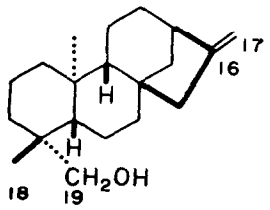
Tetrahedron Letters No.29, pp. 3395-3400, 1966. Pergamon Press Ltd.
Printed in Great Britain.

TOTAL SYNTHESIS OF THE RACEMATES OF KAUR-16-EN-19-OL, MONOGYNOL AND SOME OXYGENATED KAURANES*

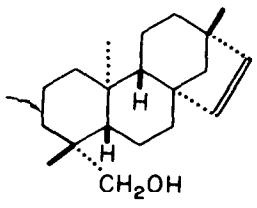
Kenji Mori,** Masanao Matsui, Nobuo Ikekawa*** and Yusuke Sumiki***
Department of Agricultural Chemistry
The University of Tokyo, Bunkyo-ku, Tokyo, Japan

(Received 19 May 1966)

(-)-Kaur-16-en-19-ol (I)(1) has been reported to be biologically active as a gibberellin-like substance (2) and its role as a precursor of the gibberellins has also been clarified (3). Our work which resulted in the total synthesis of (±)-16-oxo-17-norkauran-19-oic acid (4) has been extended now to the synthesis of (±)-kaur-16-en-19-ol (I) itself. This communication describes the synthesis and biological activity of the kaurenol (I) and its conversion to other oxygenated kauranes from Ricinocarpus stylosus (1), together with a synthesis of (±)-monogynol (II), the racemate of a diterpene isolated from Erythroxylon monogynum (5), by a skeletal



I



II

* Diterpenoid Total Synthesis - VII. This work was presented at the Annual Meeting of the Agricultural Chemical Society of Japan, Kyoto, April 2, 1966. Part VI, K. Mori, M. Matsui, Tetrahedron Letters, No.15, 1633 (1966).

** To whom inquiries concerning this paper should be adressed.

*** Institute of Physical and Chemical Research, Bunkyo-ku, Tokyo.

rearrangement.

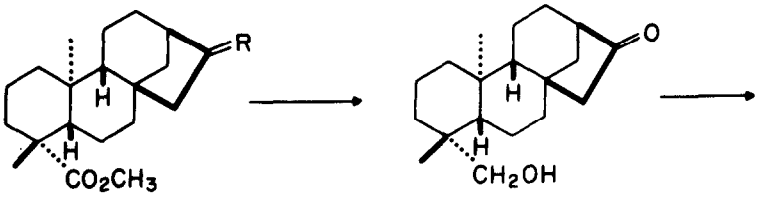
Methyl (±)-16-oxo-17-norkauran-19-oate (IIIa)* (4) in boiling dichloroethylene was treated with ethylene glycol and p-toluenesulfonic acid to give the corresponding ethylene ketal (IIIb), m.p. 133-134°, $\nu_{max.}$ (mujol) 1736, 1153, 1110, 1025 cm^{-1}. Reduction of this in tetrahydrofuran with lithium aluminum hydride in ether followed by acid hydrolysis afforded (±)-16-oxo-17-norkauran-19-ol (IV), m.p. 155-156°, $\nu_{max.}$ (mujol) 3460, 1735, 1038, 1008; (CS_2) ca. 3650, 1747, 1028, 1007 cm^{-1}. Treatment of the ketol in tetrahydrofuran with a great excess of methylenetriphenylphosphorane in ether gave (±)-kaur-16-en-19-ol (I), m.p. 144-145°, $\nu_{max.}$ (mujol) ca. 3320 broad, 3060, 1662, 1023, 1014, 1005, 870; (CS_2) ca. 3650, 3060, 1658, 1026, 1014, 1006, 874 cm^{-1}, in 47% yield after chromatography over alumina and repeated recrystallization from methanol. The solution infrared spectrum (in CS_2) of the synthetic material was identical with that of (-)-kaur-16-en-19-ol. The corresponding racemic acetate (V), m.p. 88-90°, $\nu_{max.}$ (mujol) 1742, 1662, 1252, 1035, 870 cm^{-1}, was also prepared. The racemates (I) and (V) were tested for biological activity and compared with (-)-kaur-16-en-19-ol (I) employing d-5 dwarf mutants of Zea mays L. as the assay plants.** The racemic alcohol (I) was about 50% as active as the optically active one and the lengths of leaf sheaths of treated mutants were on the average 2.4 cm greater than those of non-treated dwarf controls. The acetate (V) was a little more active (3.9 cm elongation) than the alcohol. This is the first description of the gibberellin-activity of racemates of synthetic origin.

