columns*[3] with the authentic XXIII, derived from (−)-kaurene.*[4] The formation of a cyano compound (XXIV), m.p. 103~104°, ν_{max}^{KBr} : 2220 cm^{-1} (*Anal.* Calcd. for $C_{20}H_{31}N$: C, 84.14; H, 10.95; N, 4.91. Found : C, 83.87; H, 10.90; N, 4.72) was observed in 20~40% yield during the drastic alkali degradation of XXII.

Since (−)-kaurene has been inter-related to phyllocladene[9] through XXV and correlated to podocarpic acid by way of garryfoline[7] and atisine,[10~12] the present work has established the absolute configuration of enmein. As the backbone stereochemistry of the compound (XIV) was determined beyond doubt, conversion of enmein to the diterpene alkaloids is in progress.

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Received May 26, 1965

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11) D. Dvornik, O. E. Edwards : Chem. & Ind. (London), **1958**, 623; *Idem* : Can. J. Chem., **42**, 137 (1964).
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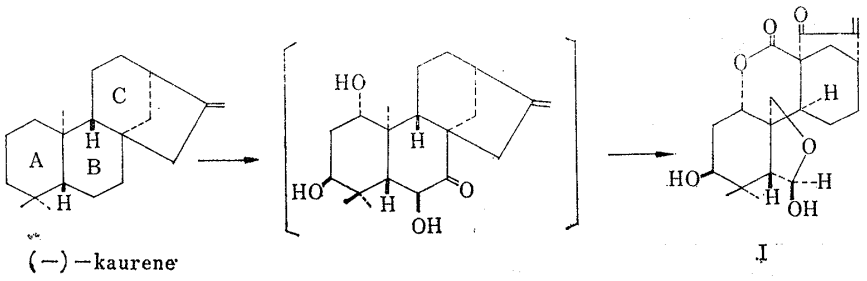
Chem. Pharm. Bull. 13(8)1023~1027(1965)

UDC 547.597.02.07

The Absolute Configuration of Enmein
Transformation of Enmein into (−)-Kaurane

Recently, it was shown by chemical methods[1] and X-ray analysis[2] that the structure and stereochemistry of enmein, a bitter principle of *Isodon trichocarpus* KUDO could be represented as shown in formula (I). Its absolute configuration was also proposed on the basis of optical rotatory dispersion data and conformational analysis, but no chemical evidence on it has been provided.

It may be assumed that enmein is biogenetically derived from (−)-kaurene by oxidative cleavage of its B ring followed by recyclization, as shown in Chart 1.

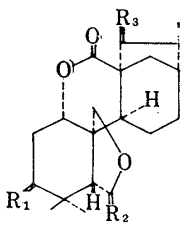


(−)-kaurene I

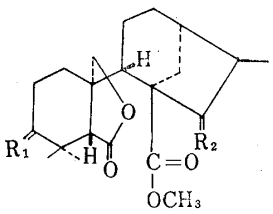
Chart 1.

1) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Fujita, T. Okamoto, M. Natsume, Y. Kawazoe, K. Sudo, T. Ikeda, M. Tomoeda, S. Kanatomo, T. Kosuge, K. Adachi : Tetrahedron Letters, No. 20, 1243 (1964).
2) Y. Iitaka, M. Natsume : *Ibid.*, No. 20, 1257 (1964).

