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Stereoselective Total Synthesis of (+)-Norrisolide

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Table of Contents

General Techniques

All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2) and benzene (PhH) were purified by passage through a bed of activated alumina.[1] *N,N*-diisopropylethylamine (DIPEA), diisopropylamine, pyridine and triethylamine (TEA) were distilled from calcium hydride prior to use.[2] Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4Å molecular sieves until needed. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm^{-1} units. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: $[\alpha]^{T}_{\lambda}$ (c: g/100ml, solvent). High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

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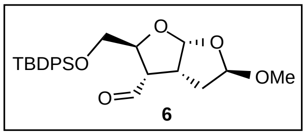
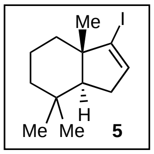
[1]. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15,* 1518-1520.

[2]. Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, **1988**.



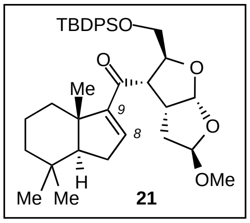
6

To a solution of alkene **20** (1.85 g, 4.22 mmol) in 110 ml of a mixture of acetone and water (10/1) was added a 2.5 wt% solution of OsO_4 in *t*-BuOH (0.51 g, 0.050 mmol), NMO (0.63 g, 5.2 mmol) and a catalytic amount of pyridine (3 drops). The reaction mixture was stirred for 10 h. The reaction was quenched with sodium thiosulfate, diluted with water (50 ml) and extracted with ether (3 x 50 ml). The organic layers were dried over $MgSO_4$, and concentrated to give the corresponding diol. A solution of crude diol in 100 ml of dichloromethane was treated with $Pb(OAc)_4$ (2.63 g, 5.64 mmol) at 0 °C for 30 minutes under argon. The mixture was quenched by a few drops of ethylene glycol, washed with water (2 x 30 ml), and purified by silica gel chromatography to yield aldehyde **6** (1.75 g**,** 94% yield). **6**: $[\alpha]^{25}_{D}$: –28.7 (c= 4.18, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (d, 1H, *J*=1.6 Hz), 7.69-7.66 (m, 4H), 7.45-7.38 (m, 6H), 5.86 (d, *J*= 5.0 Hz, 1H), 5.18 (d, *J*= 5.0 Hz, 1H), 4.47-4.44 (m, 1H), 3.91 (dd, *J*= 11.0, 4.0 Hz, 1H), 3.82 (dd, *J*= 11.0, 3.0 Hz, 1H), 3.42-3.35 (m, 2H), 3.35 (s, 3H), 2.04 (ddd, *J*= 13.5, 9.0 Hz, 1H), 1.91-1.86 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 135.5, 135.4, 133.0, 132.8, 129.7 (2), 127.7, 127.6, 108.3, 105.9, 77.8, 63.6, 55.2, 54.8, 42.4, 32.9, 26.7, 19.1; HRMS, calcd for $C_{25}H_{32}O_5Si$ (M+ H^+) 441.2097, found 441.2081.



5

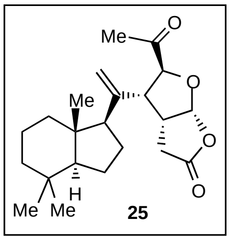
To a solution of hydrazone **14** (129.3 mg, 0.666 mmol) in THF (4.0 ml) was added Et_3N (0.84 ml). To the above solution was added I_2 until nitrogen evolution is ceased. The reaction mixture was diluted with ether and washed with 5% HCl (aq), aqueous saturated $NaHSO_3$, and aqueous saturated $NaHCO_3$. The ether layer was dried over $MgSO_4$ and concentrated to give after purification on silica gel (100% hexane) pure vinyl iodide **5** as a light yellow liquid (119.7 mg, 62% yield). **5**: $[\alpha]^{25}_{D}$: –5.9 (c= 4.85, CH_2Cl_2); IR (film) ν_{max} 2997, 2928, 2863, 1457, 1373, 987, 847, 803, 680 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 5.97 (t, *J*= 2.4 Hz, 1H), 1.83-1.73 (m, 2H), 1.53-1.39 (m, 3H), 1.28-1.24 (m, 2H), 1.09-1.02 (m, 1H), 0.94-0.87 (m, 1H), 0.79 (s, 3H), 0.77 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 137.1, 114.4, 58.0, 50.5, 41.5, 37.3, 33.2, 32.6, 31.3, 21.4, 20.3, 17.4; HRMS, calcd for $C_{12}H_{19}I$ (M+ H^+) 291.0569, found 291.0551.



21

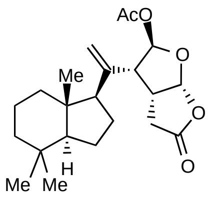
To a solution of vinyl iodide **5** (200 mg, 0.69 mmol) in THF (15 ml) at –78 °C was added under argon 0.82 ml of *t*-BuLi (1.7 M, pentane). The reaction was then allowed to warm at –40 °C and stirred for 30 minutes. The reaction mixture was cooled at –78 °C and treated with a solution of aldehyde **6**, (200 mg, 0.45 mmol) in THF (3 ml) added dropwise. After stirring at –78 °C for 30 minutes, the reaction was quenched with aqueous saturated NH_4Cl (10 ml) and diluted with ether (20 ml). The aqueous phase was extracted with ether (3 x 20 ml) and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (ether/hexane: 4/6) to afford the corresponding allylic alcohol (203 mg, 75%); *Rf* =

0.55 (ether/hexane: 1/1). To a solution of this alcohol (203 mg, 0.33 mmol) in dichloromethane (10 ml) was added portionwise Dess-Martin periodinane (280 mg, 0.66 mmol) and the reaction was stirred for a total of 10 h. After disappearance of the starting material (monitor by tlc), the reaction was treated with aqueous saturated sodium thiosulfate (15 ml) and aqueous saturated sodium bicarbonate (5 ml) and the mixture was stirred until the organic layer was clear (45 minutes). The aqueous layer was extracted with dichloromethane (3 x 10 ml), dried over Na_2SO_4, and concentrated. The residue was purified on silica (hexane/ether: 7/3) to afford ketone **21** as a colorless liquid (190 mg, 95%). **21**: *Rf* = 0.65 (hex/ether: 1/1); $[\alpha]^{25}_{D}$: –38.1 (c= 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.61 (m, 4H), 7.43-7.32 (m, 6H), 6.77 (dd, *J*= 3.6, 2.0 Hz, 1H), 5.84 (d, *J*= 5.2 Hz, 1H), 5.13 (dd, *J*= 4.0, 0.8 Hz, 1H), 4.48 (dt, *J*= 9.6, 2.8 Hz, 1H), 3.96-3.88 (m, 2H), 3.73-3.69 (m, 1H), 3.34 (s, 3H), 3.30-3.24 (m, 1H), 2.27-2.19 (m, 3H), 1.80-0.87 (m, 8H), 1.03 (s, 12H), 0.97 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 155.2, 144.1, 135.5, 135.3, 133.3, 133.0, 129.5, 127.5, 107.9, 105.6, 78.6, 63.1, 59.2, 55.0, 50.3, 45.4, 41.3, 35.1, 33.2, 32.8 (2), 30.1, 26.9, 21.2, 19.9, 19.4, 17.9; HRMS, calcd for $C_{37}H_{50}O_5Si$ (M+ H$^+$) 603.3505, found 603.3511.



