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Regio- and Stereocontrolled Syntheses of Cyclic Chiral cis-Amino Alcohols from 1,2-Diols or Epoxides

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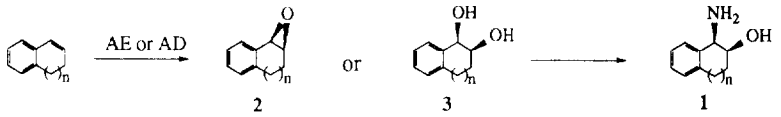
Abstract: *The behavior of 1,2-dioxygen derivatives of indane, tetralin, and benzosuberane in acetonitrile-strong acid media is exploited in the regio- and stereocontrolled syntheses of chiral cis-amino alcohols.*

Chiral amino alcohols serve as versatile chiral reagents in a variety of asymmetric processes.[1] The rigid benzocycloalk-1-ene-derived *cis*-1-amino-2-alcohols **1** represent a chemically[2] and biologically[3] appealing subclass of these amino alcohols. Despite the potential utility of these conformationally constrained reagents, their availability has been limiting.[4,2b] Recently, the chiral 1,2-dioxygen analogues have become available by either asymmetric epoxidation (AE) or asymmetric dihydroxylation (AD) of the corresponding prochiral olefins (Scheme 1).[5] These adducts are excellent precursors to such *cis*-amino alcohols; however, an effective stereo- and regioselective conversion of the dioxygen moiety to the *cis*-amino alcohol has not been developed. Herein, we disclose a practical preparation of these chiral *cis*-amino alcohols, either from the epoxides **2** or diols **3** in acetonitrile-strong acid media.

Scheme 1



a: n = 0; b: n = 1; c: n = 2

We recently reported a highly selective process for the preparation of *cis*-1-amino-2-indanol (**1a**) by subjecting indene oxide **2a** to a Ritter reaction.[6] This process proceeds through the acid-induced ring opening of chiral indene oxide where an equilibrium exists between the C-1 carbenium ion **4a** and the C-1 nitrilium intermediate **5a**.[7] The apparent selective *syn*-addition of the nitrile is actually governed by the conformationally driven formation of the *cis*-5,5-ring derived methyl oxazoline **6a**.

If the *cis*-selectivity of the indane system is controlled by the ring closure to the oxazoline then the larger ring analogues, such as tetralin or benzosuberane, should give poorer *cis*-selectivity due to their ability to form both *cis*- and *trans*-systems (**6b** and **6c**). First, tetralin oxide **2b** in acetonitrile with two equivalents of triflic acid at -40 °C was observed by low temperature NMR studies to generate the *trans*-methyloxazoline **6b**, *cis*-methyloxazoline **6b** and amido alcohol **8** in a ratio of 8:5:1 (Table 1). Warming the reaction mixture did not change the reaction profile. Hydrolysis provided a mixture of *cis*- and *trans*-amino alcohols **1b**. Interestingly, the less reactive acid methanesulfonic acid at -40 °C formed not only *trans*-**6b**, *cis*-**6b**, and amido alcohol **8** but also the mesylate **7b** in a ratio of 44:6:6:44 (Scheme 2).[8] Upon slowly warming this reaction mixture the mesylates converted mostly to the *cis*-methyloxazoline **6b** providing a 1:1 ratio of *cis*-/*trans*-**6b**. Similarly, benzosuberene

oxide **2c** provided a ~ 1:1 ratio of the *cis-/trans*-methyloxazolines **6c**. With indene oxide low temperature NMR revealed that the same intermediate **7a** is formed. However, only the *cis*-methyloxazoline **6a** was obtained.[7] This confirms that the source of the high selectivity in the indane system is from the favored *cis*-5,5-ring formation.

