Synthesis of Illudinine from Dimedone

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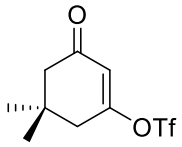
Supporting Information

Contents:

I. General Information

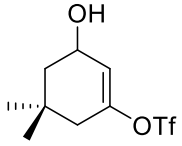
^{1}H-NMR and ^{13}C-NMR spectra were obtained on a 400 or 600 MHz spectrometer using $CDCl_3$ as the deuterated solvent (≥99.8 atom % D, contains 0.03% (v/v) TMS. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.26 ppm for ^{1}H-NMR and 77.0 ppm for ^{13}CNMR). Coupling constants (J) are reported in Hertz (Hz). IR spectra were recorded on an FT-IR spectrometer with diamond ATR accessory as thin film. Mass spectra were recorded using electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). Microwave experiments were performed using a CEM Discover SP microwave reactor at a fixed temperature setting in a sealed vial and the temperature was monitored using an external IR sensor. Melting points were taken using an electrothermal Mel-Temp© apparatus. All chemicals were used as received without further purification and all reactions were run under nitrogen atmosphere. Glassware was oven-dried prior to use and all purifications were performed by flash chromatography using silica gel with 40-63 micron particle size.

II. Literature Preparation of Fragmentation/Olefination Precursors



5,5-dimethyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (1si)

To a suspension of 5,5-dimethyl-1,3-cyclohexanedione (***dimedone***, 3.00 g, 21.4 mmol, 1 equiv.) in dichloromethane (107 mL) was added pyridine (3.46 mL, 42.8 mmol, 2 equiv.). The resulting mixture was stirred at -78 ˚C for 10 minutes before trifluoromethanesulfonic anhydride (4.3 mL, 260 mmol, 1.2 equiv.) was added dropwise via syringe. The reaction was stirred at -78 ˚C for 20 minutes, warmed to 0˚C for 20 minutes, and room temperature for 30 minutes. When complete consumption of the starting dione was observed by TLC, the reaction was quenched using 1 M HCl solution and extracted 3 times with diethyl ether. The organic layers were combined and washed with aqueous Na_2CO_3 solution and water, dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography (eluent mixture: EtOAc/Hexane = 2/98) to yield 5.54 g vinyl triflate **1si** in ≥95% yield as a colorless oil. Spectroscopic data were identical to the previously reported data.[1]



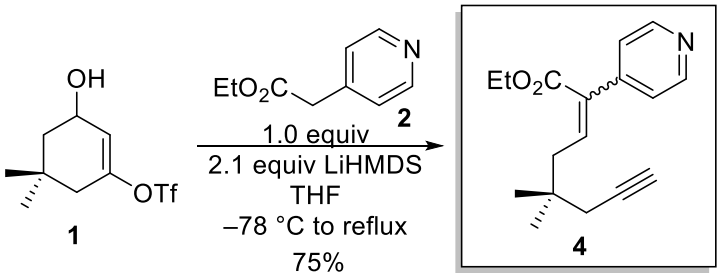
3-hydroxy-5,5-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (1)

To 86 mL THF solution of vinyl triflate **1si** (5.54 g, 20.3 mmol, 1 equiv.) at -78 ˚C was slowly added 24 mL DIBAL-H (1.0 M solution in toluene, 1.2 equiv.). The reaction mixture was stirred at -78 ˚C for 10 minutes, warmed to 0 ˚C for 10 minutes, and room temperature for 30 minutes. The reaction was diluted with ether, cooled to 0 ˚C and quenched by adding 15% NaOH and water. The mixture was stirred for 15

[1] Hoang, T. T.; Dudley, G. B. *Org. Lett.* **2013**, *15*, 4026.

minutes until a gel formed, and $MgSO_4$ was then added. After the addition of $MgSO_4$, the mixture was stirred for an additional 15 minutes. Vacuum filtration and evaporation gave the crude vinylogous hemiacetal triflate **1**. Purification flash column chromatography with gradient eluent from EtOAc/Hexane = 5/95 to EtOAc/Hexane = 20/80 yielded 5.41 g of **1** (97%). Spectroscopic data were identical to the reported data from the literature.[1]

III. Methods for The Synthesis of Illudinine



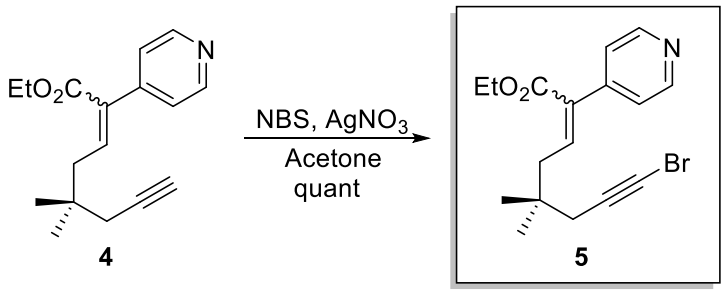
Ethyl 5,5-dimethyl-2-(pyridine-4-yl)oct-2-en-7-ynoate (4)

To a 118 mL THF solution of 11.3 mL lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 11.3 mmol, 2.1 equiv) at -78 ˚C was added 1.62 g vinylogous hemiacetal triflate **1** (5.90 mmol, 1.1 equiv) and 886 mg ethyl-4-pyridylacetate **2** (5.36 mmol, 1 equiv) successively. The resulting mixture was stirred at -78 °C for 10 minutes, warmed to 0 °C for 10 minutes, room temperature for 30 minutes, and heated in an oil bath at 60 °C for 2 hours. After 2 hours, the reaction mixture was cooled to room temperature and half-saturated NH_4Cl was added to quench the reaction. The mixture was extracted with diethyl ether 3 times. The organic layers were combined and washed with water, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (eluent mixture: EtOAc/Hexane = 10/90) to give the desired enyne **4** as a 2:1 mixture of alkene isomers (1.09 g, 75%).

^{1}HNMR major isomer (400MHz, $CDCl_3$): δ 8.62 (dd, J = 4.6, 1.30Hz, 2H), 7.20 (t, J = 7.90Hz, 1H), 7.11 (dd, J = 4.40, 1.5Hz, 2H), 4.22 (q, J = 7.10Hz, 2H), 2.12 (d, J = 7.90Hz, 2H), 2.06 (d, J = 2.60Hz, 2H), 1.92 (t, J = 2.60Hz, 1H), 1.25 (t, J = 7.10Hz, 3H), 0.98 (s, 6H) ppm

^{13}CNMR of major isomer (400MHz, $CDCl_3$): δ 165.76, 149.42, 143.70, 142.70, 133.56, 124.91, 81.40, 70.58, 61.14, 40.19, 34.36, 31.61, 26.69, 14.11 ppm

HRMS (ESI+) calcd for $C_{17}H_{22}NO_2^+$ [$(M+H)^+$]: 272.1651, found 272.1641



Ethyl 8-bromo-5,5-dimethyl-2-(pyridine-4-yl)oct-2-en-7-ynoate (5)

