Synthesis of both isomers of aziridine derived from the mixture of *cis*- and *trans*-limonene oxide

Hossein Mehrabi

Abstract: A short and efficient route is described for both isomers of aziridine derived from the commercially available 1:1 mixture of limonene oxides. The process is amenable to scale-up and allows easy access to multigram quantities of these useful chiral building blocks.

Key words: cis- and *trans*-limonene oxide, β-amino alcohol, *o*-tosylation, limonene aziridine.

Résumé : On a décrit une méthode courte et efficace d'obtention des deux isomères de l'aziridine qui peut être obtenue à partir d'un mélange 1 :1 commercialement disponible d'oxydes de limonène. Le processus pourrait être amener à produire de grandes quantités et il permet d'accéder facilement à des quantités multigrammes de ces importants intermédiaires chiraux.

Mots-clés : oxydes des *cis*- et *trans*-limonène, β-amino alcool, *o*-tosylation, aziridine du limonène.

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Terpenes, particularly limonenes, are an important class of naturally occurring chiral compounds widely used in organic synthesis either as starting materials in the synthesis of optically pure molecules[1] or as the chiral core of the numerous chiral auxiliaries or asymmetric ligands employed in enantioselecive transformations.[2] In the majority of cases, the ligands derived from terpenes are amino alcohols as opposed to diamines, and the use of diamines as ligands in asymmetric synthesis is well-established.[3] The simplest way to access diamines in an enantiomerically pure form is from stereoselective ring opening of chiral aziridines.[4]

While methods for the synthesis of chiral epoxides, and thus chiral amino alcohols, have been an area of active research interest for some time, the area of asymmetric aziridination has only recently become implemented.[4] An alternative to this approach would be to utilize molecules from the chiral pool and develop chemistry to transform them into optically active aziridines. The most obvious starting materials to carry out such transformations would be amino acids, and indeed numerous methods have been developed for the transformation of amino acids into the corresponding optically pure aziridines[4,5] via the corresponding amino alcohols. Although, this would offer simple, rapid access to a number of diamines, the flexible nature of the amino acids side chain would not be suitable for developing chiral ligands.[6] Thus, the attention of our group was turned to the naturally occurring terpenes, the substituents of which are in geometrically defined environments as a result of the rigidity of the ring systems. In conjunction with our program to develop ligands for such asymmetric transformations, as well as our general interest in the chemistry of these naturally occurring chiral building blocks,[7] our group aimed to obtain the aziridines derived from limonene in diastereomericaly pure form. While several methods for the preparation of terpene aziridines have been reported, they vary in their degree of regio- and diastereo-selectivity.[8]

Herein, a method is reported for the selective synthesis of either diastereomer of aziridine from the commercially available 1:1 mixture of limonene oxides.

The separation of limonene oxide diastereomers by distillation is difficult,[9] though partial separation has been achieved by this method.[10] However, to separate the epoxides, there are chemical methods of isomer resolution based on the difference in rates of the *cis*-limonene oxide and *trans*-limonene oxide opening either by amines[10,11] or via hydrolysis.[12,13] Trans-diaxial ring opening of the *trans*-limonene oxide is more facile; hence, this isomer reacts faster than the other one, and this difference can be exploited in the separation of the corresponding products.

The reaction of a 1:1 mixture of *trans*-limonene oxide (**1a**) and *cis*-limonene oxide (**1b**) with ethanolamine gave a mixture of the β-amino alcohol (**2a**) and the unreacted *cis*-limonene oxide (**1b**).[12a] The *cis*-limonene oxide was recovered from the reaction mixture in 85% yield after a simple distillation in greater than 98% purity. The crude β-amino alcohol was purified by isolation of the oxalate salt, followed by treatment with potassium hydroxide to give the free base,[10b] which was subsequently recrystallizad (Scheme 1).

The selectivity observed in these reactions can be explained by the inherent conformational difference between *cis*- and *trans*-limonene oxides (Scheme 2). Because of its large *A* value, the isopropenyl group prefers the equatorial orientation in both the *cis*- and *trans*-isomers. For the *trans*-isomer, **1a**, an S_N2-type reaction with ethanolamine can be envisioned to occur at the less hindered C-2 carbon through a thermodynamically stable chair-like transition state (Scheme 2A). In contrast, for S_N2-type attack at the C-2 carbon atom to occur, the *cis*-isomer would have to attain the unfavorable, energetically demanding "boat-like" transition state. Consequently, the *cis*-isomer is left largely unreacted (Scheme 2B).

