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Published on Web 04/17/2007

Practical Synthesis of Enantiomerically Pure β^2-Amino Acids via Proline-Catalyzed Diastereoselective Aminomethylation of Aldehydes

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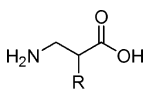
Abstract: Proline-catalyzed diastereoselective aminomethylation of aldehydes using a chiral iminium ion, generated from a readily prepared precursor, provides α-substituted-β-amino aldehydes with 85:15 to 90:10 dr. The α-substituted-β-amino aldehydes can be reduced to β-substituted-γ-amino alcohols, the major diastereomer of which can be isolated via crystallization or column chromatography. The amino alcohols are efficiently transformed to protected β^2-amino acids, which are valuable building blocks for β-peptides, natural products, and other interesting molecules. Because conditions for the aminomethylation and subsequent reactions are mild, β^2-amino acid derivatives with protected functional groups in the side chain, such as β^2-homoglutamic acid, β^2-homotyrosine, and β^2-homolysine, can be prepared in this way. The synthetic route is short, and purifications are simple; therefore, this method enables the preparation of protected β^2-amino acids in useful quantities.

Introduction

β^2-Amino acids are 3-aminopropanoic acids bearing a single substituent adjacent to the carboxylic acid group. β^2-Amino acid residues can be found embedded within natural products that exhibit interesting biological activities.[1] In addition, β^2-residues are essential for the formation of specific β-peptide secondary structures[2] (e.g., 12/10-helix, β^2/β^3 reverse turn[3]). Designed β-peptides containing β^2-residues display useful functions including mimicry of somatostatin signaling[4] and inhibition of viral infection.[5] Many routes to enantio-enriched β^2-amino acids or protected derivatives have been described; however, most of these routes involve tedious chromatographic purifications (e.g., isolation of diastereomers from alkylation of chiral enolates), and few of these synthetic approaches are amenable to large-scale synthesis or diversity in side-chain functionality.[6,7]



ß^2-amino acid

We recently reported a new route to protected β^2-amino acids[8] that is based on enantioselective aminomethylation of aldehydes[9] via an organocatalytic Mannich reaction.[10−12] The Mannich reaction involves diphenylprolinol TMS ether (**1**) as catalyst and a formaldehyde-derived iminium generated in situ from *N*,*O*-acetal **2** as the electrophile. Our route to protected β^2-amino

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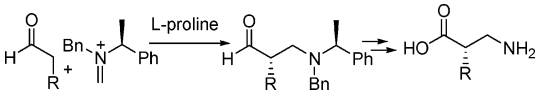
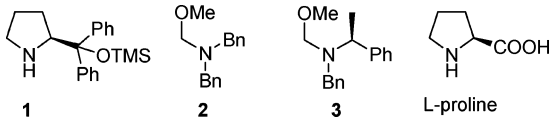
10.1021/ja070063i CCC: $37.00

Scheme 1. Diastereoselective Aminomethylation of Aldehydes and Its Application in β^2-Amino Acid Synthesis



acids is efficient, as illustrated by a multigram synthesis of Boc-β^2-homonorvaline. This synthetic approach has been very valuable in our exploration of structure and function among β-peptides and α/β-peptides; however, some drawbacks have become apparent as we have tried to expand the scope of this new route, that is, to generate protected β^2-amino acids with diverse side chains. The use of achiral iminium precursor **2** leads to γ-amino alcohols with ~90% ee under the optimal conditions; this level of enantioselectivity is excellent for an organocatalytic reaction but inadequate for some applications. Multiple crystallizations of γ-amino alcohol salts provide material with >99% ee in a number of cases, but not all derivatives are readily crystallized, and not all crystallization attempts lead to improvement of ee. Thus, in our hands this approach is very effective for generating substantial quantities of some protected β^2-amino acids in enantio-pure form, but other protected β^2-amino acids are difficult to prepare in this way.



