Novel Methodology for the Synthesis of *trans*-Alkene Dipeptide Isosteres

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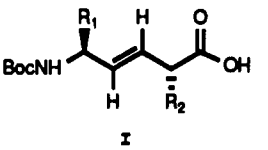
Natural amino acids were converted to the corresponding allylic alcohols A, from which key precursors C were obtained via a three-step sequence [(a) Ac_2O/Py or CbzOSu/Et_3N/DMAP; (b) NMO/$NaIO_4$/OsO_4(cat.); (c) $Ph_3P{=}CR_2CO_2Bn$]. The allylic alcohols D were further transformed to the desired pseudodipeptides I through the corresponding bromo derivatives E via a reductive deconjugation process.

The use of peptides as drugs is hampered by the poor stability, lack of oral absorption, and marginal ability to cross the blood-brain barrier. These shortcomings have been attributed to the presence of peptide bonds which impart high polarity to the molecule and render it susceptible to degradation by the peptidase presence in biological tissues. To circumvent some of the therapeutic limitations of peptides, a great deal of effort has been devoted to replacing amide bonds in peptides with suitable isosteric units. Among the several mimics which have been reported, the trans carbon-carbon double bond appears to be the most suitable moiety to mimic the linkage in terms of geometry and bond angles and length.[1,2] Furthermore, unlike the amide bond, which has some degree of flexibility and possesses hydrogen bonding capability, the trans double bond will fix the replaced peptide linkage in a trans conformation and eliminate its hydrogen bonding properties. Therefore, trans double bond isostere analogues can provide valuable information concerning the role of an amide bond at a specific site in a peptide. Several successful examples have been demonstrated in the syntheses of analogue of enkephalin,[2a,3] substance P[3], angiotensin-converting enzyme inhibitors,[4] and inhibitors of protein kinase.[5] To date only two highly functionalized analogues (Asn-Val and Ser-Asn[5]) have been reported, and no Trp-containing analogues were demonstrated by utilizing the existing methodologies. Herein we report a novel methodology[6a] for highly functionalized *trans*-alkene isosteres of dipeptides having the general structure I.

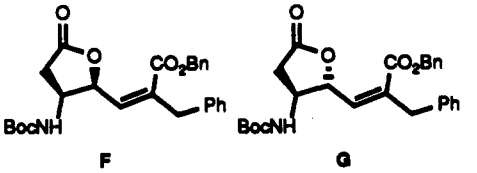
Synthetic Strategy. In designing the syntheses of trans double bond isosteres of general structure I, it is important to employ reaction schemes that are compatible with sensitive functionalities present in certain natural amino acids (e.g., Trp, Asp, etc.). In addition, it is highly desirable to control the stereochemistry at either one or both α-centers and at the double bond. Our synthetic strategy designed to address these issues is outlined in Scheme I. Specifically, protected allylic alcohols of general structure A, derived from natural amino acids, were converted to the key precursors C via a three-step sequence [(a) Ac_2O/Py or CbzOSu/Et_3N/DMAP, (b) NMO/$NaIO_4$/OsO_4(cat.), (c) $Ph_3PC{=}CR_2CO_2Bn$]. Removal of the protecting group (acetyl or benzyloxycarbonyl) of compounds C afforded the allylic alcohol derivatives D, which possessed the necessary handle to place the unsaturation at the β-γ position. This was achieved through their bromo counterparts E via a reductive deconjugation process.



I

R_1	R_2
a. $CH_2CO_2C(CH_3)_3$	$CH_2C_6H_5$
b. $CH_2CH(CH_3)_2$	$CH_2CO_2C(CH_3)_3$
c. H	3-Indolylmethyl

Aspψ[*E*-CH=CH]Phe. Boc-β-*tert*-butylaspartic acid 1 was converted to optically pure Boc-β-*tert*-butylaspartic acid-α-carboxaldehyde 3 via its 3,5-dimethylpyrrazolide 2 according to literature procedure.[7] Addition of vinylmagnesium bromide to 3 afforded allylic alcohol 4 as a mixture of diastereomers. For practical purposes, the allylic alcohol 4 was carried through the reaction sequence as a mixture of diastereomers. The alcohol 4 was protected as the acetate 5, which was converted to aldehyde 7 via a modified Rudloff oxidation [NMO/$NaIO_4$/OsO_4(cat.)].[8] The intermediate diol 6 was cleaved with $NaIO_4$ in situ as soon as it was formed to avoid any side reaction which may occur at its γ-acetoxy moiety. Compound 7 was condensed with Wittig reagent 8[9] to afford allylic acetate 9,[10] which possesses all the necessary elements for the targeted double bond isostere but in a different oxidation state. Careful methanolysis of the acetyl blocking group of compound 9 provided the corresponding allylic alcohol 10.[11] The



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(11) The reaction conditions for this hydrolysis are crucial. With longer reaction times (>1 h), the newly formed allylic alcohol 9 will convert further to lactones F and G plus other byproducts, i.e., Michael addition and transesterification of the α,β-unsaturated benzyl ester will occur.

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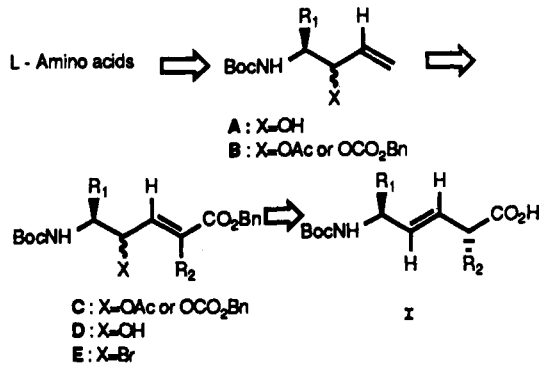
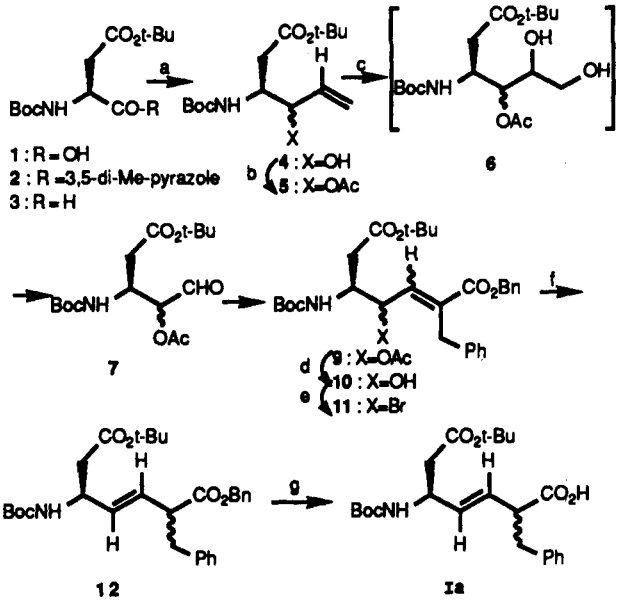
Scheme I



