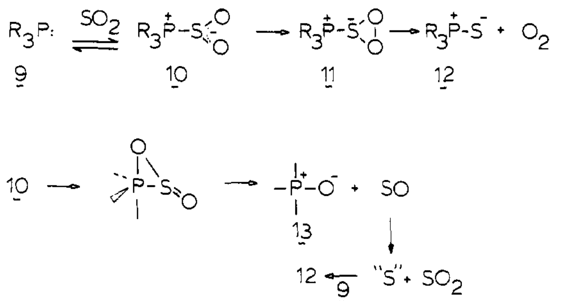

of **11** and its subsequent fragmentation. However, when this reaction was carried out under the same conditions in the presence of an equimolar amount of *o*-dibromobenzene the yield was unchanged but the ratio of **13** to **12** was 3:7. It is amusing to speculate that in this case an external heavy atom catalyst was responsible for an increased intersystem crossing efficiency in the fragmentation of an intermediate such as **11**.

**Acknowledgment.** We wish to thank the NSF and NIH for generous financial support and Drs. Charles Liotta and Kent Barefield for their interest and suggestions.

# Two-Flask Preparation of α-Lithio Cyclic Ethers from γ- and δ-Lactones. Reductive Lithiation as a Route, via Radical Intermediates, to Axial 2-Lithiotetrahydropyrans and Their Equilibration to the Equatorial Isomers

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In this paper, we report a two-flask procedure for preparing α-lithio derivatives of tetrahydrofurans and tetrahydropyrans by a two-stage reduction of widely available γ- and δ-lactones, we demonstrate the utility of this method by describing a very efficient stereospecific total synthesis, the first recorded,[1] of (±)-*trans*-rosoxide (**6**), which also includes a new procedure for the vinylation of carbanions, and we reveal that axial 2-lithiotetrahydropyrans are the proximate products of reductive lithiation of 2-(phenylthio)tetrahydropyrans but that they can be equilibrated to the more stable equatorial organolithiums.

A recent report from this laboratory revealed that reductive lithiation of α-phenylthio ethers, preferably by readily preparable lithium 1-(dimethylamino)naphthalenide (LDMAN), constitutes the first general method for preparing α-lithio ethers.[2] The general method reported here for producing α-phenylthio cyclic ethers in both the five- and six-member ring series and the demonstration that α-lithio ethers can be produced from them and trapped by aldehydes and ketones should have considerable value in synthesis since five- and six-member oxygen heterocycles are distributed widely in nature.

The procedure is demonstrated by a three-flask preparation of (±)-*trans*-rosoxide (Scheme I),[3] a substance that is found in roses and geraniums[4] and is used in the perfume industry. Commercially available lactone **1** is reduced with diisobutylaluminum hydride, and the resulting aluminum salt of the lactol is treated directly with 1.2 M equiv of thiophenol containing 2–3 M equiv of $BF_3 \cdot OEt_2$ to yield the mixture of stereoisomers **2**. Reductive lithiation of the mixture with LDMAN yields only the *trans*-2-lithio-4-methyltetrahydropyran (**3**) which adds in a 1,2 fashion to methacrolein; the resulting alkoxide salt **4** reacts with $CS_2$, and the methyl xanthate, produced by S-methylation of the product, undergoes a [3,3]-sigmatropic rearrangement[5] to yield a single isomer, assumed to have an *E* double bond (**5**), in very satisfactory yield. Reductive desulfurization[6] produces racemic *trans*-rosoxide (**6**).[1] This novel method of vinylation of carbanions is quite promising;[7] a preliminary experiment has shown that methyl vinyl ketone can be substituted for methacrolein.

