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An efficient synthesis of *N*-protected *threo* (2*R*,3*S*)-3-amino-1,2-epoxy phenylbutane

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Abstract—A precise and versatile method was developed for the synthesis of *threo* amino epoxide derivatives, which are useful intermediates for protease inhibitors. It involves the diastereoselective reduction of the carbonyl group of γ-*N*,*N*-dibenzyl amino α-hydroxy β-keto sulfide prepared from an amino acid, and its subsequent stereospecific conversion to an amino epoxide via acetoxy halogenation in high yield.

Optically active α-amino epoxides have been widely used as key building blocks for pharmaceuticals, particularly for HIV protease inhibitors. For instance, *erythro* (*S*,*S*)-amino epoxide can be used as the key intermediate for saquinavir,[1] nelfinavir,[2] and fosamprenavir,[3] whereas *threo* (*R*,*S*) can be used for atazanavir.[4] Several methods have been reported for the synthesis of *threo* amino epoxides, for example, the halomethylation of optically active amino aldehydes[5] and the asymmetric epoxidation of olefins.[6] However, there are various difficulties associated with the industrial application of these methods, such as the multi-step transformation required to produce the amino aldehyde as the raw material, the requirement for a cryogenic reaction, the use of expensive reagents, etc. In the pursuit of synthetic approaches to the intermediates for HIV protease inhibitors,[7] we recently reported a practical synthesis of a β-amino α-hydroxy acid involving a Pummerer rearrangement of a β-keto sulfoxide followed by a stereoselective acyl migration.[8] The α-hydroxy β-keto sulfide that is the Pummerer product of this reaction can be reduced to an amino diol which in turn forms the precursor for an amino epoxide—the *N*-Cbz derivative thereof being reduced by sodium borohydride to an *erythro* diol preferentially in the ratio of *erythro*/*threo* = 2/1.[9,10] In this present paper, we report a new approach to the synthesis of the *threo* diol involving selective reduction followed by efficient epoxidation.[10]

β-Keto sulfoxide **2** was prepared by the reaction between *N*,*N*-dibenzyl L-phenylalanine benzyl ester **1** and dimsyl anion, followed by a Pummerer rearrangement under HCl acidic conditions affording the α-hydroxy sulfide **3**.[8] Crude **3** was easily reduced with sodium borohydride in an alcoholic solvent to give the amino diol derivative **4a**, in which the *threo* (*R*,*S*)-isomer was predominantly formed in a ratio of about 10/1[11] (Scheme 1). Each diastereomer could be isolated by means of silica gel column chromatography. As the *tert*-butoxycarbonyl (Boc) group is more commonly utilized in the synthesis of HIV protease inhibitor intermediates,[4] the *N*-Boc derivative (*R*,*S*)-**4b** was also prepared by hydrogenolysis of the dibenzyl group of (*R*,*S*)-**4a** followed by treatment with di-*tert*-butoxy dicarbonate (Scheme 1). Amongst the known procedures for the epoxidation of 1,2-diols, methods involving Mitsunobu conditions[12] appear the most efficient, but the use of expensive reagents as well as safety concerns prohibit their application on an industrial scale. Cyclization under basic conditions after activation of either of the hydroxy groups has been generally used,[13] although the complete regioselective introduction of the leaving group to the specified hydroxy group is difficult to achieve and leads to a reduction in diastereomeric purity during epoxidation. Furthermore, *threo* (*R*,*S*)-amino epoxide is especially difficult to isolate as pure crystals having a higher solubility than the corresponding *erythro* isomer. The stereospecific conversion of (*R*,*S*)-amino diols to