Scheme 2

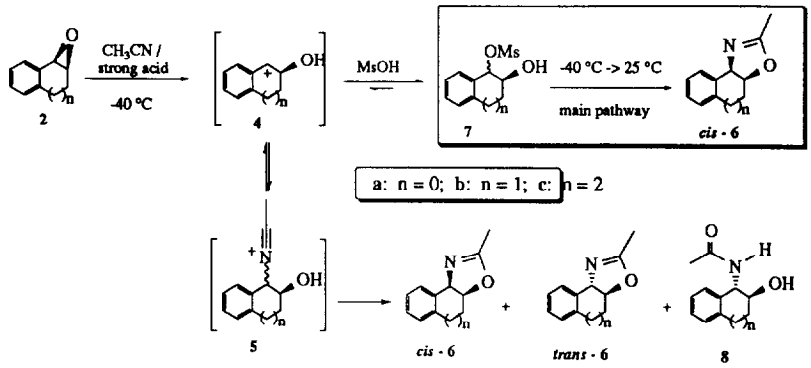


Table 1 Epoxides in Acetonitrile/Strong Acid Media

Epoxide	Acid	*cis /trans* 6[a]
2a, n = 0	TfOH	100:0
	MsOH	100:0
2b, n = 1	TfOH	37:63
	MsOH	50:50
2c, n = 2	TfOH	41:59
	MsOH	53:47

a) Measured by NMR at 25 °C

The salient feature of this study is the selective conversion of the mixture of *cis-/trans*-mesylates **7b** to the *cis*-methyloxazoline **6b**. This indicated that the high reactivity of epoxides may be the cause of the overall non-selective process with the tetralin and benzosuberane systems. Perhaps, the less reactive diol substrates, in analogy to the mesylate intermediates, could provide a more selective reaction. Indeed, when the *cis*- or *trans*-1,2-tetralindiol **3b** was exposed to two equivalents of triflic acid in acetonitrile at -40 °C followed by warming to room temperature, >95% *cis*-methyloxazoline **6b** was obtained[9]. Hydrolysis of **6b** followed by isolation, afforded pure *cis*-**1b** (Scheme 3). The other analogues behaved similarly (Table 2). As expected, either *cis*- or *trans*-indandiol **3a** provided only the *cis*-methyl oxazoline **6a**.[7] The more conformationally flexible benzosuberane diols **3c** gave lower *cis*-selectivity (85%) but certainly higher than obtained with the epoxide **2c**.

Key to asymmetric syntheses of these amino alcohols is the stereochemical integrity of the carbon-oxygen bond at C-2. Thereby, chirality is effectively transferred from the C-2 position to C-1 of the amino alcohol. When either chiral epoxides or *cis- /trans*-diols were used in this process the resultant amino alcohol **1** had the same optical purity as the starting 1,2-dioxygen-styrene derivatives.[10]

Since the stereochemistry at the C-1 position of the diols is irrelevant to the resultant stereochemistry of the amino alcohol, the conversion of a chiral epoxide to a mixture of *cis/trans* diols could be followed by the amination conditions to provide a higher ratio of *cis*- to *trans*-amino alcohols over that from the epoxide-Ritter reaction. Indeed, when **2b** (84% ee) was first exposed to acid hydrolysis (1N H_2SO_4 at 0 °C in CH_2Cl_2) a

mixture of *cis*-and *trans*-diols **3b** was generated.[11] The diol mixture when subjected to the acetonitrile/triflic acid media, followed by hydrolysis of the oxazoline, was converted to >97% *cis*-amino alcohol **1b**, which had an unchanged optically purity of 84%.

Scheme 3

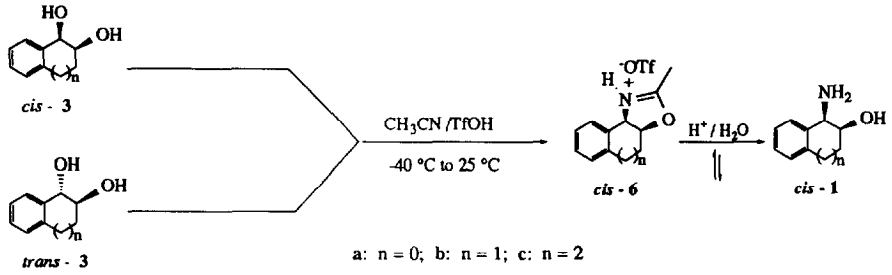


Table 2 Conversion of Diols 3 to Amino Alcohols 1.

