A Stereocontrolled, Convergent Synthesis of Hydroxyethylene Dipeptide Isosteres

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Received March 31, 1997[⊗]

A simple, convergent, and stereoselective synthesis of hydroxyethylene dipeptide isosteres **1** and **2** from scalemic α-hydroxy esters has been developed. The method is short (six steps), efficient (≈15−25% overall), and highly diastereoselective (86−94% de) and enantioselective (>95% ee).

Introduction

For the past two decades there has been an ever increasing interest in the use of enzyme inhibitors as therapeutic agents.[1] Since proteases are known to mediate a wide variety of disease states, protease inhibitors have become common starting points for drug discovery efforts related to those diseases.[2] A recurring design element in protease inhibitors is replacement of the scissile amide bond in a substrate peptide with another functional group. The resulting peptide isostere can bind strongly in the active site of the protease, but hydrolysis (and thus release and turnover) is not possible, thus inhibiting the normal function of the protease.[2]

Inhibitors of aspartate proteases have been of particular interest recently, since the aspartate protease renin is involved in the regulation of blood pressure,[3] and the aspartate protease HIV-1 protease plays a crucial role in the replication cycle of the AIDS virus.[4] Replacement of the scissile amide bond with a hydroxyethylene group is a common structural motif in aspartate protease inhibitors (Figure 1). The hydroxyl group serves as a mimic for the tetrahedral intermediate of proteolysis and is bound tightly in the active site, but the hydroxyethylene group is incapable of hydrolytic cleavage.[2a]

A synthesis of hydroxyethylene peptide isosteres must focus on the dipeptide core which is a 2-alkyl-4-hydroxy-5-amino acid derivative. Moreover the control of stereochemistry at three stereogenic centers is a central requirement of any preparative method. The 4*S*,5*S* stereochemistry[5] is generally preferred in hydroxyethylene peptide isostere inhibitors of aspartate proteases.[2a,6] The chiral center at C-2 may be either the 2*R* (**1**) or 2*S* (**2**) configuration. The 2*R* configuration in **1** has the same stereochemical disposition as the alkyl group of the natural peptide (containing an L-amino acid) and is most common. However, the stereocontrolled synthesis of both 2*R* and 2*S* diastereomers is desirable for the study of structure−activity relationships[7] and in the preparation of several potential HIV-1 protease inhibitors.[8]

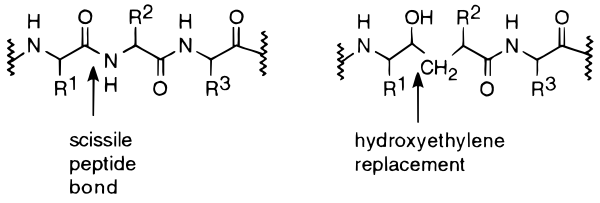
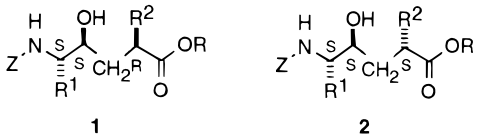


Figure 1. Hydroxyethylene isosteric replacement.



1 **2**

A second prerequisite of synthetic methodology for the preparation of **1** and **2** is the latitude to incorporate a wide range of R^2 groups at C-2. The use of R^1 and R^2 groups not commonly found in amino acids can lead to increased intrinsic inhibitory potency and improved antiviral activity.[9]

Beginning with the pioneering work of Szelke[10] and Rich[11] in 1983, a number of approaches have been reported for the synthesis of **1**. The most common approach is to construct the 3,4-carbon−carbon bond by reacting an N-protected amino aldehyde with a homoenolate equivalent.[12] The alkyl group at C-2 is installed by an alkylation of an intermediate lactone in a stereospecific *trans* fashion (Scheme 1).

A less common approach to **1** is to construct the 2,3-carbon−carbon bond by the reaction of a two-carbon fragment with amino ketones,[13] α-amino epoxides,[14] α-hydroxy-β-amino aldehydes,[15] or 4-amino-3-keto phos-

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1997.

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(5) The *S* stereochemical designation may change to *R* for certain side chains because of Cahn−Ingold−Prelog priority rules, but the stereochemical orientation of the side chain would be the same.

(6) It has been found that extended binding regions can alter the *S* preference in HIV-1 protease and potentially other proteases as well. Rich, D. H.; Sun, C.-Q.; Vara Prasad, J. V. N.; Pathiasseril, A.; Toth, M. V.; Marshall, G. R.; Clare, M.; Mueller, R. A.; Houseman, K. *J. Med. Chem.* **1991**, *34*, 1222.

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(9) Danielmeier, K.; Schierle, K.; Steckhan, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2247 and references therein.