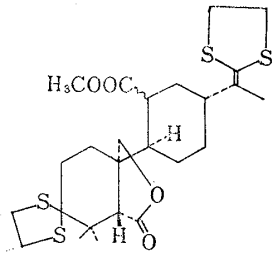
We have now succeeded in chemical transformation of enmein (I) into (−)-kaurane ((−)-α-dihydrokaurene) (XXIX)[3,4] *via* a reverse biogenetic sequence of reactions.*1 According to the method of Kubota, *et al.*,[5] enmein*2 was hydrogenated to dihydroenmein (II) and the latter was converted to the known diketolactone methyl ester (III). Thioketalization of III led to the formation of monothioketal (IV), m.p. 220°, ν_{max}^{Nujol} cm^{-1} : 1755, 1711, and unsaturated dithioketal (V), a product from cleavage of the five-membered ketone ring, m.p. 264~266.5°, $\nu_{max}^{CHCl_3}$ cm^{-1} : 1765, 1725, NMR^{CDCl_3} δ : 1.20 (s), 1.48 (s), 1.70 (s, >C=C<^{CH_3}), 2.68 (s, >CH-COO-), 3.25 (br, S-CH_2-CH_2-S), 3.30 (s, S-CH_2-CH_2-S), 3.67 (s, -$COOCH_3$), 3.96 (s, -CH_2-O-CO-). Desulfurization of IV and V yielded ketolactonic ester (VI), m.p. 132~134°, ν_{max}^{Nujol} cm^{-1} : 1765, 1744, 1711, NMR^{CDCl_3} δ : 0.98 (s), 1.10 (d, J=7 c.p.s., >CH-CH_3) 1.18 (s), 2.13 (s, >CH-CO-O-), 3.78 (s, -$COOCH_3$), 4.97 (s, -CH_2-O-CO-), and isopropyl derivative (VII), m.p. 106.5~107.5°, $\nu_{max}^{CHCl_3}$ cm^{-1} : 1770 (inf.), 1768, 1728, NMR^{CDCl_3} δ :



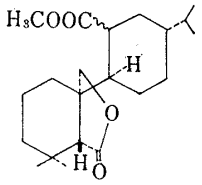
II : $R_1=R_2=$<H, OH, $R_3=O$
IX : $R_1=$<H, OH, $R_2=R_3=O$
X : $R_1=$<H, OH, $R_2=O$, $R_3=H_2$
XI : $R_1=$<H, OAc, $R_2=R_3=O$
XII : $R_1=$<H, OAc, $R_2=O$, $R_3=H_2$
XIII : $R_1=R_2=O$, $R_3=H_2$



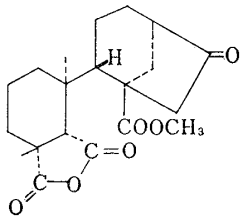
III : $R_1=R_2=O$
IV : $R_1=$<S, S, $R_2=O$
VI : $R_1=H_2$, $R_2=O$
XVIII : $R_1=R_2=H_2$



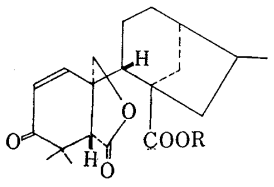
V



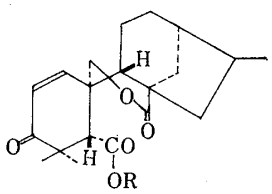
VII



VIII



XIV : R=H
XVI : R=CH_3



XV : R=H
XVII : R=CH_3

Chart 2.

*1 Prof. T. Okamoto, Faculty of Pharm. Sciences, University of Tokyo, kindly informed us of his group's success in conversion of enmein to (−)-kaurane.

*2 Part of the starting material was kindly supplied by Prof. S. Uyeo, Faculty of Pharm. Sciences, Kyoto University. We wish to express our deep gratitude for his encouragements and helpful advices.

3) B. E. Cross, R. H. B. Galt, J. R. Hanson : J. Chem. Soc., **1963**, 2937, 2944.
4) L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge, J. K. Wilmshurst : *Ibid.*, **1963**, 1345.
5) T. Kubota, T. Matsuura, T. Tsutsui, K. Naya : Nippon Kagaku Kaishi, **84**, 353 (1963).

0.84 (d, J=5.5 c.p.s., $-CH(C\underline{H}_3)_2$), 0.96 (s), 1.19 (s), 2.32 ($>C\underline{H}-COO-$), 3.68 (s, $-COOC\underline{H}_3$), 3.92 (s, $-C\underline{H}_2-O-CO-$) (*Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.67; H, 9.88), respectively. The optical rotatory dispersion curve*3 of compound (Ⅵ) exhibited a negative Cotton effect, which is almost antipodal to that of derivative (Ⅷ)[6] of fujenoic acid, a metabolite from *Gibberella fujikuroi*. Thioketalization of compound (Ⅵ) and subsequent desulfurization also produced undesired cleaved product (Ⅶ).

