

Concise Enantioselective Synthesis of Absciscic Acid and a New Analogue

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Supplementary Information

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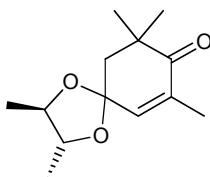
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General Experimental

Unless otherwise noted, all materials were obtained from commercial sources and used without further purification. Toluene was freshly distilled from sodium and THF from potassium. Column chromatography was performed on Merck silica gel 60 H (230-400 mesh). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations (given in 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$) were measured on an Optical Activity AA-1000 polarimeter. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR instrument. ^1H and ^{13}C NMR spectra were recorded using a Bruker DPX400 at 400 MHz and 100 MHz respectively. NMR spectra were recorded in the indicated solvent and chemical shifts (δ) are reported in ppm relative to residual non-deuterated solvent as an internal standard. J -values are given in Hz. Elemental analysis was performed on an Exeter Analytical CE440 machine by the Warwick Analytical Service. LSIMS and EI mass spectroscopy was performed on a Micromass Autospec mass spectrometer. GC-MS data was collected on a Varian 4000 GC-MS fitted with an autosampler and a FactorFour™ Capillary column number VF-5ms operating a temperature programme from 50 – 250°C increased at 5°C per minute.

I) Synthesis of (*R*)-(-)-abscisic acid

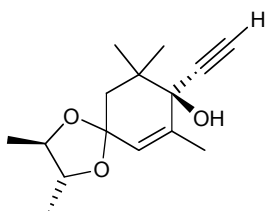
(*2R, 3R*)-2,3,7,9,9-Pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-one, **13**



4-Oxoisophorone, **4** (1.30 g, 8.5 mmol, 1 eq), 2*R,3R*-(-)-2,3-butanediol, **12** (1.0 g, 11.0 mmol, 1.3 eq) and *p*-toluenesulfonic acid (50 mg) in toluene (15 ml) were heated under reflux for 24 hours using a Dean-Stark trap. The mixture was cooled and washed with saturated NaHCO_3 solution (20 ml). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 20 ml). The combined organics were dried over MgSO_4 and the solvent removed under reduced pressure. The crude

product was purified by column chromatography (silica, 20% diethyl ether in hexane) to yield the *title product* **13** as a pale yellow oil (1.80 g, 94%). R_f 0.49 (30% diethyl ether in hexane); $[\alpha]_D^{20} = +16.5$ (c 1.75, MeOH); $\nu_{\max}(\text{film})$ 1676, 1093, 970 cm^{-1} ; δ_H (400 MHz, CDCl_3) 1.17 (s, 3H), 1.22 (s, 3H), 1.27-1.30 (m, 6H), 1.79 (d, $J = 1.5$, 3H), 2.05 (dd, $J = 1.5$, 13.8, 1H), 2.13 (d, $J = 13.8$, 1H), 3.62-3.72 (m, 2H), 6.33 (t, $J = 1.5$, 1H); δ_C (100 MHz, CDCl_3) 16.2 (CH_3), 16.6 (CH_3), 16.8 (CH_3), 26.3 (CH_3), 26.8 (CH_3), 42.1 (CH_2), 47.5 (C), 78.4 (2x CH), 102.9 (C), 135.2 (C), 141.3 (CH), 204.4 (C); MS (EI): m/z requires ($\text{C}_{13}\text{H}_{21}\text{O}_3$) 225, found 225, 100%, $[\text{M} + \text{H}]^+$.

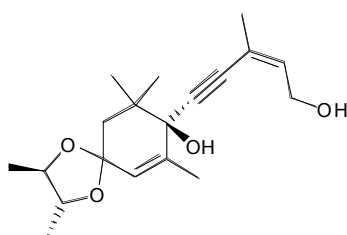
(2R,3R,8S)-8-(Ethynyl)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol, 14



Trimethylsilylacetylene (1.44 g, 14.6 mmol, 2 eq) was added slowly to a stirred solution of LDA (8.1 ml of a 1.8 M solution of LDA in THF/heptane/ethylbenzene, 2 eq) in THF (75 ml) at -78°C under a nitrogen atmosphere. The mixture was stirred for 15 minutes, then (2R, 3R)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-one, **13** (1.64 g, 7.3 mmol, 1 eq) in THF (10 ml) was introduced dropwise and the mixture allowed to attain room temperature. After 1 hour the reaction was quenched with saturated NH_4Cl (50 ml) and extracted with diethyl ether (3 x 60 ml). The combined organic extracts were washed with water (100 ml), then brine (100 ml) and dried over MgSO_4 . The solvent was removed under reduced pressure to yield a pale yellow residue that was dissolved in methanol (50 ml) and treated with K_2CO_3 (7.0 g). The suspension was stirred vigorously for 2 hours, then concentrated under reduced pressure. Water (50 ml) was added and the product extracted with diethyl ether (3 x 50 ml). The combined organics were washed with water (100 ml) then brine (100 ml) and dried over MgSO_4 . The solvent was removed under reduced pressure and the residue recrystallised slowly from petroleum ether ($40\text{-}60^\circ$) to give the *title product* **14** as white needles (1.10 g, 60%). (Found: C, 71.97; H, 8.85% $\text{C}_{15}\text{H}_{22}\text{O}_3$ requires C, 71.97; H, 8.86%); m.p. $138\text{-}140^\circ\text{C}$ ($40\text{-}60^\circ$ petroleum ether); $[\alpha]_D^{20} = -117.2$ (c 1.00,

MeOH); $\nu_{\max}$ (solid) 3424, 3285, 1090, 991, 947 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 1.08 (s, 3H), 1.16 (s, 3H), 1.23-1.25 (m, 6H), 1.82 (dd, $J = 1.3, 14.0$, 1H), 1.91 (d, $J = 1.5$, 3H), 1.99 (s, 1H), 2.06 (d, $J = 14.0$, 1H), 2.49 (s, 1H), 3.53-3.63 (m, 2H), 5.38-5.39 (m, 1H); δ_{C} (100 MHz, CDCl_3) 16.7 (CH_3), 16.8 (CH_3), 18.4 (CH_3), 22.0 (CH_3), 25.5 (CH_3), 39.2 (C), 45.5 (CH_2), 74.0 (CH), 74.5 (C), 77.9 (CH), 78.0 (CH), 84.2 (C), 103.8 (C), 125.3 (CH), 140.0 (C); HRMS (EI): m/z requires ($\text{C}_{15}\text{H}_{22}\text{O}_3$) 250.1569, found 250.1571, 72%, $[\text{M}]^+$.

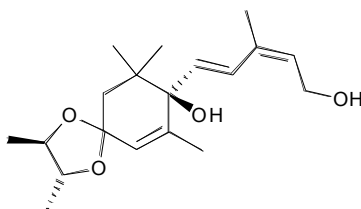
(2*R*,3*R*,8*S*)-8-(5-Hydroxy-3-methylpent-3-en-1-ynyl)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol, **20**



Copper iodide (114 mg, 15% mol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (281 mg, 10% mol), in dry deoxygenated toluene (40 ml) under a nitrogen atmosphere was treated with (*Z*)-3-iodobut-2-en-1-ol, **8**, (1.58 g, 8.0 mmol, 2 eq) and (2*R*,3*R*,8*S*)-8-(ethynyl)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol **14** (1.0 g, 4.0 mmol, 1 eq). Diisopropylamine (1.12 ml, 8.0 mmol, 2 eq) was added dropwise and the mixture stirred for 1.5 hours. Saturated NH_4Cl solution (40 ml) was added and the organic layer separated. The aqueous layer was extracted with diethyl ether (3 x 40 ml) and the combined organics dried over MgSO_4 . The solvent was removed under reduced pressure and the product purified by column chromatography (silica, 30% EtOAc in hexane) to yield the *title product* **20** as a pale yellow oil (1.23 g, 96%). R_f 0.19 (40% EtOAc in hexane); $[\alpha]_{\text{D}}^{20} = -121.6$ (c 0.76, MeOH); $\nu_{\max}$ (film) 3382, 1090, 983, 948 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 1.09 (s, 3H), 1.15 (s, 3H), 1.23-1.26 (m, 6H), 1.83 (d, $J = 14.0$, 1H), 1.86 (s, 3H), 1.90 (s, 3H), 2.04 (d, $J = 14.0$, 1H), 2.25 (s, br, 1H), 3.53-3.63 (m, 2H), 4.26 (d, $J = 6.3$, 2H), 5.37 (s, 1H), 5.86-5.89 (m, 1H); δ_{C} (100 MHz, CDCl_3) 16.7 (CH_3), 16.7 (CH_3), 18.6 (CH_3), 22.2 (CH_3), 23.0 (CH_3), 25.7 (CH_3), 39.6 (C), 45.7 (CH_2), 61.1 (CH_2), 75.0 (C), 77.9 (CH), 78.0 (CH), 83.9 (C), 94.7 (C), 103.9 (C),

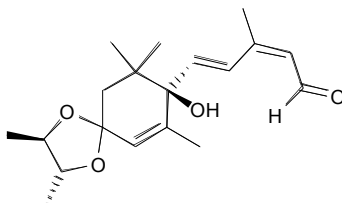
120.7 (C), 125.0 (CH), 136.1 (CH), 140.5 (C); HRMS (LSIMS): m/z requires ($C_{19}H_{29}O_4$) 321.2066, found 321.2076, 12%, $[M+H]^+$.

(2R,3R,8R)-8-(5-Hydroxy-3-methyl-2,4-pentadienyl)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol, **21**



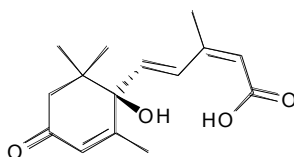
To a stirred solution of (2R,3R,8S)-8-(5-hydroxy-3-methylpent-3-en-1-ynyl)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol, **20** (640 mg, 2.0 mmol, 1 eq) in dry deoxygenated THF (15 ml) at -78°C under a nitrogen atmosphere was added Red-Al[®] (1.25 ml of a 3.2 M solution in toluene, 4.0 mmol, 2 eq) *via* syringe. The reaction was allowed to warm to room temperature and stirred for 3 hours. It was then cooled on an ice bath and water (15 ml) was carefully added dropwise and stirring continued at room temperature for 1 hour. (CAUTION: unreacted Red-Al[®] reacts violently with water). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 15 ml). The combined organics were washed with brine (50 ml) and dried over MgSO_4 . The solvent was removed under reduced pressure and the product purified by column chromatography (silica, 25% hexane in diethyl ether) to yield the *title alcohol* **21** as a viscous oil (531 mg, 82%). R_f 0.16 (25% hexane in diethyl ether); $[\alpha]_D^{20} = -219.5$ (c 0.41, MeOH); ν_{max} (film) 3379, 1092, 978, 952 cm^{-1} ; δ_H (400 MHz, CDCl_3) 0.90 (s, 3H), 1.10 (s, 3H), 1.23 (d, $J = 5.5$, 3H), 1.26 (d, $J = 5.5$, 3H), 1.67 (d, $J = 1.5$, 3H), 1.69 (dd, $J = 1.5$, 14.3, 1H), 1.85 (d, $J = 1.0$, 3H), 1.93 (d, $J = 14.3$, 1H), 2.12 (s, br, 1H), 3.52-3.62 (m, 2H), 4.24-4.36 (m, 2H), 5.44 (t, $J = 1.5$, 1H), 5.58 (t, $J = 7.5$, 1H), 5.72 (d, $J = 15.8$, 1H), 6.66 (d, $J = 15.8$, 1H); δ_C (100 MHz, CDCl_3) 16.6 (2 x CH_3), 18.1 (CH_3), 20.7 (CH_3), 23.2 (CH_3), 24.9 (CH_3), 39.3 (C), 46.3 (CH_2), 58.3 (CH_2), 77.6 (CH), 78.0 (CH), 79.4 (C), 104.0 (C), 125.5 (CH), 126.1 (CH), 128.4 (CH), 132.2 (CH), 134.9 (C), 141.6 (C); HRMS (LSIMS): m/z requires ($C_{19}H_{31}O_4$) 323.2222, found 323.2212, 24%, $[M+H]^+$.

