

Chemo- and stereospecific solid-state dimerization of lithium *trans*-2-butenolate and lithium *trans*-2-butenolate formamide solvateWen Shang,^a Magali B. Hickey,^a Volker Enkelmann,^b Barry B. Snider^{*a} andBruce M. Foxman^{*a}^a *Department of Chemistry, MS015, Brandeis University, Waltham, MA 02454-9110 USA and*^b *Max-Planck-Institut für Polymerforschung, Postfach 3148, D-55021 Mainz, Germany*snider@brandeis.edu, foxman1@brandeis.edu**Supporting Information**

Experimental Procedures	S2-S10
Tables S1-S5 Showing Assignment of the ¹H NMR Spectra of 13b, 22a, 24b, 26 and 28	S11-S15
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General methods and Instrumentation. ^1H and ^{13}C NMR spectra were recorded on either a Varian Unity Inova-400 (400 MHz) or Varian Unity Inova-600 (600MHz) spectrometer. NOESY, ROESY and GCOSY experiments were recorded on a Varian Unity Inova-400 (400 MHz) or -600 (600MHz) spectrometer. Chemical shifts are given in δ (ppm upfield from TMS). NMR spectra in D_2O were referenced to HDO or acetone at δ 4.79 and δ 2.08, respectively. ^{13}C NMR multiplicities were assigned by APT experiments. The following abbreviations are used to indicate signal multiplicity (NMR) or spectral characteristics (IR): s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplet; dq, doublet of quartet; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; m, multiplet; br, broad; sh, shoulder. A Gammacell 220 Irradiator (Atomic Energy of Canada, Ltd.) equipped with a ^{60}Co source, nominal activity 2.6 kGy/d as of June 1, 2002, was used for some γ -irradiation experiments. The facility at the Radiation Laboratory, University of Massachusetts Lowell with nominal activity of 20 kGy/h was used for other experiments. Diazomethane was prepared by adding *N*-nitroso-*N*-methylurea to a mixture of 40% by weight aqueous KOH solution and ether.³² All purchased starting materials were used without further purification. To seal salts under nitrogen, the salt was placed in a 3 mm inside diameter glass tube. A septum is placed at the rim of the tube. The sample is then evacuated for 2 min and purged with nitrogen for 1 min. The glass tubes are sealed using an air/glass flame.

Preparation of Crystalline Lithium *trans*-2-Butenoate (11). Lithium hydroxide monohydrate (2.52 g, 0.06 mol) was added to *trans*-2-butenoic acid (5.42 g, 0.063 mol) in 100 mL of 1:1 $\text{H}_2\text{O}/\text{EtOH}$. The reaction mixture was stirred at room temperature for two hours and the resulting solution was filtered. The filtrate was then allowed to evaporate at room temperature in a tissue-covered crystallization dish. Thin, plate-like colorless crystals were obtained within two weeks.

X-Ray data collection, solution, and refinement for 11. Data collection was carried out at room temperature (low temperature apparatus was not available) on a CAD-4U diffractometer equipped with $\text{CuK}\alpha$ radiation,^{28a} completeness was 99.8%. The structure was solved by direct

methods (SIR92).²⁹ From the systematic absences, the observed metric constants and intensity statistics, space group *I2/a* was chosen initially; subsequent solution and refinement confirmed the correctness of this choice. The unit cell setting differs from that published by Beck and Trübenbach on the identical material;¹⁶ in that case space group *C2/c* was chosen, with a very large β angle (158.97°). In order to avoid the correlations associated with refinement in oblique unit cells,²⁷ we chose the non-standard *I2/a* setting, with $\beta = 96.37^\circ$. Full-matrix least squares refinement was carried out using the Oxford University *Crystals for Windows* system.³⁰ All non-hydrogen atoms were refined using anisotropic displacement parameters. After preliminary location on electron density difference maps, hydrogen atoms were first regularized with the use of restraints and subsequently allowed to ride on the corresponding C atoms. The final least-squares refinement converged to $R_1 = 0.0552$; $wR_2 = 0.0680$ ($I > 2\sigma(I)$, 644 data) and $R_1 = 0.0981$; $wR_2 = 0.1190$ (F , all 1011 data, 64 parameters). The final CIF file is available as supporting material.

γ -Irradiation of **11.** A sample of **11** (1 gram, 10.9 mmol) was put into a small glass vial, capped under air, and irradiated at 2.6 kGy/day for 170 d with aliquots removed for NMR spectroscopic analysis at various times. The conversion of **11** to **13a** was as follows: 1% after 1 d (2.6 kGy), 5.5% after 12 d (31.2 kGy), 9.7% after 26 d (67.6 kGy), 14.1% after 34 d (88.4 kGy), 18.6% after 61 d (158 kGy), 24.0% after 89 d (231.4 kGy), and 31.6% after 170 d (442 kGy)

The ¹H NMR spectrum of a sample of γ -irradiated **11** (γ -ray dose 88 kGy, 34 d) indicated the presence of an 86:14 mixture of unreacted **11** and dilithium *trans*-5-methyl-2-heptenedioate (**13a**): ¹H NMR (D₂O) 0.86 (d, 3, $J = 6.1$), 1.91-2.06 (m, 3), 2.11-2.20 (m, 2), 6.58 (dt, 1, $J = 15.3, 7.3$); H₂ is obscured by residual **11**.

A sample of γ -irradiated **11** (γ -ray dose 231.4 kGy, 89 d) was converted to the free acid by dissolving 10 mg in 1 mL of D₂O and adding two drops of DCl (20% in D₂O). The NMR spectrum indicated the presence of a 74:26 mixture of unreacted *trans*-2-butenoic acid and *trans*-5-methyl-2-heptenedioic acid (**13b**): ¹H NMR (D₂O/DCl) 0.92 (d, 3, $J = 6.7$), 2.03-2.12 (m, 1), 2.19 (dd, 1, $J = 15.2, 7.9$), 2.15-2.28 (m, 2), 2.34 (dd, 1, $J = 15.2, 6$), 6.95 (dt, 1, $J = 15.2, 7.3$);

H₂ is obscured by residual *trans*-2-butenoic acid.

