Reduction of Epoxides. IV. Lithium Aluminum Hydride Reduction of Cyclohexene Oxides Containing Neighboring Oxygen Groups[1]

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The effects of β-hydroxy and methoxy substituents on the lithium aluminum hydride reduction of cyclohexene oxides have been examined. Contrary to reports in the literature, these reactions in flexible systems exhibit little regioselectivity. Some conformationally rigid epoxy alcohols were also reduced; a small amount of "abnormal" opening product is observed in some instances, presumably formed *via* a boatlike transition state and facilitated by metal–oxygen bridging. *cis*- and *trans*-1,3-cyclohexadiene diepoxides were also subjected to lithium aluminum hydride reduction, and the diol product distributions are analyzed in terms of a two-step reduction mechanism.

The lithium aluminum hydride reductions of cyclohexene oxides generally yield alcohol products predictable on the basis of trans coplanar (diaxial) opening. In our earlier work,[1] we examined in detail the effects of alkyl substituents attached either at an oxirane position or a more remote carbon; these studies allowed the determinations of the energetic preference for various chair and boat transition states in the reduction, and established some factors which lead to "abnormal" opening of the epoxide ring.

The literature contains a number of reports of hydride reductions of β-oxygen substituted cyclohexene oxides where the substituent appears to play a major role in the direction of oxirane opening[2] An example is found in the work of Fales and Wildman[3] on the alkaloid crimamidine and its *o*-tetrahydropyranyl derivative, where the two materials exhibit different regioselectivity on hydride attack. The epoxide oxygen and the β-hydroxyl group are trans in crimamidine, and reduction *via* initial reaction of the alcohol function and subsequent intramolecular attack by *O*-aluminate may explain the observed selective formation of 1,3-diol. The model system, *trans*-3-hydroxycyclohexene oxide, has been reported by Henbest and Wilson[4] to yield mostly *trans*-1,2-diol, accompanied by some *trans*-1,3-diol, with the latter product presumed to arise by the intramolecular mechanism mentioned above. The corresponding *O*-methyl ether (*trans*-3-methoxycyclohexene oxide) has been reported[5] to give "mainly" *trans*-2-methoxycyclohexanol on $LiAlH_4$ reduction, in apparent agreement with the result obtained with the crimamidine *o*-THP derivative.[3]

A different feature may arise in the reduction of a *cis*-3-hydroxycyclohexene oxide, namely intramolecular aluminum complex assisted opening. Henbest[4] has reported that the simple model, *cis*-3-hydroxycyclohexene oxide, yields more than 90% of *cis*-1,2-diol on $LiAlH_4$ reduction, and postulated that the product arises from diaxial opening of the half-chair conformer in which the hydroxyl group (or its *O*-metalated derivative) exists in the pseudoequatorial position. On the other hand, a more recent study[6] involving 3α,4α-epoxy-5α-hydroxycholestane (where the 5-hydroxy group is fixed in the pseudoaxial position), indicates similar regioselectivity; the preferred formation of 4α,5α-diol in this instance constitutes a formal violation of the rule of diaxial opening.

Many of the pertinent reactions were carried out prior to the widespread use of vapor phase chromatography, or with materials which did not lend themselves readily to complete analysis of product mixtures. In order to establish more precisely the features leading to regioselectivity in these reductions, and to examine the possibilities of oxidative inversion[7] and syn opening on reduction, we have reexamined some of the earlier work and also made use of fixed conformation derivatives in $LiAlH_4$ reductions.

