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Yonemitsu-type condensations catalysed by proline and $Eu(OTf)_3$

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Supplementary Information

Contents

General information

Lanthanum *tris*-dodecylsulfate was prepared according to literature procedure.[1] All reagents were obtained from Aldrich, Acros, and Alfa Aesar, and used without further purification. Solvents were dried and purified by standard literature methods prior to use. Reactions under ultrasounds were performed in a sonicating bath (Cole Parmer, 100W, 42 kHz ± 6%). All reactions were monitored by thin layer chromatography (TLC) using precoated plates (Merck silica gel 60 F-254, 0.25 mm). TLCs were visualised using UV light (254 nm) first, then a solution of ammonium cerium sulfate in sulfuric acid and nitric acid under heating. Column chromatography was performed on Merck silica gel 60 (particle size 0.040-0.063 mm, 70-230 mesh). Chiral HPLC was done on a Chiralcel OD-H column following the procedure reported in the literature.[2]

Melting points were determined on a hot-stage Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer (300 or 400 MHz and 75 or 100 MHz, respectively) at room temperature. NMR chemical shifts (δ) were reported in parts per million (ppm) and referenced to TMS as an internal standard or the solvent residual signals. IR spectra were measured on KBr pastille with a Bomem FTIR instrument and reported in wave numbers (cm^{-1}). Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained on a VG Autospec mass spectrometer with electron-spray ionization (ESI) or electronic impact (EI) at −70 eV. Elemental analyses were performed on a FISONS Instrument EA 108 or a Perkin Elmer 240C elemental analyser.

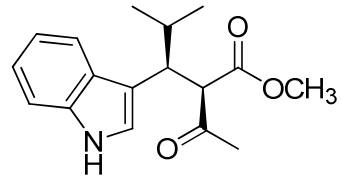
General procedure for the trimolecular condensation

L-proline (0.1 eq) was dissolved in alcohol (20 mL) under stirring at room temperature in the presence of molecular sieves 4Å (3.00 g). Active methylene compound (1.0 equiv.) and isobutyraldehyde (1.0 equiv.) were added to the solution. After 24 h of stirring at room temperature, indole (1.0 equiv.) and Lewis acid (0.1 equiv.) were added. After an additional 120 h of stirring, the mixture was filtered over celite to remove molecular sieves. The filtrate was concentrated at reduced pressure. Purification of the crude mixture by flash chromatography or recrystallisation afforded the condensation product.

[1] K. Deleersnyder, D. Shi, K. Binnemans and T. N. Parac-Vogt, *J. Alloys Comp.* 2008, **451**, 418-421.
[2] J. Zhou and T. Yong, *J. Am. Chem. Soc.* 2002, **124**, 9030-9031.

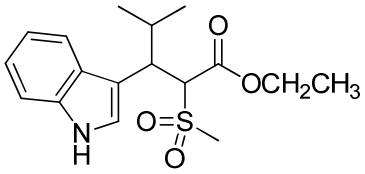
Preparation of 1–9b and 14

***(2R*,3S*)*-Methyl 2-acetyl-3-(1*H*-indol-3-yl)-4-methylpentanoate (1)**



Prepared according to the general procedure using methanol, *L*-proline (101 mg, 0.87 mmol), methyl acetoacetate (946 μL, 8.76 mmol), isobutyraldehyde (800 μL, 8.76 mmol), indole (1.025 g, 8.76 mmol), and $Eu(OTf)_3$ (521 mg, 0.87 mmol). Purification of the crude mixture by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1→8/2) followed by recrystallisation from a mixture of hexane/ethyl acetate [1/4 (v/v)] afforded **1** as a white solid (1.963 g, 78% yield). Spectroscopic data of **1** are consistent with those reported in the literature.[3] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (d, 6H, J = 5.6 Hz), 1.91 (s, 3H), 2.01 (m, 1H), 3.78 (s, 3H), 3.89 (dd, 1H, J = 12.0 Hz, J = 3.9 Hz), 4.07 (d, 1H, J = 12.0 Hz), 6.89 (d, 1H, J = 2.4 Hz), 7.11–7.20 (m, 3H), 7.34 (d, 1H, J = 7.6 Hz), 7.68 (d, 1H, J = 7.6 Hz), 8.17 (br, 1H). ESI-HRMS calcd. for $C_{17}H_{21}NNaO_3$ $[M + Na]^+$: 310.1418; found: 310.1414.

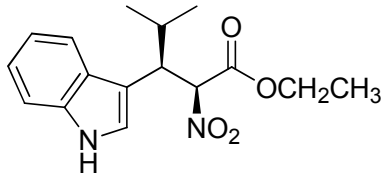
Ethyl 3-(1*H*-indol-3-yl)-4-methyl-2-(methylesulfonyl)pentanoate (2)



Prepared according to general procedure using ethanol, *L*-proline (101 mg, 0.87 mmol), ethyl methylsulfonyl acetate (1.16 mL, 8.76 mmol), isobutyraldehyde (800 μL, 8.76 mmol), indole (1.025 g, 8.76 mmol), and $Bi(OTf)_3$ (574 mg, 0.87 mmol). Purification of the crude mixture by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1→8/2) afforded **2** as a brown liquid (1.182 g, 40% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.01 (d, 3H, J = 6.6 Hz), 1.12 (d, 3H, J = 6.6 Hz), 2.65 (m, 1H), 3.16 (dd, 1H, J = 8.4 Hz, J = 3.8 Hz), 3.17 (s, 1H), 4.26 (d, 1H, J = 8.4 Hz), 4.36 (q, 2H, J = 7.1 Hz), 7.00–7.16 (m, 4H), 7.64 (d, 1H, J = 7.9 Hz), 7.93 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 21.4, 21.6, 29.2, 32.7, 43.0, 62.1, 81.8, 110.8, 118.6, 119.3, 119.4, 121.2, 121.5, 127.5, 136.0, 160.6. IR (KBr): ν (cm^{-1}) = 3413, 2962, 1714, 1455, 1310, 1214, 1133, 740. MS (EI): *m/z* (%) 360 (20), 291 (40), 288 (40), 252 (30), 245 (20), 174 (100), 167 (20), 123 (20). EI-HRMS calcd for $C_{17}H_{23}NO_4S$ $[M]^{+\bullet}$: 337.1348; found 337.1328.

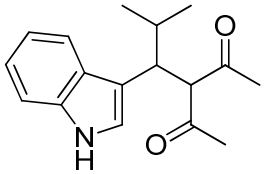
[3] A. Renzetti, E. Dardennes, A. Fontana, P. De Maria, J. Sapi and S. Gérard, *J. Org. Chem.* 2008, **73**, 6824-6827.

***(2R*,3R*)*-Ethyl 3-(1*H*-indol-3-yl)-4-methyl-2-nitropentanoate (3)**



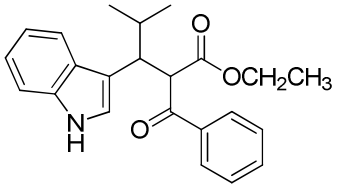
A 10-mL microwave vial was charged with *L*-proline (101 mg, 0.87 mmol), ethyl nitroacetate (972 μL, 8.76 mmol), isobutyraldehyde (800 μL, 8.76 mmol), and indole (1.025 g, 8.76 mmol). The vial was sealed and dimmed in an ultrasonic bath at room temperature during 12 h. Purification of the crude mixture by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1→7/3) followed by recrystallisation from a mixture of diethyl ether/petroleum ether [1/5 (v/v)] afforded **3** as a pale yellow solid (826 mg, 38% yield). Spectroscopic data of **1** are consistent with those reported in the literature.[3] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 6.7 Hz), 1.23 (t, 3H, J = 6.8 Hz), 2.14 (m, 1H), 3.99 (dd, 1H, J = 10.1 Hz, J = 5.6 Hz), 4.22 (m, 2H), 5.64 (d, 1H, J = 10.1 Hz), 7.12–7.18 (m, 3H), 7.33 (d, 1H, 8.0 Hz), 7.64 (d, 1H, J = 7.6 Hz), 8.14 (br, 1H). ESI-HRMS calcd. for $C_{16}H_{20}KN_2O_4$ $[M + K]^+$: 343.1060; found: 343.1055.

3-(1-(1*H*-Indol-3-yl)-2-methylpropyl)pentane-2,4-dione (4)



Prepared according to general procedure using methanol, *L*-proline (101 mg, 0.87 mmol), pentane-2,4-dione (900 μL, 8.76 mmol), isobutyraldehyde (800 μL, 8.76 mmol), indole (1.025 g, 8.76 mmol), and $Bi(OTf)_3$ (574 mg, 0.87 mmol). Purification of the crude mixture by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1→8/2) afforded **3** as a red-brown liquid (357 mg, 15% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81 (d, 6H, J = 6.8 Hz), 1.78 (s, 3H), 1.89 (m, 1H), 2.34 (s, 3H), 3.99 (dd, 1H, J = 12.2 Hz, J = 3.6 Hz), 4.41 (d, 1H, J = 12.2 Hz), 6.84–7.69 (m, 5H), 8.39 (br, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.2, 22.2, 27.4, 30.5, 30.8, 41.7, 74.0, 111.1, 112.2, 119.3, 119.6, 122.0, 123.2, 128.3, 135.6, 204.1, 204.2. IR (KBr) : ν (cm^{-1}) 3405, 2959, 1692, 1457, 1355, 1190, 743. MS (EI): *m/z* (%) 271 ($M^{+\bullet}$, 10), 226 (10), 186 (100), 172 (40), 170 (15), 130 (10). EI-HRMS calcd for $C_{17}H_{21}NO_2$ $[M]^{+\bullet}$: 271.1572; found: 271.1587.

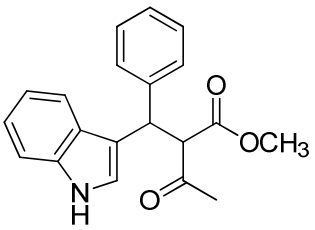
Ethyl 2-benzoyl-3-(1*H*-indol-3-yl)-4-methylpentanoate (5)



Prepared according to general procedure using ethanol, *L*-proline (101 mg, 0.87 mmol), ethyl benzoylacetate (1673 μL, 8.76 mmol), isobutyraldehyde (800 μL, 8.76 mmol), 1.0, 25 g (8.76 mmol) of

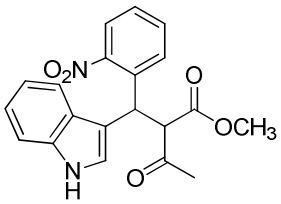
indole, and 521 mg (0.87 mmol) of $Eu(OTf)_3$. Purification of the crude mixture by flash chromatography on silica gel (petroleum ether/ethyl acetate = 9/1→8/2) afforded **5** as a white solid (636 mg, 20% yield). mp 174–176°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.57 (t, 3H, J = 7.2 Hz), 0.80 (d, 3H, J = 6.8 Hz), 0.83 (d, 3H, J = 6.8 Hz), 2.03 (m, 1H), 3.64 (dq, 2H, J = 7.2 Hz, J = 3.6 Hz), 4.19 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 5.04 (d, 1H, J = 11.6 Hz), 7.09–7.18 (m, 3H), 7.33 (d, 1H, J = 8.0 Hz), 7.49–7.53 (m, 2H), 7.61 (m, 1H), 7.74 (d, 1H, J = 8.0 Hz), 8.08 (br, 1H), 8.16 (d, 2H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.2, 18.2, 22.2, 30.6, 41.9, 58.9, 61.1, 110.7, 113.5, 119.3, 120.0, 121.7, 122.9, 128.7, 128.8, 133.6, 135.6, 136.9, 168.3, 194.1. IR (KBr) : ν (cm^{-1}) 3237, 3014, 2999, 1724, 1684, 1223, 1158. MS (EI): m/z (%) 363 $[M]^{+\bullet}$, 320, 274, 171, 130, 105, 77. EI-HRMS calcd for $C_{23}H_{25}NO_3$ $[M]^{+\bullet}$: 363.1834; found: 363.1826.

