Tetrahedron Letters No.2, pp. 175-180, 1966. Pergamon Press Ltd.
Printed in Great Britain.

TOTAL SYNTHESIS OF (±)-KAUR-16-EN-19-OIC ACID*

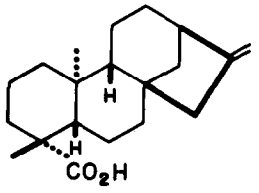
Kenji Mori and Masanao Matsui

Department of Agricultural Chemistry
The University of Tokyo, Tokyo, Japan

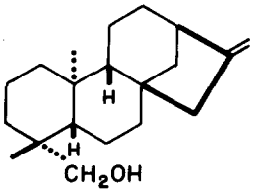
(Received 15 November 1965)

(-)-Kaur-16-en-19-oic acid (I) is one of the tetracyclic diterpenes isolated from Ricinocarpus stylosus DIELS (1). Its gibberellin-like activity as well as that of (-)-kaur-16-en-19-ol (II)(1) has recently been discovered (2). We now wish to describe the total synthesis of the racemates of these two compounds. This is the first total synthesis of compounds with appreciable gibberellin-like activity.

Condensation of 1-methyl-5-methoxytetrahydronaphthalen-2-one with methyl acroylacetate in the presence of sodium methoxide (3) afforded a keto ester (III),** m.p. 185-186°, $\nu_{max.}$ (nujol) 1745, 1680, 1638, 1608, 1590, 1270, 1055, 796, 777 cm^{-1}. This was methylated with methyl iodide and potassium



I



II

---

* Diterpenoid Total Synthesis - IV. This paper is heartily dedicated to Professors T. Yabuta and Y. Sumiki who first isolated the gibberellins in 1938 in this Department. Part III, K. Mori and M. Matsui, Tetrahedron, in the press.

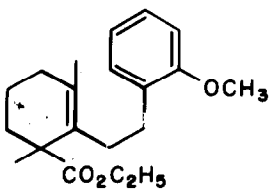
** Although the formulae depicted represent only one enantiomer, they are taken to mean a racemate in every case unless otherwise specified. The numbering system used in this paper for kauranoids is that of the Australian workers (1). For podocarpanoids, Klyne's nomenclature (4) is employed.

t-butoxide to give an oily ester (IVa), $\nu_{max.}$ (film) 1742, 1720, 1670, 1605, 1590, 1055, 790, 720 cm^{-1}. Removal of the carbonyl oxygen and saturation of the non-conjugated double bond were accomplished through two different routes. First, the oily ester (IVa) was treated with ethanedithiol and boron trifluoride etherate to yield a thioketal (IVb), m.p. 193-194°, $\nu_{max.}$ (mujol) 1732, 1672, 1604, 1582, 1234, 1055, 784, 720 cm^{-1}, which in dioxane was refluxed with Raney nickel to give an ester (Vb),* m.p. 124-125°, $\nu_{max.}$ (mujol) 1730, 1600, 1580, 1260, 1190, 1152, 1060, 785, 780 cm^{-1}. Secondly, the oily ester (IVa) in acetic acid was hydrogenated over palladium-charcoal to afford a keto ester (Va), m.p. 155-156°, $\nu_{max.}$ (mujol) 1736, 1718, 1602, 1585, 1260, 1055, 785, 780, 720 cm^{-1}. The Clemmensen reduction of this gave the ester (Vb), identical in every respect with the above mentioned product. Demethylation of the ester (Vb) by refluxing hydriodic acid in acetic acid afforded an acid (VIa), m.p. 223-224°, $\nu_{max.}$ (mujol) 3530, 3200-2400, 1680, 1610, 1580, 1272, 782, 725 cm^{-1}. This was esterified with diazomethane to give methyl (±)-8-methoxydesoxypodocarpate (VIb), m.p. 191-192°, $\nu_{max.}$ (mujol) 3380, 1702, 1582, 787, 728 cm^{-1}.

