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Substituted Alkenediols by Alkylative Double Ring Opening of Dihydrofuran and Dihydropyran Epoxides

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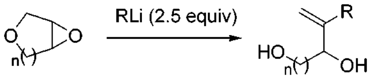
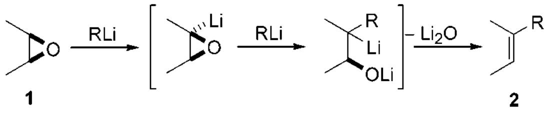
ABSTRACT



Dihydrofuran and dihydropyran epoxides undergo alkylative double ring opening with organolithiums to provide a new route to substituted alkenediols.

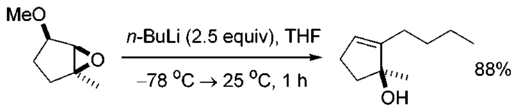
Epoxides are widely utilized as versatile synthetic intermediates.[1] Their reactions are dominated by the electrophilic nature of the epoxide, generally involve cleavage of the strained three-membered ring, and include a wide range of nucleophilic ring openings and acid- and base-induced isomerization reactions. The alkylative deoxygenation of epoxides **1** using organolithiums to give substituted alkenes **2** (Scheme 1) was originally discovered by Crandall and Lin,[2] and a number of research groups have subsequently made contributions to this area.[3]

Scheme 1



In one development of this methodology, Mioskowski and co-workers reported in 1996 that the reaction of organolithiums with cyclopentene- and cyclohexene-derived epoxides possessing a β-methoxy substituent results in the elimination of methoxide and formation of substituted cyclic allylic alcohols (e.g., Scheme 2).[4]

Scheme 2



Arising out of these previous observations, and in connection with our studies concerning the reactions of organolithiums with cycloalkene- and heterocycloalkene-derived epoxides,[5] we considered whether the chemistry illustrated in Scheme 2 could be extended to elimination from a cyclic ether **3** (Scheme 3). Both ethereal oxygens would be retained

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(1) Erden, I. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 1A, pp 97−171.

(2) (a) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4526−4257. (b) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4527−4528. (c) Crandall, J. K.; Apparu, M. *Org. React. (N.Y.)* **1983**, *29*, 345−443.

(3) Reviews: (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325. (b) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337−343.

(4) Dechoux, L.; Doris, E.; Mioskowski, C. *Chem. Commun.* **1996**, 549−550.

(5) (a) Hodgson, D. M.; Lee, G. P.; Marriott, R. E.; Thompson, A. J.; Wisedale, R.; Witherington, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2151−2161. (b) Hodgson, D. M.; Robinson, L. A. *Chem. Commun.* **1999**, 309−310. (c) Hodgson, D. M.; Cameron, I. D. *Org. Lett.* **2001**, *3*, 441−444. (d) Hodgson, D. M.; Cameron, I. D.; Christlieb, M.; Green, R.; Lee, G. P.; Robinson, L. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2161−2174.

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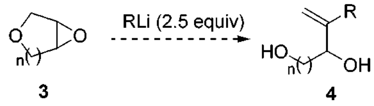
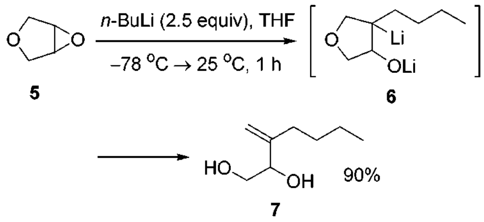
Scheme 3



as hydroxyl groups in the product, and the overall process would represent a new strategy to substituted alkenediols **4**.

