Chemoselective Conversion from α-Hydroxy Acids to α-Keto Acids Enabled by Nitroxyl-Radical-Catalyzed Aerobic Oxidation

Keisuke Furukawa, Haruki Inada, Masatoshi Shibuya* and Yoshihiko Yamamoto

Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8601, Japan

Supporting Information

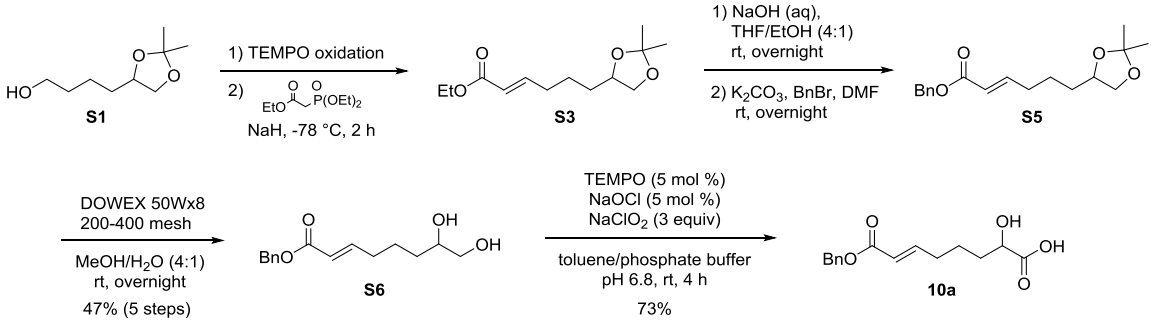
1. General considerations

Reagents were purchased from commercial suppliers and used without purification. Column chromatography was performed on SO_3H silica gel (CHROMATOREX®, Fuji Silysia Chemical LTD) for α-hydroxy acids, α-keto acids and neutral silica gel (Cica silica gel 60N) for others with solvents specified below. ^1H and ^{13}C NMR spectra were obtained for samples in $CDCl_3$ or MeCN-d_3 solutions at 25 ˚C. ^1H NMR chemical shifts are reported in terms of chemical shift (δ, ppm) relative to the singlet at δ 0.00 ppm for tetramethylsilane as an internal standard substance or 1.94 ppm for acetonitrile. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are reported in Hz. ^{13}C NMR spectra were fully decoupled and are reported in terms of chemical shift (δ, ppm) relative to the triplet at δ 77.0 ppm for $CDCl_3$ or 1.30 ppm for MeCN-d_3.

2. Preparation of α-hydroxy acids

α-Hydroxy acids **2a**, **7a**, **8a**, **9a** and **12a** were purchased from commercial suppliers and used without purification. α-Hydroxy acids **3a**, **4a**, **6a**, **13a** and **15a** were prepared according to previous report by us.[1] α-Hydroxy acids **5a** was prepared according to the reported procedure.[2] The other α-hydroxy acids were prepared following procedures.

(*E*)-8-(Benzyloxy)-2-hydroxy-8-oxooct-6-enoic acid (**10a**)



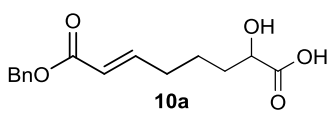
To a solution of the 4-(2,2-dimethyl-1,3-dioxolan-4-yl)butan-1-ol (**S1**, 1122 mg, 6.44 mmol), TEMPO (10.1 mg, 0.322 mmol) in CH_2Cl_2/sat. $NaHCO_3$ (aq) (19 mL/13 mL) were added 1.63 M NaOCl (aq) (4.7 mL) in sat. $NaHCO_3$ (6 mL) at 0 °C. After 20 min stirring at 0 °C, the reaction was quenched with sat. $Na_2S_2O_3$ (aq) and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford aldehyde **S2**, which was used to the next reaction without further purification. A suspension of NaH (60%, 283 mg, 7.08 mmol) and THF (30 mL) were added triethyl phosphonoacetate (1.42 mL, 7.08 mmol) at 0 °C, and stirred 30 min. The mixture were added

aldehyde **S2** in THF (15 mL) at -78 °C. After 2 h stirring, the reaction was quenched with H_2O and extracted with AcOEt (15 mL x 3). The combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford ester **S3**, which was used to the next reaction without further purification.

To a solution of ethyl ester **S3** in THF/EtOH (6.9 mL/1.7 mL) were added 2.5 M NaOH (aq) (8.6 mL, 21.5 mmol) at room temperature and stirred overnight. The reaction mixture were acidified using NaH_2PO_4 and extracted with AcOEt (10 mL x 3). The combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford carboxylic acid **S4**. The carboxylic acid **S4** was dissolved in DMF (10.8 mL) and added K_2CO_3 (713 mg, 5.16 mmol) and benzyl bromide (766 µL, 6.45 mmol). After overnight stirring, the reaction mixture were added H_2O and extracted with hexane:AcOEt (2:1) (10 mL x 3). The combined organic layer were washed with H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford benzyl ester **S5**.

To a solution of benzyl ester **S5** in MeOH/H_2O (11.5 mL/2.8 mL) were added DOWEX 50Wx8 200-400 mesh (215 mg) and the resulting mixture were stirred at room temperature. After 8 h stirring, DOWEX was filtered off and filtrate was concentrated under reduced pressure. The crude materials were purified by column chromatography on silica gel (hexane:AcOEt = 2:1) to give diol (**S6**) (513 mg, 47%, 5 steps).

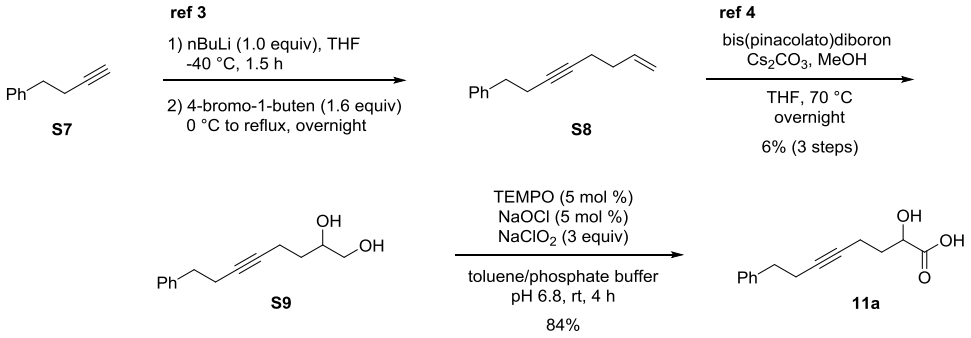
A mixture of diol (**S6**) (190 mg, 0.718 mmol) and TEMPO (5.61 mg, 35.9 µmol) in toluene (3.6 mL) and 1 M sodium phosphate buffer (pH = 6.8, 2.2 mL) was stirred at 25 °C. Then $NaClO_2$ (80%, 244 mg, 2.16 mmol) in H_2O (1.0 mL) and dilute bleach (0.168 M, 220 µL, 35.9 µmmol) were added simultaneously over 1 minute. The mixture was stirred at 25 °C for 4 h. The reaction was quenched with 1 M sodium phosphate buffer (pH = 2.1) and extracted with AcOEt (10 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude materials were purified by column chromatography on silica gel (SO_3H, hexane:AcOEt = 3:1 to 2:1) to give (*E*)-8-(Benzyloxy)-2-hydroxy-8-oxooct-6-enoic acid (**10a**) (147 mg, 73%).



10a

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 7.00 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.89 (dt, *J* = 15.6, 1.2 Hz, 1H), 5.17 (s, 2H), 4.26 (dd, *J* = 6.6, 4.0 Hz, 1H), 4.13 (br s, 2H), 2.34-2.18 (m, 2H), 1.97-1.79 (m, 1H), 1.78-1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 166.6, 149.2, 135.9, 128.5, 128.2, 121.4, 69.9, 66.2, 33.4, 31.7, 23.1; IR (neat, cm^{-1}): 3740-3120, 2950, 1718, 1652; HRMS (ESI^+, m/z) Calcd. for $C_{15}H_{18}O_5$•Na ($[M+Na]^+$): 301.1052, found 301.1043.

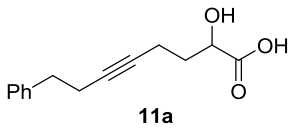
2-Hydroxy-8-phenyloct-5-ynoic acid (**11a**)



Under Ar atmosphere, 4-pheyl-1-butyne (**S7**, 1014 mg, 7.79 mmol) was dissolved in THF (8.7 mL). After cooling to -40 °C, *n*-BuLi (1.6 M, 4.87 mL, 7.79 mmol) was added dropwise to the solution. After 1.5 h stirring, the reaction mixture was warmed to 0 °C, 4-bromo-1-butene (1.26 mL, 12.5 mmol) in THF (8.7 mL) was added dropwise to the reaction mixture, and the solution was stirred 2 h and refluxed for 12 h. The reaction was quenched with ice/H_2O and acidified with 1 M HCl (aq) and extracted with AcOEt (15 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude materials were passed silica gel (hexane). The resulting materials included starting material **S7** and desired eneyn **S8** (**S7**:**S8** = 1.4:1) which was used to the next reaction without further purification.

To a solution of the eneyne (**S8**), bis(pinacolato)diboron (1.98 g, 7.79 mmol), Cs_2CO_3 (381 mg, 1.17 mmol) in THF (15 mL) were added MeOH (790 µL, 19.5 mmol) and stirred for 10 h at 70 °C. The mixture was allowed to cool until 0 °C, followed by the dropwise addition of 30% H_2O_2 (aq) (2.16 mL, 19.5 mmol) and 2.5 M NaOH (aq) (7.79 mL, 19.5 mmol). After 30 min stirring, the reaction mixture was added AcOEt and H_2O. The aqueous layer was extracted with AcOEt (15 mL x 3). The extracted organic layer was combined, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude compounds were purified by column chromatography on silica gel (hexane:AcOEt = 1:0 to 1:2) to give diol (**S9**) (146 mg, 6%, 3 steps).

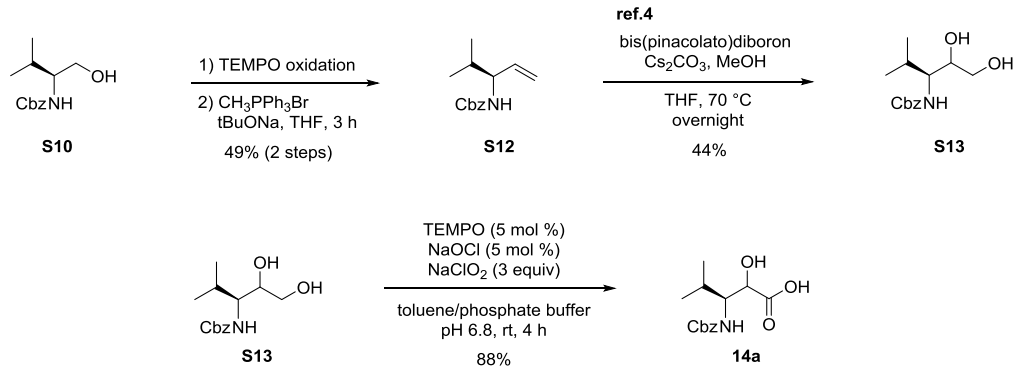
A mixture of diol (**S9**) (146 mg, 0.668 mmol) and TEMPO (5.23 mg, 33.4 µmol) in toluene (3.3 mL) and 1 M sodium phosphate buffer (pH = 6.8, 2.3 mL) was stirred at 25 °C. Then $NaClO_2$ (80%, 227 mg, 2.01 mmol) in H_2O (1.0 mL) and dilute bleach (0.163 M, 205 µL, 33.4 µmmol) were added simultaneously over 1 minute. The mixture was stirred at 25 °C for 1 h. The reaction was quenched with 1 M sodium phosphate buffer (pH = 2.1) and extracted with AcOEt (10 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude materials were purified by column chromatography on silica gel (SO_3H, hexane:AcOEt = 3:1) to give 2-hydroxy-8-phenyloct-5-ynoic acid (**11a**) (84.2 mg, 84%).



11a

White solid; mp: 102-104 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 2H), 7.25-7.16 (m, 3H), 4.32 (dd, *J* = 8.6, 4.0 Hz, 1H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.45 (tt, *J* = 7.2, 2.4 Hz, 2H), 2.41-2.28 (m, 2H), 2.12-1.95 (m, 1H), 1.91-1.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 140.8, 128.4, 128.3, 126.2, 81.1, 79.1, 69.2, 35.2, 33.0, 20.8, 14.7; IR (neat, cm^{-1}): 3700-3100, 2928, 2249, 1725; HRMS (ESI^+, m/z) Calcd. for $C_{14}H_{16}O_3$•Na ($[M+Na]^+$): 255.0997, found 274.0992 .

N-(Benzyloxycarbonyl)-3-amino-4-methyl-3-oxopentanoic acid (**14a**)

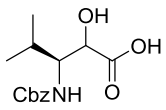


To a solution of the *N*-Cbz-L-valinol (**S10**, 8.99 g, 37.9 mmol), TEMPO (118 mg, 0.758 mmol) in CH_2Cl_2/sat. $NaHCO_3$ (aq) (95 mL/50 mL) were added 1.63 M NaOCl (aq) (25.6 mL) in sat. $NaHCO_3$ (45 mL) at 0 °C. After 15 min stirring at 0 °C, the reaction was quenched with sat. $Na_2S_2O_3$ (aq) and extracted with CH_2Cl_2 (30 mL x 3). The combined organic layer were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford aldehyde **S11**, which was used to the next reaction without further purification. A mixture of *t*-BuOK (9.10 g, 94.7 mmol) and THF (60 mL) were added methyltriphenylphosphonium bromide (52.8 g, 148 mmol) at -78 °C, and stirred 30 min. The mixture was warmed to 0 °C and added aldehyde **S11** in THF (34 mL) at 0 °C. After 2 h stirring, the reaction mixture was warmed to room temperature. After 1 h stirring, the reaction was quenched with H_2O and extracted with AcOEt (30 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude materials were purified by column chromatography on silica gel (hexane:AcOEt = 15:1 to 10:1) to give olefin (**S12**) (4.35 g, 49%, 2 steps).

To a solution of the olefin (**S12**, 4.35 g, 18.7 mmol), bis(pinacolato)diboron (9.48 g, 37.3 mmol), Cs_2CO_3 (1.82 mg, 5.60 mmol) in THF (62 mL) were added MeOH (3.78 mL, 93.3 mmol) and stirred for 9 h at 70 °C. The mixture was allowed to cool until 0 °C, followed by the dropwise addition of 30% H_2O_2 (aq) (19 mL, 171 mmol) and 2.5 M NaOH (aq) (70 mL, 175 mmol). After 1 h stirring, the

reaction was added AcOEt and H_2O. The aqueous layer was extracted with AcOEt (30 mL x 3). The extracted organic layer was combined, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude compounds were purified by column chromatography on silica gel (hexane:AcOEt = 2:1 to 1:1) to give diol (**S13**) (2.22 mg, 44%).

A mixture of diol (**S13**) (149 mg, 0.557 mmol) and TEMPO (4.35 mg, 27.8 μmol) in toluene (2.8 mL) and 1 M sodium phosphate buffer (pH = 6.8, 2.0 mL) was stirred at 25 °C. Then $NaClO_2$ (80%, 189 mg, 1.67 mmol) in H_2O (0.8 mL) and dilute bleach (0.163 M, 171 μL, 27.8 μmmol) were added simultaneously over 1 minute. The mixture was stirred at 25 °C for 3 h. The reaction was quenched with 1 M sodium phosphate buffer (pH = 2.1) and extracted with AcOEt (10 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude materials were purified by column chromatography on silica gel (SO_3H, hexane:AcOEt = 2:1 to 1:1) to give *N*-(Benzyloxycarbonyl)-3-amino-4-methyl-3-oxopentanoic acid (**14a**) (137 mg, 88%).

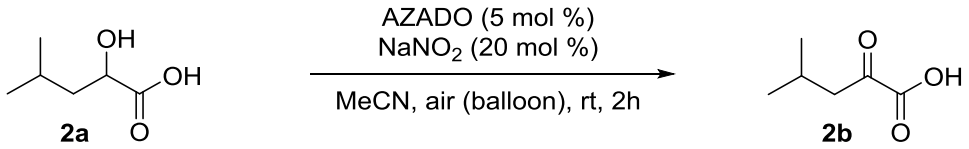


14a

White solid; mp: 122-123 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 6.03 (d, *J* = 10.4 Hz, 0.2H), 5.19 (d, *J* = 9.2 Hz, 0.8H), 5.12 (d, *J* = 12.6 Hz, 1H), 5.08 (d, *J* = 12.6 Hz, 1H) 5.22-5.04 (m, 2H), 4.39 (d, *J* = 4.0 Hz, 0.8H), 4.33 (d, *J* = 3.2 Hz, 0.2H), 3.85-3.68 (m, 1H), 2.14-1.86 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 157.8, 135.9, 128.6, 128.3, 128.0, 72.7, 67.5, 59.9, 28.9, 20.2, 18.8; IR (neat, cm^{-1}): 3700-3190, 3401, 3327, 2965, 1719, 1523; HRMS (ESI^+, m/z) Calcd. for $C_{14}H_{19}NO_5$•Na ($[M+Na]^+$): 304.1161, found 304.1166.

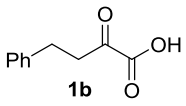
3. Oxidation of α-hydroxy acids to α-keto acids

Typical procedure



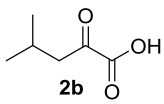
To a solution of the 2-hydroxy-4-methylvaleric acid (**2a**, 26.4 mg, 0.200 mmol), AZADO (1.52 mg, 10 μmol) in MeCN (1 mL) were added $NaNO_2$ aqueous solution (1 M, 40 μL, 40 μmol) and stirred at room temperature under air atmosphere. After 2 h stirring, the reaction was quenched with 1 M sodium phosphate buffer (pH = 2.1, 5 mL) and extracted with AcOEt (5 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude materials were purified by column chromatography on silica gel (SO_3H, hexane:AcOEt = 10:1) to give 4-methyl-2-oxopentanoic acid (**2b**) (23.1 mg, 89%).

2-Oxo-4-phenylbutanoic acid (**1b**)[5]



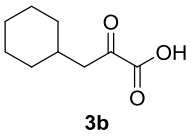
White Solid; mp: 49-51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2H), 7.24-7.17 (m, 3H), 4.30 (br s, 1H), 3.29 (t, J = 7.2 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 159.3, 139.5, 128.6, 128.3, 126.6, 39.0, 29.0; IR (KBr, cm^{-1}): 3710-3150, 2927, 1728; HRMS (DART, m/z) Calcd. for $C_{10}H_{10}O_3$•NH_4 ([M+NH_4]$^+$): 196.0974, found 196.0976 .

4-Methyl-2-oxopentanoic acid (**2b**)[6]



Keto acid **2b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 10:1) in 89% yield (23.1 mg). Pale yellow oil; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.03 (br s, 1H), 2.82 (d, J = 7.2 Hz, 2H), 2.30-2.16 (m, 1H), 0.98 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 159.7, 45.8, 24.5, 22.4; IR (neat, cm^{-1}): 3700-3300, 2961, 1727; HRMS (DART, m/z) Calcd. for $C_6H_{10}O_3$•NH_4 ([M+NH_4]$^+$): 148.0974, found 148.0973.

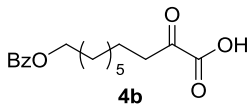
3-Cyclohexyl-2-oxopropanoic acid (**3b**)[7]



3b

Keto acid **3b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 10:1) in 86% yield (33.8 mg). White solid; mp: 45-46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (d, J = 7.2 Hz, 2H), 2.04-1.84 (m, 1H), 1.83-1.59 (m, 5H), 1.40-1.22 (m, 2H), 1.21-1.09 (m, 1H), 1.08-0.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 160.5, 44.8, 33.6, 33.0, 25.9(1), 25.8(6); IR (neat, cm^{-1}): 3710-3450, 3450-3030, 2925, 1727, 1449; HRMS (ESI$^+$, m/z) Calcd. for $C_9H_{14}O_3$•Na ([M+Na]$^+$): 193.0841, found 193.0836.

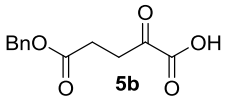
10-(Benzoyloxy)-2-oxodecanoic acid (**4b**)[8]



4b

Keto acid **4b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 5:1) in 77% yield (49.4 mg). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.01 (m, 2H), 7.60-7.52 (m, 1H), 7.48-7.40 (m, 2H), 4.32 (t, J = 6.4 Hz, 2H), 2.94 (t, J = 6.8 Hz, 2H), 1.77 (tt, J = 6.8, 6.4 Hz, 2H), 1.72-1.59 (m, 2H) 1.53-1.29 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 166.9, 159.6, 133.0, 130.5, 129.6, 128.4, 65.2, 37.4, 29.2, 29.1, 28.9, 28.7, 26.0, 23.1; IR (neat, cm^{-1}): 3700-3350, 3350-3130, 2932, 2857, 1715; HRMS (ESI$^+$, m/z) Calcd. for $C_{17}H_{22}O_5$•Na([M+Na]$^+$): 329.1365, found 329.1361.

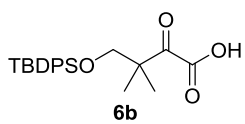
5-(Benzyloxy)-2,5-dioxopentanoic acid (**5b**)



5b

Keto acid **5b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 3:1) in 88% yield (46.5 mg). White solid; mp: 72-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.29 (m, 5H), 5.13 (s, 2H), 3.26 (t, J = 6.4 Hz, 2H), 2.79 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 171.8, 159.4, 135.4, 128.6, 128.4, 128.3, 67.0, 32.5, 27.9; IR (neat, cm^{-1}): 3700-3400, 2957, 1730; HRMS (ESI$^+$, m/z) Calcd. for $C_{12}H_{12}O_5$•Na ([M+Na]$^+$): 259.0582, found 259.0574.

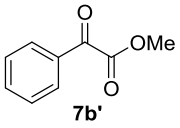
4-((*tert*-butyldiphenylsilyl)oxy)-3,3-dimethyl-2-oxobutanoic acid (**6b**)



6b

Keto acid **6b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 5:1) in 87% yield (43.9 mg). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.58 (m, 4H), 7.50-7.36 (m, 6H), 3.94 (s, 2H), 1.28 (s, 6H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 160.0, 135.6, 132.7, 129.8, 127.7, 70.4, 48.9, 26.7, 21.3, 19.2; IR (neat, cm^{-1}): 3700-3130, 2960, 2932, 1715; HRMS (ESI$^+$, m/z) Calcd. for $C_{22}H_{28}O_4Si$•Na ([M+Na]$^+$): 407.1655, found 407.1650.

