Synthesis of α-Corocalene†

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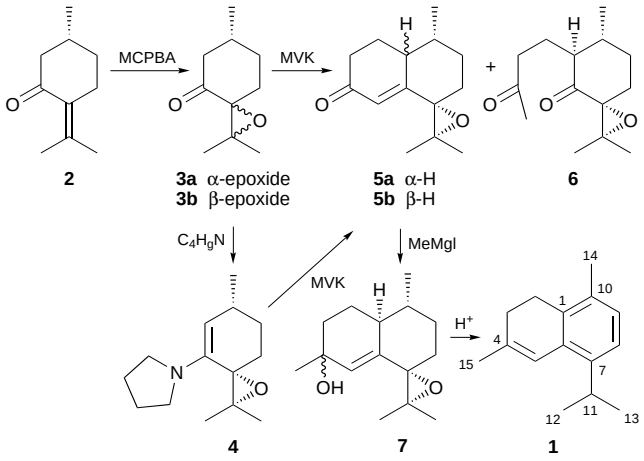
α-Corocalene, a constituent of hop oil, has been synthesized in four steps from the monoterpene (+)-pulegone.

The sesquiterpene α-corocalene (**1**) was first isolated as a constituent of hop oil by Japanese workers in 1969[1] and has been subsequently reported in essential oils and Juniper[2] and members of the Lauraceae family.[3] No synthesis of this compound has been reported following its isolation as a natural product, although preparations of the isomeric sesquiterpene hydrocarbons γ-calacorene and α-calacorene have appeared.[4,5] The completely aromatized naphthalene system of cadalene (with one extra degree of unsaturation as compared to α-corocalene) has also been obtained by synthesis.[6]

A common synthetic strategy in the synthesis of sesquiterpenes is to perform Robinson annulation of commercially available menthane monoterpenes.[7,8] It has been reported that the pyrrolidene enamine of (+)-pulegone (**2**) undergoes such a reaction,[9] but we were unable to form the enamine of **2** despite repeated attempts. Pulegone α-epoxide (**3a**), however, did readily form the desired enamine **4** in good yield (Scheme 1). Interestingly, the β-epoxide (**3b**), which was normally present in combination with the α-epoxide (MCPBA epoxidation of pulegone showed no diastereoselectivity), completely failed to react with pyrrolidine even under the most forcing conditions. Compounds **3a** and **3b** were separated by HPLC. X-Ray crystallographic analysis (Fig. 1)‡ showed that the C-1 methyl group and the new epoxide functionality were *trans* to one another in **3b** and *cis* in **3a**. Since the absolute stereochemistry at C-1 is known for (+)-pulegone starting material and this chiral centre is not expected to undergo alteration during the course of epoxidation, the absolute stereochemistry for **3a** and **3b** can be determined as shown.

The enamine **4** underwent smooth Robinson annulation with methyl vinyl ketone (MVK), as expected, to give the



Scheme 1 Synthetic route to α-corocalene from (+)-pulegone

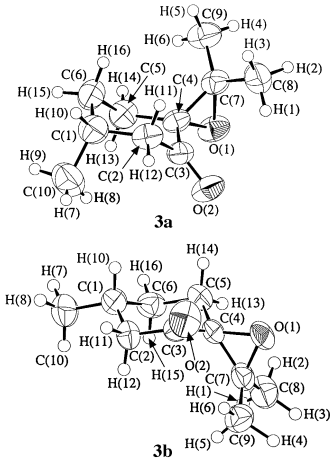


Fig. 1 ORTEP diagrams for **3a** and **3b**

bicyclic unsaturated ketone **5a**. It was later discovered that **5a** could be made directly by Robinson annulation of the **3a**–**3b** epoxide mixture with MVK in the presence of base. As previously, the β-epoxide (**3b**) was completely unreactive. Direct Robinson annulation also resulted in production of small amounts of the 1β-epimer (**5b**) and uncyclized product **6**. The two epimers **5a** and **5b** were very clearly distinguished from their ^{13}C NMR spectra (see Table 1) which showed a pronounced upfield shift (*ca.* 5 ppm) in the 14-methyl group of **5b** as a result of *gauche* effects when this substituent is forced to adopt an axial conformation. NOESY spectra for **5b** also demonstrated strong axial–axial correlations from 14-H to 8α-H and 2α-H, which were absent from compound **5a**. The appearance of diastereoisomers at this step in the synthesis was considered unimportant as this new chiral centre would be eliminated in the final product.

