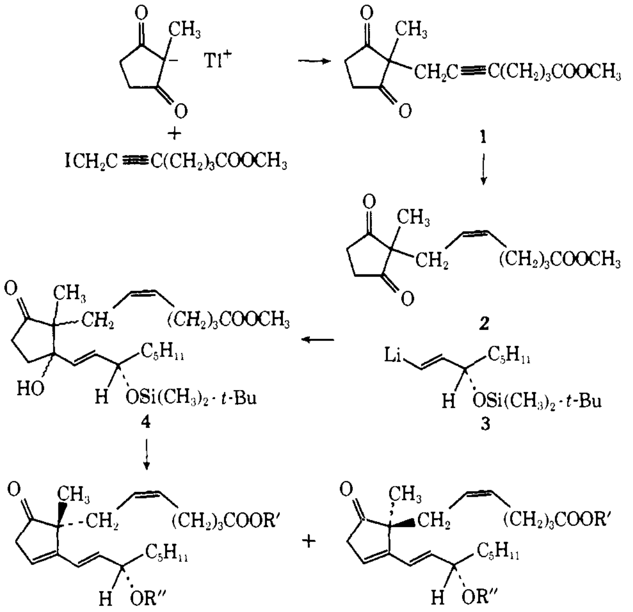
235 nm ($\epsilon$ 19,200) (in $CH_3OH$), ir$_{max}$ 1734 cm$^{-1}$ (in $CHCl_3$). Hydrolysis of the mixture of **5** and **6** using acetic acid–THF–water (3:1:1) at 22–23° for 20 hr produced the corresponding hydroxy esters **7** and **8** which could be separated by careful thin-layer chromatography on silica gel using two developments with methylene chloride–ethyl acetate (20:1). The isomers of higher $R_f$ (0.31) and lower $R_f$ (0.25) are provisionally assigned structures **7** and **8**, respectively, on the basis of biological activities (see below).[8] The more polar isomer, obtained as a colorless air-sensitive oil, had $[\alpha]^{25}D$ $+10.32°$ (*c*, 1.74 in $CHCl_3$) and showed uv$_{max}$ at 235 nm ($\epsilon$ 19,000) (in $CH_3OH$) and ir$_{max}$ at 1742 cm$^{-1}$ with a shoulder at 1733 cm$^{-1}$ (in $CH_2Cl_2$), whereas the less polar isomer was somewhat less dextrorotatory, $[\alpha]^{25}D$ $+2.8°$ (*c*, 1.36 in $CHCl_3$), and showed the same ultraviolet and infrared carbonyl absorption. The methyl esters **7** and **8** were converted in high yield to the corresponding free acids **9**, $[\alpha]^{25}D$ $+2.45°$ (*c*, 1.3 in $CHCl_3$), and **10**, $[\alpha]^{25}D$ $+13.6°$ (*c*, 1.1 in $CHCl_3$), by the action of porcine pancreatic lipase[9] at pH 7.5 and 25° in water containing a small amount of dimethylformamide. Both **9** and **10** showed infrared carbonyl absorption at 1742 and 1710 cm$^{-1}$ (in $CH_2Cl_2$) and ultraviolet absorption at 234 nm ($\epsilon$ 14,500) (in $CH_3OH$). In the solvent system benzene–dioxane–acetic acid (90:10:1) on a silica gel thin layer, samples of **9**, **10**, and PGA$_2$ showed $R_f$ values of 0.175, 0.216, and 0.145, respectively. The biological activity of **9** was 10–30 times greater than that of **10** in tests of stimulation of contraction of smooth muscle (guinea pig uterus), suggesting the tentative configurational assignments indicated herein.[10]



