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A Regio- and Stereodivergent Synthesis of *vic*-Amino Alcohols

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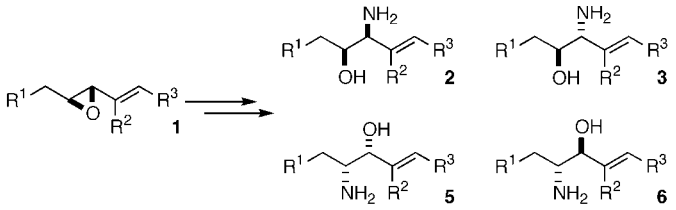
ABSTRACT



A regio- and stereodivergent synthesis of *vic*-amino alcohols starting from vinylepoxides is described. The developed strategy focuses on the propensity of vinylepoxides and vinylaziridines to be ring-opened at the allylic position by suitable nucleophiles and makes use of reactions that perform such tasks selectively with either retention or inversion of configuration.

The β-amino alcohol moiety is found in a wide variety of biologically active alkaloids and peptides.[1] The importance of vicinal amino alcohols is also well recognized in asymmetric synthesis, where the need for chiral auxiliaries and ligands is continually increasing.[2] Existing synthetic routes to enantiopure amino alcohols rely heavily on the derivatization of the available pool of amino acids, inherently limiting the number of accessible derivatives.[3] Large efforts to develop asymmetric routes circumventing these drawbacks have been made[4] and can be divided into two strategically different categories. First, the amino alcohol moiety can be formed by concomitant creation of a new C−C bond; this can be accomplished by stereoselective addition of nucleophiles to α-aminocarbonyls,[3] nitroalkenes,[5] or imines[1,6] or by reaction of chiral aminoallylboranes with aldehydes.[7] Alternatively, the segment may be constructed without alteration of the carbon skeleton, which can be done by Sharpless aminohydroxylation[8] or by ring opening of epoxides,[9] aziridines,[10] or cyclic sulfates[11] with appropriate nucleophiles. Despite the great interest in this field, no divergent route from a common starting material toward all possible regio- and stereoisomers of a vicinal amino alcohol has been documented, thus complicating the synthetic planning substantially by the requirement of a conceptually different synthesis route for each isomer. A divergent route would be a great simplification for studies on structure−activity relationships for pharmacologically active derivatives

(1) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431−432 and references therein.
(2) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.
(3) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546.
(4) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561−2576.
(5) Enders, D.; Haertwig, A.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **1998**, 1771−1792. Enders, D.; Haertwig, A.; Runsink, J. *Eur. J. Org. Chem.* **1998**, 1793−1802.
(6) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785−2792.
(7) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P. *J. Org. Chem.* **1996**, *61*, 2677−2685.
(8) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326−329. Li, G.; Chang, H.-T.; Sharpless, B. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451.
(9) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420−7421. Mitsunobu, O. *Synthesis of Amines and Ammonium Salts*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp Chapter 1.3. Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792−3794. Zwanenburg, B. *Pure Appl. Chem.* **1999**, *71*, 423−430. Hayakawa, H.; Okada, N. M., M.; Miyashita, M. *Tetrahedron Lett.* **1999**, *40*, 4589−4592. Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287−289.
(10) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 2* **1981**, 121−126. Ibuka, T.; Nakai, K.; Akaji, M.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron* **1996**, *52*, 11739−11752. Hwang, G.-I.; Chung, J.-H.; Lee, W. K. *J. Org. Chem.* **1996**, *61*, 6183−6188.
(11) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623−2626. Lohray, B. B.; Ahuja, J. R. *J. Chem. Soc., Chem. Commun.* **1991**, 95−97. Chang, H.-T.; Sharpless, B. *Tetrahedron Lett.* **1996**, *37*, 3219−3222. Cho, G. Y.; Ko, S. Y. *J. Org. Chem.* **1999**, *64*, 8745−8747.

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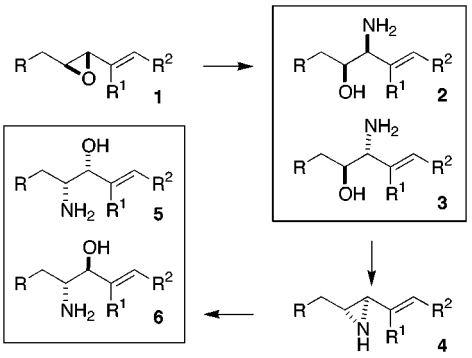
incorporating this structural motif and for optimizing the performance of chiral ligands containing this substructure. We therefore set out to develop a route leading to all eight possible isomers of a given 1,2-amino alcohol starting from a common substrate, and herein we present our preliminary results.

