A general approach to the amnesic shellfish toxins: total synthesis of (–)-isodomoic acid B, (–)-isodomoic acid E and (–)-isodomoic acid F.

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Supplementary information

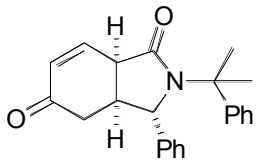
Contents:

1. General experimental information

NMR spectra were recorded on a Bruker Ultrashield 300, 400 or 500 MHz spectrometer. The chemical shifts (δ) are reported in ppm downfield of trimethylsilane and coupling constants (*J*) reported in hertz and rounded to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septuplet (sep), multiplet (m), broad (br), or a combination of these. Solvents were used as internal standard when assigning NMR spectra (δ H: $CDCl_3$ 7.26 ppm, D_2O 4.87 ppm; δ C: $CDCl_3$ 77.0 ppm). Low and high resolution mass spectra were recorded by staff at the University of Manchester. EI and CI spectra were recorded on a Micromass Trio 2000; ES and APCI spectra were recorded on a Micromass Platform II; high resolution mass spectra (HRMS, EI and ES) were recorded on a Thermo Finnigan MAT95XP mass spectrometer. Infrared spectra were recorded on a Perkin Elmer Spectrum RX I FTIR spectrometer as a film on a potassium bromide plate. Absorptions reported are sharp and strong, only absorption maxima of interest are reported. Melting points (M.P.) were determined on a Gallenkamp apparatus and are uncorrected. Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram Sil G/UV254) and visualised with UV light at 254 nm or phosphomolybdic acid dip (5 % in ethanol) or potassium permanganate. Flash chromatography was carried out using Fluorochem Davisil 40-63u 60 Å. All reactions were conducted under an atmosphere of dry nitrogen in flame-dried glassware. Tetrahydrofuran (THF) was distilled under nitrogen from sodium using benzophenone as indicator. Dichloromethane and toluene were obtained by distillation from calcium hydride under nitrogen. Petrol refers to the fraction of light petroleum ether boiling between 40-65 °C. All other solvents and commercially obtained reagents were used as received or purified using standard procedures.

2. Experimental procedures and characterisation

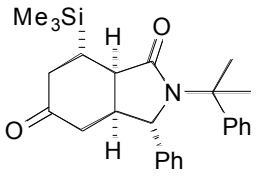
(3*R*, 3a*R* , 7a*S*)-2,3,3a,4-Tetrahydro-3-phenyl-2-(2-phenylpropan-2-yl)-7a*H*isoindol-1,5-dione 7.



$C_{23}H_{23}NO_2$
Mol. Wt.: 345,43

To a suspension of chiral amine **6** (1.7 g, 10.44 mmol) in THF (120 mL) at 0 °C, was added *n*-butyl lithium (2.5 M in hexanes 3.6 mL, 9.05 mmol), dropwise. The resulting mixture was allowed to stir for 15 minutes, resulting in a clear yellow solution. This was then cooled to –78 °C, and a solution of amide **5** (2.5 g, 6.96 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at –78 °C for 30 minutes before being slowly warmed to ~20°C over 4 hours. The reaction was first quenched with NH_4Cl (2 mL) and followed by the addition of 20 mL of HCl (3 M), the layers separated and the aqueous layer extracted with ether. The combined organic fractions were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (6:4 petrol:ethyl acetate) gave the title compound (1.61 g, 67 %) as a white solid. Mp 127-129 °C. Analytical HPLC (β-GEM, Regis), eluting with IPA and hexane (30:70), showed it to consist of a 7:93 mixture of two enantiomers, *t*R 7.96 and 8.57 min (ee=86%). Recrystallisation from ethyl acetate afforded **7** (0.820 g, 51 %) of ee >99%, $[\alpha]_D^{26} = -224.0$ (c = 1.05 in $CHCl_3$). m/z (CI+) 346 (MH+, 20 %), 176 (100 %); ^{1}H NMR (300MHz; $CDCl_3$) δ_H: 7.5-7.2 (10H, m, ArH), 6.94 (1H, dd, *J* 10. 5, C*H*=CHCO), 6.17 (1H, dd, *J* 10. 2, CH=C*H*CO), 4.48 (1H, d, *J* 2.5, NC*H*Ph), 3.70 (1H, m, COC*Ha*H), 2.83-2.52 (3H, m, COCH*Hb* + PhCHC*H* + NCOC*H*), 1.86 (3H, s, C*H*$_3$), 1.53 (3H, s, C*H3*); ^{13}C NMR (75MHz; $CDCl_3$) δ_C : 197.0, 171.9, 145.9, 144.7, 141.8, 130.6, 129.4(2C), 128.5(5C), 127.3, 126.2(2C), 125.6(2C), 67.6, 60.3, 42.7, 41.8, 39.4, 28.6, 27.5. All data correspond to those described in the literature.[1]

(3*S*,3a*S*,7a*R*)-3-phenyl-2-(2-phenylpropan-2-yl)-7-(trimethylsilyl) hexahydro-1H-isoindole-1,5(6H)-dione 8.



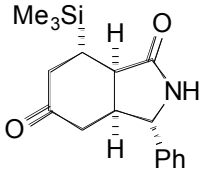
$C_{26}H_{33}NO_2Si$
Mol. Wt.: 419,63

A solution of HMPA (3.2 ml) and hexamethyldisilane (HMDS) (1.49 ml, 7.26 mmol) was cooled to 0 °C. Methyllithium (4.1 ml, 6.6 mmol) was added dropwise and the red solution was left to stir for 15 minutes at the same temperature. After this time, THF (13 mL) was added followed by the addition in one portion of copper cyanide (295 mg, 3.3 mmol) and the reaction was left to stir for 30 minutes at 0°C. After this time the reaction was cooled to -78 °C and a solution of enone **7** (1 g, 2.90 mmol) and TMSCl (1.1 ml, 9.0 mmol) in THF (12 mL) was added dropwise. The mixture was allowed to stir at -78 °C for 30 minutes and then quenched with NH_4OH/NH_4Cl (1/1) solution. Diethyl ether was added and the aqueous layer was extracted twice with diethyl ether. The organic layers were combined and washed with NH_4OH/NH_4Cl, brine, dried over magnesium sulfate and concentrated under reduced pressure to afford the silyl enol ether intermediate.

The enol intermediate was dissolved in 20 mL of THF and HCl 3M (~ 10mL) was added at room temperature. The reaction was allowed to stir 15 minutes and the aqueous layer was extracted twice with diethyl ether. The organic layers were combined and washed with a saturated solution of $NaHCO_3$, brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (petroleum ether/ethyl acetate 8:2) gave the title compound **8** (1.05 g, 86 %) as a white solid, m.p. 119-121 °C; $[\alpha]_D^{24}$ = 58.0 (c = 1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2947.8, 1722.58, 1694.38, 1495.20, 1455.90 and 1390.22; ^{1}H NMR (400MHz; $CDCl_3$) δ_H: 7.45-7.24 (10H, m, ArH), 4.43 (1H, s, NC*H*Ph), 3.05 (1H, dd, *J* 4.0, 4.0, COC*H*), 2.59 (1H, dd, *J* 4.0, 12.0, C*Ha*HCHCHPh), 2.48-2.40 (1H, m, CHC*H*Ph), 2.39-2.28 (2H, m, CH*Hb*CHCHPh + C*Ha*HCHSi), 2.15-2.04 (1H, m, CH*Hb*CHSi), 1.90 (3H, s, C*H*$_3$), 1.75-1.69 (1H, m, C*H*Si), 1.55 (3H, s, C*H*$_3$), 0.00 (9H, s, 3 SiC*H*$_3$); ^{13}C NMR (100MHz, $CDCl_3$) δ_c: 211.4. 175.6, 146.1, 141.8, 129.1 (2C), 128.2 (2C), 127.9, 127.0, 125.6 (2C), 125.4 (2C), 67.4, 62.3, 59.3, 43.1, 39.6, 38.7, 28.1, 27.1, 19.9, -2.5 (3C); *m/z* (ES^+) 442.2 (100%, MNa^+); Found MH^+ 420.2367, $C_{26}H_{33}NO_2Si$ requires MH^+ 420.2353.

Crystallisation of **8** gave material suitable for single crystal X-ray analysis. Data have been deposited with the Cambridge Crystallographic Database, deposition number 785966.

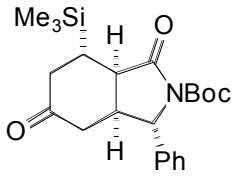
(3*S*,3a*S*,7a*R*)-3-phenyl-7-(trimethylsilyl)hexahydro-1H-isoindole-1,5(6H)-dione



$C_{17}H_{23}NO_2Si$
Mol. Wt.: 301,46

Lactam **7** (1.23 g, 2.935 mmol) was dissolved in TFA (12 ml). The reaction was heated at reflux for 1 hour and then allowed to cool to R.T.. The TFA was removed under reduced pressure and the crude was dissolved in DCM. The organic was washed twice with a saturated solution of $NaHCO_3$, brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (1:1 petroleum ether/ethyl acetate) gave the free lactam (0.819 g, 93 %) as a white solid, $[\alpha]_D^{25}$ = 95.2 (c = 1 in $CHCl_3$); m.p 99-101 °C; ν_{max} (film)/cm^{-1} 3440, 2952, 1714, 1687 and 1651; ^{1}H NMR (400MHz; $CDCl_3$) δ_H: 7.41-7.27 (5H, m, ArH), 6.92 (1H, bs, NH), 4.36 (1H, d, *J* 3.0, NC*H*Ph), 2.80-2.69 (2H, m, COC*H* + NCHC*H*), 2.61 (1H, dd, *J* 6.0, 16.0 [A of ABX], C*Ha*HCHCHPh), 2.50 (1H, dd, *J* 9.5, 16.0 [B of ABX], CH*Hb*CHCHPh), 2.40 (1H, dd, *J* 5.0, 15.5, C*Ha*HCHSi), 2.15 (1H, dd, *J* 10.5, 15.5, CH*Hb*CHSi), 1.64 (1H, ddd, *J* 5.5, 7.5, 10.5, C*H*Si), 0.00 (9H, s, 3 SiC*H*$_3$); ^{13}C NMR (100MHz, $CDCl_3$) δ_C: 211.1, 178.6, 140.3, 128.8 (2C), 128.1, 125.5 (2C), 61.8, 45.5, 41.7, 39.7, 39.3, 20.7, -2.5; *m/z* (ES^+) 324 (100%, MNa^+); Found MNa^+ 324.1389, $C_{17}H_{23}NO_2$ requires MNa^+ 324.1390.

(1*S*,3a*R*,7a*S*)-tert-butyl 3,6-dioxo-1-phenyl-4-(trimethylsilyl)hexahydro-1H-isoindole-2(3H)-carboxylate 9

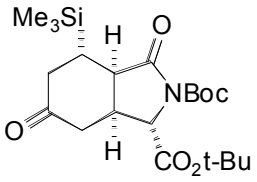


$C_{22}H_{31}NO_4Si$
Mol. Wt.: 401,57

The above lactam (1.75 g, 5.81 mmol) was dissolved in DCM (50 ml). Boc_2O (1.52 g, 6.97 mmol), triethylamine (0.81 ml, 5.81 mmol) and DMAP (142 mg, 1.16 mmol) was added and the reaction was allowed to stir for 18 hours. The reaction was quenched with water and extracted with DCM. The organic layer was washed with water, brine, dried over magnesium

sulfate and concentrated under reduced pressure. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) gave the title compound **9** (2.01 mg, 86%) as a white solid, $[\alpha]_D^{25}$ = 93.6 (c = 1 in $CHCl_3$); m.p 168 °C; ν_{max} (film)/cm^{-1} 1782, 1751, 1716 and 1636; ^1H NMR (400MHz; $CDCl_3$) δ_H: 7.39-7.35 (2H, m, ArH), 7.32-7.28 (2H, m, ArH), 7.19-7.17 (2H, m, ArH), 4.79 (1H, s, NC*H*), 2.92 (1H, dd, *J* 6.5, 6.5, COC*H*), 2.66 (1H, dd, *J* 5.0, 15.0, C*Ha*HCHSi), 2.58-2.52 (1H, m, C*H*CHPh), 2.46-2.38 (2H, m, CH*Hb*CHSi, C*Ha*HCHCHPh), 2.11 (1H, dd, *J* 9.0, 15.5, CH*Hb*CHCHPh), 1.73 (1H, dt, *J* 6.0, 12.0, C*H*Si), 1.31 (9H, s, *t*Bu), 0.00 (9H, s, 3 SiC*H*$_3$); ^{13}C NMR (100MHz, $CDCl_3$) δ_C: 210.0, 174.9, 149.6, 139.8, 128.9 (2C), 127.9, 124.7 (2C), 83.3, 65.2, 42.5, 41.0, 40.8, 38.5, 27.6 (3C), 19.9, -2.7 (3C); *m/z* (ES^+) 424.3 (100%, MNa^+); Found MNa^+ 424.1927, $C_{22}H_{31}NO_4$ requires MNa^+ 424.1915.

(1*S*,3a*R*,7a*S*)-di-*tert*-butyl 3,6-dioxo-4-(trimethylsilyl)hexahydro-1H-isoindole-1,2(3H)-dicarboxylate 10



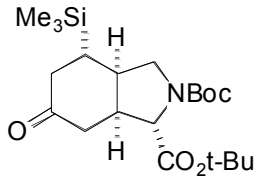
$C_{21}H_{35}NO_6Si$
Mol. Wt.: 425,59

To a solution of $NaIO_4$ (19.8 g, 90 mmol) in distilled water (52 ml) and acetonitrile (26 ml), $RuCl_3.xH_2O$ (100 mg mg, 0.50 mmol) was added in one portion. A solution of lactam **9** (2.01 g, 5.02 mmol) in ethyl acetate (26 ml) was added dropwise. The reaction was allowed to stir for 24 hours. After this time the reaction was filtered over a pad of celite and the organic was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography (4:1 petroleum ether/ethyl acetate) was performed to recover remaining starting material and the column was flushed with ethyl acetate to obtain the acid intermediate (1.41 g)**.**

The crude acid was dissolved in DCM (22 ml). DCC (1.64 g, 7.96 mmol), DMAP (97 mg, 0.79 mmol) and *tert*-Butanol (0.95 ml, 9.94 mmol) were added and the reaction was allowed to stir for 18 hours. After this time the reaction was filtered and water was added. The aqueous layer was extracted twice with DCM. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (4:1 petroleum ether/ethyl acetate) gave the title compound **10** (1.37 g, 64 %) as a colourless oil, $[\alpha]_D^{25}$ = 76.4 (c = 1 in $CHCl_3$); ^1H NMR (400MHz; $CDCl_3$) δ_H: 4.13 (1H, s, NC*H*), 2.88 (1H, dd, *J* 5.5, 7.0, COC*H*), 2.70 (1H, ddd, *J* 5.5, 12.5, C*H*CHN), 2.57 (1H, dd, *J* 5.5, 16.0 [A of ABX], C*Ha*HCHCHN), 2.41 (1H, dd, *J* 6.5, 15.5 [A of ABX], C*Ha*HCHSi),

2.28 (1H, dd, *J* 12.5, 16.0 [B of ABX], CH*Hb*CHCHN), 2.17 (1H, dd, *J* 8.0, 15.0 [B of ABX], CH*Hb*CHSi), 1.74 (1H, dt, *J* 6.0, 7.5, C*H*Si), 1.52 (9H, s, *t*Bu), 1.49 (9H, s, tBu), 0.05 (9H, s, 3 SiC*H*$_3$); ^{13}C NMR (100MHz, $CDCl_3$) δ_C: 209.4, 173.9, 168.9, 149.5, 83.8, 82.9, 63.5, 60.4, 42.2, 41.8, 38.4, 36.1, 27.9, 19.8, 14.2, -2.6; *m/z* (ES^+) 448.5 (100%, MNa^+); Found MNa^+ 448.2134, $C_{21}H_{35}NO_6Si$ requires MNa^+ 448.2126.

(1*S*,3a*R*,7a*S*)-di-tert-butyl 6-oxo-4-(trimethylsilyl)hexahydro-1H-isoindole-1,2(3H)-dicarboxylate 11



$C_{21}H_{37}NO_5Si$
Mol. Wt.: 411,61

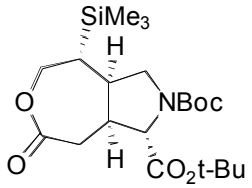
Lactam **10** (380 mg, 0.890 mmol) was dissolved in THF (9 ml) and cooled to 0 °C. Super-H (1M in THF, 3.5 ml, 3.56 ml) was added dropwise and the solution was allowed to stir for 1 hour. After this time the reaction was quenched with $NaHCO_3$ solution at 0 °C and 10 drops of H_2O_2 (30%) were added. The reaction was allowed to stir 30 min at room temperature. The organic was extracted twice with ethyl acetate. The combined layers were washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure to afford the crude aminol intermediate.

The crude aminol was dissolved in DCM (6 ml) and cooled to -78 °C. Freshly distilled $BF_3.OEt_2$ (125 µl, 0.979 ml) and Et_3SiH (160 µl, 0.979 ml) was added and the reaction was stirred for 30 minutes. After this time $BF_3.OEt_2$ (125 µl, 0.979 ml) and Et_3SiH (160 µl, 0.979 ml) was added again and the reaction was left to stir for 2 hours. After this time the reaction was quenched with $NaHCO_3$ solution and allowed to warm to room temperature. The organic was extracted twice with DCM. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification of the alcohols was performed by column chromatography (5:5 petroleum ether/ethyl acetate) to afford 250 mg of the intermediate alcohol.

The alcohol (250 mg, 0.605 mmol) was dissolved in DCM (2 ml). Dess-Martin periodinane (0.3M in DCM, 4 ml, 1.2 mmol) was added dropwise and the reaction was allowed to stir for 2 hours. After this time the reaction was quenched with $NaHCO_3$ solution and the organic was extracted with DCM). The combined organic layers were washed brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (3:1 petroleum ether/ethyl acetate) gave the title compound **11** (181 mg, 50%

over 3 steps) as a colourless oil, $[\alpha]_D^{25}$ = 95.2 (c = 1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2978.6, 1738.9, 1733.3 and 1701.5; ^1H NMR (400MHz; $CDCl_3$), 2 rotamers, δ_H: 3.94 (0.3H, bs, NC*H*), 3.84 (0.7H, dd, *J* 1.5, NC*H*), 3.78 (0.7H, dd, *J* 7.0, 10.5, C*Ha*HN), 3.68 (0.3H, dd, *J* 7.5, 10.3, C*Ha*HN), 3.29-3.25 (1H, m, CH*Hb*N), 2.60-2.53 (2H, m, C*H*CHSi + C*H*CHN), 2.46-2.42 (2H, m, CH_2CHCHN), 2.29 (1H, dd, *J* 4.5, 15.9 [A of ABX], C*Ha*HCHSi), 2.10 (1H, dd, *J* 12.5, 16.0 [B of ABX], CH*Hb*CHSi), 1.46 (9H, bs, *t*Bu), 1.43 (9H, bs, *t*Bu), 1.11-1.05 (1H, m, C*H*Si), 0.03 (9H, s, 3 SiCH_3) ; ^{13}C NMR (100MHz, $CDCl_3$) δ_C: 211.6, 171.2, 154.0, 81.6, 80.3, 64.8, 52.0, 43.4, 41.0, 38.7, 35.3, 28.3 (3C), 28.0 (3C), 23.9, 14.2, -2.9 (3C); *m/z* (ES^+) 412 (80%, MH^+), 434.4 (100%, MNa^+); Found MH^+ 412.2505, $C_{21}H_{27}NO_5Si$ requires MH^+ 412.2514.