Scheme II[a]

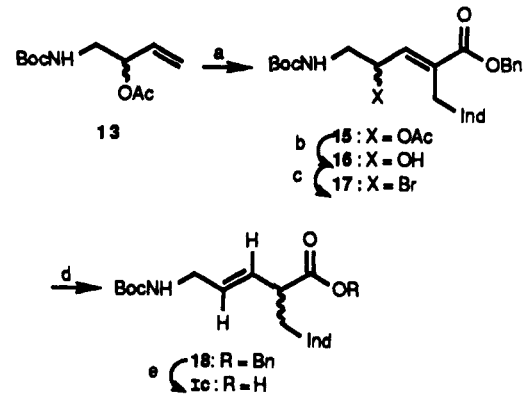


[a] Reagents: (a) LAH/−78 °C then vinyl GR (66%) from 2; (b) Ac_2O/Py/DMAP (89%); (c) NMO/$NaIO_4$/OsO_4(cat.), Ph_3P=CCH_2PhCO_2Bn 8 (70%); (d) Na_2CO_3/CH_3OH/rt/45 min (64%); (e) Ph_3P/CBr_4/THF (75%); (f) Zn/HOAc (97%); (g) 1,4-cyclohexadiene/Pd/C/MeOH (84%).

allylic alcohol **10** was transformed to the relatively unstable allylic bromide **11**, from which the fully protected Boc-Asp(β-O-tBu)ψ[*E*-CH=CH]Phe-OBn **12** was obtained in quantitative yield via a zinc-induced reductive isomerization in acetic acid medium.[12] A catalytic transfer hydrogenation.[13] afforded the properly protected double bond isostere Boc-Asp(β-O-tBu)ψ[*E*-CH=CH]Phe-OH Ia suitable for incorporation into peptides. The newly created α-center at the Phe residue was racemic, and attempts to separate the diastereomers of either the benzyl ester **12** or acid Ia failed. The coupling constants between the pairs of olefinic protons in compound **12** and Ia were found to be 15.4 and 15.8 Hz, respectively, thus establishing the trans stereochemistry for the newly formed double bond. This was consistent with literature precedent.[12]

Glyψ[*E*-CH=CH]Trp. Boc-Glyψ[*E*-CH=CH]Trp-OBn **18** was prepared in an identical fashion to Boc-Asp(β-OtBu)ψ[*E*-CH=CH]Phe-OBn **12**. The coupling constant between the pair of olefinic protons in compound **18** was found to be 15 Hz, consistent with the trans stereochemistry at the newly formed double bond. However, during the final transfer hydrogenation of **18**, isomerization and saturation of the internal trans double bond became serious side reactions. Therefore, the final transfer hydrogenation of **18** was carefully monitored, and the reaction was quenched prior to saturation of the double bond. A substantial amount of Boc-Glyψ[*E*-CH=CH]Trp-OBn **18** was recycled without appreciable loss.

Scheme III[a]



[a] Reagents: (a) NMO/$NaIO_4$/OsO_4(cat.), then Ph_3P=CCH_2IndCO_2Bn[14] **14** (70%); (b) Na_2CO_3/MeOH/rt/1 h (75%); (c) Ph_3P/CBr_4/THF (71%); (d) Zn/HOAc (97%); (e) 1,4-cyclohexadiene/Pd/C/MeOH (14%).

Leuψ[*E*-CH=CH]Asp. The synthesis of Boc-Leuψ[E-CH=CH]Asp(β-O-tBu)-OH **Ib** was carried out using the same reaction sequence with only minor modifications. Allylic alcohol **21** was prepared by a two-step, one-pot procedure (Dibal, then vinylmagnesium bromide added in situ) from Boc-Leu methyl ester **19**.[15] The acetyl blocking group used for the Aspψ[*E*-CH=CH]Phe isostere was found to be incompatible for synthesis of Ib since the sequence bears an aspartic side chain at the second residue. Methanolysis of the acetyl group of compound **25** did give the desired alcohol **27**, but in very low yield. Another protecting group (trichloroacetyl) was found to be too labile under the oxidative cleavage procedure [NMO/$NaIO_4$/OsO_4(cat.)]. Finally, the benzyloxycarbonyl moiety was determined to be the protecting group of choice for synthesis of this analogue. The allylic carbonate **26** was prepared in a similar fashion to its acetyl counterpart **25**. A catalytic transfer hydrogenation of **26** produced the desired allylic alcohol **27** in good yield and leaving the benzyl ester moiety of **26** untouched. Compound **27** was carried through the identical reaction sequence used for the Aspψ[*E*-CH=CH]Phe analogue to afford pseudodipeptide **29**. Again, the trans double bond stereochemistry was established through the coupling constant (16 Hz) between the olefinic protons in compound **29**. As in the case of compound **18**, transfer hydrogenation of compound **29** must be carefully controlled. The reaction proceeds very slowly using 1,4-cyclohexadiene. When ammonium formate was used as the hydrogen donor, the reaction proceeded rapidly (within minutes), but saturated compound **30** and desired Ib were obtained in a ratio of 1:2.[16] The difficulty in removing the benzyl ester of compound

