Tetrahedron Letters, Vol.32, No.26, pp 3127-3130, 1991 Printed in Great Britain

TRICYCLO[5.2.1.0^{2,6}]DECADIENONE EPOXIDES: RIGID, HIGHLY CONGESTED α , β -EPOXYCYCLOPENTANONES WITH DISTINCTIVE CHEMICAL BEHAVIOR.

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<u>Abstract</u>: Tricyclodecadienone epoxides $\underline{5}$ do not form an enolate on treatment with lithium diisopropyl amide, but instead undergo an unusual stereoselective β -hydride transfer leading to alcohols $\underline{6}$. The same type of epoxy endo-alcohol was obtained from parent epoxy ketone $\underline{5}$ on reaction with metal hydrides and organolithium reagents. These alcohols readily undergo an intramolecular epoxide migration by a Payne-type rearrangement, to give endo-epoxides $\underline{9}$.

Tricyclo[5.2.1.0^{2,6}]decadienones $\underline{1}$ are synthetic equivalents of cyclopentadienones and as such serve as synthons for cyclopentanoid natural products¹. Regio- and stereoselective epoxidation of the enone moiety in $\underline{1}$, using hydrogen peroxide in alkaline medium, conveniently leads to tricyclic α,β -epoxy cyclopentanones $\underline{2}$. These



epoxides have successfully been applied for the synthesis of both *trans*- and *cis*-4,5-dihydroxy-2-cyclopentenones². In order to extend the use of these tricyclic α,β -epoxyketones for the synthesis of cyclopentanoids, we studied their possible angular substitution and their chemical reactivity towards metallic hydrides and organolithium reagents.

In recent papers³, we showed that angular functionalization of tricyclic ester $\underline{3}$ is conveniently achieved using lithiumdiisopropyl amide in THF to form enolate $\underline{4}$. Quenching this enolate with appropriate electrophiles afforded α '-alkyltricyclodecadienones and bridged oxapropellanes, which turned out to be suitable precursors for 2-alkyl-3-carboethoxycyclopentadienones and sarkomycins⁴.

Treatment of tricyclic epoxide $\underline{5a}$ with lithiumdiisopropyl amide in THF at -78 °C and subsequent quenching with methyl iodide, however, did not produce the expected α '-methylated product. Instead, complete reduction of the ketone function was observed, affording a single alcohol in 80% yield. The same alcohol was obtained when water was used as quenching agent instead of methyl iodide. In order to secure the structure of this alcohol unequivocally, it was acylated with acetic anhydride in pyridine and the crystalline acetate was subjected to an X-ray diffraction analysis⁵. This analysis showed that the acetate has structure <u>7a</u> and therefore its precursor must have structure <u>6a</u> (Scheme I). When parent tricyclic epoxide <u>5b</u> was treated with LDA in the same way as <u>5a</u>, reduction of the ketone function, producing <u>6b</u> in 60% yield, was again the only reaction observed. No products suggesting the formation of enolate <u>8</u>, were observed.

Scheme I



Since enone $\underline{3}$ only leads to enolate $\underline{4}$ and does not give any reduction product on treatment with LDA, it is suggested that in epoxy ketones $\underline{5}$ such an enolate formation by LDA is apparently strongly disfavored and the alternative, *viz.* a reduction, is preferred. Molecular modeling⁶ showed that deprotonation of enone $\underline{2}$ is indeed sterically more favorable than that of epoxyketones $\underline{5}$. The *exo*-epoxide function together with the C₁₀-methylene bridge severely hinder the approach of LDA needed to abstract the bridgehead α '-proton in either $\underline{5a}$ or $\underline{5b}$. In addition to these steric considerations, the thermodynamic stability of the produced enolates may also be of importance. The formation of enolate $\underline{4}$ is probably considerably more favored than epoxy enolate $\underline{8}$, which lacks the conjugative stabilization present in $\underline{4}$.

