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A Simple, Stereoselective Synthesis of Ketomethylene Dipeptide Isosteres

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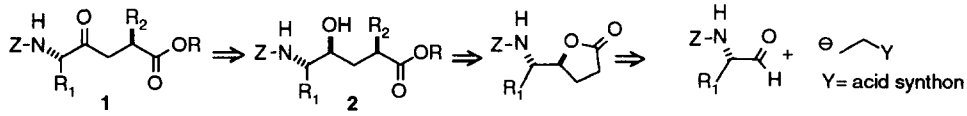
Abstract: An exceedingly simple, general, and stereoselective method for the preparation of ketomethylene dipeptide isosteres (5-(carbobenzyloxyamino)-2-alkyl-γ-ketoesters) from Cbz-protected amino acids and scalemic 2-triflyloxy esters has been developed. The method is short (three steps), efficient, and highly diastereoselective and enantioselective. © 1997 Elsevier Science Ltd.

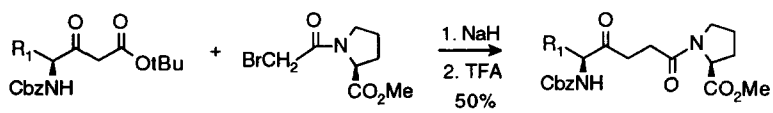
Introduction

Because of their interest as protease inhibitors and hence potential therapeutic agents,[1] ketomethylene peptide isosteres have been the focus of a variety of synthetic efforts.[2] Ketomethylene peptide isosteres are characterized by a 1,4-disposition of the oxygenated functional groups (ketone and acid derivative), and they bear an amino functionality at chiral center C-5 and an alkyl group at chiral center C-2. Thus they are functionally related to chiral 2-alkyl-4-ketoesters. The majority of syntheses reported for these types of compounds have utilized construction of the 3,4 carbon-carbon bond by reaction of an amino aldehyde with a three carbon nucleophilic species (Scheme 1).[1c,2] The resulting 4-hydroxy ester is lactonized and alkylated at C-2 with chiral induction to give hydroxyethylene peptide isosteres **2**, which upon mild oxidation give ketomethylene peptide isosteres.



Scheme 1

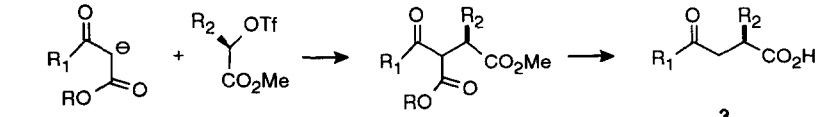
A much less common approach is to construct the 2,3-bond of the 4-ketoester. It was reported that the alkylation of *tert*-butyl 3-ketoesters with ethyl bromoacetate followed by decarboxylation gives γ-ketoesters,[3] which have the 1,4- oxygen functionality of ketomethylene peptide isosteres. It was also shown that 4-amino-3-ketoesters could be alkylated with α-bromoacetamides to give γ-ketoamides in one step in very satisfactory yields (eq 1, for example).[3] Similar approaches have since been reported by others.[4,5] Alkyl groups at C-2



(1)

must still be installed by alkylation of a lactone enolate to produce scalemic ketomethylene peptide isosteres.[5]

Scalemic α-triflyloxy esters react with β-ketoester enolates to give 2-alkyl-4-keto esters in good yields and high ee's.[6] This utilization of 2-triflyloxy esters as scalemic alkylating agents provided an excellent new method for the synthesis a variety of 2-alkylated γ-ketoacids **3** (Scheme 2).[7]

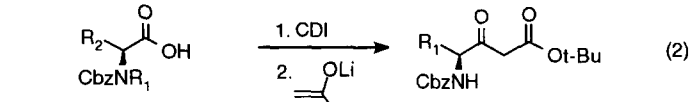


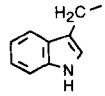
Scheme 2

These results have provided the foundation for a new, simple, and short synthesis of protected ketomethylene dipeptide isosteres with high enantiomeric and diastereomeric purity. This methodology provides the most direct and efficient access to these compounds yet described.

