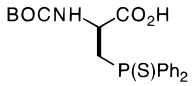
New and Efficient Synthesis of an Amino Acid for Preparing Phosphine-Functionalized Peptidomimetics

Alexander M. Porte, Wilfred A. van der Donk,† and Kevin Burgess*

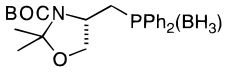
Department of Chemistry, Texas A & M University, College Station, Texas 77843

Received February 18, 1998

Gilbertson and co-workers have used the *N*-protected amino acid **1** as the key building block in syntheses of peptidomimetics having one or more phosphine-containing side chains.[1,2] These products have conformational properties that may be conveniently modulated by adding metals to coordinate with the phosphine moieties. Moreover, libraries of peptidomimetics derived from **1** can be produced via combinatorial methods;[3,4] hence, they are obvious targets for high-throughput catalyst screening, an interest shared by our group[5−7] and by Gilbertson et al.[8,9]



1

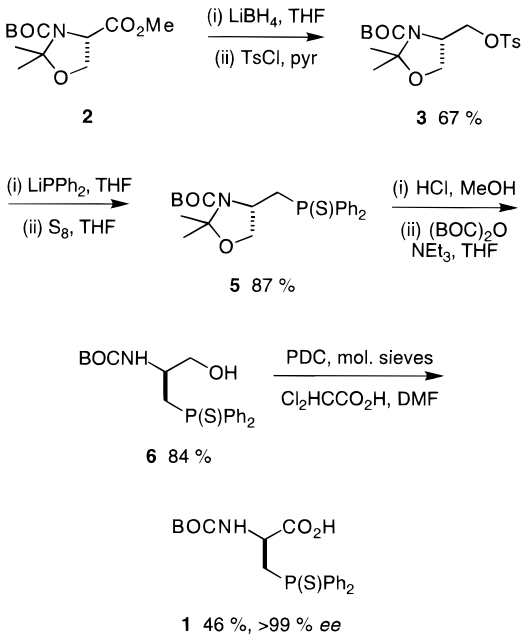


4

The published route to the phosphine sulfide **1** involves diastereoselective transfer of an azido group[10] to an oxazolidinone enolate.[1] This paper describes an alternative procedure that does not involve expensive chiral auxiliaries, or diastereoselective reactions which are critically dependent upon reaction conditions and workup procedures. It does, however, give optically pure product via a protocol amenable to scale-up.

Serine was converted into the BOC-protected ester **2** (Scheme 1) via a practical improvement[11] of earlier procedures.[12,13] Reduction of the ester and tosylation gave the intermediate **3**, which was conveniently purified via recrystallization. A phosphine functionality was then introduced via a nucleophilic displacement using phosphide. The resulting phosphine needed to be protected immediately to shelter it from oxidation in the subsequent steps in this synthesis and in solid-phase syntheses of peptidomimetics. Phosphine boranes have been used extensively to protect phosphorus(III) centers,[14−16] but in our studies the derivative **4** was insufficiently robust to tolerate the unavoidable oxidation steps that follow later in the synthesis. Consequently, the intermediate phosphine was oxidized to the corresponding phosphine sulfide **5**. Treatment with aqueous acid had the desired effect of cleaving the oxazolidine ring, but removal of the *tert*-butyloxycarbonyl *N*-protection was an undesired consequence. The latter group was therefore reinstated to give the alcohol **6**, which was purified via flash chromatography.

Scheme 1. Synthesis of Chiron 1



Oxidation of alcohol **6** to the corresponding acid without racemization of the adjacent chiral center was a nontrivial challenge. The Moffatt oxidation[17,18] has been used in similar situations where stereochemical integrity is an issue;[19] this step, followed by further oxidation of the aldehyde produced using buffered permanganate,[20] gave the corresponding BOC-protected amino acid **1** in 94% ee. The best method identified for oxidation of the alcohol, however, was a pyridinium dichromate oxidation[21] in the presence of molecular sieves, giving the product **1** in >99% ee as assessed via chiral-phase

† Present address: University of Illinois at Urbana−Champaign, Department of Chemistry, 600 South Mathews Ave., Urbana, IL 61801.

