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# Scale-Up of the Preparation of (1*R*,2*R*,4*S*)-1-Methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol§

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**Abstract:**

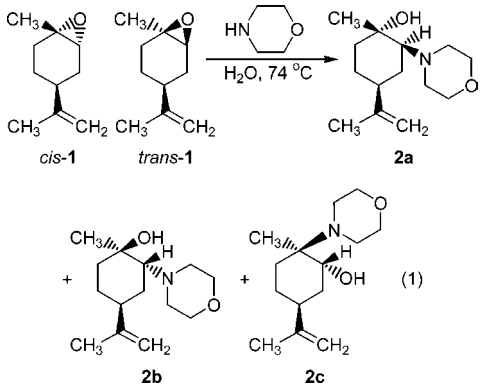
**Chiral β-amino alcohols are widely recognized as effective chiral auxiliaries for a variety of asymmetric organic transformations. Recently, (1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol has been reported to be an effective chiral auxiliary for the asymmetric addition of diethylzinc to benzaldehyde and the asymmetric addition of lithium cyclopropylacetylide to 4-(trifluoromethyl)-2(1H)-quinazolinones. This paper describes the scale-up of the reaction of morpholine with *cis*/*trans*-(*S*)-(-)-limonene oxide (99% ee) in the presence of water to produce 125 g of (1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol of 99.6% diastereomeric purity.**

## Introduction

The rapid development of single enantiomer pharmaceutical agents and agricultural chemicals over the last 10 years had led to the development of numerous asymmetric organic chemical transformations. One of the most useful of these methods is the asymmetric addition of organometallic reagents to aldehydes to generate optically active secondary alcohols, and this subject has been widely reviewed.[1−4] We recently described the synthesis of a series of chiral β-amino alcohols based on commercially available *cis*/*trans*-limonene oxide,[5] and demonstrated their utility as chiral auxiliaries in the asymmetric addition of diethylzinc to benzaldehyde[6] and the enantioselective alkynylation of aromatic and aliphatic aldehydes.[7] They have also been shown to be useful for the asymmetric addition of lithium cyclopropylacetylide to 4-(trifluoromethyl)-2(1H)-quinazolinones.[8] In this paper, we would like to present the scale-up of one of these amino alcohols derived from limonene oxide, (1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol (**2b**), to the 125 g scale.

## Results and Discussion

The reaction of morpholine with *cis*/*trans*-(*S*)-(-)-limonene oxide in the presence of water[9] was conducted at 74 °C.[10] At this temperature it took 24 h for nearly all of the *trans*-**1** to be consumed (see Table 1). There were three amine products, **2a**, **2b**, and **2c** formed in the ratio of 2:85:13 (eq 1).




The major amine product, **2b**, arises from *trans*-(*S*)-(-)-limonene oxide (*trans*-**1**), and the minor amine products, **2a**

§ This paper is dedicated to Professor Clinton F. Lane who passed away suddenly on May 19, 2007.

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(9) The reaction is extremely slow in the absence of water. The reaction was run in a separate study with 0, 1, 2, 3, 4, and 8 equiv of water to limonene oxide. The rate of the reaction was found to steadily increase up to 8 equiv of water. This study was reported at the *ACS Prospectives, Process Chemistry in the Pharmaceutical Industry*, Barcelona, Spain, February 24−27, 2002, in a paper entitled "The Design and Process Optimization of a Series of β-Amino Alcohols Based on Limonene Oxide," by Christian T. Goralski, Robert B. Appell, Dennis L. Hasha, Lawrence W. Nicholson, Philip R. Rudolf, Karen K. Borodychuck, Bakthan Singaram, Jason N. Camara, Will Chrisman, and Kim Marcellini. Since our work was reported, several other groups have reported the opening of epoxides with amines in the presence of water. See: Azizi, N.; Saidi, M.R. *Org. Lett.* **2005**, *7*, 3649 and Azoulay, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2005**, *7*, 4593.

(10) This particular reaction was run at 74 °C. This temperature is not critical, and the reaction has been run in the range of 60−100 °C in a separate study which was reported as indicated in ref 9.


