preparation of cold material yielded yellow needles, mp 221–223°.)

Anal. Calcd for $C_{31}H_{38}O_6$: C, 75.89; H, 7.81. Found: C, 75.78; H, 7.66.

Ir (KBr) showed 1669, 1680, 1708, 1280, and a shoulder at 1698 cm^{-1}; uv λ_{max} 272.5 mμ (log ϵ = 3.95).

Equilibration of 22,23,24,25,26,27-Hexanor-3-benzoyloxy-7,11,20-triketolanost-8-ene with Basic Methanol. A mixture of 22,23,24,25,26,27-hexanor-3-benzoyloxy-7,11,20-triketolanost-8-ene (9 mg, 0.018 mmol), 0.5 ml of 8% potassium hydroxide in methanol, and 0.5 ml of 50% aqueous methanol was refluxed for 4.5 hr, and the methanol then distilled. An additional 0.5 ml of methanol was added to the residue and distilled. The procedure was repeated with two 0.2-ml portions of methanol. The combined distillate, totaling about 1.8 ml, was counted in toluene to which an additional 4 ml of ethanol had been added to get a homogeneous solution.

To the residue of the distillation was added 8 ml of water and 0.1 ml of acetic acid. The mixture was extracted several times with a total of 25 ml of ether. After washing with a saturated solution of sodium bicarbonate and a saturated solution of sodium chloride, and drying over anhydrous sodium sulfate, the ether was distilled to leave a slightly brown residue which was purified by thin layer chromatography (E. Merck Darmstadt, tlc plates, silica gel F_{254}–0.5 mm of eluent 20% hexane–ether) to give 4.65 mg of a white solid, which was recrystallized from absolute ethanol and counted (uv λ_{max} 272 mμ (log ϵ = 3.93).

Stereochemistry of the Base-Induced Rearrangement of Epoxides to Allylic Alcohols

Randolph P. Thummel and Bruce Rickborn[1]

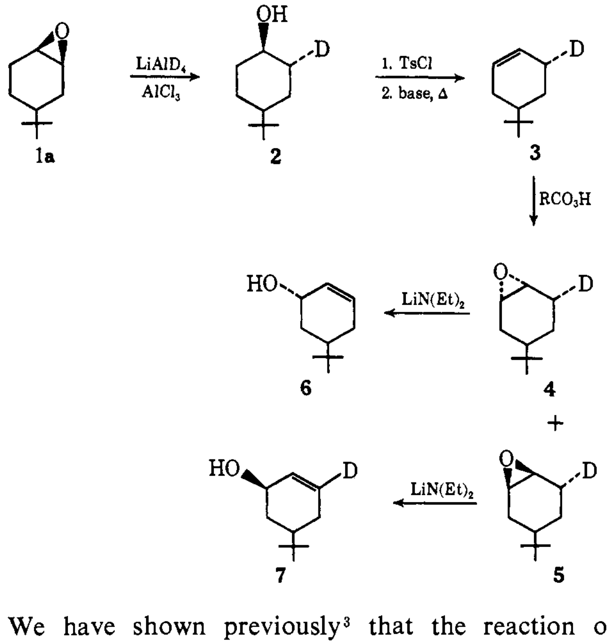
Contribution from the Department of Chemistry, University of California, Santa Barbara, California 93106. *Received September 9, 1969*

Abstract: The epoxide–allylic alcohol rearrangement of *cis*- and *trans*-4-*t*-butylcyclohexene oxide by lithium diethylamide is shown through appropriate deuterium substitution to occur by a *syn*-elimination process. Thus *cis*-3-deuterio-*trans*-5-*t*-butylcyclohexene oxide was converted to *trans*-5-*t*-butyl-2-cyclohexenol with loss of deuterium, while *trans*-3-deuterio-*cis*-5-*t*-butylcyclohexene oxide gave *cis*-5-*t*-butyl-2-cyclohexenol-3-*d* (loss of a proton).

The lithium diethylamide induced rearrangement of epoxides to allylic alcohols has two highly selective features which add greatly to its synthetic potential. Cope and Heeren[2] have shown that only *trans*-olefinic product is obtained from either *cis*- or *trans*-4-octene oxide. More recently, we have described[3] the very high selectivity of this base for proton abstraction from the least substituted β-carbon atom of an unsymmetrically substituted epoxide. These features in combination are unique to this elimination reaction, and consequently the mechanism is of considerable interest. This paper deals with a study of the stereochemistry of the lithium diethylamide induced rearrangement of substituted cyclohexene oxides.

