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SELECTIVE SYNTHESIS OF CARVONE AND CRYPTOMERLONE FROM α-PINENE

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Carvone and cryptomerlone were synthesized selectively using electrochemical oxidation of α-pinene in the key step.

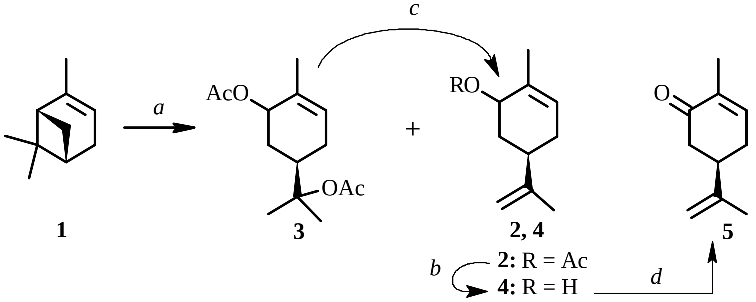
Key words: mono- and sesquiterpenoids, α-pinene, carvone, cryptomerlone, electrochemical oxidation.

The use of Pt or RuO_2/TiO_2 anodes and an electrolyte (AcOH-AcONa—$NaClO_4$) for electrochemical oxidation of α-pinene (**1**) has been previously reported [1].

We investigated anodic oxidation of α-pinene using Ac_2O in combination with AcOH-AcONa and carbon electrodes.

The reaction product was predominantly a mixture of two compounds that could be isolated by chromatography and characterized.

The less polar product was eluted from a SiO_2 column and turned out to be carveol acetate **2**. The more polar compound eluted from the column was sobrerol diacetate (**3**). Ester **3** eliminates AcOH on boiling in Ac_2O to form an additional amount of **2**.



a. Ac_2O, AcOH, AcONa, e^-; *b.* 10% NaOH, EtOH; *c.* Ac_2O, boiling 8 h; *d.* MnO_2

Electrochemical oxidation of **1** was also carried out using carbon electrodes in AcOH-AcONa [2]. However, the yield of **4** was less than 12%.

Hydrolysis of **2** gave in high yield alcohol **4**, oxidation of which by MnO_2 in CH_2Cl_2 led to carvone **5**, which was identified by its spectral and chromatographic properties compared with an authentic sample.

Silyl ether of carveol **6** was brominated using NBS in benzene to give **7**. Its IR spectrum contained bands characteristic of siloxy (1265 cm^{-1}) and a trisubstituted double bond (1650 cm^{-1}). Its PMR spectrum contained a multiplet at 0.54-2.67 ppm for protons of ethyls on Si, a methyl, and two methylenes. Furthermore, signals for a methylene on Br were observed at 3.77 ppm. The allyl proton H-6 resonated at 4.03 ppm. Broadened signals of vinyls H-9 and H-2 appeared at 4.73 and 5.50 ppm, respectively.

Bromide **7** reacted with 3-methyl-2-butenylmagnesium bromide in the presence of CuBr to form triene **8**. Removal of the silyl protection and subsequent treatment with PDC completed the synthesis of cryptomerlone **9**, the spectral properties of which agreed with those in the literature [3].

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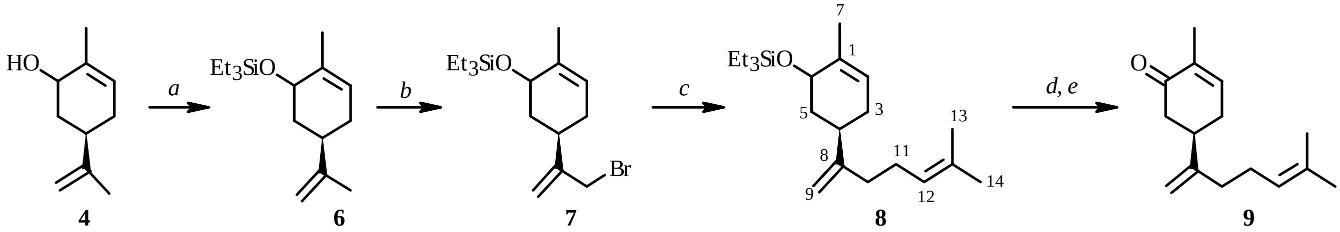

a. Et_3SiCl, Im; *b.* NBS; *c.* Grignard reagent, CuBr, THF; *d.* AcOH/THF/H_2O; *e.* PDC

Thus, we carried out a specific synthesis of carvone and cryptomerlone using electrochemical oxidation of α-pinene to construct the *p*-menthane fragment of the target products.

EXPERIMENTAL

IR spectra were recorded on a Specord 75 spectrophotometer; PMR and ^{13}C NMR spectra, on Bruker AC-E200 (200.13 and 50.32 MHz) and Bruker AC-80 (80 and 20 MHz) spectrometers for $CDCl_3$ solutions (2-3%) with TMS internal standard. Specific rotation was measured on a Perkin-Elmer 241 polarimeter. Column chromatography used SiO_2 L40/100, 100/160 μ (Czech Rep.) and 40/63 μ (Fluka); TLC, Silufol plates (Czech Rep.) developed using phosphomolybdic acid in EtOH (5%) with subsequent heating or acidification with aqueous $KMnO_4$ (2%).

