QUARTERLY REVIEWS

THE SYNTHESIS OF DI- AND TRI-TERPENES

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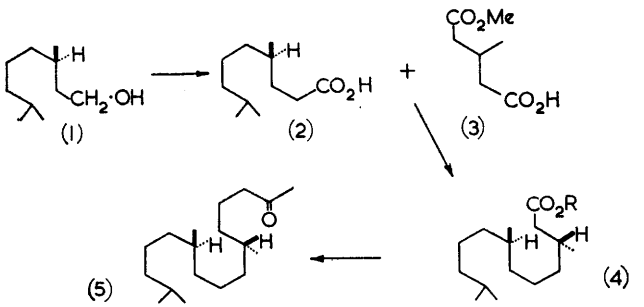
THE total synthesis of terpenoid compounds, as in other fields, provides the final confirmation of structural investigations. In some cases it enables an unambiguous choice to be made between two or more structures, each in itself consistent with the degradative evidence.

Apart from this utilitarian purpose, however, there is an aspect of greater appeal. The higher terpenes are complex molecules, and as such provide a considerable intellectual challenge to the aspiring synthetic chemist. Also, the measure of a successful synthesis is not simply in that its object is achieved, but in the elegance of the route chosen. More perhaps than any other branch of the subject, synthesis remains a field where aesthetic as well as scientific satisfaction may be enjoyed. In the opinion of the present authors, this aspect of the subject provides a powerful stimulus, the reaction to which is well illustrated in the field under review.

Acyclic Diterpenes

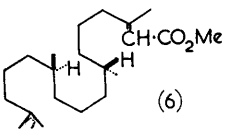
Phytol.—This diterpene (7) contains two asymmetric carbon atoms and earlier synthetic operations[1] led to mixtures of the various epimeric modifications. However, the work of Burrell, Jackman, and Weedon[2] not



[1] Simonsen and Barton, "The Terpenes," Cambridge Univ. Press, 1952, Vol. III; Lukes and Zubacova, *Chem. Listy*, 1957, **51**, 330; Weichet, Hodrova, and Kvita, *ibid.*, p. 568; Sacrycheva, Vorobeva, Kuznetzova, and Preobrazhenskii, *Zhur. obshchei Khim.*, 1958, **28**, 147; Nazarov, Gusev, and Gunar, *ibid.*, p. 1444.

[2] Burrell, Jackman, and Weedon, *Proc. Chem. Soc.*, 1959, 263.

only gave the naturally occurring, optically active compound but also permitted an assignment of absolute configuration at these asymmetric centres. By a nitrile synthesis, D-(+)-dihydrocitronellol (1) was converted into the acid (2) which, by anodic cross-coupling with the L-(+)-, D-(−)-, and DL-forms of the glutaric half ester (3) gave rise to three epimeric forms of the ester (4; R=Me). A further anodic synthesis with lævulic acid gave three forms of the ketone (5). A comparison of the rotations of these ketones with the ketone obtained by degrading phytol showed both the asymmetric centres in phytol to have the D-configuration. The synthesis was completed by treating this ketone with methoxyacetylene, and rearranging the methoxyethynylcarbinol with acid, to give a separable mixture of *cis*- and *trans*-methyl phytenoates (6), the *trans*-isomer of which with lithium aluminium hydride afforded natural phytol (7).



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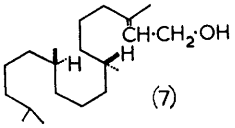
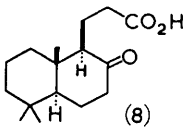


(7)

Sclareol and Labdanolic Acid.—The problem of synthesising[3] these compounds is primarily one of controlling the configuration at the five asymmetric centres. The keto-acid (8) was obtained by ozonolysis of a tricyclic ketone (41; R = H) to be described below. Treatment of it with methyl-lithium followed by dehydration led, through the hydroxy-ketone (9) to the unsaturated ketone (10; R = Ac). This, on oxidation with hypoiodite, gave the corresponding unsaturated acid (10; R = CO_2H)



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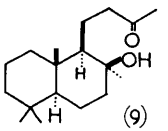

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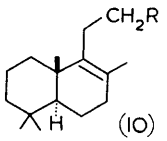


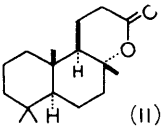
(10)

which was cyclised under acidic conditions to (±)-ambreinolide (11). This furnished a relay. (+)-Ambreinolide was hydrolysed to the lithium salt of the related hydroxy-acid which with methyl-lithium gave the ketone (12). This ketone was converted into a mixture of epimeric acetoxyethynylcarbinols (13; R^1 = Ac, R^2 = C:CH), which, on being separated and reduced with lithium aluminium hydride, gave rise to sclareol (13; R^1 = H; R^2 = $CH{:}CH_2$) and 13-episclareol. Through the dehydration[4] of sclareol to manool (16) this work also constitutes a formal total synthesis of the latter compound.

The ketol (12) was also transformed into methyl labdanolate (15) and

[3] Bigley, Rogers, and Barltrop, *J.*, 1960, 4613.
[4] Büchi and Biemann, *Croat. Chem. Acta*, 1957, **29**, 163.

its 13-epimer by reaction with ethoxyacetylene, acid-catalysed rearrangement of the ethoxyethynylcarbinol (13; R^2 = C:C·OEt, R^1 = H) to the unsaturated ester (14), and hydrogenation.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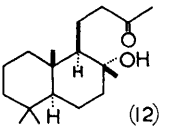
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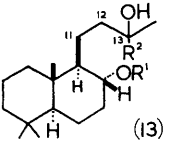
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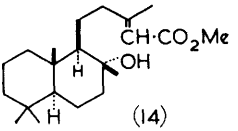
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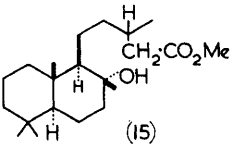
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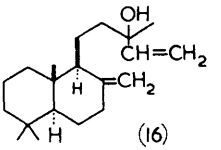
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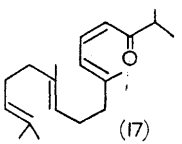
Tricyclic Diterpenoids

