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GROUP SELECTIVE REDUCTION OF ACETALS RELATED TO THE ANSA CHAIN OF THE STREPTOVARICINS: CONFORMATIONAL AND STEREOCHEMICAL ANALYSIS

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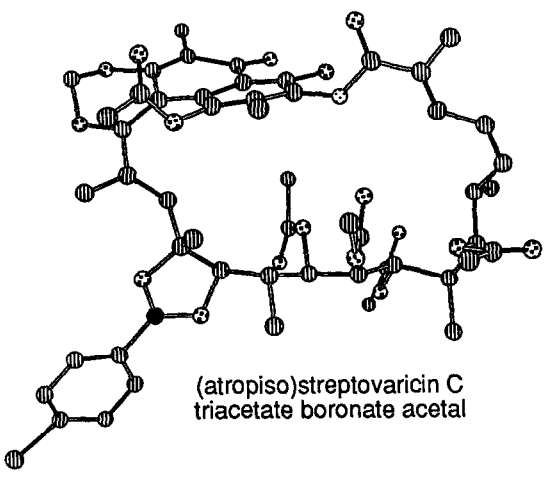
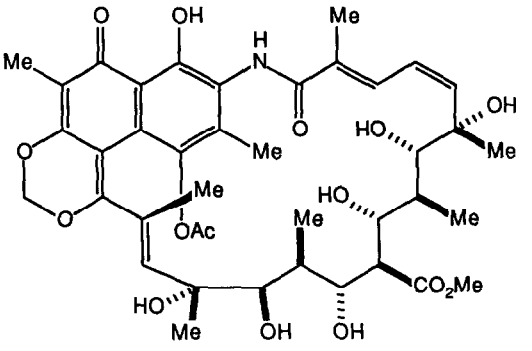
Abstract The group selective reductive cleavage of benzylidene acetals derived from diols containing chains equipped with a central chirotopic, nonstereogenic carbon atom is reported. The stereochemistry that is obtained at the central carbon is suitable for application to the synthesis of members of the streptovaricin class of antibiotics.

We are currently engaged in studies directed towards the total synthesis of members of the streptovaricin class of ansamycin antibiotics (Figure).[1] In the course of these studies, we required the stereoselective and sequential functionalization of the unsaturated termini of the two-directionally homologated class C chain (-)-**1** (Scheme 1).[2] The selective engagement of one of the homoallylic alcohols as its benzyl ether was deemed an attractive solution to this problem since the remaining alcohol function was expected to direct an epoxidation reagent to the nearest-neighbor olefin in a chemo- and stereoselective fashion.

Figure



(atropiso)streptovaricin C
triacetate boronate acetal

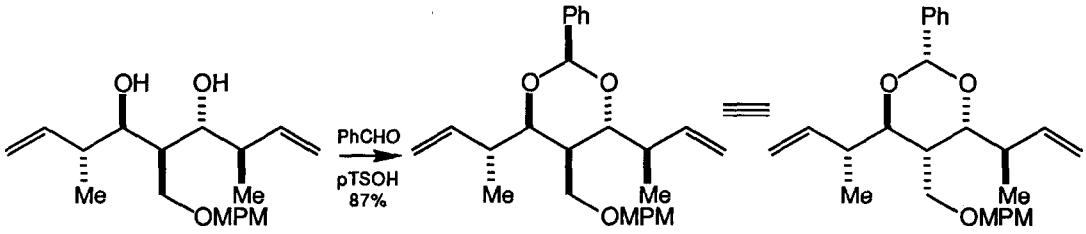


streptovaricin G
(natural atropisomer)

The monobenzyl ether synthesis described in this Letter relies on the group selective reductive cleavage of benzylidene acetals. The acetalization of **1**[3] ($[\alpha]_D^{23}$ = -1.64°, c = 3.3, $CHCl_3$) with benzaldehyde was promoted by the action of a catalytic quantity of p-toluenesulfonic acid in benzene (0 °C). Under these conditions, one major diastereomer of the acetal was formed (87%

yield). The structure of the product **2** ($[\alpha]_D^{23}$ = +7.6°, c = 5.4, $CHCl_3$, mp = 55-56 °C) was shown to have the cis-relationship of the phenyl and (p-methoxy)benzyloxymethyl substituents by X-ray diffractometry (**3**, Scheme 2). We have not determined the extent to which these conditions reflect kinetic or equilibrium-control in the formation of product.

