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Stereoselective Synthesis of 2,6-Disubstituted 3-Piperidinols: Application to the Expedient Synthesis of (+)-Julifloridine

Alexandre Lemire and André B. Charette*

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec H3C 3J7, Canada

andre.charette@umontreal.ca

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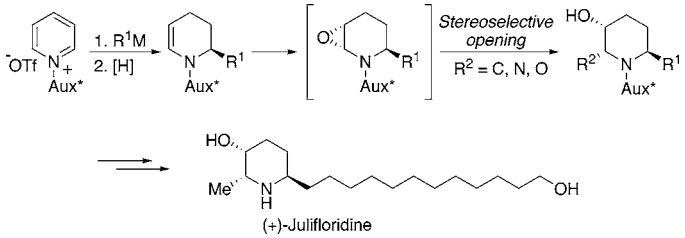
ABSTRACT



The asymmetric synthesis of 2,6-disubstituted 3-piperidinols having a 2,3-cis and 2,6-trans relative stereochemistry was accomplished in three steps using the following sequence: stereocontrolled nucleophilic addition of an organomagnesium reagent to a chiral pyridinium salt; monohydrogenation of the resulting 2-substituted 1,2-dihydropyridine; and a one-pot, highly diastereoselective epoxidation–nucleophilic addition with a heteroatom nucleophile or an organometallic reagent. This methodology was applied to the expedient asymmetric synthesis of (+)-julifloridine in four steps.

The piperidine subunit is among the most important pharmacophores found in biologically active molecules and natural products. The stereoselective synthesis of polysubstituted piperidines remains a substantial challenge in organic chemistry.[1,2] Among this class of products, 2,6-disubstituted 3-piperidinol alkaloids such as **1**−**7** are frequently encountered in biologically active natural products (Figure 1).[3,4] Our research program directed toward the expedient synthesis of polysubstituted piperidines from cheap and readily available starting materials[5] prompted us to develop a general approach for the stereocontrolled synthesis of substituted piperidinols.

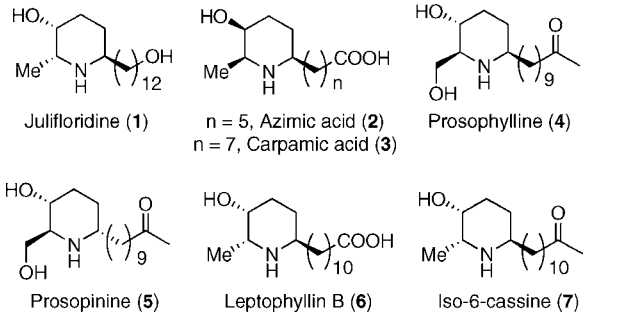


Figure 1. 2,6-Disubstituted 3-piperidinols natural products.

(1) For recent reviews on the stereoselective synthesis of piperidines, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989.

(2) For recent examples: (a) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 1897−1900. (b) Toure, B. B.; Hall, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 2001−2004. (c) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 11808−11809. (d) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240−6241. See also: (e) Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574−2576. (f) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052−2057.

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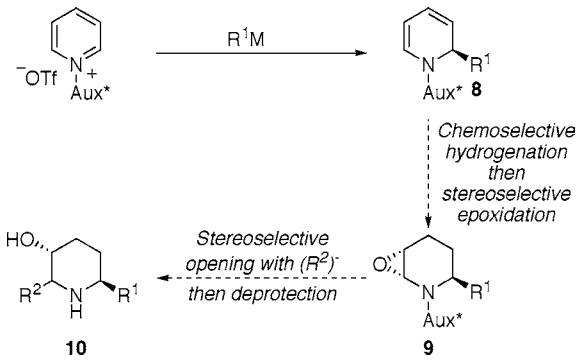
The realization of this goal and an application to the expedient synthesis of julifloridine (**1**) is presented herein. The approach is based on our ability to chemoselectively functionalize various positions of the chiral dihydropyridine **8** obtained by diastereoselective nucleophilic 1,2-addition of organometallic reagents to chiral pyridinium salts (Scheme 1).[5a,d] A chemoselective hydrogenation of the dihydropyridine