(2*R*,3*R*,8*R*)-8-(3-Methylpenta-2,4-dienal)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol, **22**



(2*R*,3*R*,8*R*)-8-(3-Methylpenta-2,4-dienal)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol, **21** (500 mg, 1.55 mmol, 1 eq) was dissolved in DCM (15 ml) and treated with 4-methylmorpholine-*N*-oxide (270 mg, 2.3 mmol, 1.5 eq), powdered 4Å molecular sieves (500 mg) and tetra-*N*-propyl ammonium perruthenate (TPAP) (55 mg, 10% mol). The mixture was stirred under nitrogen for 20 minutes, then filtered through a short column of silica. The column was washed with DCM and the filtrate and washings combined. The solvent was removed under reduced pressure and the product recrystallised from cyclohexane to yield the *title aldehyde* **22** as off-white crystals (490 mg, 98%). (Found: C, 71.34; H, 8.86%. C₁₉H₂₈O₄ requires C, 71.22; H, 8.81%); m.p. 126-127°C (cyclohexane); [α]_D²⁰ = -324.2 (c 0.78, MeOH); ν_{max}(solid) 3518, 1664, 1628, 1132, 1091, 956 cm⁻¹; δ_H (400 MHz, CDCl₃) 0.92 (s, 3H), 1.12 (s, 3H), 1.24 (d, *J* = 5.5, 3H), 1.27 (d, *J* = 5.5, 3H), 1.67 (s, 3H), 1.75 (dd, *J* = 1.3, 14.4, 1H), 1.95 (d, *J* = 14.4, 1H), 2.07 (s, 3H), 3.53-3.63 (m, 2H), 5.47 (t, *J* = 1.3, 1H), 5.86 (d, *J* = 8.1, 1H), 6.12 (d, *J* = 15.6, 1H), 7.34 (d, *J* = 15.6, 1H), 10.22 (d, *J* = 8.1, 1H); δ_C (100 MHz, CDCl₃) 16.6 (2 x CH₃), 17.8 (CH₃), 21.6 (CH₃), 23.2 (CH₃), 25.1 (CH₃), 39.4 (C), 46.3 (CH₂), 77.7 (CH), 78.1 (CH), 79.3 (C), 103.6 (C), 124.9 (CH), 126.4 (CH), 128.9 (CH), 139.4 (CH), 140.4 (C), 154.0 (C), 190.6 (CH); HRMS (LSIMS): *m/z* requires (C₁₉H₂₉O₄) 321.2066, found 321.2063, 70%, [M+H]⁺.

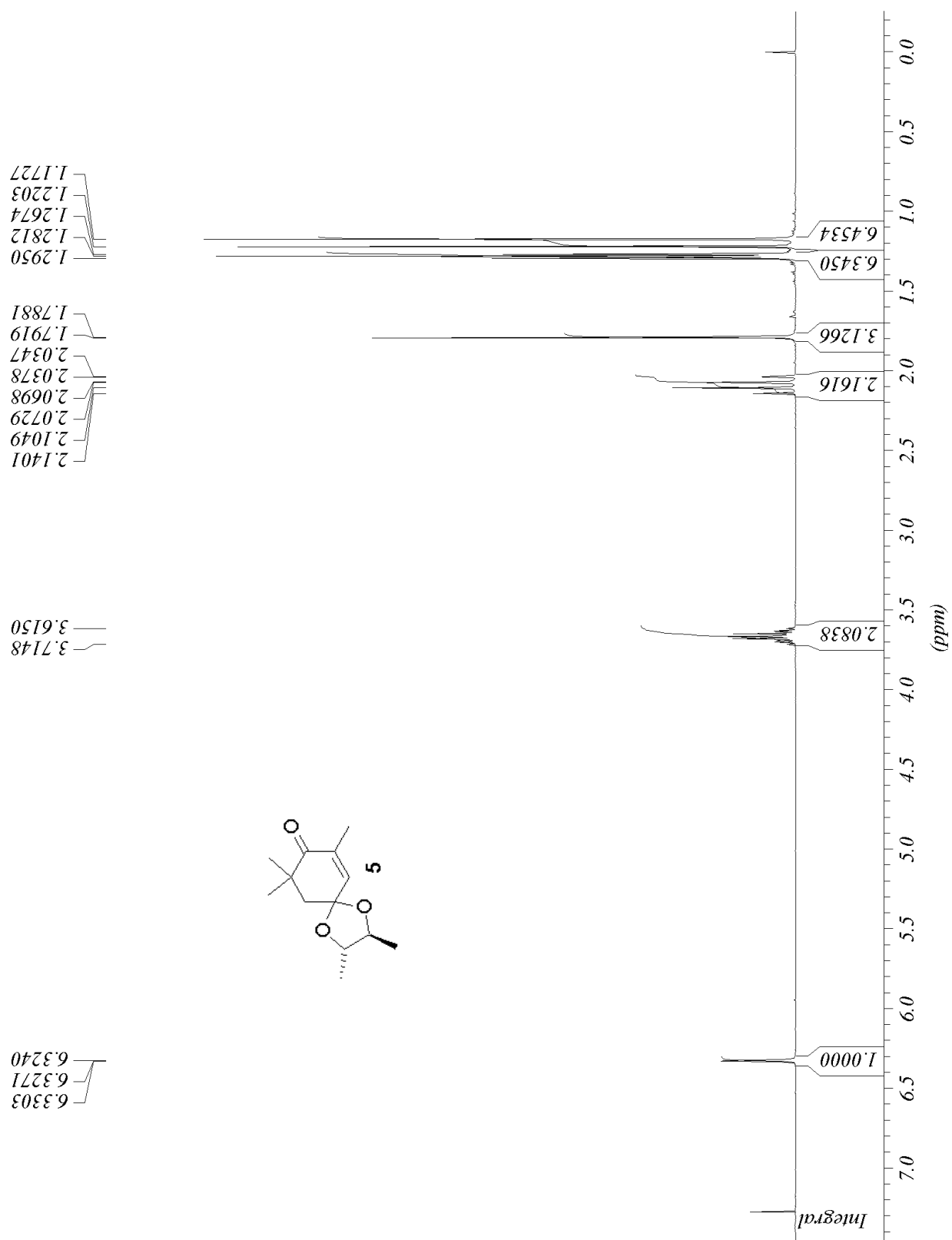
(*R*)-5-(1-Hydroxy-2,6,6-trimethyl-4-oxo-2-cyclohexen-1-yl)-3-methyl-(2*Z*,4*E*)-pentadienoic acid, **2, (*R*)-(-)-abscisic acid**

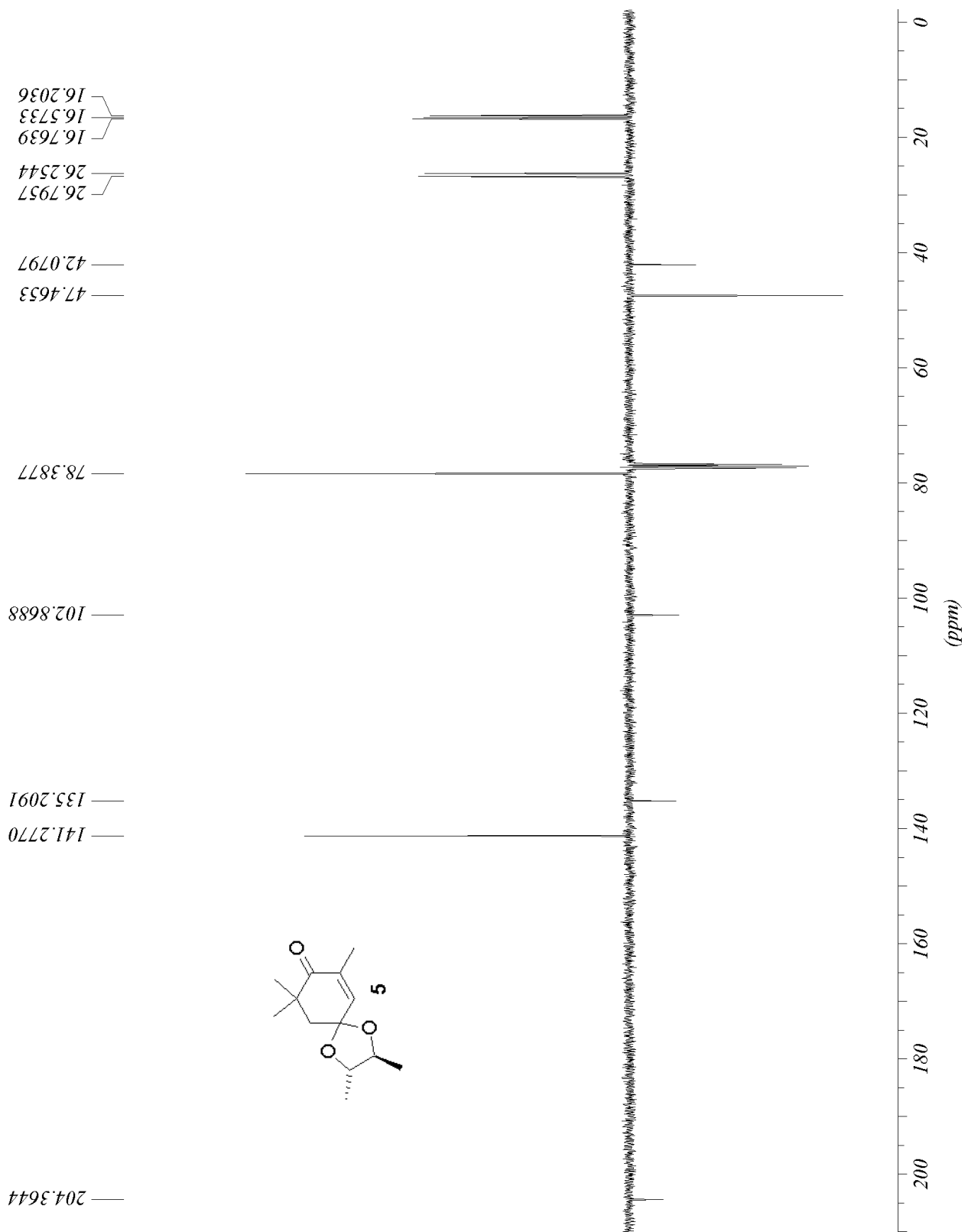


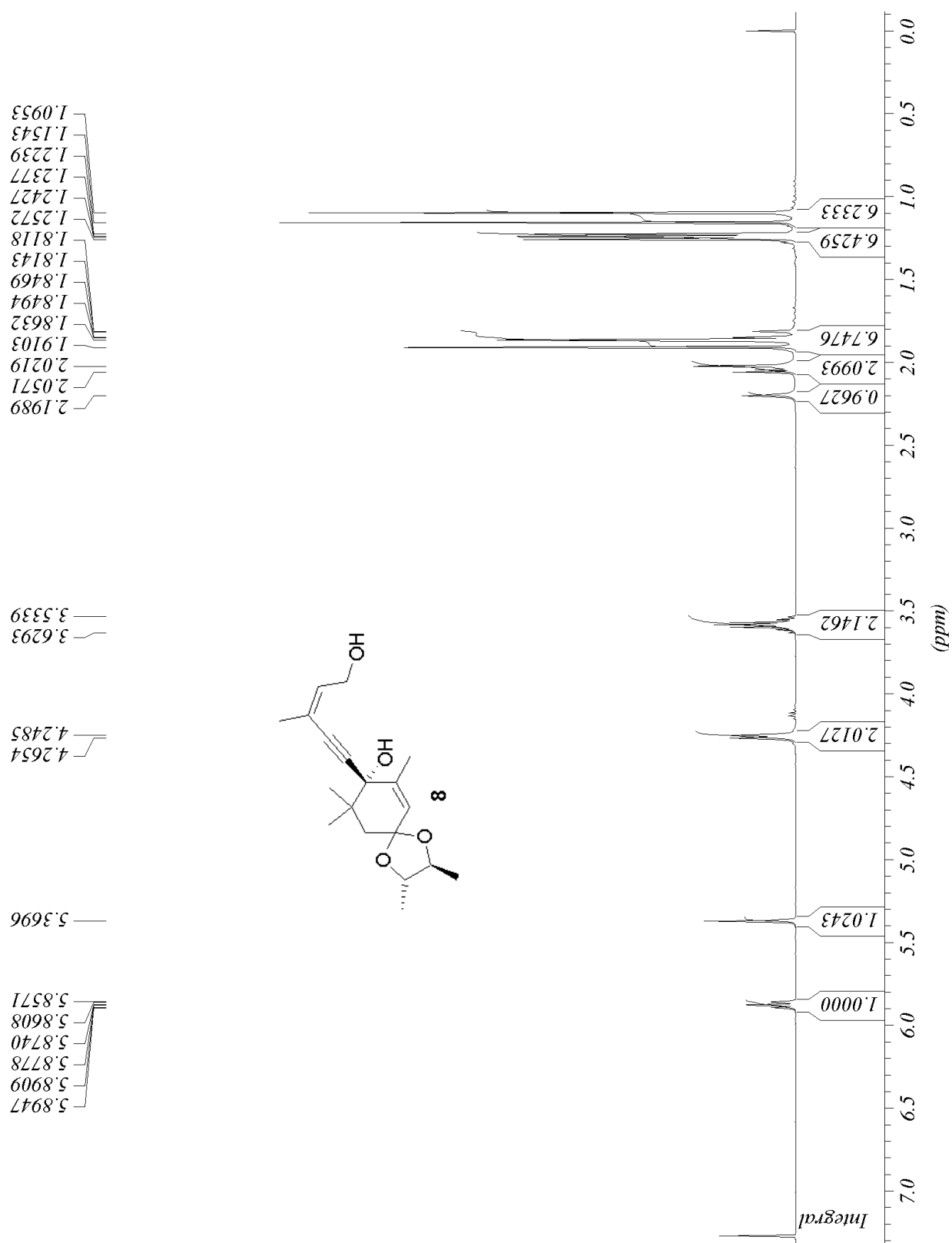
A solution of KH_2PO_4 (850 mg, 6.2 mmol, 5 eq) and sodium chlorite (1.13 g, 12.5 mmol, 10 eq) in water (10 ml) was added dropwise over a period of ten minutes to a stirred solution of (2*R*,3*R*,8*R*)-8-(3-methylpenta-2,4-dienal)-2,3,7,9,9-pentamethyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol, **22** (400 mg, 1.3 mmol, 1 eq) and 2-methyl-2-butene (8.0 ml) in $t\text{BuOH}$ (20 ml). The mixture was stirred for 20 hours, then concentrated under reduced pressure. Methanol (10 ml) was added and the mixture carefully acidified to pH 3 with concentrated HCl (aq). After 15 minutes the mixture was extracted with EtOAc (3 x 20 ml) and the combined organics washed in brine (50 ml) and dried over MgSO_4 . The solvents were removed under reduced pressure and the residue purified by column chromatography (silica, 30% EtOAc and 3% AcOH in hexane). The solid obtained was recrystallised from EtOAc / hexane to give (*R*)-(-)-abscisic acid as white crystals (189 mg, 57%). (Found: C, 68.11; H, 7.58%. $\text{C}_{15}\text{H}_{20}\text{O}_4$ requires C, 68.16; H, 7.63%); m.p. 159-160°C (hexane) (lit. m.p. 162-163°C);¹ R_f 0.27 (40% EtOAc and 3% AcOH in hexane), $[\alpha]_D^{20} = -413.4$ (c 1.00, EtOH); ν_{max} (solid) 3371, 1647, 1623, 1598, 1249 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 1.04 (s, 3H), 1.12 (s, 3H), 1.93 (s, 3H), 2.05 (d, $J = 1.0$, 3H), 2.30 (d, $J = 16.8$, 1H), 2.50 (d, $J = 16.8$, 1H), 5.77 (s, 1H), 5.98 (s, 1H), 6.17 (d, $J = 16.0$, 1H), 7.81 (d, $J = 16.0$, 1H); δ_{C} (100 MHz, CDCl_3) 19.1 (CH_3), 21.4 (CH_3), 23.1 (CH_3), 24.3 (CH_3), 41.6 (C), 49.7 (CH_2), 79.9 (C), 117.9 (CH), 127.1 (CH), 128.3 (CH), 136.8 (CH), 151.6 (C), 162.6 (C), 170.6 (C), 198.1 (C); HRMS (LSIMS): m/z requires ($\text{C}_{15}\text{H}_{20}\text{O}_4$) 264.1362, found 264.1364, 100%, $[\text{M}]^+$.

