Eur. J. Org. Chem. **2006** · © WILEY-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, 2006 · ISSN 1434–193X

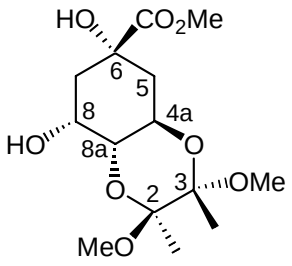
SUPPORTING INFORMATION

Title: Total Synthesis of Altenuene and Isoaltenuene
Author(s): Martina Altemöller, Joachim Podlech,* Dieter Fenske
Ref. No.: O200500904

Content

Experimental procedures and ^{1}H NMR-spectroscopic data for all previously reported compounds. UV/Vis and CD spectra of authentic and synthesized altenuene. ^{1}H and ^{13}C NMR spectra of altenuene and isoaltenuene.

Methyl (2*S*,3*S*,4aR,6*S*,8R,8a*R*)-Octahydro-6,8-dihydroxy-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxin-6-carboxylate[1]

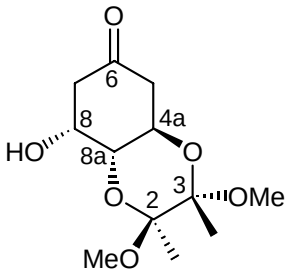


$HC(OEt)_3$ (9.41 ml, 28.6 mmol) and TosOH (0.55 g, 2.9 mmol) was added under an argon atmosphere to a soln of (–)-quinic acid (**11**, 5.00 g, 26.0 mmol) and 2,3-butandione (2.51 mL, 28.6 mmol) in MeOH (50 mL). The mixture was heated to reflux over night. After cooling to rt, Et_3N (0.5 mL) was added, the solvents were removed in vacuo and the residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 20:1) to yield the title compound (6.00 g, 18.7 mmol, 72%) as a white solid.

R_f (CH_2Cl_2/MeOH, 10:1) = 0.26.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.87–1.97 (m, 2 H), 2.00–2.23 (m, 2 H), 3.06–3.08 (m, 1 H, OH), 3.26 (s, 6 H, OMe), 3.60 (dd, 1 H, ^{3}J = 2.8 Hz, ^{3}J = 10.1 Hz), 3.79 (s, 3 H, OMe), 4.18–4.22 (m, 2 H), 4.31 (ddd, 1 H, ^{3}J = 4.7 Hz, ^{3}J = 10.1 Hz, ^{3}J = 12.2 Hz).

(2*S*,3*S*,4a*R*,8*R*,8a*R*)-2,3,4a,5,6,7,8,8a-Octahydro-8-hydroxy-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxin-6-one[1]

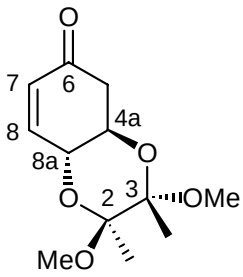


DIBAL-H (46.8 mL of a 1 M soln in THF, 46.8 mmol) was added at –78 ºC with exclusion of moisture and air within 30 min to a soln of the acetal described above (3.00 g, 9.36 mmol) in anhydrous Et_2O (60 mL). The soln was stirred for 30 min at –78 ºC and for further 30 min at 0 ºC. The mixture was hydrolyzed with H_2O (60 mL) and the precipitating aluminium hydroxide was removed by filtration through Celite®. The filter cake was stirred for 1 h in H_2O (200 mL) and filtered again. The combined aqueous layers were treated with $NaIO_4$ (3.42 g, 16.0 mmol), stirred for 1 h at rt, extracted with CH_2Cl_2 (4×40 mL) and the organic layers were dried (Na_2SO_4). The solvents were removed in vacuo to yield crude title compound (1.85 g, 7.10 mmol, 75%) as a white solid which was used without further purification.

