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One-Pot Direct Conversion of 2,3-Epoxy Alcohols into Enantiomerically Pure 4-Hydroxy-4,5-dihydroisoxazole 2-Oxides

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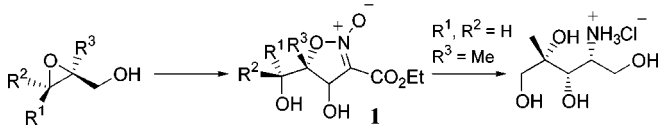
ABSTRACT



A new methodology for the one-pot direct conversion of 2,3-epoxy alcohols into enantiomerically pure 4-hydroxy-4,5-dihydroisoxazole 2-oxides 1 has been found. The reaction works at room temperature and can be run at the 5–10 g scale. The mixture of 4,5-cis and 4,5-trans isomers obtained can be separated as such or as the bis-TDS ethers. A preliminary example of reductive cleavage of 1 to the corresponding amino polyol is also reported.

4-Hydroxy-4,5-dihydroisoxazoles (Figure 1) represent a very interesting subclass of the dihydroisoxazole family,[1] since

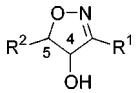


Figure 1. General structure of 4-hydroxy-4,5-dihydroisoxazoles.

the several manipulations possible at the heterocyclic ring can lead to expeditious preparations of biologically interesting compounds.[2,3]

Unfortunately, the usual method for the preparation of 4,5-dihydroisoxazoles, nitrile oxide cycloaddition to alkenes, cannot be applied to the synthesis of 4-hydroxy derivatives. In fact, when vinyl ethers are employed, 5-oxygenated rather than 4-oxygenated heterocycles are obtained with cycloaddition to furans being an exception.[2b,e]

An even more difficult problem is represented by the preparation of enantiomerically pure products. Some approaches to this problem have been devised,[2,4,5] but each one of these methodologies suffers from one or more of the following disadvantages: lack of generality, chiral auxiliries that require several steps to prepare and are not readily available in both enantiomerically pure forms, and low ee values of the products.

For the past 10 years we have been investigating a new approach for the synthesis of 2-oxide derivatives of these heterocycles based on the tandem nitroaldol−intramolecular cyclization reaction between an activated primary nitroalkane and an aldehyde bearing a leaving group on the α-position (Scheme 1).[6,7]

(1) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1069.

(2) For examples, see: (a) Vogel, P.; Schaller, C. *Synlett* **1999**, 1219. (b) Schaller, C.; Vogel, P.; Jäger, V. *Carbohyr. Res.* **1998**, *314*, 25. (c) Wade, P. A.; Shah, S. S.; Govindarajan, L. *J. Org. Chem.* **1994**, *59*, 7199. (d) Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898. (e) Yin, H.; Franck, R. W.; Chen, S.-L.; Quigley, G. J.; Todaro, L. *J. Org. Chem.* **1992**, *57*, 644. (f) Jäger, V.; Schröter, D. *Synthesis* **1990**, 556. (g) Schwab, W.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603.

(3) Recently, it has also been found that a 4-oxygenated-4,5-dihydroisoxazole derivative is itself biologically active as a galactosidase inhibitor. Schaller, C.; Demange, R.; Picasso, S.; Vogel, P. *Bioorg. Chem. Med. Lett.* **1999**, 277.

(4) Davis, F. A.; Kumar, A.; Reddy, R. E.; Chen, B.-C.; Wade, P. A.; Shah, S. W. *J. Org. Chem.* **1993**, *58*, 7591.

(5) Zhang, A.; Kan, Y.; Zhao, G.-L.; Jiang, B. *Tetrahedron* **2000**, *56*, 965. (b) Wallace, R. H.; Liu, J.; Zong, K. K.; Eddings, A. *Tetrahedron Lett.* **1997**, *38*, 6791. (c) Liu, J.; Eddings, A.; Wallace, R. H. *Tetrahedron Lett.* **1997**, *38*, 6795.

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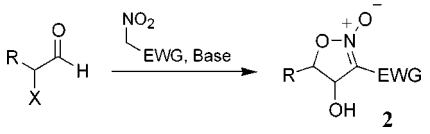
Scheme 1. Tandem Nitroaldol−Intramolecular Cyclization Preparation of 4-Hydroxy-4,5-dihydroisoxazole 2-Oxides



In our continuing efforts to perform the "chiral switch" of the tandem procedure depicted in Scheme 1,[8] we turned our attention to 2,3-epoxy aldehydes. These substrates, which can be obtained by oxidation of the corresponding glycidols, are very interesting starting materials for this process. During the intramolecular cyclization they undergo a stereospecific epoxide ring opening, affording 4,5-dihydroisoxazoles of type **1**, possessing an additional acyclic and stereochemically defined chiral center bearing a hydroxy group.[6a] A drawback of this procedure is that, in many cases, these aldehydes are difficult to isolate from the oxidation medium, if at all, as is the case for simple glycidols, such as **3a** and **3b**. The overall yields for the glycidol oxidation−tandem sequence is usually in the range 0−40%.