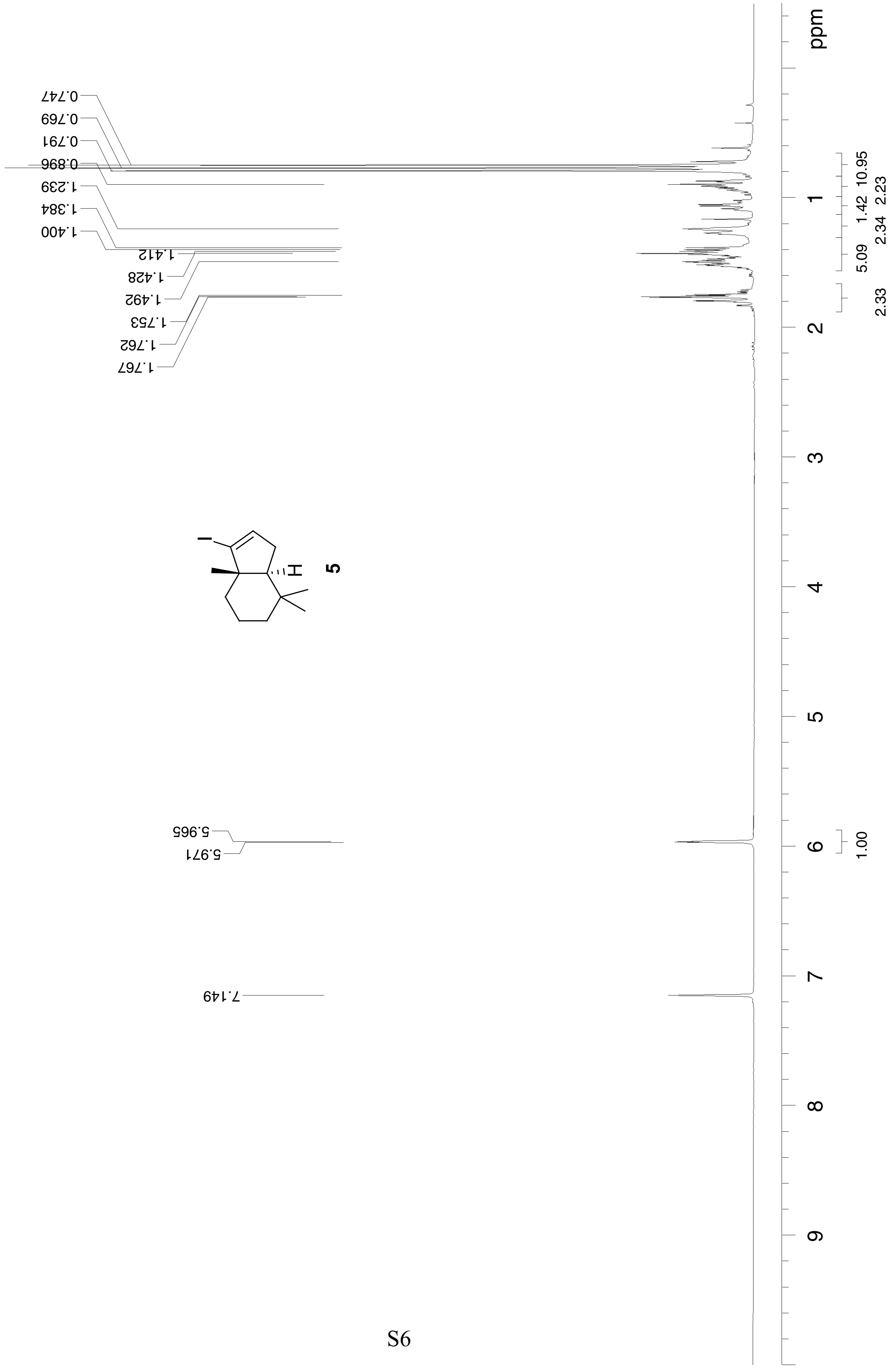
25

A solution of ketone **24** (6 mg, ~0.02 mmol) in 0.2 ml of acetic acid was treated with a solution of chromic acid (15 mg) in 1.5 ml acetic acid containing 0.5 ml of water and the reaction was stirred for 6 h at room temperature. The solution was then diluted with dichloromethane (10 ml) and washed with water (10 ml), followed by aqueous saturated sodium bicarbonate (2 x 20 ml). The organic layer was dried over Na_2SO_4 and concentrated on the rotavap. The residue was purified on silica gel to yield lactone **25** as a colorless liquid (4.5 mg, 80%). **25**: *Rf* = 0.6 (hex/ether/dcm: 1/1/0.02); $[\alpha]^{25}_{D}$: +22.4 (c= 0.16, CH_2Cl_2); IR (film) ν_{max} 2924, 1788, 1721, 992 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J*= 5.6 Hz, 1H), 5.31 (s, 1H), 5.04 (s, 1H), 4.46 (d, *J*= 10.8 Hz, 1H), 3.32-3.25 (m, 1H), 2.93 (t, *J*= 10.4 Hz, 1H), 2.74 (dd, *J*= 18.8, 4.0 Hz, 1H), 2.56 (dd, *J*= 19.2, 10.8 Hz, 1H), 2.25 (s, 3H), 2.08 (t, *J*= 9.2 Hz, 1H), 1.72-1.02 (m, 11H), 0.86 (s, 6H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 174.2, 142.9, 117.4, 107.3, 85.2, 59.6, 58.1, 49.6, 44.5, 42.2, 41.5, 38.9, 33.3, 33.2, 30.5, 27.0, 24.7, 20.7, 20.6, 19.8, 14.2; HRMS, calcd for $C_{22}H_{32}O_4$ (M+ H$^+$) 361.2378, found 361.2391.



