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THE STEREOCHEMISTRY OF L-LANCEOL AND THE SYNTHESIS OF ITS RACEMATE

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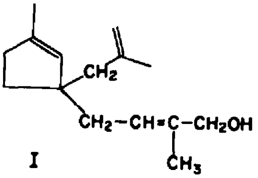
Abstract—The *trans*-configuration of the isopropenyl carbinol group in D-lanceol has been established by means of NMR, UV and IR spectral determinations and by the synthesis of racemic lanceol.

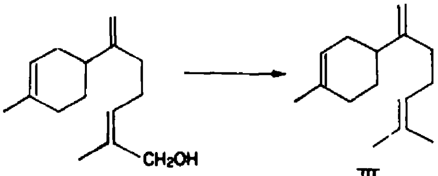
The sesquiterpenic alcohol lanceol, $C_{15}H_{24}O$, was isolated in 1928 by Penfold[1] from the essential oil of the wood of *Santalum lanceolatum*. Later, in 1954, Nave[2] obtained lanceol from the essential oil of *Osyris teunofolia.*

Lanceol was first investigated by Bradfield *et al.*[3] who proposed structure I, based on the reactions performed.



I

Later, Owen,[4] and Birch and Murray,[5] proved the correct structure to be II.



II

III

This formula contains the classic skeleton of the monocyclic sesquiterpenes as was proved by Birch *et al.* by reduction of lanceol to *β*-bisabolene (III).

Mills[6] correlated the molecular rotations of *β*-bisabalene (−157°), limonene (−169°) and lanceol (−152°), establishing the configuration of L-lanceol as shown in IV.

However, since this structure was based, mainly, on the different products obtained by ozonolysis, it was not possible to establish the orientation of the isopropenyl

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* Taken in part from a D.Sc. thesis to be presented to the Universidad Nacional Autónoma de México.

[1] A. R. Penfold, *Chem. Abstr.* **23**, 474 (1929).

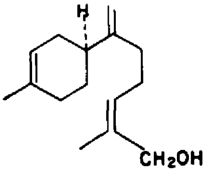
[2] Y. R. Nave and P. Ardizio, *Bull. Soc. Chim. Fr.* D.1-**107**, 334 (1954).

[3] A. E. Bradfield, E. M. Francis, A. R. Penfold and J. L. Simonsen, *J. Chem. Soc.* 1619 (1936).

[4] L. N. Owen, *J. Chem. Soc.* 1582 (1949).

[5] A. J. Birch and A. R. Murray, *J. Chem. Soc.* 1888 (1951).

[6] J. A. Mills, *J. Chem. Soc.* 4976 (1962).



IV

alcohol. In the present paper, complete proof of the structure is sought by application of the following information. The configuration of tiglic and angelic acids have been unequivocally established[7,8] and Cason[9] has determined the UV maxima of several 2-methyl-2-alkene acids (Table 1).

TABLE 1. ULTRAVIOLET SPECTRAL MAXIMA FOR SOME 2-METHYL-2-ALKENE ACIDS[9]

	$\lambda_{max}^{(Hexane)}$	ε
Tiglic acid	214	12600
Angelic acid	217	9000
trans-2-Methyl-2-pentenoic acid	215·5	13200
trans-2-Methyl-2-hexenoic acid	217	13580
cis-2-Methyl-2-hexenoic acid	218	8780
trans-2-Methyl-2-heptenoic acid	217	13800

These data are in agreement with the stuctures of the other acids, as proposed by different authors (Table 2).

