Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information



69451 Weinheim, Germany

# A Serendipitous Discovery: Nickel Catalyst for the Cycloaddition of Diynes with Unactivated Nitriles**

*Puneet Kumar, Simon Prescher, and Janis Louie**

anie_201104475_sm_miscellaneous_information.pdf

## SUPPORTING INFORMATION

**General Experimental**:

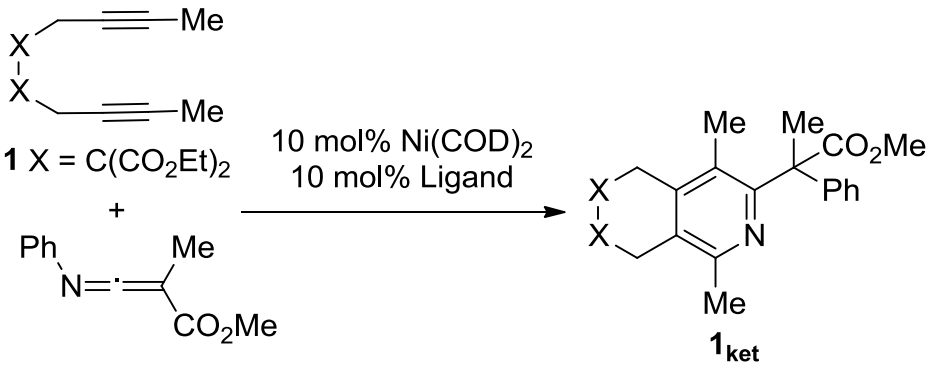
All reactions were conducted under an atmosphere of $N_2$ using standard Schlenk techniques or in a $N_2$ filled glove-box unless otherwise noted. Toluene was dried over neutral alumina under $N_2$ using a Grubbs type solvent purification system. THF was freshly distilled from Na/benzophenone. $Ni(COD)_2$ was purchased from Strem and used without further purification. The diynes were prepared according to literature procedure.[1] All other reagents were purchased and used without further purification unless otherwise noted.

$^1H$ and $^{13}C$ Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 125 MHz, respectively unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for $^1H$ and to the center line of a triplet at 77.23 ppm for $^{13}C$. The abbreviations s, d, dd, dt, dq, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, quartet, and quintet, in that order. All $^{13}C$ NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

Gas Chromatography was performed on an Agilent 6890 gas chromatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 50 ºC/min.; final temperature: 300 ºC held for 7 minutes; detector temperature: 250 ºC.

**Ligand Screening:**

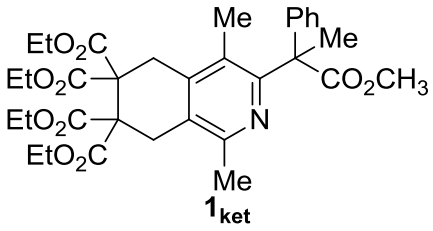
In nitrogen filled glove-box, diyne **1** (10 mg, 1 equiv.) and ketenimine[2] (1.2 equiv.) were added to an oven-dried screw-cap vial equipped with a magnetic stir bar. In separate vials, $Ni(COD)_2$ and ligand were weighed and dissolved in toluene. Catalyst solution (10 mol%) was added to the reaction mixtures. The vials were sealed, brought out of the glove-box, and stirred @ 100 °C for 24 h. The reactions were analyzeed by GC.




| Entry | Ligand[a] | % Conv.[b] | % Yield[b] |
|---|---|---|---|
| 1 | $PPh_3$ | 100 | - |
| 2 | P(*o*-Tol)$_3$ | 100 | - |
| 3 | $PCy_3$ | 67 | - |
| 4 | DPPB | 100 | - |
| 5 | Ph-Xantphos | 92 | 33 |
| 6 | *t*-Bu-Xantphos | 97 | - |
| 7 | P(O*i*-Pr)$_3$ | 95 | 22 |

[a] 20 mol% ligand was used except for entries 4-6, where 10 mol% ligand was used. [b]Analyzed by GC using decane as an internal standard.

**Tetraethyl 3-(1-methoxy-1-oxo-2-phenylpropan-2-yl)-1,4-dimethylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate ($1_{ket}$):**



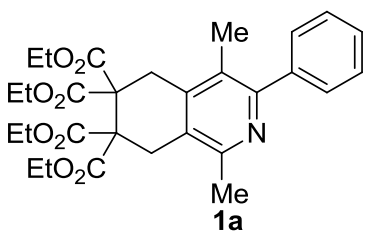
**$1_{ket}$**

In nitrogen filled glove-box, diyne (52.1 mg, 0.12 mmol, 0.1M) and ketenimine[2] (28.0 mg, 0.14 mmol) were added to an oven-dried screw-cap vial equipped with a magnetic stir bar. In a separate vial $Ni(COD)_2$ and Xantphos were weighed (in 1:1 molar ratio) and dissolved in toluene. 10 mol% Catalyst solution was added to the reaction mixture. The reaction vessel was sealed, brought out of the glove-box, and stirred @ 100 °C for 24 h. The resulting reaction mixture was concentrated, and purified by flash column chromatography using first 15% EtOAc, and then 30 % EtOAc in hexanes to afford the title compound **$1_{ket}$** as pale oil, 29%yield. $^1$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.25 (m, 5H), 4.20 (m, 8H), 3.68 (s, 3H), 3.33 (s, 2H), 3.30 (s, 2H), 2.42 (s, 3H), 1.98 (s, 3H), 1.68 (s, 3H), 1.24 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 175.7, 170.1, 169.9, 157.7, 151.9, 143.0, 142.3, 128.1, 128.0, 126.5, 125.2, 62.2, 59.7, 57.5, 56.6, 52.5, 32.8, 32.1, 24.7, 22.8, 15.7, 14.0. IR ($CH_2Cl_2$, $cm^{-1}$): 2984, 2935, 1735, 1600, 1575, 1446, 1368, 1270, 1241, 1203, 1096, 1036, 864, 700. HRMS (ESI): calcd for $C_{33}H_{42}NO_{10}$ $[M+1]^+$ 612.2809, found 612.2806.

**General Procedure for Cycloaddition of Diynes and Nitriles:**

In nitrogen filled glove-box, diyne (1 equiv., 0.1M) and nitrile (1.5 equiv.) were added to an oven-dried screw-cap vial equipped with a magnetic stir bar. In a separate vial $Ni(COD)_2$ and Xantphos were weighed (in 1:1 molar ratio) and dissolved in toluene. 3 mol% Catalyst solution was added to the reaction mixture. The vial was sealed and brought out of the glove-box. The reaction was stirred @ RT for 3 h. The resulting reaction mixture was concentrated and purified by flash column chromatography.

**Tetraethyl 1,4-dimethyl-3-phenylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (1a):**



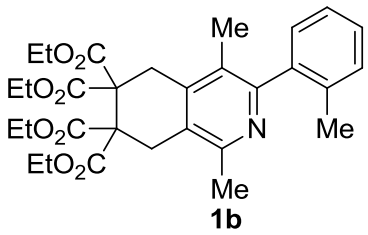
**1a**

The general procedure was used with 51.3 mg (0.12 mmol, 0.1 M) of diyne **1**, 18.7 mg (0.18 mmol) of nitrile **a**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash

column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **1a** as colorless oil, 98% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.43 (m, 4H), 7.36 (m, 1H), 4.23 (m, 8H), 3.43 (s, 4H), 2.50 (s, 3H), 2.17 (s, 3H), 1.25 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 169.99, 169.95, 155.6, 153.0, 141.42, 141.39, 129.4, 128.2, 127.6, 125.9, 125.3, 62.2, 57.1, 56.9, 33.1, 32.2, 22.5, 15.9, 13.9. IR ($CH_2Cl_2$, $cm^{-1}$):2984, 1736, 1568, 1447, 1368, 1271, 1240, 1203, 1095, 1053, 864, 702. HRMS (ESI): calcd for $C_{29}H_{36}NO_8$ $[M+1]^+$ 526.2441, found 526.2441.

**Tetraethyl 1,4-dimethyl-3-(o-tolyl)isoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (1b):**

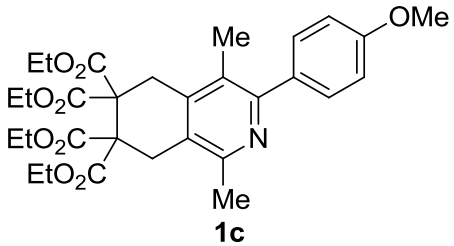


**1b**

The general procedure was used with 49.0 mg (0.11 mmol, 0.1 M) of diyne **1**, 20.3 mg (0.17 mmol) of nitrile **b**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **1b** as colorless oil, 87% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.32 (d, 2H, *J*= 8Hz), 7.23 (d, 2H, *J*= 8Hz), 4.23 (m, 8H), 3.43 (s, 4H), 2.49 (s, 3H), 2.39 (s, 3H), 2.17 (s, 3H), 1.25 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.0, 169.9, 155.6, 152.9, 141.2, 138.5, 137.2, 129.3, 128.9, 125.8, 62.1, 57.1, 56.9, 33.1, 32.2, 22.5, 21.4, 15.9, 13.9. IR ($CH_2Cl_2$, $cm^{-1}$):2983, 2924, 1734, 1445, 1367, 1205, 1095, 1039, 864, 734, 578. HRMS (ESI): calcd for $C_{30}H_{38}NO_8$ $[M+1]^+$ 540.2597, found 540.2591.

**Tetraethyl 3-(4-methoxyphenyl)-1,4-dimethylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (1c):**

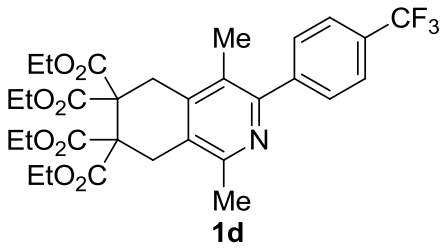


**1c**

The general procedure was used with 48.4 mg (0.11 mmol, 0.1 M) of diyne **1**, 20.3 mg (0.17 mmol) of nitrile **c**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **1c** as colorless oil, 90% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.37 (d, 2H, *J*= 8Hz), 6.96 (d, 2H, *J*= 8Hz), 4.23 (m, 8H), 3.84 (s, 3H), 3.43 (s, 4H), 2.49 (s, 3H), 2.18 (s, 3H), 1.26 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.0, 169.9, 159.2, 155.3, 152.9, 141.3, 134.0, 130.7, 125.8, 125.0, 113.7, 62.20, 62.19, 57.2, 56.9, 55.5, 33.1, 32.2, 22.5, 16.0, 13.9. IR ($CH_2Cl_2$, $cm^{-1}$):2984, 2938, 2838, 1734, 1610, 1573, 1513, 1427, 1367, 1247, 1203, 1110, 1036, 965. HRMS (ESI): calcd for $C_{30}H_{38}NO_9$ $[M+1]^+$ 556.2547, found 556.2551.

**Tetraethyl 1,4-dimethyl-3-(4-(trifluoromethyl)phenyl)isoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (1d):**

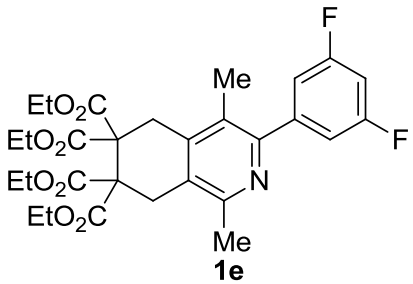


**1d**

The general procedure was used with 53.9 mg (0.12 mmol, 0.1 M) of diyne **1**, 32.7 mg (0.19 mmol) of nitrile **d**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **1d** as colorless oil, 99% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.68 (d, 2H, *J*= 8Hz), 7.58 (d, 2H, *J*= 8Hz), 4.24 (m, 8H), 3.44 (d, 4H, *J*= 3.2 Hz), 2.50 (s, 3H), 2.17 (s, 3H), 1.26 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 169.93, 169.89, 154.1, 153.4, 145.0, 141.7, 129.9, 126.1, 126.0, 125.29 (q, *J* = 2.85 Hz), 62.29, 62.26, 57.1, 56.8, 33.1, 32.3, 22.5, 15.8, 13.9. IR ($CH_2Cl_2$, $cm^{-1}$):2985, 2940, 1735, 1618, 1565, 1428, 1392, 1367, 1325, 1271, 1203, 1165, 1123, 1064, 966, 853. HRMS (ESI): calcd for $C_{30}H_{35}NO_8F_3$ $[M+1]^+$ 594.2315, found 594.2321.

