A $TiCl_4/Et_3N$ Promoted Three Component Condensation Between Aromatic Heterocycles, Aldehydes and Active Methylene Compounds

Andrea RENZETTI,[†,‡] Emmanuel DARDENNES,[†] Antonella FONTANA,[‡]

Paolo De MARIA,[‡] Janos SAPI,[†*] and Stéphane GERARD [†*]

janos.sapi@univ-reims.fr

Tel + 33 (0)3 26 91 80 22

Fax + 33 (0)3 29 91 80 29

stephane.gerard@univ-reims.fr

Tel + 33 (0)3 26 91 87 07

Fax + 33 (0)3 29 91 80 29

[†] *Institut de Chimie Moléculaire de Reims, UMR CNRS 6229, Université de Reims-Champagne-Ardenne, Faculté de Pharmacie, 51 rue Cognacq-Jay, F-51096 Reims, Cedex, France*

[‡] *Dipartimento di Scienze del Farmaco, Università "G. d'Annunzio", via dei Vestini 31, I-66013 Chieti, Italia*

Supporting Information

Contents :

Experimental Section

General : All solvents were dried and purified by standard literature methods prior to use. Melting points were determined on an hot-stage apparatus and are uncorrected. Reactions were monitored on silicagel plates (Kieselgel $60F_{254}$) and preparative chromatographies were carried out on silica gel 60 (70-230 mesh ASTM). ^{1}H NMR and ^{13}C NMR spectra were acquired at 300 MHz and 75 MHz, respectively, in $CDCl_3$, with TMS as internal standard. IR spectra (thin film or KBr pastille) were measured with a Fourrier Transformed instrument. Mass spectra were recorded with an ESI mass spectrometer.

Typical procedure for the three-component reaction: In a typical procedure, the malonester derivative is added to a solution of $TiCl_4$ (1 equiv) in dry dichloromethane (20 mL / 10 mmol), at 0°C, under nitrogen using 3Å molecular sieves. Et_3N (1.0 equiv) was added after formation of a yellow suspension. The solution became red. The aldehyde (1.0 equiv) was then dropwise added and the mixture was stirred at this temperature until its disappearance (monitored by TLC). The heterocycle (1.0 equiv) was then added and the mixture is allowed to reach room temperature until the reaction was completed. After quenching by an aqueous solution of 1M HCl, the organic layer was dried over $MgSO_4$ and concentrated under vacuum to give crude products which were purified either by column chromatography on silica gel or by recrystallization to furnish the corresponding trimolecular adduct.

Caracterisation of compounds 1-7 ; 10-14 ; 16-22 :

Methyl 2-methoxycarbonyl-3-(3-indolyl)-3-(2-propyl)propanoate 1 (Table 1, Entry 5)
Prepared according to procedure using 1 mL (1.156 g, 8.75 mmol) of dimethyl malonate, 960 µL (1.660 g, 8.75 mmol) of $TiCl_4$, 1.23 mL (885 mg, 8.75 mmol) of Et_3N, 800 µL (631 mg, 8.75 mmol) of isobutyraldehyde and 1.025 g (8.75 mmol) of indole to yield **1** (2.146 g; 81 % yield) as a white solid; mp = 128-129 °C; **^{1}H NMR** ($CDCl_3$): δ 0.86 (d, 3H, *J* = 6.8 Hz), 0.88 (d, 3H, *J* = 6.8 Hz), 2.08 (m, 1H), 3.35 (s, 3H), 3.74 (s, 3H), 3.82 (dd, 1H, *J* = 11.0 Hz, *J* = 4.8

Hz), 3.99 (d, 1H, *J* = 11.0 Hz), 7.03 (d, 1H,), 7.14 (m, 2H), 7.33 (d, 1H, *J* = 7.4 Hz), 7.68 (d, 1H, *J* = 7.6 Hz), 8.08 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 17.9, 21.8, 30.5, 42.1, 52.1, 52.6, 56.2, 110.8, 112.8, 119.2, 119.5, 121.7, 122.7, 128.3, 135.5, 168.7, 169.3. **IR** (KBr): ν 3401, 3048, 2952, 1727, 1432, 1335, 1269, 1150, 1018, 741 cm^{-1}. **MS (EI)**: *m/z* 303, 260, 171, 156, 130, 101. **HRMS** calcd for $C_{17}H_{21}NO_4$ 303.1471; found 303.1463. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(3-indolyl)-3-(3-pentyl)propanoate 2 (Table 2, Entry 1)
Prepared according to the general procedure using 1 mL (1.156 g, 8.75 mmol) of dimethyl malonate, 960 μL (1.660 g, 8.75 mmol) of $TiCl_4$, 1.23 mL (885 mg, 8.75 mmol) of Et_3N, 1.076 mL (876 mg, 8.75 mmol) of 2-ethylbutyraldehyde and 1.025 g (8.75 mmol) of indole to yield **2** (1.767 g; 61 % yield) as a dark pink oil; **^{1}H NMR** ($CDCl_3$): δ 0.82 (t, 3H, *J* = 7.2 Hz), 0.97 (t, 3H, *J* = 7.2 Hz), 1.35 (m, 5H), 3.32 (s, 3H), 3.72 (dd, 1H, *J* = 7.4 Hz, *J* = 1.5 Hz), 3.75 (s, 3H), 4.05 (d, 1H, *J* = 1.5 Hz), 6.99 (d, 1H, *J* = 2.5 Hz), 7.09 (m, 2H), 7.25 (t, 1H, *J* = 7.4 Hz), 7.68 (d, 1H, *J* = 7.6 Hz), 8.21 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 11.9, 12.2, 23.1, 23.6, 38.1, 44.5, 52.1, 52.4, 56.2, 110.8, 113.1, 119.2, 119.3, 121.5, 122.8, 128.3, 135.4, 168.7, 169.3. **IR** (KBr): ν 3397, 2956, 2927, 1750, 1739, 1454, 1432, 1336 cm^{-1}. **MS (EI)**: *m/z* 331, 260, 201, 170, 130. **HRMS** calcd for $C_{19}H_{25}NO_4$ 331.1784; found 331.1807. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(3-indolyl)-3-cyclohexylpropanoate 3 (Table 2, Entry 2)
Reaction of dimethyl malonate (1 mL, 1.156 g, 8.75 mmol), $TiCl_4$ (960 μL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), cyclohexanecarbaldehyde (1.060 mL, 982 mg, 8.75 mmol) and indole (1.025 g, 8.75 mmol) yielded **3** (1.890 g; 63 %) as a yellow solid; mp = 128-129 °C; **^{1}H NMR** ($CDCl_3$): δ 0.92 (m, 2H), 1.19 (m, 2H), 1.66 (m, 7H), 3.34 (s, 3H), 3.73 (s, 3H), 3.78 (dd, 1H, *J* = 10,9 Hz, *J* = 4.7 Hz), 4.04 (d, 1H, *J* = 10.9 Hz), 7.02 (d, 1H, *J* = 2.4 Hz), 7.13 (m, 2H), 7.32 (d, 1H, *J* = 7,5 Hz), 7.66 (d, 1H, *J* = 7,6 Hz), 8.06 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 26.1, 26.3, 26.6, 28.5, 32.2, 40.9, 41.8, 52.1, 52.5, 55.5, 110.8, 113.8, 119.3, 119.6, 121.7, 122.6, 128.3, 135.5, 168.8, 169.4. **IR** (KBr): ν 3404, 2924, 2851, 1749, 1431, 1262 cm^{-1}. **MS (EI)**: *m/z* 343, 260, 211, 168, 130, 129, 101. **HRMS** calcd for $C_{20}H_{25}NO_4$ 343.1784; found 343.1787. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(3-indolyl)-3-phenylpropanoate 4 (Table 2, Entry 3)

Yield from dimethyl malonate (1 mL, 1.156 g, 8.75 mmol), $TiCl_4$ (960 μL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), benzaldehyde (890 μL, 929 mg, 8.75 mmol) and indole (1.025 g, 8.75 mmol): 1.594 g (54 %) as a pink solid; mp = 149-151 °C; **^{1}H NMR** ($CDCl_3$): δ 3.52 (s, 3H), 3.55 (s, 3H), 4.31 (d, 1H, *J* = 11.7 Hz), 5.09 (d, 1H, *J* = 11.7 Hz), 7.20 (m, 9H), 7.51 (d, 1H, *J* = 7,5 Hz), 8.03 (sl, 1H); **^{13}C NMR** ($CDCl_3$): δ 42.8, 52.5, 52.7, 58.1, 111.0, 116.8, 119.3, 119.5, 120.7, 122.3, 126.5, 126.8, 128.0, 128.4, 136.2, 141.1, 168.1, 168.4. **IR (KBr)**: ν 3386, 2947, 1752, 1754, 1457, 1433, 1252, 1014 cm^{-1}. **MS (CI)**: *m/z* 337, 246, 206, 178, 149. **$C_{20}H_{19}NO_4$** (337.28): calcd. C 71.20, H 5.68, N 4.15; found C 71.18, H 5.83, N 4.21. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(3-indolyl)-3-(*p*-nitrophenyl)propanoate 5 (Table 2, Entry 4)

Reaction of dimethyl malonate (1 mL, 1.156 g, 8.75 mmol), $TiCl_4$ (960 μL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), 4-nitrobenzaldehyde (1.322 g, 8.75 mmol) and indole (1.025 g, 8.75 mmol) yielded **5** (2.105 g; 63 %) as a red pale solid; mp = 145-146 °C; **^{1}H NMR** ($CDCl_3$): δ 3.57 (s, 3H), 3.59 (s, 3H), 4.34 (d, 1H, *J* = 11.5 Hz), 5.21 (d, 1H, *J* = 11.5 Hz), 7.08 (m, 1H), 7.17 (m, 1H), 7.22 (m, 1H), 7.28 (m, 1H), 7.44 (m, 1H), 7.53 (m, 2H), 8.11 (m, 2H), 8.13 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 42.4, 52.8, 52.9, 57.4, 111.3, 115.2, 118.8, 119.9, 121.0, 122.7, 123.7, 126.1, 129.0, 136.2, 146.4, 148.9, 167.7, 167.8. **IR** (KBr): ν 3401, 3048, 2952, 1736, 1516, 1344, 1270, 1150, 741 cm^{-1}. **MS (EI)**: *m/z* 382, 355, 251, 161, 149, 133, 101. **HRMS** calcd for $C_{20}H_{18}N_2O_6$ 382.1165; found 382.1153. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(3-indolyl)-3-(phenethyl)propanoate 6 (Table 2, Entry 5)

Yield from dimethyl malonate (1 mL, 1.156 g, 8.75 mmol), $TiCl_4$ (960 μL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), phenylpropionaldehyde (1.22 mL, 8.75 mmol) and indole (1.025 g, 8.75 mmol): 2.152 g (68 %) as a yellow oil; **^{1}H NMR** ($CDCl_3$): δ 2.10 (m, 4H), 2.48 (m, 1H), 3.39 (s, 3H), 3.63 (s, 3H), 3.85 (d, 1H, *J* = 10.1 Hz), 7.15 (m, 8H), 7.38 (d, 1H, *J* = 7,8 Hz), 7.65 (d, 1H, *J* = 7,8 Hz), 8.03 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 30.5, 32.2, 42.0, 52.3, 52.5, 56.5, 110.8, 112.8, 119.2, 119.8, 121.2, 122.5, 128.3, 135.6, 136.1, 168.6, 169.5. **IR** (KBr): ν 3412, 3051, 2986, 2952, 1725, 1435, 1280, 1016, 750 cm^{-1}. **MS**

(CI): *m/z* 366, 235, 234, 144, 131. **$C_{22}H_{23}NO_4$** (365.16): calcd. C 72.31, H 6.34, N 3.83; found C 71.98, H 5.96, N 4.11. A copy of the ^{1}H NMR spectrum is provided.

(3*RS*, 3a'*R*, 5'*R*, 6'*S*, 6a'*R*) Methyl 2-methoxycarbonyl-3-(3-indolyl)-3-(6'-benzyloxy-2',2'-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5'-yl)propanoate 7 (Table 2, Entry 6)

Reaction of dimethyl malonate (400 µL, 462 mg, 3.5 mmol), $TiCl_4$ (380 µL, 664 mg, 3.5 mmol), Et_3N (490 µL, 354 mg, 3.5 mmol), aldehyde (0.938 g, 3.5 mmol) and indole (0.407 g, 3.5 mmol) yielded **7** (1.170 g; 66 %) as a yellow oil; **^{1}H NMR** ($CDCl_3$): δ 1.27 (s, 3H), 1.48 (s, 3H), 3.45 (m, 4H), 3.62 (s, 3H), 3.75 (m, 1H), 3.91 (d, 1H, *J* = 3.4 Hz), 3.97 (d, 1H, *J* = 3.0 Hz), 4.16 (m, 1H), 4.51 (m, 4H), 5.83 (m, 1H), 7.07 (m, 2H), 7.32 (m, 7H), 7.65 (d, 1H, *J* = 7.9 Hz), 8.04 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 26.6, 26.8, 36.9, 50.1, 52.3, 52.5, 71.1, 80.6, 82.4, 104.6, 111.0, 112.1, 119.1, 121.6, 127.3, 127.6, 128.4, 135.6, 137.1, 168.7, 169.1. **IR** (KBr): ν 3401, 2987, 1740, 1454, 1432, 1370, 1256, 1018 cm^{-1}. **MS (EI)**: *m/z* 509, 387, 305, 243, 211, 129. **HRMS** calcd for $C_{28}H_{31}NO_8$ 509.2050; found 509.1956. A copy of the ^{1}H NMR spectrum is provided.

COSY ^{1}H NMR spectrum, measured in CD_3OD allowed the identification of the two C-3 epimers as follows:

7a (major): **^{1}H NMR** (CD_3OD): δ 1.28 (s, 3H), 1.45 (s, 3H), 3.59 (s, 3H), 3.68 (s, 3H), 3.84 (d, 1H, *J* = 3.2 Hz), 4.16 (d, 1H, *J* = 7.8 Hz), 4.34 (dd, 1H, *J* = 7.8, 7.8 Hz), 4.44 and 4.70 (d, 2H, *J* = 11.6 Hz), 4.68-4.75 (m, 2H), 5.88 (d, 1H, *J* = 3.9 Hz), 6.98 (t, 1H, *J* = 7.8 Hz), 7.08 (s, 1H), 7.31 (d, 1H, *J* = 6.9 Hz), 7.32-7.47 (m, 6H), 7.55 (d, 1H, *J* = 7.8 Hz).

7b (minor): **^{1}H NMR** (CD_3OD): δ 1.30 (s, 3H), 1.45 (s, 3H), 3.45 (dd, 1H, *J* = 4.7, 9.3 Hz), 3.68 (s, 3H), 3.89 (d, 1H, *J* = 3.1 Hz), 4.09 (d, 1H, *J* = 4.7 Hz), 4.45 and 4.72 (d, 2H, *J* = 11.8 Hz), 4.68-4.75 (m, 2H), 5.88 (d, 1H, *J* = 3.9 Hz), 7.00 (s, 1H), 7.05 (t, 1H, *J* = 8.2 Hz), 7.32-7.47 (m, 8H). A copy of the COSY ^{1}H NMR spectrum of **7** (zoomed between δ = 3.0 and δ= 5.0 ppm) in CD_3OD is provided.

Ethyl 2-ethoxycarbonyl-3-(3-indolyl)-3-(2-propyl)propanoate 10 (Table 3, Entry 1)

Yield from diethyl malonate (1.33 mL, 1.400 g, 8.75 mmol), $TiCl_4$ (960 µL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), isobutyraldehyde (800 µL, 631 mg, 8.75 mmol) and indole (1.025 g, 8.75 mmol): 1.506 g (52 %) as a white solid; mp = 75-76 °C; **^{1}H NMR** ($CDCl_3$): δ 0.74 (t, 3H, *J* = 7.1 Hz), 0.87 (m, 6H), 1.26 (t, 3H, *J* = 7.1 Hz), 2.09 (m, 1H, H3), 3.83 (dd, 1H, *J* = 11.3 Hz, *J* = 4.7 Hz), 3.97 (d, 1H, *J* = 11.0 Hz), 4.21 (q, 4H, *J* = 7.1 Hz),

6.98 (d, 1H), 7.11 (m, 2H), 7.30 (d, 1H, *J* = 7.4 Hz), 7.68 (d, 1H, *J* = 7.6 Hz), 8.19 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 13.4, 14.0, 17.8, 21.9, 30.5, 42.0, 56.6, 61.0, 61.4, 110.8, 113.0, 119.2, 119.7, 121.6, 122.8, 128.6, 135.5, 168.3, 169.0. **IR** (KBr): ν 3392, 3048, 2960, 1727, 1454, 1366, 1177, 1027, 736 cm^{-1}. **MS (EI)**: *m/z* 331, 288, 171, 156, 130, 115. **HRMS** calcd for $C_{19}H_{25}NO_4$ 331.1784; found 331.1745. A copy of the ^{1}H NMR spectrum is provided.

***i*-Propyl 2-*i*-propyloxycarbonyl-3-(3-indolyl)-3-(2-propyl)propanoate 11** (Table 3, Entry 2)

Prepared according to the general sprocedure using 1.645 g of diisopropyl malonate (8.75 mmol), 960 μL of $TiCl_4$ (1.660 g, 8.75 mmol), 1.23 mL of Et_3N (885 mg, 8.75 mmol), 800 μL of isobutyraldehyde (631 mg, 8.75 mmol) and 1.025 g of indole (8.75 mmol) to yield **11** (1.735 g; 56 % yield) as a white solid; mp = 104-106 °C; **^{1}H NMR** ($CDCl_3$): δ 0.70 (d, 3H, *J* = 6.2 Hz), 0.88 (m, 9H), 1.26 (t, 6H, *J* = 6.3 Hz), 2.13 (m, 1H), 3.85 (dd, 1H, *J* = 11.4 Hz, *J* = 4.3 Hz), 3.97 (d, 1H, *J* = 11.4 Hz), 4.67 (sept, 1H, *J* = 6.3 Hz), 5.12 (sept, 1H, *J* = 6.3 Hz), 6.92 (d, 1H, *J* = 2.4 Hz), 7.15 (m, 2H), 7.29 (d, 1H, *J* = 7.5 Hz), 7.69 (d, 1H, *J* = 7.5 Hz), 8.36 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 17.6, 20.8, 21.1, 21.6, 21.9, 30.5, 41.8, 57.0, 68.3, 68.8, 110.8, 112.9, 119.1, 119.8, 121.6, 122.8, 128.7, 135.6, 168.0, 168.6. **IR** (KBr): ν 3463, 2977, 2933, 1725, 1586, 1450, 1263 cm^{-1}. **MS (EI)**: *m/z* 359, 316, 188, 170, 130. **HRMS** calcd for $C_{21}H_{29}NO_4$ 359.2097; found 359.2108. A copy of the ^{1}H NMR spectrum is provided.

