

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

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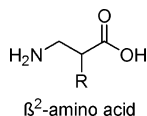
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Abstract: Proline-catalyzed diastereoselective aminomethylation of aldehydes using a chiral iminium ion, generated from a readily prepared precursor, provides α -substituted- β -amino aldehydes with 85:15 to 90:10 dr. The α -substituted- β -amino aldehydes 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

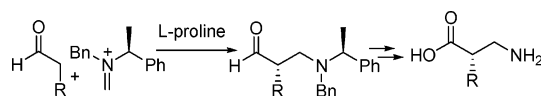
β^2 -Amino acids are 3-aminopropanoic acids bearing a single substituent adjacent to the carboxylic acid group. β^2 -Amino acid residues can be found embedded within natural products that exhibit interesting biological activities.¹ In addition, β^2 -residues are essential for the formation of specific β -peptide secondary structures² (e.g., 12/10-helix, β^2/β^3 reverse turn³). Designed β -peptides containing β^2 -residues display useful functions including mimicry of somatostatin signaling⁴ 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}



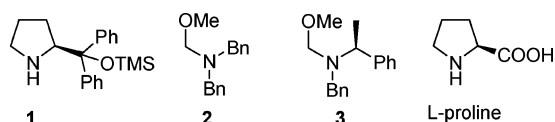
We recently reported a new route to protected β^2 -amino acids⁸ that is based on enantioselective aminomethylation of aldehydes⁹ via an organocatalytic Mannich reaction.^{10–12} The Mannich reaction involves diphenylprolinol TMS ether (**1**) as catalyst and a formaldehyde-derived iminium generated in situ from *N,O*-acetal **2** as the electrophile. Our route to protected β^2 -amino

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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 $\sim 90\%$ 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.



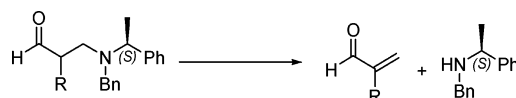
We turned our attention to a *diastereoselective* version of the Mannich reaction (Scheme 1), since the major stereoisomer from such a reaction should be readily isolated via column chromatography or crystallization. Our experience suggested that such a process would be very valuable for rapid preparation 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.

Table 1. Diastereoselective Mannich Reaction

entry ^a	catalyst	T	yield ^c	dr ^c	avored diastereomer ^d
1		room temp	<1		
2	HOAc	room temp	>90	57:43	<i>S, S</i>
3	HOAc	−25 °C	<1		
4	L-proline	−25 °C	>90	86:14	<i>S, S</i>
5 ^b	L-proline	−25 °C	>90	76:24	<i>S, S</i>
6	D-proline	−25 °C	>90	23:77	<i>R, S</i>
7 ^b	(<i>R</i>)-1-HOAc	−25 °C	>90	$\sim 95:5$	<i>S, S</i>

^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 ¹H 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 commercially 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.

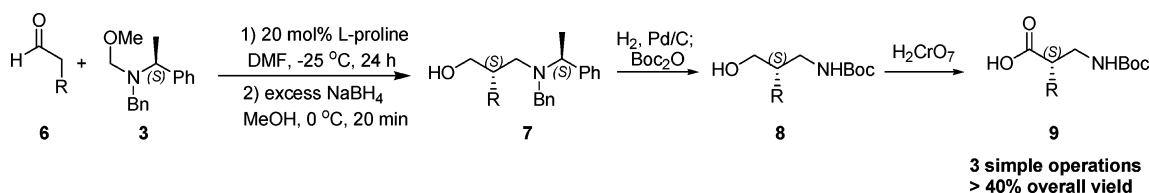
We used the aminomethylation of pentanal (**4**) for initial investigation of diastereoselective Mannich reaction protocols involving **3** (Table 1). No reaction could be detected when **3** and **4** were combined in DMF and allowed to stand for 24 h at room temperature. The addition of acetic acid 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 -methylbenzylamine¹³) 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**, epimerization¹⁴ of the Mannich adduct **5**,¹⁵ and retro-Michael reaction of the Mannich adduct (Scheme 2).

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(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

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 ¹H NMR of the crude reaction mixture before reduction; the reductions were quantitative. ^b Determined by ¹H NMR of the crude reaction mixture before reduction. ^c Isolated via crystallization or column chromatography.