We turned our attention to a *diastereoselective* version of the Mannich reaction (Scheme 1), since the major stereoisomer from such a reaction should be readily isolated via column chromatography or crystallization. Our experience suggested that such a process would be very valuable for rapid preparation of a diverse set of β^2-amino acids, including those bearing protected functional groups in the side chain. A single example of a diastereoselective Mannich reaction was reported in the Supporting Information of our original publication;[8] this reaction was used to establish the stereochemical outcome of an enantioselective Mannich reaction. Here we describe the development of a general approach to diastereoselective β^2-amino acid synthesis. We have focused on substrates and catalysts that are commercially available or easily prepared in large quantity and at low cost so that this approach will be attractive to other chemists.

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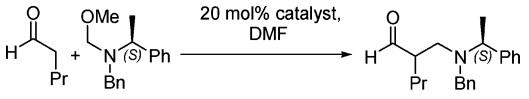
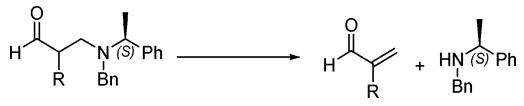
Table 1. Diastereoselective Mannich Reaction



entry[a]	catalyst	T	yield[c]	dr[c]	favored diastereomer[d]
1		room temp	<1		
2	HOAc	room temp	>90	57:43	*S, S*
3	HOAc	−25 °C	<1		
4	**L-proline**	**−25 °C**	**>90**	**86:14**	***S, S***
5[b]	L-proline	−25 °C	>90	76:24	*S, S*
6	D-proline	−25 °C	>90	23:77	*R, S*
7[b]	*(R)*-**1**-HOAc	−25 °C	>90	~95:5	*S, S*

[a] Reaction run using 2.0 equiv aldehyde; reaction for 24 h except entry 7 (2 h). [b] Reaction with 1 M LiCl DMF as solvent. [c] Yield% (sum of two diastereomers) was measured by ^{1}H NMR of the crude reaction mixture. [d] See Supporting Information for details.

Scheme 2. Retro-Michael Reaction of the Mannich Product



Results and Discussion

Development of a Diastereoselective Mannich Reaction. *N,O*-Acetal **3** was prepared by allowing enantiomerically pure *N*-benzyl-α-methylbenzylamine to react with paraformaldehyde in anhydrous methanol. Since both enantiomers of *N*-benzyl-α-methylbenzylamine are commerically available, both enantiomers of **3** are easily accessible. Compound **3** is a chiral analogue of **2**, the iminium precursor used in our enantioselective route to protected β^2-amino acids.[8] *N,O*-Acetal **3** can be isolated from the reaction mixture in >100 g quantities via simple distillation.

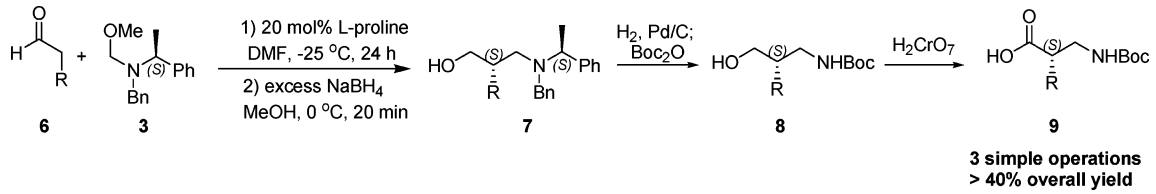
We used the aminomethylation of pentanal (**4**) for initial investigation of diastereoselective Mannich reaction protocols involving **3** (Table 1). No reaction could be detected when **3** and **4** were combined in DMF and allowed to stand for 24 h at room temperature. The addition of acetic acid to the DMF solution, to promote iminium ion formation from **3**, caused nearly complete conversion of **3** to Mannich product **5**, albeit with virtually no diastereoselectivity (Table 1, entry 2). The low stereoselectivity under these conditions suggests that Mannich reaction between the chiral iminium electrophile and the enol of aldehyde **4** (or enamine derived from **4** and *N*-benzyl-α-methylbenzylamine[13]) proceeds with little stereoinduction. In contrast to these results obtained at room temperature, no reaction occurs when **3**, **4**, and acetic acid are combined in DMF at −25 °C. In addition to this suppression of the "background" Mannich reaction, low-temperature minimizes other undesired processes, such as the self-aldol reaction of aldehyde **4**, epimerization[14] of the Mannich adduct **5**,[15] and retro-Michael reaction of the Mannich adduct (Scheme 2).

