ORGANIC LETTERS

2005
Vol. 7, No. 12
2305−2308

2-Ene-1,4-diols by Dimerization of Terminal Epoxides using Hindered Lithium Amides

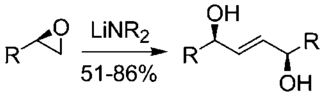
David M. Hodgson,* Christopher D. Bray, and Nicholas D. Kindon[†]

Department of Chemistry, University of Oxford, Chemistry Research Laboratory,
Mansfield Road, Oxford OX1 3TA, U.K.

david.hodgson@chem.ox.ac.uk

Received February 24, 2005

ABSTRACT

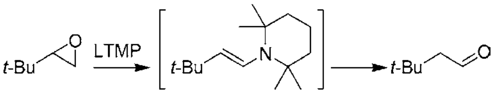


Reaction of hindered lithium amides with readily available (enantiopure) terminal epoxides gives 2-ene-1,4-diols via carbenoid dimerization of the corresponding α-lithiated epoxides. D-Mannitol and D-iditol were synthesized using this method in three steps from (*S*)-tritylglycidyl ether.

Methods for the construction of carbon−carbon double bonds are of major importance.[1] One such method is the dimerization of carbenes/carbenoids, a process that has long been known as a decomposition pathway of such species.[2] The most widely studied methodology to achieve this transformation is the metal-catalyzed decomposition of diazo compounds,[3] though dimerization of α-halo anions is also known.[4] Despite these advances and the fact that it is potentially a powerful method for the construction of double bonds, carbene/carbenoid dimerization has been largely overlooked as a synthetic tool.[5] α-Lithiated epoxides (also called oxiranyl anions) constitute an alternative to diazo compounds as a carbene source,[6] and there have been isolated reports of their dimerization as an undesired side reaction to give 2-ene-1,4-diols.[7]

During our recent studies on the synthesis of enamines from terminal epoxides and hindered lithium amides,[8] we attempted to form an enamine from (racemic) *tert*-butyloxirane. The isomerization of this epoxide to 3,3-dimethylbutyraldehyde (60%) using lithium 2,2,6,6-tetramethylpiperidide (LTMP) (2.5 equiv, THF, 25 °C, 16 h) has been reported,[9] and we presumed it would proceed via the hydrolysis of enamine **1** (Scheme 1). Indeed, enamine **1** was observed by ^{1}H NMR monitoring of the reaction mixture [δ 5.78 (d, $J = 14$, 1H), 5.30 (d, $J = 14$, 1H)], although it was

Scheme 1



1

[†] AstraZeneca R&D Charnwood Medicinal Chemistry, Bakewell Road, Loughborough, Leics LE11 5RH, U.K.

(1) *Preparation of Alkenes*; Williams, J. M. J., Ed.; Oxford University Press: Oxford, 1996.

(2) Grundmann, C. *Ann.* **1938**, *536*, 29−36.

(3) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons: New York, 1997; pp 624−627.

(4) For a recent example, see: Satoh, T.; Osawa, A.; Kondo, A. *Tetrahedron Lett.* **2004**, *45*, 6703−6707.

(5) For a recent example in synthesis, see: Li, G.-Y.; Che, C.-M. *Org. Lett.* **2004**, *6*, 1621−1623.

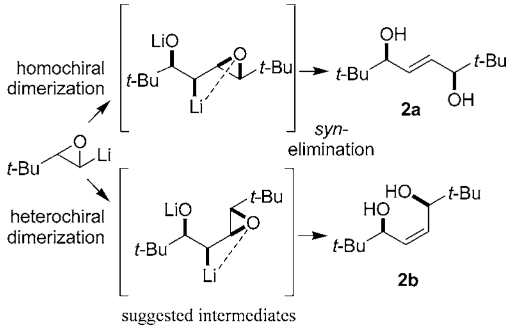
(6) (a) Cope, A. C.; Lee, H.-H.; Petree, H. E. *J. Am. Chem. Soc.* **1958**, *80*, 2849−2852. (b) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4526−4527. (c) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc.* **2004**, *126*, 8664−8665. For recent reviews, see: (d) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625−1642. (e) Chemla, F.; Vrancken, E. In *The Chemistry of Organolithium Reagents*; Rappoport, Z., Marek, I., Eds.; Wiley and Sons: New York, 2004; pp 1165−1242.

(7) (a) Dhawan, K. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* **1980**, *45*, 922−924. (b) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615−618. (c) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445−2448. (d) Capriati, V.; Florio, S.; Luisi, R.; Nuzzo, I. *J. Org. Chem.* **2004**, *69*, 3330−3335. (e) Hodgson, D. M.; Reynolds, N. J.; Coote, S. J. *Org. Lett.* **2004**, *6*, 4187−4189.