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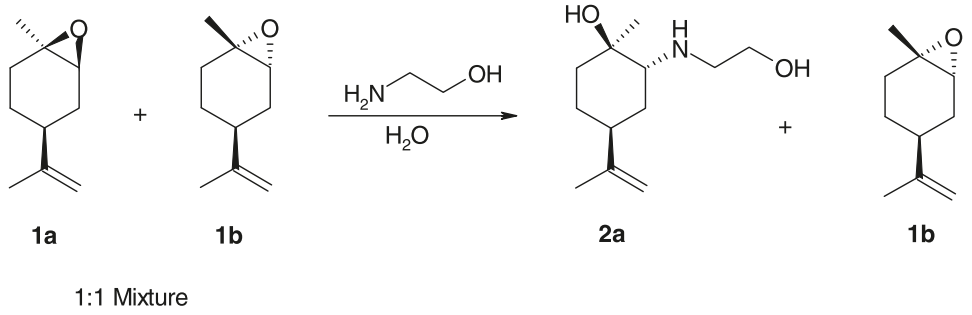
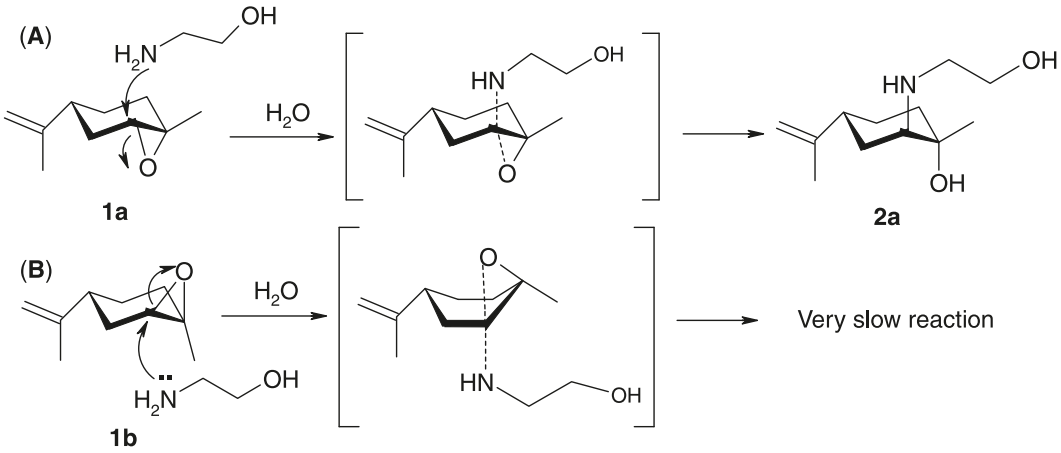
H. Mehrabi. Department of Chemistry, Rafsanjan Vali-e-Asr University, Rafsanjan 77176, Iran. (e-mail: mehraby_h@yahoo.com).

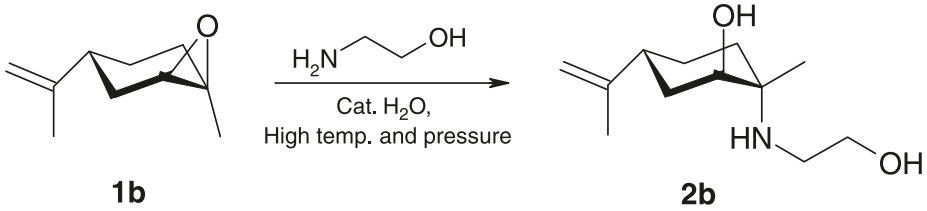
Scheme 1.



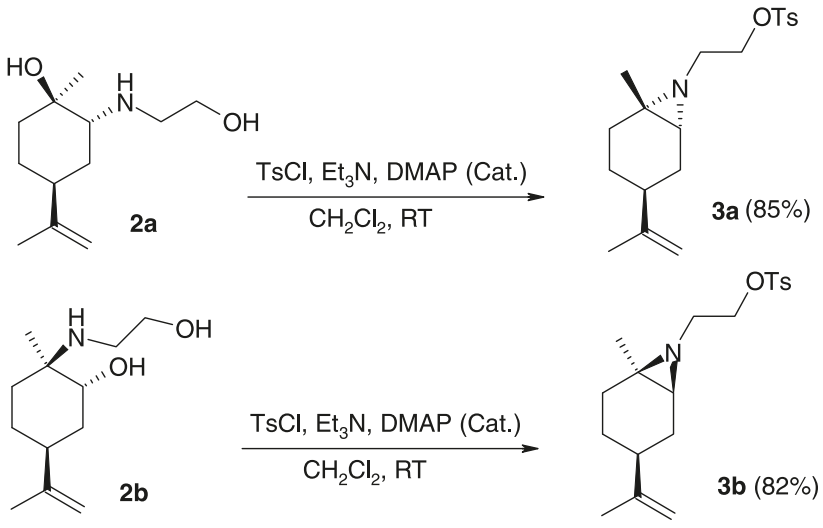
Scheme 2.



