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Regio- and diastereoselective synthesis of bifunctionalized limonenes

Michael V. Voronkov,[a,*] Ramanaiah C. Kanamarlapudi[a] and Paul Richardson[a,b]

[a]*Lexicon Pharmaceuticals, 250 Carter Road, Princeton, NJ 08540, USA*
[b]*Pfizer, 10578 Science Center Drive, San Diego, CA 92121, USA*

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Abstract—High regio- and diastereoselective ring opening of limonene aziridines with a variety of nucleophiles is described. The resulting novel chiral derivatives are readily accessible from limonene aziridine in either enantiomeric form in 35–94% yield.

1. Introduction

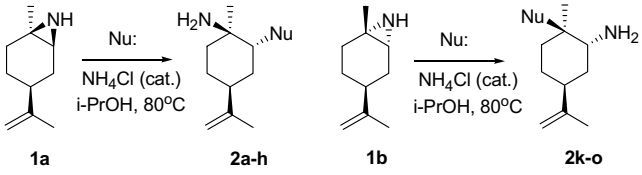
Terpenes and limonene in particular, are an important class of naturally occurring chiral compounds widely used in organic synthesis either as starting materials for optically pure molecules[1] or as a core of chiral auxiliaries or asymmetric ligands employed in enantioselective transformations.[2]

The stereoselective functionalization of the endocyclic double bond in limonene has presented a formidable challenge, thus severely limiting its application in synthesis. To the best of our knowledge there are no literature examples of limonene based chiral diamine or aminophosphine ligands.

We recently reported a method for synthesis of either isomer of limonene aziridines in a highly selective manner.[3] Now we have expanded the chemistry of these chiral building blocks to the synthesis of bifunctionalized limonenes with examples of regio- and diastereoselective opening of these aziridines with various nucleophiles including *N*-, *P*-, and *S*-nucleophiles.

2. Results and discussion

In the presence of a catalytic amount of ammonium chloride, limonene aziridines **1a** and **1b** reacted with various nucleophiles using isopropanol as solvent (Scheme 1). Limonene aziridines require no protective groups and/or additional activation and the reaction generally proceeded for 2–96 h depending on the nature of the nucleophiles. Aziridine consumption was monitored by LC/MS and the desired products were isolated either by vacuum distillation from the reaction mixture (products **2a**–**e**,**n**,**o**) or by chromatography (products **2f**,**h**,**i**,**k**–**m**) in 35–94% yields (Table 1). In all reactions no regioisomeric products were observed with the exception of reaction of isomer **1a** with thiophenol.



Scheme 1. Nucleophilic opening of aziridines **1a** and **1b**.

We observed that the nucleophilic opening of the limonene aziridines **1a** and **1b** was both regio- and diastereoselective and proceeded by the same stereochemical constraints that dictate the opening of the epoxides. Thus, reaction of amines and azide on the *trans*-aziridine **1a** occurred at the less sterically encumbered secondary carbon center (C-2). In the case of the *cis*-aziridine **1b**, the incoming nucleophile attacked exclusively at C-1 (Scheme 1). Proton NMR spectra of products **2a**–**h** showed a characteristic C-1 methyl signal at 1.03–1.28 ppm. In comparison, for products **2k**–**o** the

* Corresponding author. Tel.: +1 609 466 5557; fax: +1 609 466 3562; e-mail: mvoronkov@lexpharma.com

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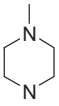
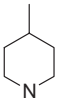
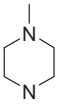
Table 1. Nucleophilic opening of aziridines **1a** and **1b**

Product	Aziridine	Nucleophile	Conditions (h)	Yield (%)
2a	**1a**		48	72
2b	**1a**		48	85
2c	**1a**		24	92
2d	**1a**		48	74
2e	**1a**		24	66
2f	**1a**	$HPPh_2$	96	57
2g	**1a**	PhCN	72	Decomp.
2h	**1a**	HSPh	48	65[a]
2i	**1a**	NaN_3	48	68
2j	**1b**	$HPPh_2$	96	Decomp.
2k	**1b**	PhCN	72	35
2l	**1b**	HSPh	2	94
2m	**1b**	NaN_3	48	63
2n	**1b**		24	65
2o	**1b**		24	71

[a] Regioisomer **3l** was isolated in 22% yield.

same methyl signal shifted downfield to 1.41–1.51 ppm, possibly reflecting steric congestion at this carbon. The geometry of these products was confirmed by NOESY.

