c = 1.0$, CHCl_3).

(2S,5R,6R)-Methyl 6-(2-bromophenyl)-5-methyl-2-(2-phenylallyl)-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 20: This compound was synthesized by general procedure 1 and isolated



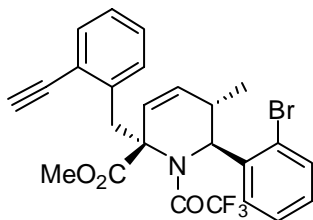
in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.91-7.89 (m, 1H), 7.52-7.50 (m, 2H), 7.40-7.24 (m, 5H), 7.11-7.09 (m, 1H), 5.69 (dd, $J = 10.3, 1.4$ Hz, 1H), 5.62 (dd, $J = 10.2, 4.6$ Hz, 1H), 5.33 (d, $J = 1.5$ Hz, 1H), 5.18 (b s, 1H), 5.08 (d, $J = 4.7$ Hz, 1H), 3.74 (d, $J = 14.3$ Hz, 1H), 3.65 (s, 3H), 3.40 (d, $J = 14.3$ Hz, 1H), 2.52-2.43 (m, 1H), 1.12 (d, $J = 7.26$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 160.1 (q, $J = 37$ Hz), 144.1, 142.6, 142.3, 132.7, 129.8, 128.8, 128.8, 128.0, 127.9, 127.3, 127.1, 123.6, 115.7 (q, $J = 286.5$ Hz), 119.9, 67.0, 61.6 (q, $J = 2.3$ Hz), 52.6, 42.0, 37.7, 19.4. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{25}\text{H}_{23}\text{NO}_3\text{F}_3\text{Br}+\text{Na}]$ 544.0711, found 544.0724. IR (thin film) ν_{max} 2953, 1742, 1689, 1202, 1157 cm^{-1} . $[\alpha]_{\text{D}}^{20} +27.9^\circ$ ($c = 1.0$, CHCl_3).

(2S,5R,6R)-Methyl 6-(2-bromophenyl)-5-methyl-2-((E)-pent-2-enyl)-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 21: This compound was synthesized by general procedure 1 and



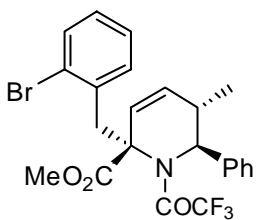
isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.01 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.52 (dd, $J = 7.9, 1.2$ Hz, 1H), 7.26-7.22 (m, 1H), 7.11-7.07 (m, 1H), 5.93 (dd, $J = 10.2, 6.4$ Hz, 1H), 5.83 (d, $J = 10.3$ Hz, 1H), 5.54-5.38 (m, 3H), 3.84 (s, 3H), 3.10 (dd, $J = 14.2, 5.9$ Hz, 1H), 2.97 (dd, $J = 14.2, 8.1$ Hz, 1H), 2.60-2.53 (m, 1H), 2.07-2.0 (m, 2H), 1.39 (d, $J = 7.3$ Hz, 3H), 0.97 (t, $J = 7.45$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 158.9 (d, $J = 36.5$ Hz), 143.1, 137.3, 132.7, 128.9, 128.6, 128.2, 127.3, 127.1, 123.1, 122.5, 116.0 (d, $J = 288.4$ Hz), 66.3, 61.1 (q, $J = 3.2$ Hz), 52.8, 41.3, 36.4, 25.7, 20.3, 13.5. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{21}\text{H}_{23}\text{NO}_3\text{BrF}_3+\text{Na}]$ 496.0711, found 496.0726. IR (thin film) ν_{max} 2964, 1746, 1696, 1202, 1153 cm^{-1} . $[\alpha]_{\text{D}}^{20} +33.1^\circ$ ($c = 1.0$, CHCl_3).

(2R,5S,6S)-Methyl 2-(2-ethynylbenzyl)-5-methyl-6-phenyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 22:



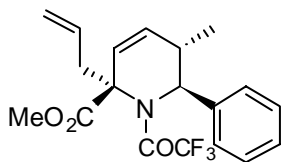
This compound was synthesized by general procedure 1 and isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.99 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 2H), 7.37-7.05 (m, 2H), 7.11-7.05 (m, 2H), 6.08 (d, $J = 10.5$ Hz, 1H), 5.82 (dd, $J = 10.4, 6.6$ Hz, 1H), 5.33 (s, 1H), 4.08 (d, $J = 14.0$ Hz, 1H), 4.02 (d, $J = 14.0$ Hz, 1H), 3.89 (s, 3H), 3.29 (s, 1H), 2.26 (app. p, $J = 7.2$ Hz, 1H), 0.31 (d, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 170.7, 159.5 (q, $J = 36.1$ Hz), 143.9, 138.4, 133.4, 132.7, 131.7, 129.0, 128.7, 128.4, 127.8, 127.3, 127.2, 125.9, 124.9, 122.1, 116.0 (q, $J = 286.9$ Hz), 83.2, 81.2, 68.5, 60.9 (q, $J = 3.3$ Hz), 53.1, 38.4, 36.4, 19.2. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{25}\text{H}_{21}\text{NO}_3\text{NaBrF}_3]$ 542.0555, found 542.0566. IR (thin film) ν_{max} 2955, 1748, 1694, 1198, 1153 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ -76.0° ($c = 1.0$, CHCl_3).

(2R,5S,6S)-Methyl 2-(2-bromobenzyl)-5-methyl-6-phenyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 23:



This compound was synthesized by general procedure 1 and isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.56 (d, $J = 8.0$ Hz, 1H), 7.40 (d, $J = 6.8$ Hz, 2H), 7.29-7.24 (m, 4H), 7.13-7.07 (m, 2H), 6.19 (d, $J = 10.4$ Hz, 1H), 6.08 (dd, $J = 10.2, 6.4$ Hz, 1H), 4.94 (s, 1H), 4.15 (d, $J = 14.4$ Hz, 1H), 3.85 (d, $J = 14.3$ Hz, 1H), 3.39 (s, 3H), 2.57 (app. p, $J = 6.6$ Hz, 1H), 0.38 (d, $J = 7.12$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 169.9, 159.3 (q, $J = 34.9$ Hz), 140.1, 135.5, 133.3, 132.7, 130.4, 128.9, 128.4, 127.8, 127.6, 127.2, 127.1, 126.7, 116.6 (q, $J = 287.8$ Hz), 67.8, 61.3 (q, $J = 2.8$ Hz), 52.4, 38.7, 33.7, 18.2. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{23}\text{H}_{21}\text{NO}_3\text{BrF}_3+\text{Na}]$ 518.0555, found 518.0519. IR (thin film) ν_{max} 2953, 1732, 1693, 1263, 1190 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ -41.5° ($c = 1.0$, CHCl_3).

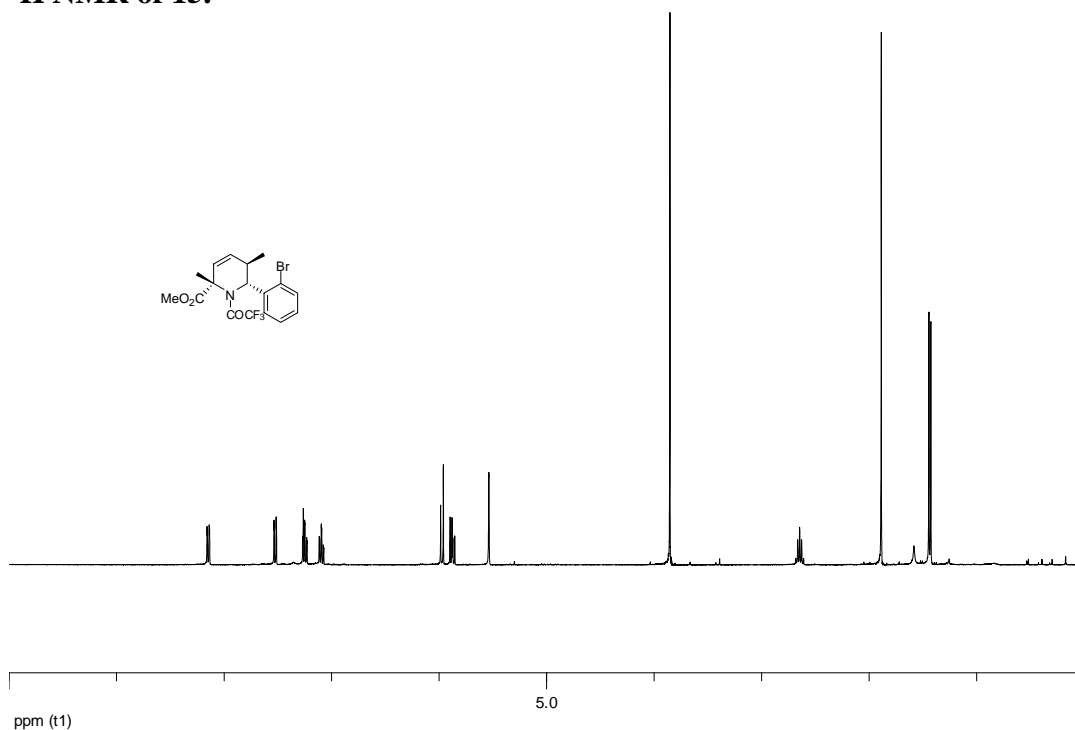
(2R,5S,6S)-Methyl 2-allyl-5-methyl-6-phenyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate 24:



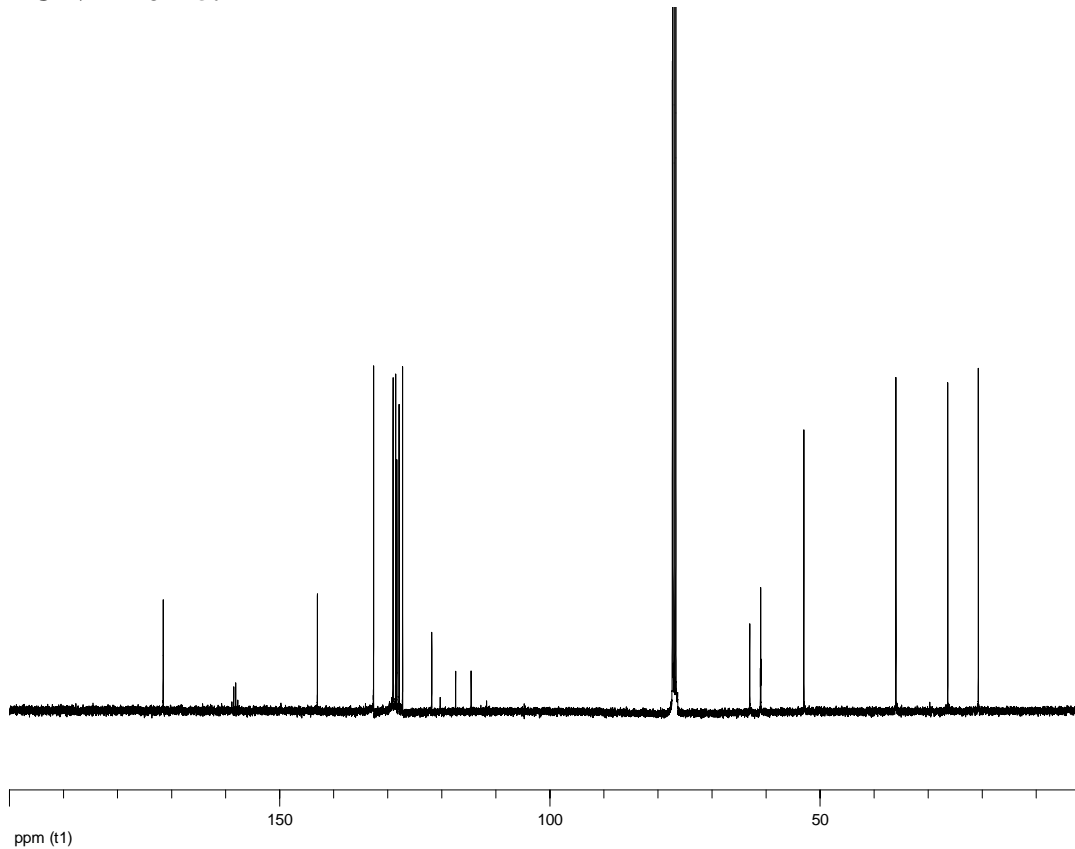
This compound was synthesized by general procedure 1 and isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.39 (m, 2H), 7.29-7.21 (m, 3H), 6.24 (dd, $J = 10.3, 6.0$ Hz, 1H), 5.79 (dd, $J = 10.3, 0.9$ Hz, 1H), 5.61 (dddd, $J = 16.9, 10.1, 9.4, 5.6$ Hz, 1H), 5.18-5.07 (m, 3H), 5.01 (s, 1H), 3.56 (dd, $J = 14.2, 9.3$ Hz, 1H), 3.19 (s, 3H), 2.59 (dd, $J = 14.2, 5.5$ Hz, 1H), 1.24 (d, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 170.2, 158.0 (q, $J = 34.8$ Hz), 139.1, 131.6, 130.7, 128.6 (q, $J = 2.5$ Hz), 128.0, 127.7, 127.6, 116.6 (q, $J = 287.6$ Hz), 119.8, 65.3, 60.5 (q, $J = 2.6$ Hz), 52.1, 39.8, 33.1, 19.2. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{19}\text{H}_{20}\text{NO}_3\text{F}_3+\text{Na}]$ 390.1293, found 390.1330. IR (thin film) ν_{max} 2953, 1729, 1702, 1262, 1146 cm^{-1} . $[\alpha]_{\text{D}}^{20}$ -52.1° ($c = 1.0$, CHCl_3).

3. ^1H and ^{13}C NMR Spectra of Alkylated Tetrahydropyridines.

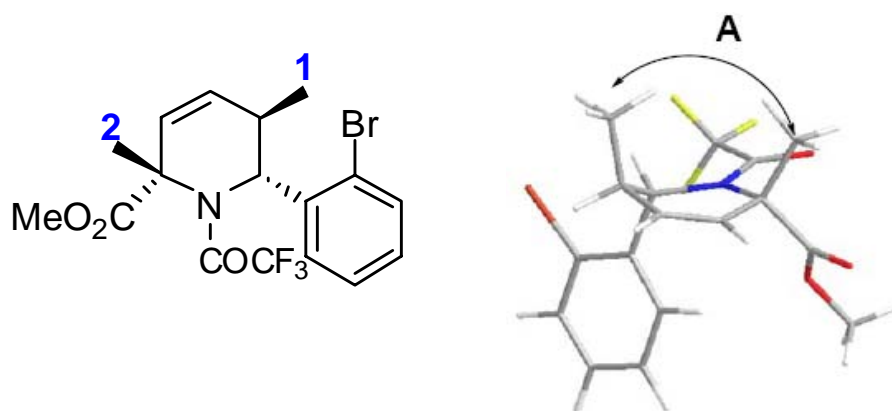
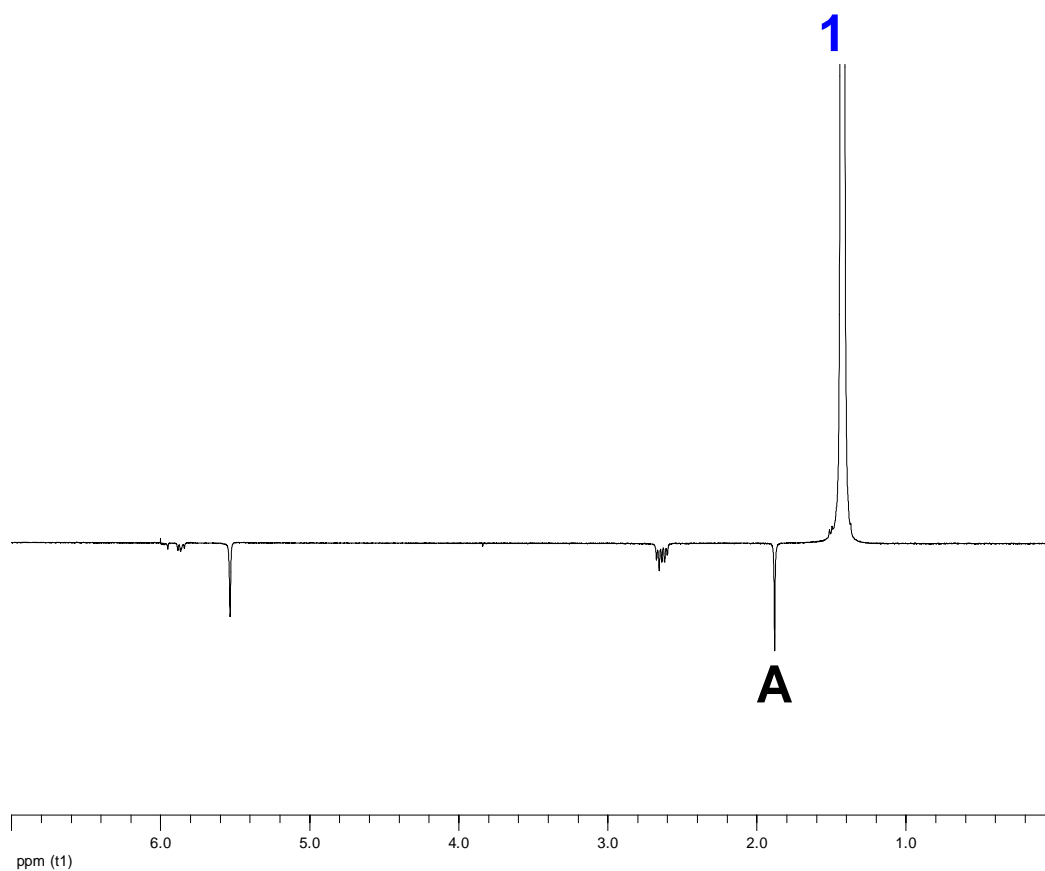
^1H NMR of 15.