Results and Discussion

A series of Cbz-protected amino acids **4a-g** was converted to the corresponding t-butyl β-ketoesters **5a-g** by reaction with 1,1'-carbonyldiimidazole (CDI) followed by treatment with the lithium enolate of t-butyl acetate (eq 2).[8] A variety of branched and unbranched sidechains as well as heteroatom-containing amino acids were utilized to demonstrate generality. The ee's of the β-keto esters were not determined as the literature suggests that this conversion takes place without any racemization of the α-position.[8] Moreover, the optical purities determined subsequently for the γ-ketoester products show this to be true as well.



4a, R_1=H, R_2= i-Bu (Leucine)
b, R_1, R_2= $(CH_2)_3$ (Proline)
c, R_1=H, R_2= i-Pr (Valine)
d, R_1=H, R_2= BnOBn (Tyrosine, OBn)
e, R_1=H, R_2=  (Tryptophan)
f, R_1=H, R_2= Bn (Phenylalanine)
g, R_1=H, R_2= Me (Alanine)

Ketoesters **5a-g** were converted to their enolates with sodium hydride and then reacted with two equivalents of an α-triflyloxy ester **6a-f** to give tricarbonyl derivatives **7**. These were simply isolated and treated with TFA to afford decarboxylated ketomethylene peptide isosteres in fair yields (40-62%) for the two steps (eq 3) (Table 1).

Several points need to be noted about the method. Firstly, it is much more efficient to use isolated 2-triflyloxy esters than to use 2-triflyloxy esters produced *in situ* from the reaction of 2-hydroxyesters, triflic anhydride and 2,6-lutidine.[3,9] Previous work on the synthesis of γ-ketoesters [7] utilized this *in situ* preparation as

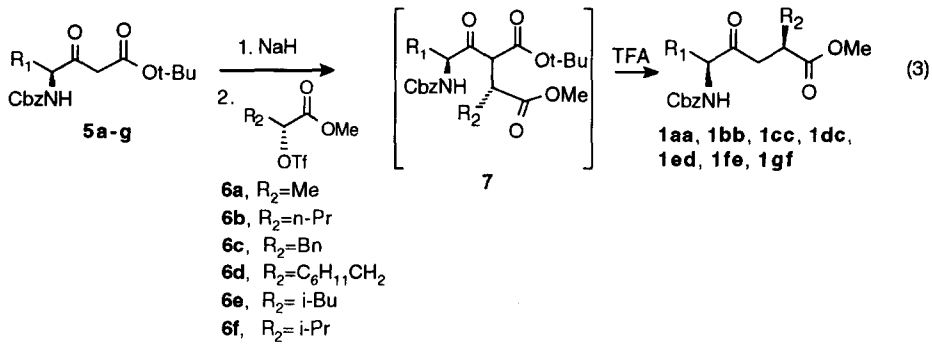


Table 1. Stereochemical Results of the Preparation of Peptide Isosteres by Chiral Alkylation

Entry	Product	Yield (%)[a]	de(%)[b]	ee(%)[c]
1	**1aa**	48	96	95
2	**1bb**	45	92	>95
3	**1cc**	52	84	>95
4	**1dc**	45	88	>95
5	**1ed**	43	90	>95
6	**1fe**	62	90	>95
7	**1gf**	40	74	92

a. Isolated yields of chromatographed mixtures of diastereomers. b. Determined by ^{1}H nmr and HPLC of the crude products. c. Determined by chiral LIS study on separated major diastereomer.

the source of the 2-triflyloxy ester. However, due to the presence of the lutidinium salt in this mixture, an excess of the enolate was needed to neutralize this salt as well as serve as a nucleophile. For readily available β-ketoesters, this poses no real problem, however, the use of isolated 2-triflyloxyesters maximizes the conversion of **5** to **7**. Moreover, 2-triflyloxy esters are easily isolated and are quite stable to storage in the freezer.

Second, while not every combination of β-ketoester and 2-triflyloxy ester was used, the similar yields for all cases studied (Table 1) indicate that this method is very tolerant of structural diversity. Similar results would be expected for other combinations of interest.