As shown in Table 1, limonene aziridine **1a** reacted with a variety of *N*-nucleophiles to afford products **2a**–**e**,**i** in good yields. In most cases we observed small amounts of unreacted aziridine **1a** as the major impurity. However, prolonging reaction time or using stronger acids such as PSA or PPA, as a catalyst did not improve the yields of the desired products.

The reactions of isomer **1b** under similar conditions employing sodium azide, piperidine and *N*-methyl piperazine afforded the desired products **2m**–**o** in 63–94% yield. However, reactions of isomer **1b** with morpholine, 4-methylpiperidine, or pyrrolidine generated complex mixtures of products and vacuum distillation yielded trace amounts of the expected products. Although such differences in chemical reactivity between stereoisomers has been reported for the corresponding limonene oxides,[4] the difference in stability of these aziridine derivatives at elevated temperature could not be ruled out. In reactions of isomer **1b** with other nucleophiles significant amounts of a single impurity was observed. The LC/MS data (M+1 = 170.1) for this impurity corresponded to opening of aziridine ring by water present in the reaction solvent. Therefore somewhat lower yields in the reactions of isomer **1b** can be due to its inferior stability under the reaction conditions.

The bulkier diphenylphosphine in reactions with the limonene aziridine isomer **1a** gave derivative **2f** in accordance with previous reported aziridine opening by phosphines.[5] After 96 h, the transformation proceeded in 57% yield with what we suspected was the corresponding phosphine oxide derivative as a major impurity, based on LC/MS data (M+1 = 354.1). On the other hand, diphenylphosphine completely failed to react with more sterically congested isomer **1b**.

A much stronger nucleophile thiophenol reacted with both isomer **1a** and **1b** to afford the desired products **2h** and **2l** in 65% and 94% yields, respectively. Of note, the reaction of isomer **1a** with thiophenol also produced a minor product **3l** in 22% yield, where aziridine was opened at C-1 position. Such behavior in aziridine opening reactions with strong nucleophiles has been previously reported.[6] The structure of **3l** was tentatively assigned based on NMR analysis and comparisons with that of the expected **2h** and **2l** (Fig. 1).

Finally, we attempted aziridine opening with a nitrile.[7] While isomer **1a** underwent excessive decomposition under the reaction conditions, isomer **1b** formed dihydroimidazoyl derivative **2k** as the single product in

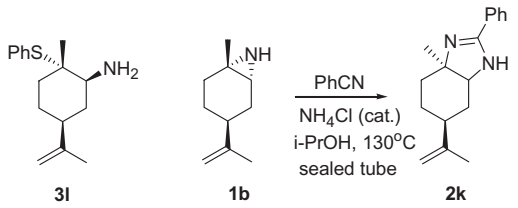


Figure 1. Unexpected products of aziridine opening.

35% yields (Fig. 1). Although it was expected that nucleophilic attack would take place at C-1 position, no strong NOE was observed. Remarkably, we did not observe any other Ritter-like products reported for terpene oxides.[8]

In conclusion, we have demonstrated synthetic utility of these aziridines by regioselective ring opening with various nucleophiles in 35–94% yield. The limonene aziridines require no protective groups and/or additional activation. The ease and scope of functionalization of this transformation allows for an efficient entry to novel bifunctional limonenes. The further use of these functionalized terpenes as chiral ligands in asymmetric synthesis is currently under evaluation.

