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TERPENOIDS—XII[1]

THE STEREOCHEMISTRY OF SOME ALCOHOLS DERIVED FROM ENMEIN[2]

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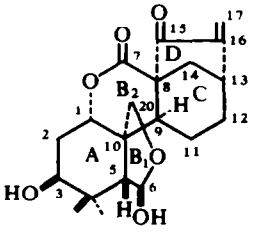
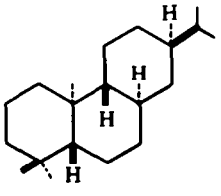
Abstract—The reduction of ketone **9** with LiAl (t-BuO)$_3$H in absolute THF gave alcohols **11** and **13**, while the reduction of ketone **9** with $NaBH_4$ in THF–H_2O gave an alcohol **10**. Alcohol **11** on weak alkaline treatment was epimerized to **10**. Similarly, alcohol **13** was epimerized to **15** under similar conditions. Ketolactone ester **20** was reduced with LiAl (t-BuO)$_3$H in anhydrous solvent to give alcohol **24**, while it was reduced with $NaBH_4$ in MeOH–H_2O to give alcohol **3**. Alcohol **24** was epimerized to **3** in weak alkaline conditions. Two other epimeric alcohols **29** and **31** were derived from **3** *via* a series of reactions. Alcohol **29** was epimerized to **31** by treatment with weak alkali, although the reaction rate was much slower.

RECENTLY, we converted enmein (**1**), a major bitter diterpenoid of the leaves of *Isodon trichocarpus* Kudo (Japanese name "Kurobanahikiokoshi") and *I. japonicus* Hara ("Hikiokoshi"), into *enantio*-abietane (**2**),[4] in which we used alcohol **3** as an important key intermediate. The necessity for establishing the absolute configurations of the C-15 OH group and C-16 Me group prompted us to carry out the present research. We have derived four possible epimeric alcohols including **3** from enmein (**1**) and clarified their structure and absolute configuration.

CHART 1



1



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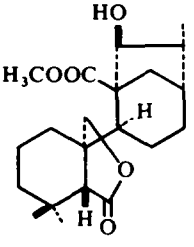

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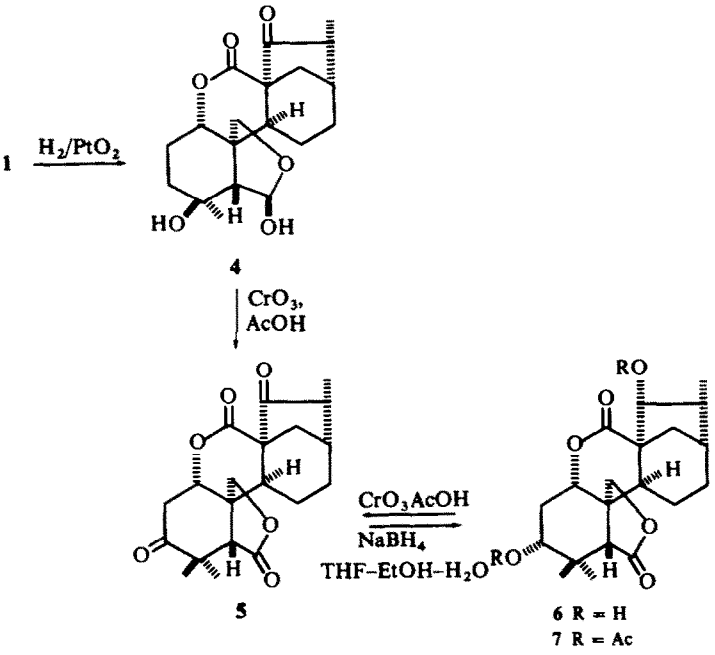
Enmein (**1**) was hydrogenated with Adams' catalyst to dihydroenmein (**4**),* which was converted into bisdehydro-derivative **5** by CrO_3 oxidation. Compound **5** on reduction with $NaBH_4$ in THF–EtOH–H_2O gave diol **6**, whose NMR spectrum supported the *cis* relationship between C-15 OH and C-16 Me-groups. This is also supported from the NMR data of its diacetate **7**. Diol **6** on CrO_3 oxidation gave the

* The absolute confuguration of dihydroenmein, especially of its C-16 Me group, has been established by an X-ray analysis (C-16 : R).[5]

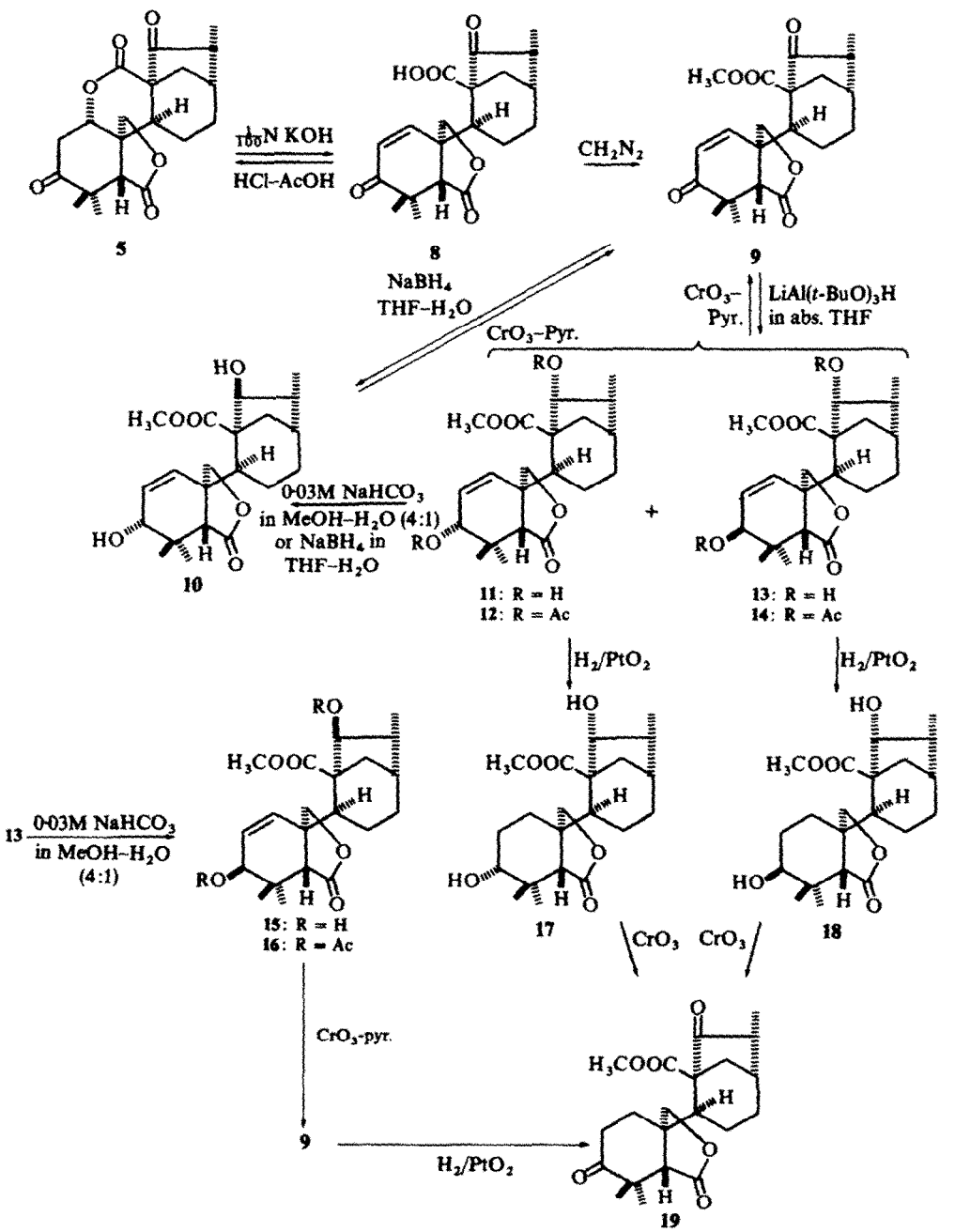
original ketone **5**, which showed that the configuration of C-16 in compounds **5**, **6** and **7** is completely same and should be assigned R as in **4**.