Results

The determination of the stereochemical course (*i.e.*, whether *syn* or *anti*) of any elimination reaction requires that the relative configurations of the two asymmetric reaction sites and the geometry of the olefin product be known. The strong preference for proton abstraction from the least substituted center[3] adds to the difficulty of determining the preferred stereochemical course of the base-promoted epoxide rearrangement. Thus, under the usual reaction conditions (several hours in refluxing ether–hexane), no rearrangement of 2,5-dimethyl-3-hexene oxide (only tertiary β-protons available) is observed. Consequently it was necessary for the purposes of the present study to construct a model compound with a known H–D asymmetric secondary center. Scheme I outlines the major features of the synthesis used to obtain the model systems **4** and **5** and results obtained on rearrangement of these materials by lithium diethylamide. The precise details are somewhat more complicated than indicated here and require further discussion.



We have shown previously[3] that the reaction of lithium diethylamide with mixed *cis*- and *trans*-4-*t*-butylcyclohexene oxide (**1a**, **b**) is kinetically selective, such that the *trans* isomer **1b** is completely consumed in a time which allows only part of **1a** to react. This feature proved to be extremely useful in the present

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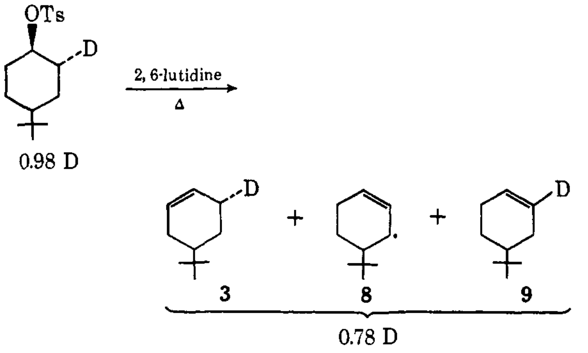
[1] Alfred P. Sloan Fellow, 1967–1969.

[2] A. C. Cope and J. K. Heeren, *J. Amer. Chem. Soc.*, **87**, 3125 (1965).

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

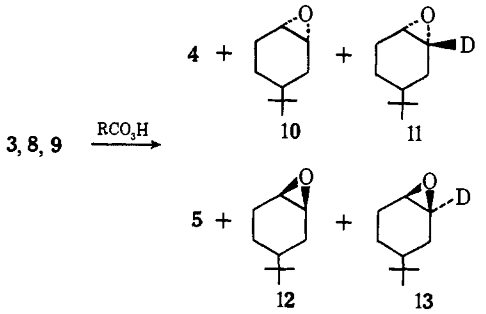
work. It allowed a ready source of nearly pure **1a** from the epoxide mixture (55–60% **1a**)[4] obtained on peracid treatment of the olefin, and further greatly simplified product separation from the rearrangement reaction of **4** and **5**.

The starting epoxide **1a** used in this work was 97.2% *cis*, as shown by lithium aluminum hydride reduction and vpc analysis of the alcohol product as the acetate derivative.[5] Reduction of **1a** by aluminum deuteride (3:1 LAD:AlCl$_3$)[7] gave **2** which was 96.6% *cis*-4-*t*-butylcyclohexanol and contained 0.98 atom of D per mole. The *trans* geometry of the deuterium in **2** is assured by the observation that even epoxides with tertiary centers give only inversion opening with the relatively electrophilic aluminum hydride reagent.[8] This factor assumes greater importance since the subsequent elimination of the recrystallized tosylate of **2** gave a mixture of allylic- and vinyl-deuterated cyclohexene (eq 1), as shown by the two sharp C–D stretching frequencies appearing in the ir spectrum at 2235 and 2110 cm^{-1} and the epoxide rearrangement results discussed later. The higher frequency (vinyl) band had approximately one-third the intensity of the other band; although ε values are not known for these absorptions, other evidence presented later in this paper indicates that, at least semiquantitatively, this ratio reflects directly the relative amounts of **3** and **9** formed. The effective *syn* elimination leading to **9** was not anticipated for this lutidine-catalyzed reaction. We have used this procedure several times previously for elimination of 4-alkylcyclohexanol sulfonate derivatives, and found it to be a clean, high-yield process. Specifically, no indication of carbonium ion rearrangement (*i.e.*, formation of 3-alkylcyclohexene) products was ever observed; however, the lack of stereospecificity obtained in the present instance implies that a nonselective, E1-type mechanism was involved.[9] Although the presence of **9** in the sample of **3** somewhat complicated the stereochemical analysis, this still proved feasible.