A third sample sealed under nitrogen was irradiated at 20 kGy/h for a total dose of 500 kGy (1 d). The ¹H NMR spectrum showed an 85:15 mixture of **11** and **13a**. A portion (180 mg) was dissolved in 10 mL of 1 M HCl, which was extracted with eight 10 mL portions of methylene chloride. The combined organic layers were dried (MgSO₄), filtered, and treated with ethereal diazomethane³² until the yellow color persisted. Dilute aqueous acetic acid was then added to quench the residual diazomethane. The layers were separated and the aqueous layer was washed with methylene chloride three times. The combined organic layer were dried (MgSO₄) and concentrated to remove methyl *trans*-2-butenoate affording 10 mg of dimethyl *trans*-5-methyl-2-heptenedioate (**13c**): ¹H NMR (CDCl₃) 0.98 (d, 1, *J* = 5.5), 2.10-2.36 (m, 5), 3.67 (s, 3), 3.73 (s, 3), 5.85 (d, 1, *J* = 15.2), 6.92 (dt, 1, *J* = 15.2, 7.3); ¹³C NMR (CDCl₃) 19.7 (CH₃), 29.7 (CH), 39.0 (CH₂), 40.8 (CH₂), 51.4 (OCH₃), 51.5 (OCH₃), 122.8 (CH), 146.9 (CH), 166.8 (CO₂), 173.0 (CO₂). The data are identical to those previously reported.^{17a}

Preparation of Crystalline Lithium *trans*-2-Butenoate•Formamide (12**).** Lithium hydroxide monohydrate (1.28 grams, 0.03 mol) was added to a solution of *trans*-2-butenoic acid (2.64 grams, 0.03 mol) in 40 mL of H₂O. The mixture was stirred at room temperature for ten min. Formamide (8.11 grams, 0.18 mol) was then added to the solution and the mixture was stirred at room temperature for three h. The resulting solution was filtered and the filtrate was allowed to evaporate in air at room temperature. In some cases, colorless acicular, good quality crystals of **12** were obtained from the filtrate within two weeks. Only those crystals were used for X-ray structure determination and further solid-state reactivity study. In other cases, however, plate-like crystals, rather than acicular crystals, were obtained that tended to have poor crystallographic quality. The ¹H NMR spectrum of the acicular crystals indicated that the molar ratio of formamide ligand to *trans*-2-butenoate ligand was about 1:1. The ¹H NMR spectrum of the plate-like crystals did not indicate the presence of formamide in the crystals. An intensive study of the crystal growth of **12** revealed that high-quality, crystalline **12** could only be obtained in a very dry atmosphere in which crystal growth by evaporation was relatively fast (within one

week). When the crystal growth was slow (over several weeks), plate-shaped crystals were usually formed. In some situations, even when **12** was obtained, the crystals would automatically transform from acicular to plate-like morphology when allowed to remain in contact with solvent for more than one month. From these observations, we believe that the acicular crystal **12** is a metastable phase. The plate-like crystals may simply be **11**, although crystals of **11** prepared by from water as described above are extremely thin plates.

X-Ray data collection, solution, and refinement for 12. Data collection was carried out at 120K on a Nonius KappaCCD diffractometer at the Max-Planck-Institut für Polymerforschung, Mainz, Germany, using omega scans and graphite-monochromated MoK α radiation;^{28b,28c} completeness was 98.5%. The structure was solved by direct methods (SIR92).²⁹ From the lack of systematic absences, the observed metric constants and intensity statistics, space group *C2/c* was chosen initially; subsequent solution and refinement confirmed the correctness of this choice. Full-matrix least squares refinement was carried out using the Oxford University *Crystals for Windows* system.³⁰ All non-hydrogen atoms were refined using anisotropic displacement parameters. After preliminary location on electron density difference maps, hydrogen atoms were refined using isotropic displacement parameters. The final least-squares refinement converged to $R_1 = 0.0336$; $wR_2 = 0.0864$ ($I > 2\sigma(I)$, 1587 data) and $R_1 = 0.0498$; $wR_2 = 0.0925$ (F^2 , all 2124 data, 123 parameters). The final CIF file is available as supporting material.

γ -Irradiation of 12. Crystalline **12** is unstable in air. After filtration, crystals of **12** (~1 gram) were immediately transferred to a small glass vial, capped to prevent loss of formamide, and irradiated at 2.6 kGy/day for 111 days with aliquots removed for NMR spectroscopic analysis at various times. The conversion of **12** to **13d** was as follows: 29.6% after 0.67 d (1.7 kGy), 50.9% after 1.67 d (4.3 kGy), 61.5% after 4 d (10 kGy), 65.4% after 7 d (18 kGy), 68.4% after 18 d (47 kGy), 77.9% after 36 d (94 kGy), 78.8% after 47 d (122 kGy), 81.5% after 85 d (221 kGy), and 81.5% after 111 d (288 kGy). The NMR spectrum of a mixture of γ -irradiated **11** and **12** showed the presence of a single dimer confirming that the products are identical. A 200 mg sample of **12** that had been irradiated for 1 d was acidified with concentrated HCl until

the pH reached 4 (2 drops). The solution was extracted with 3 × 5 mL of methylene chloride. The organic layers were combined, dried (MgSO₄), and concentrated under reduced pressure to give 115 mg of a 2:1 mixture of *trans*-2-butenic acid and **13b** as a colorless solid. The data for **13b** were determined from the mixture: ¹H NMR (CDCl₃) 1.03 (d, 3, *J* = 5.5), 2.20-2.35 (m, 5), 5.84 (d, 1, *J* = 15.8), 7.04 (dt, 1, *J* = 15.8, 7.4).

***tert*-Butyl 3-Hydroxybutanoate-2,2-*d*₂ (17)**. A 7:1 mixture of THF/D₂O (80 mL) was added to *tert*-butyl acetoacetate (**16**, 10 g, 63 mmol) and the resulting mixture was stirred at room temperature for 24 h. THF was then removed under reduced pressure and the partially deuterated acetoacetate and aqueous layers were separated and the aqueous layer was discarded. The cycle described above was repeated. The partially deuterated acetoacetate was stirred for 24 h for a third time with 7:1 THF/D₂O without the evaporation step to give a solution of *tert*-butyl acetoacetate-2,2-*d*₂ (**17**). The solution was cooled to 0 °C and sodium borohydride (1.18 g, 31 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h and THF was removed under reduced pressure. The remaining oil was treated dropwise with concentrated hydrochloric acid (2 mL) until the pH was 4 and was then extracted with 3 × 50 mL of methylene chloride. The organic extracts were combined, dried (MgSO₄), and concentrated under reduced pressure to give 7.8 g of **17** as a light yellow oil. Bulb-to-bulb distillation (55 °C, 0.5 torr) gave 7.4 g (73%) of **17** as a colorless oil: ¹H NMR (CDCl₃) 1.20 (d, 3, *J* = 6.1), 1.47 (s, 9), 4.13 (q, 1, *J* = 6.1).

***tert*-Butyl 3-Methanesulfonyloxybutanoate-2,2-*d*₂ (18)**. Triethylamine (4.49 g, 44 mmol) was added to a stirred solution of **17** (6.00 g, 37 mmol) in 50 mL of dry methylene chloride at room temperature. The reaction mixture was stirred at room temperature for 10 minutes, cooled in an ice bath to 0 °C, and methanesulfonyl chloride (4.24 g, 37 mmol) was added dropwise. After stirring at 0 °C for 1 h, the reaction mixture was slowly poured into 25 mL of 1 M NaHCO₃ and the aqueous and organic layers were separated. The aqueous layer was further extracted with 3 × 30 mL of methylene chloride, and the combined organic extracts were washed with water, dried (MgSO₄), and concentrated under reduced pressure to give 7.56 g (75%) of **18** as an orange oil: ¹H NMR (CDCl₃) 1.46 (s, 9), 1.48 (d, 3, *J* = 6.1), 3.04 (s, 3), 5.08 (q, 1, *J*

= 6.1). Deuterium incorporation was determined by integration of the residual peaks for the CH₂ group at δ 2.67-2.78, and was calculated to be 96-97%.