TABLE 2. ULTRAVIOLET SPECTRAL MAXIMA FOR SOME UNSATURATED ACIDS

	$\lambda_{max}^{(Hexane)}$	ε
trans-2,4-Dimethylheneicosenoic acid	216	12600[10]
trans-2,5-Dimethylheneicosenoic acid	217–218	12600[10]
2-Methyl-2-eicosenoic acid	217	13500[9]
2-Methyl-2-hexacosenoic acid	217	14000[9]
C_{22}-Phtienoic acid	216	11140[9]
2,5-Dimethylheptadecenoic acid	218·5	12700[11]

When lanceal[*,3] was oxidized with silver oxide, lanceolic acid, $C_{15}H_{22}O_2$, was obtained; n_D^{25} 1·5099, $[\alpha]_D^{25}$ −55·5, λ_{max} 219, ε 12,788 (hexane). This acid was characterized as its methyl ester, for which the spectroscopic data agree with a *trans*-2-methylalkene acid, in accordance with the following observations. Freeman,[12] Stenhagen[10] and Cason[9] have found characteristic differences in the IR spectra of the *trans*-2-methylalkene acids and their corresponding *cis*-isomers. The most important difference is that the carbon-carbon stretching band for the cis-acids is at 6·11 μ, and for the *trans*, at 6·09 μ. Another region characteristic for all the *trans*-isomers is the double band at 6·85 and 7·03 μ with the band at 6·85 μ much weaker and sometimes

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[*] The aldehyde was obtained from lanceol, kindly given to us by Professor Y. R. Navé, Switzerland

[7] L. Crombie, *Quart Revs.* VI–2, 101 (1952).

[8] C. S. Marvel, in Gilman's *Organic Chemistry* (2nd Edition) p. 444 (1943).

[9] J. Cason and M. J. Kalm, *J. Org. Chem.* 1950 (1959).

[10] S. S. Stenhagen, *Arkiv Kemi* **6**, 537 (1954).

[11] J. Cason, N. L. Allinger and C. F. Allen, *J. Org. Chem.* **18**, 857 (1953).

[12] N. K. Freeman, *J. Amer. Chem. Soc.* 1859 (1953).

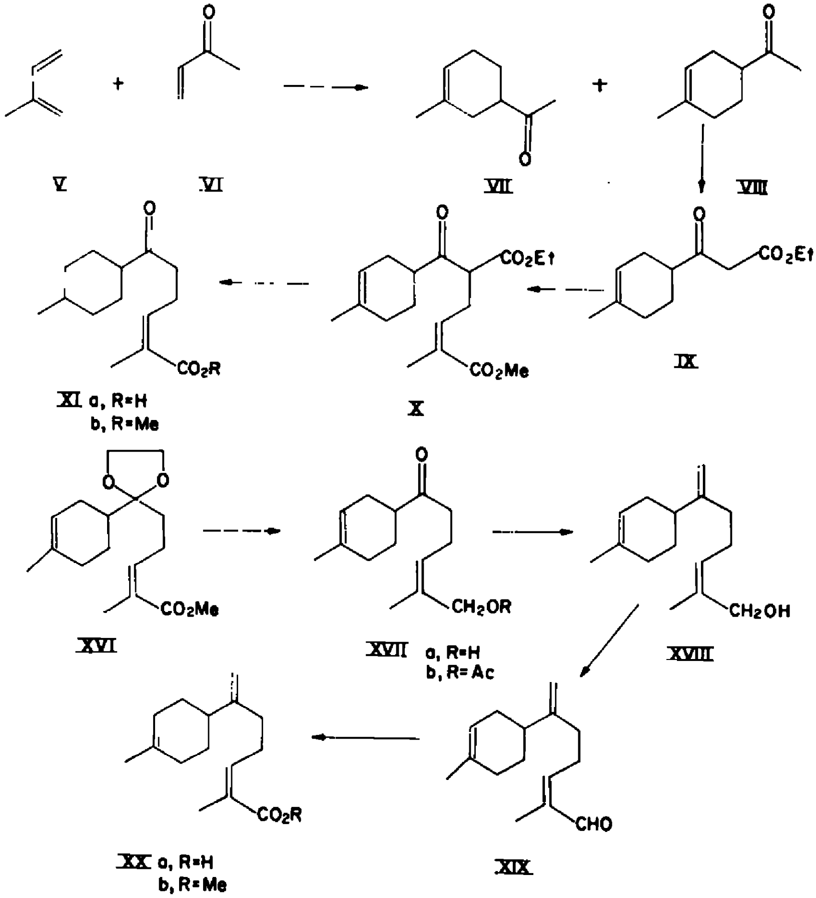
even as a shoulder. In the *cis*-isomers the band at 6·80 μ is the stronger of the two. Another double band which serves to differentiate between the *cis* and *trans*-isomers is the two overlapping carboxyl bands at about 7·8 and 8 μ. Freeman[12] has pointed out that in all the *trans*-α-methyl-α,β-unsaturated acids, the second band is the weaker, while the opposite holds for the *cis*-isomers. Thus, the relative intensities of two pairs of bands are reversed in the *cis* and *trans*-isomers.

