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STEREOCHEMICAL REQUIREMENTS FOR FRAGMENTATION OF HOMOALLYLIC EPOXY ALCOHOLS

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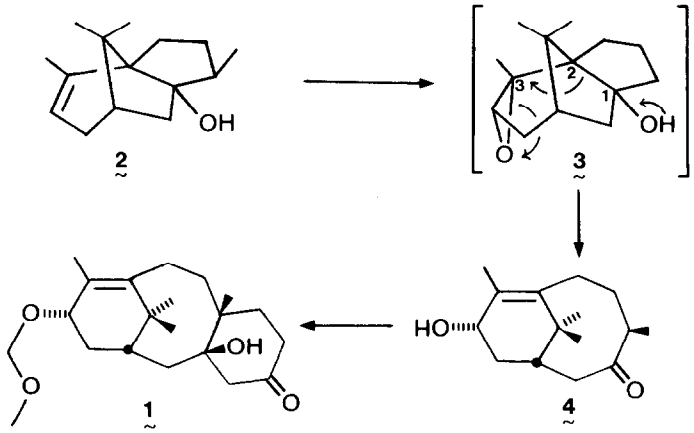
Abstract: The fragmentation of 5,6-epoxynorbornan-2-ol and 5,6-epoxynorbornan-2-one have been studied under both acidic and basic conditions. These processes show a clear preference for syn periplanar alignment of breaking bonds.

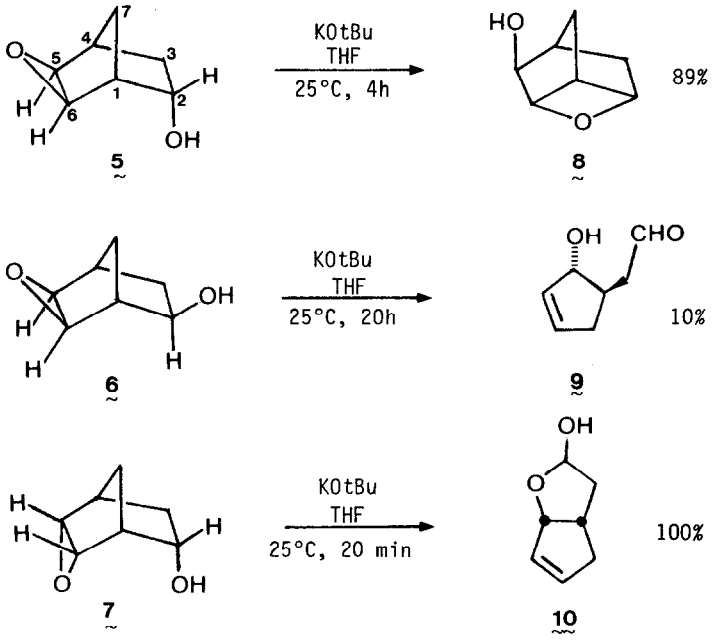
We have recently reported a short and efficient synthesis of the ketol 1,[1] embodying all of the skeletal features of the taxane ring system.[2] The key step of this synthetic sequence involved the hydroxyl-directed epoxidation[3] of 2, presumably giving intermediate epoxy alcohol 3 which underwent fragmentation in situ to provide a quantitative yield of 4. The ease of this fragmentation is surprising since the C1-C2 bond and the C3-O bond (the breaking bonds) in 3 have a syn periplanar relationship. We have attempted, unsuccessfully, to prepare the isomeric β epoxide by epoxidation of the TMS ether of 2. Presumably both faces of this olefin are sterically shielded; the β-face is shielded by the geminal methyl group, and the α-face is shielded by the silyl ether.



Fragmentation reactions have been the subject of numerous studies. In several of these a clear preference for the anti periplanar alignment of breaking bonds has been observed.[4] There exists no study, to our knowledge, in which a preference has been demonstrated for syn periplanar alignment of breaking bonds in a fragmentation process.[5]

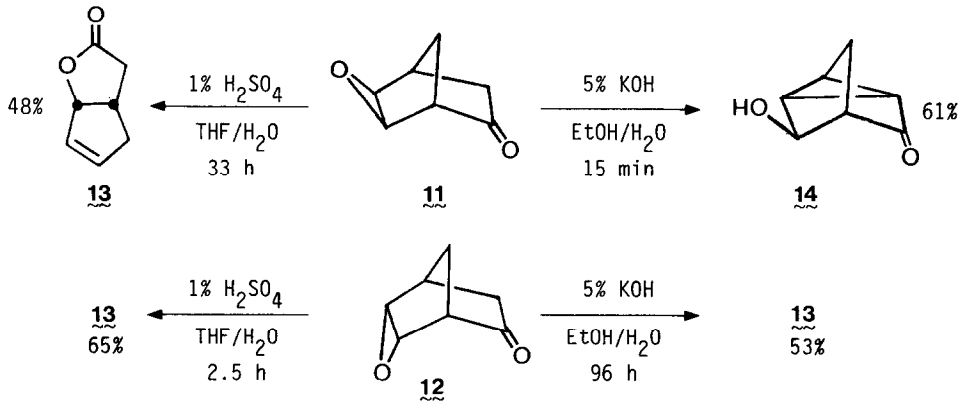
A few examples of the fragmentation of homoallylic epoxy alcohols have been previously reported.[6] However, none of these experiments were conducted under conditions which allowed evaluation of the stereochemical requirements for this process. For the purpose of such an evaluation we have prepared isomeric epoxy alcohols 5-7.[7] Exo epoxides 5 and 6 were readily available via peracid epoxidation of the corresponding alcohols.[8,9] The endo epoxy endo alcohol 7 was prepared from endo norbornen-2-ol via directed epoxidation.[3,8,10]