**5**, R' = $CH_3$; R'' = $Si(CH_3)_2$·*t*-Bu
**7**, R' = $CH_3$; R'' = H
**9**, R' = R'' = H

**6**, R' = $CH_3$; R'' = $Si(CH_3)_2$·*t*-Bu
**8**, R' = $CH_3$; R'' = H
**10**, R' = R'' = H

The simple and effective synthesis of 8-MePGC$_2$ (**9**) described above makes available a biologically active member of the PGC$_2$ family which in contrast to the highly sensitive PGC$_2$ cannot undergo deactivation *via* a PGB structure.[11,12]

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[8] The diastereomers (former in *ca.* 1:1 ratio) were cleanly separated by high-pressure liquid chromatography using a Waters Associates ALC-202 instrument fitted with a Porasil T column. Retention times using an 8 ft × 0.125 in column, 5% ether in methylene chloride as solvent and a flow rate of 1.2 ml/min were 83 min and 60 min for **7** and **8**, respectively.

[9] Obtained as a gift from Dr. H.-J. Hess of the Chas. Pfizer Co.

[10] We are indebted to Dr. H.-J. Hess and associates of the Chas. Pfizer Co. Medical Research Laboratories for the biological tests. The isomer designated as **9** was one-thirtieth as active as PGE$_2$ in the smooth muscle test. Both esters **7** and **8** were found to be active in inhibition of gastric acid secretion in rats (*ca.* 60% of PGE$_2$ or PGA$_2$).

[11] For a synthetic route to PGC$_2$ itself, see, E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, **95**, 7185 (1973).

[12] This work was assisted financially by the National Institutes of Health and the Chas. Pfizer Co.

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## Retention in the Combination of Optically Active 2-Butyl-*tert*-Butoxy Radical Pairs

*Sir:*

We wish to report the results of our investigation of the optical purity of *S*-(+)-2-butyl *tert*-butyl ether obtained from thermolysis of *S*-(+)-*tert*-butylperoxy 2-methylbutyrate at 101.8° in solvents of varying fluidity. The results allow an estimation of the ratios of the rate constants for internal rotation ($k_r$) and tumbling ($k_t$) to that for combination of the 2-butyl-*tert*-butoxy radical pair. The $k_t/k_c$ ratio was found to be *ca.* ten times that reported[1] for benzylic radical pairs. The fluidity dependence of the ratio is *ca.* 100 times that estimated from data recently reported for a fluorenyl–diazenyl pair.[2]

The specific optical rotation of the ether was obtained by relating it to *S*-(+)-2-butanol. Sodium pivalate was oxidatively decarboxylated in an electrolysis cell containing 0.02 *M* *S*-(+)-2-butanol ($[\alpha]^{23°}{}_{589}$ $+9.31 \pm 0.08°$ (*c*, 2.60, $CCl_4$), 67.1% optically pure[3]) dimethylformamide solution. The resulting 2-butyl *tert*-butyl ether showed a specific rotation of $+6.17 \pm 0.06°$ (*c*, 2.76, $CCl_4$; 23°, 589 nm). A sample of this material was cleaved by trifluoroacetic acid and the resulting *S*-(+)-2-butanol ($[\alpha]^{23°}{}_{589}$ $+9.27 \pm 0.08°$ (*c*, 3.38, $CCl_4$), 66.9% optically pure) was essentially unchanged in optical purity relative to unreacted alcohol recovered from the electrolysis ($[\alpha]^{23°}{}_{589}$ $+9.35 \pm 0.05°$ (*c*, 6.41, $CCl_4$), 67.4% optically pure). The specific rotation of optically pure *S*-(+)-2-butyl-*tert*-butyl ether ($[\alpha]^{23°}{}_{589}$ $+9.19 \pm 0.10°$) was thus calculated from the known optical purity of the *S*-(+)-2-butanol used in this sequence.

The *S*-(+)-2-butanol was obtained from *S*-(+)-2-methylbutanoic acid through a carboxy inversion–hydrolysis sequence[4] *via* the mixed peroxide with *m*-

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[1] (a) K. R. Kopecky and T. Gillian, *Can. J. Chem.*, 47, 2371 (1969); (b) F. D. Greene, M. A. Berwick, and J. C. Stowell, *J. Amer. Chem. Soc.*, **92**, 867 (1970).

