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TERPENOIDS—XI[1]

THE STRUCTURE AND ABSOLUTE CONFIGURATION OF TRICHOKAURIN AND ITS CHEMICAL CONVERSION INTO (—)-KAURENE AND DITERPENE ALKALOIDS[2]

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Abstract—The structure and absolute configuration **22** of trichokaurin have been established on the basis of spectral and chemical evidence. The chemical conversion of trichokaurin into *ènt*-16-oxo-17-norkauran-20-oic acid (**40**) has been accomplished, which means the transformation of trichokaurin into (—)-kaurene (**41**), atisine (**42**), garryine (**43**) and veatchine (**44**).

RECENTLY, we isolated eight kinds of diterpenoids from the leaves of *Isodon japonicus* Hara (Japanese name: "Hikiokoshi") and *I. trichocarpus* Kudo (Japanese name: "Kurobana-hikiokoshi"), and clarified the structure and stereochemistry of six kinds among them.[3–7]

Subsequently, we isolated a new kaurene-type diterpenoid from the leaves of *I. trichocarpus* Kudo, which we gave the name "trichokaurin"*, and investigated its structure and stereochemistry. This paper deals with the details of the research which led to an assignment of the structure and absolute configuration **22** to trichokaurin.

Trichokaurin was obtained as crystals having m.p. 184–185° (decomp.) and $[\alpha]_D^{17}$ −93°. The molecular formula, $C_{24}H_{34}O_7$, was established by the mass spectrum determination and analysis. In the IR spectrum (KBr), the absorption bands at 3550, 3450 and 3350 cm^{-1} due to hydroxy groups were observed.

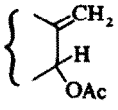
The IR absorption bands at 1730 and 1230 cm^{-1} and two singlet signals at δ 2·19 and 2·06 ppm due to methyl protons of acetoxy groups as well as one proton doublet at δ 5·21 ppm and one proton triplet signal at δ 5·62 ppm due to the protons on the acetoxylated carbons in the NMR spectrum gave an information that trichokaurin has two secondary acetoxy groups. Trichokaurin on acetylation gave an acetate, whose NMR spectrum exhibited singlet signals at δ 2·18, 2·09 and 2·06 ppm indicating the presence of three acetoxy groups. The one proton signal at δ 3·58 ppm in trichokaurin's spectrum caused a paramagnetic shift to δ 4·64 ppm by acetylation. Chromic acid oxidation of trichokaurin yielded a monoketo-derivative (IR: 1700 cm^{-1}).

* Prof. T. Okamoto and his collaborators, University of Tokyo, isolated a new diterpenoid from the same plant source and called it enmenin, which was proved to be identical with trichokaurin by a direct comparison with each other.

These facts suggested the presence of a secondary hydroxy group in the diterpenoid.

The foregoing acetate still had a hydroxy group, as shown in the IR (3500 cm^{-1}) and NMR (δ 3·76 ppm) spectra. The presence of a hydroxy group also in the foregoing keto-derivative was shown by the NMR (δ 3·38 ppm) and IR (3400 cm^{-1}) spectra. Accordingly, a tertiary hydroxy group is present in trichokaurin. Thus, six oxygens in trichokaurin were characterized. Subsequently, the remaining one was shown to be an ether-type oxygen, because a singlet signal of two protons due to an ether-type methylene group was observed at δ 3·93 ppm in the NMR spectrum.

The IR (1660 cm^{-1}) and NMR spectra (each one proton signal at δ 5·04 and 4·91 ppm) suggested an exocyclic methylene group in trichokaurin. As couplings of each of exocyclic methylene protons to the foregoing proton at δ 5·62 ppm were recognized, a partial structure **1** was proposed.



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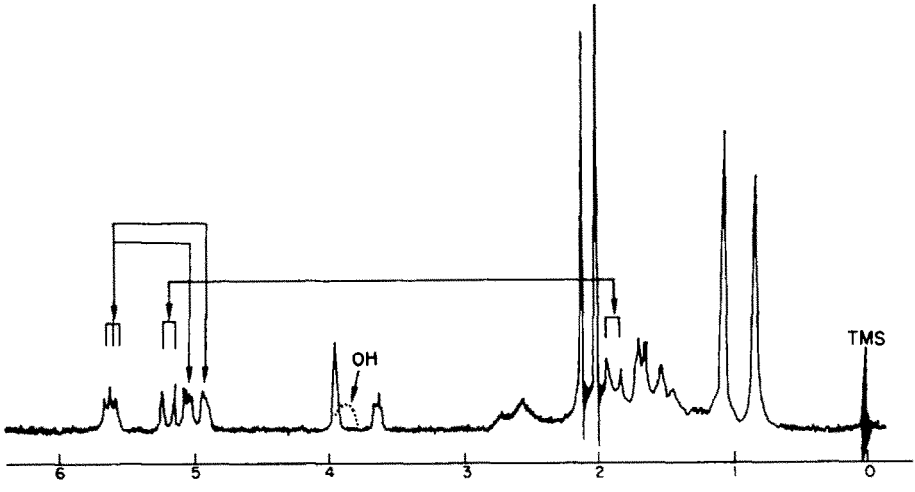
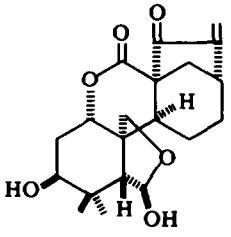


FIG. 1. The NMR spectrum of trichokaurin.

It is very characteristic and different from enmein (**2**)-type that trichokaurin contains neither a five-membered hemiacetal ring nor a δ-lactone ring, but does bear a tertiary hydroxy group. From its molecular formula the number of sites of unsaturation is calculated as eight. Since no other unsaturated bonds than one exomethylene and two carbonyls in acetoxy groups were found, trichokaurin must have five rings.

Trichokaurin was also shown to have two tertiary methyl groups from the NMR spectrum. Moreover, the proton at δ 5·21 ppm appeared as a doublet with a coupling (J = 7·0 Hz) to the proton at δ 1·93 ppm.

The foregoing data and a biogenetic consideration led to an assumption that trichokaurin might have a kaurene-type 7-hemiketal structure; a partial structure **3** was proposed.



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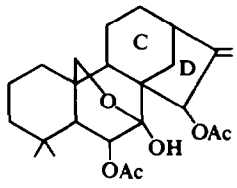
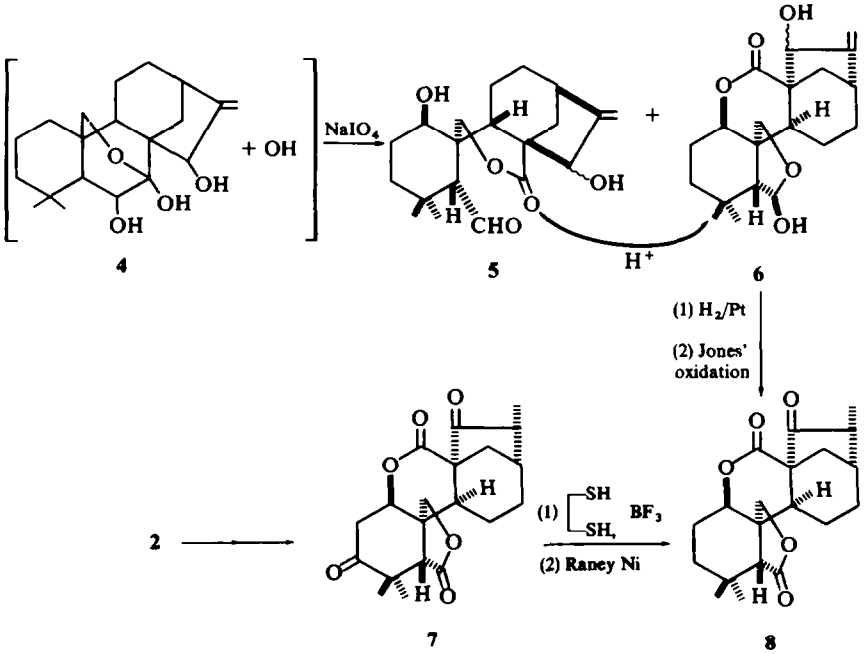


3

+ A Secondary OH

An alkaline hydrolysis of trichokaurin was tried in order to get tetraol **4**, but only a low yield of the desired product was obtained. The major product was an unsaturated aldehyde, which was yielded by the cleavage of the D-ring. A satisfactory yield of the tetraol was achieved by the treatment of trichokaurin with $LiAlH_4$. The acetate of trichokaurin on treatment with the same reagent also gave the tetraol in good yield.

