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ORGANOBORANES IN ORGANIC SYNTHESIS

IX *. CARBONYLATION PRODUCTS OF ORGANOBORANES DERIVED FROM MYRCENE

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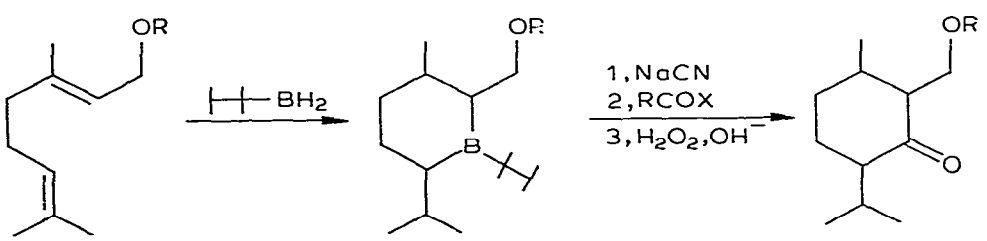
Summary

Myrcene and thexylborane react in the ratio 2/3 to give a mixture of two boranes, only one of which is carbonylated with cyanide/trifluoroacetic anhydride, followed by oxidation, to give 3-hydroxymethyl-6-isopropyl-2-methylcyclohexanone (A). The positions of hydroboration are established by synthesis of the hydroboration/oxidation products. The cyanidation of the organoboranes derived from myrcene and diborane leads to a 2/3 mixture of A and 5-(2′-hydroxyethyl)-2-isopropylcyclohexanone, the structures of which are established by independent synthesis. The hydroboration of myrcene is shown to be relatively non-stereospecific.

Introduction and discussion

In Part IV of this series [1] we investigated the utility of the readily available diene geraniol as a precursor of cyclic ketones via hydroboration—cyanidation [2]. We now report the extension of this work to the readily available triene,



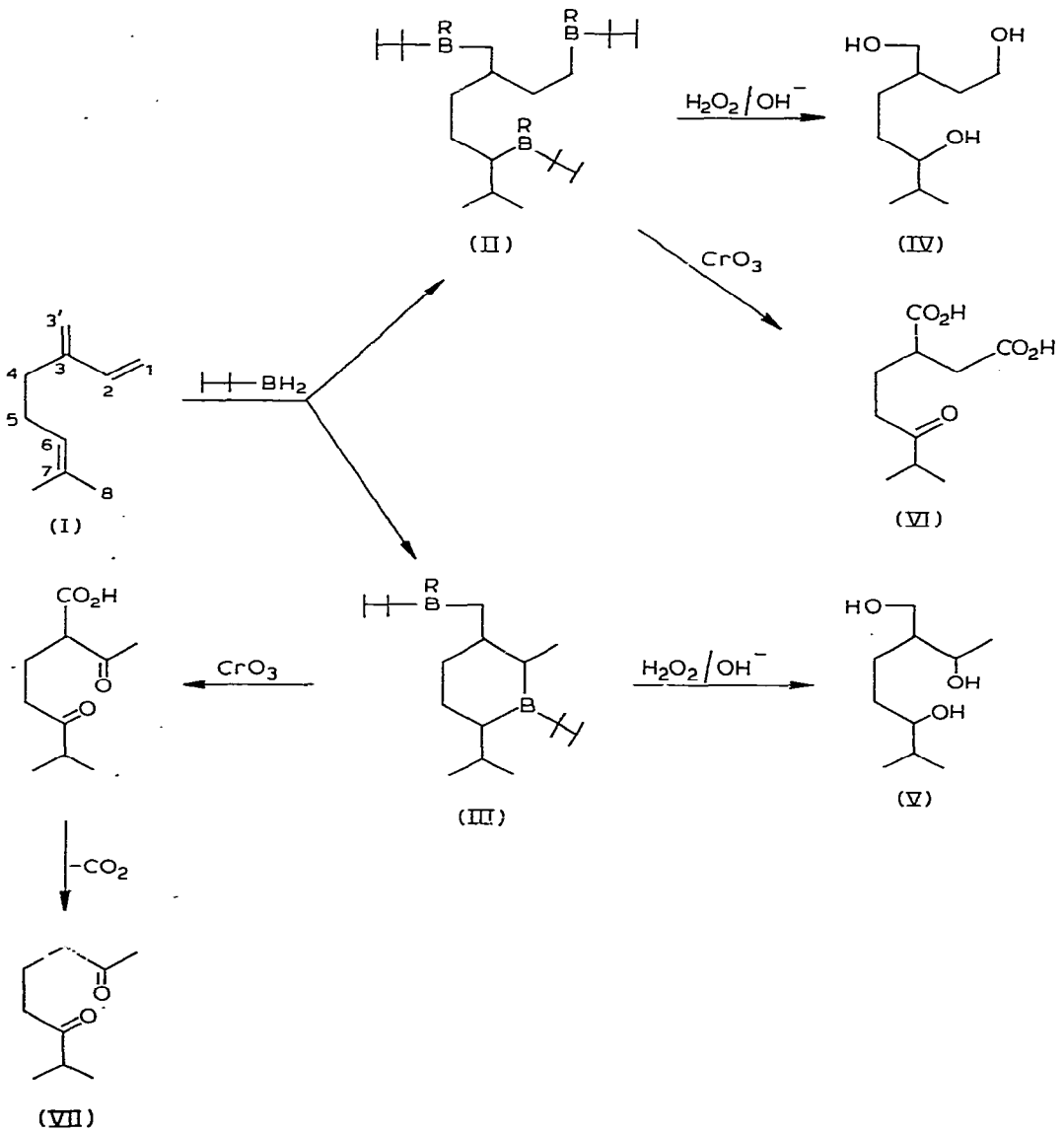
myrcene (I).

* Dedicated to Professor H.C. Brown on the occasion of his 66th birthday. (For Part VIII, see ref. 7).

When myrcene is hydroborated with thexylborane (1,1,2-trimethylpropylborane) in a 1/1 molar ratio, only two thirds of the myrcene is utilised, indicating that all three double bonds within the molecule are attacked by the reagent. Since hydroboration of conjugated dienes frequently gives rise to mixtures of cyclic and acyclic boranes [3,4], the position of hydroboration was first established by oxidation.

Oxidation of the hydroboration mixture gave the triols IV (20%), and V (80%) (Scheme 1), which could not be adequately separated by distillation or chromatography, and their trimethylsilyl ethers were only partially resolved by gas—liquid chromatography (GLC).