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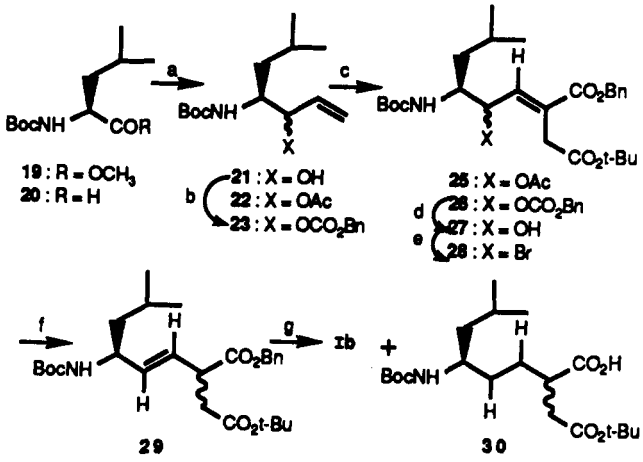
(16) Alternatively, an improved synthetic route[6b] was developed specifically for the synthesis of Boc-Leuψ[*E*-CH=CH]Asp(β-OtBu)-OH Ib.

Scheme IV[a]



[a] Reagents: (a) Dibal then vinyl GR (53%); (b) CbzOSu/DIEA/DMAP/CH_2Cl_2 (85%); (c) NMO/$NaIO_4$/OsO_4(cat.), then $Ph_3P{=}CCH_2CO_2t$-$BuCO_2Bn$ **24** (63%); (d) 1,4-cyclohexadiene/10% Pd/C/MeOH (66%); (e) Ph_3P/CBr_4 (88%); (f) Zn/HOAc (72%); (g) ammonium formate/Pd/C/MeOH.

29 and the unusual selectivity toward a benzyloxycarbonyl moiety over a benzyl ester group in **26**, which were observed in catalytic transfer hydrogenation, are presumably due to the steric effect. The bulkness of the *tert*-butyl-protected Asp side chain in compounds **26** and **29** effectively shielded the catalyst from approaching the benzyl ester moiety of both compounds.

Conclusion

The methodology described above affords pseudodipeptides containing highly functionalized side chains for incorporation into a variety of peptides of biological interest. The methodology involved is fully compatible with sensitive functionalities existing in many natural amino acids as demonstrated in the first successful synthesis of Trp and Asp containing trans-alkene dipeptide isosteres. The only shortcoming is the lack of stereocontrol at the α-center of the second amino acid residue. However, in some cases pseudopeptides containing the desired stereochemistry at the second residue can be obtained by chromatographic separation at the tripeptide or higher stage. This new reaction sequence provides access to a wide range of biologically significant pseudopeptide analogues and allows one to gain information concerning the role of the amide linkage in the receptor recognition and transduction process.

Experimental Section

Proton magnetic resonance spectra were recorded in $CDCl_3$ unless otherwise noted. Thin-layer chromatography (TLC) was carried out by using E. Merck precoated silica gel F-254 plates (thickness 0.25 mm). Flash chromatography was carried out with Merck silica gel 60, 70–230 mesh. Melting points are uncorrected. Protected amino acids were purchased from Bachem (Torrance, CA) or Chemical Dynamics Corp. (S. Plainfield, NJ). Anhydrous solvents were purchased from Aldrich (Milwaukee, WI), and reactions requiring anhydrous conditions were performed under a nitrogen atmosphere. Final product solutions were dried over Na_2SO_4, filtered, and evaporated under reduced pressure.

***tert*-Butyl (3*S*,4*RS*)-3-[(*tert*-Butoxycarbonyl)amino]-4-hydroxy-5-hexenoate (4).** To a suspension of LAH (498 mg, 13.1 mmol) in anhydrous THF (160 mL) was cooled to −78 °C under a N_2 atmosphere. A solution of 3,5-dimethylpyrrazolide **2** (4.82 g, 13.1 mmol) in anhydrous THF (60 mL) was added to the above LAH suspension with vigorous stirring. The reaction mixture was stirred at −78 °C for 40 min, quenched with MeOH (5 mL) at −78 °C, poured into aqueous solution of 10% citric acid (150 mL), and extracted with EtOAc. The organic layer was dried, filtered and evaporated. The residue was passed through a Florisil pad (EtOAc/Hx, 1/1, 700 mL). Solvents were removed, and the residue was dried at high vacuum for 2 h to provide the desired aldehyde **3** (3.52 g) in crude form, which was used immediately for the next reaction without further purification. A solution of vinylmagnesium bromide (1 M, 80 mL, 80 mmol) in anhydrous THF (80 mL) was cooled to −5 to −10 °C (acetone–ice bath). A solution of the aldehyde (3.52 g) in anhydrous THF (30 mL) was slowly added to the above Grignard solution with the cooling bath temperature maintained between −5 and −10 °C. Following the completion of addition, the reaction mixture was allowed to stir at that temperature for 40 min, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The organic layer was washed with brine, dried, filtered, and evaporated. The residue was chromatographed (EtOAc/toluene, 1/16 to 1/6) to give the desired diastereomeric allylic alcohol (2.63 g, 66.5%) as a colorless oil. Limited attempts to separate this diastereomeric mixture were unsuccessful; therefore, the spectrum reported here was a mixture of two isomers; ^1H NMR δ 1.43, 1.44, 1.45, 1.46 (4 s, 18 H), 2.46–2.6 (m, CH_2CO_2tBu, 2 H), 2.90 (br d, 1 H), 3.96 (m, 1 H), 4.23 (m, 1 H), 5.12 (br, 1 H), 5.23 (ddt, 1 H), 5.33 (ddt, 1 H), 5.28–5.92 (2 ddd, 1 H); exact mass calcd for $C_{15}H_{28}NO_5$ 302.1967, found 302.1970. Anal. Calcd for $C_{15}H_{27}NO_5 \cdot 0.5H_2O$: C, 58.05; H, 9.09; N, 4.51. Found: C, 57.90; H, 8.71; N, 4.45.

