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Stereocontrolled Synthesis of 2,3-Diaminobutanoic Acids.

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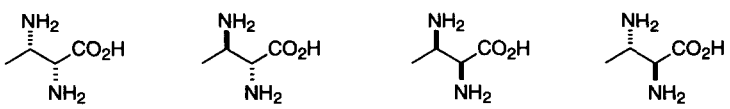
Abstract: A straightforward synthesis of 2,3-diaminobutanoic acids is reported. The synthesis is based on the nucleophilic addition of methylmagnesium bromide to differentially protected nitrones derived from L-serine. The change of the protecting groups in the starting nitrone is crucial for the stereocontrol of the reaction.

α,β-Diamino acids occupy a notable place among the non-proteinogenic amino acids due to their presence in a variety of natural products.[1] They are constituents of several antibiotics,[2] antifungal dipeptides[3] as well as other biologically active molecules.[4] In particular, 2,3-diaminobutanoic acids **1** have proven to be of interest because they form part of some peptide antibiotics and toxins.[5]

Though several methods of preparing α,β-diamino acids are known,[4-6] only a few offer the possibility of accessing to both *syn* and *anti* diamino acid units. Schmidt and co-workers[6f,g] reported the synthesis of 2,3-diaminobutanoic acids **1** starting from threonine. Since the introduction of the second amino group is made by a Mitsunobu reaction, only the *anti* isomers **1b,d** were accessible (depending on the enantiomer used as starting material) and *allo*-threonine had to be used in order to obtain the *syn* isomers **1a,c**. Shin and co-workers[5a,b] described the synthesis of the four possible isomers of **1** using as starting material L-threonine and its antipode. However, this methodology seems to be too intricate since a double inversion was needed to achieve the desired absolute configuration in the preparation of the *syn* diastereomers **1a,c**. More recently, Davies and co-workers[5c] have reported the synthesis of both epimers **1a,d** based on the asymmetric addition of a chiral lithium amide to tert-butyl crotonate, the introduction of the second amino group being achieved either by using trisyl azide as an electrophilic nitrogen source or by a Mitsunobu reaction.



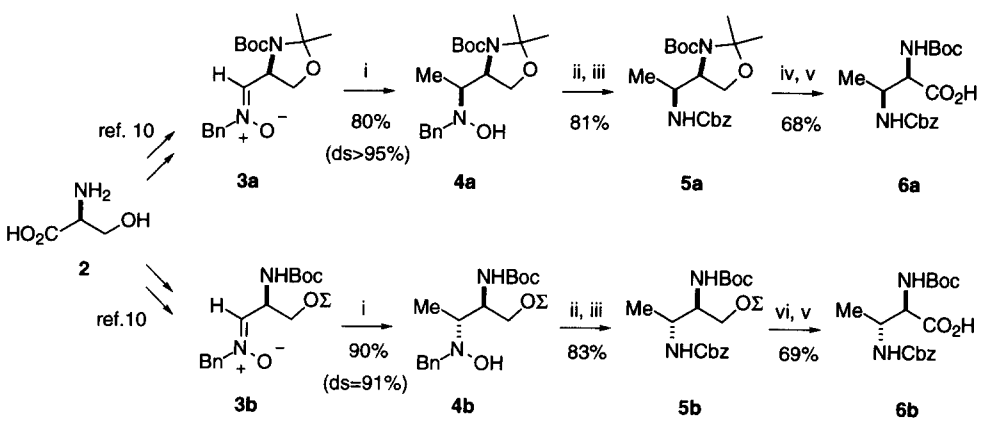
(2R,3S)-**1a** (2R,3R)-**1b** (2S,3R)-**1c** (2S,3S)-**1d**

Recent work from this laboratory has demonstrated the utility of nitrones as electrophilic substrates towards the stereoselective synthesis of several nitrogen-containing compounds of interest.[7] Moreover, in a recent communication[8] we showed that the stereocontrolled synthesis of a 1,2-diamino unit is possible making use of

diferentially protected nitrones derived from L-serine.[9] The wide scope of that reactivity prompted us to extend our investigations to different nucleophiles and apply them to the synthesis of α,β-diamino acids. In this communication we report a stereodivergent approach to both (2R,3S) and (2R,3R)-2,3-diaminobutanoic acids **1a** and **1b**, respectively, using L-serine as the only starting material. Since D-serine is available commercially the methodology described herein also constitutes a formal synthesis of (2S,3R) and (2S,3S)-2,3-diaminobutanoic acids **1c** and **1d**.

