GEOMETRIC REQUIREMENTS FOR 3,4-EPOXY ALCOHOL FRAGMENTATION

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ABSTRACT

Grobe-type fragmentation of 3,4-epoxy alcohols is a potentially useful synthesis reaction. In this paper, we provide new evidence that the bonds involved in the base-catalyzed elimination must take on *anti* or *syn* coplanar geometry.

INTRODUCTION

Epoxy alcohols have been the subject of many recent and vigorous investigations. Of paramount importance has been Sharpless' (1983) work on the asymmetric syntheses and subsequent reactions of 2,3-epoxy alcohols. The related *3,4*-epoxy alcohols(*1*) have received much less attention (Waddell, Ross, 1987). This year, however, Holton et al.(1988) have reported an elegant synthesis of taxusin enroute to taxol, a rare and very promising antitumor natural product. The key step in this preparation is the fragmentation reaction (Scheme 1) of a tricyclic 3,4-epoxy alcohol.

Scheme 1

1

The reaction of Scheme 1, then, has potential synthetic utility. What are the geometric requirements for this fragmentation? For example, do the bonds involved in the elimination (a and b) need to project in an *anti* coplanar fashion, as in most Grobe-type fragmentations? (Grobe, 1969). Or, might the strain of the epoxide ring serve to relax this usual restriction? In this paper, we present new evidence that *syn* coplanar (Holton, Kennedy, 1984) or *anti* coplanar bonds a and b (Dev, et al., 1983) suffice to allow this chemical change.

2

3

In an earlier study, Holton and Kennedy (1984) reported that epoxy alcohol 2 yielded a complex mixture when treated with potassium t-butoxide in THF. The

bonds a,b in *2* deviate from *anti* coplanarity by ca 10 degrees. In contrast, *3* smoothly fragmented (as shown) with the same reagent. The a,b angle in *3* is very close to *syn* coplanarity. With these results, Holton proposed that *syn* coplanar a,b geometry is required for base-catalyzed fragmentation of 3,4-epoxy alcohols.

RESULTS AND DISCUSSION

It occurred to us that bridging of a K+ ion between the two oxygen atoms of *3* might contribute to the efficacy of its fragmentation. To test this notion, we prepared dicyclopentadien-10-ol-8,9-epoxide(*5*), which can clearly bridge a K+ ion. Moreover, the a,b bond angle in *5* deviates from *syn* coplanarity by ca 35 degrees. If *5* fails to fragment, then, the smooth reactivity of *3* is due to *syn* coplanar geometry (Holton, Kennedy, 1984) and not to K+ bridging. Compound *5* was prepared by treating the known 10-ol precursor *4* (Woodward, Katz, 1959) with VO(AcAc)$_2$/ t-butyl hydroperoxide (Sharpless, Verhoeven, 1979). The structure of *5* is
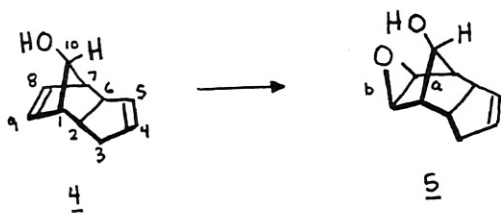
indicated by the established directive effect of the OH (Sharpless, Verhoeven, 1979), the IR spectrum, and comparison of the NMR spectrum of *5*(listed in the Methods section) with numerous model dicyclopentadienyl and epoxide compounds. *Compound 5 was stable to the V^{+5} reagent (Holton, 1984) and was recovered unchanged after treatment with potassium t-butoxide in THF. Therefore, the syn geometry of 3 is the factor responsible for its successful fragmentation.*

As reported in the Methods section, the synthesis of the 10-ol *4* was achieved by refluxing the known dicyclopentadien-3-ol (Woodward, Katz, 1959) in toluene, followed by column chromatography on alumina. A by-product(12% yield) of this Cope-rearrangement was a new dimeric ether whose structure *6* is indicated by IR, NMR, and elemental analysis (see Methods).
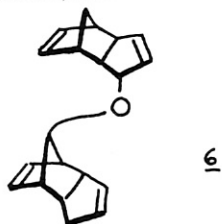