1: norrisolide

To a solution of ketone **25** (2.5 mg, 0.007 mmol) in 3 ml dichloromethane at 0 °C was added solid sodium hydrogen carbonate (42.1 mg, 0.5 mmol). The heterogeneous mixture was stirred for 5 minutes and then treated with a solution of *m*-CPBA (43.0 mg, 0.25 mmol) in 1 ml of dichloromethane. After stirring for 4 h, the reaction was quenched by the addition of 10 ml of saturated aqueous sodium thiosulfate and the mixture was stirred for an additional 30 minutes. The reaction mixture was diluted with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane (3 x 5 ml). The organic layer was dried over Na_2SO_4 and the solvent removed on the rotavap. The crude residue was purified on silica gel (hexane/ether: 2/1) to yield synthetic norrisolide (**1**) as a white powder (1.5 mg, 60%). **1**: R_f = 0.61 (hexane/ether: 3/7); $[\alpha]^{25}_{D}$: +3.5 (c= 0.13, CH_2Cl_2); IR (film) ν_{max} 1793, 1755, 1222 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.63 (dd, *J*= 4.0, 1.6 Hz, 1H), 5.66 (dd, *J*= 6.4, 1.6 Hz, 1H), 4.90 (s, 1H), 4.77 (s, 1H), 2.70 (dd, *J*= 8.8, 3.6 Hz, 1H), 2.40-2.33 (m, 1H), 2.15 (dd, *J*= 18.0, 4.0 Hz, 1H), 1.76 (dd, *J*= 18.4, 10.8 Hz, 1H), 1.58 (s, 3H), 1.45-0.60 (m, 12H), 0.85 (s, 3H), 0.79 (s, 3H), 046 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 173.5, 168.5, 143.4, 116.9, 107.1, 101.8, 58.7, 57.7, 50.0, 45.0, 41.7, 40.5, 