(1*S*,3a*R*,4*R*,8a*S*)-di-tert-butyl hexahydro-4-(trimethylsilyl)-7-oxo-1H-oxepino[4,5-c]pyrrole-1,2(7H)-dicarboxylate 12

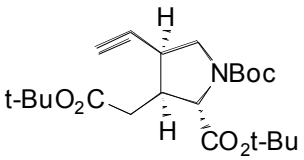


$C_{21}H_{37}NO_6Si$
Mol. Wt.: 427,61

Ketone **11 (**288 mg, 0.7 mmol) was dissolved in DCM (5 mL). *m*CPBA (240 mg, 1.4 mmol) was added in one portion and the reaction was left to stir for 2 days. The reaction was quenched with sodium thiosulfite and extracted with DCM. The organic layer was washed twice with $NaHCO_3$ and brine, dried over magnesium sulfate and concentrated under reduced pressure to give 288 mg of an inseparable mixture of the title compound **12** (83% yield) and the overoxidised by-product (10% yield) as a white solid; m.p. 191-195 °C. $[\alpha]_D^{25}$ = -4.4° (c = 1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2979, 2936, 1733, 1728 and 1705 ; ^1H NMR (400 MHz, $CDCl_3$), 2 rotamers, δ_H : 4.63-4.57 (1H, m, OC*Ha*H), 4.28-4.23 (1H, m, OCHa*Hb*), 3.99 (0.35, s, NC*H*CO_2*t*Bu), 3.84 (0.65, s, NC*H*CO_2*t*Bu), 3.69 (0.65H, A of ABX, *J* 10.7, 8.4, NCHaHCO*t*Bu), 3.61 (0.35H, A of ABX, *J* 10.5, 8.6, NC*Ha*HCO_2*t*Bu), 3.40 (0.65H, B of ABX, *J* 10.6, 10.6 , NCH*Hb*CO_2*t*Bu), 3.36 (0.35H, B of ABX, *J* 10.6, 10.6, NCH*Hb*CO_2*t*Bu), 2.99 (0.65H, A' of A'B'X', *J* 13.3, 13.3, C*Ha*HCO_2*t*Bu), 2.95 (0.35H, A' of A'B'X', *J* 13.5, 13.5, C*H*aHCO_2*t*Bu), 2.75-2.69 (1H, m, NCH_2C*H*), 2.58 (1H, B' of A'B'X', *J* 13.6, 1.3, CH*Hb*CO_2*t*Bu), 2.52 (1H, dd, *J* 13.0, 5.4, NCHC*H*), 1.47-1.43 (18H, m, 2 *t*Bu), 1.13 (0.65H, bs, C*H*SiMe_3) and 1.08 (0.35H, bs, C*H*SiMe_3) ; ^{13}C NMR (100 MHz, $CDCl_3$, 2 rotamers, δ_C : 173.2, 173.1, 170.5, 170.2, 154.4, 154.1, 81.9, 81.8, 80.4, 80.2, 66.9, 66.6, 66.1, 65.9, 48.5,

48.3, 40.3, 39.3, 36.7, 35.9, 35.6, 35.4, 28.2, 27.9 (2C), 27.8, 27.3, 27.2, -2.0 (6C) ; m/z (ES^+) 450 (100%, MNa^+); Found MNa^+ 450.2286, $C_{21}H_{37}NO_6Si$ requires MNa^+ 450.2282

(2*S*,3*S*,4*R*)-di-tert-butyl 3-((tert-butoxycarbonyl)methyl)-4-vinylpyrrolidine-1,2-dicarboxylate 13

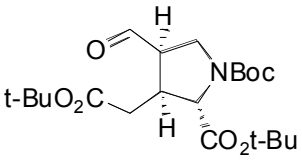


$C_{22}H_{37}NO_6$
Mol. Wt.: 411,53

To a solution of lactone **12** (165 mg, 0.38 mmol) in dry THF (3.5 mL) was added tetrabutylammonium fluoride dropwise at 0°C. The mixture was stirred for 5 min and then the cold bath was removed and the stirring continued for 2 hours. The reaction was quenched with NH_4Cl and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the acid intermediate.

To a solution of the intermediate acid in *tert*-butanol (4 mL) was added DMAP (14 mg, 0.11 mmol) and Boc_2O (163 mg, 0.76 mmol). The reaction was allowed to stir overnight at room temperature and the mixture was concentrated under reduced pressure. Purification by column chromatography (9:1 petroleum ether/ethyl acetate) gave the title alkene **13** (94 mg, 70 % yield over 2 steps) as a colourless oil. $[\alpha]_D^{25} = -3.6$ (c = 1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2978, 2930, 1735, 1723 and 1700; ^1H NMR (400 MHz, $CDCl_3$), 2 rotamers, δ_H : 5.68-5.59 (1H, m, CH_2=C*H*), (1H, m, CHH_{cis}=CH), (1H, m, CH_{trans}H=CH), 3.84 (0.35H, d, *J* 6.0, NC*H*CO_2tBu), 3.80 (0.65H, d, *J* 5.7, NC*H*CO_2tBu), 3.60 (0.65H, A of ABX, *J* 10.8, 6.6, NC*Ha*HCO*t*Bu), 3.56 (0.35H, A of ABX, *J* 10.7, 6.5, NC*Ha*HCO_2tBu), 3.43 (0.65H, B of ABX, *J* 10.8, 5.4 , NCH*Hb*CO_2tBu), 3.33 (0.35H, B of ABX, *J* 10.7, 5.0, NCH*Hb* CO_2tBu), 3.06-2.97 (1H, m, =CHC*H*), 2.68-2.62 (1H, m, NCHC*H*), 2.37-2.26 (2H, m, CH_2CO_2tBu) and 1.45-1.41 (27H, m, 3 *t*Bu) ; ^{13}C NMR (100 MHz, $CDCl_3$), 2 rotamers, δ_C : 171.3, 171.2, 171.0, 171.0, 154.1, 153.8, 134.9, 134.5, 117.8, 117.7, 81.3, 81.2, 80.7, 80.7, 79.9, 79.7, 63.7, 63.7, 50.2, 49.5, 44.1, 44.0, 43.1, 43.0, 35.0, 34.9, 28.3, 28.2, 28.0 (3C) and 27.9 ; m/z (ES^+) 434 (100%, MNa^+); Found MH^+ 412.2694, $C_{22}H_{35}NO_6$ requires MH^+ 412.2694.

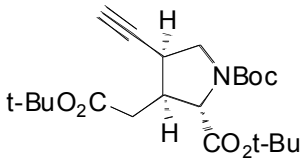
(2*S*,3*S*,4*R*)-di-tert-butyl 3-((tert-butoxycarbonyl)methyl)-4-formylpyrrolidine-1,2-dicarboxylate 14



$C_{21}H_{35}NO_7$
Mol. Wt.: 413,51

In a three-neck round bottom flask, alkene **13** (130 mg, 0.32 mmol) was dissolved in dry DCM (5 mL). The solution was cooled down to -78 °C and O_3 was bubbled for 15 min. After the appearance of deep blue colour, the mixture was allowed to stir 5 more min. Then O_2 was bubbled for 5 min at the same temperature until the total disappearance of the blue colour. N_2 was then flushed for 5 min and Me_2S (1 mL, 15.8 mmol) was added in once. The solution was then warmed up to room temperature and allowed to stir for 24 hours. The solvents were removed under reduced pressure to give the crude aldehyde **14** (128 mg, 98% yield). $[\alpha]_D^{25}$ = –3.8 (c = 1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2977, 2930, 1735, 1727 and 1703 ; ^{1}H NMR (400 MHz, $CDCl_3$), 2 rotamers, δ_H : 9.70 (1H, d, *J* 1.3, CO*H*), 3.97 (0.35H, d, *J* 4.6, NC*H*CO_2tBu), 3.91 (0.65H, d, *J* 5.4, NC*H*CO_2tBu), 3.84 (0.65H, A of ABX, *J* 11.4, 5.4, NC*Ha*HCO_2tBu), 3.76 (0.35H, A of ABX, *J* 11.2, 6.4, NC*Ha*HCO_2tBu), 3.60 (0.65H, B of ABX, *J* 11.4, 7.3 , NCH*Hb*CO_2tBu), 3.56 (0.35H, B of ABX, *J* 11.2, 7.5, NCH*Hb*CO_2tBu), 3.36-3.28 (1H, m, =CHC*H*), 3.00-2.87 (1H, m, NCHC*H*), 2.55-2.41 (2H, m, C*H*$_2$$CO_2t$Bu),1.46-1.401 (27H, m, 3 *t*Bu) ; ^{13}C NMR (100 MHz, $CDCl_3$), 2 rotamers, δ_C : 199.9, 199.9, 170.7, 170.6, 170.5, 170.5, 154.0, 153.7, 81.8, 81.8, 81.5, 81.4, 80.4, 80.3, 64.5, 64.3, 51.6, 50.6, 44.9, 44.8, 42.0, 40.6, 35.1, 35.0, 28.3, 28.2, 28.0, 27.9 (2C), 27.9 ; m/z (ES^+) 436 (100%, MNa^+), 468 (50%, M(MeOH)Na^+); Found MNa^+ 436.2308, $C_{21}H_{35}NO_7$ requires MNa^+ 436.2307.

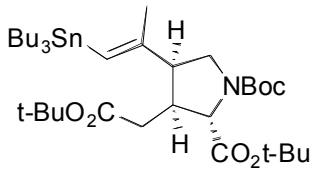
(2*S*,3*S*,4*S*)-di-tert-butyl 3-((tert-butoxycarbonyl)methyl)-4-ethynylpyrrolidine-1,2-dicarboxylate 4



$C_{22}H_{35}NO_6$
Mol. Wt.: 409,52

To a solution of Ohira-Bestmann reagent (188 mg, 0.99 mmol) in dry THF (4 mL) at -78°C was added a solution of freshly prepared NaOMe (500 μL, 0.99 mmol, 2N in MeOH) in dry THF (1 mL), the solution turned yellow. To this mixture, a solution of aldehyde **14** (100 mg, 0.24 mmol) in dry THF (3 mL) was added dropwise. The reaction was allowed to stir 1 hour at the same temperature and then warmed up to room temperature over 1 hour. After this time, the reaction was quenched with NH_4Cl and extracted twice with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (85:15 petroleum ether/ethyl acetate) gave the title compound **4** (88 mg, 89 % yield) as a colourless oil, $[\alpha]_D^{25} = -4.1$ (c = 1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3273, 2980, 2932, 1738, 1732 and 1700 ; ^{1}H NMR (400 MHz, $CDCl_3$), 2 rotamers, δ_H : 3.93 (0.35H, d, *J* 5.5, NC*H*CO_2tBu), 3.87 (0.65H, d, *J* 5.6, NC*H*CO_2tBu), 3.70-3.59 (1.65H, m, NC*Ha*HCO_2tBu + NCH*Hb*CO_2tBu), 3.53-3.49 (0.35H, m, NC*Ha*HCO_2tBu), 3.32-2.23 (1H, m, CHCC*H*), 2.77-2.72 (1H, m, C*H*HCO_2tBu), 2.68-2.62 (1H, m, NCHC*H*), 2-47-2.40 (1H, m, CH*H*CO_2tBu), 2.17 (d, *J* 2.4, CC*H*), 1.46-1.43 (27H, m, 3 *t*Bu) ; ^{13}C NMR (100 MHz, $CDCl_3$), 2 rotamers, δ_C : 171.0, 170.9, 170.8 (2C), 154.0, 153.7, 81.5 (2C), 81.0 (3C), 80.8, 80.3, 80.0, 72.9, 72.9, 63.4, 63.3, 51.3, 50.8, 43.5, 42.3, 35.5, 35.4, 32.7, 32.0, 28.3 (3C), 28.3(3C), 28.0 (6C), 28.0 (3C), 27.9 (3C) ; m/z (ES^+) 432 (100%, MNa^+); Found MNa^+ 432.2371, $C_{22}H_{35}NO_6$ requires MNa^+ 432.2357

(2*S*,3*S*,4*S*)-di-tert-butyl 3-((tert-butoxycarbonyl)methyl)-4-((*E*)-1-(tributylstannyl)prop-1-en-2-yl)pyrrolidine-1,2-dicarboxylate 15

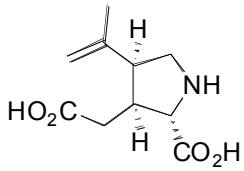


$C_{35}H_{65}NO_6Sn$
Mol. Wt.: 714,6

To a mixture of CuCN (27 mg, 0.3 mmol) in THF (1.5 ml) at -78 °C was added BuLi (1.6M, 375 μl, 0.6 mmol) and the mixture was stirred for 15 min affording a colourless solution. The mixture was warmed to -60 °C and Bu_3SnH (161 μL, 0.6 mmol) was added and the yellow

solution that resulted was stirred for 10 min before being cooled again to -78 °C. Alkyne **4** (35 mg, 0.086 mmol) in THF (200 µl) was added slowly to the reaction. The reaction was slowly warmed to -10 °C (approx. 40 mins) and MeI (78 µl, 1.2 mmol) was then added. The reaction was stirred for 2 h at 0 °C then quenched with a solution of NH_4Cl/NH_4OH (1/1) and extracted twice with ether. The combined organic layers were washed with a solution of NH_4Cl/NH_4OH (1/1) and brine and concentrated under reduced pressure. Purification by column chromatography (98/2 petroleum ether/ethyl acetate) gave the title stannane **15** (40 mg, 65%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$), 2 rotamers, δ_H : 5.48 (0.7H, s, J_{Sn-H} 64, C*H*Sn), 5.44 (0.3H, s, J_{Sn-H} 64, C*H*Sn), 4.00 (1H, bs, NC*H*), 3.62 (0.7H, A of ABX, *J* 10.5, 7.5, NC*Ha*Hb), 3.58 (0.3H, dd, *J* 9.9, 7.5, NC*Ha*Hb), 3.52 (0.7H, B of ABX, *J* 10.0, 10.0, NC*Ha*Hb), 3.41 (0.3H, bt, *J* 9.5, NCHa**Hb**), 3.08 (1H, m, NCH_2CH), 2.75-2.66 (1H, m, NCHC*H*) and 2.17-2.04 (2H, m, CH_2CO_2tBu), 1.71 (3H, s, $=CCH_3$), 1.47-1.43 (33H, m, $3CH_2$ + 3*t*Bu), 1.35-1.24 (6H, m, $3CH_2$), 0.93-0.82 (15H, m, $3CH_2Sn$ + $3CH_3$) ; ^{13}C NMR (125 MHz, $CDCl_3$), 2 rotamers, δ_C : 171.5, 171.4 (2C), 171.3, 154.2, 154.0, 150.1, 149.4, 125.9, 125.6, 81.2 (2C), 80.8, 80.7, 79.8, 79.7, 64.3 (2C), 49.1, 48.3, 47.7, 42.9, 41.7, 34.6, 34.6, 29.2 (J_{Sn-C} = 20 Hz, 6C), 28.4 (3C), 28.3 (3C), 28.0 (6C), 28.0 (3C), 28.0 (3C), 27.3 (J_{Sn-C} = 56 Hz, 6C), 24.6, 24.5, 13.7 (6C), 10.2 (J_{Sn-C} = 333 Hz, 6C); Found MNa^+ 734.3722, $C_{35}H_{65}NO_6{}^{116}Sn$ requires MNa^+ 734.3728.

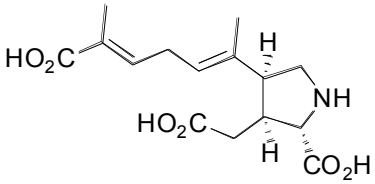
(−)-Kainic acid (3)



$C_{10}H_{15}NO_4$
Mol. Wt.: 213,23

To a solution of stannane **15** (5.0 mg, 0.007 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL) at room temperature. The reaction was allowed to stir 15 h. After this time the reaction was concentrated under reduced pressure. The crude product was dissolved in water and added to a column containing Dowex-50 H^+ (WX8-200, 8% crosslinking, 100-200 wet mesh). The product was eluted with NH_4OH (1M). Evaporation, followed by passage through a column of Amberlite CG-50 with water afforded, after evaporation, (−)-kainic acid **3** (1.5 mg, quantitative) as a white solid. $[\alpha]_D^{25}$ = −14.0 (c = 0.15 in H_2O) [lit.[2] $[\alpha]_D$ = −13.9 (*c* 0.18, H_2O)]. All spectroscopic data were consistent with literature values.[2]

(−)-Isodomoic acid B (2B)



$C_{15}H_{21}NO_6$
Mol. Wt.: 311,33

To a solution of stannane **15** (19.0 mg, 0.0266 mmol) and bromide **16** (12.5 mg, 0.053 mmol) in degassed DMF (250 µl) was added $PdCl_2(CH_3CN)_2$ (50 µL of a solution 0.015 M in DMF, 0.00075 mmol). The reaction was stirred 5 h at room temperature and water was added. The aqueous layer was extracted twice with ethyl acetate. The organic layers were combined and washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (petroleum ether/ethyl acetate 95/5 to 9/1) gave the diene **17B** (11.0 mg, 71%) as a colourless oil.; ^{1}H NMR (500 MHz, $CDCl_3$), 2 rotamers, δ_H : 6.60-6.53 (1H, m, COC=C*H*), 5.14-5.09 (1H, m, CHC=C*H*), 3.98 (0.3H, d, *J* 4.5, NC*H*), 3.97 (0.7H, d, *J* 4.5, NC*H*), 3.61 (0.7H, dd, *J* 13.5, 9.5, NC*Ha*H), 3.57 (0.3H, dd, *J* 13.5, 9.5, NC*Ha*H), 3.47 (0.7H, dd, *J* 13.0, 10.0, NCH*Hb*), 3.39 (0.3H, dd, *J* 13.5, 10.0, NCH*Hb*), 3.02-2.94 (1H, m, C*H*), 2.87 (2H, bt, J 7.0, CHC*H*$_2$CH), 2.76-2.69 (1H, m, C*H*), 2.16-2.11 (2H, m, C*H*$_2$CO), 1.80 (3H, bs, C*H*$_3$), 1.61 (3H, bs, C*H*$_3$), 1.50-1.43 (36H, m, 4*t*Bu); m/z (ES$^+$) 602 (100%, MNa$^+$); Found MNa$^+$ 602.3672, $C_{32}H_{53}NO_8$ requires MNa$^+$ 602.3663.

To a solution of diene **17B** (11.0 mg, 0.0190 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL) at room temperature. The reaction was allowed to stir 15 h. After this time the reaction was concentrated under reduced pressure to afford the trifluoroacetate salt of isodomoic acid B (8.0 mg, quant.) as an oil. $[\alpha]_D^{25}$ = +2.8 (c = 1.0 in H_2O). ^{1}H and ^{13}C NMR data are reported in Table S1.

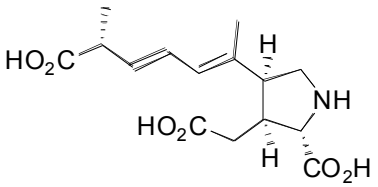
The salt was dissolved in water and added to a column containing Dowex-50 H$^+$ (WX8-200, 8% crosslinking, 100-200 wet mesh). The product was eluted with NH_4OH (1M). Evaporation, followed by passage through a column of Amberlite CG-50 with water afforded, after evaporation, (–)-isodomoic acid B, $[\alpha]_D^{25}$ = ï 2.0 (c 1.0 in H_2O) [lit^3 [$\alpha\{_D^{25}$ = –8.1 (c = 0.14 in H_2O)]; m/z (ES$^-$) 310 (100%, M–H$^+$); Found M–H$^+$ 310.1304, $C_{15}H_{21}NO_6$ requires M–H$^+$ 310.1296. ^{1}H and ^{13}C NMR data are reported in Table S1.

