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Asymmetric Synthesis of *syn*-(2*R*,3*S*)- and *anti*-(2*S*,3*S*)-Ethyl Diamino-3-phenylpropanoates from *N*-(Benzylidene)-*p*-toluenesulfinamide and Glycine Enolates†

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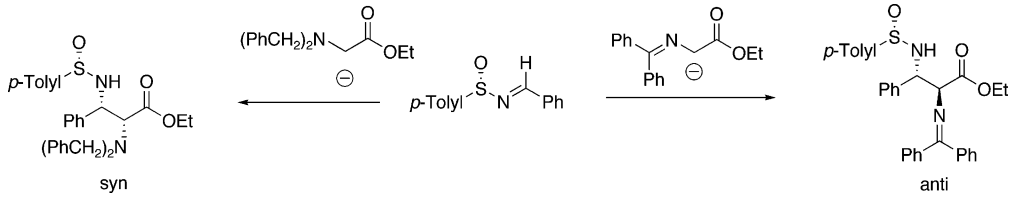
ABSTRACT



Addition of differentially *N*-protected glycine enolates to enantiopure sulfinimines affords *syn- and* anti-α,*β*-diamino esters with high diastereoselectivities and good yields.

α,*β*-Diamino acids are important structural units found in natural products, in peptides,[1] in peptide antibiotics,[1,2] and in medicinally valuable compounds.[3,4] As such, a number of methods, with varying degrees of efficiency, have been devised for their preparation in enantiomerically pure form.[5] Routes to optically active *syn*- and *anti*-α,*β*-diamino acids generally begin with a suitably protected α- or *β*-amino acid.[6,7] The second amino group is then introduced by azide displacement on derived aziridines, on mesylates, or on hydroxyl groups under Mitsunobu conditions, followed by reduction of the azide moiety.[1,6,7] α,*β*-Diamino acids have also been prepared by a catalytic aza-Henry reaction, which involved the addition of alkyl nitro anions to imines.[8,9] Benzophenone imines of glycine are reported to react with certain *N*-sulfonyl imines, in the presence of catalytic chiral copper(I) complexes, to give the syn α,*β*-diamino acids in high ee.[10] Viso and co-workers explored the 1,3-dipolar cycloaddition of glycine iminoester enolates to sulfinimines (*N*-sulfinyl imines) in the presence of $BF_3{\cdot}Et_2O$ to give *N*-sulfinylimidazolidines with good levels of diastereoselectivity.[11] This group recently devised a procedure to transform the 1,3-imidazolidines into *syn*-α,*β*-diamino acids.[5a]

† This work is dedicated to Professor Amos B. Smith III, University of Pennsylvania, on the occasion of his 60th birthday.

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(5) For summaries of the existing literature of the syntheses of α,*β*-diamino acids, see: (a) Viso, A.; de la Pradilla, R. F.; Lopez-Rodrigues, M. L.; Garcia, A.; Flores, A.; Alonso, M. *J Org. Chem.* **2004**, *69*, 1542. (b) Reference 1. (c) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Lett.* **1997**, *38*, 4671.

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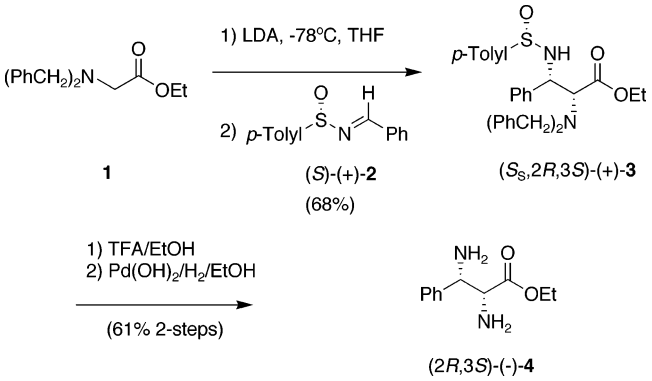
Scheme 1



Glycine ester derivatives are valuable building blocks for the preparation of amino acids via the alkylation and Michael additions of the derived enolates.[12] Therefore, the diastereoselective addition of glycine ester enolates to enantiopure sulfinimines[13] appeared to us to be a potentially attractive method for the asymmetric synthesis of α,*β*-diamino acids because two stereogenic centers could be created in a single operation. Furthermore, there was the possibility that both the syn and anti isomers could be created from a single sulfinimine precursor. We describe here the realization of this objective in concise, highly diastereoselective asymmetric syntheses of *syn*-(2*R*,3*S*)- and *anti*-(2*S*,3*S*)-diamino-3-phenylpropanoates from a benzaldehyde-derived sulfinimine. These diamino acids have been considered to be analogues of the Taxol side chain and provide a way to improve the water solubility of this antitumor compound.[14]