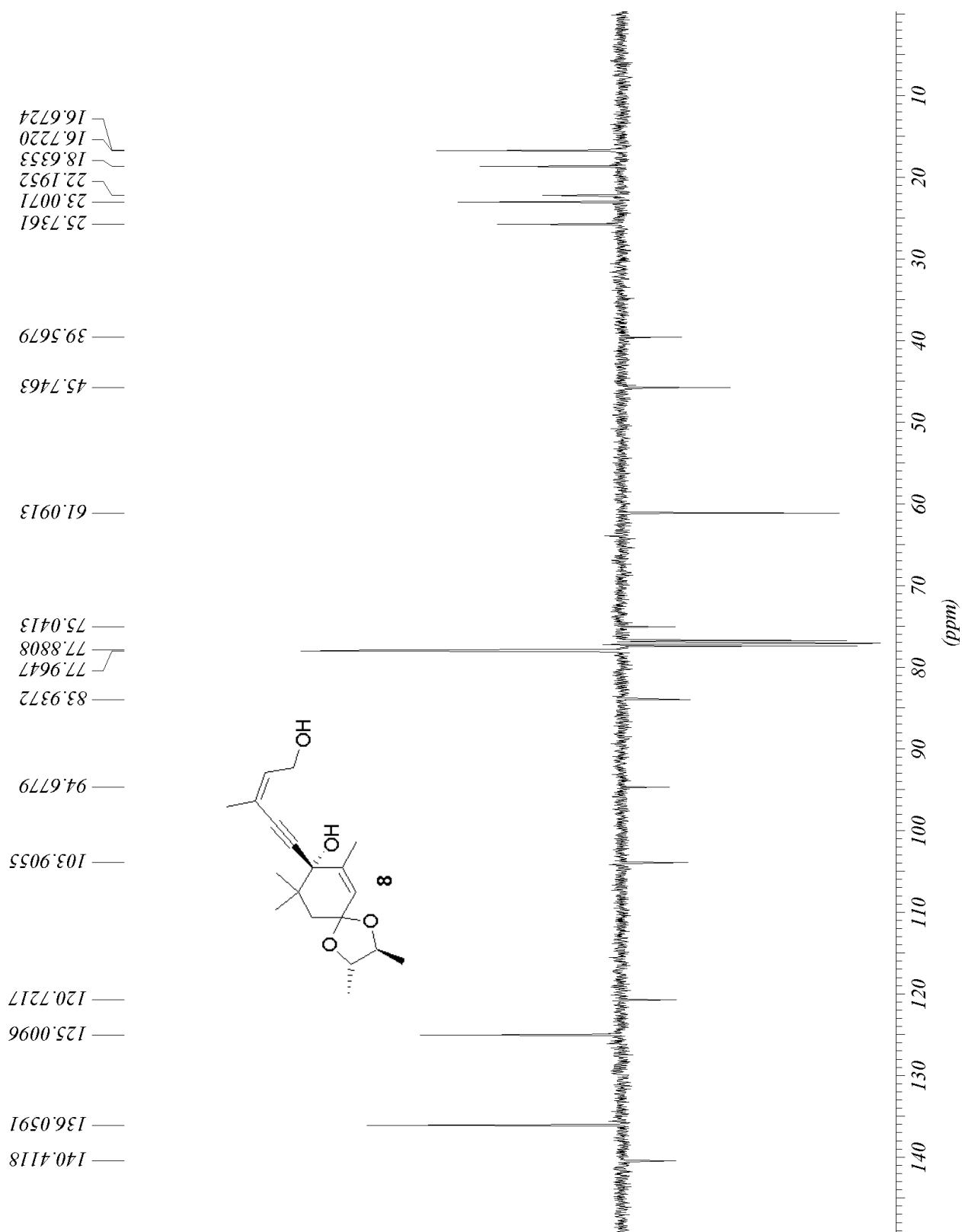
¹ F. Kienzle, H. Mayer, R. E. Minder, H. Thommen, *Helv. Chim. Acta*, 1978, **61**, 2616.

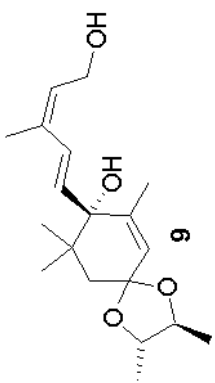
II) NMR spectra for compounds without elemental analysis

