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STRIKING CONTRASTS IN STEREOSELECTIVITIES OF SPIRO-CLAISEN REARRANGEMENTS OF PYRANOSIDES VERSUS CARBOCYCLES.

Bert Fraser-Reid*, Deen B. Tulshian, Ray Tsang and Derek Lowe
Paul M. Gross Chemical Laboratory
Duke University, Durham, NC 27706

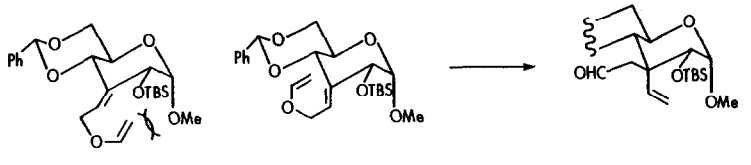
and

Vernon G. S. Box*
Department of Chemistry
City University of New York, City College
New York, NY 10031

Structurally equivalent derivatives of pyranosides and cyclohexanes undergo the spiro-Claisen rearrangement with different stereochemical results. A rationalization for the course observed with the pyranosides is suggested, which invokes interaction of the oxygen lone pair with a (developing) electron deficient centre at the spiro carbon.

The burgeoning interest in the use of carbohydrates in organic synthesis is undoubtedly related to the fact that reactions of sugars invariably proceed with high stereoselectivities,[1] a property which has given rise to their description as "chiral templates".[2] In the case of alkyl pyranosides, this property has been attributed to the fact that the sugar ring is held rigidly in a favored conformation wherein the polar anomeric substituent is axially oriented,[3,4] a circumstance which would cause the α-face (e.g. of 1, Scheme 1) to be more sterically hindered than the -face. However, in this communication we disclose some experimental results which suggest an important role for the ring oxygen in ensuring stereoselectivities at trans-annular sites.

SCHEME I



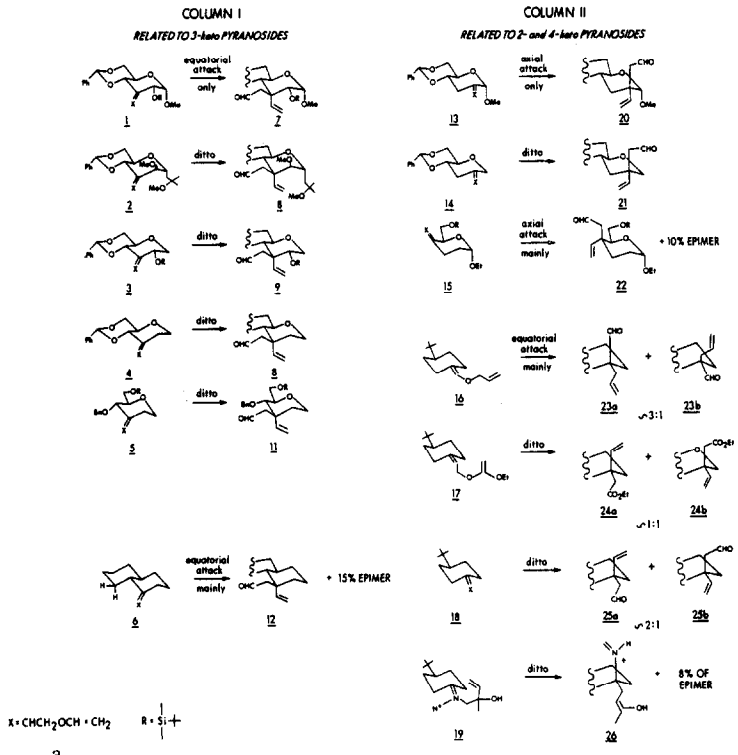
1a 1b 7

In connection with a synthetic project in our laboratory we had occasion to carry out the spiro-Claisen rearrangement of 1 in which 7 was obtained as the only product.[5] We initially rationalized this stereoselectivity on the ground that the fold in 1a (Scheme 1) is disfavored by steric interaction with the axial anomeric methoxyl, and hence rearrangement occurred through 1b to give 7. This result seemed to be reinforced by the exclusive formation of 8 from

2 (Table). However, when complete stereoselectivity continued even when the anomeric substituent was removed, as in 3 and 4, it became apparent that the rationalization in Scheme 1 was inadequate. Conformational rigidity also did not appear to be a factor since the rearrangement was equally stereoselective in the absence of the trans-fused ring, i.e. 5 11. **Thus in all of these substrates 1-5, the reacting appendage folds from the β-face exclusively resulting in equatorial attack.**

T A B L E[a]

SPIRO-CLAISEN REARRANGEMENTS



[a]In all cases, the ally vinyl ethers used in our studies were prepared as described previously[6,7]. Refluxing benzonitrile was used as the solvent, reactions were monitored by TLC, and the isolated yields were uniformly 85-95%. Only the isomer(s) indicated were detected by ^{1}H NMR(250 MHz).