**Tetraethyl 3-(3,5-difluorophenyl)-1,4-dimethylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (1e)**:

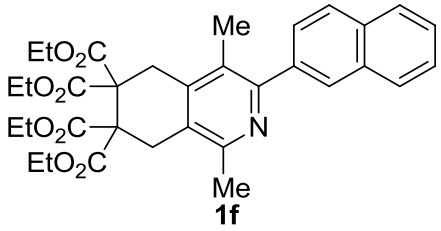


**1e**

The general procedure was used with 53.4 mg (0.12 mmol, 0.1 M) of diyne **1**, 26.3 mg (0.18 mmol) of nitrile **e**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **1e** as colorless oil, >99% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 6.97 (m, 2H), 6.80 (m, 1H), 4.23 (m, 8H), 3.42 (d, 4H, *J*= 4.4 Hz), 2.49 (s, 3H), 2.17 (s, 3H), 1.26 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 169.89, 169.86, 162.89 (dd, $J_1$ = 185 Hz , $J_2$ = 9.65 Hz), 153.4, 153.1 (t, $J_1$ = 1.95 Hz), 141.8, 126.2, 112.6 (m), 103.1 (t, *J* = 18.75 Hz)), 57.0, 56.8, 33.1, 32.2, 22.5, 15.7, 13.9. IR ($CH_2Cl_2$, $cm^{-1}$):3084, 2985, 2939, 1733, 1624, 1594, 1428, 1368, 1269, 1203, 1116, 1053, 987, 864, 736, 699.93. HRMS (ESI): calcd for $C_{29}H_{34}NO_8F_2$ $[M+1]^+$ 562.2252, found 562.2253.

**Tetraethyl 1,4-dimethyl-3-(naphthalen-2-yl)isoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (1f):**

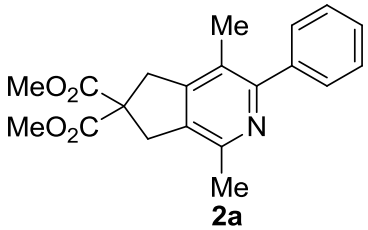


**1f**

The general procedure was used with 42.4 mg (0.10 mmol, 0.1 M) of diyne **1**, 23.0 mg (0.15 mmol) of nitrile **f**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **1f** as colorless oil, 96% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.90 (m, 4H), 7.60 (m, 1H), 7.50 (m, 2H), 4.23 (m, 8H), 3.42 (d, 4H, *J*= 3.2 Hz), 2.55 (s, 3H), 2.20 (s, 3H), 1.26 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.0, 155.5, 153.1, 141.4, 138.8, 133.3, 132.9, 128.5, 128.4, 127.85, 127.80, 127.6, 126.1, 125.4, 62.2, 57.0, 33.1, 32.2, 22.6, 16.0, 13.9. IR ($CH_2Cl_2$, $cm^{-1}$):3056, 2984, 2938, 1733, 1565, 1429, 1367, 1270, 1203, 1095, 1052, 912, 863, 823, 732. HRMS (ESI): calcd for $C_{33}H_{38}NO_8$ $[M+1]^+$ 576.2597, found 576.2606.

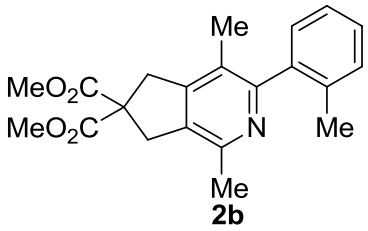
**Dimethyl 1,4-dimethyl-3-phenyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2a):**



**2a**

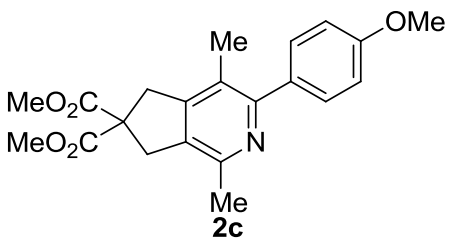
The general procedure was used with 46.0 mg (0.19 mmol, 0.1 M) of diyne **2**, 30.1 mg (0.29 mmol) of nitrile **a**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **2a** as solid, 92% yield. $^{1}$H NMR and $^{13}$CNMR was consistent with reported data.[3]

**Dimethyl 1,4-dimethyl-3-(o-tolyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2b):**



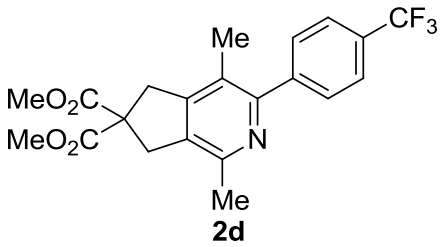

The general procedure was used with 45.6 mg (0.19 mmol, 0.1 M) of diyne **2**, 33.9 mg (0.28 mmol) of nitrile **b**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **2b** as solid, 85% yield. $^{1}$H NMR and $^{13}$CNMR was consistent with reported data. [3]

**Dimethyl 3-(4-methoxyphenyl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2c):**



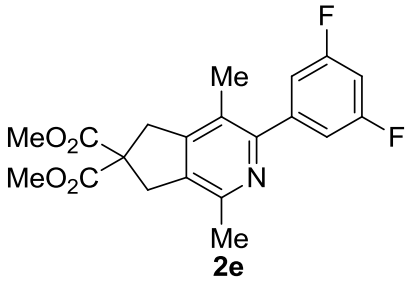

The general procedure was used with 45.3 mg (0.19 mmol, 0.1 M) of diyne **2**, 38.2 mg (0.28 mmol) of nitrile **c**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **2c** as solid, 89% yield. $^{1}$H NMR and $^{13}$CNMR was consistent with reported data. [3]

**Dimethyl 1,4-dimethyl-3-(4-(trifluoromethyl)phenyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2d):**




The general procedure was used with 49.1 mg (0.20 mmol, 0.1 M) of diyne **2**, 53.3 mg (0.31 mmol) of nitrile **d**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **2d** as solid, 98% yield. $^{1}$H NMR and $^{13}$CNMR was consistent with reported data. [3]

**Dimethyl 3-(3,5-difluorophenyl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2e):**

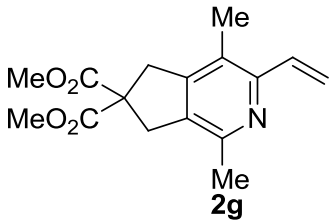


**2e**

The general procedure was used with 54.4 mg (0.23 mmol, 0.1 M) of diyne **2**, 48.0 mg (0.34 mmol) of nitrile **e**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **2e** as solid, >99% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 6.99 (m, 2H), 6.81 (m, 1H), 3.80 (s, 6H), 3.63 (s, 2H), 3.60 (s, 2H), 2.47 (s, 3H), 2.20 (s, 3H).$^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 171.9, 163.3 (dd, $J_1$ = 321 Hz , $J_2$ = 12.3 Hz), 154.6, 151.0, 149.8, 144.0 (t, $J$ = 8.1 Hz), 133.5, 124.4, 112.5 (m), 103.2 (t, $J$= 25.2 Hz), 59.5, 53.4, 40.2, 39.2, 22.0, 16.1. IR ($CH_2Cl_2$, $cm^{-1}$): 2956, 1737, 1624, 1589, 1434, 1351, 1268, 1201, 1166, 1117, 1063, 986, 866, 738. HRMS (ESI): calcd for $C_{20}H_{20}NO_4F_2$ $[M+1]^+$ 376.1360, found 376.1360.

**Dimethyl 1,4-dimethyl-3-vinyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2g):**

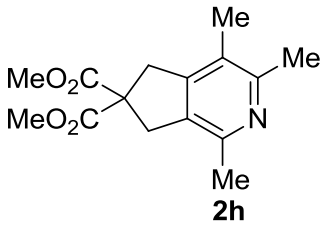


**2g**

The general procedure was used with 46.1 mg (0.19 mmol, 0.1 M) of diyne **2**, 15.5 mg (0.29 mmol) of nitrile **g**, and 3 mol% of catalyst in toluene but reaction mixture was heated and stirred @ 100 °C. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **2g** as solid, >99% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 6.9 (dd, 1H, $J1$= 10.5 Hz, $J2$= 16.8 Hz), 6.26 (d, 1H, $J$=15.6 Hz), 5.4 (d, 1H, $J$=10.8 Hz), 3.77 (s, 6H), 3.56 (s, 2H), 3.55 (s, 2H), 2.43 (s, 3H), 2.23 (s, 3H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 172.0, 151.8, 150.7, 148.9, 133.2, 124.0, 118.9, 59.5, 53.3, 40.0, 39.3, 22.1, 14.6. IR ($CH_2Cl_2$, $cm^{-1}$): 2955, 1737, 1578, 1434, 1268, 1201, 1164, 1066, 929. HRMS (ESI): calcd for $C_{16}H_{20}NO_4$ $[M+1]^+$ 290.1392, found 290.1392.

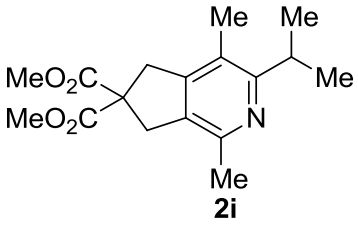
**Dimethyl 1,3,4-trimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2h):**



**2h**

The general procedure was used with 63.4 mg (0.26 mmol, 0.1 M) of diyne **2**, 16.5 mg (0.40 mmol) of nitrile **h**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **2h** as solid, 94% yield. $^{1}$H NMR and $^{13}$CNMR was consistent with reported data.[3]

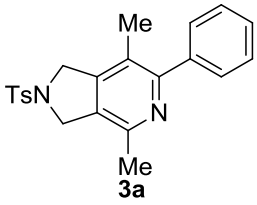
**Dimethyl 3-isopropyl-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2i):**



**2i**

The general procedure was used with 61.1 mg (0.25 mmol, 0.1 M) of diyne **2**, 26.8 mg (0.38 mmol) of nitrile **i**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **2i** as colorless oil, 90% yield. $^{1}$H NMR and $^{13}$CNMR was consistent with reported data. [3]

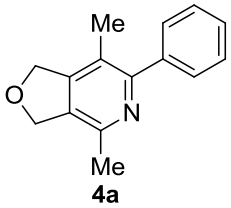
**4,7-Dimethyl-6-phenyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (3a):**



**3a**

The general procedure was used with 53.4 mg (0.19 mmol, 0.1 M) of diyne **3**, 29.9 mg (0.29 mmol) of nitrile **a**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **3a** as solid, 73% yield. $^{1}$H NMR and $^{13}$CNMR was consistent with reported data. [3]

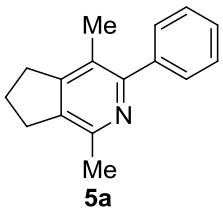
**4,7-Dimethyl-6-phenyl-1,3-dihydrofuro[3,4-c]pyridine (4a)**:



**4a**

The general procedure was used with 45.5 mg (0.37 mmol, 0.1 M) of diyne **4**, 57.6 mg (0.55 mmol) of nitrile **a**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **4a** as solid, 80% yield. $^{1}$H NMR and $^{13}$CNMR was consistent with reported data. [3]

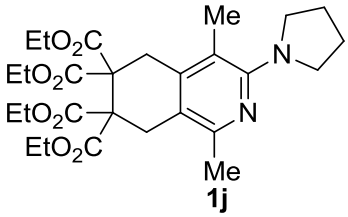
**1,4-Dimethyl-3-phenyl-6,7-dihydro-5H-cyclopenta[c]pyridine (5a):**



**5a**

The general procedure was used with 38.7 mg (0.32 mmol, 0.1 M) of diyne **5**, 49.8 mg (0.48 mmol) of nitrile **a**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **5a** as solid, 93% yield. $^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.45 (m, 3H), 7.36 (m, 2H), 2.95 (t, 2H, *J*=7.6 Hz), 2.92 (t, 2H, *J*=7.6 Hz), 2.50 (s, 3H), 2.21 (s, 3H), 2.17 (q, 2H, *J*= 7.6 Hz). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 156.2, 153.5, 150.6, 141.4, 136.5, 129.3, 128.2, 127.5, 124.4, 32.3, 31.2, 24.4, 22.1, 16.4. IR ($CH_2Cl_2$, $cm^{-1}$): 2943 (br), 1580, 1413, 744, 700. HRMS (ESI): calcd for $C_{16}H_{18}N$ $[M+1]^+$ 224.1439, found 224.1442.

**Tetraethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)isoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (1j):**

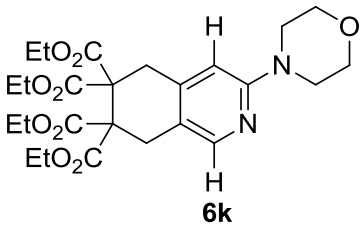


**1j**

The general procedure was used with 52.0 mg (0.12 mmol, 0.1 M) of diyne **1**, 14.1 mg (0.14 mmol) of nitrile **j**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using first 15%, 30% and then 50% ethyl acetate in hexanes to afford the title compound **1j** as colorless oil (it starts to turn pale yellow on standing), >99% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 4.19 (m, 8H), 3.37 (m, 6H), 3.30 (s, 2H), 2.34 (s, 3H), 2.12 (s, 3H), 1.87 (q, 4H, *J*= 3.2 Hz), 1.23 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.2, 170.1, 158.0, 150.2, 141.6, 118.1, 115.8, 62.0, 61.9, 57.4, 57.1, 50.4, 33.1, 31.8, 25.5, 22.4, 14.8, 13.9. IR ($CH_2Cl_2$, $cm^{-1}$): 2982, 1735, 1571, 1429, 1271, 1203, 1051. HRMS (ESI): calcd for $C_{27}H_{39}N_2O_8$ $[M+1]^+$ 519.2706, found 519.2706.

**Tetraethyl 3-morpholinoisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (6k):**



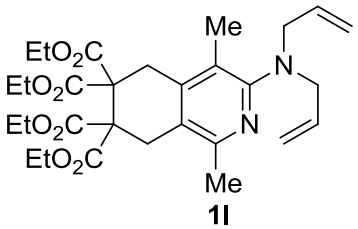
**6k**

The general procedure was used with 52.0 mg (0.13 mmol, 0.1 M) of diyne **6**, 22.1 mg (0.19 mmol) of nitrile **k**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using first 15%, 30% and then 50% ethyl

acetate in hexanes to afford the title compound **6k** as slightly pale yellow oil, 75% yield.

$^1$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.97 (s, 1H), 6.37 (s, 1H), 4.20 (m, 8H), 3.80 (t, 4H, *J*= 4.8 Hz), 3.43 (d, 2H, *J*= 12.4 Hz), 3.42 (d, 2H, *J*= 4.8 Hz), 1.23 (m, 12H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 169.8, 169.7, 158.7, 147.5, 143.9, 119.3, 105.5, 66.9, 62.13, 62.10, 57.7, 57.2, 46.1, 34.7, 31.5, 13.9. IR ($CH_2Cl_2$, cm$^{-1}$): 2982, 1735, 1608, 1492, 1425, 1367, 1264, 1118, 1041. HRMS (ESI): calcd for $C_{25}H_{35}N_2O_9$ $[M+1]^+$ 507.2343, found 507.2346.

**Tetraethyl 3-(diallylamino)-1,4-dimethylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (1l):**

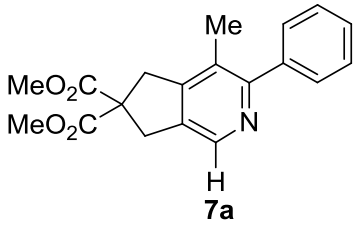


**1l**

The general procedure was used with 51.3 mg (0.12 mmol, 0.1 M) of diyne **1**, 17.8 mg (0.14 mmol) of nitrile **l**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using first 15%, 30% and then 50% ethyl acetate in hexanes to afford the title compound **1l** as slightly pale yellow oil, 76% yield.

$^1$H NMR (300 MHz,$CDCl_3$): δ (ppm) 5.89 (m, 2H), 5.17 (d, 2H, *J*= 17.2 Hz), 5.07 (d, 2H, *J*= 10.2 Hz), 4.20 (m, 8H), 3.71 (d, 2H, *J*= 6Hz), 3.32 (d, 2H, *J*= 12.4 Hz), 2.35 (s, 3H), 2.14 (s, 3H), 1.22 (t, 12H, *J*= 6.8 Hz). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.17, 170.10, 158.6, 150.7, 142.0, 136.3, 120.6, 119.8, 116.5, 62.08, 62.04, 57.3, 57.1, 54.0, 33.2, 31.9, 22.3, 13.9. IR ($CH_2Cl_2$, cm$^{-1}$): 2983, 1736, 1570, 1443, 1367, 1443, 1367, 1269, 1205, 1095, 1038, 864. HRMS (ESI): calcd for $C_{29}H_{41}N_2O_8$ $[M+1]^+$ 545.2863, found 545.2865.

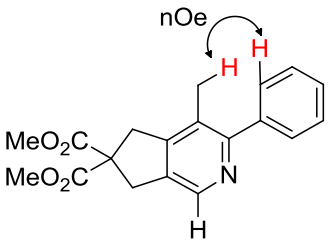
**Dimethyl 4-methyl-3-phenyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (7a):**



**7a**

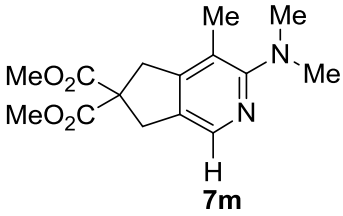
Solution of 49.0 mg (0.23 mmol, 0.1 M) of diyne **7** in toluene, was added dropwise (over a period of 1 h) to the vial containing 36.4 mg (0.35 mmol) of nitrile **a**, and 3 mol% of catalyst in toluene. Then, the reaction was stirred @ RT for another 3 h. The reaction mixture was purified via flash column chromatography using first 15%, and then 30% ethyl acetate in hexanes to afford the title compound **7a** as colorless oil, 79% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 8.37 (s, 1H), 7.42 (m, 5H), 3.79 (s, 6H), 3.70 (s, 2H), 3.61 (s, 2H), 2.25 (s, 3H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 171.8, 157.4, 149.7, 142.4, 140.5, 134.4, 129.2, 128.2, 127.8, 126.9, 59.9, 53.3, 39.9, 38.7, 16.5. IR ($CH_2Cl_2$, $cm^{-1}$): 2954, 1736, 1595, 1435, 1401, 1269, 1201, 1164, 1072, 1022, 911, 854. HRMS (ESI): calcd for $C_{19}H_{20}NO_4$ $[M+1]^+$ 326.1392, found 326.1392.



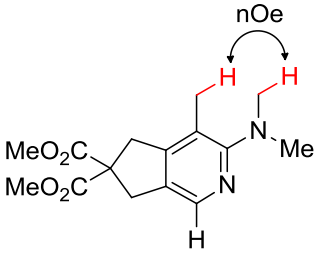

Regioselectivity was assigned on the basis of nOe of the methyl protons with aryl protons.

**Dimethyl 3-(dimethylamino)-4-methyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (7m):**




**7m**

Solution of 52.0 mg (0.23 mmol, 0.1 M) of diyne **7** was added dropwise (over a period of 1 h) to the vial containing 19.6 mg (0.28 mmol) of nitrile **m**, and 3 mol% of catalyst in toluene. Then, the reaction was stirred @ RT for another 3 h. The reaction mixture was purified via flash column chromatography using first 15%, 30% and then 50% ethyl acetate in hexanes to afford the title compound **7m** as oil, 86% yield.

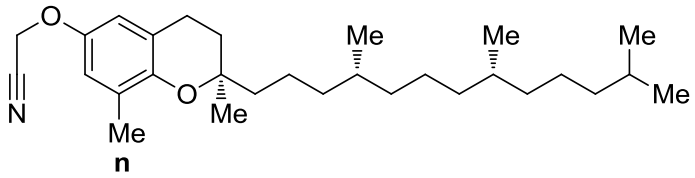



The regioselectivity was assigned on the basis of nOe of pyridyl methyl protons with cyanamide methyl protons.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.94 (s, 1H), 3.73 (s, 6H), 3.54 (s, 2H), 3.46 (s, 2H), 2.76 (s, 6H), 2.17 (s, 3H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 171.9, 161.8, 150.6, 139.7, 129.4, 120.1, 60.3, 53.2, 42.4, 39.7, 38.2, 15.1. IR ($CH_2Cl_2$, $cm^{-1}$): 2953, 1737, 1606, 1483, 1438, 1396,

1273, 1242, 1199, 1164, 1061. HRMS (ESI): calcd for $C_{15}H_{21}N_2O_4$ $[M+1]^+$ 293.1501, found 293.1501.

**2-(((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)acetonitrile (n):**

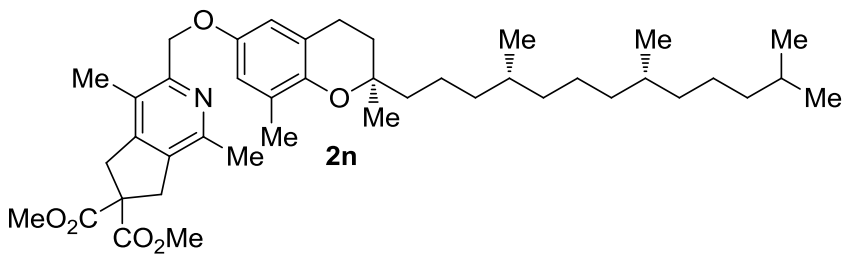


**n**

To a suspension of pre-washed and dried NaH (15.9 mg) in THF (4 mL), *delta*-tocopherol (177.7 mg, technical grade, about 90% purity) in THF (3 mL) was added dropwise @ 0 °C. The resulting pale yellow solution was stirred for 15 min, and then bromoacetonitrile (0.5 mL) was added and stirred overnight @ RT. The reaction mixture was purified via flash column chromatography using 10% ethyl acetate in hexanes to afford the title compound **n** as an oily compound, 146.7 mg.

$^1$H NMR (300 MHz,$CDCl_3$): δ (ppm) 6.65 (d, 1H, *J*= 3 Hz), 6.55 (d, 1H, *J*= 3 Hz), 4.68 (s, 2H), 2.73 (t, 2H, *J*= 6 Hz), 2.16 (s, 3H), 1.77-0.86 (m, 36H) . $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 149.3, 148.2, 127.9, 121.4, 116.5, 115.8, 113.1, 76.1, 55.1, 40.2, 39.5, 37.6, 37.5, 37.4, 32.9, 32.8, 31.2, 28.1, 24.9, 24.6, 24.2, 22.9, 22.82, 22.80, 21.1, 19.9, 19.8, 16.4. IR ($CH_2Cl_2$, $cm^{-1}$): 2927, 2864, 1742, 1607, 1478, 1377, 1223, 1152, 1068, 857. HRMS (ESI): calcd for $C_{29}H_{47}NO_2$ $[M+K]^+$ 480.3244, found 480.3252.