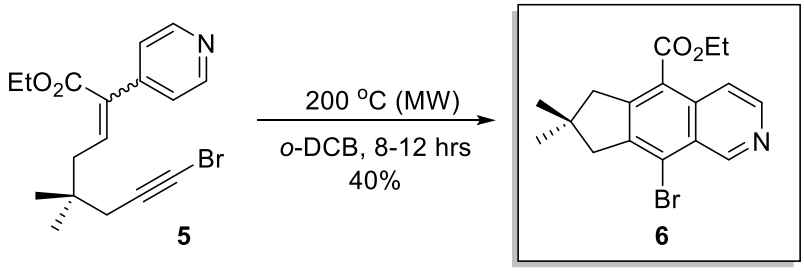
To a solution of 575 mg enyne **4** in 10.6 mL acetone was added $AgNO_3$ (109 mg, 0.3 equiv) and NBS (452 mg, 1.1 equiv) consecutively. The flask was wrapped in aluminum foil and stirred at room temperature for 1 hour. The reaction mixture was filtered through a 1 inch silica plug using diethyl ether as the eluent and then concentrated under reduced pressure. Purification by flash column chromatography using gradient eluent from 5% to 30% EtOAc in hexane yielded bromoalkyne **5**[2] (740 mg, >99%) as yellow oil.[3]

^{1}HNMR major isomer (400MHz, $CDCl_3$): δ 8.63 (d, J = 5.12Hz, 2H), 7.18 (t, J = 7.90, 1H), 7.11 (d, J = 5.92Hz, 2H), 4.22 (q, J = 7.10Hz, 2H), 2.10 (d, J = 7.92Hz, 2H), 2.07 (s, 2H), 1.25 (t, J = 7.10Hz, 3H), 0.97 (s, 6H) ppm

^{1}HNMR minor isomer (400MHz, $CDCl_3$): δ 8.56 (d, J = 3.84Hz, 2H), 7.26 (d, J = 6.00Hz, 2H), 6.39 (t, J = 7.94Hz, 1H), 4.32 (q, J = 7.12Hz, 2H), 2.52 (d, J = 8.00Hz, 2H), 2.19 (s, 2H), 1.34 (t, J = 7.12Hz, 3H), 1.06 (s, 6H) ppm

^{13}CNMR of mixture of major and minor isomers (400MHz, $CDCl_3$): δ 166.74, 165.67, 149.68, 149.36, 145.21, 143.61, 142.43, 138.58, 134.51, 133.56, 124.82, 121.62, 77.80, 77.52, 61.10, 61.07, 40.97, 40.14, 39.89, 39.75, 34.75, 34.64, 32.99, 32.67, 26.78, 26.70, 14.13, 14.06 ppm

HRMS (ESI+) calcd for $C_{17}H_{21}NO_2Br^+$ $[(M+H)^+]$: 350.0756, found 350.0759



Ethyl 9-bromo-7,7-dimethyl-7,8-dihydro-6H-cyclopenta[g]isoquinoline-5-carboxylate (6)

[2] Major and minor isomers were not separated and the E/Z ratio was not determined. ^{1}HNMR data of major and minor isomers are listed separately in the text for clarity but the data was taken from a 2:1 isomeric mixture (vide infra).

[3] Best results were obtained when using new glassware and a new stir bar as trace metals adversely affected the reaction.

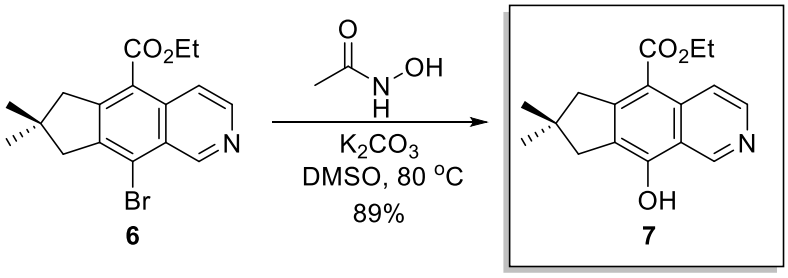
A solution of 328 mg of bromoalkyne **5** (0.939 mmol, 1 equiv) in 15.6 mL *o*-dichlorobenzene (*o*-DCB) was heated in a sealed reaction vessel in a microwave reactor at 200 ˚C. After 12 hours, the reaction was cooled and transferred directly into a flash column equipped with silica gel and 1% EtOAc/Hexane. The eluent was maintained at 1% until all of the *o*-DCB was out. Then the polarity of the eluent was gradually increased to 30% EtOAc/Hexane to obtain bromoisoquinoline **6** (130 mg, 40%) as a brown solid.

^{1}HNMR (400MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.58 (d, J = 6.00Hz, 1H), 8.15 (d, J = 6.00Hz, 1H), 4.49 (q, J = 7.10Hz, 2H), 3.17 (s, 2H), 2.98 (s, 2H), 1.46 (t, J = 7.10Hz, 3H), 1.20 (s, 6H) ppm

^{13}CNMR (600MHz, $CDCl_3$): δ 166.91, 151.32, 149.57, 145.36, 144.42, 134.80, 126.19, 123.46, 122.80, 117.67, 61.53, 49.76, 49.22, 39.16, 28.52, 14.41 ppm

HRMS (ESI+) calcd for $C_{17}H_{19}NO_2Br^+$ $[(M+H)^+]$: 348.0599, found 348.0611

MP: 107-110˚C



Ethyl 9-hydroxy-7,7-dimethyl-7,8-dihydro-6H-cyclopenta[g]isoquinoline-5-carboxylate (7)

To a screw-cap vial under N_2 was added 111 mg acetohydroxamic acid (1.48 mmol, 6 equiv), 341 mg K_2CO_3 (2.47 mmol, 10 equiv), and 86 mg of bromoisoquinoline **6** (0.247 mmol, 1 equiv). The vial was purged and refilled with N_2 before the addition of 0.82 mL of DMSO, such that the final substrate concentration was 0.3M. The mixture was heated at 80 ˚C for 20 hours before being cooled to room temperature and slowly quenched with 4.2 mL 1M HCl (4.20 mmol, 17 equiv). After stirring at room temperature for 10 minutes, the vial was placed in an ice bath without stirring for a further 10 minutes. The precipitate was filtered, washed with cold water, and dried under vacuum. Purification by flash column chromatography using gradient eluent from 20% to 80% EtOAc in hexane yielded hydroxyisoquinoline **7** (63 mg, 89%) as a bright yellow solid.

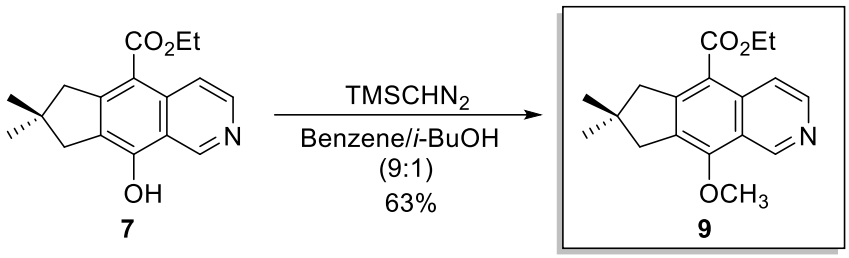
^{1}HNMR (600MHz, $CDCl_3$)[4]: δ 9.76 (s, 1H), 8.55 (d, J = 6.00Hz, 1H), 8.39 (d, J = 6.00Hz, 1H), 4.46 (q, J = 7.12Hz, 2H), 3.16 (s, 2H), 2.90 (s, 2H), 1.45 (t, J = 7.08Hz, 3H), 1.18 (s, 6H) ppm