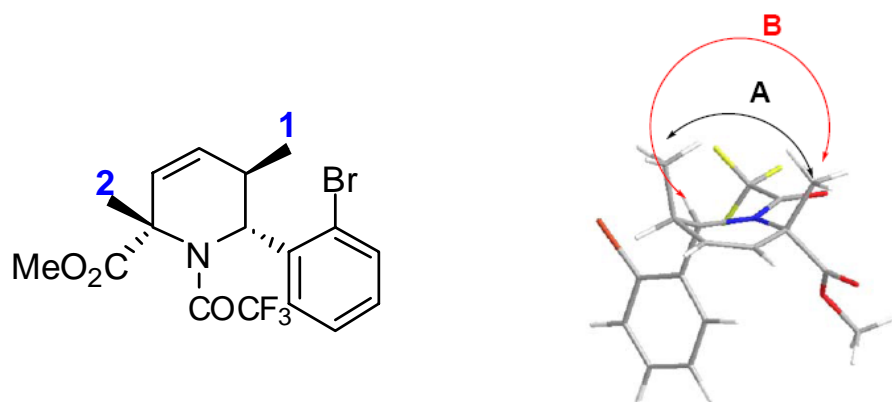
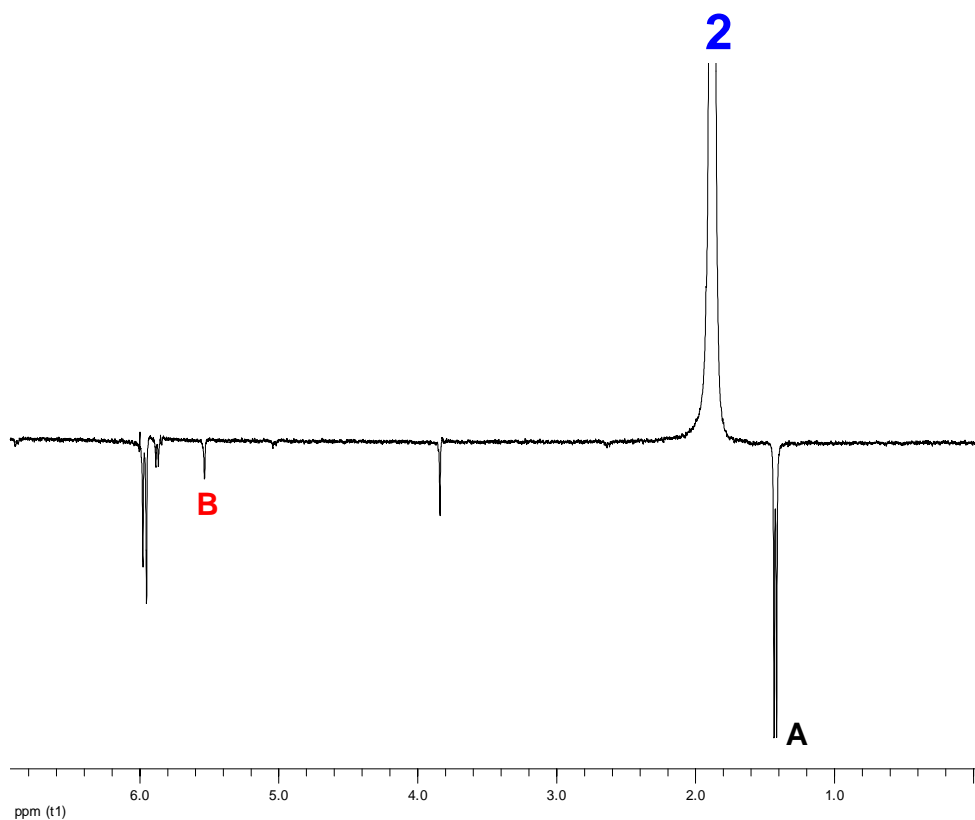
^{13}C NMR of 15.



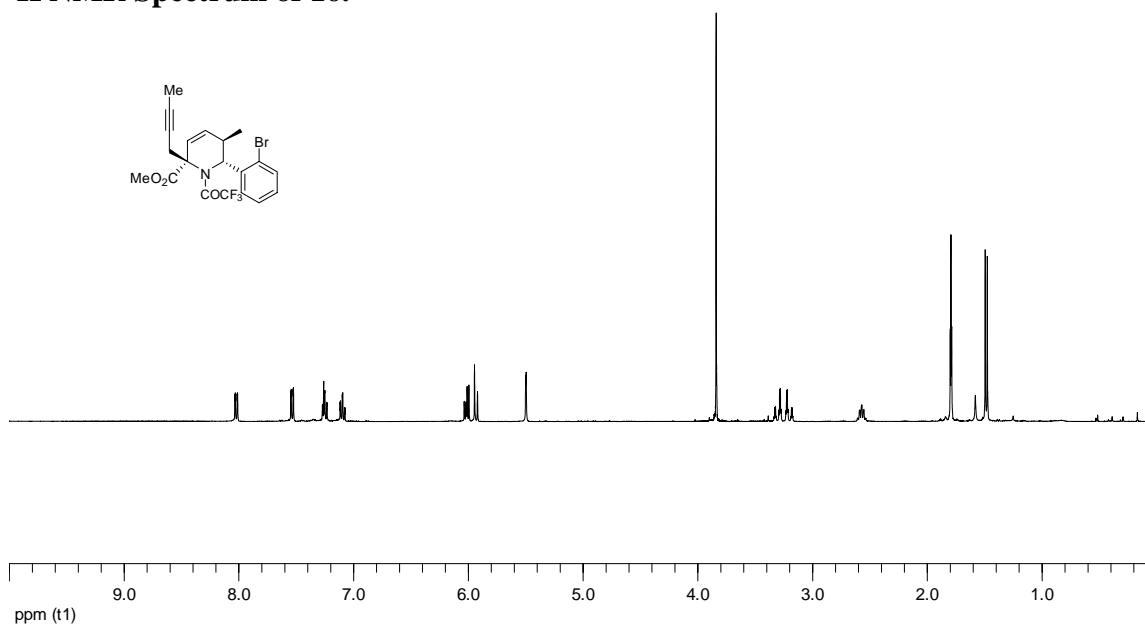
1D NOE Spectrum of 15 indicating a *syn* relationship of the two methyl groups:
 (doublet at 1.43 ppm (**Peak 1**) irradiated)



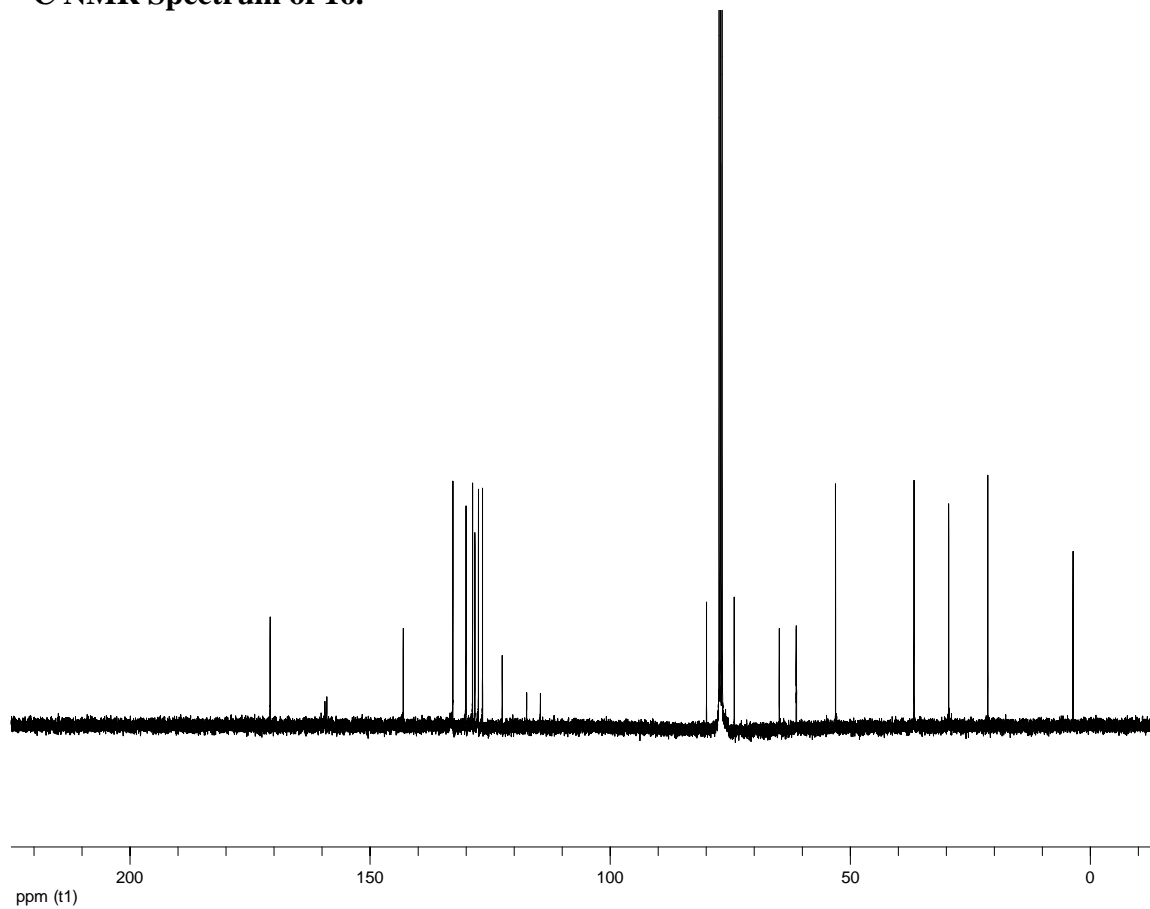
1D NOE Spectrum of 15 indicating a *syn* relationship of the two methyl groups:
 (Singlet at 1.89 ppm (**Peak 2**) irradiated)



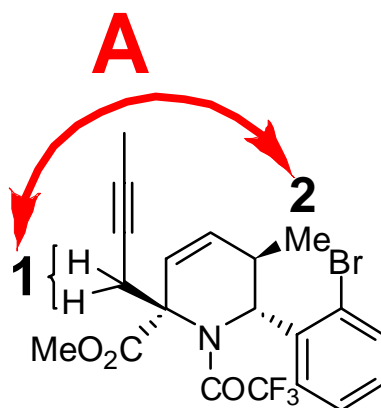
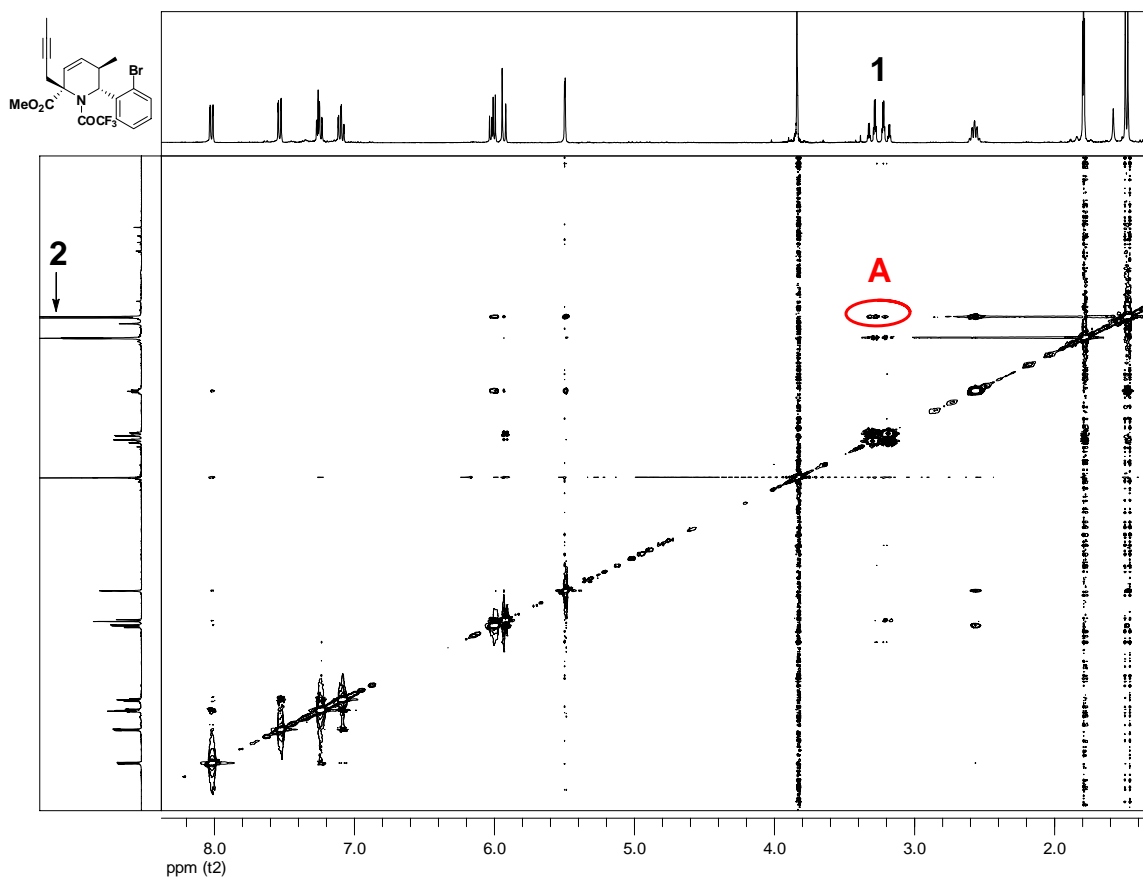
^1H NMR Spectrum of 16.



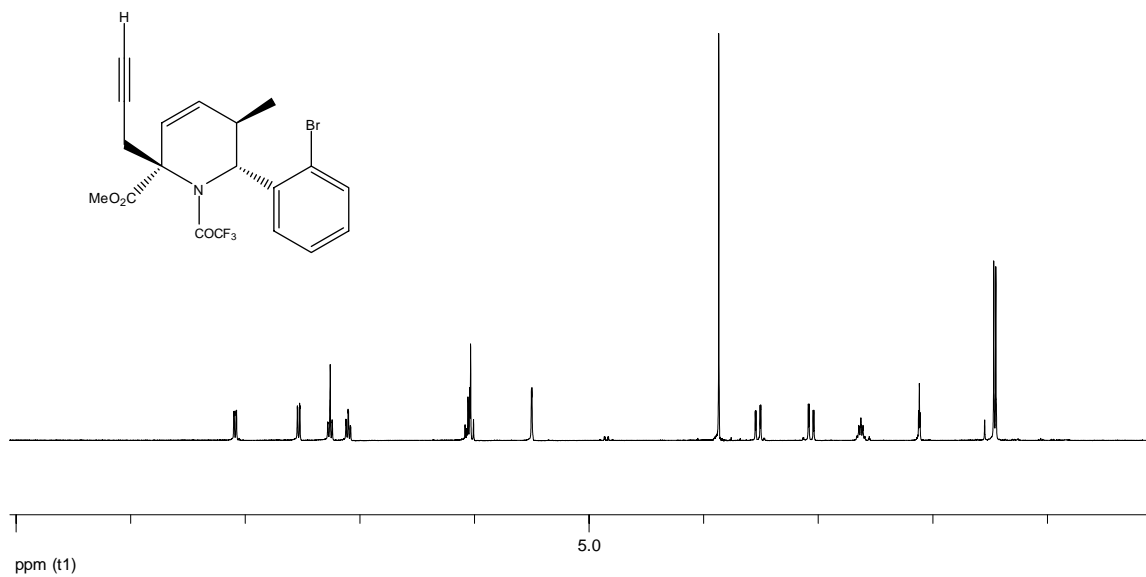
^{13}C NMR Spectrum of 16.



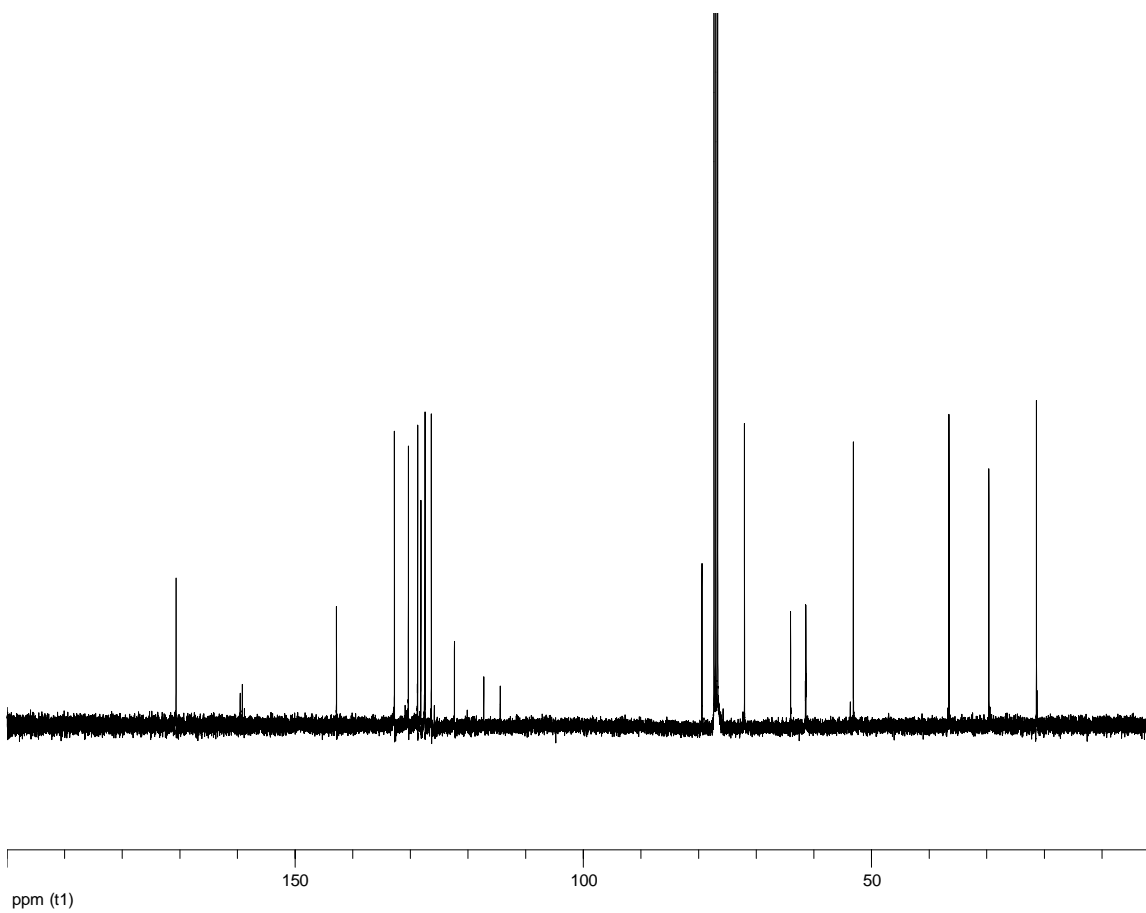
Expanded Segment of NOESY Spectrum of 16.



