Supporting Information

Asymmetric organocatalytic formation of protected and unprotected tetroses under potentially prebiotic conditions.

Laurence Burroughs,† Paul A. Clarke,*† Henrietta Forintos,‡ James A. R. Gilks,‡ Christopher J. Hayes,*‡ Matthew E. Vale, †‡ William Wade† and Myriam Zbytniewski †

Department of Chemistry, University of York, Heslington, York, North Yorks, UK, YO10 5DD.

School of Chemistry, University of Nottingham, University Park, Nottingham, UK, NG7 2RD.

E-mail: paul.clarke@york.ac.uk, chris.hayes@nottingham.ac.uk

Contents

General

Melting points were determined using a Stuart SMP3 apparatus. Infrared spectra were recorded on a ThermoNicolet 100IR spectrometer using NaCl plates, or on a JASCO FT/IR-4100 spectrometer as a solid. Optical rotations were carried out using a JASCO-DIP370 polarimeter; concentrations are given in g 100 ml^{-1} and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High-performance liquid chromatography was carried out on an Agilent 1100 Series system using a Chiralcel OD-H column and OD-H guard with hexanes/isopropanol as the mobile phase. Gas chromatography was carried out on a Varian 430-GC system using a CP-Chirasil-Dex CB or SGE BP-5 column as indicated. Nuclear magnetic resonance spectra were recorded on a Jeol EX-270 (270 MHz), a Jeol ECX-400 (400 MHz), Jeol ECS400 (400 MHz) or a Bruker DRX 500 (500 MHz) spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-d, 7.26 ppm; deuterium oxide, 4.79 ppm; dimethyl sulfoxide-d, 2.50 ppm; methanol-d, 3.31 ppm for ^{1}H NMR data; chloroform-d, 77.0 ppm; dimethyl sulfoxide-d, 39.5 ppm; methanol-d, 49.1 ppm; deuterium oxide was referenced to an internal standard of 1,4-Dioxane at 67.4 ppm for ^{13}C NMR data. Coupling constants (*J*) are quoted in Hertz. ^{13}C NMR spectra were assigned using DEPT and HSQC experiments. Mass spectrometry was performed by the University of York mass spectrometry service ESI ionisation techniques. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F_{254}. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich as stated. Dichloromethane was used distilled from calcium chloride, methanol and ethanol were used distilled from magnesium turnings/iodine and tetrahydrofuran was used distilled from sodium/benzophenone unless otherwise stated. Buffer solutions were made up to the desired pH using mixtures of 0.1 mol dm^{-3} potassium dihydrogen orthophosphate and 0.1 mol dm^{-3} sodium hydroxide. All other solvents

and reagents were used as received from commercial suppliers. All numbering on the structures below is for the benefit of characterisation and does not conform to IUPAC rules. However, the compound names are standardised and correspond to IUPAC rules.

General procedure for the formation of (*L*)-*N*-Boc proline aliphatic esters

N-Methylmorpholine (0.15 mL, 1.40 mmol) was added to a stirred solution of icosanol or heneicosanol (0.35 mmol), (*L*)-*N*-Boc proline (151 mg, 0.70 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (134 mg, 0.70 mmol) and 4-dimethylamino pyridine (5.0 mg, 0.035 mmol) in dichloromethane (3 mL) under nitrogen. The reaction mixture was stirred for 24 hours, after which ethyl acetate (50 mL) was added. The organic mixture was then washed with citric acid (1 mol dm^{-3}, 50 mL) followed by saturated aqueous potassium carbonate solution (50 mL). The separated organic layer was dried with magnesium sulfate, filtered and solvent removed *in vacuo* to provide the crude ester. This was then purified by flash column chromatography using silica gel 60 (220–240 mesh) supplied by Fluorochem (7:3 pentane:diethyl ether) to provide the pure title compound.

(L)-N-Boc proline heneicosyl ester

The title compound was obtained in 94 % yield as a clear, colourless oil. $\mathbf{[\alpha]_D^{25}}$ -20.0 (c 4.5, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3421, 2955, 2923, 2852, 1744, 1703, 1639, 1465, 1396, 1366, 1256, 1196, 1164, 1122, 1087 cm-1; **^{1}H NMR** (270 MHz, $CDCl_3$): δ 4.87 (1H, p, 6.0 Hz), 4.22 (1H, dd, 3.0 Hz, 8.5 Hz), 3.58-3.31 (2H, m), 2.20-1.82 (4H, m, H-5), 1.51-1.48 (4H, m), 1.41 (9H, s), 1.23 (32H, s), 0.86 (6H, t, 6.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.1 (C), 155.0 (C) 79.7 (C), 75.0 (CH), 58.9 (CH), 45.8 (CH_2), 33.4 (CH_2), 31.2 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.6 (CH_2), 24.4 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **MS** (ESI): m/z 510 ($M^+ + H^+$); HRMS: found 510.4515

$C_{31}H_{60}NO_4$ requires 510.4517; m/z 532 (M^+ + Na); HRMS: found 532.4334 $C_{31}H_{59}NNaO_4$ requires 532.4336.

(L)-N-Boc proline icosyl ester

The title compound was obtained in 94 % yield as a clear, colourless oil. **$[\alpha]_D^{25}$** -18.0 (c 4.6, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3420, 2923, 2852, 1747, 1703, 1464, 1395, 1366, 1278, 1256, 1163, 1122, 1088, 1033 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl3): δ 4.21-4.17 (1H, dd, 4.0 Hz, 8.5 Hz), 4.15-4.01 (2H, m), 3.65-3.30 (2H, m), 1.99-1.78 (2H, m), 1.65-1.54 (2H, m), 1.39 (9H, s), 1.23 (36H, s), 0.86 (3H, t, 7.0 Hz); **^{13}C NMR** (100 MHz, CDCl3): δ 172.8 (C), 154.28 (C), 79.8 (C), 75.2 (CH_2), 59.3 (CH), 46.3 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 28.4 (CH_3), 25.3 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **MS** (ESI): m/z 496 (M^+ + H^+); HRMS: found 496.4352 $C_{30}H_{58}NO_4$ requires 496.4360; m/z 518 (M^+ + Na); HRMS: found 518.4172 $C_{30}H_{57}NNaO_4$ requires 518.4180.

General procedure for the formation of (*L*)-proline aliphatic esters (6 and 7)

A sample of (*L*)-*N*-Boc proline ester (0.34 mmol) was dissolved in dichloromethane (3 mL) under nitrogen at 0 °C, and trifluoroacetic acid (0.53 mL, 6.87 mmol) added to the stirred solution. After 13 hours the reaction mixture was washed with saturated aqueous potassium carbonate solution (10 mL) and extracted with dichloromethane (3 × 3 mL). The combined organics were dried with magnesium sulfate and concentrated *in vacuo* to furnish the pure title compound.

*(L)-Proline heneicosyl ester (**6**)*

The title compound was obtained in 91 % yield as an off-white solid. **mp** 38.2-39.9 °C; **$[\alpha]_D^{25}$** -15.3 (c 2.6, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3435, 2924, 2854, 1731, 1688, 1466, 1378, 1333, 1204, 1126 cm-1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.88 (1H, p, 9.0 Hz), 3.75 (1H, dd, 7.5 Hz, 12.5 Hz), 3.11-2.87

(3H, m, H-2), 2.17-2.08 (1H, m), 2.20-2.07 (1H, m), 1.88-1.67 (2H, m), 1.53-1.47 (4H, m), 1.30-1.11 (32H, m), 0.86 (6H, t, 9.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.6 (C), 75.5 (CH), 59.8 (CH), 46.9 (CH_2), 37.5 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **MS** (ESI): m/z 410 ($M^+ + H^+$); HRMS: found 410.3992 $C_{26}H_{52}NO_2$ requires 410.3993.

(L)-Proline icosyl ester (7)

The title compound was obtained in 82 % overall yield as a yellow solid. **mp** 40.4-41.7 °C; **$[\alpha]_D^{25}$** -16.7 (c 2.3, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3345, 2920, 2852, 1734, 1678, 1467, 1339, 1204, 1181, 1118 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl3): δ 4.14-4.05 (2H, m), 3.77 (1H, dd, 5.5 Hz, 8.0 Hz), 3.11-3.05 (1H, m), 2.99 (1H, br s), 2.94-2.88 (1H, m), 2.17-2.08 (1H, m), 1.87-1.80 (1H, m), 1.77-1.71 (2H, m), 1.31-1.23 (36H, m), 0.85 (t, 3H, 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.2 (C), 65.1 (CH_2), 61.5 (CH), 46.9 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 25.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **MS** (ESI): m/z 396 ($M^+ + H^+$); HRMS: found 396.3853 $C_{25}H_{50}NO_2$ requires 396.3836.

General procedure for 2-(tri*iso*propylsilyloxy)acetaldehyde aldol reactions in pH = 7 phosphate buffer, catalysed by (*L*)-proline icosyl ester (7). Formation of acetal (8)

(*L*)-Proline icosyl ester (50.9 mg, 0.129 mmol) was added to 2-(tri*iso*propylsilyloxy)acetaldehyde (280 mg, 1.29 mmol) in pH = 7 phosphate buffer (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude reaction mixture. This was then purified by flash column chromatography using silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich (30:1:1:0.32 pentane:diethyl ether:dichloromethane:acetic acid) to provide the acetal product (**8**) 5-tri*iso*propylsilanyloxy-2,6-bis-tri*iso*propylsilanyloxymethyl-[1,3]dioxan-4-ol (89.6 mg,

0.138 mmol) in 32 % yield, 23 % *e.e.* ((2*S*, 5*S*, 6*S*)-enantiomer), as a clear, colourless oil. $[\alpha]_D^{25}$ = +4.6 (c 0.50, $CHCl_3$); **IR** (NaCl, film) υ_{max} 2945, 2892, 2868, 2360, 1734, 1684, 1653, 1635, 1576, 1559, 1540, 1521, 1506, 1464, 1386, 1368, 1249 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.35-5.31 (1H, m), 5.25 (1H, t, 4.5 Hz), 4.06-3.99 (2H, m), 3.85-3.74 (3H, m, H-6), 3.67 (1H, dd, 16.5 Hz, 7.5 Hz), 3.12-3.09 (1H, m), 1.12-1.09 (63H, m); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 98.2 (CH), 93.6 (CH), 81.4 (CH), 69.1 (CH), 65.3 (CH_2), 62.8 (CH_2), 17.9 (CH), 12.0 (CH_3); **MS** (ESI): m/z 666 (M^+ + NH_4^+); HRMS: found 666.4961 $C_{33}H_{76}NO_6Si_3$ requires 666.4975; enantiomeric excess was determined using Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] and further ^{1}H NMR analysis.

General procedure for 2-(tri*iso*propylsilyloxy)acetaldehyde aldol reactions in water, catalysed by (*L*)-proline icosyl ester (7). Formation of acetal (8)

(*L*)-Proline icosyl ester (50.9 mg, 0.129 mmol) was added to 2-(tri*iso*propylsilyloxy)acetaldehyde (280 mg, 1.29 mmol) in water (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude reaction mixture. This was then purified by flash column chromatography using silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich (30:1:1:0.32 pentane:diethyl ether:dichloromethane:acetic acid) to provide the acetal product (**8**) 5-tri*iso*propylsilanyloxy-2,6-bis-tri*iso*propylsilanyloxymethyl-[1,3]dioxan-4-ol (112 mg, 0.172 mmol in 40 % yield, 17 % *e.e.* ((2*S*, 5*S*, 6*S*)-enantiomer), as a clear, colourless oil. $[\alpha]_D^{25}$ = +4.6 (c 0.50, $CHCl_3$); **IR**, **^{1}H**, **^{13}C** and **MS** data found to be the same as previously reported for 5-tri*iso*propylsilanyloxy-2,6-bis-tri*iso*propylsilanyloxymethyl-[1,3]dioxan-4-ol; enantiomeric excess was determined using Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] and further ^{1}H NMR analysis.

