JOC*Note*

Asymmetric Synthesis of the Carbapenam Core from Serine

Barry P. Hart,*[,1] Sharad K. Verma,[1] and Henry Rapoport[†]

Department of Chemistry, University of California, Berkeley, Berkeley, California 94720

barry.hart.b@bayer.com

Received September 30, 2002

Abstract: The stereospecific synthesis of the functionalized carbapenam core **16** from the serine-derived trisubstituted pyrrolidine **9** is reported. The synthetic strategy relies on synthesizing an appropriately functionalized pyrrolidine, followed by an intramolecular azetidone formation utilizing a modified Mukiyama reagent. The efficient one-pot conversion of the benzenesulfonamide-protected pyrrolidine **9** to the Cbz-protected pyrrolidine **10** is also reported.

Since the discovery of penicillin in 1928, β-lactam antibiotics have remained a class of drugs used for the treatment of bacterial infections.[2] The discovery of thienemycin,[3] reported in 1976, by a Merck research group[4] provided the impetus for an intensive derivitization program to identify carbapenams having potent, broad spectrum antibacterial properties. Because of the inaccesibility associated with obtaining carbapenams in large quantity from naturally occurring sources, there has been a great deal of interest to develop routes to this class of synthetically challenging compounds. It is remarkable that commercially utilized carbapenams are still most efficiently produced from multistep total synthesis, instead of processes such as fermentation or semisynthesis.[5] In this note we wish to report an enantioselective approach to the carbapenam core **6** from the amino acid

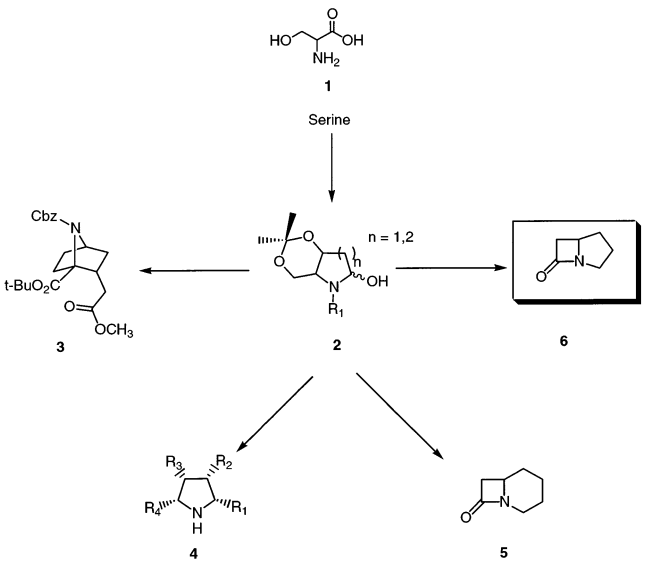


FIGURE 1. Serine-derived heterocycles.

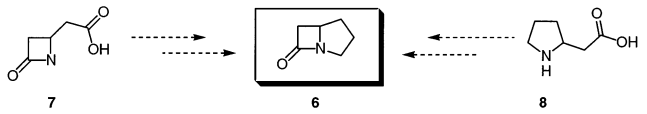


FIGURE 2. Approaches to the carbapenam core.

serine **1**. Variations of this approach have been described in previous reports from this laboratory for the enantioselective preparation of numerous chiral heterocycles, including conformationally constrained azabicyclo[2.2.1]-heptane amino acids **3**, tetrasubstituted pyrrolidines **4**, and carbacephems **5** (Figure 1).[6]

Unlike many approaches to carbapenams that entail five-membered ring closure of a substituted azetidinone (such as **7**),[7] the method reported herein involves closure of a four-membered ring from a five-membered ring intermediate,[8] such as **8**. The primary advantage conferred by four-membered ring closure late in the synthesis is that it allows for reaction conditions that might otherwise be incompatible with the labile azetidinone (Figure 2).

A functionalized pyrrolidine intermediate containing the γ-amino-carboxy terminus as in **8** was envisaged to be attainable from **9**, whose enantioselective preparation from D-serine has previously been reported from this laboratory.[6a] Because of difficulties associated with benzenesulfonamide deprotection later in the synthesis, it was determined to exchange protecting groups at an

[†] Dedicated to the memory of Professor Henry Rapoport (1918−2002).

(1) Present address: Bayer Pharmaceuticals, Department of Chemistry, 400 Morgan Lane, West Haven, CT 06516.

