Supporting information for

Non Lewis acid catalyzed epoxide ring opening with amino acids

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Table of contents

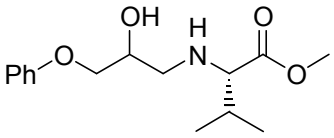
General methods

Melting points were determined on a Stuart® SMP10 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker® ARX 200 apparatus at respectively 300 and 75 MHz in $CDCl_3$. The following abbreviations are used for the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, oct = octuplet, m = multiplet, br s = broad singlet, dd = doublet doublet. Chemical shifts unit is ppm. Mass spectra were performed on a Bruker® Esquire-LC apparatus. IR spectra were recorded on a Bruker® Vector 22 apparatus. Microanalyses were done on an Ankersmit CAHN® 25 apparatus. Opical activity was determined on an Optical Activity LTD Automatic polarimeter polAAr 32 apparatus. TLC monitoring was performed with Merk® silica gel aluminium sheets (type 60 F_{254}). Visualization were performed under a SVL Bioblock Scientific lamp at 254 nm and/or by developing the plates with $KMnO_4$ solution followed by heating. Purifications were done by column chromatography at atmospheric pressure with Merk® silica gel (60 µm). Trifluoroethanol was purchased from Fluorochem. N-(2,3-Epoxypropyl)phtalimide, purchased from Aldrich, and Benzyl (R)-(-)-glycidyl ether, purchased from Alfa Aesar, were used after purification on silica gel. Unless otherwise noted, commercially available reagents were used without further purification.

Experimental procedure and characterisation of products 2-10

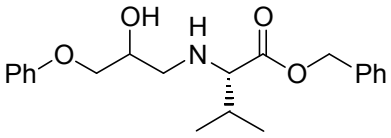
The *C*-protected amino acid salt (1.5 mmol) and potassium carbonate (2.5 mmol) were suspended in water (3 mL). The free amino acid was extracted with diethyl ether (3x15 mL). The organic phase was then dried with magnesium sulphate and concentrated under reduced pressure at ambient temperature. The free amino acid (2 eq.) was immediately diluted in 1.25 mL of trifluoroethanol. Then, epoxide (1 eq.) was added. The reaction mixture was stirred at reflux until the disappearance of the starting material (monitored by TLC). The reaction medium was concentrated under reduced pressure and the resulting oil was then purified by chromatography on silica gel. All products, except **2e**, were obtained in the form of two diastereoisomers in a 1:1 ratio which was determined from the ratio integrals from 1H NMR spectra.

(R)-methyl 2-(2-hydroxy-3-phenoxypropylamino)-3-methylbutanoate (2a)



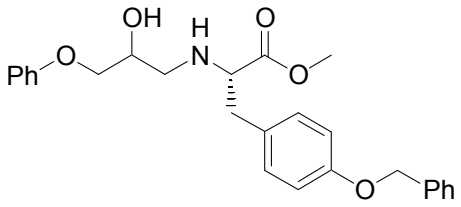
Epoxide **1a** (0.38 mmol, 0.058 g) and L-H-Val-OMe (0.76 mmol, 0.099 g) gave, after 10 min of heating and after purification (cyclohexane/AcOEt : 8/2), the product **2a** (0.098 g, 92%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85-0.89 (m, 12H), 1.82-1.93 (m, 2H), 2.40-2.47 (m, 1H), 2.55 (dd, 1H, *J* = 3.8, 12.4 Hz), 2.77 (dd, 1H, *J* = 6.9, 12.4 Hz), 2.87-2.92 (m, 1H), 2.94 (d, 1H, *J* = 5.7 Hz), 2.95 (d, 1H, *J* = 6.0 Hz), 3.64 (s, 6H), 3.87-3.94 (m, 6H), 6.81-6.88 (m, 6H), 7.18 (t, 4H, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 19.2, 19.2, 31.4, 31.5, 50.4, 51.0, 51.4, 67.0, 67.7, 68.0, 68.9, 69.7, 70.2, 114.4, 120.8, 129.3, 158.5, 175.2, 175.3; LRMS (APCI) m/z 282.1 $(MH)^+$; IR (cm-1) 2956, 1732, 1599, 1496, 1461, 1244, 1156, 755, 693; Anal. Calcd for $C_{15}H_{23}NO_4$ (%): C, 64.03; H, 8.24; N, 4.98. Found: C, 64.43; H, 8.19; N, 4.65.

(R)-benzyl 2-(2-hydroxy-3-phenoxypropylamino)-3-methylbutanoate (3a)



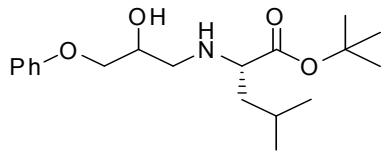
Epoxide **1a** (0.58 mmol, 0.088 g) and L-H-Val-OBn (1.16 mmol, 0.240 g) gave, after 1h30 of heating and after purification (cyclohexane/AcOEt : 8/2), the product **3a** (0.190 g, 92%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 3H, *J* = 7.2 Hz), 0.84 (d, 3H, *J* = 6.6 Hz), 0.86 (d, 3H, *J* = 6.9 Hz), 0.87 (d, 3H, *J* = 6.3 Hz), 1.84-1.95 (m, 2H), 2.43 (dd, 1H, *J* = 7.5, 12.3 Hz), 2.55 (dd, 1H, *J* = 3.9, 12.3 Hz), 2.77 (dd, 1H, *J* = 6.8, 12.3 Hz), 2.89 (dd, 1H, *J* = 3.6, 12.3 Hz), 2.97 (d, 1H, *J* = 5.7 Hz), 2.98 (d, 1H, *J* = 6.3 Hz), 3.83-3.92 (m, 6H), 5.05 (d, 2H, *J* = 12.3 Hz), 5.11 (d, 2H, *J* = 12.3 Hz), 6.79-6.89 (m, 6H), 7.15-7.27 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 19.3, 19.3, 31.5, 31.6, 50.4, 51.0, 66.4, 66.4, 67.0, 67.8, 67.9, 68.9, 69.7, 70.2, 114.4, 120.9, 128.3, 128.5, 129.3, 135.6, 158.5, 174.6, 174.8; MS (APCI) m/z 358.2 $(MH)^+$; IR (cm-1) 3421, 2960, 2926, 1730, 1599, 1496, 1457, 1245, 1175, 1152, 1042, 754, 694; Anal. Calcd for $C_{21}H_{27}NO_4$ (%): C, 70.56; H, 7.61; N, 3.92. Found: C, 70.63; H, 7.63; N, 3.85.

(S)-methyl2-(2-hydroxy-3-phenoxypropylamino)-3-(4-phenethylphenyl) propanoate (4a)



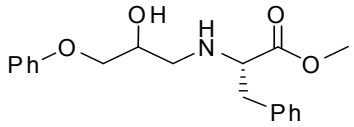
Epoxide **1a** (0.51 mmol, 0.076 g) and L-H-Tyr(Bn)-OMe (1.02 mmol, 0.291 g) gave, after 1h30 of heating and after purification (cyclohexane/AcOEt : 8/2), the product **4a** (0.212 g, 96%) as a white gel; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31-2.53 (br s, 2NH), 2.53-3.02 (m, 8H), 3.48-3.55 (m, 2H), 3.69 (s, 6H), 3.91-3.97 (m, 6H), 5.04 (s, 4H), 6.88-6.99 (m, 10H), 7.10-7.13 (m, 4H), 7.26-7.45 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.7, 38.8, 50.0, 50.4, 51.7, 62.7, 63.4, 68.1, 68.7, 69.7, 69.9, 70.1, 114.5, 114.8, 120.9, 127.4, 127.8, 128.5, 129.3, 130.1, 136.9, 157.6, 158.5, 174.8, 174.9; MS (ESI) m/z 436.2 $(MH)^+$, 458.1 $(MNa)^+$, 474.1 $(MK)^+$; IR (cm-1) 2926, 1730, 1598, 1511, 1496, 1454, 1241, 1171, 1042, 755, 735, 693; Anal. Calcd for $C_{26}H_{29}NO_5$ (%): C, 71.70; H, 6.71; N, 3.22. Found: C, 71.35; H, 6.73; N, 3.01.

tert-butyl 2-(2-hydroxy-5-methyl-1-phenoxyhexan-3-ylamino)acetate (5a)



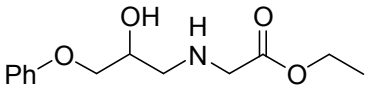
Epoxide **1a** (0.52 mmol, 0.078 g) and L-H-Leu-O*t*Bu (1.04 mmol, 0.195 g) gave, after 10 min of heating and after purification (cyclohexane/AcOEt : 8/2), the product **5a** (0.161 g, 92%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-0.86 (m, 12H), 1.33-1.44 (m, 4H), 1.39 (s, 18H), 1.62-1.75 (m, 2H), 2.36-2.78 (br s, 2NH), 2.48 (dd, 1H, *J* = 7.7, 12.2 Hz), 2.61 (dd, 1H, *J* = 4.1, 12.3 Hz), 2.75 (dd, 1H, *J* = 7.2, 12.3 Hz), 2.89 (dd, 1H, *J* = 3.5, 12.2 Hz), 3.03-3.10 (m, 2H), 3.87-3.95 (m, 6H), 6.81-6.88 (m, 6H), 7.15-7.21 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 22.6, 24.8, 28.0, 42.7, 49.9, 50.4, 60.2, 60.9, 68.0, 68.8, 69.8, 70.2, 81.0, 114.4, 120.8, 129.3, 158.6, 174.9, 175.1; MS (APCI) m/z 338.2 $(MH)^+$; IR (cm-1) 2930, 1726, 1640, 1599, 1494, 1244, 1170, 1041, 748, 693; Anal. Calcd for $C_{19}H_{31}NO_4$ (%): C, 67.63; H, 9.26; N, 4.15. Found: C, 67.87; H, 8.94; N, 4.03.

(S)-methyl 2-(2-hydroxy-3-phenoxypropylamino)-3-phenylpropanoate (6a)



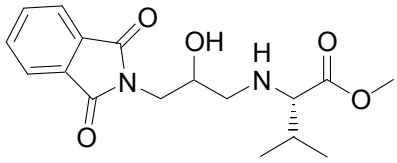
Epoxide **1a** (0.50 mmol, 0.075 g) and L-H-Phe-OMe (1.00 mmol, 0.179 g) gave, after 45 min of heating and after purification (cyclohexane/AcOEt : 8/2), the product **6a** (0.140 g, 85%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26-2.49 (br s, 2NH), 2.46 (dd, 1H, *J* = 7.2, 12.3 Hz), 2.57-2.62 (m, 1H), 2.70-2.96 (m, 6H), 3.41-3.47 (m, 2H), 3.59 (s, 6H), 3.78-3.87 (m, 6H), 6.76-6.88 (m, 6H), 7.07-7.22 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6, 39.6, 50.0, 50.5, 51.7, 62.6, 63.3, 68.0, 68.7, 69.7, 70.0, 114.4, 120.9, 126.7, 128.4, 129.0, 129.3, 137.1, 158.5, 174.7, 174.8; MS (APCI) *m/z* : 330.1 $(MH)^+$; IR (cm-1) 2928, 1735, 1599, 1496, 1455, 1244, 1173, 1042, 755, 694; Anal. Calcd for $C_{13}H_{23}NO_4$ (%): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.67; H, 6.95; N, 4.15.

methyl 2-(2-hydroxy-3-phenoxypropylamino)acetate (7a)



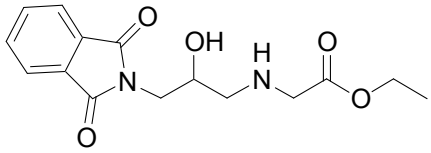
Epoxide **1a** (0.50 mmol, 0.075 g) and H-Gly-OEt (1.00 mmol, 0.103 g) gave, after 24h at ambient temperature and after purification (cyclohexane/AcOEt : 1/1), the product **7a** (0.068 g, 54%) as a white solid (mp. 144°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 3H, *J* = 7.2 Hz), 2.58-2.86 (br s, NH), 2.72 (dd, 1H, *J* = 5.1, 7.7 Hz), 2.83 (dd, 1H, *J* = 3.6, 7.7 Hz), 3.38 (s, 2H), 3.90 (d, 2H, *J* = 9.3 Hz), 3.94-4.04 (m, 1H), 4.12 (q, 2H, *J* = 7.2 Hz), 6.81-6.90 (m, 3H), 7.17-7.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 50.8, 51.8, 60.9, 68.5, 70.1, 114.5, 121.0, 129.4, 158.5, 172.4. MS (ESI) m/z 254.2 $(MH)^+$, 276.1 $(MNa)^+$; IR (cm-1) 2928, 1737, 1640, 1599, 1494, 1238, 1042, 747, 693; Anal. Calcd for $C_{13}H_{19}NO_4$ (%): C, 61.64; H, 7.56; N, 5.53. Found: C, 62.04; H, 7.21; N, 5.85.

methyl (2S)-2-{[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-hydroxypropyl]amino}-3-methylbutanoate (2b)



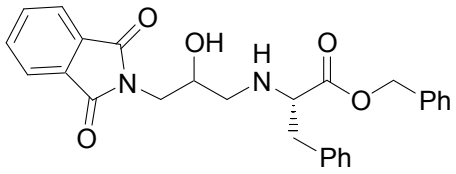
Epoxide **1b** (0.52 mmol, 0.106 g) and L-H-Val-OMe (1.04 mmol, 0.136 g) gave, after 1h of heating and after purification (cyclohexane/AcOEt : 6/4), the product **2b** (0.142 g, 82%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 3H, *J* = 6.9 Hz), 0.90 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.9 Hz), 1.84-1.97 (m, 2H), 2.30-2.90 (br s, 2NH), 2.33 (dd, 1H, *J* = 7.5, 12.4 Hz), 2.50 (dd, 1H, *J* = 3.9, 12.6 Hz), 2.68 (dd, 1H, *J* = 7.2, 12.6 Hz), 2.85 (dd, 1H, *J* = 3.6, 12.4 Hz), 2.96 (d, 1H, *J* = 6.0 Hz), 2.97 (d, 1H, *J* = 5.7 Hz), 3.67 (s, 3H), 3.68 (s, 3H), 3.69-3.79 (m, 4H), 3.84-3.93 (m, 2H), 7.65-7.71 (m, 4H), 7.78-7.84 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 18.3, 19.3, 31.4, 31.6, 41.5, 41.7, 51.0, 51.5, 51.5, 51.8, 67.0, 67.5, 67.7, 68.5, 123.2, 131.9, 133.9, 168.5, 175.1, 175.3; MS (ESI) m/z 335.3 $(MH)^+$, 357.2 $(MNa)^+$; IR (cm-1) 2958, 1704, 1392, 1191, 724; Anal. Calcd for $C_{17}H_{22}N_2O_5$ (%): C, 61.07; H, 6.63; N, 8.38. Found: C, 60.71; H, 6.79; N, 8.02.

ethyl {[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-hydroxypropyl]amino}acetate (7b)



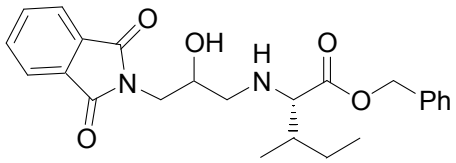
Epoxide **1b** (0.50 mmol, 0.102 g) and Gly-OEt (1.00 mmol, 0.103 g) gave, after 1h of heating and after purification (cyclohexane/AcOEt : 3/7), the product **7b** (0.080 g, 52%) as white needless (mp: 139°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J* = 7.2 Hz), 2.64 (dd, 1H, *J* = 7.5, 12.6 Hz), 2.76 (dd, 1H, *J* = 3.8, 12.6 Hz), 2.61-2.79 (br s, NH), 3.40 (s, 2H), 3.71 (dd, 1H, *J* = 5.4, 14.1 Hz), 3.79 (dd, 1H, *J* = 6.8, 14.1 Hz), 3.90-3.97 (m, 1H), 4.14 (q, 2H, *J* = 7.2 Hz), 7.67-7.70 (m, 2H), 7.79-7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 41.7, 50.7, 52.4, 60.8, 68.1, 123.3, 131.9, 133.9, 168.5, 172.4; MS (APCI) m/z 307.1 $(MH)^+$; IR (cm-1) 2917, 1731, 1708, 1393, 1202, 1135, 1023, 723; Anal. Calcd for $C_{15}H_{18}N_2O_5$ (%): C, 58.82; H, 5.92; N, 9.15. Found: C, 59.21; H, 5.88; N, 8.80.

benzyl (2S)-2-{[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-hydroxypropyl]amino}-3-phenylpropanoate (8b)



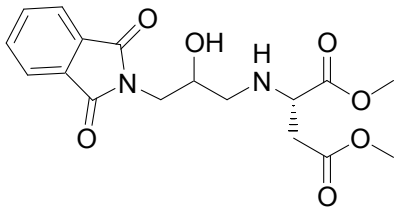
Epoxide **1b** (0.51 mmol, 0.104 g) and L-H-Val-OMe (1.02 mmol, 0.260 g) gave, after 2h of heating and after purification (cyclohexane/AcOEt : 6/4), the product **8b** (0.168 g, 72%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26-2.63 (br s, 2NH), 2.31 (dd, 1H, *J* = 7.8, 12.3 Hz), 2.50 (dd, 1H, *J* = 4.1, 12.7 Hz), 2.59 (dd, 1H, *J* = 6.6, 12.7 Hz), 2.76-2.95 (m, 5H), 3.44-3.49 (m, 2H), 3.53-3.81 (m, 6H), 5.01 (s, 4H), 7.01-7.08 (m, 4H), 7.11-7.20 (m, 10H), 7.22-7.29 (m, 6H), 7.60-7.66 (m, 4H), 7.72-7.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6, 41.5, 41.6, 50.6, 51.3, 62.8, 63.2, 66.6, 66.7, 67.7, 68.4, 123.3, 126.7, 128.3, 128.4, 128.5, 129.1, 131.9, 134.0, 168.5, 174.0, 174.2; MS (APCI) m/z 459.1 $(MH)^+$; IR (cm-1) 1704, 1393, 1169, 698; Anal. Calcd for $C_{27}H_{26}N_2O_5$ (%): C, 70.73; H, 5.72; N, 6.11. Found: C, 70.37; H, 6.00; N, 5.92.

benzyl (2S)-2-{[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-hydroxypropyl]amino}-3-ethylbutanoate (9b)



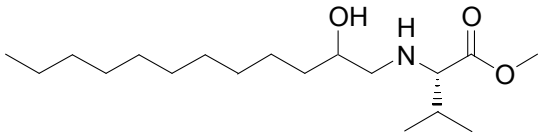
Epoxide **1b** (0.50 mmol, 0.102 g) and L-H-Ile-OBn (1.00 mmol, 0.221 g) gave, after 1h30 of heating and after purification (cyclohexane/AcOEt : 6/4), the product **9b** (0.176 g, 83%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80-0.89 (m, 12H), 1.09-1.20 (m, 2H), 1.40-1.52 (m, 2H), 1.65-1.75 (m, 2H), 2.36 (dd, 1H, *J* = 7.2, 12.3 Hz), 2.52 (dd, 1H, *J* = 4.2, 12.3 Hz), 2.68 (dd, 1H, *J* = 6.9, 12.3 Hz), 2.86 (dd, 1H, *J* = 3.8, 12.3 Hz), 3.09 (d, 1H, *J* = 6.0 Hz), 3.10 (d, 1H, *J* = 5.7 Hz), 3.64-3.79 (m, 4H), 3.84-3.93 (m, 2H), 5.07-5.18 (m, 4H), 7.26-7.34 (m, 10H), 7.66-7.72 (m, 4H), 7.79-7.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 11.3, 15.7, 25.1, 25.1, 38.1, 38.2, 41.5, 41.6, 51.0, 51.8, 66.0, 66.3, 66.3, 66.6, 67.6, 68.4, 123.2, 128.2, 128.2, 128.4, 131.8, 133.9, 135.5, 135.6, 168.4, 174.4, 174.7; MS (APCI) m/z 425.2 $(MH)^+$; IR (cm-1) 2963, 1713, 1395, 726; Anal. Calcd for $C_{24}H_{28}N_2O_5$ (%): C, 67.91; H, 6.65; N, 6.60. Found: C, 67.55; H, 6.54; N, 6.56.

dimethyl (2S)-2-{[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-hydroxypropyl]amino}succinate (10b)



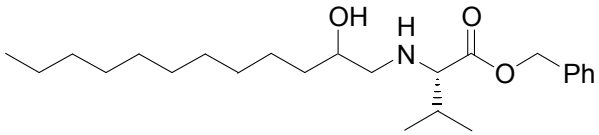
Epoxide **1b** (0.50 mmol, 0.104 g) and L-H-Asp(OMe)-OMe (1.00 mmol, 0.161 g) gave, after 3h30 of heating and after purification (cyclohexane/AcOEt : 6/4), the product **10b** (0.124 g, 68%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42-2.96 (m, 10H), 3.61-3.81 (m, 16H), 3.84-3.94 (m, 2H), 7.65-7.71 (m, 4H), 7.78-7.83 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.8, 41.4, 41.5, 50.7, 51.4, 51.9, 51.9, 52.1, 52.2, 57.5, 58.0, 67.8, 68.7, 123.2, 131.9, 133.9, 168.5, 171.2, 171.3, 173.7, 173.9; MS (APCI) m/z 365.1 $(MH)^+$; IR (cm-1) 2953, 1703, 1434, 1393, 1169, 1025, 725, 629; Anal. Calcd for $C_{17}H_{20}N_2O_7$ (%): C, 56.04; H, 5.53; N, 7.69. Found: C, 56.06; H, 5.60; N, 7.42.