(3*RS*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-6-methyl-1-hepten-3-ol (21). To a cooled (−78 °C) solution of Boc-Leu-OMe **19** (4.91 g, 20.0 mmol) in toluene (46 mL) was added 1.0 M Dibal in toluene (28 mL) over 20 min via syringe. The reduction was allowed to proceed for 30 min at −78 °C, after which 1.0 M vinylmagnesium bromide in THF (120 mL, 120 mmol) was added over 15 min at −78 °C. The reaction mixture was stored overnight at −20 °C, and then was quenched with the slow addition of methanol (10 mL) and 20% aqueous Rochelle's salt (35 mL). The salts were removed by vacuum filtration through Celite and rinsed thoroughly with EtOAc. This filtrate was washed with water (2 × 200 mL), and the aqueous layer was back-washed with EtOAc (2 × 100 mL). The combined extracts were washed with brine, dried, filtered, and evaporated. The residue was chromatographed (EtOAc/Hx, 1/5 to 1/3) to yield a clear yellow oil (2.57 g, 53%), which solidified upon storage: mp 50–53 °C; ^1H NMR δ 0.93 (d, J = 7 Hz, 6 H), 1.34–1.41 (m, 2 H), 1.44 (s, 9 H), 1.61–1.75 (m, 1 H), 2.36 (d, J = 4 Hz), 3.60–3.72 (m, 1 H), 4.03–4.10 (m, 1 H), 4.59 (d, J = 9 Hz, 1 H), 5.20 (d, J = 11 Hz, 1 H), 5.30 (d, J = 17 Hz, 1 H), 5.90 (ddd, J = 6, 11, 17 Hz, 1 H); MS (EI) m/e 244 (M + H)$^+$. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.15; H, 10.35; N, 5.76. Found: C, 64.04; H, 10.23; N, 5.65.

***tert*-Butyl (3*S*,4*RS*)-4-Acetoxy-3-[(*tert*-butoxycarbonyl)amino]-5-hexenoate (5).** A mixture of allylic alcohol **4** (1.56 g, 5.18 mmol), Ac_2O (10 mL), Py (2.5 mL), and DMAP (50 mg) was stirred at room temperature overnight. Water (30 mL) was added, followed by Et_2O (5 × 30 mL) extraction. The Et_2O layer was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. The residue was chromatographed (EtOAc/Hx, 1/7 to 1/3) to give a colorless oil (1.58 g, 89%, a mixture of diastereomers): ^1H NMR δ 1.43, 1.45 (2 s, 18 H), 2.09, 2.10 (2 s, 3 H), 2.33–2.50 (m, 2 H), 4.19 (m, 1 H), 4.92, 5.08 (2 br s, 1 H), 5.25–5.35 (m, 2 H), 5.48 (t, 1 H), 5.79 (m, 1 H); exact mass calcd for $C_{17}H_{30}NO_6$ 344.2073, found 344.2076.

(3*RS*,4*S*)-3-[(Benzyloxycarbonyl)oxy]-4-[(*tert*-butoxycarbonyl)amino]-6-methyl-1-heptene (23). To a cooled (ice–water bath) solution of allylic alcohol **21** (1.00 g, 4.11 mmol) in CH_2Cl_2 (10 mL) were added DIEA (0.72 mL, 4.1 mmol), CbzOSu (2.23 g, 8.95 mmol) and DMAP (0.1 g, 0.82 mmol). The reaction mixture was allowed to stir overnight in the ice bath with warming to room temperature. The chilled reaction mixture was treated with 10% aqueous citric acid (20 mL). The layers were separated, and the aqueous phase was further extracted with $CHCl_3$ (4 × 20 mL). The combined organics were dried filtered and concentrated. The crude oil was chromatographed (EtOAc/Hx, 1/15 to 1/10) to give a clear oil (1.32 g, 85%): ^1H NMR δ 0.91 (d, J = 7 Hz, 6 H), 1.23–1.37 (m, 2 H), 1.40 (s, 9 H), 1.58–1.74 (m, 1 H), 3.85–3.97 (m, 1 H), 4.52 (d, J = 10 Hz, 1 H), 5.07–5.15 (m, 1 H), 5.17 (s, 2 H), 5.26 (d, J = 11 Hz, 1 H), 5.32 (d, J = 17 Hz, 1 H), 5.83 (ddd, J = 6, 11, 17 Hz, 1 H), 7.33–7.40 (m, 5 H); exact mass calcd for $C_{21}H_{32}NO_5$ 378.2280, observed 378.2277. Anal.

Calcd for $C_{21}H_{32}NO_3$: C, 66.80; H, 8.28; N, 3.71. Found: C, 66.90; H, 7.89; N, 3.71.

General Procedure To Prepare γ-Acetoxy 9, 15, or (Benzyloxycarbonyl)vinyl Pseudodipeptides 26. NMO (300 mg, 2.55 mmol) and OsO_4 (1 mL, 2% solution in t-BuOH) were added to a solution of 0.1 M allylic acetate (10 mL, 1 mmol) in acetone and stirred at room temperature for 5 min. $NaIO_4$ (1 g, 4.65 mmol in 7.5 mL of H_2O) was added to the above reaction mixture with a white precipitate forming during the course of the reaction. The progress of the reaction was monitored by TLC which indicated that the majority of the starting material was consumed within 2–4 h. The reaction mixture was poured into ice-cold water (12 mL) and extracted with $CHCl_3$ (10 mL × 3), dried, filtered, and evaporated. The residue was chromatographed (EtOAc/Hx as eluents) to afford the desired aldehyde which was reacted with (α-substituted carbobenzyloxymethylene)triphenylphosphorane (2 mmol) in CH_2Cl_2 (2 mL) at room temperature overnight. Purification was accomplished by flash chromatography using EtOAc/Hx as eluents.