Analytical data of all synthesized compounds agreed with those calculated.

Starting α-pinene (**1**, Fluka) was a mixture of enantiomers with n_D^{20} 1.466, $[\alpha]_D^{20}$ -45° (l = 1, pure).

Electrochemical Oxidation of α-Pinene. Compound **1** (15.44 g, 113.5 mmol), Ac_2O (50 mL), AcOH (1 mL), and AcONa (0.4 g) were placed in a 30-mm diameter cylinder. Two graphite electrodes (10-mm diameter) were inserted with a distance of 5 mm between them. Electrical current (100 mA) was passed for 120 h. The reaction mixture was poured into saturated NaCl solution (250 mL), treated with saturated $NaHCO_3$ solution (100 mL), left for 3 d, extracted with $CHCl_3$ (4 × 100 mL), and washed with water (100 mL) and saturated $NaHCO_3$ solution (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was distilled off to afford a solid (18.8 g) that was charmatographed over SiO_2 with elution by ethylacetate:petroleum ether (1:20) to give **4** (6.5 g, 30%) and **6** (6.7 g, 23%).

Mixture of Diastereomers 2. n_D^{20} 1.4715. IR spectrum (mineral oil, ν, cm^{-1}): 1380, 1735 (OAc), 1650 (=CH_2).

PMR spectrum of the predominant isomer (200 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.17-2.19 (5H, m, H-4, H-3, H-5), 1.63, 1.66 (6H, 2 s, H-7, H-10), 1.99 (3H, s, H-Ac), 4.61-4.67 (2H, m, H-9), 5.15 (1H, m, H-6), 5.55 (1H, m, H-2).

^{13}C NMR of the predominant isomer (50 MHz, $CDCl_3$): 16.59 (C-7), 20.39 (C-10), 20.61 (CO$\underline{Me}$), 30.73 (C-3), 33.52 (C-4), 40.13 (C-5), 70.39 (C-6), 109.04 (C-9), 127.60 (C-2), 130.79 (C-1), 148.42 (C-8), 170.54 ($\underline{C}$OMe).

Mixture of Diastereomers 3. n_D^{20} 1.4660. IR spectrum (mineral oil, ν, cm^{-1}): 1385, 1720 (OAc), 1670 (C=CH).

PMR spectrum of the predominant isomer (200 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.18, 1.19 (6H, 2 s, H-9, H-10), 1.43-1.56 (1H, m, H-4), 1.62 (3H, s, H-7), 1.70-2.30 (4H, m, H-3, H-5), 1.93, 2.04 (6H, 2 s, 2 Ac), 5.15 (1H, m, H-6), 5.64 (1H, m, H-2).

^{13}C NMR spectrum of the predominant isomer (50 MHz, $CDCl_3$): 18.29 (C-7), 22.00, 20.94 (2CO$\underline{Me}$), 22.61 (C-10), 23.16 (C-9), 26.20 (C-3), 29.78 (C-5), 37.18 (C-4), 70.37 (C-6), 83.35 (C-8), 127.23 (C-2), 130.63 (C-1), 170.57, 169.85 (2$\underline{C}$OMe).

Mixture of Diastereomers 4. A solution of NaOH (0.48 g, 12 mmol) in ethanol (30 mL) was stirred and treated with **2** (0.93 g, 4.79 mmol), stirred for 48 h, diluted with saturated NaCl solution (60 mL), and extracted with ether (4 × 25 mL). The ether extract was washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. Solvent was distilled off to afford **4** (0.63 g, 95%), n_D^{20} 1.4945.

IR spectrum (mineral oil, ν, cm^{-1}): 3390 (OH), 1650 (=CH_2).

PMR spectrum of the predominant isomer (80 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.91-2.34 (11H, m, H-10, H-7, H-3, H-5, H-4), 4.06 (1H, m, H-6), 4.78 (2H, m, H-9), 5.59 (1H, m, H-2).

^{13}C NMR spectrum of the predominant isomer (20 MHz, $CDCl_3$): 18.81 (C-7), 20.68 (C-10), 30.82 (C-3), 36.53 (C-4), 40.37 (C-5), 70.56 (C-6), 108.76 (C-9), 125.02 (C-2), 134.12 (C-1), 149.00 (C-8).

Carvone 5. A solution of **4** (0.69 g, 4.54 mmol) in anhydrous CH_2Cl_2 (50 mL) was stirred and treated in portions with MnO_2 (25 g, 5 g portions) over 24 h. The MnO_2 was filtered off and washed with CH_2Cl_2. The combined extract was evaporated to afford **5** (0.42 g, 70%), n_D^{20} 1.4961, $[\alpha]_D^{20}$ -1.5° (*c* 1.1, $CHCl_3$).

