Synthesis of Aromatic Sesquiterpenes, (±)-Cuparene and (±)-Laurene by Means of an Intramolecular Carbenoid Displacement (ICD) Reaction[1]

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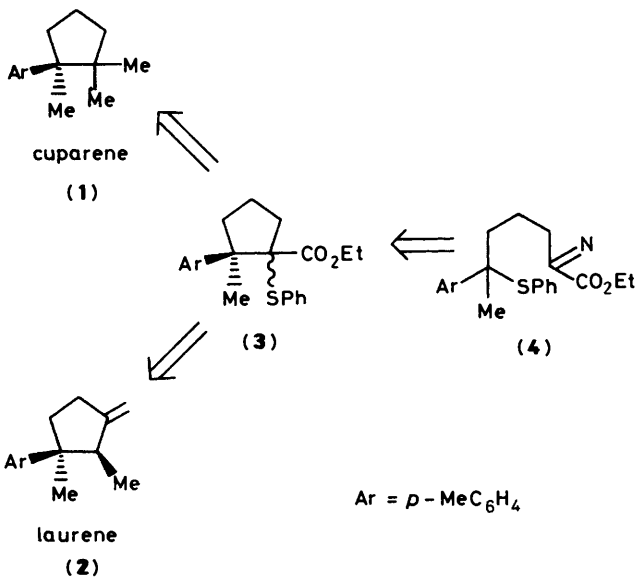
The synthesis of (±)-cuparene and (±)-laurene was accomplished by means of an intramolecular carbenoid displacement (ICD) reaction of the benzyl sulphide (**12**) as a key reaction.

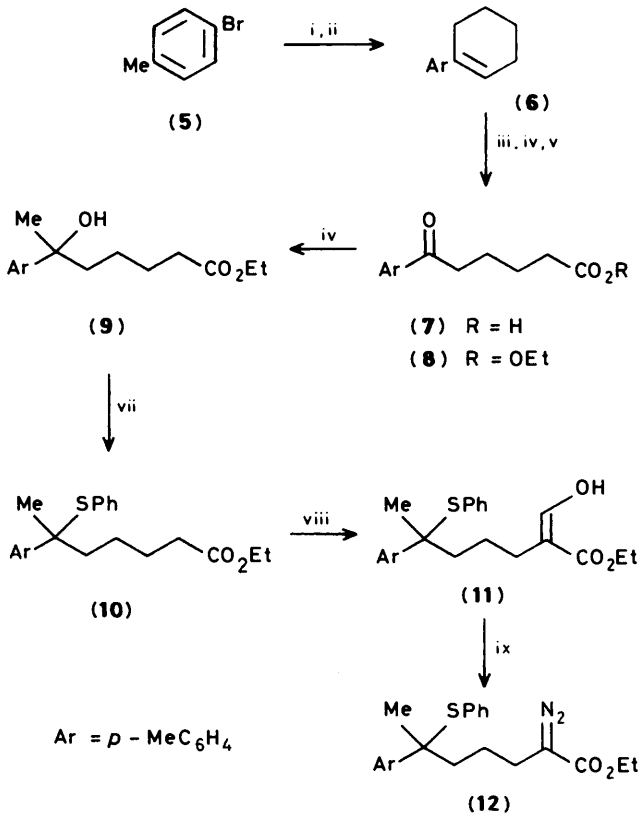
The development of new methods for the construction of quaternary carbon centres is one of the most interesting objectives in organic synthesis, and has been widely studied[2] not only for synthetic reasons but also because of the observation of such centres in a variety of natural products. During the course of our work[3] on the ICD reaction, we have been interested in the synthesis of the 1-aryl-1,2,2-trimethylcyclopentane ring system, a basic skeleton of aromatic sesquiterpenes such as cuparene (**1**) and laurene (**2**), which contain a quaternary carbon centre.

The key feature of our synthesis is the formation of a new carbon–carbon bond at a benzylic position to construct the quaternary carbon centre by using an ICD reaction of the benzyl sulphide (**4**) (Scheme 1).



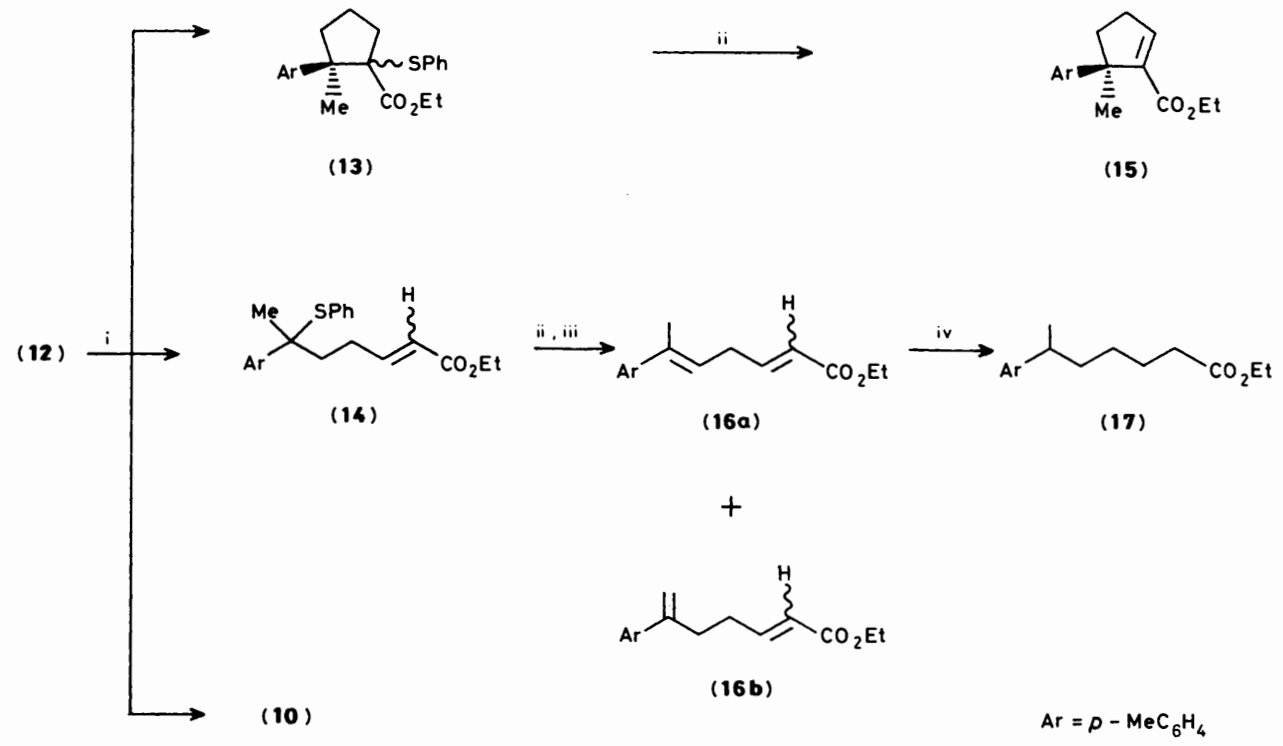
Scheme 1.

