mmol) was added with rapid stirring a nitrogen-purged solution of rhodium octanoate dimer (20 mg), triethylamine (40 μL), and ethanol (2.5 mL, 0.0428 mol) in ethyl acetate (10 mL). The mixture was stirred for 20 min and consecutively washed with 1% aqueous H_3PO_4 (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to afford a viscous oil, which was chromatographed on silica gel with hexanes/ethyl acetate (3/1) as the eluent. The first component isolated contained to 880 mg (86%) of a crystalline solid, mp 85.0 °C (EtOAc/hexanes), whose structure was assigned as *tert*-butyl 1,1-dioxo-*trans*-7-ethoxycephalosporanate on the basis of its spectral properties. ^1H NMR ($CDCl_3$): δ 5.21 (d, 1 H, J = 1.7), 5.01 (d, 1 H, J = 13.6), 4.70 (dd, 1 H, J = 1.7, J = 1.0), 4.67 (d, 1 H, J = 13.6), 3.99 (dd, 1 H, J = 18.0, J = 1.0), 3.67–3.87 (m, 2 H, CH_2), 3.69 (d, 1 H, J = 18.0), 2.10 (s, 3 H), 1.56 (s, 9 H), 1.3 (t, 3 H). Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 49.35; H, 5.95; N, 3.60; S, 8.23. Found: C, 49.28; H, 5.97; N, 3.55; S, 8.09.

The second component isolated contained 110 mg (11%) of a crystalline solid, mp 155.5–156.0 °C (EtOAc/hexanes), identified as *tert*-butyl 1,1-dioxo-*cis*-7-ethoxycephalosporanate. ^1H NMR ($CDCl_3$): δ 5.16 (d, 1 H, J = 4.4), 5.15 (d, 1 H, J = 13.9), 4.77 (d, 1 H, J = 4.4), 4.74 (d, 1 H, J = 13.9), 3.92 (d, 1 H, J = 18.5), 3.76–3.94 (m, 2 H, CH_2), 3.66 (d, 1 H, J = 18.5), 2.1 (s, 3 H), 1.54 (s, 9 H), 1.33 (t, 3 H, J = 7.0). Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 49.35; H, 5.95; N, 3.60; S, 8.23. Found: C, 49.44; H, 6.00; N, 3.56; S, 8.20.

Reaction of 7 with 2-Propanol. To a cooled (−5 °C) solution of the diazo compound 7 in ethyl acetate (13.2 mL containing 2.75 mmol) was added with rapid stirring a nitrogen-purged solution of rhodium octanoate dimer (20 mg), triethylamine (40 μL) and 2-propanol (3.3 mL, 42.8 mmol) in ethyl acetate (10 mL). The mixture was stirred for 20 min and washed consecutively with 1% aqueous H_3PO_4 (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo to afford a viscous oil, which was was chromatographed on silica gel with hexanes/ethyl acetate (3/1) as the eluant. The first component isolated contained 571 mg (54%) of a crystalline solid, mp 118.5–119.0 °C (EtOAc/hexanes), whose structure was assigned as *tert*-butyl 1,1-dioxo-*trans*-7-(isopropyloxy)cephalosporanate on the basis of its spectral characteristics. ^1H NMR ($CDCl_3$): δ 5.22 (d, 1 H, J = 1.4), 5.00 (d, 1 H, J = 13.5), 4.67 (d, 1 H, J = 13.5), 4.65 (br d, 1 H, J = 1.4), 3.99 (br d, 1 H, J = 18.2), 3.90 (septet, 1 H, J = 6.0), 3.67 (d, 1 H, J = 18.2), 2.10 (s, 3 H), 1.56 (s, 9 H), 1.29 (d, 3 H, J = 6.0), 1.26 (d, 3 H, J = 6.0). Anal. Calcd for $C_{17}H_{25}NO_8S$: C, 50.61; H, 6.25; N, 3.47; S, 7.95. Found: C, 50.51; H, 6.30; N, 3.42; S, 7.88.

The second component isolated contained 53 mg (5%) of a crystalline solid, mp 149–150 °C (EtOAc/hexanes), identified as *tert*-butyl 1,1-dioxo-*cis*-7-(isopropyloxy)cephalosporanate. ^1H NMR ($CDCl_3$): δ 5.20 (d, 1 H, J = 4.7), 5.11 (d, 1 H, J = 14.0), 4.76 (dd, 1 H, J = 4.7, J = 1.1), 4.73 (d, 1 H, J = 14.0), 3.93 (septet, 1 H, J = 6.1), 3.90 (dd, 1 H, J = 18.5, J = 1.1), 3.64 (d, 1 H, J = 18.5), 2.09 (s, 3 H), 1.54 (s, 9 H), 1.30 (d, 6 H, J = 6.1). Anal. Calcd for $C_{17}H_{25}NO_8S$: C, 50.61; H, 6.25; N, 3.47; S, 7.95. Found: C, 50.78; H, 6.26; N, 3.41; S, 7.89.