Table S1: Spectroscopic comparison of natural[3] and synthetic (–)-isodomoic acid B.

^{1}H NMR (D_2O)		
Natural[3] (360 MHz)	TFA salt of synthetic material (500 MHz)	Neutralised synthetic material (400 MHz)
6.70 (1H, t, *J* 7.0)	6.77 (1H, t, *J* 7.5)	6.73 (1H, t, *J* 7.5)
5.25 (1H, t, *J* 7.0)	5.29 (1H, t, *J* 7.1)	5.23 (1H, t, *J* 7.1)
4.04 (1H, d, *J* 3.5)	4.33 (1H, bs)	4.02 (1H, d, *J* 3.9)
3.60 (1H, dd, *J* 12.0, 7.0)	3.63 (1H, dd, *J* 11.8, 7.1)	3.56 (1H, dd, *J* 12.1, 7.5)
3.46 (1H, dd, *J* 12.0, 12.0)	3.48 (1H, dd, *J* 11.8, 10.0)	3.42 (1H, dd, *J* 11.9, 10.3)
2.99 (1H, dddd, *J* 8.6, 7.5, 7.0, 3.5)	3.20-3.12 (2H,m)	3.07-3.00 (2H, m)
2.91 (3H, m)	3.00 (2H, dd, *J* 7.2, 7.2)	2.96 (2H, dd, *J* 7.5, 7.5)
2.38 (2H, d, *J* 7.0)	2.55 (dd, 1H, *J* 17.0, 6.6)	2.43-2.40 (2H, m)
	2.49 (dd, 1H, *J* 17, 6.9)	1.80 (3H, s)
1.82 (3H, s)	1.84 (3H, s)	1.67 (3H, s)
1.72 (3H, s)	1.71 (3H, s)	

^{13}C NMR (D_2O)	
Natural[3] (90 MHz)	Synthetic (100 MHz)
176.3	176.3
173.1	173.3
173.0	172.4
142.6	142.6
132.2	132.0
125.5	128.4
125.3	125.6
65.7	65.0
47.8	47.8
47.3	47.5
41.6	41.4
33.9	33.8
28.1	28.1
16.8	16.8
12.5	12.5

(−)-Isodomoic acid E (2E)



$C_{15}H_{21}NO_6$
Mol. Wt.: 311,33

To a solution of stannane **15** (19.0 mg, 0.0266 mmol) and vinyl iodide *E*-**18** (11 mg, 0.040 mmol) in degassed DMF (250 µl) was added $PdCl_2(CH_3CN)_2$ (50 µL of a solution 0.015 M in DMF, 0.00075 mmol). The reaction was stirred 48 h at 50°C and water was added. The aqueous layer was extracted twice with ethyl acetate. The organic layers were combined and washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (petroleum ether/ethyl acetate 98/2 to 95/5) gave the diene **17E** (7.9 mg, 51%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$), 2 rotamers, δ_H : 6.33-6.27 (1H, m, CO_2tBuCHC*H*=), 5.75 (1H, bd, *J* 13.5, CH=C*H*CH=), 5.70-5.62 (1H, m, CHC=C*H*), 3.98 (0.3H, d, *J* 5.0, NC*H*), 3.96 (0.7H, d, *J* 4.5, NC*H*), 3.64 (0.7H, dd, *J* 13.5, 9.0, NC*Ha*H), 3.58 (0.3H, dd, *J* 13.5, 9.0, NC*Ha*H), 3.51 (0.7H, dd, *J* 13.5, 10.5, NCH*Hb*), 3.43 (0.3H, dd, *J* 13.0, 9.5, NCH*Hb*), 3.11-2.98 (2H, m, 2C*H*), 2.78-2.73 (1H, m, C*H*), 2.19-2.13 (2H, m, CH_2CO), 1.70 (3H, bs, CH_3), 1.47-1.44 (36H, m, 4*t*Bu), 1.23 (3H, d, *J* 9.0, CHCH_3); m/z (ES$^+$) 602 (100%, MNa$^+$); Found MNa$^+$ 602.3664, $C_{32}H_{53}NO_8$ requires MNa$^+$ 602.3663.

To a solution of diene **17E** (7.9 mg, 0.0136 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL) at room temperature. The reaction was allowed to stir 15 h. After this time the reaction was concentrated under reduced pressure to afford the trifluoroacetate salt of isodomoic acid E (5.8 mg, quant.) $[\alpha]_D^{25} = -5.1$ (c = 1 in H_2O). ^{1}H and ^{13}C NMR data are reported in Table S2.

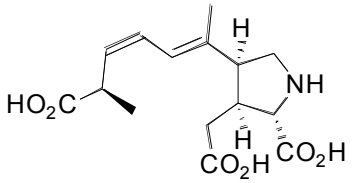
The salt was dissolved in water and added to a column containing Dowex-50 H$^+$ (WX8-200, 8% crosslinking, 100-200 wet mesh). The product was eluted with NH_4OH (1M). Evaporation, followed by passage through a column of Amberlite CG-50 with water afforded, after evaporation, (–)-isodomoic acid E, $[\alpha]_D^{25} = -20.0$ (c = 0.5 in H_2O) [lit[4] $[\alpha]_D^{25} = -19.5$ (H_2O, *c* not reported)]; m/z (ES$^-$) 310 (100%, M–H$^+$); Found M–H$^+$ 310.1286, $C_{15}H_{21}NO_6$ requires M–H$^+$ 310.1296. ^{1}H and ^{13}C NMR data are reported in Table S2.

Table S2: Spectroscopic comparison of natural[4] and synthetic (–)-isodomoic acid E.

^{1}H NMR (D_2O)		
Natural[4] at pH = 1.8 (300 MHz)	TFA salt of synthetic material (400 MHz)	Neutralised synthetic material (400 MHz)
6.55 (1H, dd)	6.55 (1H, dd, *J* 15.2, 10.5)	6.54 (1H, dd, *J* 15.1, 10.5)
5.95 (1H, d)	5.95 (1H, d, *J* 10.5)	5.94 (1H, d, *J* 10.6)
5.87 (1H, dd)	5.87 (1H, dd, *J* 15.3, 8.0)	5.87 (1H, dd, *J* 15.3, 7.5)
4.36 (1H, d)	4.32 (1H, d, *J* 4.0)	4.14 (1H, bs)
3.72 (1H, dd)	3.72 (1H, dd, *J* 12.0, 7.2)	3.70 (1H, dd, *J* 11.3, 7.1)
3.58 (1H, dd)	3.57 (1H, dd, *J* 11.8, 10.3)	3.55 (1H, dd, *J* 11.2)
3.38 (1H, dq)	3.38 (1H, dq, *J* 7.1, 7.1)	3.38 (1H, dq, *J* 7.1, 7.1)
3.26 (1H, dddd)	3.28-3.18 (2H, m)	3.12-3.20 (2H, m)
3.23 (1H, ddd)		
2.57 (1H, dd)	2.57 (1H, dd, *J* 16.9, 7.0)	2.48 (2H, d, *J* 6.9)
2.53 (1H, dd)	2.53 (1H, dd, *J* 17.0, 7.0)	
1.85 (3H, s)	1.85 (3H, s)	1.85 (3H, s)
1.33 (3H, d)	1.33 (3H, d, *J* 7.0)	1.32 (3H, d, *J* 7.0)

^{13}C NMR (D_2O)	
Natural[4] (75 MHz)	Synthetic (100 MHz)
181.9	182.0
177.7	177.8
173.3	173.9
135.6	135.3
134.2	134.2
130.0	129.6
129.5	129.5
66.1	66.4
49.6	49.5
49.2	48.8
45.0	45.0
43.3	43.3
35.3	35.3
18.9	18.9
18.7	18.7

(−)-Isodomoic acid F (2F)



$C_{15}H_{21}NO_6$
Mol. Wt.: 311,33

To a solution of stannane **15** (23.0 mg, 0.032 mmol) and vinyl iodide *Z*-**18** (14 mg, 0.046 mmol) in degassed DMF (250 µl) was added $PdCl_2(CH_3CN)_2$ (50 µL of a solution 0.023 M in DMF, 0.00075 mmol). The reaction was stirred 48 h at 50°C and water was added. The aqueous layer was extracted twice with ethyl acetate. The organic layers were combined and washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (petroleum ether/ethyl acetate 98/2 to 95/5) gave the diene **17F** (9.0 mg, 49%) as a colourless oil. ; 6.28-6.20 (1H, m, CO_2tBuCHC*H*=), 5.75 (1H, m, CH=C*H*CH=), 5.49-5.38 (1H, m, CHC=C*H*), 3.99 (1H, bd, *J* 4.4, NC*H*), 3.71-3.36 (3H, m, NCH_2 + C*H*), 3.10-3.01 (1H, m, C*H*), 2.81-2.73 (1H, m, C*H*), 2.19-2.13 (2H, m, CH_2CO), 1.73 (3H, bs, CH_3), 1.48-1.43 (36H, m, 4*t*Bu), 1.18 (3H, d, *J* 9.2, CHCH_3); m/z (ES^+) 602 (100%, MNa^+); Found MNa^+ 602.3672, $C_{32}H_{53}NO_8$ requires MNa^+ 602.3664.

To a solution of diene **17F** (9.0 mg, 0.0190 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL) at room temperature. The reaction was allowed to stir 15 h. After this time the reaction was concentrated under reduced pressure to afford the trifluoroacetate salt of isodomoic acid F (6.5 mg, quant.) as an oil. $[\alpha]_D^{25}$ = −33.2 (c = 1 in H_2O) [lit[4] for neutral amino acid $[\alpha]_D^{25}$ = −85 (H_2O, *c* not reported)]; m/z (ES^-) 310 (100%, $M–H^+$); Found $M–H^+$ 310.1287, $C_{15}H_{21}NO_6$ requires $M–H^+$ 310.1296. ^1H and ^{13}C NMR data are reported in Table S3.

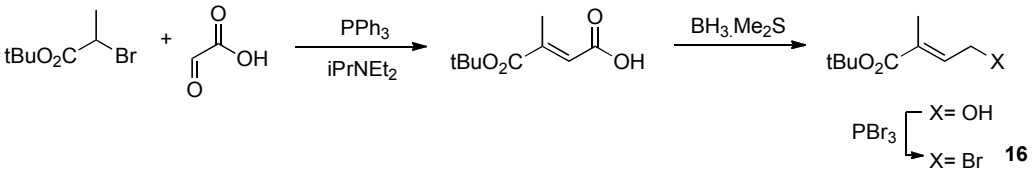
Table S3: Spectroscopic comparison of natural[4] and synthetic (–)-isodomoic acid F.

^{1}H NMR (D_2O)	
Natural[4] at pH = 1.6 (300 MHz)	TFA salt of synthetic material (400 MHz)
6.47 (1H, dd)	6.47 (1H, dd, *J* 11.0, 11.0)
6.19 (1H, d)	6.19 (1H, bd, *J* 11.0)
5.60 (1H, dd)	5.60 (1H, dd, *J* 10.2, 10.2)
4.39 (1H, d)	4.43 (1H, d, *J* 5.0)
3.77 (1H, dd)	3.78-3.71 (2H, m)
3.73 (1H, dq)	
3.63 (1H, dd)	3.63 (1H, dd, *J* 1.9, 9.8)
3.32 (1H, ddd)	3.36-3.25 (2H, m)
3.27 (1H, dddd)	
2.63 (1H, dd)	2.64 (1H, dd, *J* 17.0, 7.0)
2.53 (1H, dd)	2.53 (1H, dd, *J* 17.0, 7.0)
1.87 (3H, s)	1.87 (3H, s)
1.33 (3H, d)	1.33 (3H, d, *J* 7.0)

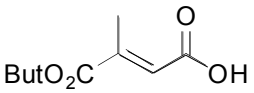
^{13}C NMR (D_2O)	
Natural[4] (75 MHz)	Synthetic (100 MHz)
181.8	182.1
177.6	177.8
173.1	173.7
136.7	136.7
133.1	133.0
127.8	127.8
125.2	124.9
66.0	66.3
50.0	49.9
49.3	48.9
43.3	43.3
40.7	40.6
35.3	35.3
19.7	19.7
18.6	18.6

Preparation of the side chain 16[5]

Synthetic route



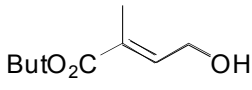
(*E*)-3-(*tert*-butoxycarbonyl)but-2-enoic acid



$C_9H_{14}O_4$
Mol. Wt.: 186,21

To a solution of *tert*-butyl methyl 2-bromopropionate (7.94 ml, 47.83 mmol) in acetonitrile (65 ml) was added triphenylphosphine (11.41 g, 43.52 mmol). The mixture was heated to 65 °C for 24 h. The reaction was cooled to 0 °C and diisopropylethylamine (15.17 ml, 87.05 mmol) was added followed by portion-wise addition of glyoxylic acid monohydrate (8.01 g, 87.05 mmol). The reaction was stirred for 2 h at 0 °C and 72 h at room temperature. EtOAc (34ml) was added to the reaction mixture extracted with $NaHCO_3$ until no more gas was evolved. The aqueous phase was washed with EtOAc (5 x 10 ml) and acidified to pH 1-2 with conc. HCl and then extracted with EtOAc once more (5 x 10 ml) The combined organic layers were dried over $MgSO_4$ and the solvent removed to afford the title compound (3.00 g, 33 %) as an orange oil. ν_{max}(film)/cm^{-1} 2980,1699, 1643; ^{1}H NMR (300 MHz; $CDCl_3$) δ_H : 6.70 (1 H, m, C*H*), 2.23 (3 H, d, *J* 3.0, CH_3), 1.51 (9 H, s, $(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C : 171.6, 166.0, 148.0, 124.8, 82.2, 27.4, 14.6; *m/z* (ES^-) 185 (100 %, MH^-); Found M^-: 185.0819 $C_9H_{14}O_4$ requires M^- 185.0817.

(*E*)-*tert*-butyl 4-hydroxy-2-methylbut-2-enoate

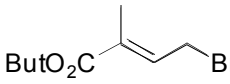


$C_9H_{16}O_3$
Mol. Wt.: 172,22

To a solution of the above acid (1.00 g, 5.37 mmol) in THF (20 ml) was added dropwise BH_3 .Me_2S (2M in toluene, 5.91 ml) at -15 °C. The reaction was gradually allowed to warm to rt and stirred for 16 h before being quenched with methanol (2 ml). The solvent was removed *in vacuo*, more methanol was added and the solvent removed again. This was repeated once more and the crude residue was purified by column chromatography (7:3 EtOAc-Petrol) to afford the title compound (631 mg, 68 %). ν_{max}(film)/cm^{-1} 3500, 2966, 2927, 1708; ^{1}H NMR

(300 MHz; $CDCl_3$) δ_H: 6.73 (1 H, t, *J* 6.0, C*H*), 4.33 (2 H, d, *J* 6.2, CH_2OH), 1.80 (3 H, s, CH_3), 1.49 (9 H, s, $(CH_3)_3$); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C : 138.6, 92.9, 59.7, 31.2, 29.7, 28.1, 12.7.

(*E*)-*tert*-butyl 4-bromo-2-methylbut-2-enoate

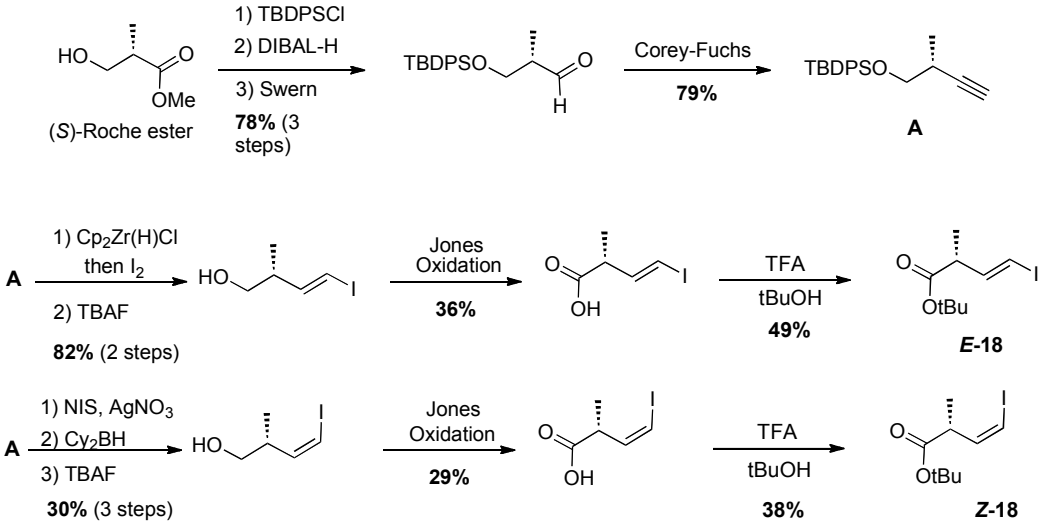


$C_9H_{15}BrO_2$
Mol. Wt.: 235,12

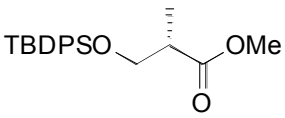
Tribromophosphine (22 μl, 0.23 mmol, 0.33 eq) in CCl_4 (2 ml), was added to a solution of (E)-methyl 4 hydroxy-2-methylbut-2-enoate (120 mg, 0.70 mmol, 1 eq) in CCl_4 (0.2 ml) at 0 °C. The reaction was stirred at rt for 2 h and quenched with $NaHCO_3$ (0.5 ml). The aqueous layer was extracted with pentane (2 x 2ml), the combined organic layers were washed with brine and dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the title compound[87] (35 mg, 21 %) as a pale yellow oil. R_F (Petrol-EtOAc 7:3) 0.66; ν_{max}(film)/cm^{-1} 2981, 2928, 1709; ^{1}H δ_H (400 MHz; $CDCl_3$) 6.82 (1 H, tq, *J* = 8.7, 1.5, C*H*), 4.02 (2 H, d, *J* = 8.4, CH_2), 1.88 (3 H, s, CH_3), 1.49 (9 H, s, $(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 166.4, 133.8, 81.0, 28.1, 28.0, 26.4, 12.2.

