A Practical and Diastereoselective Synthesis of Ketomethylene Dipeptide Isosteres of the Type AAΨ[COCH$_2$]Asp

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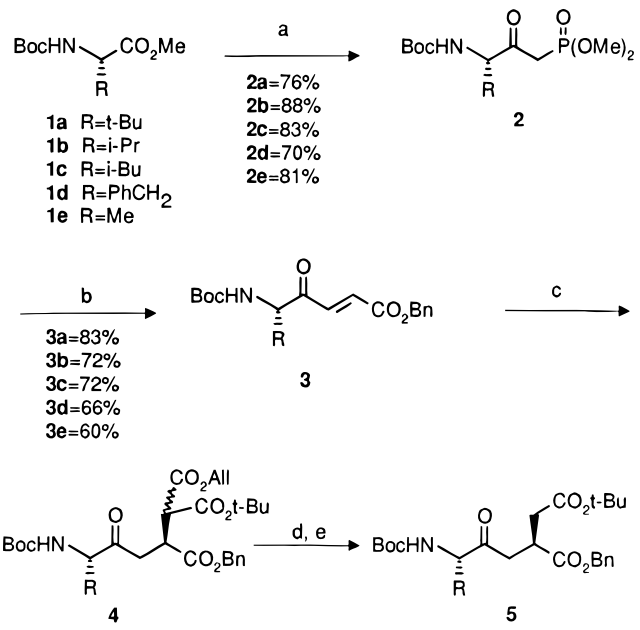
In recent years much attention has been focused on the synthesis of ketomethylene isosteres and their use in biologically active peptides.[1] In the course of our studies on peptidomimetic inhibitors we needed a facile synthesis of aspartic acid ketomethylene dipeptide isosteres (AAΨ[COCH$_2$]Asp). Here we report a practical synthesis of this type of isostere that features a diastereoselective Michael addition and provides suitably protected functionalities for subsequent transformations.[2]

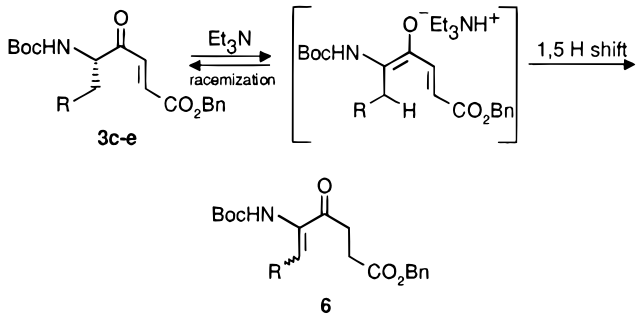
The synthesis, outlined in Scheme 1, began with the *N*-Boc protected amino acid methyl esters **1a**−**e** which were converted into the ketophosphonates **2a**−**e** in good yield by treatment with 8 equiv of lithium dimethyl methylphosphonate in THF at −78 °C. The *trans*-Michael acceptors **3a**,**b** were prepared by treating the ketophosphonates **2a**,**b** with 1.05 equiv of benzyl glyoxylate[3] in the presence of 2.0 equiv of triethylamine in acetonitrile at room temperature. However, we found that the above reaction conditions were not suitable for the preparation of Michael acceptors bearing smaller alkyl groups **3c**−**e**. We observed racemization[4] and formation of the corresponding rearranged products **6**.[5] We believed that products **6** were formed *via* a based-catalyzed 1,5-hydrogen shift as shown in Scheme 2.

Scheme 1[a]



[a] Reagents and Conditions: (a) LiCH$_2$PO(OMe)$_2$ (8 equiv), THF, −78 °C; (b) **3a**,**b** HCOCO$_2$Bn·0.3H$_2$O, CH$_3$CN, Et$_3$N 23 °C; **3c**−**e** HCOCO$_2$Bn·0.3H$_2$O, NMM, CH$_2$Cl$_2$, 0 °C; (c) reaction conditions of entry 1, Table 1; (d) Pd(PPh$_3$)$_4$ (0.01% mol), pyrrolidine (1.05 equiv), toluene; (e) xylenes, 130 °C.