^{13}CNMR (600MHz, CD_3OD): δ 167.27, 154.98, 148.61, 145.98, 142.77, 140.49, 138.13, 136.20, 125.85, 113.45, 60.51, 49.93, 42.92, 39.18, 27.46, 13.35 ppm

HRMS (ESI+) calcd for $C_{17}H_{20}NO_3^+$ $[(M+H)^+]$: 286.1443, found 286.1441

MP: 198-202˚C

[4] ^{1}HNMR was run at a concentration of 4.6 mg of substrate per 1 mL of $CDCl_3$



Ethyl 9-methoxy-7,7-dimethyl-7,8-dihydro-6H-cyclopenta[g]isoquinoline-5-carboxylate (9)

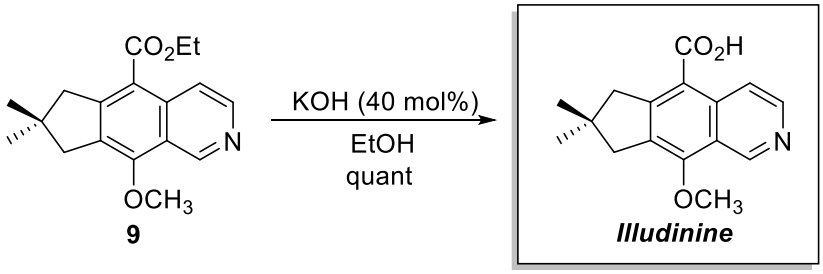
To a solution of 19.2 mg of hydroxyisoquinoline **7** (0.067 mmol, 1 equiv) in 0.7 mL *i*-BuOH/benzene (1:9) at room temperature was slowly added 0.05 mL of (trimethylsilyl)diazomethane (2M solution in hexane, 0.1 mmol, 1.5 equiv). Once complete consumption of the starting alcohol was observed by TLC (12-18h), the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (eluent mixture: EtOAc/Hexane = 40/60) to give illudinine ethyl ester **9** (12.6 mg, 63%) as a slightly orange solid.

^{1}HNMR (600MHz, $CDCl_3$): δ 9.54 (bs, 1H), 8.54 (bs, 1H), 8.24 (d, J = 4.70Hz, 1H), 4.48 (q, J = 7.10Hz, 2H), 4.06 (s, 3H), 3.08 (s, 2H), 2.98 (s, 2H), 1.46 (t, J = 7.10Hz, 3H), 1.18 (s, 6H) ppm

^{13}CNMR (600MHz, $CDCl_3$)[5]: δ 167.23, 155.16, 153.31, 147.48, 144.06, 135.16, 130.72, 118.93, 61.12, 60.92, 49.05, 44.71, 40.18, 28.34, 14.45 ppm

HRMS (ESI+) calcd for $C_{18}H_{22}NO_3^+$ [$(M+H)^+$]: 300.1600, found 300.1600

MP: 63-65˚C



Illudinine

To a solution of 10 mg illudinine ethyl ester **9** in 1 mL 95% EtOH was added 20 drops of 40% KOH at room temperature. The mixture was stirred for 20 hours before being neutralized (to ca. pH 3) with 10% HCl, and poured into pH 7 buffer (14 mL). The aqueous mixture was extracted with Et_2O (x4) and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give illudinine (9 mg, 99%) as a white solid.

^{1}HNMR (400MHz, CD_3OD)[6]: δ 9.72 (s, 1H), 9.01 (d, J = 6.96Hz, 1H), 8.51 (d, J = 6.92Hz, 1H), 4.30 (s, 3H), 3.28 (s, 2H), 3.25 (s, 2H), 1.22 (s, 6H) ppm

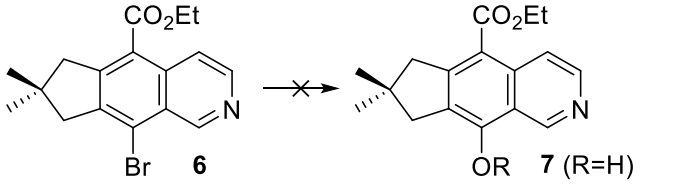
[5] Consistent with Dieters' report, not all quaternary carbons observed (see main text, ref 5).

^{13}CNMR (600MHz, CD_3OD)[6]**:** δ 168.64, 163.68, 157.27, 143.37, 139.44, 133.71, 132.87, 123.89, 123.15, 120.78, 61.77, 50.78, 46.28, 41.28, 28.23 ppm

HRMS (ESI+) calcd for $C_{16}H_{18}NO_3^+$ [$(M+H)^+$]: 272.1287, found 272.1277

MP: 218 to 225˚C

IV. Select S_NAr and Metal-catalyzed Aryl Ether Formation Efforts[7]



Entry	S_NAr/[Cu]	Entry	[Cu]/[Pd]
1	KOMe DMF, 150°C	6	CuI, 1,10-phenanthroline Cs_2CO_3, MeOH, 110°C
2	KOMe MeOH, 80°C	7	$Pd(dppf)Cl_2$, NaOH vinyltrimethoxysilane
3	KOH, CuI DMSO/H_2O, 100°C	8	$Pd(OAc)_2$, Cs_2CO_3 XPhos, Toluene/MeOH
4	NaOMe, CuI DMF, 110°C	9	$Pd(OAc)_2$, Cs_2CO_3 *t*-BuXPhos, Toluene/MeOH
5	KOMe, CuI 1,10-phenanthroline DMSO	10	$Pd(OAc)_2$, Cs_2CO_3 Singer's Ligand[a] Toluene/MeOH

[a] Under "**Pd-catalyzed**", see ref f)