The propensity to fragment of 3,4-epoxy alcohols

with *anti* coplanar a,b geometry remains to be further demonstrated. In 1983, Dev reported an example where such an event occurred. Thus, epoxy alcohol *7*, with ideal *anti* coplanarity, gave the aldehyde *8* when treated with NaH/THF. Now,
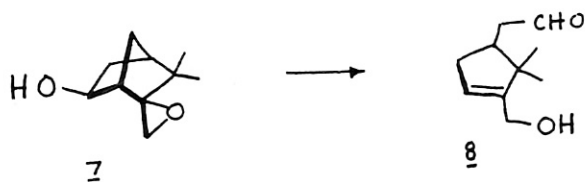

compound *2*(*anti* but not coplanar) does not easily fragment. However, molecular models reveal that the insertion of one CH$_2$ group to make *9* rotates the a,b bonds to near *anti* coplanarity. If *9* fragments (and *2* does not), an *anti* coplanarity requirement would be established.
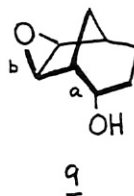
The synthesis of epoxy alcohol *9*(in the mixture *13*) is outlined in Scheme 2. 2-Cyano-bicyclo[2.2.1]hept-5-ene(*10*)(Alder, et al., 1958) was reduced with LiAlH$_4$/ ether to give the amine *11*(Hall, 1960) in 77% yield. Parenthetically, we were surprised to note that reaction of *10* with NaBH$_4$/CoCl$_2$ in methanol reduced both the nitrile *and* the alkene groups to give an 89% yield of the *saturated* analog of *11*.This NaBH$_4$/CoCl$_2$ reagent was reported previously to *not* reduce alkene double bonds(Satoh, et al., 1969). Treatment of *11* with acetic acid/NaNO$_2$ affected a Demjanov ring expansion providing known alcohols *12*(72% yield)(Hall, 1960) as an equimolar mixture of 2-OH and 3-OH regio- and stereoisomers. Compounds

Scheme 2
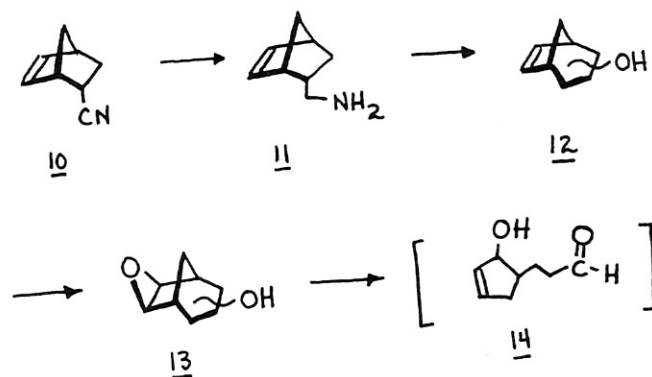
12 were obtained as an unstable, volatile, and partially water-soluble oil and immediate epoxidation with m-chloroperbenzoic acid in CH_2Cl_2 gave *13*(60%) as the corresponding mixture. The *exo* orientation of the epoxide follows from the epoxidation of closely related bicyclic alken-ols(Holton, Kennedy, 1984).

The mixture *13* contains approximately 50% of the potentially fragmentable 2-ol(*9*) but separation of the mixture was impeded by the unstable nature of *13* along with its volatility and partial water-solubility. Nevertheless, the efficient fragmentation of *9* could be clearly demonstrated by spectral studies of the mixture.