Results and Discussion

The product distributions obtained on reduction of *cis*- and *trans*-3-hydroxy- and 3-methoxycyclohexene oxides by $LiAlH_4$ in ether solvent are displayed in Table I. These data show clearly that, in these flexible

TABLE I[a]

	Epoxide	cis-1,2	trans-1,2	trans-1,3	cis-1,3
1		60	0	0	40
2		43	0	0.5[b]	57
3		0.3[b]	22	77	0.8[b]
4		0	52	47	1[b]

[a] The products were analyzed as the acetates by vpc. [b] Products attributed to oxidative inversion.[7]

derivatives, neither the hydroxy nor the methoxy substituent exhibits any strong directing influence on the reduction. In fact, the cis compounds **1** and **2** react in

(1) (a) Part III: D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Amer. Chem. Soc.*, **91**, 2649 (1969). (b) Supported in part by grants from the National Science Foundation, GP 9383, and the Petroleum Research Fund, administered by the American Chemical Society (AC-5744).

(2) For a recent excellent review of epoxide chemistry, see H. Z. Sable and J. G. Buchanan in "Selective Organic Transformations," Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1972.

(3) H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 181 (1961).

(4) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(5) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, *J. Amer. Chem. Soc.*, **80**, 2237 (1958).

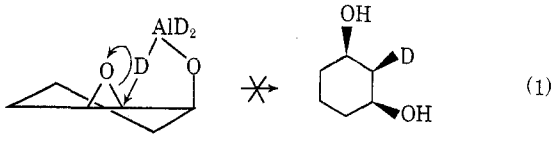
(6) E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Lett.*, 5261 (1967).

(7) B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 3185 (1964).

a less regioselectivity manner than *cis*-3-methylcyclohexene oxide, which gives 98% of 2-methylcyclohexanol.[8] The regioselectivity of the trans alcohol **3** is very similar to that observed with *trans*-3-methylcyclohexene oxide.[8] In the cases of the ethers **2** and **4**, the nearly equal amounts of 1,2 and 1,3 products suggests that either steric, polar, and conformational effects are slight, or that a subtle balancing of these effects leads to the observed absence of selectivity.

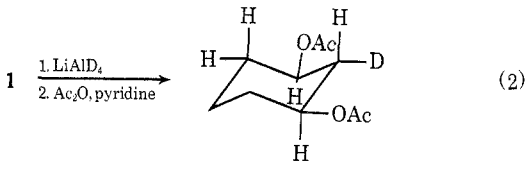
One interesting feature of the data in Table I is the absence or very low level of oxidative inversion[7] which occurs during reaction. It might be argued that, in the alcohols **1** and **3**, initial reaction of $LiAlH_4$ with the hydroxyl group forms some aluminum hydride, which is known to diminish this epimerization process.[7] However, the similar behavior of the ethers **2** and **4** indicates that some other explanation must be involved. In simple alkyl-substituted cyclohexene oxides, oxidative inversion occurs to the extent of *ca.* 10% of overall reduction. Apparently the electronegative oxygen substituent makes the lithium alkoxide (initially generated on reduction of the epoxide) less prone to act as a hydride donor; this view is supported by the observation that electronegative substituents enhance the rate of sodium borohydride reduction of cyclohexanone.[9]

The minor but still significant (40%) product formed on reduction of **1** could conceivably arise by intramolecular syn opening of the oxirane ring through the *O*-aluminate derivative as shown in eq 1. To test this



(1)

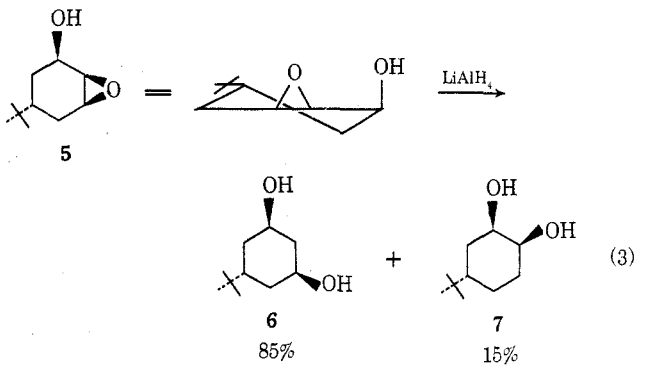
possibility **1** was reduced with lithium aluminum deuteride. The isolated *cis*-1,3-diol was analyzed, as the diacetate, by nmr, which demonstrated that this product contained the 2 deuterium in the trans position, thus ruling out eq 1 as an appreciable pathway (we estimate that $\geq$10–15% would have been detected). The nmr spectrum of the HCOAc protons showed a