Methyl 2-((1*H*-indol-3-yl)(phenyl)methyl)-3-oxobutanoate (6a, 6b)



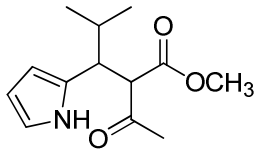
Prepared according to general procedure using methanol, *L*-proline (50.5 mg, 0.44 mmol), methyl acetoacetate (473 μL, 4.38 mmol), benzaldehyde (447 μL, 4.38 mmol), indole (513 mg, 4.38 mmol), and $Eu(OTf)_3$ (260 mg, 0.44 mmol). Purification of the crude mixture by flash chromatography on silica gel (hexane→hexane/ethyl acetate = 8/2) afforded **6a** as a pale yellow solid and **6b** as a yellow solid (182 and 183 mg, respectively; 26% overall yield). **6a**: mp 128–130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H), 3.52 (s, 3H), 4.42 (d, 1H, J = 12.0 Hz), 5.08 (d, 1H, J = 12.0 Hz), 7.05–7.36 (m, 9H), 7.54 (d, 1H, J = 11.6 Hz), 8.13 (br, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.4, 43.0, 52.5, 66.5, 111.4, 116.0, 119.1, 119.8, 121.7, 122.5, 126.5, 127.0, 128.0, 128.6, 136.4, 141.5, 168.8, 203.4. IR (KBr) : ν (cm^{-1}) 3385, 1753, 1459, 1357, 1282, 1243, 1172, 756, 702. Anal. calcd. for $C_{20}H_{19}NO_3$: C 74.75; H 5.96; N 4.36; found: C 74.41; H 6.20; N 4.27. **6b**: mp 166–168 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02 (s, 3H), 3.54 (s, 3H), 4.52 (d, 1H, J = 11.6 Hz), 5.10 (d, 1H, J = 11.6 Hz), 7.01–7.32 (m, 9H), 7.52 (d, 1H, J = 7.6 Hz), 8.06 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.6, 42.9, 52.7, 65.7, 111.2, 117.2, 119.4, 119.6, 120.8, 122.4, 126.6, 127.0, 128.3, 128.8, 136.4, 141.4, 168.8, 202.6. IR (KBr) : ν (cm^{-1}) 3388, 1744, 1714, 1459, 1407, 1360, 1295, 1246, 1173, 1145, 760, 705. Anal. calcd. for $C_{20}H_{19}NO_3$: C 74.75; H 5.96; N 4.36; found: C 74.54; H 6.23; N 4.27.

Methyl 2-((1*H*-indol-3-yl)(2-nitrophenyl)methyl)-3-oxobutanoate (7a, 7b)



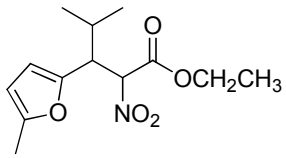
Prepared according to general procedure using methanol, *L*-proline (48 mg, 0.4 mmol), methyl acetoacetate (432 μL, 4 mmol), 2-nitrobenzaldehyde (616 mg, 4 mmol), indole (468 mg, 4 mmol), and $Eu(OTf)_3$ (243 mg, 0.4 mmol). Purification of the crude mixture by flash chromatography on silica gel (hexane/ethyl acetate = 8/2) afforded an inseparable mixture of **7a** and **7b** (513 mg, 35% yield; 55/45 diastereomeric mixture). Spectroscopic data of **7a** and **7b** are consistent with those reported in the literature.[4] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s, 3H) (2.15), 3.52 (s, 3H) (3.56), 4.40 (d, J = 12.1 Hz, 1H) (4.61), 5.91 (d, J = 12.1 Hz, 1H) (5.98), 7.05–7.80 (m, 9H), 8.09 (br, 1H) (8.12).

Methyl 2-acetyl-4-methyl-3-(1*H*-pyrrol-2-yl)pentanoate (8)



Prepared according to general procedure using methanol, *L*-proline (50.5 mg, 0.44 mmol), methyl acetoacetate (473 μL, 4.38 mmol), isobutyraldehyde (400 μL, 4.38 mmol), pyrrole (304 μL, 4.38 mmol), and $Eu(OTf)_3$ (260 mg, 0.44 mmol). Purification of the crude mixture by flash chromatography on silica gel (hexane→hexane/ethyl acetate = 8/2) afforded **7** as a white solid (488 mg, 47% yield). mp 126–128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (d, 3H, J = 6.8 Hz), 0.86 (d, 3H, J = 6.8 Hz), 1.98 (m, 1H), 2.07 (s, 3H), 3.24 (dd, 1H, J = 16.4 Hz, J = 9.2 Hz), 3.68 (s, 3H), 4.02 (d, 1H, J = 9.2 Hz), 5.85 (m, 1H), 6.06 (m, 1H), 6.65 (m, 1H), 8.46 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.5, 21.5, 29.9, 30.0, 45.5, 52.6, 62.3, 107.4, 107.9, 117.0, 128.7, 169.6, 203.6. IR (KBr) : ν (cm^{-1}) 3376, 2964, 1744, 1431, 1359, 1315, 1260, 1215, 1149, 1031, 998, 727. Anal. calcd. for $C_{13}H_{19}NO_3$: C 65.80; H 8.07; N 5.90; found: C 65.70; H 8.14; N 5.85.

Ethyl 4-methyl-3-(5-methylfuran-2-yl)-2-nitropentanoate (9a, 9b)

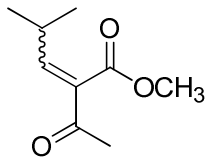


Prepared according to general procedure using methanol, *L*-proline (48 mg, 0.4 mmol), ethyl nitroacetate (450 μL, 4 mmol), isobutyraldehyde (370 μL, 4 mmol), 2-methylfuran (360 μL, 4 mmol), and $Eu(OTf)_3$ (243 mg, 0.4 mmol). Purification of the crude mixture by flash chromatography on silica gel (CH_2Cl_2/ethyl acetate = 95/5) afforded an inseparable mixture of **9a** and **9b** as a pale yellow liquid (295 mg, 35% yield; diastereomeric mixture 55/45). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80 (d, 3H, J = 3.0 Hz), 0.82 (d, 3H, J = 3.0 Hz), 0.83 (d, 3H, J = 1.8 Hz), 0.85 (d, 3H, J = 1.8 Hz), 1.02 (t, 3H, J = 6.9 Hz), 1.21 (t, 3H, J = 6.9 Hz), 1.83 (m, 2H), 2.10 (d, 3H, J = 0.9 Hz), 2.12 (d, 3H, J = 0.9 Hz), 3.50 (dd, 1H, J

[4] S. Gérard, A. Renzetti, B. Lefevre, A. Fontana, P. De Maria and J. Sapi, *Tetrahedron*, 2010, **66**, 3065-3069.

= 10.5 Hz, *J* = 4.0 Hz), 3.54 (dd, 1H, *J* = 10.5 Hz, *J* = 4.5 Hz), 3.90 (dq, 2H, *J* = 6.9 Hz, *J* = 2.1 Hz), 4.12 (dq, 2H, *J* = 6.9 Hz, *J* = 1.2 Hz), 5.31 (d, 1H, *J* = 10.5 Hz), 5.33 (d, 1H, *J* = 10.5 Hz), 5.62 (m, 2H), 5.79 (d, 1H, *J* = 3.0 Hz), 5.81 (d, 1H, *J* = 3.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.5 (13.8), 17.7 (17.9), 21.0 (21.5), 28.8 (28.7), 46.1, 62.9 (63.1), 88.9 (89.4), 106.0 (106.1), 110.3 (109.9), 147.0 (147.6), 151.9 (151.7), 163.4 (163.7). IR (KBr) : ν (cm^{-1}) 2985, 1764, 1548, 1204, 1035. MS (EI): m/z (%) 269 $[M]^{+\bullet}$, 222, 136, 121, 94. EI-HRMS calcd for $C_{13}H_{19}NO_5$ $[M]^{+\bullet}$: 269.1263; found: 269.1279.

Methyl 2-acetyl-4-methylpent-2-enoate (14)



E/*Z* = 1:2

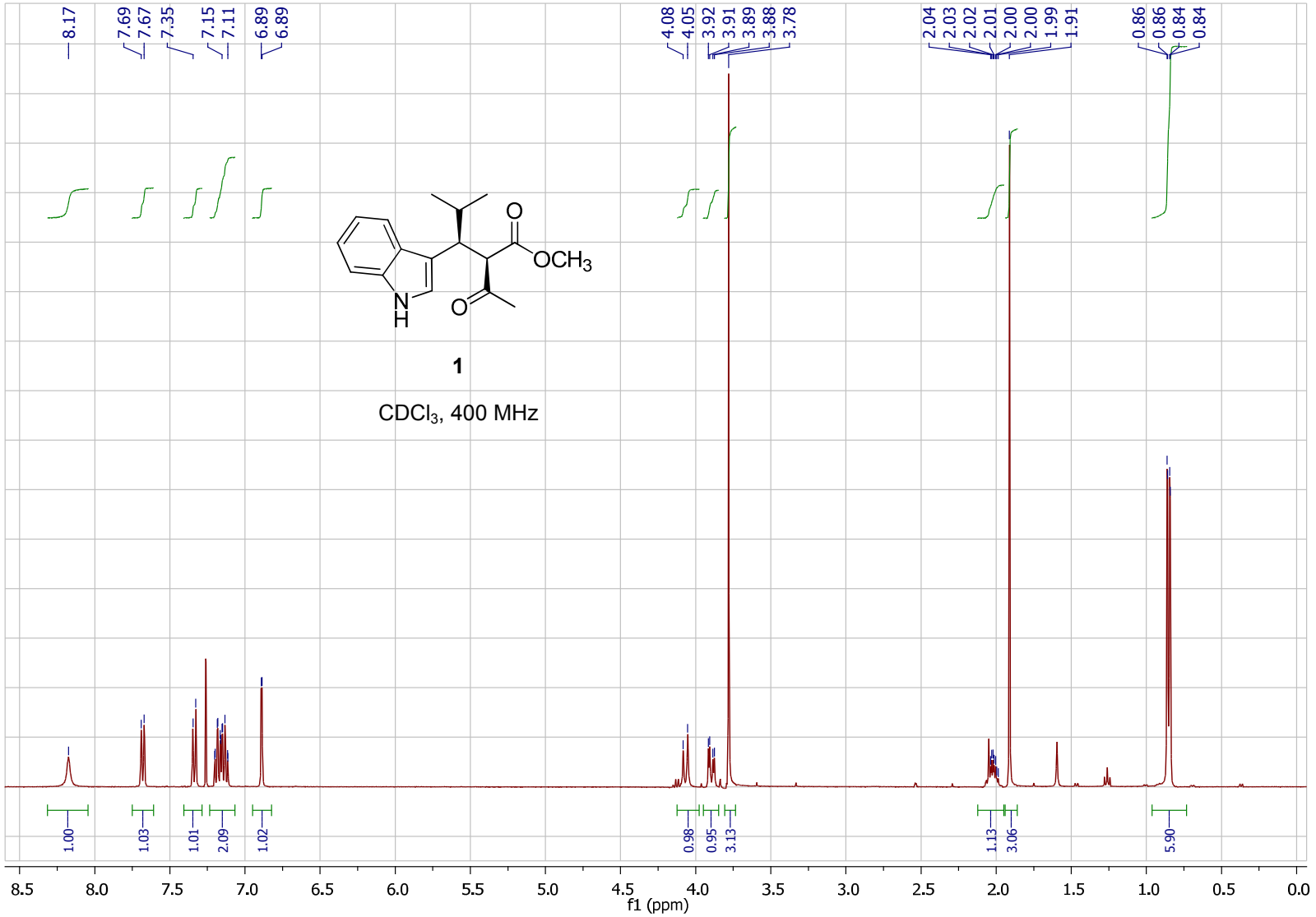
L-proline (101 mg, 0.87 mmol, 0.1 equiv.) was dissolved in methanol (20 mL) under stirring at room temperature in the presence of molecular sieves 4Å. Methyl acetoacetate (946 µL, 8.76 mmol, 1.0 equiv.) and isobutyraldehyde (800 µL, 8.76 mmol, 1.0 equiv.) were added to the solution. After 24 h of stirring at room temperature, the mixture was filtered over celite to remove molecular sieves. The filtrate was concentrated at reduced pressure. Purification of the crude mixture by flash chromatography (hexane/diethyl ether = 6/4) afforded **14** as an uncoloured liquid (mixture of diastereomers, *E*/*Z* = 1:2, 625 mg, 37% yield). Spectroscopic data of **14** are in agreement with those reported in the literature.[5] ^{1}H NMR ($CDCl_3$, 400 MHz) isomer *E*: δ 1.02 (d, 6H, *J* = 6.8 Hz), 2.33 (s, 3H), 2.61 (m, 1H), 3.75 (s, 3H), 6.68 (d, 1H, *J* = 10.4 Hz); isomer *Z*: δ 1.05 (d, 6H, *J* = 6.4 Hz), 2.28 (s, 3H), 2.65 (m, 1H), 3.80 (s, 3H), 6.59 (d, 1H, *J* = 10.0 Hz). ESI-HRMS calcd. for $C_9H_{14}NaO_3$ $[M + Na]^+$: 193.0835; found: 193.0835.