The tetraol **4** in methanol was allowed to react with periodate at room temperature for three days to afford an enmein-type hemiacetal lactone **6** as a major product and a lactone aldehyde **5** as a minor product. The latter on treatment with a weak acid was easily converted into the former. Product **6** on hydrogenation using Adams' catalyst followed by oxidation with Jones' reagent gave a crystalline keto-dilactone, which was proved to be identical with 3-deoxy-1-*epi*-dehydrodihydro-enmein **8**, a product prepared from 1-*epi*-bisdehydrodihydroenmein **7**[8] by thioketalization and subsequent desulfurization. Thus, the structures and absolute configurations of **5** and **6** were confirmed as shown in Chart 1. Accordingly, the unidentified secondary



4 5 6 7 8

CHART 1

hydroxy group was proved to be located at C-1 and to have β-orientation (*axial*); the R-configuration of C-1 was established.

Hereupon, the structure of trichokaurin can be represented as formula **9**, the stereochemistry of the acetoxy groups at C-6 and C-15 being unsolved.

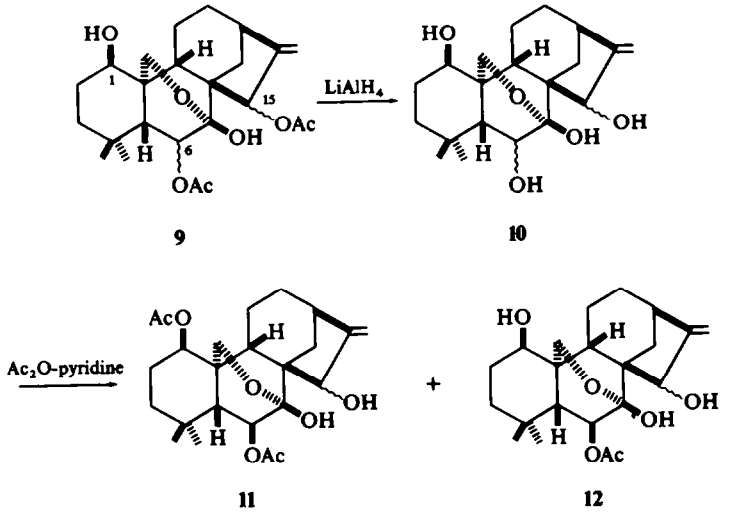


CHART 2

Tetraol **10** (=**4**) on acetylation yielded a crystalline diacetate **11** and an oily 6-monoacetate **12**. The fact suggests that the C-6 hydroxy group in compound **10** has β-configuration, because α-hydroxy group at C-6 would be more hardly acetylated than β-hydroxy group at C-1. Thus, the β-configuration is assigned to the acetoxy group at C-6 in trichokaurin as shown in formula **13**. It was reconfirmed that this assignment is correct, as will be later mentioned.

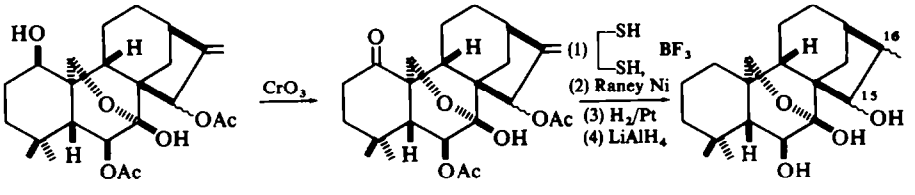


CHART 3

1-Keto-derivative **14**, a chromic acid oxidation product of trichokaurin **13**, was subjected to thioketalization followed by desulfurization with Raney nickel. The crude product was subjected to catalytic hydrogenation on Adams' catalyst, then to treatment with $LiAlH_4$ to give a saturated triol **15**. The *trans* relationship between C-15 and C-16 hydrogens in the triol was recognized based on the coupling constant (J = 5·0 Hz) in the NMR spectrum, hence the C-15 hydroxy group and the C-16 methyl group are *trans* each other. According to the usual examples[9] of hydrogenation on the exo-methylene at the D-ring in the series of compounds, we supposed β-

configuration of the methyl group at C-16. On the basis of the assumption, we first gave an assignment of α-configuration to the C-15 acetoxy group in trichokaurin,[2a] but we reached the conclusion that the assignment was incorrect, from the evidence given below.*

The methanesulfonate **16** of trichokaurin on oxidation with Lemieux-Johnson's reagent[11] gave a ketone **17**, which was also obtained from trichokaurin by Lemieux–Johnson's oxidation followed by mesylation. Treatment of the compound **17** with

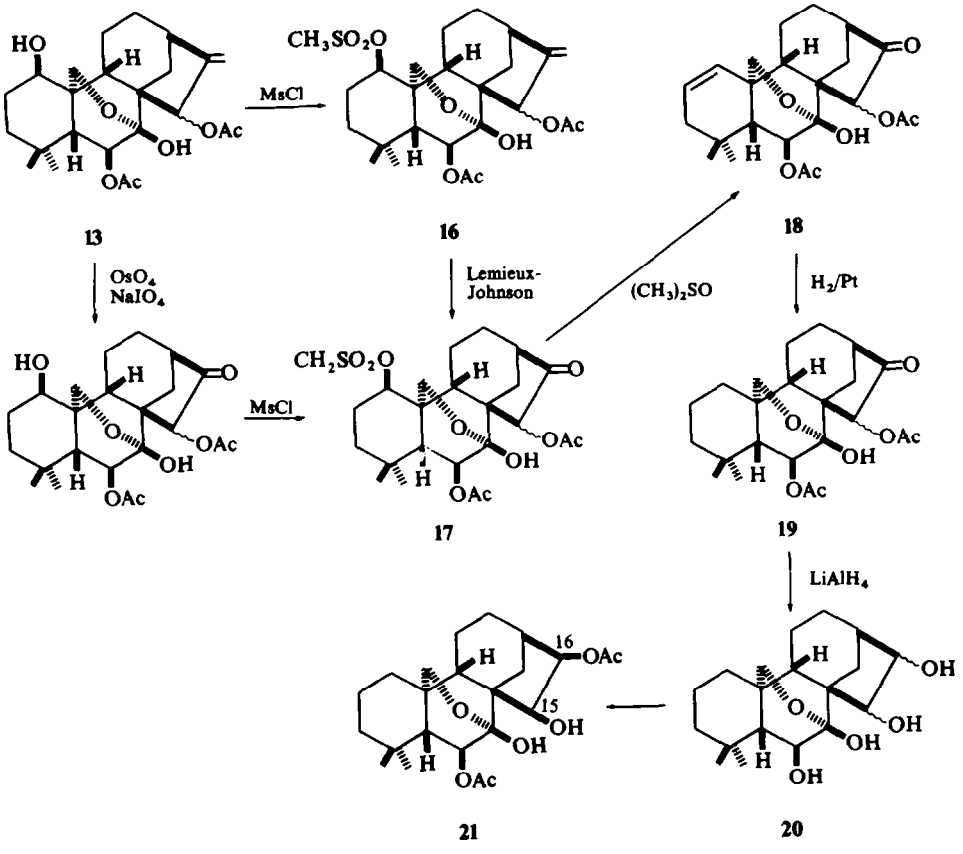
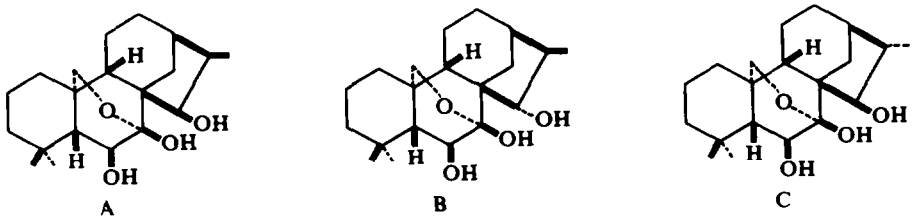