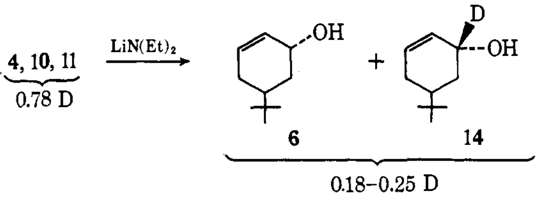
(1)

The deuterated olefin was next treated with peracetic acid[10] to give the epoxide mixture shown in eq 2. This product also exhibited two C–D stretch bands in the ir spectrum, at 2215 (presumably from **11**, **13**) and 2145 cm^{-1}. Analysis[6] demonstrated that the mixture consisted of 45.7% *trans*- and 54.3% *cis*-epoxide.[11] Our earlier work with 3-methylcyclohexene, which yields equal amounts of *cis*- and *trans*-epoxides,[12] leaves little doubt that the deuterium in **3** should have no effect on the *cis,trans*-epoxide ratio, *i.e.*, this measured overall ratio should be identical to that for **5**:**4** (or **13**:**11**). This total epoxide sample contained 0.78 deuterium atoms per mole, identical with the olefin precursor.



(2)

The epoxide mixture was treated with lithium diethylamide in ether–hexane, under conditions identical with those used previously.[3] The first indication that deuterium was being lost from the *trans*-epoxide **4** was the slower rate relative to earlier runs with undeuterated **10**. Although the latter is completely consumed after 7 hr, the present sample still contained 10% of *trans*-epoxide after 10 hr.[5] This reaction was run for 23 hr to assure complete consumption of *trans*-epoxide,[13] giving the results shown in eq 3. The *trans*-5-*t*-butyl-2-cyclohexenol was isolated and analyzed for deuterium by combustion, mass spectrometry, and nmr, giving the range shown in eq 3. The nmr spectrum was particularly useful in demonstrating that, within experimental error, the retained deuterium in this sample was attached to the carbinol carbon (*i.e.*, as in **14**). This conclusion was confirmed by the ir spectrum, which showed only a single band in the C–D stretching region, at 2140 cm^{-1}. Further, Jones oxidation of the



(3)

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(4) B. Rickborn and S. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

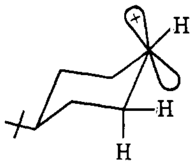
(5) The *cis*-epoxide is cleanly reduced to 4-*t*-butylcyclohexanol isomers (*cis* and *trans*) by LAH; conversely the *trans*-epoxide yields only 3-ol products.[6]

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

(7) This reagent avoids the complications associated with the use of LAD alone, *i.e.*, formation of appreciable equatorial alcohol and dideuterated product.[6]

(8) D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Amer. Chem. Soc.*, **91**, 2649 (1969).

(9) One might have expected the 4-*t*-butyl group to exert some conformational control on even a pure E1 reaction, inasmuch as *anti* elimination appears to be geometrically favored from a structure such as i. An alternate explanation is that a substantial amount of the *cis*-tosylate rearranged to the *trans* derivative prior to elimination.



i

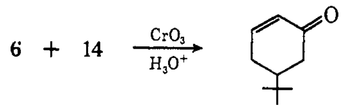
(10) M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Amer. Chem. Soc.*, **82**, 4328 (1960).

(11) The formation of more *cis*- than *trans*-epoxide from this olefin with other peracids has been noted previously.[5]

(12) B. Rickborn and W. E. Lamke, *J. Org. Chem.*, **32**, 537 (1967).

(13) This was necessary to avoid complications due to the kinetic isotope effect; a significant amount of *cis*-epoxide had also rearranged after this time, making it necessary to isolate product **6** by preparative vpc.

allylic alcohol mixture (eq 4) gave enone which by nmr and ir spectral analysis was free of deuterium.