(S)-methyl 2-(2-hydroxydecylamino)-3-methylbutanoate (2c)



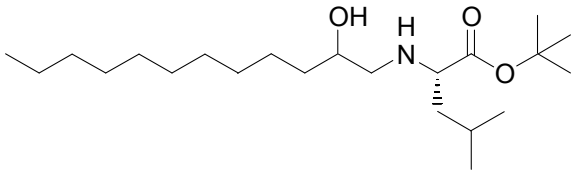
Epoxide **1c** (0.50 mmol, 0.092 g) and L-H-Val-OMe (1.00 mmol, 0.131 g) gave, after 3h of heating and after purification (cyclohexane/AcOEt : 8/2), the product **2c** (0.151 g, 96%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, 6H, *J* = 6.6 Hz), 0.90 (d, 6H, *J* = 6.9 Hz), 0.91 (d, 6H, *J* = 6.9 Hz), 1.22 (s, 24H), 1.25-1.39 (m, 12H), 1.85-1.94 (m, 2H), 2.06-2.13 (m, 1H), 2.44-2.47 (m, 2H), 2.79 (dd, 1H, *J* = 2.4, 11.7 Hz), 2.92 (d, 1H, *J* = 5.7 Hz), 2.97 (d, 1H, *J* = 6.0 Hz), 2.43-2.55 (m, 2H), 3.69 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.3, 18.4, 19.3, 22.6, 25.4, 25.6, 29.2, 29.5, 29.6, 31.4, 31.6, 31.8, 34.5, 34.8, 51.4, 53.5, 54.8, 66.3, 67.9, 68.6, 70.2, 175.3, 175.5; MS (APCI) m/z 316.2 $(MH)^+$; IR (cm-1) 2923, 2854, 1736, 1465, 1196, 678; Anal. Calcd for $C_{18}H_{37}NO_3$ (%): C, 68.53; H, 11.82; N, 4.44. Found: C, 68.83; H, 11.61; N, 4.48.

(S)-benzyl 2-(2-hydroxydodecylamino)-3-methylbutanoate (3c)



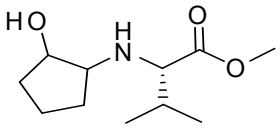
Epoxide **1c** (0.54 mmol, 0.099 g) and L-H-Val-OBn (1.08 mmol, 0.223 g) gave, after 4h of heating and after purification (cyclohexane/AcOEt : 8/2), the product **3c** (0.165 g, 78%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86-0.95 (m, 18H), 1.26-1.41 (m, 36H), 1.89-2.01 (m, 2H), 2.09-2.48 (br s, 2NH), 2.13 (dd, 1H, *J* = 9.6, 11.7 Hz), 2.47-2.49 (m, 2H), 2.81 (dd, 1H, *J* = 2.7, 11.7 Hz), 2.99 (d, 1H, *J* = 16.2 Hz), 3.04 (d, 1H, *J* = 6.0 Hz), 3.43-3.57 (m, 2H), 5.14 (d, 2H, *J* = 12.3 Hz), 5.19 (d, 2H, *J* = 12.3 Hz), 7.33-7.37 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.2, 18.3, 19.4, 22.6, 25.4, 25.6, 29.3, 29.5, 29.7, 31.4, 31.7, 31.8, 34.5, 34.8, 53.4, 54.8, 66.4, 67.9, 68.6, 70.2, 128.3, 128.5, 135.6, 135.6, 174.7, 174.9; MS (ESI) m/z 392.4 $(MH)^+$; IR (cm-1) 2924, 2853, 1732, 1465, 1150, 734, 698, 669; Anal. Calcd for $C_{24}H_{41}NO_3$ (%): C, 73.61; H, 10.55; N, 3.58. Found: C, 74.00; H, 10.57; N, 3.47.

(R)-tert-butyl 2-(2-hydroxydodecylamino)-4-methylpentanoate (5c)



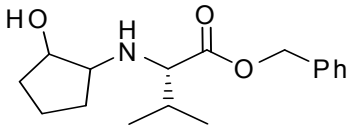
Epoxide **1c** (0.38 mmol, 0.070 g) and L-H-Leu-O*t*Bu (0.76 mmol, 0.142 g) gave, after 2h30 of heating and after purification (cyclohexane/AcOEt : 8/2), the product **5c** (0.127 g, 90%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83-0.92 (m, 18H), 1.24 (s, 28H), 1.32-1.42 (m, 12H), 1.45 (s, 18H), 1.66-1.82 (m, 2H), 2.12-2.56 (br s, 2NH), 2.16 (dd, 1H, *J* = 9.8, 11.9 Hz), 2.45 (dd, 1H, *J* = 8.3, 12.5 Hz), 2.53 (dd, 1H, *J* = 3.6, 12.5 Hz), 2.80 (dd, 1H, *J* = 2.9, 11.9 Hz), 3.02-3.15 (m, 2H), 3.41-3.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.2, 22.6, 22.7, 24.9, 24.9, 25.6, 25.7, 28.1, 29.3, 29.6, 29.7, 31.9, 34.6, 34.9, 42.8, 43.0, 53.0, 54.3, 59.7, 61.1, 68.9, 70.1, 81.0, 81.0, 175.1, 175.4; MS (ESI) m/z 372.4 $(MH)^+$; IR (cm-1) 2924, 2855, 1730, 1367, 1152; Anal. Calcd for $C_{22}H_{45}NO_3$ (%): C, 71.11; H, 12.21; N, 3.77. Found: C, 71.23; H, 12.21; N, 3.74.

(R)-methyl 2-(2-hydroxycyclopentylamino)-3-methylbutanoate (2d)



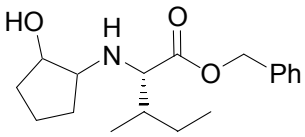
Epoxide **1d** (0.52 mmol, 0.044 g) and L-H-Val-OMe (1.04 mmol, 0.136 g) gave, after 18h of heating and after purification (cyclohexane/AcOEt : 8/2), the product **2d** (0.072 g, 64%) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 12H, *J* = 6.9 Hz), 1.22-2.01 (m, 14H, 2NH), 2.66-2.75 (m, 2H), 3.02 (d, 1H, *J* = 6.0 Hz), 3.09 (d, 1H, *J* = 6.0 Hz), 3.71 (s, 6H), 3.77-3.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 18.6, 19.2, 20.1, 20.5, 29.6, 30.7, 31.7, 32.2, 32.4, 51.5, 51.5, 65.4, 65.5, 65.8, 66.1, 78.0, 78.7, 176.2, 176.5; MS (APCI) m/z 216.2 $(MH)^+$; IR (cm-1) 2957, 1733, 1153, 625; Anal. Calcd for $C_{11}H_{21}NO_3$ (%): C, 61.37; H, 9.83; N, 6.51. Found: C, 61.75; H, 9.88; N, 6.14.

(R)-benzyl 2-(2-hydroxycyclopentylamino)-3-methylbutanoate (3d)



Epoxide **1d** (0.50 mmol, 0.042 g) and L-H-Val-OBn (1.00 mmol, 0.207 g) gave, after 18h of heating and after purification (cyclohexane/AcOEt : 8/2), the product **3d** (0.078 g, 54%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87-0.94 (m, 12H), 1.21-2.02 (m, 14H, 2NH), 2.66-2.76 (m, 2H), 3.06 (d, 1H, *J* = 6.3 Hz), 3.14 (d, 1H, *J* = 6.0 Hz), 3.81 (q, 2H, *J* = 5.6 Hz), 5.11-5.21 (m, 4H), 7.31-7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 18.5, 19.3, 20.0, 20.4, 29.5, 30.7, 31.7, 31.7, 32.1, 32.4, 65.4, 65.6, 65.8, 66.2, 66.4, 66.4, 77.9, 78.7, 128.3, 128.4, 128.5, 135.7, 135.8, 175.6, 175.9; MS (APCI) m/z 292.2 $(MH)^+$; IR (cm-1) 2971, 1639, 1598, 1492, 1340, 1244, 1170, 1041, 747, 694; Anal. Calcd for $C_{17}H_{25}NO_3$ (%): C, 70.07; H, 8.65; N, 4.81. Found: C, 69.71; H, 8.60; N, 4.67.

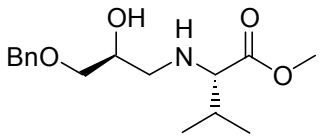
(2S,3R)-benzyl 2-(2-hydroxycyclopentylamino)-3-methylpentanoate (9d)



Epoxide **1d** (0.50 mmol, 0.042 g) and L-H-Ile-OBn (1.00 mmol, 0.221 g) gave, after 18h of heating and after purification (cyclohexane/AcOEt : 8/2), the product **9d** (0.120

g, 79%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-0.88 (m, 12H), 1.10-2.00 (m, 18H, 2NH), 2.65-2.75 (m, 2H), 3.14 (d, 1H, *J* = 6.3 Hz), 3.21 (d, 1H, *J* = 6.3 Hz), 3.77-3.84 (m, 2H), 5.10-5.22 (m, 4H), 7.32-7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 15.6, 20.0, 20.4, 25.3, 25.4, 29.5, 30.7, 32.1, 32.4, 38.4, 38.4, 64.5, 64.8, 65.4, 66.1, 66.3, 66.4, 77.9, 78.8, 128.3, 128.5, 128.5, 135.7, 135.8, 175.5, 175.9; MS (APCI) m/z 306.1 $(MH)^+$; IR (cm-1) 2960, 1729, 1454, 1233, 1127, 735, 699; Anal. Calcd for $C_{18}H_{27}NO_3$ (%): C, 70.79; H, 8.91; N, 4.59. Found: C, 70.39; H, 8.78; N, 4.52.

2-(3-Benzyloxy-2-hydroxy-propylamino)-3-methyl-butyric acid methyl ester (2e)



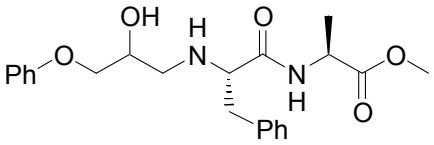
Epoxide **1e** (0.50 mmol, 0.082 g) and L-H-Val-OMe (1.00 mmol, 0.131 g) gave, after 45 min of heating and after purification (cyclohexane/AcOEt : 8/2), the product **2e** (0.118 g, 80%) as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 3H, *J* = 6.6 Hz), 0.85 (d, 3H, *J* = 6.6 Hz), 1.84 (oct, 1H, *J* = 6.6 Hz), 2.19-2.40 (br s, NH), 2.34 (dd, 1H, *J* = 12.0, 7.8 Hz), 2.76 (dd, 1H, *J* = 12.0, 3.9 Hz), 2.90 (d, 1H, *J* = 6.6 Hz), 3.37-3.46 (m, 2H), 3.63 (s, 3H), 3.68-3.75 (m, 1H), 4.47 (s, 2H), 7.17-7.28 (m, 5H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 19.2, 31.5, 51.1, 51.4, 67.7, 69.4, 72.2, 73.3, 127.5, 127.6, 128.2, 138.0, 175.3 ; MS (ESI) m/z 296.0 $(MH)^+$, 318.0 $(MNa)^+$, 333.9 $(MK)^+$.; IR (cm-1) 2960, 1732, 1454, 1199, 1095, 700; Anal. Calcd for $C_{16}H_{25}NO_4$ (%): C, 65.06; H, 8.53; N, 4.74. Found: C, 65.14; H, 8.69; N, 4.59; $[\alpha]_{589}^{18.2}$ = -6° (c=1 in CH_2Cl_2).

Experimental procedure and characterisation of products 12

L-Z-Phe-Ala-OMe (0.385 g, 1 mmol, 2 eq.) was suspended in methanol (8 mL). After addition of Pd/C, the solution was placed under a hydrogen atmosphere and was vigorously stirred during 40 minutes. The crude product was then filtrated several times on celite. The filtrate was concentrated under reduced pressure at ambient temperature. The dipeptide L-H-Phe-Ala-OMe thus obtained was immediately diluted in 1.25 mL of trifluoroethanol and epoxide (0.5 mmol) was added. The reaction mixture was stirred at reflux until the disappearance of the starting material

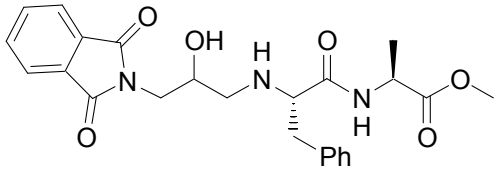
(monitored by TLC). The reaction medium was concentrated under reduced pressure and the resulting oil was then purified by chromatography on silica gel. Products were obtained in the form of two diastereoisomers in a 1:1 ratio which was determined from the ratio integrals from 1H NMR spectra.

2-[2-(2-Hydroxy-3-phenoxy-propylamino)-3-phenyl-propionylamino]-propionic acid methyl ester (12a)



Epoxide **1a** (0.50 mmol, 0.075 g) and L-H-Phe-Ala-OMe (1.00 mmol, 0.250 g) gave, after 1h30 of heating and after purification (cyclohexane/AcOEt : 1/1), the product **12a** (0.168 g, 84%) as a yellow gel; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (d, 6H, *J* = 7.2 Hz), 2.41-2.84 (br s, 2NH), 2.41-2.84 (m, 6H), 3.14-3.24 (m, 2H), 3.35-3.43 (m, 2H), 3.70 (s, 6H), 3.83-4.05 (m, 6H), 4.56-4.66 (m, 2H), 6.85 (t, 4H, *J* = 8.7 Hz), 6.93 (t, 2H, *J* = 7.2 Hz), 7.22-7.31 (m, 14H), 7.83 (d, NH, *J* = 8.4 Hz), 7.87 (d, NH, *J* = 8.4 Hz) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 39.1, 39.2, 47.3, 50.9, 51.1, 52.3, 63.6, 64.0, 68.9, 69.9, 70.0, 114.3, 120.9, 126.8, 128.5, 128.8, 128.9, 129.2, 137.0, 137.1, 158.3, 158.3, 173.3, 173.6, 173.6 ; MS (ESI) m/z 401.0 $(MH)^+$, 422.9 $(MNa)^+$; IR (cm-1) 3311, 2968, 1744, 1645, 1495, 1453, 1209, 1150, 1056, 755, 696, 613 ; Anal. Calcd for $C_{22}H_{28}N_2O_5$ (%): C, 65.98; H, 7.05; N, 7.00. Found: C, 65.84; H, 6.88; N, 6.75.

2-{2-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-hydroxy-propylamino]-3-phenyl-propionylamino}-propionic acid methyl ester (12b)

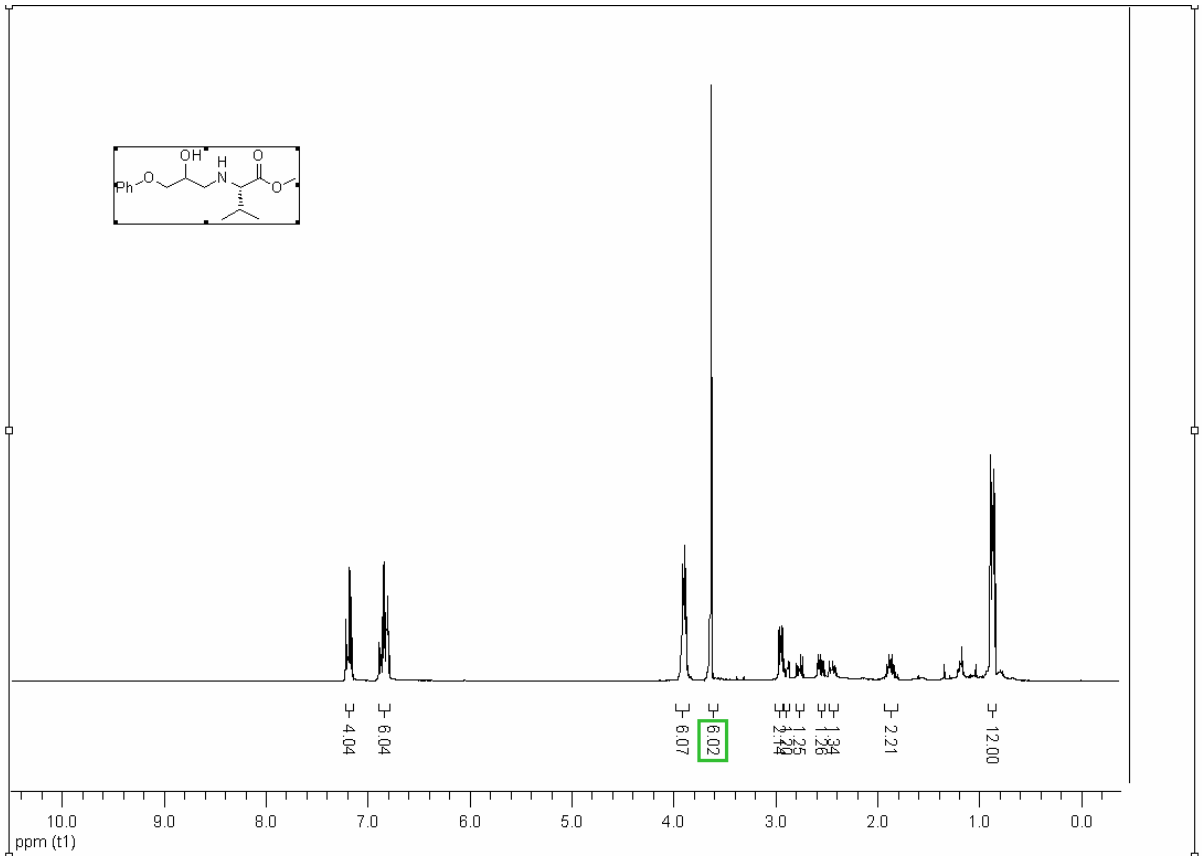


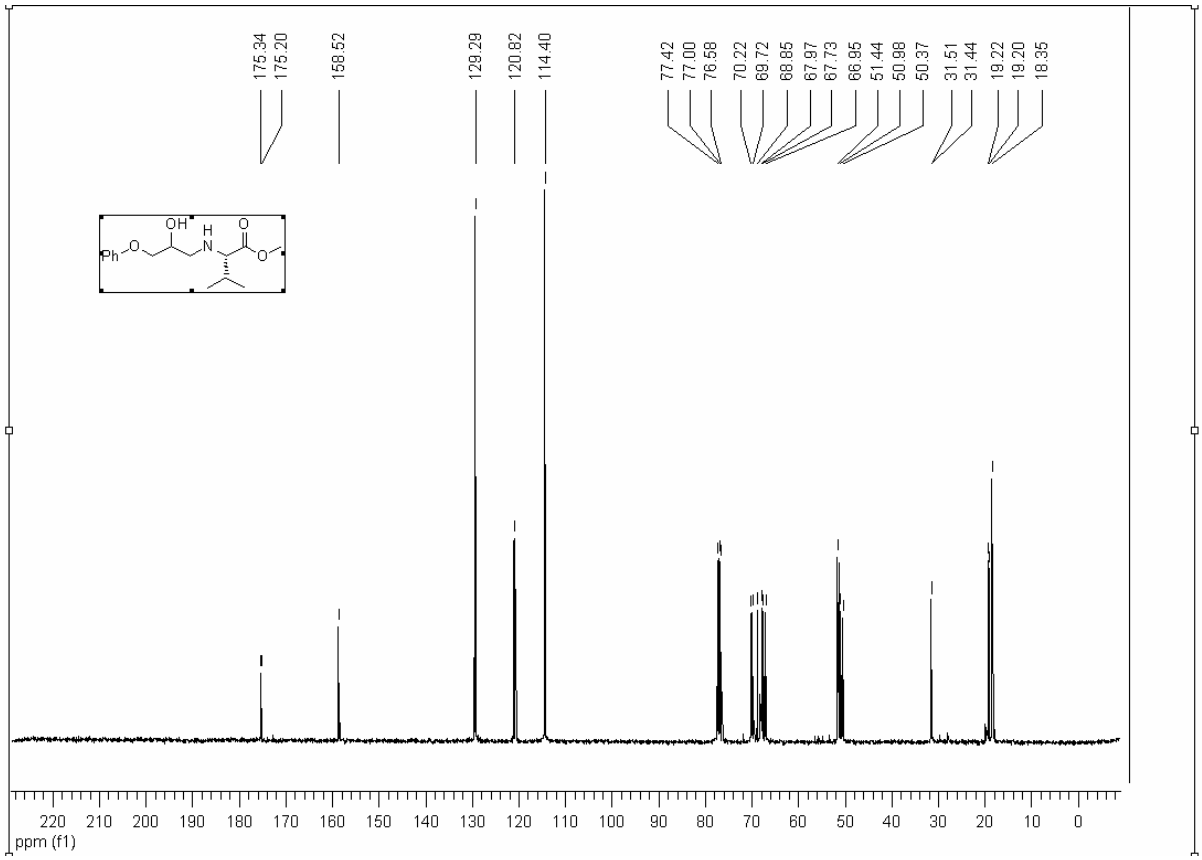
Epoxide **1b** (0.50 mmol, 0.102 g) and L-H-Phe-Ala-OMe (1.00 mmol, 0.250 g) gave, after 3h30 of heating and after purification (cyclohexane/AcOEt : 6/4), the product **12b** (0.204 g, 90%) as a white solid (mp:125-126°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, *J* = 7.2 Hz), 1.31 (d, 3H, *J* = 7.5 Hz), 1.75-2.16 (br s, 2NH), 2.45-2.72 (m, 6H), 3.05 (t, 1H, *J* = 3.9 Hz), 3.10 (t, 1H, *J* = 3.6 Hz), 3.24-3.30 (m, 2H), 3.53 (s, 3H), 3.56 (s, 3H), 3.59-3.63 (m, 2H), 3.68-3.70 (m, 2H), 3.80-3.91 (m, 2H), 4.44-4.56 (m, 2H), 7.11-7.21 (m, 10H), 7.59-7.65 (m, 3H), 7.69-3.77 (m, 5H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 17.8, 18.0, 39.2, 39.3, 41.5, 41.7, 47.2, 51.6, 51.7, 52.2, 52.2, 63.8, 63.9, 68.7, 68.8, 123.2, 126.7, 126.8, 128.5, 128.5, 129.0, 129.0, 131.8, 131.8, 133.9, 137.1, 137.2, 168.5, 168.6, 173.3, 173.4, 173.6 ; MS (ESI) m/z 454.2 $(MH)^+$, 476.2 $(MNa)^+$; IR (cm-1) 3313, 2269, 1739, 1687, 1642, 1541, 1400, 1316, 1232, 1152, 1072, 1025, 716, 693 ; Anal. Calcd for $C_{24}H_{27}N_3O_6$ (%): C, 63.56; H, 6.00; N, 9.27. Found: C, 63.42; H, 6.00; N, 8.98.

