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OXIRANYLCARBINYL REARRANGEMENT: THE EFFECT OF PRECURSOR STEREOCHEMISTRY

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Rigid, bisected oxiranylcarbinyl mesylates solvolyzed *via* an apparent oxiranylcarbinyl cation which rearranged to a 2-oxahomoallyl cation, while the perpendicular isomers gave displacement with inversion.

The prediction[1] that the bisected oxiranylcarbinyl cation would be greatly stabilized with respect to its perpendicular partner, a stereochemical trend similar to that experimentally observed in cyclopropylcarbinyl cations,[2] provided an impetus for studying the solvolyses[3-9] of oxiranylcarbinyl sulfonates. Product studies have implicated both oxiranylcarbinyl-to-oxetanyl and oxiranylcarbinyl-to-oxahomoallyl cation rearrangements. The former was postulated to proceed from a conformation as shown in **1**.[7] However, the original issue remains despite these studies.[2] As part of our interest in the antimalarial[10,11,12] quing-hao-su (arteannuin),[13] we suspected that the preferred rearrangement route during solvolysis under proper conditions of a model of arteannuin B[14,15] would lead to 2-oxahomoallyl-derived products. Therefore, we synthesized epoxymesylates **6**, **7**, **8**, and **9**,[16] and report here the products of their solvolysis at 60 °C in methanol containing excess diisopropylethylamine and their conformations based on single-crystal X-ray diffraction studies of **6** and **9**.[17] Our results confirm our suspicion and indicate a way to examine experimentally the original prediction.

The straightforward syntheses involved reducing Δ-1(10)-2-octalone[18] with lithium tetrahydridoaluminate in ether and epoxidizing the crude mixture of allylic alcohols with vanadium acetylacetonate/*tert*-butyl hydroperoxide[19] in toluene. The resulting epoxyalcohols were separated by careful flash chromatography[20] to give an approximately 1:10 ratio of the less polar **4** to the more polar **2**. The alcohols **2** and **4** were converted to their crystalline mesylates with methanesulfonyl chloride in methylene chloride/triethylamine.[21] Inversion of alkoxy configuration with tetra-*n*-butylammonium formate[22,23] in refluxing acetone and methanolysis of the resulting formates gave the corresponding alcohols 3 and **5**. Finally, these were converted to their corresponding crystalline mesylates **7** and 9 with methanesulfonyl chloride in methylene chloride/triethylamine.[20]