(1) Gilbertson, S. R.; Chen, G.; McLoughlin, M. *J. Am. Chem. Soc.* **1994**, *116*, 4481−2.
(2) Gilbertson, S. R.; Chen, G. H.; Kao, J.; Beatty, A.; Campana, C. F. *J. Org. Chem.* **1997**, *62*, 5557−5566.
(3) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−51.
(4) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385−401.
(5) Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220−2.
(6) Burgess, K.; Moye-Sherman, D.; Porte, A. M. In *Molecular Diversity and Combinatorial Chemistry*; Chaiken, I. M., Janda, K. D., Eds.; American Chemical Society: Washington, DC, 1996; pp 128−36.
(7) Burgess, K.; Porte, A. M. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2, pp 69−82.
(8) Gilbertson, S. R.; Wang, X. *Tetrahedron Lett.* **1996**, *36*, 6475−8.
(9) Gilbertson, S. R.; Chang, C.-W. T. *Chem. Commun.* **1997**, 975−6.
(10) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881−3.
(11) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31−3.
(12) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18−28.
(13) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−4.
(14) Pellon, P. *Tetrahedron Lett.* **1992**, *33*, 4451−2.
(15) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244.
(16) Corey, E. J.; Chen, Z.; Tanoury, G. J. *J. Am. Chem. Soc.* **1993**, *115*, 11000−1.
(17) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661−5669.
(18) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670−5678.
(19) Fearon, K.; Spaltenstein, A.; Hopkins, P. B.; Gelb, M. H. *J. Med. Chem.* **1987**, *30*, 1617−1622.
(20) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537−4540.
(21) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399−402.

S0022-3263(98)00307-7 CCC: $15.00 © 1998 American Chemical Society
Published on Web 06/25/1998

analytical HPLC of the corresponding methyl ester (formed via treatment of **1** with diazomethane).

Only one chromatographic separation was used in the synthesis of **1** from serine. The intermediate preceding this separation, i.e., compound **5**, could be prepared on a very large scale, and purification of **6** is the only major restriction on the amounts of **6** and **1** that can be produced. The synthesis begins with serine, which is fortunate because *both* enantiomers of this amino acid are relatively cheap. In this synthesis, L-serine was used as a starting material, giving the phosphine sulfide in the D-series. The overall yield of the product **1** from serine was 22%.

Chiron **1** can be used in the typical reactions involved in peptide syntheses, and the phosphine sulfide side chains can be reduced to the corresponding phosphines using Raney nickel[1] or via an alkylation of the sulfur and reaction with a phosphorus(III) compound.[22]

Experimental Section

General Procedures. Melting points were uncorrected. Proton NMR spectra were recorded at 200 or 300 MHz; ^{13}C spectra at 50 or 75.4 MHz; ^{31}P spectra were recorded at 121 MHz referenced to H_3PO_4 external standard. Where necessary, the carbon multiplicities were determined via APT experiments. Thin-layer chromatography was performed using silica gel 60 F_{254} plates. Flash chromatography was performed using silica gel (230−600 mesh). DMF was stored over 4 Å molecular sieves for 1 week before use; CH_2Cl_2, THF, and methanol were distilled from appropriate drying agents. 4-Methyl-(*S*)-*N*-(*tert*-butyloxycarbonyl)-2,2-dimethyl-4-oxazolidinecarboxylate **2** was synthesized via a literature procedure,[11] and it is also available from Aldrich Chemical Co. Other chemicals were purchased from commercial suppliers and used as received.

(*S*)-*N*-*tert*-Butoxycarbonyl-4-[[(4′-methylbenzenesulfonyl)oxy]methyl]-2,2-dimethyloxazolidine (3). A solution of **2** (2.59 g, 10.0 mmol) in 10 mL of THF was added dropwise to a stirred suspension of lithium borohydride (650 mg, 30 mmol) at 0 °C in 15 mL of THF. The reaction was allowed to warm to room temperature and stirred until all starting material was consumed as determined by TLC (ca. 4 h). The solution was diluted with 200 mL of ethyl acetate. Dropwise addition of 1 M HCl gave an emulsion. This dropwise addition was continued until the emulsion disappeared and layers separated. The aqueous layer was removed, and the organic layer was washed with brine, dried over Na_2SO_4, and filtered. Removal of solvent gave an oil that was used for the next step without further purification. Thus, this oil was dissolved in 20 mL of dry pyridine and cooled to 0 °C. 4-Methylbenzenesulfonyl chloride (2.09 g, 11 mmol) was added, and the resulting yellow solution was stored at 0 °C for 24 h. The solvent was then removed, and remaining material was redissolved in ethyl acetate (100 mL) and washed three times with 1 M HCl (20 mL), one time with brine (20 mL), dried over Na_2SO_4, and filtered. After removal of solvent, the remaining solid was recrystallized from ethyl acetate/hexanes to provide 2.58 g of colorless crystals (67%): mp 108−109 °C; R_f 0.2 (9:1 hexanes/ethyl acetate); ^{1}H NMR (200 MHz, C_6D_6, 60 °C) δ 7.74 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 2H), 4.22−4.27 (m, 1H), 3.88−4.08 (m, 2H), 3.73−3.78 (m, 1H), 3.52−3.59 (m, 1H), 1.91 (s, 3H), 1.52 (s, 3H), 1.37 (s, 12H); ^{13}C NMR (50 MHz, C_6D_6, 60 °C) δ 151.8, 144.6, 134.3, 130.0, 128.5, 128.0, 127.6, 94.3, 80.2, 68.3, 65.0, 56.2, 28.4, 27.1, 23.6, 21.2; IR 3021, 1692, 1389, 1377, 1366, 1175, 653 cm^{-1}; HRMS (FAB/acc. mass) *m*/*z* calcd 385.4790 for $C_{18}H_{27}NO_6S$, found 385.4773; $[\alpha]_D$ −79.2 (c = 2.01, $CHCl_3$, 25 °C).