The biosynthesis of tricyclic diterpenoids appears[5] to take place through the cyclisation of acyclic polyisoprenoid precursors and, in the attempt to parallel such processes *in vitro*, numerous farnesol derivatives have been shown[6] to give rise to bi- and tri-cyclic systems under acidic conditions. For example, the ketone (17) has been converted[7] into an abietatriene (20).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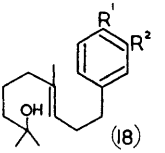
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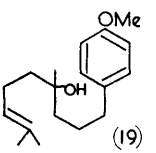
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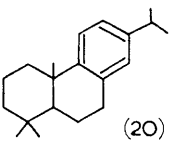

(20)

Similarly, the unsaturated alcohols (18; R^1 = OMe, R^2 = H) and (19) gave rise[8,9] to A/B-*cis*- and -*trans*-methoxypodocarpatriene (33; X = H). The related compound (18; R^1 = H, R^2 = Pr^i) was cyclised to *cis*- and *trans*-abietatriene.[9] Such syntheses appear to offer little control over the configurations of the ring junctions and have not been extended, so far, to include the introduction of the tertiary 1-carboxyl group characteristic of the diterpenoid acids.

Cyclisation of phenethylcyclohexanols and ring extension of naphtha-

[5] Barltrop and Rogers in "Progress in Organic Chemistry," Butterworths Scientific Publns., London, 1961, Vol. V, pp. 96-131 and refs. cited therein.

[6] Ruzicka in "Perspectives in Organic Chemistry," Interscience Publ., Inc., London, 1956, p. 265; Eschenmoser in "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," Churchill Ltd., London, 1959, p. 217; Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1955, **77**, 5068; Barton and de Mayo, *Quart. Rev.*, 1957, **11**, 190, and refs. cited therein.

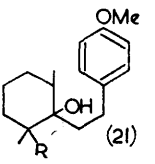
[7] Caliezi and Schinz, *Helv. Chim. Acta*, 1952, 35, 1649.

[8] Fetizon and Delobelle, *Compt. rend*, 1958, **246**, 2776.

[9] Ansell and Gadsby, *J.*, 1959, 2994.

lene derivatives have been much more productive from the standpoint of the total synthesis of naturally occurring tricyclic diterpenoids.

Podocarpic Acid.—Podocarpic acid (22; R^1 = OH, R^2 = H), though not strictly a diterpenoid, has been a key compound in these studies. King, King, and Topliss[10] prepared the ethynylcarbinol from *p*-methoxyphenylacetylene and ethyl 1,3-dimethyl-2-oxocyclohexanecarboxylate, and reduced it to the cyclohexanol (21; R = CO_2Et) which was cyclised with polyphosphoric acid. This gave a mixture of three stereoisomeric esters, one of which was identified as (±)-*O*-methylpodocarpic ester (22; R^1 = OMe, R^2 = Et), identical with a substance which had been earlier synthesised by an essentially similar route.[11,12]



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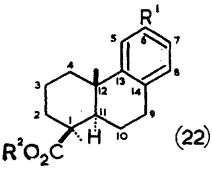

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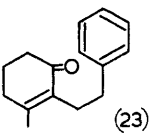
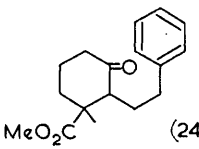


(23)

In a further synthesis[13] of podocarpic acid, the addition of hydrogen cyanide to the unsaturated ketone (23), followed by hydrolysis and esterification, gave the keto-ester (24). Reaction with methylmagnesium iodide then gave a hydroxy-ester and thence, on cyclisation, a mixture of tricyclic epimers from which was isolated deoxypodocarpic acid (22; $R^1 = R^2 = H$), shown to be identical with the acid obtained by Haworth and Barker,[14]



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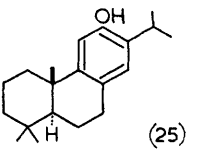


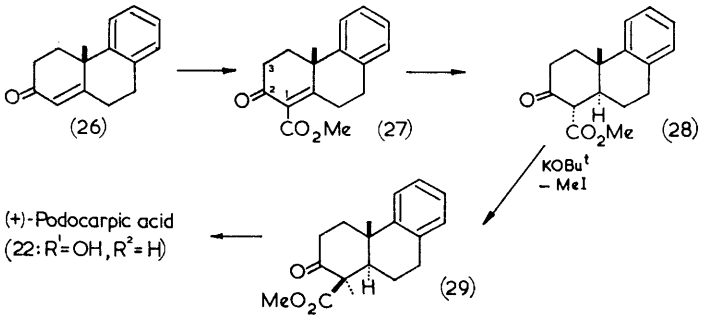
(25)

and *cis*-deoxypodocarpic acid (45). The synthesis was completed by a Friedel–Crafts acetylation, giving the ketone (22; R^1 = Ac, R^2 = Me) which, oxidised by peracetic acid, gave the acetate (22; R^1 = OAc, R^2 = Me) of podocarpic ester.