(2*S, 3R*) Methyl 2-(acetyl)-3-(3-indolyl)-3-(2-propyl)propanoate 12** (Table 3, Entry 3)

Reaction of methyl acetoacetate (940 μL, 1.016 g, 8.75 mmol), $TiCl_4$ (960 μL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), isobutyraldehyde (800 μL, 631 mg, 8.75 mmol) and indole (1.025 g, 8.75 mmol) yielded **12** (966 mg; 45 %) as a white solid; mp = 128-130 °C; **^{1}H NMR** ($CDCl_3$): δ 0.84 (d, 6H, *J* = 5.6 Hz), 1.90 (s, 3H), 2.05 (m, 1H), 3.78 (s, 3H), 3.88 (dd, 1H, *J* = 12.2 Hz, *J* = 3.8 Hz), 4.05 (d, 1H, *J* = 12.2 Hz), 6.89 (d, 1H, *J* = 2.4 Hz), 7.12 (m, 3H), 7.32 (d, 1H, *J* = 4.8 Hz), 7.67 (d, 1H, *J* = 7.5 Hz), 8.14 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 17.2, 21.9, 30.7, 52.6, 64.8, 111.1, 111.9, 119.2, 119.6, 122.2, 128.2, 135.6, 169.8, 203.4. **IR** (KBr): ν 3277, 3048, 2977, 2951, 1727, 1696, 1423, 1253 cm^{-1}. **MS (EI)**: *m/z* 287, 202, 170, 156, 130, 115. **HRMS** calcd for $C_{17}H_{21}NO_3Na$ 310.1419; found 310.1414. A copy of the ^{1}H NMR spectrum is provided.

(2*R, 3R*) Ethyl 2-nitro-3-(3-indolyl)-3-(2-propyl)propanoate 13** (Table 3, Entry 4)

Yield from ethyl nitroacetate (1 mL, 1.164 g, 8.75 mmol), $TiCl_4$ (960 μL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), isobutyraldehyde (800 μL, 631 mg, 8.75 mmol) and indole (1.025 g, 8.75 mmol): 1.267 g (48 %) as a yellow solid; mp = 124-125 °C; **^{1}H NMR**($CDCl_3$): δ 0.90 (d, 3H, *J* = 6.7 Hz), 0.92 (d, 3H, *J* = 6.7 Hz), 1.23 (t, 3H, *J* = 6.9 Hz), 2.14 (m, 1H), 3.99 (dd, 1H, *J* = 10.1 Hz, *J* = 5.5 Hz), 4.23 (m, 2H), 5.63 (d, 1H, *J* = 10.1 Hz), 7.25 (m, 4H), 7.62 (d, 1H, *J* = 7.5 Hz), 8.13 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 13.7, 18.5, 21.7, 29.9, 43.7, 62.9, 91.3, 110.1, 111.1, 118.9, 119.6, 122.1, 122.9, 128.1, 135.6, 164.3. **IR** (KBr): ν 3424, 2962, 1754, 1562, 1190, 1018, 741 cm^{-1}. **MS (CI)**: *m/z* 305, 259, 172, 141, 82. **$C_{16}H_{20}N_2O_4$** (304.34): calcd. C 63.14, H 6.62, N 9.20; found C 63.46, H 6.76, N 9.13. A copy of the ^{1}H NMR spectrum is provided.

(3*RS*, 3a'*R*, 5'*R*, 6'*S*, 6a'*R*) Ethyl 2-diethylphosphono-3-(3-indolyl)-3-(6'-benzyloxy-2',2'-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5'-yl)propanoate 14 (Table 3, Entry 5)

Reaction of triethyl phosphonoacetate (560 μL, 628 mg, 2.8 mmol), $TiCl_4$ (310 μL, 531 mg, 2.8 mmol), Et_3N (390 μL, 283 mg, 2.8 mmol), aldehyde (0.783 g, 2.8 mmol) and indole (0.330 g, 2.8 mmol) yielded **14** (915 mg; 54 %) as a white solid; mp = 101-103 °C; **^{1}H NMR** ($CDCl_3$): δ 0.94 (m, 3H), 1.05 (m, 3H), 1.18 (m, 3H), 1.30 (m, 3H), 1.43 (s, 3H), 1.50 (s, 3H), 3.80 (m, 8H), 4.55 (m, 4H), 4.90 (dd, 1H, *J* = 6.8 Hz, *J* = 3.4 Hz), 5.79 (d, 2H, *J* = 3.7 Hz), 7.30 (m, 10H), 8.21 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 13.9, 15.9, 16.1, 26.3, 26.8, 34.2, 35.1, 49.4, 61.4, 62.1, 62.4, 71.1, 81.6, 82.5, 104.6, 110.8, 111.3, 112.2, 119.4, 124.0, 125.1, 127.2, 135.5, 137.1, 168.2, 169.3. **IR** (KBr): ν 3268, 2925, 1731, 1454, 1366, 1251, 1163 cm^{-1}. **MS (EI)**: *m/z* 601, 528, 496, 464, 378. **$C_{31}H_{40}NO_9P$** (601.61): calcd. C 61.88, H 6.70, N 2.33; found C 62.06, H 6.76, N 2.11. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(*N*-methyl-3-indolyl)-3-(2-propyl)propanoate 16 (Table 4, Entry 1)

Yield from dimethyl malonate (500 μL, 578 mg, 4.375 mmol), $TiCl_4$ (480 μL, 830 mg, 4.375 mmol), Et_3N (615 μL, 443 mg, 4.375 mmol), isobutyraldehyde (400 μL, 316 mg, 4.375 mmol) and *N*-methylindole (560 μL, 4.375 mmol): 0.570 g (43 %) as a red solid; mp = 105-107 °C; **^{1}H NMR** ($CDCl_3$): δ 0.85 (d, 3H, *J* = 6.7 Hz), 0.87 (d, 3H, *J* = 6.7 Hz), 2.06 (m, 1H), 3.36 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.79 (dd, 1H, *J* = 11.0 Hz, *J* = 4.9 Hz), 3.97 (d, 1H, *J* = 11.0 Hz), 6.88 (s, 1H), 7.09 (m, 1H), 7.18 (m, 1H), 7.25 (d, 1H, *J* = 7.0 Hz), 7.65 (d, 1H, *J* =

7.9 Hz). **^{13}C NMR** ($CDCl_3$): δ 17.9, 21.8, 30.5, 32.7, 42.1, 52.1, 52.4, 56.2, 108.8, 111.3, 118.7, 119.6, 121.2, 127.3, 128.9, 136.3, 168.6, 169.3. **IR** (KBr): ν 2951, 1736, 1432, 1322, 1155, 741 cm^{-1}. **MS (EI)**: *m/z* 317, 274, 215, 186, 144. **HRMS** calcd for $C_{18}H_{23}NO_4$ 317.1627; found 317.1636. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(2-methyl-3-indolyl)-3-(2-propyl)propanoate 17 (Table 4, Entry 2)

Prepared according to procedure using 1 mL (1.156 g, 8.75 mmol) of dimethyl malonate, 960 μL (1.660 g, 8.75 mmol) of $TiCl_4$, 1.23 mL (885 mg, 8.75 mmol) of Et_3N, 800 μL (631 mg, 8.75 mmol) of isobutyraldehyde and 1.148 g (8.75 mmol) of 2-methylindole to yield **17** (1.248 g; 45 % yield) as a yellow oil; **^{1}H NMR** ($CDCl_3$): δ 0.89 (d, 6H, *J* = 6.8 Hz), 2.20 (m, 1H), 2.31 (s, 3H), 3.58 (dd, 1H, *J* = 11.1 Hz, *J* = 6.0 Hz), 3.73 (s, 3H), 3.78 (s, 3H), 4.36 (d, 1H, *J* = 11.1 Hz), 7.00 (m, 2H), 7.18 (m, 1H), 7.57 (m, 1H), 8.19 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 12.2, 19.4, 21.5, 31.9, 43.6, 51.9, 52.6, 55.2, 108.7, 110.1, 118.8, 119.7, 120.3, 127.4, 133.8, 135.3, 169.2, 169.7. **IR** (KBr): ν 3393, 2954, 1752, 1458, 1267, 742 cm^{-1}. **MS (EI)**: *m/z* 317, 274, 187, 186, 185, 170, 144, 101. **HRMS** calcd for $C_{18}H_{23}NO_4$ 317.1627; found 317.1692. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(3-methyl-2-indolyl)-3-(2-propyl)propanoate 18 (Table 4, Entry 3)

Yield from dimethyl malonate (1 mL, 1.156 g, 8.75 mmol), $TiCl_4$ (960 μL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), isobutyraldehyde (800 μL, 631 mg, 8.75 mmol) and 3-methylindole (1.148 g, 8.75 mmol): 2.524 g (91 %) as a red solid; mp = 103-104 °C; **^{1}H NMR** ($CDCl_3$): δ 0.73 (d, 3H, *J* = 6.6 Hz), 1.02 (d, 3H, *J* = 6.6 Hz), 2.21 (m, 1H), 2.21 (s, 1H), 3.30 (dd, 1H, *J* = 10.3 Hz, *J* = 6.4 Hz), 3.45 (s, 3H), 3.78 (s, 3H), 4.07 (d, 1H, *J* = 6.4 Hz), 7.08 (m, 2H), 7.32 (d, 1H, *J* = 7.9 Hz), 7.48 (d, 1H, *J* = 7.4 Hz), 9.36 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 8.5, 21.1, 21.5, 30.5, 43.7, 52.5, 52.7, 53.6, 109.5, 110.8, 118.2, 118.4, 121.2, 128.4, 132.5, 135.7, 168.9, 170.2. **IR** (KBr): ν 3402, 2956, 1732, 1462, 1271, 742 cm^{-1}. **MS (EI)**: *m/z* 318, 317, 275, 274, 242, 215, 186, 154. **HRMS** calcd for $C_{18}H_{23}NO_4$ 317.1627; found 317.1638. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(1,2-dimethyl-3-indolyl)-3-(2-propyl)propanoate 19 (Table 4, Entry 4)

Prepared according to procedure using 1 mL of dimethyl malonate (1.156 g, 8.75 mmol), 960 μL of $TiCl_4$ (1.660 g, 8.75 mmol), 1.23 mL of Et_3N (885 mg, 8.75 mmol), 800 μL of isobutyraldehyde (631 mg, 8.75 mmol) and 1.270 g of dimethylindole (8.75 mmol) to yield **19** (1.804 g; 72 % yield) as a white solid; mp = 100-101 °C; **^{1}H NMR** ($CDCl_3$): δ 0.88 (d, 3H, *J* = 6.7 Hz), 0.89 (d, 3H, *J* = 6.7 Hz), 2.20 (m, 1H), 2.40 (s, 3H), 3.22 (s, 3H), 3.62 (dd, 1H, *J* = 11.1 Hz, *J* = 6.1 Hz), 3.64 (s, 3H), 3.80 (s, 3H), 4.36 (d, 1H, *J* = 11.1 Hz), 7.07 (m, 2H), 7.23 (d, 1H, *J* = 8.0 Hz), 7.60 (d, 1H, *J* = 7.9 Hz). **^{13}C NMR** ($CDCl_3$): δ 10.7, 20.4, 21.5, 29.7, 31.9, 43.9, 51.9, 52.6, 55.3, 108.0, 108.5, 118.4, 119.9, 120.4, 126.6, 135.6, 136.8, 168.8, 169.9. **IR** (KBr): ν 3040, 2952, 1753, 1731, 1467, 1432, 1252, 1155, 1014, 736 cm^{-1}. **MS (EI)**: *m/z* 331, 288, 229, 200, 198, 158. **HRMS** calcd for $C_{19}H_{25}NO_4$ 331.1784; found 331.1741. A copy of the ^{1}H NMR spectrum is provided.

(3*RS*, 3a'*R*, 5'*R*, 6'*S*, 6a'*R*) Methyl 2-methoxycarbonyl-3-[3-(2-ethoxycarbonyl)indolyl]-3-(6'-benzyloxy-2',2'-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5'-yl)propanoate 20 (Table 4, Entry 5)

Reaction of dimethyl malonate (740 μL, 859 mg, 6.5 mmol), $TiCl_4$ (710 μL, 1.233 g, 6.5 mmol), Et_3N (910 μL, 658 mg, 6.5 mmol), aldehyde (1.799 g, 6.5 mmol) and 2-ethoxycarbonylindole (1.223 g, 6.5 mmol) yielded **20** (2.590 g; 66 %) as a yellow oil; **^{1}H NMR** ($CDCl_3$): δ 1.20-1.45 (m, 9H), 3.23 (s, 3H), 3.55 (s, 3H), 3.75 (m, 5H), 4.38 (m, 3H), 4.43 (dd, 1H, *J* = 9.4 Hz, *J* = 6.8 Hz), 5.82 (d, 1H, *J* = 3.8 Hz), 7.35 (m, 8H), 7.84 (d, 1H, *J* = 8.2 Hz), 8.79 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 14.2, 26.4, 33.0, 36.9; 50.1, 52.4, 54.5, 60.8, 71.7, 77.9, 79.3, 81.6, 83.0, 111.2, 111.8, 119.9, 120.2, 124.1, 124.8, 125.2, 126.6; 127.3, 127.5, 128.3, 128.8, 135.8, 137.7, 161.2, 168.3, 169.0. **IR** (KBr): ν 3374, 2987, 2951, 1736, 1709, 1454, 1375, 1247, 1159, 855 cm^{-1}. **MS (EI)**: *m/z* 581, 509, 387, 305, 273, 243, 129. **HRMS** calcd for $C_{31}H_{35}NO_{10}$ 581.2274; found 581.2261. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(2-furyl)-3-(2-propyl)propanoate 21 (Table 4, Entry 6)

Yield from dimethyl malonate (1 mL, 1.156 g, 8.75 mmol), $TiCl_4$ (960 μL, 1.660 g, 8.75 mmol), Et_3N (1.23 mL, 885 mg, 8.75 mmol), isobutyraldehyde (800 μL, 631 mg, 8.75 mmol) and furan (640 μL, 596 mg, 8.75 mmol): 1.378 g (62 %) as a yellow oil; **^{1}H NMR** ($CDCl_3$): δ

0.82 (d, 3H, *J* = 6.9 Hz), 0.86 (d, 3H, *J* = 6.9 Hz), 1.92 (m, 1H), 3.46 (dd, 1H, *J* = 11.1 Hz, *J* = 4.5 Hz), 3.53 (s, 3H), 3.78 (s, 3H), 3.94 (d, 1H, *J* = 11.1 Hz), 6.05 (d, 1H, *J* = 3.3 Hz), 6.28 (m, 1H), 7.32 (d, 1H, *J* = 1.9 Hz). **^{13}C NMR** ($CDCl_3$): δ 17.5, 21.4, 29.5, 44.7, 52.4, 52.6, 54.0, 107.9, 109.9, 141.4, 152.7, 168.2, 168.6. **IR (KBr)**: ν 3120, 2985, 1755, 1731, 1438, 1023 cm^{-1}. **MS (CI)**: *m/z* 255, 245, 242, 211, 123. **$C_{13}H_{18}O_5$** (254.28): calcd. C 61.40, H 7.14; found C 60.98, H 6.75. A copy of the ^{1}H NMR spectrum is provided.

Methyl 2-methoxycarbonyl-3-(5-methyl-2-furyl)-3-(2-propyl)propanoate 22 (Table 4, Entry 7)

Prepared according to procedure using 1 mL of dimethyl malonate (1.156 g, 8.75 mmol), 960 μL of $TiCl_4$ (1.660 g, 8.75 mmol), 1.23 mL of Et_3N (885 mg, 8.75 mmol), 800 μL of isobutyraldehyde (631 mg, 8.75 mmol) and 789 μL of 2-methylfuran (718 mg, 8.75 mmol) to yield **22** (2.110 g; 90 % yield) as a pale yellow oil; **^{1}H NMR** ($CDCl_3$): δ 0.84 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 6.8 Hz), 1.90 (m, 1H), 2.12 (s, 3H), 3.44 (dd, 1H, *J* = 11.2 Hz, *J* = 4.5 Hz), 3.57 (s, 3H), 3.77 (s, 3H), 3.91 (d, 1H, *J* = 11,2 Hz), 5.84 (m, 1H), 5.94 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 13.5, 17.6, 21.5, 29.4, 44.8, 52.4, 52.6, 54.1, 105.7, 108.5, 150.7, 150.8, 168.4, 168.7. **IR (KBr)**: ν 3101, 2952, 1753, 1736, 1560, 1432, 1260, 1023, 785 cm^{-1}. **MS (EI)**: *m/z* 268, 225, 181, 166, 137, 135, 125. **HRMS** calcd for $C_{14}H_{20}O_5$ 268.1311; found 268.1302. A copy of the ^{1}H NMR spectrum is provided.

Determination of the stereochemistry of 7

(3*S*, 3a'*R*, 5'*R*, 6'*S*, 6a'*R*) Methyl 2-methoxycarbonyl-3-(3-indolyl)-3-(6'-hydroxy-2',2'-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5'-yl)propanoate 8a (Scheme 1)

A diastereomeric mixture (60/40) of **7** (150 mg, 0.295 mmol) dissolved in ethyl acetate (8 mL) hydrogenated at room temp and 4 bar in the presence of 50 mg of 10% Pd on charcoal as catalyst. After 48 h the catalyst was filtered off, the filtrate was evaporated and the residue was purified by flash-chromatography (elution: cyclohexan/ethyl acetate 8/2 to 6/4) affording two main fractions. From the higher running one, a modified diastereomeric mixture (**7a/7b** = 1/1) of the starting material **7** (98 mg, 65 %) was identified.

The lower running fraction corresponded to the diastereomerically enriched alcohol **8a** (33 mg, 27%) resulting from the debenzylation of **7a**.

