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Supporting Information

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New Tricks for the Carboxylic Acid. Efficient Synthesis and Resolution of Pyrrolizidines

Renata Marcia de Figueiredo, Roland Fröhlich and Mathias Christmann*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany

christmann@oc.rwth-aachen.de

General

All reactions were carried out under an argon atmosphere in absolute solvents with syringe and Schlenk techniques in oven-dried glassware. THF was distilled under argon from lead/sodium in the presence of benzophenone. Bulk solvents for chromatography and extraction were distilled prior to use. Reagents were obtained from commercial sources and used without further purification unless otherwise stated. TLC was performed on E. Merck precoated plates (SiO_2 60 F_{254}, layer thickness 0.2 mm), and chromatography was performed with E. Merck SiO_2 60 (0.040–0.063 mm) in the flash mode with a nitrogen pressure of 0.2 bar.

Melting points were determined with a Büchi 510 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300, a Varian Mercury 300, a Varian Inova 400 and a Varian Unity 500 instrument. ^{1}H chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet at 7.26 ppm for *d*-chloroform (residual $CHCl_3$) and the singlet (0.00 ppm) for TMS. ^{13}C Chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for *d*-chloroform. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; m, multiplet; and l, large and combinations thereof. Coupling constants are recorded in Hertz (Hz). IR spectra were recorded neat on a Perkin-Elmer PE 1759 FT instrument; absorptions are given in wavenumbers (cm^{-1}). Low resolutions mass spectra were recorded on a Varian MAT 212 S instrument using either electron impact ionisation (EI, 70 eV), or chemical ionisation (CI, CH_4, isobutane or NH_3). High resolution mass spectra were recorded either on a Varian MAT 95 mass spectrometer or on a Micromass LCT Spectrometer (ESI, TOF). Optical rotations were measured with a Perkin-Elmer model 241 polarimeter in a 1-dm cell and the sodium D line (589 nm) at the temperature, solvent, and concentration indicated using solvents of Merck UVASOL-quality. Elemental analyses were performed by the Microanalytical Laboratory of the Institute of Organic Chemistry.

Data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods in Enzymology*, **1997**, *276*, 307-326), absorption correction Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Cryst.* **2003**, *A59*, 228-234), structure solution SHELXS-97 (G.M. Sheldrick, *Acta Cryst.* **1990**, *A46*, 467-473), structure refinement SHELXL-97 (G.M. Sheldrick, Universität Göttingen, 1997), graphics SCHAKAL (E. Keller, Universität Freiburg, 1997).

CCDC 623489 and 632725 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk].

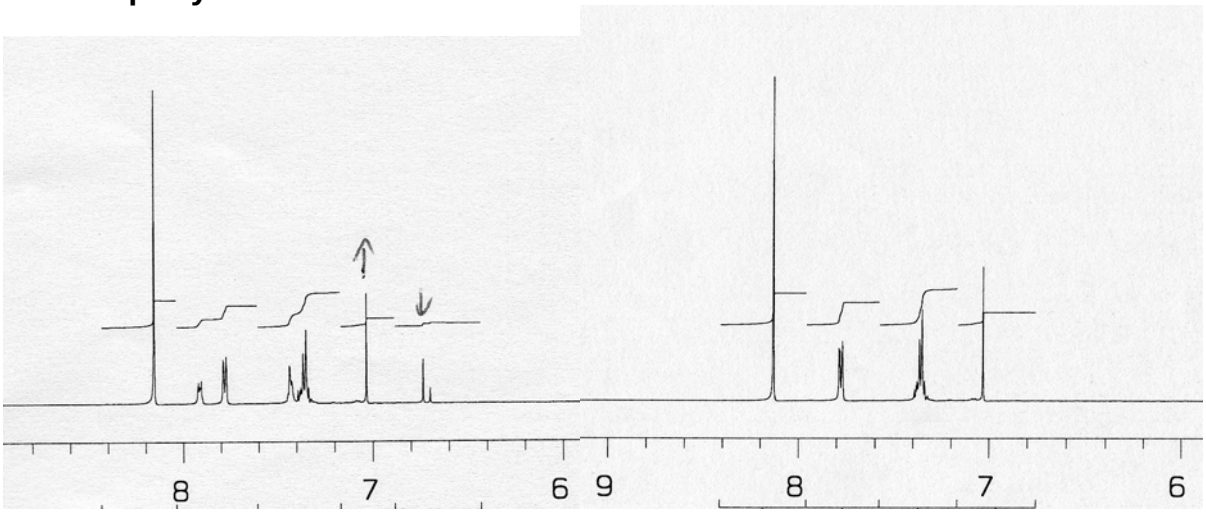
General procedure for the cyclization of maleimidoalkanoic acids (in NMR solvents)

To a suspension of pre-**7d** (131 mg, 0.51 mmol) in $CDCl_3$ (1,3 mL) is added Et_3N (180 mg, 1.78 mmol) upon which the solution became clear. After completed formation of the amide (NMR analysis), TBSOTf (402 mg, 1.52 mmol) is slowly added with a syringe. At the end of the addition the solution has turned red brown and it further darkens as the reaction proceeds. After 3 h, the reaction is diluted with $CDCl_3$ (10 mL) and extracted with 1N HCl (in order to remove the Et_3N). The aqueous layer is back extracted with 10 mL $CDCl_3$. The combined organic layers are dried (Na_2SO_4), filtered and evaporated in vacuo. The solid residue is suspended in d^4-MeOH (10 mL) and a catalytic amount of K_2CO_3 is added. As the reaction proceeds, a clear solution is obtained. After completion (NMR), solvent is evaporated in vacuo. The residue is portioned between 1N HCl and $CDCl_3$ (10 mL each). The layers are separated and the organic layer is dried (Na_2SO_4). From this solution, a crude NMR was obtained (see next page). The crude products can be further purified by flash chromatography (EtOAc/pentane 1:1). In large scale, these reactions were carried out in undeuterated solvents.

General Procedure for the Oxa-Michael lactonization

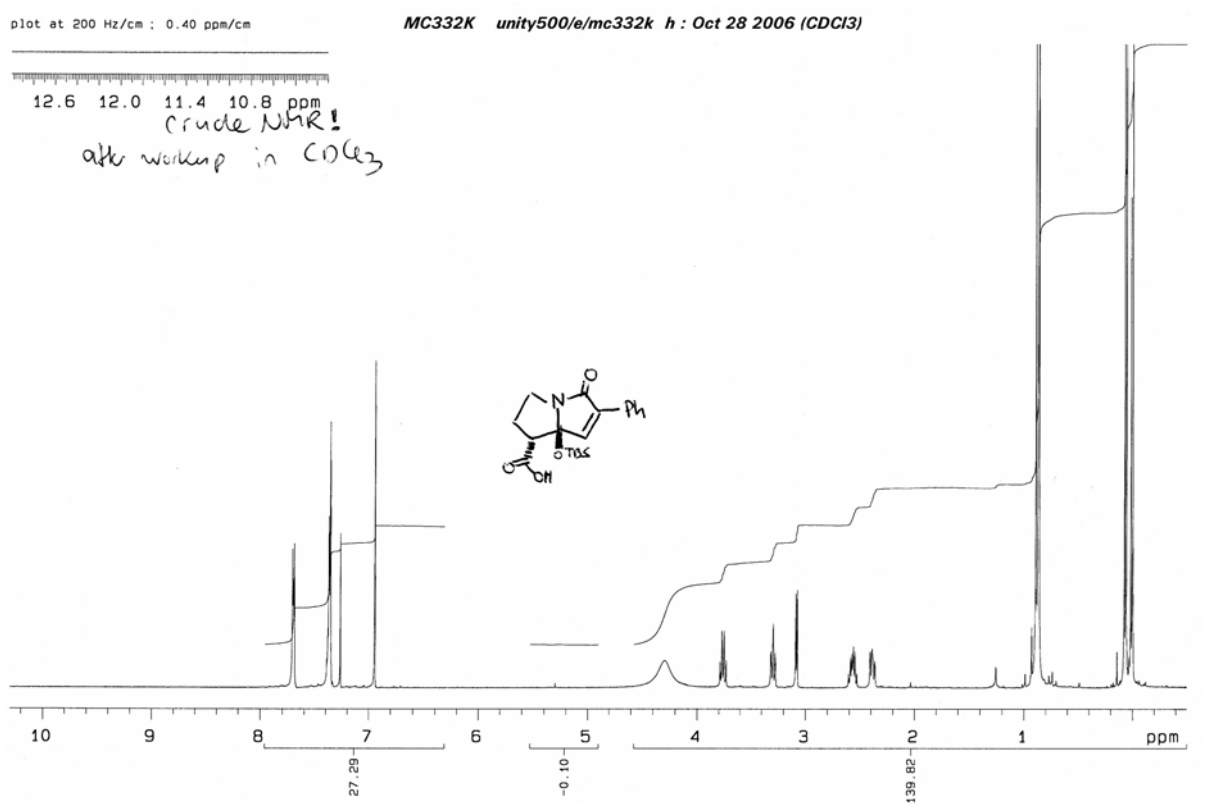
A solution of acid (±)-**7b** (20 mmol) and the cinchona alkaloid (10 mmol) in the appropriate solvent (15 mL) are stirred for the time indicated in table 1. The reaction progress can be monitored by removing a small sample, evaporating the solvent and taking an NMR in $CDCl_3$. Upon desired conversion, the reaction mixture is extracted with 0.1M HCl. The organic layer is dried, filtered and evaporated in vacuo to give a solid residue. This material is triturated in hot pentane. This procedure is eventually repeated once. The residue consists of the racemic starting material (±)-**7b**. The pentane solution is evaporated to give the lactone **9** and enantiopure acid **7b**, which are easily separated by a short column (ethyl acetate/pentane 1:1→ethyl acetate).

First step: Cyclization



after 15 min **after 3 h**

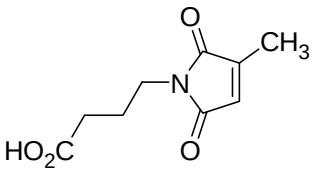
Second step: hydrolysis



Synthesis of the cyclization precursors

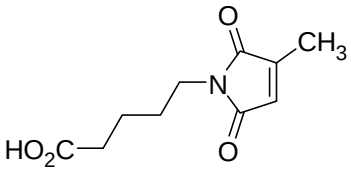
The maleimide carboxylic acid precursors (pre-**7x**) for the TBSOTf-mediated cyclization were synthesized according to the procedure of Rich et al.[1] and – unless described in the literature – completely characterized.

4-(3-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoic acid (pre-7b)



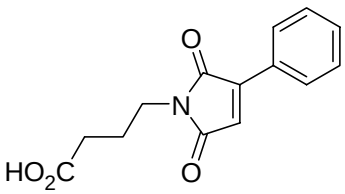
Colorless solid; mp 61-64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (q, J = 1.8 Hz, 1H), 3.55 (t, J = 6.7 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 2.06 (d, J = 2.1 Hz, 3H), 1.90 (qn, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 171.8, 170.9, 145.7, 127.2, 36.9, 31.1, 23.6, 10.9; IR 1709, 1446, 1288, 1215, 926, 871, 750, 713 cm^{-1}; MS (EI) 197 (M^+, 30), 179 (53), 151 (25), 138 (59), 137 (33), 124 (100); Anal calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10; Found: C, 54.74; H, 5.61; N, 7.01.

5-(3-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)pentanoic acid (pre-7c)



Colorless solid; mp 51-54 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (q, J = 1.8 Hz, 1H), 3.49 (t, J = 6.4 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), 2.05 (d, J = 1.8 Hz, 3H), 1.66-1.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 171.8, 170.9, 145.5, 127.2, 37.3, 33.3, 27.8, 21.6, 10.9; IR (KBr) 3099, 2946, 1707, 1444, 1407, 1256, 1209, 1043, 908, 871 cm^{-1}; MS (EI) 211 ([M]$^+$, 34), 193 (20), 165 (34), 137 (21), 124 (100), 96 (18); Anal calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63; Found: C, 56.85; H, 6.01; N, 6.59.

