Supporting Information

Tandem multi-step synthesis of C-carboxyazlactones promoted by N-heterocyclic carbenes

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Experimental Procedures and Analytical Data

General Information

Rearrangement protocols using Et_3N (General Procedure A) were performed under an atmosphere of argon *via* standard vacuum line techniques and with freshly purified solvent and Et_3N. Tetrahydrofuran (THF) was obtained dry from a solvent purification system (MBraun, SPS-800). Et_3N was distilled from calcium hydride. All other procedures used THF and Et_3N as supplied without purification. Petrol is defined as petroleum ether 40-60 ˚C. All solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Ambient temperature refers to 20-25 ˚C. *In vacuo* refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC_2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

Analytical thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica. TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining 1% aqueous $KMnO_4$ solution. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ^1H, 75.4 MHz ^{13}C) or a Bruker Avance II 400 (400 MHz ^1H, 100 MHz ^{13}C) spectrometer and in the deuterated solvent stated. Coupling constants (*J*) are reported in Hz. Multiplicities are indicated by: br s (broad singlet), s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) and m (multiplet). The abbreviation Ar is used to denote aromatic.

Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrometer using either thin films on NaCl plates (thin film) or KBr discs (KBr disc) as stated. Only the characteristic peaks are quoted. Melting points were recorded on an Electrothermal apparatus and are uncorrected.

Mass spectrometric (*m/z*) data were acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI), at the University of St Andrews Mass Spectrometry facility. Low and high resolution ESI MS was carried out on a Micromass LCT spectrometer and low and high resolution CI MS was carried out on a Micromass GCT spectrometer.

General Experimental Procedures

General Procedure A – Two-step tandem protocol from azlactones

To a mixture of azlactone (1 eq) and triazolium salt **5** (5 mol%) in THF was added Et_3N (1.5 eq) followed by phenyl chloroformate (1.3 eq). The mixture was stirred at ambient temperature, then $Et_3N.HCl$ was removed by filtration and the filtrate concentrated *in vacuo*. Purification by chromatography on silica (EtOAc/petrol or Et_2O/petrol) gave the desired product.

General Procedure B – Multi-step tandem protocol from *N*-(4-methoxybenzoyl) amino acids

A mixture of *N*-(4-methoxybenzoyl) amino acid (1 eq) and DCC (1.01 eq) were stirred in THF for 2 hours then filtered (to remove dicyclohexylurea), followed by addition of triazolium salt **5** (5 mol%), Et_3N (1.5 eq) and then phenyl chloroformate (1.3 eq). The mixture was stirred at ambient temperature, then $Et_3N.HCl$ was removed by filtration and the filtrate concentrated *in vacuo*. Purification by chromatography on silica (Et_2O/petrol) gave the desired product.

General Procedure C – Alternative multi-step tandem protocol from *N*-(4-methoxybenzoyl) amino acids

To a mixture of *N*-(4-methoxybenzoyl) amino acid (1 eq) and triazolium salt **5** (5 or 10 mol%) in THF was added Et_3N (3.5 eq) followed by phenyl chloroformate (3 eq), with significant exotherm and effervescence. The mixture was stirred at ambient temperature, then $Et_3N.HCl$ was removed by filtration and the filtrate concentrated *in vacuo*. Purification by chromatography on silica (Et_2O/petrol) gave the desired product.

Determination of the carbon acid pK_a value for 2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate 5

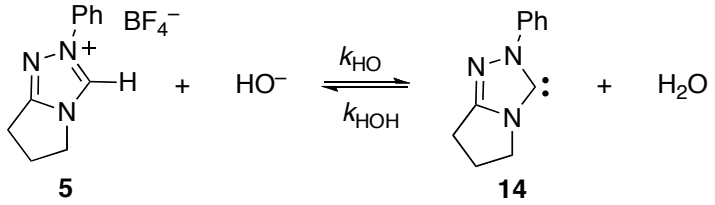
Materials and preparation of solutions

Deuterium oxide (99.9% D) was purchased from Apollo Scientific Ltd. Deuterium chloride (35%, 99.5% D) was purchased from the Aldrich Chemical company. The internal standard, tetramethylammonium deuteriosulfate, was a generous gift from Prof. Tina Amyes, University of Buffalo, New York. Stock solutions of deuterium chloride were prepared by dilution and titration of commercial concentrated solutions.

The pDs of the deuterium chloride solutions were determined at 25 ºC using a MeterLab^{TM} PHM 290 pH-Stat Controller equipped with a radiometer (pH 4-7-10 @ 25 ºC) combination electrode, that could be standardised between pH 1-4 to encompass the pD of the solution. The pD was calculated by adding 0.4 to the observed reading of the pH meter. The deuteroxide concentration was calculated from the equation $[DO^-] = (10^{pD - pKw})/\gamma_{DO}$, where $K_w = 10^{-14.87}$ M^2 is the ion product of D_2O at 25 ºC and $\gamma_{DO} = 0.727$ is the apparent activity coefficient of deuteroxide ion under our experimental conditions. The estimated error on the observed pseudo-first-order rate constant (k_{ex}, s^{-1}) is ±10% based on the error of the ^1H NMR measurement. Although the measurements of k_{ex} and the calculation of pK_a are single determinations, the calculated error in similar measurements and calculations performed by Amyes *et al.*[1] is ±10% for k_{ex} and ±0.5 units for the pK_a.

The carbon acid pK_a value for triazolium salt **5** was determined using the method of Amyes *et al*.[1] According to Equation S1 which is derived for Scheme S1, the second order rate constant for hydroxide-ion catalysed carbene formation from triazolium ion **5** (k_{HO}, $M^{-1}s^{-1}$) and the first order rate constant for the reverse protonation of the carbene conjugate base (k_{HOH}, s^{-1}) can be combined to yield the pK_a value for ionisation at the C3 position. In Equation S1, $K_w = 10^{-14}$ is the ion product of water at 25°C.

Scheme S1



5 **14**

$$pK_a = pK_w + \log \frac{k_{HOH}}{k_{HO}}$$ **Equation S1**

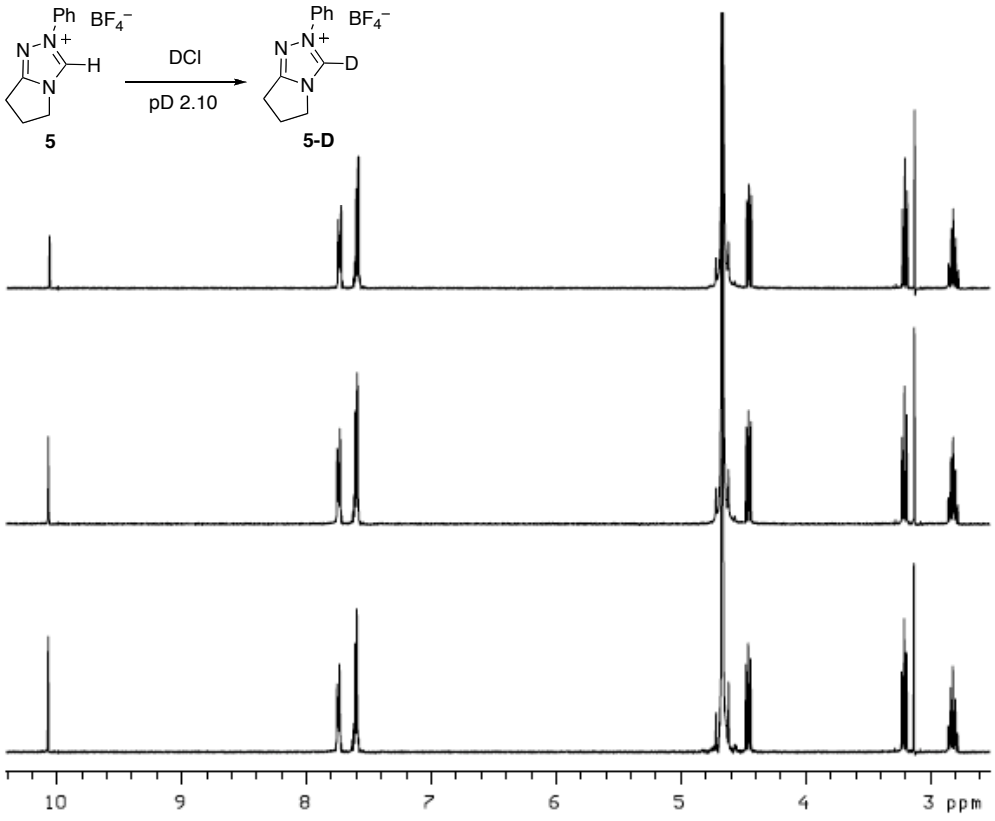
Rate constants for carbene formation

Rates of carbene formation were measured by hydrogen exchange in D_2O solution. ^1H NMR spectroscopy was used to monitor the decrease in the area of the singlet at 10.06 ppm due to the C3-H over time in solutions at different pD values as a result of H/D exchange.

H/D exchange reactions were carried out in 12.5 mL vials which were incubated at 25 ±0.1 ºC in a thermostated water bath. All reactions were carried out in D_2O with the ionic strength maintained at I = 1.0 with potassium chloride. Owing to the lability of triazolium ion **5** towards deuteroxide ion-catalysed H/D-exchange, the deuterium exchange reactions were monitored in deuterium chloride solutions of low pD values. Reactions were run on a 5 mL scale and were initiated by injection of deuterium chloride solution containing internal standard tetramethylammonium deuteriosulfate to solid substrate. The final substrate and internal standard concentrations in the reaction solutions were 10 mM and 1 mM, respectively. This ensured an approximately 1:1 ^1H NMR integration ratio of the singlet due to the C3 acidic hydrogen of substrate and the broad triplet at 3.12 ppm due to the 12 methyl hydrogens of internal standard. The reaction progress was monitored over time by withdrawing aliquots (~800 μL) at timed intervals. These aliquots were quenched to pD 0.5-1 by addition of 5 M DCl solution. The samples were analysed immediately by ^1H NMR spectroscopy.

Chemical shifts were referenced to HOD at δ 4.67 ppm, and spectra (32 transients, 20 s relaxation delay) were obtained using a sweep width of 7000 Hz, a 90° pulse angle, and an acquisition time of 4 s. The integrated area of the C3-H signal was referenced to the area of the broad triplet at δ 3.12 ppm due to the twelve methyl hydrogens of internal standard, tetramethylammonium deuteriosulfate (Figure S1). Disappearance of the C3-H signal conformed well to the first-order rate law.

Figure S1 Representative ^{1}H NMR spectra at 400 MHz obtained during the H/D exchange of the C3H of triazolium ion **5** in 8 mM DCl solution (pD 2.10) at 25 °C and ionic strength, I = 1.0 (KCl).



Values of the fraction of remaining unexchanged substrate **5** could be calculated using Equation S2 by comparing the integrated areas of the singlet at 10.06 ppm due to the C3-H ($A_{C3–H}$) with that of the broad triplet at 3.12 ppm due to internal standard (A_{IS}). The observed first order rate constant for deuterium exchange, k_{ex} (s^{-1}), could be obtained as the slope of a semilogarithmic plot of the fraction of remaining substrate (f(s)) against time according to Equation S3. These plots at different pD values are illustrated in Figure S2.

$$f(\mathrm{s}) = \frac{(A_{\mathrm{C3\text{-}H}} / A_{\mathrm{IS}})_t}{(A_{\mathrm{C3\text{-}H}} / A_{\mathrm{IS}})_0} \qquad \textbf{Equation S2}$$

$$\ln f(\mathrm{s}) = -k_{ex} t \qquad \textbf{Equation S3}$$

Figure S2 Semilogarithmic plots of the fraction of remaining substrate **5** (*f*(s)) against time at different pD values: ■, 0.002 M DCl, pD 2.72; ▲, 0.004 M DCl, pD 2.37; ●, 0.006 M DCl, pD 2.23; □, 0.008 M DCl, pD 2.10; ◆, 0.010 M DCl, pD 2.00.

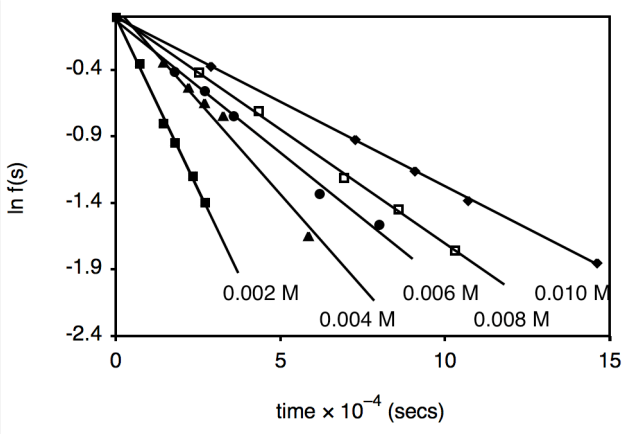
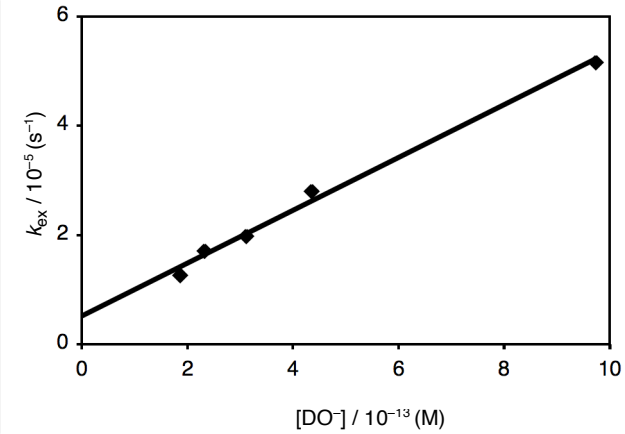