We, therefore, chose the following route. Dehydrodihydroenmein (Ⅸ)[1] was converted to the thioketal, which was desulfurized with Raney nickel to give hydroxydilactone derivative (X)*4, m.p. 236~239°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450, 1766, 1723, NMR^{CDCl_3} δ: 1.00 (d, J=5 c.p.s.), 1.03 (s), 1.26 (s), 2.57 (s, $>C\underline{H}-COO-$), 3.80~4.31 (m, $-C\underline{H}_2-OCO-$, $>C\underline{H}-OH$), 4.97 (q, J=11 and 6.8 c.p.s., $-CH_2-C\underline{H}-O-CO-$) (*Anal.* Calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.98; H, 7.89). Compound (X) was also derived *via* an alternative route. Dehydrodihydroenmein acetate (Ⅺ),[1] which was derived from dihydroenmein diacetate by partial hydrolysis and oxidation, was thioketalized and the resulting thioketal was desulfurized with Raney nickel to give deoxo acetate (Ⅻ), m.p. 206~209°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1725 (br), NMR^{CDCl_3} δ: 2.12 (s, $C\underline{H}_3COO-$), 4.76 (q, J=11.5 and 7 c.p.s., $-CH_2-C\underline{H}-O-CO-$), 4.96 (q, J=3.5 and 2 c.p.s., $-CH_2-C\underline{H}-OAc$) (*Anal.* Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.68; H, 7.99). This acetate on hydrolysis yielded alcohol (X).

Chromium trioxide oxidation of X gave deoxobisdehydrodihydroenmein (XIII), m.p. 196~200°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1773, 1740, 1721 (*Anal.* Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.59. Found: C, 69.63; H, 7.38). Hydrolysis of the latter with *N*/100 potassium hydroxide solution afforded a mixture of α,β-unsaturated ketocarboxylic acids (XIV) and (XV). Main product (XIV), ν_{max}^{KBr} cm^{-1}: 3200, 1770, 1720, 1680, resisted crystallization, while minor acid (XV)*5 easily crystallized. (m.p. 267~269°). On methylation the product (XIV) gave methyl ester (XVI), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1723, 1682, λ_{max}^{EtOH} $m\mu$ (ε): 223 (9180), NMR^{CDCl_3} δ: 3.66 (s, $-COOC\underline{H}_3$), 6.98, 6.17 (each d, J=10 c.p.s., $-C\underline{H}=C\underline{H}-$). Acid (XV) could be converted to (XIV) by hydrolysis with *N*/100 potassium hydroxide.

Thioketal of the dihydro derivative, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1715, derived from unsaturated keto ester (XVI) by catalytic hydrogenation, was desulfurized with Raney nickel to give lactone ester (XVIII), m.p. 90.5~92°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1715, NMR^{CDCl_3} δ: 3.68 (s, $-COOC\underline{H}_3$), 3.91 (s, $-C\underline{H}_2-O-CO-$) (*Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.08; H, 9.23).

The cyclization was achieved by acyloin condensation of lactone ester (XVIII) with sodium in liquid ammonia[7] in the nitrogen atmosphere. The reaction product was shown to be a mixture of at least five kinds of compounds on thin-layer chromatogram. A product which had the largest Rf value was separated as crystals after purification by column chromatography on silica gel. Ether structure (XIX) was assigned to this compound, m.p. 130~131°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1045, 1020, NMR^{CDCl_3} δ: 3.62, 4.00 (each d, J=9 c.p.s., $-C\underline{H}_2-O-$), 4.23 (m, $-O-C\underline{H}<$).

The substance which had the second largest Rf value was also separated as crystals, m.p. 152~154°, ν_{max}^{KBr} cm^{-1}: 3300 (br), NMR^{CDCl_3} δ: 1.00 (d, J=5 c.p.s.), 1.06 (s), 1.15 (s),

*3 We are indebted to Dr. D. Sato of the Research Laboratory, Shionogi & Co., Ltd. for the optical rotatory dispersion data.

*4 The compound was compared and identified with the sample which was supplied by Mr. A. Numata, Faculty of Pharm. Sciences, Kyoto University, to whom we wish to express our thanks.

*5 This acid was converted to methyl ester (XVII), which was characterized by infrared and NMR spectra. Hydrogenation, thioketalization, and desulfurization led to a saturated deoxolactonic ester, m.p. 161~161.5°.