CHART 4

* Recently, we tried the IR comparisons of the product **15** (m.p. 232–235°) with the authentic samples A (m.p. 204–210°) and B (m.p. 200–202°), which were supplied by Prof. T. Okamoto,[10] University of Tokyo, and recognized the unidentity in each case. The stereochemistry of **15** is most probably represented as C.



dimethylsulfoxide at 150° for three hours[12] afforded an unsaturated compound **18**. On catalytic hydrogenation, the latter gave a saturated ketone **19**, which was treated with $LiAlH_4$ to afford tetraol **20**. In the NMR spectrum of diacetate **21** which was derived from the tetraol **20** by acetylation, a quartet [J = 3·5 (coupling to OH) and 9·0 Hz] at δ 4·26 ppm assignable to the C-15 proton and a quartet (J = 6·5 and 9·0 Hz) at δ 4·97 ppm assignable to the C-16 proton were observed. On the basis of the investigation on the stereomodel, only a steric configuration shown as formula **21**, in which the C-15 and C-16 hydrogens are α-*cis*-oriented, can provide a reasonable interpretation for the NMR data. Hence, the configuration of the C-15 acetoxy group in trichokaurin must be β as shown in formula **22**; the asymmetric center C-15 must have the R configuration.

Chemical evidence was provided to support this. Dehydrotrichokaurin (**23** = **14**) on treatment with $LiAlH_4$ gave tetraol **24**, whose periodate oxidation resulted in the formation of an enmein-type product. The structure and absolute configuration of the product were proved to be represented as **25**, because the derivative prepared by a partial acetylation followed by the catalytic hydrogenation was shown to be identical with tetrahydroisodocarpin-6-acetate (**26**) by IR and NMR spectral comparisons and the mixed melting point test; tetrahydroisodocarpin-6-acetate (**26**) was derived from isodocarpin **27**[7] through dihydroisodocarpin **28**[7] and tetrahydro-

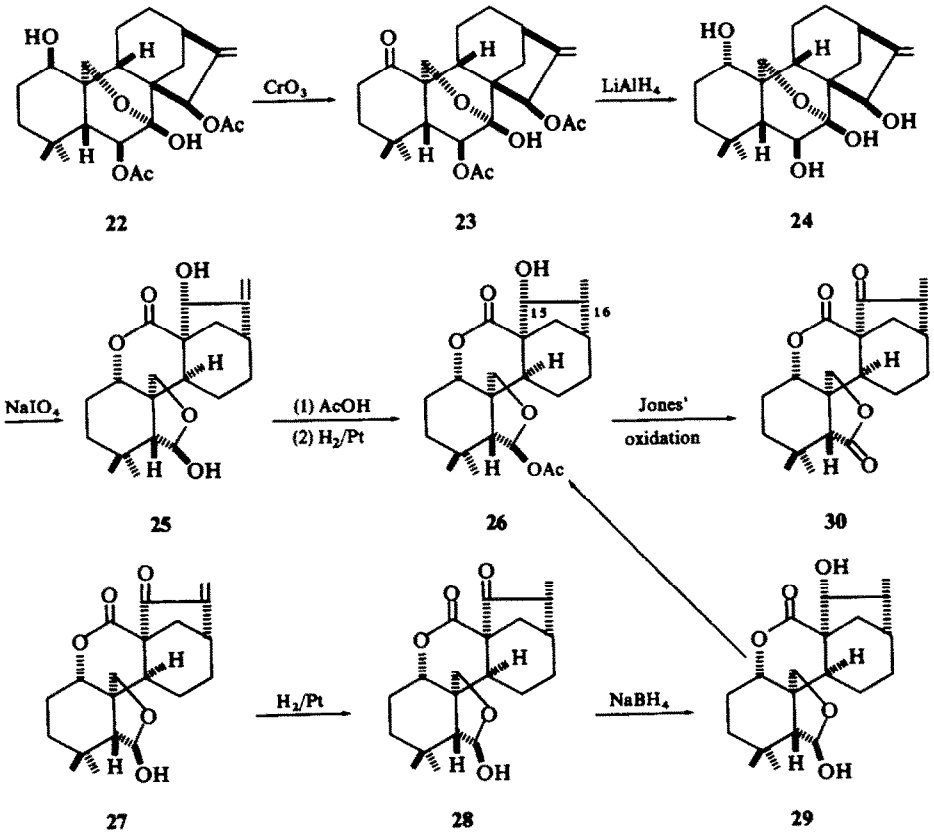
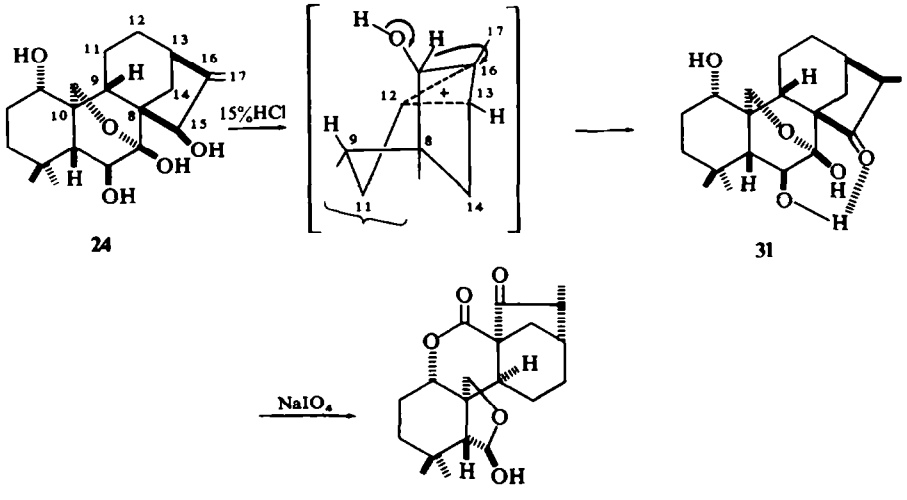


CHART 5

isodocarpin **29**. Moreover, compound **26** derived from trichokaurin (**22**), on Jones' oxidation, gave a product which was proved to be identical with the known dehydrodihydroisodocarpin (**30**).[7]

The C-15 proton in tetrahydroisodocarpin-6-acetate (**26**) being coupled to the C-16 proton with splitting of 10 Hz, gives rise to a doublet at δ 4·93 ppm. Thus, the C-15 hydroxy group has *cis*-relationship with α-oriented methyl group at C-16 as shown in formula **26**, that is, the absolute configuration of C-15 must be R.

Another evidence also supported this conclusion; tetraol **24** on treatment with 15% hydrochloric acid yielded a saturated ketone **31** quantitatively, which means easy hydride shift from C-15 to C-16 due to a favorable steric environment[13] (see Chart 6). Thus, the fact established the β-orientation of the C-15 hydroxy group in **24**, hence of the equivalent acetoxy group in trichokaurin. The ketone **31** on periodate oxidation gave dihydroisodocarpin (**28**), which confirmed the structure and absolute configuration of the ketone to be represented as formula **31**. An unusual IR absorption



24 **31** **28**

CHART 6

of cyclopentanone at 1715 cm^{-1} of compound **31** can be attributed to the hydrogen-bonding with the C-6 hydroxy group.* This fact provides another support to the β-assignment of the C-6 acetoxy group in trichokaurin; the asymmetric center C-6 must have the S-configuration. Thus, the chemical structure and absolute configuration of trichokaurin was established as shown in formula **22**.

