Tetrahedron Letters No.47, pp. 4091-4093, 1970. Pergamon Press. Printed in Great Britain.

A SYNTHESIS OF STEVIOL

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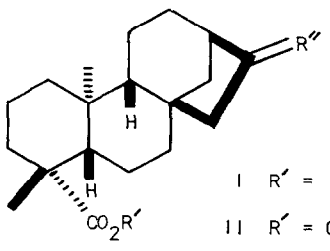
(Received in UK 13 August 1970; accepted for publication 10 September 1970)

There is a continuing interest[1,2] in the development of methods for synthesis of the unusual bicyclo[3.2.1]octane system forming the C/D rings of steviol (V a)[3] and some gibberellins. House and Darms[2] attempted to form a 1-hydroxybicyclo[3.2.1]octane-7-one or a reduced variant in a gibbane skeleton by acyloin-like condensation of a keto ester but the results were inconclusive as to the usefulness of the approach due to complexities in their system. We have used a cyclization of this type as a key step in a convenient sequence leading to the first synthesis of steviol (Va).

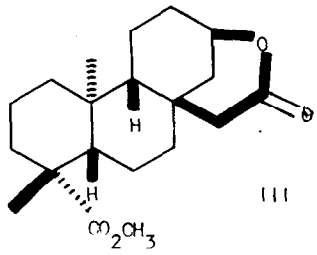
The ketodiester (IV) required for the cyclization reaction was obtained from (-)-kaur-16-en-19-oic acid (I)[4]. Conversion of the methyl ester of (I) to the nor-ketone (II)[5] and subsequent Baeyer-Villiger oxidation afforded the lactone (III) $C_{20}H_{30}O_4$, m.p. 152-3°, $[\alpha]_D$-88° which showed a broad one proton signal at 4.78δ (H-13) in the n.m.r. spectrum and i.r. peaks at 1730 and 1725 cm^{-1}. Further transformation by hydrolysis of the lactone functionality followed by careful methylation and oxidation (CrO_3 / pyridine) gave the keto diester (IV) $C_{21}H_{32}O_5$, m.p. 116-8° $[\alpha]_D$ -45°. Evidence for the structure of IV came from the close correspondence of the physical constants with literature values[3] and also from i.r. and n.m.r. evidence for two methyl ester functionalities and a ketone in a six-membered ring.

The acyloin-like condensation of IV) proved to be complex. With the help of model compounds it was found that the major competing reactions leading to undesired products involved dimerization, reductive loss of a bridgehead hydroxyl and formation of a nor-beyerane nucleus through isomerization. The conditions chosen for the reduction of IV are as follows: Sodium (400mg) was stirred with liq. NH_3 (150ml) and THF (200ml) for 15 min. and then a solution of the keto diester (400mg) in THF (50ml) was added over 1-2 min.After 5 min.

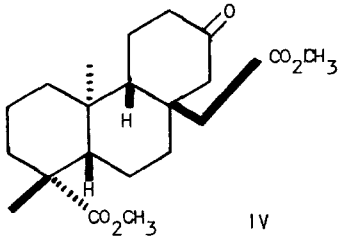


I R' = H, R'' = CH_2

II R' = CH_3, R'' = O



III



IV

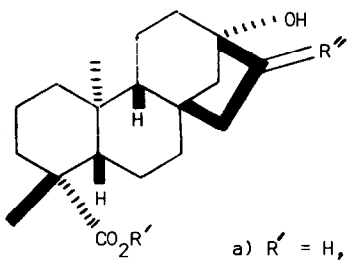
t-BuOH was added and the acidic material recovered (96% weight yield). A portion of this fraction was converted to the ^{14}C - labelled methyl esters ($^{14}CH_3I$ / K_2CO_3 / acetone) and the distribution of radioactivity determined through a t.l.c. scanning technique. In this way it was shown that the yields of the major products were: the epimeric nor-kaurane diols VIa and VIIa 27% and 3% respectively, the beyerane diol (acid corresponding to IX) 10% and a dimer of uncertain structure 54%.

