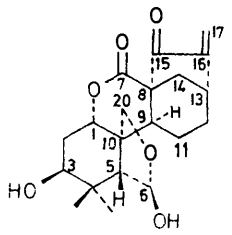
Terpenoids. Part XXIX.[1] Chemical Conversion of Enmein into an Important Relay Compound for Its Total Synthesis

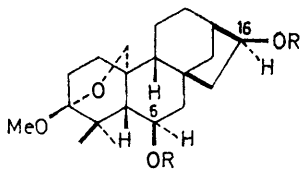
By **Masayuki Shibuya** and **Eiichi Fujita,*** Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan

The conversion of enmein (1) into *ent*-3β,20-epoxy-3-methoxy-17-norkaurane-6α,16α-diol (2), an important relay compond in its total synthesis, is reported.

In the preceding paper,[1] we reported the total synthesis of enmein (1), in which we used *ent*-3β,20-epoxy-3α-methoxy-17-norkaurane-6α,16α-diol (2) as an important relay compound. In this paper, we report the chemical conversion of enmein (1) into (2).



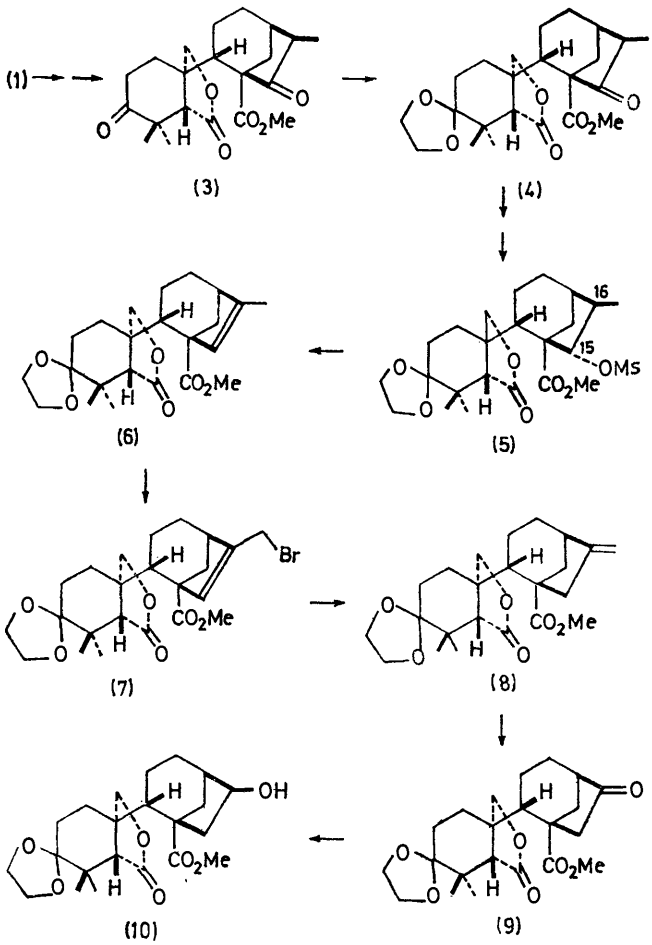
(1)



(2) R = H
(12) R = Ac

In order to synthesise (2) from (1), removing the C-17 carbon and forming of a C(6)–C(7) bond are necessary. The first problem was solved by the steps shown in the Scheme.

The known diketo-lactone ester (3)[2] derived from enmein was subjected to partial acetalisation to yield 3-acetal (4), which was reduced by sodium borohydride in aqueous methanol.† The product, *i.e.* the 15α-ol, was converted into the mesylate (5). The *trans*-relationship between the 15-mesyloxy- and 16-methyl groups was shown by the coupling constant (4 Hz) of the doublet at δ 4·55 p.p.m. due to C(15)H in its n.m.r. spectrum. Heating (5) in dimethyl sulphoxide afforded the 15-ene (6) quantitatively. The overall yield of (6) from (3) was 72%. Migration of a double bond from an *endo*- to an *exo*-position had been observed in an equilibrium between similar double bond isomers,[4] but it seemed difficult to apply such an equilibrium for synthetic purposes in our case. Then, we selected allylic bromination of (6) followed by zinc-dust reduction. Thus, the desired exocyclic methylene compound (8) was obtained from (7) in almost quantitative yield, with none of *endo*-derivative (6) present (confirmed by n.m.r.). Ozonolysis of (8) in ethyl acetate and subsequent catalytic reduction of the ozonide gave the 17-nor-16-one (9). The overall yield of (9) from (6) was 52%. The ketone (9) on sodium borohydride reduction gave alcohol (10) in 78% yield. The 16β-ol assignment was based on; (i) the hydride attack from the less hindered α-side was expected in the reduction, (ii) in the n.m.r. spectrum, the C(16)H signal



