Tetrahedron Letters No. 8, pp 727 - 730, 1978. Pergamon Press. Printed in Great Britain.

STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF THE IONOPHORE ANTIBIOTIC A-23187

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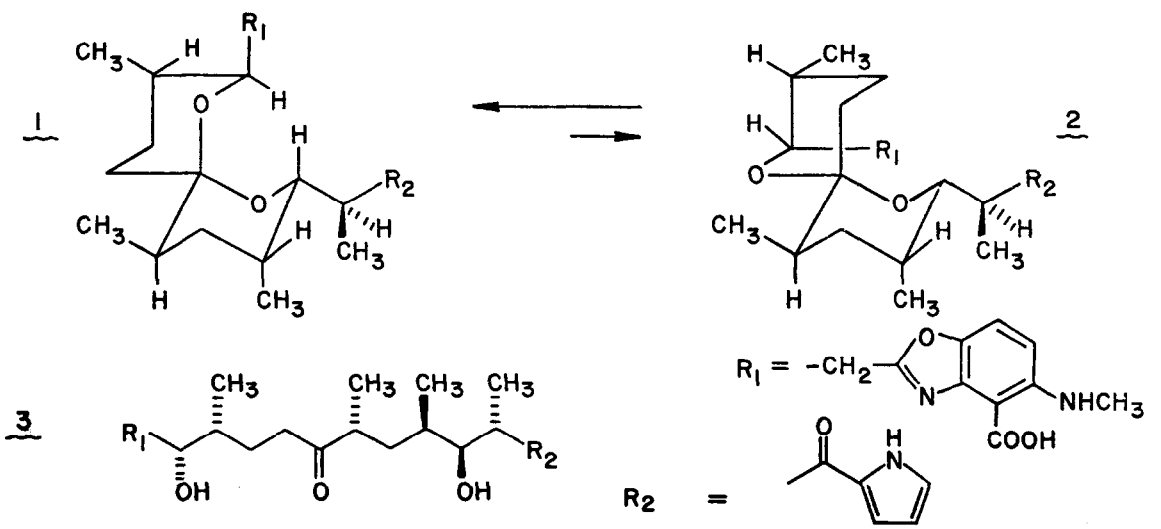
(Received in USA 1 December 1977; received in UK for publication 5 January 1978)

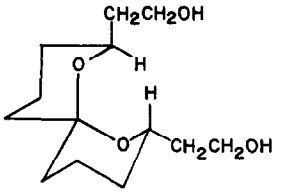
The carboxylic acid antibiotic A-23187 (1) is a divalent cation ionophore which has been isolated from cultures of Streptomyces chartreusensis.[2] The structure and proposed absolute configuration[2] have shown it to be one of a limited group of natural products, including oligomycin B[3] and aplysiatoxin,[4] which contains the unusual 1,7-dioxaspiro[5.5]undecane ring system (c.f. 1) as an integral structure feature. As a consequence of our intentions to engage in the total synthesis of A-23187 and related ion carriers we have initiated studies related to the construction of such spirane ring systems.[5] The general approach under consideration for the assemblage of the dioxaspirane skeleton involves the intramolecular ketalization shown in Scheme I wherein diol 3 might be expected to undergo ring closure to either of two possible diastereomeric spiroketals 1 or 2. The purpose of this communication is to demonstrate that this approach to the synthesis of dioxaspiranes related to A-23187 will proceed in a highly stereoselective fashion to afford bicyclic ketals possessing the stereochemistry associated with A-23187 (1) rather than the diastereomer 2.

SCHEME I

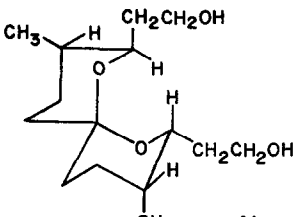


A rough estimate of the relative free energy differences between the two dioxaspiranes 1 and 2[6] suggested that the potentially labile asymmetric carbon at the spirane fusion in A-23187 (1) could be stereoselectively constructed under equilibrium condensation conditions from suitable acyclic precursors such as 3. Accordingly, pursuant to the total synthesis of this target molecule we have undertaken a study which would test the validity of these assumptions.[5]

The model compounds chosen as targets for this study were the dioxaspiranes 4a and 4b. The general approach to the synthesis of the acyclic precursors to both 4a and 4b is outlined in Scheme II.