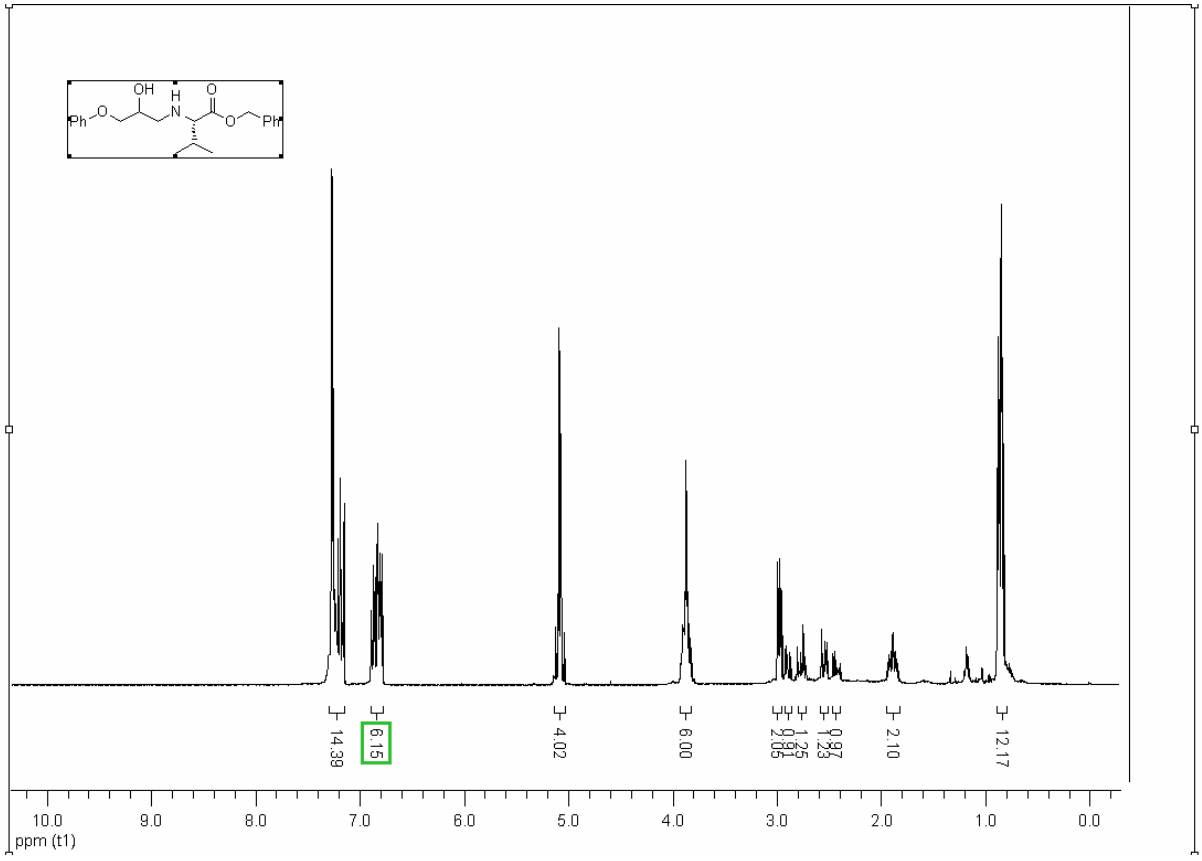
1H and 13C NMR spectra

Compound 2a





Compound 3a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1.25
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0.93
2.10
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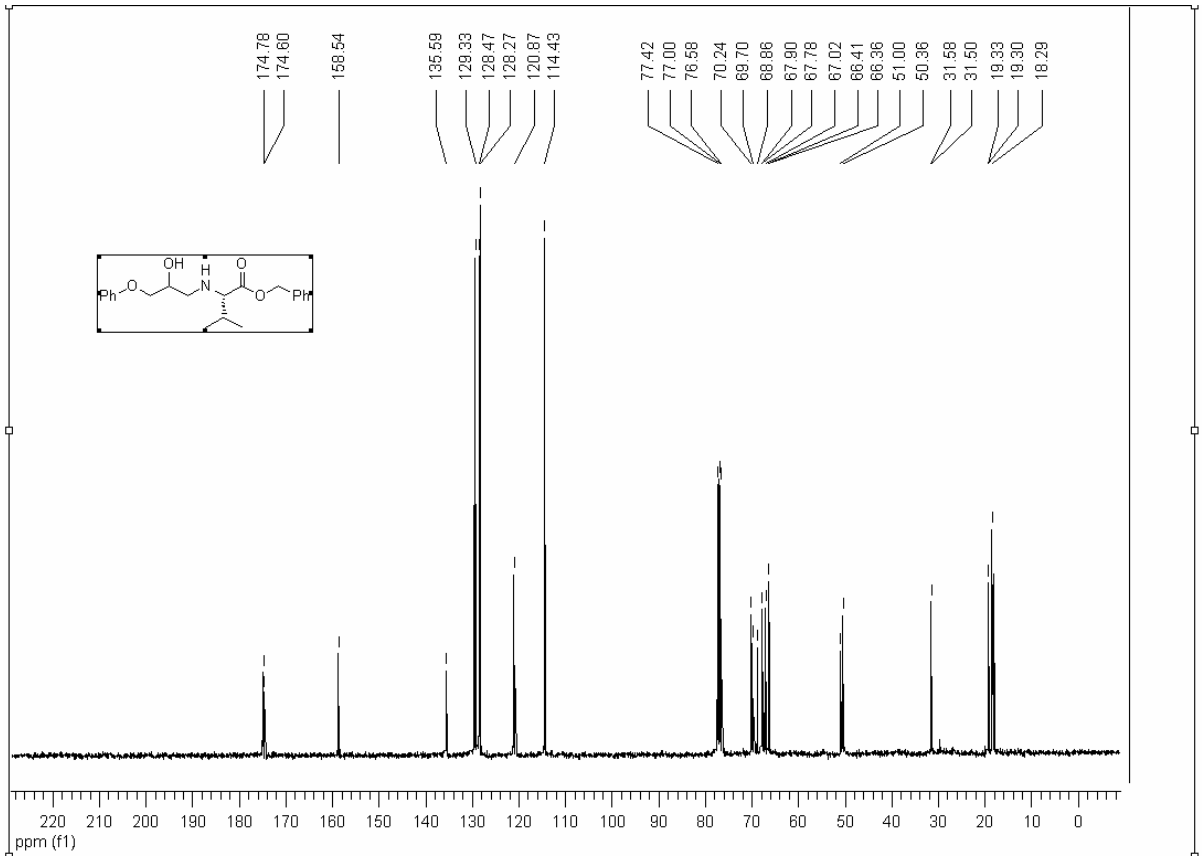
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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128.27
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114.43
77.42
77.00
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69.70
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67.90
67.78
67.02
66.41
66.36
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31.58
31.50
19.33
19.30
18.29
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200
190
180
170
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110
100
90
80
70
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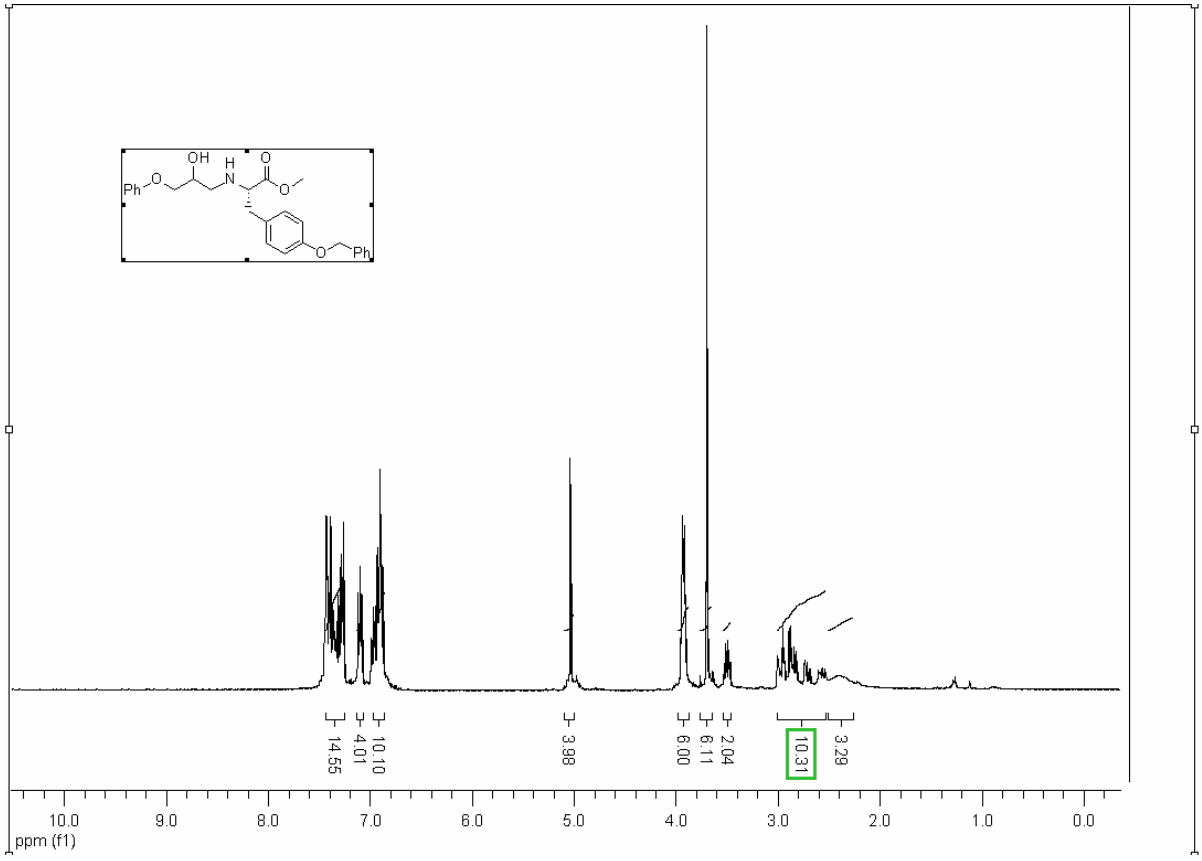
40
30
20
10
0
ppm (f1)

Compound 4a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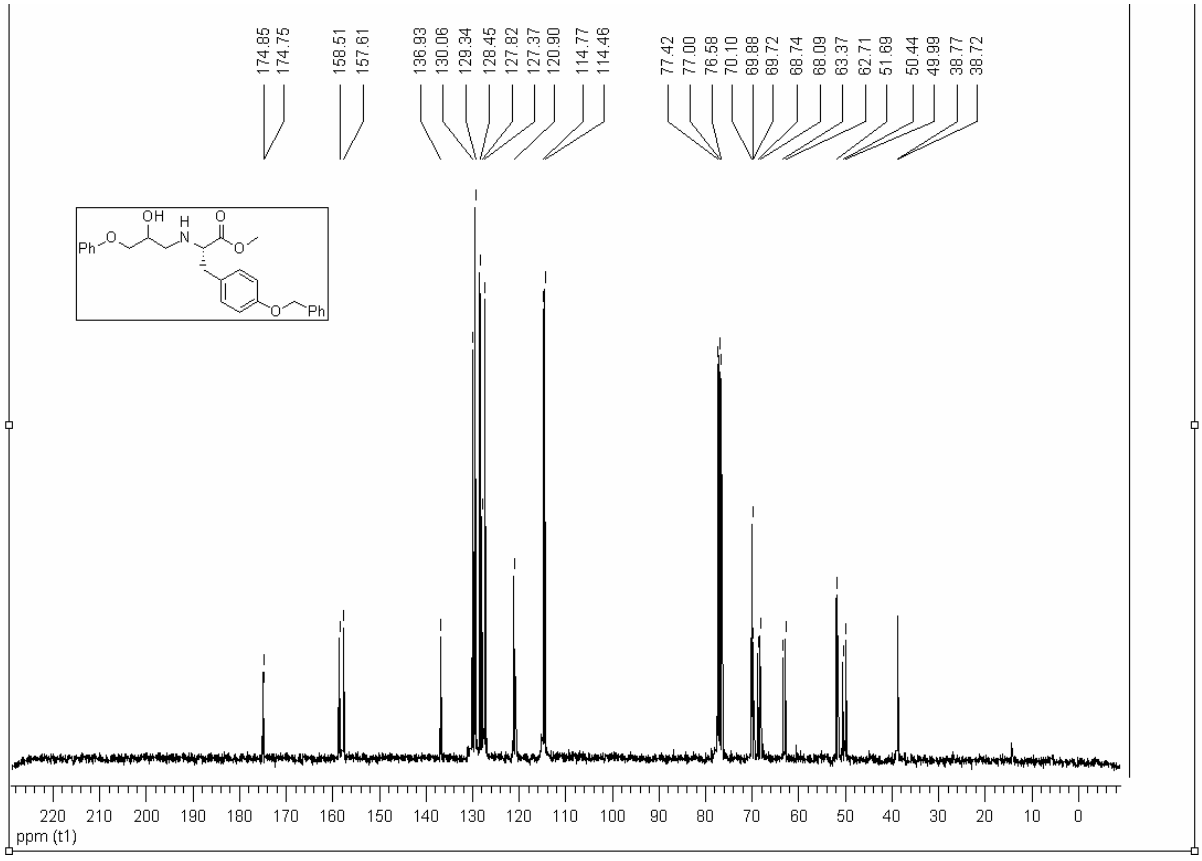
ppm (f1)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160
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30
20
10
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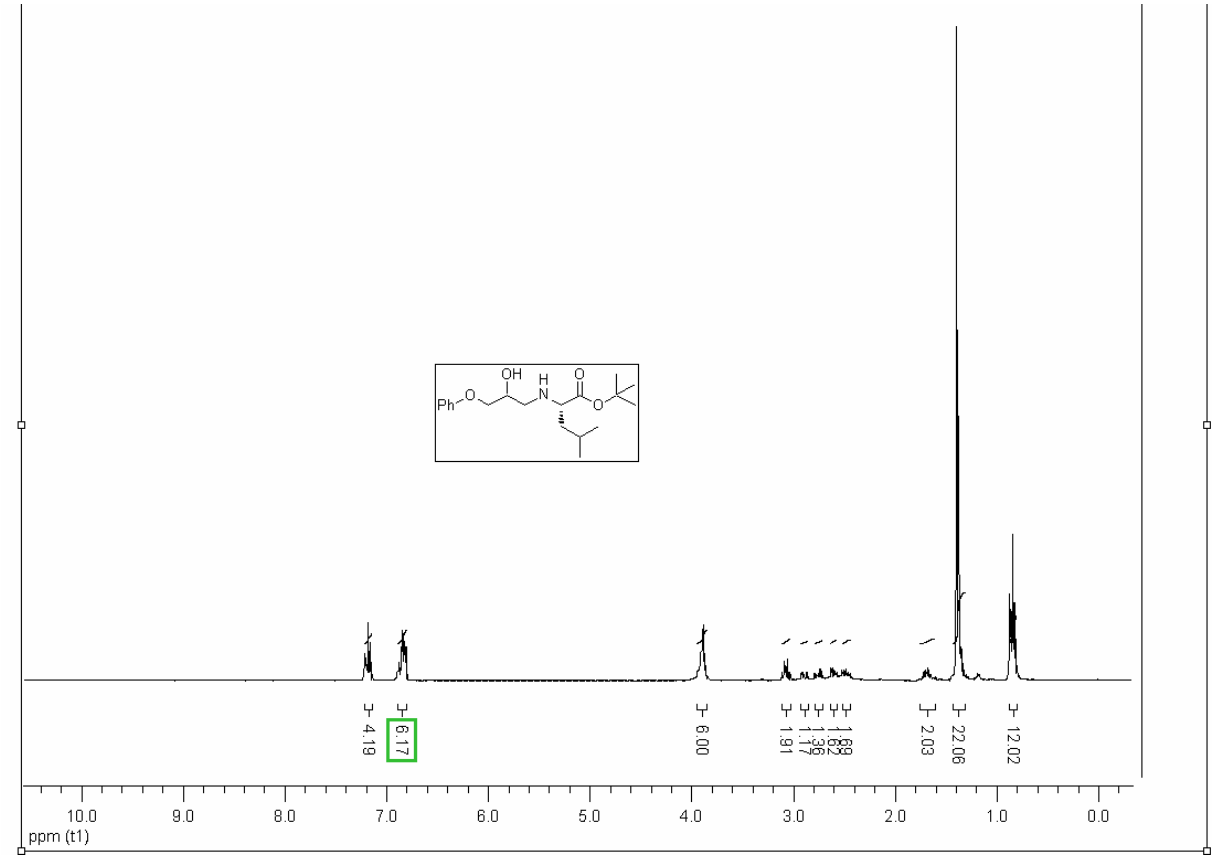
ppm (t1)