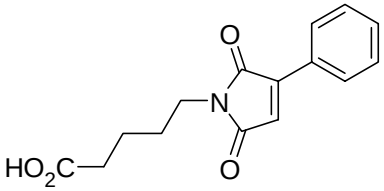
4-(2,5-dioxo-3-phenyl-2,5-dihydro-1*H*-pyrrol-1-yl)butanoic acid (pre-7d)



Colorless solid; mp 129-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.89 (m, 2H), 7.47-7.38 (m, 3H), 6.74 (s, 1H), 3.64 (t, J = 6.7 Hz, 2H), 2.38 (t, J = 7.3 Hz, 2H), 1.95 (qn, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 170.6, 170.4, 143.7, 131.1, 128.9 (2C), 128.6 (3C), 123.6, 37.0, 31.2, 23.5; IR 1702, 1610, 1445, 1407, 1288, 791 cm^{-1}; MS (EI) 259 (M^+, 24), 85 (98), 83 (89), 69 (100), 55 (93); Anal calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40; Found: C, 65.11; H, 4.96; N, 5.40.

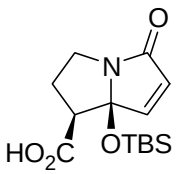
[1] D. H. Rich, P. D. Gesellchen, A. Tong, A. Cheung, C. K. Buckner, *J. Med. Chem.* **1975**, *18*, 1004.

5-(2,5-dioxo-3-phenyl-2,5-dihydro-1*H*-pyrrol-1-yl)pentanoic acid (pre-7f)



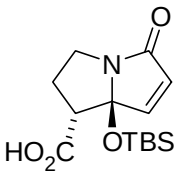
Colorless solid; mp 99-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.88 (m, 2H), 7.48-7.43 (m, 3H), 6.73 (s, 1H), 3.64-3.56 (m, 2H), 2.44-2.36 (m, 2H), 1.75-1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 170.5, 170.3, 143.6, 131.0, 128.8 (2C), 128.6, 128.5 (2C), 123.7, 37.5, 33.4, 28.0, 21.8; IR (KBr) 1702, 1443, 1408, 1250, 794 cm^{-1}; MS (EI) 273 (M^+, 14), 181 (71), 153 (45), 109 (42), 105 (100), 55 (26); Anal calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13 Found: C, 65.98; H, 5.47; N, 5.01.

(1*S*,7a*S*)-7a-(*tert*-butyldimethylsilyloxy)-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylic acid (7a)



Colorless solid; mp 58-61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 5.8 Hz, 1H), 6.02 (d, J = 5.8 Hz, 1H), 3.55-3,48 (m, 1H), 3.39-3.33 (m, 1H), 2.90-2.80 (m, 1H), 2.60 (dd, J = 11.9, 7.3 Hz, 1H), 2.48-2.41 (m, 1H), 0.83 (s, 9H), 0.08 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 173.3, 150.4, 126.8, 98.5, 52.0, 41.0, 39.4, 25.3 (3C), 17.9, -3.6, -4.2; IR (KBr) 2937, 2861, 1733, 1670, 1381, 1344, 1143, 836 cm^{-1}; MS (EI) 297 (M^+, 1), 282 ([M-CH_3]$^+$, 1) 240 ([M-*t*Bu]$^+$, 100), 196 (39), 166 ([M-TBSO]$^+$, 4), 75 (51); Anal calcd for $C_{14}H_{23}NO_4Si$: C, 56.54; H, 7.79; N, 4.71; Found: C, 56.91; H, 7.96; N, 4.72

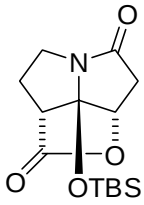
(1*R*,7a*S*)-7a-(*tert*-butyldimethylsilyloxy)-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylic acid (7b)



This compound has been described previously.[2]

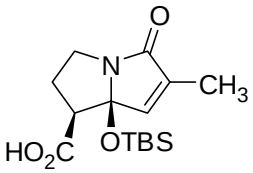
[2] T. H. Lambert, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 426.

(2a*R*,2a^1*R*,7a*S*)-2a^1-(*tert*-butyldimethylsilyloxy)tetrahydrofuro[4,3,2-*gh*]pyrrolizine-2,6(2a*H*,2a^1*H*)-dione (9)



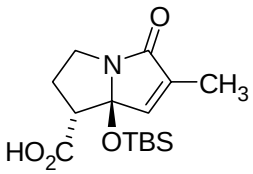
Colorless solid; mp 100-103 °C; R_f 0.41 (pentane/EtOAc 4:1); $[\alpha]^{23}_D$ –26.1 (*c* 1.13 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (d, *J* = 4.4 Hz, 1H), 3.81 (dddd, *J* = 2.5, 6.6, 9.0, 15.7 Hz, 1H), 3.23 (m, 1H), 3.16 (dd, *J* = 2.2, 8.2 Hz, 1H), 3.01 (d, *J* = 4.4 Hz, 1H), 2.55 (d, *J* = 17.8 Hz, 1H), 2.47 (m, 2H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 173.6, 102.7, 80.5, 49.7, 42.8, 38.6, 29.8, 25.4 (3C), 17.8, –3.4, –3.7; IR ($CHCl_3$) 2953, 2858, 1785, 1719, 1363, 1328, 1135, 1032, 839, 777 cm^{-1}; MS (EI): m/z (%) 438 ([M^+– 57], 100), 75 (19); HRMS calcd for $C_{10}H_{14}NO_4Si$ (M^+–57), 240.06921; found, 240.06921.

(1*S*,7a*S*)-7a-(*tert*-butyldimethylsilyloxy)-6-methyl-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylic acid (10a)



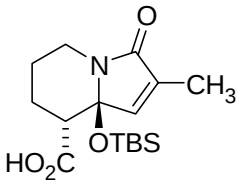
Colorless solid; mp 88-91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (q, *J* = 1.5 Hz, 1H), 3.52-3.45 (m, 1H), 3.39-3.33 (m, 1H), 2.88-2.77 (m, 1H), 2.61 (dd, *J* = 12.2, 7.3 Hz, 1H), 2.44-2.37 (m, 1H), 1.86 (d, *J* = 1.8 Hz, 3H), 0.82 (s, 9H), 0.04 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 174.3, 143.1, 135.4, 96.7, 52.3, 41.1, 29.2, 25.4, 17.9, 10.7, -3.6, -4.2; IR (KBr) 1705, 1131, 1074, 841, 779 cm^{-1}; MS (EI) 311 (M^+, 2), 254 ([M-*t*Bu]$^+$, 100), 210 (51), 180 ([M-TBSO]$^+$, 6), 136 (15), 75 (50); Anal calcd for $C_{15}H_{25}NO_4Si$: C, 57.85; H, 8.09; N, 4.50; Found: C, 57.85; H, 7.89; N, 4.42.

(1*R*,7a*S*)-7a-(*tert*-butyldimethylsiloxy)-6-methyl-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylic acid (10b)



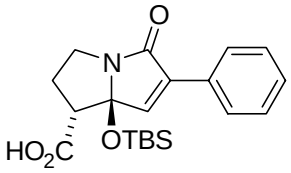
Colorless solid; mp 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (q, *J* = 1.6 Hz, 1H), 3.76-3.66 (m, 1H), 3.30-3.22 (m, 1H), 3.06 (d, *J* = 6.6 Hz, 1H), 2.64-2.53 (m, 1H), 2.50-2.42 (m, 1H), 1.80 (d, *J* = 1.6 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), –0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 174.3, 140.2, 136.7, 98.7, 52.5, 41.9, 31.0, 25.5 (3C), 17.9, 10.7, –3.4, –4.0; IR (KBr) 2953, 2860, 1739, 1676, 1473, 1440, 1411, 1382, 1254, 1093, 839 cm^{-1}; MS (EI) 311 (M^+, 2), 296 ([M-CH_3]$^+$, 1), 254 [M-*t*Bu]$^+$, 100), 236 (50), 210 (42), 75 (51); Anal calcd for $C_{15}H_{25}NO_4Si$: C, 57.85; H, 8.09; N, 4.50; Found: C, 57.88; H, 7.99; N, 4.46.

(8*R*,8a*S*)-8a-(*tert*-butyldimethylsiloxy)-2-methyl-3-oxo-3,5,6,7,8,8a-hexahydroindolizine-8-carboxylic acid (10c)



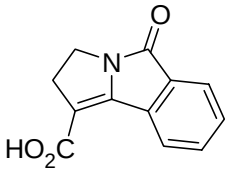
Colorless solid; mp 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (q, J = 1.7 Hz, 1H), 4.07 (dd, J = 11.7, 5.5 Hz, 1H), 2.99-2.87 (m, 2H), 2.22-2.11 (m, 1H), 1.96-1.88 (m, 2H) 1.86 (d, J = 1.7 Hz, 3H), 1.54-1.46 (m, 1H), 0.88 (s, 9H), 0.01 (s, 3H), –0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 168.0, 139.7, 136.9, 86.5, 48.6, 35.7, 25.7 (3C), 22.0, 19.6, 18.2, 10.8, –2.6, –3.8; IR (KBr) 3280, 2935, 2859, 1734, 1685, 1651, 1437, 1060, 837, 670 cm^{-1}; MS (EI) 325 (M^+, 5), 310 ([M-CH_3]$^+$, 2), 268 [M-*t*Bu]$^+$, 97), 250 (91), 224 (70), 176 (46), 75 (100); Anal calcd for $C_{16}H_{27}NO_4Si$: C, 59.04; H, 8.36; N, 4.30; Found: C, 58.80; H, 8.19; N, 4.14.

(1*R*,7a*S*)-7a-(*tert*-butyldimethylsilyloxy)-5-oxo-6-phenyl-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylic acid (**10d**)



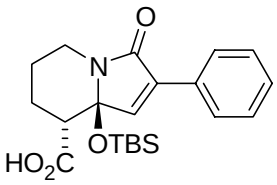
Colorless solid; mp 170-172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.67 (m, 2H), 7.38-7.33 (m, 3H), 6.93 (s, 1H), 3.76 (q, J = 9.1 Hz, 1H), 3.29 (t, J = 9.4 Hz, 1H), 3.08 (d, J = 6.1 Hz, 1H), 2.61-2.52 (m, 1H), 2.41-2.34 (m, 1H), 0.86 (s, 9H), 0.05 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 172.4, 139.1, 137.7, 130.4 (d, J = 2.1 Hz), 129.2, 128.5 (2C), 127.6 (2C), 97.9, 52.6, 42.1, 30.7, 25.5 (3C), 17.8, -3.3, -4.1; IR (KBr) 2939, 2860, 1735, 1667, 1623, 1385, 1255, 1197, 1091, 911, 840, 786, 686 cm^{-1}; MS (EI) 373 (M^+, 1), 358 ([M-CH_3]$^+$, 2), 316 ([M-*t*Bu]$^+$, 100), 75 (89); EA Anal calcd for $C_{20}H_{27}NO_4Si$: C, 64.31; H, 7.29; N, 3.75; Found: C, 64.33; H, 7.47; N, 3.68.

5-oxo-3,5-dihydro-2*H*-pyrrolo[2,1-a]isoindole-1-carboxilic acid (10e)



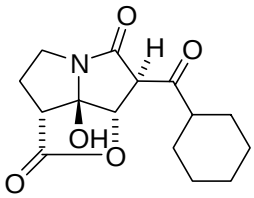
Colorless solid; mp 229-231 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (sb, 1H), 8.56 (d, J = 8.55 Hz, 1H), 7.74-7.88 (m, 3H), 3.95 (t, J = 8.24 Hz, 2H), 3.33 (t, J = 8.24 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 162.7, 147.5, 136.0, 132.4, 131.7, 129.8, 126.6, 123.2, 111.9, 40.1, 34.5; IR (KBr) 1723, 1621, 1450, 1312, 1268, 1222, 750, 687 cm^{-1}; MS (EI) 215 (M^+, 100), 170 ([M-CO_2H]$^+$, 75), 142 (16), 115 (21); Anal calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51; Found: C, 66.77; H, 4.59; N, 6.48.