3. Experimental

3.1. 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 atmosphere under anhydrous conditions. LC/MS analysis was conducted on HP1100 with Polaris C18 A-5 μm column.

3.2. General procedure for preparation of limonene derivatives 2a–f

To a solution of the corresponding of limonene aziridine isomer **1a** or **1b** (70 mmol) in 2-propanol (20 mL) was added (210 mmol) of the corresponding nucleophile, followed by addition of a catalytic amount 0.27 g (5.0 mmol) of ammonium chloride. The reaction mixture was heated at the appropriate temperature with magnetic stirring for 1–2 days (the reaction was monitored by GC). After cooling, the reaction mixture was concentrated in vacuo to remove the solvent and excess of nucleophile. The products were isolated from the residue by vacuum distillation or column chromatography.

3.3. 4-Isopropenyl-1-methyl-2-piperidin-4-yl-cyclohexylamine 2a

^{1}H (300 MHz, $CDCl_3$): δ 1.01 (s, 3H), 1.22–1.51 (m, 9H), 1.61 (s, 3H), 1.74 (d, 1H, $J = 10.4$ Hz), 1.74 (d, 1H, $J = 10.4$ Hz), 2.12–2.39 (m, 5H), 2.52 (br s, 2H), 4.74 (s, 1H), 4.82 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 21.8, 22.0, 24.1, 24.4, 26.5, 36.5, 38.8, 52.8, 53.1, 68.1, 110.4, 145.3; bp at 135 °C/1 mm.

3.4. 4-Isopropenyl-1-methyl-2-(4-methyl-piperazin-1-yl)-cyclohexylamine 2b

^{1}H (300 MHz, $CDCl_3$): δ 1.03 (s, 3H), 1.31–1.41 (m, 2H), 1.43–1.54 (m, 4H), 1.64 (s, 3H), 1.92 (dd, 1H, $J = 10.5$, 3.1 Hz), 2.11 (d, 1H, $J = 10.5$, 3.1 Hz), 2.32 (s, 3H), 2.39–2.52 (m, 7H), 2.73 (m, 2H), 4.84 (s, 1H), 4.93 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 22.2, 22.3, 24.3, 24.5, 36.7, 39.0, 45.9, 53.5, 55.8, 67.5, 110.7, 145.6; bp at 133 °C/1 mm.

3.5. 4-Isopropenyl-1-methyl-2-morpholin-4-yl-cyclohexylamine 2c

^{1}H (300 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.32–1.39 (m, 2H), 1.49–1.55 (m, 4H), 1.67 (s, 3H), 1.87 (dd, 1H, $J = 10.5$ Hz, 3.1 Hz), 1.98 (d, 1H, $J = 10.5$ Hz, 3.1 Hz), 2.22 (dd, 1H, $J = 10.4$ Hz, 3.7 Hz), 2.47–2.61 (m, 3H), 2.68–2.79 (m, 2H), 3.66–3.78 (m, 4H), 4.83 (s, 1H), 4.91 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 22.8, 23.0, 24.8, 24.9, 37.2, 39.5, 52.5, 53.9, 63.5, 68.0, 68.7, 111.3, 146.0; bp at 130 °C/1 mm.

3.6. 4-Isopropenyl-1-methyl-2-(4-methylpiperidin-1-yl)-cyclohexylamine 2d

^{1}H (300 MHz, $CDCl_3$): δ 0.84 (d, 3H, $J = 2.2$ Hz), 1.03 (s, 3H), 1.22–1.44 (m, 4H), 1.47–1.55 (m, 5H), 1.64 (s, 3H), 1.77 (d, 1H, $J = 11.1$ Hz), 2.08 (d, 1H, $J = 11.1$ Hz), 2.13 (t, 1H, $J = 9.6$ Hz), 2.23 (d, 1H, $J = 10.9$ Hz), 2.42–2.64 (m, 3H), 2.23 (d, 1H, $J = 9.6$ Hz), 4.78 (s, 1H), 4.85 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 21.9, 22.2, 22.4, 24.5, 24.5, 31.1, 35.0, 35.7, 36.8, 39.2, 48.7, 53.5, 56.1, 67.9, 110.8, 145.6; bp at 120 °C/1 mm.