Table S1 summarises the resulting first order rate constants for exchange (k_{ex}, s^{-1}) at different experimental pD values. A plot of the k_{ex} values against deuteroxide concentration was linear (Figure S3) with slope equivalent to k_{DO}, the second order rate constant for deuteroxide ion–catalysed exchange according to Equation S4.[2] The resulting experimental second order rate constant k_{DO} was obtained as 4.83×10^7 $M^{-1}s^{-1}$. A value for $k_{HO} = 2.01 \times 10^7$ $M^{-1}s^{-1}$ was calculated from the corresponding value for deprotonation of triazolium ion **5** by deuteroxide ion in D_2O, k_{DO}, using a secondary solvent isotope effect of $k_{DO}/k_{HO} = 2.4$ for proton transfer that is limited by the solvent reorganisation step.[1,3,4]

Table S1: First-order rate constants (k_{ex}) for the deuteroxide ion-catalysed exchange of the C3-H of triazolium ion **5**

pD	[DO^-] (M^{-1})	k_{ex} (s^{-1})	R^2
2.72	9.74×10^{-13}	5.17×10^{-5}	9.97×10^{-1}
2.37	4.35×10^{-13}	2.81×10^{-5}	9.86×10^{-1}
2.23	3.12×10^{-13}	1.98×10^{-5}	9.94×10^{-1}
2.10	2.33×10^{-13}	1.71×10^{-5}	9.99×10^{-1}
2.00	1.86×10^{-13}	1.27×10^{-5}	9.99×10^{-1}

Figure S3 Determination of the second order rate constant for deuteroxide ion–catalysed exchange.



$$k_{ex} = k_{DO}[DO^-] + k_{D_2O} \qquad \textbf{Equation S4}$$

Rate constants for carbene protonation

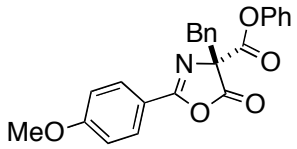
As discussed by Amyes *et al.*[1] there is good evidence that the reverse proton transfer from solvent water to C3 of the imidazolyl carbene to give the imidazolium cation is limited by the rate of reorganisation of the solvent (k_{reorg}) and occurs with a limiting rate constant of $k_{HOH} = k_{reorg} = 10^{11}$ s^{-1}. In particular, the absence of detectable buffer catalysis of exchange strongly supports the conclusion that $k_{HOH} = k_{reorg}$ for the protonation of imidazol-2-yl carbenes by solvent water. We have performed similar buffer catalysis experiments for a range of cyclic azolium ions including imidazolium, dihydroimidazolium and trihydropyrimidinium ions.[5] Buffer catalysis of exchange was not detectable in any case and thus it is reasonable to assume that protonation of triazolyl carbenes is also limited by solvent reorganisation and occurs with a limiting rate constant of $k_{HOH} = k_{reorg} = 10^{11}$ s^{-1}. Furthermore, our experimental rate constants for exchange for triazolium ion **5** are very similar to values obtained for N-substituted thiazolium ions for which it was also concluded that the reverse protonation by solvent water is limited largely by the physical "encounter" of a molecule of HOH with the carbene.[6]

Combining values for the second order rate constant for hydroxide-ion catalysed carbene formation from triazolium ion **5** ($k_{HO} = 2.01 \times 10^7$ $M^{-1}s^{-1}$) and the first order rate constant for the reverse protonation of the carbene conjugate base ($k_{HOH} = 10^{11}$ s^{-1}) according to Equation S1 yields a pK_a value of 17.7 ±0.5.

Experimental Procedures for Compounds

Literature procedures were used for the preparation of compounds **4**,[7] **5**,[8] **9**,[7] **10**,[7] **11**,[9] **19**,[7] **20**[7] and **21**[7] and gave spectroscopic data in accordance with the literature.

Phenyl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-7



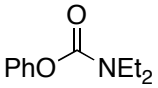
(±)-**7**

Following general procedure A, azlactone **4** (200 mg, 0.711 mmol), triazolium salt **5** (9.70 mg, 0.0355 mmol), THF (2 mL), Et_3N (128 μL, 0.924 mmol) and phenyl chloroformate (88.0 μL, 0.782 mmol) gave, after chromatography (EtOAc/petrol, 10:90), ester (±)-**7** as a colourless oil (231 mg, 81%) with spectroscopic data in accordance with the literature.[7]

Following general procedure B, DL-*N*-(4-methoxybenzoyl)phenylalanine **19** (300 mg, 1.00 mmol), DCC (208 mg, 1.01 mmol), triazolium salt **5** (13.7 mg, 0.0500 mmol), THF (3 mL), Et_3N (182 μL, 1.30 mmol), and phenyl chloroformate (123 μL, 1.10 mmol) gave, after chromatography (Et_2O/petrol, 20:80), ester (±)-**7** as a colourless oil (285 mg, 71%).

Following general procedure C, DL-*N*-(4-methoxybenzoyl)phenylalanine **19** (300 mg, 1.00 mmol), Et_3N (0.487 mL, 3.51 mmol), triazolium salt **5** (13.7 mg, 0.0500 mmol), THF (3 mL) and phenyl chloroformate (0.340 mL, 3.01 mmol) gave, after chromatography (Et_2O/petrol, 20:80), ester (±)-**7** as a colourless oil (286 mg, 71%).

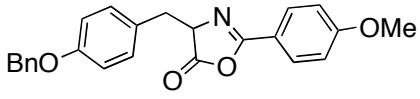
Phenyl diethylcarbamate 8



8

To a solution of Et_3N (0.750 mL, 5.34 mmol) in dry THF (20 mL) at 0 ˚C was added phenyl chloroformate (0.650 mL, 5.14 mmol) and the resultant solution stirred overnight with warming slowly to ambient temperature. Water was added and the aqueous layer extracted with Et_2O (× 3). The organic extracts were combined and washed successively with 0.1 M HCl(aq), $NaHCO_3$ (sat. aq) and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (Et_2O/petrol, 10:90) afforded carbamate **11** as a pale yellow liquid (0.672 g, 68%). Carbamate **8** has been prepared by alternative methods and characterised in the literature previously.[10,11] $\boldsymbol{\delta_H}$ (400 MHz; $CDCl_3$) 7.36-7.19 (2H, m, 3,5-Ph*H*), 7.12-7.08 (1H, m, 4-Ph*H*), 7.06-7.02 (2H, m, 2,6-Ph*H*), 3.43-3.24 (4H, m, C*H*$_2$CH$_3$) and 1.23-1.06 (6H, m, CH$_2$C*H*$_3$).

4-(4-Benzyloxyphenyl)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole 12

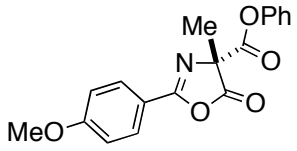


12

A mixture of DL-*N*-(4-methoxybenzoyl)-*O*-tyrosine **23** (2.50 g, 6.17 mmol) and Ac_2O (5.00 mL, 52.9 mmol) were heated at 80 ºC for 1 hour before concentration *in vacuo*. The remaining AcOH/Ac_2O was removed azeotropically with toluene (20 mL × 5) to afford the azlactone **12** (2.39 g, quantitative) as a colourless solid and was used without further purification. ***m.p.*** 118-119 ºC; $\boldsymbol{\nu_{max}}$ (KBr disc)/cm^{-1} 3059 (CH), 3014 (CH), 2917 (CH), 2860 (CH), 2841 (CH), 1814 (C=O), 1654. 1609, 1512, 1332, 1247 (C-O), 1149, 1057, 1020, 997, 954, 883, 850, 836, 742 and 697; $\boldsymbol{\delta_H}$ (400 MHz; $CDCl_3$) 7.87 (2H, d, *J* 8.8, 4-OMeAr(2,6)*H*), 7.41-7.28 (5H, m, Ph*H*), 7.18 (2H, d, *J* 8.5, 4-OBnAr(2,6,)*H*), 6.94 (2H, d, *J* 8.8, 4-OMeAr(3,5)*H*), 6.86 (2H, d, *J* 8.5, 4-OBnAr(3,5)*H*), 5.00 (2H, s, PhC*H*$_2$*),* 4.62 (1H, dd, *J* 6.3, 4.9, *H*-4), 3.86 (3H, s, OC*H*$_3$), 3.30 (1H, ABX, J_{AB} 14.0, J_{AX} 4.9, ArC*H*$_A$) and 3.13 (1H, ABX, J_{BA} 14.0, J_{BX} 6.3, ArC*H*$_B$); $\boldsymbol{\delta_C}$ (100 MHz; $CDCl_3$) 178.0, 163.2, 161.4, 158.0, 137.1, 130.8, 129.9, 128.7, 128.0, 127.8, 127.6, 118.2, 114.8, 114.3, 70.0, 66.8, 55.6 and 36.7;

m/z (CI+) 388.15 (28, M + H^+) and 255 (100, 4-OBnC$_6$H$_4$C(=NH_2^+)CH$_2$OMe); HRMS (CI+) $C_{24}H_{22}NO_4$ requires 388.1543, found 388.1549 (-1.5 ppm).

Phenyl 2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-15



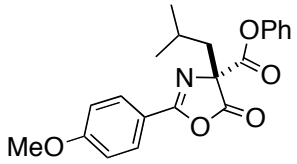
(±)-15

Following general procedure A, azlactone **9** (300 mg, 1.46 mmol), triazolium salt **5** (39.9 mg, 0.146 mmol), THF (3 mL), Et_3N (305 μL, 2.19 mmol) and phenyl chloroformate (214 μL, 1.90 mmol) gave, after chromatography (EtOAc/petrol, 10:90), ester (±)-**15** as a colourless oil (385 mg, 81%) with spectroscopic data (^{1}H NMR) in accordance with the literature.[7]

Following general procedure B, DL-*N*-(4-methoxybenzoyl)alanine **20** (200 mg, 0.896 mmol), DCC (187 mg, 0.905 mmol), triazolium salt **5** (12.2 mg, 0.0448 mmol), THF (2 mL), Et_3N (186 μL, 1.34 mmol), and phenyl chloroformate (132 μL, 1.17 mmol) gave, after chromatography (Et_2O/petrol, 20:80), ester (±)-**15** as a colourless oil (201 mg, 69%).

Following general procedure C, DL-*N*-(4-methoxybenzoyl)alanine **20** (500 mg, 2.24 mmol), Et_3N (1.09 mL, 7.84 mmol), triazolium salt **5** (30.5 mg, 0.112 mmol), THF (4 mL) and phenyl chloroformate (760 μL, 6.72 mmol) gave, after chromatography (Et_2O/petrol, 20:80), ester (±)-**15** as a colourless oil (568 mg, 78%).

Phenyl 4-*iso*-butyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-16



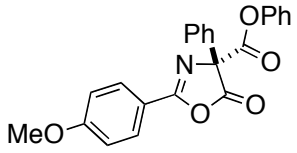
(±)-16

Following general procedure A, azlactone **10** (200 mg, 0.809 mmol), triazolium salt **5** (11.1 mg, 0.0405 mmol), THF (2 mL), Et_3N (157 μL, 1.13 mmol) and phenyl chloroformate (119 μL, 1.05 mmol) gave, after chromatography (Et_2O/petrol, 15:85),

ester (±)-**16** as a colourless oil (252 mg, 85%) with spectroscopic data (^{1}H NMR) in accordance with the literature.[9]

Following general procedure B, DL-*N*-(4-methoxybenzoyl)leucine **21** (300 mg, 1.13 mmol), DCC (236 mg, 1.14 mmol), triazolium salt **5** (15.1 mg, 0.0552 mmol), THF (3 mL), Et_3N (236 μL, 1.70 mmol) and phenyl chloroformate (166 μL, 1.47 mmol) gave, after chromatography (Et_2O/petrol, 15:85), ester (±)-**16** as a colourless oil (290 mg, 70%).

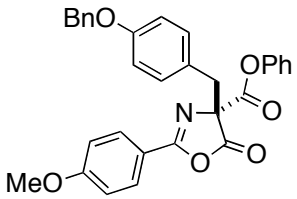
Phenyl 2-(4-methoxyphenyl)-4-phenyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-**17**



(±)-**17**

Following general procedure A, azlactone **11** (200 mg, 0.748 mmol), triazolium salt **5** (10.0 mg, 0.0374 mmol), THF (2 mL), Et_3N (135 μL, 0.972 mmol) and phenyl chloroformate (93.0 μL, 0.823 mmol) gave, after chromatography (Et_2O/petrol, 20:80), ester (±)-**17** as a colourless oil (217 mg, 75%) with spectroscopic data in accordance with the literature.[8]

Phenyl 4-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-**18**



(±)-**18**

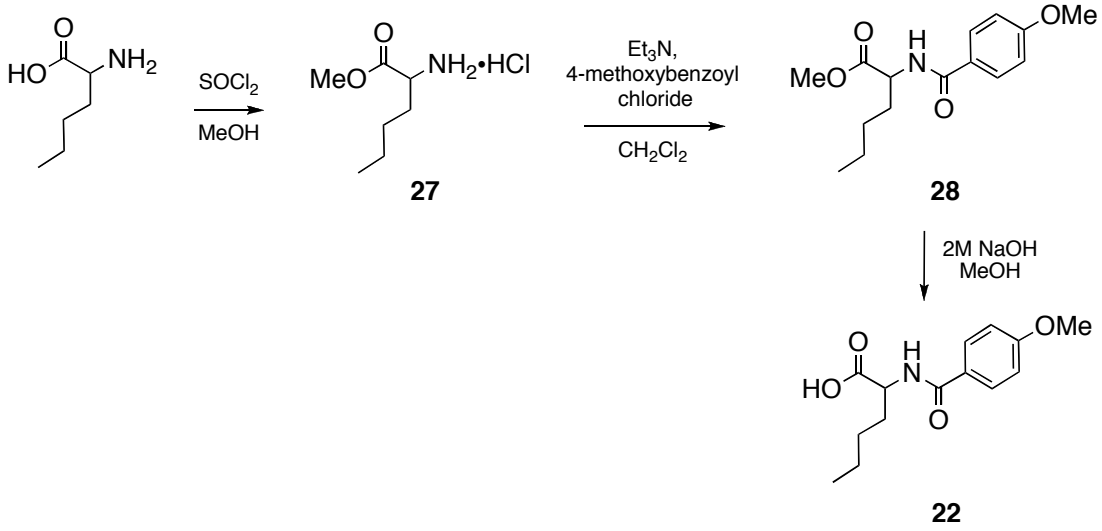
Following general procedure A, azlactone **12** (200 mg, 0.516 mmol), triazolium salt **5** (7.04 mg, 0.0258 mmol), THF (2 mL), Et_3N (108 μL, 0.774 mmol) and phenyl chloroformate (76.0 μL, 0.671 mmol) gave, after chromatography (Et_2O/petrol, 20:80), ester (±)-**18** as a colourless oil (231 mg, 81%).