***syn*-Ethyl Diamino-3-phenylpropanonate**. The lithium enolate of ethyl (dibenzylamino)acetate (**1**) was prepared at −78 °C by treatment with the appropriate base and allowed to react at this temperature with (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**2**) (Scheme 1).[15] The formation of four diastereoisomers are possible on the addition of the enolate of **1** to **2**, and ^{1}H NMR of the crude reaction mixtures indicated the presence of all four isomers (Table 1, entries 1−6). Best results were observed using 5.0 equiv of the lithium enolate of **1** generated from LDA or LiHMDS as shown in Table 1. Quenching and chromatographic workup afforded the major syn adduct (+)-**3** in 68% isolated yield (Table 1, entry 2). Subsequent treatment of (+)-**3** with TFA/EtOH to remove the sulfinyl auxiliary and hydrogenation over $Pd(OH)_2$ afforded ethyl (2*R*,3*S*)-(−)-*syn*-2,3-diamino-3-phenylpropanonate (**4**) in 61% yield for the two steps (Scheme 1). The absolute stereochemistry of **4** was established by converting it into a product of known absolute configuration as will be subsequently discussed.

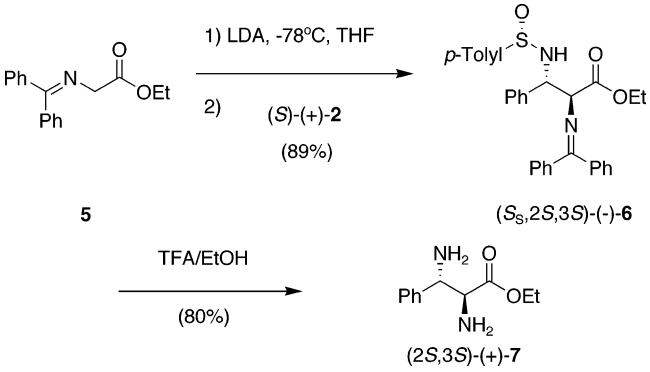
Table 1. Reaction of Glycine Enolates with (*S*)-(+)-*N*-(Benzylidene)-*p*-toluenesulfinamide (**2**) at −78 °C

entry	glycine	conditions base/equiv/solvent	α,*β*-diamino ester (isomer ratio)[a] % isolated yield[b]
1	1	LDA/1.6/THF	(+)-**3** (20:3:2:4) 30[c]
2		LDA/5.0/THF	(20:3:2:3) 68
3		LDA/5.0/Et_2O	(20:4:3:0) 50
4		LiHMDS/5.0/THF	(20:2:2:4) 65
5		NaHMDS/5.0/THF	(20:7:6:7) 80[c]
6		KHMDS/5.0/THF	(20:3:10:6) 76[c]
7	5	LDA/1.1/THF	(−)-**6** (10:0:5:3) 36
8		LDA/1.6/THF	(100:0:2:2) 89
9		LDA/2.0/THF	(10:0:4:3) 34

[a] Estimated from the ^{1}H NMR of the crude reaction mixture by monitoring the C(3) and NH protons. [b] Isolated yield of the pure major diastereoisomer. [c] Conversion yield, isomers not separated.

***anti*-Ethyl Diamino-3-phenylpropanoate.** Addition of the lithium enolate of *N*-(diphenylmethylene)glycine ethyl ester (**5**) to (*S*)-(+)-**2** gave the anti isomer ethyl (2*S*,3*S*)-(−)-*anti*-2,3-diamino-3-phenylpropanonate (**6**) (Scheme 2). The optimum conditions for the synthesis of (+)-**6** required 1.6 equiv of the lithium enolate, which resulted in the formation of a single isomer that was isolated in 89% yield (Table 1, entry 8). Interestingly, when 1.1 or 2.0 equiv of the enolate, respectively, were employed, the diastereoselectivity and yield were significantly reduced (Table 1, entries 7 and 9). Concomitant removal of the *N*-sulfinyl group and hydrolysis of the imine was accomplished on treatment of (+)-**6** with TFA/EtOH affording the diamino ester (+)-**7** in 80% yield (Scheme 2). The absolute stereochemistry of (+)-**7** was

Scheme 2



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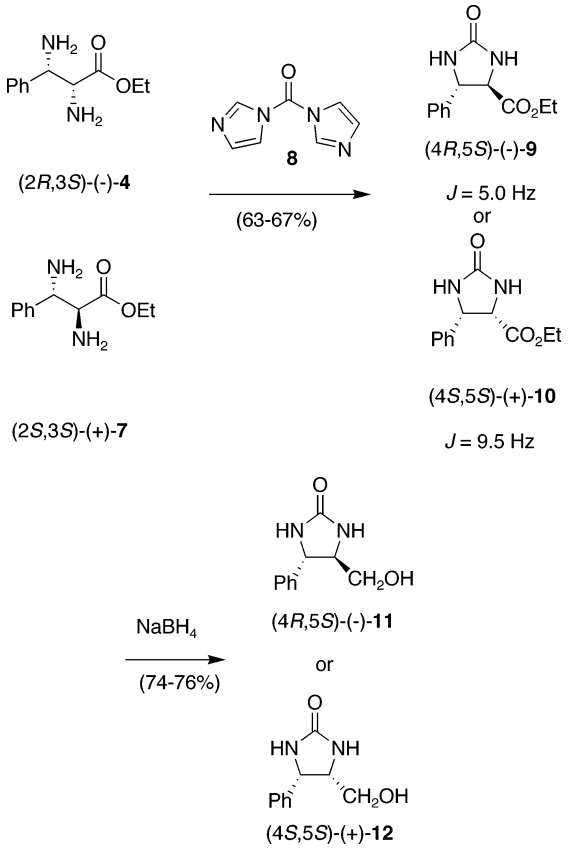
Scheme 3