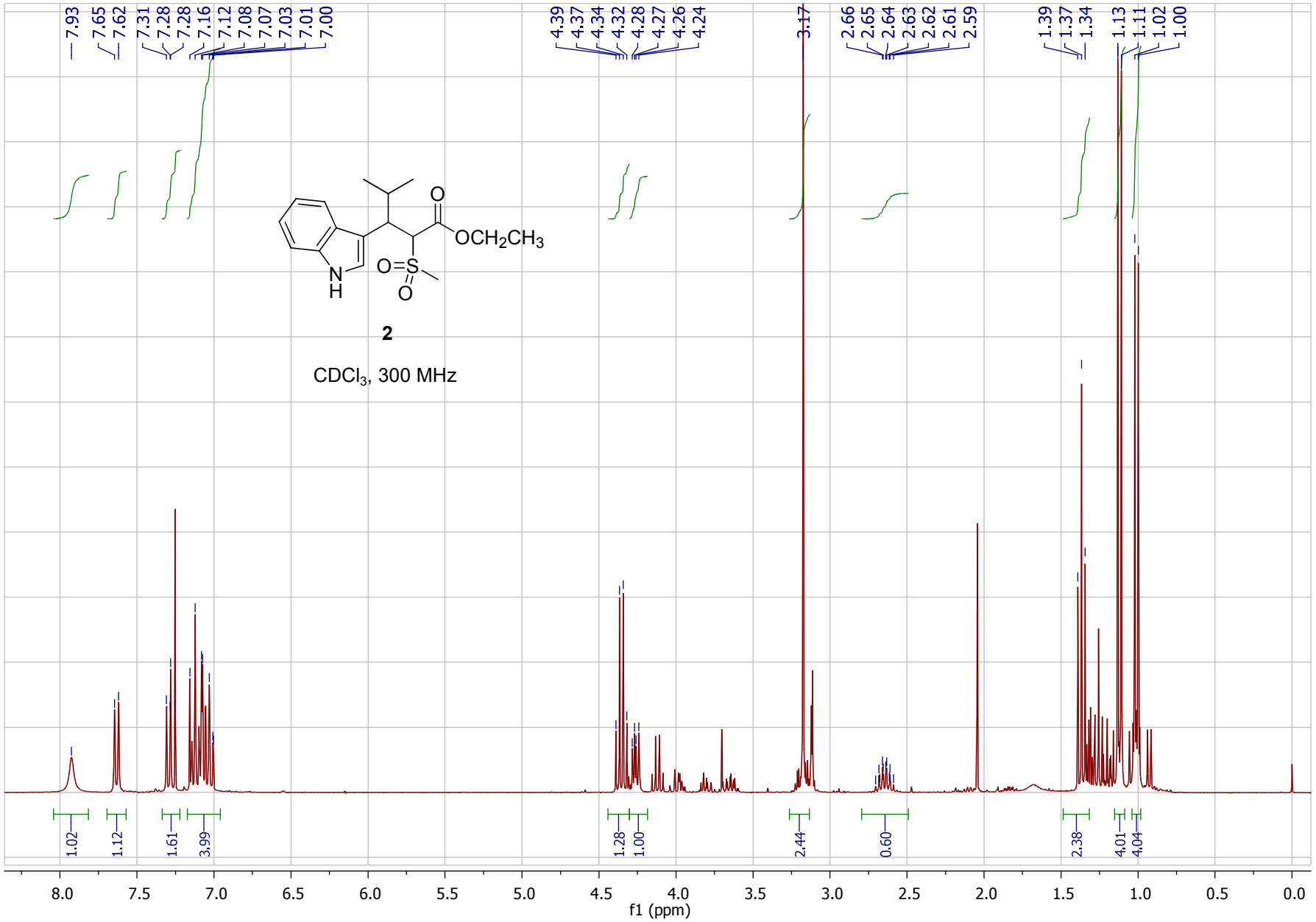
Preparation of 1 from 14

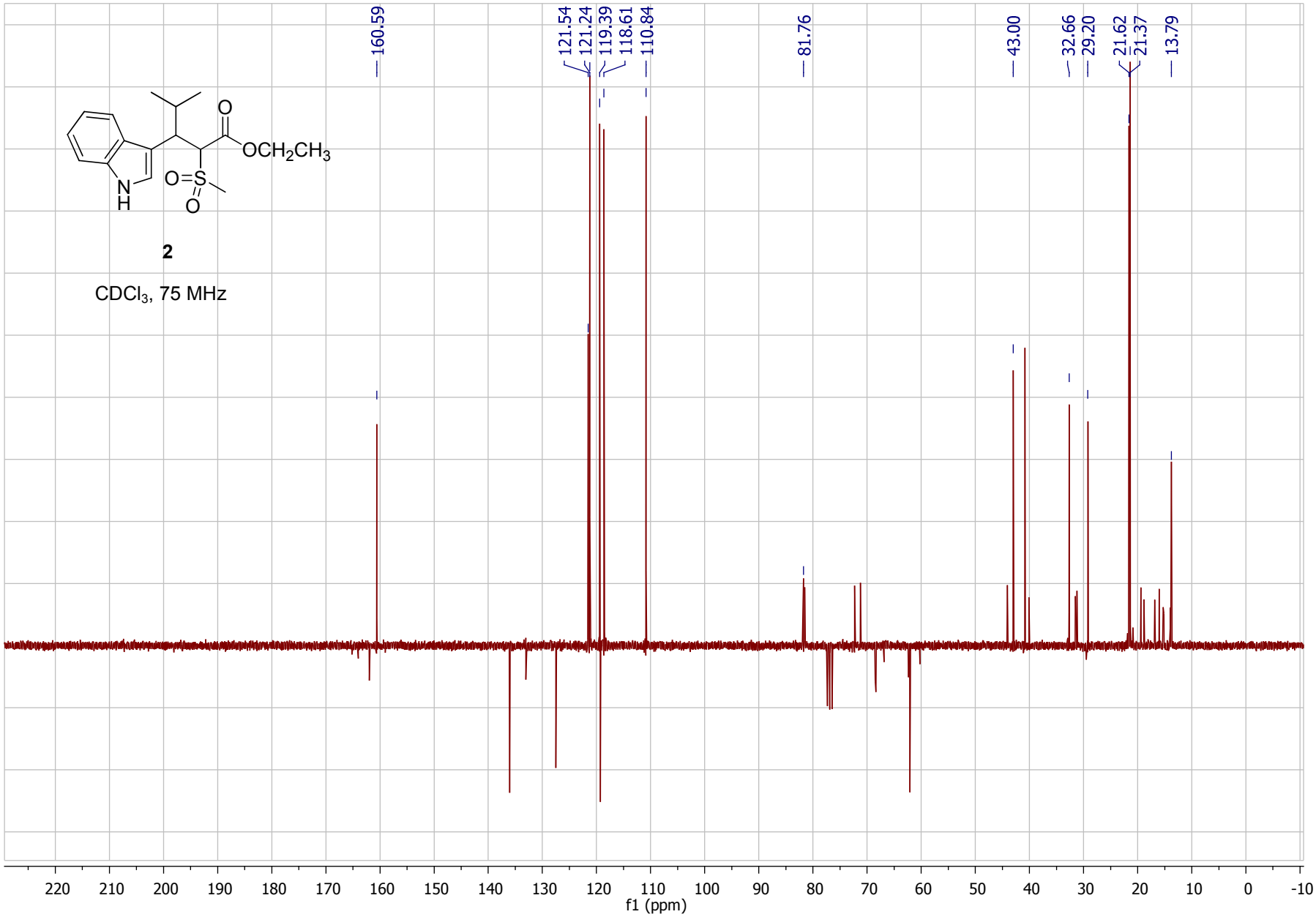
Compound **14** (71 mg, 417 µmol, 1.0 equiv.) was dissolved in methanol (5 mL) under stirring at room temperature in the presence of molecular sieves 4Å. Indole (48.9 mg, 417 µmol, 1.0 equiv.) and $Eu(OTf)_3$ (24.6 mg, 41.7 µmol, 0.1 equiv.) were added to the solution. After five days of stirring at room temperature, the mixture was filtered over celite® to remove molecular sieves. The filtrate was concentrated at reduced pressure. Purification of the crude mixture by PTLC on silica gel (petroleum ether/ethyl acetate = 8/2) afforded **1** as a white solid (12 mg, 10% yield). Spectroscopic data of **1** are consistent with those reported in the literature.[3]