Compound 5a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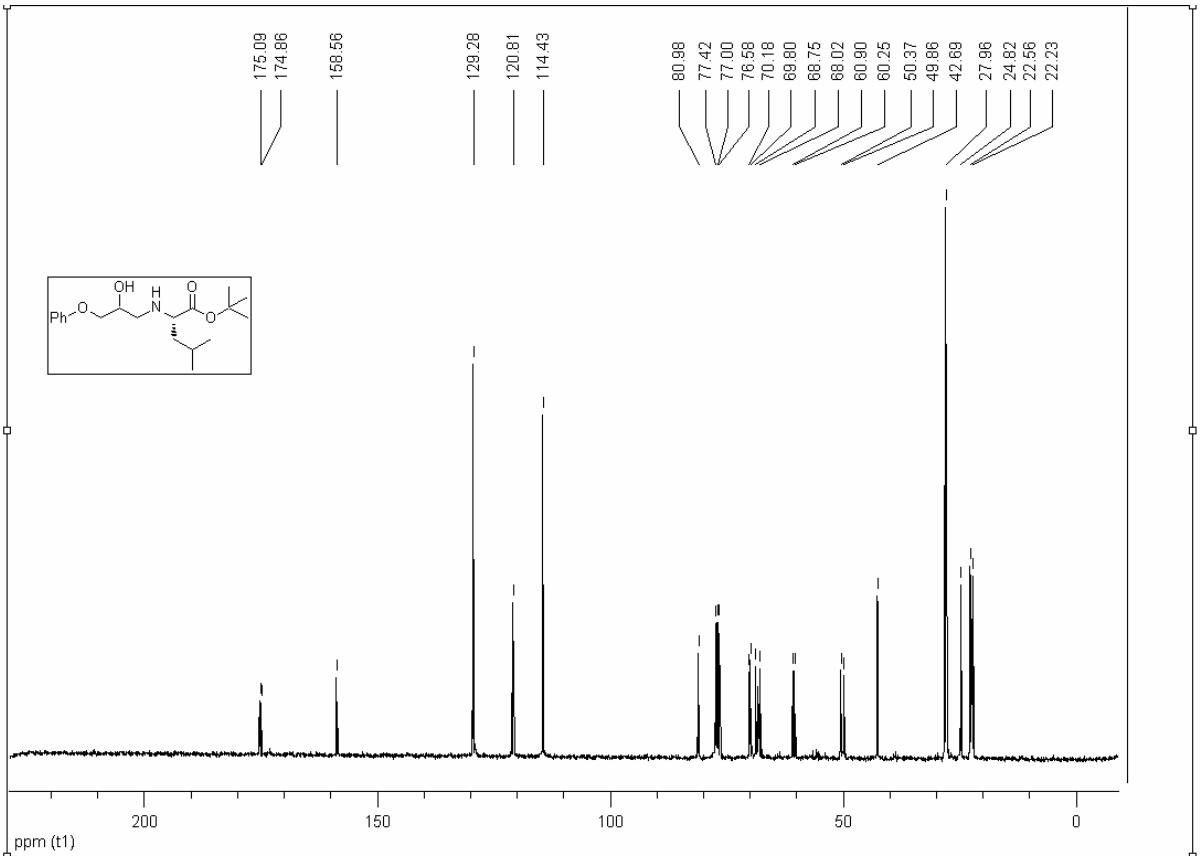
ppm (t1)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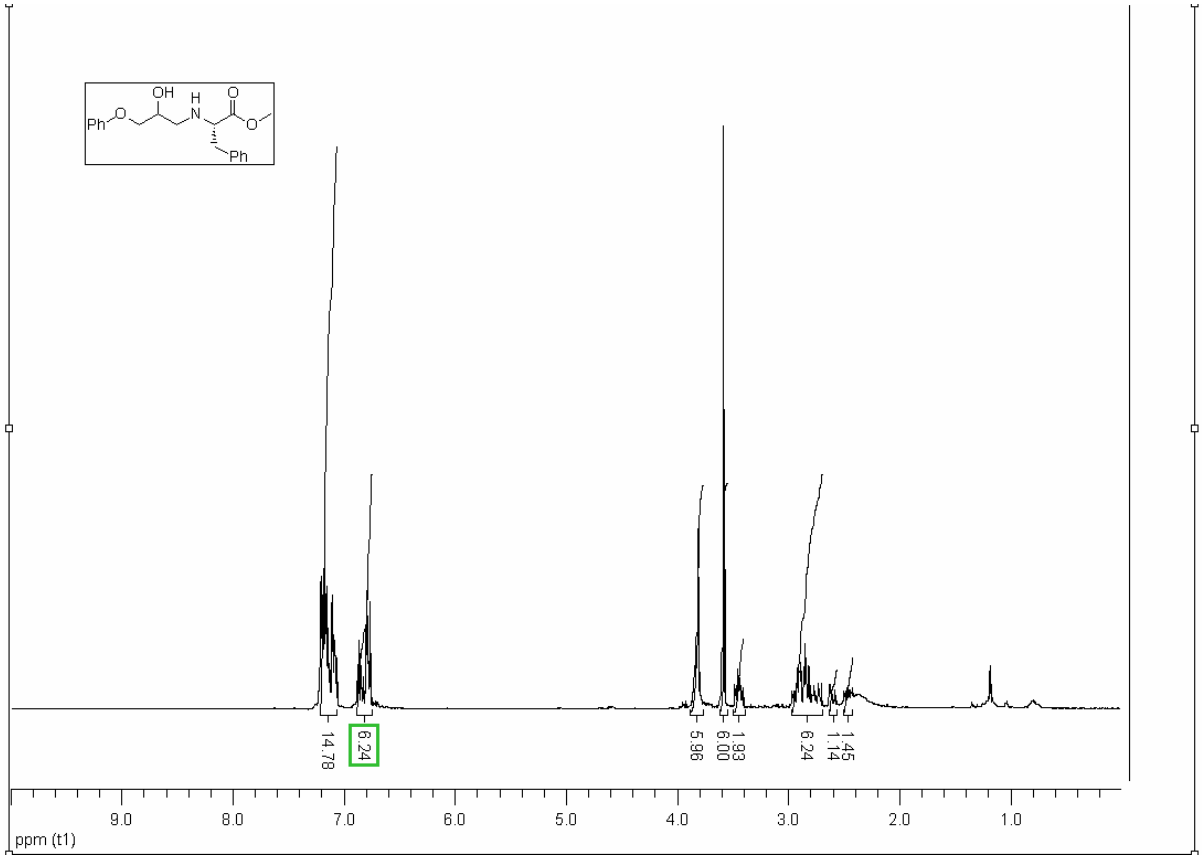
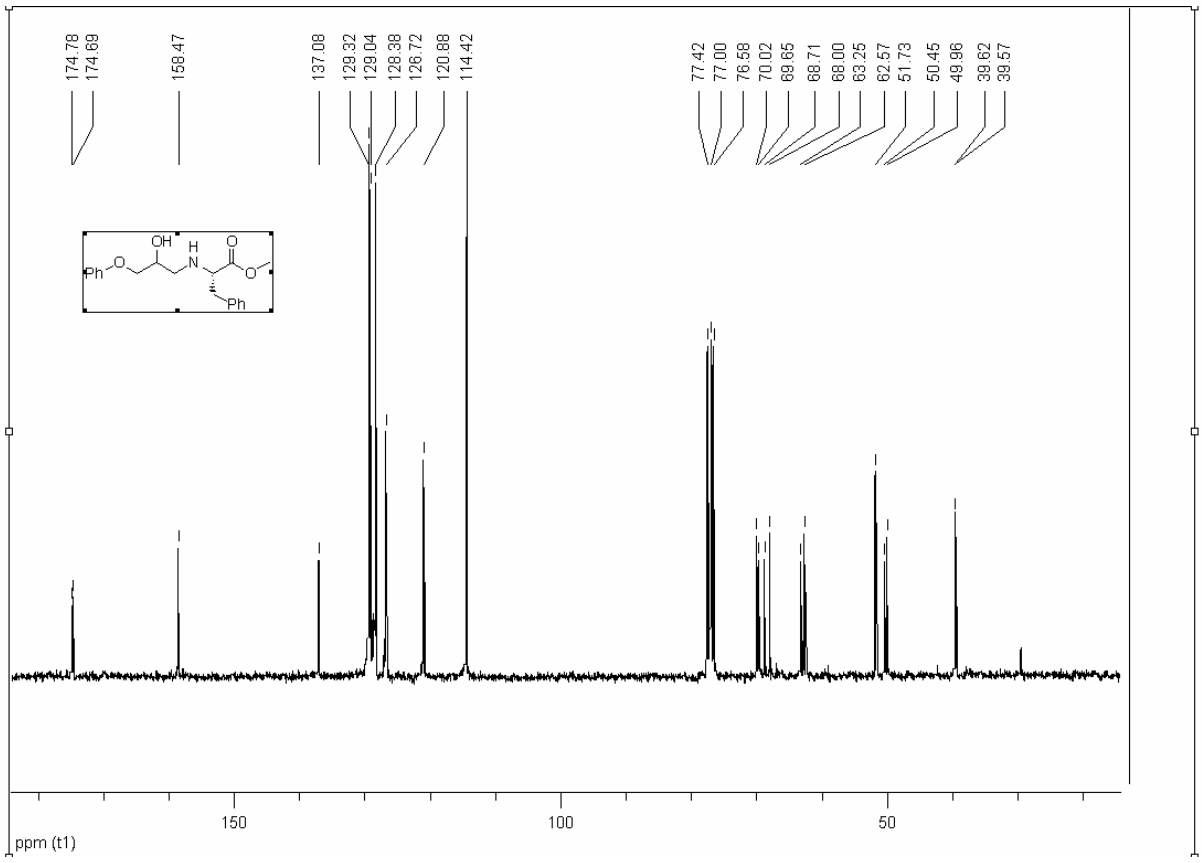
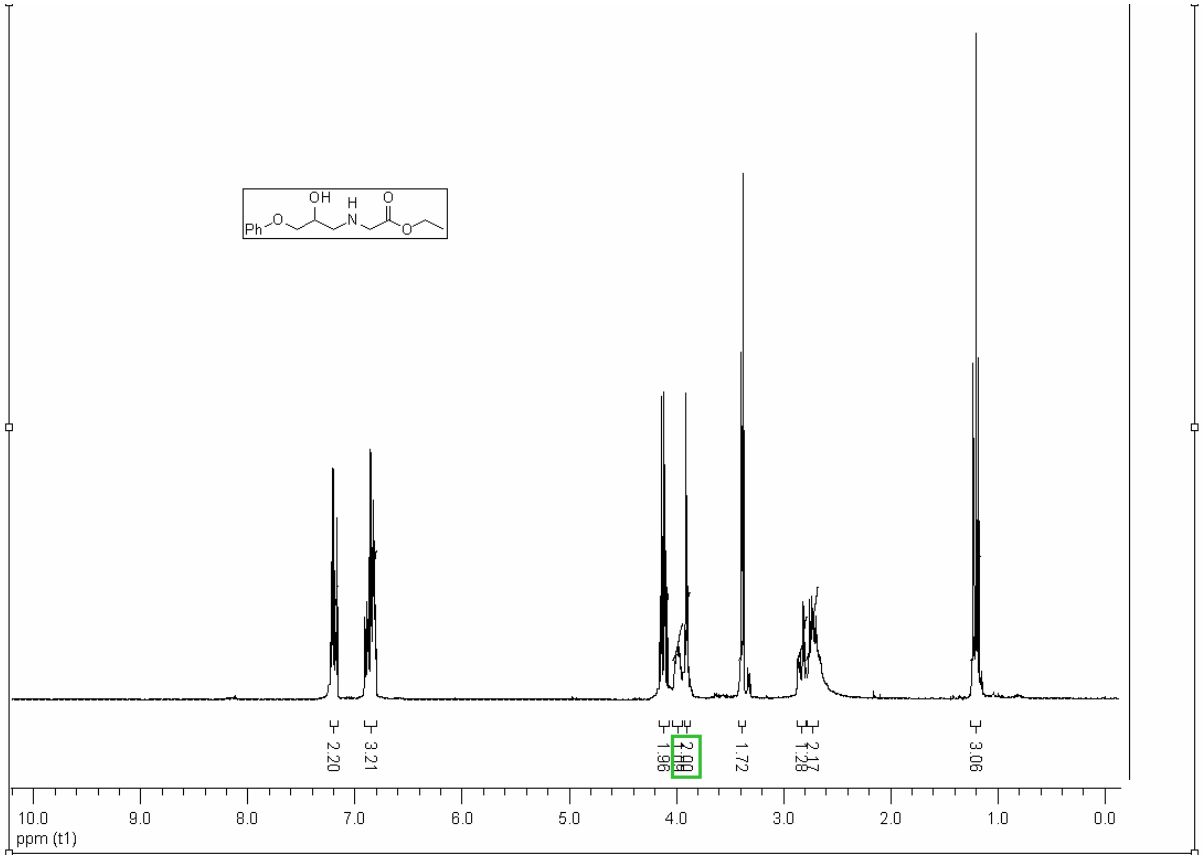
68.02
60.90
60.25
50.37
49.86
42.69
27.96
24.82
22.56
22.23
200
150
100
50
0
ppm (t1)

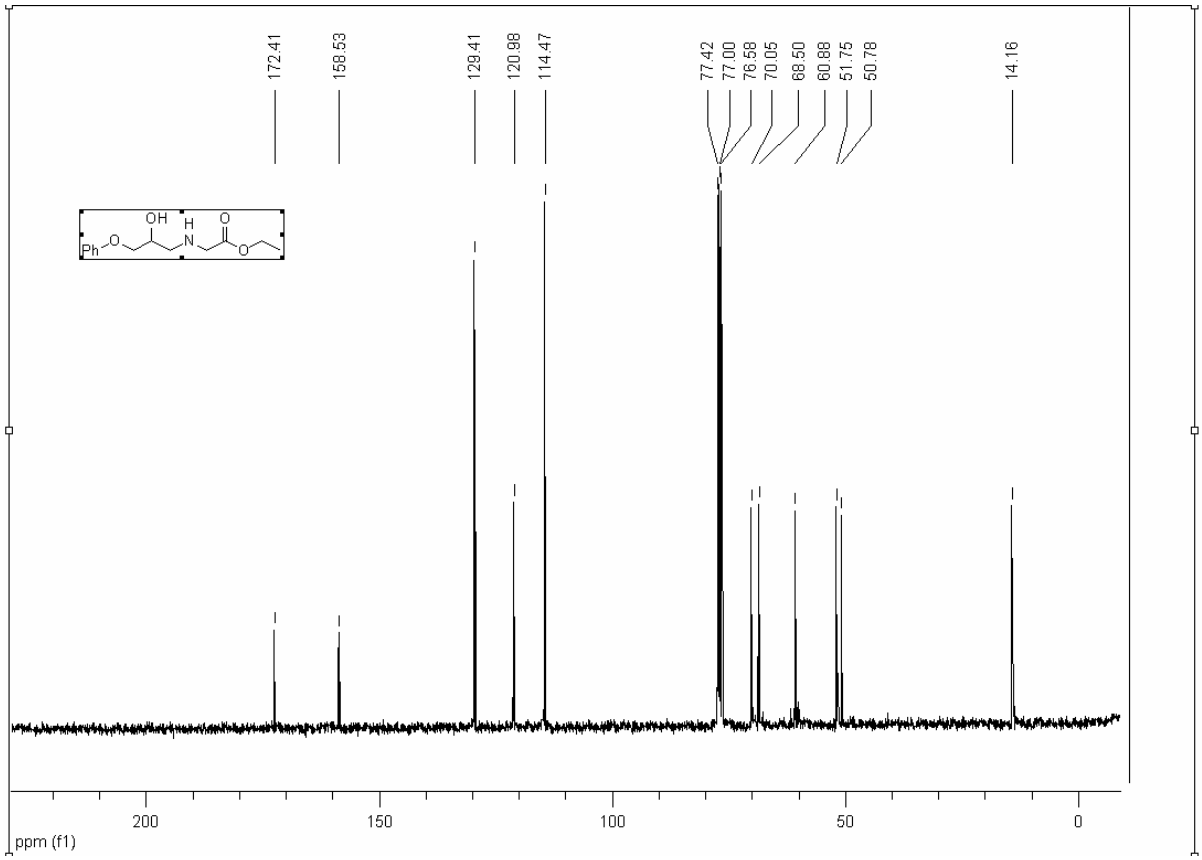
Compound 6a


OH
H
N
O
Ph
O
O
Ph
14.78
6.24
5.96
8.00
1.93
6.24
1.45
1.14
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

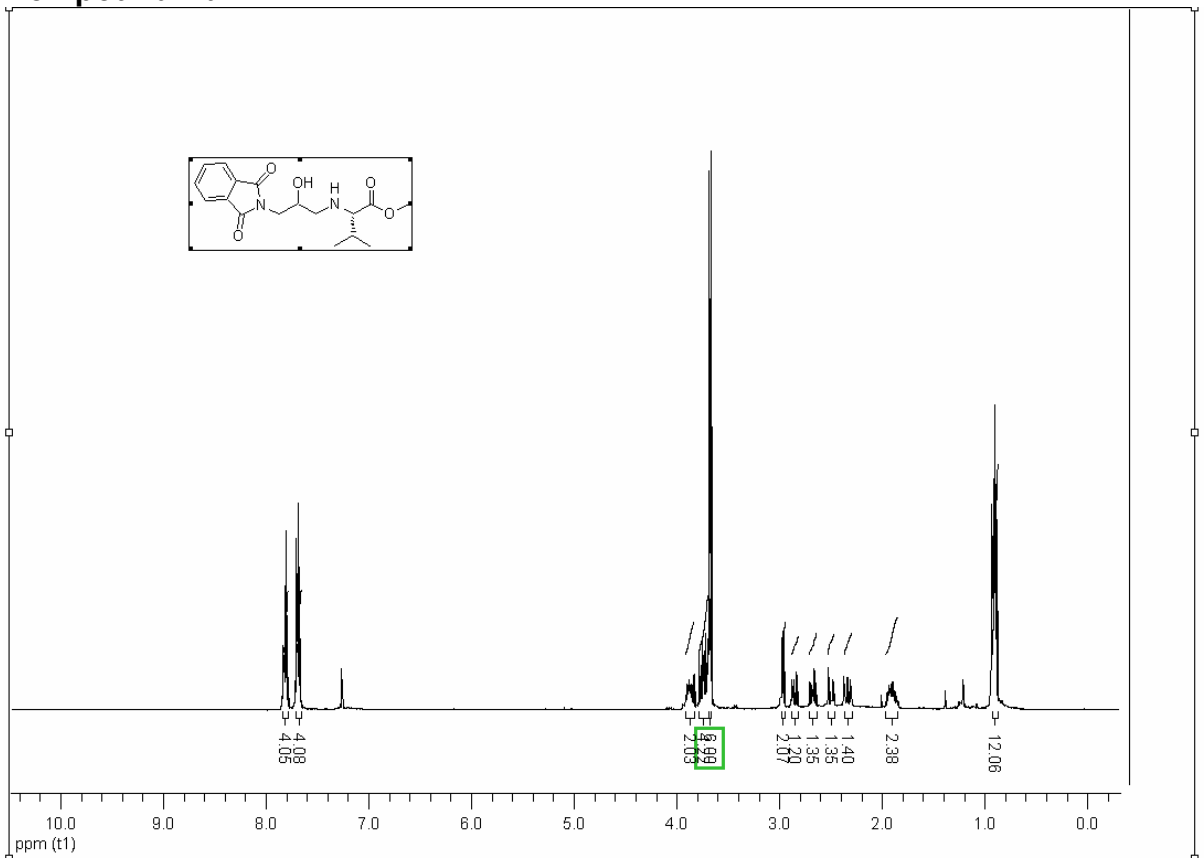

174.78
174.69
158.47
137.08
129.32
129.04
128.38
126.72
120.88
114.42
77.42
77.00
76.58
70.02
69.65
68.71
68.00
63.25
62.57
51.73
50.45
49.96
39.62
39.57
OH
H
N
O
Ph
O
O
Ph
150
100
50
ppm (t1)

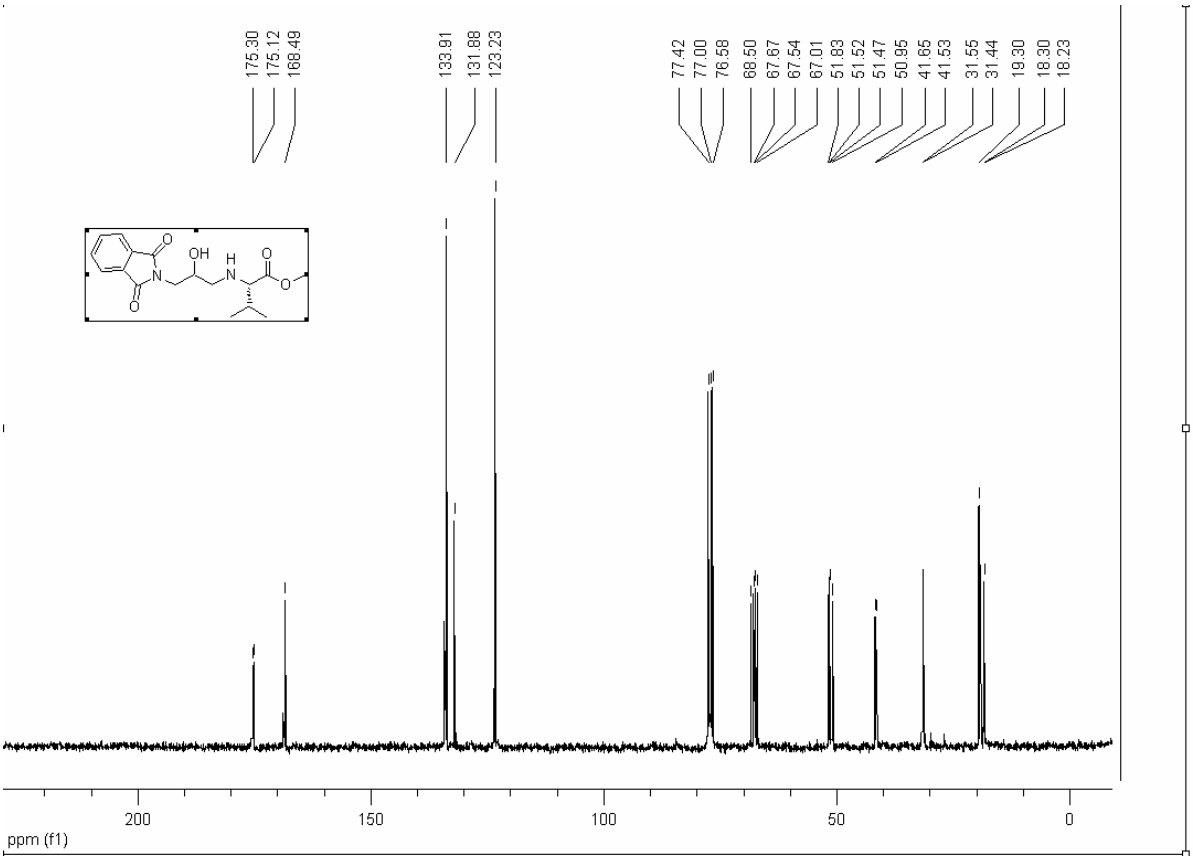
Compound 7a


OH
H
N
O
Ph
O
O
2.20
3.21
1.98
2.00
1.72
2.17
1.28
3.06
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