Scheme 1. Strategy to Access 2,6-Disubstituted 3-Piperidinols

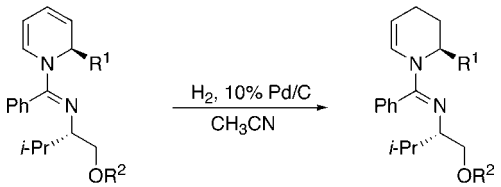


followed by a diastereoselective epoxidation should generate epoxide **9** that could be opened with a nucleophile to afford, after deprotection, piperidinol **10**. The versatility of this approach should allow the rapid synthesis of substituted piperidinols with four easily modified substituents (R^1, R^2, OH, NH).

2-Substituted nitrogen heterocycles protected with an electron-withdrawing group are known to place their substituents in axial positions to minimize the $A^{1,3}$ strain.[6] This suggests that the epoxidizing reagent should react on the face opposite to R^1 (Scheme 1). The resulting labile epoxide **9** should undergo ring opening upon nucleophilic attack, leading to 2,6-disubstituted 3-piperidinols **10**. One potential issue was the stereoselectivity of the nucleophilic attack on the epoxide, which could afford **10** as a mixture of epimers.

The first step of the sequence involved a chemoselective reduction of one of the two endocyclic alkenes of dihydropyridine **11**[5a] to afford tetrahydropyridine **12**. Hydrogenation of the alkenes proceeded at significantly different rates, and selective hydrogenation afforded good yields of 2-substituted 1,2,3,4-tetrahydropyridines (Table 1).[7] To the best of our knowledge, this regioselective hydrogenation has no precedent for monosubstituted 1,2-dihydropyridines.[8,9]

Table 1. Regioselective Hydrogenation of 1,2-Dihydropyridines[a]



entry	R^1	R^2	yield (%)	product
1	Ph	Bn	77	**12a**
2	Me	Me	86	**12b**
3	Et	Me	58	**12c**
4	2-furyl	Me	79	**12d**
5	Ph	Me	78	**12e**

[a] Substrate and catalyst were stirred in acetonitrile under a hydrogen atmosphere (1 atm) for 2 h. See Supporting Information for details.

Initial attempts to epoxidize the enamine were conducted with 2-phenyl-1,2,3,4-tetrahydropyridine **12a**. However, only decomposition products resulted when attempting to isolate the epoxide if *m*-chloroperoxybenzoic acid (MCPBA) or dimethyldioxirane (DMDO) was used as the epoxidizing agent. Use of the Camps reagent (MCPBA-KF) did not lead to either the desired epoxide or its epoxide opening product

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(4) For recent syntheses, see: (a) Cassidy, M. P.; Padwa, A. *Org. Lett.* **2004**, *6*, 4029−4031. (b) Randl, S.; Blechert, S. *Tetrahedron Lett.* **2004**, *45*, 1167−1169. (c) Chavan, S. P.; Praveen, C. *Tetrahedron Lett.* **2004**, *45*, 421−423. (d) Jourdant, A.; Zhu, J. *Heterocycles* **2004**, *64*, 249−259. Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001−6009. (e) Wang, Q.; Sasaki, N. A. *J. Org. Chem.* **2004**, *69*, 4767−4773. (f) Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27−29. (g) Sato, T.; Aoyagi, S.; Kibayashi, C. *Org.* Lett. **2003**, *5*, 3839−3842. (h) Lee, H. K.; Chun, J. S.; Pak, C. S. *Tetrahedron* **2003**, *59*, 6445−6454. (i) Ma, D.; Ma, N. *Tetrahedron Lett.* **2003**, *44*, 3963−3965. (j) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855−3857. (k) Sengupta, S.; Mondal, S. *Tetrahedron* **2002**, *58*, 7983−7986. (l) Singh, R.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 7711−7715. (m) Toyooka, N.; Nemoto, H. *Drugs Future* **2002**, *27*, 143−158. (n) Bailey, P. D.; Smith, P. D.; Morgan, K. M.; Rosair, G. M. *Tetrahedron, Lett.* **2002**, *43*, 1071−1074. (o) Comins, D. L.; Sandelier, M. J.; Grillo, T. A. *J. Org. Chem.* **2001**, *66*, 6829−6832. (p) Enders, D.; Kirchhoff, J. H. *Synthesis* **2000**, 2099−2105. (q) Agami, C.; Couty, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783−8796. (r) Kiguchi, T.; Shirakawa, M.; Honda, R.; Ninomiya, I.; Naito, T. *Tetrahedron* **1998**, *54*, 15589−15606 and references therein.