Preparation of the side chains *E*-18 and *Z*-18

Synthetic route



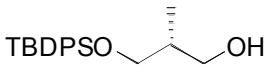
Methyl (2*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropionate



$C_{21}H_{28}O_3Si$
Mol. Wt.: 356,53

To a solution of (*S*)-Roche ester (2.5 ml, 22.6 mmol) and imidazole (605 mg, 8.89 mmol, 1.05 eq) in DMF (30 ml) at 0 °C was added TBDPSCl (5.85, 24.9 mmol) over 10 min. The solution was stirred for 2 h before quenching with water and pentane. The aqueous layer was extracted twice with pentane and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate 9:1) to afford the title compound (7.9 g, 98 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H : 7.56-7.80 (4 H, m, Ar), 7.31-7.36 (6 H, m, Ar), 3.70 (2H, m, C*H*$_2$), 3.61 (3 H, s, C*H*$_3$), 2.59-2.70 (1 H, m, C*H*), 1.08 (3 H, d, *J* 6.9, C*H*$_3$), 0.96 (9 H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$), δ_C : 175.4, 135.6, 133.6, 133.5, 129.7, 127.7, 65.9, 51.5, 42.5, 26.7, 19.3,1 3.5; *m/z* (ES^+) 379 (100 %, MNa).The data correspond to those described in the literature.[6]

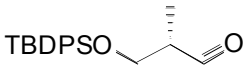
(*S*)-3-[(*tert*-butyldiphenyl)silyloxy]-2-methylpropanol



$C_{20}H_{28}O_2Si$
Mol. Wt.: 328,52

To a solution of ester (7.9 g, 22.19 mmol) in CH_2Cl_2 (80 ml) at -15 °C was added dropwise DIBAlH (1.0 M toluene solution, 57.3 ml). The mixture was stirred for 2h at -15 °C then poured into Rochelle's salt and the mixture stirred vigorously until the organic phase was clear. The aqueous phase was extracted with diethyl ether and the combined organic layers were washed with brine, dried over magnesium sulfate and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (9:1 petroleum ether/ethyl acetate) to afford the title compound (6.5 g, 89 %) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H : 7.68 (4 H, m, Ar*H*), 7.46-7.34 (6 H, m, Ar*H*), 3.73 (1 H, dd, *J* 5.5, 10, C*H*), 3.68 (2 H, d, *J* = 6.0, CH_2), 3.60 (1 H, t, *J* 9, C*H*), 2.00 (1 H, m, C*H*), 1.06 (9 H, s, $(CH_3)_3$), 0.83 (3 H, d, *J* 7.0, CH_3), 2.48 (1 H, t, *J* 3.0, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$), δ_C : 135.6, 133.2, 129.8, 127.8, 68.7, 67.6, 37.4, 26.9, 19.2 and 13.2; *m/z* (ES^+) 351.0 (100 %, MNa^+). The data correspond to those described in the literature.[7]

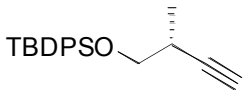
(2*S*)-3-(*tert*-butyldiphenylsilylsilyloxy)-2-methylpropanal



$C_{20}H_{26}O_2Si$
Mol. Wt.: 326,5

To a solution of oxalyl chloride (2.06 ml, 23.61 mmol, 2.2 eq) in CH_2Cl_2 (200 ml) cooled to -78 °C was added a solution of DMSO (4.26 ml, 60 mmol, 2.8 eq) in CH_2Cl_2 (10 ml) followed by stirring for approx 5 mins before adding alcohol (6.5 g, 19.8 mmol) in CH_2Cl_2 dropwise and the mixture stirred for 1h 20 mins. Et_3N (11.0 mL, 100 mmol) was then added. The mixture was stirred at rt for 30 min before being quenched with $NaHCO_3$ and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over sulfate magnesium, filtered and the solvent removed. The residue was purified by column chromatography (9:1 Petrololeum ether/ ethyl acetate) to afford the title aldehyde (5.75 g, 89 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H : 9.70 (1 H, d, *J* = 1.8, C*H*O), 7.62-7.56 (4 H, m, Ar*H*), 7.37-7.29 (6 H, m, Ar*H*), 3.81 (2 H, m, CH_2), 2.22-2.44 (1 H, m, C*H*), 1.03 (3 H, d, *J* = 6.9, CH_3), 0.97 (9 H, s, $(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C : 204.4, 135.6, 133.2, 129.8, 127.8, 64.2, 60.4, 48.83, 26.8, 10.31; Found MNa^+ 349.1601, $C_{20}H_{26}O_2Si$ requires MNa^+ 349.1594. The data correspond to those described in the literature.[6]

(*R*)-2-methylbut-3-ynyloxy)(*tert*-butyl)diphenylsilane A

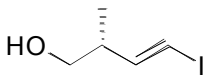


$C_{21}H_{26}OSi$
Mol. Wt.: 322,52

CBr_4 (9.95 g, 30 mmol) in CH_2Cl_2 (10 ml) was added to a suspension of zinc powder (1.96 g, 30 mmol) and triphenylphosphine (7.9 g, 30 mmol) in CH_2Cl_2 (30 ml) at 0 °C and the mixture stirred for 20 min. A solution of the above aldehyde (3.7 g, 11.3 mmol) in CH_2Cl_2 (10 ml) was then added and the mixture stirred for 4h at rt. The reaction mixture was poured into pentane (150 ml) filtered to remove the precipitate and concentrated *in vacuo*.

The crude residue was dissolved in THF (20 ml) and cooled to -78 °C. n-BuLi (2.3 M in hexanes, 14.0 ml, 28.25 mmol) was added to the solution. After being stirred for 1H at -78°C the reaction was quenched with $NaHCO_3$ and extracted twice with ether. The organic layers were combined and washed with brine, dried over magnesium sulfate and concentrated. The crude residue was purified by column chromatography (100 % pentane to 95:5 pentane-ethyl acetate) to afford the title alkyne **A** (2.88 g, 79 %) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$), δ_H : 7.62-7.59 (5 H, m Ar), 7.36-7.28 (6 H, m, Ar), 3.66 (1 H, dd, *J* 5.7, 9.6. C*H*), 3.47 (1 H, dd, *J* 7.5, 9.6, C*H*), 2.65-2.52 (1 H, m, C*H*), 1.95 (1 H, d, *J* 2.4, C*H*), 1.16 (3 H, d, *J* = 6.9, CH_3), 0.99 (9 H, s, (CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), δ_C : 135.6, 133.63, 129.65, 127.7, 86.58, 69.0, 67.5, 28.8, 26.8, 19.3 and 17.4; *m/z* (ES^+) 345.0 (100 %, MNa^+); Found: MNa^+ 345.1632, $C_{21}H_{26}ONaSi$ requires MNa^+ 345.1645.

(*R*,*E*)-4-iodo-2-methylbut-3-en-1-ol



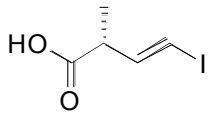
C_5H_9IO
Mol. Wt.: 212,03

To a solution of protected alkyne **A** (1 g, 3.10 mmol) in CH_2Cl_2 (11 ml) at rt was added the Schwartz reagent (960 mg, 3.72 mmol). The solution was stirred for 25 min, iodine (983 mg, 3.87 mmol) was added and the reaction stirred for 30 min before being quenched with Na_2SO_3 (16 ml). The aqueous phase was extracted twice with CH_2Cl_2, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to afford the crude vinyl iodide.

The crude product (1.4 g, 3.10 mmol) was dissolved in THF (5 ml) and TBAF (1M in THF, 4.65 ml, 4.65 mmol) was added dropwise to the above mixture and the reaction stirred for 1 h before being quenched with water. The aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 75:25) to afford the title alcohol (510 mg, 82 %) as an oil. ^{1}H

NMR (400 MHz, $CDCl_3$) δ_H : 6.40 (1 H, dd, *J* 14.6, 8.0, C*H*), 6.09 (1 H, d, *J* 14.6, C*H*), 3.47-3.38 (2 H, m, CH_2), 2.41-2.31 (1 H, m, C*H*), 1.48 (1 H, brs, CH_2OH), 0.96 (3 H, d, *J* 6.8, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C : 148.5, 76.1, 66.5, 43.4, 15.5.

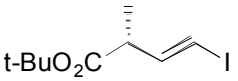
(*R*,*E*)-4-iodo-2-methylbut-3-enoic acid



$C_5H_7IO_2$
Mol. Wt.: 226,01

Jones reagent was prepared by the addition of H_2SO_4 (2.3 ml) added dropwise to a solution of CrO_3 (2.78 g) in H_2O (7.7 ml). The above alcohol (520 mg, 2.45 mmol) was dissolved in acetone (15 ml) and cooled to -10 °C. Jones reagent (3 ml) was added dropwise to the mixture and the reaction stirred for 1 h. *i*-PrOH (10 eq) was added to the reaction followed by water (30 ml). The aqueous phase was extracted thrice with EtOAc and then washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 7:3) to afford the title compound (200 mg, 36 %) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.63-6.60 (1 H, dd, *J* 8.0, 14.4, C*H*), 6.31 (1 H, d, *J* 14.6, C*H*), 3.24-3.17 (1 H, m, C*H*), 1.32 (3 H, d, *J* = 7.2, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C : 178.8, 143.1, 78.2, 45.7, 16.3. *m/z* (ES^-) 225 (100 %, M^-); Found: M^- 224.9426, $C_5H_6O_2$ requires M^- 224.9418.

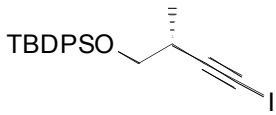
(*R*,*E*)-tert-butyl 4-iodo-2-methylbut-3-enoate *E*-18



$C_9H_{15}IO_2$
Mol. Wt.: 282.1187

TFA anhydride (252 µl, 1.8, mmol) was added dropwise to a solution of acid (80 mg, 0.35 mmol) in *t*-butanol (1 ml), the mixture was stirred at rt for 1 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted thrice with ethyl acetate and then washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/ethyl acetate 9:1) to afford the ester ***E*-18** (48 mg, 36 %) as an colourless oil. $[\alpha]_D^{25}$ = –3.2 (c = 1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3435.4, 2971.5, 2923.4, 1722.9 ^{1}H NMR (400 MHz, $CDCl_3$) δ_H : 6.59 (1H, dd, *J* 14.4, 8.0, =C*H(I)*), 6.19 (1H, d, *J* = 14.4, CHC*H*=), 3.06-2.99 (1H, m, CH_3CH), 1.44 (9H, s, tBu), 1.22 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 172.0, 144.6, 81.0, 47.0, 27.0 (3C), 16.5. Found: $(M\text{-}tBu)^+$, 208.9448, $C_9H_{15}OI$ requires $(M\text{-}tBu)^+$, 208.9458.

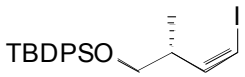
((*R*)-4-iodo-2-methylbut-3-ynyl oxy)(*tert*- butyl)diphenylsilane



$C_{21}H_{25}IOSi$
Mol. Wt.: 448,41

Alkyne **A** (1.00 g, 3.11 mmol) was dissolved in acetone (13 ml) and treated with *N*-iodosuccinimide (770 mg, 3.42 mmol) and $AgNO_3$ (53 mg, 0.31 mmol). The mixture was stirred at rt for 2.5 h then diluted with hexane (21 ml) and filtered through a pad of celite. Water was added and the aqueous layer was extracted with hexane. The organic layers were combined, washed with brine and dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the title compound (1.28 g, 92 %) as a yellow oil which turned crystalline on standing. mp 56 °C; ν_{max}(film)/cm^{-1} 2929, 2857, 1427; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H : 7.61-7.59 (4 H, m, Ar*H*), 7.36-7.29 (6 H, m, Ar*H*), 3.65-3.60 (1 H, m, C*H*), 3.50-3.45 (1 H, m, C*H*), 2.80-2.70 (1 H, m, C*H*), 1.14 (3 H, d, *J* 7.2, CH_3), 0.99 (9 H, s, (CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C : 135.7, 133.6, 129.6, 127.7, 67.5, 31.2, 26.8, 19.3, 17.2; *m/z* (ES$^+$) 471.0 (100 %, MNa$^+$); Found (M-tBu)$^+$: 390.9993 $C_{21}H_{25}OISi$ requires (M-tBu)$^+$ 391.0010.

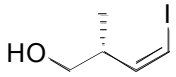
((*R*,*Z*)-4-iodo-2-methylbut-3-enyloxy)(*tert*-butyl)diphenylsilane



$C_{21}H_{27}IOSi$
Mol. Wt.: 450,43

BH_3 .SMe_2 (2M in toluene 1.58 ml, 3.16 mmol) was added to a stirred solution of cyclohexene (0.64 ml, 6.33 mmol) in diethyl ether (3 ml) at 0 °C. The reaction mixture was stirred at rt for 1 h before adding the iodo-alkyne (473 mg, 1.05 mmol) in diethyl ether (2 ml) at 0 °C. After 1 h glacial acetic acid (1.30 ml) was added and the reaction stirred for 30 min at 0 °C. Diethyl ether was added followed by aqueous $NaHCO_3$ at 0 °C. The aqueous layer was washed with brine, dried ($MgSO_4$) filtered and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (Petroleum ether to 98:2 PE-EtOAc) to afford the title compound (264, mg, 58 %) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H : 7.68-7.65 (4H, m, Ar*H*), 7.43-7.35 (6H, m, Ar*H*), 6.20 (1H, d, *J* 8.1, C*H*), 6.06 (1H, t, *J* 7.5, C*H*), 3.58 (2H, dd, *J* 5.7, 2.1, CH_2), 2.83-2.68 (1H, m, C*H*), 1.05 (12H, br s, CH_3 and (CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C : 143.9, 135.6, 133.7, 129.6, 127.6, 81.7, 67.0, 42.2, 26.8, 19.3, 15.7; *m/z* (GCMS) 393 (M –^{t}Bu), Found: (M-tBu) 393.0168 $C_{17}H_{18}OISi$ requires (M-tBu) 393.0166).

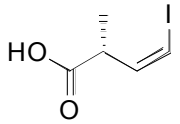
(*R*,*Z*)-4-iodo-2-methylbut-3-en-1-ol



C_5H_9IO
Mol. Wt.: 212,03

TBAF (2.16 ml) was added dropwise to a solution of protected alcohol (628 mg, 1.44 mmol) in THF (0.8 ml) at 0 °C. the mixture was stirred at rt for 2h and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography (Petroleum ether/Ethyl acetate 75:25) to afford the title compound (204 mg, 67 %) as a pale yellow oil. ν_{max}(film)/cm^{-1} 3349.1, 2914.7, 2851.4; ^{1}H NMR (400 MHz, $CDCl_3$), δ_H : 6.31 (1H, d, *J* = 6, C*H*), 6.04 (1H, d, *J* = 9, C*H*), 3.58-3.55 (2H, m, CH_2), 2.83-2.69 (1H, m, C*H*), 1.04 (3H, d, *J* = 6, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ_C : 143.4, 82.9, 66.5, 42.2, 15.4.

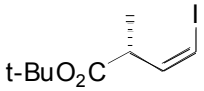
(*R*,*Z*)-4-iodo-2-methylbut-3-enoic acid



$C_5H_7IO_2$
Mol. Wt.: 226,01

Jones reagent was prepared by adding H_2SO_4 (0.88 ml) to a solution of CrO_3 (1.06 g) in water (2.96 ml). 1.15 ml of this solution was added dropwise to a solution of the above alcohol (200 mg, 0.94 mmol) in acetone (2.93 ml) at 0 °C. The mixture was stirred for 1 h at this temperature then isopropanol (0.70 ml, 10 eq) and water were added. The aqueous phase was extracted thrice with EtOAc and then washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography (75:25 Petroleum ether/Ethyl acetate) to afford the title compound (62 mg, 29 %) as a pale yellow oil. ν_{max}(film)/cm^{-1} 2981, 1706; ^{1}H NMR (400 MHz, $CDCl_3$), δ_H : 6.62 (1H, dd, *J* 14.4 8.0, CHC*H*=), 6.31 (1H, d, *J* 14.6, =C*H*(I)), 3.24-3.17 (1H, m, C*H*CH_3), 1.32 (3H, d, *J* 7.2, CH_3); δ_C (100 MHz; $CDCl_3$) 139.3, 84.3, 45.3, 30.9, 16.7.

***(R,Z)*-tert-butyl 4-iodo-2-methylbut-3-enoate *Z*-18**



$C_9H_{15}IO_2$
Mol. Wt.: 282.1187

TFA anhydride (0.19 ml, 1.37 mmol, 5 eq) was added dropwise to a stirring solution of the above acid (62 mg, 0.27 mmol) in *t*-butanol (0.8 ml). The mixture was stirred for 1.5 h at rt and monitored by TLC. The reaction was cooled to 0 °C and a further 3 eq of TFA anhydride was added and the mixture stirred for 30 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted thrice with ethyl acetate

and then washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate 7:3) to afford the title ester *Z*-**18** (18 mg, 38 % brsm) as a colourless oil. ν_{max}(film)/cm^{-1} 3434.0, 2975.7, 2921.8, 1723.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H : 6.34-6.296 (2H, m, CH_2), 3.39-3.29 (1H, m, C*H*), 1.45 (9H, s, (CH_3)$_3$), 1.25 (3H, d, *J* 9.0, CH_3); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C: 172.7, 140.5, 83.1, 80.9, 46.5, 28.0, 16.8.

Discussion of the structure of domoic acid and the isodomoic acids

X-ray crystallography proved the structure of domoic acid,[8] and showed that the originally proposed structure[8] had incorrect (*E* rather than *Z*) geometry at the trisubstituted double bond. It also confirmed the stereochemistry of the C5' side chain stereogenic centre. The originally proposed structure later turned out to be a natural product and was named isodomoic acid E, though with undefined C5' stereochemistry.[4] Ohfune's synthesis and proof of structure of domoic acid[8] was accompanied by a demonstration that natural isodomoic acid was not identical with either C5' epimer of the *E*,*E* isomer later referred to as isodomoic acid E, and Ohfune's 1982 paper describes a synthesis of a protected form of isodomoic acid E (though not isodomoic acid E itself).

Side chain C5' stereochemistry has never been unequivocally proved for isodomoic acids E and F, but since isodomoic acids E and F (and not their epimers) are produced by photolysis of (–)-domoic acid,[10] it is safe to assume that they have the same *R* stereochemistry as (–)-domoic acid at C5'.