(8*R*,8a*S*)-8a-(*tert*-butyldimethylsilyloxy)-3-oxo-2-phenyl-3,5,6,7,8,8a-hexahydroindolizine-8-carboxylic acid (10f)



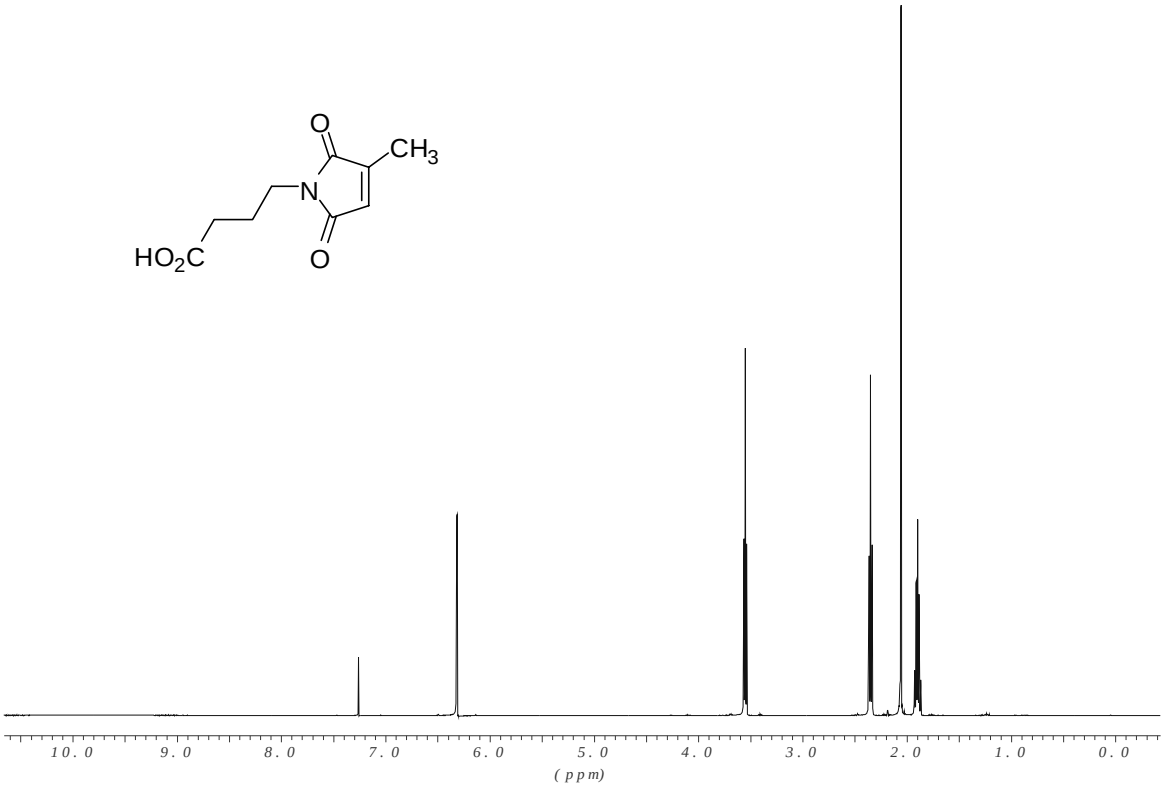
Colorless solid; mp 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.74 (m, 2H), 7.40-7.34 (m, 3H), 6.85 (s, 1H), 4.14 (dd, J = 13.0, 5.4 Hz, 1H), 3.02-2.88 (m, 2H), 2.22-2.12 (m, 1H), 1.92-1.75 (m, 2H), 1.57-1.44 (m, 1H), 0.89 (s, 9H), 0.02 (s, 3H), –0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 166.1, 139.0, 137.6, 130.7, 128.9, 128.4 (2C), 127.5 (2C), 85.8, 48.5, 35.7, 25.7 (3C), 22.0, 19.6, 18.2, –2.4, –3.8; IR (KBr) 2932, 2863, 1739, 1672, 1428, 1164, 1068, 832 cm^{-1}; MS (EI) 387 (M^+, 1), 330 ([M-*t*Bu]$^+$, 19), 312 (12), 286 (16), 255 (19), 211 (48), 182 (18), 75 (100); Anal calcd for $C_{21}H_{29}NO_4Si$: C, 65.08; H, 7.54; N, 3.61; Found: C, 65.15; H, 7.38; N, 3.51.

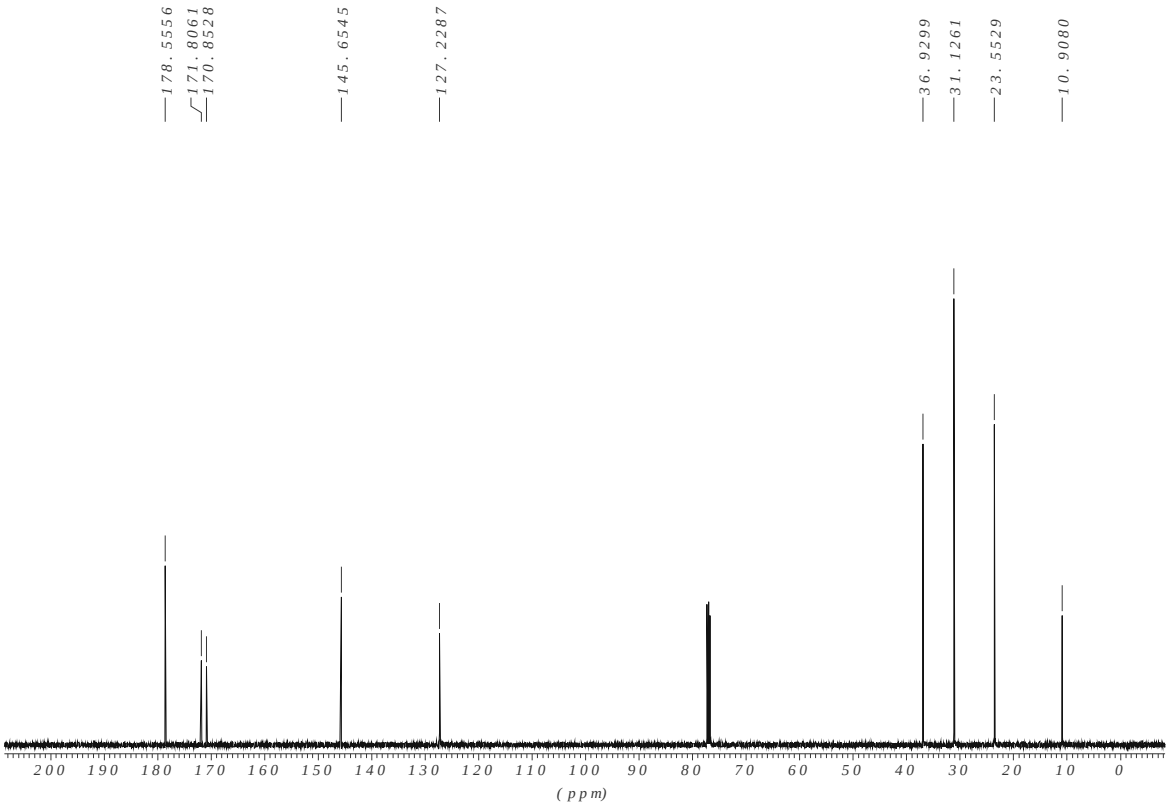
(2a*R*,2a^1*R*,7*R*,7a*S*)-7-(Cyclohexanecarbonyl)-2a^1-hydroxytetrahydrofuro[4,3,2-gh]pyrrolizine-2,6(2a*H*,2a^1*H*)-dione (11)



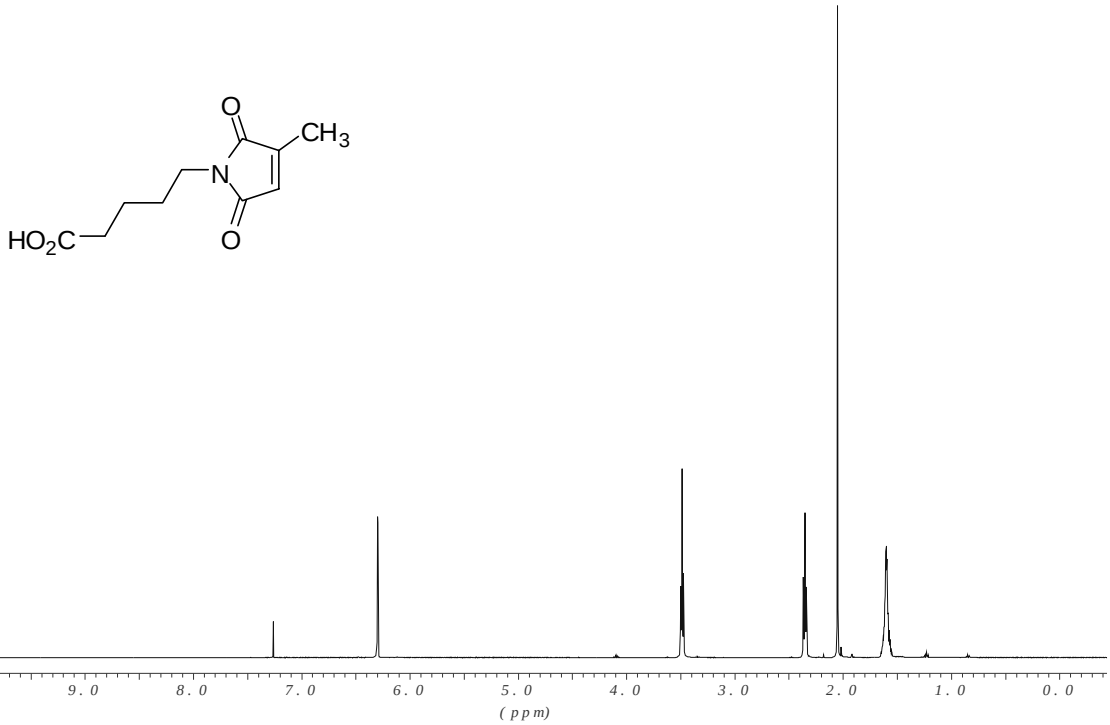
Colorless solid; R_f 0.41 (pentane/EtOAc 1:1); $[\alpha]^{24}_D$ = – 22.2 (*c* 0.90 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (s), 4.73 (s), 4.18 (s), 3.87 (dddd, J = 5.8, 9.2, 11.9, 15.0 Hz), 3.78 (dddd, J = 5.2, 8.9, 11.6, 15.0 Hz), 3.44 (dddd, J = 5.5, 9.8, 12.2, 15.3 Hz), 3.29 (dddd, J = 5.2, 9.8, 12.0, 15.0 Hz), 3.22 (td, J = 1.8, 7.3 Hz), 2.94 (tdd, J = 3.9, 11.3, 15.0 Hz), 2.68 (m), 2.51 (m), 2.00 (m), 1.81 (m), 1.69 (m), 1.27 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 200.3, 174.8, 172.8, 167.1, 166.9, 100.9, 98.8, 83.9, 80.5, 62.7, 51.3, 48.1 (2C), 47.7, 42.6, 41.7, 30.3, 30.0, 29.7, 29.4, 29.1, 28.5, 28.3, 26.9, 25.6 (3C), 25.2, 24.9; IR ($CHCl_3$) 3241, 2929, 2858, 1802, 1722, 1690, 1326, 1309, 1217, 1164, 1042, 758 cm^{-1}; MS (EI): m/z (%) 293 (M^+, 5), 275 (8), 111 (58), 83 (100), 55 (36); HRMS calcd for $C_{15}H_{19}NO_5$ (M^+), 293.12632; found, 293.12632.

