carboxylate esters. The discovery of a reaction pathway involving 2 equiv of base was followed by speculation about implications for general reactivity patterns.[4-6,9-11] Our work establishes product patterns that define the structure and general reactivity of intermediates in this pathway. Product and reactivity patterns in related cases of phosphate ester hydrolysis involving other catalysts such as Brønsted bases[17] and metal ions[18-21] remain to be elucidated. Since these pathways are likely to be important components of enzymatic catalysis of the reactions of phosphate esters, nucleotides, and nucleic acids, their elucidation will be of continuing importance.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for support through an operating grant. Nick Plavac provided us with assistance in obtaining the NMR results.

Registry No. Methyl ethylene phosphate, 2196-04-5.

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Mechanism of Cyclopentene-1-carboxaldehyde Formation by Ring Contraction of 2,3-Epoxycyclohexanols. Improved Synthetic Procedures

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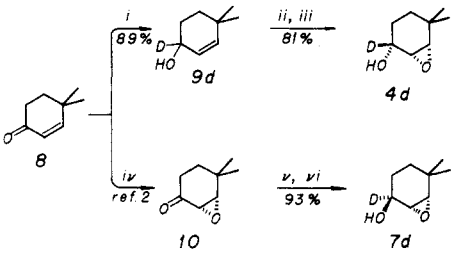
Complete analysis of the reaction mixtures from lithium bromide induced skeletal rearrangement of *cis*- and *trans*-1-deuterio-4,4-dimethyl-2,3-epoxycyclohexanol (**4d** and **7d**) showed that the formation of specifically deuterated 5,5- and 3,3-dimethylcyclopentene-1-carboxaldehydes (**1d**, **2d**, and **2**) occurred by a route that requires the participation of practically all possible configurational and conformational halohydrin intermediates. Small amounts of cyclohexenones were formed by intramolecular hydride (or deuteride) shifts in the lithium alcoholates of the epoxy alcohols and halohydrins. Nondeuterated trans epoxy alcohols were found to produce one aldehyde (**1** or **2**) almost exclusively whereas cis epoxy alcohols gave mixtures of **1** and **2**. Both *cis*- and *trans*-5,5-dimethyl-2,3-epoxycyclohexanol (**6** and **15**) gave isomer-free 4,4-dimethylcyclopentene-1-carboxaldehyde (**3**).

Although many examples of epoxide rearrangements are known,[1] skeletal rearrangements of epoxy alcohols seem to be rather neglected. We reported[2] a synthesis of the cyclopentene-1-carboxaldehydes **1-3** by lithium bromide mediated rearrangement of the *cis*-2,3-epoxycyclohexanols **4-6**. The last one gave access to *isomer-free* 4,4-dimethylcyclopentene-1-carboxaldehyde (**3**; Table I). This aldehyde (and the isomer **1**) has since then been utilized as a starting material in several natural product syntheses.[3] We have now improved the preparation of these aldehydes and obtained experimental evidence that suggests a rather intricate mechanism for the rearrangement of both *cis*- and *trans*-2,3-epoxycyclohexanols (Schemes 2 and 3).

The ring-opening, formation, and rearrangement reactions of epoxides[1] under basic or neutral conditions are governed by a few empirical "rules": (i) the ring opening reaction is S_N2 (or borderline S_N2) in character; (ii) Lewis acids catalyze these reactions (e.g., Li^+, Mg^{2+}, H^+, BF_3); (iii) in cyclohexane epoxides, the ring-opening is trans-1,2-diaxial in character (Fürst-Plattner rule); (iv) epoxide-ring formation from halohydrin salts requires a 1,2-trans-diaxial arrangement of the participating groups (microscopic reversibility of the Fürst-Plattner rule[1]); (v) in the rearrangement of cyclohexane derivatives, the migrating group and the leaving group must have an antiperiplanar relationship.

Scheme I[a]



[a] (i) $LiAlD_4$; (ii) *m*-CPBA; (iii) preparative gas chromatography; (iv) H_2O_2; (v) $NaBD_4/CeCl_3$; (vi) preparative liquid chromatography.

It is known from our earlier work[2] that the isomeric *cis*-2,3-epoxycyclohexanols **4** and **5**, on treatment with lithium bromide/hexamethylphosphoric triamide (HMPA), rearrange to give the aldehydes **1** and **2** in the approximate ratio 4:1 and 1:4, respectively. However, the **1**/**2** ratios per se do not give any clues to the detailed mechanism of the reaction. We now report a highly probable route to the cyclopentene-1-carboxaldehydes **1** and **2** (and **3**) based on rearrangement of the specifically deuterated cis and trans epoxy alcohols **4d** and **7d**, followed

(1) Buchanan, J. G.; Sable, H. Z. "Selective Organic Transformations"; Thyagarayan, B. S., Ed.; Wiley: New York, 1972; Vol. 2.
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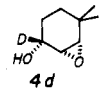
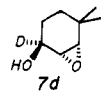
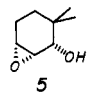
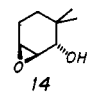
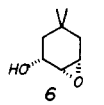
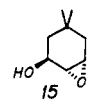
(3) Lactaral: Froborg, J.; Magnusson, G.; Thoren, S. *Acta Chem. Scand., Ser. B* **1974**, *28*, 265. Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1982**, *23*, 5509. Marasmic acid: Greenlee, W. J.; Woodward, R. B. *Tetrahedron* **1980**, *36*, 3367, 3361. Hirsutene: Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351. Capnellene: Stevens, K. E.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 4393. Silphinene: Paquette, L. A.; Leone-Bay, A. *J. Am. Chem. Soc.* **1983**, *105*, 7352. Isovelleranes: Bergman, R.; Wickberg, B., unpublished results.