(13) There are two possible sources of *N*-benzyl-α-methylbenzylamine in the reaction mixture: hydrolysis of the iminium by residual water, and retro-Michael reaction of the Mannich adduct as shown in Scheme 2.

(14) For examples of epimerization of α-substituted aldehydes: (a) Chi, Y.; Peelen, T. J.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 3469. (b) Chi, Y.; Gellman, S. H. *Org. Lett*. **2005**, *7*, 4253. (c) List, B. *J. Am. Chem. Soc*. **2002**, *124*, 5656.

(15) Although the Mannich reaction at room temperature with L-proline as catalyst can give dr comparable to that at −25 °C, epimerization leads to poor reproducibility of Mannich reaction product diastereoselectivity at this temperature.

Table 2. Synthesis of Boc-β^2-Amino Acids with Hydrophobic Side Chains



6 3 7 8 9

			isolated yield % (major diastereomer)		
entry[a]	R	dr[b]	7[c]	8	9
a	Pr	86:14	62	92	85
b	^{n}Hex	89:11	51	92	89
c	Bn	88:12	62	99	92
d	^{i}Pr	90:10	49	95	91
e	$CH_2{}^i$Pr	83:17	51	96	90
f		84:16	52	91	95

[a] Reaction using 2.0 equiv (entry a−d) or 1.5 equiv (entry e−f) aldehyde; yields (sum of two diastereomers) of the Mannich reaction were >90% as determined by ^{1}H NMR of the crude reaction mixture before reduction; the reductions were quantitative. [b] Determined by ^{1}H NMR of the crude reaction mixture before reduction. [c] Isolated via crystallization or column chromatography.

The Mannich reaction occurs at −25 °C in DMF when **3**, **4**, and L-proline are combined in 1:2:0.2 ratio (i.e., L-proline is present in a catalytic amount, 20 mol % relative to iminium precursor **3**). This reaction generates desired product **5** with 86:14 dr (Table 1, entry 4).[16] Optimal results for the proline-mediated Mannich reaction require the use of excess (e.g., 1.5 equiv) aldehyde, relative to *N,O*-acetal **3**.[17] The presence of excess aldehyde slows two undesired reactions of the Mannich product: epimerization and retro-Michael reaction, processes that are promoted by L-proline and by *N*-benzyl-α-methylbenzylamine.[12,18] When the proline-catalyzed Mannich reaction is carried out in the presence of 1 M LiCl, the diastereoselectivity declines somewhat, to 76:24 dr (Table 1, entry 5). This diminution in stereoselectivity in the presence of salt is consistent with our previously reported observations regarding salt effects on the enantioselective Mannich reaction catalyzed by L-proline.[8] This salt effect suggests that non-hydrogen-bonded ionic interactions[19] in the transition state influence the stereochemical outcome of the reaction.[8]

Switching chirality of the catalyst (D-proline) had little impact on the yield of product **5** but altered and diminished the stereoselectivity of the Mannich reaction. The reaction catalyzed by D-proline favored the diastereomer of **5** with *R* configuration at the newly formed stereocenter, while L-proline favored *S* configuration at this center. With D-proline, the dr was 23:77, while L-proline gave a product with 86:14 dr. This difference in stereoselectivity likely arises from a matched/mismatched relationship between the chirality of the iminium ion and the chirality of the proline-derived enamine in the transition state for the Mannich reaction.[20] Diphenylprolinol TMS ether (*R*)-**1**[21,22] gave improved diastereoselectivity (~95:5 dr; Table 1, entry 7) relative to L-proline in the matched case; however, we decided to develop our β^2-amino acid synthesis with L-proline rather than **1** as the Mannich reaction catalyst because proline is very inexpensive.

Synthesis of Boc-Protected β^2-Amino Acids. If the diastereoselective Mannich reaction is to be useful for the synthesis of enantio-enriched β^2-amino acid derivatives, then isolation of the major diastereomer from the aminomethylation reaction must be straightforward. To avoid epimerization at the newly created

(16) A three-component Mannich reaction using pentanal, formaldehyde and (*S*)-*N*-benzyl-α-methylbenzylamine in the presence of L-proline as catalyst gave the desired Mannich product in 60% yield with ~80:20 dr, along with side product α,β-unsaturated aldehyde (Scheme 2).