(2)

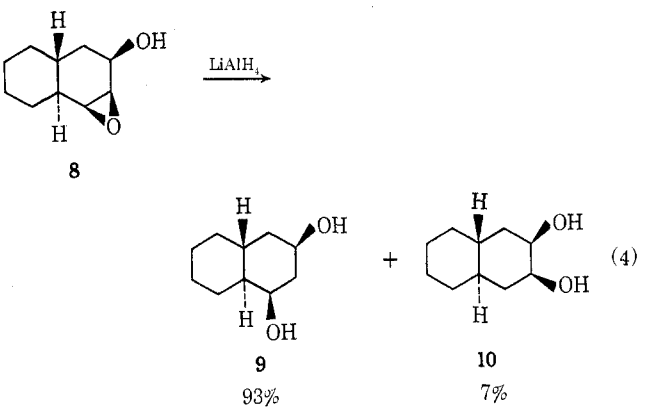
well-defined triplet (J = 11 Hz) with each line further split into a doublet (J = 4.2 Hz), centered at δ 4.68 ppm, the result of two axial–axial and one axial–equatorial couplings. This product thus most reasonably arises by normal diaxial opening of the half-chair conformer shown in eq 1, but by anti attack by a second molecule of $LiAlH_4$. Note that this implies that the initially formed *O*-aluminate does not have a very large conformational preference.

Fixed conformation model systems were examined to further delineate the effects of pseudoaxial and pseudoequatorial cis hydroxyl groups in the $LiAlH_4$ reduction. Compound **5**, in which the conformational preference of the remote *tert*-butyl group forces the hydroxyl group to assume the pseudoaxial position, gives the product distribution shown in eq 3. The major prod-



(3)

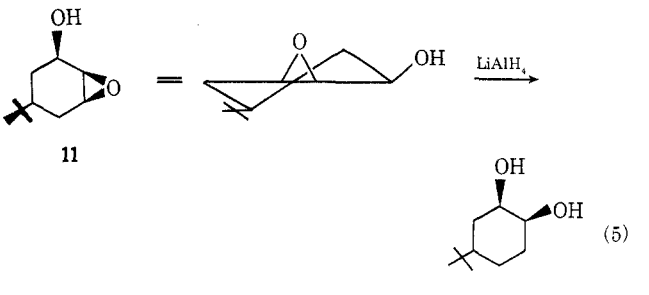
uct **6** is that derived by normal diaxial opening of the oxirane ring. The minor product **7** arises by the abnormal mode involving a boat transition state.[1] Although only 15% of the latter process occurs, this would still be unexpected in the absence of some specific directive effect of the pseudoaxial hydroxyl group, since the parent system, *trans*-4-*tert*-butylcyclohexene oxide, gives >99% of normal diaxial opening.[7] A conformationally analogous system **8** was also subjected to $LiAlH_4$ reduction. The results, shown in eq 4, are com-



(4)

parable to those obtained with **5**; the somewhat greater percentage of normal as compared to abnormal opening in the octalin oxide reduction may be ascribed to the lower flexibility of the bicyclic compound, making the boat transition state process even more unfavorable.

When the hydroxyl group is fixed in the pseudoequatorial position, as in compound **11**, the cis epoxide ring is cleaved exclusively (or nearly so; the experimental uncertainty is greater in this case owing to working with a sample containing isomeric impurities) in the normal diaxial mode (eq 5).