As described above, trichokaurin on alkaline hydrolysis gave an oily unsaturated aldehyde **32** as a major product, while the desired tetraol **10** was obtained as a minor product. The pathway to **32** from trichokaurin **22** is shown in Chart 7. The hemiketal **32** on acetylation gave triacetate **33**.

Subsequently, we carried out the chemical conversion of trichokaurin into (−)-kaurene and diterpene alkaloids. The ketone **34** (=**19**) derived from trichokaurin through four steps as shown in Chart 4, on hydrogenolysis with calcium in liquid

* cf. IR spectrum of oridonin[5].

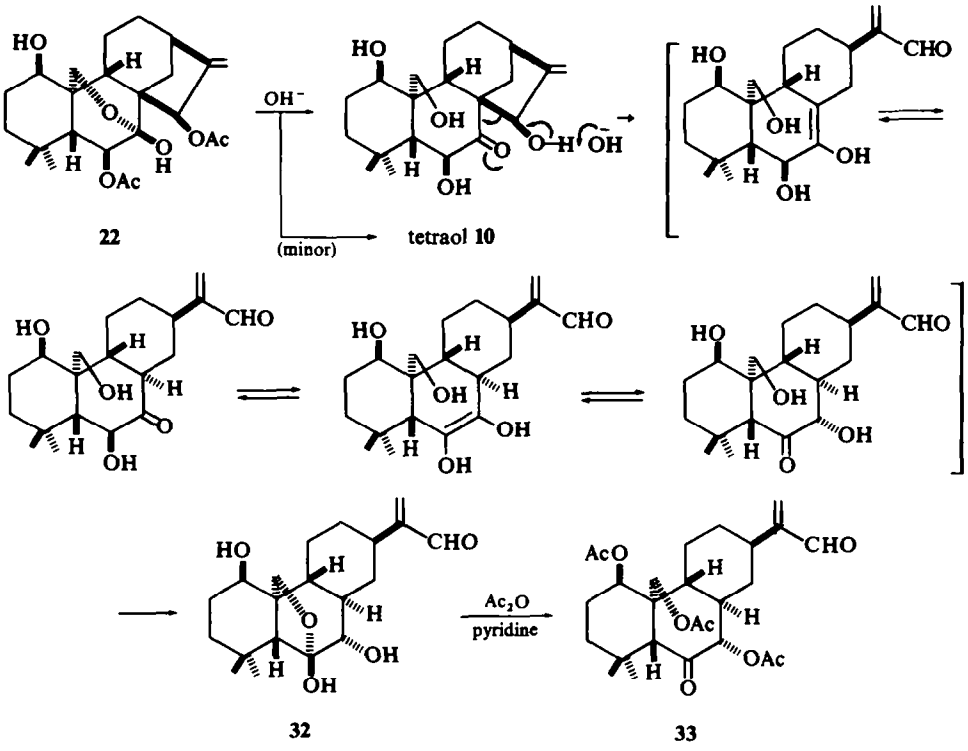


CHART 7

ammonia gave a ketone **35** and a triol **36**. The structures of both compounds were assigned on the basis of the spectral data* of their acetates, **37** and **38**. Triol **36** was subjected to Wolff–Kishner reduction modified by Nagata *et al.*,[14] then to catalytic

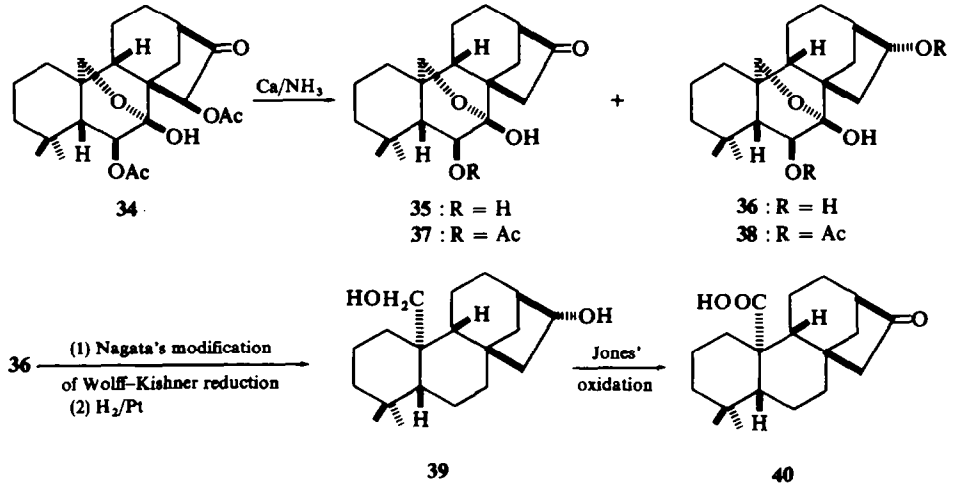
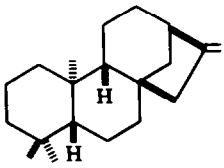


CHART 8

* See experimental section.

hydrogenation using Adams' catalyst to give diol **39**, which was oxidized with Jones' reagent to afford a keto carboxylic acid. The latter product was proved to be identical with *ent*-16-oxo-17-norkauran-20-oic acid (**40**)[15] by the mixture melting point determination and IR and mass-spectral comparisons. Since this compound **40** has already been converted into (−)-kaurene (**41**),[15] atisine (**42**),[16] garryine (**43**)[17a,b] and veatchine (**44**)[17a,18] the present transofrmation means the accomplishment of the chemical conversion of trichokaurin into (−)-kaurene and those diterpene alkaloids.



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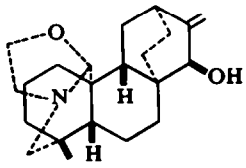

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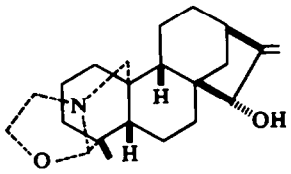

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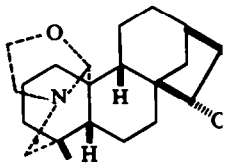

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CHART 9

EXPERIMENTAL

All m.ps were determined by a micro m.p. apparatus (Yanagimoto) and were uncorrected. UV spectrum was recorded in MeOH on a Hitachi model EPS-3 spectrophotometer. Unless otherwise stated, IR spectra were run in KBr discs on a Hitachi model EPI-S2 spectrophotometer and NMR spectra in $CDCl_3$ with TMS as an internal standard on a Varian A-60 spectrometer.

Extracts were dried over anhydrous Na_2SO_4.

Mallinckrodt silicic acid was used for column chromatography. TLC plates were coated with Nakarai silica layer G.

Isolation of trichokaurin (**22**) *from Isodon trichocarpus Kudo*

The dried leaves (1 kg) of *Isodon trichocarpus* Kudo which were collected at Ishikawa prefecture in 1963 were digested in Et_2O (5 l) at room temp for a few months. Evaporation of Et_2O gave a green residue (11 g), which was dissolved in acetone and refluxed with charcoal (3 g) for 1 hr then filtered. The filtrate was evaporated. This procedure was again carried out to give a yellow syrup (10 g). The latter was chromatographed on silica gel (400 g' column and the eluate with acetone-$CHCl_3$ (1 :9) was collected. As isodocarpin precipitated from the fraction, it was filtered off. The filtrate was evaporated to give a residue (1 g), which was chromatographed on silica gel (40 g) column. An amorphous and apparently homogeneous fraction (400 mg) was again chromatographed on silica gel (15 g) column to give crude crystals, which were recrystallized from Et_2O to yield very fine crystals (85 mg) of *trichokaurin*. M.p. 184 ~ 185°, $[\alpha]_D^{17}$ − 93° (*c*, 1; $CHCl_3$); IR ν_{max}: 3550, 3450, 3350, 1730, 1630 cm^{-1}; NMR δ_{ppm}: 0·87, 1·13 (each 3H, s), 1·93 (1H, d, J = 7, C-5—H), 2·06, 2·19 (each 3H, s), 3·58 (1H, t, J = 2, C-1—H), 3·29 (2H, s, —CH_2—O—), 4·91, 5·04 (each 1H, q, J = 1·2, >C=CH_2), 5·21 (1H, d, J = 7, coupling to a doublet proton at 1·93 ppm), 5·62 (1H, t, J = 2, coupling to quartet protons at 4·91 and 5·04 ppm) (Found: C, 66·25; H, 8·06. $C_{24}H_{34}O_7$ requires: C, 66·34; H, 7·89%).

