Terpenoids. Part XXVIII.[1] Total Synthesis of Enmein [2]

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The total synthesis of enmein (1) is reported. The diol acetal, *ent*-3β,20-epoxy-3-methoxy-17-norkaurane-6α,16α-diol (3) was used as the important relay compound.

ENMEIN (1) is a major bitter principle [3] of the leaves of *Isodon trichocarpus* Kudo and *I. japonicus* Hara,[4] and its complicated B-secokaurene-type structure and absolute configuration have been elucidated on the basis of the chemical [5] and *X*-ray [6] studies. Additional evidence for the structure and absolute configuration of enemin was given by the chemical conversion of enmein into *ent*-kaurane [7,8a] and *ent*-kaur-16-ene.[8b]

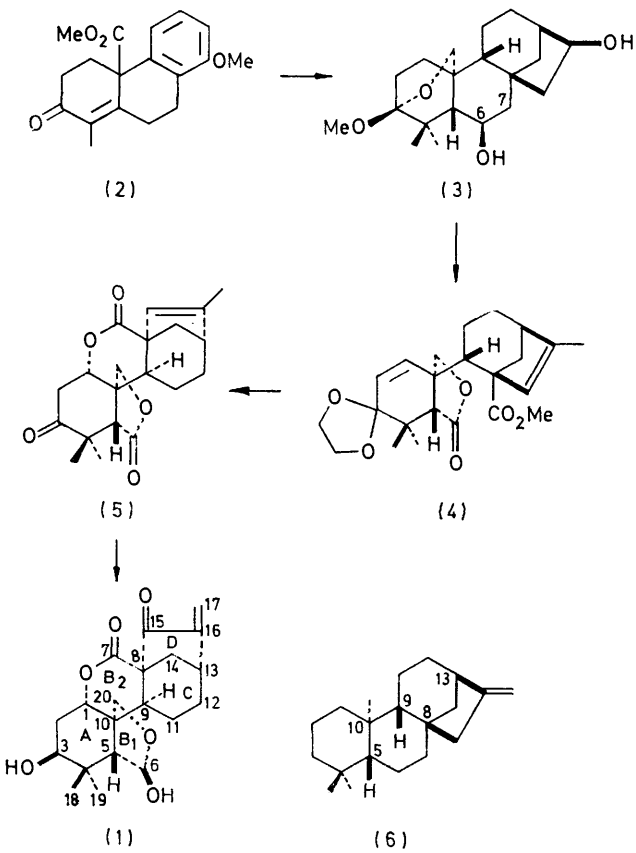
We now report a total synthesis of enmein (1).

Prior to the synthesis, we decided on a general synthetic route as shown in Scheme 1.

Enmein had been thought to be biosynthesised *via* cleavage of the C(6)–C(7) bond of the kaurene skeleton. A recent tracer experiment [9] has shown *ent*-kaur-16-ene (6) to be a precursor of enmein. Among the eight asymmetric centres of enmein, the absolute configurations at the 5-, 8-, 9-, 10-, and 13-carbon atoms are identical with those in *ent*-kaur-16-ene. It is reasonable, therefore, to choose the norkaurane derivative (3), which is obtained in good yield from enmein,† as an important relay compound in this synthesis. We first synthesised the racemic compound (3) from the phenanthrene derivative (2), and then the optically active enantiomer (3) derived from enmein was transformed into the B-secokaurene derivative (4) by a pathway containing a cleavage of the C(6)–C(7) bond. Compound (4) was then converted into the keto-dilactone (5), and this was transformed into enmein (1) *via* the stereoselective formation of two hydroxy-groups at C-3 and C-6 followed by modification of ring D.

Synthesis of the Intermediate (3).—The keto-ester (2) was synthesised in *ca.* 60% overall yield by a route involving methoxycarbonylation of 5-methoxy-2-tetralone [10] by dimethyl carbonate, alkylation with 1-chloropentan-3-one,[11] and heating in toluene in the presence of toluene-*p*-sulphonic acid.

Methoxycarbonylation at C-1 of 5-methoxy-2-tetralone was demonstrated by an A_2B_2 signal centred at δ 2·62 in the n.m.r. spectrum of the product, indicating the presence of methylene groups at C-3 and C-4. Methylation of (2) by methyl iodide yielded the product (7), whose n.m.r. spectrum showed a triplet assignable to the vinylic proton at C-6. If methoxycarbonylation had occurred at C-3 of 5-methoxy-2-tetralone, the n.m.r. spectrum of the corresponding compound (7a) should



SCHEME 1

† The preparation of (3) from enmein is described in the following paper.

[1] Part XXVII, E. Fujita, M. Taoka, M. Shibuya, T. Fujita, and T. Shingu, *J.C.S. Perkin I*, 1973, 2277.

[2] Preliminary communication, E. Fujita, M. Shibuya, S. Nakamura, Y. Okada, and T. Fujita, *J.C.S. Chem. Comm.*, 1972, 1107.

[3] (*a*) T. Ikeda and S. Kanatomo, *J. Pharm. Soc. Japan*, 1958, **78**, 1128; (*b*) K. Naya, *J. Chem. Soc. Japan*, 1958, **79**, 885; (*c*) M. Takahashi, T. Fujita, and Y. Koyama, *J. Pharm. Soc. Japan*, 1958, **78**, 947.

[4] E. Fujita, T. Fujita, and M. Shibuya, *Chem. Comm.*, 1966, 297; *J. Pharm. Soc. Japan*, 1967, **87**, 1076.

[5] (*a*) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Fujita, T. Okamoto, M. Natsume, Y. Kawazoe, K. Shudo, T. Ikeda, M. Tomoeda, S. Kanatomo, T. Kosuge, and K. Adachi, *Tetrahedron Letters*, 1964, 1243; (*b*) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, H. Irie, A. Numata, T. Fujita, and T. Suzuki, *Tetrahedron*, 1966, **22**, 1659.

[6] Y. Iitaka and M. Natsume, *Tetrahedron Letters*, 1964, 1257; *Acta Cryst.*, 1966, **20**, 197.

[7] K. Shudo, M. Natsume, and T. Okamoto, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1019.

[8] (*a*) E. Fujita, T. Fujita, K. Fuji, and N. Ito, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1023; *Tetrahedron*, 1966, **22**, 3423; (*b*) E. Fujita, T. Fujita, and Y. Nagao, *Tetrahedron*, 1972, **28**, 555.

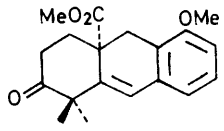
[9] T. Fujita, S. Takao, and E. Fujita, *J.C.S. Chem. Comm.*, 1973, 434.

[10] J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1949, 1855.

[11] E. M. McMahon, J. N. Roper, jun., W. P. Utermohlen, jun., R. H. Hasket, R. C. Harris, and J. H. Brant, *J. Amer. Chem. Soc.*, 1948, **70**, 2977.

have shown a singlet or a doublet with a small coupling constant assignable to the vinylic proton.

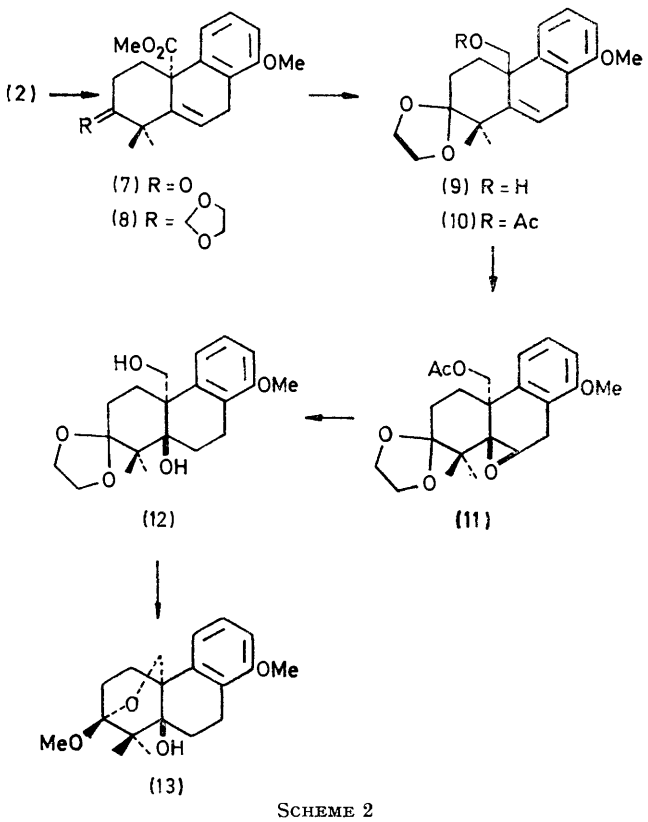
Compound (7) has suitably positioned functional



(7a)

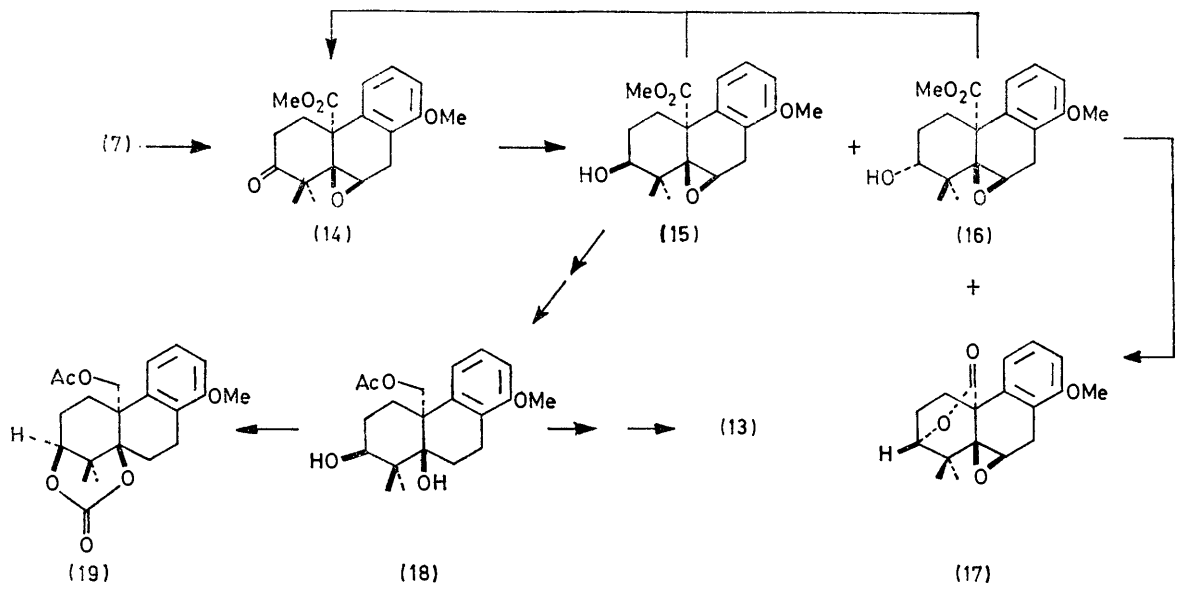
groups for the synthesis of (3). In order to carry out the reduction of the aromatic ring and the synthesis of ring D stereoselectively and in good yields, some modifications of these functional groups were necessary. Ethylene acetalisation of (7), lithium aluminium hydride reduction of acetal (8), acetylation of alcohol (9), and then epoxidation of acetate (10) with *m*-chloroperbenzoic acid in chloroform to give (11) proceeded in 48% overall yield. Because of the instability of compounds (7)—(10) in air, they were used without extensive purification. Epoxide (11) on reduction with lithium aluminium hydride gave diol (12) in 71% yield, which on heating in methanol under the presence of toluene-*p*-sulphonic acid afforded a 91% yield of the methyl acetal (13). The sequence is shown in Scheme 2.

