

S0040-4039(96)00518-7

A Novel Approach to Homochiral β -Amino Acids¹

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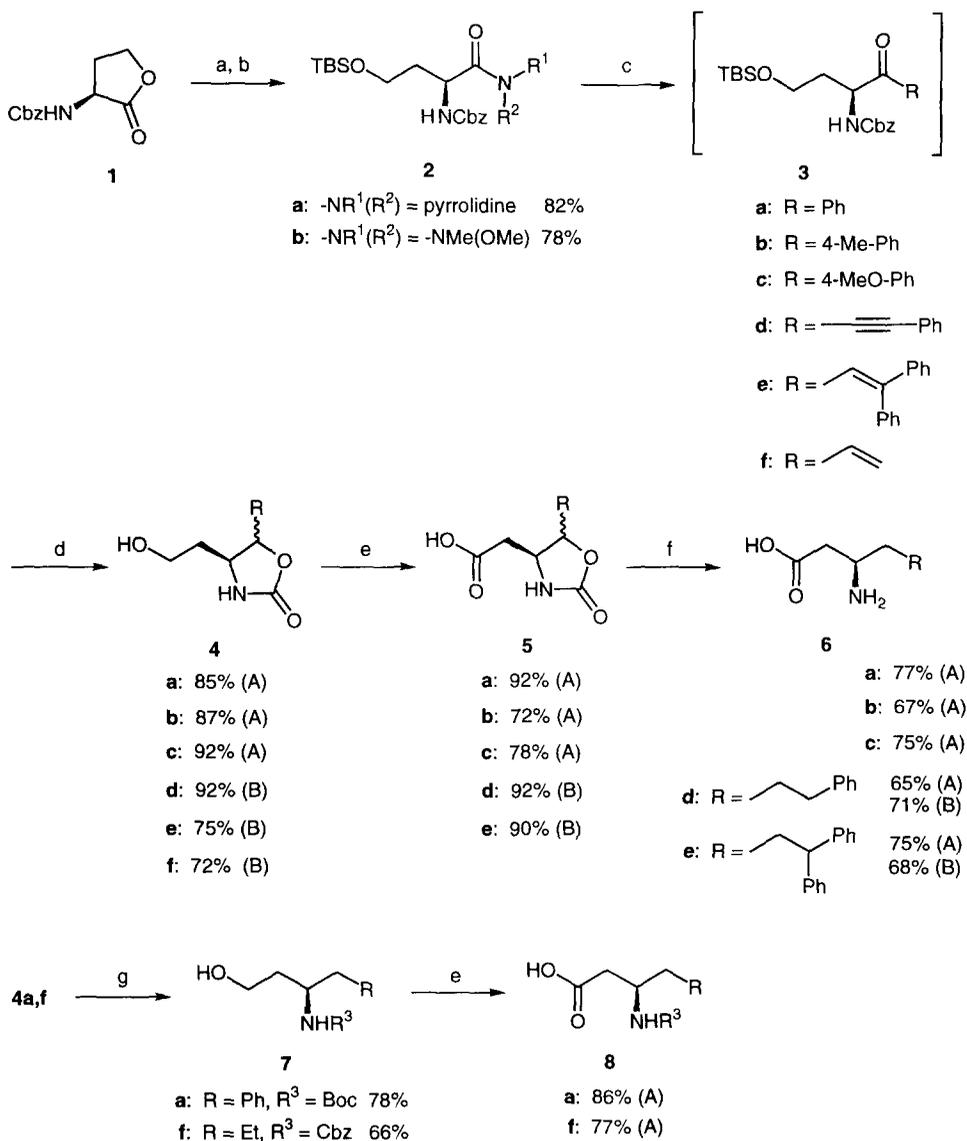
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Abstract: An efficient synthesis of γ -aryl or alkyl substituted β -amino acids starting from *N*-Cbz-L-homoserine lactone via the formation of α -amino aryl, alkenyl or alkynyl ketones with the original α -carbon chirality retained as such is described. Copyright © 1996 Elsevier Science Ltd

