A New Asymmetric Synthesis of α-Methylcysteines via Chiral Aziridines

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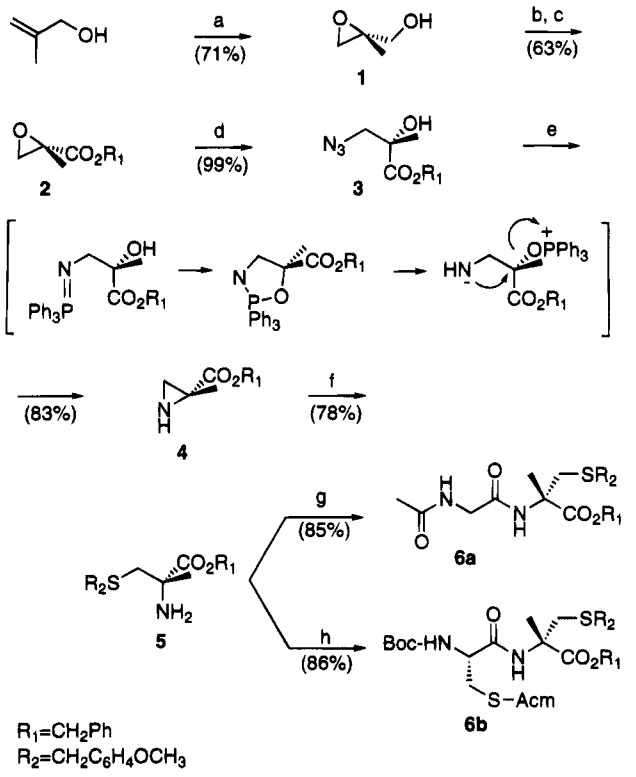
Received December 16, 1994

An important rationale for peptidomimetic ligand design involves the incorporation of conformationally constrained amino acids into the peptide sequences.[1] The employment of a chiral α,α-disubstituted amino acid in a peptide severely restricts rotation around the N–C^{α} (ϕ) and C^{α}–C(O) (ψ) bonds of the amino acid and stabilizes preferred conformations of the peptide backbone. Such unnatural amino acids in peptide hormone sequences can also make peptide bonds more resistant to enzymatic degradation. Among them, α-methylcysteine and derivatives are attractive target molecules because they can form further constrained cyclic peptide structures via disulfide bridge formation. This α-methyl amino acid residue will facilitate conformational analysis and the development of structure–activity relationships of bioactive peptides by molecular modeling and NMR studies. In addition, Heathcock and Pattenden showed that α-methylcysteine is an important building block for a new family of natural products, thiangazole, tantazoles, and mirabazoles, which exhibit antitumor and anti-HIV-1 activities.[2] Heathcock has recently reported the total syntheses of (−)-thiangazole[2a] and (−)-mirabazole B[2b] and C.[2c] At the same time, Pattenden and co-workers described their syntheses of thiangazole,[2d] didehydromirabazole A,[2e,f] and (*S*)-desferrithiocin[2g] with α-methylcysteines by a completely different strategy.

Because of the labile nature of the sulfhydryl group, very few routes have been successfully applied for the asymmetric synthesis of α-methylcysteine.[3] Seebach and co-workers[4] were unsuccessful in their attempts to prepare such molecules by asymmetric alkylation of chiral thiazolidines because of β-elimination under the reaction conditions. But Pattenden *et al.* observed that *N*-formylthiazolidine can produce the desired α-methylcysteine under similar conditions,[2g] and they also showed the result of the X-ray examination of the intermediate and the synthetic route for other α-substituted cysteine analogs.[5] Our desire to prepare protected α-substituted amino acids suitable for peptide syntheses leads us to explore a general synthetic strategy. In this paper, we describe a new asymmetric synthesis of protected α-methylcysteine derivatives based on chiral aziridine synthons.

Scheme 1[a]



[a] Reagents: (a) tBuOOH, D-DET, $Ti(OiPr)_4$, CH_2Cl_2; (b) $RuCl_3{\cdot}H_2O$, $NaIO_4$; (c) DCC, DMAP, BnOH; (d) NaN_3, EtOH, H_2O; (e) PPh_3, CH_3CN; (f) $BF_3{\cdot}(Et)_2O$, $CH_3OC_6H_4CH_2SH$, CH_2Cl_2; (g) acetylglycine, EDC·HCl, HOBt, DIEA, CH_2Cl_2; (h) Boc-(*R*)-Cys(Acm)-OH, EDC·HCl, HOBt, DIEA, CH_2Cl_2. The enantiomers of compounds **1**–**5** were also prepared with comparable yields by the same procedure as shown above.

Starting with the allylic alcohol, 2-methyl-2-propen-1-ol (Scheme 1), the (*R*)-2-methylglycidol (**1**) was readily obtained in high enantiomeric purity[6] by Sharpless asymmetric epoxidation.[7] Oxidation of **1** with ruthenium(VIII) oxide[8] provided the corresponding carboxylic acid **2** (R_1 = H). The carboxylic acid was converted without further purification to the benzyl ester **2** by the standard carbodiimide esterification method.[9] Treatment of benzyl (*S*)-2-methyl-2-oxirane carboxylate (**2**) with sodium azide resulted in regioselective ring opening to form the azido alcohol **3** as was first shown by Rapoport[10] and later by others.[11,12] No partial hydrolysis or trans-

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esterification was observed. Refluxing the azido alcohol **3** with triphenylphosphine in acetonitrile[12] generated the benzyl aziridinecarboxylate (**4**). Overall, the transformation of the epoxide to the aziridine occurs with no loss of enantiomeric purity[6,12] and in good to excellent overall yields.

With the aid of a Lewis acid, the ring opening of benzyl aziridine-2-carboxylate with a thiol predominantly occurs at C-3 in an S_N2 fashion.[6,12] Regioselective ring opening of the chiral aziridine **4** with 4-methoxy-α-toluenethiol and boron trifluoride etherate resulted in the desired (*S*)-α-methylcysteine (**5**). The enantiomers of **1**–**5** were also synthesized based on Scheme 1 using diethyl L-tartrate in Sharpless asymmetric epoxidation. Both enantiomers were obtained in excellent optical purities. These protected α-methylcysteine derivatives are useful building blocks for peptide synthesis. For example, two dipeptides (**6a** and **6b**) containing (*S*)-2-methyl-S-(*p*-methoxybenzyl)cysteine were prepared in excellent yield[13] (Scheme 1).

In summary, we have developed a novel and efficient approach for the asymmetric synthesis of α-methylcysteine derivatives using chiral aziridines. We demonstrated that these compounds can be applied to the preparation of peptide derivatives. This methodology provides a general strategy for the design of other α-substituted amino acid derivatives starting from appropriate allylic alcohols.

Acknowledgment. We thank Drs. K. Barry Sharpless, Zhi-min Wang (Scripps Research Institute), and Yitzhak Tor (UC, San Diego) for helpful discussions. We also thank Drs. Richard Kondrat (UC, Riverside) and Yunfei Zhu (Bioresearch, Inc.) for mass spectroscopic analyses and IR spectra, respectively. This work was supported by NIHDK-15410.

Supplementary Material Available: Experimental procedures and characterization data (6 pages).

JO942119U

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