CHART 2



Enonoic acid **8**, a product from hydrolysis of **5**, on treatment with HCl–AcOH[6] gave the original compound **5**, although the yield was very poor; the stereochemistry of C-16 in **8** has been kept unchanged. Its methyl ester **9** was reduced with $NaBH_4$ in THF–H_2O to yield a sole diol **10**, while **9** with LiAl (t-BuO)$_3$H in anhydrous THF gave two C-3 epimers of C-15: C-16 *cis*-α-alcohol, that is, **11** and **13** in a ratio of 1:3·4. All of the alcohols, **10**, **11** and **13**, on oxidation with CrO_3–pyridine complex, reproduced ketone **9**; the R-configuration of C-16 has been kept in these alcohols. Alcohol **11** was treated with 0·03M $NaHCO_3$ in MeOH–H_2O (4:1) to give an epimerized alcohol **10**. Quite similarly, **11** on treatment with $NaBH_4$ in THF–H_2O gave **10**. The same treatment of alcohol **13** with weak alkali resulted in its epimerization into **15**. The steric configuration of C-3 in compounds **10**, **11**, **13** and **15** was assigned by the investigation of allylic coupling of C-3 proton to C-1 olefinic proton in their NMR spectra; allylic coupling of C-1 proton to C-3 proton with coupling constant of 2–2·5 Hz was observed in the spectra of **10** and **11**, while such a coupling was not observed in those of **13** and **15**. But this observation is based on the assumption that the A-ring should be present in half-chair form. The NMR investigation of hydrogenation products **17** and **18** confirmed this to be correct: C-3 proton signal appeared at δ 3·39 ppm as a triplet (J = 7·0 Hz) in **17**, while it appeared at δ 3·53 ppm as a triplet (J = 2·5 Hz) in **18**. These data supported that the A-ring is present as chair form in both compounds, and **17** has α-equatorial C-3 OH, while **18** has β-axial C-3 OH.

CHART 3


5
1/100N KOH
HCl–AcOH
8
CH2N2
9
NaBH4
THF–H2O
CrO3–Pyr.
LiAl(t-BuO)3H
in abs. THF
CrO3–Pyr.
10
0·03M NaHCO3
in MeOH–H2O (4:1)
or NaBH4 in
THF–H2O
11: R = H
12: R = Ac
13: R = H
14: R = Ac
H2/PtO2
H2/PtO2
13 0·03M NaHCO3
in MeOH–H2O
(4:1)
15: R = H
16: R = Ac
17
18
CrO3
CrO3
CrO3-pyr.
9
H2/PtO2
19

The comparisons of C-5 protons chemical shifts about four pairs of C-3 epimeric alcohols and one pair of C-3 epimeric acetates were presented in Table 1. The C-5 proton chemical shift of C-3 β alcohol series is in the lower magnetic field than that of C-3 α alcohol series, due to the effect of the OH or OAc oxygen in 1,3-diaxial relationship to the C-5 H. This fact gave a further evidence for the above assignment of the stereochemistry to **10**, **11**, **13** and **15** and also half chair conformation of their A-ring.

TABLE 1. THE C-5 PROTONS CHEMICAL SHIFTS OF C-3 EPIMERIC ALCOHOLS AND ACETATES[a]

C-3-α-OH (or OAc) compds	Chemical shifts of C-5-H (δ_{ppm})	C-3-β-OH (or OAc) compds	Chemical shifts of C-5-H (δ_{ppm})
3-*epi*-6-dehydro-dihydroenmein[b]	2·56 (pyr) 4·96 (C-1—H)	6-dehydro-dihydroenmein[c]	2·85 (pyr) 5·29 (C-1—H)
11	2·95	**13**	3·28
12	2·93	**14**	3·14
10	2·84	**15**	3·22
17	2·27	**18**	2·36

[a] Unless otherwise stated, NMR spectra were taken in $CDCl_3$.
[b] See Ref 6.
[c] See Refs 6 and 7.

Alcohols **17** and **18** on chromic acid oxidation gave a same diketone **19**,[7] a hydrogenation product of **9**.

Ester **9** on treatment with ethanedithiol and BF_3-etherate gave ethylenedithioketal, which was desulphurized with Raney Ni followed by hydrogenation on Adams' catalyst to give a ketolactone ester **20**.[7] Compound **9** on treatment with only BF_3-etherate did not change at all. Moreover, **9** was subjected to monothioketalization by its treatment with ethylene monothioglycol and BF_3–etherate to yield an ethylene monothioketal, whose desulphurization with Raney Ni also recovered the original material **9**. Hence, this interconversion is expressed as **9** ⇄ **21**, and the steric configuration of C-16 Me group was proved to be unchanged under these reaction conditions. An attempted epimerization of C-16 Me group of compound **20** with CH_3ONa in MeOH resulted in an easy opening of the D-ring, and the products **22**[8] and **23** were obtained after esterification.

Now, the ketone **20** was reduced with $NaBH_4$ in MeOH–H_2O to yield only a *trans*-β-alcohol **3**, while it was converted into only a *cis*-α-alcohol **24** by reduction with LiAl $(t\text{-}BuO)_3H$ in anhydrous THF. Sodium borohydride reduction of **20** in absolute MeOH gave **24** and **3**. The alcohol **24** was epimerized into **3** under the same condition as in the epimerization of **11** into **10**. The epimerization of **24** into **3** also occurred by treatment of **24** with $NaBH_4$ in MeOH–H_2O. Both alcohols, **3** and **24**, on oxidation with CrO_3–pyridine complex gave the original ketone **20**, which proved the maintenance of the R-configuration of C-16 in these alcohols.

