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A stereoselective synthesis of bis-β-amino acids

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Abstract

Enantiopure bis-β-amino acids (**5a–c**) were prepared from chiral bis-sulfinimines (**3a–c**) in >97% ee via stereoselective addition of the sodium enolate of methyl acetate followed by hydrolysis. © 1998 Elsevier Science Ltd. All rights reserved.

β-Amino acids are emerging as an important class of compounds due to their presence in a number of interesting natural products as well as for their utility in a variety of critical applications both in synthesis and medicine.[1] Generally, peptidic molecules containing β-amino acids are more stable to enzymatic hydrolysis due to the inability of peptidases to cleave amide bonds adjacent to β-amino acids.[1] Furthermore, recent studies of peptides containing β-amino acids have suggested that the β-peptide helical secondary structure[2] has a richer conformational energy surface than the α-counterpart.[3] The increased biological stability of β-peptides suggests that compounds of this type with recognition-specific side chains will be able to bind to α-peptide receptors.[3] β-Peptides are therefore, intriguing candidates for the development of novel drugs. In view of the above prospects, bis-β-amino acids with *syn/anti* stereochemistry are important building blocks. In this paper, we describe a stereoselective synthesis of (*R*,*R*)-bis-β-amino acids (**5a–c**) from (*S*,*S*)-bis-sulfinimines (**3a–c**).

The strategy for the synthesis of bis-β-amino acids (**5**) (Scheme 1) involves stereoselective addition of the sodium enolate of methyl acetate[4] to a bis-sulfinimine (**3**) to give bis-sulfinamide (**4**), followed by removal of the sulfinate auxiliary. The required bis-sulfinimines (**3a–c**) were realized from the chiral sulfinate ester (Andersen reagent **1**) according to the procedure developed by Davis et al.[5] for the preparation of mono-sulfinimines. Thus, (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate (**1**) was treated (Table 1) with LiHMDS in THF at −78°C and the mixture was stirred for 5 h at room temperature. A solution of bis-aldehyde (**2a–c**, 0.5 equiv.) in THF was then added at −78°C. After stirring the mixture for 3 h at −78°C, the reaction was quenched with water and the crude product was purified by silica gel column chromatography or crystallization[6] to afford (*S*,*S*)-bis-sulfinimines (**3a–c**, entries 1, 2 and 4) in 43–46% yield and >97% ee.[7,8] Similarly, the (*R*,*R*)-(+)-bis-sulfinimine (**3b**, entry 3) was also prepared

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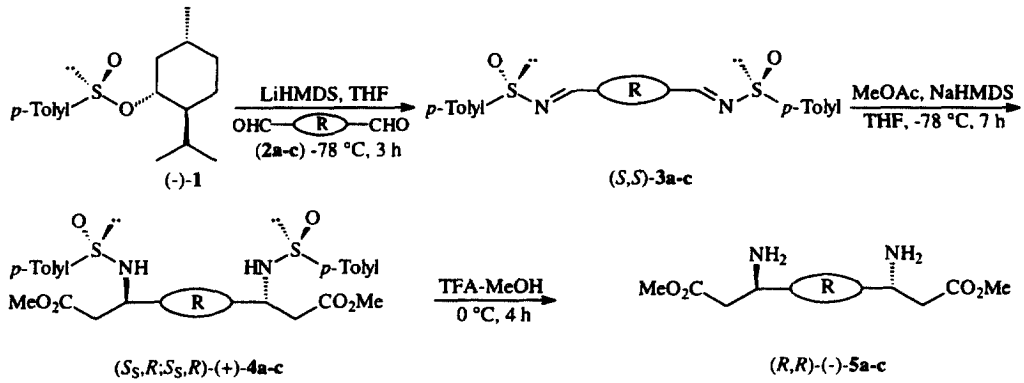
from (1*S*,2*R*,5*S*)-(+)-menthyl-(*R*)-*p*-toluenesulfinate (**1**) and teriphthaladehyde (**2b**) in 40% yield and >97% ee as a crystalline product.[6,8]



2a: Isophthaladehyde; **2b**: Teriphthaladehyde; **2c**: 2,6-Naphthalenedicarboxaldehyde
R = **a**: 1,3-Phenyl; **b**: 1,4-Phenyl; **c**: 2,6-Naphthyl

Scheme 1.

