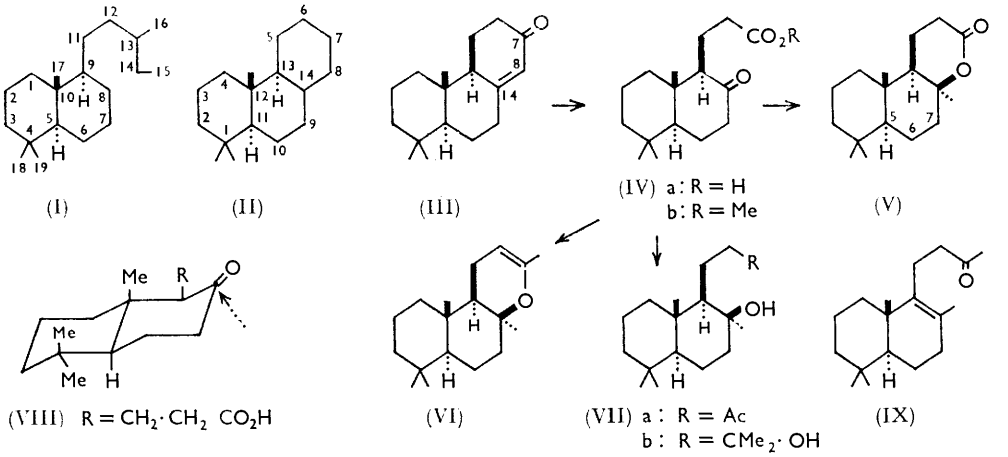
893. *Synthesis of Diterpenes. Part III.* The Synthesis, and Configuration at Position 13, of Diterpenes of the Labdane Group.*

By D. B. Bigley, N. A. J. Rogers, and J. A. Barltrop.

Sclareol (XXIIIb), methyl labdanolate (XXVIIIc), isomanoöl (XXVIIb), and their 13-epimers have been synthesised from podocarp-8(14)-en-7-one † (III), with (+)-ambreinolide (XIII), and the hydroxy-ketone (XV) as relays. From a study of the intramolecular hydrogen-bonding of the acetoxyethynylcarbinol (XXIIIc), and an analysis of the molecular rotations of manoöl, isomancöl and (*R*)(+)-linaloöl (XXIV), it emerges that sclareol, and manoöl have the (*R*)-configuration at position 13. A limitation of the method of molecular-rotation comparison is revealed.

Consideration of possible approaches to the synthesis of the manoöl–sclareol groups of diterpenes suggested that ambreinolide (XIII) would be a useful relay, as would the ketol (XV) and the unsaturated ketone (XXb) which are degradation products of sclareol [3] and manoöl [4] respectively. The synthesis of these compounds was therefore undertaken.

The starting material in this synthesis was podocarp-8(14)-en-7-one † (III), the synthesis of which has been reported in Part I of this series.[5] This necessitated the production of fairly large quantities of *m*-methoxyphenylacetylene, hitherto available only by long and tedious reactions from acetophenone.[6,7] We have now developed a convenient procedure



for its preparation from *m*-methoxycinnamic acid, by adding bromine photochemically,[8] converting the dibromide by sodium carbonate solution into ω-bromo-3-methoxystyrene and dehydrobrominating this with sodamide in liquid ammonia. An alternative procedure, involving *m*-methoxyphenylpropiolic acid as an intermediate, has recently been published.[9]

* Part II, Barltrop and Day, *J.*, 1959, 671.

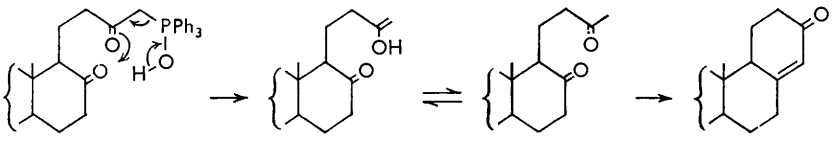
† The nomenclature of all compounds in this paper is based on that of the unknown hydrocarbons abdane [1] (I) and podocarpane [2] (II).

[1] Cocker and Halsall, *J.*, 1956, 4262.
[2] Klyne, *J.*, 1953, 3073.
[3] Ruzicka, Seidel, and Engel, *Helv. Chim. Acta*, 1942, **25**, 621.
[4] (*a*) Hosking and Brandt, *New Zealand J. Sci. Technol.*, 1936, **17**, 750; (*b*) Schenk, Gutmann, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 817.
[5] Barltrop and Rogers, *J.*, 1958, 2566.
[6] Collins, B.Sc. Thesis, Oxford, 1955.
[7] Johnson, Bannerjee, Schneider, Gutsche, Shelberg, and Chinn, *J. Amer. Chem. Soc.*, 1952, **74**, 2843.
[8] Jones and James, *J.*, 1935, 1600.
[9] Exner, Simak, Jilek, and Protiva, *Coll. Czech. Chem. Comm.*, 1954, **19**, 331.

Ozonolysis of podocarp-8(14)-en-7-one (III), under the conditions devised by Turner,[10] gave a high yield of the keto-acid (IVa). Esterification with dimethyl sulphate, under alkaline conditions, gave the methyl ester (IVb), the infrared spectrum of which was apparently identical with that published for the degradation product of manoöl.[4b]

Our first approach to ambreinolide (XIII) envisaged attack of methylmagnesium iodide on the carbonyl group of the keto-acid (IVa), or of its methyl ester, to give, after dehydration, a mixture of ambreinolide (XIII) and 8-epiambreinolide (V). In practice, only the latter lactone was obtained, accompanied, in the reaction on the acid, by the ketol (VIIa). This stereospecificity is not surprising in terms of the diagram (VIII), which shows that attack from the β-face of the molecule would be very hindered. The production of the ketol (VIIa), on reaction of an excess of Grignard reagent with the keto-acid, is surprising in view of the known lack of reaction between acids, or their salts, and Grignard reagents. This may be attributed to an equilibrium between the normal anion of the keto-acid, and the anion (XVII), which should react as a lactone with the Grignard reagent.

A second approach to ambreinolide, employing the Wittig reaction between methylenetriphenylphosphorane and the keto-ester (IVb), was attempted. It was expected that this reaction would give rise to the unsaturated ester (X; R = Me), the acid from which, a degradation product of manoöl, was known [4b] to cyclise to ambreinolide in high yield in acidic conditions. In practice, however, preferential attack at the ester function occurred, to give the organophosphorus compound (XI). Pyrolysis of this compound gave rise, possibly by the mechanism shown, to an αβ-unsaturated ketone, which, from its b. p. and spectrum, was probably podocarp-8(14)-en-7-one (III).



(XI) + Ph_3PO (III)

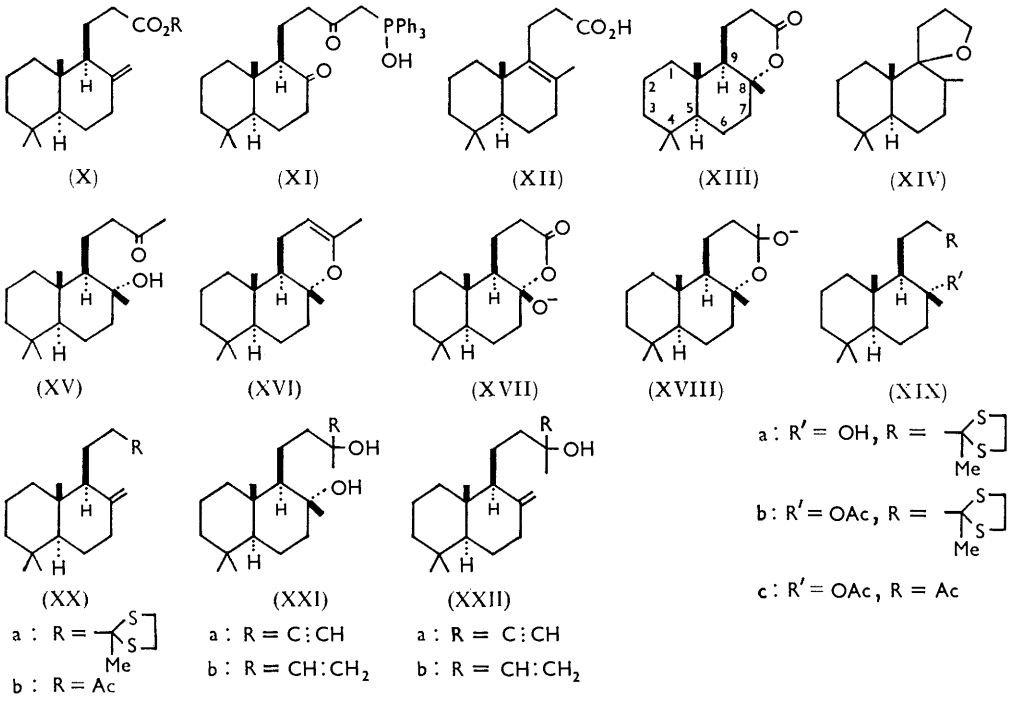
Attempted Wittig reactions on the lithium salt of the keto-acid (IVa) in various refluxing solvents gave only unchanged starting material. This failure of the 8-oxo-group to react even under forcing conditions may perhaps be attributed partly to the presence of the anion (XVII) in the solution of the lithium salt, and partly to the large steric requirements of the Wittig reagents.