Reaction of 7 with Triethylborane. The following reaction was patterned after the procedure of Weiring and Wynberg.[16] To a cooled (−78 °C) solution of the diazo compound 7 in ethyl acetate (13.2 mL containing 2.75 mmol) was added with rapid stirring a triethylborane/tetrahydrofuran solution (5.5 mL, 1.0 M, 5.5 mmol). The reaction mixture was allowed to warm to 0 °C, and the reaction was quenched with the addition of 30% H_2O_2 (0.5 mL). The mixture was washed with brine (20 mL) and dried over Na_2SO_4, and the solvent was removed in vacuo to afford a viscous oil, which was chromatographed on silica gel with hexanes/ethyl acetate (6/1) as the eluant. The first eluted component contained 456 mg (46%) of a crystalline solid, mp 109–110 °C (EtOAc/hexanes), whose structure was assigned as *tert*-butyl 1,1-dioxo-*trans*-7-ethylcephalosporanate on the basis of its spectral characteristics. ^1H NMR ($CDCl_3$): δ 5.05 (d, 1 H, J = 13.5), 4.66 (d, 1 H, J = 13.5), 4.51 (br d, 1 H, J = 1.4), 3.95 (d, 1 H, J = 18.6), 3.85 (dt, 1 H, J = 1.4, J = 7.4), 3.70 (d, 1 H, J = 18.6), 2.08 (s, 3 H), 1.92 (p, 2 H, J = 7.4), 1.54 (s, 9 H), 1.09 (t, 3 H, J = 7.4). Anal. Calcd for $C_{16}H_{23}NO_7S$: C, 51.46; H, 6.21; N, 3.75; S, 8.59. Found: C, 51.29; H, 6.25; N, 3.73; S, 8.56.

The second eluted component contained 454 mg (45%) of a crystalline solid, mp 117.5–118.0 °C (EtOAc/hexanes), identified as *tert*-butyl 1,1-dioxo-*cis*-7-ethylcephalosporanate on the basis of its spectral properties. ^1H NMR ($CDCl_3$): δ 5.05 (d, 1 H, J = 13.5), 4.73 (dd, 1 H, J = 5.3, J = 1.0), 4.66 (d, 1 H, J = 13.50), 3.93 (dd, 1 H, J = 18.3, J = 1.0), 3.78 (dt, 1 H, J = 5.3, J = 7.9), 3.61 (d, 1 H, J = 18.3), 2.16 (p, 2 H, J = 7.9), 2.09 (s, 3 H), 1.54 (s, 9 H), 1.14 (t, 3 H, J = 7.4). Anal. Calcd for $C_{16}H_{23}NO_7S$: C, 51.46; H, 6.21; N, 3.75; S, 8.59. Found: C, 51.37; H, 6.26; N, 3.70; S, 8.70.

Acknowledgment is made to Drs. James B. Doherty, Paul E. Finke, and Shrenik K. Shah for many helpful discussions regarding their initial synthesis of *trans*- and *cis*-cephems 8 and 9.

An Efficient Synthesis of Novel α-Diketone and α-Keto Ester Derivatives of N-Protected Amino Acids and Peptides

Michael R. Angelastro,* Norton P. Peet, and Philippe Bey

Merrell Dow Research Institute, 2110 E. Galbraith Road, Cincinnati, Ohio 45215

Received March 31, 1989

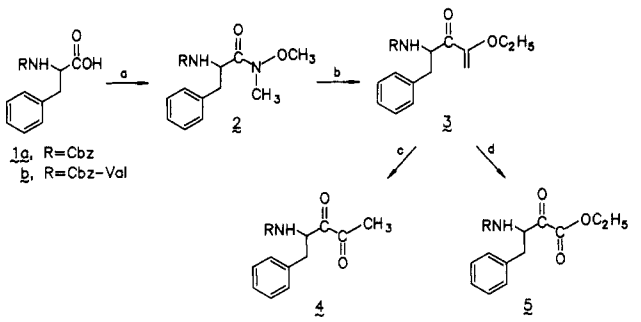
A novel synthetic approach to α-diketone and α-keto ester derivatives of N-protected amino acids and peptides via a common intermediate is described. Conversion of the carboxyl group of N-protected amino acids and peptides into an α-keto vinyl ether functionality and subsequent hydrolysis or ozonolysis produces α-diketone or α-keto ester functionalities, respectively. Preparation of the α-keto vinyl ether intermediates was achieved by conversion of the protected amino acids and peptides to the corresponding *N*-methoxy-*N*-methylamides and alkylation with (α-ethoxyvinyl)magnesium bromide.