**Dimethyl 3-((((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)methyl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (2n):**



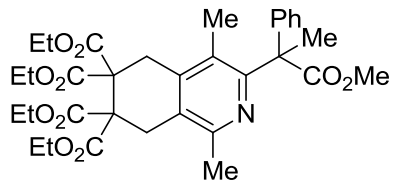
**2n**

The general procedure was used with 26.0 mg (0.11 mmol, 0.1 M) of diyne **2**, 48.7 mg (0.11 mmol) of nitrile **n**, and 3 mol% of catalyst in toluene. The reaction mixture was purified via flash column chromatography using first 15% and then 30% ethyl acetate in hexanes to afford the title compound **2n** as colorless oil, 94% yield.

$^{1}$H NMR (300 MHz,$CDCl_3$): δ (ppm) 6.67 (d, 1H, *J*= 3.2 Hz), 6.57 (d, 1H, *J*= 3.2 Hz), 5.05 (s, 2H), 3.78 (s, 6H), 3.58 (s, 2H), 3.57 (s, 2H), 2.71 (t, 2H, *J*= 9.6 Hz), 2.45 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 1.74-0.87 (m, 36H). $^{13}$C NMR (75 MHz , $CDCl_3$): δ (ppm) 171.9, 152.8, 151.5, 150.2, 149.5, 146.5, 133.9, 127.2, 127.1, 121.0, 115.8, 112.3, 75.7, 71.4, 59.6, 53.3, 40.3, 39.9, 39.5, 39.3, 37.68, 37.65, 37.64, 37.4, 33.0, 32.9, 31.5, 28.1, 25.0, 24.6, 24.3, 22.9, 22.8, 21.8, 21.2, 19.9, 19.8, 16.4, 14.6. IR ($CH_2Cl_2$, $cm^{-1}$): 2927, 1739, 1479, 1273, 1155, 1055. HRMS (ESI): calcd for $C_{42}H_{64}NO_6$ $[M+1]^+$ 678.4734, found 678.4750.

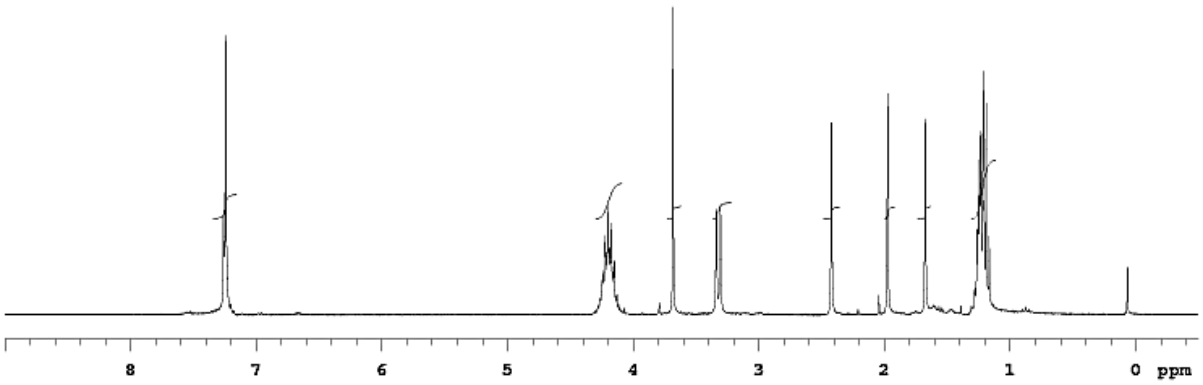
# References:

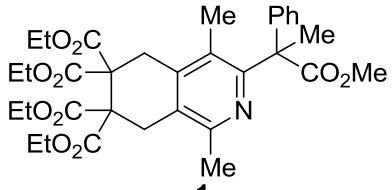

1) See references cited in supporting information in: P. Kumar, D. M. Troast, R. Cella, J. Louie, *J. Am. Chem. Soc.* **2011**, *133*, 7719–7721.
2) Y. Cheng, Y. –G. Ma, X. –R. Wang, J. –M. Mo, *J. Org. Chem.* **2009**, *74*, 850-855.
3) M. M. McCormick, H. A. Duong, G. Zuo, J. Louie, *J. Am. Chem. Soc.* **2005**, *127*, 5030–5031.




