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Communications to the Editor

Scaleable Syntheses of Isomeric Limonene Aziridines from the Commercially Available Mixture of *cis*- and *trans*-Limonene Oxides

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Abstract:

A short and efficient route to both isomers of limonene aziridine is described. The process is amenable to scale-up and allows easy access to multigram quantities of these highly useful chiral building blocks.

Introduction

Terpenes, and in particular limonene, 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 enantioselective transformations.[2] In the majority of cases, the ligands derived from terpenes are amino-alcohols as opposed to diamines. The use of diamines as ligands in asymmetric synthesis is well established,[3] although the use of the naturally occurring terpenes to provide such ligands has been underutilized. The simplest way to access diamines in enantiomerically pure form is from stereoselective ring opening of the corresponding 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 a major focus.[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, we believed that the flexible nature of the amino acids side chain would not be suitable for developing chiral ligands.[6] Thus, we turned our attention to the naturally occurring terpenes, the substituents of which are in geometrically defined environments as a result of their cyclic nature. In conjunction with our programme to develop ligands for such asymmetric transformations, as well as our general interest in the chemistry of these naturally occurring chiral building blocks,[7] we required a scaleable, economical method to obtain the aziridines derived from limonene in diastereomerically pure form. However, the stereoselective functionalization of the endocyclic double bond of limonene has presented a formidable challenge thus severely limiting its application in synthesis. For example, most of the olefin epoxidation methods, whilst displaying moderate to excellent regioselectivity, give an almost equimolar mixture of diastereomeric limonene epoxides.[8]

Limonene oxides have been used as key intermediates en route to the corresponding vicinal amino-alcohols that have also found application as ligands in asymmetric

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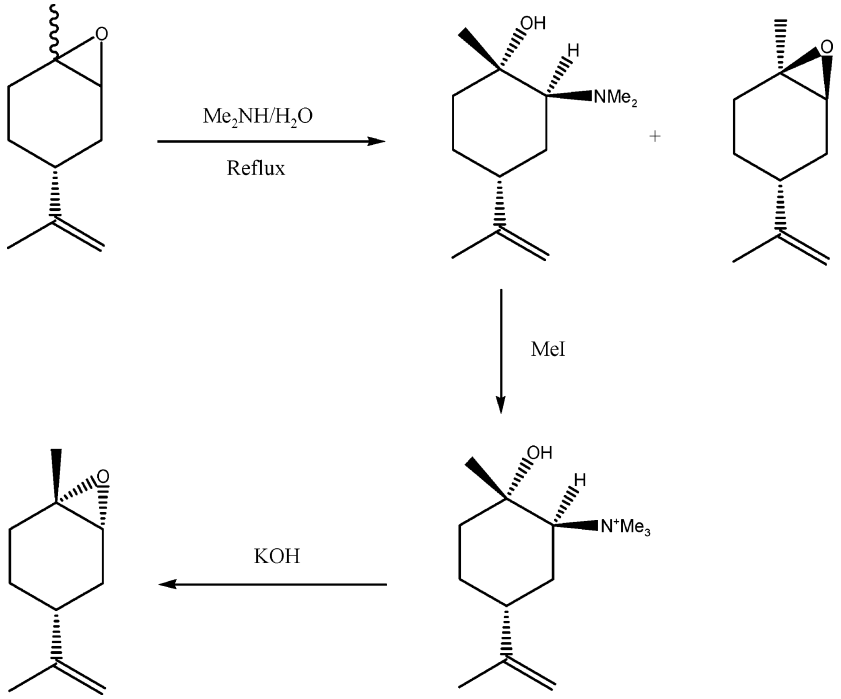
Scheme 1. **Separation of limonene oxides**



catalysis.[9,10] The separation of the mixture of limonene oxide isomers by distillation is difficult,[11] though partial separation by distillation has been achieved on a commercial scale. However, to separate the epoxides, there are chemical methods of isomer resolution based on the differences in rates of the *cis*-limonene oxide and *trans*-limonene oxide opening either by secondary amines[9,12] or via hydrolysis.[13,14] *trans*-Diaxial ring opening of the *trans*-limonene oxide is more facile, so this isomer reacts much faster than the other one, and this difference can be exploited to separate the isomers. After nucleophilic ring opening, simple acid−base extraction allows the unreacted cis isomer to be separated from the reaction. The *trans*-limonene oxide can then be obtained from the amino-alcohol, by quaternisation of the amine to generate a leaving group followed by nucleophilic ring closure[12] (Scheme 1).

