Tetrahedron Letters No.28, pp. 2347-2350. Pergamon Press Ltd.
Printed in Great Britain.

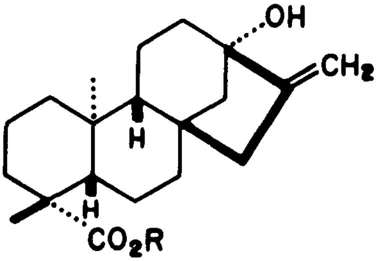
TOTAL SYNTHESIS OF METHYL (±)-8α-CARBOXYMETHYLPODOCARPAN-13-ONE-4β-CARBOXYLATE, A DEGRADATION PRODUCT OF STEVIOL*

Kenji Mori and Masanao Matsui

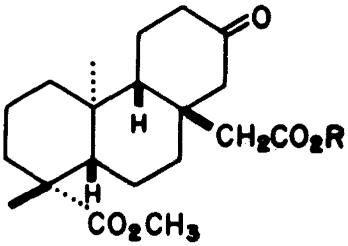
Department of Agricultural Chemistry
The University of Tokyo, Tokyo, Japan

(Received 17 May 1965)

Steviol (Ia) is the aglycone of stevioside, a glycoside abundant in Stevia rebaudiana (1). Its structure, including absolute stereochemistry, has been determined by degradative studies coupled with ORD measurements (2,3). Recent discoverty of its gibberellin-like activity (4) prompted us to search a possible route to the total synthesis of steviol, as well as that of kaurenoic acid (Ia, C-13-H instead of -OH). In this communication, a stereoselective total synthesis of (±)-seco acid (IIa)** will be described. The seco acid (IIa) has been obtained as one of the ozonolysis products of steviol methyl ester (Ib) and retains all the asymmetric centers of steviol except one at C-13 (3).



Ia R = H
b R = CH$_3$



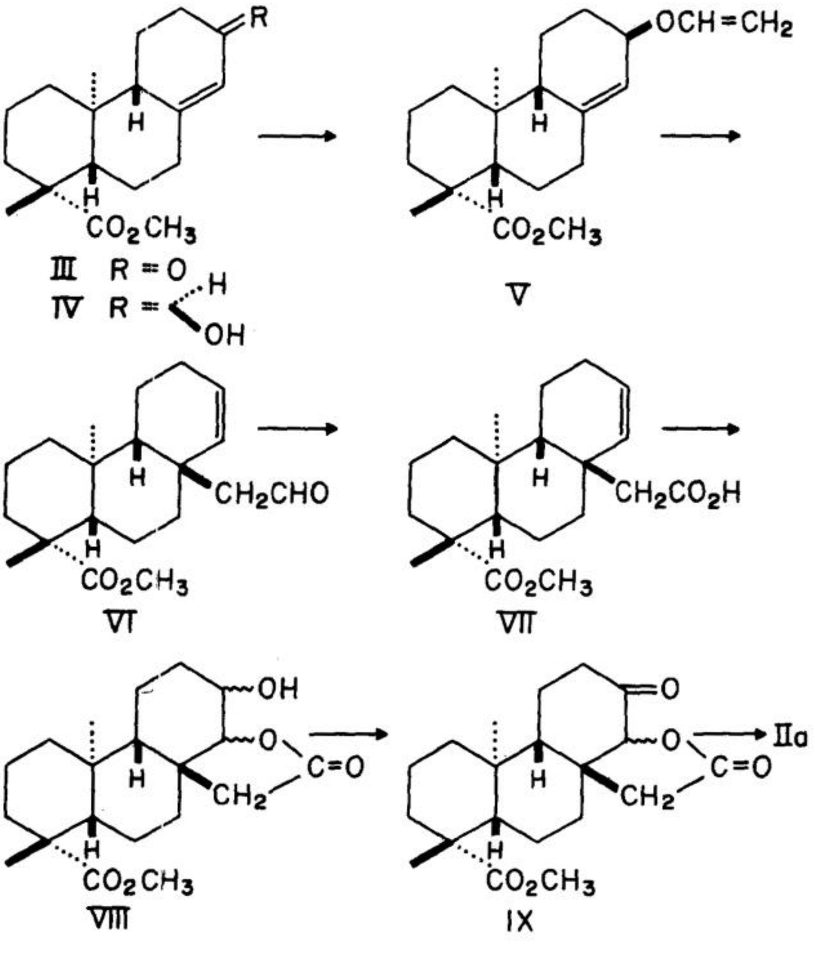
IIa R = H
b R = CH$_3$

---

* Diterpenoid Total Synthesis, Part 1.

** Although the formulae depicted represent only one enantiomer, they are taken to mean a racemate in every case unless otherwise specified. The steroid numbering is used throughout the paper.

Methyl (±)-podocarp-8(14)-en-13-one-4β-carboxylate (III), m.p. 91-94°, $\nu_{max.}$ (Nujol) 1722, 1674, 1618 cm^{-1} (5)*, was reduced with lithium tri-t-butoxyaluminum hydride (6) to afford the corresponding hydroxy ester



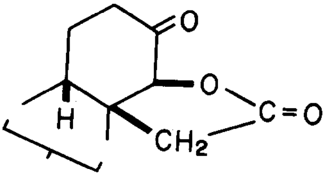
---

* Our synthetic route differs from that of the English authors (5). (±)-Desoxypodocarpic acid was employed as the starting material. Details will be described in a full paper. The keto ester (III) was identified with the natural (−)-ester by gas chromatography.