***tert*-Butyl *trans*-2-Butenoate-2-*d* (19).** 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (7.83 g, 51 mmol) was added dropwise to a stirred solution of **18** (7.00 g, 26 mmol) in 50 mL of dry methylene chloride. The reaction mixture was stirred at room temperature for 24 h and was quenched by the addition of 30 mL of 1 M acetic acid. The aqueous and organic layers were separated and the aqueous layer was further extracted with 3 \times 30 mL of methylene chloride. The combined organic extracts were washed with water, dried (MgSO₄), and concentrated under reduced pressure to give 3.48 g of **19** as a light orange oil. Bulb-to-bulb distillation (55 °C, 0.5 torr) gave 3.41 g (92%) of **19** as a colorless oil: ¹H NMR (CDCl₃) 1.48 (s, 9), 1.84 (d, 3, *J* = 7.3) 6.83 (qt [1:1:1], 1, *J* = 7.3, *J*_{H-D} = 2.1). Deuterium incorporation was determined from integration of the residual peaks for the CH group at δ 5.76 (br d, 1, *J* = 16), and was calculated to be 93-94%.

***trans*-2-Butenoic-2-*d* Acid (20).** Ester **19** (3.40 g, 23 mmol) was dissolved in 25 mL of benzene and *p*-toluenesulfonic acid (0.7 g, 3.8 mmol) was added. The reaction mixture was heated at reflux using a flask fitted with a Dean-Stark trap and condenser for 1 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give a mixture of *trans*-2-butenoic-2-*d* acid (**20**) and *p*-toluenesulfonic acid as a light yellow solid. The solid was purified by filtration through 25 g of silica gel (7:3 hexane/ethyl acetate) to give 1.6 g (81%) of **20** as a colorless solid, with the *p*-toluenesulfonic acid retained on the silica gel: ¹H NMR (CDCl₃) 1.92 (d, 3, *J* = 6.7), 7.10 (qt [1:1:1], 1, *J* = 6.7, *J*_{H-D} = 2.1). Deuterium incorporation determined from integration of the residual peaks for the CH group at δ 5.86 (br d, 1, *J* = 16) was calculated to be 94-95%.

Lithium *trans*-2-Butenoate-2-*d* (21). Acid **20** (1.00 g, 12 mmol) was dissolved in 20 mL of water and lithium hydroxide monohydrate (0.49 g, 12 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure to give a colorless solid which was washed with acetone to remove any excess **20** and dried to give 0.98

g (92%) of **21** as a colorless solid, mp > 220 °C.

γ -Ray Induced Irradiation of Lithium *trans*-2-Butenoate-2-*d* (21**) Under Nitrogen. Preparation of *trans*-(5*R*,6*S*)-*rel*-4-Methyl-2-heptenedioic-2,6-*d*₂ Acid (**22b**).** Salt **21** (100 mg, 1.00 mmol) was sealed in a glass tube under nitrogen and irradiated at 20 kGy/h for 10 h (200 kGy). NMR analysis revealed that the solid consisted of 98.5% unreacted salt **21** and 1.5% of lithium *trans*-5-methyl-2-heptenedioate-2,6-*d*₂ (**22a**). For analysis, a portion was dissolved in 1 mL of D₂O and 4 drops of DCl (20% in D₂O) were added. Data for the free acid **22b** were determined from the mixture: ¹H NMR (D₂O/DCl) 0.92 (d, 3, *J* = 6.7), 2.08 (dddq, 1, *J* = 6, 7, 7, 6.7), 2.17 (ddd, 1, *J* = 14, 7, 7), 2.24 (ddd, 1, *J* = 14, 7, 7), 2.32 (d, 1, *J* = 6), 6.94 (t, 1, *J* = 7).

Lithium *trans*-2-Butenoate-2-*d*•Formamide (23**).** Lithium hydroxide monohydrate (0.642 g, 15 mmol) was added to a solution of *trans*-2-butenoic acid-2-*d* (**20**, 1.318 g, 15 mmol) in 20 mL of water. The mixture was stirred at room temperature for 10 min and treated with formamide (4.056 g, 90 mmol). The solution was stirred at room temperature for 3 h and filtered through sintered glass. The filtrate was placed in a 30 mL beaker, which was covered with a tissue held in place with a rubber band. Several holes were placed in the tissue with a needle. After 1 week, crystals were observed. Vacuum filtration gave acicular crystals of **23** (664 mg).

γ -Ray Induced Irradiation of Lithium *trans*-2-Butenoate-2-*d*•Formamide (23**) under nitrogen. Preparation of *trans*-(5*R*,6*R*)-*rel*-4-Methyl-2-heptenedioic-2,6-*d*₂ Acid (**24b**).** Formamide complex **23** (664 mg) was sealed under nitrogen in a glass tube and irradiated for 162 h (19.1 kGy). For analysis, a 20 mg portion was dissolved in 1 mL of D₂O and 4 drops of DCl (20% in D₂O) were added. The spectrum showed a 3:1 mixture of *trans*-2-butenoic acid-2-*d* and dimer **24b** indicating that the reaction proceeded to 40% conversion since there is only one methyl group in the dimer: ¹H NMR (D₂O/DCl) 0.92 (d, 3, *J* = 6.7), 2.08 (dddq, 1, *J* = 7, 7, 7.9, 6.7), 2.18 (ddd, 1, *J* = 14, 7, 7), 2.18 (d, 1, *J* = 7.9, H_{6 β}), 2.24 (ddd, 1, *J* = 14, 7, 7), 6.94 (t, 1, *J* = 7). A small peak (<5%) at δ 2.34 (dd, 1, *J* = 15.2, 6.1) was observed for undeuterated material. A peak for formamide was observed at δ 8.03. Peaks for unreacted *trans*-2-butenoic acid-2-*d* were observed at δ 1.85 (d, 1, *J* = 6.7) and δ 7.01 (br q, 1, *J* = 6.7).

(2*R*, α *R*,4*R*)-rel-Tetrahydro- α -Iodo-4-Methyl-6-Oxo-2*H*-Pyran-2-Acetic Acid (26) and **(2*S*, α *S*,4*R*)-rel-Tetrahydro- α -Iodo-4-Methyl-6-Oxo-2*H*-Pyran-2-Acetic Acid (27)**. To a crude mixture of *trans*-2-butenic acid and **13b** (100 mg, 0.5 mmol [based on the molecular weight of (**12**)] in 25 mL of water was added NaHCO₃ (0.04 mg, 0.05 mmol), iodine (412 mg, 1.5 mmol), and potassium iodide (865 mg, 7.5 mmol). The solution was stirred at 25 °C for 24 h, and treated with small portions of Na₂SO₃ until the mixture became colorless. The resulting mixture was acidified with concentrated hydrochloric acid (1.5 mL) until the pH reached 2, and extracted with 3 × 30 mL of methylene chloride. The organic layers were combined, dried (MgSO₄), and concentrated under reduced pressure to give 65 mg (44% overall) of a mixture of **13b** (60%) and **26** and **27** (35%) as a 2:1 mixture of diastereomers.