***R**_f* (hexane/EtOAc, 2:1) = 0.36.

^{1}H NMR (250 MHZ, $CDCl_3$): δ = 1.28 (s, 1 H), 1.32 (s, 1 H), 2.36–2.38 (m, 1 H, OH), 2.41–2.53 (m, 2 H), 2.60–2.67 (m, 2 H), 3.21 (s, 3 H, OMe), 3.29 (s, 3 H, OMe), 3.86 (dd, 1 H, ^3J = 2.4 Hz, ^3J = 10.1 Hz), 4.18–4.31 (m, 2 H).

(2*S*,3*S*,4a*R*,8a*R*)-2,3,4a,5,6,8a-Hexahydro-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxin-6-one[1]

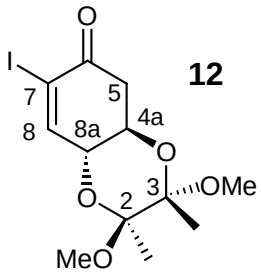


DMAP (42 mg, 0.3 mmol), *N*-ethyldiisopropylamin (1.93 g, 14.9 mmol) and acetic anhydride (0.87 g, 8.5 mmol) was added at 0 ºC to a soln of hydroxyketone described above (1.85 g, 7.10 mmol) in CH_2Cl_2 (10 mL) under an argon athmosphere. After stirring for 1 h at 0 ºC was added satd $NaHCO_3$ soln (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×6 mL). The combined organic layers were dried (Na_2SO_4), the solvents were removed in vacuo and the residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to yield the title compound (1.23 g, 5.08 mmol, 72%) as a white solid. In some runs we used the crude material without any chromatography in the further course of the synthetic sequence with virtually identical yields.

R_f (hexane/EtOAc, 2:1) = 0.31.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 2.49 (dd, 1 H, ^3J = 13.6 Hz, ^2J = 16.4 Hz, 5-H_{ax}H$_{eq}$) 2.75 (ddd, 1 H, ^5J = 1.1 Hz, ^3J = 4.9 Hz, ^2J = 16.4 Hz, 5-H$_{ax}$$H_{eq}$), 3.26 (s, 6 H, OMe), 4.05 (ddd, 1 H, ^3J = 4.9 Hz, ^3J = 9.1 Hz, ^3J = 13.6 Hz, 4a-H) 4.51 (ddd, 1 H, ^4J = 1.8 Hz, ^3J = 2.7 Hz, ^3J = 9.1 Hz, 8a-H), 6.00 (ddd, 1 H, ^5J = 1.1 Hz, ^2J = 2.7 Hz, ^3J = 10.1 Hz, 8-H), 6.87 (dd, 1 H, ^4J = 1.8 Hz, ^3J = 10.1 Hz, 7-H).

(2*S*,3*S*,4a*R*,8a*R*)-2,3,4a,5,6,8a-Hexahydro-7-iodo-2,3-dimethoxy-2,3-dimethylbenzo[*b*][1,4]dioxin-6-one[2] (12)



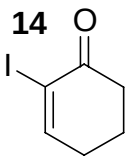
12

K_2CO_3 (166 mg, 1.20 mmol), DMAP (24 mg, 0.20 mmol) and iodine (381 mg, 1.50 mmol) were added a soln of the enone described above (242 mg, 1.00 mmol) in THF/H_2O (1:1, 10 mL). 20% Aqueous sodium thiosulfate soln (10 mL) was added after stirring for 5 h at rt. Extraction with CH_2Cl_2 (3×10 mL), drying of the combined organic layers ($NaSO_4$), removal of the solvents in vacuo and purification of the residue by chromatography on SiO_2 (hexane/EtOAc, 10:1) yielded the iodo compound **12** (354 mg, 0.96 mmol, 96 %) as a yellowish solid.

R_f (hexane/EtOAc, 2:1) = 0.61.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 2.61 (dd, 1 H, ^3J = 13.6 Hz, ^2J = 16.4 Hz, 5-H_{ax}H$_{eq}$), 2.97 (dd, 1 H, ^3J = 4.8 Hz, ^2J = 16.4 Hz, 5-H$_{ax}$$H_{eq}$), 3.25 (s, 3 H, OMe), 3.31 (s, 3 H, OMe), 4.05 (ddd, 1 H, ^3J = 4.8 Hz, ^3J = 9.1 Hz, ^3J = 13.6 Hz, 4a-H), 4.48 (dd, 1 H, ^3J = 1.8 Hz, ^3J = 9.1 Hz, 8a-H), 7.63 (d, 1 H, ^3J = 1.8 Hz, 8-H).