The synthesis of ambreinolide was finally achieved in the following manner. The keto-acid (IVa) with an excess of methyl-lithium gave three products: (*a*) a single ketol, which, by analogy with the production of 8-epiambreinolide (V), must be assigned structure (VIIa); (*b*) the enol ether (VI) arising from cyclodehydration of this ketol, and (*c*) the glycol (VIIb). Dehydration of the ketol (VIIa) with a trace of iodine in benzene, or treatment of the enol ether (VI) with mineral acid, led to the unsaturated ketone (IX), which with hypoiodite gave a good yield of the unsaturated acid (XII). Treatment [4b] of this acid with a solution of sulphuric acid in glacial acetic acid at 0° gave a mixture of lactones which was resolved by chromatography on deactivated alumina. A γ-lactone (possibly XIV), which did not crystallise, was not further examined. A second fraction crystallised spontaneously, to give a good yield of (±)-ambreinolide (XIII). This substance had previously been synthesised by Dietrich and Lederer [11] and by Wolff,[12] and partial syntheses of (+)-ambreinolide from manoöl [4b] and sclareol [13] have also been reported. The experiments reported in the present paper [14] represent the first systematic, total synthesis of the racemic lactone.

[10] Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 579.
[11] Dietrich and Lederer, *Compt. rend.*, 1952, **234**, 637.
[12] Wolff, *Compt. rend.*, 1954, **238**, 1041.
[13] Lederer and Stoll, *Helv. Chim. Acta*, 1950, **33**, 1345.
[14] Cf. Bigley, Barltrop, and Rogers, *Chem. and Ind.*, 1958, 558.

The same sequence of reactions performed with the dextrorotatory form of the unsaturated ketone (IX) yielded (+)-ambreinolide. The required ketone was obtained from sclareol, which is reported [3,15,16] to yield, by oxidation, a mixture of the hydroxy-ketone (XV) and the enol ether (XVI) derived from the hydroxy-ketone by dehydration. This dehydration occurs very readily, appreciably even in solution in light petroleum at room temperature, and quantitatively in ether in the presence of a trace of mineral acid. By taking advantage of these facts, the oxidation of sclareol may be made to yield predominantly either the hydroxy-ketone or the enol ether at will. Ruzicka *et al.*[3] report that the enol ether (XVI) may be hydrated to the ketol (XV) by means of aqueous-methanolic acetic acid or methanolic semicarbazide acetate. In our hands, these conditions gave only starting material. Partial conversion was achieved by hydrolysis with aqueous-methanolic oxalic acid at room temperature. Dehydration of the ketol or treatment of the enol ether with mineral acid then gave the required dextrorotatory form of the unsaturated ketone (IX), the infrared spectrum of which was identical with that of the racemic ketone described above.

From this point, only the optically pure forms are considered. (+)-Ambreinolide (XIII) was hydrolysed with aqueous-methanolic lithium hydroxide, to the lithium salt of the corresponding hydroxy-acid. Treatment of this with methyl-lithium gave the crude hydroxy-ketone (XV) which was partially converted into the corresponding enol ether during purification. Since these compounds are identical with the oxidation products of



sclareol, the subsequent stages of the synthesis made use of the ketol (XV), prepared from sclareol, as a relay.

Ethynylation of the ketol (XV), with lithium acetylide in liquid ammonia, or with ethynylmagnesium bromide, proved to be very difficult, a good yield of the ethynylcarbinols (XXIa) being obtained only under forcing conditions. This marked lack of reactivity can probably be attributed to the presence, in solution, of the anion (XVIII).

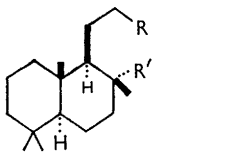
[15] Janot, *Ann. Chim. Phys.*, 1932, **17**, 5.
[16] Ruzicka and Janot, *Helv. Chim. Acta*, 1931, **14**, 645.

In this context, it is pertinent that the sodium salt of the ketol (XV), on treatment with chloromethyl methyl ether, gave an oil showing no carbonyl absorption in the region (1700—1725 cm.$^{-1}$). Reduction of the ethynylcarbinols (XXIa) with lithium aluminium hydride gave sclareol and 13-episclareol (XXIb) as mixed crystals which could not be resolved, even by graded elution chromatography. The mixture had a sharp m. p., which was depressed on admixture with authentic sclareol. The infrared spectrum was identical with that of the natural product, when measured in carbon disulphide solution, but was quite different in Nujol mull.

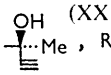
Ethynylation of the acetoxy-ketone (XIXc) (see below) gave a mixture of acetoxy-ethynylcarbinols (XXIIIa and c). Careful chromatography on deactivated alumina gave the two epimeric ethynylcarbinols, A and B. A study of the infrared spectra (measured for CCl_4 solution) of these two isomers revealed that isomer B contained an intramolecular hydrogen bond (bands at 3540 and 3440 cm.$^{-1}$; relative intensities unaffected by dilution). There was also a slight lowering of the C=O stretching frequency (~7 cm.$^{-1}$) in the spectrum of isomer B. The latter shift may be illusory, since the spectra were measured at different times, and the possibility of experimental error must not be excluded. The importance of the observed hydrogen-bonding of isomer B is discussed below.

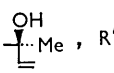
Reduction of isomer A with lithium aluminium hydride gave sclareol (XXIIIb), identical with the natural material. In view of the recent conversions of sclareol into manoöl and manoyl oxide, this constitutes a formal total synthesis of the more important diterpenes of the labdane group. Similar reduction of isomer B gave 13-episclareol. The infrared spectra of the two diastereoisomers were identical in carbon disulphide solution, but different in Nujol mull.

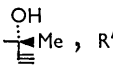
A careful analysis of the intramolecular hydrogen bonding of isomer B made possible an allocation of configuration at position 13 in this compound and in sclareol. This bonding can, in principle, involve either the ether- or the carbonyl-oxygen of the acetate residue

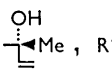


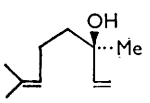
(XXIII)

a: R =  , R′ = OAc

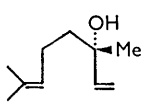
b: R =  , R′ = OH

c: R =  , R′ = OAc

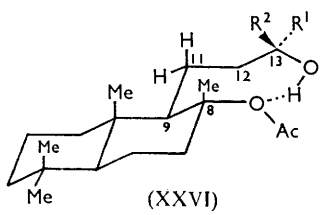
d: R =  , R′ = OH



(XXIV)



(XXV)



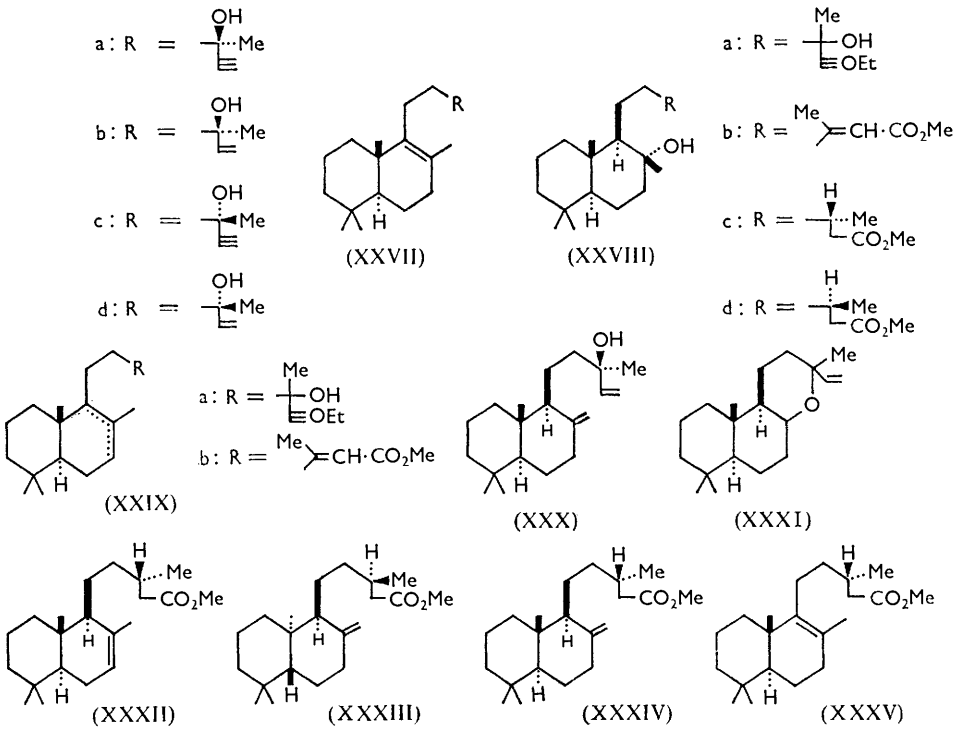
(XXVI)

giving rise to an effective seven- or nine-membered ring respectively. On general grounds, the seven-membered ring formulation is to be preferred, and this contention is supported experimentally by the fact that the ketol (XV) gives evidence of a strong intramolecular hydrogen bond, thus providing a precedent for such a system in a seven-membered ring in this series. Further, neither methyl labdanolate (XXVIIIc) nor methyl 13-epilabdanolate (XXVIIId), in which hydrogen-bonding would require an effective nine-membered ring, exhibits such a bond (see below): nevertheless this cannot be regarded as conclusive evidence, since in such a nine-membered ring a tetrahedral carbon atom would replace an oxygen atom of the ring of isomer B. However, an unshared pair of electrons is believed

to have a greater steric requirement than a hydrogen atom.[17] The apparent lowering of the carbonyl-oxygen stretching frequency of isomer B, which might be taken as evidence [18] of hydrogen-bonding to the carbonyl-oxygen atom, is of doubtful significance (see above) in this instance.