NMR data for the major isomer **26** were determined from the mixture: ¹H NMR (CDCl₃) 1.11 (d, 3, *J* = 6.1, Me), 1.21 (ddd, 1, *J* = 13.4, 11.8, 11.4, H_{3 β}), 2.05 (dd, 1, *J* = 17.1, 11.6, H_{5 β}), 2.12-2.18 (m, 1, H₄), 2.55 (ddd, 1, *J* = 13.4, 3.2, 1.8, H_{3 α}), 2.70 (ddd, 1, *J* = 17.1, 4.9, 1.8, H_{5 α}), 4.40 (d, 1, *J* = 8.3, H _{α}), 4.59 (ddd, 1, *J* = 11.4, 8.3, 3.2, H₂). Irradiation of the peak at δ 1.11 showed NOEs to the peaks at δ 1.21, 2.05, 2.12-2.18 and 2.55. Irradiation of the peak at δ 1.21 showed NOEs to the peaks at δ 1.11, 2.05 (small), 2.55, 4.40 and 4.59 (small). Irradiation of peak at δ 2.55 showed NOEs to the peaks at δ 1.11, 1.21, 2.12-2.18 (small), 4.40 (small) and 4.59. Irradiation of the peak at δ 2.70 showed NOEs to the peaks at δ 1.11, 2.05 and 2.12-2.18 (small).

NMR data for minor isomer **27** was determined from the mixture: ¹H NMR (CDCl₃) 1.17 (d, 3, *J* = 6.3), 1.99 (ddd, 1, *J* = 13.7, 9.3, 5.9), 2.21-2.36 (m, 3), 2.55-2.62 (m, 1), 4.38 (d, 1, *J* = 9.3), 4.77 (ddd, 1, *J* = 9.3, 9.3, 4.4).

(2*R*, α *R*,4*R*,5*R*)-rel-Tetrahydro- α -Iodo-4-Methyl-6-Oxo-2*H*-Pyran-2-Acetic Acid-5, α -d₂ (28) and **(2*S*, α *S*,4*R*,5*R*)-rel-Tetrahydro- α -Iodo-4-Methyl-6-Oxo-2*H*-Pyran-2-Acetic Acid-5, α -d₂ (29)**. Crude irradiated **23** (644 mg) containing 40% of dimer **24a** was dissolved in 30 mL of water, which was acidified with concentrated HCl until the pH reached 4. The solution was extracted with 3 × 30 ml of methylene chloride. The organic layers were combined, dried (MgSO₄), and concentrated under reduced pressure to give 370 mg of a 2:3 mixture of the free

acid **24b** and *trans*-2-butenic acid-2-*d* (**20**).

To the above mixture of *trans*-2-butenic acid-2-*d* (**20**) and **24b** (100 mg) in 20 mL of water was added NaHCO₃ (390 mg, 4.6 mmol), iodine (290 mg, 1.2 mmol) and potassium iodide (760 mg, 4.6 mmol). The solution was stirred at 25 °C for 24 h, and treated with small portions of Na₂SO₃ until the mixture became colorless. The resulting mixture was acidified with concentrated HCl until the pH reached 2, and extracted with 3 × 25 mL of methylene chloride. The organic layers were combined, dried (MgSO₄), and concentrated under reduced pressure to give 60 mg (44% overall) of a mixture of *trans*-2-butenic acid-2-*d* (**20**, 84%) and **28** and **29** (16%) as a 2:1 mixture of diastereomers.

NMR data for the major isomer **28** were determined from the mixture: ¹H NMR (CDCl₃) 1.09 (d, 3, *J* = 6.5), 1.24 (dd, 1, *J* = 13, 12, 12), 2.05-2.17 (m, 1), 2.55 (br dd, 1, *J* = 13, 2), 2.69 (br d, 1, *J* = 5), 4.58 (dd, 1, *J* = 12, 2).

NMR data for minor isomer **29** were determined from the mixture: ¹H NMR (CDCl₃) 1.15 (d, 3, *J* = 7), 1.95-2.26 (m, 3), 2.55-2.62 (m, 1), 4.75 (dd, 1, *J* = 8, 4).

References

32. F. Arndt, *Org. Synth., Coll. Vol. II*, 165 (see note 3).

Table S1 Chemical Shifts and Coupling Constants for 13b		
Proton	Chemical Shift (ppm)	Coupling Constants (Hz)
Me	0.92	(d, 3, $J = 6.7$)
H ₃	6.95	(dt, 1, $J = 15.2, 7.3$)
H _{4α}	2.15-2.28	(m, 1)
H _{4β}	2.15-2.28	(m, 1)
H _{5α}	2.03-2.12	(m, 1)
H _{6α}	2.34	(dd, 1, $J = 15.2, 6.1$)
H _{6β}	2.19	(dd, 1, $J = 15.2, 7.9$)

H₂ is obscured by residual **11**.

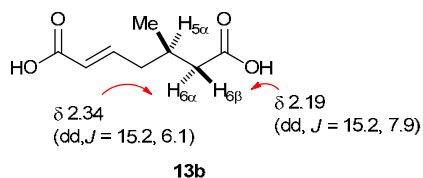


Table S2. Chemical Shifts and Splitting Patterns for 22b		
Proton	Chemical shift (ppm)	Splitting pattern
Me	0.93	(d, 3, $J = 6.7$)
H ₃	6.94	(t, 1, $J = 7$)
H _{4α} or H _{4β}	2.19	(ddd, 1, $J = 14, 7, 7$)
H _{4α} or H _{4β}	2.24	(ddd, 1, $J = 14, 7, 7$)
H _{5α}	2.09	(dddq, 1, $J = 7, 7, 6.1, 6.7$)
H _{6α}	2.32	(d, 1, $J = 6.1$)

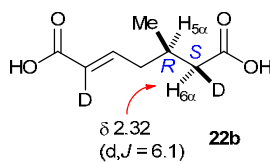


Table S3. Chemical Shifts and Splitting Patterns for 24b		
Proton	Chemical shift (ppm)	Splitting pattern
Me	0.92	(d, 3, $J = 6.7$)
H ₃	6.94	(t, 1, $J = 7$)
H _{4α} or H _{4β}	2.18	(ddd, 1, $J = 14, 7, 7$)
H _{4α} or H _{4β}	2.24	(ddd, 1, $J = 14, 7, 7$)
H _{5α}	2.08	(dddq, 1, $J = 7.9, 7, 7, 6.7$)
H _{6β}	2.18	(d, 1, $J = 7.9$)