2-Iodocyclohex-2-enone[3] (14)



14

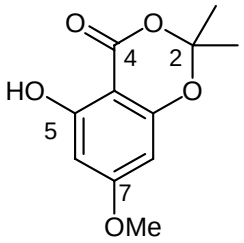
I_2 (13.2 g, 102 mmol) in pyridine/CCl_4 (1:1, 25 mL) was added dropwise at 0 °C to a soln of cyclohex-2-enone (5.00 g, 51.9 mmol) in pyridin/CCl_4 (1:1, 50 mL). The mixture was stirred at rt overnight, treated with 20% aqueous $Na_2S_2O_3$ soln (150 mL), and extracted with CH_2Cl_2 (3×20 mL). The organic layers were dried (Na_2SO_4), the solvents were removed in vacuo and the residue was purified by chromatography on SiO2 (hexane/EtOAc, 10:1) yielding **14** as a dark yellow solid (4.00 g, 18.0 mmol, 34%).

m.p. = 108–110 ºC.

R_f (hexane/EtOAc, 2:1) = 0.58.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.02–2.15 (m, 2 H), 2.39–2.46 (m, 2 H), 2.63–2.68 (m, 2 H), 7.74–7.77 (m, 1 H, 5-H).

5-Hydroxy-7-methoxy-2,2-dimethyl-benzo[*d*][1,3]dioxin-4-one[3]

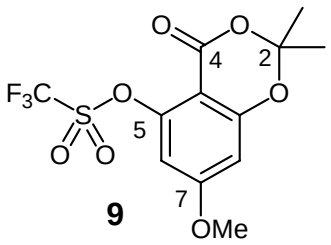


DIAD (2.58 g, 12.8 mmol) was added dropwise at 0 ºC to a soln of acetal **8** (2.50 g, 11.9 mmol), MeOH (410 mg, 12.8 mmol) and Ph_3P (3.35 g, 12.8 mmol) in anhydrous THF (40 ml) under an argon athomsphere. The mixture was stirred for 5 h while it slowly warmed to rt. EtOAc (30 mL) was added and the organic layer was extracted with H_2O (3×15 mL) and dried (Na_2SO_4). Removal of the solvents in vacuo and purification of the residue by chromatography on silica gel (hexane/EtOAc, 10:1) yielded the title compound (2.09 g, 9.32 mmol, 78 %) as a white solid.

R_f (hexane/EtOAc, 3:1) = 0.28.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.71 (s, 6 H, 2 CH_3), 3.80 (s, 3 H, OMe), 5.98 (d, 1 H, ^4J = 2.3 Hz), 6.13 (d, 1 H, ^4J = 2.3 Hz), 10.4 (s, 1 H, OH).

7-Methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl Trifluoromethanesulfonate[3] (9)



9

Trifluoromethanesulfonic anhydride (4.13 g, 14.6 mmol) was added dropwise with a syringe at –10 ºC with exclusion of moisture and air to a soln of the methyl ether described above (2.96 g, 13.2 mmol) in pyridine (70 mL). The mixture was stirred for 4 h at 0 ºC, hydrolyzed with ice water (60 mL), and extracted with Et_2O (4×30 mL). The combined organic layers were extracted with 1 N HCl and dried (Na_2SO_4). The solvents were removed in vacuo and the residue was purified by chromatography on silica gel (hexane/EtOAc, 2:1) to yield triflate **9** (4.44 g, 12.5 mmol, 95 %) as a colorless white solid.

R_f (hexane/EtOAc, 3:1) = 0.20.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.74 (s, 6 H, 2 CH_3), 3.88 (s, 3 H, OMe), 6.49 (d, 1 H, ^4J = 2.4 Hz), 6.53 (d, 1 H, ^4J = 2.4 Hz).