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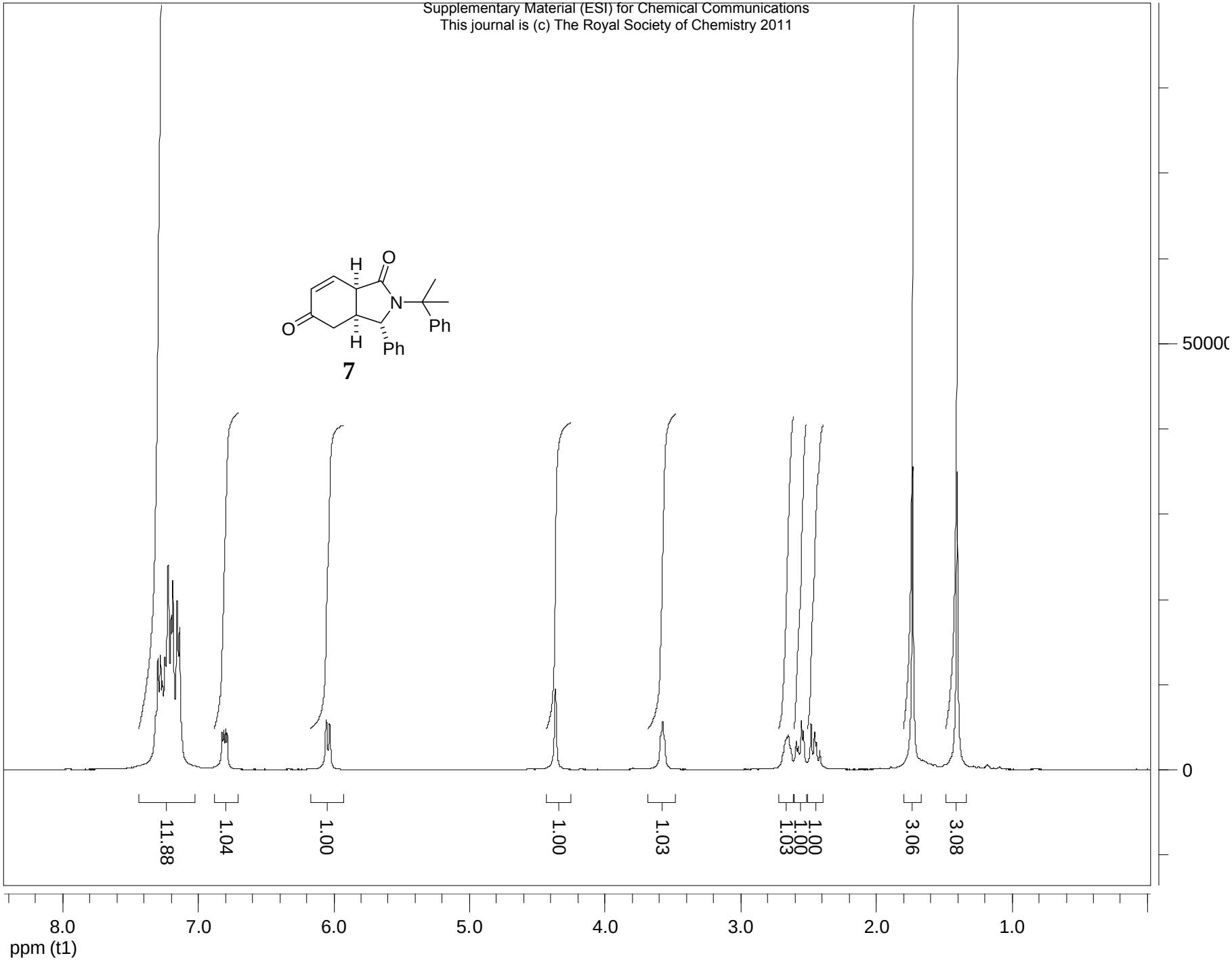

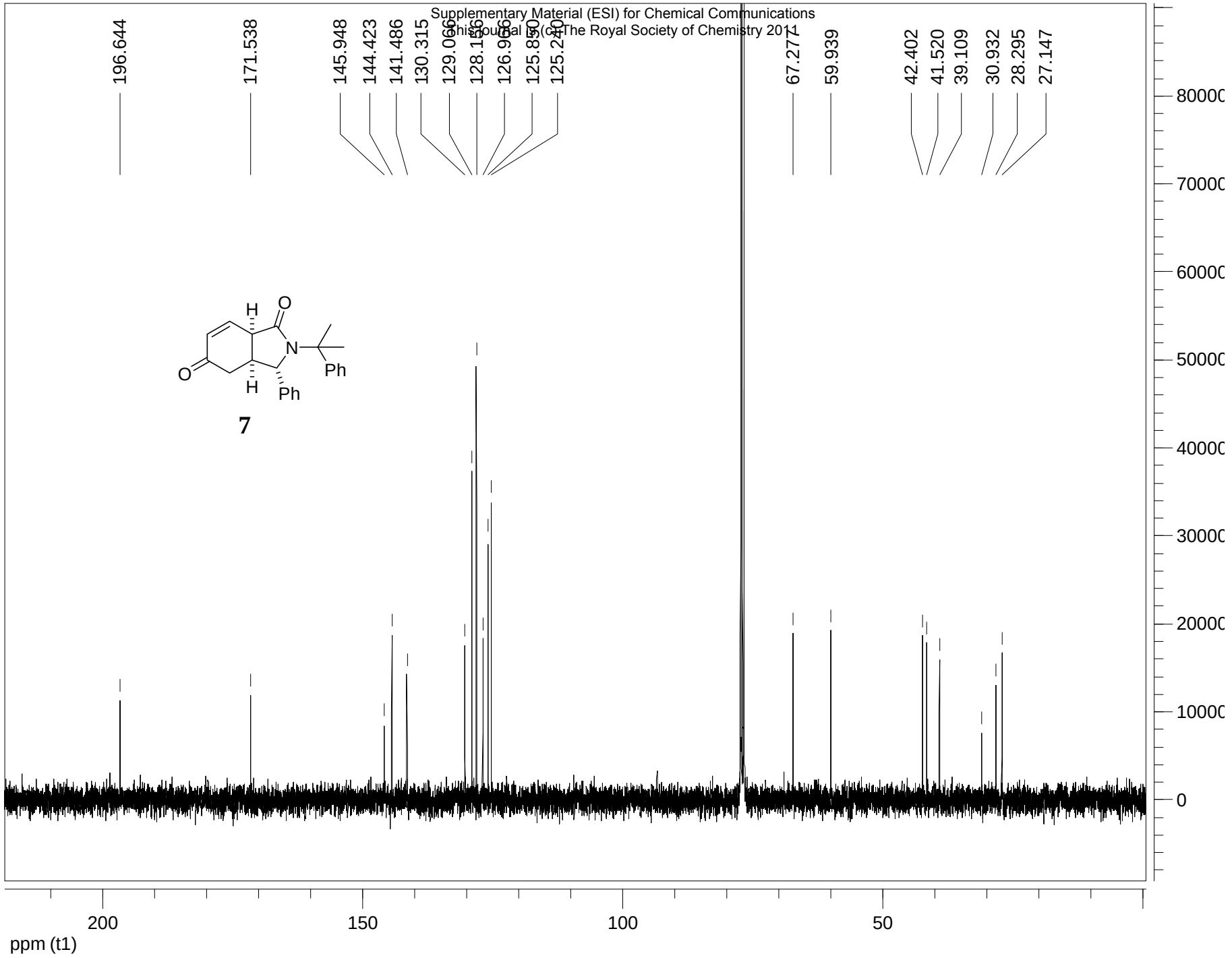

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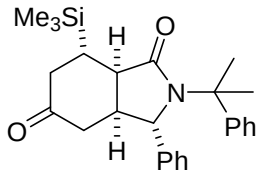

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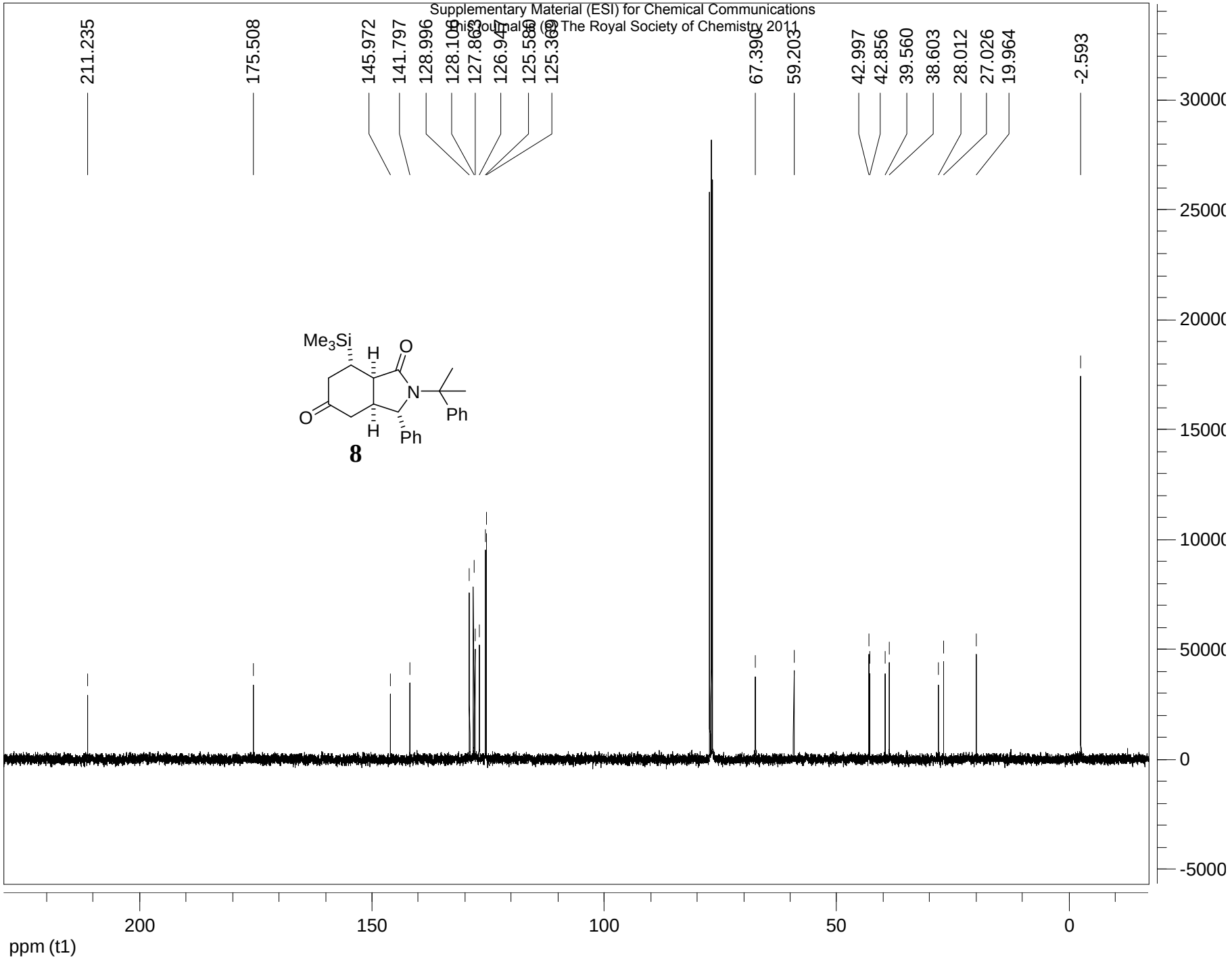
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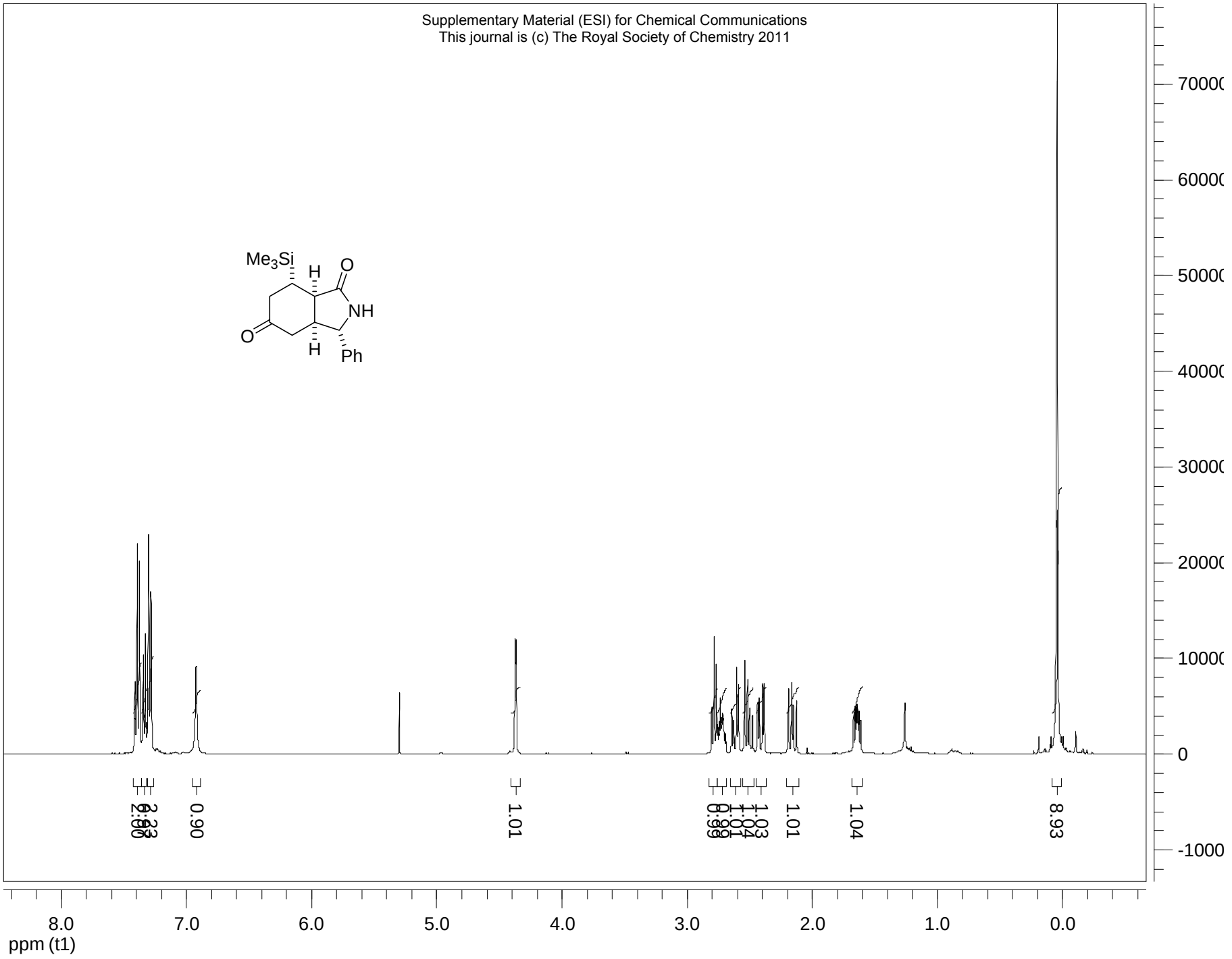

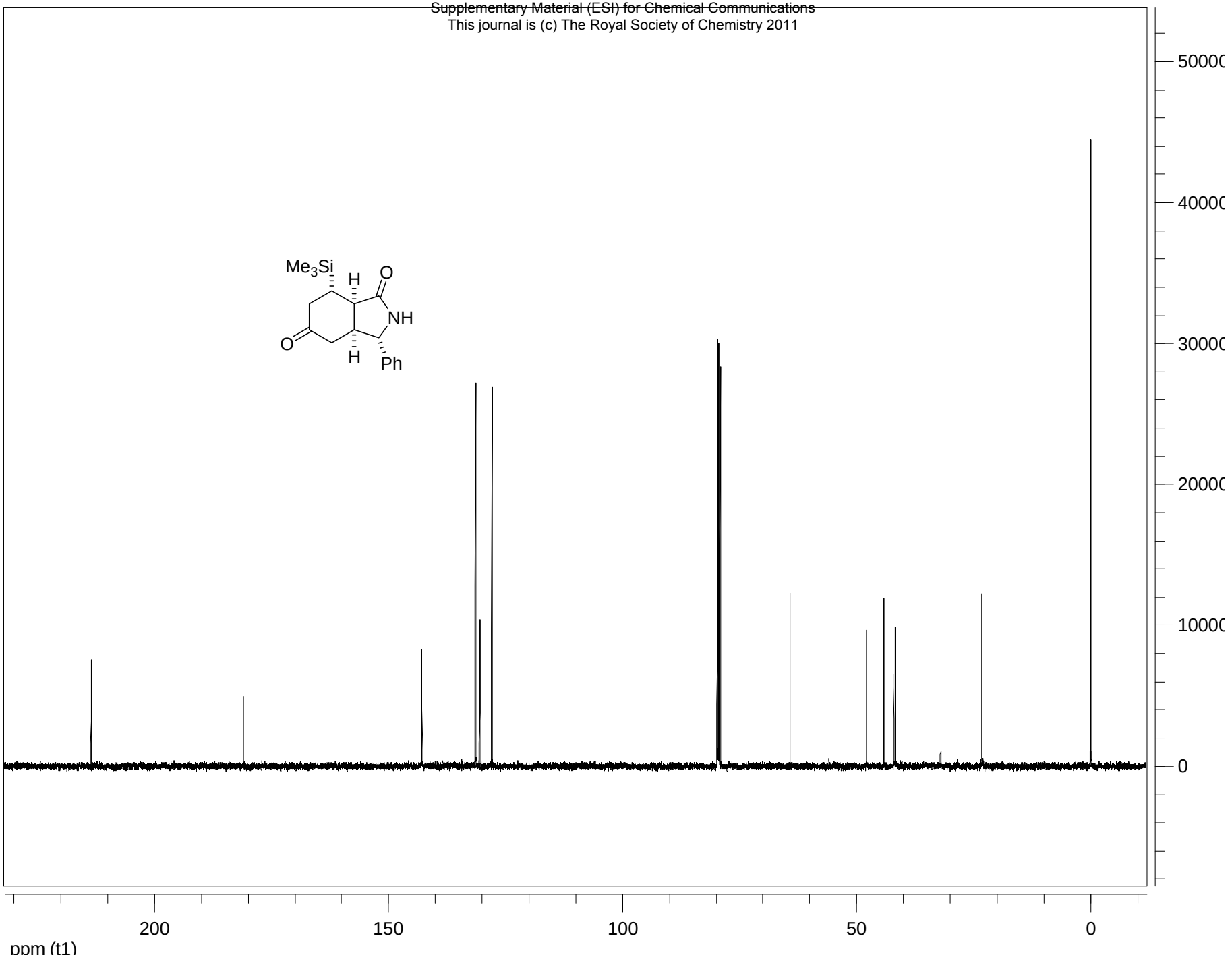

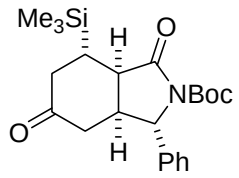

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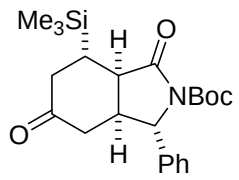
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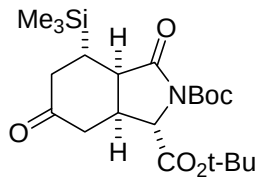
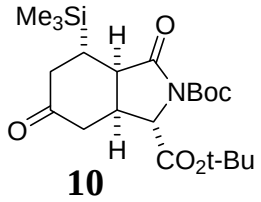
0
ppm (t1)

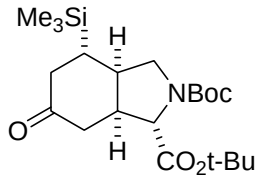

Me3Si
H
O
NBoc
O
H
CO2t-Bu

10

15000
10000
5000
0
1.00
1.03
1.02
1.01
1.08
1.03
1.10
1.05
18.12
9.39
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

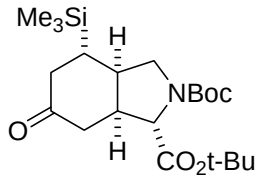


10



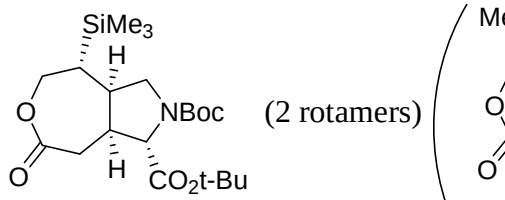
(2 rotamers)

11


Me3Si
H
NBoc
O
H
CO2t-Bu

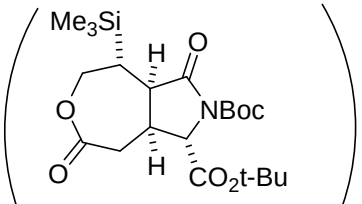
11

50000
40000
30000
20000
10000
0
200
150
100
50
0
ppm (t1)

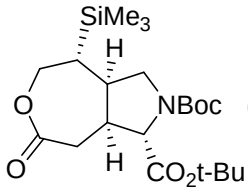


12

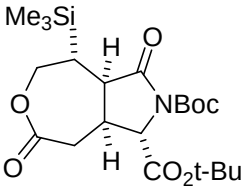
(2 rotamers)



+ ~10% of **X**

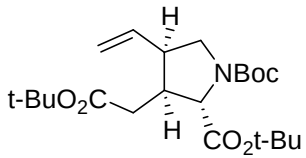


(2 rotamers)



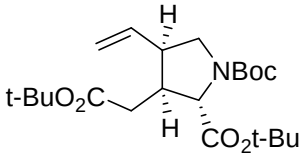
+ ~10% of **X**

12



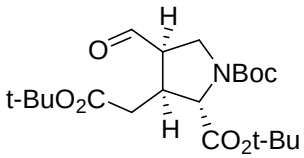
(2 rotamers)