A different approach to the synthesis of (+)-podocarpic acid is illustrated by the work of Wenkert and his co-workers.[15] The unsaturated

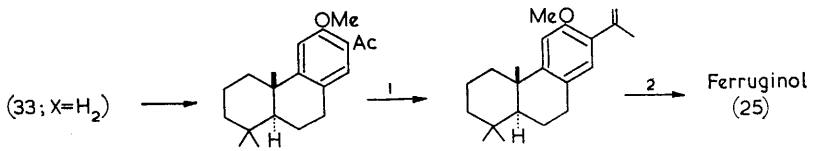
[10] King, King, and Topliss, *Chem. and Ind.*, 1956, 119.
[11] Haworth and Moore, *J.*, 1946, 633.
[12] Bhattacharyya, *J. Indian Chem. Soc.*, 1945, **22**, 165.
[13] Ghatak, *Tetrahedron Letters*, 1959, No. 1, 19; Ghatak, Datta and Ray, *J. Amer. Chem. Soc.*, 1960, **82**, 1728.
[14] Haworth and Barker, *J.*, 1939, 1299.
[15] Wenkert and Jackson, *J. Amer. Chem. Soc.*, 1958, **80**, 217; 1959, **81**, 5601; Wenkert and Tahara, *ibid.*, 1960, **82**, 3229.

ketone (26), prepared by a Robinson ring-extension reaction from the corresponding 2-tetralone, was carboxylated with triphenylmethylsodium



and carbon dioxide and then esterified to give a mixture of the ester (27) and the isomeric 3-carboxylic ester. Catalytic hydrogenation of the ester (27) gave the saturated β-keto-ester (28) which, by methylation, afforded a mixture of the keto-ester (29) and (mainly) its 1-epimer. Clemmensen reduction of the former followed by resolution then gave (+)-deoxypodocarpic acid (22; $R^1 = H$, $R^2 = H$). The introduction of the 6-hydroxyl group, by acetylation and per-acid oxidation followed the lines of the Ghatak synthesis[13] just discussed.

Ferruginol.—The first synthesis[16] of ferruginol (25) proceeded similarly. The ring closure of the alcohol (21; R = Me), obtained in two stages from *p*-methoxyphenylacetylene and 2,2,6-trimethylcyclohexanone, gave a mixture of the *cis*- and *trans*-isomers of 6-methoxypodocarpatriene (33; $X = H_2$) from which (±)-ferruginol was obtained by the reactions shown.

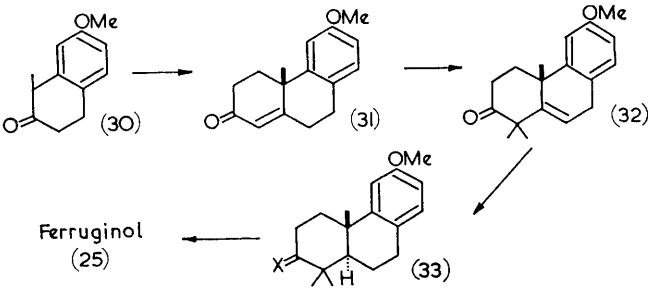


Reagents: 1, MeMgI, then $-H_2O$. 2, H_2–catalyst, then HBr.

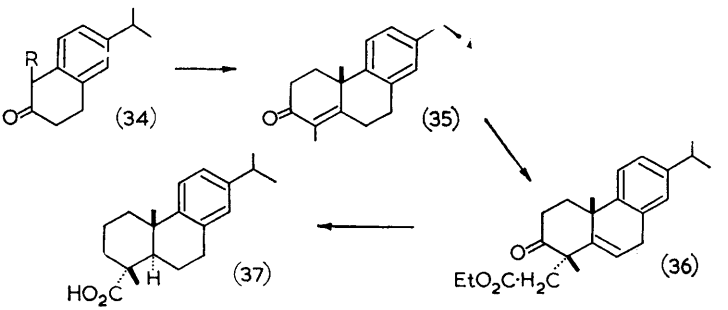
A later, but stereospecific, synthesis[17] of (±)-6-methoxypodocarpatriene (33; $R = H_2$) and hence of (±)-ferruginol, used the naphthalene approach. The β-tetralone (30), by a Robinson annellation followed by methylation of the resulting $\alpha\beta$-unsaturated ketone (31), gave the ketone (32). In this compound, the β-oriented methyl groups ensured that the subsequent catalytic hydrogenation took place on the back face of the molecule.

[16] King, King, and Topliss, *Chem. and Ind.*, 1954, 108; *J.*, 1957, 573.
[17] Raman and Rao, *Experientia*, 1956, **12**, 472; *Tetrahedron*, 1958, **4**, 294.

Removal of the carbonyl group then afforded *trans*-6-methoxypodocarpatriene (33; X = H_2). The transformation of this compound into ferruginol followed standard procedure.



Dehydroabietic Acid.—The higher degree of stereospecificity obtained in synthesis from β-tetralones and exemplified in the foregoing synthesis is shown again in the stereospecific synthesis of (±)-dehydroabietic acid (37) devised by Stork and Schulenberg.[18] This synthesis, which was a milestone in diterpene chemistry, proceeded according to the sequence (34→37).

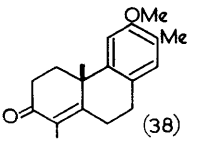


After methylation of the β-tetralone (34; R = H) by the enamine method[19] to the ketone (34; R = Me), a ring-extension using ethyl vinyl ketone gave the tricyclic compound (35) in which the 12β-methyl group forced the subsequent alkylation with bromoacetic ester to occur from the less hindered rear face of the molecule. Catalytic hydrogenation of the ester (36) so obtained also occurred from the rear and removal of the carbonyl group and a Barbier–Wieland degradation of the side chain finally gave (±)-dehydroabietic acid (37).

Nimbiol.—The synthesis[20] of nimbiol methyl ether (39; X = O, R = Me) followed a parallel course. The compound (38) obtained by annellating the corresponding β-tetralone was methylated and reduced. Oxidation by chromic acid of the product (39; X = H_2, R = Me) then gave nimbiol

[18] Stork and Schulenberg, *J. Amer. Chem. Soc.*, 1956, **78**, 250.
[19] Stork, Terrell, and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1954, **76**, 2029.
[20] Ramachandran and Dutta, *J.*, 1960, 4766.

methyl ether. This compound, which has been obtained[21] from podocarpic acid, has also been synthesised[22] from *trans*-6-methoxypodocarpatriene (33; X = H_2) by oxidation to the ketone (39; X = O, R = H) followed by insertion of the 7-methyl group through the 7-chloromethyl derivative.