Following general procedure B, DL-*N*-(4-methoxybenzoyl)-*O*-benzyltyrosine **23** (200 mg, 0.493 mmol), DCC (103 mg, 0.498 mmol), triazolium salt **5** (7.04 mg, 0.0258 mmol), THF (2 mL), Et_3N (104 μL, 0.747 mmol), and phenyl chloroformate

(72.0 μL, 0.641 mmol) gave, after chromatography (Et_2O/petrol, 20:80), ester (±)-**18** as a colourless oil (210 mg, 84%).

ν_{max} (thin film)/cm^{-1} 3064 (CH), 3035 (CH), 2935 (CH), 2841 (CH), 1823 (C=O), 1766 (C=O), 1647, 1609, 1512, 1493, 1325, 1307, 1262 (C-O), 1178, 1067, 1027, 980, 841, 741, 689 and 608; δ_H (300 MHz; $CDCl_3$) 7.84-7.78 (2H, m, 4-OMeAr(3,5)*H*), 7.33-7.21 (7H, m, Ar*H*), 7.20-7.14 (1H, m, Ar*H*), 7.14-7.07 (2H, m, Ar*H*), 7.04-7.00 (2H, m, Ar*H*), 6.89-6.84 (2H, m, Ar*H*), 6.77-6.71 (2H, m, 4-OMeAr(2,6)*H*), 4.89 (2H, s, PhCH_2), 3.78 (3H, s, OCH_3), 3.59 (1H, ABq, *J* 13.8, 4-OBnArCH_A) and 3.47 (1H, ABq, *J* 13.8, 4-OBnArCH_B); δ_C (100 MHz; $CDCl_3$) 173.8, 164.7, 163.8, 163.3, 158.4, 150.4, 137.0, 131.8, 130.4, 129.7, 128.7, 128.1, 127.6, 126.7, 125.2, 121.3, 117.4, 114.8, 114.5, 77.8, 70.0, 55.7 and 39.7; ***m/z*** (ESI+) 508.17 (10, $M+H^+$), 135.1 (38, $ArC{\equiv}O^+$) and 95.1 (100); HRMS (ESI+) $C_{31}H_{26}NO_6$ requires 508.1763, found 508.1760 (+0.6 ppm).

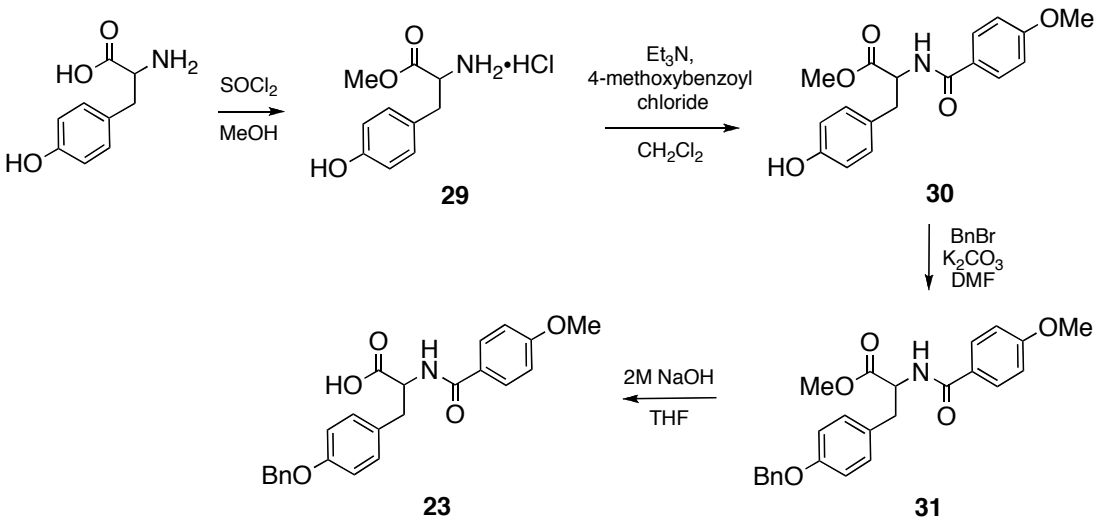
DL-*N*-(4-Methoxybenzoyl)norleucine 22



A solution of DL-norleucine (15.0 g, 115 mmol) in methanol (150 mL) was cooled to 0 ºC and thionyl chloride (12.5 mL, 172 mmol) was added dropwise over 45 minutes. The mixture was allowed to warm to ambient temperature over 16 hours then concentrated *in vacuo* to afford the methyl ester hydrochloride **27** as a pale yellow oil (20.8 g, quantitative) and was used without further purification. To a solution of ester hydrochloride **27** (20.5 g, 113 mmol) in dichloromethane (150 mL) was added Et_3N (36.3 mL, 261 mmol) and the solution cooled to 0 ºC. A solution of 4-methoxybenzoyl chloride (14.8 mL, 109 mmol) in dichloromethane (30 mL) was added over 30 min then the mixture was allowed to warm to ambient temperature over 16 hours. 0.1 M HCl(aq) (125 mL) was added and the product was extracted

with dichloromethane (100 mL × 3). The organics were combined then washed with $NaHCO_3$ (sat. aq) (100 mL) and brine (100 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the desired amide **28** as a colourless solid (26.7 g, 87%), which was used without further purification. A solution of amide **28** (25.7 g, 91.8 mmol) in methanol (300 mL) was treated with 2 M NaOH(aq) (68.9 mL) for 1 hour then concentrated to ~70 mL *in vacuo*, then 5 M HCl(aq) was added to pH <3, inducing precipitation of the product on scratching. The product was collected by filtration then dried azeotropically with toluene (100 mL × 5), giving acid **22** as a colourless solid (23.1 g, 87%). ***m.p.*** 135-138 ºC; $\boldsymbol{\nu_{max}}$ (KBr disc)/cm^{-1} 3373 (v. br, OH), 2923 (CH), 2963 (CH), 2348, 1721 (C=O), 1704 (C=O), 1615, 1575, 1539, 1506, 1456, 1417, 1309, 1256 (C-O), 1202, 1179, 1033, 842, 761 and 633; $\boldsymbol{\delta_H}$ (400 MHz; d_6-DMSO) 12.51 (1H, br s, COO*H*), 8.41 (1H, d, *J* 7.7, CON*H*), 7.91-7.86 (2H, m, 4-OMeAr(3,5)*H*), 7.04-6.96 (2H, m, 4-OMeAr(2,6)*H*), 4.38-4.29 (1H, m, C*H*COOH), 3.79 (3H, s, OCH_3), 1.87-1.66 (2H, m, $CHCH_2$), 1.44-1.20 (4H, m, CH_2CH_2) and 0.85 (3H, t, *J* 7.0, CH_3); $\boldsymbol{\delta_C}$ (100 MHz; d_6-DMSO) 174.1, 166.0, 161.7, 129.4, 126.3, 113.4, 55.4, 52.6, 30.4, 28.1, 21.8 and 13.9; ***m/z*** (ESI+) 294.2 (35, M+MeOH+H^+), 266.1 (100, M+H^+), 248.1 (40, M^+-OH) and 135.1 (40, ArC≡O^+); HRMS (ESI+) $C_{14}H_{20}NO_4$ requires 266.1388, found 266.1392 (-1.6 ppm).

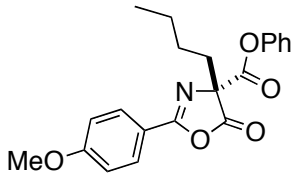
DL-*N*-(4-Methoxybenzoyl)-*O*-benzyltyrosine 23



A solution of DL-tyrosine (30.0 g, 166 mmol) in methanol (350 mL) was cooled to 0 ºC and thionyl chloride (48.0 mL, 662 mmol) was added dropwise over 45 minutes. The mixture was allowed to warm to ambient temperature over 16 hours then concentrated *in vacuo* to afford the methyl ester hydrochloride **29** as a pale cream solid (39.1 g, quantitative). Without further purification, the ester hydrochloride **29** (38.0 g, 164 mmol) was suspended in dichloromethane (400 mL) then Et_3N (53.6 mL,

385 mmol) was added and the solution cooled to 0 ºC. A solution of 4-methoxybenzoyl chloride (21.8 mL, 161 mmol) in dichloromethane (40 mL) was added over 30 minutes then the mixture was allowed to warm to ambient temperature over 16 hours. 0.1 M HCl(aq) (250 mL) was added and the product was extracted with dichloromethane (200 mL × 3). The organics were combined then washed with saturated $NaHCO_3$ (sat. aq) (100 mL) and brine (100 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude product. Recrystallisation from EtOAc (130 mL) with scratching gave the amide product **30** as a colourless solid (38.0 g, 70%). A suspension of amide **30** (5.00 g, 15.2 mmol) and K_2CO_3 (2.31 g, 16.7 mmol) in DMF (40 mL) were stirred together for 30 min then benzyl bromide (1.91 mL, 16.0 mmol) was added. The suspension was stirred for 16 hours then water (50 mL) was added to induce precipitation. The colourless precipitate was collected by filtration and washed exhaustively with water then dried azeotropically with toluene (50 mL × 5) to afford the benzyl ether product **31** as a colourless solid (6.00 g, 78%), which was used without further purification. To a solution of benzyl ether **31** (4.00 g, 9.54 mmol) in THF (40 mL) was added 2 M NaOH(aq) (5.70 mL) and the mixture stirred for 1 hour then concentrated to ~6 mL *in vacuo*, then 2 M HCl(aq) was added to pH <3, inducing precipitation of the product on scratching. The product was collected by filtration then dried azeotropically with toluene (50 mL × 5), giving acid **23** as a colourless solid (3.62 g, 94%). ***m.p.*** 140-142 ºC; $\boldsymbol{\nu_{max}}$ (KBr disc)/cm^{-1} 3332 (OH), 3062 (CH), 3035 (CH), 2927 (CH), 1734 (C=O), 1632 (C=O), 1608, 1527, 1505, 1255 (C-O), 1175, 1027, 841, 772 and 731; $\boldsymbol{\delta_H}$ (300 MHz; CD_3OD) 7.62-7.58 (2H, m, 4-OMeAr(2,6)*H*), 7.28-7.13 (5H, m, Ph*H*), 7.07-7.04 (2H, m, 4-OBnAr(2,6)*H*), 6.83-6.80 (2H, m, 4-OMeAr(3,5)*H*), 6.77-6.74 (2H, m, 4-OBnAr(3,5)*H*), 4.86 (2H, s, PhCH_2), 4.83 (3H, s, OCH_3), 4.68 (1H, dd, *J* 9.0, 5.0, C*H*COOH), 3.14 (1H, ABX, J_{AB} 14.0, J_{AX} 5.0, ArCH_A) and 2.94 (1H, ABX, J_{BA} 14.0, J_{BX} 9.0, ArCH_B); $\boldsymbol{\delta_C}$ (75 MHz; $CDCl_3$) 175.2, 169.5, 163.9, 159.0, 138.7, 131.2, 130.9, 130.2, 129.4, 128.7, 128.5, 127.3, 115.8, 114.6, 70.9, 55.8 and 37.4; ***m/z*** (ESI-) 404.2 (100, M-H^+); HRMS (ESI-) $C_{24}H_{22}NO_5$ requires 404.1496, found 404.1498 (-0.5 ppm).

Phenyl 4-*nor*-butyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-**24**



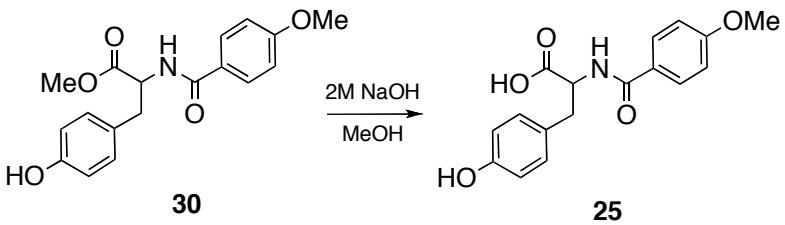
(±)-**24**

Following general procedure B, DL-*N*-(4-methoxybenzoyl)norleucine **22** (300 mg, 1.13 mmol), DCC (236 mg, 1.14 mmol), triazolium salt **5** (15.5 mg, 0.0568 mmol), THF (3 mL), Et_3N (236 μL, 1.70 mmol), and phenyl chloroformate (166 μL, 1.47 mmol) gave, after chromatography, ester (±)-**24** as a colourless oil (303 mg, 73%).

Following general procedure C, DL-*N*-(4-methoxybenzoyl)norleucine **22** (900 mg, 3.39 mmol), Et_3N (1.65 mL, 11.9 mmol), triazolium salt **5** (46.3 mg, 0.170 mmol), THF (9 mL) and phenyl chloroformate (1.14 mL, 10.2 mmol) gave, after chromatography (Et_2O/petrol, 3:97 then ramped to 20:80), ester (±)-**24** as a colourless oil (934 mg, 75%).