Epoxidation of (10) was assumed to proceed under steric control to form a product with the epoxide ring *trans* to the acetoxymethyl group, and hence, the *trans* A/B ring junction in compounds (12) and (13) was assumed. Unambiguous confirmation of this stereochemistry was required, however, because the steric control of the succeeding synthetic steps depended on the compounds



SCHEME 2

over platinum oxide in acetic acid gave alcohols (15) and (16), and a lactone (17) ($\nu_{max.}$ 1740 cm^{-1}). Jones oxidation of (15) and (16) regenerated ketone (14), which



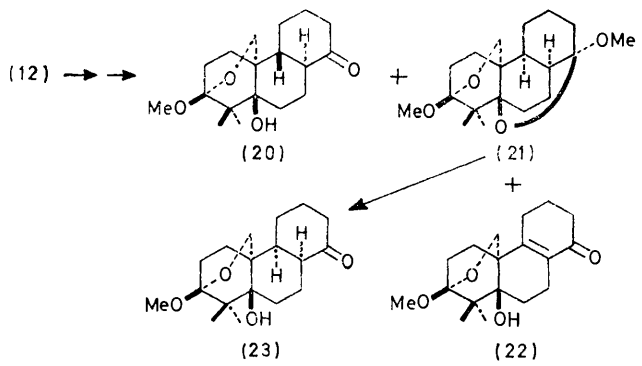
SCHEME 3

possessing the correct stereochemistry. This confirmation was achieved by the transformations shown in Scheme 3.

Epoxide (14) [derived from the olefin (7)] on reduction showed the epimeric relationship of the two alcohols. The *cis* relationship between the 3-hydroxy- and 10-methoxycarbonyl groups in alcohol (16) was demonstrated by a conversion of (16) into the lactone (17) on

heating in acetic acid for 5 min. Alcohol (15) on tetrahydropyranylation, lithium aluminium hydride reduction, acetylation, and subsequent acidic hydrolysis gave diol (18), which on treatment with phosgene yielded a cyclic carbonate (19) ($\nu_{max.}$ 1730 cm^{-1}). Thus, two hydroxy-groups at C-3 and C-5 in (18) were shown to have the *cis* diaxial stereochemistry. The diol (18) was then converted into (13) *via* chromic acid oxidation, hydrolysis with sodium carbonate, and methyl acetalisation. Thus, the stereochemistry of compounds (12) and (13) was established.

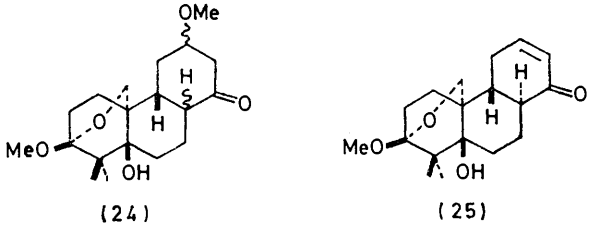
Subsequently, we reduced (12) with lithium in liquid ammonia; treatment of (12) with *ca.* 18 equiv. of lithium in ammonia gave a mixture of products, which, after hydrolysis with dilute hydrochloric acid in acetone, was heated in methanol in the presence of toluene-*p*-sulphonic acid. Chromatography of the crude mixture resulted in the separation of three products. The major product was assigned the most stable *trans,transoid,trans* structure (20) for rings A, B, and C, because it was recovered without any epimerisation after refluxing with sodium methoxide in methanol. One of the minor products (21) contained two methyl acetal groups. This compound was subjected to acidic hydrolysis under mild conditions to yield ketone (23). The diacetal structure is only possible when rings A, B, and C have *trans,cisoid,cis* fusion. The structures (21) and (23) are thus reasonable. Another minor product was assigned as (22). This compound was hydrogenated to (20) by treatment with lithium in liquid ammonia (Scheme 4).



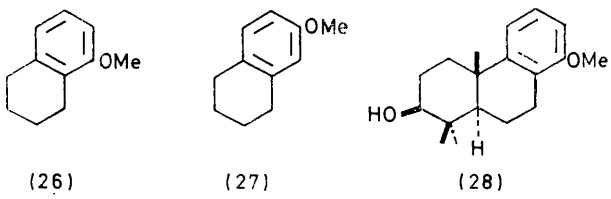
SCHEME 4

The reduction of (13) required stronger conditions than for (12), but it afforded an oily product of molecular weight 338 in addition to the foregoing compounds (20) and (22). This oil on heating with potassium t-butoxide in t-butyl alcohol gave an αβ-unsaturated ketone, which on hydrogenation over Adams catalyst yielded the foregoing product (20). The structures (24) and (25) were therefore assigned to the oil and the αβ-unsaturated ketone, respectively.

Generally, the reduction of 5-methoxy-1,2,3,4-tetrahydronaphthalene (26) derivatives with alkali metal in liquid ammonia is much more difficult than that of 6-methoxy-1,2,3,4-tetrahydronaphthalene (27) derivatives.



For instance, Birch reduction [12] of (26) gave only a trace of reduction products, and Birch reduction has been little used [13] for the derivatives of (26).



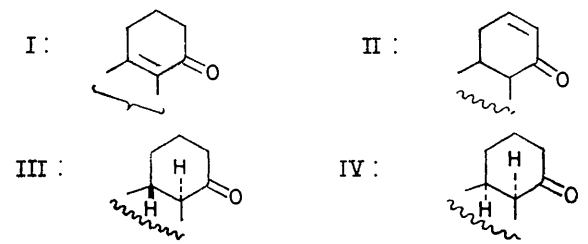
In the Table, the reaction conditions and results in these reductions are compared with those reported for the reduction of compound (28).[13b] The unusually high reactivity of (12) and (13) may be due to intramolecular participation by the hydroxy-group(s), and examples in which a hydroxy-group influences reduction with lithium in liquid ammonia have been reported.[14] The suitable location and stereochemistry of the hydroxy-group appears to control the configuration of the products. The most probable transition states are thought to be A and B for the first step of the reduction and C for the second step. The following factor(s) in these transition

Reaction conditions and products

No.	Starting material	Li [a] (equiv.)	EtOH (equiv.)	Time (min)	Products [b] (yields/%)
i	(12)	10	50	3	I(18), III(34), IV(29) [c]
ii	(12)	18	120	40	I(9), III(64), IV(22)
iii	(13)	100	300	120	I(10), II(13), III(28) [d]
iv	(28)	600	780	120	I(8), II(11)

[a] Concentration (w/v) of lithium in liquid ammonia was 0·3% for i and ii, 0·7% for iii, and *ca.* 5% for iv.

[b]



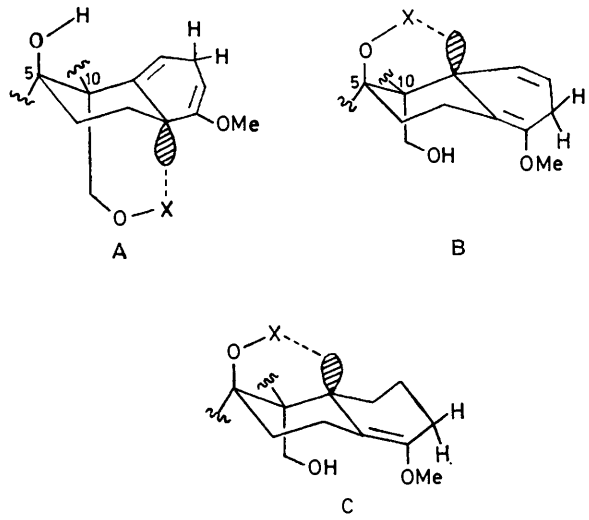
[c] Recovery of the starting material was 9%. [d] Recovery of the starting material was 44%.

[12] A. J. Birch, *J. Chem. Soc.*, 1944, 430.

[13] (*a*) W. S. Johnson, R. Pappo, and W. F. Johns, *J. Amer. Chem. Soc.*, 1956, **78**, 6339, 6354; (*b*) R. B. Turner, K. H. Gänshirt, P. E. Shaw, and J. D. Tauber, *ibid.*, 1966, **88**, 1776.

[14] (*a*) D. F. MacSweeney and R. Ramage, *Tetrahedron*, 1971, **27**, 1481; (*b*) T. B. Windholz, R. D. Brown, and A. A. Patchett, *Steroids*, 1965, **6**, 409.

states may accelerate the reaction and control the stereochemistry of the products: (i) when X = H, stabilisation of the carbanion or transfer of the proton by bridge



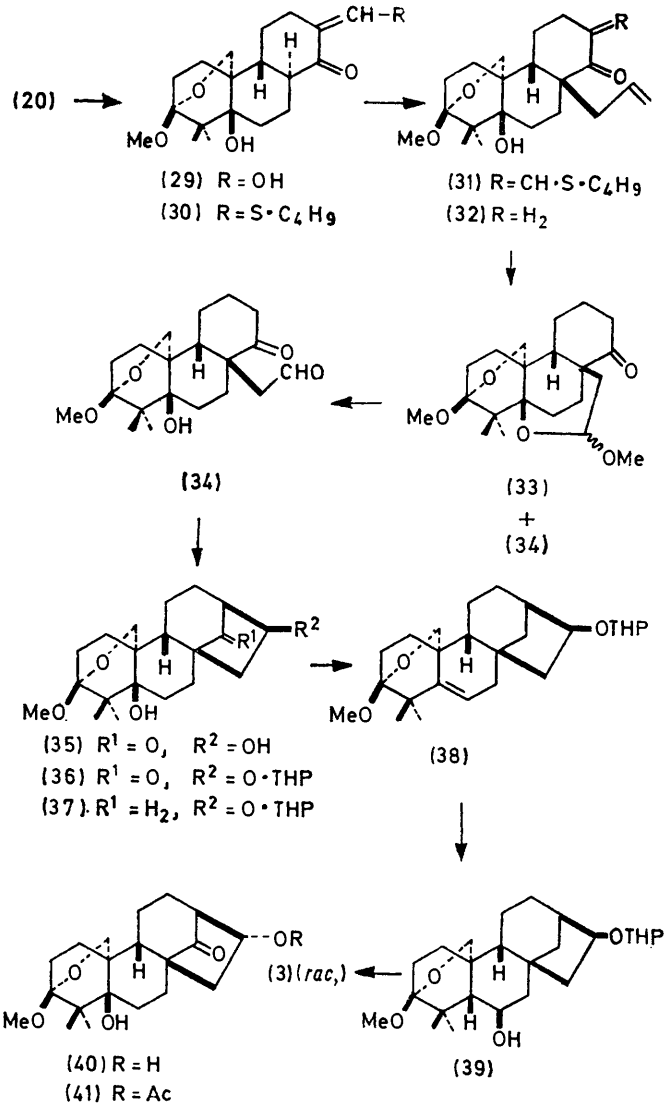
formation between the hydroxy-proton and the carbanion, and/or (ii) when X = Li, stabilisation of the carbanion by lithium bridge formation between the hydroxy-group and the carbanion, and/or (iii) acceleration of the formation of the carbanion by electron-transfer through the hydroxy-group. Investigation of the detailed mechanism is under progress.

The active methylene at C-13 of compound (20) was protected [15] to give (30), which was subjected to allylation at C-8 to yield (31). Elimination of the protecting group at C-13 by heating with potassium hydroxide in aqueous methanol afforded (32) [36% overall yield from (20)]. Ozonisation of (32) in methanol–chloroform followed by treatment with dimethyl sulphide gave a keto-diacetal (33) in addition to aldehyde (34). Thus, it was directly proved that compounds (32) and (33) had the desired *trans,transoid,cis* stereochemistry (Scheme 5).

An acidic partial hydrolysis of (33) gave aldehyde (34), which was treated with 0·2% (w/v) sodium methoxide in methanol for 0·5 h at room temperature to yield the 16β-hydroxy-derivative (35), the product from a kinetically controlled reaction, in good yield [64% from (32)]. The same reaction under more drastic conditions (2·5% sodium methoxide methanol–tetrahydrofuran at reflux) was thermodynamically controlled to yield the 16α-ol (40). The configurations of the new hydroxy-groups of (35) and (40) were assigned on the basis of the following findings: (i) The n.m.r. ($CDCl_3$) spectrum of the acetate (41) gave a quartet (J 3 and 8·5 Hz) at δ 5·08 assignable to C(16)H; (ii) alcohol (35) was epimerised into (40) under the foregoing drastic conditions.

These reactions can be tentatively explained by consideration of their transition states, D and E in Scheme 6. The transition state D, where two oxygen functions are far apart, is more stable than E, where they are close and parallel. Hence, the 16β-ol (35) predominates over the 16α-ol (40) under kinetically controlled conditions, in spite of unfavoured endosteric interaction [16] in the former.