Scheme 2



These problems were overcome by replacing triethylamine by a weaker base, *N*-methylmorpholine, and by lowering the reaction temperature to 0 °C. These modifications necessitated longer reaction times and since these Michael acceptors were somewhat unstable, we found that the use of dichloromethane and molecular sieves reduced the quantity of minor byproducts. It should be noted that the use of *N*-methylmorpholine in the Wadsworth−Emmons reaction of phosphonates **2a**,**b** gave a substantial amount of the *cis* isomer. We found that the *cis* isomer was not a suitable substrate for the subsequent reaction.

The first step in the stereoselective introduction of the *tert*-butyl acetate side chain involved the conjugate addition of the sodium salt of allyl *tert*-butyl malonate[6] to **3a**−**e** to give the adducts **4a**−**e** in >90% yields. However, at this stage the unsymmetrical malonate moiety made the assessment of the diastereoisomeric purity of **4a**−**e** difficult. We thus assessed the degree of

(1) For pertinent references on this topic see: González-Muñiz, R.; García-López, M. T.; Gómez-Monterry, I.; Herranz, R.; Jimeno, M. L.; Suárez-Gea, M. L.; Johansen, N. L.; Madsen, K.; Thogersen, H.; Suzdak. P. *J. Med. Chem.* **1995**, *38*, 1015. Casimir, J. R.; Turetta, C.; Ettouati, L.; Paris, J. *Tetrahedron Lett.* **1995**, *36*, 4797. Groeger, C.; Wenzel, H. R.; Tschesche, H. *Int. J. Protein Res.* **1994**, *44*, 166. Kim, B. H.; Chung, Y. J.; Ryu, E. J. *Tetrahedron Lett.* **1993**, *34*, 8465. Dominguez, M. J.; González-Muñiz, R.; García-López, M. T. *Tetrahedron* **1992**, *48*, 2761. Hoffman, R. V.; Kim, H-O. *Tetrahedron Lett.* **1992**, *33*, 3579. Cheng, L.; Goodwin, C. A.; Shully, M. F.; Kakkar, V. V.; Claeson, G. *J. Med. Chem.* **1992**, *35*, 3364. DiMaio, J.; Gibbs, B.; Lefebvre, J.; Konishi, Y.; Munn, D.; Yue, S. Y. *J. Med. Chem.* **1992**, *35*, 3331. Kaltenbronn, J. S.; Hudspeth, E. A.; Lunney, B. M.; Michniewicz, E. D.; Nicolaides, J. T.; Repine, J. T.; Roark, W. H.; Stier. M. A.; Tinner, F. J.; Woo, P. K.W.; Essenburg, A. D. *J. Med. Chem.* **1990**, *33*, 838. Harbeson, S. L.; Rich, D. H. *J. Med. Chem.* **1989**, *32*, 1378. García-López, M. T.; González-Muñiz, R.; Harto, J. R. *Tetrahedron Lett.* **1988**, *29*, 1577. García-López, M. T.; González-Muñiz, R.; Harto, J. R. *Tetrahedron Lett.* **1988**, *44*, 5138. Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 374. McMurray, J. S.; Dyckes, D. F. *J. Org. Chem.* **1985**, *50*, 1112. Holladay, M. W.; Rich, D. H. *Tetrahedron Lett.* **1983**, *24*, 4401. Jennings-White, C.; Almquist, R. G. *Tetrahedron Lett.* **1982**, *23*, 2533.

(2) For the selective removal of a *N*-Boc protecting group in the presence of a *tert*-butyl ester see: Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216.

(3) Benzyl glyoxylate (containing 0.3 equiv of H$_2$O) was prepared by oxidation of benzyl tartrate with periodic acid: Shuda, P. F.; Ebner, C. B.; Potlock, S. J. *Synthesis* **1987**, *25*, 2183.