$\boldsymbol{\nu}_{\mathbf{max}}$ (thin film)/cm^{-1} 2961, 2934, 2874, 1823 (C=O), 1771 (C=O), 1653, 1609, 1513, 1308, 1262 (C-O), 1173, 1049, 1029, 967, 884, 842, 742 and 688; $\boldsymbol{\delta}_{\mathbf{H}}$ (400 MHz; $CDCl_3$) 8.06-8.02 (2H, m, 4-OMeAr(3,5)*H*), 7.69-7.34 (2H, m, 3,5-Ph*H*), 7.26-7.22 (1H, m, 4-Ph*H*), 7.13-7.10 (2H, m, 2,6-Ph*H*), 7.03-6.99 (2H, m, 4-OMeAr(2,6)*H*), 3.88 (3H, s, OCH_3), 2.45-2.38 (1H, m, C(4)CH_A), 2.34-2.28 (1H, m, C(4)CH_B), 1.44-1.35 (3H, m, $CH_3CH_2CH_AH_B$), 1.31-1.21 (1H, m, $CH_3CH_2CH_AH_B$) and 0.91 (3H, t, *J* 7.1, CH_3); $\boldsymbol{\delta}_{\mathbf{C}}$ (100 MHz; $CDCl_3$) 174.5, 164.8, 163.9, 163.3, 150.4, 130.5, 129.6, 126.6, 121.2, 117.4, 114.5, 76.8, 55.7, 34.3, 25.5, 22.6 and 13.9; ***m/z*** (ESI+) 386.2 (100, M+H$^+$), 248.1 (72, M-COOPh+H$^+$) and 135.1 (38, ArC≡O$^+$); HRMS (ESI+) $C_{21}H_{22}NO_5$ requires 368.1489, found 368.1498 (-2.4 ppm).

DL-*N*-(4-Methoxybenzoyl)tyrosine 25

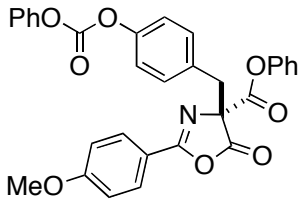


30 **25**

To a solution of methyl ester **30** (see S14-15 for preparation) (5.00 g, 15.2 mmol) in methanol (30 mL) was added 2 M NaOH(aq) (17.1 mL, 34.2 mmol) and the mixture

stirred for 1 hour. The solution was concentrated to ~20 mL *in vacuo* then 2 M HCl(aq) was added to pH <3, inducing precipitation of the product which was collected by filtration then dried azeotropically with toluene (50 mL × 5), giving acid **25** as a colourless solid (4.20 g, 88%). ***m.p.*** 152-154 ºC; $\boldsymbol{\nu}_{\mathbf{max}}$ (KBr disc)/cm^{-1} 3335 (OH), 3019 (CH), 2936 (CH), 1717 (C=O), 1636 (C=O), 1610, 1538, 1507, 1262 (C-O), 1181, 1028, 847, 824 and 767; $\boldsymbol{\delta}_{\mathbf{H}}$ (300 MHz; CD_3OD) 7.74-7.68 (2H, m, 4-OMeAr(3,5)*H*), 7.08-7.02 (2H, m, 4-OHAr(3,5)*H*), 6.97-6.92 (2H, m, 4-OHAr(2,6)*H*), 6.71-6.63 (2H, m, 4-OHAr(2,6)*H*), 4.72 (1H, dd, *J* 8.1, 5.1, C*H*COOH), 3.83 (3H, s, OCH_3), 3.21 (1H, ABX, J_{AB} 13.9, J_{AX} 5.1, ArCH_A), 3.02 (1H, ABX, J_{BA} 13.9, J_{BX} 8.1, ArCH_B); $\boldsymbol{\delta}_{\mathbf{C}}$ (75 MHz; d_6-DMSO) 173.7, 166.0, 161.8, 155.9, 130.1, 129.3, 128.4, 126.3, 115.1, 113.6, 55.4, 54.8 and 35.7; ***m/z*** (ESI+) 316.1 (72, M+H$^+$) , 298.1 (M$^+$ - H_2O) and 135.1 (100, ArC≡O$^+$); HRMS (CI+) $C_{17}H_{18}NO_5$ requires 316.1193, found 316.1185 (+2.5 ppm).

Phenyl 2-(4-methoxyphenyl)-5-oxo-4-(4-phenoxycarbonyloxy)benzyl-4,5-dihydrooxazole-4-carboxylate (±)-**26**



(±)-**26**

Following a stoichiometric modification to general procedure C, DL-*N*-(4-methoxybenzoyl)tyrosine **25** (250 mg, 0.793 mmol), Et_3N (661 μL, 4.76 mmol), triazolium salt **5** (10.8 mg, 0.0397 mmol), THF (2.5 mL) and phenyl chloroformate (493 μL, 4.36 mmol) gave, after chromatography (Et_2O/petrol, 20:80), ester (±)-**26** as a colourless oil (281 mg, 66%). $\boldsymbol{\nu}_{\mathbf{max}}$ (thin film)/cm^{-1} 2934 (CH), 2824 (CH), 2360 (CH), 1823 (C=O), 1773 (C=O), 1771 (C=O), 1646, 1608, 1513, 1493, 1259, 1236 (C-O), 1185, 1161, 980, 841, 742 and 687; $\boldsymbol{\delta}_{\mathbf{H}}$ (300 MHz; $CDCl_3$) 7.91-7.86 (2H, m, 4-OMeAr(2,6)*H*), 7.43-7.32 (5H, m, Ar*H*), 7.32-7.27 (2H, m, Ar*H*), 7.26-7.22 (3H, m, Ar*H*), 7.21-7.08 (4H, m, Ar*H*), 6.97-6.92 (2H, m, 4-OMeAr(3,5)*H*), 3.86 (3H, s, OCH_3), 3.74 (1H, ABq, *J* 13.8, ArCH_AH$_B$) and 3.59 (1H, ABq, *J* 13.8, ArCH$_a$$H_B$); $\boldsymbol{\delta}_{\mathbf{C}}$ (75 MHz; $CDCl_3$) 173.8, 164.6, 164.0, 163.6, 152.0, 151.2, 150.7, 150.5, 132.0, 131.3, 130.5, 129.8, 126.8, 126.6, 121.4, 121.2, 121.1, 121.0, 117.2, 114.6, 77.6, 55.8 and 39.7; ***m/z*** (ESI+) 538.07 (100, M+H$^+$), HRMS (ES+) $C_{31}H_{24}NO_8$ requires 538.1501, found 538.1502 (-0.2 ppm).

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[2] In Equation S4, the term k_{D2O} refers to the uncatalysed pH-independent exchange reaction with solvent acting as a base and this value is obtained as the intercept of the plot of k_{DO} against deuteroxide concentration. This term was also significant for the deuterium exchange reactions of *N*-alkylthiazolium ions which demonstrate similar reactivity towards deuteroxide-catalysed exchange to triazolium ion **5** (M. W. Washabaugh and W. P. Jencks, *J. Am. Chem. Soc.* **1989**, *111*, 683).

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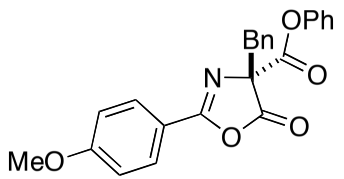
7.899 7.894 7.882 7.877 7.409 7.404 7.391 7.389 7.388 7.375 7.370 7.282 7.279 7.277 7.271 7.268 7.262 7.258 7.251 7.248 7.245 7.244 7.243 7.240 7.235 7.231 7.229 7.223 7.221 7.217 7.210 7.208 7.204 7.200 7.191 7.188 7.136 7.133 7.130 7.124 7.113 7.111 7.108 6.969 6.962 6.957 6.945 6.939 6.932 3.871 3.753 3.719 3.626 3.591