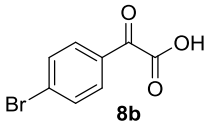
Methyl benzoylformate (**7b'**)[9]



7b'

Keto ester **7b'** was isolated by column chromatography on silica gel (hexane:AcOEt = 10:1) in 95% yield (31.1 mg). Pale yellow oil; ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.07-7.99 (m, 2H), 7.71-7.63 (m, 1H), 7.55-7.49 (m, 2H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 164.0, 135.0, 132.4, 130.1, 128.9, 52.8; IR (neat, cm^{-1}): 2956, 1740, 1692; HRMS (ESI^+, m/z) Calcd. for $C_9H_8O_3$•Na ($[M+Na]^+$): 187.0371, found 187.0371.

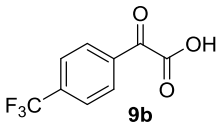
2-(4-bromophenyl)-2-oxoacetic acid (**8b**)



8b

Keto acid **8b** was isolated by column chromatography on silica gel (SO_3H, hexane:AcOEt = 2:1) in 98% yield (31.1 mg). White solid; mp: 100-102 °C ^{1}H NMR(400 MHz, MeCN-d_3) δ 7.95 (dd, J = 8.4, 2.4 Hz, 2H), 7.72 (dd, J = 8.4, 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 164.4, 133.2, 132.6, 132.4, 130.8; IR (neat, cm^{-1}): 3640-3240, 1719, 1669; HRMS (DART, m/z) Calcd. for $C_8H_5BrO_3$•NH_4 ($[M+NH_4]^+$): 245.9766, found 245.9769.

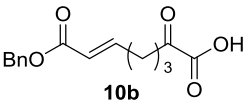
2-oxo-2-(4-(trifluoromethyl)phenyl)acetic acid (**9b**)



9b

Keto acid **9b** was isolated by column chromatography on silica gel (SO_3H, hexane:AcOEt = 2:1) in 99% yield (54.2 mg). White solid; mp: 53-55 °C ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 162.5, 136.3 (q, J = 33.4 Hz), 134.6, 131.2, 125.9 (q, J = 3.8 Hz), 123.2 (q, J = 272 Hz); IR (neat, cm^{-1}): 3750-3300, 1737, 1695; HRMS (DART, m/z) Calcd. for $C_9H_8F_3O_3$•NH_4 ($[M+NH_4]^+$): 236.0535, found 236.0537.

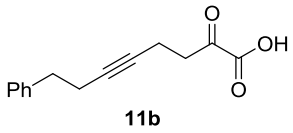
(*E*)-8-(Benzyloxy)-2, 8-dioxooct-6-enoic acid (**10b**)



10b

Keto acid **10b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 5:1 to 3:1) in 79% yield (63.5 mg). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 6.96 (dt, J = 16.0, 6.8 Hz, 1H), 5.91 (dt, J = 16.0, 1.2 Hz, 1H), 5.18 (s, 2H), 2.98 (t, J = 6.8 Hz, 2H), 2.27 (q, J = 7.2, 2H), 1.90-1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 166.6, 160.3, 148.4, 135.7, 128.5, 128.2(2), 128.1(9), 121.9, 66.4, 37.0, 31.0, 21.1; IR (neat, cm^{-1}): 3750-3000, 2949, 1720, 1651; HRMS (ESI^+, m/z) Calcd. for $C_{15}H_{16}O_5$•Na ($[M+Na]^+$): 299.0895, found 299.0896.

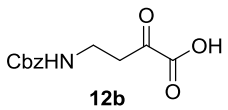
2-Oxo-8-phenyloct-5-ynoic acid (**11b**)



11b

Keto acid **11b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 5:1) in 83% yield (23.5 mg). Colorless oil; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2H), 7.24-7.16 (m, 3H), 4.78 (br s, 1H), 3.12 (t, *J* = 6.8 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.51 (tt, *J* = 6.8, 2.4 Hz, 2H), 2.41 (tt, *J* = 7.2, 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 159.2, 140.7, 128.4, 128.3, 126.2, 81.0, 78.0, 37.2, 35.2, 20.8, 12.9; IR (neat, cm^{-1}): 3730-3130, 2925, 1731; HRMS (ESI^+, m/z) Calcd. for $C_{14}H_{14}O_3$•Na ($[M+Na]^+$): 253.0841, found 253.0835.

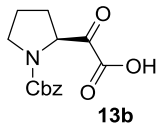
N-(Benzyloxycarbonyl)-4-amino-2-oxobutyric acid (**12b**)



12b

Keto acid **12b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 2:1) in 88% yield (44.2 mg). Pale yellow oil; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5H), 5.17 (br s, 1H), 5.08 (s, 2H), 3.61-3.48 (m, 2H), 3.21-3.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 160.3, 156.7, 136.0, 128.6, 128.3, 128.2, 67.1, 38.8, 35.6; IR (neat, cm^{-1}): 3700-3200, 2954, 1727; HRMS (ESI^+, m/z) Calcd. for $C_{12}H_{17}NO_5$•Na ($[M+Na]^+$): 274.0691, found 274.0688.

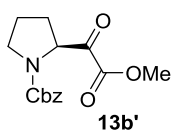
α-Keto acid (**13b**)



13b

Keto acid **13b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 2.5:1) in 85% yield (42.3 mg). Colorless oil; $[\alpha]_D^{27}$ = −37.8 (c = 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.22 (m, 5H), 6.79 (br s, 1H), 5.21-5.00 (m, 3H), 3.69-3.49 (m, 2H), 2.43-2.30 (m, 1H), 2.12-2.01 (m, 1H), 2.00-1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 192.7, 160.0, 155.5, 154.3, 135.9(0), 135.8(6), 128.5(2), 128.4(5), 128.2, 128.1, 127.9, 67.9, 67.6, 62.1, 61.6, 47.2, 46.8, 29.8, 29.0, 24.2, 23.4; IR (neat, cm^{-1}): 3730-3300, 2958, 1731, 1688; HRMS (ESI, m/z) Calcd. for $C_{14}H_{15}NO_5$•Na ($[M+Na]^+$): 300.0848, found 300.0840.

α-Keto ester (**13b'**)



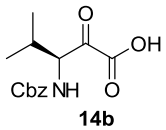
13b'

Colorless oil; $[\alpha]_D^{26}$ = −23.8 (c = 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.22 (m, 5H), 5.20-4.90 (m, 3H), 3.86 (s, 1.5 H), 3.76 (s, 1.5 H), 3.69-3.48 (m, 2H), 2.43-2.25 (m, 1H), 2.12-1.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 191.9, 160.9, 160.8, 154.8, 153.8, 136.5, 136.2, 128.4(4), 128.3(8), 128.0(0), 127.9(6), 127.8, 67.3, 67.2, 62.4, 62.1, 52.9(2), 52.9(0), 47.1, 46.6, 29.9, 28.9, 24.4, 23.5; IR (neat,

cm^{-1}): 2956, 1733, 1706; HRMS (ESI, m/z) Calcd. for $C_{14}H_{15}NO_5$•Na ([M+Na]$^+$): 314.1004, found 314.1008.

The enantiometric ratio of **13b'** was determined to be >99:1 by chiral HPLC analysis using DAICEL CHIRALPAK AS-H. The conditions used for the analysis were as follow; Solvent: *i*-PrOH-hexane (5:95 v/v). Flow rate: 1.0 mL/min. Retention time: major enantiomer (*S*)-**13b'**: 29.2 min, minor enentiomer (*R*)-**13b'**: 33.2 min.

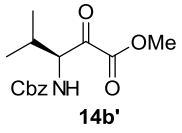
N-(Benzyloxycarbonyl)-3-amino-2-oxo-4-melylpentanoic acid (**14b**)



14b

Keto acid **14b** was isolated by column chromatography (SO_3H, hexane:AcOEt = 5:1 to 4:1) in 86% yield (49.2 mg). Colorless oil; $[\alpha]_D^{26}$ = +63.5 (c = 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 6.37 (d, *J* =6.4 Hz, 0.3H), 5.41 (d, *J* = 8.8 Hz, 0.7H), 5.22-5.06 (m, 2H), 5.00 (dd, *J* = 8.8, 4.4 Hz, 0.7H), 4.76-4.65 (m, 0.3H), 2.44-2.20 (m, 1H), 1.12-0.98 (m, 3H), 0.94-0.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 160.3, 156.7, 135.7, 128.6, 128.4, 128.2, 67.7, 61.5, 29.9, 19.7, 16.8; IR (neat, cm^{-1}): 3700-3130, 3392, 3333, 2967, 1733, 1520; HRMS (ESI$^+$, m/z) Calcd. for $C_{14}H_{17}NO_5$•Na ([M+Na]$^+$): 302.1004, found 302.1001.

Methyl *N*-(Benzyloxycarbonyl)-3-amino-2-oxo-4-melylpentanoate (**14b'**)



14b'

Colorless oil; $[\alpha]_D^{27}$ = +54.1 (c = 0.10, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 5.31 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 5.00 (dd, *J* = 9.0, 4.4 Hz, 1H), 3.89 (s, 3H), 2.39-2.05 (m, 1H), 1.05 (d, *J* = 6.8, 3H), 0.82 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 161.0, 156.2, 136.0, 128.5, 128.2, 128.1, 67.2, 61.9, 53.2, 29.8, 19.7, 16.7; IR (neat, cm^{-1}): 3700-3130, 3391, 3333, 2966, 1733, 1520; HRMS (ESI$^+$, m/z) Calcd. for $C_{15}H_{19}NO_5$•Na ([M+Na]$^+$): 316.1161, found 316.1162.

The enantiometric ratio of **14b'** was determined to be 95:5 by chiral HPLC analysis using DAICEL CHIRALPAK OD-H. The conditions used for the analysis were as follow; Solvent: *i*-PrOH-hexane (10:90 v/v). Flow rate: 1.0 mL/min. Retention time: major enantiomer (*R*)-**14b'**: 12.2 min, minor enentiomer (*S*)-**14b'**: 19.3 min.

Reference

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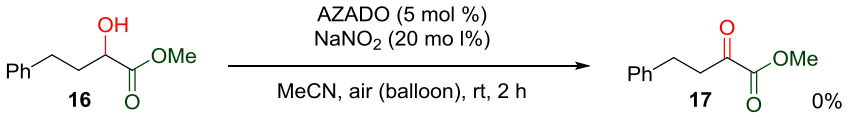
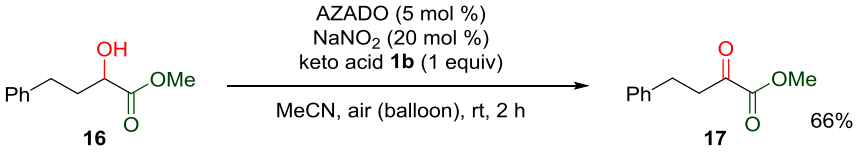
4. Control experiments

α-Hydroxy ester **16** under the optimal condition



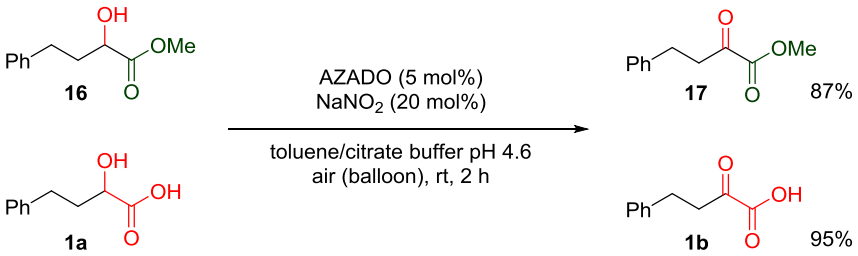
To a solution of the methyl 2-hydroxy-4-phenylbutanoate (**16**, 38.6 mg, 0.199 mmol), AZADO (1.51 mg, 9.9 μmol) in MeCN (1 mL) were added $NaNO_2$ aqueous solution (1 M, 40 μL, 40 μmol) and stirred at room temperature under air atmosphere. After 2 h stirring, the reaction was quenched with 1 M sodium phosphate buffer (pH = 2.1, 5 mL) and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was added *n*-octyl ether as an internal standard for determining NMR yield. The result of NMR analysis indicated α-keto ester **17** was not observed and starting material was recovered.

α-Hydroxy ester **16** and α-keto acid **1b** under the optimal condition



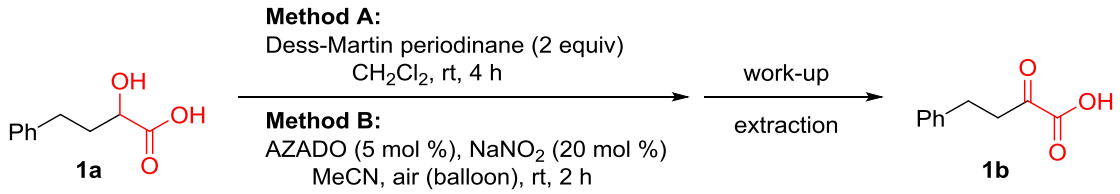
To a solution of the methyl 2-hydroxy-4-phenylbutanoate (**16**, 37.5 mg, 0.193 mmol), AZADO (0.1 M MeCN solution, 97 μL, 9.65 μmol) and 2-oxo-4-phenylbutanoic acid (**1b**, 34.4 mg, 0.193 mmol) in MeCN (970 μL) were added $NaNO_2$ aqueous solution (1 M, 39 μL, 39 μmol) and stirred at room temperature under air atmosphere. After 2 h stirring, the reaction was quenched with sat. $NaHCO_3$ aqueous solution (3 mL) and extracted with AcOEt (5 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was added *n*-octyl ether as an internal standard for determining NMR yield. The result of NMR analysis showed 66% of α-keto ester **17** and 23% of starting material.

α-Hydroxy ester **16** and α-hydroxy acid **1a** in toluene/buffer biphasic condition



To a solution of the methyl 2-hydroxy-4-phenylbutanoate (**16**, 32.3 mg, 0.166 mmol), AZADO (1.27 mg, 8.3 μmol) and 2-hydroxy-4-phenylbutanoic acid (**1a**, 30.0 mg, 0.166 mmol) in toluene (420 μL) and 20 mM citrate buffer (pH 4.6, 420 μL) were added $NaNO_2$ aqueous solution (1 M, 40 μL, 40 μmol) and stirred at room temperature under air atmosphere. After 2 h stirring, the reaction was quenched with 1 M sodium phosphate buffer (pH = 2.1, 5 mL) and extracted with AcOEt (5 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was added *n*-octyl ether as an internal standard for determining NMR yield. The result of NMR analysis showed 87% of α-keto ester **17** and 95% of α-keto acid **1b**.

5. Dess-Martin oxidation vs the AZADO-catalyzed aerobic oxidation



Method A

To a solution of the 2-hydroxy-4-phenylbutanoate (**1a**, 50.0 mg, 0.277 mmol) in CH_2Cl_2 (1.4 mL) was added Dess-Martin periodinane (237 mg, 0.559 mmol) at 0 °C. After 4 h stirring at room temperature, the reaction was quenched with MeOH (53 µL, 1.4 mmol), and added 10% NaOH aqueous solution (3 mL) and AcOEt (5 mL). The aqueous layer was acidified by 1 M HCl aqueous solution, and extracted with AcOEt (5 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The ^{1}H NMR spectrum of the crude material was shown in **Figure S1**.

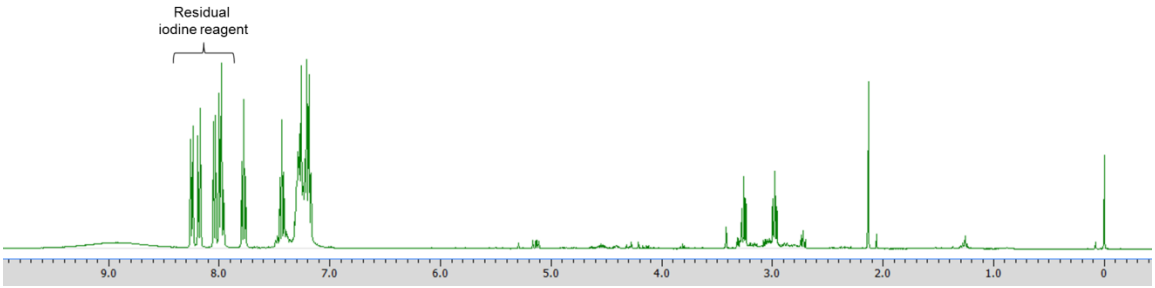


Figure S1. ^{1}H NMR spectrum of the crude material after Dess-Martin oxidation.

Method B

To a solution of the 2-hydroxy-4-phenylbutanoate (**1a**, 50.0 mg, 0.257 mmol) and AZADO (1.96 mg, 12.8 µmol) in MeCN (1.3 mL) added $NaNO_2$ aqueous solution (1 M, 40 µL, 40 µmol) and stirred at room temperature under air atmosphere. After 2 h stirring, the reaction mixture was added 10% NaOH aqueous solution (3 mL) and AcOEt (5 mL). The aqueous layer was acidified by 1 M HCl aqueous solution, and extracted with AcOEt (5 mL x 3). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The ^{1}H NMR spectrum of the crude material was shown in **Figure S2**.

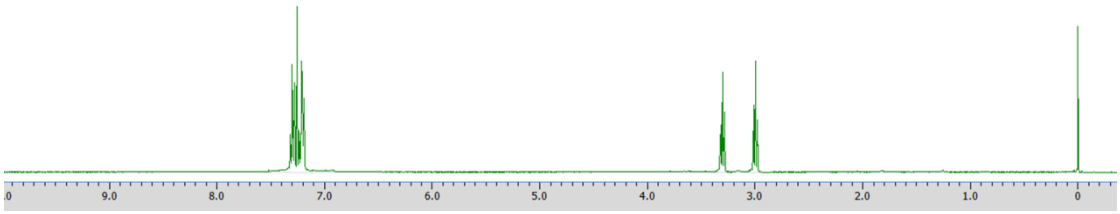
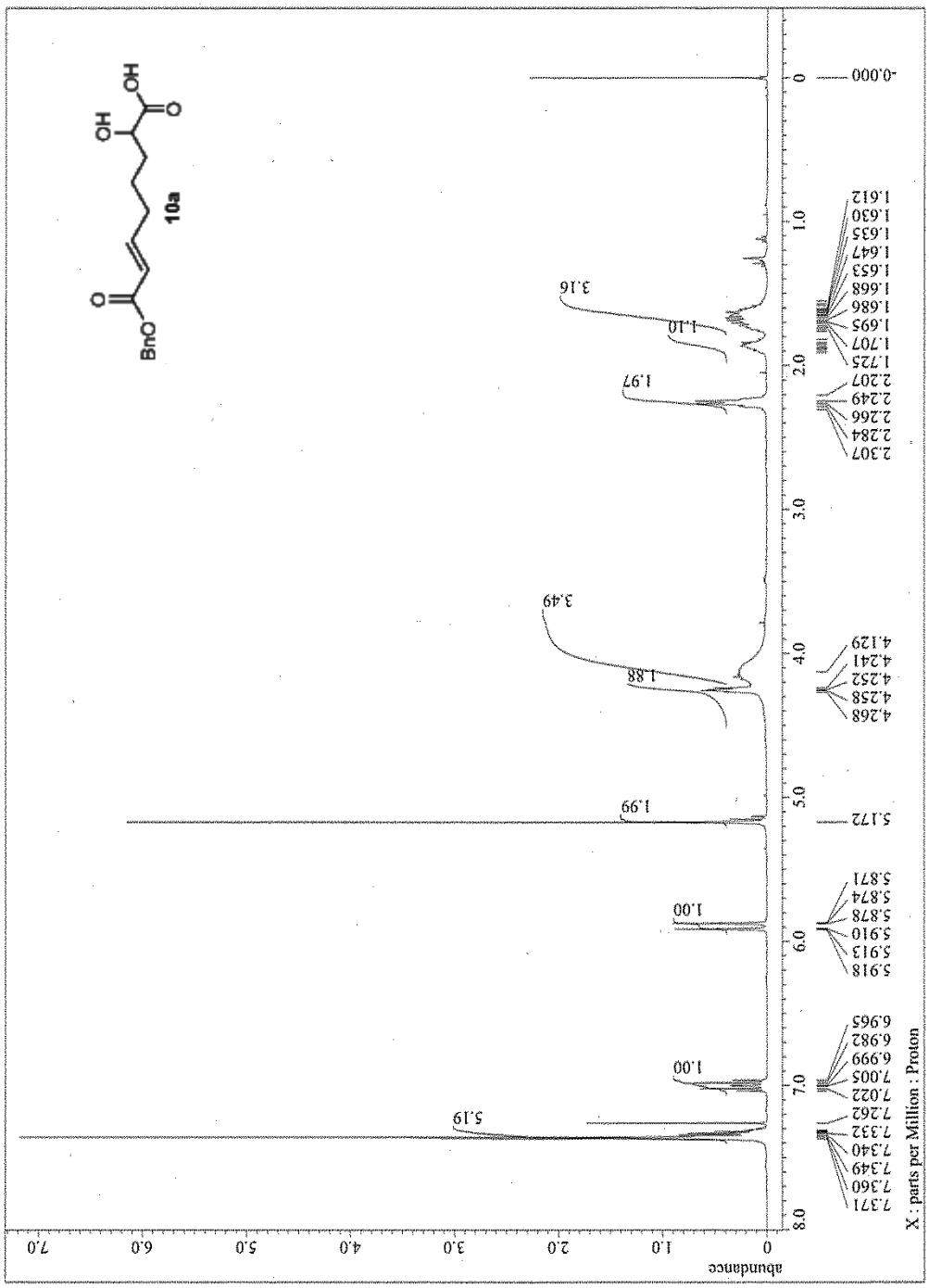
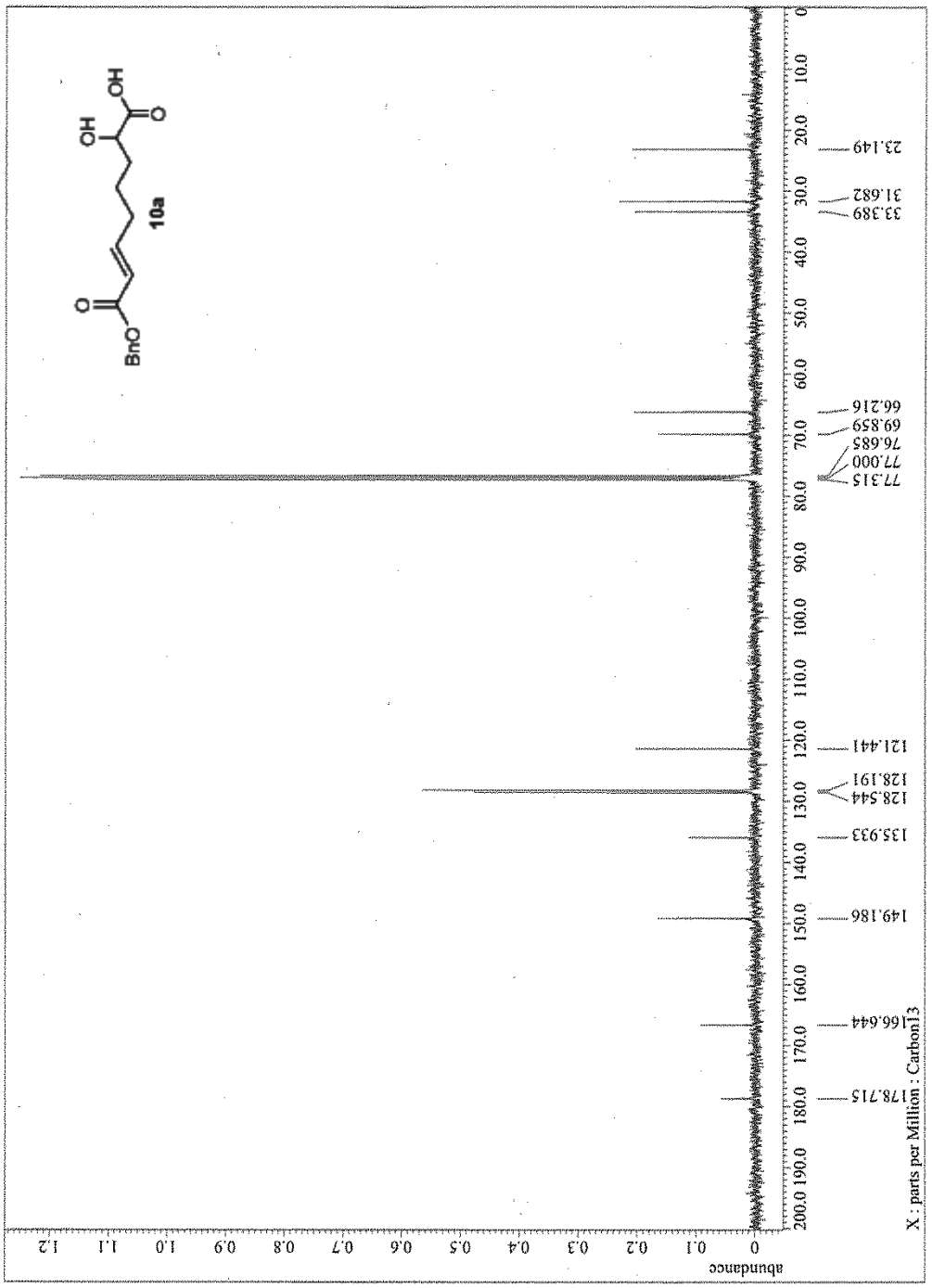


Figure S2. ^{1}H NMR spectrum of the crude material after the aerobic oxidation.