**$1_{ket}$**

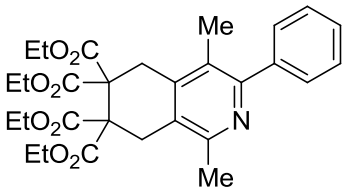
**$^{1}$H-NMR**



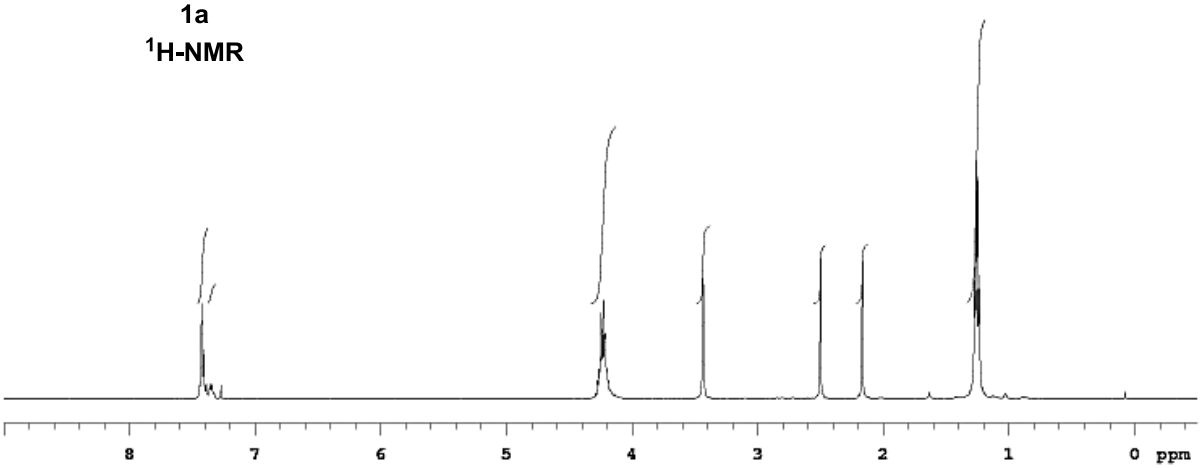

**$1_{ket}$**

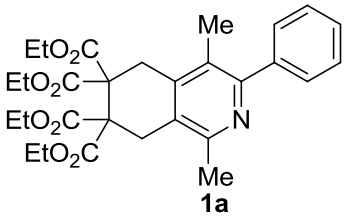
**$^{13}$C-NMR**




**1a**

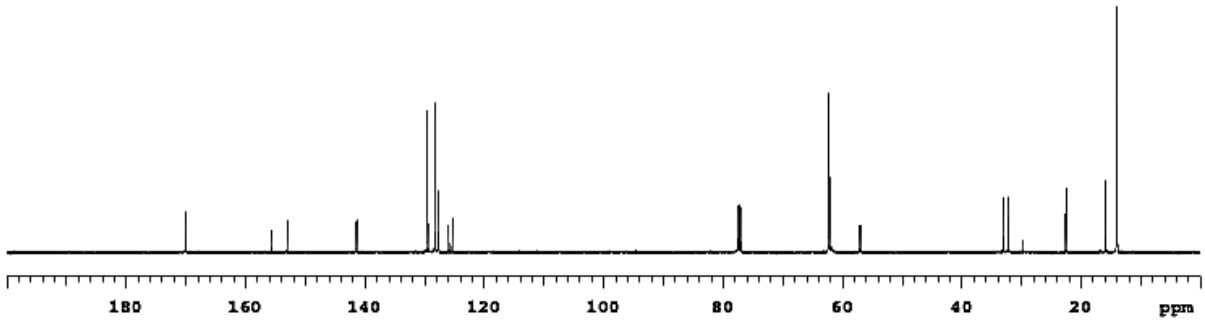
**$^{1}$H-NMR**

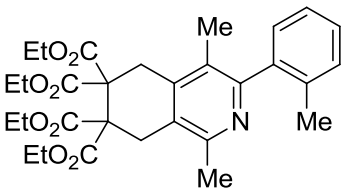



**1a**

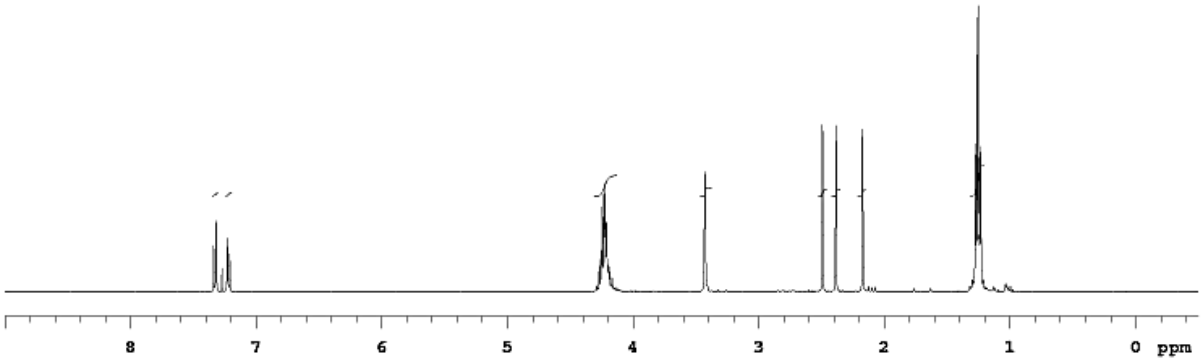
**$^{13}$C-NMR**

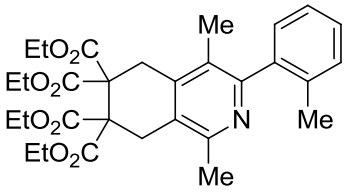





**1b**

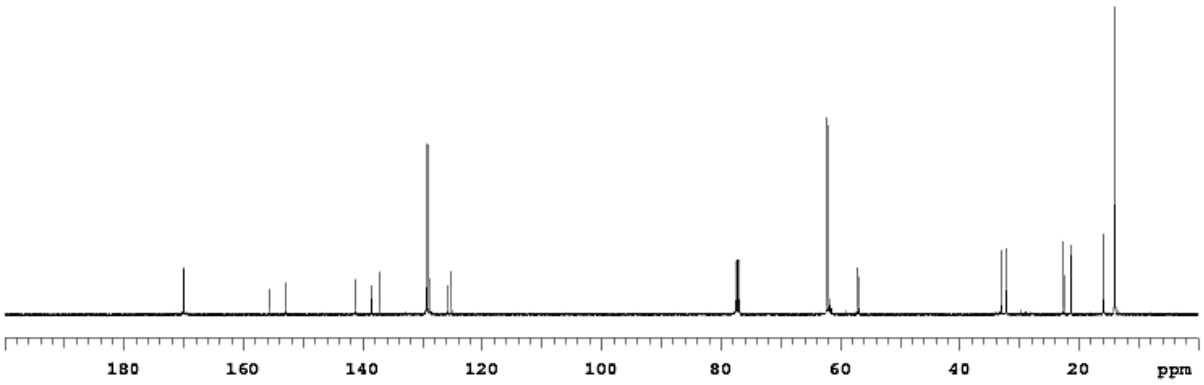
**$^{1}$H-NMR**

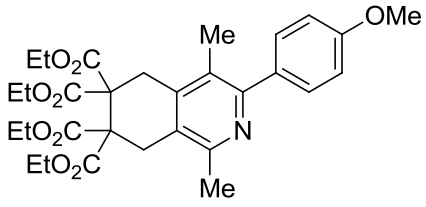



**1b**

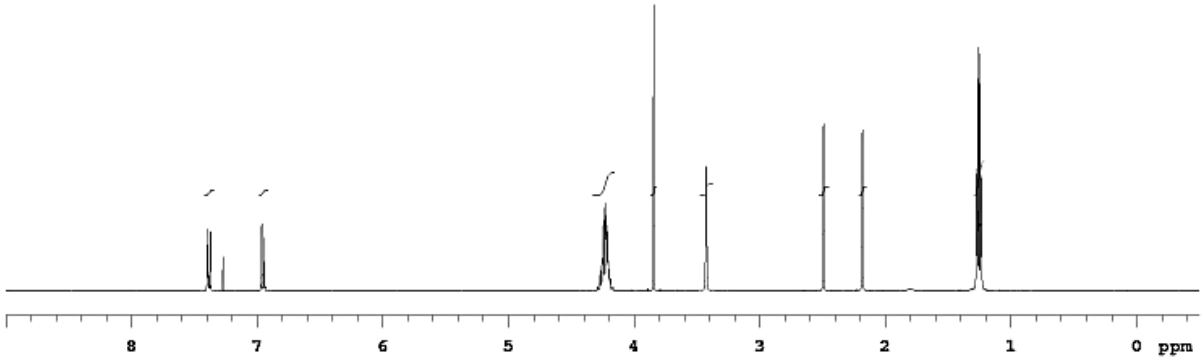
**$^{13}$C-NMR**

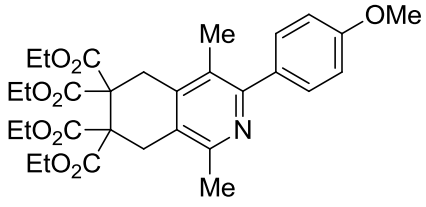





**1c**

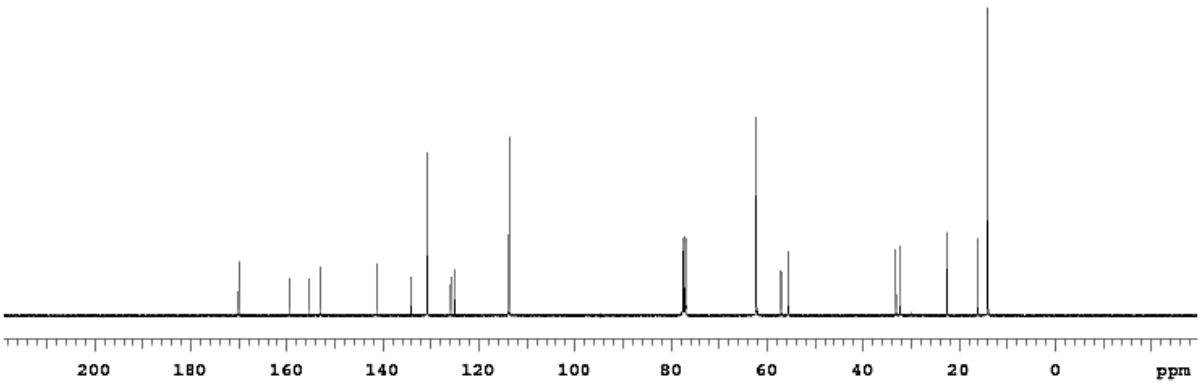
**$^{1}$H-NMR**

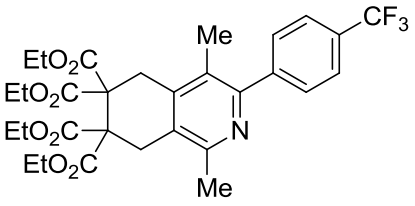



**1c**

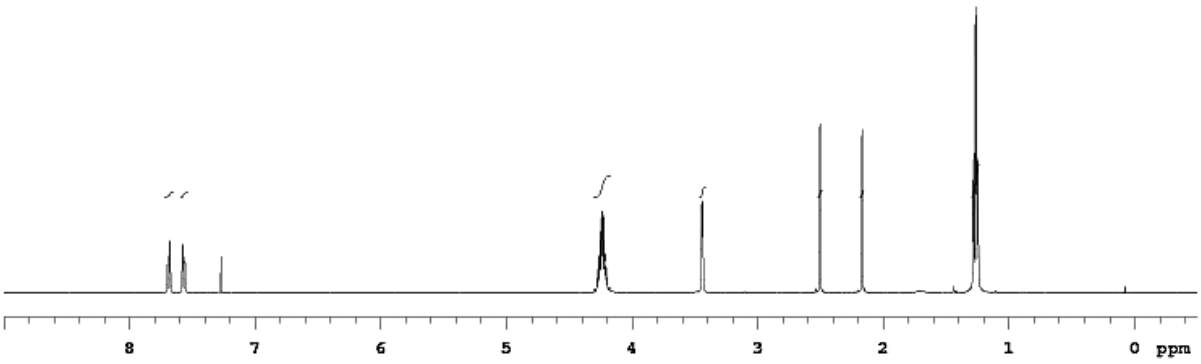
**$^{13}$C-NMR**

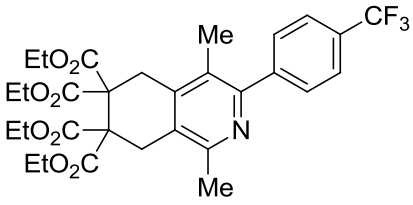