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[6] CD_3OD + 1 drop TFA

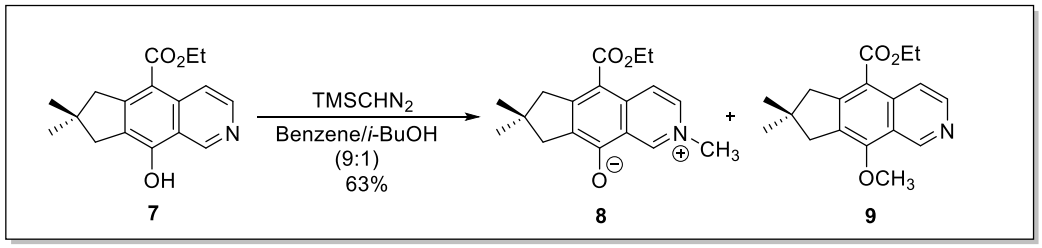
[7] **Cu-catalyzed (entries 3-6):**

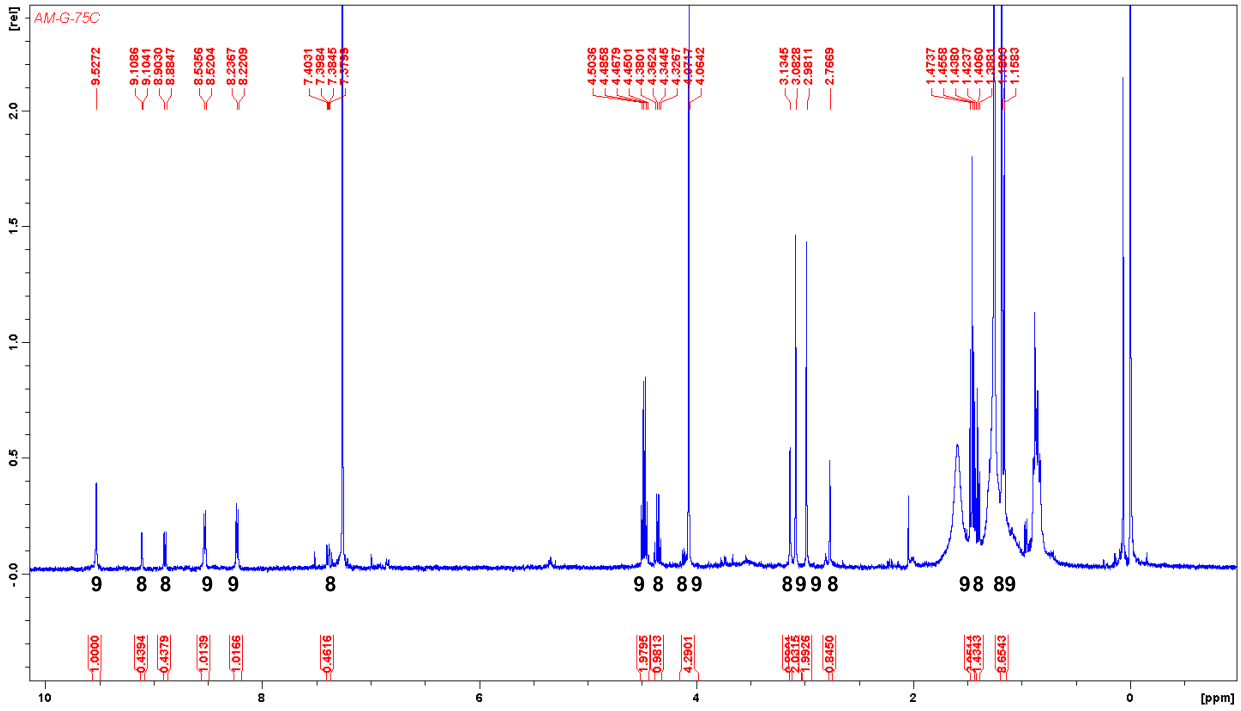
a) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. b) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284. c) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. d) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

Pd-catalyzed (entries 7-10):

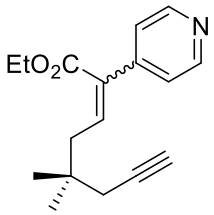
a) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. b) Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 11592. c) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770. d) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146. e) Withbroe, G. J.; Singer, R. A.; Sieser, J. E. *Org. Process Res. Dev.* **2008**, *12*, 480. f) Singer, R. A.; Caron, S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis* **2003**, *11*, 1727.

V. [1]HNMR of Crude Mixture of 7 to 9 Optimization (Table 1, entry 9)

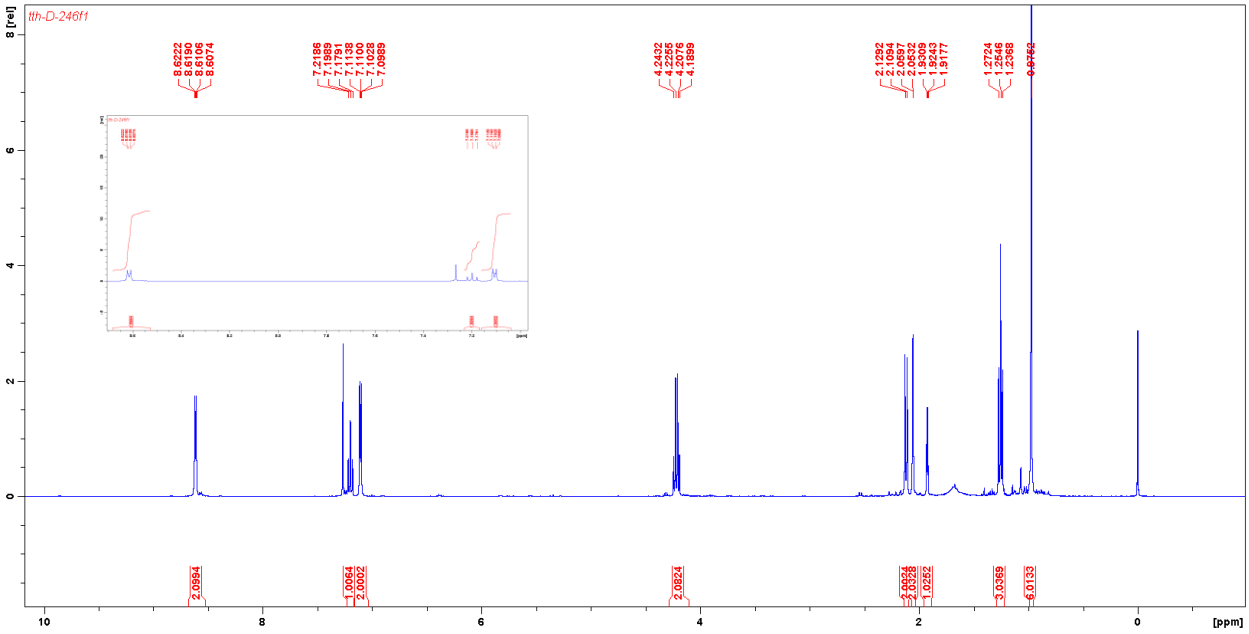


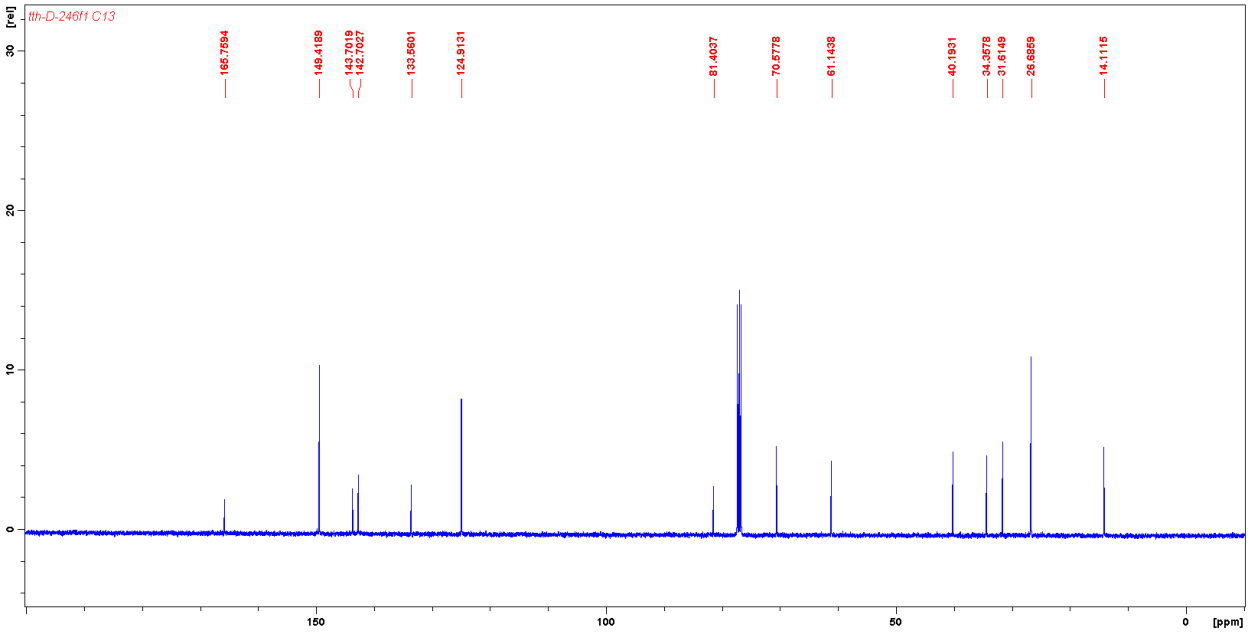


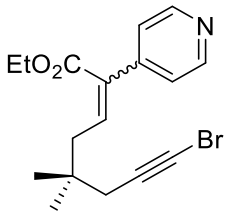
VI. Copy of ^{1}H-NMR and ^{13}C-NMR Data