CHART 4

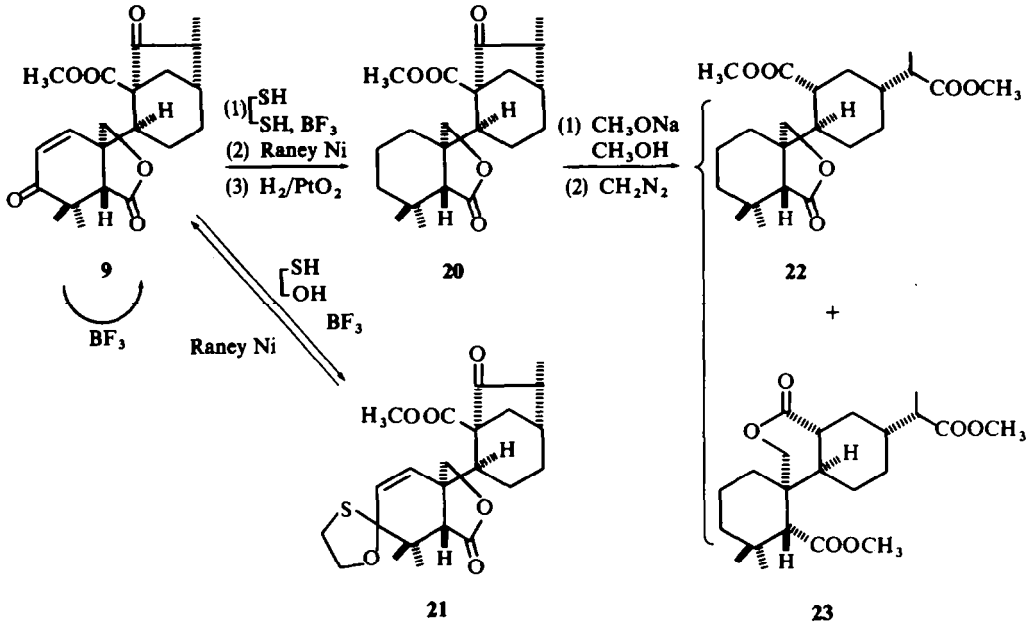
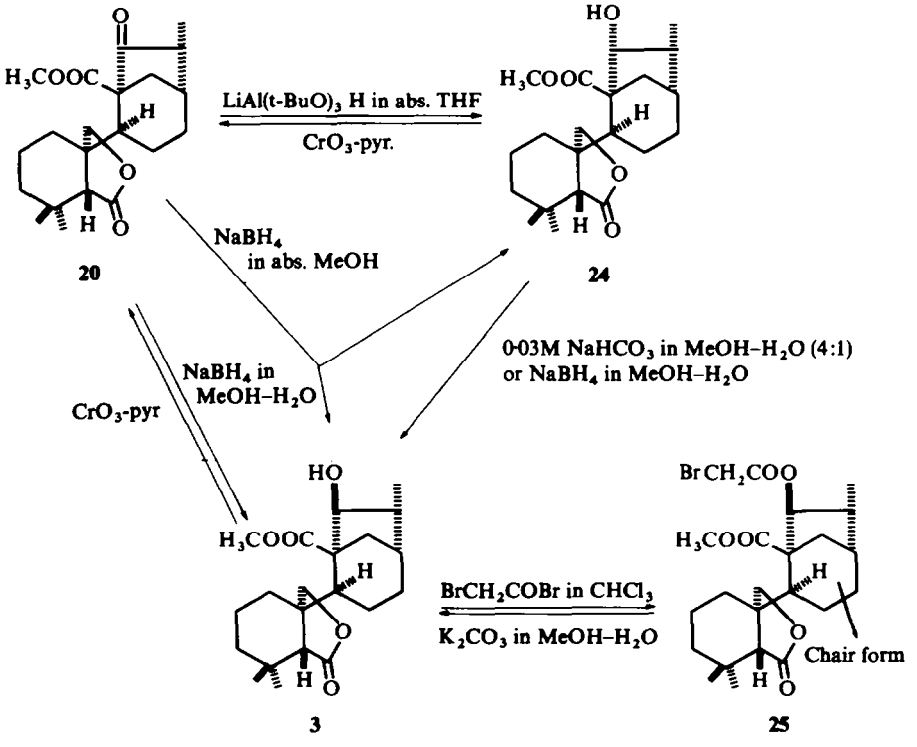


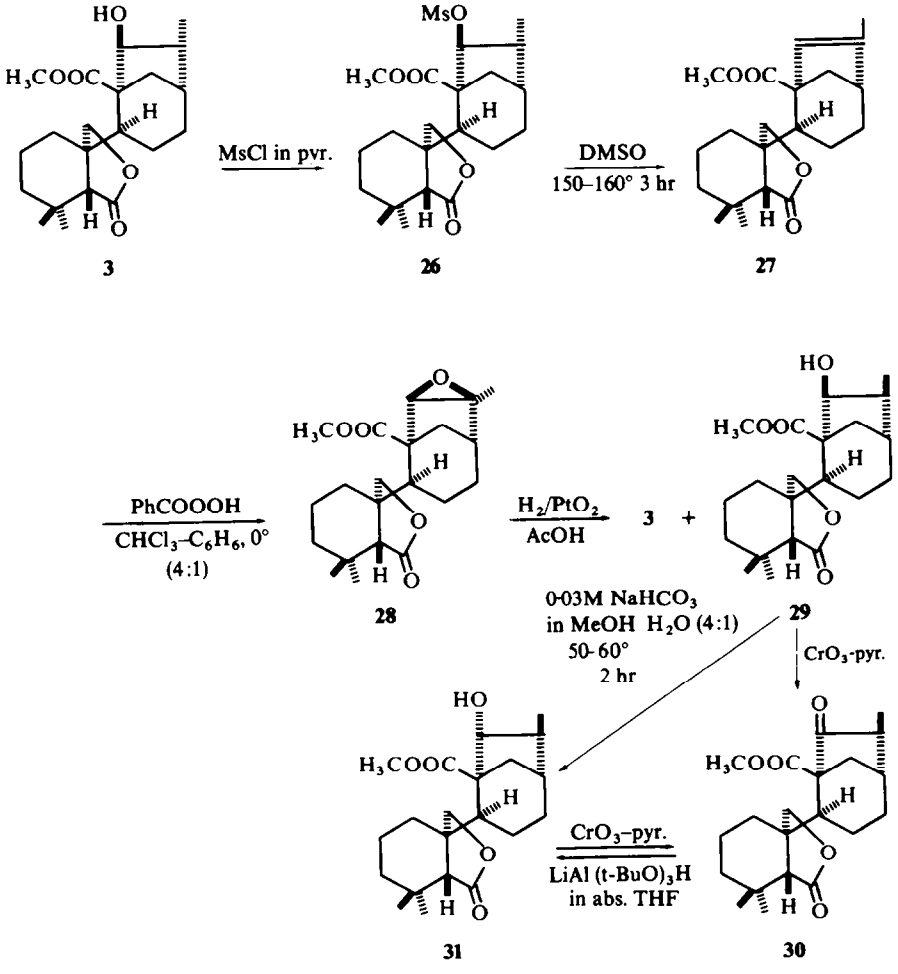
CHART 5



An X-ray analysis of the bromoacetate of alcohol **3**, which was carried out by courtesy of Professor Sim and Dr. Coggan of University of Sussex, established its structure and absolute configuration as **25**.[9] This constitutes a further evidence for the chemical assignment. These epimeric alcohols, **3** and **24**, have been obtained by Okamoto *et al.*[10] They carried out reduction of **20** with $NaBH_4$, then separated these alcohols by silica gel column chromatography. Now, it was reconfirmed that their assignments were correct.

Subsequently, alcohol **3** was converted into methane sulphonate **26**,[4,10] which was heated in DMSO at 150–160° for 3 hr[11] to afford an unsaturated product **27**[10] in a good yield. On treatment with perbenzoic acid in a mixture of chloroform and benzene, **27** gave epoxide **28**, which was subjected to hydrogenolysis on Adams' catalyst in acetic acid to yield alcohol **3** and a new *cis*-β-alcohol **29** in a ratio of 4:3. The structure and absolute configuration of **29** were reasonably assigned on the basis

CHART 6

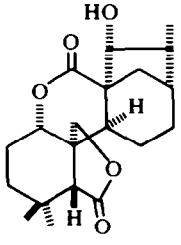


of a potential reaction mechanism[12] and the spin–spin coupling constant of 8·5 Hz of C-15 proton to C-16 proton in its NMR spectrum.

Alcohol **29** on oxidation with CrO_3–pyridine complex gave a new ketone **30**, which on reduction with LiAl (t-BuO)$_3$H in anhydrous THF gave the fourth epimer *trans*-α-alcohol **31**. On oxidation with CrO_3–pyridine complex, **31** regenerated ketone **30**. Moreover, it was recognized that the foregoing alcohol **29** was epimerized into **31** under an weak alkaline condition, although the reaction rate was much slower than that of **24** to **3**. These facts confirmed the structure and absolute configuration of each of alcohols, **29** and **31**, and ketone **30** to be represented as shown in Chart 6.

Thus, it was proved that a stereospecific hydride attack occurred from the less-hindered β-side of each molecule of ketones, **9**, **20** and **30**, when they were treated with LiAl $(t\text{-}BuO)_3H$ in anhydrous THF or with $NaBH_4$ in absolute MeOH, and also that the original products, *cis*-alcohols, were epimerized into more stable *trans*-isomers under weak alkaline condition in the case of presence of H_2O.

