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Large Scale Preparation of (2S,3S)-N-Boc-3-Amino-1,2-Epoxy-4-Phenylbutane: A Key Building Block for HIV-Protease Inhibitors

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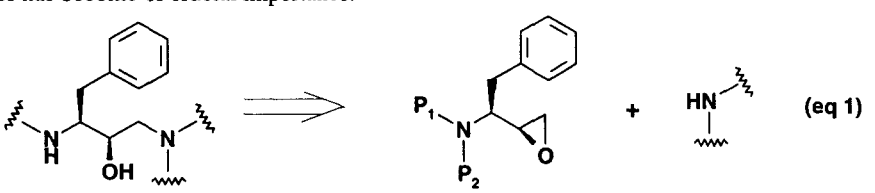
Abstract: *(2S,3S)-N-Boc-3-amino-1,2-epoxy-4-phenylbutane is prepared in four steps from commercially available N,N-dibenzyl-L-phenylalaninol. The synthesis is amenable to the preparation of kilogram quantities of enantiomerically pure material.*

The inhibition of HIV-protease by peptidomimetic structures incorporating a hydroxyethylamine (HEA) isostere offers a promising area for therapeutic intervention against acquired immunodeficiency syndrome (AIDS).[1] Many potent members of this class of inhibitors incorporate a phenylalanine-derived unit possessing an R- configuration at the critical hydroxyl-bearing carbon atom.[1,2] As studies of several HEA-based HIV-protease inhibitors have advanced from the laboratory to preclinical and clinical stages, the need for efficient syntheses has become of crucial importance.

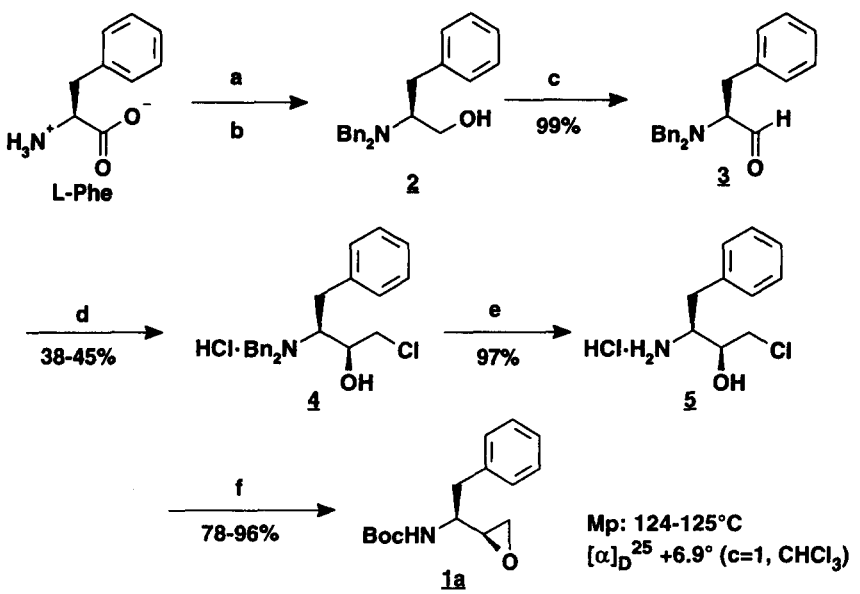


1: (a) P_1 = H, P_2 = Boc
(b) P_1 = H, P_2 = Cbz
(c) P_1, P_2 = Bn

Not surprisingly, considerable effort has been directed towards the development of efficient synthetic routes to HEA isosteres that can provide a good control of stereogenic centers. Convergent approaches usually involve coupling between a protected form of aminoepoxide **1** and a nitrogen nucleophile (eq 1).[1] Recent reports[3] addressing the synthesis of aminoalkylepoxides such as **1** have prompted us to disclose our own findings. In particular, we describe herein a new approach to (2S,3S)-N-Boc-3-amino-1,2-epoxy-4-phenylbutane (**1a**) in isomerically pure form. The method is amenable to the preparation of kilogram quantities of this versatile building block and avoids the use of dangerous or expensive reagents, unstable intermediates and chromatographic purifications.

