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SULFONE MEDIATED SYNTHESIS OF CYCLOPENTADIENONE EPOXIDES FROM 10-OXATRICYCLO[5.2.1.$0^{2,6}$]DECADIENONES. A CONVENIENT ROUTE TO epi-PENTENOMYCINS

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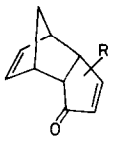
Abstract: Sulfonylmethylation of 10-oxatricyclodecadienone 6 *leads to sulfone* 4 *which forms the key intermediate in the synthesis of 5-alkoxymethylcyclopentadienone epoxides* 5. *Acid catalyzed hydrolysis of* 5 *followed by acylation affords epi-pentenomycin derivatives* 15

Tricyclo[5.2.1.$0^{2,6}$]decadienones 1 have great potential as synthetic equivalents of cyclopentadienone and serve as building blocks in cyclopentanoid natural product synthesis. *E.g.*, stereoselective chemical transformation of the enone moiety in 1, followed by thermal cycloreversion, produces functionalized cyclopentenones. Based on this strategy we recently reported the total synthesis of (±)terrein[1] and (±)pentenomycin[2]. Key intermediates in these syntheses are tricyclodecadienone epoxides 2 which are readily obtained from 1 by nucleophilic epoxidation.



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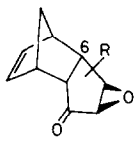

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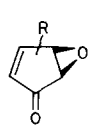

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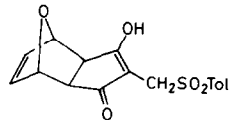

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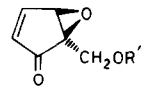
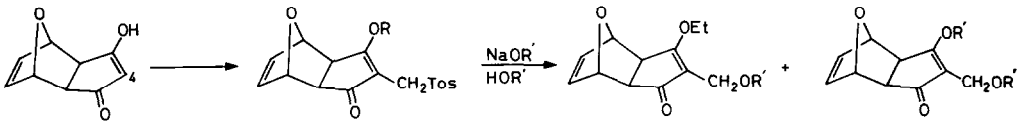


5

Thermal cycloreversion of these tricyclic epoxides applying flash vacuum thermolysis, generates cyclopentadienone epoxides 3, which, however, can only be isolated as such, if the temperature, required for efficient cycloreversion, is sufficiently low to prevent their thermal rearrangement to the corresponding α-pyrones[3]. The scope of this approach turned out to be limited to tricyclodecadienone epoxides 2 which possess a π-containing functionality R at C_6 (*e.g.* R: CH=O, CO_2Et or $C{=}CCH_3$)[3]. This severe limitation prompted us to explore synthetic routes to the 10-oxa-analogues of 1 and 2. These furan derived Diels-Alder adducts will presumably allow [4+2] cycloreversions at lower temperatures[4] and hence offer a more general route to functionalized cyclopentadienone epoxides. In this communication we wish to report on the synthesis of oxatricyclodecadienone sulfone 4 and its ultimate transformation into 5-alkoxymethyl cyclopentadienone epoxides 5. These latter structures serve as precursors for *epi*- pentenomycin analogues 15.

The 10-oxatricyclodecadienone system can readily be prepared by a Diels-Alder reaction of furan and cyclopentene-3,5-dione[4]. A single adduct 6 is formed which is completely enolic and possesses the *exo*- configuration. This structure is ideally suited for functionalization of the active methylene position at C_4. With the object to eventually synthesize *epi*- pentenomycins, the introduction of a hydroxymethyl function at this position was investigated. Direct hydroxymethylation of 6 using formaldehyde failed and led to minor amounts of polar products, which according to ^{1}H-NMR, did not contain any of the desired hydroxymethyl alcohol. A more successful result was achieved by utilizing a modification of Hellmann's method for the β-sulfonylmethylation of 1,3-diketones[5]. Treatment of 6 with sodium p-toluene sulfinate and paraformaldehyde in glacial acetic acid/DMF at room temperature afforded sulfone 4 which precipitated from the reaction mixture (yield 85%; Scheme I).