0022-3263/86/1951-0212$01.50/0

Table I. Product Distribution in the Lithium Bromide Induced Rearrangement of Epoxycyclohexanols

starting material[a]	entry[b]	product yield,[c] %									
		 1d	 1	 2d	 2	 8d	 8	 11d	 11	 3	 16
 4d	A	70		10	19	0.4	0.5	0.1			
	B	63		6	19	7	4	1			
	C	52		2	9	27	8	2			
	D					11[d]					
	E	72		28							
	F	88		12							
 7d	G	78		1.5	1.4	7	12	0.1			
	H	41		5	29	6	4	15			
	I	75		6		18		1			
	J	94		2		4					
 5	K		19		73		2		6		
	L		3		34				63		
	M		26		59		6		9		
 14	N		0.5		88				11.5		
	O		4		71				25		
	P		2		87				11		
 6	Q									89	11
	R									88	12
	S									81	19
	T									5	95
 15	U									89	11

[a] Purity of starting materials (the impurity was the corresponding cis or trans compound): entries A, G, H, >99%; entries B–F, ~95%; entries I, J, ~87%; entries K–M, ~82%; entries N–P, ~96%; entries Q–T, ~99%; entry U, ~86%. [b] Entries A, G, K, N, Q, epoxy alcohol/LiBr/HMPA (1/2/2), refluxing toluene; entry B, **4d**/LiBr/HMPA/*t*-BuOLi (1/2/2/0.5), refluxing toluene; entries C, H, L, O, T, epoxy alcohol/LiBr/HMPA/*t*-BuOLi (1/2/2/1), refluxing toluene; entry D, **4d**/*t*-BuOLi (1/1), refluxing toluene; entries E, I, R, epoxy alcohol/LiBr/TMU (1/2/4), refluxing toluene; entries F, J, M, P, S, U, epoxy alcohol/LiBr (1/3), refluxing dimethoxyethane. [c] Yields were determined by capillary column gas chromatography and mass spectrometry; GC peaks <1% were omitted except for entries A, G, and N. [d] >50% of **4d** remained; some unidentified products were formed.

by complete analysis of the reaction mixtures. An important finding from a preparative point of view is that trans epoxy alcohols are more suitable as starting materials than the corresponding cis compounds that we used before.[2] The former gives the desired aldehyde (**1** or **2**) virtually free of the unwanted isomer.

Results and Discussion

The cyclohexenone **8** (Scheme I) was reduced with lithium aluminum deuteride, yielding the deuterated cyclohexenol **9d** (89%), which was then treated with *m*-chloroperbenzoic acid to give a mixture of *cis*- and *trans*-epoxycyclohexanols **4d** and **7d** (81%) in the ratio 95:5. Pure **4d** (>99%) was prepared by preparative gas chromatography. Oxidation of **8** with hydrogen peroxide gave the epoxy ketone **10** (90%), which was then reduced in the presence of cerium(III) chloride[4] by sodium borodeuteride to give a mixture of the trans and cis epoxy alcohols **7d** and **4d** (96%) in the ratio 87:13. Pure **7d** (>99%) was obtained by liquid chromatography. In the absence of cerium chloride, **10** gave approximately equal amounts of **4d** and **7d**.

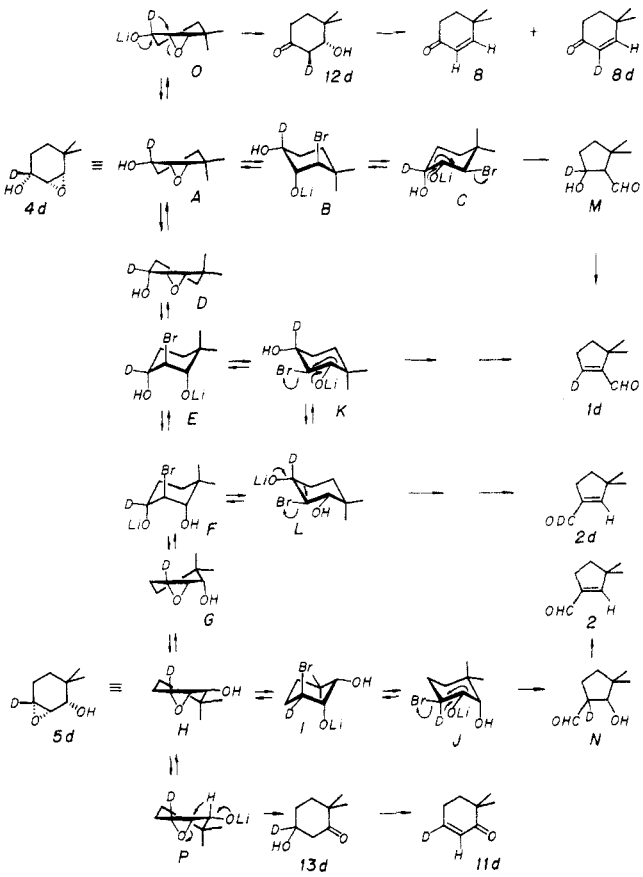
Table I shows the outcome of the rearrangement of **4d** and **7d**. With the cis compound **4d** (entries A–F), three aldehydes were formed, namely, the main product **1d**, which carried a vinylic deuterium atom, the isomeric aldehyde **2**, which had lost the deuterium label, and the aldehyde **2d**, with a deuterium atom in the formyl position. Furthermore, three ketones (total yield/ca. 1% of the reaction mixture; entry A) were formed, namely, ketone **8**, which had lost the deuterium label, ketone **8d**, carrying a vinylic α-deuterium atom, and ketone **11d**, with a vinylic β-deuterium atom. The structures were determined by a combination of ^{1}H NMR and GC–MS methods in comparison with the unlabeled material reported earlier.[2] The vinylic proton NMR signal had disappeared in the main product (**1d**) but was present in the isomers (**2** and **2d**). The presence of a formyl deuterium atom in **2d** was indicated by a slightly reduced intensity of the formyl ^{1}H NMR signal of the unseparable mixture **2**/**2d** as compared to the unlabeled material. GC–MS separated **1d** from **2**/**2d** and the relative intensities of the fragments showed that the ratio **2**/**2d** is roughly 2:1. The amounts of the ketones **8**, **8d**, and **11d** were determined by analogous reasoning (see Experimental Section).