(4) The degree of racemization of Michael acceptors **3b**−**e** was assessed by chiral HPLC. The enantiomers of **3b**−**e** were made from the corresponding D-amino acids in order to identify the elution time of both enantiomers. The assessement of optical purity of **3a** was made by proton NMR analysis (400 MHz) of its corresponding Mosher amide. HPLC conditions: Chiracel OD-H column (0.46 cm × 25 cm, Daicel Chemical Industries Ltd.); 1.0% ethanol/hexanes (0.5 mL/min, 250 psi), $\lambda = 220$ nm.

(5) Compounds **6** were characterized by 400 MHz proton NMR analysis.

(6) Allyl *tert*-butylmalonate was prepared by addition of allyl chloroformate to the lithium salt of *tert*-butyl acetate generated with LiHMDS in THF at −78 °C.

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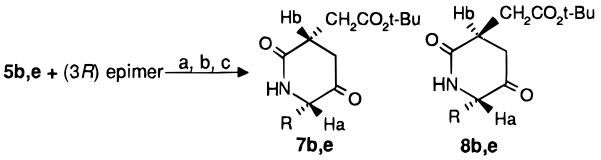
Table 1. Synthesis of the Ketomethylene Isosteres 5a-e from 3a-e

entry	electrophile	solvent	base (0.25 equiv)	*T*, °C	ratio[a] **5**:(3*R*) epimer	yield[b] (%) of **5** from **3**
1	**3a**	THF	NaH	−78	>50:1	77
2	**3b**	THF	NaH	−78	10:1	68
3	**3c**	THF	NaH	−78	9:1	62
4	**3d**	THF	NaH	−78	5:1	68
5	**3e**	THF	NaH	−78	5:1	76
6	**3b**	THF	NaHMDS	−78	10:1	74
7	**3b**	THF	KH	−78	1.5:1	72
8	**3b**	THF	LiHMDS	−78	3:1	59
9	**3b**	THF	NaH	0	4:1	70
10	**3b**	Et_2O	NaH	−78	4:1	59
11	**3b**	toluene	NaH	−78	3.5:1	60

[a] Ratio assessed by HPLC and ^1H NMR (400 MHz) analysis of crude **5**. [b] Yields of **5** and 3*R* epimers obtained after purification by silica gel column chromatography.

Scheme 3[a]



[a] Reagents and Conditions: (a) HCl, EtOAc, (b) H_2, Pd/C, solvent (c) (i) TBTU, *N*-methylmorpholine, (ii) separation.

diastereoselectivity after deallylation[7] and decarboxylation. The desired aspartic acid ketomethylene isosteres **5a**−**e** were obtained in 62−77% yields from the Michael acceptors **3a**−**e**. As shown in Table 1 (entry 1), conjugate addition to the Michael acceptor bearing the bulkiest alkyl group can occur with remarkably high diastereoselectivity (>50:1). Conjugate addition to Michael acceptors bearing smaller alkyl groups proceeded with selectivities ranging from 5−10:1. Surprisingly, the addition to the Michael acceptor bearing a methyl group occurred with a respectable 5:1 selectivity.

Several reaction conditions for the Michael addition were investigated, and the use of sodium hydride and THF at −78 °C gave the highest selectivity. Results from entries 6−11 show that the diastereoselectivity of the conjugate addition greatly depends on the base counterion, solvent, and temperature. The sodium counterion proved superior to either potassium and lithium (*cf.* entries 2, 6−8). So far THF appears to be the solvent of choice in this particular reaction (*cf.* entries 2, 10, and 11). Not surprisingly, better selectivity was obtained at lower temperature (*cf.* entries 2 and 9).

The assessment of the relative configuration of the two asymmetric centers in **5b** and **5e** was made by analyzing the corresponding lactams **7b** and **7e** prepared as shown in Scheme 3. For the lactam **7b** we obtained crystals and the stereochemistry assigned was confirmed by X-ray analysis.[8] NOE analysis of lactam **7e** showed a 4.5% enhancement between Ha and Hb whereas none was observed with the minor isomer **8e**. On the basis of these results, we assume the same relative stereochemistry for compounds **5a**,**c**,**d**. Since we found that the Michael acceptors **3c**−**e** were susceptible to base-catalyzed enolization during the Wadsworth−Emmons reaction, it was important to assess the enantiomeric purity of the final products. Chiral HPLC analysis of compounds **5b**−**d** indicated only 2−4% enantiomeric contamination.[9] Compound **5e** was shown to contain 10% enantiomeric contamination; however, that contamination was already present in phosphonate **2e**.