(5)

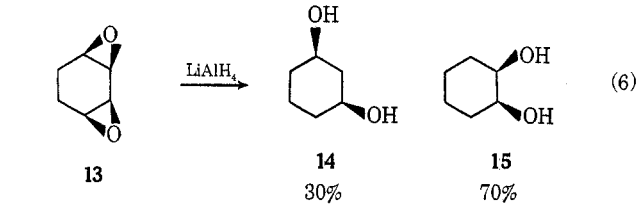
(8) B. Rickborn and W. E. Lamke, II, *J. Org. Chem.*, **32**, 537 (1967).
(9) H. Kwart and T. Takeshita, *J. Amer. Chem. Soc.*, **84**, 2833 (1962).

The data from eq 3 and 4 indicate that the pseudoaxial hydroxyl group does exert an effect on the $LiAlH_4$ reduction process which causes the usually large[1] difference in activation energies between normal (chair) and abnormal (boat) opening to be diminished. Whether the effect has its origin in some kind of specific neighboring group participation (intramolecular complex formation involving either lithium or aluminum) or is simply a polar effect of adjacent alkoxide remains unanswered. It is clear, however, that the effect is not sufficiently large to overcome the preference for normal diaxial (chair) opening in the absence of other (*e.g.*, conformational or steric) influences. Examination of models of the more complex systems where "abnormal" $LiAlH_4$ openings have been reported[3,6] in fact suggests that conformational and remote steric effects are likely the features most responsible for the observed regioselectivity.

Using the data from the reduction of compounds **5** and **11**, *i.e.*, by assuming that the *tert*-butyl group does not exert some undeterminable effect on the course of reduction, one may calculate that the simple system **1** is reduced *via* 53% of the pseudoequatorial and 47% of the pseudoaxial hydroxyl conformer. Thus regardless of the state of hydroxyl group, whether present as a lithium salt or aluminate derivative, it does not appear to have an energetically large conformational preference.

Although we have not examined conformationally fixed model systems in which the hydroxyl group and oxirane function are trans related, the mixture of diols obtained on reduction of **3** (Table I) can easily be accommodated by assuming that both half-chair conformers contribute appreciably to the reduction process in this flexible compound.

Finally, we have briefly explored the question of selectivity on reduction of *cis*- and *trans*-1,3-cyclohexadiene diepoxides. These data are shown in eq 6 and 7.



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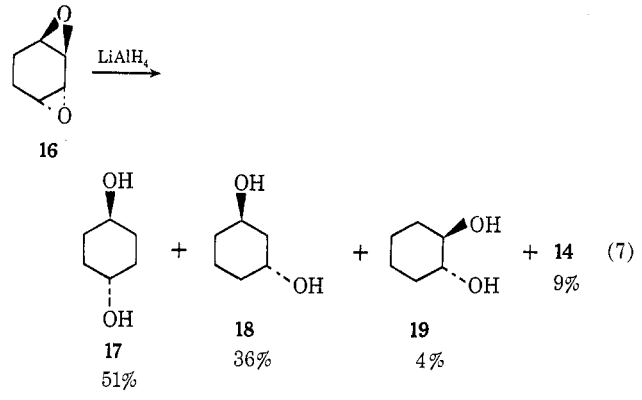
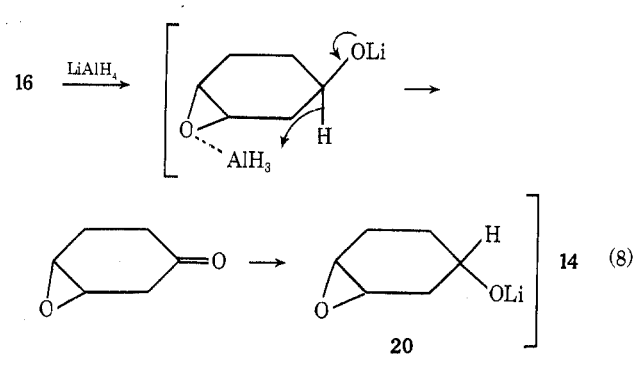


(7)