4a



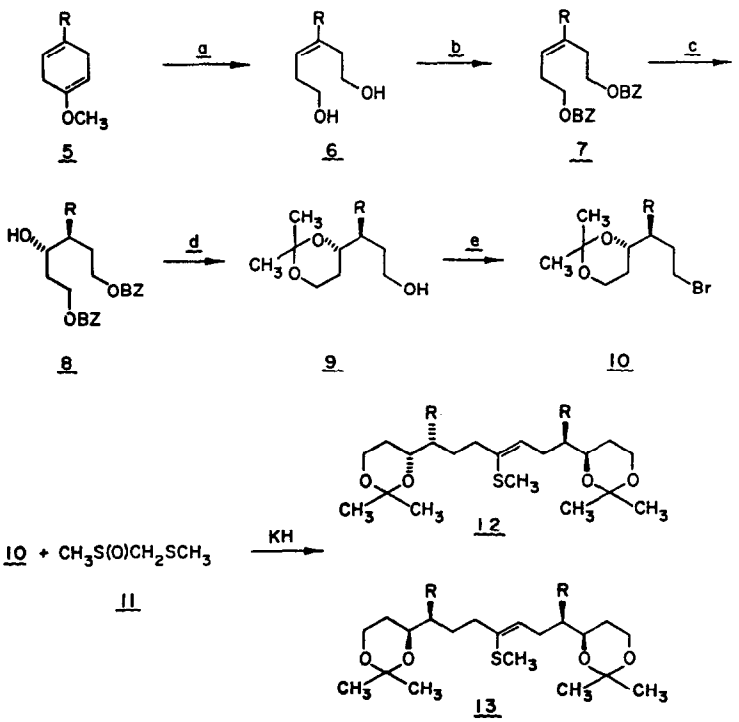
4b

The dihydroanisoles 5a and 5b, obtained by dissolving metal reduction of the appropriate anisole,[7] were treated with ozone (1 equiv.) at -78° in ether and the resultant ozonides were reduced *in situ* with an excess of lithium aluminum hydride to give the diols 6a and 6b in 40-50% yields after distillation.[8] Benzylation (NaH, $PhCH_2Cl$, THF, reflux, 18 h) gave the corresponding ethers 7a and 7b (84-92%) which were subsequently hydroborated (B_2H_6, THF, 10 h, 25°) to give the alcohols 8a and 8b in 90% yields.[8] Direct conversion of 8a,b to the acetonides 9a,b was achieved by hydrogenolysis (10% Pd on charcoal, H_2, 30 p.s.i.) in acetone (86-95%). The racemic bromoacetonides 10a and 10b which were required for subsequent cross-coupling were conveniently prepared *via* the method of Servis.[9]

The assemblage of the carbon backbone of the desired dioxaspiranes 4a and 4b was then accomplished *via* bis-alkylation of the carbonyl anion equivalent derived from methyl methylthiomethyl sulfoxide (11).[10] Treatment of 11 with racemic bromides 10a and 10b (2.1 equiv.) and excess potassium hydride (0°, .5 h, 50° 1 h, THF) gave the racemic vinyl sulfides 12 and 13 as a 1:1-mixture of E- and Z-olefin isomers (72-75%).[8,11] The use of lithio-1,3-dithiane to prepare the thioketals related to 12 and 13 proved to be inferior both in terms of overall yields and operational simplicity.