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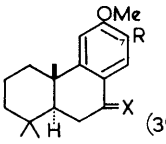

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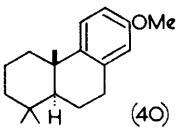

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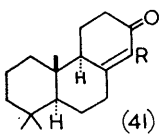
Totarol.—This resinol (43), which does not follow the classical isoprene rule, was synthesised by Barltrop and Rogers[23] from the tricyclic ether (40), itself prepared by the cyclisation of 1-*m*-methoxyphenethyl-2,2,6-trimethylcyclohexanol. The ether, submitted to a Birch reduction, gave a mixture of the unsaturated ketones (41; R = H) and (42; R = H), each of which when alkylated with sodium t-pentyl oxide and isopropyl iodide gave a mixture of the isopropylated ketones (41 and 42; R = Pr^i). Dehydrogenation of the mixture then gave (±)-totarol.



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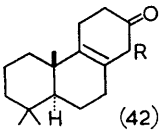

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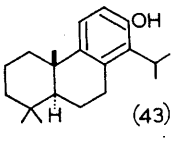
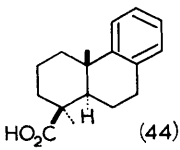


(43)

Compounds Related to the Tricyclic Diterpenoids

The four possible racemates represented by structures (44—47) are now all known. *trans*- (44) and *cis*-Deoxypodocarpic acid (45), which have



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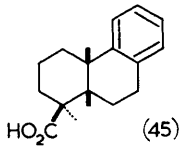

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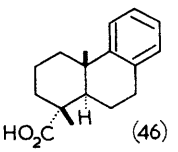

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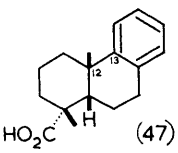


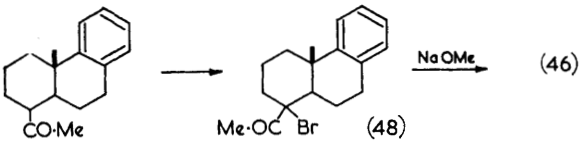
(47)

been synthesised as racemates by methods described earlier in this Review, have also been obtained in optically active forms. Deoxygenation of podocarpic acid[24] gave *trans*-(+)-deoxypodocarpic acid; removal of the isopropyl group from dehydroabietic acid[25] (37) and its nitrile[26,27] with

[21] Bible, *Tetrahedron Letters*, 1960, No. 9, 20; Wenkert and Stenhagen, Abs. 137th Amer. Chem. Soc. Meeting, 1960, 36.
[22] Fetizon and Delobelle, *Tetrahedron Letters*, 1960, No. 9, 16.
[23] Barltrop and Rogers, *J.*, 1958, 2566.
[24] Wenkert and Jackson, *J. Amer. Chem. Soc.*, 1958, **80**, 217.
[25] Ohta and Ohmori, *Pharm Bull. (Japan)*, 1957, **5**, 96.
[26] Wenkert and Chamberlin, *J. Amer. Chem. Soc.*, 1959, **81**, 688.
[27] Wenkert and Jackson, *J. Amer. Chem. Soc.*, 1958, **80**, 211.

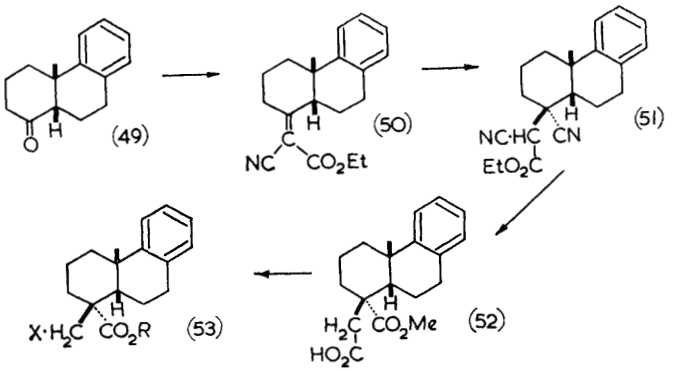
aluminium chloride gave, as main product, the enantiomorph of acid (45) and the corresponding nitrile. The latter transformation has been explained by invoking two retro-Friedel–Crafts reactions; the first causes the expected replacement of isopropyl by hydrogen, and the second a fission of the 12,13-bond and subsequent re-formation of ring B.

Deisopropyldehydroabietic acid (46), prepared[28] by oxidative removal of the isopropyl group from dehydroabietic acid, has been synthesised by two methods; first,[13] from 1-methyl-2-tetralone by a sequence analogous to the previously described synthesis[18] of dehydroabietic acid and, secondly,[29] by a route through the ketone (48). Favorskii rearrangement of this



bromo-ketone gave a mixture of esters from which was isolated a small amount of methyl deisopropyldehydroabietate.

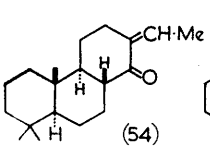
The fourth isomer was prepared[30] from Stork and Burgstahler's ketone[31] (49), a compound which appears to exist mainly in the *cis*-form. A condensation with cyanoacetic ester gave the unsaturated ester (50) to which hydrocyanic acid added stereospecifically from the unhindered back face of the molecule to give the adduct (51), from which the acid (52) was



obtained. Bromination of the silver salt of this acid gave a bromomethyl compound (53; X = Br, R = Me) (and some nuclear brominated material) which when reduced gave the required (±)-*cis*-deisopropyldehydroabietic ester (53; R = Me, X = H).

[28] Ohta, *Pharm. Bull. (Japan)*, 1956, **4**, 273; Ohta and Ohmori, *ibid.*, 1957, **5**, 91.
[29] Barltrop and Day, *Tetrahedron*, 1961, **14**, 310.
[30] Saha, Ganguly, and Dutta, *J. Amer. Chem. Soc.*, 1959, **81**, 3670.
[31] Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1951, **73**, 3544.