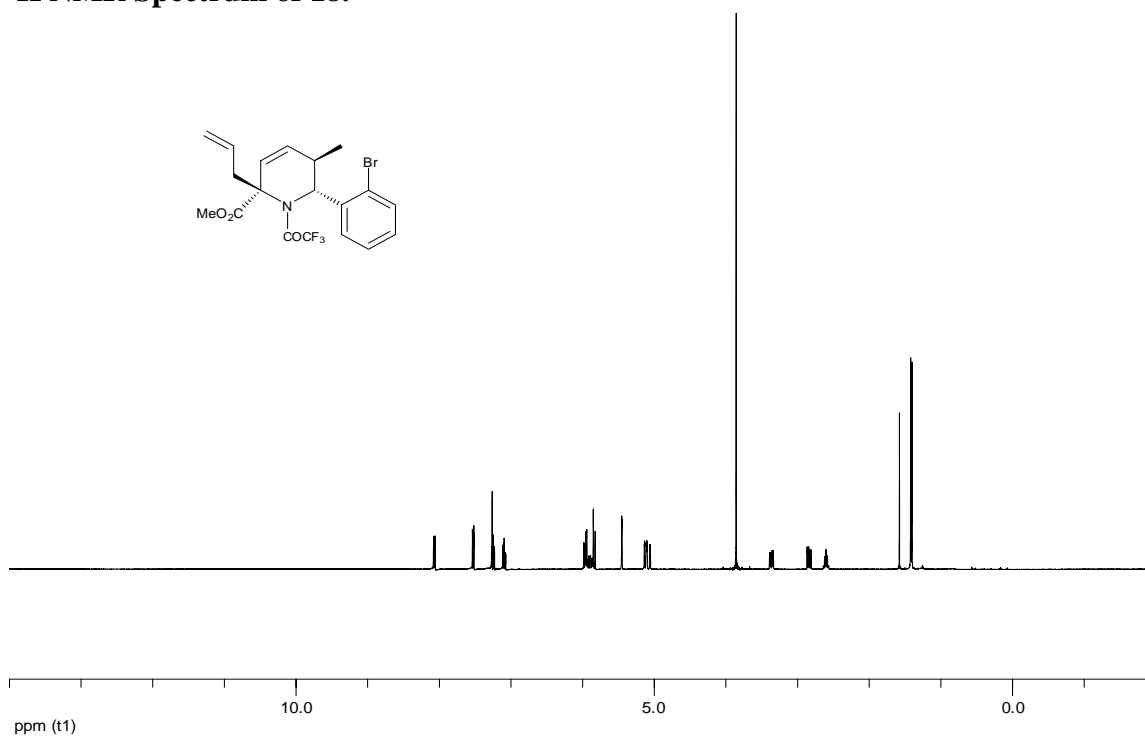
^1H NMR Spectrum of 17.



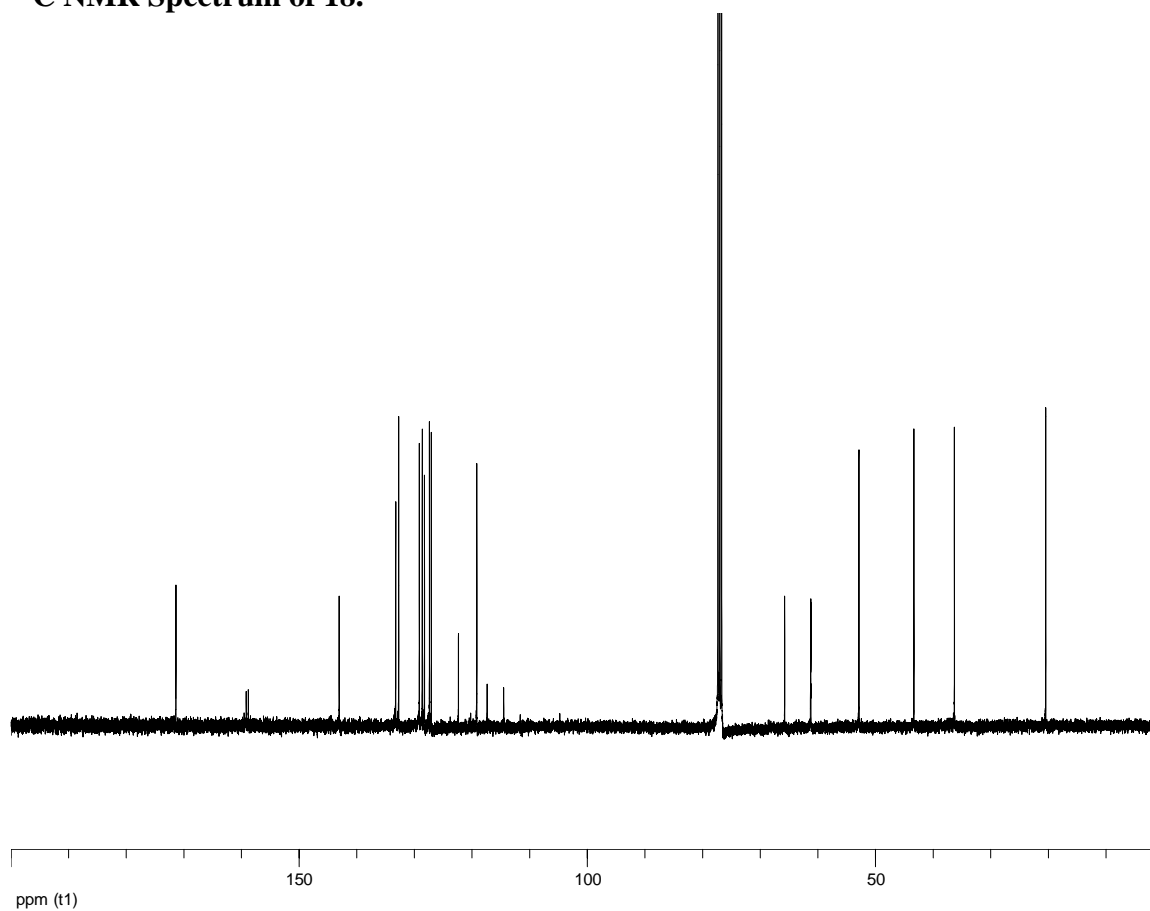
^{13}C NMR Spectrum of 17.



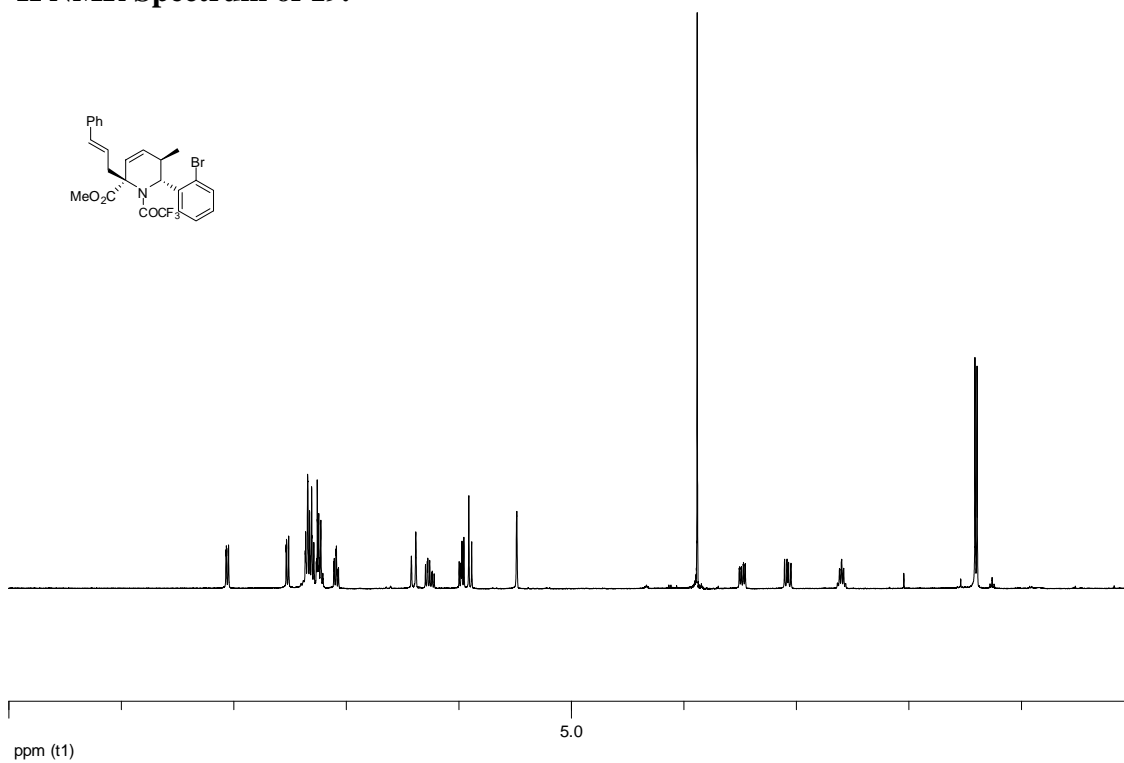
^1H NMR Spectrum of 18.



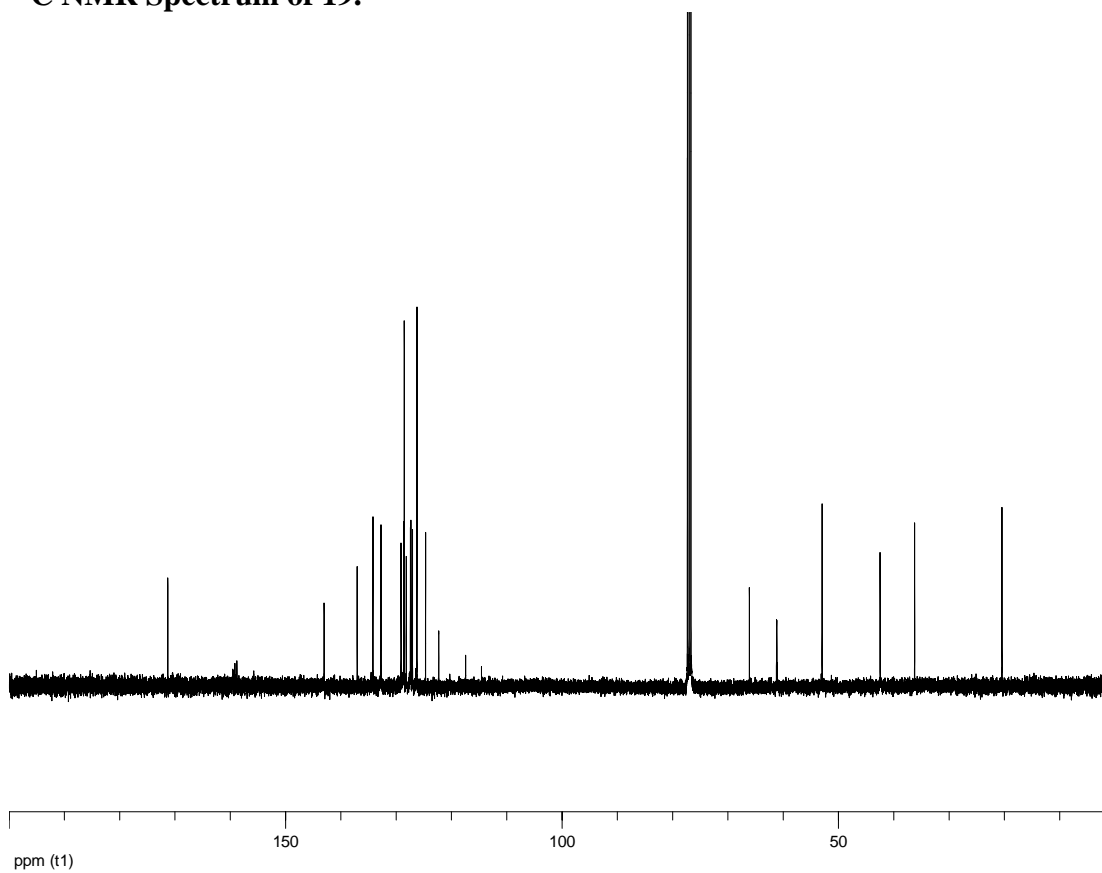
^{13}C NMR Spectrum of 18.



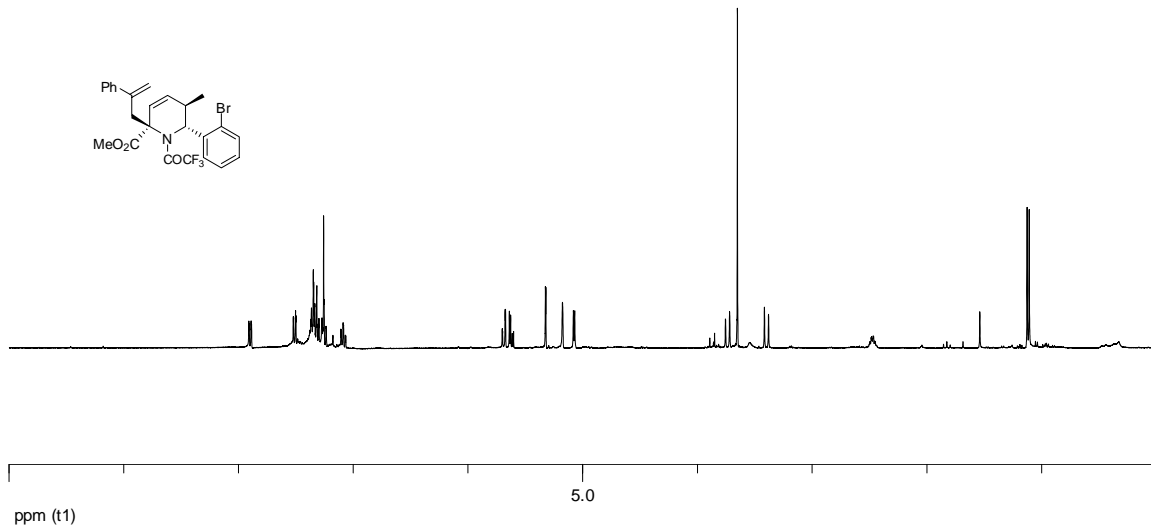
^1H NMR Spectrum of 19.



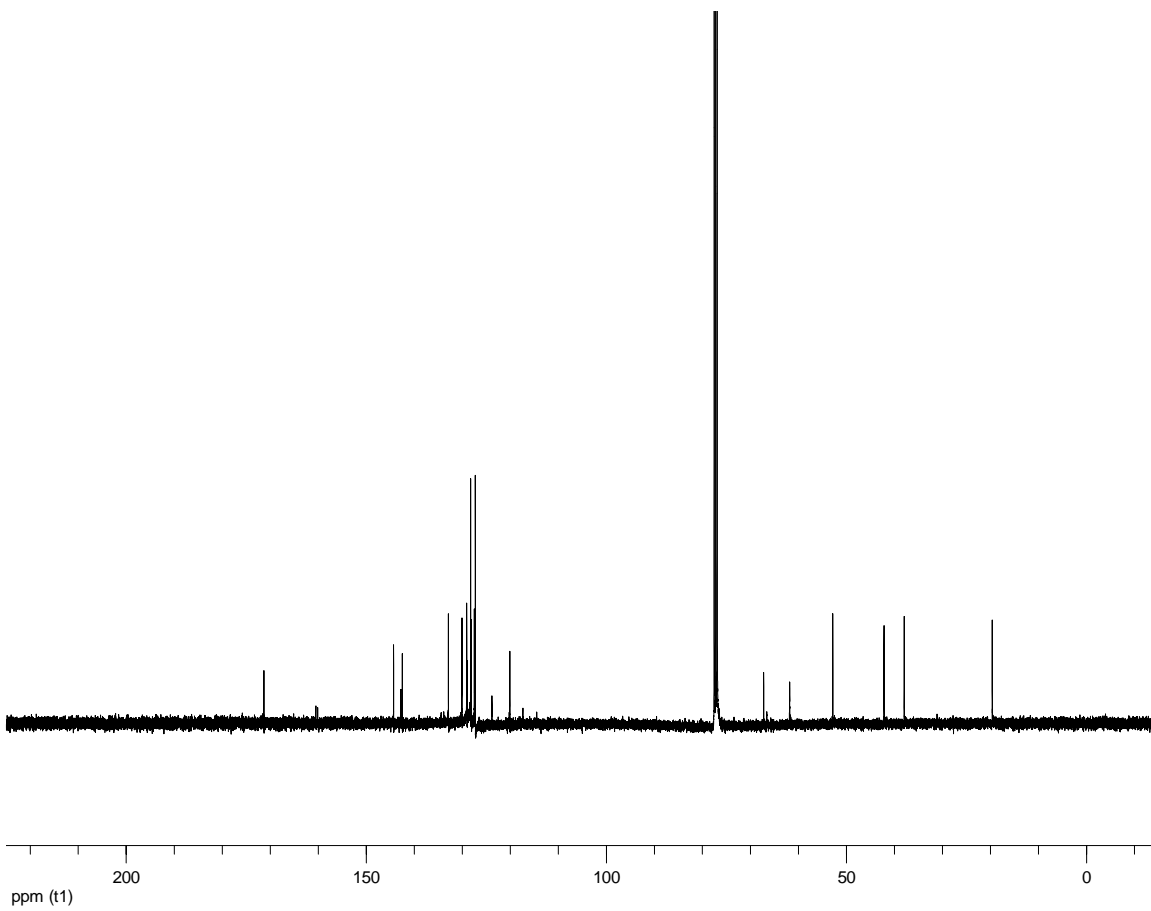
^{13}C NMR Spectrum of 19.



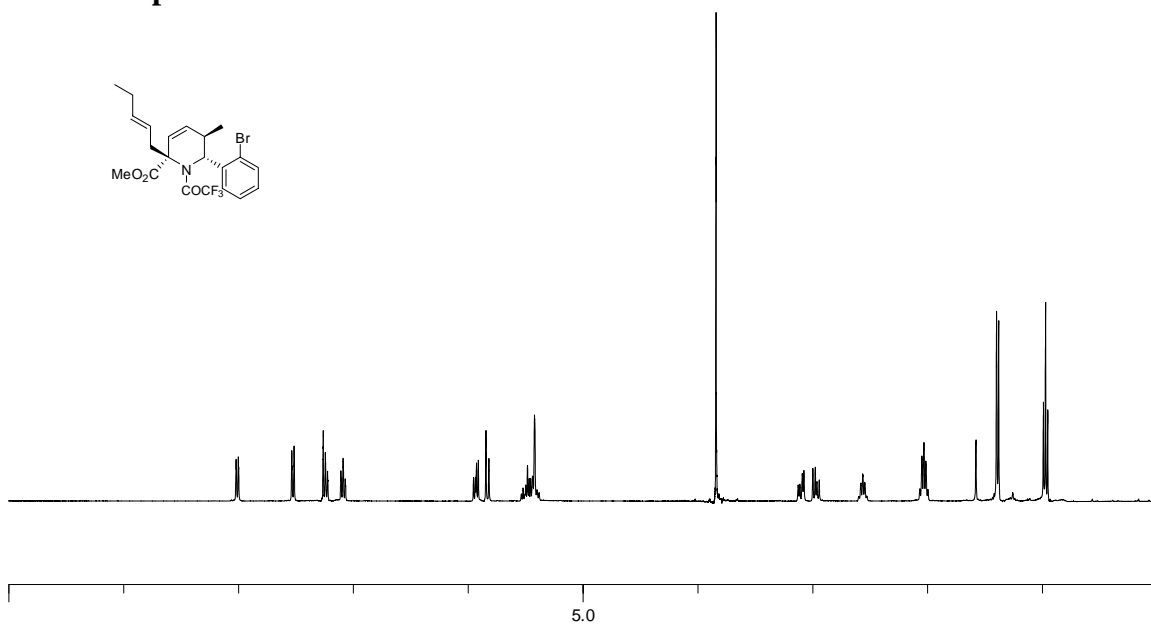
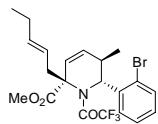
^1H NMR Spectrum of 20.