The required α-amino nitrones **3a** and **3b** were readily prepared, in large quantities, from L-serine **2** as described.[10] Treatment of **3a** with 3.0 equivalents of methylmagnesium bromide at -50°C in THF as a solvent afforded hydroxylamine **4a** as a single diastereomer[11] (Scheme 1). Catalytic hydrogenation of **4a** at 70 psi and further N-protection as the corresponding N-benzyloxycarbonyl derivative by standard methods (CbzCl, K_2CO_3, H_2O) gave diamine **5a** in 81% yield. Finally, acid-catalyzed cleavage of the acetonide moiety and subsequent ruthenium-mediated oxidation of the resulting primary alcohol afforded the protected (2R,3S)-2,3-diaminobutanoic acid[11] **6a**. The overall yield of the sequence was 41.9% from the starting nitrone **3a**. The absolute configuration of both **5a** and **6a** was established by comparison of their spectroscopic properties and optical rotations to those known for the same compounds, previously described.[5b]

Scheme 1



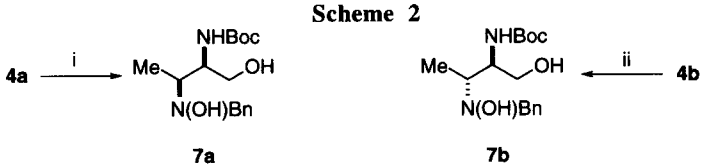
Bn = benzyl; Boc = tert-butoxycarbonyl; Σ = tert-butyldiphenylsilyl

Reagents and conditions: (i) MeMgBr, THF, -50°C, 90 min. (ii) H_2, $Pd(OH)_2$-C, MeOH, 70 psi, 3 days. (iii) CbzCl, K_2CO_3, H_2O, 15 min, 0°C. (iv) p-TosOH, MeOH, reflux, 1 h. (v) RuO_2, $NaIO_4$, CH_3CN-CCl_4-H_2O, 5 min, r.t. (vi) Bu_4NF, THF, 2 h, r.t.

On the other hand, when nitrone **3b** was treated with methylmagnesium bromide in the same conditions that those described for **3a**, a complete reversal of the diastereofacial selectivity was observed, and the hydroxylamine **4b** was obtained in excellent yield (90%) and high diastereoselectivity (ds=91%).[11] The later was determined by ^1H NMR spectroscopy. Again, catalytic hydrogenation of hydroxylamine **4b** and N-protection gave rise to the corresponding diamine **5b** in good yield (83%). Removal of the tert-butyldiphenylsilyl group with tetrabutylammonium fluoride in THF was achieved at ambient temperature in 2 h, and afforded an intermediate primary alcohol that was oxidized with the system RuO_2-$NaIO_4$ to give the (2S,3R)-2,3-diaminobutanoic acid derivative **6b**.[11] The overall yield from the nitrone **3b** was 46.9%. The absolute configuration was determined by comparison of the spectroscopic properties and optical rotation of the

diamino alcohol **7a**, obtained from **4a**, and its epimer **7b** obtained from the hydroxylamine **4b** (Scheme 2); both the physical and spectroscopic (^{1}H and ^{13}C NMR) properties were quite different.[12] In addition, the spectroscopic properties and optical rotation of compound **6b** were in good agreement with those described in the literature for the same compound.[5b]

Scheme 2



Bn = benzyl; Boc = tert-butoxycarbonyl

Reagents and conditions: (i) p-TosOH, MeOH, reflux, 1 h. (ii) Bu_4NF, THF, 2 h, r.t.

To explain the opposite and almost complete diastereofacial selectivity in the formation of hydroxylamines **4** the following transition states can be discussed. On the one hand, a transition state model **A** can be envisaged for nitrone **3a**, while on the other models **B** and **C** can be considered for nitrone **3b** (Figure 1). Model **A** is similar to that invoked by Houk for electrophilic additions to alkenes[13] and it is in concordance with the chelating properties of the Grignard reagents. Model **A** allows the formation of a chelate between the oxygen of the carbamate group and the nitrone oxygen;[14] the attack by the less hindered *Si* face leads to the corresponding *syn* hydroxylamine. In the case of nitrone **3b** it seems plausible to consider model **B** in addition to the model **C**, previously proposed by us.[8] Both semiempirical calculations[15] (PM3) and structural analyses carried out on quite similar compounds[16] indicate that a chelate between the nitrogen of the carbamate group and the nitrone oxygen could be preferred. These studies also suggest that the tert-butyldiphenylsiloxy group is oriented in such a way that the *Si* face is completely hindered (Figure 1, model **B**); as a consequence the attack by the less hindered *Re* face leads to the *anti* hydroxylamine.

