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SYNTHESIS OF HASTATOSIDE TETRAACETATE

Yoshiki Umehata and Toshio Miwa*

Faculty of Science, Osaka City University, Sumiyoshiku, Osaka 558, Japan

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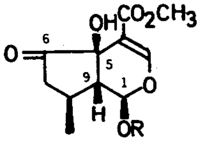
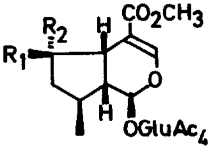
In 1973, Rimpler and Schäfer[1] isolated hastatoside, an iridoid glucoside, from Verbena hastata and proposed the structure 1 of 5-hydroxyverbenalin for the glucoside. We report here the synthesis of the tetraacetate (2) of the glucoside from verbenalin tetraacetate to confirm its stereochemistry.

Reduction of verbenalin tetraacetate[2] with sodium borohydride according to the procedure of Büchi and Manning[3], followed by plc [10 developments with benzene-ethyl acetate (9 : 1)], gave two epimeric alcohols 3a and 3b[4,5] (ca 1 : 1). Alcohol 3a, mp 151-152°, was mesylated with mesyl chloride in pyridine to give crystalline mesylate 4a, mp 155-156°[6]. On the other hand, alcohol 3b, amorphous powder, gave amorphous mesylate 4b.



1: R = Glu
2: R = GluAc$_4$



3a: R_1 = OH; R_2 = H
3b: R_1 = H; R_2 = OH
4a: R_1 = OMs; R_2 = H
4b: R_1 = H; R_2 = OMs

Heating mesylate 4b with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in xylene at 155° for 1 hr caused complete elimination to give Δ^5-olefin 5 as a sole product. The nmr spectrum of this product showed one olefinic proton signal at δ 6.18 ppm. On the other hand, mesylate 4a was reluctant to elimination. Heating it with DBU in xylene at 155° for 2.5 hr gave a mixture of Δ^5- and Δ^6-olefin in a ratio of 2 : 3 with recovery of 20% of the mesylate. The structure of the latter olefin was confirmed by two olefinic proton signals (δ 5.55 and 5.85 ppm) in the nmr spectrum. The difference in the elimination rates of the mesylates is apparently due to the different orientations of the glycosyl group[7]; the equatorial orientation of the group is favorite to loss of the C-5 proton for the stereo-electronic effect (Fig 1).

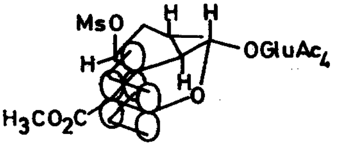
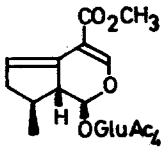


Fig 1



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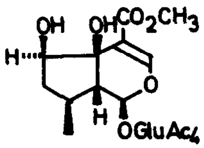
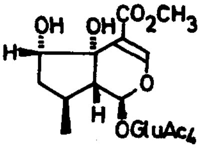
Δ^5-Olefin 5 was immediately oxidized with osmium tetraoxide in ether under catalysis of pyridine, followed by reduction of the resulting osmate with hydrogen sulfide, to a mixture of cis diols. Plc [4 developments with benzene-ethyl acetate (8 : 2)] separated the mixture into



6a



6b

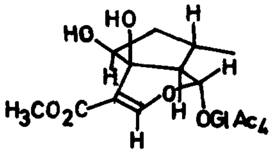


Fig 2

6a (26% based on 4b), mp 150-152°, as a more polar fraction and 6b (36% based on 4b), amorphous powder, as a less polar fraction. The nmr spectra of diols, 6a and 6b, revealed a doublet for H-1 of coupling constant of 2 Hz and 7 Hz, respectively, proposing that the glycosyl group is axial in the former and equatorial in the latter. Since the glycosyl group in axial in α-<u>cis</u> diol would cause the dihydropyranyl ring to assume a boat form (Fig 2), 6a was assigned to be β-<u>cis</u> diol and 6b α-<u>cis</u> diol.

The oxidation of diol 6a with dimethyl sulfoxide and acetic anhydride at room temperature for 24 hr gave, after purification by plc [5 developments with benzene-ethyl acetate (8 : 2)], hastatoside tetraacetate, mp 180-181° (lit. mp 180-182°[1]), $[\alpha]_D^{23}$ -245° (c = 0.388, chloroform), in 27% yield. The nmr spectrum of this material was completely identical with that of the authentic sample. It may be pointed out that all the compounds with the axial glycosyl group crystallized more readily than those with equatorial glycosyl group through this work.

Acknowledgment: The authors are much indebted to professor Hiroyuki Inouye of the Kyoto University for helpful discussions and gift of the nmr chart of hastatoside tetraacetate.

REFERENCES AND FOOTNOTES

1. H. Rimpler and B. Schäfer, Tetrahedron Lett., 1463 (1973).
2. Verbenalin was extracted from the leaves of Symplocos glauca Koidz. E. Kato, Y. Ueda, S. Isoe, and T. Sakan, Abstracts of the 24th Annual Meeting of the Chemical Society of Japan, Osaka, April 1971, p 1801.
3. G. Büchi and R. E. Manning, Tetrahedron, 18, 1049 (1962).
4. S. R. Jensen, A. Kjaer, and B. J. Nielsen, Acta Chem. Scand., 27, 2581 (1973).
5. The stereochemistry, proposed by Jensen et al.[4], of the epimeric dihydroverbenalins was further confirmed by two facts: (1) Mesylation of a mixture of epimeric alcohols (1 : 1) at 0° for 1 hr gave a mixture of mesylates (57%; 4a : 4b = 8 : 2) with recovery of a mixture enriched in 3b (37%; 3a : 3b = 2 : 8), indicating that 3b was more hindered for mesylation. (2) Mesylate 4a and the corresponding benzoate, mp 127°, showed a doublet (J = 9 Hz, each peak with $w_{1/2}$ = ca 4 Hz) for C-5 proton, while the epimeric counterparts showed a quartet (J = ca 9 and 4 Hz) for the proton. The small coupling constants for the former series can be rationalized only when alcohol 3a has 6β-OH configuration.
6. Satisfactory elemental analyses were obtained for all the crystalline compounds.
7. The coupling constants between H-1 and H-9 prtons of alcohol 3b and its derivatives (ca 8 Hz) are larger compared with those of alcohol 3a and its derivatives (ca 2 Hz), suggesting that the glycosyl group is equatorial in the former and axial in the latter.