(17) It is possible to use 1.0 equiv of aldehyde when the starting aldehyde is difficult to prepare. In this case, close monitoring of the reaction by ^{1}H NMR (Supporting Information) is necessary.

(18) The aldehyde starting material is more reactive towards the amine catalyst than is the Mannich product (α-substituted aldehyde) because of steric effects.

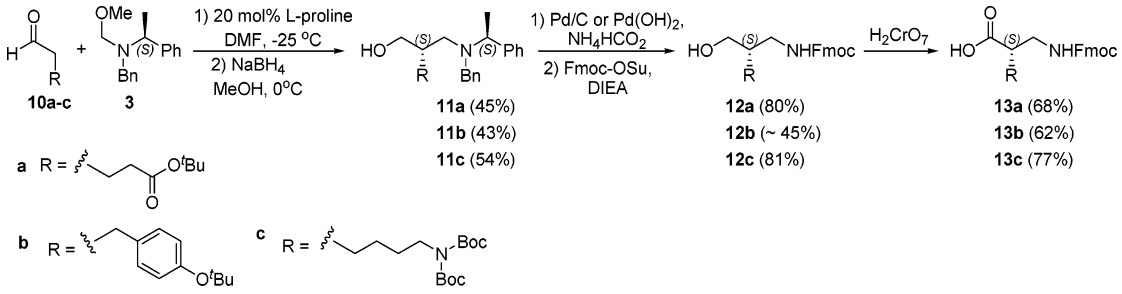
(19) For examples of non-covalent interactions in catalysis: (a) Tian, S.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (c) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (d) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (e) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (f) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (g) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (h) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101. (i) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (j) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 947. (k) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368. (l) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (m) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (n) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (o) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758. (p) Cao, C.; Ye, M.; Sun, X.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (q) Hansen, H. M.; Longbottom, D. A.; Ley, S. V. *Chem. Commun.* **2006**, *46*, 4838.

(20) For discussion of "double diastereoselectivity" in reactions with matched/mismatched chirality of reaction components, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(21) For a recent summary of the use of diaryl prolinol ethers as asymmetric catalysts: Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

(22) For recent examples using diaryl prolinol ethers as asymmetric catalysts: (a) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (b) Gotoh, H.; Masui, R.; Ogino, H.; Shoji, M.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 6853. (c) Bertelsen, S.; Marigo, M.; Brandes, S.; Diner, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (d) Marigo, M.; Bertelsen, S.; Landa, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (e) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (f) Zu, L.; Li, H.; Wang, J.; Yu, X.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 5131. (g) Enders, D.; Huttl, M. R. M.; Gronda, C.; Raabe, G. *Nature* **2006**, *441*, 861. (h) Chen, W.; Yuan, X. H.; Li, R.; Du, W.; Wu, Y.; Ding, L. S.; Chen, Y. C. *Adv. Synth. Catal.* **2006**, *348*, 1818. (i) Xie, J. W.; Yue, L.; Xue, D.; Ma, X. L.; Chen, Y. C.; Wu, Y.; Zhu, J.; Deng, J. G. *Chem. Commun.* **2006**, 1563. (j) Wang, J.; Li, H.; Zu, L.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 425. (k) Ho, C. Y.; Chen, Y. C.; Wong, M. K.; Yang, D. *J. Org. Chem.* **2005**, *70*, 898. (l) Ref 8 and 14b.

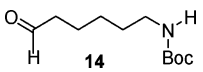
Scheme 3. Synthesis of Fmoc-β^2-Amino Acids with Protected Functionalized Side Chains



stereocenter during reaction workup and purification, we immediately reduced the aldehydes to the corresponding alcohols with $NaBH_4$. To our delight, for all the substrates described here the major γ-amino alcohol diastereomer was readily isolated via column chromatography. Furthermore, a number of the derivatives could be easily isolated by crystallization, either as the γ-amino alcohol itself or as the corresponding HCl salt. Isolation via crystallization is very attractive for large-scale synthesis. In addition, the availability of crystalline, stereochemically pure γ-amino alcohols or salts thereof allowed confirmation of product configuration through X-ray diffraction analysis for **7a**, **7c**, **7e**, and **7f** (see Supporting Information).