The methodology relies on the N,N-dibenzylaminoaldehyde chemistry developed by Reetz to establish the *anti-* relationship between the two stereogenic centers.[4] N,N-Disubstitution of α-aminoaldehydes with bulky groups stabilizes these sensitive molecules towards racemization and directs nucleophilic attack on the carbonyl according to the non-chelating model of Felkin-Anh,[4,5] thus producing aminoalcohols with the desired orientation of the hydroxyl group.

SCHEME



(a) $NaBH_4$ / H_2SO_4. (b) BnBr (2.2 equiv.) / K_2CO_3 (3 equiv.) / aq. EtOH / 60 °C. (c) Pyr.SO_3 (1.4 equiv.) / Et_3N (2 equiv.) / DMSO / RT. (d) Li (15 equiv.) / $BrCH_2Cl$ / (1.12 equiv.) / THF / -65 °C then 6N HCl. (e) H_2 (1 atm.) / 20% $Pd(OH)_2$ on C (10% w/w) / MeOH. (f) Boc_2O (1.1 equiv.) / Et_3N (2.0 equiv.) / THF / 5 °C then methanolic KOH (4 equiv.).

The starting N,N-dibenzyl-L-phenylalaninal 3 was prepared by reduction of L-phenylalanine to L-phenylalaninol[6] followed by N,N-dibenzylation[7] and oxidation to the aldehyde using pyridine-sulfur trioxide complex at room temperature.[8] This sequence for the preparation of 3 is more convenient for large scale preparations than the original procedure[4] since it minimizes the use of benzyl groups, avoids pyrophoric reagents ($LiAlH_4$) and does not require a low temperature Swern oxidation. As a more direct approach to the desired epoxide, we investigated first the addition of sulfur ylides to 3 under non-chelating conditions. Although desired epoxide 1c was produced (70 % yield) as an 86:14 mixture of (2S,3S) and (2R,3S) diastereomers,[9] on scale up we encountered various degrees of racemization of 3 due to the strongly basic conditions required for ylide formation which made this chemistry unsuitable for the preparation of large quantities of material.

Chloromethyllithium generated *in situ* has been used to convert aldehydes and ketones into one carbon homologated epoxides.[10] Until recently however, the use of this reagent with sensitive, racemization-prone chiral α-aminoaldehydes had not been investigated.[3c,d, 11] We now report that when a large excess of lithium shot was stirred in a solution of aldehyde 3 and bromochloromethane in THF at -65°C and the reaction subsequently allowed to warm up to room temperature, an 86:14 mixture of diastereomeric epoxides was produced with 1c as major constituant. Unlike sulfur ylides, these conditions did not lead to products derived from racemization of 3.[12,13] As observed previously by Reetz, the two diastereomers could only be separated in low yield by careful, repetitive chromatography.[9] However, when a solution of crude 1c in THF was added to

an equal volume of 6N aqueous HCl, a precipitate formed after standing overnight in the cold. Recrystallization from methanol gave isomerically homogeneous dibenzylaminochlorohydrin hydrochloride **4** in 38-45 % overall yield from aminoalcohol **2**. Subsequently, we found that direct quenching of the intermediate chlorohydrin alkoxide with 6N HCl gave comparable yields of diastereomerically pure **4**.[14] Hydrogenolysis under standard conditions gave deprotected aminochlorohydrin hydrochloride **5** as a stable, crystalline, white solid (Mp: 204-208 °C; $[\alpha]_D^{25}$ -42.5°(c = 1, MeOH)). Final conversion to the desired Boc-epoxide **1a** was accomplished by sequential introduction of the Boc group followed by methanolic hydroxide ring closure in a two step - one pot operation. Crystalline epoxide **1a** was isolated by simple precipitation in a large volume of water.[15]

This four step sequence from commercially available N,N-dibenzyl-L-phenylalaninol[7] gives epoxide **1a** in 28-35% yield overall and proceeds without purification of intermediates except for one recrystallization of **4**. It has been used successfully for the preparation of kilogram quantities of epoxide **1a**. The methodology has been applied to the synthesis of aminoalkylepoxides derived from other amino acids and results will be reported elsewhere in more detail.