For lanceolic acid the band at 6·84 μ is weaker than that at 7·03 μ, and absorption at 7·8 μ stronger than that at 8 μ.

Jackman[13] has observed differences between the vinyl and allylic proton resonances in the NMR spectra of methyl tiglate and methyl angelate. The vinyl proton resonance for the methyl angelate is at 6·05 p.p.m. and for methyl tiglate at 6·8 p.p.m. Methyl lanceolate, obtained by treatment of lanceolic acid with diazomethane, presents vinylic proton absorption at 6·64 p.p.m.

The excellent correlation of the data obtained in the UV, IR and NMR spectra is in agreement with a *trans*-configuration for the isopropenyl carbinol group of lanceol.

To substantiate the conclusions arrived at by consideration of spectral evidence, lanceol was synthesized as follows:



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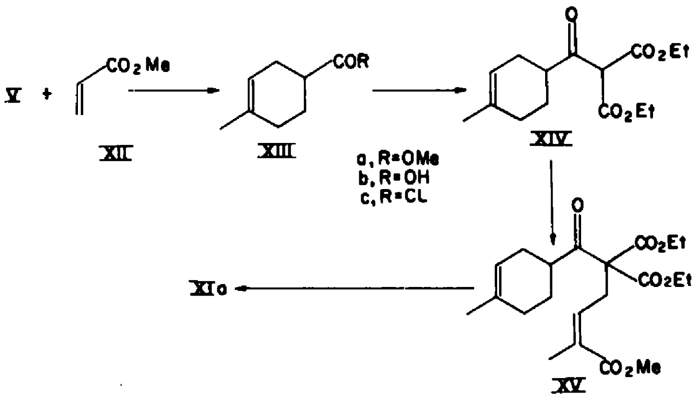
[13] L. M. Jackman, *Applications of nuclear magnetic resonance spectroscopy in organic chemistry* p. 122. Pergamon Press (1959).

A Diels–Alder addition reaction between isoprene (V) and methyl vinyl ketone (VI) was carried out according to Alder and Vogt,[14] and the ketonic products (VII and VIII) were separated by fractional crystallization of the semicarbazones, followed by acid hydrolysis. Ethyl β-keto-β-(4-methyl-Δ^3-cyclohexenyl) propionate (IX), obtained earlier by Eschenmoser *et al.*[15] in 49% yield, was prepared from the ketone (VIII) by treatment with diethyl carbonate and sodium hydride, in a mixture of benzene–dimethyl formamide 3 : 1, with 68% yield. Condensation of the keto ester (IX) with methyl γ-bromotiglate, prepared by the method of Inhoffen,[16] was effected using sodium hydride as condensing agent. In the NMR spectrum of methyl γ-bromotiglate a signal for the vinyl proton at 6·95 p.p.m. was observed. Therefore, it was assumed that the methyl α-methylcarbethoxy-ε-keto-ε-(4-methyl-Δ^3-cyclohexenyl)-Δ^2-hexenoate (X) obtained, has the desired *trans*-configuration. The ester (X) was hydrolysed and decarboxylated, yielding α-methyl-ε-keto-ε-(4-methyl-Δ^3-cyclohexenyl)-Δ^2-hexenoic acid (XIa) which was characterized as the semicarbazone. This acid (XIa) was also prepared in accordance with the following route:



The acid (XIIIb) obtained previously by Meldrum and Perkin,[17] was prepared by hydrolysis of the ester (XIIIa) which was in turn synthesized by condensation of isoprene and methyl acrylate.[14] Condensation of the derived acid chloride (XIIIc) with diethyl malonate yielded ethyl α-carbethoxy-β-keto-β-(4-methyl-Δ^3-cyclohexenyl) propionate (XIV). This keto diester was condensed with methyl γ-bromotiglate to yield methyl α-methyldicarbethoxy-ε-keto-ε-(4-methyl-Δ^3-cyclohexenyl)-Δ^2-hexenoate (XV); semicarbazone m.p. 83–86°. After hydrolysis and decarboxylation, the acid (XIa) was obtained. The carboxyl group was esterified with diazomethane to afford the keto methyl ester (XIb, characterized as its semicarbazone m.p. 157–159°) which showed in the NMR spectrum a peak at 6·7 p.p.m.

The UV and the NMR data are consistent with a *trans*-configuration of both intermediates (XIa and XIb).

When the keto ester (XIb) was treated with an ethereal solution of triphenylmethylenephosphonium, a mixture of products was obtained which showed a very

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[14] K. Alder and W. Vogt, *Liebigs Ann.* **564**, 109 (1949).

[15] A. Eschenmoser, J. Schreiber and W. Keller, *Helv. Chim. Acta* **34**, 1667–71 (1951).

[16] H. H. Inhoffen, S. Bork and M. Schwieter, *Liebigs Ann.* **580**, 1 (1953)

[17] A. N. Meldrum and W. H. Perkin, *J. Chem. Soc.* **93**, 1425 (1908).

weak band of methylene at 890 cm^{-1} in the IR spectrum. To improve the yield of the Wittig reaction, the keto ester (XIb) was ketalized with ethylene glycol and reduced with lithium aluminium hydride to the corresponding alcohol. Acid hydrolysis yielded the keto alcohol (XVIIa) and the Wittig reaction was then carried out with the acetate (XVIIb). The reaction product was treated with lithium aluminum hydride giving 54% of an alcohol, b.p. 113–116/0·1 mm, n_D^{25} 1·5102 and an IR spectrum identical with that of natural lanceol. The aldehyde[3] obtained by oxidation with chromium trioxide–pyridine complex gives the same semicarbazone (m.p. and IR) as that obtained from natural lanceol.

EXPERIMENTAL[*]

Lanceal (XIX). To a cold solution of 500 mg chromium trioxide in 25 ml pyridine, 1 g natural lanceol (b.p. 114–116°/0·1 mm; n_D^{25} 1·5087; [α] −67°) was added with mechanical stirring.

After 24 hr at 5°, the mixture was filtered, and the clear solution diluted with water and extracted with ether. The ethereal solution was washed successively with 10% HCl and water, then concentrated to give 920 mg of an oil which was chromatographed on 50 g alumina, F-20. From the fractions eluted with benzene, 840 mg of an oil was obtained, which showed ν_{max} 2950, 2750, 1710, 1660, 1450, 1385, 1120 and 890 cm^{-1}; λ_{max}^{EtOH} 230 mμ, ε 5420; and [α] −69·5°. The semicarbazone, crystallized from methanol–water, m.p. 151–153°; reported, 151–153°.[3]

Lanceolic acid (XXa). A solution of 820 mg lanceal in 4 ml ethanol was mixed with 2·34 g silver nitrate in 20 ml water. Potassium hydroxide (1·55 g) dissolved in 20 ml water was then added dropwise with stirring (2 hr), and stirring continued for 4 hr. After filtration (washing filter with water) the solution was acidified and extracted, yielding 620 mg of an oil which was chromatographed over 30 g silica gel. From the benzene fractions 520 mg of an oily acid was obtained, ν_{max} 2960, 1695, 1650, 1460, 1430, 1280, 1250 and 892 cm^{-1}; λ_{max}^{Hex} 219 mμ, ε 12788; n_D^{25} 1·5099; $[\alpha]_D^{25}$ −56.