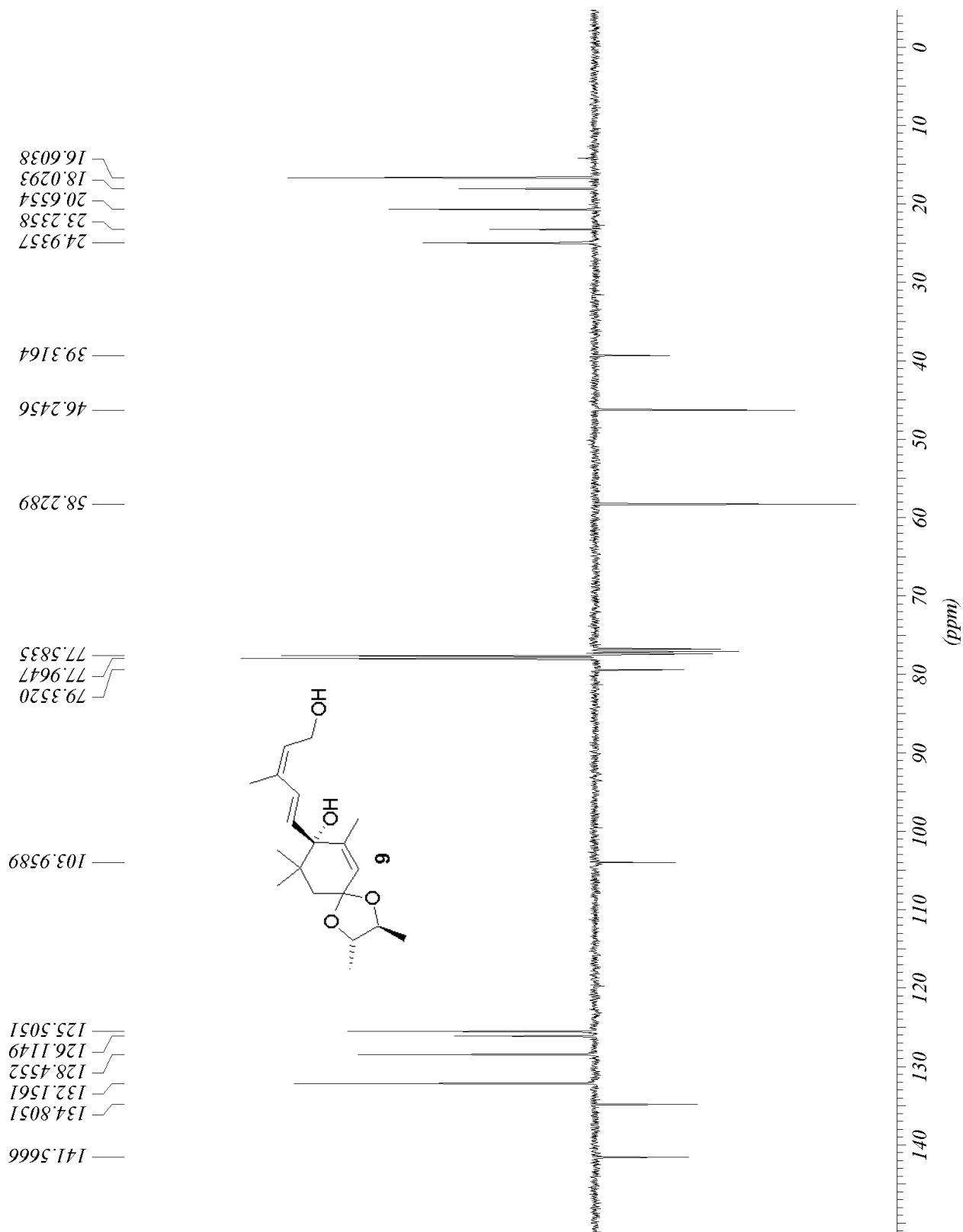


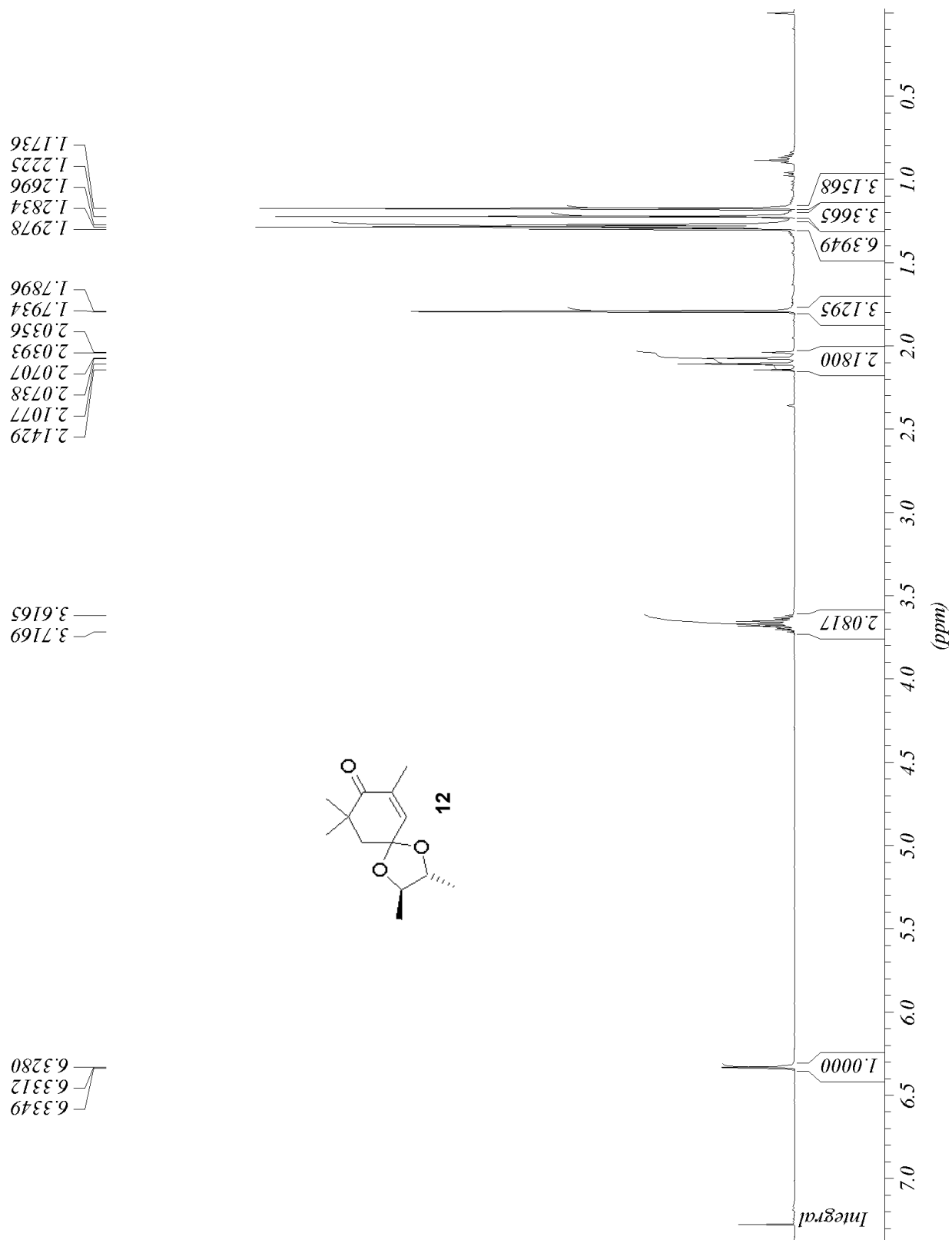


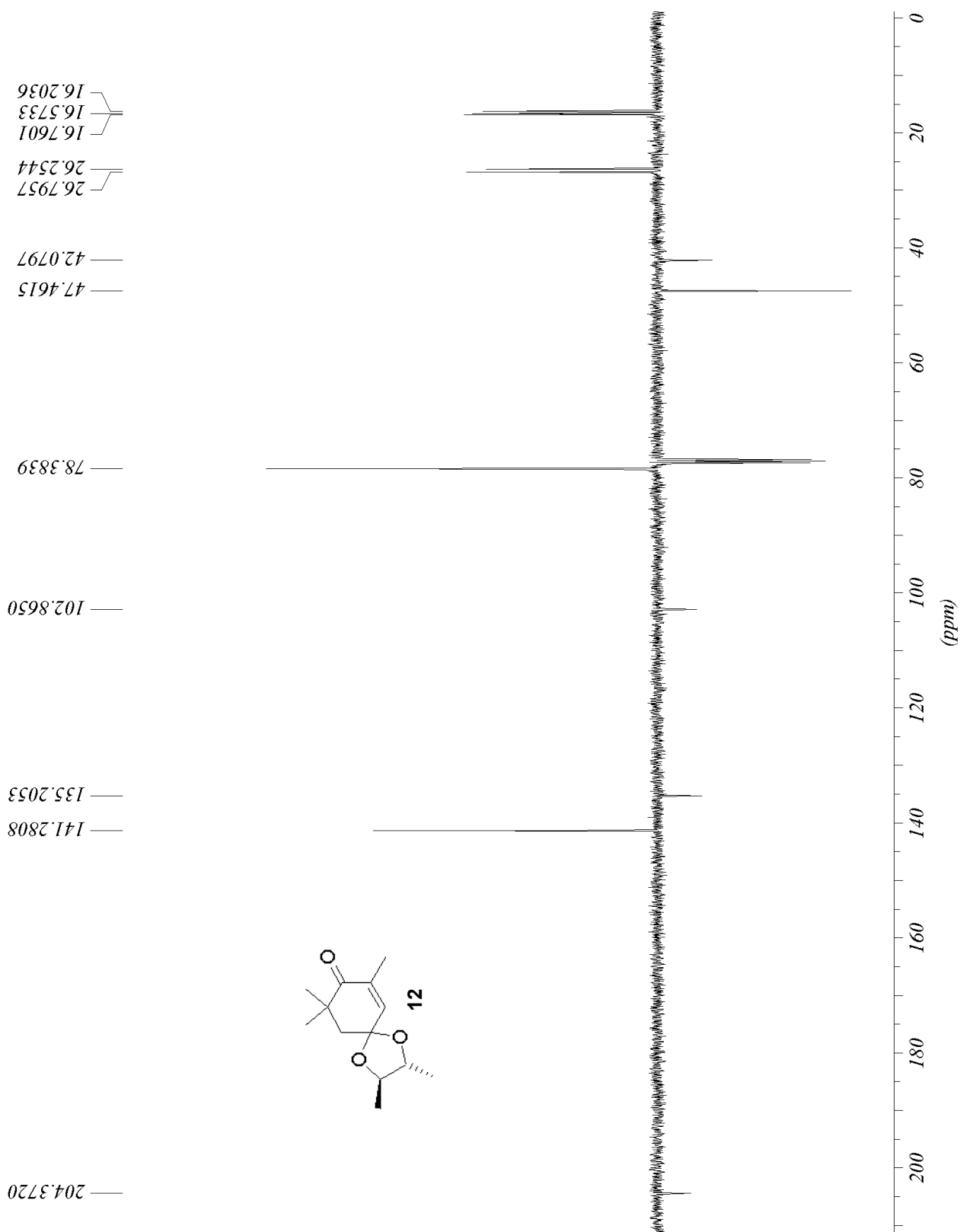


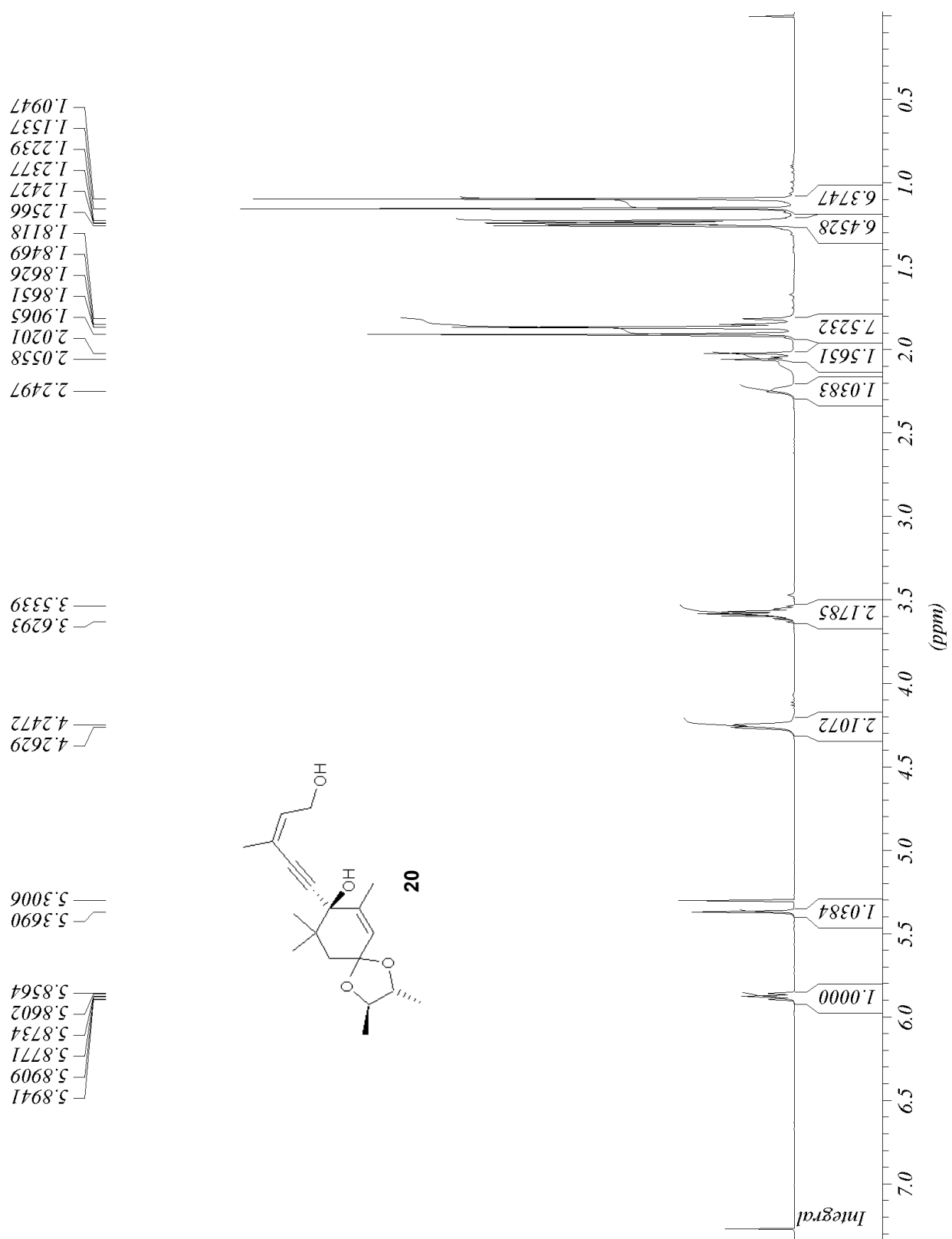


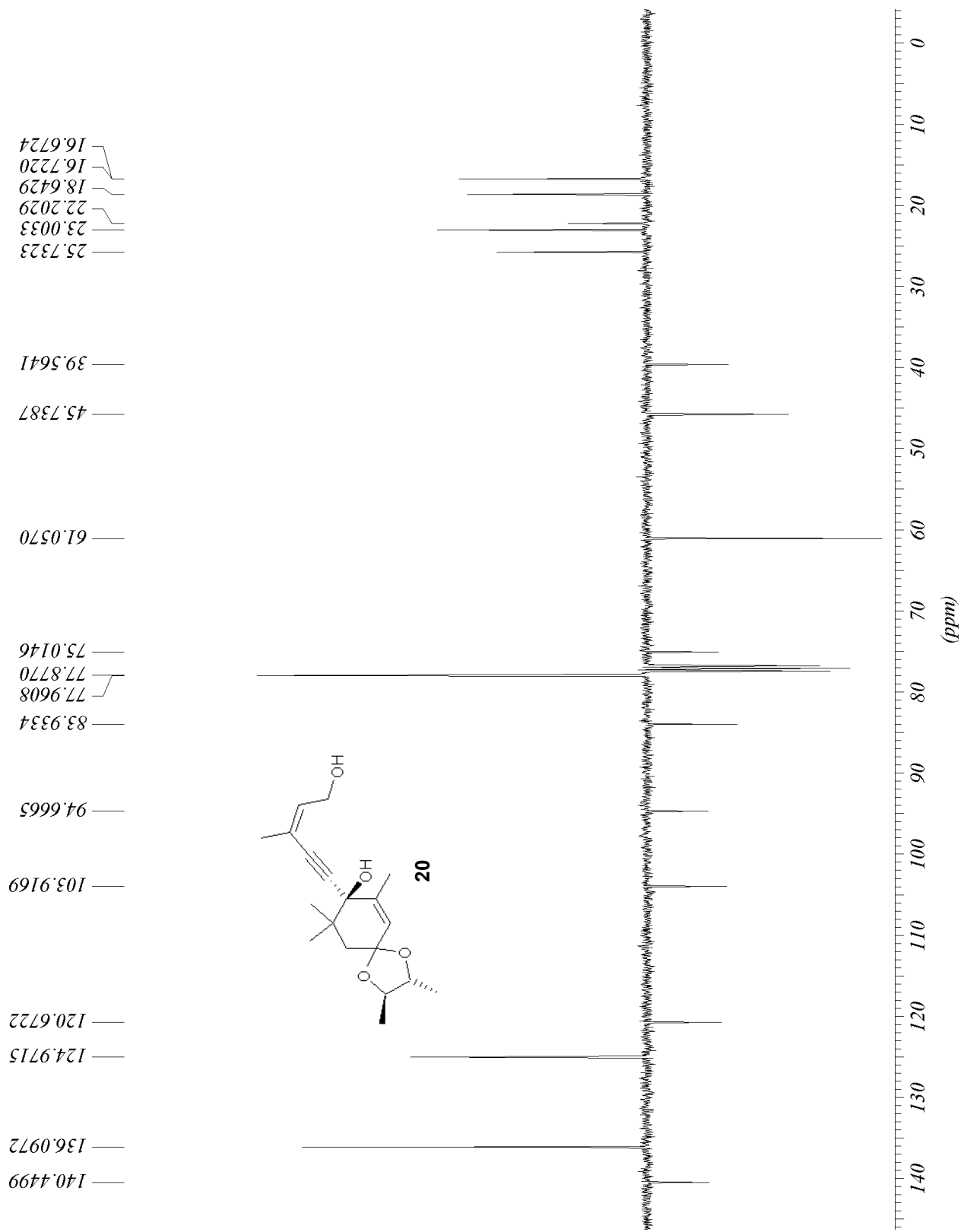