From the experimental results and the rules for epoxide opening and rearrangement described above, we deduced a probable mechanism for the rearrangement of **4d** (Scheme II).

Compound **4d** is present in the two conformations A and D, A probably being the more stable one due to the pseudoequatorial position of the hydroxyl group. Nucleophilic attack on A by bromide ion (probably paired with lithium ion which is solvated by complexation with HMPA or *N,N,N',N'*-tetramethylurea, TMU) can only give

(4) Rucker, G.; Hörster, H.; Gajewski, W. *Synth. Commun.* **1980**, *10*, 623.

Scheme II



B (because of rule iii above), which inverts to give C. The latter is probably more stable than B due to fewer axial substituents and has the proper antiperiplanar arrangement of migrating and leaving groups necessary for ring contraction to give M. Expulsion of water (Li^+ catalyzed) gives the observed product **1d**. Bromide ion attack on the minor epoxycyclohexanol conformer D gives the bromohydrin salt E which can easily equilibrate to give either the isomeric salt F or the all-equatorial conformer K. The latter can rearrange to give M and then **1d**. However, the importance of this route cannot be evaluated from the deuterium-labeling experiment since the expected labeling pattern is the same as for **1d** obtained by the main route. The halohydrin salt F either gives L, which in turn rearranges to the observed product **2d**, or it forms the isomeric epoxycyclohexanol **5d** in the conformation G. Bromide ion attack on the more stable conformer H gives the bromohydrin salt I, which inverts to give J having the proper geometry for ring contraction to give N. Loss of HDO gives the observed product **2**. When the unlabeled epoxycyclohexanol **5** is used instead of **4d**, the same product mixture results but with reversed proportions of **1** and **2** (entry K in Table I).

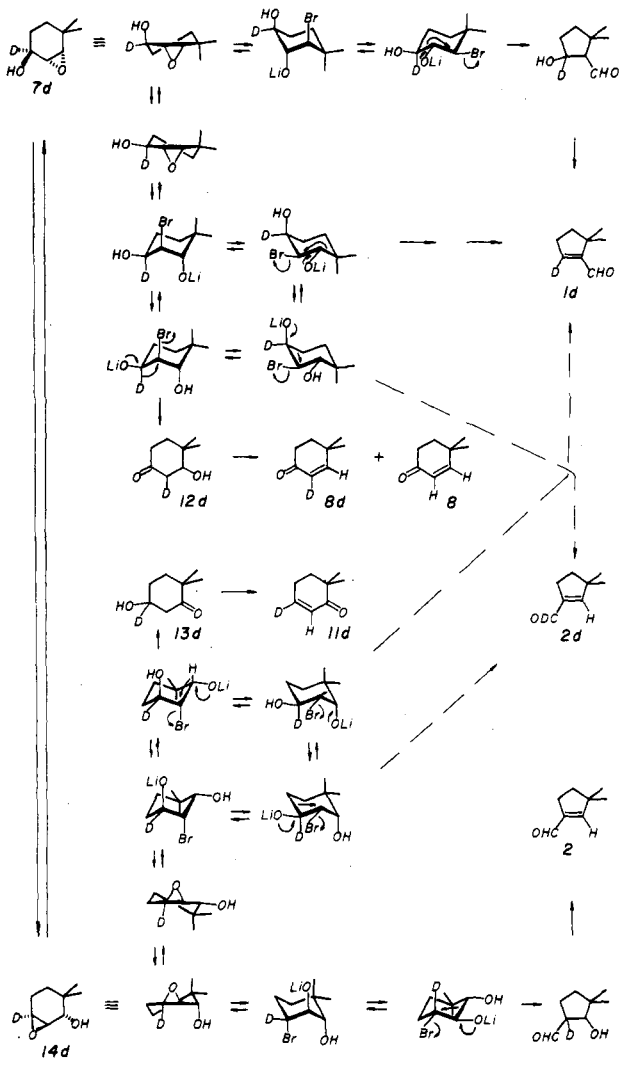
We conclude that on treatment of *cis*-epoxycyclohexanols with nucleophiles that are also good leaving groups (such as bromide ion), all possible halohydrin and epoxide conformers exist in equilibrium. When **4d** is used as starting material, the formation of epoxide G is slow, due to a kinetic "blockade" in one or several of the preceeding steps, which results in a higher proportion of the aldehyde **1d** as compared to the aldehyde **2**/**2d**. Such a blockade exists for the formation of (nondeuterated) D when **5** is used as starting material, and consequently aldehyde **2** is formed in preponderance of **1**. When a halohydrin salt conformer attains the proper geometry, an irreversible rearrangement occurs which finally leads to the observed products. It should be noted that substituent effects[1] (steric and polar) that are considered to be important in epoxide openings with nucleophiles that lack leaving-group properties are of little significance in the present type of *reversible* reactions. Only the relative concentrations and reaction rates of the precursors C, J, K, L, O, and P (Scheme II) determine the ratio of the products. It should also be noted that the bromohydrin conformations shown in Scheme II do not permit vicinal bromine and hydrogen atoms to attain an antiperiplanar relationship necessary for hydride migration, and indeed, only a very small amount of ketone was observed. (entry A, Table I). When extra base was added (entries B and C) more of **8**/**8d** was formed. Ketone **8**/**8d** was formed even when lithium bromide was omitted (entry D). This probably occurred by a direct deuteride shift/epoxide ring opening in the lithium salt of O, resulting in the β-hydroxy ketone **12d** (Scheme II). It is interesting to note that the ratio **8**/**8d** decreased in the basic reaction mixture as compared to the normal one. Water elimination from **12d** by a lithium ion assisted E2 mechanism should produce an excess of **8**. At high basicity, however, selective formation of the deuterated enolate of **12d** due to the primary isotope effect[5] (H is removed several times faster than D) should result in formation of **8d** as the main ketonic product, which was indeed observed (Table I). The ratio **8**/**8d** was easily determined by mass spectrometry. We also find that lithium ion complexation in the 1,3-diols E and F is not strong enough to prevent the existence of conformers K and L (since **2d** was formed). This is in agreement with the finding[6] that the lithium ion has two "catalytically active sites"; one is probably permanently occupied by the strong ligand HMPA.

