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The Conformation of Ring C in 8-Podocarpenes

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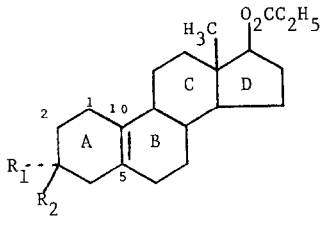
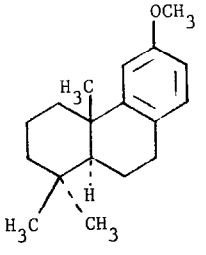
Ring A of the 5(10)-unsaturated steroid system is subject to an unusual type of conformational control which has been ascribed[1] primarily to non-bonded interactions between the C-1 and C-11 hydrogen substituents. Preference for one of the two possible half-chair forms of ring A has been established experimentally[1] for several derivatives including the 3-alcohols 1a and 1b. A more exact understanding of this phenomenon has very recently been sought by semi-empirical computor calculations of preferred geometry for this ring system[2]; the results of these two approaches are thus far in qualitative agreement only. We now report evidence that ring C of the structurally analogous 8-podocarpene system (as 3a-3c) is subject to similar conformational control.



1a R_1=OH, R_2=H
1b R_1=H, R_2=OH
1c R_1, R_2=O



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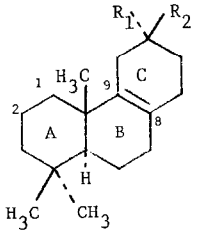


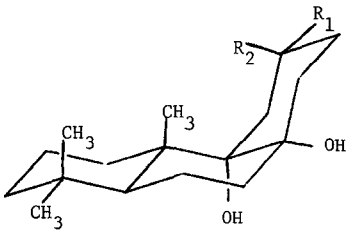
3a R_1, R_2=O
3b R_1=OH, R_2=H
3c R_1=H, R_2=OH

Treatment of 13-methoxy-podocarpa-8,11,13-triene (2)[3] with lithium in ammonia, tetrahydrofuran, and t-butanol gave a mixture of reduction products which was directly hydrolyzed by brief heating with acetic acid in aqueous methanol. Chromatography on silica gel then furnished podocarp-8-en-12-one(3a) along with several earlier eluted by-products. This ketone, obtained as an easily autoxidized oil, was homogeneous by several chromatographic procedures and gave infrared, ultraviolet, nmr, and mass spectral results consistent with its structure.

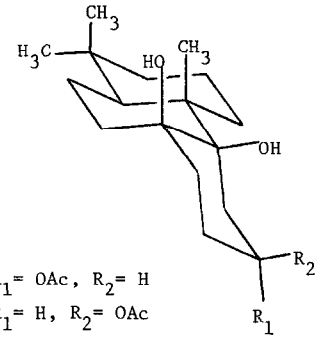
Reduction of ketone 3a with $LiAl(Ot\text{-}Bu)_3H$ in THF at room temperature produced the correspond-

ing epimeric alcohols as a mixture which was separated on a silica gel column by elution with benzene in hexane in a continuous solvent gradient system. Pure epimeric alcohols A, m.p. 111-112° (68% yield) and B, m.p. 95-96° (23% yield) were thus obtained. The observed stereoselectivity of ketone reduction is, in itself, indicative of a preferred conformation in ring C.

Following earlier developed methodology[1], we attempted to determine the C-12 configurations of the epimeric alcohols A and B *via* their conversion to products having saturated ring systems of fixed conformation. The unsaturated alcohol A was acetylated and them treated with OsO_4 in pyridine. A single 8,9-cis diol, (A') m.p. 183-184° was produced which must be assigned structure 4a, 4b, 5a or 5b. An nmr spectrum of this product disclosed the C-12 proton as a multiplet centered at δ5.04 whose broadness (W_H 24 Hz) was more than sufficient to denote an axial hydrogen substituent[4]. The oxygen attachment to C-12 must, therefore, be equatorial and reference to these structures discloses that it must have the 12α-configuration[5] (4a or 5a)[6].



4a R_1= OAc, R_2= H
4b R_1= H, R_2= OAc
4c R_1= $O_3SC_6H_4Br$



5a R_1= OAc, R_2= H
5b R_1= H, R_2= OAc

The unsaturated alcohol B, after acetylation followed by OsO_4 hydroxylation, gave a 12-acetoxy-8,9-cis diol (B'), m.p. 123-124°, as the only product. An nmr spectrum of this product revealed the C-12 proton as a complex multiplet centered at δ5.45 whose broadness (W_H 17 Hz) was, contrary to expectation, likewise within the range characteristic of axial protons in such systems. These data present a conflict in interpretation by implying that products A' and B' have the same (α) configuration at C-12 whereas they derive from alcohols A and B which are epimeric at this center. We turned to the X-ray crystallographic method for structural clarification.