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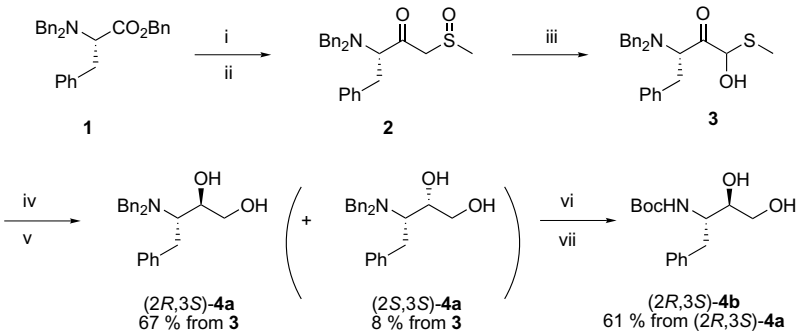
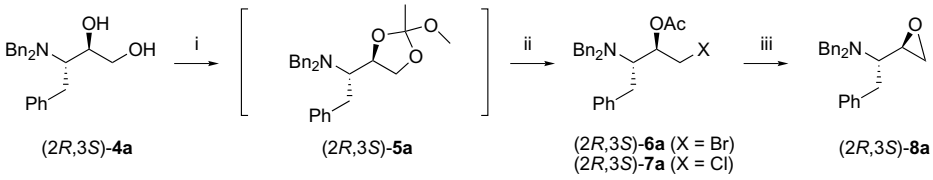


Scheme 1. Preparation of the *N*-protected *threo* (2*R*,3*S*)-amino diols **4a** and **b**. Reagents and conditions: (i) DMSO, $NaNH_2$, THF, 0 °C; (ii) 10% citric acid aq; (iii) 2 M HCl, DMSO, ambient temp; (iv) $NaBH_4$, EtOH, H_2O, 0 °C; (v) 1 M HCl; (vi) H_2, 5% Pd–C, MeOH, ambient temp; (vii) $(Boc)_2O$, Et_3N, MeOH, ambient temp.

(*R*,*S*)-amino epoxides is thus a target of significant interest. Acetoxy halogenation reactions of vicinal hydroxy groups are occasionally used for the derivatization of nucleosides and sugars[14]—the most common methodology being transformation with α-acetoxyisobutyryl halide. Ghosh et al. reported the application of this method to the synthesis of amino epoxides in moderate yields.[15] We had previously developed an efficient acetoxy bromination method that proceeds via the methoxy ethylidene derivative for the synthesis of 2′,3′-dideoxynucleosides.[16] This selective reaction has advantages in terms of the fact that the milder reaction conditions produce fewer by-products and thus presented itself as a potentially promising means of producing (*R*,*S*)-amino epoxides from (*R*,*S*)-amino diols (Scheme 2 and Table 1). The reaction of *N*,*N*-dibenzyl (*R*,*S*)-amino epoxide **4a** with trimethyl orthoacetate in the presence of trifluoroacetic acid afforded the methoxy ethylidene derivative **5a**. Acetyl bromide was then added to the reaction mixture containing **5a**. Regioselective bromination took place at the less sterically hindered carbon and 2-acetoxy 1-bromide **6a** was successfully obtained in 80% from **4a** in two steps. Compound **6a** was treated with potassium carbonate in alcohol to give the desired (*R*,*S*)-amino epoxide **8a** in 98%.[17] No other diastereomeric/enantiomeric isomers of **8a** were detected by HPLC. Compound (*R*,*S*)-**8a** proved readily convertible to the diastereomeric isomer (*S*,*S*)-**8b** by Beaulieu and Wernic's method.[5c] The same sequence of reactions using chlorotrimethyl silane instead of acetyl bromide also gave (*R*,*S*)-**8a** via the acetoxy chloride **7a**. *N*-Boc (*R*,*S*)-amino epoxide **8b** was also synthesized from (*R*,*S*)-**4b**, by using pyridinium *p*-toluenesulfonate for methoxy ethylidene formation (Scheme 3). The lower yield in the case of acetoxy bromination is likely to be due to the partial degradation of the Boc group under acidic conditions. The remarkable difference in the acetoxy chlorination reaction was the significant formation of regio isomer (*S*,*S*)-**7c**, which was confirmed[18] by separation of each isomer by silica gel column (Scheme 4).