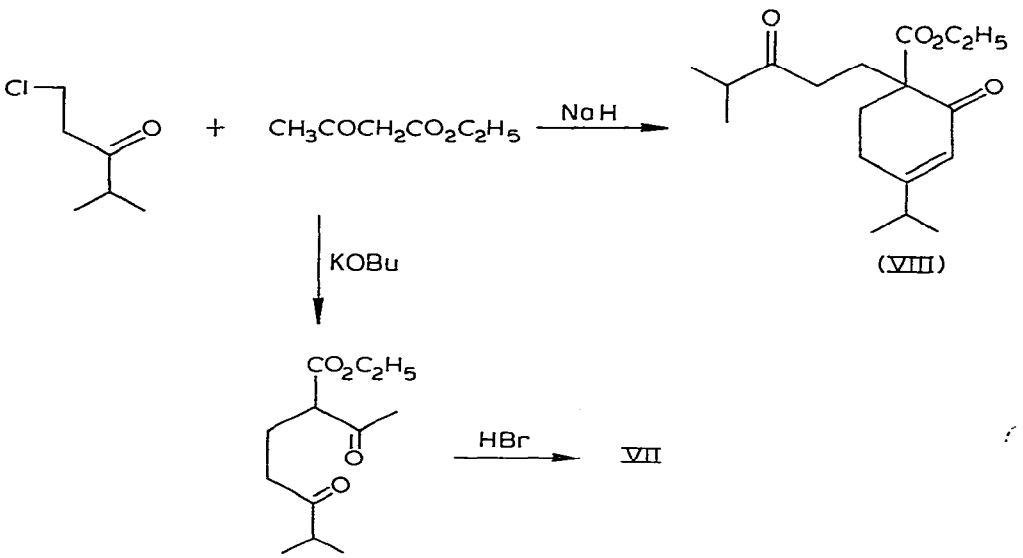
SCHEME 1



Oxidation of the boranes with acidic chromium trioxide [5] gave easily separable products, the dione VII and the ketodiacid VI, which formed the anhydride when dry.

An authentic sample of the diketone VII was prepared as shown in Scheme 2. Alkylation of ethyl acetoacetate with 1-chloro-4-methylpentan-3-one in the presence of a variety of bases led to the formation of VIII *, but reaction in the presence of potassium t-butoxide in tetrahydrofuran gave the required product IX, which was readily decarboxylated to VII.

SCHEME 2



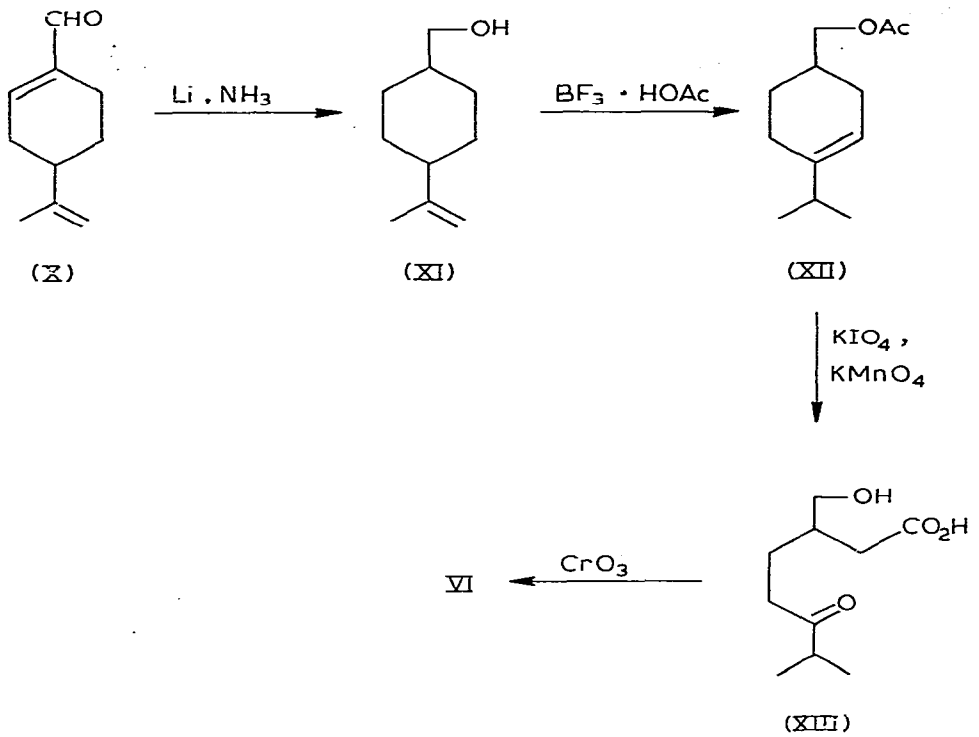
The diacid VI was prepared as shown in Scheme 3. Perillaldehyde (X) was reduced to shisool (XI) by lithium in anhydrous ammonia in the presence of isopropanol [7], and this gave the double-bond rearranged acetate XII (82%) with boron trifluoride/acetic acid [7]. The acetate XII was oxidised to the ketoacid XIII (71%) by potassium permanganate/periodate [8,9], and XIII gave the ketodiacid VI (64%) on oxidation with chromic acid, or the triol IV on reduction with lithium aluminium hydride.

Cyanidation of the borane mixture II + III gave the readily separable mixture of XIV and IV, the latter arising from the polymeric borane II which does not undergo cyanidation. The structure of the ketone XIV was confirmed by synthesis as is shown in Scheme 4.

Hydroboration of the acetate XII, followed by in situ oxidation with chromic acid [5,10] gave the ketoester XV (89%, *cis/trans*, 1/4). Various attempts to introduce a formyl group α to the ketone group of XV were unsuccessful, but treatment with two equivalents of lithium diisopropylamide in ether [11], followed by iodomethane, gave XIV (91%). GLC analysis of XIV showed the presence of three isomers in the ratio of 1/2/4, which changed to 1/4/0.5 after equilibration with acid. This is interpreted in terms of Scheme 5.

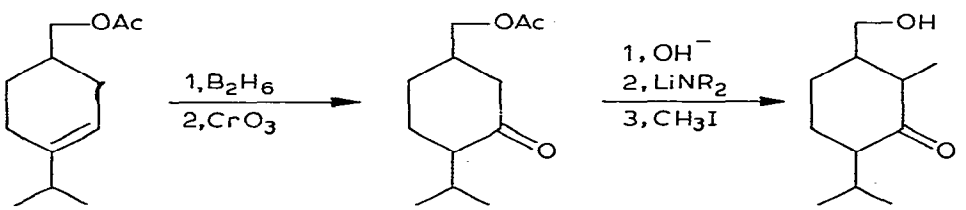
* Sharma et al. [6] claimed a different structure for this product, which was not characterised.

