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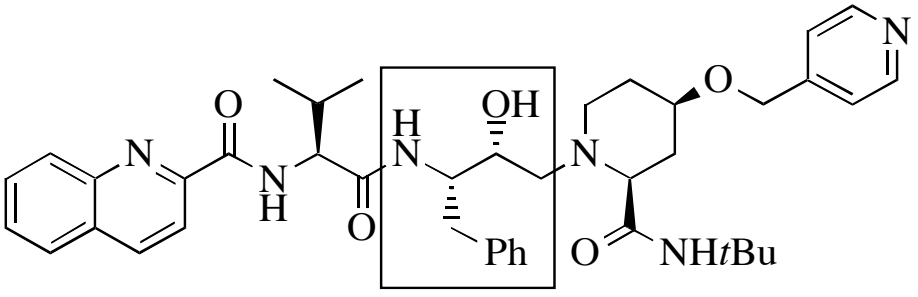
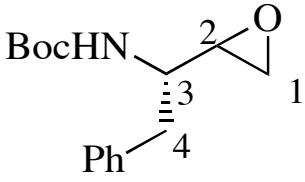
Abstract- The stereocontrolled synthesis of the title alkylaminoepoxide was achieved starting from (*3S*)-hydroxy-γ-butyrolactone by efficient utilization of the Hofmann rearrangement followed by intramolecular oxazolidinone ring formation as a key step.

Aminobenzylepoxide **(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 (*2S,3S*)- and (*2R,3S*)-alkylaminoepoxide **(1)** have been described in recent literature starting from either chiral precursors such as amino acids[2] 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



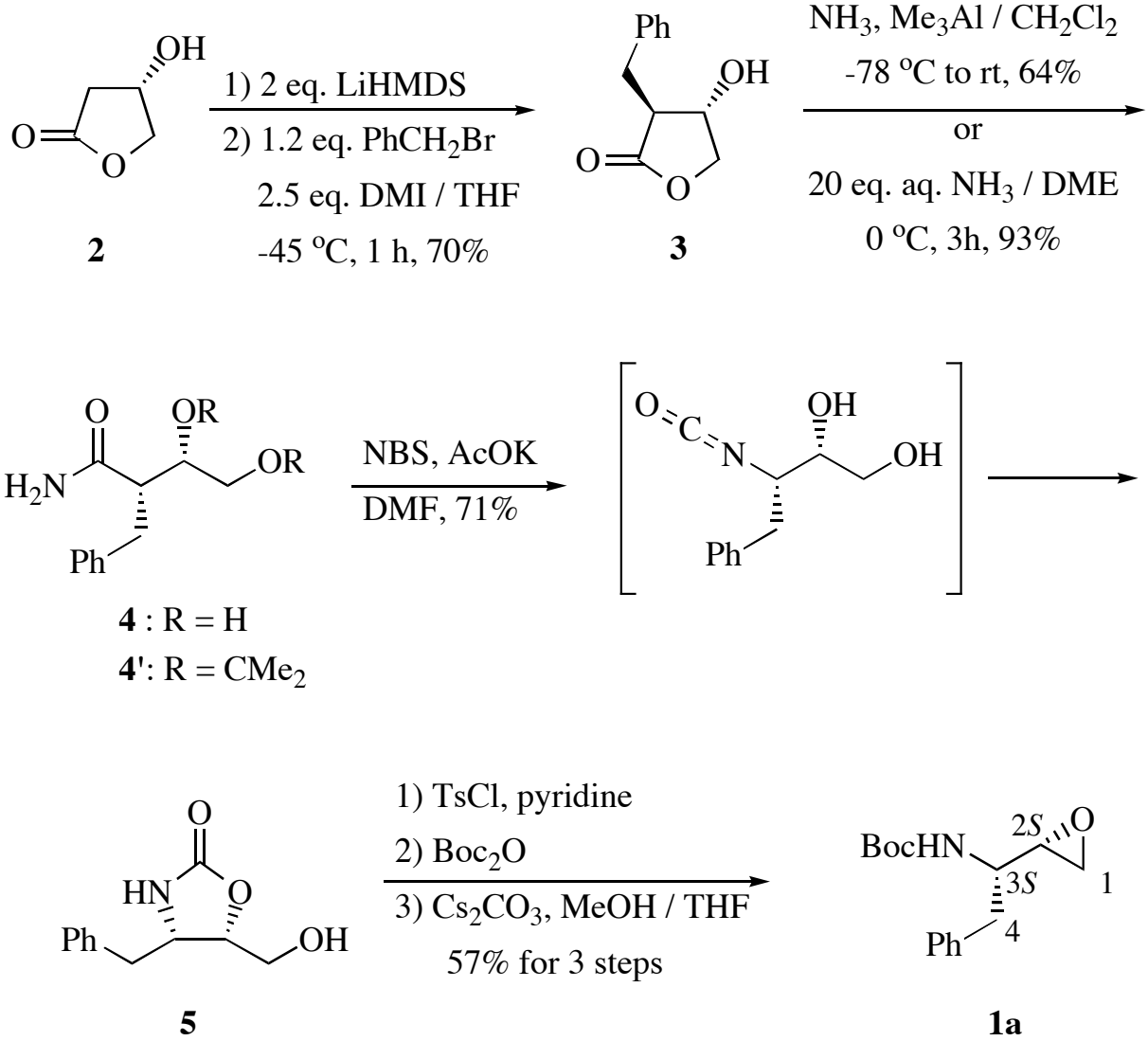
palinavir



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

compound **(1)** starting from commercially available (*3S*)-hydroxy-γ-butyrolactone **(2)** through the disubsutituted 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



2 **3**

4 : R = H

4': R = CMe_2

5 **1a**

The introduction of a benzyl group at the a position of (*3S*)-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° (c 1.24, $CHCl_3$). 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 °C in CH_2Cl_2 gave the desired amide **(4)**, mp 103-105 °C and $[\alpha]_D^{22.5}$ -41.2° (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 °C gave a mixture of **4** and its diastereomer at the a-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 158-159 °C and $[a]_D^{22.5}$ –67.2° (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 MeCN-H_2O [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 (*2S,3S*)-*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 (*2R,3S*) 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 (*3R*)-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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