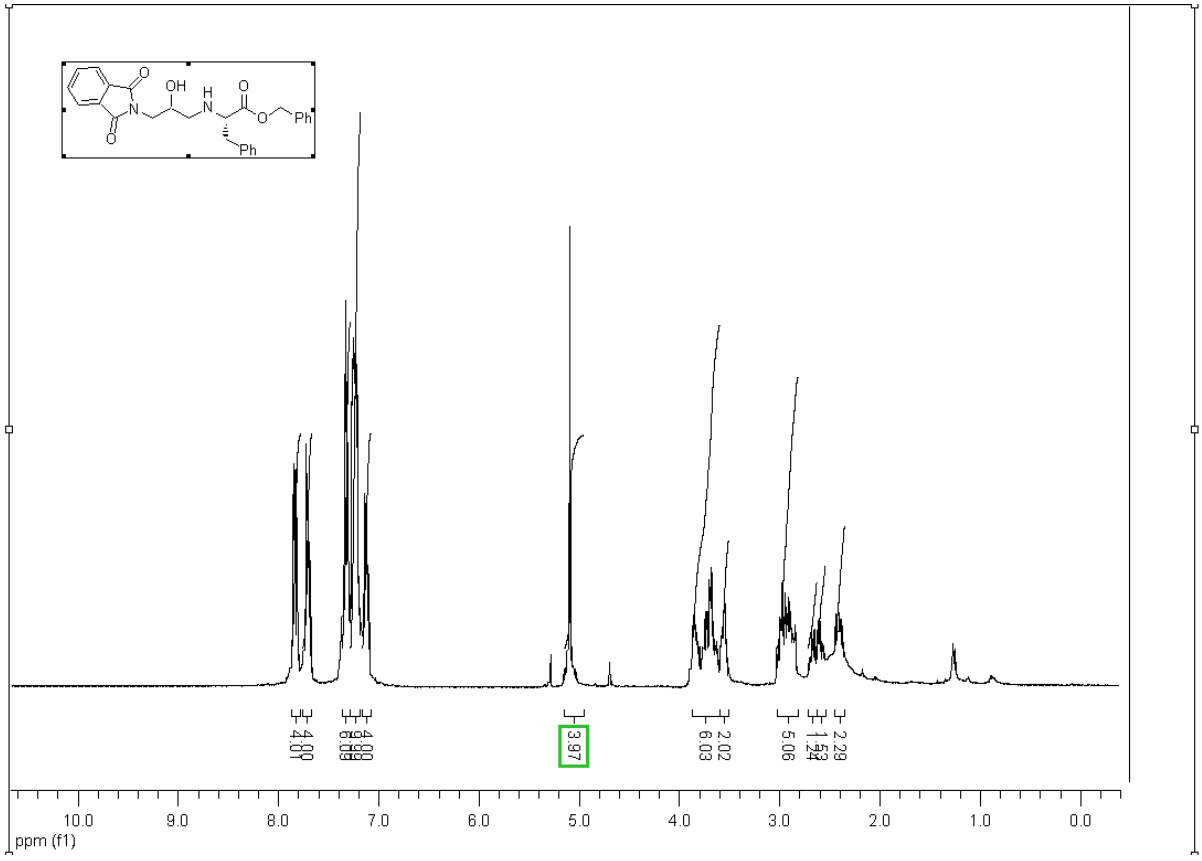

172.41
158.53
129.41
120.98
114.47
77.42
77.00
76.58
70.05
68.50
60.88
51.75
50.78
14.16
OH
H
N
O
Ph
O
O
200
150
100
50
0
ppm (f1)

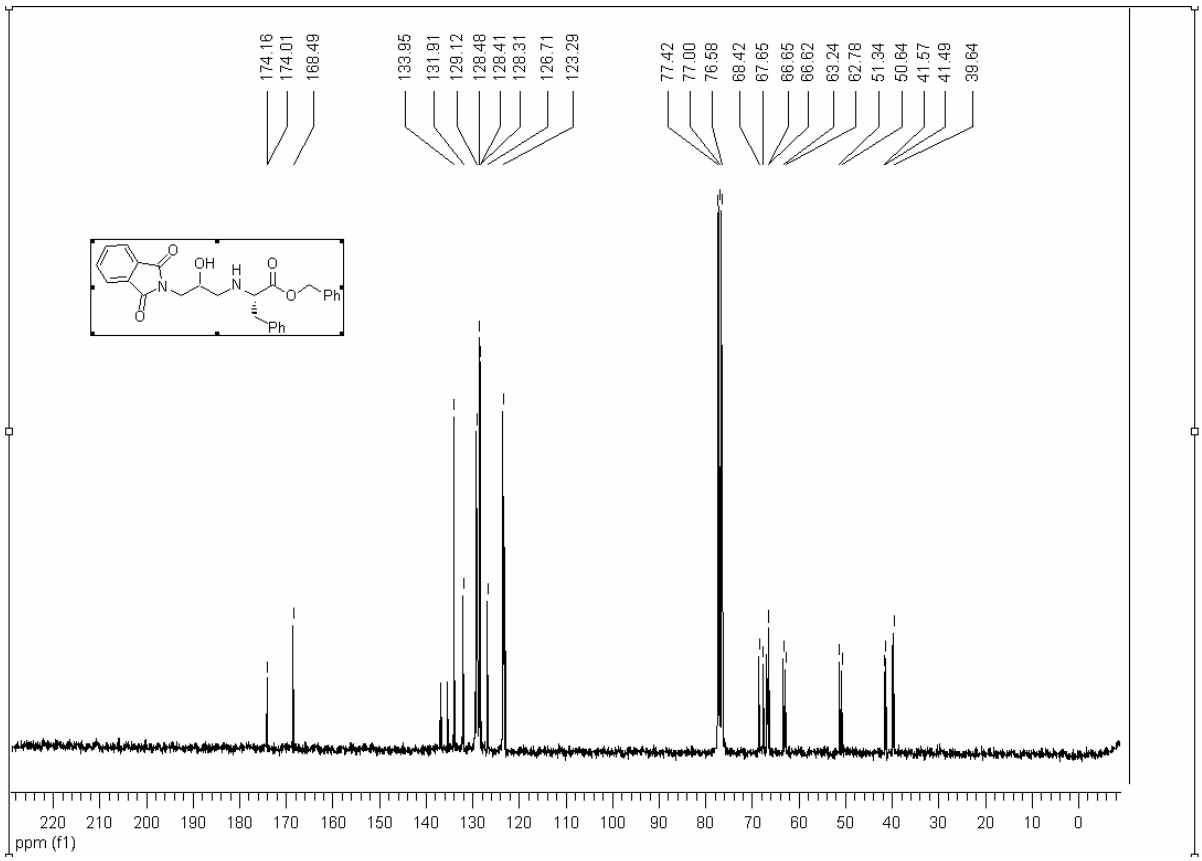
Compound 2b


4.05
4.09
2.03
6.80
2.07
1.20
1.35
1.40
2.38
12.06
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

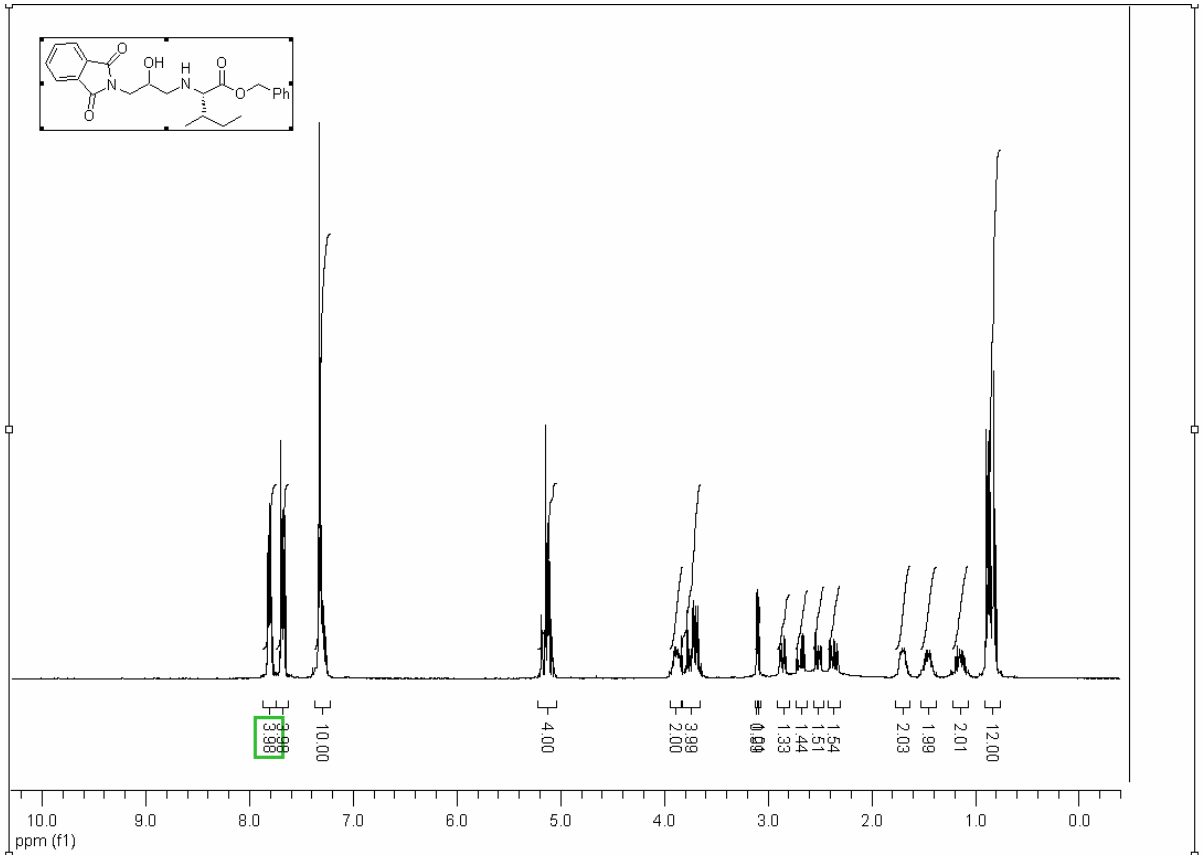

175.30
175.12
168.49
133.91
131.88
123.23
77.42
77.00
76.58
68.50
67.67
67.54
67.01
51.83
51.52
51.47
50.95
41.65
41.53
31.55
31.44
19.30
18.30
18.23
200
150
100
50
0
ppm (f1)

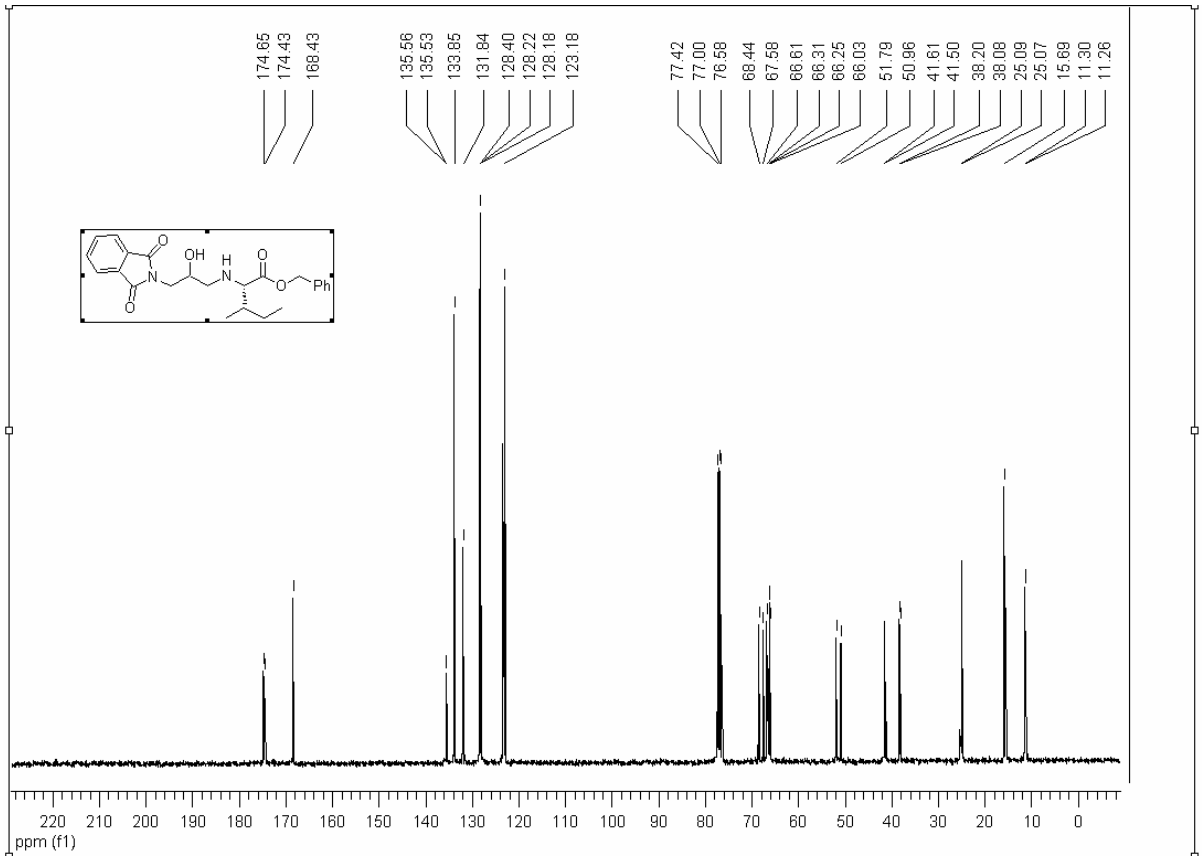
Compound 8b


4.00
4.00
6.09
3.67
6.03
2.02
5.06
1.53
1.54
2.29
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

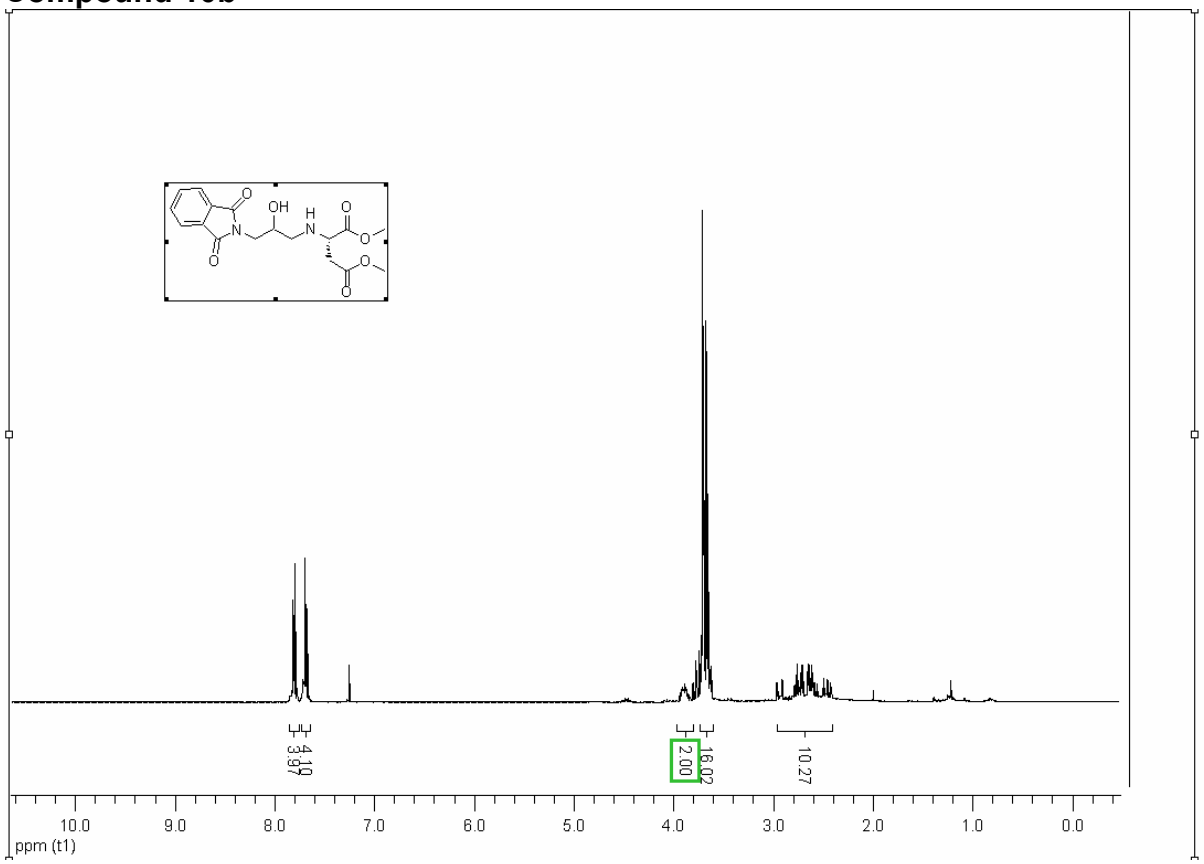

174.16
174.01
168.49
133.95
131.91
129.12
128.48
128.41
128.31
126.71
123.29
77.42
77.00
76.58
68.42
67.65
66.65
66.62
63.24
62.78
51.34
50.64
41.57
41.49
39.64
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)

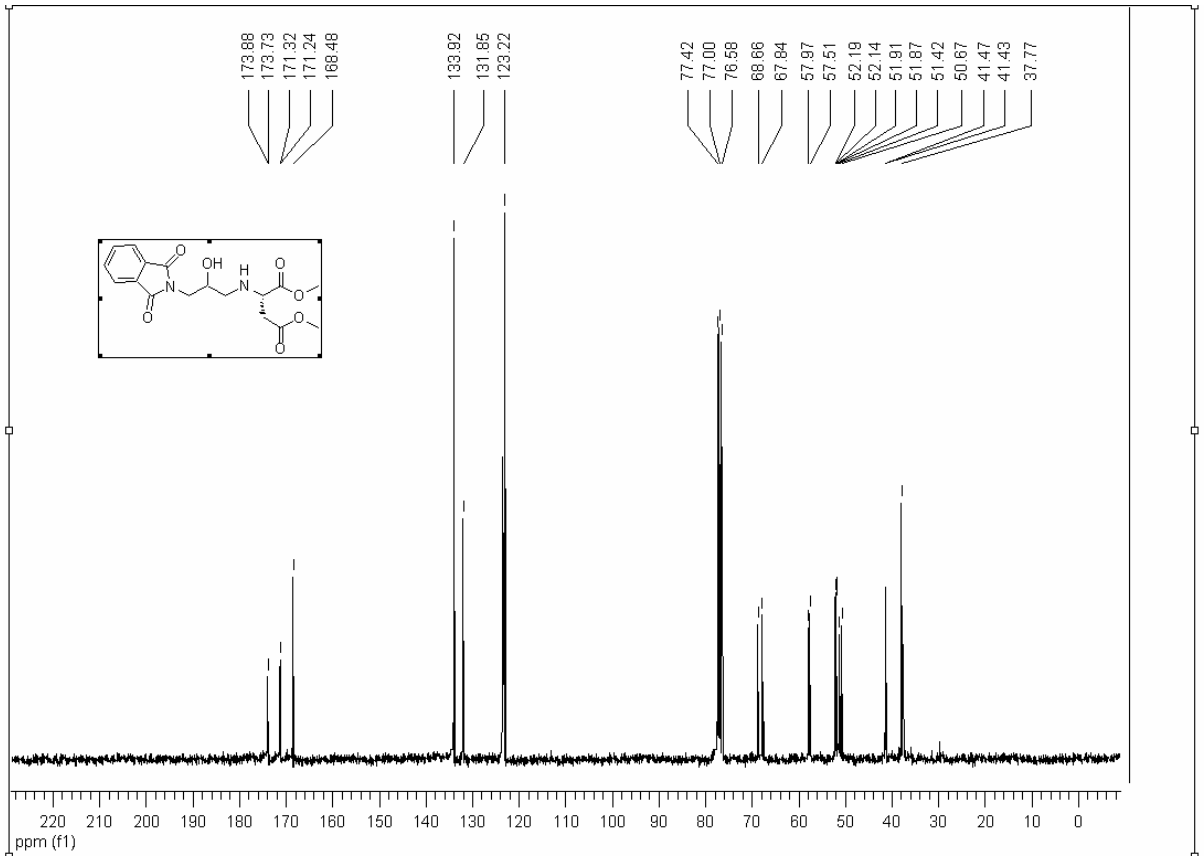
Compound 9b


OH
H
N
O
O
Ph
3.88
3.88
10.00
4.00
2.00
3.89
1.33
1.44
1.51
1.54
2.03
1.99
2.01
12.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