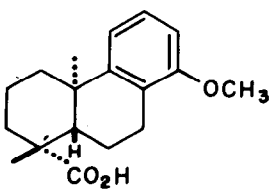
Catalytic hydrogenation of the ester (VIb) over rhodium-platinum catalyst (6) afforded an oily epimeric (at C-8) mixture of saturated hydroxy esters (VII), $\nu_{max.}$ (film) 3440, 1732, 1155 cm^{-1}, accompanied with a hydrogenolysis product. Jones oxidation (7) of the crude mixture gave crystalline methyl (±)-8-oxopodocarpan-16-oate (VIII), m.p. 155-156°, $\nu_{max.}$ (mujol) 1728, 1708,

---

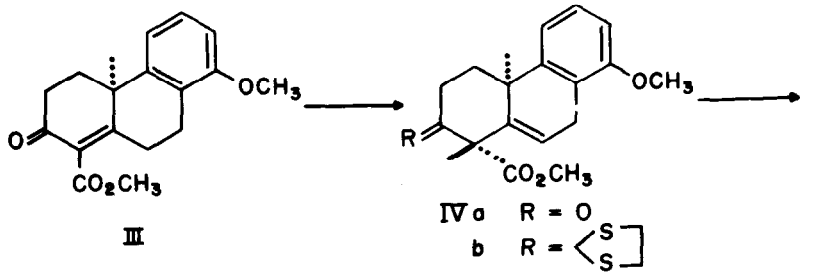
* At this stage, the stereochemistry (Vb) assigned to the ester was confirmed by the comparison with an authentic ester (Vb) which was prepared by treatment of the acid (ii), m.p. 243-244°, $\nu_{max.}$ (mujol) 1695, 1600, 1590, 782, 725 cm^{-1}, with diazomethane. The acid (ii) was obtained in a low yield by the acid-catalyzed cyclization (5) of an unsaturated ester (i), b.p. 160-170°/0.4 mm, n_D^{26} 1.5260, $\nu_{max.}$ (film) 1735, 1608, 1592, 755 cm^{-1}.