Third, two equivalents of the 2-triflyloxy ester were used in the chiral alkylation although no real attempts were made to optimize the yield of this step. It is clear, however, that the excess 2-triflyloxy ester cannot be isolated after the normal reaction time of 24 h. It is suspected that the 2-triflyloxy ester first alkylates the β-ketoester enolate and the second equivalent O-alkylates the Cbz group to produce an imidate salt. The imidate is hydrolyzed back to the Cbz group and an α-hydroxyester on workup. This scenario is suggested by the presence of the α-hydroxyester in the crude products.[10]

The diastereoselectivity of the process is very good with de's generally ranging from 84-96% (Table 1).The lowest de (74%) was found for alkylation using triflate **6f** which contains a branched chain at the α-position. For this sterically hindered electrophile the reaction time is increased to 48 h and this leads to increased epimerization at C-2. The diastereomers of **1** are readily separable by chromatography and the major diastereomer was examined with the chiral lanthanide shift reagent Eu(hfc)3 in order to determine the ee's. (Table 1). Both **1aa** and **1gf** were prepared in racemic form for comparison purposes. In most cases only a

single enantiomer was detected (ee>95%) and the lowest ee was 92% for **1gf**, the example which required 48 h for completion (Table 1). Thus there is usually no epimerization of the amino acid unit during the entire sequence.

This study utilized all (S)-amino acids and (R)-triflyloxy esters. Since it is well established that the chiral alkylation proceeds with inversion of configuration,[7] the major diastereomers have the 2R, 5S configuration (except **1gf**). Thus the ketomethylene peptide isostere products all have the same stereochemical sense as normal dipeptides.[11] Based on the apparent structural generality of the method, however, it should be possible to prepare dipeptide isosteres of any needed configurations by the appropriate choice of amino acids and triflyloxy esters. The products are easily unmasked for coupling into longer peptide sequences by standard means.

In summary, an exceedingly simple, general, and stereoselective method for the preparation of ketomethylene dipeptide isosteres from Cbz-protected amino acids and scalemic 2-triflyloxy esters has been developed. The method is short (three steps), efficient, and highly diastereoselective and enantioselective.

Experimental Section

Infrared spectra were taken on as neat liquids or as KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz respectively in $CDCl_3$ solution. 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 x 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). Optical rotations were determined on a Perkin-Elmer 241 polarimeter. 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.

(*S*)-*tert*-Butyl 4-[(benzyloxycarbonyl)amino]-3-oxo-6-methylheptanoate, 5a.[12] **General Procedure.** To a stirred solution of Cbz-protected amino acid **4a** (2.65 g, 10.0 mmol) in THF (40 mL) was added CDI (1.71 g, 10.5 mmol) at room temperature under a N_2 atmosphere. The resulting solution was stirred for 1 h at room temperature. Meanwhile, a solution of lithium *tert*-butylacetate was made from BuLi (2.50 M, 12.6 mL, 31.5 mmol), diisopropylamine (4.55 mL, 31.5 mmol), and *tert*-butyl acetate (4.27 mL, 31.5 mmol). The above imidazole solution was added dropwise to this pale yellow solution of lithium enolate at -78 °C under a N_2 atmosphere. The resulting mixture was stirred at -78° C for 40 min, quenched with 1 N HCl (100 mL), and extracted with ethyl acetate (3 x 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 **5a** as a pale yellow oil (2.83 g, 76% based on **4a**) after purification by flash chromatography (hexane:ethyl acetate = 4:1): $[\alpha]^{25}_D$ -0.38 (*c* 1.05, $CHCl_3$); ^{1}H NMR δ 0.93 (d, 3H, *J* = 6.2 Hz), 0.96 (d, 3H, *J* = 6.3 Hz), 1.36 (m, 1H), 1.45 (s, 9H), 1.62 (m, 2H), 3.38 (d, 1H, *J* = 13.6 Hz), 3.50 (d, 1H, *J* = 13.6 Hz), 4.46 (m, 1H), 5.10 (s, 2H), 5.41 (d, 1H, *J* = 8.7 Hz), 7.33 (s, 5H); ^{13}C NMR δ 21.8, 23.6, 25.1, 28.2, 40.4, 47.9, 59.0, 67.4, 82.7, 128.5, 36.6, 156.6, 166.5, 203.3; FTIR (neat) 3356, 2977, 1715 (br), 1630 cm^{-1}.