**1d**

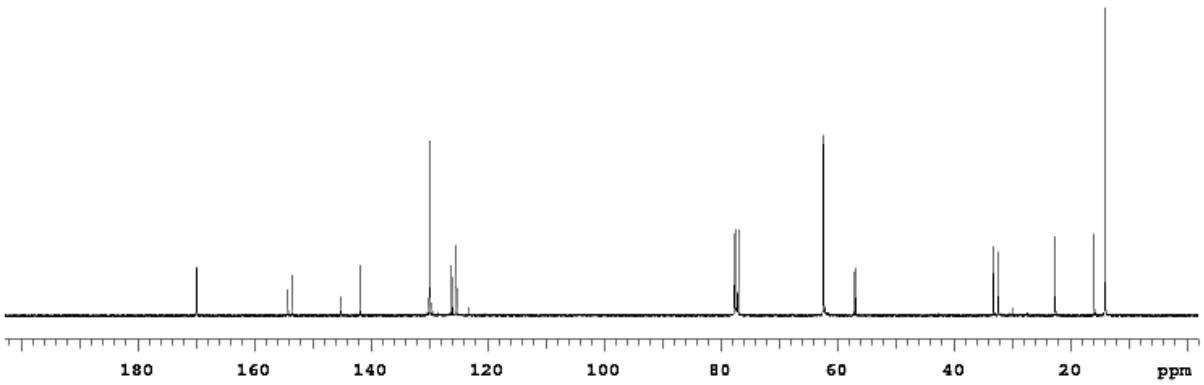
**$^{1}$H-NMR**

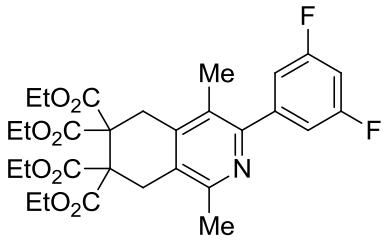



**1d**

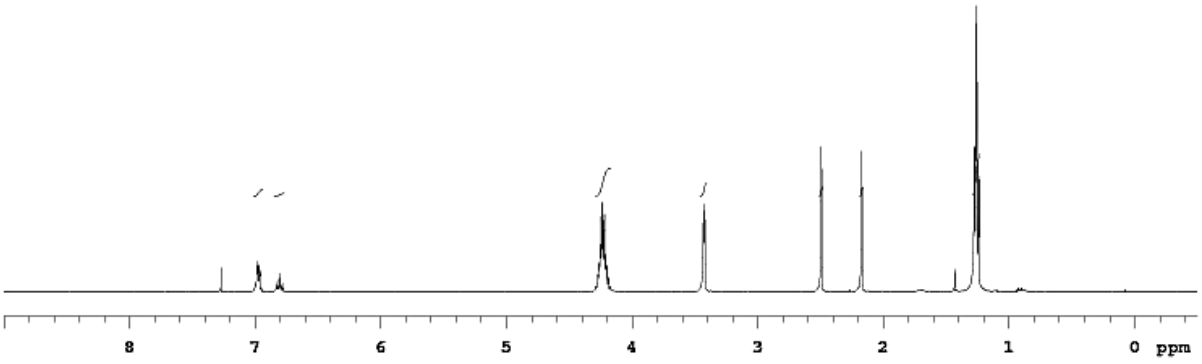
**$^{13}$C-NMR**

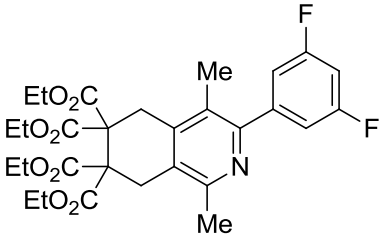





**1e**

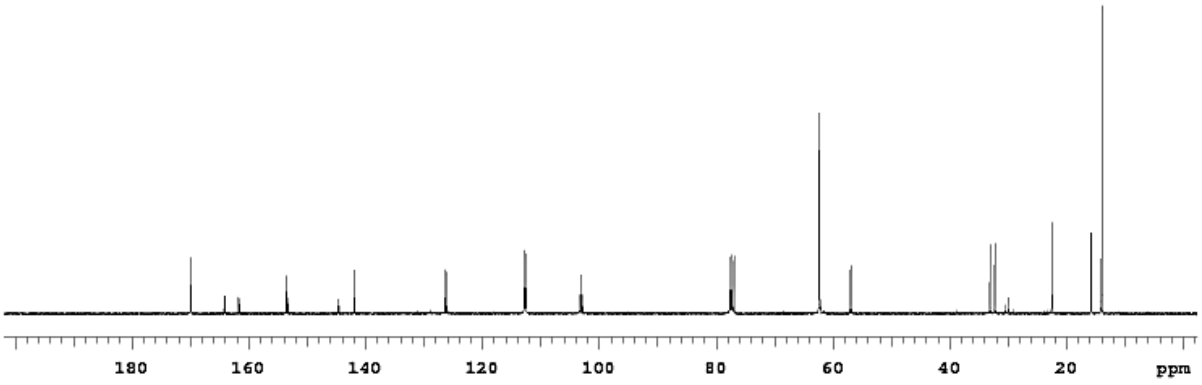
**$^{1}$H-NMR**

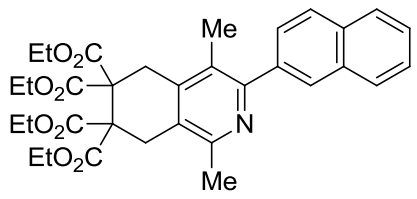



**1e**

**$^{13}$C-NMR**

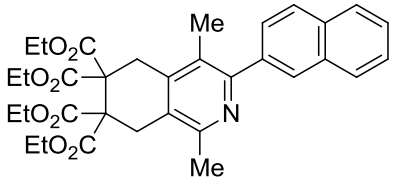





**1f**

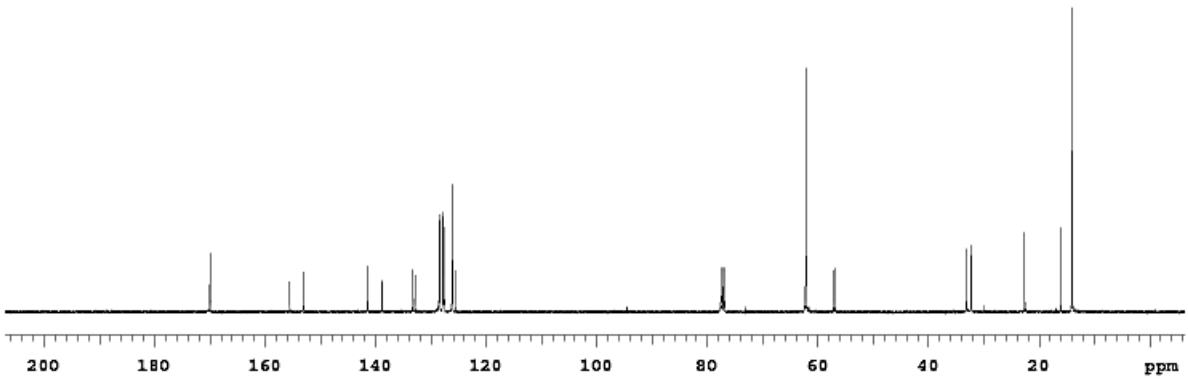
**$^{1}$H-NMR**

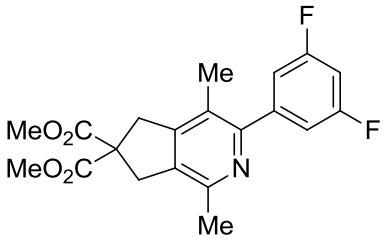



**1f**

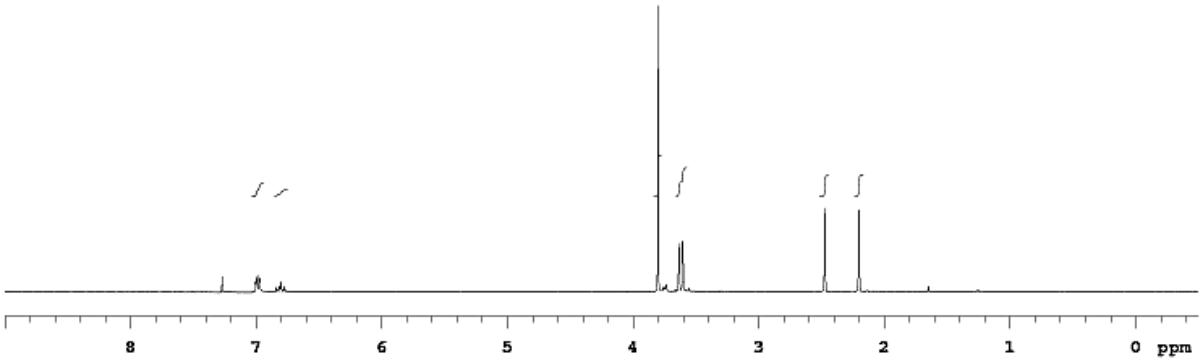
**$^{13}$C-NMR**

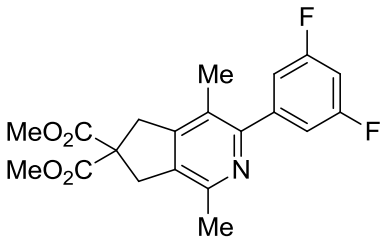





**2e**

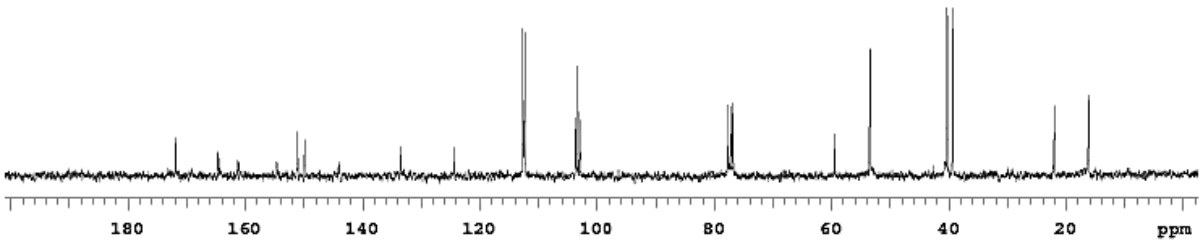
**$^{1}$H-NMR**

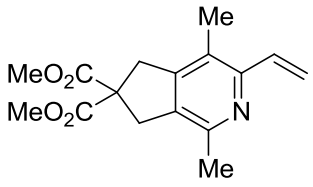



**2e**

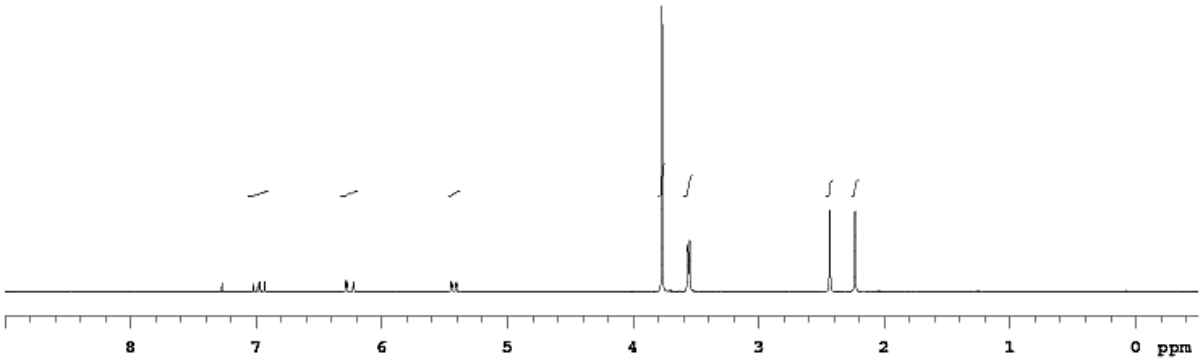
**$^{13}$C-NMR**

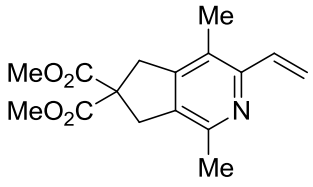





**2g**

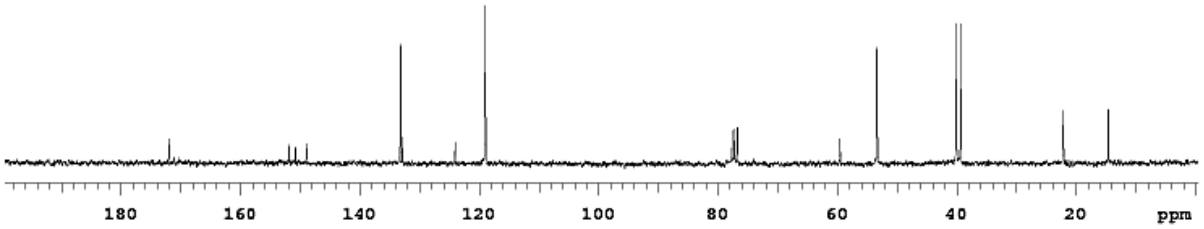