References

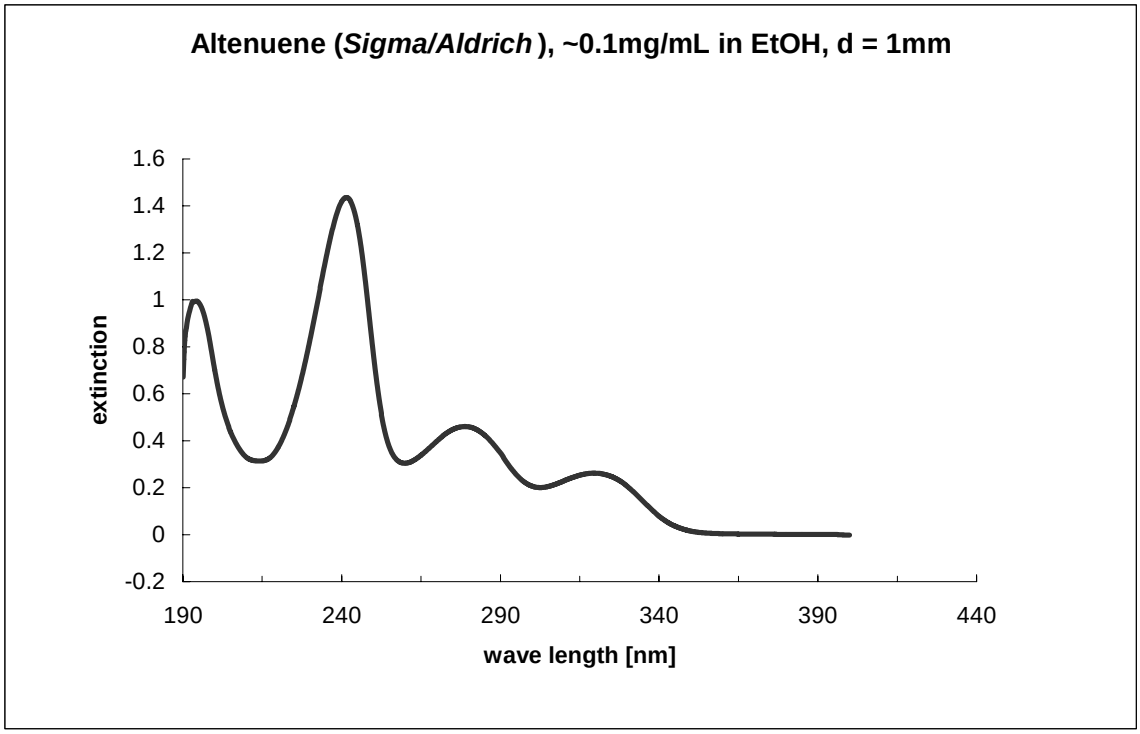
1 L. M. Murray, P. O'Brien, R. J. K. Taylor, *Org. Lett.* **2003**, *5*, 1943–1946.