Peptidyl α-keto esters are receiving considerable attention due to their potent inhibition of various proteolytic enzymes.[1-6] Recently, we found that peptidyl α-diketones are also potent inhibitors of cysteine and serine proteinases.[6] By analogy to the mechanism established for the inhibition of serine-dependent proteases by peptidyl tri-

(1) Berndt, M. C.; de Jersey, J.; Zerner, B. *J. Am. Chem. Soc.* **1977**, *99*, 8334.
(2) Hori, H.; Yasutake, A.; Minematsu, Y.; Powers, J. C. In *Peptides, Structure and Function (Proceedings of the Ninth American Peptide Symposium)*; Deber, C. M., Hruby, V. J., Kopple, K. D., Eds.; Pierce Chemical Co.: Rockford, IL, 1985; p 819.
(3) Trainor, D. A. *TIPS* **1987**, *8*, 303.
(4) Burkhart, J. P.; Peet, N. P.; Bey, P. *Tetrahedron Lett.* **1988**, *29*, 3433 and references cited therein.
(5) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.*, in press.
(6) Angelastro, M. R.; Mehdi, S.; Burkhart, J. P.; Bey, P.; Peet, N. P., manuscript in preparation.

0022-3263/89/1954-3913$01.50/0

Scheme I[a]



[a] (a) *i*-BuOCOCl, *N*-methylmorpholine, *N,O*-dimethylhydroxylamine hydrochloride; (b) *t*-BuLi, ethyl vinyl ether, $MgBr_2$, THF; (c) HCl, dioxane/H_2O; (d) O_3, CH_2Cl_2/pyr.

fluoromethyl ketones,[5,7] these peptidyl substrate analogues are proposed to produce inhibition of proteases via the formation of a stable tetrahedral adduct between the electrophilic carbonyl of the inhibitor molecule and the catalytic hydroxyl or thiol group.[2,6] Inhibitor potency and specificity are achieved through the optimization of the binding interaction between the peptide recognition unit and the binding region of a target protease. No general synthesis of peptidyl α-diketones exists. In fact, prolylmethyl diketone[8] is the only reported example of an α-amino acid derivative where the carboxylic acid group is replaced by an α-methyl diketone functionality. Herein we report an efficient approach, from common intermediates to the synthesis of α-diketone and α-keto ester derivatives of N-protected amino acids and peptides that allows the convenient manipulation of the amino acid sequence of the peptide portion.

Results and Discussion

Our primary objective was to develop a synthetic method that would allow the transformation of the carboxyl group of an N-protected peptide or amino acid into α-keto ester and α-diketone functionalities. The previously reported preparations of 1,2-diones have entailed the selenium dioxide mediated oxidation of ketones,[9] the copper(II) acetate oxidation[10] of α-hydroxy ketones, the hydrolysis of α-methoxy vinyl ketones,[11] and the photooxygenation of α-enamino ketones.[8] Oxidation of α-hydroxy esters is the major route to the preparation of α-keto esters.[4] Several reagents are available for this oxidation,[4] including the Dess–Martin periodinane[4] and dimethyl sulfoxide and oxalyl chloride.[5] Alternatively, α-keto esters have been prepared via the hydrolysis of enol esters obtained from α-amino acids and ethyl oxalyl chloride via the Dakin–West reaction.[12] Of these methods, the formation of 1,2-diones via the hydrolysis of α-methoxy vinyl ketones was particularly attractive, for peptidyl α-alkoxy vinyl ketones could also serve as precursors to peptidyl α-keto esters via ozonolysis.

The α-ethoxy vinyl ketones **3** were conveniently prepared from the corresponding N-protected dipeptide or amino acids as depicted in Scheme I. The *N*-methoxy-*N*-methylamide group, introduced by Nahm and Weinreb,[13] was used to activate the carboxylic acid function. Thus, *N*-methoxy-*N*-methylamides **2**, obtained by mixed anhydride coupling (isobutyl chloroformate) of commercially available *N*-[(phenylmethoxy)carbonyl]-L-phenylalanine (**1a**) and *N*-[(phenylmethoxy)carbonyl]-L-valyl-L-phenylalanine (**1b**) to *N,O*-dimethylhydroxylamine hydrochloride, were alkylated by excess (α-ethoxyvinyl)-magnesium bromide (EVMgBr), derived from the treatment of (α-ethoxyvinyl)lithium[10,14] with magnesium bromide etherate, to afford the desired peptidyl α-ethoxy vinyl ketones **3** in good yield. The stability of the Val-Phe amide bond to excess EVMgBr is noteworthy. We propose that protection occurs via salt formation with excess reagent as suggested by our inability to obtain intact peptidyl α-ethoxy vinyl ketones from peptidyl-*N*-methoxy-*N*-methylamides containing proline. Finally, the hydrolysis of **3** with hydrochloric acid in dioxane/water proceeded smoothly to give α-diketones **4**, whereas the ozonolysis of **3** afforded the α-keto esters **5**.