IR spectrum (mineral oil, ν, cm^{-1}): 1715 (C=O), 1645 ($=CH_2$).

PMR spectrum (80 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.56 (6H, br. s, H-7, H-10), 2.07-2.53 (5H, m, H-3, H-5, H-4), 4.60-4.65 (2H, m, H-9), 6.59 (1H, m, H-2).

^{13}C NMR spectrum (20 MHz, $CDCl_3$): 15.48 (C-7), 20.30 (C-10), 31.04 (C-3), 42.28 (C-4), 42.94 (C-5), 110.26 (C-9), 135.30 (C-1), 144.37 (C-2), 146.47 (C-8), 199.43 (C-6).

Mixture of Diastereomers 6. A solution of **4** (1 g, 6.57 mmol) and imidazole (0.48 g, 7.05 mmol) in anhydrous CH_2Cl_2 (20 mL) was stirred and treated with Et_3SiCl (1.06 g, 7.05 mmol) and left overnight. The solid was filtered off. The solvent was evaporated. The solid was chromatographed over SiO_2 with elution by hexane to afford a light yellow oil (**6**, 1.62 g), yield 87%.

IR spectrum (mineral oil, ν, cm^{-1}): 1260 (C–O–Si), 1660 ($=CH_2$).

PMR spectrum of the predominant isomer (80 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.46-2.31 (26H, m, H-Et_3, H-7, H-10, H-3, H-5, H-4), 4.25 (1H, m, H-6), 4.71 (2H, m, H-9), 5.45 (1H, m, H-2).

^{13}C NMR spectrum of the predominant isomer (20 MHz, $CDCl_3$): 5.07 $[Si(CH_2\underline{C}H_3)_3]$, 6.91 $[Si(\underline{C}H_2CH_3)_3)]$, 19.46 (C-7), 20.31 (C-10), 31.08 (C-3), 38.63 (C-4), 40.95 (C-5), 71.43 (C-6), 108.93 (C-9), 123.43 (C-2), 136.92 (C-1), 149.12 (C-8).

Mixture of Diastereomers 7. A mixture of **6** (0.8 g, 3 mmol), NBS (0.56 g, 3.15 mmol), and benzoyl peroxide (0.02 g) in CCl_4 (10 mL) was boiled for 4 h. The solid was washed with CCl_4. The combined filtrate was washed with saturated NaCl solution (3 × 5 mL) and dried over anhydrous Na_2SO_4. Solvent was distilled. The solid was chromatographed over SiO_2 (hexane eluent) to afford an unstable yellow oily product (**7**, 0.46 g), yield 44%.

IR spectrum (mineral oil, ν, cm^{-1}): 580 (C–Br), 1265 (C–O–Si), 1650 ($=CH_2$).

PMR spectrum of the predominant isomer (80 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.54-2.67 (23H, m, H-7, H-3, H-5, H-4), 3.77 (2H, s, H-10), 4.03 (1H, m, H-6), 4.73 (2H, m, H-9), 5.50 (1H, m, H-2).

Mixture of Diastereomers 8. A solution of 3-methyl-2-butenylmagnesium bromide in dry THF (10 mL), prepared from 3-bromo-2-methyl-2-butene (0.592 g, 4 mmol) and Mg (0.3 g), was added dropwise with stirring to a cold (icewater) solution of **7** (1.06 g, 4 mmol) and CuBr (25 mg). The mixture was stirred for an additional 6 h, left overnight at room temperature, treated with saturated NH_4Cl solution (10 mL), extracted with ether, and dried over anhydrous Na_2SO_4. Solvent was evaporated to afford **8** (1.15 g), which was used without further purification.

PMR spectrum of the predominant isomer (80 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.34-1.08 (15H, m, H-Et_3), 1.63 (3H, br. s, H-7), 1.83-1.85 (6H, m, H-13, H-14), 3.89-4.01 (1H, m, H-6), 5.50-5.89 (4H, H-2, H-9, H-12).

Cryptomerlone 9. A solution of **8** (1.15 g, 3.44 mmol) in THF (5 mL) was treated dropwise with aqueous AcOH (10 mL, 50%). The mixture was stirred for 8 h, extracted with ether (3 × 50 mL), and dried over anhydrous Na_2SO_4. Solvent was distilled. The solid was dissolved in CH_2Cl_2 (5 mL), treated with cooling (icewater) with pyridinium dichlorochromate (PDC) (720 mg), stirred for 14 h, treated with H_2O (10 mL), extracted with CH_2Cl_2 (3 × 25 mL), washed with saturated NaCl solution, and dried over anhydrous Na_2SO_4. Solvent was evaporated. The solid was chromatographed over SiO_2 to afford a colorless liquid (**9**, 134 mg), yield 20% calculated for **8**, n_D^{20} 1.5035, $[\alpha]_D^{20}$ -4.0° (*c* 0.2, $CHCl_3$), lit. [3]: n_D^{20} 1.5041.

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