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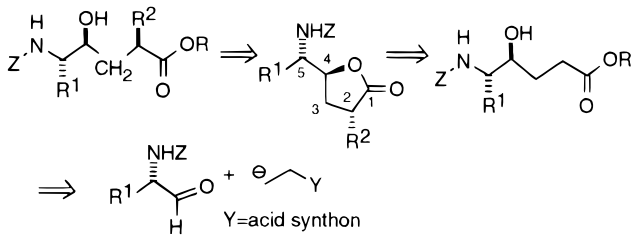
S0022-3263(97)00579-3 CCC: $14.00

Scheme 1

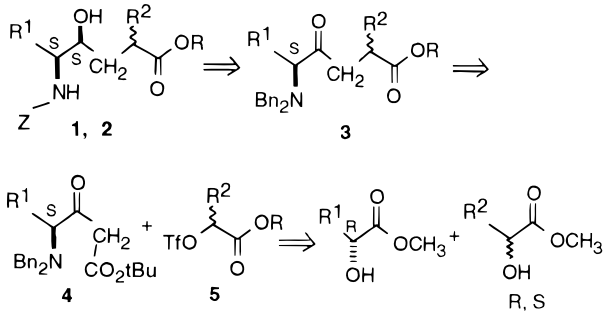


phonates[16] which themselves were generally obtained from α-amino aldehydes. Other approaches have utilized a variety of starting materials including carbohydrates,[17] acid chlorides,[18] glutamic acid,[19] and isovaleryl aldehyde.[20] These methodologies often are long (>10 steps) and thus inefficient, sometimes have poor diastereoselectivity, and are limited in the choice of side chains R^1 and R^2. In addition, virtually all of these syntheses install the R^2 group by alkylation of a lactone intermediate which occurs diastereoselectively to give **1**. Few preparations of the diastereomer **2** have been attempted.[18] An efficient and convergent synthesis of **1** and **2** has yet to be described.

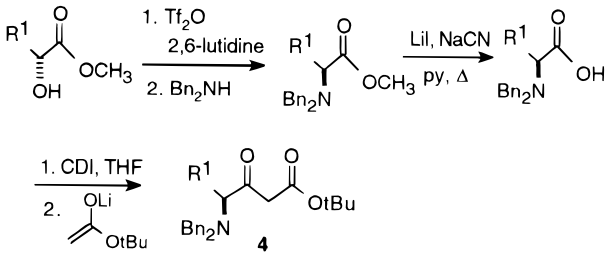
We reported earlier that the alkylation of 4-amino-3-keto esters with ethyl bromoacetate followed by decarboxylation produced 2-unsubstituted 5-amino-4-keto esters.[21] Subsequently we found that scalemic 2-triflyloxy esters react with *β*-keto ester enolates to give 2-alkyl-4-keto esters in high ee's.[22,23] These results provided a simple entry into ketomethylene dipeptide isosteres,[24] but these could not be reduced to hydroxyethylene dipeptide isosteres with high diastereoselectivity.[21]

Reetz reported that α-*N*,*N*-dibenzylamino ketones can be reduced to the corresponding *syn*-vicinal amino alcohol with high diastereoselectivity.[25] This reduction method gives the correct stereochemical relationship between the amine and hydroxyl groups of hydroxyethylene peptide isosteres as demonstrated by Liotta.[13a]

Scheme 2



Scheme 3



By linking our scalemic triflate alkylation results with the reduction studies of Reetz,[25] we are pleased to describe the first convergent synthesis of **1** and **2** which is short, efficient, and highly stereoselective.

Results and Discussion

The synthetic approach we have developed to **1** and **2** is shown in Scheme 2. As rewritten to emphasize the more common 4*S*,5*S*-*syn* relationship of the amine and hydroxyl groups, **1** is derived from reduction of keto ester **3**, which in turn results from the chiral alkylation of the enolate of *β*-keto ester **4** and a scalemic triflate **5** (*R* or *S*). Both **4** and **5** ultimately come from α-hydroxy esters which can be obtained optically pure from a variety of sources.[26]

We previously disclosed an efficient three step synthesis of 4-(*N*,*N*-dibenzylamino)-3-keto esters **4** from scalemic α-hydroxy esters (Scheme 3). This sequence gives good overall yields (55−61%) with no detectable racemization (>95% ee) and provides an extraordinarily short route to statine derivatives.[27]

Keto esters **4** were converted to their enolates with NaH and alkylated with scalemic 2-triflyloxy esters **5**, also prepared from α-hydroxy esters.[24] Both *R* and *S* enantiomers of **5** were used to demonstrate convergency. The intermediate tricarbonyl derivatives **6** were treated immediately with TFA to effect decarboxylation and give ketomethylene peptide isosteres **3** in moderate yields for the two steps (40−57%) (Scheme 4). For the various combinations used, reaction of keto ester **4x** with triflate **5y** gives isostere **3xy**.