The requisite starting material (**12**) was prepared as shown in Scheme 2. Grignard reaction of *p*-tolylmagnesium bromide (**5**) with cyclohexanone afforded the tertiary alcohol, dehydration of which with toluene-*p*-sulphonic acid furnished the cyclohexene (**6**) in quantitative yield. Compound (**6**) was then transformed into the oxo ester (**8**), *via* the oxo acid (**7**), by ozonolysis, Jones oxidation, and esterification following standard procedures. Treatment of compound (**8**) with methyl-lithium gave the benzyl alcohol (**9**), phenylthionylation[4] of which with thiophenol in the presence of zinc iodide yielded the sulphide (**10**) in quantitative yield. Formylation[5] of the sulphide (**10**) with ethyl formate in the presence of lithium di-isopropylamide, followed by treatment of the formyl compound (**11**) with toluene-*p*-sulphonyl azide and triethylamine afforded the desired diazo-compound (**12**) (78%) from compound (**10**).



Scheme 2. *Reagents:* i, cyclohexanone, Mg, THF; ii, *p*-TsOH, PhH, reflux; iii, O_3, CH_2Cl_2, −78 °C; Me_2S; iv, Jones oxidation; v, EtOH, H_2SO_4, reflux; vi, MeLi, PhH; vii, ZnI_2, PhSH, $ClCH_2CH_2Cl$; viii, $LiNPr^i_2$, THF, HCO_2Et, −78 °C; ix, *p*-$Me_6H_4SO_2N_3$, Et_3N, CH_2Cl_2, room temp.

The ICD reaction for the diazo-compound (**12**) was investigated under the various conditions.[6] The desired cyclopentane derivative (**13**) together with the α,β-unsaturated ester (**14**)[7] and the dediazotised compound (**10**) were obtained, the results of which are summarised in Table 1 (Scheme 3). Because of the difficulty in the separation of those products, the mixture was subjected to oxidative elimination of the phenylthio group to give the cyclopentene derivative (**15**) and the inseparable alkenes [(**16a**) and (**16b**), in a *ca.* 1:1 ratio]. Hydrogenation of the dienes [(**16a**) and (**16b**)] over platinum oxide in methanol under an atmosphere of hydrogen afforded the ester (**17**) as a single compound; this result suggested that the dienes (**16a**) and (**16b**) were the olefinic position isomers. Although the chiral induction was also studied by using a chiral copper catalyst R-1648[8] in this reaction, the chemical yield of compound (**15**) decreased to 10.8% and its specific rotation was $[\alpha]_D^{25}$ 0°.

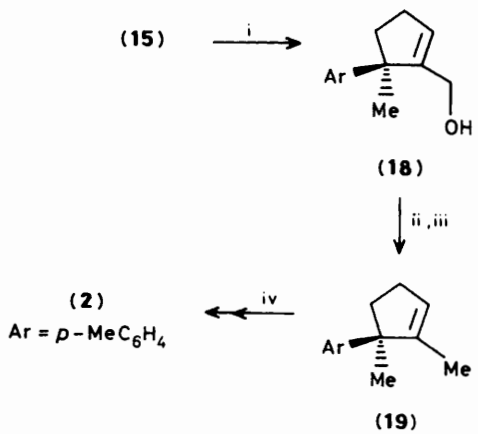


Scheme 3. *Reagents:* i, catalyst (see Table 1), PhH, reflux, 2 h; ii, *m*-CPBA, CH_2Cl_2, aq. $NaHCO_3$; iii, toluene, $CaCO_3$, reflux; iv, H_2, PtO_2, MeOH, 1 atm

Table 1. Data for ICD reaction

	Product yield (%)		
Catalyst	(10)	(15)	(16)
$Rh_2(OAc)_4$	15.8	52.2	11.4
$Cu(acac)_2$	20.0	58.0	10.0
R-1648	36.0	10.8	30.0

We now turned our attention to the conversion of compound (**15**) into cuparene and laurene. Reduction of compound (**15**) with di-isobutylaluminium hydride[9] gave the allyl alcohol (**18**), methanesulphonylation of which with methanesulphonyl chloride and triethylamine, and subsequent super-hydride reduction[10] afforded the cyclopentene derivative (**19**) (34.8%)