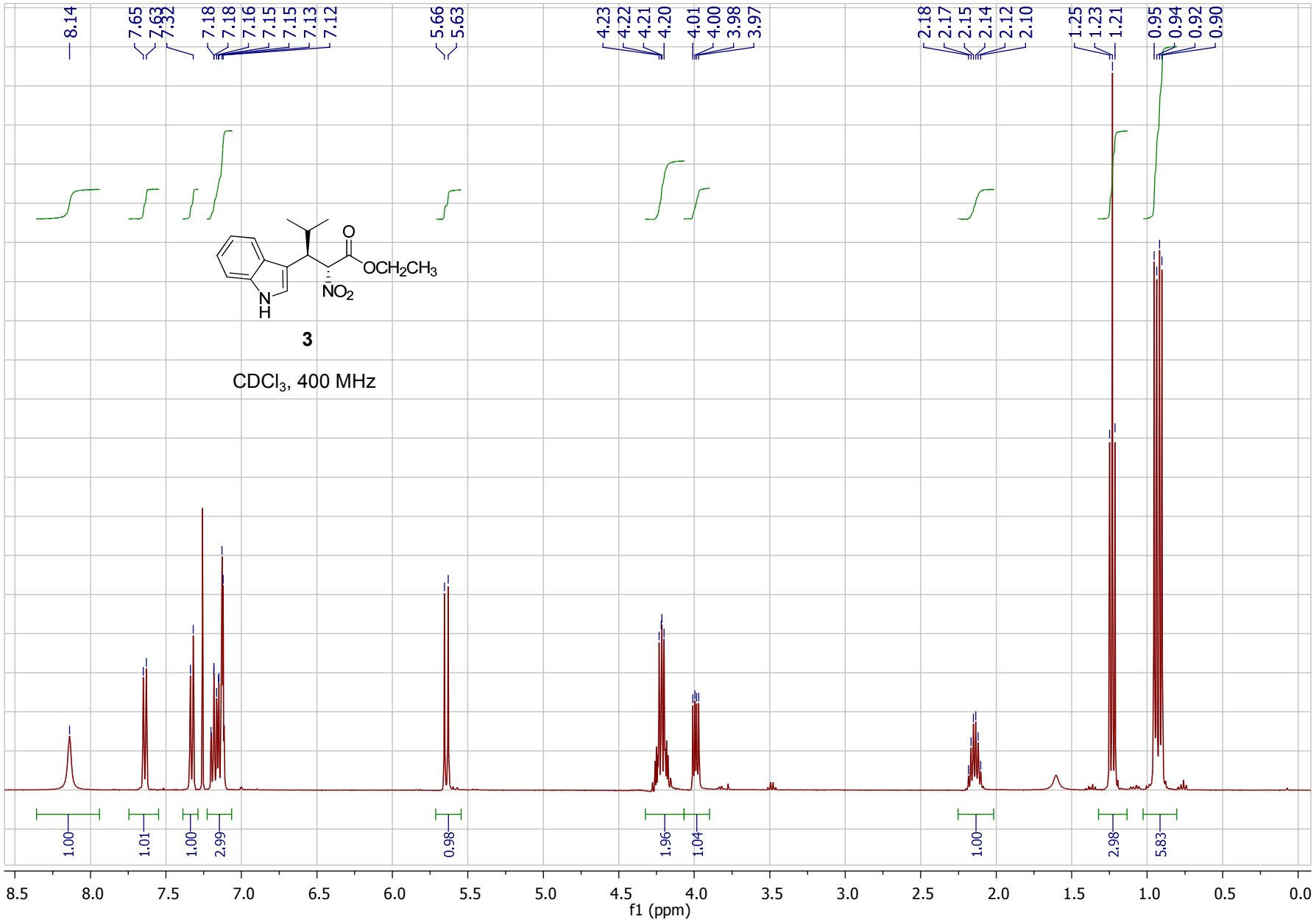
[5] R. Antonioletti, P. Bovicelli and S. Melancona *Tetrahedron* 2002, **58**, 589-596.