8a: Pale yellow oil; **^{1}H NMR** ($CDCl_3$): δ 1.28 (s, 3H), 1.46 (s, 3H), 3.38 (s, 3H), 3.78 (s, 3H), 3.84 (d, 1H, *J* = 3.2 Hz), 4.14 (m, 2H), 4.24 (d, 1H, *J* = 10.1 Hz), 4.38 (dd, 2H, *J* = 5.5, 10.1 Hz), 4.45 (d, 1H, *J* = 3.7 Hz), 4.54 (dd, 1H, *J* = 2.6, 5.5 Hz), 5.83 (d, 1H, *J* = 3.7 Hz), 7.12-7.18 (m, 2H), 7.22 (d, 1H, *J* = 2.5 Hz), 7.23-7.27 (m, 1H), 7.72 (dd, 1H, *J* = 2.5, 6.6 Hz), 8.32 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 26.2, 26.8, 35.5, 52.4, 52.9, 55.5, 76.0, 80.5, 85.3, 104.2, 111.2, 111.6, 111.7, 118.9, 119.8, 122.2, 123.8, 126.5, 135.7, 168.4, 170.3. **IR** (KBr): ν 3836, 3732, 3379, 2992, 1728, 1634, 1545, 1522, 1426, 1116, 1064, 1036 cm^{-1}. **MS (EI)**: *m/z* 419, 388, 387, 371, 345, 322, 313, 271, 270. **HRMS** calcd for $C_{21}H_{25}NO_8$ 419.1580; found 419.1552. A copy of the ^{1}H NMR spectrum is provided.

(3a*R*, 3b*S*, 6*S*, 7*S*, 7a*R*, 8a*R*) 7-(3-Indolyl)-2,2-dimethyl-5-oxo-hexahydro-1,3-dioxolo[4,5]furo[3,2-*b*]pyran-6-carboxylic acid methyl ester 9a (Scheme 1)

To an ice-cooled suspension of freshly sublimated ^{t}BuOK (19 mg, 0.17 mmol) in dry THF was added dropwise alcohol **8a** (30 mg, 0.071 mmol), dissolved in THF (2 mL). After 1 h stirring under nitrogen, the reaction mixture was quenched with 10% NH_4Cl, the solvent was partially evaporated and the residue was extracted with CH_2Cl_2 (3x3 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash-chromatography (elution: cyclohexan/ethyl acetate 8/2 to 7/3) affording **9a** (19 mg, 69 %), as a viscous oil. **^{1}H NMR** ($CDCl_3$): δ 1.33 (s, 3H), 1.44 (s, 3H), 3.78 (s, 3H), 3.90 (d, 1H, *J* = 4.8 Hz), 4.41 (dd, 1H, *J* = 4.0, 4.1 Hz), 4.74- 4.83 (m, 3H), 5.90 (d, 1H, *J* = 3.6 Hz), 7.03 (d, 1H, *J* = 2.1 Hz), 7.19 (t, 1H, *J* = 7.8 Hz), 7.28 (t, 1H, *J* = 7.8 Hz), 7.47 (d, 1H, *J* = 7.4 Hz), 7.65 (d, 1H, *J* = 7.8 Hz), 8.38 (sl, 1H). **^{1}H NMR** (CD_3OD): δ 1.31 (s, 3H), 1.37 (s, 3H), 3.63 (s, 3H), 3.98 (dd, 1H, *J* = 3.5, 10.3 Hz), 4.18 (d, 1H, *J* = 10.3 Hz), 4.70 (dd, 1H, *J* = 3.1, 3.2 Hz), 4.83 (d, 1H, *J* = 3.8 Hz) 4.98 (d, 1H, *J* = 2.9 Hz), 5.97 (d, 1H, *J* = 3.8 Hz), 7.03 (t, 1H, *J* = 7.8 Hz), 7.09 (d, 1H, *J* = 1.2 Hz), 7.13 (t, 1H, *J* = 7.1 Hz), 7.37 (d, 1H, *J* = 8.0 Hz), 7.63 (d, 1H, *J* = 7.8 Hz), 10.42 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 26.2, 26.7, 35.7, 49.5, 52.9, 76.3, 82.8, 83.6, 105.0, 111.6, 112.6, 112.8, 118.4, 120.2, 121.0, 122.9, 125.8, 136.3, 166.1, 168.3. **IR** (KBr): ν 3721, 3390, 2985, 1745, 1644, 1535, 1520, 1458, 1166, 1081, 1011 cm^{-1}. **MS (EI)**: *m/z* 387, 371, 345, 329, 313, 271, 269, 255, 237, 218. **HRMS** calcd for $C_{20}H_{21}NO_7$ 387.1318; found 387.1329. $[\alpha]^{26}_D$ +3.2 (*c* 0.72, MeOH). A copy of the ^{1}H NMR spectrum is provided. A copy of the COSY ^{1}H NMR spectrum of **9a** (zoomed between δ = 3.0 and δ= 5.5 ppm) in CD_3OD is provided.

Typical procedures for the synthesis of tryptophan analogues 15

(2*R, 3*R**) Ethyl 2-amino-3-(3-indolyl)-3-(2-propyl)propanoate 15a** (Scheme 2)

Method a :

To a solution of **13** (39 mg, 0.13 mmol) in a mixture of EtOH (5 mL), concd HCl (0.37 mL) and water (4 mL) was added at 0°C Zn dust (190 mg, 2.9 mmol), followed by stirring for 3 h at 0°C. The Zn dust was filtered off, the reaction mixture was diluted with CH_2Cl_2 and washed with water and satd aq Na_2CO_3. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product which was purified by flash chromatography (eluent: CH_2Cl_2/MeOH, 97/3) to furnish **15a** in 67 % yield (24 mg).

Yellow oil; **^{1}H NMR** ($CDCl_3$): δ 0.82 (d, 3H, *J* = 6.6 Hz), 1.10 (d, 3H, *J* = 6.6 Hz), 1.15 (t, 3H, *J* = 6.8 Hz), 1.91 (sl, 2H), 2.25 (m, 1H), 3.18 (dd, 1H, *J* = 9.6 Hz, *J* = 4.6 Hz), 3.90 (m, 3H), 7.10 (m, 3H), 7.32 (d, 1H, *J* = 8.0 Hz), 7.60 (d, 1H, *J* = 7.5 Hz), 8.15 (sl, 1H). **^{13}C NMR** ($CDCl_3$): δ 14.0, 21.4, 30.1, 47.2, 55.9, 60.8, 109.9, 111.0, 118.9, 119.3, 121.9, 128.22, 135.9, 175.2. **IR** (KBr): ν 3408, 3380, 3354, 2973, 2872, 1724, 1368, 1153 cm^{-1}. **MS (CI)**: *m/z* 274, 216, 201, 172, 157, 130. **HRMS** calcd for $C_{16}H_{22}N_2O_2$ 274.1681; found 274.1678. A copy of the ^{1}H NMR spectrum is provided.

Method b :

A solution of (2*R**, 3*R**) *tert*-butyl 2-amino-3-(3-indolyl)-3-(2-propyl)propanoate[16] (45 mg, 0.15 mmol) was treated in boiling EtOH-HCl for 4h. After evaporation of the solvent the residue was dissolved in CH_2Cl_2 (5 mL) and extracted with satd aq Na_2CO_3. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give crude product which was purified by flash chromatography (eluent: CH_2Cl_2/MeOH, 97/3) to give **15a** (29 mg, 72 %) identical all respects with the product obtained from **13** by Zn-mediated reduction.

(2*R, 3*S**) Ethyl 2-amino-3-(3-indolyl)-3-(2-propyl)propanoate 15b**

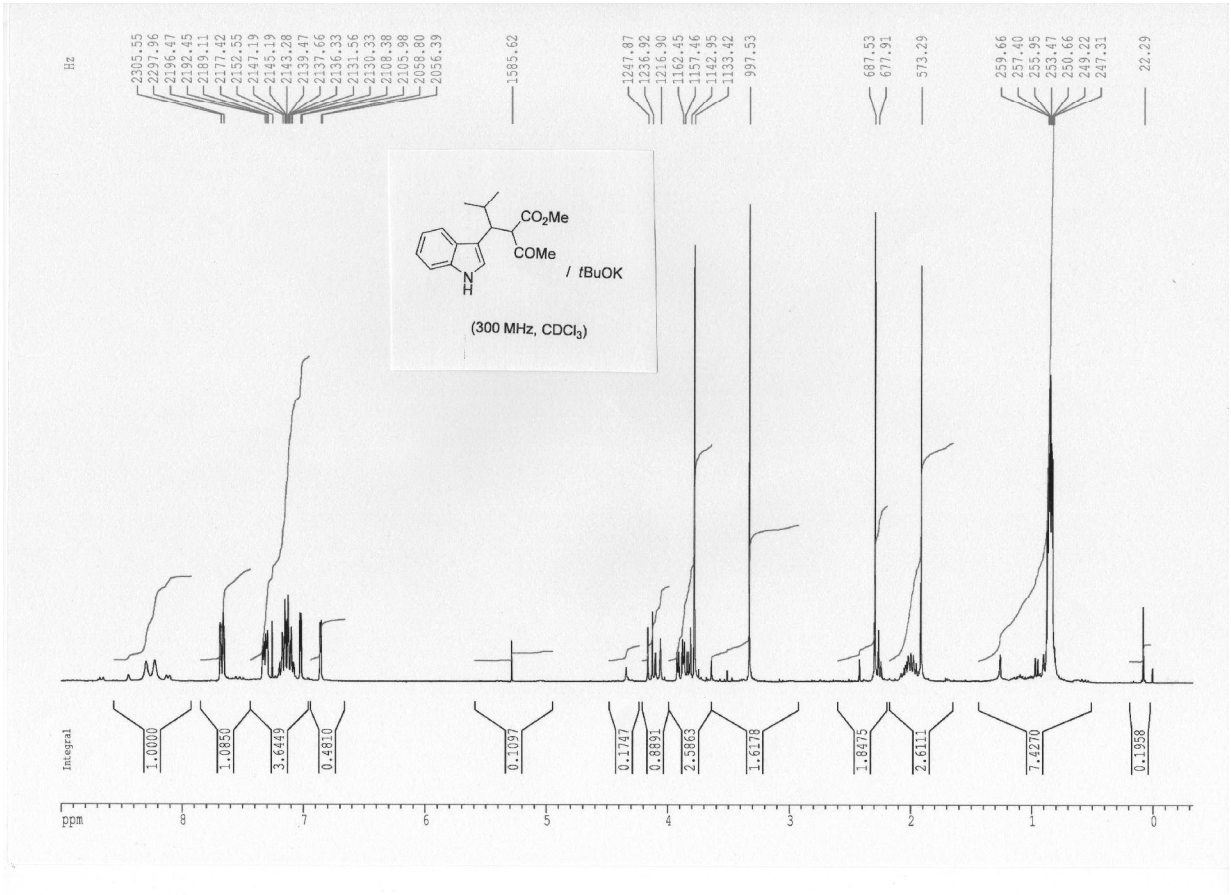
Obtained from (2*R**, 3*S**) *tert*-butyl 2-amino-3-(3-indolyl)-3-(2-propyl)propanoate[16] according to the procedure used for (2*R**, 3*R**) diastereisomer as a yellowish oil; **^{1}H NMR** ($CDCl_3$): δ 0.82 (d, 3H, *J* = 6.6 Hz), 1.02 (m, 6H), 1.90 (sl, 2H), 2.45 (m, 1H), 3.11 (t, 1H, *J* = 6.6 Hz), 3.85 (d, 1H, *J* = 6.6 Hz), 3.95 (q, 2H, *J* = 7.2 Hz), 6.98 (d, 1H, *J* = 2.4 Hz), 7.12 (m, 2H), 7.32 (d, 1H, *J* = 7.8 Hz), 7.61 (d, 1H, *J* = 7.9 Hz), 8.15 (sl, 1H). **IR** (KBr): ν 3415, 3362, 2957, 2870, 1722, 1628, 1370, 1150 cm^{-1}. **MS (CI)**: *m/z* 274, 228, 201, 172, 157, 130. **HRMS**

calcd for $C_{16}H_{22}N_2O_2$ 274.1681; found 274.1679. A copy of the ^1H NMR spectrum is provided.

Epimerization studies of compounds 12 and 13

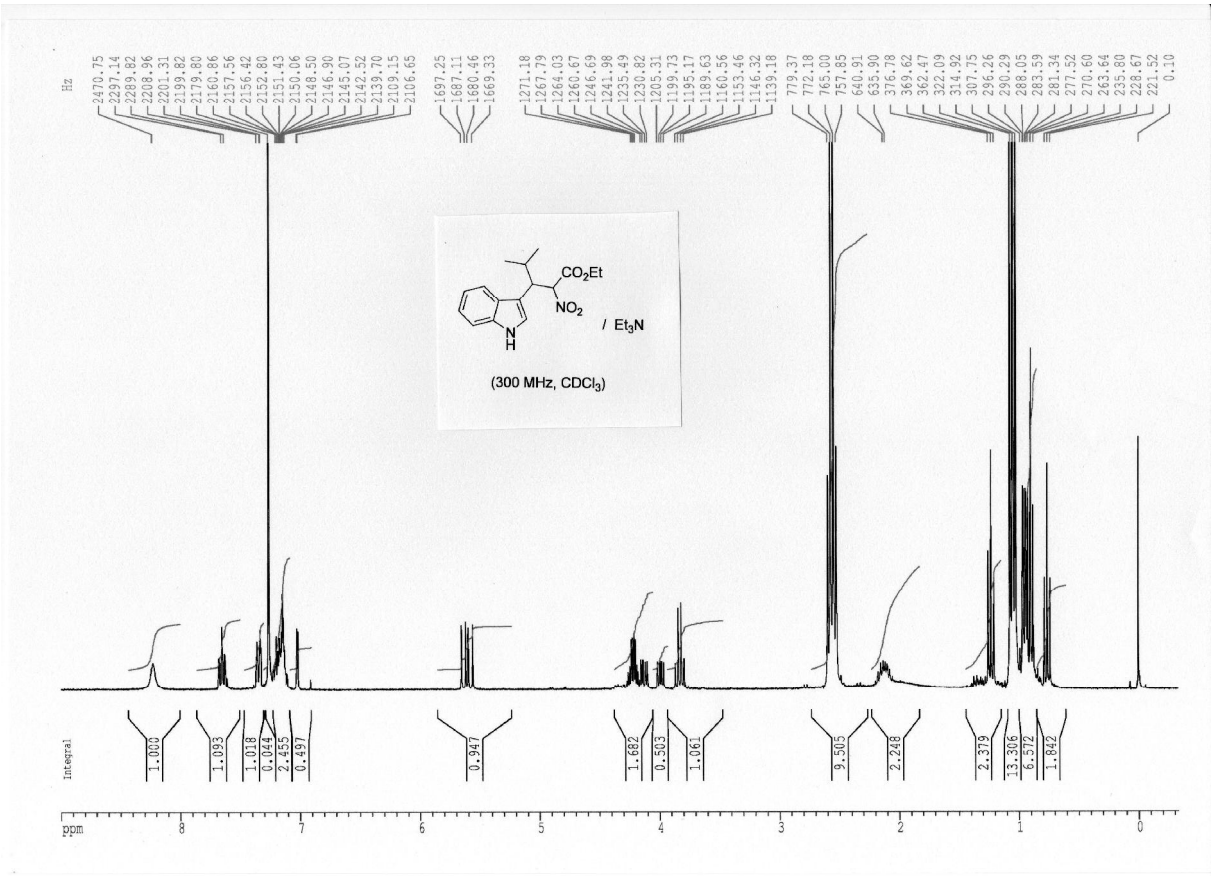
Treatment of **12** with ^{t}BuOK at 0°C

A solution of **12** (40 mg, 0.139 mmol) in dry THF (2 mL) was added dropwise at 0°C to a suspension of freshly sublimated ^{t}BuOK (35 mg, 0.303 mmol) in dry THF. After stirring for 15 min at 0°C under nitrogen, the reaction mixture was quenched with 10 % NH_4Cl, partially evaporated and the residue was extracted with CH_2Cl_2 (2x3 mL). The organic layers were dried ($MgSO_4$), filtered and evaporated to dryness to give 38 mg crude product. The ^1H NMR spectrum of the residue proved a partial epimerisation of the C-3 carbon:



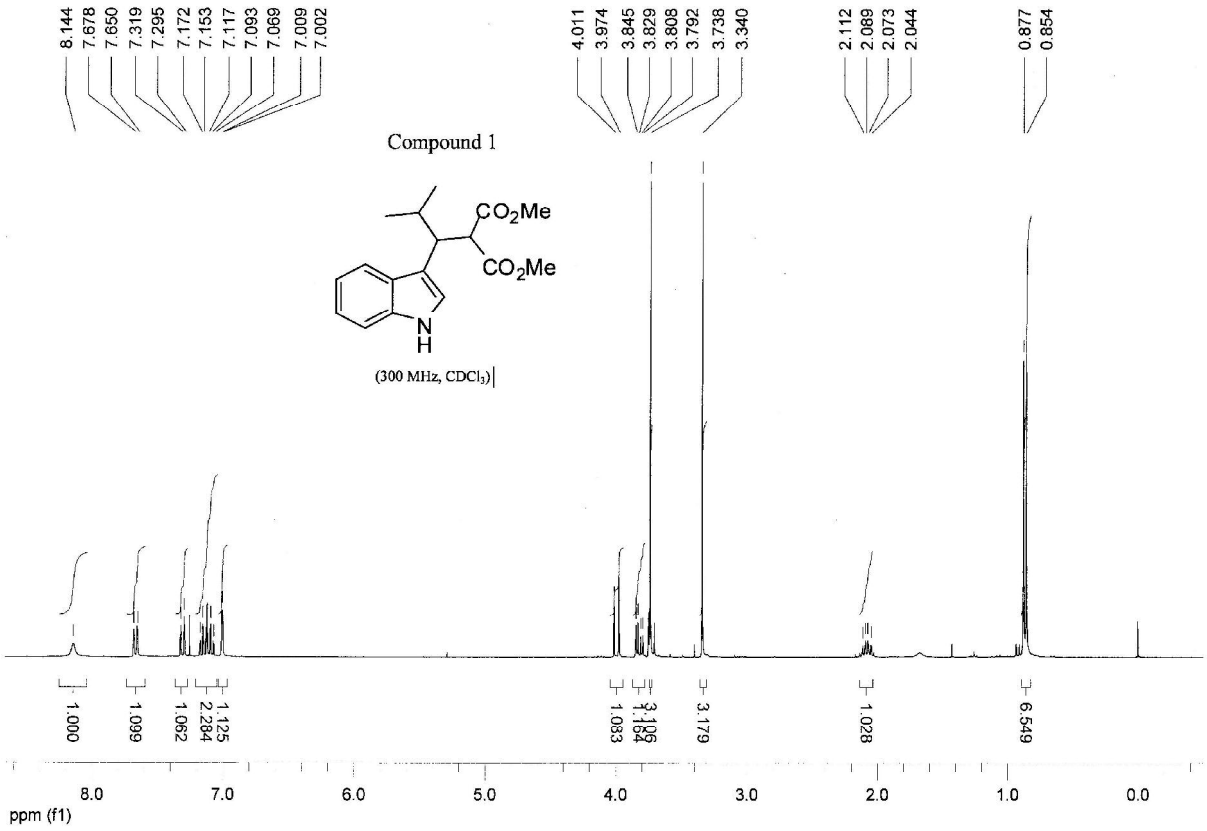
Treatment of **13** with triethylamine at 0°C

