

Supporting Information

A Concise Asymmetric Total Synthesis of Obolactone

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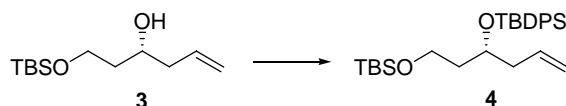
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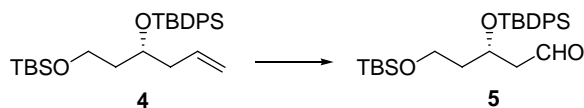
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1. Experimental procedure and spectroscopic data

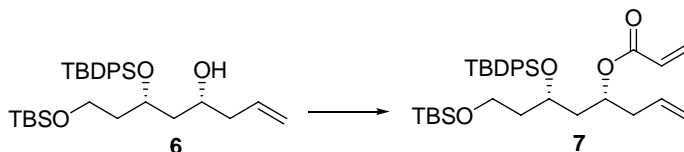
General Methods: Oxygen- and moisture-sensitive reactions were carried out under argon atmosphere. Solvents were purified and dried by standard methods prior to use. All commercially available reagents were used without further purification unless otherwise noted. Column chromatography was performed on silica gel (200-300 mesh). Optical rotations were measured on a precision automated polarimeter. Infrared spectra were recorded on a FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz and a 400 MHz spectrometer. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26 for ^1H and 77.0 for ^{13}C).



(3R)-1-[(*tert*-Butyldimethylsilyl)oxyl]-3-[(*tert*-Butyldiphenyl)oxyl]hex-5-ene (4). A stirred solution of alcohol **3** (2.663 g, 11.6 mmol) in dry DMF (5.8 mL) at rt was treated with imidazol (2.36g, 34.3 mmol) followed by TBDPSCl (4.46g, 16.2 mmol). After stirring overnight, the reaction mixture was diluted with EtOAc (50 mL). The resulting mixture was washed with brine (10 \times 5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes / EtOAc, 100:1) to give silyl ether **4** (5.21 g, 96%) as a colorless oil: $[\alpha]_{\text{D}}^{25}$ -11° (c 2.45, CHCl_3); IR (KBr) 2955, 2931, 2858, 1254, 1108 835, 704 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 0.02 (s, 6H), 0.85 (s, 9H), 1.07 (s, 9H), 1.72 (q, J = 6.3 Hz, 2H), 2.15-2.26 (m, 2H), 3.57-3.68 (m, 2H), 3.93-3.97 (m, 1H), 4.88-4.98 (m, 2H), 5.68-5.77 (m, 1H), 7.35-7.45 (m, 6H), 7.69 (d, J = 7.2 Hz); ^{13}C NMR (75 MHz, CDCl_3) δ -5.4, 18.2, 19.4, 39.2, 4.4, 60.0, 70.4, 116.9, 127.5, 129.5, 134.3, 134.8, 135.9; HRMS m/z calcd for $\text{C}_{28}\text{H}_{44}\text{O}_2\text{Si}_2\text{Na}$ 491.2773 $[\text{M} + \text{Na}]^+$, found 491.2781.



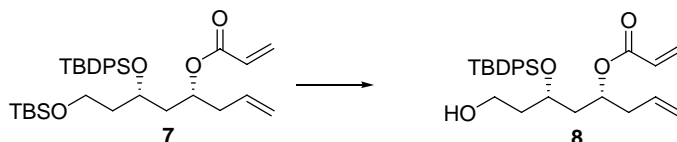
(3S)-3-[(*tert*-Butyldiphenyl)oxyl]-5-[(*tert*-Butyldimethylsilyl)oxyl]hexanal (5). To a solution of silyl ether **4** (2.81g, 6.00 mmol) in 3:1 THF-H₂O (120 mL) was added N-methyl morpholine N-oxide (844 mg, 7.20mmol) and aqueous OsO₄ (0.1 M, 3 mL, 0.3 mmol). The resulting solution was stirred 10 h at rt before being stopped by the addition of excess solid sodium sulfite. The reaction mixture was then diluted with EtOAc and the layers were separated. The aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic phase were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The resultant oil was dissolved in 120 mL 3:1 THF-H₂O, to which was added NaIO₄ (3.85g, 18.0mmol). The reaction mixture was stirred 2 h at rt before being diluted with H₂O and EtOAc. The layers were separated, and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic phase were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes / EtOAc, 50:1) to give aldehyde **5** (2.37g, 84%) as a colorless oil: $[\alpha]_D^{25}$ -2° (c 1.45, CHCl₃); IR (KBr) 2955, 2951, 1727, 1107 835, 704 cm⁻¹; ¹HNMR (300 MHz, CDCl₃) δ 0.01 (s, 6H), 0.85 (s, 9H) 1.09 (s, 9H), 1.75-1.89 (m, 2H), 2.55 (ddd, *J* = 15.6, 5.5, 2.9 Hz, 1H), 2.59 (ddd, *J* = 15.6, 5.7, 1.7 Hz, 1H), 3.57-3.69 (m, 2H), 4.42-4.46 (m, 2H), 7.38-7.48 (m, 6H), 7.70 (d, *J* = 6.6 Hz, 4H), 9.70 (t, *J* = 2.1 Hz, 1H); ¹³CNMR (75 MHz, CDCl₃) δ -5.5, 18.1, 19.3, 25.8, 26.9, 40.0, 50.4, 59.4, 67.2, 127.7, 129.8, 133.7, 135.8, 202.1; HRMS *m/z* calcd for C₂₇H₄₃O₃Si₂ 471.2751 [M + H]⁺, found 471.2758.



(3S,5R)-1-[(*tert*-Butyldimethylsilyl)oxyl]-3-[(*tert*-Butyldiphenyl)oxyl]oct-7-ene-5-yl