(*S*)-*N*-(*tert*-Butoxycarbonyl)-4-[(methylenediphenylphosphino)sulfide]-2,2-dimethyloxazolidine (5). A flask was charged with diphenylphosphine (7.25 g, 20 mmol), and 150 mL of THF was added. The solution was cooled to −78 °C, and 2 mL of a 10 M solution of *n*-butyllithium in hexanes was added, providing a bright orange solution of the phosphine anion. After being stirred for 0.5 h, the solution was warmed to 0 °C and added via cannula dropwise to a solution of **3** (5.0 g, 13 mmol) in 150 mL of THF. The addition was continued until the orange color persisted and TLC showed complete consumption of the sulfonyl starting material. The reaction mixture was then treated with a stoichiometric amount of elemental sulfur (416 mg, 13 mmol) at 0 °C. The reaction was followed by TLC and stopped when the phosphine starting material had disappeared (approximately 1 h). The solvent was removed, giving a crude oil that was then recrystallized from ethyl acetate/hexanes, providing 3.42 g of colorless crystals. Recovery of material from the mother liquor and recrystallization of this gave 1.02 g slightly yellow crystals (pure enough for use in the next stage in this sequence). The combined yield of these materials was 4.44 g (87%): mp 133−134.5 °C; R_f 0.24 (9:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $C_6D_5CD_3$, 90 °C) δ 8.05−8.25 (b, 2H), 7.72−7.90 (m, 2H), 6.94−7.25 (m, 6H), 4.20−4.80 (b, 2H), 3.65−3.80 (b, 1H), 3.25−3.70 (b, 1H), 2.40−2.70 (b, 1H), 1.60 (s, 3H), 1.45 (s, 12H); ^{13}C NMR (75.4 MHz, $C_6D_5CD_3$, 90 °C) δ 152.1, 132.1−128.6, 80.1, 67.6, 54.8, 35.6 (d, J_{CP} = 51.6 Hz), 28.7, 27.8; ^{31}P NMR (121 MHz, $C_6D_5CD_3$, 90 °C) δ 37.4; IR 3054, 2975, 1688, 1396, 1166, 1099 cm^{-1}; HRMS (FAB/acc. mass) *m*/*z* calcd 454.1582 for $C_{23}H_{30}NO_3PS$ + Na, found 454.1605; $[\alpha]_D$ −13.2 (c = 1.12, $CHCl_3$, 25 °C).

