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# Stereoselective synthesis of β-amino alcohols: diastereoselective reduction of chiral α′-amino enones derived from amino acids

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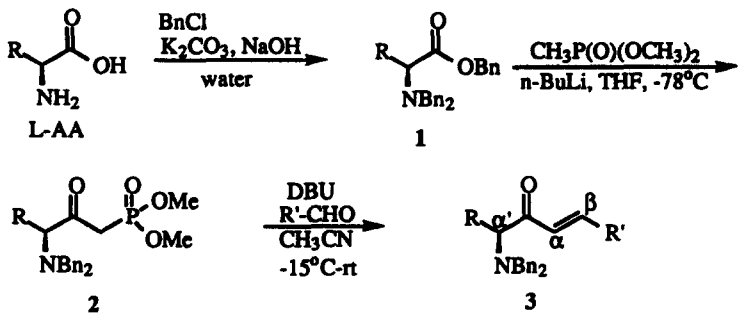
***Abstract:*** α-Amino acids are doubly benzylated at nitrogen to give *N,N*-dibenzyl amino acids, which can readily be converted to α′-amino enones **3**. The α′-amino enones are very resistant to racemization, and undergo highly diastereoselective reduction to afford chiral amino alcohols upon treatment with L-Selectride under non-chelation control. © 1997 Elsevier Science Ltd

Among the unnatural or non-proteinogenic amino acids, those incoorporating the β-amino α-hydroxy unit are receiving much attention due to their presence in many biologically important compounds such as the potent anticancer agents, taxol and taxotere, numerous protease inhibitors such as pepstatine, bestatine, and amastatine, and various hydroxymethylene dipeptide isosteres that are renin inhibitors or active against the human immunodeficiency virus type-1 (HIV-1), the virus responsible for AIDS.[1]

The diastereoselective synthesis of β-amino alcohols via *N*-protected chiral α-amino aldehydes has been extensively studied.[2] It is now well known that additions of organometallics to *N,N*-dibenzylamino aldehydes lead to *anti* adducts, in contrast to the α-alkoxy derivatives.[3] This behavior of *N,N*-dibenzylamino aldehydes has been observed repeatedly and is explained on the basis of a non-chelated transition state. Obtaining a high degree of the opposite diastereoselectivity via a chelation control still remains a challenge. Furthermore, chiral α-amino aldehydes are known to be prone to racemization. Only partial success has been achieved through a combination of sterically less demanding protecting groups on the nitrogen or monoprotected aminoaldehydes and cuprates, manganese or chrominium reagents as the nucleophile.[4] Allyltins and allysilanes in the presence of various Lewis acids have also been used in this connection.[5] On the other hand, phenyl or vinyl addition to aluminoxy acetals derived from α-amino esters leads to the chelation control products.[6] We wish to report herein a highly flexible and efficient synthetic route to the *syn* β-amino alcohols via γ-amino-β-ketophosphonates.

Requisite substrate **3** was synthesized in three steps from L-amino acids (Scheme 1).




**Scheme 1.**

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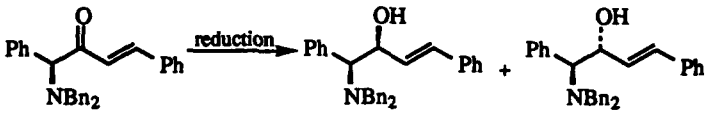
**Table 1.** The HWE reaction of the γ-amino-β-ketophosphonates


**2a-d** **3a-j**

| entry | R | R' | product | Y(%) |
|---|---|---|---|---|
| 1 | $CH_3$ | $C_6H_5$ | 3a | 75 |
| 2 | " | p-$CF_3C_6H_4$ | 3b | 72 |
| 3 | " | m-$NO_2C_6H_4$ | 3c | 74 |
| 4 | $C_6H_5CH_2$ | p-$CHOC_6H_4$ | 3d | 58 |
| 5 | " | p-$CH_3OC_6H_4$ | 3e | 70 |
| 6 | " | α-Naphthyl | 3f | 72 |
| 7 | " | $C_6H_5$ | 3g | 62 |
| 8 | " | p-$CHOC_6H_4$ | 3h | 58 |
| 9 | $C_6H_5$ | $C_6H_5$ | 3i | 73 |
| 10 | $(CH_3)_2CHCH_2$ | $C_6H_5$ | 3j | 74 |

**Table 2.** Reduction of α′-amino enone **3i** with various reducing agents




**3i** *syn*-**4i** *anti*-**4i**

| entry | reducing agents | syn : anti | Y(%) |
|---|---|---|---|
| 1 | L-Selectride/THF | >39 : 1 | 96 |
| 2 | $NaBH_4$/MeOH | 9.3 : 1 | 94 |
| 3 | $NaCNBH_3$/MeOH | 8.2 : 1 | 91 |
| 4 | $ZrCl_4/NaBH_4$/THF | 4.9 : 1 | 93 |
| 5 | $SnCl_4/NaBH_4$/THF | 4.7 : 1 | 92 |
| 6 | $ZnCl_2/NaBH_4/Et_2O$ | 3.9 : 1 | 94 |
| 7 | $TiCl_4/NaBH_4/Et_2O$ | 2.3 : 1 | 93 |

Syntheses of several related compounds by similar routes have been reported.[7] Tribenzylation of L-amino acids with BnCl (78–89% yields) followed by addition of the lithium anion of dimethyl methylphosphonate (5.0 eq) produced β-ketophosphonate **2** in 90–96% yields.