**$^{1}$H-NMR**

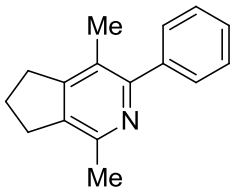



**2g**

**$^{13}$C-NMR**

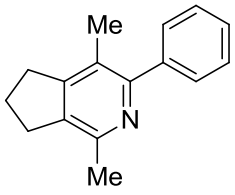





**5a**

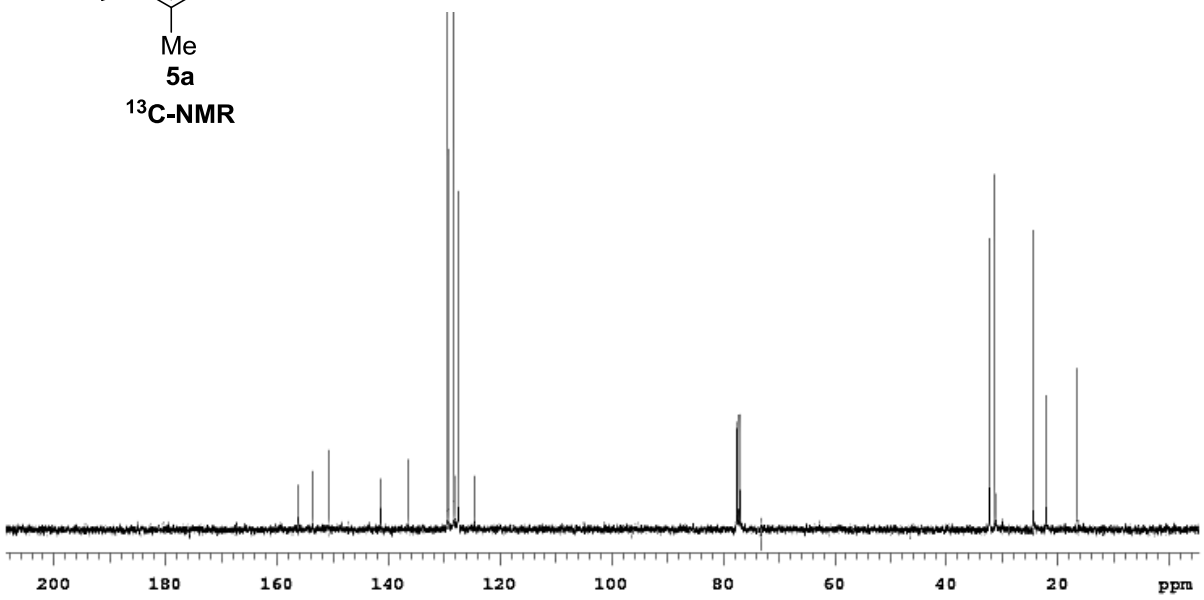
**$^{1}$H-NMR**

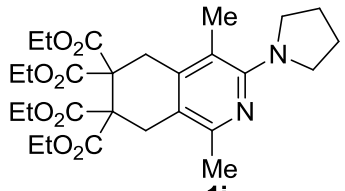



**5a**

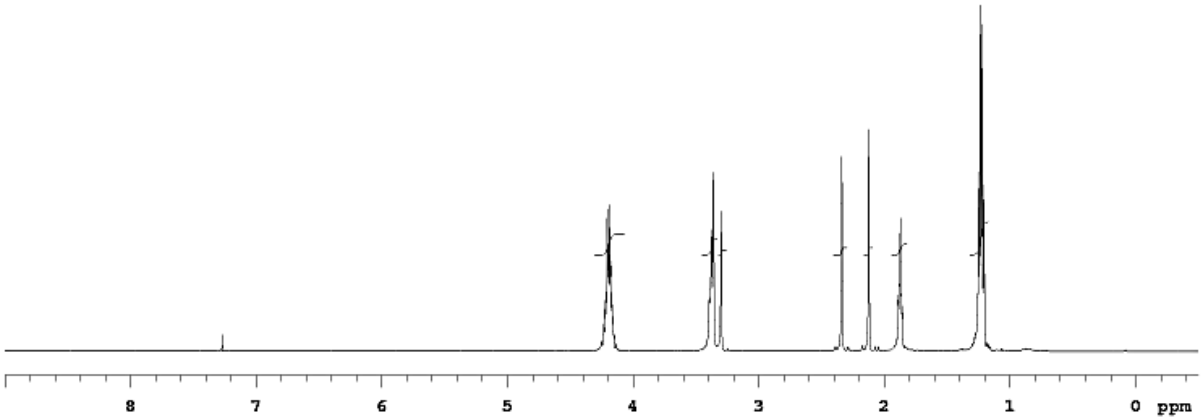
**$^{13}$C-NMR**

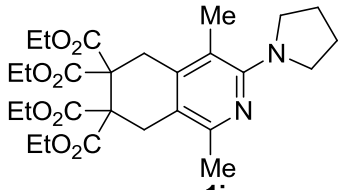





**1j**

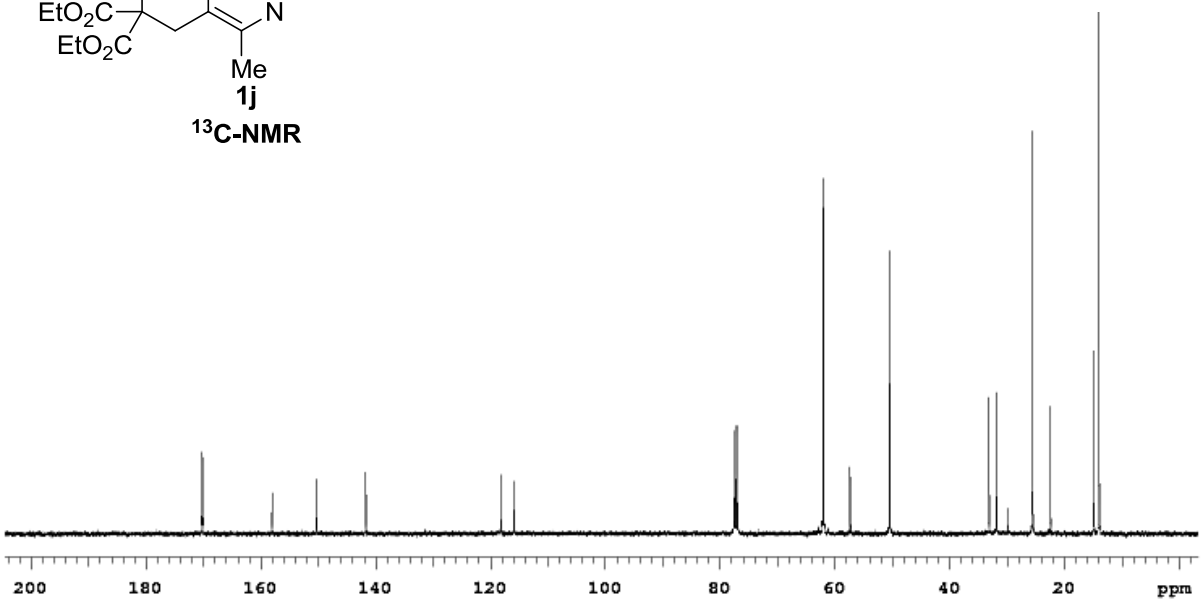
**$^{1}$H-NMR**

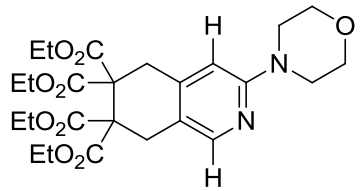



**1j**

**$^{13}$C-NMR**

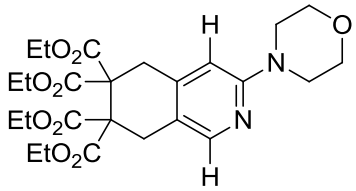





**6k**

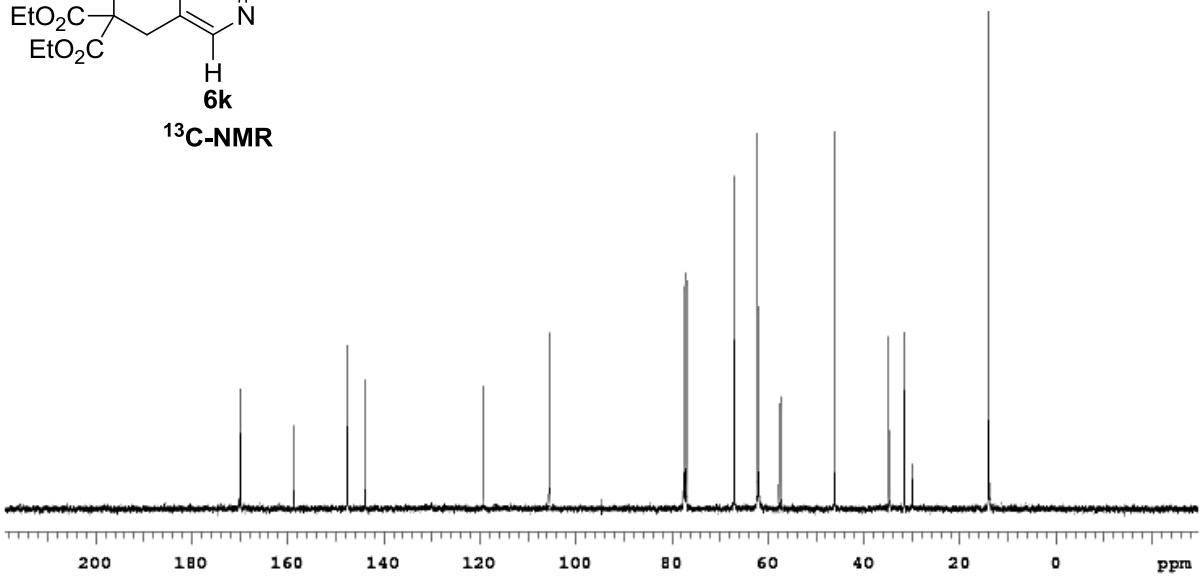
**$^{1}$H-NMR**

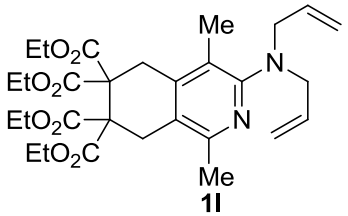



**6k**

**$^{13}$C-NMR**

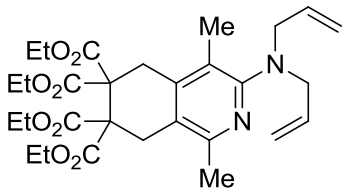





**1l**

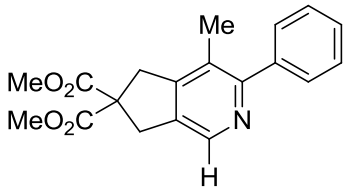
**$^{1}$H-NMR**




**1l**

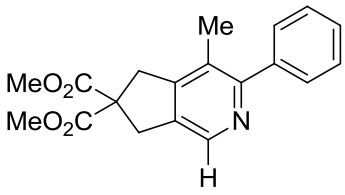