General procedure for 2-(tri*iso*propylsilyloxy)acetaldehyde aldol reactions in brine, catalysed by (*L*)-proline heneicosyl ester (6). Formation of acetal (8)

2-(Tri*iso*propylsilyloxy)acetaldehyde (280 mg, 1.29 mmol) was added to (*L*)-proline heneicosyl ester **(6)** (51.0 mg, 0.129 mmol) in brine (5 mL). After 5 hours the reaction mixture was extracted with chloroform (3 × 10 mL). The organic extracts were combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. This was then purified by flash column chromatography using silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich (15:1 pentane:diethyl ether) to provide the major product, acetal (**8**) 5-tri*iso*propylsilanyloxy-2,6-bis-tri*iso*propylsilanyloxymethyl-[1,3]dioxan-4-ol (113 mg, 0.175 mmol, 41%, 15 % *e.e*). ((2*S*, 5*S*, 6*S*)-enantiomer), as a clear, colourless oil. **IR**, **^{1}H**, **^{13}C** and **MS** data found to be the same as previously reported for 5-tri*iso*propylsilanyloxy-2,6-bis-tri*iso*propylsilanyloxymethyl-[1,3]dioxan-4-ol; enantiomeric excess was determined using Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] and further ^{1}H NMR analysis. The minor product aldol dimer 3-hydroxy-2,4-bis(tri*iso*propylsilyloxy)butanal (50.2 mg, 0.116 mmol) was isolated in 18 % yield, 0 % *e.e*. (*anti*), 1.0:1.0 *anti*:*syn* mixture of diastereomers as a clear, colourless oil. **IR**, **^{1}H**, **^{13}C** and **MS** data found to be the same as previously reported for 3-hydroxy-2,4-bis(tri*iso*propylsilyloxy)butanal; enantiomeric excess was determined using Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] and further ^{1}H NMR analysis, after conversion of the isolated *anti* isomer to the 1-hydroxy-3-*p*-nitrobenzoate-derivative**.**

General procedure for the formation of (*L*)-*N*-Boc amino acid ethyl esters

Sodium bicarbonate (3.13 g, 37.3 mmol) was added to the (*L*)-amino acid ethyl ester hydrochloride (13.0 mmol) in tetrahydrofuran (30 mL, not distilled) and water (30 mL) at 0 ^{o}C. Di-*tert*-butyl dicarbonate (2.84 g, 13.0 mmol) was then added in one portion to the reaction mixture. After 1.0 hour the reaction was allowed to warm to room temperature. After a further 23 hours the mixture was acidified to pH 4-5 with citric acid and extracted with diethyl ether (3 × 20 mL). The combined

organic extracts were dried with magnesium sulfate, filtered and concentrated *in vacuo* to furnish the (*L*)-*N*-Boc amino acid ethyl ester as a colourless oil which was used without further purification.

(L)-N-Boc alanine ethyl ester

The title compound was obtained in 94 % yield as a colourless oil. $[\alpha]_D^{25}$ +0.74 (c 0.99, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3373, 2981, 2937, 1695, 1518, 1454, 1391, 1367, 1344, 1301, 1250, 1214, 1164, 1114, 1095, 1068, 1025 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.04 (1H, br s), 4.31-4.23 (1H, m), 4.18 (2H, q, 7.0 Hz), 1.43 (9H, s), 1.36 (3H, d, 7.0 Hz), 1.26 (3H, t, 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5 (C), 155.2 (C), 79.9 (C), 61.4 (CH_2), 49.3 (CH), 28.4 (CH_3), 18.8 (CH_3), 14.2 (CH_3); **MS** (ESI): m/z 240 (M^+ + Na); HRMS: found 240.1209 $C_{10}H_{19}NNaO_4$ requires 240.1212.

(L)-N-Boc leucine ethyl ester

The title compound was obtained in 98 % yield as a colourless oil. $[\alpha]_D^{25}$ -2.7 (c 0.90, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3367, 2961, 2872, 2099, 1711, 1645, 1517, 1470, 1454, 1390, 1368, 1272, 1252, 1226, 1164, 1119, 1048, 1025 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.88 (1H, br s), 4.27 (1H, dd, 5.5 Hz, 13.5 Hz), 4.17 (2H, q, 7.0 Hz), 1.79-1.64 (1H, m), 1.62-1.47 (2H, m), 1.43 (9H, s), 1.26 (3H, t, 7.0 Hz), 0.94 (3H, d, 6.5 Hz), 0.93 (3H, d, 6.5 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6 (C), 155.5 (C), 79.8 (C), 61.2 (CH_2), 52.2 (CH), 42.0 (CH_2), 28.4 (CH_3), 24.9 (CH), 22.9 (CH_3), 22.0 (CH_3), 14.3 (CH_3); **MS** (ESI): m/z 282 (M^+ + Na); HRMS: found 282.1677 $C_{13}H_{25}NNaO_4$ requires 282.1681.

(L)-N-Boc valine ethyl ester

The title compound was obtained in 71 % yield as a colourless oil. $[\alpha]_D^{25}$ +9.0 (c 0.75, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3379, 2977, 2936, 2878, 2081, 1809, 1703, 1503, 1468, 1392, 1369, 1310, 1249, 1211, 1159, 1119, 1073, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.02 (1H, d, 8.5 Hz), 4.13 (2H,

q, 7.0 Hz), 2.19-2.00 (1H, m), 1.43 (9H, s), 1.27 (3H, t, 7.0 Hz), 0.95 (3H, d, 7.0 Hz), 0.88 (3H, d, 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.5 (C), 155.6 (C), 79.8 (C), 61.2 (CH_2), 58.6 (CH), 31.4 (CH), 28.4 (CH_3), 19.1 (CH_3), 17.6 (CH_3), 14.3 (CH_3); **MS** (ESI): m/z 268 (M^+ + Na); HRMS: found 268.1527 $C_{12}H_{23}NNaO_4$ requires 268.1525.

General procedure for the formation of (*L*)-*N*-Boc *N*-methyl amino acid ethyl esters

Potassium bis(trimethylsilyl)amide 0.5 M in toluene (13.3 mL, 6.65 mmol) was added to the (*L*)-*N*-Boc amino acid ethyl ester (6.65 mmol) in tetrahydrofuran (35 mL) under argon at -78 ^{o}C. After 0.5 hours iodomethane (0.455 mL, 7.32 mmol) was added to the solution. The reaction mixture was then allowed to warm to room temperature overnight. After 18 hours the solution was washed with saturated potassium carbonate solution (30 mL), then brine (30 mL) followed by 1 M sodium hydroxide solution (30 mL). The aqueous washes were each extracted with ethyl acetate (3 × 10 mL). The organic fractions were then combined, dried with magnesium sulfate, filtered and concentrated *in vacuo* to give the crude title compound as an orange oil which was then purified by Kugelrohr distillation to provide the pure (*L*)-*N*-Boc *N*-methyl amino acid ethyl ester as a colourless oil.

(L)-N-Boc N-methyl alanine ethyl ester

The title compound was obtained in 66 % yield as a colourless oil. **$[\alpha]_D^{25}$** +0.19 (c 1.3, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3394, 2981, 2368, 2119, 1740, 1682, 1391, 1368, 1252, 1214, 1158, 1094, 1023 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.74 (1H, q, 7.0 Hz), 4.11 (2H, q, 7.0 Hz), 2.74 (3H, s), 1.38 (9H, s), 1.31 (3H, d, 7.0 Hz), 1.21 (3H, t, 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4 (C), 156.0 (C), 80.1 (C), 61.0 (CH_2), 53.6 (CH), 30.4 (CH_3), 28.4 (CH_3), 14.8 (CH_3), 14.2 (CH_3); **MS** (ESI): m/z 254 (M^+ + Na); HRMS: found 254.1370 $C_{11}H_{21}NNaO_4$ requires 254.1368.

(L)-N-Boc N-methyl leucine ethyl ester

The title compound was obtained in 72 % yield as a colourless oil. **$[\alpha]_D^{25}$** -8.2 (c 0.74, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3443, 2976, 2079, 1740, 1692, 1645, 1442, 1391, 1367, 1326, 1220, 1154, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.79 (1H, t, 7.5 Hz), 4.11 (2H, q, 7.0 Hz), 2.91 (3H, s), 1.67-1.59 (1H, m), 1.56-1.45 (2H, m), 1.39 (9H, s), 1.22 (3H, t, 7.0 Hz), 0.90 (3H, d, 7.0 Hz), 0.89 (3H, d, 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3 (C), 155.8 (C), 80.2 (C), 61.0 (CH_2), 57.3 (CH), 36.5 (CH_2), 31.5 (CH_3), 28.4 (CH_3), 24.7 (CH), 23.3 (CH_3), 22.9 (CH_3), 14.3 (CH_3); **MS** (ESI): m/z 296 (M^+ + Na); HRMS: found 296.1833 $C_{14}H_{27}NNaO_4$ requires 296.1838.

(L)-N-Boc N-methyl valine ethyl ester

The title compound was obtained in 53 % yield as a colourless oil. **$[\alpha]_D^{25}$** -56.4 (c 0.97, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3391, 2976, 2936, 2878, 2125, 1737, 1692, 1444, 1390, 1368, 1313, 1258, 1202, 1150, 1094, 1028 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.37 (1H, d, 10.5 Hz), 4.11 (2H, q, 7.0 Hz), 2.76 (3H, s), 2.23-2.02 (1H, m), 1.41 (9H, s), 1.23 (3H, t, 7.0 Hz), 0.91 (3H, d, 7.0 Hz), 0.84 (3H, d, 7.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.4 (C), 155.7 (C), 79.9 (C), 61.1 (CH_2), 60.6 (CH), 31.4 (CH_3), 28.4 (CH_3), 27.7 (CH), 19.0 (CH_3), 18.9 (CH_3), 14.2 (CH_3); **MS** (ESI): m/z 282 (M^+ + Na); HRMS: found 282.1676 $C_{13}H_{25}NNaO_4$ requires 282.1681.

General procedure for the formation of (*L*)-*N*-methyl amino acid ethyl esters (10, 11 and 12)

Trifluoroacetic acid (15.3 mL, 206 mmol) was added to the (*L*)-*N*-Boc *N*-methyl amino acid ethyl ester (10.3 mmol) in dichloromethane (40 mL) at 0 ^oC under nitrogen and stirred for 4 hours. The solution was then concentrated *in vacuo*, washed with 50 mL saturated sodium bicarbonate solution and extracted with ethyl acetate (3 × 20 mL). The organic extracts were then combined, dried with magnesium sulfate, filtered and concentrated *in vacuo*. The crude amino acid derivative was then

purified by Kugelrohr distillation to provide the pure (*L*)-*N*-methyl amino acid ethyl ester as a colourless oil.

*(L)-N-Methyl alanine ethyl ester (**10**)*

The title compound was obtained in 67 % yield as a colourless oil. $[\alpha]_D^{25}$ +0.34 (c 0.84, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3583, 3457, 3391, 1727, 1693, 1660, 1645, 1551, 1442, 1219, 1058 cm^{-1}; **^{1}H NMR** (270 MHz, $CDCl_3$): δ 4.23 (2H, q, 2.0 Hz), 3.59 (1H, q, 7.0 Hz), 2.60 (3H, s), 1.48 (3H, d, 7.0 Hz), 1.30 (3H, t, 2.0 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.6 (C), 60.6 (CH_2), 58.3 (CH), 34.5 (CH_3), 18.8 (CH_3), 14.2 (CH_3); **MS** (ESI): m/z 132 ($M^+ + H^+$); HRMS: found 132.1022 $C_6H_{14}NO_2$ requires 132.1019.