SCHEME 3



(X) (XI) (XII) (XIII)

SCHEME 4

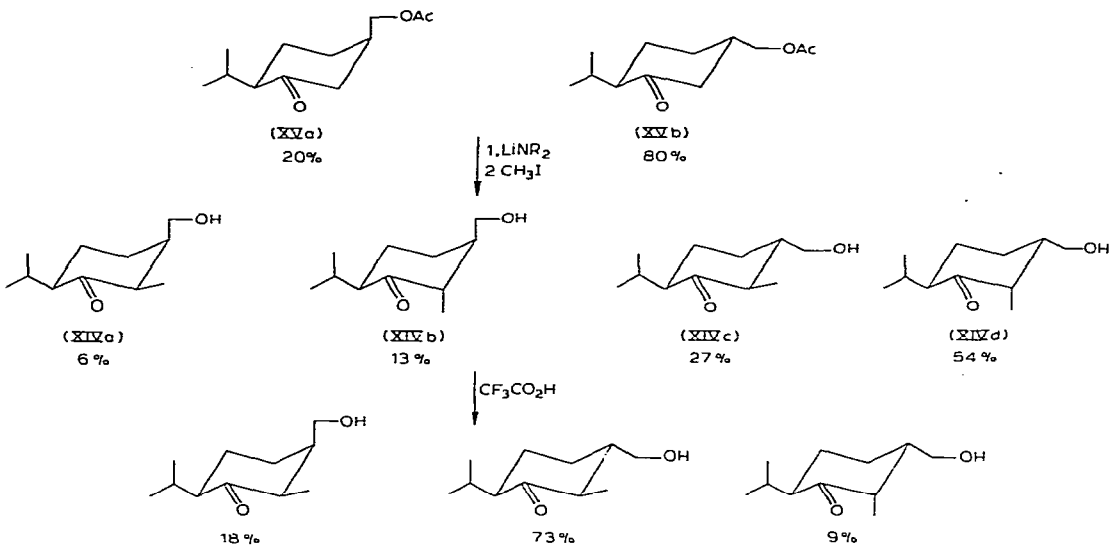


(XII) (XV) (XIV)

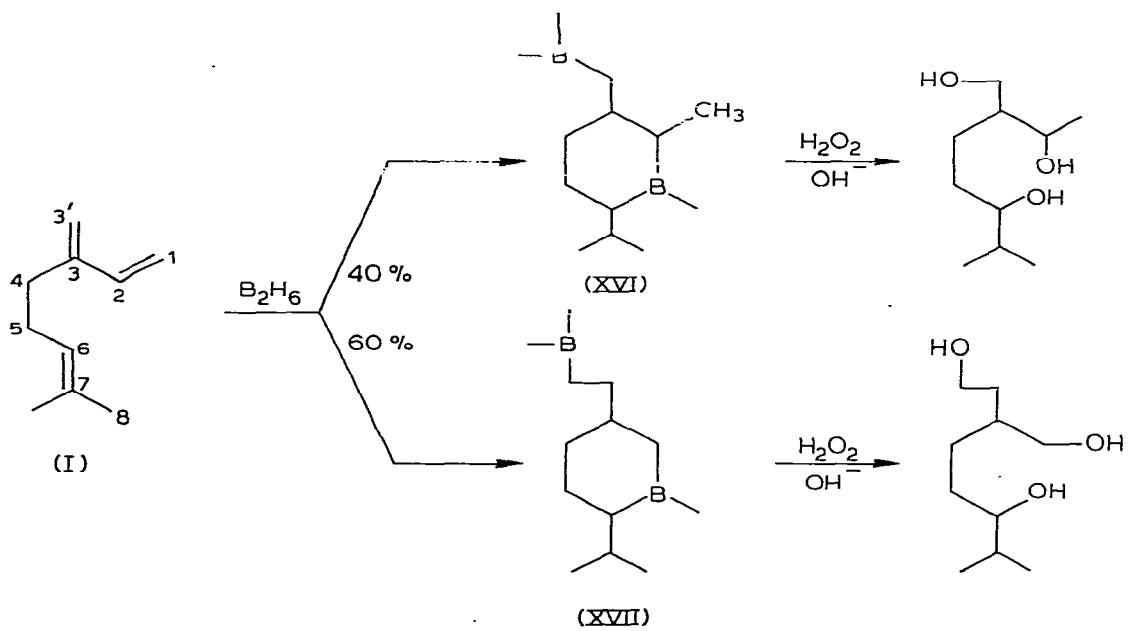
Analysis of the cyanidation product from myrcene showed the presence of XIVa and/or XIVb (20%), XIVc (40%) and XIVd (40%). The relative lack of stereospecificity in the hydroboration of myrcene is presumably due to the stepwise addition of the thexylborane to each double bond.

Hydroboration of myrcene with diborane in 1/1 molar ratio utilizes all available substrate to give a mixture of organoboranes assigned the structures XVI and XVII on the basis of their oxidation products and that both underwent cyanidation. Oxidation with alkaline hydrogen peroxide gave the same mixture of triols as obtained from myrcene and thexylborane, and this was confirmed by oxidation with acidic chromium trioxide which again gave the dione VII and the ketodiacid VI. The absence of B—H groups in the boranes, the structure of the oxidation products, and the nature of the cyanidation products

SCHEME 5



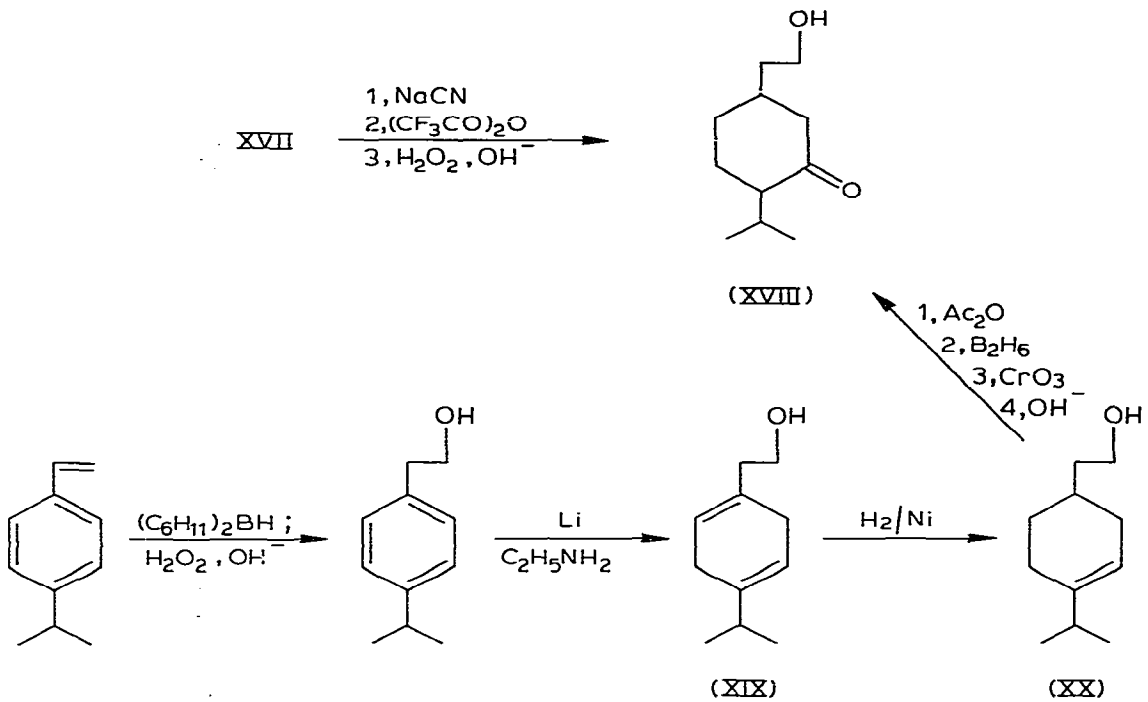
described below then logically leads to structures XVI and XVII for the hydroboration products.