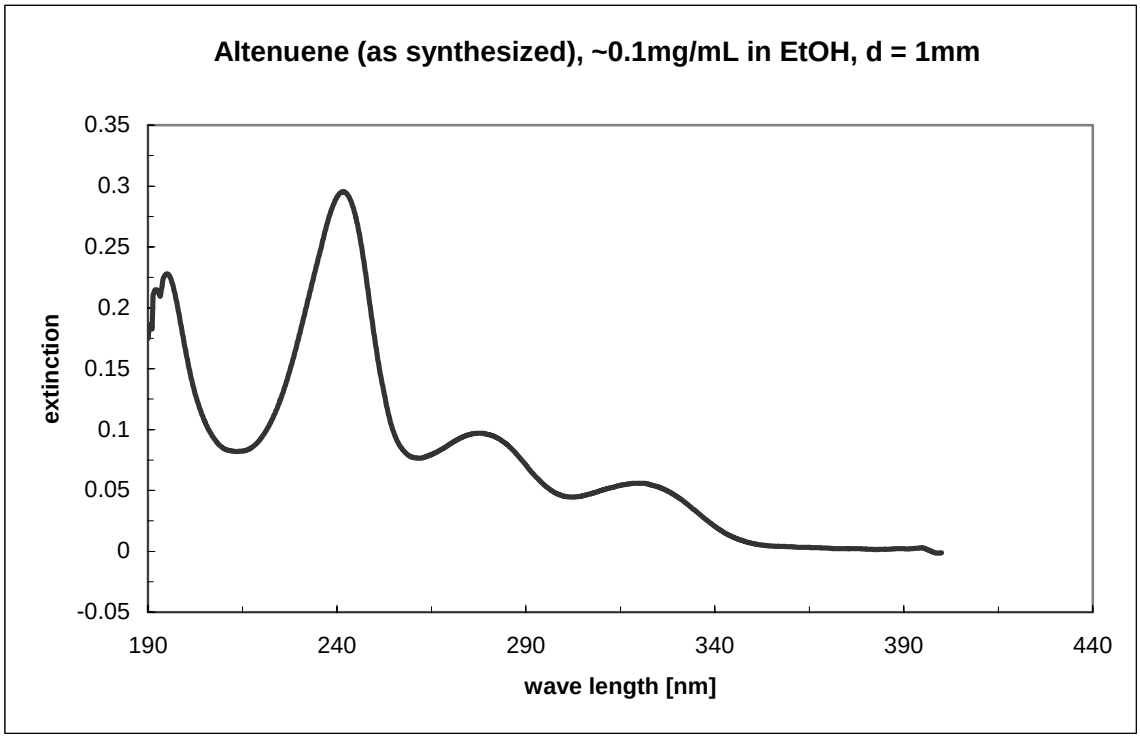
2 M. T. Barros, C. D. Maycock, M. R. Ventura, *J. Chem. Soc., Perkin Trans. 1* **2001**, 166–173.

3 F. S. Ruel, M. P. Braun, C. R. Johnson, *Org. Synth.* **1998**, *75*, 69–77; **2004**, *Coll. Vol. X*, 467.

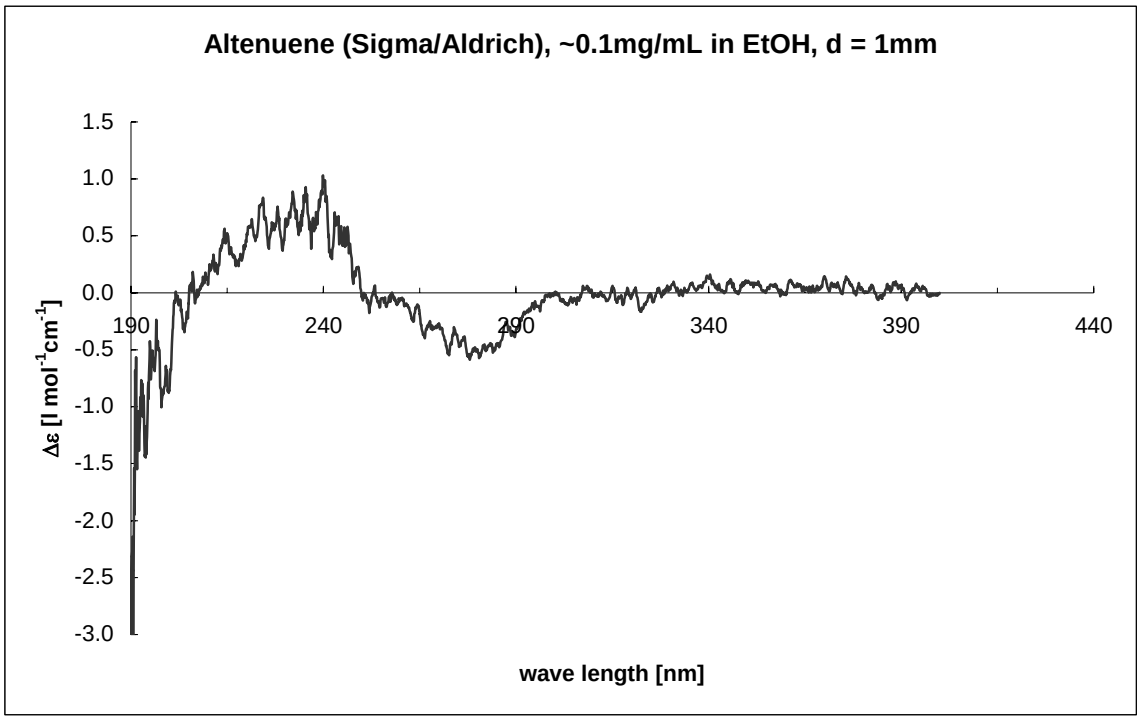
4 S. Kamisuki, S. Takahashi, Y. Mizushina, S. Hanashima, K. Kuramochi, S. Kobayashi, K. Sakaguchi, T. Nakata, F. Sugawara, *Tetrahedron* **2004**, *60*, 5695–5700.