38.6, 33.4, 33.3, 30.5, 24.2, 21.2, 20.7, 20.4, 19.9, 14.1; HRMS, calcd for $C_{22}H_{32}O_5$ (M-AcOH$^+$) 316.2038, found 316.2051.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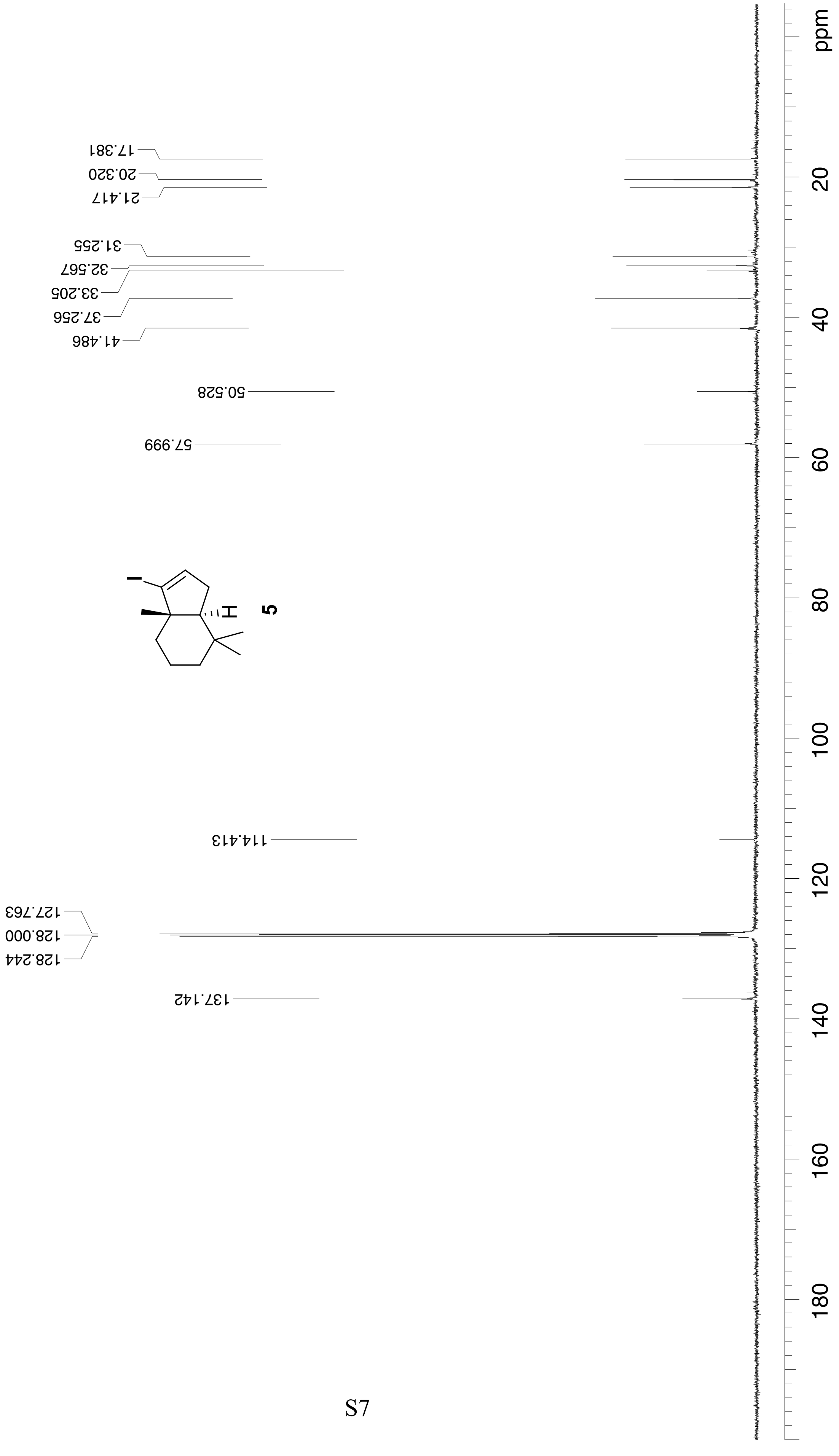
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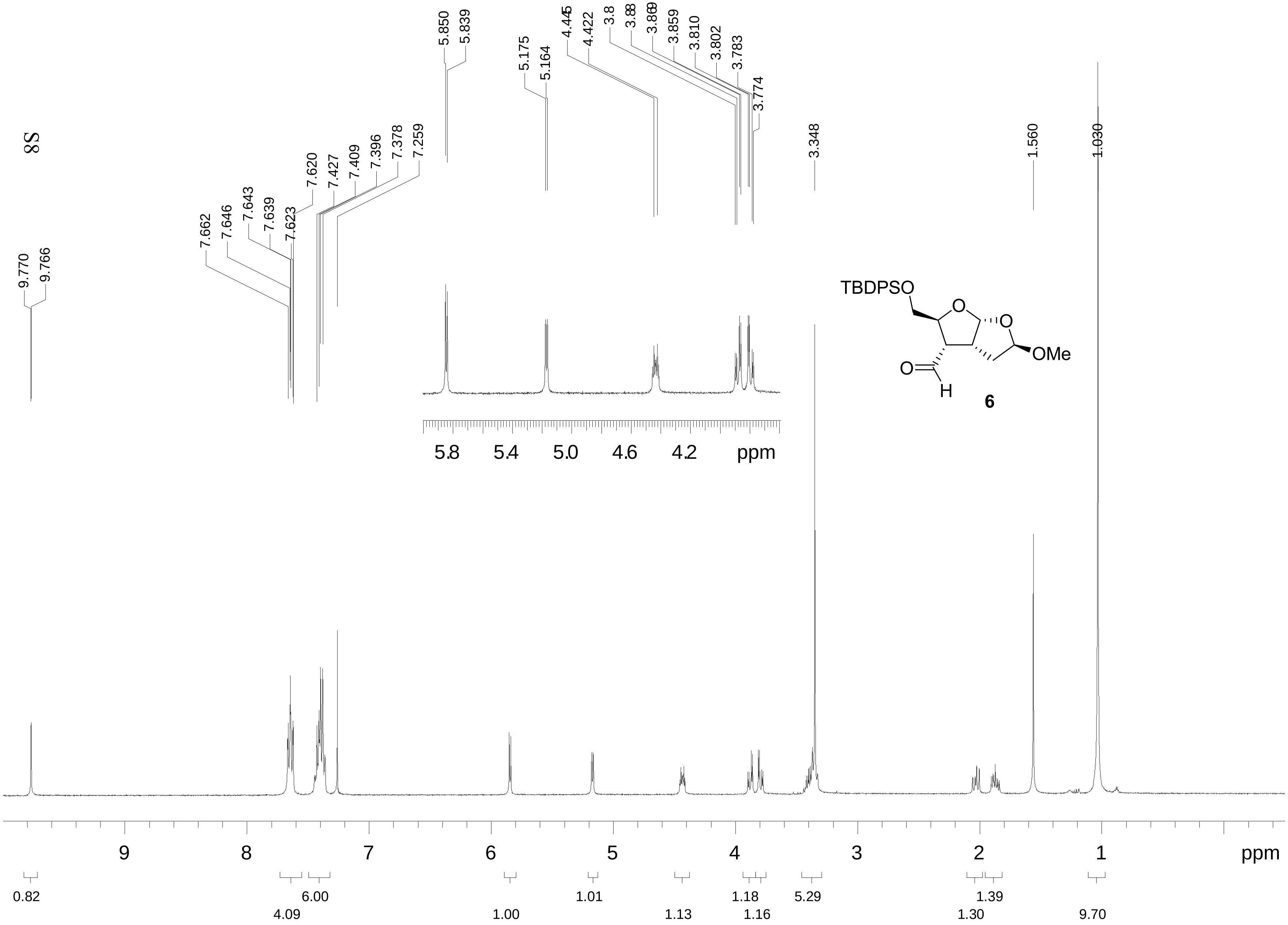
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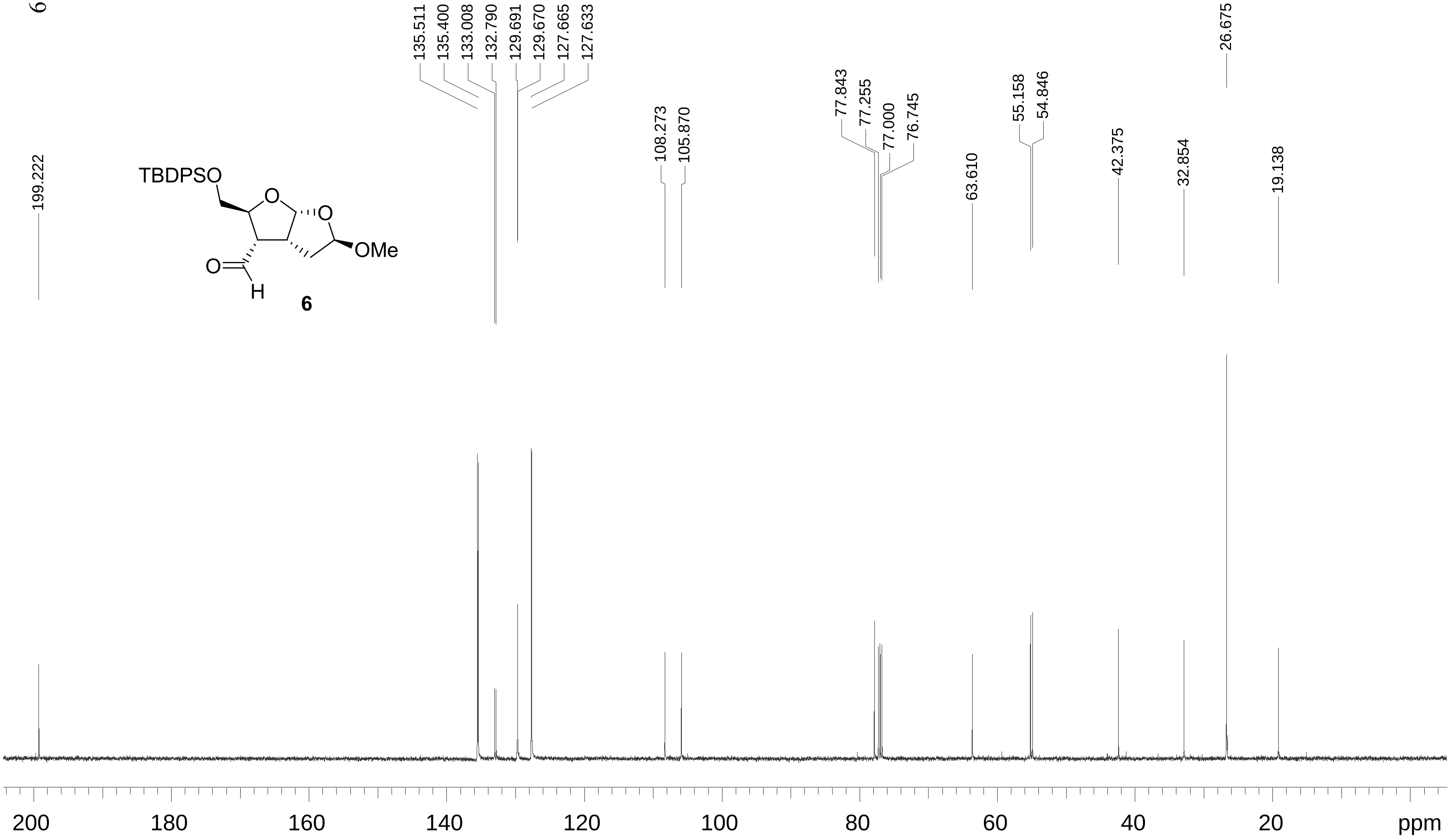
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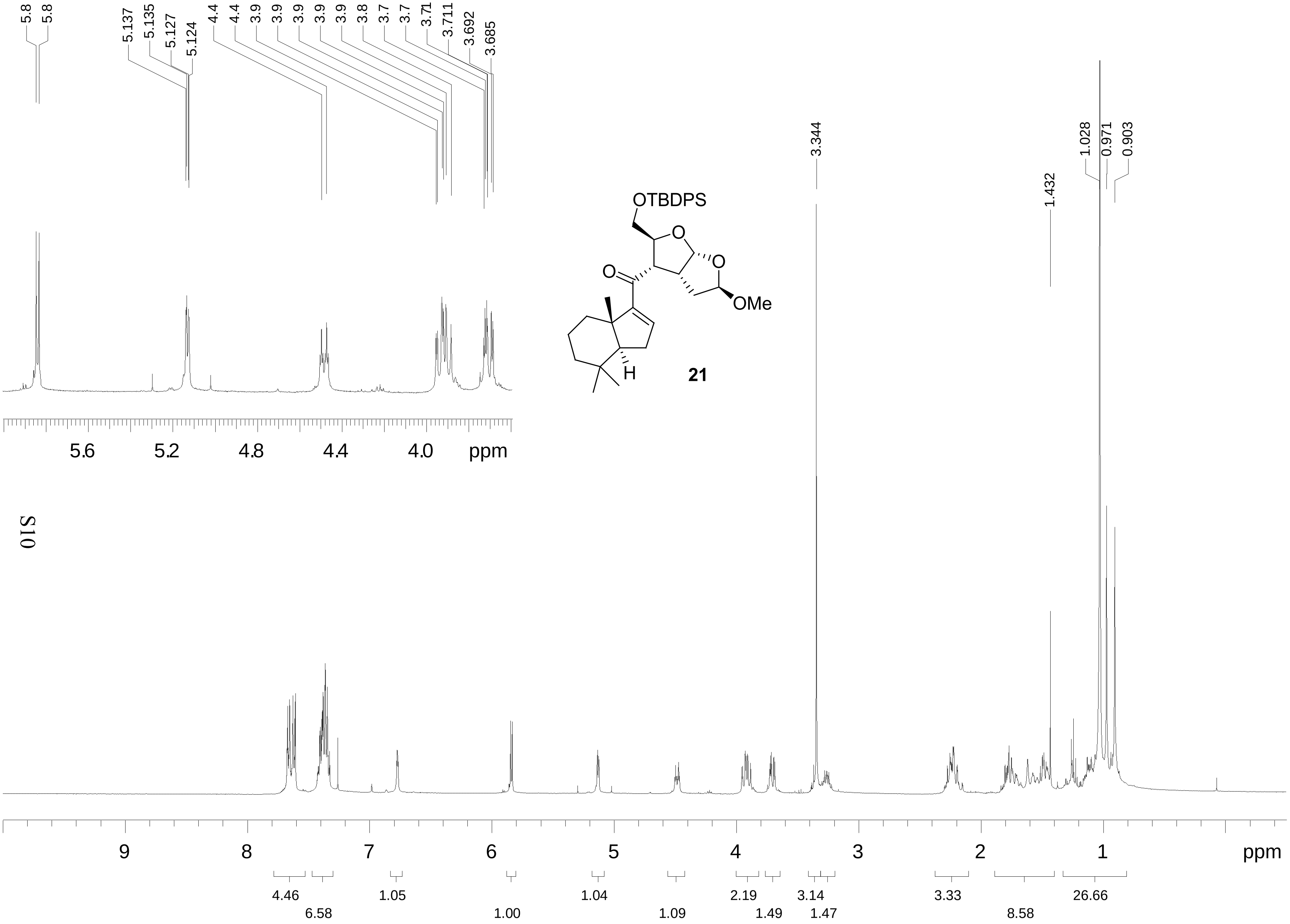