Acetylation of trichokaurin. A solution of trichokaurin (**22**) (20 mg) in Ac_2O(1 ml)-pyridine (1 ml) was allowed to stand overnight at room temp, and evaporated *in vacuo* to give a syrupy residue, which was chromatographed on silica gel column to give *acetate* as crystals (20 mg). Recrystallization from MeOH gave the analytical sample, m.p. 189 ~ 191°. IR ν_{max}: 3475, 1730, 1660 cm^{-1}; NMR δ_{ppm}: 0·89, 1·15 (each 3H, s), 1·95 (1H, d, J = 7), 2·06, 2·09, 2·18 (each 3H, s), 3·76 (1H, br s, OH), 3·97 (2H, s), 4·64 (1H, br s), 4·93, 5·04 (each 1H, dd, J = 1, 2), 5·21 (1H, d, J = 7, coupling to proton at 1·95 ppm), 5·64 (1H, t, J = 2, coupling to protons at 4·93 and 5·04 ppm). (Found: C, 65·84; H, 7·95. $C_{26}H_{36}O_8$ requires: C, 65·53; H, 7·61%).

Oxidation of trichokaurin. Trichokaurin (**22**) (40 mg) was dissolved in pyridine (1 ml), and to this solution was added a complex prepared from CrO_3 (150 mg) and pyridine (1·5 ml), then the mixture was allowed to stand overnight at room temp. About three times of volume of H_2O were added and extracted with $CHCl_3$. The extract was treated as usual to give a crude product, which was chromatographed on silica

gel column to yield crystals. Purification by recrystallization from MeOH afforded pure crystals (35 mg) of *oxo-compound* **14**, m.p. 177 ~ 179°. IR ν_{max}: 3400, 1740, 1700, 1655 cm^{-1}; NMR δ_{ppm}: 0·94, 1·00 (each 3H, s), 2·07, 2·23 (each 3H, s), 3·96, 4·35 (each 1H, AB-type, J = 10), 3·39 (1H, br s, OH), 5·11 (1H, d, J = 7, C-6-H). (Found: C, 66·38; H, 7·59. $C_{24}H_{32}O_7$ requires: C, 66·65; H, 7·46%).

ent-7β,20-Epoxykaur-16-ene-1α,6α,7α,15α-tetraol (**4**). Trichokaurin (**22**) (120 mg) was dissolved in dry Et_2O (20 ml) and the solution was dropwise added into a suspension of LAH (240 mg) in Et_2O (10 ml). The mixture was refluxed for 3 hr on a water-bath. After cooling, AcOEt (20 ml) was added and the solution was washed with dil. HCl and then H_2O. The organic layer was dried over anhydrous Na_2SO_4, then the solvent was evaporated off to give a solid, which was recrystallized from MeOH to yield fine crystals (25 mg) of tetraol **4**. IR ν_{max} cm^{-1}: 3500, 3300, 3050, 1660. M^+ m/e 350 (mass spectrum).

Periodate oxidation of tetraol **4**

(i) Tetraol **4** (100 mg) was dissolved in MeOH (10 ml) and $NaIO_4$ (300 mg) was added into the solution. The mixture was kept stirring for 3 days at room temp. The usual treatment of the AcOEt extract gave a syrupy crude product (120 mg), which gave two spots on silica gel TLC. Chromatographic separation on silica gel column gave polar (20 mg) and less polar (60 mg) compounds as crystals. The polar compound was recrystallized from MeOH to afford analytical sample of **5**. IR ν_{max}: 3450, 2725, 1705 cm^{-1}; NMR (100 MHz) δ_{ppm}: 1·06 (6H, s) 3·15 (1H, d, J = 4, >CH—CHO), 4·23 (1H, br s, >CH— OH), 4·61 (2H, s, —CH_2—O—), 4·93 (2H, m, >C=CH_2), 5·10 (1H, br s, >CH—OH), 9·92 (1H, d, J = 4, —CHO).

The less polar compound was recrystallized from MeOH to yield *diol* **6** (40 mg), m.p. 207 ~ 209°. IR ν_{max}: 3400, 1700 cm^{-1}; NMR (100 MHz) δ_{ppm}: 1·03, 1·06 (each 3H, s), 3·40 (1H, m, —OH), 3·76, 3·99 (each 1H, AB-type, J = 10, —CH_2—O—), 4·92 (1H, q, J = 3·5, C—15—H), 5·06 (2H, m, >C=CH_2), 5·34 (1H, s, C-6-H). (Found: C, 68·92; H, 8·22. $C_{20}H_{28}O_5$ requires: C, 68·94; H, 8·10%). (ii) After having kept standing a solution of **5** (5 mg) in AcOH (1 ml) for 30 min at room temp, AcOH was evaporated off to give a crystalline residue (5 mg), which was recrystallized from MeOH to yield diol **6** (3 mg).

The conversion of hemiacetal lactone **6** *into 3-deoxy-1-epidehydrodihydroenmein* **8**. Compound **6** (20 mg) was dissolved in MeOH (5 ml) and was subjected to hydrogenation on PtO_2 (2 mg) catalyst for 1 hr. After filtration from the catalyst, the solution was evaporated off to give a syrupy residue (20 mg), which was dissolved in acetone (1 ml) and oxidized with Jones' reagent (0·1 ml) to afford a crude crystalline product (15 mg) by usual treatment. It was recrystallized from MeOH to yield pure crystals (9 mg), m.p. 199 ~ 204°, which proved to be identical with 1-*epi*-3-deoxy-dehydrodihydroenmein (**8**) by comparisons of IR spectra and mixture melting point determination.

1-Epi-3,6-bisdehydro-dihydroenmein-3-ethylenedithioketal

A mixture of 1-*epi*-bisdehydrodihydroenmein (**7**) (200 mg), ethanedithiol (0·1 ml) and BF_3-etherate (0·1 ml) was allowed to stand at room temp for 1 night. The reaction mixture was poured into ice water containing Na_2CO_3, and alkaline mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give the crude crystalline product (152 mg), which was chromatographed on silica gel (4 g) column. Elution with $CHCl_3$ gave an ethylenedithioketal (111 mg) which was crystallized from $CHCl_3$-hexane as needles, m.p. 298 ~ 301°, IR ν_{max}: 1750, 1717 cm^{-1}. (Found: C, 60·82; H, 6·47. $C_{22}H_{28}O_5S_2$ requires: C, 60·54; H, 6·59%).

1-Epi-6-dehydro-3-deoxy-dihydroenmein (**8**). A mixture of ethylenedithioketal (109 mg) and Raney Ni W_2 (2 g) in EtOH (50 ml) was refluxed for 12 hr. The catalyst was filtered off. The filtrate was evaporated *in vacuo* to give a gum, which was chromatographed on a silica gel column, then purified by recrystallization from MeOH to give 1-*epi*-6-*dehydro*-3-*deoxy-dihydroenmein* (**8**) as needles, m.p. 199 ~ 204°. IR ν_{max}: 1775 1740, 1705 cm^{-1}; NMR δ_{ppm}: 4·48 (1 H, t, J = 3·0, C-1-H), 4·13, 3·95 (each 1 H, AB-type, J = 10·0, C-20 H_2). (Found: C, 69·06; H, 7·70. $C_{20}H_{26}O_5$ requires: C, 69·34; H, 7·57%).