(*S*)-*tert*-Butyl 3-[(*N*-benzyloxycarbonyl)pyrrolidine-2]-3-oxo-propanoate, 5b:[12] yield 85% (based on **4b**) as a colorless oil after purification by flash chromatography (hexane:ethyl acetate = 4:1); $[\alpha]^{25}_D$ -64.4 (*c* 3.85, $CHCl_3$); ^{1}H NMR (major rotamer) δ 3.56 (s, 2H), 3.60 (m, 2H), 4.48 (dd, 1H, *J* = 7.4, 9.0

Hz), 5.09 (s, 2H), 7.31 (m, 5H); ^{13}C NMR (mixture of rotamers) δ 23.9, 24.6, 28.3, 28.8, 29.9, 47.2, 48.2, 59.6, 65.4, 65.7, 67.6, 75.7, 81.3, 82.2, 128.1, 128.9, 136.6, 136.9, 154.7, 155.5, 166.5, 166.8, 203.1; FTIR (neat) 2976, 1720 (br), 1642 (m) cm^{-1}.

(*S*)-tert-Butyl 4-[(benzyloxycarbonyl)amino]-3-oxo-5-methylhexanoate, 5c:[12] yield 82% (based on **4c**) as a pale yellow oil after purification by flash chromatography (hexane:ethyl acetate = 4:1): $[\alpha]^{25}_D$ +30.9 (*c* 2.80, $CHCl_3$); ^1H NMR δ 0.80 (d, 2H, *J* = 6.9 Hz), 1.02 (d, 2H, *J* = 6.7 Hz), 1.45 (s, 9H), 1.48 (enol) (s, 9H). 2.26 (m, 1H), 3.44 (s, 2H), 4.46 (dd, 1H, *J* = 3.8, 8.9 Hz), 5.10, (s, 2H), 5.48 (d, 1H, *J* = 8.9 Hz), 7.34 (s, 5H); ^{13}C NMR(major) δ 16.9, 20.4, 28.4, 30.1, 48.7, 65.2, 67.5, 82.8, 128.6, 136.7, 157.0, 166.3, 202.5; FTIR 3335, 2987, 1731 (br), 1648 (m) cm^{-1}.

(*S*)-*tert*-Butyl 4-[(benzyloxycarbonyl)amino]-3-oxo-5-(4-benzyloxy)phenylpentanoate, 5d:[12] yield 79% (based on **4d**) as a white solid after purification by flash chromatography (hexane:ethyl acetate = 4:1); mp 63.5-64.5 °C; $[\alpha]^{25}_D$ +15.7 (*c* 6.25, $CHCl_3$); ^1H NMR δ 1.42 (s, 9H), 3.05 (m, 2H), 3.38 (s, 2H), 4.62 (dd, 1H, *J* = 6.7, 8.8 Hz), 4.95 (s, 2H), 5.03 (s, 2H), 5.56 (br, 1H); 6.82-7.36 (m, 10H); ^{13}C NMR δ 28.4, 36.6, 48.6, 61.5, 70.3, 82.7, 115.5, 128.5, 129.0, 130.8, 136.8, 137.5, 156.4, 158.3, 166.6, 202.4; FTIR 3356, 2987, 1721 (br), 1661 (m) cm^{-1}.

(*S*)-*tert*-Butyl 4-[(benzyloxycarbonyl)amino]-3-oxo-5-(3-indolyl)pentanoate, 5e:[12] yield 78% (based on **4e**) as a glassy, colorless oil after purification by flash chromatography (hexane:ethyl acetate = 4:1 to 2:1); $[\alpha]^{25}_D$ +12.0 (*c* 0.55, $CHCl_3$); ^1H NMR δ 1.38 (s, 9H), 3.18 (m, 2H), 3.32 (s, 2H), 4.72 (m, 1H), 5.00 (s, 2H), 5.67 (d, 1H, *J* = 6.6 Hz), 6.81-7.56 (m, 10H), 8.59 (br, 1H); ^{13}C NMR δ 27.4, 28.4, 48.6, 60.9, 67.5, 82.8, 109.8, 112.0, 119.0, 120.2, 122.6, 123.8, 127.9, 128.6, 129.2, 136.8, 156.6, 166.9, 203.3; FTIR (neat) 3376, 2947, 1725 (br), 1636 (m) cm^{-1}.