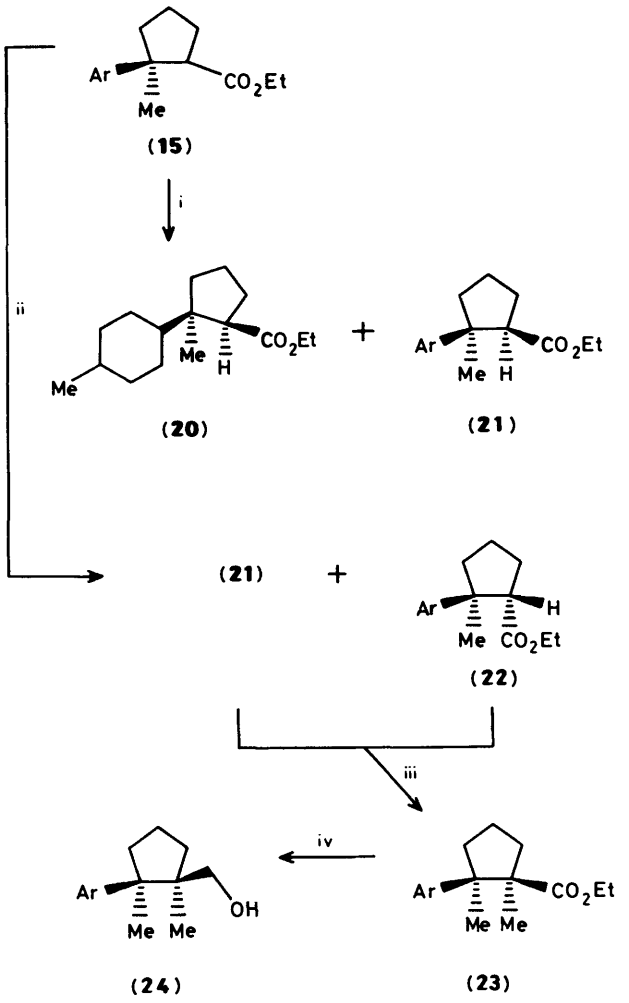
Scheme 4. *Reagents:* i, DIBAL, PhMe, −78 °C; ii, MsCl, Et_3N, CH_2Cl_2; iii, $LiBEt_3H$, THF; iv, see ref. 11

Table 2. Reduction of compound (**15**)

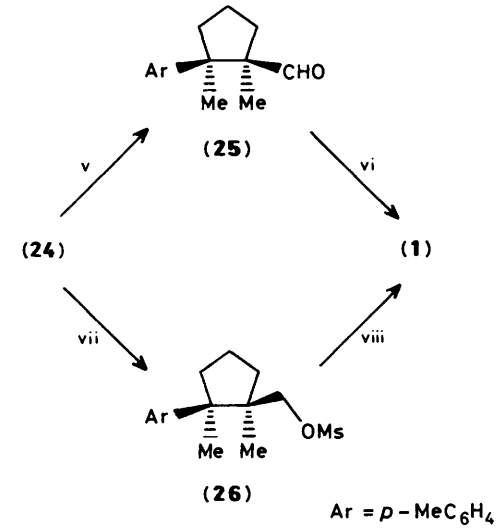
	Product yield (%)			
Reaction conditions	(15)	(20)	(21)	(22)
PtO_2/H_2, MeOH 4 atm, r.t., 48 h	Recovery	—	Trace	—
PtO_2/H_2, AcOH 1 atm, r.t., 3 h	—	100	—	—
PtO_2/H_2, AcOEt 3 atm, r.t., 18 h	—	71	26.5	—
$NaBH_4$, $NiCl_2 \cdot 6H_2O$ MeOH, r.t., 24 h	—	—	90 [(21):(22) = 9:2]	

from (**15**) (Scheme 4). Since compound (**19**) has already been converted[11] into laurene (**2**), this synthesis constitutes its formal total synthesis.

The conversion of compound (**15**) into cuparene was achieved as follows (Scheme 5-I). First the reduction of (**15**) was investigated, the results are summarised in Table 2. Although catalytic hydrogenation of compound (**15**) over platinum oxide gave the cyclohexane derivative (**20**) as a major product together with the desired compound (**21**), the 1,4-conjugate reduction of compound (**15**) with sodium borohydride in the presence of nickel chloride[12] in methanol afforded the expected products (**21**) and (**22**), as an inseparable epimeric mixture in 90% yield. Treatment of both esters [(**21**) and (**22**)] with methyl iodide in the presence of lithium di-isopropylamide[13] gave the ester (**23**) (89.5%) as the sole product, which was further converted into cuparene (**1**) (39%) by a known procedure,[14] *via* the alcohol (**24**) and the aldehyde (**25**) (Scheme 5-II). Alternatively, cuparene (**1**) was synthesized from the alcohol (**24**) by treatment with methanesulphonyl chloride and sub-



Scheme 5-I. *Reagents:* i, see Table 2; ii, $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, room temp.; iii, $LiNPr^i_2$, THF, HMPA, MeI; iv, $LiAlH_4$, Et_2O



Scheme 5-II. *Reagents:* v, PCC, CH_2Cl_2; vi, Na, $N_2H_4 \cdot H_2O$, EG, 185 °C; vii, MsCl, Et_3N, CH_2Cl_2; viii, $LiBEt_3H$, THF, heat

sequent super-hydride[15] reduction of the methanesulphonate (**26**) (Scheme 5-II).

Thus, an efficient method was developed for the construction of a quaternary carbon centre at the benzylic position using an ICD reaction, and this synthetic strategy was successfully applied to the synthesis of aromatic sesquiterpenes, (±)-cuparene and (±)-laurene.

Experimental

I.r. spectra were obtained with a Hitachi 260-10 spectrophotometer, n.m.r. spectra with JEOL PMX-60 and JEOL JNM FX-100 instruments (tetramethylsilane as internal reference), and mass spectra with a JEOL JMS D-300 spectrometer. M.p.s were determined with a Yanagimoto micro apparatus.

1-p-*Tolylcyclohex*-1-*ene* (**6**).—A solution of cyclohexanone (53 g, 0.54 mol) in anhydrous tetrahydrofuran (THF) (600 ml) was added dropwise to a stirred solution of *p*-tolylmagnesium bromide (**5**) [prepared from magnesium (14.2 g, 0.585 mol) and *p*-bromotoluene (100 g, 0.585 mol)] in anhydrous THF (230 ml) under nitrogen at room temperature. After being stirred for 1 h at room temperature, the mixture was treated with solid ammonium chloride (50 g) and water (500 ml), and extracted with diethyl ether (800 ml). The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded an oily residue which was used directly in the next reaction without further purification. A small portion of the crude oil was chromatographed on silica gel with benzene as eluant, to give 1-*p*-tolylcyclohexan-1-ol as a colourless oil; $\nu_{max.}(CHCl_3)$ 3 400 cm^{-1} (OH); $\delta(CDCl_3)$ 1.10—2.10 (10 H, m, $-CH_2-$), 3.40 (3 H, s, Ar*Me*), 7.10 (2 H, d, *J* 8 Hz, ArH), and 7.38 (2 H, d, *J* 8 Hz, ArH); *m/z* 190 (M^+).

