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THE STRUCTURE OF THE ANTIBIOTIC HEDAMYCIN. IV. RELATIVE CONFIGURATIONS IN THE DIEPOXIDE SIDE CHAIN [1)]

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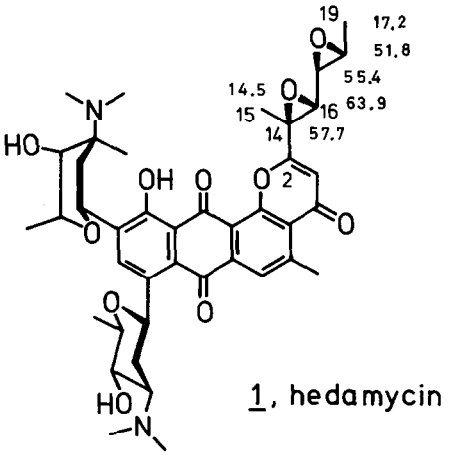
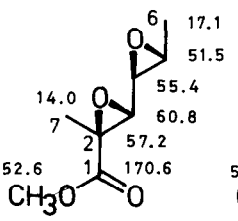
Summary: The relative configurations in the diepoxide side chain of the antibiotic hedamycin have been shown to be rel-(14R,16S,17R,18S).

The structure of the antibiotic hedamycin (1) has recently been elucidated in our laboratory. [2-4)] However, the relative configurations in the unique diepoxide side chain at C(2) could not yet be determined. We now wish to present evidence in support of the configurations shown in formula 1. *)

Several epoxidized methyl 2-methyl-2,4-hexadienoates were synthesized as model compounds for spectral comparisons. The esters 2, 3, and 4 were obtained by direct epoxidation of the parent diene 8 with m-chloroperbenzoic acid (MCPBA). After a short reaction period, 4 could be isolated; prolonged treatment with



1, hedamycin



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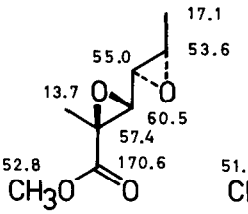
"O-cis"



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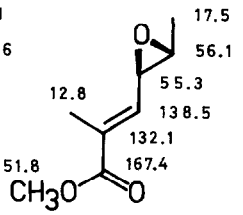
"O-trans"



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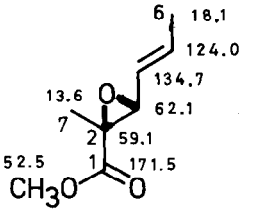
*) All compounds shown in the schemes are racemic, except 1.
Carbon chemical shifts are given in ppm downfield from internal TMS.

MCPBA in refluxing dichloromethane yielded a mixture of 2 and 3, which could be separated by chromatography on a florisil column. The compounds 5, 6, and 7, on the other hand, were prepared by Darzens condensations.



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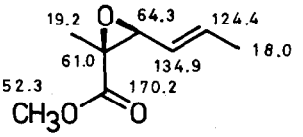

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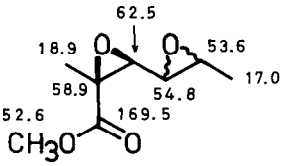

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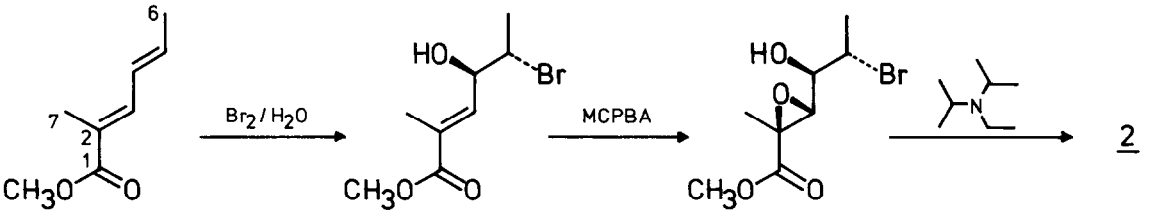
A comparison of the carbon chemical shifts of the methyl groups C(15) and C(19) in hedamycin (1) with the chemical shifts of C(7) and C(6) in the model compounds 2 - 7 clearly shows that both oxirane rings in hedamycin must be trans-substituted. [5] This is further corroborated by the coupling constants measured for the H-C(17) / H-C(18) interaction ($^3J_{HH}$ = 2.2 Hz [4]) and the C(15) / H-C(16) interaction ($^3J_{CH}$ = not observed, i.e. <1 Hz under the experimental conditions used). Both values are in the typical ranges for trans-H-H [6] and trans-C-H [7] couplings, respectively.