The reactions of 5, 6, and 7 with potassium t-butoxide were carried out under nitrogen at 25°C in THF solution. Epoxy alcohol 5 cyclized over a 4 h period to provide oxetane 8 in 89% yield.[9,11] Epoxy alcohol 6 reacted very slowly (20 h at 25°C was required for complete consumption of 6) to provide a multitude of products from which the aldehyde 9[12] could be isolated in 10% yield.[11] In contrast to this result, epoxide 7 reacted within 20 min to provide a quantitative yield[11] of lactol 10.[12] Under these conditions fragmentation of the exo epoxides 5 and 6 (anti periplanar alignment of breaking bonds) is at least an order of magnitude slower than fragmentation of the endo epoxide 7 (syn periplanar alignment of breaking bonds).



Under acidic conditions, the fragmentation of 5, 6, and 7 generally did not proceed cleanly. For example, treatment of 7 with protic acids and strong Lewis acids (e.g., $BF_3 \cdot Et_2O$) gave low yields of a mixture of allylic alcohols. However, epoxide 7 was converted to lactol 10 in 60% yield[11] in the presence of titanium tetraisopropoxide ($Ti(OiPr)_4$) in benzene at reflux for 9 h. Epoxy alcohol 5 reacted very slowly with $Ti(OiPr)_4$; over a period of 22 h in refluxing mesitylene (163°C) 5 was converted to oxetane 8 in 50% yield.[11] Epoxide 6 did not react even under these harsh conditions.

Sarett oxidation of 5 and 6 gave exo epoxy ketone 11,[7] and Sarett oxidation of 7 provided endo epoxy ketone 12.[7] These oxidations served to further confirm the stereochemical assignments of 5, 6, and 7 and also provided isomeric epoxy ketone substrates for further fragmentation studies.



Epoxy ketones 11 and 12 were both treated with aqueous acid and aqueous base. As previously reported,[13] epoxy ketone 11 was converted to lactone 13[12] in the presence of dilute acid. However, treatment of 11 with 5% KOH solution gave alcohol 14[7] in 61% yield.[11] Alcohol 14 was also formed in 70% yield upon treatment of 11 with LDA in THF. Expoy alcohol 12 fragmented to provide lactone 13 under both acidic and basic conditions. The sluggish conversion of 12 to 13 under basic conditions may be attributed to the steric difficulty of generating a tetrahedral hydrate from 12. Under acidic conditions, the conversion of 12 to 13 is at least an order of magnitude faster than the conversion of 11 to 13. Once again, the syn periplanar alignment of breaking bonds appears to be preferred.

The faster and cleaner fragmentation of the endo epoxides 7 and 12 might be interpreted as a general preference for syn elimination of epoxides.[14] However, the norbornane skeleton is constrained so that the C1-C2 bond and the C6-O bond are more nearly coplanar in endo epoxides 7 and 12 than in exo epoxides 5, 6, and 11. This fact could be solely responsible for the observations we have described. We plan further investigation of this fragmentation in systems in which this bias has been removed.

Acknowledgment. We thank the National Cancer Institute for their generous financial support of our program.

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7. Characterized by IR, PMR and combustion analysis or high resolution mass spec analysis.

8. 5-Norbornen-2-ol was purchased from Aldrich Chemical Co. as a 4:1 mixture of endo:exo alcohols. These could be separated by careful flash chromatography.

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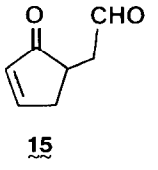
10. Directed epoxidation[3] of the mixture[8] of alcohols gave 7 and a mixture of recovered olefinic alcohols enriched in the exo isomer.

11. Isolated yield of spectrally (PMR) and chromatographically (TLC) homogeneous material.

12. Sarett oxidation of 6 gave lactone 13 in high yield. Sarett oxidation of 9 provided 15, in accord with the trans stereochemistry of 9. Hydrogenation of 13 gave 16, which was identical with an authentic sample.[15]



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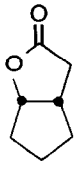

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