The bis-β-amino esters **5a–c** were prepared by addition of (*S*,*S*)-bis-sulfinimines **3a–c** in THF to a −78°C solution of the sodium enolate of methyl acetate generated using NaHMDS in THF. After stirring the mixture for 7 h at −78°C, the reaction was quenched with saturated aq. NH_4Cl. The resulting diastereomeric mixture of sulfinamides **4a–c** were separated by preparative reverse phase HPLC (see footnotes c and d in the table) followed by lyophilization to afford the major (S_S,*R*;S_S,*R*)-bis-sulfinamides **4a–c**[9] in up to 46% yield as colorless amorphous powders (Table 1). The diastereomeric ratio of bis-sulfinamides **4a–c** [(S_S,*R*;S_S,*R*):(S_S,*R*;S_S,*S*)] varied from 60:40 to 70:30 (entries 1–4), but the mixture (**4a–c**) was separable by preparative HPLC. The minor (S_S,*R*;S_S,*S*)-bis-sulfinamide diastereomers (**4a–c**), were also isolated in 13–21% yield.[10,11] Although it was previously shown that the enolate addition to mono-sulfinimines in ether solvent proceeds in high stereoselectivity (de>97%),[4] unfortunately, in the present study the insolubility of bis-sulfinimines **3a–c** in ether precluded attempts to reproduce these conditions. Addition of HMPA to the enolate/bis-sulfinimine reaction (ex., **3a**) in THF further lowered

Table 1
Synthesis of bis-β-amino acids (**5a–c**) from bis-sulfinimines (**3a–c**)

Entry	Bis-aldehyde (2), R =	Bis-sulfinimine (3) Yield (%)[a]	Bis-Sulfinamide (4) Isomer ratio[b,c]/Yield (%)[a,d]	Bis-β-amino acids (5) Yield (%)[a,e]/ee (%)[f]/$[\alpha]^{20}_D$[g]		
1.	1,3-Ph	(+)-(*S*,*S*)-**3a** 44	(+)-(S_S,*R*;S_S,*R*)-**4a** 60:40/33	(*R*,*R*)-**5a** 82	>97	-8.0
2.	1,4-Ph	(-)-(*S*,*S*)-**3b** 43	(+)-(S_S,*R*;S_S,*R*)-**4b** 70:30/46	(*R*,*R*)-**5b** 86	>97	-8.87
3.	1,4-Ph	(+)-(*R*,*R*)-**3b** 40	(-)-(R_S,*S*;R_S,*S*)-**4b** 67:33/45	(*S*,*S*)-**5b** 90	>97	+8.71
4.	2,6-Naphthyl	(+)-(*S*,*S*)-**3c** 46	(+)-(S_S,*R*;S_S,*R*)-**4c** 68:32/24	(*R*,*R*)-**5c** 93	>97	-12.9

a) Isolated yield. b) Ratio determined by ^1H NMR and HPLC and the stereochemistry of the minor diastereomer is (S_S,*R*;S_S,*S*), see also Ref. 10, 11. c) The diastereomers were separated by preparative reverse phase HPLC on a Waters Symmetry column (40 x 100 mm) [MeCN:H_2O/40:60/45 mL/min at 254 nm] for **4a-b** and, [MeCN:H_2O/45:55/45 mL/min at 254 nm] for **4c**. d) Yield of the major diastereomer. e) Isolated as bis-TFA salt. f) Ee determined by converting to bis-Mosher's amide. g) Optical rotations were measured in MeOH.

the stereoselectivity. A six-membered chair like transition state mechanism was proposed for the addition of sodium enolate of methyl acetate to mono-sulfinimines by Davis et al.[4a] Therefore, by analogy, the stereochemistry of the major bis-sulfinamide diastereomers **4a–c** was assigned to be (S_S,R;S_S,R) which were obtained from (S,S)-sulfinimines **3a–c**.