i



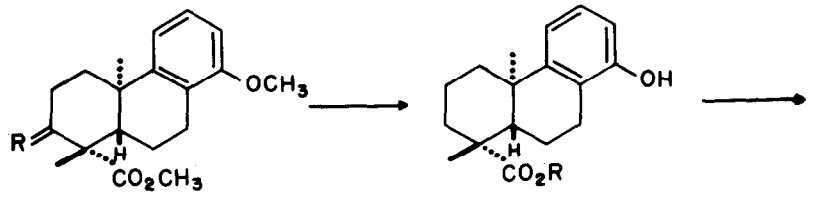
ii



III

IV a R = O

b R = S, S

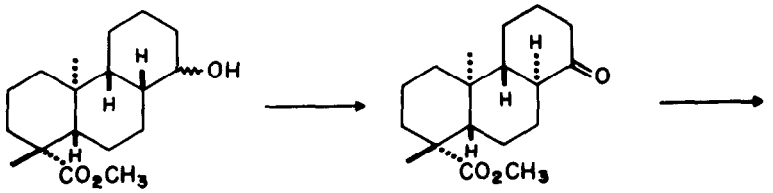


V a R = O

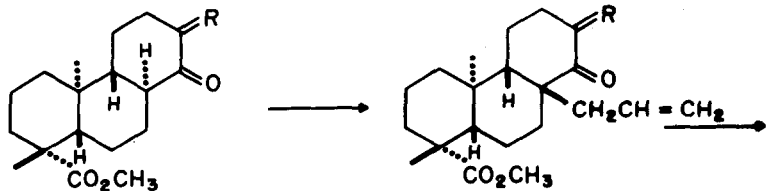
b R = H_2

VI a R = H

b R = CH_3



VII VIII

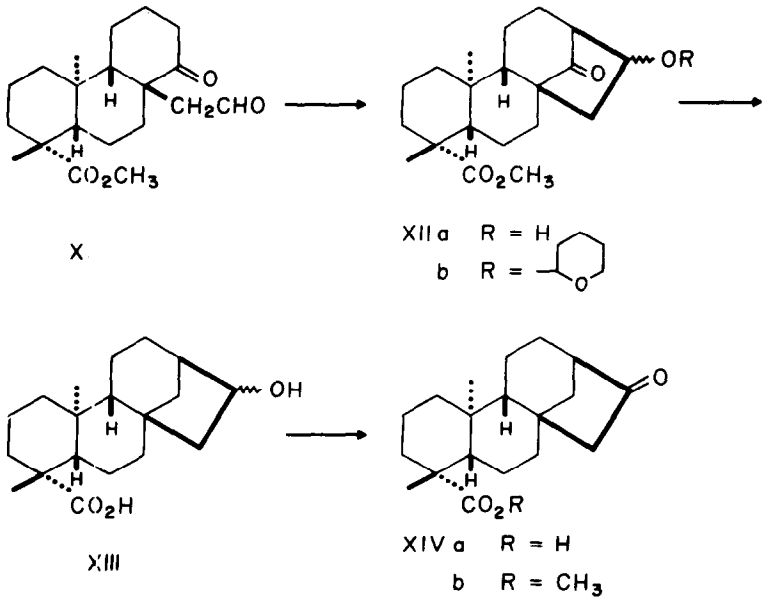


IX a R = CHOH

b R = $CHSC_4H_9$

X a R = $CHSC_4H_9$

b R = H_2



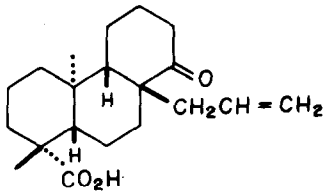
1166 cm^{-1}. The B/C trans stereochemistry of this ketone (VIII) was proved by the fact that equilibration with methanolic sodium methoxide gave back the starting material.

The construction of the D ring was carried out by the method developed by Ireland et al. (8) referring its application in the total synthesis of garryine (9). Prior to the introduction of a substituent at C-14, the C-7 methylene was blocked by employing the n-butylthiomethylene protective group (10). Thus formylation of the ketone (VIII) with ethyl formate in the presence of sodium methoxide gave a formyl ketone (IXa), m.p. 122-123°, νmax. (mujol) 1718, 1645, 1590 cm^{-1}, which in benzene was refluxed with n-butyl mercaptan and p-toluenesulfonic acid to yield an n-butylthiomethylene ketone (IXb), m.p. 86-87°, νmax. (mujol) 1728, 1670, 1554 cm^{-1}. This was treated with a great excess of allyl bromide and potassium t-butoxide to afford an oily keto ester (Xa), νmax. (film) 1730, 1674, 1642, 1550, 915 cm^{-1}. Removal of the protective group was effected by refluxing the ketone (Xa) in aqueous ethanol with potassium hydroxide to give an oily allyl ketone (Xb), νmax. (film) 1730, 1712,

1648, 915 cm^{-1}.* Osmium tetroxide-sodium periodate oxidation (11) of the allyl ketone (Xb) afforded a crystalline keto aldehyde (XI),** m.p. 110-111°, $\nu_{max.}$ ($CHCl_3$ film) 2740, 1730, 1708 cm^{-1}, which was treated with hot methanolic sodium methoxide to give an oily epimeric mixture (at C-16) of the tetracyclic hydroxyketones (XIIa), $\nu_{max.}$ (film) 3420, 1745, 1732 cm^{-1}. This in benzene was treated with dihydropyran and p-toluenesulfonic acid to give an epimeric mixture (at C-16) of the tetrahydropyranyl ethers (XIIb), one of which crystallized, m.p. 165-166°, $\nu_{max.}$ (mujol) 1745, 1725, 1242, 1198, 1140, 1026, 1015 cm^{-1}. The modified Wolff-Sishner reduction (13) of the crystalline ketone (XIIb) followed by acid-hydrolysis yielded a crystalline hydroxy acid (XIII), m.p. (crude) 255-258°, $\nu_{max.}$ (mujol) 3400, 3200-2400, 1708, 1270, 1260, 1030, 1020 cm^{-1}. Without further purification this was oxidized with the Jones reagent (7) to give (±)-16-oxo-17-norkauran-19-oic acid (XIVa), m.p. 247-248°, $\nu_{max.}$ (mujol) 3200-2400, 1743, 1700 ($CHCl_3$) 3200-2400, 1740, 1698

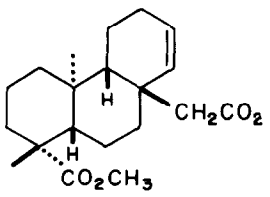
---

* As a minor product was obtained the corresponding acid (iii), m.p. 226-227°, $\nu_{max.}$ (mujol) 3200-2400, 1704, 1648, 934, 915 cm^{-1}.