(*S*)-*tert*-Butyl 4-[(benzyloxycarbonyl)amino]-3-oxo-5-phenylpentanoate, 5f:[12] yield 81% (based on **4f**) after purification by flash chromatography (hexane:ethyl acetate = 4:1); $[\alpha]^{25}_D$ +11.1 (*c* 5.00, $CHCl_3$); ^1H NMR δ 1.44 (s, 9H), 3.09 (m, 2H), 3.38 (s, 2H), 4.66 (m, 1H), 5.03 (s, 2H), 5.59 (d, 2H, *J* = 7.5 Hz), 7.24 (m, 5H); ^{13}C NMR δ 28.4, 38.2, 48.5, 61.3, 67.4, 82.7, 127.4, 128.5, 129.2, 129.8, 136.5, 156.4, 166.4, 202.3; FTIR 3317, 2976, 1720 (br), 1661 cm^{-1}.

(*S*)-*tert*-Butyl 4-[(benzyloxycarbonyl)amino]-3-oxo-pentanoate, 5g:[12] yield 80% (based on **4g**)as a pale yellow oil after purification by flash chromatography (hexane:ethyl acetate = 4:1); $[\alpha]^{25}_D$ +10.2 (*c* 3.60, $CDCl_3$); ^1H NMR δ 1.35 (d, 3H, *J* = 7.2 Hz), 1.44 (s, 9H), 3.46 (s, 2H), 4.45 (m, 1H), 5.09 (s, 2H), 5.73 (d, 1H, *J* = 6.7 Hz), 7.32 (s, 5H); ^{13}C NMR δ 17.5, 28.3, 47.5, 56.2, 67.3, 82.7, 128.5, 128.9, 136.6, 156.3, 166.5, 202.8; FTIR (neat) 3326, 2977, 1710 (br), 1648 cm^{-1}.

(*R*)-Methyl 2-triflyloxypropanoate, 6a. General Procedure. To a stirred solution of (*R*)-methyl 2-hydroxypropanoate (520 mg, 5.00 mmol) in dichloromethane (20 mL) at 0 °C under a N_2 atmosphere was added triflic anhydride (0.90 mL, 5.25 mmol), followed by 2,6-lutidine (0.61 mL, 5.25 mmol). After stirring for 20 min, the mixture was concentrated by rotary evaporation. The residue was dissolved in pentane (150 mL), filtered to remove the lutidinium salt, and concentrated again to provide triflate **6a** as a pale pink oil (1.05 g, 89% based on 2-hydroxy ester). ^1H NMR ($CDCl_3$) δ 1.72 (d, 3H, *J* = 7.0 Hz), 3.86 (s, 3H), 5.25 (q, 1H, *J* = 7.0 Hz) was the same as the reported spectrum.[9] This material was used without further purification.

(*R*)-Methyl 2-triflyloxypentanoate, 6b: yield 94% based on (*R*)-methyl 2-hydroxypentanoate; ^1H NMR ($CDCl_3$) δ 0.99 (t, 3H, *J* = 7.4 Hz), 1.50 (m, 2H), 1.97 (m, 2H), 3.85 (s, 3H), 5.14 (t, 1H, *J* = 6.7 Hz).

(*R*)-Methyl 2-triflyloxy-3-phenylpropanoate, 6c: yield 95% based on (*R*)-methyl 2-hydroxy-3-phenylpropanoate; ^{1}H NMR ($CDCl_3$) δ 3.29 (m, 2H), 3.83 (s, 3H), 5.25 (dd, 1H, *J* = 4.2, 4.5 Hz), 7.32 (m, 5H) was the same as the reported spectrum.[9]

(*R*)-Methyl 2-triflyloxy-3-cyclohexylpropanoate, 6d: yield 86% based on (*R*)-methyl 2-hydroxy-3-cyclohexylpropanoate; ^{1}H NMR ($CDCl_3$) δ 0.97-1.71 (set of m, 11H), 1.90 (m, 2H), 3.84 (s, 3H), 5.20 (dd, 1H, *J* = 4.5, 5.4 Hz).

(*R*)-Methyl 2-triflyloxy-4-methylpentanoate, 6e: yield 90% based on (*R*)-methyl 2-hydroxy-4-methylpentanoate; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 6H, *J* = 8.1 Hz), 1.80 (m, 2H), 1.97 (m, 1H), 3.85 (s, 3H), 5.16 (dd, 1H, *J* = 3.6, 5.4 Hz).

