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SYNTHESIS OF A NEW SULFUR-CONTAINING DIPEPTIDE ANALOGUE

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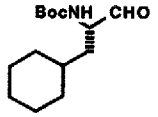
Summary: The synthesis of a sulfur-containing Cha-Ala isostere is reported (Cha = cyclohexylalanine). The diastereoconversion of a *N*-2-Boc-amino alcohol has been achieved by treatment with methanesulfonyl chloride in pyridine resulting in the corresponding oxazolidin-2-one with inverted stereochemistry at the carbinol carbon.

Dipeptide analogues are currently the subject of much interest both in the pharmaceutical industry and in academia[1]. This is warranted by the potential for obtaining therapeutically active drugs by incorporating these moieties in transition state analogues[2] and metabolically stable peptides[3]. Our interest in this field derives from our involvement in the search for orally active renin inhibitors. Based on structure-activity relationships, short Cha-Ala derived isosteres were considered to be of interest[4]. We now wish to report the synthesis of one such sulfur-containing replacement, **8**.



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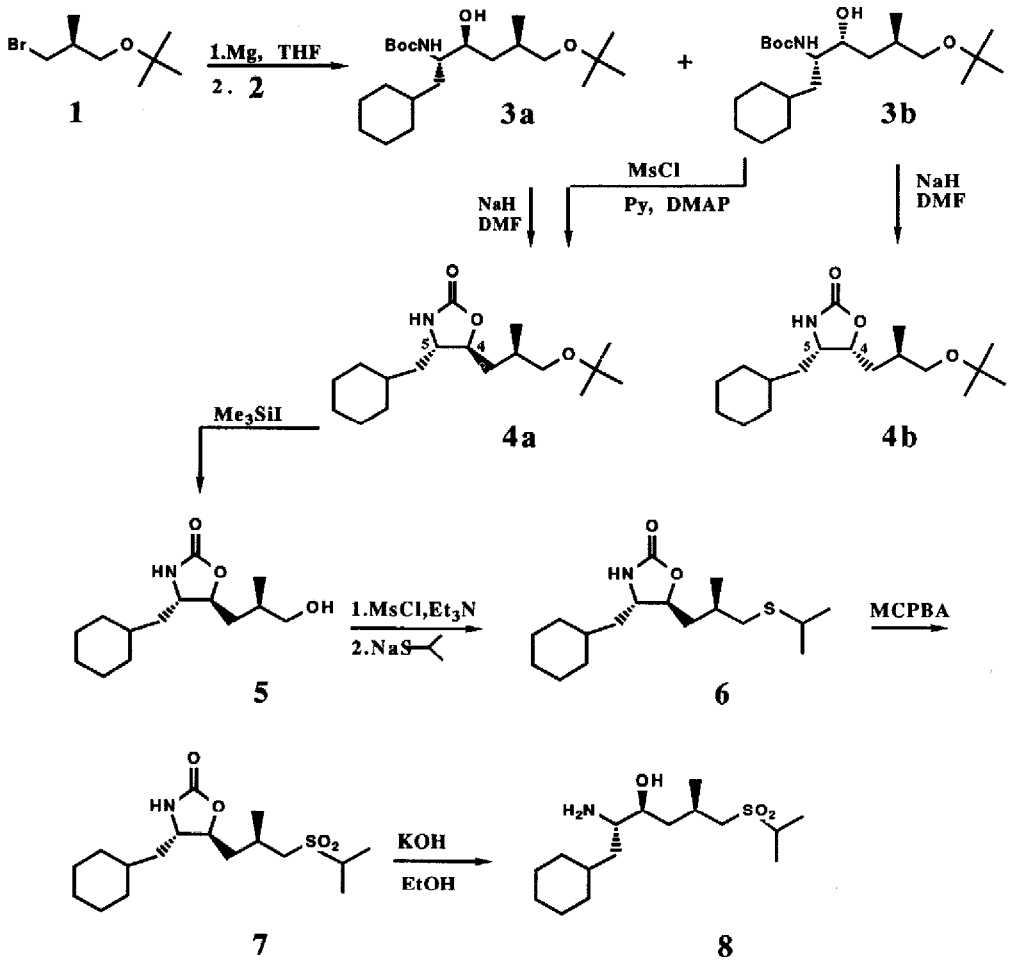
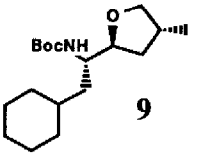
The key step in the synthesis was the addition of 2.5 eq of the Grignard reagent derived from the bromo ether **1**[5] to Boc-(*S*)-cyclohexylalaninal **2**[6,7] (THF, <10°C) (Scheme 1). The diastereomeric alcohols **3** were obtained in a 6:1 ratio (threo:erythro) and were separated by flash chromatography on silica gel (petroleum ether 40-60°C - EtOAc 5:1) giving the desired threo alcohol **3a** in 40 % yield and the epimer **3b** in 7 % yield, both as oils. The preference for the threo alcohol could be explained by a chelation-controlled addition of the Grignard reagent to the aldehyde[8]. Treatment of **3a** and **3b** with sodium hydride in dry DMF at room temperature overnight effected ring closure to **4a** and **4b**, respectively. The stereochemistry at the hydroxy-substituted carbon of the epimers **3** was assigned on the basis of $J_{4,5}$ in the ^{1}H-NMR spectra of these oxazolidinones. Thus, **4a** showed a coupling constant of 5.7 Hz, clearly indicative of the desired threo configuration, while the corresponding value for **4b** was 7.5 Hz, which suggests an erythro configuration[9].