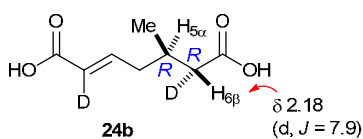


Table S4. Chemical Shift Assignments and COSY and NOESY Data for 26		
H#, Chemical Shift (ppm), splitting pattern	COSY cross peaks	1D NOESY cross peaks
H _α 4.40 (d, 1, <i>J</i> = 8.3)	4.59	----
H _{2a} 4.59 (ddd, 1, <i>J</i> = 11.4, 8.3, 3.2)	1.21, 2.55, 4.40	-----
H _{3α} 2.55 (ddd, 1, <i>J</i> = 13.4, 3.2, 1.8)	1.21, 2.12-2.18, 4.59	1.11, 1.21, 2.12-2.18 (w), 4.40 (w), 4.59
H _{3β} 1.21 (ddd, 1, <i>J</i> = 13.4, 11.8, 11.4)	2.12-2.18, 2.55, 4.59	1.11, 2.05 (w), 2.55, 4.40, 4.59 (w)
H ₄ 2.12-2.18 (m, 1)	1.11, 1.21, 2.05, 2.55, 2.70	-----
H _{5α} 2.70 (ddd, 1, <i>J</i> = 17.1, 4.9, 1.8)	1.21, 2.05, 2.55	1.11, 2.05, 2.12-2.18 (w)
H _{5β} 2.05 (dd, 1, <i>J</i> = 17.1, 11.6)	2.12-2.18, 2.70	-----
Me 1.11 (d, 3, <i>J</i> = 6.1)	2.12-2.18	1.21, 2.05, 2.12-2.18, 2.55

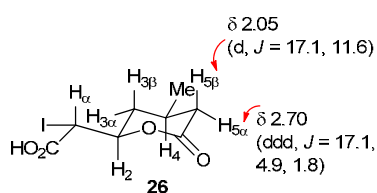
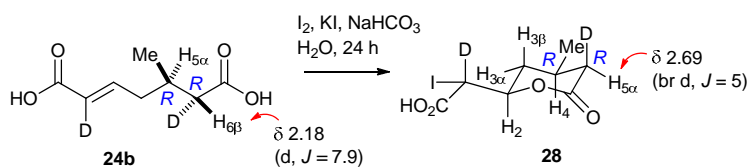
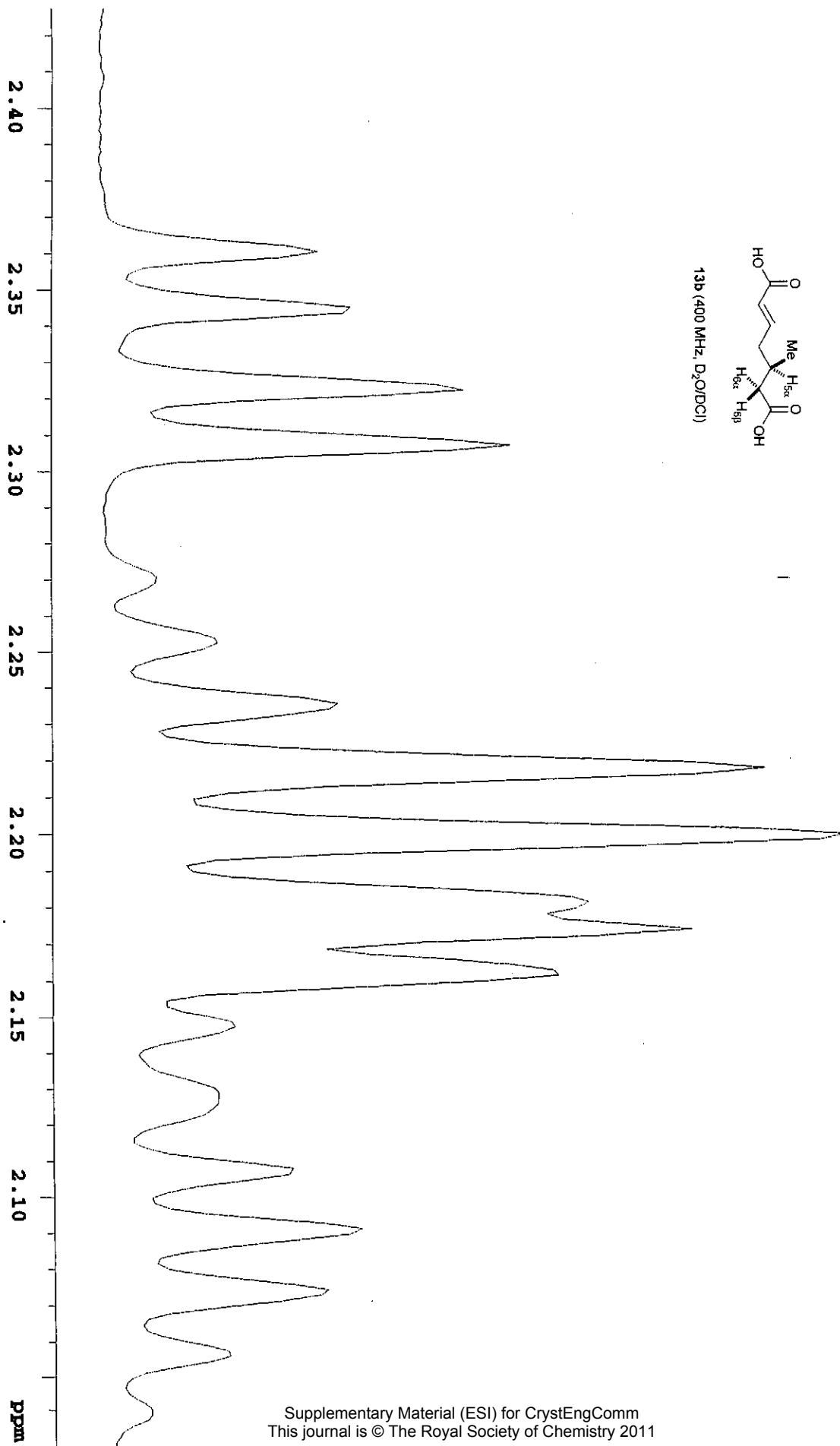
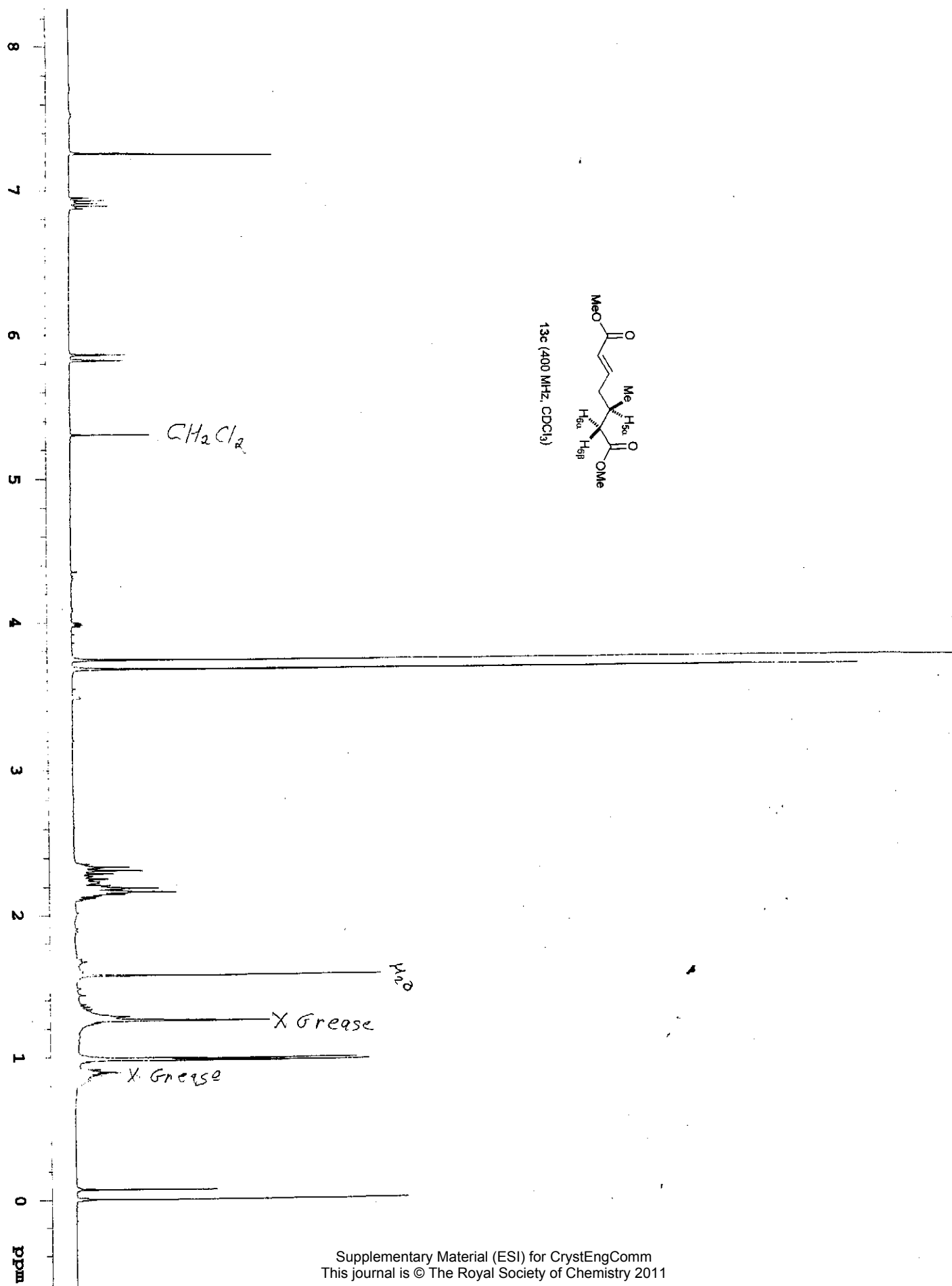