The major nor-kaurane product (VIa) $C_{19}H_{30}O_4$, m.p. 265-7°, $[\alpha]_D$-82° was obtained by careful chromatography of the acidic fraction from the cyclization reaction. Treatment with diazomethane gave the methyl ester (VIb) $C_{20}H_{32}O_4$, m.p. 185-7°, $[\alpha]_D$-85° which had i.r. absorption (nujol) at 3375 (OH) and 1725 cm^{-1} (ester) and signals in the n.m.r. spectrum at 3.63δ (s, 3H, CO_2Me) and 3.95δ (br, 1H, H-16) consistent with the structural assignment. Furthermore, the product of oxidation of VIb was identified as the ketol (VIIIb) by elemental analysis and the close correspondence of the m.p. (224-6°) and rotation ($[\alpha]_D$-100°) with literature values (m.p. 224-7°, $[\alpha]_D$-102°)[3]. It was thus established that the cyclization product (VIa) had the required 13,16-dioxygenated-17-nor-kaurane structure. The β-configuration of the 16-hydroxyl followed from the exclusive formation of VIb by $NaBH_4$ reduction of the ketol (VIIIb). This reagent is known to reduce 13-deoxy analogues by exclusive exo attack[6] and it is unlikely that a 13-hydroxyl substituent would reverse this preference.

The ketol acid (VIIIa) $C_{19}H_{28}O_4$, m.p. 221-2°, $[\alpha]_D$-96° was obtained by careful oxidation of VIa. To complete the synthesis of steviol it remained necessary to generate the exocyclic methylene functionality by a Wittig reaction. This was best achieved through the silyl ether which prevented the formation of a small amount of the Wittig product of the isomeric nor-beyerane ketol. The silyl ether was readily prepared (hexamethyldisilazane and trimethylsilyl chloride in pyridine) and underwent smooth Wittig reaction with triphenylmethylene phosphorane followed by hydrolysis of the silyl ether in the work-up. The product m.p. 208-10°, $[\alpha]_D$ -91° was identified as steviol (Va)[3] by m.m.p. and i.r. spectral comparison with an authentic sample.

The minor nor-kaurane product from the cyclization of IV was isolated as the gummy methyl ester (VIIb), m.s. peak at m/e 336 (M^+). Careful oxidation gave the ketol (VIIIb) thus establishing that VIIb is the 16α-epimer of VIb. The n.m.r. spectra of the epimers are very similar except for the signal due to the 16- proton which occurs at higher field (3.60δ) in the spectrum of VIIb.

Two nor-beyerane derivatives were also isolated by chromatography of the methylated products from the cyclization reaction. One compound m.p. 197-9°, $[\alpha]_D$ -62.5° was obtained



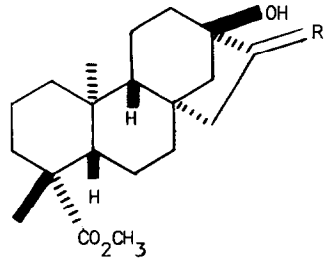
a) R' = H, b) R' = CH_3

V R'' = CH_2

VI R'' = $<^{OH(\beta)}_{H}$

VII R'' = $<^{OH(\alpha)}_{H}$

VIII R'' = O



IX R = $<^{OH(\beta)}_{H}$

X R = O

in trace amounts and had i.r. absorption due to hydroxyl, ester and cyclopentanone functionalities. Mechanistic considerations as well as our experience with model compounds suggested that it was the ketol (X). The close correspondence of the physical constants with literature values for the compound of this structure[3] provided firm evidence for the deduction. The other compound (IX) $C_{20}H_{32}O_4$, m.p. 136-7°, $[\alpha]_D$ - 77° formed the ketol (X) by careful oxidation; it is consequently one of the epimeric 16-hydroxy compounds. This compound is different from the gummy diol obtained from $NaBH_4$ reduction of the ketol (X). The stereochemistry of the $NaBH_4$ reduction is presumably the same as with the nor-kaurane compounds and consequently the hydroxyl group of IX is tentatively assigned the 16β- configuration.

Acknowledgements

We are indebted to Professor M. Ruddat and Dr. J.R. Hanson for samples of steviol.

References

1. R.A. Bell, R.E. Ireland and L.N. Mander, J. Org. Chem., 31, 2536 (1966); G. Stork, S. Malhotra, H. Thompson and M. Uchibayashi, J. Amer. Chem. Soc., 87, 1148 (1965); E.J. Corey, M. Narisada, T. Hiraoka and R.A. Ellison, J. Amer. Chem. Soc., 92, 396 (1970); K. Mori, M. Matsui and Y. Sumiki, Tetrahedron Letters, 429 (1970).
2. H.O. House and R. Darms, J. Org. Chem., 30, 2528 (1965).
3. E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt and J.A. Waters, J.Amer.Chem. Soc., 85, 2305 (1963).
4. For the total synthesis of I and IV see: K. Mori and M. Matsui, Tetrahedron, 24, 3095 (1968); K. Mori and M. Matsui, Tetrahedron Letters, 2347, (1965).
5. P.R. Jefferies and T.G. Payne, Aust. J. Chem., 18, 1441 (1965).
6. J.R. Hanson, Tetrahedron, 23, 801 (1967).