β -Amino acids have recently attracted considerable attention due to their crucial role to exhibit potent pharmacological activities in such drugs as immunological response modifier,² antihypertensive,³ antiplatelet,⁴ or anticancer agents,⁵ and this has spurred intense synthetic studies of amino acids of this important class.⁶ One of the steadiest approaches to the optically active β -amino acids comprises an elaboration from inexpensive L-aspartic acid⁷ which already bears the required β -amino acid fragment in its molecule.⁸ In these syntheses, activated L- β -homoserine derivatives, obtained from L-aspartic acid, have allowed to substitution with organocuprates to afford a variety of γ -substituted β -amino acids in from moderate to good yields. Although they represent the most direct approach obtained so far, there are some limitations concerning the incorporated substituents. Alkylcuprates reacted smoothly with the L- β -homoserine derivative to afford the desired substituted products, however, the reaction with arylcuprates was not realized in most cases, only a substrate having an *N,N*-dibenzyl protective group gave a poor yield of the product.^{8a} In addition, they all need excess organocuprates (7 equivalents or more) for the successful substitution. Since there are many pharmacologically important aromatic β -amino acids comparable to their alkyl counterparts,²⁻⁵ a more efficient and versatile synthetic method of β -amino acids especially carrying an aryl group is currently in eager demand. We report herein a novel and practical synthesis of optically pure γ -aryl or alkyl substituted β -amino acids starting from *N*-Cbz-L-homoserine lactone.

The starting material, *N*-Cbz-L-homoserine lactone **1** was readily prepared from easily accessible L-methionine or L-aspartic acid according to the reported procedures.^{9, 10} Introduction of the required substituent to *N*-Cbz-L-homoserine lactone **1** was undertaken through the formation of the α -amino ketones **3** (Scheme 1). The reaction must be conducted without effecting overreaction of the organolithiums to the carbonyl group (carbinol formation) and with complete conservation of the α -carbon chirality. Taking such requirements into consideration, the substrate of choice for the reaction was considered to be L- α -homoserinamide **2**¹¹ which was readily derived from **1** by the treatment with dimethylaluminumamide¹² followed by silylation of the hydroxy group. The pyrrolidinamide **2a** was subjected to the reaction with various aryllithiums to afford assuredly the aryl ketones **3a-c**. In the case of less reactive alkenyl or alkynyl lithiums for the nucleophile, use of *N,O*-dimethylhydroxamide **2b** smoothly gave corresponding ketones

Scheme 1



a: i) Me_3Al (1.1 eq.), HNR^1R^2 (1.1 eq.), CH_2Cl_2 , 25°C, 17 h; b) TBS-Cl, imidazole, DMF; c) R-Br (R-H for **3d**) (2.2 eq.), *n*-BuLi (2.2 eq.), -78--20°C, 2 h, THF; d) i) NaBH_4 , EtOH (Method A); $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, NaBH_4 , MeOH (Method B), 5°C ii) NaOMe, THF, 25°C iii) c-HCl, MeOH, 5°C; e) $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (6 mol%), NaIO_4 (4eq.), CH_3CN , CCl_4 , H_2O (2:2:3), 25°C, 1 h (Method A), Jones reagent (excess), acetone, 5°C, 20 min. (Method B); f) H_2 (1 atm), Pd-C, MeOH, 25°C, 1 h (Method A); Et_3SiH , Pd(OAc) $_2$, EtOH, reflux, 20 min. (Method B); g: i) H_2 (1 atm), Pd-C, MeOH, 25°C, 4 h ii) $(\text{Boc})_2\text{O}$, Et_3N , THF, H_2O or Cbz-Cl, NaHCO_3 , AcOEt, H_2O .

3d-f. Practically, these ketones **3a-f** were not isolated by such means as silica-gel column chromatography and were directly subjected to reduction with NaBH₄ for **3a-c** and CeCl₃-NaBH₄^{11b} for **3d-f**. Cyclization of the resulting hydroxy carbamate with NaOMe and subsequent removal of the silyl group by simple acidifying the reaction mixture were conducted to afford **4a-f** in good yields as a mixture of diastereomers (*cis:trans*=3:1 to 6:1).¹³ Ruthenium catalyzed oxidation¹⁴ of **4a-c** gave the carboxylic acids **5a-c** in good yields. For the compounds **4d,e** bearing labile unsaturated substituents, Jones oxidation was successfully applied to afford **5d,e** in good yields. Mild catalytic hydrogenation of **5a-c** afforded γ -aryl β -amino acids **6a-c** in good yields.¹⁵ Hydrogenation of **5d,e** did not yield the corresponding β -amino acids. However, fortunately, the β -amino acids with a saturated γ -substituent **6d,e** were obtained in good yields by this reaction.¹⁵ Reductive cleavage of the oxazolidones **5d,e** without reducing the alkenyl or alkynyl groups were attempted by the use of Et₃SiH and Pd(OAc)₂,¹⁶ however, they all gave saturated products **6d,e** in good yields. Although it shows a limitation of the present synthesis, it is evident that the reductive cleavage of the oxazolidones proceeded prior to the saturation of the olefinic side chain. This provides a general access to γ -alkyl substituted β -amino acids *via* the formation of corresponding α -amino alkenyl or alkynyl ketones. As an alternative route, we examined the reductive cleavage of hydroxy oxazolidones **4a,f**. Hydrogenation over Pd-C as well gave alkyl or aralkyl substituted *N*-protected γ -aminoalcohols **7a,f** in good yields after protection of the amino group. The desired *N*-Cbz or *N*-Boc- β -amino acids **8a,f**¹⁷ were obtained in good yields by the ruthenium catalyzed oxidation of **7a,f**.