On these grounds, we are inclined to favour the seven-membered ring structure for isomer B (XXVI, XXIIIc), although the matter must be regarded as unproved. Fortunately, this is not important, as the arguments of the next paragraph, developed on the basis of a seven-membered ring formulation for isomer B, apply with almost equal force to a structure possessing a nine-membered ring.

An examination of models (see diagram XXVI) explains why isomer B alone exhibits intramolecular hydrogen-bonding. It is apparent that if the hydrogen bond is incorporated in a seven-membered ring, then a bulky β-orientated 13-group R^2 can interact strongly with the "axial" 11-hydrogen atom and with the 8-methyl group. This interaction, which appears to be significant even when R^2 is the slim ethynyl group, becomes enhanced



when R^2 is methyl, probably to the extent that the intramolecular hydrogen-bond must break in order to relieve this strain. On this basis then, the conclusion was reached that isomer B has a β-oriented ethynyl group in structure (XXVI), *i.e.*, that it has the (*S*)-configuration [19] at position 13 (XXIIIc), and hence that sclareol has the (*R*)-configuration at this centre (XXIIIb).

If the above arguments about the configuration at position 13 of isomer B are accepted, then it follows, from the recent conversion of sclareol into manoöl,[20] that the latter also has the (*R*)-configuration at position 13. Although it has been reported [21] that sclareol can be

[17] (*a*) Aroney and Le Fèvre, *Proc. Chem. Soc.*, 1958, 82; (*b*) Barton, *Quart. Rev.*, 1956, **10**, 72.
[18] Henbest and Lovell, *J.*, 1957, 1965.
[19] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[20] Büchi and Biemann, *Croat. Chem. Acta*, 1957, **29**, 163.
[21] Ohloff, *Annalen*, 1958, **617**, 134.

transformed also into manoyl oxide (XXXI), in the absence of evidence as to the mechanism of this cyclisation the configuration of this compound at positions 8 and 13 remains in doubt. Since Prelog and Watanabe assigned the (*R*)-configuration to (+)-linaloöl [22] (XXIV), it follows that the establishment of a relation between manoöl and (+)-linaloöl would provide confirmatory evidence for their assignment. On the other hand, if we regard the (*R*)-configuration of (+)-linaloöl as proved, such a relation would add weight to our conclusions, which are in conflict with the tentative suggestion by Büchi and Biemann [20] that sclareol has the (*S*)-configuration at position 13.

At this point, it is pertinent that a consideration of the difference in molecular rotation between sclareol and 13-episclareol ($\Delta[M]_D = +10{\cdot}3°$), and that between (−)- and (+)-linaloöl (XXV) and (XXIV) [($\Delta[M]_D = +39°$], suggest, in view of Prelog and Watanabe's work,[22] that sclareol has the (*S*)-configuration at position 13. The incompatibility of this result with our work on isomer B led us to believe that the method of molecular-rotation differences cannot be applied with confidence to comparisons between systems which contain an intramolecular hydrogen-bond and systems not bonded in this way. Büchi and Biemann's conclusions [20] were based on rotation comparisons in the annexed Table. Now the two comparisons (i and ii) which support Büchi and Biemann's conclusions are between sclareol compounds (in which intramolecular hydrogen-bonding is likely) and linaloöl compounds (in which such bonding is impossible). The rotation differences in comparison (iii) are probably too small to be meaningful, although they are in conflict with Büchi and Biemann's conclusions. Comparison (iv) is, in our view, the only one which is valid, and this clearly relates manoöl, and hence sclareol, to (*R*) (+)-linalool.

(i) Sclareol ⟶ Dihydrosclareol $\Delta[M]_D$ = +9°
(ii) Sclareol monoacetate ⟶ Sclareol diacetate $\Delta[M]_D = +17{\cdot}2°$
(iii) Sclareol diacetate ⟶ Dihydrosclareol diacetate $\Delta[M]_D = -2{\cdot}1°$
(iv) Manoöl ⟶ Manoyl acetate $\Delta[M]_D$ = −12·7°
(v) Sclareol ⟶ 13-Episclareol $\Delta[M]_D$ = +10·3°

(*S*)(−)-Linaloöl ⟶ (*R*)(−)-Tetrahydrolinaloöl $\Delta[M]_D = +21{\cdot}7°$
(*S*)(−)-Linaloöl ⟶ (*S*)(−)-Linaloyl acetate $\Delta[M]_D = +9{\cdot}4°$
(*S*)(−)-Linaloöl acetate ⟶ (*R*)(−)-Tetrahydrolinaloyl acetate $\Delta[M]_D = +7{\cdot}6°$
(*S*)(−)-Linaloöl ⟶ (*S*)(−)-Linaloyl acetate $\Delta[M]_D = +9{\cdot}4°$
(*S*)(−)-Linaloöl ⟶ (*R*)(+)-Linaloöl $\Delta[M]_D$ = + 39°

The most direct way of relating this series of compounds with linaloöl, in an unambiguous manner, appeared to be the synthesis of manoöl and 13-epimanoöl from the unsaturated ketone (XXb). This approach involved difficulties which were not readily overcome (see below). The more readily available ketone (IX) was ethynylated, to give a mixture of ethynylcarbinols (XXVIIa and c) which were separated on deactivated alumina. Partial reduction of these two isomers with Lindlar's catalyst gave the vinylcarbinols (XXVIIb and d) which, for convenience, we name isomanoöl and 13-epi-isomanoöl respectively. Isomanoöl had $[\alpha]_D^{22}$ +73·5°; 13-epi-isomanoöl had $[\alpha]_D^{22}$ +27·5°. It follows that isomanoöl must have the same configuration at position 13 as (*R*)(+)-linaloöl (XXIV), and is therefore (XXVIIb).

It remained to relate natural manoöl to either isomanoöl or 13-epi-isomanoöl and this was done in three ways. First, the molecular rotation difference between methyl labd-8-(20)-en-15-oate (XXXIV), and methyl labd-8-en-15-oate (XXXV) ($\Delta[M]_D$ +118°), clearly relates manoöl to isomanoöl ($\Delta[M]_D$ +113°) rather than to 13-epi-isomanoöl ($\Delta[M]_D$ −15°).

Secondly, the reduction of the ethynylcarbinols (XXVIIa and c) to the vinylcarbinols resulted in a rotation change so small as to be within the limits of experimental error. By analogy, the ethynylcarbinol which on reduction would give rise to manoöl ($[\alpha]_D$ +33°) should have a specific rotation of approximately +33°. The epimeric ethynylcarbinol would have a rotation ~33° + 39° = 72° if manoöl has the (*S*)-configuration at position 13 and a rotation of ~33° − 39° = −6° if manoöl has the (*R*)-configuration at this centre

[22] Prelog and Watanabe, *Annalen*, 1957, **603**, 1.

{because for the change (*S*)-(−)-linaloöl ⟶ (*R*)-(+)-linaloöl $\Delta[M]_D = +39°$}. It follows that if manoöl has the (*R*)-configuration at position 13 the mixture of ethynylcarbinols (XXIIa) (see below) should have a specific rotation of less than 33°. In practice the mixture had a specific rotation of +16°.

Thirdly, dehydration of sclareol has been reported [20] to give a small proportion of isomanoöl. This work was repeated in the hope of isolating isomanoöl with the " natural " configuration at position 13. Complete separation could not be achieved, but repeated chromatography gave an increasing proportion of isomanoöl, which could be estimated by measuring the diminution in the extinction coefficient of the infrared band at 887 cm.$^{-1}$ due to the exocyclic double bond of manoöl. The relation between the specific rotation and isomanoöl content of the various mixtures is shown in Fig. 1. Extrapolation shows that pure isomanoöl should have a specific rotation of approximately +80°, clearly relating it to our synthetic isomanoöl, and hence to (*R*)(+)-linaloöl. The relation between the isomanoöl content of the various mixtures, and the appearance of the infrared spectrum in the relevant region, is shown in Fig. 2. It will be seen that the band at 7·25 μ, which is characteristic of a methyl group attached to a double bond, is absent in the spectrum of

FIG. 1. *Infrared bands of (a) manoöl, (c) isomanoöl, and (b) mixtures of the two, in* CS_2.