The 16β-ol (35) was converted into the tetrahydropyranyl derivative (36), which on Huang-Minlon reduction gave the deoxo-product (37) [70% from (35)]. Dehydration of (37) with thionyl chloride in pyridine afforded the 5-ene (38) (87%), which was converted into the 6β-ol (39) *via* hydroboronation. Finally, the 6β-ol



SCHEME 5

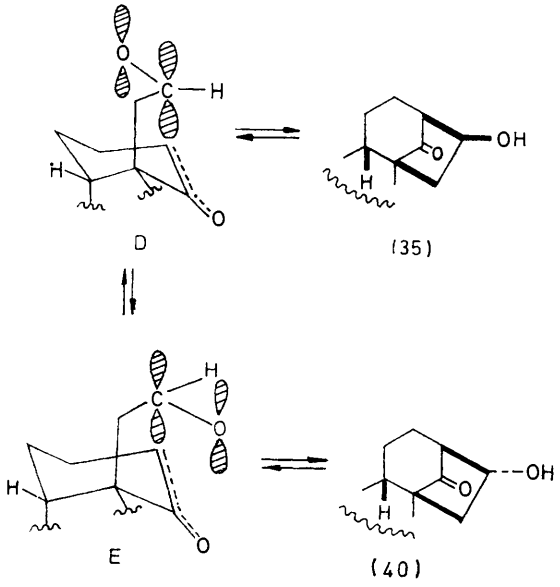
(39) was heated in methanol with toluene-*p*-sulphonic acid to yield the desired diol (3), m.p. 196—197° [18% from (38)]. Comparison of this racemic product (3) with

[15] R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1615.

[16] J. MacMillan and E. R. H. Walker, *J.C.S. Perkin I*, 1972, 1272.

the optically active compound (3), m.p. 220—225°, $[\alpha]_D^{20}$ −137°, derived from enmein confirmed their identity; their i.r. ($CHCl_3$), n.m.r., and mass spectra and their behaviour on t.l.c. were identical.

Synthesis of Enmein (1) *from the Intermediate* (3).—The optically active compound (3) on partial tetrahydropyranylation and subsequent dehydration gave a mixture



SCHEME 6

of isomers, (42) and (43), in a ratio of *ca.* 1 : 2 [30% from (3)]. These were separated by column chromatography on silica gel impregnated with silver nitrate. The desired isomer (43) was refluxed in ethylene glycol with toluene-*p*-sulphonic acid to afford diol (44) (49%), which was identical with an authentic sample derived through another route from enmein. Jones oxidation of the ozonolysis product from (44), followed by methylation with diazomethane yielded the expected B-seco-compound (45) (13%), which on Wittig reaction gave the exocyclic methylene compound (46) (80%). Treatment of (46) with dilute hydrochloric acid gave the ketol (47) (47%). The new hydroxy-group at C-16 was useful to protect the double bond during the next step. Bromination of (47) gave a mixture (48) of two products (85%), which, without purification, was heated in collidine at 160° to afford an αβ-unsaturated ketone (49) (68%). Since the product (50) from dehydration of (49) with dimethyl sulphoxide [17] was contaminated by a small quantity of the undesired *exo*-double bond isomer, its purification by recrystallisation was required. Dehydration of (49) with phosphoryl chloride in pyridine gave a crystalline product almost quantitatively which was a 50 : 50 mixture of the *exo*- and *endo*-ene isomers (n.m.r.). Separation of this mixture was difficult.

[17] V. J. Traynelis, W. L. Hergenrother, T. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, 1964, **29**, 123.

Hydrolysis of (50) with 0·01N-sodium hydroxide or 0·1N-sodium carbonate solution gave a δ-lactone (63) as the major product. Conversion of (63) into (54) was not successful. On the other hand, hydrolysis of acetal (51) [derived in 88% yield from (50)] did not proceed under the foregoing conditions, but under more drastic conditions using 10% potassium hydroxide it gave the desired carboxylic acid (52) quantitatively. The reason why ester (50) is hydrolysed more easily than ester (51) may be due to (i) intramolecular participation [18] of the carbonyl group at C-3, or (ii) predominance of the concerted reaction shown in formula (64) owing to some influence of the ketone at C-3.

Previously, lactonisation at C-1 of compound (65) was tried,[5] but the epimeric lactone (having a β C–O bond at C-1) was the major product, while the desired 1α-equatorial lactone was obtained only in 6% yield. We got a high yield (72%) of the desired lactone (53) by treatment of (52) with boron trifluoride–ether complex. The reaction produced a single product, uncontaminated by the C-1 epimer. The high yield on cyclisation is probably attributable to the easy formation of a favoured transition state (F) which satisfies the stereoelectronic requirement for maximum overlapping of the carboxy-group, the π-bond of the double bond, and the C–O bond of the acetal in the α-side of the molecule (Scheme 8).

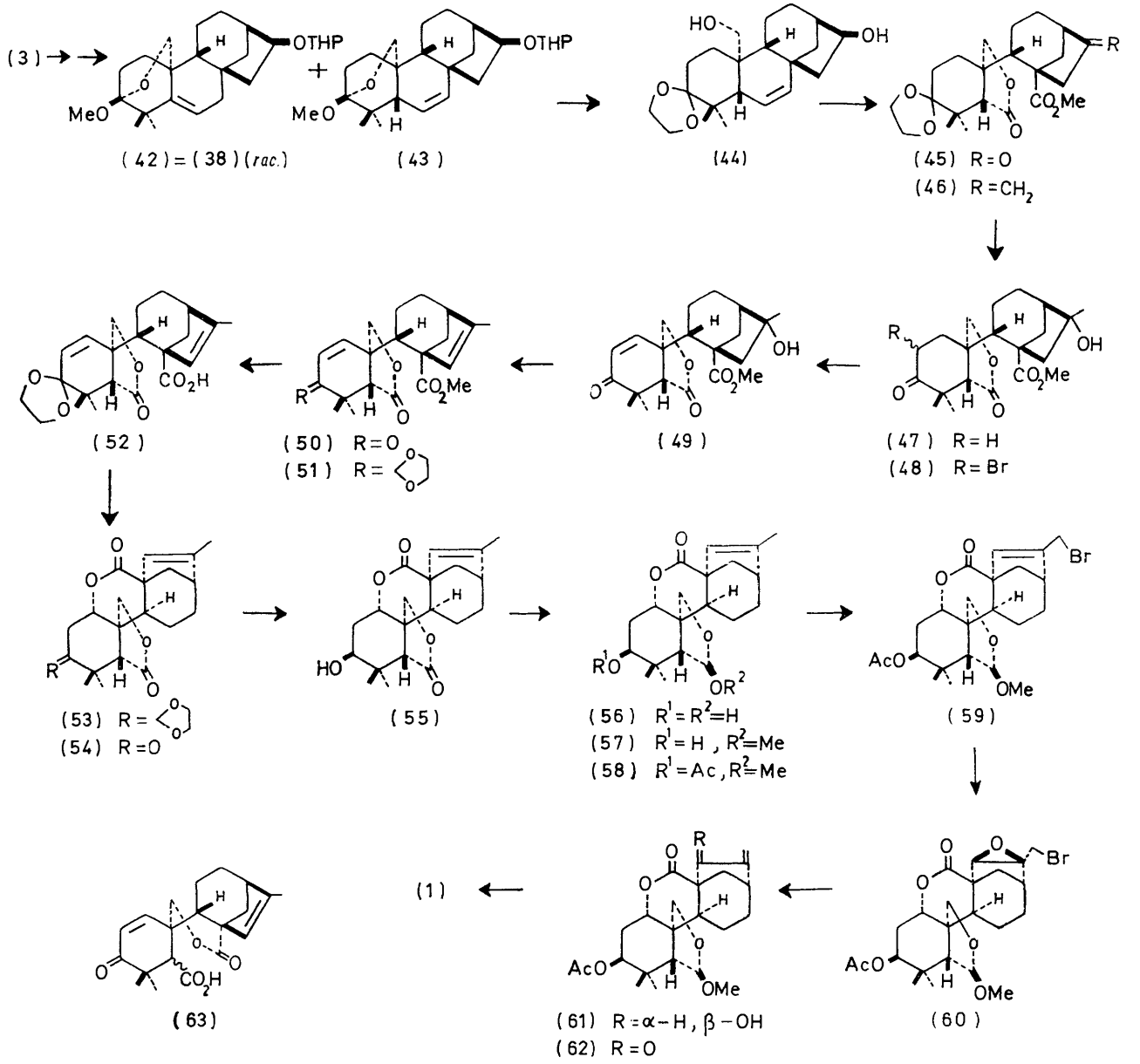
The structure of (53) was confirmed by chemical conversion of the known enmein derivative (66) into (53) *via* (67), (68), and (69) (overall yield 56%).

Ketone (54) (yield 22%) obtained by acidic hydrolysis of (53) was subjected to Meerwein–Ponndorf reduction to yield the desired 3β-axial hydroxy-compound (55) (92%). A selective reduction [19] of the γ-lactone of (55) with lithium aluminium hydride in tetrahydrofuran at −30° gave hemiacetal (56) (50%). The β-configuration of the new hemiacetal hydroxy-group was shown by the singlet n.m.r. signal due to 6-H.

The final problem was only the formation of an αβ-unsaturated ketone on ring D. In order to protect the two hydroxy-groups during the following reactions, (56) was converted into (58) *via* (57) (86% overall yield). Bromination at the allylic C-17 of (58) with *N*-bromosuccinimide gave (59) (61%), which was treated with perbenzoic acid to afford an epoxide (60) (51%). The epoxide ring must have the β-configuration because of the attack of the reagent from the less-hindered *exo*-side. The epoxide (60) on treatment with zinc dust in ethanol at reflux gave an allyl alcohol (61) (91%), whose oxidation with chromium trioxide–pyridine complex afforded an αβ-unsaturated ketone (62) (24%) with some recovery of starting material. The compound derived from (62) by deacetylation with sodium carbonate solution and subsequent hydrolysis with aqueous acetic acid was obtained as crystals of m.p. 300° (decomp.), which were identical with an authentic sample of enmein (1).

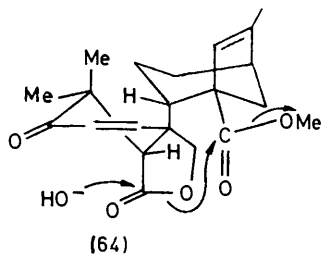
Thus, the total synthesis of enmein was achieved. We

[18] U. R. Ghatak and J. Chakravarty, *Chem. Comm.*, 1966, 184.
[19] E. Fujita, T. Fujita, and H. Katayama, *J. Chem. Soc.* (*C*), 1970, 1681.



SCHEME 7

have reported chemical conversions of enmein into several natural diterpenoids, *i.e.*, enmein 3-acetate,[4] isodocarpin,[19,20] isodotricin,[21] *ent*-kaur-16-ene,[8b,22] *ent*-kaur-



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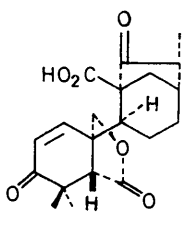

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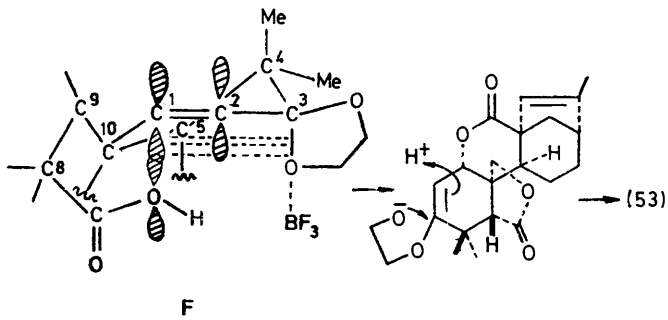

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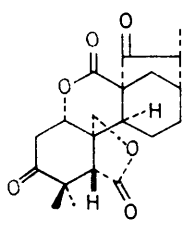
SCHEME 8

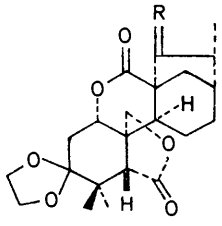
[20] E. Fujita, T. Fujita, and M. Shibuya, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 1573.

[21] E. Fujita, T. Fujita, Y. Okada, S. Nakamura, and M. Shiubya, *Chem. and Pharm. Bull.* (*Japan*), 1972, **20**, 2377.

[22] A formal chemical conversion: E. Fujita, T. Fujita, and H. Katayama, *Tetrahedron*, 1970, **26**, 1009.



(66)



(67) R = O
(68) R = α-OH, β-H
(69) R = α-O·SO_2Me, β-H

15-ene,[8b] atisine,[22] garryine,[22] and veatchine,[22] and the transformation of enmein into gibberellin A_{15} has also been reported;[23] the present work thus constitutes formal total syntheses of these natural products.

