

Accessory Publication

Concise synthesis of a hydroxylated nine-membered lactone from tartaric acid using the Claisen rearrangement

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Accessory Publication: Experimental procedures for **12**→**15** (both routes), characterisation data for all new compounds, and ¹H and ¹³C JMOD NMR data for **15**.

Experimental

General

Proton (¹H) and carbon (¹³C) NMR spectra were recorded on a Bruker AV400SX spectrometer at 400 and 100 MHz, respectively. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterated chloroform (CDCl₃) or deuterated acetonitrile (CD₃CN) at 20°C. For ¹H NMR spectra, the peak from residual CHCl₃ (δ_{H} 7.26) or CH₃CN (δ_{H} 1.94) was used as the internal reference, while for proton-decoupled ¹³C NMR spectra the central peak of the CDCl₃ triplet (δ_{C} 77.16) or CD₃CN multiplet (δ_{C} 1.32) was used as the reference.^[1] ¹H NMR spectroscopic data are recorded as follows: chemical shift (δ_{H}) [multiplicity, coupling constant(s) *J* (Hz), relative integration, assignment] whereby multiplicity is defined as: s for singlet; d for doublet; t for triplet; q for quartet; m for multiplet; br for broad, or combinations thereof. Assignment of ¹H and ¹³C NMR spectra, except where obvious, were aided by COSY, NOESY, JMOD, HSQC and HMBC experiments. Melting points were recorded on an Electrothermal IA9300 digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer

SPECTRUM 2000 FTIR Spectrometer. Oils were analysed neat as thin films on sodium chloride plates, whereas solids were dissolved in chloroform and deposited on sodium chloride plates; solvent was allowed to evaporate before measurement of the spectra. Positive ion EI mass spectra were run on a ThermoQuest MAT95XL mass spectrometer using ionisation energy of 70 eV. Accurate mass measurements were obtained with a resolution of 5000-10000 using PFK as the reference compound. Positive and negative ion APCI mass spectra were acquired with a VG Platform mass spectrometer using a cone voltage of 50 V and the source was maintained at 100°C. Nitrogen was used as the nebulizer and sheath gas and the probe temperature was 400°C. The solvent system used was acetonitrile with a flow rate of 0.3 mL/min. Positive and negative ion electrospray mass spectra were acquired with a VG Platform mass spectrometer using a cone voltage of 50 V and the source was maintained at 80°C. The solvent system used was acetonitrile with a flow rate of 0.04 mL/min. Where indicated, reactions were heated on an oil bath or were sealed and then heated in a Biotage Initiator 60 operating at a frequency of 2.45 GHz, with a maximum power output of 400 W. The external temperature of reaction vessels under microwave irradiation was measured by an infrared thermal camera, and heating was carried out at the desired temperature for the stated reaction time. After the stated time, the reaction vessel was cooled rapidly (~1-2 min) to room temperature by exposure to a stream of compressed air. Analytical thin-layer chromatography (TLC) was conducted on Merck Kieselgel 60 F₂₅₄ on aluminium sheets. All starting materials, reagents and solvents were obtained from commercial sources and used as supplied unless otherwise noted. Molecular sieves were dried by heating in a domestic microwave oven; the hot sieves were allowed to cool to room temperature under vacuum until ready to use.^[2] Dichloromethane, diethyl ether, tetrahydrofuran and toluene were dried by passage through two sequential columns of activated neutral alumina. Dimethyl-2,3-*O*-isopropylidene-*L*-tartrate,^[3] zinc(II) chloride,^[4] divinyl zinc,^[5] diol **12**,^[5] dimethyltitanocene,^[6] Tebbe reagent^[7] and (2,2-diethoxyethylselanyl)benzene^[8] were prepared according to literature procedures. Petroleum spirits refers to that fraction with a boiling range of 40–60 °C.

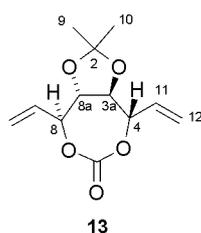
Crystallography

Intensity data were collected with a Bruker SMART Apex CCD detector using Mo-K α radiation (graphite crystal monochromator λ 0.71073). Data were reduced using

the program SAINT. The temperature during data collection was maintained at 130.0(1) K using an Oxford Cryostream cooling device. The structures were solved by direct methods and difference Fourier synthesis. Thermal ellipsoid plots were generated using the program ORTEP-3^[9] integrated within the WinGX^[10] suite of programs.