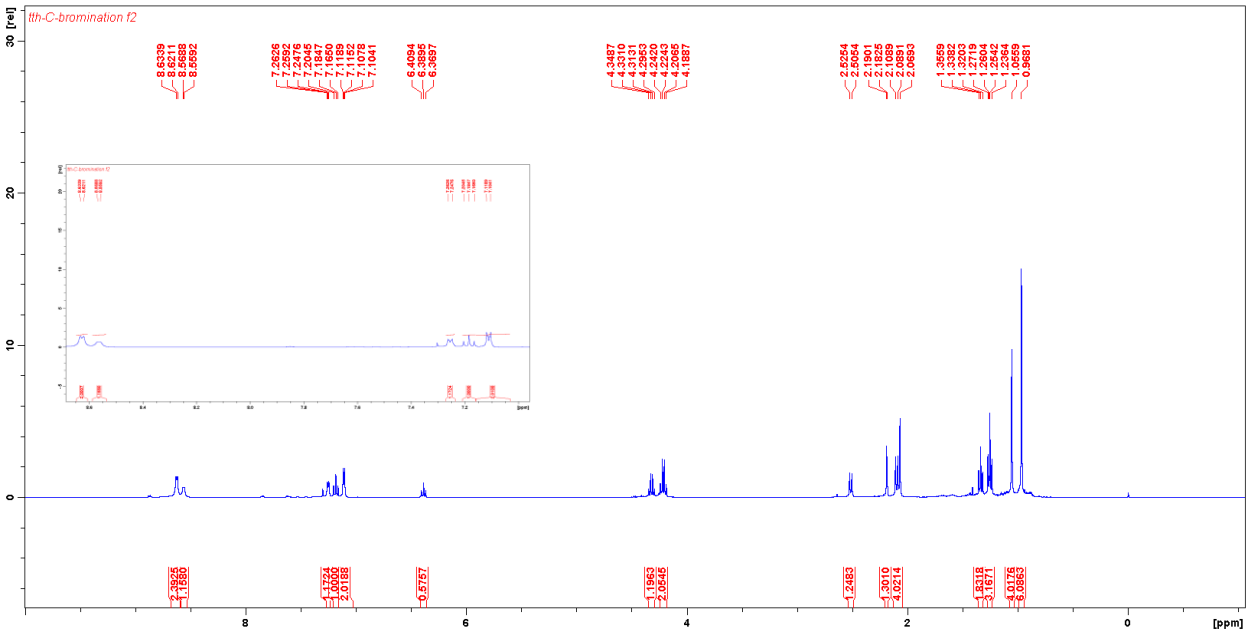
Ethyl 5,5-dimethyl-2-(pyridine-4-yl)oct-2-en-7-ynoate (4)