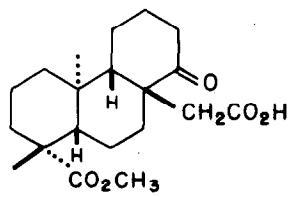


iii

** Again at this stage the stereochemistry (XI) assigned to the keto aldehyde was confirmed by proving the identity of the corresponding keto acid obtained by the Jones oxidation (7) of the aldehyde (XI) with an authentic sample of the keto acid (v), m.p. 201-202°, $\nu_{max.}$ (mujol) 3200-2400, 1725, 1705, 1695 (sh.) cm^{-1}. This was prepared from the previously described acid (iv)(12) via iodolactonization, hydrogenolytic removal of the iodine, reduction with sodium borohydride to a diol and its Jones oxidation. Details of this process together with a less successful conversion of the keto acid (V) into the tetracyclic hydroxyketone (XIIa) will be described in a full paper.



iV



V

cm^{-1}. The corresponding methyl ester (XIVb) m.p. 127-128°, ν_{max}. (nujol) 1745, 1728 ; ($CHCl_3$) 1738, 1726 cm^{-1}, was prepared by esterification with diazomethane. The solution infrared spectra (in $CHCl_3$) of the acid (XIVa) and the ester (XIVb) were completely identical with those of the natural products (1)(14). Since the (-)-ester (XIVb) had been converted to (-)-kaur-16-en-19-ol (II)(14) which in turn had been transformed into (-)-kaur-16-en-19-oic acid (I)(1), this completed the total synthesis of both the (±)-acid (I) and (±)-alcohol (II) with gibberellin-like activity.

Preparation of (±)-kaur-16-en-19-ol (II) is now in progress to test its biological activity.

Acknowledgment. We are indebted to Prof. P.R. Jefferies (University of Western Australia) and Dr. R.H.B. Galt (Imperial Chemical Industries) for their kind gifts of the authentic samples of (-)-16-oxo-17-norkauran-19-oic acid (XIVa) and its ester (XIVb).

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) I.N. Nazarov, S.I. Zavyalov. Zhur. Obsch. Khim., 23, 1703 (1953).
   b) E. Wenkert, A. Afonso, J. B-son Bredenberg, C. Kaneko, A. Tahara, J. Amer. Chem. Soc., 86, 2038 (1964).
4. W. Klyne, J. Chem. Soc., 3072 (1953).
5. K. Mori, M. Matsui, Tetrahedron, in the press.
6. S. Nishimura, Bull. Chem. Soc. Japan, 34, 1544 (1961).
7. A. Bowers, T.G. Halsall, E.R.H. Jones, A.J. Lewis, J. Chem. Soc., 2548 (1953).
8. a) R.A. Bell, R.E. Ireland, R.A. Partyka, J. Org. Chem., 27, 3741 (1962).
   b) R.A. Bell, R.E. Ireland, Tetrahedron Letters, No. 14, 269 (1963).
9. Z. Valenta, K. Wiesner, C.M. Wong, ibid., No. 36, 2437 (1964).
10. R.E. Ireland, J.A. Marshall, J. Org. Chem., 27, 1615 (1962).
11. R. Pappo, D.S. Allen, Jr., R.U. Lemieux, W.S. Johnson, ibid., 21, 478 (1956).
12. K. Mori, M. Matsui, Tetrahedron Letters, No. 28, 2347 (1965).
13. D.H.R. Barton D.A.J. Ives, B.R. Thomas, J. Chem. Soc., 2056 (1955).
14. R.H.B. Galt, ibid., 3143 (1965).