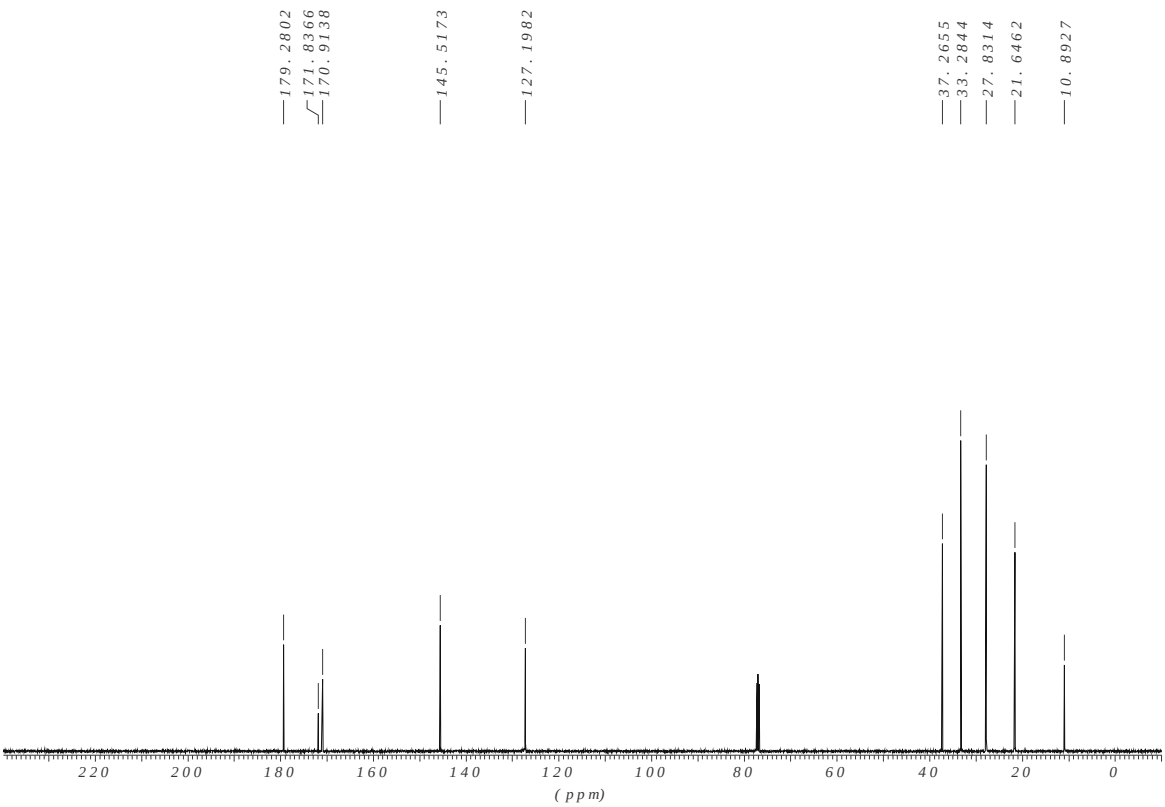
pre-7b


O
CH3
N
HO2C
O
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

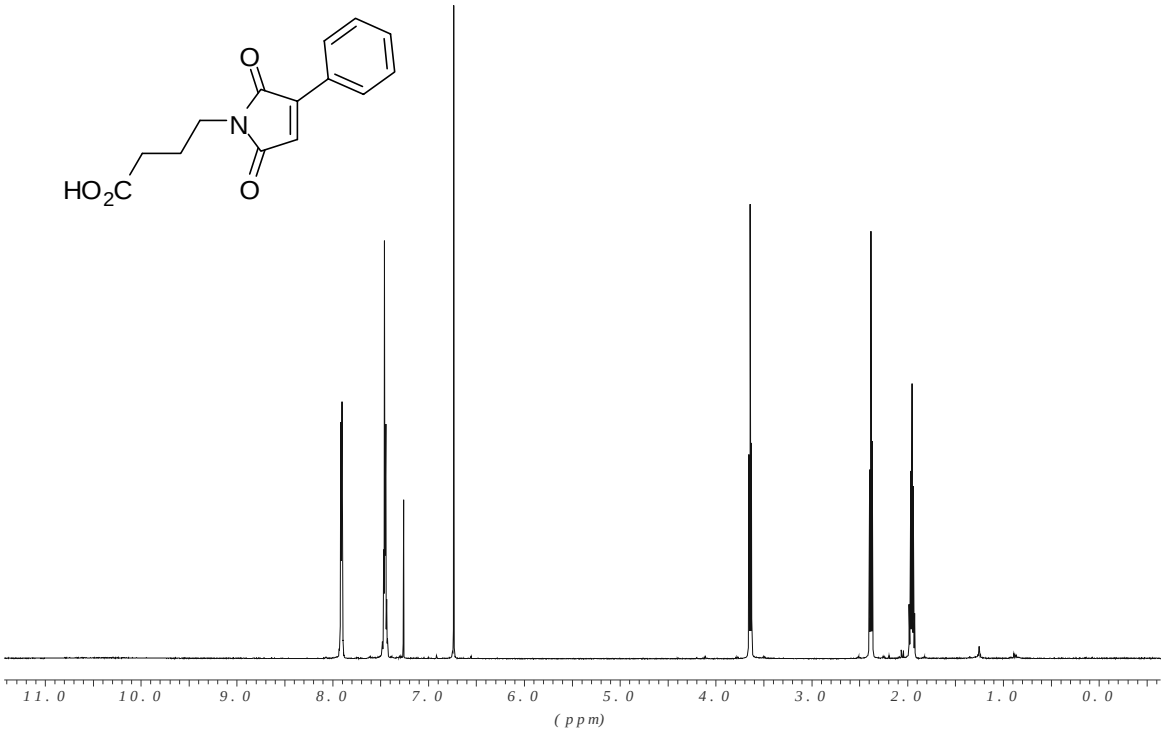

178.5556
171.8061
170.8528
145.6545
127.2287
36.9299
31.1261
23.5529
10.9080
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

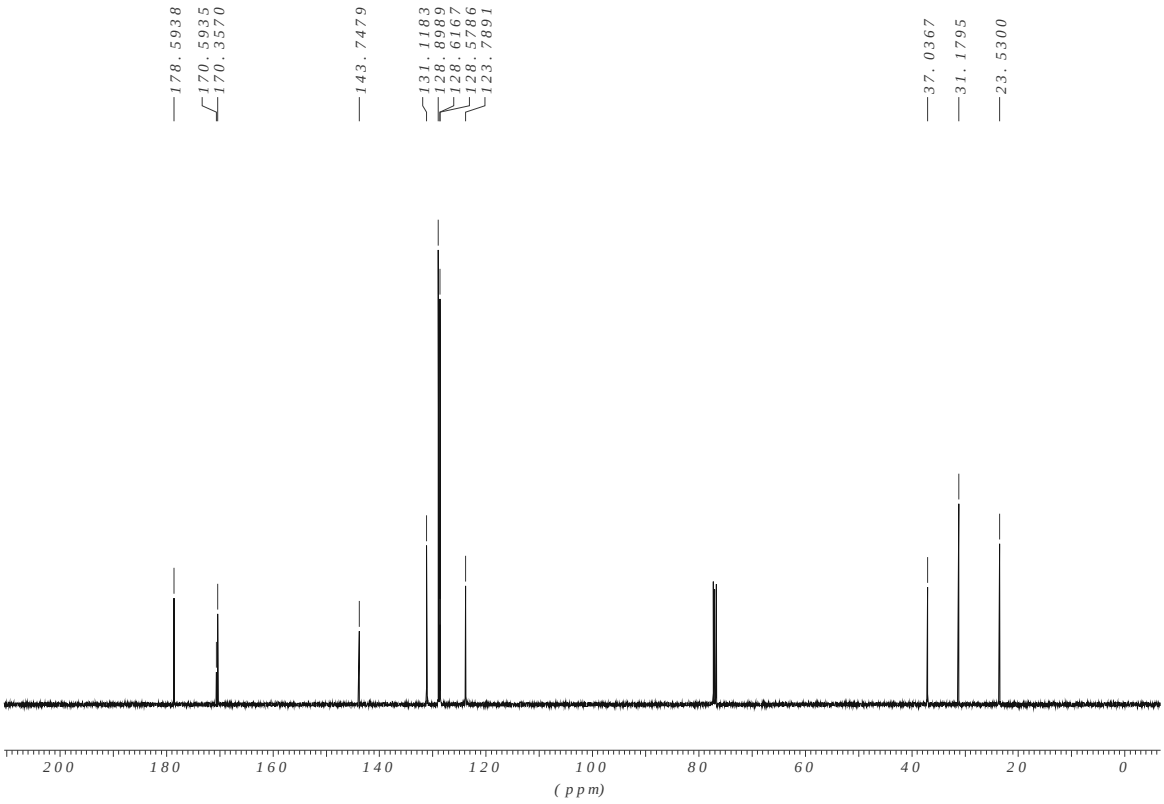
pre-7c


O
CH3
N
HO2C
O
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

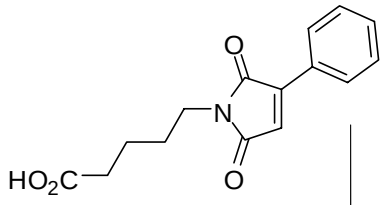

179.2802
171.8366
170.9138
145.5173
127.1982
37.2655
33.2844
27.8314
21.6462
10.8927
220
200
180
160
140
120
100
80
60
40
20
0
(ppm)

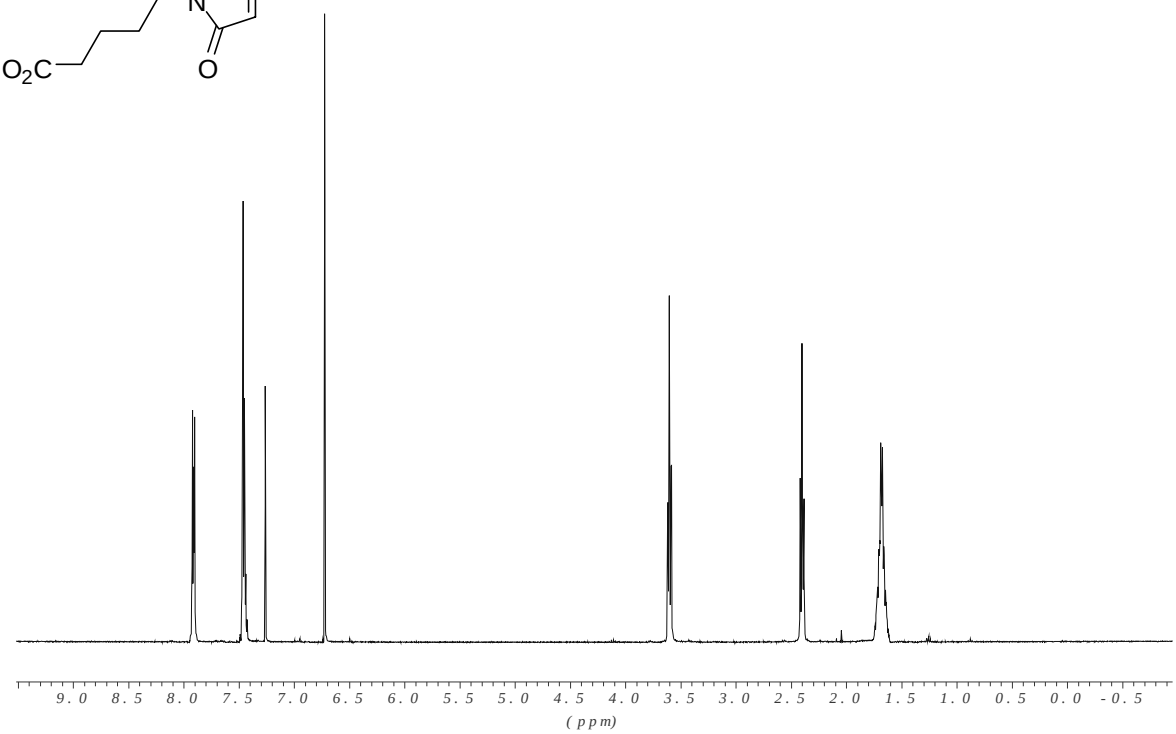
pre-7d


O
N
O
HO2C
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

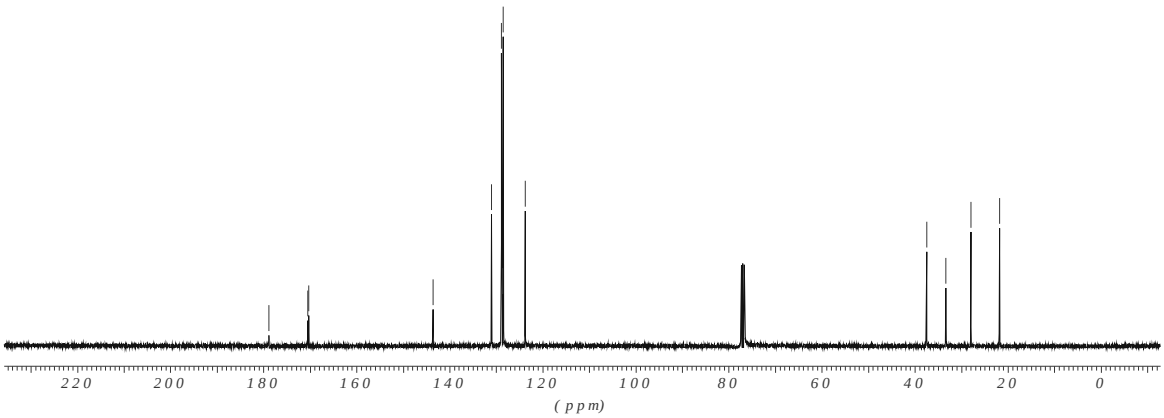

178.5938
170.5935
170.3570
143.7479
131.1183
128.8989
128.6167
128.5786
123.7891
37.0367
31.1795
23.5300
200
180
160
140
120
100
80
60
40
20
0
(ppm)