Scheme I

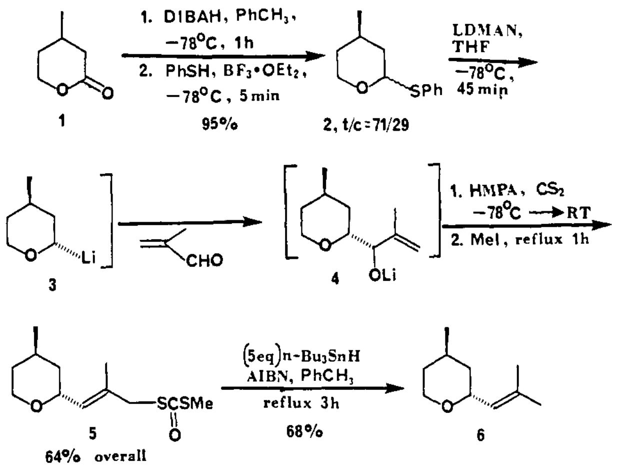
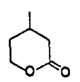
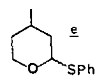
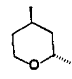
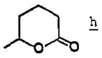
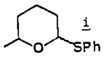
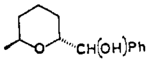
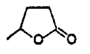
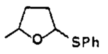
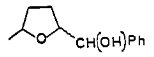
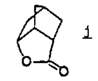
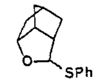
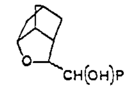
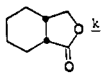
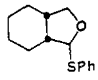
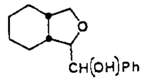


Table I. Conversion of Lactones to α-Lithio Ethers

| lactone[a] | α-phenylthio ether[b] | yield, % | product of RLi + electrophile[b-d] | yield, % |
|---|---|---|---|---|
|  |  [e] | 95 |  Y = PhCH(OH)<br>Y = Ph2C(OH)[f]<br>Y = Me2C(OH)[g] | 63<br>65<br>68 |
|  [h] |  [i] | 74 |  | 56 |
|  |  | 97 |  | 51 |
|  [j] |  | 94 |  | 46 |
|  [k] |  | 76 |  | 56 |

[a] The lactones are commercially available except where noted. [b] Wavy lines indicate mixture of stereoisomers. [c] Except in the cases noted, the electrophile was benzaldehyde. [d] The products of trapping with aldehydes were pairs of threo and erythro isomers. [e] Cis:trans = 29:71. [f] The electrophile was benzophenone. [g] The electrophile was acetone. [h] Reference 23. [i] Cis:trans = 9:91. [j] Reference 24. [k] Reference 25.

As indicated by the representative examples in Table I, other δ-lactones as well as γ-lactones behave in a similar fashion,[3] but we have been unable to convert ε-caprolactone to the seven-membered ring α-phenylthio ether by this method.

The apparently stereospecific production of trans products in the reductive lithiation of the 4- and 6-methyl-2-(phenylthio)-

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(1) In all syntheses, the trans isomer is produced as a mixture with the cis isomer in which the latter is usually the major component. For example, see: Eschinasi, E. H. *J. Org. Chem.* **1970**, *35*, 1097.

(2) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900.

(3) New compounds have been characterized by $^1H$ NMR, IR, and mass spectroscopy and either by their exact masses or by combustion analyses.

(4) Naves, Y.-R.; Lamparsky, D.; Ochsner, P. *Bull. Soc. Chim. Fr.* **1961**, 645. Seidel, C. F.; Felix, D.; Eschenmoser, A.; Biemann, K.; Palluy, E.; Stoll, M. *Helv. Chim. Acta* **1961**, *44*, 598.

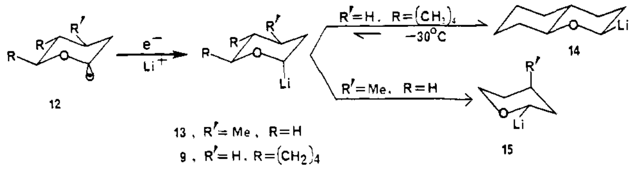
(5) Harano, K.; Taguchi, T. *Chem. Pharm. Bull. (Tokyo)* **1972**, *20*, 2348, 2357.

(6) Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* **1981**, *53*, 1081. Ueno, Y.; Sano, H.; Okawara, M. *Tetrahedron Lett.* **1980**, 1767.