**$^{13}$C-NMR**




**7a**

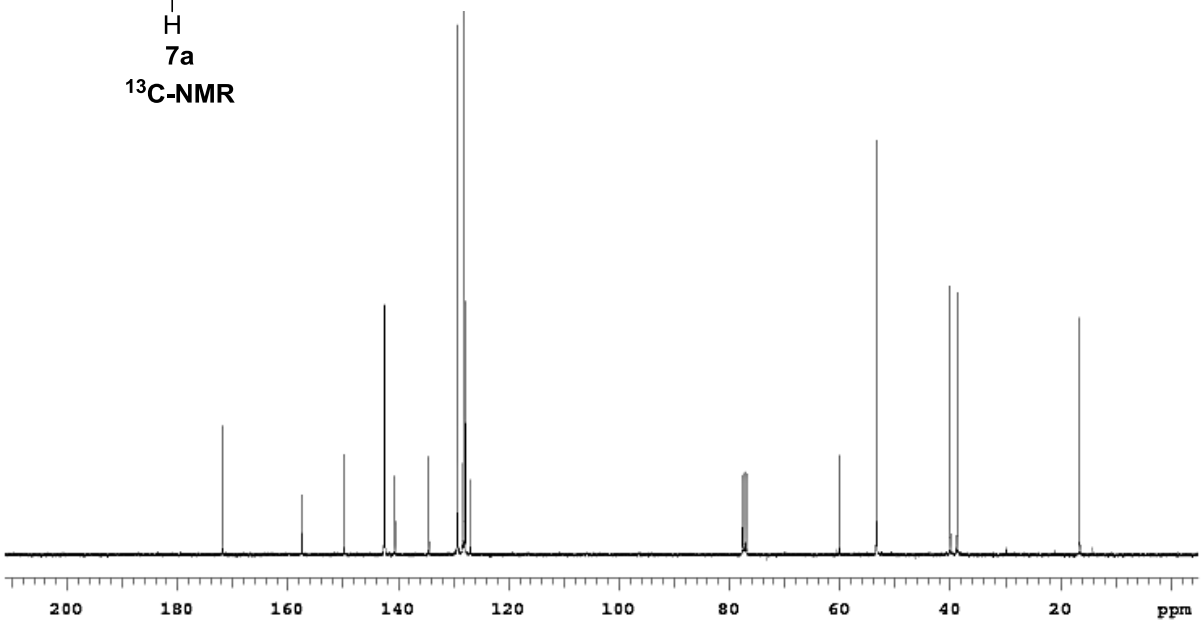
**$^{1}$H-NMR**

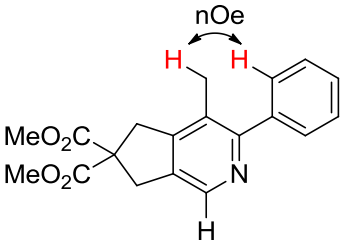



**7a**

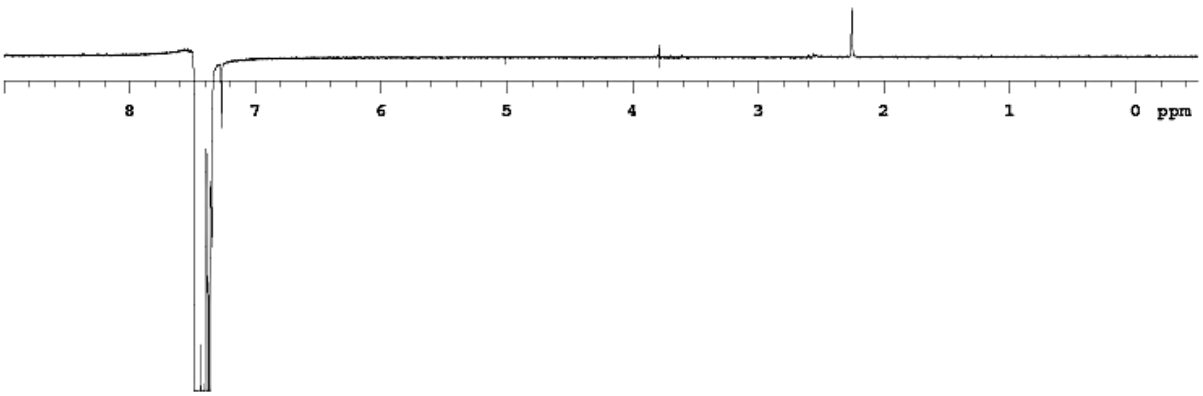
**$^{13}$C-NMR**

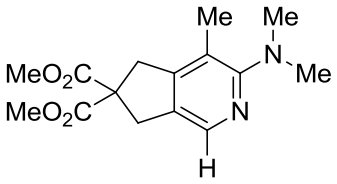





**7a**

**1*d*-NOESY**

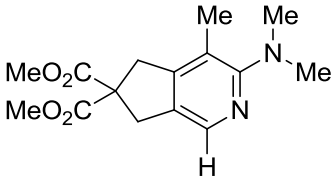





**7m**

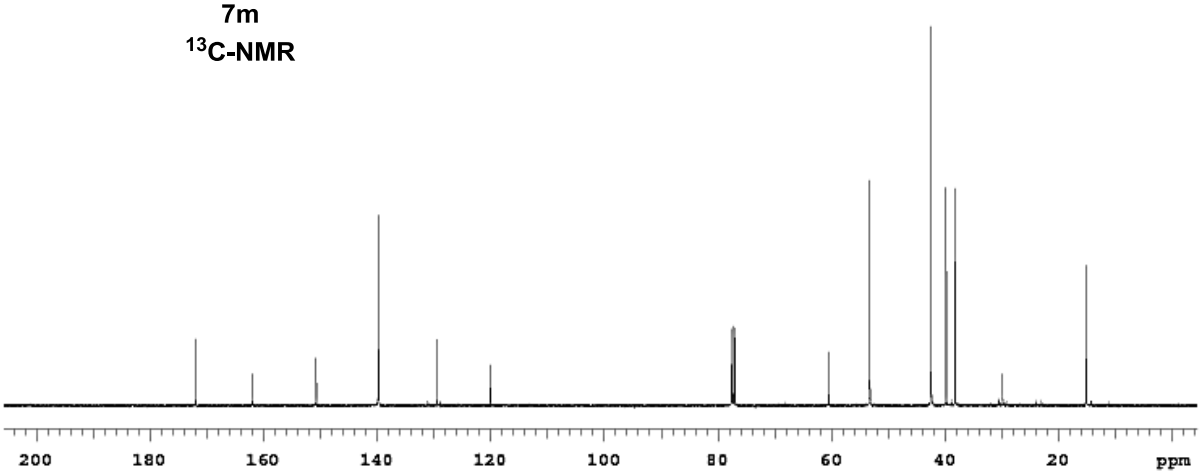
**$^{1}$H-NMR**

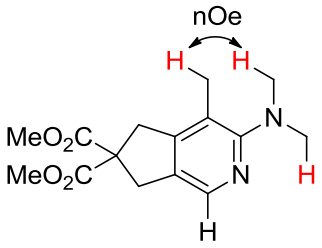



**7m**

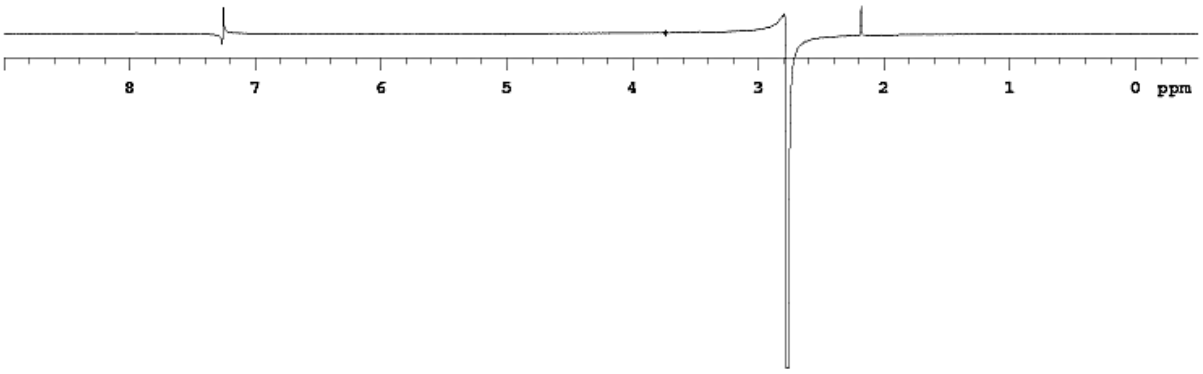
**$^{13}$C-NMR**

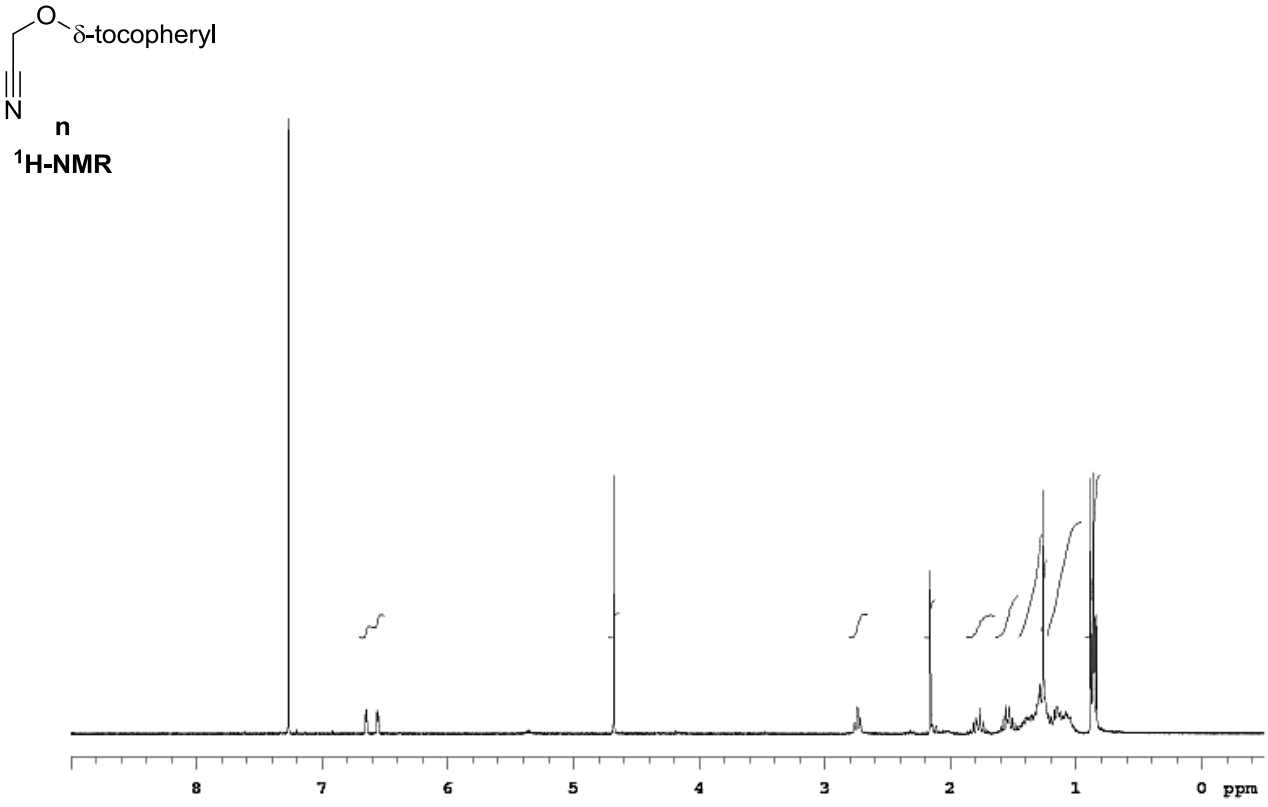


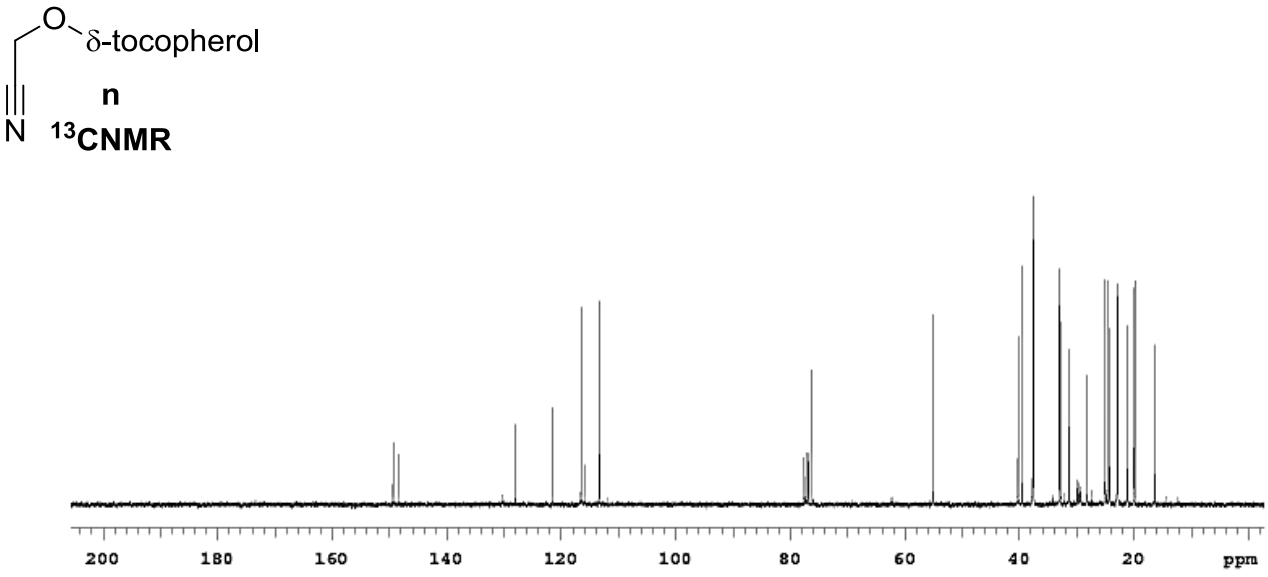


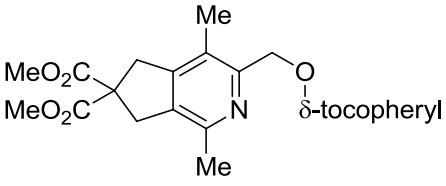

**7m**

**1*d*-NOESY**



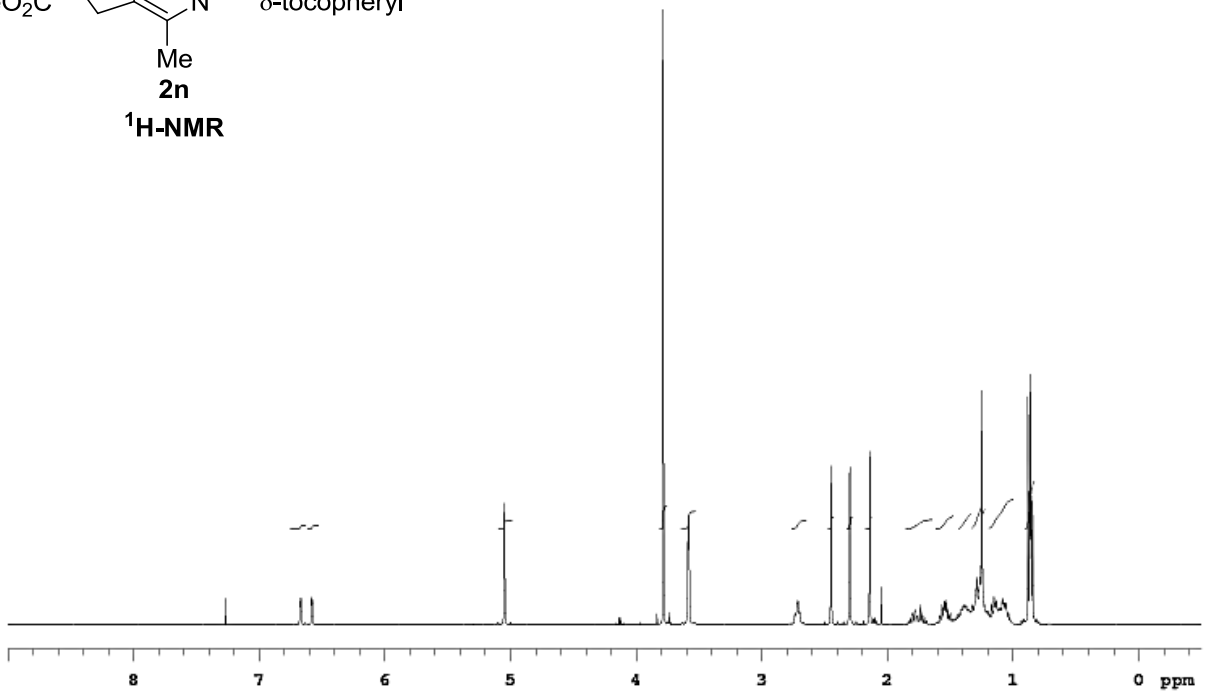

O
δ-tocopheryl
N
n
1H-NMR
8
7
6
5
4
3
2
1
0 ppm

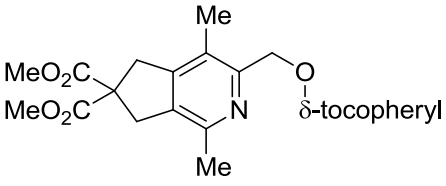

O
δ-tocopherol
n
N
13CNMR
200
180
160
140
120
100
80
60
40
20
ppm




**2n**

**$^{1}$H-NMR**




**2n**

**$^{13}$C-NMR**