A stirred solution of the above oil in benzene (800 ml) was refluxed for 16 h in the presence of a catalytic amount of toluene-*p*-sulphonic acid. After being cooled, the reaction mixture was washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a brownish oil, which was chromatographed on silica gel (1.5 kg) with hexane as eluant and distilled, to give 1-p-*tolylcyclohex*-1-*ene* (**6**) (75.4 g, 81.2%) as a colourless oil, b.p. 81—82 °C (4 mmHg) (Found: C, 90.65; H, 9.35. $C_{13}H_{16}$ requires C, 90.35; H, 9.45%); $\nu_{max.}(CHCl_3)$ 1 640 cm^{-1} (C=C); $\delta(CDCl_3)$ 1.50—1.90 (4 H, m, 4-H_2 and 5-H_2), 2.00—2.57 (4 H, m, 3-H_2 and 6-H_2), 2.30 (3 H, s, Ar*Me*), 5.90—6.13 (1 H, m, >C=CH–), 6.98 (2 H, d, *J* 9 Hz, ArH), and 7.20 (2 H, d, *J* 9 Hz, ArH); *m/z* 172 (M^+).

6-*Oxo*-6-p-*tolylhexanoic Acid* (**7**).—A stirred solution of compound (**6**) (10 g, 0.058 mol) in dichloromethane (400 ml) was saturated with ozone at −78 °C. The solution was stirred for 10 min, the ozone removed by exchange with nitrogen, and the mixture treated with an excess of dimethyl sulphide (10 ml) then warmed to room temperature. The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded a greenish solid, which was used directly in the next reaction without further purification. A small portion of the crude solid was chromatographed on silica gel with benzene as eluant to give 6-oxo-6-*p*-tolylhexanal as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 720 (CHO), 1 680 (ArCO), and 1 600 cm^{-1} (Ar); δ ($CDCl_3$) 1.10—2.10 (4 H, m, 3-H_2 and 4-H_2), 2.20—2.66 (2 H, m, 2-H_2), 2.42 (3 H, s, Ar*Me*), 2.77—3.20 (2 H, m, 5-H_2), 7.25 (2 H, d, *J* 8 Hz, ArH), 7.82 (2 H, d, *J* 8 Hz, ArH), and 9.75 (1 H, t, *J* 2 Hz, CHO); *m/z* 204 (M^+).

Jones reagent (4M; 50 ml) was added dropwise at 0 °C to a stirred solution of the above residue in acetone (300 ml) and the resultant mixture stirred for 30 min at the same temperature. The reaction mixture was treated with isopropyl alcohol (50 ml) and evaporated under reduced pressure to give a residue, which

was diluted with water (300 ml) and treated with 95% sulphuric acid (10 ml). The resultant precipitate was extracted with ethyl acetate and the organic layer was treated with 20% aqueous sodium hydroxide (150 ml). The aqueous layer was washed with ether, acidified with 95% sulphuric acid, and the resultant precipitate extracted with ethyl acetate. The ethyl acetate extract was dried (Na_2SO_4) and evaporated under reduced pressure to afford a yellow powder, which was recrystallised from ether to give 6-*oxo*-6-p-*tolylhexanoic acid* (**7**) (6.23 g, 49%) as a white powder, m.p. 154—155 °C (from ether) (Found: C, 69.95; H, 7.35. $C_{13}H_{16}O_3 \cdot 0.2\ H_2O$ requires C, 69.75; H, 7.4%); $\nu_{max.}$($CHCl_3$) 3 200 (OH), 1 710 (CO_2H), and 1 680 cm^{-1} (ArCO); δ($CDCl_3$) 1.53—1.94 (4 H, m, 3-H_2 and 4-H_2), 2.16—2.60 (2 H, m, 2-H_2), 2.40 (3 H, s, Ar*Me*), 2.83—3.15 (2 H, m, 5-H_2), 7.23 (2 H, d, *J* 8 Hz, ArH), and 7.82 (2 H, d, *J* 8 Hz, ArH); *m/z* 220 (M^+).

Ethyl 6-*Oxo*-6-p-*tolylhexanoate* (**8**).—A stirred solution of compound (**7**) (20 g, 0.091 mol) in ethanol (800 ml) was refluxed for 5 h in the presence of a catalytic amount of 95% sulphuric acid. The reaction mixture was concentrated under reduced pressure and diluted with ether. The organic solution was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallised from hexane to give *ethyl* 6-*oxo*-6-p-*tolylhexanoate* (**8**) (19.7 g, 87.2%) as colourless prisms, m.p. 44.5—45 °C (from hexane) (Found: C, 72.55; H, 8.1. $C_{15}H_{20}O_3$ requires C, 72.7; H, 8.2%); $\nu_{max.}$($CHCl_3$) 1 720 (CO_2Et), 1 670 (ArCO), and 1 600 cm^{-1} (Ar); δ($CDCl_3$) 1.24 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.53—1.96 (4 H, m, 3-H_2 and 4-H_2), 2.14—2.54 (2 H, m, 2-H_2), 2.37 (3 H, s, Ar*Me*), 2.75—3.10 (2 H, m, 5-H_2), 4.05 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 7.10 (2 H, d, *J* 8 Hz, ArH), and 7.70 (2 H, d, *J* 8 Hz, ArH); *m/z* 248 (M^+).

Ethyl 6-*Hydroxy*-6-p-*tolylheptanoate* (**9**).—Methyl-lithium [1.5M ethereal solution (66.7 ml, 0.1 mol)] was added dropwise to a stirred solution of compound (**8**) (25.1 g, 0.1 mol) in anhydrous toluene (400 ml) under nitrogen at −78 °C; the resultant mixture was stirred for 30 min at the same temperature. The reaction mixture was treated with saturated aqueous ammonium chloride, washed with water and brine, then dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (500 g) with benzene–ethyl acetate (10:1 v/v) as eluant to give *ethyl* 6-*hydroxy*-6-p-*tolylheptanoate* (**9**) (20.1 g, 75%) as a colourless oil (Found: M^+, 264.1725. $C_{16}H_{24}O_3$ requires M^+, 264.1735); $\nu_{max.}$($CHCl_3$) 3 400 (OH) and 1 720 cm^{-1} (C=O); δ($CDCl_3$) 1.00—1.93 (6 H, m, 3-H_2, 4-H_2, and 5-H_2), 1.20 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.48 (3 H, s, 6-Me), 2.03–2.46 (2 H, m, 2-H_2), 2.29 (3 H, s, Ar*Me*), 4.01 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 6.97 (2 H, d, *J* 8 Hz, ArH), and 7.17 (2 H, d, *J* 8 Hz, ArH); *m/z* 264 (M^+).