These systems are complicated by the fact that a double reduction must occur in two distinct steps; we can refer to attack at either the 1 or 4 (equivalent) positions as "exterior" and at the 2 or 3 position as "interior." Looking first at the cis diepoxide, initial exterior attack will lead to (presumably) the same intermediate as formed in the reduction of **1**, which should in turn be reduced to 60% 1,2-diol (**15**) and 40% 1,3-diol (**14**). This suggests that 50% of the initial hydride attack is exterior and 50% interior, *i.e.*, that the initial reduction of **13** is completely void of regioselectivity. The data in eq 6 further imply that the intermediate formed by initial interior attack must lead exclusively, or nearly so, to 1,3-diol (**14**).[10]

The trans diepoxide, by analogous reasoning, appears to undergo much more regioselective interior initial hydride attack. The small amount of *trans*-1,2-diol (**19**) formed, when viewed in connection with the reduction of compound **3**, implies that little more than 10% of exterior initial hydride attack takes place. The intermediate formed by initial hydride attack is further reduced to **17** and **18**, along with, interestingly, 9% of oxidative inversion product **14** (see eq 7).[10] The formation of this appreciable quantity of *cis*-1,3-diol, considered in connection with the absence of *cis*-1,2- and *cis*-1,4-diol, suggests that some special geometrical feature leads to oxidative inversion in the reduction of **16**. A reasonable explanation is that the epimerization takes place in the initial reduction step, as outlined in eq 8.



(8)

It should be noted that the proposed epimerized intermediate **20** is identical with the initially formed intermediate in the reduction of **13**, which in turn is converted exclusively to **14** (*i.e.*, no *cis*-1,4-diol should be formed, and none is observed).

Experimental Section

All lithium aluminum hydride reductions were carried out in ether solvent using 1 mol of $LiAlH_4$ per mole of substrate. The isolation procedure was that recommended by Fieser and Fieser.[12] The crude alcohol products were converted directly to acetate derivatives for further analysis.

Epoxidation of 3-acetoxycyclohexene with *m*-chloroperbenzoic

(10) We were unable to effect the separation of *cis*-1,3- and *cis*-1,4-cyclohexanediol diacetate by vpc; however, the preparative vpc collected sample of **14** had an ir spectrum identical with that of authentic *cis*-1,3-diol, and different from that of the *cis*-1,4-diol. This observation is somewhat disturbing, since Henbest and Nicholls[11] have reported that the $LiAlH_4$ reduction of *cis*-4-hydroxycyclohexene oxide gives *cis*-1,4-diol; they obtained a recrystallized dibenzoate ascribed to this material. It appears that either Henbest's conclusion is incorrect or our assumption that the intermediate formed from the diepoxide is identical with that obtained from the analogous hydroxy epoxide needs to be modified.

(11) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 4608 (1957).

(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1968, p 584.

acid afforded a mixture[13] (68% cis, 32% trans), which was saponified and subjected to spinning band distilation to give pure cis (**1**), bp 83° (10 Torr), and trans (**3**) compounds, bp 92° (10 Torr).[14]

Lithium aluminum deuteride reduction of **1** followed by acetylation gave a mixture, separated by preparative vpc, consisting of 67% of *trans-3-d-cis*-2-acetoxycyclohexyl acetate, nmr δ 1.3–2.0 (m, 9 H), 2.01 (s, 6 H), 4.81–5.13 (m, 2 H), and 33% of *trans-2-d-cis*-3-acetoxycyclohexyl acetate, nmr δ 1.0–2.1 (m, 9 H), 2.01 (s, 6 H), 4.68 ppm (d of t, J = 4.2 and 11 Hz, 2 H).