5. NMR charts




10a
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OH
O
O
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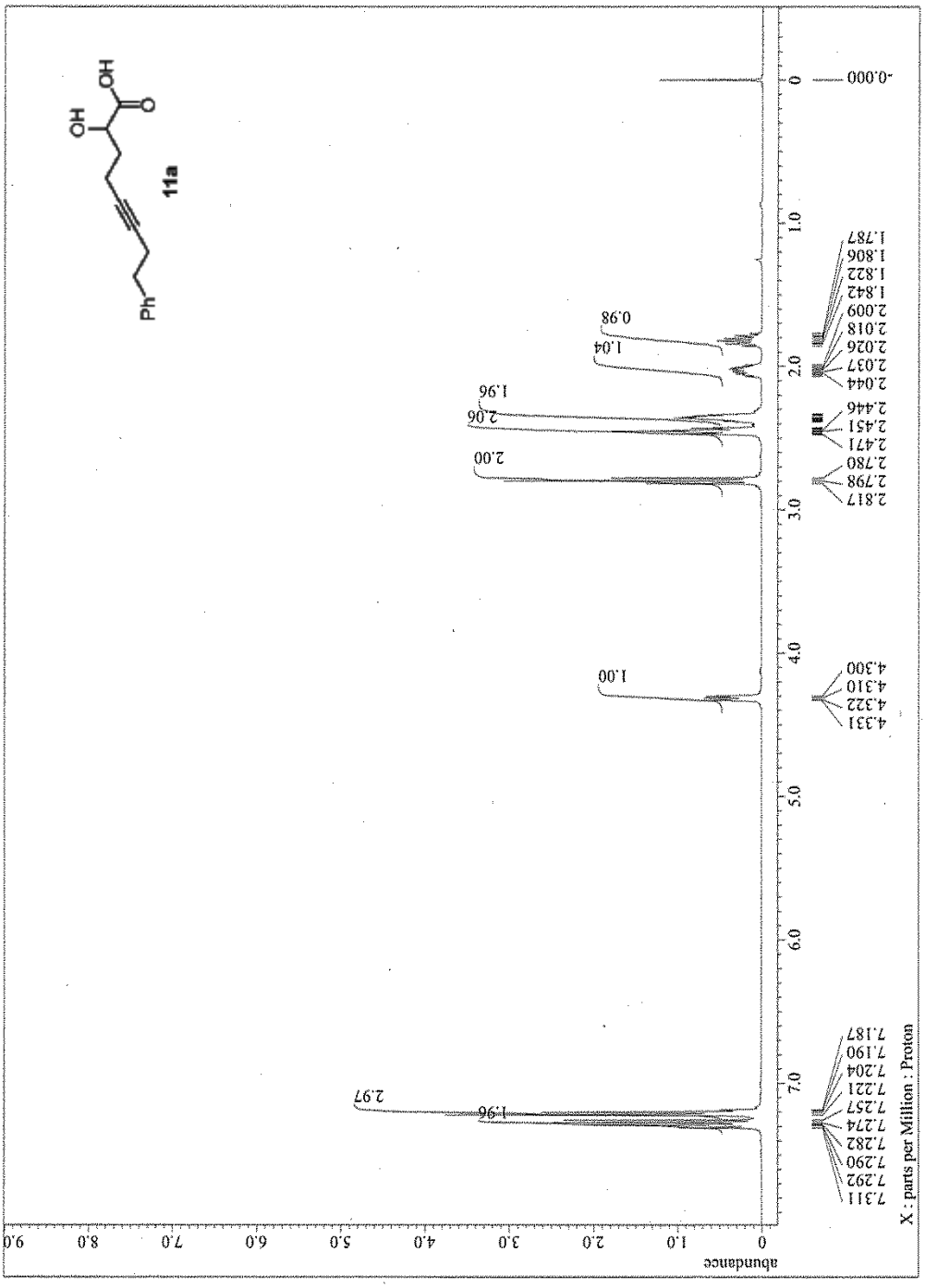
31.682
33.389
66.216
69.859
76.685
77.000
77.315
121.441
128.191
128.544
135.933
149.186
166.644
178.715
X : parts per Million : Carbon13
abundance


11a
OH
OH
O
Ph
X : parts per Million : Proton
abundance
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7.204
7.190
7.187
4.331
4.322
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2.471
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2.026
2.018
2.009
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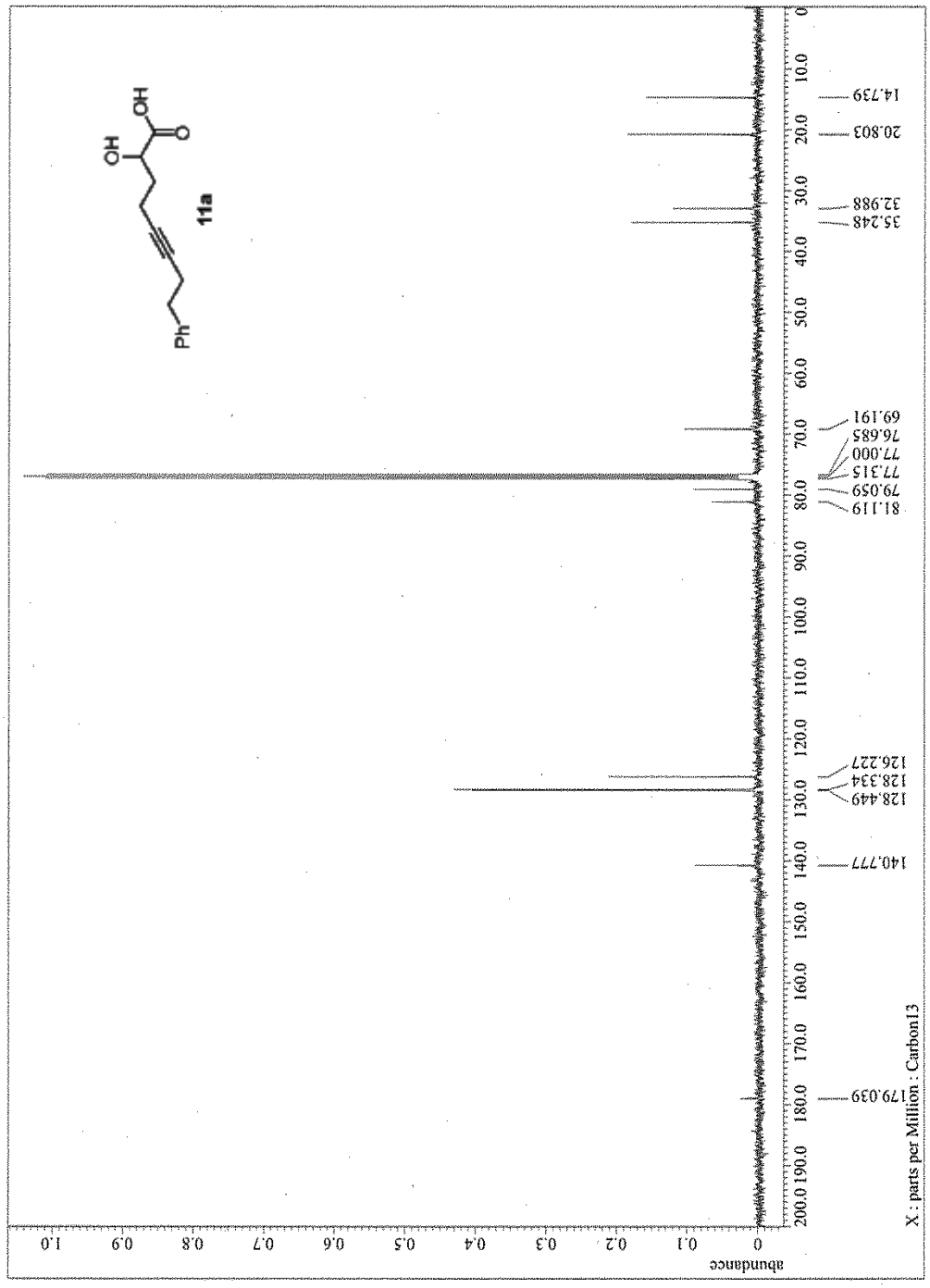
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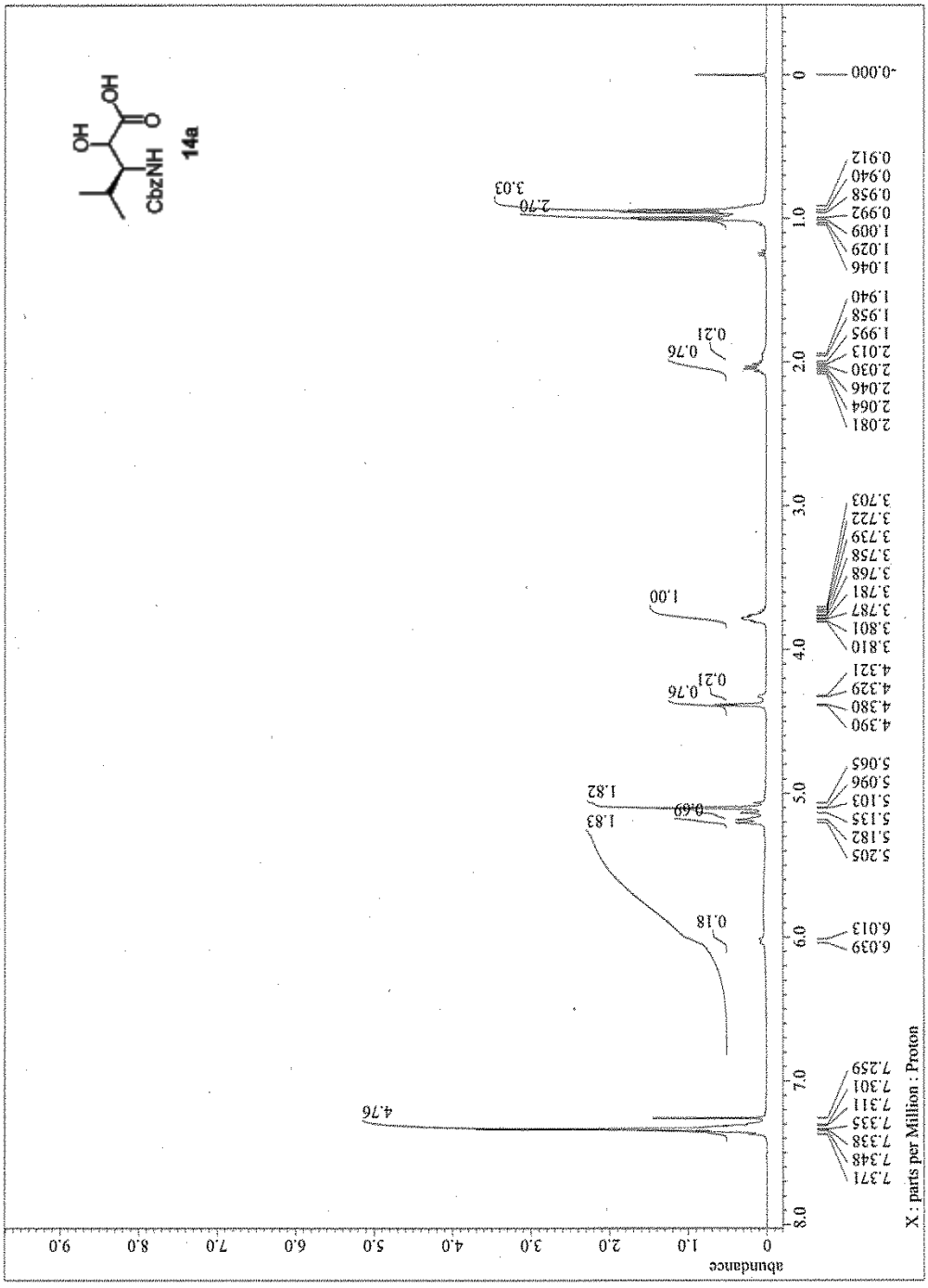
140.777
179.039
X : parts per Million : Carbon13
abundance


