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ENANTIOSELECTIVE SYNTHESIS OF 3-DEMETHOXYARANCIAMYCINONE VIA ASYMMETRIC EPOXIDATION [1)]

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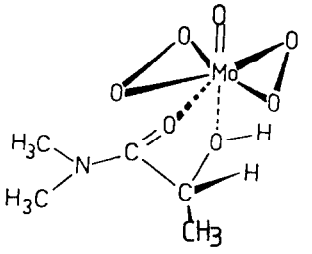
Abstract: The tetracyclic olefin 1 was enantioselectively epoxidized using a molybdenum(VI)-oxodiperoxo complex containing a chiral lactamide. Conversion to the glycosides 8 and 9 showed the epoxide 2 to be the predominant (3 : 1) enantiomer.

Relatively few methods for the enantioselective total synthesis of anthracyclinones are known, including asymmetric reductions[2)], microbial reduction[3)], asymmetric halolactonization[4)], Diels-Alder[5)] or mixed aldol reactions[6)], as well as asymmetric epoxidations[7,8)].

In connection with our synthesis of aranciamycinone[1,9)] we have considered the possibility to obtain this anthracyclinone in an enantiomerically enriched form using the established synthetic procedure[1,9)]. It should be very promising to employ the enantioselective epoxidation of the readily available prochiral intermediate 1. However, the olefin 1 lacks any allylic alcoholic functionality which is a prerequisite for the employment of the method of Sharpless[10)]. Only a few methods are available for the asymmetric epoxidation of nonfunctionalized olefins[11)]. One possibility is the stoichiometric reaction with optically active molybdenum(VI)-oxodiperoxo complexes[12)]. The molecular structure of such a complex containing (S)-dimethyl lactamide has been determined by X-ray analysis (figure I)[13)].



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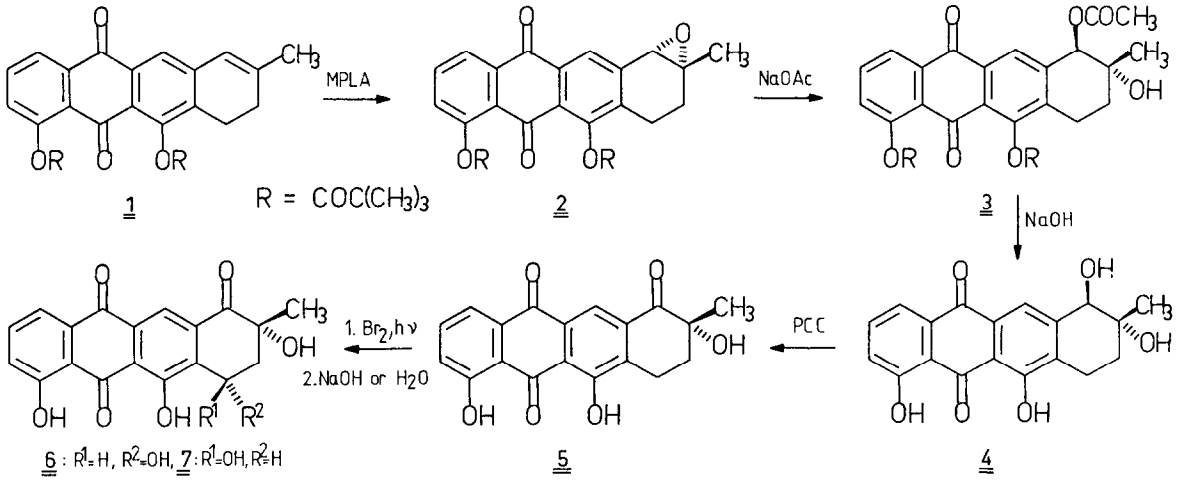
Two different mechanisms for the epoxidation with these transition metal complexes have been proposed[14,15], and various complexes with optically active bidentate ligands were tested for asymmetric epoxidations, the enantiomeric yields depending on the nature of the chiral ligand and the olefin[11b,12,16].

In our synthesis, olefin 1 was treated with diluted solutions (1 mmole in 300 mL of dichloromethane) of the molybdenum(VI)-oxodiperoxo complexes containing (S)-dimethyl lactamide, (S)-dimethylphenyl lactamide, (S)-N-acetylprolinol, (S)-N-benzoylprolinol, and (S)-piperidine lactamide (MPLA).

With the exception of the dimethyl lactamide (7 ± 3 % e.e.) and the piperidine lactamide complex (40 ± 3 % e.e.) only low asymmetric inductions were observed. Decreasing the temperature to 0° C raised the enantiomeric yield with the MPLA complex to 53 ± 3 % e.e.