The diastereoselectivity of the alkylation−decarboxylation is generally quite good, ranging from 86 to 94% de (Table 1); moreover the diastereomers can easily be separated by chromatography on silica gel. The lowest de was found for the alkylation of **4d** with triflate **5c**

(12) Representative examples: (a) Ciapetti, P.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1994**, *35*, 3183. (b) Konieczny, M. T.; Toma, P. H.; Cushman, M. *J. Org. Chem.* **1993**, *58*, 4619. (c) Jones, D. M.; Nilsson, B.; Szelke, M. *J. Org. Chem.* **1993**, *58*, 2286. (d) D'Aniello, F.; Gehanne, S.; Taddei, M. *Tetrahedron Lett.* **1992**, *33*, 5621. (e) Thompson, W. J.; Ball, R. G.; Darke, P. L.; Zugay, J. A.; Thies, J. E. *Tetrahedron Lett.* **1992**, *33*, 2957. (f) Kano, S.;Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **1991**, *32*, 233. (g) Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4828. (h) Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921.

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Scheme 4

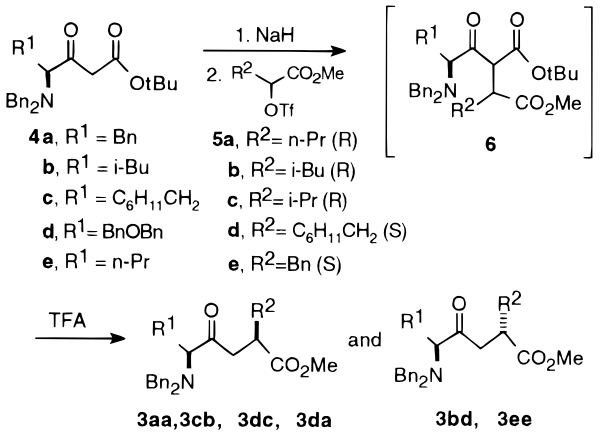
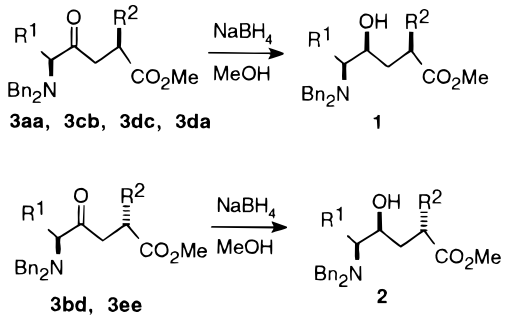


Table 1. Stereochemical Results of the Preparation of Ketomethylene Dipeptide Isosteres 3

entry	product	yield (%)[a]	de (%)[b]	ee (%)[c]
1	**3aa**	50	94	>95
2	**3cb**	46	90	>95
3	**3dc**	40	70	>95
4	**3da**	42	94	>95
5	**3bd**	57	86	>95
6	**3ee**	46	90	>95

[a] Isolated yields of chromatographed mixtures of diastereomers. [b] Determined by ^{1}H NMR of the mixture of diastereomers in corroboration with chromatographic separation. [c] Determined by chiral LIS study using Eu(hfc)$_3$ on separated major diastereomer.

Scheme 5



(entry 3) which has a branched chain next to the triflate leaving group. In this sterically hindered case the reaction time was increased to 48 h. In each case the major diastereomer of **3** was separated and examined by the chiral shift reagent Eu(hfc)$_3$. Within the limits of NMR detection only one enantiomer was present (>95% ee), indicating that no epimerization at C-5 takes place during the reaction sequence.[28]

Reduction of the major diastereomers of amino ketones **3** with sodium borohydride in absolute methanol gave *N*,*N*-dibenzyl-protected hydroxyethylene dipeptide isosteres **1aa, 1cb, 1dc, 1da**, and **2bd, 2ee** in good yields and excellent diastereoselectivity (Scheme 5, Table 2). Only a single diastereomer was observed in the ^{1}H NMR spectrum, indicating both that the reduction is highly stereoselective (>95%) and that no epimerization at C-2 or C-5 occurs.

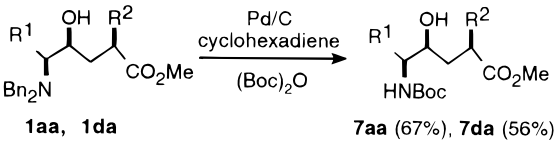
From previous studies it is known that the reduction of *N*,*N*-dibenzylamino ketones takes place with *syn* stereochemistry,[13a,25] and *syn* stereochemistry was assumed for the reduction of **3**. Although the chiral center at C-2 could influence the reduction stereochemistry, the data suggest this is not the case. Only a single diastereomer is observed in the reduction. Thus the alkyl group at C-2 must either completely reverse the *syn* diastereoselectivity known for α-dibenzylamino ketones or have no observable effect. Since it is unlikely that a chiral center two atoms away from the carbonyl group would completely reverse the stereochemical control effected by the bulky dibenzylamino group vicinal to the carbonyl group, the assumption of *syn* stereochemistry in **1** is a sound one. Because *R*-α-hydroxy esters were used as starting materials, the stereochemistry in **3** is 5*S* and consequently *syn* reduction products **1** and **2** both have the 4*S*,5*S* stereochemistry common in hydroxyethylene dipeptide isosteres.