3.7. 4-Isopropenyl-1-methyl-2-pyrrolidin-1-yl-cyclohexylamine 2e

^{1}H (300 MHz, $CDCl_3$): δ 1.04 (s, 3H), 1.34–1.87 (m, 12H), 1.97 (d, 1H, $J = 10.6$ Hz), 2.31–2.57 (m, 2H), 2.23 (d, 4H, $J = 6.4$ Hz), 4.79 (s, 1H), 4.88 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 22.2, 23.9, 25.1, 25.2, 37.1, 39.4, 51.4, 53.8, 64.2, 110.7, 146.5; bp at 170 °C/1 mm.

3.8. 2-Diphenylphosphanyl-4-isopropenyl-1-methyl-cyclohexylamine 2f

^{1}H (300 MHz, $CDCl_3$): δ 1.04 (s, 3H), 2.42 (s, 3H), 2.52–2.94 (m, 5H), 2.22 (t, 1H, $J = 11.2$ Hz), 2.37–2.42 (m, 1H), 2.62–2.66 (m, 1H), 4.59 (s, 1H), 4.64 (s, 1H), 7.43–7.57 (m, 6H), 7.80 (t, 2H, $J = 8.2$ Hz), 7.91 (t, 2H, $J = 8.2$ Hz); ^{13}C (75 MHz, $CDCl_3$): δ 21.7, 26.3, 28.7, 38.2, 39.6, 44.2, 45.1, 52.8, 109.8, 128.8, 128.9, 129.0, 129.1, 131.4, 131.6, 135.5, 136.7, 148.7.

3.9. 4-Isopropenyl-1-methyl-2-phenylsulfanyl-cyclohexylamine 2h

^{1}H (300 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.63 (s, 3H), 1.61–1.91 (m, 9H), 2.07 (d, 1H, $J = 10.7$ Hz), 2.21 (s, 1H), 2.37–2.39 (m, 1H), 3.37 (br s, 1H), 4.62 (s, 1H), 4.72 (s, 1H), 7.25–7.31 (m, 3H), 7.47–7.51 (m, 2H), 7.96

(br s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 21.6, 25.6, 29.3, 29.5, 33.6, 38.9, 51.2, 55.2, 111.8, 127.4, 129.3, 132.0, 134.5, 147.8.

3.10. 2-Azido-4-isopropenyl-1-methyl-cyclohexylamine 2i

^{1}H (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.61–1.73 (m, 2H), 1.71 (s, 3H), 1.76–1.82 (m, 2H), 1.85–1.93 (m, 1H), 2.07 (td, 1H, $J = 10.1$, 3.4 Hz), 2.34 (br s, 1H), 3.42 (s, 1H), 3.78 (br s, 1H), 4.74 (s, 1H), 4.83 (s, 1H), 7.93 (br s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 21.6, 24.9, 30.1, 31.7, 37.9, 57.4, 62.4, 111.3, 145.7.

3.11. 6-Isoprenyl-3a-methyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-benzoimidazole 2k

^{1}H (300 MHz, $CDCl_3$): δ 1.62 (s, 3H), 1.64–1.70 (m, 2H), 1.72 (s, 3H), 1.91–2.17 (m, 3H), 2.22–2.36 (m, 2H), 2.47 (td, 1H, $J = 10.4$, 3.1 Hz), 4.71 (s, 1H), 4.76 (s, 1H), 5.82 (br s, 1H), 7.43–7.67 (m, 5H); ^{13}C (75 MHz, $CDCl_3$): δ 21.1, 21.4, 30.8, 30.9, 32.6, 35.4, 53.5, 68.1, 110.4, 127.3, 128.6, 128.9, 132.8, 147.5, 167.5.

