

Regio- and Stereoselectivity in Metal Hydride Reduction of the Diels–Alder Adduct of Ergosteryl Acetate and Maleic Anhydride

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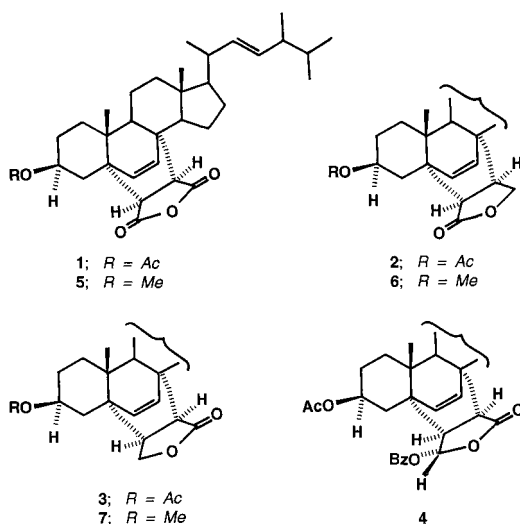
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Received October 17, 1997

Some years ago^{1,2} we investigated reactions of derivatives of the Inhoffen adduct **1**³ of ergosteryl acetate and maleic anhydride with metal hydride reducing agents, with a view to predicting which of the two possible lactones would be formed in such anhydride reductions. Compound **1** with lithium aluminum hydride/THF at -55



°C or sodium borohydride/dioxane at 95 °C gave only one lactone, to which structure **2** was assigned, mainly on the basis of shielding effects observed in 100 MHz ¹H NMR spectra.

Recently Anastasia and co-workers⁴ have proposed on the basis of 1D and 2D NMR at 500 MHz that this reduction product is **3**. To corroborate this revision and to shed light on the reduction mechanism, we have investigated the X-ray structure of the lactol (as its derived benzoate¹) formed by treatment of **1** with lithium aluminum tri-*tert*-butoxy hydride/THF. This compound has been related to the above-mentioned lactone by further reduction.¹ We have now shown the lactol benzoate to have structure **4**. This confirms the structure revision proposed by Anastasia and necessitates a modification of the reduction mechanism we proposed previously.^{1,2}

Several factors are believed to influence the course of metal hydride reductions of cyclic anhydrides. Chiefly, they are the relative reactivity of each carbonyl, steric

hindrance at carbonyl substituents, a directional approach of hydride to the carbonyl, an antiperiplanar effect when the anhydride ring is flexible, and the nature of the counterion of the hydride reagent.^{5,6}

The Inhoffen adduct **1** is highly rigid. The two carbonyls are similar in steric environment, although the 15-CH₂ group is a little nearer to one carbonyl than the 4-CH₂ is to the other (cf. ref 4).

Our earlier work^{1,2} revealed the important effects of 3-substituents and the counterion on regioselectivity. With the 3-methyl ether analogue **5**, sodium borohydride/dioxane at 95 °C gave lactones **6** and **7** in roughly equal amounts; with lithium aluminum hydride/THF at -55 °C the ratio of **6** to **7** was 1:13, and with sodium aluminum hydride/THF at -55 °C it was 1:10.² These data suggest that the acetoxy group in **1** directs hydride, possibly via a complex involving solvent and a counterion, completely to the carbonyl nearer ring-A. The methoxy group in **5** has a lesser directing effect with sodium borohydride but a significant one with lithium and sodium aluminum hydrides.

With regard to stereoselectivity, NMR data on lactols from the earlier work,^{1,2} together with the lactol configuration in structure **4**, suggest that in all these reductions the hydride may approach from the β -face of the anhydride ring, on the same side as the etheno bridge. This is consistent with involvement of the β -oriented 3-oxygenated substituents in the hydride-delivering complexes, although epimerization at the lactol chiral center during workup of the reactions cannot be ruled out.

Experimental Section

Data were collected on a Siemens SMART diffractometer with a CCD area detector. The data collection covered a nominal sphere of reciprocal space by a combination of four sets of exposures. Crystal decay was monitored by repeating the initial frames at the end of data collection and analyzing duplicate reflections; no evidence of decay was found. Unit cell parameters were obtained by least-squares fit to all data with $I > 10\sigma(I)$. The data were corrected for Lorentz and polarization factors and no absorption correction was considered necessary. The 34 092 measured reflections were averaged to give 7551 unique reflections ($R_{\text{int}} = 0.053$) of which 4773 had $I > 2\sigma(I)$ and were considered observed.

The structure was solved by direct methods⁷ and refined by full-matrix least-squares⁸ fit on F^2 . All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed geometrically and refined with a riding model (including free rotation for methyl groups) with U_{iso} greater than U_{eq} of the carrier atom (50% for methyl groups). Refinement converged to conventional $R = 0.0585$ for the observed data.

Supporting Information Available: X-ray structural data for compound **4** including summaries of crystallographic parameters and bond lengths and angles (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9719230

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