The requirements for a generally applicable synthetic route were readily available starting materials, flexibility, predictability, and high regio- and stereoselectivity. These demands could be met by choosing vinylepoxides as substrates, both enantiomers being readily available in high enantiomeric excess, as they are known to be ring opened selectively at the allylic position by hard nucleophiles.[12] As depicted in Scheme 1, the synthesis strategy designed to fulfill these

Scheme 1. Synthetic Strategy



specifications starts by ring opening of epoxide **1** with a nitrogen nucleophile. The opening can be performed either with retention or inversion of stereochemistry, giving *syn*- and *anti*-amino alcohols **2** and **3**, respectively. Ring closure of **3** to the corresponding vinylaziridines **4** and subsequent ring opening with an oxygen nucleophile, either with retention or inversion, would then give *syn*- and *anti*-amino alcohols **5** and **6**, all reactions taking place regioselectively at the allylic position. The remaining set of enantiomeric amino alcohol isomers can simply be obtained by starting from *ent*-**1**.

Aminolysis of vinylepoxides **1**[13] was accomplished with NH_4OH under microwave irradiation[14] to afford *anti*-amino alcohols **3** regioselectivity (>20:1) and in high yields (Scheme 2, Table 1).[15] Alternatively, Pd(0)-catalyzed ring

Scheme 2. Opening of Vinylepoxides **1**

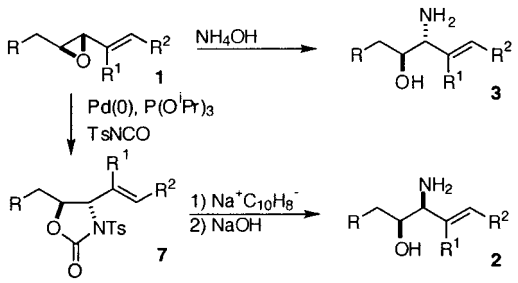


Table 1. Data for the Opening of Vinylepoxides **1**[a]

				yield (%)[b]		
substrate	R	R^1	R^2	**3**	**7**	**2**
a	BnO	H	H	87	88[c]	73
b	$PhCH_2$	H	H	93	82[c]	93
c	BnO	H	CH_2OPMB	88	87	66
d	PMBO	CH_2OBn	H	86	93	73

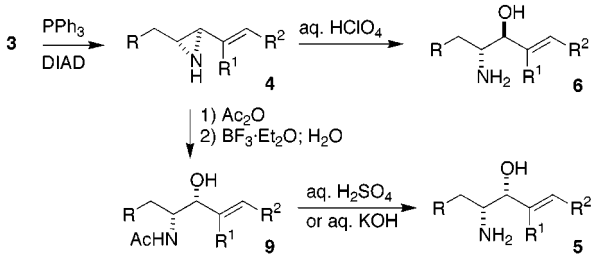
[a] For experimental details, see Supporting Information. [b] Isolated yields. [c] Diasteromeric mixture; see text.

opening of **1** in the presence of tosyl isocyanate, according to the Trost procedure,[16] gave oxazolidinones **7** with retention of configuration.

Conversion of **1** to **7** took place with complete stereoselectivity (>20:1) when **1** contained additional vinylic substituents (**1c**,**d**), whereas the unsubstituted vinylepoxides **1a**,**b** gave a diastereomeric mixture. In these cases the kinetically obtained, poor selectivity could be improved by equilibration of the initial product mixture (**1a** ds 2:1 → 14:1, **1b** ds 2:1 → 6:1).[17] Oxazolidinones **7** were detosylated to the corresponding *N*-H derivatives,[18] the relative stereochemistry of which could be determined from the ^{1}H NMR coupling constants.[7] At this stage the diastereomers could be separated by flash chromatography, and subsequent basic hydrolysis yielded *syn*-amino alcohols **2** (Scheme 2, Table 1).

To obtain regioisomers **5** and **6**, amino alcohols **3** were ring closed to give *N*-H aziridines **4** (Scheme 3, Table 2).[19]

Scheme 3. Formation and Opening of Vinylaziridines **4**



Cyclization of primary amines into aziridines is known to be difficult,[20] but good yields of **4** were obtained under optimized Mitsunobu conditions followed by careful puri-

(12) Jaime, C.; Ortuno, R. M.; Font, J. *J. Org. Chem.* **1988**, *53*, 139−141.

(13) Vinylepoxides **1a**,**b** were obtained from the allylic alcohols using Sharpless asymmetric epoxidation followed by the Swern/Wittig procedure, see: Díez-Martin, D.; Kotecha, N. R.; Ley, S. L.; Mantegani, S.; Menéndez, J. C.; Organ, H. M.; White, A. D.; Banks, J. B. *Tetrahedron* **1992**, *48*, 7899−7938; **1c** was obtained from the corresponding dienol; for **1d**, see: Weigand, S.; Brückner, R. *Synlett* **1997**, 225−228. All vinylepoxides had ee > 95%.