CHART 7



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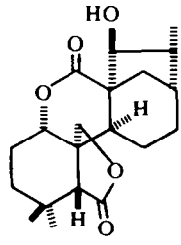
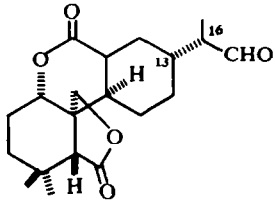
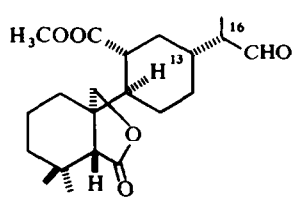


33



34



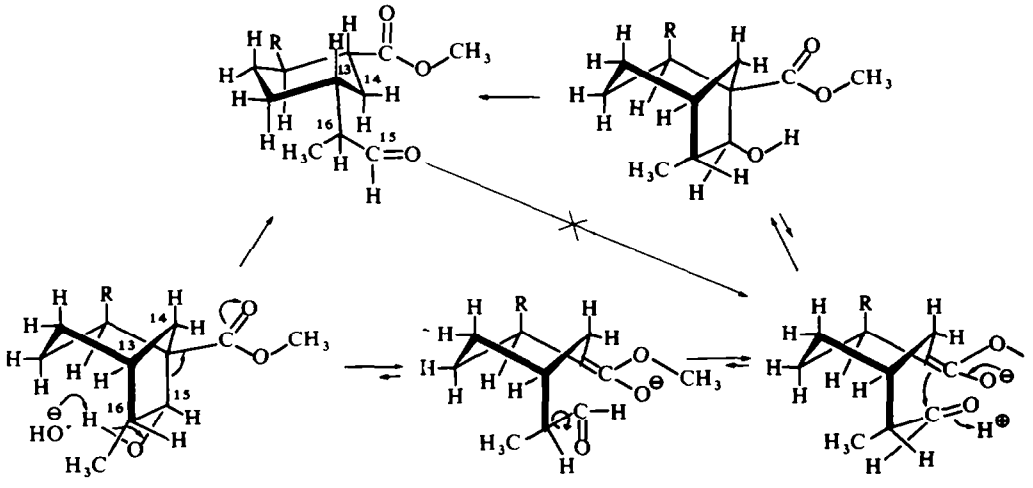
35

Finally, compound **32**[13] possessing a δ-lactone on its treatment under the same condition as in the foregoing epimerizations did not give the epimerized alcohol **33**, but only the recovered material. The use of stronger condition, that is, an attempted epimerization at reflux resulted in the formation of aldehyde **34** with cleaved D-ring. Thus, it was recognized that the free rotational carbomethoxy group in **11**, **13**, **24** and **29** is more favourable to the transition state for epimerization of C-15 OH than the rigid lactone ring in **32**.

Neither of aldehydes **34** and **35**, which was derived from alcohol **3**, was recyclized by 0·03M $NaHCO_3$ in MeOH–H_2O (4:1) at room temp. Each aldehyde has a stable *equatorial* substituent at C-13. This is why no recyclization occurred in such a mild condition.

The afore-mentioned epimerizations, that is **11** to **10**, **24** to **3**, **13** to **15** and **29** to **31** may proceed through a retroaldol-type transition state and recyclization. In order to release an unfavourable *cis* eclipsed interaction between C-15 OH and C-16 Me groups, a turning of the orientation of C-15 substituent around the bond between C-15 and C-16 must occur and give a *trans* product in each case.[14] These processes are depicted in Chart 8. It is noteworthy that C-15 β-OH group of **29** was epimerized into the thermodynamically less favourable α-orientation, although the rate was much slower.

CHART 8



EXPERIMENTAL

All m.ps were determined by a micro m.p. apparatus (Yanagimoto) and were uncorrected. All specific rotations were measured by JASCO model ORD/UV-5. Unless otherwise stated, IR spectra were recorded in KBr disk on a Hitachi model EPI-S2 spectrophotometer, NMR spectra in $CDCl_3$ with TMS as an internal standard on a Varian A-60 spectrometer and Mass spectra on a Hitachi RMU 6D mass spectrometer. Shimadzu GC-1C was used for gaschromatography and QF-1 for column packing. Extracts were dried over Na_2SO_4. Mallinckrodt silisic acid was used for column chromatography. TLC plates were coated with Nakarai Silica Layer G and Merck Kieselgel G.

$NaBH_4$ reduction of bisdehydrodihydroenmein

To a soln of **5** (552 mg) in THF (40 ml) and EtOH (20 ml) a soln of $NaBH_4$ (120 mg) in aqueous EtOH (10 ml) was added and the mixture was stirred at room temp for 2 days. After neutralization with 10% HCl, the solvent was distilled off leaving a residue, to which H_2O was added, then extracted with $CHCl_3$. The extract, treated as usual, gave a crude crystalline product (350 mg), which was purified by recrystallization from acetone–light pet ether to yield **6** as colourless needles (200 mg), m.p. 258–259°; IR ν_{max}: 3415; 1771; 1721 cm^{-1}; NMR $\delta^{D_5\text{-}pyr}_{ppm}$: 0·97 (3H, d, J = 7); 1·33 (3H, s); 1·60 (3H, s); 2·67 (1H, s, C-5—H); 3·78 (1H, q, J = 5·5, 9·5, C-3—H); 4·60 (2H, s, C-20—H_2); 4·96 (1H, q, J = 7, 9·5, C-1—H); 5·34 (1H, d, J = 10, C-15—H). (Found: C, 65·93; H, 8·00. Calc. for $C_{20}H_{28}O_6$: C, 65·91; H, 7·74%).

Diacetate **7**. To a soln of **6** (80 mg) in anhyd pyridine (2 ml) Ac_2O (2 ml) was added and the mixture kept

overnight. The solvent was evaporated after addition of H_2O and benzene. The residue was purified by silica gel chromatography and elution by $CHCl_3$. A purified sample (39 mg) of **7** was obtained from EtOH, m.p. 131–133°; IR ν_{max}: 1777; 1735; 1225 cm^{-1}, NMR δ_{ppm}: 0·79 (3H, d, J = 7); 1·12 (3H, s); 1·21 (3H, s); 2·12 (3H, s); 2·15 (3H, s); 2·43 (1H, s, C-5—H); 3·98, 4·28 (each 1H, AB type, J = 10, C-20—H_2); 4·60 (1H, q, J = 4·5, 11, C-3—H); 4·70 (1H, q, J = 6·5, 11, C-1—H); 5·78 (1H, d, J = 10, C-15—H). (Found: C, 62·03; H, 7·09. Calc. for $C_{24}H_{32}O_8 \cdot H_2O$: C, 61·79; H, 7·35%).

Chromic acid oxidation of diol **6**. Diol **6** (52 mg) was dissolved in AcOH (1·5 ml), and a soln of CrO_3 (50 mg) in a small amount of AcOH was added. The mixture was stirred at room temp overnight and then extracted with AcOEt after addition of a little H_2O. The extract, treated as usual, gave colourless fine crystals (20 mg), identical with **5** (IR and TLC).

Treatment of enonoic acid **8** *with* HCl.* Acid **8** (1 g) was dissolved in AcOH (40 ml), and conc HCl (2·5 ml) was added and the mixture stirred at room temp for 54 hr. A ppt of colourless fine crystals (190 mg) proved identical with the known enonoic diacid,[6] a product with cleaved D-ring. The filtrate was extracted with $CHCl_3$. During this procedure, further crystals (145 mg) of diacid precipitated and were separated. The $CHCl_3$ extract, treated as usual, was separated into neutral (39 mg) and acidic (547 mg) fractions. From the neutral fraction, **5** (21 mg) was obtained as pure crystals. The crude acidic fraction was purified by recrystallization from MeOH to recover acid **8** (301 mg). 1-*Epi* derivative of **5** was also observed on TLC, but it was not investigated in detail, because of the small amount and contamination.