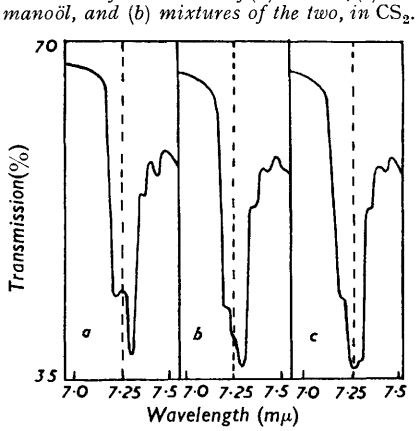
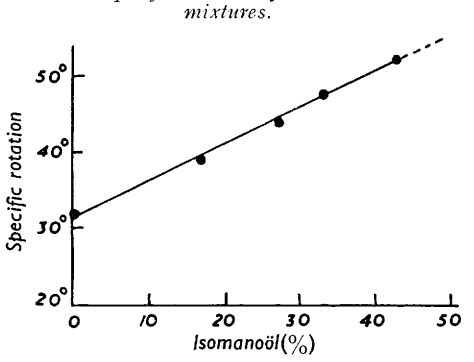


FIG. 2. *Specific rotation of manoöl–isomanoöl mixtures.*



manoöl, but increases in intensity as the percentage of isomanoöl in the mixture increases. Further, the possibility that the mixture contains more extensively rearranged material is slight, since there are no bands in the spectrum of the mixture which are not present in the spectra of either manoöl or isomanoöl.

These results show that manoöl (XXX), sclareol (XXIIIb), and isomanoöl (XXVIIb) have the (*R*)-configuration at position 13.

The clearly untrustworthy nature of conclusions based on the analysis of molecular-rotation data, where hydrogen bonding may be involved, led us to re-investigate Bory and Lederer's work on the configuration at position 13 of labdanolic ester.[23] The published spectra were for potassium bromide suspensions, which are inadequate to reveal the presence of intramolecular hydrogen-bonding. Accordingly, the synthesis of methyl labdanolate and methyl 13-epilabdanolate was undertaken.

Reaction of the hydroxy-ketone (XV) with ethoxyethynylmagnesium bromide gave a mixture of hydroxyethoxyethynylcarbinols (XXVIIIa) and unsaturated ethoxyethynylcarbinols (XXIXa) which was rearranged, without purification, to a mixture of the unsaturated esters (XXVIIIb and XXIXb), by briefly refluxing it with methanol.[24] These esters were separated by chromatography, the two hydroxy-esters having melting points

[23] Bory and Lederer, *Croat. Chem. Acta*, 1957, **29**, 157.
[24] Wallach and Beschke, *Annalen*, 1906, **347**, 338.

in agreement with those quoted by Bory and Lederer.[23] Reduction of the combined hydroxy-esters (XXVIIIb) gave a readily separable mixture of methyl labdanolate and methyl 13-epilabdanolate. Neither of these compounds gave evidence of intramolecular hydrogen-bonding. There is therefore no reason to suppose that Lederer's assignment of configuration to labdanolic ester is incorrect and we may write methyl labdanolate as (XXVIIIc) with the (*R*)-configuration at position 13 and methyl 13-epilabdanolate as (XXVIIId). It follows that methyl cativate must be (XXXII), since it has been related to methyl labdanolate by a process [1] which does not involve position 13. Also, methyl eperuate has been shown [25] to be epimeric with methyl labd-8(20)-en-15-oate (XXXIV) at all centres except $C_{(9)}$, and hence can be written as (XXXIII).

Attempts were also made to synthesise manoöl by similar methods from the unsaturated ketone (XXb). Although this compound could not be prepared directly from the ketol (XV) by dehydration, a process which led solely to the enol ether (XVI), the requisite transformation was effected in the following way. The ketol (XV) was protected as the dithiolan (XIXa). Dehydration with phosphorus oxychloride in pyridine [1] gave the unsaturated thioketal (XXa), which, treated with mercuric acetate, gave the desired product (XXb). This material had properties identical with those recorded [4] for the oxidation product of manoöl. A further valuable intermediate (see above) obtained during this synthesis was the keto-acetate (XIXc), prepared *via* the acetoxydithiolan (XIXb). This compound was also prepared, in low yield, by the action of keten on the ketol (XV). Pyrolysis of the keto-acetate (XIXc), expected to yield the unsaturated ketone (XXb), gave a complex mixture of double-bond isomers. This result was surprising in view of Bailey's work,[26] but more recent publications [27] have suggested that his results are not of general applicability. A third approach to the unsaturated ketone, involving the pyrolysis of the enol ether (XVI), gave only the ketone (IX).

Ethynylation of the unsaturated ketone (XXb) gave a mixture of diastereoisomeric ethynylcarbinols (XXIIa) (see above). It was hoped that reduction would give manoöl and 13-epimanoöl (XXIIb), but in fact lithium aluminium hydride caused extensive rearrangements of the double-bond system and no useful product was isolated.

Experimental

Deactivated alumina refers to alumina treated with 5% of 10% aqueous acetic acid. M. p.s are measured on a Kofler block and are corrected.

m-*Methoxyphenylacetylene.*—3-Methoxycinnamic acid (10 g.), dissolved in carbon tetrachloride (50 c.c.) in a Pyrex flask, was treated with bromine (3·1 c.c.) by Jones and James's method,[8] a powerful ultraviolet source being substituted for the less readily available sunshine. The dibromide (17·1 g., 90%), m. p. 166°, was recrystallised from carbon tetrachloride. When boiled in water (120 c.c.) for 20 min. with its own weight of potassium carbonate, it gave ω-*bromo*-3-*methoxystyrene* (70%), b. p. 140—150°/20 mm. (Found: C, 50·9; H, 4·5; Br, 37·0. C_9H_9OBr requires C, 50·7; H, 4·2; Br, 37·5%).

A solution of the ω-bromostyrene (20 g.) in dry ether (500 c.c.) was added slowly to a stirred solution of sodamide (from 23 g. of sodium) in liquid ammonia (1·5 l.). The mixture was stirred during 30 min., then treated with ammonium chloride (40 g.) and worked up in the usual way, to give *m*-methoxyphenylacetylene (9·9 g. 80%), b. p. 93—95°/21 mm. (Found: C, 81·8; H, 6·1. Calc. for C_9H_8O: C, 81·8; H, 6·1%).

The overall yield from *m*-hydroxybenzaldehyde in this procedure was 41%.

8-*Oxo*-14,15,16,20-*tetranorlabdan*-13-*oic Acid* (IVa).—Podocarp-8(14)-en-7-one [5] (III) (1·73 g.) was ozonised according to Turner's directions,[10] to give the desired *product* in 96% yield as a glass, b. p. 155—160° (bath-temp.)/0·1 mm. (Found: C, 71·9; H, 9·7. $C_{16}H_{26}O_3$ requires C,

[25] Djerassi and Marshall, *Tetrahedron*, 1957, **1**, 238.
[26] Bailey, *J. Amer. Chem. Soc.*, 1955, **77**, 75, 357.
[27] Royals, *J. Org. Chem.*, 1958, **23**, 1822; Froemsdorf, Collins, Hammond, and DePuy, *J. Amer. Chem. Soc.*, 1959, **81**, 643; Bailey and Hales, *ibid.*, 647, 651; Eglinton and Rodger, *Chem. and Ind.*, 1959, 256.

71·8; H, 9·8%). Distillation of this keto-acid in quantities greater than 1·5 g. through a Vigreux column was found to give a mixture of enol lactone (b. p. 182—187°/0·25 mm.) and some charred material. The lactone was hydrolysed to the keto-acid by warm 2N-sodium hydroxide for 3 hr.; acidification afforded the product which was isolated in ether.

The keto-acid with dimethyl sulphate and alkali at room temperature gave the *methyl ester* (IVb) (85%) as a pale yellow oil, b. p. 138—145° (bath-temp.)/0·25 mm., $n_D^{25\cdot5}$ 1·4945 (Found: C, 72·6; H, 9·8. $C_{17}H_{28}O_3$ requires C, 72·8; H, 10·0%).

8-*Epiambreinolide* (V).—(*A*) A solution of methylmagnesium iodide (from 0·05 g. of magnesium) in dry ether (12 c.c.) was added dropwise to a stirred solution of the keto-ester (IVb) (0·52 g.) in dry ether (25 c.c.), under nitrogen. The mixture was refluxed for 1½ hr., cooled, mixed with ice, and acidified with dilute sulphuric acid. Extraction with ether gave a pale brown oil (0·45 g.) which was chromatographed on deactivated alumina. Elution with 1 : 1 light petroleum–benzene gave successively unchanged starting material (205 mg.) and an oil (120 mg.), which crystallised. Recrystallisation from light petroleum gave 8-*epiambreinolide* (V), as needles, m. p. 144—146° (Found: C, 77·3; H, 10·4. $C_{17}H_{28}O_2$ requires C, 77·3; H, 10·6%), ν (in CS_2) 1730s cm.$^{-1}$. The region 700—1400 cm.$^{-1}$ was entirely different from that of ambreinolide, measured under the same conditions.

Further elution with 1 : 1 benzene–ether gave colourless crystals (110 mg.), showing no absorption in the region 1700—1750 cm.$^{-1}$, but a complicated band around 3500 cm.$^{-1}$. Recrystallisation from ether gave 15-norlabdane-8β,13-diol (VIIb), m. p. 139—140°.