14a
CbzNH
OH
OH
X : parts per Million : Proton
abundance
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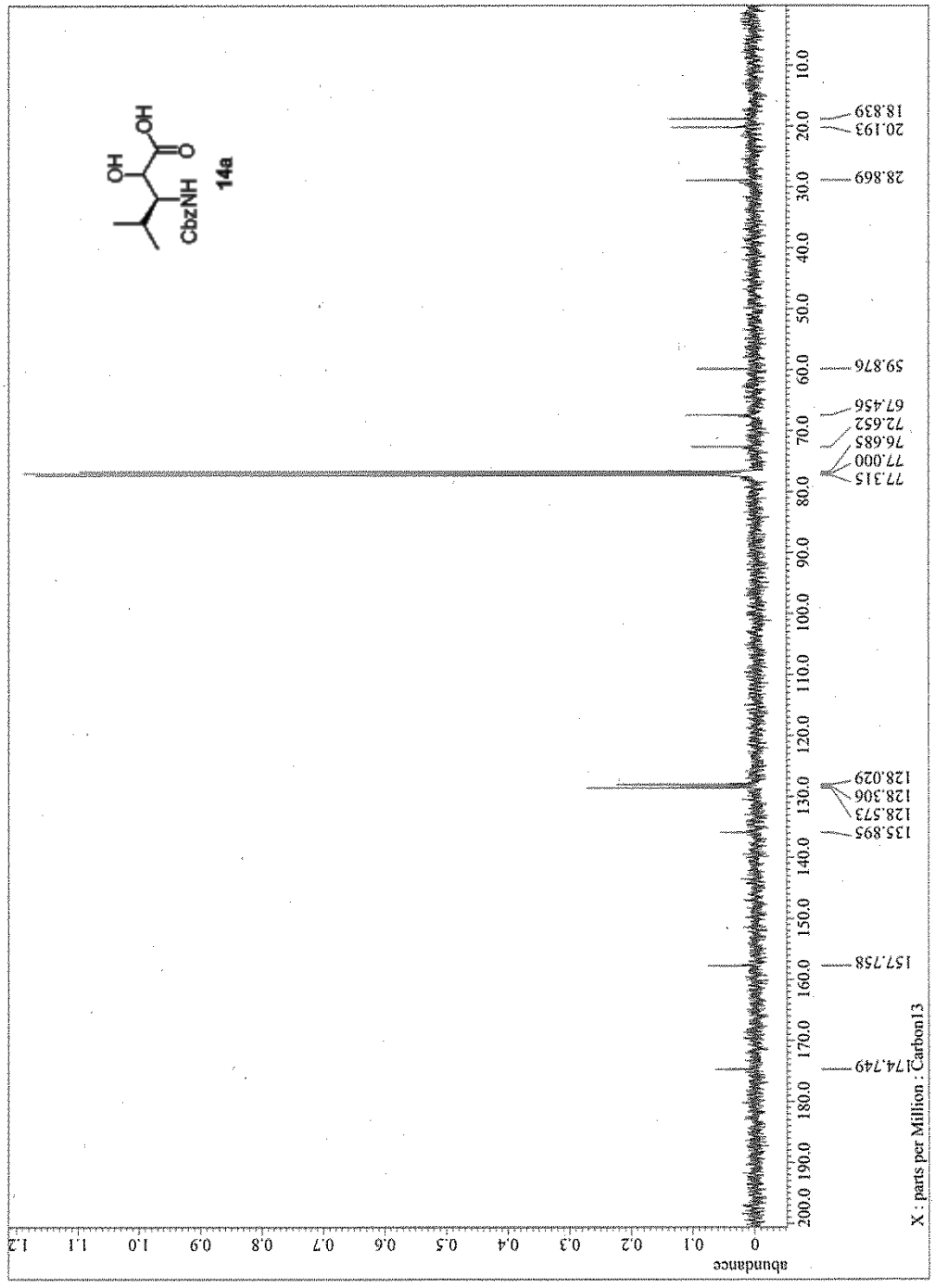
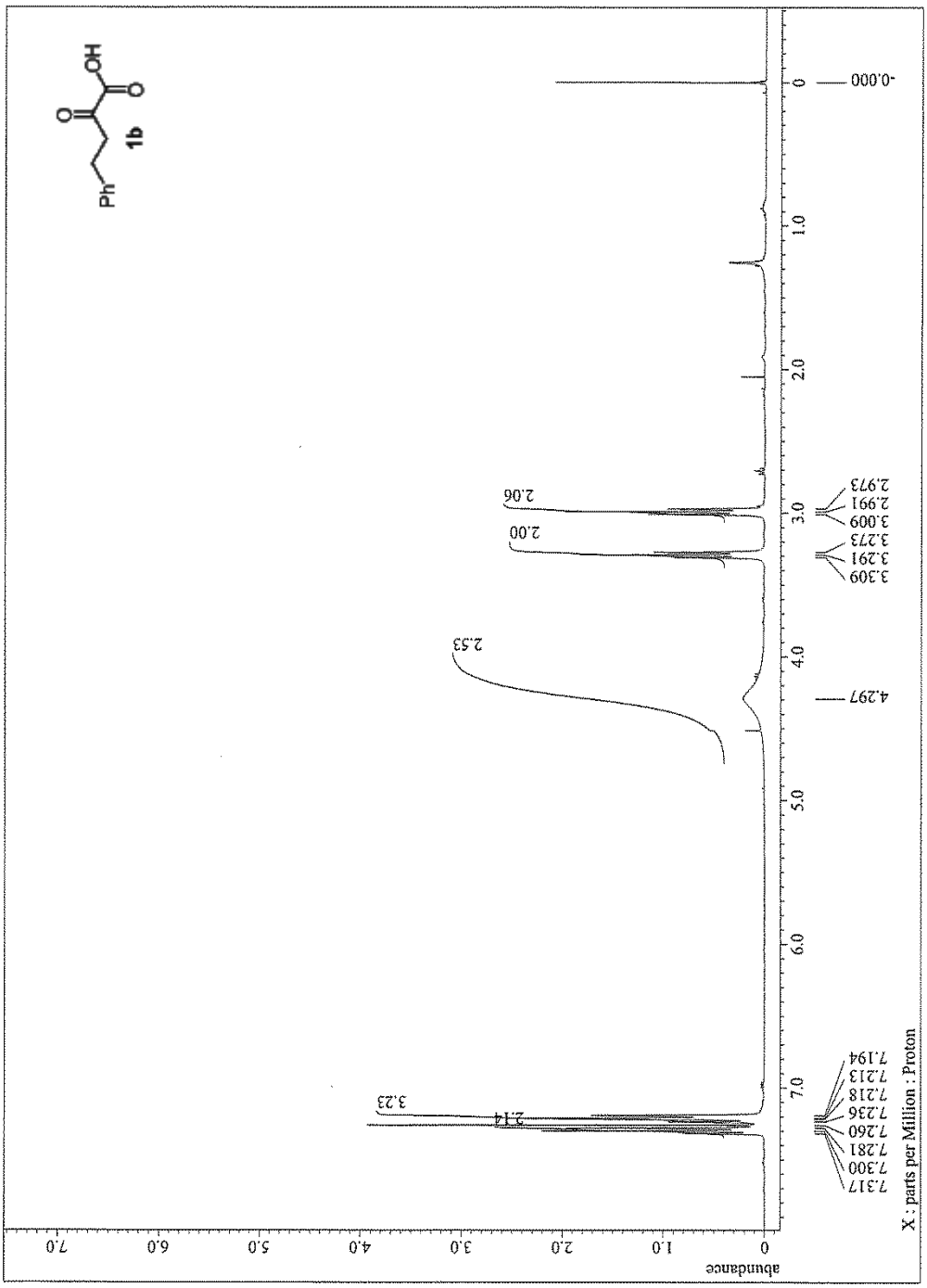
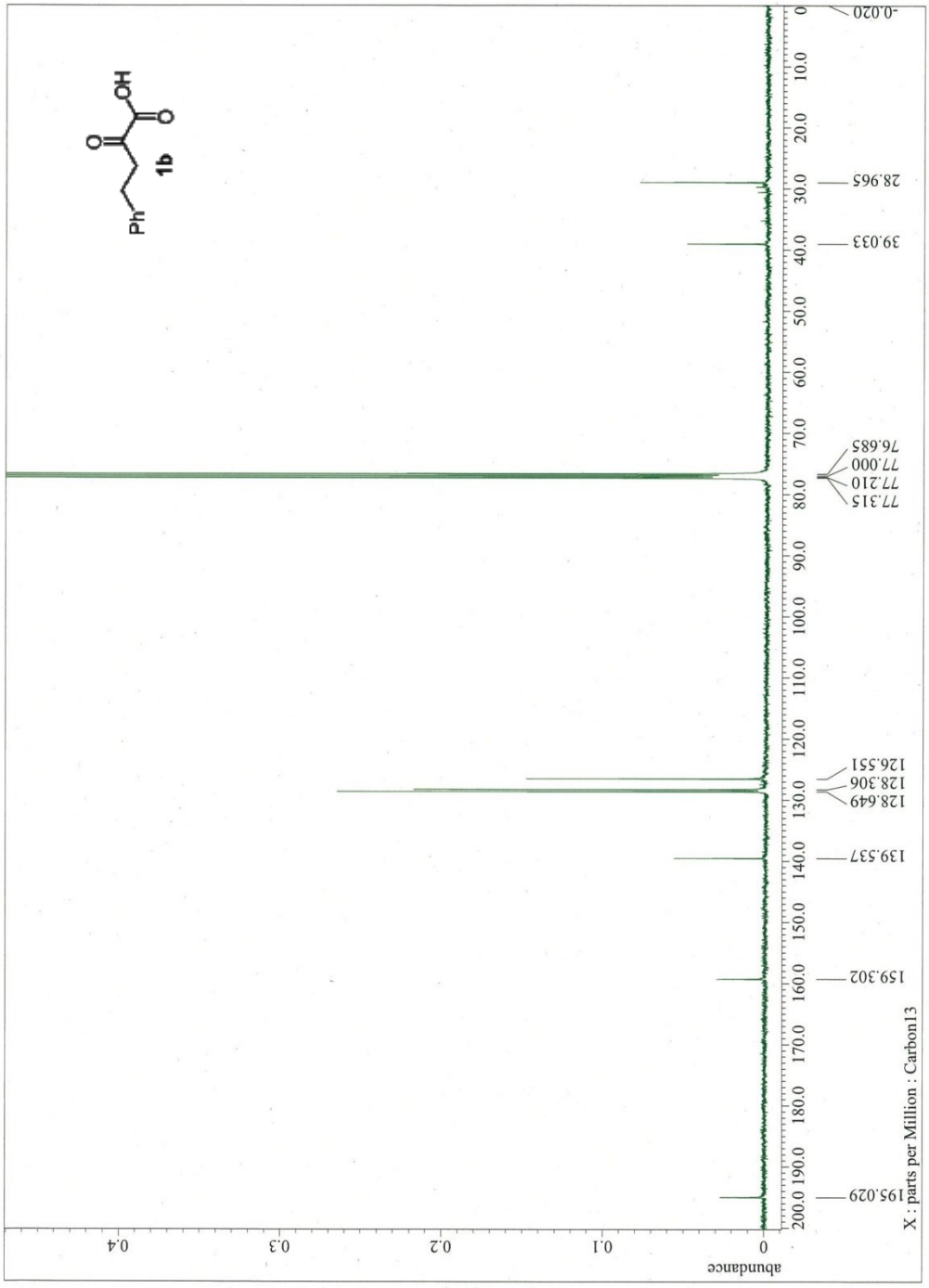
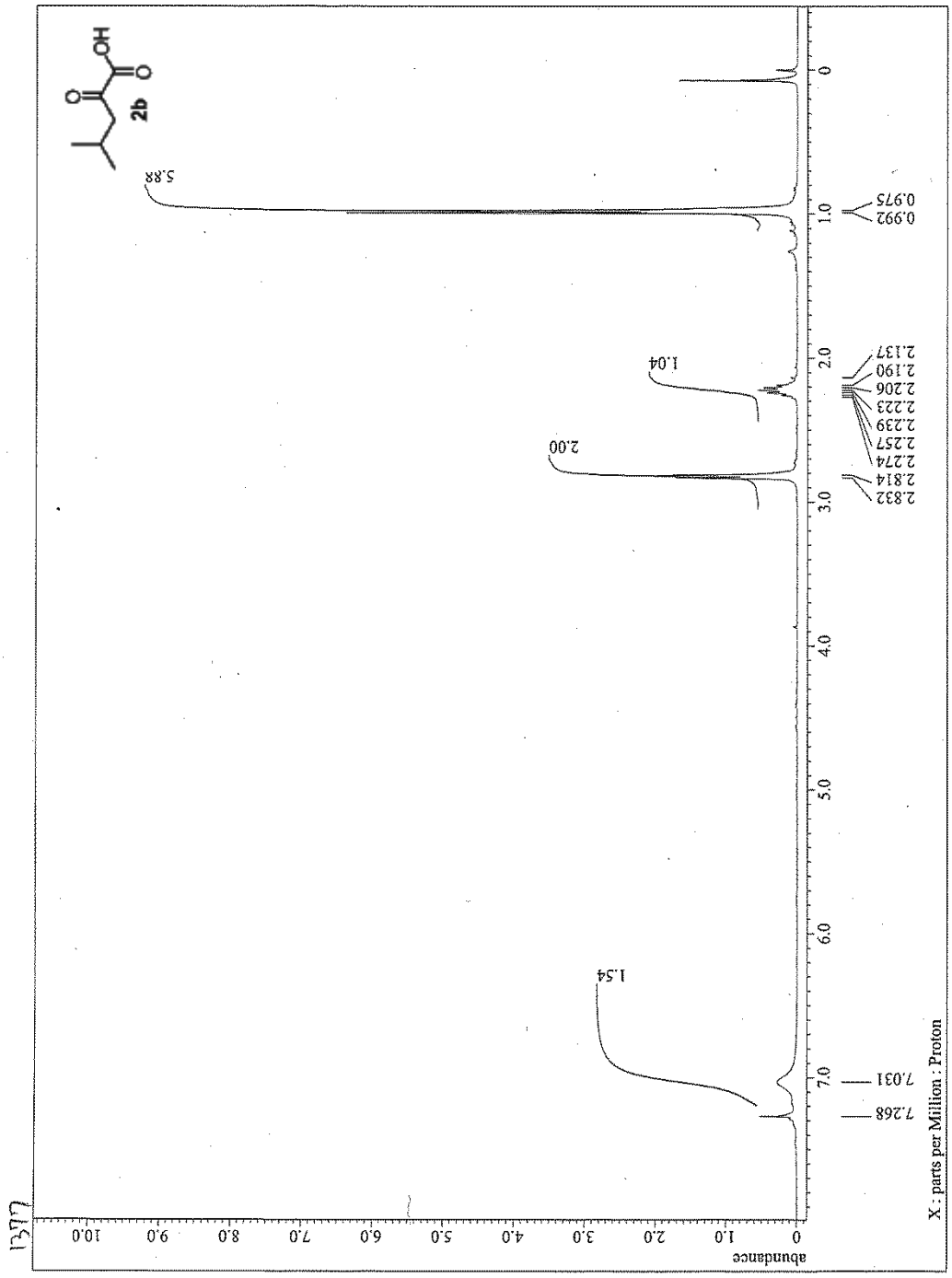
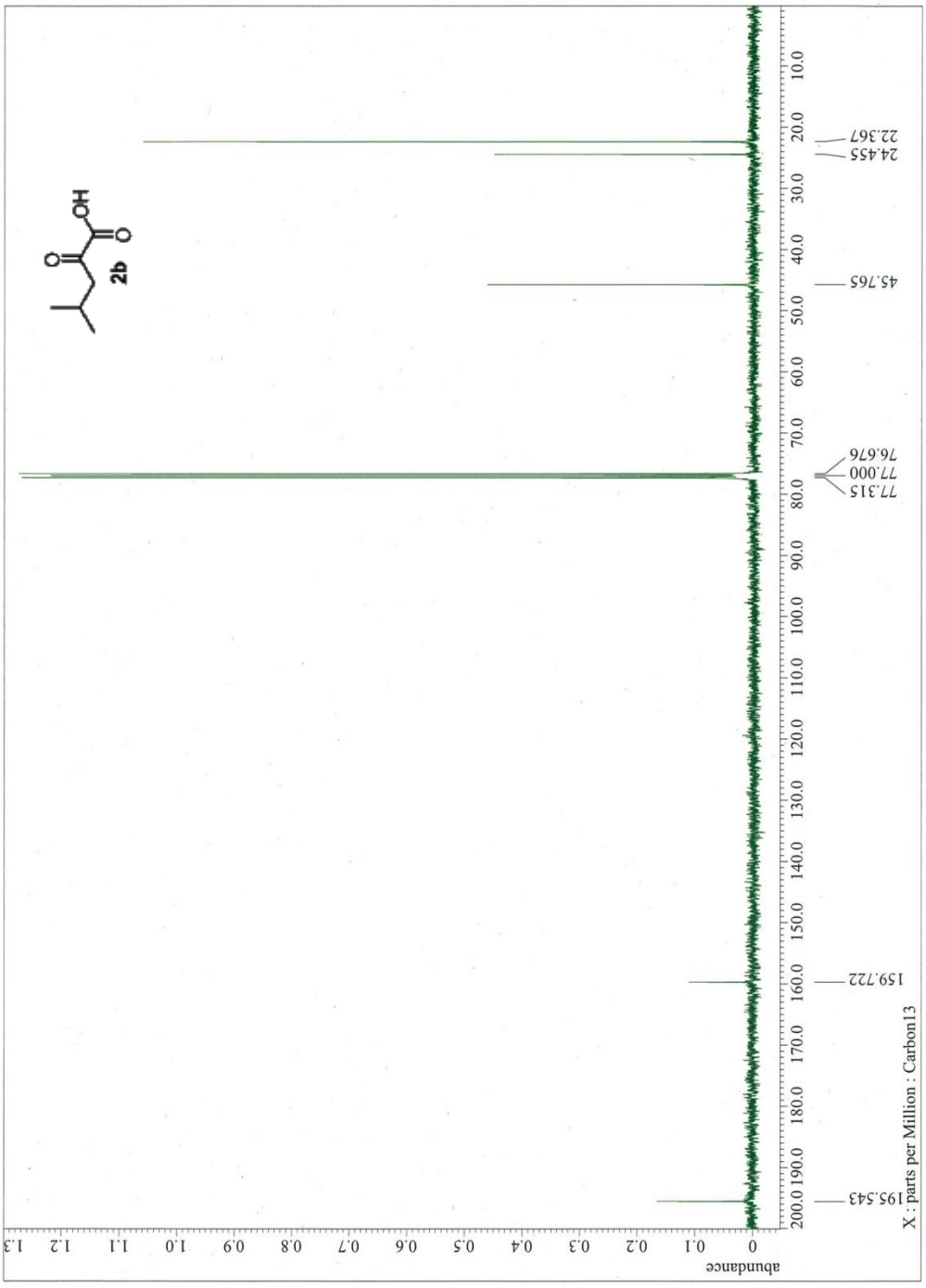
3.03
2.70
1.83
1.82
1.00
0.76
0.21
0.18
0.69
-0.000

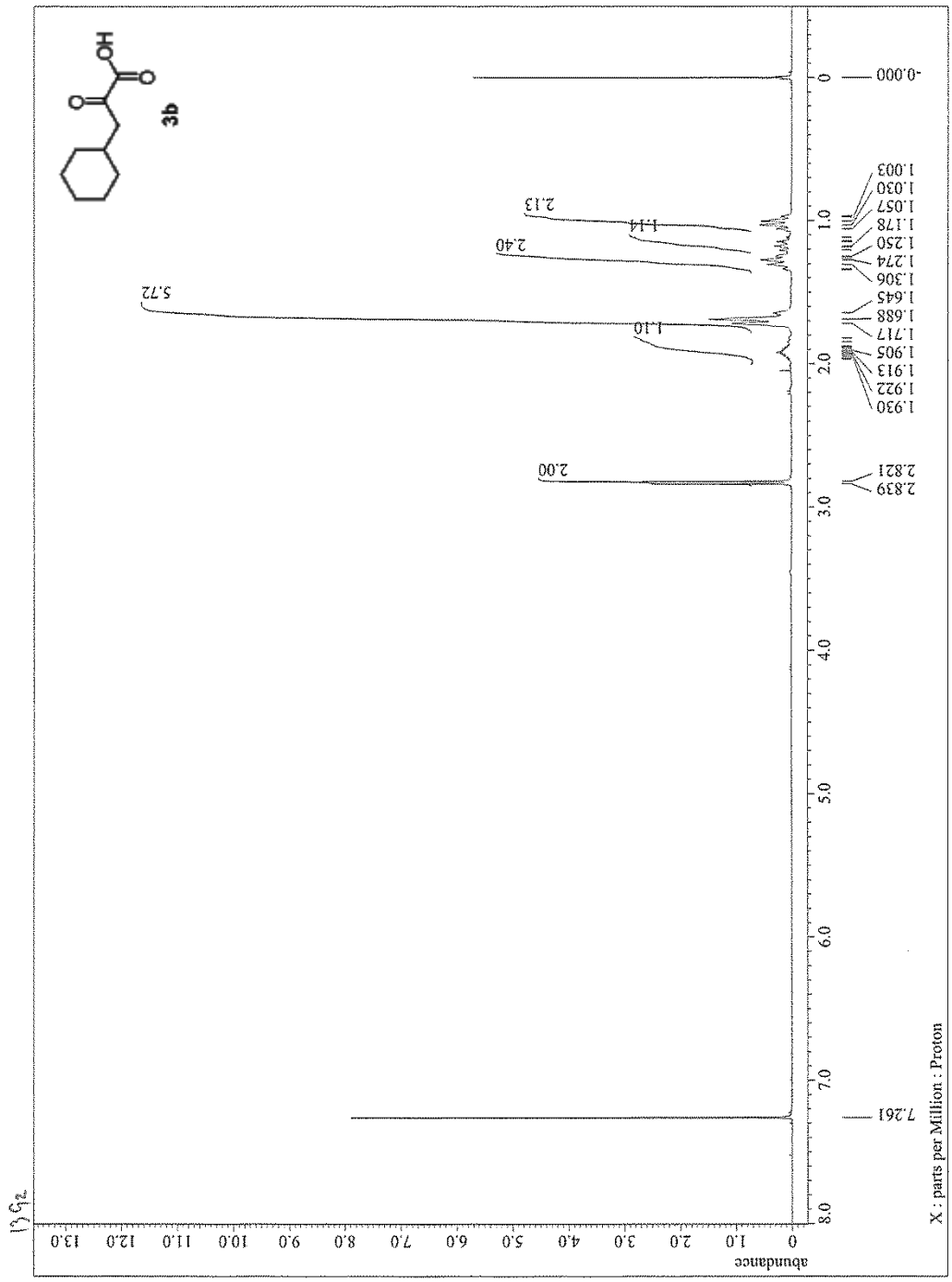

OH
OH
O
CbzNH
14a
abundance
X : parts per Million : Carbon13
18.839
20.193
28.869
59.876
67.456
72.652
76.685
77.000
77.315
128.029
128.306
128.573
135.895
157.758
174.749

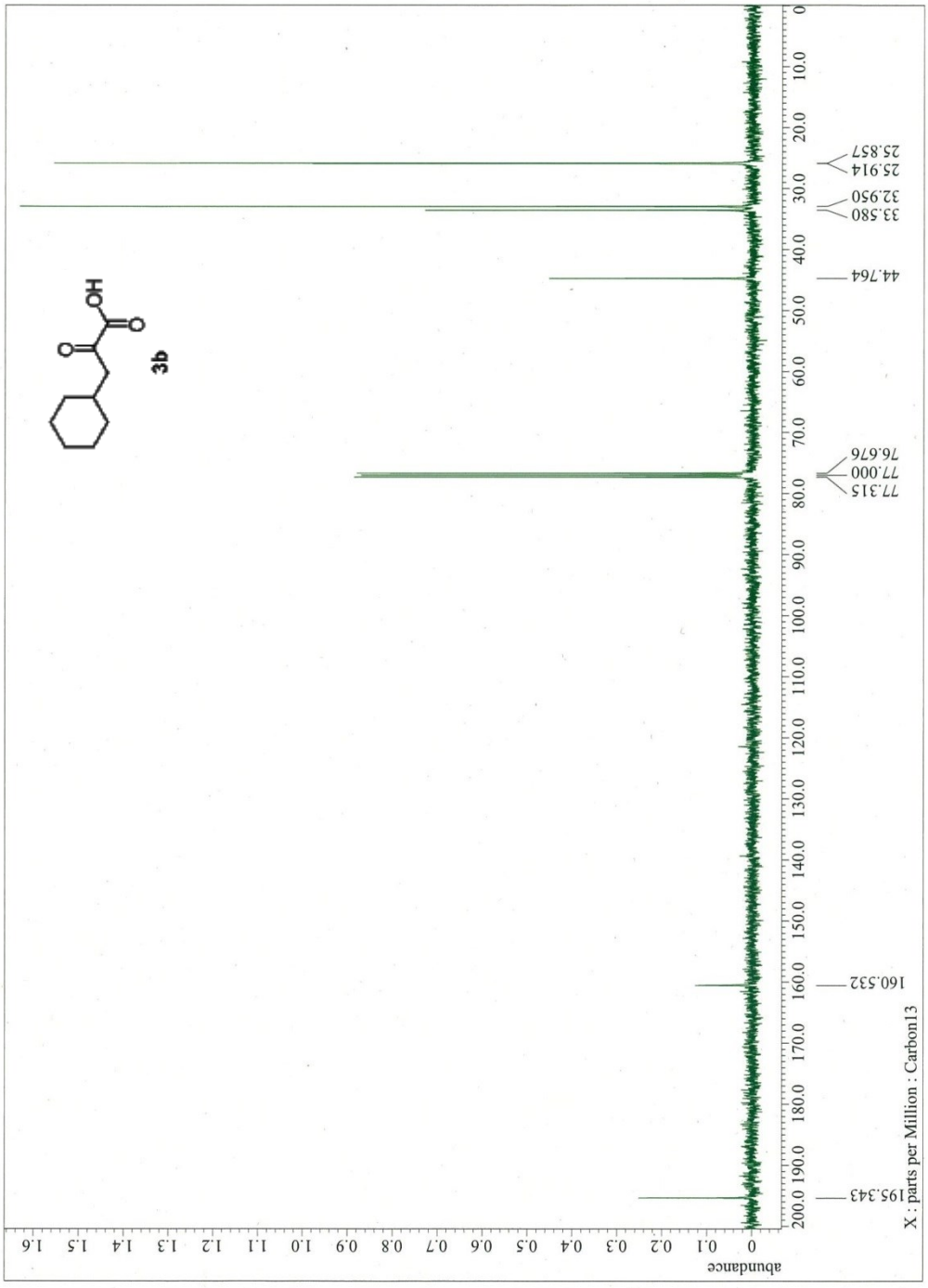

1b
Ph
OH
O
O
X : parts per Million : Proton
abundance
7.317
7.300
7.281
7.260
7.236
7.218
7.213
7.194
4.297
3.309
3.291
3.273
3.009
2.991
2.973
2.53
2.14
3.23
2.06
2.00
-0.000

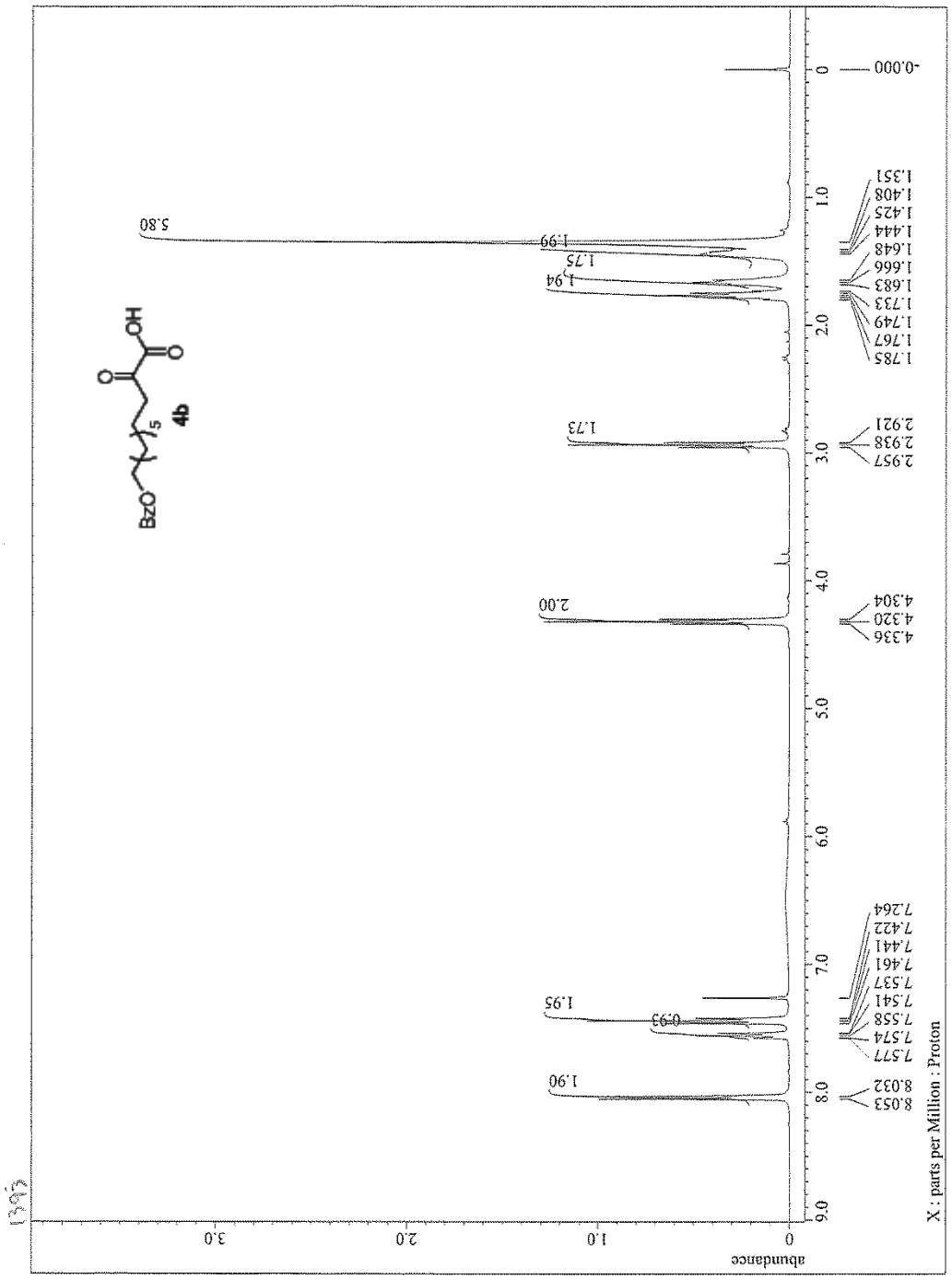

1b
Ph
OH
O
O
abundance
0
0.1
0.2
0.3
0.4
X : parts per Million : Carbon13
195.029
159.302
139.537
128.649
128.306
126.551
77.315
77.210
77.000
76.685
39.033
28.965
-0.020

