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Synthesis of Enantiopure α,α-Disubstituted Amino Acids from the Asymmetric Strecker Reaction Products of Aldehydes

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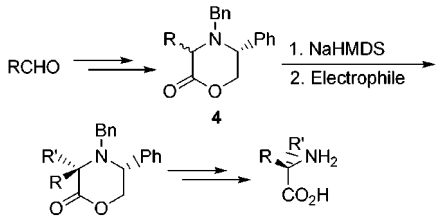
ABSTRACT



Treatment of the enolates of 4 generated from the asymmetric Strecker reaction products with alkyl halides or aldehydes provided the corresponding functionalized products with high diastereoselectivity. Deprotection of these products afforded the corresponding enantiopure α,α-dialkyl amino acids.

The asymmetric synthesis of α,α-disubstituted amino acids continues to challenge an ever growing group of chemists.[1−10] The driving force behind much of this work is based on their remarkable pharmacological and conformational properties.[1] One of the most popular emerging methods[1−10] is dia-

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(1) For reviews, see (a) Cativiela, M. D.; Diaz-De-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (c) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (d) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.

(2) By alkylation of acyclic chiral esters: (a) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A.; Lapena, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 311. (b) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233.

(3) By self-regeneration of stereogenic center strategy: (a) Schollkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799. (b) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586. (c) Zhang, L.; Finn, J. M. *J. Org. Chem.* **1995**, *60*, 5719. (d) Smith, A. B.; Benowitz, A. B.; Favor, D. A.; Sprengeler, P. A.; Hirschmann, R. *Tetrahedron Lett.* **1997**, *38*, 3809. (e) Acton, J. J.; Jones, A. B. *Tetrahedron Lett.* **1996**, *37*, 4319. (f) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Najera, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 995. (g) Juaristi, E.; Lopez-Ruiz, H.; Madrigal, D.; Ramirez-Quiros, Y.; Escalante, J. *J. Org. Chem.* **1998**, *63*, 4706.

(4) By enzymatic resolution: Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1996**, *61*, 7398.

(5) By Sharpless epoxidation or dihydroxylation: (a) Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240. (b) Hatakeyama, S.; Fukuyama, H.; Mukugi, Y.; Irie, H. *Tetrahedron Lett.* **1996**, *37*, 4047.

(6) By asymmetric Strecker reactions: (a) Ma, D.; Tang, G.; Tian, H. *Tetrahedron Lett.* **1999**, *40*, 5753 (published erratum appeared in *Tetrahedron Lett.* **1999**, *40*, 9385). (b) Ma, D.; Tian, H. Zou, G. *J. Org. Chem.* **1999**, *64*, 120. (c) Ohfune, Y.; Moon, S.; Horikama, M. *Pure Appl. Chem.* **1996**, *68*, 645. (d) Ohfune, Y.; Horikawa, M. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 982. (e) Cordi, A. A.; Lacoste, J.-M.; Borgne, F. L.; Herve, Y.; Vaysse-Ludot, L.; Descombes, J.-J. Courchay, C.; Laubie, M.; Verbeuren, T. J. *J. Med. Chem.* **1997**, *40*, 2931, and references therein.

(7) Through chiral sulfinamides: (a) Hua, D. H.; Miao, S.; Chen, J.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4. (b) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771.

(8) By chiral memory strategy: (a) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373. (b) Ferey, V.; Toupet, L.; Gall, T. L.; Mioskowski, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 430.

(9) By chiral phase transfer catalysts: (a) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671. (b) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Parmar, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851.

(10) By rearrangement reactions: (a) Frutos, R. P.; Spero, D. M. *Tetrahedron Lett.* **1998**, *39*, 2475. (b) Imogai, H.; Petit, Y.; Larcheveque, M. *Tetrahedron Lett.* **1996**, *37*, 2573.

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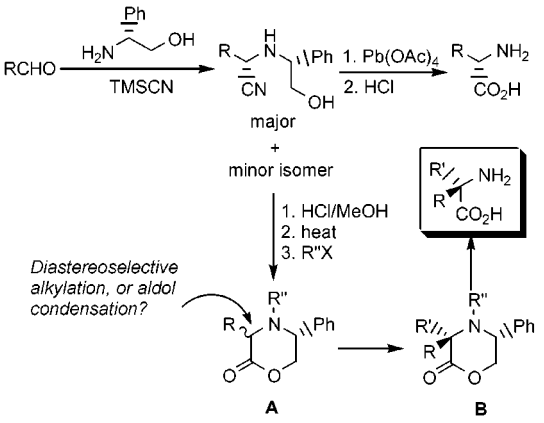
stereolective functionallization of an enantiopure α-amino acids via a nonracemic enolate.[3] However, this method is restricted by the lack of enantiopure α-amino acids. On the other hand, although asymmetric Strecker reactions starting with chiral amines have been successfully used in synthesizing chiral α-monosubstituted α-amino acids from aldehydes with good diastereoselectivity (Scheme 1),[11] this reaction's