Methyl lanceolate (XXb). A solution of 500 mg lanceolic acid in 50 ml ether was mixed with an ethereal solution of diazomethane prepared from 1 g N-nitrosomethylurea. After 30 min, the excess diazomethane was destroyed with acetic acid. The ethereal solution was washed with dil NaOH and water, and evaporated to dryness. The oily residue (420 mg) was purified by chromatography over 25 g alumina, F-20. From the hexane–benzene 1:1 fractions, 350 mg of an oil was obtained, ν_{max} 2950, 1740, 1650, 1445, 1380, 1145 and 892; λ_{max}^{Hex} 217 mμ, ε 11496; n_D^{25} 1·5058; $[\alpha]_D^{25}$ −62; NMR. 6·64 p.p.m. (Found: C, 77·63; H, 9·93; O, 12·64; $C_{16}H_{24}O_2$ requires: C, 77·37; H, 9·74; O, 12·88%).

4-*Methyl*-1-*acetyl*-Δ^3-*cyclohexene* (VIII). A mixture of 100 g methyl vinyl ketone, 103·5 g isoprene and 2 g hydroquinone was heated at 150° during 5 hr in a sealed tube. The liquid obtained was distilled and the fraction b.p. 45–47°/0·5 mm (68 g) was refluxed for 1 hr with 250 ml alcohol, 70 g semicarbazide hydrochloride and 20 ml water. The solution crystallized on cooling and the crystals were washed with hot water and extracted with hot benzene. The insoluble material (3·8 g) was recrystallized from alcohol m.p. 165–169°. This semicarbazone corresponds with that of the ketone VII.[14]

The benzene solution was concentrated and 63 g of a crystalline material was obtained; recrystallization from alcohol gave 62·3 g pure semicarbazone of the ketone VIII, m.p. 147–149° (reported 149[illegible]). Hydrolysis of the semicarbazone was effected on 62 g suspended in 800 ml hexane by the addition of 715 ml 1N H_2SO_4. The mixture was stirred at room temp until all the solid had disappeared (48 hr). The organic layer was separated, washed thoroughly with water and evaporated yielding 44·5 g of a liquid, which was purified by distillation (45–47°/0·5 mm) to afford 37 g of oil; n_D^{25} 1·4710; ν_{max} 2900, 1720, 1435, 1355 and 1165 cm^{-1}.

Ethyl-β-keto-β-(4-methyl-Δ^3*-cyclohexenyl) propionate* (IX). A solution of 50 g ethyl carbonate in 300 ml anhydrous, thiophene free benzene and 100 ml dimethyl formamide was placed in a 3-necked

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[*] M.ps were determined in a Kofler block. IR spectra were determined in film on a Perkin-Elmer model 21 spectrophotometer, and the UV spectra with a Beckman D-K 2 or a D.U. spectrophotometer. The NMR spectra were determined in CCl_4 solution containing T.M.S. as internal standard using a Varian A-60 machine. Chemical shifts are given in p.p.m. (δ). Unless otherwise specified, distillations were carried out through a 20 cm Wiedmer column. Microanalysis were determined by Dr. F. Pascher, Bonn, Germany.

flask, fitted with a mechanical stirrer, a dropping funnel, and a condenser, through which a stream of N_2 was passed. To this solution, 22 g of a 50% sodium hydride suspension in Nujol was added. The mixture was heated to boiling and then 30 g of ketone VIII was added dropwise; hydrogen being evolved immediately. After the addition was complete (30 min) heating was prolonged for another 30 min. The mixture was cooled and poured into water and the organic layer was separate, washed with water and dried (Na_2SO_4). After removal of the solvent 36·6 g of a reddish liquid was obtained. This was purified by distillation, b.p. 98–100°/1 mm; n_D^{25} 1·4760 (31 g) reported 142–143°/11 mm n_D^{24} 1·4760.[16] This liquid gave a positive $FeCl_3$ test; ν_{max} 2895, 1740, 1710, 1650, 1600, 1440, 1370, 1260, 1115, 1030, 1015, 915 and 845 cm^{-1}.