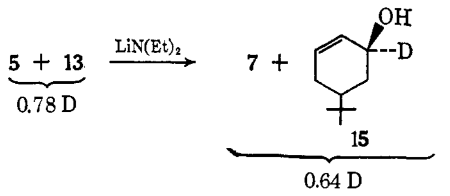


(4)

These data show that the preferred course of the lithium diethylamide induced rearrangement of **4** to **6** involves loss of deuterium, or effective *syn* elimination.

In order to demonstrate that this observation is not an artifact, *i.e.*, to rule out the possibility that deuterium is lost through some extra-rearrangement process, it was necessary to examine a system which, on *syn* elimination, would retain the isotopic label. Compound **5** has the requisite geometry. Our earlier studies[3] have shown that *cis*-4-*t*-butylcyclohexene oxide, unlike its *trans*-geometric isomer, gives a rather complex mixture of products consisting of two allylic alcohols and two ketones. The desired product, *cis*-5-*t*-butyl-2-cyclohexenol, is the minor allylic alcohol product (*ca.* 25% of the total mixture),[3] but its relatively long vpc retention time allows fairly easy separation from the other components.

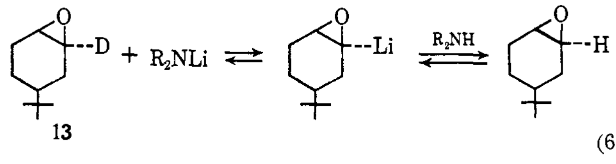
When a sample of **4** and **5** (plus **10–13**) was treated with lithium diethylamide in refluxing ether–hexane for 67 hr, the epoxides were totally consumed. The *cis*-5-*t*-butyl-2-cyclohexenol was isolated by preparative vpc, and analyzed to give the results shown in eq 5. The ir spectrum of this product showed two C–D stretching bands, at 2240 (**7**) and 2120 cm^{-1} (**15**), the former more intense by a factor of 3–5.



(5)

This result confirms that obtained in the rearrangement of **4** to **6**, *i.e.*, the lithium diethylamide induced rearrangement of cyclohexene oxides to allylic alcohols, occurs preferentially *via syn* elimination. Some deuterium is lost in the reaction (eq 5), precluding an exact conclusion regarding the degree of specificity for the process **5** → **7**. However, it appears that this loss of deuterium may be due to a side reaction, unrelated to formation of allylic alcohol, in which either **5** or **13** undergoes D–H exchange. Thus, when a sample of **5** + **13** was recovered from the initial epoxide mixture after 23 hr and analyzed by MS for deuterium content, it had decreased from 0.78 to 0.69 D/mole.

A significant amount of 3-*t*-butylcyclohexanone is formed in the rearrangement of this *cis*-epoxide; if the ketone arises by an α-proton abstraction process, it is conceivable that this step might be reversible, allowing exchange of the amine proton for deuterium in compound **13**. Similar reaction of the *trans*-epoxide **11** could easily have escaped detection because of the much faster elimination to give allylic alcohol which occurs with this system.



(6)

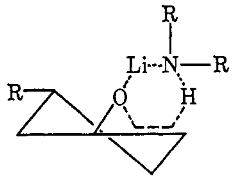
Discussion

Recent work by Sicher and his coworkers[14] has stressed the importance of *syn*-elimination mechanisms in many olefin-forming reactions previously thought to strongly prefer *anti* pathways. The known factors which can affect the relative importance of *syn* and *anti* mechanisms include base strength,[15] solvent,[16] leaving group,[16] and conformational aspects as exemplified by ring size.[17] The base–solvent system used in the present work is expected to favor strongly ion pairs, for which a cyclic transition state, *syn*-elimination pathway, may be drawn.[16] On the other hand, Sicher's work[14] suggests that *syn* elimination is usually associated with formation of *trans*-olefins, and conversely *cis*-olefins may be primarily formed by *anti* elimination.[17] Inasmuch as cyclohexene is constrained *cis*, its formation by *anti* elimination appears reasonable on this basis, and many cyclohexene-forming reactions undoubtedly occur in this manner.[18]