Scheme 3.



Scheme 4.



The amino alcohol **2b** can be prepared from the recovered pure *cis*-limonene oxide and ethanolamine under high temperature and pressure (sealed tube) in the presence of a catalytic amount of water.[14] Epoxide ring opening of the cis-diastereomer provides amino alcohol where the amine is attached to the more C-1 carbon atom (Scheme 3).

The products **2a** and **2b** were fully characterized by elemental analyses, IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry (see Appendix I).

It was thought that the *o*-tosylation and cyclization could be performed in a single operation starting from the β-amino alcohols **2a** and **2b** (Scheme 4). Therefore, the reaction involved 1.0 equiv. of β-amino alcohol with 2.5 equiv. of tosyl chloride and excess (3.0 equiv.) triethylamine in CH_2Cl_2 and in the presence of a catalytic amount of DMAP (see Appendix II), observing that the expected chiral aziridines **3a** and **3b** were formed cleanly after 24 h with high yields. When these conditions were applied at a larger scale (10 g), the reaction showed to be equally effective, giving comparable yields of the final compound (**3a,** 8.5 g and **3b,** 8.2 g).

The structure of compounds **3a** and **3b** were confirmed by their analytical and spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, and MS) (see Appendix II). The coupling constants of the aziridinyl proton of **3b** (2.62, dd, $^3J_{HH}$= 16.8 Hz, $^3J_{HH}$= 2.4 Hz, N–C**H**) showed a clear difference from the aziridinyl proton of **3a** (2.62, dd, $^3J_{HH}$= 10.4 Hz, $^3J_{HH}$= 5.6 Hz, N–C**H**).

In conclusion, this paper reports an efficient and convenient procedure for the highly selective synthesis of either diastereomer of aziridine derived from limonene starting from the commercially available 1:1 mixture of limonene oxides. It is important to point out that the reaction was performed on a 10 g scale, which allowed the preparation of high quantities of the target aziridines in a single step and using a simple protocol.

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Appendix I

The data for 2a

Pale yellow oil, yield: 9.0 g (85%). $[\alpha]_D^{25}$ –29.8 (*c*1.0, $CHCl_3$). IR ν(cm^{-1}, KBr): 3332 (broad), 1441, 1044, 887. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.27 (3H, s, CH_3), 1.46–1.90 (6H, m, $3CH_2$), 1.72 (3H, s, CH_3), 2.27 (1H, m, CH), 2.73 (2H, td, $^3J_{HH}$= 6.4 Hz, $^2J_{HH}$= 2.8 Hz, N–CH_2), 3.64 (2H, td, $^3J_{HH}$= 6.4 Hz, $^2J_{HH}$= 2.8 Hz, O–CH_2), 3.81 (1H, t, $^3J_{HH}$= 7.2 Hz, N–CH), 4.68 (2H, s, =CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3 (CH_3), 26.6 (CH_3), 29.5 (CH_2), 33.8 (CH_2), 37.1 (CH_2), 43.2 (CH), 48.9 (N–CH_2), 63.6 (C), 65.4 (O–CH_2), 78.7 (N–CH), 115.3 (C=**C**H_2), 150.6 (**C**=CH_2) ppm. MS (EI, 70 eV) *m*/*z* (%): 213 (M^+, 27), 156 (55), 143 (39), 114 (100), 83 (52). Anal. calcd. for $C_{12}H_{23}NO_2$ (213.3): C, 67.57; H, 10.87; N, 6.57. Found: C, 67.68; H, 10.91; N, 6.54.

The data for 2b

Pale orange oil, yield: 8.3 g (78%). $[\alpha]_D^{25}$ –46.3 (*c*1.0, $CHCl_3$). IR ν(cm^{-1}, KBr): 3334 (broad), 1440, 1044, 884. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.11 (3H, s, CH_3), 1.49–1.99 (6H, m, $3CH_2$), 1.73 (3H, s, CH_3), 2.30 (1H, m, CH), 2.69 (2H, td, $^3J_{HH}$= 5.2 Hz, $^2J_{HH}$= 2.4 Hz, N–CH_2), 3.61 (2H, td, $^3J_{HH}$= 5.2 Hz, $^2J_{HH}$= 2.4 Hz, O–CH_2), 3.64 (1H, t, $^3J_{HH}$= 6.8 Hz, O–CH), 4.74 (2H, s, =CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.0 (CH_3), 26.5 (CH_3), 30.1 (CH_2), 35.5 (CH_2), 37.9 (CH_2), 42.3 (CH), 47.3 (N–CH_2), 59.4 (C), 66.5 (O–CH_2), 81.7 (O–CH), 113.7 (C=**C**H_2), 153.5 (**C**=CH_2) ppm. MS (EI, 70 eV) *m*/*z* (%): 213 (M^+, 14), 156 (87), 143 (22), 114 (100), 83 (38). Anal. calcd. for $C_{12}H_{23}NO_2$ (213.3): C, 67.57; H, 10.87; N, 6.57. Found: C, 67.73; H, 10.77; N, 6.52.

