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REMOTE ELECTRONIC CONTROL IN THE $LiAlH_4$ REDUCTION OF TRICYCLIC p-TOLYLSULFONYLMETHYL ENONES

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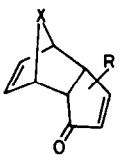
Abstract: The $LiAlH_4$ reduction of 4-p-tolylsulfonylmethyl-oxatricyclo[5.2.1.$0^{2,6}$]decadienones 3 *and* 8 *leads regioselectively and stereospecifically to exo-methylene tricyclodecenols* 6 *and* 11. *The sulfone function is essential for this bis-hydride reduction process. Flash vacuum thermolysis of* 6 *and* 11 *affords quantitatively the exo-methylene cyclopentenols* 13 *and* 14.

Tricyclic enones 1 (X= CH_2,O) allow the stereo- and enantioselective synthesis of a variety of potentially valuable cyclopentenoids[1]. The strategy underlying these syntheses involves stereocontrolled transformations in the annelated cyclopentenone ring of 1, followed by thermal [4+2] cycloreversion utilizing the flash vacuum thermolysis technique. In a recent paper we showed that the oxatricyclodecadienone system 1 (X=O) is particularly suited for the synthesis of *thermally labile* cyclopentenones such as cyclopentadienone epoxides 2[2]. Key structure in the route to 2 is sulfone 3, which is readily available from the Diels-Alder adduct of furan and cyclopentene-1,3-dione, by a modified Mannich reaction using paraformaldehyde and p-toluenesulfinate[2].



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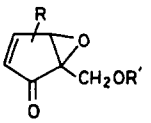

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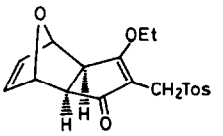

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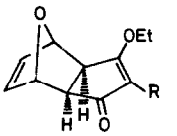


4 R = CH_2OR', CH_2SR'
5 R = H

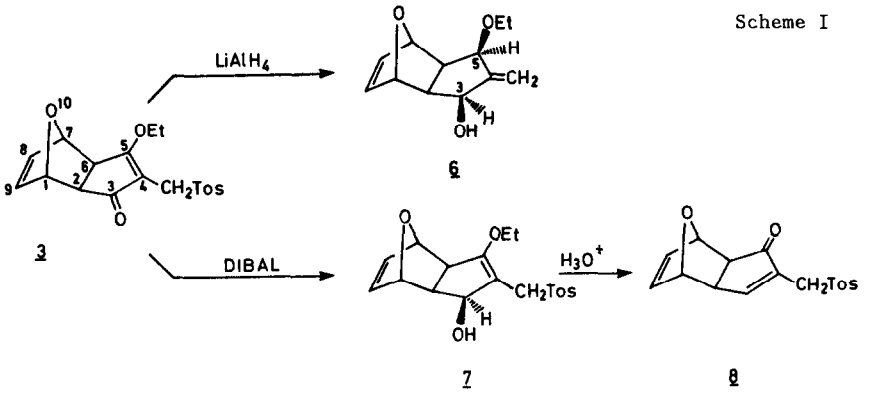
The versatility of this sulfone as a synthon is primarily due to its unique behaviour towards nucleophiles. Upon treatment with alkoxides and thiolates, it undergoes a rapid and efficient displacement of the p-tolylsulfonyl function to form the corresponding tricyclic ethers and thioethers 4, which are essential intermediates in the route to *epi*-pentenomycins[2]. In this communication, we will show that the unique structural moiety consisting of an α,β-enone function with a p-tolylsulfonylmethyl group at the α-position, is responsible for the exceptional behaviour of sulfone 3 during the reduction with $LiAlH_4$.

Complex metal hydride reduction of β-alkoxy enones to the corresponding enones is a well documented process which usually proceeds with high efficiency[3]. The first step involves reduction of the ketone function to produce the corresponding γ-hydroxy enol

ether which on hydrolysis yields the enone. This last reaction is often very fast and the intermediate alcohol is seldom intercepted. The $LiAlH_4$-reduction of the 'parent' tricyclic β-ethoxy enone 5 conforms entirely to this pattern and leads to the corresponding enone 1 (X= O)[4].

Sulfone 3 gave upon treatment with $LiAlH_4$ in THF/Et_2O (3:2) a single crystalline product in a yield of 70% (m.p. 132-134°, from ethylacetate/hexane (1:5)). The IR spectrum showed an OH-absorption at 3355 cm^{-1} but no C=O absorption, indicating complete reduction of the C_3-carbonyl function. The ^1H-NMR spectrum[5] revealed the absence of the p-tosyl group and a β-enone proton. The spectral data strongly suggested the formation of *exo*-methylene-tricyclodecenol 6 (Scheme I).