While there is no direct analogy for the epoxy oxygen as a leaving group in elimination, some similarity may be drawn with the elimination of methanol, induced by *n*-butyllithium, from *cis*- and *trans*-2-methoxy-1-phenylcyclohexane.[19] The faster reaction of the *trans* isomer led to the suggestion that *syn* elimination was preferred in this reaction.[19]

The present work establishes experimentally that *syn* elimination is the preferred pathway in the lithium diethylamide induced rearrangement of cyclohexene oxides to the corresponding allylic alcohols. The generality of this result remains open to question. However, the very high stereoselectivity (formation of *trans*-olefin) reported earlier by Cope and Heeren[2] taken in conjunction with Sicher's observations[14] suggests that all epoxides, cyclic and acyclic, undergo this reaction preferentially by the *syn* mechanism.

Finally, two aspects of the rearrangement reported previously require further comment. The very high positional selectivity[3] (proton abstraction from the least-substituted carbon) is in keeping with a cyclic *syn*-elimination mechanism where the base has substantial steric requirements. The conformational selectivity,[3] *e.g.*, in the reaction of *trans*-4-*t*-butylcyclohexene oxide or *trans*-Δ^2-octalin oxide, also fits this picture nicely; the favored direction of elimination is accounted



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[14] J. Sicher, J. Závada, and M. Pánková, *Chem. Commun.*, 1147 (1968), and earlier references.

[15] J. Sicher and J. Závada, *Collect. Czech. Chem. Commun.*, 33, 1278 (1968).

[16] M. Svoboda, J. Závada, and J. Sicher, *ibid.*, 33, 1415 (1968).

[17] J. Sicher and J. Závada, *ibid.*, 32, 2122 (1967).

[18] D. J. Cram in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, Chapter 6.

[19] R. L. Letsinger and E. Bobko, *J. Amer. Chem. Soc.*, **75**, 2649 (1953).

for by the preferred geometry of the cyclic transition state involving abstraction of the quasiaxial C_5 proton, at the same time avoiding steric interactions of the base with C_3. The suggested transition state is shown (**16**).

Experimental Section

cis-**4-*t*-Butylcyclohexene Oxide (1a).** A 60:40 *cis*:*trans* mixture of 4-*t*-butylcyclohexene oxide,[6] 151 g (0.98 mole), was treated with 1.5 equiv of lithium diethylamide;[3] after 5.5 hr at reflux (ether–hexane), analysis[5] indicated that all of the *trans*-epoxide had been consumed. The solution was washed successively with water, dilute acid, and water again, dried over magnesium sulfate, and evaporated. Spinning band distillation of the residue gave 45.9 g of epoxide, bp 82.5° (8 mm). Analysis[5,6] showed that the epoxide was at least 97.2% *cis*.

A by-product of this procedure was 36.3 g of ~90% pure *trans*-5-*t*-butyl-2-cyclohexenol, bp 103–104° (8 mm).

trans-**2-Deuterio-*cis*-4-*t*-butylcyclohexanol.** Into a thoroughly dried 1-l. reaction flask equipped with a mechanical stirrer, condenser, and dropping funnel was placed 5.8 g (0.138 mole) of lithium aluminum deuteride and 150 ml of ether. After cooling in an ice bath, a mixture of 2 g of aluminum chloride in ether was added. With continued cooling, the *cis*-4-*t*-butylcyclohexene oxide, 42.8 g (0.278 mole), was added slowly; stirring was continued at ambient temperature for an additional 6 hr. Dilute hydrochloric acid was then added to hydrolyze the excess hydride, and the ether solution separated. The aqueous phase was extracted three times with small portions of ether, and the combined ether solution was washed with sodium bicarbonate solution and water. After drying, the solvent was evaporated to give a quantitative yield of the alcohol, mp 76–78° (lit.[20] mp 82–82°). A small sample was converted to the acetate derivative and analyzed by vpc (TCEOP, 110°); the product consisted to 1.0% *trans*-3-, 96.6% *cis*-4-, 1.8% *cis*-3-, and 0.4% *trans*-4-*t*-butylcyclohexanol.

Combustion and falling-drop deuterium analysis[21] indicated 4.90 atom % excess D, corresponding to 98% d_1 material. Mass spectral analysis showed 98.5% d_1 content, in excellent agreement.