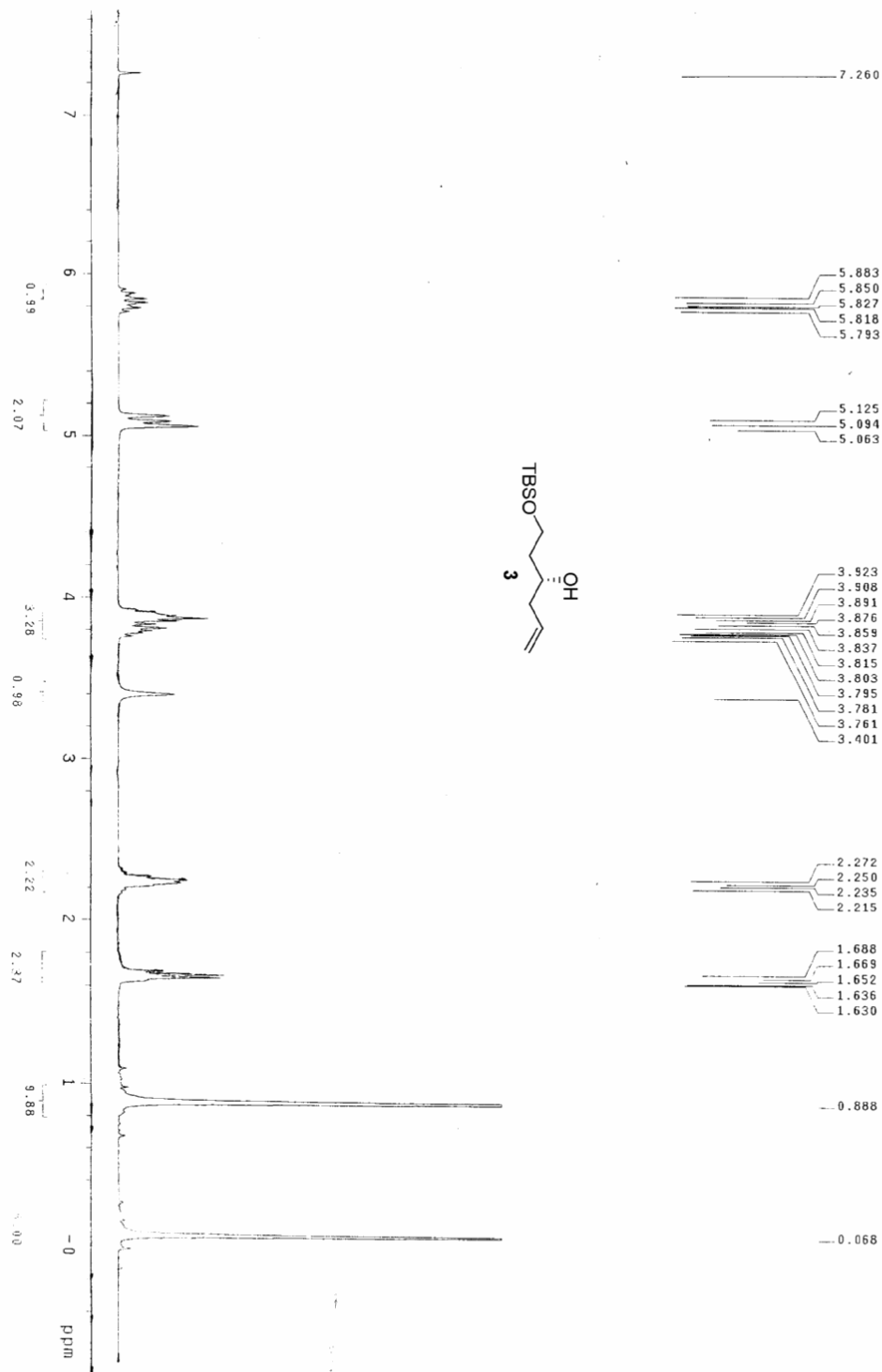
Acrylate (7). Under Ar, to a solution of alcohol **6** (1.35 g, 2.60 mmol) in dry CH₂Cl₂ (20 mL) at 0°C was added Et₃N (1.47mL, 10.5 mmol) and acryloyl chloride (0.43 mL, 5.2 mmol). The reaction mixture was stirred at 0°C for 2 h and diluted with CH₂Cl₂ (20 mL), Saturated NaHCO₃, and water. The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes / EtOAc, 50:1) to give ester **7** (1.38 g, 94%) as a colorless oil: $[\alpha]_D^{25}$ -12° (c 2.65, CHCl₃); IR (KBr) 2955, 2931, 2858, 1725, 1469, 1428, 1405, 1256, 1193, 1108, 837, 705 cm⁻¹; ¹HNMR (400 MHz, CDCl₃) δ -0.02 (s, 6H), 0.84 (s, 9H), 1.07 (s, 9H), 1.69-1.84 (m, 4H), 2.09-2.23 (m, 2H), 3.64 (ddt, *J* = 16.8, 6.6, 3.2 Hz, 2H), 3.94-3.98 (m,

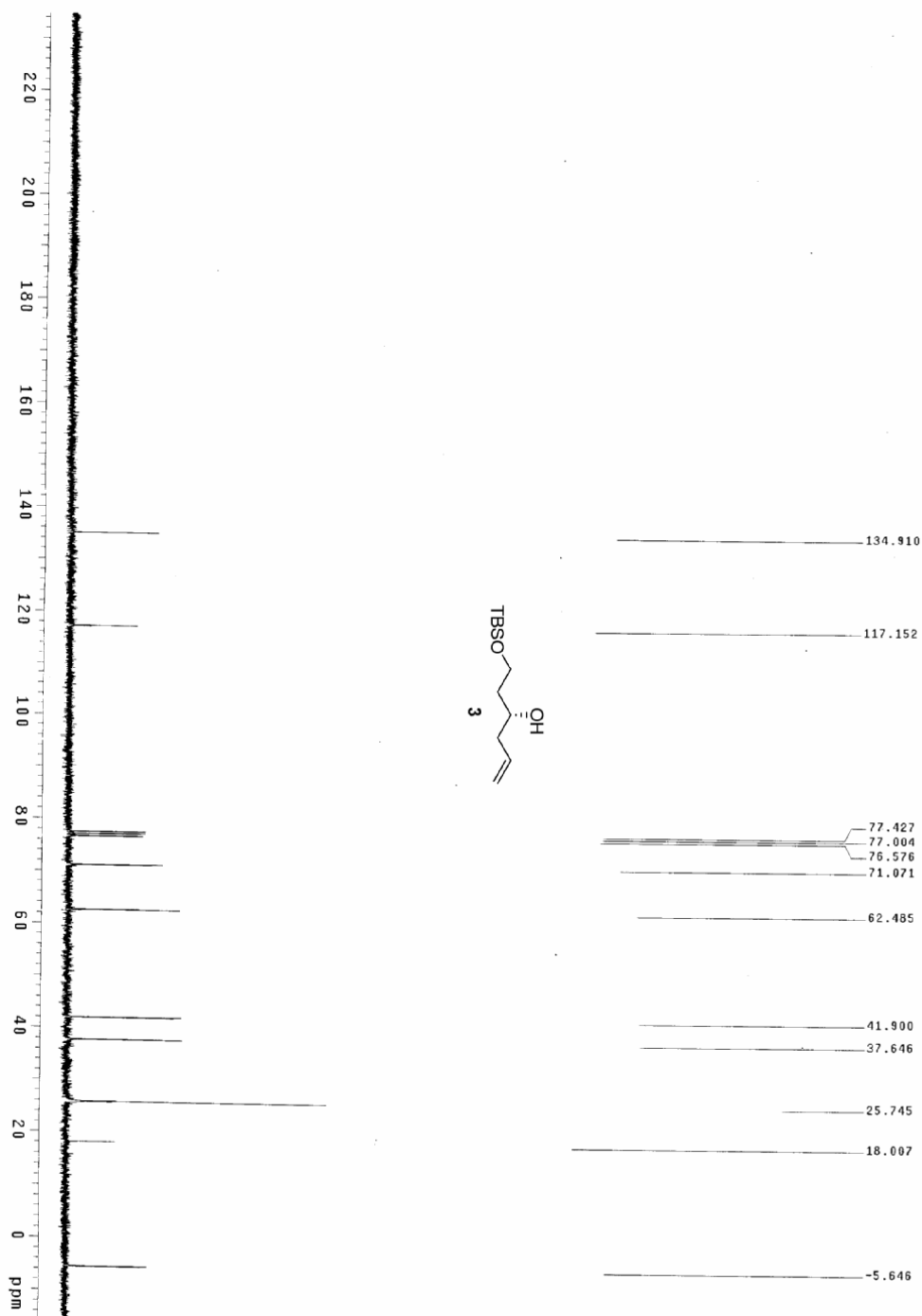
2H), 4.92-4.99 (m, 2H), 5.08-5.11 (m, 1H), 5.57-5.63 (m, 1H), 5.73 (d, $J = 10.8$ Hz), 5.94 (dd, $J = 17.2, 10.4$ Hz, 1H), 6.23 (d, $J = 17.6$ Hz, 1H), 7.34-7.66 (m, 6H), 7.67-7.69 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ -5.4, 18.2, 19.4, 25.9, 27.0, 38.8, 39.2, 40.5, 59.5, 67.9, 70.5, 117.8, 127.5, 128.7, 129.5, 130.2, 133.3, 134.1, 134.3, 135.9, 165.4; HRMS m/z calcd for $\text{C}_{33}\text{H}_{50}\text{O}_4\text{Si}_2\text{Na}$ 589.3146 $[\text{M} + \text{Na}]^+$, found 589.3142.

