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Synthesis of Substituted (*D*)-Phenylalanine Derivatives by Regioselective Reduction of Enantiomerically Pure *cis*-2,3-Disubstituted Aziridines

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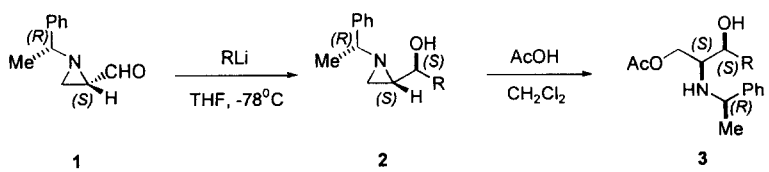
Abstract: Various *N*-(*R*)-(+)-(α-methylbenzyl)-(2*R*,3*R*)-disubstituted aziridines were prepared by intramolecular cyclization. The regioselective reduction of the ring C(3)-*N* bond in the presence of $(Boc)_2O$ by catalytic hydrogenation with atmospheric pressure of hydrogen provides (*D*)-phenylalaninol analogues in good yields.

Keywords: Amino acids and derivatives; Chiral aziridine; Reduction

The importance of unnatural, enantiomerically pure amino acids is increasing especially in the syntheses of peptide-based biologically active compounds.[1] In connection with our research toward enzyme inhibitors, we became interested in the efficient preparation of substituted phenylalanines and their derivatives. Most aromatic modification of phenylalanine uses transition metal catalyzed cross coupling reactions starting from tyrosine or arylboronic acid.[2] The need for various phenyl substituted α-amino acids prompted us to investigate more general and efficient preparative method for those molecules.

We recently showed that a variety of enantiomerically pure aziridine-2-methanols (**2**) were prepared by organometallic addition to the aziridine-2-carboxaldehyde (**1**) in high yields. The aziridine ring C-N bond can be regioselectively cleaved by AcOH to provide various 2-amino-1,3-propanediols (**3**) (Scheme 1).[3]

Scheme 1



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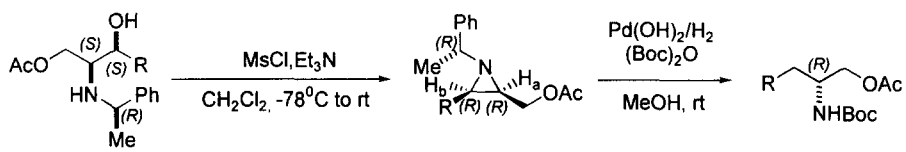
The selective reduction of the hydroxyl group at C-1 of **3** would provide β-amino alcohols which can be transformed to α-amino acids after oxidation of the primary alcohol. Since a variety of aromatic groups can be introduced in the first addition step, the reduction of the C-1 hydroxyl group and *N*-α-methylbenzyl group will provide phenylalaninol analogues.

Recently, the preparation of enantiomerically pure 2,3-disubstituted aziridines from amino acids and their derivatives by intramolecular cyclization was reported.[4] Treatment of the amino alcohol **3** with MsCl and Et_3N in CH_2Cl_2 at −78°C provides various *cis*-2,3-disubstituted chiral aziridines (**4**) by a stereospecific intramolecular cyclization in high yields (Scheme 2).[5] Yamamoto[4a,4b] reported that *cis*-2,3-disubstituted aziridines are thermodynamically more stable than the corresponding *trans*-2,3-disubstituted aziridines and we

Scheme 2



3 **4** **5**

Entry	R	Yield (% isolated)	
		4	**5**
a	Phenyl	93	85
b	4-Chlorophenyl	81	
c	4-Fluorophenyl	81	80
d	1-Naphthyl	76	67
e	2-Naphthyl	82	71
f	2-Methoxyphenyl	56	81
g	3-Methoxyphenyl	76	85
h	*p*-Trifluoromethylphenyl	77	82
i	4-Biphenyl	72	78
j	2-Thiazolyl	80	
k	Methyl	83	75

confirmed that by observing the smooth cyclization of the mesylate of **3** to give high yields of the *cis*-aziridines (**4**). However, we could not isolate the corresponding *trans*-2,3-disubstituted aziridines from the cyclization of (1*R*,2*S*) stereoisomers of **3** when R was an aromatic substituent.[6] The chemical shifts of the two ring protons of the aromatic substituted aziridines are very similar which makes the coupling constant measurement difficult. However, the two ring protons of the methyl substituted aziridine (**4k**) are well resolved and show 6.5 Hz of coupling constant which confirms *cis* relationship of those two protons (J_{cis} ~ 7 Hz, J_{trans} ~ 4 Hz).[4a]