(2) (a) Overviews of β-lactam antibiotics: *The Chemistry of β-Lactams*; Page, M. I., Ed.; Blackie Academic & Professional: New York, 1992. (b) *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Press: New York, 1993. (c) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1−3. (d) Samarendra, C. I.; Maiti, N.; Micetich, R. G.; Daneshtalab, M.; Atchison, K.; Phillips, O. A.; Kunugita, C. *J. Antibiot.* **1994**, *47*, 1030.

(3) Kahan, J. S.; Kahan, F.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1.

(4) (a) Ratcliffe, R. W.; Albers-Schonberg, G. The Chemistry of Thienamycin and Other Carbapenem Antibiotics. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, p 227. (b) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463. (c) Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

(5) For a review on the state of carbapenem antibiotics, see: (a) Coulton, S.; E. Hunt. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier: New York, 1996; Vol. 33, pp 99−145. (b) Kim, O.; Fung-Tomc, J. *Expert Opin. Ther. Pat.* **2001**, *11*, 8. (c) Bonfiglio, G.; Russo, G.; Nicoletti, G. *Expert Opin. Invest. Drugs* **2002**, *11*, 4.

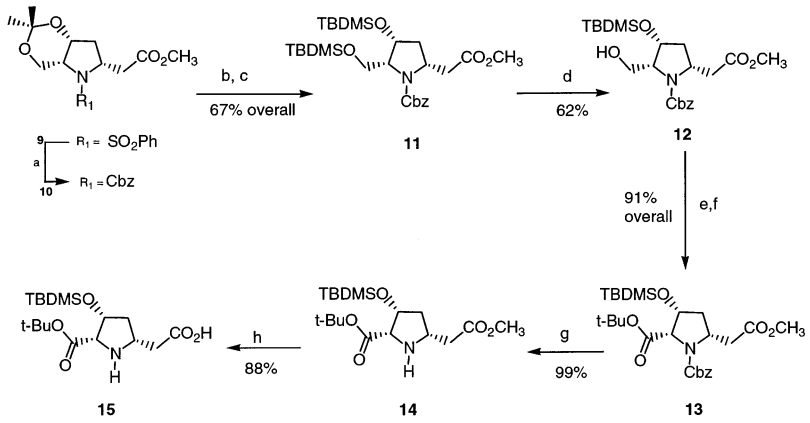
(6) (a) Hart, B. P.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2050. (b) Verma, S. K.; Atanes, M. N.; Busto, J. H.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **2002**, *67*, 1314. (c) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170.

(7) (a) Berks, A. H. *Tetrahedron* **1996**, *52*, 331. (b) Humphrey, G.; Miller, R. A.; Pye, P. J.; Rossen, K.; Reamer, R. A.; Maliakal, A.; Ceglia, S. S.; Grabowski, E. J. J.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1999**, *121*, 11261 and references therein.

(8) (a) Tanaka, H.; Sakagami, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 93. (b) Miyashita, M.; Chida, N.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1984**, 195.

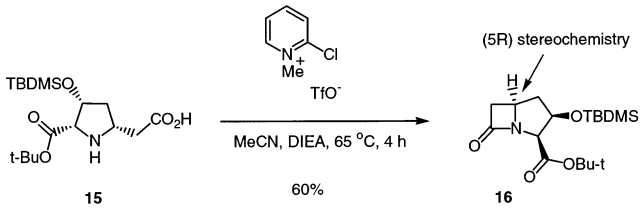
10.1021/jo026499s CCC: $25.00
Published on Web 11/26/2002

SCHEME 1[a]



[a] Conditions: (a) (1) sodium naphthalenide, DME, −78 °C, (2) 1 M AcOH, warm to rt, (3) EtOAc, K_2CO_3, CbzCl; (b) HCl, MeOH, rt, 3 h; (c) TBDMSCl, DMF, imidazole, rt, 12 h; (d) AcOH/H_2O/THF (13:7:3), rt, 24 h; (e) $NaIO_4$, $RuCl_3$·*x*H_2O, CH_3CN/CCl_4 (1:1), rt, 3 h; (f) *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, *tert*-butanol, rt, 2 h; (g) H_2, Pd/C, MeOH, rt, 2 h; (h) LiOH, 4:1 THF/H_2O, rt, 3 h.

SCHEME 2



appropriate point earlier in the synthesis. The criteria for an alternative protecting group were that it provide robust enough protection through ensuing reaction conditions and it's removal conditions be mild enough so as not to affect other functionality present in the molecule. The chlorobenzyloxycarbonyl (Cbz) group was found to be suitable for this purpose. Reductive cleavage of the sulfonamide bond in **9** via sodium naphthalenide reduction and reprotection as the Cbz derivative proceeded smoothly, giving **10** in 70% yield from **9** (Scheme 1).