(*R*)-Methyl 2-triflyloxy-3-methylbutanoate, 6f: yield 85% based on (*R*)-methyl 2-hydroxy-3-methylbutanoate; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3H, *J* = 2.2 Hz), 1.03 (d, 3H, *J* = 2.3 Hz), 2.40 (m, 1H), 3.85 (s, 3H), 4.98 (d, 1H, *J* = 4.0 Hz).

(2R, 5S) Cbz-LeuΨ[COCH$_2$]Ala-OMe, 1aa.[12] **General Procedure**. A solution of 3-oxo ester **5a** (726 mg, 2.00 mmol) in THF (10 mL) was added dropwise to a stirred suspension of NaH (84.0 mg of 60% in mineral oil, 2.10 mmol) in dry THF (30 mL) at 0 °C under a N_2 atmosphere. The mixture was stirred for 10 min. Then a solution of triflate **6a** (949 mg, 4.02 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), extracted with ethyl acetate (3 x 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 into dichloromethane (10 mL) and treated with TFA (1.5 mL) at room temperature for 24 h. After dilution with dichloromethane (50 mL), the resulting solution was washed with saturated $NaHCO_3$ (2 x 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated. Isostere **1aa** was obtained as a colorless oil (314 mg, 48% based on **5a**) after purification by flash chromatography (hexane:ethyl acetate = 4:1 to 2:1) 96% de based on ^{1}H NMR. HPLC analysis (normal phase, 1.5 mL/min, hexane:ethyl acetate = 1:1) corroborated the diastereoselectivity found by ^{1}H nmr. t_R 3.99 (major), 4.16 (minor); ratio 98:2. After separation by flash chromatography using a 40 cm column, the major diastereomer had ee 95% by a chiral LIS study using Eu(hfc)$_3$ in comparison with a racemic sample; $[\alpha]^{25}_D$ -6.00 (*c* 0.40, $CHCl_3$); ^{1}H NMR δ 0.92 (d, 3H, *J* = 6.3 Hz), 0.97 (d, 3H, *J* = 6.0 Hz), 1.18 (d, 3H, *J* = 6.8 Hz), 1.40 (m, 1H), 1.62 (m, 2H), 2.57 (m, 1H), 2.96 (m, 2H), 3.65 (s, 3H), 4.39 (m, 1H), 5.10 (s, 2H), 5.46 (d, 1H, *J* = 8.1 Hz), 7.34 (s, 5H); ^{13}C NMR δ 17.4, 22.0, 23.6, 25.2, 35.0, 40.6, 42.9, 52.3, 58.8, 67.3, 128.5, 128.9, 136.8, 156.6, 176.4, 208.7; FTIR (neat) 3336, 2947, 1736, 1721 (br) cm^{-1}.

(2R, 5S) Cbz-ProΨ[COCH$_2$]Nva-OMe, 1bb,[12] was obtained as a colorless oil in 45% yield (based on **5b**) after purification by flash chromatography (hexane:ethyl acetate = 9:1 to 3:2); 92% de based on ^{1}H NMR. HPLC analysis (normal phase, 1.5 mL/min, hexane:ethyl acetate = 1:1) t_R 2.89 (minor), 5.87 (major); ratio 96:4 corroborated the diastereoselectivity found by ^{1}H nmr. After separation by flash chromatography using a 40 cm column, the major diastereomer had e.e. >95% determined by LIS; $[\alpha]^{25}_D$ -46.8 (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 0.86 (major rotamer) (t, 3H, *J* = 7.3 Hz), 0.90 (minor) (t, 3H, *J* = 7.2 Hz), 1.27 (m, 2H), 1.50 (m, 2H), 2.14 (m, 2H), 2.25 (m, 2H), 2.61 (m, 1H), 2.97 (m, 2H), 3.56 (m, 2H), 3.64 (minor) (s, 3H), 3.66 (major) (s, 3H), 4.37 (minor) (dd, 1H, *J* = 4.5, 5.0 Hz), 4.47 (major) (dd, 1H, *J* = 4.4, 5.1 Hz), 5.02 (d, 1H, *J* = 11.5 Hz), 5.12 (d, 1H, *J* = 11.5 Hz), 5.07 (d, 1H, *J* = 14.0 Hz), 5.16 (d, 1H, *J* = 14.0 Hz), 7.33 (m, 5H);

^{13}C NMR (mixture of rotamers) δ 14.3, 20.5, 23.9, 24.6, 28.8, 30.0, 34.4, 39.6, 41.7, 42.1, 47.0, 47.6, 52.1, 64.8, 65.1, 67.6, 128.5, 128.9, 136.6, 136.8, 154.7, 155.4, 176.2, 176.5, 208.0, 208.3; FTIR (neat) 2957, 1727, 1711 cm^{-1}.