$NaBH_4$ *reduction of* **9** *in* THF–H_2O. To a soln of **9** (266 mg) in THF (9 ml), a soln of $NaBH_4$ (60 mg) in THF (1 ml)–H_2O (0·5 ml) was added, and the mixture stirred at room temp for 1·3 hr. The mixture was neutralized with 10% HCl, the solvent was distilled off and a small amount of H_2O was added to the residue. The mixture was extracted with $CHCl_3$ and the extract, treated as usual, gave *an oily product* **10** (226 mg); IR $\nu_{max}^{CHCl_3}$: 3550; 1755; 1724 cm^{-1}, NMR $\delta_{ppm}^{CDCl_3-C_6H_6}$: 0·83 (3H, s); 1·00 (3H, d, J = 7); 1·3 (3H, s); 2·74 (1H, s); 3·44 (1H, d, J = 4·5, C-15—H); 3·56 (3H, s); 3·68, 3·92 (each 1H, AB-type, J = 10, C-20—H_2); 3·97 (1H, dd, J = 1·5, 2·0, C-3—H); 5·25 (1H, dd, J = 2, 10, C-1—H); 5·52 (1H, dd, J = 1·5, 10·0, C-2—H).

Oxidation of **10** *into* **9**. To a soln of **10** (27 mg) in anhyd pyridine (1 ml) excess of CrO_3–pyridine complex in pyridine was added, and the mixture kept overnight. Usual treatment afforded colourless needles (15 mg), identical with **9** by IR, TLC, m.p. comparisons.

Reduction of **9** *with* LiAl(t-BuO)$_3$H *in* THF. To a soln of **9** (545 mg) in anhyd THF (15 ml) LiAl(t-BuO)$_3$H (1 g), was added, and the mixture kept at room temp for 6 hr. It was then poured into ice-cooled 10% HCl, while the acidity was maintained. The solvent was evaporated off leaving a residue, to which a small volume of H_2O was added. The mixture was extracted with $CHCl_3$. Usual treatment gave a crude residue (699 mg), which was chromatographed on silica gel (35 g) and elution by $CHCl_3$ gave a crystalline first fraction (343 mg). The latter was recrystallized from MeOH to yield diol **13** as colourless plates (290 mg); IR $\nu_{max}^{CHCl_3}$: 3500; 1765; 1715 cm^{-1}, NMR δ_{ppm}: 0·84 (3H, s); 1·00 (3H, d, J = 7); 1·39 (3H, s); 2·82 (1H, d, J = 5, C-15—OH, disappeared with D_2O); 3·28 (1H, s, C-5—H); 3·53 (1H, d, J = 6, C-3—H); 3·68 (3H, s); 3·90, 4·12 (each 1H, AB-type, J = 10, C-20—H_2); 4·04 (1H, dd, J = 5, 10, d, J = 10, with D_2O, C-15—H); 5·46 (1H, d, J = 10, C-1—H); 5·99 (1H, dd, J = 6, 10, C-2—H). (Found: C, 66·64; H, 7·99. $C_{21}H_{30}O_6$ requires: C, 66·69; H, 8·18%). The second eluate gave *an oily product* **11** (101 mg); IR $\nu_{max}^{CHCl_3}$: 3600; 1760; 1725 cm^{-1}, NMR $\delta_{ppm}^{C_6H_6}$: 0·94 (3H, s); 0·95 (3H, d, J = 7); 1·43 (3H, s); 2·95 (1H, s, C-5—H); 3·38 (3H, s); 3·58, 3·84 (each 1H, AB-type, J = 10, C-20—H_2); 3·79 (1H, d, J = 11, C-15—H); 3·99 (1H, dd, J = 1·0, 2·5, C-3—H); 5·12 (1H, dd, J = 2·5, 10, C-1—H); 5·53 (1H, dd, J = 1·0, 10, C-2—H).

Both diols, **11** and **13** on oxidation with CrO_3–pyridine complex gave the original ketone **9**.

Diacetate **12**. Diol **11** (31 mg) was dissolved in Ac_2O (1 ml) and dry pyridine (1 ml) and kept for 4 days. Usual treatment followed by purification with silica gel chromatography using $CHCl_3$ for elution gave *diacetate* **12** as colourless needles (30 mg), which was recrystallized from EtOH, m.p. 185–187°; IR $\nu_{max}^{CHCl_3}$: 1760; 1735; 1235 cm^{-1}; NMR δ_{ppm}: 0·85 (3H, d, J = 7); 0·98 (3H, s); 1·28 (3H, s); 2·14 (6H, s); 2·93 (1H, s, C-5—H); 3·63 (3H, s); 3·90, 4·16 (each 1H, AB-type, J = 10, C-20—H_2); 5·26 (1H, d, J = 11, C-15—H); 5·29 (1H, s, C-3—H); 5·58 (2H, s, C-1—H, C-2—H). (Found: C, 64·65; H, 7·65. $C_{25}H_{34}O_8$ requires: C, 64·92; H, 7·41%).

Diacetate **14**. Diol **13** (41 mg) was dissolved in Ac_2O (2 ml), and dry pyridine (2 ml) was added and the mixture was kept at room temp for 2 days. Usual treatment and purification of the crude product by silica gel chromatography and elution with $CHCl_3$ gave a crystalline product (50 mg), which was recrystallized from EtOH to yield *diacetate* **14** as colourless needles (30 mg), m.p. 183–184°; IR $\nu_{max}^{CHCl_3}$: 1760; 1730; 1230 cm^{-1}; NMR δ_{ppm}: 0·86 (3H, d, J = 6·5); 0·98 (3H, s); 1·32 (3H, s); 2·12 (3H, s); 2·13 (3H, s); 3·14

* This part was carried out by Mr. H. Katayama, to whom we express our thanks.

(1H, s, C-5—H); 3·54 (3H, s); 3·92, 4·18 (each 1H, AB-type, C-20—H_2); 4·60 (1H, d, J = 5·5, C-3—H); 5·21 (1H, d, J = 10·5, C-15—H); 5·72 (1H, d, J = 10, C-1—H); 6·02 (1H, dd, J = 5·5, 10, C-2—H). (Found: C, 64·86; H, 7·41. $C_{25}H_{34}O_8$ requires: C, 64·92; H, 7·41%).

Epimerization of **13** *into* **15**. Diol **13** (150 mg) was dissolved in 0·03M $NaHCO_3$ in MeOH–H_2O (4:1) (8 ml), and the soln was stirred at room temp overnight. The mixture was neutralized with 10% HCl and the solvent evaporated leaving a residue, to which a small amount of H_2O was added. The mixture was extracted with $CHCl_3$ and the extract, treated as usual, gave a crude product (140 mg), which was chromatographed on silica gel with elution by $CHCl_3$–acetone (30%) to give a crystalline substance (130 mg). The latter was recrystallized from MeOH to yield *epimeric alcohol* **15** as colourless plates (98 mg), m.p. 167–168°; IR $\nu_{max}^{CHCl_3}$: 3460; 1765; 1718 cm^{-1}; NMR δ_{ppm}: 0·84 (3H, s); 1·12 (3H, d, J = 7); 1·37 (3H, s); 3·22 (1H, s, C-5—H); 3·58 (1H, d, J = 6, C-3—H); 3·63 ~ 3·75 (1H, C-15—H); 3·70 (3H, s); 3·90, 4·08 (each 1H, AB-type, J = 10, C-20—H_2); 5·55 (1H, d, J = 10, C-1—H); 6·03 (1H, dd, J = 6, 10, C-2—H). (Found: C, 66·69; H, 7·93. $C_{21}H_{30}O_6$ requires: C, 66·64; H, 7·99%). Diol **15** was oxidized with CrO_3–pyridine complex in pyridine as usual to regenerate diketone **9**.