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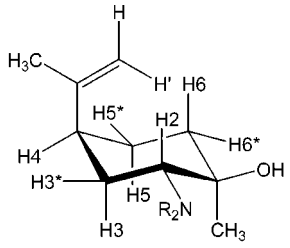
***Table 1.*** **Capillary GC data for the reaction of *cis*/*trans*-(*S*)-(-)-limonene oxide with morpholine in the presence of water (area % of the peak for the given material)**

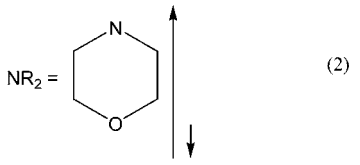
| | | | amine products | | |
|---|---|---|---|---|---|
| time, h | *cis*-limonene oxide (8.08 min) | *trans*-limonene oxide (8.19 min) | **2a** (17.31 min) | **2b** (17.60 min) | **2c** (17.96 min) |
| 0 | 46.2 | 53.8 | – | – | – |
| 1 | 45.6 | 49.5 | – | 4.9 | – |
| 2 | 44.4 | 43.9 | – | 11.1 | 0.6 |
| 3 | 43.2 | 38.2 | – | 17.5 | 1.1 |
| 4 | 42.4 | 33.8 | – | 22.3 | 1.5 |
| 5.5 | 40.8 | 27.6 | – | 29.5 | 2.1 |
| 6 | 40.2 | 25.5 | 0.3 | 31.8 | 2.3 |
| 8 | 38.7 | 19.3 | >0.1 | 38.8 | 3.2 |
| 9 | 37.9 | 16.5 | – | 42.0 | 3.7 |
| 23 | 31.0 | 3.1 | 1.3 | 56.3 | 8.3 |
| 24 | 30.7 | 2.7 | 1.4 | 56.7 | 8.6 |

and **2c**, arise from *cis*-(*S*)-(-)-limonene oxide (*cis*-**1**).[11] The excess morpholine and the unreacted *cis*-**1** were removed by distillation at reduced pressure, leaving the mixture of **2a**−**c**.[12] The mixture of **2a**−**c** was treated with oxalic acid in methanol, and the oxalate salt of **2b** separated as a white, crystalline solid. The oxalate salt of **2b** was then treated with aqueous potassium hydroxide to give **2b** as a white solid, mp 42−44 °C, in 32% yield (based on the amount of *cis*/*trans*-(*S*)-(-)-limonene oxide charged, or 64% yield based on the amount of *trans*-(*S*)-(-)-limonene oxide charged), and 99.6% diastereomeric purity.

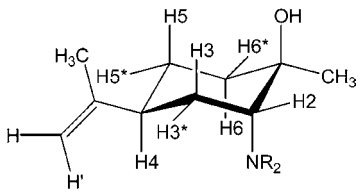
The $^{1}$H, $^{13}$C, $^{13}$C-DEPT, and HMQC spectra coupled with incremental chemical shifts allowed unambiguous assignment of all resonances of the morpholine-derived amino alcohol **2b** except the carbons and the protons at the 3- and 5-positions (eq 2). These assignments were made by a self-




**I**




(2)




**II**

consistency check using the $^{1}$H NOESY spectrum. The two nonequivalent methylene protons corresponding to positions 3 and 5 are located at 1.86, 1.60 and 1.71, 1.42 ppm, respectively. Initially it is assumed that the general rule regarding the downfield position of the equatorial protons 3* and 5* relative to its geminal axial partner 3 and 5 is obeyed. The methyl geminal to the OH group exhibits NOE cross-peaks to the resonances at 1.60 and 1.42, indicating that the methyl position is axial. Thus, it is not surprising that an NOE cross-peak is not detected between 2 and 4. The ambiguity between 2 and 4 is removed by observing which of these resonances exhibit a NOE cross-peak with proton 2 (geminal to the morpholine group). It is clear from the NOESY spectrum that proton 2 exhibits a cross-peak to the resonance located at 1.86 ppm, meaning resonances at 1.71 and 1.42 ppm are attributed to protons 5* and 5, respectively. Proton 4 exhibits a weak NOE cross-peak to protons 3 and 5, while the upfield vinylic proton, H′, shows an NOE cross-peak to protons 2 and 6. Protons 6 and 6* exhibit an identical chemical shift. Thus, it is concluded that the isopropenyl group is on the same side of the ring as protons 2 and 6. With the assumptions we have made regarding chemical shifts of equatorial protons and their axial partners, conformer I is consistent with the NOE data. The other conformer, II, would be expected to produce NOE cross-peaks between the morpholine protons and proton 4.