Table 2. Stereochemical Results of the Preparation of Hydroxyethylene Dipeptide Isosteres 1 and 2 by the Reduction of 3

entry	Product	Yield (%)[a]	de (%)[b]
1	**1aa**	89	>95
3	**1cb**	80	>95
4	**1dc**	90	>95
6	**1da**	91	>95
2	**2bd**	80	>95
5	**2ee**	84	>95

[a] Isolated yields of chromatographically pure diastereomers. [b] Determined by ^{1}H NMR, only one diastereomer observed.

Scheme 6



Solely for demonstration purposes, the *N*,*N*-dibenzyl protecting group was removed and converted to the Boc group, **7**, in a one-pot procedure (Scheme 6).[29] No attempts were made to optimize the yields of **7**. *N*-Boc-protected hydroxyethylene dipeptide isosteres **7** tend to lactonize during removal of the Boc group under acidic conditions; thus Boc protection is not very useful for these compounds.[11c,13] This protecting group interchange simply shows that *N*,*N*-dibenzyl groups provide good orthogonal protection for **7** and they can be removed readily.

There are several points that should be noted. First, the starting α-hydroxy esters are available commercially, from amino acids, or from a variety of other sources.[26] Thus the structure of R^1 and R^2 and the chirality of the product are not restricted to those available in amino acid precursors. Furthermore the methodology is convergent so that diastereomers epimeric at C-2 can be produced from a single precursor.

Second, the diastereoselectivity of the process is generally good (86−94% de) and the enantioselectivity is very high (>95% ee); thus good stereocontrol can be exerted at three chiral centers. This control is based on clean stereochemical inversion in the alkylation of **4** by scalemic triflate **5**[23] and by highly diastereoselective *syn* reduction of **3**.[13a,25]

Third, differential reactivity is used to create the functional groupings in **1** and **2** without the need for extensive protection−deprotection schemes. This contributes to the overall efficiency of the method.

(28) For calibrating the LIS method to determine enantioselectivity, racemic **4a** was prepared and converted to racemic **3aa** which was examined by the LIS reagent.

(29) Bajwa, J. S. *Tetrahedron Lett.* **1992**, *33*, 2955.

In summary, a simple, convergent, and stereoselective synthesis of hydroxyethylene dipeptide isosteres **1** and **2** from scalemic α-hydroxy esters has been developed. The method is short (six steps from α-hydroxy esters), efficient (≈15−25% overall), and highly diastereoselective (86−94% de) and enantioselective (>95% ee).

Experimental Section

Infrared spectra were taken as neat liquids or as KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irradiation and/or iodine. Analytical HPLC was performed with the indicated solvent systems and flow rates on 8 mm × 25 mm cm silica gel columns using UV detection. Preparative thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irradiation. Flash chromatography was performed using silica gel 60 (230−400 mesh). Tetrahydrofuran was distilled from benzophenone ketyl. Other solvents were HPLC grade and were used without further purification. Starting materials were purchased from Aldrich, Sigma, or Novabiochem and used as received. Elemental analyses were carried out by M-H-W laboratories, Phoenix, AZ.

The synthesis of 3-oxo esters **4** and triflates **5** has been reported previously.[27]

***N,N*-Dibenzyl-PheΨ[COCH$_2$](2*R*,5S)Nva-OMe, 3aa. General Procedure**. A solution of 3-oxo ester **4a** (970 mg, 2.19 mmol) in THF (10 mL) was added dropwise to a stirred suspension of NaH (92.0 mg of 60% in oil, 2.30 mmol) in dry THF (30 mL) at 0 °C under nitrogen. The mixture was stirred for 10 min. A solution of triflate **5a** (607 mg, 2.30 mmol) in dichloromethane (10 mL) was added dropwise to the gray suspension. The resulting mixture was stirred at room temperature for 24 h and then quenched with 1 N HCl (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide a pale yellow oil. Without further purification, the above oil was dissolved in dichloromethane (10 mL) and treated with TFA (3.2 mL) at room temperature for 24 h. After dilution with dichloromethane (50 mL), the resulting solution was washed with saturated $NaHCO_3$ (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated to provide **3aa** as a colorless oil (500 mg, 50% based on **4a**) after purification by flash chromatography (hexane:ether = 85:10). Product **3aa** had 94% de on the basis of the separated diastereomers in corroboration with the ^{1}H NMR of the crude product. The major diastereomer had ee > 95% by a chiral LIS study using Eu(hfc)$_3$ in comparison with a racemic sample: $[\alpha]^{25}_D$ −83.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR δ 0.81 (t, 3H, *J* = 7.0 Hz), 1.18−1.43 (set of m, 4H), 2.09 (m, 1H), 2.66 (m, 1H), 2.90 (m, 1H), 3.20 (m, 2H), 3.54 (m, 1H), 3.60 (d, 2H, *J* = 13.6 Hz), 3.59 (s, 3H), 3.80 (d, 2H, *J* = 13.6 Hz), 7.35 (m, 15H); ^{13}C NMR δ 13.5, 19.9, 29.3, 33.7, 39.3, 43.2, 51.2, 54.1, 67.5, 125.8, 127.0, 128.1, 128.7, 129.3, 138.9,175.5, 196.6; FTIR (neat) 1738, 1719 cm^{-1}. Anal. Calcd for $C_{30}H_{35}O_3N$: C, 78.78; H, 7.71; N, 3.06. Found: C, 78.92; H, 7.59; N, 3.14.