The *cis*- and *trans*-3-methoxycyclohexene oxides (**2** and **4**) were prepared by the procedure of Bannard and Hawkins.[15]

Authentic samples of the methoxy acetates and diacetates derived from **1**–**4** by reduction and acylation were available from earlier work.[16]

The procedure of Chamberlain and coworkers was followed to prepare *cis*-2,3-epoxy-*trans*-5-*tert*-butylcyclohexanol (**5**).[14] The product obtained from one recrystallization of the *p*-nitrobenzoate derivative followed by saponification was contaminated with 2% of the isomeric *trans*-2,3-epoxy-*trans*-5-*tert*-butylcyclohexanol. This material was used directly in the $LiAlH_4$ reduction, giving a mixture of diols which was in turn converted to diacetates for vpc analysis (Carbowax 20M, 150°). The product consisted of 14% of *trans*-5-*tert*-butyl-*cis*-1,2-cyclohexanediol (**7**),[17] nmr (diacetate) δ 0.85 (s, 9 H), 1.0–2.1 (m, 7 H), 1.93 and 2.04 (s, 3 H each), 4.6–4.8 (m, 1 H), 5.1–5.4 ppm (m, 1 H), further characterized as having the same retention time as the *cis*-1,2-diacetates (not separated under our vpc conditions) derived by applying the Woodward–Brutcher procedure[18] to 4-*tert*-butylcyclohexene; 84% of *trans*-5-*tert*-butyl-*cis*-1,3-cyclohexanediol (**6**),[19] diacetate having identical properties with those of material obtained by oxymercuration–reduction[19] of *trans*-5-*tert*-butyl-2-cyclohexenol; and 2% of a peak assumed to te *trans*-5-*tert*-butyl-*trans*-1,3-cyclohexanediol (from the isomeric impurity in the starting material).

The sample of *cis*-2,3-epoxy-*cis*-5-*tert*-butylcyclohexanol (**11**)[14] obtained by epoxidation of 95% pure *cis*-5-*tert*-butyl-2-cyclohexenol (5% trans isomer) contained 4% of *trans*-2,3-epoxy-*cis*-5-*tert*-butylcyclohexanol[14] and 5% of **5**. Reduction of this mixture gave *cis*-5-*tert*-butyl-*cis*-1,2-cyclohexanediol (**12**), 91%, having identical retention time with that of the authentic cis diol derivative obtained by the Woodward–Brutcher procedure as described above, and two other peaks (4 and 5%) attributed to reduction of the isomeric impurities in the starting material.

Epoxidation of *trans*-bicyclo[4.4.0]dec-4-en-*trans*-3-ol[20] with *m*-chloroperbenzoic acid gave a mixture (97:3); the major product, based on analogy with the work of Chamberlain, *et al.*,[14] the reduction data, and other evidence presented below, was *trans*-bicyclo[4.4.0]dec-*trans*-4,5-epoxy-*trans*-3-ol (**8**), while the 3% contaminant was the isomer in which the hydroxyl group and epoxide were trans related. Reduction of this material gave a mixture, again analyzed as the diacetates, with vpc retention times of 20, 23, and 34 min (relative peak area 6, 3, and 91%, respectively) using a 2M 18% XF-1150 column at 175°. The shortest retention time peak proved to be that of *trans*-decalin-*cis*-2,3-diol (**10**), by comparison with an authentic sample prepared by the Woodward–Brutcher reaction on *trans*-2-octalin. The minor (3%) productwas *trans*-decalin-*trans*-2,3-diol, demonstrated by comparison with a sample obtained by acid-catalyzed hydration of *trans*-2-octalin oxide.[21] The major product was *trans*-bicyclo[4.4.0]decane-*cis*,*cis*-2,4-diol (**9**), nmr (diacetate) δ 0.8–2.1 (m, 14 H), 1.96 (two s, separated by 1 Hz, 3 H each, acetates), 4.8–5.1 ppm (m, 2 H), and had identical spectral properties with those of material prepared by oxymercuration–reduction[19] of the starting allylic alcohol.

cis-1,3-Cyclohexadiene diepoxide (**13**)[22] was prepared by thermal rearrangement of the endoperoxide formed by the reaction of singlet oxygen with 1,3-cyclohexadiene. We found it convenient to simply inject the endoperoxide into a vpc instrument (Carbowax 20M, 150°) and to preparatively collect the effluent of **13** rather than to work with the usual thermal rearrangement mixture.