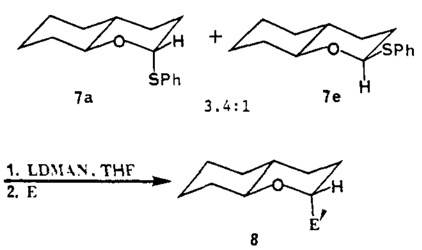
(7) For a discussion of some other methods, see: Hudrlik, P. F.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 6251.

0002-7863/84/1506-1130$01.50/0

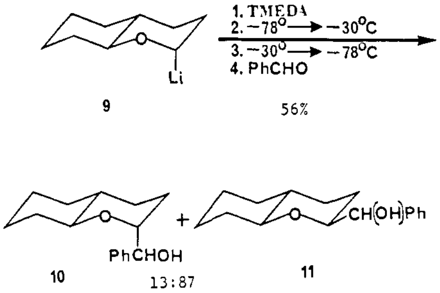
Scheme II



tetrahydropyrans prompted a study of reductive lithiation of the epimeric pair **7** (produced as a mixture with the two cis-fused epimers in 93% yield from the cis–trans lactone mixture[8]) in which the products are incapable of chair–chair interconversion because of the trans ring fusion. Treatment of the products with methacrolein gave in 63% yield the erythro and threo alcohols **8** (E′ = $CH_2$=CMeCHOH–). When benzaldehyde was used, instead, there was isolated a 78% yield of adduct that was composed of 95% of the axial alcohol **10** and 5% of the epimeric alcohol **11**. Treatment of the organolithium intermediate with $D_2O$ or $CD_3CO_2D$ provided the axial deuterio compound (**8**; E′ = D); no detectable quantity of the equatorial deuterium compound was produced.[9]



The conclusion is inescapable that both the axial and equatorial epimers of **7** yield very predominantly the axial lithio derivative **9** upon reductive lithiation. In view of the expectation[10,11] that the equatorial epimer of **9** would be the stable one, **9** was warmed to −30 °C in the presence of 1 M equiv of *N*,*N*,*N′*,*N′*-tetramethylethylenediamine and then cooled to −78 °C and quenched with benzaldehyde whereupon a 56% yield of adduct containing 13% of the erythro and threo axial alcohols (**10**) and 87% of the corresponding equatorial epimers (**11**) was produced along with



a 17% yield[12] of **8** (E′ = H). Thus, a 127-fold change in product ratio was attained by heating the intermediate. A similar attempt to effect equilibration of **3** was unsuccessful; addition of benzaldehyde to the intermediate that had been heated to −30 °C resulted in the same trans erythro–threo pair that was obtained (Table I) without heating.

It has been pointed out[2] that the present method of producing complex organolithium compounds differs fundamentally from the methods in widest use in synthetic methodology in that a carbon radical,[13] formed in the rate-determining step,[2] is a precursor to the anion. The intermediate radical in the present system is expected to be nonplanar,[14-16] to be capable of rapid equilibration between the quasi-equatorial and quasi-axial epimers,[16,17] and to exist largely or entirely in the axial configuration (see **12**).[15-18] When the radical accepts an electron from the LDMAN, the resulting organolithium species (e.g., **9** or **13**) is thus produced in the axial arrangement.[19] In contrast to the radical, the α-lithio ether would certainly be configurationally stable at −78 °C.[20] In the case of the bicyclic α-lithio ether **9**, which cannot undergo chair–chair interconversion, axial products are obtained upon treatment with a carbonyl compound at −78 °C. When **9** is heated to −30 °C, epimerization (inversion)[21] occurs to the more stable equatorial epimer **14**, a process that accompanies or competes with reaction with THF to yield **8** (E′ = H) (Scheme II). On the other hand, **13** can undergo a chair–chair interconversion to **15** and thereby attain the stable equatorial arrangement of the carbon–lithium bond thus eliminating the driving force for epimerization; the trans arrangement of the ring substituents is thus maintained in the product of reaction with carbonyl compounds. It appears that the driving force for the epimerization of **9** to **14** is the thermodynamically unfavorable axial arrangement of the lithio substituent as indicated by the stability to inversion at −30 °C of **15** and of noncyclic analogues, as reported by Still.[20a]

This work provides powerful evidence for the validity of Lehn's conclusion[10] based on ab initio calculations that 2-lithiotetrahydropyrans exist preferentially in the equatorial conformation. It also provides evidence for the theoretically predicted[18] conformation **13**[15-17,19] of the corresponding radical.