(2R, 5S) Cbz-ValΨ[COCH$_2$] Phe-OMe, 1cc,[12] was obtained as a colorless oil in 52% yield (based on **5c**) after purification by flash chromatography (hexane:ethyl acetate = 4:1); 84% de based on ^1H NMR. HPLC analysis (1.5 mL/min, hexane:ethyl acetate = 1:1) t_R 2.96 (major), 4.07 (minor); ratio 92:8 corroborated the diastereoselectivity found by ^1H nmr. After separation by flash chromatography using a 40 cm column, the major diastereomer had ee >95% by LIS; $[\alpha]^{25}_D$ +32.3 (*c* 0.65, $CHCl_3$); ^1H NMR δ 0.74 (d, 3H, *J* = 6.9 Hz), 0.99 (d, 3H, *J* = 6.6 Hz), 2.22 (m, 1H), 2.60 (m, 1H), 3.02 (m, 1H), 3.17 (m, 2H), 3.62 (s, 3H), 4.30 (dd, 1H, *J* = 4.5, 6.7 Hz), 5.06 (s, 2H), 5.28 (d, 1H, *J* = 4.5 Hz), 7.32 (m, 10H); ^{13}C NMR δ 16.6, 19.2, 30.6, 38.2, 41.9, 59.1, 64.5, 67.4, 74.0, 128.6, 129.0, 127.3, 136.7, 156.9, 175.4, 207.5; FTIR (neat) 3366, 2977, 1728, 1711 cm^{-1}.

(2R, 5S) Cbz-Tyr(Bn)Ψ(COCH$_2$) Phe-OMe, 1dc,[12] was obtained as a colorless oil in 45% yield (based on **5d**) after purification by flash chromatography (hexane:ethyl acetate = 4:1 to 2:1); 88% de based on ^1H NMR. HPLC analysis (1.5 mL/min, hexane:ethyl acetate = 1:1) t_R 2.10 (minor), 2.86 (major); ratio 94:6 corroborated the diastereoselectivity found by ^1H nmr. After separation by flash chromatography using a 40 cm column, the major diastereomer had ee >95%; $[\alpha]^{25}_D$ +24.4 (*c* 0.45, $CHCl_3$); ^1H NMR δ 2.50 (m, 2H), 2.66-3.12 (set of m, 5H), 3.60 (s, 3H), 4.53 (dd, 1H, *J* = 6.7, 7.2 Hz), 5.00 (s, 2H), 5.06 (s, 2H), 6.52-7.40 (set of m, 19 H); ^{13}C NMR (major) δ 37.2, 37.7, 38.0, 41.4, 42.4, 52.4, 61.2, 67.3, 115.4, 127.2, 127.9, 128.5, 129.0, 130.6, 136.8, 137.3, 138.7, 156.2, 158.3, 175.2, 207.4; FTIR (neat) 3346, 2967, 1726 (br), 1611 (m) cm^{-1}.

(2R, 5S) Cbz-TrpΨ[COCH$_2$] Cha-OMe, 1ed,[12] was obtained as a pale pink oil in 43% yield (based on **5e**) after purification by flash chromatography (hexane:ethyl acetate = 4:1 to 2:1); 90% de based on ^1H NMR. HPLC analysis (1.5 mL/min, hexane:ethyl acetate = 1:1) t_R 2.80 (major), 3.24 (minor); ratio 95:5 corroborated the diastereoselectivity found by ^1H nmr. the major diastereomer had ee >95% by LIS; $[\alpha]^{25}_D$ +11.0 (*c* 0.01, $CHCl_3$); ^1H NMR δ 0.74-1.64 (set of m, 13H), 2.37 (m, 1H), 2.82 (m, 2H), 3.22 (d, 2H, *J* = 6.5 Hz), 3.62 (s, 3H), 4.68 (m, 1H), 5.08 (s, 2H), 5.54 (d, 1H, *J* = 7.2 Hz), 6.92-7.10 (set of m, 9H), 8.22 (br, 1H); ^{13}C NMR δ 26.5, 28.0, 33.4, 35.4, 37.7, 39.9, 43.0, 52.2, 60.4, 67.3, 110.4, 111.7, 119.0, 120.3, 122.8, 123.2, 128.6, 136.7, 156.3, 176.7, 208.6; FTIR (neat) 3416, 2927, 1711 (br), 1648 cm^{-1}.