Table S5. Chemical Shift Assignments for **28**

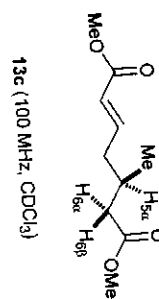
H _# , Chemical Shift (ppm), splitting pattern
H _α Deuterium
H _{2a} 4.58 (dd, 1, <i>J</i> = 12, 2)
H _{3α} 2.55 (br dd, 1, <i>J</i> = 13, 2)
H _{3β} 1.24 (ddd, 1, <i>J</i> = 13, 12, 12)
H ₄ 2.05-2.17 (m, 1)
H _{5α} 2.69 (br d, 1, <i>J</i> = 5)
H _{5β} Deuterium
Me 1.09 (d, 3, <i>J</i> = 6.5)





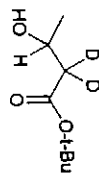


INDEX	FREQUENCY	PPM	HEIGHT
1	17390.438	172.995	35.0
2	16764.045	166.764	26.2
3	14767.371	146.901	69.1
4	12341.913	122.774	67.2
5	7772.529	77.319	157.8
6	7740.485	77.000	165.1
7	7708.440	76.681	166.5
8	5176.167	51.491	83.6
9	5171.589	51.445	84.1
10	4096.575	40.751	133.5
11	3918.041	38.975	107.6
12	2987.990	29.724	97.3
13	2981.123	29.655	23.1
14	1977.827	19.675	119.6
15	98.650	0.981	29.7



tert-1,3-hydroxybutanoate-2-2-d2

Pulse Sequence: zgpg1

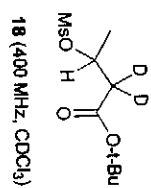


17 (400 MHz, CDCl₃)