Diacetate **16**. Diol **15** (20 mg) was dissolved in Ac_2O (1 ml), and dry pyridine (1 ml) was added. After standing at room temp for 4 days, usual treatment and recrystallization of the crude product from EtOH afforded *diacetate* **16** as colourless needles (17 mg), m.p. 145–146°; IR $\nu_{max}^{CHCl_3}$: 1765; 1730; 1235 cm^{-1}; NMR δ_{ppm}: 0·94 (3H, s); 1·11 (3H, d, J = 7); 1·30 (3H, s); 1·96 (3H, s); 2·16 (3H, s); 3·09 (1H, s, C-5—H); 3·55 (3H, s); 3·90, 4·14 (each 1H, AB-type, J = 10, C-20—H_2); 4·57 (1H, d, J = 6, C-3—H); 4·97 (1H, d, J = 5, C-15—H); 5·74 (1H, d, J = 10, C-1—H); 6·02 (1H, dd, J = 6, 10, C-2—H). M^+ m/e 462 (mass spectrum).

Epimerization of **11** *into* **10**. (i) Diol **11** (16 mg) was dissolved in 0·03M $NaHCO_3$ in MeOH–H_2O (4:1) (1 ml), and the soln was stirred overnight at room temp. The mixture was neutralized with 10% HCl and the solvent evaporated leaving a residue, to which a small amount of H_2O was added, and the mixture extracted with $CHCl_3$. The extract, treated as usual, yielded an oily epimeric diol, whose IR and TLC were identical with those of an authentic sample of **10**.

(ii) Diol **11** (30 mg) was dissolved in THF (2 ml), and a soln of $NaBH_4$ (10 mg) in EtOH (0·5 ml) and H_2O (0·5 ml) was added and the mixture stirred at room temp overnight. After acidification with 10% HCl, the solvent was distilled off leaving a residue, which was extracted with CH_2Cl_2 after addition of a small amount of H_2O. The extract, on usual treatment, gave an oily product (22 mg), whose IR spectrum coincided with that of the authentic sample of **10**.

Catalytic hydrogenation of **11**. To a soln of **11** (90 mg) in MeOH (2 ml), PtO_2 (10 mg) was added, and the mixture was stirred overnight in a stream of H_2. The filtrate from the catalyst was evaporated leaving a residue (50 mg), which was purified by silica gel chromatography and elution by $CHCl_3$ to yield a pure oily **17** (30 mg); IR $\nu_{max}^{CHCl_3}$: 3575; 1765; 1722 cm^{-1}; NMR δ_{ppm}: 0·95 (3H, d, J = 7); 0·96 (3H, s); 1·23 (3H, s); 2·27 (1H, s, C-5—H); 3·39 (1H, t, J = 7, C-3—H); 3·72 (3H, s); 3·92 (2H, s, C-20—H_2); 4·07 (1H, d, J = 10, C-15—H).

Jones' oxidation of **17**. Diol **17** (25 mg) was dissolved in acetone (1·5 ml), and an equivalent amount of Jones' reagent was added dropwise under ice-cooling. The mixture was stirred for 0·5 hr and then poured into a cold sat NaCl aq and extracted with $CHCl_3$. The extract, on usual treatment, gave a crude crystalline product, which was recrystallized from MeOH to yield **19** as colourless needles (15 mg). The identity was confirmed by TLC and IR comparisons with those of an authentic sample **19**.[7]

Catalytic hydrogenation of **13**. Unsaturated diol **13** (45 mg) was dissolved in MeOH (2 ml), and PtO_2 (10 mg) was added. The mixture was stirred overnight in a stream of H_2. The filtrate from catalyst was evaporated leaving a residue (55 mg), which was chromatographed on silica gel using $CHCl_3$ for elution to give a crystalline product. The latter was recrystallized from MeOH to yield saturated alcohol **18** as colourless needles (24 mg), m.p. 155–157°; IR $\nu_{max}^{CHCl_3}$: 3570; 1760; 1722 cm^{-1}; NMR δ_{ppm}: 0·96 (3H, d, J = 7); 0·96 (3H, s); 1·25 (3H, s); 2·36 (1H, s, C-5—H); 3·53 (1H, t, J = 2·5, C-3—H); 3·73 (3H, s); 3·93 (2H, s, C-20—H_2); 4·07 (1H, d, J = 10·5, C-15—H).

Jones' oxidation of **18**. To a soln of **18** (20 mg) in acetone (1·5 ml), an equivalent amount of Jones' reagent was added dropwise, and the mixture stirred for 0·5 hr; then poured into a cold sat NaCl aq, and extracted with $CHCl_3$. The extract, on usual treatment, gave a crystalline product as colourless needles (16 mg), which was identical with an authentic sample of **19**.

Treatment of **9** *with* BF_3*–etherate*. To a soln of **9** (100 mg) in $CHCl_3$ (1 ml) BF_3–etherate (1 ml) was added, and the mixture kept for 2 weeks, and then neutralized with cold 5% Na_2CO_3 aq. Subsequently, the mixture was extracted with $CHCl_3$ and the extract, treated as usual, gave a crude crystalline product, which was

recrystallized from MeOH to yield colourless needles (95 mg). Their IR, TLC and m.p. were completely identical with those of **9**.

Ethylene monothioketal **21**. Ethylene monothioglycol (1 ml) was added to a soln of **9** (500 mg) in $CHCl_3$ (1 ml) and BF_3–etherate (1 ml). The mixture was stirred at room temp for 2 hr, and then poured into a small excess of cold 10% Na_2CO_3 aq. The mixture was extracted with $CHCl_3$, and the extract, treated as usual, gave a crude product (548 mg), which was chromatographed on silica gel using $CHCl_3$ for elution to yield a crystalline product. The latter was recrystallized from MeOH to afford colourless needles (300 mg) of *monothioketal* **21**, m.p. 186–189°; IR ν_{max}: 1764 (shoulder); 1753; 1715 cm^{-1}. (Found: C, 63·39; H, 7·24. $C_{23}H_{30}O_6S$ requires: C, 63·58; H, 6·96%).

Desulphurization of **21**. Monothioketal **21** (137 mg) was dissolved in 99% EtOH (8 ml), and a soln of Raney-Ni (W_2) (0·6 g) in EtOH (1 ml) was added. The mixture was heated for 4 hr under reflux, and the catalyst filtered off. The solvent was evaporated leaving a crystalline residue, which was purified by chromatography on silica gel using $CHCl_3$ for elution. It was recrystallized from $CHCl_3$–MeOH to yield **9** as colourless needles (60 mg), whose IR and NMR spectra were identical with those of the authentic sample. The mixture m.p. also confirmed their identity.