1-Benzyl 7-*tert*-Butyl (4*RS*,5*S*)-(*E*)-4-Acetoxy-5-[(*tert*-butoxycarbonyl)amino]-2-phenyl-2-heptenedioate (9). This compound was prepared from **5** on a 2-mmol scale. Flash chromatography (EtOAc/Hx, 1/10 to 1/5) provided more mobile isomer (isomer A, 205 mg, 18%), mixed fractions (210 mg, 19%), less mobile isomer (isomer B, 381 mg, 33%) [total yield 796 mg, 70% from **5**]: ^{1}H NMR (isomer A) δ 1.38 (s, 9 H), 1.43 (s, 9 H), 2.05 (s, 3 H), 2.4 (dd, *J* = 4.5, 15 Hz, 1 H), 2.49 (dd, *J* = 9, 15 Hz, 1 H), 3.85 (dd, *J* = 15 Hz, 1 H), 4.2 (m, 1 H), 5.05 (br d, 1 H), 5.72 (dd, *J* = 8.5, 9 Hz, 1 H), 6.7 (d, *J* = 9.5 Hz, 1 H), 7.15–7.40 (m, 10 H); (isomer B) δ 1.40 (s, 18 H), 2.04 (s, 3 H), 2.31 (dd, *J* = 9, 16 Hz, 1 H), 2.45 (dd, *J* = 6, 16 Hz, 1 H), 3.82 (dd, *J* = 15 Hz, 2 H), 4.24 (m, 1 H), 4.94 (br d, *J* = 9.5 Hz, 1 H), 5.09 (s, 2 H), 5.8 (br dd, *J* = 6, 9 Hz, 1 H), 6.72 (d, *J* = 9.2 Hz, 1 H), 7.1–7.4 (m, 10 H); exact mass calcd for $C_{32}H_{42}NO_8$ 568.2910 (M + H)$^+$, found 568.2913. Anal. Calcd for $C_{32}H_{41}NO_8 \cdot 0.5H_2O$: C, 66.65; H, 7.34; N, 2.43. Found: C, 66.57; H, 7.21; N, 2.65.

Benzyl (4*RS*)-(*E*)-4-Acetoxy-5-[(*tert*-butoxycarbonyl)amino]-2-(3-indolylmethyl)-2-pentenoate (15). This compound was prepared from **13** on a 5.02-mmol scale to yield a pale yellow oil (1.74 g, 70% from **13**). The isolated product also contained approximately 10% *Z* isomer: ^{1}H NMR δ 1.40 (s, 9 H), 2.04 (s, 3 H), 3.23 (t, *J* = 6 Hz, 2 H), 3.94 (s, 2 H), 4.66 (br s, 1 H), 5.12 (s, 2 H), 5.72 (dt, *J* = 6, 9 Hz, 1 H), 6.67 (d, *J* = 9 Hz, 1 H), 6.97 (s, 1 H), 7.10 (t, *J* = 8 Hz, 1 H), 7.14–7.22 (m, 3 H), 7.24–7.30 (m, 3 H), 7.33 (d, *J* = 8 Hz, 1 H), 7.64 (d, *J* = 8 Hz, 1 H), 8.00 (s, 1 H); exact mass calcd for $C_{28}H_{32}N_2O_6$ 531.1897 (M + K)$^+$, found 531.1889. Anal. Calcd for $C_{28}H_{32}N_2O_6 \cdot 0.25H_2O$: C, 67.66; H, 6.60; N, 5.64. Found: C, 67.55; H, 6.57; N, 5.46.

1-Benzyl 4-*tert*-Butyl (*E*)-2-[(2*RS*,3*S*)-2-[(Benzyloxycarbonyl)oxy]-3-[(*tert*-butoxycarbonyl)amino]-5-methylhexylidene]succinate (26). This compound was prepared from **22** on a 3.50-mmol scale to yield a clear oil (1.39 g, 63% from **22**). This isolated product contained approximately 10% *Z* isomer: ^{1}H NMR δ 0.91 (d, *J* = 7 Hz, 6 H), 1.30–1.40 (m, 2 H), 1.39 (s, 18 H), 1.57–1.73 (m, 1 H), 3.44 (s, 2 H), 3.94–4.06 (m, 1 H), 4.65–4.77 (m, 1 H), 5.13 (d, *J* = 7 Hz, 2 H), 5.19 (s, 2 H), 5.33 (dd, *J* = 10 Hz, 1 H), 6.82 (d, *J* = 9 Hz, 1 H), 7.30–7.44 (m, 10 H); exact mass calcd for $C_{35}H_{48}NO_9$ 626.3329 (M + H)$^+$, found 626.3329. Anal. Calcd for $C_{35}H_{47}NO_9 \cdot 0.25H_2O$: C, 66.70; H, 7.60; N, 2.22. Found: C, 66.84; H, 7.79; N, 2.34.

1-Benzyl 7-*tert*-Butyl (4*RS*,5*S*)-(*E*)-5-[(*tert*-Butoxycarbonyl)amino]-4-hydroxy-2-phenyl-2-heptenedioate (10). Sodium carbonate (3 g) was added to a solution of **9** (210 mg, 0.37 mmol) in MeOH (9 mL) at room temperature. After the mixture was stirred for 45 min, sodium carbonate was removed by filtration and rinsed thoroughly with CH_2Cl_2. The filtrate was added to saturated NH_4Cl (20 mL), and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layer was washed with brine, dried, filtered, and concentrated. The residue was chromatographed (EtOAC/Hx, 1/9 to 1/4) to afford the desired allylic alcohol **10** (125 mg, 64%) and the recovered starting material **9** (30 mg, 14%): ^{1}H NMR (isomer A, an oil) δ 1.40 (s, 9 H), 1.43 (s, 9 H), 2.52 (dd, *J* = 5.6, 1.2 Hz, 2 H), 3.15 (br, 1 H), 3.78 (dd, *J* = 14.5 Hz, 2 H), 3.94 (m, 1 H), 4.68 (m, 1 H), 5.13 (dd, *J* = 12.5 Hz, 2 H), 5.24 (br d, 1 H), 6.86 (d, *J* = 9 Hz, 1 H), 7.15–7.34 (m, 10 H); (isomer B, a solid) δ 1.41 (s, 9 H), 1.42 (s, 9 H), 2.46 (dd, 1 H), 2.62 (dd, 1 H), 3.16 (br d, *J* = 4.8 Hz), 3.77 (br s, 2 H), 3.92 (m, 1 H), 4.65 (m, 1 H), 5.12 (br s, 1 H), 5.19 (br d, *J* = 8.9 Hz, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 7.16–7.33 (m, 10 H). Anal. Calcd for $C_{30}H_{39}NO_7$: C, 68.55; H, 7.48; N, 2.67. Found: C, 68.23; H, 7.49; N, 2.61.