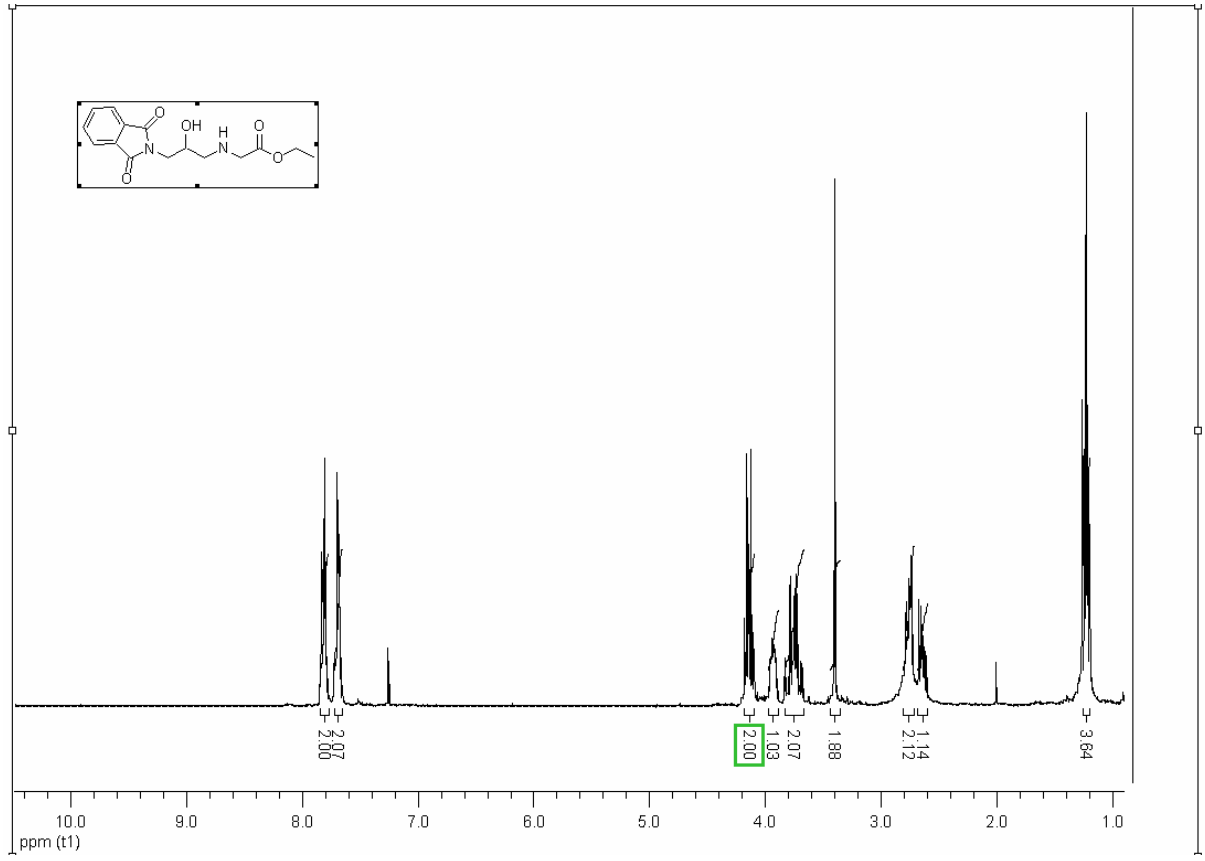

174.65
174.43
168.43
135.56
135.53
133.85
131.84
128.40
128.22
128.18
123.18
77.42
77.00
76.58
68.44
67.58
66.61
66.31
66.25
66.03
51.79
50.96
41.61
41.50
38.20
38.08
25.09
25.07
15.69
11.30
11.26
OH
H
N
O
O
Ph
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)

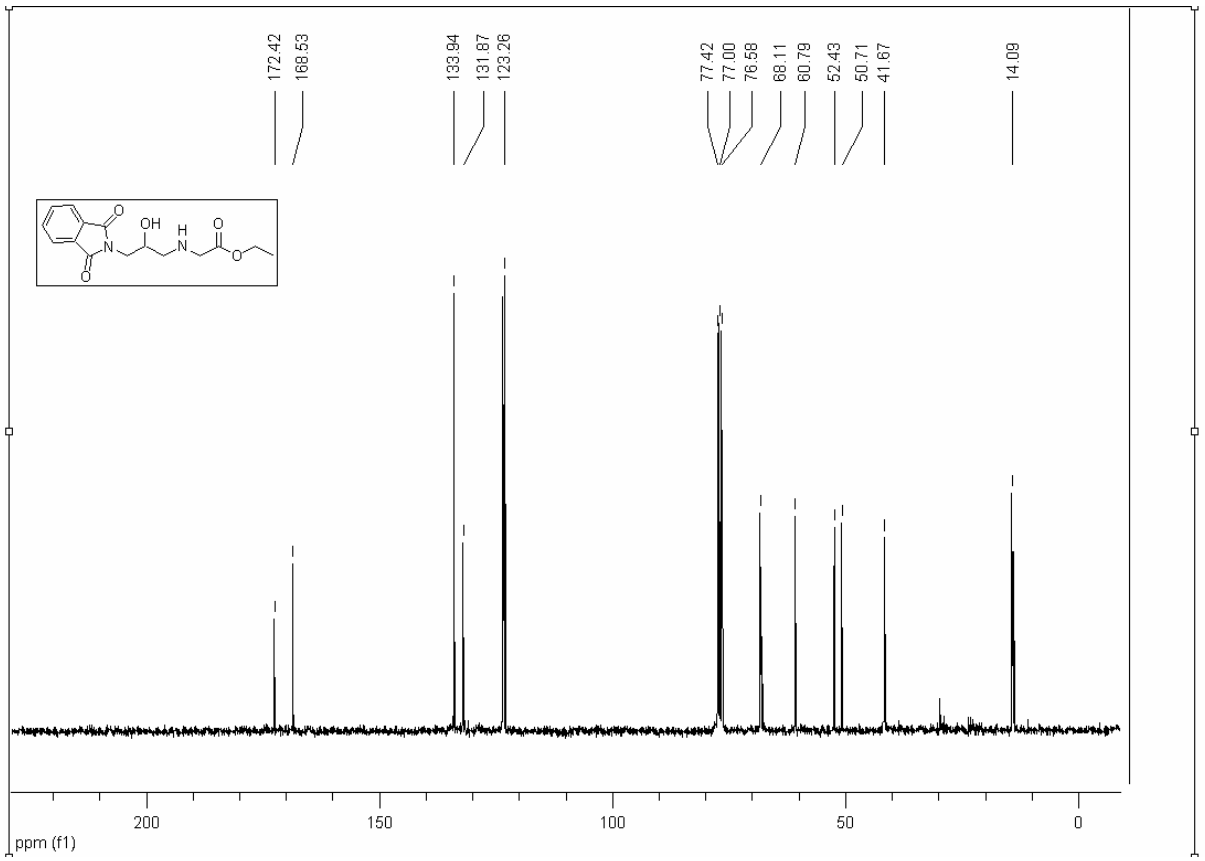
Compound 10b



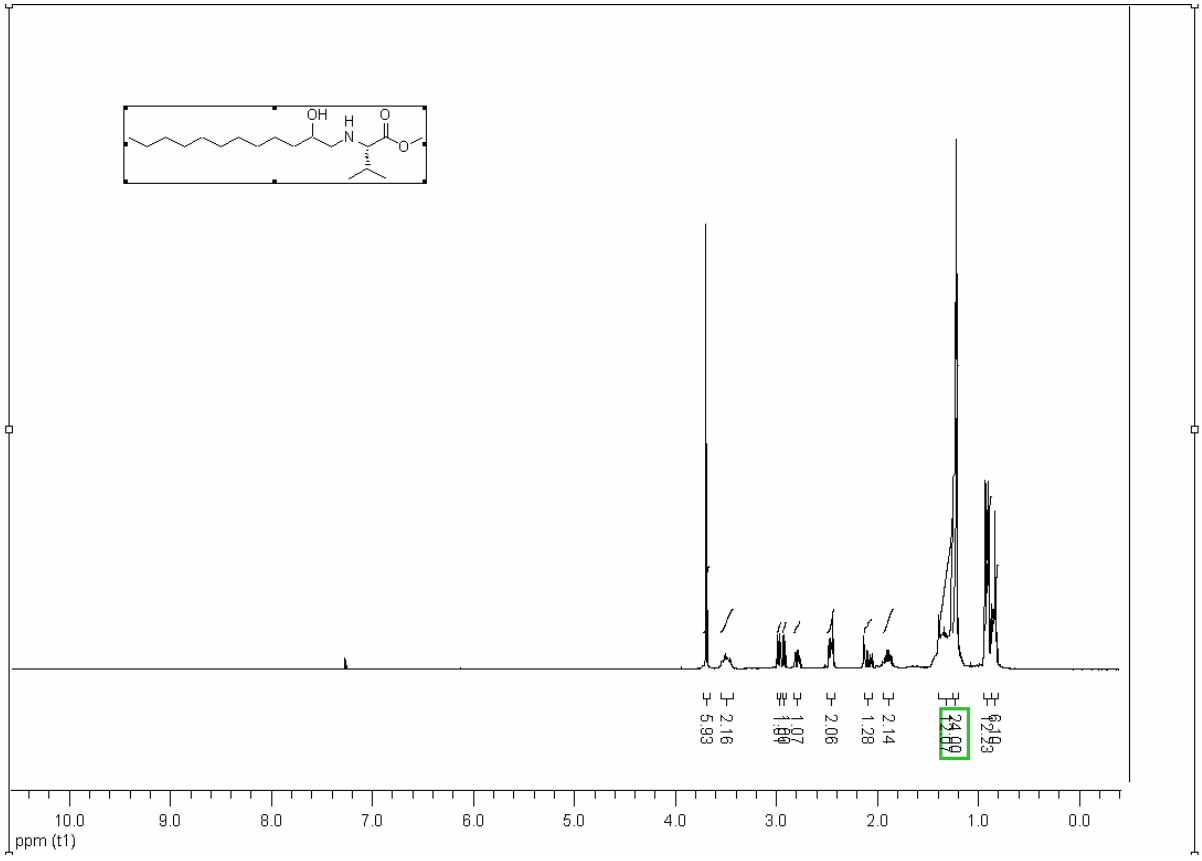


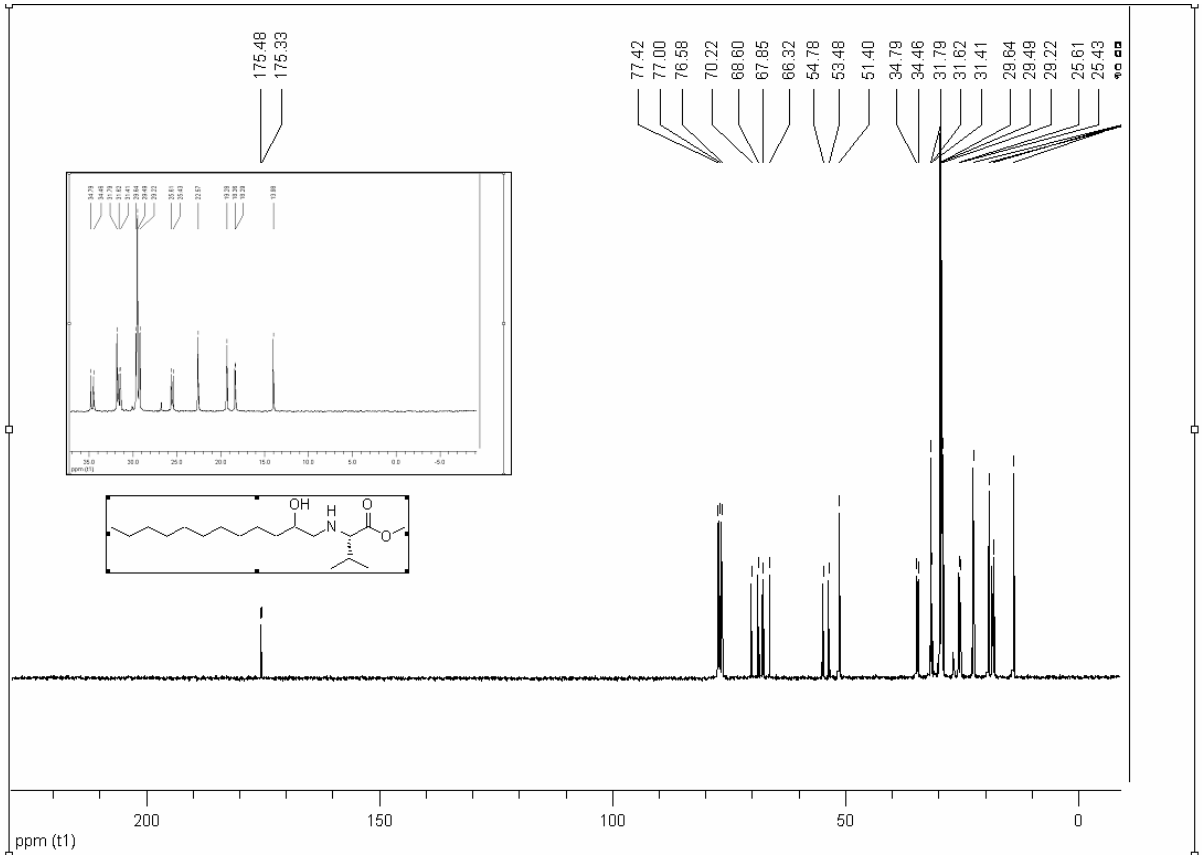
Compound 7b


2.07
2.00
1.03
2.07
1.88
2.12
1.14
3.64
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

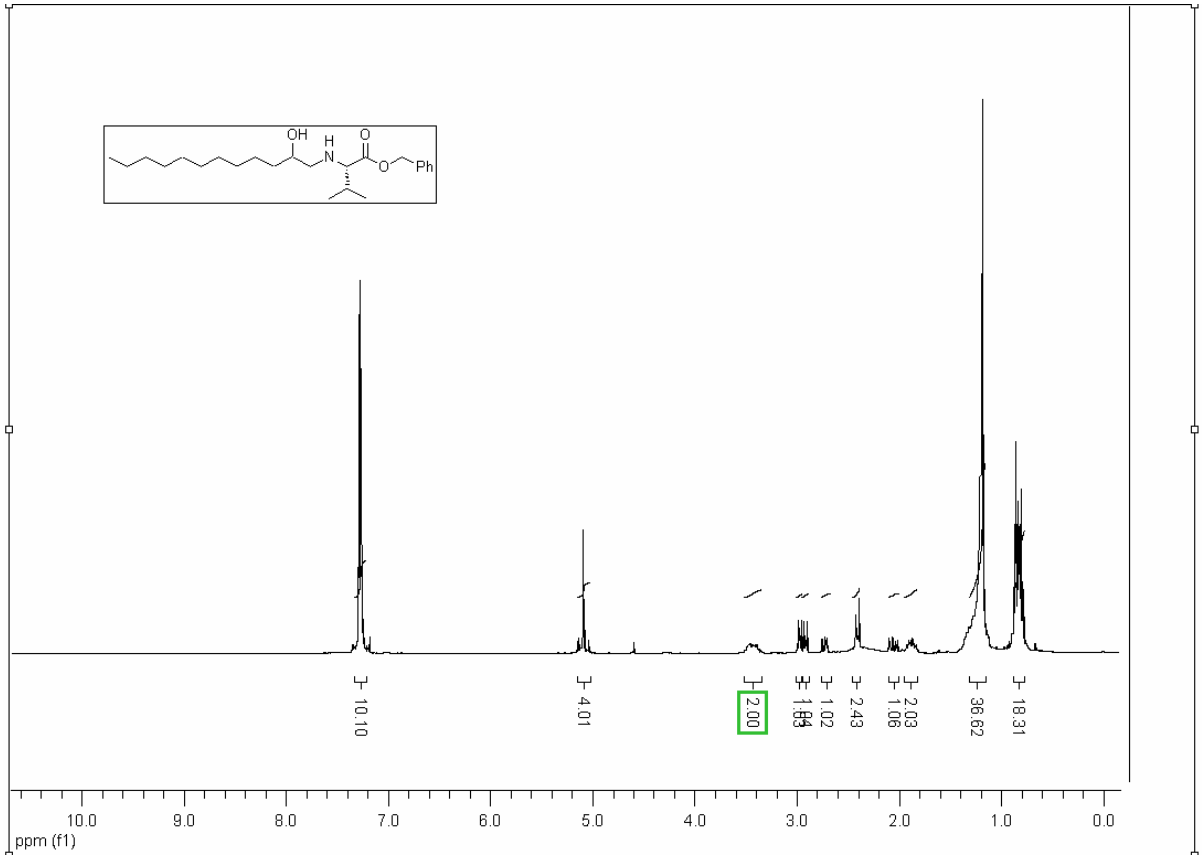

172.42
168.53
133.94
131.87
123.26
77.42
77.00
76.58
68.11
60.79
52.43
50.71
41.67
14.09
200
150
100
50
0
ppm (f1)

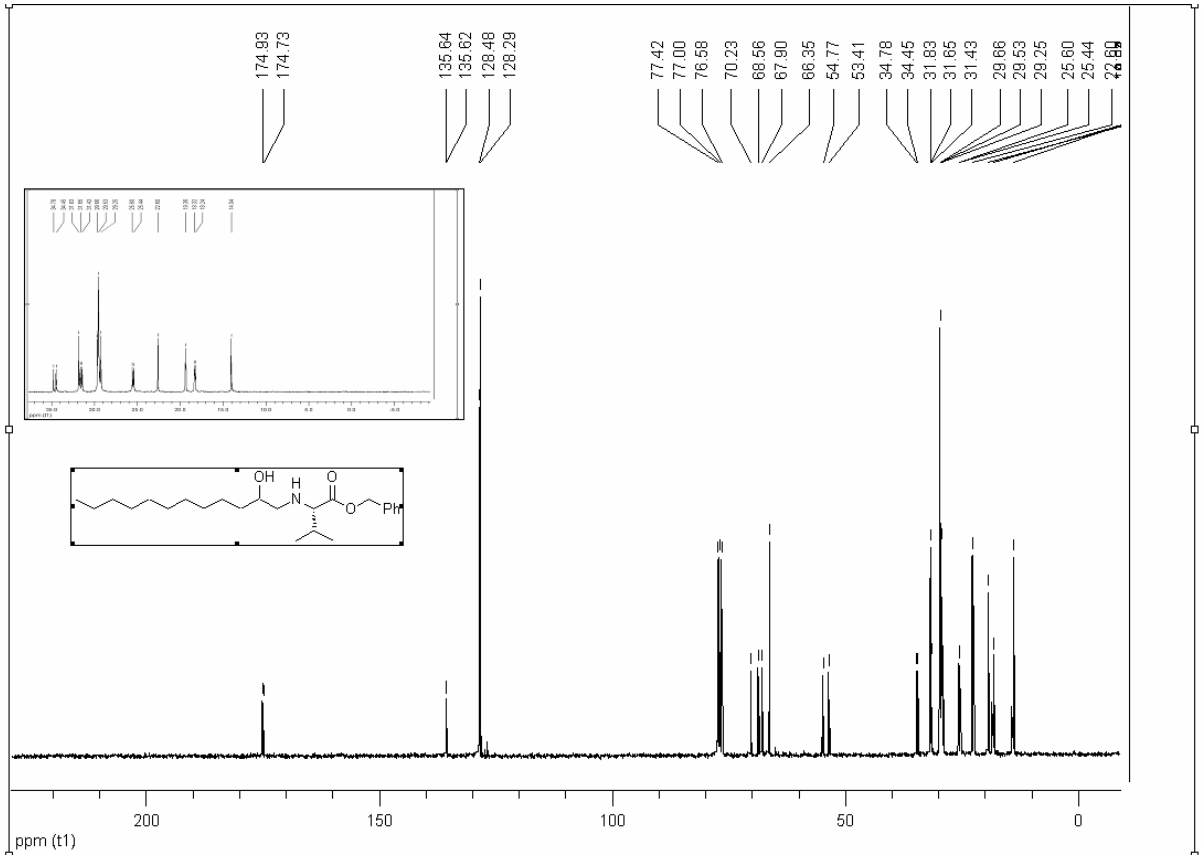
Compound 2c


OH
H
N
O
O
5.83
2.16
1.07
1.00
2.06
1.28
2.14
12.00
6.23
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