(11) The compounds **2a** and **2c** are the two isomeric amino alcohols that can arise from reaction of morpholine with *cis*-**1**. The reaction of pure *cis*-**1** with pyrrolidine in the presence of water was carried out in a separate study (see ref 7), and the major product of the reaction was conclusively identified as (1*R*,2*R*,5*S*)-2-methyl-5-(1-methylethenyl)-2-(1-pyrrolidinyl)-cyclohexanol resulting from attack occurring at the tertiary carbon center (the carbon bearing the methyl group). The epoxide opening requires that the attacking nucleophile and the leaving oxygen be in a *trans*-diaxial orientation. Attack at the least-substituted carbon requires that the ring assume a boat conformation to obtain the *trans*-diaxial orientation, a situation which is energetically less favorable than attack at the tertiary carbon center A key diagnostic tool for determining the location of the amino group and the hydroxyl group in this series of compounds is the chemical shift of the methyl group in the $^{1}$H NMR spectrum of the compound. In compounds such as **2b** (hydroxyl group on the carbon bearing the methyl group) the methyl signal occurs at 1.1−1.2 $\delta$, and in compounds such as **2c** (amino group on the carbon bearing the methyl group) the methyl signal occurs at 0.8−0.9 $\delta$. Thus, examining the $^{1}$H NMR spectrum of the mixture of amino alcohols prior to treatment with oxalic acid allows one to assign the structure of the amino alcohol arising from *cis*-**1** that is in excess.

(12) The *cis*-**1** can be recovered and purified for use in the preparation of other chiral amino alcohols. See: Steiner, D.; Ivison, L.; Goralski, C. T.; Appell, R. B.; Gojkovic, J. R.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2359.

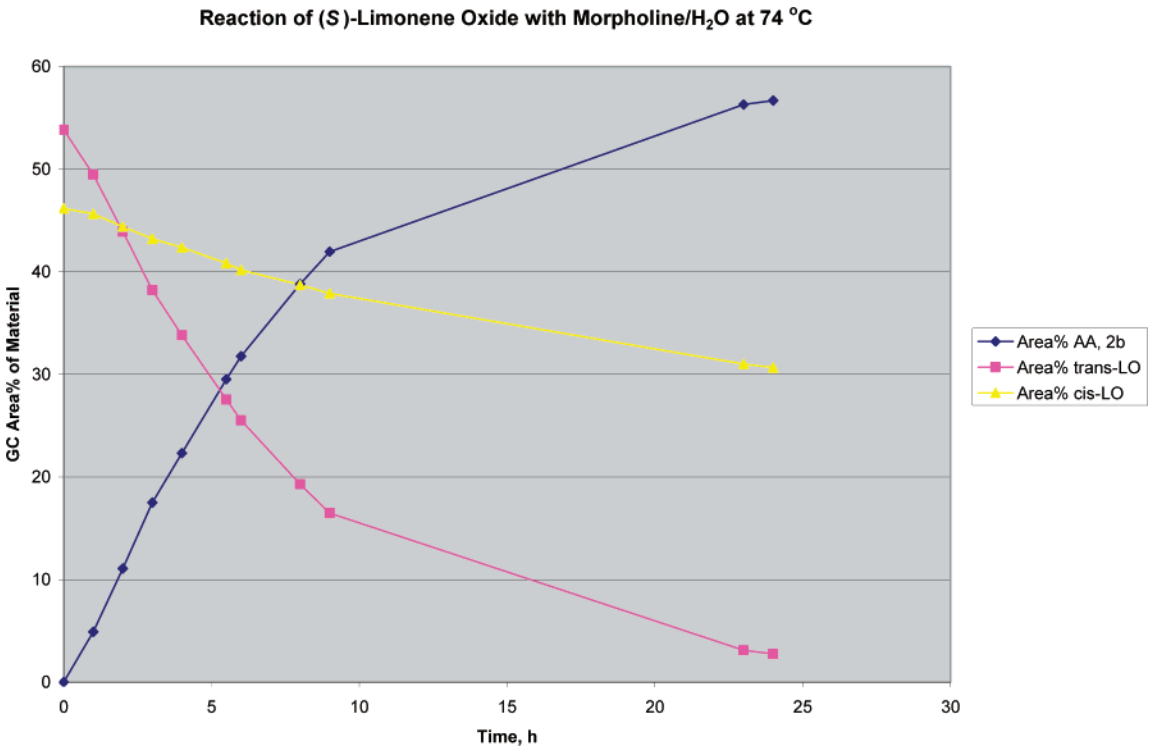



***Figure 1.*** **Graphical presentation of the data from Table 1.**

Since no such cross-peaks exist, it is concluded that conformer II is not present in appreciable concentration.