*(L)-N-Methyl leucine ethyl ester (**11**)*

The title compound was obtained in 59 % yield as a colourless oil. $[\alpha]_D^{25}$ +0.57 (c 1.2, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3437, 2959, 2872, 2802, 1731, 1669, 1468, 1385, 1368, 1308, 1257, 1182, 1141, 1095, 1025 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.06 (2H, q, 7.0 Hz), 3.03 (1H, t, 7.5 Hz), 2.50 (3H, s), 1.62-1.51 (1H, m), 1.36-1.28 (2H, m), 1.15 (3H, t, 7.0 Hz), 0.79 (3H, d, 6.5 Hz), 0.77 (3H, d, 6.5 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.9 (C), 61.8 (CH), 60.5 (CH_2), 42.7 (CH_2), 34.7 (CH_3), 24.9 (CH), 21.4 (CH_3), 14.2 (CH_3); **MS** (ESI): m/z 174 ($M^+ + H^+$); HRMS: found 174.1492 $C_9H_{20}NO_2$ requires 174.1489.

*(L)-N-Methyl valine ethyl ester (**12**)*

The title compound was obtained in 84 % yield as a colourless oil. $[\alpha]_D^{25}$ +3.6 (c 0.75, $CHCl_3$); **IR** (NaCl, film) υ_{max} 3583, 3389, 2964, 2797, 1731, 1466, 1388, 1369, 1271, 1218, 1182, 1097, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.12 (2H, q, 7.0 Hz), 2.80 (1H, d, 6.0 Hz), 2.27 (3H, s), 1.94 (1H, heptd, 6.0 Hz, 7.0 Hz), 1.20 (3H, t, 7.0 Hz,), 0.88 (3H, d, 7.0 Hz), 0.85 (3H, d, 7.0 Hz); **^{13}C**

NMR (100 MHz, $CDCl_3$): δ 175.0 (C), 69.4 (CH), 60.3 (CH_2), 35.3 (CH_3), 31.5 (CH), 19.2 (CH_3), 18.7 (CH_3), 14.4 (CH_3); **MS** (ESI): m/z 160 ($M^+ + H^+$); HRMS: found 160.1333 $C_8H_{18}NO_2$ requires 160.1332.

General procedure for preparation of the silylated standards (2-*syn* and 2-*anti*)

Aldol adducts **2**-*syn* and **2**-*anti* (both enantiomers) were prepared according to the procedure of Northrup and MacMillan.[12, 13]

General procedure for preparation of the acylated tetrol standards (17, (D)-18 and (L)-18)

Pyridine (0.05 mL, 0.618 mmol) was added to *meso*-erythritol (10.0 mg, 0.0819 mmol) in acetic acid anhydride (1.0 mL) under nitrogen, followed by 4-(dimethylamino)pyridine (0.50 mg, 4.1 mol). After 5 hours the reaction mixture was diluted with dichloromethane (10 mL), and washed with water (10 mL). The separated organic layer was then washed with saturated sodium bicarbonate solution (10 mL), 1 mol dm^{-3} hydrochloric acid (10 mL) followed by brine (10 mL). The aqueous layers were each extracted with dichloromethane (3 × 4 mL) and combined with the washed organic layer. The combined organic extracts were then dried with magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude title compound. This was then purified by flash column chromatography using silica gel 60 (220–240 mesh) supplied by Fluorochem (1:1 hexane:ethyl acetate) to provide the pure title compound

*meso-Erythritol tetraacetate (**17**)*

The title compound was obtained in 99 % yield as a white, crystalline solid. **mp** 85.1-86.9 °C; $[\alpha]_D^{25}$ 0.0 (c 1.0, $CHCl_3$); **IR** (NaCl, film) υ_{max} 2917, 2849, 1740, 1650, 1633, 1454, 1434, 1373, 1214, 1067, 1021 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.24 (2H, t, 2.5 Hz), 4.30 (2H, dd, 2.5 Hz, 12.0 Hz), 4.16 (2H, dd, 5.5 Hz, 12.0 Hz), 2.07 (6H, s), 2.04 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ

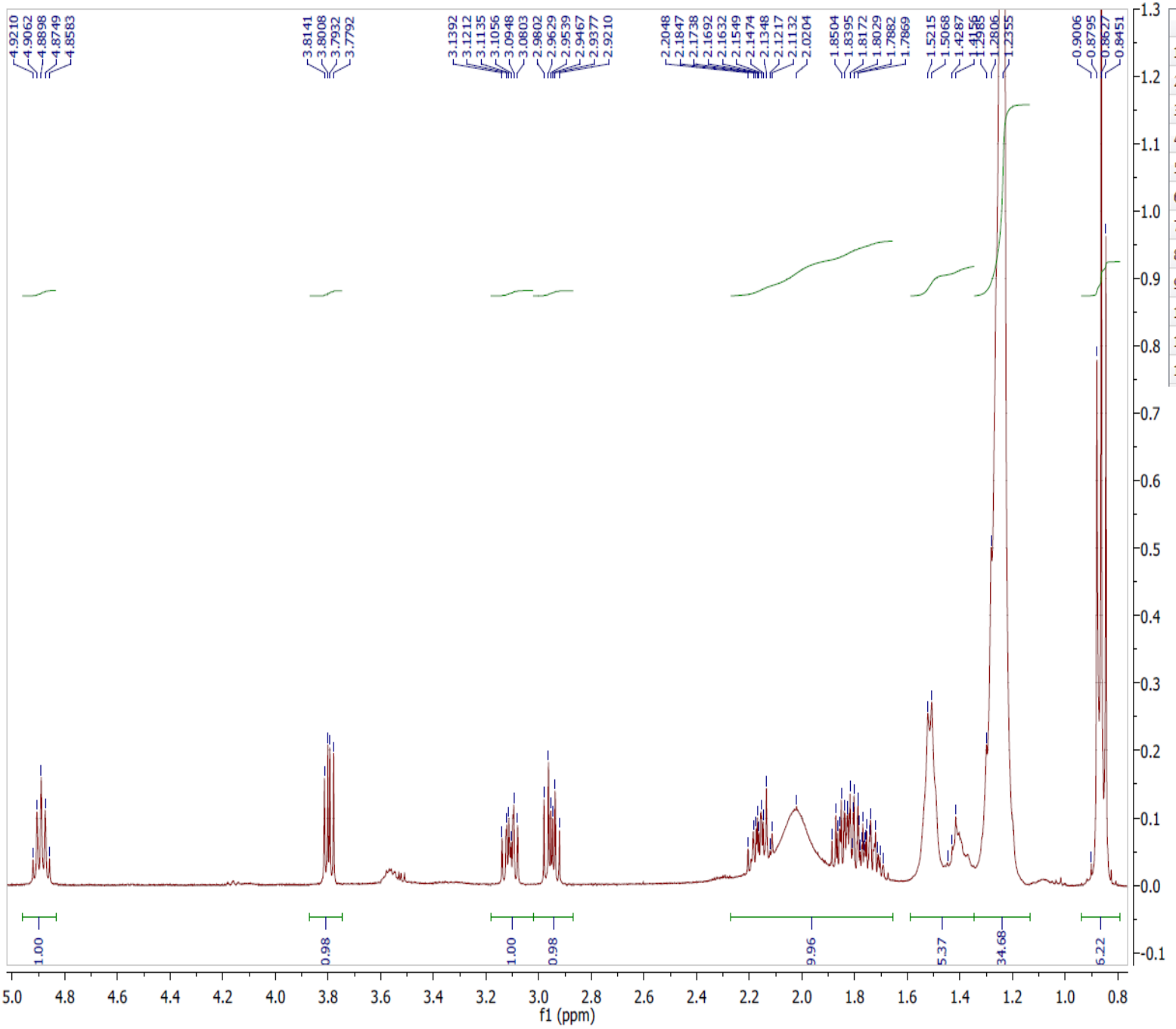
170.8 (C), 170.4 (C), 68.6 (CH), 62.1 (CH_2), 21.1 (CH_3), 20.9 (CH_3); **MS** (ESI): m/z 313 (M^+ + Na); HRMS: found 313.0888 $C_{12}H_{18}NaO_8$ requires 313.0894.

*(D)-Threitol tetraacetate ((D)-**18**)*

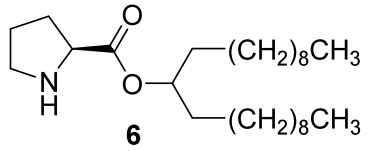
The title compound was obtained in 98 % yield as an off-white oil. $[\alpha]_D^{25}$ +22.3 (c 1.0, $CHCl_3$); **IR** (NaCl, film) υ_{max} 2965, 2363, 1740, 1646, 1437, 1372, 1215, 1050 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.24 (2H, t, 2.5 Hz), 4.30 (2H, dd, 2.5 Hz, 12.0 Hz), 4.16 (2H, dd, 5.5 Hz, 12.0 Hz), 2.07 (6H, s), 2.04 (6H, s); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.8 (C), 170.4 (C), 69.4 (CH), 62.0 (CH_2), 21.1 (CH_3), 20.9 (CH_3); **MS** (ESI): m/z 313 (M^+ + Na); HRMS: found 313.0900 $C_{12}H_{18}NaO_8$ requires 313.0894.

*(L)-Threitol tetraacetate ((L)-**18**)*

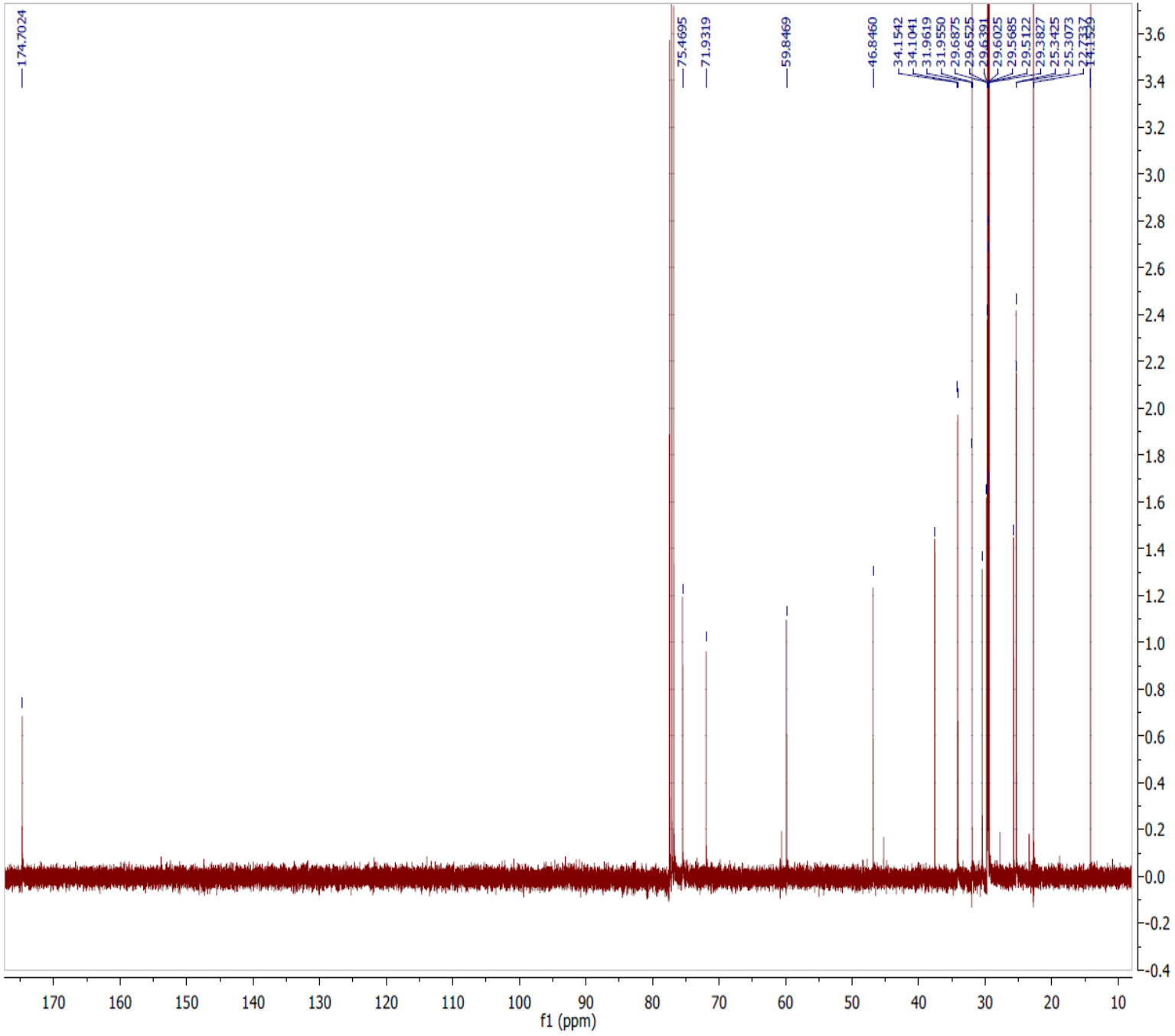
The title compound was obtained in 99 % yield as an off-white oil. $[\alpha]_D^{25}$ -20.7 (c 1.0, $CHCl_3$); **IR**, **^{1}H**, **^{13}C** and **MS** data found to be the same as previously reported for (*D*)-Threitol tetraacetate.