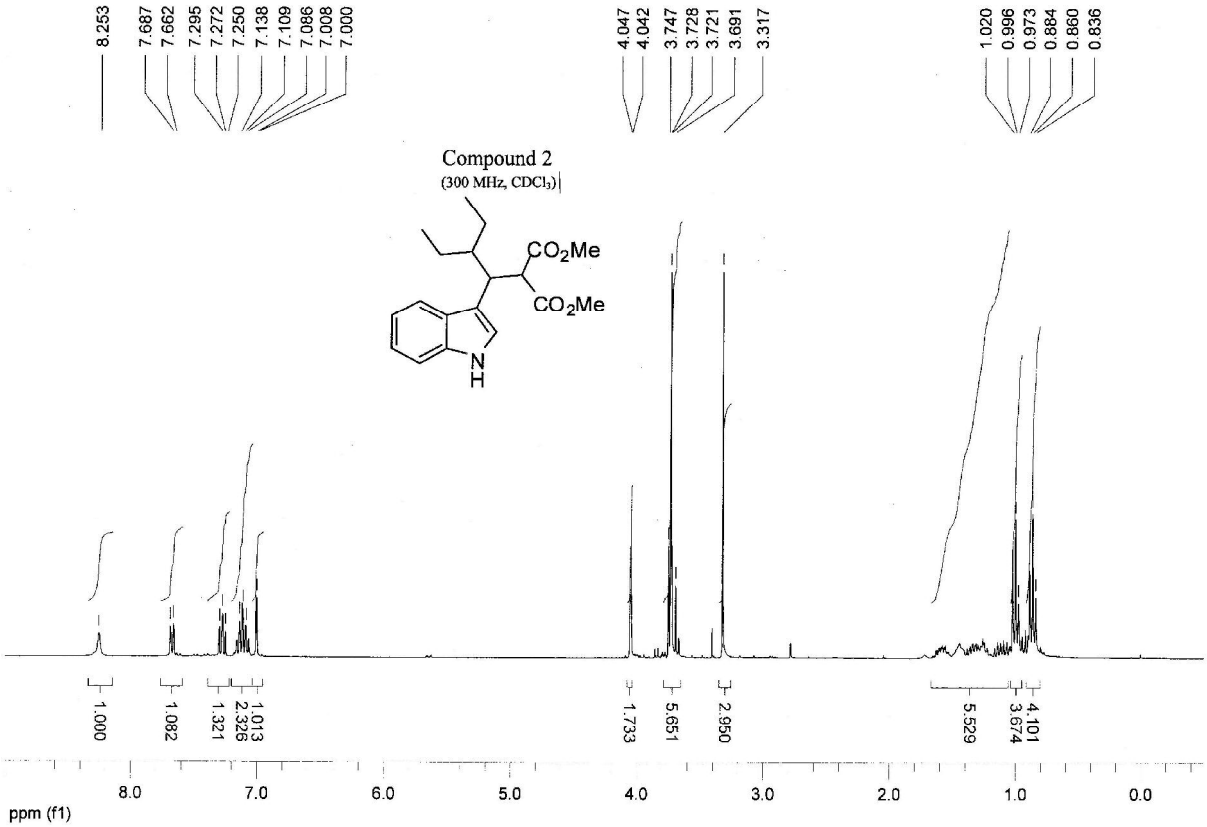
To a solution of **13** (20 mg, 0.064 mmol) in $CDCl_3$ in an NMR tube was added at 0°C triethylamine (10 µL, 0.13 mmol). After 15 min at 0°C, the enregistered ^1H NMR spectrum evidenced a partial epimerisation of the C-3 carbon:



Copies of ^{1}H NMR SPECTRA

for Compounds 1 - 22

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3.728
3.721
3.691
3.317
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0.884
0.860
0.836
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H
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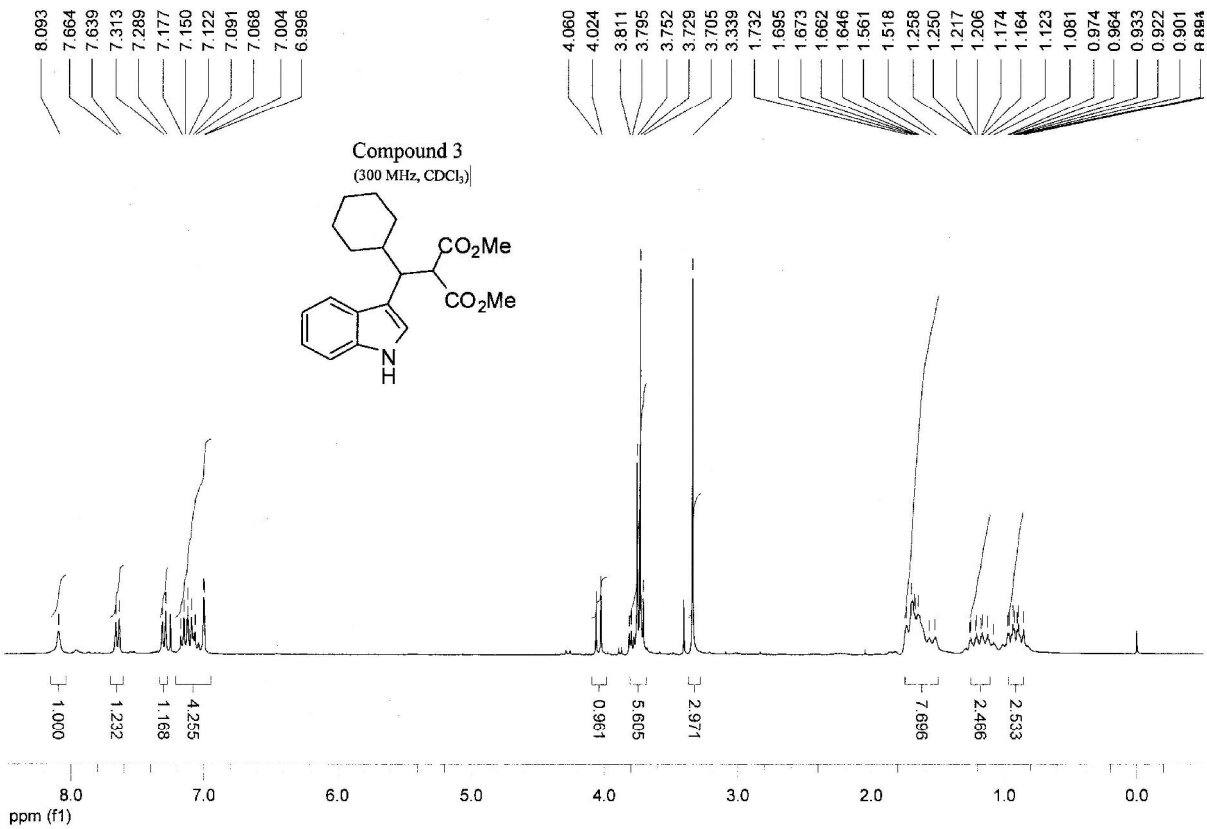
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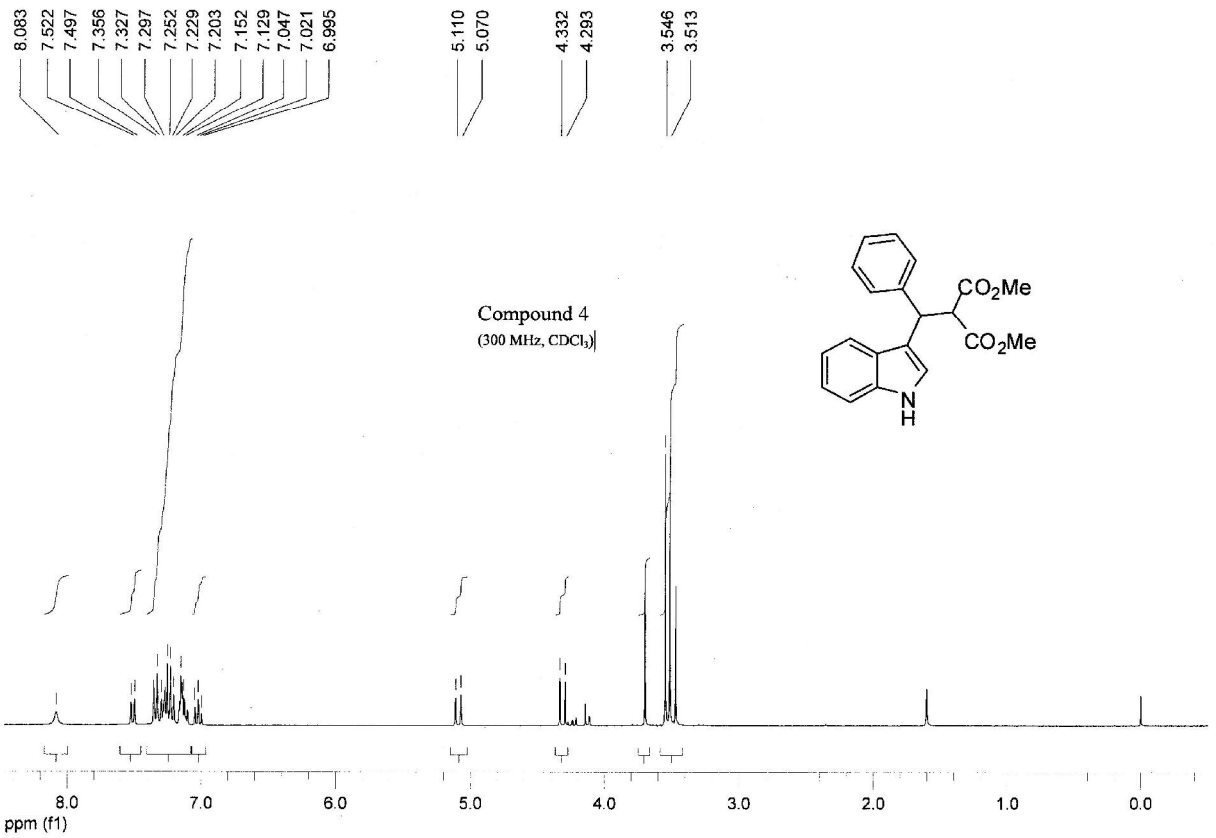
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5.070
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4.293
3.546
3.513
Compound 4
(300 MHz, CDCl3)
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CO2Me
N
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6.0
5.0
4.0
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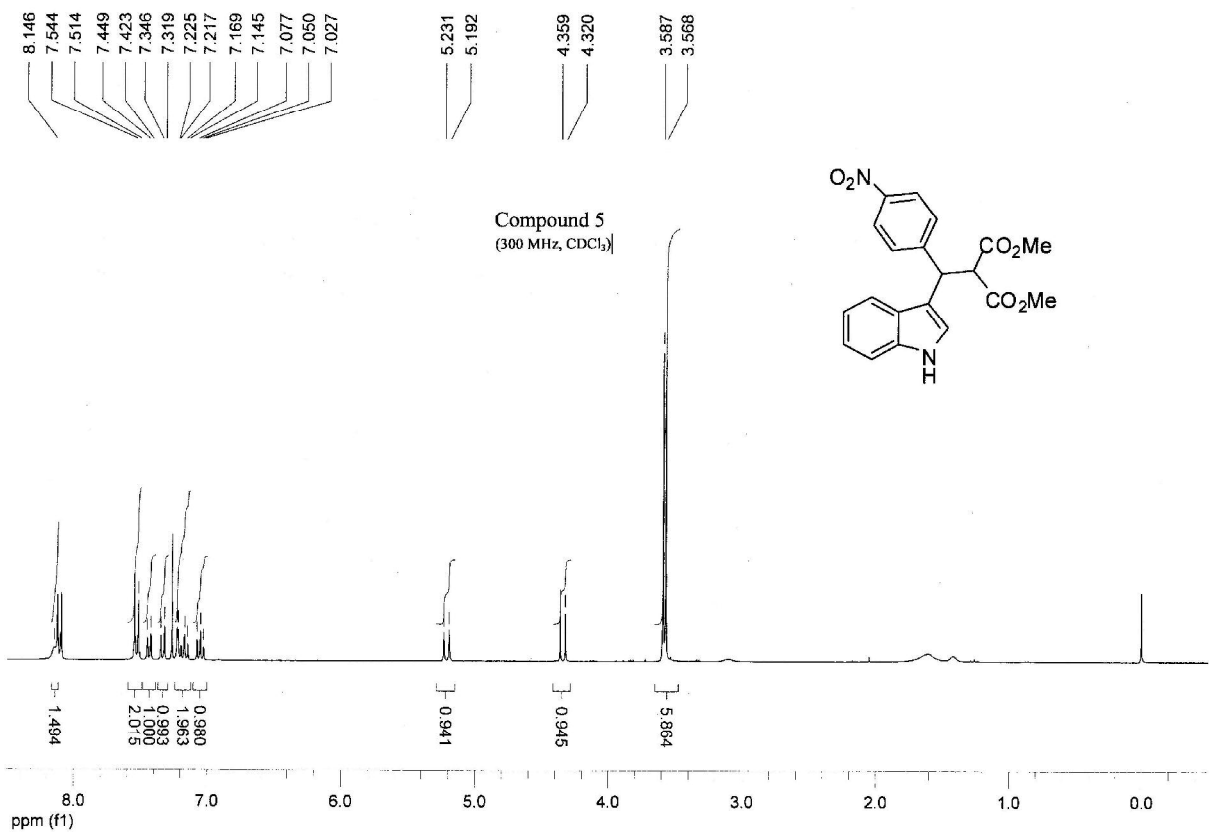
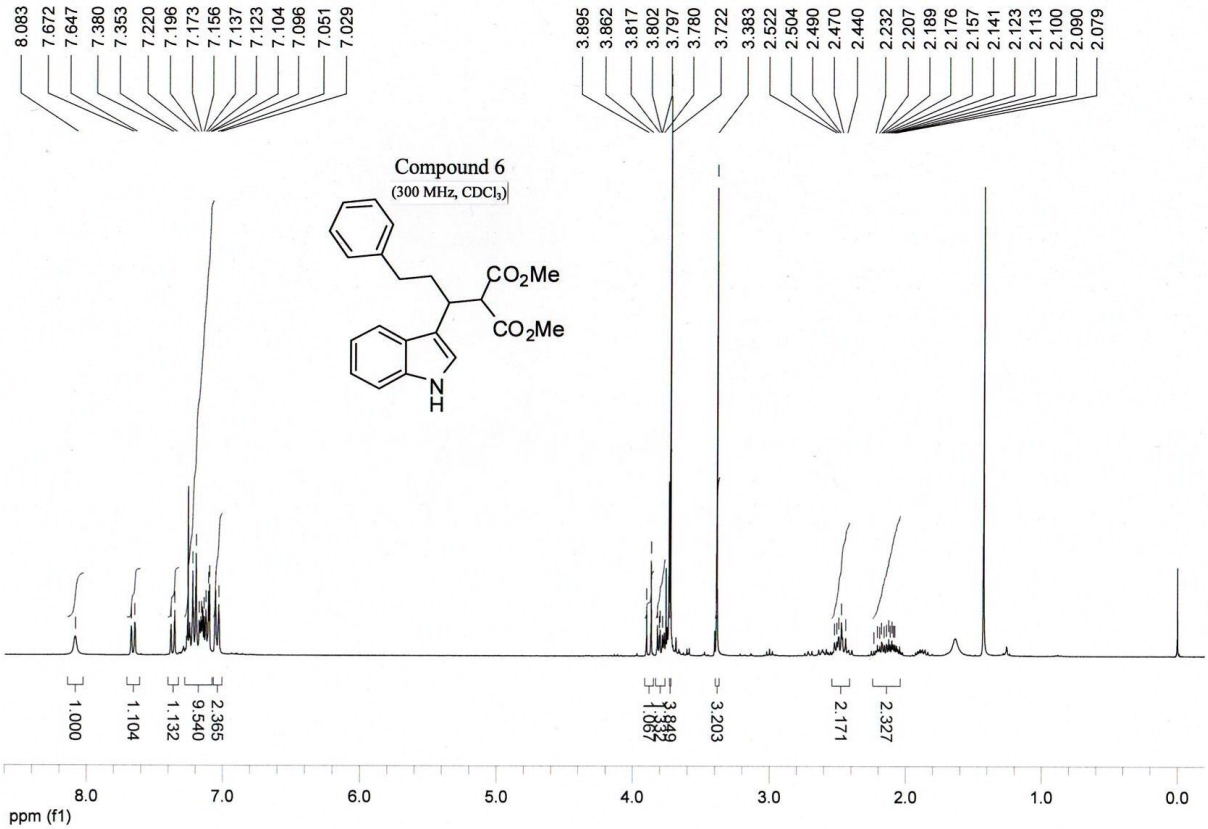
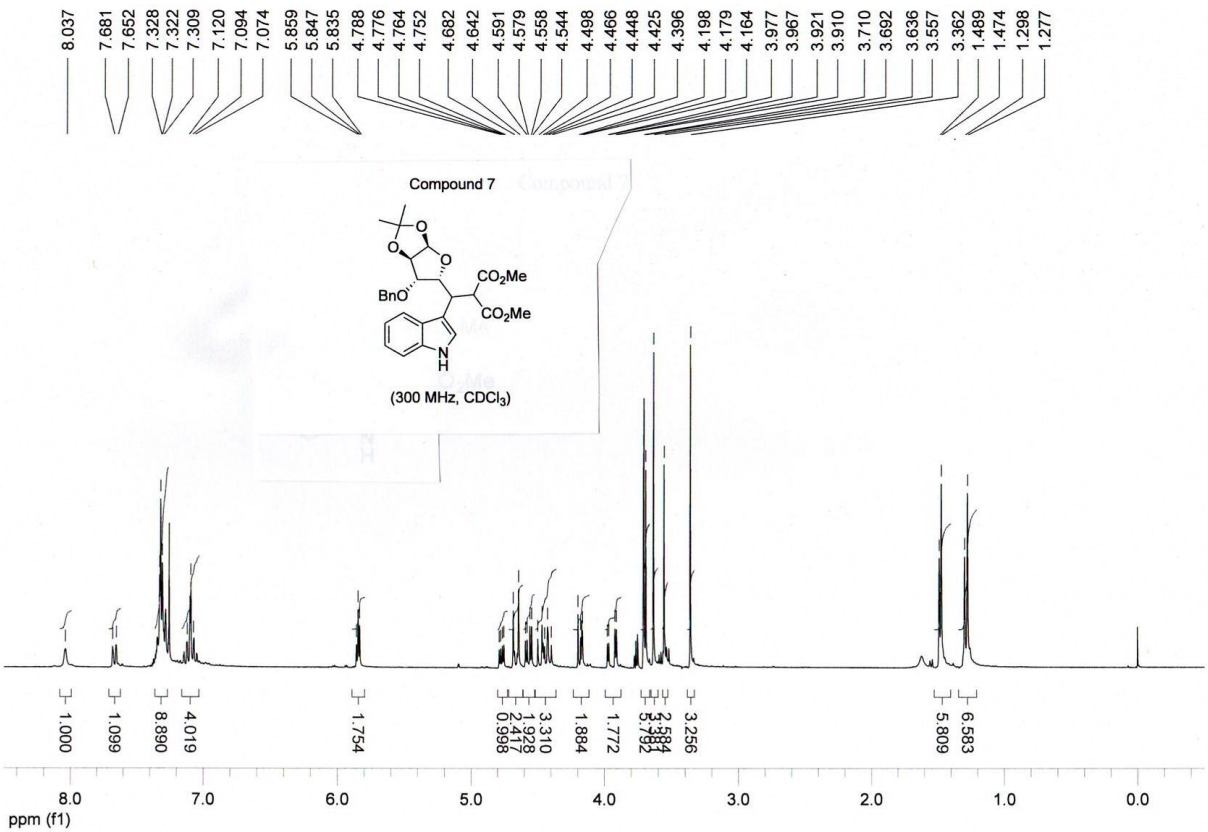
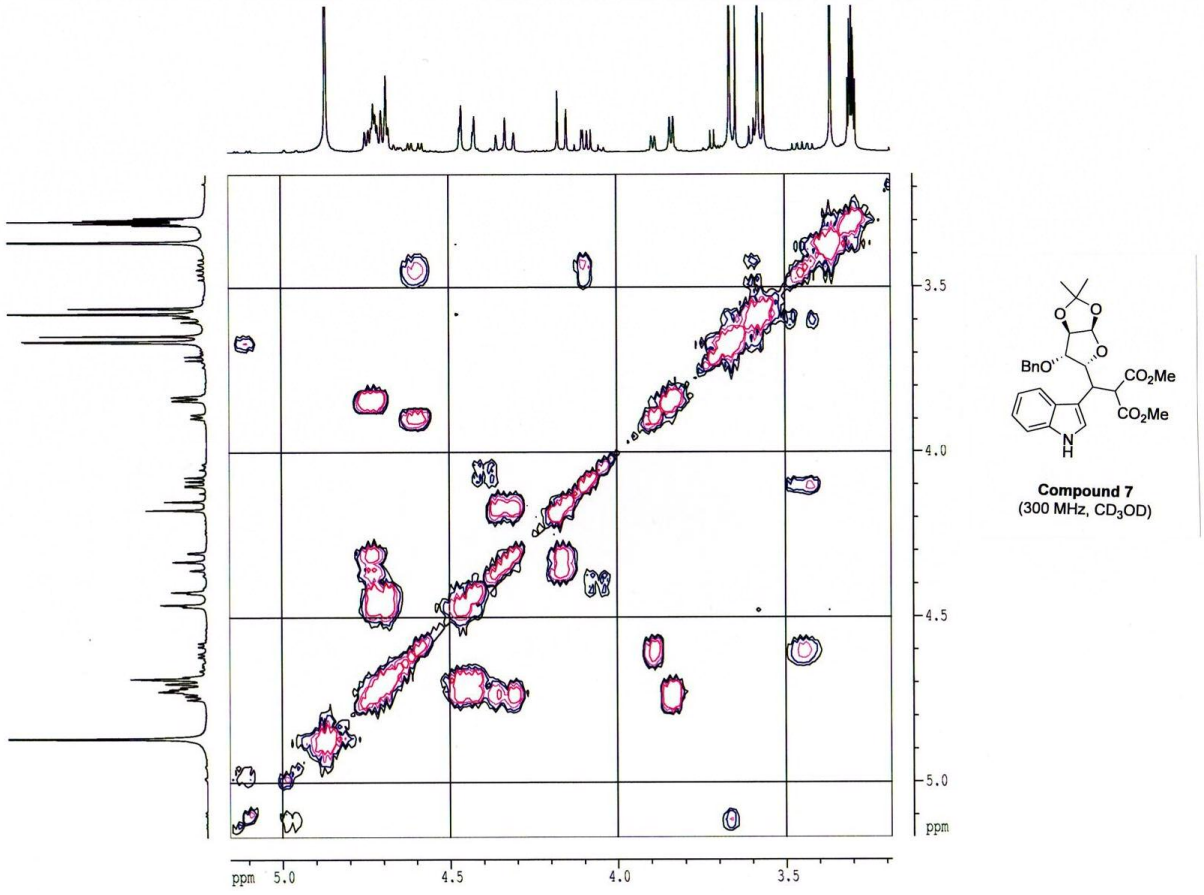
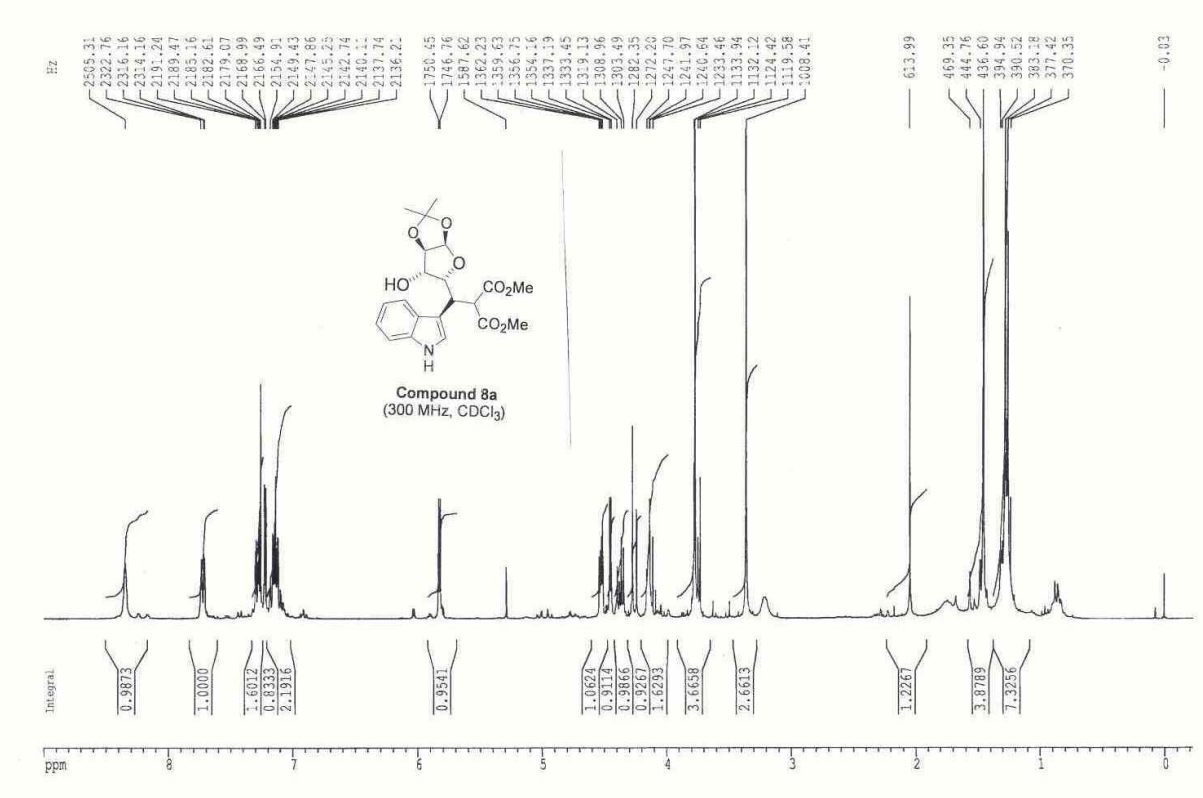
2.0
1.0
0.0
ppm (f1)