6) B. E. Cross, R. H. B. Galt, J. R. Hanson: J. Chem. Soc., **1963**, 5052.

7) cf. E. E. van Tamelen, T. A. Spencer, Jr., D. S. Allen, Jr., R. L. Orvis: Tetrahedron, **14**, 8 (1961).

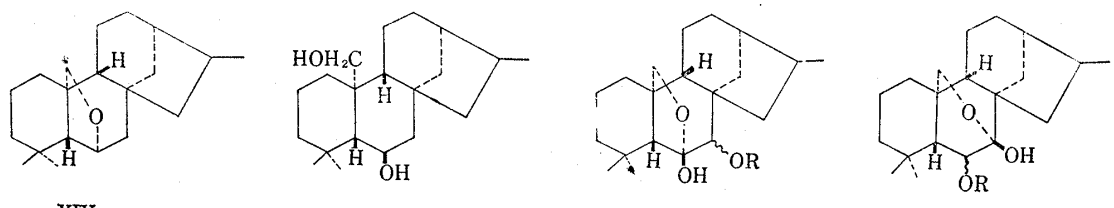


Chart 3.

3.60~4.20 (m, >CH-OH), 4.02 (s, $-CH_2-OH$) (*Anal.* Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found : C, 78.50; H, 11.08). The compound was shown to be a diol with one primary and one secondary alcoholic hydroxyl groups. On the basis of its conversions to diacetate, m.p. 92~94°, $\nu_{max}^{CHCl_3}$ cm^{-1} : 1725, NMR^{CDCl_3} δ : 0.92 (s), 1.00 (d, J=6 c.p.s.), 1.06 (s), 2.04 (s, $-O-COCH_3$), 2.10 (s, $-OCOCH_3$), 4.42, 4.47 (each d, J=12 c.p.s., $-CH_2-O-$), 5.27 (oct, J=11, 9 and 5 c.p.s., $-CH_2-CH\langle^{O-}_{CH\langle}$), and to ketoaldehyde (XXV), $\nu_{max}^{CHCl_3}$ cm^{-1} : 2750, 1710, NMR^{CDCl_3} δ : 10.0 (s, -CHO), structure (XX) was assigned to this diol.

The third product which had a Rf value close to that of XX was isolated in the pure state and 6-hemiketal structures (XXI) and (XXII) were reasonably assigned to this compound, m.p. 190~194°, $\nu_{max}^{CHCl_3}$ cm^{-1} : 3600, 3350, NMR^{CDCl_3} δ : 3.30 (s, >CH-OH), 3.89 (s, $-CH_2-O-$), and its monoacetate, m.p. 167~168°, $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500, 1720, NMR^{CDCl_3} δ : 2.09 (s, CH_3COO-), 3.88, 4.00 (each d, J=9 c.p.s., $-CH_2-O-$), 4.69 (s, >CH-OAc), respectively.

Another product having the smallest Rf value was isolated as pure crystals, and 7-hemiketal structures (XXIII) and (XXIV) were reasonably assigned to this compound, m.p. 219°, ν_{max}^{KBr} cm^{-1} : 3550, 3375, $NMR^{C_5H_5N}$ δ : 3.90, 4.11 (each d, J=11 c.p.s., $-CH_2-O-$), 4.17 (d, J=4 c.p.s., $>CH-\underset{|}{C}H-OH$) (*Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found : C, 75.02; H, 10.02), and its monoacetate, m.p. 174~177°, $\nu_{max}^{CHCl_3}$ cm^{-1} : 3550, 1730, NMR^{CCl_4} δ : 2.07 (CH_3COO-), 3.78, 3.96 (each d, J=9 c.p.s., $-CH_2-O-$), 5.01 (d, J=4 c.p.s., $>CH-\underset{|}{C}H-OAc$), respectively.

Generally, the main product of this reaction was either diol (XX) or 7-hemiketal (XXIII). Presence of another minor product, the Rf value of which on thin-layer chromatogram was between those of XXI and XXVI, was observed, however, isolation of this substance was not successful. Attempted Huang-Minlon reduction of keto aldehyde (XXV) to (—)-kaurane (XXIX) resulted in failure.