## Experimental Section

**Scale-Up of the Preparation of (1*R*,2*R*,4*S*)-1-Methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol (2b).**[13] A 2-L, three-neck flask equipped with a mechanical stirrer, a reflux condenser equipped with a nitrogen bubbler, and a thermometer was charged with 250 g (1.64 mol) of *cis*/*trans*-(*S*)-(-)-limonene oxide (99% ee), 572 g (6.57 mol) of morpholine, and 240 g of deionized water. The mixture was stirred and heated with a heating mantle set to control at 120 °C (this gave a reaction temperature of 74 °C). The progress of the reaction was followed by capillary GC, and a summary of the data collected is given in Table 1. (See Figure 1 for a graphical representation of the data.) After 25 h, the heat was turned off. The reaction was cooled to room temperature. The stirrer was stopped, and the reaction mixture separated into two phases. The phases were separated to give 376 g of a slightly cloudy, pale-yellow organic layer. The organic layer was transferred to a 1-L, single-neck flask equipped with a simple distillation head. The excess limonene oxide, along with a small amount of water and morpholine, was distilled off at reduced pressure (1.5−2.0 Torr, bp 20−70 °C; the pot heating mantle was taken to 195 °C). The distillate, 158 g, consisted of two colorless layers. There was 193 g of crude amino alcohol remaining in the pot as a pale-yellow, viscous liquid. The crude amino alcohol was dissolved in 270 mL of methanol, and the solution was charged to a 5-L, three-neck flask equipped with a mechanical stirrer, a pressure-equalizing addition funnel, and a glass stopper. A solution of 99 g (1.1 mol) of oxalic acid in 900 mL of methanol was prepared. The solution of the amino alcohol was cooled with an ice bath, and the solution of oxalic acid was slowly added. No solid crystallized. The reaction mixture was stirred for 0.5 h, and still no solid crystallized. The reaction mixture was seeded with a few crystals of (1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol oxalate, and a heavy slurry of white solid formed immediately. The slurry was stirred for 0.5 h. The solid was isolated by filtration, air-dried, washed with two 100-mL portions of cold (ice bath) methanol, air-dried, and vacuum-dried at 60 °C to give 183 g of (1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)cyclohexanol oxalate as a white, crystalline solid, mp 204−206 °C dec.

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 21.78, 22.05, 24.29, 25.07, 37.45, 38.27, 51.55, 64.18, 69.58, 71.42, 110.93, 145.51, 163.62.

A 5-g sample of the (1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol oxalate was retained for reference. The remainder of the sample was transferred to a 2-L separatory funnel and mixed with 1.4 L of 1 M potassium hydroxide. The mixture was swirled, and a very pale-yellow oil separated. The mixture was mixed with 200 mL of diethyl ether.[14] The mixture was shaken, and the layers were separated. The aqueous layer was extracted with two, 200-mL portions of diethyl ether. The three ether layers were combined and dried over anhydrous magnesium sulfate. The ether was removed in vacuo (rotary evaporator) leaving 126 g of very pale-yellow oil. The oil was cooled to room

(13) A very recent paper appeared in which the nucleophilicity of primary and secondary amines in water was measured, and this information is of value to one planning to synthesize other amino alcohols from limonene oxide or other epoxides. See: Brotzel, F.; Chu, Y. C.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 3679.

(14) If this chemistry were to be operated on a larger scale it would be desirable to replace diethyl ether with a solvent such as methyl *tert*-butyl ether.

temperature. A few seed crystals of (1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol were added, and crystals began to form. After approximately 2 h, the entire sample had crystallized. The solid mass was broken up with a spatula and transferred to a crystallizing dish. The solid was dried in vacuo at room temperature to give 125 g of (1*R*,2*R*,4*S*)-1-methyl-4-(1-methylethenyl)-2-(4-morpholinyl)cyclohexanol as a white, crystalline solid, mp 42−44 °C.

$^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 21.4 ($CH_3$ geminal to OH), 24.8 ($\underline{C}H_3C$═), 24.9 (C5), 25.3 (C3), 36.3 (C6), 39.4 (C4), 52.1 (morpholine ring carbons adjacent to N), 66.8 (morpholine ring carbons adjacent to O), 67.1 (*C*2), 71.6 (C1), 109.6 (═*C*HH′), 147.62 ($CH_3\underline{C}$═).

$^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 1.14 ($CH_3$ geminal to OH), 1.42 (H5), ∼1.45 (H6*, H6), 1.60 (H3), 1.70 ($C\underline{H}_3C$═), 1.71 (H5*), 1.86 (H3*), 2.25 (H4), 2.30 (H2), 2.48 and 2.65 (morpholine ring protons adjacent to N), 3.53 and 3.58 (morpholine ring protons adjacent to O), 3.93 (O<u>H</u>), 4.75 (H′), 4.79 (H).

Capillary GC Analysis: 99.6% diastereomeric purity. $[\alpha]^{23}_D = -35.1$.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