To establish the generality of this synthetic approach to protected β^2-amino acids, we carried out multigram syntheses of six compounds bearing hydrophobic side chains (Table 2). Four commercially available aldehydes (**6a**−**d**) and two aldehydes prepared in one step from commercially available alcohols via PCC oxidation (**6e** and **6f**)[23] were subjected to the optimized L-proline-catalyzed Mannich reaction/reduction sequence.[24] In each case, the major diastereomer of the γ-amino alcohol (**7a**−**f**) was isolated in 50−60% yield. Hydrogenolytic removal of the benzyl groups followed by Boc-protection of the resulting primary amine yielded Boc-protected γ-amino alcohols **8a**−**f**. Subsequent Jones oxidation[25] provided the protected β^2-amino acids **9a**−**f** after extractive workup. The complete synthetic routes involve only three or four simple operations and provide the enantio-pure β^2-amino acid derivatives in >40% overall yield.

Synthesis of Fmoc-Protected β^2-Amino Acids with Functionalized Side Chains. A major limitation of most synthetic approaches to β^2-amino acids is the difficulty of introducing sensitive functional groups, such as protected carboxylic acid or amino groups, into the side chain. Our method does not involve strongly acidic or basic conditions, which should make this route well-suited for synthesis of β^2-amino acids bearing side-chain functionality. We demonstrated this utility through the synthesis of Fmoc-protected derivatives of β^2-homoglutamic acid, β^2-homotyrosine, and β^2-homolysine with orthogonally protected side chains (Scheme 3). Aldehydes **10a**−**c**, each prepared in a few steps from commercially available materials (see Supporting Information), were used in the L-proline-catalyzed Mannich reaction, with subsequent $NaBH_4$ reduction, to yield γ-amino alcohols **11a**−**c**.[26] The yields for these Mannich/reduction sequences were a little lower than those observed for the analogous processes involving hydrocarbon side chains (Table 2); however, the diastereoselectivites were comparable to those in Table 2. Moreover, the subsequent transformations leading to Fmoc-β^2-amino acid derivatives **13a**−**c** proceeded efficiently. Careful workup of the Jones oxidation reactions that generate **13a**−**c** was necessary to avoid loss of acid-sensitive side-chain protecting groups. Alternatively, oxidation can be achieved with $NaIO_4/RuCl_3$ under neutral conditions.[9b,27] We were unsuccessful in our attempts to prepare Fmoc-β^2-homolysine with a single Boc protecting group on the side chain, starting from aldehyde **14**. No Mannich reaction product could be obtained. Moreover, the synthesis of **14** from the corresponding mono-Boc-protected aminohexanol gave only low yields, perhaps because the urethane adds intramolecularly to the carbonyl carbon.



Conclusions

We have developed a concise and versatile route for the synthesis of enantiomerically pure β^2-amino acids bearing useful protecting groups. The route features a diastereoselective Mannich reaction. L-Proline is employed as the catalyst, and the stoichiometric chiral component, an *N*,*O*-acetal derived from α-methlybenzylamine, is readily prepared on large scale. Diastereomerically and enantiomerically pure β-substituted-γ-amino alcohols resulting from the Mannich reaction/reduction sequence can be isolated by chromatography or crystallization. The reaction conditions are mild, the synthetic route is short, and purifications are generally straightforward; therefore, this protocol is suitable for large-scale synthesis of β^2-amino acids with diverse side chains, including those containing sensitive functional groups. Our catalytic diastereoselective method provides practical access to enantiomerically pure β^2-amino acid building blocks for use in foldamer synthesis, as well as access to other chiral molecules of potential value, such as α-substituted β-amino aldehydes and β-substituted γ-amino alcohols.

Experimental Section

Materials. Fmoc-OSu was purchased from Advanced ChemTech; other commercially available materials were purchased from Sigma-

(23) The aldehyde prepared from PCC oxidation was filtered through a silica pad; the filtrate was collected, concentrated, and subjected to Mannich reaction without further purification.