The alcohol was converted to its tosylate derivative by treating with *p*-toluenesulfonyl chloride in pyridine; the crude product, 73.4 g (86%), had mp 76–78°. One recrystallization from low-boiling petroleum ether gave 65.6 g of nice white crystals, without detectable change in melting point (lit.[20] mp 79–80°).

trans-**6-Deuterio-4-*t*-butylcyclohexene (3).** The tosylate of **2** (0.21 mole) was taken up in 200 ml of dry 2,6-lutidine and heated to reflux. After 9 hr heating the mixture was cooled and enough water added to dissolve the solid salt which had formed. The pentane solution obtained by combining extracts was washed with dilute acid, base, and water, dried, and evaporated. The residue was distilled on a Teflon spinning band column to give 25.3 g (87%) of the olefin: bp 85° (40 mm); nmr doublet 5.47 (1.8 H), multiplet 2.1–0.9 (6.5 H), singlet 0.73 (9 H); ir (thin film) 2235, 2110 cm^{-1}; mass spectrum *m/e* 138 (31.5), 139 (100), 140 (11.0), 75.5% d_1; deuterium by combustion[21] 4.32 atom % excess (77.7% d_1).

6-Deuterio-4-*t*-butylcyclohexene Oxides (4 + 5). A sample of the olefin described above (**3** + vinyl deuterated material), 15.0 g (0.108 mole), was converted to the epoxide mixture by treatment with peracetic acid.[10] Distillation gave 14.2 g (85%) of product: bp 86–87° (7 mm); nmr doublet 3.04 (2 H), multiplet 2.3–1.0 (6 H), and singlet 0.86 (*ca.* 9 H); ir (thin film) 2215, 2145 cm^{-1}; mass spectrum *m/e* 138 (32.8), 139 (100), 140 (10.9),[22] 74.7% d_1; deuterium by combustion[21] 4.35, 4.36 atom % excess (78.3% d_1).

Lithium Diethylamide Promoted Rearrangements. The procedure used was identical with that described previously,[3] except that the acid-wash step was omitted.

(**a**) Treatment of 5.0 g (0.032 mole) of 6-deuterio-4-*t*-butylcyclohexene oxides with 0.81 mole of the base for 25 hr gave *trans*-5-*t*-butyl-2-cyclohexenol among other products. This allylic alcohol (**6**) was isolated by preparative vpc using a 5-m Carbowax 6M column at 160° (retention time 41 min): nmr singlet 5.73 (1.82 H), singlet 4.59 (1.0 H), singlet 4.13 (0.69 H), multiplet 2.3–1.0, singlet 0.8 ppm; ir (thin film) 2140 cm^{-1}; mass spectrum *m/e* 153 (75), 154 (100), 155 (41), 156 (5), 25.6% d_1; deuterium by combustion[21] 1.03 atom % excess (18.5% d_1).

(**b**) Treatment of 3.5 g (0.023 mole) of the same epoxide mixture with 0.057 mole of lithium diethylamide for 67 hr gave the anticipated[3] mixture of products from which *cis*-5-*t*-butyl-2-cyclohexenol (**7**) was isolated by preparative vpc (column and conditions noted above): retention time 48 min; nmr singlet 5.6 (1.33 H), singlet 5.0 (1.0 H), singlet 4.15 (0.83 H), multiplet 2.3–10, singlet 0.8 ppm; ir (thin film) 2240, 2120 cm^{-1}; mass spectrum *m/e* 154 (54), 155 (100), and 156 (17), 63.5% d_1.

Oxidation of 6. A portion (56 mg) of the *trans*-5-*t*-butyl-2-cyclohexenol (**6**) described above was subjected to Jones oxidation,[23] and the product, shown by comparison with an authentic sample to be 5-*t*-butyl-2-cyclohexenone, was examined by nmr. The integrated areas for the 2 and 3 protons were identical, indicating no vinyl deuterium in this material or its precursor **6**.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation (9383). The authors also wish to thank Professor Donald Aue for helpful discussions.

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(20) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 77, 5562 (1955).

(21) These analyses were carried out by J. Nemeth, Urbana, Ill.

(22) The epoxide exhibited a relatively weak parent peak at *m/e* 155 (154 for the undeuterated material), and hence analyses were carried out using the $P - 16$ reference. The close agreement with the combustion analysis data indicates the validity of this treatment.

(23) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).