(5) (a) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830. (b) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360−6361. (c) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517−3520. (d) Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 2368−2371.

(6) (a) Comins, D. L.; Joseph, S. P. *Advances in Nitrogen Heterocycles*; Moody, C. J., Ed.; JAI Press, Inc.: Greenwich, CT, 1996; Vol. 2, pp 251−294. (b) Hoffmann, H. R. *Chem. Rev.* **1989**, *89*, 1841−1860. (c) Johnson, F. *Chem.* Rev. **1968**, *68*, 375−413.

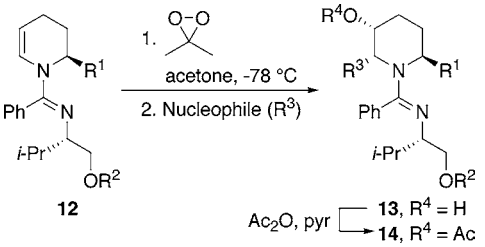
(7) For a review on stereocontrolled additions to di- and tetrahydropyridines, see: (a) Kumar, R.; Chandra, R. *Adv. Heterocycl. Chem.* **2001**, *78*, 269−313. For a review on dihydropyridines, see: (b) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141−1156. For stereoselective synthesis of 1,2,5,6-tetrahydropyridines, see: (c) Huang, H.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 626−627. (d) Felpin, F.-X.; Lebreton, J. *Curr. Org. Synth.* **2004**, *1*, 83−109.

(8) For 2,6-disubstituted 1,2-dihydropyridines, see: (a) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506−2512. (b) Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.-i.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215−222. For 3,5-disubstituted dihydropyridines, see: (c) Comins, D. L.; Williams, A. L. *Org. Lett.* **2001**, *3*, 3217−3220.

(9) For disubstituted 1,2-dihydropyridines substituted with an electron-withdrawing group, see: (a) Kita, Y.; Maekawa, H.; Yamasaki, Y.; Nishiguchi, I. *Tetrahedron* **2001**, *57*, 2095−2102. (b) Lavilla, R.; Gotsens, T.; Gullón, F.; Bosch, J. *Tetrahedron* **1994**, *50*, 5233−5244. (c) Naito, T.; Lida, N.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1986**, 99−104.

when 2-propanol was subsequently added.[10] However, the reaction with DMDO using methanol as a cosolvent led to **13a** in 82% yield. Isolation of the product as its acetate (**14a**) afforded an excellent yield of the product as a single diastereomer (Table 2, entry 1). The stereochemical outcome of the reaction was determined by NMR and was rather surprising since the expected axial attack would have led to the 2,3-trans isomer.