^{13}C NMR, 100 MHz,$CDCl_3$

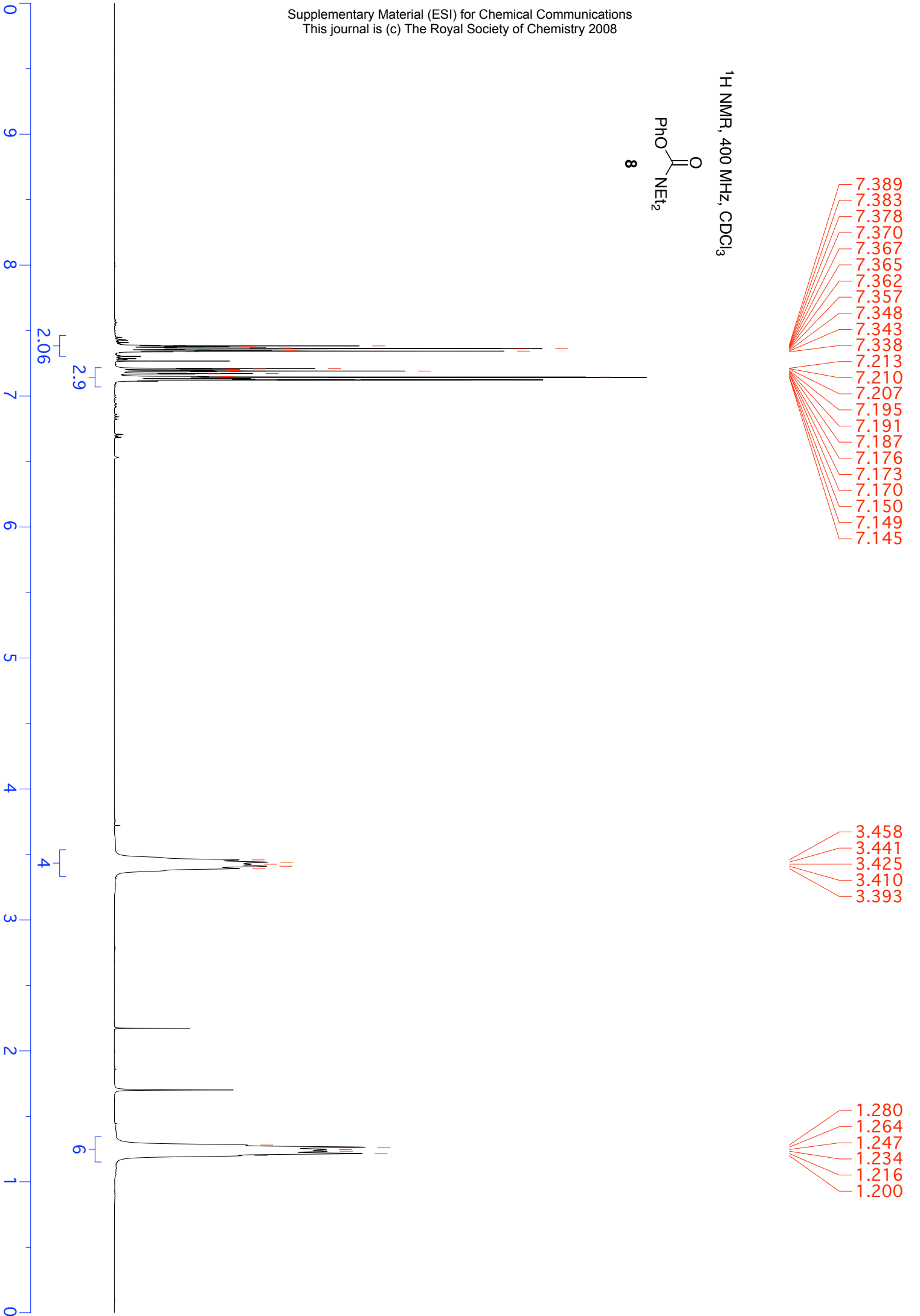


(±)-**7**

2.18 2.05 3.26 1

2.07 7.46 2.23 1.01

0 9 8 7 6 5 4 3 2 1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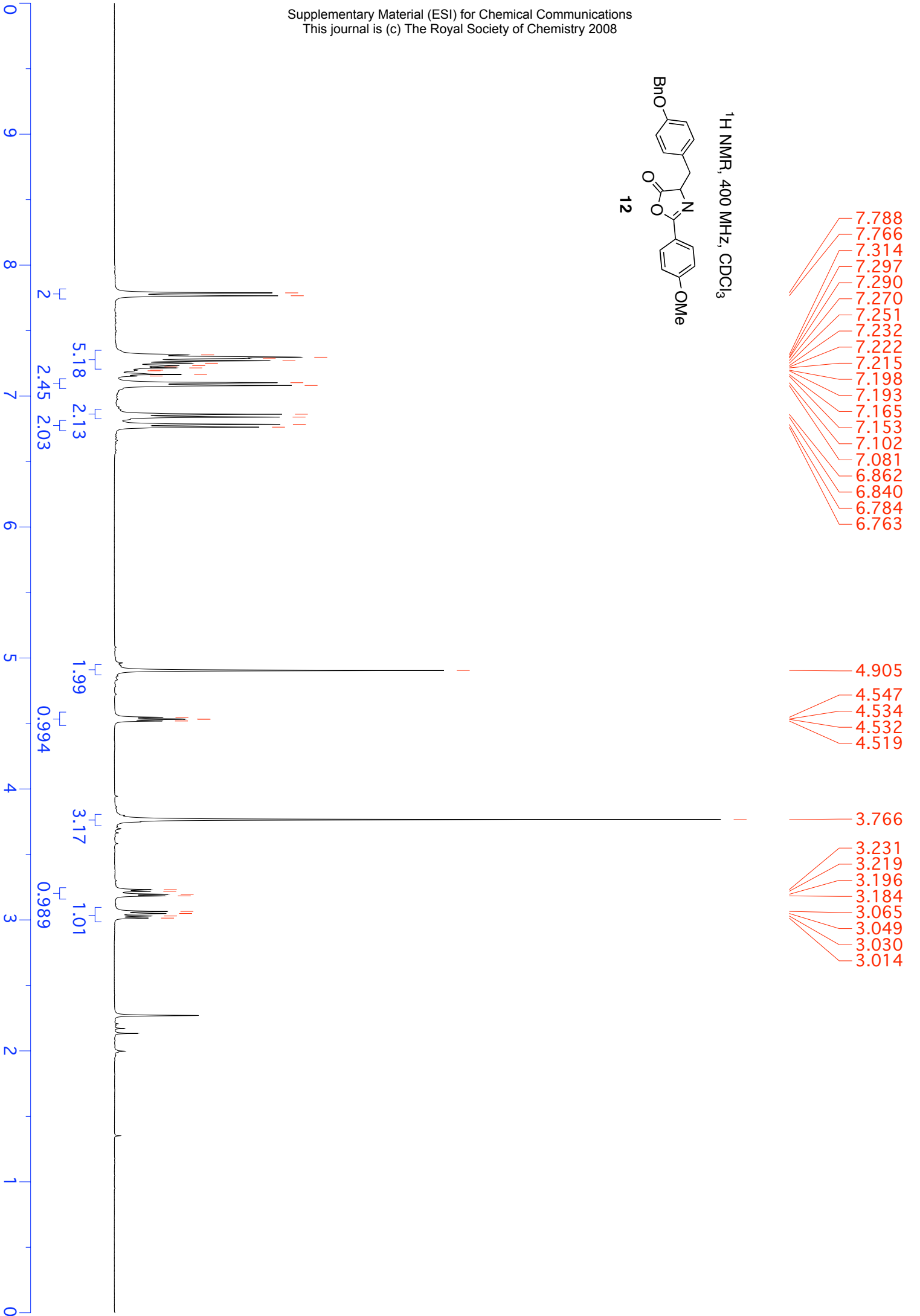
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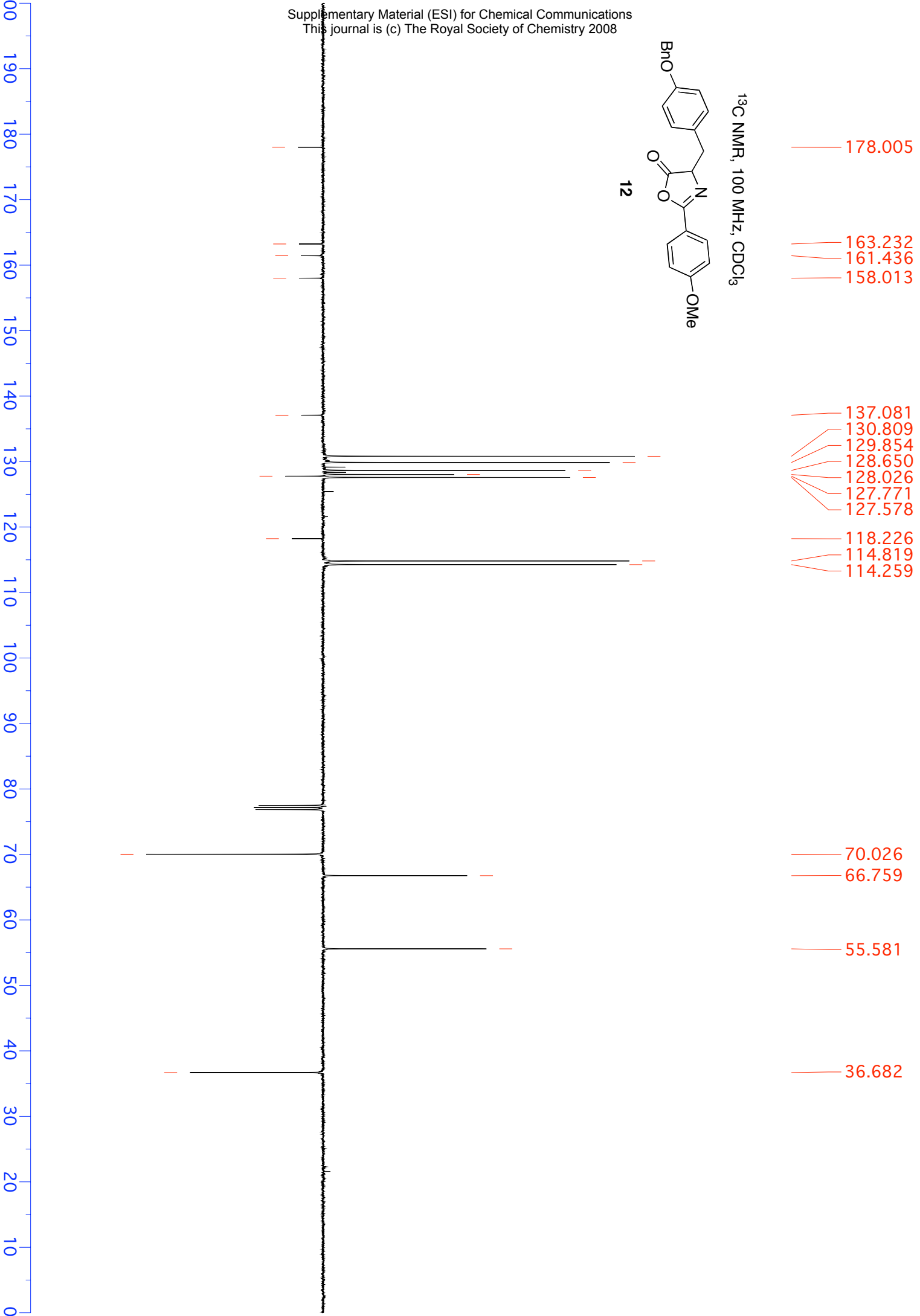
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OMe
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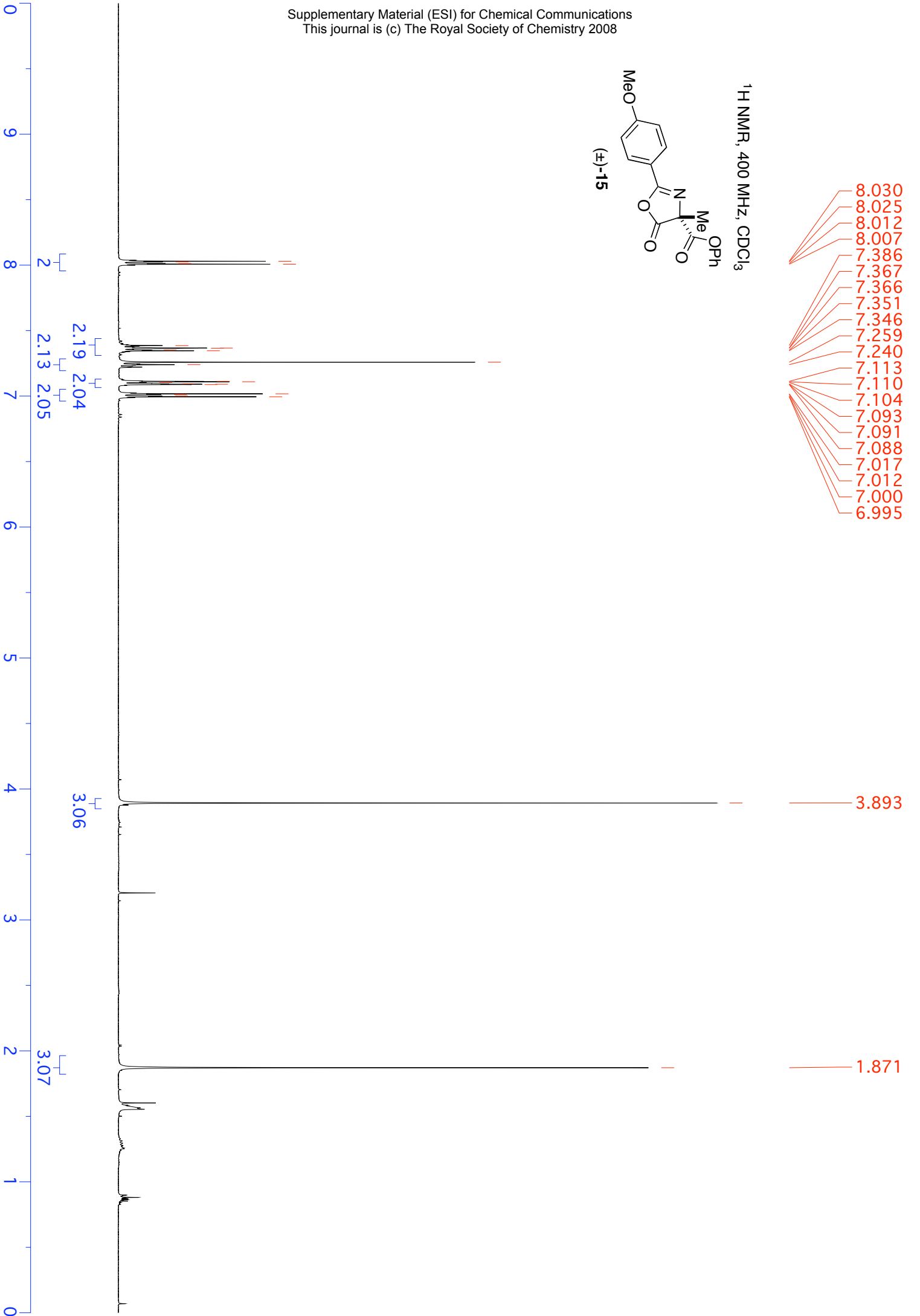
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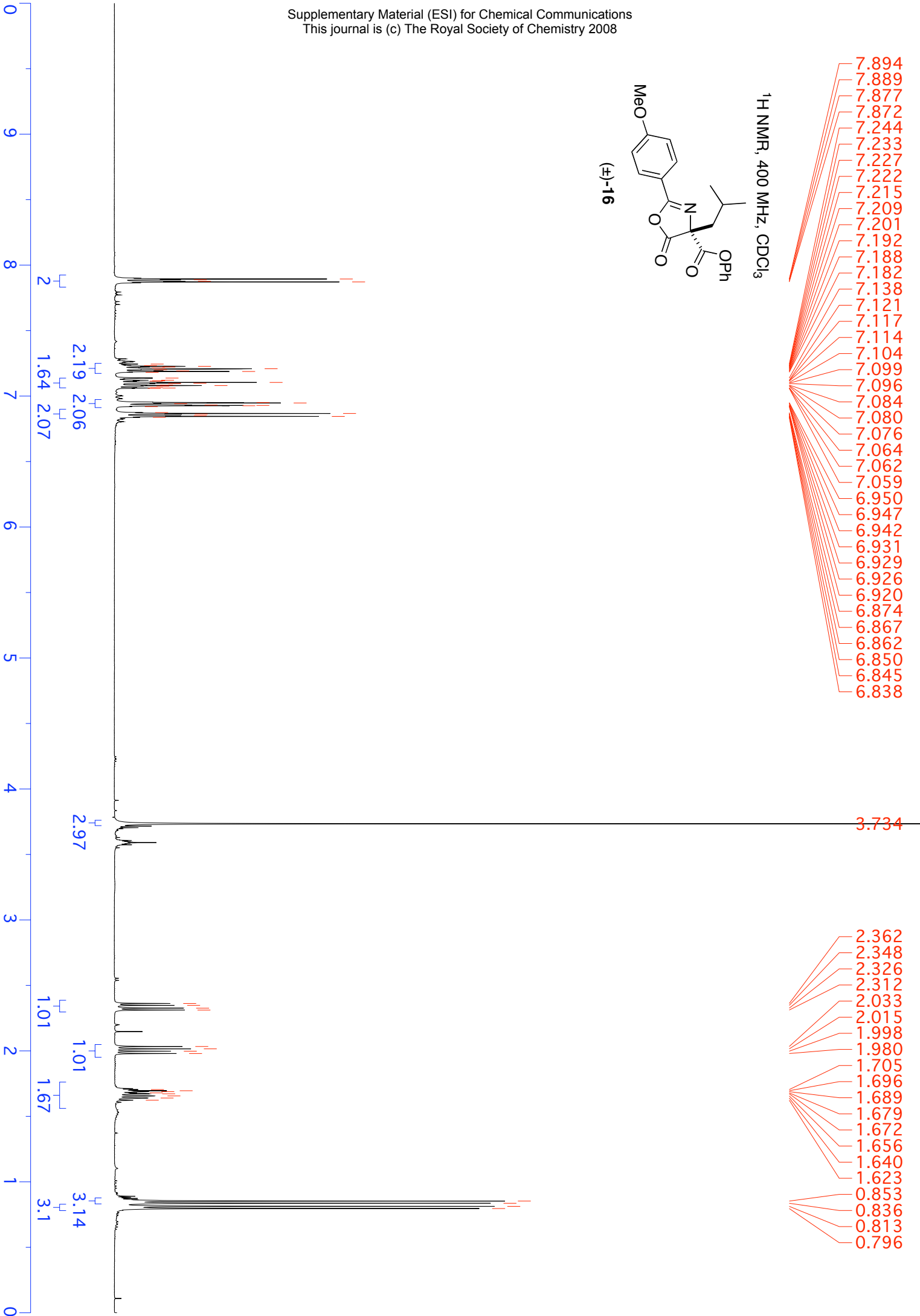
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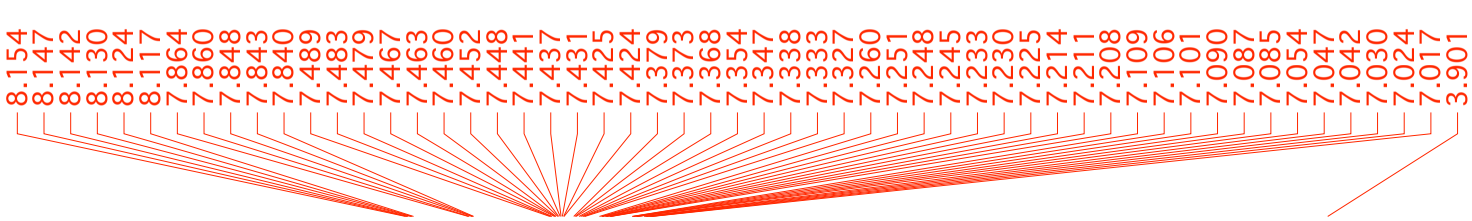
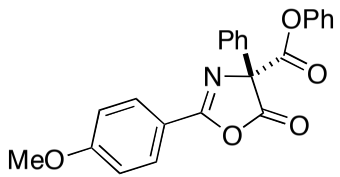
6.920
6.874
6.867
6.862
6.850
6.845
6.838
3.734
2.362
2.348
2.326
2.312
2.033
2.015
1.998
1.980
1.705
1.696
1.689
1.679
1.672
1.656
1.640
1.623
0.853
0.836
0.813
0.796
2
2.19
2.06
1.64
2.07
2.97
1.01
1.01
1.67
3.14
3.1