The initial attempts of the Horner–Wadsworth–Emmons (HWE) reaction with γ-amino-β-ketophosphonates **2** under a variety of conditions ($K_2CO_3$/18-Crown-6/$CH_2Cl_2/H_2O$; NaH/THF; NaOMe/MeOH; DBU/$PhCH_3$; $CsCO_3$/isopropanol; $Et_3N/CH_3CN$) gave either none or only very low yields of olefinic products. A report by Masamune *et al.*[8] describing the HWE reaction in the presence of lithium chloride and either DBU or diisopropylethylamine prompted us to examine a related HWE reaction of **2** in the presence of magnesium or lithium halides together with DBU (Table 1). It was found that the γ-amino-β-ketophosphonates smoothly underwent the HWE reaction with aromatic aldehydes to give α′-amino enones in 58–75% yields (DBU, LiCl, $CH_3CN$). The *E* stereochemistry of the α′-amino enones **3** was assigned on the basis of $^1$H-NMR ($J$=15–16Hz, *trans* vinyl CH).

Treatment of the α′-amino enone **3i** with reducing agents provided the β-amino-α-hydroxy

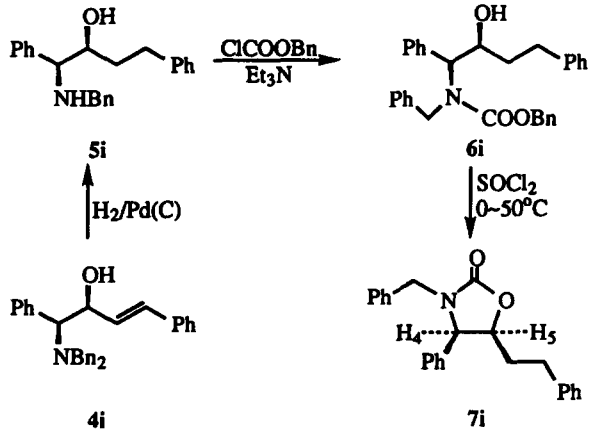
**Table 3.** Reduction of α′-amino enones with L-Selectride


**3a-j** **4a-j**

| entry | R | R' | product | Y(%) |
|---|---|---|---|---|
| 1 | $CH_3$ | $C_6H_5$ | **4a** | 95 |
| 2 | " | p-$CF_3C_6H_4$ | **4b** | 94 |
| 3 | " | m-$NO_2C_6H_4$ | **4c** | 92 |
| 4 | $C_6H_5CH_2$ | p-$CHOC_6H_4$ | **4d** | 93 |
| 5 | " | p-$CH_3OC_6H_4$ | **4e** | 95 |
| 6 | " | α-Naphthyl | **4f** | 96 |
| 7 | " | $C_6H_5$ | **4g** | 96 |
| 8 | " | p-$CHOC_6H_4$ | **4h** | 94 |
| 9 | $C_6H_5$ | $C_6H_5$ | **4i** | 96 |
| 10 | $(CH_3)_2CHCH_2$ | $C_6H_5$ | **4j** | 94 |

compound (*syn*- and *anti*-**4i**) in high yield. As expected, the diastereomeric ratio of **4i**, which was heavily dependent on the reducing agents used, ranged from better than 39:1 to 2.3:1; L-Selectride gave the best *syn*/*anti* ratio (Table 2). Thus, the other α′-amino enones **3a–j** were also reduced with L-Selectride in THF at −78°C. Indeed, the desired diastereomers **4a–j** were obtained with high degrees of stereoselectivity, presumably via non-chelation control. The crude products were purified by simple crystallization from ethyl acetate–hexane, and the purity of the β-amino alcohol products were found to be >98% de on the basis of the $^1$H-NMR analysis (Table 3).

The stereochemistry of the new stereogenic center in **4i** was determined in the following manner (Scheme 2).[9]




**Scheme 2.** Determination of the stereochemistry of **4i**.

Compound **4i** was hydrogenated over Pd/C, and the product was treated with benzyl chloroformate and $Et_3N$ to give product **6i** in good yield. Compound **6i** was then treated with thionyl chloride (0–50°C, 5 h) to give the corresponding *cis*-4,5-disubstituted oxazolidin-2-one **7i**. The relative configurations

at the 4- and 5-positions of **7i** were clearly determined on the basis of the chemical shifts and the coupling constants for 4-H (δ 4.46, d, *J*=*8.23* Hz) and 5-H (δ 4.59, ddd, *J*=10.89, *8.23*, 3.75 Hz).

**Acknowledgements**

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