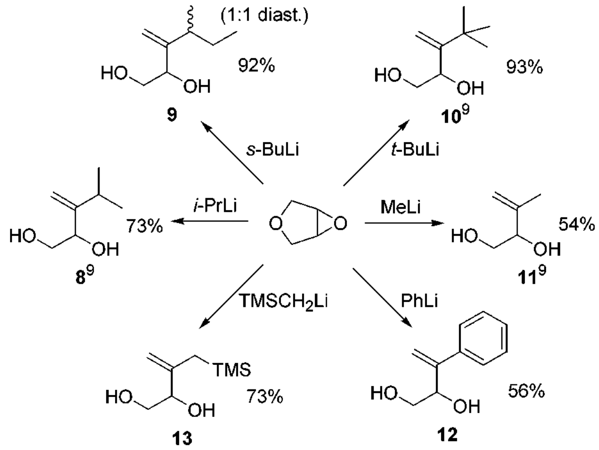
Initially we chose to probe the above hypothesis with readily available 3,4-epoxytetrahydrofuran **5**.[6] Pleasingly, reaction of 3,4-epoxytetrahydrofuran **5** with *n*-BuLi (2.5 equiv) in THF at −78 °C gave 3-butylbut-3-ene-1,2-diol **7**[7] in excellent yield (90%, Scheme 4). As in Mioskowski's work (Scheme 2), the current reaction proceeds via ether cleavage rather than loss of Li_2O;[4] this is despite β-elimination from the presumed lithiated intermediate **6** (Scheme 4) being the reverse of a stereoelectronically disfavored 5-*endo-trig* cyclization.[8]

Scheme 4



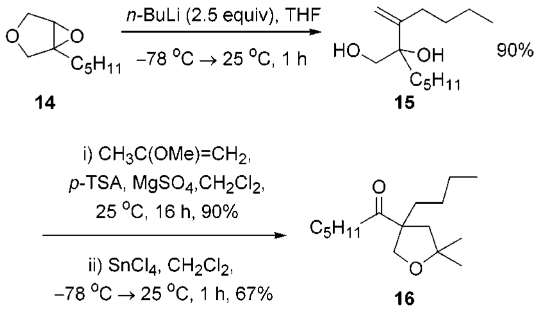
The new alkylative double ring opening process exhibits scope with respect to the type of organolithium that can be used. Primary, secondary, and tertiary alkyllithiums, as well as phenyllithium and (trimethylsilylmethyl)lithium, all underwent successful reaction with 3,4-epoxytetrahydrofuran **5** under the above conditions (Scheme 5).[7,9] Given the utility of allylsilanes in synthesis,[10] the straightforward synthesis of allylsilane **13** (in one step from commercial materials) is noteworthy.

Scheme 5



An alkyl substituent on the epoxide ring of 3,4-epoxydihydrofuran is tolerated in the reaction. Pentyl-substituted epoxide **14**,[11] when treated with *n*-BuLi, was found to undergo the transformation to give tertiary allylic alcohol **15** (Scheme 6), in comparable yield to that of the parent system **5**. The Prins-pinacol rearrangement[12] of **15** to the 3-acyl-substituted tetrahydrofuran **16** (Scheme 6) demonstrates one application of such a tertiary allylic alcohol formed in this reaction.

Scheme 6



A study of 2,5-disubstituted-3,4-epoxytetrahydrofurans was undertaken to further examine the effect of substituents on the rearrangement and as a probe of the stereospecificity[3b] of the process. Methylation and epoxidation[13] of *cis*-2,5-bis(hydroxymethyl)-2,5-dihydrofuran (**17**)[14] gave a chromatographically separable mixture of epoxides **18** and **19**.[15]

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[6] 3,4-Epoxytetrahydrofuran **5** is commercially available from Acros Organics. It can be prepared by epoxidation of widely available 2,5-dihydrofuran (Barili, P. L.; Berti, G.; Mastrorilli, E. *Tetrahedron* **1993**, *49*, 6263−6276).