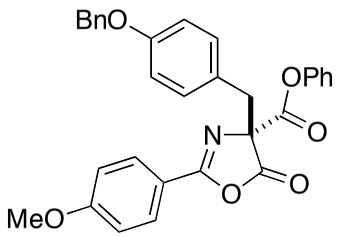


^{1}H NMR, 400 MHz, $CDCl_3$

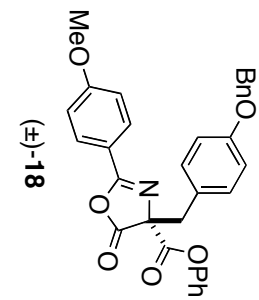


(±)-**17**

^{1}H NMR, 300 MHz, $CDCl_3$



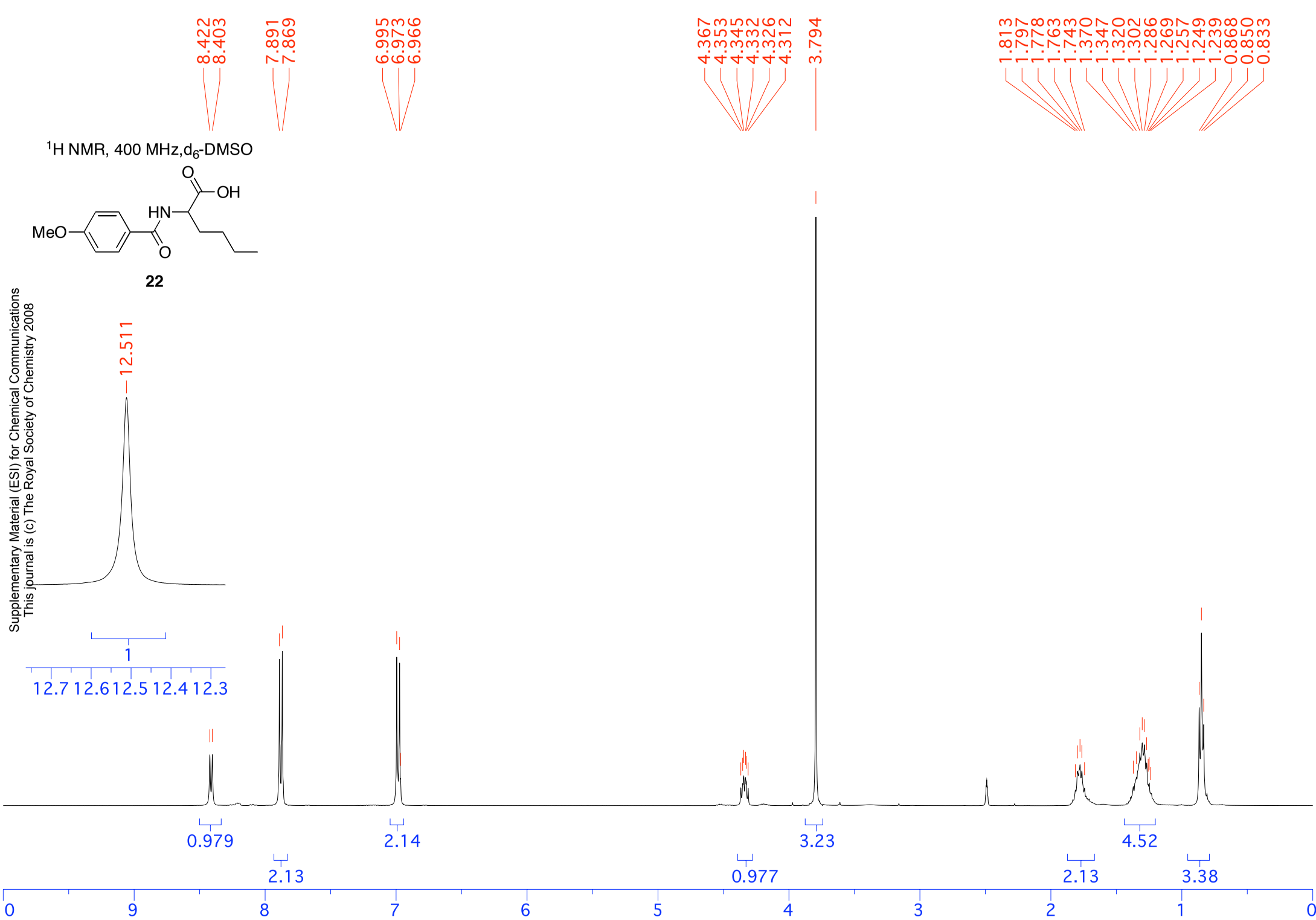
(±)-**18**

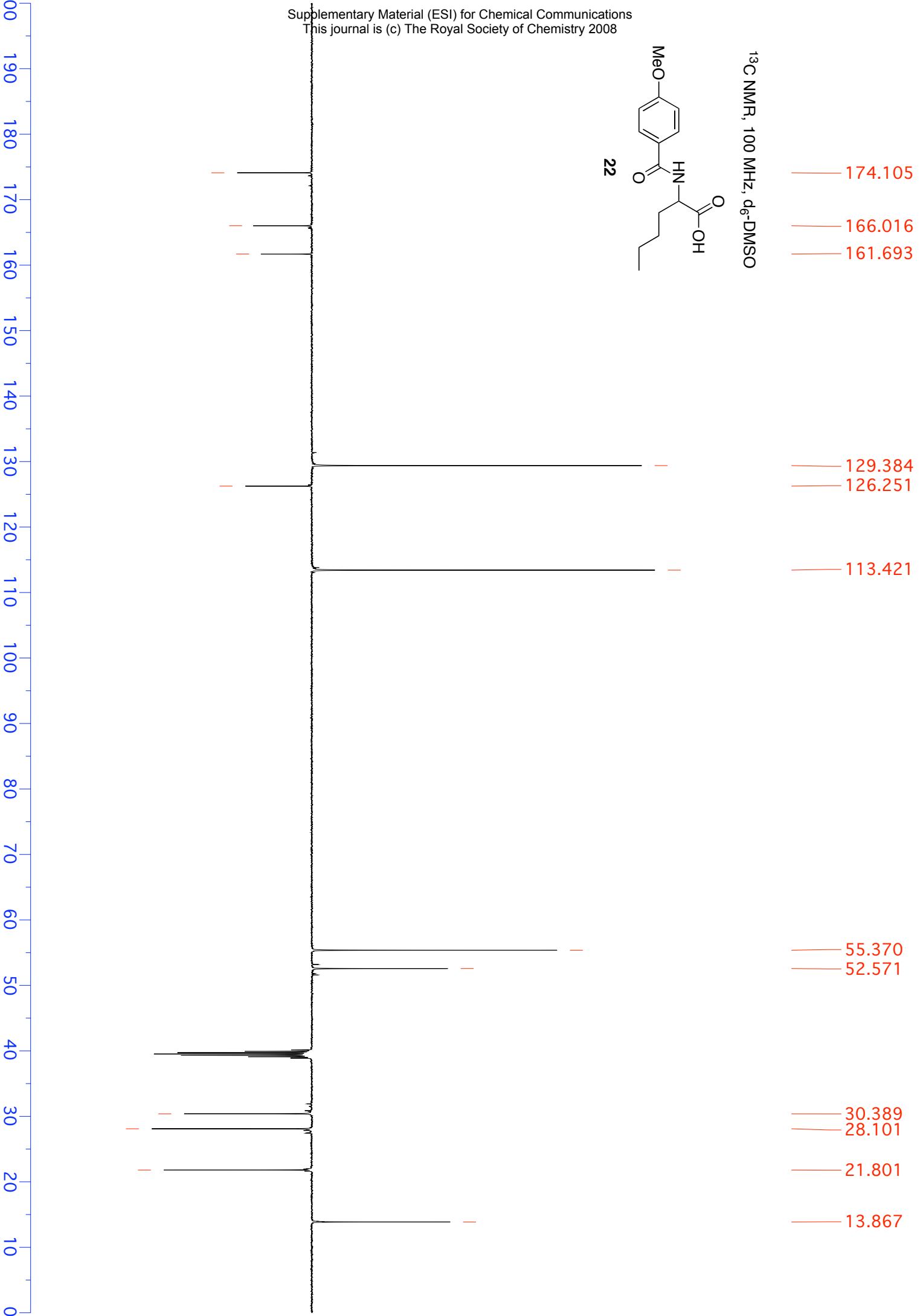


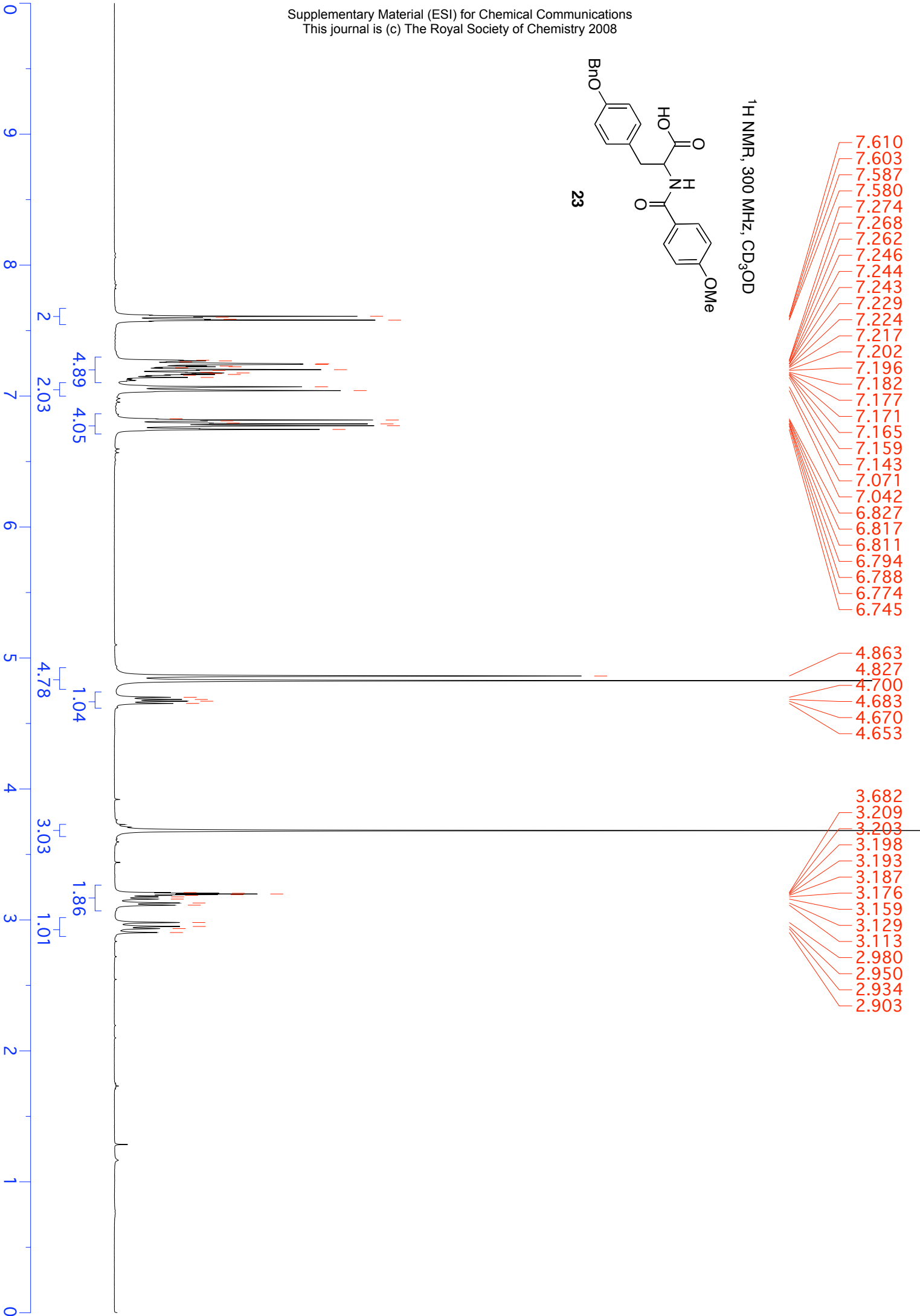
(±)-**18**

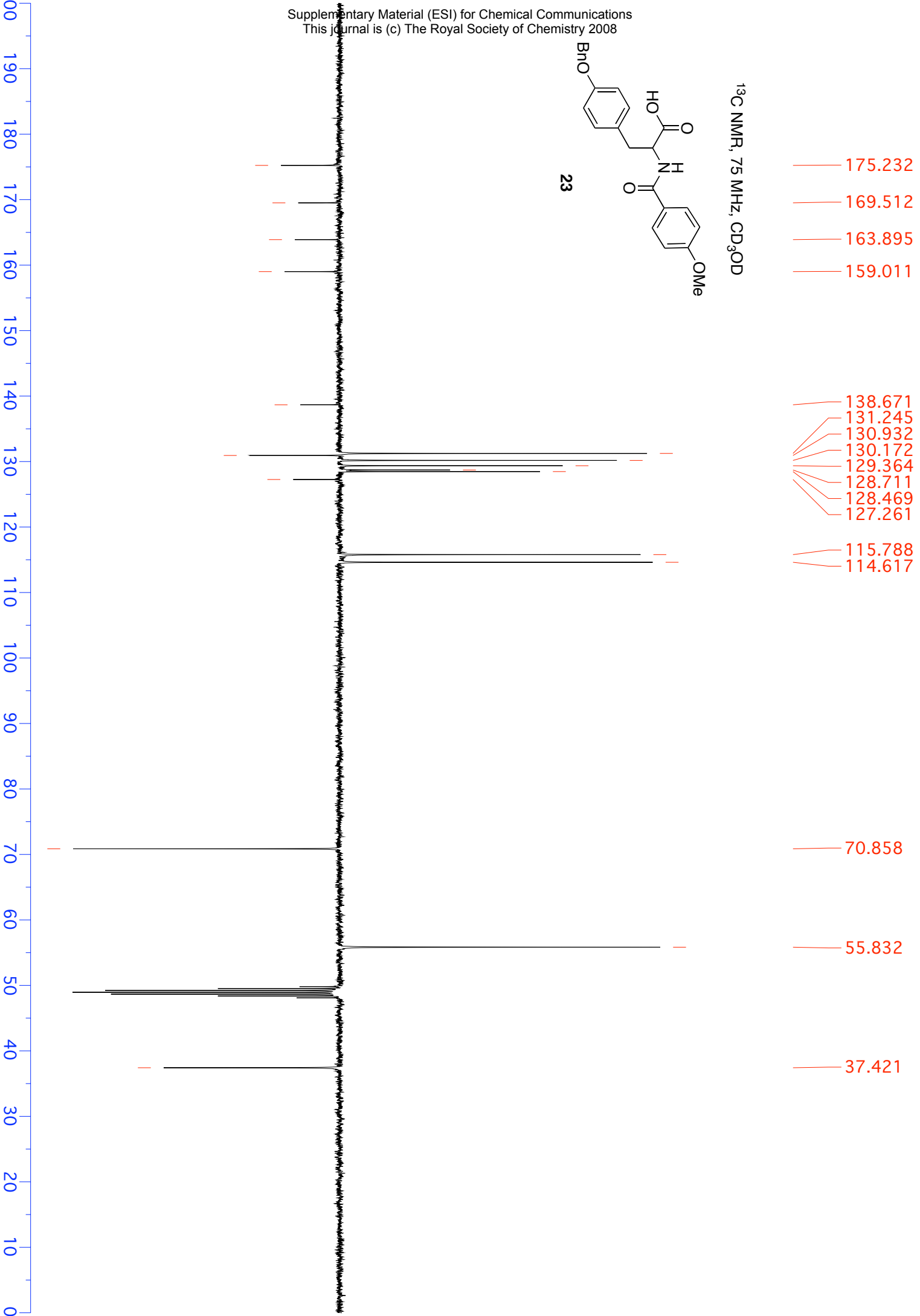
^{13}C NMR, 100 MHz, $CDCl_3$

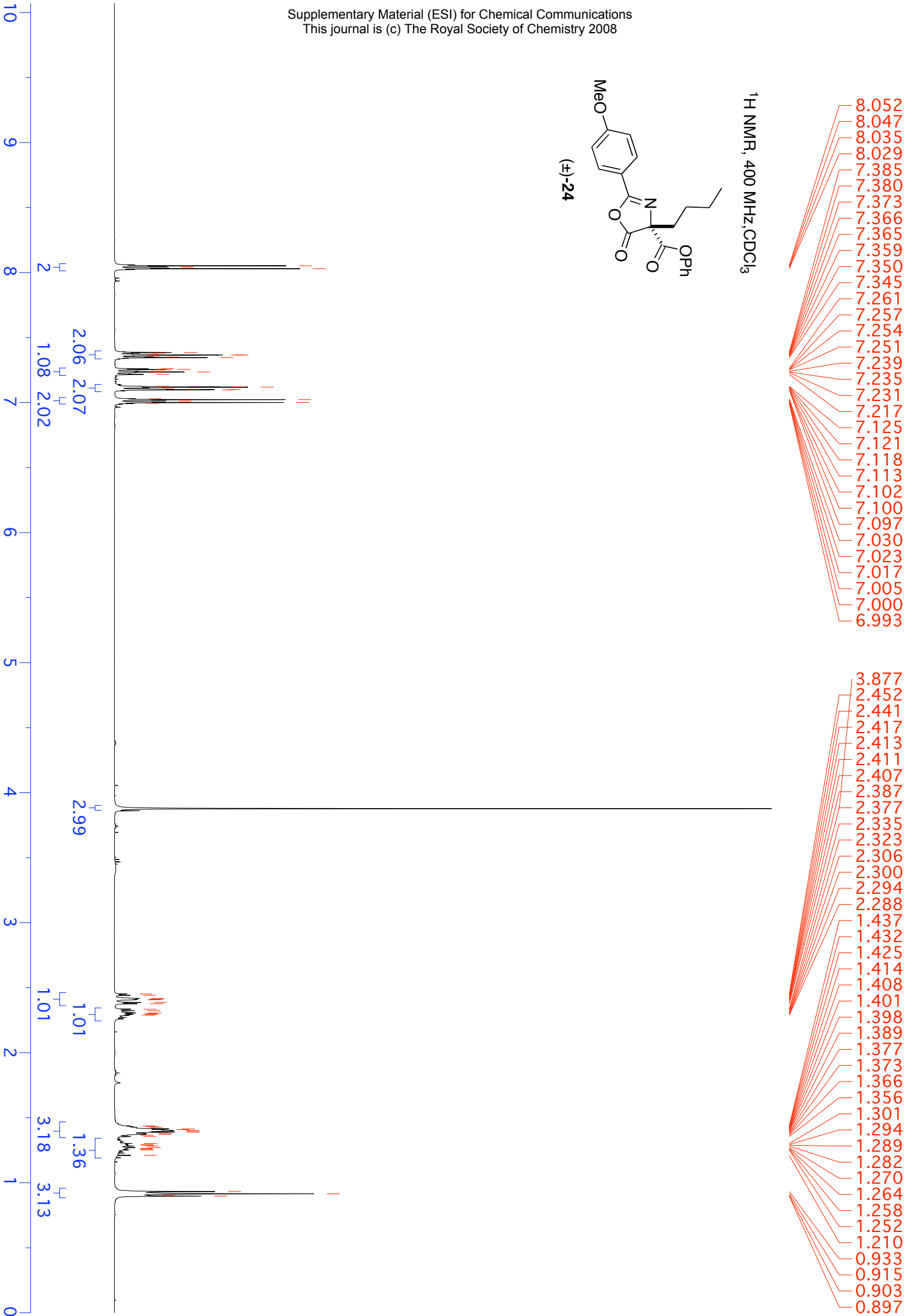