Alkaline hydrolysis of triol monacetate A' gave a triol , m.p. 218-219° which was treated, in pyridine with a small excess of p-bromobenzenesulfonyl chloride. The resulting monobrosylate, m.p. 92-93° from ether-hexane, was subjected to single crystal X-ray analysis *and found to have structure* 4c. Brosylate 4c crystallizes in the triclinic system, space group *P*1, with a=6.75, b=8.22, c=13.75Å, α=107.3, β=80.0, γ=128.7°, *D*m=1.47g.cm.$^{-3}$, *Z*=1, *D*c=1.47g.cm.$^{-3}$. The structure

was solved by the heavy-atom method and refined (anisotropic Br, isotropic S,C,O) by full-matrix least squares calculations. Anomalous dispersion corrections have been included in the structure-factor calculations for which the present *R* is 0.122 over 1913 independent observed reflections. Based on the brosylate structure 4c, the triol monoacetate A' may be assigned structure 4a and its precursor, *the major ketone reduction product* A, *is identified as the 12a-alcohol* 3b. The minor reduction product B is, then, the 12 β-alcohol 3c. (Osmium tetroxide product B' is presumed to have structure 4b; ring distortion due to severe crowding of the β-side of 4b could account for its unexpected 12α-proton spectrum.)

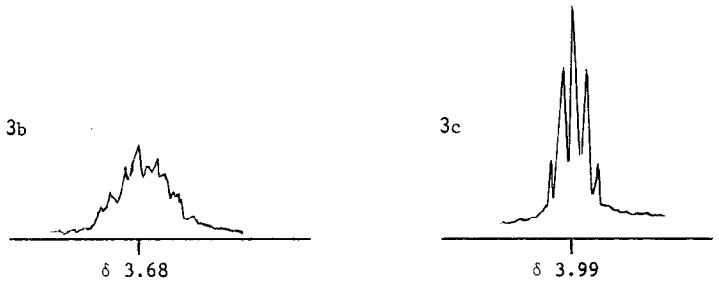
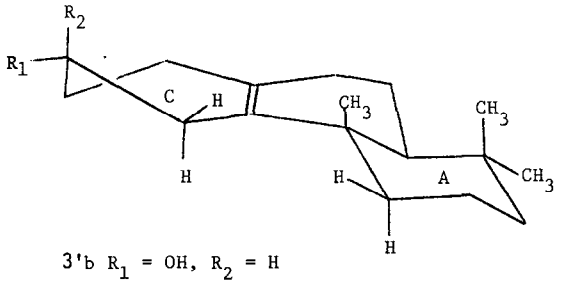


Figure 1. NMR Spectra of Podocarp-8-en-12-ols 3b and 3c in the C-12 Proton Region

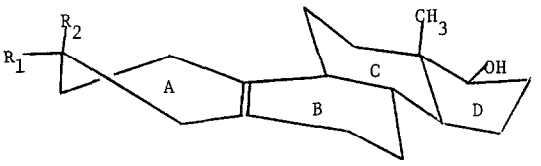
Having established the C-12 configurations of alcohols 3b and 3c, we may now consider those aspects of their nmr spectra which are of conformational significance. The 12β-proton of alcohol 3b appears as a complex multiplet centered at δ3.68 whose broadness (W_H 20 Hz) betokens it axial orientation. On the other hand, the C-12 proton of the epimeric alcohol 3c presents a closely spaced (4 Hz) apparent quintet centered at δ3.99. The narrowness of this band and its appearance at lower field point to an equatorial orientation of the 12α-proton in alcohol 3c. Alcohols 3b and 3c may then be represented by stereostructures 3'b and 3'c in which ring C is shown in the preferred half-chair conformation. This conformation is exactly analogous to that preferred in ring A of the 5(10)-estrene series, with C-3 of the latter case corresponding to C-12 of the former (cf. 3'b,3'c and 7a,7b). The close correspondence of molecular rotation differences between these two series (Table 1) provides further support for these conclusions.

Table 1. Molecular Rotations in the 8-Podocarpene and 5(10)-Estrene Series

Compound	OH Orientation	M	ΔM
Podocarp-8-en-12α-ol(3'b)	equatorial	+564	223
Podocarp-8-en-12β-ol(3'c)	axial	+341	
Estr-5-ene-3α,17β-diol(7a)	equatorial	+514	204
Estr-5-ene-3β,17β-diol(7b)	axial	+310	



3'b R_1 = OH, R_2 = H
3'c R_1 = H, R_2 = OH



7a R_1 = OH, R_2 = H
7b R_1 = H, R_2 = OH

Measurements on a Dreiding model reveal that the half-chair ring C form shown in 3'b and 3'c is free of any serious non-bonded interactions. The enantiomeric ring C conformation, however, places the equatorial 11α- and equatorial 1β-hydrogen substituents at 1.8Å internuclear distance. A destabilizing interaction of the same magnitude (within errors of measurement) is found[1] for the unstable half-chair ring A conformation of the steroid series. However, the extent of conformational preference in the steroid case is somewhat greater than that in the 8-podocarpenes based on the relative stereoselectivity of reduction of ketones 1c[1] and 3a[7].

The 8-podocarpene ring system is probably simpler than the 5(10)-estrene system for the purpose of *a priori* calculation of equilibrium geometry and we hope that these results will stimulate such efforts.

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REFERENCES AND FOOTNOTES

1. See S.G. Levine and N.H. Eudy, *J. Org. Chem.*, 35, 549 (1970) and references therein.

2. N. Cohen, *Tetrahedron*, 27, 789 (1971).

3. E. Wenkert, V.I. Stenberg, and P. Beak, *J. Amer. Chem. Soc.*, 83, 2320 (1961).

4. L.M. Jackman and S. Sternhell, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Second Edition, *Pergamon Press*, Oxford, p.288.

5. The side of the molecule carrying the angular methyl group is defined as "β", the opposite side "α".

6. It is assumed that rings are in the chair form.

7. The use and limitations of this criterion of conformational integrity are discussed in Reference 2.