[7] **Typical experimental procedure:** To a stirred solution of 3,4-epoxytetrahydrofuran **5** (80 mg, 0.93 mmol) in THF (5.0 mL) at −78 °C was added dropwise over 10 min *n*-BuLi (2.20 M in hexanes, 1.06 mL, 2.33 mmol). The reaction mixture was then allowed to warm to 25 °C over 1 h, followed by addition of MeOH (0.5 mL) and preabsorption onto silica gel (2.5 g). Purification by column chromatography on silica gel (petroleum ether/diethyl ether 1/9) gave 3-butylbut-3-ene-1,2-diol **7** as a colorless oil (121 mg, 90%): R_f 0.35 (diethyl ether); IR (neat) 3368, 2957, 2930, 1458, 1074, 1029, 903 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.87 (s, 1H), 4.12 (d, 1H, $J = 7.0$ Hz), 3.97 (br s, 1H), 3.89 (br s, 1H), 3.62 (d, 1H, $J = 11.0$ Hz), 3.44 (dd, 1H, $J = 11.0$ and 7.0 Hz), 2.05−1.88 (m, 2H), 1.43−1.36 (m, 2H), 1.33−1.24 (m, 2H), 0.87 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 110.2, 75.1, 66.2, 32.3, 30.5, 22.5, 13.9; CIMS *m*/*z* (relative intensity) 162 ($M + NH_4+$, 100), 128 (50); HRMS cald for $C_8H_{20}NO_2$ 162.1494, found 162.1494.

[8] Calaza, M. I.; Paleo, M. R.; Sardina, F. J. *J. Am. Chem. Soc.* **2001**, *123*, 2095−2096.

[9] Alkenediols **8**, **10**, and **11** are known compounds (Schulte-Elte, K. H.; Muller, B. L.; Pamingle, H. *Helv. Chim. Acta* **1979**, *62*, 816−829).

[10] Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React. (N.Y.)* **1989**, *37*, 57−575.

[11] Prepared in three steps from 2-methylidene heptanol (Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167−4170): (i) Allyl bromide, NaH, THF, 25 °C, 16 h, 96%; (ii) $(PCy_3)_2Cl_2RuCHPh$, CH_2Cl_2, 25 °C, 5 days, 56% (91% based on recovered diene); (iii) CF_3COCH_3, Oxone, $NaHCO_3$, Na_2EDTA, MeCN, H_2O, 0 °C, 3 h, 73%.

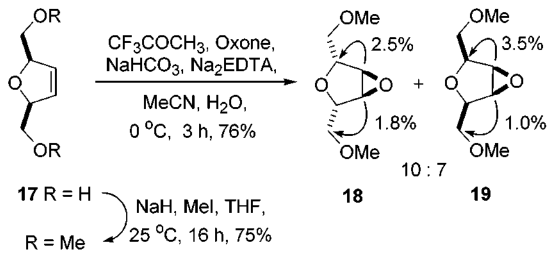
[12] Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354−5365.

[13] Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887−3889.

[14] Prepared via cycloaddition of furan with vinylidene carbonate: de Micheli, C.; de Amici, M.; Grana, E.; Zonta, F.; Giannella, M.; Piergentili, A. *Farmaco* **1993**, *48*, 1333−1348.

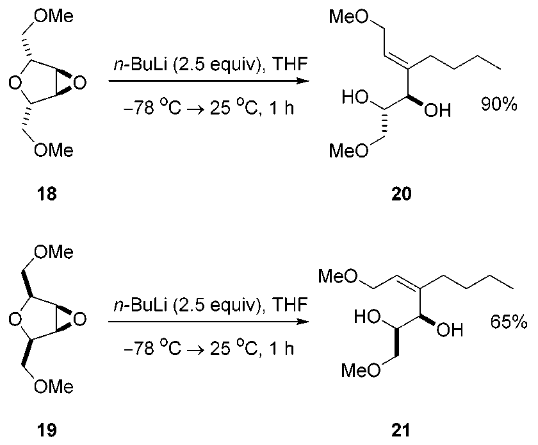
The relative stereochemistry of **18** and **19** was determined by ^{1}H NOE studies (Scheme 7).

Scheme 7



On treatment with *n*-BuLi, each diastereomeric epoxide gave a geometric isomer of the same trisubstituted olefin. These reactions are stereospecific: *cis*,*trans*-**18** exclusively gave the *E*-olefin **20** in 90% yield, and *cis*,*cis*-**19** exclusively gave the *Z*-olefin **21** in 65% yield (Scheme 8).[16]