Treatment of ketolactone ester **20** *with* MeONa. To a soln of **20** (50 mg) in anhyd MeOH (10 ml) a soln of Na (ca. 3 mg) in anhyd MeOH (3 ml) was added, and the mixture heated under reflux for 45 min under anhyd conditions. The mixture was neutralized with 10% HCl and the solvent was distilled off leaving a residue, to which H_2O was added. The mixture was extracted with $CHCl_3$. The extract, treated as usual, gave a mixture of crude carboxylic acids, which were dissolved in MeOH (3 ml) and esterified with CH_2N_2–Et_2O soln to yield a mixture of methyl esters. The latter was chromatographed on silica gel (1·5 g) using $CHCl_3$–acetone (20:1) for elution to give a first crystalline eluate, which was recrystallized from MeOH to yield colourless fine needles (10 mg), m.p. 155–156°. Their IR, TLC, and VPC were identical with those of an authentic sample of **22**.[8] The second crystalline eluate was recrystallized from MeOH to yield colourless needles (20 mg), m.p. 200–202°, of **23**.*

Reduction of **20** *with* LiAl $(t\text{-BuO})_3H$ *in abs.* THF. To a soln of **20** (50 mg) in dry THF (1 ml), a soln of LiAl $(t\text{-BuO})_3H$ (70 mg) in dry THF (0·5 ml) was added. After the mixture was stirred for 3 hr under ice-cooling, it was acidified with cold 10% HCl, and the solvent was evaporated to give a residue, which, after addition of some H_2O, was extracted with $CHCl_3$. The extract, treated as usual, gave a crude crystalline product (45 mg), which was recrystallized from MeOH to afford **24**[10] as colourless needles (25 mg), m.p. 134–135°, $[\alpha]_D^{20}$ +31·3° (c, 0·46; dioxan); IR $\nu_{max}^{CHCl_3}$: 3600; 1769; 1725 cm^{-1}, NMR δ_{ppm}: 0·97 (3H, d, J = 7); 0·98 (3H, s); 1·19 (3H, s); 2·18 (1H, s); 3·73 (3H, s); 3·93 (2H, s); 4·08 (1H, d, J = 10·5, C-15—H). (Found: C, 69·35; H, 8·98. Calc. for $C_{21}H_{32}O_5$: C, 69·20; H, 8·85%).

Reduction of **20** *with* $NaBH_4$ *in abs* MeOH. To a soln of **20** (500 mg) in abs MeOH (10 ml), a soln of $NaBH_4$ (33 mg) in abs MeOH (1 ml) was added, and the mixture was stirred at room temp for 5·5 hr. After usual treatment, a crude product (481 mg) was isolated from the $CHCl_3$ extract. It was chromatographed on silica gel (30 g) using $CHCl_3$ and $CHCl_3$–acetone (9:1) for elution. The first eluate was crystallized from MeOH and purified by recrystallization to yield **24** as colourless needles (138 mg). The second eluate was also crystallized and purified from MeOH to yield **3**[4] as colourless needles (127 mg).

Reduction of **20** *with* $NaBH_4$ *in* MeOH–H_2O. To a soln of **20** (500 mg) in MeOH (10 ml), a soln of $NaBH_4$ (42 mg) in a small quantity of MeOH and H_2O (1 ml) was added. The mixture was stirred at room temp for 5 hr. Neutralization with 10% HCl, evaporation of the solvent, extraction of the products with $CHCl_3$ and usual treatment gave **3** (481 mg), which was recrystallized from MeOH to give pure colourless needles (360 mg).

Regeneration of **20** *from* **24** *and* **3** *by oxidation.* To a soln of **24** (50 mg) in pyridine (1·5 ml), excess of CrO_3–pyridine complex was added, and the mixture was kept at room temp overnight. Usual treatment gave **20** (26 mg). Similarly, **3** (50 mg) was oxidized to give **20** (25 mg).

Epimerization of **24** *into* **3**. (i) A soln of **24** (24 mg) in 0·03M $NaHCO_3$ in MeOH–H_2O (4:1) (2 ml) was stirred at room temp for 2 hr. The mixture, treated as usual, gave a crude crystalline product, which was recrystallized from MeOH to yield epimer **3** (16 mg).

(ii) To a soln of **24** (30 mg) in MeOH (2 ml), a soln of $NaBH_4$ (10 mg) in a mixture of MeOH (0·5 ml) and H_2O (0·5 ml) was added, and the mixture stirred at room temp for 5 hr. After acidification with 10%

* This compound was orally reported at the Annual Meeting of the Kinki Branch of the Pharmaceutical Society of Japan held on 20 November, 1966, by E. Fujita, T. Fujita, H. Katayama and S. Kunishima, and will be published elsewhere.

HCl, the solvent was distilled off to give a residue, to which a small quantity of H_2O was added. The mixture was extracted with CH_2Cl_2, and the extract, treated as usual, gave an oily product, which was crystallized and purified from MeOH to yield **3** as colourless needles (18 mg).

(iii) To a soln of **20** (50 mg) in anhyd MeOH (1 ml), $NaBH_4$ (4 mg) was added, and the mixture left for 1 hr under anhyd conditions. TLC of the mixture showed the formation of **24**. After addition of 2 drops H_2O, the mixture was stirred for 5 min. TLC of the mixture showed the formation of about equal quantity of **24** and **3**. After further stirring for 1 hr, the TLC of the mixture showed a large spot of **3** and a very small spot of **24**. Then, $NaBH_4$ (3 mg) was added, and the mixture was stirred for 2 hr. TLC of the mixture showed only one spot of **3**. The usual treatment afforded a crystalline product (45 mg), which was recrystallized from MeOH to yield pure colourless needles (30 mg). The latter proved to be pure **3** by mixture m.p. with an authentic sample and comparison of their IR spectra.

Bromoacetate **25** *from* **3**. To a soln of **3** (100 mg) in $CHCl_3$ (10 ml) bromoacetyl bromide (0·3 ml) was added, and the mixture heated under reflux for 3·5 hr. After washing with ice–H_2O (10 ml) 3 times, the mixture, treated as usual, gave a crude product (85 mg), which was chromatographed on silica gel column using $CHCl_3$ for elution to give a crystalline eluate. The latter was recrystallized from EtOH to yield *bromoacetate* **25** as colourless plates (36 mg), m.p. 146–147°; IR ν_{max}: 1770; 1758; 1728 cm^{-1}: NMR δ_{ppm}: 0·99 (3H, s); 1·15 (3H, d, J = 7); 1·20 (3H, s); 2·07 (1H, s); 3·72 (3H, s); 3·73 (2H, s, $BrC\underline{H}_2COO$—); 3·91, 4·05 (each 1H, AB-type, J = 11, C-20—$\underline{H}_2$), 4·92 (1H, d, J = 5, C-15—$\underline{H}$). Beilstein test: positive. (Found: C, 56·62; H, 6·94. $C_{23}H_{33}O_6Br$ requires: C, 56·91; H, 6·85%).

Regeneration of **3** *from* **25**. Bromoacetate **25** (19 mg) was suspended in 5% K_2CO_3 in MeOH–H_2O (1 ml), and the mixture was stirred overnight. After neutralization with 10% HCl, the solvent was evaporated leaving a residue, which after addition of a small quantity of H_2O was extracted with $CHCl_3$. The extract, treated as usual, gave a crystalline product, which was recrystallized from MeOH to yield pure colourless needles (12 mg), identical with **3** by comparison with an authentic sample (m.p. TLC, IR and VPC).

Conversion of mesylate **26** *into olefin* **27**. Mesylate **26** (124 mg) was dissolved in anhyd DMSO (ca. 1·5 ml), and the mixture was heated in a sealed tube at 150–160° for 2–3 hr. (Or the mixture was heated at 180° under reflux for 0·5 hr with air cooling.) A small quantity of H_2O was added and the mixture was evaporated *in vacuo* to a yellow oily product (143 mg), which was chromatographed on silica gel using $CHCl_3$ for elution to yield a crystalline eluate. The latter was purified by recrystallization from MeOH–Et_2O to afford **27** as colourless needles, m.p. 128–130°; IR ν_{max}: 1765, 1725 cm^{-1}; NMR δ_{ppm}: 0·97 (3H, s); 1·19 (3H, s); 1·72 (3H, d, J = 1·6); 2·12 (1H, s, C-5—$\underline{H}$); 3·73 (3H, s); 3·93 (2H, s, C-20—$\underline{H}_2$); 5·38 (1H, m, C-15—$\underline{H}$). (Found: C, 73·07; H, 8·73. Calc. for $C_{21}H_{30}O_4$: C, 72·80; H, 8·73%).