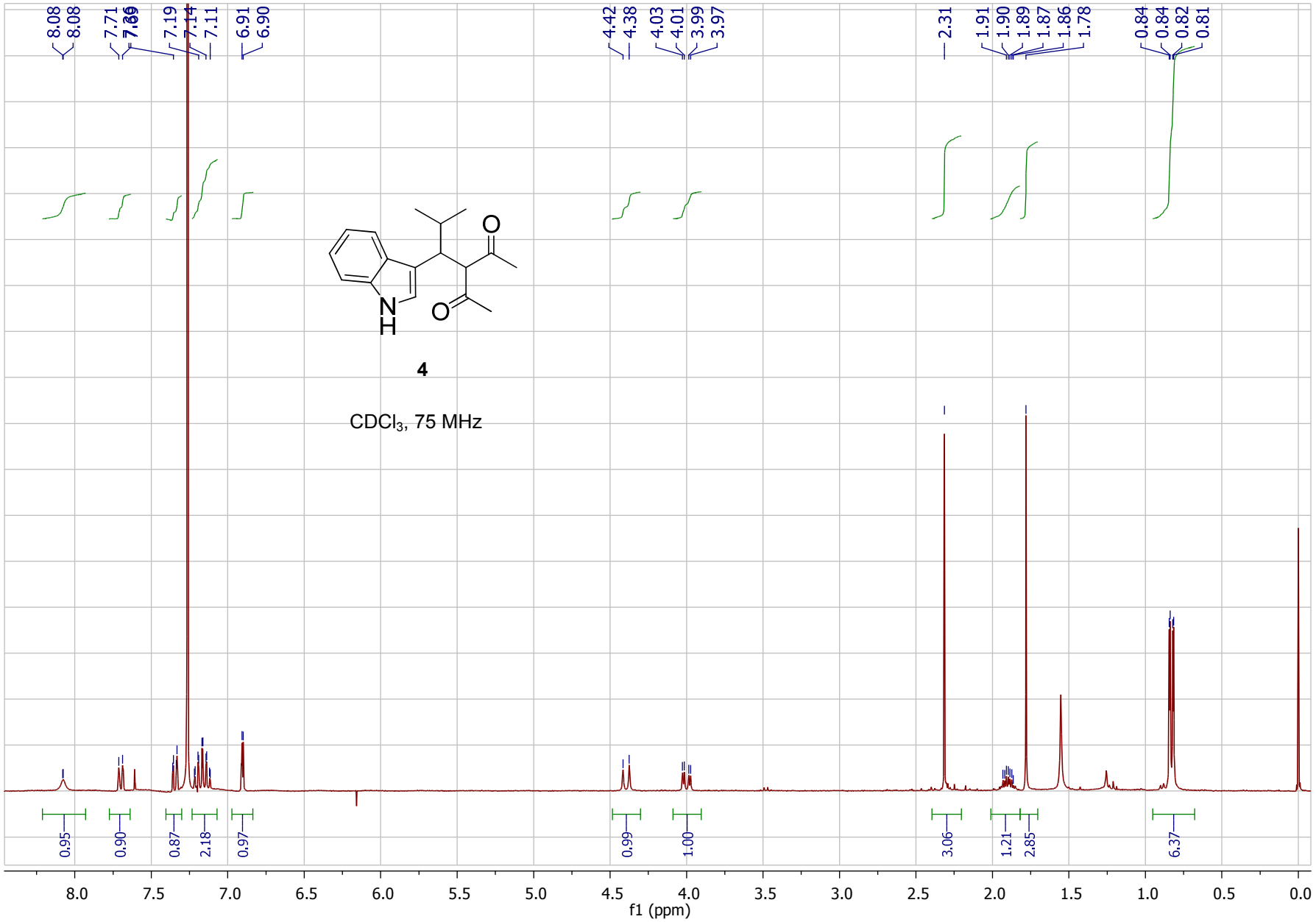
NMR spectra of 1–6b and 8–9b

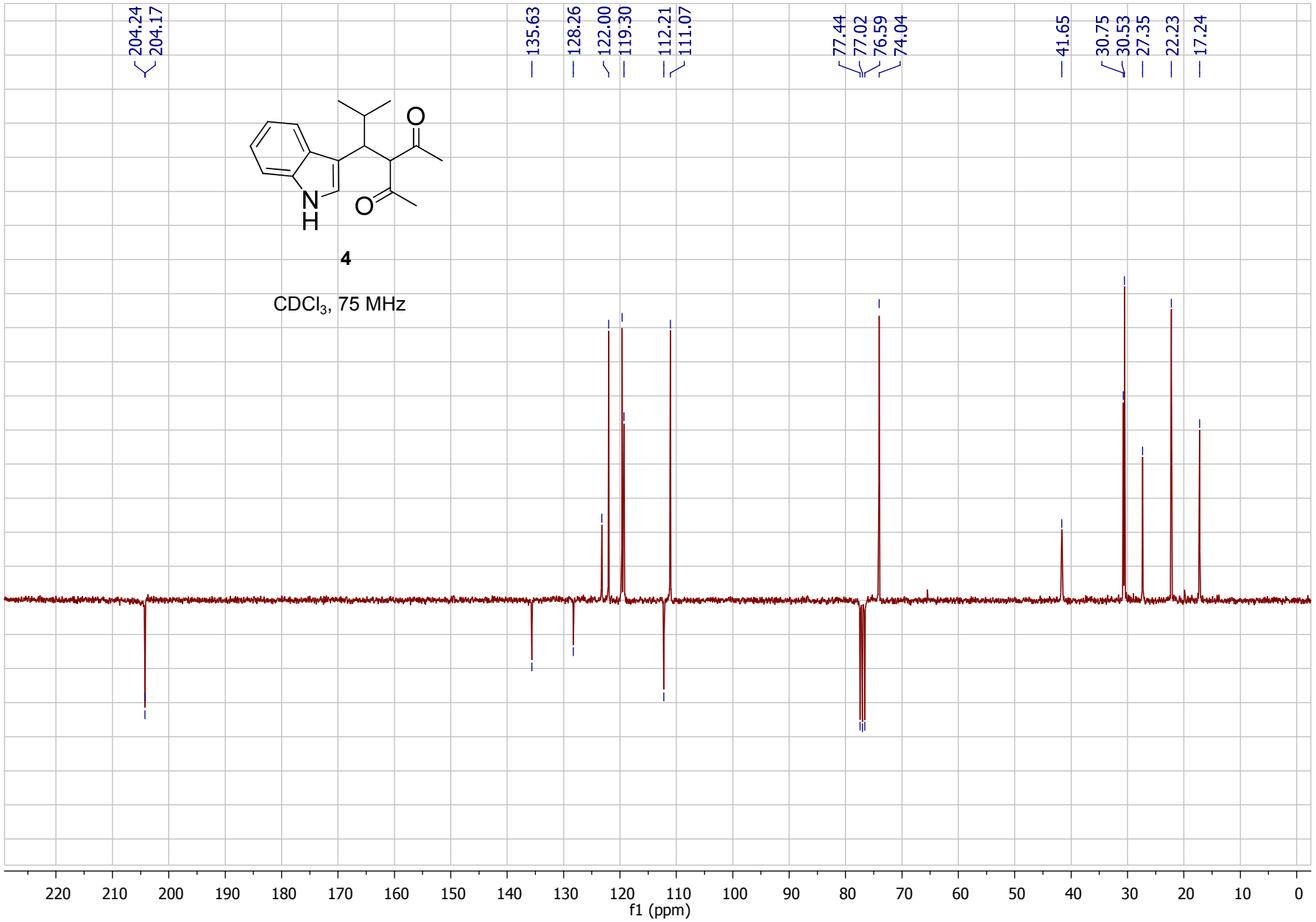


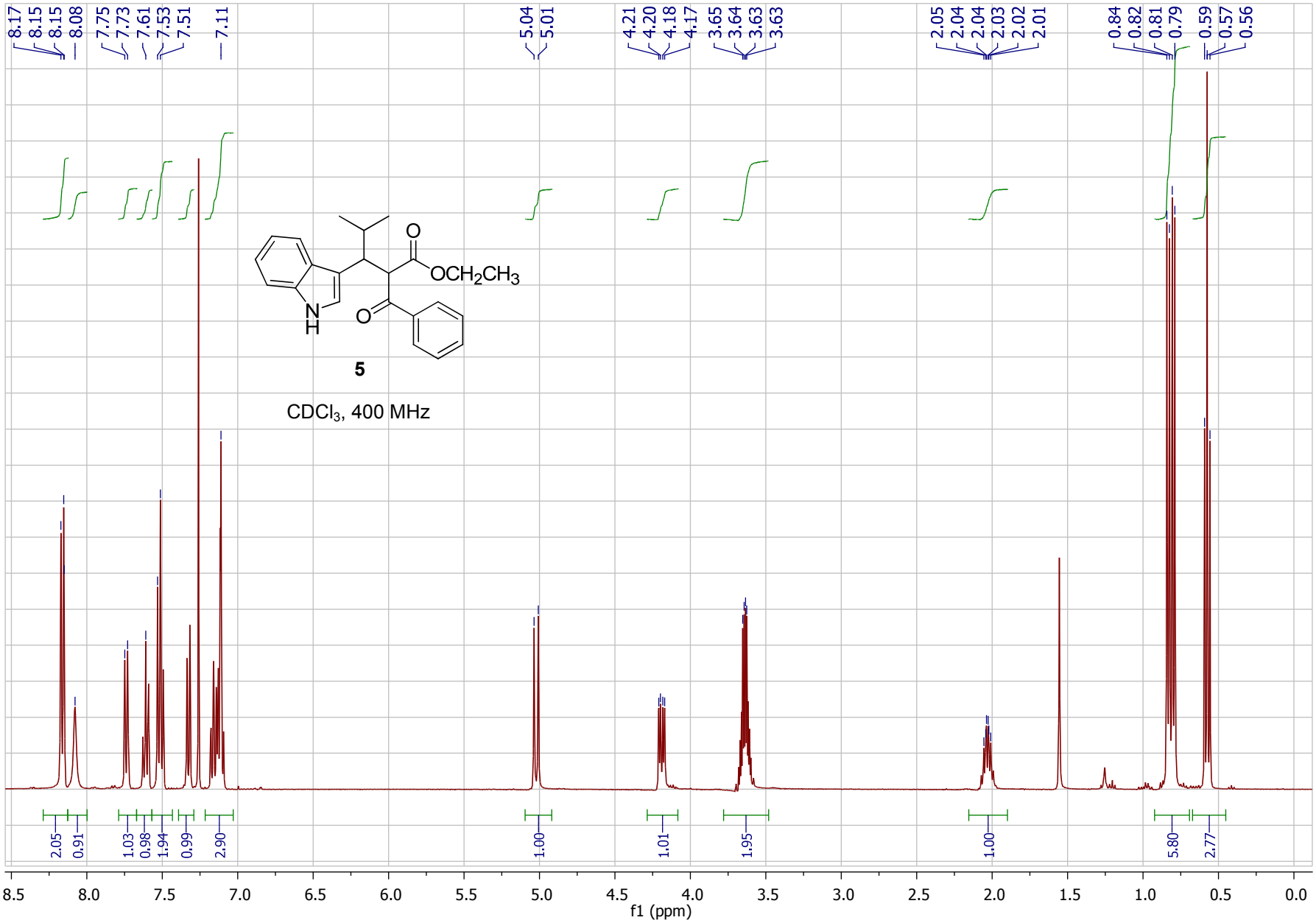

7.93
7.65
7.62
7.31
7.28
7.28
7.16
7.12
7.08
7.07
7.03
7.01
7.00
4.39
4.37
4.34
4.32
4.28
4.27
4.26
4.24
3.17
2.66
2.65
2.64
2.63
2.62
2.61
2.59
1.39
1.37
1.34
1.13
1.11
1.02
1.00
O
OCH2CH3
O=S
O
N
H
2
CDCl3, 300 MHz
1.02
1.12
1.61
3.99
1.28
1.00
2.44
0.60
2.38
4.01
4.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

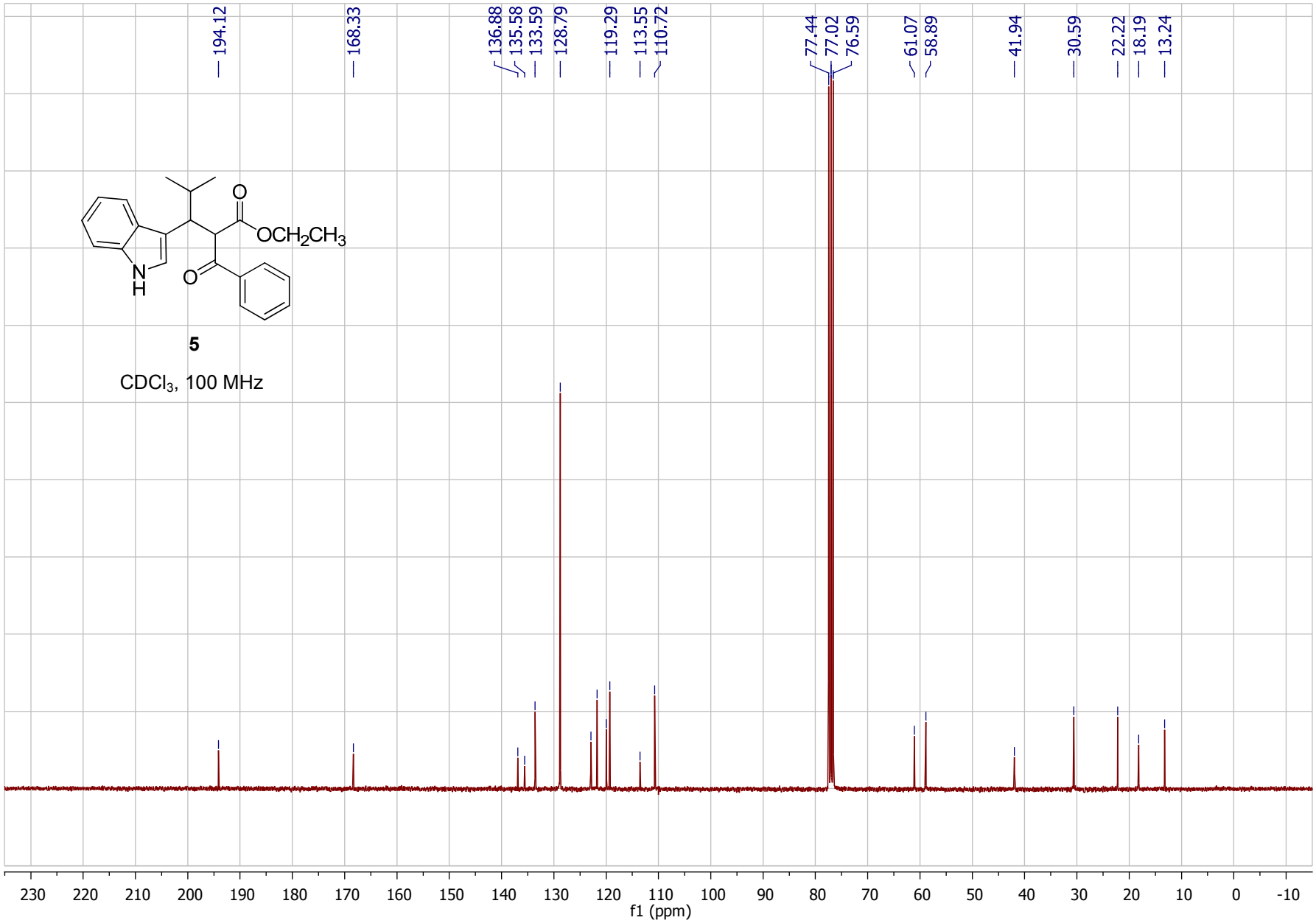

160.59
121.54
121.24
119.39
118.61
110.84
81.76
43.00
32.66
29.20
21.62
21.37
13.79
O
OCH2CH3
O=S
O
N
H
2
CDCl3, 75 MHz
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

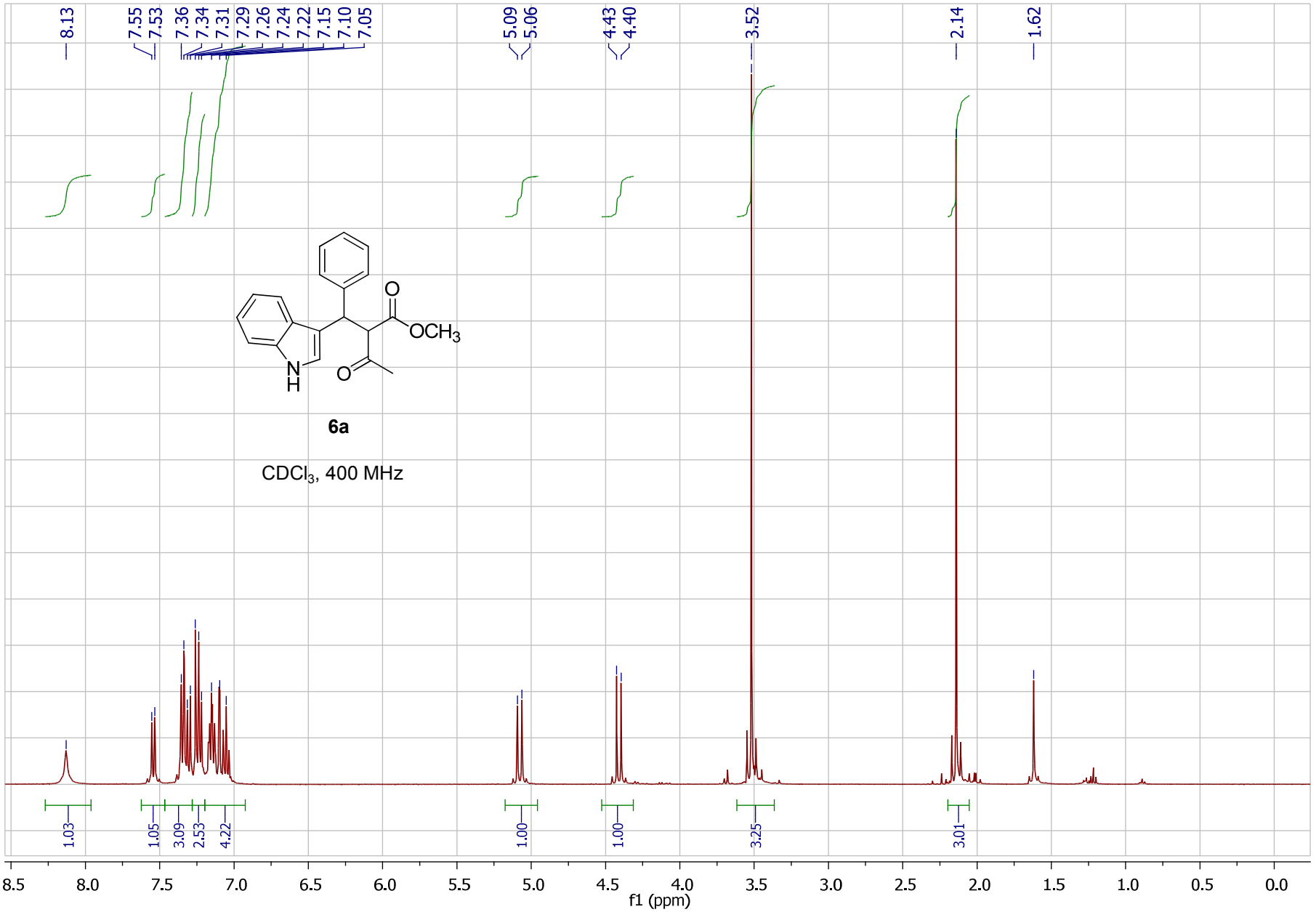

8.14
7.65
7.63
7.32
7.18
7.18
7.16
7.15
7.15
7.13
7.12
5.66
5.63
4.23
4.22
4.21
4.20
4.01
4.00
3.98
3.97
2.18
2.17
2.15
2.14
2.12
2.10
1.25
1.23
1.21
0.95
0.94
0.92
0.90
O
OCH2CH3
NO2
N
H
3
CDCl3, 400 MHz
1.00
1.01
1.00
2.99
0.98
1.96
1.04
1.00
2.98
5.83
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