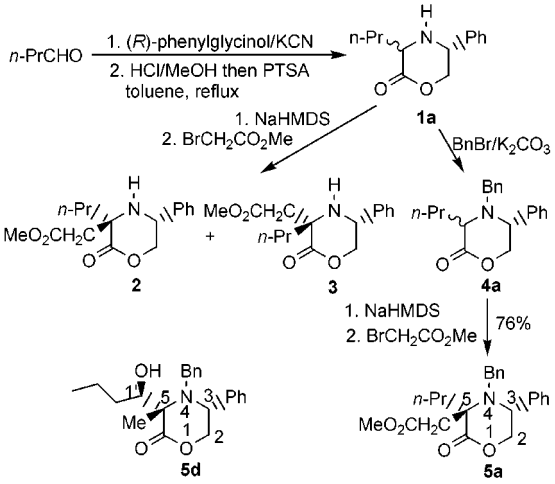
Scheme 1



capability to afford chiral α,α-disubstituted α-amino acids from ketones is still limited because of the low reactivity of ketones and low diastereoselectivity of the products.[6] Our idea is to combine these two methods to prepare enantiopure α,α-disubstituted amino acids as shown in Scheme 1. The asymmetric Strecker reaction products of an aldehyde could be converted into lactone **A** under the conditions indicated in Scheme 1, which can serve as a nonracemic enolate upon the treatment of a suitable base. The reactions of this enolate with various electrophiles would provide functionalized products **B**. If the diastereoselectivity in this step was good we would be able to obtain enantiopure α,α-disubstituted amino acids after deprotection of **B**.

With this idea in mind, we prepared the lactone **1a** as a mixture of two diastereomers from butyraldehyde according to the known procedure except for using KCN instead of TMSCN and cyclization of the resultant ester under refluxing in toluene.[11] Initially, direct alkylation of **1a** with methyl bromoacetate mediated by NaHMDS was attempted and it was found that two diastereomers **2** (45%) and **3** (14%) were formed (Scheme 2). To improve the diastereoselectivity, we tried to modify the structure of **1a**. Thus it was converted into **4a** by treatment with benzyl bromide and potassium carbonate in DMF. As we expected, the alkylation of **4a** with methyl bromoacetate provided a single diastereomer **5a**, with

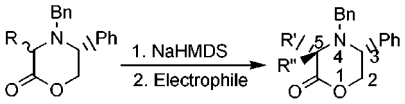
Scheme 2



the diastereoselectivity of over 200:1 as detected by HPLC. Its stereochemistry was assigned by its single-crystal X-ray analysis in which the 5-*n*-propyl group is *cis* to the 3-phenyl group. This result indicated that the configuration of 5-position is *R*.

Encouraged by this result, we tested several different electrophiles and substrates, and the results are summarized in Table 1. Other alkyl halides such as benzyl bromide and

Table 1. Diastereoselective Functionallization of **4**[12]



4a: R = *n*-Pr
4b: R = Me

5a: R' = *n*-Pr, R" = CH_2CO_2Me
5b: R' = Bn, R' = Me
5c: R' = Et, R' = Me
5d: R' = (*S*)-CH(OH)Pr-*n*, R" = Me
5e: R' = Me, R" = CH_2CO_2Me
5f: R' = Bn, R" = *n*-Pr
5g: R = (*S*)-CH(OH)Me, R" = *n*-Pr

entry	substrate	electrophile	product	yield (%)[a]
1	**4a**	$BrCH_2CO_2Me$	**5a**	76
2	**4b**	BnBr	**5b**	90
3	**4b**	EtI	**5c**	50
4	**4b**	*n*-PrCHO	**5d**	80[b]
5	**4b**	$BrCH_2CO_2Me$	**5e**	87
6	**4a**	BnBr	**5f**	85
7	**4a**	CH_3CHO	**5g**	85[b]

[a] Isolated yield. [b] Based on 50% starting material recovery.