173.794
164.736
163.824
163.266
158.400
150.420
136.989
131.860
131.758
130.408
129.697
128.692
128.096
127.605
126.679
125.161
121.312
117.354
114.832
114.498
114.427
77.827
70.036
55.696
39.655

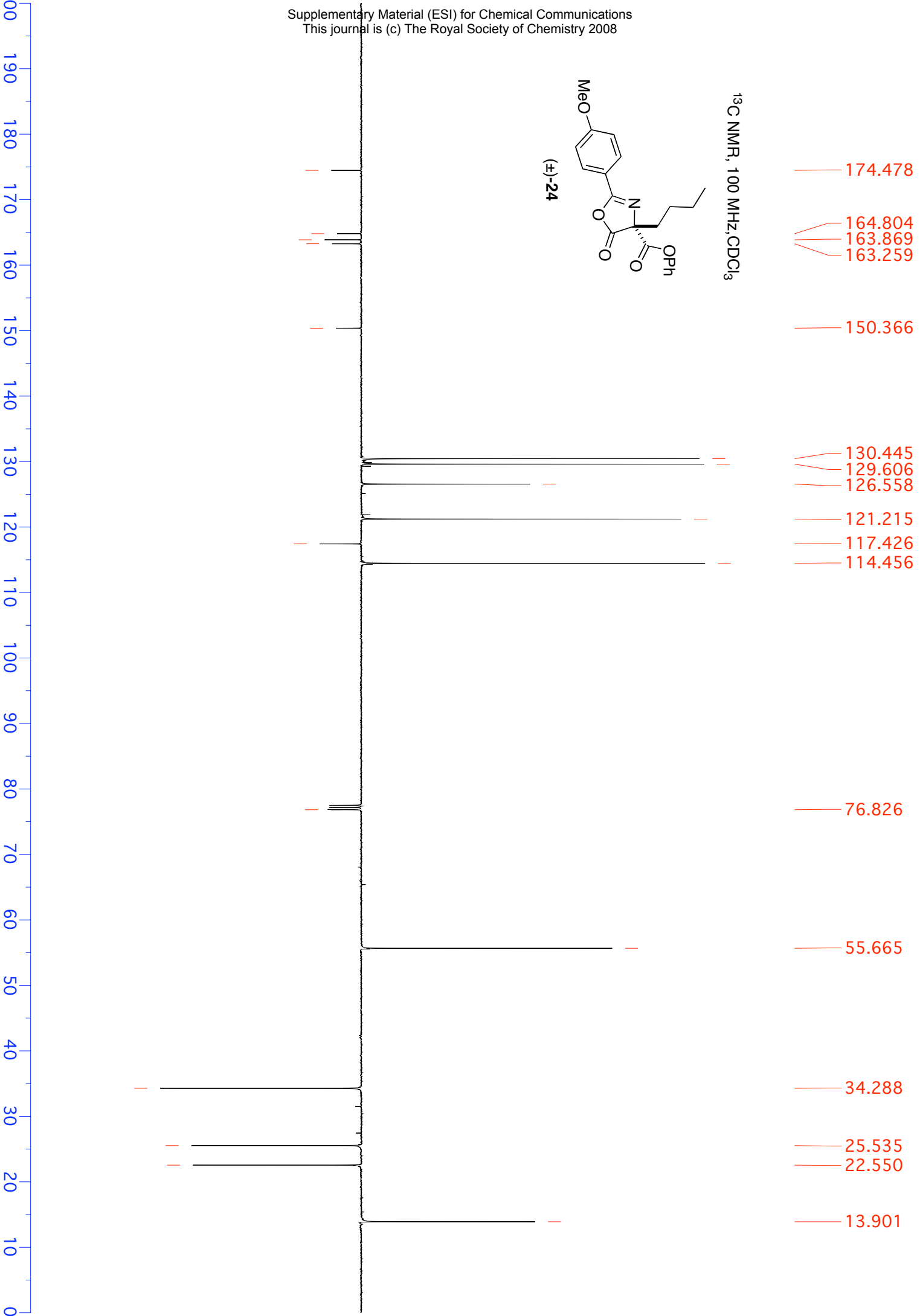


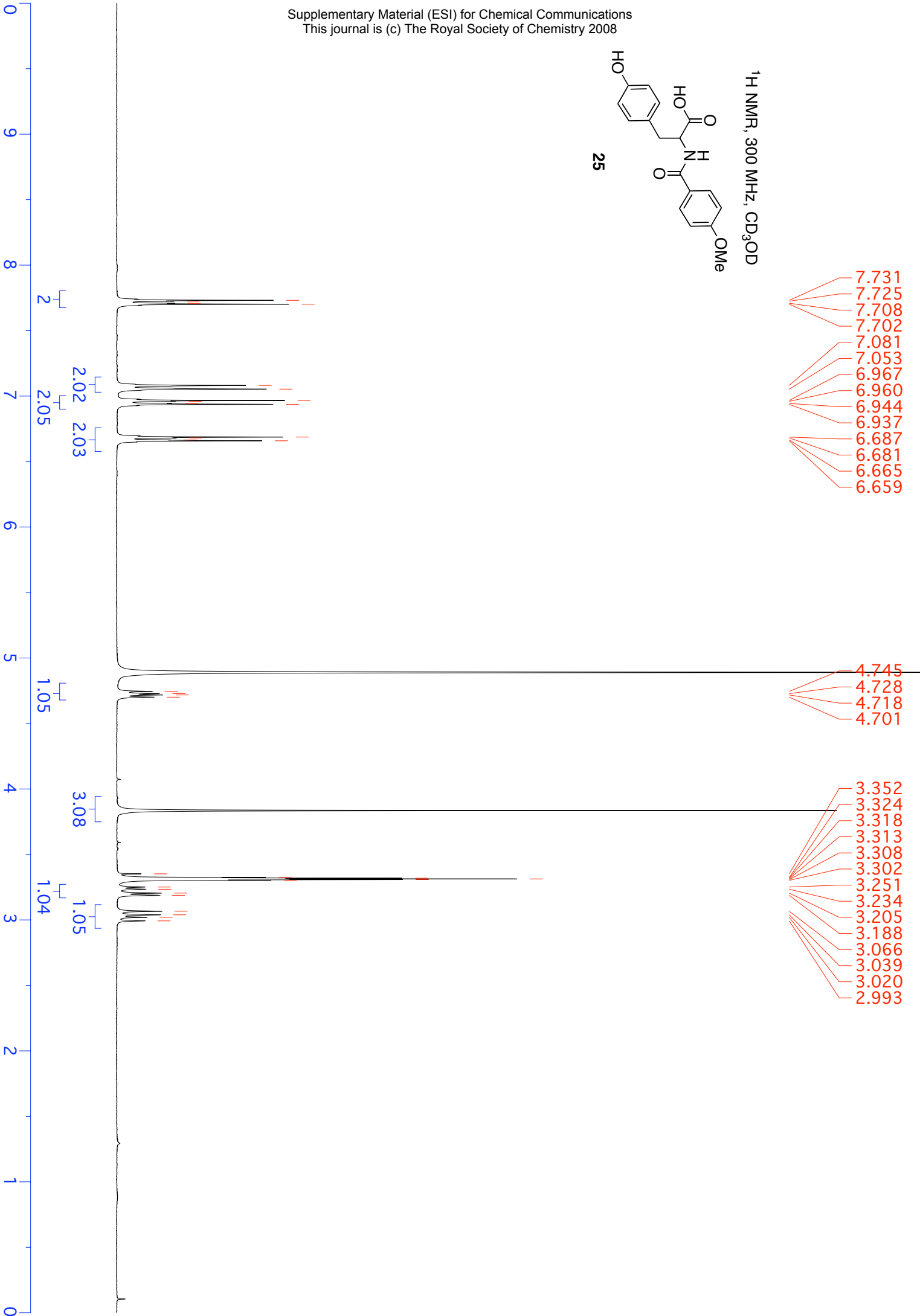

MeO
HN
O
O
OH
22
^{13}C NMR, 100 MHz, d_6-DMSO
174.105
166.016
161.693
129.384
126.251
113.421
55.370
52.571
30.389
28.101
21.801
13.867