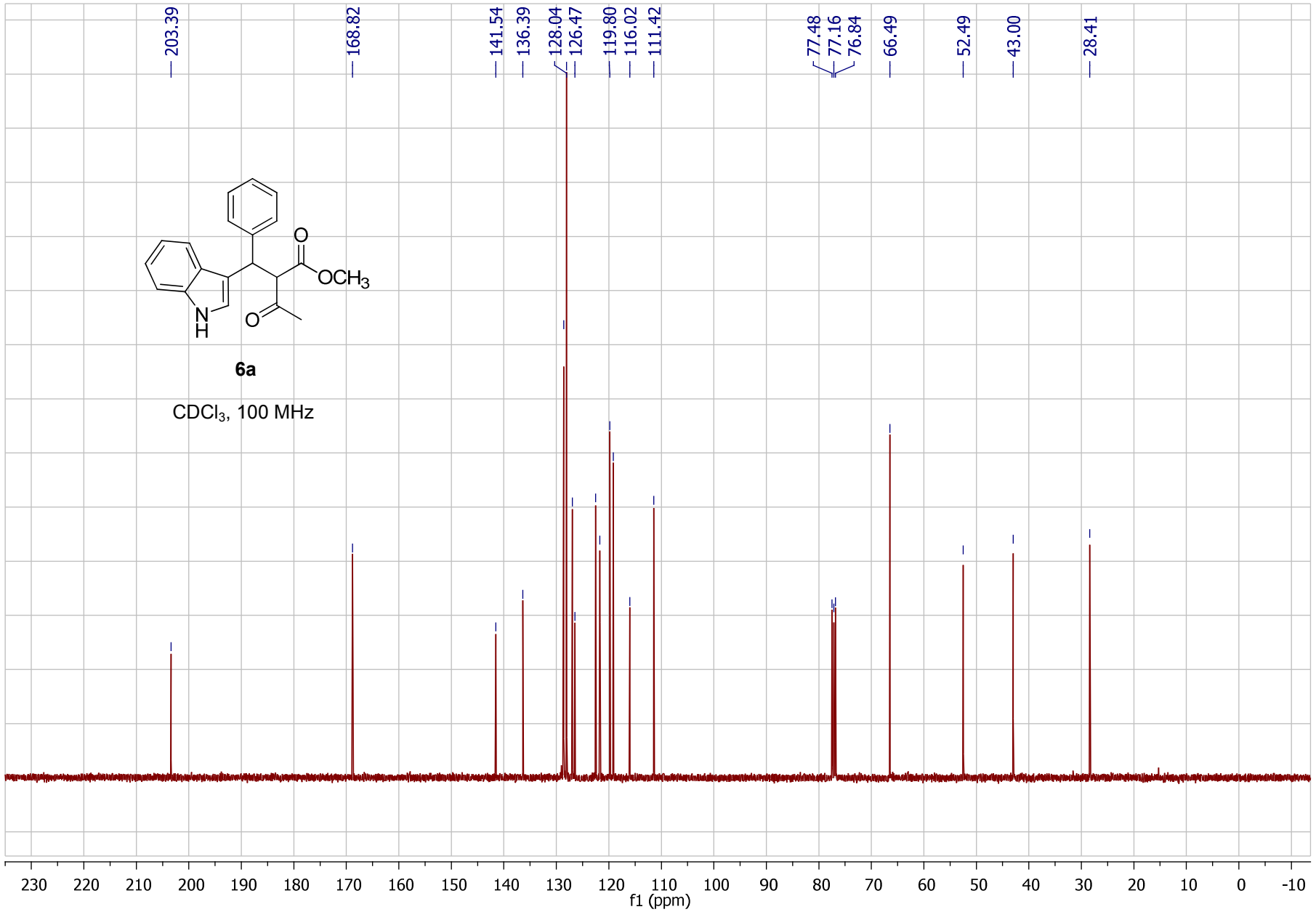

8.08
8.08
7.71
7.19
7.14
7.11
6.91
6.90
4.42
4.38
4.03
4.01
3.99
3.97
2.31
1.91
1.90
1.89
1.87
1.86
1.78
0.84
0.84
0.82
0.81
O
O
N
H
4
CDCl3, 75 MHz
0.95
0.90
0.87
2.18
0.97
0.99
1.00
3.06
1.21
2.85
6.37
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

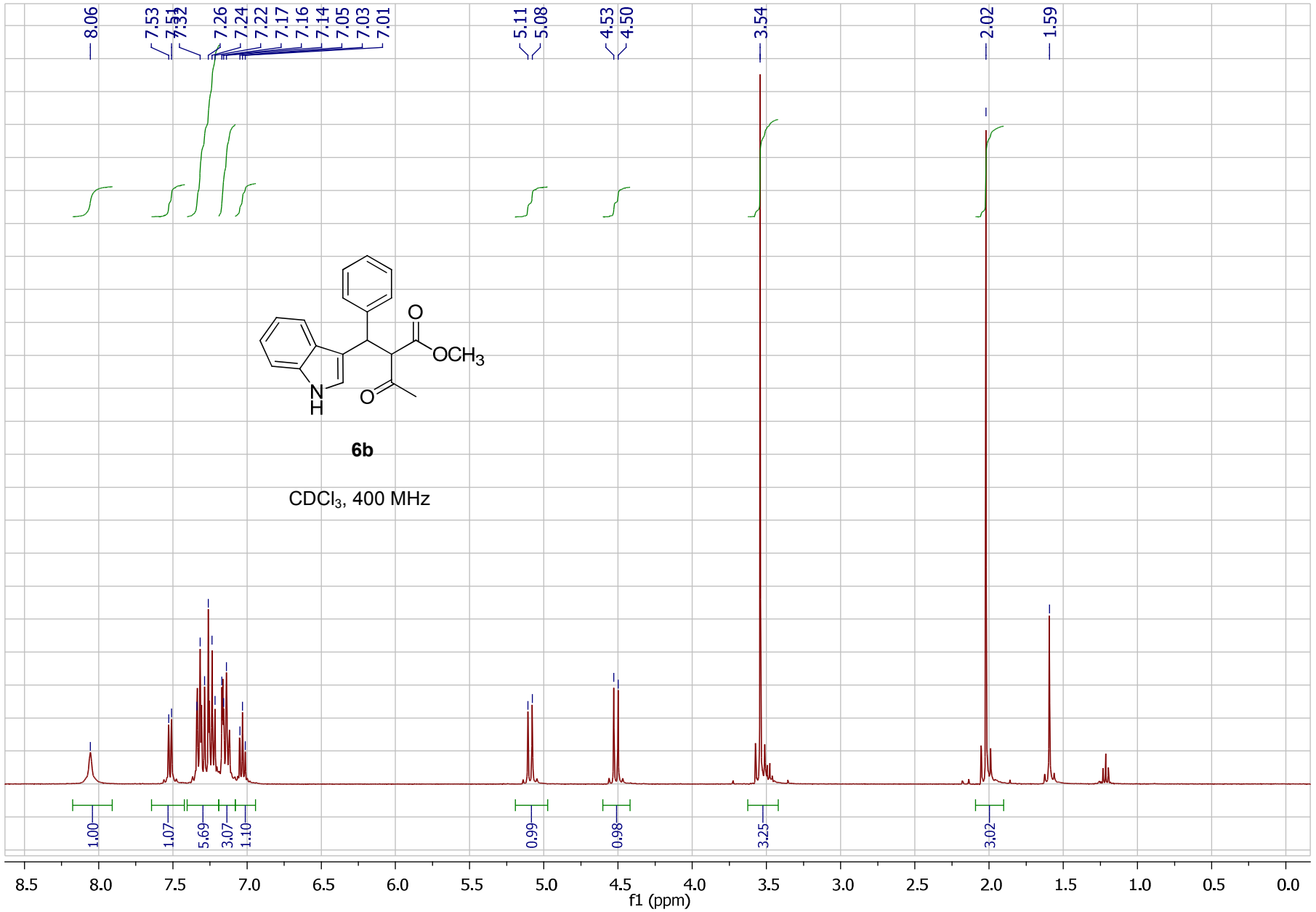

204.24
204.17
135.63
128.26
122.00
119.30
112.21
111.07
77.44
77.02
76.59
74.04
41.65
30.75
30.53
27.35
22.23
17.24
O
N
H
O
4
CDCl3, 75 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

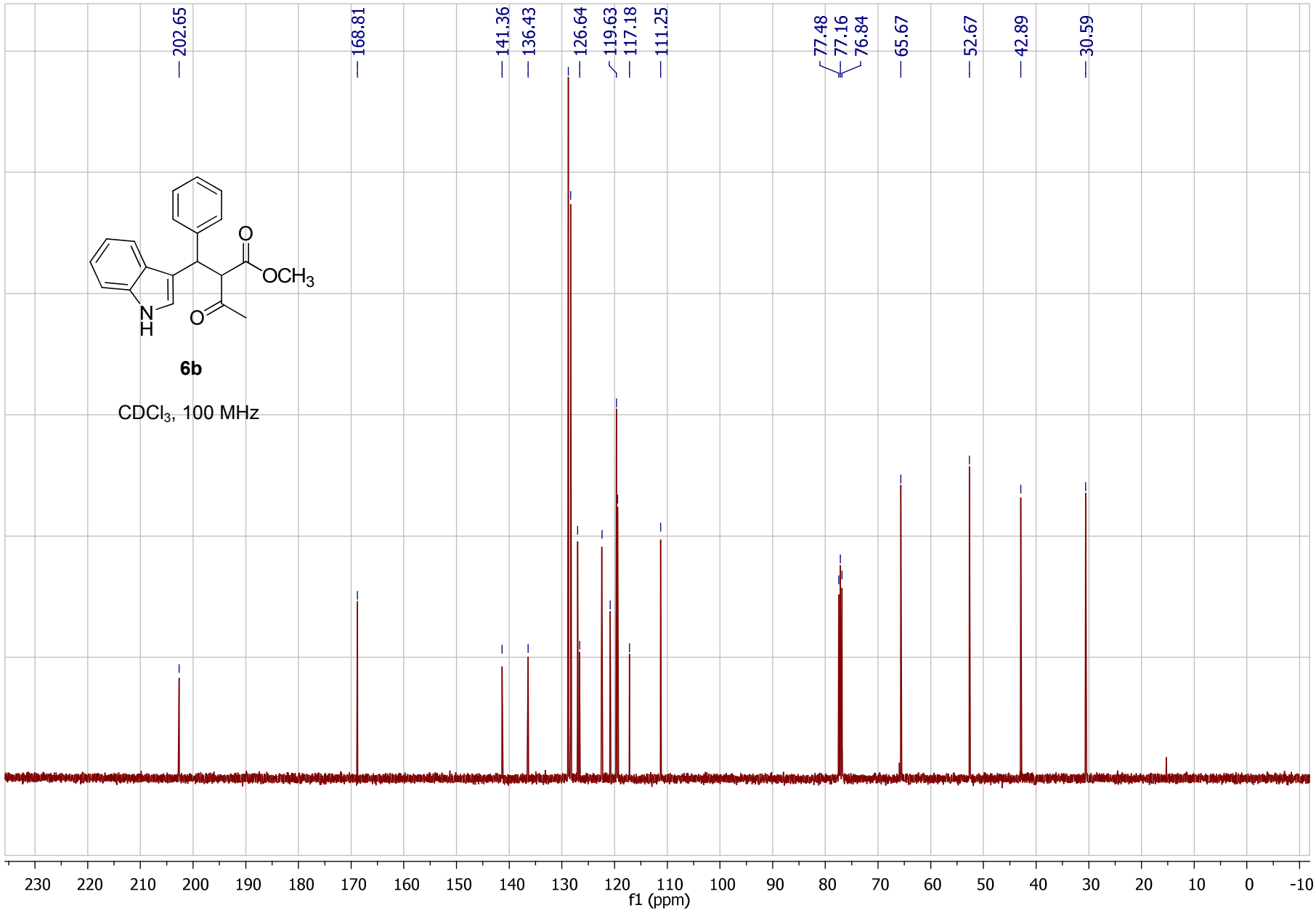

8.17
8.15
8.15
8.08
7.75
7.73
7.61
7.53
7.51
7.11
5.04
5.01
4.21
4.20
4.18
4.17
3.65
3.64
3.63
3.63
2.05
2.04
2.04
2.03
2.02
2.01
0.84
0.82
0.81
0.79
0.59
0.57
0.56
O
OCH2CH3
N
H
O
5
CDCl3, 400 MHz
2.05
0.91
1.03
0.98
1.94
0.99
2.90
1.00
1.01
1.95
1.00
5.80
2.77
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