Table 2. Stereoselective Epoxidation/Opening Sequence[a]



entry	substrate	nucleophile (R^3)	yield (%)[b]	product
1	**12a**	MeOH (MeO)	89	**14a**
2	**12a**	*i*-PrOH (*i*-PrO)	92	**14b**
3	**12a**	4-$BrC_6H_4CH_2OH$ (4-$BrC_6H_4CH_2O$)	60	**14c**
4	**12a**	phthalimide	77	**14d**
5	**12a**	MeZnBr (Me)	67	**13e**
6	**12a**	Me_2Zn (Me)	91	**13e**
7	**12a**	Et_2Zn (Et)	75	**13f**
8	**12b**	Et_2Zn (Et)	57	**13g**
9	**12c**	Me_2Zn (Me)	75	**13h**
10	**12c**	Et_2Zn (Et)	60	**13i**
11	**12d**	Et_2Zn (Et)	65	**13j**
12	**12e**	Me_2Zn (Me)	92	**13k**
13	**12e**	PhZnBr (Ph)	91	**13l**
14	**12e**	CH_2=CHZnBr (vinyl)	89	**13m**

[a] Entries 1 and 2: the substrate and nucleophile (used as a cosolvent) were stirred at −78 °C, and then 1.1 equiv of DMDO (ca. 0.08 M in acetone) was added. Entries 3 and 4: the substrate and nucleophile (2.0 equiv) were stirred at 0−5 °C, and then 1.1 equiv of DMDO (ca. 0.08 M in acetone) was added. Entries 5−14: the substrate was stirred at −78 °C, and 1.1 equiv of DMDO (ca. 0.08 M in acetone) was added. After 5 min, the nucleophile (5−10 equiv) was added. [b] Entries 1−4: isolated yield of acetylated product **14** (two steps). Entries 5−14: isolated yield of the free alcohol **13**. See Supporting Information for details.

We then decided to explore the reactivity of various heteroatom nucleophiles to examine the scope of this oxidation/epoxide opening sequence as well as the generality of the sense of induction of the stereochemical induction. As shown in Table 2, various alcohols reacted equally well, producing the ring-opened products as single diastereomers (entries 2 and 3). Phthalimide was also found to react in a similar fashion, producing the N-substituted adduct (entry 4). For more valuable or nonvolatile nucleophiles, the number of equivalents could be lowered to 2 (entries 3 and 4). In all the examples we tested, the 2,3-cis product was always formed as the exclusive diastereomer.[11]

Having established that heteroatom nucleophiles could efficiently react with the epoxide, we then examined methods for the introduction of carbon-based nucleophiles. Spectroscopic studies have shown that the epoxide is moderately stable at −78 °C in the absence of Lewis acids or nucleophiles. However, all our efforts to remove acetone upon concentration under reduced pressure at low temperature led to epoxide decomposition. Furthermore, our attempts to induce a BF_3·OEt_2- or TMSOTf-mediated epoxide opening in the presence of allylstannanes or allylsilanes were unsuccessful. This failure may be attributed to the presence of acetone as a solvent in these reactions since the epoxide could not be isolated. Since DMDO was used as a dilute solution in acetone, our attention turned to nucleophiles that were compatible with acetone at low temperature. Gratifyingly, methylzinc bromide reacted with the in situ-generated epoxide to afford **13e** in good yield, again as a single diastereomer (Table 2, entry 5). Interestingly, a cis relative stereochemistry was observed, which is consistent with the stereochemistry obtained using heteroatom nucleophiles. The organozinc halide generated from methylmagnesium bromide and zinc chloride reacted equally well, but the use of zinc triflate proved to be less effective. Furthermore, generation of the methylzinc bromide from organometallic reagents other than Grignards led to lower yields. Addition of magnesium bromide dimethylcuprate or magnesium bromide methylcyanocuprate also led to **13e**, albeit in a 1:1 mixture of 2,3-cis and 2,3-trans isomers. Diorganozinc reagents added nicely to the epoxides generated from **12a**−**e** (Table 2, entries 6−12). Phenylzinc bromide and vinylzinc bromide gave excellent yields of the piperidinols **13l** and **13m** (entries 13 and 14).

Selected NOE correlations demonstrating the structures of **14a** and **13f** are illustrated in Figure 2. As expected,

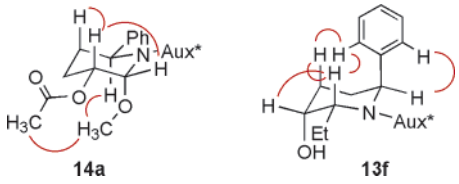


Figure 2. Selected NOEs for **14a** and **13f**.