EXPERIMENTAL

M.p.s were taken on a micro hot-stage. Unless otherwise stated, i.r. spectra were recorded in KBr discs on a Hitachi model EPI-S2 spectrometer and n.m.r. spectra with a Varian A-60 or T-60 spectrometer in [^{2}H]chloroform; signals are reported in p.p.m. from tetramethylsilane as internal standard. The mass spectra were determined on a JEOL model JMS-OISG double-focusing mass spectrometer, and u.v. spectra on a Hitachi model EPS-3 spectrometer in ethanol. Rotations were measured on a JASCO DIP-180 automatic polarimeter. Extracts were dried over anhydrous $MgSO_4$. Mallinckrodt silicic acid was used for column chromatography. T.l.c. plates were coated with Nakarai Silica Layer G.

Methyl 2,3,4,4a,9,10-*Hexahydro*-8-*methoxy*-1-*methyl*-2-*oxophenanthrene*-4a-*carboxylate* (2).—To a mixture of benzene (22 ml), ether (11 ml), and sodium hydride (50% in oil; 3·3 g) was added dimethyl carbonate (6·7 g), and a solution of 5-methoxy-2-tetralone (10 g) in benzene (55 ml) was added dropwise. After refluxing the mixture for 3 h, 1-chloropentan-3-one (8 g) was added dropwise, and the mixture was refluxed for further 3 h. After cooling, ice–water (*ca.* 100 ml) and 5% hydrochloric acid were added to weak acidity, then the mixture was extracted with ethyl acetate. Usual work-up gave a crude substance (17 g), which was dissolved in toluene (1 l). Toluene-*p*-sulphonic acid (200 mg) was added, and refluxed for 30 min with a water-separator. To the mixture was added benzene (1 l), and usual work-up of the benzene solution gave a crude product, which was recrystallised from isopropyl ether to give the *ester* (2) (6·5 g). The mother liquor was purified by chromatography to give second crop of (2) (3·5 g), m.p. 102—103°, $\nu_{max.}$ 1720, 1660, 1610, and 1590 cm^{-1} (Found: C, 72·25; H, 6·7. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%).

Methylation of (2).—Potassium (3·3 g) was dissolved in t-butyl alcohol (120 ml) under heating, and a solution of (2) (5·1 g) in t-butyl alcohol was added. The mixture was stirred for 10 min at room temperature, then methyl iodide (12·4 g) was added dropwise, and stirring was continued for 2 h. After neutralisation by acetic acid, the mixture was extracted with ethyl acetate to give an oily product (5·2 g), which was crystallised from isopropyl ether to yield methyl *ent*-14-methoxy-3-oxopodocarpa-5,8,11,13-tetraen-17-oate (7) (3·1 g). Chromatography of the mother liquor also gave (7) (0·4 g) (total yield 65%), δ 1·25, 1·36, 3·57, 3·82 (each 3H, s) and 6·11 (1H, t, *J* 4 Hz, 6-H) p.p.m. This was used without further purification for the following reaction.

Ethylene-acetalisation of (7).—To a solution of (7) (5 g) in toluene (70 ml) and ethylene glycol (9 ml) was added toluene-*p*-sulphonic acid (90 mg), and the mixture was refluxed for 3 h under a water separator. Extraction with benzene (1 l) and evaporation of the solvent after usual work-up gave crystals of methyl *ent*-3,3-ethylenedioxy-14-methoxypodocarpa-5,8,11,13-tetraen-17-oate (8) (5·2 g), which was homogeneous on t.l.c. and n.m.r., δ 1·14, 1·23, 3·51, 3·81 (each 3H, s), 3·92 (4H, s), and 6·04 (1H, t, *J* 4 Hz) p.p.m.

Lithium Aluminium Hydride Reduction Followed by Acetylation of (8).—To a solution of (8) (5·2 g) in ether (100 ml) and tetrahydrofuran (100 ml) was added lithium aluminium hydride (LAH) (5 g), and the mixture was refluxed for 3 h. After cooling, the mixture was added to a large quantity of cold ethyl acetate. Evaporation, after washing with water and drying, left *ent*-3,3-ethylenedioxy-14-methoxypodocarpa-5,8,11,13-tetraen-17-ol (9) as an oil (4·8 g), which was homogeneous on t.l.c. and n.m.r. Without further purification, (9) was dissolved in pyridine (50 ml), and acetic anhydride (50 ml) was added. The mixture was left for 1 h, and the solvent was evaporated off *in vacuo* to leave an oil, which was chromatographed to yield oily *ent*-17-acetoxy-3,3-ethylenedioxy-14-methoxypodocarpa-5,8,11,13-tetraene (10) (4·6 g), δ 1·30, 1·18, 1·87, 3·79 (each 3H, s), 3·93 (4H, s), 4·22 (2H, s, $-CH_2OAc$), and 6·21 (1H, q, *J* 2·5 Hz, 6-H) p.p.m.

Epoxidation of (10).—Acetate (10) (4·6 g) was dissolved in chloroform (250 ml), to which *m*-chloroperbenzoic acid (4 g) was added. The mixture was left under nitrogen overnight, and then added to a large quantity of chloroform. After washing with sodium carbonate and water and drying, the solvent was evaporated off to leave an oil (3·5 g), which was purified by chromatography to give *ent*-17-acetoxy-5α,6α-epoxy-3,3-ethylenedioxy-14-methoxypodocarpa-8,11,13-triene (11) as a homogeneous oil [2·9 g, 48% from (7)], δ 0·85, 1·28, 1·83, 3·74 (each 3H, s), 3·95 (4H, s), 4·30 and 4·42 (ABq *J* 10 Hz, $-CH_2OAc$).

ent-3,3-*Ethylenedioxy*-14-*methoxypodocarpa*-8,11,13-*trien*-5α,17-*diol* (12).—To a solution of epoxide (11) (500 mg) in tetrahydrofuran (THF) (10 ml) was added LAH (500 mg), and the mixture was heated for 3 h under reflux. The mixture, after cooling, was added to ethyl acetate (*ca.* 500 ml), and evaporation, after washing with water and drying, left a crystalline residue (450 mg), which was purified by chromatography to yield *diol* (12) (320 mg, 71%) as plates, m.p. 175—176° (from ethyl acetate), $\nu_{max.}$ 3450 and 1580 cm^{-1}, δ 1·00, 1·13, 3·80 (each 3H, s) and 3·97 (4H, s) p.p.m. (Found: C, 68·7; H, 8·2. $C_{20}H_{28}O_5$ requires C, 68·95; H, 8·1%).

ent-3β,17-*Epoxy*-3,14-*dimethoxypodocarpa*-8,11,13-*trien*-5α-*ol* (13).—To a solution of diol (12) (200 mg) in absolute methanol (100 ml) was added toluene-*p*-sulphonic acid (10 mg), and the mixture was heated for 1 h under reflux. After cooling and neutralisation with sodium carbonate, almost all the methanol was evaporated off *in vacuo*, and the residue was extracted with acetic acid. After usual work-up, the crude product was purified by chromatography to yield the *methyl acetal* (13) (165 mg, 91%) as plates, m.p. 190—191° (from MeOH), $\nu_{max.}$ 3400 and 1580 cm^{-1}, δ 1·10, 1·05,

[23] M. Somei and T. Okamoto, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 2135; *J. Pharm. Soc. Japan*, 1972, **92**, 397.

3·35, 3·80 (each 3H, s) and 3·97 (2H, s, $-OCH_2-$) p.p.m. (Found: C, 71·45; H, 8·2. $C_{19}H_{26}O_4$ requires C, 71·65; H, 8·25%).

Epoxidation of (7).—To a solution of (7) (2·5 g) in chloroform (100 ml) was added a *ca.* 5% solution (30 ml) of perbenzoic acid in chloroform, and the mixture was left overnight. After washing with aqueous sodium carbonate and water, the solvent was evaporated off to leave an oil (3·2 g), which was purified by chromatography to yield *methyl* ent-5α,6α-*epoxy*-14-*methoxy*-3-*oxopodocarpa*-8,11,13-*trien*-17-*oate* (14) (560 mg, 12%) as plates, m.p. 152—153° (from MeOH), $\nu_{max.}$ 1720 and 1585 cm^{-1}, δ 1·05, 1·23, 3·60, and 3·80 (each 3H, s) p.p.m. (Found: C, 68·85; H, 6·75. $C_{19}H_{22}O_5$ requires C, 69·05; H, 6·7%).

Reduction of Epoxide (14).—Platinum oxide (*ca.* 100 mg) was added to a solution of (14) (500 mg) in acetic acid (50 ml), and hydrogenation was continued for 12 h. Evaporation left a residue, which was chromatographed to isolate three components. The most polar product was *methyl* ent-5α,6α-*epoxy*-3β-*hydroxy*-14-*methoxypodocarpa*-8,11,13-*trien*-17-*oate* (16) (220 mg, 44%), m.p. 215—218° (from ethyl acetate), $\nu_{max.}$ 3550, 1710, and 1585 cm^{-1}, δ 1·00 (6H, s), 3·56 and 3·80 (each 3H, s) p.p.m. (Found: C, 68·85; H, 7·45. $C_{19}H_{24}O_5$ requires C, 68·65; H, 7·3%). The second substance was *methyl* ent-5α,6α-*epoxy*-3α-*hydroxy*-14-*methoxypodocarpa*-8,11,13-*trien*-17-*oate* (15) (105 mg, 21%), which was obtained as needles, m.p. 128—129° (from ethyl acetate), $\nu_{max.}$ 3250, 3350, 1720, and 1580 cm^{-1}, δ 1·03 (6H, s), 3·55, and 3·80 (each 3H, s) p.p.m. (Found: C, 68·4; H, 7·35. $C_{19}H_{24}O_5$ requires C, 68·65; H, 7·3%). The least polar compound was ent-5α,6α-*epoxy*-14-*methoxypodocarpa*-8,11,13-*trien*-17,3β-*olactone* (17) (95 mg, 19%), obtained as needles, m.p. 200—202° (from methanol), $\nu_{max.}$ 1740 and 1590 cm^{-1}, δ 1·14, 0·96, 3·78 (each 3H, s), and 4·33 (1H, t, *J* 2 Hz, 3-H) p.p.m. (Found: C, 72·1; H, 7·0. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%).

Oxidation of (15) *and* (16).—To a solution of (15) (20 mg) in acetone (0·5 ml) was added Jones reagent (2 drops) with ice-cooling, and the mixture was stirred for 10 min. After addition of methanol (0·5 ml), the mixture was extracted with ethyl acetate. After washing with water and drying, evaporation gave (14) (18 mg, 90%). Similar oxidation of (16) (50 mg) also gave (14) (45 mg, 90%).

Lactonisation of (16).—A solution of (16) (20 mg) in acetic acid (1 ml) was refluxed for 1 h. Usual work-up gave (17) (20 mg).

Conversion of (15) *into the Diol* (18).—Compound (15) (320 mg) was dissolved in chloroform (5 ml) (pre-dried over phosphorus pentoxide), and dihydropyran (100 mg) was added. After stirring for 3 h, the mixture was poured into aqueous sodium carbonate, and extracted with chloroform. Usual work-up of the chloroform layer gave the crude tetrahydropyranyl derivative, whose solution in THF (5 ml) was heated with LAH (300 mg) under reflux for 1 h. After cooling, the mixture was added to a large quantity of cold ethyl acetate. Washing with water, drying, and evaporation left an oil (250 mg), which was treated with acetic anhydride (1 ml) in pyridine (1 ml) for 1 h at room temperature. The crude acetate obtained, without further purification, was dissolved in acetone (3 ml), to which 5% hydrochloric acid (1 ml) was added. The acidic mixture was warmed for 1 h at *ca.* 40°, and neutralised. After concentration *in vacuo*, extraction with ethyl acetate, washing with water, and drying, evaporation left an oil (250 mg), which was purified by chromatography to give ent-17-*acetoxy*-14-*methoxypodocarpa*-8,11,13-*triene*-3α,5α-*diol* (18) (70 mg, 21% overall yield) as plates, m.p. 195—196° (from ethyl acetate), $\nu_{max.}$ 3250, 1740, and 1585 cm^{-1}, δ 1·04, 1·20, 1·82, 3·80 (each 3H, s), 4·04 and 4·24 (each 1H, ABq, *J* 10 Hz, $-CH_2OAc$) p.p.m. (Found: C, 68·95; H, 8·15. $C_{20}H_{28}O_5$ requires C, 68·95; H, 8·1%).

ent-17-*Acetoxy*-3α,5α-*carbonyldioxy*-14-*methoxypodocarpa*-8,11,13-*triene* (19).—Diol (18) (50 mg) was dissolved in chloroform (1 ml) and pyridine (1 ml), to which phosgene in toluene (1·5 ml) was added. The mixture was stirred for 1 h with ice-cooling, then was left overnight. It was added to ice–water and extracted with chloroform. The usual work-up gave a crystalline mass (35 mg), which was chromatographed to yield the *carbonate* (19) (15 mg, 28%) as plates, m.p. 155—160° (from methanol), $\nu_{max.}$ 1730 and 1585 cm^{-1}, δ 1·27. 1·87, 3·80 (each 3H, s), 4·26, 4·35 (each 1H, ABq, *J* 11 Hz, $-CH_2OAc$), and 4·20br (1H, m, 3-H) p.p.m. (Found: M^+, 374·173. $C_{21}H_{26}O_6$ requires *M*, 374·173).