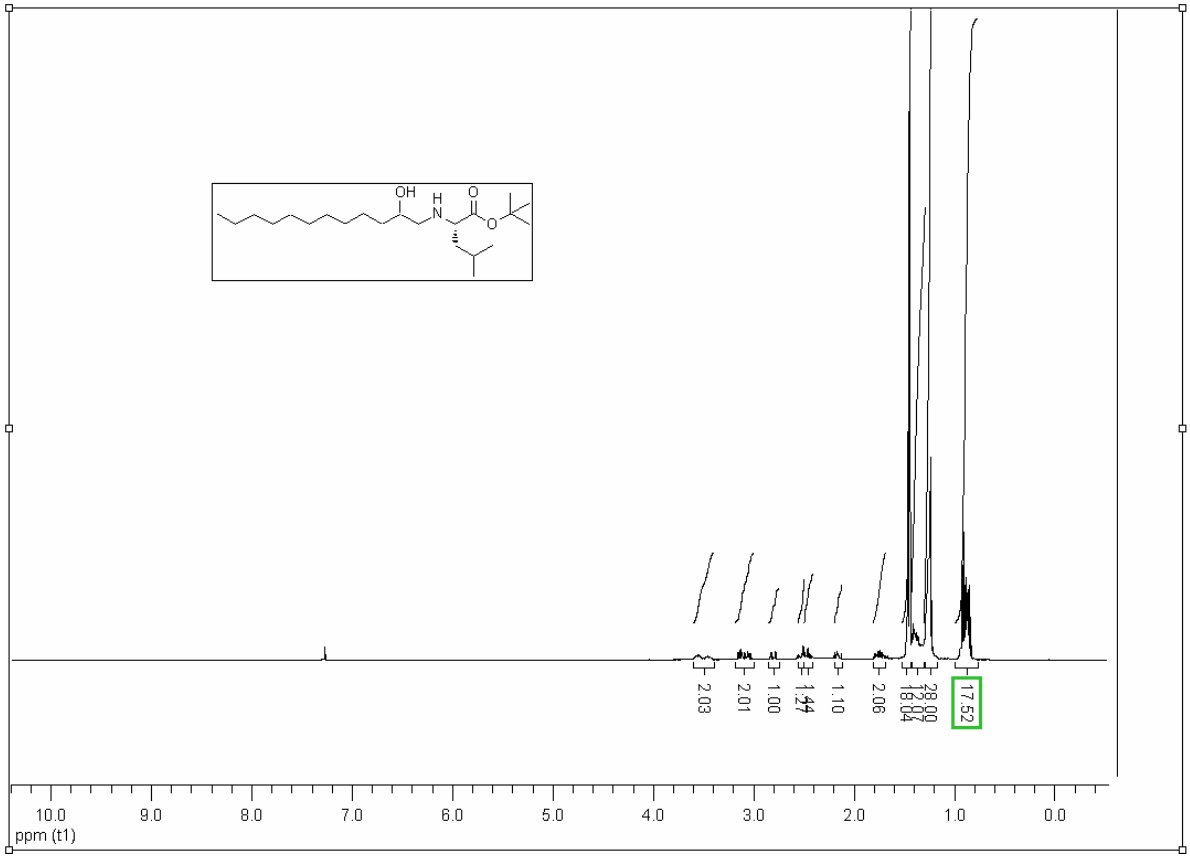

175.48
175.33
77.42
77.00
76.58
70.22
68.60
67.85
66.32
54.78
53.48
51.40
34.79
34.46
31.79
31.62
31.41
29.64
29.49
29.22
25.61
25.43
OH
H
N
O
O
200
150
100
50
0
ppm (t1)

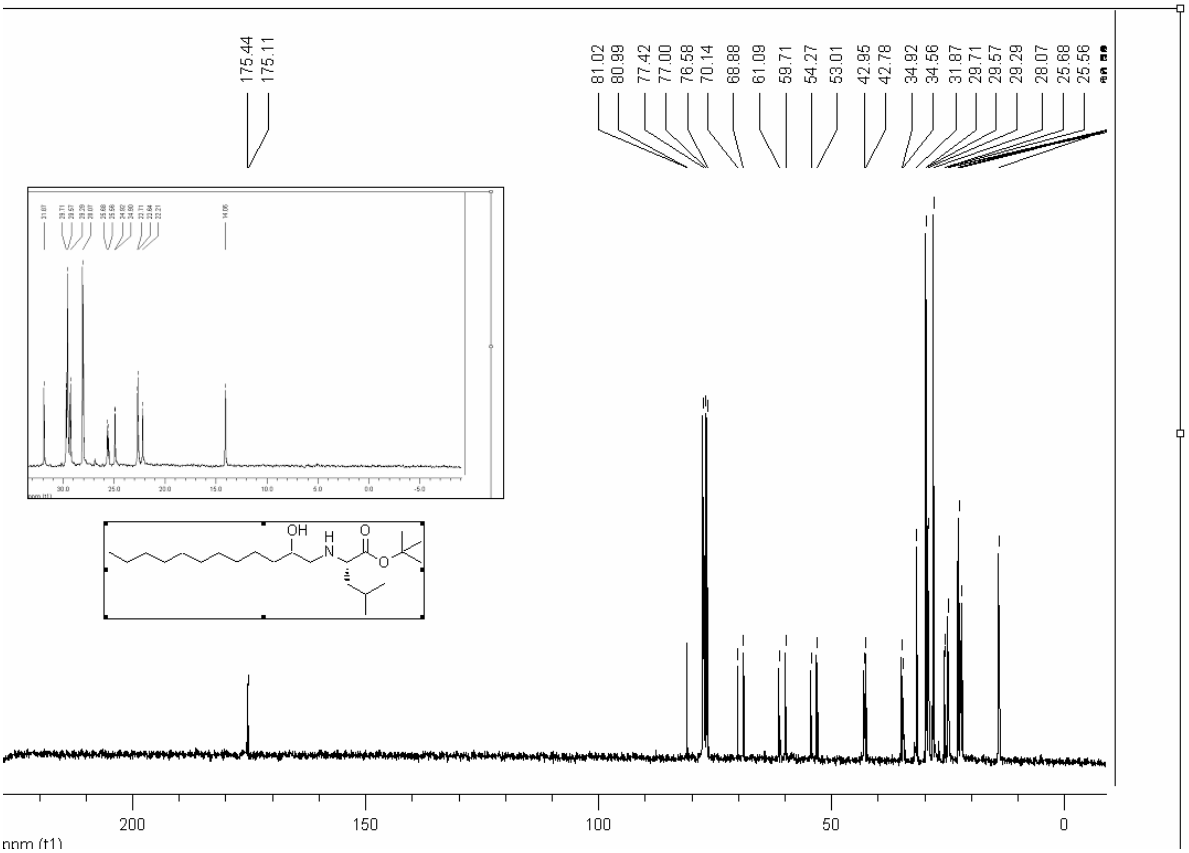
Compound 3c


OH
H
N
O
O
Ph
10.10
4.01
2.00
1.84
1.02
2.43
2.03
1.06
36.62
18.31
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

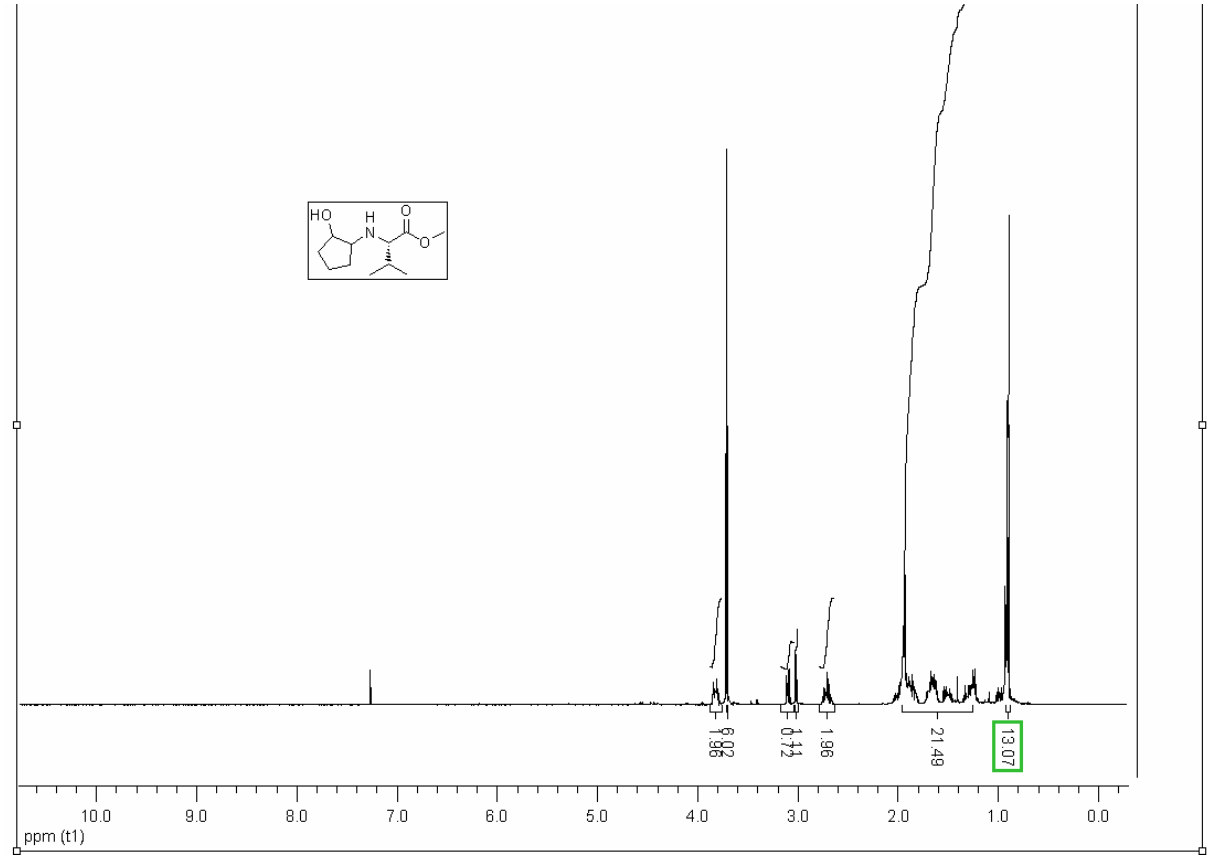

174.93
174.73
135.64
135.62
128.48
128.29
77.42
77.00
76.58
70.23
68.56
67.90
66.35
54.77
53.41
34.78
34.45
31.83
31.65
31.43
29.66
29.53
29.25
25.60
25.44
OH
H
N
O
O
Ph
200
150
100
50
0
ppm (t1)

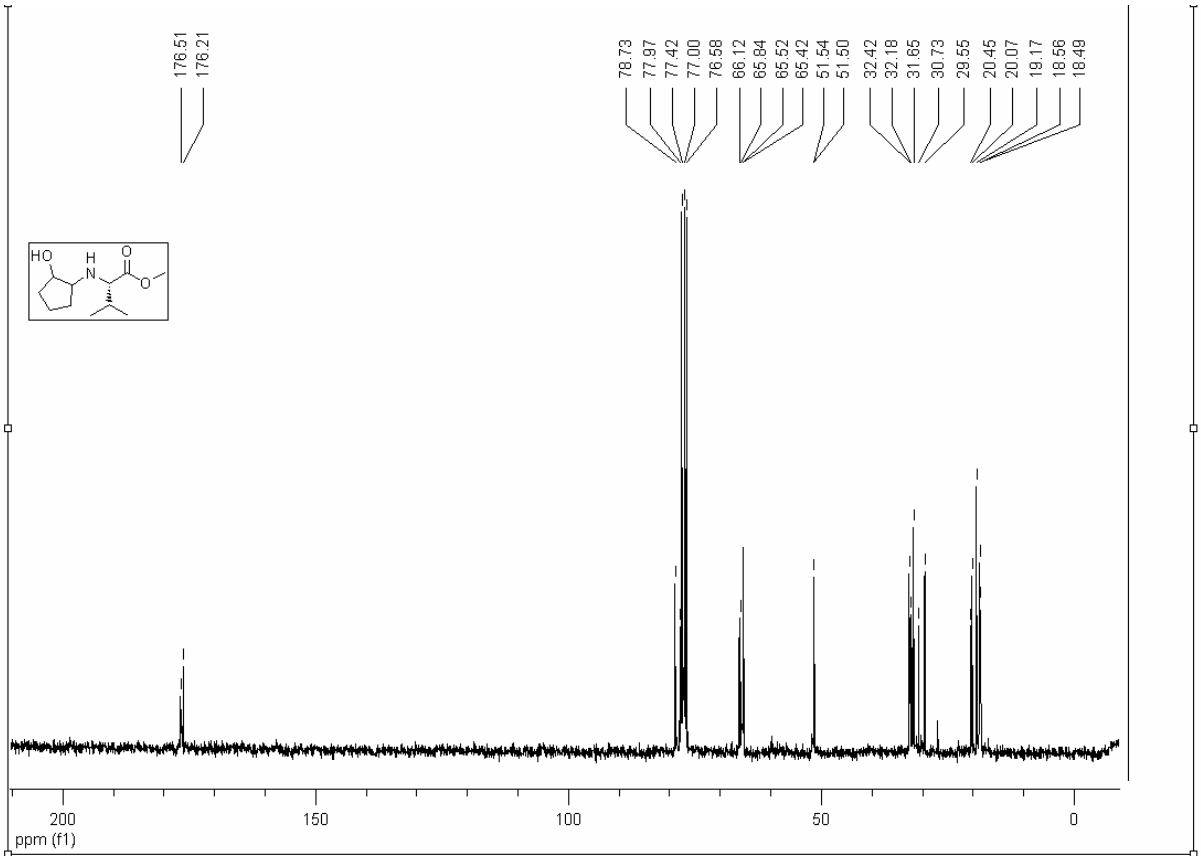
Compound 5c


OH
H
N
O
O
2.03
2.01
1.00
1.44
1.10
2.06
28.00
16.04
17.52
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

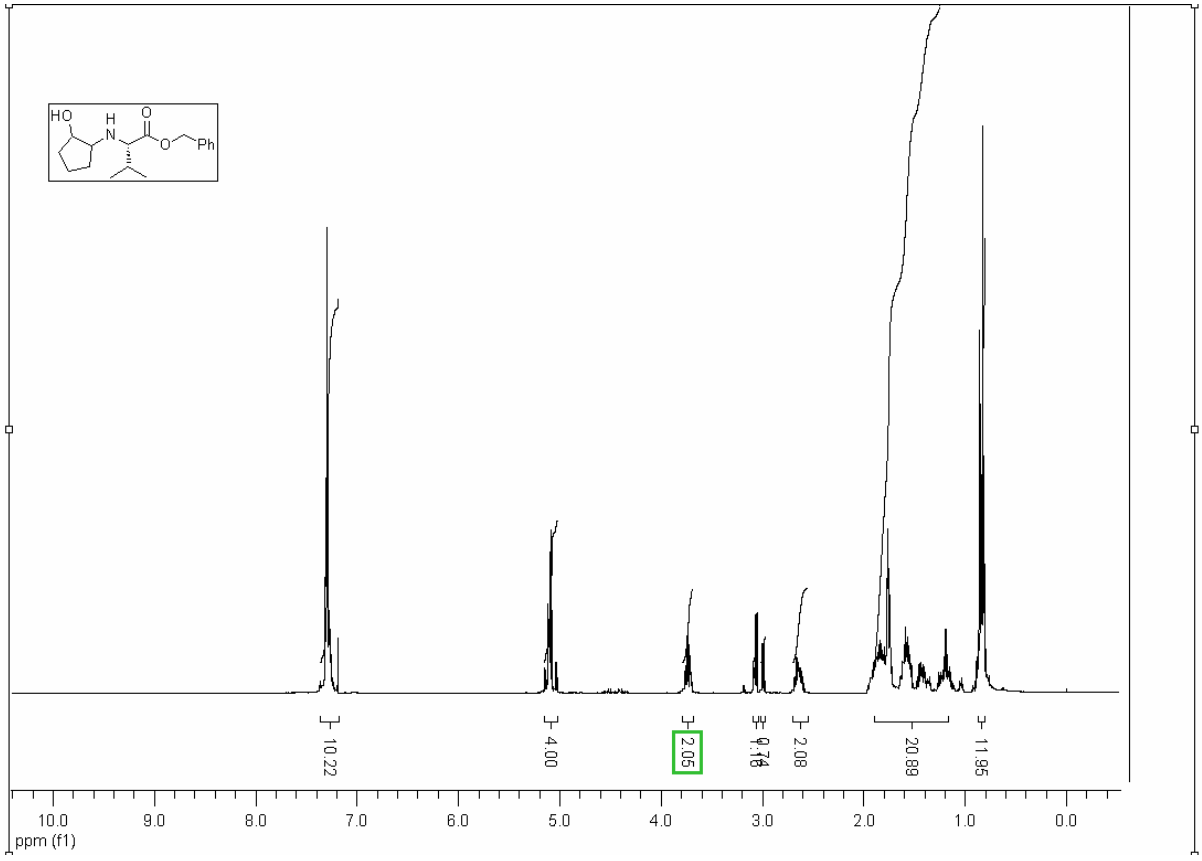

175.44
175.11
81.02
80.99
77.42
77.00
76.58
70.14
68.88
61.09
59.71
54.27
53.01
42.95
42.78
34.92
34.56
31.87
29.71
29.57
29.29
28.07
25.68
25.56
OH
H
N
O
O
200
150
100
50
0
ppm (t1)

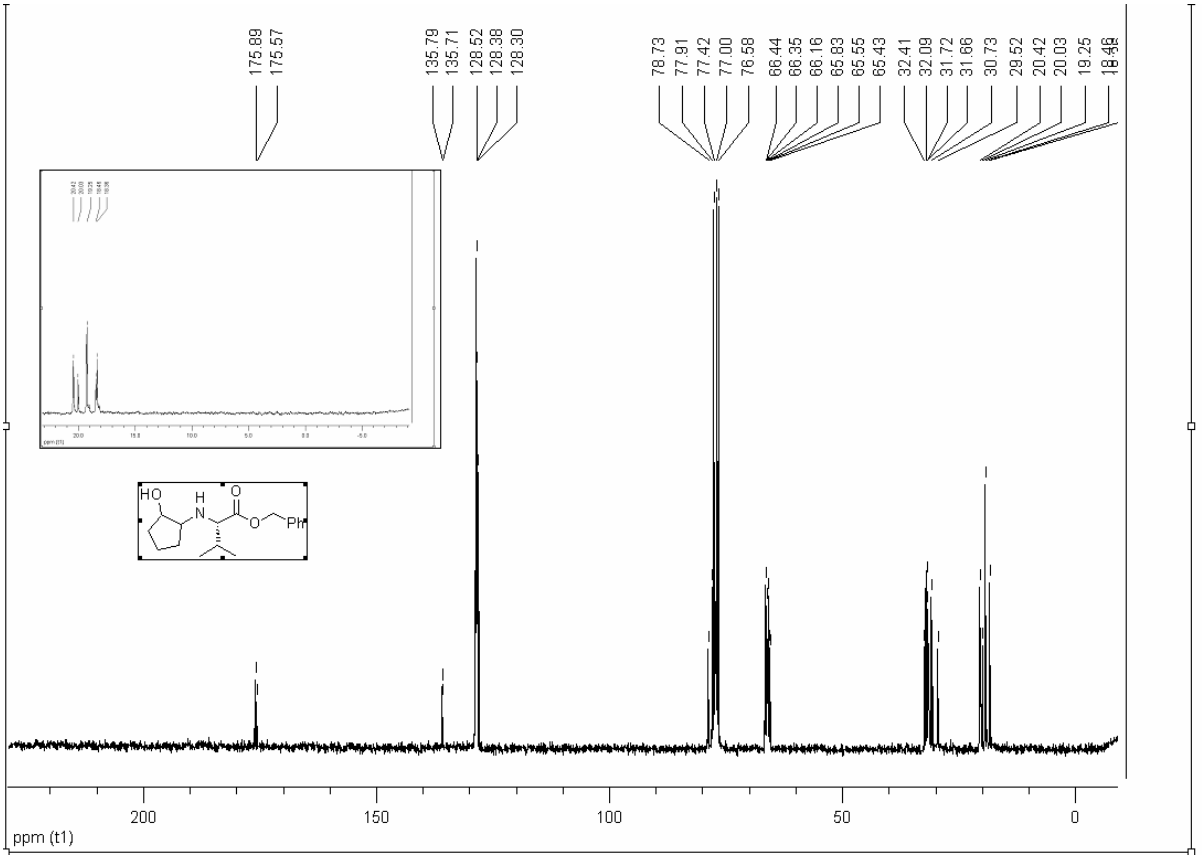
Compound 2d


HO
H
N
O
O
6.02
1.11
1.12
1.96
21.49
13.07
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