Scheme I



6 — 4 R=H, 7 R=Et — 8 R'= Me,Et,i-Pr,t-Bu — 9

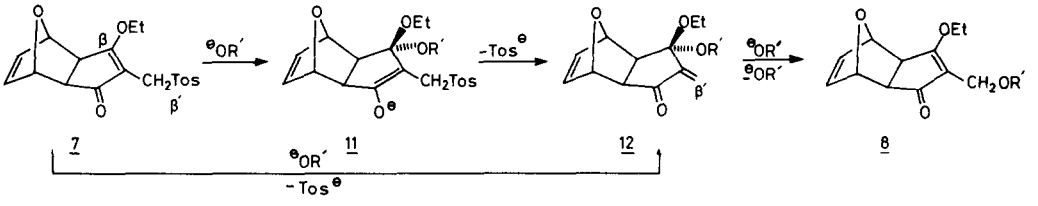
The poorly soluble sulfone was converted into a more convenient material by reacting it with Meerwein's reagent to give the crystalline enolether 7 (m.p. 170- 172 °C, yield 90%). This multiply functionalized compound turned out to be a synthetically promising species as the tolylsulfonyl function can be readily replaced by other heteroatom containing groups.

Heating 7 in EtOH with 1.2 equivalent of NaOEt for 10 min. under reflux gave diethoxy ether 8 (R'= Et) in almost quantitative yield. When NaOMe in MeOH was used under identical conditions ethoxymethoxy ether 8 (R'= Me) was obtained also in high yield. Longer reaction times produced mixtures of 8 (R'= Me) and the bismethoxy ether 9 (R'= Me). The latter ether was isolated as the only product after 15 hrs of heating under reflux, but in considerably lower yield (60%)[6]. Similar behavior was observed for other alcohols *i.e.* iso-propyl and t-butyl alcohol. Thiols *e.g.* benzylthiol and thiophenol also reacted smoothly with sulfone 7 to give the corresponding thioethers in excellent yields.

For the sulfone displacement in 7 two pathways can be envisaged, *viz.* conjugate addition/elimination and vinylogeous substitution (Sn_2')[7]. Initial β-attack of the nucleophile on sulfone 7 will occur exclusively from the sterically less hindered *exo*-side[8] leading either to enolate anion 11 (β-addition product) or directly to methylene ketone 12 (SN_2' process)(Scheme II). In case of initial formation of 11, subsequent β'-elimination also leads to 12. As under the applied reaction conditions, the enone 12 could not be detected, it will have a very short lifetime and will rapidly react with a second nucleophile at the β'-position to form eventually enolether 8 under the expulsion of the *exo*-β-substituent introduced at the outset. This second transformation can again be envisaged either as a conjugate addition followed by elimination or as a SN_2'-type substitution. The high stereoselectivity observed in the expulsion of the *exo*-β-alkoxy

group when applying relatively short reaction times, indicates the SN_2' reaction to be the most important one.

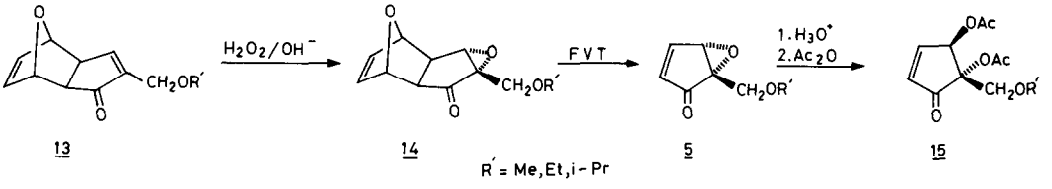
Scheme II



The nature of the β'-function strongly effects the course of this nucleophilic process. Whereas replacement of the β'-tosyl group is almost instantaneous, treatment of bis-methoxy ether 9 (R'=Me) under identical conditions with NaOEt in EtOH, only showed a relatively slow exchange of the β'-methoxy group. Even by applying extended reaction times (heating for 2 days) substitution of the β'-methoxy group could only partly be accomplished. Studies to further unravel the mechanism of the nucleophilic transformation in the uniquely functionalized tricyclic system 7 are currently under way[10].