In this Letter we describe a new one-pot consecutive[9] conversion of enantiomerically pure 2,3-epoxy alcohols into 4-hydroxy-4,5-dihydroisoxazole 2-oxides **1** that requires no isolation of the intermediate aldehyde. For this purpose we screened several oxidation methodologies to find one that is compatible with the rest of the new one-pot procedure and found the Piancatelli oxidation[10] to be the one of choice. Under these conditions—bisacetoxyiodobenzene (BAIB) as the stoichiometric oxidant and tetramethylpiperidinyloxy radical (TEMPO) as the catalyst—2,3-epoxy alcohols **3** were smoothly converted at room temperature to the corresponding aldehydes in 4−5 h. Addition of ethyl nitroacetate and imidazole at this stage completed the one-pot consecutive process and afforded, after another 18−24 h stirring at room temperature, the corresponding 4-hydroxy-4,5-dihydroisoxazole 2-oxides **1** as a mixture of 4,5-cis and 4,5-trans isomers (Scheme 2 and Table 1), where the former slightly predominates.

These reactions could usually be carried out on a 5−10 g scale, and Table 1 reports the isolated yields and diastereoisomer ratios of the products for the reactions with four different 2,3-epoxy alcohols, chosen to demonstrate the generality of this approach. Yields of this new one-pot procedure are much better than those obtained for the two-step sequence, and especially for 4,5-dihydroisoxazoles **1a** and **1b** which could not be obtained with the previous methodology.

Scheme 2. One-Pot Consecutive Transformation of 2,3-Epoxy Alcohols **3** into 4-Hydroxy-4,5-dihydroisoxazole 2-Oxides **1**

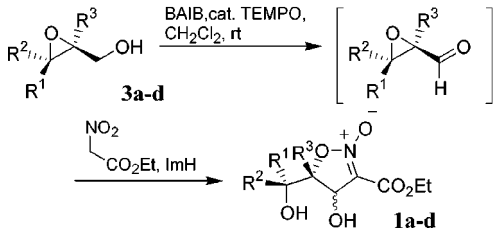
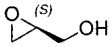
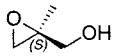
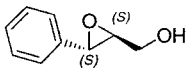
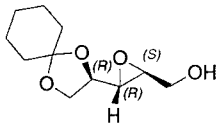


Table 1. Results of the One-Pot Reactions Depicted in Scheme 2

entry	epoxy alcohol (3)	yield (%)	d.r.[a]
a		81	60/40
b		97	72/28
c		71	70/30
d[b]		62	56/44

[a] 4,5-Cis/4,5-trans ratio. [b] Prepared according to ref 11.

The 4,5-cis or 4,5-trans stereochemical configuration of the dihydroisoxazoles obtained has been assigned by means of the coupling constant between the protons on C4 and C5 and through NOE experiments. The low selectivity of this process is of course a drawback, but it can also be considered an advantage since both diastereoisomers are easily available in gram quantities. Moreover, considering that starting 2,3-epoxy alcohols can be obtained in every stereochemical configuration through Sharpless asymmetric epoxidation, this procedure makes available 4,5-dihydroisoxazole of type **1** in every absolute stereochemical configuration at C4 and C5 of the heterocyclic ring.

The mixture of diastereoisomeric products could be separated directly by flash column chromatography in the case of 4,5-dihydroisoxazoles **1c** and **1d**, while products **1a** and **1b** required preliminary derivatization as the bis-*tert*-butyldimethylsilyl (TDS) ethers **4a** and **4b**. If needed, the stereoisomerically pure 4,5-*cis*- and 4,5-*trans*-**4a**,**b** can be deprotected to the corresponding free diols **1a**,**b**, under the usual conditions (anhydrous tetrabutylammonium fluoride in THF) in yields ranging from 78% to 90%.[12]

(6) (a) Rosini, G.; Marotta, E.; Righi, P.; Seerden, J.-P. *J. Org. Chem.* **1991**, *56*, 6258. (a) Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*, 781. For a review on the nitroaldol reaction, see: Rosini, G. The Henry (Nitroaldol) Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds; Pergamon Press: Oxford, 1991; Vol. 2, p 321.

(7) (a) Righi, P.; Marotta, E.; Rosini, G. *Chem. Eur. J.* **1998**, *4*, 2501. (b) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446.

(8) Marotta, E.; Baravelli, M.; Maini, L.; Righi, P.; Rosini, G. *J. Org. Chem.* **1998**, *63*, 8235.

(9) For a clear explanation of the terms tandem, consecutive, and domino process, see: Tietze, L. *Chem. Rev.* **1996**, *96*, 115.