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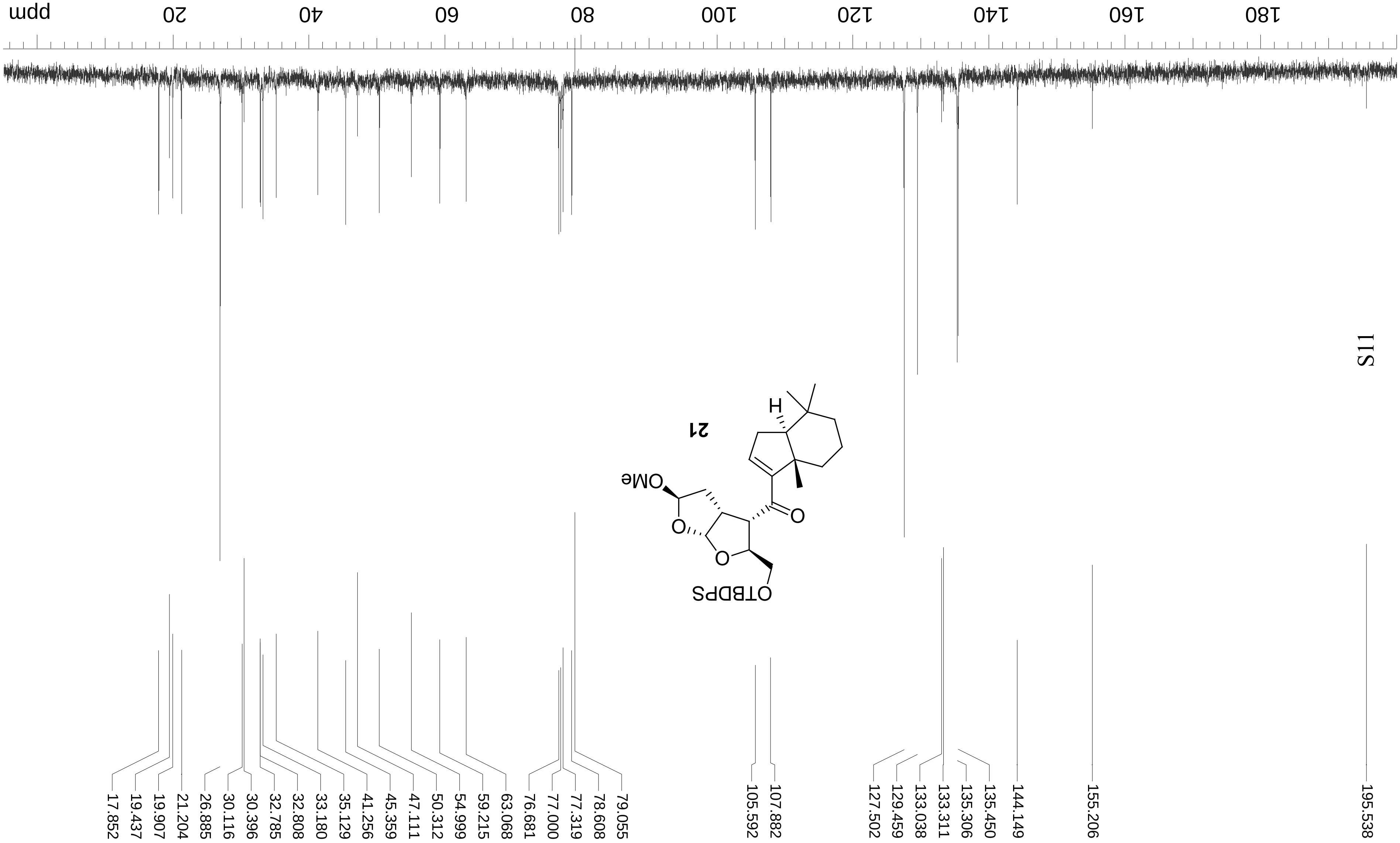
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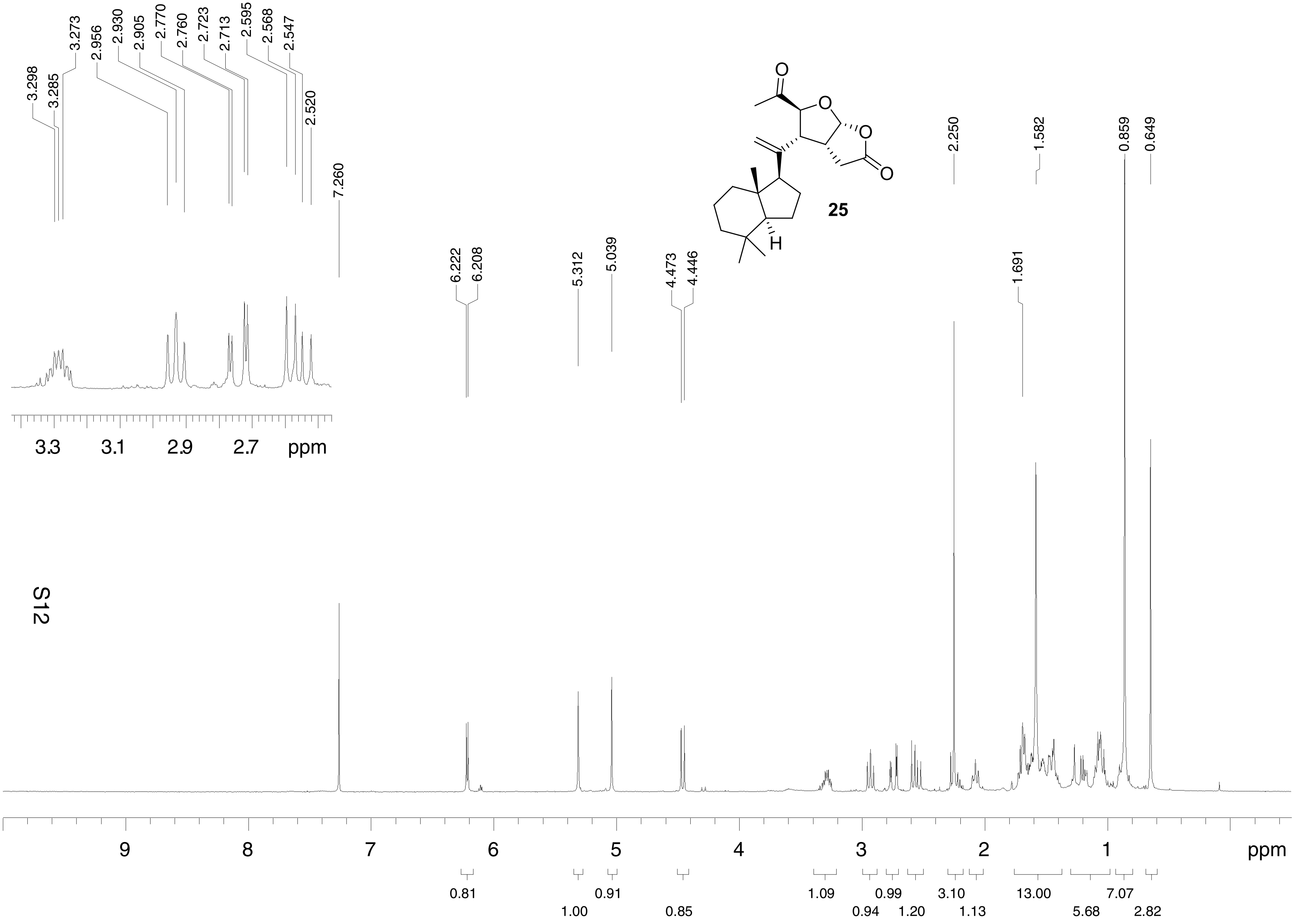
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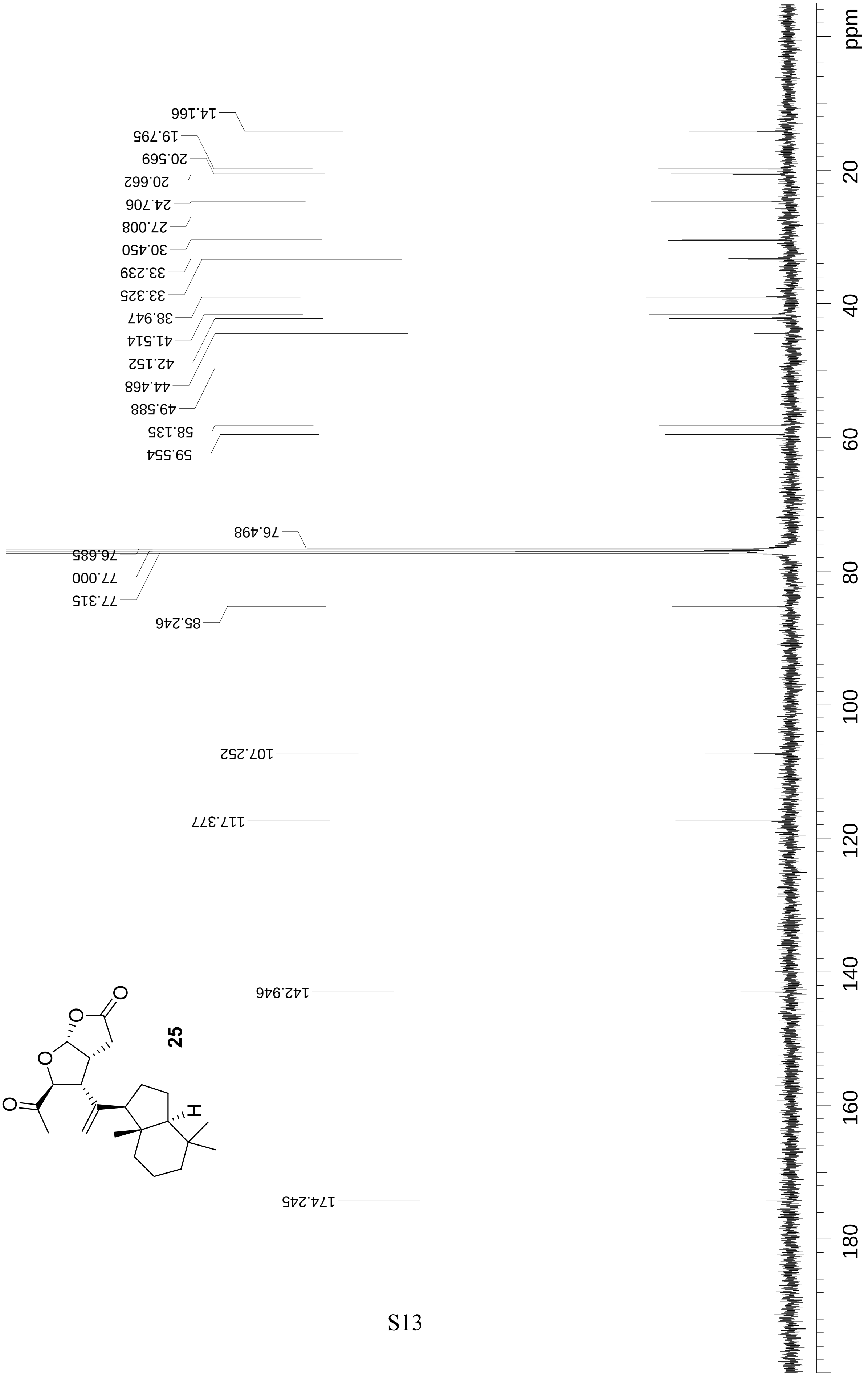
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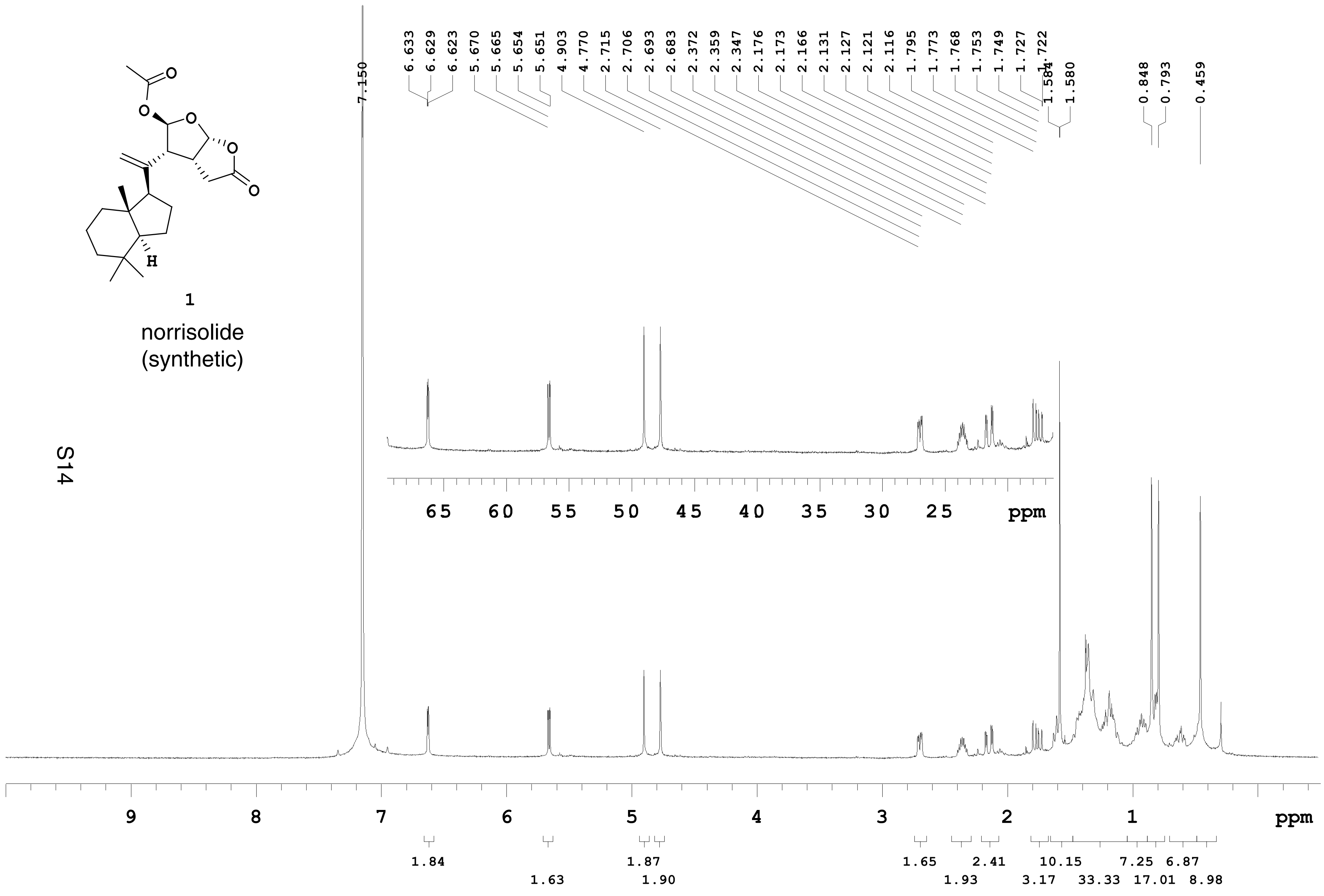
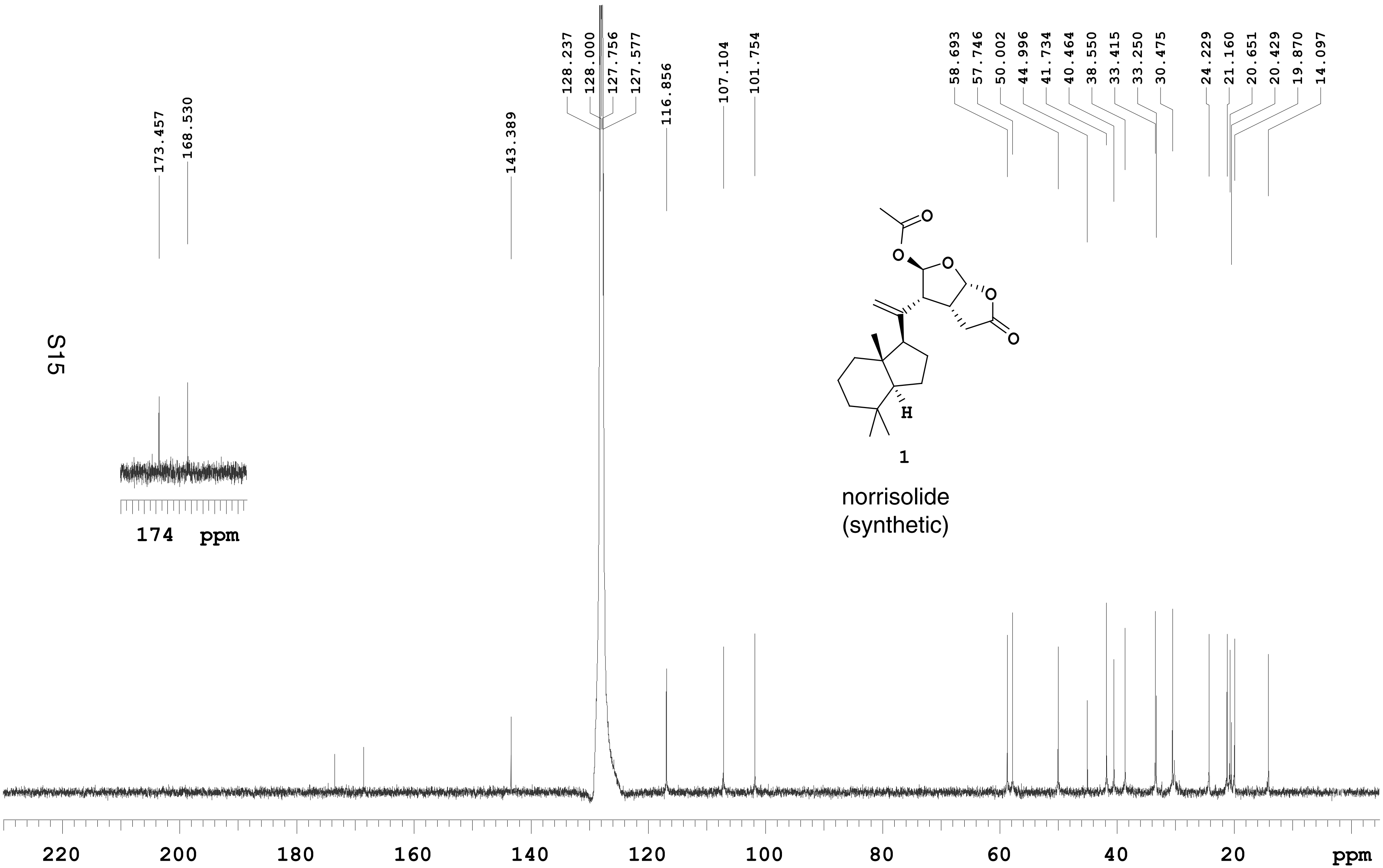