Conversion of (18) *into* (13).—To a solution of (18) (60 mg) in acetone (3 ml) was added Jones reagent (2 drops) at room temperature, and the mixture was stirred for 10 min. It was extracted with ethyl acetate after addition of methanol (0·5 ml), and usual work-up of the extract yielded an oily 3-ketone (56 mg, 93%), $\nu_{max.}$ ($CHCl_3$) 3550, 1730, 1705, and 1580 cm^{-1}. This ketone (20 mg) was dissolved in methanol (1 ml), to which aqueous 10% sodium carbonate (1 ml) was added. Subsequent stirring for 3 h, neutralisation with dil. hydrochloric acid, and evaporation of methanol *in vacuo* left a residue, which was extracted with ethyl acetate. The extract, after usual treatment, was chromatographed to give the crude 3-hemiacetal (8 mg, 45%), whose solution in methanol (2 ml) was refluxed with toluene-*p*-sulphonic acid (2 mg) for 1 h. After cooling, methanol was evaporated off *in vacuo* to leave a residue, which was extracted with ethyl acetate. Usual treatment of the organic layer gave a crystalline mass, which was recrystallised from methanol to afford the foregoing methyl acetal (13) (4 mg).

Reduction of (12) *with Lithium in Liquid Ammonia.*—(a) The diol (12) (200 mg) was dissolved in ethanol (1·7 ml) and liquid ammonia (20 ml) (which was distilled in the presence of sodium). To the solution was added lithium (40 mg) at *ca.* −70°, and the mixture was stirred for 3 min. After the bronze colour disappeared, ammonia was evaporated off at room temperature to leave a residue, which was extracted with chloroform. Usual treatment of the chloroform layer gave a crude mixture (195 mg), which, dissolved in acetone (3 ml), was heated with the addition of water (0·2 ml) and conc. hydrochloric acid (0·06 ml) at gentle reflux for 1 h. The mixture, after cooling, was neutralised with sodium carbonate, and extracted with chloroform. The extract was treated as usual to give a crystalline mixture (190 mg), which, without purification, was dissolved in methanol (3 ml), and refluxed for 1 h in the presence of toluene-*p*-sulphonic acid. After neutralisation with sodium carbonate, methanol was evaporated off *in vacuo* to leave a residue, which was extracted with ethyl acetate and treated as usual to yield a mixture. Chromatography separated three products besides acetal (13) (17 mg, 9%). The least polar product, 3α,17;-5β,14β-*diepoxy*-3,14-*dimethoxy*-8α,10α-*podocarpane* (21), was obtained as needles (53 mg, 29%), m.p. 110—111° (from methanol), δ 0·97, 1·08, 3·26, 3·30 (each 3H, s), 3·60 and 3·70 (each 1H, ABq, *J* 9 Hz, 17-H_2) p.p.m. (Found: C, 70·85; H, 9·55. $C_{19}H_{30}O_4$ requires C, 70·75; H, 9·4%). The second polar compound was the major product, ent-3β,17-*epoxy*-5α-*hydroxy*-3-*methoxypodocarpan*-14-*one* (20) (61

mg, 34%), obtained as needles, m.p. 185—190° (from methanol), $\nu_{max.}$ 3450 and 1695 cm^{-1}, δ 0·98, 1·00, 3·28 (each 3H, s), 3·97 and 4·05 (each 1H, ABq, *J* 9 Hz, 17-H_2) p.p.m. (Found: C, 70·0; H, 9·25. $C_{18}H_{28}O_4$ requires C, 70·1; H, 9·15%). The most polar product, ent-3β,17-*epoxy*-5α-*hydroxy*-3-*methoxypodocarp*-8-*en*-14-*one* (22), was obtained as plates (32 mg, 18%), m.p. 198—200° (from MeOH), $\nu_{max.}$ 3450, 1650, and 1620 cm^{-1}, $\lambda_{max.}$ 249 nm (ε 14,000), δ 1·00, 1·05, 3·34 (each 3H, s), 3·86 and 4·00 (each 1H, AB type, *J* 9 Hz, 17-H_2) p.p.m. (Found: C, 70·3; H, 8·55. $C_{18}H_{26}O_4$ requires C, 70·55; H, 8·55%).

(b) The reaction using (12) (140 mg), ethanol (5 ml), liquid ammonia (60 ml), and lithium (80 mg), was complete in 40 min, and usual treatment of the mixture gave a crude product (125 mg). Treatment with acid and subsequent methyl-acetalistion yielded (20) (74 mg, 64%), (21) (29 mg, 22%), and (22) (11 mg, 9%).

Reduction of Methyl-acetal (13) *with Lithium in Liquid Ammonia.*—Methyl-acetal (13) (4·5 g) was dissolved in liquid ammonia (600 ml) and ethanol (100 ml), to which lithium (3 g) was added at −70°, and the mixture was stirred for 1 h. Further lithium (2·6 g) was added, then ethanol (150 ml) was added dropwise over *ca.* 1 h. The bronze colour disappeared. Evaporation of ammonia at room temperature, chloroform extraction, and usual treatment of the extract gave a crystalline mass (4·7 g), which was subjected to acidic hydrolysis followed by methanolysis to give a mixture of four compounds. Chromatography separated starting material (13) (2·0 g, 44%), (20) (1·2 g, 28%), (22) (450 mg, 10%), and an epimeric mixture (24) (620 mg, 13%), $\nu_{max.}$ 3500 and 1700 cm^{-1}, M^+, 338.

Treatment of (20) *with Sodium Methoxide.*—To a solution of (20) (30 mg) in methanol (3 ml) was added sodium methoxide (3 mg), and the mixture was refluxed for 1 h. Concentration *in vacuo*, extraction of the residue with ethyl acetate, and usual treatment of the extract gave the starting material (20) (28 mg).

Partial Hydrolysis of Dimethyl-acetal (21).—To a solution of dimethyl-acetal (21) (550 mg) in acetone (6 ml) was added water (0·8 ml) and conc. hydrochloric acid (0·03 ml), and the mixture was stirred for 30 min. Neutralisation with sodium carbonate, evaporation of acetone *in vacuo*, extraction of the residue with ethyl acetate, and usual work-up gave a crystalline product, which was purified by chromatography to yield 3α,17-*epoxy*-5β-*hydroxy*-3-*methoxy*-8α,10α-*podocarpan*-14-*one* (23) (500 mg, 95%) as needles, m.p. 138—139° (from ethyl acetate), $\nu_{max.}$ 3500, 3400, and 1650 cm^{-1}, δ 1·00 (6H, s), 3·30 (3H, s), 3·50 and 41·5 (each 1H, AB part of ABX, *J* 9 and 3 Hz) p.p.m. (Found: C, 70·35; H, 9·35. $C_{18}H_{28}O_4$ requires C, 70·1; H, 9·15%).

ent-3β,17-*Epoxy*-5α-*hydroxy*-3-*methoxypodocarp*-12-*en*-14-*one* (25).—The methyl ether (24) (30 mg) was dissolved in a mixture of benzene (1 ml) and t-butyl alcohol (0·2 ml), to which potassium t-butoxide (5 mg) was added, and the mixture was refluxed for 1 h. After cooling, it was added to ice–water, and extracted with ethyl acetate. The extract was treated as usual, and the crude product was purified by chromatography to yield the αβ-*unsaturated ketone* (25) (15 mg, 45%) as needles, m.p. 238—239° (from methanol), $\nu_{max.}$ 3450 and 1660 cm^{-1}, $\lambda_{max.}$ 225 nm (ε 9500), δ 1·01 (6H, s), 3·29 (3H, s), 3·92, 4·08 (each 1H, ABq, *J* 9 Hz, 17-H_2), 6·00, and 6·95 (each 1H, AB part of ABXY, *J* 10, 5, and 2 Hz, 12- and 13-H) p.p.m. (Found: C, 70·45; H, 8·5. $C_{18}H_{26}O_4$ requires C, 70·55; H, 8·55%).

Catalytic Hydrogenation of (25).—Unsaturated ketone (25) (100 mg), dissolved in methanol (6 ml), was hydrogenated over platinum oxide (*ca.* 5 mg) for 1 h to give a residue, which was chromatographed to yield ketone (20) (81 mg, 81%) as crystals.

Reduction of (22) *with Lithium in Liquid Ammonia.*—Unsaturated ketone (22) (100 mg) was reduced by lithium (10 mg) and ethanol (1 ml) in liquid ammonia (30 ml) for 5 min, and the mixture was treated as usual to yield saturated ketone (20) (85 mg, 85%) as crystals.

Formylation of (20).—To a solution of (20) (100 mg) in dry benzene (2 ml) and dry THF (2 ml) was added sodium methoxide (100 mg) and subsequently ethyl formate (0·3 ml), and the mixture was stirred for 1 h at room temperature and for a further 1 h at 40°. After cooling, it was added to ice–water and acidified with aqueous 5% tartaric acid. Extraction with ethyl acetate, usual treatment of the extract, and purification of the product by chromatography gave *ent*-3β,17-epoxy-5α-hydroxy-13-hydroxymethylene-3-methoxypodocarpan-14-one (29) as a homogeneous oil (96 mg, 87%), δ 1·00, 1·03, 3·28 (each 3H, s), 3·81, 3·99 (each 1H, ABq, *J* 9 Hz), and 8·50br (1H, s) p.p.m.

ent-13-*Butylthiomethylene*-3β,17-*epoxy*-5α-*hydroxy*-3-*methoxypodocarpan*-14-*one* (30).—To a solution of (29) (96 mg) in dry benzene (3 ml) was added toluene-*p*-sulphonic acid (2 mg) and butane-1-thiol (0·2 ml), and the mixture was refluxed with water-separation for 1 h. Extraction with ethyl acetate, treatment of the extract in the usual way, and purification of the crude product by chromatography yielded the *butylthio-ether* (30) (65 mg, 56%) as crystals, m.p. 148—149° (from MeOH), $\nu_{max.}$ 3450 and 1640 cm^{-1}, δ 1·00 (6H, s), 2·83 (2H, t, *J* 6 Hz, $-CH_2-S-$), 3·28 (3H, s), 3·86, 3·99 (each 1H, ABq, *J* 9 Hz), and 7·53br (1H, s, $=CH\cdot S-$) p.p.m. (Found: C, 67·4; H, 9·0. $C_{23}H_{36}O_4S$ requires C, 67·65; H, 8·8%).

Allylation of (30).—Potassium t-butoxide [prepared from potassium (100 mg)] was added to a solution of (30) (300 mg) in t-butyl alcohol (3 ml). After stirring for 5 min, a solution of allyl bromide (0·8 ml) in benzene (4 ml) was added, and the mixture was stirred for 3 h. Neutralisation of the mixture with 5% tartaric acid under cooling, extraction of the mixture with ethyl acetate, and usual treatment of the extract gave a crude substance, which was purified by chromatography to yield *ent*-8α-allyl-13-butylthiomethylene-3β,17-epoxy-5α-hydroxy-3-methoxypodocarpan-14-one (31) as an oil (310 mg, 95%), δ 0·97 (6H, s), 3·27 (3H, s), 2·88 (2H, t, *J* 6 Hz, $-S-CH_2-$), 3·74 (2H, s), and 7·61 (1H, t, *J* 2 Hz, $=CH-S-$).