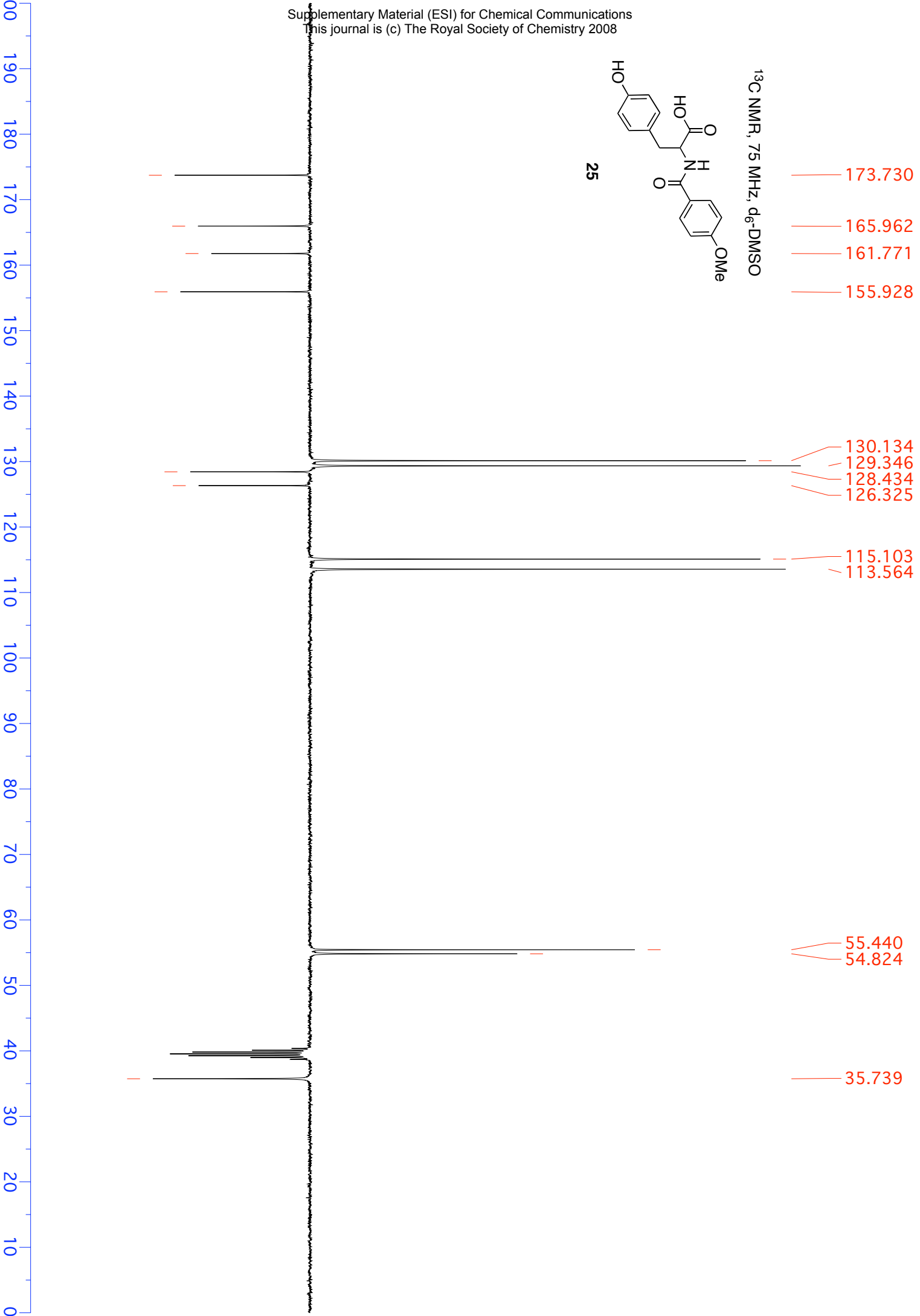

BnO
HO
O
N
H
O
OMe
23
^{1}H NMR, 300 MHz, CD_3OD
7.610
7.603
7.587
7.580
7.274
7.268
7.262
7.246
7.244
7.243
7.229
7.224
7.217
7.202
7.196
7.182
7.177
7.171
7.165
7.159
7.143
7.071
7.042
6.827
6.817
6.811
6.794
6.788
6.774
6.745
4.863
4.827
4.700
4.683
4.670
4.653
3.682
3.209
3.203
3.198
3.193
3.187
3.176
3.159
3.129
3.113
2.980
2.950
2.934
2.903
2
4.89
2.03
4.05
4.78
1.04
3.03
1.86
1.01

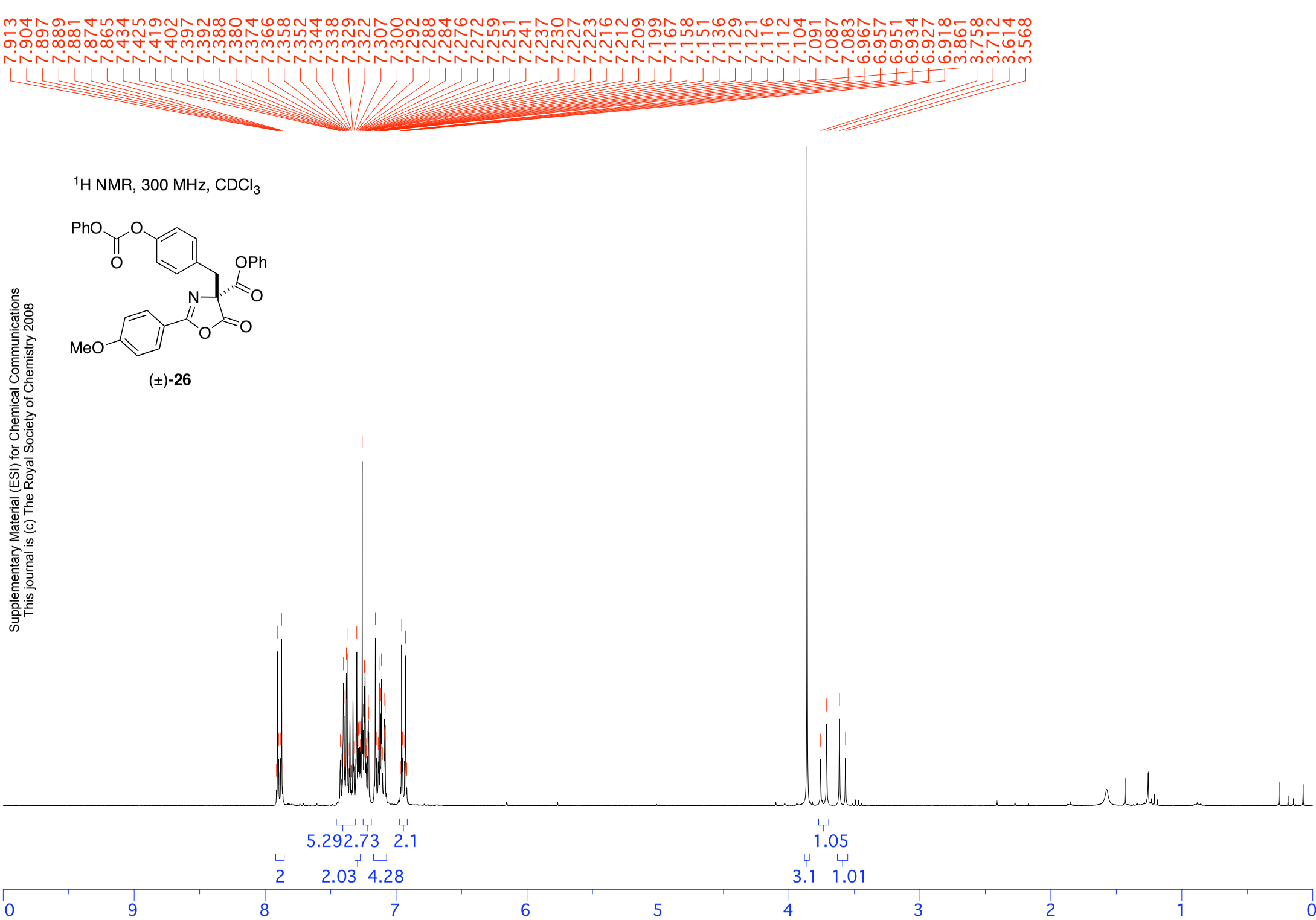

BnO
HO
O
H
N
O
OMe
23
^{13}C NMR, 75 MHz, CD_3OD
175.232
169.512
163.895
159.011
138.671
131.245
130.932
130.172
129.364
128.711
128.469
127.261
115.788
114.617
70.858
55.832
37.421
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

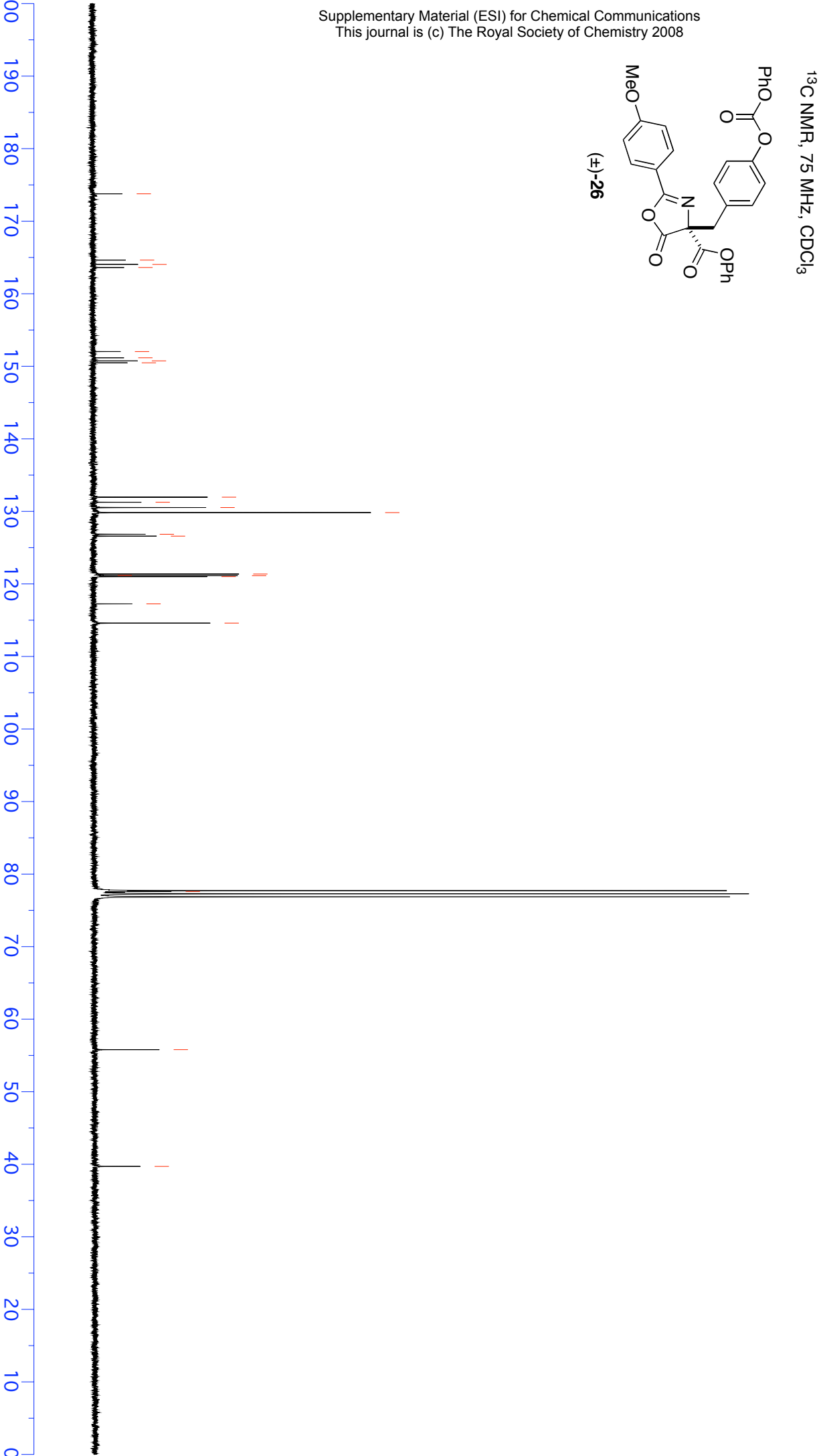

(±)-24
MeO
N
O
O
O
OPh
^{1}H NMR, 400 MHz, $CDCl_3$
8.052
8.047
8.035
8.029
7.385
7.380
7.373
7.366
7.365
7.359
7.350
7.345
7.261
7.257
7.254
7.251
7.239
7.235
7.231
7.217
7.125
7.121
7.118
7.113
7.102
7.100
7.097
7.030
7.023
7.017
7.005
7.000
6.993
3.877
2.452
2.441
2.417
2.413
2.411
2.407
2.387
2.377
2.335
2.323
2.306
2.300
2.294
2.288
1.437
1.432
1.425
1.414
1.408
1.401
1.398
1.389
1.377
1.373
1.366
1.356
1.301
1.294
1.289
1.282
1.270
1.264
1.258
1.252
1.210
0.933
0.915
0.903
0.897
2
2.06
2.07
1.08
2.02
2.99
1.01
1.01
3.18
1.36
3.13
10
9
8
7
6
5
4
3
2
1
0


MeO
N
O
O
O
OPh
(±)-24
^{13}C NMR, 100 MHz, $CDCl_3$
174.478
164.804
163.869
163.259
150.366
130.445
129.606
126.558
121.215
117.426
114.456
76.826
55.665
34.288
25.535
22.550
13.901


25
^{1}H NMR, 300 MHz, CD_3OD
HO
HO
O
N
H
O
OMe
7.731
7.725
7.708
7.702
7.081
7.053
6.967
6.960
6.944
6.937
6.687
6.681
6.665
6.659
4.745
4.728
4.718
4.701
3.352
3.324
3.318
3.313
3.308
3.302
3.251
3.234
3.205
3.188
3.066
3.039
3.020
2.993
2
2.02
2.05
2.03
1.05
3.08
1.04
1.05


25
^{13}C NMR, 75 MHz, d_6-DMSO
173.730
165.962
161.771
155.928
130.134
129.346
128.434
126.325
115.103
113.564
55.440
54.824
35.739




MeO
PhO
O
N
OPh
(±)-26
^{13}C NMR, 75 MHz, CDCl$_3$
173.778
164.638
164.041
163.617
152.028
151.171
150.746
150.479
131.956
131.259
130.528
129.828
126.843
126.587
121.362
121.178
121.138
121.009
117.249
114.598
77.606
55.801
39.706