3.12. 5-Isopropenyl-2-methyl-2-phenylsulfanyl-cyclohexylamine 2l

^{1}H (300 MHz, $CDCl_3$): δ 1.51 (s, 3H), 1.61 (s, 3H), 1.61–1.64 (m, 1H), 1.66–1.91 (m, 5H), 2.13 (td, 1H, $J = 10.8$, 3.3 Hz), 2.39 (t, 1H, $J = 10.0$ Hz), 3.64 (s, 1H), 4.67 (s, 1H), 4.73 (s, 1H), 7.21–7.29 (m, 3H), 7.40–7.43 (m, 2H), 8.02 (br s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 21.4, 24.8, 25.5, 32.4, 32.7, 38.6, 52.6, 58.2, 110.6, 127.6, 129.4, 131.9, 134.5, 147.2.

3.13. 2-Azido-5-isopropenyl-2-methyl-cyclohexylamine 2m

^{1}H (300 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.70 (s, 3H), 1.71–1.79 (m, 2H), 1.81–1.85 (m, 2H), 2.09 (td, 1H, $J = 8.8$, 3.6 Hz), 2.25 (br s, 1H), 3.21 (br s, 1H), 3.48 (s, 1H), 4.75 (s, 1H), 4.85 (s, 1H), 7.86 (br s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 21.5, 25.6, 29.9, 31.5, 37.2, 54.5, 61.6, 111.1, 145.9.

3.14. 5-Isopropenyl-2-methyl-2-piperidin-4-yl-cyclohexylamine 2n

^{1}H (300 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.24–1.66 (m, 11H), 1.67(s, 3H), 1.92 (d, 1H, $J = 3.0$ Hz), 2.12 (d, 1H, $J = 3.0$ Hz), 2.32–2.52 (m, 4H), 2.71–2.82 (m, 3H), 4.81(s, 1H), 4.92 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 22.6, 22.8, 24.9, 25.3, 27.4, 37.3, 39.7, 53.6, 59.9, 68.9, 111.2, 146.3; bp at 132 °C/1 mm.

3.15. 5-Isopropenyl-2-methyl-2-(4-methyl-piperazin-1-yl)-cyclohexylamine 2o

^{1}H (300 MHz, $CDCl_3$): δ 1.43 (s, 3H), 1.27–1.61 (m, 6H), 1.68 (s, 3H), 1.93 (d, 1H, $J = 3.1$ Hz), 2.11 (d, 1H, $J = 3.1$ Hz), 2.34 (s, 3H), 2.34–2.55 (m, 6H), 2.73–2.81 (m, 3H), 4.86 (s, 1H), 4.95 (s, 1H); ^{13}C (75 MHz, $CDCl_3$): δ 22.3, 22.5, 24.8, 24.9, 27.4, 37.3, 39.5, 46.0, 53.4, 59.1, 68.5, 111.2, 146.6.

3.16. 5-Isopropenyl-2-methyl-2-phenylsulfanyl-cyclohexylamine 3l

^{1}H (300 MHz, $CDCl_3$): δ 1.41 (s, 3H), 1.62 (q, 1H, $J = 7.3$ Hz), 1.66 (s, 3H), 1.71–1.83 (m, 2H), 1.96 (t, 1H, $J = 9.4$ Hz), 2.05–2.09 (m, 2H), 3.33 (dd, 1H, $J = 12.3$ Hz, 4.3 Hz), 3.48 (s, 1H), 4.67 (s, 1H), 4.72 (s, 1H), 7.28–7.32 (m, 3H), 7.46–7.49 (m, 2H), 7.89 (br s, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 18.4, 21.2, 27.3, 36.2, 36.9, 44.8, 56.2, 58.5, 110.1, 128.5, 129.6, 132.5, 132.9, 147.5.

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