Synthetic studies

2,2-Dimethyl-4,8-divinyltetrahydro-[1,3]dioxolo[3a,8a-e][5,7]dioxepin-6-one **13**



A solution of diol **12** (2.11 g, 9.86 mmol) in CH₂Cl₂ (700 mL) was added to a mixture of NaHCO₃ (3.13 g, 37.2 mmol) and 4Å molecular sieves (~2 g) in CH₂Cl₂ (300 mL). The resulting mixture was cooled to -78°C before adding pyridine (16 mL, 198 mmol), followed by a solution of triphosgene (0.10 M in CH₂Cl₂, 48 mL, 480 mmol). The resulting solution was stirred for a further 1 h before warming slowly to 25 °C. The resulting mixture was stirred for 2 h before quenching with saturated aqueous NaHCO₃ (200 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 200 mL) and the combined organic layers were dried over Na₂SO₄ before concentrating *in vacuo*. Filtration through a short plug of silica (gradient elution, 10:90 to 20:80 EtOAc:petroleum spirits) provided the carbonate **13** (1.71 g, 72%) as a white solid (1.71 g, 72%), *R*_F 0.28 (20:80 EtOAc:petroleum spirits), mp 47–49°C (from EtOAc/petroleum spirits). $[\alpha]_{\text{D}}^{25}$ -17.5 (*c* 1.0 in CHCl₃). $\nu_{\text{max}}/\text{cm}^{-1}$ 3089, 2989, 2936, 2874, 1762, 1229, 1197, 1092, 1063. δ_{H} (CD₃CN) 5.95 (ddd, *J* 17.2, 10.6, 6.6, 2H, H-11), 5.52 (d, *J* 17.2, 2H, H-12_{trans}), 5.41 (d, *J* 10.6, 2H, H-12_{cis}), 4.80 (m, 2H, H-4), 3.78 (dm, *J* 6.4, 2H, H-3a), 1.40 (s, 6H, 2 × CH₃). δ_{C} (CD₃CN) 152.3 (C), 133.3 (CH), 120.7 (CH₂), 112.5 (C), 81.1 (CH), 80.9 (CH), 26.7 (CH₃). *m/z* (EI) 225 (17%, [*M*-CH₃]⁺), 182 (21, [*M*-(CH₃)₂CO]⁺), 139 (48), 82 (100). HRMS *m/z* (EI): calcd for C₁₁H₁₃O₅ [*M*-CH₃]⁺: 225.0758; found 225.0766.

Further elution afforded recovered starting material (371 mg, 18%).

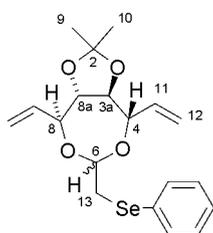
Procedure for methylenation-Claisen rearrangement of carbonate 13: Petasis method

A solution of carbonate **13** (84 mg, 0.35 mmol) in THF (70 mL) was degassed by the freeze-pump-thaw method (3 times) before addition of dimethyltitanocene (0.85 M in PhMe, 0.53 mL, 0.45 mmol). The resulting solution was stirred at 25°C for 5 min before heating to 130°C under microwave irradiation for 30 min. The resulting solution was concentrated *in vacuo* and purified by flash chromatography (gradient elution, 5:95 to 10:90 EtOAc:petroleum spirits), to give the lactone **15** (23 mg, 28%) as a colourless crystalline solid. The product obtained from this reaction was identical by TLC and ¹H NMR to that obtained by selenoxide elimination (**17** → **15**). See below for full characterisation details.

Procedure for methylenation-Claisen rearrangement of carbonate 13: Tebbe method

A solution of carbonate **13** (100 mg, 0.42 mmol), 4-(dimethylamino)pyridine (130 mg, 1.07 mmol) and powdered 4Å molecular sieves (~20 mg) in THF (85 mL) was stirred at 0°C before addition of Tebbe reagent (0.65 M in PhMe, 1.40 mL, 0.91 mmol). The resulting solution was stirred for 4 h before quenching with aqueous NaOH (25% w/v, 2 mL). The resulting mixture was allowed to warm to 25°C over 30 min before filtration through a plug of silica and rinsing with Et₂O. The crude product was purified by flash chromatography (gradient elution, 5:95 to 10:90 EtOAc:petroleum spirits), to give the lactone **15** (57 mg, 57%) as a colourless crystalline solid. The product obtained from this reaction was identical by TLC and ¹H NMR to that obtained by selenoxide elimination (**17** → **15**). See below for full characterisation details.