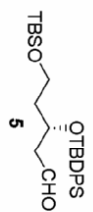


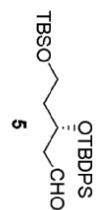
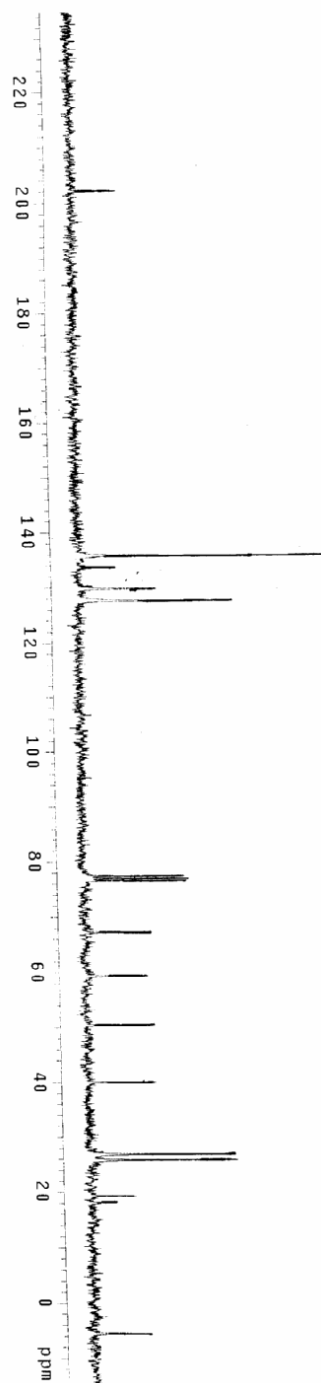
(3S,5R)-3-[(*tert*-Butyldiphenyl)oxyl]oct-7-ene-1-ol-5-yl Acrylate (8). To a solution of ester **7** (1.13g, 2.00 mmol) in 20:1 THF- H_2O (10.5 mL) was added $\text{TsOH} \cdot 2\text{H}_2\text{O}$ (38 mg, 0.2 mmol). The resulting solution was stirred at rt for 7 h. Saturated NaHCO_3 was added, and the mixture was extracted with EtOAc (4×30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (hexanes / EtOAc, 10:1) to give **8** (805 mg, 89%) as a colorless oil: $[\alpha]_{\text{D}}^{25} -20^\circ$ (c 1.80, CHCl_3); IR (KBr) 3425, 2931, 1722, 1428, 1406, 1272, 1195, 1108, 1066, 704 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.06 (s, 9H), 1.66-1.92 (m, 4H), 2.01 (s, 1H), 2.15 (dd, $J = 12.2, 6.2$ Hz), 3.68-3.74 (m, 2H), 3.97-4.00 (m, 1H), 4.94-5.00 (m, 3H), 5.54-5.61 (m, 1H), 5.73 (dd, $J = 10.6, 1.4$ Hz, 1H), 5.89 (dd, $J = 17.2, 10.0$ Hz, 2H), 6.19 (dd, $J = 9.2, 1.2$ Hz, 1H), 7.36-7.46 (m, 6H), 7.68 (d, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 19.2, 27.0, 37.5, 39.0, 40.2, 59.5, 69.1, 70.3, 118.1, 127.6, 127.7, 128.4, 129.8, 130.6, 133.0, 133.5, 133.7, 135.9, 135.9, 165.5; HRMS m/z calcd for $\text{C}_{27}\text{H}_{36}\text{O}_4\text{SiNa}$ 475.2281 $[\text{M} + \text{Na}]^+$, found 475.2276.