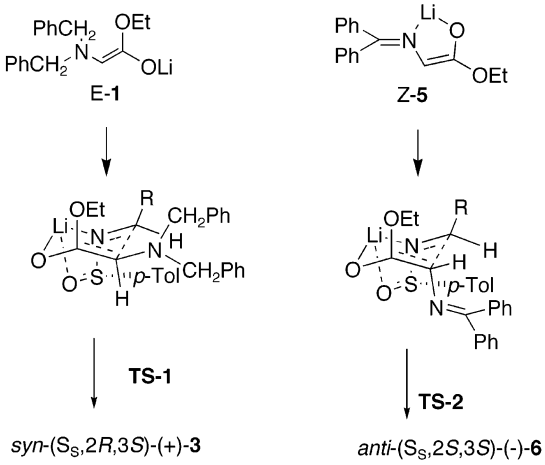


determined by transforming it into a product of known configuration, as discussed in the next section.

Determination of Product Absolute Configuration. The absolute configurations of *syn*- and *anti*-**4** and -**7** were determined as outlined in Scheme 3. Heating **4** and **7** with carbonyl diimidazole (**8**) afforded the corresponding imidazolidin-2-ones **9** and **10** in 62−66% yield. The C-4, C-5 proton- coupling constants of 5 Hz for **9** and 9 Hz for **10** are consistent with their trans and cis relationship, respectively.[14] Finally, reduction of the carbethoxy groups with $NaBH_4$ gave the corresponding alcohols (−)-**11** and (+)-**12**, which were prepared previously by Rossi and co-workers in an unequivocal manner.[16]

Mechanism. The absolute stereochemistry of the product resulting from the addition of organometallic reagents (CN, enolates, Grignard reagents) to sulfinimines is controlled by the *N*-sulfinyl group and predicted by a six-membered chairlike transition state.[13] The opposite sense of stereoinduction is observed for the addition of benzyl Grignards,[17] α-metallo phosphonates,[18] and chloromethyl phosphonate anions[19] to sulfinimines and steric arguments have been

Scheme 4



evoked to explain this stereochemical preference. The 1,3-dipolar cycloaddition of glycine iminoester enolates to sulfinimines, reported by Viso et al. and that leads to *syn*-α,*β*-diamino esters, falls into the latter category.[11]

Nearly exclusive *Re* face addition was observed for reaction of the enolates derived from **1** and **5** to (*S*)-(+)-**2** resulting in the *S*-configuration at C-3 (Table 1). These results are in accord with the six-membered chelate chairlike transition state model (Scheme 4). The syn/anti diastereoselectivity at C-2, which is dependent on the protecting group on the glycine nitrogen atom, can be readily interpreted in terms of the geometry of the enolate. We suggest that the syn/anti selectivity can be explained if **1** and **5** adopt the (*E*)- and (*Z*)-enolate geometries, respectively, in transition states **TS-1** and **TS-2** (Scheme 4).[20] Intramolecular chelation is expected to favor the (*Z*)-geometry in (*Z*)-**5**.[21,22] Garcia Ruano et al. used related arguments to explain the diastereoselectivity of the addition of dienolates to sulfinimines that affords *syn*- and *anti*-α-alkyl *β*-amino esters.[23]

In summary, new methodology has been introduced for the concise asymmetric synthesis of diamino acids, key structural units in natural products, and other biologically active materials. Our procedure calls for the addition of glycine enolates of ethyl (dibenzylamino)acetate (**1**) and *N*-(diphenylmethylene)glycine ethyl acetate (**5**) to enantiopure sulfinimine (*S*)-(+)-**2**. The resulting *syn*- and *anti*-α,*β*-diamino esters are produced in good yield and excellent diastereoselectivity. A mechanistic hypothesis involving the

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(22) Instead of reacting with the sulfinimine as the five membered 1-oxaallylanion (*Z*)-**5** it could also react as the six-membered 2-azaallylanion. See: Ezquerra, J.; Pedregeal, C.; Merino, I.; Florez, J.; Barluenga, J.; Garcia-Granda, S.; Llorca, M.-A. *J. Org. Chem.* **1999**, *64*, 6554.

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addition of the (*E*)- and (*Z*)-enolates of **1** and **5**, respectively, to **2** via a six-membered chairlike transition state is proposed.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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