trans-1,3-Cyclohexadiene diepoxide (**16**),[23] bp 60° (4 Torr), was obtained in 57% yield by *m*-chloroperbenzoic acid epoxidation of 1,3-cyclohexadiene monoepoxide.[24] The product contained 5% of an impurity having the same retention time and identical ir spectrum with that of the cis diepoxide; in view of the overall yield, a significant pot residue, and the observation that the cis diepoxide appears to be more acid sensitive than the trans material, the stereoselectivity of the epoxidation reaction remains unclear.[13] The trans diepoxide had nmr δ 1.84 (broad s, 4 H), 2.99 (m, 2 H), and 3.17 ppm (d of d, J = 3.2, 1.6 Hz, 2 H); ir 740, 785, 840, 887, 930, 970, 1195, 1245, 1430 cm^{-1}.

Lithium aluminum hydride reduction of **13** gave a mixture of diols in high yield consisting of 29.7% of **15**,[10] 70% of **14**, and 0.3% of material having the same retention time as that of *trans*-1,3-cyclohexanediol diacetate (oxidative inversion); the major products were characterized by comparison of vpc and spectral properties with those of authentic samples.

Reduction of **16** gave a mixture, analyzed as the diacetates, as shown in eq 7. A sample of commercial *cis*-1,4-cyclohexanediol was converted to the diacetate and proved to have an identical ir spectrum with that of preparatively collected **20** diacetate.[10]

Registry No.—**1**, 26828-72-8; **2**, 2867-30-3; **3**, 26828-73-9; **4**, 2699-17-4; **7** diacetate, 36736-20-6; **9** diacetate, 36736-21-7; **16**, 36736-23-9; *trans-3-d-cis*-2-acetoxycyclohexyl acetate, 36736-22-8; *trans-2-d-cis*-3-acetoxycyclohexyl acetate, 36736-24-0; lithium aluminum hydride, 16853-85-3.

(13) The literature contains conflicting reports regarding the stereospecificity of epoxidation of allylic alcohols. In our hands, 2-cyclohexenol invariably gave a mixture of isomers in which the cis material predominated (*ca.* 90%), but in general the ratio of products depends on the peracid, solvent and other reaction conditions. The acid-catalyzed decomposition of oxiranes is strongly influenced by these same variables and often exhibits considerable stereoselectivity;[8] this subsequent step may in fact be responsible for misleading reports of stereospecificity in epoxidation. The mixture we obtained from epoxidation of 3-acetoxycyclohexene differs substantially from that reported by Chamberlain, Roberts, and Whitham;[14] we have repeated this epoxidation using their conditions and obtain the same ratio of isomers reported by the English group.

(14) P. Chamberlain, M. L. Roberts, and G. H. Whitham, *J. Chem. Soc. B*, 1374 (1970).

(15) R. A. B. Bannard and L. R. Hawkins, *Can. J. Chem.*, **36**, 1241 (1958).

(16) M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **34**, 2781 (1969).

(17) C. W. Davey, E. L. McGinnis, J. M. McKeown, G. D. Meakins, M. W. Pemberton, and R. N. Young, *J. Chem. Soc. C*, 2674 (1968).

(18) R. B. Woodward and F. V. Brutcher, *J. Amer. Chem. Soc.*, **80**, 209 (1958).

(19) P. Chamberlain and G. H. Whitham, *J. Chem. Soc. B*, 1382 (1970).

(20) B. Rickborn and R. P. Thummel, *J. Org. Chem.*, **34**, 3583 (1969).

(21) M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2119 (1958).

(22) K. K. Mashewari, P. DeMayo, and D. Wiegand, *Can. J. Chem.*, **48**, 3265 (1970).

(23) P. Bedox and A. Ruyer, *C. R. Acad. Sci.*, **196**, 625 (1933); these authors proposed the diepoxide structure but proof of stereochemistry was not provided.

(24) J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971).