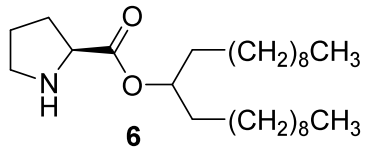
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	21.3
3	Pulse Sequence	single_pulse.ex2
4	Number of Scans	16
5	Relaxation Delay	4.0000
6	Pulse Width	5.5000
7	Spectrometer Frequency	399.78
8	Spectral Width	5997.4
9	Lowest Frequency	-999.8
10	Nucleus	1H
11	Acquired Size	16384
12	Spectral Size	32768



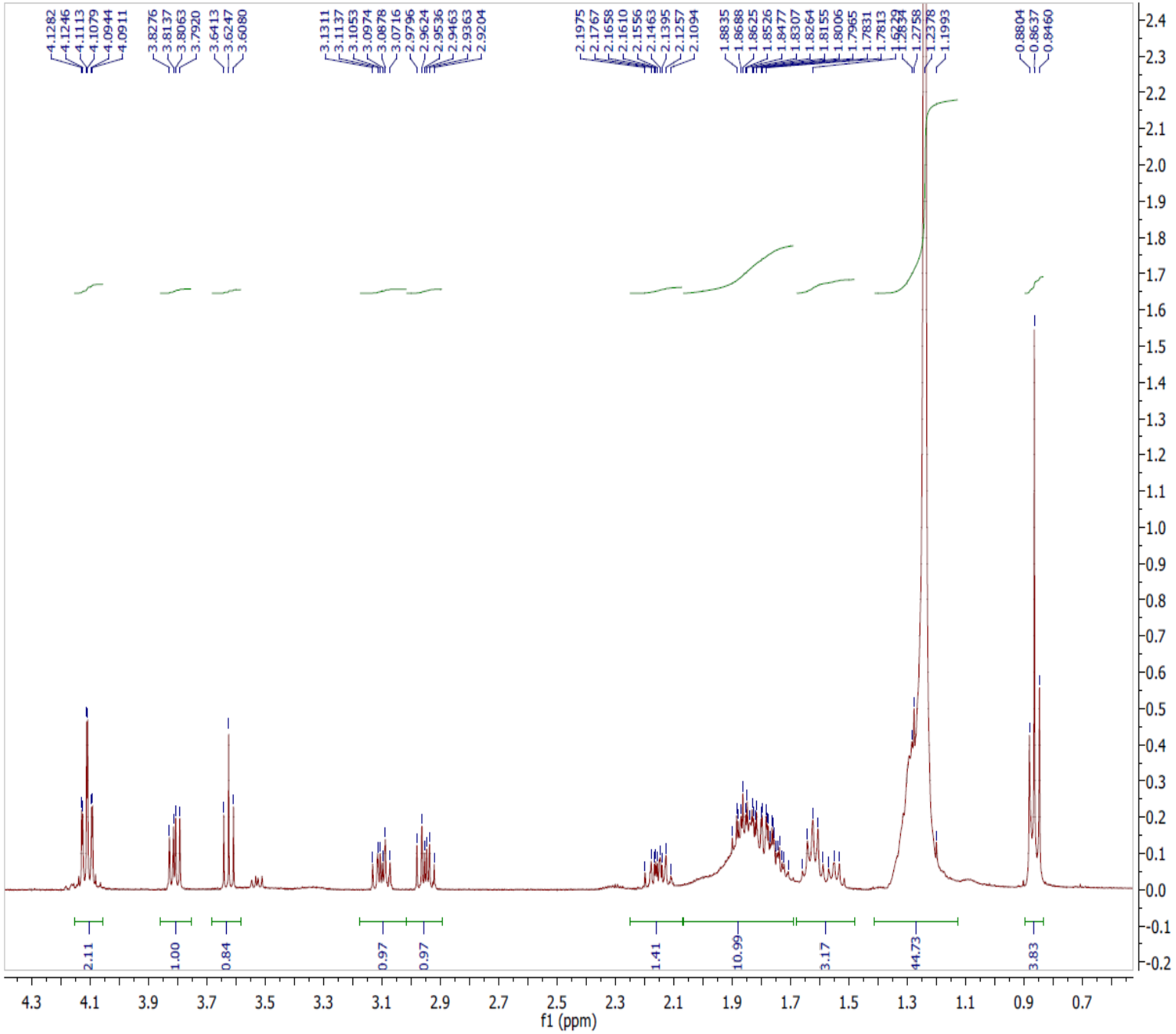
6



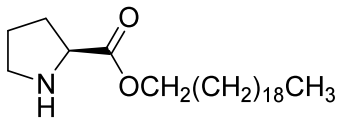
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	23.1
3	Pulse Sequence	single_pulse_dec
4	Number of Scans	256
5	Relaxation Delay	2.0000
6	Pulse Width	2.7333
7	Spectrometer Frequency	100.53
8	Spectral Width	25138.3
9	Lowest Frequency	-2516.6
10	Nucleus	13C
11	Acquired Size	32768
12	Spectral Size	65536



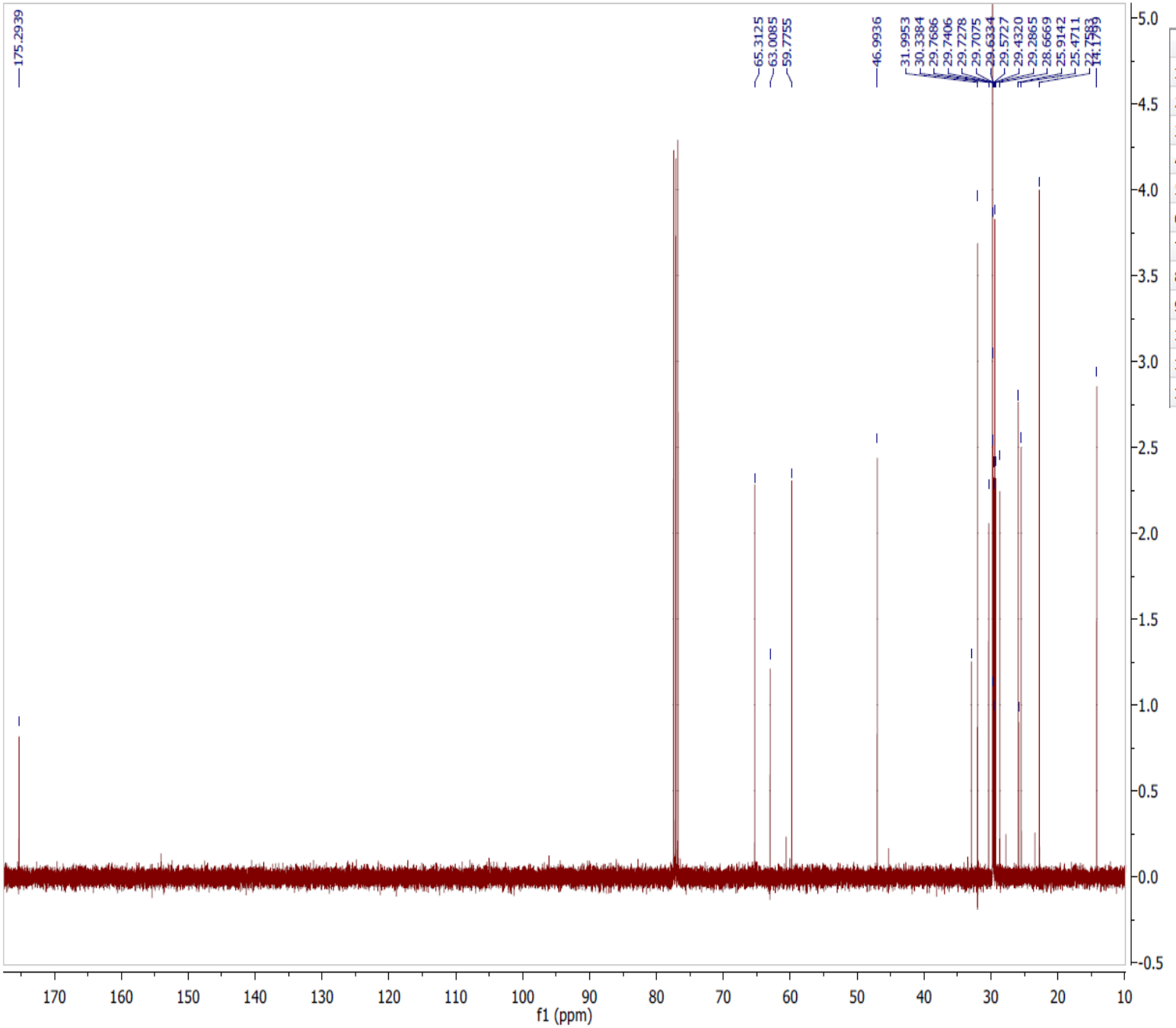
6



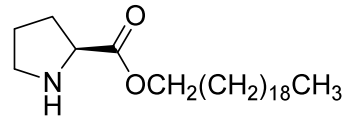
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	21.4
3	Pulse Sequence	single_pulse.ex2
4	Number of Scans	16
5	Relaxation Delay	4.0000
6	Pulse Width	5.5000
7	Spectrometer Frequency	399.78
8	Spectral Width	5997.4
9	Lowest Frequency	-999.8
10	Nucleus	1H
11	Acquired Size	16384
12	Spectral Size	32768