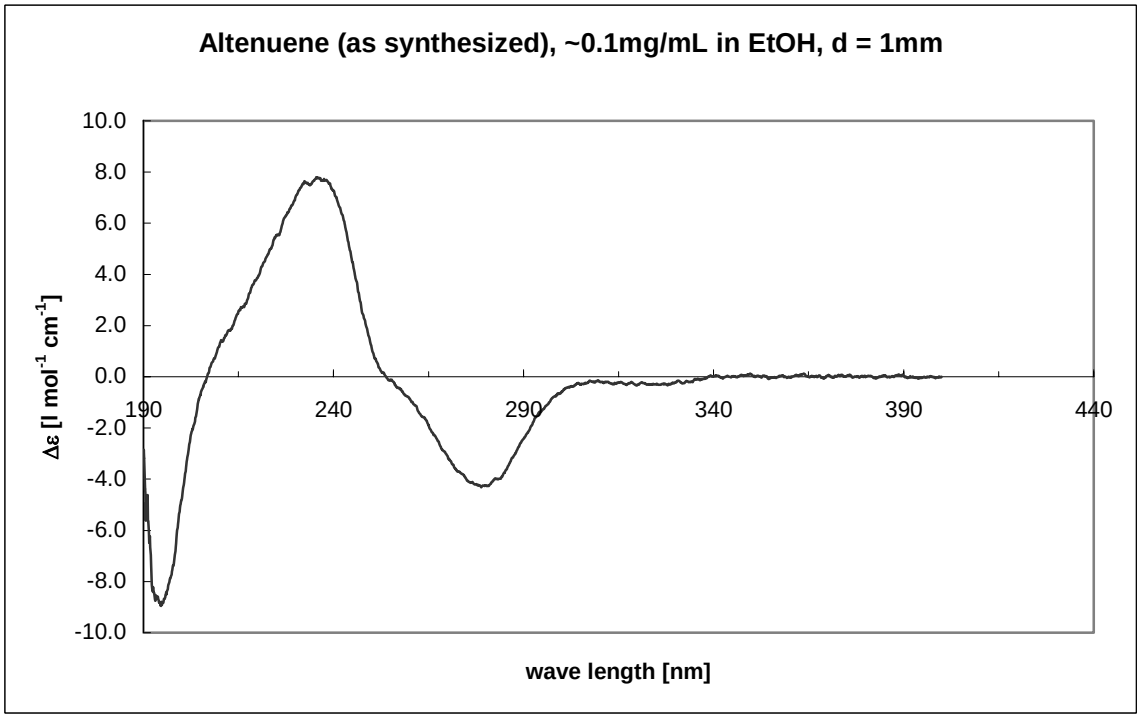
Qualitative UV/Vis Spectra of Authentic (top) and Synthesized (bottom) Altenuene (4)