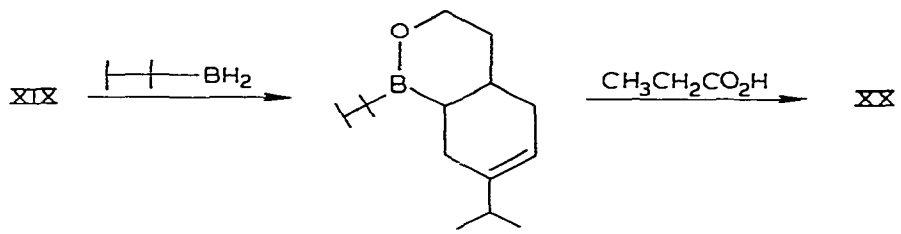
Cyanidation of the mixture of boranes XVI and XVII gave the hydroxyketones XIV and XVIII, separable by chromatography. The former was identical with that obtained above, and the structure of the ketone XVIII was confirmed by an independent synthesis as outlined in Scheme 6.

The isopropylstyrene was synthesised from isopropylacetophenone. Acylation of cumene with acetic anhydride and aluminium chloride gave 4-isopropyl-

SCHEME 6



acetophenone (54%) together with considerable 2,4,6-triisopropylacetophenone and acetophenone, formed by disproportionation. Similar rearrangements under Friedel—Crafts conditions have been observed previously [12]. Hydroboration of 4-isopropylstyrene with dicyclohexylborane gave the 2-phenylethanol (68%), which was reduced almost quantitatively by lithium in anhydrous ethylamine to 2-(2′,5′-dihydro-4′-isopropylphenyl)ethanol (XIX). Partial hydrogenation of



(XXI)

XIX to give XX was achieved in two ways. Treatment of XIX with thexylborane resulted in the formation of the cyclic borinate XXI, which underwent protonolysis with propionic acid to give XX in 60% overall yield.

A more efficient conversion could be achieved by hydrogenation of XIX over P-2 nickel [13], which selectively reduced only the C(1)—C(6) double bond, yielding XX in 84% yield. Presumably the regioselectivity is due to prior coordination of the hydroxyl group to the catalyst. The synthesis was then completed by hydroboration/oxidation of the acetate of XX. GLC analysis of the

synthetic XVIII showed the presence of two isomers in the ratio 3/2, which were also present in the product from cyanidation of myrcene, but in the ratio 2/1, As noted above, the stepwise nature of the hydroboration of myrcene precludes the reaction being stereospecific.

Experimental

General experimental details have been given in Parts I and II [14]. Columns used for GLC analysis were A, 2 m 30% FFAP; B, 3 m 5% Carbowax 20M; C, 3 m 20% Carbowax 20M; D, 3 m 5% Silicone GE XE-60.

Hydroboration of myrcene with thexylborane

Myrcene (1.84 g, 13 mmol) and thexylborane (20 mmol in THF, 20 ml) were added simultaneously [15], over a period of 3 h, to rapidly stirred THF (20 ml) under nitrogen, stirring being continued for a further 20 h. When equimolar quantities of reagents were used, GLC analysis (column A) indicated 34% of the myrcene remained unreacted. The product was a mixture of the boranes II and III.

Oxidation of the products II and III

The combined products II and III were oxidised by stirring the mixture with aqueous 3 *M* potassium hydroxide (25 ml) and hydrogen peroxide (25 ml, 30%) for 3 h at 20°C. Extraction with ether gave a colourless oil (2.06 g, 81%). To a drop of the reaction mixture in dry ether (0.5 ml) was added trimethylsilyl chloride (1 drop) and dry pyridine (2 drops). The sample was allowed to stand for 1 h, and was then subjected to GLC analysis (column A). Complete resolution could not be achieved, but two compounds, IV and V were shown to be present in the approximate ratio of 1 to 4.

Chromic acid oxidation of the boranes II and III

The combined products II and III were subjected to oxidation with chromium trioxide in sulphuric acid [14] (20 ml, 2.67 *M*) by the method of Brown and Garg [5]. The product was extracted with ether (2 × 50 ml), and the ether extracts were washed with aqueous potassium hydroxide (10%, 2 × 50 ml). Removal of the ether gave a ketonic product (1.2 g, 59%) identified as 7-methyl-2,6-octanedione (VII) by direct comparison with the sample synthesized below. ν_{max} 1710s cm^{-1}; NMR: d, 6H, 0.95 (7 Hz), $C\underline{H}_3$; e, 7H, 1.2—2.6, CH; s, 3H, 2.1, $C\underline{H}_3$—CO.

Acidification of the alkaline aqueous extract, followed by extraction with ether, yielded an acidic compound (0.42 g, 15%) identified as 3-carboxy-6-oxo-7-methyloctanoic acid (VI) by comparison with the sample synthesized below. ν_{max} 3450s, 1760s, 1710s, NMR: m, 0.9, 6H, $C\underline{H}_3$; m, 1.5, 2H, $C\underline{H}_2$; m, 2.4, 6H, C<u>H</u>—CO; broad s, 12.9, 2 exchangeable H, $CO_2\underline{H}$.

Synthesis of 7-methyloctan-2,6-dione (VII)

(a) Alkylation of ethyl acetoacetate by 1-chloro-4-methylpentan-3-one. Two representative procedures are given; the results are collected in Table 1.

