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Synthesis of α-Substituted β-Amino Acids Using Pseudoephedrine as a Chiral Auxiliary

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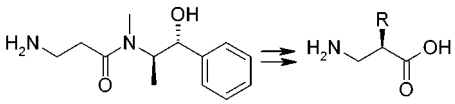
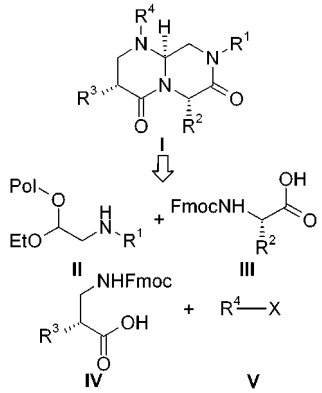
ABSTRACT



β-Amino acids are becoming increasingly attractive as intermediates in the synthesis of a variety of molecular structures. However, few methods are available for the synthesis of α-substituted β-amino acids that are both readily scalable and highly stereoselective. Herein we report a new method for synthesizing α-substituted β-amino acids that satisfies both of these requirements using enantiomerically pure pseudoephedrine as a chiral auxiliary.

During the course of our investigations of mimetics for a number of protein motifs,[1] we have identified the [4.4.0]-heterobicyclic system **I** as a new class of constrained β-turn mimetics.[1c] These compounds were synthesized on a solid support from components **II**−**V** as shown in the retrosynthetic scheme (Scheme 1).

Scheme 1



This approach to the synthesis of **I** allowed for a considerable amount of diversity at the *i*, *i* + 2, and *i* + 3 positions, **V**, **III**, and **II**, respectively, from commercially available intermediates. However, the amount of diversity at the *i* + 1 position (**IV**) from commercially available materials was severely limited. The few commercially available α-substituted β-amino acids were racemic mixtures or prohibitively expensive or both. Hence we initiated a program to identify methods for the rapid and efficient enantioselective synthesis of α-substituted β-amino acids.

The synthetic methods used to obtain compounds such as **IV** should be useful for synthesizing β-amino analogues of most natural and many unnatural α-amino acids. Ideally the synthesis of these derivatives would proceed through a common intermediate. Of the two most commonly used asymmetric methods for synthesizing α-substituted β-amino acids, enolate alkylation,[2] or Mannich chemistry,[3] only the former would allow several analogues of **IV** to be prepared from a common intermediate. Unfortunately, there have been

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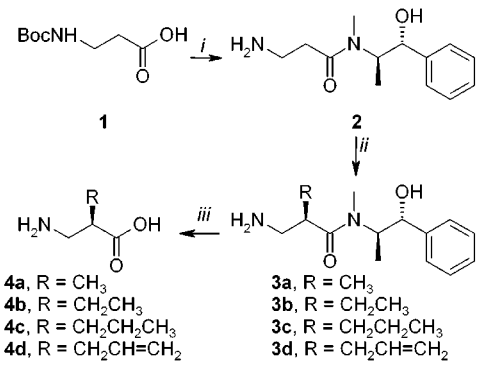
relatively few reports of the asymmetric alkylation of β-alanine or its derivatives. Those syntheses described in the literature using Oppolzer's sultam,[4] Evans' chiral auxiliary,[5] or Seebach and Juaristi's chiral pyrimidinone methodology appeared to give highly scalemic α-substituted β-amino acids.[6] However, the enolate derived from Oppolzer's sultam was reportedly unstable at temperatures greater than −45 °C. Moreover, Evans' chiral auxiliary was prohibitively expensive for the large-scale synthesis of these derivatives, while the hydrogenation conditions required for the preparation of the chiral pyrimidinone derivatives did not scale well in our hands. Hence, these methodologies appeared to be unacceptable for the preparation of bulk quantities (>100 g) of these β-amino acid analogues.