Dibenzyl-LeuΨ[COCH$_2$](2*S*,5*S*)Cha-OMe, 3bd: yield 57% (based on **4b**) of a colorless oil that had de 86% on the basis of flash chromatography (hexane:ether = 85:10). The major diastereomer had ee > 95%; $[\alpha]^{25}_D$ +55.5 (*c* 0.81, $CHCl_3$); ^{1}H NMR δ 0.79 (d, 3H, *J* = 6.4 Hz), 0.82 (d, 3H, *J* = 7.6 Hz), 0.86−1.72 (set of m, 16H), 2.52−2.90 (set of m, 3H), 3.30 (dd, 1H, *J* = 4.5, 6.8 Hz), 3.52 (d, 2H, *J* = 13.6 Hz), 3.62 (s, 3H), 3.69 (d, 2H, *J* = 13.6 Hz), 7.31 (m, 10H); ^{13}C NMR δ 22.4, 23.0, 25.3, 26.2, 27.8, 31.9, 33.2, 37.4, 39.6, 43.0, 51.6, 54.5, 63.7,127.1,128.3, 128.7, 128.9, 139.5, 176.4, 209.8; FTIR (neat) 1741, 1721 cm^{-1}. Anal. Calcd for $C_{31}H_{43}O_3N$: C, 77.95; H, 9.07; N, 2.93. Found: C, 77.78; H, 9.19; N, 2.78.

Dibenzyl-ChaΨ[COCH$_2$](2*R*,5*S*)Leu-OMe, 3cb: yield 46% (based on **4c**) of a colorless oil that had de 90% on the basis of flash chromatography (hexane:ether = 85:10). The major diastereomer had ee > 95%; $[\alpha]^{25}_D$ −40.8 (*c* 0.80, $CHCl_3$); ^{1}H NMR δ 0.82 (d, 3H, *J* = 8.1 Hz), 0.86 (d, 3H, *J* = 5.4 Hz), 0.82−1.69 (set of m, 16H), 2.63−2.82 (set of m, 3H), 3.33 (dd, 1H, *J* = 4.8, 6.7 Hz), 3.53 (d, 2H, *J* = 13.8 Hz), 3.62 (s, 3H), 3.65 (d, 2H, *J* = 13.8 Hz), 7.31 (m, 10H); ^{13}C NMR δ 22.7, 26.7, 27.0, 31.0, 33.6, 34.1, 35.1, 38.8, 41.7, 43.6, 52.0, 54.9, 63.5, 127.6, 128.8, 129.1, 129.4, 140.0, 176.8, 210.3; FTIR (neat) 1744, 1716 cm^{-1}. Anal. Calcd for $C_{31}H_{43}O_3N$: C, 77.95; H, 9.07; N, 2.93. Found: C, 78.06; H, 8.81; N, 2.98.

Dibenzyl-Ser(Bzl)Ψ[COCH$_2$](2*S*,5*S*)Val-OMe, 3dc: yield 40% (based on **4d**) of a colorless oil that had de 70% on the basis of flash chromatography (hexane:ether = 85:10 to 80:15). The major diastereomer had ee 95%: $[\alpha]^{25}_D$ +21.5 (*c* 1.36, $CHCl_3$); ^{1}H NMR δ 0.87(d, 6H, *J* = 5.9 Hz), 1.90 (m, 1H), 2.86 (dd, 1H, *J* = 3.3, 15.2 Hz), 2.66 (m, 1H), 3.25 (dd, 1H, *J* = 10.8, 15.2 Hz), 3.59 (t, 1H, *J* = 6.1 Hz), 3.64 (s, 3H), 3.69 (d, 2H, *J* = 13.6 Hz), 3.80 (d, 2H, *J* = 13.6 Hz), 3.88 (d, 2H, *J* = 6.1 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.54 (d, 2H, *J* = 12.0 Hz), 7.32 (m, 15H); ^{13}C NMR δ 19.7, 20.2, 30.0, 40.3, 45.9, 51.4, 54.9, 65.1, 67.0, 73.5, 127.1, 127.7, 128.3, 129.0, 138.1, 139.5, 175.3, 209.9; FTIR (neat) 1739, 1721 cm^{-1}. Anal. Calcd for $C_{31}H_{37}O_4N$: C, 76.36; H, 7.65; N, 2.87. Found: C, 76.11; H, 7.89; N, 2.87.