With the *trans*-epoxycyclohexanol **7d** (Scheme III), the equilibrium situation is even more complicated, because *trans*-epoxycyclohexanols are known to interconvert (so-called epoxide migration) and bromide ion attack on the central carbon atom gives rise to *cis*-bromohydrins. This means that one conformer must exist where a ring hydrogen atom and the bromine atom are trans diaxially situated and thus a hydride (or deuteride) shift with displacement of bromide ion could occur, which should lead to ketone formation. This is indeed what we observe (Scheme III). Treatment of the deuterium-labeled trans epoxy alcohol **7d** with lithium bromide/HMPA in toluene (entry G, Table I) as before resulted in a mixture of the labeled and unlabeled aldehydes **1d**, **2d**, and **2**, together with the cyclohexenones **8**, **8d**, and **11d**, the last of which carried a full deuterium label as predicted. Since **7d** was free of **4d**, epoxide migration must be the reason for the formation of aldehyde **2** and ketone **11d** (there is no route from **7d** to **14d** that goes via bromohydrins!). Addition of lithium *tert*-butoxide augmented the equilibrium between **7d** and **14d**, which resulted in a drastic increase in the amount of the aldehyde **2**/**2d** and the ketone **11d** (entry H in Table I). The mechanism for the rearrangement of the *trans*-epoxycyclohexanol **7d** as described in Scheme III is based on the same set of rules as was used above for the cis compound **4d**.

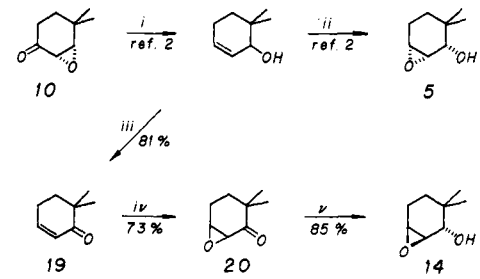
5d and **14d** were implied as transient intermediates in the reactions of **4d** and **7d**, respectively (Scheme II and III). However, since **4d** and **5d** happened to be coeluted on the capillary column used in the GC analyses, possible buildup of small amounts of the latter could not be demonstrated when **4d** was used as starting material. Buildup

(5) Melander, L.; Saunders, W. H. "Reacton Rates of Isotopic Molecules"; Wiley: New York, 1980.
(6) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693.

Scheme III

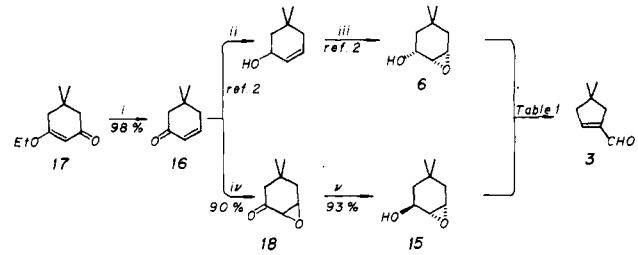


Scheme IV[a]



[a] (i) H_2NNH_2; (ii) *m*-CPBA; (iii) MnO_2; (iv) H_2O_2; (v) $NaBH_4/CeCl_3$.

Scheme V[a]



[a] (i) $LiAlH_4$, 0 °C; (ii) $LiAlH_4$, 25 °C; (iii) *m*-CPBA; (iv) H_2O_2; (v) $NaBH_4$.

of **14d** in the reaction of **7d** should be negligible in the absence of extra base (entry G, Table I) since very little material was found that originated from **14d**. However, when extra base was added the situation changed drastically (entry H). It was found in a separate experiment that **7d** could be partly transformed into **14d** by treatment with lithium *tert*-butoxide in toluene.