The optical integrity of the products **6a-e** and **8a,f** were confirmed on corresponding amino esters by 200 MHz ¹H-NMR analysis after deprotection (for **8a,f**), esterification and derivatization with (*S*)-(-)- α -methylbenzylisocyanate.^{8a} This revealed that the γ -substituted β -amino acids **6a-e** and **8a,f** obtained by the present methodology were virtually optically pure (>95% e.e.). The β -amino acid **6a** had an optical rotation $[[\alpha]_D^{25} -8.6^\circ(c, 0.86, H_2O)]$ in good accordance with the reported value $[Lit. 8a [\alpha]_D^{25} -8.5^\circ(c, 0.2, H_2O)]$.

In conclusion, the present synthesis represents a novel and efficient approach to the biologically important β -amino acids from easily accessible *N*-Cbz-*L*-homoserine lactone. The simple procedure and economical operation with higher overall yields provide easier access to β -amino acids of recent interest.

References and Notes

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13. A general procedure, synthesis of **4a**: Into a solution of PhBr (1.87 g, 12 mmol) in THF (20 ml) was added *n*-BuLi (1.6M in hexane, 7.4 ml, 12 mmol) at -78°C , and the mixture was stirred at the same temperature for 1 h. The amide **2a** (2g, 4.8 mmol) in THF (10 ml) was added at -78°C and the mixture was warmed up to -20°C for 2h. After the reaction, 10% aq. citric acid was added and the mixture was extracted with AcOEt, washed successively with water, sat. aq. NaHCO_3 , dried over anhydrous MgSO_4 , and evaporated. The residue was treated with NaBH_4 (91 mg, 2.4 mmol) in EtOH (20 ml) at 5°C . After being stirred at 5°C for 1 h, the mixture was evaporated *in vacuo*, dissolved in AcOEt, washed with water, dried and evaporated. Into the residue was added THF (5 ml) and NaOMe (24% in MeOH, 2.16g, 9.6 mmol) at 25°C and the mixture was stirred at 25°C for 5 min. After addition of MeOH (25 ml) and *c*-HCl (2.5 ml) at 5°C , the mixture was neutralized by adding 2N aq. NaOH at 10°C . The mixture was evaporated and the residue was extracted with CH_2Cl_2 , dried, and evaporated. The residue was purified by silica-gel column chromatography (*n*-hexane:AcOEt=2:1 to CHCl_3 :MeOH=20:1) to afford **4a** (835 mg, 85%) in colorless crystals. *cis/trans*=4.1/1. mp $98-100^{\circ}\text{C}$. **4b**: *cis/trans*=4.5/1. mp $79-80^{\circ}\text{C}$. **4c**: *cis/trans*=6/1. mp $99-101^{\circ}\text{C}$. **4d**: *cis/trans*=5/1. mp $92-94^{\circ}\text{C}$. **4e**: *cis/trans*=6/1. mp $98-101^{\circ}\text{C}$. **4f**: *cis/trans*=3/1. oil.
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15. **6a**: mp $222-225^{\circ}\text{C}$ (dec.). $[\alpha]_{\text{D}}^{25} -8.6^{\circ}$ (*c*, 0.86, H_2O)[Lit. $[\alpha]_{\text{D}}^{25} -8.5^{\circ}$ (*c*, 0.2, H_2O)**8a**]. **6b**: mp $212-213^{\circ}\text{C}$ (dec.). $[\alpha]_{\text{D}}^{25} -7.4^{\circ}$ (*c*, 0.5, H_2O). **6c**: mp $210-212^{\circ}\text{C}$ (dec.). $[\alpha]_{\text{D}}^{25} -6.6^{\circ}$ (*c*, 0.4, H_2O). **6d**: mp $198-202^{\circ}\text{C}$ (dec.). $[\alpha]_{\text{D}}^{25} -16.3^{\circ}$ (*c*, 0.28, H_2O). **6e**: mp $205-207^{\circ}\text{C}$ (dec.). $[\alpha]_{\text{D}}^{25} -4.4^{\circ}$ (*c*, 0.23, MeOH).
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17. **8a**: mp $99-101^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} +19.7^{\circ}$ (*c*, 0.67, MeOH). **8f**: mp $82-83^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} +12.9^{\circ}$ (*c*, 0.55, MeOH).

(Received in Japan 27 February 1996; revised 14 March 1996; accepted 15 March 1996)