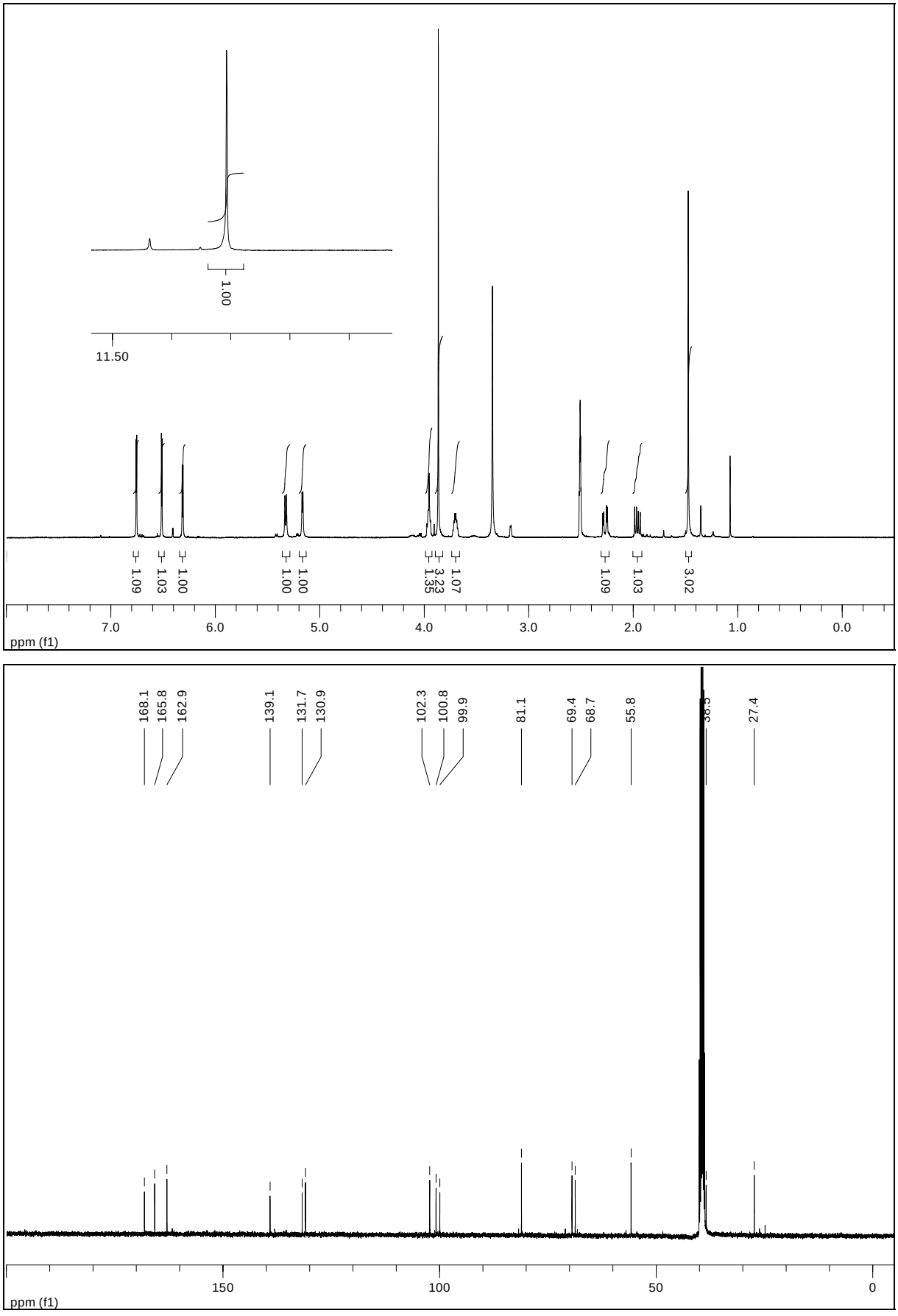
CD Spectra of Authentic (top) and Synthesized (bottom) Altenuene (4) [samples as used for UV/Vis spectra (page 6)]





NMR Spectra of Altenuene (4)

Top: ^{1}H NMR (400 MHz, d_6-DMSO); Bottom: ^{13}C NMR (100 MHz, d_6-DMSO)



NMR Spectra of Isoaltenuene (5)

Top: ^{1}H NMR (500 MHz, $CDCl_3$); Bottom: ^{13}C NMR (125 MHz, $CDCl_3$).