In summary, we have developed a diastereoselective and straightforward synthesis of ketomethylene dipeptide isosteres of the type AAΨ[$COCH_2$]Asp bearing suitably protected functionalities for subsequent transformations. The key feature of this new synthesis involves a diastereoselective conjugate addition on Michael acceptors **3a**−**e**. Studies toward expanding the scope of this reaction and understanding the parameters dictating facial selectivity are currently in progress.

Experimental Section

Dimethyl [(3*S*)-4,4-Dimethyl-3-[(*tert*-butyloxycarbonyl)amino]-2-oxopentyl]phosphonate (2a). (General Procedure for the Synthesis of 2 from 1). To a solution of dimethyl methylphosphonate (4.04 g, 32.6 mmol) in THF (30 mL) and cooled to −78 °C was added 1.6 N *n*-BuLi (20.4 mL, 32.6 mmol) dropwise. The solution was stirred at −78 °C for 20 min, and then a THF (20 mL) solution of **1a** (1.00 g, 4.07 mmol) was slowly added. The mixture was stirred at −78 °C for 1 h and then at room temperature for 15 min. The solution was acidified with 10% AcOH (20 mL), extracted with EtOAc, washed with 10% $NaHCO_3$ and brine, and dried over $MgSO_4$. After concentration, the residue was triturated in hexanes to give **2a** (1.05 g, 76%) as a white solid: mp 82−83 °C; $[\alpha]^{22}_D = +20.1°$ (*c*, 1.82, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.23 (d, J = 9.5 Hz, 1 H), 4.25 (d, J = 9.5 Hz, 1 H), 3.81 (d, J = 2 Hz, 3 H), 3.78 (d, J = 2 Hz, 3 H), 3.32 (dd, J = 22 Hz, 14.5 Hz, 1 H), 3.12 (dd, J = 22 Hz, 14.5 Hz, 1 H), 1.44 (s, 9 H), 1.00 (s, 9 H); HRMS *m*/*z* calcd for $C_{14}H_{29}NO_6P$ (MH^+) 338.1732, found 338.1721. Anal. Calcd for $C_{14}H_{28}NO_6P$: C, 49.85; H, 8.37; N, 4.15. Found: C, 49.77; H, 8.56; N, 4.09.

Dimethyl [(3*S*)-4-methyl-3-[(*tert*-butyloxycarbonyl)amino]-2-oxopentyl]phosphonate (2b): colorless oil; $[\alpha]^{22}_D = +16.8°$ (*c*, 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.30 (d, 8.5 Hz, 1 H), 4.32 (dd, J = 8.5 Hz, 4 Hz, 1 H), 3.81 (d, J = 2 Hz, 3 H), 3.78 (d, J = 2 Hz, 3 H), 3.29 (dd, J = 22 Hz, 14.5 Hz, 1 H), 3.09 (dd, J = 22 Hz, 14.5 Hz, 1 H), 2.32−2.28 (m, 1 H), 1.45 (s, 9 H), 1.00 (d, J = 7 Hz, 3 H), 0.82 (d, J = 7 Hz, 3 H); HRMS *m*/*z* calcd for $C_{13}H_{27}NO_6P$ (MH^+) 324.1576, found 324.1554. Anal. Calcd for $C_{13}H_{26}NO_6P$: C, 48.29; H, 8.11; N, 4.33. Found: C, 47.83; H, 8.36; N, 4.21.