In summary, this approach provides a new, relatively simple, and versatile access to α-diketone and α-keto ester derivatives of N-protected amino acids and peptides.

Experimental Section

General Methods. TLC analyses were performed with Merck-DC-F_{254} plates, with visualization by alkaline permanganate and UV irradiation with a Mineralight UVS 11; flash chromatography was performed with Merck silica gel 60 (0.040–0.063 mm). IR spectra were recorded with a Perkin-Elmer Model 1800 spectrophotometer; ^1H and ^{13}C NMR spectra with a Varian VXR-300 (^{13}C = 75.4 MHz) or a Varian EM-390; MS at 70 eV with a Finnigan MAT 4600 and HRMS at 70 eV with a VG ZABZ-SE spectrometer, using computerized peak matching with perfluorokerosene as the reference.

Solvents and reagents were dried prior to use, and all reactions were run under inert atmosphere.

L-*N*-[(Phenylmethoxy)carbonyl]-*N'*-methoxy-*N'*-methylphenylalaninamide (2a). To a solution of *N*-Cbz-L-phenylalanine (25.0 g, 0.084 mol) in methylene chloride (300 mL) was added *N*-methylmorpholine (18.4 mL, 0.167 mol). The mixture was cooled to −15 °C, and isobutylchloroformate (10.8 mL, 83.6 mmol) was added. The mixture was stirred at −15 °C for 15 min followed by the addition of *N,O*-dimethylhydroxylamine hydrochloride (8.5 g, 0.087 mol). The mixture was stirred at −15 °C for 1 h, allowed to warm to room temperature, and stirred for 3 h. The reaction mixture was poured into H_2O (300 mL), and the aqueous phase was extracted with methylene chloride (2 × 150 mL). The combined organic extracts were dried over Na_2SO_4, reduced in volume to 100 mL, and filtered through silica gel (2 in.). The solvent was removed in vacuo to give 26.1 g (91%) of **2a** as a clear oil: ^1H NMR ($CDCl_3$) δ 7.35–7.12 (m, 10 H, aromatic), 5.42 (d, 2 H, *J* = 8.8 Hz, NH), 5.07 (s, 2 H, CH_2 benzyl), 5.04 (s, 2 H, CH_2 benzyl), 5.04 (m, 2 H, CH phenylalanine), 3.67 (s, 6 H, OCH_3), 3.17 (s, 6 H, NCH_3), 3.08 (dd, 2 H, *J* = 13.4 Hz, *J* = 6.0 Hz, CH phenylalanine), 2.90 (dd, 2 H, *J* = 13.4 Hz, *J* = 7.0 Hz, CH phenylalanine); ^{13}C NMR ($CDCl_3$) δ 155.75, 136.33, 136.24, 129.40, 128.46, 128.40, 128.05, 127.95, 126.88, 66.77, 61.54, 52.09, 38.68, 32.07; MS (DCI/CH_4) *m/z* (rel intensity) 343 (MH^+, 49), 299 (20), 282 (33), 235 (15), 91 (100); MS *m/z* (MH^+) calcd 343.1658, obsd 343.1656.

Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.58; H, 6.46; N, 8.06.

***N*-[(Phenylmethoxy)carbonyl]-L-valyl-*N'*-methoxy-*N'*-methyl-L-phenylalaninamide (2b).** To a suspension of *N*-Cbz-L-valyl-L-phenylalanine (2.5 g, 6.25 mmol) in methylene chloride (25 mL) was added *N*-methylmorpholine (1.5 mL, 13.7 mmol). The solution was cooled to −15 °C, followed by the

(7) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813.
(8) Conrow, P.; Portoghese, P. S. *J. Org. Chem.* **1986**, *51*, 938.
(9) (a) Rabjohn, N. *Org. React.* **1959**, *5*, 331. (b) Corey, E. J.; Schaefer, J. P. *J. Am. Chem. Soc.* **1960**, *82*, 918.
(10) (a) Blomquist, A. T.; Goldstein, A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 1963. (b) Wiberg, K. B.; Nigh, W. G. *J. Am. Chem. Soc.* **1965**, *87*, 3849.
(11) Baldwin, J. E.; Höfle, G. A.; Lever, W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.
(12) Charles, I.; Latham, D. W. S.; Hartley, D.; Oxford, A. W.; Scopes, D. I. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1139.
(13) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Davies, D. T.; O'Hanlon, P. J. *Syn. Commun.* **1988**, *18*, 2273.
(14) Chavdarian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822.