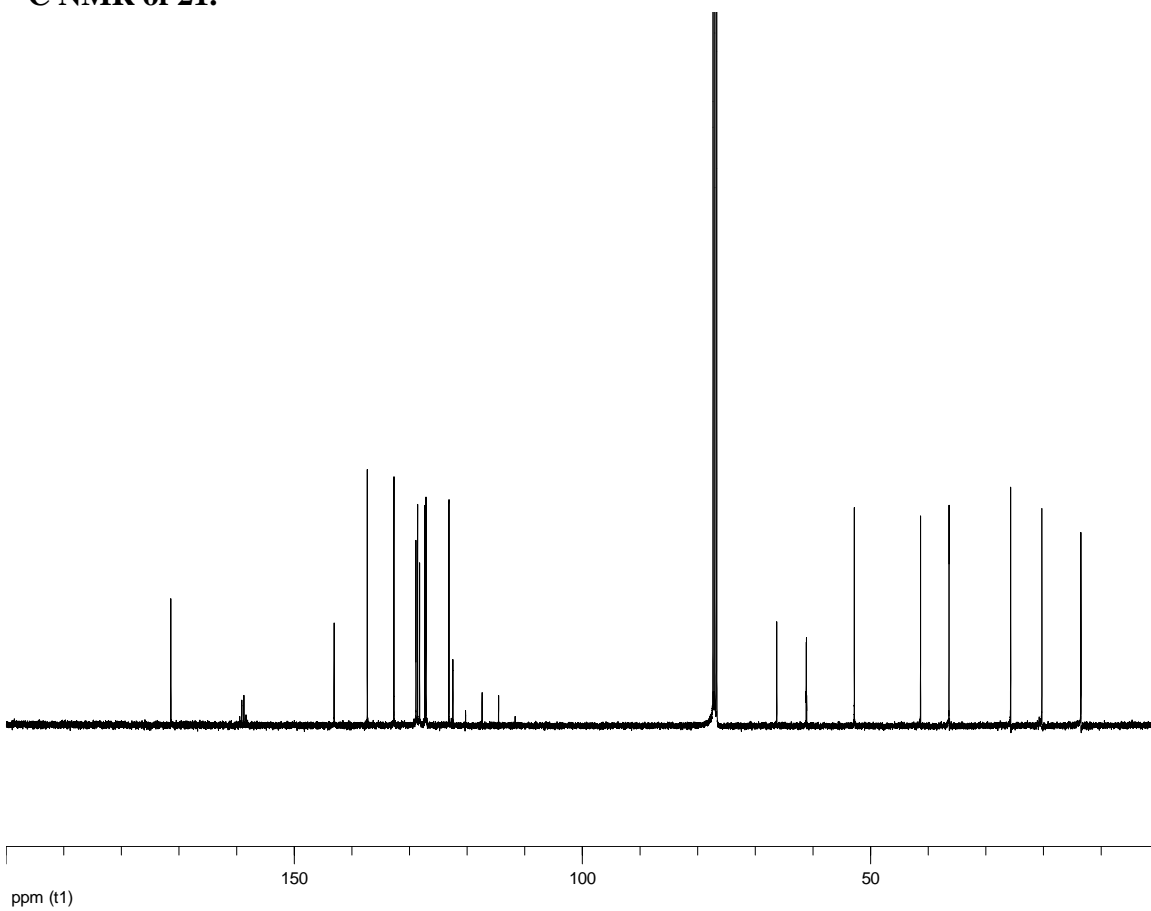
^{13}C NMR Spectrum of 20.



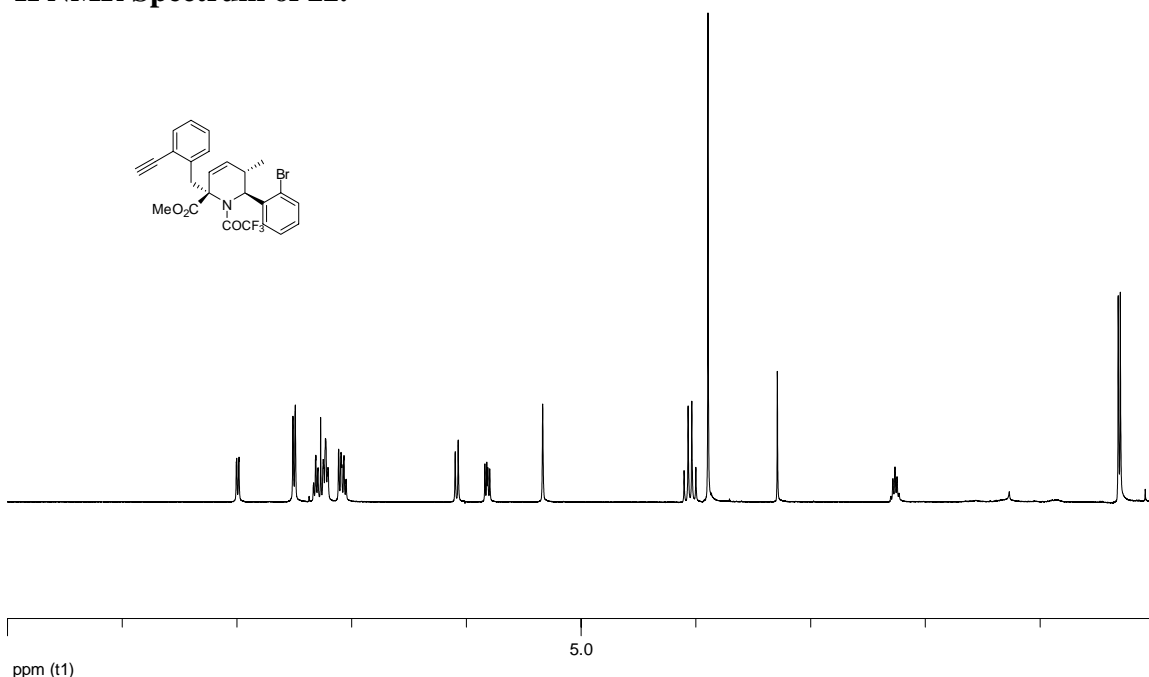
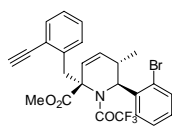
^1H NMR Spectrum of 21.



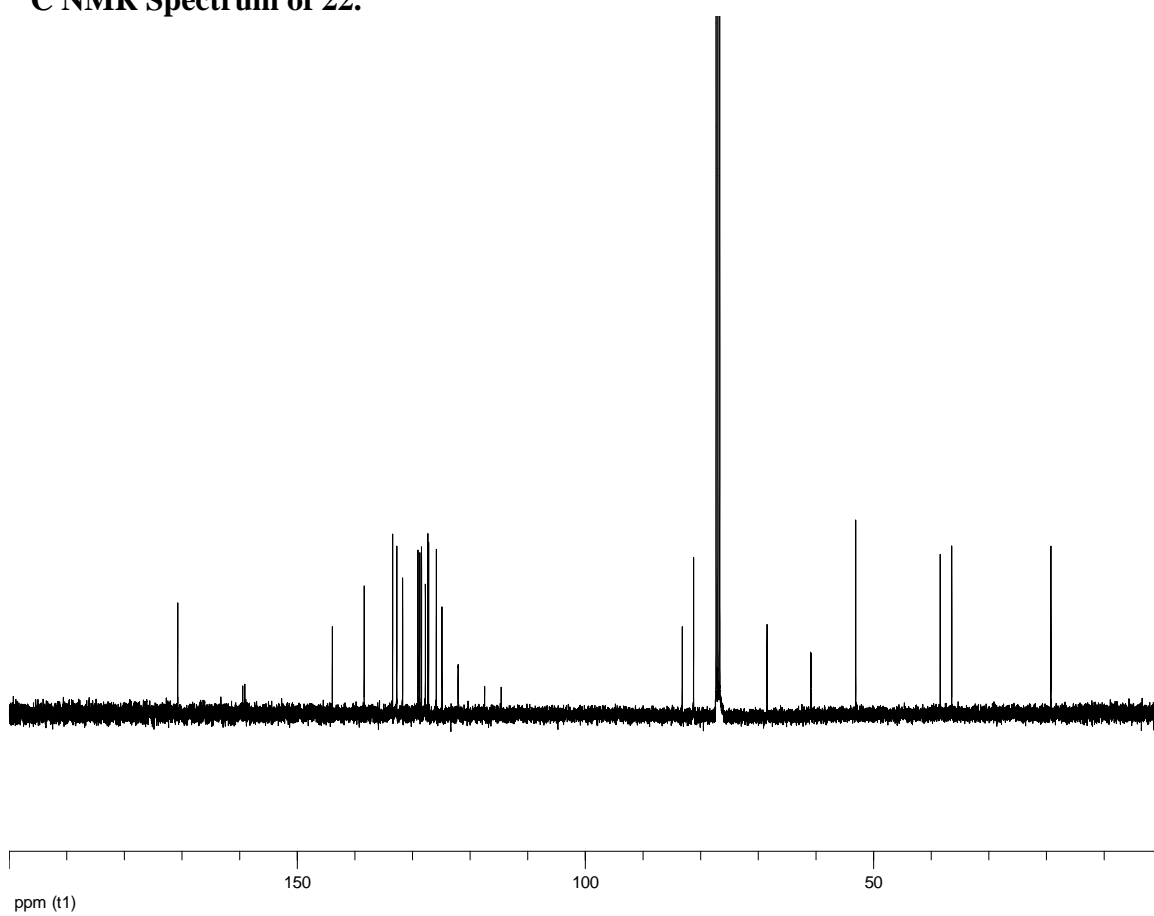
^{13}C NMR of 21.



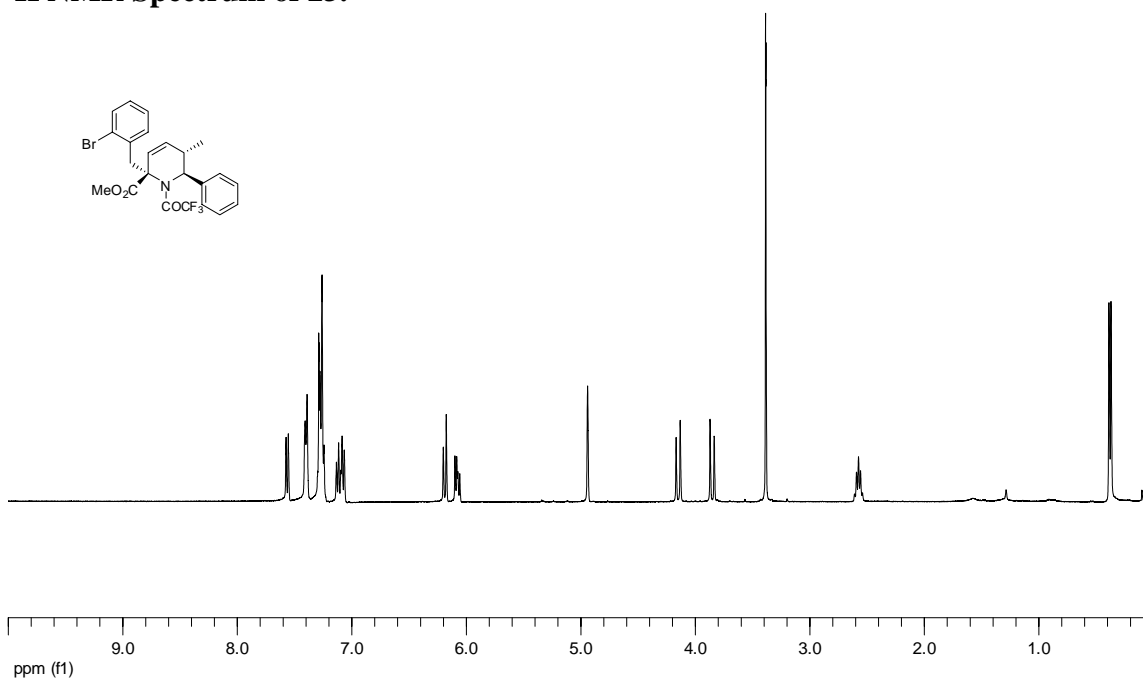
^1H NMR Spectrum of 22.



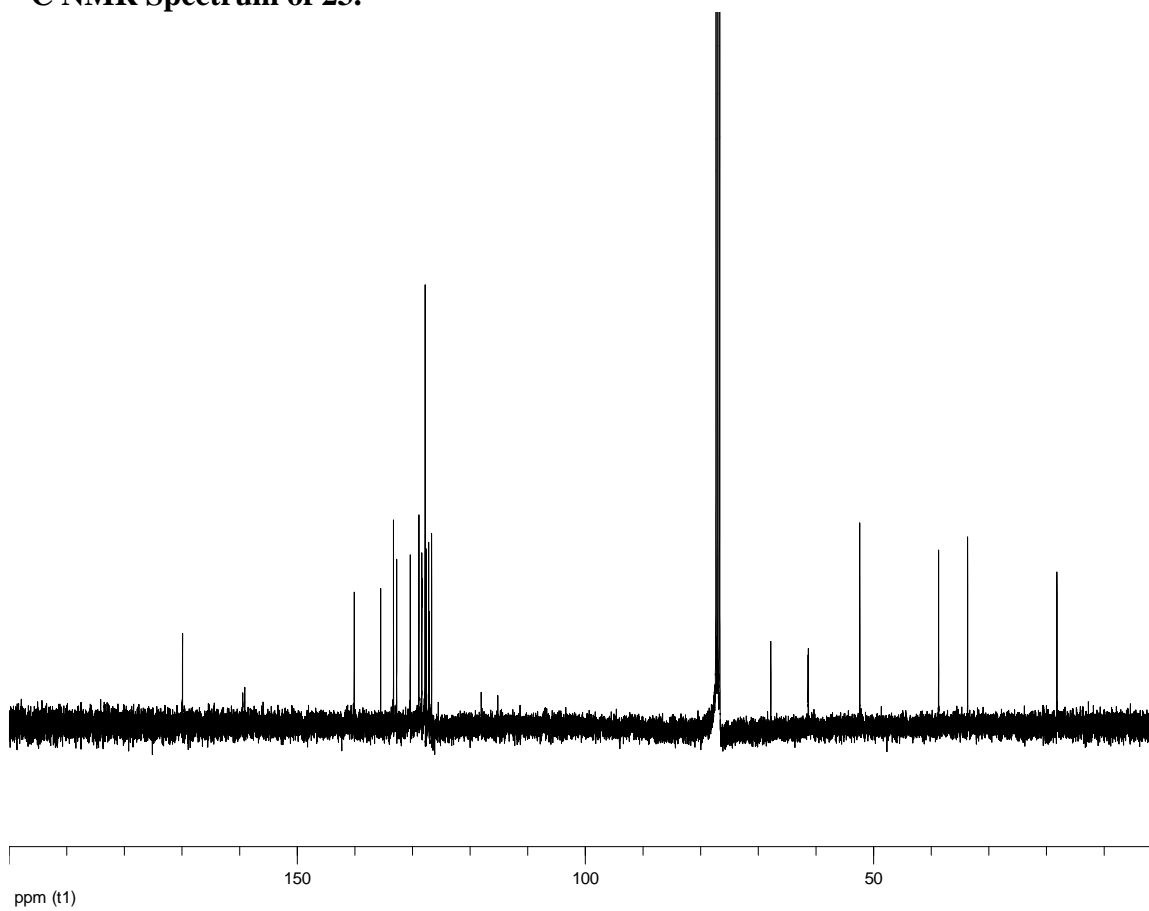
^{13}C NMR Spectrum of 22.



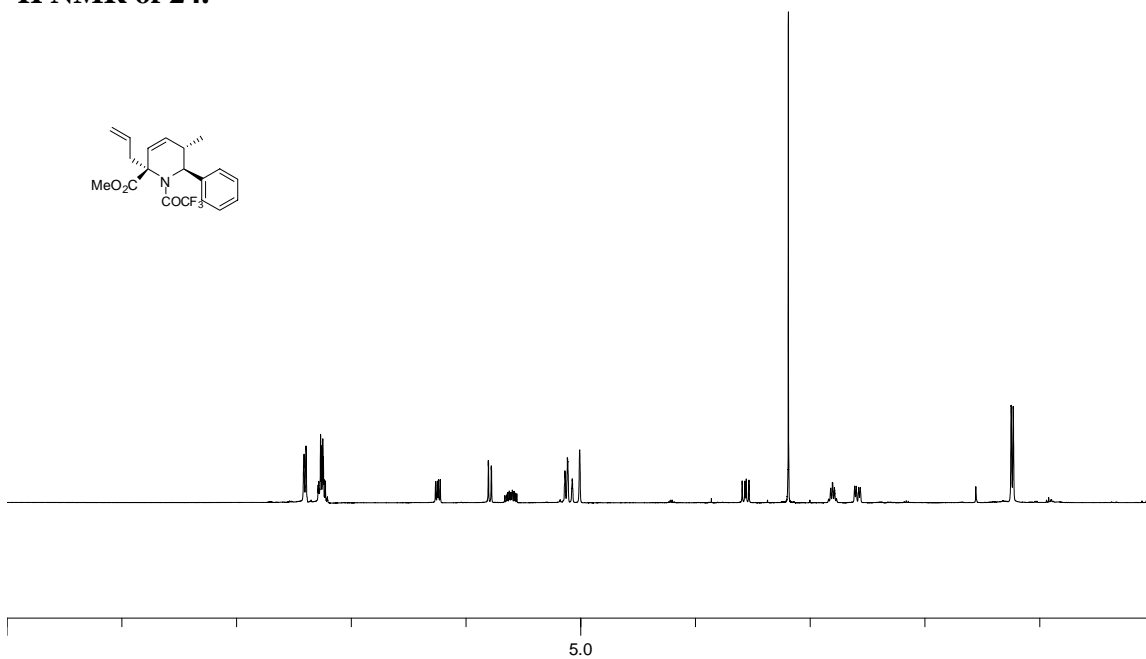
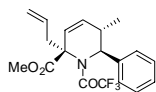
^1H NMR Spectrum of 23.