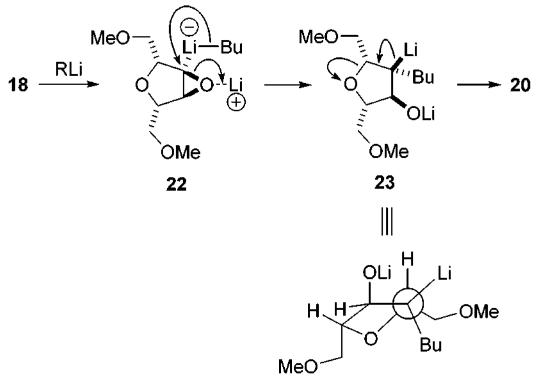
Scheme 8



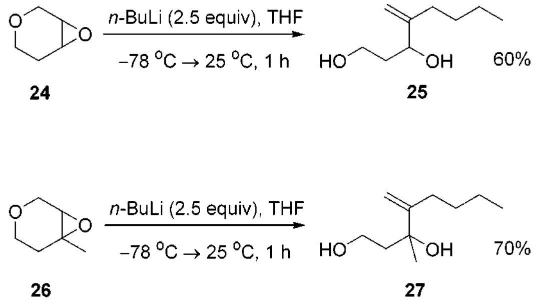
The above results are consistent with a reaction mechanism which proceeds from the lithiated epoxide (e.g., **22** from **18**, Scheme 9) via a 1,2-metalate shift[17] (with concomitant epoxide opening), followed by *anti*-*β*-elimination of Li and furanyl O from alkoxide **23**.[18]

While the process failed with cyclic and acyclic derivatives of the epoxide of *cis*-but-2-ene-1,4-diol,[19] the reaction could be successfully extended to dihydropyran epoxides (Scheme 10). Treatment of dihydropyran epoxides **24**[20] and **26**[21] with *n*-BuLi yields the corresponding substituted pentene-1,3-diols **25** (70% yield) and **27** (60% yield). Formation of pentenediol **25** suggests that the "cyclic" alkoxy substituent *β* to the epoxide directs the epoxide lithiation vicinal to itself.[22]

Scheme 9



Scheme 10



In conclusion, we have demonstrated that dihydrofuran and dihydropyran epoxides undergo alkylative double ring opening with organolithiums to provide a new route to substituted alkenediols. Extensions of the process to other epoxides, organolithiums, and asymmetric transformations and manipulation of the adducts toward targets of biological interest are under investigation.

Acknowledgment. We thank the EPSRC and Roche for a CASE award (to M.A.H.S.) and the EPSRC National Mass Spectrometry Service Centre for mass spectra.

Supporting Information Available: ^{13}C NMR spectra for previously unreported epoxides (**14**, **18**, **19**, **26**) and alkenediols (**7**, **9**, **12**, **13**, **15**, **20**, **21**, **25**, **27**). This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Epoxidation with *m*CPBA (1.1 equiv, CH$_2$Cl$_2$, 25 °C, 16 h) gave epoxides **18** and **19** (**18**:**19**, 1:2) in 75% yield.

[16] Stereochemistry was determined by ^{1}H NOESY studies on both isomers: diol **20** showed strong correlations between the olefinic proton and the protons α-OH, while **21** showed correlations between the olefinic proton and the butyl chain only.

[17] (a) Kasatkin, A. N.; Whitby, R, J. *Tetrahedron Lett.* **2000**, *41*, 5275−5280. (b) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697−756.

[18] Assuming an early transition state for the elimination, then the required *anti* alignment of bonds is easily achieved (Scheme 9). *Syn* elimination is not possible.

[19] The corresponding acetonide and dimethyl and bis(^{t}BuMe$_2$Si) ethers all underwent decomposition. The failure of noncyclic substrates to react via oxiranyl anion chemistry has been previously observed (refs 4 and 22).

[20] Berti, G.; Catelani, G.; Ferretti, M.; Monti, L. *Tetrahedron* **1974**, *30*, 4013−4020.

[21] Dihydropyran oxide **26** was prepared by epoxidation (*m*CPBA, 1.1 equiv, CH$_2$Cl$_2$, 25 °C, 16 h, 35% yield) of the corresponding dihydropyran (Booth, H.; Khedhair, K. A.; Readshaw, S. A. *Tetrahedron* **1987**, *43*, 4699−4723).

[22] Doris, E.; Dechoux, L.; Mioskowski, C. *J. Am. Chem. Soc.* **1995**, *117*, 12700−12704.