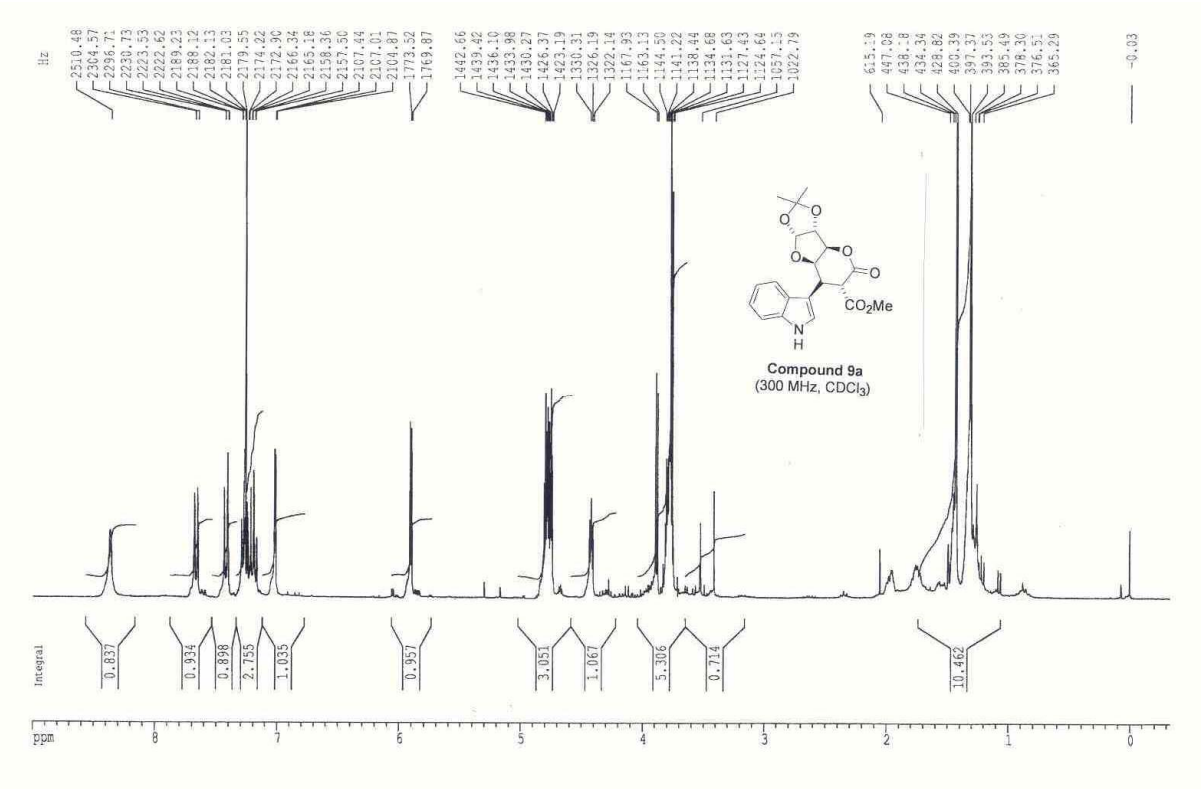

8.146
7.544
7.514
7.449
7.423
7.346
7.319
7.225
7.217
7.169
7.145
7.077
7.050
7.027
5.231
5.192
4.359
4.320
3.587
3.568
Compound 5
(300 MHz, CDCl3)
O2N
CO2Me
CO2Me
N
H
1.494
2.015
1.000
0.983
1.963
0.680
0.941
0.945
5.864
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

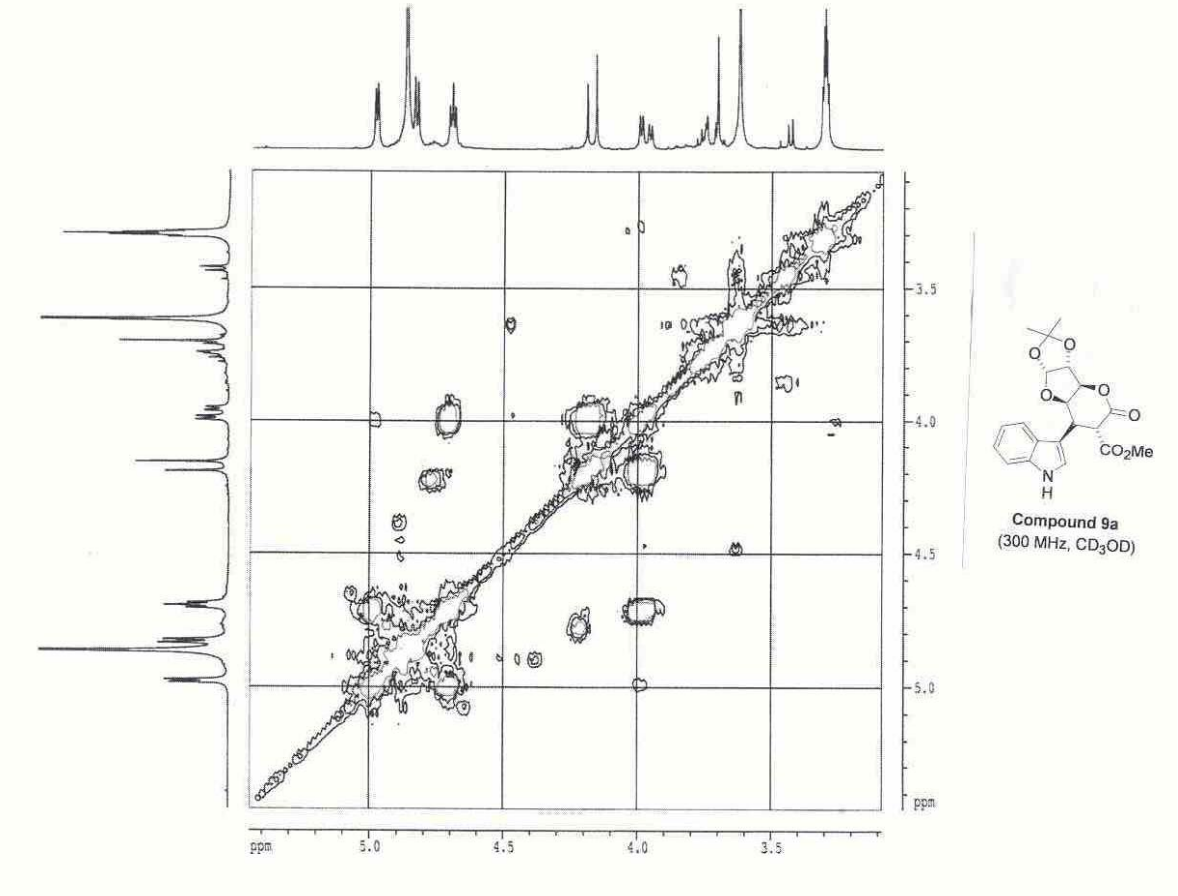

8.083
7.672
7.647
7.380
7.353
7.220
7.196
7.173
7.156
7.137
7.123
7.104
7.096
7.051
7.029
3.895
3.862
3.817
3.802
3.797
3.780
3.722
3.383
2.522
2.504
2.490
2.470
2.440
2.232
2.207
2.189
2.176
2.157
2.141
2.123
2.113
2.100
2.090
2.079
Compound 6
(300 MHz, CDCl3)
CO2Me
CO2Me
N
H
1.000
1.104
1.132
9.540
2.365
3.203
2.171
2.327
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