Enol ethers 8 were subjected to hydride reduction, in order to remove the enolic ether function. With DIBAL in hexane, a regioselective reduction led to the expected enones 13 (R'= Me; Et; i-Pr) in 90% overall yields[11](Scheme III).

Scheme III



Alkaline epoxidation of these enones with H_2O_2 led to the corresponding epoxides 14 in almost quantitative yield. ^{1}H-NMR analysis of these tricyclic epoxides established the predicted *exo* -configuration of the epoxide ring[3]. Thermal cycloreversion of tricyclic epoxides 14, using flash vacuum thermolysis, proceeds at considerably lower temperatures than for 2. At temperatures as low as 330 °C complete cycloreversion of 14 (R'= Me; Et; i-Pr) was observed and the cyclopentadiene epoxides 5 could be isolated in almost quantitative yield. At this temperature no α-pyrones were detected at all. Cyclopentadienone epoxides 5 were unequivocally characterized by their IR and ^{1}H-NMR spectra. Typically, the ^{1}H-NMR (CCl_4) spectrum of 5 (R'= CH_3) displays a doublet of doublets (JH_3H_2=6 Hz; JH_3H_4=1.5 Hz) at δ7.52 for β-proton H_3, a doublet of doublets (JH_2H_3=6 Hz; JH_2H_4=2.3 Hz) at δ5.96 for α-proton H_2, a narrow multiplet at δ3.97 for H_4, AB-doublets at δ4.04 and 3.61 (J=11.4 Hz) for the diastereotopic methylene protons and a singlet at δ3.33 ppm for the methoxy group.

This efficient synthesis of alkoxymethyl cyclopentadienone epoxides **5** (overall yields from **6** are > 65%) shows the potential of the 10-oxatricylodecadienone system as a synthetic equivalent for cyclopentadienones.

The applicability of 4-alkoxymethyl cyclopentadienone epoxides **5** in natural product synthesis is demonstrated by their conversion into acylated alkyl *epi*- pentenomycin derivatives **15** by acid catalyzed hydrolysis followed by acylation[12]. The moderate yields (25-30%) observed for this epoxide ring opening reaction are attributable to the reactive nature of these cyclopentenones.

NOTES AND REFERENCES

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5. H. Hellmann and K. Mueller, Chem. Ber. **88**, 638 (1965).
6. It is very likely that under the basic conditions applied, β-elimination of the 10-oxabridge becomes competitive, *cf.* F. Brion, Tetrahedron Lett., **1982**, 5299.
7. Direct SN_2-type replacement of the sulfone function is sterically and electronically excluded[8].
8. See J. Strating in 'Organic Sulfur Compounds I', p. 146-153; Ed. by N. Kharash, NY (1961); F.G. Bordwell and G.D. Cooper, J. Amer. Chem. Soc., **73**, 5184 (1951).
9. We found that the alkaline epoxidation of *exo*- tricyclodecadienones **1** [3] and *exo*-oxatricyclodecadienone **13** *(vide infra)* both proceed with complete *exo*- stereoselectivity.
10. Related processes are the 1,4-conjugate addition to β-functionalized enones and the bis-β,β'-1,4-conjugate addition to β'-functionalized enones; see for leading references on both processes: C.J. Kowalski and K.W. Fields, J. Org. Chem., **46**, 197 (1981) and A.B. Smith, III, B.A. Wexler, and J.S. Slade, Tetrahedron Letters **1980**, 3237.
11. The hydride reduction of enolether sulfone **7** using $LiAlH_4$ in THF deviated from the expected reaction pattern and did not lead to the anticipated enone. Details on this interesting reaction will be reported in a forthcoming paper.
12. See for other approaches to *epi*- pentenomycins: T. Shono, Y. Matsumura, S. Yamnae and M. Suzuki, Chem. Lett. **1980**, 1619; A.B. Smith III, S.J. Branca, N.N. Pilla and M.A. Guaciaro, J. Org. Chem. **47**, 1855 (1982).

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