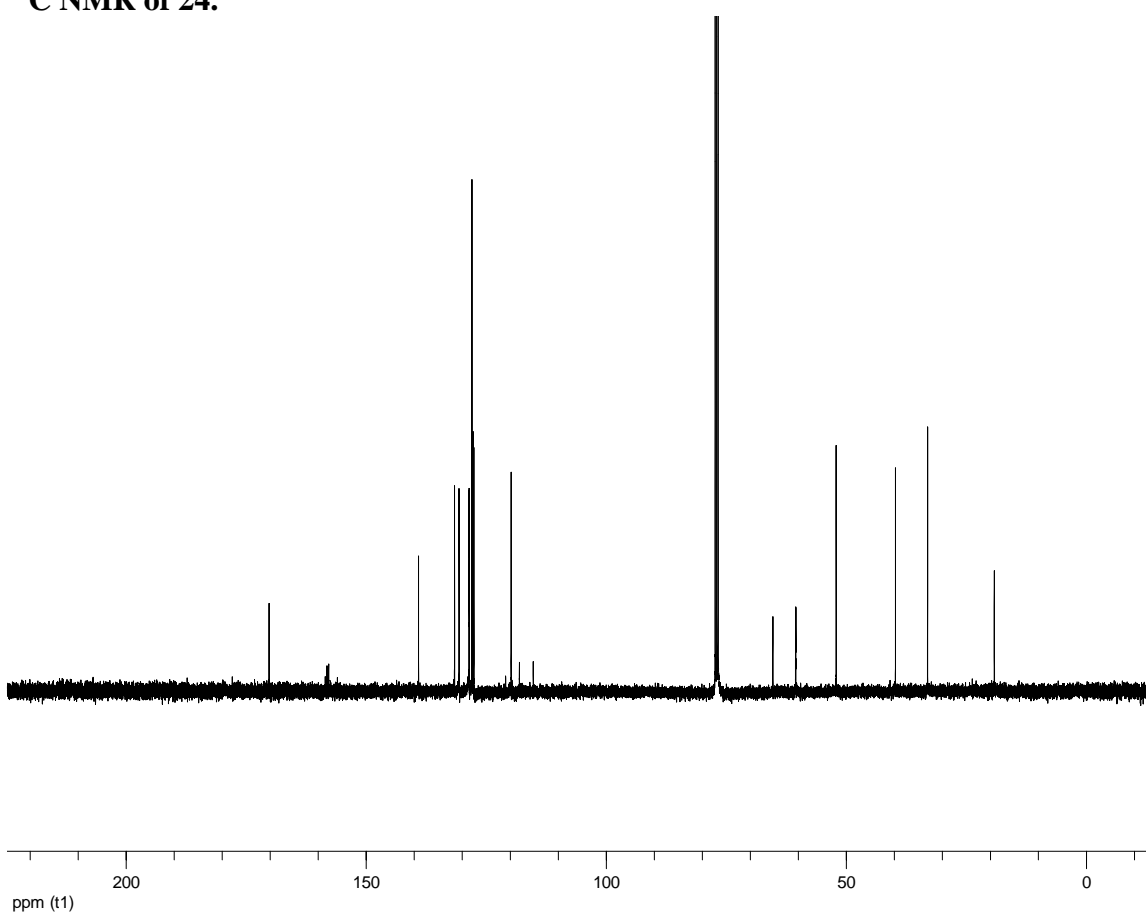
^{13}C NMR Spectrum of 23.



^1H NMR of 24.



ppm (t1)
 ^{13}C NMR of 24.



4. Radical Cyclizations and Hydantoin formation

General Procedure 2 - Radical cyclization of 23: A solution of (2*R*,5*S*,6*S*)-methyl 2-(2-bromobenzyl)-5-methyl-6-phenyl-1-(2,2,2-trifluoroacetyl)-1,2,5,6-tetrahydropyridine-2-carboxylate **23** (70 mg, 0.14 mmol, 1 equiv), 2,2'-azo-bis(isobutyronitrile) (2.3 mg, 0.014 mmol, 0.01 equiv.) and tri(*n*-butyl)tin hydride (56 μ L, 0.21 mmol, 1.5 equiv.) in degassed benzene (5 mL) were heated at 80 °C for 4 h. The reaction mixture was concentrated. Silica gel chromatography with ethyl acetate in hexane (from 0% to 10%) gave the desired product (2*S*,3*S*,4*aS*,9*aR*)-methyl 3-methyl-2-phenyl-1-(2,2,2-trifluoroacetyl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-indeno[2,1-*b*]pyridine-9*a*-carboxylate **25** as a viscous oil (48 mg, 81% yield).

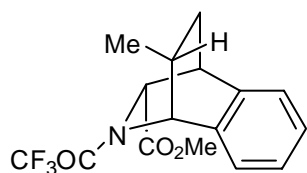
(2*S*,3*S*,4*aS*,9*aR*)-Methyl 3-methyl-2-phenyl-1-(2,2,2-trifluoroacetyl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-indeno[2,1-*b*]pyridine-9*a*-carboxylate **25:** This compound was synthesized by general procedure 2 and isolated in pure form as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.73-7.71 (m, 2H), 7.44-7.40 (m, 2H), 7.37-7.31 (m, 1H), 7.26-7.22 (m, 4H), 4.75 (d, *J* = 8.0 Hz, 1H), 4.43 (d, *J* = 16.7 Hz, 1H), 3.64 (s, 3H), 3.60 (dd, *J* = 12.5, 5.0 Hz, 1H), 3.09 (d, *J* = 16.7 Hz, 1H), 2.28-2.10 (m, 2H), 1.51-1.42 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 173.7, 160.8 (q, *J* = 36.9 Hz), 143.1, 141.5, 138.9, 128.5, 128.2, 127.8, 127.6, 126.9, 124.2, 123.1, 116.2 (q, *J* = 286.2 Hz), 72.1, 66.2 (q, *J* = 2.9 Hz), 52.5, 49.7, 43.1, 36.5, 35.4, 19.8. HRMS (CI/NH₃) *m/z* calculated for [C₂₂H₂₂NO₃F₃+Na] 440.1449, found 440.1462. IR (thin film) ν_{\max} 2959, 1760, 1688, 1192, 1143 cm⁻¹. [α]_D²⁰ +86.2 ° (c = 0.8, CHCl₃).

(1*R*,3*S*,4*R*,6*R*)-*N*-(2,2,2-Trifluoroacetyl)-3-methoxycarbonyl-3,6-dimethyl-7,8-benzo-2-azabicyclo[2.2.2]octane **26:** This compound was synthesized by general procedure 2 and isolated in pure form as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.20 (m, 3H), 7.10-7.08 (m, 1H), 4.90-4.88 (m, 1H), 3.22 (s, 3H), 3.16 (t, *J* = 2.8 Hz, 1H), 1.92 (s, 3H), 1.91-1.85 (m, 1H), 1.82-1.75 (m, 2H), 1.25 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.2, 156.32 (q, *J* = 35.79 Hz), 137.9, 137.9, 128.2, 127.6, 123.9, 122.7, 116.37 (q, *J* = 288.3 Hz), 65.5, 58.59 (q, *J* = 3.3 Hz), 52.1, 45.2, 32.1, 26.7, 20.0, 18.5. HRMS (CI/NH₃) *m/z* calculated for [C₁₇H₁₈NO₃F₃+Na] 364.1136, found 364.1163. ν_{\max} 2963, 1733, 1691, 1201, 1140 cm⁻¹. [α]_D²⁰ -62.3 ° (c = 0.9, CHCl₃).

(1*R*,3*R*,4*R*,6*R*)-*N*-(2,2,2-Trifluoroacetyl)-3-methoxycarbonyl-6-methyl-7,8-benzo-2-azabicyclo[2.2.2]octane **27:** This compound was synthesized by general procedure 2 with the following exception. Tris(trimethylsilyl)silane was used in the place of tri(*n*-butyl)tin hydride. Compound **27** was isolated in the pure form as a viscous oil. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.25 (m, 3H), 7.22-7.20 (m, 1H), 4.91-4.89 (m, 1H), 4.11-4.08 (m, 1H), 3.84 (s, 3H), 3.56 (dd, *J* = 5.4, 2.6 Hz, 1H), 1.92 (dddd, *J* = 11.4, 6.8, 4.8, 2.0 Hz, 1H), 1.79-1.72 (m, 1H), 1.41-1.37

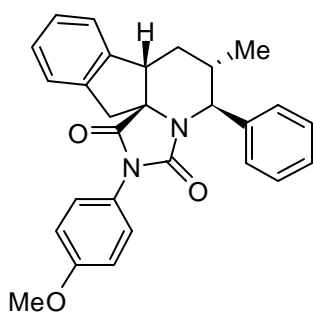
(overlp m, 1H), 1.37 (d, $J = 6.95$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 157.4 (q, $J = 36.6$ Hz), 139.5, 138.9, 128.6, 127.8, 124.5, 122.7, 116.52 (q, $J = 287.4$ Hz), 61.0, 58.73 (q, $J = 3.0$ Hz), 52.7, 37.6, 33.2, 27.7, 18.0. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{16}\text{H}_{16}\text{NO}_3\text{F}_3+\text{Na}]$ 350.0980, found 350.0994. ν_{max} 2956, 1757, 1691, 1206, 1143 cm^{-1} . $[\alpha]_{\text{D}}^{20} +9.0^\circ$ ($c = 1.2$, CHCl_3).

(1R,3S,4R,6R)-N-(2,2,2-Trifluoroacetyl)-3-methoxycarbonyl-6-methyl-7,8-benzo-2-



azabicyclo[2.2.2]octane 29: This compound was synthesized by general procedure 2 with the following exception. Tris (trimethylsilyl)silane was used in the place of tri(*n*-butyl)tin hydride. Compound **29** was isolated in the pure form as a viscous oil. ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.21 (m, 3H), 7.15-7.13 (m, 1H), 4.92-4.90 (m, 1H), 4.52 (b m, 1H), 3.53 (dd, $J = 5.6, 2.5$ Hz, 1H), 3.44 (s, 3H), 2.03-1.86 (m, 2H), 1.37 (ddd, $J = 12.5, 4.4, 2.3$ Hz, 1H), 1.17 (d, $J = 6.67$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 168.1, 155.9 (q, $J = 36.6$ Hz), 138.2, 136.4, 128.4, 127.7, 124.5, 122.9, 116.3 (q, $J = 285.6$ Hz), 57.9 (q, $J = 3.0$ Hz), 60.8, 52.2, 38.1, 33.2, 31.7, 19.2. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{16}\text{H}_{16}\text{NO}_3\text{F}_3+\text{Na}]$ 350.0980, found 350.1003. ν_{max} 2959, 1760, 1689, 1192, 1143 cm^{-1} . $[\alpha]_{\text{D}}^{20} -41.2^\circ$ ($c = 0.9$, CHCl_3).

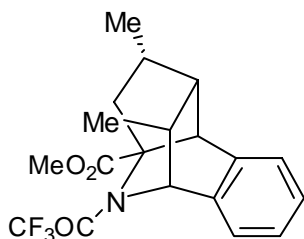
Hydantoin 35: A solution of potassium hydroxide in water (3.3 M, 2 mL) was added to a



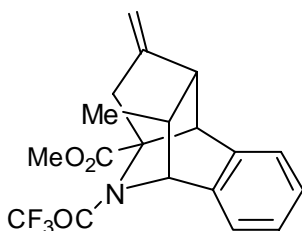
solution of (2*S*,3*S*,4*aS*,9*aR*)-methyl 3-methyl-2-phenyl-1-(2,2,2-trifluoroacetyl)-2,3,4,4*a*,9,9*a*-hexahydro-1*H*-indeno[2,1-*b*]pyridine-9*a*-carboxylate **25** (10 mg, 0.024 mmol, 1 equiv.) in methanol (3 mL) and stirred at room temperature for 2 h. A solution of aqueous hydrochloric acid (6 M, 0.3 mL) was added and the reaction mixture was concentrated. 4-Methoxyphenylisocyanate (5 μL , 0.04 mmol, 1.7 equiv.), triethylamine (10 μL , 0.07 mmol, 3 equiv) and THF (1 mL) were added and the reaction mixture was heated at 45 $^\circ\text{C}$ for 6

h. The reaction was quenched by the addition of water (2 mL) and the crude reaction mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with sodium sulfate, concentrated. Silica gel chromatography with ethyl acetate in hexane (gradient elution from 0% to 50%) gave the desired product **35** (5 mg, 68% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.45-7.19 (m, 11H), 6.89-6.83 (m, 2H), 3.90 (d, $J = 11.1$ Hz, 1H), 3.76 (s, 3H), 3.67 (dd, $J = 7.9, 5.8$ Hz, 1H), 3.63-3.59 (d, 2H), 2.72-2.59 (m, 1H), 2.29 (ddd, $J = 14.9, 5.9, 5.9$ Hz, 1H), 1.81 (ddd, $J = 15.0, 7.6, 7.6$ Hz, 1H), 0.78 (d, $J = 6.71$ Hz, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 174.6, 158.9, 153.8, 144.1, 138.8, 135.6, 129.5, 128.0, 127.9, 127.6, 127.5, 127.4, 124.8, 124.3, 123.8, 114.0, 70.7, 62.1, 55.4, 46.7, 39.1, 35.4, 31.6, 19.5. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_3\text{F}_3]$ 439.2022, found 439.2027. ν_{max} 2926, 1770, 1721, 1514, 1411, 1250, 1173 cm^{-1} . $[\alpha]_{\text{D}}^{20} -39.4^\circ$ ($c = 0.6$, CHCl_3).

Compound 36. This compound was synthesized by general procedure 2 with the following exception. Tris(trimethylsilyl)silane was used in the place of tri(*n*-butyl)tin hydride. Compound **36** was isolated in the pure form as a viscous oil. Viscous oil. ^1H NMR (400 MHz, C_6D_6) δ 7.07-7.03 (m, 2H), 6.95-6.91 (m, 1H), 6.90-6.88 (m, 1H), 4.53 (b, 1H), 3.39 (d, $J = 3.9$ Hz, 1H), 3.00 (s, 3H), 2.55-2.45 (m, 2H), 1.93-1.84 (m, 1H), 1.41-1.33 (m, 2H), 0.90 (d, $J = 7.1$ Hz, 3H), 0.67 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 169.8, 155.1 (q, $J = 36.1$ Hz), 139.4, 133.7, 128.1, 127.4, 125.8, 121.8, 116.3 (q, $J = 286.1$ Hz), 71.7, 58.1 (q, $J = 3.0$ Hz), 52.2, 49.2, 45.1, 39.8, 37.9, 29.5, 23.4, 14.7. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{19}\text{H}_{20}\text{NO}_3\text{F}_3+\text{Na}]$ 320.1293, found 320.1299. ν_{max} 2962, 1739, 1684, 1203, 1143 cm^{-1} . $[\alpha]_{\text{D}}^{20} +21.0^\circ$ ($c = 1.0$, CHCl_3).

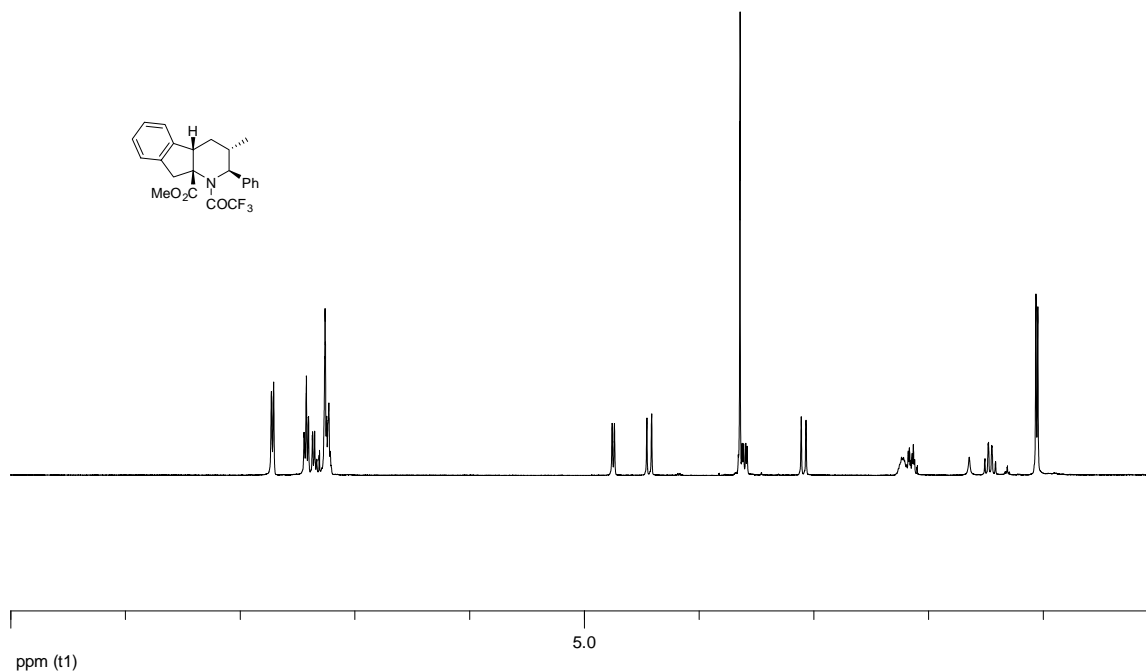


Compound 37. This compound was synthesized by general procedure 2 and isolated in pure form as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.31 (m, 2H), 7.30-7.23 (m, 1H), 7.22-7.17 (m, 1H), 5.11 (app t, $J = 2.4$ Hz, 1H), 5.07 (app t, $J = 2.4$ Hz, 1H), 4.77 (b s, 1H), 3.51 (d, $J = 4.7$ Hz, 1H), 3.45 (ddd, $J = 18.3, 2.4, 2.4$ Hz, 1H), 3.36 (s, 3H), 2.87 (ddd, $J = 18.3, 2.4, 2.4$ Hz, 1H), 2.77 (dd, $J = 9.8, 4.7$ Hz, 1H), 1.95-1.87 (m, 1H), 1.02 (d, $J = 7.21$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.2, 155.33 (q, $J = 36.47$ Hz), 145.8, 139.1, 133.3, 128.3, 127.7, 125.8, 121.9, 116.20 (q, $J = 287.8$ Hz), 110.9, 70.6, 58.01 (q, $J = 3.2$ Hz), 52.3, 51.1, 45.3, 38.7, 37.8, 15.5. HRMS (CI/ NH_3) m/z calculated for $[\text{C}_{19}\text{H}_{18}\text{NO}_3\text{F}_3+\text{Na}]$ 388.1136, found 388.1183. ν_{max} 2962, 1739, 1684, 1203, 1143 cm^{-1} . $[\alpha]_{\text{D}}^{20} +31.0^\circ$ ($c = 1.0$, CHCl_3).

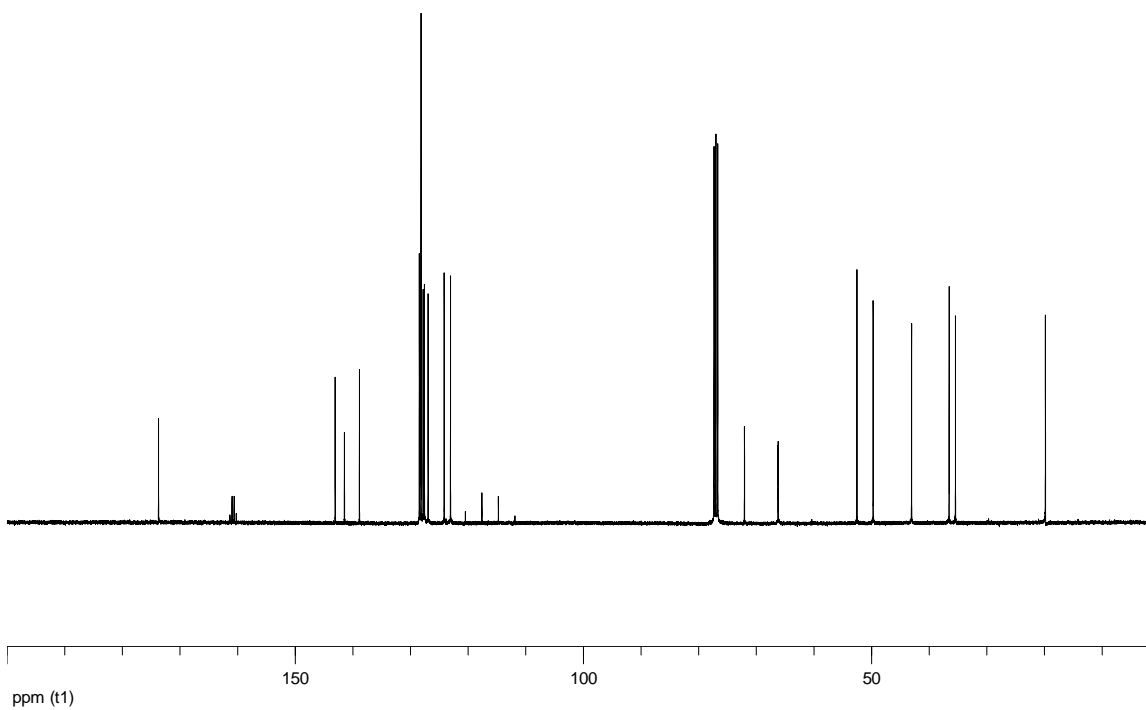


5. ^1H , ^{13}C and 2D NMR Spectra of Products of Radical Cyclizations and Hydantoin 35.