1

norrisolide
(synthetic)



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norrisolide
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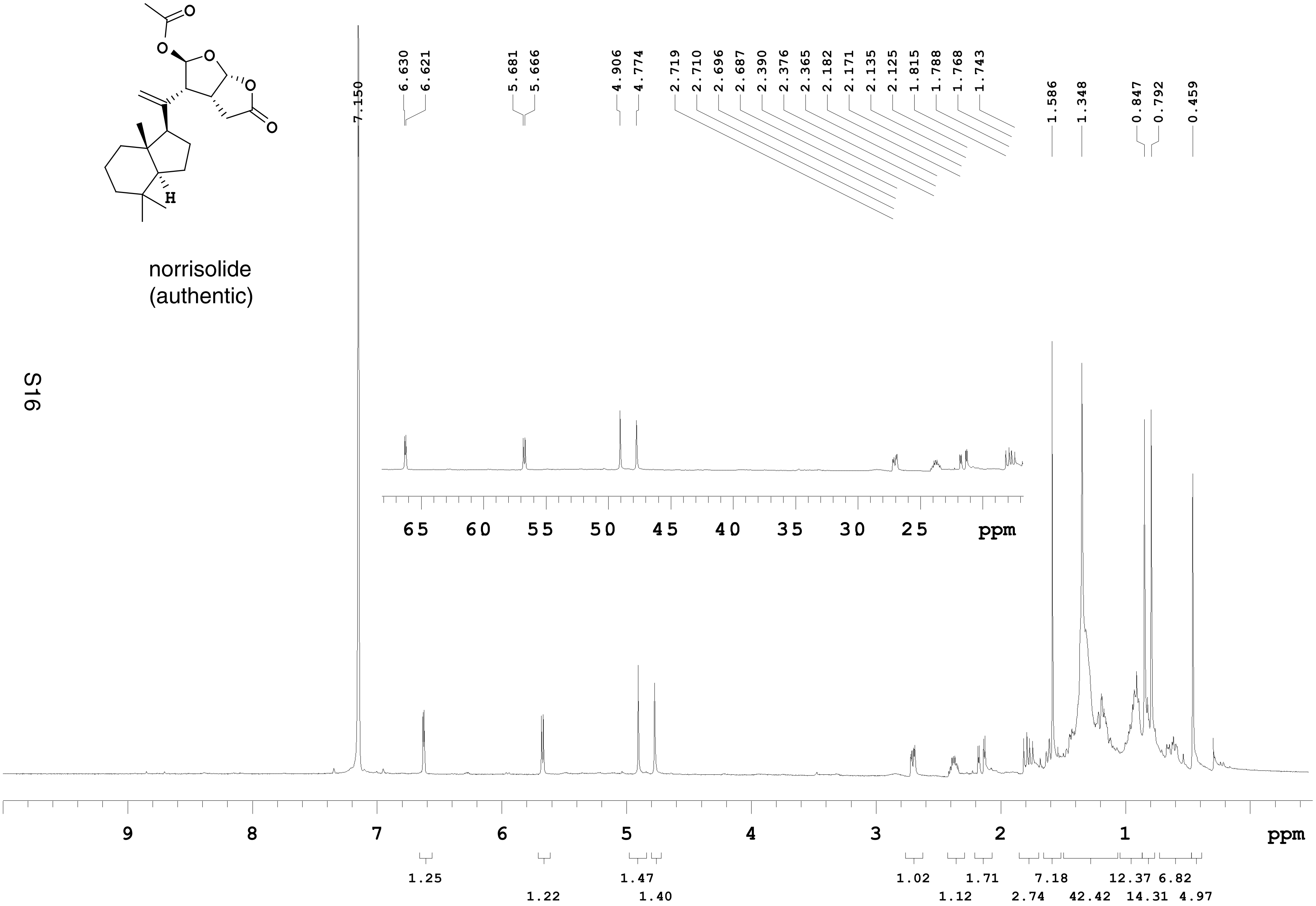

norrisolide
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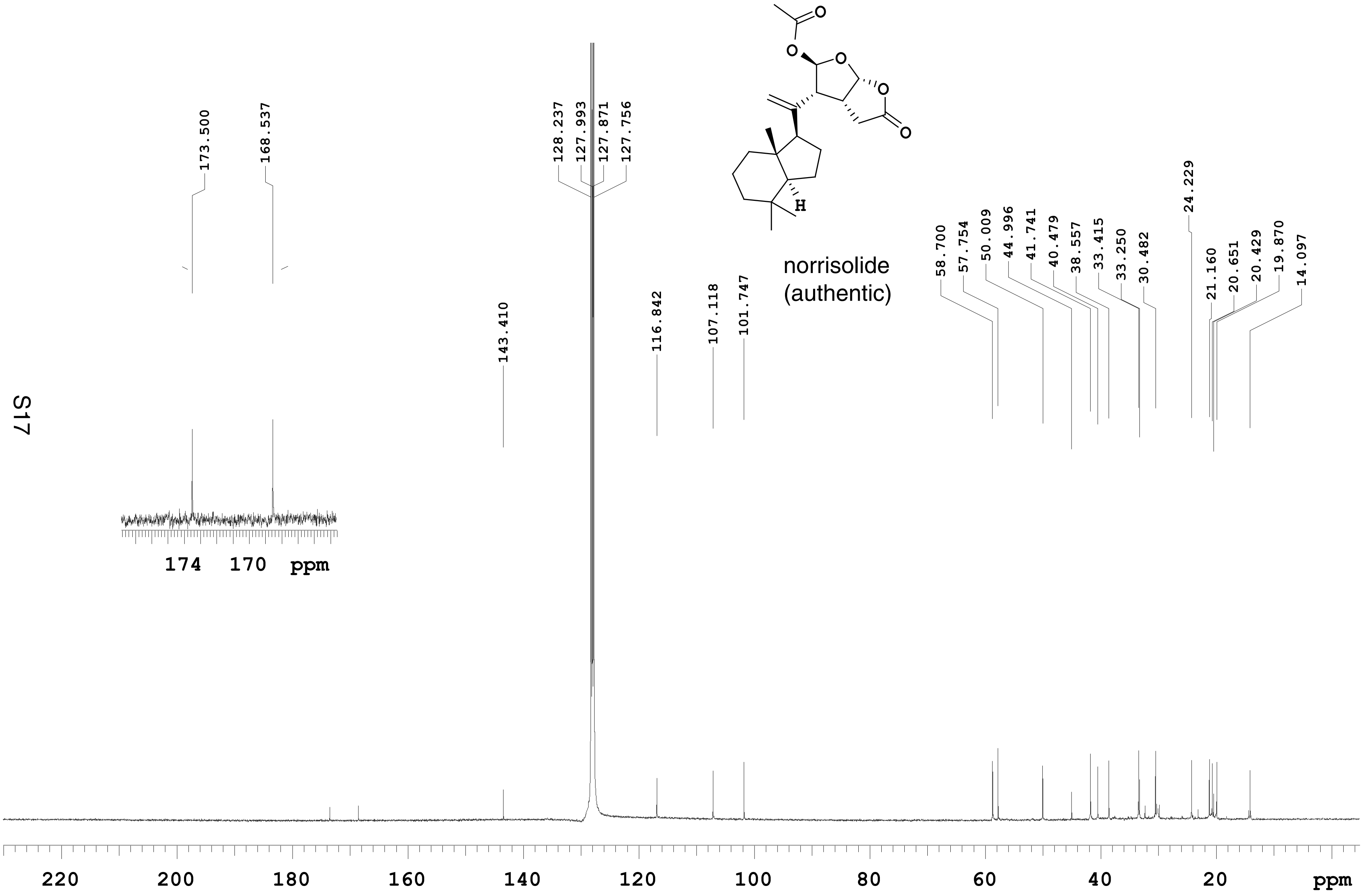

norrisolide
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