In conclusion, a practical synthesis of *N*-protected *threo* (2*R*,3*S*)-3-amino-1,2-epoxy phenylbutane has been developed. It involves the diastereoselective reduction of γ-*N*,*N*-dibenzyl amino α-hydroxy β-keto sulfide followed by stereospecific conversion to the amino epoxide via

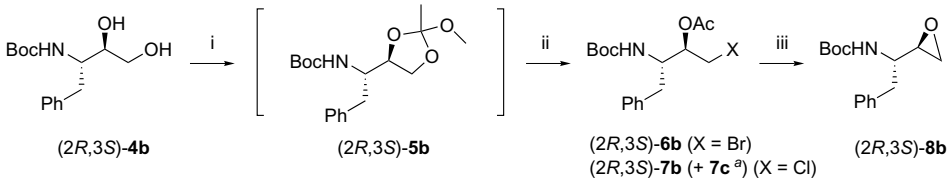


Scheme 2. Preparation of the *N*,*N*-dibenzyl *threo* (2*R*,3*S*)-amino epoxide **8a**. Reagents and conditions: (i) $CH(OMe)_3$, CF_3CO_2H, CH_2Cl_2, ambient temp; (ii) AcBr (X = Br) or Me_3SiCl (X = Cl), CH_2Cl_2, ambient temp; (iii) K_2CO_3, MeOH, ambient temp.

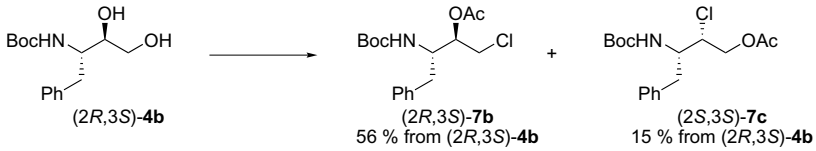
Table 1. Preparation of the *threo* amino epoxide from the *threo* amino diol

Entry	Amino diol	Acetoxy halide			Amino epoxide	
			X	Yield (%)		Yield[a] (%)
1	(*R*,*S*)-**4a**	(*R*,*S*)-**6a**[b]	Br	80	(*R*,*S*)-**8a**	98
2	(*R*,*S*)-**4a**	(*R*,*S*)-**7a**[b]	Cl	71	(*R*,*S*)-**8a**	80
3	(*R*,*S*)-**4b**	(*R*,*S*)-**6b**[b]	Br	57	(*R*,*S*)-**8b**	99
4	(*R*,*S*)-**4b**	(*R*,*S*)-**7b** + (*S*,*S*)-**7c**	Cl	76	(*R*,*S*)-**8b**	89

[a] The optical purity (ee) and the diastereomeric excess (de) of each compound were higher than 98%, as determined by chiral HPLC.
[b] Detailed analysis of the formation of regio isomers was not undertaken. No impurity larger than 5% (peak area vs. product) was detected in HPLC.



Scheme 3. Preparation of the *N*-Boc *threo* (2*R*,3*S*)-amino epoxide **8b**. Reagents and conditions: (i) $CH(OMe)_3$, *p*-TsOH–pyridine, CH_2Cl_2, ambient temp; (ii) AcBr (X = Br) or Me_3SiCl (X = Cl), CH_2Cl_2, ambient temp; (iii) K_2CO_3, MeOH, ambient temp. ([a]See Scheme 4.)



Scheme 4. Formation of the regio isomers **7b** and **c**. Reagents and conditions shown in Scheme 3.

acetoxy halogenation. This method also represents a potential industrial manufacturing process for *threo* amino epoxides, providing a versatile synthesis using safe and inexpensive reagents without the need for a cryogenic reaction.