Dibenzyl-NvaΨ[COCH$_2$](2*S*,5*S*)Phe-OMe, 3ee: yield 46% (based on **4e**) of a colorless oil that had de 90% on the basis of flash chromatography (hexane:ether = 85:10). The major diastereomer had ee 95%: $[\alpha]^{25}_D$ +57.5 (*c* 3.94, $CHCl_3$); ^{1}H NMR δ 0.85 (t, 3H, *J* = 7.2 Hz), 1.14−1.71 (set of m, 4H), 2.63 (m, 3H), 3.03 (m, 2H), 3.17 (dd, 3H, *J* = 4.4, 8.0 Hz), 3.45 (d, 2H, *J* = 13.6 Hz), 3.56 (d, 2H, *J* = 13.6 Hz), 3.61 (s, 3H), 7.24 (m, 15H); ^{13}C NMR δ 14.6, 20.7, 25.5, 28.2, 38.2, 42.2, 52.2, 54.9, 65.8, 127.1, 127.6, 128.7, 129.0, 129.1, 139.1, 139.8, 175.6, 210.3; FTIR (neat) 1734, 1716 cm^{-1}. Anal. Calcd for $C_{30}H_{35}O_3N$: C, 78.74; H, 7.71; N, 3.06. Found: C, 78.88; H, 7.86; N, 3.16.

Dibenzyl-Ser(Bzl)Ψ[COCH$_2$](2*R*,5*S*)Nva-OMe, 3da: yield 42% (based on **4d**) of a colorless oil that had de 94% on the basis of flash chromatography (hexane:ether = 85:10 to 75:20). The major diastereomer had ee 95%: $[\alpha]^{25}_D$ −12.2 (*c* 1.10, $CHCl_3$); ^{1}H NMR δ 0.87 (t, 3H, *J* = 7.2 Hz), 1.26 (m, 2H), 1.40 (m, 2H), 2.41 (dd, 1H, *J* = 4.1, 18.1 Hz), 2.77 (m, 1H), 3.18 (dd, 1H, *J* = 9.5, 18.1 Hz), 3.58 (t, 1H, *J* = 6.1 Hz), 3.63 (s, 3H), 3.68 (d, 2H, *J* = 13.6 Hz), 3.80 (d, 2H, *J* = 13.6 Hz), 3.88 (d, 2H, *J* = 6.1 Hz), 4.45 (d, 1H, *J* = 11.8 Hz), 4.53 (d, 1H, *J* = 11.8 Hz), 7.32 (m, 15H); ^{13}C NMR δ 14.3, 20.7, 34.7, 40.1, 43.7, 52.0, 55.5, 65.5, 67.4, 74.0, 127.6, 128.2, 128.8, 129.5, 138.5, 140.0, 176.5, 209.7; FTIR (neat) 1746, 1726 cm^{-1}. Anal. Calcd for $C_{31}H_{37}O_4N$: C, 76.36; H, 7.65; N, 2.87. Found: C, 76.32; H, 7.72; N, 2.86.

Dibenzyl-PheΨ[CHOHCH$_2$](2*R*,4*S*,5*S*)Nva-OMe, 1aa. General Prodedure. Oxo ester **3aa** (100 mg, 0.22 mmol) was dissolved in dry methanol (5.0 mL).[30] The resulting solution was cooled to −20 °C and treated with $NaBH_4$ (17.0 mg, 0.44 mmol). The reaction was monitored by TLC. After 4.0 h, the solution was quenched with H_2O (100 mL), extracted by ether (3 × 100 mL), washed by brine (100 mL), dried ($MgSO_4$), and concentrated to provide **1aa** as a colorless oil (90.0 mg, 89% based on **3aa**) after purification by flash chromatography (hexane:ether = 85:15 to 80:25): de >95% on the basis of ^{1}H NMR; $[\alpha]^{25}_D$ −8.36 (*c* 2.44, $CHCl_3$); ^{1}H NMR δ 0.86 (t, 3H, *J* = 7.0 Hz), 1.21 (m, 2H), 1.47 (m, 4H), 2.47 (m, 1H), 2.80 (m, 2H), 3.05 (m, 1H), 3.36 (d, 2H, *J* = 13.4 Hz), 3.56 (s, 3H), 3.59 (m, 1H), 3.90 (d, 2H, *J* = 13.4 Hz), 4.21 (s, 1H), 7.24 (m, 15H); ^{13}C NMR δ 14.0, 20.4, 32.3, 34.1, 37.0, 42.2, 51.4, 54.0, 64.1, 68.7, 126.3, 127.3, 128.5, 129.0, 129.4, 138.8, 140.3, 171.2; FTIR (neat) 3426, 1738 cm^{-1}. Anal. Calcd for $C_{30}H_{37}O_3N$: C, 78.40; H, 8.11; N, 3.05. Found: C, 78.75; H, 8.16; N, 3.06.