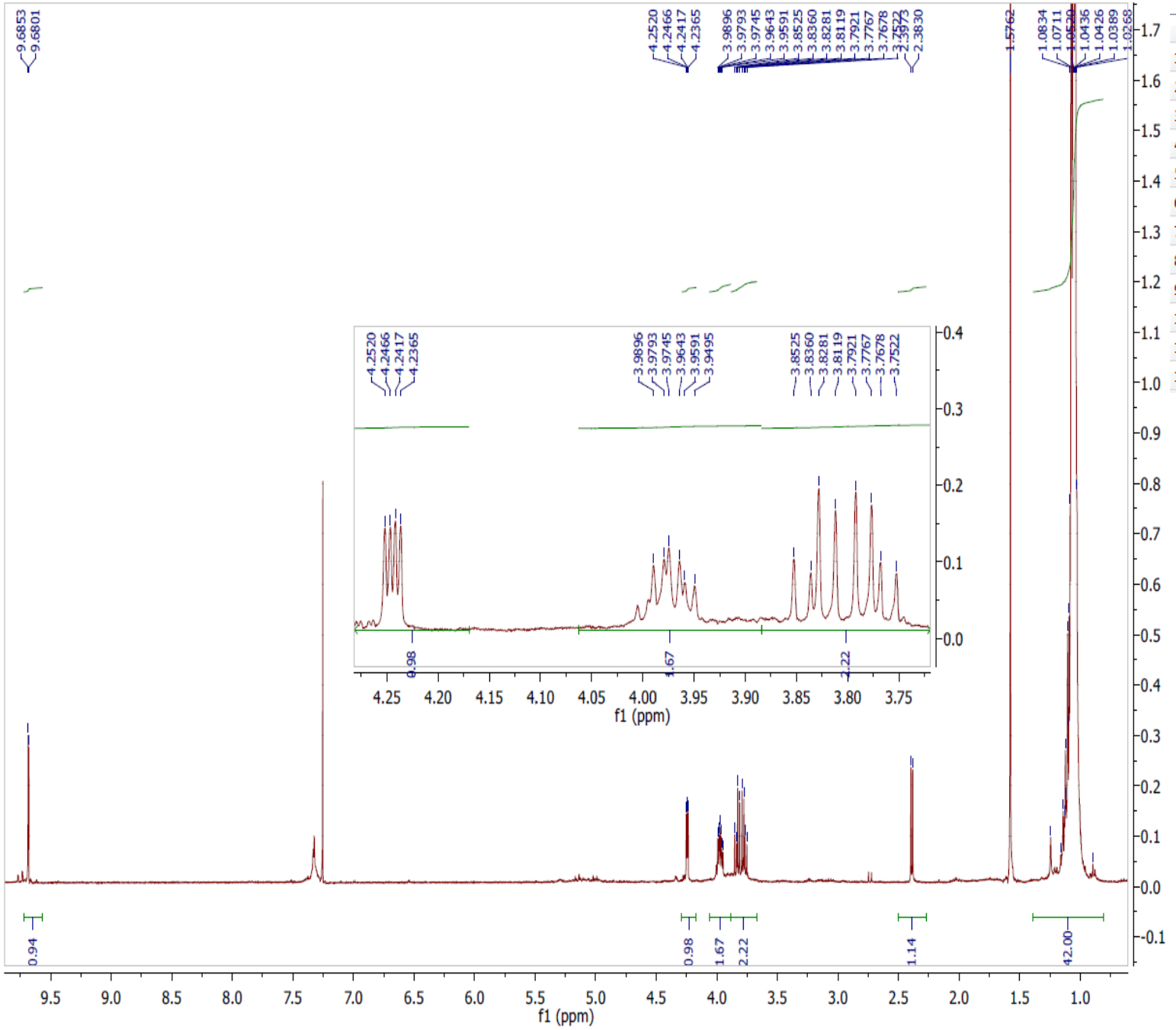
7



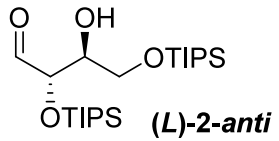
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	23.2
3	Pulse Sequence	single_pulse_dec
4	Number of Scans	256
5	Relaxation Delay	2.0000
6	Pulse Width	2.7333
7	Spectrometer Frequency	100.53
8	Spectral Width	25138.3
9	Lowest Frequency	-2516.6
10	Nucleus	13C
11	Acquired Size	32768
12	Spectral Size	65536



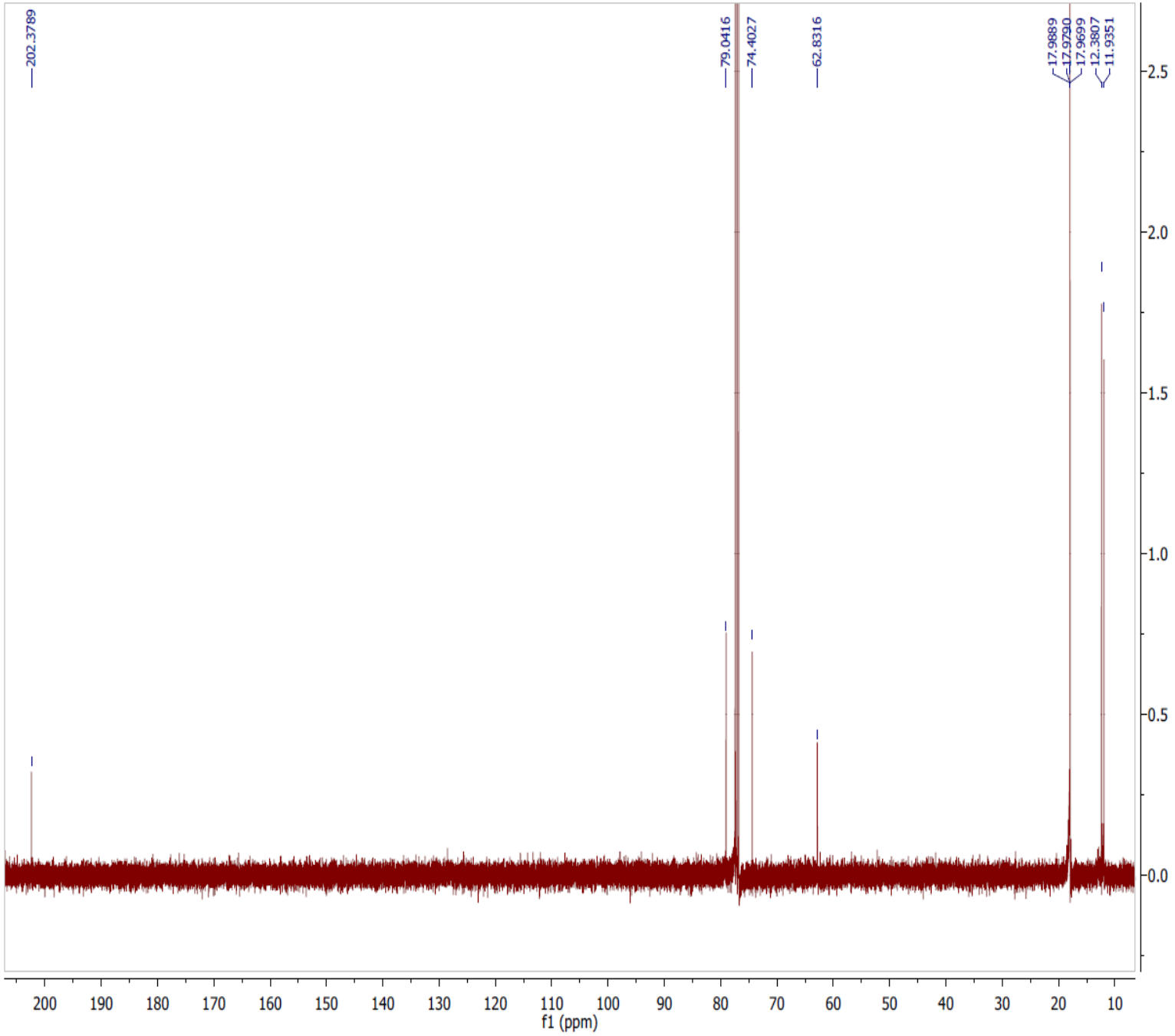
7



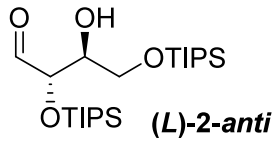
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	19.6
3	Pulse Sequence	single_pulse.ex2
4	Number of Scans	16
5	Relaxation Delay	4.0000
6	Pulse Width	5.3400
7	Spectrometer Frequency	399.78
8	Spectral Width	5997.4
9	Lowest Frequency	-999.8
10	Nucleus	1H
11	Acquired Size	16384
12	Spectral Size	32768



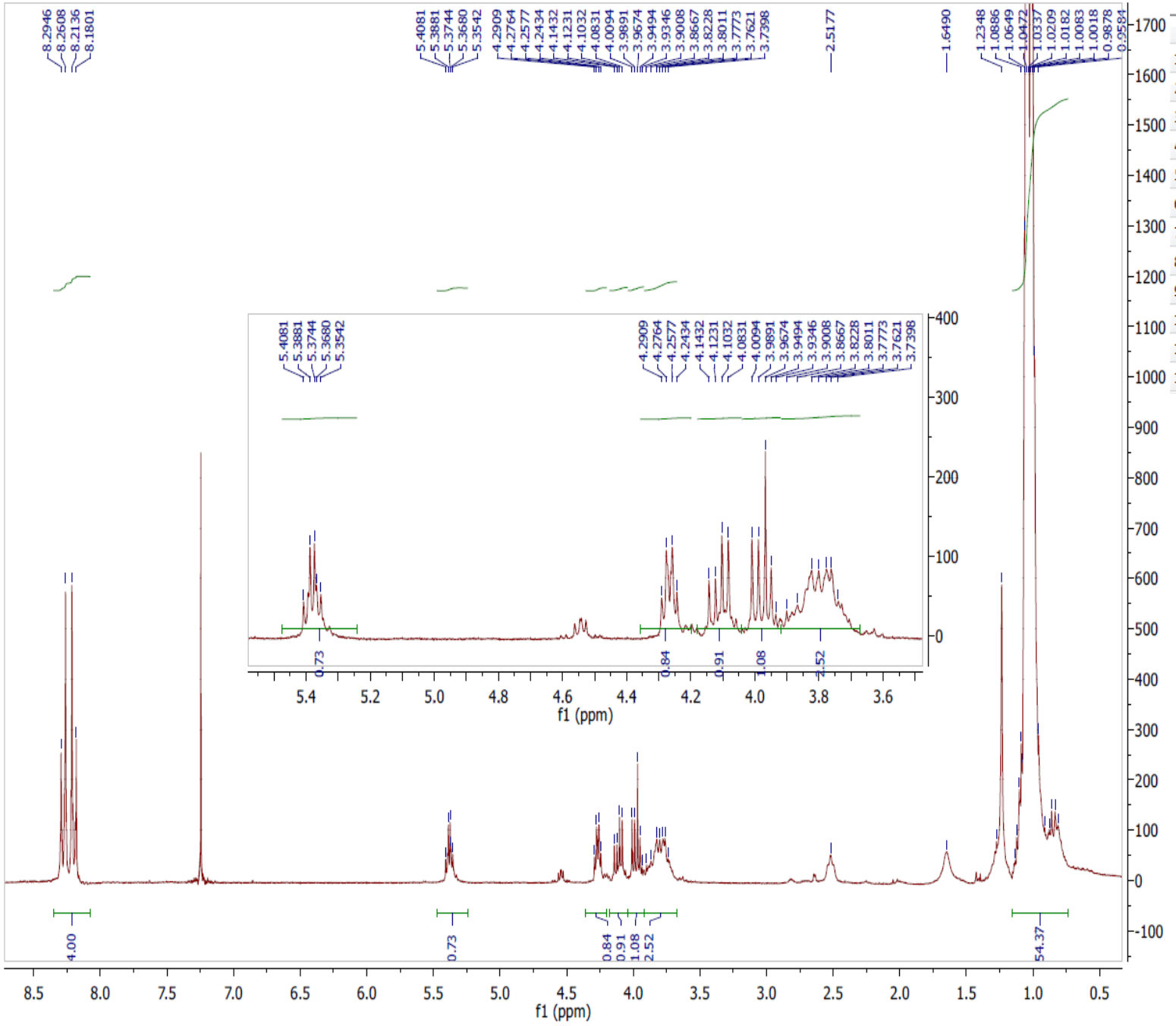
(L)*-2-*anti



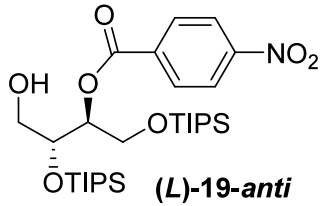
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	21.7
3	Pulse Sequence	single_pulse_dec
4	Number of Scans	512
5	Relaxation Delay	1.5000
6	Pulse Width	3.2667
7	Spectrometer Frequency	67.93
8	Spectral Width	17006.8
9	Lowest Frequency	-1710.1
10	Nucleus	13C
11	Acquired Size	16384
12	Spectral Size	32768