(24) We did not attempt to isolate the aldehyde product or directly oxidize it to carboxylic acid, because it is easier to separate the major diastereomer as the alcohol form. The aldehyde intermediates are subject to epimerization and side reactions such as retro-Michael reaction.

(25) Oxidation of chiral α-substituted aldehydes and alcohols to carboxylic acids without epimerization: (a) Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 3286. (b) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598. (c) See also refs 8, 14a,b.

(26) About 1.5 equiv aldehyde was used. Excess starting aldehyde reactant can be recycled (via the corresponding alcohol) after the Mannich reaction/reduction sequence.

(27) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479.

Aldrich and used as received. Catalyst **1** was prepared from diphenylmethyl prolinol according to a literature procedure.[28]

***N,O*-Acetal (3)** was prepared by using procedures analogous to those previously described for the synthesis of **2**.[8,29] To 150 mL (0.70 mol) of (*S*)-*N*-benzyl-α-methylbenzylamine dissolved in ~500 mL anhydrous MeOH in a 1000 mL round-bottom flask at room temperature was added 53 g (2.5 equiv) of paraformaldehyde, followed by 100 g of anhydrous K_2CO_3 and 100 g of anhydrous Na_2SO_4. The reaction proceeded immediately upon the addition of all reactants, and ^{1}H NMR analysis indicated complete conversion of the amine to *N,O*-acetal **3** within 1 h (typically within 5 min). The heterogeneous mixture was stirred for another 12 h (overnight) to ensure that H_2O produced during the reaction was completed absorbed by the anhydrous Na_2SO_4 and anhydrous K_2CO_3. The mixture was filtered through a pad of anhydrous Na_2SO_4 (~50 g) to remove solid materials, and the remaining solids were washed with about 300 mL of anhydrous MeOH and filtered. All filtrates were combined to give a light milky mixture. The mixture was concentrated to give a mixture of oil and white solid (the white solid is mainly paraformaldehyde). This mixture was mixed with about 150 mL of anhydrous Et_2O (paraformaldehyde remains as a solid in the Et_2O solution) and filtered through a pad of anhydrous Na_2SO_4. The remaining solid in the flask was washed with another 150 mL of anhydrous Et_2O and filtered. All filtrates were collected, combined, and concentrated to give a clear oil (181 g, 98% yield). ^{1}H NMR analysis of this oil indicated >95% purity of the *N,O*-acetal; this oil can be used for the Mannich reaction without further purification. From the above oil, pure *N,O*-acetal **3** was obtained via vacuum distillation (168−170 °C at 36−37 mmHg) as a colorless oil (168 g, 92% yield). This material can be stored at 4 °C for several months without observable decomposition. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22−7.45 (m, 10H), 4.18 and 4.21 (s, 1H), 4.08 (q, J = 6.6 Hz, 1H), 3.93 and 3.97 (s, 1H), 3.70−3.78 (m, 2H), 3.17 (s, 3H), 1.46 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3, 140.0 129.0, 128.5, 128.3, 127.7, 127.1, 127.0, 82.8, 59.5, 55.2, 52.9, 20.0. TOF-MS-ESI: the compound decomposes to amine under the conditions of this analysis; however, a trace amount of *N,O*-acetal was detected at 278.5 ($[M+Na]^+$ calculated 278.2. Optical rotation: $[\alpha]^{rt}_D$ −6.5 (*c* 2.0, MeOH).

General Procedure for the Diastereoselective Mannich Reaction (Table 1). To 0.1 mmol catalyst in 1 mL of HPLC grade DMF (or 1 M LiCl in DMF[30]) in an 8 mL vial cooled to −25 °C was added 1 mmol (110 μL) aldehyde. The mixture was stirred for a few minutes, and then 0.5 mmol (130 μL) *N,O*-acetal **3** was added. The mixture was stirred at −25 °C for 2 or 24 h, as indicated in Table 1. Yield and dr of the reaction were determined by ^{1}H NMR analysis of the crude reaction mixture.[31] Absolute stereochemistry of the reaction product was determined as described in our original publication[8]