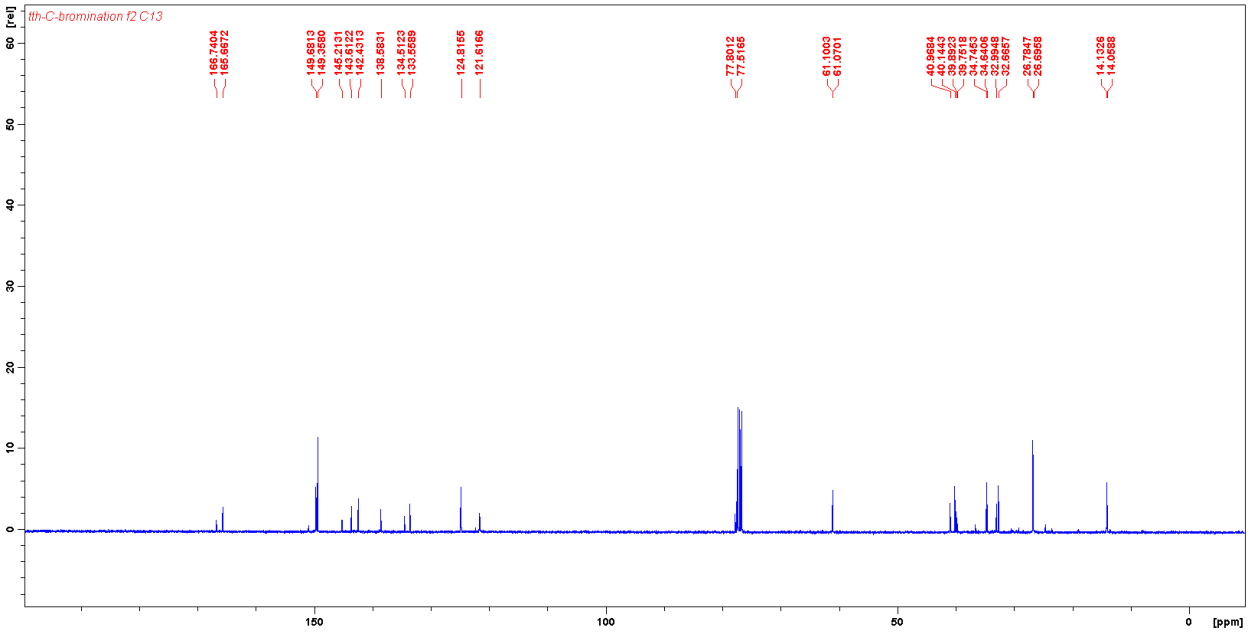


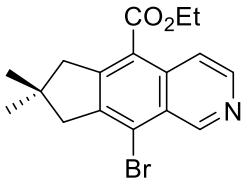




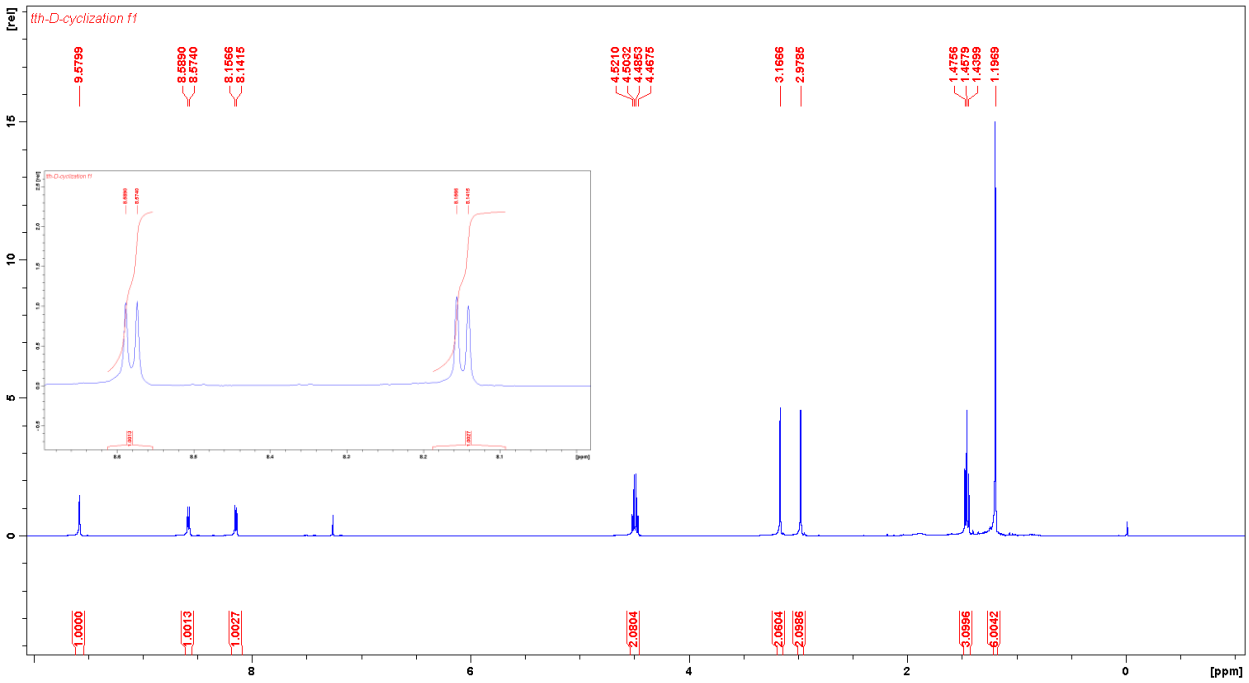
Ethyl 8-bromo-5,5-dimethyl-2-(pyridine-4-yl)oct-2-en-7-ynoate (5)

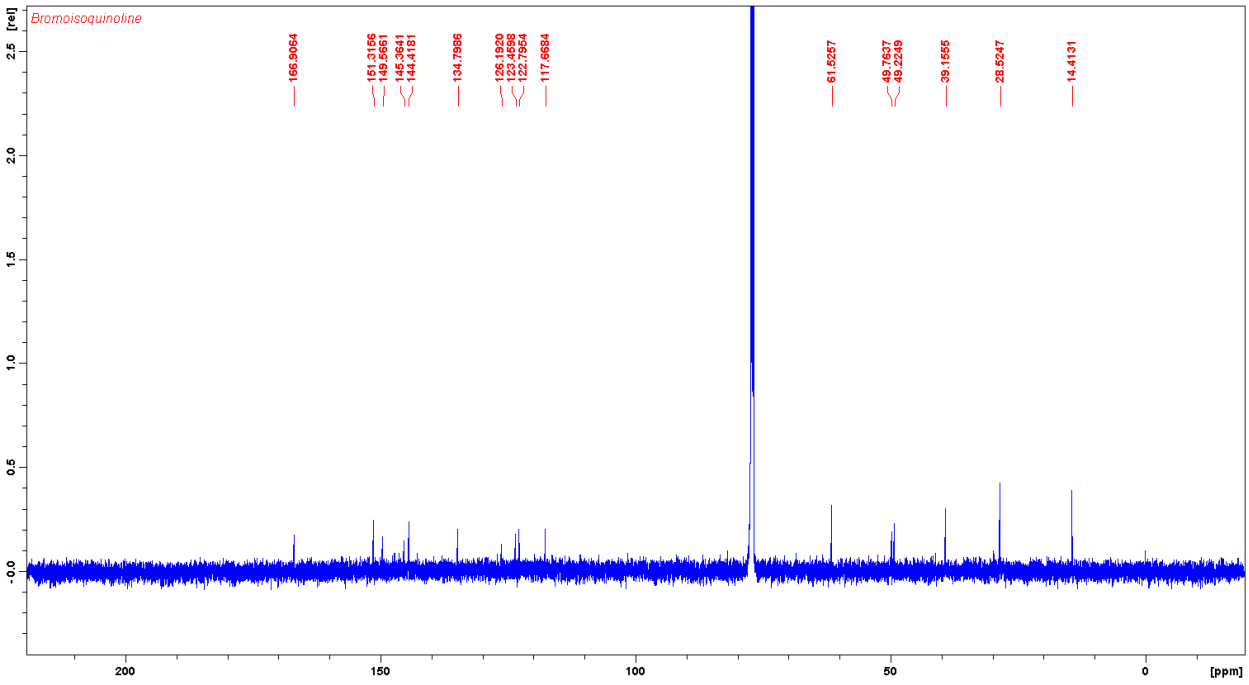


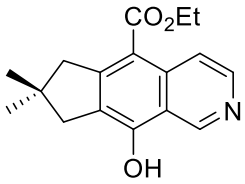




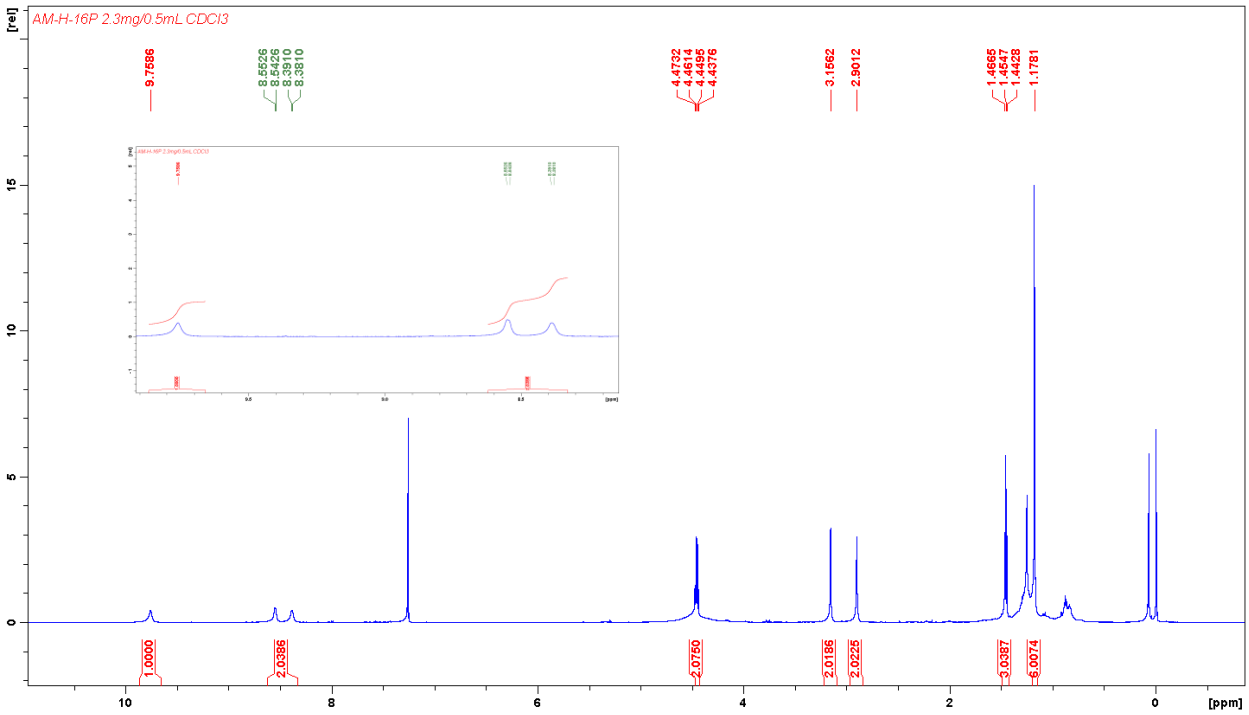
Ethyl 9-bromo-7,7-dimethyl-7,8-dihydro-6H-cyclopenta[g]isoquinoline-5-carboxylate (6)

