A New Approach to the Synthesis of (±)-Cuparene

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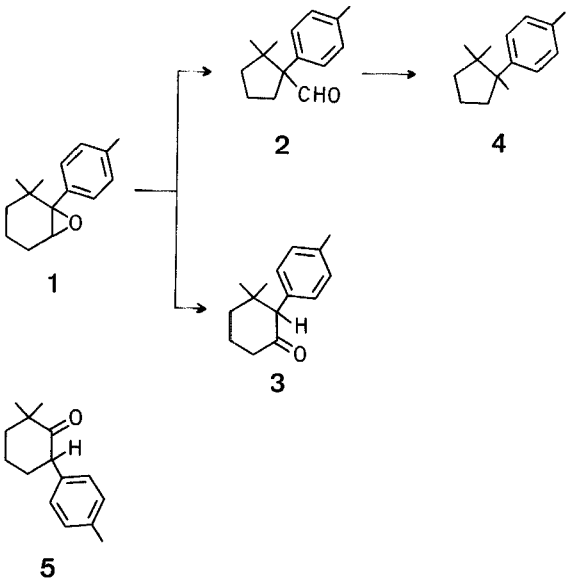
The generation of two vicinal quaternary centres as encountered in sesquiterpenes of the cuparene type poses a synthetic challenge which has been approached in several ways[1-3]. The present communication offers an original solution to the synthetic problem which is exemplified by the synthesis of (±)-cuparene (**4**).

The key step entails the boron trifluoride catalysed rearrangement of the epoxide (**1**), which was synthesised by conventional methods. Brief treatment of the epoxide (**1**) with boron trifluoride etherate in benzene gave a mixture of the desired aldehyde (**2**) and the ketone (**3**). Conversion of the aldehyde (**2**) to the semicarbazone, followed by heating with potassium hydroxide gave an acceptable yield of (±)-cuparene (**4**), whose infrared[4] and N.M.R.[5] spectroscopic properties were identical with those reported.

The conditions used for the rearrangement of the epoxide (**1**) are critical since the aldehyde (**2**) readily undergoes further rearrangement to the ketone (**5**).



1 2 3 4 5

6,6-Dimethyl-1-*p*-tolylcyclohexene:
2,2-Dimethylcyclohexanone was reacted with *p*-tolyllithium, following the general procedure of Garbisch[6], to give 2,2-dimethyl-*p*-tolylcyclohexanol; yield: 62%; m.p. 49–53° (from petroleum ether).

$C_{15}H_{22}O$	calc.	C 82.5	H 10.2
	found	82.6	10.1

Dehydration of the carbinol (25 g) by heating with potassium hydrogen sulphate (1 g) at 160° for two hours gave 6,6-dimethyl-1-*p*-tolylcyclohexene; yield 18 g (78%); b.p. 88°/0.25 torr.

$C_{15}H_{20}$	calc.	C 89.9	H 10.1
	found	89.7	9.9

3,3-Dimethyl-1,2-epoxy-2-*p*-tolylcyclohexane (1):
6,6-Dimethyl-1-*p*-tolylcyclohexene (11 g) was slowly added with stirring to a cooled solution of perbenzoic acid in chloroform

(170 ml, 0.28 *M*), and the reaction mixture then allowed to stand at room temperature overnight. The chloroform solution was thoroughly washed with dilute aqueous sodium hydroxide, dried over sodium sulfate and evaporated. Distillation of the residue gave the epoxide; yield: 10.6 g (89%); b.p. 94°/0.2 torr.

$C_{15}H_{20}O$	calc.	C 83.3	H 9.3
	found	82.9	9.0

Rearrangement of the Epoxide (1):

The epoxide (4.5 g) in benzene (200 ml) was treated with freshly distilled boron trifluoride etherate (4.5 ml) for 45 seconds and then quenched by rapidly shaking with dilute aqueous sodium hydroxide. The dried benzene layer was evaporated and the residual oil was separated by preparative T.L.C. using seven 20 × 20 cm plates coated (2 mm) with silica gel, which were developed (× 3) with benzene. The leading band contained unreacted epoxide (1.3 g). The second band yielded 2,2-dimethyl-1-*p*-tolylcyclopentanecarboxaldehyde (**2**, 0.7 g, 22% on unrecovered epoxide) as an oil.

I.R. (liquid film): ν_{max} = 2820, 2720, 1720, 1522, 820 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.66 (s, 3H), 1.24 (s, 3H), 1.4 to 2.0 (broad hump, 6H), 2.3 (s, 3H), 7.28 (s, 4H), 9.9 ppm (s, 1H).

The aldehyde was converted to its semicarbazone, m.p. 193–195° (from methanol).

$C_{16}H_{23}N_3O$	calc.	C 70.3	H 8.4	N 15.3
	found	70.1	8.5	15.2

The remaining material was rechromatographed on three plates using benzene/ethyl acetate (19:1) as eluant. The leading band contained 3,3-dimethyl-2-*p*-tolylcyclohexanone (**3**, 0.8 g, 25% on unrecovered epoxide) m.p. 71–73° (from cold petroleum ether).

$C_{15}H_{20}O$	calc.	C 83.3	H 9.3
	found	82.9	9.3

I.R. (Nujol): ν_{max} = 1700, 1520, 1175, 1085, 815, 760 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.82 (s, 3H), 0.85 (s, 3H), 1.7 to 2.2 (broad hump, 4H), 2.31 (s, 3H), 7.23 ppm (s, 4H), the signal due to the remaining two protons is obscured by the aromatic methyl resonance.

The second band provided 2,2-dimethyl-6-*p*-tolylcyclohexanone (**5**, 0.1 g) m.p. 45° (from cold petroleum ether).

$C_{15}H_{20}O$	calc.	C 83.3	H 9.3
	found	83.5	9.4

I.R. (Nujol): ν_{max} = 1700, 1520, 1060, 1020, 1000, 830, 810, 750 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.02 (s, 3H), 1.24 (s, 3H), 1.8 (br. 4H), 2.05 (br. 2H), 2.31 (s, 3H), 3.5 4.0 (m, 1H), 7.0–7.4 ppm (m, 4H).

Preliminary experiments monitored by G.L.C. showed that longer reaction times resulted in the formation of increasing amounts of the ketone (**5**), with complete disappearance of the aldehyde (**2**) after five minutes.

(±)-Cuparene (4):

The semicarbazone of 2,2-dimethyl-1-*p*-tolylcyclopentanecarboxaldehyde (0.45 g) was heated with potassium hydroxide (1 g) at 220° for fifteen minutes. The reaction mixture was cooled, water added and then extracted with ether. The total organic material was transferred to a 20 × 20 cm preparative T.L.C. plate coated (2 mm) with silica gel. After development with cyclohexane the principle band (R_F ~ 0.5) was removed and eluted with ether to give (±)-cuparene; yield: 0.24 g (72%).

I.R. (liquid film): ν_{max} = 1520, 1465, 1390, 1380, 1370, 1190, 1020, 820, 725 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 0.54 (s, 3H), 1.04 (s, 3H), 1.22 (s, 3H), 1.65 (br. 6H), 2.25 (s, 3H), 7.1–7.4 ppm (m, 4H).

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