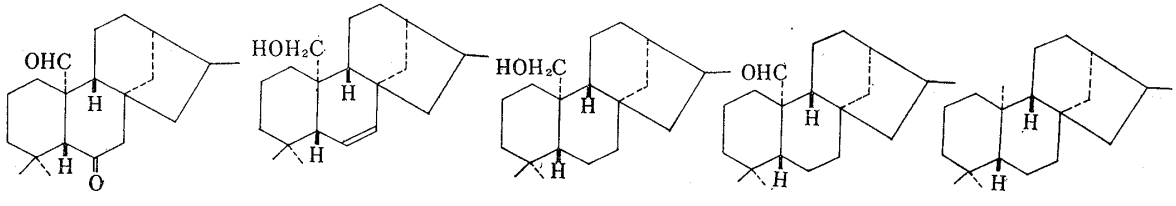


Chart 4.

Subsequently, Wolff-Kishner reduction[8] of α-hydroxyhemiketal (XXIII) was tried to give an expected unsaturated alcohol (XXVI), m.p. 56~57°, $\nu_{max}^{CHCl_3}$ cm^{-1} : 3650, 3550, 1650, NMR^{CDCl_3} δ : 3.87 (s, $-CH_2-OH$), 5.53 (oct, $>CH-CH=CH-$), which gave a monoacetate,

8) D. H. R. Barton, C. H. Robinson : J. Chem. Soc., **1954**, 3045.

NMR^{CDCl_3} δ: 2.10 (s, $C\underline{H}_3COO$-). Hydrogenation of XXVI in platinum oxide in ethanol afforded saturated alcohol (XXVII), m.p. 78~79°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640, 3475, NMR^{CDCl_3} δ: 4.11 (s, -$C\underline{H}_2$-OH). This alcohol was also prepared by hydrogenation of the acetate of unsaturated alcohol (XXVI) to saturated acetate, $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, NMR^{CDCl_3} δ: 2.08 (s, $C\underline{H}_3COO$-), and subsequent hydrolysis of the latter. Alcohol (XXVII) was oxidized with chromium trioxide-pyridine complex in the nitrogen atmosphere to aldehyde (XXVIII), m.p. 96~98°, $\nu_{max}^{CHCl_3}$ cm^{-1}: 2750, 1700. This aldehyde was heated with 98.5% hydrazine in ethylene glycol-ethanol at 180° in a sealed tube for 42 hours. After addition of potassium hydroxide pellets (85%), the temperature was gradually raised to 217° by distilling the low boiling material out, and the solution was heated at this temperature for two days. The purification of the reaction mixture by column chromatography on acidic alumina and recrystallization from acetonitrile gave colorless needles of a hydrocarbon, m.p. 87.5~88.5°, $[\alpha]_D^{22}$ −28.7° (c=0.25, CH_3OH),*6 whose molecular weight was determined as 274 ($C_{20}H_{34}$, Calcd. 274) by mass spectrometry.*7 This hydrocarbon showed a negative plain curve,*8 and its identity with (−)-kaurane (XXIX)*9 was established by mixed melting point determination, infrared spectral comparison, and mixed vapor phase chromatography using SE 30 Golay column (45 m.).

Since the absolute stereochemistry of (−)-kaurene[3,4,9] had been confirmed, the present work has established the absolute configuration of enmein.

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Received June 10, 1965

6 Physical data of (−)-kaurane have been reported as follows: m.p. 84~85°,[4] 85~87°,[3] 87.5~88.5°; $[\alpha]_D$ −33° ($CHCl_3$),[3] −32° ($CHCl_3$).*
*F. Dolder, H. Lichti, E. Mosettig, P. Quitt: J. Am. Chem. Soc., 82, 246 (1960).

*7 Thanks are due to Mr. T. Ibuka, Faculty of Pharm. Sciences, Kyoto University, for measurement of mass spectrum.

*8 (−)-Kaurane also gave a negative plain curve.

*9 We are indebted to Prof. L. H. Briggs, The University of Auckland, New Zealand, for supplying us the authentic specimen of (−)-kaurane.

9) J. R. Hanson: J. Chem. Soc., **1963**, 5061.