Scheme

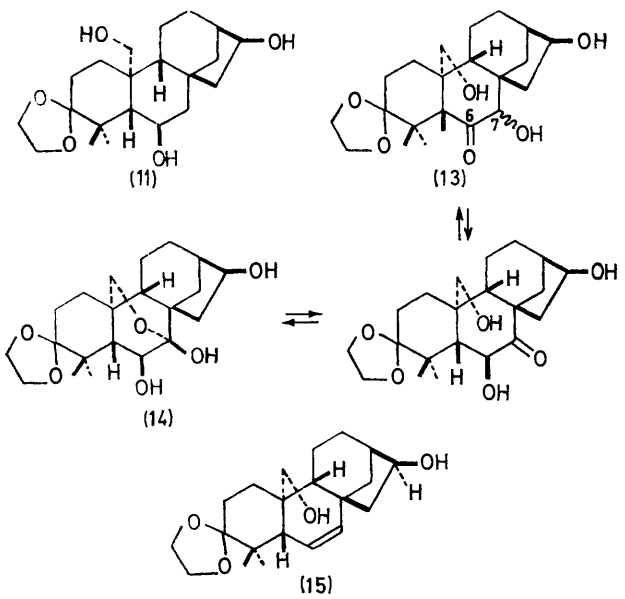
was observed as a quintet (*J* 5, 5, and 10 Hz) at δ 4·27 p.p.m.

The second problem, *i.e.* formation of a bond between C-6 and C-7 was solved by the acyloin condensation.[2,5-7]

† The sodium borohydride reduction of (4) in absolute methanol gave the 15β-ol as the main product. On the other hand, the same reduction in aqueous methanol yielded the 15α-ol as the only product, formed by epimerisation of the 15β-ol.[3]

[1] Part XXVIII, preceding paper.
[2] E. Fujita, T. Fujita, K. Fuji, and N. Ito, *Tetrahedron*, 1966, **22**, 3423.
[3] (*a*) E. Fujita, T. Fujita, and Y. Nagao, *Tetrahedron*, 1969, **25**, 3717; (*b*) E. Fujita and Y. Nagao, *J. Chem. Soc.* (*C*), 1971, 2902.
[4] R. A. Appleton, A. J. McAlees, A. McCormick, R. McCrindle, and R. D. H. Murray, *J. Chem. Soc.* (*C*), 1966, 2319.
[5] E. Fujita, T. Fujita, and Y. Nagao, *Tetrahedron*, 1972, **28**, 555.
[6] E. Fujita, T. Fujita, Y. Nagao, H. Katayama, and M. Shibuya, *Tetrahedron Letters*, 1969, 2573.
[7] E. Fujita, T. Fujita, and H. Katayama, *Tetrahedron*, 1970, **26**, 1009.

Thus, the lactone ester (10) was treated with sodium in liquid ammonia to give two major products, together with some by-products. The product of the highest yield (30%) was obtained as crystals, while that of the second highest yield (14%) remained as an oil. The crystalline product was probably the triol (11), on the basis of its analysis, spectroscopic data, and consideration of the reaction mechanism. The presence of the original 16-ol and a new 20-ol was easily assumed. Another secondary hydroxy-group should be located at C-6 or C-7, but a preference for C-6 was supported by analogy with other examples.[2,5,6] The compound was refluxed in a mixture of methanol and chloroform in the presence of conc. sulphuric acid to yield a methyl acetal diol (2) in 59% yield. Its structure and stereochemistry were confirmed by the n.m.r. spectrum of its diacetate (12) in which a sextet (J 5, 11, and 11 Hz) at δ 5·08 p.p.m. and a quintet (J 5, 5, and 10 Hz) signal at δ 5·03 p.p.m. were observed. These signals were reasonably assigned to 6α-H * and 16α-H, respectively, in structure (12). Thus, it was established that the foregoing triol had the structure and absolute configuration formulated as (11), and that compound (2) was the desired *ent*-3β,20-epoxy-3α-methoxy-17-norkaurane-6α,16α-diol. The triol (11) was thought to be formed from an initial acyloin product (13) by hydrogenolysis at C-7 followed by reduction of the C-6 ketone. The steric hindrance at C-7 is bigger than that at C-6. This may be the reason why the predominant hydrogenolysis occurs at C-7.