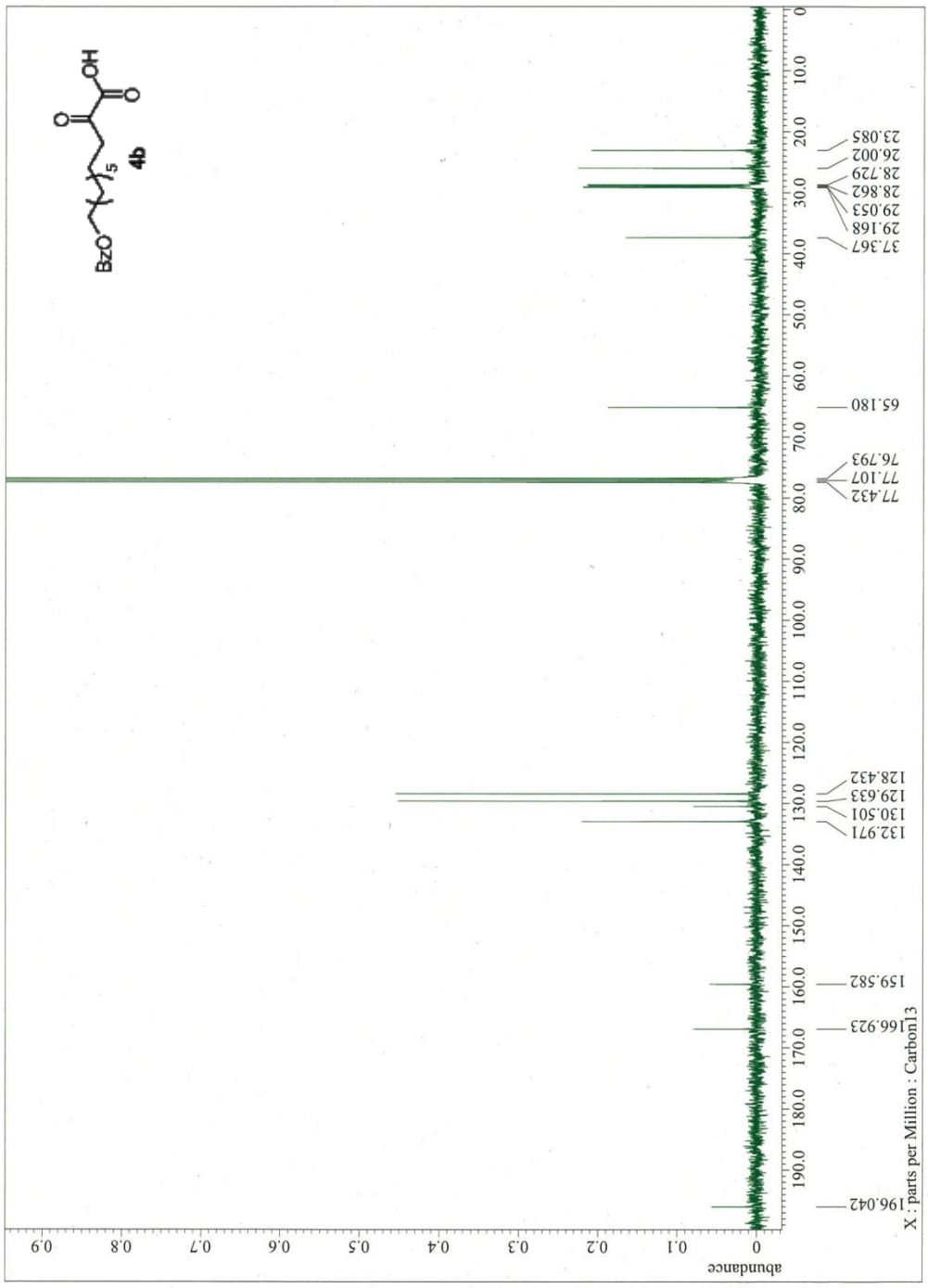

2b
5.88
2.00
1.54
1.04
0.992
0.975
2.832
2.814
2.274
2.257
2.239
2.223
2.206
2.190
2.137
7.268
7.031
X : parts per Million : Proton
abundance


2b
195.543
159.722
77.315
77.000
76.676
45.765
24.455
22.367
X : parts per Million : Carbon13
abundance

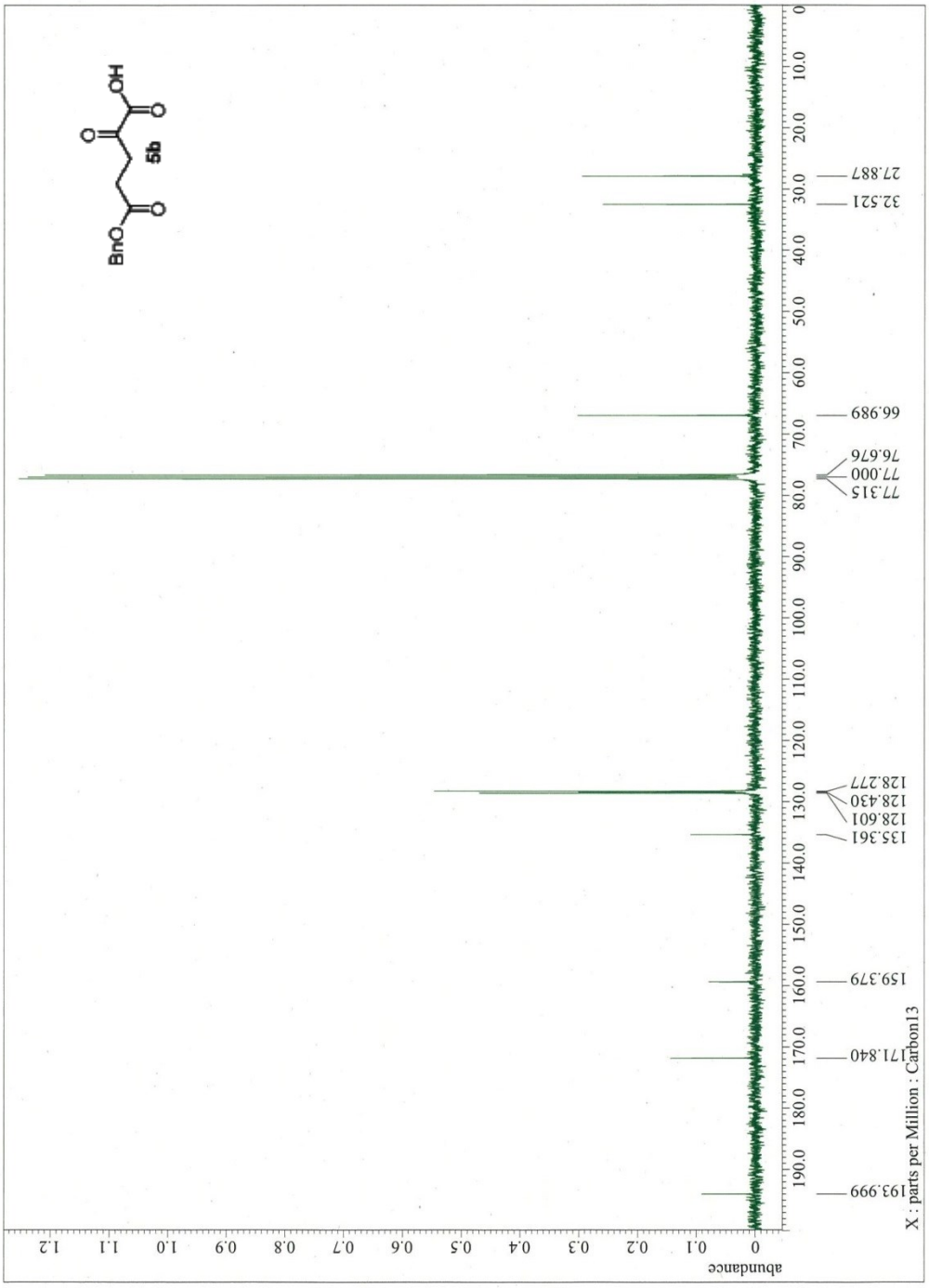

3b
OH
O
O
-0.000
1.003
1.030
1.057
1.178
1.250
1.274
1.306
1.645
1.688
1.717
1.905
1.913
1.922
1.930
2.821
2.839
2.00
1.10
5.72
2.40
1.14
2.13
7.261
X : parts per Million : Proton
abundance


3b
X : parts per Million : Carbon13
abundance
195.343
160.532
77.315
77.000
76.676
44.764
33.580
32.950
25.914
25.857
3b


4b
X : parts per Million : Proton
abundance
BzO
4b
-0.000
1.351
1.408
1.425
1.444
1.648
1.666
1.683
1.733
1.749
1.767
1.785
2.921
2.938
2.957
4.304
4.320
4.336
7.264
7.422
7.441
7.461
7.537
7.541
7.558
7.574
7.577
8.032
8.053
1.90
0.93
1.95
2.00
1.73
1.94
1.75
1.99
5.80

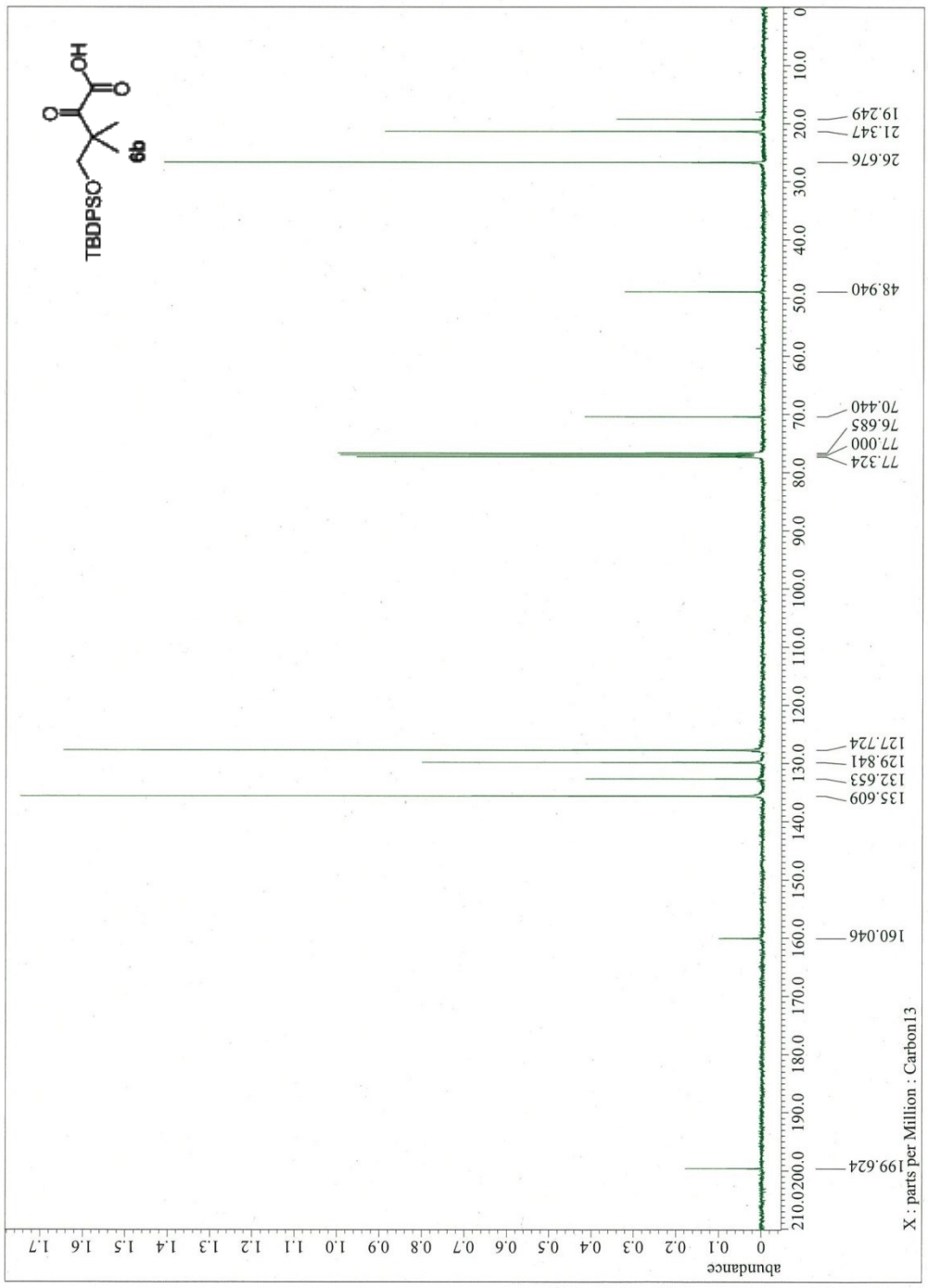

4b
BzO
OH
O
O
5
196.042
166.923
159.582
132.971
130.501
129.633
128.432
77.432
77.107
76.793
65.180
37.367
29.168
29.053
28.862
28.729
26.002
23.085
X : parts per Million : Carbon13
abundance

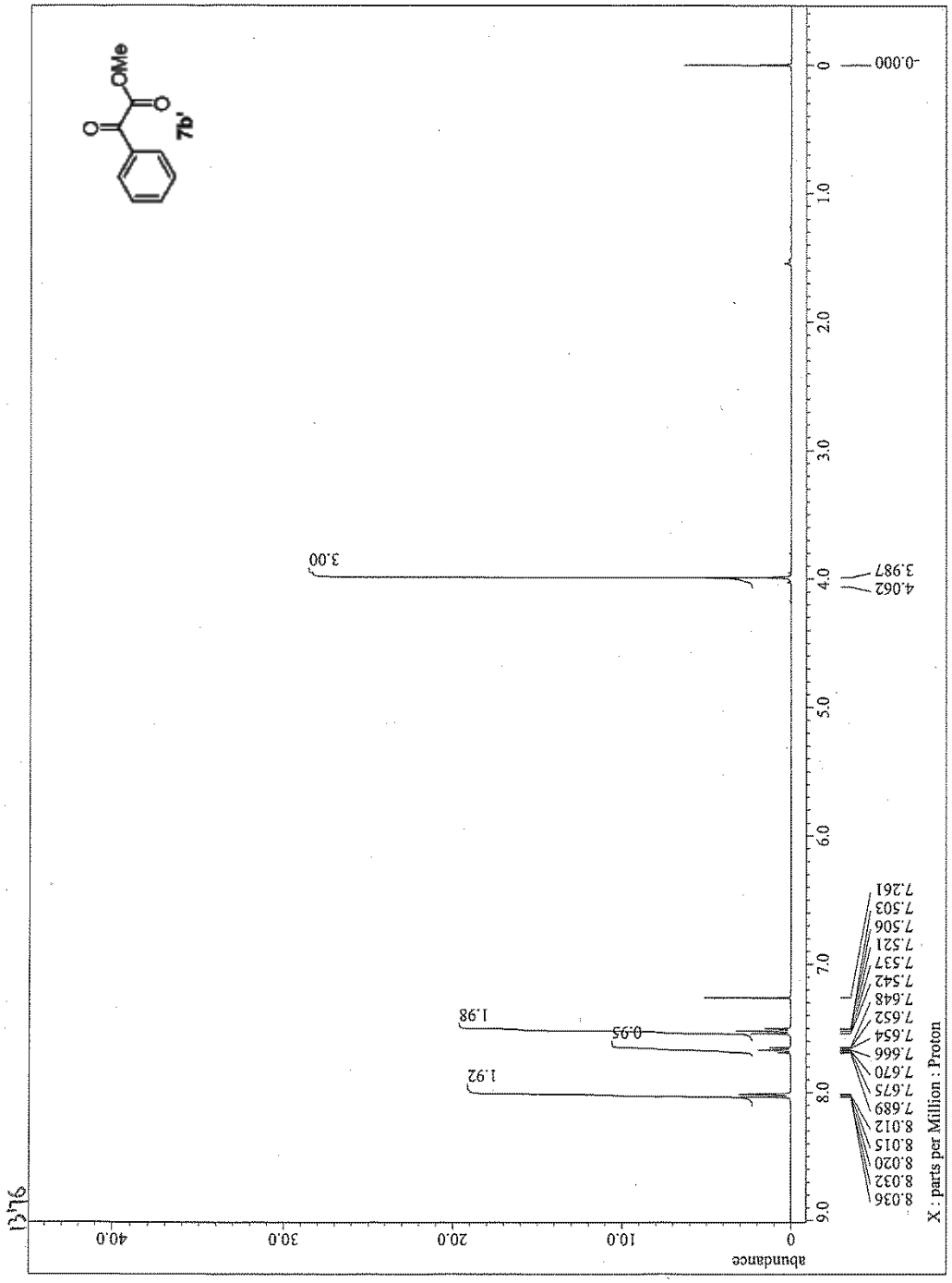
5b
BnO
OH
X : parts per Million : Proton
abundance
7.392
7.386
7.379
7.375
7.361
7.349
7.339
7.331
7.320
7.260
5.133
3.273
3.257
3.241
2.809
2.793
2.777
2.00
2.00
1.93
5.61
-0.000


5b
BnO
OH
193.999
171.840
159.379
135.361
128.601
128.430
128.277
77.315
77.000
76.676
66.989
32.521
27.887
X : parts per Million : Carbon13
abundance

5b

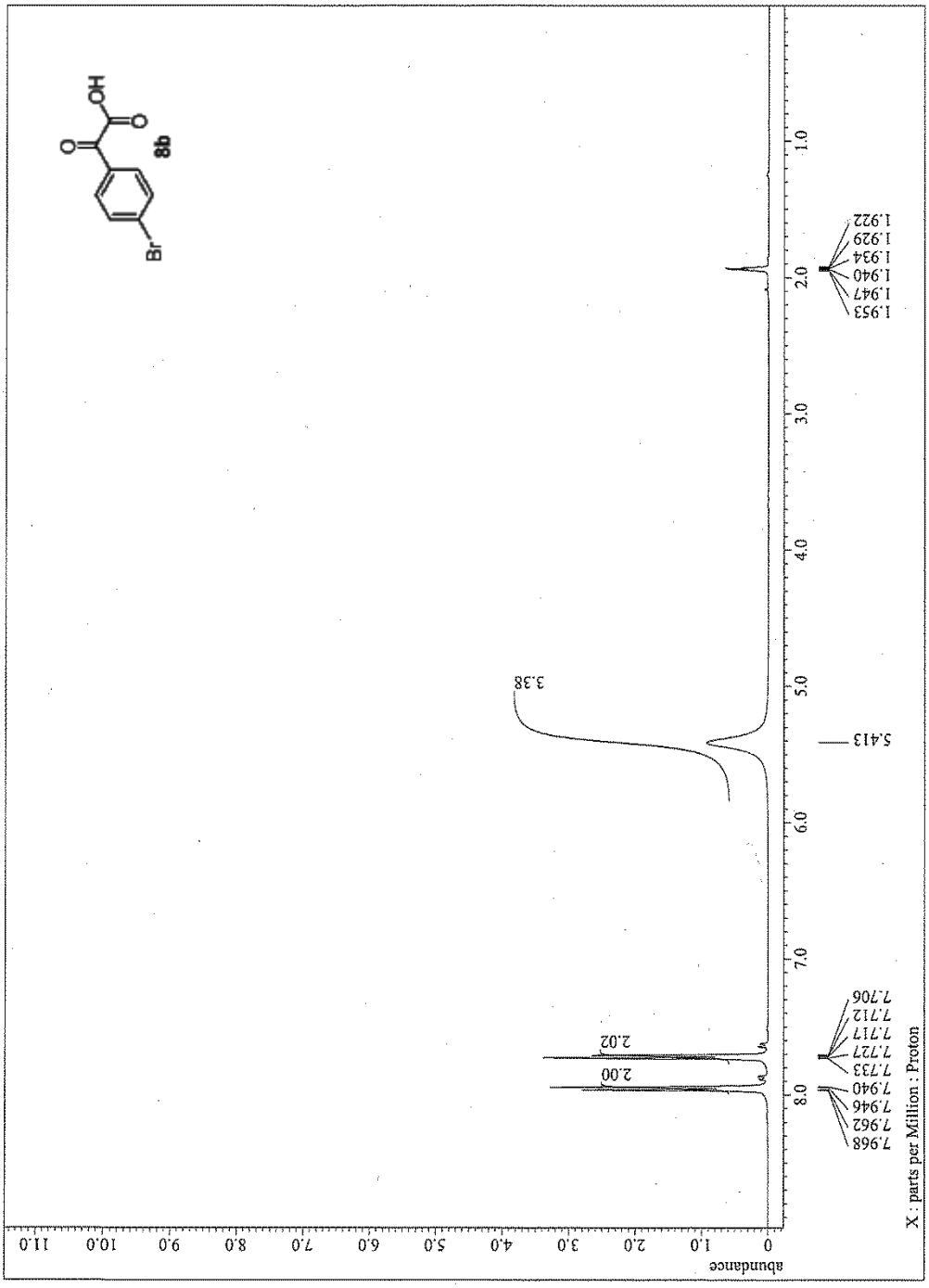
TBDPSO
6b
9.07
6.14
7.10
4.43
2.00
3.940
1.277
0.999
0.000
7.618
7.614
7.598
7.593
7.435
7.422
7.417
7.414
7.402
7.384
7.368
7.363
X : parts per Million : Proton
abundance


TBDPSO
6b
199.624
160.046
135.609
132.653
129.841
127.724
77.324
77.000
76.685
70.440
48.940
26.676
21.347
19.249
X : parts per Million : Carbon13
abundance