The present method is the only general one for producing five- and six-membered α-phenylthio and nontransient α-lithio ethers. Alkyllithiums are capable of deprotonating the α-position of tetrahydrofurans but the temperatures required are such that the resulting α-lithio ethers completely fragment to olefin and enolate anions.[22] Of course the present method allows complete regiospecificity in such anion formation as well as a choice as to the use of the anion.

**Acknowledgment.** We thank Prof. Kendall N. Houk for helpful discussions and useful references, Dr. Alvin Marcus for determining the mass spectral data, the National Institutes of Health for providing financial support (GM 22760), and the National Science Foundation for funds used to purchase the 300-MHz Bruker NMR instrument used in this study (CHE 7905185).

**Supplementary Material Available:** 300 MHz $^1H$ NMR spectra and exact masses of compounds **2**, **5**, **7a**, **7e**, **8** (E′ = $CH_2$=CMeCHOH–), **8** (E′ = D), **10**, and **11** (2 pages). Ordering information is given on any current masthead page.

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(8) Dev, S.; Rai, C. *J. Ind. Chem. Soc.* **1957**, *34*, 266.

(9) About 5% of the epimer would have been detectable. The completely protium material **9** (E′ = H) was available by quenching with $H_2O$.

(10) Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498. See also: Epiotis, N. D.; Yates, R. L.; Bernardi, F.; Wolfe, S. *Ibid.* **1976**, *98*, 5435.

(11) (a) Meyers, A. I.; Campbell, A. L.; Abatjoglou, A. G.; Eliel, E. L. *Tetrahedron Lett.* **1979**, 4159. (b) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614.

(12) Some **8** (E′ = H) was undoubtedly lost during the evaporation of solvent.

(13) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064.

(14) Dobbs, A. J.; Gilbert, B. C.; Norman, R. O. C. *J. Chem. Soc. A* **1971**, 124. Beckwith, A. L. J.; Tindal, P. K. *Aust. J. Chem.* **1971**, *24*, 2099.

(15) Brunton, G.; Ingold, K. U.; Roberts, B. P.; Beckwith, A. L. J.; Krusic, P. J. *J. Am. Chem. Soc.* **1977**, *99*, 3177.

(16) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609. Beckwith, A. L. J.; Easton, C. J. *Ibid.* **1981**, *103*, 615.

(17) Hayday, K.; McKelvey, R. D. *J. Org. Chem.* **1976**, *41*, 2222. Malatesta, V.; McKelvey, R. D.; Babcock, B. W.; Ingold, K. U. *Ibid.* **1979**, *44*, 1872.

(18) Gregory, A. R.; Malatesta, V. *J. Org. Chem.* **1980**, *45*, 122.

(19) Two reports that appeared after our manuscript was submitted lend credence to this explanation. Pyranosyl radicals have been trapped by acrylonitrile and by tributyltin hydride to give largely or exclusively the product of capture of the α-radical. Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622. Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210.

(20) (a) For the first example of the preparation of diastereomerically related α-lithio ethers, see: Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5420.

(21) Lambert, J. B. *Topics Stereochem.* **1971**, *6*, 19.

(22) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.

(23) Pyysalo, H.; Enqvist, J.; Honkanen, E.; Pippuri, A. *Finn. Chem. Lett.* **1975**, 129.

(24) Beckmann, S.; Geiger, H. *Chem. Ber.* **1961**, *94*, 48.

(25) Bloomfield, J. J.; Lee, S. L. *J. Org. Chem.* **1967**, *32*, 3919.