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A Convergent, Stereocontrolled Synthesis of C_2-Symmetrical and Pseudosymmetrical Sulfur-Tethered Bis(amino alcohols)

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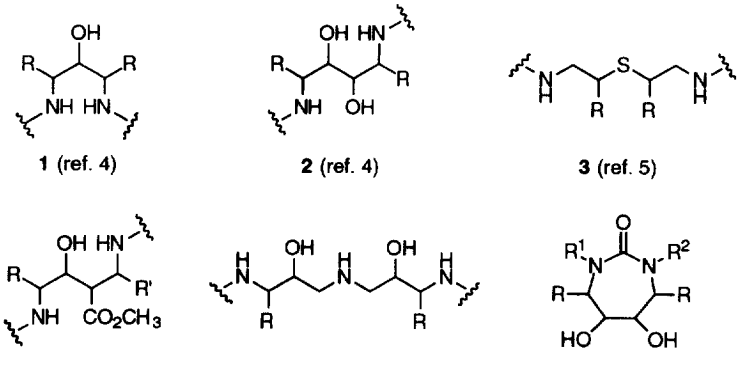
Abstract: The totally enantiocontrolled preparation of C_2-symmetrical and pseudosymmetrical sulfur-tethered bis(amino alcohols) from *anti*-3-amino-1,2-alkane diols is described. The key step in the synthetic procedure involves the use of triphenylsilanethiol as a sulfide or hydrogenosulfide equivalent in the regioselective nucleophilic ring opening of both *anti*- and *syn*-aminoalkyl epoxides.

Key words: *Amino alcohols; asymmetric synthesis; enzyme inhibitors; sulfides*

In recent years, much effort has been devoted to the search of clinically effective inhibitors of the essential aspartic protease of the human immunodeficiency virus (HIVPR).[1] As result of these studies, several potent HIVPR inhibitors have been identified, and some of these are currently being used, in combination with reverse transcriptase inhibitors, as chemotherapeutic agents for the treatment of acquired immune deficiency syndrome (AIDS).[2] One of the most successful strategies in the design of HIVPR inhibitors has been based on the inherent C_2 symmetry of the enzyme homodimer, first disclosed in 1989.[3] Since then, a great variety of compounds having C_2-symmetrical or pseudosymmetrical cores have been synthesized and their biological activity has been studied (Fig. 1).[4-8]



1 (ref. 4) **2** (ref. 4) **3** (ref. 5)

4 (ref. 6) **5** (ref. 7) **6** (ref. 8)

Fig.1: Selected types of C_2-symmetrical and pseudosymmetrical amino alcohol-based HIVPR inhibitors.

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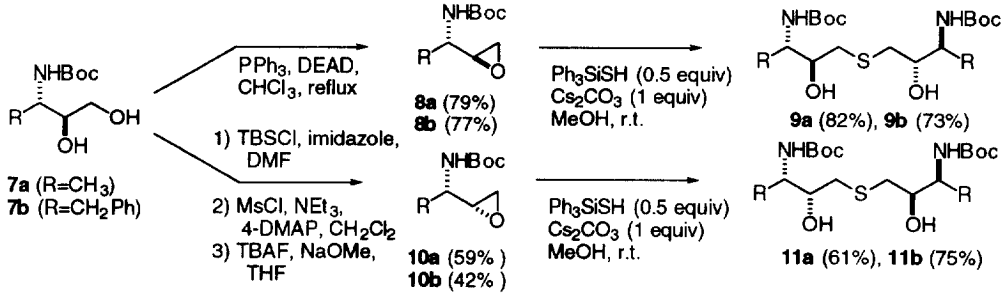
However, since it has been shown that HIV can easily generate mutant varieties with diminished sensitivity to the known protease inhibitors,[9] there is currently an urgent need for uncovering new structural types of inhibitors. We have recently described the application of enantiopure *anti*-3-amino-1,2-alkanediols, easily available chiral synthons[10] whose chemistry we have been exploring over the past few years, to the synthesis of the hydroxyethylene dipeptide isostere unit present in several aspartic protease inhibitors.[11] We report here a convergent and totally enantiocontrolled approach to both C_2-symmetrical and pseudosymmetrical sulfur-tethered bis(amino alcohols), a new class of diamino diol dipeptide isostere that combines structural features present in several pseudopeptide HIVPR inhibitors and that can also be of interest from the point of view of asymmetric catalysis.[12,13] In the following paper,[14] we describe the preparation of the structurally related 1,6-diamino-2,5-diols.