Introduction of the final carbon atom required in the structure of **1** was achieved by Grignard reaction to yield the unstable alcohol **7**. Treatment of **7** with mild acid resulted in dehydration at both the tertiary hydroxide and epoxide groups accompanied by double bond migration to yield the aromatic B ring of α-corocalene. In fact, this reaction is so facile that it can be affected by the acidic impurities in $CDCl_3$: thus, simply allowing a solution of **7** in an NMR tube to stand overnight resulted in conversion into **1**.

Low-field ^1H NMR data reported for the natural product α-corocalene[1] agreed with that for **1** obtained through synthesis. Complete ^{13}C and ^1H NMR assignments for **1** and for all of the intermediates in the synthesis (Table 1) were rigorously determined by means of the 2D-NMR techniques HSQC (which shows ^{13}C connected to ^1H by a single bond) and HMBC (2- and 3-bond couplings between ^{13}C and ^1H). ^1H–^1H COSY spectra were normally used to confirm these assignments and NOESY and ^1H–^1H *J*-resolve experiments were used to determine the relative stereochemistries.

Experimental

Chemical shifts are expressed in ppm (δ) relative to Me_4Si as internal standard. All NMR experiments were run on a Bruker DRX 500 instrument. Two-dimensional spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. Mass spectra were

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡Full crystallographic details, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Research (S)*, 1998, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 423/6.

Table 1 NMR data for **1, 5a, 5b, 6**

	δ_C				δ_H			
Atom	**1**	**5a**	**5b**	**6**	**1**	**5a**	**5b**	**6**
1	132.7	42.7	41.6	57.5		2.28	2.55	1.97
2α	24.9	25.3	25.3	19.87	2.73	1.81	1.95	1.86
2β					2.73	2.13	2.15	1.82
3α	28.1	35.8	36.2	40.9	2.19	2.33	2.30	2.58
3β					2.19	2.46	2.50	2.43
4	137.8	199.3	199.4	208.7				
5	119.0	123.9	125.3	29.8	6.51	5.83	6.08	2.12
6	132.0	165.0	162.0	207.8				
7	140.5	68.2	67.8	70.7				
8α	122.3	29.4	25.7	30.1	7.01	1.91	2.05	2.01
8β						1.76	1.70	1.90
9α	128.0	31.1	31.8	33.0	6.94	1.53	1.80	1.56
9β						1.92	1.80	2.00
10	131.6	35.0	34.6	38.1		1.62	2.28	1.73
11	28.2	65.2	64.7	62.7	3.24			
12	23.6	20.4	19.7	19.93	1.21	1.31	1.19	1.17
13	23.6	21.7	20.4	19.2	1.21	1.42	1.45	1.42
14	19.6	19.5	14.7	20.3	2.24	1.05	1.02	1.14
15	24.1				1.95			

recorded in the EI mode at 70 eV on a Finnigan-MAT 95 MS spectrometer. IR spectra were recorded in solution on a Shimadzu FTIR-8201 PC-7 spectrometer. TLC plates were developed using *p*-anisaldehyde. Column chromatography was performed using silica gel 60–200 μm (Merck). HPLC separations were performed using a PREP-SIL 20 mm × 25 cm column, flow-rate 8 ml min^{-1}.