DMDO reacts with the enamine on the opposite face of the C-2 substituent. An interesting feature of this reaction is the cis stereochemistry observed between the newly formed C-2 and C-3 asymmetric centers. To our knowledge, this represents the first intermolecular cis stereoselective epoxidation-ring opening and nucleophilic substitution of an endocyclic amino-substituted epoxide.[12−16] The 2,3-cis ster-

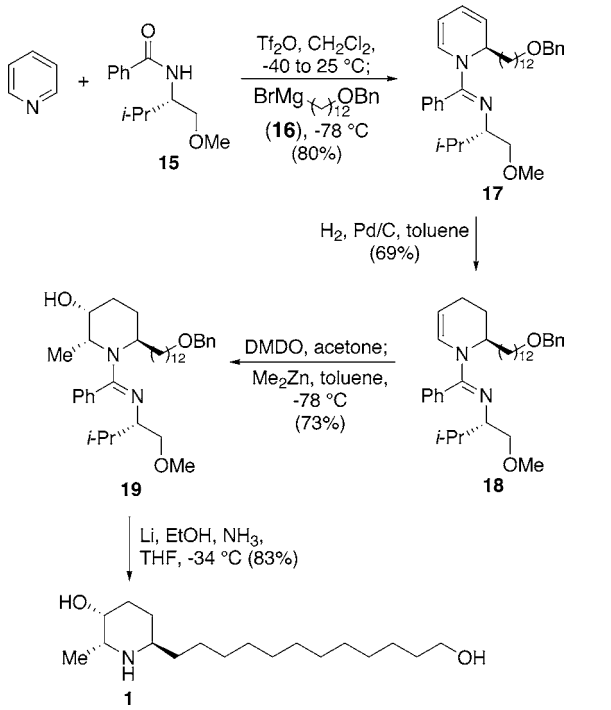
(10) Camps, F.; Coll, J.; Messeauer, A.; Pujol, F. *J. Org. Chem.* **1982**, *47*, 5402−5404. 2-Propanol was used as a nucleophile since methanol is described to be incompatible with this epoxidation procedure. Furthermore, both nucleophiles were shown to cleanly react with **12** (with DMDO, see Table 2). This KF−MCPBA complex was shown to cleanly epoxidize diverse glucals; see: Bellucci, G.; Catelani, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron Lett.* **1994**, *35*, 8433−8436.

(11) Cis product is the kinetic product since treatment of **13a** with TFA in EtOH for 76 h led to the 2,3-*trans*-ethanol adduct in 74% yield.

eochemistry would suggest that epoxide **9** opens before the nucleophilic attack, generating an iminium-alkoxide.[17,18]

Having shown that we can efficiently epoxidize **12** and open **9** with organozinc nucleophiles, we turned our attention to a demonstration of the applicability of this methodology in the context of total synthesis. (+)-Julifloridine (**1**, Scheme 2) is a 2,6-disubstituted 3-piperidinol alkaloid isolated from *Prosopis juliflora* by Ahmad.[19] The synthesis of julifloridine is straightforward and has been realized in four steps from pyridine as depicted in Scheme 2.[20] The synthesis began with the regio- and diastereoselective addition of Grignard reagent **16** on the chiral pyridinium salt generated from amide **15**. Dihydropyridine **17** was then monohydrogenated, affording tetrahydropyridine **18**. The epoxidation−methylation procedure produced **19** in excellent yield given the complexity of the product formed. Simultaneous removal of the amidine chiral auxiliary and benzyl ether cleavage, leading to (+)-julifloridine, was achieved upon treatment with lithium in ammonia. Expedient total synthesis of (+)-julifloridine was realized in four steps and 33% overall yield, from pyridine.

