

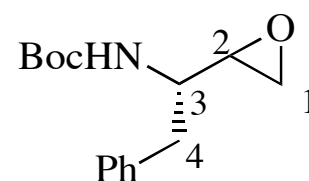
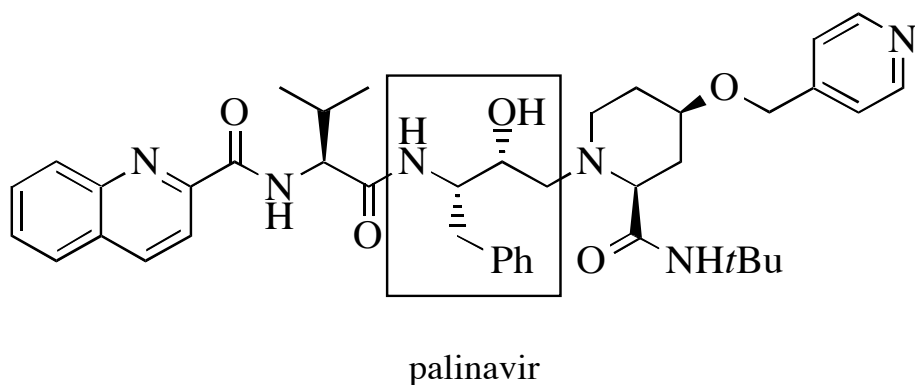
SYNTHESIS OF *N*-BOC-3-AMINO-1,2-EPOXY-4-PHENYLBUTANE FROM (3*S*)-HYDROXY- γ -BUTYROLACTONE BY MEANS OF THE HOFMANN REARRANGEMENT^{#), †)}

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Abstract- The stereocontrolled synthesis of the title alkylaminoepoxide was achieved starting from (3*S*)-hydroxy- γ -butyrolactone by efficient utilization of the Hofmann rearrangement followed by intramolecular oxazolidinone ring formation as a key step.

Aminobenzylepoxyde (**1**), the title compound, has been paid much attention because it is well recognized as a versatile chiral building block for the preparation of peptide isosteres incorporating a hydroxyethylamine moiety, which is a core structure of HIV-protease inhibitors represented by palinavir.¹ A number of stereoselective syntheses of both (2*S*,3*S*)- and (2*R*,3*S*)-alkylaminoepoxide (**1**) have been described in recent literature starting from either chiral precursors such as amino acids² or achiral olefins.³ Although some of them may be useful for large-scale preparation of **1**, the development of new methods applicable for the preparation of a wide variety of enantiomerically pure alkylaminoepoxides is still required. We now report the stereocontrolled synthesis of the title