(*B*) The keto-acid (IVa) (60 mg.) was added, in dry ether (10 c.c.), to methylmagnesium iodide (from 80 mg. of magnesium) in ether. The mixture, diluted with tetrahydrofuran (3 c.c.), was refluxed under dry nitrogen for 2 hr., worked up in the usual way, and divided into neutral and alkali-soluble fractions. The neutral material, after chromatography on a short column of deactivated alumina, gave the ketol (VIIa) (20 mg.) (see below), m. p. and mixed m. p. 90—91°. The alkali-soluble fraction gave a viscous oil, the infrared spectrum of which was typical of a carboxylic acid; this when distilled from a small crystal of potassium hydrogen sulphate gave 8-epiambreinolide (15 mg.).

Wittig Reaction on the Keto-ester (IVb).—A solution of redistilled bromobenzene (15·7 g.) in dry ether (50 c.c.) was added dropwise to a stirred suspension of freshly cut lithium (1·47 g.) in dry ether (25 c.c.) under dry nitrogen. After the initial reaction had subsided, the mixture was refluxed until the remaining lithium was black. The solution was then filtered, under nitrogen, through glass wool, into a separatory funnel.

This solution was added, dropwise, under nitrogen, to a stirred suspension of methyltriphenylphosphonium bromide (5·1 g.) in dry ether (25 c.c.) until only a small amount of solid remained. The mixture was then stirred for 1 hr., to ensure that some solid remained (no excess of phenyl-lithium present), then added to a stirred solution of the keto-ester (IVb) (0·5 g.) in dry ether (100 c.c.), giving rise to a heavy yellow precipitate. Stirring was continued overnight. The ether was then replaced by dry tetrahydrofuran, and the mixture was refluxed for 6 hr. The solvents were then removed, water was added, and the product taken up in ether. Adsorption on deactivated alumina and elution with benzene–ether gave, successively, triphenylphosphine oxide, m. p. 154°, and a yellow viscous oil, prolonged evacuation of which gave the *dioxophosphonium hydroxide* (XI) as a resinous solid (Found: C, 78·8; H, 8·3; P, 5·2. $C_{35}H_{43}O_3P$ requires C, 78·1; H, 8·0; P, 5·7%). The infrared spectrum had a single band at 1719 cm.$^{-1}$ and was otherwise very similar to the published spectra of phenacylphosphonium compounds.

Pyrolysis of the phosphonium hydroxide (XI) (100 mg.) at 140°/4 × 10^{-5} mm. for 2 hr. gave (i) a colourless oil (2 mg.) which had an infrared spectrum similar to that of podocarp-8(14)-en-7-one (III) and gave a red precipitate with Brady's reagent, and (ii) triphenylphosphine oxide, (20 mg.), m. p. 156° (from ether).

(±)-8β-*Hydroxy*-14,15-*bisnorlabdan*-13-*one* (VIIa).—Methyl-lithium was prepared by cutting lithium metal (3 g., 60 mol.) into dry ether (50 c.c.) under dry nitrogen, and adding methyl iodide (40 g.) in dry ether (100 c.c.) at such a rate that refluxing was maintained. The mixture was boiled until the remaining lithium was black, then filtered under nitrogen, through glass wool, into a solution of the keto-acid (IVa) (1·7 g.) in dry ether (50 c.c.), refluxed for 5 hr., cooled, and poured on ice. The product was taken up with ether and washed with dilute sodium hydroxide and water. Evaporation gave a pale yellow oil (1·66 g.), which was adsorbed on deactivated alumina. Elution with light petroleum gave a colourless oil (121 mg.), b. p.

120—125° (bath-temp.)/0·03 mm., having a strong infrared band at 1695 cm.$^{-1}$ but no absorption in the region of 3500 cm.$^{-1}$. This material was formulated as 8β,13-epoxy-14,15-bisnorlabd-12-ene (VI). Elution with benzene gave colourless needles (1·1 g.). These chromatographic fractions were all spectroscopically identical (in Nujol), having strong bands at 3450 (OH) and 1720 (C=O) cm.$^{-1}$. Recrystallisation from ether gave (±)-8β-*hydroxy*-14,15-*bisnorlabdan*-13-*one* (VIIa) as needles, m. p. 90—91° (Found: C, 76·7; H, 11·2. $C_{18}H_{32}O_2$ requires C, 77·1; H, 11·4%). Elution with ether gave colourless needles (120 mg.), m. p. 141—142° (from ether), believed to be 15-norlabdane-8β,13-diol (VIIb), ν (in Nujol) 3450 (OH) cm.$^{-1}$, no carbonyl absorption.

(±)-14,15-*Bisnorlabd*-8-*en*-13-*one* (IX).—(*A*) The enol ether (VI) (121 mg.), dissolved in ethanol (7 c.c.), was treated with 5N-hydrochloric acid (1 c.c.) and kept at 70° for 1 hr., cooled, and poured into water. The product, isolated with ether, gave (±)-14,15-*bisnorlabd*-8-*en*-13-*one* (IX) (109 mg.), b. p. 127—132° (bath-temp.)/0·01 mm., n_D^{25} 1·5110 (Found: C, 82·0; H, 11·3. $C_{18}H_{30}O$ requires C, 82·4; H, 11·5%), ν 1718s (C=O) cm.$^{-1}$.

(*B*) The (±)-hydroxy-ketone (VIIa) (0·3 g.) was refluxed in benzene (10 c.c.) for 3 hr. with a small crystal of iodine, then cooled and washed with sodium thiosulphate solution. Removal of the solvent gave the unsaturated ketone (IX) (0·27 g.), n_D^{25} 1·5107.

Oxidation of (−)-*Sclareol.*—The general conditions described by Ruzicka, Seidel, and Engel [3] were followed, apart from the stated variations which permit a high yield of either the ketol (XV) or the corresponding enol ether (XVI) to be obtained. The sclareol used was supplied by Firmenich et Cie., Geneva, and had m. p. 100—102°.

(*A*) All apparatus was cleaned with chromic acid and washed with water before use. Finely ground " AnalaR " potassium permanganate and " AnalaR " acetone were used, and the oxidation was conducted at 0°. Working up in the usual way gave the enol ether (XVI) (5·2 g. from 10·0 g. of sclareol), b. p. 120—125° (bath-temp.)/0·03 mm., which crystallised from methanol at −40° as needles, m. p. 44—46°, $[\alpha]_D^{20}$ +5° ± 2°, n_D^{20} 1·5137.

(*B*) All apparatus was cleaned with chromic acid and washed with sodium carbonate solution and water before use. The " AnalaR " acetone was further purified by distillation from " AnalaR " potassium permanganate. The oxidation was performed as in (*A*) except that the temperature was never allowed to exceed 25°. The product crystallised spontaneously, without distillation. Crystallisation from light petroleum gave the ketol (XV), m. p. 89—90°.

(*C*) The sodium carbonate washings from (*A*) and (*B*) were combined and acidified, and the product was isolated with ether. This material (0·29 g.), dissolved in glacial acetic acid (1·1 c.c.), was maintained at 70° in the presence of red lead (0·83 g.) for 15 min. then treated with aqueous glycerol. The organic product, isolated with ether, gave crude ketol (XV) (0·15 g.), m. p. 65—70°.

Interconversion of the Ketol (XV) *and the Enol Ether* (XVI).—(*A*) The ketol (XV), on treatment with mineral acid, or on distillation, gave a quantitative yield of the enol ether (XVI). (*B*) The enol ether (XVI) (0·7 g.), dissolved in methanol (210 c.c.), was treated with a solution of oxalic acid dihydrate (3·22 g.) in water (42 c.c.), stirred for 45 min. at 25°, and poured into water (3 l.). The product, isolated with ether, was adsorbed on deactivated alumina. Elution with light petroleum gave unchanged starting material (0·29 g.). Elution with ether and removal of the solvent at room temperature gave the ketol (XV) (0·27 g.), m. p. 89°. The conditions described by Ruzicka, Seidel, and Engel [3] gave only starting material in our hands.

(+)-14,15-*Bisnorlabd*-8-*en*-13-*one* (IX).—(*A*) The enol ether (XVI) was treated with hydrochloric acid, under the conditions (*A*) described for the preparation of the racemic ketone. Working up in the normal way gave the product, n_D^{24} 1·5105, $[\alpha]_D^{19}$ +4·5° ± 2°. The infrared spectrum (liquid film) was identical with that of the racemic unsaturated ketone. The 2,4-dinitrophenylhydrazone had m. p. 150—151°.

(*B*) The hydroxy-ketone (XV) (4·0 g.), treated in the same way as the enol ether in (*A*), gave the unsaturated ketone (3·7 g.).

(±)-14,15,16-*Trisnorlabd*-8-*en*-13-*oic Acid* (XII).—The (±)-unsaturated ketone (IX) (0·66 g.), dissolved in pure dioxan (175 c.c.), was stirred at room temperature for 1 hr., during which were added in 2 c.c. portions at 3-minute intervals (*a*) iodine (4·83 g.) and potassium iodide (9·9 g.) in water (40 c.c.), and (*b*) potassium hydroxide (4·0 g.) in water (40 c.c.). The mixture was stirred for 2 hr., the colour was discharged with aqueous sodium hydrogen sulphite, and the solution made slightly alkaline with aqueous sodium hydroxide. The organic solvent was

removed, the solution was acidified, and the product was taken up in ether. The ethereal layer was then extracted with aqueous sodium hydroxide, the aqueous layer acidified, and the product isolated with ether. Removal of the solvent gave the acid (XII) (550 mg.) as a pale brown oil, ν 1718s cm.$^{-1}$, with the broadening of the C–H stretching region typical of carboxylic acids. The product was used, without further purification, in the preparation of (±)-ambreinolide.