pre-7f

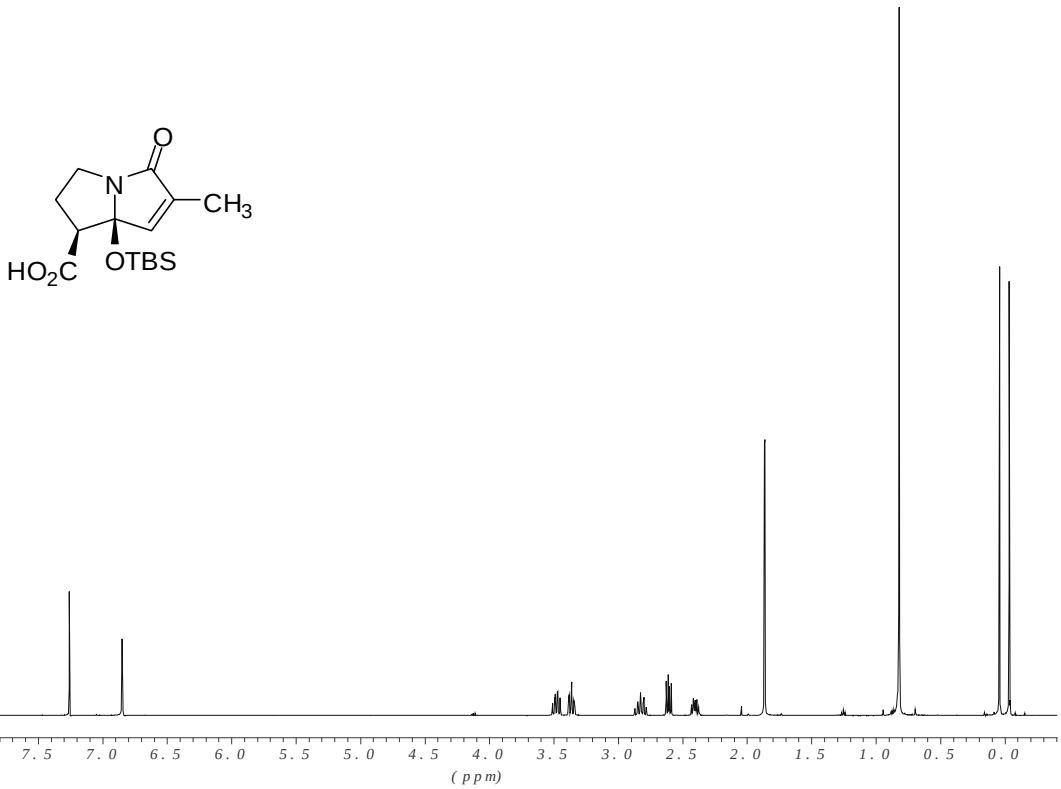


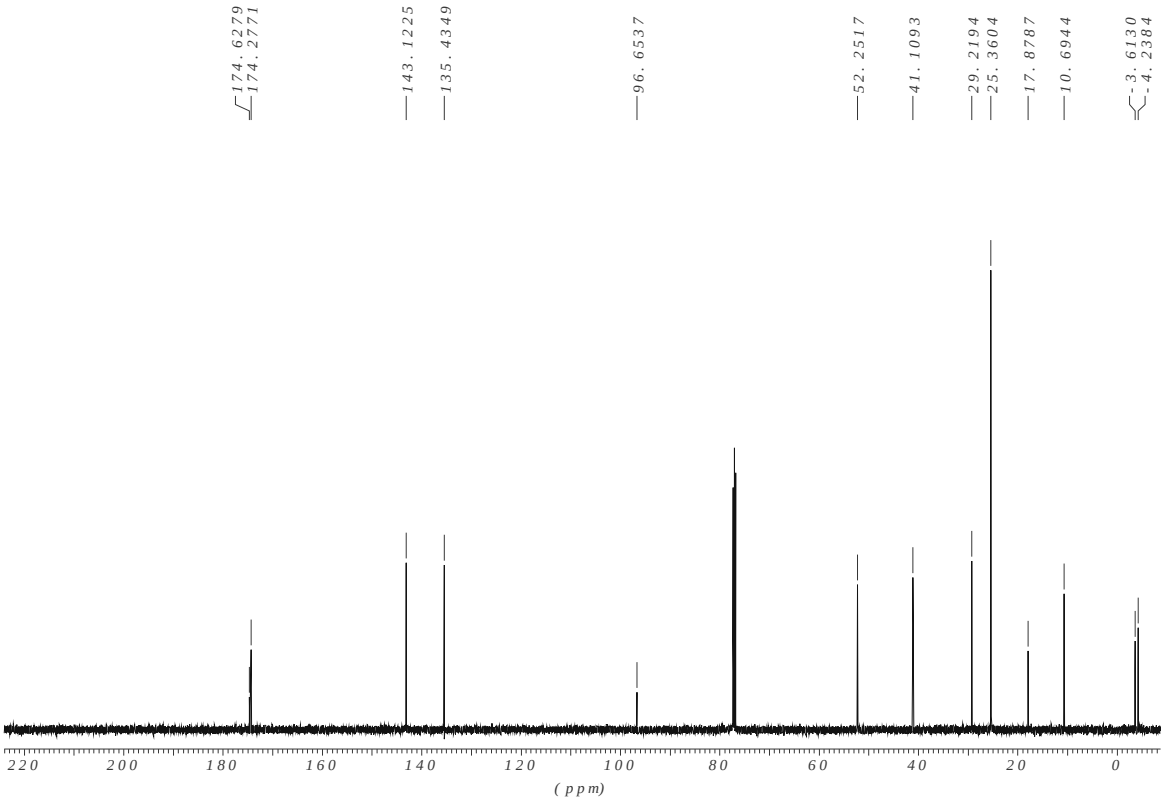


178.8853
170.5181
170.2830
143.6188
131.0111
128.8340
128.6292
128.5078
123.7439
37.4778
33.3663
27.9652
21.8434

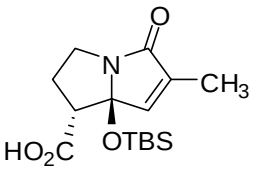


7a

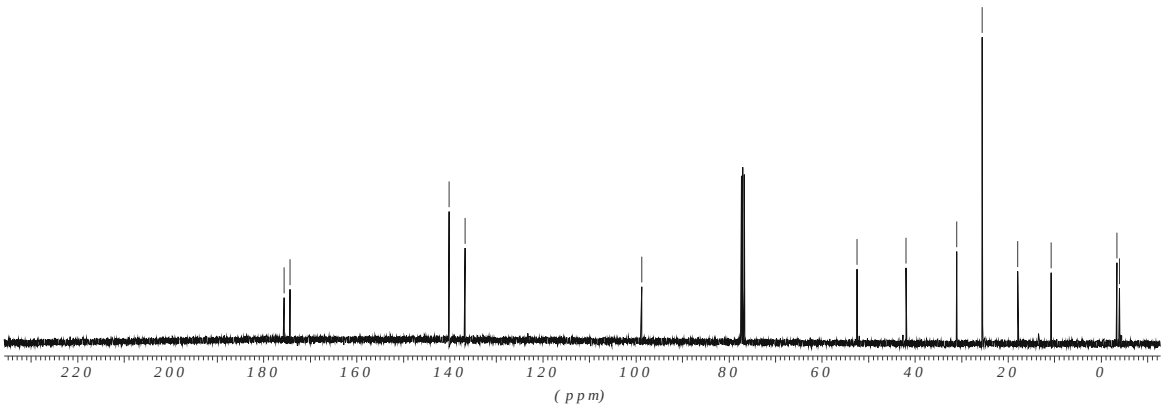

O
N
CH3
HO2C
OTBS
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)


174.6279
174.2771
143.1225
135.4349
96.6537
52.2517
41.1093
29.2194
25.3604
17.8787
10.6944
-3.6130
-4.2384
220 200 180 160 140 120 100 80 60 40 20 0
(ppm)

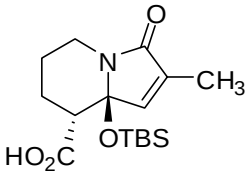
7b



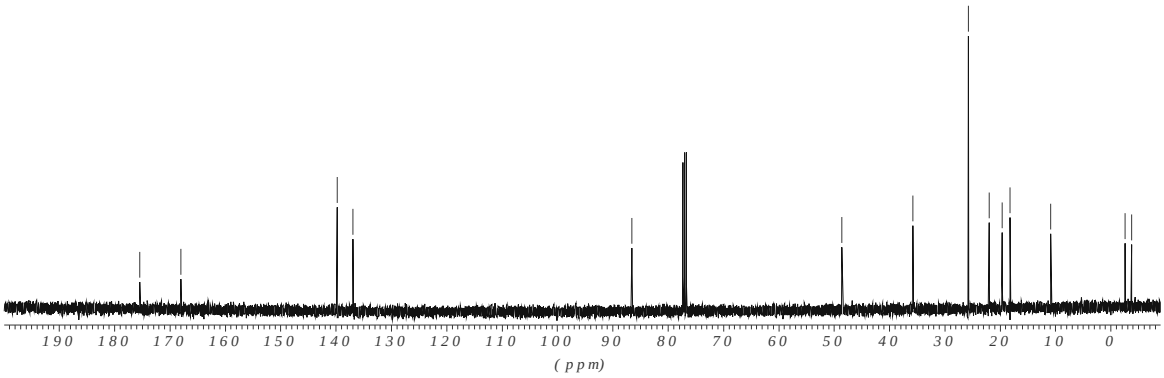
175.5779
174.2959
140.1824
136.7460
98.7562
52.4902
41.9080
31.0375
25.5074
17.8685
10.7529
-3.3719
-3.9939