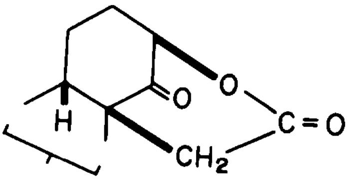
(IV), oil, $\nu_{max.}$ (film) 3400, 1724, 1662 cm^{-1}. This was converted to a crystalline vinyl ether (V), m.p. 88-89°, $\nu_{max.}$ (Nujol) 1718, 1660, 1632, 1608 (sh.)cm^{-1}, by mercuric acetate-catalyzed vinyl transetherification reaction in ethyl vinyl ether (7). The ether (V) in decalin was heated at 200° for several hours to give a crystalline aldehyde (VI), m.p. 84-85°, $\nu_{max.}$ (Nujol) 1722, 1650 cm^{-1}, which was oxidized with silver oxide to an unsaturated acid (VII), m.p. 161-162°, $\nu_{max.}$ (Nujol) ~2700, 1720, 1698 cm^{-1}. This acid (VII), upon performic acid oxidation, alkaline hydrolysis and acid-catalyzed lactonization (8), afforded an oil, $\nu_{max.}$ (film) 3500, 1774 (γ-lactone), 1722 cm^{-1}, consisting mainly of a hydroxy lactone (VIII). This was oxidized with Jones reagent (9) to the corresponding semi-solid keto lactone (IX)*, $\nu_{max.}$ 1782, 1724 cm^{-1}, which in turn was treated with zinc dust in acetic acid to give methyl (±)-8α-

---

* Fractional crystallization of the crude keto lactone (IX) gave keto lactones A and B in about 3:1 ratio. The keto lactone A was more soluble in ethyl acetate than B and crystallized from ethyl acetate-petroleum ether as prisms, m.p. 176-177°, $\nu_{max.}$ (Nujol) 1786 (γ-lactone), 1732, 1725 (sh.) cm^{-1}. The lactone B separeted from ethyl acetate-petroleum ether as needles, m.p. 236-238°, $\nu_{max.}$ (Nujol) 1762, 1730; (CHCl$_3$) 1740 (sh., δ-lactone), 1728, 1718(sh.) cm^{-1}. When the crude keto lactone was treated with zinc dust in acetic acid, the lactone B was recovered from the neutral fraction, while the seco acid (IIa) was the only component of the acidic fraction of the reaction product. The lactone A was most probably the desired γ-lactone (i). Inspection of a molecular model indicated the cis-lactone structure as shown with an equatorially oriented ethereal lactone oxygen atom. Hence in the parent hydroxy lactone (VIII), the C-13 hydroxyl group and the C-14 ethereal lactone oxygen atom were in trans-diequatorial relationship. The lactone B was assumed to be a δ-lactone (ii) with a hindered carbonyl group and an axially oriented ethereal lactone oxygen atom. The hindered nature of the ketone function was shown by the fact that the lactone B remained unchanged during the zinc dust reduction. No further structure elucidation was attempted since the available amounts of the pure lactones were very small.



(i)



(ii)

carboxymethylpodocarpan-13-one-4β-carboxylate (IIa), m.p. 190-191° (softening at 172°), $\nu_{max.}$ (Nujol) ~2700, 1722, 1706, 1698 (sh.) cm^{-1}. Its solution infrared spectrum ($CHCl_3$, 1722(sh.), 1712, 1704(sh.) cm^{-1}) was identical with that of the seco acid (IIa) obtained from steviol. The corresponding racemic dimethyl ester (IIb), m.p. 93-95°, $\nu_{max.}$ (Nujol) 1728, 1706 cm^{-1}, prepared from the acid (IIa) by treatment with diazomethane, also showed an identical infrared spectrum ($CHCl_3$ solution, $\nu_{max.}$ 1720 cm^{-1}) with that of the natural product.

Acknowledgement. We are indebted to Dr. James A. Waters, National Institutes of Health, U.S.A., for his generous supply of the comparison samples (IIa and IIb) and a copy of the infrared spectrum of the seco acid. We also thank Drs. A. Tahara and O. Hoshino, Institute of Physical and Chemical Research, Tokyo, for gas chromatographic comparison of the keto ester (III).

REFERENCES

1. H. B. Wood,Jr., R. Allerton, H. W. Diehl, H. G. Fletcher,Jr., J. Org. Chem., 20, 875 (1955).
2. C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge, L. H. Briggs, J. Amer. Chem. Soc., 83, 3720 (1961).
3. E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt, J. A. Waters, J. Amer. Chem. Soc., 85, 2305 (1963).
4. M. Ruddat, A. Lang, E. Mosettig, Naturwissenschaften, 50, 23 (1963).
5. J. A. Barltrop, A. C. Day, J. Chem. Soc., 1959, 671.
6. H. C. Brown, R. F. McFarlin, J. Amer. Chem. Soc., 80, 5372 (1958).
7. A. W. Burgstahler, I. C. Nordin, J. Amer. Chem. Soc., 83, 198 (1961); R. F. Church, R. E. Ireland, J. Org. Chem., 28, 17 (1963).
8. K. Mori, M. Matsui, Y. Sumiki, Agr. Biol. Chem. (Tokyo), 25. 213 (1961).
9. A. Bowers, T. G. Halsall, E. R. H. Jones, A. J. Lewis, J. Chem. Soc., 1953, 2548.