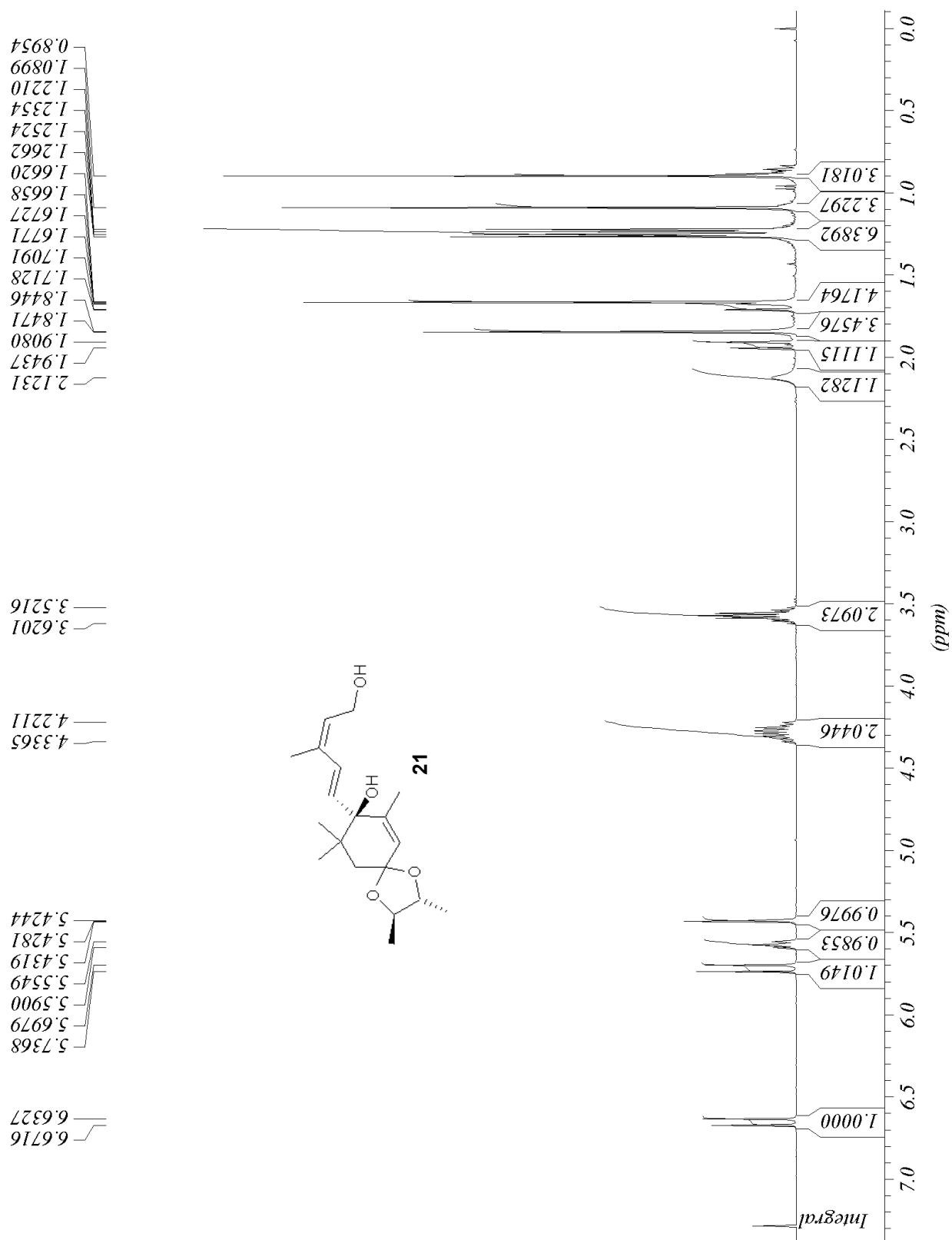


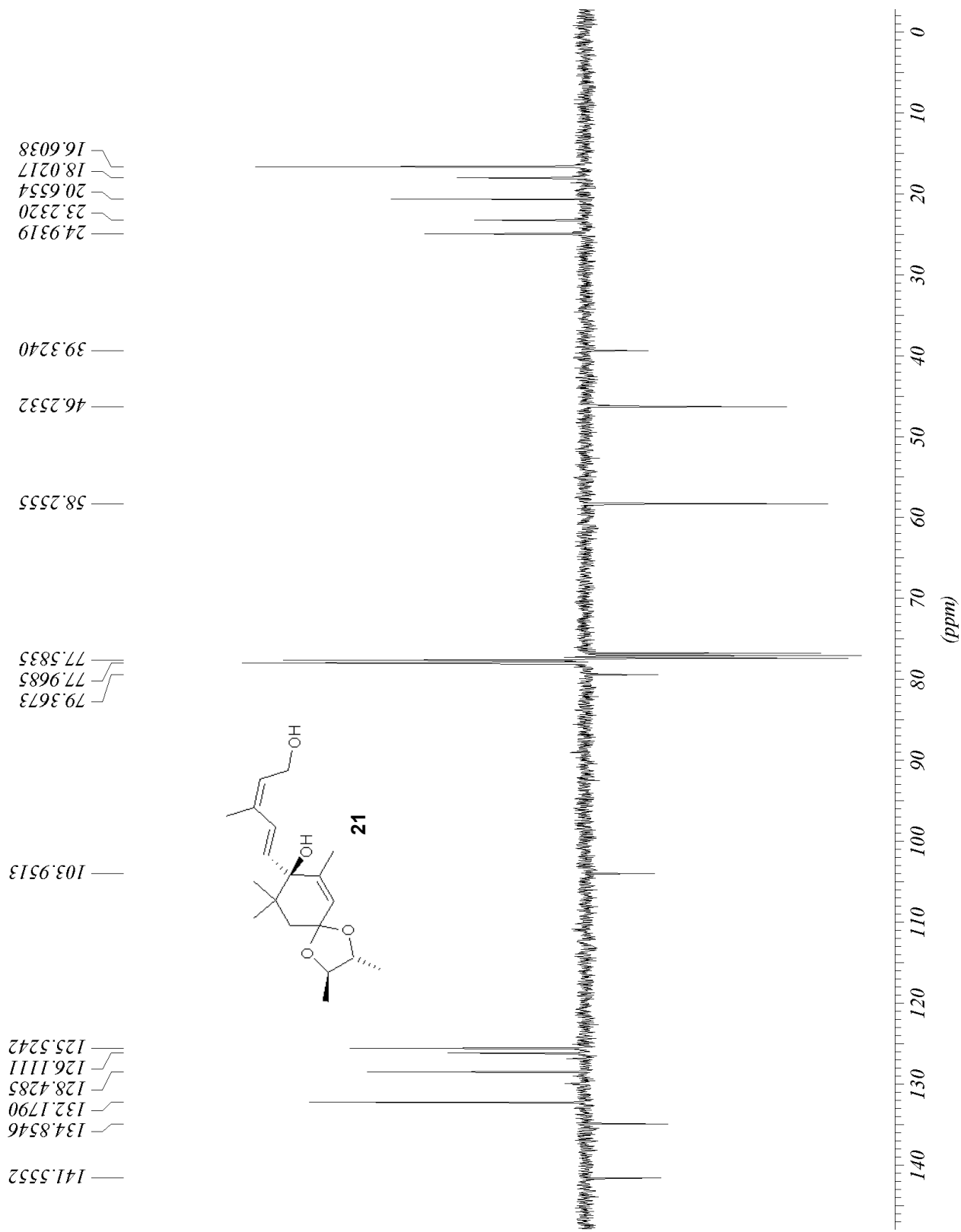


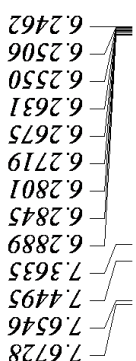


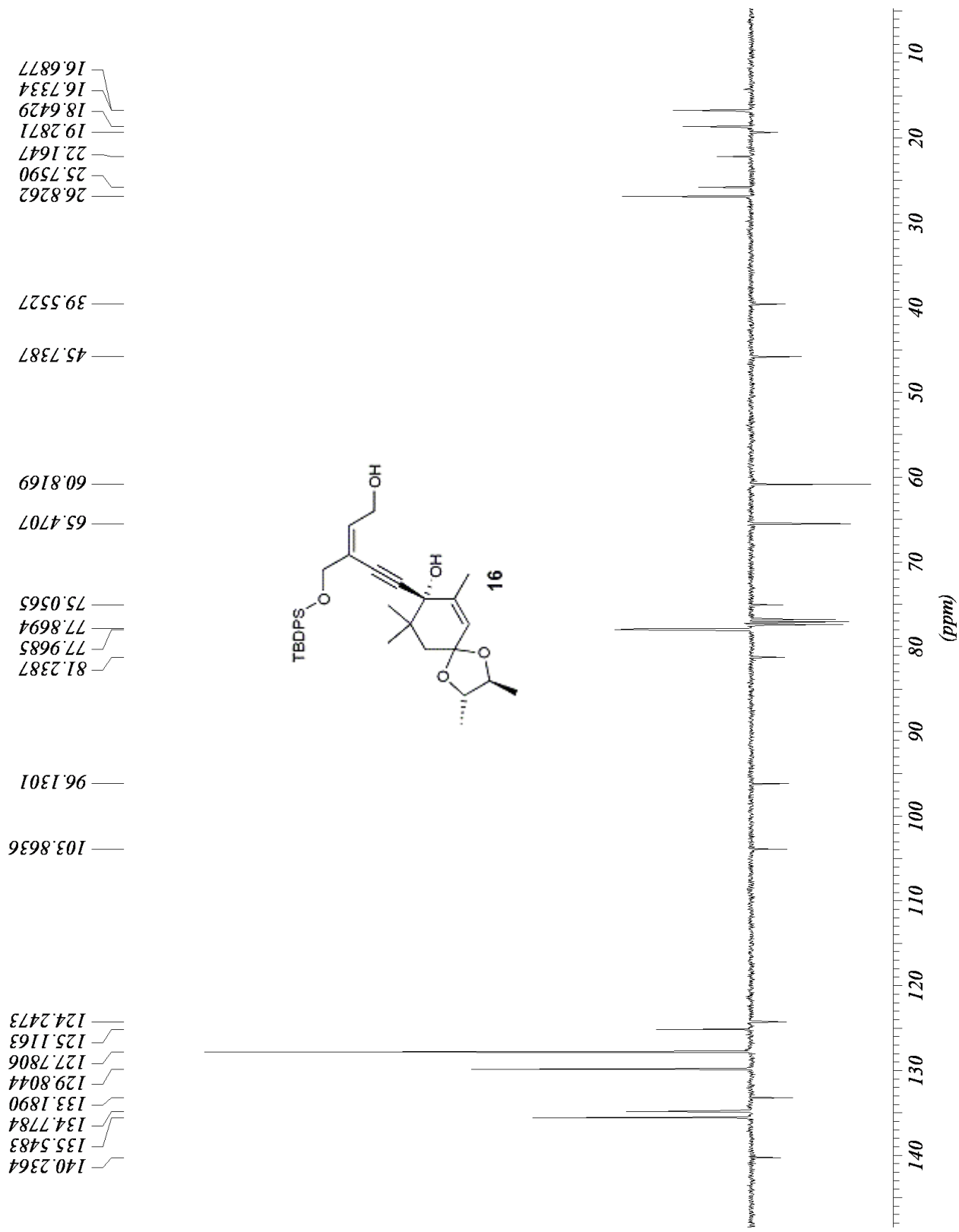


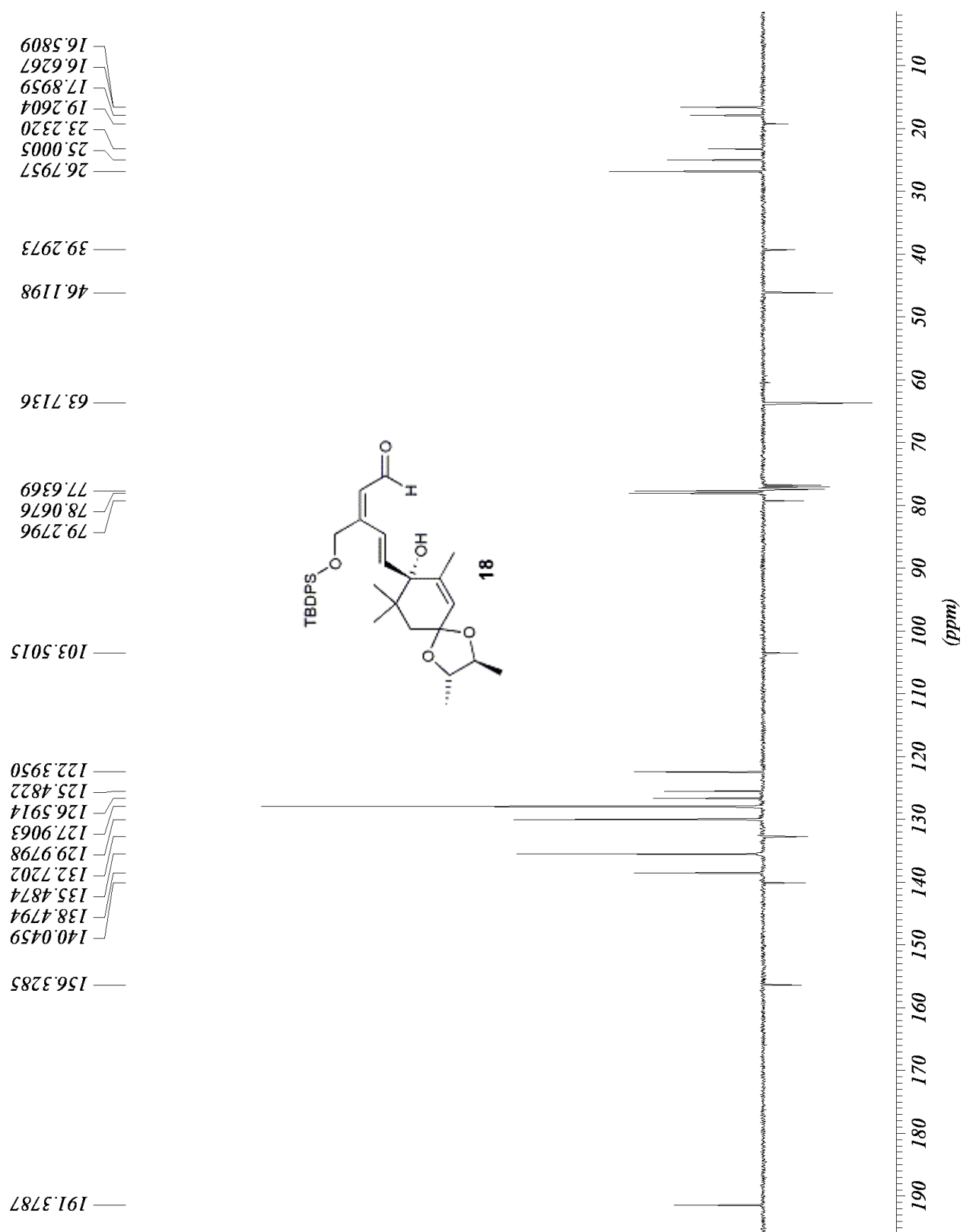