13



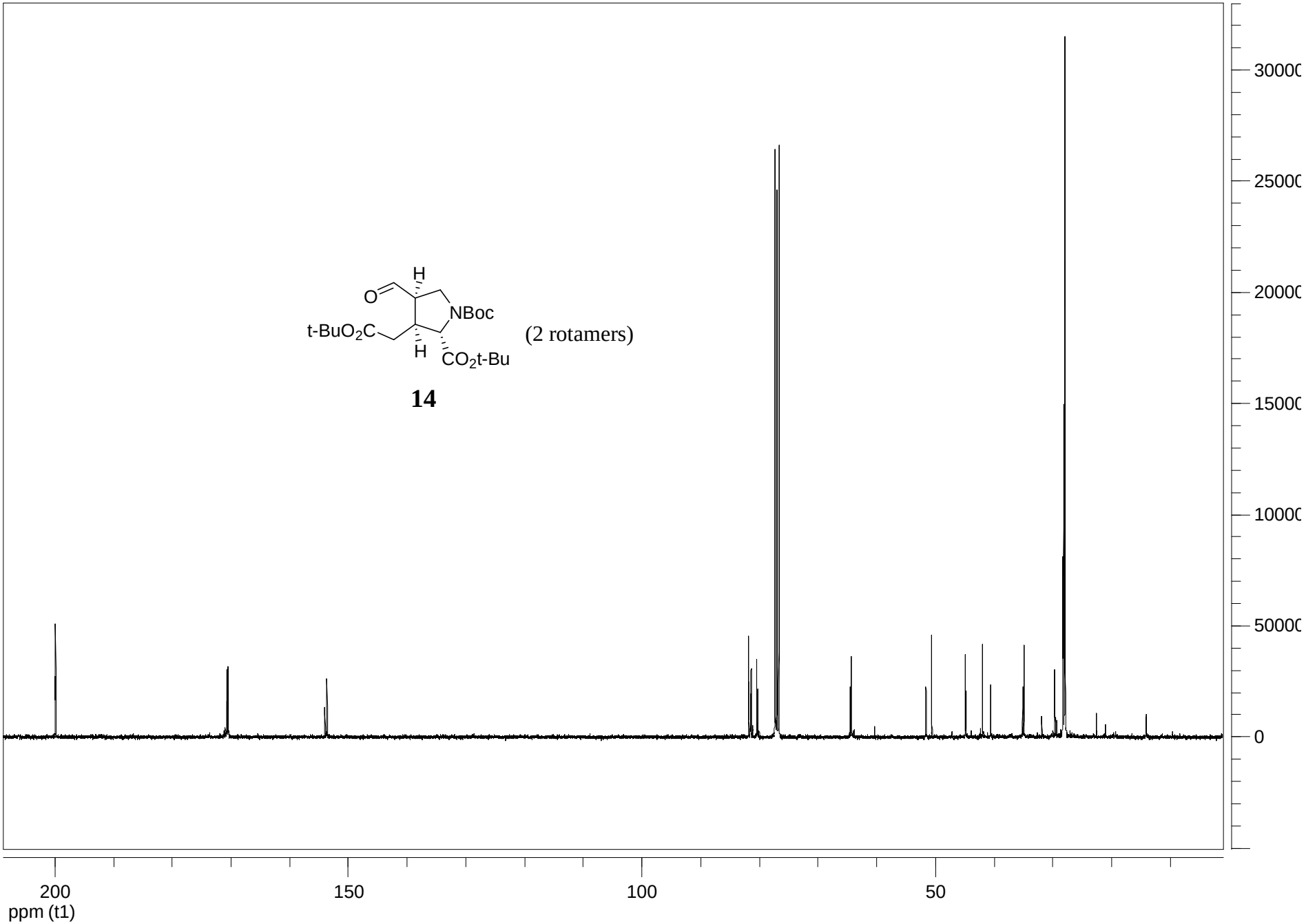
(2 rotamers)

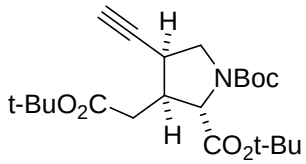
13



(2 rotamers)

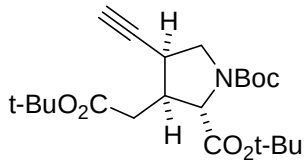
14


H
O
NBoc
t-BuO2C
H
CO2t-Bu
(2 rotamers)
14
30000
25000
20000
15000
10000
50000
0
200
150
100
50
ppm (t1)



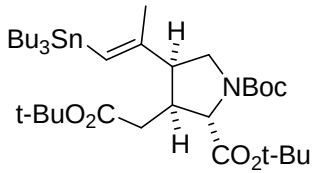
(2 rotamers)

4



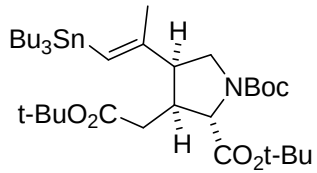
(2 rotamers)

4



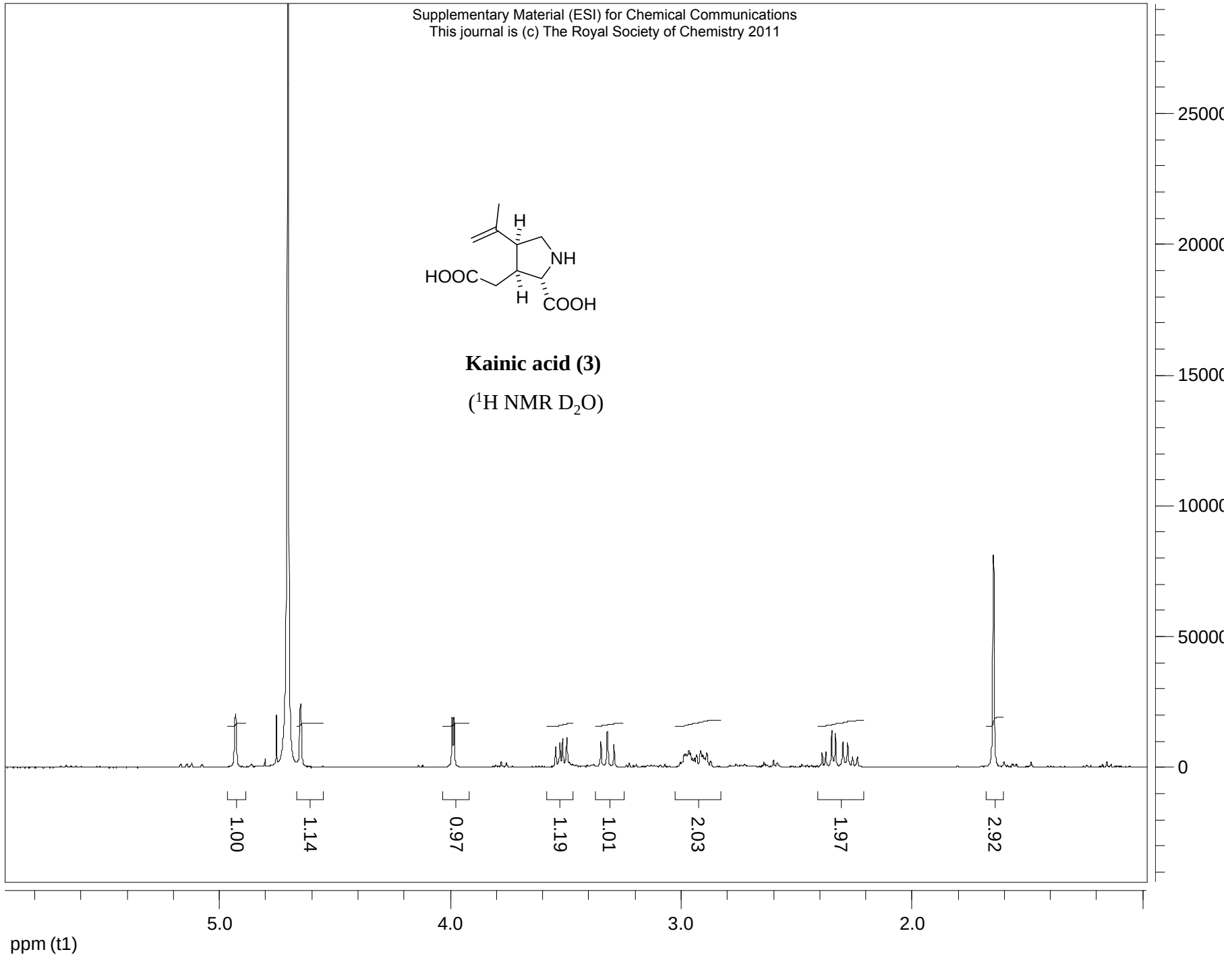
(2 rotamers)

15



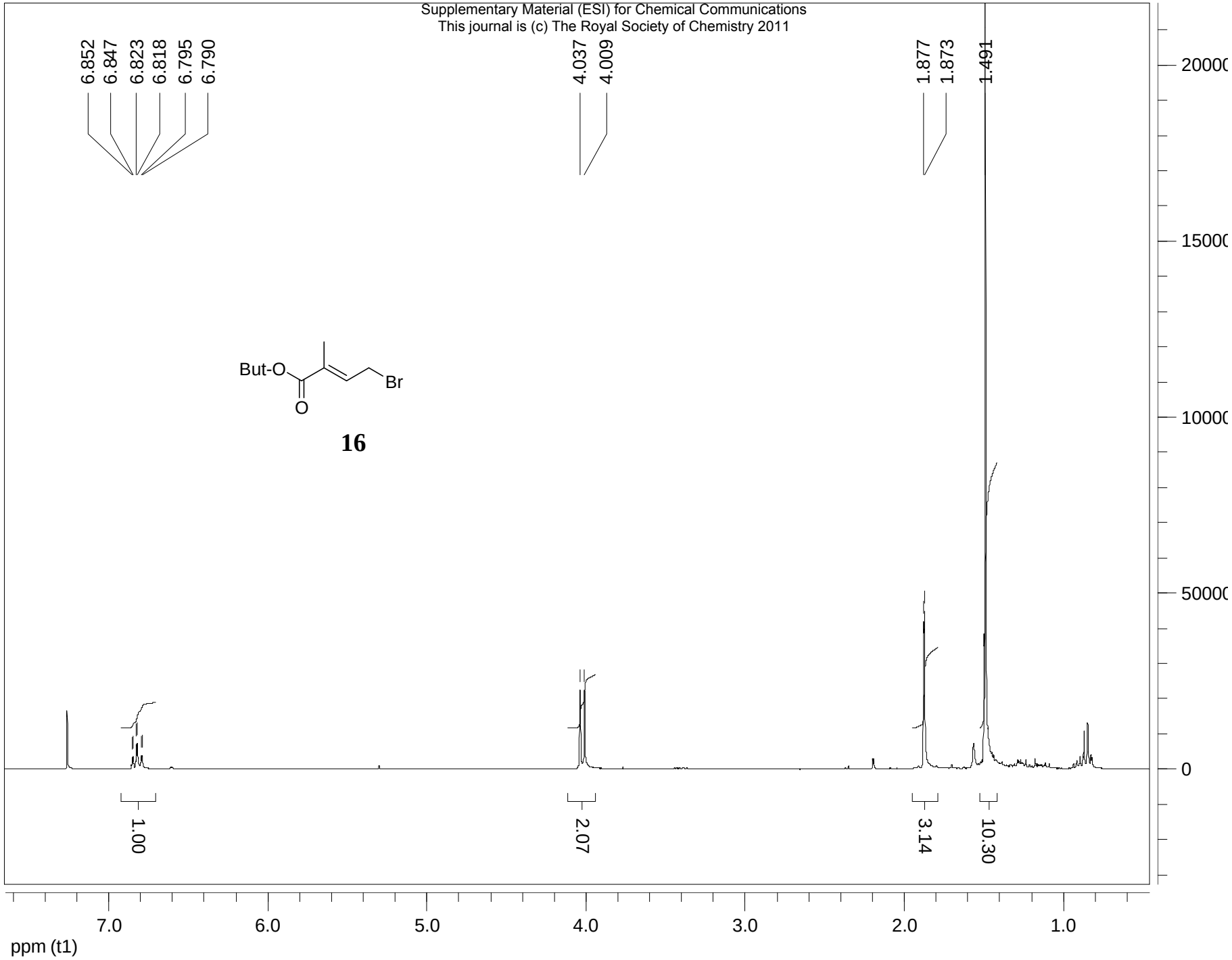
(2 rotamers)

15

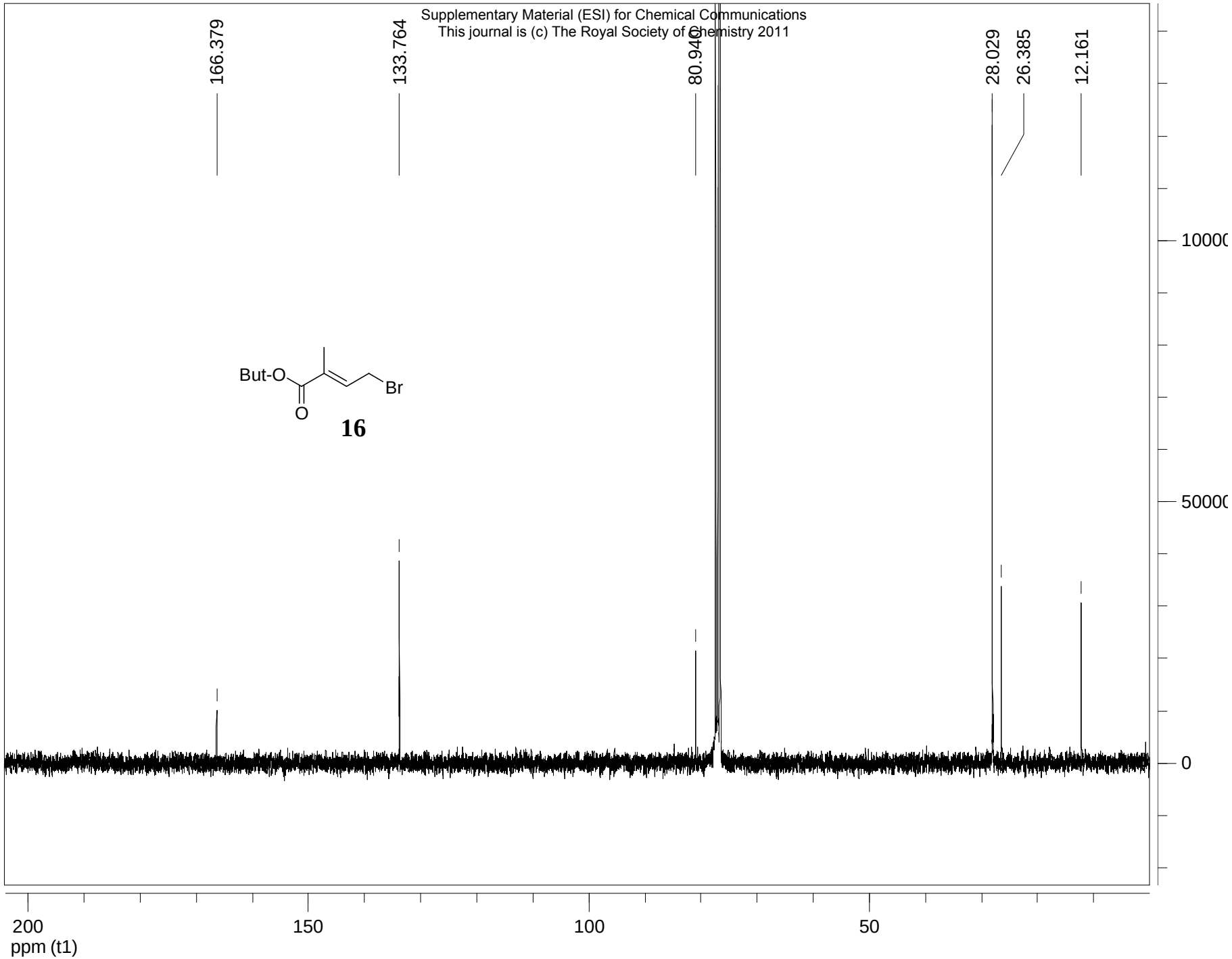


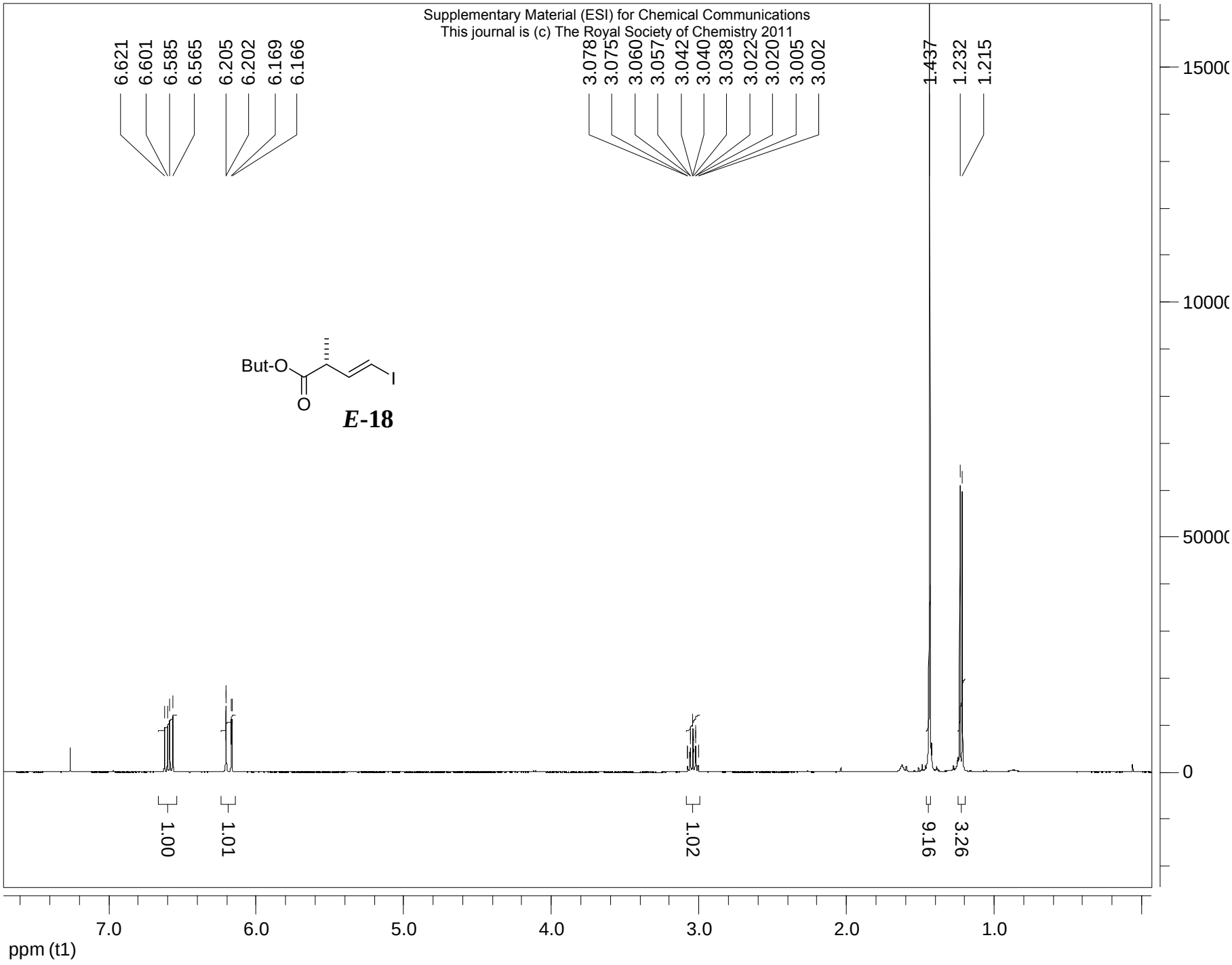
Kainic acid (3)