Ethyl 6-*Phenylthio*-6-p-*tolylheptanoate* (**10**).—To a stirred solution of compound (**9**) (7.87 g, 0.03 ml) in 1,2-dichloroethane (80 ml) was added, in one portion, zinc iodide (4.8 g, 0.015 mol), followed by thiophenol (3.96 g, 0.036 mol) dropwise at room temperature. After being stirred for 10 min under the same reaction conditions, the mixture was diluted with dichloromethane (500 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate, aqueous 2% sodium hydroxide, and brine, then dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (300 g) with benzene as eluant to give *ethyl* 6-*phenylthio*-6-p-*tolylheptanoate* (**10**) (8.65 g, 81.5%) as a colourless oil (Found: C, 74.1; H, 7.9. $C_{22}H_{28}O_2S$ requires C, 74.35; H, 8.05%); $\nu_{max.}$($CHCl_3$) 1 730 cm^{-1} (CO_2Et); δ($CDCl_3$) 1.17 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.57 (3 H, s, 6-Me), 2.28 (3 H, s, Ar*Me*), 4.20 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 6.95 (2 H, d, *J* 8 Hz, ArH), 7.07 (5 H, s, SPh), and 7.17 (2 H, d, *J* 8 Hz, ArH); *m/z* 247 (M^+ − 109).

Ethyl 2-*Hydroxymethylene*-6-*phenylthio*-6-p-*tolylheptanoate* (**11**).—A solution of compound (**10**) (8.4 g, 0.0234 mol) in anhydrous THF (70 ml) was added dropwise to a stirred solution of lithium di-isopropylamide [prepared from di-isopropylamine (11.2 ml, 0.08 mol) and n-butyl-lithium–hexane solution (114 mg ml^{-1}) (26.4 ml, 0.047 mol) at 0 °C] in anhydrous THF (70 ml) under nitrogen at −78 °C; the resultant mixture was stirred for 1 h at this temperature, a solution of ethyl formate (11.2 ml, 0.165 mol) in anhydrous THF (20 ml) was added dropwise, and the resultant mixture stirred for 1 h at −78 °C and warmed to room temperature. The reaction mixture was treated with saturated aqueous ammonium chloride and aqueous 10% hydrochloric acid, and then extracted with ether. The organic layer was washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (300 g) with benzene–hexane (4:1 v/v) as eluant to give the title compound (**11**) (7.8 g, 87%) as a colourless oil; $\nu_{max.}$($CHCl_3$) 1 720 (CO_2Et) and 1 660 cm^{-1} (>C=CHOH); δ($CDCl_3$) 1.18 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.56 (3 H, s, 6-Me), 2.30 (3 H, s, Ar*Me*), 3.15 (0.22 H, m, 2-H), 4.12 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 6.86 (0.78 H, d, *J* 12 Hz, >C=CHO*H*), 6.99 (2 H, d, *J* 9 Hz, ArH), 7.10 (5 H, s, SPh), 7.20 (2 H, d, *J* 9 Hz, ArH), 9.56 (0.22 H, d, *J* 2 Hz, CHO), and 11.33 (0.78 H, d, *J* 12 Hz, >C*H*OH); *m/z* 275 (M^+ − 109).

Ethyl 2-*Diazo*-6-*phenylthio*-6-p-*tolylheptanoate* (**12**).—A solution of toluene-*p*-sulphonyl azide (14.48 g, 73.44 mmol) in dichloromethane (50 ml) at 0 °C was added dropwise to a stirred solution of compound (**11**) (14.1 g, 36.72 mmol) in dichloromethane (250 ml) and the resultant mixture was stirred for 4 h at room temperature. The reaction mixture was evaporated under reduced pressure and diluted with ether. The organic layer was washed with aqueous 10% potassium hydroxide, brine, and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silica gel (500 g) with hexane–dichloromethane (7:3 v/v) and hexane–ethyl acetate (9:1 v/v) as eluant to afford the *title compound* (**12**) (14 g, 100%) as a bright yellow oil (Found: C, 69.1; H, 6.85; N, 7.3. $C_{22}H_{26}N_2O_2S$ requires C, 68.9; H, 6.8; N, 6.85%); $\nu_{max.}$($CHCl_3$) 2 080 (N_2) and 1 680 cm^{-1} (CO_2Et); δ($CDCl_3$) 1.23 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.58 (3 H, s, 6-Me), 2.32 (3 H, s, Ar*Me*), 4.18 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 7.02 (2 H, d, *J* 9 Hz, ArH), 7.12 (5 H, s, SPh), and 7.28 (2 H, d, *J* 9 Hz, ArH); *m/z* 354 (M^+ − 28) and 368 (M^+ − 14).

Treatment of Compound (**12**) *with a Catalytic Amount of Transition Metal Complex.*—(*a*) *Reaction of Compound* (**12**) *with Rhodium Acetate.* A catalytic amount of rhodium(II) acetate was added in one portion to a stirred solution of (**12**) (3 g, 7.85 mmol) in dry benzene (200 ml) under nitrogen at reflux, and reflux was continued for 2 h. The reaction mixture was evaporated under reduced pressure to afford a residue, which was chromatographed on silica gel (100 g) with benzene–hexane (7:3 v/v) as eluant. The first elution afforded a mixture (2.174 g), of compounds (**13**) and (**14**), as an oil; $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1} (CO_2Et); 354 (M^+). The second elution afforded (**10**) (440 mg, 15.8%) as a colourless oil; t.l.c. and spectral data were identical with those of an authentic sample.