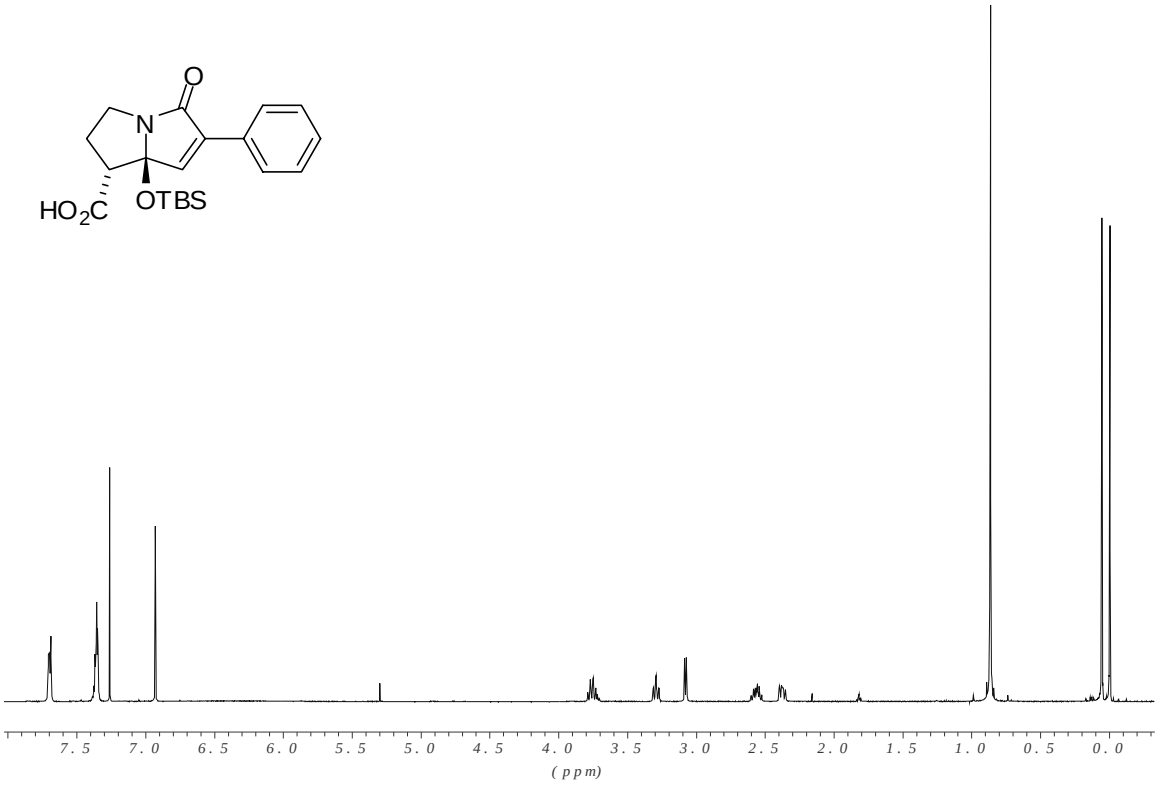
7c

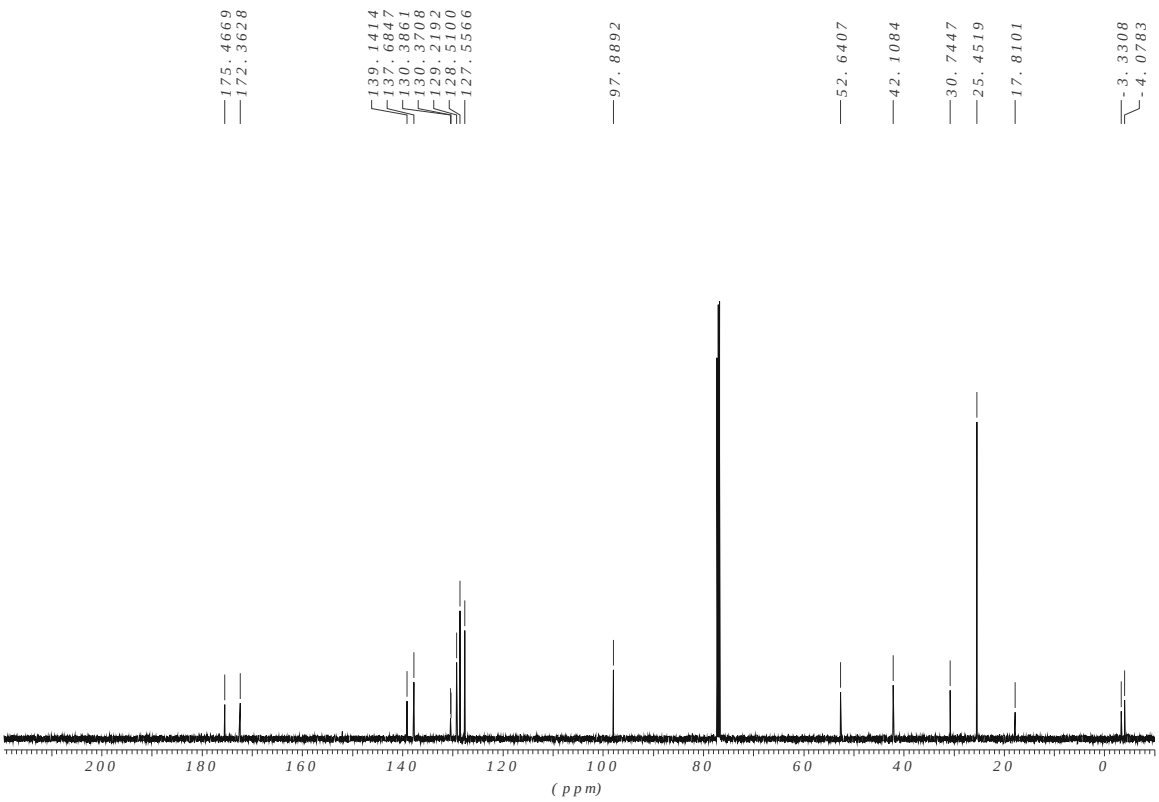


175.4034
167.9769
139.7500
136.8901
86.4975
48.5607
35.7103
25.7425
22.0027
19.6435
18.1795
10.8364
-2.5829
-3.7739

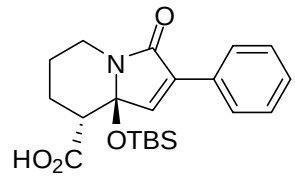


7d

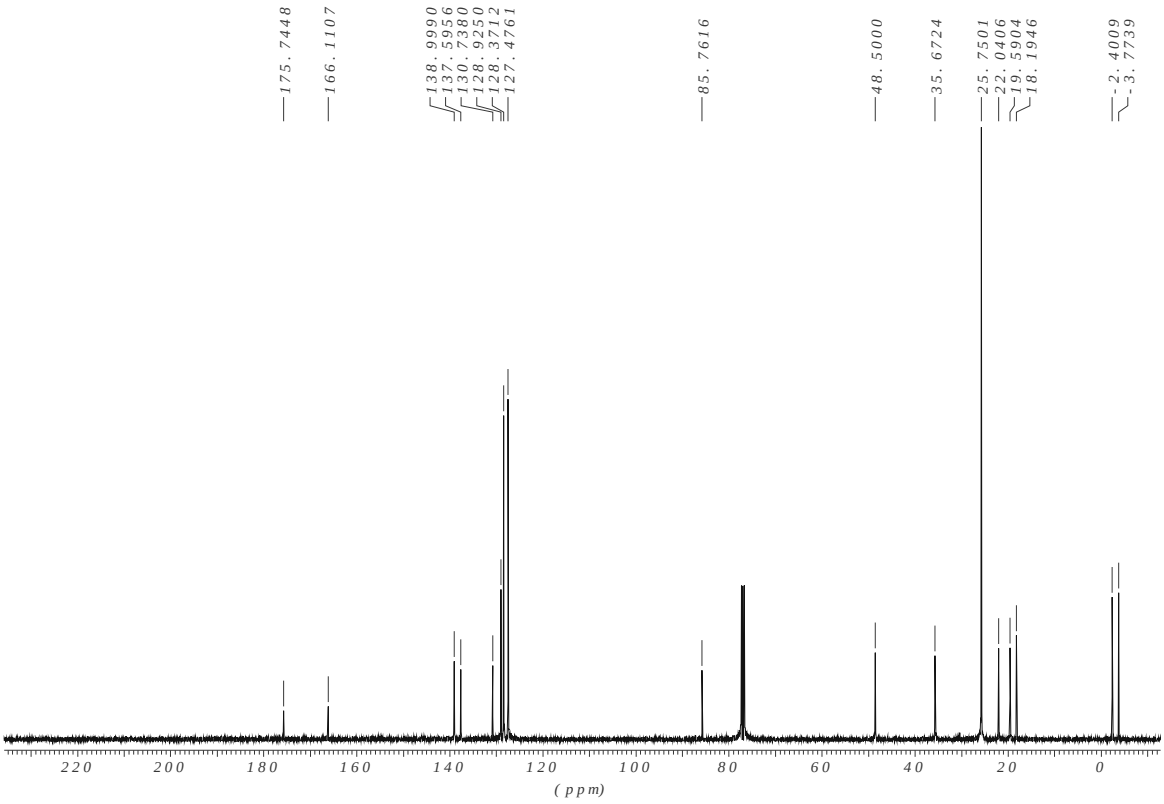

O
N
HO2C
OTBS
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


175.4669
172.3628
139.1414
137.6847
130.3861
130.3708
129.2192
128.5100
127.5566
97.8892
52.6407
42.1084
30.7447
25.4519
17.8101
-3.3308
-4.0783
200
180
160
140
120
100
80
60
40
20
0
(ppm)

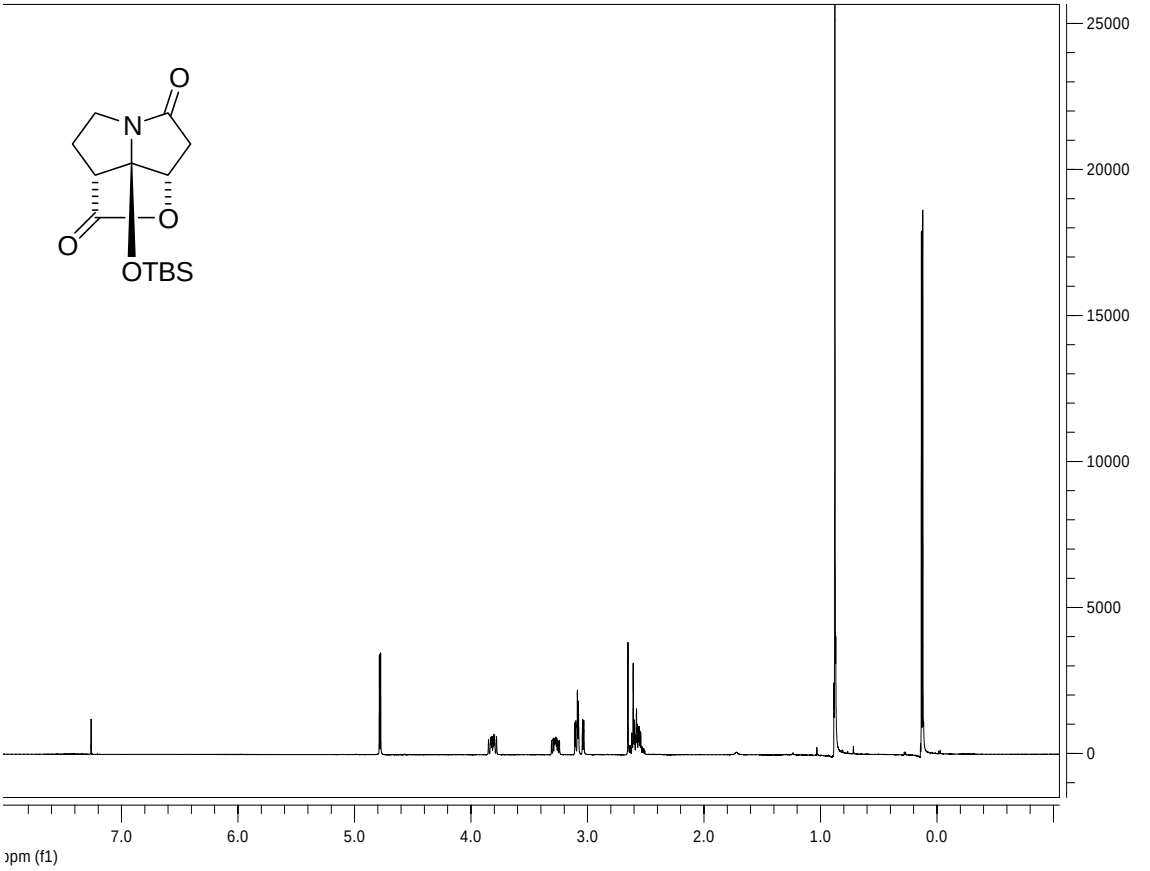
7f

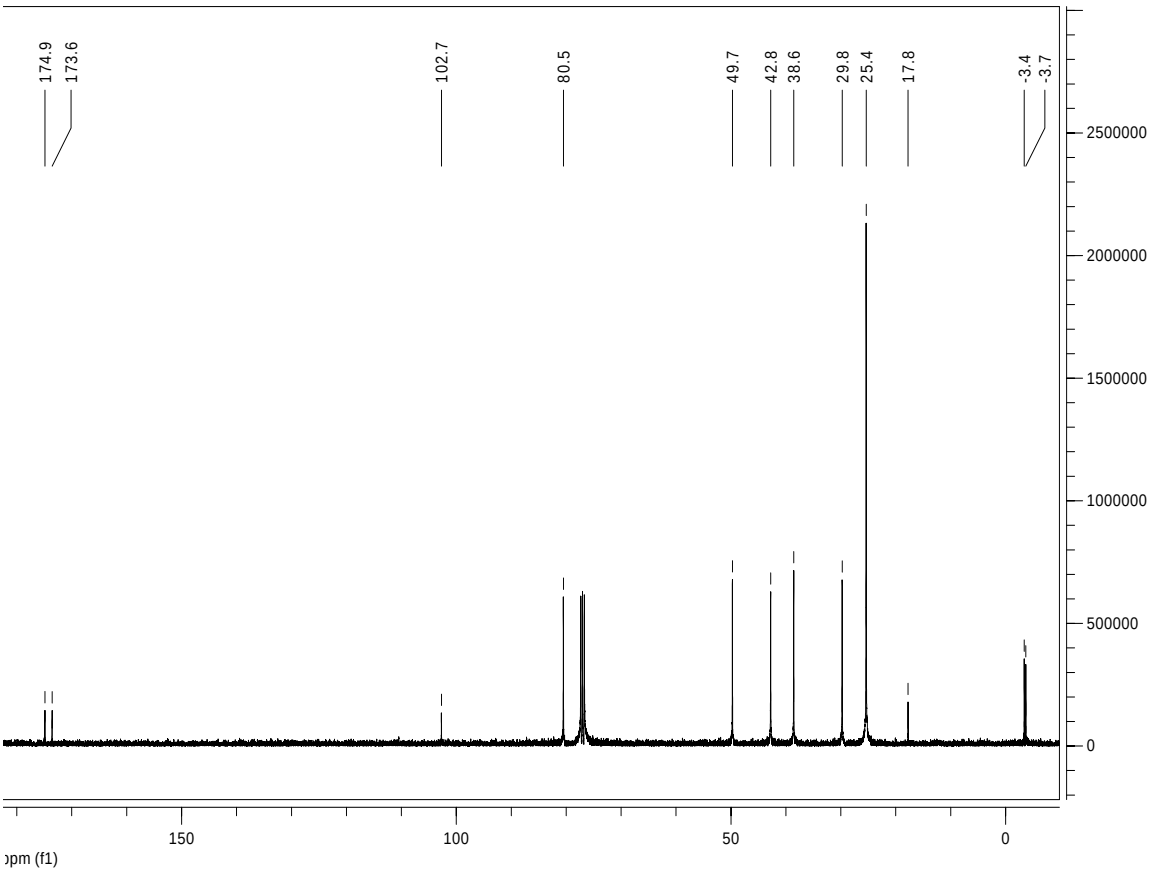

O
N
OTBS
HO2C

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
(ppm)