Scheme 2. Total Synthesis of (+)-Julifloridine



In conclusion, the asymmetric synthesis of 2,6-disubstituted 3-piperidinols having a 2,3-cis-2,6-trans stereochemistry was accomplished in three steps using the following sequence: stereocontrolled nucleophilic addition of an organomagnesium reagent to a chiral pyridinium salt; chemoselective monohydrogenation of a 2-substituted 1,2-dihydropyridine; and a tandem, highly diastereoselective epoxidation−nucleophilic addition with a heteroatom nucleophile or an organometallic reagent. Highly substituted 3-piperidinol derivatives can be prepared using this approach, which was demonstrated by a rapid and stereoselective total synthesis of (+)-julifloridine.

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Supporting Information Available: Experimental procedures and data for each reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Blaauw and co-workers reported an oxone-mediated epoxidation−methanol opening of a related tetrahydropyridine, but the cis−trans ratio was not specified. See: Botman, P. N. M.; Dommerholt, F. J.; de Gelder, R.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2004**, *6*, 4941−4944.

(13) Related cis stereoselective pyridinone epoxide intramolecular opening with an alcohol, leading to an oxazolopiperidine, has been reported: Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett.* **2001**, *3*, 3257−3260.

(14) Asymmetric epoxidation of unsubstituted *N*-tosyl-1,4,5,6-tetrahydropyridirines has been reported, but the yields or enantioselectivities are modest; see: Sunose, M.; Anderson, K. M.; Orpen, A. G.; Gallagher, T.; Macdonald, S. J. F. *Tetrahedron Lett.* **1998**, *39*, 8885−8888.

(15) DMDO and MCPBA epoxidation of unsubstituted *N*-ethylcarbamoyl-1,4,5,6-tetrahydropyridines has been reported, but the cis−trans selectivity of the nucleophilic substitution of the epoxide is low (1:1.5 to 1:1.8), see: (a) Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* **1998**, *39*, 3413−3416. (b) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255−3258.

(16) (a) Treatment of *N*-acetyl-1,4,5,6-tetrahydropyridines with peroxybenzoic acid gave *N*-acetyl-2-benzoyloxy-3-hydroxypiperidine, but the cis−trans ratio was not specified; see: Masamune, T.; Hayashi, H.; Takasugi, M.; Fukuoka, S. *J. Org. Chem.* **1972**, *57*, 2343−2345. (b) A related MCPBA epoxidation of *N*-methylcarbamoyl-1,4-dihydropyridine has been shown to give the corresponding addition products with trans relative stereochemistry. However, use of DMDO afforded a dioxane dimer from dimerization of the opened epoxide; see: Lavilla, R.; Barón, X.; Coll, O.; Gullón, F.; Masdeu, C.; Bosch, J. *J. Org. Chem.* **1998**, *63*, 10001−10005.

(17) For a related cis stereoselective glycal epoxide opening using organozinc triflate or organozinc chloride, see: Xue, S.; Han, K.-Z.; Guo, Q.-X. *Synlett* **2003**, 870−872. Use of organoaluminum and organoboron reagents, see: Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997−2009. Use of sodium thiophenolate, see: Marzabadi, C. H.; Spilling, C. D. J. *Org. Chem.* **1993**, *58*, 3761−3766.

(18) For an interesting DMDO/$TiCl_4$ semipinacol-type rearrangement of 2-cycloalkanol-substituted *N*-tosyl-1,4,5,6-tetrahydropyridines, see: Dake, G. R.; Fenster, M. D. B.; Fleury, M.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5676−5683.

(19) Isolation: (a) Ahmad, V. U.; Basha, A.; Haque, W. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1978**, *33B*, 347−348. (b) Ahmad, V. U.; Usmanghani, K.; Najmus-Saqib, Q. *Sci. Pharm.* **1979**, *47*, 333−334. Absolute configuration determination: (c) Ahmad, V. U.; Qazi, S. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1983**, *38B*, 347−348.

(20) For asymmetric synthesis of **1**, see ref 4r. For racemic synthesis, see: Paterne, M.; Brown, É. *C. R. Séances Acad. Sci., Ser. 2* **1983**, *296*, 433−434.