The next objective was the conversion of (±)-kaur-16-en-19-ol (I) into other oxygenated kaurenes. Thus the alcohol (I) in tetrahydrofuran was hydroborated with sodium borohydride and boron trifluoride etherate. The resulting alkylborane was oxidized with alkaline hydrogen peroxide to give a diol (VI) as a crude oil, $\nu_{max.}$ (film)~3300, 1035, 1010 cm^{-1}. Jones' oxidation of the diol yielded a crystalline diacid, (±)-16β-kaurane-17,19-dioic acid (VIIa), m.p. 279-280°, $\nu_{max.}$ (mujol)~3200-~2600, 1705,~940 cm^{-1}. The solution infrared spectrum (in CS_2) of the corresponding dimethyl

---

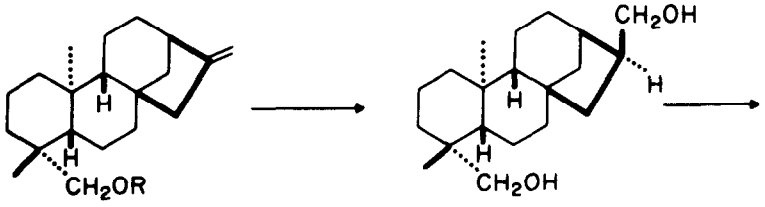
* Although the formulae depicted represent only one enantiomer, they are taken to mean a racemate in every case. The numbering system used in this paper for kauranes is that of the Australian workers (1).

** Dr. M. Katsumi of International Christian University, Tokyo, kindly performed the bioassay.



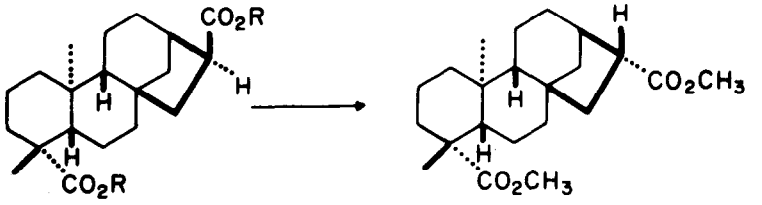
IIIa R = O
b R = 

IV



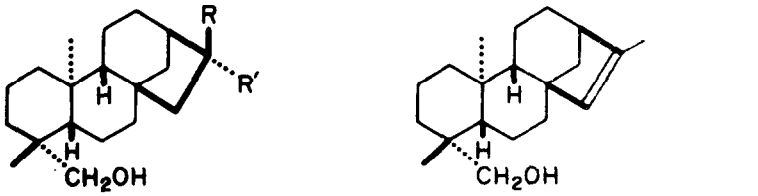
I R = H
V R = $COCH_3$

VI



VIIa R = H
b R = CH_3

VIII



IX R = H, R′ = CH_2OH
X R = CH_2OH, R′ = OH

XI

ester (VIIb), m.p. 165-166°, $\nu_{max.}$ (mujol) 1740, 1722, 1190; (CS_2) 1734, 1235, 1214, 1190, 1175, 1160, 1152 cm^{-1}, was different from that of methyl (-)-16α-kaurane-17,19-dioate (VIII), $\nu_{max.}$ (CS_2) 1734, 1236, 1193, 1176 (sh.), 1168 (sh.), 1152, 1026 cm^{-1}, in finger print regions. This suggested that the hydroboration proceeded stereoselectively from less hindered α-side of the D-ring affording 16β-alcohol as the sole product, which, upon Jones oxidation, gave 16β-acid (VIIa)*. Inspection of a molecular model clearly indicates that the 16β-ester (VIIb) is less stable than the 16α-ester (VII). Accordingly, the dimethyl ester (VIIb) was equilibrated with sodium methoxide in methanol to give a few mg of crude epimeric diester (VIII), m.p. 79-83°, of which solution infrared spectrum (in CS_2) was identical with that of the optically active diester (VIII). Gas chromatographic analysis of the diesters gave a further evidence supporting the identity of the epimerized racemate (VIII) and the natural diester (VIII). The retention time of the former coincided with that of the latter as shown in the Table, while that of the 16β-ester (VIIb) differred slightly. The parent diacid ((-)-16α-kaurane-17,19-dioic acid) of the diester (VIII) is one of the diterpenes isolated from Ricinocarpus stylosus (1). Since both the conversion of the diester (VIII) into (-)-16α-kaurane-17,19-diol (IX) and that of (-)-kaur-16-en-19-ol (I) into (-)-16β-kaurane-16α, 17,19-triol (X) had been reported by Henrick and Jefferies (1), the present work completed the total synthesis of those two diterpenes from the Australian shrub.