Dibenzyl-ChaΨ[CHOHCH$_2$](2*R*,4*S*,5*S*)Leu-OMe, 1cb: yield 80% (based on **3cb**) of a colorless oil after flash chromatography (hexane:ether = 85:10 to 75:20); de >95%; $[\alpha]^{25}_D$ +23.8 (*c* 0.504, $CHCl_3$); ^{1}H NMR δ 0.84 (d, 3H, *J* = 5.9 Hz), 0.87 (d, 3H, *J* = 6.2 Hz), 0.91−1.83 (set of m, 18H), 2.44 (m, 1H), 2.48 (m, 1H), 2.79 (m, 1H), 3.26 (m, 1H), 3.42 (d, 2H, *J* =

(30) Distilled from absolute methanol using Mg turnings and iodine. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* Pergamon Press: Oxford, U.K., 1988; p 217.

13.5 Hz), 3.64 (s, 3H), 3.79 (d, 2H, J = 13.5Hz), 4.52 (br, 1H), 7.26 (m, 10H); ^{13}C NMR δ 22.4, 23.5, 26.7, 34.3, 36.7, 38.2, 40.8, 43.4, 51.8, 54.4, 54.8, 60.9, 69.6, 127.6, 128.9, 129.5, 139.6, 177.8; FTIR (neat) 3446, 1735 cm^{-1}. Anal. Calcd for $C_{31}H_{45}O_3N$: C, 77.62; H, 9.46; N, 2.92. Found: C, 77.80; H, 9.31; N, 2.95.

Dibenzyl-Ser(Bzl)Ψ[CHOHCH$_2$](2*S*,4*S*,5*S*)Val-OMe, 1dc: yield 90% (based on **3dc**) of a colorless oil after flash chromatography (hexane:ether = 75:20); de >95%; $[\alpha]^{25}_D$ −24.5 (*c* 0.714, $CHCl_3$);^{1}H NMR δ 0.84 (d, 3H, J = 4.0 Hz), 0.86 (d, 3H, J = 2.6 Hz), 1.64 (m, 2H), 1.82 (m, 1H), 2.37 (m, 1H), 2.68 (m, 1H), 3.52 (d, 2H, J = 13.3 Hz), 3.59 (s, 3H), 3.68 (m, 1H), 3.69 (d, 2H, J = 4.1 Hz), 3.95 (d, 2H, J = 13.3 Hz), 4.50 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 12.0 Hz) 7.25−7.37 (m, 15H); ^{13}C NMR δ 18.5, 19.8, 29.4, 32.9, 47.9, 50.4, 53.9, 61.6, 65.8, 72.7, 126.4, 127.0, 127.7, 128.4, 137.3, 138.4, 175.6; FTIR (neat) 3436, 1735 cm^{-1}. Anal. Calcd for $C_{31}H_{39}O_4N$: C, 76.04; H, 8.03; N, 2.86. Found: C, 76.16; H, 8.23; N, 2.89.

Dibenzyl-Ser(Bzl)Ψ[CHOHCH$_2$](2*R*,4*S*,5*S*)Nva-OMe, 1da: yield 91% (based on **3da**) of a colorless oil after flash chromatography (hexane:ether = 75:20); de >95%; $[\alpha]^{25}_D$ +36.0 (*c* 0.644, $CHCl_3$);^{1}H NMR δ 0.86 (t, 3H, J = 7.1 Hz), 1.25 (m, 2H), 1.51 (m, 4H), 2.67 (m, 3H), 3.53 (d, 3H, J = 13.5 Hz), 3.60 (s, 3H), 3.68 (d, 2H, J = 5.1 Hz), 3.95 (d, 2H, J = 13.5 Hz), 4.13 (br, 1H), 4.49 (d, 1H, J = 11.8 Hz), 4.57 (d, 1H, J = 11.8 Hz), 7.25−7.37 (m, 15H); ^{13}C NMR δ 14.0, 20.4, 33.8, 36.3, 41.9, 51.4, 54.5, 62.5, 65.2, 66.4, 73.4, 127.2, 127.6, 128.4, 129.2, 138.1, 139.0, 177.2; FTIR (neat) 3436,1731 cm^{-1}. Anal. Calcd for $C_{31}H_{39}O_4N$: C, 76.04; H, 8.03; N, 2.86;. Found: C, 76.16; H, 8.12; N, 2.91.