Treatment of *13* in THF with potassium t-butoxide gave a product *14* whose IR spectrum showed absorption at 3350 cm^{-1}(OH), 1720(C=O), and 1645(C=C). The presence of the alkene group in *14* was confirmed by a distinctly positive Baeyer test. The NMR spectrum of *14* was definitive. A triplet at 9.83 ppm(CH_2CHO) accompanied by a singlet at 11.00(COOH) established the aldehyde(partially air oxidized) functional group. Moreover, a broadened AB quartet at 5.27 and 5.50 ppm for the alkene protons in *14* had an appearance very similar to corresponding signals in numerous model cyclopentenol analogs.

The successful fragmentation of *9* allows us to conclude that base-catalyzed fragmentation of 3,4-epoxy alcohols requires *syn* coplanar *or anti* coplanar geometry of the bonds a,b involved in the elimination. We hope that this clarification will enhance the use of this organic reaction in synthesis applications.

METHODS

IR spectra were recorded with a Beckman FT 1100 or Perkin-Elmer Model 710-B instrument. Proton NMR data were obtained on a JNM-PMX60 JEOL spectrometer (signals reported in ppm from TMS). The combustion analyses were performed by Galbraith Labs, Knoxville, Tennessee. The gas chromatograph was a Carle Analytical, col. temp. 200 degrees C, 10% CW-20M on Chrom W, 80/100 mesh, 1/8"×8'.

Dicyclopentadien-10-OL(*4*).

Dicyclopentadien-3-ol (Woodward, Katz, 1959) (2.108 g) was taken up in 45 ml of dry, distilled toluene and the solution was refluxed under nitrogen for 21 hours. Removal of the solvent provided the oily product mixture. A 0.820 g sample of the product was chromatographed on a column of neutral alumina (2.2×27 cm) made up and eluted with benzene. Fractions of 10 ml each were collected (nos. 1-36). Fractions 5-6 gave 0.038 g of *6*; nos. 16-26 (0.261 g *4*); nos. 27-36 (0.387 g starting 3-ol). *4*: mp 50.5-51.5 deg C; tosylate ester mp 95-6(lit. values 52-3, 96-7 deg, respectively) (Woodward, Katz, 1959).

Compound *4* formed a phenylurethan derivative, mp 108-110 deg C,

Calc. for C17H$_{17}$NO$_2$: C 76.40, H 6.37%
Found: C 76.28, H 6.36%

6: one spot on TLC, Rf 0.7(5% methanol in benzene); IR (neat)-1625, 1580 cm^{-1}(C=C), 1125(C-O-C). NMR(CCl_4)- 5.5-6.0 ppm(8H), 1.3-4.0(14H). The IR and complex NMR spectra were nearly identical to those of a 10-ol/3-ol mixture, suggesting ether structure *6*.

Calc. for $C_{20}H_{22}O \cdot 1.4H_2O$: C 79.16, H 8.17%

Found: C 79.23, H 7.78%

Dicyclopentadien-10-ol-8,9-epoxide(*5*).

To 50 mg of *4* in 2 ml benzene containing ca 2 mg vanadyl acetylacetonate(VO(acac)$_2$) was added dropwise 0.08 ml of 90% t-butyl hydroperoxide in 2 ml benzene. The blood-red solution was stirred at room temperature for 1.5 hours and 15 ml of diethyl ether was added. The organic solution was extracted 2×20 ml with sat. NaHSO$_3$, then once with water. The combined aqueous phase was extracted with an equal volume of ether. The organic layers were combined, dried(MgSO$_4$), filtered, and evaporated to give 35 mg of *5*(one spot on TLC, Rf 0.55(5% methanol in benzene)).

5: IR(neat)-3500 cm^{-1}(OH), 1620(C=C), 840(epoxide). NMR(CCl_4)-

5.63 ppm(2H, complex)(alkene H), 3.50, 3.36(2H, broadened AB pattern)(epoxy H), 3.50(1H, s)(H-C-O), 1.0-3.0(complex). Comparison of these data to those of numerous model dicyclopentadienes and epoxides strongly indicated structure *5*.