Epoxidation of Pulegone (**2**).—*m*-Chloroperbenzoic acid (MCPBA) (15.96 g) was added to pulegone (**2**) in CH_2Cl_2 (7.61 g, 130 ml) and the mixture was cooled in an ice bath. The mixture was stirred for 1 h (a white precipitate appeared after 15 min), then washed with Na_2SO_3 (10%; 2 × 100 ml) and $NaHCO_3$ (2 × 100 ml). The combined aqueous washings were back-extracted with CH_2Cl_2 (2 × 50 ml) and combined organic layers, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield **3a**/**3b** in a 1:1 ratio (8.38 g, 99.8%). The two isomers were separated by HPLC in 25% (v/v) EtOAc–hexane [R_t (**3a**) 13.6 min; R_t (**3b**) 14.6 min]. Pulegone α-epoxide (**3a**): crystals, mp < 40 °C; $[\alpha]_D - 17.3°$ (*c* 3.5, $CHCl_3$); *m*/*z* (intensity %): 168.1146 (M^+, Δ = 0.4 mmu for $C_{10}H_{16}O_2$) (35), 153 (100), 126 (10), 125 (11); ν_{max}/cm^{-1} 3015, 2964, 2932, 1720; δ_H ($CDCl_3$) 2.43 (3 H, br m), 2.21 (1 H, ddd, *J* 15.3, 12.3, 4.3 Hz), 1.98 (1 H, m), 1.44 (3 H, s), 1.23 (3 H, s), 1.06 (3 H, d, *J* 7.1 Hz); δ_C ($CDCl_3$) 207.6 (C), 70.2 (C), 63.5 (C), 49.5 (CH_2), 30.7 (CH), 30.2 (CH_2), 26.3 (CH_2), 20.0 (CH_3), 19.6 (CH_3), 18.9 (CH_3). Pulegone β-epoxide (**3b**): crystals mp < 40 °C; $[\alpha]_D$ 26.0° (*c* 3.1, $CHCl_3$). *m*/*z* (intensity %) 168 (28) 153.0925 (100) ($M^+ - CH_3$, Δ = − 1.0 mmu for $C_9H_{13}O_2$), 126 (10), 111 (5); ν_{max}/cm^{-1} ($CHCl_3$) 3015, 2963, 2930, 1720; δ_H ($CDCl_3$) 2.50 (1 H, dt, *J* 12.8, 2.8 Hz), 1.44 (3 H, s), 1.22 (3 H, s), 1.08 (3 H, d, *J* 6.1 Hz). δ_C ($CDCl_3$) 206.5 (C), 70.3 (C), 63.3 (C), 51.4 (CH_2), 34.0 (CH), 33.0 (CH_2), 30.0 (CH_2), 22.1 (CH_3), 19.8 (CH_3), 19.4 (CH_3).

Reaction of Pyrrolidine with Pulegone Epoxide (**3a**/**3b**).—Pyrrolidine (1.07 g), pulegone epoxide (**3a**/**3b**) (0.465 g) and benzene (5 ml; sodium-dried) were mixed together and allowed to stand over molecular sieve (3 g; 4 Å). The reaction was monitored by TLC; after 5 days, molecular sieve was removed and washed with benzene (2 × 5 ml) and the combined organic fractions evaporated under reduced pressure to give a crude product (139 mg). ^1H NMR showed this to consist of the enamine of pulegone α-epoxide (**4**) and unreacted pulegone β-epoxide (**3b**). No unreacted pulegone α-epoxide could be detected. Compound **4**: dark brown oil (isolated as a mixture with **3b**); δ_H ($CDCl_3$) 4.48 (1 H, d, *J* 2.2 Hz), 3.17 (2 H, dt, *J* 15.5, 6.9 Hz), 1.35 (3 H, s), 1.33 (3 H, s), 1.03 (3 H, d, *J* 7.1 Hz); δ_C ($CDCl_3$) 145.1 (C), 107.9 (CH), 66.6 (C), 62.2 (C), 49.4 (CH_2 × 2), 30.0 (CH_2), 28.0 (CH_2), 26.0 (CH_2), 24.4 (CH_2 × 2), 22.8 (CH_3), 21.2 (CH_3), 19.7 (CH_3).