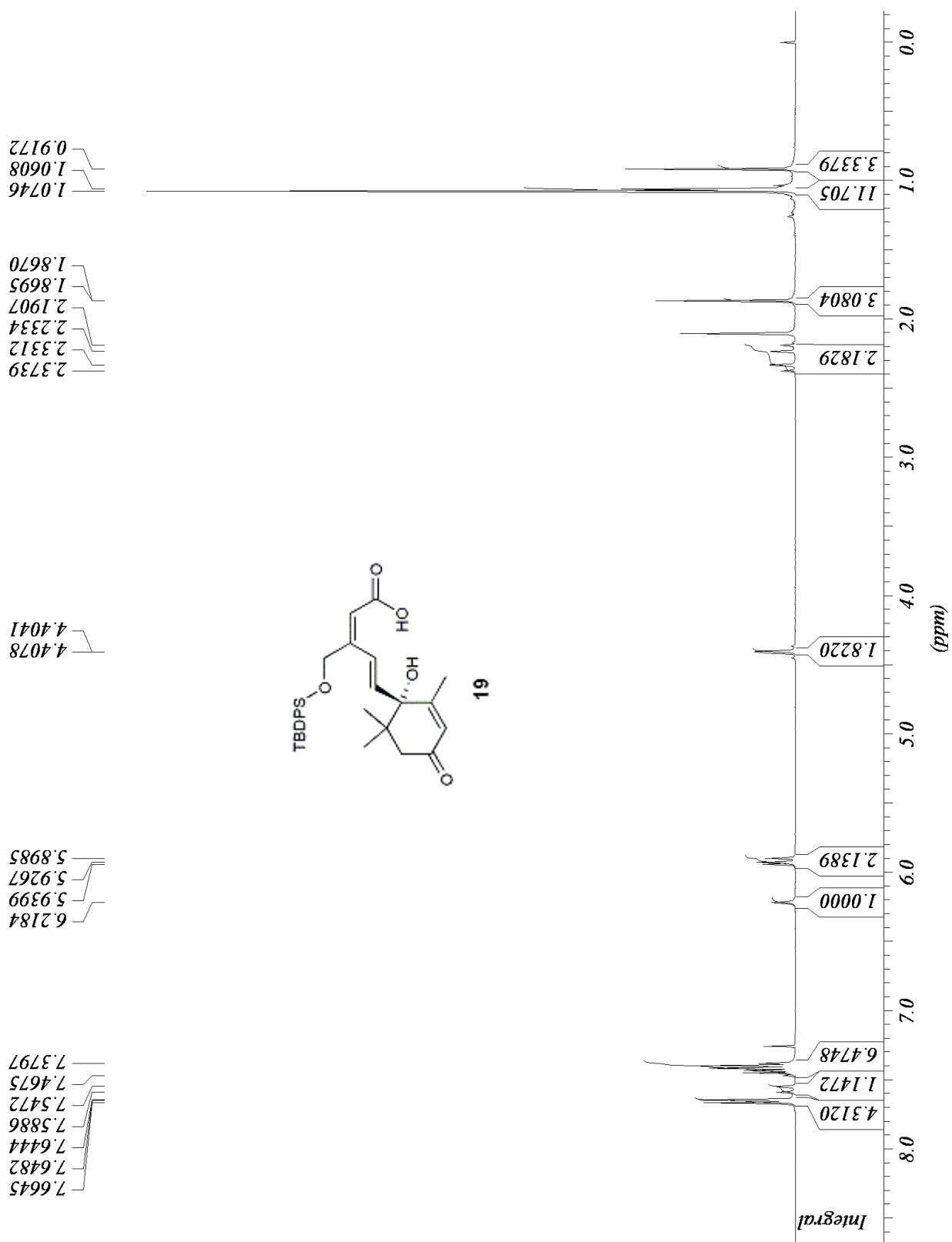


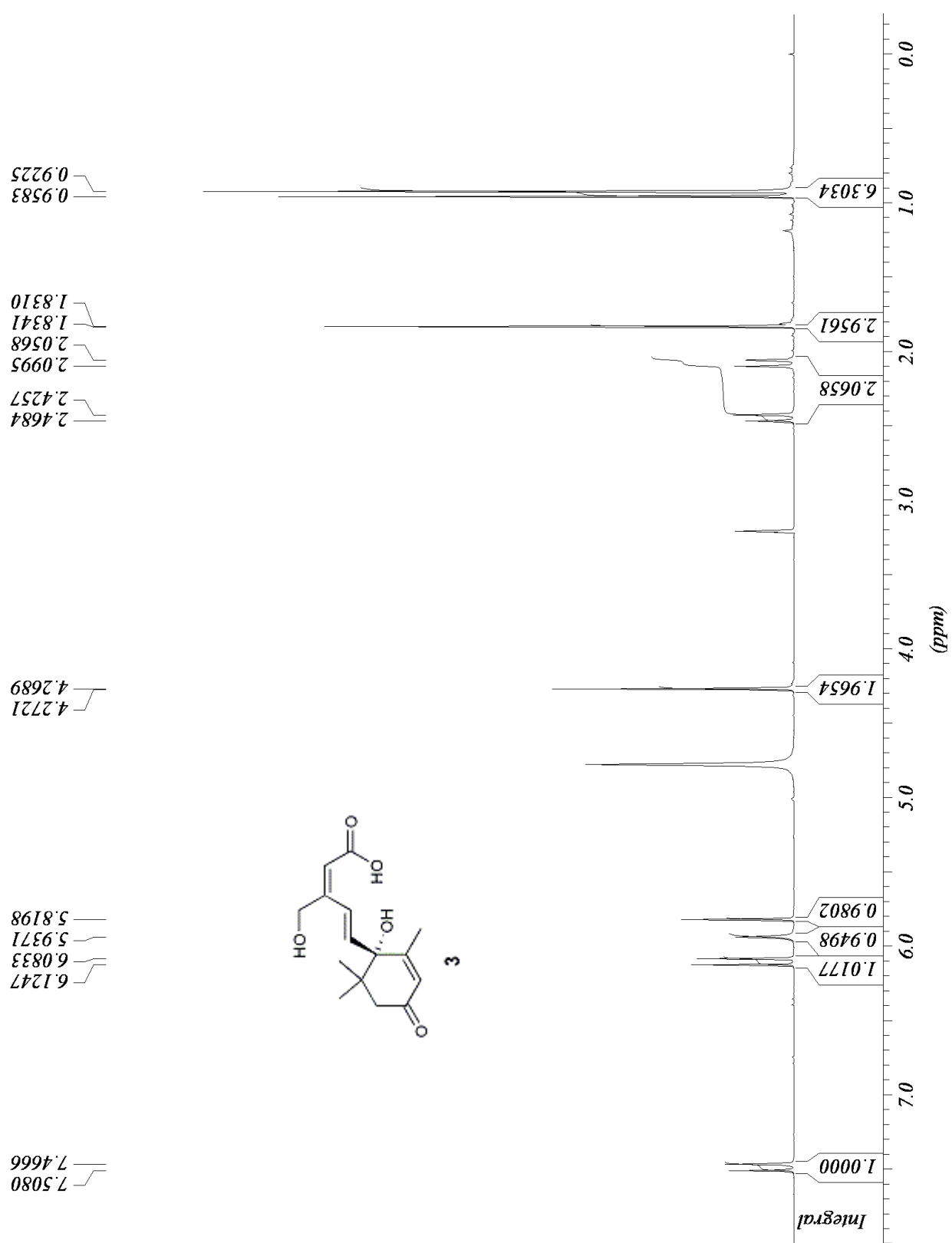


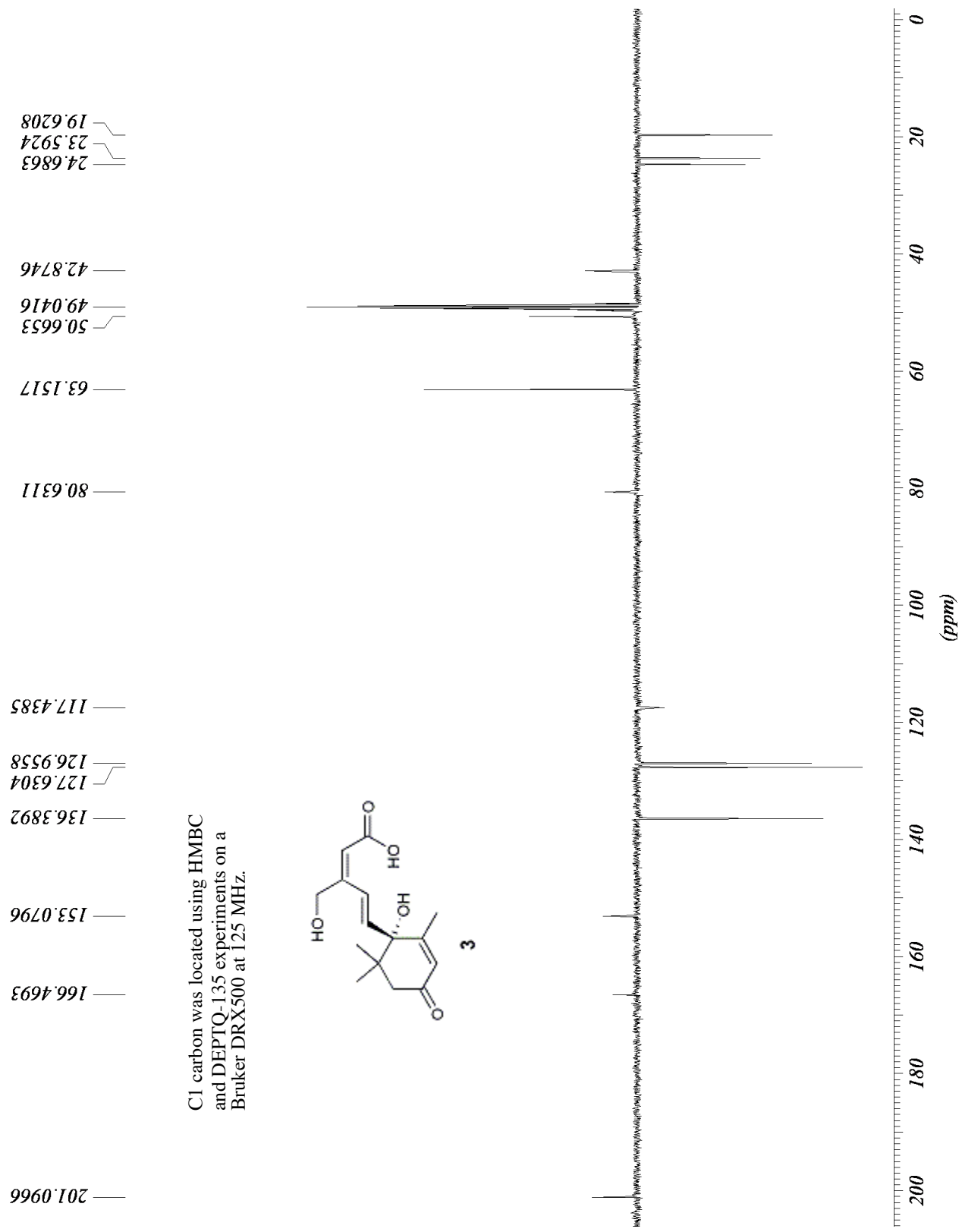




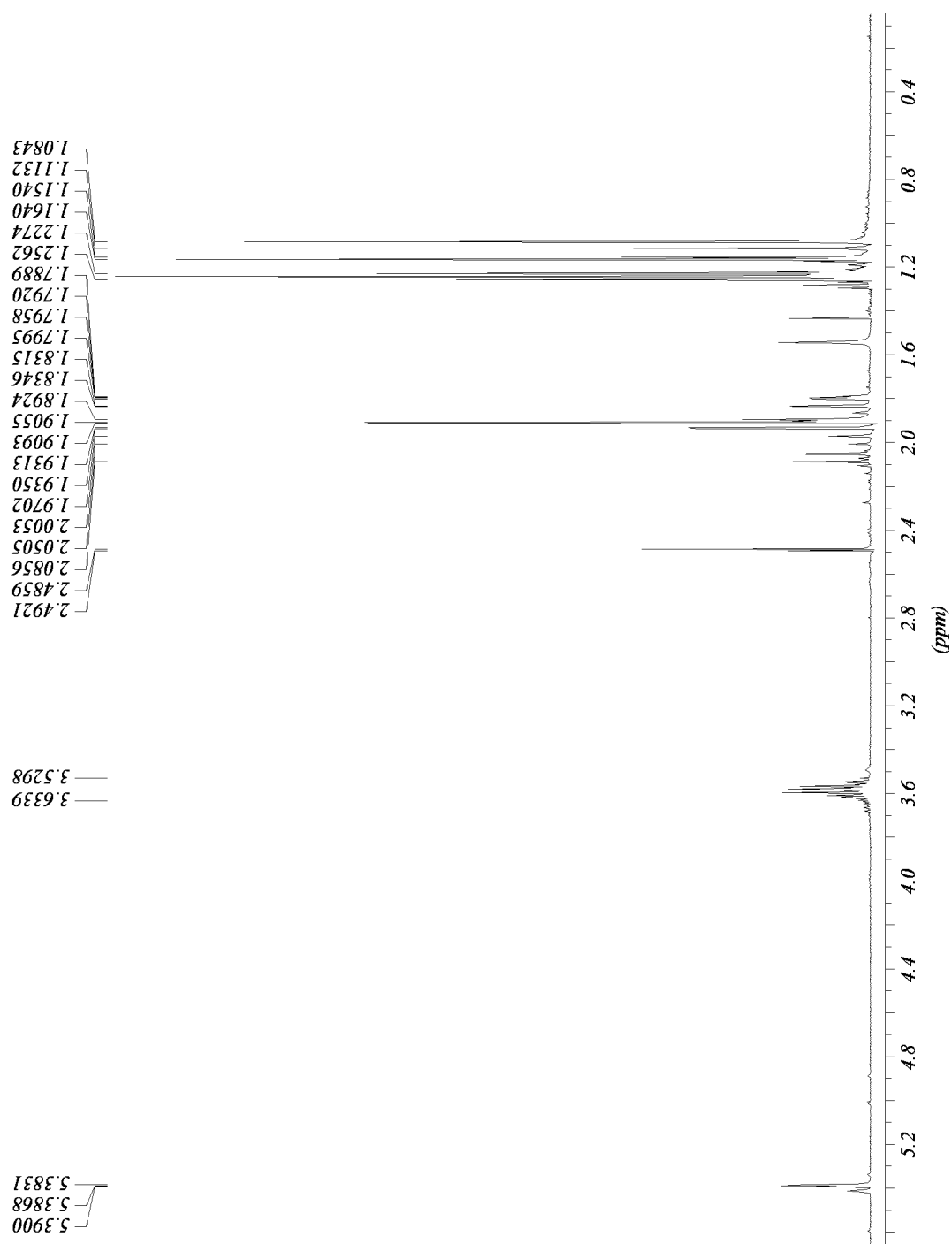