General Procedure for Mannich Reaction/Reduction (Table 2). A mixture of 6 mmol (0.69 g) L-proline in 60 mL of HPLC grade DMF was stirred at room temperature for several hours,[32] and then this mixture was cooled to −25 °C. To the cooled catalyst mixture was added aldehyde (60 mmol, neat), and the mixture was stirred for a few minutes. *N,O*-Acetal **3** (30 mmol, 7.8 mL) was then added, and the mixture was stirred at −5 °C for 24 h. ^{1}H NMR analysis of the crude reaction mixture at this point revealed complete conversion of the limiting reagent, **3**. The product diastereomer ratio was determined by ^{1}H NMR. Excess $NaBH_4$ (90 mmol, 3.4 g) was added, followed by ~20 mL of MeOH. The mixture was stirred for a few minutes; the −25 °C bath was then replaced by an ice bath, and the mixture was stirred for an additional 20 min. The mixture was then slowly poured into a 1000 mL beaker containing 50−100 mL of saturated NH_4Cl at 0 °C to quench excess $NaBH_4$. The resulting mixture was extracted several times with Et_2O, until TLC indicated that all product had been removed into the organic phase. The Et_2O layers were combined, washed with water and then brine, dried over $MgSO_4$, filtered, and concentrated to give crude β-substituted γ-amino alcohols (the remaining DMF was removed under vacuum[33]). The major diastereomer (Table 2, **7a**−**f**) was isolated via column chromatography or crystallization as described below.

Isolation of the Major Diastereomer via Crystallization (Table 2). In some cases the major diastereomer from the Mannich reaction/reduction sequence could be directly crystallized by evaporation of a hexane solution (Table 2, entries 1 and 3). A more general protocol for crystallization was realized via vapor diffusion of Et_2O into a EtOAc−MeOH solution of the amino alcohol-HCl salt as described in detail below. The crude amino alcohol (or the diastereomeric mixture of the amino alcohols obtained after preliminary column chromatographic purification, if the crude sample could not be directly crystallized) was dissolved in Et_2O in a 150 mL flask at 0 °C. To this solution was added 4 N HCl in dioxane with stirring until the solution turned acidic as indicated by pH paper. The resulting mixture was stirred for a few minutes, and the solvent was removed under reduced pressure to give a viscous oil (or solid depending on the substrate and initial purity). To this viscous oil, was added 50 mL of EtOAc. The flask was shaken with heating (heat gun) until the oil solidified to give a milky mixture. A minimal amount (a few drops) of MeOH was added until a clear solution was obtained. The open flask with the hot EtOAc−MeOH solution was then placed in a large glass gar containing hot Et_2O. The container was sealed and left to stand at room temperature for crystallization, which took from minutes to days. White crystals from this procedure were isolated by filtration, washed with EtOAc, and dried in vacuo to afford the major diastereomer; no minor diastereomer was detected by ^{1}H NMR analysis.[34] This crystallization protocol generally gave the major diastereomer in 40−60% overall yield for the Mannich reaction/reduction sequence. X-ray crystal structures of several amino alcohols (**7a**, **7c**, **7e**, and **7f**) were determined (see Supporting Information).

One-Pot Hydrogenolysis and Boc Protection (Table 2). To about 1.0 g of wet 10% Pd/C in 50 mL of MeOH in a hydrogenation flask was added 15 mmol amino alcohol (as either the free base or the HCl salt) (Table 2, **7a**−**f**). The heterogeneous mixture was placed under 40−60 psi H_2 at room temperature overnight. After the hydrogenolysis was complete, as indicated by TLC and ^{1}H NMR analysis, the mixture was diluted with 50 mL of CH_2Cl_2, and DIEA (18 mmol, 3.2 mL for free amino alcohol; or 36 mmol, 6.4 mL for HCl salt of the amino alcohol) and Boc_2O (18 mmol, 4.0 g) were added. The mixture was stirred at room temperature overnight and then filtered through a pad of celite to remove Pd/C, and the celite was washed with MeOH extensively. The combined filtrate was concentrated and applied to a silica chromatography column eluted with EtOAc/hexane to give Boc protected β-substituted γ-amino alcohols (Table 2, **8a**−**f**) in excellent yield.