Elimination of the Protecting Group of (31).—Potassium hydroxide (5 g) was added under nitrogen to a solution of (31) (400 mg) in ethanol (15 ml) and water (15 ml), and the mixture was refluxed for 15 h. Evaporation of almost all the ethanol, extraction of the residue with methylene chloride, treatment of the extract as usual, and chromatography of the crude product thus obtained yielded ent-8α-*allyl*-3β,17-*epoxy*-5α-*hydroxy*-3-*methoxypodocarpan*-14-*one* (32) (206 mg, 67%) as plates, m.p. 210—211° (from methanol), $\nu_{max.}$ 3450, 1690, and 1640 cm^{-1}, δ 0·98 (6H, s), 3·26 (3H, s), 3·79, and 3·92 (each 1H, ABq, *J* 8·5 Hz) p.p.m. (Found: C, 72·05; H, 9·6. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%).

Ozonolysis of (32).—Ozone was passed through a solution of (32) (300 mg) in chloroform (6 ml) and dry methanol (20 ml) at −50° for 1 h. After replacement of the air in the flask by nitrogen and addition of dimethyl sulphide (1 ml) at −50°, the temperature was raised to room temperature, then

the mixture was stirred for 12 h. The solvent was evaporated off *in vacuo*, and the residue was chromatographed to separate the less polar substance, ent-3β,17-*epoxy*-5α,8α-(*epoxyethano*)-3α,19-*dimethoxypodocarpan*-14-*one* (33) (174 mg, 55%) as plates, m.p. 167—168° (from methanol), $\nu_{max.}$ 1690 cm^{-1}, δ 0·97, 1·12, 3·28, 3·54 (each 3H, s), 3·78 (2H, s, $-OCH_2-$), and 4·98 (1H, q, *J* 4 and 8·5 Hz, $-O-\underset{|}{C}H-OMe$) p.p.m. (Found: C, 69·3; H, 9·85. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·85%), and the more polar substance, ent-3β,17-*epoxy*-8α-*formylmethyl*-5α-*hydroxy*-3-*methoxypodocarpan*-14-*one* (34) (118 mg, 39%) as fine crystals, m.p. 173—175° (from ethyl acetate), $\nu_{max.}$ 3450, 1715, and 1690 cm^{-1}, δ 0·97 (6H, s), 3·13 (3H, s), 3·78, 3·89 (each 1H, ABq, *J* 8 Hz), and 9·68 (1H, t, *J* 2 Hz, $-CHO$) p.p.m. (Found: C, 68·4; H, 8·65. $C_{20}H_{30}O_5$ requires C, 68·55; H, 8·65%).

Partial Hydrolysis of (33).—To a solution of (33) (100 mg) in acetone (3 ml) was added 5% hydrochloric acid (0·03 ml) and water (0·12 ml), and the mixture was stirred for 1 h. Neutralisation, extraction with ethyl acetate, usual treatment of the extract, and purification by chromatography yielded aldehyde (34) (85 mg, 88%).

ent-3β,20-*Epoxy*-5α,16α-*dihydroxy*-3-*methoxy*-17-*norkauran*-14-*one* (35).—To a solution of (34) (100 mg) in methanol (6 ml) was added sodium methoxide (12 mg), and the mixture was stirred for 30 min. Neutralisation with dil. hydrochloric acid under ice-cooling, evaporation, extraction of the residue with ethyl acetate, and purification through chromatography of the crude crystalline product obtained by usual treatment of the extract yielded the *norkaurane derivative* (35) (75 mg, 75%) as needles, m.p. 250—253° (from methanol), $\nu_{max.}$ 3450 and 1720 cm^{-1} (Found: C, 68·05; H, 8·7. $C_{20}H_{30}O_5$ requires C, 68·55; H, 8·65%).

ent-3β,20-*Epoxy*-5α,16β-*dihydroxy*-3-*methoxy*-17-*norkauran*-14-*one* (40), *an Epimer of* (35).—To a solution of (34) (100 mg) in THF (3 ml) and methanol (4 ml) was added sodium methoxide [from sodium (100 mg)], and the mixture was refluxed for 30 min. Neutralisation of the mixture with dil. hydrochloric acid under cooling, evaporation of the solvent *in vacuo*, extraction of the residue with ethyl acetate, usual treatment of the extract, and purification of the crude product by chromatography gave the *norkauranone* (40) (85 mg, 85%) as plates, m.p. 235—236° (from methanol), $\nu_{max.}$ 3450 and 1720 cm^{-1}, δ (C_5D_5N) 1·33 (6H, s) and 3·40 (3H, s) p.p.m. (Found: C, 68·35; H, 8·9. $C_{20}H_{30}O_5$ requires C, 68·55; H, 8·65%).

Epimerisation of (35) *into* (40).—After refluxing a mixture of sodium methoxide (50 mg) and (35) (10 mg) dissolved in methanol (1 ml) and THF (1 ml) for 30 min, the same treatment as above yielded (40) (8 mg, 80%).

Acetylation of (40).—Acetylation of (40) (50 mg) with acetic anhydride (1 ml) in pyridine (1 ml) was carried out as usual to give ent-16β-*acetoxy*-3β,20-*epoxy*-5α-*hydroxy*-3-*methoxy*-17-*norkauran*-14-*one* (41) (48 mg, 86%) as needles, m.p. 191—192° (from methanol), $\nu_{max.}$ 3500 and 1735 cm^{-1}, δ 0·95, 1·04, 2·00, 3·27 (each 3H, s), 3·67, 4·02 (each 1H, ABq, *J* 9 Hz), and 5·08 (1H, q, *J* 3 and 8·5 Hz) p.p.m. (Found: C, 67·1; H, 8·4. $C_{22}H_{32}O_6$ requires C, 67·3; H, 8·2%).

Tetrahydropyranylation of (35).—To a solution of (35) (48 mg) in chloroform (3 ml) (pre-dried with phosphorus pentoxide) was added dihydropyran (0·1 ml), and the mixture was stirred for 1 h. It was made alkaline by aqueous sodium carbonate and added to a large quantity of methylene chloride. The organic layer was washed with water and dried. Evaporation left an oil, which was chromatographed to yield ent-3β,20-*epoxy*-5α-*hydroxy*-3-*methoxy*-16α-(*tetrahydropyran*-2-*yloxy*)-17-*norkauran*-14-*one* (36) (60 mg, quantitative) as fine crystals, m.p. 178—180° (from ether), $\nu_{max.}$ 3450 and 1735 cm^{-1} (Found: C, 69·25; H, 8·9. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

Huang-Minlon Reduction of (36).—To a mixture of (36) (60 mg), diethylene glycol (1 ml), and anhydrous hydrazine (150 mg) was added sodium (45 mg), and the mixture was heated at 180—190° for 14 h. Then, the temperature was raised to 220—230° over 2 h to remove the excess of hydrazine by distillation. After further heating at 180—190° for 8 h, the reaction mixture was added to ice–water, and extracted with methylene chloride. The extract was treated as usual, and evaporated to leave a crude residue, which was chromatographed to yield ent-3β,20-*epoxy*-3-*methoxy*-16α-(*tetrahydropyran*-2-*yloxy*)-17-*norkauran*-5α-*ol* (37) (40 mg, 70%) as fine crystals, m.p. 153—155° (from ethyl acetate), $\nu_{max.}$ 3400 cm^{-1} (Found: C, 71·35; H, 9·75. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·6%).

Dehydration of (37).—To a solution of (37) (35 mg) in dry pyridine (0·5 ml) was added thionyl chloride (0·06 ml), and the mixture was left for 5 min. Evaporation *in vacuo* left a residue, which was chromatographed to yield ent-3β,20-*epoxy*-3-*methoxy*-16α-(*tetrahydropran*-2-*yloxy*)-17-*norkaur*-5-*ene* (38) (29 mg, 87%) as fine needles, m.p. 158—160° (from ether), δ 1·07, 1·13, 3·14 (each 3H, s) and 5·50 (1H, q, *J* 2·6 Hz, 6-H) p.p.m. (Found: C, 74·7; H, 9·8. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%).

Hydroboronation Followed by Depyranylation of (38).—A solution of (38) (20 mg) in THF (1·2 ml) was added dropwise into a mixture of sodium borohydride (24 mg), boron trifluoride–ether complex (150 mg), and THF (1 ml). After stirring at room temperature for 3 h and at *ca.* 40° for 3 h, aqueous 10% sodium hydroxide (1·2 ml) was added dropwise at room temperature. Then, 30% hydrogen peroxide (1·6 ml) was added dropwise under ice-cooling over 10 min. The mixture was stirred at 0° for 1 h. Extraction with methylene chloride, washing with water, drying, and evaporation left a viscous residue, which was chromatographed to yield *ent*-3β,20-epoxy-3-methoxy-16-(tetrahydropyran-2-yloxy)-17-norkauran-6α-ol (39) as a homogeneous but amorphous substance (5 mg, 24%), δ 1·13, 1·22, and 3·28 (each 3H, s) p.p.m. Compound (39) (5 mg) was dissolved in dry methanol (1 ml), and toluene-*p*-sulphonic acid (2 mg) was added. The mixture was refluxed for 1 h, and, after cooling, was neutralised with aqueous sodium carbonate. Methanol was evaporated off *in vacuo* and the residue was extracted with ethyl acetate. The extract was treated as usual, and the crude product was chromatographed to yield ent-3β,20-*epoxy*-3-*methoxy*-17-*norkaurane*-6α,16α-*diol* (3) (3 mg, 75%) as needles, m.p. 196—197° (from ethyl acetate) (Found: M^+, 336·230. $C_{20}H_{32}O_4$ requires *M*, 336·230), whose i.r. ($CHCl_3$), n.m.r., and mass spectra and behaviour on t.l.c. were identical with those of the authentic sample of optically active (3), m.p. 220—225°, which was derived from enmein.

Partial Tetrahydropyranylation Followed by Dehydration of (3).—Dihydropyran (0·5 ml) was added to a solution of (3) (200 mg) in chloroform (pre-dried with phosphorus pentoxide), and the mixture was stirred for 1 h. It was then made alkaline with aqueous sodium carbonate and added to a large quantity of methylene chloride. Washing with water, drying, and evaporation gave a residue (two spots on t.l.c.). Chromatography separated the main product (180 mg, 72%), m.p. 175—180° (from ethyl acetate) (Found: M^+, 420·287. $C_{25}H_{40}O_5$ requires *M*, 420·287), whose n.m.r.

spectrum was identical with that of racemic (39), and the minor product, *i.e.*, the dipyranyl derivative (25 mg, 8%) as an amorphous substance, (M^+ 504). The major product (150 mg) was dissolved in dry pyridine (3 ml), to which thionyl chloride (0·1 ml) was added. The mixture was left for 5 min, evaporated, and extracted with methylene chloride. Usual treatment of the extract gave a mixture (60 mg, 72%) of two components (checked by n.m.r.), which were separated by column chromatography on silica gel impregnated with silver nitrate (12%) to yield the major product ent-3β,20-*epoxy*-3-*methoxy*-16α-(*tetrahydropyran*-2-*yloxy*)-17-*norkaur*-6-*ene* (43) as needles, m.p. 199—200° (from ether), δ 0·97, 1·02, 3·31 (each 3H, s), and 3·48 (2H, s, $-CH=CH-$) p.p.m. (Found: C, 74·35; H, 9·7. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%), and the minor product (42) whose n.m.r. spectrum was identical with that of racemic compound (38).

ent-3,3-*Ethylenedioxy*-17-*norkaur*-6-*ene*-16α,20-*diol* (44).—To a solution of (43) (7 mg) in toluene (5 ml) was added ethylene glycol (1 ml) and toluene-*p*-sulphonic acid (2 mg), and the mixture was refluxed for 1 h under water-separation. After cooling, it was poured into a large quantity of ethyl acetate and washed with water. Drying and evaporation left a residue, which was chromatographed to yield diol (44) (3 mg, 49%) as crystals, m.p. 188—189°, identical (i.r. and mixed m.p.) with an authentic sample of (44) derived from enmein.*

ent-3,3-*Ethylenedioxy*-20-*hydroxy*-16-*oxo*-17-*nor*-6,7-*seco*-*kaurane*-6,7-*dioic Acid* 6,20-*Lactone* 7-*Methyl Ester* (45).—Diol (44) (100 mg) was dissolved in methanol (20 ml), and ozone was passed through at −50° for 5 h. After replacement of the air in the flask by nitrogen, the solvent was evaporated off *in vacuo* to leave an oil, which was oxidised in acetone (3 ml) with Jones reagent. Usual treatment of the mixture gave an oily product, which, dissolved in methanol (1 ml), was treated with diazomethane in ether. Chromatography of the crude product yielded the *lactone-ester* (45) (15 mg, 13%) as plates, m.p. 194—195° (from methanol), $\nu_{max.}$ 1770, 1740, and 1725 cm^{-1}, δ 1·12, 1·14, 3·76 (each 3H, s), 3·99 (4H, s), and 4·03 (2H, s, $-CH_2-O-$) p.p.m. (Found: C, 65·15; H, 7·4. $C_{22}H_{30}O_4$ requires C, 65·0; H, 7·45%).