Dimethyl [(3*S*)-5-methyl-3-[(*tert*-butyloxycarbonyl)amino]-2-oxohexyl]phosphonate (2c): colorless oil; $[\alpha]^{22}_D = -15.7°$ (*c*, 2.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.19 (d, J = 7.5 Hz, 1 H), 4.36−4.32 (m, 1 H), 3.81 (d, J = 4 Hz, 3 H), 3.78 (d, J = 4 Hz, 3 H), 3.33 (dd, J = 22 Hz, 14 Hz, 1 H), 3.10 (dd, J = 22 Hz, 14 Hz, 1 H), 1.68−1.60 (m, 2 H), 1.45 (s, 9 H), 1.41−1.37 (m, 1 H), 0.95 (d, J = 6 Hz, 3 H), 0.94 (d, J = 6 Hz, 3 H); HRMS *m*/*z* calcd for $C_{14}H_{29}NO_6P$ (MH^+) 338.1732, found 338.1721. Anal. Calcd for $C_{14}H_{28}NO_6P$: C, 49.85; H, 8.37; N, 4.15. Found: C, 48.87; H, 8.50; N, 4.08.

Dimethyl [(3*S*)-4-phenyl-3-[(*tert*-butyloxycarbonyl)amino]-2-oxobutyl]phosphonate (2d): white solid, mp 76−78 °C; $[\alpha]^{22}_D = -5.94°$ (*c*, 1.80, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.31−7.17 (m, 5 H), 5.28 (d, J = 7 Hz, 1 H), 4.54−4.57 (m, 1 H), 3.77 (d, J = 11.5 Hz, 3 H), 3.76 (d, J = 11.5 Hz, 3 H), 3.29−2.92 (m, 4 H), 1.39 (s, 9 H); HRMS *m*/*z* calcd for $C_{17}H_{27}NO_6P$ (MH^+) 372.1576, found 372.1587. Anal. Calcd for $C_{17}H_{26}NO_6P$: C, 54.98; H, 7.06; N, 3.77. Found: C, 54.60; H, 7.09; N, 3.75.

Dimethyl [(3*S*)-3-[(*tert*-butyloxycarbonyl)amino]-2-oxobutyl]phosphonate (2e): colorless oil; $[\alpha]^{22}_D = -1.18°$ (*c*, 2.62, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.36 (broad s, 1 H), 4.39−4.35 (m, 1

(7) Déziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371

(8) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(9) In order to make sure that we were indeed measuring ratios of enantiomers and not diastereoisomers, we made the enantiomers of **5b**−**e** from the corresponding D-amino acids and compared their elution time with **5b**−**e**. See footnote 4 for HPLC conditions.

H), 3.81 (d, J = 2.5 Hz, 3 H), 3.78 (d, J = 2.5 Hz, 3 H), 3.31 (dd, J = 22.5 Hz, 14 Hz, 1 H), 3.12 (dd, J = 22.5 Hz, 14 Hz, 1 H), 1.45 (s, 9 H), 1.36 (d, J = 7 Hz, 3 H); HRMS m/z calcd for $C_{11}H_{23}NO_6P$ (MH^+) 296.1263, found 296.1269. Anal. Calcd for $C_{11}H_{22}NO_6P$: C, 44.75; H, 7.51; N, 4.74. Found: C, 44.47; H, 7.65; N, 4.62.

Benzyl (*E*)-(5*S*)-6-Methyl-5-[(*tert*-butyloxycarbonyl)amino]-4-oxo-2-heptenoate (3b) (General Procedure for the Synthesis of 3a,b). To a solution of phosphonate **2b** (24.7 mmol, 8.00 g) in acetonitrile (120 mL) were added triethylamine (49.4 mmol, 6.88 mL) and a solution of benzyl glyoxylate[3] (24.7 mmol, 4.05 g) in acetonitrile (30 mL). The solution was stirred at room temperature for 1 h, poured into hexane−EtOAc, washed with 0.1 M aqueous HCl and brine, and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography (hexane−EtOAc 7:1, *trans*-isomer elutes faster than the *cis*) to give **3b** (6.43 g, 72%) as a light yellow oil: $[\alpha]^{22}_D$ = +53° (*c*, 2.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39−7.35 (m, 5 H), 7.23 (d, J = 16 Hz, 1 H), 6.83 (d, J = 16 Hz, 1 H), 5.28−5.21 (m, 2 H), 5.13 (d, J = 8.5 Hz, 1 H), 4.51 (dd, J = 8.5 Hz, 4 Hz, 1 H), 2.19−2.16 (m, 1 H), 1.43 (s, 9 H), 1.02 (d, J = 7 Hz, 3 H), 0.79 (d, J = 7 Hz, 3 H); HRMS m/z calcd for $C_{20}H_{28}NO_5$ (MH^+) 362.1967, found 362.1979. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.60; H, 7.39; N, 4.33.