On the other hand, a doublet (J 4·5 Hz) was observed at δ 4·23 p.p.m. in the n.m.r. spectrum of the oily second product. This observation together with other spectroscopic data led to the assumption of the 7-hemiacetal structure (14) by analogy with the products of the similar acyloin condensations.[2,5-7] The Huang-Minlon reduction of (14) yielded a diol, whose n.m.r. spectrum revealed an AB part of an ABX signal at δ 5·56 and 5·40 p.p.m. (J 1·5, 2, and 10 Hz) due to protons on a C(6)–C(7) double bond and signals assignable to acetal ethylene, 16α-H and 20-methylene protons. Thus, it is certain that this diol is the acetal (15).† This compound may also be useful as an intermediate for the synthesis of highly functionalised diterpenoids.

* Ring B was considered to be in the stable chair conformation.
† See also ref. 1.

EXPERIMENTAL

General details are given in ref. 1.

Ethylene-acetalisation of Diketo-lactone ester (3).—To a solution of diketo-lactone ester (3) (4·5 g) in dry toluene (68 ml) were added ethylene glycol (9 ml) and toluene-*p*-sulphonic acid (90 mg), and the mixture was refluxed for 6 h under a water separator. After cooling, the mixture was poured onto ice–water and extracted with ethyl acetate. Usual work-up gave a crude crystalline product, and recrystallisation from methanol afforded ent-3,3-*ethylenedioxy*-20-*hydroxy*-15-*oxo*-6,7-*secokaurane*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (4) (4·0 g), m.p. 213—214°, $\nu_{max.}$ 1770, 1740, and 1720 cm^{-1}, δ 3·96 (4H, s, $-OCH_2CH_2O-$) and 3·77 (3H, s) p.p.m. (Found: C, 65·9; H, 7·45. $C_{23}H_{32}O_7$ requires C, 65·7; H, 7·65%).

Conversion of (4) *into Mesylate* (5).—To a solution of (4) (4·0 g) in methanol (50 ml) and water (5 ml) was added sodium borohydride (500 mg). After stirring for 5 h at room temperature, methanol was distilled off at *ca.* 30° *in vacuo* to leave a residue, which was extracted with chloroform. Usual work-up gave a crystalline mass (3·8 g), which, without purification, was dissolved in pyridine (50 ml). Mesyl chloride (5 ml) was added to the solution, and the mixture was left overnight. Evaporation *in vacuo* left a residue, which was chromatographed to give plates (4·1 g). Recrystallisation from methanol yielded pure ent-3,3-*ethylenedioxy*-20-*hydroxy*-15β-*mesyloxy*-6,7-*secokaurane*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (5), m.p. 143—144°, $\nu_{max.}$ 1770 and 1730 cm^{-1}, δ 4·55 (1H, d, J 4, 15-H), 3·98 (4H, s), 3·73, 2·96, 1·12, 1·08 (each 3H, s), and 1·20 (3H, d, J 6 Hz) p.p.m. (Found: C, 57·7; H, 7·45. $C_{24}H_{36}O_9S$ requires C, 57·6; H, 7·2%).

Demesyloxylation of (5).—A solution of mesylate (5) (4·1 g) in dimethyl sulphoxide (20 ml) was heated at 150° for 10 min in an oil-bath. The solvent was evaporated off at *ca.* 60—70° *in vacuo* to leave a residue, which was chromatographed to yield ent-3,3-*ethylenedioxy*-20-*hydroxy*-6,7-*secokaur*-15-*ene*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (6) (3·5 g) as crystals, m.p. 144—145° (from methanol), $\nu_{max.}$ 1765 and 1725 cm^{-1}, δ 5·37br (1H, m, 15-H), 3·97 (4H, s), 3·71 (3H, s), and 1·71 (3H, d, J 2 Hz, 17-H_3) p.p.m. (Found: C, 68·05; H, 8·05. $C_{23}H_{32}O_6$ requires C, 68·3; H, 7·95%).