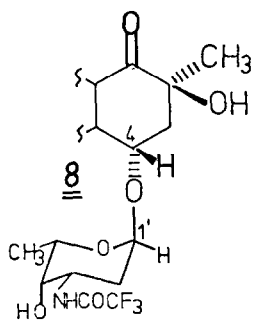
The enantiomeric excess was determined by ^{1}H NMR spectroscopy [addition of the chiral europium complex Eu(hfc)$_3$] employing the signals of the methyl group or H-1 of the oxiranering. In contrast to similar reactions in nitromethane[11b], no significant degradation of the epoxide was observed, and 2 could be isolated in 70-75 % chemical yield.

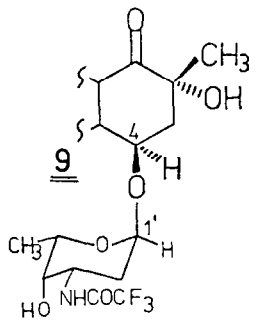
In order to establish the absolute configuration of the predominantely formed enantiomer (2 or ent-2)[17], the epoxide was transformed by an unequivocal sequence of reactions into the L-daunosamide glycosides 8 and 9 of 3-demethoxy-aranciamycinone 7. The absolute configurations of the glycosides 8 and 9 have previously been determined by comparison with the L-daunosamine glycoside of natural steffimycinone[18].

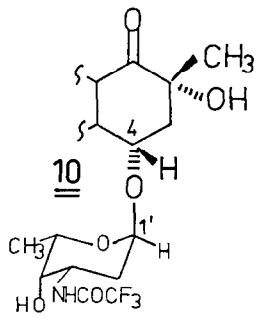
Thus, the mixture of enantiomeric epoxides 2 (76.5 %) and ent-2 (23.5 %) was treated with sodium acetate in acetic acid to afford a mixture of acetates 3 and ent-3 quantitatively. It is important to note, that the opening of the epoxide proceeds with absolute regio- and stereoselectivity. A nonregioselective ring opening would result in a subsequent loss of optical yield. In fact, the e.e. of about 50 % was preserved in the acetates as shown by ^{1}H NMR mea-

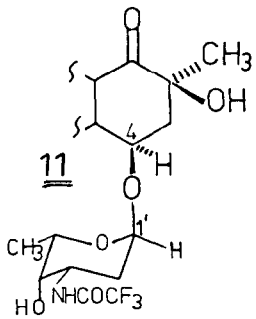
surements. Saponification of 3 and PCC oxidation of the trans-diol 4 were effected in 75 % yield to give the ketol 5 as previously described[9]. The benzylic hydroxy group was introduced via photolytic bromination. Solvolysis of the bromide with 0.25 N NaOH gave the 2,4-cis-diol 6 with 96 % d.e., whereas the 2,4-trans-diol 7 was the main product after treatment with water[1].

The trans-diols 7 and ent-7 (corresponding to the natural configuration of aranciamycinone) were subjected to glycosidation with trifluoroacetyl protected daunosamyl chloride as described for rac-7 [18]. The mixture of the α-L-glycosides was separated to yield 26 % of 8 and 74 % of 9. Thus, the 7(S), 8(R)-epoxide 2 was predominantely formed in the asymmetric epoxidation step and the 53 % e.e., as determined by ^{1}H NMR, was confirmed by the ratio of the products 8 and 9. Furthermore, the cis-diols 6 and ent-6 were converted to the diastereomeric glycosides 10 (72 %) and 11 (28 %). The glycosidation of the cis-diols shows that the (S)-lactamide complex used in our investigation leads to anthracyclinones of the natural absolute configuration (aranciamycinone and steffimycinone with inverted configuration at C-3 are rare exceptions [19]).









$[\alpha]_D^{25}$ = + 112.5 (C = 0.21 in $CHCl_3$) $[\alpha]_D^{25}$ = - 155.3 (C = 0.24 in $CHCl_3$) $[\alpha]_D^{25}$ = +72.9 (C=0.21 in $CHCl_3$) $[\alpha]_D^{25}$ = 79.2 (C=0.17 in $CHCl_3$)

Finally, the optical rotation of the glycosides 9 - 11 were measured, providing a third independent determination of the optical yield in the epoxidation step.

Further improvements of the enantiomeric yield, which already ranges among the highest found for nonfunctionalized olefins, as well as the extension to other types of anthracyclinones, is under investigation. One important advantage of the procedure described here is the fact, that no additional steps in various anthracyclinone syntheses via olefins are necessary. Instead of the 1:1-mixture of the achiral synthesis, a 3:1 mixture in favor of the biologically active anthracycline of natural configuration may be obtained.

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