Diol **3** (% ee)	Acid	*cis*-selectivity (%) of **6**[a]	Yield (%)[b], % ee of *cis*-aminoalcohol **1**[e]
cis-**3a** (>99)	TfOH	100	87, >99
	97% H_2SO_4[c]	100	81, >99
trans-**3a** (85)	TfOH	100	78, 85
cis-**3b** (>99)	TfOH	99	80, >99
	97% H_2SO_4[d]	98	75, >99
trans-**3b** (99)	TfOH	95	71, 99
cis-**3c**	TfOH	86	63, -
trans-**3c** (90)	TfOH	85	62, 90

a) Measured by ^1H NMR; b) wt% assay by HPLC; c) Indene oxide with 97% H_2SO_4/CH_3CN, 55% yield of *cis*-**1a** was provided; d) Tetralin oxide with 97% H_2SO_4/CH_3CN, ~1:1 mixture of *cis/trans*-**1b** was provided.; e) A three-necked flask under nitrogen atmosphere is charged diol 3 (10 mmol) and acetonitrile (16.5 mL) and cooled to -40 °C. To this slurry is added triflic acid (20 mmol) while maintaining the internal temperature at <-30 °C. The reaction mixture is warmed to 22 °C and aged for 1.0 h. Water (16.5 mL) is added to the reaction mixture and aged for 10 minutes. The reaction mixture is concentrated until the internal temperature reaches 100 °C by atmospheric distillation and the aqueous reaction mixture is then refluxed at 100 °C for 5.0 h. After cooling to 22 °C, CH_2Cl_2 (10.0 mL) is added and stirred for 10 minutes. The two phases are separated and the aqueous layer is assayed by HPLC for *cis*-amino alcohol **1**. The *cis*-amino alcohol is isolated after basification of the aqueous layer to pH 12.5- 13.

The valuable findings described herein clearly offer a simple practical solution to the preparation of chemically and pharmacologically useful chiral *cis*-amino alcohols from the corresponding prochiral olefins. The mechanism of this highly *cis*-selective process via the diols is currently under investigation.

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(7) In the case of the 5,5-ring system the *trans*-closure is conformationally difficult.
(8) These results suggest that the tetralin oxide first generates the C-1 carbenium ion which is trapped by nucleophiles present in the media. In the case of methanesulfonic acid, the C-1 carbenium ion **4b** is trapped by acetonitrile or methanesulfonic acid to provide the C-1 nitrilium intermediate **5b** or C-1 mesylate **7b**, respectively. The nitrilium intermediates generate the corresponding *cis*- and *trans*-oxazoline **7b** and amido alcohol **8**.
(9) Unlike the tetralin oxide, there is no *trans*-amido alcohol **8** observed in this reaction.
(10) (a) The chiral epoxides **2a, b** and **c** were prepared with a modified procedure (Senanayake, C. H. et al., manuscript in preparation) of Jacobson's chiral Mn-salen catalyst as follows: To 12% NaOCl ([OH]= 0.3) cooled to 0 °C was added a PhCl mixture of 4-(3-phenylpropyl)pyridine-*N*-oxide (P_3NO) and Mn-*S,S*-salen catalyst. The olefin was added at 0 °C. The reaction progress was followed by HPLC. The absolute stereochemistry of epoxide **2** was established as in reference 5c. (b) The diols were obtained as follows: For the preparation of 1-(*S*)-2-(*R*)-indandiol (*cis*-**3a**) in >99% ee, see ref. 5k. Similarly for *trans*-**3a**, see ref. 11. Optically pure 1-(*R*)-2-(*S*)-dihydronapthalanediol (*cis*-**3b**) was purchased from Genencor International, Inc. The *trans*-**3b** was prepared according to ref. 5i. Chiral *cis*-**3c** could not be prepared with Sharpless's AD-β-mix technology; only 1% ee was obtained. The chiral *trans*-**3c** was prepared in 90% ee via a modification of Jacobsen's epoxidation (NaOCl, P_3NO, Mn-*S,S*-salen in PhCl) followed by epoxide opening with 1N H_2SO_4 at 0 °C. (c) Relative stereochemistry of *cis*-amino alcohol **1** was established by conducting a series of NMR experiments such as 1-D, (^1H, ^{13}C NOEDS), 2-D (COSY, HETCOR) etc. and comparing the *cis*-and *trans*-methyl oxazolines (**6**) and *cis*- and *trans*-amino alcohols **1**. The absolute stereochemistry of *cis*-amino alcohol **1** was based on the known C-2 absolute stereochemistry of epoxide **2** or diol **3**.
(11) Depending on the solvent, the acid, and the acid strength the ratio of *cis/trans* diols can differ; see, Balsamo, A.; Berti, G.; Crotti, P.; Ferretti, M.; Macchia, B.; Macchia, F. *J. Org. Chem.* **1974**, *39*, 2596.

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