Epoxy alcohol *5* was recovered unchanged when dissolved in dry, distilled(from LiAlH$_4$) THF and treated with excess potassium t-butoxide.

Preparation of *13*.

Bicyclic alcohols *12*, prepared according to the procedure of Hall(1960), were seen by GC analysis to be approximately an equimolar mixture of 2-OH and 3-OH regio- and stereoisomers. To a chilled solution of 0.218 g*12* (1.76 mmol) in 2 ml CH_2Cl_2 was added dropwise at 0 deg C with stirring, 0.426 g of m-chloroperbenzoic acid(2.1 mmol) in 5 ml CH_2Cl_2. The reaction mixture was refrigerated at 4 deg C for 3 days after which the precipitated m-chlorobenzoic acid was removed by gravity filtration. The filter cake was washed with a little cold CH_2Cl_2 and the filtrate diluted with diethyl ether. This organic solution was washed successively with 1×20 ml sat. NaHSO3 and 2×20 ml sat. NaHCO$_3$. The combined aqueous layers were back-extracted with CH_2Cl_2 and the combined organic phase was dried(MgSO$_4$), filtered, and evaporated to give

0.148 g(60%) of a colorless glass *13*. IR(neat)- 3500 cm⁻¹(OH), 850(epoxide). NMR(CCl₄)-no alkene H's. 4.07 and 3.67 ppm(1H)(H-C-O), 3.23(2H, broad s)(epoxide H).

Fragmentation of *9*.

The product *13* in 12 ml dry, distilled THF was treated with 2.06 equivalents of potassium t-butoxide. The reaction solution was vigorously stirred overnight at room temperature under nitrogen, and filtered through a column of neutral alumina, eluting with chloroform. After removal of solvents, the NMR and IR spectra(discussed in the text) were taken.

LITERATURE CITED

Alder, K., Heimbach, K. Reubke, R. 1958, Uber den Sterischen Verlauf der Addition von Acrylnitril an cyclische Diene. *Ber.* 91:1516-24.

Dev, S., Patil, D. G., Chawla, H. P. S. 1983. Heterolytic Cleavage of Homoallylic Alcohols. *Indian J. Chem.* 22B: 206-211.

Grob, C. A. 1969. Mechanisms and Stereochemistry of Heterolytic Fragmentation. *Angew. Chem. internat. Edit* 8(8): 535-46.

Hall, H. K. 1960. Synthesis and Polymerization of Atom-bridged Bicyclic Lactams. *J. Am. Chem. Soc.* 82: 1209-15.

Holton, R. A., Kennedy, R. M. 1984. Stereochemical Requirements for Fragmentation of Homoallylic Epoxy Alcohols *Tetr. Letters.* 25: 4455-8.

Holton, R. A. et al. 1988. A Synthesis of Taxusin. *J. Am. Chem. Soc.* 110: 6558-60.

Holton, R. A. 1984. Synthesis of the Taxane Ring System. *J. Am. Chem. Soc.* 106: 5731-2.

Sharpless, K. B., Verhoeven, T. R. 1979. Metal-Catalyzed Oxygenations of Olefins with t-Butyl Hydroperoxide. *Aldrichimica Acta.* 12(4): 63-74.

Sharpless, Behrens, C. H. 1983. New Transformations of 2,3-Epoxy Alcohols and Related Derivatives. *Aldrichimica Acta.* 16(4):67-79.

Satoh, T. et al. 1969. Reduction of Organic Compounds with Sodium Borohydride-Transition Metal Systems. *Tetr.Letters.* (52): 4555-8.

Waddell, T. G., Ross, P. A. 1987. Chemistry of 3,4-Epoxy Alcohols. Fragmentation Reactions. *J. Org. Chem.* 52:4802-4.

Woodward, R. B. Katz, T. J. 1959. Mechanism of the Diels-Alder Reaction.*Tetrahedron,* 5: 70-89.