Hydrolysis of the racemic mixture of diastereoisomeric vinyl sulfides 12 and 13 could lead, in principle, to the four possible dioxaspiranes illustrated in Scheme III. It was projected that diastereomer 12 would afford exclusively the desired dioxaspirane 4 while the isomer 13 should show little preference for closure to either 14 or epi-14.[6] Upon treatment of the presumed 1:1-mixture of vinyl sulfides 12a and 13a with mercuric chloride in aqueous acetonitrile (18 h, 25°) followed by azeotropic removal of water with benzene, two dioxaspiranes, A and B, were produced. After separation by column chromatography dioxaspirane A was isolated as a white crystalline solid, mp 97-8°, in 89% yield (based upon a presumed 1:1-mixture of 12a and 13a) while dioxaspirane B was isolated as an oil in 40% yield.[8] The definitive structural assignment for the desired spirane was based upon the ^{13}C-NMR spectra of the two diastereoisomeric structures. Of the four possible spiroketals which could have been obtained, only the desired dioxaspirane 4a possesses a C_2-axis of

SCHEME II: a, R=H; b, R=CH_3



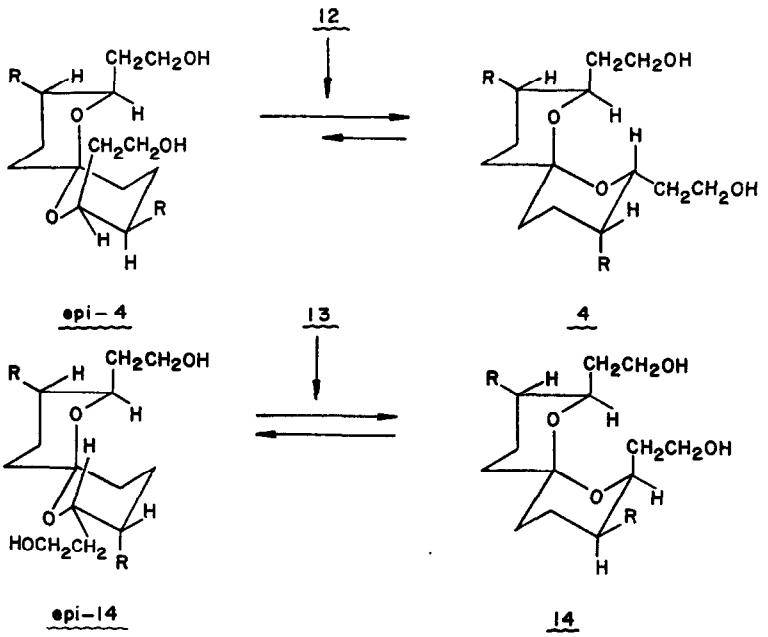
a) O_3, $LiAlH_4$; b) $PhCH_2Cl$, NaH; c) B_2H_6, ^-O_2H;
d) H_2, Pd-C, CH_3COCH_3; e) CH_3SO_2Cl, Et_3N, LiBr.

symmetry. The definitive seven-line ^{13}C-NMR spectrum of dioxaspirane A established its structure to be that illustrated in 4a. Dioxaspirane B exhibited a thirteen-line spectrum which would be consistent with either structures 14a or epi-14a. Similar results were obtained on the mercuric chloride hydrolysis of the vinyl sulfides 12b and 13b. In this instance dioxaspirane 4b was isolated in 60% yield as an oil while the diastereoisomeric spiranes 14b and epi-14b were not isolated. As with 4a, dioxaspirane 4b exhibited the expected eight-line decoupled ^{13}C-NMR spectrum.[8] In order to place these structural assignments on an unequivocal basis an X-ray structure determination was carried out on dioxaspirane 4a with the assigned structure being confirmed.[12]

The observed stereospecificity in these cyclization reactions has two important implications. The first is that a synthetic approach to A-23187 from an appropriate acyclic precursor, such as 3, will generate the requisite stereochemistry about the spirane juncture. The second relates to the biosynthesis of A-23187. This study suggests that the actual formation of the 1,7-dioxaspiro-

[5.5]undecane *in vivo* need not be enzymatically mediated, but may result from an expression of a conformational preference. On this basis one would expect predictive capabilities for structures such as aplysiatoxin[4] which contain this dioxaspirane system but for which the relative stereochemistry is at present unknown.

SCHEME III: a, R = H; b, R = CH_3



Acknowledgement. Support for this study was made possible through an unrestricted research grant from the Eli Lilly Company.

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11. The probable mechanism of this fragmentation will be discussed in the following communication, ref. 5.
12. The structure was solved by direct methods using MULTAN 74 and refined by full-matrix least squares to a final R value of 0.065.