2,2-Dimethyl-6-phenylselanylmethyl-4,8-divinyltetrahydro[1,3]dioxolo[4,5-e][1,3]dioxepine 16

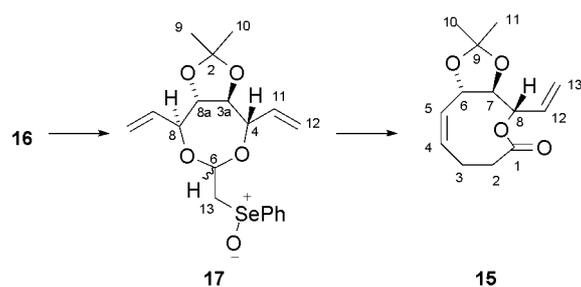


16

To a solution of diol **12** (3.09 g, 14.4 mmol) and (2,2-diethoxyethylselanyl)benzene (5.02 g, 18.4 mmol) in PhMe (40 mL) was added pyridinium *p*-toluenesulfonate (187 mg, 0.74 mmol). The resulting mixture was heated at reflux under a Dean–Stark

apparatus for 1 h before cooling to room temperature. Water (50 mL) was added and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated brine (50 mL) and dried with MgSO₄, and solvent was removed *in vacuo*. The crude product was dissolved in CH₂Cl₂ and filtered through a short pad of silica, eluting with 20:80 EtOAc:petroleum spirits, and concentrated to give crude selenoacetal (6.21 g, >100%) as a brown oil. This compound was used in the next step without further purification. On a smaller scale reaction this compound was purified by chromatography (gradient elution 2.5:97.5 to 5:95 EtOAc:petroleum spirits) to give the selenoacetal **16** (70%) as a yellow oil, *R*_F 0.28 (2.5:97.5 EtOAc:petroleum spirits), [α]_D²⁶ -15.4 (*c* 0.7 in CHCl₃). *v*_{max}/cm⁻¹ 2986, 2892, 1232, 1084, 1011, 930, 736. δ_H (CDCl₃) 7.58–7.45 (m, 2H, Ph), 7.30–7.19 (m, 3H, Ph), 6.08–5.87 (m, 2H, H-11), 5.39 (dd, *J* 17.2, 11.8, 2H, H-12_{trans}), 5.27 (d, *J* 10.5, 2H, H-12_{cis}), 5.01 (dd, *J* 5.0, 5.0, 1H, H-4), 4.26 (m, 1H, H-8), 4.04–3.93 (m, 2H, H-3a, H-8a), 3.87 (dd, *J* 8.9, 8.9, 1H, H-6), 3.14 (m, 2H, H-13), 1.42 (s, 3H, CH₃), 1.41 (s, 3H, CH₃). δ_C (CDCl₃) 136.7 (CH), 134.5 (CH), 132.6 (CH), 130.6 (C), 129.2 (CH), 127.1 (CH), 117.8 (CH₂), 116.9 (CH₂), 111.1 (C), 98.8 (CH), 81.2 (CH), 81.1 (CH), 80.1 (CH), 77.1 (CH), 33.3 (CH₂), 27.2 (CH₃), 27.1 (CH₃). *m/z* (EI) 396 (37%, [M(⁸⁰Se)]⁺), 394 (19, [M(⁷⁸Se)]⁺), 392 (7, [M(⁷⁶Se)]⁺), 111 (100). HRMS *m/z* (EI): calcd for C₁₉H₂₄O₄⁸⁰Se [M]⁺: 396.0834; found 396.0828.

(4*Z*,6*S*,7*R*,8*S*)-4,5-didehydro-9,9-dimethyl-8-vinyl-6,7-[1,3]dioxolo-oxonan-1-one **15**



The selenoacetal **16** from the previous step (6.21 g, 14.41 mmol) was dissolved in CH₂Cl₂:MeOH (3:7, 120 mL) before addition of H₂O (30 mL). To the resulting cloudy mixture was added NaHCO₃ (2.86 g, 34.0 mmol) and NaIO₄ (9.66 g, 45.1 mmol). A thick white precipitate formed after about 1 minute. The resulting mixture was allowed to stir for 2 h before removing volatile solvents *in vacuo*. The crude product was quenched with H₂O (150 mL) and extracted into CH₂Cl₂ (4 × 100 mL).