Myers has shown pseudoephedrine to be an efficient and inexpensive chiral auxiliary in the stereoselective synthesis of unnatural α-amino acids.[7] Moreover, this methodology has been extended to the synthesis of chiral β-hydroxy acids[8] and chiral α-substituted acids.[9] These reports suggested that the use of pseudophedrine as a chiral auxiliary should be applicable to a wide variety of substrates, including β-amino acids.

We have found that the extension of this method to the alkylation of β-alanine provides an inexpensive, efficient, and enantioselective route to α-alkyl β-amino acids (Scheme 2). Boc-β-alanine (**1**) was coupled to (*R*,*R*)-pseudoephedrine

Scheme 2[a]



[a] (*i*) (1*R*,2*R*)-(+)-Pseudoephedrine, PvCl, TEA, THF, 0 °C; HCl, 1:1 H_2O/CH_3OH; (*ii*) R−X (X = Br, I), LHMDS, LiCl, THF, −5−0 °C; (*iii*) H_2O, △.

(**2**) using a mixed anhydride method.[7b] Deprotection of the amine was accomplished with HCl, and the final product was obtained after recrystallization from toluene. Lithiation of the pseudoephedrine amide **2** was accomplished with LiHMDS in the presence of excess LiCl.[8] The alkylation step generally gave the desired product in good yield and with a high degree of stereoselectivity (Table 1).

Table 1. Overall Yields from **2** and Optical Rotations and Enantiomeric Excesses of **4a**−**d**

product	R−X	yield (%)[a]	$[\alpha]^n_D$ (deg), *n*	ee (%)
4a	CH_3I	74	−12.6, 26[b]	84
4b	CH_3CH_2I	74	−2.9, 26	94
4c	$CH_3(CH_2)_2I$	63	3.5, 27	>99
4d	$CH_2{=}CHCH_2Br$	52	−4.6, 26	75

[a] Yield from pseudoephedrine amide **2**. [b] Lit. $[\alpha]^{29}_D = -11.8$ (c = 1, 1.1 M HCl).[2]

Analysis of the diastereomeric excesses of **3a**−**d** proved to be nontrivial. Determination of the de values of the pseudoephedrine amides by their ^{1}H NMR spectra was complicated by the presence of rotational isomers.[7a] These rotational isomers sufficiently complicated the ^{1}H NMR spectra of the amides such that key signals could not be resolved. Moreover, the diastereomeric protons of MTPA ester **5** (from the reduction/esterification of Fmoc-**4a**) were also unresolvable by ^{1}H NMR. The diastereomeric separations of Marfey's derivative **6**,[10] pseudoephedrine amide **3a**, and **7** were not achieved by HPLC (Figure 1). The diastereomeric separations of **5**−**7** by chiral HPLC on a Leucine Pirkle column were also unsuccessful. The enantiomeric excess was finally determined by GC/MS of the trifluoroacetamide−isopropyl ester derivatives **8a**−**d** of amino acids **5a**−**d** on a Chirasil-Val capillary GC column (Table 1).

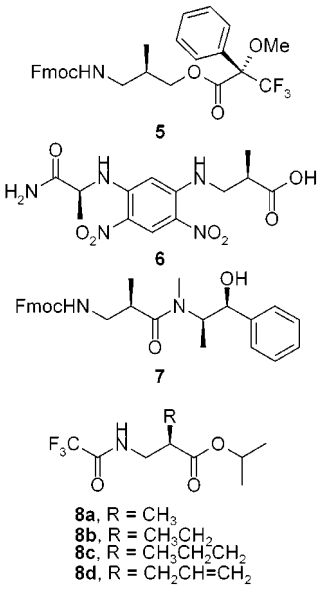


Figure 1. β-Amino acid derivatives used to determine ee values.

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In conclusion, (*R*,*R*)-pseudoephedrine appears be an effective chiral auxiliary for the enantioselective preparation of α-substituted *β*-amino acids from *β*-alanine. Further examples are being explored as part of our efforts to mimic both natural and unnatural amino acid side chains and will be reported in due course.

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Supporting Information Available: Experimental details and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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