Wittig Reaction with (45).—Potassium (630 mg) was added to t-butyl alcohol (20 ml) and ether (15 ml) and refluxed for 1 h, then the mixture was concentrated to 22 ml. Methyltriphenylphosphonium iodide (1·07 g) was added to this solution and stirred for 30 min. Then, a solution of (45) (195 mg) in ether (15 ml) was added slowly and stirred for 3 h. Ice–water (1 ml) was added and the mixture was neutralised with dil. hydrochloric acid under ice-cooling. Extraction with ethyl acetate, drying, and evaporation left a viscous residue (600 mg), which was chromtographed to yield ent-3,3-*ethylenedioxy*-20-*hydroxy*-6,7-*secokaur*-16-*ene*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (46) (155 mg, 80%) as plates, m.p. 129—130° (from methanol), $\nu_{max.}$ 1760, 1720, and 1655 cm^{-1}, δ 1·12, 1·15, 3·72 (each 3H, s), 3·98 (4H, s), 4·01 (2H, s, $-CH_2-O-$), and 4·85 (2H, m, $C=CH_2$) p.p.m. (Found: C, 68·5; H, 8·25. $C_{23}H_{32}O_6$ requires C, 68·25; H, 7·95%).

Acidic Hydrolysis of (46).—To a solution of (46) (200 mg) in acetone (12 ml) was added 5% hydrochloric acid (12 ml), and the mixture was refluxed for 6 h. After concentration to *ca.* half volume, extraction with ethyl acetate, washing with water, drying, and evaporation left a residue, which was chromatographed to yield ent-16,20-*dihydroxy*-3-*oxo*-6,7-*secokaurane*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (47) (88 mg, 47%) as plates, m.p. 171—172° (from methanol), $\nu_{max.}$ 3450, 1780sh, 1745, 1725, and 1700 cm^{-1}, δ 1·19, 1·29, 1·36, 3·70 (each 3H, s), 4·05 and 4·07 (each 1H, ABq, *J* 10 Hz) p.p.m. (Found: C, 66·9; H, 8·25. $C_{21}H_{30}O_6$ requires C, 66·65; H, 8·0%).

Bromination of (47).—To a solution of (47) (300 mg) in acetic acid (30 ml) was added dropwise a solution of bromine (140 mg) in acetic acid (15 ml) with stirring over 2 h. The mixture was poured onto water (100 ml) and extracted with ethyl acetate. The usual treatment of the extract gave viscous 2-epimeric bromides, *ent*-2-bromo-16,20-dihydroxy-3-oxo-6,7-secokaurane-6,7-dioic acid 6,20-lactone 7-methyl ester (48) (310 mg, 85%), which showed an n.m.r. pattern of a mixture of two components, $\nu_{max.}$ ($CHCl_3$) 1770 and 1725 cm^{-1}.

ent-16,20-*Dihydroxy*-3-*oxo*-6,7-*secokaur*-1-*ene*-6,7-*dioic Acid* 6,20-*Lactone* 7-*Methyl Ester* (49).—Bromide (48) (100 mg) was dissolved in 2,4,6-collidine (1 ml) and was heated in a sealed tube at 160° for 2 h. Evaporation *in vacuo* left a residue, which was chromatographed to yield the *unsaturated ketone* (49) (56 mg, 68%) as needles, m.p. 119—120° (from methanol), $\nu_{max.}$ 3450, 1760, 1705, and 1685 cm^{-1}, δ 1·23, 1·39, 1·42, 3·72 (each 3H, s), 4·13, 4·26 (each 1H, ABq, *J* 10 Hz, $-CH_2-O-$), 6·03 and 6·69 (each 1H, ABq, *J* 10·5 Hz, $-CO-CH=CH-$) p.p.m. (Found: C, 66·75; H, 7·75. $C_{21}H_{28}O_6$ requires C, 67·0; H, 7·5%).

Dehydration of (49).—A solution of (49) (100 mg) in dimethyl sulphoxide (2 ml) was heated at 170° for 5 h in a sealed tube filled with nitrogen. Evaporation *in vacuo* left a viscous residue, which was chromatographed to give a crystalline substance, which was shown by n.m.r. to be contaminated by a trace of the *exo*-double bond isomer. Recrystallisation from methanol gave ent-20-*hydroxy*-3-*oxo*-6,7-*secokaura*-1,15-*diene*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (50) (14 mg, 15%), m.p. 120—121°, $\nu_{max.}$ 1780, 1715, and 1680 cm^{-1}, δ 1·20, 1·40, 3·63 (each 3H, s), 1·73 (3H, d, *J* 2 Hz, 17-H_3), 4·22, 4·13 (each 1H, ABq, *J* 10 Hz, 20-H_2), 5·46br (1H, s, 15-H), 6·00 and 6·61 (each 1H, d, *J* 10 Hz, 1-H, 2-H) p.p.m. (Found: C, 70·15; H, 7·35. $C_{21}H_{26}O_6$ requires C, 70·35; H, 7·3%).

Acetalisation of (50).—To a solution of (50) (2 g) in toluene (30 ml) was added ethylene glycol (5 ml) and toluene-*p*-sulphonic acid (50 mg), and the mixture was heated at reflux under water-separation for 5 h. After cooling, it was made weakly alkaline by aqueous sodium carbonate and extracted with ethyl acetate. After washing with water and drying, evaporation left a crystalline residue, which gave ent-3,3-*ethylenedioxy*-20-*hydroxy*-6,7-*secokaura*-1,15-*diene*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (51) (1·85 g, 88%) as needles (from methanol), m.p. 170—171°, δ 1·20, 1·40, 3·63 (each 1H, s), 1·73 (1H, d, *J* 2 Hz, 17-H_3), 4·13, 4·22 (each 1H, ABq, *J* 10 Hz), 5·46 (1H, m, 15-H), 6·00 and 6·11 (each 1H, ABq, *J* 10 Hz, 1-H, 2-H) p.p.m. (Found: C, 68·65; H, 7·75. $C_{23}H_{30}O_6$ requires C, 68·65; H, 7·5%).

Hydrolysis of (50).—When a mixture of (50) (100 mg) and 0·01N-aqueous potassium hydroxide (30 ml) was heated at 100° for 2 h, the starting material dissolved. The mixture, after cooling, was washed with chloroform, and the aqueous layer was acidified with hydrochloric acid, then extracted with ethyl acetate. The organic layer was treated as usual and evaporation left a crystalline residue, which gave ent-20-*hydroxy*-3-*oxo*-6,7-*secokaura*-1,15-*diene*-6,7-*dioic acid* 7,20-*lactone* (63) (65 mg, 68%) as needles, m.p. 235—240° (from methanol), $\nu_{max.}$ 1735 and 1660 cm^{-1}, δ (C_5D_5N), 1·47, 1·60

* See following paper.

(each 3H, s), 1·67 (3H, d, *J* 2 Hz), 4·76, 5·12 (each 1H, ABq, *J* 12 Hz, 20-H_2), 5·68 (1H, m, 15-H), 6·37 and 7·01 (each 1H, ABq, *J* 10·5 Hz, 1-H, 2-H) p.p.m. (Found: C, 79·75; H, 7·2. $C_{20}H_{24}O_5$ requires C, 69·75; H, 7·0%). Hydrolysis with 0·1N-aqueous sodium carbonate gave the same result.

Hydrolysis of (51).—A mixture of (51) (1 g) and 10% methanolic potassium hydroxide (30 ml) was heated under reflux for 3 h, and concentrated *in vacuo* to one tenth its volume. After cooling, it was acidified with hydrochloric acid and extracted with ethyl acetate. Usual treatment of the extract gave ent-3,3-*ethylenedioxy*-20-*hydroxy*-6,7-*seco*-*kaura*-1,15-*diene*-6,7-*dioic acid* 6,20-*lactone* (52) as a homogeneous, viscous oil (960 mg, quantitative), $\nu_{max.}$ ($CHCl_3$) 1760 and 1695 cm^{-1}.

Lactonisation of (52) *at* C-1.—To a stirred solution of (52) (900 mg) in chloroform (15 ml) was added boron trifluoride–ether complex (2 ml), and stirring was continued for 10 h. The mixture was poured onto a large quantity of methylene chloride and, after washing with water and drying, evaporation gave a viscous residue (910 mg), which was chromatographed to yield ent-3,3-*ethylenedioxy*-6,7-*secokaur*-15-*ene*-6,20;7,1β-*diolactone* (53) (650 mg, 72%) as plates, m.p. 192—195° (from methanol), $\nu_{max.}$ 1770 and 1735 cm^{-1}, δ 1·13 (6H, s), 1·77 (3H, d, *J* 2 Hz, 17-H_3), 3·71, 43·4 (each 1H, ABq, *J* 10 Hz, 20-H_2), 4·03 (4H, s), 4·78 (1H, t, *J* 9 Hz, 1-H), and 5·66 (1H, m, 15-H) p.p.m. (Found: C, 67·85; H, 7·15. $C_{22}H_{28}O_6$ requires C, 68·0; H, 7·25%).

Acetalisation of Diketo-lactone (66).—To a solution of (66) (10 g) in dry toluene (150 ml) was added ethylene glycol (20 ml) and toluene-*p*-sulphonic acid (200 mg), and the mixture was heated at reflux under water-separation for 6 h. After cooling it was added to a large quantity of ethyl acetate and, after washing with water and drying, evaporation gave ent-3,3-*ethylenedioxy*-15-*oxo*-6,7-*secokaurane*-6,20;7,1β-*diolactone* (67) (11 g, 98%) as needles, m.p. 256—258° (from methanol), $\nu_{max.}$ 1760 and 1720 cm^{-1} (Found: C, 64·8; H, 7·3. $C_{22}H_{28}O_7$ requires C, 65·35; H, 7·0%).

Sodium Borohydride Reduction of (67).—A solution of sodium borohydride (7 g) in methanol (100 ml) was added slowly to a solution of (67) (10 g) in methanol (300 ml) and THF (100 ml), and stirred overnight. Evaporation of methanol *in vacuo* at *ca.* 30° and, after addition of water (100 ml), neutralisation with hydrochloric acid, and extraction with ethyl acetate, the usual treatment of the extract yielded ent-3,3-*ethylenedioxy*-15α-*hydroxy*-6,7-*secokaurane*-6,20;7,1β-*diolactone* (68) (9·6 g, 96%) as needles, m.p. 273—275° (from methanol), $\nu_{max.}$ 3500, 1760, and 1725 cm^{-1} (Found: C, 65·3; H, 7·6. $C_{22}H_{30}O_7$ requires C, 65·0; H, 7·45%).

Conversion of (68) *into* (53).—Mesyl chloride (5 ml) was added to a solution of (68) (8 g) in dry pyridine (100 ml) and, after standing overnight, evaporation *in vacuo* gave a residue, which was chromatographed to yield the crystalline mesylate (69) (7·5 g, 79%). The mesylate (69) (4 g), without further purification, was dissolved in 2,4,6-collidine (20 ml), and was heated at 170° for 6 h in a sealed tube filled with nitrogen. Evaporation of the solvent at 100° under reduced pressure left a residue, which was dissolved in ethyl acetate and washed with 5% hydrochloric acid then water. Evaporation, after drying, and the usual treatment gave (53) (2·4 g, 75%) identical with the product derived from (52).