(i) A solution of ethyl acetoacetate (1.56 g, 12 mmol) and sodium (0.23 g,

10 mmol) in ethanol (10 ml) was stirred at room temperature for 15 min [6]. 1-Chloro-4-methylpentan-3-one [16,17] (1.06 g, 8 mmol) was then added and the mixture stirred at room temperature for a further 6 h. After acidification with hydrochloric acid (2 *M*), the solution was extracted with ether and the organic extract washed thoroughly with water. The extracts were then dried and the solvent removed to give a yellow oil (0.31 g, 27%), 5-isopropyl-2-carbethoxy-2-(4-methyl-3-oxopentyl)cyclohex-5-enone (VIII), b.p. 122—123°C/0.6 mmHg. (Found: C, 69.8; H, 9.6. $C_{18}H_{28}O_4$ calcd.: C, 70.10; H, 9.15%). ν_{max} 1730, 1710, 1670 cm^{-1}; NMR: m, 15H, 1.1, CH_3; e, 10H, 1.3—2.6, CH_2, CH; q, 2H, 4.2 (7 Hz), CH_2—O; s, 1H, 5.8, =CH; mass spectrum: *m/e* 308 (M^+, 8%).

Refluxing the reaction mixture for 2 h, instead of allowing it to stand at room temperature for 6 h, gave the same product (IR, NMR) but in higher yield (0.49 g, 40%).

(ii) The chloroketone (0.135 g, 1 mmol) was added to a stirred solution of ethyl acetoacetate (0.130 g, 1 mmol) and potassium t-butoxide (0.112 g, 1 mmol) in dry THF (5 ml). The solution was stirred for 15 min and then acidified with hydrochloric acid. The organic layer was separated, washed with water and dried. Removal of the solvent gave a colourless oil (0.150 g, 66%), 7-methyl-3-carbethoxy-2,6-octanedione (IX), characterized as the bis(2,4-dinitrophenyl)-hydrazone, m.p. 124—125°C. (Found: C, 49.5; H, 4.9; N, 19.85. $C_{24}H_{26}N_8O_{10}$ calcd.: C, 49.0; H, 4.8; N, 19.1%). IX: ν_{max} 1730, 1700 cm^{-1}; NMR: d, 6H, 1.0 (7 Hz), CH_3; t, 3H, 1.3 (6 Hz), CH_3; s, 3H, 2.1, CH_3; e, 5H, 1.4—2.6, CH_2, CH; t, 1H, 3.3 (7 Hz), CO—CH—CO; q, 2H, 4.1 (6 Hz), CH_2—O; mass spectrum: *m/e* 228 (M^+, 1%). GLC analysis (column B, 150°C) indicated the presence of only one compound with retention time of 6.45 min.

(b) 7-Methyl-2,6-octanedione (VII). Compound IX (0.228 g, 1 mmol) was heated under reflux in hydrobromic acid (48% w/v, 10 ml) for 1 h. The solution was diluted with water and extracted with ether. The organic extracts were washed with water, dried and the solvent removed to give a very pale yellow oil (0.122 g, 79%), 7-methyl-2,6-octanedione (VII), b.p. 64—65°C/1.0 mmHg) (Found: C, 69.5; H, 10.3. $C_9H_{16}O_2$ calcd.: C, 69.2; H, 10.3%). ν_{max} 1710 cm^{-1}; NMR: d, 6H, 1.0 (7 Hz), CH_3; s, 3H, 2.1, CO—CH_3; e, 7H, 1.2—2.6, CH_2, CH; mass spectrum: *m/e* 156 (M^+, 4%). GLC analysis (columns C and D, 100°C) confirmed the identity of VII with the product isolated from the chromic acid oxidation above.

TABLE 1

BASE CATALYSED ALKYLATION OF ETHYL ACETOACETATE BY 1-CHLORO-4-METHYL-PENTAN-3-ONE

Base	Solvent	Reaction time (h)	Temperature (°C)	Product	Yield (%)
Sodium ethoxide	Ethanol	2	78	VIII	40
		6	20	VIII	27
Potassium t-butoxide	t-Butyl alcohol	3	80	VIII	59
		16	20	VIII	42
	Tetrahydrofuran	0.25	20	IX	66
Sodium hydride	Tetrahydrofuran	3	65	VIII	63
Triethylamine	Ether	18	20	VIII	31

3-Oxo-7-acetoxy-p-menthane (XV)

A solution of diborane in anhydrous THF (2.6 *M*, 0.8 ml) was added dropwise to a stirred solution of XII (0.392 g, 2 mmol) in tetrahydrofuran (10 ml) maintained under a nitrogen atmosphere. The solution was stirred for 40 min at room temperature. Chromium trioxide (0.5 g) in aqueous sulphuric acid (50%, 8 ml) was then added [5,10], and the solution warmed to 65°C, and maintained at this temperature for 1 h. After cooling, the solution was extracted with ether and the organic extracts were washed with aqueous 10% sodium carbonate, and water. After drying, removal of the solvent gave 3-oxo-7-acetoxy-*p*-menthane (XV), b.p. 49—50°C/0.01 mmHg as a pale yellow oil (0.37 g, 89%). (Found: C, 67.7; H, 9.15. $C_{12}H_{20}O_3$ calcd.: C, 67.88; H, 9.50%). ν_{max} 1735, 1705 cm^{-1}; NMR: d, 6H, 0.9 (7 Hz), CH_3; e, 9H, 1.2—2.5, CH_2, CH; s, 3H, 2.0, CO—CH_3; m, 2H, 3.9, CH_2—O; mass spectrum: *m/e* 152 ($M^+ - CH_3CO_2H$, 8%). GLC analysis (column D, 120°C) indicated the presence of two isomers (*cis* and *trans*) in the ratio 1/4.

3-Oxo-7-hydroxy-p-menthane

The acetate XV (2.12 g, 10 mmol) was allowed to stand at room temperature for 18 h in methanolic potassium hydroxide (2 *M*; 20 ml). The solution was then diluted with water and extracted with ether. The ether extracts were washed with water, dried and the solvent removed to give 3-oxo-7-hydroyx-*p*-menthane, b.p. 40—41°C/0.01 mmHg as a colourless oil (1.48 g, 87%). (Found: C, 70.8; H, 10.8. $C_{10}H_{18}O_2$ calcd.: C, 70.54; H, 10.66%). ν_{max} 3350, 1705 cm^{-1}; NMR: s, exch., 1H, 3.0, OH; m, 2H, 3.5, CH_2—O; mass spectrum: *m/e* 152 ($M^+ - H_2O$, 12%). GLC analysis (column D, 150°C) indicated no change in the ratio of isomers present.