Scheme 1

In view of the fairly low yield of **3a** it was highly desirable to find a way of making use of both epimers by inverting the stereochemistry of the hydroxy group of **3b**. Recently, Kano et al.[10] published a method for converting (1*R*,2*S*)-*N*-Cbz-2-amino alcohols into the epimeric (1*S*,2*S*)-2-amino alcohols. The former were treated with trifluoromethanesulfonic anhydride in methylene chloride, or better yet with thionyl chloride, giving (1*S*,2*S*)-oxazolidinones via a cyclocarbamation reaction. We wished to convert **3b** into **4a** in a similar reaction. However, treatment of **3b** with thionyl chloride in toluene, in the presence of triethylamine to conserve the Boc group, at 70°C for 12 h gave mainly the tetrahydrofuran **9** with a minor amount of **4a**. On the other hand, when **3b** was reacted with methanesulfonyl chloride and 1 mol% of DMAP in pyridine at 60–65°C for 4.5 h compound **4a** was obtained in 72 % yield after flash chroma-

tography (silica gel, petroleum ether 40–60°C – EtOAc 4:1), thus allowing us to use both diastereomeric alcohols obtained from the Grignard addition. A small amount of compound **9** was formed even under these conditions. The stereochemistry of **9** was determined by NOE enhancement studies.



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Cleavage of the t-butyl group of **4a** by trimethylsilyl iodide in methylene chloride for 30 min gave the alcohol **5** as an oil which crystallized upon standing. The overall yield from **3a** after flash chromatography on silica gel (EtOAc) was 75 %. Compound **5** was mesylated (MsCl, Et_3N, CH_2Cl_2) and subsequently treated with sodium isopropylthiolate in dry THF. The resulting sulfide **6** was oxidized with meta-chloroperbenzoic acid to give sulfone **7**. Finally, we obtained compound **8** by refluxing **7** overnight in ethanolic potassium hydroxide. Flash chromatography on silica gel (MeOH–EtOAc 1:1) gave the desired compound as a crystalline material in 68 % overall yield from **5**[11].

In conclusion, a potentially useful and effective method for synthesizing novel types of Cha–Ala derived isosteres has been achieved. The isostere prepared above has subsequently been successfully incorporated into a number of renin-inhibiting structures. The results of this work will be published elsewhere.

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