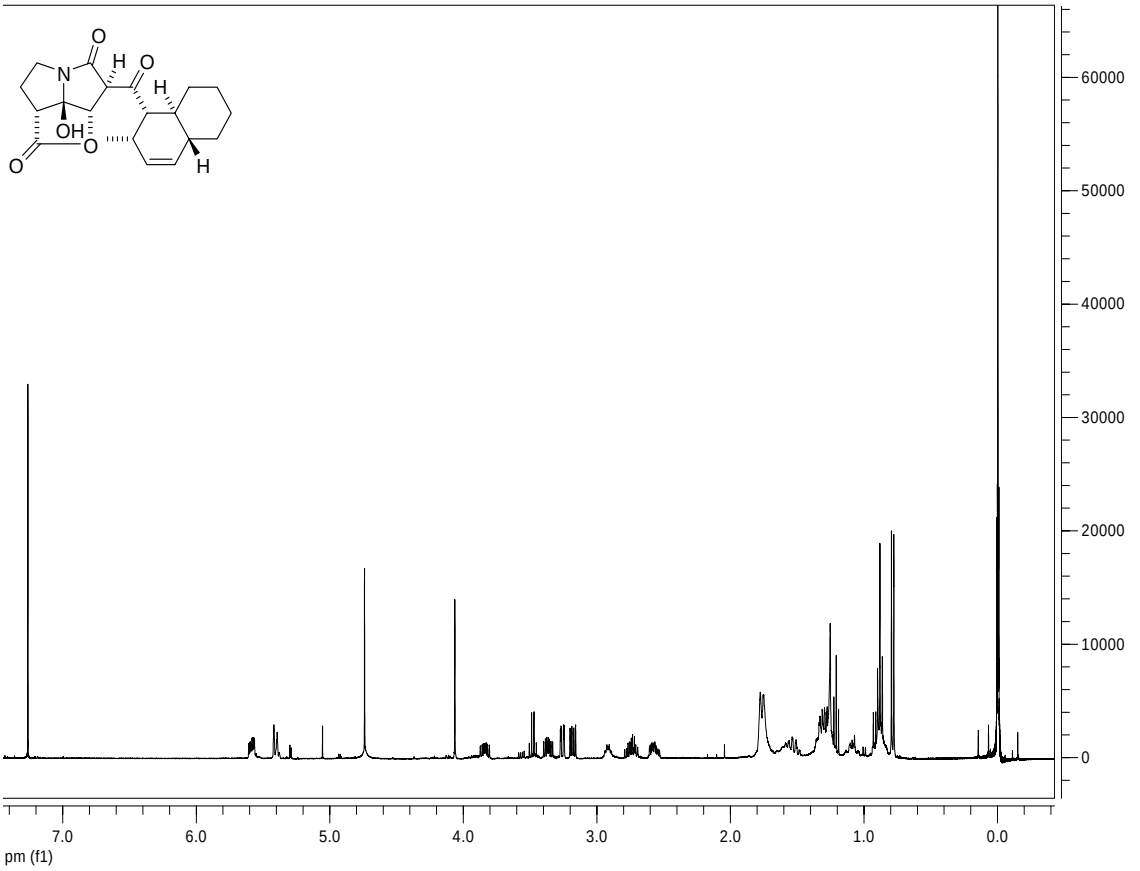

175.7448
166.1107
138.9990
137.5956
130.7380
128.9250
128.3712
127.4761
85.7616
48.5000
35.6724
25.7501
22.0406
19.5904
18.1946
-2.4009
-3.7739
220 200 180 160 140 120 100 80 60 40 20 0
(ppm)

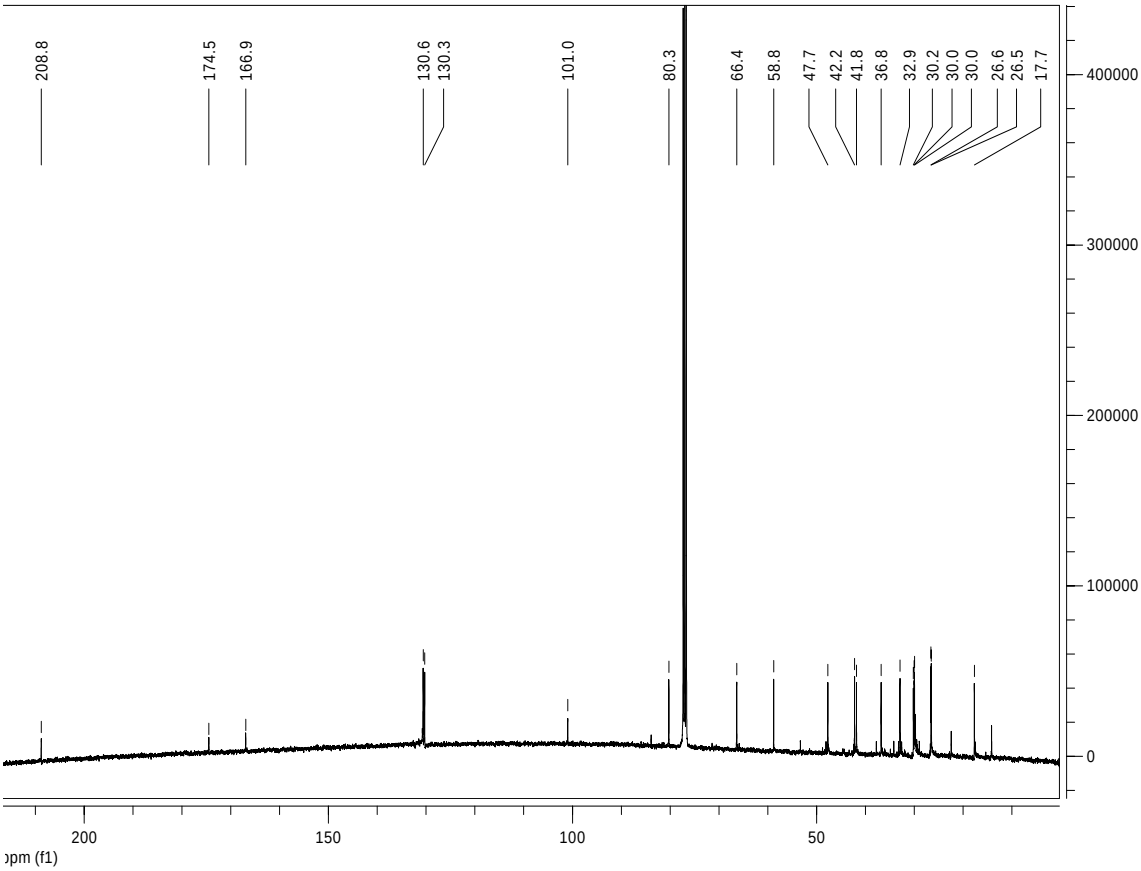
9


O
N
O
O
OTBS
25000
20000
15000
10000
5000
0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

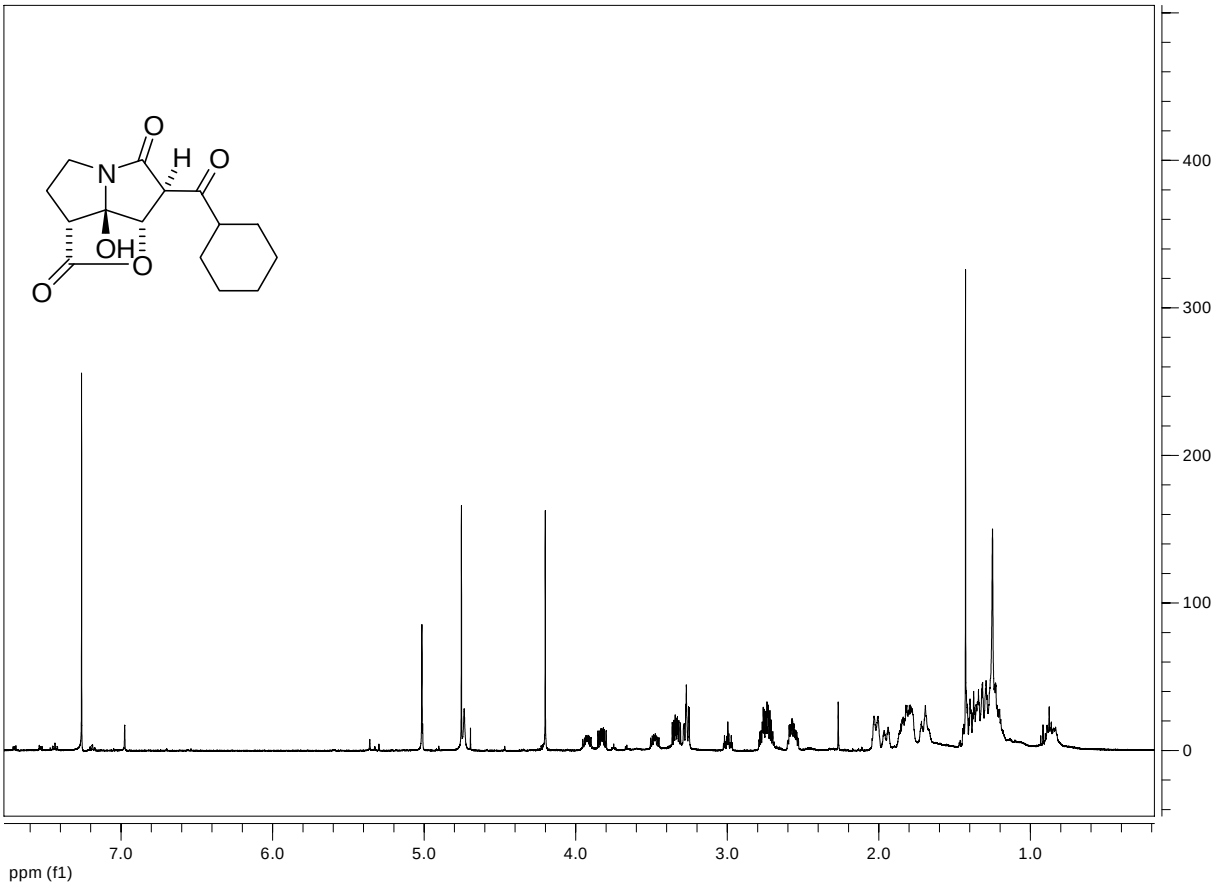

174.9
173.6
102.7
80.5
49.7
42.8
38.6
29.8
25.4
17.8
-3.4
-3.7
2500000
2000000
1500000
1000000
500000
0
150
100
50
0
ppm (f1)

UCS1025A


O
N
H
O
H
OH
O
O
H
60000
50000
40000
30000
20000
10000
0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
pm (f1)


208.8
174.5
166.9
130.6
130.3
101.0
80.3
66.4
58.8
47.7
42.2
41.8
36.8
32.9
30.2
30.0
30.0
26.6
26.5
17.7
400000
300000
200000
100000
0
200
150
100
50
ppm (f1)

11


O
N
H
O
OH
O
O
400
300
200
100
0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