[2] R. A. Johnson and S. Seltzer, *J. Amer. Chem. Soc.*, **95**, 938 (1973).

[3] (a) All optical rotation samples were purified by glpc. (b) P. J. Leroux and H. J. Lucas, *J. Amer. Chem. Soc.*, **73**, 41 (1951).

[4] (a) D. B. Denny and N. Sherman, *J. Org. Chem.*, 30, 3760 (1965); (b) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 323–325.

chloroperbenzoic acid. The optically active acid was generated by nitric acid oxidation[5] of commercially available $S$-(−)-2-methyl-1-butanol (79% yield, $[\alpha]^{23°}{}_{589}$ −19.74 ± 0.01° ($c$, 18.56, $CCl_4$), 100% optically pure[6]).

It was established that conversion of the acid to acid chloride ($[\alpha]^{23°}{}_{589}$ +7.47 ± 0.04° ($c$, 6.74, $CCl_4$)) and subsequent hydrolysis could be accomplished without change in the specific rotation of the acid. The $S$-(+)-*tert*-butylperoxy 2-methylbutyrate (**1**) ($[\alpha]^{23°}{}_{589}$ +16.31 ± 0.01° (neat)) obtained from the acid chloride and *tert*-butyl hydroperoxide[7] was assumed to have the same optical purity as the starting acid (100%).

The perester decompositions were carried out in degassed, sealed tubes with and without added styrene or cumene. Products were isolated by bulb-to-bulb distillation, followed by preparative glpc. Ether yields were determined by quantitative glpc analysis of crude decomposition solutions. The fractional yields and optical purities are summarized in Table I.

**Table I**

| Solvent | $\eta$,[a] cP | Yield (Y) **2** | Optical purity (OP) **2** | $k_d/k_c$[b] | $k_t/k_c$[c] |
|---|---|---|---|---|---|
| Paraffin oil | 5.30 | 0.287 (0.282)[d] | 0.0600 (0.0596)[d] | 0.4 | 23 |
| Dodecane | 0.52 | 0.184 (0.180) | 0.0192 (0.0200) | 2.4 | 138 |
| Decane | 0.37 | 0.159 (0.161) | 0.0170 | 3.2 | 178 |
| Octane | 0.26 | (0.141) | (0.0150) | 4.1 | 232 |

[a] W. K. Smith, Ph.D. Thesis, Louisiana State University, 1969. [b] Calculated, using 2.1 for $k_2k_c$ from Figure 1. [c] Calculated, using 4.2 for $k_r/k_c$ from Figure 1. [d] Parenthetical values are from decomposition mixtures containing 0.1 $M$ cumene or 0.2 $M$ styrene.

The insensitivity of the ether optical purity and yields to the presence of scavangers (styrene or cumene) suggests that chain processes, which would destroy or racemize either the starting perester or the ether product, are not serious problems in the present system.[8] This result also indicates that no significant fraction of the ether is formed *via* random combination of radicals which have diffusively escaped the initial solvent cage. The inverse relationship of increasing ether yield with decreasing solvent fluidity suggests that the ether formation process is a radical pair combination.[9] The net retention in the ether product excludes the possibility of an $S_H2$ displacement of carbon dioxide from a carboxy radical intermediate.