Bromination of (6).—A solution of (6) (544 mg) in anhydrous carbon tetrachloride (35 ml) was azeotropically concentrated to 20 ml, and *N*-bromosuccinimide (260 mg) and dibenzoyl peroxide (20 mg) were added. The mixture was refluxed for 1 h. After cooling, the solid which precipitated was filtered off and the filtrate was extracted with methylene chloride (10 ml). Usual work-up afforded a viscous oily bromide (7) (690 mg), δ 4·02, 4·01 (each 2H, s), 3·98 (4H, s), and 3·74, 1·15, and 1·11 (each 3H, s) p.p.m.

Reductive Debromination of (7).—To a solution of the

bromo-compound (7) (200 mg) in ethanol (3 ml) were added zinc-dust (1 g) and acetic acid (0·012 ml), and the mixture was stirred for 2 h at room temperature. After filtration and washing the zinc with excess of ethanol, the filtrate and washings were combined. The solvent was distilled off *in vacuo* to leave a residue (260 mg), which was chromatographed to give ent-3,3-*ethylenedioxy*-20-*hydroxy*-6,7-*secokaur*-16-*ene*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (8) (185 mg), as needles, m.p. 129—130° (from methanol), $\nu_{max.}$ 1760, 1720, and 1655 cm^{-1}, δ 4·85 (2H, m, 17-H$_2$), 4·01 (2H, s, 20-H$_2$), 3·98 (4H, s), and 3·72, 1·15, and 1·12 (each 3H, s) p.p.m. (Found: C, 68·5; H, 8·25. $C_{23}H_{32}O_6$ requires C, 68·3; H, 7·95%).

Ozonolysis of Olefin (8).—Ozone was introduced to a solution of (8) (400 mg) in dry ethyl acetate (70 ml) at −60°. When (8) was consumed (t.l.c.) the reaction was stopped. After warming to the room temperature, platinum oxide (*ca.* 5 mg) was added and the mixture was hydrogenated overnight. After filtration, evaporation *in vacuo* gave a viscous residue (455 mg), which was purified by column chromatography and recrystallisation from methanol to yield ent-3,3-*ethylenedioxy*-20-*hydroxy*-16-*oxo*-17-*nor*-6,7-*secokaurane*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (9) as plates (210 mg), m.p. 194—195°, $\nu_{max.}$ 1770, 1740, and 1725 cm^{-1}, δ 4·03 (2H, s, 20-H$_2$), 3·99 (4H, s), and 3·76, 1·14, and 1·12 (each 3H, s) p.p.m. (Found: C, 65·15; H, 7·4. $C_{22}H_{30}O_7$ requires C, 65·0; H, 7·45%).

Reduction of Ketone (9).—To a solution of (9) (170 mg) in ethanol (10 ml) was added a solution of sodium borohydride (80 mg) in ethanol (3 ml) with cooling. After stirring at room temperature for 1 h, the mixture was concentrated to *ca.* one fifth volume *in vacuo*. Extraction with ethyl acetate and usual treatment of the extract gave a crude product (165 mg), which was purified by column chromatography followed by recrystallisation from ethyl acetate to yield crystalline ent-3,3-*ethylenedioxy*-16α,20-*dihydroxy*-17-*nor*-6,7-*secokaurane*-6,7-*dioic acid* 6,20-*lactone* 7-*methyl ester* (10) (132 mg), m.p. 228—229°, $\nu_{max.}$ 3420, 1765sh, and 1725 nm^{-1}, δ 4·27 (1H, quintet, *J* 5, 5, and 10 Hz, 16-H), 3·98 (4H, s), and 3·69, 1·15, and 1·10 (each 3H, s) p.p.m. (Found: C, 64·45; H, 7·85. $C_{22}H_{33}O_7$ requires C, 64·7; H, 7·9%).