Jones Oxidation of Boc Protected β-Substituted γ-Amino Alcohols to Boc-β²-amino Acids (Table 2). To 10 mmol Boc protected β-substituted γ-amino alcohol (Table 2, **8a**−**f**) dissolved in 100 mL of acetone at 0 °C was added 15 mmol $H_2Cr_2O_7$ (30 mL of Jones

(28) (a) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(29) (a) Hosomi, A.; Iijima, S.; Sakurai, H. *Tetrahedron. Lett.* **1982**, *23*, 547. (b) Enders, D.; Ward, D.; Adam, J.; Raabe, G. *Angew. Chem., Int. Ed. Eng.* **1996**, *35*, 981. (c) Rehn, S.; Ofial, A. R.; Mayr, H. *Synthesis* **2003**, 1790.

(30) Concentration of LiCl refers to room temperature concentration. At - 25 °C, LiCl partially precipitates.

(31) See Supporting Information for details regarding use of ^{1}H NMR to monitor the reaction.

(32) Proline has poor solubility in DMF and is not completely dissolved even after it is stirred overnight. The Mannich reaction time can vary from a few to 24 h partially because of the limited solubility of proline.

(33) It is important to remove DMF completely to achieve efficient crystallization. When using column chromatography for purification, a small amount residual DMF does not affect the purification.

(34) Recrystallization may be necessary if the crystals contain the minor diastereomer at this point.

reagent).[35] The mixture was stirred for 12 h, during which time the mixture warmed to room temperature. Excess isopropanol was then added, and the mixture was stirred overnight. The mixture was filtered, and the filtrate was concentrated to about 20 mL under reduced pressure at room temperature. The concentrate was diluted with 20 mL of 2 N aqueous HCl and extracted with Et_2O until TLC indicated that all product had been removed from the aqueous phase. The combined Et_2O layers were concentrated to about 50 mL. Except in the case of **9b**, the concentrated Et_2O solution was extracted with 2 M aqueous NaOH (monitored by TLC). The combined basic aqueous extracts were washed with 2 × 10 mL Et_2O, and the organic layers were discarded. The basic aqueous solution was then acidified with 2 N aqueous HCl and extracted with Et_2O (monitored by TLC). The combined Et_2O layers were washed with saturated NaCl, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give Boc-β^2-amino acid that was pure by TLC and NMR analysis.

For **9b**, the Et_2O layers from the first extraction were washed with saturated NaCl, dried over $MgSO_4$, filtered, and concentrated to give a viscous oil, from which the desired compound was purified via column chromatography eluted with MeOH/CH_2Cl_2 (1/10, v/v; TLC $R_f = 0.29$) to give pure product in 89% yield.

Synthesis of β²-Homoglutamic Acid, β²-Homotyrosine, and β²-Homolysine. The synthesis of the above three β^2-amino acids, with acid- or base-sensitive functional groups in the side chain, involved procedures analogous to those described above for preparing β^2-amino acids with hydrocarbon side chains (Table 2). Detailed procedures are provided in the Supporting Information.

(35) Jones reagent preparation: To 50 mmol $Na_2Cr_2O_7$ dissolved in 50 mL of H_2O, was slowly added 200 mol concentrated H_2SO_4. The solution was then diluted to 100 mL to give the Jones reagent (0.5 M $H_2Cr_2O_7$).

Acknowledgment. This research was supported by NIH Grant GM56414 and NSF Grant CHE-0551920. NMR equipment purchase was supported in part by grants from NIH and NSF, and X-ray equipment by NSF. Additional support was provided by the UW-Madison Nanoscale Science and Engineering Center (NSF Grant DMR-0425880). Y.C. was supported in part by a fellowship from Abbott Laboratories; E.P.E. was supported in part by NIH chemistry and biology interface training Grant NIGMS T32 GM008505; and W.S.H. was supported in part by an NIH postdoctoral fellowship CA119875. We thank Josh Price, Li Guo, and other Gellman group members for helpful discussions during their use of this chemistry, and Dr. Ilia Guzei for X-ray crystallographic analysis.

Supporting Information Available: Experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

JA070063I