Methods have recently been developed[32] for introducing the methyl and vinyl groups at position 7 characteristic of the pimaradiene diterpenoids. Methylation of the ethylidene ketone (54) with methyl iodide and potassium t-butoxide gave a mixture of epimeric ketones (55; R^1 = Me, R^2 = $CH{:}CH_2$ and *vice versa*), from which were obtained by reduction and



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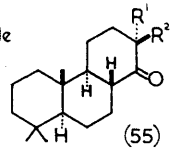

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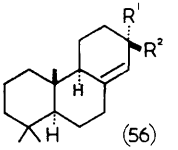

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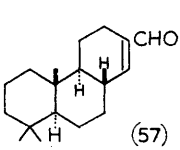


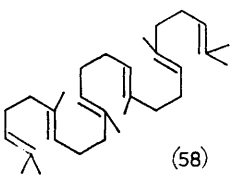
(57)

dehydration the corresponding epimers, pimaradiene and sandaracopimaradiene (56), neither being identical with rimuene.

Similarly, methylation of the aldehyde[32,33] (57) gave the epimeric methyl derivatives (56; R^1 = CHO, R^2 = Me, and *vice versa*) which were transformed into the corresponding pimaradienes by a Wittig reaction with methylenetriphenylphosphorane.

Acyclic Triterpenes

Squalene.—The great importance of squalene (58) in the biosynthesis of the steroids and triterpenes[5] has stimulated much interest in its synthesis.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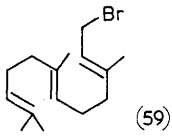


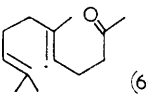
(59)

Early experiments[34] in which two molecules of farnesyl bromide (49) of doubtful homogeneity were coupled in a Wurtz reaction gave a hydrocarbon resembling squalene, but further developments had to await the discovery that natural squalene gave a crystalline clathrate compound with thiourea, an *X*-ray investigation of which showed[35] that squalene had the all-*trans*-geometry (58).

The coupling of farnesyl bromide was repeated by Isler and his coworkers,[36] a synthetic halide being used and the coupling effected with lithium. From its method of synthesis, the farnesyl bromide was largely the all-*trans*-isomer (59), and in this case it was possible to isolate the all-*trans*-squalene, in low yield, as the thiourea adduct.

[32] Ireland and Schiess, *Tetrahedron Letters*, 1960, No. 25, 37.
[33] Barltrop, Giles, Hanson, and Rogers, *J.*, 1962, in the press.
[34] Karrer and Helfenstein, *Helv. Chim. Acta*, 1931, **14**, 78.
[35] Nicolaides and Laves, *J. Amer. Chem. Soc.*, 1954, **76**, 2596.
[36] Isler, Rüegg, Chopard-dit-Jean, Wagner, and Bernhard, *Helv. Chim. Acta*, 1956, **39**, 897.

A different approach has been used by three groups of workers.[37] This employed the Wittig reaction between geranylacetone (60) and the ylide



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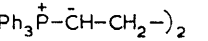
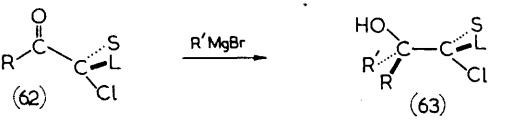


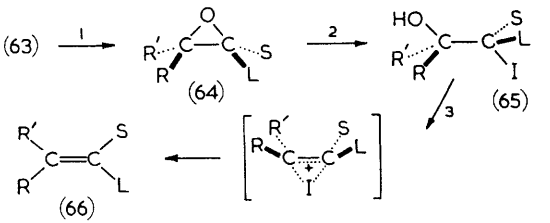
(61)

(61) derived from 1,4-dibromobutane. This reaction is known to give a mixture of geometrical isomers, and in fact only a low yield of all-*trans*-squalene was obtained. Purification through the thiourea adduct yielded a product identical with natural squalene. Further refinements in this field awaited a general stereoselective synthesis of olefins. The elegant researches of Cornforth and his co-workers[38] have supplied this need and resulted in a total stereoselective synthesis of squalene.[39] This synthesis is based on the ideas that an α-chloro-ketone will be most reactive in the conformation (62), even though this rotational isomer may be present in only low concentration, and that attack on such a ketone by a Grignard reagent will occur preferentially from the less hindered side to give predominantly the product (43) (S and L are the smaller and the larger group). The stages shown lead through (64) and (65) to the olefin (66),



(62) (63)

80—85% overall selectivity being normal. The three final reactions in this

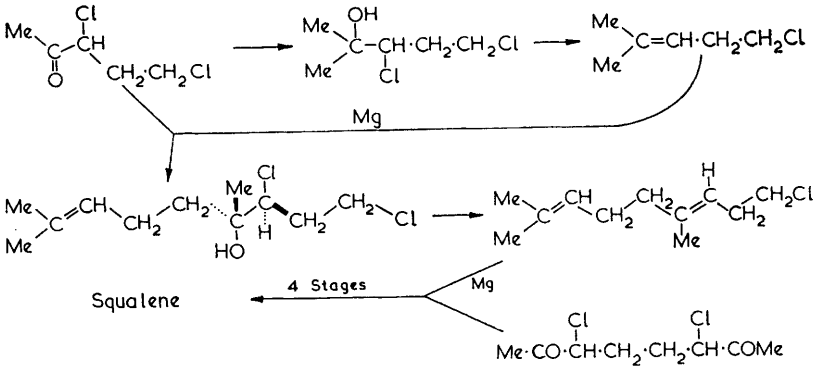


Reagents: 1, OH^-. 2, NaI–AcOH. 3, $POCl_3$–C_5H_5N, $SnCl_2$.

sequence are 100% stereoselective. By use of this principle, squalene has been synthesised as illustrated; 18—20% of the product formed a clath-