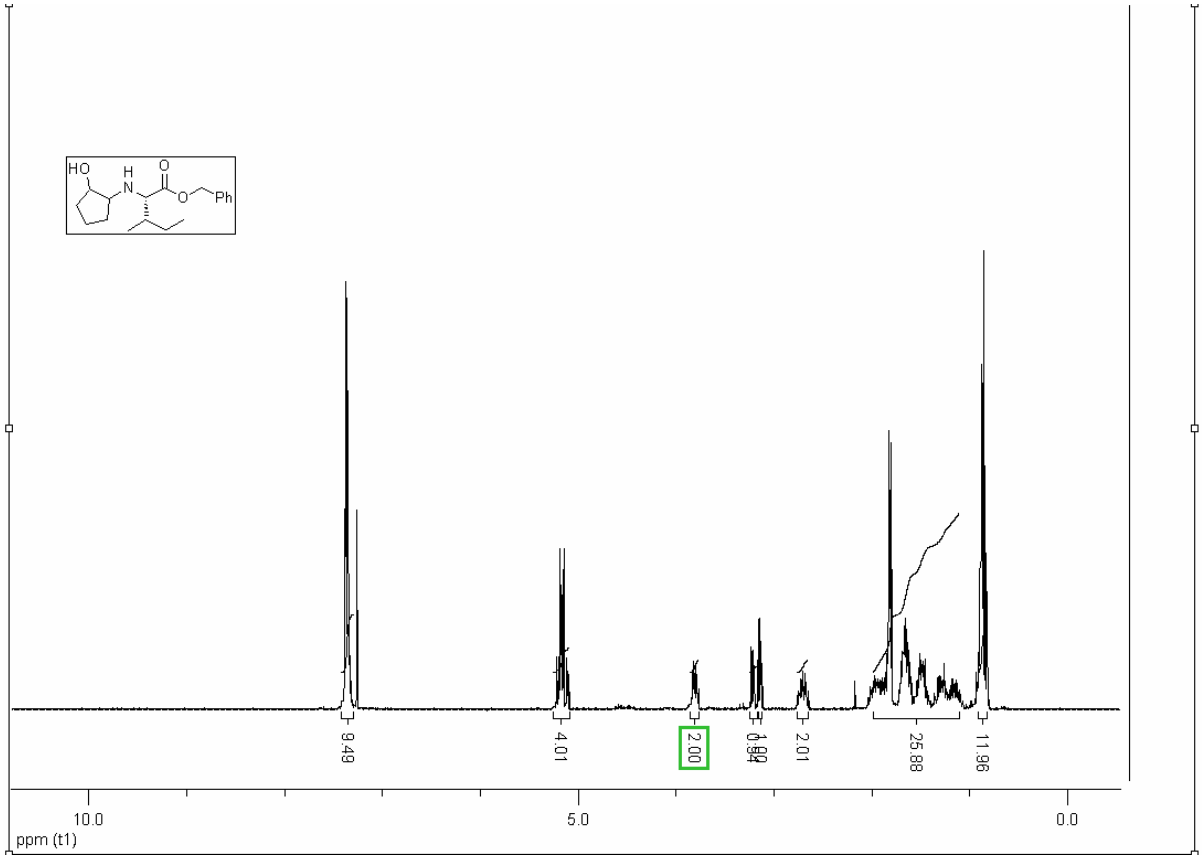

176.51
176.21
78.73
77.97
77.42
77.00
76.58
66.12
65.84
65.52
65.42
51.54
51.50
32.42
32.18
31.65
30.73
29.55
20.45
20.07
19.17
18.56
18.49
HO
H
N
O
O
200
150
100
50
0
ppm (f1)

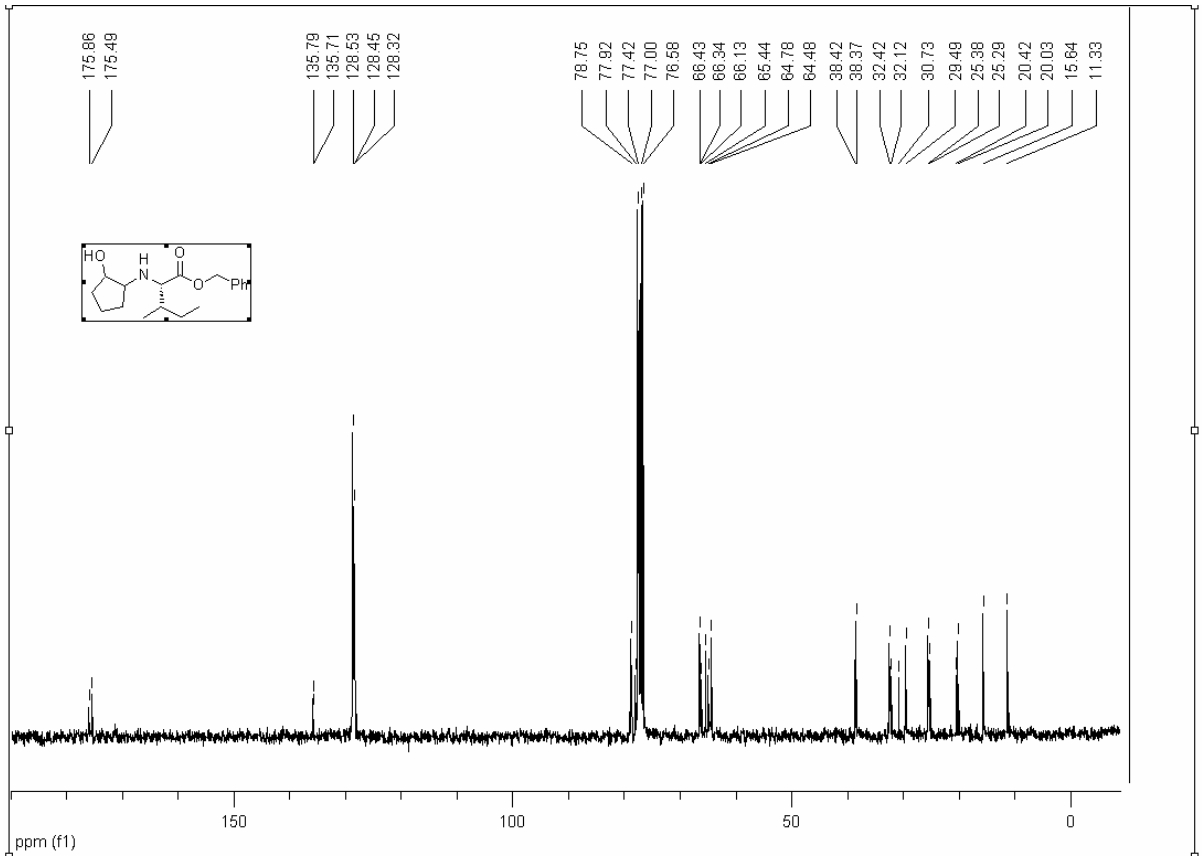
Compound 3d


HO
H
N
O
O
Ph
10.22
4.00
2.05
0.74
2.08
20.89
11.95
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

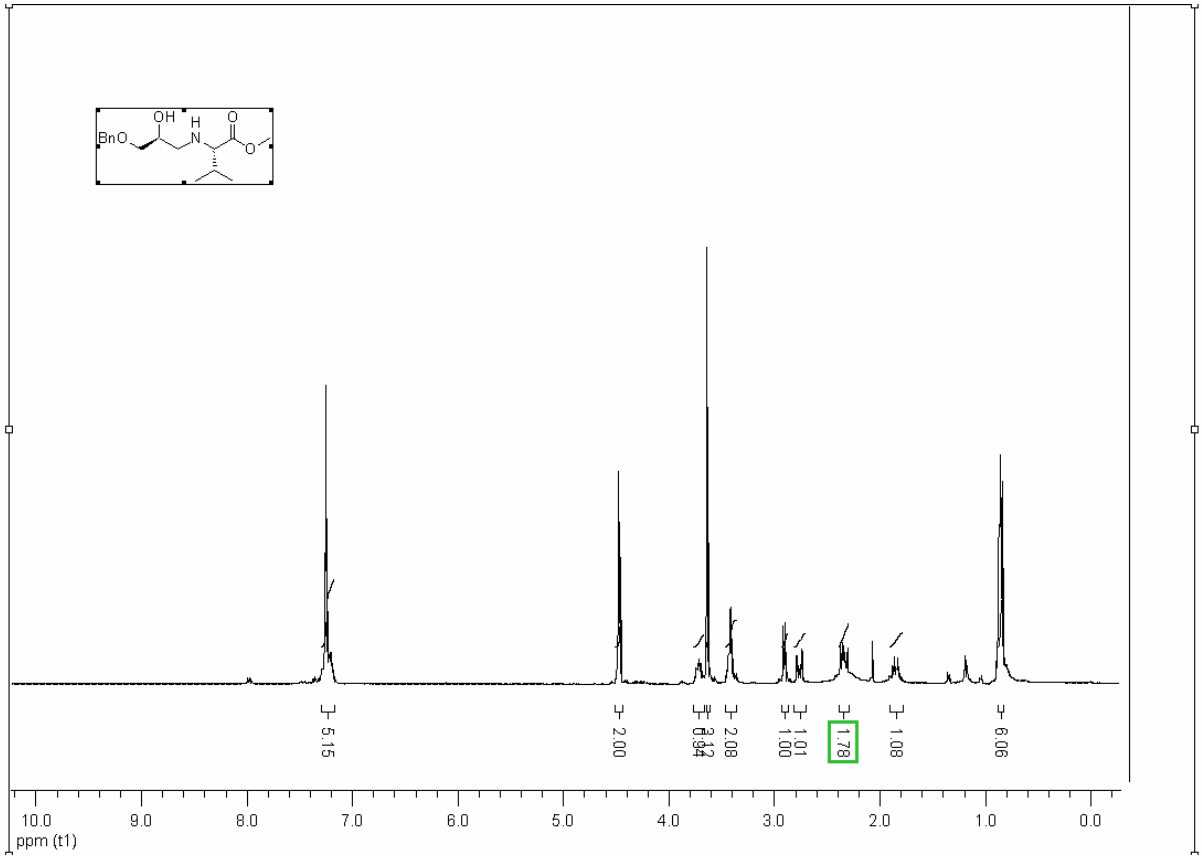

175.89
175.57
135.79
135.71
128.52
128.38
128.30
78.73
77.91
77.42
77.00
76.58
66.44
66.35
66.16
65.83
65.55
65.43
32.41
32.09
31.72
31.66
30.73
29.52
20.42
20.03
19.25
HO
H
N
O
O
Ph
200
150
100
50
0
ppm (t1)

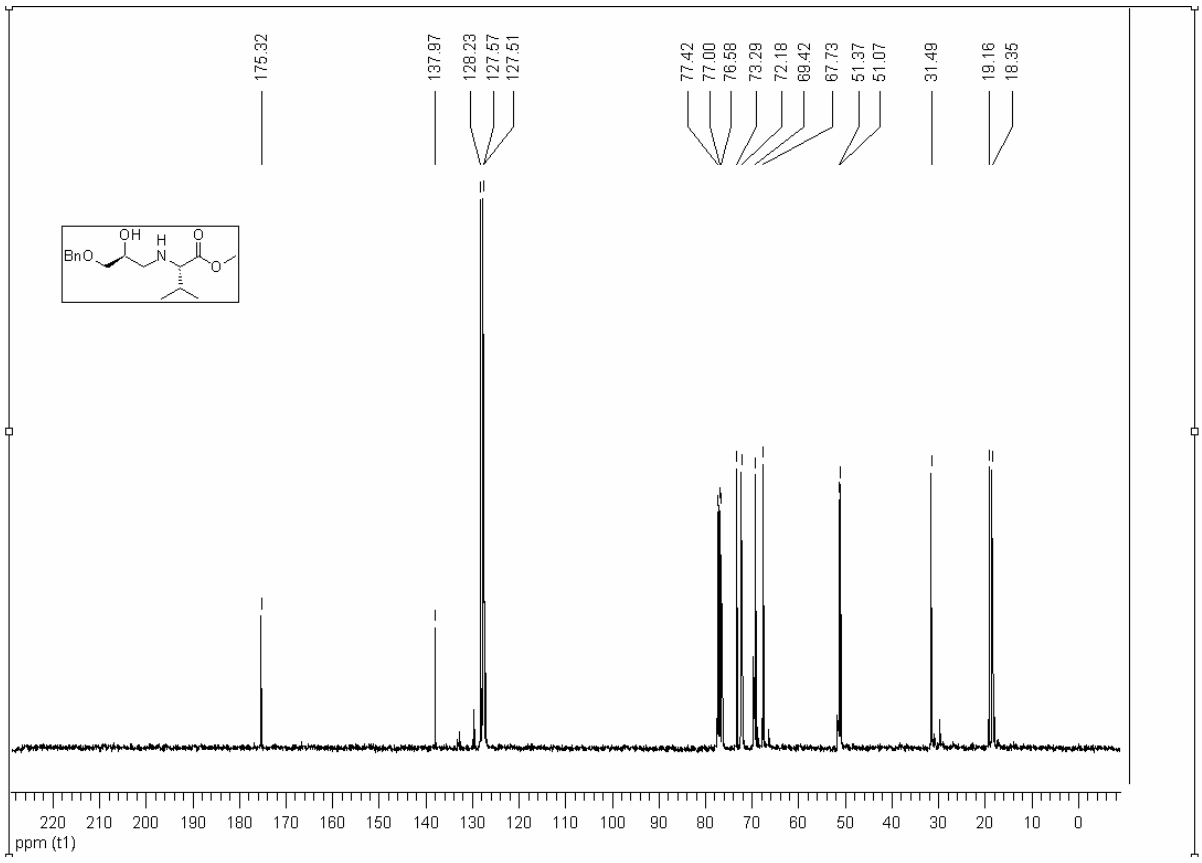
Compound 9d


HO
H
N
O
O
Ph
9.49
4.01
2.00
2.01
25.88
11.96
10.0
5.0
0.0
ppm (t1)

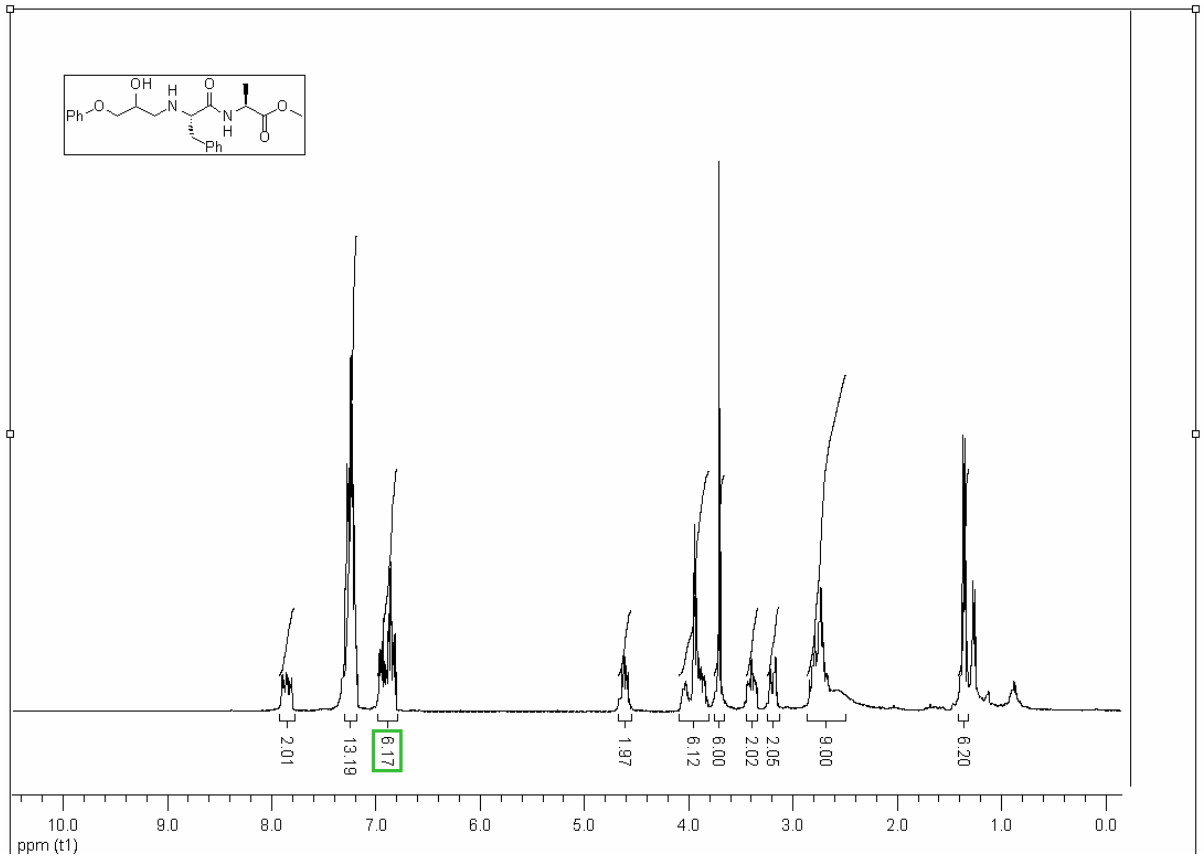

175.86
175.49
135.79
135.71
128.53
128.45
128.32
78.75
77.92
77.42
77.00
76.58
66.43
66.34
66.13
65.44
64.78
64.48
38.42
38.37
32.42
32.12
30.73
29.49
25.38
25.29
20.42
20.03
15.64
11.33
HO
H
N
O
O
Ph
150
100
50
0
ppm (f1)

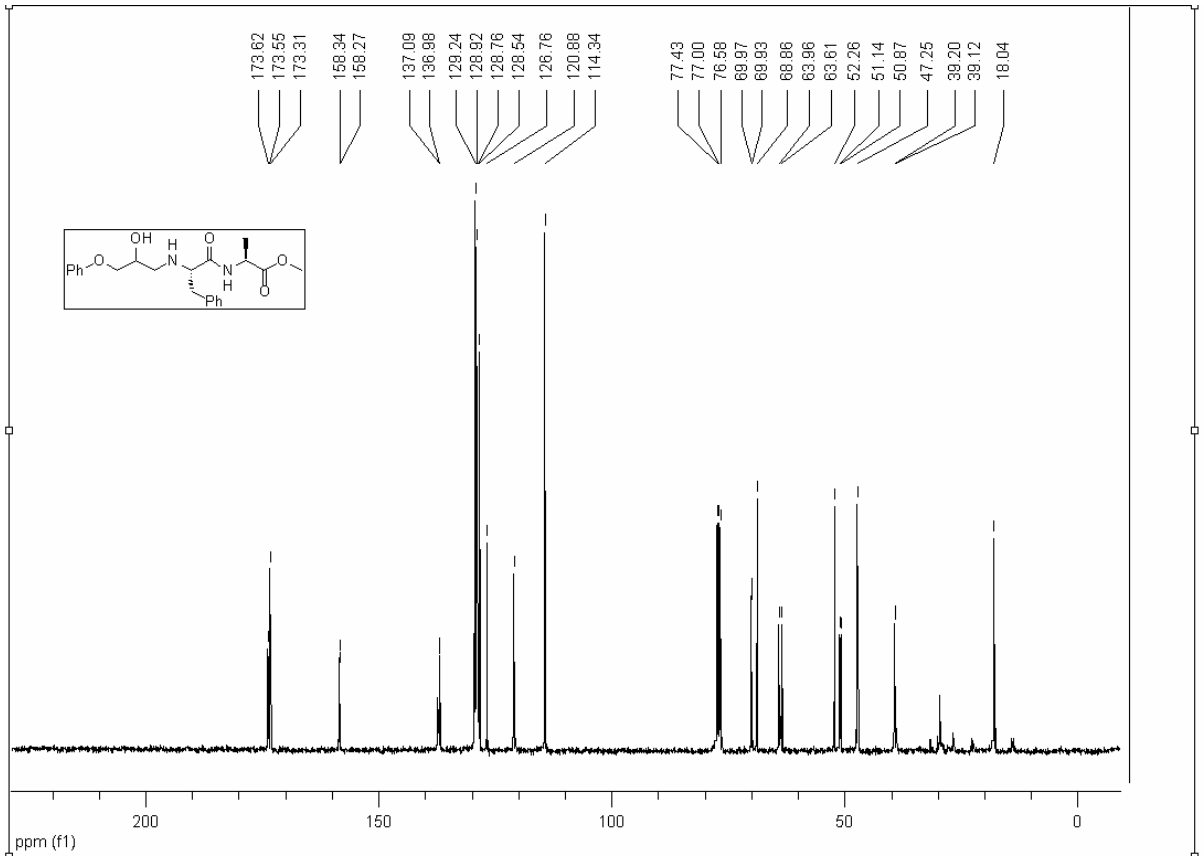
Compound 2e


BnO
OH
H
N
O
O
5.15
2.00
2.08
1.01
1.00
1.78
1.08
6.06
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


175.32
137.97
128.23
127.57
127.51
77.42
77.00
76.68
73.29
72.18
69.42
67.73
51.37
51.07
31.49
19.16
18.35
BnO
OH
H
N
O
O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (t1)

Compound 12a





Compound 12b