Given the versatility of the pure epoxides, we envisioned that in a similar manner the closely related terpene aziridines also have the potential to become useful intermediates in organic synthesis, as well as source of both chiral diamine or aminophosphine chiral ligands. Unfortunately, this area of terpene chemistry remains relatively unexplored. While several methods for the preparation of terpene aziridines have been reported, they all vary in their degree of regio- and diastereoselectivity, and as such there is no general, efficient, safe, and selective route to such systems.[15]

Herein, we report a method for the highly selective synthesis of either isomer of limonene aziridine starting from the cheap, commercially available 1:1 mixture of limonene oxides.

Results and Discussion

The epoxides were converted to the aziridines through the intermediate azido-alcohols, which were cyclized by reaction with triphenylphosphine. The transformation begins with the opening of the limonene oxide mixture **1** with sodium azide in the presence of ammonium chloride as the catalyst (Scheme 2). The opening of each isomer is stereoselective, and the stereochemistry of the opening arising from

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(11) Fractional distillation is possible but extremely inefficient. Royals, E. E.; Leffingwell, J. C. *J. Org. Chem.* **1966**, *31*, 1937.

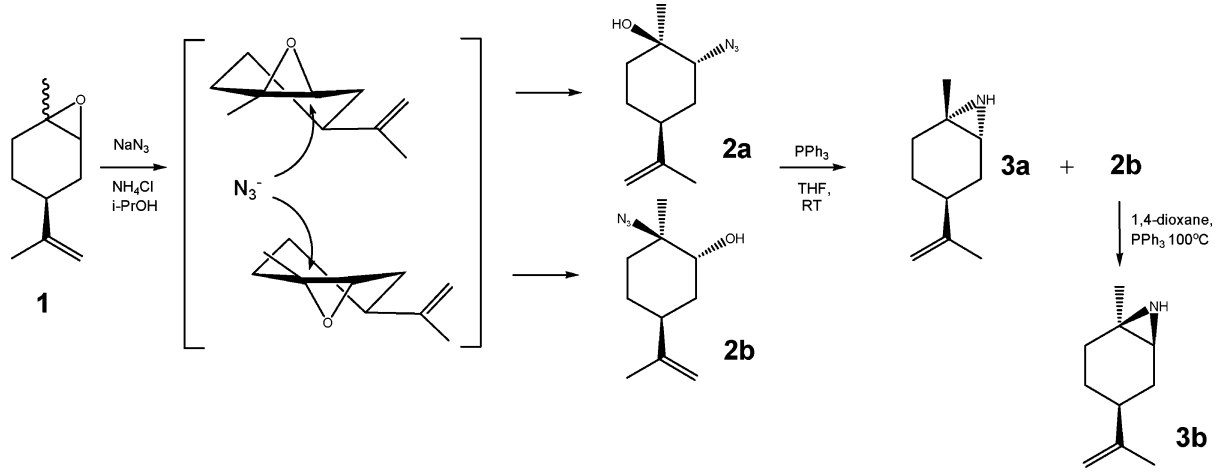
(12) Under harsh conditions, both epoxides can be opened with dimethylamine, and the corresponding amino-alcohols can be separated by salt formation and crystallization. For examples of this and the susbsequent conversion of the amino-alcohols back to the diastereomerically pure epoxides, see: (a) Baker, R.; Borges, M.; Cooke, N. G.; Herbert, R. H. *J. Chem. Soc., Chem. Commun.* **1987**, 414. (b) Newhall, W. F. *J. Org. Chem.* **1964**, *29*, 185. (c) Kuczynski, H.; Piatkowski, K. *Roczniki Chem.* **1959**, *33*, 299. (d) Patrick, R.; Newhall J. *J. Agric. Food Chem.* **1960**, *8*, 397.

(13) For examples, see: (a) Steiner, D.; Ivison, L.; Goralski, C. T.; Appell, R. B.; Gojkovic, J. R.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2359. (b) Jones, J.; dos Santos, A. G.; de Lima Castro, F. *Synth. Commun.* **1996**, *26*, 2651. (c) Cole-Hamilton, D. J.; Salles, L.; Nixon, A. F.; Russell, N. C.; Clarke, R.; Pogorzelec, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1471. (d) Van der Warf, M. J.; Jongejan, H.; Franssen, M. C. R. *Tetrahedron Lett.* **2001**, *42*, 5521.