Robinson Annulation of Pulegone Epoxide (**3a**/**3b**) *with Methyl Vinyl Ketone*.—To a mixture of pulegone epoxide (**3a**/**3b**) (1.68 g), methanol (20 ml, anhydrous) and methyl vinyl ketone (0.73 g) was added potassium hydroxide (0.1 g). The mixture was stirred for 1 h at 50–60 °C and refluxed for a further 3 h. Solvent was removed by distillation at reduced pressure, and the residue was taken up into $CHCl_3$. The organic layer was washed and dried and the solvent was removed to yield a product consisting predominantly of unreacted β-pulegone epoxide (**3b**) and the annulation product **5a**, together with a little of the 1-epimer **5b** and cyclohexanedione **6**. Compound **5a** was purified by column chromatography in 30% (v/v) EtOAc–hexane (398 mg, 36% yield from **3a**): oil; $[\alpha]_D + 95.0°$ (*c* 0.65, $CHCl_3$); *m*/*z* (intensity %) 192.1513 ($M^+ - CO$, Δ = 0.1 mmu for $C_{13}H_{20}O$) (100), 177 (62), 164 (62), 150 (37), 122 (18); ν_{max}/cm^{-1} ($CHCl_3$) 2995, 2961, 2924, 2860, 1668; δ_H ($CDCl_3$) 5.83 (1 H, d, *J* 1.3 Hz), 2.46 (1 H, ddd, *J* 17.0, 8.6, 8.6 Hz), 2.33 (1 H, ddd, *J* 17.0, 7.9, 4.8 Hz), 2.28 (1 H, ddd, *J* 11.2, 6.0, 6.0 Hz), 1.42 (3 H, s), 1.31 (3 H, s), 1.05 (3 H, d, *J* 6.3 Hz). Compound **5b**: oil; $[\alpha]_D + 5.7°$ (*c* 5.5, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ 3013, 2964, 2936, 1670; δ_H ($CDCl_3$) 6.08 (1 H, d, *J* 2.4 Hz), 1.45 (3 H, s), 1.19 (3 H, s), 1.02 (3 H, d, *J* 7.1 Hz). Compound **6**: δ_H($CDCl_3$) 2.12 (3 H, s), 1.42 (3 H, s), 1.17 (3 H, s), 1.14 (3 H, d, *J* 6.4 Hz).

Grignard Reaction of **5a** *and Conversion into* **1**.—A methyl Grignard reagent (Mg 0.56 g; CH_3I, 3.6 g; Et_2O, 30 ml) was prepared by standard procedures. A solution of **5a** (0.37 g) in Et_2O (25 ml) was added to the Grignard reagent and the mixture was stirred at room temperature for 1.5 h, and then worked up by standard procedures. Following washing, drying and concentration of the organic phase, compound **7** (180 mg) was isolated without need for further purification: colourless oil, δ_H ($CDCl_3$) 1.52 (3 H, s), 1.43 (3 H, s), 1.14 (3 H, s), 0.96 (3 H, d, *J* 6.9 Hz). On standing overnight in $CDCl_3$, compound **7** was converted into α-corocalene **1**; *m*/*z* (intensity %) 200.1567 (M^+, Δ = − 0.2 for $C_{15}H_{20}$) (100), 185 (65), 157 (13); ν_{max}/cm^{-1} ($CHCl_3$) 3013, 2967, 2924, 2870, 1601, 1475, 1452; δ_H ($CDCl_3$) 7.01 (1 H, d, *J* 8.0 Hz), 6.94 (1 H, d, *J* 8.0 Hz), 6.51 (1 H, d, *J* 1.4 Hz), 3.24 (1 H, septet, *J* 7.0 Hz), 2.73 (2 H, t, *J* 8 Hz), 2.24 (3 H, s), 2.19 (2 H, m), 1.95 (3 H, d, *J* 0.9 Hz), 1.21 (6 H, d, *J* 7.0 Hz).

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