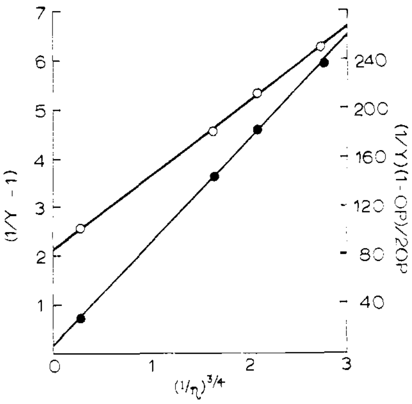
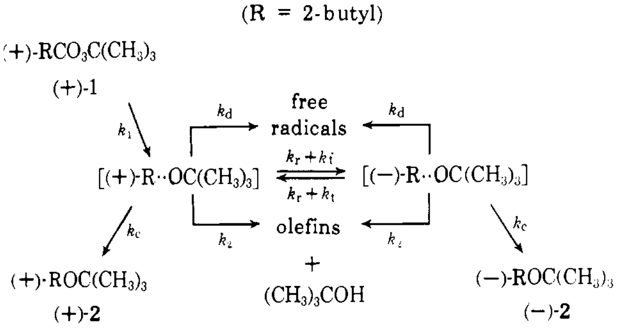


Figure 1. Fluidity variation of yield (Y, eq 1 and 2) and optical purity (OP, eq 2): ○, eq 1; ●, eq 2.

These results may be quantitatively interpreted in terms of eq 1 and 2, derived[13] from Scheme I.

**Scheme I**



$$(1/Y) - 1 = k_d/k_c + k_2/k_c \qquad (1)$$

$$(1/Y)(1 - OP)/2OP = k_r/k_c + k_t/k_c \qquad (2)$$

The reciprocal yield function (1) is linear with the 0.75 power of fluidity,[14] as shown in Figure 1. The intercept may be interpreted in terms of the competition between disproportionation and combination ($k_2/k_c$). The value, 2.1, is very similar to that reported with other peresters.[15, 16] The slope (1.49) is a measure of the fluidity sensitivity of the diffusion–combination competition ($k_d/k_c$), and is in good agreement with that obtained with 2-propyl–*tert*-butoxy pairs.[16]

The optical purity function (2) is also linear with the 0.75 power of fluidity. We interpret the slope (Figure 1) as a reflection of the sensitivity to fluidity changes of the *formal* rate constant for the relative tumbling ($k_t$) of the 2-butyl radical with respect to the *tert*-butoxy radical.[17] The small positive intercept (4.2) may be

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(5) H. Gilman and A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 168.

(6) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **103**, 1923 (1913).

(7) P. D. Bartlett and C. Ruchart, *J. Amer. Chem. Soc.*, **82**, 1762 (1960).

(8) Infrared spectra of the exhausted decomposition solutions show none of the carbonyl absorptions which would be expected if chain formation of the $\alpha$-lactone were occurring.

(9) The ether yield data may be rationalized by assuming a concerted process with an activation volume of −22 $cm^3$/mol. The increase with viscosity could thus be a reflection of the change in internal solvent pressure[10] of *ca.* 1000 atm over the range of solvents employed. The solvent dependence of optical purity requires a difference in activation volumes of −2.9 $cm^3$/mol for the formation of the $S$-(+) and $R$-(−) optical isomers. The negative activation volume is possible,[11] but the difference in activation volumes for the $S$- and $R$-enantiomer formations is of *opposite* sign from that predicted from conformational considerations.[12]

(10) S. Glasstone, "Textbook of Physical Chemistry," 2nd ed, Van Nostrand, New York, N. Y., 1966, p 479.

(11) (a) S. D. Hamann, "Physico-Chemical Effects of Pressure," Butterworth, London, 1957; (b) R. S. Bradley, Ed., "High Pressure Physics and Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963.

(12) R. J. Oullette and S. H. Williams, *J. Amer. Chem. Soc.*, **93**, 466 (1971).

(13) Both equations follow directly from a steady-state assumption on the (+) radical pair and on the (−) radical pair, and from the definitions: $Y = [\mathbf{2}]_\infty/[\mathbf{1}]_0$; $OP = \{[(+)\text{-}\mathbf{2}]_\infty - [(-)\text{-}\mathbf{2}]_\infty\}/\{[(+)\text{-}\mathbf{2}]_\infty + [(-)\text{-}\mathbf{2}]_\infty\}$.