(^{1}H NMR D_2O)

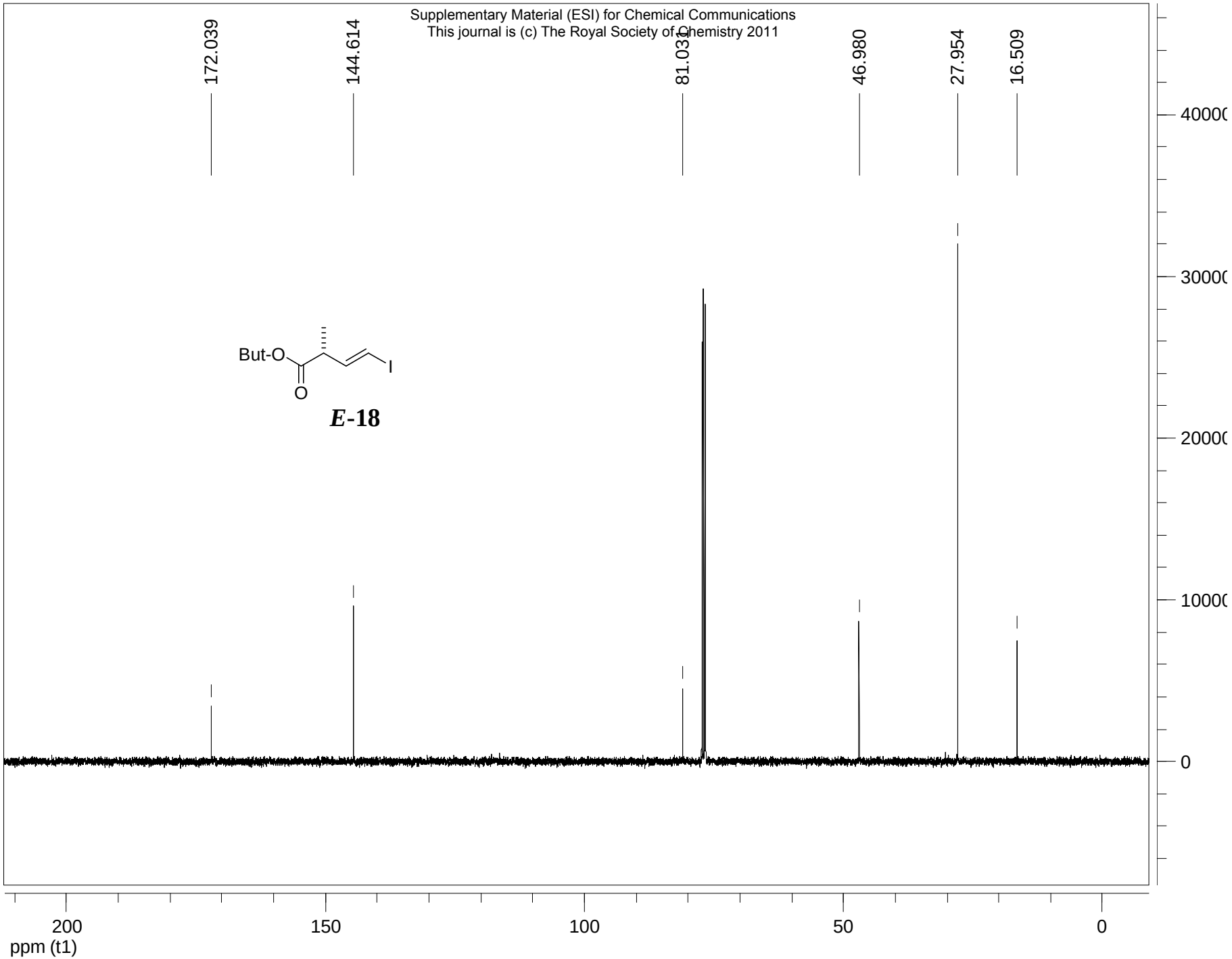


16

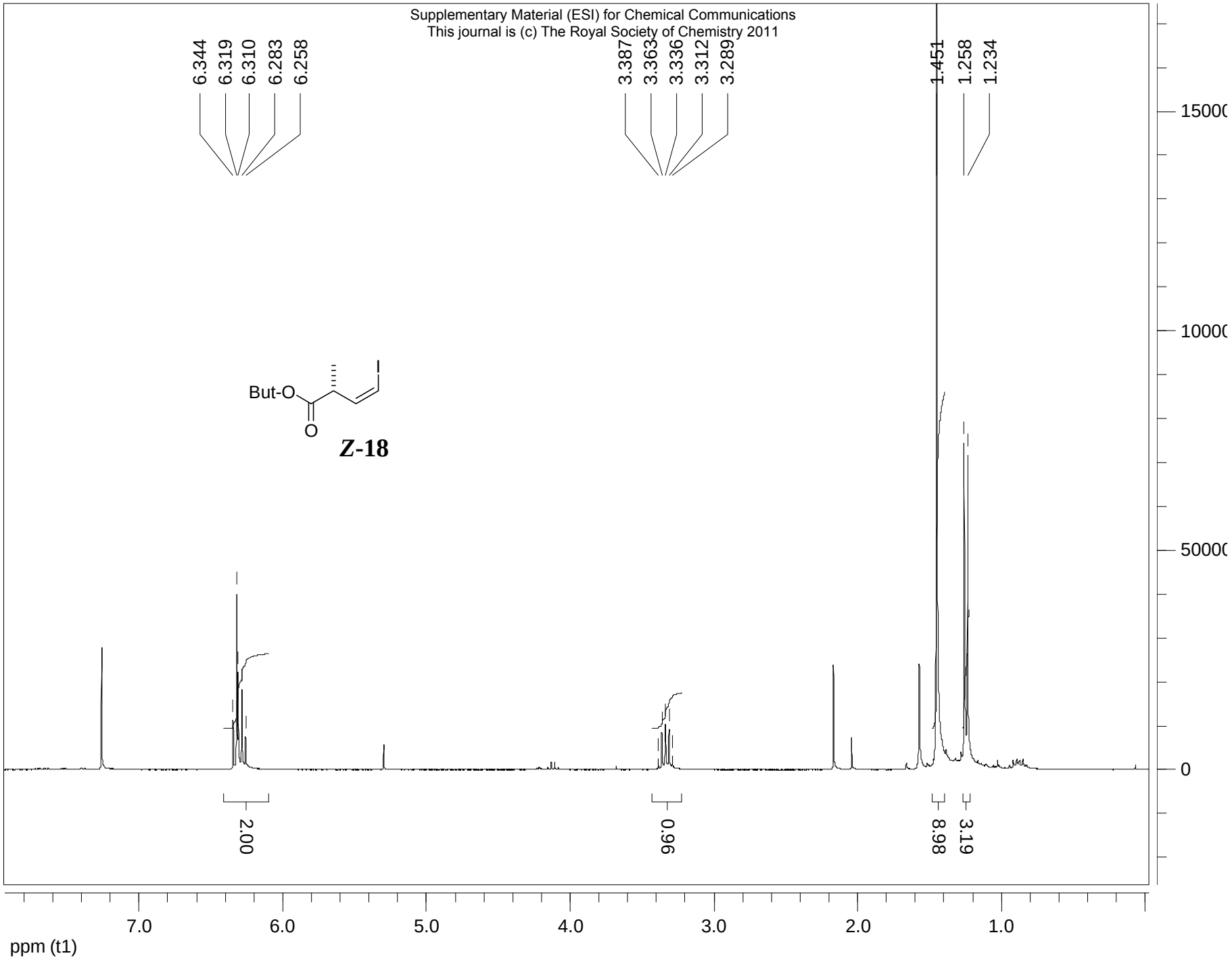




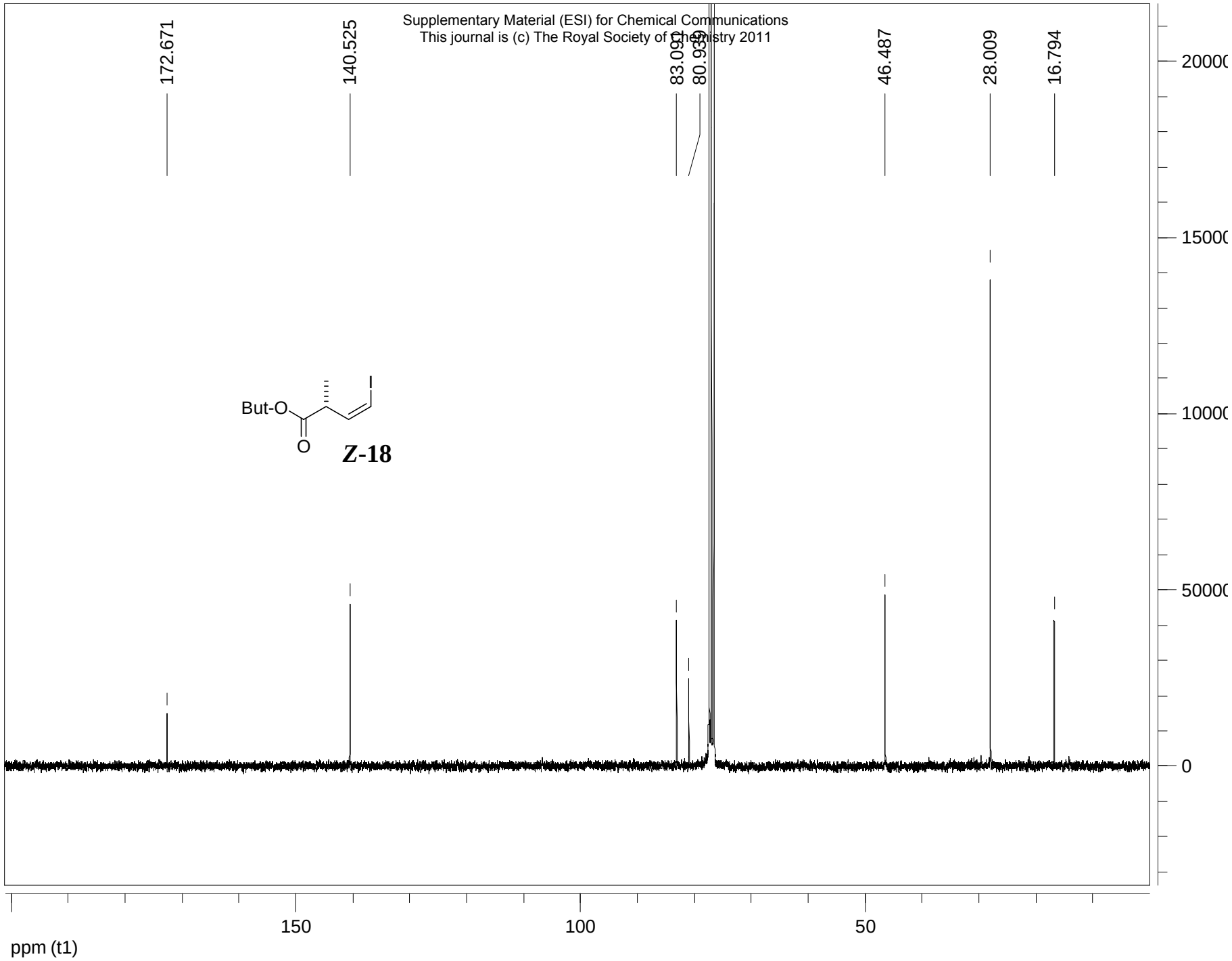
***E*-18**



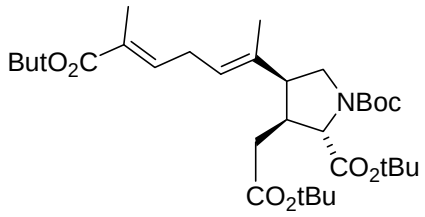
***E*-18**



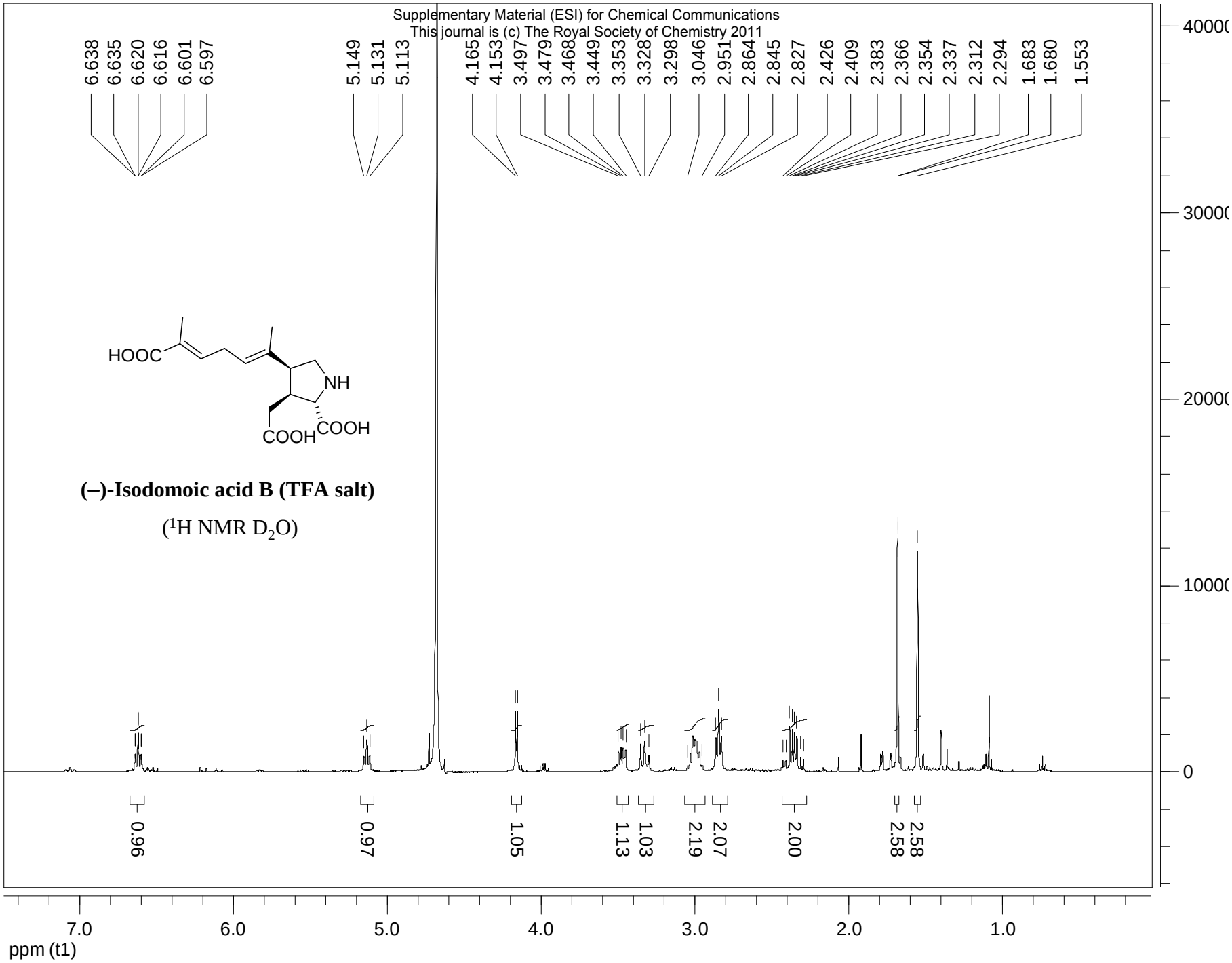
***Z*-18**



***Z*-18**

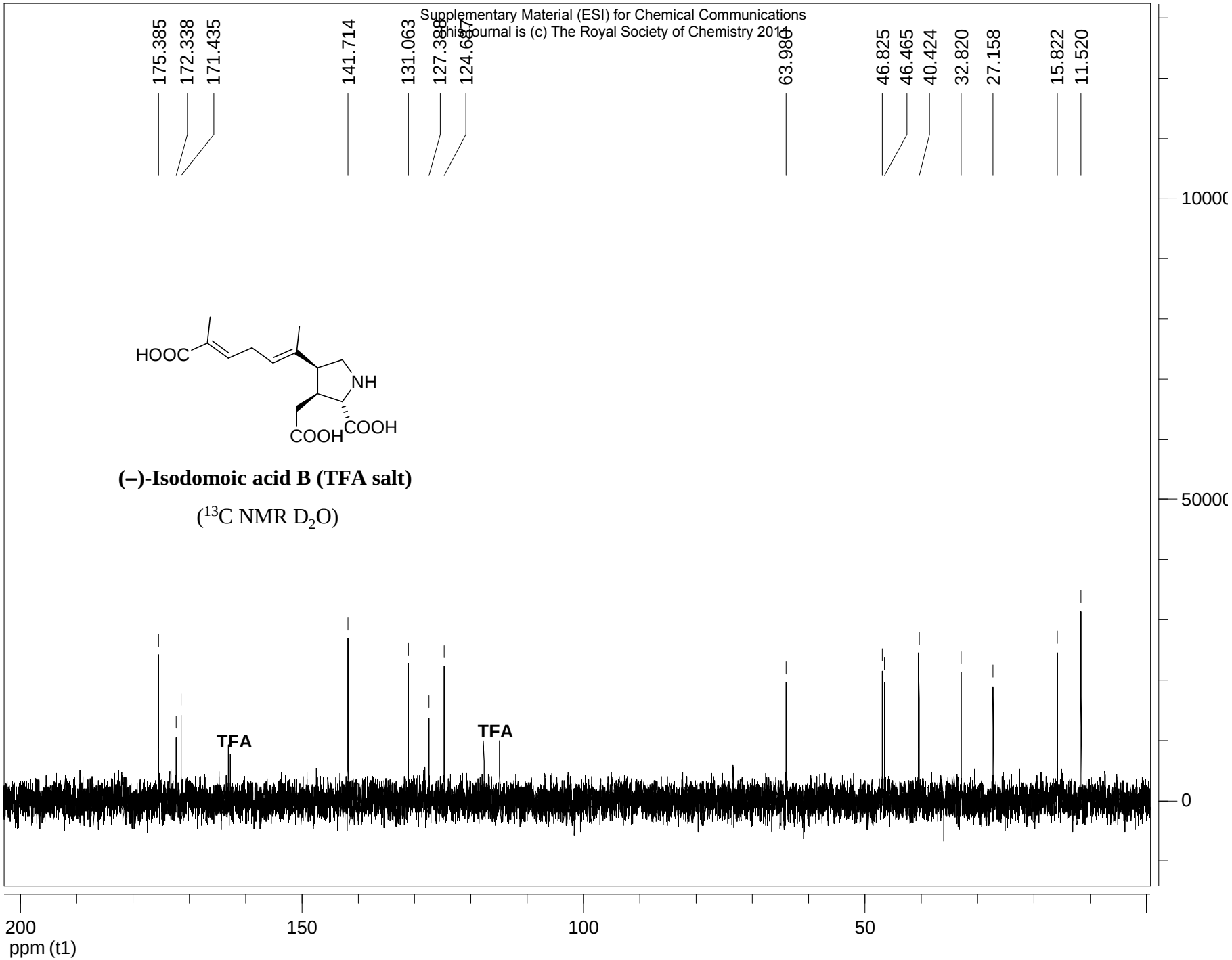


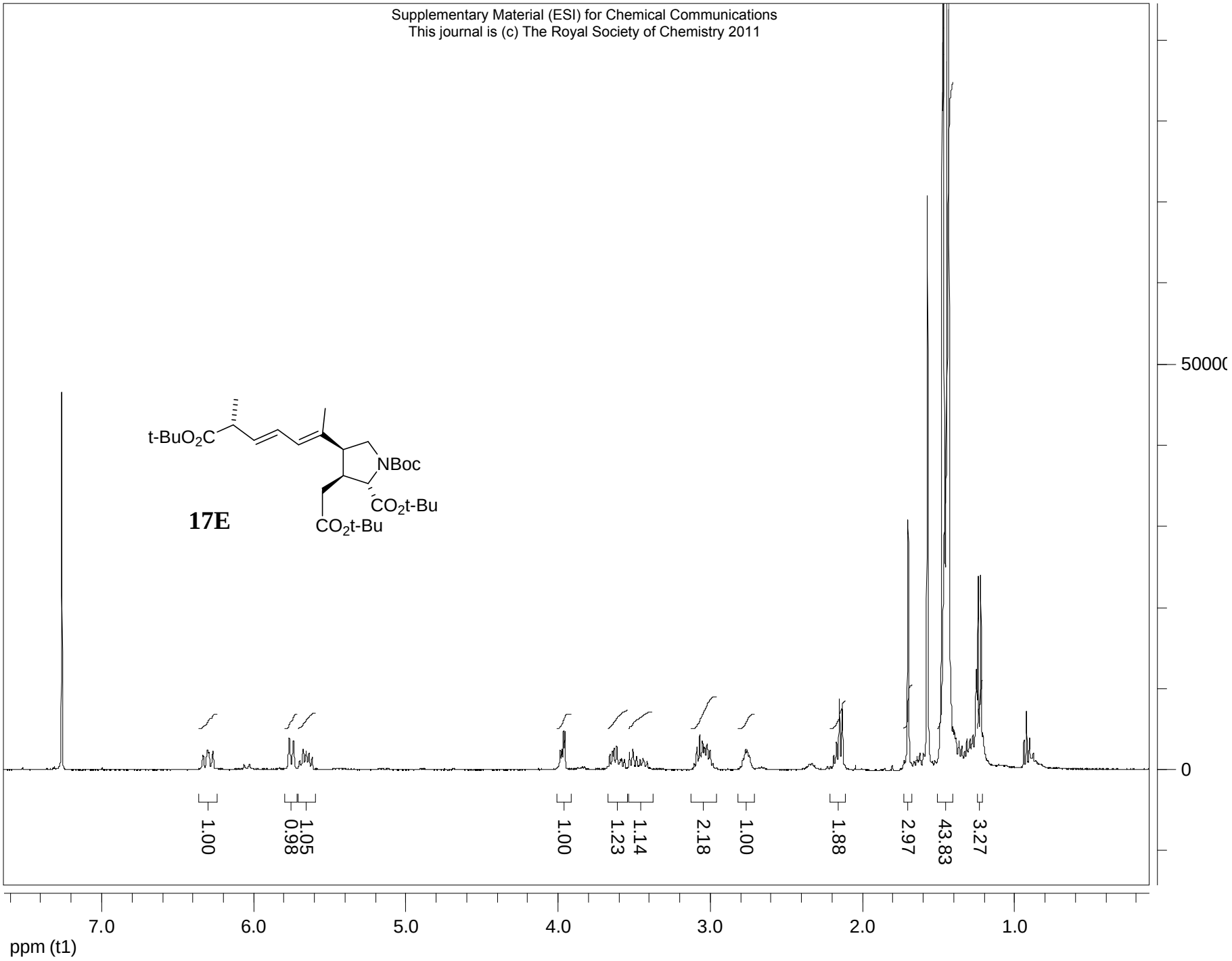
17B

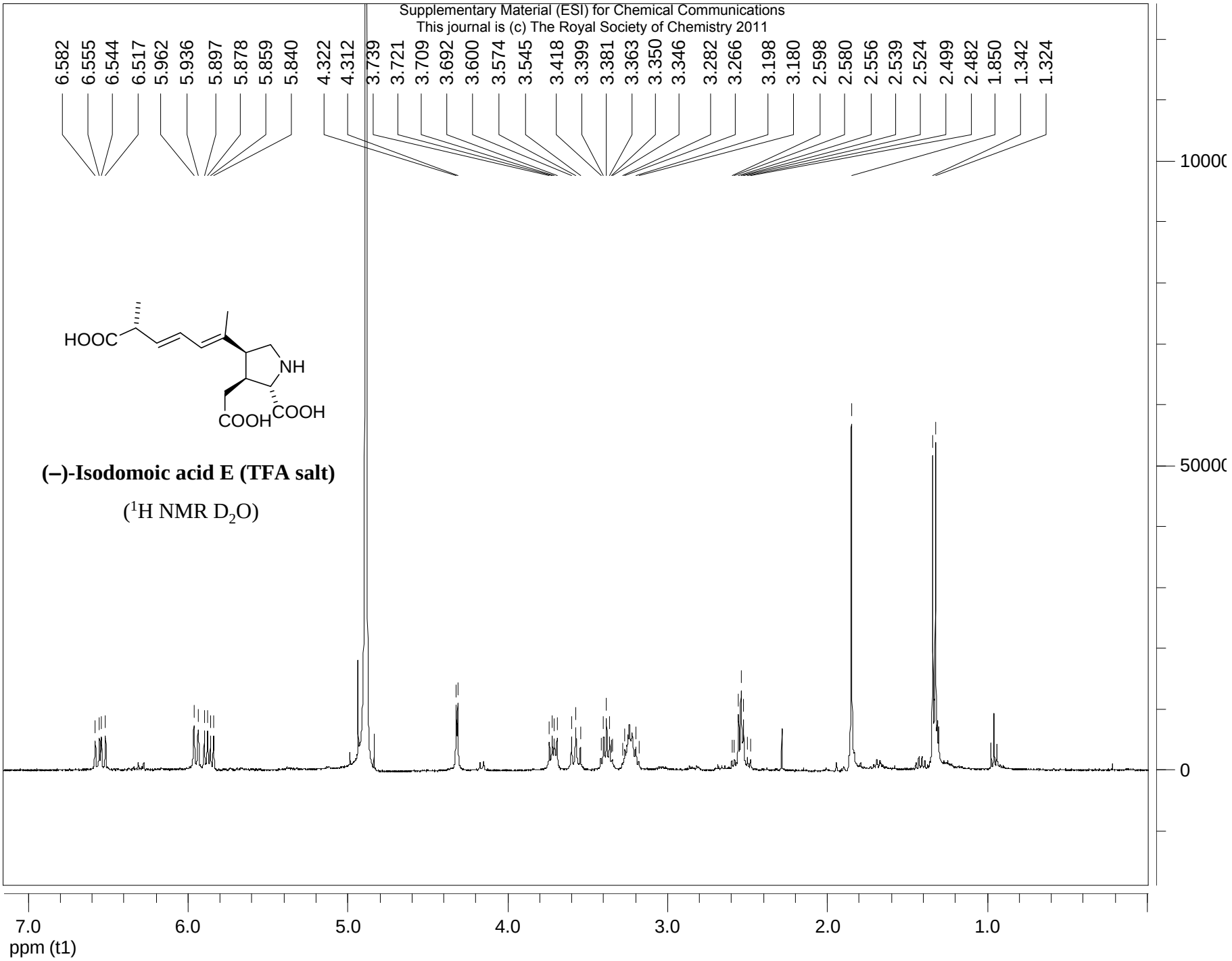