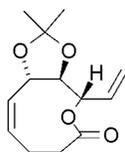
The combined organic layers were washed with saturated brine (100 mL) then dried with MgSO₄ before concentrating *in vacuo* to give the crude product **17** (6.19 g, 96%) as a colourless foam. This product was used in the next step without further purification. The following data are reported for the crude selenoxide **17**, which exhibits as a pair of diastereomers by ¹H and ¹³C NMR: *R*_F 0.00 (50:50 EtOAc:petroleum spirits). *v*_{max}/cm⁻¹ 2986, 2887, 1231, 1082, 1011, 931, 825, 743. δ_{H} (CDCl₃) 7.76–7.69 (m, 2H, Ph), 7.54–7.47 (m, 3H, Ph), 6.13–5.83 (m, 2H, H-11), 5.56–5.14 (m, 5H), 4.31–3.80 (m, 4H), 3.23 (dd, *J* 12.0, 7.6, 1H), 3.15 (d, *J* 4.6, 1H), 1.42 (s, 6H). δ_{C} (CDCl₃) 141.2 (C), 140.8 (C), 135.9 (CH), 135.9 (CH), 134.1 (CH), 134.1 (CH), 131.5 (CH), 131.4 (CH), 129.8 (CH), 126.2 (CH), 126.0 (CH), 118.3 (CH₂), 118.0 (CH₂), 118.0 (CH₂), 116.9 (CH₂), 111.3 (C), 111.2 (C), 94.4 (CH), 94.4 (CH), 81.0 (CH), 80.9 (CH), 80.9 (CH), 80.2 (CH), 80.2 (CH), 77.8 (CH), 77.4 (CH), 59.8 (CH₂), 59.5 (CH₂), 27.1 (2 × CH₃), 27.0 (CH₃), 27.0 (CH₃).

The crude selenoxide **17** (6.19 g, 14.4 mmol) was dissolved in PhMe (720 mL) before addition of 1,8-diazabicycloundecane (7.0 mL, 47 mmol). The resulting solution was heated at reflux under a Dean–Stark apparatus, after discarding the first 10 mL of cloudy distillate, for 17 h. The resulting solution was allowed to cool to 25°C before removing solvent *in vacuo*. The product was obtained pure by chromatography (5:95 EtOAc:petroleum spirits) to give the lactone **15** (2.60 g, 53% from diol **12**) as a colourless crystalline solid, *R*_F 0.21 (10:90 EtOAc:petroleum spirits), mp 88–90°C (from CDCl₃); [α]_D²⁵ +49.0 (*c* 0.1 in CHCl₃). *v*_{max}/cm⁻¹ 3021, 2987, 2936, 2880, 1739, 1381, 1372, 1252, 1196, 1167, 1139, 1073, 1006, 988, 871, 740. δ_{H} (CDCl₃) 6.01 (ddd, *J* 17.2, 10.7, 5.5, 1H, H-12), 5.84–5.76 (m, 1H, H-4), 5.64 (dd, *J* 10.3, 9.9 Hz, 1H, H-5), 5.46–5.38 (m, 2H, H-8, H-13_{cis}), 5.30 (ddd, *J* 10.7, 1.2, 1.2, 1H, H-13_{trans}), 4.49 (ddd, *J* 9.2, 8.3, 1.1, 1H, H-6), 3.79 (dd, *J* 9.3, 8.4, 1H, H-7), 2.50–2.40 (m, 3H, H-2 and H-3_{αβ}), 2.18–2.08 (m, 1H, H-3_{βα}), 1.43 (s, 6H, 2 × CH₃). δ_{C} (CDCl₃) 174.6 (C), 134.2 (CH), 132.6 (CH), 129.5 (CH), 118.2 (CH₂), 111.5 (C), 82.4 (CH), 77.8 (CH), 75.5 (CH), 34.0 (CH₂), 27.3 (CH₃), 26.9 (CH₃), 25.9 (CH₂). *m/z* (EI) 238 (9%, [*M*]⁺), 223 (27, [*M*-CH₃]⁺), 169 (27), 124 (59), 111 (63), 96 (100). HRMS *m/z* (EI): calcd for C₁₃H₁₈O₄ [*M*]⁺: 238.1200; found 238.1198.