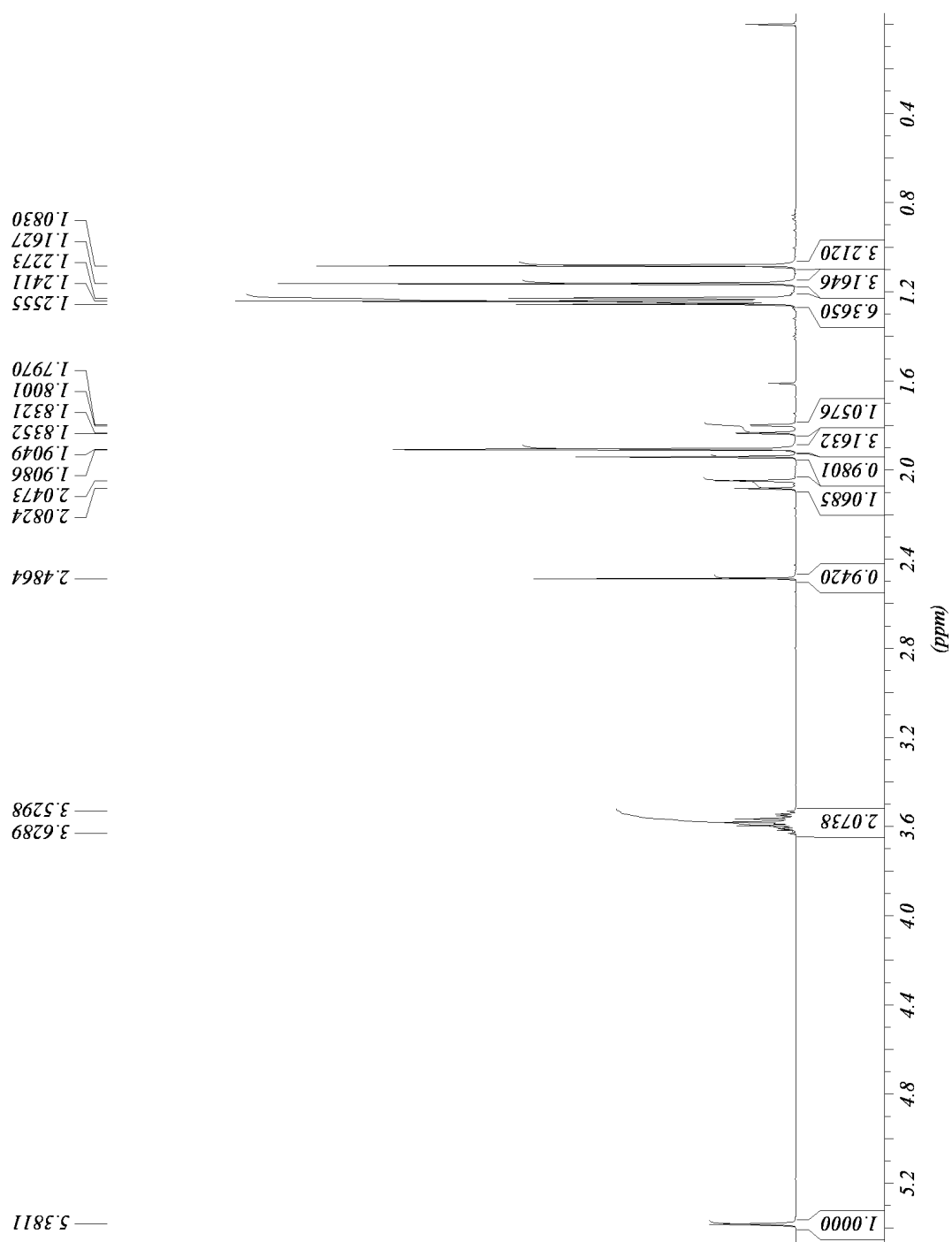




^1H NMR spectrum of crude compound **7**.



^1H NMR spectrum of **7** after one recrystallisation from 40-60° petroleum ether.



GC-MS of recrystallised compound 7.