Compound **10** was treated with HCl in MeOH to afford its corresponding diol, which was converted to the bissilyl ether **11** under standard conditions. Selective deprotection of the primary silyl group furnished **12**.[10] The primary alcohol of **12** was oxidized to the corresponding carboxylic acid, and esterification afforded the functionalized pyrrolidine **13**. Deprotection of the Cbz group was carried out under mild conditions, by way of hydrogenation, affording **14** in excellent yield**.** Hydrolysis of the methyl ester in **14** was accomplished with LiOH, from which the pyrrolidine amino acid **15**, the envisaged carbapenam precursor, was isolated after pH adjustment and extraction.

The intramolecular cyclization of **15**, employing a modified Mukiyama reagent developed in the Rapoport laboratory,[6c] afforded carbapenam **16** in 60% yield (Scheme 2). This carbapenam has the desired 5*R* absolute stereochemistry at the C-5 position, required for antibiotic activity. Conversely, the synthesis of a carbapenam derived from L-serine would afford the diastereomer, having *S* absolute stereochemistry at C-5, and C-2 and C-3 substituents as a single enantiomer.

We have reported a method for the enantioselective synthesis of a functionalized carbapenam core from D-serine-derived pyrrolidines. The methods reported herein provide an efficient, stereocontrolled route to the carbapenam core, with substitution at C-2, and C-3. These methods complement previous efforts of the group in illustrating the synthetic utility of pyrrolidines derived from amino acids. This core can be further functionalized to provide a variety of novel synthetic carbapenems and their analogues aimed at increasing potency, metabolic stability, and activity against resistant bacteria.

Experimental Section

General. All reactions were conducted under an atmosphere of nitrogen, and solvents were distilled before use unless otherwise noted. THF and Et_2O were distilled from sodium/benzophenone; CH_3CN was distilled from P_2O_5 and then from CaH_2; DMF was dried over 4 Å molecular sieves; CH_2Cl_2 was distilled from CaH_2; EtOAc, hexane, 2-propanol, and chloroform were used as purchased. ^1H and ^{13}C NMR were taken in $CDCl_3$ at room temperature, unless otherwise stated. Chemical shifts are reported in ppm (δ) in reference to tetramethylsilane (TMS). Coupling constants are reported in Hertz. Column chromatography was performed using EM Science silica gel (230−400 mesh). Melting points were taken in duplicate and are uncorrected. Elemental analyses were determined by the Microanalytical Laboratories, University of California, Berkeley.

(2*R*,4*R*,5*R*)-4-Hydroxy-5-hydroxymethyl-2-methoxycarbonylmethyl-1-(benzyloxycarbonyl)-isopropylidene Ketal-pyrrolidine (10). To a −78 °C THF solution of **9**[6a] (1.0 g, 2.7 mmol) was added 8 mL of a DME solution of sodium naphthalenide, dropwise via syringe, until the end point was reached (indicated by persistence of a dark olive green color).[9a] The contents were quenched with a 50% solution of 1 M aqueous AcOH/THF (16 mL) at −78 °C and were allowed to warm to room temperature with stirring. The homogeneous mixture was then diluted with EtOAc (24 mL), followed by the addition of K_2CO_3 (0.94 g, 6.7 mmol) and benzyl chloroformate (0.85 mL, 6.0 mmol). After stirring at room temperature for 2 h, the contents were diluted with 1 M KH_2PO_4 (50 mL). The aqueous layer was separated and extracted with EtOAc (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (1:2 EtOAc/hexanes) afforded 693

(9) Sodium naphthalenide was generated as described by: (a) Bergmeir, S. C.; Seth, P. P. *Tetrahedron Lett.* **1999**, *40*, 6181. (b) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

(10) Kawai, A.; Hara, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 6331.

mg (70%) of **10** as a pale oil: $[\alpha]^{23}_D$ −70.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, rotomers) δ 1.33−1.38 (m, 12H), 1.94 (dd, J = 14.2, 3.1, 2H), 2.10−2.19 (m, 2H), 2.79−2.97 (m, 4H), 3.60 (s, 3H), 3.64 (s, 3H), 3.66−3.69 (m, 1H), 3.79−3.82 (m, 1H), 3.86−3.90 (m, 1H), 3.97−4.07 (m, 2H), 4.12 (dd, J = 12.5, 5.4, 1H), 4.36−4.43 (m, 4H), 5.06−5.17 (m, 4H), 7.32−7.34 (m, 10H); ^{13}C NMR (100 MHz, rotomers) δ 172.2, 172.1, 155.2, 154.6, 136.5, 136.3, 128.5, 128.2, 128.1, 127.8, 99.2, 98.6, 71.3, 70.3, 67.2, 67.0, 62.3, 61.0, 57.8, 57.6, 55.9, 55.2, 51.5 (2C), 40.0, 39.4, 36.3, 35.5, 26.8, 25.6, 21.9, 20.9. Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.8; H, 6.9; N, 3.9. Found: C, 62.5; H, 6.9; N, 3.7.