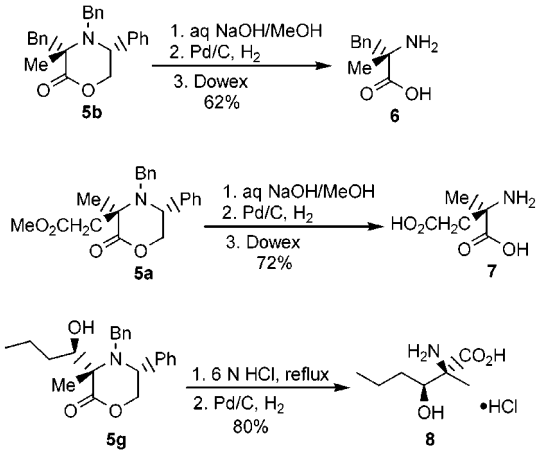
ethyl iodide were found to be suitable for functionallization of **4** and gave the corresponding alkylation products in similar diastereoselectivities (entries 2−3, 5−6). When aldehydes were used as the electrophiles, the reaction gave two isomers and the ratio for them ranged from 8:1 to 10:1 (entries 4 and 7). By recrystallization the pure major isomer **5d** or **5g** was obtained. To determine the stereochemistry of two

(11) (a) Chakraborty, T. K.; Reddy, G. V.; Hussain, K. A. *Tetrahedron Lett.* **1991**, *32*, 7597. (b) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179.

(12) **Typical Procedure for Functionalization of 4.** A solution of **4** (5 mmol) in DME−THF (1:1, 1 mL) was cooled to −78 °C under argon before NaHMDS in THF (6 mmol) was added over 15 min. The stirring was continued for 1 h and then benzyl bromide (6 mmol) was added. After the reaction was completed as monitored by TLC, ether workup followed by chromatography afforded **5**.

stereogenic centers in this coupling reaction, the alcohol **5d** was recrystallized to give a single crystal. X-ray analysis showed that the configuration of **5d** was 3*R*,5*S*,1′*S* (Scheme 2). This stereochemistry was quite surprising, because in compound **5a** the configuration of the 5-position was *R*! Obviously, the reason for this difference was that different electrophiles were employed. These results promoted us to check the stereochemistry of **5b**, **5c**, and **5f** that were generated by alkylation with simple alkyl halides. We decided to solve this problem by conversion of **5b** to the known amino acid **6**. Thus, treatment of **5b** with aqueous NaOH opened the lactone ring. The generated sodium salt was neutralized with HCl before being deprotected by Pd/C-catalyzed hydrogenation (40 atm and 40 °C) to give the crude amino acid, which was purified with Dowex-50W to afford **6** ($[\alpha]^{19}_D$ −22.2 (*c* 2.8, H_2O), lit. $[\alpha]^{25}_D$ −22 (*c* 1.0, H_2O) for (*S*)-α-methylphenylalanine) in 62% yield (Scheme 3). This result implied that the quarternary carbon in **5b**, **5c**, and **5f** might have *S*-form configuration.

Scheme 3



At this stage we concluded that when sodium enolates of **4** reacted with aldehydes or some simple alkyl halides, the (3*R*,5*S*)-products were formed. This stereochemistry could be explained by Figure 1. When **4** was used as a substrate, the generated enolate would prefer the conformation **C**, in which the *N*-benzyl group and the phenyl group are *trans* to each other. This enolate would attack favorably the electrophile from the backside of the benzyl group and give the (3*R*,5*S*)-product. However, as mentioned above, when sodium enolates of **4** attacked methyl bromoacetate, the coupling products had (3*R*,5*R*)-configuration. The reason for this exception is not clear, but one possible explanation is that this stereochemistry might come from some chelation between the ester moiety of methyl bromoacetate and sodium enolates.

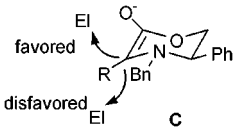


Figure 1. Asymmetric induction of the enolates **C** derived from **4**.

According to the procedure for preparing **6** from **5b**, the lactone **5a** was transformed into (*R*)-α-methylaspartic acid in 72% yield (Scheme 3). From the functionalized products α,α-disubstituted amino acids could be obtained in another manner as demonstrated by the conversion of **5g** to **8**. Refluxing of **5g** in 6 N HCl to open the lactone ring followed by Pd/C-catalyzed hydrogenation to cleavage the benzyl groups afforded **8** in 80% yield.

In conclusion, we have developed a five-step method to synthesize α,α-diasubstituted amino acids from aldehydes, using chiral phenylglycinol as a chiral auxiliary. The key step is the diastereoselective functionalization of the lactones **4** with some highly reactive electrophiles. This method is suitable for preparing enantiopure α-dialkyl amino acids, especially α-alkyl aspartic acids and α,α-disubstituted analogues of serine and threine.

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Supporting Information Available: Experimental details for the synthesis and product characterizations and X-ray structures of **5a** and **5d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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