(+)-14,15,16-*Trisnorlabd*-8-*en*-13-*oic Acid* (XII).—The above procedure, repeated with the (+)-unsaturated ketone (IX) (1·7 g.), gave the product (1·4 g.). This was used without purification, in the preparation of (+)-ambreinolide.

(±)-*Ambreinolide* (XIII).—The (±)-unsaturated acid (XII) (550 mg.) was stirred in sulphuric (7·0 c.c.) and glacial acetic acid (17·5 c.c.) at 0° for 5 hr., and then poured on ice, and the product was taken up in ether. Unchanged acids (270 mg.), recovered by washing the ethereal layer with sodium hydrogen carbonate solution, were treated again with mixed sulphuric and acetic acid. The combined neutral products were adsorbed on deactivated alumina. Elution with 40% benzene in light petroleum gave a yellow oily γ-lactone (43 mg.) (XIV?), b. p. 110—120° (bath-temp.)/0·03 mm., ν 1770 cm.$^{-1}$. Further elution with 1 : 1 benzene–light petroleum gave colourless crystals (201 mg.), that from light petroleum gave (±)-ambreinolide as prisms, m. p. 136·5—138·5° (Found: C, 77·6; H, 10·4. Calc. for $C_{17}H_{26}O_2$: C, 77·3; H, 10·6%). The infrared spectrum of a CS_2 solution was identical with that of (+)-ambreinolide measured under the same conditions.

(+)-*Ambreinolide* (XIII).—The (+)-unsaturated acid (XII) (1·3 g.) was treated as in the previous experiment, to give unchanged starting material (300 mg.), and a neutral fraction (1·0 g.), from which was isolated by chromatography a γ-lactone (174 mg.), which was not further investigated, and (+)-*ambreinolide* (440 mg.), which recrystallised from light petroleum as needles, m. p. 143—144°, $[\alpha]_D^{18}$ +29·5° ± 2°, mixed m. p. with authentic (+)-ambreinolide (m. p. 140—142°) 142—143·5° (Found: C, 77·0; H, 10·6. $C_{17}H_{26}O_2$ requires C, 77·3; H, 10·6%).

(+)-8α-*Hydroxy*-14,15-*bisnorlabdan*-13-*one* (XV).—A solution of lithium hydroxide (from 0·04 g. of lithium) in water (25 c.c.) was added to one of (+)-ambreinolide (430 mg.) in methanol (25 c.c.) and the mixture was kept at 50—60° for 15 min. It was then diluted with water (25 c.c.) and kept at the same temperature until it became homogeneous (a further 40 min.). The solvent having been removed by freeze-drying, the resultant solid was washed with light petroleum, to extract unchanged ambreinolide (93 mg.).

The lithium salt (360 mg.), suspended in dry ether (25 c.c.), and a filtered solution of methyl-lithium (from 1·0 g. of lithium) in dry ether (35 c.c.) were refluxed together for 6 hr., under dry nitrogen, cooled, and poured on ice. The product was extracted with ether and crystallised from light petroleum to give the ketol (XV) (1·5 mg.), m. p. 78—80°, mixed m. p. with authentic ketol (m. p. 77—79°) 77—79°. The mother-liquors were combined and distilled, to give the enol ether (XVI), b. p. 115—120° (bath-temp.)/0·03 mm., n_D^{20} 1·5140, $[\alpha]_D^{20}$ +4° ± 2°. Recrystallised from methanol at −40°, this material had m. p. 44—46°, alone or mixed with the authentic enol ether.

8α-*Acetoxy*-14,15-*bisnorlabdan*-13-*one* (XIXc).—(*A*) A solution of the ketol (XV) (400 mg.) in dry pyridine (1·62 c.c.) and acetic anhydride (4·5 c.c.) was protected from the air and refluxed for 6½ hr. Cooling and digestion with saturated sodium hydrogen carbonate solution gave an oil, the spectrum of which gave no indication of the presence of an acetate group. This material was not further investigated.

(*B*) The ketol (XV) (52·8 mg.), dissolved in acetic anhydride (1 c.c.), was treated with one drop of perchloric acid (60% w/v), then left at room temperature for 45 min. and poured on ice; the acetic anhydride was allowed to hydrolyse. The product, b. p. 120—125° (bath-temp.)/0·03 mm., was identified as the enol ether (XVI).

(*C*) The ketol (XV) (0·21 g.) in dry ether (20 c.c.) was cooled to 0°, a small crystal of toluene-*p*-sulphonic acid was added, and keten (from a 500 w keten lamp) was passed into the solution through a sintered-glass bubbler for 45 min. A second addition of the catalyst (50 mg.) was then made, keten was passed for a further 15 min., and the mixture was poured into N-sodium hydroxide. The products isolated with ether gave, after chromatography, the enol ether (XVI) (184 mg.), and the desired *keto-acetate* (XIXc) (12 mg.), m. p. 119·5—122° (Found: C, 74·7; H, 10·7. $C_{20}H_{34}O_3$ requires C, 74·6; H, 10·6%).

(*D*) A solution of the ketol (XV) (3·5 g.) in a mixture of ethanedithiol (5·0 c.c.) and dry benzene (10 c.c.) was cooled to 0° and kept at this temperature for 30 min., during which

hydrogen chloride was bubbled through the mixture. The supply of hydrogen chloride was then cut off, and the mixture left at 0° for 1 hr. Volatile materials were removed under reduced pressure, and the product was adsorbed on deactivated alumina. Elution with 3 : 17 benzene–light petroleum gave the *ethylene dithioketal* of 14,15-bisnorlabd-8-en-13-one (IX) (2·15 g.), b. p. 145—155° (bath-temp.)/0·01 mm. (Found: S, 18·5. $C_{20}H_{34}S_2$ requires S, 18·95%). The infra-red spectrum of this product gave no evidence of hydroxyl or carbonyl bands. Hydrolysis with mercuric acetate (see below) gave the parent unsaturated ketone (IX), identified as its dinitrophenylhydrazone, m. p. and mixed m. p. 150—152°.

Further elution with benzene gave colourless crystals (2·34 g.). Recrystallisation from light petroleum gave the *ethylene dithioketal* of 8α-hydroxy-14,15-bisnorlabdan-13-one (XIXa) as needles, m. p. 113—114° (Found: C, 67·7; H, 10·2; S, 17·8. $C_{20}H_{36}OS_2$ requires C, 67·4; H, 10·1; S, 18·0%).

A solution of ethylmagnesium bromide (from 0·2 g. of magnesium) in dry ether (5 c.c.) was added slowly to a solution of the hydroxythioketal (XIXa) (272 mg.) in dry ether (10 c.c.), under dry nitrogen. The mixture was refluxed for 1 hr., cooled to 0° and treated cautiously with a solution of acetic anhydride (2·5 c.c.) in dry ether (10 c.c.), then left overnight. The product, taken up into ether, was washed with dilute alkali until the washings remained alkaline. Distillation of the solvent gave the *ethylene dithioketal* of 8α-acetoxy-14,15-bisnorlabdan-13-one (XIXb), which crystallised from light petroleum as needles, m. p. 132—134° (Found: C, 66·7; H, 9·9; S, 15·8. $C_{22}H_{38}O_2S_2$ requires C, 66·4; H, 9·6; S, 16·1%).

A solution of mercuric acetate (720 mg.) in water (10 c.c.) was added to a stirred solution of the acetoxythioketal (XIXb) (154 mg.) in acetone (50 c.c.). The mixture was stirred at room temperature for 1 hr., then filtered into water (300 c.c.), and the product was taken up into ether. Evaporation of the solvent, and extraction with boiling light petroleum, gave needles (107 mg.), which, recrystallised from ether, gave 8α-acetoxy-14,15-bisnorlabdan-13-one (XIXc), m. p. 119·5—122°, identical with the material described above.

(+)-14,15-*Bisnorlabd*-8(20)-*en*-13-*one* (XXb).—(*A*) The ketol (XV) (190 mg.) in dry pyridine (1 c.c.) was added to a cooled mixture of phosphorus oxychloride (0·63 c.c.) and pyridine (2·25 c.c.). The vessel was then sealed and left at −14° for 17 hr. Pouring the mixture into water and isolating the product with ether led to a brown oil which on distillation gave the enol ether (XVI) (115 mg.).

(*B*) The keto-acetate (XIXc) (20 mg.) was kept at 350° under dry nitrogen for 45 min., giving a yellow oil, $\nu_{max.}$ 3170w, 1710s, 1640w, 1250m, 975w, 945w, 930w, 890w, and 830w cm.$^{-1}$, that was not investigated further.

(*C*) The enol ether (XVI) (363 mg.) was refluxed at atmospheric pressure (bath-temp. 350°) under nitrogen for 45 min. The resulting yellow oil was identified as 14,15-bisnorlabd-8-en-13-one (IX), n_D^{19} 1·5108 (2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 149—150°).