Deacetalisation of (53).—To a solution of (53) (600 mg) in acetone (9 ml) was added 5% sulphuric acid (9 ml), and the mixture was heated at reflux for 5 h. After concentration to *ca.* half volume, extraction with ethyl acetate and usual treatment of the extract gave a crude viscous product, which was a mixture of two components (t.l.c.). Chromatography separated the less polar ent-3-*oxo*-6,7-*secokaur*-15-*ene*-6,20;7,1β-*diolactone* (54) (150 mg, 22%) as needles, m.p. 202—205° (from methanol), $\nu_{max.}$ 1770, 1740, and 1715 cm^{-1}, δ 1·26, 1·28 (each 3H, s), 1·77 (3H, d, *J* 2 Hz, 17-H_3), 3·94, 4·58 (each 1H, ABq, *J* 10 Hz), 4·86 (1H, q, *J* 8 and 11 Hz, 1-H), and 5·72 (1H, m, 15-H) p.p.m. (Found: C, 69·65; H, 7·05. $C_{20}H_{24}O_5$ requires C, 69·75; H, 7·0%), and the more polar compound (350 mg) as crystals, m.p. 202—204° (from methanol), $\nu_{max.}$ 3350, 1775, 1730, and 1720 cm^{-1}, δ 1·26, 1·28, 1·43 (each 3H, s), 2·52 (1H, s, 6-H), 3·93, 4·58 (each 1H, ABq, *J* 10 Hz, 20-H_2), and 4·97 (1H, q, *J* 7 and 11 Hz, 1-H) p.p.m. (Found: C, 66·5; H, 7·3. Calc. for $C_{20}H_{26}O_6$: C, 66·3; H, 7·25%). This compound was tentatively assigned as the 16-ol derivative of (54), formed by hydration at the 15,16-double bond of (54).

Meerwein–Ponndorf Reduction of (54).—Ketone (54) (70 mg) was dissolved in dry isopropyl alcohol (80 ml), to which aluminium isopropoxide (200 mg) was added. The mixture was heated and gently distilled, keeping the volume constant at 80 ml by occasional additions of isopropyl alcohol. About 50 ml was distilled over 1 h, then the mixture was concentrated *in vacuo* to *ca.* 5 ml, and was poured into a large quantity of ethyl acetate. Washing with water, drying, and evaporation gave ent-3α-*hydroxy*-6,7-*secokaur*-15-*ene*-6,20;7,1β-*diolactone* (55) (65 mg, 92%) as needles, m.p. 290—291° (from ethyl acetate), $\nu_{max.}$ 3400, 1780, and 1710 cm^{-1}, δ 1·03, 1·25 (each 3H, s), 1·77 (3H, d, *J* 1·5 Hz, 17-Hz), 3·74, 4·34 (each 1H, ABq, *J* 10 Hz, 20-H_2), 3·76br (1H, s, 3-H), and 5·17 (1H, m, 15-H) p.p.m. (Found: C, 69·6; H, 7·35. $C_{20}H_{26}O_5$ requires C, 69·35; H, 7·55%).

Partial Reduction of (55) *with Lithium Aluminium Hydride and Methyl-acetalisation of the Product.*—A solution of (55) (100 mg) in dry THF (5 ml) was cooled to −30°, and a solution of LAH (45 mg) in THF (8 ml) was added dropwise with stirring. The mixture was warmed to −15° over 3 h, then cooled again to −40°, and the excess of LAH was decomposed by addition of ethyl acetate (10 ml). After raising the temperature to room temperature, a large quantity of water was added and the mixture was extracted with ethyl acetate. The extract was treated as usual to give the crude product, which was chromatographed to yield *ent*-6,20-epoxy-3α,6α-dihydroxy-5,7-secokaur-15-en-7,1β-olactone (56) (35 mg, 50%) as plates, m.p. 228—232° (from methanol), $\nu_{max.}$ 3400 and 1710 cm^{-1}. Without further purification, (56) (30 mg) was dissolved in methanol (2 ml), to which conc. hydrochloric acid (0·03 ml) was added. The mixture was warmed for 1 h at *ca.* 40°, and, after cooling, it was added to a large quantity of ethyl acetate. Washing with water, drying, and evaporation gave a residue, which was purified by chromatography to yield ent-6,20-*epoxy*-3α-*hydroxy*-6α-*methoxy*-6,7-*secokaur*-15-*en*-7,1β-*olactone* (57) (30 mg, 92%) as plates, m.p. 200—203° (from ether), $[\alpha]_D^{20}$ −147° (*c* 0·58, chloroform), $\nu_{max.}$ 3425 and 1715 cm^{-1}, δ 0·95, 1·10, 3·30 (each 3H, s), 1·75 (3H, d, *J* 2 Hz, 17-H_3), 3·63 (1H, m, 3-H), 3·60, 4·06 (each 1H, ABq, *J* 9 Hz, 20-H_2), 4·89 (1H, s, 6-H), 5·02 (1H, q, *J* 8 and 10·5 Hz, 1-H), and 5·67br (1H, s, 15-H) p.p.m. (Found: C, 69·35; H, 8·45. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·35%).

Acetylation of (57).—Usual acetylation of (57) (1·01 g), with acetic anhydride (8 ml) and pyridine (8 ml) gave ent-3α-*acetoxy*-6,20-*epoxy*-6α-*methoxy*-6,7-*secokaur*-15-*en*-7,1β-*olactone* (58) (1·01 g, 89·3%) as prisms, m.p. 136—138° (from ether–isopropyl ether), $[\alpha]_D^{20}$ −84° (*c* 0·32, chloroform),

$\nu_{max.}$ 1733 cm^{-1}, δ 2·12 (3H, s) and 4·90 (1H, m, 3-H) p.p.m. (Found: C, 68·0; H, 8·05. $C_{23}H_{32}O_6$ requires C, 68·3; H, 7·95%).

Bromination of (58).—Compound (58) (1·435 g) was dissolved in dry benzene (75 ml), and benzene (10 ml) was evaporated off to give a dry solution, to which *N*-bromosuccinimide (650 mg) and dibenzoyl peroxide (10 mg) were added. The mixture was heated at reflux for 45 min and, after cooling, was added to dil. aqueous sodium carbonate. Extraction with ethyl acetate, washing with water, drying, and evaporation left a crystalline residue, which was chromatographed to yield ent-3α-*acetoxy*-17-*bromo*-6,20-*epoxy*-6α-*methoxy*-6,7-*secokaur*-15-*en*-7,1β-*olactone* (59) (1·04 g, 60·5%) as needles, m.p. 181—183° (from ether–isopropyl ether), $[\alpha]_D^{20}$ −111° (*c* 0·34, chloroform), $\nu_{max.}$ 1735 cm^{-1}, δ 0·98, 1·03, 2·15, 3·32 (each 3H, s), 3·60, 4·04 (each 1H, ABq, *J* 10 Hz, 20-H_2), 4·09 (2H, s, 17-H_2), 4·77 (1H, q, *J* 8 and 10·5 Hz, 1-H), 4·80 (1H, s, 6-H), 4·92 (1H, m, 3-H), and 6·13br (1H, s, 15-H) p.p.m. (Found: C, 57·2; H, 6·55. $C_{23}H_{31}BrO_6$ requires C, 57·15; H, 6·5%).

Epoxidation of (59).—A solution of perbenzoic acid (320 mg) in chloroform (5 ml) was added to a solution of (59) (508 mg) in chloroform (1 ml), and left for 2 days. Extraction with methylene chloride after neutralisation with dil. aqueous sodium carbonate, the usual treatment of the extract, and evaporation left a crude product, which was chromatographed to yield ent-3α-*acetoxy*-17-*bromo*-6,20;15β,16β-*diepoxy*-6α-*methoxy*-6,7-*secokauran*-7,1β-*olactone* (60) (270 mg, 51·2%) as needles, m.p. 199·5—201° (from ether), $[\alpha]_D^{20}$ −40° (*c* 0·20, chloroform), $\nu_{max.}$ 1740sh and 1728 cm^{-1}, δ 1·00, 1·02 (each 3H, s), 2·10 (3H, s), 3·32 (3H, s), 3·64, 4·10 (each 1H, ABq, *J* 9·0 Hz, 20-H_2), 3·48, 4·08 (each 1H, ABq, *J* 12 Hz, 17-H_2), 5·53 (1H, s, 15-H), 4·65 (1H, q, *J* 11 and 7 Hz, 1-H), 4·82 (1H, s, 6-H), and 4·90 (1H, m, 3-H) p.p.m. (Found: C, 55·4; H, 6·3. $C_{23}H_{31}BrO_7$ requires C, 55·3; H, 6·25%).

Reaction of (60) *with Zinc Dust in Ethanol.*—To a solution of (60) (220 mg) in absolute ethanol (15 ml) was added zinc dust (5·0 g), and the mixture was refluxed for 7 h, and filtered. The filtrate was evaporated *in vacuo* to leave a viscous residue, which was chromatographed to yield ent-3α-*acetoxy*-6,20-*epoxy*-15β-*hydroxy*-6α-*methoxy*-6,7-*secokaur*-16-*en*-7,1β-*olactone* (61) (169 mg, 91·2%) as an oil, $\nu_{max.}$ ($CHCl_3$) 3400, 1727, and 1700 cm^{-1}, δ 1·00, 1·04, 2·11, 3·30 (each 3H, s), 3·74, 4·05 (each 1H, ABq, *J* 10 Hz), 4·30 (1H, s, 15-H), 4·79 (1H, q, *J* 11 and 7 Hz, 1-H), 4·82 (1H, s, 6-H), 4·93 (1H, m, 3-H), 5·23, 5·37 (each 1H, 17-H_2), and 5·81 (1H, s, OH) p.p.m.

Oxidation of (61) *with Chromium Trioxide–Pyridine Complex.*—To a solution of (61) (75 mg) in pyridine (2 ml) was added chromium trioxide (200 mg)–pyridine (2 ml) complex, and the mixture was stirred at room temperature for 2 days. Water (10 ml) was added, and the mixture was extracted with methylene chloride. Washing with water, drying, and evaporation left an oil, which was chromatographed to yield ent-3α-*acetoxy*-6,20-*epoxy*-6α-*methoxy*-15-*oxo*-6,7-*secokaur*-16-*en*-7,1β-*olactone* (62) (18 mg, 24%) as plates, m.p. 195—197° (from methanol), $\nu_{max.}$ 1745 and 1715 cm^{-1}, $\lambda_{max.}$ (MeOH) 233 nm (ε 9300), δ 1·00, 1·04, 2·10, 3·25 (each 3H, s), 3·90, 4·06 (each 1H, ABq, *J* 10 Hz), 4·67 (1H, q, *J* 11 and 7 Hz, 1-H), 4·80 (1H, s, 6-H), 4·87 (1H, m), and 5·49 and 6·08 (each 1H, 17-H_2) p.p.m. (Found: C, 66·0; H, 7·3. $C_{23}H_{30}O_7$ requires C, 66·0; H, 7·25%).

Hydrolysis of (62) *into Enmein* (1).—To a solution of (62) (102 mg) in methanol (25 ml) was added 5% aqueous sodium carbonate (5 ml), and the mixture was stirred overnight. Neutralisation with 5% hydrochloric acid, evaporation *in vacuo*, extraction with chloroform, and after drying, evaporation left an oil (119 mg), which was chromatographed to yield ent-6,20-*epoxy*-3α-*hydroxy*-6α-*methoxy*-15-*oxo*-6,7-*secokaur*-16-*en*-7,1β-*olactone* (81 mg, 90%), as plates, m.p. 240—242° (from methanol), $\nu_{max.}$ 3400, 1743, and 1700 cm^{-1}, $\lambda_{max.}$ (MeOH) 233 nm (ε 4300), δ (C_5D_5N) 1·00, 1·26, 3·21 (each 3H, s), 3·75 (1H, m, 3-H), 4·34 (2H, s, 3-H), 4·34 (2H, s, 20-H_2), 4·90 (1H, OH), 5·04 (1H, s, 6-H), 5·33 (1H, q, *J* 11 and 7·5 Hz, 1-H), and 5·32 and 6·00 (each 1H, 17-H_2) p.p.m. (Found: C, 67·0; H, 7·55. $C_{21}H_{28}O_6$ requires C, 67·0; H, 7·5%). The 6-acetal-3-ol compound (204 mg) was heated in a mixture of acetic acid (8 ml) and water (3 ml) for 2·5 h. Neutralisation with aqueous sodium carbonate, extraction with ethyl acetate, washing with water, drying, and evaporation of the solvent left a hydrolysed product, which was recrystallised twice from methanol to yield the pure compound (67 mg), m.p. 300° (decomp.) $[\alpha]_D^{20}$ −134·5° (*c* 0·35, pyridine), (Found: C, 66·1; H, 7·5. Calc. for $C_{20}H_{26}O_6$: C, 66·3; H, 7·25%), whose m.p., i.r. and n.m.r. spectra, and behaviour on t.l.c. were identical with those of natural enmein (1).

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