addition of isobutylchloroformate (0.8 mL, 6.17 mmol). The mixture was stirred at −15 °C for 15 min followed by the addition of *N,O*-dimethylhydroxylamine hydrochloride (1.0 g, 10.2 mmol). The solution was stirred at −15 °C for 1 h, allowed to warm to room temperature, and stirred for an additional 3 h. The reaction mixture was poured into dilute $NaHCO_3$ and extracted with ethyl acetate (3 × 75 mL). The combined extracts were dried over Na_2SO_4, the solvent was removed in vacuo, and the crude product was purified by chromatography on silica gel. The product was eluted with 75% EtOAc/hexane to give 1.8 g (65%) of **2b** as a white solid: mp 115–116 °C; ^1H NMR ($CDCl_3$) δ 7.36–7.10 (m, 10 H, aromatic), 6.56 (d, 1 H, J = 8.0 Hz, NH), 5.28 (m, 2 H, CH phenylalanine + NH), 5.08 (s, 2 H, CH_2 benzyl), 4.08 (m, 1 H, $CH(CH_3)_2$), 3.69 (s, 3 H, OCH_3), 3.17 (s, 3 H, NCH_3), 2.90 (dd, 1 H, J = 12.7 Hz, J = 7.7 Hz, CH_2 phenylalanine), 2.06 (m, 1 H, $CH(CH_3)_2$), 0.90 (d, 3 H, J = 6.7 Hz, CH_3 valine), 0.82 (d, 3 H, J = 6.7 Hz, CH_3 valine); IR (thin film) ν 3310, 29.65, 29.40, 2370, 2345, 1715, 1650; MS (DCI/CH_4) m/z (rel intensity) 442 (MH^+, 66), 409 (15), 381 (100), 334 (14), 234 (8), 91 (18); MS m/z (MH^+) calcd 442.2341, obsd 442.2381.

Anal. Calcd for $C_{24}H_{31}N_3O_5$: C, 65.29; H, 7.08; N, 9.51. Found: C, 65.75; H, 7.20; N, 9.39.

2-Ethoxy-5-phenyl-4-[[(phenylmethoxy)carbonyl]amino]-3-oxo-1-pentene (3a). A solution of ethyl vinyl ether (3.0 mL, 31.5 mmol) in tetrahydrofuran (40 mL) was cooled to −78 °C, and *tert*-butyllithium (18.0 mL, 30.6 mmol, 1.7 M in pentane) was added. The mixture was warmed to 0 °C over a 1-h period, stirred for 45 min, and cooled to −30 °C, and magnesium bromide etherate (7.5 g, 29.1 mmol) was added. The mixture was warmed to 0 °C over a 15-min period followed by the addition of **2a** (2.0 g, 5.8 mmol) dissolved in tetrahydrofuran (5 mL). The mixture was allowed to warm to room temperature and stirred for 2 h. The mixture was poured into dilute NH_4Cl and extracted with diethyl ether (3 × 100 mL). The combined extracts were dried over Na_2SO_4, and the removal of solvent yielded 1.85 g of crude product, which was purified by chromatography on silica gel. Elution with 25% EtOAc/hexane gave 1.5 g (73%) of **3a** as a white solid: mp 110–112 °C; ^1H NMR ($CDCl_3$) δ 7.36–7.02 (m, 10 H, aromatic), 5.44 (d, 1 H, J = 8.1 Hz, NH), 5.34 (m, 1 H, CH), 5.29 (d, 1 H, J = 2.6 Hz, vinyl), 5.12 (d, 1 H, J = 12.2 Hz, CH_2 benzyl), 5.04 (d, 1 H, J = 12.2 Hz, CH_2 benzyl), 4.50 (d, 2 H, J = 2.6 Hz, vinyl), 3.83 (m, 2 H, CH_2 ethyl), 3.21 (dd, 1 H, J = 14.0 Hz, J = 5.6 Hz, CH_2 phenylalanine), 2.92 (dd, 1 H, J = 14.0 Hz, J = 6.2 Hz, CH_2 phenylalanine), 1.40 (t, 3 H, J = 7.4 Hz, CH_3 ethyl); ^{13}C NMR ($CDCl_3$) δ 195.10, 156.05, 155.52, 136.42, 135.84, 129.62, 129.50, 128.44, 128.29, 128.04, 127.99, 126.84, 92.68, 66.72, 63.99, 56.63, 38.04, 14.29; IR (KBr) 3340, 1718, 1695, 1610, 1540, 1288, 1260, 1029 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 354 (MH^+, 93), 338 (14), 310 (100), 91 (30); MS m/z (MH^+) calcd 354.1705, obsd 354.1739.

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.28; N, 3.97. Found: C, 71.53; H, 6.64; N, 3.83.