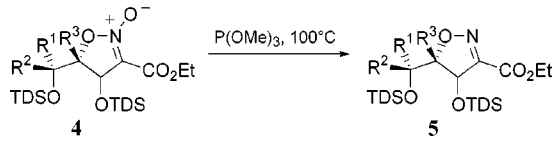
(10) Piancatelli, G.; Margherita, R.; De Mico, A.; Parlanti, L.; Vescovi, A. *J. Org. Chem.* **1997**, *62*, 6974.

(11) Kim, Y. J.; Ichikawa, M.; Ichikawa, Y. *J. Org. Chem.* **2000**, *65*, 2599.

(12) See Supporting Information for full details.

Each of the bis-TDS ethers, 4,5-*cis*- and 4,5-*trans*-**4a**−**c**, could be deoxygenated in very good yields,[6a,8] by exposure to hot trimethyl phosphite, to obtain the corresponding 4,5-dihydroisoxazoles **5a**−**c** (Table 2). Again, if needed, deprotection of these compounds can afford the stereoisomerically pure free diols.[12]

Table 2. Deoxygenation of 4,5-Dihydroisoxazole 2-Oxides



4 **5**

substrate	yield (%)
4,5-*cis*-**4a**	quant
4,5-*trans*-**4a**	quant
4,5-*cis*-**4b**	quant
4,5-*trans*-**4b**	95
4,5-*cis*-**4c**	94
4,5-*trans*-**4c**	93

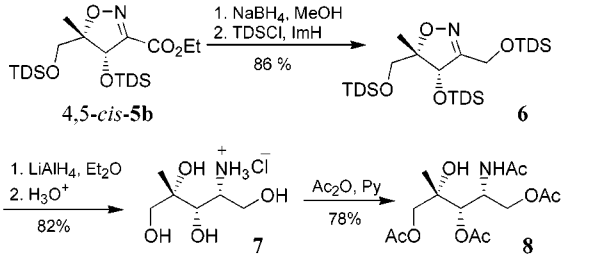
One the most important transformations that a 4,5-dihydroisoxazole can undergo is the lithium aluminum hydride reductive ring cleavage of the heterocycle.[2f] This reaction results in the stereoselective reduction of the C,N double bond with concomitant N,O bond cleavage.

To demonstrate the viability of this new approach to the synthesis of amino polyhydroxylated compounds, we performed the conversion of compound 4,5-*cis*-**5b** to the corresponding amino polyol (Scheme 3).

Thus, the ester functionality of dihydroisoxazole 4,5-*cis*-**5b** was preliminarily reduced[13] with sodium borohydride and the crude alcohol protected to afford **6** in a 86% overall yield. Lithium aluminum hydride reduction in diethyl ether followed by an acid workup resulted in ring cleavage and deprotection to give the corresponding amino polyol **7** as the predominating isomer (de > 9/1), which was fully characterized as the tetraacetate **8**. The stereochemical

(13) When compound 4,5-*cis*-**5b** was directly subjected to the $LiAlH_4$ ring cleavage, a reduction−elimination of the ester function with concomitant ring opening afforded the corresponding 3-hydroxy nitrile in moderate yields.

Scheme 3. Linearization of a 4,5-Dihydroisoxazole Derivative



4,5-*cis*-**5b** **6** **7** **8**

configuration of the newly formed chiral center was assigned on the basis of known steric considerations,[2e,f,g] assuming that the reducing agent attacks from the opposite side of the two bulky silyloxy groups on C4 and C5.

To summarize, in this Letter we reported a new gram-scale one-pot preparation of enantiomerically pure 5-hydroxylakyl-4-hydroxy-4,5-dihydroisoxazole 2-oxides **1**. The advantage of this new approach is the establishment of a direct link between one of the more easily available enantiomerically pure substrates, 2,3-epoxy alcohols, and 4-hydroxy-4,5-dihydroisoxazoles, intermediates of great synthetic potentiality for the preparation of biologically interesting substrates. Further work is now underway to expand this one-pot methodology to other starting materials and to the synthesis of linear amino polyols.

Acknowledgment. This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Italy, the Consiglio Nazionale delle Ricerche (CNR), Italy, and by the University of Bologna, Italy (Progetto d'Ateneo: Biomodulatori Organici and National Project Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni).

Supporting Information Available: (1) Detailed descriptions of experimental procedures for the preparation of compounds 4,5-*trans*- and 4,5-*cis*-**1a**−**d**, 4,5-*trans*- and 4,5-*cis*-**4a**,**b**, 4,5-*trans*- and 4,5-*cis*-**5a**,**b**, **6**, and **8**; (2) actual ^1H and ^{13}C NMR spectra of compounds 4,5-*trans*- and 4,5-*cis*-**1a**−**d**, 4,5-*trans*- and 4,5-*cis*-**4a**,**b**, 4,5-*trans*- and 4,5-*cis*-**5a**,**b**, **6** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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