(14) Lindström, U. M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* **1999**, *40*, 9273−9276.

(15) The stereochemistry was confirmed by converting amino alcohols **3**, **5**, and **6** into the corresponding oxazolidinones; see ref 18.

(16) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792−3794.

Table 2. Formation and Opening of Vinylaziridines 4[a]

substrate	R	R^1	R^2	yield (%)[b] 4	6	9	5
a	BnO	H	H	72	84	73	92[c]
b	$PhCH_2$	H	H	80	80	71	95[c]
c	BnO	H	CH_2OPMB	78[d]	82	73	91[e]
d	PMBO	CH_2OBn	H	63	71	73	84[e]

[a] For experimental details, see Supporting Information. [b] Isolated yields. [c] Acidic hydrolysis. [d] Based on recovered starting material. [e] Basic hydrolysis.

fication on deactivated silica. Vinylaziridines **4** could then be regioselectively hydrolyzed into *anti*-amino alcohols **6** under acidic conditions. Initial attempts to hydrolyze **4** using TsOH gave **6** in modest yields and regioselectivity (9:1), whereas complete regioselectivity (>20:1) was obtained with $HClO_4$ (1 equiv) in THF/H_2O.[15] Finally, *syn*-isomer **5** was obtained via acetylation of **4** into the corresponding acylaziridines, which was unstable to standard purification and therefore used as crude product in the subsequent step.[21] When the acylaziridines were treated with $BF_3{\cdot}OEt_2$ in THF, a clean rearrangement into oxazolines **8** (ds > 20:1) ensued,[22] which surprisingly proved to be unstable toward workup and purification (Figure 1).[23]

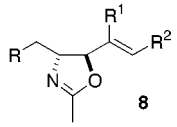


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Figure 1. Structure of oxazoline **8**.

This could be circumvented by in situ hydrolysis of **8** into hydroxyamide derivatives **9**, which could be isolated in 70−73% yield from **4**. The timing of the water addition is crucial for the successful outcome of the reaction; when added too early the diastereoselectivity is diminished as water opens the acylaziridine, and when added too late the formation of byproducts increases. Interestingly, attempts to effect the rearrangement of **4a** using Brønsted acids proved inferior because of increased byproduct formation. The stereoselectivity of this rearrangement (>20:1) is gratifying and has been explained by invoking an S_Ni mechanism.[22] The complete regioselectivity, which is of equal importance, can be rationalized by the stabilizing effect of the vinyl group on the transition state, thus favoring attack of the carbonyl oxygen at the allylic position. Finally, mild acidic or basic hydrolysis of **9**, depending on the stability of the protective groups, gave the remaining *syn*-amino alcohols **5**.[15,24]

In conclusion, we have presented a synthetic strategy that provides a straightforward route from vinylepoxides **1** to the four isomeric *vic*-amino alcohols **2**, **3**, **5** and **6**. Since *ent*-**1** is available from the same starting material as **1**, this protocol has the potential of delivering all eight possible isomers of a given amino alcohol. The presented strategy focuses on the propensity of vinylepoxides and vinylaziridines to be ring-opened at the allylic position by suitable nucleophiles, using reactions that perform such transformations selectively with either inversion or retention of configuration. Further investigations to define the scope and limitations of this protocol are underway, as is the application to natural product synthesis.

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Supporting Information Available: Representative procedures for the preparation of compounds **2**−**7** and **9** and characterization of **2**, **3**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Cook, G. R.; Shanker, S. *Tetrahedron Lett.* **1998**, *39*, 3405−3408.
(18) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548−1562.
(19) Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109.
(20) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127−164. Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−619. Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715. Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. *Aziridines and Azirines: Monocyclic*; Padwa, A., Ed.; Pergamon: Elmsford, NY, 1996; Vol. 1A, pp 1−96.
(21) Lindström, U. M.; Somfai, P. *J. Am. Chem. Soc.* **1997**, *119*, 8385−8386.
(22) Hori, K.; Nishiguchi, T.; Nabeya, A. *J. Org. Chem.* **1997**, *62*, 3081−3088. Ferraris, D.; Drury, W. J., III; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568−4569.
(23) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450−9458. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.
(24) Lai, C. K.; Buckanin, R. S.; Chen, S. J.; Zimmerman, D. F.; Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1982**, *47*, 2364−2369. Koft, E. R.; Dorff, P.; Kulling, R. *J. Org. Chem.* **1989**, *54*, 2936−2940.