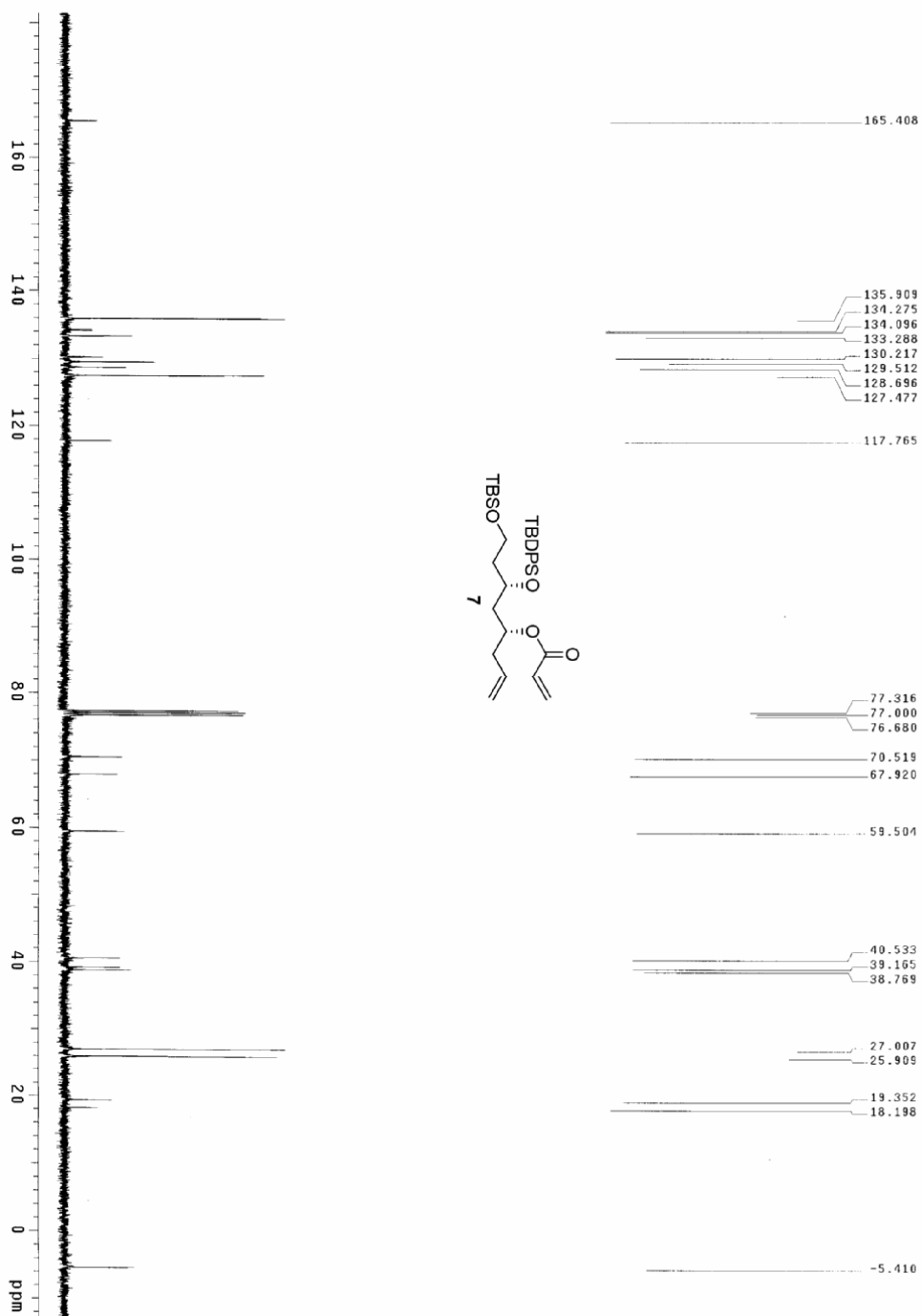
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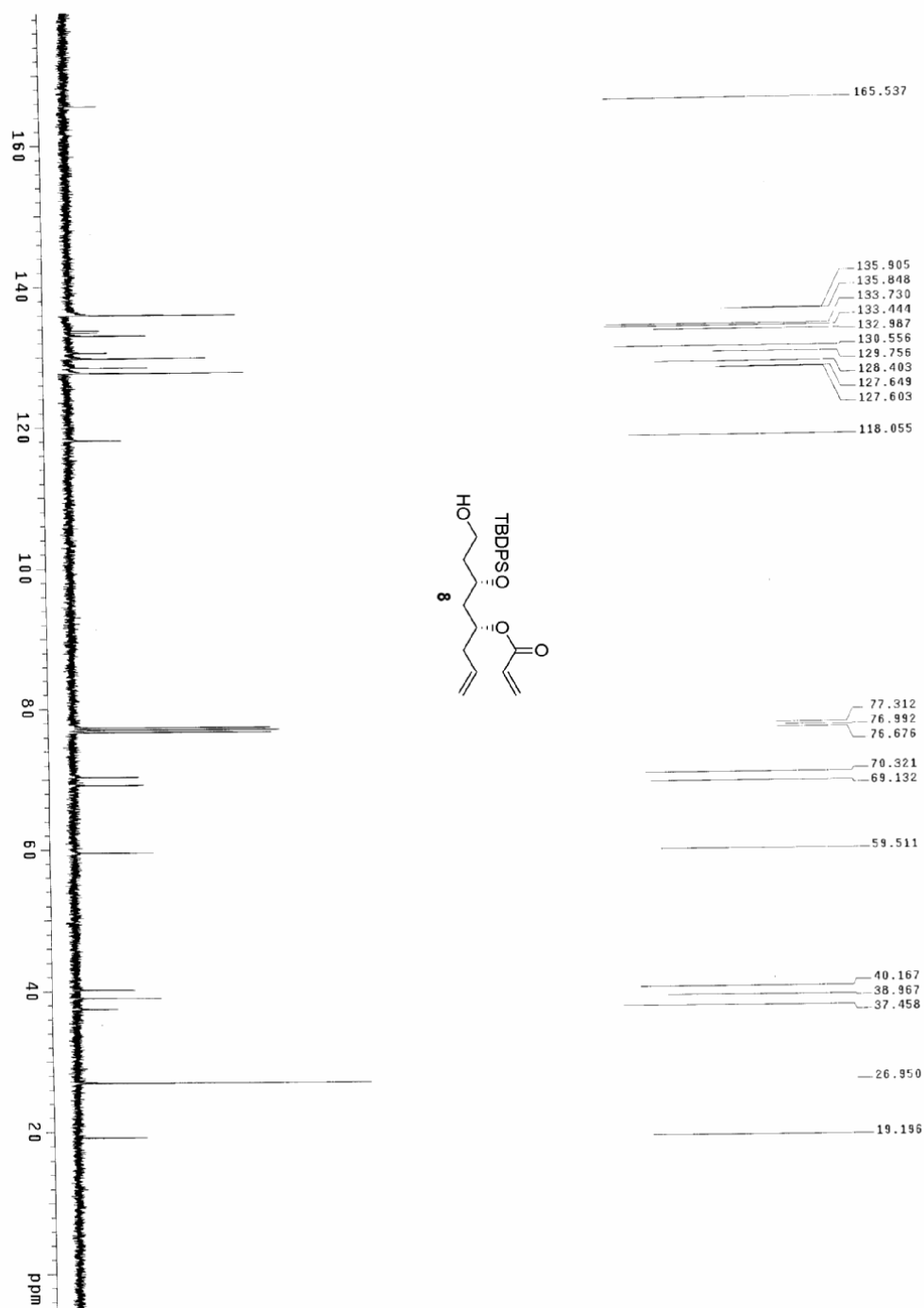