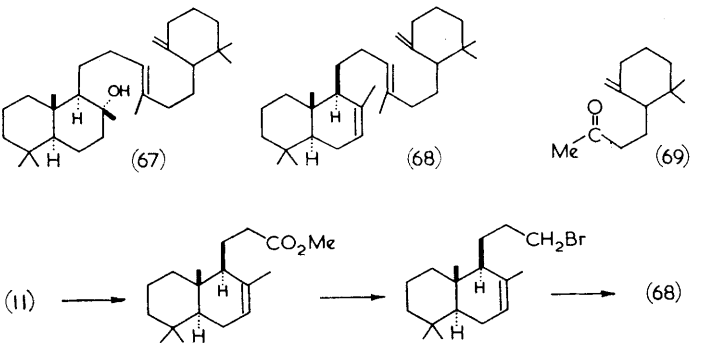
[37] (*a*) Dicker and Whiting, *Chem. and Ind.*, 1956, 351; *J.*, 1958, 1994; (*b*) Trippett, *Chem. and Ind.*, 1956, 80; (*c*) Mondon, *Annalen*, 1957, **603**, 115.
[38] Cornforth, Cornforth, and Mathew, *J.*, 1959, 112.
[39] Cornforth, Cornforth and Mathew, *J.*, 1959, 2539.

rate. Since pure all-*trans*-squalene gives only a 70% yield of clathrate, it follows that an overall stereoselectivity of > 25%, or > 70% per double bond, was achieved.



Tricyclic Triterpenes

Ambrein.—Ambrein (67) is a triterpene derived from ambergris. No synthesis of this compound has been achieved, but the dehydration product ambratriene (68) has been synthesised[40] from the ambrein degradation products ambreinolide (11) and dihydro-γ-ionone (69) by the route shown. The last stage involved formation of the Grignard reagent, reaction with the ketone (69), and dehydration. Both ambreinolide[41] and dihydro-γ-ionone[42] have been independently synthesised.

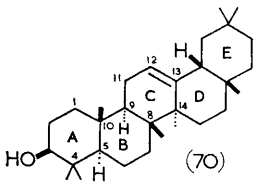


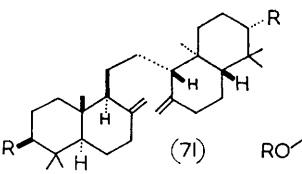
[40] Dürst, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 46.
[41] (*a*) Dietrich and Lederer, *Compt. rend.*, 1952, **234**, 637; (*b*) Wolff, *ibid.*, 1954, **238**, 1041; (*c*) Barltrop, Bigley, and Rogers, *Chem. and Ind.*, 1958, 558; *J.*, 1960, 4613.
[42] Ruzicka, Büchi, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 293.

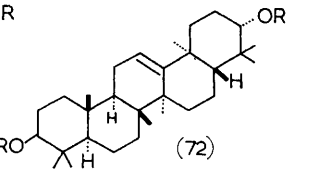
Lanosterol Group.—The four triterpenes of this group have been partially synthesised from cholesterol.[43] In view of the earlier syntheses[44] of cholesterol, this constitutes a formal total synthesis. Further discussion of this topic is here omitted since, for reasons of space, full justice could not be done to the many complexities of what is, essentially, an exercise in steroid chemistry.

Onocerin and the Pentacyclic Triterpenes

The problem of total synthesis of the pentacyclic triterpenes, *e.g.*, β-amyrin (70), by stepwise ring-extension would be one of great complexity, a feature of particular difficulty being the vicinal quaternary centres at positions 8 and 14. Halsall and Thomas[45] suggested that this difficulty could be overcome by constructing a tetracyclic (AB—DE) system which would be expected to cyclise under acidic conditions to form ring C. This suggestion was supported by the finding[46] that α-onocerin (71; R = OH) under acidic conditions gave the pentacyclic γ-onocerin (72; R = H).





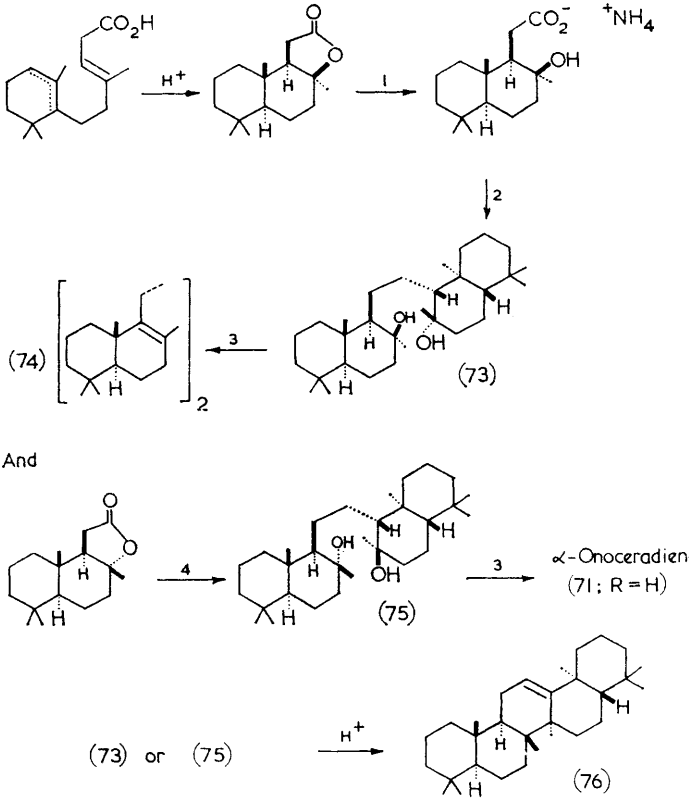


Several successful approaches to the onocerin skeleton have been published in recent years.