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(diphenylphosphino)sulfide]propan-1-ol (6). The protected intermediate **5** (812 mg, 1.9 mmol) was placed in 10 mL of MeOH and cooled to 0 °C. Gaseous HCl was bubbled through the reaction for 5 min, whereupon the starting material was consumed (TLC). The solvent was then removed and the residue was redissolved in 10 mL of THF and cooled to 0 °C. Triethylamine (1.05 mL, 7.5 mmol) was added, followed by di-*tert*-butyl dicarbonate (615 mg, 2.8 mmol), and the solution was stirred for 2 h. The reaction was diluted with EtOAc (40 mL) and washed with 0.5 M HCl and brine. The organic layer was dried over Na_2SO_4, and filtered, and the solvent was removed. Purification was performed via flash chromatography on silica gel (3:2 hexanes/EtOAc), providing 621 mg (84%) of **6** as a white solid: mp 106−107.5 °C; R_f 0.21 (3:2 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−8.00 (m, 2H), 7.75−7.85 (m, 2H), 7.38−7.55 (m, 6H), 5.22 (d, J = 9.4 Hz, 1H), 3.92 (m, 2H), 3.62 (m, 1H), 3.45 (m, 1H), 3.15 (m, 1H), 2.70 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 133.8, 132.7, 131.7 (d, J_{CP} = 14.5 Hz), 131.6 (d, J_{CP} = 14.6 Hz), 131.3 (d, J_{CP} = 10.5 Hz), 130.7 (d, J_{CP} = 10.5 Hz), 128.8 (d, J_{CP}=9.1 Hz), 128.7 (d, J_{CP} = 9.0 Hz), 79.7, 64.3 (d, J_{CP} = 6.5 Hz), 49.4, 33.8 (d, J_{CP} = 54.6 Hz), 28.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ 38.3; IR 3392, 2968, 1685, 1509, 1165, 750 cm^{-1}; HRMS (FAB/acc. mass) *m*/*z* calcd 414.1269 for $C_{20}H_{26}NO_3PS$ + Na, found 414.1277; $[\alpha]_D$ 0.11 (c = 2.85, $CHCl_3$, 25 °C).

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(diphenylphosphino)sulfide]-1-propanoic Acid (1). Alcohol **6** (293 mg, 0.75 mmol) in 1.5 mL of DMF was added to a slurry of PDC (1.41 g, 3.75 mmol) and 3 Å powdered molecular sieves (1 g) in 2 mL of DMF. Dichloroacetic acid (30 μL, 0.37 mmol) was then added to the mixture. The solution was stirred for 12 h, after which time all the alcohol starting material was consumed but some intermediate aldehyde remained (TLC). Attempts to completely oxidize this aldehyde intermediate under more forcing conditions were unsuccessful. The solution was diluted in ether (30 mL) and filtered through Celite. The filtrate was washed two times with 0.5 M HCl (10 mL). The acid was extracted into aqueous base by washing the organic solution three times with 1 N NaOH (15 mL). This aqueous base layer was then carefully acidified with 1 M HCl until the solution became turbid and an acidic pH was observed. The organic material was extracted three times with ether (15 mL), and the combined organic layers were then washed with brine and dried over Na_2SO_4. Removal of the solvent gave 139 mg (46%) of **1** as a fluffy white crystalline solid. The optical purity of this material was determined by formation of the methyl ester (diazomethane) and separation via HPLC ((*S*,*S*)-Whelk-O1 analytical column; eluting with 95:5−90:10 for 15 min then isocratic 90:10 hexanes/2-propanol, flow rate 0.8 mL/min, 254 nm, t_1 = 16.5 min, t_2 = 18.2 min). The HPLC separation was calibrated using racemic material. None of the

(22) Gilbertson, S. R.; Wang, X. F.; Hoge, G. S.; Klug, C. A.; Schaefer, J. *Organometallics* **1996**, *15*, 4678−4680.

other enantiomer was observed in the analysis of the optically active material: mp 70−73 °C; R_f 0.22 (9:1 $CHCl_3$/ MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.75−7.85 (m, 4H), 7.20−7.35 (m, 6H), 5.56 (d, J = 9.6 Hz, 1H), 4.42 (m, 1H), 3.15 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 (d, J_{CP} = 16.1 Hz), 155.2, 133.1 (d, J_{CP} = 31.1 Hz), 131.9 (d, J_{CP} = 30.5 Hz), 131.6, 131.1, 131.0, 130.9, 130.8, 130.7, 128.8, 128.7, 128.7, 128.6, 80.3, 50.2, 32.7 (d, J_{CP} = 57.6 Hz), 28.1; ^{31}P NMR (121 MHz,$CDCl_3$) δ 39.4; IR 3318, 2979, 1718, 1501, 1170, 790 cm^{-1}; HRMS (FAB/acc. mass) *m/z* calcd 428.1061 for $C_{20}H_{26}NO_3PS$ + Na, found 428.1067; $[\alpha]_D$ 0.01 (c = 3.16, $CHCl_3$, 25 °C).

Acknowledgment. We thank The Petroleum Research Foundation, administered by The American Chemical Society, The National Institutes of Health (GM 50772 and DA 06554), and The Robert A. Welch Foundation for support for this research, and K.B. thanks the NIH for a Research Career Development Award and the Alfred P. Sloan Foundation for a fellowship. NMR facilities were provided by the NSF via the chemical instrumentation program.

JO9803075