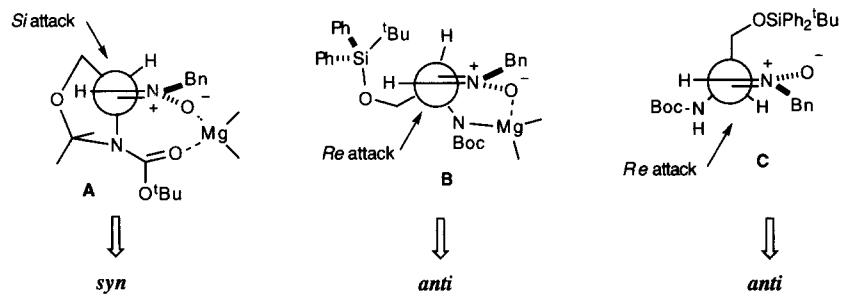


Figure 1. Transitions state models for the addition of methylmagnesium bromide to nitrones **3**.

To summarize, it has been shown that 2,3-diaminobutanoic acids can be prepared stereoselectively in high enantiomeric purity and excellent overall yields by the procedure detailed here. The extension of the method leading to the preparation of other α,β-diamino acids of interest is currently the object of our investigations.

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9. The tunable selectivity achieved by changing the nitrogen-protecting groups has also been successfully applied to the reduction of chiral α-amino ketones (see: Dondoni, A.; Perrone, D.; Merino, P. *Chem. Commun.* **1991**, 1313-1314) and to the addition of 2-(trimethylsilyl)thiazole to α-amino aldehydes (see: Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074-8080).
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11. All new compounds exhibited consistent spectral (^1H and ^{13}C NMR, IR) and analytical data. **4a**: $[\alpha]_D^{20}$ = -5.9 (c 0.50, $CHCl_3$). **4b**: $[\alpha]_D^{20}$ = -1.3 (c 0.41, $CHCl_3$). **5a**: $[\alpha]_D^{20}$ = -4.3 (c 0.72, MeOH). **5b**: $[\alpha]_D^{20}$ = -24.0 (c 0.35, $CHCl_3$). **6a**: $[\alpha]_D^{20}$ = -14.7 (c 0.61, MeOH) (Lit.[5b] $[\alpha]_D^{20}$ = -11.8 (c 1.50, MeOH)). **6b**: $[\alpha]_D^{20}$ = +22.7 (c 0.17, MeOH) (Lit.[5b] $[\alpha]_D^{20}$ = +21.1 (c 1.0, MeOH)).
12. **7a**: $[\alpha]_D^{20}$ = -9.2 (c 0.13, $CHCl_3$); R_f (Et_2O) = 0.50; mp 126°C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, 3H, J = 6.6 Hz), 1.44 (s, 9H), 2.20 (bs, 1H, ex. D_2O), 2.91 (dq, 1H, J = 6.8, 6.6 Hz), 3.59 (dddd, 1H, J = 8.9, 6.8, 3.6, 3.4 Hz), 3.69 (dd, 1H, J = 11.3, 3.4 Hz), 3.72 (d, 1H, J = 13.3 Hz), 3.76 (dd, 1H, J = 11.3, 3.6 Hz), 3.91 (d, 1H, J = 13.3 Hz), 5.4 (d, 1H, J = 8.9 Hz), 6.1 (bs, 1H, ex. D_2O), 7.35-7.41 (m, 5H) . **7b**: $[\alpha]_D^{20}$ = -49.8 (c 0.15, $CHCl_3$); R_f (Et_2O) = 0.22; oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9H), 1.55 (d, 3H, J = 6.9 Hz), 1.90 (bs, 1H, ex. D_2O), 3.49-3.61 (m, 3H), 4.14 (d, 1H, J = 12.9 Hz), 4.64 (dq, 1H, J = 6.9, 6.1 Hz), 5.20 (d, 1H, J = 12.9 Hz), 5.50 (d, 1H, J = 7.0 Hz), 6.12 (bs, 1H, ex. D_2O), 7.38-7.45 (m, 5H).
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