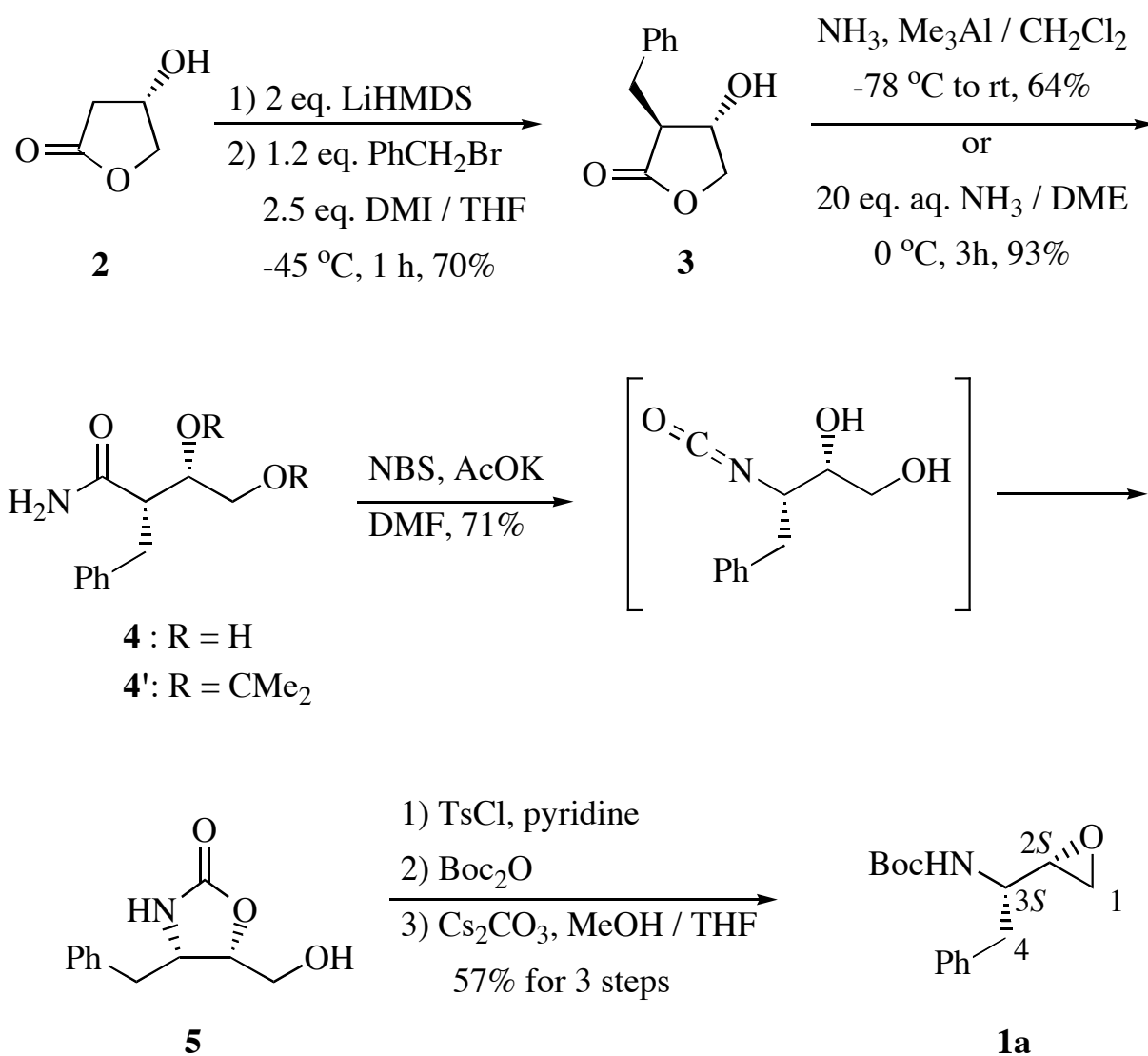


1a : (2*S*,3*S*)

1b : (2*R*,3*S*)

compound (**1**) starting from commercially available (3*S*)-hydroxy- γ -butyrolactone (**2**) through the disubstituted oxazolidinone derivative (**5**), which was produced by an intramolecular selective trap with the secondary hydroxy group of the intermediary isocyanate resulting from the Hofmann rearrangement of 2-benzyl-3,4-dihydroxybutanoic amide (**4**).

Scheme 1



The introduction of a benzyl group at the α position of (3*S*)-hydroxy- γ -butyrolactone (**2**) was improved by reinvestigation of the reported reaction conditions.⁴ Thus, the lactone (**2**) was treated with lithium hexamethylsilazide (2 equivalents) in the presence of 1,3-dimethyl-2-imidazolidinone (2.5 equivalents) in THF at -45 °C, and then the benzyl bromide was reacted with the dianion generated at the same temperature to produce the alkylated product (**3**), mp 90-91 °C and $[\alpha]_D^{22.5} +18.2^\circ$ (c 1.24, CHCl₃). Under these reaction conditions, the yield was improved from 34 to 70% and no stereoisomer was detected. In order to achieve the synthesis of **1** from **3**, the stereocontrolled intramolecular rearrangement of an amide group was very attractive for introduction of the amino group. Accordingly, two methods were studied for the formation of the amide (**4**). Treatment of **3**

with liquid NH_3 (one equivalent) in the presence of trimethylaluminum (one equivalent, 2.0 M solution in toluene) at $-78\text{ }^\circ\text{C}$ in CH_2Cl_2 gave the desired amide (**4**), mp $103\text{-}105\text{ }^\circ\text{C}$ and $[\alpha]_{\text{D}}^{22.5} -41.2^\circ$ (c 0.85, CHCl_3), in 64% yield without any isomerization, after the reaction mixture was warmed to room temperature.⁵ On the other hand, treatment of **3** with aqueous NH_3 (20 equivalents) in DME at $0\text{ }^\circ\text{C}$ gave a mixture of **4** and its diastereomer at the α -position in 93% yield in the ratio of 5:1, which was determined after acetonide formation at the vicinal diols.

The successful Hofmann rearrangement of **4** was achieved by reaction with NBS in the presence of KOAc in DMF at room temperature, and the disubstituted oxazolidinone (**5**), mp $158\text{-}159\text{ }^\circ\text{C}$ and $[\alpha]_{\text{D}}^{22.5} -67.2^\circ$ (c 1.33, CHCl_3), was obtained in 74% yield in one pot.⁶ In this rearrangement, the use of AgOAc instead of KOAc or [bis(trifluoroacetoxy)iodo]benzene treatment in $\text{MeCN-H}_2\text{O}$ ⁷ gave **5** in 61 or 65% yield, respectively. Reaction with lead tetraacetate in pyridine and sodium hypochlorite in water gave none of the desired product. Treatment of the acetonide (**4'**), which was derived from **4** by the usual method, with [bis(trifluoroacetoxy)iodo]benzene also gave **5** in 54% yield. The reactive isocyanate resulting from the Hofmann rearrangement must be selectively trapped with the secondary hydroxy group in an intramolecular fashion.⁸ This is a novel and effective method for the stereocontrolled disubstituted oxazolidinone formation, and is very useful for the vicinal amino alcohol synthesis from substituted γ -butyrolactones.^{9,10} The synthesis of (2*S*,3*S*)-*N*-Boc-3-amino-1,2-epoxy-4-phenylbutane (**1a**) was achieved by tosylation of **5** followed by the introduction of a *tert*-butoxycarbonyl group at the oxazolidinone nitrogen and then cesium carbonate treatment in MeOH and THF in 57% yield for three steps.^{11, 12} The compound (**5**) would be led to the (2*R*,3*S*) compound (**1b**) by a sequence of protection of the hydroxy group with dihydropyran, introduction of a *tert*-butoxycarbonyl group at the amide nitrogen, ring-opening with cesium carbonate treatment, mesylation of the resulting secondary hydroxy group, acid treatment, and then potassium *tert*-butoxide treatment.¹³

Since (3*R*)-hydroxy- γ -butyrolactone is also obtainable,¹⁴ the present method is valuable for the synthesis of all stereoisomers of *N*-Boc-3-amino-1,2-epoxy-4-phenylbutane.

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REFERENCES AND NOTES

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