α-Methyl-ε-keto-ε-(4-methyl-Δ³-cyclohexenyl)Δ² hexenoic acid (XIa). To a suspension of 7 g sodium hydride in Nujol (50%) in 300 ml of a mixture benzene–dimethylformamide 3:1 30 g of the keto ester IX were slowly added with stirring. After the addition was complete, gentle reflux was started and 27·5 g methyl γ-bromotiglate were added. Reflux was maintained during 3 hr and then the mixture was poured into water. The organic layer was worked up as usual to afford 52 g of a red-brown material, 35 g of which distilled at 152–160/0.05 mm; ν_{max} 2895, 1740, 1710, 1630, 1440, 1370, 1260, 1155, 1030, 1015, 915 and 845 cm^{-1}. This material was hydrolysed with a solution of 9 g KOH in 50 ml water and 100 ml methanol. After 6 hr refluxing, the mixture was concentrated and poured into water. The acidic material was isolated in the usual manner and chromatographed over acidic alumina. By elution with 4:1 benzene–ether mixture, 20·5 g of an oily acid was obtained (λ_{max}^{Hex} 221 mμ, ε 12608; ν_{max} 2895, 1740, 1710, 1650, 1600, 1440, 1370, 1030, 915 and 845 cm^{-1}). The derived semicarbazone had m.p. 203–204°. (Found: C, 61·89; H, 7·83; O, 16·30; N, 14·05; $C_{15}H_{23}O_3N_3$ requires: C, 61·41; H, 7·90; O, 16·36; N, 14·33%.)

4-*Methyl*-1-*carboxy-Δ³-cyclohexene* (XIIIb). A mixture of 30 g isoprene, 26 g methyl acrylate and 2 g hydroquinone was heated at 150° for 5 hr in a sealed tube, and then distilled affording 42·2 g of oil b.p. 60–63°/6 mm (reported 83–86°/13 mm); ν_{max} 2850, 1735, 1430, 1375, 1165, 1050 and 920 cm^{-1}. This product was saponified in methanol (100 ml) with 20 ml 50% KOH aq. After refluxing 4 hr, the acidic material was isolated in the usual way to give 31·6 g of a solid which was recrystallized from hexane; m.p. 97–99° (reported 98–99°); $\nu_{max}^{CCl_4}$ 2900, 1710, 1440, 1380, 1140, 1075 and 1025 cm^{-1}.

Ethyl α-carbethoxy-β-keto-(methyl-Δ³-cyclohexenyl) propionate (XIV). Thionyl chloride (70 g) was added dropwise, at room temp to a solution of 30 g of the acid (XIIIb) in 60 ml benzene. Vigorous evolution of hydrogen chloride commenced immediately and after 1 hr at room temp the mixture was distilled yielding 26 g of a liquid b.p. 95–104°/30 mm, ν_{max} 2900, 1795, 1440, 1380, 1140, 1075, 1025 and 918 cm^{-1}.

Condensation of this acid chloride and diethyl malonate was achieved using the same 3-necked flask arrangement described above, to which 6 g of a sodium hydride suspension in Nujol (50%) and 150 ml of a benzene–dimethyl formamide 3:1 mixture had been added. To this suspension were slowly added at room temp, 20 g diethyl malonate; when the addition was completed (30 min) 20 g of the acid chloride were added and the mixture refluxed for 3 hr. The organic layer was washed with water, dried and evaporated yielding 25 g of a liquid which was distilled affording a fraction (16 g) b.p. 136–140°/0·75 mm; ν_{max} 2895, 1740, 1710, 1440, 1370, 1260, 1155, 1030 and 845 cm^{-1}, and showing a positive $FeCl_3$ test.

Methyl α-methyl-δ,δ-dicarbethoxy-ε-keto,ε-(methyl-Δ³-cyclohexenyl)-Δ²-hexenoate (XV). Condensation of 15 g of the ketone (XIV) with 11 g methyl γ-bromotiglate was achieved as above giving 21 g of an oil which was chromatographed over 1 Kg of alumina, F-20. From the fractions eluted with hexane–ether 1:1, 10 g of a clear oil was obtained; ν_{max} 2950, 1750, 1730, 1720, 1650, 1430, 1365, 1320, 1210, 1075 and 1030 cm^{-1}, showing a negative $FeCl_3$ test. The semicarbazone had m.p. 83–86°. (Found: C, 58·79; H, 7·57; O, 23·90; N, 10·21; $C_{22}H_{33}O_7N_3$ requires: C, 58·52; H, 7·37; O, 24·81; N, 9·31%). This keto triester was hydrolysed and decarboxylated as above, to yield 3 g of the acid (XIa).