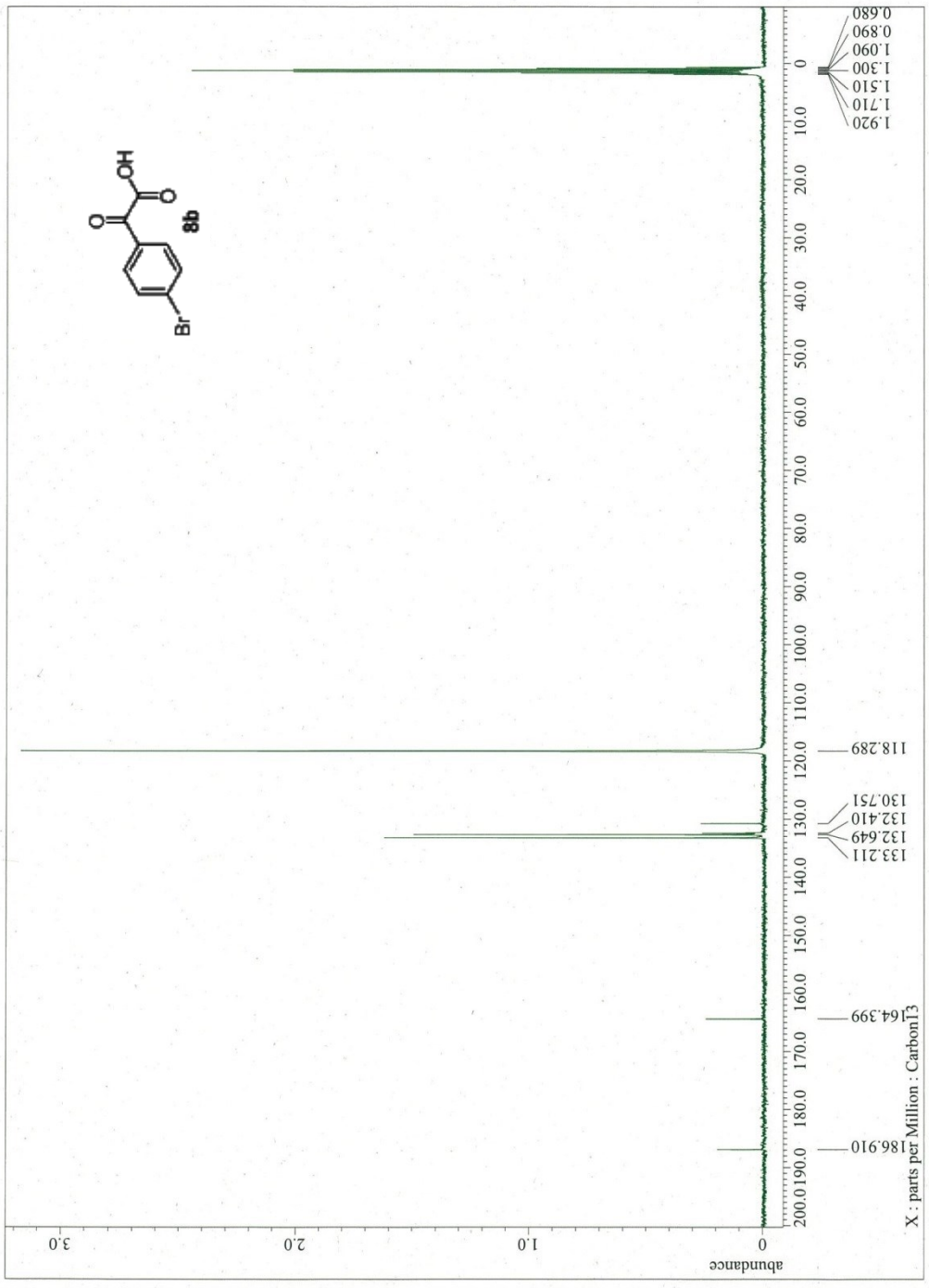

7b'
OMe
X : parts per Million : Proton
abundance
-0.000
3.987
4.062
3.00
1.98
0.95
1.92
8.036
8.032
8.020
8.015
8.012
7.689
7.675
7.670
7.666
7.654
7.652
7.648
7.542
7.537
7.521
7.506
7.503
7.261

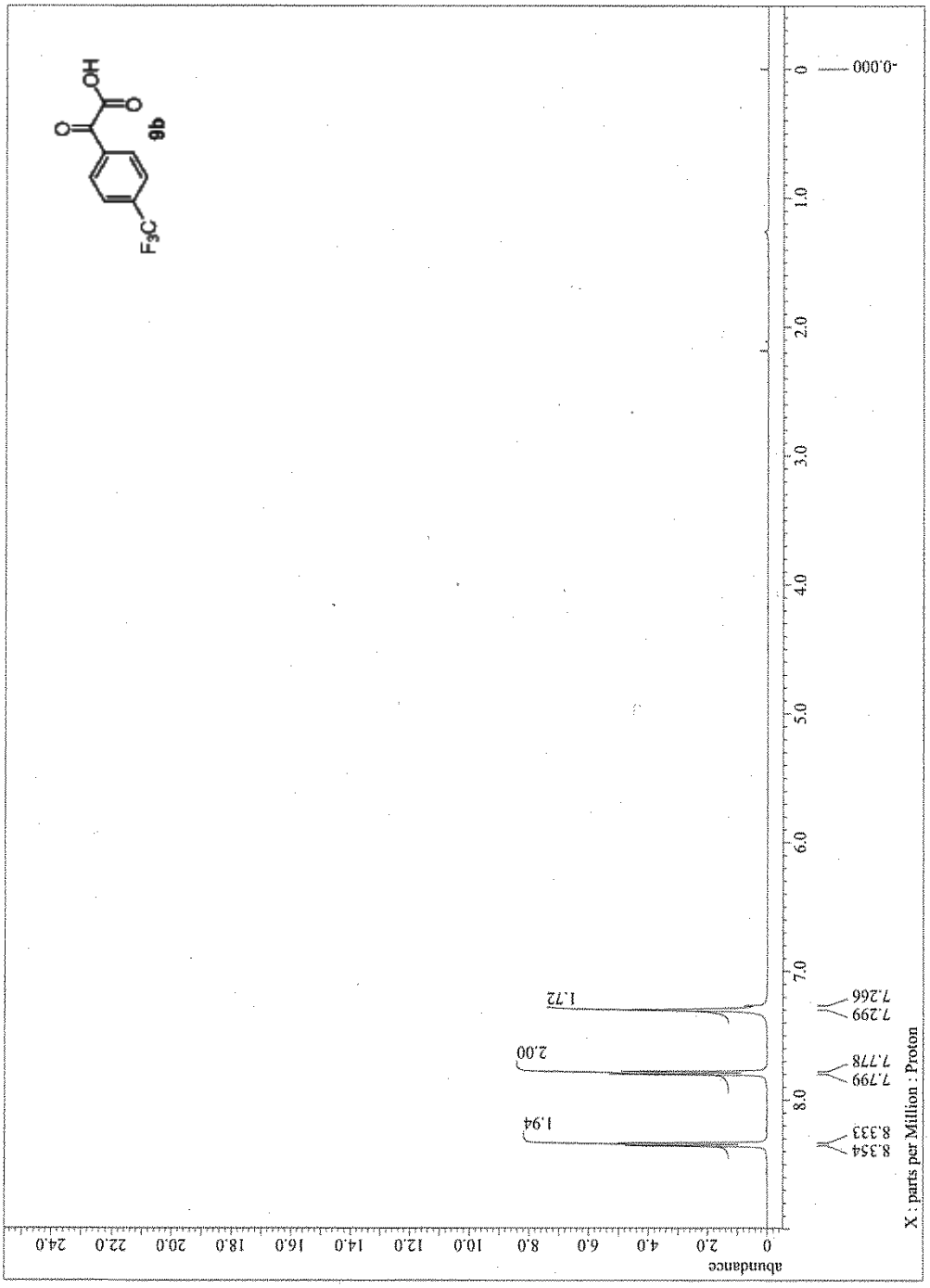
7b'
OMe
52.773
76.685
77.000
77.315
128.887
130.069
132.386
134.980
164.013
186.028
X : parts per Million : Carbon13
abundance

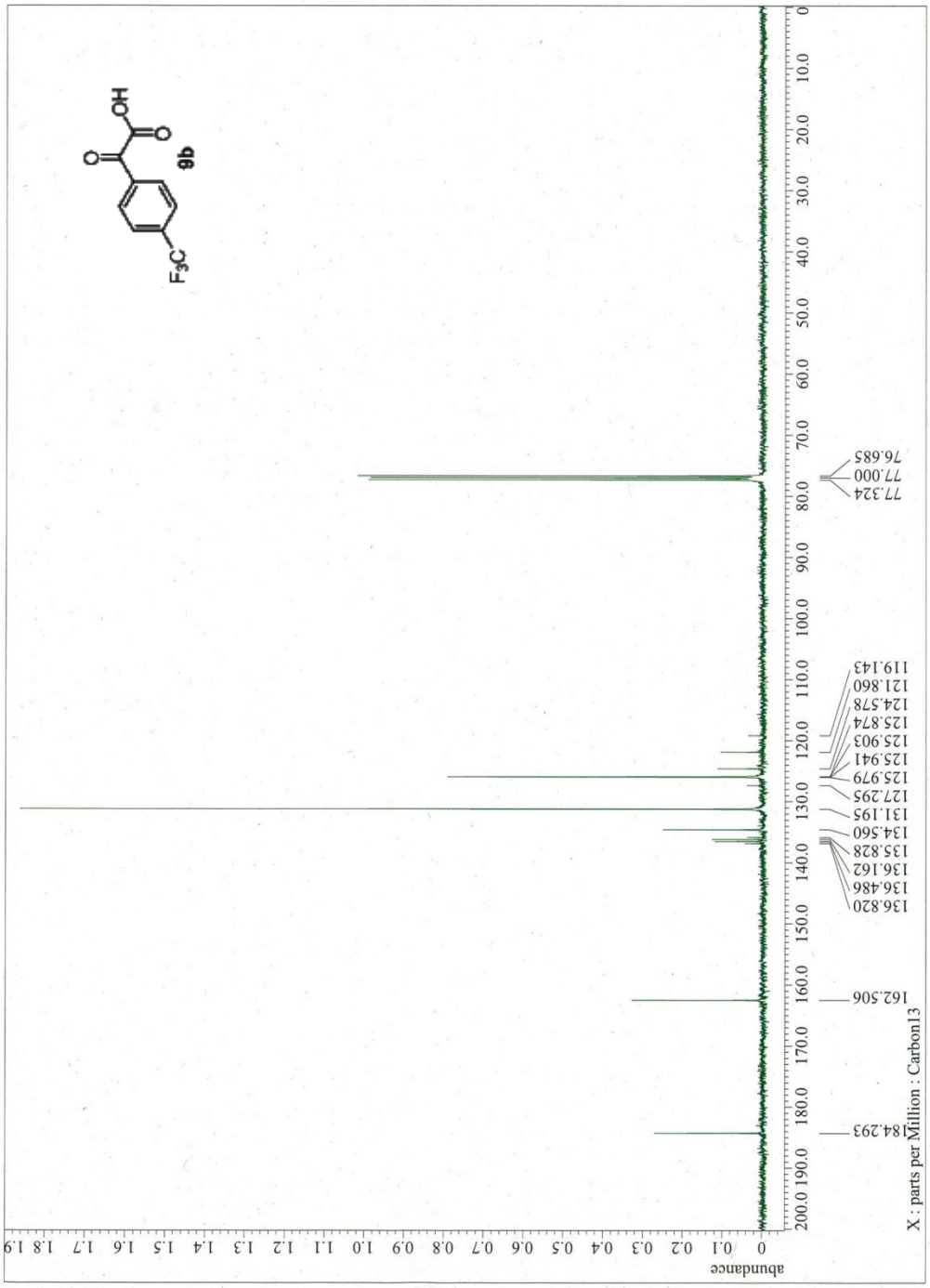
7b'

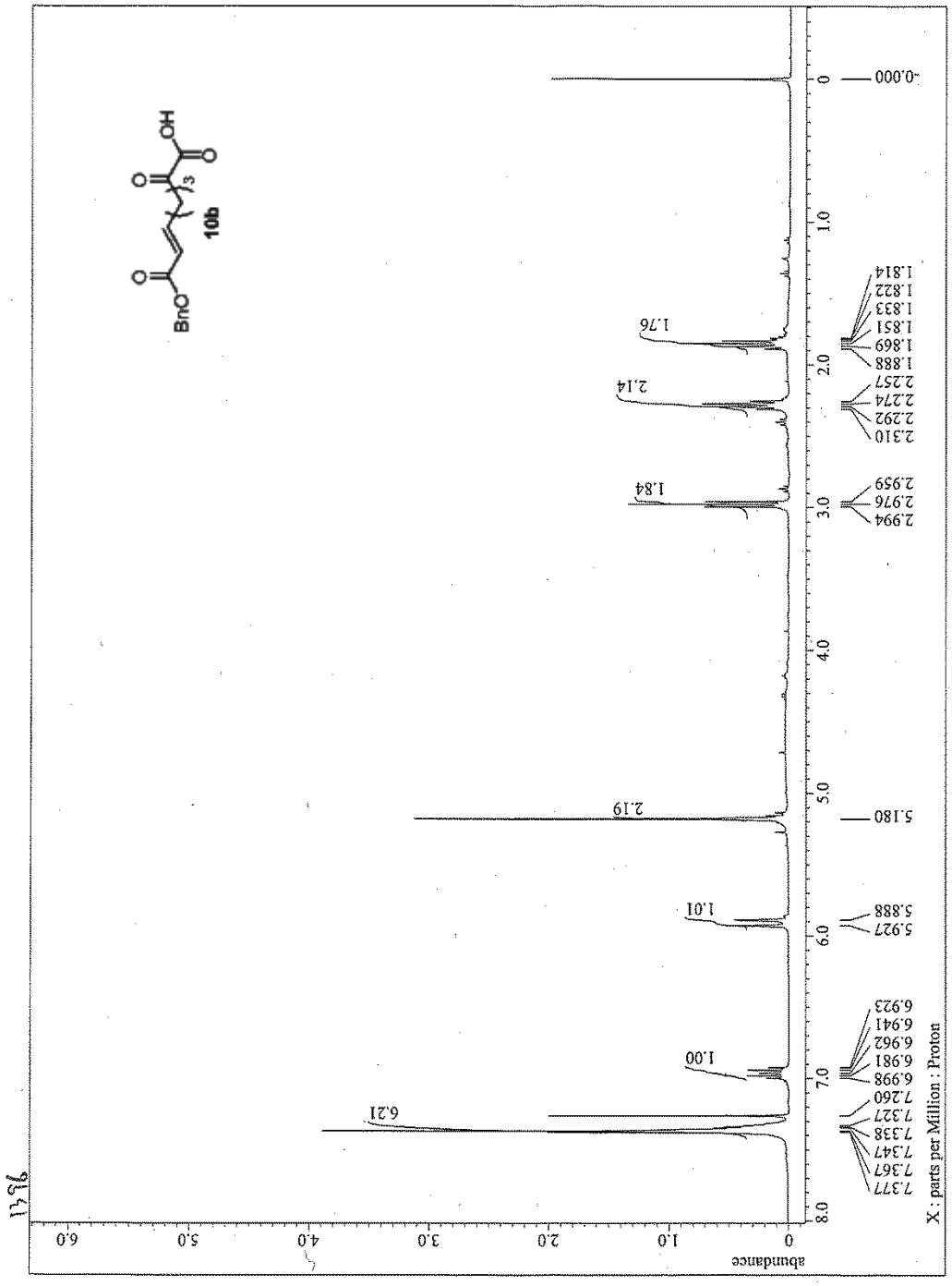

8b
Br
OH
O
O
abundance
X : parts per Million : Proton
7.968
7.962
7.946
7.940
7.733
7.727
7.717
7.712
7.706
1.953
1.947
1.940
1.934
1.929
1.922
5.413
3.38
2.00
2.02

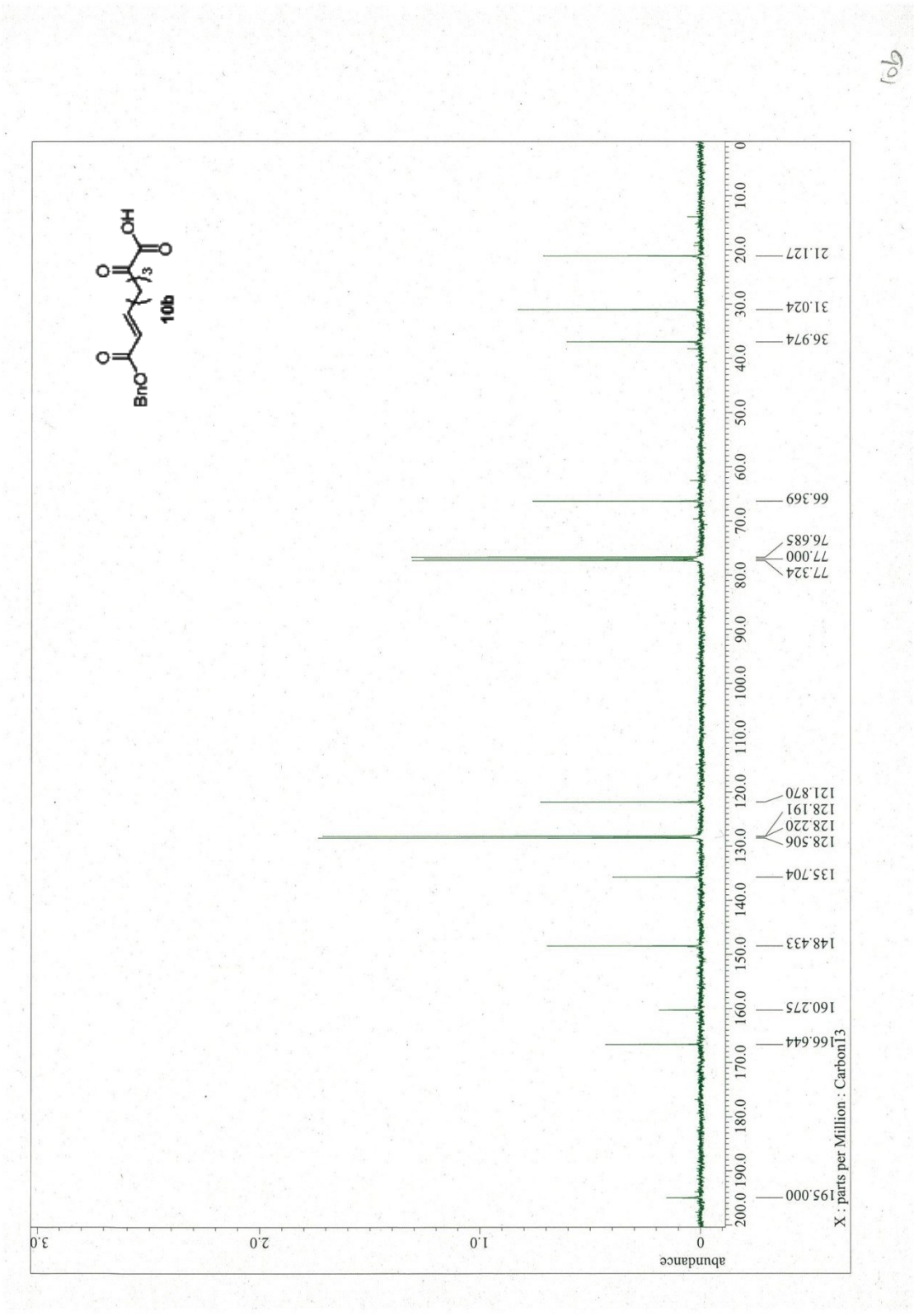
8b

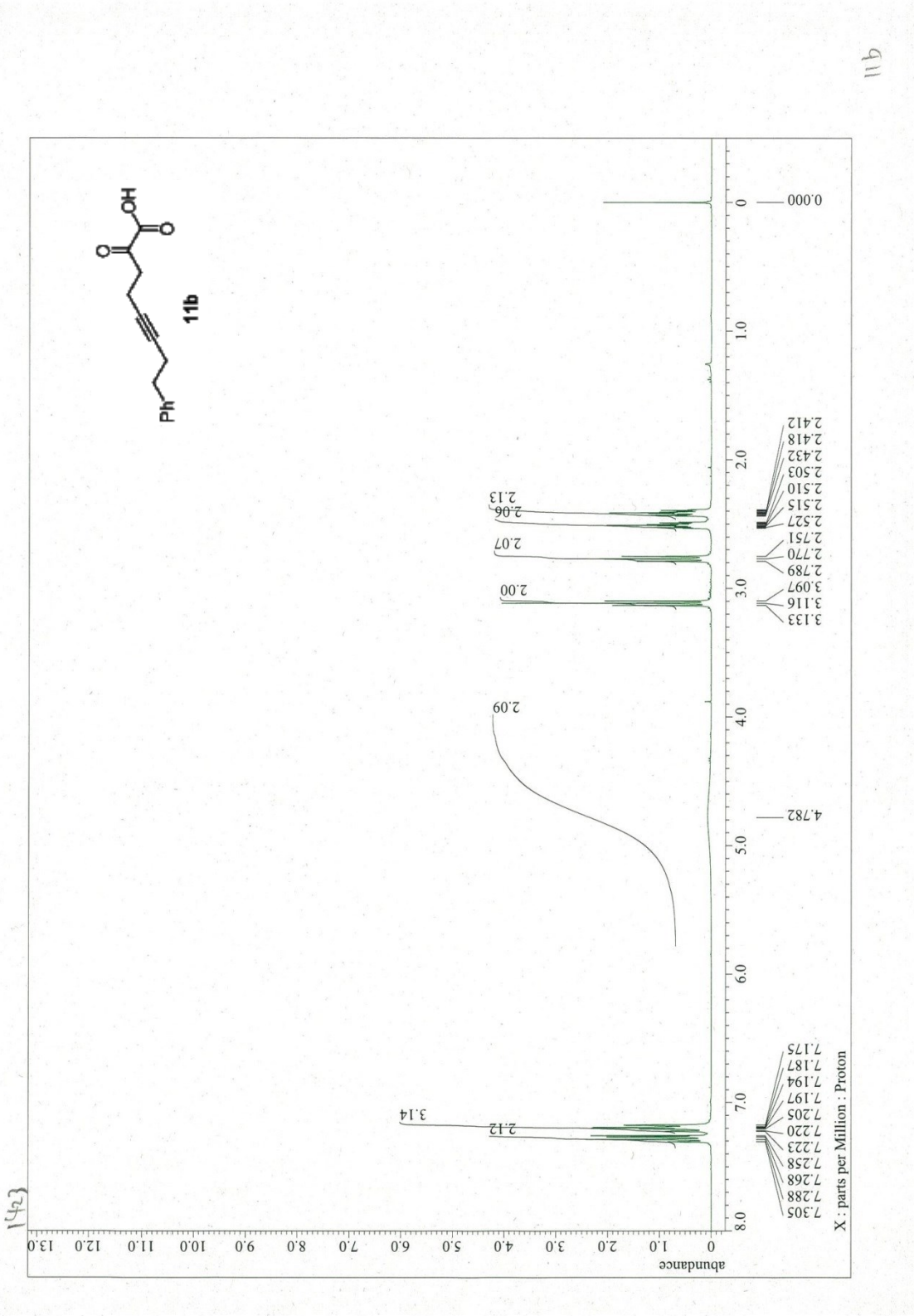

8b
Br
OH
O
O
1.920
1.710
1.510
1.300
1.090
0.890
0.680
118.289
133.211
132.649
132.410
130.751
164.399
186.910
X : parts per Million : Carbon13
abundance