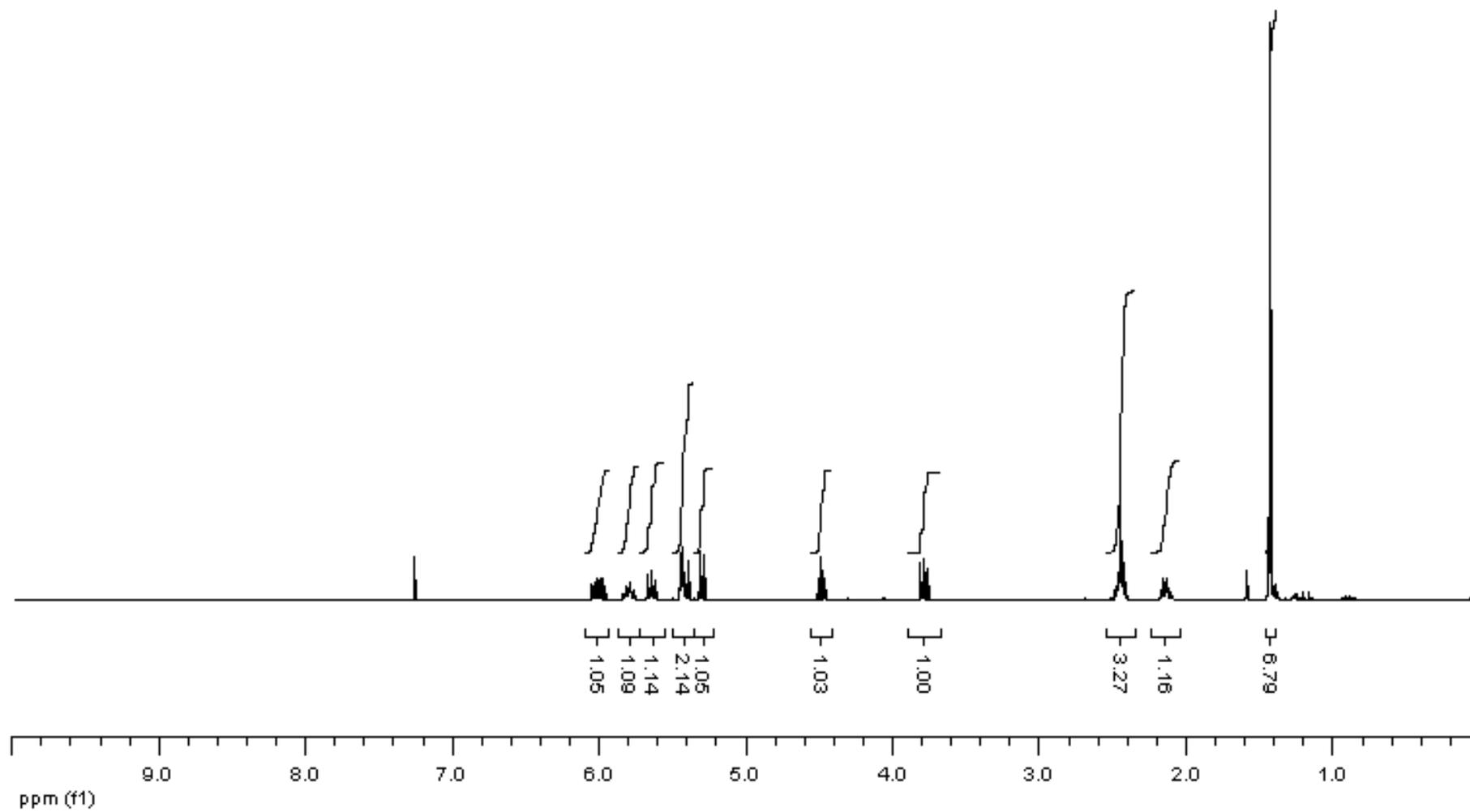
Crystals suitable for x-ray crystallography were grown by slow evaporation from a concentrated solution of **15** in chloroform to give colourless prisms. Crystal data for **15**: C₁₃H₁₈O₄, *M* 238.27, *T* 130.0(1) K, λ 0.71073, tetragonal, space group P4(3)2(1)2,

a 8.1249(3), b 8.1249, c 37.575(3) Å, V 2480.5(2) Å³, Z 8, D_c 1.276 mg M⁻³, $\mu(\text{Mo-K}\alpha)$ 0.094 mm⁻¹, $F(000)$ 1024, crystal size 0.4 × 0.3 × 0.3 mm. 12621 Reflections were measured, with 2195 independent reflections (R_{int} 0.057); the final R was 0.0284 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.0688 (all data).