(*D*) A solution of the hydroxythioketal (XIXa) (330 mg.) in dry pyridine (2 c.c.) was added to a well-cooled mixture of phosphorus oxychloride (1·4 c.c.) and dry pyridine (5·2 c.c.). The mixture, protected from the air, was left at −14° for 15 hr., then poured into ice-cold sodium hydrogen carbonate solution. The oily product, isolated with ether, was dissolved in light petroleum and filtered through a short column of deactivated alumina (30 g.). Distillation gave the ethanedithioketal (297 mg.) of 14,15-bisnorlabd-8(20)-en-13-one (XXa) as a colourless oil, b. p. 155—165° (bath-temp.)/0·03 mm., $n_D^{19\cdot5}$ 1·5536, ν (liquid film) 3070w, 1645m, 890s cm.$^{-1}$.

A solution of mercuric acetate (0·9 g.) in water (5 c.c.) was added slowly to a stirred solution of the unsaturated thioketal (XXa) (450 mg.) in acetone (25 c.c.); stirring was continued for 1 hr. The mixture was filtered into water, and the product, isolated with ether, was adsorbed on deactivated alumina and eluted with 3 : 17 benzene–light petroleum to give unchanged starting material (130 mg.). Elution with benzene gave 14,15-bisnorlabd-8(20)-en-13-one (XXb), b. p. 100—110° (bath-temp.)/0·01 mm., n_D^{21} 1·5092, $[\alpha]_D^{19}$ +36·5° ± 1° (semicarbazone, m. p. 187—189°; 2,4-dinitrophenylhydrazone, m. p. 148—150°) (Found: C, 82·5; H, 11·6. Calc. for $C_{18}H_{30}O$: C, 82·4; H, 11·5%). The infrared spectrum, measured as a natural film, was identical with a published spectrum.[4b] Hosking *et al.*[28] give b. p. 114—115°/0·12 mm., n_D^{19} 1·5093, $[\alpha]_D$ +37°, semicarbazone, m. p. 191·5—193° (185—186°), and 2,4-dinitrophenylhydrazone, m. p. 146—146·5°.

[28] Hosking and Brandt, *Ber.*, 1935, **68**, 37; 1936, **69**, 780; cf. ref. 4*a*.

Labd-14-*yne*-8α,13-*diol* (XXIa).—(*A*) A solution of lithium acetylide (from 1·0 g. of lithium) in liquid ammonia (100 c.c.) was mixed with a solution of the (+)-ketol (XV) (0·8 g.) in dry tetrahydrofuran (50 c.c.) and poured into a bomb cooled to −70°. The vessel was then sealed, warmed to room temperature, and left for 2 days. The ammonia was allowed to evaporate, and the organic material from the bomb was isolated with ether, giving a dark brown oil, which, dissolved in 3 : 2 ether–light petroleum, was filtered through a short column of deactivated alumina. Distillation gave the product (XXIa) (0·79 g.), b. p. 125—135° (bath-temp.)/0·03 mm.

(*B*) A solution of the (+)-ketol (XV) (0·8 g.) in dry tetrahydrofuran (100 c.c.) was added slowly, with stirring, to a solution of ethynylmagnesium bromide (from 200 mg. of magnesium) in the same solvent (100 c.c.). The mixture was stirred under reflux overnight, then worked up in the normal way to give a viscous yellow oil which was adsorbed on deactivated alumina. Elution with light petroleum gave the enol ether (XVI) (210 mg.). Further elution with 1 : 19 ether–light petroleum gave the unchanged ketol (XV) (53 mg.), and elution with 1 : 1 ether–light petroleum gave the desired product (XXIa) (405 mg.).

This material was reduced without further purification.

Sclareol and 13-*Episclareol* (XXIb).—A mixture of the above mixed ethynylcarbinols (0·75 g.), lithium aluminium hydride (1·0 g.), and dry dioxan (100 c.c.) was refluxed for 5 hr., then cooled, and the unchanged hydride was decomposed with ethyl acetate. Ether (150 c.c.) and a few drops of water were added, the suspension was filtered, the residue was washed with ether, and the combined filtrates were poured into water. The product, isolated with ether, was chromatographed on deactivated alumina. Elution with 13 : 7 ether–light petroleum gave crystals (206 mg.). Further chromatography on deactivated alumina or magnesium trisilicate, or graded elution chromatography on deactivated alumina, failed to resolve this material further. The infrared spectrum (in Nujol) of the various fractions was always identical.

All the fractions were combined and recrystallised twice from light petroleum to give a mixture of sclareol and 13-episclareol (XXIb) as rods, m. p. 97—98° [mixed m. p. with authentic sclareol (m. p. 101—102°), 92—93°], $[\alpha]_D^{16}$ +2° ± 2° (Found: C, 77·8; H, 11·9. Calc. for $C_{20}H_{36}O_2$: C, 77·9; H, 11·7%). The infrared spectrum, measured for a CS_2 solution, was almost identical with that of authentic 13-episclareol (see below). In Nujol mull, all three spectra were different. Equal weights of sclareol and 13-episclareol were mixed together and recrystallised from light petroleum to give rods, m. p. and mixed m. p. with the above product 96—98°. The infrared spectrum of this mixture (in Nujol mull) was identical with that of the above product.

Further elution with a 13 : 7 ether–light petroleum gave unchanged starting material (XXIa) (188 mg.).

(+)-*Labd*-8(20)-*en*-14-*yn*-13-*ol* (XXIIa) *and its Reduction.*—The (+)-unsaturated ketone (XXb) (150 mg.) in dry ether (20 c.c.) was added, with stirring, to lithium acetylide (from 0·2 g. of lithium) in liquid ammonia (200 c.c.). Stirring was continued for 2 hr., and the ammonia then removed. The product (XXIIa), isolated in the normal way, was a colourless oil (145 mg.), $[\alpha]_D^{19}$ +16°, ν (in CS_2) 3620m, 3320m, 3100w, 1645m (C=C), 1112m (>C=CH_2), 887s (>C=CH_2) cm.$^{-1}$.

This product was reduced with lithium aluminium hydride as described in the previous experiment, to a crude product with an infrared spectrum (in CS_2) very similar to that of manoöl (XXX), but with differences in the intensities of the double-bond absorptions. Chromatography on deactivated alumina gave three partly separated viscous oils, the infrared spectra of which indicated that extensive double-bond rearrangements had occurred. These products were not further investigated.

8α-*Acetoxylabd*-14-*yn*-13-*ol* (XXIIIa *and* c).—The keto-acetate (XIXc) (620 mg.) in dry ether (60 c.c.) was added slowly to a stirred solution of lithium acetylide (from 0·8 g. of lithium) in liquid ammonia (300 c.c.). After 3 hr., evaporation of the ammonia, dilution with water, and isolation with ether gave brown crystals (619 mg.). Two recrystallisations from ether gave colourless needles, m. p. 161—169°, that were adsorbed on deactivated alumina (110 g.). Elution with 1 : 19 light petroleum–benzene gave successively " isomer A " (235 mg.) [(13-R)-8α-*acetoxylabd*-14-*yn*-13-*ol*] (XXIIIa) which when rechromatographed and recrystallised from light petroleum at −10° gave needles (190 mg.), m. p. 138—140° (Found: C, 76·1; H, 10·4. $C_{22}H_{36}O_2$ requires C, 75·9; H, 10·4%), ν (in CCl_4) 3625w, 3320m, 1735s cm.$^{-1}$, ν (in Nujol) 3410m, 3250m, 1715s, and 1270s cm.$^{-1}$. Further elution gave " isomer B " (277 mg.) [(13-S)-8α-*acetoxylabd*-14-*yn*-13-*ol*] (XXIIIc) which when rechromatographed and recrystallised from ether

at −10° gave needles (157 mg.), m. p. 180·5—181·5° (Found: C, 75·9; H, 10·2%), ν (in CCl_4) 3540w (OH), 3440w (OH), 3250m (C≡CH), 1725s (acetate), and 1240 (acetate) cm.$^{-1}$ (the relative intensities of the first two bands were unaffected by dilution), ν (in Nujol), 3365m, 3260w, 1702s, and 1274s cm.$^{-1}$.

(13-R)-*Labd*-14-*ene*-8α,13-*diol* (*Sclareol*) (XXIIIb).—A mixture of the acetoxyethynylcarbinol ("isomer A"; XXIIIa) (135 mg.) and lithium aluminium hydride (0·75 g.) in dry dioxan (25 c.c.) was refluxed for 3½ hr. The product was isolated with ether in the normal way and filtered through deactivated alumina (12 g.) prepared in the same solvent. Removal of the solvent and recrystallisation from light petroleum gave *sclareol* (XXIIIb) as needles, m. p. and mixed m. p. 103—104°, $[\alpha]_D^{19}$ −3° ± 1° (Found: C, 77·9; H, 11·5. $C_{20}H_{36}O_2$ requires C, 77·9; H, 11·7%). The infrared spectra of this compound and of natural sclareol were identical in all respects when measured for CS_2 solution and Nujol mull.

(13-S)-*Labd*-14-*ene*-8α,13-*diol* (13-*Episclareol*) (XXIIId).—The acetoxyethynylcarbinol ("isomer B"; XXIIIc) (120 mg.) was treated as described in the previous experiment, and gave, after recrystallisation from light petroleum, 13-*episclareol* (XXIIId) as needles, m. p. 130—131·5°, mixed m. p. with sclareol 91—93°, $[\alpha]_D^{18}$ +7·2° ± 1° (Found: C, 78·0; H, 11·7%). The infrared spectrum of this material in CS_2 solution was almost identical with that of sclareol, but was different when measured in Nujol mull.