2-Methyl-3-oxo-7-hydroxy-p-menthane (XIV)

The hydroxy-ketone above (0.170 g, 1 mmol) in anhydrous tetrahydrofuran (2 ml) was added to a solution of lithium diisopropylamide (2 mmol) in tetrahydrofuran, generated from diisopropylamine (0.202 g, 2 mmol) and n-butyllithium, and the resultant solution was maintained under a nitrogen atmosphere at 0°C for 20 min [11]. Iodomethane (0.142 g, 1 mmol) was added and the solution stirred at 0°C for a further 70 min. The solution was acidified with hydrochloric acid (2 *M*) and the organic layer separated and washed thoroughly with water. After drying, removal of the solvent gave 2-methyl-3-oxo-7-hydroxy-*p*-menthane (XIV), b.p. 65—66°C/0.1 mmHg as a colourless oil (0.168 g, 91%). (Found: C, 71.9; H, 11.0. $C_{11}H_{20}O_2$ calcd.: C, 71.69; H, 10.94%). ν_{max} 3400, 1700 cm^{-1}; NMR: m, 6H, 0.9, CH_3; m, 3H, 1.1, CO—C—CH_3; e, 8H, 1.2—2.4, CH_2, CH; s, exch., 1H, 2.3, OH; dd, 3H, 3.3 (6 Hz), CH_2—O; mass spectrum: *m/e* 184 (M^+, 2%). GLC analysis (column D, 150°C) indicated the presence of three isomers, with retention times of 5.4, 6.0 and 6.3 min. respectively, in the ratio 1/2/4. These were shown to be the same as the isomers present in the product of hydroboration—cyanidation of myrcene.

A small sample of the product was dissolved in trifluoroacetic acid and allowed to stand at room temperature for 6 h. After dilution with ether the sample was analyzed by GLC, which indicated the presence of the same isomers as previously observed, but in the ratio of 2/8/1.

3-Hydroxymethyl-6-oxo-7-methyloctanoic acid (XIII)

Olefin XII (0.196 g, 1 mmol) in dioxane (20 ml) was added to a stirred solution of potassium periodate (0.75 g), potassium permanganate (0.05 g) and sodium carbonate (0.03 g) in water (20 ml) [8,9]. The mixture was stirred at room temperature for 40 h, after which excess reagent was decomposed by the dropwise addition of aqueous hydrogen peroxide (30% w/v, 1 ml). After acidification the mixture was extracted with ether and the organic layer was washed with water and then dried. Removal of the solvent gave a pale yellow oil which was molecularly distilled to give 3-hydroxymethyl-6-oxo-7-methyloctanoic acid (XIII) (0.143 g, 71%). (Found: C, 59.3; H, 9.0. $C_{10}H_{18}O_4$ calcd.: C, 59.38; H, 8.97%) ν_{max} 2800, 1750, 1710 cm^{-1}; NMR: d, 6H, 0.9 (7 Hz), CH_3; e, 8H, 1.2—2.4, CH_2, CH; broad s, exch., 2H, 3.3, OH, CO_2H; d, 2H, 3.5 (6 Hz), CH_2—O; mass spectrum: *m/e* 184 ($M^+ - H_2O$, 7%).

3-Carboxy-6-oxo-7-methyloctanoic acid (VI)

Compound XIII (0.202 g, 1 mmol) in acetone (5 ml) was added to an aqueous solution of chromic acid (8 *M*, 5 ml), and the solution was stirred at room temperature for 1 h. Excess reagent was decomposed by the addition of isopropanol (2 ml) and the resultant mixture was diluted with water. Extraction with ether gave a pale yellow syrup (0.137 g, 64%), 3-carboxy-6-oxo-7-methyloctanoic acid (VI), b.p. 128—129°C/0.05 mmHg (Found: C, 55.8; H, 7.35. $C_{10}H_{16}O_5$ calcd.: C, 55.54; H, 7.46%). ν_{max} 3100, 1760, 1710 cm^{-1}; NMR: d, 6H, 0.9 (7 Hz), CH_3; e, 8H, 1.4—2.4, CH_2, CH; broad s, exch., 2H, 9.1, CO_2H; mass spectrum: *m/e* 198 ($M^+ - H_2O$, 1%).

3-Hydroxymethyl-7-methyl-1,6-octanediol (IV)

Compound XIII (0.202 g, 1 mmol) in anhydrous ether (5 ml) was added dropwise to a rapidly stirred suspension of lithium aluminium hydride (0.38 g, 10 mmol) in ether (10 ml). After completion of the addition the reaction mixture was refluxed for 1 h, and the excess reagent was destroyed by the dropwise addition of acetone (3 ml). The mixture was acidified with aqueous sulphuric acid (15% w/v) and the organic layer was separated and washed with water. After drying, the removal of the solvent gave 3-hydroxymethyl-7-methyl-1,6-octanediol (IV), as a viscous syrup (0.079 g, 46%), b.p. 117—120°C/0.01 mmHg (Found: C, 63.5; H, 11.55. $C_{10}H_{22}O_3$ calcd.: C, 63.12; H, 11.65%). ν_{max} 3400 cm^{-1}; NMR: d, 6H, 0.9 (7 Hz), CH_3; e, 8H, 1.2—2.0, CH_2, CH; broad s, exch., 3H, 2.7, OH; m, 5H, 3.9, CH—O; mass spectrum: *m/e* 172 ($M^+ - H_2O$, 3%). GLC analysis (columns A and D, 100°C) of the tris(trimethylsilyl) ether of IV showed it to be identical with the minor product isolated below from the hydroboration-cyanidation of myrcene.

2,6-Dihydroxy-3-hydroxymethyl-7-methyloctane (V)

The diketo ester IX (0.20 g) was reduced by sodium borohydride in ethanol in the usual way to yield the octanediol, which was reduced in benzene by sodium bis(methoxyethoxy)aluminium hydride (REDAL) at 0°C for 1 h. The mixture was worked up by cautious addition of 3 *M* HCl, and ether extraction then gave the triol V, which was purified by TLC (CH_2Cl_2/ether 1/1) to give an oil (0.15 g), b.p. 125°C/0.1 mmHg (Found: C, 63.0; H, 11.8. $C_{10}H_{22}O_3$

calcd.: C, 63.12; H, 11.65%). The NMR spectrum had integrals consistent with structure V, but was poorly resolved due to the presence of the diastereoisomers. GLC analysis (column D, 100°C) of the tris(trimethylsilyl) ether showed it to be identical with the major product isolated below from the hydroboration cyanidation of myrcene.

Cyanidation of the products II and III

The combined product II and III was treated with sodium cyanide (0.98 g, 25 mmol) followed by trifluoroacetic acid anhydride (4.23 ml, 30 mmol) under the conditions described previously. Oxidation with aqueous potassium hydroxide (3 *M*, 25 ml) and hydrogen peroxide (30%, 25 ml) was carried out as previously described [1]. Extraction with ether gave a pale yellow oil, which was chromatographed on alumina, eluting with increasing concentrations of ether in light petroleum. Two colourless oils were obtained. The first (1.44 g, 60%) was identified as 2-methyl-3-hydroxymethyl-6-isopropylcyclohexanone (XIV) by direct comparison with the sample synthesized above. ν_{max} 3400s, 1700s, cm^{-1}; NMR: m, 0.9, 9H, $C\underline{H}_3$; m, 1.5, 6H, $C\underline{H}_2$; m, 2.0, 2H, $C\underline{H}$—CO; broad s, 2.9, 1 exchangeable H, OH; d, 3.6, *J* 6 Hz, 2H, $C\underline{H}_2$—OH.