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7. N,N-Dibenzyl-L-phenylalaninol **2** is commercially available from the *Nutrasweet®* *Company.*

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9. Reetz, M.T.; Binder, J.; *Tetrahedron Lett.* **1989**, *30*, 5425-5428. When performed on a small scale as described by Reetz, the epoxides were obtained free of epimeric contaminants. However, when scaled-up to larger quantities (> 10 g), the reaction was found to be very sensitive to temperature control and became unreliable.

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11. While our work was in progress, the addition of chloromethyllithium (generated *in situ* from alkyllithiums and chloroiodomethane) to chiral N,N-dibenzylaminoaldehydes was reported (ref. 3c and 3d). In both cases, diastereomerically pure epoxides were obtained only after careful chromatography. In addition, the use of highly pyrophoric alkyllithiums in the metal-halogen exchange reaction, the cost of chloroiodomethane and the fact that iodoalkanes are generated as by-products made these procedures less attractive on a large scale.

12. All compounds gave analytical and spectroscopic data consistent with their structure. Enantiomeric and diastereomeric purities were determined by HPLC using a Chiralcel OD column.

13. No improvement in yield was obtained when the same reaction was performed under sonochemical conditions as reported by Luche (ref. 10d).

14. Experimental procedure for the preparation of **4**: Aldehyde **3** (2233 g, 6.77 mole) in THF (22 L, reagent grade) was cooled to -76 °C under an argon atmosphere. Lithium shot (4-16 mesh, bruised with mortar / pestle; 4 X 180 g, 104 mole) and bromochloromethane (4 X 245 g, 7.57 mole) were added alternatingly in four equal portions while maintaining an internal temperature below -65 °C at all times (additions were done at 45 min intervals). After complete addition, stirring was continued for 50 min at -70 °C. The solution was separated from floating lithium residues (the excess metal can be recovered for future use) and transferred into 6N HCl (7 L). The mixture was concentrated *in vacuo* until a clear aqueous layer separated from a gummy, brown residue. The aqueous layer was removed and the residue crystallized from hot methanol (3 L). The crude product was collected, washed with 10% methanol in ether (1 L) and recrystallized from methanol (4 L) to give pure **4** in three crops (1064 g, 38% yield) as a white, crystalline solid. Mp: 172-174 °C. $[a]_D^{25}$ -7.3°(c=1, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 2.69 (t, J = 10.3 Hz, 1H), 3.05 (dd, J = 11.0, 7.0 Hz, 1H), 3.31 (m, 1H), 3.39 (dd, J = 13.7, 4.0 Hz, 1H), 3.53 (dd, J = 14.0, 9.9 Hz, 1H), 3.99 (broad d, J = 6.3 Hz, 1H), 4.5 (m, 3H), 4.72 (broad d, J = 14.0 Hz, 1H), 5.03 (broad d, J = 13.2 Hz, 1H), 7.13 (m, 2H), 7.28 (m, 3H), 7.5 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.6, 45.7, 48.6, 54.6, 62.5, 68.8, 126.9, 128.4, 128.5, 129.1, 129.3, 130.0, 130.2, 131.2, 131.8, 136.8. FAB-MS: m/z 380 (MH^+). Elemental analysis calc. for $C_{24}H_{27}Cl_2NO$: %C, 69.23; %H, 6.54; %N, 3.36; found: %C, 69.14; %H, 6.41; %N, 3.22 (recrystallized analytical sample).

15. The free base of **5** must be generated in presence of the acylating agent to prevent decomposition. Epoxide **1a** is of acceptable purity for most purposes but can be purified further by recrystallization from EtOAc-hexane or precipitation of a methanolic solution in a large volume of water. The product was found to be identical in all respects to material produced by other methods (ref. 3a). HPLC analysis (Chiralcel-OD) and comparison to authentic samples of all four possible isomers gave an isomeric purity in excess of 99.5%.

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