Acetylation of tetraol **10** (=**4**). Tetraol **10** (50 mg) was dissolved in a mixture of Ac_2O (1 ml) and pyridine (1 ml). Evaporation *in vacuo* after standing overnight at room temp gave a syrupy residue (55 mg), which gave two spots on TLC (silica layer G). It was chromatographed on silica gel column to yield an oily polar substance and a less polar crystalline substance. The former proved to be *monoacetate* **12**. IR ν_{max}; 3350, 1690 cm^{-1}; NMR (100 MHz) δ_{ppm}: 0·86, 1·13 (each 3H, s), 2·12 (3H, s), 3·13 (1H, br s, —OH), 3·46 (1H, br s, C-1-H), 4·36 (1H, br s, C-15-H), 5·02 (2H, m, >C=CH_2), 5·15 (1H, d, J = 6, C-6-H). The latter was

recrystallized from MeOH to give pure *diacetate* **11**, m.p. 175 ~ 178°. IR ν_{max}: 3550, 3400, 1760, 1740, 1665 cm^{-1}; NMR δ_{ppm}: 0·89, 1·17 (each 3H, s), 2·07, 2·18 (each 3H, s), 3·21, 3·50 (each 1H, br s, OH), 3·97 (2H, s, —CH_2—O—), 4·44 (1H, m, C-15-H), 4·62 (1H, br s, C-1-H), 5·10 (2H, m, >C=CH_2), 5·27 (1H, d, J = 6, C-6-H). (Found: C, 66·33; H, 7·88. $C_{24}H_{34}O_7$ requires: C, 66·34; H, 7·89%).

Triol **15**. 1-Keto-derivative **14** (80 mg) was dissolved in a mixture of ethanedithiol (0·5 ml) and BF_3-etherate (0·5 ml) and kept standing for 10 min at room temp. The reaction mixture was treated as usual to give a crude product, which was dissolved in EtOH (30 ml). Raney Ni (6 g) was added into the solution and the mixture was heated at reflux for 8 hr, then the catalyst was filtered off. The filtrate was evaporated to give a residue, which was dissolved in absolute Et_2O (10 ml). A suspension of LAH (160 mg) in Et_2O (5 ml) was added into the solution and heated at reflux for 3 hr. A crude syrupy product which was obtained by usual treatment of the reaction mixture was chromatographed on silica gel column to yield a crystalline product. The latter was recrystallized from MeOH to afford pure *triol* **15** as crystals (30 mg), m.p. 232 ~ 235°. IR ν_{max}: 3300 cm^{-1}; NMR $\delta_{pm}^{D_5pyridine}$: 4·07 (2H, s), 4·18 (1H, d, J = 5·5), 4·31 (1H, d, J = 5). (Found: C, 71·09; H, 9·66. $C_{20}H_{32}O_4$ requires: C, 71·39; H, 9·59%).

ent-7β,20-*Epoxy*-6α,15α-*diacetoxy*-1α-*mesyloxykaur*-16-*en*-7α-*ol* (**16**). Methanesulfonyl chloride (0·5 ml) was added into a solution of trichokaurin (110 mg) in pyridine (2 ml), and the mixture was kept standing overnight at room temp. The reaction mixture was thrown into ice-water and extracted with AcOEt. Washing of the extract with H_2O, drying, and evaporation of the solvent gave a crude crystalline product (80 mg), which was recrystallized from AcOEt to afford *mesylate* **16** as colorless plates, m.p. 190 ~ 191°. IR ν_{max}: 3500, 1740, 1725, 1660 cm^{-1}; NMR δ_{ppm}: 2·07, 2·18 (each 3H, s), 3·06 (3H, s, —OSO_2CH_3), 4·67 (1H, m, >CH—OSO_2CH_3). (Found: C, 58·86; H, 7·17. $C_{25}H_{36}O_9S$ requires: C, 58·59; H, 7·03%).

ent-7β,20-*Epoxy*-6α,15α-*diacetoxy*-16-*oxo*-1α-*mesyloxy*-17-*norkauran*-7α-*ol* (**17**). Mesylate **16** (100 mg) was dissolved in a mixture of tetrahydrofuran (25 ml) and H_2O (25 ml), and OsO_4 (5 mg) was added into the solution under stirring. When the mixture was kept stirring for ½ hr, the solution got black. To this solution was added $NaIO_4$ (1·5 g) and the mixture was kept stirring for 3 hr at room temp. The solution got pale yellow and colorless crystals precipitated. After a treatment with H_2S, the reaction mixture was extracted with Et_2O (200 ml), and the extract was treated as usual to give a crude product (100 mg), which was chromatographed on silica gel column to yield *a ketone* **17** as crystals (70 mg). Recrystallization from acetone gave an analytical sample, m.p. 192 ~ 193°. IR ν_{max}: 3500, 1750, 1735 cm^{-1}; NMR δ_{ppm}: 2·05, 2·22 (each 3H, s), 3·06 (3H, s), 4·65 (1H, m, >CH—OSO_2Me), 5·26 (1H, d, J = 7·5, C-6-H), 5·44 (1H, d, J = 1, C-15-H). (Found: C, 56·25; H, 6·62. $C_{24}H_{34}O_{10}S$ requires: C, 56·03; H, 6·61%).

ent-7β,20-*Epoxy*-6α,15α-*diacetoxy*-16-*oxo*-17-*norkaur*-1-*en*-7α-*ol* (**18**). A solution of mesylate **17** (100 mg) in DMSO (2 ml) was heated in a sealed tube at 150° for 3 hr. After cooling, DMSO was evaporated off *in vacuo* to give a syrupy residue, which was chromatographed on silica gel column to afford colorless crystals (60 mg) of *compound* **18**, m.p. 203 ~ 204°. IR ν_{max}: 3475, 1755, 1735 cm^{-1}; NMR δ_{ppm}: 2·04, 2·21 (each 3H, s), 5·18 (1H, d, J = 8·5, C-6-H), 5·47 (1H, s, C-15-H), 5·32, 5·78 (each 1H, AB part of ABX_2, —CH_2—CH=CH—). (Found: C, 65·93; H, 7·35. $C_{23}H_{30}O_7$ requires: C, 66·01; H, 7·23%).

ent-7β,20-*Epoxy*-6α,15α-*diacetoxy*-16-*oxo*-17-*norkauran*-7α-*ol* (**19**). Unsaturated ketone **18** (20 mg), dissolved in AcOH (2 ml), was subjected to hydrogenation on PtO_2 (5 mg) catalyst for 12 hr. After filtration from catalyst, the solvent was evaporated off to give a saturated crystalline product, which was recrystallized from MeOH to yield pure *compound* **19** as needles (15 mg), m.p. 186 ~ 187° IR ν_{max}: 3350, 1755, 1735 cm^{-1}; NMR δ_{ppm}: 2·02, 2·21 (each 3H, s), 5·02 (1H, d, J = 7·5, C-6-H), 5·45 (1H, d, J = 1, C-15-H). (Found: C, 65·58; H, 7·49. $C_{23}H_{32}O_7$ requires: C, 65·69; H, 7·67%).

ent-7β,20-*Epoxy*-6α,16α-*diacetoxy*-17-*norkaurane*-7α,15α-*diol* (**21**). (i) Ketone **19** (20 mg) was dissolved in absolute Et_2O (5 ml), and a suspension of LAH (30 mg) in Et_2O (2 ml) was added to the solution under stirring. The mixture was heated at reflux for 3 hr on a water-bath. After cooling, AcOEt was added and washed with H_2O. Drying followed by evaporation gave a crystalline residue (20 mg), which was recrystallized from EtOH to yield colorless needles of *tetraol* **20**, m.p. 195 ~ 200°. IR ν_{max}: 3350 cm^{-1}. (ii) Tetraol **20** (18 mg) was dissolved in a mixture of Ac_2O (1 ml) and pyridine (1 ml) and allowed to stand overnight. Evaporation of the solution gave a syrupy residue (20 mg), which was chromatographed on silica gel column to afford crude crystals. Recrystallization from MeOH yielded pure crystals (14 mg) of *diacetate* **21**, m.p. 205 ~ 206°. IR ν_{max}: 3400, 1720 cm^{-1}; NMR δ_{ppm}: 0·80, 1·10 (each 3H, s), 2·11, 2·13 (each 3H, s), 2·76 (1H, d, J = 3·5, OH), 3·30 (1H, s, —OH), 3·92 (2H, br s, —CH_2—O—), 4·26 (1H, q, J = 3·5, 9,