Finally, isomerization of (±)-kaur-16-en-19-ol (I) was carried out to obtain (±)-monogynol (II). The acetate (V) in xylene containing a small amount of iodine was heated under reflux for 9 hrs (6)**. After alkaline hydrolysis, the resulting mixture of alcohols were separated by chromatography over silica gel impregnated with silver nitrate (7). An unidentified saturated alcohol, m.p. 153-156°, $\nu_{max.}$ (mujol) ~3300, 1022, 1015; (CS_2) ca. 3640, 1028, 1015 cm^{-1}, was first eluted with benzene-petroleum ether (1:2). Then (±)-kaur-16-en-19-ol (I), identified by m.m.p. and I.R. comparison, was eluted with benzene-petroleum ether (25:15). Elution with benzene-ether

---

* The steric course of the hydroboration reaction had also been studied by Professor Jefferies (private communication to K.M. dated 11th, March, 1966). We thank him for kindly informing us of his results on the synthesis of (-)-diester (VIII) prior to publication.

** Kaurene-hibaene transformation by this method had been reported by Yoshikoshi and his co-workers (6b).

(9:1) afforded (±)-kaur-15-en-19-ol (isokaurenol, XI), m.p. 162-163°, $\nu_{max.}$ (nujol)~3300, ca. 3020, 1655, 1022, 1007, 815; (CS_2) ca. 3640, ca. 3020, 1655, 1025, 1007, 816 cm^{-1}. The last fraction yielded (±)-monogynol (II), m.p. 123-124°, ν_{max} (nujol)~3280, ca. 3035, 1580, 1025, 749; (CS_2) ca.~3640, ca. 3020, 1580, 1022, 750 cm^{-1}. The solution infrared spectrum (in CS_2) of the purified racemate was identical with that of (+)-monogynol. The identity was also proved by gas chromatographic comparison as shown in the Table. The ratio of the obtained kaurenol, isokaurenol and monogynol was 1:2:1. This added another example to the rings C/D rearrangement of tetracyclic diterpenes via bridged carbonium ion intermediates (8).

TABLE 1. Gas Chromatographic Data

Compound	Retention times (min.) 1.5% XE-60*	1% XE-61**	1.5% SE-30***
VIIb synthetic	23.6[a]	30.35[b]	48.3[c]
VIII synthetic	23.4[a]	29.7[b]	47.8[c]
VIII natural	23.4[a]	29.7[b]	47.7[c]
II synthetic	24.8[d]	16.25[e]	
II natural	24.8[d]	16.25[e]	

(Note 1) All retention times are determined on Shimadzu Seisakusho model GC1C, hydrogen flame detectors, stainless steel columns, *180 cm x 4 mm i.d., **400 cm x 3 mm i.d., ***300 cm x 3 mm i.d.

(Note 2) Column temperature : a, 180°; b, 190°; c, 197°; d, 160°; e, 170°.

Carrier gas : N_2

Flow rate of N_2 (ml/min.): a, 35; b, 20; c, 17.5; d, 40; e, 25.

Pressure (kg/cm^2): a, 0.9; b, 2.75; c, 0.45; d, 0.8; e, 2.8.

Acknowledgments. Our thanks are due to Professor P.R. Jefferies (University of Western Australia) for gifts of (-)-kaur-16-en-19-ol and methyl (-)-16α-kaurane-17,19-dioate and also to Dr. Sukh Dev (National Chemical Laboratory, India) and Dr. R.D.H. Murray (The University, Glasgow) for gifts of (+)-monogynol. We are indebted to Dr. M. Katsumi (International Christian University, Tokyo) for bioassay.

REFERENCES

1. C.A. Henrick, P.R. Jefferies, Aust. J. Chem., 17, 915 (1964).

2. M. Katsumi, B.O. Phinney, P.R. Jefferies, C.A. Henrick, Science, 144, 849 (1964).

3. a) R.H.B. Galt, J. Chem. Soc., 3143 (1965).
   b) J.E. Graebe, O.T. Dennis, C.D. Upper, C.A. West, J. Biol. Chem., 240, 1847 (1965).

4. K. Mori, M. Matsui, Tetrahedron Letters, No. 2, 175 (1966).

5. a) R.D.H. Murray, R. McCrindle, Chem. & Ind., 500 (1964).
   b) A.H. Kapadi, Sukh Dev, Tetrahedron Letters, No.19, 1171, No.38, 2751 (1964).

6. a) L.H. Briggs, B.F. Cain, R.C. Cambie, B.R. Davis, P.S. Rutledge, J. Chem. Soc., 1850 (1962).
   b) A. Yoshikoshi, M. Kitaya, Y. Kitahara, Abstracts of Papers, p. 83, 9th Symposium on Terpenes and Essential Oils held by the Chemical Society of Japan (October, 1965).

7. H.L. Goering, W.D. Glosson, A.C. Olson, J. Amer. Chem. Soc., 83, 3507 (1961).

8. For recent examples see
   a) A.H. Kapadi, Sukh Dev, Tetrahedron Letters, No.18, 1255 (1965).
   b) A.J. McAlees, R. McCrindle, R.D.H. Murray, Chem. & Ind., 240 (1966).