Figure

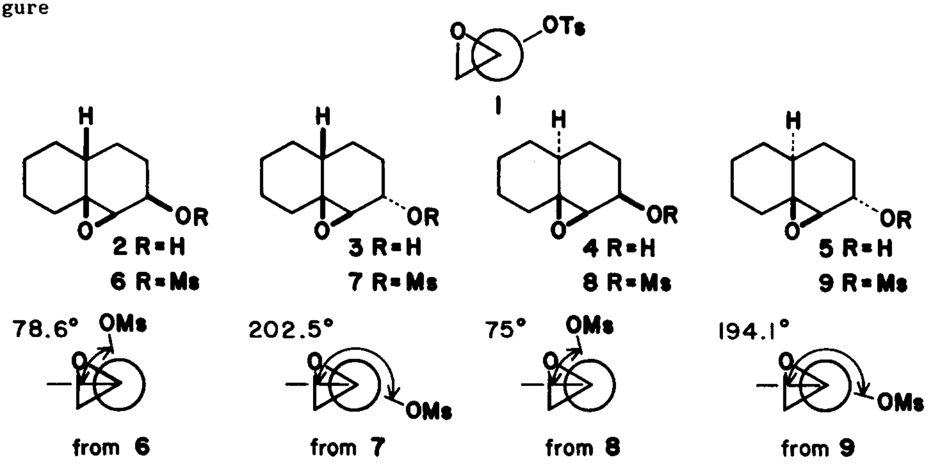


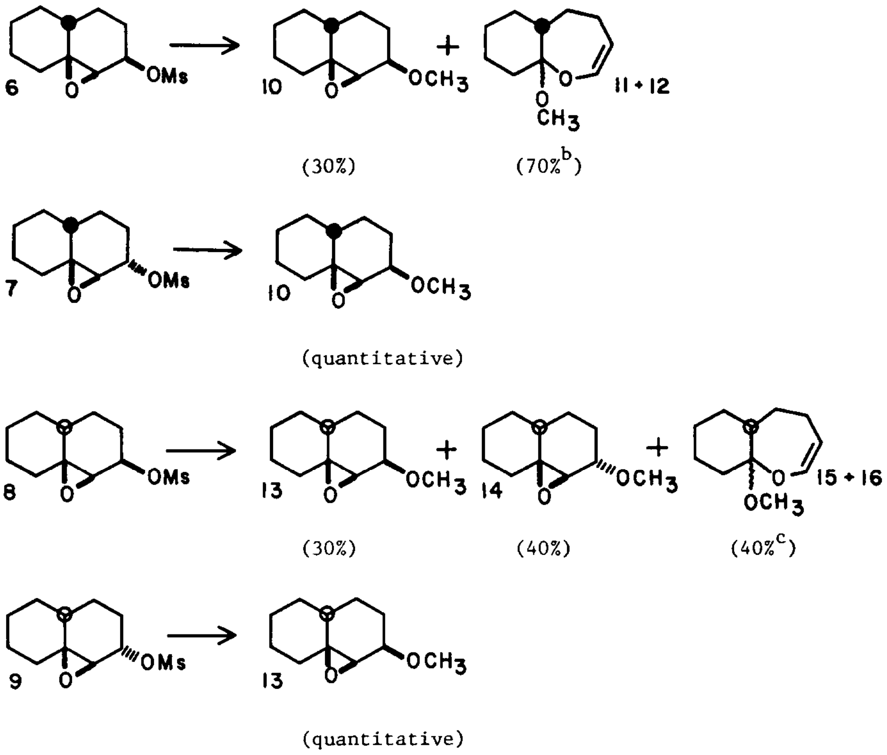
Figure. (1) The conformation proposed by Santielli[7] for the oxiranylcarbinyl-to-oxetanyl rearrangement; (2-**9**) the configurations of the substrates used for solvolysis, and the conformations of the epoxymesylate units therein.

If the pairs 6 and **7**, and 8 and **9**, are assumed to have identical ring conformations, the torsion angles from crystal structures of **6** and 9[17] allows coomputation of the "dihedral" angles shown in Figure 1 for the molecules in the solid state. Thus, **6** and 8 are approximately bisected $(\theta=90^{o})$ and **7** and 9 are approximately perpendicular $(\theta=180^{o})$. The ^{1}H NMR data for all four configurations indicate that the solid-state and predominant solution conformations are the same ($J(H_1H_2)$ for **6** = 3.4 Hz; for **3** = ca. 0 Hz; for **8** = 4.5 Hz; for **9** = ca. 0 Hz).

The solvolyses of compounds **6**, 7, **8**, and 9 were carried out in anhydrous methanol at 60 ^{o}C with excess diisopropylethylamine added. The results are shown in the Scheme.

This information provides for the first time a stereochemical distinction between different reaction modes of these rigid oxiranylcarbinyl sulfonates. When the epoxide is anti as in **7** and 9, and therefore perpendicular, there is exclusive displacement by methanol with inversion implying Sn2-type reaction. The syn epoxide in the trans-fused system **8** gives a stereo-and regio-randon methanolysis indicating the intermediacy of a carbocation. The reactivity difference between the syn and anti epoxides[24] does not necessarily represent the

Scheme



(a) Yields were determined by integration of the O-CH_3 peaks vs internal standard in the ^1H NMR spectra

(b) Produced in an approximately 5:1 ratio. We have so far been unable to assign the relative configuration of the major isomer.

(c) Produced in a 1:1 ratio; yields corrected for starting material not observed, at 74% conversion.

acceleration of carbocation formation by the bisected versus perpendicular oxirane, but rather a comparison of these two different reaction modes.[25] Since carbocation formation from a precursor with the bisected conformation is implicated, and the preferred rearrangement pathway leads to the 2-oxahomoallyl cation, a potential biochemical predcursor for both arteannuin B[15] and quinghaosu[12,13] may undergo this type of rearrangement to give the quinghaosu skeleton.

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24. Under these conditions, the half-life for **9** was about 48 hours while two half-lives of **8** were complete in approximately 12 hours. Action of the epoxide as in internal base may accelerate displacement with inversion for **7** and **9**. But, if such an effect does exist, its magnitude is smaller than the stereoelectronic preference for ionization displayed by **6** and **8**.
25. Assuming that the *anti* isomer reacted with methanol *via* the oxiranylcarbinyl carbocation up to the limit of detection in the present study (5%), one can conservatively estimate the minimum acceleration of carbocation formation from the bisected *versus* perpendicular oxirane to be a factor of about 100. Danen has calculated the energy difference between prototypes of these two carbocations to be in excess of 30 Kcal/mol (reference 1); the true rate enhancement could thus be much greater than a factor of 100.

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