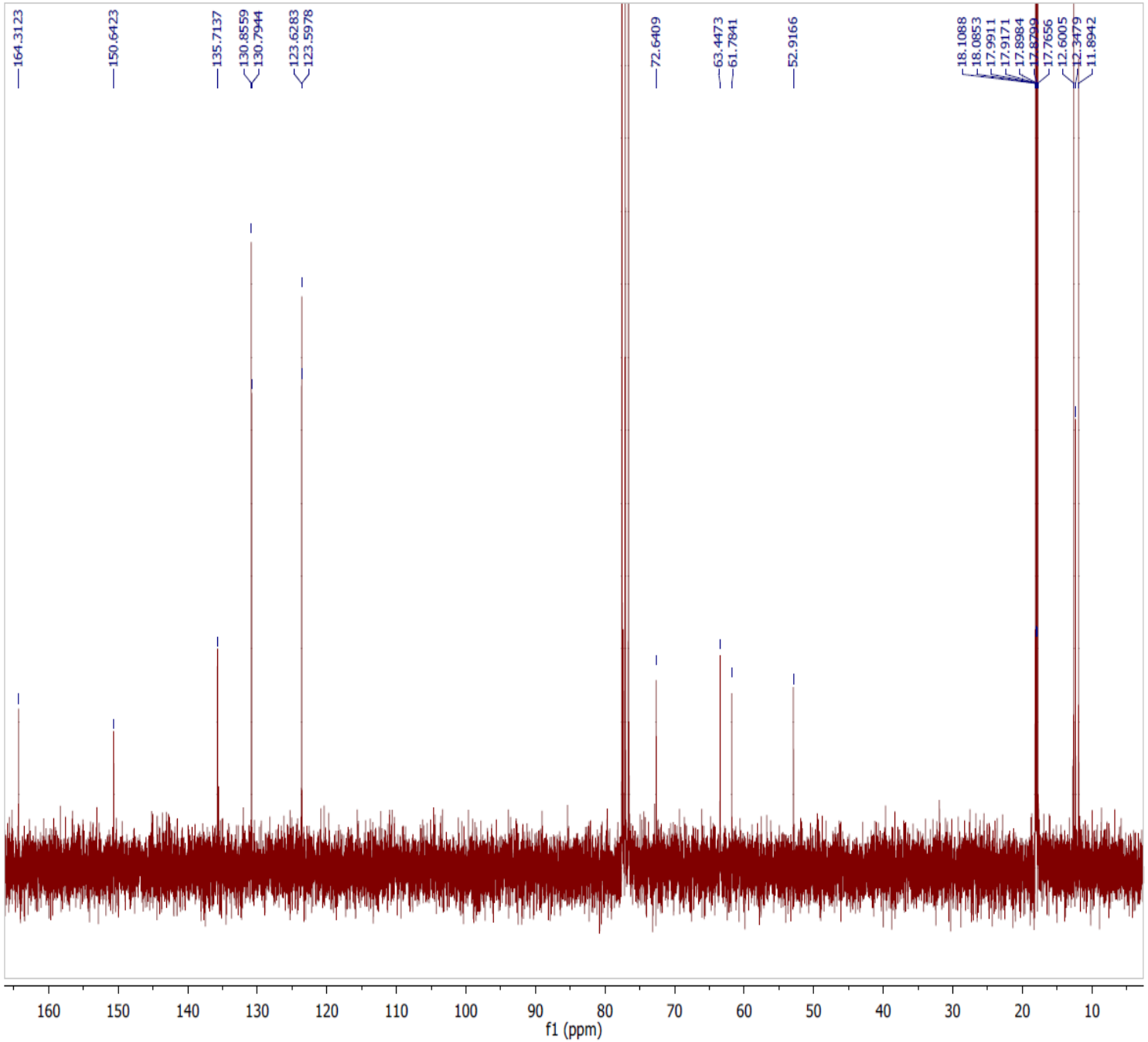
(L)*-2-*anti



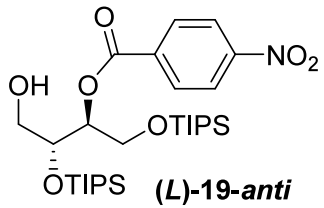
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	20.9
3	Pulse Sequence	single_pulse.exp
4	Number of Scans	32
5	Relaxation Delay	1.0000
6	Pulse Width	3.4000
7	Spectrometer Frequency	270.17
8	Spectral Width	12165.5
9	Lowest Frequency	-6758.1
10	Nucleus	1H
11	Acquired Size	32768
12	Spectral Size	65536



(*L*)-19-*anti*

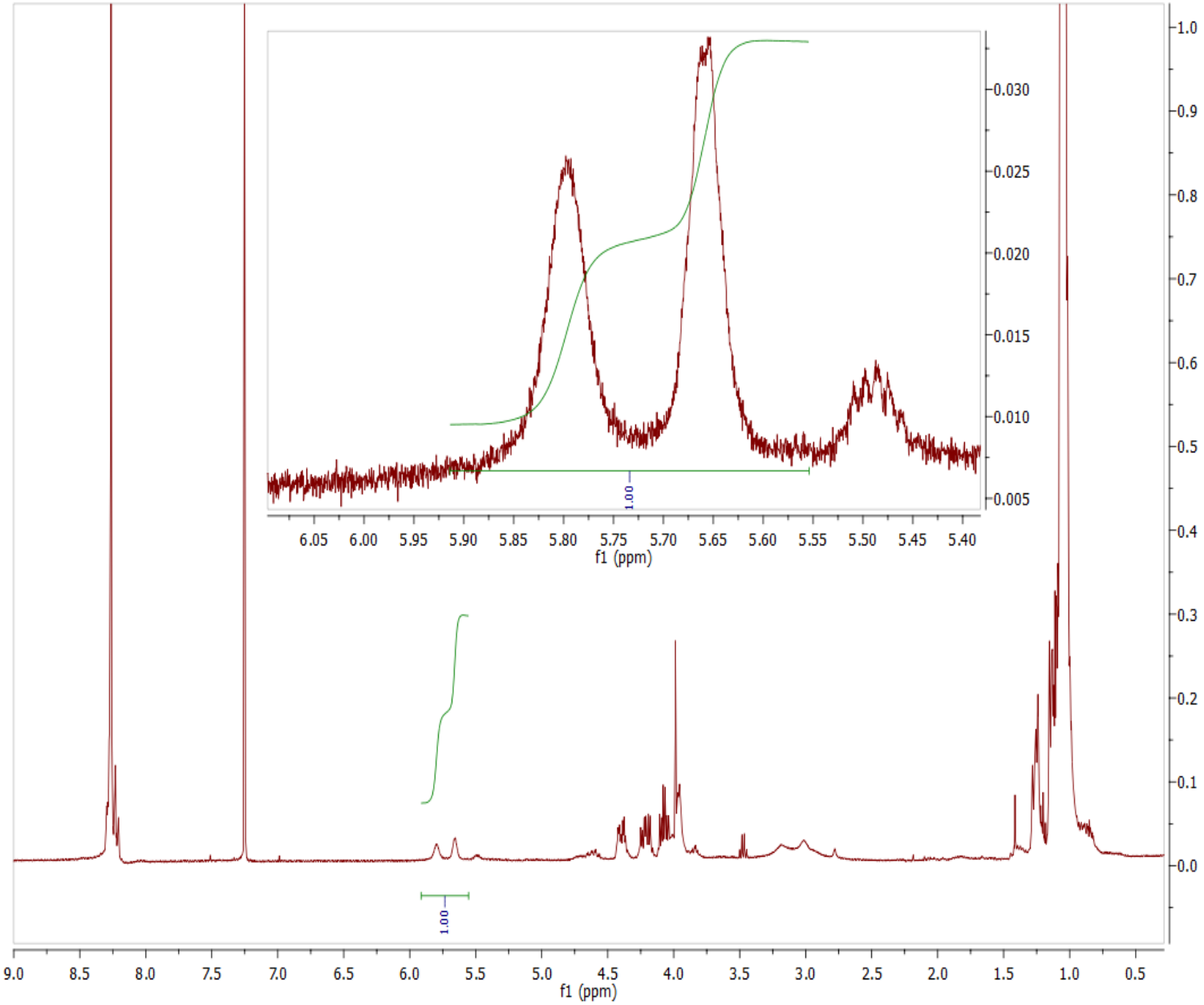


	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	22.6
3	Pulse Sequence	single_pulse_dec
4	Number of Scans	256
5	Relaxation Delay	1.5000
6	Pulse Width	3.2667
7	Spectrometer Frequency	67.93
8	Spectral Width	17006.8
9	Lowest Frequency	-1710.1
10	Nucleus	13C
11	Acquired Size	16384
12	Spectral Size	32768

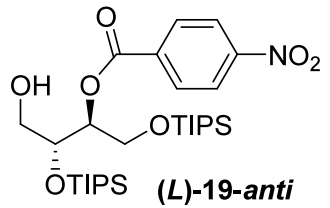


(*L*)-19-*anti*

Chiral shift ^{1}H NMR of racemic erythrose derivative

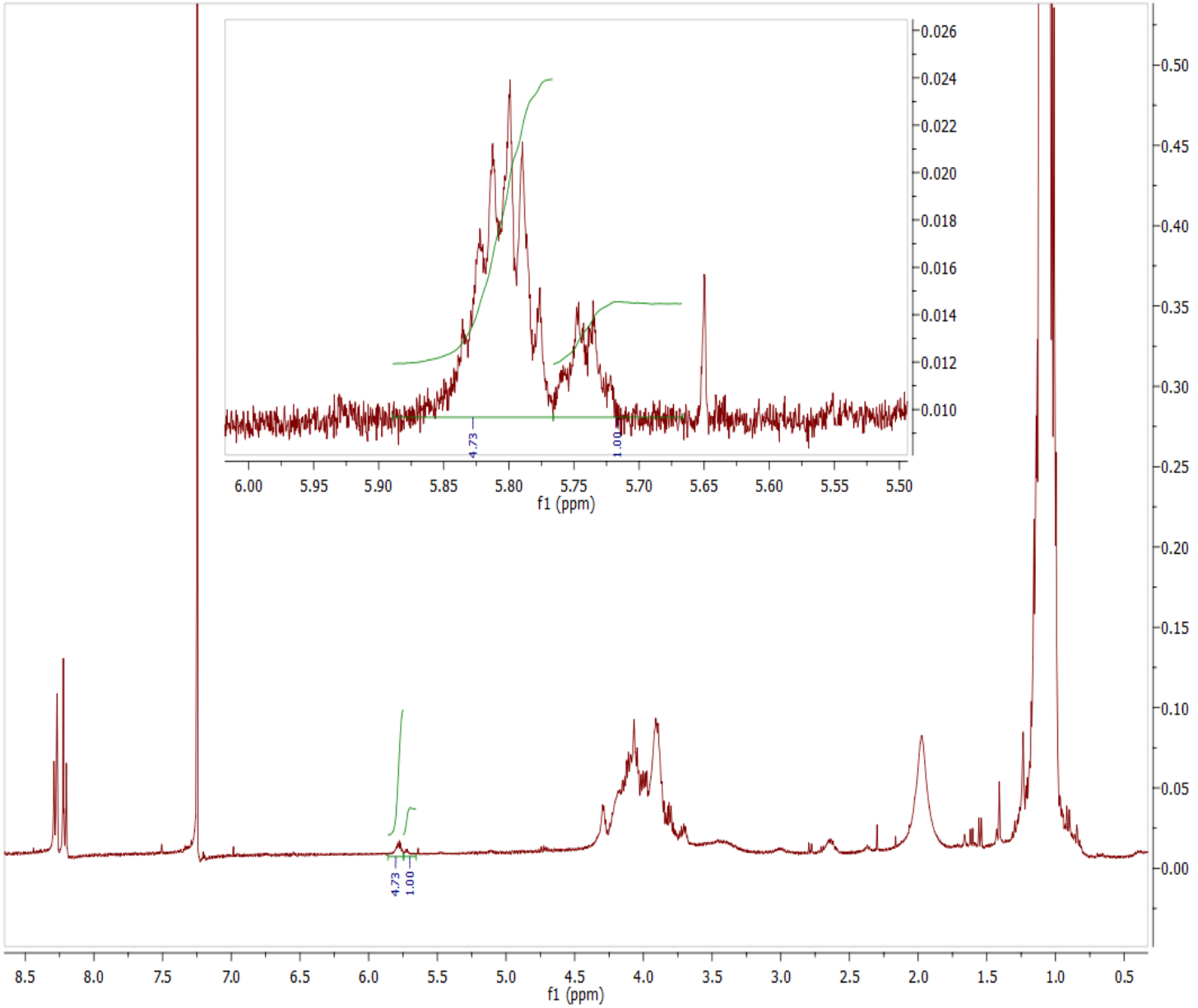


	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	22.0
3	Pulse Sequence	single_pulse.ex2
4	Number of Scans	32
5	Relaxation Delay	1.0000
6	Pulse Width	4.2000
7	Spectrometer Frequency	399.78
8	Spectral Width	9996.0
9	Lowest Frequency	-1999.6
10	Nucleus	1H
11	Acquired Size	32768
12	Spectral Size	65536