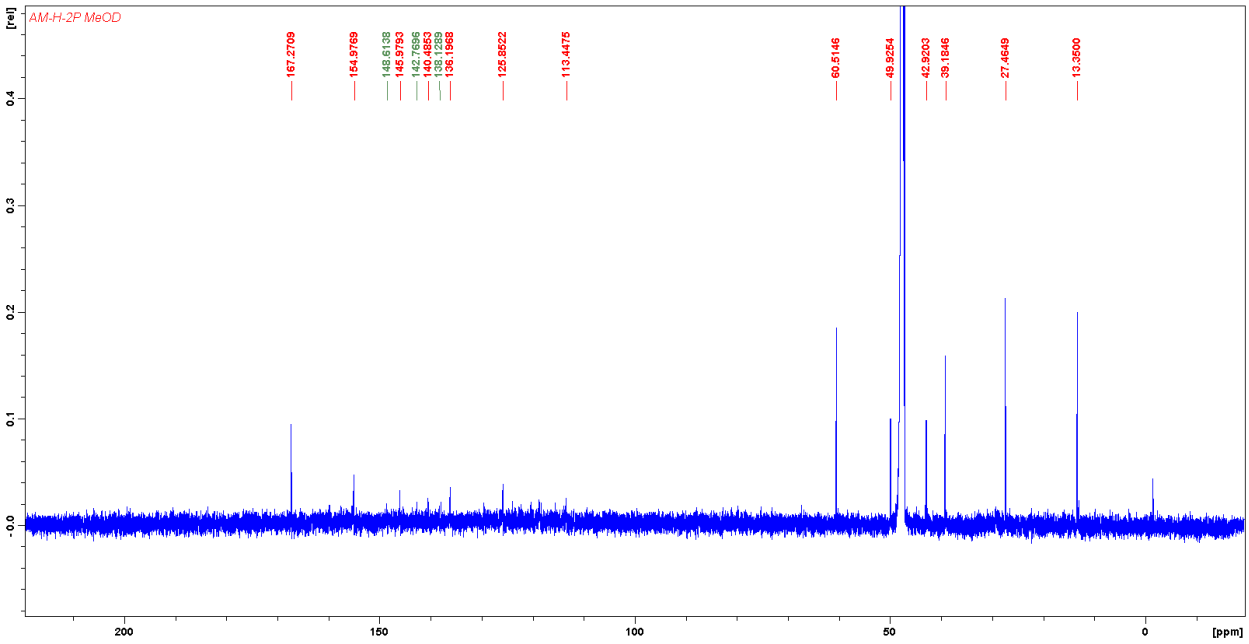


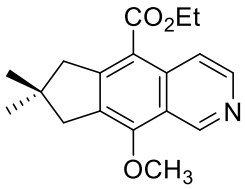




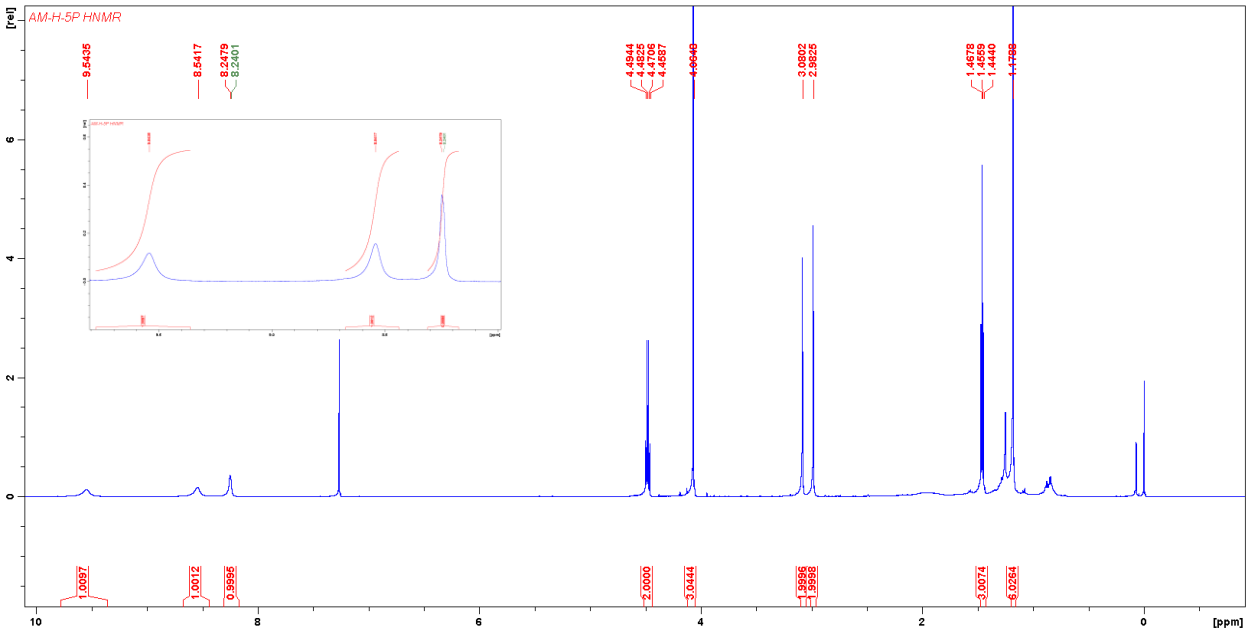
Ethyl 9-hydroxy-7,7-dimethyl-7,8-dihydro-6H-cyclopenta[g]isoquinoline-5-carboxylate (7)