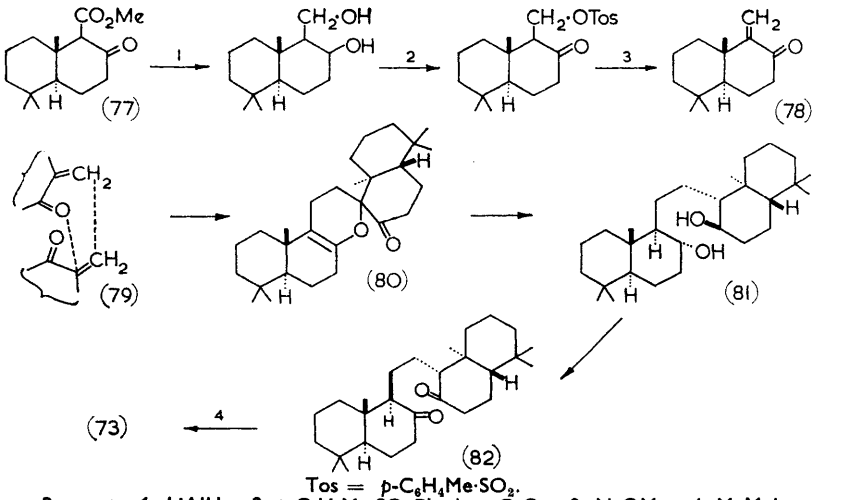
α- and β-Onoceradiene (71; R = H, and 74), and their cyclisation product pentacyclosqualene (76), already known as degradation products of the onocerins,[46] were synthesised[47] by the elegant route illustrated, the crucial step being a Kolbe electrolytic coupling reaction to the " doubled " compounds (73), (74), and (75).

The glycol (73) has been obtained by another group of workers[48] using the following ingenious reaction sequence from (77) through (82).

[43] Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852; *Chem. and Ind.*, 1954, 605; *J.*, 1957, 1131.
[44] Woodward, Sondheimer, and Taub, *J. Amer. Chem. Soc.*, 1951, **73**, 3548; Woodward, Sondheimer, Taub, Heusler, and McClamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223; Cardwell, Cornforth, Duff, Holtermann, and Robinson, *J.*, 1953, 361.
[45] Halsall and Thomas, *J.*, 1956, 2431.
[46] Barton and Overton, *J.*, 1955, 2639.
[47] Corey and Sauers, *J. Amer. Chem. Soc.*, 1957, **79**, 3925.
[48] Romann, Frey, Stadler, and Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 1900.



Reagents: 1, Resolve, then NH_3. 2, Electrolysis. 3, $POCl_3$–C_5H_5N. 4, Two stages.

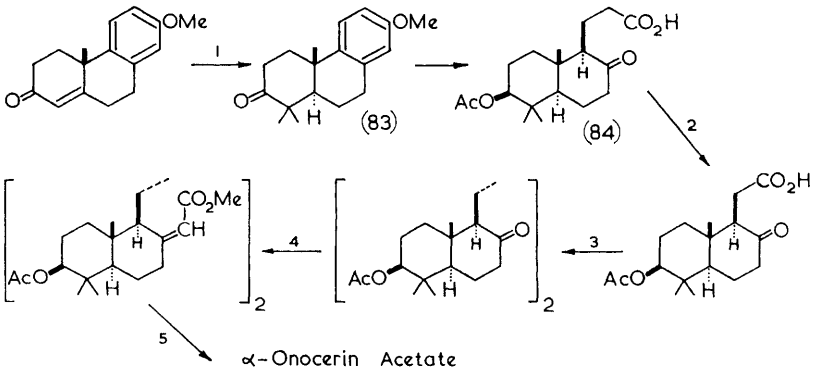


Tos = p-$C_6H_4Me{\cdot}SO_2$.

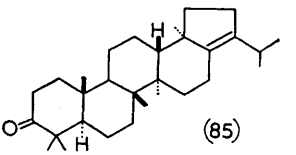
Reagents: 1, $LiAlH_4$. 2, p-$C_6H_4Me{\cdot}SO_2Cl$, then CrO_3. 3, NaOMe. 4, MgMeI.

The dimerisation (79) of the ketone (78) appears[49] to be governed by the principle of "maximum accumulation of π-bonds," as is the normal Diels–Alder reaction, leading only to the *endo*-products. Of the four possible dimers, only two (80) appear to have been formed, one of which led to racemic bisnoronoceranediol (81), and the other to the *meso*-compound. Resolution and oxidation to bisnoronoceranedione (82), followed by a Grignard reaction, gave the glycol (83).

α-Onocerin itself has been synthesised[50] by an anodic coupling, similar to that used by Corey and Sauers. The main reaction sequence is as shown.



Reagents: 1, MeI–KOBu^t, then H_2–Pd–C. 2, Barbier–Wieland degradation. 3, Resolve, then electrolyse. 4, EtO·C:C·MgBr, then H_2SO_4–MeOH. 5, OH^-, then decarboxylate.

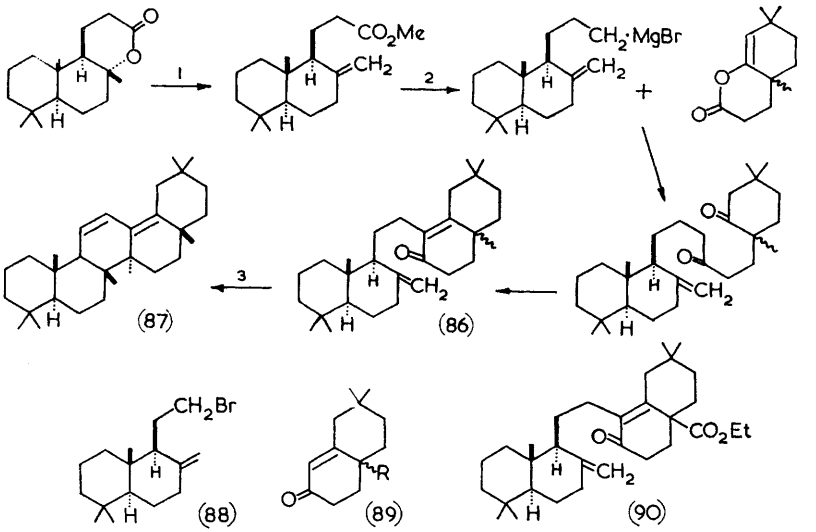


The degradation of the ether (83) to the acid (84) followed the sequence (40)→(41; R = H)→(8) described earlier. An ingenious feature of this synthesis is the conversion of a carbonyl group into an exocyclic methylene *via* an $\alpha\beta$-unsaturated acid. This constitutes a total synthesis of the three onocerins, and, since γ-onocerin (72; R = H) has been converted[51] into hopen-1-one-1 (85), also the first total synthesis of a naturally occurring pentacyclic triterpene.