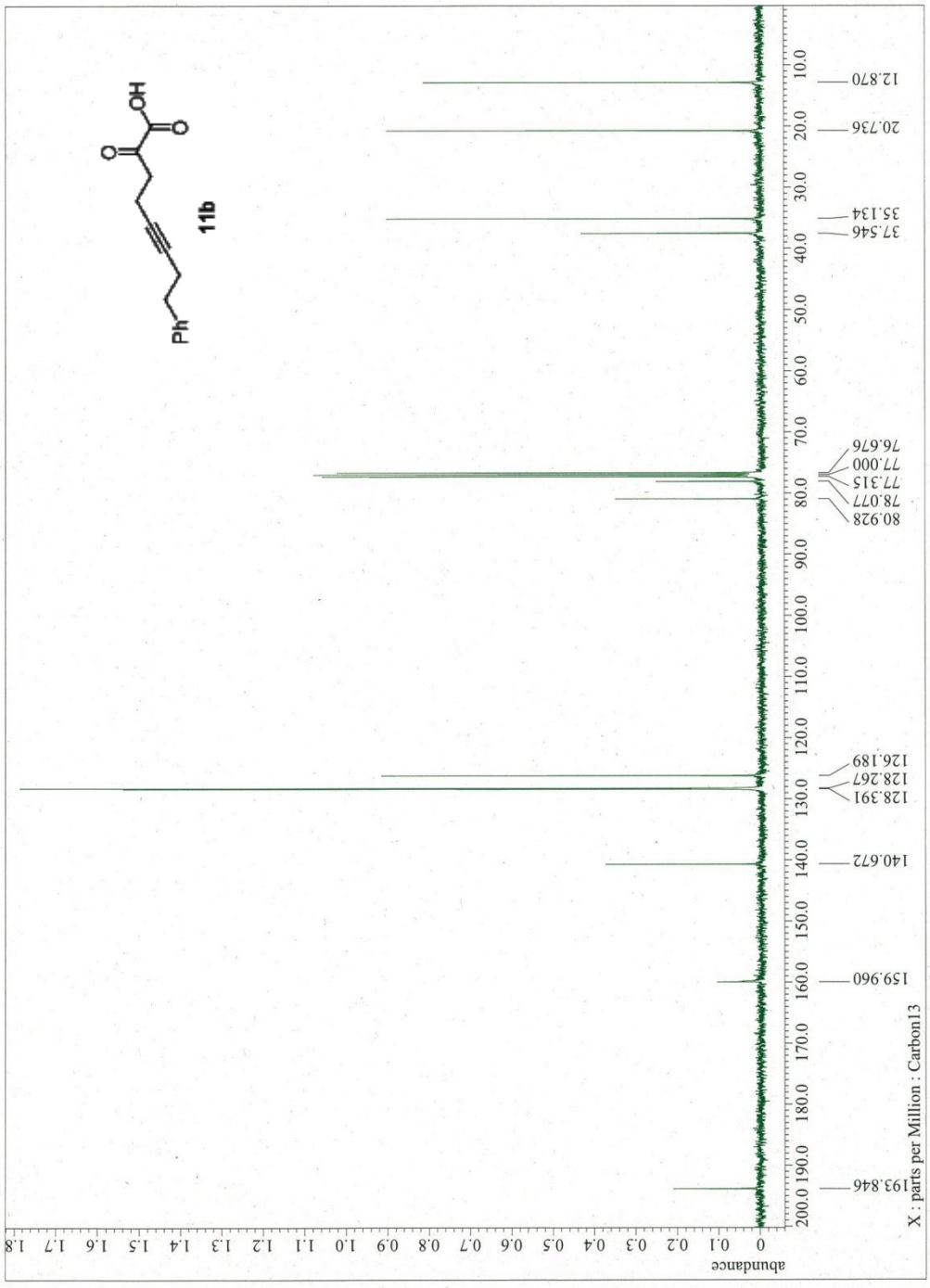

abundance
X : parts per Million : Proton
8.354
8.333
7.799
7.778
7.299
7.266
1.94
2.00
1.72
F3C
OH
9b

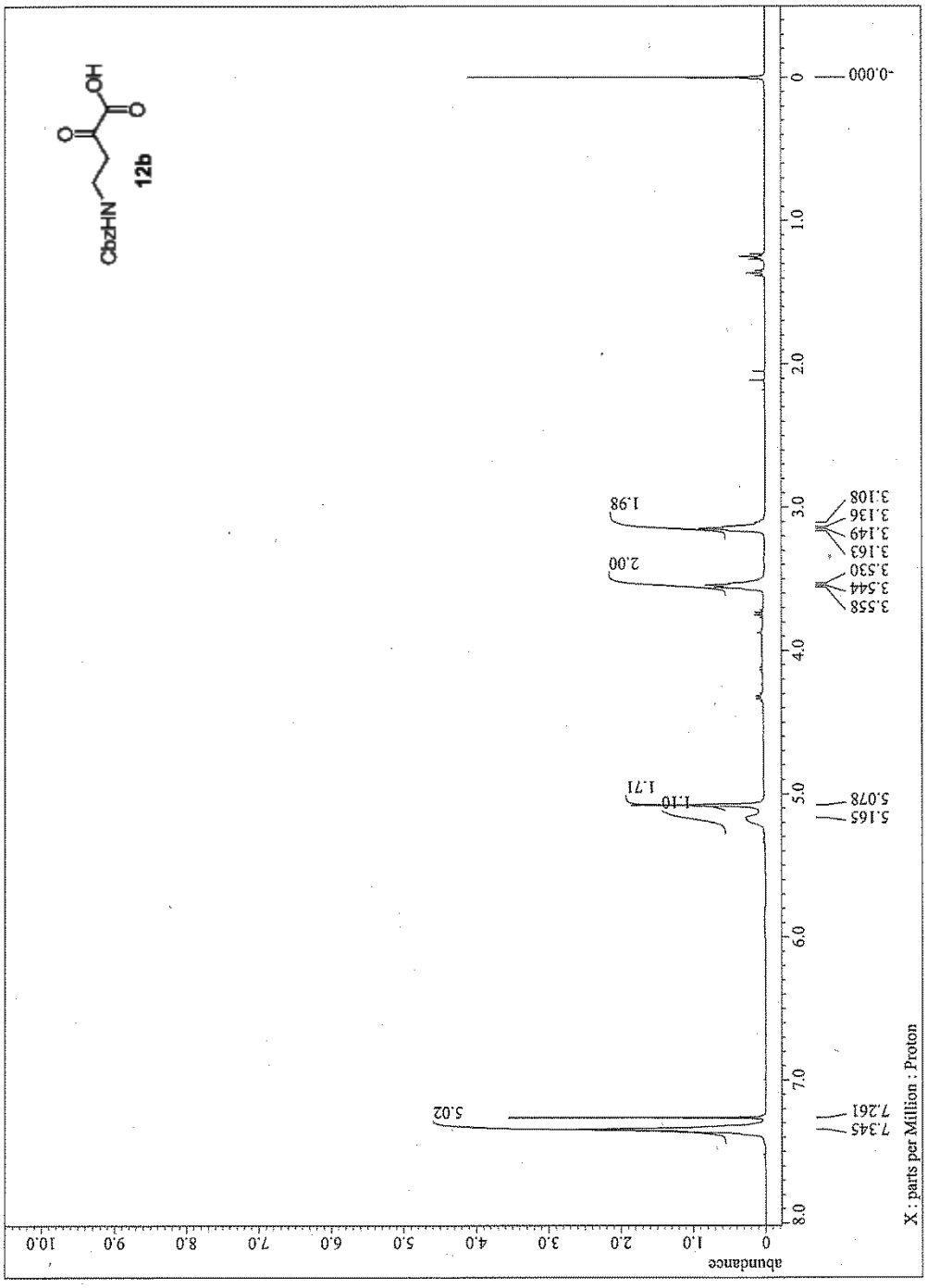

9b
F3C
OH
O
O
abundance
X : parts per Million : Carbon13
184.293
162.506
136.820
136.486
136.162
135.828
134.560
131.195
127.295
125.979
125.941
125.903
125.874
124.578
121.860
119.143
77.324
77.000
76.685


10b
BnO
OH
X : parts per Million : Proton
7.377
7.367
7.347
7.338
7.327
7.260
6.998
6.981
6.962
6.941
6.923
5.927
5.888
5.180
2.994
2.976
2.959
2.310
2.292
2.274
2.257
1.888
1.869
1.851
1.833
1.822
1.814
-0.000
6.21
1.00
1.01
2.19
1.84
2.14
1.76
abundance

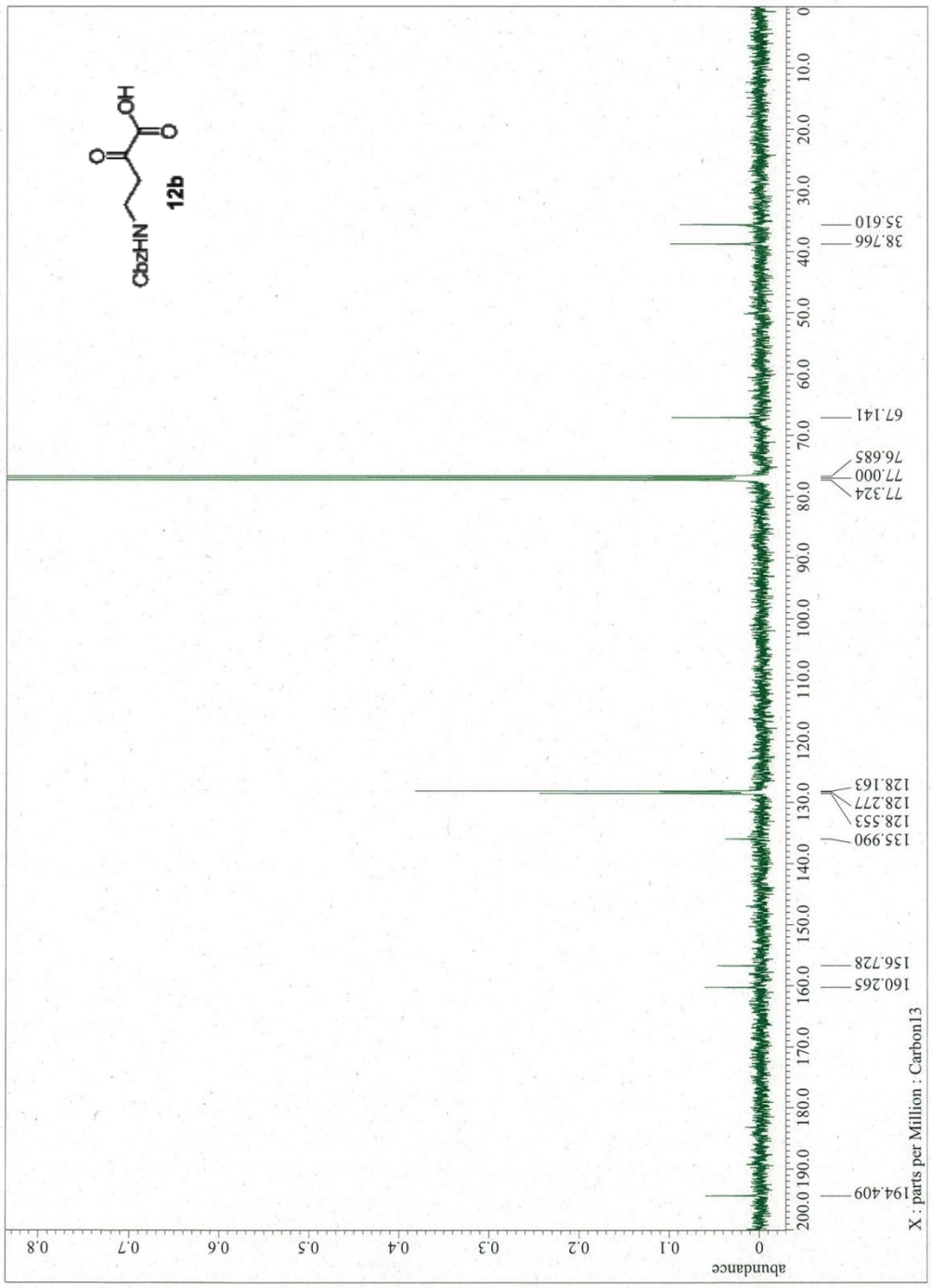

10b
BnO
OH
abundance
X : parts per Million : Carbon13
195.000
166.644
160.275
148.433
135.704
128.506
128.220
128.191
121.870
77.324
77.000
76.685
66.369
36.974
31.024
21.127

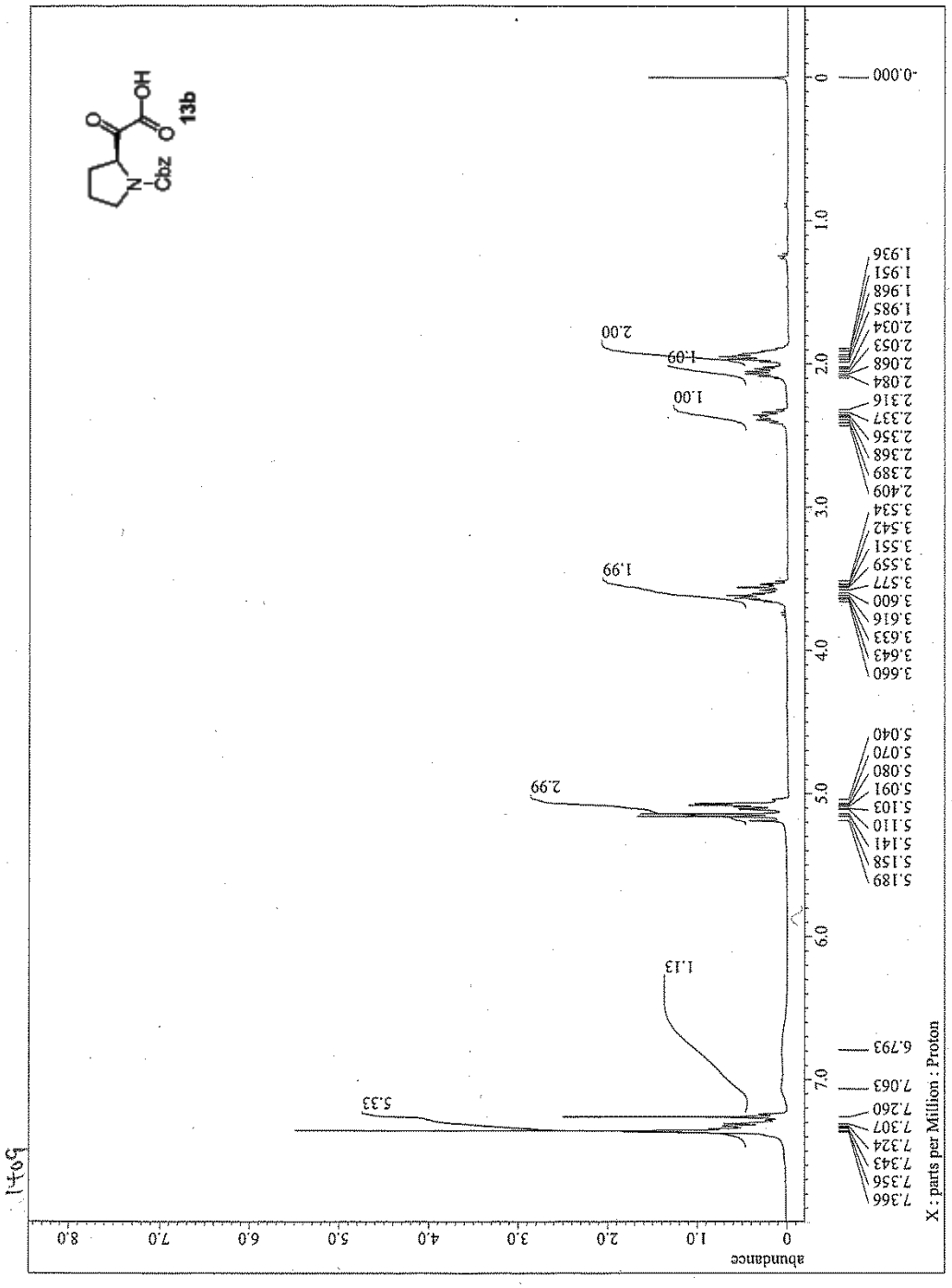

11b
Ph
OH
O
O
X : parts per Million : Proton
abundance
7.305
7.288
7.268
7.258
7.223
7.220
7.205
7.197
7.194
7.187
7.175
4.782
3.133
3.116
3.097
2.789
2.770
2.751
2.527
2.515
2.510
2.503
2.432
2.418
2.412
0.000
3.14
2.12
2.09
2.00
2.07
2.06
2.13

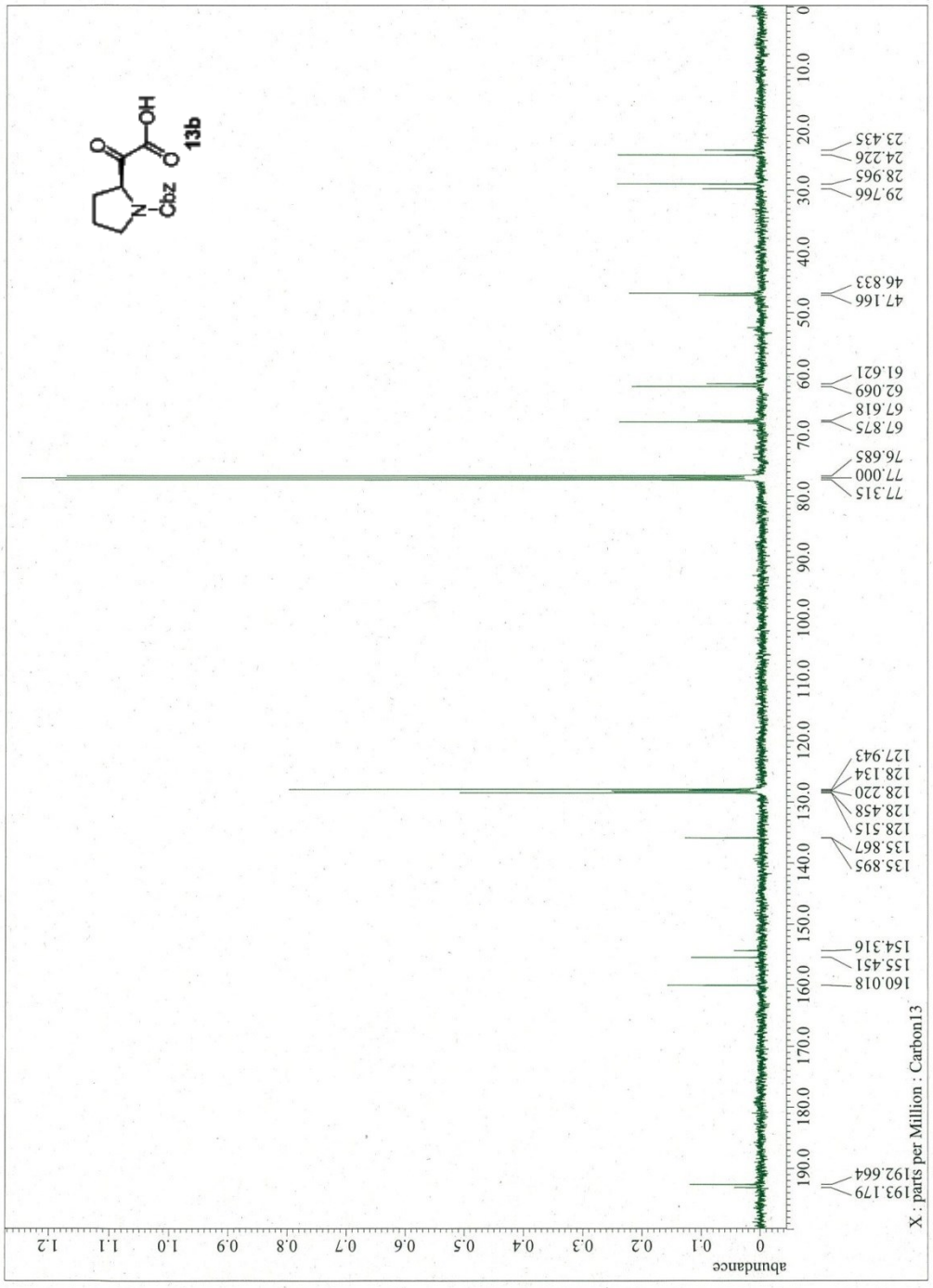

11b
Ph
OH
O
O
193.846
159.960
140.672
128.391
128.267
126.189
80.928
78.077
77.315
77.000
76.676
37.546
35.134
20.736
12.870
X : parts per Million : Carbon13
abundance


12b
CbzHN
OH
O
O
X : parts per Million : Proton
abundance
-0.000
7.345
7.261
5.165
5.078
3.558
3.544
3.530
3.163
3.149
3.136
3.108
5.02
1.71
1.10
2.00
1.98