[1-[[[3-Ethoxy-2-oxo-1-(phenylmethyl)-3-butenyl]amino]carbonyl]-2-methylpropyl]carbamic Acid Phenylmethyl Ester (3b). A solution of ethyl vinyl ether (3 mL) in tetrahydrofuran (20 mL) was cooled to −78 °C, and *tert*-butyllithium (10 mL, 17 mmol, 1.7 M in pentane) was added. The mixture was warmed to 0 °C and stirred for 0.75 h. Magnesium bromide etherate (4.38 g, 17 mmol) was added, and the mixture was stirred for 20 min before a solution of **2b** (1.75 g, 3.98 mol) dissolved in tetrahydrofuran (5 mL) was added. After being stirred for 1.5 h, the reaction mixture was poured into dilute NH_4Cl, and the aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were washed with dilute $NaHCO_3$. The removal of solvent in vacuo yielded 1.7 g of crude product. Purification by recrystallization from 40% EtOAc/hexane gave 1.1 g (61%) of **3b**: mp 120–122 °C; ^1H NMR ($CDCl_3$) δ 7.39–7.00 (m, 11 H, aromatic + NH), 6.35 (d, 1 H, J = 8.1 Hz, NH), 5.52 (m, 1 H, CH phenylalanine), 5.30 (d, 1 H, J = 3.4 Hz, vinyl) 5.13 (s, 2 H, CH_2), 4.52 (d, 1 H, J = 3.4 Hz, vinyl), 3.97 (m, 1 H, CH valine), 3.85 (m, 2 H, CH_2 ethyl), 3.22 (dd, 1 H, J = 13.9 Hz, J = 5.9 Hz, CH_2 phenylalanine), 2.96 (dd, 1 H, J = 13.9 Hz, J = 5.9 Hz, CH_2 phenylalanine), 2.05 (m, 1 H, $CH(CH_3)_2$), 1.42 (t, 3 H, J = 6.8 Hz, ethyl), 0.90 (d, 3 H, J = 6.7 Hz, CH_3 valine), 0.85 (d, 3 H, J = 6.7 Hz, CH_3 valine); ^{13}C NMR ($CDCl_3$) δ 194.79, 170.45, 156.00, 135.61, 129.50, 128.55, 128.38, 128.31, 128.18, 128.07, 126.98, 92.92, 67.02, 64.08, 60.33, 55.08, 37.78, 31.20, 19.10, 17.65, 14.32; IR (KBr) ν 3298, 1693, 1656, 1610, 1538, 1294, 1248 cm^{-1}; M/S (DCI/CH_4) m/z (rel intensity) 453 (MH^+, 100), 409 (13), 345 (918), 220 (20), 91 (60); MS m/z (MH^+) calcd 453.2389, obsd 453.2388.

Anal. Calcd for $C_{26}H_{32}N_2O_5$: C, 69.00; H, 7.13; N, 6.19. Found: C, 68.68; H, 7.08; N, 6.03.

[2,3-Dioxo-1-(phenylmethyl)butyl]carbamic Acid Phenylmethyl Ester (4a). To a solution of **3a** (100 mg, 0.28 mmol) in methanol (10 mL) was added concentrated HCl (0.1 mL). The mixture was stirred for 24 h and poured into H_2O, and $NaHCO_3$ was added. The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, and removal of solvent in vacuo gave 95 mg of crude product, which was purified by flash chromatography (30% EtOAc/hexane) to give 65 mg (71%) of **4a** as a yellow solid: mp 51–53 °C; ^1H NMR ($CDCl_3$) δ 7.36–7.01 (m, 10 H, aromatic), 5.20 (m, 2 H, CH + NH), 5.06 (s, 2 H, CH_2 benzyl), 3.18 (dd, 1 H, J = 14.1 Hz, J = 5.4 Hz, CH_2 phenylalanine), 2.99 (dd, 1 H, J = 14.1 Hz, J = 8.0 Hz, CH_2 phenylalanine), 2.30 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 196.56, 196.26, 155.74, 136.00, 135.45, 129.65, 129.58, 129.36, 129.22, 128.80, 128.71, 128.54, 128.46, 128.41, 128.28, 128.11, 127.35, 127.29, 67.20, 55.94, 37.41, 24.00; IR (KBr) ν 3406, 17.16, 1515, 1498, 1455, 751, 699 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 326 (MH^+, 23), 310 (8), 282 (85), 264 (13), 91 (100); MS m/z (MH^+) calcd 326.1392, obsd 326.1394.

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.09; H, 5.80; N, 4.33.