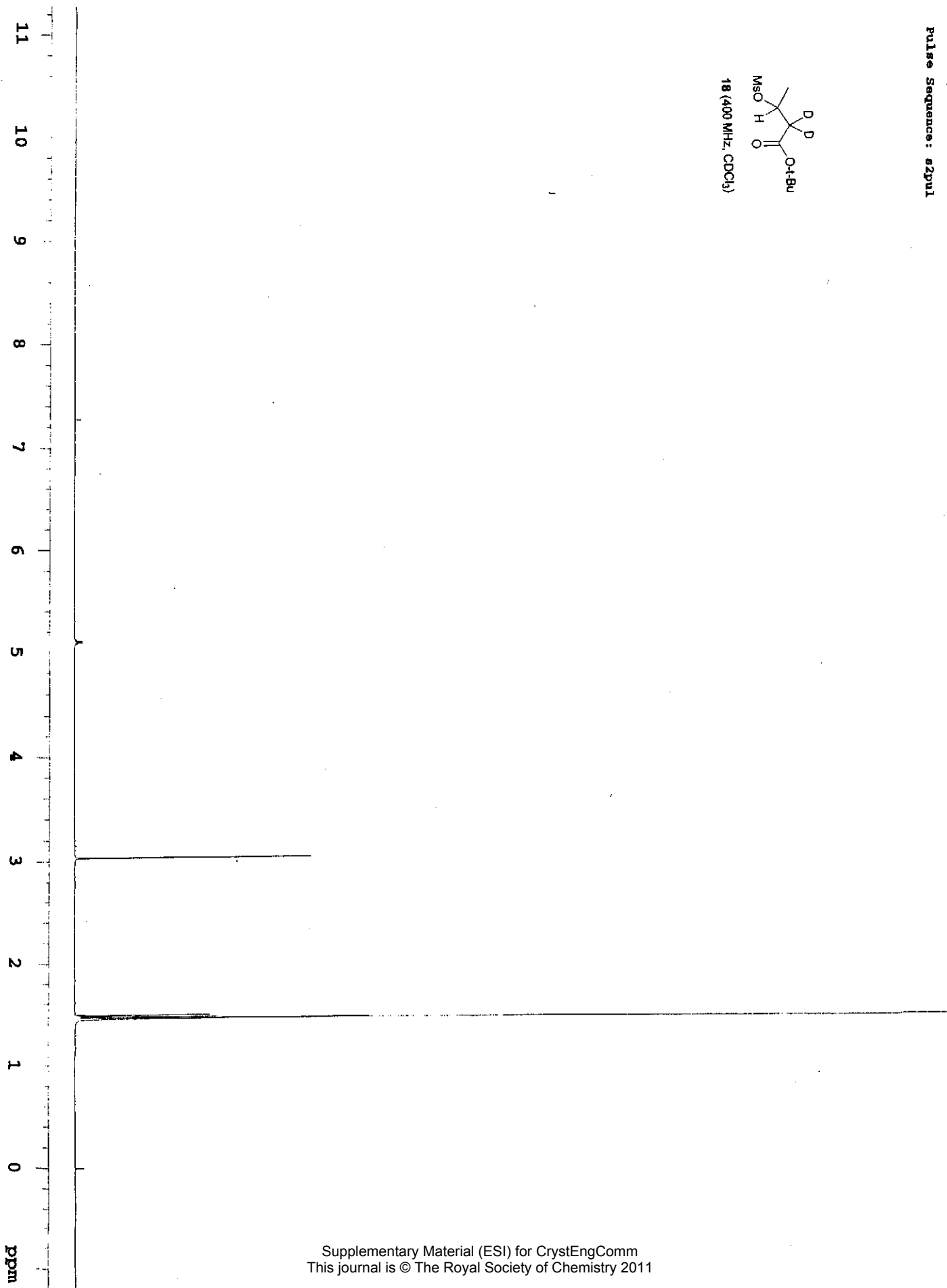


tert. /1-3-methanesulfonyloxypentanoate-2-2-d2

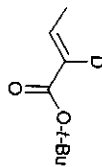
Pulse Sequence: s2pu1



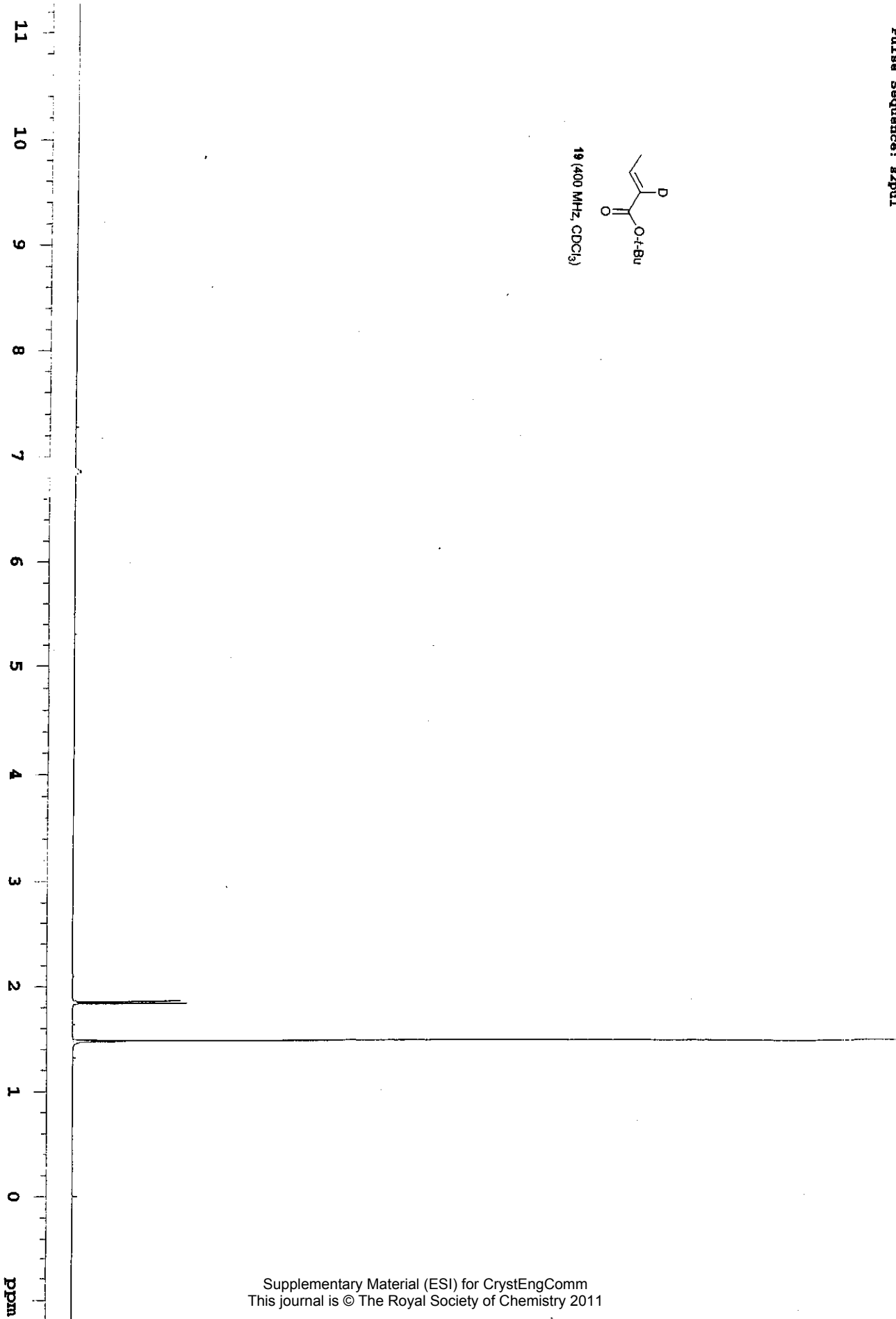
18 (400 MHz, CDCl₃)



cert Y1-(R)-2-Butenoate-2-d
Pulse Sequence: szpu1

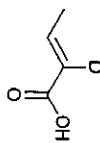


19 (400 MHz, CDCl₃)