10.1021/ol050402h CCC: $30.25

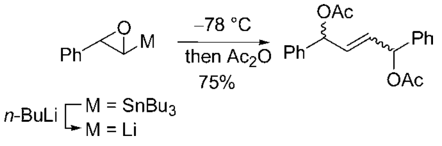
not possible to isolate it. However, when *tert*-butyloxirane was added neat to LTMP (2.0 equiv, 0.05 M in THF) at −15 °C and the reaction was allowed to warm to 25 °C over 2 h, the major product was not the expected aldehyde but rather a chromatographically inseparable mixture of enediols **2a** and **2b** in 37% yield (**2a**:**2b** = 4:1)[10] (Scheme 2). These enediols were initially identified by NMR spectroscopy[11] and ultimately by X-ray crystallography.[12]

Scheme 2



The major (chiral but racemic) enediol **2a** is the result of homochiral dimerization of *trans*-α-lithiated *tert*-butyloxirane, whereas the minor *meso*-enediol **2b** results from heterochiral dimerization. If one lithiated epoxide acts as a nucleophile to another acting as an electrophile, as previously suggested,[7a,b] then the olefin geometry of enediols **2a** and **2b** can be rationalized in terms of exclusive *syn*-elimination (Scheme 2). These observations are similar to those of Pfaltz and co-workers,[7b] who reported that the carbenoid dimerization of (racemic)-*trans*-lithiated styrene oxide (generated from the corresponding epoxystannane and *n*-BuLi in THF) gave an (*E*)-chiral-enediol (∼30%) and a (*Z*)-*meso*-enediol (∼36%) as the major products (Scheme 3).[13]

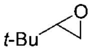
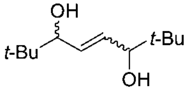
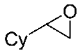
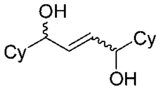
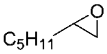
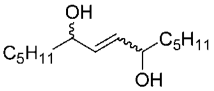
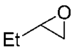
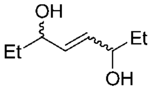
Scheme 3[a]



[a] See ref 7b.

Given the utility of symmetrical 2-ene-1,4-diols[14] and of the corresponding saturated 1,4-diols,[15] we sought to examine the scope of this process. The yield of enediols **2a** and **2b** could be improved to 57% by increasing the reaction concentration (from 0.05 to 0.13 M in THF). A change of solvent to hexane (0.25 M) led to a further improvement to 64% yield. LTMP precipitates from hexane when generated at these concentrations and so *t*-BuOMe was added as a solubilizing cosolvent to enable further concentration increases. Within the scope of the present study, the best reaction conditions[16] were when neat *tert*-butyloxirane was slowly added to LTMP (1.3 equiv; 0.76 M in hexane/*t*-BuOMe (∼1.6:1)) at −5 °C, resulting in a 75% yield of enediols **2a** and **2b** (Table 1, entry 1).[17]

Table 1. 2-Ene-1,4-diols by Dimerization of Racemic Terminal Epoxides using LTMP[a]

entry	epoxide	enediol	yield (%)
1		 **2**	75
2		 **3**	63
3		 **4**	55
4		 **5**	53

[a] See ref 16.

Under these reaction conditions cyclohexyloxirane, 1,2-epoxyheptane, and 1,2-epoxybutane all underwent dimer-

---

(8) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870−6871.

(9) For the isolated yield of 2,4-DNP derivative (57% in our hands), see: Katritzky, A. R.; Fang, Y.; Prakash, I. *J. Indian Chem. Soc.* **2000**, *77*, 635−636.

(10) For a related example of mutual kinetic resolution, see: Alickmann, D.; Fröhlich, R.; Würthwein, E. U. *Org. Lett.* **2001**, *3*, 1527−1530.

(11) Bach, J.; Berenguer, R.; Garcia, J.; López, M.; Manzanal, J.; Vilarrasa, J. *Tetrahedron* **1998**, *54*, 14947−14962.

(12) See Supporting Information.

(13) The (*E*)-*meso*-enediol was also observed to a lesser extent (∼9%, ref 7b), but the corresponding enediol was not observed in our dimerization of *tert*-butyloxirane.

(14) For examples of the uses of symmetric 2-ene-1,4-diols in total synthesis, see: (a) Masaki, Y.; Arasaki, H.; Itoh, A. *Tetrahedron Lett.* **1999**, *40*, 4829−4832. (b) Ariza, X.; Garcia, J.; López, M.; Montserrat, L. *Synlett* **2001**, 120−122. (c) Amador, M.; Ariza, X.; Garcia, J.; Sevilla, S. *Org. Lett.* **2002**, *4*, 4511−4514. (d) Ariza, X.; Fernández, N.; Garcia, J.; López, M.; Montserrat, L.; Ortiz, J. *Synthesis* **2004**, 128−134. (e) Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *J. Org. Chem.* **2004**, *69*, 8172−8175.