(14) W. A. Pryor, E. H. Morkved, and H. T. Bickley, *J. Org. Chem.*, **37**, 1999 (1972).

(15) R. Sheldon and J. Kochi, *J. Amer. Chem. Soc.*, **92**, 5175 (1970).

(16) T. Koenig, J. Huntington, and W. R. Mabey, *Tetrahedron Lett.*, in press.

(17) Using the Stokes model for the viscosity dependence of rotation,[18] the correlation time for a particle of 3 Å *effective* rotational radius, in a solvent of 1 cP viscosity, is 2.2 × $10^{-11}$ sec. This leads to a rate constant for combination of 2-butyl–*tert*-butoxy of 5.5 × $10^8$ $sec^{-1}$ which compares well with that estimated[15] for the combination of cyclopropylmethyl–*tert*-butoxy pairs. Using this value of $k_c$,

interpreted in terms of the path leading to $R$-(−)-**2** by internal rotation of the radical center with respect to the largest (ethyl) substituent ($k_r$). This motion should be less sensitive to fluidity changes than the gross tumbling of the radical species.[19]

The $k_t/k_c$ slope estimated from the data reported for the fluorenyl–diazenyl pair[2] (<1) is not readily reconciled with that found here (84) by purely rotational radius differences. We suggest that the difference is largely due to a lower $k_c$ for the present system, which may be a result of the initial intervention of the $CO_2$ molecule between the radical pair.

**Acknowledgment.** We are grateful to the National Science Foundation and the E. I. Du Pont Company for financial support of this work.

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$k_d$ corresponds to a particle of *effective* Stokes–Einstein diffusion radius of 4.7 Å.

(18) P. Debye, "Polar Molecules," Dover Publications, New York, N. Y., 1945, p 85.

(19) D. Gegiou, K. A. Muszkat, and E. Fischer, *J. Amer. Chem. Soc.*, **90**, 12 (1968). A referee has suggested this intercept is a measure of the rotation of the 2-butyl radical about its long axis which is certainly a possibility at this point.

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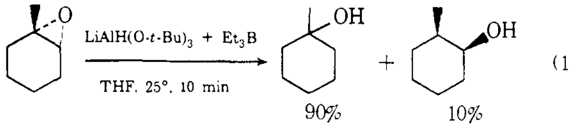
## Lithium Triethylborohydride as a Convenient Reagent for the Facile Reduction of Both Hindered and Bicyclic Epoxides Prone to Electrophilically Induced Rearrangement

*Sir:*

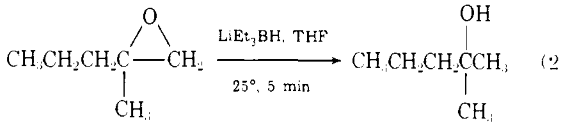
Bicyclic epoxides, such as norbornene oxide and benzonorbornadiene oxide, are highly resistant to the usual reducing agents, reacting sluggishly, incompletely, and often with rearrangement. These epoxides, as well as highly hindered labile epoxides, can be reduced by lithium triethylborohydride relatively rapidly with exceptionally high regio- and stereospecificity, to the desired products.

Difficulties are frequently encountered in the reductive opening of hindered and bicyclic epoxides with lithium aluminum hydride.[1e,f,g] In addition to the sluggishness of the reaction, there is frequently observed rearrangement. For example, treatment of *exo*-2,3-epoxynorbornane with lithium aluminum hydride in ether is reported to give a mixture of 7-norbornanol and *exo*-2-norbornanol.[1a]

Attempts to apply the reagent, lithium tri-*tert*-butoxyaluminohydride, plus triethylborane[2] failed in the case of electrophilically labile epoxides. For example, both 1-methylcyclohexene oxide and styrene oxide gave significant amounts of the anti-Markovnikov products. Evidently the monomeric aluminum *tert*-butoxide formed in the reaction is capable of inducing the electrophilic rearrangement of such epoxides[3] (eq 1).