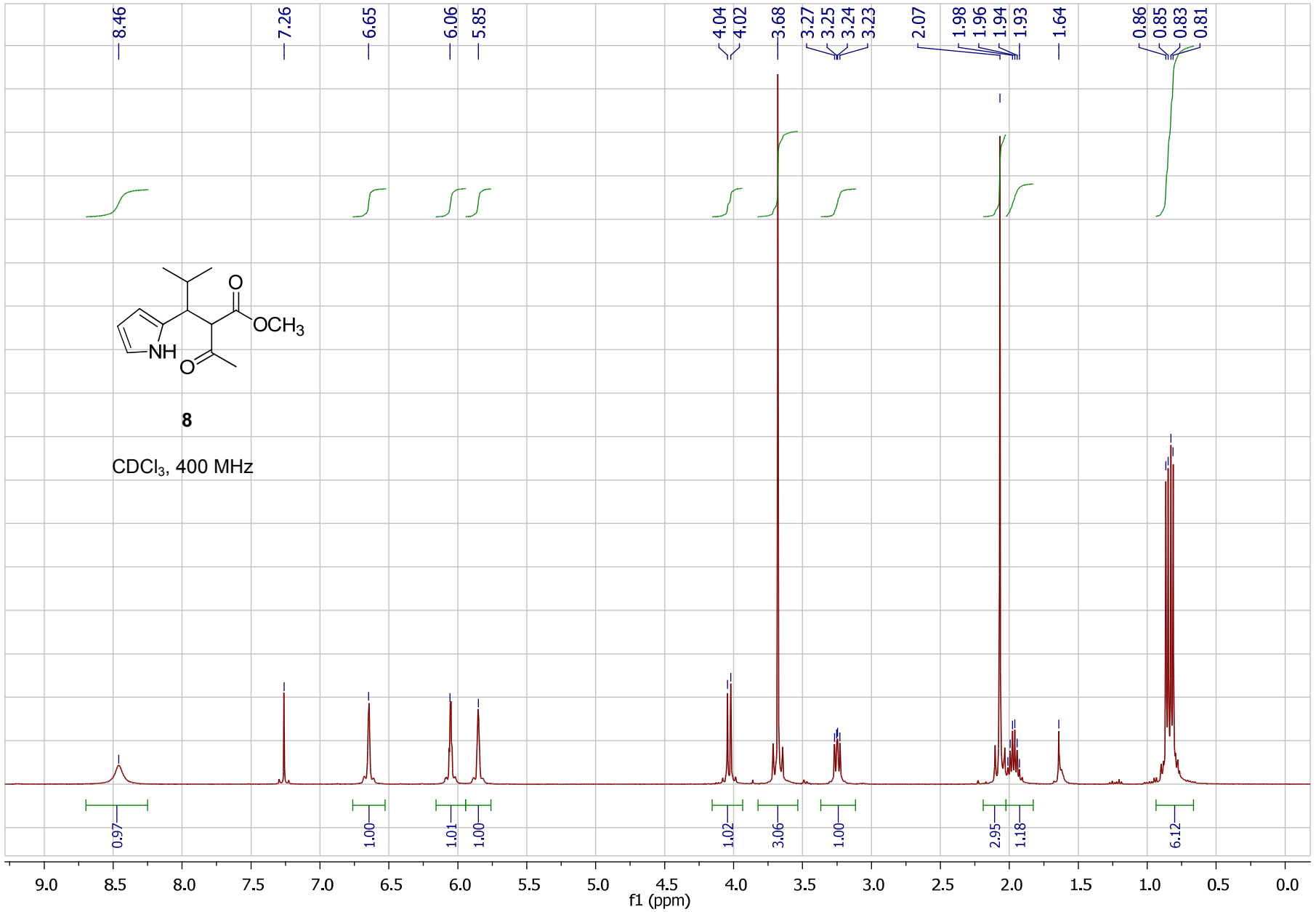

194.12
168.33
136.88
135.58
133.59
128.79
119.29
113.55
110.72
77.44
77.02
76.59
61.07
58.89
41.94
30.59
22.22
18.19
13.24
O
OCH2CH3
N
H
O
5
CDCl3, 100 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

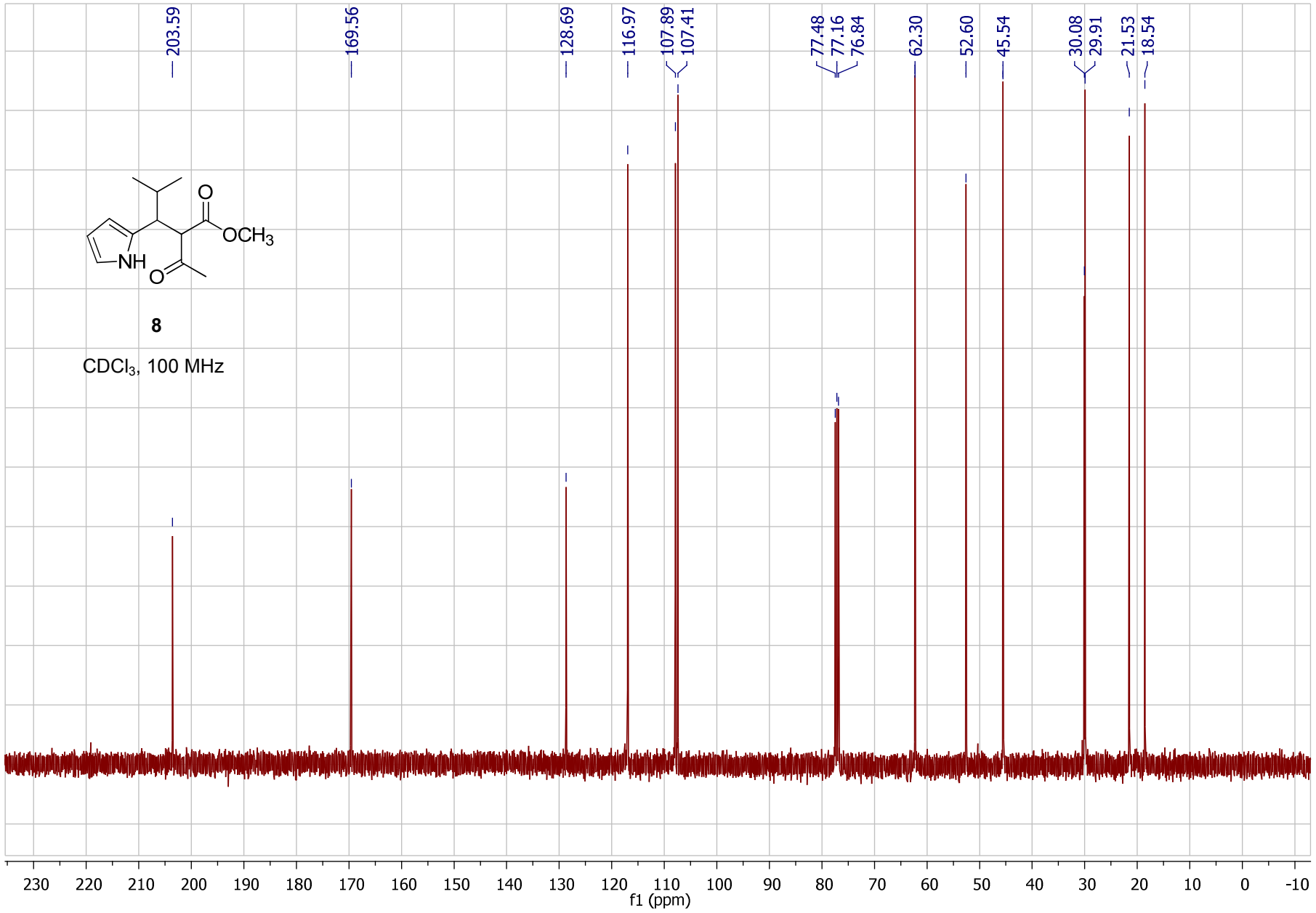

8.13
7.55
7.53
7.36
7.34
7.31
7.29
7.26
7.24
7.22
7.15
7.10
7.05
5.09
5.06
4.43
4.40
3.52
2.14
1.62
O
OCH3
N
H
O
6a
CDCl3, 400 MHz
1.03
1.05
3.09
2.53
4.22
1.00
1.00
3.25
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