Benzyl (*E*)-(5*S*)-6,6-dimethyl-5-[(*tert*-butyloxycarbonyl)amino]-4-oxo-2-heptenoate (3a): yellow oil; $[\alpha]^{22}_D$ = +50° (*c*, 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39−7.33 (m, 5 H), 7.22 (d, J = 16 Hz, 1 H), 6.79 (d, J = 16 Hz, 1 H), 5.27−5.21 (m, 2 H), 5.20 (d, J = 9 Hz, 1 H), 4.41 (d, J = 9 Hz, 1 H), 1.42 (s, 9 H), 0.97 (s, 9 H); HRMS m/z calcd for $C_{21}H_{30}NO_5$ (MH^+) 376.2124, found 376.2142. Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 66.82; H, 7.92; N, 3.61.

Benzyl (*E*)-(5*S*)-5-[(*tert*-butyloxycarbonyl)amino]-4-oxo-2-hexenoate (3e) (General Procedure for the Synthesis of 3c−e). To a solution of **2e** (3.40 mmol, 1.00 g) in dichloromethane (5 mL) were added a dichloromethane (4 mL) solution of benzyl glyoxylate (3.40 mmol, 560 mg) and 4 Å molecular sieves (1 g). The mixture was stirred at room temperature for 1 h, cooled to 0 °C, and *N*-methylmorpholine (3.40 mmol, 354 μL) was added. After 16 h of stirring at 0 °C, the reaction mixture was worked-up as above and purified by flash chromatography (hexane−EtOAc 5:1) to give **3e** (684 mg, 60%) as a light yellow oil: $[\alpha]^{22}_D$ = +6.0° (*c*, 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39−7.34 (m, 5 H), 7.24 (d, J = 16 Hz, 1 H), 6.86 (d, J = 16 Hz, 1 H), 5.28−5.22 (m, 2 H), 5.21 (d, J = 6 Hz, 1 H), 4.57−4.54 (m, 1 H), 1.43 (s, 9 H), 1.35 (d, J = 7.5 Hz, 3 H); HRMS m/z calcd for $C_{18}H_{24}NO_5$ (MH^+) 334.1654, found 334.1664. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.36; H, 7.01; N, 4.19.

Benzyl (*E*)-(5*S*)-7-methyl-5-[(*tert*-butyloxycarbonyl)amino]-4-oxo-2-octenoate (3c): yellow oil; $[\alpha]^{22}_D$ = −0.3° (c 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39−7.34 (m, 5 H), 7.24 (d, J = 16 Hz, 1 H), 6.85 (d, J = 16 Hz, 1 H), 5.28−5.21 (m, 2 H), 4.98 (d, J = 7.5 Hz, 1 H), 4.60−4.52 (m, 1 H), 1.78−1.68 (m, 1 H), 1.58−1.50 (m, 1 H), 1.43 (s, 9 H), 1.39−1.32 (m, 1 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H); HRMS m/z calcd for $C_{21}H_{30}NO_5$ (MH^+) 376.2124, found 376.2111. Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.29; H, 7.89; N, 3.73.

Benzyl (*E*)-(5*S*)-6-phenyl-5-[(*tert*-butyloxycarbonyl)amino]-4-oxo-2-hexenoate (3d): white solid, mp 113−114 °C; $[\alpha]^{22}_D$ = +12.6° (c 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39−7.09 (m, 10 H), 7.16 (d, J = 16 Hz, 1 H), 6.78 (d, J = 16 Hz, 1 H), 5.23 (s, 2 H), 5.10 (d, J = 7.5 Hz, 1 H), 4.79−4.75 (m, 1 H), 3.13 (dd, J = 14 Hz, 6.5 Hz, 1 H), 3.00 (dd, J = 14 Hz, 6.5 Hz, 1 H), 1.40 (s, 9 H); HRMS m/z calcd for $C_{24}H_{28}NO_5$ (MH^+) 410.1967, found 410.1975. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.38; H, 6.67; N, 3.37.