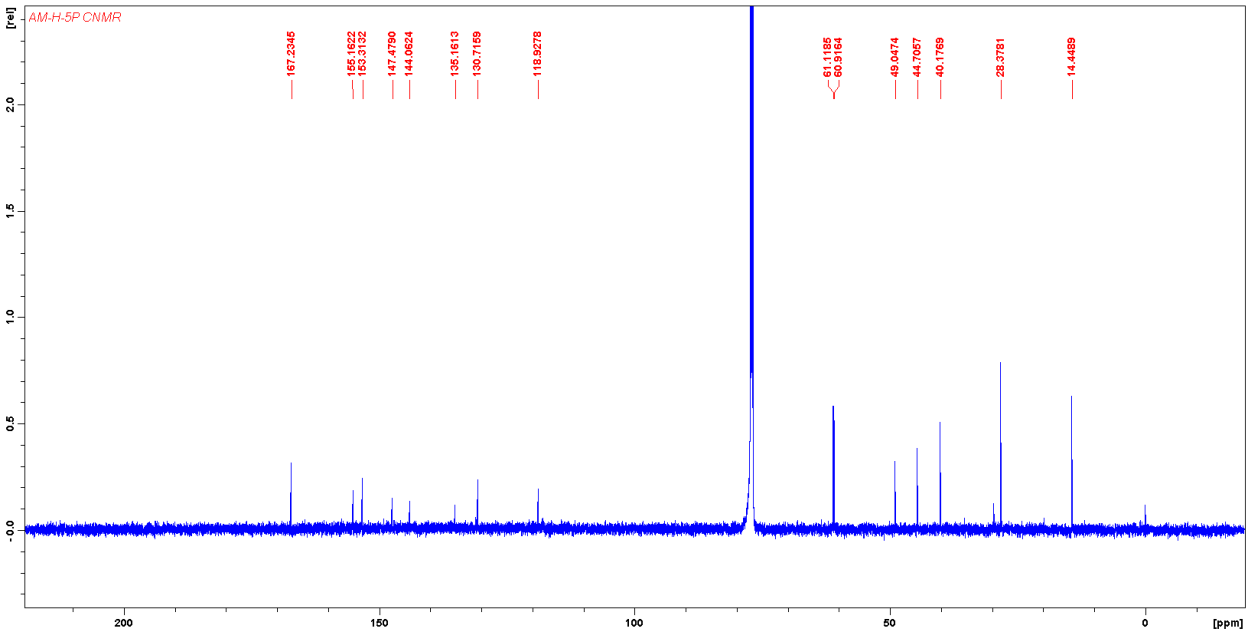


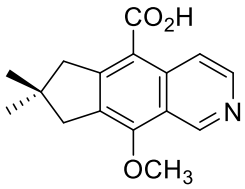




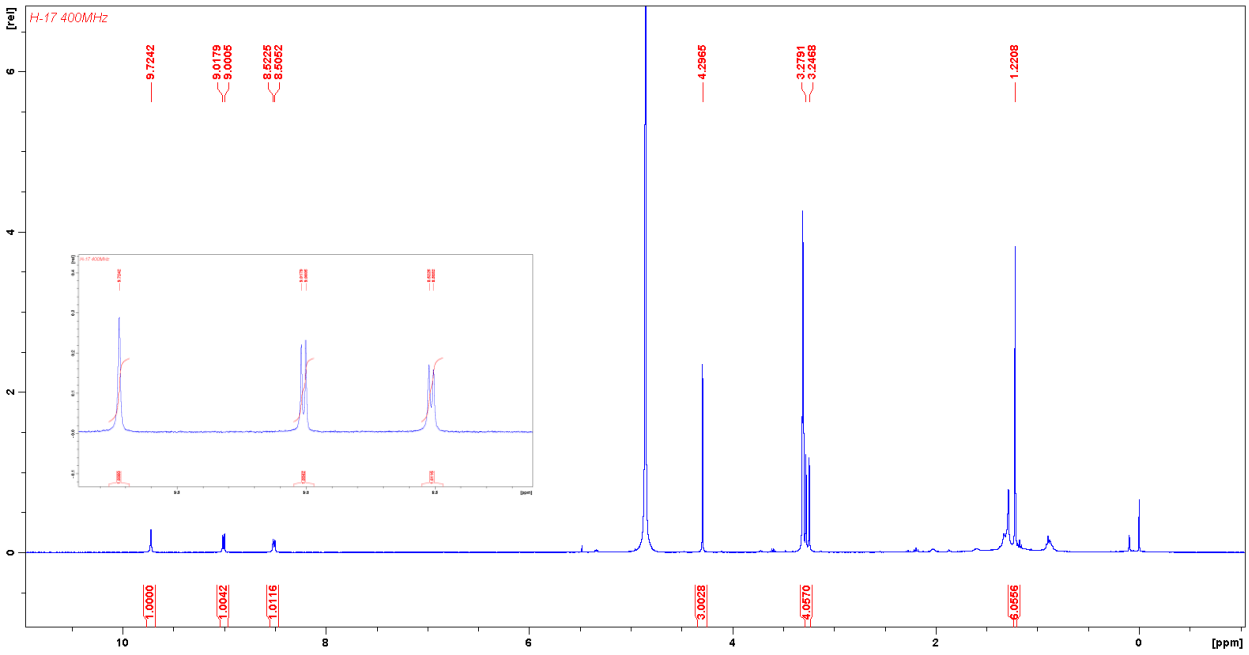
Ethyl 9-methoxy-7,7-dimethyl-7,8-dihydro-6H-cyclopenta[g]isoquinoline-5-carboxylate (9)

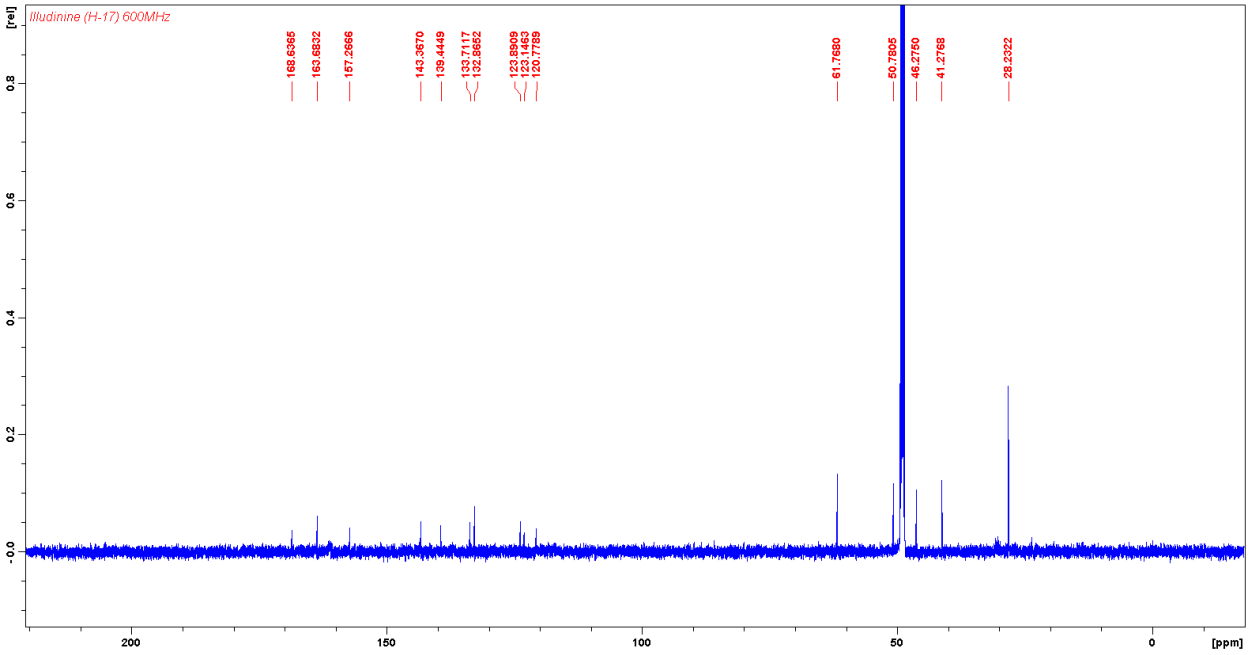





CO2H
N
OCH3

Illudinine


H-17 400MHz
[rel]
9.7242
9.0179
9.0065
8.5225
8.5052
4.2965
3.2791
3.2468
1.2208
1.0000
1.0042
1.0116
3.0026
4.0570
6.0556
[ppm]


Illudinine (H-17) 600MHz
[rel]
168.6365
163.6832
157.2666
143.3670
139.4449
133.7417
132.8552
123.8909
123.1463
120.7789
61.7680
50.7805
46.2750
41.2768
28.2322
[ppm]