(14) Enzyme mediated hydrolyses has also been reported. See: (a) Weijers, C. A. G. M. *Tetrahedron: Asymmetry* **1997**, *8*, 639. (b) Van der Werf, M. J.; Orru, R. V. A.; Overcamp, K. M.; Swarts, H. J.; Osprian, A.; de Bont, J. A. M.; Faber, K. *Appl. Microbiol. Biotechnol.* **1999**, *52*, 38.

(15) For examples, see: (a) Davis, C. E.; Bailey, J. L.; Lockner, J. W.; Coates, R. M. *J. Org. Chem.* **2003**, *68*, 75. (b) Bochvic, B.; Kapuscinski, J.; Olejniczak, B. *Roczniki Chem.* **1971**, *45*, 869. (c) Subbaraj, A.; Rao, O. S.; Lwowski, W. *J. Org. Chem.* **1989**, *54*, 3945. (c) Bergmeier, S. C.; Seth, P. P. *Tetrahedron Lett.* **1999**, *40*, 6181. (d) Corey, E. J.; Ortiz de Montellano, P. R.; Lin, K.; Dean, P. D. G. *J. Am. Chem. Soc.* **1967**, *89*, 2797. (e) Avruch, L.; Oehlschlager, A. C. *Synthesis* **1973**, 622. (f) van Ende, D.; Krief, A. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 279. (g) Parrish, E. J.; Nes, W. D. *Synth. Commun.* **1988**, *18*, 221. (h) Nes, W. D.; Parrish, E. J. *Lipids* **1988**, *23*, 375. (i) Corey, E. J.; Riddiford, L. M.; Ajami, A. M.; Yamamoto, H.; Anderson, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 1815.

Scheme 2



the trans-diaxial approach of the nucleophile has long been established.[11,12b,16] As such, nucleophilic attack of *trans*-limonene oxide occurs exclusively at the secondary C-2 carbon and leads to formation of **2a**. Similarly, opening of the *cis*-limonene oxide, leading to formation of **2b**, occurs at the tertiary carbon (C-1) and, therefore, is slower. This rate difference can be exploited when bulkier amines are employed as the nucleophile, as it is sufficiently large to allow clean separation of the unreacted *cis*-limonene oxide (Scheme 2). However, the reaction of the smaller and extremely nucleophilic azide anion is extremely rapid with both epoxide isomers making kinetic resolution at this stage impossible.[15a,17]

The subsequent step, the aziridine formation, involves a pseudo-Staudinger reaction[18] between the mixture of azides **2a** and **2b**, with triphenylphosphine to effect both azide reduction with concomitant ring closure to yield the aziridine.[19] Interestingly, the ring closure has previously been achieved by conversion of the azido-alcohol to the corresponding mesylate, and reductive cyclisation,[20] though using such a protocol here may not allow the azido-alcohol diastereomers to be distinguished. We found that the reactivities of the two isomeric azido alcohols toward triphenylphosphine differ significantly enough to allow a highly efficient kinetic resolution of the mixture. The Staudinger reaction of the secondary azide is much faster, so azido alcohol **2a** is converted completely to the corresponding aziridine **3a** at room temperature over a period of 48 h. The resulting aziridine **3a** is easily separated from the unreacted azido-alcohol **2b** by a simple acid−base extraction. Conversion of the azido-alcohol **2b** to the *cis*-aziridine **3b** requires elevated temperatures and proceeds smoothly in refluxing dioxane over a period of 16 h. Both aziridine isomers, **3a** and **3b**, were purified by vacuum distillation to afford the desired products in greater than 98% purity and in high yield.

(16) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 5.
(17) Coates[15a] reports modest selectivity in the ring opening of the mixture of aziridines at low temperature using diethylaluminium azide as the nucleophile.
(18) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437.
(19) For a similar transformation, see: Sommerdijk, N. A. J. M.; Buynsters, P. J. J. A.; Akdemir, H.; Geurts, D. G.; Nolte, R. J. M.; Zwanenburg, B. *J. Org. Chem.* **1997**, *62*, 4955. Interestingly the authors report that the success of the transformation is dependent on the scale on which the reaction is run and that the transformation is not amenable to being run on large scale. This is not the case with our procedure.
(20) Ferrero, L.; Geribaldi, S.; Rouillard, M.; Azzaro, M. *Can. J. Chem.* **1975**, *53*, 3227.

Conclusions

In conclusion, we have developed a practical, scaleable method for the preparation of either isomer of limonene aziridine from the commercially available mixture of limonene oxides. This methodology is extremely efficient and avoids the separation of the limonene oxides (and subsequent separate processing of each diastereomer) by either physical or chemical methods. The key to the efficiency of the separation is the exploitation of the differences in rate between the two azido-alcohol diastereomers in the ring closure.