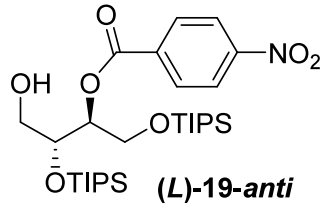


(*L*)-19-*anti*

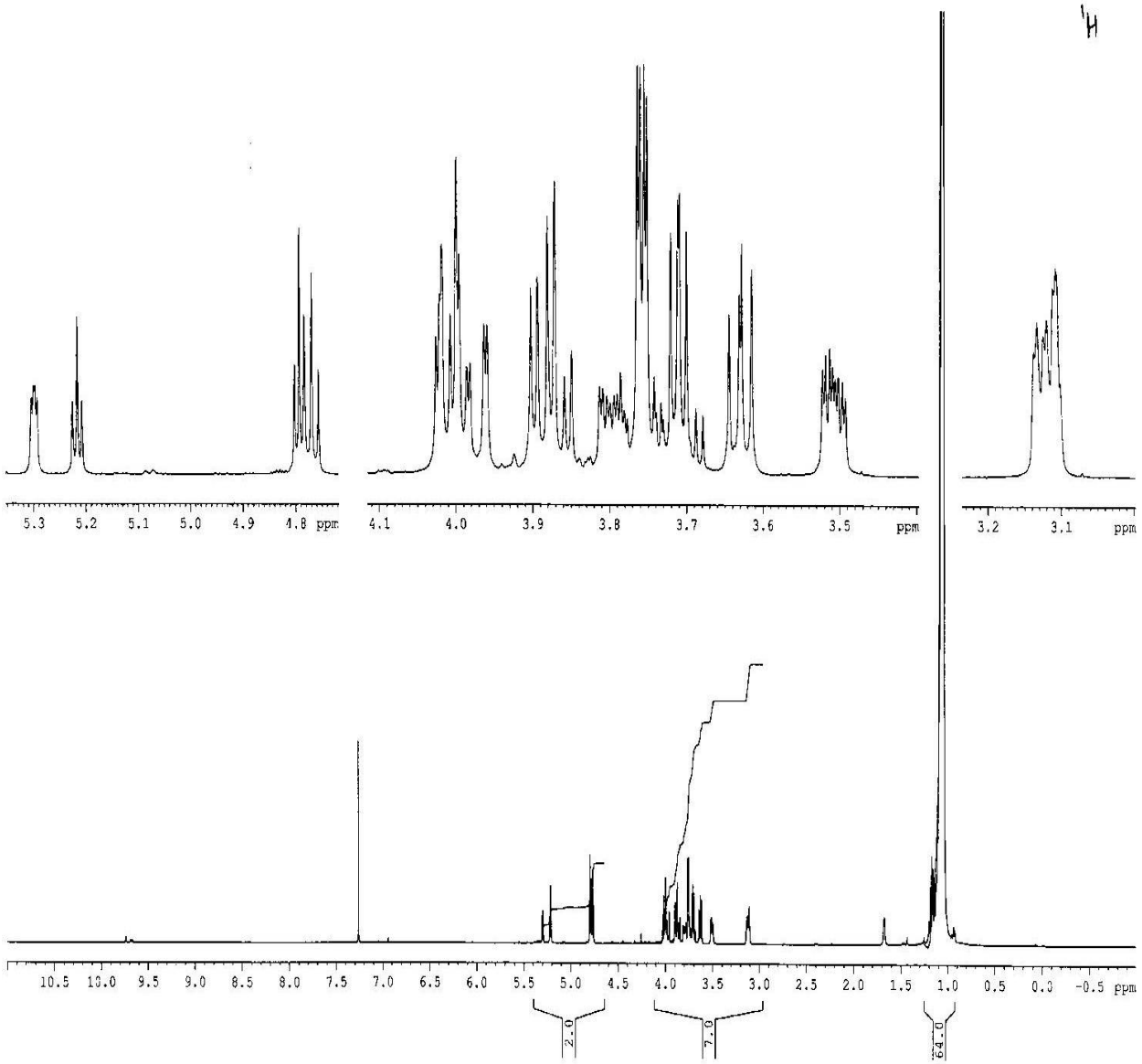
Chiral shift ^{1}H NMR of erythrose derivative formed by catalyst **12** at pH = 7



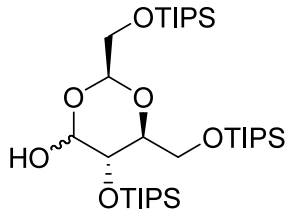
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	19.3
3	Pulse Sequence	single_pulse.ex2
4	Number of Scans	64
5	Relaxation Delay	1.0000
6	Pulse Width	4.2000
7	Spectrometer Frequency	399.78
8	Spectral Width	9996.0
9	Lowest Frequency	-1999.6
10	Nucleus	1H
11	Acquired Size	32768
12	Spectral Size	65536



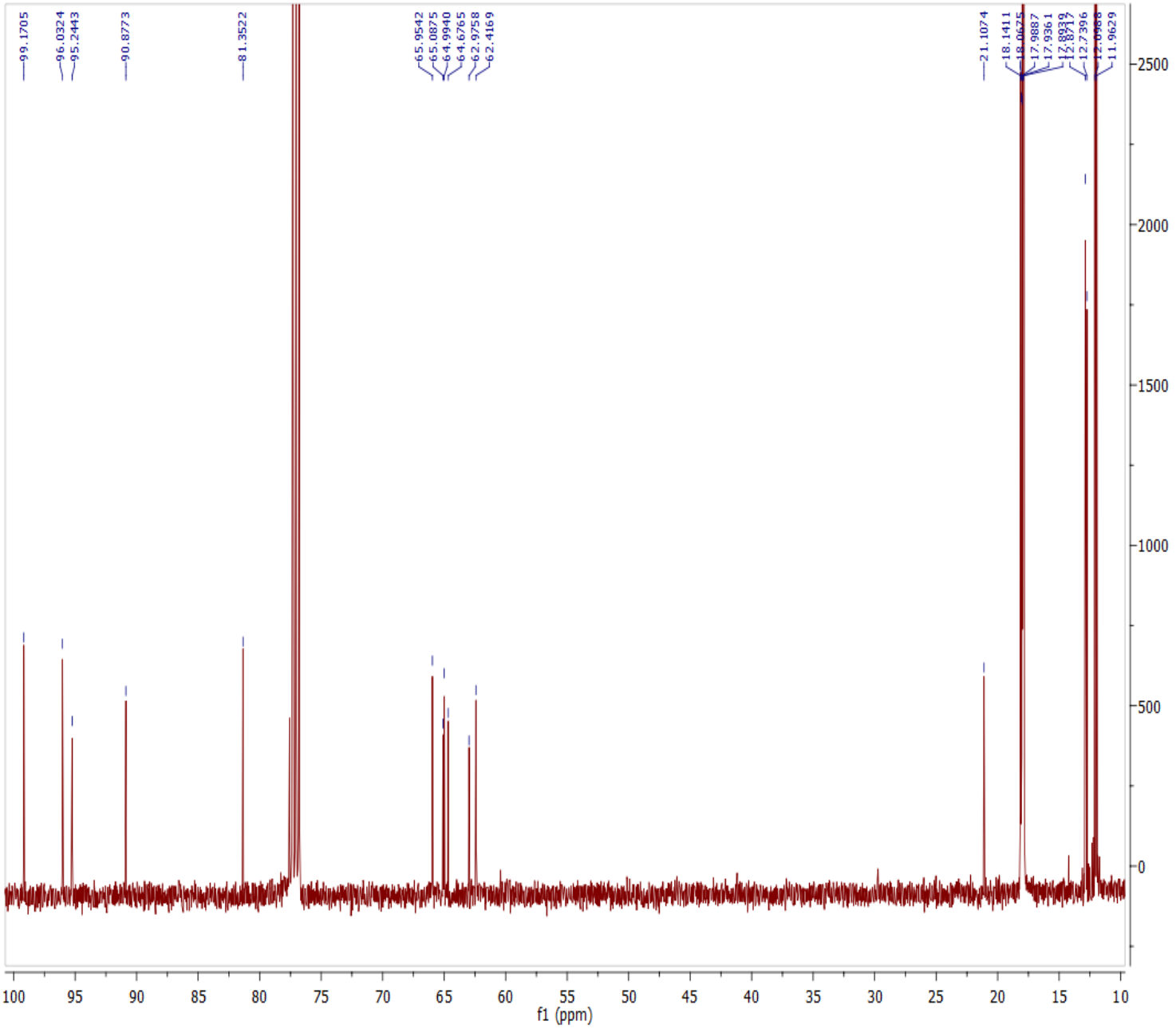
(*L*)-19-*anti*



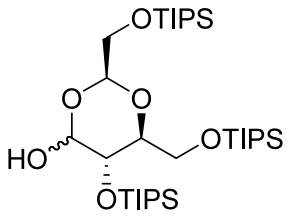
	Parameter	Value
1	Spectrometer	av500
2	Solvent	CDCl3
3	Temperature	300.0
4	Pulse Sequence	zg30
5	Number of Scans	64
6	Relaxation Delay	1.0000
7	Pulse Width	7.5000
8	Modification Date	2009-06-02T01:00:00
9	Spectrometer Frequency	500.23
10	Spectral Width	8012.8
11	Lowest Frequency	-917.3
12	Nucleus	1H
13	Acquired Size	32768
14	Spectral Size	65536