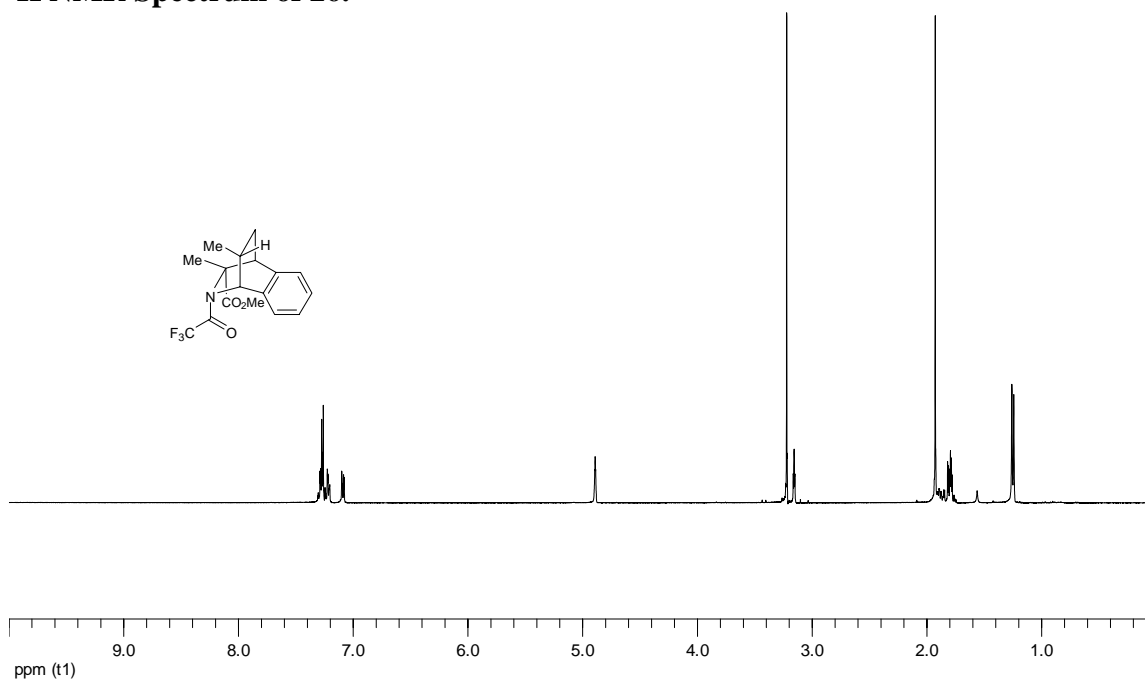
^1H NMR of 25.



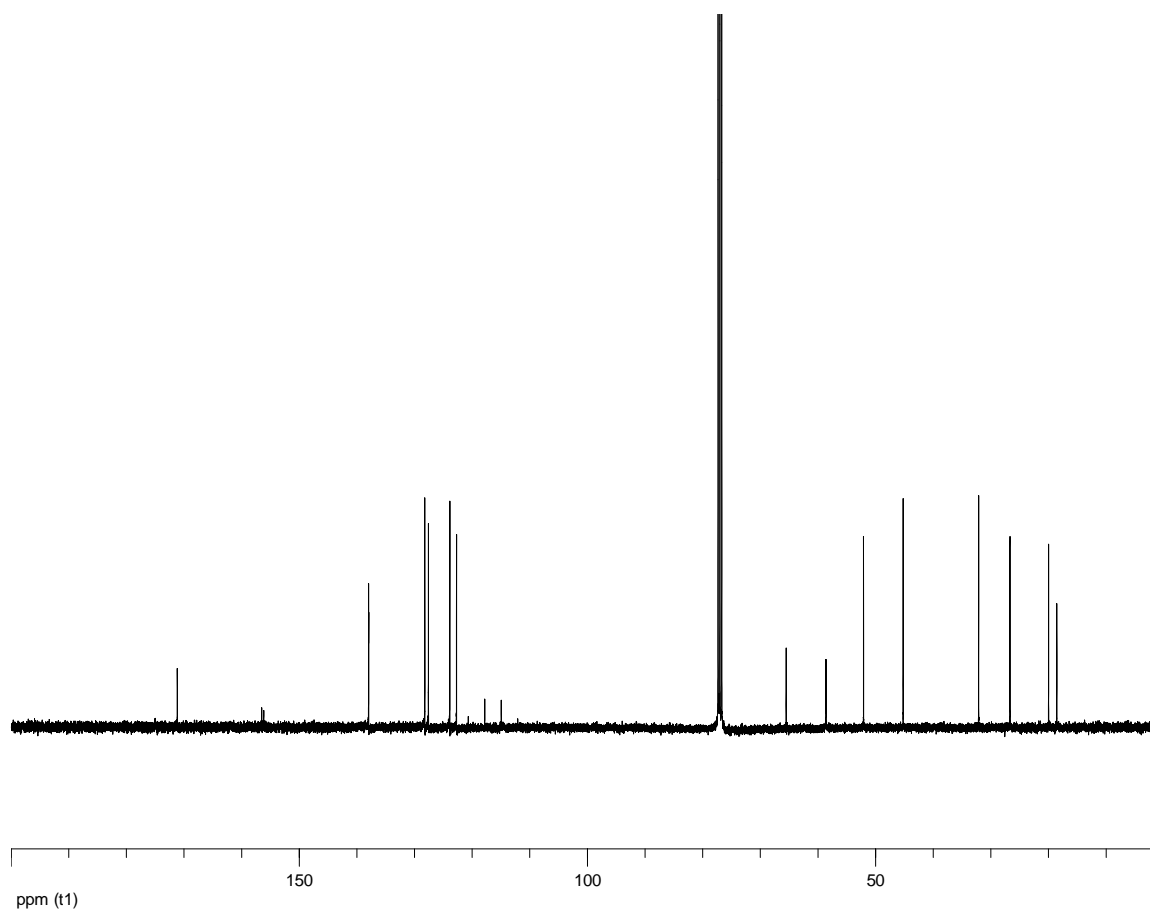
^{13}C NMR Spectrum of 25.



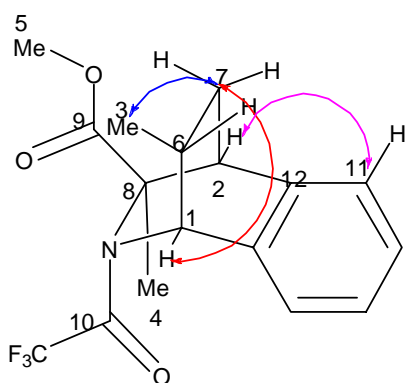
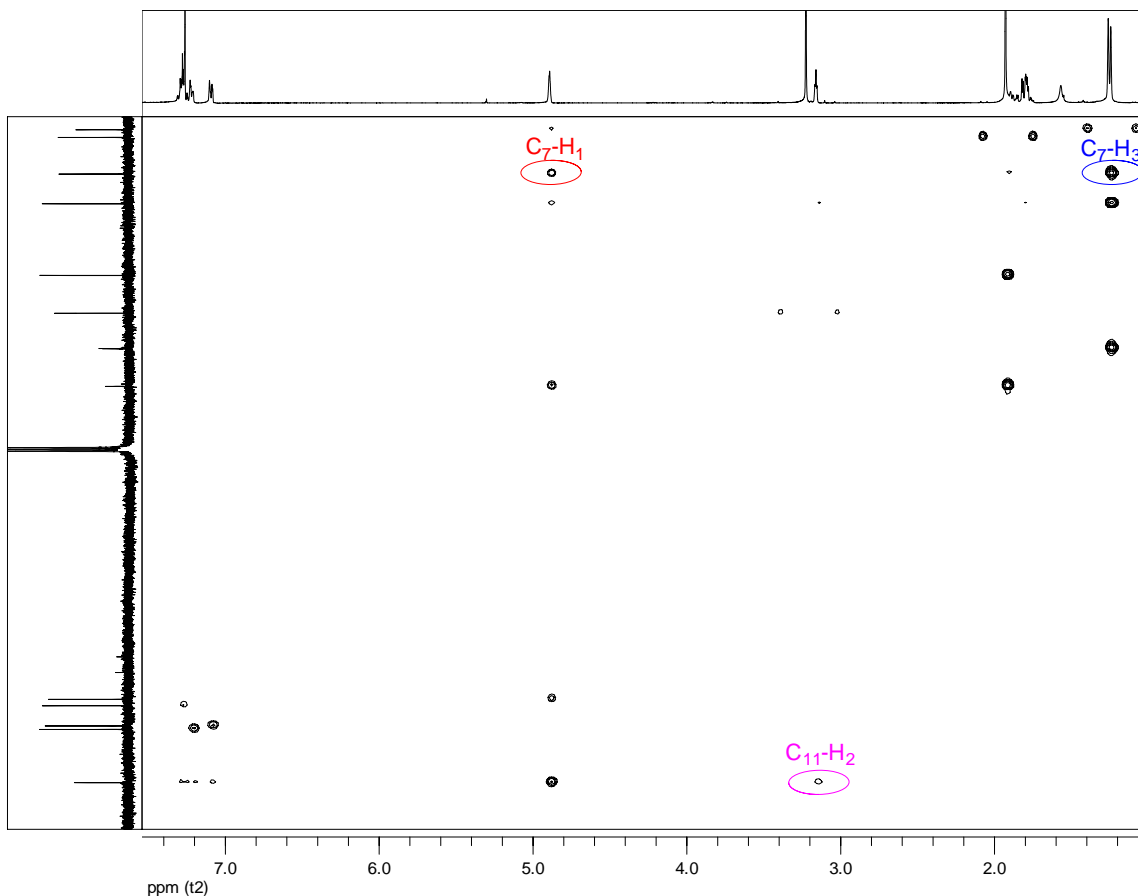
^1H NMR Spectrum of 26.



^{13}C NMR Spectrum of 26.

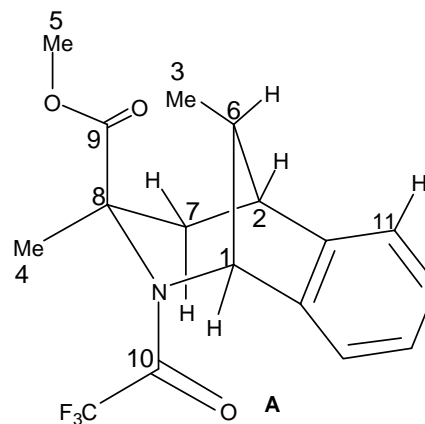


Expanded Segment of HMBC Spectrum of 26.



$C_{11}-H_2$ cross peak provides evidence for the C_2-C_{12} bond formed in this reaction

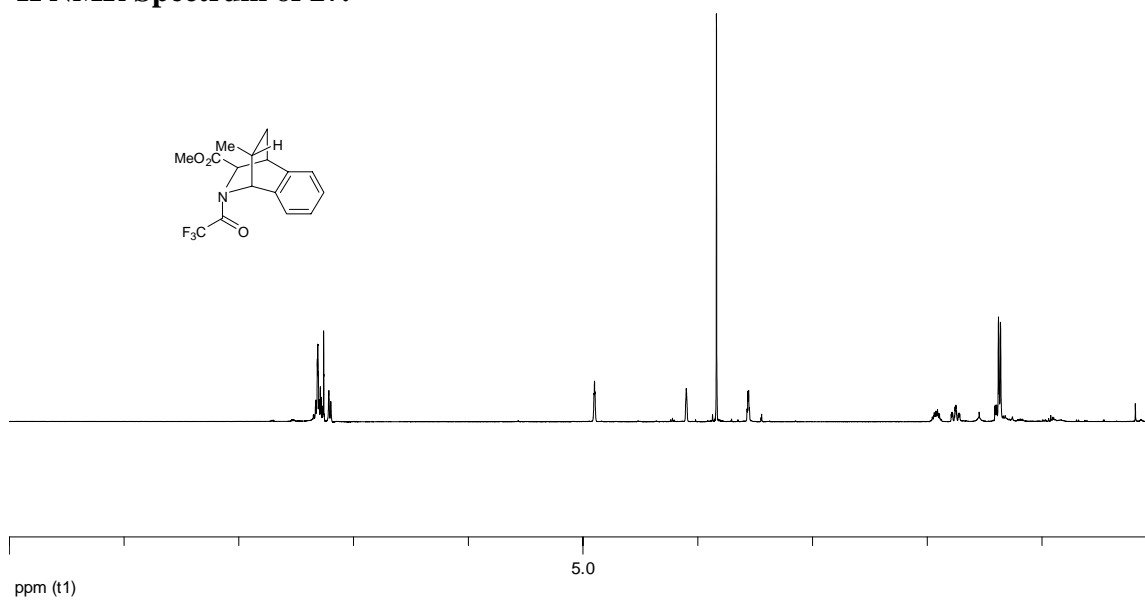
The strong three-bond HMBC cross peaks across C_7-H_3 and C_7-H_1 provide evidence for the [2,2,2]-bicyclo product as opposed to the [3,2,1]-bicyclo product A shown on the right.



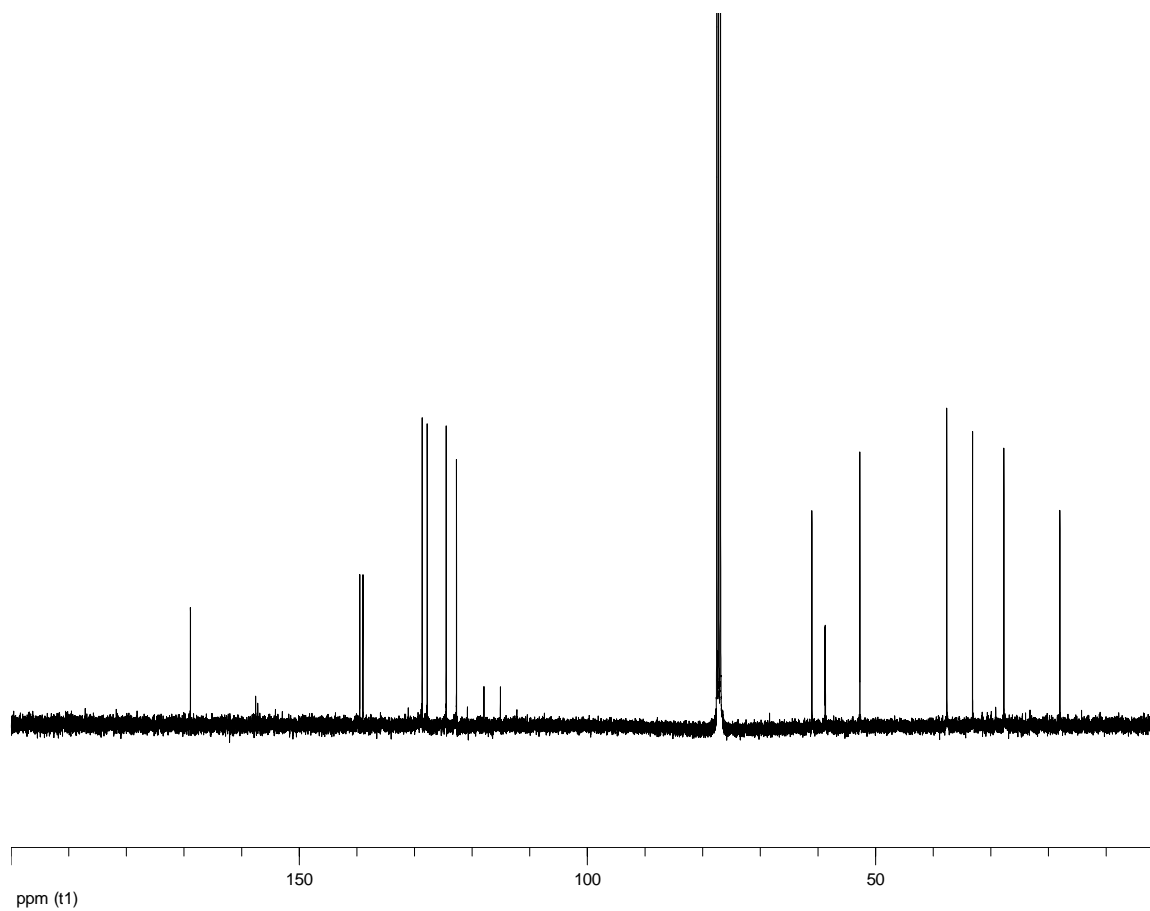
(This compound is not formed)

C_7-H_3 and C_7-H_1 are four bonds away in this structure and will not show (or show extremely weak) HMBC crosspeaks. The observed strong HMBC cross peaks for these bonds discount this structure.

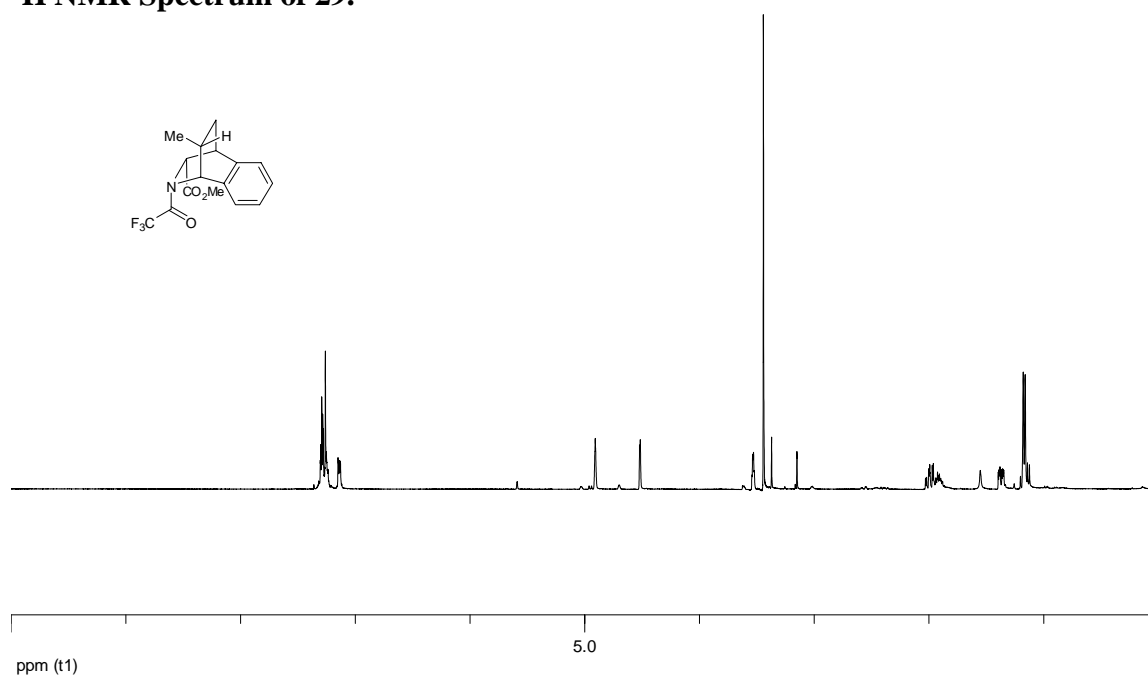
^1H NMR Spectrum of 27.