Experimental Section

General Comments. NMR experiments were conducted with a Bruker ARX300 spectrometer at 75 MHz for ^{13}C and 300 MHz for ^{1}H spectra. Samples were dissolved in $CDCl_3$ with TMS as the internal reference. Reactions were carried out under nitrogen under anhydrous conditions. LC/MS analysis was conducted on a HP1100 with a Polaris C18 A-5μ column.

Preparation of Azido-5-isopropenyl-2-methyl-cyclohexanols 2a and 2b: To a solution of a commercial mixture of (−)-*cis*-limonene oxide and (−)-*trans*-limonene oxide **1** (76 g, 0.50 mol, Acros, 1:1 mixture) in methanol (200 mL) was added sodium azide (65 g, 1.0 mol) (Caution: highly toxic chemical; handle and dispose according to OSHA and your state regulations) and ammonium chloride (27 g, 0.50 mol). The resulting mixture was heated at reflux with magnetic stirring for 24 h (the reaction was monitored by GC). The mixture was allowed to cool to rt, and the solids were removed by filtration. Methanol was removed in vacuo, and the oily residue was diluted with ether (200 mL) and filtered through a 1-in Celite plug. The ether solution was dried over magnesium sulfate and concentrated to yield 96 g of a crude 1:1 mixture (98% yield; 94% purity by GC) of

azides **2a** and **2b** as yellow viscous oil, which was used without further purification.

Preparation 4-Isopropenyl-1-methyl-7-aza-bicyclo-[4.1.0]heptane 3a. The crude mixture (96 g, 0.492 mol) of **2a** and **2b** was dissolved in 200 mL of THF, and triphenylphosphine (75 g, 0.28 moL) was added. The reaction mixture was stirred at rt for 2 days (the reaction was monitored by GC) and then concentrated in vacuo. The residue was dissolved in ether (200 mL) and filtered through a cotton plug. The filtrate was washed twice with an aqueous solution of citric acid (2 × 100 mL, 96 g in 200 mL of water). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting oil contained unreacted azido-alcohol, **2b**, and was used directly in the next reaction without further purification. The aqueous layer was washed with DCM (2 × 150 mL), and then the pH was adjusted to ca. 7 by adding NaOH solution (1 N aq, ~90 mL). The crude aziridine was extracted with ether (2 × 200 mL), and the organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was distilled under vacuum (bp 60−65 °C/2 mm) to yield 25 g (67%) of the aziridine **3a** as a colorless oil. ^{1}H (300 MHz; $CDCl_3$): 1.27 (s, 3H), 1.33−1.57 (m, 4H), 1.61 (s, 3H), 1.79 (td, 1H, J = 10.5 Hz, 2.9 Hz), 1.93−2.07 (m, 3H), 4.62 (s, 2H). ^{13}C (75 MHz; $CDCl_3$): 20.1, 24.6, 26.1, 30.3, 30.7, 34.8, 37.3, 41.2, 108.4, 149.3.

Preparation 4-Isopropenyl-1-methyl-7-aza-bicyclo-[4.1.0]heptane 3b. The crude azido-alcohol **2b** isolated from the preparation of **3a** was dissolved in reagent grade 1,4-dioxane (ca. 200 mL), and the solution was heated with triphenylphosphine (75 g, 0.28 mol) at reflux for 36 h (again the reaction could be easily monitored by GC). Upon completion, the reaction was allowed to cool to rt before being diluted with ether (300 mL). The triphenylphosphine oxide, which precipitated, was filtered off, and the organic filtrate was washed with an aqueous solution of citric acid (2 × 100 mL, 96 g in 200 mL of water). The aqueous layer was separated and washed with DCM (2 × 150 mL), and its pH was adjusted to pH 7 by addition of 1 N aq NaOH solution. The product was extracted with ether (2 × 200 mL). The organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo, and the residue was purified by vacuum distillation (bp 55−60 °C/2 mm) to yield 22 g (59%) of the aziridine **3b** as a colorless oil. ^{1}H (300 MHz; $CDCl_3$): 1.11−1.19 (m, 1H), 1.25 (s, 3H), 1.41−1.58 (m, 1H), 1.67 (s, 3H), 1.74−1.85 (m, 3H), 1.91−2.13 (m, 3H), 4.68 (s, 1H), 4.71 (s, 1H). ^{13}C (75 MHz; $CDCl_3$): 21.4, 26.8, 27.8, 29.8, 30.8, 34.7, 36.9, 39.5, 109.2, 149.6.

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