A solution of *m*-chloroperbenzoic acid (1.27 g, 7.36 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of the above mixture (2.174 g) in dichloromethane (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml) at room temperature, and stirring was continued for 1 h. The reaction mixture was extracted with dichloromethane, and the organic layer was washed with brine, and dried (Na_2SO_4). After

evaporation of the solvent, the residue was chromatographed on silica gel (50 g) with benzene–hexane (7:3 v/v) and ethyl acetate as eluant. Elution with benzene–hexane furnished *ethyl 5-methyl-5-p-tolylcyclopent-1-ene-1-carboxylate* (**15**) (1 g, 52.2%) as a colourless oil (Found: C, 78.65; H, 8.25. $C_{16}H_{20}O_2$ requires C, 78.4; H, 8.3%); $\nu_{max.}$($CHCl_3$) 1 710 (CO_2Et) and 1 620 cm^{-1} (C=C); δ($CDCl_3$) 1.12 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.66 (3 H, s, 5-Me), 1.93—2.70 (4 H, m, 3-H_2 and 4-H_2), 2.30 (3 H, s, Ar*Me*), 4.03 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 6.90 (1 H, t, *J* 2 Hz, >C=CH–), and 7.09 (4 H, s, ArH); *m/z* 244 (M^+).

Elution with ethyl acetate furnished an oil (785 mg), which was refluxed in toluene (30 ml) in the presence of a trace of calcium carbonate for 12 h with stirring. The reaction mixture was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (30 g) with benzene–hexane (7:3 v/v) as eluant to furnish an inseparable geometrical mixture [218 mg, 11.4% from (**12**)] of *ethyl* 6-p-*tolyl*-2,5-*heptadienoate* (**16a**) and its isomer, the 2,6-*diene* (**16b**), as a colourless oil [(**16a**):(**16b**) = 1:1 w/w]; $\nu_{max.}$($CHCl_3$) 1 710 (CO_2Et) and 1 640 cm^{-1} (C=C); δ($CDCl_3$) 1.24 and 1.28 (each 3 H, each t, each *J* 7 Hz, each CO_2CH_2Me), 2.04 (3 H, s, 6-Me), 2.3 (6 H, s, Ar*Me* × 2), 2.52—3.00 (4 H, m, 4-H_2 and 5-H_2), 3.57 (2 H, t, *J* 7 Hz, 4-H_2), 4.10 and 4.17 (each 2 H, each q, each *J* 7 Hz, each CO_2CH_2Me), 5.02 and 5.25 (each 1 H, each d, each *J* 2 Hz, >C=CH_2), 5.54—6.47 (5 H, m, 2-H × 2, 3-H × 2, and 5-H), and 6.90—7.10 (8 H, m, ArH × 2); *m/z* 244 (M^+).

(*b*) *Reaction of Compound* (**12**) *with Copper Acetylacetonate.* Reaction of compound (**12**) (3.4 g, 8.9 mmol) in the presence of copper acetylacetonate as catalyst was carried out as described above and subsequent oxidative elimination of the crude product gave the compounds (**10**), (**15**), and (**16**) in 20, 58, and 10% yields, respectively.

(*c*) *Reaction of Compound* (**12**) *with* R-1648. Reaction of (**12**) (0.5 g, 1.31 mmol) in the presence of R-1648 as catalyst was carried out as described above. The yields of the compounds (**10**), (**15**), and (**16**) were 36, 10.8, and 30%, respectively.

Ethyl 6-p-*Tolylheptanoate* (**17**).—A suspension of the mixture of (**16a**) and (**16b**) (60 mg) and platinum oxide (10 mg) in methanol (3 ml) was stirred for 10 h under hydrogen (1 atm) at room temperature. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (10 g) with benzene–hexane (1:1 v/v) as eluant to afford *ethyl* 6-p-*tolylheptanoate* (**17**) (45 mg, 74%) as a colourless oil (Found: M^+, 248.1792. $C_{16}H_{24}O_2$ requires M^+, 248.1777); $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1} (CO_2Et); δ($CDCl_3$) 1.20 (3 H, d, *J* 7 Hz, 6-Me), 1.21 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 2.30 (3 H, s, Ar*Me*), 4.08 (2 H, q, *J* 7 Hz, CO_2CH_2Me), and 7.06 (4 H, s, ArH); *m/z* 248 (M^+).

1-*Hydroxymethyl*-5-*methyl*-5-p-*tolylcyclopent*-1-*ene* (**18**).—Di-isobutyl aluminium hydride (25% solution in hexane, 5.76 ml, 10.12 mmol) was added dropwise to a stirred solution of compound (**15**) (1.233 g, 5.06 mmol) in dry toluene (30 ml) under nitrogen at −78 °C, and stirring was continued for 30 min at −78 °C. The reaction mixture was treated with saturated aqueous ammonium chloride with stirring for 2 h, and the resultant white precipitate was filtered, the filtrate diluted with ethyl acetate, and the organic layer washed with brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (5 g) with benzene as eluant to give the *title compound* (**18**) (557 mg, 54.5%) as a colourless oil (Found: M^+, 202.1357. $C_{14}H_{18}O$ requires M^+, 202.1357); $\nu_{max.}$($CHCl_3$) 3 400 (OH) and 1 640 cm^{-1} (C=C); δ($CDCl_3$) 1.33 (1 H, s, OH), 1.43 (3 H, s, 5-Me), 1.83—2.56 (4 H, m, 3-H_2 and 4-H_2), 2.25 (3 H, s, Ar*Me*), 3.86 and 3.93 (each 1 H, each d, each *J* 2 Hz, CH_2OH), 5.76 (1 H, t, *J* 2 Hz, >C=CH–), and 7.09 (4 H, s, ArH); *m/z* 202 (M^+).