The Mannich reaction occurs at $-25\text{ }^{\circ}\text{C}$ 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 interactions¹⁹ in the transition state influence the stereochemical outcome of the reaction.⁸

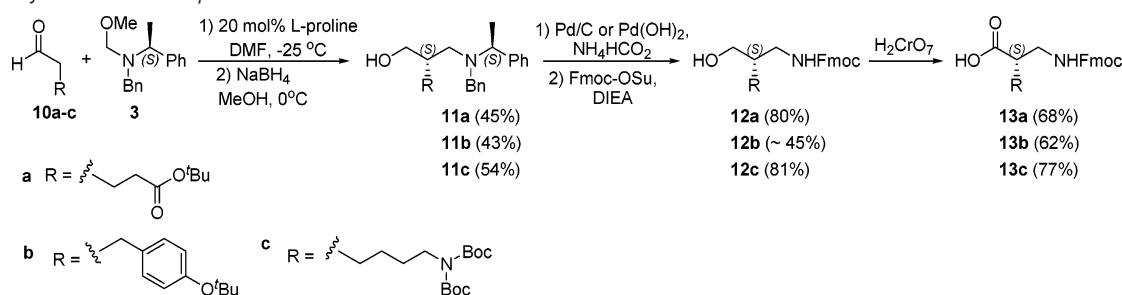
Switching chirality of the catalyst (D-proline) had little impact on the yield of product **5** but altered and diminished the stereoselectivity of the Mannich reaction. The reaction catalyzed by D-proline favored the diastereomer of **5** with *R* configuration at the newly formed stereocenter, while 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 (\sim 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 \sim 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 ¹H NMR (Supporting Information) is necessary.
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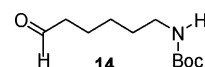
Scheme 3. Synthesis of Fmoc- β^2 -Amino Acids with Protected Functionalized Side Chains

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 oxidation²⁵ 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 diastereoselectivities 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 $\text{NaIO}_4/\text{RuCl}_3$ 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 -methylbenzylamine, 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 K₂CO₃ and 100 g of anhydrous Na₂SO₄. The reaction proceeded immediately upon the addition of all reactants, and ¹H 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 H₂O produced during the reaction was completely absorbed by the anhydrous Na₂SO₄ and anhydrous K₂CO₃. The mixture was filtered through a pad of anhydrous Na₂SO₄ (~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 Et₂O (paraformaldehyde remains as a solid in the Et₂O solution) and filtered through a pad of anhydrous Na₂SO₄. The remaining solid in the flask was washed with another 150 mL of anhydrous Et₂O and filtered. All filtrates were collected, combined, and concentrated to give a clear oil (181 g, 98% yield). ¹H 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. ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75 MHz, CDCl₃): 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: $[\alpha]_D^{25}$ –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 DMF³⁰) in an 8 mL vial cooled to –25 °C was added 1 mmol (110 μ L) aldehyde. The mixture was stirred for a few minutes, and then 0.5 mmol (130 μ L) *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 ¹H NMR analysis of the crude reaction mixture.³¹ Absolute stereochemistry of the reaction product was determined as described in our original publication⁸

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. ¹H 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

¹H NMR. Excess NaBH₄ (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 NH₄Cl at 0 °C to quench excess NaBH₄. The resulting mixture was extracted several times with Et₂O, until TLC indicated that all product had been removed into the organic phase. The Et₂O layers were combined, washed with water and then brine, dried over MgSO₄, filtered, and concentrated to give crude β -substituted γ -amino alcohols (the remaining DMF was removed under vacuum³³). 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 Et₂O 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 Et₂O 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 jar containing hot Et₂O. 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 ¹H 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 H₂ at room temperature overnight. After the hydrogenolysis was complete, as indicated by TLC and ¹H NMR analysis, the mixture was diluted with 50 mL of CH₂Cl₂, 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 Boc₂O (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- β^2 -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 H₂Cr₂O₇ (30 mL of Jones

(28) (a) Marigo, M.; Fielenbach, D.; Branton, 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. Engl.* **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 ¹H 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 Et₂O until TLC indicated that all product had been removed from the aqueous phase. The combined Et₂O layers were concentrated to about 50 mL. Except in the case of **9b**, the concentrated Et₂O solution was extracted with 2 M aqueous NaOH (monitored by TLC). The combined basic aqueous extracts were washed with 2 \times 10 mL Et₂O, and the organic layers were discarded. The basic aqueous solution was then acidified with 2 N aqueous HCl and extracted with Et₂O (monitored by TLC). The combined Et₂O layers were washed with saturated NaCl, dried over MgSO₄, 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 Et₂O layers from the first extraction were washed with saturated NaCl, dried over MgSO₄, filtered, and concentrated to give a viscous oil, from which the desired compound was purified via column chromatography eluted with MeOH/CH₂Cl₂ (1/10, v/v; TLC *R_f* = 0.29) to give pure product in 89% yield.

Synthesis of β^2 -Homoglutamic Acid, β^2 -Homotyrosine, and β^2 -Homolysine. The synthesis of the above three β^2 -amino acids, with

(35) Jones reagent preparation: To 50 mmol Na₂Cr₂O₇ dissolved in 50 mL of H₂O, was slowly added 200 mol concentrated H₂SO₄. The solution was then diluted to 100 mL to give the Jones reagent (0.5 M H₂Cr₂O₇).

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.

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

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