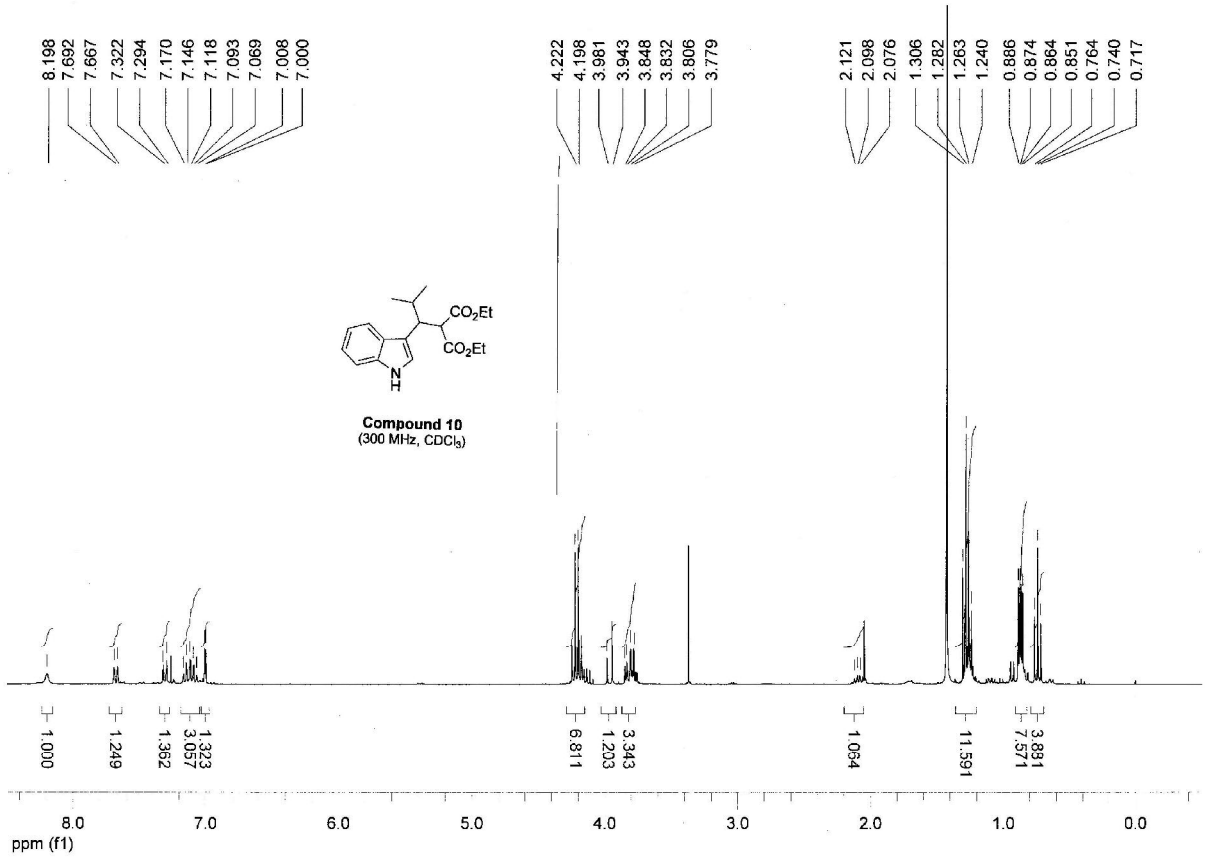

8.037
7.681
7.652
7.328
7.322
7.309
7.120
7.094
7.074
5.859
5.847
5.835
4.788
4.776
4.764
4.752
4.682
4.642
4.591
4.579
4.558
4.544
4.498
4.466
4.448
4.425
4.396
4.198
4.179
4.164
3.977
3.967
3.921
3.910
3.710
3.692
3.636
3.557
3.362
1.489
1.474
1.298
1.277
Compound 7
CO2Me
CO2Me
BnO
N
H
(300 MHz, CDCl3)
1.000
1.099
8.890
4.019
1.754
0.998
2.417
1.928
3.310
1.884
1.772
3.256
5.809
9.583
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

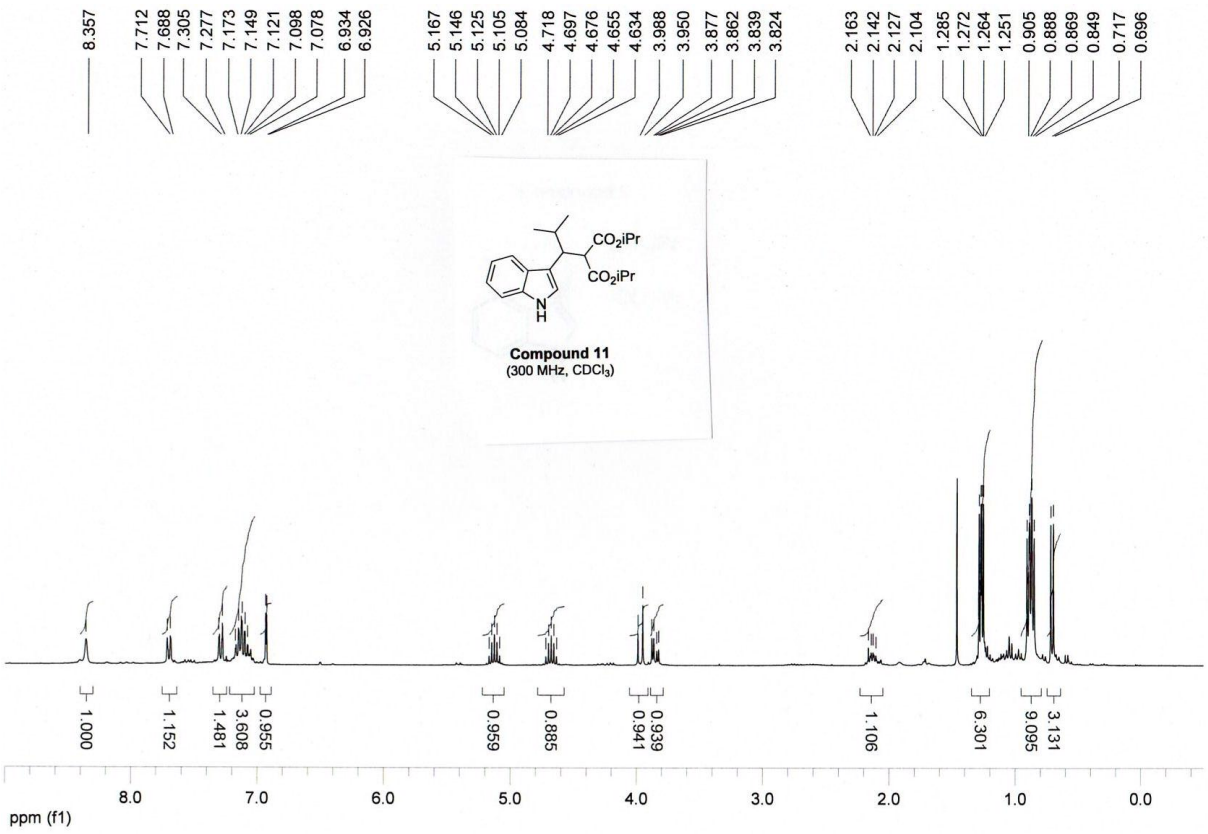

BnO
CO2Me
CO2Me
N
H
Compound 7
(300 MHz, CD3OD)
3.5
4.0
4.5
5.0
ppm
ppm 5.0
4.5
4.0
3.5

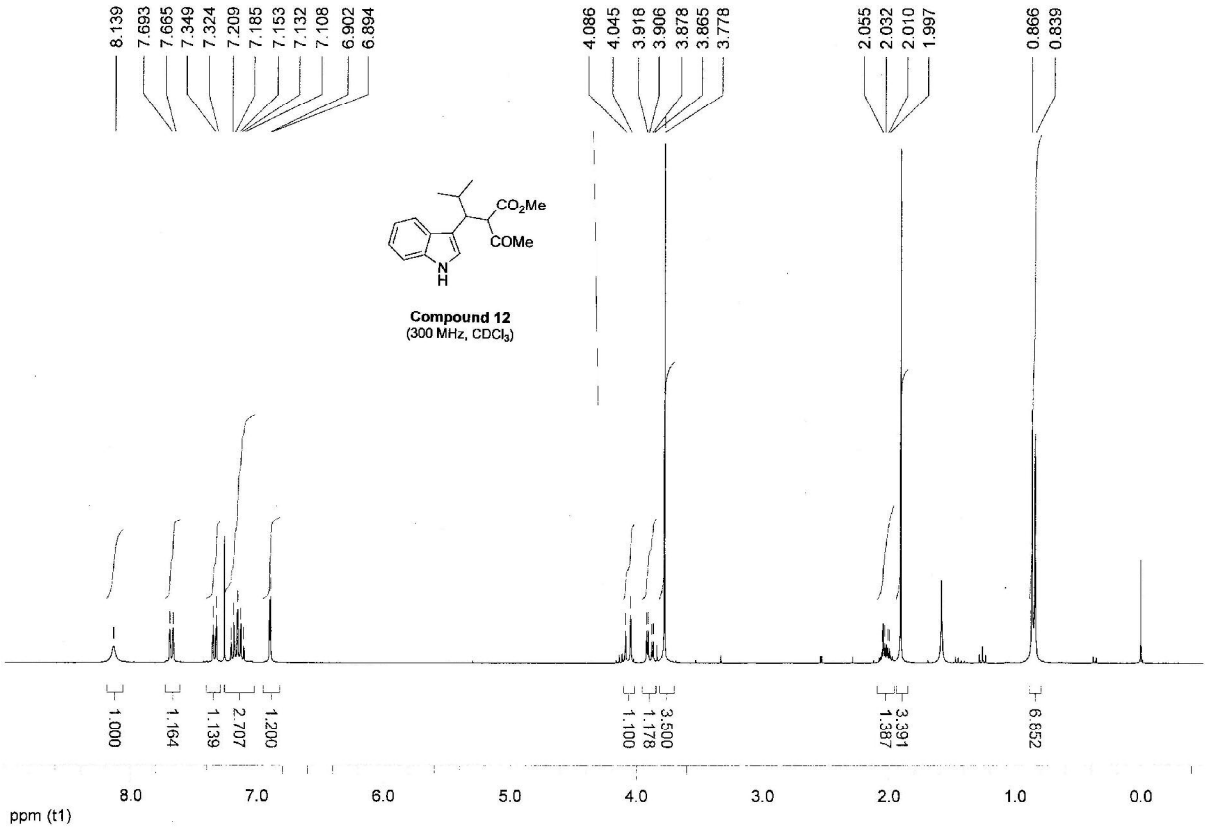

Hz
HO
CO2Me
CO2Me
N
H
Compound 8a
(300 MHz, CDCl3)
Integral
0.9873
1.0000
1.6012
0.8333
2.1916
0.9541
1.0624
0.9114
0.9866
0.9267
1.6293
3.6658
2.6613
1.2267
3.0789
7.3256
ppm

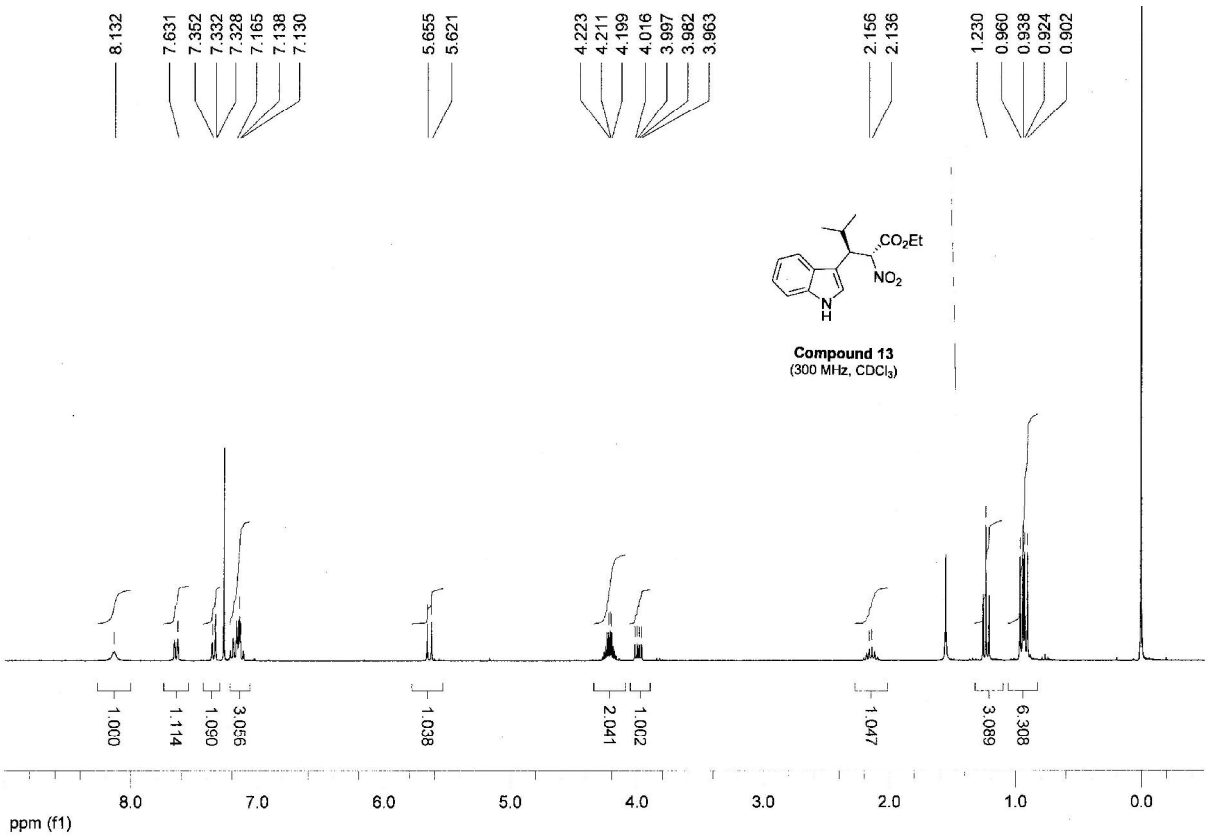

Hz
2510.48
2304.57
2296.71
2230.73
2223.53
2222.62
2199.23
2188.12
2182.13
2181.03
2179.55
2174.22
2172.90
2166.34
2165.18
2158.36
2157.50
2107.44
2107.01
2104.87
1773.52
1769.87
1442.66
1439.42
1436.10
1433.98
1430.27
1426.37
1423.19
1330.31
1326.19
1322.14
1167.93
1163.13
1144.50
1141.22
1138.44
1134.68
1131.63
1127.43
1124.64
1057.15
1022.79
615.19
447.08
438.18
434.34
428.82
400.39
397.37
393.53
385.49
378.30
376.51
365.20
-0.03
Integral
0.837
0.934
0.898
2.755
1.035
0.957
3.051
1.067
5.306
0.714
10.462
ppm
8
7
6
5
4
3
2
1
0
CO2Me
N
H
Compound 9a
(300 MHz, CDCl3)

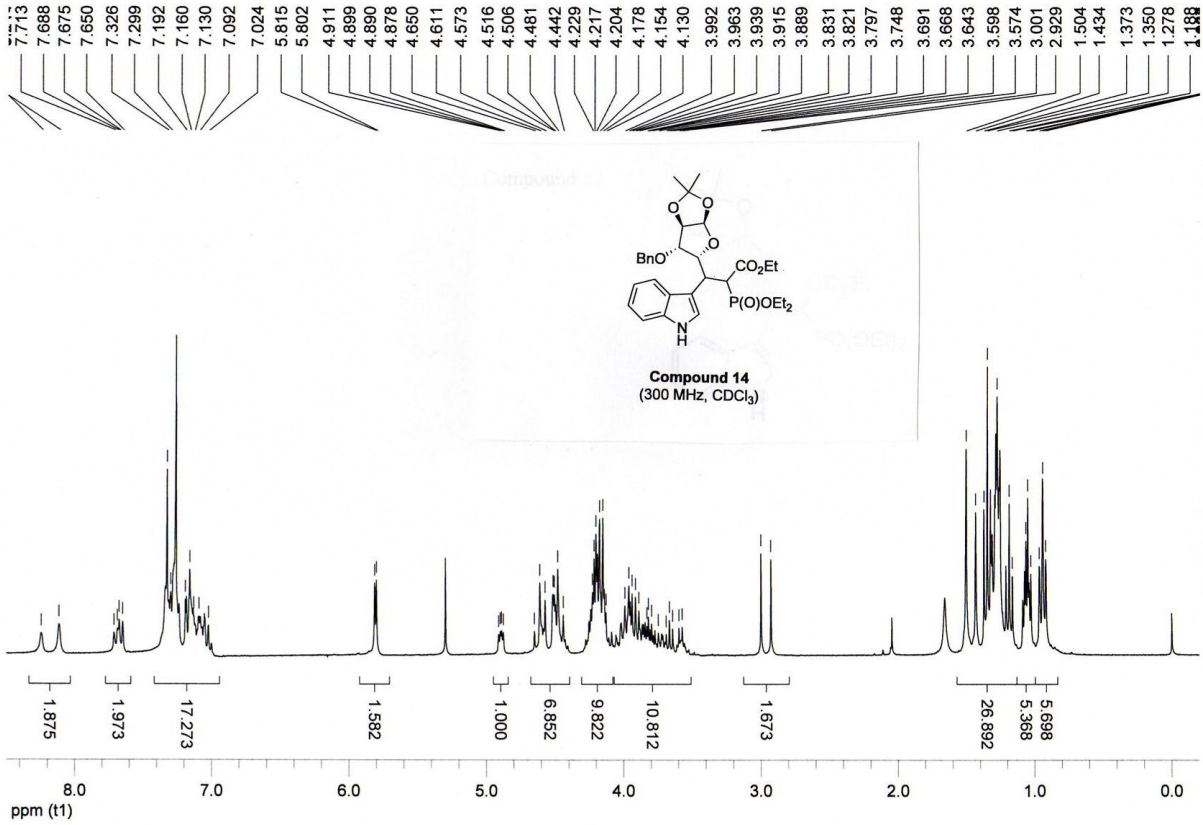

3.5
4.0
4.5
5.0
ppm
5.0
4.5
4.0
3.5
CO2Me
N
H
Compound 9a
(300 MHz, CD3OD)