Scheme 1



1 **2**

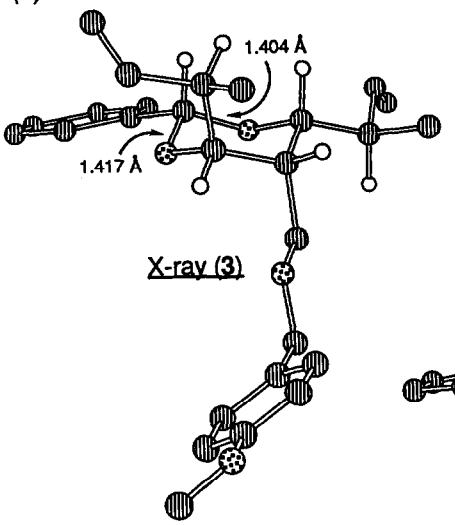
Several important features of the structure of **2** are noteworthy. First, the chirotopic, nonstereogenic center in **1** has been converted to a stereogenic center in **2** (the reaction produces a stereogenic dyad or *stereogen* with control of relative stereogenicity[4]). Second, the X-ray crystal structure **3** (=**2**) illustrates the molecule adopts the chair conformation in the solid state that places the phenyl group in an equatorial orientation and leaves the (p-methoxy)benzyloxymethyl group axially disposed. This result is fully consistent with the large difference in A values of substituents at the 2-position (methyl = 4.0) and 5-position (methyl = 0.8) of the 1,3-dioxane ring.[5] Why does the major isomer of this reaction have the cis-geometry when the alternative trans-isomer (or transition state leading to that isomer) could "benefit" from the placement of both substituents (phenyl, (p-methoxy)benzyloxymethyl) in the equatorial orientation? We believe the answer follows from a conformation analysis of **3** and **4**. This analysis suggests that a 5-substituent on this 1,3-dioxane should have a large and negative A-value.

Note that the rotamers of the carbon-carbon bond that connects the *sec*-butenyl group to the dioxane in **3** avoid the considerable steric strain associated with a "syn-pentane" (gauche(+)-gauche(-))[6] local conformation. To illustrate, relevant hydrogens have been added to the skeletal atoms whose positions were ascertained by X-ray diffractometry. The presence of the equatorial (p-methoxy)benzyloxymethyl group in the trans-isomer **4** should cause a rotation of 120° about the carbon-carbon bond that serves as the attachment site of the equatorial *sec*-butenyl substituent. However, the existence of a syn-pentane type interaction between a substituent (methyl or vinyl) on the axial *sec*-butenyl group and either a ring carbon or the methylene of the equatorial alkoxymethyl group is now unavoidable in any chair conformation with staggered exocyclic bonds.

The X-ray structure **3** reveals an asymmetry about the carbon-oxygen bonds within the 1,3-dioxane skeleton. The C-O bond bearing the axial *sec*-butenyl group is 0.014 Å longer than the partner bond of the acetal, presumably reflecting steric interactions of the axial allylic methine with the acetal methine. In accord with the findings of others concerning the stereochemical outcome of reactions of chiral acetals,[7] the reaction of **2** with 10 equiv of DIBAL-H in CH_2Cl_2 (0 °C) resulted in the formation of a single monobenzyl ether (>20:1, 89% yield), **7** (Scheme 3). In this fashion,

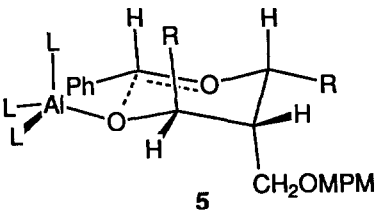
Scheme 2

(a) Diastereoselective Acetalization

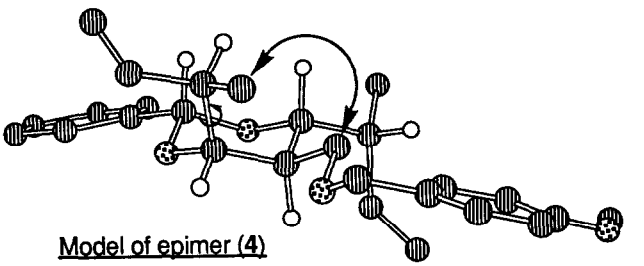


X-ray (3)