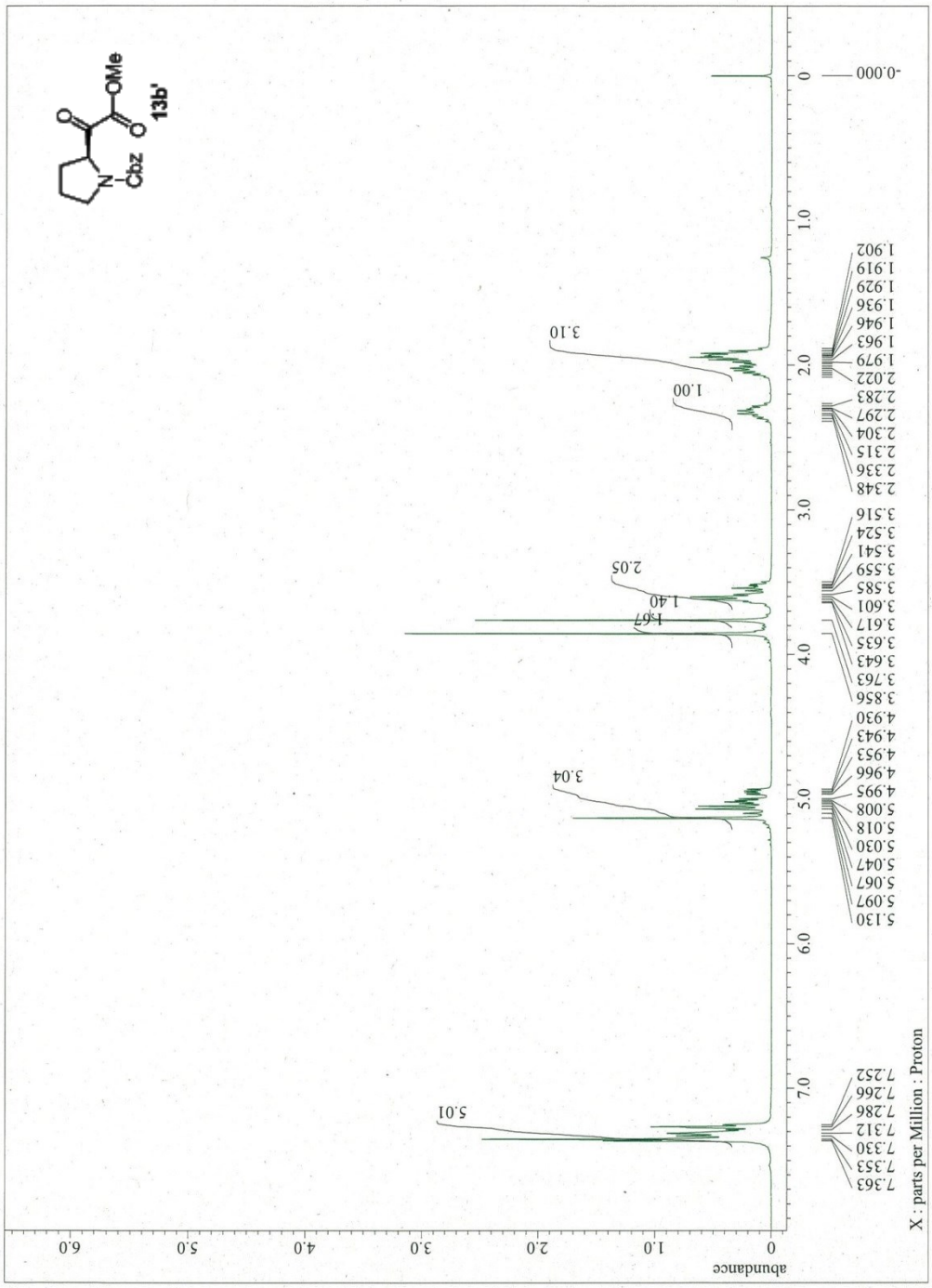
12b

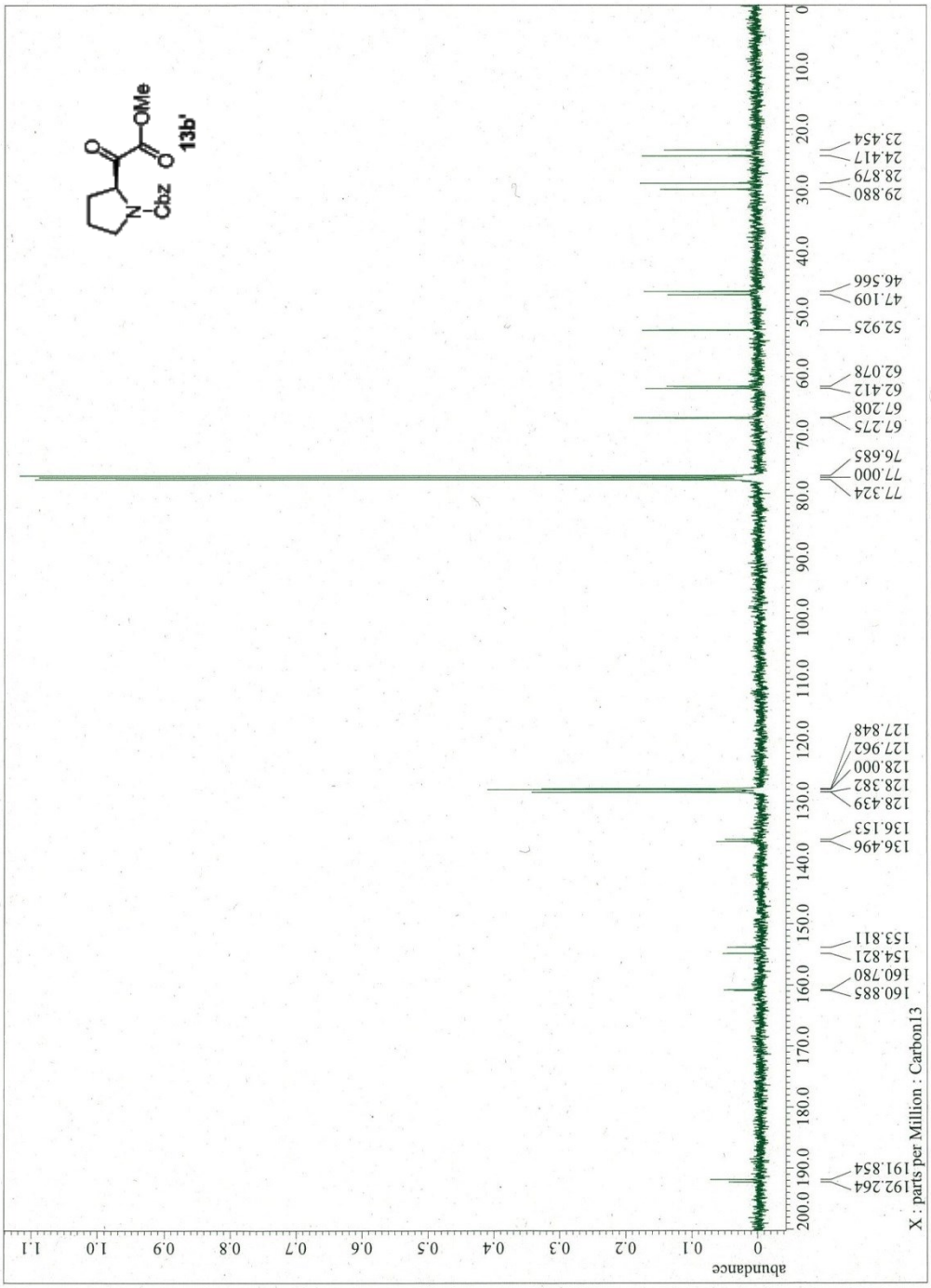

12b
CbzHN
OH
O
O
194.409
160.265
156.728
135.990
128.553
128.277
128.163
77.324
77.000
76.685
67.141
38.766
35.610
X : parts per Million : Carbon13
abundance

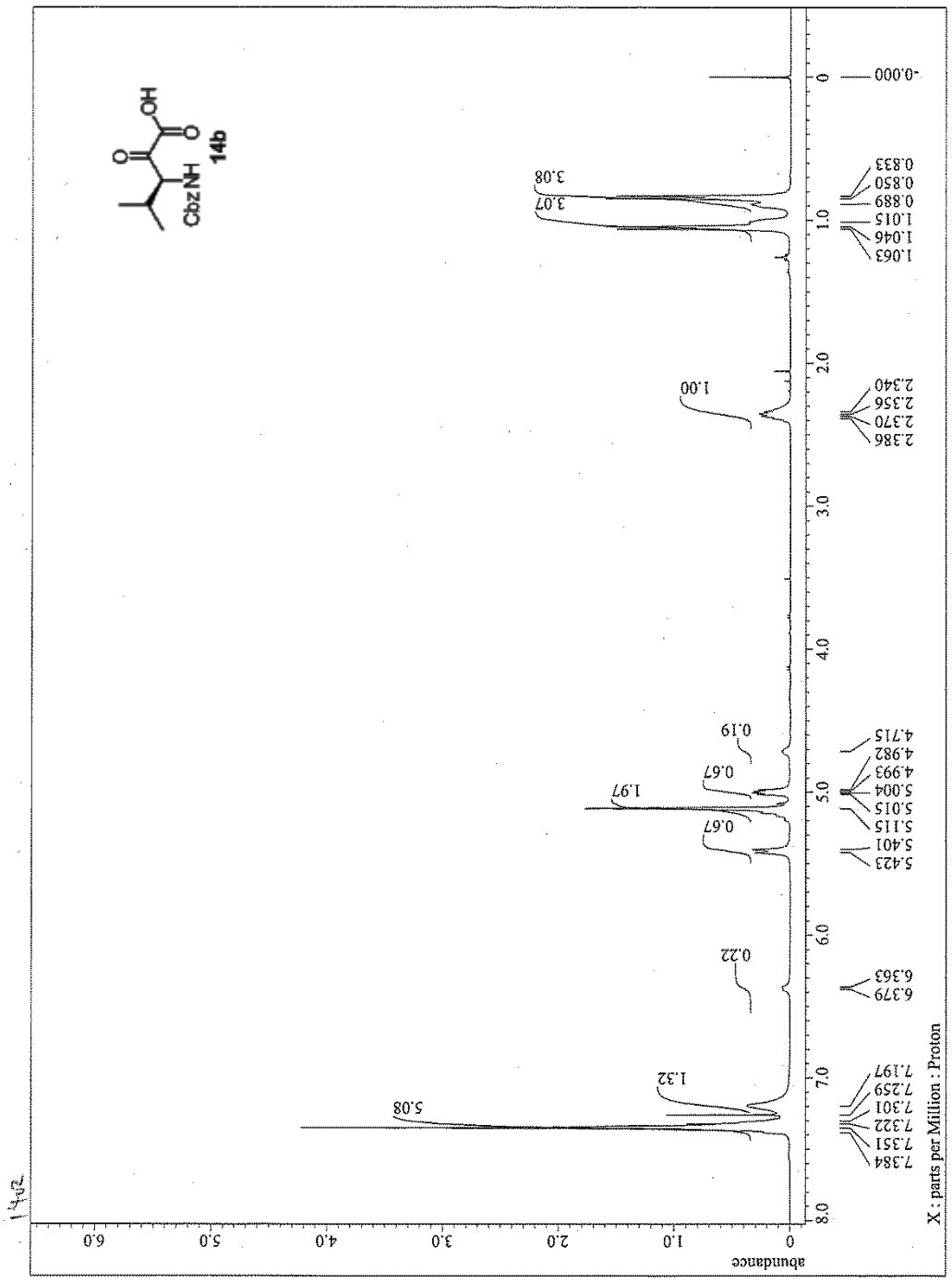

13b
Cbz
N
OH
O
O
abundance
X : parts per Million : Proton
7.366
7.356
7.343
7.324
7.307
7.260
7.063
6.793
5.333
5.189
5.158
5.141
5.110
5.103
5.091
5.080
5.070
5.040
3.660
3.643
3.633
3.616
3.600
3.577
3.559
3.551
3.542
3.534
2.409
2.389
2.368
2.356
2.337
2.316
2.084
2.068
2.053
2.034
1.985
1.968
1.951
1.936
1.13
2.99
1.99
1.00
1.09
2.00
-0.000

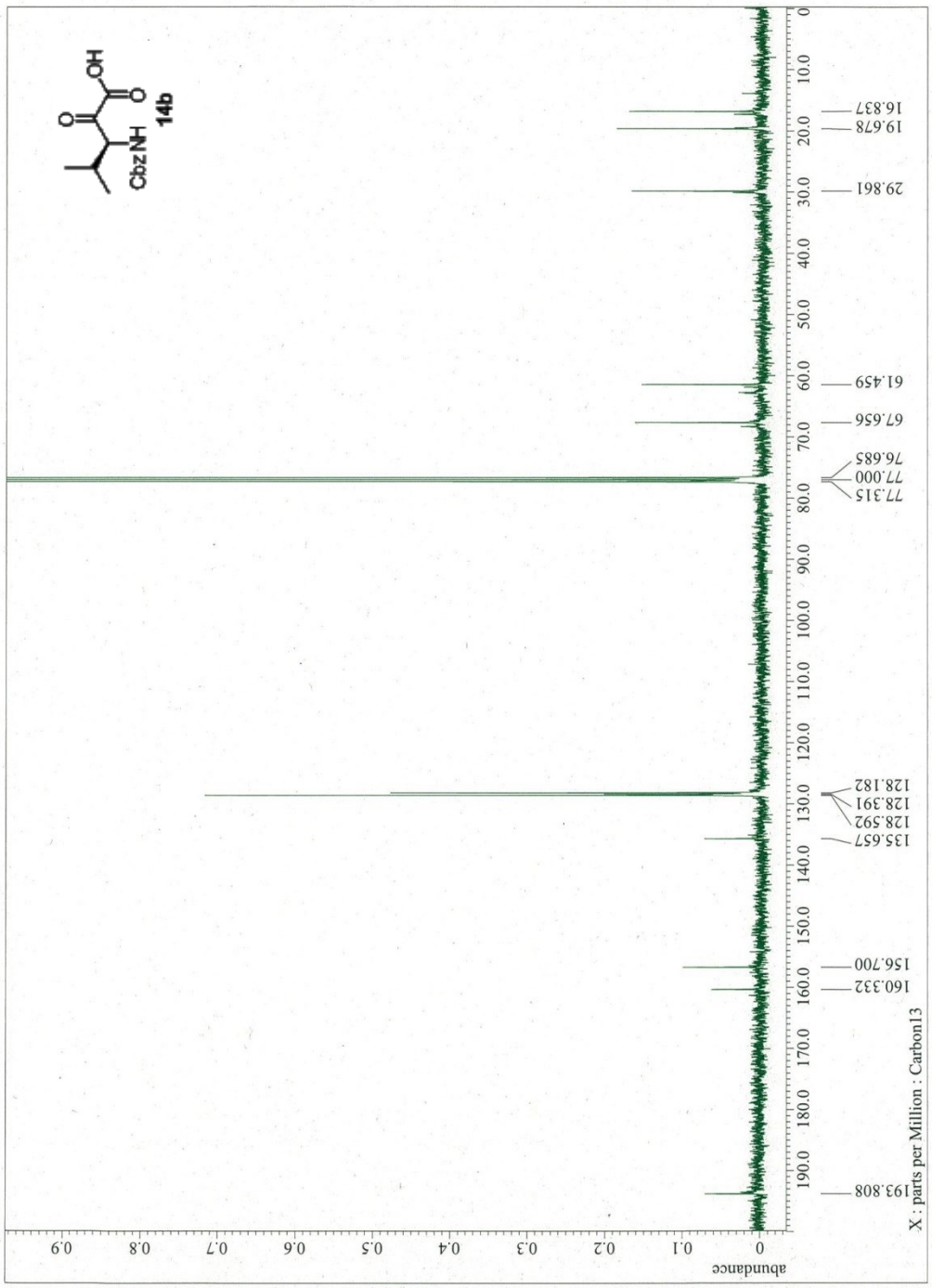

13b
Cbz
OH
O
O
N
abundance
X : parts per Million : Carbon13
193.179
192.664
160.018
155.451
154.316
135.895
135.867
128.515
128.458
128.220
128.134
127.943
77.315
77.000
76.685
67.875
67.618
62.069
61.621
47.166
46.833
29.766
28.965
24.226
23.435

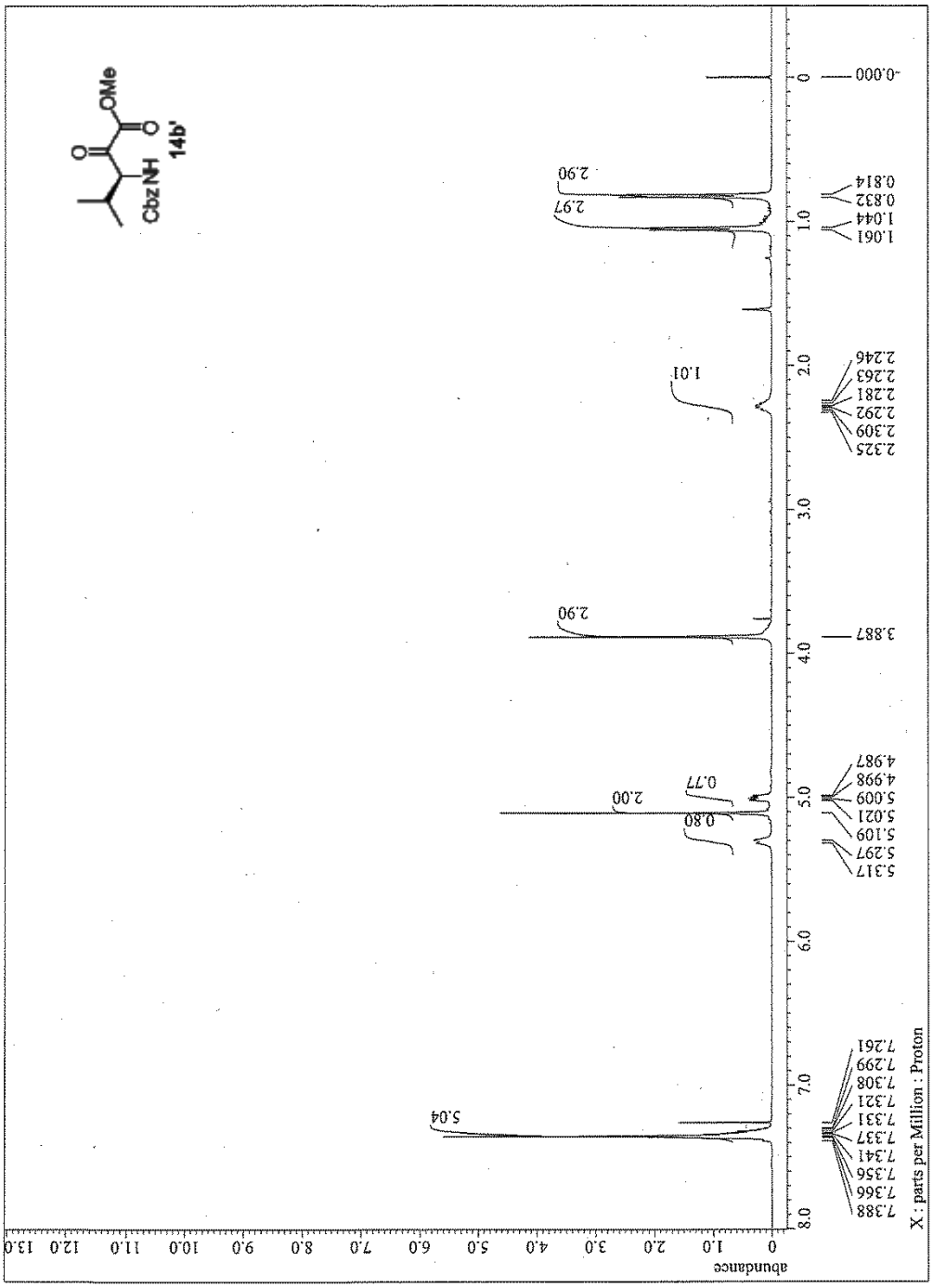
13b

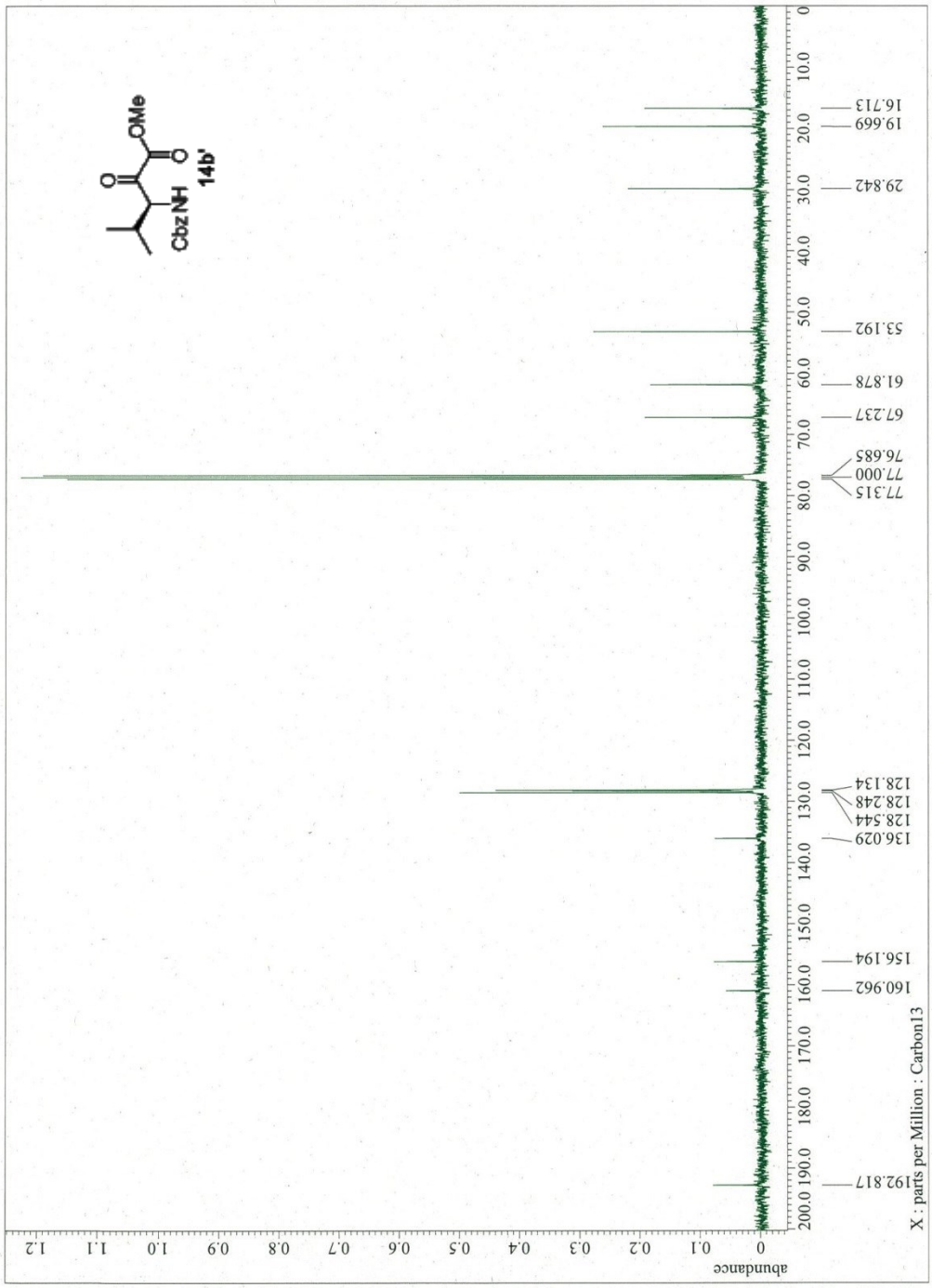

13b'
OMe
Cbz
X : parts per Million : Proton
abundance
5.01
3.04
3.10
1.00
2.05
1.40
1.67


13b'
OMe
Cbz
13b'
abundance
X : parts per Million : Carbon13
191.854
192.264
153.811
154.821
160.780
160.885
136.153
136.496
128.439
128.382
128.000
127.962
127.848
77.324
77.000
76.685
67.275
67.208
62.412
62.078
52.925
47.109
46.566
29.880
28.879
24.417
23.454


14b
CbzNH
X : parts per Million : Proton
abundance
7.384
7.351
7.322
7.301
7.259
7.197
6.379
6.363
5.423
5.401
5.115
5.015
5.004
4.993
4.982
4.715
2.386
2.370
2.356
2.340
1.063
1.046
1.015
0.889
0.850
0.833
0.000
5.08
1.32
0.22
1.97
0.67
0.67
0.19
1.00
3.07
3.08


14b
CbzNH
OH
O
O
abundance
X : parts per Million : Carbon13
193.808
160.332
156.700
135.657
128.592
128.391
128.182
77.315
77.000
76.685
67.656
61.459
29.861
19.678
16.837


14b'
OMe
O
O
CbzNH
14b'
X : parts per Million : Proton
abundance
7.388
7.366
7.356
7.341
7.337
7.331
7.321
7.308
7.299
7.261
5.317
5.297
5.109
5.021
5.009
4.998
4.987
3.887
2.325
2.309
2.292
2.281
2.263
2.246
1.061
1.044
0.832
0.814
-0.000
5.04
2.90
0.77
2.00
0.80
2.90
1.01
2.97
2.90


14b'
OMe
O
O
CbzNH
14b'
192.817
160.962
156.194
136.029
128.134
128.248
128.544
77.315
77.000
76.685
67.237
61.878
53.192
29.842
19.669
16.713
X : parts per Million : Carbon13
abundance