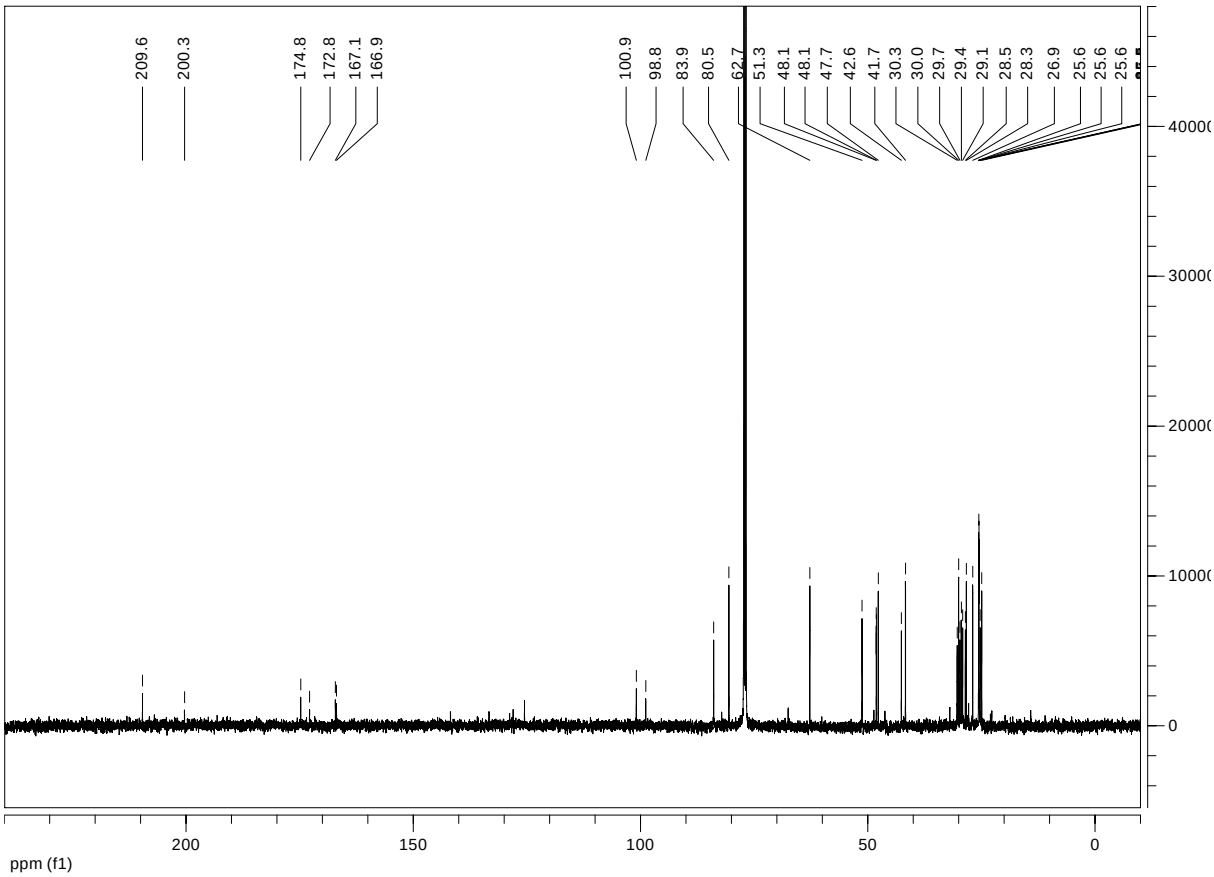
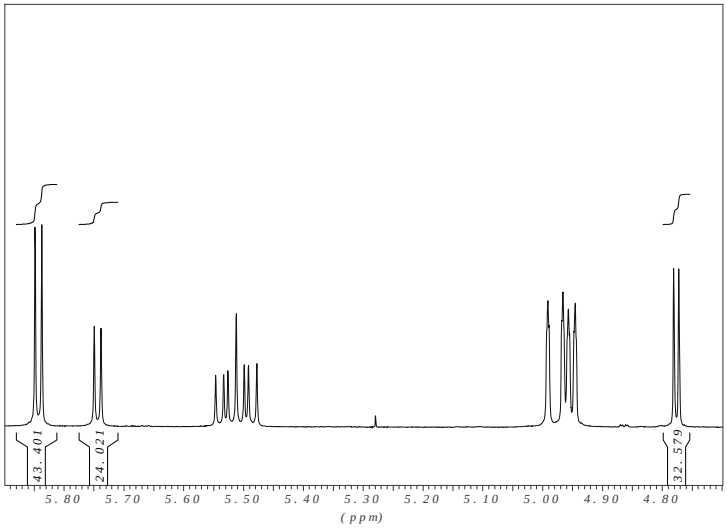
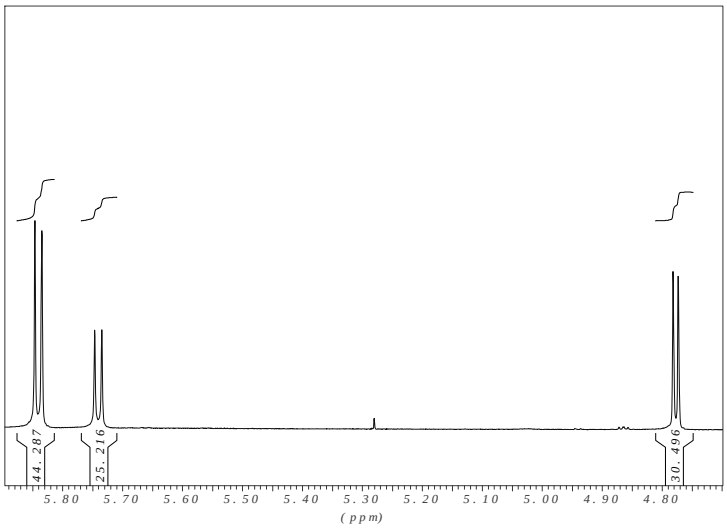

209.6
200.3
174.8
172.8
167.1
166.9
100.9
98.8
83.9
80.5
62.7
51.3
48.1
48.1
47.7
42.6
41.7
30.3
30.0
29.7
29.4
29.1
28.5
28.3
26.9
25.6
25.6
25.6
40000
30000
20000
10000
0
200
150
100
50
0
ppm (f1)

Table 1: Catalyst screening.

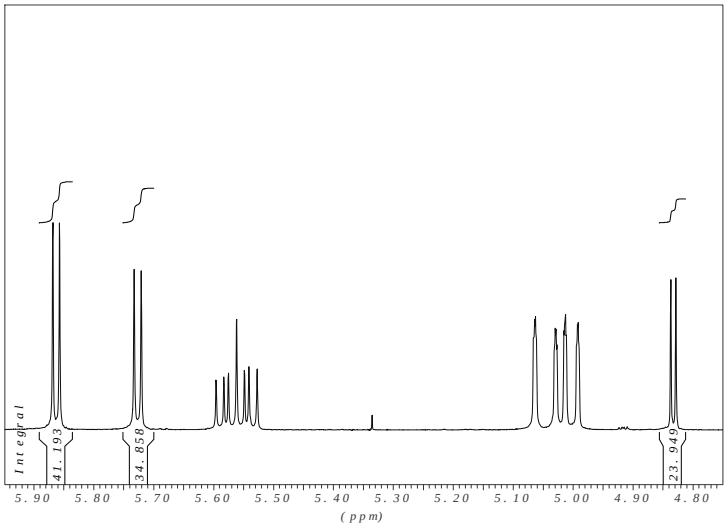
Entry 1 (Quinine, $CDCl_3$, 26 h, 25 °C)



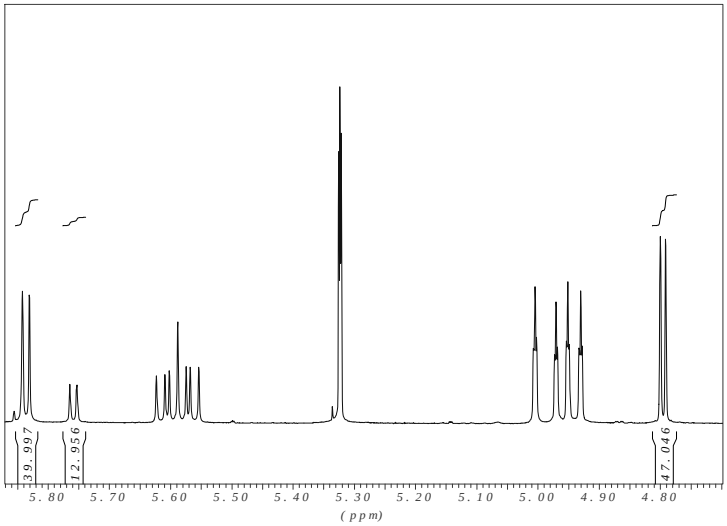
Entry 2 (Hydroquinine, $CDCl_3$, 26 h, 25 °C)



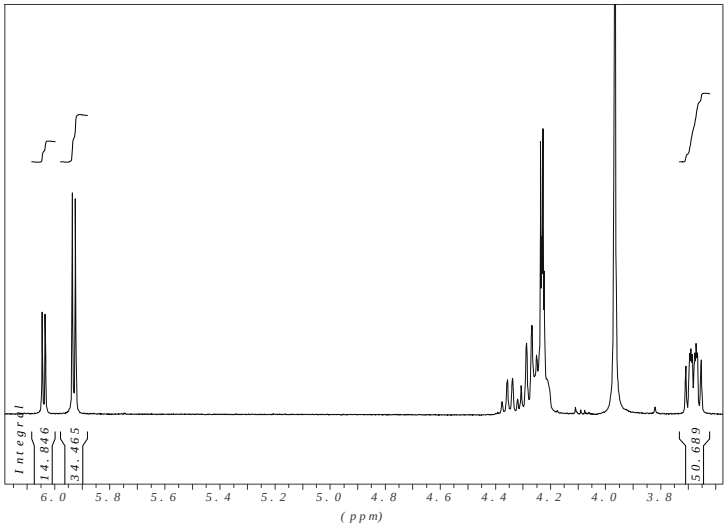
Entry 3 (Cinchonidin, $CDCl_3$, 26 h, 25 °C)

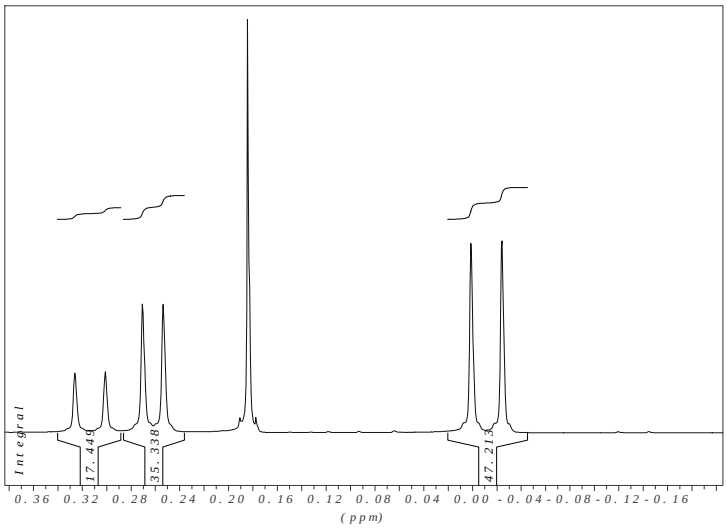


Entry 4 (Quinine, CD_2Cl_2, 26 h, 25 °C)

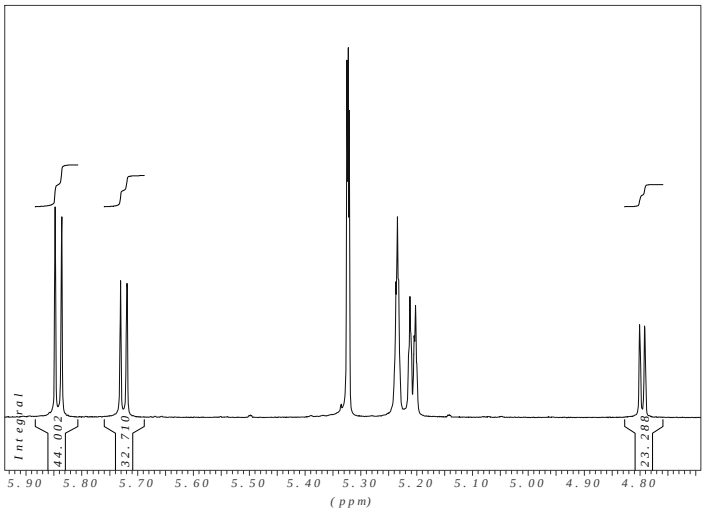


Entry 5 (Hydroquinine, C_6D_6, 26 h, 25 °C)





Entry 6 (Quinidine, CH_2Cl_2, 26 h, 25 °C)



Entry 7 (Cinchonidine, CH_2Cl_2, 26 h, 25 °C)