We recently reported regioselective reduction of the C-N bond of 2-substituted aziridines by catalytic hydrogenation with the Perlman's catalyst.[7] The same protocol applies to the 2,3-disubstituted aziridines (**4**) and the reduction of the ring C-N bond occurs at the C(3) which has an aromatic substituent. The presence of $(Boc)_2O$ provides ring nitrogen activation and facilitates the reduction of the ring C-N bond and also *N*-α-

methylbenzyl group with atmospheric pressure of hydrogen to provide 2(*R*)-*N*-Boc-phenylalaninol derivatives (**5**)[8] in high yields. However, the reduction of **4b** and **4j** yielded complex product mixtures and we failed to isolate the expected product. Interestingly, the reduction of **4k** also occurs at C(3) regioselectively to give an alaninol homologue as the only isolated product which clearly shows the presence of the ethyl group in ^{1}H and ^{13}C NMR.[9] The acetate of **5a** was hydrolyzed quantitatively by KOH in ethanol to give *N*-Boc-(*D*)-phenylalaninol. The *N*-Boc-(*D*)-phenylalaninol from **5a** was oxidized to the corresponding carboxylic acid using $RuCl_3$ and $NaIO_4$[10] and the crude carboxylic acid was converted to its methyl ester using methyl iodide in the presence of potassium hydrogen carbonate in DMF at room temperature[11] without loosing optical integrity in 81% yield.

To summarize the above results, we developed an efficient method for the preparation of a variety of substituted (*D*)-phenylalanine derivatives by regioselective reduction of *cis*-2,3-disubstituted aziridines. Since the enantiomer of **4** can be readily prepared from (*S*)-α-methylbenzylamine, the preparation of the substituted (*L*)-phenylalanine derivatives is also possible.

Acknowledgements

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5. General procedure for the preparation of **4**. To a solution of (1*S*,2*S*)-2-{*N*-[(*R*)-α-methylbenzyl]amino}-3-*O*-acetyl-1-phenyl-1,3-propanediol **3a** (109 mg, 0.348 mmol) in 3.50 mL of methylene chloride, with stirring and cooling at –78°C, was added Et_3N (0.24 mL, 1.74 mmol). The orange yellow mixture was stirred for 15 min at –78°C and was added MsCl (81 μL, 1.04 mmol). The mixture was warmed to room temperature and was stirred for 6 h and then treated with 3 mL of saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL x 5). The combined organic extracts were washed with brine, dried over anhydrous K_2CO_3, filtered, and concentrated in *vacuo*. Purification by silica gel flash chromatography (EtOAc/n-Hexane, 15:85) gave 96 mg (93%) of **4a** as a yellow oil. **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.50 (d, *J* = 6.50 Hz, 3H), 2.05 (s, 3H), 2.14 (m, 1H), 2.78 (m, 2H), 3.75 (dd, *J* = 11.7, 4.0

Hz, 1H), 3.99 (dd, J=11.8, 5.0 Hz, 1H), 7.22 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.91, 23.37, 43.82, 45.04, 63.71, 69.86, 126.91, 127.13, 127.60, 128.09, 128.39, 136.38, 144.22, 171.00. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.08; H, 7.43; N, 4.82.

6. We obtained *trans*-2,3-disubstituted aziridines as the only cyclization product when R of **3** was vinyl or hexynyl group in 81% and 84% yields, respectively. However, the chemical shifts of the two ring protons were very similar and the coupling constant measurement failed.
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8. General procedure for the preparation of **5**. To a solution of **4a** (240 mg, 0.809 mmol) in 4.00 mL of MeOH was added $Pd(OH)_2$ (30 wt%) and $(Boc)_2O$ (353 mg, 1.62 mmol). The mixture was stirred for 7 h with atmospheric pressure of hydrogen and then filtered, concentrated in *vacuo*. Purification by silica gel flash chromatography (EtOAC/n-Hexane, 15:85) gave 203 mg (85%) of **5a** as a white solid. Without $(Boc)_2O$ the reaction takes much longer time and the reduction of the α-methylbenzyl group is not completed.

   5a: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (s, 9H), 2.06 (s, 3H), 2.81 (m, 2H), 4.02 (m, 3H), 4.69 (br, NHBoc, 1H), 7.27 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.31, 23.81, 31.44, 46.11, 60.58, 75.01, 122.11, 124.06, 124.74, 132.69, 150.67, 166.35. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.77; H, 7.95; N, 4.61.
9. We do not have a clear explanation about the regioselectivity of the reduction of **4k** and we are currently working on the subject to provide a suitable explanation.
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