There remains a possibility that the six-membered halohydrin rings (with the LiO and Br groups in a 1,3-relationship) could rearrange to cyclopentene aldehydes in a two-step fashion, where an intermediate dialdehyde (such as 3,3-dimethylglutaric dialdehyde) undergoes an intramolecular aldol condensation[7] and water loss. However, since no isomeric cyclopentene aldehyde was formed when the epoxycyclohexanols **6** or **15** (Table I) were used, we prefer the mechanism shown in Schemes II and III. It has indeed been demonstrated[8] that 3,3-dimethylglutaric dialdehyde gives both possible cyclopentene aldehydes **3** and **1** under aldol condensation conditions. Furthermore, epoxycyclohexanes rearrange[6] to cyclopentanecarboxaldehydes; here, aldol intermediates are not possible.

The formation of the relatively high amount of ketone **16** from **6** (entries Q–S, Table I) was unexpected. However, the axial methyl group in the more stable conformer of **6** (corresponding to A in Scheme II) should hinder the attack by bromide ion so that the competing, base-induced hydride shift gains in importance. Addition of base to **6** (entry T, Table I) results in roughly inverted proportions of aldehyde **3** and ketone **16**.

Preparative Aspects. As can be seen in Table I, the use of the cis epoxy alcohols **4d** and **5** (entries A and K) led to a mixture of isomeric aldehydes but with very little ketone formation. The trans epoxy alcohols **7d** and **14** (entries G and N) on the other hand gave mainly one aldehyde but a substantial amount of ketone. Therefore, when "unsymmetrically" substituted aldehydes (like **1** and **2**) are desired, trans epoxy alcohols should be used since in most cases it would be easier to separate the aldehyde from the concomitantly formed ketone than to separate two isomeric aldehydes. The preparation of the "symmetrically" substituted aldehyde **3** can be performed from both the *cis*-**6** and *trans*-**15** epoxy alcohols since no isomeric aldehyde can be formed and approximately the same amount of ketone **16** was obtained with both compounds (entries Q–S and U, Table I).

Our original procedure[2] has a few drawbacks. We used hexamethylphosphoric triamide (HMPA) as lithium bromide solubilizing agent in toluene, but HMPA has since then been classified as a potent carcinogen. The synthesis of *cis*-epoxycyclohexanols calls for *m*-chloroperbenzoic acid (or possibly some other organic peroxide) oxidation of the corresponding allylic alcohol (Scheme V). The *m*-chlorobenzoic acid formed in the oxidation can be difficult to remove since it has a tendency to codistill with the desired product. As can be seen in Table I (entries E, I, and R), HMPA can be replaced by *N,N,N',N'*-tetramethylurea (TMU) for the rearrangement of both cis and trans epoxy alcohols without any drop in product yield or purity. In this case, 2 equiv of TMU are needed in order to keep the lithium bromide in solution. Even more advantageous is the finding that lithium bromide (excess) can be used without extra solubilizing agents in dimethoxyethane (or diglyme) even though this solvent has been reported to make the salt inactive for epoxide rearrangements.[6] We suspect that the hydroxyl group of the epoxy alcohols can compete favorably with the solvent for the lithium ion, thereby making it catalytically active (Table

(7) Suggested by Professor R. U. Lemieux.
(8) Wilson, S. R.; Turner, R. B. *J. Org. Chem.* **1973**, *38*, 2870.

I, entries F, J, M, P, S, and U).

We now consider the following alternative route to be the most practical one for the preparation of the synthetically valuable[3] 4,4-dimethylcyclopentene-1-carboxaldehyde (**3**): 5,5-Dimethyl-3-ethoxycyclohex-2-enone[9] (**17**) was reduced by adding $LiAlH_4$ to the ketone at 0 °C to give, after acidic workup, 5,5-dimethylcyclohexen-3-one[9] (**16**). This constitutes an improvement over the original procedure.[9] Oxidation of **16** with hydrogen peroxide[10] gave the epoxy ketone **18**. The overall yield from **17** was 90%. Reduction with sodium borohydride gave a mixture of trans and cis epoxy alcohols **15** and **6** (93%) in the ratio 86:14. Treatment of the mixture of **15** and **6** with an excess of lithium bromide in refluxing dimethoxyethane (or diglyme at 120 °C) for approximately 25 min, followed by distillation, gave pure **3** in 60% yield. For the preparation of **3** via **6**, see ref 2 and Experimental Section.

Predictions. On the basis of the mechanistic schemes put forward here, we make certain predictions regarding the scope and limitations of the rearrangements of epoxycyclohexanols to cyclopentene aldehydes: Epoxy alcohols that are locked in one preferred conformation should not rearrange to five-membered ring aldehydes because this requires a chair–chair conformational "flip" in an intermediate bromohydrin (e.g., B → C in Scheme II). Only epoxide migrations leading to isomeric epoxy alcohols and hydride shifts leading to ketones should be possible (e.g., **4d** → **5d** and 0 → **12d**, respectively; Scheme II).

Experimental Section

All liquid chromatography purifications were performed in the gravity mode. Gas chromatographic analyses of the products in Table I were performed on a Varian 3700 instrument, equipped with a 6-m SE-30 capillary column, flame ionization detector, and electronic integrator. Determinations of the ratio between deuterated and nondeuterated products were performed by gas chromatography–mass spectrometry on a modified Varian MAT 112 instrument. NMR spectra were obtained on a Varian XL 300 instrument. The lithium aluminum deuteride (Aldrich) and sodium borodeuteride (Merck) contained less than 2 mol % of hydrogen.