The synthesis of C_2-symmetrical, sulfur-tethered bis(amino alcohols) from *N*-Boc *anti*-3-amino-1,2-diols is depicted in Scheme 1. The intramolecular Mitsunobu reaction of **7a** (PPh_3, DEAD, refluxing $CHCl_3$)[15] afforded the *anti*-epoxide **8a** in 79% yield. When a methanolic solution of **8a** was treated with 0.5 equivs. of triphenylsilanethiol[16] in the presence of cesium carbonate (1 equiv.) at room temperature for 24 hours, the bis(amino alcohol) **9a**, arising from the sequential nucleophilic opening of two oxirane rings, was cleanly obtained in high yield (82%). The enantiomeric excess of **9a**, measured by differential scanning calorimetry, was higher than 98.7%. In a similar way, highly enantiopure **9b** (e.e. > 99.9%) was prepared from amino diol **7b**. It is interesting to note that the absolute stereochemistry of both **9a** and **9b** (*S,S,S,S*) corresponds to that giving maximal activity to HIVPR inhibitors within the structural class represented by **5** (see Figure 1).[7] The diastereomeric (*S,R,R,S*) bis(amino alcohols) **11a** and **11b** could also be obtained from the *syn*-(aminoalkyl)epoxides **10a** and **10b**, that were readily secured from **7a** and **7b** via a three-step synthetic sequence involving silylation of the primary alcohol, mesylation of the remaining hydroxyl and concomitant desilylation-cyclization with tetrabutylammonium fluoride-sodium methoxide.[15] Since the enantiomers of the starting amino diols can be easily accessed by simply changing the tartrate ligand of the catalytic asymmetric epoxidation step,[10] the present route allows the totally enantiocontrolled preparation of any stereoisomer of a given C_2-symmetrical, sulfur-tethered bis(amino alcohol).

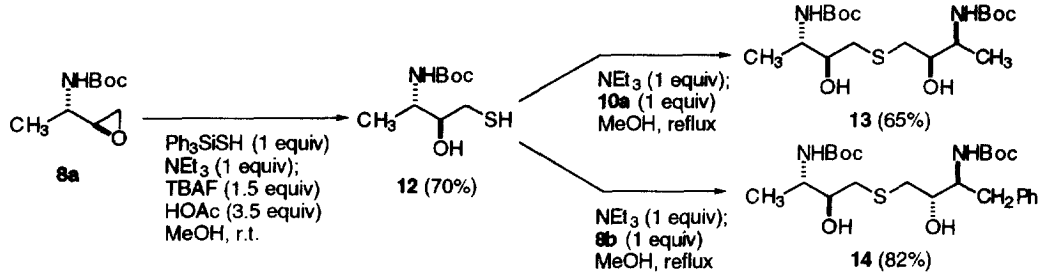
Scheme 1



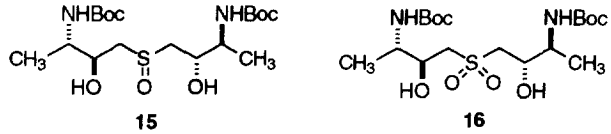
This synthetic scheme could also be easily adapted to the assembly of pseudosymmetrical bis(amino alcohols), as exemplified by the preparation of compounds **13** and **14** (Scheme 2). The reaction of epoxide **8a** with 1 equivalent of triphenylsilanethiol in the presence of triethylamine produced a mixture of *O*- and *S*-silylated hydroxythiols[16] that was desilylated *in situ* (tetrabutylammonium fluoride/acetic acid) to give the hydroxythiol **12** in good yield (70%). We were then pleased to find that the triethylammonium thiolate derived from **12** cleanly

effected the regioselective nucleophilic opening of oxiranes **10a** and **8b**, affording, respectively, the bis(amino alcohols) **13** (65% yield) and **14** (82% yield).

Scheme 2



Finally, it is worth noting that increasing the oxidation state of the sulfur atom can give rise to other types of symmetrical bis(amino alcohols). Thus, for instance, compound **9a** was easily transformed into sulfoxide **15** (2 equivs. of *tert*-butylhydroperoxide, 0.1 equivs. of camphorsulfonic acid, 93% yield) and into sulfone **16** (2.5 equivs. of *m*-chloroperbenzoic acid, 85% yield).[17]



In summary, the ready availability of the starting materials (ultimately derived from (*E*)-allyl alcohols), the complete control on the stereochemistry of all of the stereogenic centers, and the convergent nature of the synthetic scheme render the present method especially suitable for the preparation of a rich library of sulfur-tethered bis(amino alcohols). This hitherto unknown class of compounds can be of great interest both in connection with the preparation of new HIVPR inhibitors and as chiral ligands for asymmetric catalysis.

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