Epoxide **28**. Olefine **27** (122 mg) was dissolved in $CHCl_3$–C_6H_6 (4:1) (1 ml), and a cold fresh prepared soln (1·3 ml) of perbenzoic acid in $CHCl_3$ (49·95 mg/1 ml) was added. The mixture was kept for 7 hr under cooling. A small quantity of $CHCl_3$ was added and the mixture was washed with cold 5% $Na_2S_2O_3$ aq. then with cold 5% Na_2CO_3 aq, and finally with H_2O. The soln, after drying, was evaporated leaving a residue, which was chromatographed on neutral alumina column using $CHCl_3$ for elution to give a crystalline eluate. The latter was purified from Et_2O to yield *epoxide* **28** as colourless needles (112 mg), m.p. 172–173°; IR ν_{max}: 1768; 1728; 1242; 899; 862 cm^{-1}; NMR δ_{ppm}: 0·98 (3H, s); 1·20 (3H, s); 1·46 (3H, s, C-16—$C\underline{H}_3$); 2·23 (1H, s, C-5—$\underline{H}$); 3·28 (1H, s, C-15—$\underline{H}$); 3·77 (3H, s); 3·94 (2H, C-20—$\underline{H}_2$). (Found: C, 69·50; H, 8·43; $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%). M^+: *m/e* 362 (Mass spectrum).

Hydrogenolysis of epoxide **28**. A mixture of a soln of **28** (122 mg) in pure AcOH (2 ml) with Adams' catalyst (122 mg) was stirred at room temp overnight in the stream of H_2. To the filtrate from the catalyst H_2O was added, and the mixture extracted with $CHCl_3$. The extract was washed with 5% Na_2CO_3, then with H_2O, and dried. The solvent was evaporated leaving an oily residue (126 mg), which was chromatographed on silica gel (5 g) using $CHCl_3$ for elution. A first crystalline eluate was recrystallized from MeOH to give *cis-β-alcohol* **29** as colourless needles (45 mg), m.p. 141–142°, $[\alpha]_D^{20}$ +30° (*c*, 0·6; dioxan); IR $\nu_{max}^{CHCl_3}$: 3600; 1750; 1725 cm^{-1}; NMR $\delta_{ppm}^{C_6H_6}$: 0·92 (3H, s); 1·10 (3H, d, J = 7·5); 1·18 (3H, s); 2·07 (1H, s); 3·56 (3H, s); 3·73 (1H, d, J = 8·5, C-15—$\underline{H}$); 3·52, 4·04 (each 1H, AB-type, J = 11, C-20—$\underline{H}_2$). (Found: C, 69·20; H, 8·85. $C_{21}H_{32}O_5$ requires: C, 69·19; H, 8·84%); M^+: *m/e* 364 (Mass spectrum). The following crystalline eluate was recrystallized from MeOH to yield colourless needles (50 mg), whose m.p., TLC and IR were completely identical with those of an authentic sample **3**.

Oxidation of **29** *into* **30**. Alcohol **29** (60 mg) was dissolved in pyridine (1 ml) and an excess of CrO_3–pyridine complex was added. After standing at room temp overnight, the mixture was treated as usual yielding crystalline product, which recrystallized from MeOH as *ketone* **30** (colourless needles; 30 mg), m.p. 130–131°, $[\alpha]_D^{20}$ +26·9° (*c*, 0·26; dioxan); IR $\nu_{max}^{CHCl_3}$: 1770; 1758; 1716 cm^{-1}; NMR $\delta_{ppm}^{C_6H_6}$: 0·98 (3H, s);

1·13 (3H, d, J = 7); 1·19 (3H, s); 2·20 (1H, s, C-5—H); 3·80 (3H, s); 3·96 (2H, s, C-20—H_2). (Found: C, 69·49; H, 8·51. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34%); M^+: m/e 362 (mass spectrum).

Alcohol **31** *from ketone* **30**. To a soln of **30** (20 mg) in anhyd THF (1 ml), LiAl (t-BuO)$_3$H (38 mg) was added, and the mixture stirred at room temp for 3·5 hr. The mixture was added dropwise to 10% HCl, during which time the acidity was maintained. Then, the solvent was evaporated leaving a residue, which, after addition of some H_2O, was extracted with $CHCl_3$. The extract on usual treatment gave an oily substance (20 mg) which was chromatographed on silica gel (1 g) using $CHCl_3$ for elution to give *a new* trans α-*alcohol* **31** as colourless needles (11 mg), m.p. 125–126°, $[\alpha]_D^{20}$ +32° (c, 0·25; dioxan); IR $\nu_{max}^{CHCl_3}$: 3575; 1755; 1725 cm^{-1}; NMR δ_{ppm}: 0·99 (3H, s); 1·10 (3H, d, J = 7·5); 1·20 (3H, s); 2·26 (1H, s, C-5—H); 3·53 (1H, d, J = 4·5); 3·73 (3H, 5); 3·92 (2H, s, C-20—H_2): M^+: m/e 364 (mass spectrum).

Oxidation of **31** *into* **30**. Excess of CrO_3–pyridine complex was added into a soln of **31** (8 mg) in pyridine (1 ml), and the mixture kept overnight. The mixture was treated as usual to give a crystalline substance, which was recrystallized from MeOH to yield ketone **30** (4 mg) as colourless needles.

Epimerization of **29** *into* **31**. (i) Alcohol **29** (15 mg) was dissolved in 0·03M $NaHCO_3$ in MeOH–H_2O (4:1) (0·4 ml), and the soln stirred for 7 days. The crude substance, isolated by usual treatment, was chromatographed on silica gel (500 mg) using $CHCl_3$ for elution. The first crystalline eluate was recrystallized from MeOH to yield **31** as colourless needles (6 mg). The following eluate was treated as above to give the original alcohol **29** as colourless needles (4 mg).

(ii) Alcohol **29** (15 mg) was dissolved in 0·03M $NaHCO_3$ in MeOH–H_2O (4:1) (0·4 ml), and the soln was warmed at 50–60° for 2 hr. The mixture on similar treatment as above gave **31** (8 mg).

Aldehyde **34**. (i) A soln of **32**[13] (100 mg) in 0·03M $NaHCO_3$ in MeOH H_2O (4:1) (2 ml) was heated under reflux for 7·5 hr, and the soln was weakly acidified with 10% HCl, then evaporated to dryness. Some H_2O was added to the residue, and the mixture was extracted with $CHCl_3$. The extract, treated as usual, gave a crystalline substance (70 mg), which was recrystallized from MeOH–Et_2O to yield *aldehyde* **34** as colourless fine crystals (29 mg), m.p. 172–175°; IR ν_{max}: 2710; 1774; 1744; 1222 cm^{-1}; NMR δ_{ppm}: 1·09 (3H, s); 1·10 (3H, d, J = 7); 1·23 (3H, s); 2·34 (1H, s, C-5—H); 3·79, 4·47 (each 1H, AB-type, J = 10, C-20—H_2); 4·35 (1H, q, J = 5·5, 9, C-1—H); 9·68 (1H, d, J = 2, >CH—CHO). (Found: C, 68·89; H, 8·39. $C_{20}H_{28}O_5$ requires: C, 68·94; H, 8·10%).

(ii) Alcohol **32** (100 mg) in ethylene glycol (2 ml) was heated under reflux for 20 min, H_2O was added and the mixture was extracted with Et_2O. The extract, treated as usual, gave a crude product, which after silica gel column chromatography gave a crystalline substance (96 mg). The latter was recrystallized from MeOH to yield pure *aldehyde* **34** as colourless fine crystals (50 mg).

An attempted cyclization of aldehyde **34**. Aldehyde **34** (15 mg) was dissolved in 0·03M $NaHCO_3$ in MeOH–H_2O (0·5 ml), and the soln was kept at room temp overnight. Usual treatment of the soln recovered the material **34** (12 mg).

An attempted cyclization of aldehyde **35**. Aldehyde **35** (20 mg) was treated as above to recover the material **35** (18 mg).

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