(2R, 5S) Cbz-PheΨ[COCH$_2$] Leu-OMe, 1fe,[12] was obtained as a colorless oil in 62% yield (based on **5f**) after purification by flash chromatography (hexane:ethyl acetate = 9:1 to 4:1); 90% de based on ^1H NMR. HPLC analysis (1.5 mL/min, hexane:ethyl acetate = 1:1) t_R 2.12 (minor), 2.64 (major); ratio 95:5 corroborated the diastereoselectivity found by ^1H nmr. After separation by flash chromatography using a 40 cm column, the major diastereomer had e.e. >95% by LIS; $[\alpha]^{25}_D$ +15.5 (*c* 1.95, $CHCl_3$); ^1H NMR δ 0.85 (d, 3H, *J* = 6.0 Hz), 0.87 (d, 3H, *J* = 6.1 Hz), 1.20 (m, 1H), 1.55 (m, 2H), 2.34 (m, 1H), 2.83 (m, 2H), 3.07 (m, 2H), 3.64 (s, 3H), 4.60 (m, 1H), 5.08 (s, 2H), 5.32 (d, 1H, *J* = 6.7 Hz), 7.33 (m, 10H); ^{13}C NMR δ 21.8, 22.8, 23.5, 26.1, 38.4, 41.5, 52.2, 61.0, 67.3, 72.2, 127.4, 128.5, 128.9, 129.6, 136.6, 156.3, 176.4, 208.0; FTIR (neat) 3346, 2967, 1716 (br) cm^{-1}.

(2S, 5S) Cbz-AlaΨ[COCH$_2$]Val-OMe, 1gf,[12] was prepared by the same procedure using a reaction time of 48 h as a colorless oil in 40% yield (based on **5g**) after purification by flash chromatography

(hexane:ethyl acetate = 4:1); 74% de based on ^{1}H NMR. HPLC analysis (1.5 mL/min, hexane:ethyl acetate = 1:1) t_R 4.22 (major), 5.44 (minor); ratio 87:13 corroborated the diastereoselectivity found by ^{1}H nmr. After separation by flash chromatography using a 40 cm column, the major diastereomer had ee 92% by comparison with a racemic sample; $[\alpha]^{25}_D$+60.0 (*c* 0.05, $CHCl_3$); ^{1}H NMR δ 0.85 (d, 3H, *J* = 4.4 Hz), 0.88 (d, 3H, *J* = 4.5 Hz). 1.34 (d, 3H, *J* = 7.0 Hz), 2.05 (m, 1H), 2.50 (m, 1H), 2.88 (m, 2H), 3.66 (s, 3H), 4.42 (m, 1H), 5.11 (s, 2H), 5.57 (d, 1H, *J* = 5.4 Hz), 7.40 (s, 5H); ^{13}C NMR δ 17.0, 18.6, 19.5, 30.0, 36.8, 46.3, 52.1, 55.8, 66.8, 128.1, 136.3, 155.6, 174.9, 208.3; FTIR (neat) 3346, 2967, 1726 (br) cm^{-1}.

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References and Notes

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10. A referee has suggested that the second equivalent of the 2-triflyloxy ester O-alkylates the β-ketoester rather than the Cbz-group. This appears unlikely since without an amino group at C-4 or using an N,N-dibenzylamino protecting group in place of the Cbz-group requires only one equivalent of the triflate. It is the Cbz group which changes the chemistry and thus seems to be alkylated.
11. The priority rules change in the ketomethylene isostere thus the 2R configuration in the isostere chain corresponds to the 2S configuration in an analogous peptide chain.
12. Elemental analysis C, H, N ±0.4% was obtained for this compound.

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