***tert*-Butyl (3*S*/*R*,6*S*)-7-Methyl-6-[(*tert*-butyloxycarbonyl)amino]-5-oxo-3-(benzyloxycarbonyl)octanoate (5b) (General Procedure for the Synthesis of 5 from 3). (a)** To a solution of allyl *tert*-butylmalonate (1.00 mmol, 200 mg) in THF (10 mL) was added sodium hydride (60% in mineral oil, 0.25 mmol, 10 mg). After gas evolution ceased, the mixture was cooled to −78 °C and a THF solution (3 mL) of **3b** (1.00 mmol, 361 mg) was added over a period of 5 min. The mixture was stirred at −78 °C for 2 h and quenched with 0.1 M HCl (4 mL). The resulting solution was extracted with a 2:1 mixture hexane−EtOAc (75 mL), and the organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated to give **4b** (512 mg, 91%) as a colorless oil.

(b) To a solution of $Pd(PPh_3)_4$ (11 mg, 0.01 eq) and pyrrolidine (1.10 mmol, 92 μL) in toluene (6 mL) was added a toluene solution (6 mL) of crude **4b** (0.90 mmol, 505 mg). The mixture was stirred at room temperature for 2 h, diluted with EtOAc, successively washed with 0.10 M HCl, water, and brine, dried over $MgSO_4$, and concentrated. The crude carboxylic acid derivative was heated in 10 mL of xylenes at 130 °C for 4 h. After concentration the residue was flash chromatographed (hexane−EtOAc, 4:1) to give **5b** and its 3*R* epimer (322 mg, 68% from **3b**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (m, 5 H), 5.11 (s, 2 H), 5.05 (d, J = 8 Hz, 1 H), 4.23 (dd, J = 8 Hz, 4 Hz, 1 H), 3.34−3.28 (m, 1 H), 3.12 (dd, J = 18.5 Hz, 7.5 Hz, 1 H × 10/11), 3.01 (dd, J = 18.5 Hz, 6.5 Hz, 1 H × 1/11), 2.81 (dd, J = 17.5 Hz, 5.5 Hz, 1 H × 1/11), 2.71 (dd, J = 18.5 Hz, 5.5 Hz, 1 H × 10/11), 2.63−2.50 (m, 2 H), 2.21−2.18 (m, 1 H), 1.43 (s, 9 H), 1.40 (s, 9 H), 0.99 (d, J = 7 Hz, 3 H), 0.77 (d, J = 7 Hz, 3 H); HRMS m/z calcd for $C_{26}H_{40}NO_7$ (MH^+) 478.2805, found 478.2819. Anal. Calcd for $C_{26}H_{39}NO_7$: C, 65.39; H, 8.23; N, 2.93. Found: C, 65.45; H, 8.11; N, 3.38.

***tert*-Butyl (3*S*,6*S*)-7,7-dimethyl-6-[(*tert*-butyloxycarbonyl)amino]-5-oxo-3-(benzyloxycarbonyl)octanoate (5a):** white solid, mp 59−61 °C; ^{1}H NMR ($CDCl_3$) δ 7.30−7.35 (m, 5 H), 5.12 (s, 2 H), 5.06 (d, J = 9 Hz, 1 H), 4.10 (d, J = 9 Hz, 1 H), 3.25−3.31 (m, 1 H), 3.15 (dd, J = 19 Hz, J = 7.5 Hz, 1 H), 2.82 (dd, J = 19 Hz, 5 Hz, 1 H), 2.49−2.63 (m, 1 H), 1.42 (s, 9 H), 1.40 (s, 9 H), 0.96 (s, 9 H); HRMS m/z calcd for $C_{27}H_{42}NO_7$ (MH^+) 492.2961, found 492.2975. Anal. Calcd for $C_{27}H_{41}NO_7$: C, 65.96; H, 8.41; N, 2.85. Found: C, 65.75; H, 8.49; N, 2.81.