Finally, amyra-11,13(18)-diene (87) which possesses the carbon skeleton of β-amyrin (70) has been synthesised, albeit in only 2% yield, by the route formulated.[52] Its separation was facilitated by its characteristic ultraviolet spectrum. The intermediate (86) has also been obtained by

[49] Stadler, Nechvatal, Frey, and Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 1373.
[50] Stork, Davies, and Meisels, *J. Amer. Chem. Soc.*, 1959, **81**, 5516.
[51] Dunstan, Fazackerley, Halsall and Jones, *Croat. Chem. Acta*, 1957, **29**, 173; Fazackerley, Halsall, and Jones, *Proc. Chem. Soc.*, 1957, 353; Shaffner, Caglioti, Arigoni, and Jeger, *Helv. Chim. Acta*, 1958, **41**, 152.
[52] Corey, Hess, and Proskow, *J. Amer. Chem. Soc.*, 1959, **81**, 5258.

Reagents: 1, OH^-, then CH_2N_2, then $POCl_3$–C_5H_5N. 2, $LiAlH_4$, then p-$C_6H_4Me{\cdot}SO_2Cl$, then LiBr, then Mg. 3, MeLi, then H^+.

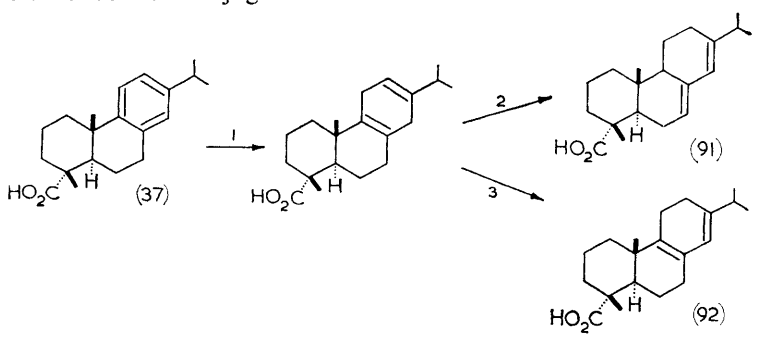


a different route.[53] The halide (88) was obtained from sclareol (13; $R^1 = H$, $R^2 = CH{:}CH_2$) and used to alkylate the $\alpha\beta$-unsaturated ketone (89; R = Me). Alkylation of the keto-ester (89; R = CO_2Et) has led[53] to the potentially valuable intermediate (90).

Addendum

Since the preparation of this manuscript, significant developments have occurred in this field, some of which are reported below.

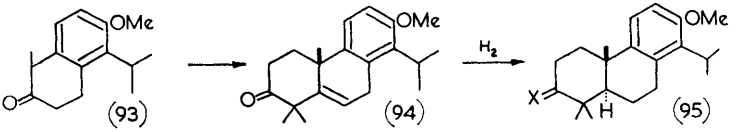
Abietic Acid (91) **and Palustric Acid** (92).—These resin acids have been prepared[54] by reducing dehydroabietic acid (37) and then isomerising the double bonds into conjugation.



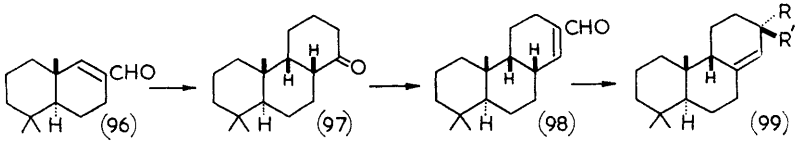
Reagents: 1, Li–$EtNH_2$–t-$C_5H_{11}{\cdot}OH$. 2, H^+. 3, OH^- at 210°.

[53] Barltrop, Rogers, Leggate and Rushton, unpublished work.
[54] Burgstahler and Worden, *J. Amer. Chem. Soc.*, 1961, **83**, 2587.

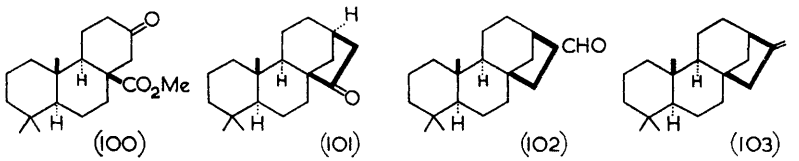
Totarol (43).—The methyl ether of this substance and 3-oxototaryl methyl ether (95; X = O) were obtained[55] by hydrogenation of the intermediate (94), itself obtained by standard methods from the β-tetralone (93).



Pimaradienes.—An ingenious reaction sequence, by which the aldehyde (96) was transformed into the tricyclic aldehyde (98) *via* the ketone (96), was devised by Church and Ireland.[56] Methylation, etc., as described above, then led to isomers (99; R = Me, R′ = $CH{:}CH_2$ and *vice versa*), epimeric at C-13 (C-9 by steroid numbering), of pimaradiene and sandaracopimaradiene, respectively. These compounds were found not to be identical with rimuene or isopimaradiene, implying the incorrectness of the formulations of these latter compounds.



Phyllocladene.—A total synthesis of this tetracyclic diterpene (103) has been published.[57] The keto-ester (100), a degradation product of phyllocladene which had already been synthesised,[58] was converted by a Reformatsky reaction followed by reduction and ring-closure into the ketone (101), and thence in several stages into the aldehyde (102). This is another degradation product of phyllocladene, convertible into the diterpene by a Wolff–Kishner reduction, the reduction being accompanied by migration of the double bond.



[55] Taylor, *J.*, 1961, 3319.
[56] Church and Ireland, *Tetrahedron Letters*, 1961, 493.
[57] Turner and Gänshirt, *Tetrahedron Letters*, 1961, 231.
[58] Turner and Shaw, *Tetrahedron Letters*, 1960, No. 18, 24; Church, Ireland, and Marshall, *ibid.*, 1960, No. 17, 1.