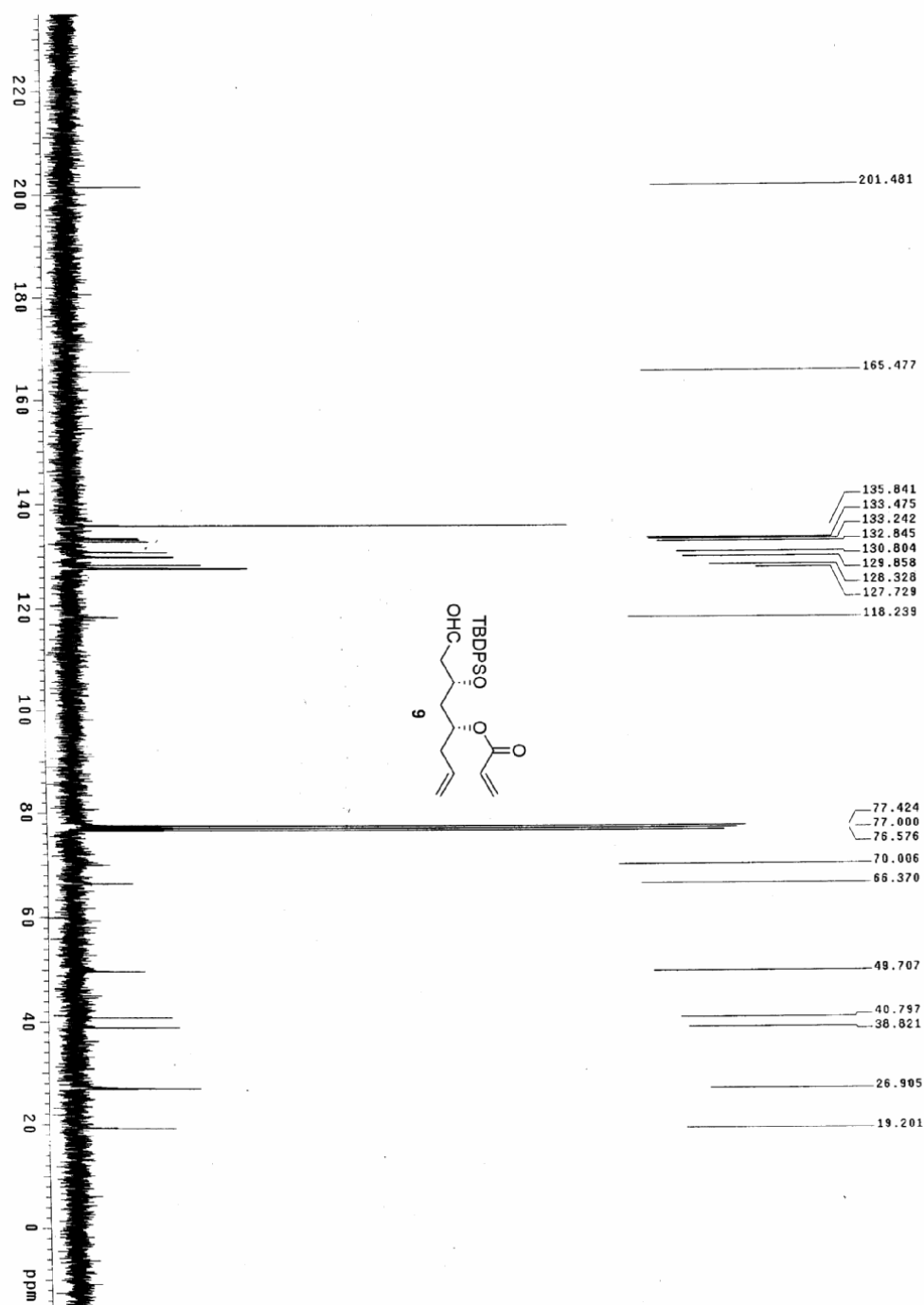


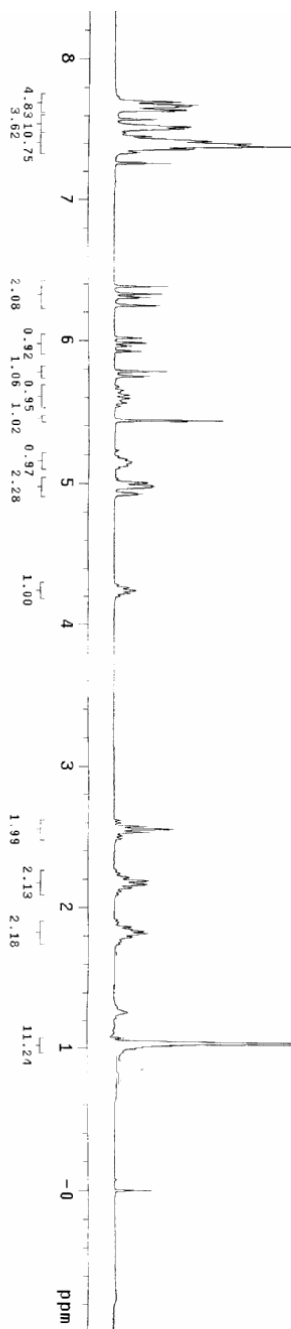
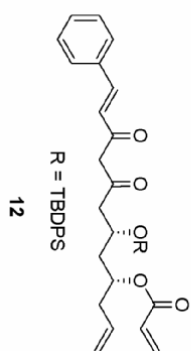
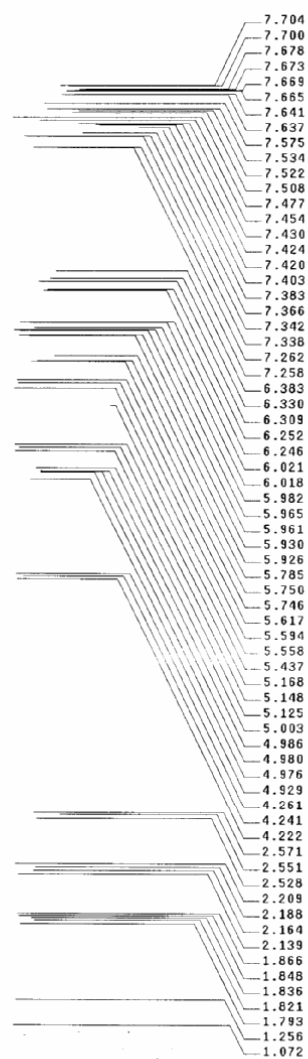