Acyloin Condensation with Lactone-ester (10).—A solution of (10) (1·2 g) in dry ether (75 ml) was added dropwise to a mixture of sodium (378 mg) in liquid ammonia (135 ml) and dry ether (90 ml) with stirring at −70° (bath temperature) over *ca.* 1 h. The blue colour disappeared, so further sodium (200 mg) was added and the mixture was stirred at −70° for 2 h. A mixture of methanol (3 ml) and ether (3 ml) was added, then ammonia was evaporated off at room temperature to leave a residue, which was extracted with ethyl acetate. Usual work-up gave a viscous oil (1·15 g), which was chromatographed to separate two products. The more polar product *ent*-7β,20-epoxy-3,3-ethylenedioxy-17-norkaurane-6α,7,16α-triol (14) (150 mg) was obtained as an oil, $\nu_{max.}$ 3400 cm^{-1}, δ (C_5D_5N), 4·60 (1H, quintet, *J* 5, 5, and 10 Hz, 16-H), 4·23 (1H, d, *J* 4·5 Hz, 6-H), 3·90 (4H, s), and 1·40 and 1·26 (each 3H, s) p.p.m. (Found: M^+, 380. $C_{21}H_{32}O_6$ requires *M*, 380). The less polar product ent-3,3-*ethylenedioxy*-17-*norkaurane*-6α,16α,20-*triol* (11) was obtained as crystals (360 mg), m.p. 181—182° (from methanol) $\nu_{max.}$ 3200 cm^{-1}, δ (C_5D_5N), 4·00 (2H, s) and 4·65—3·76 (6H, overlapped multiplet) p.p.m. (Found: C, 68·7; H, 9·4. $C_{21}H_{34}O_5$ requires C, 68·8; H, 9·35%).

Methanolysis of Triol (11).—To a solution of (11) (400 mg) in a mixture of methanol (2 ml) and chloroform (2 ml) was added conc. sulphuric acid (0·8 ml), and the mixture was refluxed for 5 h. After cooling, it was poured onto ice–water, made alkaline by sodium carbonate, and extracted with chloroform. After washing the organic layer with water and drying, the solvent was distilled off to leave a residue (380 mg), which was chromatographed to afford ent-3β,20-*epoxy*-3-*methoxy*-17-*norkaurane*-6α,16α-*diol* (2) (250 mg), m.p. 220—225° (from ethyl acetate), $[\alpha]_D^{20}$ −137° (*c* 0·5, pyridine), $\nu_{max.}$ 3350 cm^{-1}, $\nu_{max.}$ ($CHCl_3$) 3555 cm^{-1}, δ 4·60—3·75 (4H, overlapped complex signal), and 3·30, 1·26, and 1·18 (each 3H, s) p.p.m. (Found: C, 71·1; H, 9·7. $C_{20}H_{32}O_4$ requires C. 71·4; H, 9·6%).

Acetylation of Acetal Diol (2).—A solution of (2) (50 mg) in anhydrous pyridine (1 ml) and acetic anhydride (1 ml) was left at room temperature overnight. Evaporation of the solvent *in vacuo* and chromatography of the residue left a crystalline product (19 mg), which was recrystallised from methanol to yield ent-3β,20-*epoxy*-3-*methoxy*-17-*norkaurane*-6α,16α-*diyl diacetate* (12), m.p. 180—181°, $\nu_{max.}$ 1730 cm^{-1}, δ 4·33, 3·86 [each 1H, AB, *J* 8·5 Hz. Each signal showed long range couplings (*J* 2 and 1 Hz, respectively)], 3·28 (3H, s), 2·07 (6H, s), and 1·10 and 1·00 (each 3H, s) p.p.m. (Found: C, 68·6; H, 8·85. $C_{24}H_{36}O_6$ requires C, 68·55. H, 8·65%).

Wolff–Kishner Reduction of Hemiacetal (14).—A mixture of (14) (100 mg), sodium (50 mg), and anhydrous hydrazine (170 mg) in diethylene glycol (1 ml) was heated at 180° for 2 h, then refluxed at 220° for 2 h, and finally heated at 180—190° for 10 h. After cooling, the mixture was poured onto ice–water (10 ml) and extracted with methylene chloride. Usual work-up gave a viscous oil (95 mg), which was subjected to column chromatography to yield ent-3,3-*ethylenedioxy*-17-*norkaur*-6-*ene*-16α,20-*diol* (15) (62 mg), m.p. 188—190° (from ethyl acetate), $\nu_{max.}$ 3300 cm^{-1}, δ 5·56, 5·40 (each 1H, AB part of ABX, *J* 1·5, 2, and 10, 7-H and 6-H), 4·30 (1H, quintet, *J* 5, 5, and 10 Hz, 16-H), 3·95 (4H, s), 3·87 (2H, s, 20-H$_2$), and 1·01 and 0·89 (each 3H, s) p.p.m. (Found: C, 72·55; H, 9·15. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·25%).

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