The second oil (0.37 g, 15%) was identified as 6-hydroxy-3-hydroxymethyl-7-methyloctanol (IV) by comparison with the sample synthesized above.

Hydroboration of myrcene with diborane

Myrcene (20 mmol; 2.76 g) was hydroborated with diborane in THF (0.8 *M*; 25.0 ml) by the addition of the diborane over 2 h from a syringe dropping funnel at 0°C. The solution was stirred for 40 h, after which GLC analysis (column A) indicated complete utilization of starting material. The product was not isolated but was used "in situ".

Cyanidation

The product above was treated with sodium cyanide (25 mmol; 0.98 g), followed by trifluoroacetic anhydride (30 mmol; 4.23 ml) under the conditions described above. Oxidation with aqueous potassium hydroxide (3 *M*; 25 ml) and hydrogen peroxide (30%; 25 ml) was carried out in the usual manner Extraction with ether gave a pale yellow oil which was chromatographed on alumina, eluting with increasing concentrations of ether in light petroleum. Two colourless oils were obtained. The first (0.80 g; 22%) was identified as 3-hydroxymethyl-2-methyl-6-isopropylcyclohexanone, with spectral data identical with that obtained previously. The second (1.26 g; 34%) was identified as 5-(2′-hydroxyethyl)-2-isopropylcyclohexanone. ν_{max} 3400s, 1700s cm^{-1}. NMR: m, 0.9, 6H, $C\underline{H}_3$; m, 1.5, 6H, $C\underline{H}_2$; m, 2.0, 5H, $C\underline{H}$, $C\underline{H}$—CO; broad, s, 2.5, 1 exchangeable H, $O\underline{H}$; t, 3.6 (*J* 6 Hz), 2H, $C\underline{H}_2$—OH. This product had identical GLC retention times and spectral properties as the synthetic sample prepared below.

Oxidation

The hydroboration product was subjected to oxidation with aqueous potassium hydroxide (3 *M*; 25 ml) and hydrogen peroxide (30%; 25 ml) as previously described. Extraction with ether gave a pale yellow oil (3.26 g; 86.8%). GLC

analysis (columns A, B) of the product, as the trimethylsilyl ethers, indicated that the same triols were present as previously, but in the ratio 2/3.

4-Isopropylacetophenone

The method is essentially that of Kuliev [18]. Isopropylbenzene (120 g, 1 mol) in n-hexane (200 ml) was added to a stirred suspension of aluminium chloride (267 g, 2 mol) in n-hexane (400 ml), and the mixture was cooled in an ice/salt bath. Acetic anhydride (118 g, 1 mol) was added, with cooling and rapid stirring, over 1 h and the resultant mixture was stirred for a further 3 h. The reaction mixture was then poured onto ice and hydrochloric acid (36% w/v), and extracted with light petroleum. The organic extracts were washed with aqueous sodium bicarbonate solution (5% w/v) and water, and then dried. Removal of the solvent gave a yellow oil, which upon distillation gave two fractions. The first fraction (85 g, 54%) was 4-isopropylacetophenone [18], b.p. 88—90°C/1.0 mmHg. ν_{max} 1680, 1610 cm^{-1}; NMR: d, 6H, 1.2 (7 Hz), CH_3; s, 3H, 2.5, CO—CH_3; m, 1H, 3.0, CH; m, 4H, 7.5, Ar—H; mass spectrum: *m/e* 162 (M^+, 22%). The second fraction (29.5 g, 12%) was 2,4,6-triisopropylacetophenone, m.p. 83—84°C (lit. 19 m.p. 86—87°C). ν_{max} 1680, 1610 cm^{-1}; NMR: d, 18H, 1.2 (7 Hz), CH_3; s, 3H, 2.5, CO—CH_3; m, 3H, 3.0, CH; s, 2H, 7.3, Ar—H; mass spectrum: *m/e* 246 (M^+, 23%).

1-(4-Isopropylphenyl)ethanol

The acetophenone (50 g, 0.315 mol) in ethanol (100 ml) was added to a stirred suspension of sodium borohydride (13 g, 0.3 mol) in ethanol (100 ml) The mixture was stirred for 1 h and then poured onto ice and sulphuric acid (96%). The mixture was extracted with light petroleum, the extracts dried and the solvent removed. Distillation of the residue gave a colourless oil (50 g, 98%), 1-(4-isopropylphenyl)ethanol [18], b.p. 95—96°C/1.0 mmHg. ν_{max} 3400 cm^{-1}; NMR: d, 6H, 1.2 (7 Hz), CH_3; d, 3H, 1.3 (6 Hz), CH_3; s, exch., 1H, 2.8, OH; m, 1H, 2.7, CH; q, 1H, 4.6 (6 Hz), CH—O; s, 4H, 7.1, Ar—H; mass spectrum: *m/e* 164 (M^+, 34%).

4-Isopropylstyrene

(i) The above alcohol (5 g) was heated under reflux in toluene (20 ml), containing a crystal of iodine [20] for 18 h with azeotropic separation of water. After cooling, the solution was washed thoroughly with aqueous sodium bisulphite (5% w/v) and water, and dried. Distillation of the reaction mixture gave 4-isopropylstyrene, a colourless liquid (1.44 g, 31%), b.p. 44—45°C/1.0 mmHg [18]. ν_{max} 1620 cm^{-1}; NMR: d, 6H, 1.2 (7 Hz), CH_3; m, 1H, 2.8, CH; m, 2H, 5.3, $=CH_2$; m, 1H, 6.6, =CH; m, 4H, 7.2, Ar—H; mass spectrum: *m/e* 146 (M^+, 44%).

(ii) The alcohol (10 g) was added dropwise to molten potassium bisulphate (20 g) maintained at 260°C and under reduced pressure (80 mmHg). Distillate from the reaction mixture was collected and dried, and was identified as 4-isopropylstyrene [18] (7.9 g, 89%), identical in all respects to the product isolated in (i).