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11. Typical procedure: to a solution of **2** (94.3 mg, 0.233 mmol) in dimethyl sulfoxide (1.6 mL) was added 2 M HCl (0.4 mL). After the mixture had been stirred for 15 h at ambient temperature, it was cooled in an ice bath and saturated $NaHCO_3$ aqueous solution (1.5 mL) was added. Water (4 mL) and ethyl acetate (8 mL) were added to the mixture and extracted. After the organic layer had been separated, the resulting aqueous layer was extracted twice with ethyl acetate (3 mL). The combined organic layers were washed with water (5 mL) and saturated NaCl aqueous solution (5 mL), then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude **3a**. To a solution of crude **3a** in a mixed solvent of ethanol (2 mL) and water (0.2 mL) was added sodium borohydride (18.4 mg, 0.48 mmol) at 0 °C. After the mixture had been stirred for 50 min at 0–5 °C, 1 M HCl was added to adjust pH to 4.8, and the mixture was concentrated under reduced pressure. Water (5 mL) and ethyl acetate (20 mL) were added to the concentrate and extracted, and the organic layer was washed with saturated NaCl aqueous solution (5 mL), then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. HPLC analysis revealed a diastereomeric ratio of about 10/1. The resulting residue was purified through preparative silica gel thin-layer chromatography to obtain (2*R*,3*S*)-**4a** (56.2 mg, 0.155 mmol, 67% from **2**) and (2*S*,3*S*)-**4a** (7.0 mg, 0.019 mmol, 8% from **2**). ^1H NMR for (2*R*,3*S*)-**4a** (300 MHz, $CDCl_3$) $\delta = 2.7$ (m, 1H), 3.06–3.23 (m, 3H), 3.42 (d, 2H), 3.52–3.60 (m, 2H), 3.99 (d, 2H), 7.21–7.36 (m, 15H). Mass (ESI) *m*/*z* 362 (MH^+).
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17. Typical procedure: to a solution of (2*R*,3*S*)-**4a** (569.4 mg, 1.575 mmol) in dichloromethane (16 mL) were added trimethyl orthoacetate (0.5 mL) and trifluoroacetic acid (0.13 mL). After the mixture had been stirred for 4 h at ambient temperature, it was concentrated under reduced pressure. To a solution of the resulting residue in dichloromethane (14 mL) acetyl bromide (1.29 mL) in dichloromethane (2 mL) was added dropwise for 4 min. After the mixture had been stirred for 5 h at ambient temperature, saturated $NaHCO_3$ aqueous solution (16 mL) and dichloromethane (10 mL) were added to the mixture and extracted. The organic layer was washed with saturated NaCl aqueous solution (15 mL) and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography to obtain (2*R*,3*S*)-**6a** (588.4 mg, 1.262 mmol, 80% from (2*R*,3*S*)-**4a**). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.16$ (s, 3H), 2.66 (dd, 1H), 3.10 (dd, 1H), 3.17–3.25 (m, 2H), 3.49 (d, 2H), 3.59 (dd, 1H), 4.04 (d, 2H), 5.05 (m, 1H), 7.14 (m, 2H), 7.19–7.35 (m, 13H). Mass (ESI) m/z 466 (MH^+). To a solution of (2*R*,3*S*)-**6a** (75.1 mg, 0.161 mmol) in methanol (1.6 mL) was added potassium carbonate (45 mg). After the mixture had been stirred for 2 h at ambient temperature, suspended matter was removed by filtration, and the filtrate was concentrated under reduced pressure. Water (5 mL) and ethyl acetate (10 mL) were added to the residue and extracted. The organic layer was washed with saturated NaCl aqueous solution (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain (2*R*,3*S*)-**8a** (54.1 mg, 0.158 mmol, 98% from (2*R*,3*S*)-**6a**). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.20$ (dd, 1H), 2.59 (dd, 1H), 2.69–2.80 (m, 1H), 2.98 (m, 1H), 3.15 (m, 1H), 3.82 (d, 2H), 3.88 (d, 2H), 7.00–7.04 (m, 2H), 7.17–7.33 (m, 13H). Mass (ESI) m/z 344 (MH^+).
18. The structure of **7c**, which only consists of a single diastereomer was determined by NMR. Absolute configuration is based on the original configuration in L-Phe.