C-15-H), 4·97 (1H, q, J = 6·5, 9, C-16-H), 5·12 (1H, d, J = 5·5, C-6-H). (Found: C, 65·09; H, 8·05. $C_{23}H_{34}O_7$ requires: C, 65·38; H, 8·11%). M^+ m/e 422 (mass spectrum).

ent-7β,20-Epoxykaur-16-ene-1β,6α,7α,15α-tetraol (**24**). Ketone **23** (800 mg) was dissolved in anhydrous Et_2O (50 ml), and a suspension of LAH (800 mg) in Et_2O (20 ml) was added to this solution. The mixture was heated at reflux on a water-bath for 1 hr, then treated as usual to give a crude crystalline product, which was recrystallized from MeOH to yield *tetraol* **24** as needles (500 mg), m.p. 240 ~ 243°. IR ν_{max}: 3300, 1660 cm^{-1}. (Found: C, 68·33; H, 8·73. $C_{20}H_{30}O_5$ requires: C, 68·54; H, 8·63%).

Periodate oxidation of tetraol **24**. Tetraol **24** (100 mg) was dissolved in a mixture of MeOH (5 ml) and H_2O (5 ml). To this solution was added $NaIO_4$ (200 mg), then the mixture was kept stirring for 12 hr at room temp. The reaction mixture, after extraction with AcOEt, was treated as usual to give a crystalline crude product (120 mg). Recrystallization from MeOH yielded pure crystals (80 mg) of *compound* **25**, m.p. 265 ~ 269°. IR ν_{max}: 3450, 1700 cm^{-1}; NMR δ_{ppm}: 4·48 (1H, t, J = 9, C-1-H), 5·36 (1H, s, C-6-H). (Found: C, 69·11; H, 8·39. $C_{20}H_{28}O_5$ requires: C, 68·94; H, 8·10%).

Partial acetylation and catalytic reduction of compound **25**.

(i) Compound **25** (30 mg) was dissolved in AcOH (10 ml) and the solution was heated for 3 hr at 100° on a water-bath. Acetic acid was evaporated off to give crude crystalline residue (30 mg), which was recrystallized from MeOH to yield 6-*acetate* of **25**. IR ν_{max}: 3350, 1740, 1710, 1660 cm^{-1}.

(ii) The foregoing 6-acetate (10 mg) was dissolved in MeOH and subjected to catalytic hydrogenation on PtO_2 (2 mg) for 3 hr. The reaction mixture was treated as usual to give a crude crystalline product (10 mg), which was recrystallized from MeOH to yield an analytical sample of *compound* **26**, m.p. 270 ~ 272°. IR ν_{max}: 3350, 1735, 1710 cm^{-1}; NMR δ_{ppm}: 0·94 (3H, d, J = 7, $\rangle$CH CH_3), 1·00, 1·08 (each 3H, s), 2·05 (3H, s), 3·97, 4·13 (each 1H, AB-type, J = 9), 4·44 (1H, t, J = 9, C-1-H), 4·93 (1H, d, J = 10, C-15-H), 6·17 (1H, s, C-6-H). (Found: C, 67·38; H, 8·36. $C_{22}H_{32}O_6$ requires: C, 67·35; H, 8·16%).

Reduction of dihydroisodocarpin (**28**). Dihydroisodocarpin (**28**) (100 mg) was dissolved in MeOH (10 ml) and a solution of $NaBH_4$ (100 mg) in MeOH (2 ml) was added to this solution. The mixture was kept stirring for 1 hr at room temp. Three times of 10% HCl in volume were added under cooling to the reaction mixture, then extracted with AcOEt. The extract was treated as usual to give a syrupy product (110 mg), which was chromatographed on silica gel column to yield homogeneous, but oily *tetrahydroisodocarpin* (**29**) (40 mg) in addition to recovered material **28** (30 mg). *Compound* **29**. IR $\nu_{max}^{CHCl_3}$: 3400, 1710 cm^{-1}; NMR δ_{ppm}: 4·46 (1H, t, J = 8·5, C-1-H), 4·86 (1H, d, J = 10, C-15-H), 5·36 (1H, s, C-6-H).

Partial acetylation of tetrahydroisodocarpin (**29**). Tetrahydroisodocarpin (**29**) (50 mg) was dissolved in AcOH (10 ml) and heated for 3 hr on a water-bath, then AcOH was evaporated off to give a crystalline residue, which was chromatographed on silica gel column and at last purified by recrystallization from MeOH to yield 6-*acetate* **26** as pure crystals (40 mg), m.p. 271 ~ 273°. This compound proved to be identical with the sample **26** which was derived from trichokaurin by IR and NMR comparisons and mixture melting point determination.

Oxidation of 6-monoacetate **26** *derived from trichokaurin.*

6-Acetate **26** (10 mg) was dissolved in acetone (1 ml) and two drops of Jones' reagent were added to this solution. The mixture was allowed to stand for 1 hr at room temp, and extracted with AcOEt. The extract was treated as usual to give a crystalline product (8 mg), which was recrystallized from MeOH to yield pure crystals (4 mg) of compound **30**, m.p. 290 ~ 300°. The IR spectrum coincided with that of dehydrodihydroderivative **30** derived from isodocarpin.

Rearrangement of tetraol **24** *with hydrochloric acid*

ent-7β,20-Epoxy-kauran-15-one-1β,6α,7α-triol (**31**). Tetraol **24** (30 mg) was dissolved in MeOH (2 ml) and 20% HCl was added to the solution, so that the concentration of HCl was adjusted to 15%. The solution thus prepared was kept stirring for 50 hr at room temp. The extract with AcOEt was treated as usual to give a ketone **31** as a crude crystalline product (30 mg). Purification by recrystallization from MeOH yielded an analytical sample, m.p. 244 ~ 246°. IR ν_{max}: 3250, 1715 cm^{-1}; NMR $\delta_{ppm}^{D_5\text{-pyridine}}$: 1·08 (3H, d, J = 6, $\rangle$CH—CH_3), 1·09, 1·22 (each 3H, s), 3·68 (1H, t, J = 8, C-1-H), 4·13 (1H, q, J = 6, 11, C-6-H), 4·32, 4·68 (each 1H, AB-type, J = 10, —CH_2—O—), 6·54 (1H, d, J = 11, C-6-OH). (Found: C, 68·49; H, 8·66. $C_{20}H_{30}O_5$ requires: C, 68·54; H, 8·63%).

Periodate oxidation of ketone **31**. *Dihydroisodocarpin* (**28**). Ketone **31** (20 mg) was dissolved in a mixture

of MeOH (2 ml) and H_2O (2 ml), and $NaIO_4$ (50 mg) was added into this solution. The mixture was kept stirring for 20 hr at room temp. The reaction mixture was treated as usual to give a syrupy crude product (15 mg), which was chromatographed on silica gel column to yield a homogeneous crystalline substance (6 mg). Recrystallization from MeOH afforded pure crystals (3 mg), m.p. 224 ~ 230°. This compound proved to be identical with the known dihydroisodocarpin by IR comparison and mixture melting point determination.