Benzyl (4*RS*)-(*E*)-5-[(*tert*-Butoxycarbonyl)amino]-4-hydroxy-2-(3-indolylmethyl)-2-pentenoate (16). Sodium carbonate (26 g) was added to a solution of **15** (1.51 g, 3.06 mmol) in MeOH (75 mL) at room temperature. After the mixture was stirred for 1 h, sodium carbonate was removed by filtration and rinsed thoroughly with CH_2Cl_2. The filtrate was added to 20 mL of saturated NH_4Cl, and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with brine, dried, filtered, and evaporated. The residue was chromatographed (EtOAC/Hx, 1/6 to 1/1) to afford the allylic alcohol **16** (1.03 g, 75%): ^{1}H NMR δ 1.43 (s, 9 H), 2.97 (s, 1 H), 3.10–3.32 (m, 2 H), 3.87 (s, 2 H), 4.65–4.67 (m, 1 H), 4.85 (br s, 1 H), 5.16 (s, 2 H), 6.79 (d, *J* = 9 Hz, 1 H), 6.88 (s, 1 H), 7.11 (t, *J* = 8 Hz, 1 H), 7.19 (t, *J* = 8 Hz, 1 H), 7.22–7.31 (m, 6 H), 7.33 (d, *J* = 8 Hz, 1 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.99 (s, 1 H); exact mass calcd for $C_{26}H_{30}N_2O_9$ 473.2053 (M + Na)$^+$, found 473.2053. Anal. Calcd for $C_{26}H_{30}N_2O_5 \cdot 0.60H_2O$: C, 67.69; H, 6.82; N, 6.07. Found: C, 67.38; H, 6.65; N, 6.22.

1-Benzyl 4-*tert*-Butyl (*E*)-2-[(2*RS*,3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-2-hydroxy-5-methylhexylidene]succinate (27). A suspension of 1,4-cyclohexadiene (21 mL, 220 mmol) and 10% Pd/C (1.4 g) was stirred at 0 °C for 5 min, and then a solution of **26** (1.39 g, 2.22 mmol) in methanol (10 mL) was added. The reaction mixture was allowed to stir for 100 min at room temperature, after which the catalyst was removed by vacuum filtration through Celite. The filtrate was concentrated under reduced pressure. The resulting crude oil was chromatographed (EtOAc/Hx, 1/10 to 1/3), to give a clear pale yellow oil (0.72 g, 66%): ^{1}H NMR δ 0.92 (d, *J* = 7 Hz, 6 H), 1.39 (s, 9 H), 1.40 (s, 9 H), 1.40–1.55 (m, 2 H), 1.59–1.75 (m, 1 H), 3.38 (q, *J* = 16 Hz, 2 H), 3.52 (s, 1 H), 3.65–3.81 (m, 1 H), 4.28–4.38 (m, 1 H), 4.80 (d, *J* = 9 Hz, 1 H), 5.18 (s, 2 H), 7.00 (d, *J* = 8 Hz, 1 H), 7.29–7.43 (m, 5 H); exact mass calcd for $C_{27}H_{42}NO_7$ 492.2961 (M + H)$^+$, found 492.2982. Anal. Calcd for $C_{27}H_{41}NO_7$: C, 65.97; H, 8.41; N, 2.85. Found: C, 65.94; H, 8.24; N, 2.95.

General Procedure To Prepare Allylic Bromides 11, 17, 28. A solution of alcohol (1.0 mmol) in THF (10 mL) was added slowly into a freshly prepared 0.25 M suspension of dibromotriphenylphosphorane complex (6–8 equiv) in THF at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 1.5 h. The solid formed was removed by filtration and rinsed thoroughly with Et_2O. The organic layer was washed with 10% aqueous citric acid solution, and the aqueous layer was back-washed with Et_2O. The combined organic extracts were washed with 10% sodium thiosulfate solution and brine, dried, filtered, and concentrated in vacuo. Flash chromatography (EtOAc/Hx, 1/10 to 1/4) afforded the diastereomeric bromide usually as a pale-pink oil. The allylic bromides **11**, **17**, and **28** decomposed upon standing, and therefore should be used immediately for the next reaction.

1-Benzyl 7-*tert*-Butyl (4*RS*,5*S*)-(*E*)-4-Bromo-5-[(*tert*-butoxycarbonyl)amino]-2-phenylheptenedioate (11). This compound was prepared from **10** (a mixture of diastereomers) on a 1-mmol scale and afforded **11** (440 mg, 75%) as a pink oil: ^{1}H NMR δ 1.35, 1.42, 1.43 (3 s, 18 H), 2.46–2.90 (4 dd, 2 H, CH_2CO_2t-Bu), 3.67–3.86 (2 dd, 2 H, CH_2Ph), 4.2 (m, 1 H, αH), 5.0 (m, 1 H, NH), 5.10, 5.17 (2 dd, 2 H, OCH_2Bn), 5.22 (1 H, CHBr), 7.02 (2 d, 1 H, CH=C), 7.18–7.32 (m, 10 H, Ar-H); exact mass calcd for $C_{30}H_{39}NO_6Br$: 588.1961 (M + H)$^+$, found 588.1957.

Benzyl (4*RS*)-(*E*)-4-Bromo-5-[(*tert*-butoxycarbonyl)amino]-2-(3-indolylmethyl)-2-pentenoate (17). This compound was prepared from **16** on a 2.06-mmol scale and afforded **17** (0.75 g, 71%) as a pale brown oil: ^{1}H NMR δ 1.42 (s, 9 H), 3.54 (t, *J* = 6 Hz, 2 H), 3.88 (s, 2 H), 4.90 (br s, 1 H), 5.01 (dt, *J* = 6, 11 Hz, 1 H), 5.15 (s, 2 H), 6.92 (s, 1 H), 6.93 (d, *J* = 11 Hz, 1 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.17–7.25 (m, 3 H), 7.25–7.31 (m, 3 H), 7.35 (d, *J* = 7.5 Hz, 1 H), 7.63 (d, *J* = 7.5 Hz, 1 H), 7.98 (br s, 1 H); MS (DCI/NH_3) *m/e* 530 (M + NH_4)$^+$, 532 (M + 2 + NH_4)$^+$, 513 (M + H)$^+$, and 515 (M + 2 + H)$^+$.