8

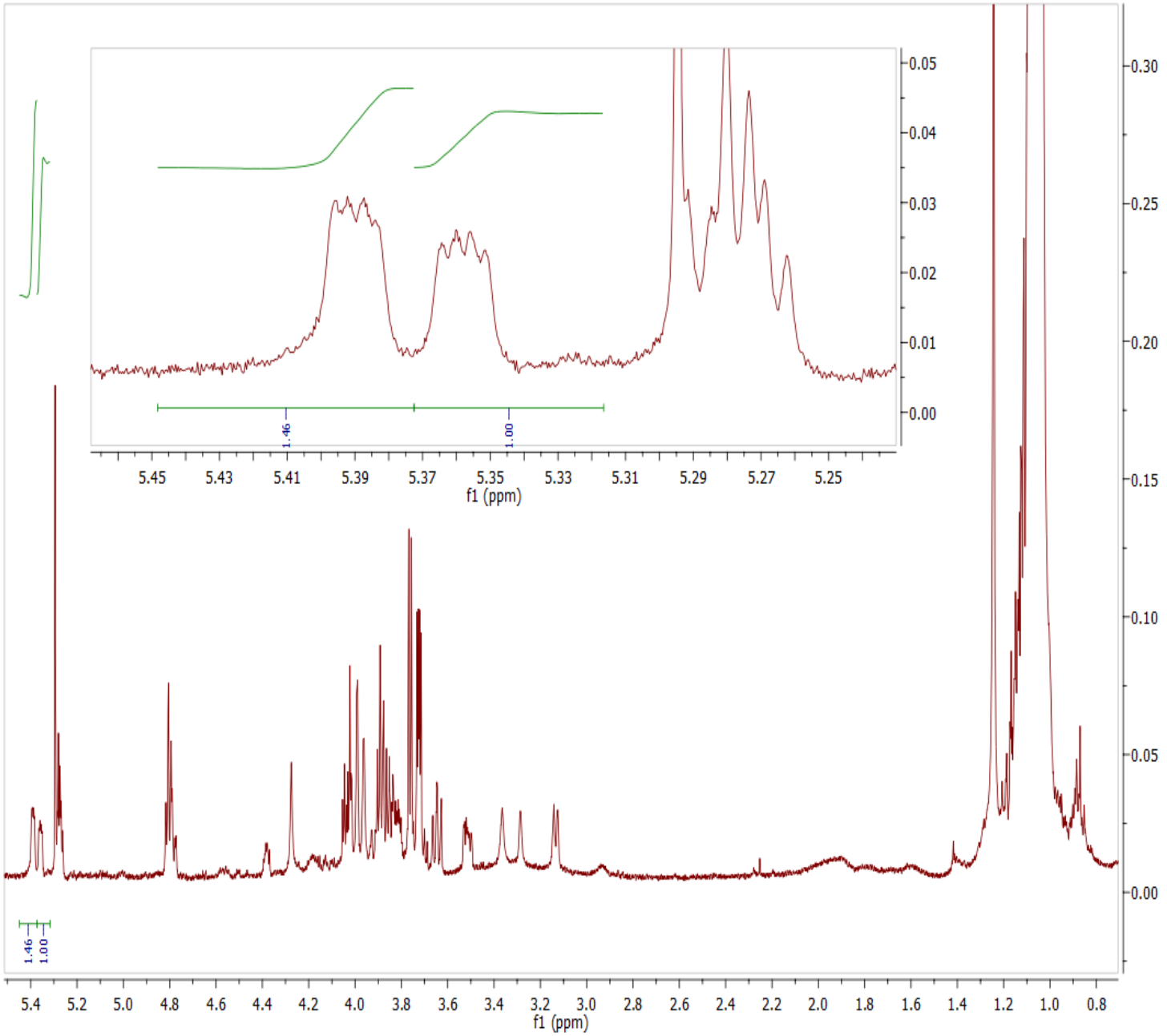


	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	22.7
3	Pulse Sequence	single_pulse_dec
4	Number of Scans	256
5	Relaxation Delay	1.5000
6	Pulse Width	3.4333
7	Spectrometer Frequency	100.53
8	Spectral Width	25137.5
9	Lowest Frequency	-2516.2
10	Nucleus	13C
11	Acquired Size	32768
12	Spectral Size	32768

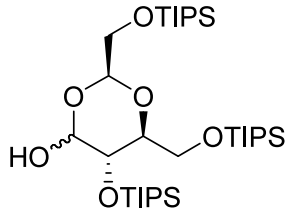


8

Chiral shift ^{1}H NMR of acetal **8** formed by catalyst **7**



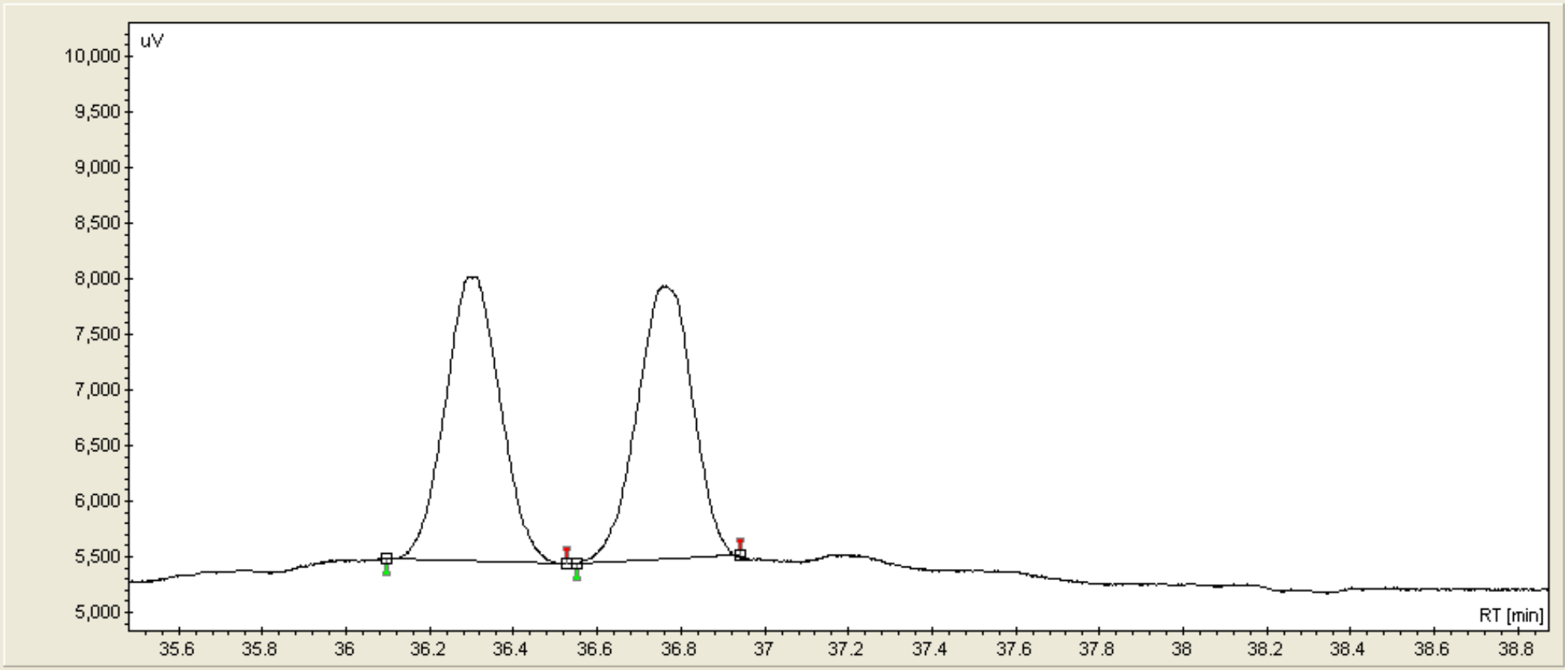
	Parameter	Value
1	Solvent	CHLOROFORM-D
2	Temperature	21.0
3	Pulse Sequence	single_pulse.ex2
4	Number of Scans	64
5	Relaxation Delay	4.0000
6	Pulse Width	4.9500
7	Spectrometer Frequency	399.78
8	Spectral Width	5997.0
9	Lowest Frequency	-999.6
10	Nucleus	1H
11	Acquired Size	16384
12	Spectral Size	16384



8

GC trace of racemic **18** standard.

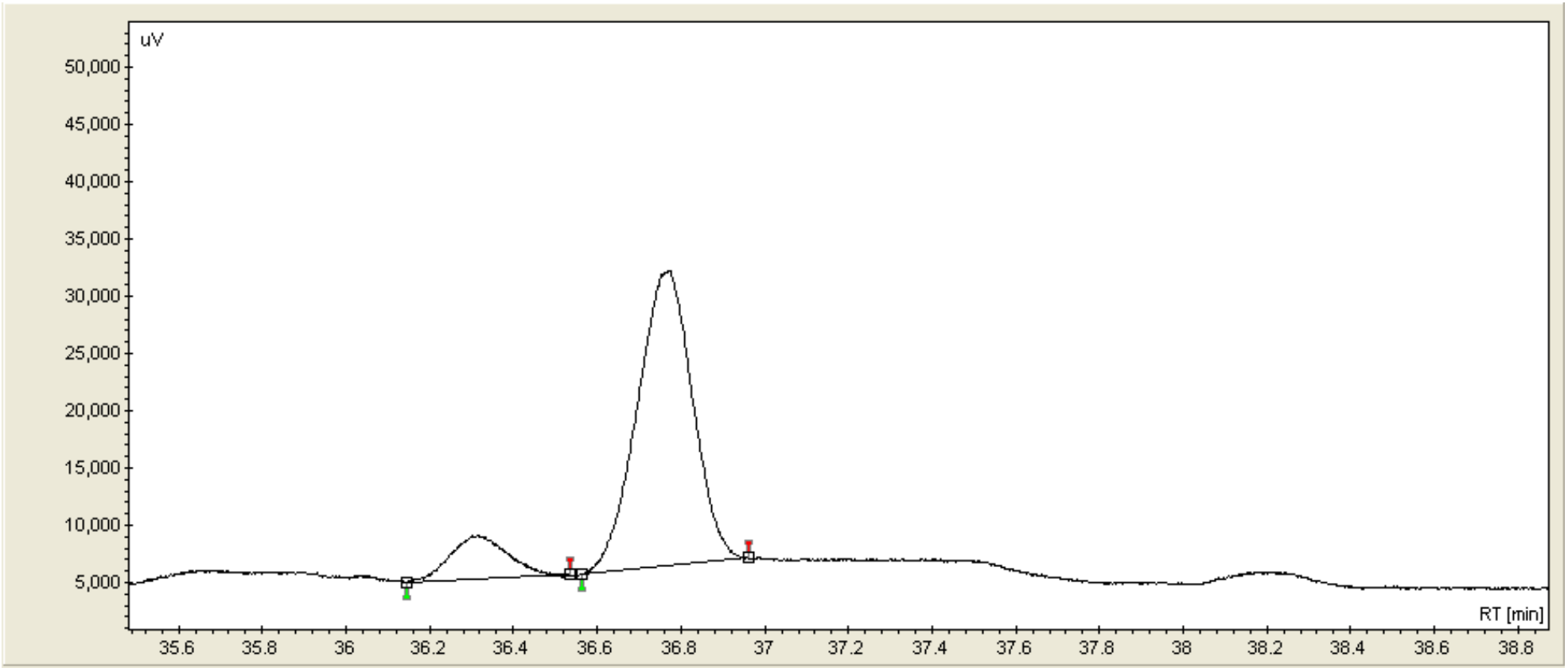
(CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.5 mL min^{-1}, t_i = 100 °C (10 min), (100 °C min^{-1}) t_f = 200 °C (40 min): (*L*)-isomer: t_R = 36.25 min; (*D*)-isomer: t_R = 36.78 min.



#	Name	Time [Min]	Quantity [% Area]	Height [uV]	Area [uV.Min]	Area % [%]
1	UNKNOWN	36.25	51.03	8203.9	1689.1	51.033
2	UNKNOWN	36.78	48.97	8173.8	1620.8	48.967
Total			100.00	16377.7	3309.9	100.000

GC trace of **18** form by catalyst **11** at pH = 7

(CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.5 mL min^{-1}, t_i = 100 °C (10 min), (100 °C min^{-1}) t_f = 200 °C (40 min): (*L*)-isomer: t_R = 36.33 min; (*D*)-isomer: t_R = 36.79 min.



#	Name	Time [Min]	Quantity [% Area]	Height [uV]	Area [uV.Min]	Area % [%]
1	UNKNOWN	36.33	17.03	10331.9	1371.3	17.033
2	UNKNOWN	36.79	82.97	29503.8	6679.4	82.967
Total			100.00	39835.7	8050.7	100.000