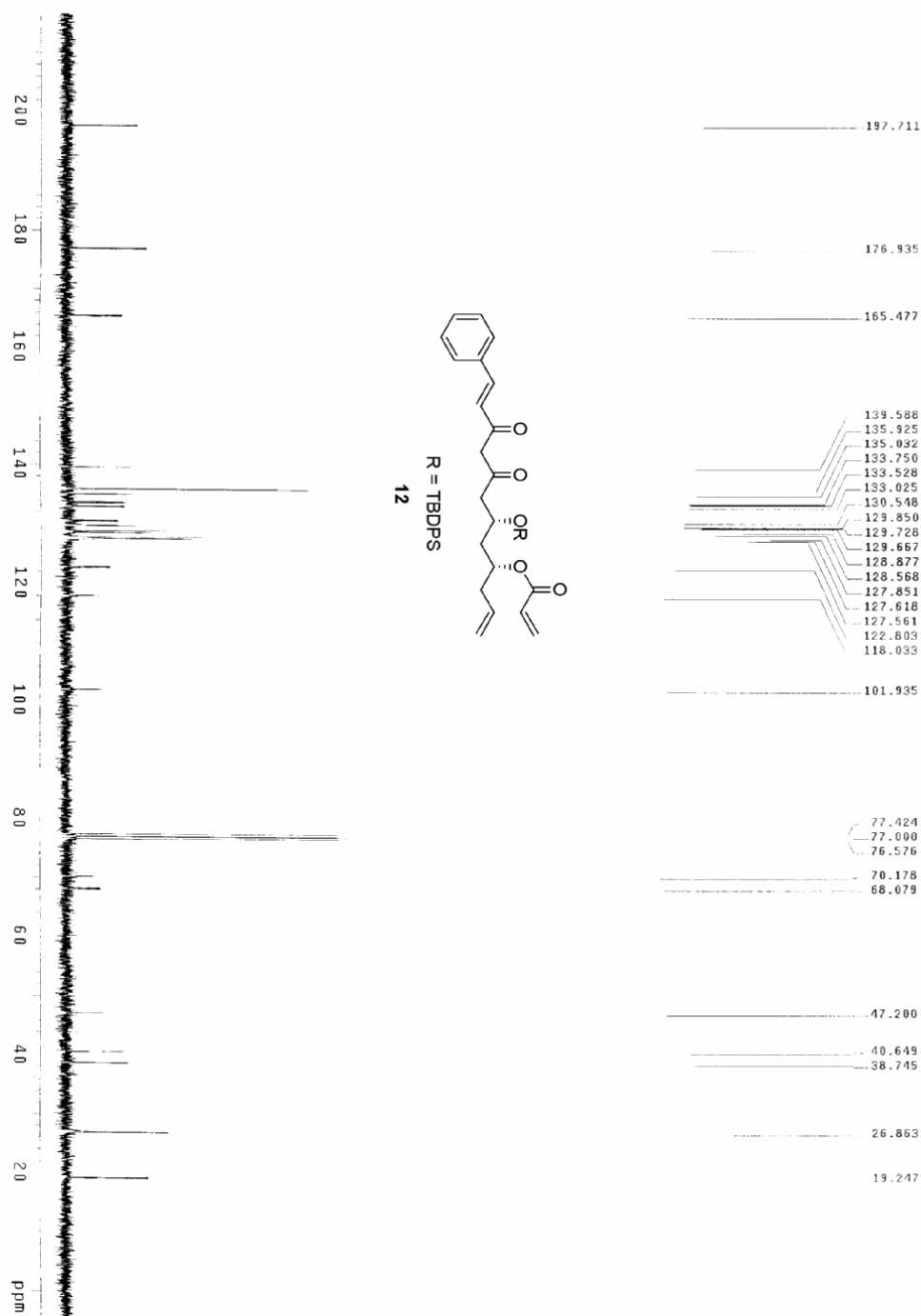


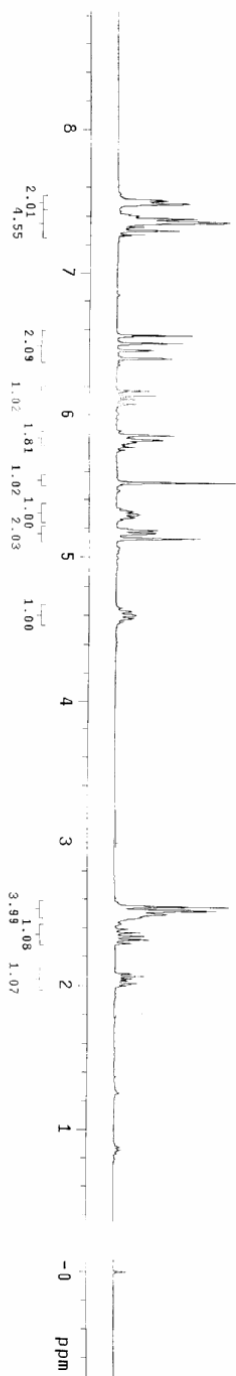
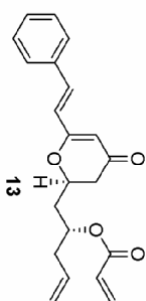
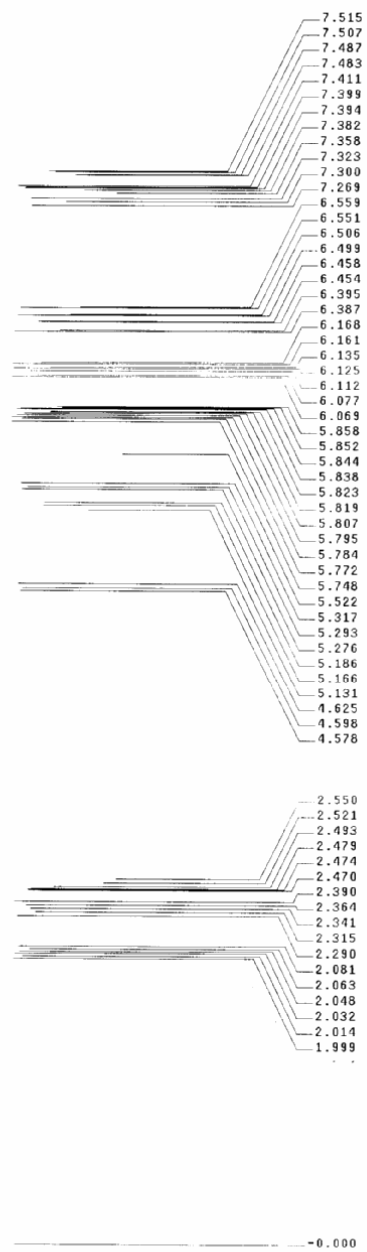