1,5-*Dimethyl*-5-p-*tolylcyclopent*-1-*ene* (**19**).—Methanesulphonyl chloride (0.08 ml, 1 mmol) was added dropwise to a stirred solution of compound (**18**) (100 mg, 0.5 mmol) and triethylamine (0.7 ml, 5 mmol) in anhydrous dichloromethane (2 ml) under nitrogen at 0 °C, and stirring was continued for 5 min at 0 °C. The reaction mixture was diluted with ether (30 ml), and the organic layer washed with water and brine, then dried (Na_2SO_4). Evaporation of the solvent afforded the almost pure methanesulphonate (130 mg, 93%), which was used directly in the next reaction without further purification; $\nu_{max.}$($CHCl_3$) 1 640 (C=C) and 1 350 cm^{-1} (SO_2); δ($CDCl_3$) 1.46 (3 H, s, 5-Me), 1.80—2.60 (4 H, m, 3-H_2 and 4-H_2), 2.25 (3 H, s, Ar*Me*), 2.70 (3 H, s, SO_2Me), 4.48 (2 H, br s, CH_2OMS), 5.97 (1 H, br s, >C=CH–), and 7.10 (4 H, s, ArH).

Lithium triethylborohydride (1.0M solution in THF, 0.93 ml) was added dropwise to a stirred solution of the above methanesulphanate (130 mg, 0.47 mmol) in anhydrous THF (1 ml) under nitrogen at 25 °C, and stirring was continued for 30 min at 25 °C. The reaction mixture was diluted with diethyl ether and treated with saturated aqueous ammonium chloride, the organic layer was washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (5 g) with hexane as eluant to furnish the *title compound* (**19**) (60 mg, 68.6%) as a colourless oil; $\nu_{max.}$($CHCl_3$) 1 655 cm^{-1} (C=C); δ(CCl_4) 1.38 (3 H, s, 5-Me), 1.43 (3 H, d, *J* 2 Hz, 1-Me), 1.83—2.55 (4 H, m, 3-H_2 and 4-H_2), 2.26 (3 H, s, Ar*Me*), 5.41 (1 H, m, >C=CH–), and 7.01 (4 H, s, ArH); *m/z* 186 (M^+).

Reduction of Compound (**15**).—(*a*) Sodium borohydride (3.102 g, 82 mmol) was added in portions to a stirred solution of compound (**15**) (996 mg, 4.1 mmol) and nickel chloride (238 mg, 1 mmol) in methanol (30 ml) at room temperature, and stirring was continued for 24 h at room temperature. The reaction mixture was filtered through Celite, and the filtrate was extracted with ether.

The organic layer was washed with saturated aqueous ammonium chloride, brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (20 g) with benzene–hexane (4:1 v/v) as eluant to furnish a mixture (901 mg, 90%) of cis-*ethyl* 2-*methyl*-2-p-*tolylcyclopentane*-1-*carboxylate* (**21**) and its *trans*-isomer (**22**) as a colourless oil [(**21**):(**22**) = 9:2 w/w] (Found: M^+, 246.1630. $C_{16}H_{22}O_2$ requires M^+, 246.1620); $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1} (CO_2Et); (one isomer) δ($CDCl_3$) 0.90 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.37 (3 H, s, 2-Me), 2.30 (3 H, s, Ar*Me*), 2.73—3.10 (1 H, m, 1-H), 3.72 (2 H, q, *J* 7 Hz, CO_2CH_2 Me), 7.00 (2 H, d, *J* 8 Hz, ArH), 7.17 (2 H, d, *J* 8 Hz, ArH); (other isomer) δ($CDCl_3$) 1.20 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.30 (3 H, s, 2-Me), 2.30 (3 H, s, Ar*Me*), 2.73—3.10 (1 H, m, 1-H), 4.10 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 7.00 (2 H, d, *J* 8 Hz, ArH), and 7.17 (2 H, d, *J* 8 Hz, ArH); *m/z* 246 (M^+).

(*b*) A suspension of compound (**15**) (150 mg, 0.61 mmol) and platinum oxide (20 mg) in ethyl acetate (5 ml) was stirred for 18 h under hydrogen (1—3 atm) at room temperature. The reaction mixture was filtered through Celite, and the filtrate was washed with brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (20 g) with benzene–hexane (1:1 v/v) as eluant. The first elution gave ethyl 2-(4-methylcyclohexyl)cyclopentane-1-carboxylate (**20**) (110 mg, 71%) as a colourless oil; δ($CDCl_3$) 0.84 (3 H, s, 2-Me), 1.14 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.30 (3 H, d, *J* 7 Hz, 4-Me), and 4.06 (2 H, q, *J* 7 Hz, CO_2CH_2Me). The second elution gave compound (**21**) (40 mg, 26.5%) as a colourless oil, the spectral data of which were identical with an authentic sample.

(*c*) A suspension of compound (**15**) (70 mg, 0.287 mmol) and platinum oxide (10 mg) in acetic acid (5 ml) was stirred for 3 h

under hydrogen (1 atm) at room temperature. The reaction mixture was filtered through Celite, and the filtrate was washed with brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (10 g) with benzene–hexane (1:1 v/v) as eluant to give compound (**20**) in quantitative yield as a diastereoisomer mixture, having spectral data identical with those of an authentic sample.

(*d*) A suspension of compound (**15**) (250 mg, 1.03 mmol) and platinum oxide (25 mg) in methanol (15 ml) was stirred for 48 h under hydrogen (4 atm) at room temperature. The filtrate was filtered through Celite, and the reaction mixture washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (10 g) with benzene–hexane (1:1 v/v) as eluant to give a trace of compound (**21**), and the unchanged starting material (**15**) as the main product; spectral data were identical with those of authentic samples.