(13-R)- *and* (13-S)-*Labd*-8-*en*-14-*yn*-13-*ol* (XXVIIa *and* c).—A solution of the (+)-unsaturated ketone (IX) (4·8 g.) in dry ether (200 c.c.) was added slowly to a stirred solution of lithium acetylide (from 5·0 g. of lithium) in liquid ammonia (600 c.c.). After 2 hr., the ammonia was removed, and the product, isolated in the normal way, was adsorbed on deactivated alumina. Elution with 1 : 4 benzene–light petroleum gave unchanged starting material (1·3 g.). Further elution with 2 : 3 benzene–light petroleum gave a colourless viscous oil (3·68 g.). The first 1·31 g. of this oil (fraction A) and the final 1·07 g. (fraction B) were separated. Fraction A was chromatographed on deactivated alumina (130 g.). The first 0·89 g. was collected and rechromatographed to give fore-run (0·41 g.) which was rechromatographed to give a new fore-run (90 mg.). The last fore-run, dissolved in methanol (10 c.c.), was diluted to faint opalescence with water and treated with a solution of silver nitrate (0·1 g.) in methanol (1 c.c.). The precipitated silver derivative was collected and decomposed by boiling it for 2½ hr. with sodium cyanide (1·0 g.) in water (7 c.c.) and ethanol (1 c.c.). The recovered ethynylcarbinol was isolated with ether, filtered in benzene through deactivated alumina (10 g.) and distilled. The (13-*R*)-ethynylcarbinol (XXVIIa) was obtained as a viscous oil, b. p. 105—110° (bath-temp.)/0·03 mm., $[\alpha]_D^{21}$ +74° ± 1°.

Fraction B was treated in the same way, the chromatographic tail fractions being collected in this case. Purification *via* the silver derivative and distillation gave the (13-*S*)-ethynylcarbinol (XXVIIc), b. p. 105—110° (bath-temp.)/0·03 mm., $[\alpha]_D^{19\cdot5}$ +28° ± 1°. The infrared absorption of these products in CS_2 was identical: ν 3540m (OH), 3250m (C≡CH), 1210 (C–O) cm.$^{-1}$. No crystalline derivatives could be obtained.

(13-R)-*Labd*-8,14-*dien*-13-*ol* (XXVIIb) (*Isomanoöl*).—A solution of the (13-*R*)-ethynylcarbinol (XXVIIa) (80 mg.) in light petroleum (3 c.c.) was hydrogenated in the presence of Lindlar's catalyst (48 mg.). After 15 min. 5·0 c.c. of hydrogen had been absorbed (calc. 6·25 c.c.) and hydrogen uptake had almost ceased. The reaction was stopped at this stage, the catalyst and solvent were removed, and the unchanged acetylene was precipitated as the silver complex as in the preceding experiment. The filtrate was distilled to give *isomanoöl* (XXVIIb), b. p. 130—135° (bath-temp.)/0·4 mm., $[\alpha]_D^{22}$ +73·5° ± 1° (Found: C, 82·5; H, 11·4. $C_{20}H_{34}O$ requires C, 82·8; H, 11·7%), $\varepsilon_{918\ cm.^{-1}}$ 179 (in CS_2).

(13-S)-*Labd*-8,14-*dien*-13-*ol* (XXVIId) (13-*Epi-isomanoöl*).—The (13-*S*)-ethynylcarbinol (XXVIIc) (100 mg.) was hydrogenated as described in the previous experiment, to give 13-*epi-isomanoöl* (XXVIId), b. p. 125—130° (bath-temp.)/0·3 mm., $[\alpha]_D^{19\cdot5}$ +27·5° ± 1° (Found: C, 82·9; H, 11·7%), $\varepsilon_{918\ cm.^{-1}}$ 175 (in CS_2).

Under the same conditions of measurements, manoöl had $\varepsilon_{918\ cm.^{-1}}$ 195.

Isomanoöl from Sclareol.—Sclareol (10 g.) was refluxed for 7 hr. with acetic anhydride and pyridine, as in the directions of Büchi and Biemann.[20] The acetyl groups in the product were then removed by reduction with lithium aluminium hydride.[20] The resulting oil was chromatographed on deactivated alumina. Elution with light petroleum gave a colourless oil (0·35 g.), assumed to be a mixture of hydrocarbons and not investigated. Further elution, with 2 : 3 benzene–light petroleum, gave an oil (4·46 g.), b. p. 120—125° (bath-temp.)/0·1 mm. whose

infrared spectrum (in CS_2) was very similar to that of manoöl, the differences being attributable to some rearrangement of the exocyclic double bond.

This material was chromatographed on deactivated alumina a further four times. In each case, the weight of adsorbent was 120 times that of the material adsorbed, and the column length was 10—15 times its diameter. The first third of the material eluted from the column, each time, was collected and distilled [b. p. 110—120° (bath temp.)/0·02 mm.]. The infrared spectrum of each fraction in CS_2 solution was measured, and the extinction coefficients of the bands at 918 and 887 $cm.^{-1}$ were calculated. The extinction coefficient of the band at 918 $cm.^{-1}$ was normalised in each case to 195, and the amount of isomanoöl in the mixture was calculated by comparing the band at 887 $cm.^{-1}$ with the corresponding band in manoöl. The results are summarised in Fig. 1.

The final fraction (85 mg.) (Found: C, 82·6; H, 11·6%) contained 43% of isomanoöl, and had an infrared spectrum intermediate between those of manoöl and isomanoöl (Fig. 2).

Methyl 8α-*Hydroxylabd*-13-*en*-15-*oate* (XXVIIIb).—A solution of ethoxyacetylene (1·5 g.) in dry ether (15 c.c.) was added slowly to a mixture of dry benzene (30 c.c.) and a solution of ethylmagnesium bromide (from 0·43 g. of magnesium) in ether (30 c.c.), at 0° under nitrogen. The mixture was refluxed for 45 min., cooled to 0°, treated with a solution of the (+)-ketol (XV) (0·44 g.) in dry ether (10 c.c.), refluxed for a further 17 hr., cooled, and decomposed with saturated ammonium chloride solution. The product (530 mg.), isolated in the normal way, was refluxed in methanol (25 c.c.) for 5 min. The solvent was then removed, and the residual oil was adsorbed on deactivated alumina. Elution with light petroleum gave the enol ether (XVI) (95 mg.). Further elution with 1 : 1 light petroleum–benzene gave an oil (221 mg.), b. p. 120—130° (bath-temp.)/0·03 mm. This material, ν (liquid film) 1720s, 1150s $cm.^{-1}$, had no absorption in the region of 3500 $cm.^{-1}$, and was considered to be a mixture of the unsaturated esters (XXIXb) (Found: C, 79·6; H, 10·9. Calc. for $C_{21}H_{34}O_2$: C, 79·3; H, 10·7%). Further elution with benzene gave successively crystals (47 mg.), which when crystallised twice from light petroleum at −11° gave isomer A of the unsaturated ester (XXVIIIb), m. p. 133—133·5° (lit.,[23] m. p. 132—134°), and an oil which recrystallised from light petroleum at −11° to give rods of isomer B of the unsaturated ester (XXVIIIb) (138 mg.), m. p. 100—101° (lit.,[23] m. p. 99—101°).

(13-R)- *and* (13-S)-*Methyl* 8α-*Hydroxylabdan*-15-*oate* (*Methyl Labdanolate and Methyl* 13-*Epilabdanolate*) (XXVIIIc *and* d).—Isomers A and B of the unsaturated ester (XXXb) were combined (185 mg.) and hydrogenated under atmospheric pressure over Adams catalyst (47·5 mg.) in ethanol (12 c.c.). The catalyst was removed and the solvent evaporated. Chromatography on deactivated alumina gave, on elution with 3 : 7 light petroleum–benzene, a single band, the end fractions of which were investigated. The first fraction (37 mg.) gave crystals of methyl 13-epilabdanolate (XXVIIId) which, after two recrystallisations from light petroleum at −15°, had m. p. 72·5—73·5°, mixed m. p. with methyl labdanolate 60—62°, $[\alpha]_D^{19}$ +3° ± 2° (lit.,[23] m. p. 72—74°, $[\alpha]_D$ +2°) (Found: C, 74·0; H, 11·1. Calc. for $C_{21}H_{33}O_3$: C, 74·6; H, 11·2%). The infrared spectrum of the compound in CS_2 solution had a single sharp band at 3540 $cm.^{-1}$, indicating the absence of intramolecular hydrogen-bonding. In Nujol mull, the spectrum was identical with that published.[23] The final fraction (33 mg.) was recrystallised from light petroleum to give methyl labdanolate (XXVIIIc) as needles, m. p. and mixed m. p. 71—73°, $[\alpha]_D^{19}$ −7·5° ± 2·5° (lit.,[29] m. p. 73—74°, $[\alpha]_D$ −8·0°) (Found: C, 74·3; H, 11·1%). The infrared spectra of this compound and of authentic labdanolic ester were identical (in CS_2 and in Nujol mull). There was a single sharp band at 3540 $cm.^{-1}$ in CS_2 solution, indicating the absence of intramolecular hydrogen-bonding.

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[29] Cocker and Halsall, *J.*, 1956, 4259.