1-Deuterio-4,4-dimethylcyclohex-2-enol (9d). 4,4-Dimethylcyclohex-2-enone[12] (**8**; 1.1 g; 8.8 mmol) was dissolved in dry ethyl ether (20 mL) and cooled (0 °C), and lithium aluminum deuteride (0.2 g; 4.7 mmol) was added. After 10 min, the cooling bath was removed, and the mixture was allowed to stand at room temperature for 15 min. Water (0.2 mL), sodium hydroxide solution (2 M; 0.2 mL), and water (0.6 mL) were added, which gave a white precipitate. After 20 min, the mixture was filtered, and the precipitate was washed with dichloromethane. The combined organic solutions were carefully concentrated to give a residue (1.1 g), which was chromatographed (SiO_2; 1:2 ethyl acetate/hexane) to give pure **9d** (1.0 g, 89%) with approximately the same physical characteristics as the nondeuterated material,[2] except for the ^1H NMR data: ($CDCl_3$, Me_4Si) δ 5.58, 5.52 (AB q, each 1 H, J_{AB} = 10.0 Hz, vinylic H), 1.01, 0.97 (s, each 3 H, CH_3).

1-Deuterio-4,4-dimethyl-*cis*-2,3-epoxycyclohexanol (4d). Alcohol **9d** (1.0 g; 7.9 mmol) was dissolved in dichloromethane (20 mL) and cooled (0 °C), and *m*-chloroperbenzoic acid (75%; 2.3 g; 10 mmol) was added. The mixture was stirred for 20 min, filtered to remove *m*-chlorobenzoic acid, and concentrated. The residue was chromatographed (SiO_2; 1:2 ethyl acetate/hexane) to give 920 mg (81%) of **4d** containing approximately 5% (by GC) of the trans compound **7d**. The mixture had approximately the same physical characteristics as the nondeuterated material.[2] Pure **4d** (>99%) was obtained by preparative gas chromatography on an SE-30 column (15% on Chromosorb A; 2.3 m): ^1H NMR ($CDCl_3$, Me_4Si) δ 3.35, 2.92 (d, each 1 H, J = 3.9 Hz, epoxy H), 1.08, 1.02 (s, each 3 H, CH_3).

1-Deuterio-4,4-dimethyl-*trans*-2,3-epoxycyclohexanol (7d). 4,4-Dimethyl-2,3-epoxycyclohexanone[2] (**10**; 1.0 g; 7.1 mmol) was dissolved in a solution of $CeCl_3 \cdot 6H_2O$[4] (3 g; 8 mmol) in methanol (20 mL). After 1 min, sodium borodeuteride (170 mg; 4 mmol) was added at room temperature (gas evolution). The reaction temperature increased to 35 °C. After 10 min, the mixture was concentrated, diluted with water (5 mL), and extracted with ethyl ether (2 × 6 mL). Removal of the solvent and chromatography of the residue (SiO_2; 1:2 ethyl acetate/hexane) gave 950 mg (93%) of **7d** containing approximately 13% of the cis compound **4d**. Rechromatography gave pure (>99%) **7d**: ^1H NMR ($CDCl_3$, Me_4Si) δ 3.13, 2.82 (d, each 1 H, J = 3.7 Hz, epoxy H), 1.06 (s, 6 H, CH_3); ^{13}C NMR δ 65.3 (t, 1 C, J_{CD} = 22 Hz, CDOH), 61.6, 57.7, 29.8, 29.2, 26.8, 26.6, 24.8. Anal. 7. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.92. Found: C, 67.2; H, 9.94.

6,6-Dimethylcyclohex-2-enone (19). 6,6-Dimethylcyclohex-2-enol[2] (6 g; 0.05 mol) was dissolved in hexane (400 mL) and active manganese dioxide[11] (20 g; 0.23 mol) was added with stirring, and the mixture was left overnight. The mixture was filtered on a Büchner funnel and then through a cotton plug, concentrated, and distilled to give pure **19** (4.75 g, 81%): bp_{12} 60–61 °C; $n^{21}{}_D$ 1.4704; IR 1685 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 6.88 (dt, 1 H, J = 10.0, 3.9 Hz, H-3), 5.91 (dt, 1 H, J = 10.0, 2.0 Hz, H-2), 2.38 (10-signal m, 2 H, H-4), 1.83 (t, 2 H, J = 6.1 Hz, H-5), 1.12 (s, 6 H, CH_3); ^{13}C NMR δ 204.6, 148.7, 128.3, 41.4, 36.2, 24.1 (2 C), 23.4. Anal. Calcd for $C_8H_{12}O$: C, 77.3; H, 9.74. Found: C, 76.6; H 9.69.

The dinitrophenylhydrazone was crystallized from ethanol/ethyl acetate and had mp 168–170 °C.

6,6-Dimethyl-2,3-epoxycyclohexanone (20). Ketone **19** (2.5 g; 0.02 mol) was dissolved in methanol (25 mL), and hydrogen peroxide solution (30%; 5.8 mL; 0.06 mol) was added. The mixture was cooled (15 °C) and sodium hydroxide solution (6 M; 1.7 mL; 0.01 mol) was added dropwise, while the temperature was kept below 16 °C. The mixture was stirred at room temperature for 3 h and then poured into water (25 mL). The water solution was extracted with ethyl ether (2 × 20 mL), and the ether phase was dried (Na_2SO_4), concentrated, and distilled to give pure **20** (2.05 g, 73%): bp_{13} 82–83 °C; $n^{21}{}_D$ 1.4611; IR 1715 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 3.56 (m, 1 H, H-3), 3.18 (d, 1 H, J = 3.9 Hz, H-2), 1.12, 1.02 (s, each 3 H, CH_3); ^{13}C NMR δ 209.6, 54.5, 53.5, 41.8, 29.2, 25.4, 25.0, 20.4. Anal. Calcd for $C_8H_{12}O_2$: C, 68.6; H, 8.63. Found: C, 69.2; H, 8.80.