Ethyl 1,2-*Dimethyl*-2-p-*tolylcyclopentane*-1-*carboxylate* (**23**).—A solution of compounds (**21**) and (**22**) (900 mg, 3.66 mmol) in anhydrous hexamethylphosphoric triamide and THF (1:2 v/v) (10 ml) was added dropwise to a stirred solution of lithium di-isopropylamide [prepared from di-isopropylamine (1.78 ml, 12.7 mmol) and n-butyl-lithium–hexane solution (114 mg ml^{-1}) (6.17 ml, 11 mmol) at 0 °C] in anhydrous hexamethylphosphoric triamide (20 ml) and anhydrous THF (40 ml) under nitrogen at 0 °C, and stirring was continued for 2 h at 0 °C. Methyl iodide (2.3 ml, 36.6 mmol) was added at 0 °C, and the resultant mixture was stirred for a further 2 h at room temperature. The reaction mixture was treated with saturated aqueous ammonium chloride and extracted with ether, and the organic layer was washed with brine several times, then dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (50 g) with benzene–hexane (4:1 v/v) as eluant to give the *title compound* (**23**) (851 mg, 89.5%) as a colourless oil (Found: C, 78.4; H, 9.3. $C_{17}H_{24}O_2$ requires C, 78.55; H, 9.45%); $\nu_{max.}(CHCl_3)$ 1 705 cm^{-1} (CO_2Et); $\delta(CDCl_3)$ 0.87 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.33 and 1.40 (each 3 H, each s, Me × 2), 2.28 (3 H, s, Ar*Me*), 3.67 (2 H, q, *J* 7 Hz, CO_2CH_2Me), 6.96 (2 H, d, *J* 9 Hz, ArH), and 7.16 (2 H, d, *J* 9 Hz, ArH); *m/z* 260 (M^+).

2-*Hydroxymethyl*-1,2-*dimethyl*-1-p-*tolylcyclopentane* (**24**).—A solution of compound (**23**) (850 mg, 3.27 mmol) in anhydrous ether (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (199 mg, 5.23 mmol) in anhydrous ether (20 ml) under nitrogen at room temperature, and stirring was continued for 2 h at room temperature. The reaction mixture was diluted with ether (100 ml) and treated with aqueous 25% sodium hydroxide until the aluminium complex decomposed. The resultant white suspension was filtered through Celite, and the filtrate washed with saturated aqueous ammonium chloride, brine, and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silica gel (10 g) with benzene as eluant to furnish the *title compound* (**24**) (650 mg, 91.2%) as a colourless oil (Found: M^+, 218.1669. $C_{15}H_{22}O$ requires M^+, 218.1669); $\nu_{max.}(CHCl_3)$ 3 505 cm^{-1} (OH); $\delta(CDCl_3)$ 0.95 (1 H, s, OH), 1.13 (6 H, s, Me × 2), 1.30 (3 H, s, Me), 2.30 (3 H, s, Ar*Me*), 3.03 (2 H, s, CH_2OH), 7.00 (2 H, d, *J* 8 Hz, ArH), and 7.23 (2 H, d, *J* 8 Hz, ArH); *m/z* 218 (M^+).

1,2-*Dimethyl*-2-p-*tolycyclopentane*-1-*carbaldehyde* (**25**).—Pyridinium chlorochromate (295 mg, 1.37 mmol) was added in one portion to a stirred solution of compound (**24**) (200 mg, 0.92 mmol) in anhydrous dichloromethane (10 ml) under nitrogen at room temperature, and stirring was continued for 3 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the resultant black residue was washed with ether until the solid became a powder. The combined ether was filtered through Celite, and the filtrate was washed with brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (10 g) with benzene–hexane (7:3 v/v) to give the title compound (**25**) (183 mg, 92.3%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 710 cm^{-1} (CHO); $\delta(CDCl_3)$ 1.27 and 1.30 (each 3 H, each s, Me × 2), 2.28 (3 H, s, Ar*Me*), 6.99 (2 H, d, *J* 9 Hz, ArH), 7.15 (2 H, d, *J* 9 Hz, ArH), and 8.92 (1 H, s, *CHO*).

Cuparene (1,2,2-*Trimethyl*-1-p-*tolylcyclopentane*) (**1**).—(*a*) Hydrazine hydrate (80%, 0.5 ml) was added to a stirred solution of compound (**25**) (150 mg, 0.695 mmol) in diethylene glycol (8 ml) and ethylene glycol (2 ml) and the resultant mixture heated at 184 °C for 1.5 h. The mixture was cooled to 70 °C and sodium (0.2 g, 8.7 mmol) in diethylene glycol (2 ml) added. The reaction mixture was heated under reflux for 4 h, cooled, and then poured into ice-cold water. The organic material was extracted with ether and the extract washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the residue was chromatographed on silica gel (10 g) with hexane as eluant to give *cuparene* (**1**) (65 mg, 46.3%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 2 850 cm^{-1} (Me and $-CH_2-$); $\delta(CDCl_3)$ 0.56 (3 H, s, 2β-Me), 1.05 and 1.25 (each 3 H, each s, Me × 2), 2.30 (3 H, s, Ar*Me*), 7.02 (2 H, d, *J* 9 Hz, ArH), and 7.22 (2 H, d, *J* 9 Hz, ArH); *m/z* 202 (M^+).

(*b*) Methanesulphonyl chloride (0.08 ml, 1 mmol) was added dropwise to a stirred solution of (**24**) (100 mg, 0.46 mmol) and triethylamine (0.64 ml, 4.6 mmol) in anhydrous dichloromethane (4 ml) under nitrogen at 0 °C, and stirring was continued for 10 min at room temperature. The reaction mixture was diluted with ether, and the organic layer was washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (5 g) with benzene as eluant to furnish the methanesulphonate (**26**) (135 mg, 99.4%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 350 cm^{-1} (OMs); δ 1.18 and 1.33 (each 3 H, each s, Me × 2), 2.73 (3 H, s, SO_2Me), 3.38 and 3.66 (each 1 H, each d, each *J* 9 Hz, CH_2OMs), 7.01 (2 H, d, *J* 9 Hz, ArH), and 7.19 (2 H, d, *J* 9 Hz, ArH); *m/z* 296 (M^+).

Lithium triethylborohydride (1.0M solution in THF, 1 ml) was added in one portion to a stirred solution of compound (**26**) (135 mg, 0.46 mmol) in anhydrous THF (2 ml) under nitrogen at room temperature, and stirring was continued for 10 h at reflux. The reaction mixture was treated with water and extracted with ether. The organic layer was washed with saturated aqueous ammonium chloride, brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was chromatographed on silica gel (10 g) with hexane and benzene–hexane (7:3 v/v) as eluant. The first elution with hexane gave cuparene (10 mg, 10.8%) as a colourless oil, the t.l.c. and spectral data of which were identical with those of an authentic sample. The second elution with benzene–hexane gave the starting material (70 mg) as a colourless oil, having spectral data identical with those of an authentic sample.

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