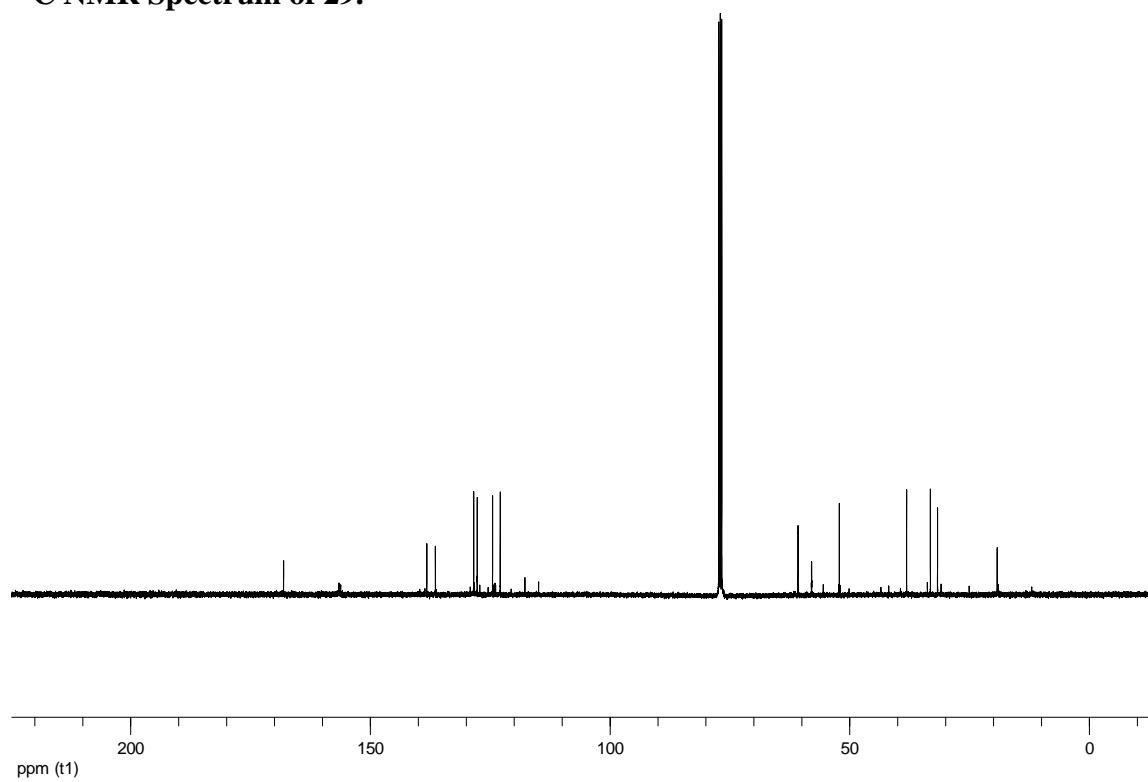
^{13}C NMR Spectrum of 27.



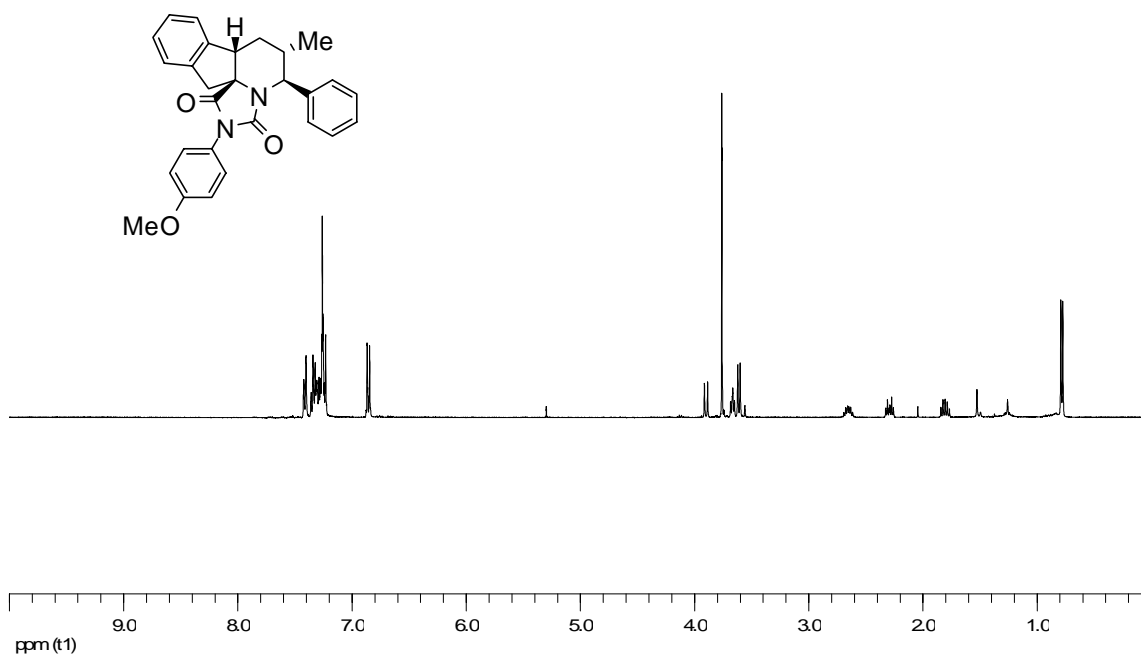
^1H NMR Spectrum of 29.



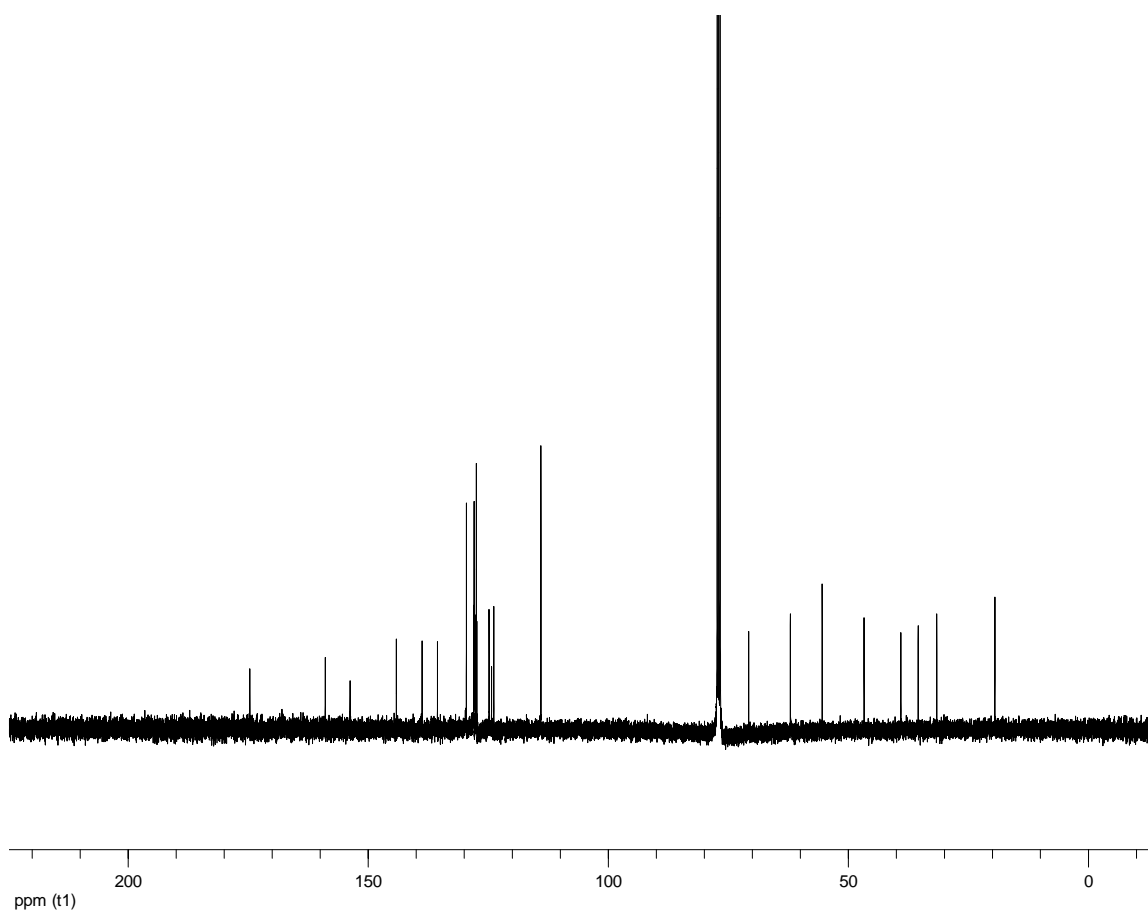
^{13}C NMR Spectrum of 29.



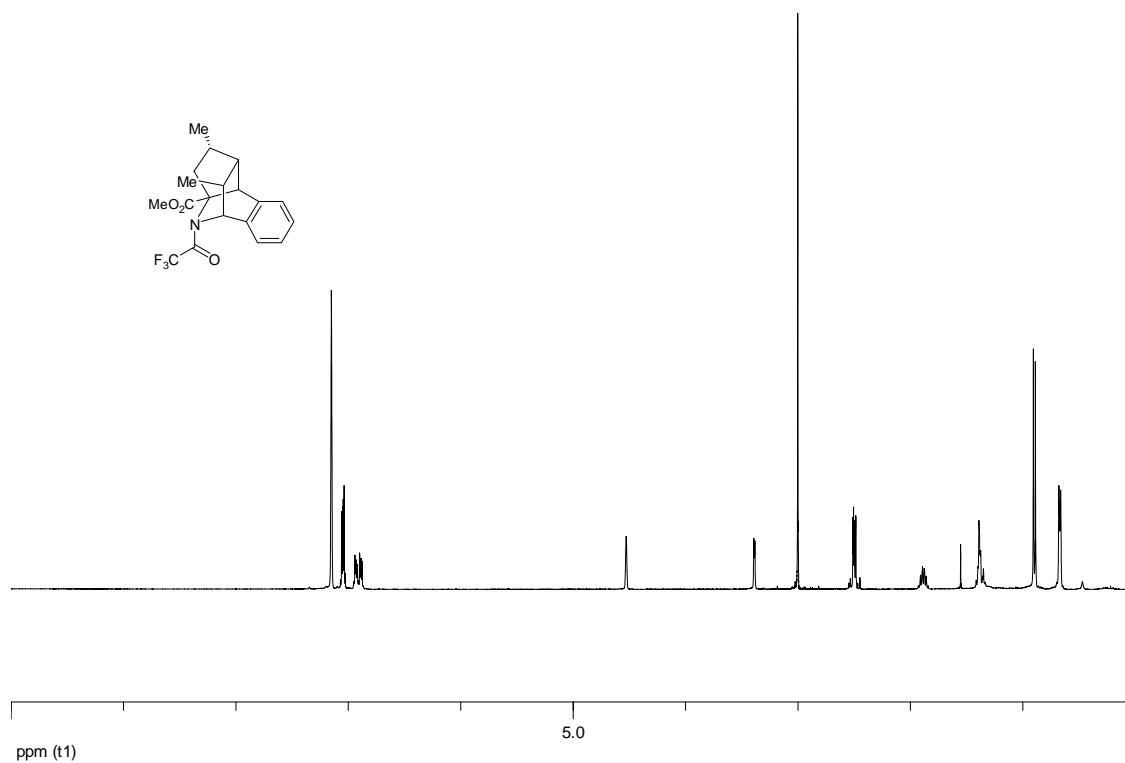
^1H NMR Spectrum of 35.



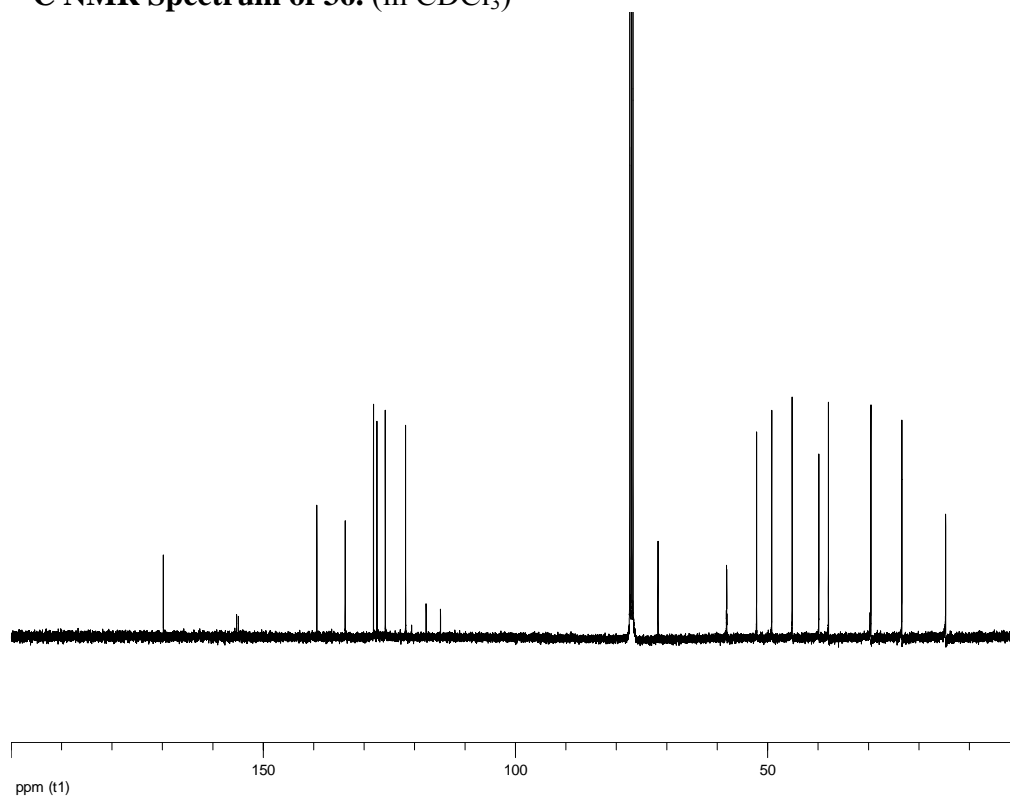
^{13}C NMR Spectrum of 35.



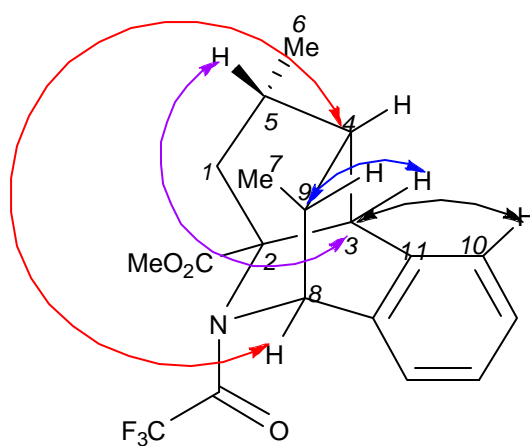
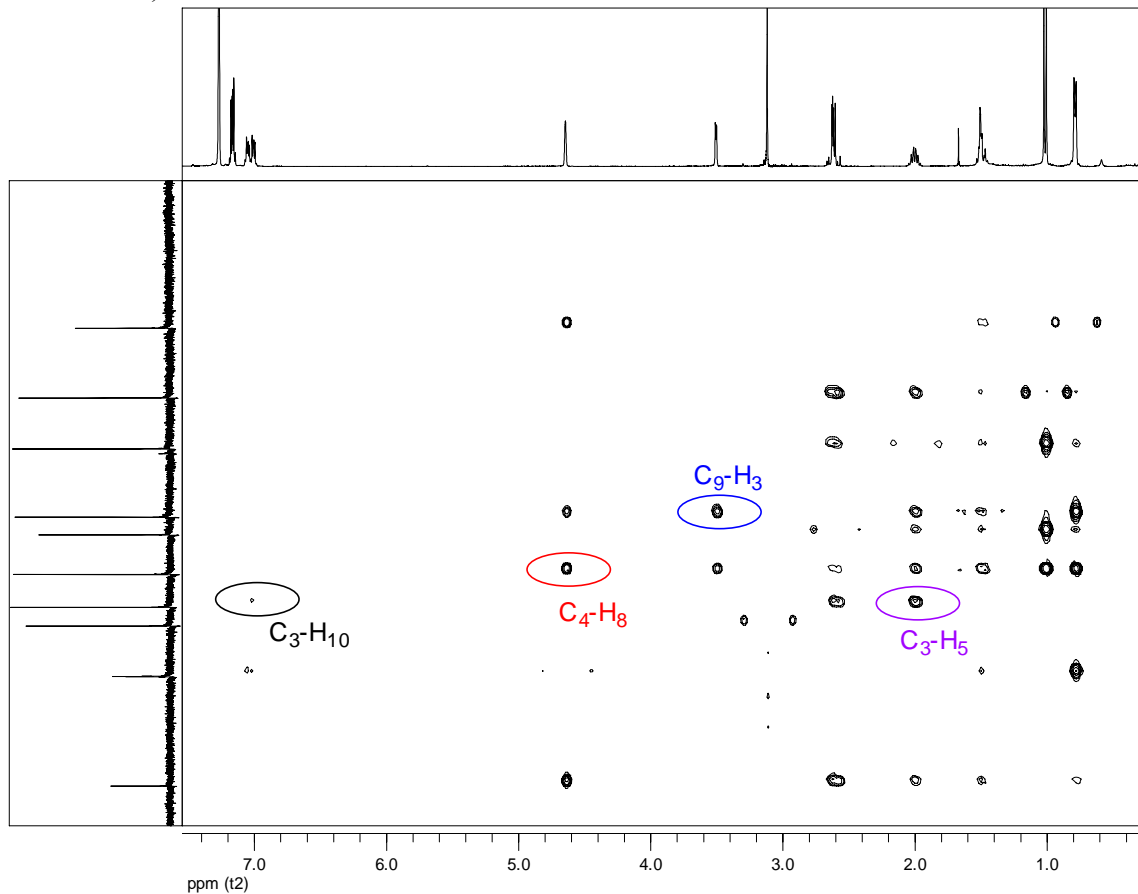
^1H NMR Spectrum of 36. (in benzene- d_6)