1-Benzyl 4-*tert*-Butyl (*E*)-2-[(2*RS*,3*S*)-2-Bromo-3-[(*tert*-butoxycarbonyl)amino]-5-methylhexylidene]succinate

(28). This compound was prepared from **27** (75 mg, 0.153 mmol) by the method described above to give a clear pale yellow oil (65 mg, 88%): ^{1}H NMR δ 0.94 (dd, J = 4, 8 Hz, 6 H), 1.27 (s, 2 H), 1.35–1.50 (m, 18 H), 1.63–1.76 (m, 1 H), 3.35 (d, J = 10 Hz, 1 H), 3.45 (d, J = 10 Hz, 1 H), 3.83–3.95 (m, 1 H), 4.64–4.73 (m, 1 H), 4.76–4.85 (m, 1 H), 5.22 (d, J = 3 Hz, 2 H), 7.06 (t, J = 7 Hz, 1 H), 7.29–7.40 (m, 5 H); MS (DCI) m/e 571, 573 $(M + NH_4)^+$, 554, 556 $(M + H)^+$.

General Procedure for Reductive Isomerization: Preparation of Trans Double-Bond Isosteres of Peptide Bonds. To a stirred solution of allylic bromide (0.1 M) in glacial acetic acid was added Zn powder (1 g) at room temperature. After the mixture was stirred at room temperature for 1 h, excess Zn powder was removed by filtration and was rinsed thoroughly with Et_2O. The filtrate was added to ice water and the layers were separated. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried, and then filtered. Solvent was removed, and the residue was purified by plug filtration through a pad of silica gel (EtOAc/Hx, 1/1) to afford the fully protected pseudodipeptide.

Boc-Asp(O-tBu)ψ[*E*-CH=CH]-D,L-Phe-OBn (12). This analogue was prepared from **11** (430 mg, 0.73 mmol) to afford **12** (360 mg, 97%) as an inseparable 1:1 mixture of diasteromers at the α-center of Phe: ^{1}H NMR δ 1.42 (s, 9 H), 1.44 (2 s, 9 H), 2.38–2.45 (m, 2 H, CH_2CO$_2$t-Bu), 2.81 (dd, 1 H, J = 7.0, 13.6 Hz, CHPh), 3.04 and 3.08 (2 dd, 1 H, CHPh), 3.30–3.36 (m, 1 H, CHCO$_2$Bn), 4.41–4.46 (br 1 H, NCH), 5.03 (br s, 2 H, OCH_2Ph), 5.49 (dt, J = 5.5, 15.4 Hz, CH=C), 5.69 (dt, J = 7.0, 15.4 Hz, C=CH), 7.08–7.34 (m, 10 H, Ar-H); exact mass calcd for $C_{30}H_{40}NO_6$ 510.2855 $(M + H)^+$, found 510, 2862. Anal. Calcd for $C_{30}H_{39}NO_6 \cdot H_2O$: C, 68.29; H, 7.83; N, 2.65. Found: C, 68.23; H, 8.15; N, 2.71.

Boc-Glyψ[*E*-CH=CH]-D,L-Trp-OBn (18). This analogue was prepared from **17** (750 mg, 1.46 mmol) to afford **18** (610 mg, 97%) as a pale yellow oil: ^{1}H NMR δ 1.44 (s, 9 H), 2.99 (dd, J = 7, 15 Hz, 1 H, CHInd), 3.25 (dd, J = 8, 15 Hz, 1 H, CHInd), 3.48 (q, J = 7.5 Hz, 1 H, CHCO$_2$Bn), 3.68 (t, J = 6 Hz, 2 H, NCH_2), 4.40 (br s, 1 H), 5.05 (s, 2 H), 5.51 (dt, J = 6, 15 Hz, 1 H, CH=C), 5.73 (dd, J = 7.5, 15 Hz, 1 H, C=CH), 6.89 (s, 1 H), 7.11 (t, J = 7 Hz, 1 H), 7.14–7.22 (m, 3 H), 7.26–7.32 (m, 3 H), 7.34 (d, J = 7 Hz, 1 H), 7.56 (d, J = 7 Hz, 1 H), 7.96 (s, 1 H); exact mass calcd for $C_{28}H_{31}N_2O_4$ 435.2284 $(M + H)^+$, found 435.2280. Anal. Calcd for $C_{26}H_{30}N_2O_4 \cdot 0.25H_2O$: C, 71.12; H, 7.02; N, 6.38. Found: C, 71.02; H, 7.10; N, 6.06.

Boc-Leuψ[*E*-CH=CH]-D,L-Asp(O-t-Bu)-OBn (29). This compound was prepared from **28** (63 mg, 0.11 mmol) by the method described above to afford **29** (28 mg, 72%): ^{1}H NMR δ 0.88 (q, J = 3 Hz, 6 H), 1.24–1.31 (m, 2 H), 1.41, 1.43 (2 s, 18 H), 1.53–1.65 (m, 1 H), 2.45 (dd, J = 6, 16 Hz, 1 H), 2.77 (dq, J = 9, 16 Hz, 1 H), 3.45–3.55 (m, 1 H), 4.11 (br s, 1 H), 4.28 (br s, 1 H), 5.14 (q, J = 12 Hz, 2 H), 5.48 (dt, J = 7, 15 Hz, CH=C, 1 H), 5.61 (dd, J = 7.5, 15 Hz, C=CH, 1 H), 7.30–7.43 (m, 5 H); exact mass calcd for $C_{27}H_{41}NO_6$ 514.2571 $(M + K)^+$, found 514.2566. Anal. Calcd for $C_{27}H_{41}NO_6 \cdot 0.25H_2O$: C, 67.54; H, 8.71; N, 2.92. Found: C, 67.26; H, 8.59; N, 2.72.