(–)-Isodomoic acid B (TFA salt)

(^{1}H NMR D_2O)

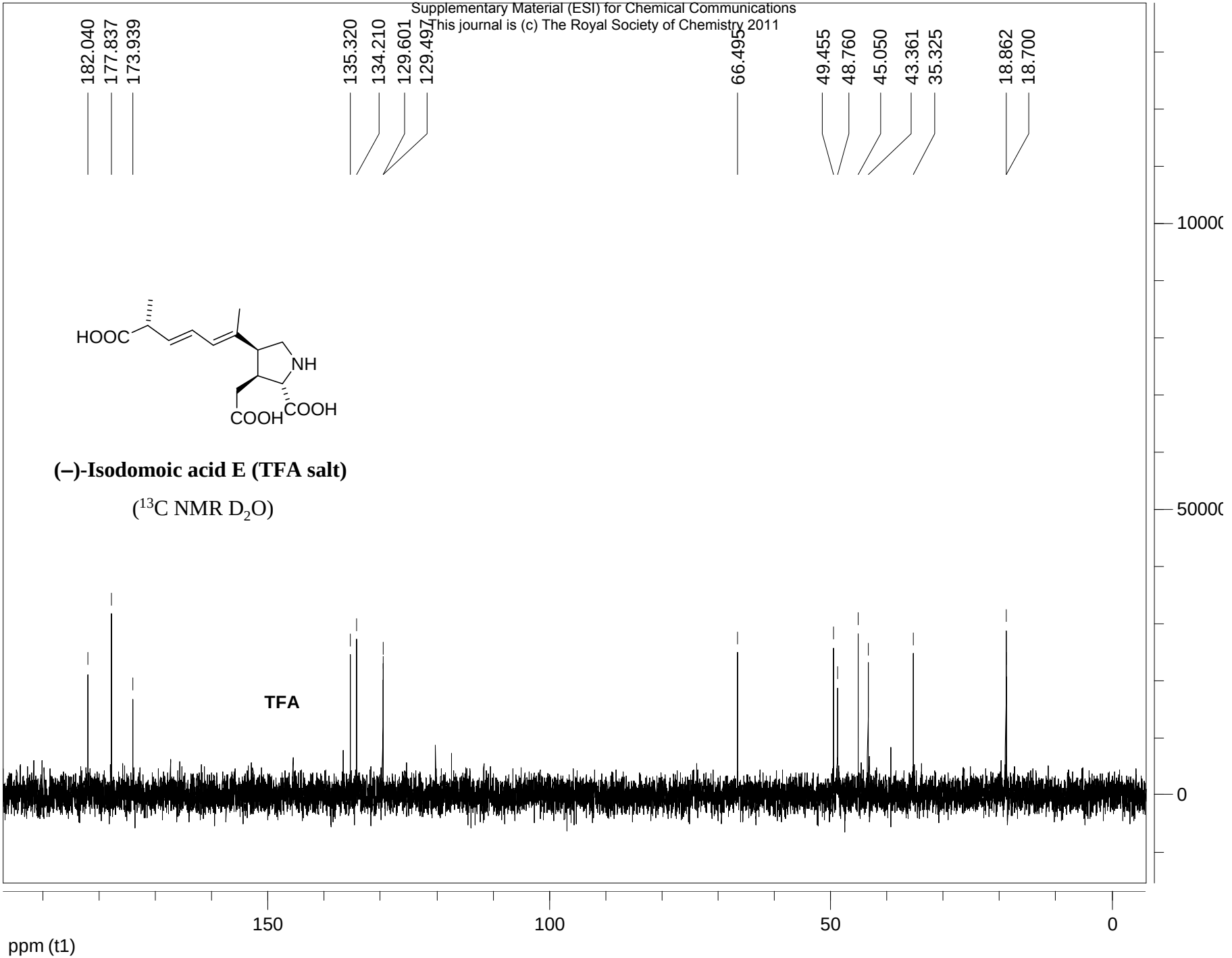






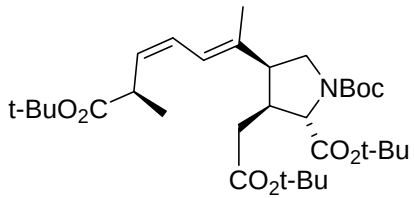
(–)-Isodomoic acid E (TFA salt)

(^{1}H NMR D_2O)



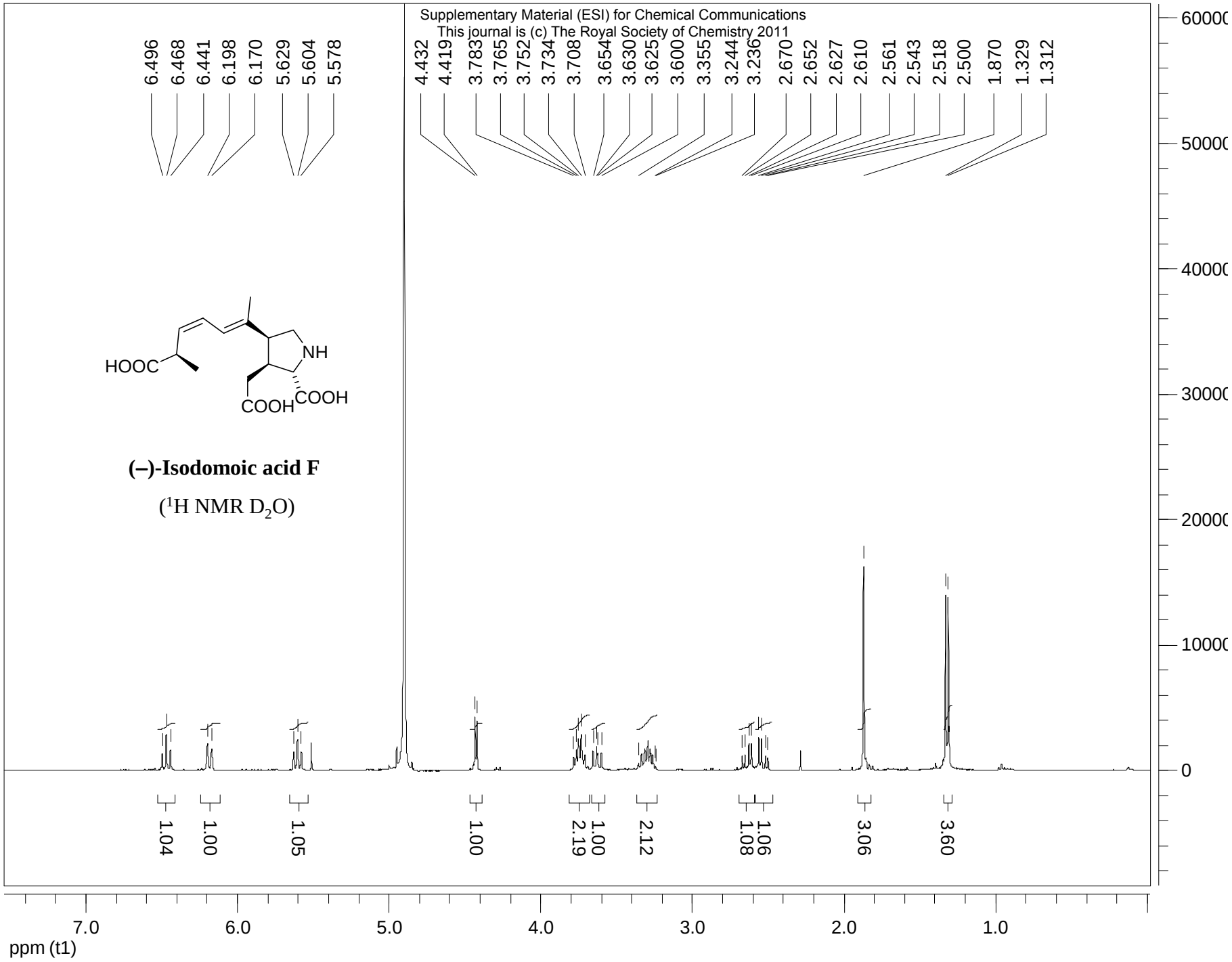
(–)-Isodomoic acid E (TFA salt)

(^{13}C NMR D_2O)



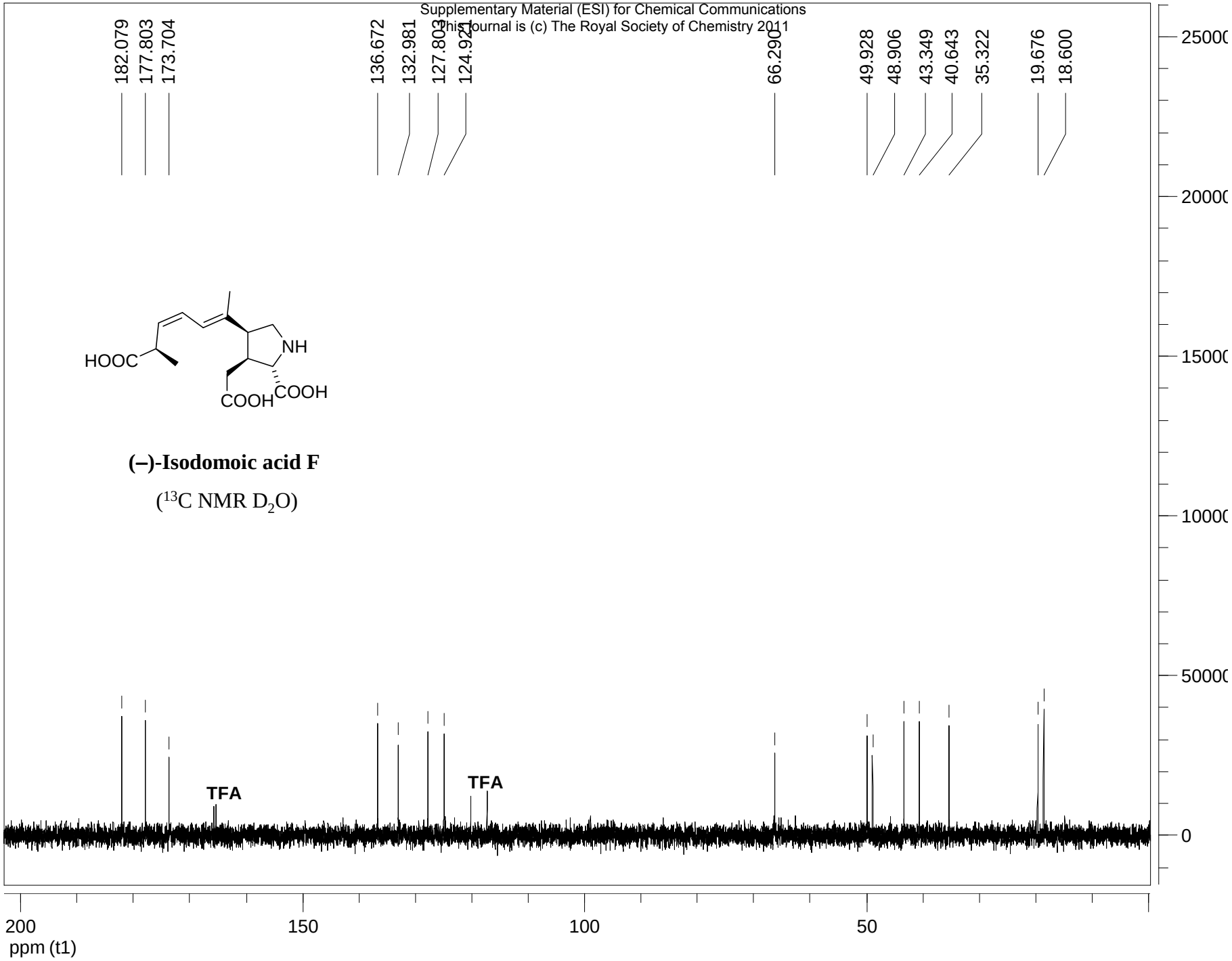
17F

(2 rotamers)



(–)-Isodomoic acid F

(^{1}H NMR D_2O)



(–)-Isodomoic acid F

(^{13}C NMR D_2O)