^{13}C NMR Spectrum of 36. (in CDCl_3)

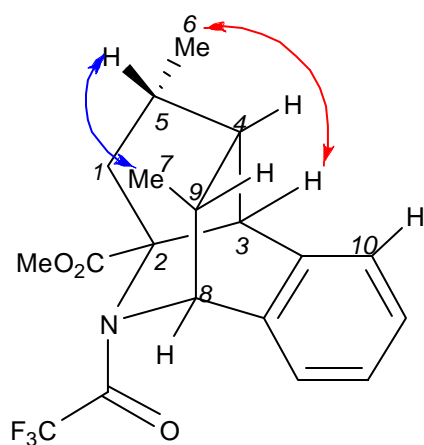
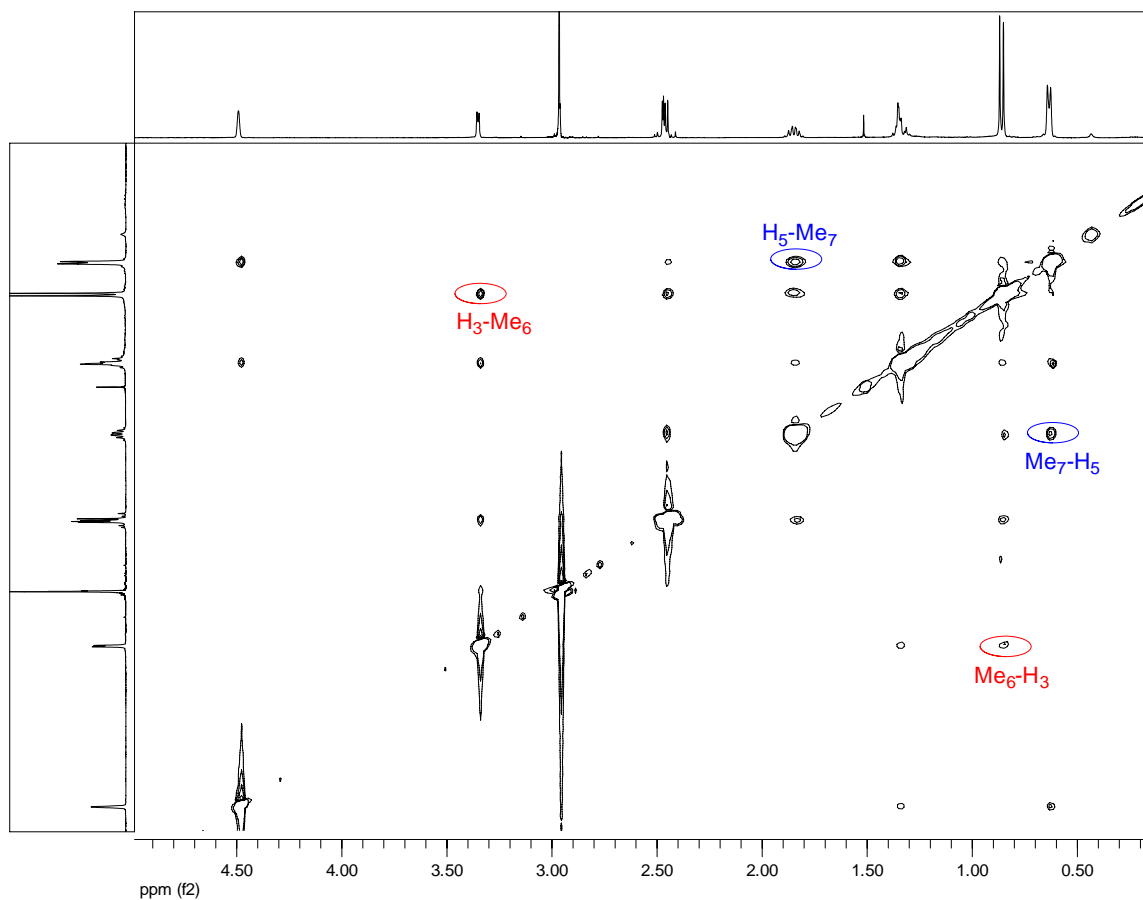


Expanded HMBC Spectrum of 36 (^1H , ^{13}C and HMBC spectra were obtained in benzene- d_6).



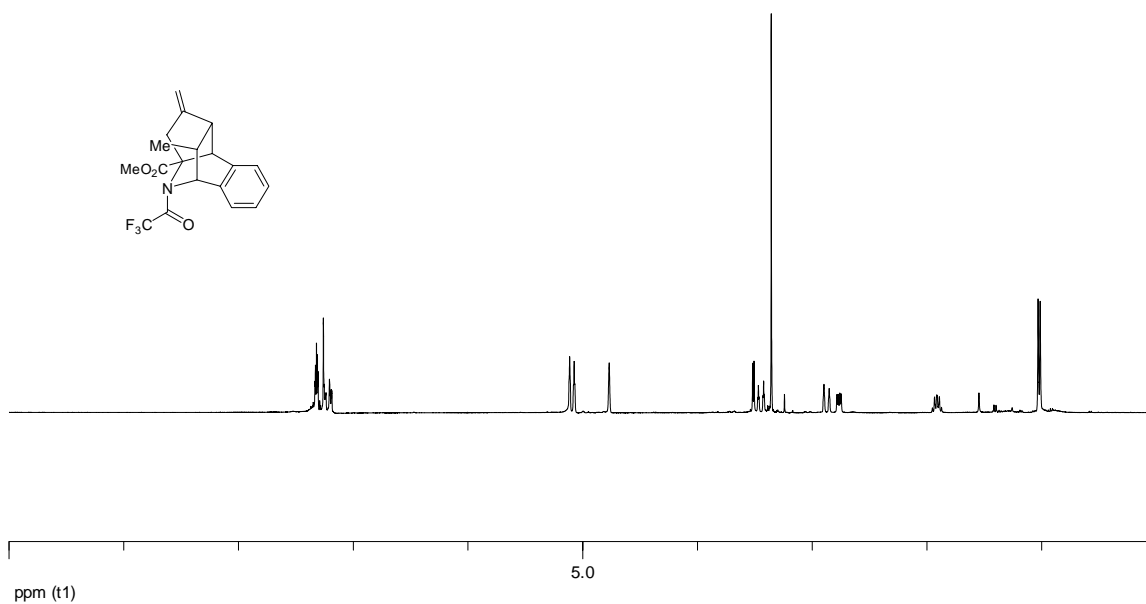
$\text{C}_3\text{-H}_{10}$ crosspeak provides evidence for the formation of $\text{C}_3\text{-C}_{11}$ bond

Expanded NOESY Spectrum of 36 (in benzene-d6)

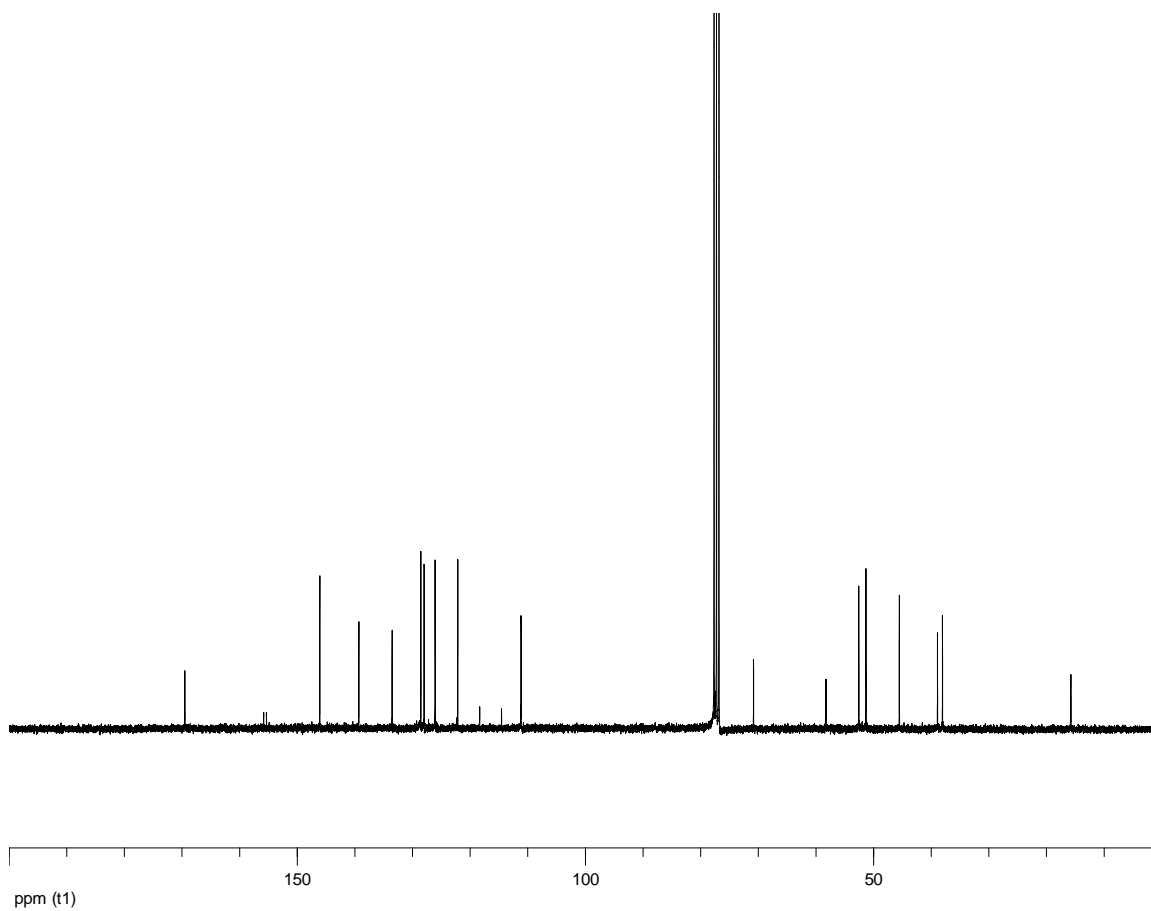


The indicated crosspeaks confirm the cis relationship between Me_6 and H_3 and Me_7 and H_5

^1H NMR Spectrum of 37.

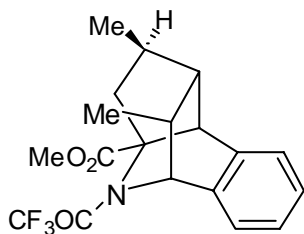


^{13}C NMR Spectrum of 37.

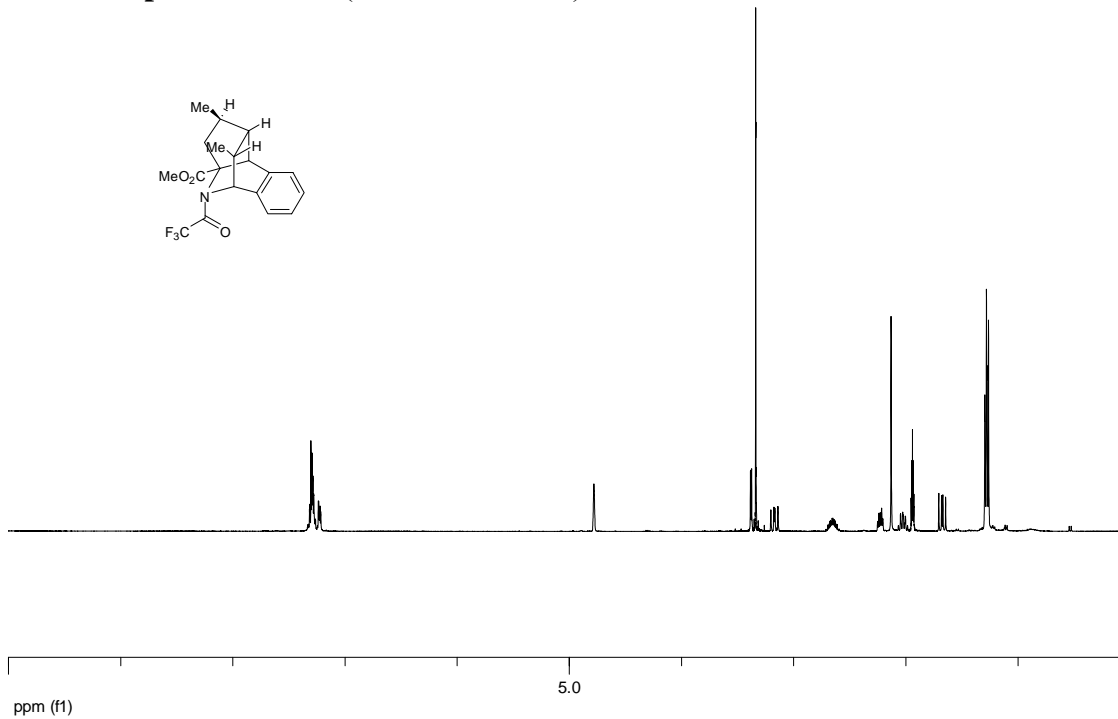


6. Hydrogenation

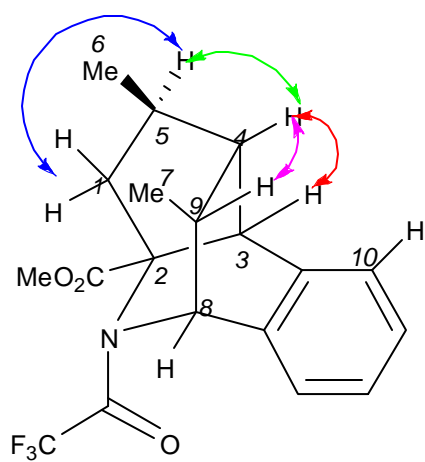
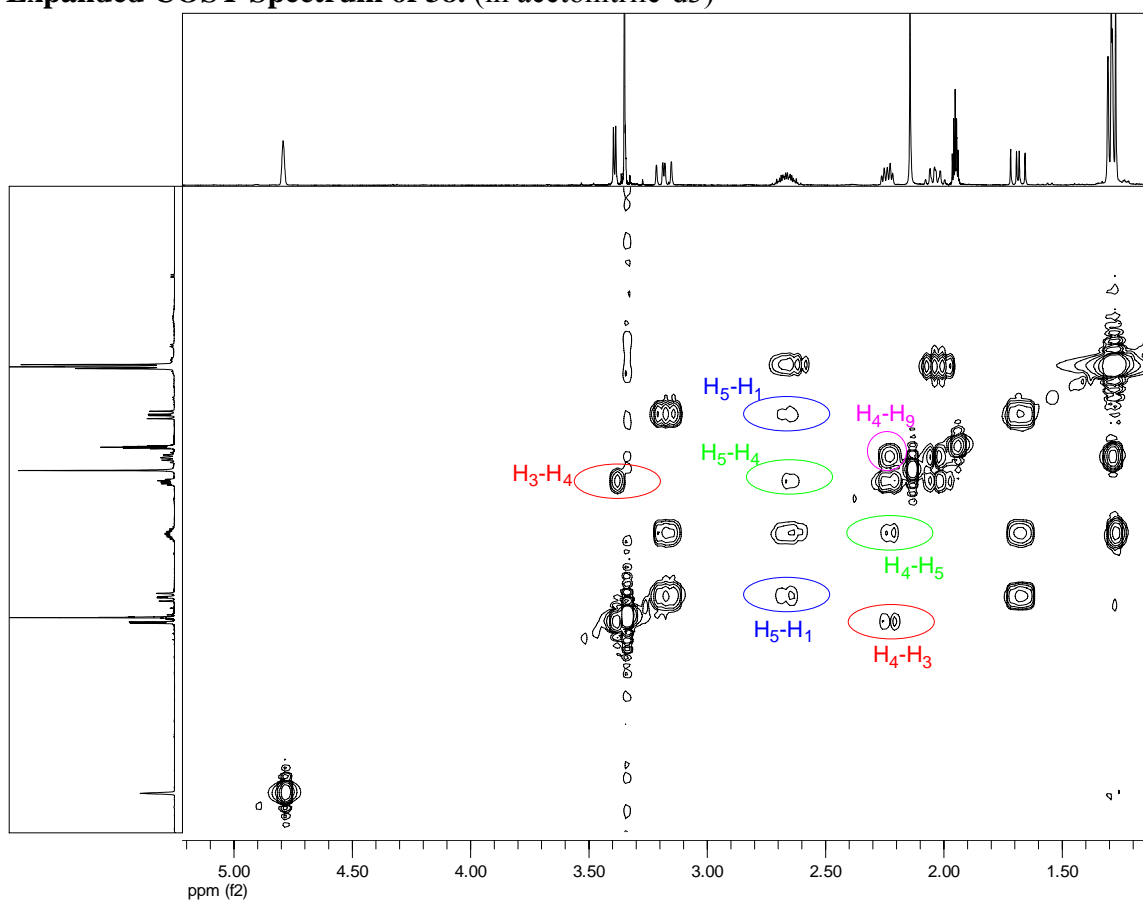
Compound 38: A solution of compound **37** (12 mg, 0.03 mmol) and PtO₂ (0.61 mg, 0.003 mmol, 0.10 equiv) in ethylacetate (2 mL) was evacuated and filled with a balloon of hydrogen. After stirring at room temperature for 5 min, the crude reaction mixture was filtered through celite and concentrated. Silica gel chromatography with ethyl acetate in hexane (from 0% to 30%) gave the desired product **38** (10 mg, 84% yield) as a viscous oil. ¹H NMR (400 MHz, CD₃CN) δ 7.34-7.25 (m, 3H), 7.25-7.20 (m, 1H), 4.78 (b s, 1H), 3.38 (d, *J* = 3.9 Hz, 1H), 3.34 (s, 3H), 3.17 (dd, *J* = 14.3, 10.9 Hz, 1H), 2.72-2.59 (m, 1H), 2.26-2.20 (m, 1H), 2.07-1.99 (m, 1H), 1.68 (dd, *J* = 14.4, 10.0 Hz, 1H), 1.29 (d, *J* = 5.61 Hz, 3H), 1.27 (d, *J* = 5.63 Hz, 3H). ¹³C NMR (100 MHz, CD₃CN) δ 170.6, 155.4 (q, *J* = 35.6 Hz), 140.4, 135.8, 128.8, 128.2, 126.8, 122.6, 117.5 (q, *J* = 282.2 Hz), 71.6, 59.3 (d, *J* = 3.0 Hz), 54.3, 52.6, 43.0, 42.2, 40.4, 38.3, 17.5, 17.0. HRMS (CI/NH₃) *m/z* calculated for [C₂₀H₂₀NO₃F₃+Na] 390.1293, found 390.1286. *v*_{max} 2962, 1740, 1684, 1203, 1143 cm⁻¹. [*α*]_D²⁰ +17.9 ° (c = 1.0, CHCl₃).



¹H NMR spectrum of 38 (in acetonitrile-d₃).



Expanded COSY Spectrum of 38. (in acetonitrile-d3)



Expanded 1D NOE Spectrum of 38 indicating *cis* relationship between H₅ and H₃:
 (in acetonitrile-d₃) (multiplet corresponding to H₅ is irradiated)