(15) For some uses of saturated symmetrical 1,4-diols, see: (a) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755−1756. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518−8519. (c) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569−592.

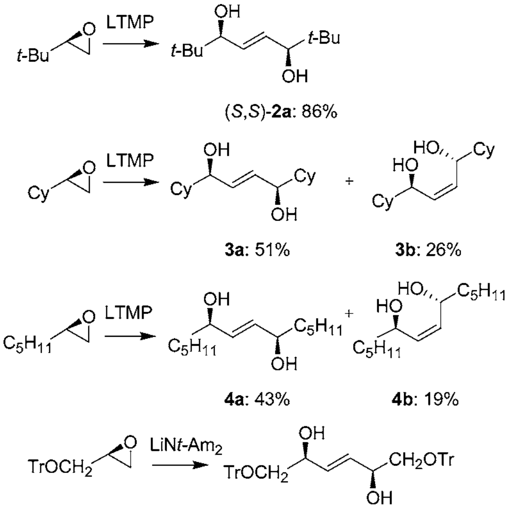
(16) **General Procedure.** To a solution of 2,2,6,6-tetramethylpiperidine (0.44 cm^3; 2.6 mmol) in *t*-BuOMe (1 cm^3) at −5 °C was added *n*-BuLi (1.6 M in hexanes, 1.63 cm^3; 2.6 mmol) dropwise over 2 min. The solution was stirred at this temperature for 5 min at which point a precipitate of LTMP was observed. The solution was then warmed to 25 °C and allowed to stir at this temperature for 15 min. The slurry of LTMP was cooled to −5 °C before addition of the epoxide (2.0 mmol) dropwise over 5 min, after which time the precipitate dissolved. The reaction was stirred at −5 °C for 16 h before the addition of MeOH (3 cm^3). This solution was dry loaded onto silica and flash chromatographed (SiO_2; EtOAc/petrol) to give the enediols.

(17) LTMP precipitated from the hexane/*t*-BuOMe mixture; however, upon addition of the epoxide, the solution became homogeneous (this did not occur at higher reaction concentrations and was detrimental to the yield).

ization to give, in each case, a complex mixture of enediols **3**−**5** (entries 2−4). The yields decrease with diminishing steric bulk at the γ-position of the epoxides, which may be due to competitive enamine formation.[8] Indeed, the dimerization of 1,2-epoxydodecane gave a complex mixture of enediols in 51% yield along with dodecanal, the product of enamine hydrolysis, in 30% yield.

On the basis of our results with *tert*-butyloxirane and those of Pfaltz and co-workers,[7b] it was considered that if our dimerization process was carried out using an enantiopure terminal epoxide, then a single (*E*)-enediol would be obtained. For (*R*)-*tert*-butyloxirane[18] this was indeed the case, and under the typical reaction conditions[16] dimerization gave (*S*,*S*)-**2a** in 86% yield (Scheme 4).

Scheme 4. 2-Ene-1,4-diols by Dimerization of Enantiopure Terminal Epoxides using LTMP[a]



(*S*,*S*)-**2a**: 86%

3a: 51% **3b**: 26%

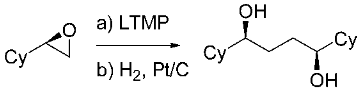
4a: 43% **4b**: 19%

6: 51%

[a] See ref 16.

Dimerization of (*R*)-cyclohexyloxirane was less stereoselective, giving a (separable) mixture of enediols **3a**[19] and **3b** in 77% combined yield. Lowering the temperature for this reaction to −78 °C did not lead to any appreciable improvement in *E*:*Z* selectivity. However, following dimerization, the (unseparated) diols **3a** and **3b** converged to a single saturated 1,4-diol[11] **7** upon hydrogenation (5 mol % Pt/C, H_2 (50 atm), EtOH, 2 h, 76% from (*R*)-cyclohexyloxirane) (Scheme 5). Thus, dimerization of a terminal epoxide followed by hydrogenation constitutes a straightforward two-step entry to C_2-symmetric enantiopure 1,4-diols.[15] Dimerization of (*R*)-1,2-epoxyheptane[20] gave a chromatographically separable mixture of enediols **4a** and **4b** in 62% combined yield (Scheme 4). The one-step synthesis of enediol **4a** is of note since (ent)-**4a** has been used as a building block in the synthesis of (−)-methylenolactocin.[14b,d]

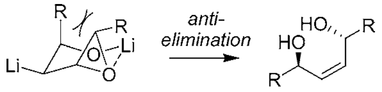
Scheme 5



7: 76%

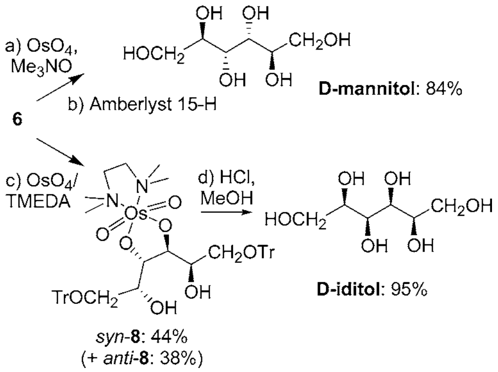
The lower stereoselectivity observed in the dimerization of epoxides that are not fully substituted in the γ-position could be due to *anti*-elimination from the dianion intermediate (Scheme 6), this being less likely when the alkyl chain of the epoxide is large as a result of the indicated steric clash.