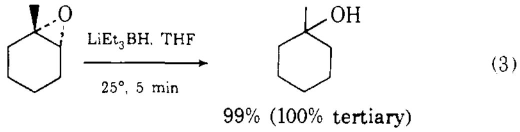


We recently reported that lithium triethylborohydride ($LiEt_3BH$, "Super-Hydride") is the most powerful nucleophile known for $S_N2$ displacement reactions with organic halides.[4,5] It appeared possible that $LiEt_3BH$ might overcome these difficulties. Indeed, we observed that the reduction of tertiary epoxides, such as 2-methyl-1-pentene oxide and 1-methylcyclohexene oxide, proceeds rapidly and cleanly at 25° (eq 2 and 3).



$$CH_3CH_2CH_2\overset{O}{\underset{CH_3}{C}}—CH_2 \xrightarrow[25°,\ 5\ min]{LiEt_3BH,\ THF} CH_3CH_2CH_2\overset{OH}{\underset{CH_3}{C}}CH_3 \quad (2)$$

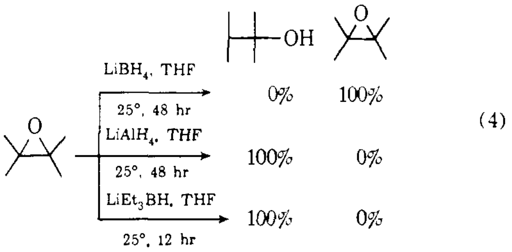
100% (100% tertiary)



99% (100% tertiary)

Yields are glpc values, except where the product was isolated, as indicated.

Even very hindered epoxides, such as 2,3-epoxy-2,3-dimethylbutane, react cleanly, considerably faster than with lithium aluminum hydride; under reflux the reaction is complete within 2 hr. Lithium borohydride was inert toward this epoxide (eq 4).



Moreover, lithium triethylborohydride reduces *exo*-2,3-epoxynorbornane reasonably rapidly, without rearrangement[6] (eq 5).

The advantage of the new reagent is especially evident for the reduction of bicyclic epoxides which are relatively labile. Thus, all of our attempts to reduce benzonorbornadiene oxide without rearrangement failed

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(1) (a) P. D. Bartlett and W. P. Giddings, *J. Amer. Chem. Soc.*, **82**, 1240 (1960); (b) H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963); (c) H. C. Brown, S. Ikegami, and J. H. Kawakami, *ibid.*, **35**, 3243 (1970); (d) W. Hückel and D. Volkman, *Justus Liebigs Ann. Chem.*, **664**, 31 (1963); (e) K. B. Wiberg, J. E. Hiatt, and G. Burgmaier, *Tetrahedron Lett.*, 5855 (1968); (f) P. G. Gassman and J. L. Marshall, *J. Amer. Chem. Soc.*, **88**, 2822 (1966); (g) L. A. Paquette and I. R. Dunkin, *ibid.*, **95**, 3067 (1973); (h) N. M. Yoon and H. C. Brown, *ibid.*, **90**, 2927 (1968).

(2) H. C. Brown, S. Krishnamurthy, and R. A. Coleman, *J. Amer. Chem. Soc.*, **94**, 1750 (1972).

(3) H. C. Brown and S. Krishnamurthy, *J. Chem. Soc., Chem. Commun.*, 868 (1972).

(4) H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **95**, 1669 (1973).

(5) Super-Hydride (lithium triethylborohydride) is now commercially available as 1 *M* solution in THF from Aldrich Chemical Co., Inc., Milwaukee, Wis.

(6) Even at 25°, $LiEt_3BH$–THF reduces *exo*-2,3-epoxynorbornane at a moderate rate, giving 37% of *exo*-2-norbornanol and 63% of the unreacted epoxide in 24 hr. However, $LiAlH_4$–THF gives only 8% *exo*-2-norbornanol at 25°, after 10 days.