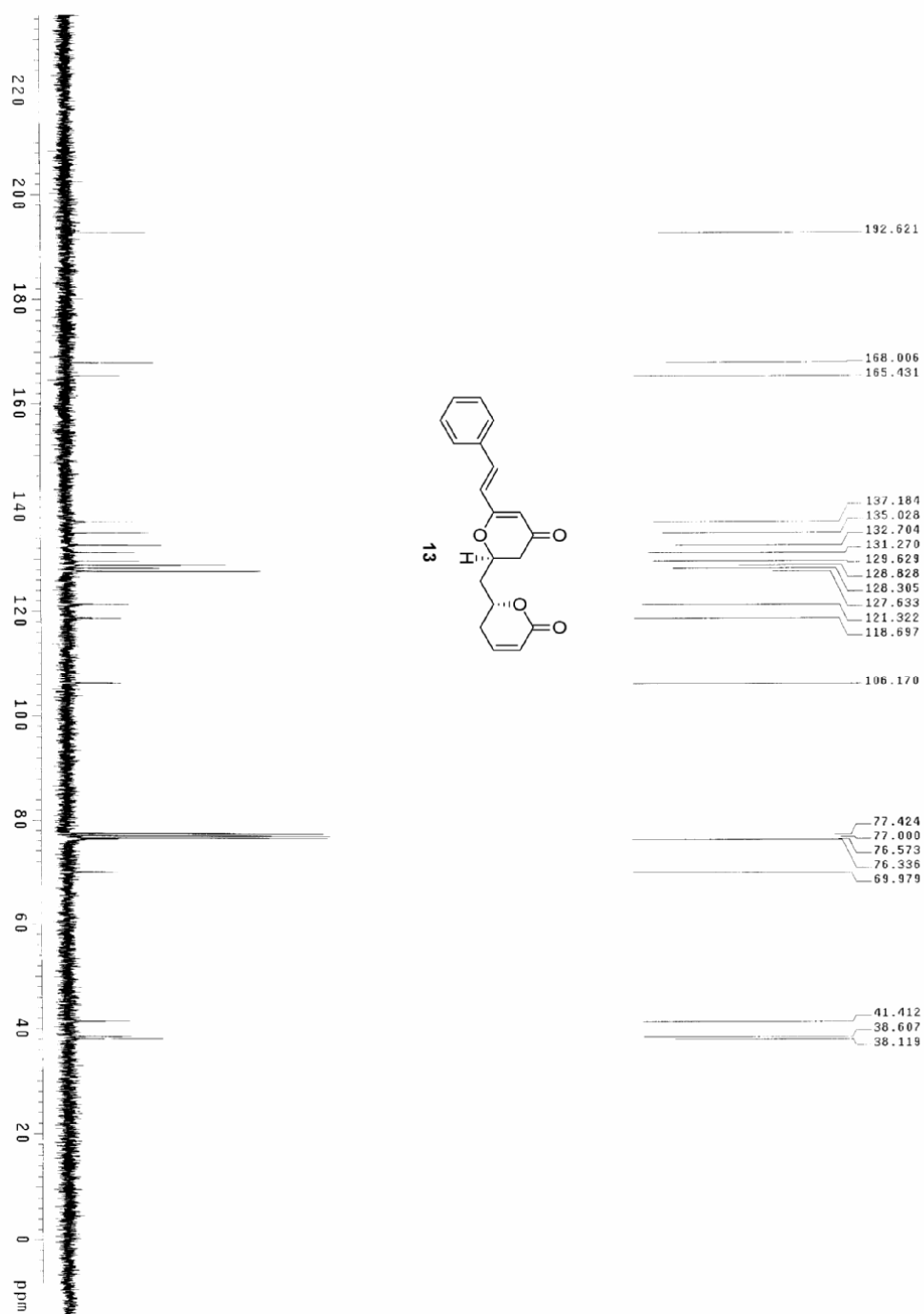


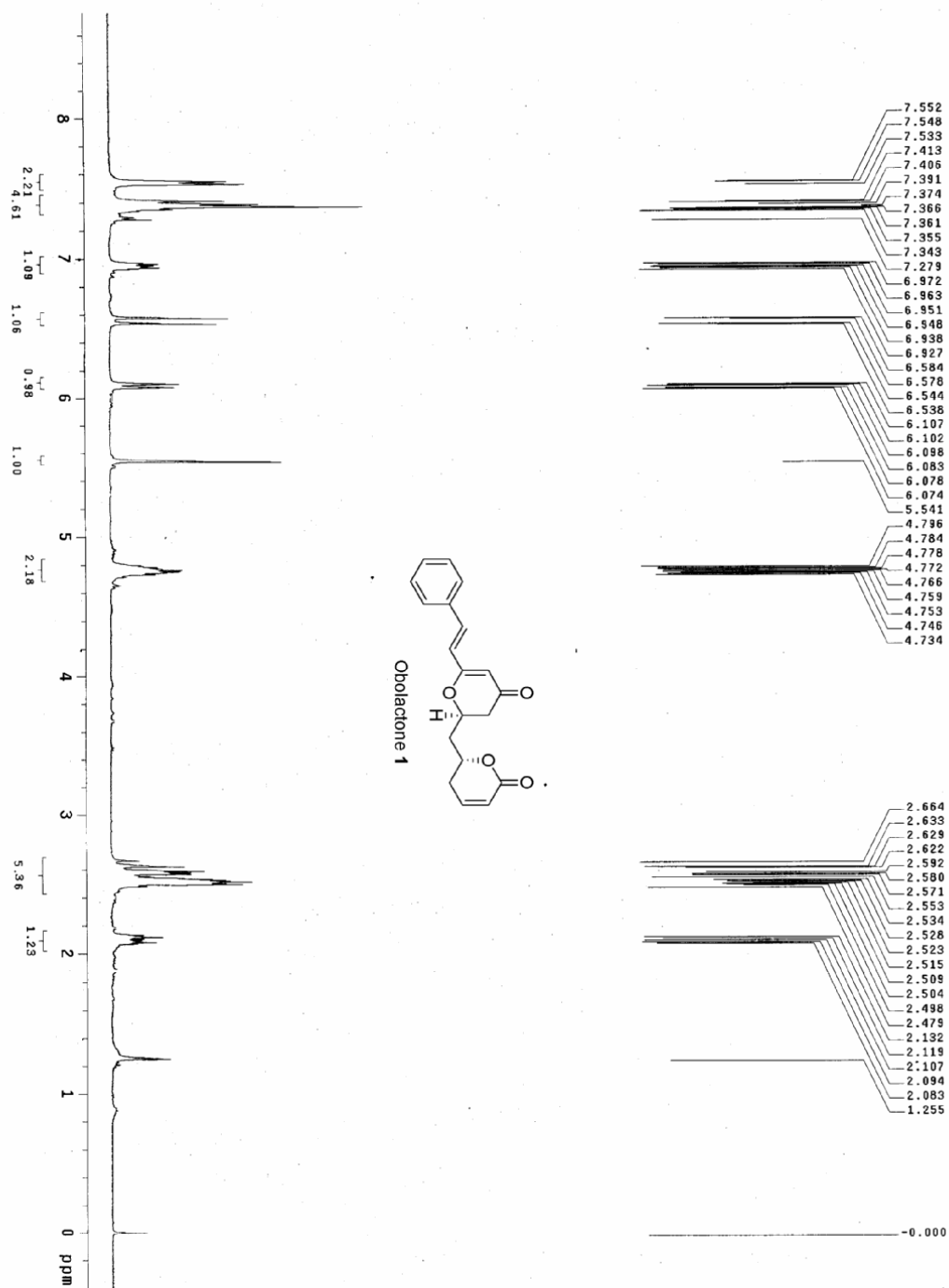












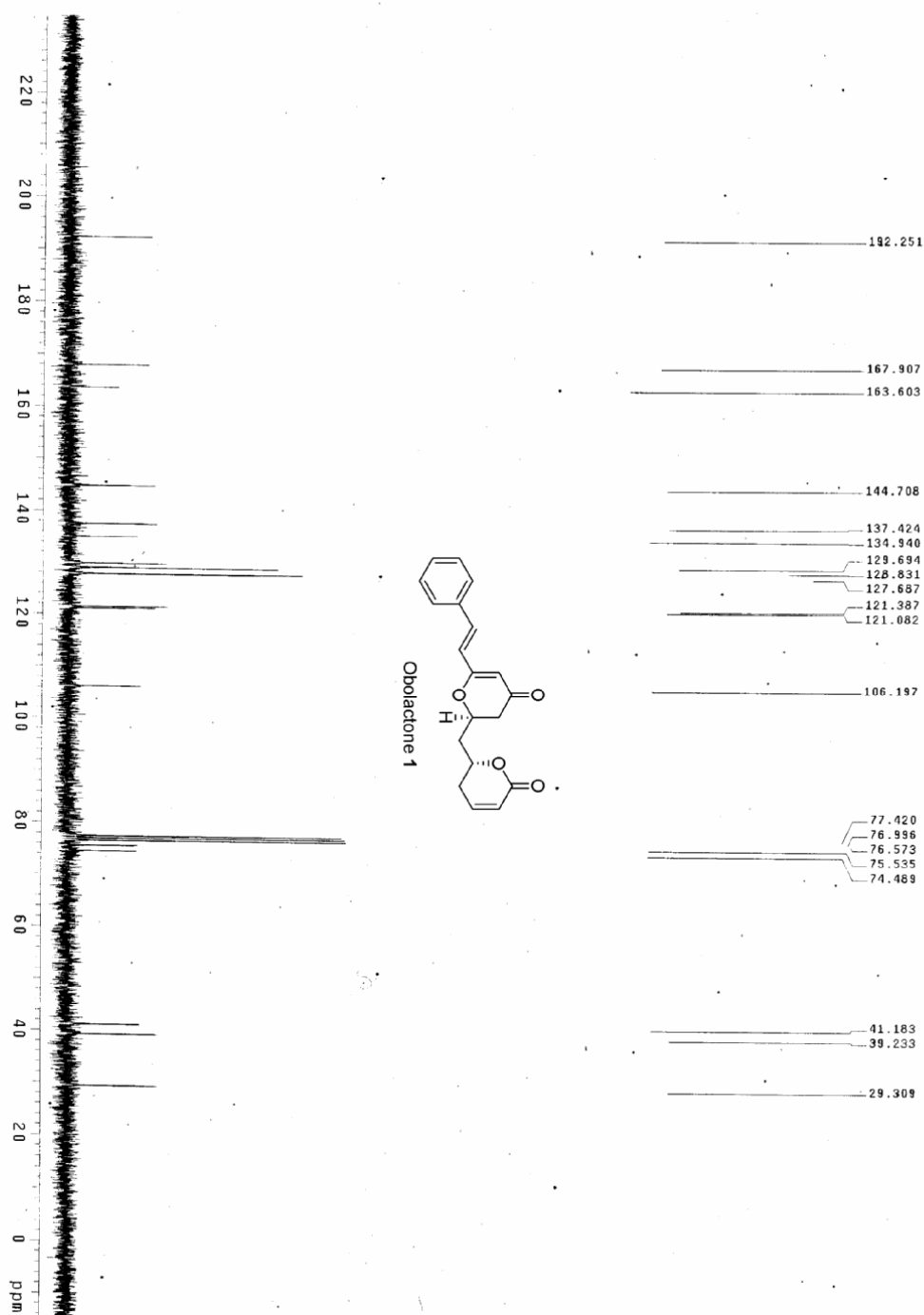
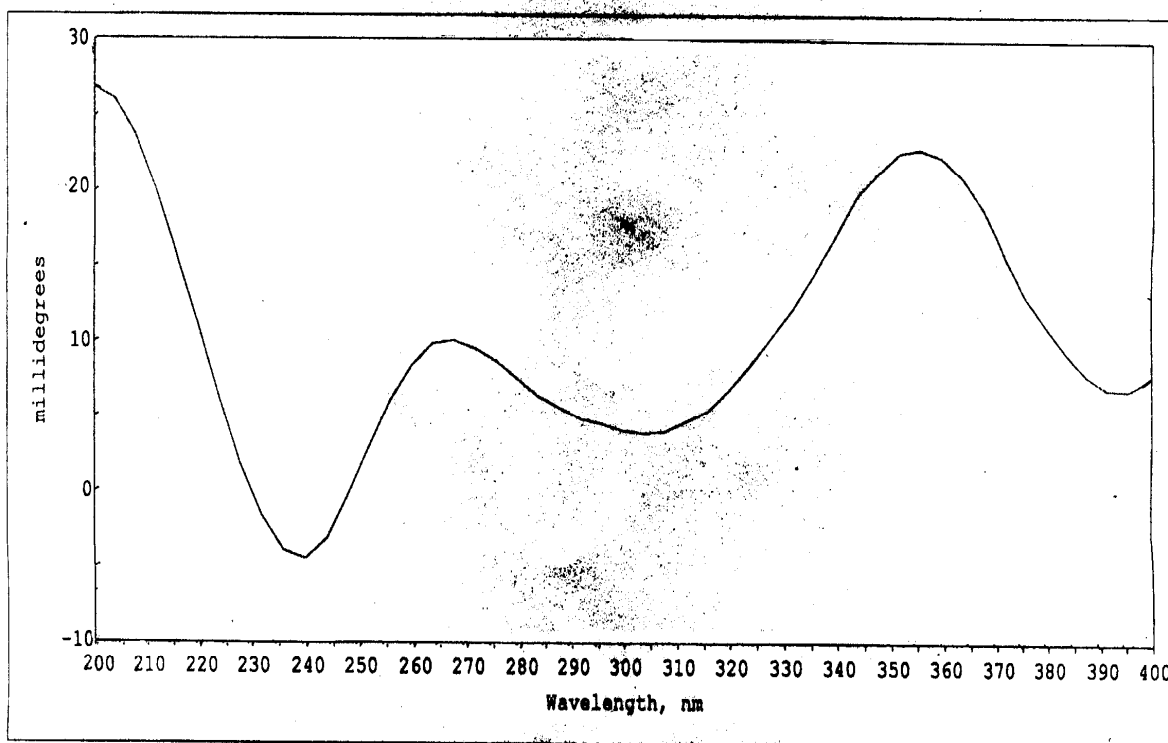