2-(4'-Isopropylphenyl)ethanol

The styrene (3.75 g, 25 mmol) in anhydrous THF (10 ml) was added to a solu-

tion of dicyclohexylborane (25 mmol) in THF [21] at 0°C under a nitrogen atmosphere and the solution was maintained at 0°C for 15 h. The reaction mixture was then heated to 65°C in the presence of aqueous potassium hydroxide (3 *M*, 30 ml) and aqueous hydrogen peroxide (30% w/v, 30 ml), and was maintained at 65°C for 3 h. After cooling, the organic layer was separated, washed with water, and dried. Removal of the solvent and distillation of the residue gave a colourless liquid (2.8 g, 68%), 2-(4′-isopropylphenyl)ethanol, b.p. 96—98°C/1.0 mmHg (lit. [22] b.p. 132°C/11 mmHg) ν_{max} 34000 cm^{-1}; NMR: d, 6H, 1.2 (7 Hz), CH_3; s, exch., 1H, 1.8, OH; m, 3H, 2.8, CH_2, CH; t, 2H, 3.7 (7 Hz), CH_2—O; s, 4H, 7.1, Ar—H; mass spectrum: *m/e* 164 (M^+, 49%).

7-Hydroxymethyl-1,4-p-menthadiene (XIX)

The alcohol above (1.64 g, 10 mmol) in anhydrous ethylamine (20 ml) at —78°C under a nitrogen atmosphere was treated with lithium (0.56 g, 0.08 g-atom), added in small pieces over 1 h [23]. The mixture was stirred at —78°C for 12 h, and was then allowed to warm to room temperature. The mixture was diluted with water, and then extracted with light petroleum. The extracts were washed thoroughly with water, dried and the solvent removed to give 7-hydroxymethyl-1,4-*p*-menthadiene (XIX), b.p. 80—81°C/0.1 mmHg as a colourless liquid (1.63 g, 98%). ν_{max} 3380 cm^{-1}; NMR: d, 6H, 1.0 (6 Hz), CH_3; s, exch., 1H, 1.9, OH; m, 3H, 2.2, CH_2, CH; s, 4H, 2.6, ring CH; t, 2H, 3.6 (6 Hz), CH_2—O; m, 2H, 5.4, =CH; mass spectrum: *m/e* 166 (M^+, 59%).

7-Hydroxymethyl-3-menthene (XX)

(i) Compound (XIX) (0.83 g, 5 mmol) in anhydrous THF (10 ml) was added to a stirred solution of thexylborane (5 mmol) in THF under a nitrogen atmosphere. The solution was maintained at room temperature for 1 h and then the solvent was removed in vacuo. The residue was dissolved in propionic acid (10 ml) and the solution heated under reflux for 3 h. After cooling, the solution was diluted with water and extracted with ether. The organic extracts were washed with aqueous sodium carbonate (10% w/v) and water, and then dried. Removal of the solvent gave 7-hydroxymethyl-4-*p*-menthene (XX), b.p. 78—79°C/0.1 mmHg as a colourless liquid (0.50 g, 60%). ν_{max} 3400 cm^{-1}; NMR: d, 6H, 1.0 (6 Hz), CH_3; e, 10H 1.2—2.0, CH_2, CH; s, exch., 1H, 2.2, OH; t, 2H, 3.5 (7 Hz), CH_2—O; m, 1H, 5.5, =CH; mass spectrum: *m/e* 168 (M^+, 7%); 3-nitrohydrogenphthalate m.p. 148—149°C. (Found: C, 62.9; H, 6.5; N, 4.1. $C_{19}H_{23}NO_6$ calcd.: C, 63.14; N, 6.42; H, 3.88%).

(ii) Diene XIX (0.83 g, 5 mmol) in ethanol (20 ml) was hydrogenated over P-2 nickel catalyst [15] at room temperature and 1 atmosphere until 5 mmol of hydrogen had been absorbed. The solution was then allowed to stand in air for 15 min and then diluted with water. Extraction with ether gave a colourless oil (0.71 g, 84%) identified as 7-hydroxymethyl-4-*p*-menthene by its spectral characteristics (IR, NMR, mass spectrum) which were identical to those of the product isolated in (i).

7-Acetoxymethyl-3-p-menthene

Alcohol XX (0.84 g, 5 mmol) was dissolved in acetic anhydride (10 ml) and the solution allowed to stand at room temperature for 18 h. It was then carefully

diluted with water and extracted with ether. The ether extracts were washed with aqueous sodium carbonate (10% w/v) and water, dried, and the solvent removed to give 7-acetoxymethyl-4-*p*-menthene (0.96 g, 91%). ν_{max} 1710 cm^{-1}; NMR: s, 3H, 2.0, $CO—CH_3$; t, 2H, 4.1 (6 Hz), $CH_2—O$.

7-Acetoxymethyl-3-oxo-p-menthane

Diborane in THF (1.5 *M*, 0.70 ml, 1.05 mmol) was added to a stirred solution of the acetate (0.21 g, 1 mmol) in anhydrous THF (10 ml) at 0°C under a nitrogen atmosphere. The reaction mixture was maintained at 0°C for 1 h, and then an aqueous solution of chromic acid [24] (8 *M*, 5 ml) was added, and the mixture was stirred at 0°C for a further 24 h. The organic layer was then separated and washed with aqueous sodium carbonate (10% w/v) and water, and then dried. Removal of the solvent gave 7-acetoxymethyl-3-oxo-*p*-menthane, b.p. 91—92°C/0.1 mmHg as a colourless oil (0.176 g, 78%). (Found: C, 68.7; H, 9.9, $C_{13}H_{22}O_3$ calcd.: C, 68.99; H, 9.80%.) ν_{max} 1710, 1700 cm^{-1}; NMR: m, 6H, 0.9, CH_3; s, 3H, 2.0, $COCH_3$; e, 11H, 1.2—2.6, CH_2, CH; m, 2H, 4.1, $CH_2—O$; mass spectrum: *m/e* 166 ($M^+ - CH_3CO_2H$, 7%).

5-(2'-Hydroxyethyl)-2-isopropylcyclohexanone (XVIII)

The above compound (0.226 g, 1 mmol) was allowed to stand in methanolic potassium hydroxide (2 *M*, 3 ml) at room temperature for 18 h. The solution was then diluted with water and extracted with ether. After washing the organic extracts with water, they were dried and the solvent removed to give a colourless oil (0.151 g, 82%), 5-(2'-hydroxyethyl)-2-isopropylcyclohexanone (XVIII), b.p. 77—78°C/0.9 mmHg (Found: C, 71.65; H, 11.0. $C_{11}H_{20}O_2$ calcd.: C, 71.69; H, 10.94%) ν_{max} 3400, 1700 cm^{-1}; NMR: m, 6H, 0.9, CH_3; s, exch. 1H, 1.9, OH; e, 11H, 1.2—2.6, CH_2, CH; m, 2H, 3.4, $CH_2—O$; mass spectrum: *m/e* 184 (M^+, 1%). GLC analysis (columns B and D, 150°C) indicated the presence of two isomers with retention times of 7.8 and 8.4 min, in the ratio 3/2. These products were shown to be identical to those obtained by the hydroboration-cyanidation of myrcene, above.

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