Appendix II

General procedure for the preparation of compounds 3a and 3b

Et_3N (0.10 mol) was added to a cooled (0 °C) solution of the starting β-amino alcohols **2a** and **2b** (0.03 mol), TsCl (0.07 mol), and DMAP (30 mg) in dry CH_2Cl_2 (200 mL). The mixture was allowed to reach RT and stirred at this temperature for 24 h after which a saturated NH_4Cl solution (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic fractions were collected, dried over Na_2SO_4, filtered, and the solvent removed in vacuo, affording the desired aziridines (**3a** and **3b**) after flash column chromatography purification (hexane/AcOEt 8:2).

The data for 3a

White powder, yield: 8.91 g (85%), mp 111–113 °C. $[\alpha]_D^{25}$ +24.7 (*c*1.0, $CHCl_3$). IR ν(cm^{-1}, KBr): 1643, 1596, 1374, 1330, 1124, 1088. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.37 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.35–1.70 and 2.21 (6H, m, $3CH_2$), 1.86 (1H, m, CH), 2.41 (3H, s, CH_3), 2.62 (1H, dd, $^3J_{HH}$= 10.4 Hz, $^3J_{HH}$= 5.6 Hz, N–CH), 2.83 and 3.90 (2H, m, N–CH_2), 3.67 and 4.08 (2H, m, O–CH_2), 4.63 and 4.68 (2H, 2s, =CH_2), 7.30 (2H, d, $^3J_{HH}$= 8.0 Hz, 2CH), 7.61 (2H, d, $^3J_{HH}$= 8.0 Hz, 2CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.4 (CH_3), 22.9 (CH_3), 23.5 (CH_3), 29.4 (CH_2), 34.0 (CH_2), 38.3 (CH_2), 46.7 (CH), 52.4 (N–CH_2), 62.3 (O–CH_2), 69.3 (N–CH), 78.8 (N–C), 112.3 (C=**C**H_2), 129.5 (CH), 130.3 (CH), 137.2 (C), 146.7 (C), 150.9 (**C**=CH_2) ppm. MS (EI, 70 eV) *m*/*z* (%): 349 (M^+, 13), 194 (100), 155 (38), 91 (42), 65 (21). Anal. calcd. for $C_{19}H_{27}NO_3S$ (349.5): C, 65.30; H, 7.79; N, 4.01. Found: C, 65.31; H, 7.73; N, 4.00.

The data for 3b

White powder, yield: 8.59 g (82%), mp 110–111 °C. $[\alpha]_D^{25}$ –56.1 (*c*1.0, $CHCl_3$). IR ν(cm^{-1}, KBr): 1645, 1597,

1374, 1333, 1123, 1087. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.38–1.73 and 2.22 (6H, m, $3CH_2$), 1.86 (1H, m, CH), 2.43 (3H, s, CH_3), 2.62 (1H, dd, $^{3}J_{HH}$= 16.8 Hz, $^{3}J_{HH}$= 2.4 Hz, N–CH), 2.85 and 3.92 (2H, m, N–CH_2), 3.67 and 4.09 (2H, m, O–CH_2), 4.66 and 4.70 (2H, 2s, =CH_2), 7.31 (2H, d, $^{3}J_{HH}$= 8.0 Hz, 2CH), 7.63 (2H, d, $^{3}J_{HH}$= 8.0 Hz, 2CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (CH_3), 23.1 (CH_3), 23.6 (CH_3), 29.5 (CH_2), 34.2 (CH_2), 39.5 (CH_2), 46.6 (CH), 52.2 (N–CH_2), 62.7 (O–CH_2), 69.2 (N–CH), 78.9 (N–C), 111.6 (C=**C**H_2), 129.3 (CH), 131.9 (CH), 138.5 (C), 145.5 (C), 150.3 (**C**=CH_2) ppm. MS (EI, 70 eV) *m*/*z* (%): 349 (M^+, 9), 194 (100), 155 (16), 91 (37), 65 (14). Anal. calcd. for $C_{19}H_{27}NO_3S$ (349.5): C, 65.30; H, 7.79; N, 4.01. Found: C, 65.32; H, 7.70; N, 4.02.