Boc-Asp(O-t-Bu)ψ[*E*-CH=CH]-D,L-Phe-OH (Ia). A suspension of 1,4-cyclohexadiene (5 mL) and 10% Pd/C (200 mg) in MeOH (10 mL) was stirred at room temperature for 10 min, and then a solution of Boc-Asp(O-t-Bu)ψ[*E*-CH=CH]-D,L-Phe-OBn **12** (210 mg, 0.41 mmol) in MeOH (10 mL) was added. The reaction mixture was allowed to stir for 1.5 h at room temperature, after which the catalyst was removed by filtration through Celite. The filtrate was concentrated under reduced pressure, and the residue was taken up in Et_2O (20 mL) and extracted with 0.4 N NaOH (4 × 7 mL). The combined organic fractions were washed with brine, dried, filtered, and evaporated to recover starting material (10 mg, 4.7%). The pH of the aqueous layer was adjusted to 2–3 with 6 N HCl at 0 °C, and this was extracted with CH_2Cl_2 (5 × 10 mL). The combined CH_2Cl_2 layer was washed with brine, dried, filtered, and evaporated to give a clear oil (146 mg, 84%): ^{1}H NMR δ 1.43 (s, 9 H), 1.45 (s, 9 H), 2.39–2.44 (m, 2 H, CH_2CO$_2$-tBu), 2.83 (dd, 1 H, J = 7.3, 13.7 Hz, CH-Ph), 3.10 (dd, J = 7.7, 13.7 Hz, CH-Ph), 3.29–3.34 (m, 1 H, CHCOOH), 4.43 (br, 1 H, N-CH), 5.51 (dd, 1 H, J = 6.0, 15.8 Hz, CH=C), 5.69 (dt, 1 H, J = 8.6, 15.8 Hz, C=CH), 7.15–7.29 (m, 10 H, Ar-H); exact mass calcd for $C_{23}H_{34}NO_6$ 420.2384 $(M + H)^+$, found 420.2386. Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.70; H, 8.16; N, 3.68.

Boc-Glyψ[*E*-CH=CH]-D,L-Trp-OH (Ic). To a suspension of 10% Pd/C (0.38 g) in 1,4-cyclohexadiene (16.4 mL) was added a solution of Boc-Glyψ[*E*-CH=CH]-D,L-Trp-OBn (**18**) in MeOH (17 mL). The reaction mixture was allowed to stir at room temperature for 5 h, at which time TLC revealed approximately 10% completion. The reaction was worke up at this point due to the fact that the product Ic is prone to over reduction and isomerization. The catalyst was removed by filtration through Celite and by filtration through a 0.45 μm PTFE filter membrane. The filtrate was concentrated under reduced pressure. The oily residue was dissolved in Et_2O (20 mL) and extracted with 0.2 N NaOH (3 × 15 mL). The aqueous extracts were back-washed with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine, dried, filtered, and concentrated to yield a clear oil (277 mg, 73% recovered starting material **18**). The combined aqueous extracts were acidifed with 2.0 N HCl until pH 2 was attained and were extracted with EtOAc (4 × 100 mL). The extracts were washed with brine, dried, filtered, and concentrated to yield a clear pale yellow oil (43 mg, 14%): ^{1}H NMR δ 1.44 (s, 9 H), 2.99 (dd, J = 7, 14 Hz, 1 H, CHInd), 3.26 (dd, J = 7.5, 15 Hz, 1 H, CHCO$_2$H), 3.43 (t, J = 8.0 Hz, 1 H, CHInd), 3.68 (br s, 2 H, NCH_2), 4.48 (br s, 1 H), 5.54 (dt, J = 5, 15 Hz, 1 H, CH=C), 5.71 (dd, J = 8.0, 15 Hz, 1 H, C=CH), 6.99 (s, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.34 (d, J = 7.5 Hz, 1 H), 7.58 (d, J = 7.5 Hz, 1 H), 8.07 (s, 1 H); exact mass calcd for $C_{19}H_{25}N_2O_4$ 345.1814 $(M + H)^+$, found 345.1813. Anal. Calcd for $C_{19}H_{24}N_2O_4 \cdot 0.5H_2O$: C, 64.56; H, 7.13; N, 7.93. Found: C, 64.81; H, 6.99; N, 7.59.

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Registry No. **2**, 131792-06-8; **4** (diastereomer 1), 114475-32-0; **4** (diastereomer 2), 114475-31-9; **5** (diastereomer 1), 131792-07-9; **5** (diastereomer 2), 131792-08-0; **8**, 114475-41-1; **9** (diastereomer 1), 131897-74-0; **9** (diastereomer 2), 131897-75-1; **10** (diastereomer 1), 131897-76-2; **10** (diastereomer 2), 131897-77-3; **11** (diastereomer 1), 131897-78-4; **11** (diastereomer 2), 131897-79-5; **12** (diastereomer 1), 114475-40-0; **12** (diastereomer 2), 114475-39-7; **13**, 131792-11-5; **14**, 131792-12-6; **15**, 131792-13-7; (*Z*)-**15**, 131792-14-8; **16**, 131792-17-1; **17**, 131031-90-8; **18**, 131792-20-6; **19**, 63096-02-6; **21** (diastereomer 1), 107599-95-1; **21** (diastereomer 2), 107600-12-4; **23** (diastereomer 1), 131792-09-1; **23** (diastereomer 2), 131792-10-4; **24**, 114475-48-8; **26** (diastereomer 1), 114475-45-5; **26** (diastereomer 2), 114475-44-4; (*Z*)-**26** (diastereomer 1), 131792-15-9; (*Z*)-**26** (diastereomer 2), 131792-16-0; **27** (diastereomer 1), 114475-47-7; **27** (diastereomer 2), 114475-46-6; **28** (diastereomer 1), 131792-18-2; **28** (diastereomer 2), 131792-19-3; **29** (diastereomer 1), 131792-21-7; **29** (diastereomer 2), 131792-22-8; Ia (diastereomer 1), 114475-30-8; Ia (diastereomer 2), 114475-29-5; Ib (diastereomer 1), 119689-14-4; Ib (diastereomer 2), 119689-13-3; Ic, 131792-23-9.