6,6-Dimethyl-*trans*-2,3-epoxycyclohexanol (14). 6,6-Dimethyl-2,3-epoxycyclohexanone (**20**; 280 mg; 2 mmol) was dissolved in a solution of $CeCl_3 \cdot 6H_2O$[4] (710 mg; 2 mmol) in methanol (10 mL). After 1 min, sodium borohydride (80 mg; 2.1 mmol) was added, and the reaction mixture was treated as for the preparation of **7d** above, to give 240 mg of a mixture of **14** and **5** (85%) in the ratio 96:4. **14**: ^1H NMR ($CDCl_3$, Me_4Si) δ 3.50 (br s, 1 H, H-1), 3.25 (br s, 1 H, H-3), 3.01 (d, 1 H, J = 3.6 Hz, H-2), 2.00–1.75 (m, 2 H, H-4), 1.26–1.05 (m, 2 H, H-5), 0.96, 0.84 (s, each 3 H, CH_3); ^{13}C NMR δ 74.5, 56.6, 53.3, 32.6, 29.6, 28.1, 20.9, 18.4. Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.92. Found: C, 66.3; H, 9.65.

5,5-Dimethylcyclohex-2-enone[9] (16). 5,5-Dimethyl-3-ethoxycyclohex-2-enone[9] (**17**; 350 g; 2.08 mol) was dissolved in dry ethyl ether (1200 mL) and cooled (0 °C). Lithium aluminum hydride (25 g; 0.67 mol) was suspended in dry ethyl ether (400 mL) and added in portions during 30 min to the ketone solution at 0 °C. The mixture was stirred at room temperature for 1 h, ethyl acetate (20 mL) was added, and the mixture was poured into ice-cold sulfuric acid solution (2 M; 1500 mL). The phases were separated, and the aqueous phase was extracted with ethyl ether (200 mL). The combined ethyl ether solutions were dried (Na_2SO_4) and concentrated, and toluene (300 mL) was added and removed to give crude, dry **16** (251 g, 98%), which was used in the next step without further purification.

5,5-Dimethyl-2,3-epoxycyclohexanone (18). Ketone **16** (98 g; 0.78 mol) was dissolved in methanol (800 mL) and cooled (15 °C). Hydrogen peroxide solution (35%; 240 mL; 2.4 mol) was

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added, followed by sodium hydroxide solution (6 M; 20 mL), which resulted in a rapid increase of the temperature. Cooling was continued (the temperature reached a maximum of 36 °C) for 10 min, which gave a final temperature of 12 °C. NMR analysis showed that the reaction was complete and that a pure epoxy ketone had been formed. The reaction mixture was diluted with brine (20%; 1.5 L) and then extracted with ethyl ether (2 × 500 mL). The ether phase was washed with brine (500 mL) and dried (Na_2SO_4). The ether was removed, which gave crude **18** (99 g, 90%; >95% pure). An aliquot was distilled to give pure **18**: bp_{15} 80–81 °C; ^1H NMR ($CDCl_3$, Me_4Si) δ 3.52 (t, 1 H, J = 4.2 Hz, H-3), 3.22 (d, 1 H, J = 4 Hz, H-2), 1.03, 0.93 (s, each 3 H, CH_3); ^{13}C NMR δ 207.5, 57.0, 54.7, 48.6, 37.3, 37.2, 31.0, 28.0. Anal. Calcd for $C_8H_{12}O_2$: C, 68.6; H, 8.63. Found: C, 68.6; H, 8.70.

5,5-Dimethyl-*trans*-2,3-epoxycyclohexanol (15). Epoxy ketone **18** (99 g; 0.71 mol) was dissolved in ethanol (600 mL) and cooled (3 °C). Sodium borohydride (9.5 g; 0.25 mol) was added in portions during 10 min. The temperature increased to 12 °C, and started to decrease, and the cooling bath was removed. At 22 °C, the temperature increased rapidly (maximum 37 °C), and the cooling was continued until the mixture had reached 10 °C. After 1 h, the mixture was poured into saturated sodium chloride solution (2 L) and extracted with three portions of dichloromethane (1000, 500, and 500 mL), and the organic phase was dried (Na_2SO_4) and concentrated to give a mixture of **15** and **6** (93 g, 93%). The trans/cis ratio was 86:14 according to GC analysis. An aliquot was distilled to give material for analysis which had $bp_{0.5}$ 70–72 °C. **15**: ^1H NMR ($CDCl_3$, Me_4Si) δ 4.28 (br q, 1 H, J = 6 Hz, H-1), 3.35 (dt, 1 H, J = 3.8, 1.5 Hz, H-3), 3.22 (d, 1 H, J = 3.8 Hz, H-2), 1.03, 0.93 (s, each 3 H, CH_3); ^{13}C NMR δ 65.0, 55.9, 53.7, 42.5, 37.1, 31.9, 29.0, 28.1. Anal. Calc. for $C_8H_{14}O_2$: C, 67.6; H, 9.92. Found: C, 67.6; H, 9.92.