Scheme I



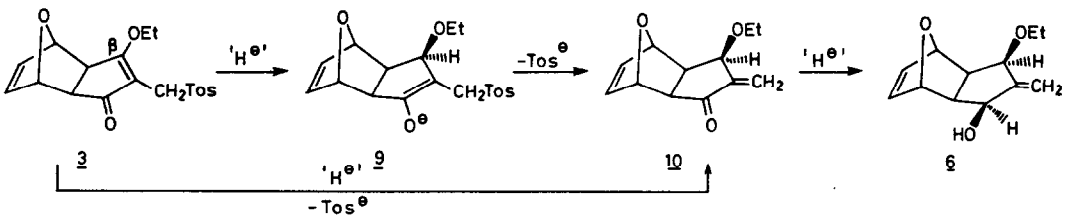
The stereochemistry around C_3 and C_5 could not be assigned unambiguously on the basis of the spectral features. Therefore, an X-ray diffraction analysis was performed[6], establishing the stereochemistry of 6 to be *syn* with respect to the 10-oxa bridge for the hydroxy as well as for the ethoxy group. This unequivocal elucidation of structure 6 proves that steric factors are decisive in determining the stereochemistry of this bis-hydride reduction process. The conceivable involvement of the 10-oxa bridge in the complexation of $LiAlH_4$ would have favoured hydride attack from the *endo*-face of the tricyclic system[7] and consequently would have led to the *anti*-isomer of 6.

The nature of the complex metal hydride appeared to be of importance for the course of the reduction. When $(i\text{-}Bu)_2AlH$ (DIBAL) was used instead of $LiAlH_4$, sulfone 3 was smoothly transformed into enone 8 (yield 90%)(Scheme I). Here, no reductive expulsion of the sulfone function was observed at all. By applying alkaline work-up conditions, alcohol 7 was isolated. This proves that the actual product of the DIBAL reduction of 3 is 7, resulting from a 1,2-hydride addition to the C_3-carbonyl function.

In order to rationalize the formation of 6 from 3 upon reduction with $LiAlH_4$, initial hydride attack at either the C_3-carbonyl function or the electrophilic C_5-position can be envisaged. 1,2-Hydride addition to the ketone function seemed most plausible in view of the normal behaviour of β-alkoxy enones[3] and will lead to the alcoholate of 7. In order to produce the exo-methylene alcohol 6, 7 should undergo a subsequent hydride substitution at the electrophilic C_5-position under the expulsion of the tosyl group (SN_2'-process). To subject this mechanism to testing, alcohol 7, which was isolated from the DIBAL reduction of 3 (see Scheme I), was treated with $LiAlH_4$. However, much to our surprise, no reaction was observed at all and the starting alcohol was recovered in almost quantitative yield. This result indicates that the first step in the $LiAlH_4$ reduc-

tion of 3 does *not* involve carbonyl reduction but conjugate hydride attack at the C_5-position instead. This β-attack leads to methylene ketone 10 by expulsion of the tosyl group either via an SN_2'-reaction or via a conjugate addition/elimination process involving 9 (Scheme II).

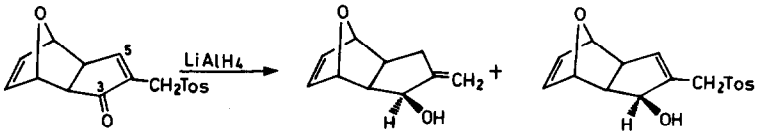
Scheme II



The formation of alcohol 6 must, therefore, proceed by an ultimate regiospecific 1,2-hydride addition to enone 10[8]. Evidence for the correctness of this mechanistic course was attained from the $LiAlH_4$ reduction of enone 10, which could be prepared by MnO_2 oxidation of alcohol 6. Under conditions identical to the reduction of sulfone 3, enone 10 was converted regiospecifically and quantitatively into alcohol 6.

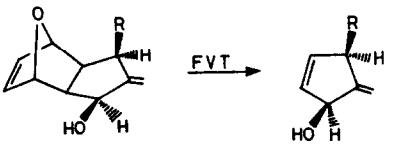
In contrast to sulfone 3, the alkoxy methyl analogues 4 behave according to the general pattern and undergo exclusively 1,2-addition to the carbonyl function upon treatment with $LiAlH_4$. This result suggests that the remarkable preference of $LiAlH_4$ to add at the C_5-position of sulfone 3 is most likely attributable to the presence of the sulfonyl group at the β'-position. Being a strong electron withdrawing substituent, it causes the electron deficiency at C_5 to be much more pronounced than in the corresponding β'-alkoxy enones 4. This remote electronic effect is apparently sufficiently large to change the regiochemical course of the $LiAlH_4$ reduction completely. Regio-electronic control is also observed in the $LiAlH_4$ reduction of sulfone 8, however less pronounced (Scheme III). Here, the bis-hydride reduction product 11, was isolated along with a minor amount of the 1,2-reduction product 12 (yields 80 and 20%, respectively). Apparently, when the alkoxy group at C_5 is lacking, hydride attack at this position and at the carbonyl function become competitive.

Scheme III



With an efficient, stereospecific route to 6 and 11 at hand, their thermal cycloreversion to the corresponding *exo*-methylene cyclopentenols 13 and 14 was considered (scheme IV). The flash vacuum thermolysis of both 6 and 11 was complete at $400^0/2x10^{-2}$ torr and afforded 13 and 14 respectively, as colourless oils in almost quantitative yield. Their spectral data unequivocally confirmed their structures[9].

Scheme IV



6 R = OEt 13
11 R = H 14

In conclusion, the unprecedented course of the $LiAlH_4$ reduction of 3 provides an interesting entry to the hitherto unknown class of alkylidene cyclopentenols. Oxidation of these alcohols may lead to functionalized *exo*-methylene cyclopentenones, which may serve as precursors for prostanoid natural products such as clavulones and punaglandins[10].

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