[1-[[[2,3-Dioxo-1-(phenylmethyl)butyl]amino]carbonyl]-2-methylpropyl]carbamic Acid Phenylmethyl Ester (4b). To a solution of **3b** (300 mg, 0.66 mmol) in 5:1 dioxane/H_2O (10 mL) was added concentrated HCl (0.1 mL). The mixture was stirred for 24 h at room temperature, poured into dilute $NaHCO_3$, and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over Na_2SO_4, and the removal of solvent in vacuo gave 330 mg of crude product, which was purified by flash chromatography (30% EtOAc/hexane) to give 210 mg (74%) of **4b** as a yellow solid: mp 135–139 °C; ^1H NMR (300 MHz) δ 7.36–7.06 (m, 10 H, aromatic), 6.47 (m, 1 H, NH), 5.26–5.10 (m, 2 H, CH phenylalanine + NH), 5.08 (s, 2 H, CH_2), 3.97 (m, 1 H, CHCO valine), 3.19 (dd, 1 H, J = 14.0 Hz, J = 5.7 Hz, CH_2 phenylalanine), 2.95 (dd, 1 H, J = 14 Hz, J = 9.2 Hz, CH_2 phenylalanine), 2.30 (s, 3 H, CH_3), 2.06 (m, 1 H, $CH(CH_3)_2$), 0.91 (d, 3 H, J = 6.5 Hz, CH_3 valine), 0.84 (d, 3 H, J = 6.5 Hz, CH_3 valine); ^{13}C NMR ($CDCl_3$) δ 196.47, 195.42, 171.29, 156.29, 136.05, 135.61, 129.16, 128.84, 128.56, 128.26, 128.06, 127.30, 67.19, 59.90, 54.63, 36.90, 36.82, 30.72, 23.84, 23.76; IR (KBr) ν 3311, 1713, 16.91, 1642, 1536, 1293, 1243 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 425 (MH^+, 100), 381 (41), 234 (15), 91 (43); MS m/z (MH^+) calcd 425.2076, obsd 425.2073.

Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.96; H, 6.59; N, 6.62.

β-[[(Phenylmethoxy)carbonyl]amino]-α-oxobenzenebutanoic Acid Ethyl Ester (5a). A solution of **3a** (180 mg, 0.51 mmol) in a mixture of CH_2Cl_2 (50 mL) and pyridine (0.5 mL) was cooled to −78 °C and treated with ozone until the appearance of a blue color. Oxygen was bubbled through the reaction mixture to remove excess ozone followed by the addition of dimethyl sulfide (0.5 mL). The mixture was stirred for 3 min, poured into H_2O, and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with 30% ethyl acetate/hexane gave 141 mg (78%) of **5a** as a pale yellow amorphous solid: ^1H NMR (90 MHz) ($CDCl_3$) δ 7.37–7.07 (m, 10 H, aromatic), 5.29 (m, 2 H, CH + NH), 4.96 (s, 2 H, CH_2 benzyl), 4.20 (q, 2 H, J = 7 Hz, CH_2CH_3), 3.10 (m, 2 H, CH_2 phenylalanine), 1.30 (t, 3 H, J = 7 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 192.18, 160.25, 155.52, 136.15, 136.02, 134.84; IR (thin film) ν 3352, 1728 (b), 1604, 1516, 1498, 1257, 1039 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 356 (MH^+, 61), 338 (12), 312 (100), 254 (15), 181 (17), 91 (100); MS m/z (MH^+) calcd 356.1497, obsd 356.1487.

β-[[3-Methyl-1-oxo-2-[[(phenylmethoxy)carbonyl]amino]butyl]amino]-α-oxobenzenebutanoic Acid Ethyl Ester (5b). A solution of **3b** (300 mg, 0.66 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C and treated with ozone until the appearance

of a blue color. Oxygen was bubbled through the reaction mixture to remove excess ozone, followed by the addition of dimethyl sulfide (0.5 mL) and pyridine (0.5 mL). The mixture was stirred for 5 min, poured into H_2O, and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with 55% ethyl acetate/hexane gave 160 mg (53%) of **5b** as an amorphous solid: ^{1}H NMR ($CDCl_3$) δ 7.37-7.07 (m, 10 H, aromatic), 6.42 (dd, 1 H, J = 24.0 Hz, J = 6.5 Hz, NH), 5.42 (m, 1 H, CH phenylalanine), 5.23 (m, 1 H, NH), 5.09 and 5.08 (2 s, 2 H, CH_2 benzyl), 4.30 and 4.29 (2 q, 2 H, J = 7.1 Hz, CH_2CH_3), 3.97 (m, 1 H, CH valine), 3.23 (dd, 1 H, J = 13.9 Hz, J = 6.4 Hz, CH_2 phenylalanine), 3.02 (m, 1 H, CH_2 phenylalanine), 2.06 (m, 1 H, $CH(CH_3)_2$), 1.35 (t, 3 H, J = 7.3 Hz, CH_2CH_3), 0.91 (d, 3 H, J = 7.2 Hz, CH_3 valine), 0.85 (d, 6 H, J = 7.2 Hz, CH_3 valine), 0.79 (d, 3 H, J = 7.2 Hz, CH_3 valine); ^{13}C NMR ($CDCl_3$) δ 191.66, 191.54, 171.04, 171.00, 160.12, 156.26, 136.06, 134.95, 134.84, 129.27, 129.22, 128.78, 128.54, 128.22, 128.05, 127.36, 67.16, 67.13, 62.89, 60.06, 65.44, 36.90, 30.85, 30.66, 19.13, 19.08, 17.59, 17.28, 13.91; IR (KBr) ν 3294, 2960, 1724, 1692, 1654, 1538, 1296, 1246 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 455 (MH^+, 100), 411 (10), 91 (10); MS m/z (MH^+) calcd 455.2182, obsd 455.2162.

Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 65.90; H, 6.74; N, 6.03.

Registry No. **1a**, 1161-13-3; **1b**, 19542-51-9; **2a**, 114744-85-3; **2b**, 121253-52-9; **3a**, 121253-53-0; **3b**, 121253-54-1; **4a**, 121253-55-2; **4b**, 121253-56-3; **5a**, 121253-57-4; **5b**, 121253-58-5; EtOCH=CH_2, 109-92-2.

Enantioselective Synthesis of α-Amino Acid Derivatives via the Stereoselective Alkylation of a Homochiral Glycine Enolate Synthon[1]

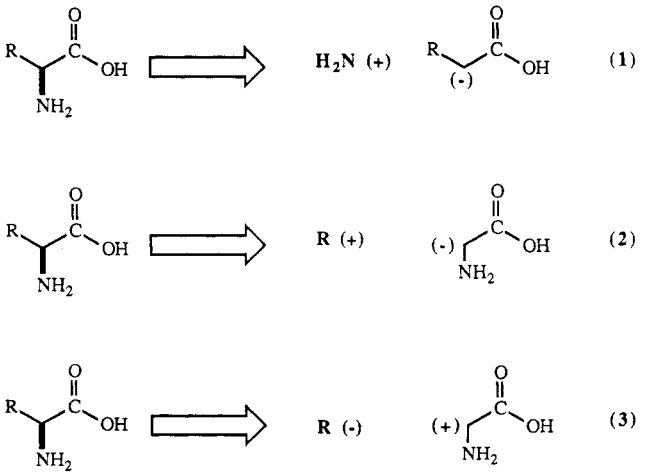
Joseph F. Dellaria, Jr.,*[,2] and Bernard D. Santarsiero[†]

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Received December 8, 1988

A new synthetic method for the enantioselective preparation of α-amino acid derivatives is presented. The key step involves the diastereoselective alkylation of the new chiral glycine enolate synthons **7** and **8** providing alkylation adducts with de of ≥97.6% in good yields (73-90%). The reactivities of the enolates of **7** and **8** were extraordinarily sensitive to the metal counterion and solvent. Experimental conditions are described to maintain high diastereoselectivities in the alkylation step for electrophiles varying from highly reactive (α-haloacetate esters) to less reactive (*n*-butyl iodide). The alkylation diastereoselectivities were established to be under kinetic control by equilibration experiments on selected alkylation products. A model is presented which hinges on an A(1,3) interaction between the termini of the N_4-acyl protecting group and the C_5-phenyl group of **7** and **8** which in turn dictates the π-facial selectivity of the enolate. The model successfully accounts for the observed results and is corroborated by the conformation of an alkylation adduct as revealed by a single-crystal X-ray determination. A simple one-pot, three-step deprotection procedure provides the desired α-amino acid as the ethyl ester hydrochloride salts (60-80% overall yield) with no attending racemization as determined by conversion of the amino acid esters to the corresponding (+)- or (-)-Mosher amides.

Current interest in developing peptide-derived chemotherapeutics has heightened the importance of rare and nonproteinogenic enantiomerically pure amino acids.[3] Consequently it has become desirabe to develop new and general synthetic methodology for the expeditious preparation of compounds in this genre. Recent advances in this endeavor have been made in the asymmetric electrophilic amination of chiral enolates (eq 1),[4] diastereoselective alkylation of chiral glycine enolate synthons (eq 2),[5] and diastereoselective nucleophilic additions to a chiral electrophilic glycinate synthon (eq 3).[6] Recently, the stereoselective alkylation of homochiral glycine enolates derived from *N*-acyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-ones (henceforth referred to as oxazinones) bearing either 5-phenyl or 5,6-diphenyl substituents were reported by us[7a] and Williams[7b] and co-workers, respectively. We now provide a full account of our studies on the alkylation of homochiral *N*-acyl oxazinones and the conversion of the resulting alkylation adducts to homochiral α-amino acid derivatives.



Design and Synthesis of the Chiral Enolate Synthon. At the outset of this investigation, it was clear that

[†] Author to whom correspondence concerning the X-ray crystal structure determination should be addressed: Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2H7.

(1) Presented in part at the International Symposium on the Chemistry of Natural Products, June 23-26, 1985, Edmonton, Alberta, Canada.

(2) (a) NIH Postdoctoral Fellow, 1982-1984, Grant GM 08803. (b) Present address: Abbott Laboratories, Department 47K, Abbott Park, IL 60064.

0022-3263/89/1954-3916$01.50/0