Scheme 6



To demonstrate the synthetic utility of this dimerization process, we have examined the use of a glycidyl ether as a common building block for the synthesis of various hexitols. As (*S*)-tritylglycidyl ether is commercially available, we turned our attention to this substrate (Scheme 4). Under the typical reaction conditions, the epoxide (2 mmol), a solid, was added as a solution in THF (1 cm^3), but unfortunately only enamine-derived products were obtained, probably as a result of the presence of THF.[8] However, lowering the reaction temperature to −78 °C and allowing it to warm to 25 °C over 16 h gave enediol **6**, encouragingly as a single geometric isomer[21] (as judged by ^{1}H NMR spectroscopy), in 39% yield. The yield for enediol **6** could be improved to 51% by using lithium di-*tert*-amylamide[22] (2 equiv) as base (0.98 M in hexane/THF (∼3:2)) at −72 °C for 40 h.[23] *anti*-Directed dihydroxylation of enediol **6** under Poli's conditions[24] (*anti*:*syn* $\approx$ 7:1, as judged by ^{13}C NMR spectroscopy) and subsequent bis-trityl deprotection gave D-mannitol[25] in 84% yield following recrystalization (Scheme 7).[26] Alterna-

Scheme 7



---

(18) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(19) The (*E*)-olefin geometry of **3a** was confirmed by X-ray crystallography; see Supporting Information.

(20) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849−851.

tively, reaction of enediol **6** with OsO_4/TMEDA[27] (1 equiv) gave a separable mixture of osmate esters, the selectivity being slightly in favor of *syn*-**8** (*syn*:*anti* = 53:47). Treatment of *syn*-**8** with HCl/MeOH gave D-iditol[28] in 95% yield.

In summary, we have developed a convenient process for the dimerization of (enantiopure) terminal epoxides to 2-ene-1,4-diols with hindered lithium amides. Furthermore, we have demonstrated this methodology in three-step syntheses of D-mannitol and D-iditol from (*S*)-tritylglycidyl ether.

Acknowledgment. We thank the EPSRC and AstraZeneca for an Industrial CASE award, Wadham College for a T. C. Keeley Senior Scholarship (to C.D.B.), the EPSRC for a research grant (GR/S46789/01), Dr. Andrew R. Cowley for obtaining X-ray crystal structures, and the EPSRC National Mass Spectrometry Service Centre for mass spectra.

Supporting Information Available: Spectral details; ^{1}H and ^{13}C NMR spectra of (*S*,*S*)-**2a**, **3a,b**, **4a,b**, **6**, and **7**; comparison of synthetic and natural D-mannitol and D-iditol; and X-ray crystal structures of (*S*,*S*)-**2a**, **2b**, and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050402H

---

[21] The (*E*)-olefin geometry of **6** was confirmed by comparison with an authentic sample synthesized by 1,6-bis-trityl protection of (*E*)-3,4-dideoxy-D-mannitol (ref 14a).

[22] Made by deprotonation of the corresponding commercially available amine with *n*-BuLi/TMEDA (1:1); see: Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1987**, *52*, 448−450.

[23] Under these conditions this base remains in solution, whereas LTMP precipitates, which results in longer reaction times and diminished yields. Application of these conditions to (*R*)-cyclohexyl oxirane did not lead to an improvement in yield or *E*:*Z* selectivity.

[24] (a) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385−7388. See also: (b) Donohoe, T. J.; Waring, M. J.; Newcombe, N. J. *Synlett* **2000**, 149−151.

[25] $[\alpha]^{24}_D$ −1.4 (*c* 0.1, H_2O) (Aldrich, −1.5 (*c* 0.1, H_2O)).

[26] For an asymmetric synthesis of D-altritol based on a related strategy, see: Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768−6769.

[27] (a) Donohoe, T. J.; Newcombe, N. J.; Waring, M. J. *Tetrahedron Lett.* **1999**, *40*, 6881−6885. (b) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946−7956.

[28] $[\alpha]^{24}_D$ +3.4 (*c* 0.8, H_2O) (Acros, −4.6 (L-iditol) (*c* 1.0, H_2O)).