The (S_S,R;S_S,R)-bis-sulfinamides **4a–c** were hydrolyzed using trifluoroacetic acid in methanol at 0°C for 4 h followed by HPLC purification[12] to afford the pure (R,R)-bis-β-amino esters (**5a–c**) in 82–93% yield as bis-TFA salts in >97% ee.[13] The enantiomeric purity of (R,R)-bis-β-amino esters (**5a–c**) was determined by converting them to the corresponding bis-β-Mosher's amides by treatment with (S)-(+)-MTP-Cl (3.0 equiv.) and triethylamine (10.0 equiv.) in methylene chloride at room temperature for 3 h, followed by preparative reverse phase HPLC purification in 75–95% yield.[14,15] Similarly, the (S,S)-(+)-bis-β-amino ester (**5b**) was also prepared in good yield and optical purity (>97% ee) from (R,R)-(+)-bis-sulfinimine (**3b**) (Table 1, entry 3) via enolate addition and subsequent hydrolysis with trifluoroacetic acid.[15] In summary, a stereoselective synthesis of enantiopure bis-β-amino acids (**5a–c**), valuable building blocks for the preparation of conformationally enriched peptide mimetics, was described from chiral bis-sulfinimines (**3a–c**) in two steps.

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6. The bis-sulfinimine **3a** was purified by silica gel column chromatography (30% ethyl acetate in hexanes) and **3b–c** were purified by crystallization (twice) from ethyl acetate.
7. All new compounds were characterized by ^{1}H, ^{13}C NMR, mass spectrometry and HPLC and the yield referred to the spectroscopically homogeneous materials.
8. Selected data for bis-sulfinimines (**3**): (S,S)-(+)-**3a**: mp 124–126°C, $[\alpha]_D^{20}$ +82.6 (c 0.64, $CHCl_3$); (S,S)-(−)-**3b**: mp 147–149°C, $[\alpha]_D^{20}$ −143.8 (c 0.92, $CHCl_3$); (R,R)-(+)-**3b**: mp 149–151°C, $[\alpha]_D^{20}$ −147.1 (c 0.85, $CHCl_3$); (S,S)-(+)-**3c**: mp 155–157°C, $[\alpha]_D^{20}$ +154.6 (c 1.12, $CHCl_3$).
9. Selected data for the major sulfinamide diastereomer (**4**): (S_S,R;S_S,R)-(+)-**4a**: mp 47–49°C, $[\alpha]_D^{20}$ +129.08 (c 0.82, $CHCl_3$); (S_S,R;S_S,R)-(+)-**4b**: mp 50–54°C, $[\alpha]_D^{20}$ +122.24 (c 0.67, $CHCl_3$); (R_S,S;R_S,S)-(−)-**4b**: mp 49–53°C, $[\alpha]_D^{20}$ −114.22 (c 0.64, $CHCl_3$); (S_S,R;S_S,R)-(+)-**4c**: mp 78–82°C, $[\alpha]_D^{20}$ +49.16 (c 0.48, $CHCl_3$).
10. Selected data for the minor sulfinamide diastereomer (**4**): (S_S,R;S_S,S)-(+)-**4a**: yield: 20%, mp 45–47°C, $[\alpha]_D^{20}$ +50.32 (c 0.62, $CHCl_3$); (S_S,R;S_S,S)-(+)-**4b**: yield: 21%, mp 50–54°C, $[\alpha]_D^{20}$ +39.84 (c 0.63, $CHCl_3$); (R_S,S;R_S,R)-(−)-**4b**: yield: 20%, mp 52–55°C, $[\alpha]_D^{20}$ −39.57 (c 0.47, $CHCl_3$); (S_S,R;S_S,S)-(−)- **4c**: yield: 13%, $[\alpha]_D^{20}$ +41.52 (c 0.46, $CHCl_3$).
11. The minor sulfinamide diastereomer (S_S,R;S_S,S)-**4** is identical to the minor (S_S,S;S_S,R)-**4** isomer.
12. Preparative reverse phase (RP) HPLC was performed on a Waters, C18 μBondpak, (40×100 mm), using MeCN:0.1% aqueous trifluoroacetic acid 10:90 45 ml min^{-1} at 254 nm.
13. Hydrolysis of the minor diastereomer of (S_S,R;S_S,S)-**4a–c** using trifluoroacetic acid in methanol gave the corresponding *meso*-bis-β-amino esters (**5a–c**) as bis-TFA salts in 75–91% yield with no optical rotation.
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15. Preparative reverse phase HPLC was performed on a Waters C18, Symmetry column (40×100 mm) using MeCN:H_2O (40:60) 40 ml min^{-1} at 254 nm.