The results with 13[6], 14[6] and 15[7] are also notable for their stereoselectivities, and comparison of 13 and 14 shows that an axial anomeric substituent is again unimportant. Furthermore, the results with 13, 14, and 15 show that the steric environment in the immediate neighborhood is also relatively unimportant. **Thus whether the adjacent substituent is axial [as in 13] or equatorial [as in 15], the acetaldehyde group in the product ends up (predominantly) axial.**

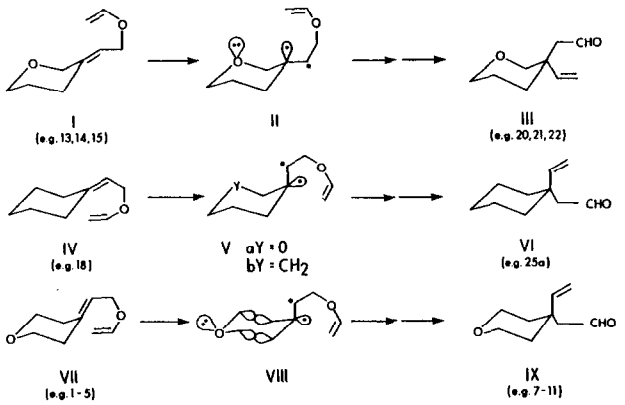
It is revealing to contrast these results with those obtained by House[8] for 16 and 17 which are conformationally-locked, carbocyclic equivalents of 13 and 14. Case 18 has also been examined by us. The results in the Table show (a) that in contrast to 13, 14 and 15, stereochemical preference is slight (as in 16 and 18, and (b) that this preference is for equatorial (rather than axial) attack, leading to 23a and 25a.

An interesting related case, reported recently by Overman[9], is 19 whose rearrangement product, 26, cyclized in situ to give an azaspirane.

In attempting to rationalize the results in the Table, we note first that the systems in column II fall into two groups, one of which (summarized as I, Scheme 2) favours axial attack,

while the other (summarized as IV) shows equatorial attack. All substrates in Column II are conformationally biased, but one group differs from the other (a) by the presence of the ring

SCHEME 2



oxygen, and, by corollary, (b) by the absence of one axial hydrogen. The latter could hardly be (solely) responsible for the overwhelming shift from equatorial to axial attack (vide infra), and we therefore sought for an electronic effect involving the former, i.e. the ring oxygen. In order to accommodate the experimental results, this effect would have to be expressed in a stereochemically biased sense.

The biradicaloid nature of sigmatropic rearrangements has been suggested by several scholars [10-13]. There is evidence, theoretical[11] and experimental,[12] that bond-making is more highly advanced than bond-breaking in the transition state. Hence early bond-making stages such as II and V would seem plausible, wherein appreciable radicaloid character would exist at the "spiro" carbon. II and Va are both β-oxygenated radicaloids RO-C-$\dot{C}$, which are homologues of the highly stabilized α-counterpart RO-$\dot{C}$.[14] However, only II is capable of enjoying the through-space interaction of the oxygen lone-pair with the electron deficient orbital at the spiro carbon, and it would seem justified that rearrangements at C2 and C4 in pyranoid systems should follow the "axial" course in Scheme 2 leading to III.

Such electronic interactions are of course irrelevant in carbocyclic systems and so the "normal preference" referred to by House[9] for equatorial attack would be exercised in 18 leading primarily to 25a.

It would therefore seem that the rearrangements in Column I of the Table are following the path of "normal preference". However, even in these systems the oxane ring oxygen could also play a significant role.# Thus, the early bond-making stage corresponds to VIII wherein the 1,4-related orbitals can couple via the intervening σ framework.[15] Operation of this effect would, therefore, heighten the "normal preference" for the equatorial product IX.

What about the oxygens in the 1,3-dioxane (benzylidene) ring? Firstly, we assume that the C6 oxygen is too remote to have any influence. The C4 oxygen should not offer any stereoelectronic bias, since it has axially and equatorially oriented lone pairs which could stabilize a C3 radicaloid centre of either axial or equatorial orientation, respectively.

In order to test the feasibility of this postulate, we examined the trans-decalin system 6 which is the carbocyclic equivalent of the bicyclic ketones 1 - 4. Interestingly, the rearrangements of 6 gave an 85:15 mixture of 12 and its epimer,[16] in contrast to the single isomers obtained in the cases 1 - 4.

STERIC EFFECTS: In the case of 14 and 18, could replacing an axial lone pair with an axial hydrogen be responsible for the overwhelming change from axial to equatorial attack? This seems unlikely since Eliel and co-workers[17] have shown that the A values for methyl groups in 3-methyloxane and methylcyclohexane differ by only 0.43 kcal.

CAUTIOUS NOTE: We are well aware of the conflicting views on the mechanistic details of the Claisen and other sigmatropic rearrangements [11-13,18,19], hence the rationalizations advanced in Scheme 2 are only one effort to account for the stereoselectivities observed.

Further studies are underway and will be reported in due course.

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