Methyl α-methyl-ε-keto-ε-(4-methyl-Δ³ cyclohexenyl)-Δ²-hexenoate (XIb). An ethereal solution of 4 g diazomethane was added to a solution of 20 g of the acid (XIa) in 60 ml ether. After 10 min, the neutral material was isolated and distilled furnishing a fraction with b.p. 125–129°/0·3 mm (17·2 g), ν_{max} 2900, 1710, 1430, 1370, 1235 and 1120 cm^{-1}; λ_{max}^{Hex} 217, ε 11408; NMR signal for the vinyl proton at C_{10}, 6·7 ppm. The semicarbazone had m.p. 157–159°. (Found: C, 62·08; H, 8·86; O, 15·91; N, 13·58; $C_{16}H_{25}O_3N_3$ requires: C, 62·52; H, 8·20; O, 15·62; N, 13·67%).

α-Methyl-ε-Keto-ε-(4-Methyl Δ^3-cyclohexenyl)Δ^2-hexeneol (XVIIa). The keto ester (XIb; 17 g) was dissolved in a mixture of 100 ml benzene, 8 g ethylene glycol and 170 mg *p*-toluenesulfonic acid. The mixture was refluxed and the water which formed was eliminated with a Stark trap. After 3 hr, the calculated amount of water (1·22 ml) had separated and the reaction mixture, was cooled and poured into 10% $NaHCO_3$ aq. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to dryness. The residual oil (16 g) showed IR bands at 2830, 1710, 1435, 1275, 1120, 1045 and 945 cm^{-1}, and was reduced with $LiAlH_4$ (2 g) in anhydrous ether (250 ml). The solution was kept 5 hr at room temp with mechanical stirring and then 100 ml 0·5N H_2SO_4 was added. The ethereal layer was worked up in the usual manner and the keto-alcohol obtained (11·3 g) showed ν_{max} 3500, 2950, 1720, 1450, 1385, 1305, 1150, 1075 and 1048 cm^{-1}. This product formed an acid phthalate the semicarbazone of which crystallized from methanol, m.p. 192–194°. (Found: C, 64·51; H, 6·64; O, 18·68; N, 9·86. $C_{23}H_{29}O_5N_3$ requires: C, 64·62; H, 6·84; O, 18·71; N, 9·83%).

Lanceol (XVIII). To a suspension of 18 g triphenylmethylphosphonium bromide in 50 ml dry ether, 21·5 ml of a 15% solution of butyllithium in hexane was added; after 30 min, 11 g of the keto-alcohol acetate (XVIIb) was added and the mixture refluxed overnight. The reaction mixture was poured into water and the organic layer isolated, washed and evaporated. The residue was treated with an excess of $LiAlH_4$ in ether during 5 hr at room temp and, after isolation in the usual way, the product was distilled, yielding a fraction (5·6 g) b.p. 113–115°/0·1 mm; n_D^{25} 1·5102; ν_{max} 3500, 2890, 1632, 1450, 1395, 1150, 1090, 1035, 945, 890 and 760 cm^{-1}.

This alcohol (1 g) was oxidized in the same manner as the natural lanceol and gave 890 mg of an aldehyde ν_{max} 2950, 2750, 1715, 1660, 1450, 1385, 1125 and 890 cm^{-1}, which formed a semicarbazone m.p. 151–153° crystallized from methanol–water. (Found: C, 69·86; H, 9·08; O, 6·26; N, 15·27; $C_{16}H_{25}ON_3$ requires: C, 69·78; H, 9·15; O, 5·81; N, 15·26%). This semicarbazone was indistinguishable from that obtained from natural lanceol, mixed m.p. and IR comparison.