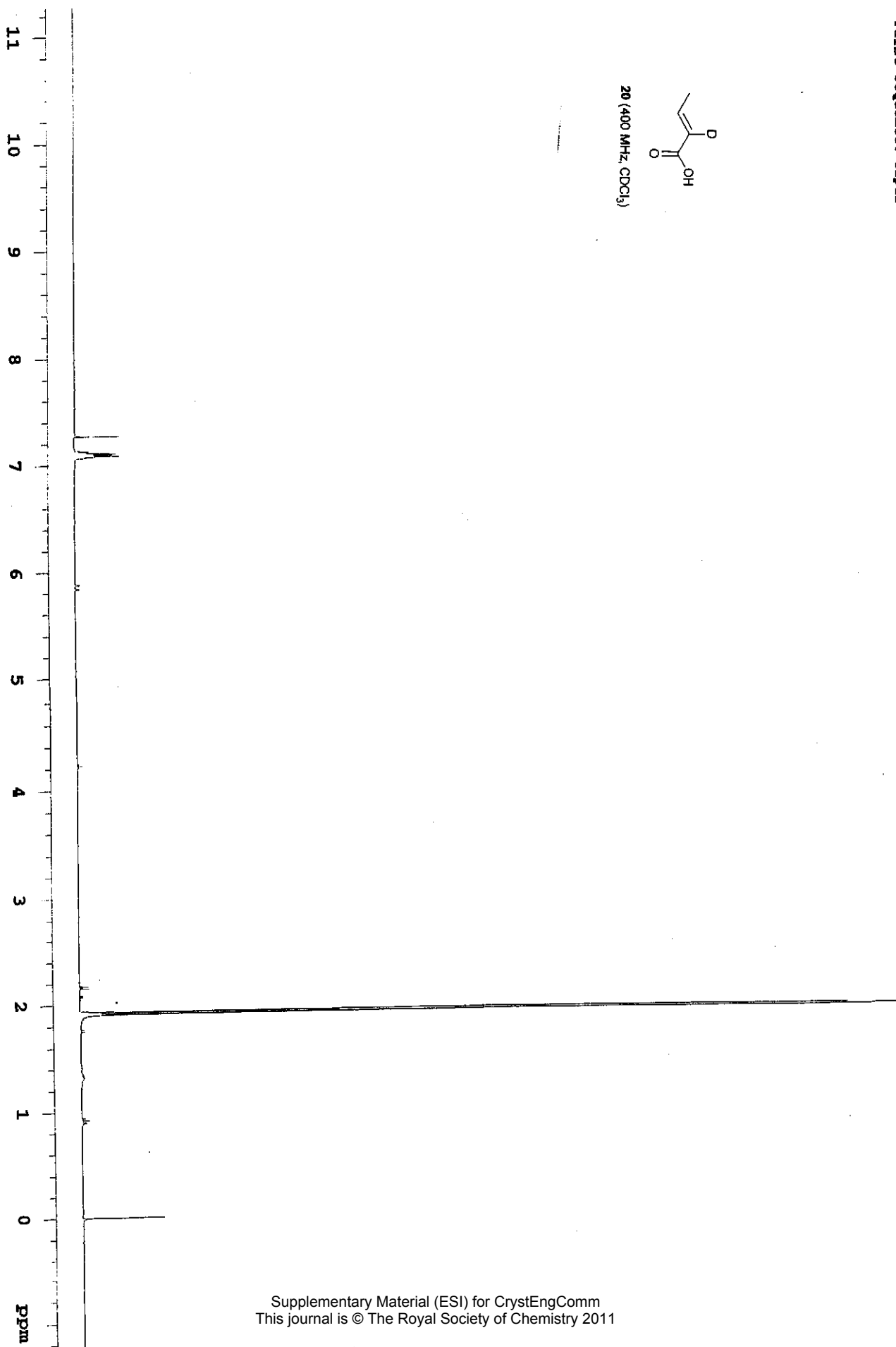


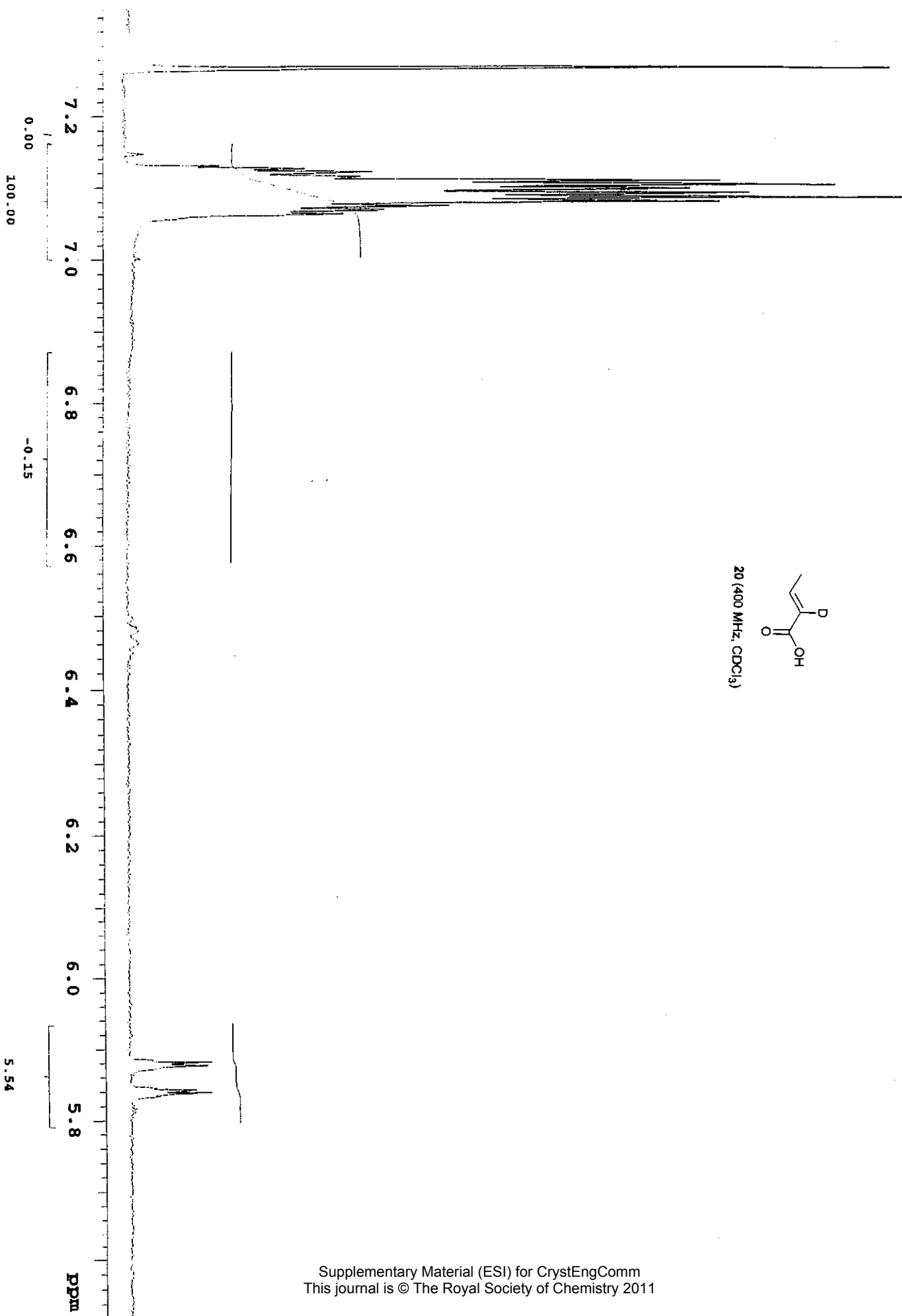
(E)-2,3,6-trimethyl-2-butenoic acid

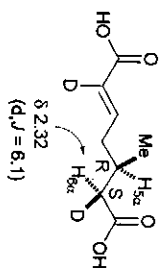
Pulse Sequence: zgpg30



20 (400 MHz, CDCl₃)







22b (400 MHz, D_2O/DCI)