The reduction of ketones by lithium diisopropyl amide has only scarcely been mentioned in the literature. It has been reported for aromatic ketones without enolizable α -hydrogens⁷, for enolizable α -halo- and alkoxy ketones⁸ and 3-alkyl substituted norbornan-2-ones⁹. Mechanistically, the stereoselective formation of *endo*-alcohols <u>6</u> in the reaction of epoxyketones <u>5</u> with LDA can be rationalized by invoking a stereospecific hydride shift from one of the isopropyl groups of LDA to the carbonyl group of <u>5</u> (Fig. 1). This hydride transfer takes place selectively



R= H, CO₂Et

at the convex side of 5. The rigid endo-tricyclic skeleton of 5 considerably hampers hydride transfer at its concave face apparently much more than the eclipsed exo-epoxide function at the convex side.

This β -hydride transfer process may energetically be more favorable than the competing enolization of $\underline{5}$. Therefore, deprotonation was also attempted with N-lithium-2,2,6,6-tetramethylpiperide (LTMP), a similar strong base as LDA, but lacking the ability of β -hydride transfer. However, under a variety of conditions again no enolization of $\underline{6}$ could be accomplished. As expected, no reduction of the ketone function was observed either.

The reduction of epoxyketones $\underline{5}$ to epoxy alcohols $\underline{6}$ was also studied with the hydride reagents NaBH₄ en LiAlH₄¹⁰. In conjunction herewith, the reaction of $\underline{5}$ with RLi reagents was also investigated in order to evaluate further the steric and electronic implications of the *exo*-epoxide function on the chemistry of the adjacent ketone function in $\underline{5}$.

Epoxyketones 5a and 5b reacted smoothly with NaBH₄ in THF at 0 °C affording *endo*-alcohols <u>6a</u> and <u>6b</u>, respectively, in nearly quantitative yields and with complete stereoselectivity. The epimeric exo-alcohols were not detected. Interestingly, when the reduction of <u>5b</u> was conducted for a longer period than strictly needed to complete the reduction, an isomeric epoxy alcohol was slowly formed. Prolonged reaction times showed this conversion to be an equilibrium with a molar ratio of 5:1 with <u>6b</u> as the major component. Approximately the same ratio was observed when epoxy ketone <u>5b</u> was treated with LiAlH₄ in ether at 0 °C for 24 hrs. Spectral data reveal that the newly formed epoxy alcohol has the inverted epoxide structure <u>9a</u> (Scheme II). Analogous results

Scheme II



were obtained when 5b was treated with methyllithium in THF at room temperature for one hr. A mixture of alcohols 8b and 9b (ratio 6:1) was obtained in nearly quantitative yield. The use of more bulky alkyllithium compounds led to an increased yield of the inverted epoxide 2 (Scheme II). In case of *t*-butyllithium, the initially formed epoxy alcohol 8e had been completely transformed into 2e after one hr of reaction only. The addition of phenyllithium afforded only a relatively small amount of inverted epoxide 2f under identical conditions. In all cases the epoxides could be separated by flash column chromatography on silica (n-hexane/ethyl acetate).

The formation of epoxy alcohols 9 can be readily explained by invoking an intramolecular epoxide opening by



the initially formed endo-alkoxide anion (Scheme III). Such an epoxide migration reaction or Payne's

rearrangement¹¹, is well known for acyclic epoxy alcohols but has not yet been described for α , β -epoxycyclopentanols. The product ratio is controlled by the relative thermodynamic stabilities of the two epoxides. Both steric and electronic effects are involved. Due to the apparent inability of the nucleophiles to attack from the endo-face of the carbonyl function in epoxy ketone 5b, exclusive endo-alcoholates 10 are formed which possess the newly introduced R at the unfavorable eclipsed position with respect to the epoxide ring. An increased bulkiness of R will shift the equilibrium towards the inverted epoxy alcoholate 11. Molecular mechanics (MM2) calculations indeed show alcohols 9 to be sterically more stable than 8. The formation of epoxy alcoholate 11 is also electronically favored (for $R \neq H$) as a secondary alcoholate is generally more stable than a tertiary one.

The formation of inverted epoxy alcohols 9 offers interesting synthetic prospects, because its epoxide function may now be readily and stereoselectively opened by appropriate nucleophiles. Thermal cycloreversion then leads to functionalized cyclopentenoids which are of interest for natural product synthesis. An application concerning the synthesis of the marine prostanoids clavulones I and II is reported in the accompanying paper¹².

Acknowledgement. This investigation was supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

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(Received in UK 3 April 1991)