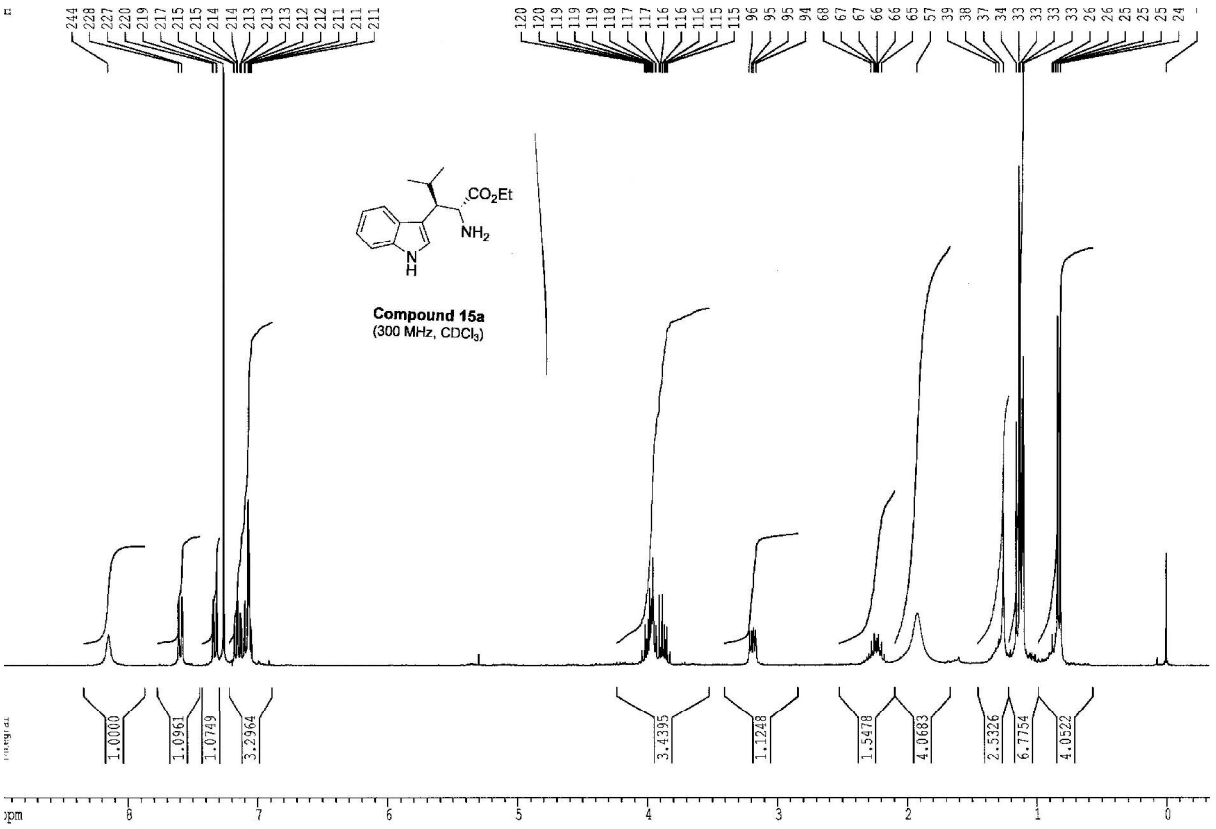

8.198
7.692
7.667
7.322
7.294
7.170
7.146
7.118
7.093
7.069
7.008
7.000
4.222
4.198
3.981
3.943
3.848
3.832
3.806
3.779
2.121
2.098
2.076
1.306
1.282
1.263
1.240
0.886
0.874
0.864
0.851
0.764
0.740
0.717
CO2Et
CO2Et
N
H
Compound 10
(300 MHz, CDCl3)
1.000
1.249
1.362
3.057
1.323
6.811
1.203
3.343
1.064
11.591
7.571
3.881
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

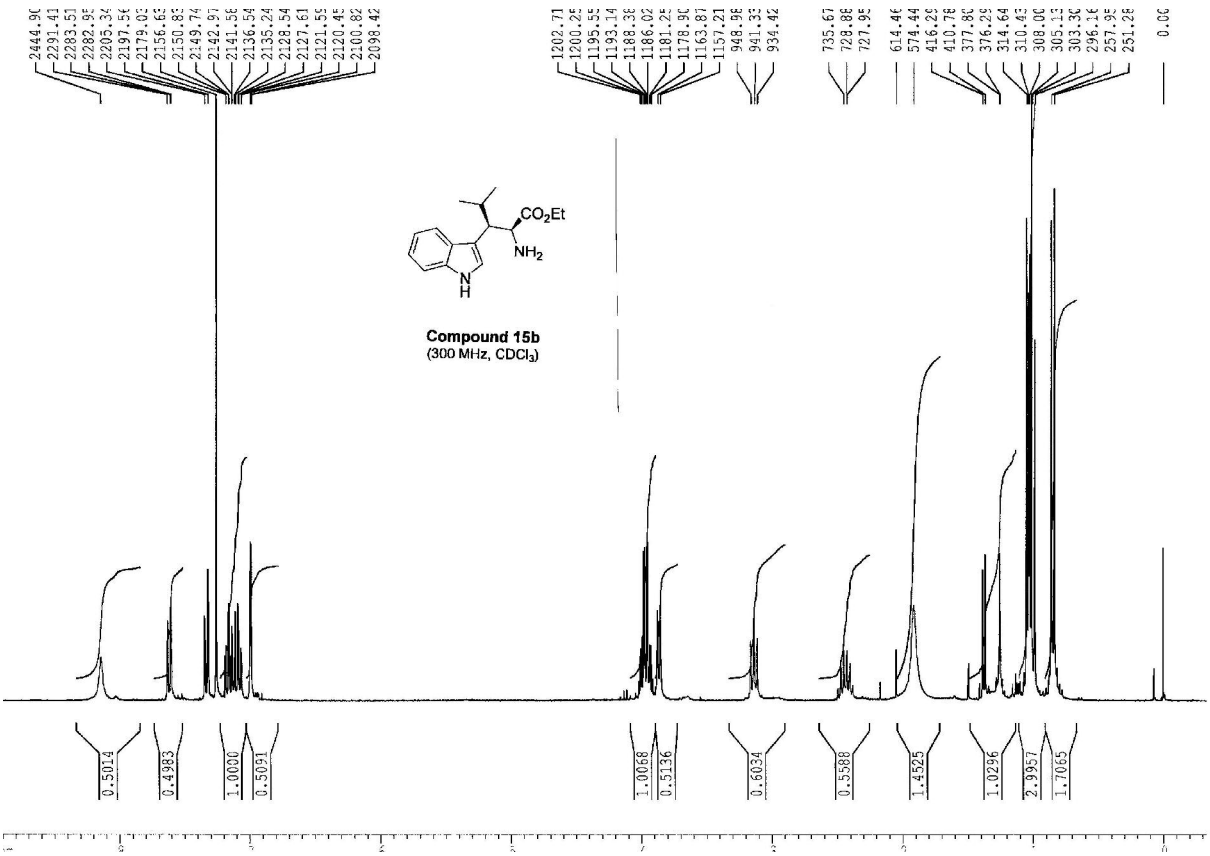

8.357
7.712
7.688
7.305
7.277
7.173
7.149
7.121
7.098
7.078
6.934
6.926
5.167
5.146
5.125
5.105
5.084
4.718
4.697
4.676
4.655
4.634
3.988
3.950
3.877
3.862
3.839
3.824
2.163
2.142
2.127
2.104
1.285
1.272
1.264
1.251
0.905
0.888
0.869
0.849
0.717
0.696
CO2iPr
CO2iPr
N
H
Compound 11
(300 MHz, CDCl3)
1.000
1.152
1.481
3.608
0.955
0.959
0.885
0.941
0.939
1.106
9.301
9.095
3.131
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

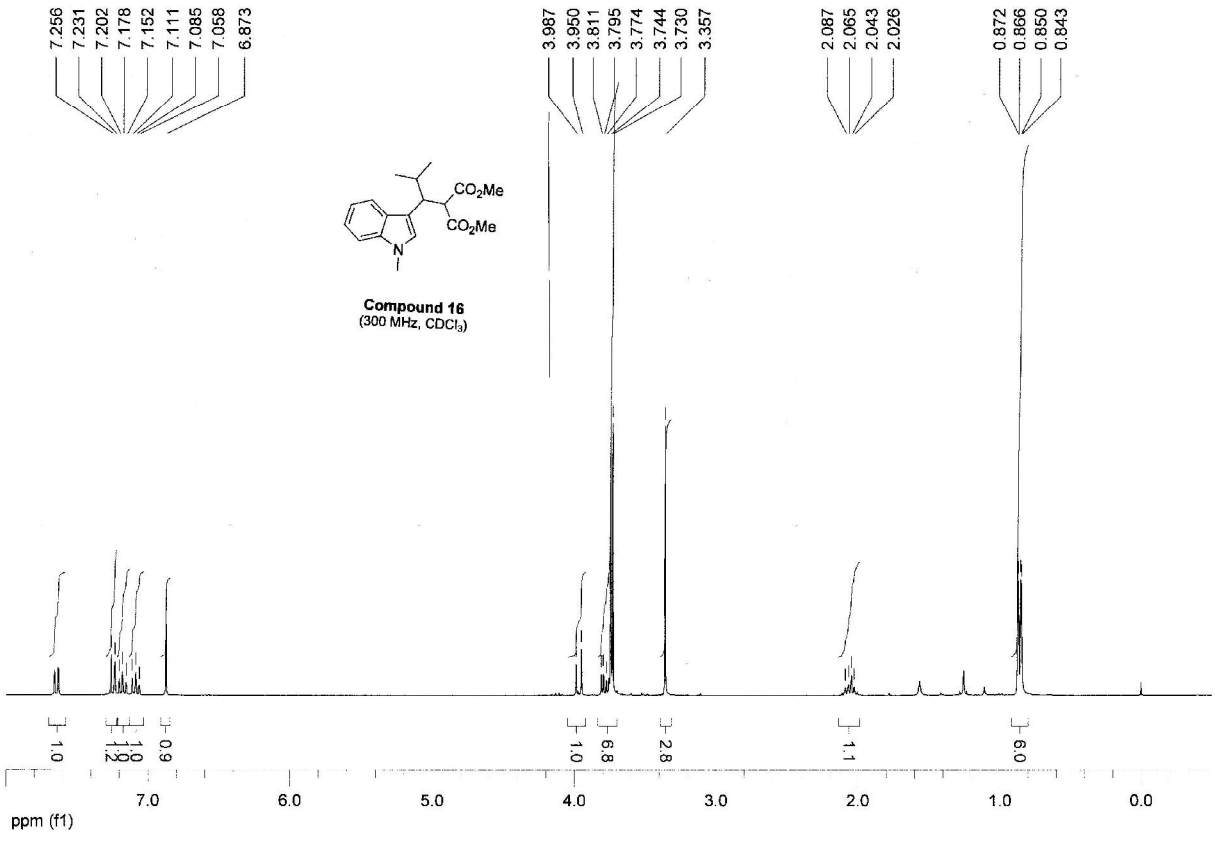

8.139
7.693
7.665
7.349
7.324
7.209
7.185
7.153
7.132
7.108
6.902
6.894
4.086
4.045
3.918
3.906
3.878
3.865
3.778
2.055
2.032
2.010
1.997
0.866
0.839
CO2Me
COMe
N
H
Compound 12
(300 MHz, CDCl3)
1.000
1.164
1.139
2.707
1.200
1.100
1.178
3.500
1.387
3.391
6.552
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

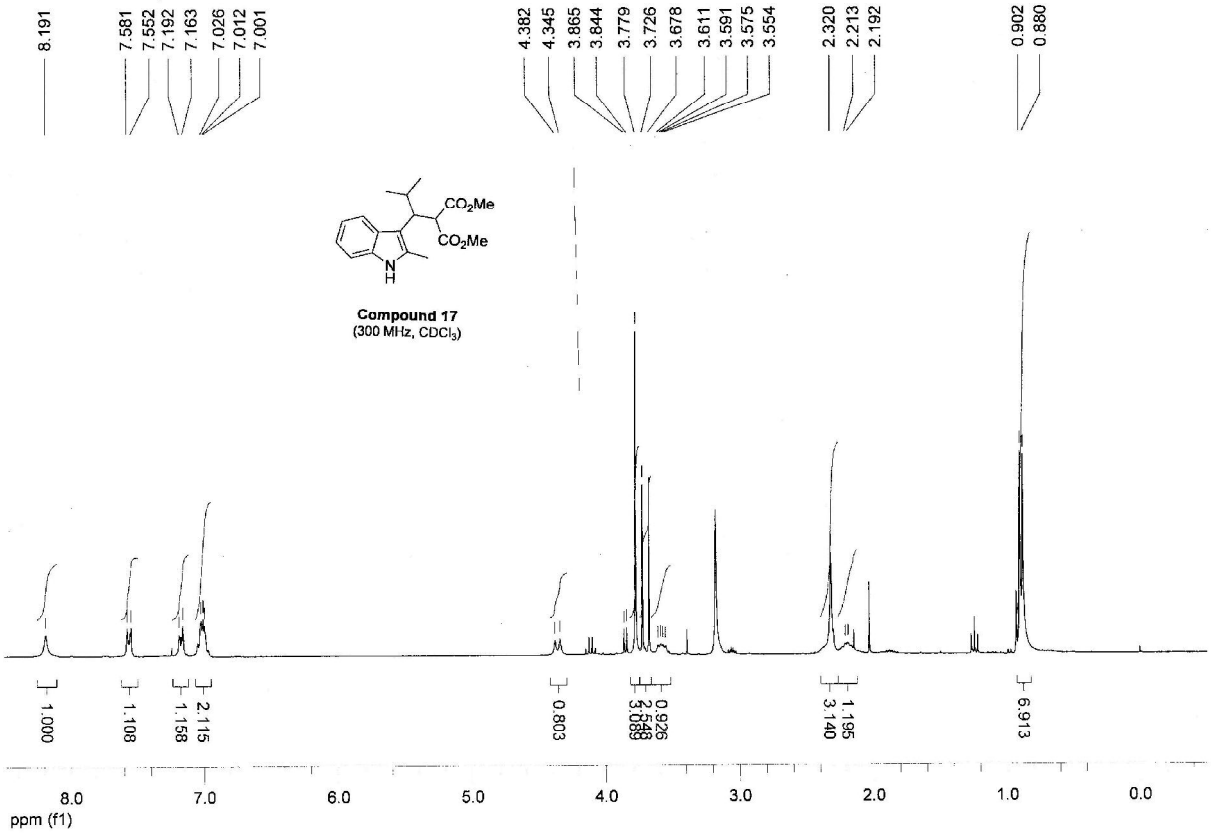

8.132
7.631
7.352
7.332
7.328
7.165
7.138
7.130
5.655
5.621
4.223
4.211
4.199
4.016
3.997
3.982
3.963
2.156
2.136
1.230
0.960
0.938
0.924
0.902
CO2Et
NO2
N
H
Compound 13
(300 MHz, CDCl3)
1.000
1.114
1.090
3.505
1.038
2.041
1.002
1.047
3.089
6.308
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

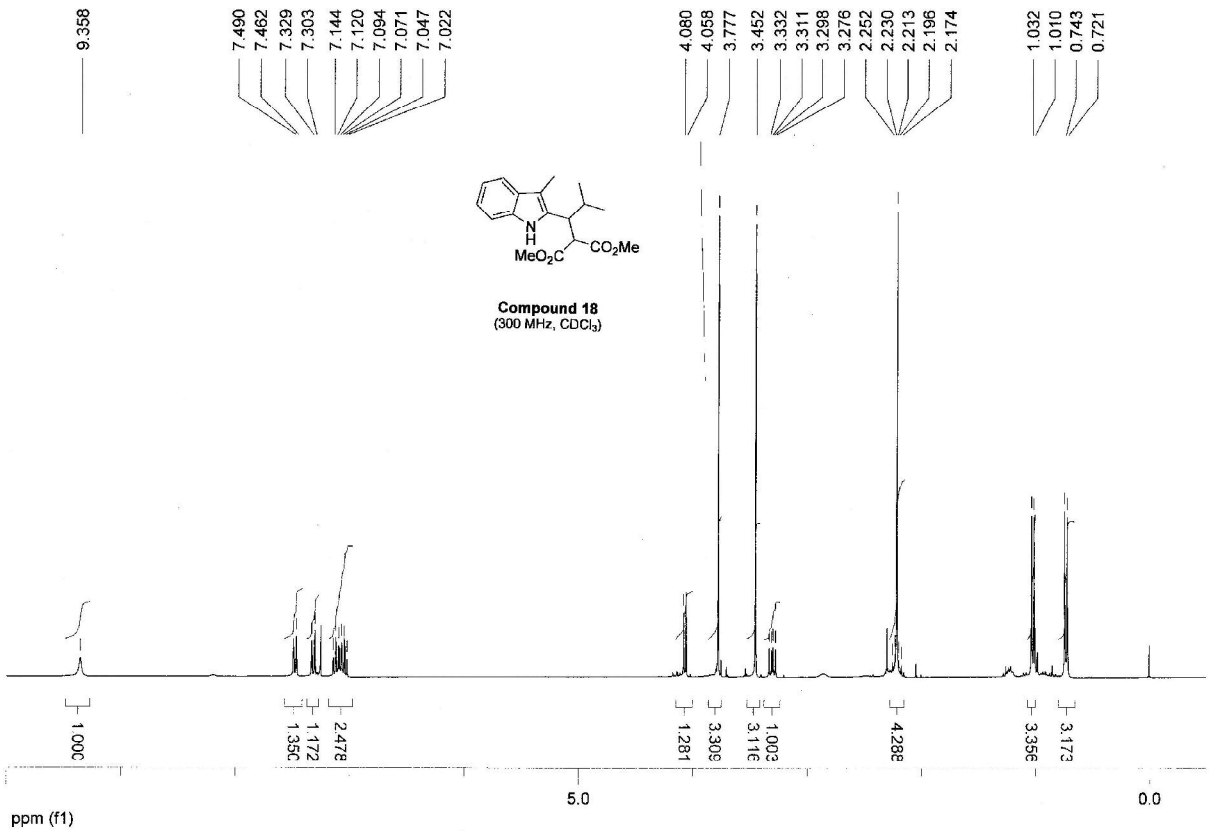

7.713
7.688
7.675
7.650
7.326
7.299
7.192
7.160
7.130
7.092
7.024
5.815
5.802
4.911
4.899
4.890
4.878
4.650
4.611
4.573
4.516
4.506
4.481
4.442
4.229
4.217
4.204
4.178
4.154
4.130
3.992
3.963
3.939
3.915
3.889
3.831
3.821
3.797
3.748
3.691
3.668
3.643
3.598
3.574
3.001
2.929
1.504
1.434
1.373
1.350
1.278
BnO
CO2Et
P(O)OEt2
N
H
Compound 14
(300 MHz, CDCl3)
1.875
1.973
17.273
1.582
1.000
6.852
9.822
10.812
1.673
26.892
5.368
5.698
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