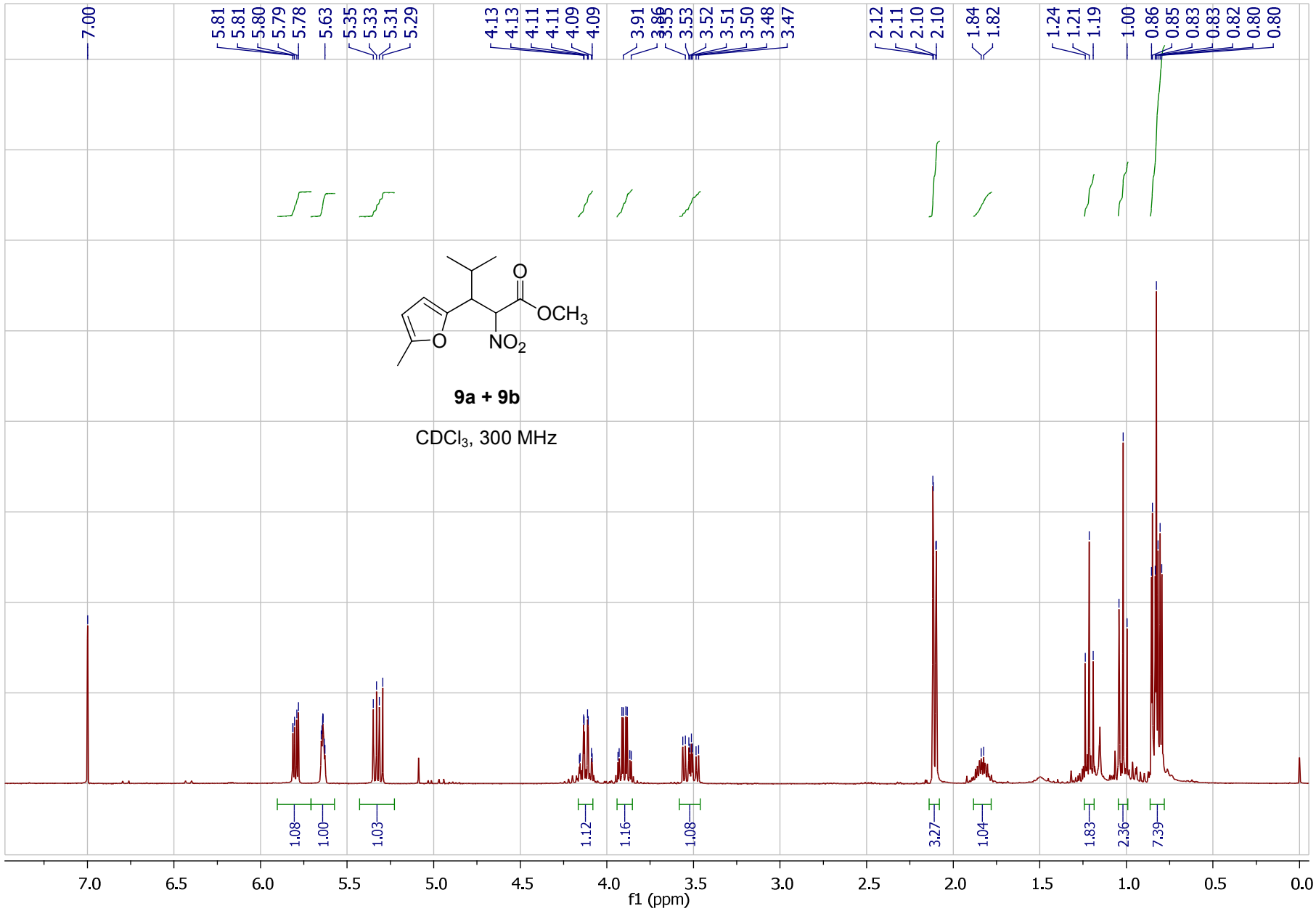

203.39
168.82
141.54
136.39
128.04
126.47
119.80
116.02
111.42
77.48
77.16
76.84
66.49
52.49
43.00
28.41
O
OCH3
N
H
O
6a
CDCl3, 100 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.06
7.53
7.51
7.32
7.26
7.24
7.22
7.17
7.16
7.14
7.05
7.03
7.01
5.11
5.08
4.53
4.50
3.54
2.02
1.59
O
OCH3
N
H
O
6b
CDCl3, 400 MHz
1.00
1.07
5.69
3.07
1.10
0.99
0.98
3.25
3.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


202.65
168.81
141.36
136.43
126.64
119.63
117.18
111.25
77.48
77.16
76.84
65.67
52.67
42.89
30.59
O
OCH3
N
H
O
6b
CDCl3, 100 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.46
7.26
6.65
6.06
5.85
4.04
4.02
3.68
3.27
3.25
3.24
3.23
2.07
1.98
1.96
1.94
1.93
1.64
0.86
0.85
0.83
0.81
O
OCH3
NH
O
8
CDCl3, 400 MHz
0.97
1.00
1.01
1.00
1.02
3.06
1.00
2.95
1.18
6.12
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


203.59
169.56
128.69
116.97
107.89
107.41
77.48
77.16
76.84
62.30
52.60
45.54
30.08
29.91
21.53
18.54
O
OCH3
NH
O
8
CDCl3, 100 MHz
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.00
5.81
5.81
5.80
5.79
5.78
5.63
5.35
5.33
5.31
5.29
4.13
4.13
4.11
4.11
4.09
4.09
3.91
3.53
3.52
3.51
3.50
3.48
3.47
2.12
2.11
2.10
2.10
1.84
1.82
1.24
1.21
1.19
1.00
0.86
0.85
0.83
0.83
0.82
0.80
0.80
O
OCH3
O
NO2
9a + 9b
CDCl3, 300 MHz
1.08
1.00
1.03
1.12
1.16
1.08
3.27
1.04
1.83
2.36
7.39
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

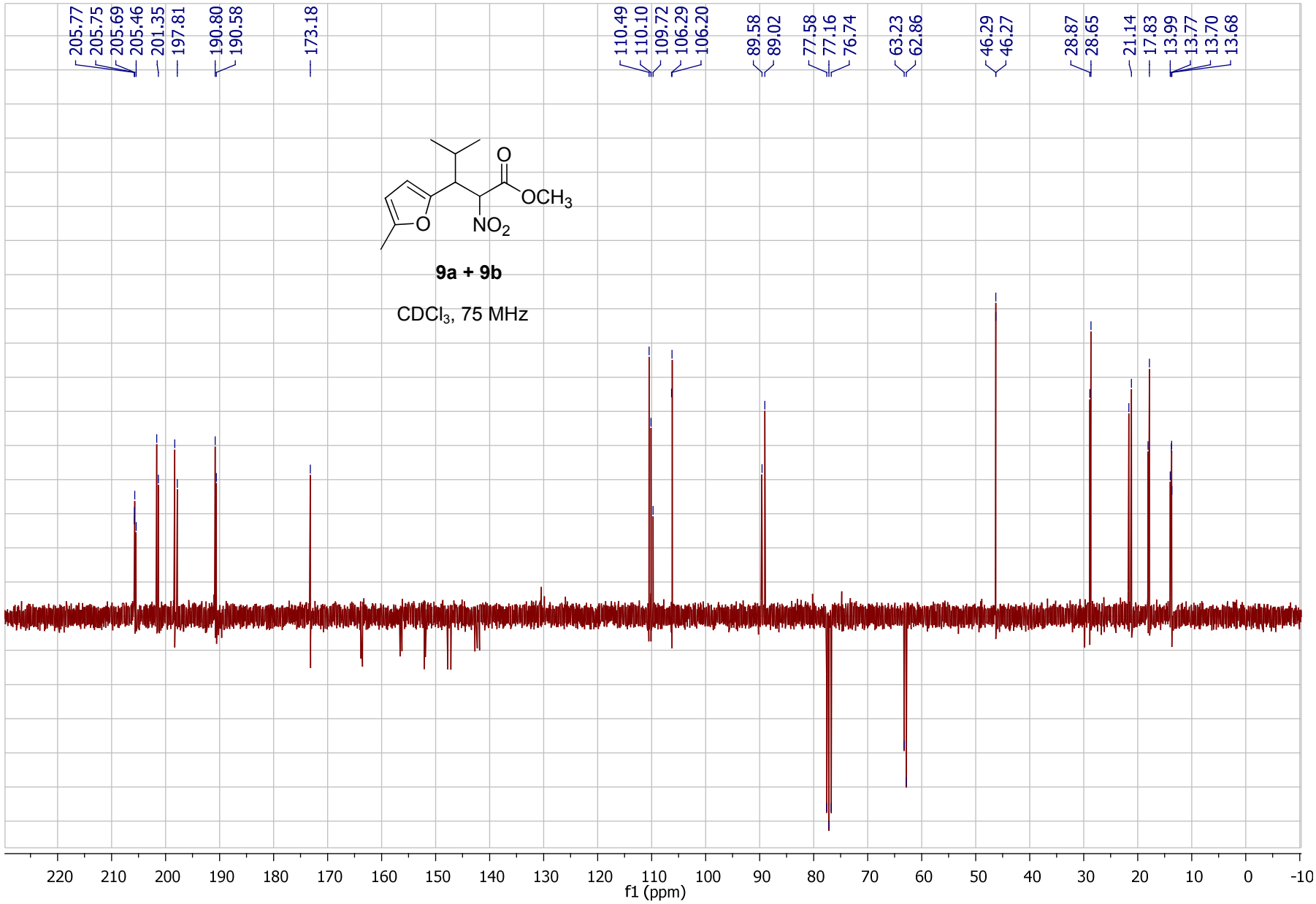
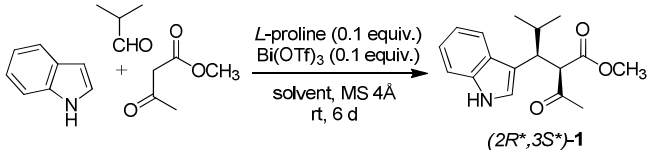

205.77
205.75
205.69
205.46
201.35
197.81
190.80
190.58
173.18
110.49
110.10
109.72
106.29
106.20
89.58
89.02
77.58
77.16
76.74
63.23
62.86
46.29
46.27
28.87
28.65
21.14
17.83
13.99
13.77
13.70
13.68
O
OCH3
O
NO2
9a + 9b
CDCl3, 75 MHz
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Table S1. Trimolecular condensation in various solvents.

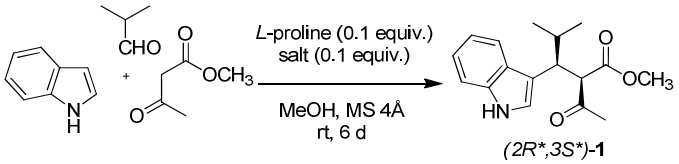


(2R,3S*)*-**1**

Entry	Solvent	Yield (%)[a]
1	none	0[e]
2[b]	none	36
3	$PhCH_3$	23
4	THF	25
5	CH_3CN	23
6	MeOH	50
7[c]	MeOH	78
8[c]	EtOH	55
9[d]	H_2O	0[e]
10[d]	MeOH/H_2O (8:2)	0[e]

[a] Yield of purified product.
[b] 0.01 equiv. of $Bi(OTf)_3$ were used.
[c] $Eu(OTf)_3$ was used in the place of $Bi(OTf)_3$.
[d] Reaction was performed without molecular sieves.
[e] A complex mixture of compounds was obtained.

Table S2. Trimolecular condensation in the presence of various europium salts.

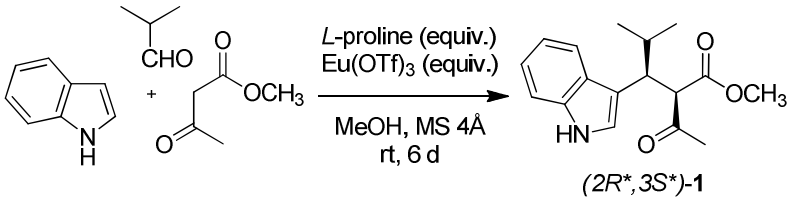


(2R,3S*)*-**1**

Entry	Salt	Yield (%)[a]
1	$Eu(OTf)_3$	78
2	$Eu(NO_3)_3$	68
3	$EuCl_3 \cdot 6H_2O$	48

[a] Yield of purified product.

Table S3. Trimolecular condensation in the presence of various amounts of $Eu(OTf)_3$ and *L*-proline.



(2R,3S*)*-**1**

Entry	Equiv.		Yield (%)[a]
	$Eu(OTf)_3$	*L*-proline	
1	0.1	0.1	78
2	0.1	0.2	19
3	0.2	0.1	67
4	0.05	0.05	48

[a] Yield of purified product.

Table S4. Calculation of the environmental factor (E-factor)[a] for the trimolecular condensation in the presence of Eu(III) and Ti(IV).

		mass (mg)	
		Eu(III)-catalyzed reaction	**Ti(IV)-promoted reaction**
Materials in	Methyl acetoacetate[b]	1016	1016
	Isobutyraldehyde[b]	631	631
	Indole[b]	1025	1025
	L-proline[c]	101	-
	$Eu(OTf)_3$[c]	521	-
	$TiCl_4$[b]	-	1660
	Et_3N[b]	-	885
	MeOH[d]	15	-
	MeOH (work-up)[d]	15	-
	CH_2Cl_2[d]	-	26
	CH_2Cl_2 (work-up)[d]	-	26
	HCl 1M[d]	-	729[f]
	Molecular sieves	3000	3000
Product out	Condensation product	1963[e]	1131[g]
E-factor[a]		2.23	6.95

[a] E-factor = [(mass of materials in) – (mass of product out)]/(mass of materials in). [b] 8.75 mmol (1.0 equiv.); [c] 0.87 mmol (0.1 equiv.); [d] 20 mL; [e] 6.83 mmol (78% yield); [f] mass of HCl (water was not included in calculations); [g] 3.94 mmol (45% yield).