Alkaline treatment of trichokaurin. Trichokaurin (100 mg) was dissolved in methanolic $\frac{1}{100}$N–NaOH solution (46 ml) (2·6 ml of H_2O was contained) and the solution was heated at reflux for 9 hr on a water-bath. The solution got neutral, so further methanolic $\frac{1}{10}$N–NaOH solution (4 ml) was added and heated at reflux for additional 3 hr. The reaction mixture was neutralized with HCl and extracted with AcOEt. The extract was treated as usual to give a crude crystalline product (83 mg), which was chromatographed on silica gel column to yield a crystalline conjugated aldehyde **32** as a major fraction. It was recrystallized from MeOH to yield pure crystals (45 mg), m.p. 160 ~ 161°. IR ν_{max}: 3400, 1690, 1625 cm^{-1}; NMR δ_{ppm}: 1·17, 1·32 (each 3H, s), 3·09 (1H, m), 3·62, 3·77 (each 1H, AB-type, J = 8·5, —C<u>H</u>$_2$—O—), 4·50 (1H, s, —O<u>H</u>), 5·98, 6·26 (each 1H, s, >C=C<u>H</u>$_2$), 9·51 (1H, s, —C<u>H</u>O). (Found: C, 68·30; H, 8·37. $C_{20}H_{30}O_5$ requires: C, 68·54; H, 8·63%). More polar crystalline fraction was recrystallized from MeOH to give pure crystals (3 mg), which proved to be identical with tetraol **10** by IR comparison.

Acetylation of hemiketal aldehyde **32**. Compound **32** (15 mg) was dissolved in Ac_2O (1 ml) and pyridine (1 ml) and the solution was allowed to stand overnight. The solvent was evaporated off to give a residue (16 mg), which was chromatographed on silica gel column to yield crude *acetate* **33** as crystals. Recrystallization from MeOH yielded pure crystals (10 mg), m.p. 145 ~ 146°. IR ν_{max}: 2700, 1740, 1690, 1620 cm^{-1}; NMR δ_{ppm}: 1·08, 1·19 (each 3H, s), 1·99, 2·14, 2·16 (each 3H, s), 2·43 (1H, s, C-5-<u>H</u>), 4·04, 4·29 (each 1H, AB-type, J = 12·5), 4·73 ~ 4·98 (2H, m, C-1-<u>H</u> and C-7-<u>H</u>), 6·01, 6·25 (each 1H, s, >C=C<u>H</u>$_2$), 9·52 (1H, s, —C<u>H</u>O). (Found: C, 65·72; H, 7·91. $C_{26}H_{36}O_8$ requires: C, 65·53; H, 7·61%). M^+ m/e 476 (mass spectrum).

Hydrogenolysis of compound **34** *with* Ca *in liquid* NH_3

Compound **34** (50 mg) was dissolved in anhydrous dioxane (5 ml: distilled with added Na), and the solution was dropwise added into a solution of Ca (100 mg) in liquid NH_3 (30 ml) under vigorous stirring. When stirring was kept for 20 min after addition of whole solution, the blue color disappeared. Ammonium chloride (500 mg) was added and NH_3 was allowed to be evaporated to give a residue, which was extracted with Et_2O (100 ml). The extract was washed with dil HCl, then H_2O, and treated as usual to give a crude mixture (30 mg), which was chromatographed on silica gel column to isolate two components. Less polar product remained as oil (6 mg) and proved to be *ent*-7β,20-*epoxy*-17-*norkauran*-16-*one*-6α,7α-*diol* (**35**). IR $\nu_{max}^{CHCl_3}$: 3400, 1735 cm^{-1}; NMR δ_{ppm}: 3·77 (1H, d, J = 5, C-6-<u>H</u>), 3·98 (2H, br s, —C<u>H</u>$_2$—O—). Another product was crystalline and recrystallized from MeOH to yield pure crystals (10 mg) of *ent*-7β,20-*epoxy*-17-*norkaurane*-6α,7α,16β-*triol* (**36**), m.p. 245 ~ 250°. IR ν_{max}: 3350 cm^{-1}. (Found: C, 70·51; H, 9·58. $C_{19}H_{30}O_4$ requires: C, 70·77; H, 9·38%).

Acetylation of ketone **35**. *ent*-6α-*Acetoxy*-7β,20-*epoxy*-17-*norkauran*-16-*on*-7α-*ol* (**37**). Ketone **35** (6·5 mg) was dissolved in a mixture of Ac_2O (0·5 ml) and pyridine (0·5 ml), and the solution was kept standing overnight. Evaporation *in vacuo* gave a residue, which was chromatographed on silica gel column to give crude crystalline *acetate* **37** (6 mg). Recrystallization from MeOH yielded an analytical sample, m.p. 210 ~ 215°. IR ν_{max}: 3350, 1740, 1720 cm^{-1}; NMR δ_{ppm}: 0·82, 1·13 (each 3H, s), 2·06 (3H, s), 3·70 (1H, s, —O<u>H</u>), 3·98 (2H, br s, —C<u>H</u>$_2$—O—), 5·06 (1H, d, J = 5). M^+ m/e 362 (mass spectrum).

Acetylation of triol **36**. *ent*-6α,16β-*Acetoxy*-7β,20-*epoxy*-17-*norkauran*-7α-*ol* (**38**). Triol **36** (10 mg) was acetylated as described above to give *diacetate* **38** as crystals (7 mg), m.p. 194 ~ 195°. IR ν_{max}: 3450, 1735, 1710 cm^{-1}; NMR δ_{ppm}: 0·83, 1·11 (each 3H, s), 2·02, 2·07 (each 3H, s), 3·56 (1H, s, —O<u>H</u>), 3·85, 3·97 (each 1H, AB-type, J = 10, —C<u>H</u>$_2$—O—), 4·80 (1H, q, J = 7, 4, C-16-<u>H</u>), 5·03 (1H, d, J = 5, C-6-<u>H</u>). (Found: C, 67·88; H, 8·46. $C_{23}H_{34}O_6$ requires: C, 67·95; H, 8·43%).

Wolff-Kishner reduction and hydrogenation of triol **36**. *ent*-17-*Norkaurane*-16β,20-*diol* (**39**). Triol **36** (40 mg) was dissolved in a mixture of anhydrous hydrazine (1700 mg), hydrazine hydrochloride (304 mg) and triethyleneglycol (2980 mg), and heated at 140° for 12 hr. After cooling, pellets of KOH (400 mg) were added and the mixture was slowly heated, so that the temp was raised up to 220° over a period of 3 hr. Then, the mixture was refluxed at 220 ~ 230° for 3 hr. After cooling, H_2O (5 ml) was added and extracted with Et_2O. The extract was treated as usual to give a crude product (50 mg), which was dissolved in MeOH

(5 ml) and subjected to hydrogenation on PtO_2 (5 mg) for 5 hr. The reaction mixture was treated as usual to give a crude product (50 mg), which was chromatographed on silica gel column to yield a homogeneous oily *diol* **39** (20 mg). NMR δ_{ppm}: 1·88 (6H, s), 4·09 (2H, s, —$\underline{CH_2}$—OH), 4·15 ~ 4·42 (1H, m, C-16-$\underline{H}$).

ent-16-Oxo-17-norkauran-20-oic acid (**40**). [(−)-16-*oxo*-10-*carboxy*-17,20-*bisnorkaurane*]. Diol **39** (6 mg) was dissolved in acetone (1 ml), and Jones' reagent (2 drops) was added into this solution. The mixture was kept stirring for 2 hr at 20°. To the reaction mixture, MeOH was added and kept stirring for 10 min, then extracted with AcOEt. The extract was treated as usual to give a crude product (6 mg), which was chromatographed on silica gel (1 g) column. Eluate with $CHCl_3$ gave a homogeneous crystalline compound (4 mg), which was recrystallized from MeOH to afford colorless pure crystals (3 mg) of keto acid **40**, m.p. 238 ~ 240°. IR ν_{max}: 3400, 1740, 1690 cm^{-1}. M^+ m/e 304 (mass spectrum). This compound proved to be identical with *ent*-16-oxo-17-norkauran-20-oic acid (**40**) by mixture melting point determination and IR and mass spectral comparisons.

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