Print Date: 20 Sep 2006 14:12:13

Unidentified Compound Report for #1 from ...6 brown 100 ci 13-52-09.sms

Reaction Screen CI

TIM-190

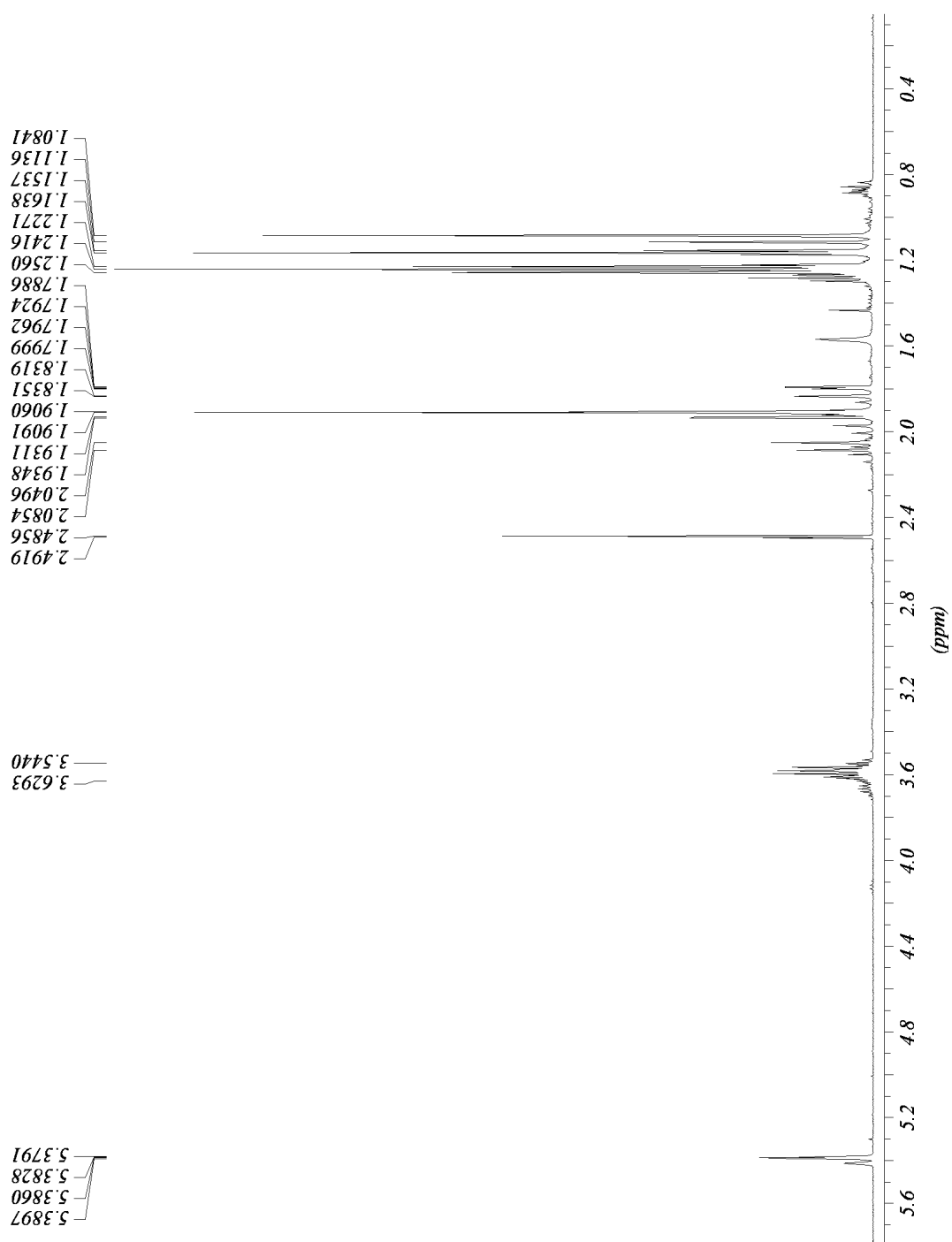
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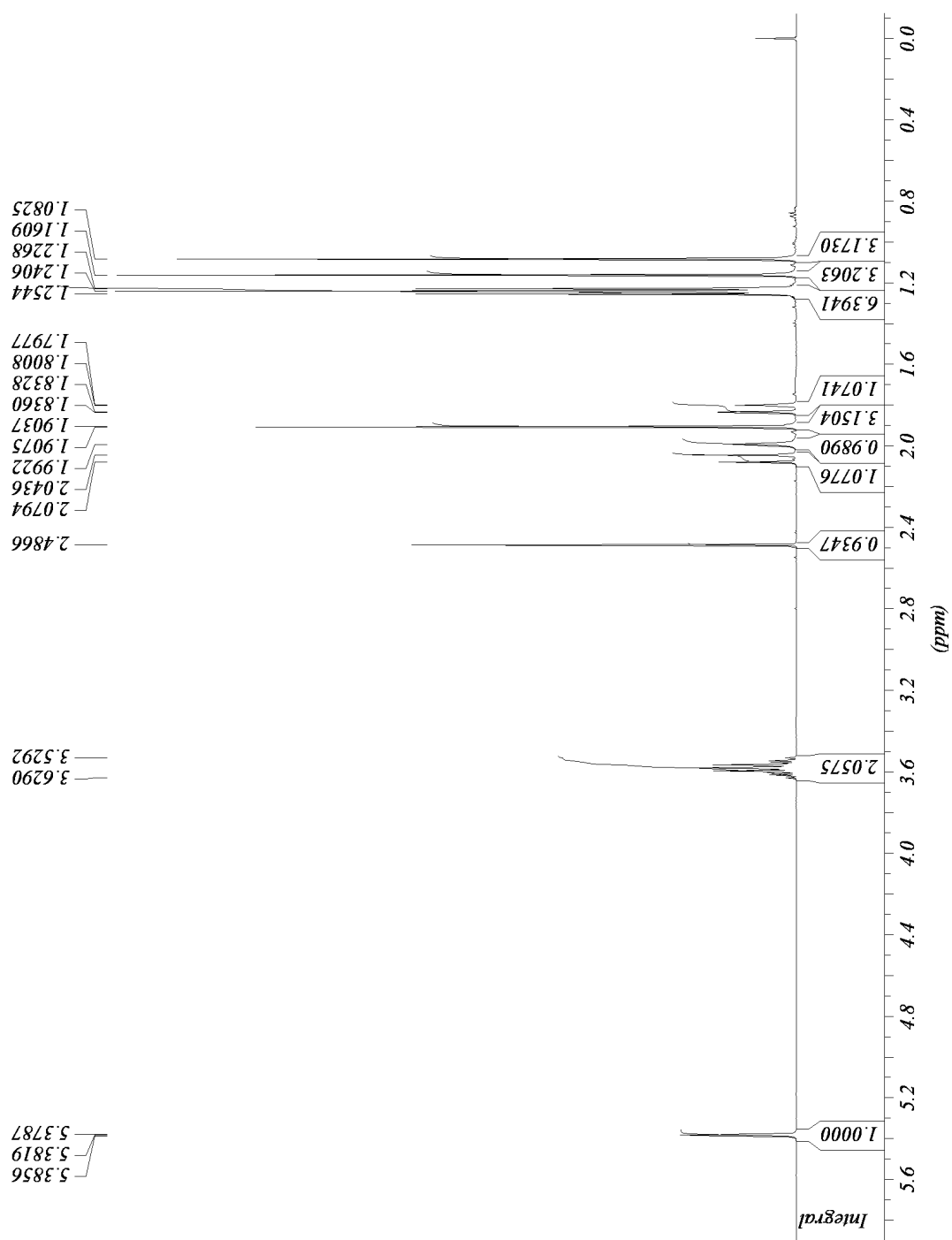
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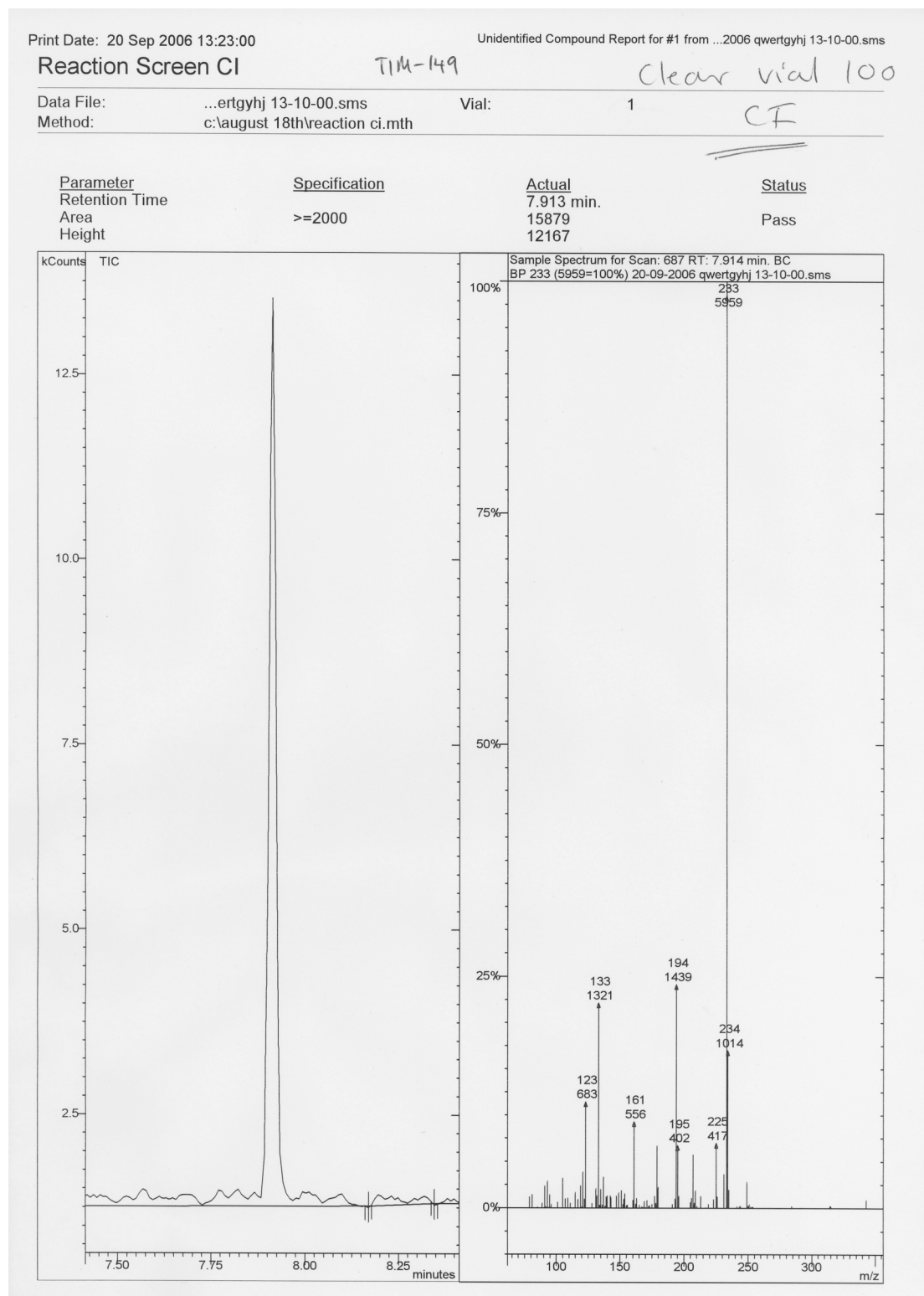
^1H NMR spectrum of crude compound **14**.



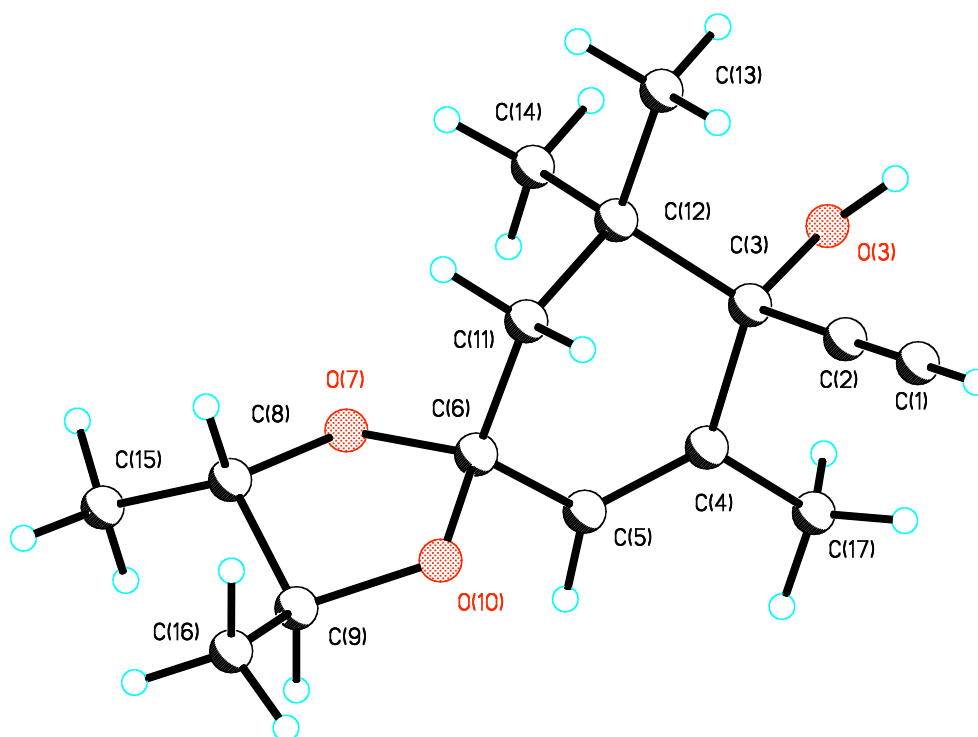
^1H NMR spectrum of **14** after one recrystallisation from 40-60° petroleum ether.



GC-MS (CI mode) of recrystallised compound **14**.



III) X-ray crystallographic data for **7** (Warwick working code ts2)



*Solid state structure of ts2, (**7**)*

The asymmetric unit contains the molecule. There are 2 molecules in the unit cell. The configuration of the diol fragment is *S,S* (from chiral pool material). The hydrogen on O3 was located in a difference map and forms an H bond to one of the dioxolane oxygens of a symmetry related molecule as tabulated below.

The Flack parameter which can be used to decide on the chiral homogeneity of a crystal has a value of -0.03(20). The large error value (0.2) means it cannot be used to reliably assign the stereochemistry of the crystal. The stereochemistry shown in the pictures was assigned from the absolute stereochemistry (*S,S*) of the diol protecting group. Sample homogeneity was conformed by optical rotation data.

Specified hydrogen bonds (with esds)

D-H	H...A	D...A	<(DHA)	
0.86(3)	2.01(3)	2.853(2)	166(3)	O3-H3A...O10

The symmetry relationship is $-x+1, y-1/2, -z+1$ to O10 and it forms an infinite H bonded helix/spiral along the b axis of the cell.

Crystal Data

C₁₅H₂₂O₃, M = 250.33, Monoclinic, space group P2(1)

a = 7.6916(3), b = 11.7602(5), c = 8.2773(4) Å,

alpha = 90 deg., beta = 95.392(3) deg., gamma = 90 deg.,

U = 745.41(6) Å³ (by least squares refinement on 1438 reflection positions),

T = 273(2)K, lambda = 1.54178 Å, Z = 2,

D(cal) = 1.115 Mg/m³, F(000) = 272.

mu(CuK-alpha) = 0.610 mm⁻¹.

Crystal character: colourless block.

Crystal dimensions 0.60 x 0.25 x 0.01 mm.

Data Collection and Processing

Bruker SMART 6000 three-circle system with CCD area detector.

Maximum theta was 70.71 deg.

The hkl ranges were -8/ 9, -12/ 14, -9/ 9.

4874 reflections measured, 2247 unique [R(int) = 0.0301].

Absorption correction by Semi-empirical from equivalents;

minimum and maximum transmission factors: 0.7002; 0.9939.

No crystal decay.

Structure Analysis and Refinement.

Systematic absences indicated space group P2(1) and shown to be correct by successful refinement. The structure was solved by direct methods using SHELXS (Sheldrick, 1990) (TREF) with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions except the OH and refined using a riding model with freely rotating methyl groups. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl or OH hydrogen atoms) times the

equivalent isotropic displacement parameter of the atom to which the H-atom is attached. The absolute structure of the individual crystal chosen was checked by refinement of a $\delta\text{-f}''$ multiplier. Absolute structure parameter $x = -0.03(20)$.

Floating origin constraints were generated automatically. The weighting scheme was calc $w=1/[\sigma^2(F_o^2)+(0.0476P)^2+0.0177P]$ where $P=(F_o^2+2F_c^2)/3$. Goodness-of-fit on F^2 was 1.060, $R1[\text{for } 2051 \text{ reflections with } I>2\sigma(I)] = 0.0348$, $wR2 = 0.0879$. Data / restraints / parameters 2247/ 19/ 171. Largest difference Fourier peak and hole 0.101 and -0.139 $\text{e.\AA}^{-3}$.

Refinement used SHELXL (Sheldrick, 2000).

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References

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