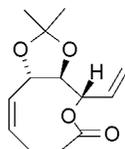
¹H NMR spectrum - 400 MHz, CDCl₃



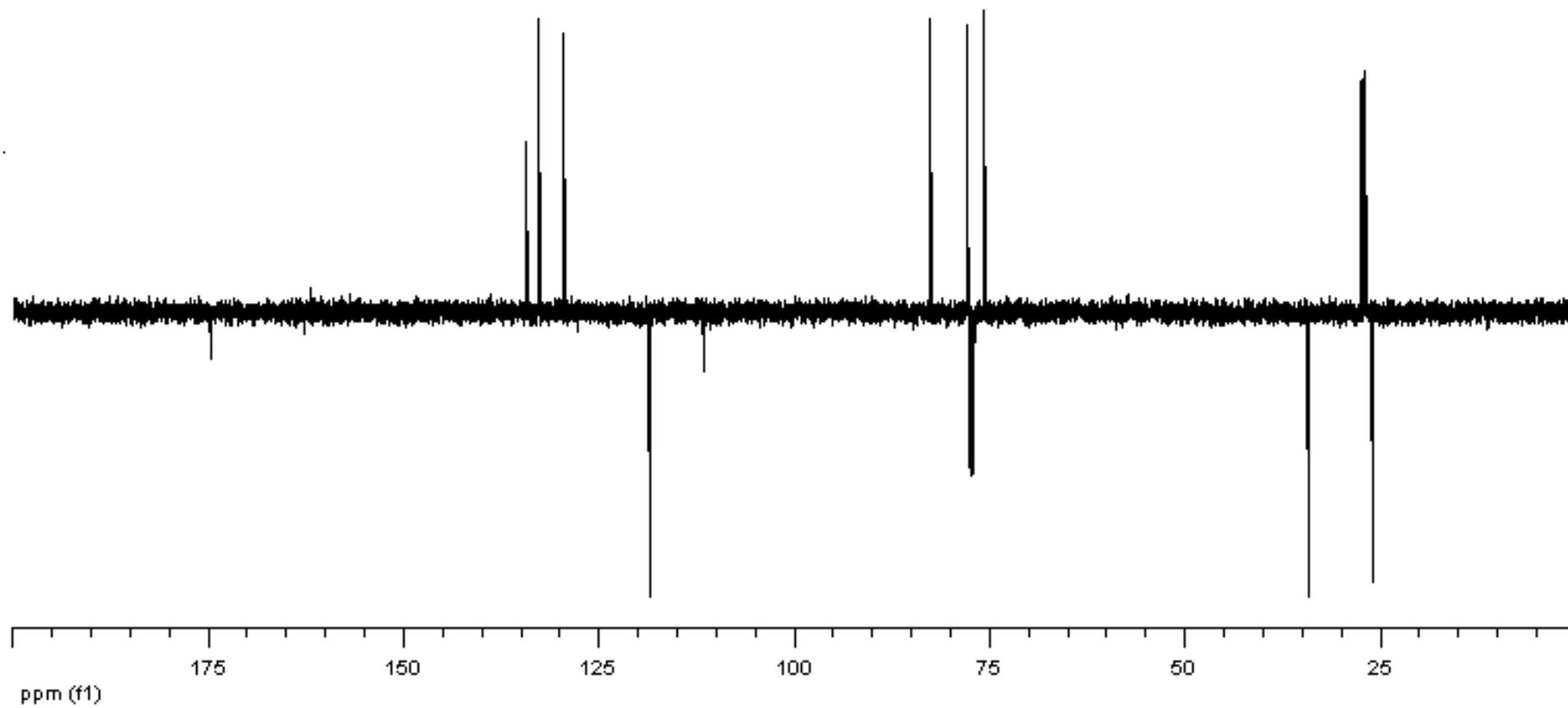
15



^{13}C JMOD NMR spectrum - 100 MHz, CDCl_3



15



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