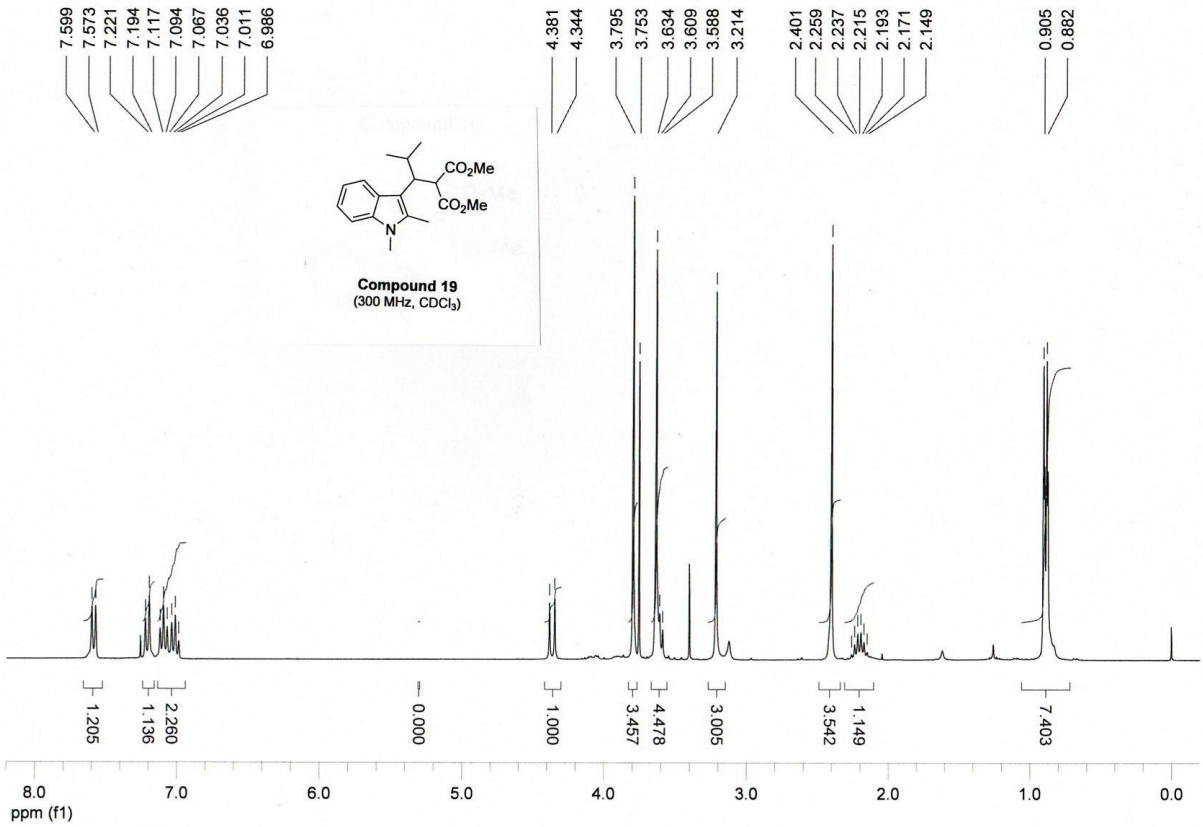

CO2Et
NH2
N
H
Compound 15a
(300 MHz, CDCl3)
1.0000
1.0961
1.0749
3.2964
3.4395
1.1248
1.5478
4.0683
2.5326
6.7754
4.0522

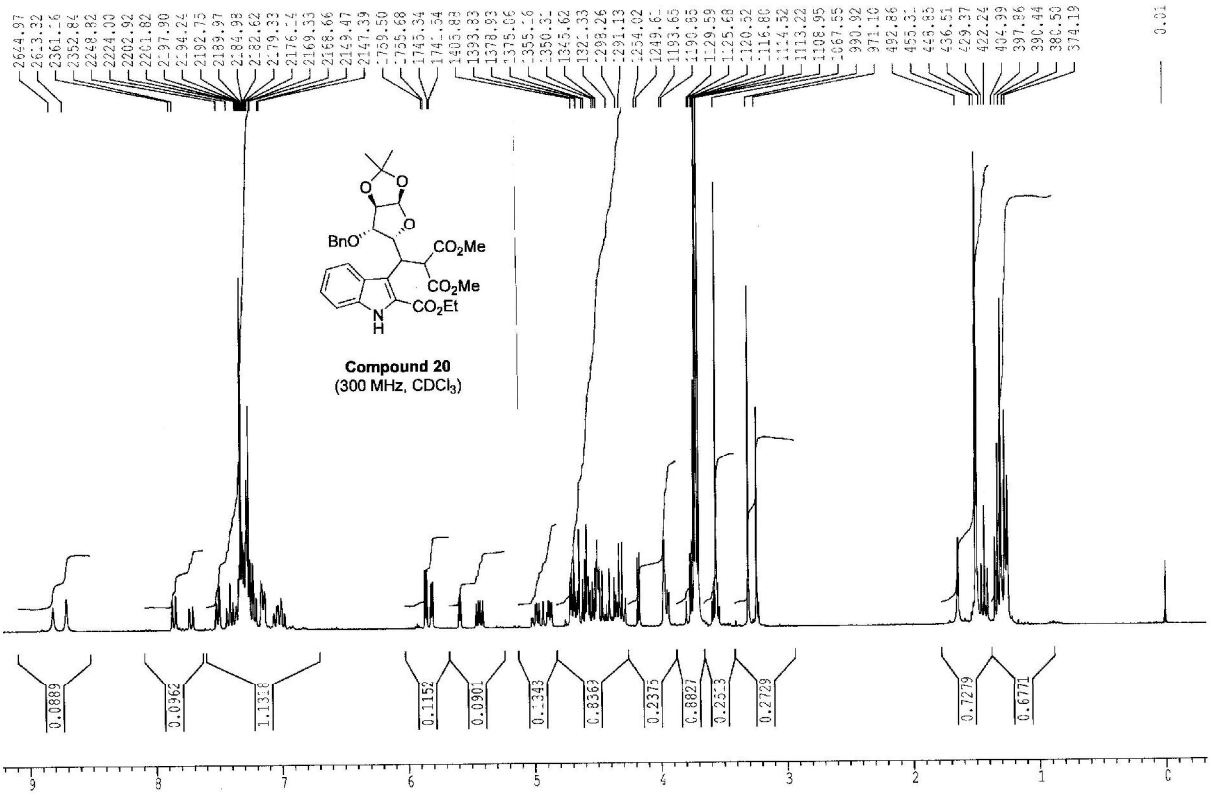

CO2Et
NH2
N
H
Compound 15b
(300 MHz, CDCl3)

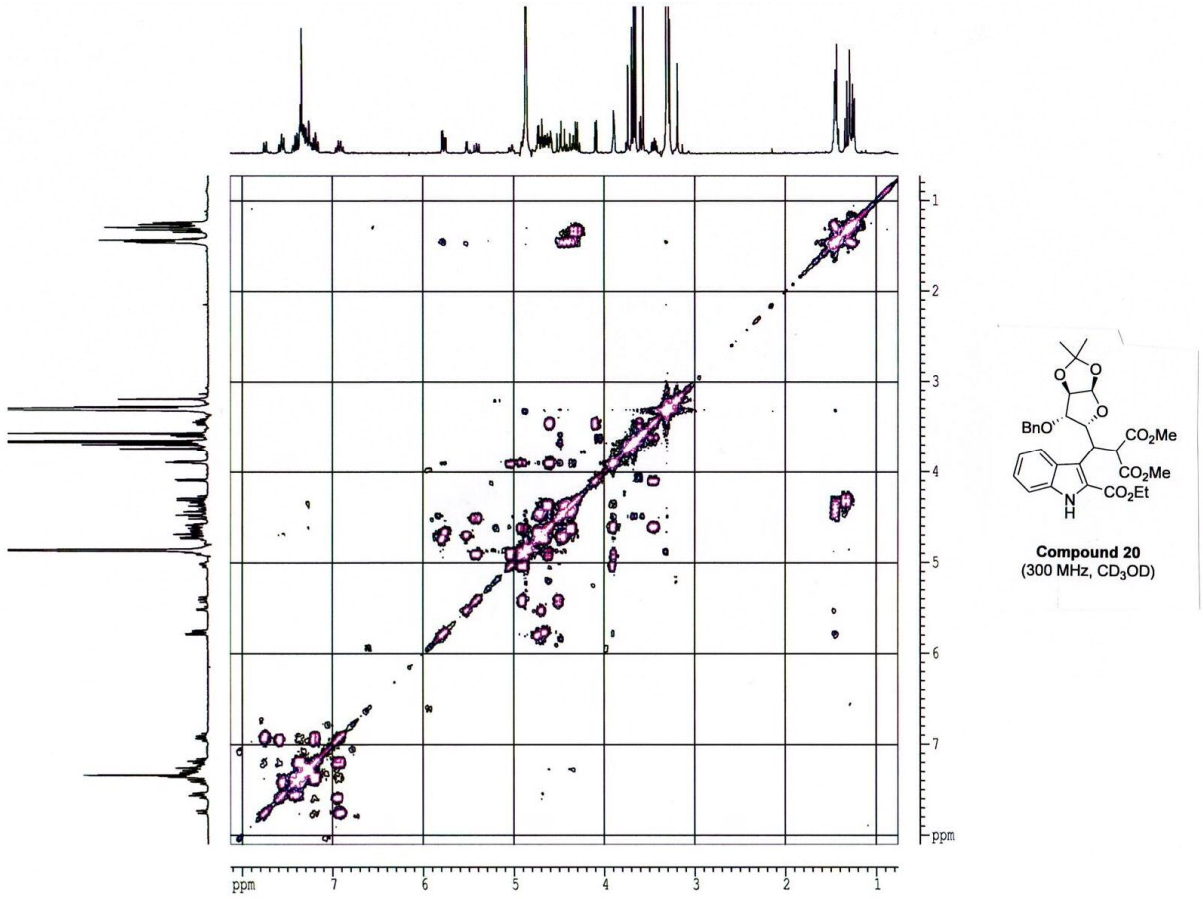

CO2Me
CO2Me
N
Compound 16
(300 MHz, CDCl3)
ppm (f1)

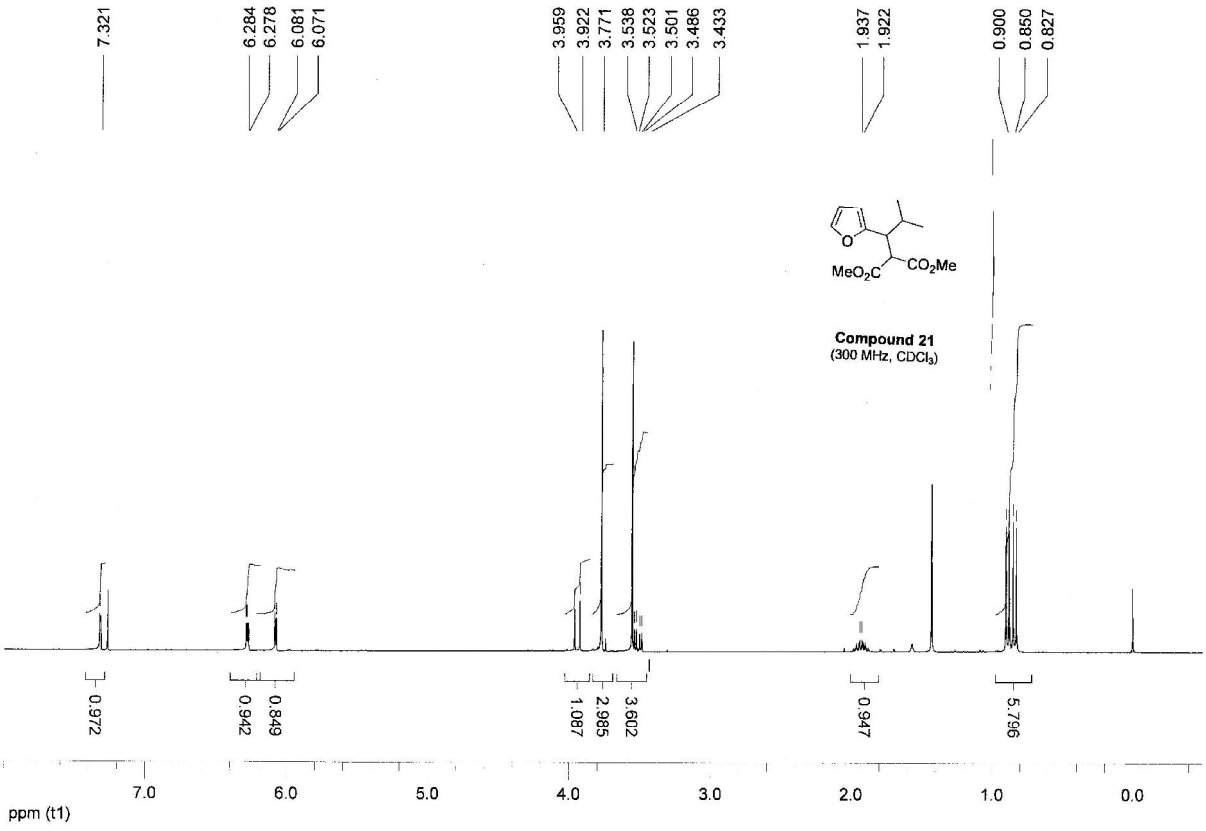

8.191
7.581
7.552
7.192
7.163
7.026
7.012
7.001
4.382
4.345
3.865
3.844
3.779
3.726
3.678
3.611
3.591
3.575
3.554
2.320
2.213
2.192
0.902
0.880
CO2Me
CO2Me
N
H
Compound 17
(300 MHz, CDCl3)
1.000
1.108
1.158
2.115
0.803
0.926
1.195
6.913
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

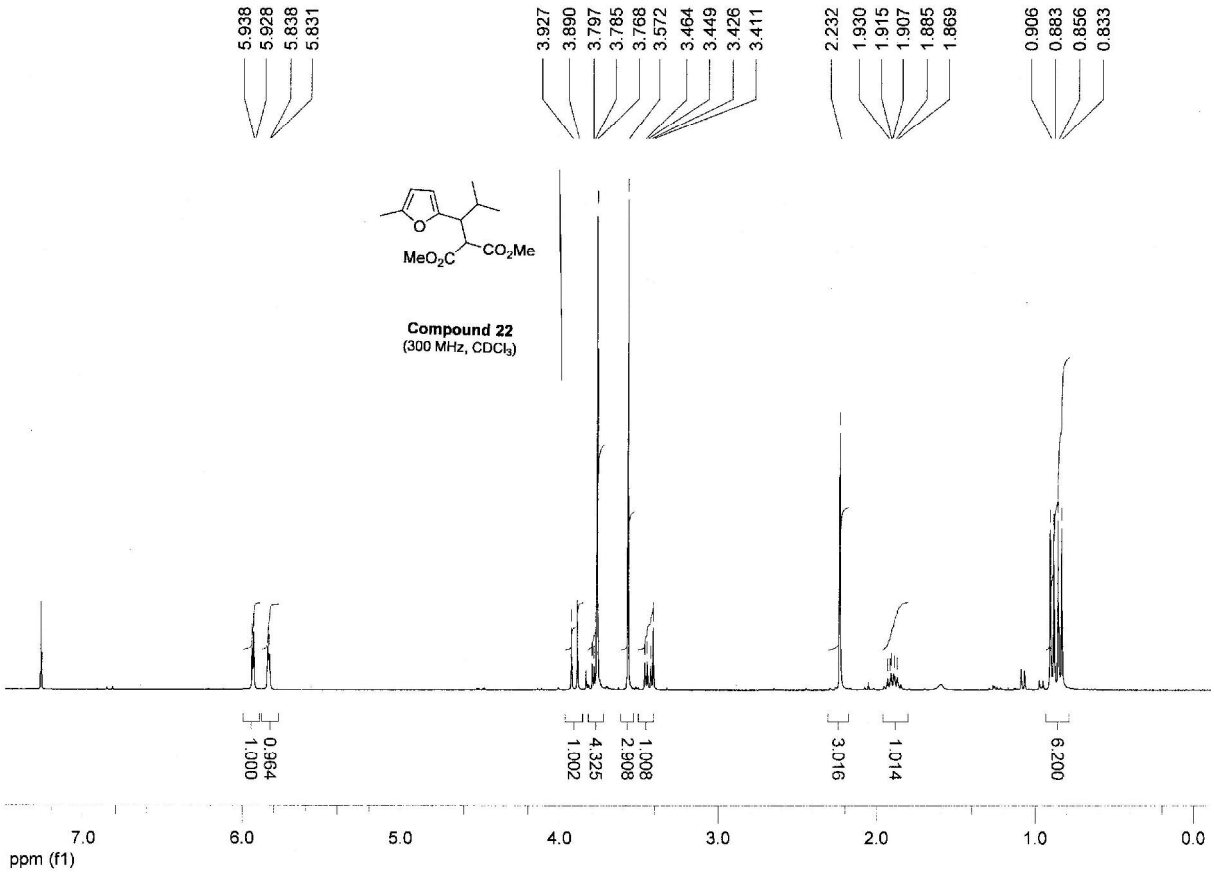

9.358
7.490
7.462
7.329
7.303
7.144
7.120
7.094
7.071
7.047
7.022
4.080
4.058
3.777
3.452
3.332
3.311
3.298
3.276
2.252
2.230
2.213
2.196
2.174
1.032
1.010
0.743
0.721
N
H
MeO2C
CO2Me
Compound 18
(300 MHz, CDCl3)
1.000
1.350
1.172
2.478
1.281
3.309
3.316
1.003
4.288
3.356
3.173
5.0
0.0
ppm (f1)


7.599
7.573
7.221
7.194
7.117
7.094
7.067
7.036
7.011
6.986
4.381
4.344
3.795
3.753
3.634
3.609
3.588
3.214
2.401
2.259
2.237
2.215
2.193
2.171
2.149
0.905
0.882
CO2Me
CO2Me
N
Compound 19
(300 MHz, CDCl3)
1.205
1.136
2.260
0.000
1.000
3.457
4.478
3.005
3.542
1.149
7.403
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


BnO
CO2Me
CO2Me
CO2Et
N
H
Compound 20
(300 MHz, CDCl3)


BnO
CO2Me
CO2Me
CO2Et
N
H
Compound 20
(300 MHz, CD3OD)
ppm
ppm


7.321
6.284
6.278
6.081
6.071
3.959
3.922
3.771
3.538
3.523
3.501
3.486
3.433
1.937
1.922
0.900
0.850
0.827
MeO2C
CO2Me
Compound 21
(300 MHz, CDCl3)
0.672
0.942
0.849
1.087
2.985
3.602
0.947
5.796
ppm (t1)


5.938
5.928
5.838
5.831
3.927
3.890
3.797
3.785
3.768
3.572
3.464
3.449
3.426
3.411
2.232
1.930
1.915
1.907
1.885
1.869
0.906
0.883
0.856
0.833
MeO2C
CO2Me
Compound 22
(300 MHz, CDCl3)
1.000
0.964
1.002
4.325
2.908
1.008
3.016
1.014
6.200
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)