Yet, the relative positions of the two epoxide oxygen atoms still remain to be determined. The decision, whether these two oxygen atoms have formally been added from the same side of the s-trans-conformer of the parent diene ("O-cis"), or from different sides ("O-trans"), should be possible with the aid of the glycidic esters 2 and 3. The configurations of these two models were assigned on the basis of the following observations: (a) Heasley et al. recently reported [8] that the "O-cis"-isomers of epoxidized 2,4-hexadienes always had longer retention times than the corresponding "O-trans"-isomers on a 17% carbowax 20 M glc column. Under similar experimental conditions (3% carbowax 20 M, 170°), the ester 2 was eluted after 3 and was therefore assigned the "O-cis"-configuration. The retention indices for 2 and 3 were 1885 and 1858, respectively. On the same glc column, but at 90°, the two diepoxides obtained from the reaction of MCPBA with trans-trans-2,4-hexadiene had retention indices of 1335 ("O-cis"-compound 11) and 1298 ("O-trans"-compound 12). Hence, the retention index differences, which reflect the differences in configurations, are almost the same with compounds 2 and 3 as with 11 and 12, and thus further corroborate the configurational assignments made. (b) Addition of HOBr to methyl 2-methyl-2,4-hexadienoate (8) yielded the bromohydrin 9, which, upon epoxidation with MCPBA, gave predominantly 10. This latter compound can readily be cyclized with

N,N-diisopropylethylamine to give the diepoxide 2. Studies with Dreiding and CPK molecular models indicate that the most stable conformation for 8 is the one in which (i) Br and OH are antiperiplanar and (ii) H-C(4) lies in the plane of the C(2)-C(3) double bond and is antiperiplanar to H-C(3) (see figure). In this conformation, the lower side of the double bond is efficiently blocked by the bromine atom, and attack of the MCPBA would rather be expected from the top side. The resulting epoxide has the configuration shown in formula 10; consequently, 2 must be the "O-cis"-isomer. (c) The chemical shifts of the carbon atoms C(5) of the glycidic esters 2 and 3 are in good agreement with the chemical shifts of the corresponding carbon atoms in the diepoxides 11 and 12, which again supports the configurations assigned to 2 and 3.



8 9 10

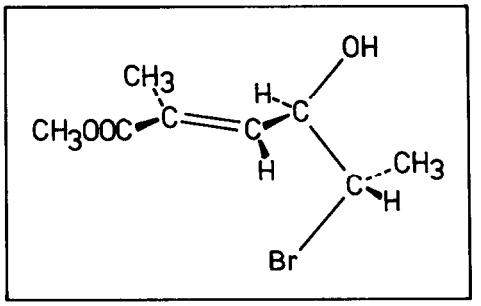
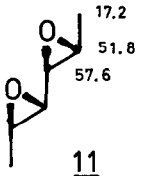


Figure: Preferred conformation of the bromohydrin 9 as deduced from studies with molecular models.

Comparison of the ^{13}C NMR data of hedamycin with those of the model compounds 2 and 3 shows a good agreement between the chemical shifts of the "O-cis" isomer 2 and those of the hedamycin side chain (± 0.5 ppm). The only exception is C(3), which has its resonance at 3.1 ppm upfield of the C(16) resonance in the antibiotic 1. This difference is due to the fact, that 2 is a glycidic ester, whereas hedamycin is actually a vinylogous glycidic ester. We could recently show that virtually the same difference (3.5 ppm) is found between the chemical shifts of C(3) in the glycidic ester 13 and C(2') in the vinylogous compound 14. [9] The correlation of the chemical shifts of hedamycin (1) and of



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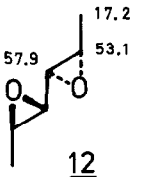

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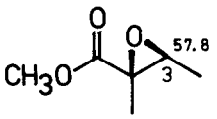

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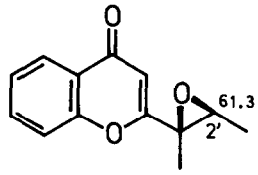

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the "O-trans"-model compound 3, on the other hand, is much less pronounced. Thus, the side chain in the antibiotic 1 must be assigned the "O-cis"-, i.e. rel-(14R,16S,17R,18S)-configuration.

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REFERENCES AND NOTES

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4) U. Séquin, Tetrahedron 34, 761 (1978).

5) cf. also S. Lesage & A. S. Perlin, Can. J. Chem. 56, 3117 (1978).

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