Dibenzyl-LeuΨ[CHOHCH$_2$](2*S*,4*S*,5*S*)Cha-OMe, 2bd: yield 80% (based on **3bd**) of a colorless oil after flash chromatography (hexane:ether = 85:10 to 75:20): de >95%; $[\alpha]^{25}_D$ −5.18 (*c* 0.580, $CHCl_3$); ^{1}H NMR δ 0.95 (d, 6H, J = 6.4 Hz), 1.50−1.82 (set of m, 18H), 2.44 (m, 1H), 2.83 (m, 1H), 3.28 (m, 1H), 3.42 (d, 2H, J = 13.4 Hz), 3.65 (s, 3H), 3.81 (d, 2H, J = 13.4 Hz), 4.49 (br, 1H), 7.26 (m, 10H); ^{13}C NMR δ 23.5, 26.6, 27.0, 33.2, 33.9, 36.0, 38.2, 40.0, 41.8, 51.8, 54.4, 61.8, 69.6. 127.6, 128.9, 129.5, 139.5, 177.9; FTIR (neat) 3396, 1736 cm^{-1}. Anal. Calcd for $C_{31}H_{45}O_3N$: C, 77.62; H, 9.46; N, 2.92. Found: C, 77.80; H, 9.41; N, 2.94.

Dibenzyl-NvaΨ[CHOHCH$_2$](2*S*,4*S*,5*S*)Phe-OMe, 2ee: yield 84% (based on **3ee**) of a colorless oil after flash chromatography (hexane:ether = 85:10 to 75:20); de >95%; $[\alpha]^{25}_D$ −8.76 (*c* 0.685, $CHCl_3$); ^{1}H NMR δ 0.94 (t, 3H, J = 7.0 Hz), 1.21−1.87 (set of m, 6H), 2.38 (m, 1H), 2.77 (m, 2H), 2.87 (m, 1H), 3.42 (d, 2H, J = 13.3 Hz), 3.52 (s, 3H), 3.73 (m, 1H), 3.82 (d, 2H, J = 13.3 Hz), 4.40 (br, 1H), 7.24 (m, 15H); ^{13}C NMR δ 14.7, 22.4, 28.4, 36.6, 39.5, 44.0, 51.4, 54.0, 63.2, 68.6, 126.3, 126.8, 127.2, 128.4, 129.0, 138.9, 176.2; FTIR (neat) 3416, 1738 cm^{-1}. Anal. Calcd for $C_{30}H_{37}O_3N$: C, 78.40; H, 8.11; N, 3.05. Found: C, 78.63; H, 8.20; N, 3.05.

Boc-PheΨ[CHOHCH$_2$](2*R*,4*S*,5*S*)Nva-OMe, 7aa. General Procedure. To a solution of dibenzyl ester **1aa** (170 mg, 0.37 mmol) and $(Boc)_2O$ (163 mg, 0.74 mmol) in absolute ethanol (2.5 mL) under an N_2 atmosphere was added 10% Pd−C (340 mg) followed by 1,4-cyclohexadiene (0.75 mL, 7.5 mmol); 36 h later, the mixture was filtered through Celite and concentrated to provide **7aa** as a colorless oil (87 mg, 67% based on **1aa**) after flash chromatography (hexane:ether = 75:20 to 60:40): $[\alpha]^{25}_D$ −32.9 (*c* 0.705, $CHCL_3$); ^{1}H NMR δ 0.84 (t, 3H, J = 6.6 Hz), 1.23−1.40 (set of m, 6H), 1.46 (s, 9H),1.87 (m, 1H), 2.34 (m, 1H), 2.71 (dd, 1H, J = 9.4, 11.0 Hz), 3.05 (br, 1H), 3.60 (s, 3H), 3.76 (m, 1H), 3.97 (m, 1H), 5.16 (br, 1H), 7.27 (m, 5H); ^{13}C NMR δ 14.3, 20.7, 22.1, 29.0, 35.0, 35.8, 43.0, 52.0, 63.5, 79.4, 80.7, 127.0, 129.0, 130.0, 138.5, 153.6, 177.0; FTIR (neat) 3495, 1736, 1701 cm^{-1}.

Boc-Ser(Bzl)Ψ[CHOHCH$_2$](2*R*,4*S*,5*S*)Nva-OMe, 7da: yield 56% (based on **1da**) of a colorless oil after flash chromatography (hexane:ether = 75:20 to 60:40); $[\alpha]^{25}_D$ +3.13 (*c* 0.575, $CHCl_3$);^{1}H NMR δ 0.90 (t, 3H, J = 6.8 Hz), 1.25−1.53 (set of m, 6H), 1.45 (s, 9H), 2.52 (m, 1H), 3.40 (m, 1H), 3.64 (s, 3H), 3.70 (d, 2H, J = 11.2 Hz), 4.24 (m, 2H), 4.54 (s, 2H), 5.12 (br, 1H), 7.32 (m, 5H); ^{13}C NMR δ 13.8, 20.4, 28.4, 34.8, 35.4, 42.7, 51.5, 60.6, 70.0, 73.2, 78.2, 80.4, 127.6, 128.4, 129.6, 138.1, 153.2, 176.8; FTIR (neat) 3495, 1736, 1701 cm^{-1}.

Acknowledgment. The authors thank the National Science Foundation (CHE 9520431) for financial support of this work.

Supporting Information Available: The ^{1}H spectra of *N*-Boc-protected hydroxyethylene dipeptide isosteres **6aa** and **6da** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970579S