Table 1: Comparison of the ^1H NMR spectrum of natural obolactone with that of the synthetic sample (400 MHz, CDCl_3).

Synthetic obolactone	Natural obolactone
2.09 (dt, $J = 14.7$, 5.0 Hz, 1H)	2.09 (dt, $J = 14.7$, 5.1 Hz, 1H)
2.48-2.53 (m, 3H)	2.50 (m, 1H) and 2.51 (m, 2H)
2.55 (dd, $J = 16.8$, 4.5 Hz, 1H)	2.55 (dd, $J = 16.7$, 4.5 Hz, 1H)
2.62 (dd, $J = 16.8$, 12.2 Hz, 1H)	2.62 (dd, $J = 16.7$, 12.2 Hz, 1H)
4.73-4.80 (m, 2H)	4.74 (m, 1H) and 4.77 (m, 1H)
5.54 (s, 1H)	5.54 (s, 1H)
6.09 (dt, $J = 9.8$, 1.8 Hz, 1H)	6.08 (dt, $J = 9.9$, 1.8 Hz, 1H)
6.55 (dd, $J = 16.0$, 2.4 Hz, 1H)	6.55 (d, $J = 16.0$, 1H)
6.95 (dt, $J = 9.9$, 3.9 Hz, 1H)	6.93 (dt, $J = 9.9$, 3.9 Hz, 1H)
7.39 (d, $J = 16.0$ Hz, 1H)	7.39 (d, $J = 15.9$ Hz, 1H)
7.34-7.41 (m, 3H)	7.37 (m, 3H)
7.53-7.55 (m, 2H)	7.53 (m, 2H)

1-Smooth

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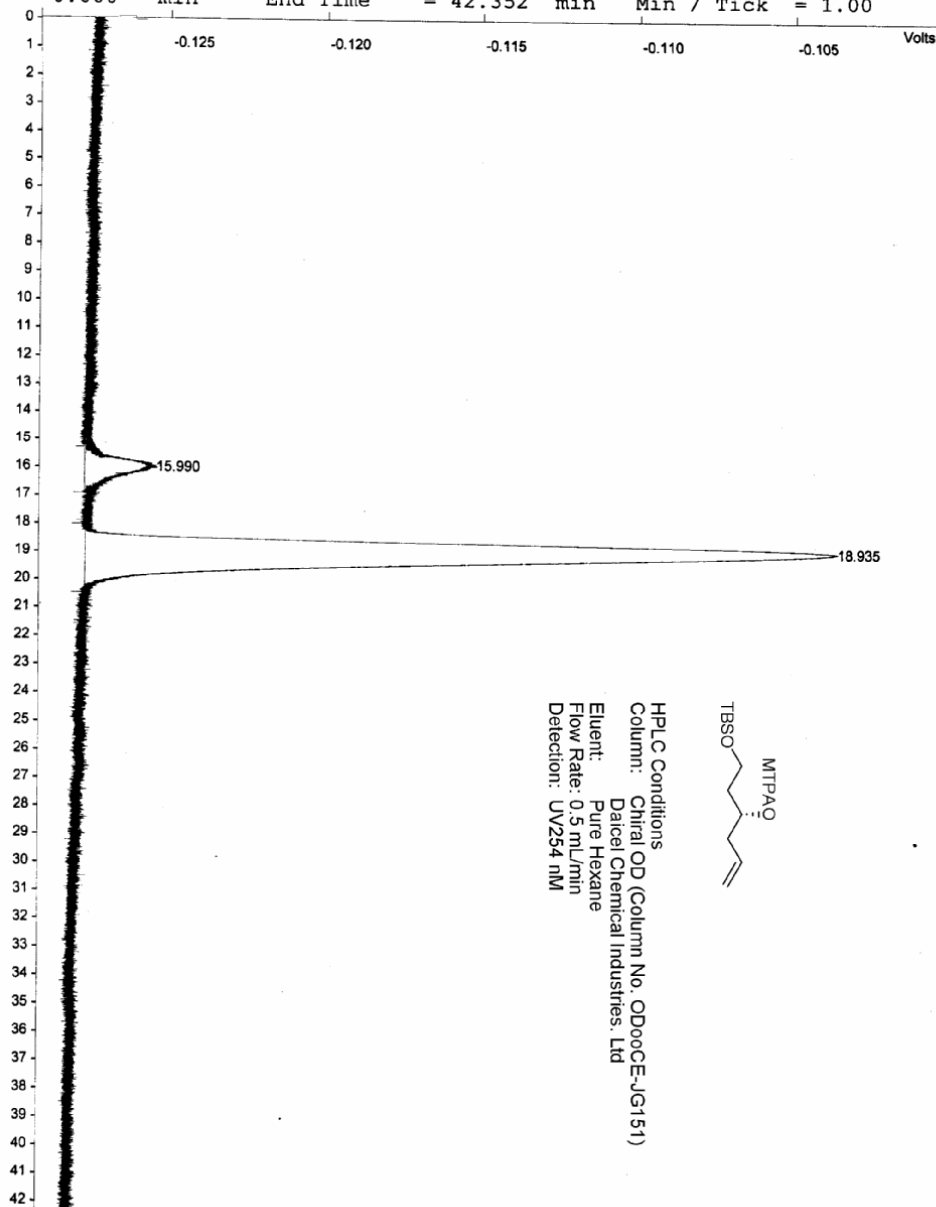
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Run Time : 42.352 min

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Print Date: Thu Dec 16 16:58:55 2004

Page 1 of 1

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Sample ID : Manual Sample

Injection Date: 04-9-4 3:30 Calculation Date: 04-12-16 16:49

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Instrument : hplc Bus Address : 24
Channel : 1 = Sample Rate : 20.00 Hz
 Run Time : 42.352 min

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Peak Measurement: Peak Area
Calculation Type: Percent

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U - User-defined peak endpoint(s)

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Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0.

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Noise (used): 641 microVolts - monitored before this run