***tert*-Butyl (3*S*,6*S*)-8-methyl-6-[(*tert*-butyloxycarbonyl)amino]-5-oxo-3-(benzyloxycarbonyl)nonanoate (5c) and (3*R*) epimer:** colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 5 H), 5.13 (d, J = 12.5 Hz, 1 H), 5.09 (d, J = 12.5 Hz, 1 H), 4.89 (d, J = 8 Hz, 1 H), 4.30−4.22 (m, 1 H), 3.34−3.30 (m, 1 H), 3.10 (dd, J = 18 Hz, 7.5 Hz, 1 H × 11/12), 3.03 (dd, J = 18.5 Hz, 7 Hz, 1 H × 1/12), 2.72 (dd, J = 18.5 Hz, 5.5 Hz, 1 H), 2.64−2.52 (m, 2 H), 1.73−1.63 (m, 1 H), 1.57−1.48 (m, 1 H), 1.42 (s, 9 H), 1.40 (s, 9 H), 1.31−1.24 (m, 1 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); HRMS m/z calcd for $C_{27}H_{42}NO_7$ (MH^+) 492.2961, found 492.2940. Anal. Calcd for $C_{27}H_{41}NO_7$: C, 65.96; H, 8.41; N, 2.85. Found: C, 65.95; H, 8.47; N, 2.84.

***tert*-Butyl (3*S*,6*S*)-7-phenyl-6-[(*tert*-butyloxycarbonyl)amino]-5-oxo-3-(benzyloxycarbonyl)heptanoate (5d) and (3*R*) epimer:** colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.37−7.12 (m, 10 H), 5.14 (s, 2 H), 4.97 (d, J = 7.5 Hz, 1 H), 4.49−4.43 (m, 1 H), 3.33−3.27 (m, 1 H), 3.10 (dd, J = 14.5 Hz, 5.5 Hz, 1 H), 3.01 (dd, J = 18 Hz, 7 Hz, 1 H), 2.84 (dd, J = 14 Hz, 7.5 Hz, 1 H), 2.71 (dd, J = 18.5 Hz, 6 Hz, 1 H), 2.62−2.48 (m, 2 H), 1.40 (s, 9 H), 1.39 (s, 9 H × 1/6), 1.38 (s, 9 H × 5/6); HRMS m/z calcd for $C_{30}H_{40}NO_7$ (MH^+) 526.2805, found 526.2791. Anal. Calcd for $C_{30}H_{39}NO_7$: C, 68.55; H, 7.48; N, 2.66. Found: C, 68.51; H, 7.58; N, 2.66.

***tert*-Butyl (3*S*,6*S*)-6-[(*tert*-butyloxycarbonyl)amino]-5-oxo-3-(benzyloxycarbonyl)heptanoate (5e) and (3*R*) epimer:** colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (m, 5 H), 5.13−5.10 (m, 3 H), 4.32−4.25 (m, 1 H), 3.37−3.30 (m, 1 H), 3.11 (dd, J = 18 Hz, 7.5 Hz, 1 H × 5/6), 3.01 (dd, J = 18 Hz, 7 Hz, 1 H × 1/6), 2.78−2.52 (m, 3 H), 1.44 (s, 9 H × 1/6), 1.43 (s, 9 H × 5/6), 1.40 (s, 9 H), 1.29 (d, J = 7 Hz, 3 H × 5/6), 1.28 (d, J = 7 Hz, 3 H × 1/6); HRMS m/z calcd for $C_{24}H_{36}NO_7$ (MH^+) 450.2492, found 450.2484. Anal. Calcd for $C_{24}H_{35}NO_7$: C, 64.12; H, 7.85; N, 3.12. Found: C, 64.20; H, 8.04; N, 3.09.

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Supporting Information Available: ^{1}H NMR of **2b**, **2c**, and **3e** (3 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.

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