Lithium Bromide Induced Rearrangement of the Epoxy Alcohols 4d, 7d, 5, 14, 6, and 15. Table I shows all products formed in the reactions described below. The purity of the epoxy alcohols is reported in footnote *a* of Table I. Analyses were made by gas chromatography. The detector response was found to be roughly the same for all the products. Compounds **1–3**, **8**, **11**, and **16** have been reported earlier[2]. The ^1H NMR spectra of the deuterated compounds showed the expected features: **1d**, lack of vinylic proton signal; **2**/**2d**, reduced intensity of formyl proton signal; **8**/**8d**, vinylic proton doublets at 6.66 and 5.84 ppm and vinylic proton singlet at 6.66 ppm, respectively; **11d**, vinylic proton singlet at 5.92 ppm. Gas chromatography–mass spectrometry with **1d**, **2d**, **8d**, and **11d** revealed a molecular ion peak at 125 mass units and the expected fragmentation patterns (comparison with the known, nondeuterated compounds).

Hexamethylphosphoric Triamide (HMPA) as Lithium Bromide Solubilizing Agent (Entries A, G, K, N, and Q; Table I). Lithium bromide (180 mg; 2 mmol) and HMPA (360 mg; 2 mmol) were dissolved in refluxing toluene (2 mL). The epoxy alcohol (1 mmol in toluene; 2 mL) was added in one portion, and the mixture was kept at reflux for 30 min. After cooling, the mixture was filtered (SiO_2; 5 g) with diethyl ether as eluent, and the filtrate was used for gas chromatographic analysis. The filtrate from entries A and G was carefully concentrated, and the residue was chromatographed (SiO_2; 1:4 ethyl acetate/hexane) to give three fractions consisting of (i) the aldehyde **1d**, (ii) the aldehydes **2**/**2d**, and (iii) the ketones **8**, **8d**, and **11d**. These fractions were submitted to NMR and GC–MS analysis. The relative amounts of the products formed are shown in Table I.

Hexamethylphosphoric Triamide (HMPA) as Lithium Bromide Solubilizing Agent and Lithium *tert*-Butoxide Added (Entries B, C, H, L, O, and T; Table I). Lithium bromide (180 mg; 2 mmol), HMPA (360 mg; 2 mmol), and lithium *tert*-butoxide (0.5 M in toluene; 0.5 mmol for entry B and 1 mmol for entries C, H, L, O, and T) were dissolved in refluxing toluene (2 mL). The epoxy alcohol (1 mmol) was added, and the reaction mixture was treated as above and then analyzed by gas chromatography (Table I).

Lithium *tert*-Butoxide Treatment of 4d in the Absence of Lithium Bromide/HMPA (Entry D; Table I). Epoxy alcohol **4d** (1 mmol) was added to refluxing toluene (2 mL) containing lithium *tert*-butoxide (1 mmol). The mixture was treated as above and then analyzed by gas chromatography. Ketone **8**/**8d** was formed (11%) together with some unidentified compounds. A substantial amount of starting material (>50%) was left unchanged.

***N,N,N′,N′*-Tetramethylurea (TMU) as Lithium Bromide Solubilizing Agent (Entries E, I, and R; Table I).** Lithium bromide (180 mg; 2 mmol) and TMU (464 mg; 4 mmol) were dissolved in refluxing toluene (2 mL). The epoxy alcohol (1 mmol) in toluene (2 mL) was added in one portion, and the mixture was left at reflux for 45 min. After cooling, the mixture was treated as above and then analyzed by gas chromatography (Table I).

Lithium Bromide in Dimethoxyethane (Entries F, J, M, P, S, and U; Table I). Lithium bromide (260 mg; 3 mmol) was dissolved in refluxing dimethoxyethane (0.5 mL). The epoxy alcohol (1 mmol) in dimethoxyethane (0.5 mL) was added, and the mixture was kept at reflux for 30 min. After cooling, the mixture was treated as above and then analyzed by gas chromatography (Table I). It is important that the lithium bromide concentration in the mixture is at least 3 M.

4,4-Dimethylcyclopentene-1-carboxaldehyde (3). Preparative Procedure. Lithium bromide (100 g; 1.15 mol) was dissolved in refluxing dimethoxyethane (200 mL), and 5,5-dimethyl-*trans*-2,3-epoxycyclohexanol (**15** containing 14% of **6**; 142 g; 1 mol) in dimethoxyethane (150 mL) was added during 10 min. The mixture was kept at reflux for another 15 min, cooled, and poured into ice–water (700 mL). The water phase was extracted with pentane (2 × 500 mL)), and the pentane solution was washed with sodium chloride solution (20%; 2 × 125 mL), dried (Na_2SO_4), and concentrated. The residue was distilled (30-cm Vigreux column) to give pure **3**[2] (75 g; 60%), Bp_{35} 80–82 °C.

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Registry No. **1**, 38312-90-2; **1d**, 99342-66-2; **2**, 38312-92-4; **2d**, 99342-67-3; **3**, 38312-94-6; **4d**, 99342-64-0; **5**, 99342-62-8; **6**, 38309-46-5; **7d**, 99396-36-8; **8**, 1073-13-8; **8d**, 99342-68-4; **9d**, 99342-63-9; **10**, 1074-26-6; **11**, 6553-64-6; **11d**, 99342-69-5; **14**, 38309-48-7; **15**, 66036-65-5; **16**, 4694-17-1; **17**, 6267-39-6; **18**, 17421-93-1; **19**, 6553-64-6; **19** DNP, 99342-65-1; **20**, 73982-30-6; 6,6-dimethylcyclohex-2-enol, 38313-10-9.