(b) Group Selective Reduction

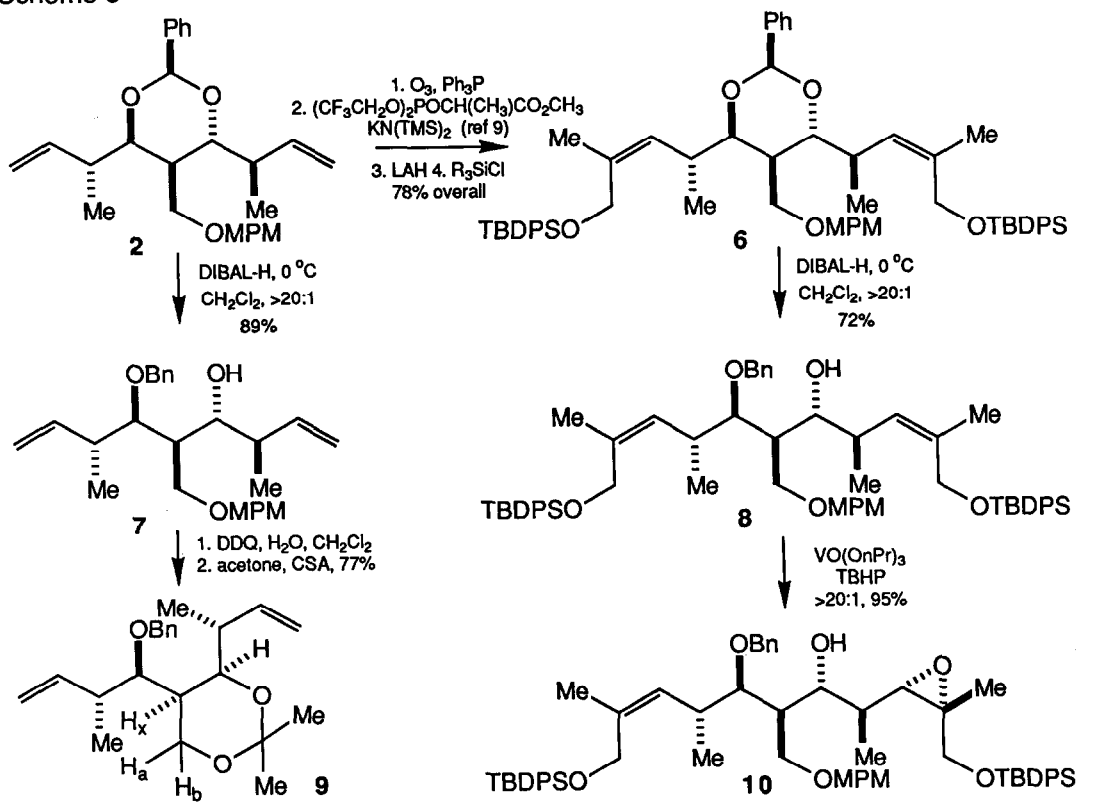


5



Model of epimer (4)

Scheme 3



control of absolute stereogenicity at the carbon bearing the (p-methoxy)benzyloxymethyl has been achieved. Evidence for the indicated stereochemistry was obtained by an analysis of the ^{1}H NMR coupling constants of the derived acetonide **9** (e.g., J_{AX} =2.4 Hz, J_{BX} = 3.6 Hz). The reductive cleavage of acetal **6** ($[\alpha]_D^{23}$ = -39.4°, c = 2.3, $CHCl_3$), obtained in four steps from **2** by two-directional chain homologation,[2] (Scheme 3) proceeded in a similar manner (20 equiv DIBAL-H) and provided a single monobenzyl ether **8** ($[\alpha]_D^{23}$ = -28.4°, c = 1, $CHCl_3$). These results are in accord with the group selective complexation of the alane reagent to the indicated ether oxygen in **5** (Scheme 2) and cleavage of the associated C-O bond.

The selective acetal cleavage provides a handle to differentiate the terminal olefins within **8** with stereochemical control that is appropriate for the streptovaricins. The directed epoxidation of **8** provided one major monoepoxide (>20:1) whose stereochemistry is suggested to be as shown in **10** ($[\alpha]_D^{23}$ = -9.7°, c = 2, $CHCl_3$) by analogy to the results of Mihelich in closely related systems.[8] Additional studies related to the synthesis of members of the streptovaricin class are ongoing.

This Letter is dedicated to Dr. Leo Sternbach on the occasion of his 80th birthday. Dr. Sternbach's contributions to biomedical research serve as an inspiration to the organic chemical community.

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