(2*R*,4*R*,5*R*)-4-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldimethylsilyloxymethyl-2-methoxycarbonylmethyl-1-(benzyloxycarbonyl)pyrrolidine (11). Compound **10** (1.1 g, 3.03 mmol) was dissolved in MeOH (27 mL), and concentrated HCl (0.8 mL) was added dropwise. After 90 min of stirring at room temperature, the mixture was concentrated to an oil. Chromatography (1:2 hexanes/EtOAc) afforded 781 mg (80%) of the diol as an oil. The diol (812 mg, 2.51 mmol) was dissolved in DMF (14 mL), followed by addition of imidazole (0.98 g, 14.4 mmol) and *tert*-butyldimethylsilyl chloride (1.07 g, 7.10 mmol) at room temperature. The reaction mixture was stirred for 12 h, after which time saturated aqueous Na_2CO_3 (1.5 mL) was added. The mixture was evaporated to dryness, and the residue was dissolved in CH_2Cl_2 (25 mL) and H_2O (25 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (4 × 25 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The resulting oil was chromatographed (1:5 EtOAc/hexanes) to give 1.16 g (84%) of **11** as a colorless oil (67% overall from **10**): $[\alpha]^{23}_D$ −18.7 (c = 3.4, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6 at 60 °C) δ −0.07 (s, 3H), −0.05 (s, 3H), 0.04 (s, 6H), 0.85 (s, 9H), 0.91 (s, 9H), 1.87−1.93 (m, 1H), 1.98−2.08 (m, 1H), 2.70−2.76 (dd, J = 9.6, 5.6, 1H), 3.27 (s, 3H), 3.70−3.80 (m, 1H), 3.86−3.88 (m, 1H), 3.92−4.03 (m, 3H), 4.28−4.38 (m, 1H), 5.00−5.03 (d, J = 12.4, 1H), 5.01−5.13 (d, J = 12.4, 1H), 6.99−7.01 (d, J = 7.6, 1H), 7.05−7.08 (dd, J = 7.6, 2H), 7.21−7.23 (d, J = 8.0, 2H); ^{13}C NMR (100 MHz, $CHCl_3$, rotomers) δ −5.3, −5.4, −4.9, −3.7, 18.0, 18.3, 25.7 (3C), 26.0 (3C), 38.5, 39.0, 40.0, 51.2, 53.4, 59.9, 60.4, 62.2, 63.2, 66.7, 70.9 (2C), 127.6, 127.9, 128.4, 136.5, 155.1, 172.2. Anal. Calcd for $C_{28}H_{49}NO_6Si_2$: C, 60.9; H, 9.0; N, 2.5. Found: C, 60.9; H, 9.0; N, 2.7.

(2*R*,4*R*,5*R*)-4-*tert*-Butyldimethylsilyloxy-5-hydroxymethyl-2-methoxycarbonylmethyl-1-(benzyloxycarbonyl)-pyrrolidine (12). To a stirring THF solution (7 mL) of **11** (1.16 g, 2.10 mmol) was added a mixture of AcOH/H_2O (29 mL:16 mL) dropwise at room temperature. The initially milky white mixture was stirred at room temperature for 24 h, after which time it was clear and homogeneous. The mixture was concentrated to an oil, which was diluted with EtOAc (50 mL) and washed with H_2O (50 mL). The aqueous layer was separated and extracted with EtOAc (4 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (2:1 hexanes/EtOAc) furnished 570 mg (62%) of **12** as a colorless oil. (Other products observed in minor amounts include the diol, which results from deprotection of both silyl groups, and starting compound **11**.) $[\alpha]^{22}_D$ −10.4 (c = 5.2, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6 at 60 °C) δ 0.20 (s, 6H), 0.77 (s, 9H), 1.67 (m, 1H), 1.85−1.95 (bs, 1H), 2.61−2.68 (m, 1H), 3.00−3.10 (bs, 1H), 3.24 (s, 3H), 3.80−3.83 (m, 2H), 3.89−3.92 (m, 3H), 4.16−4.23 (m, 1H), 4.98 (q, J = 11.4, 2H), 6.98 (d, J = 7.2, 1H), 7.03−7.07 (m, 2H), 7.20 (d, J = 7.2, 2H); ^{13}C NMR (100 MHz, $CHCl_3$, rotomers) δ −5.3, −4.7, 17.9, 25.7 (3C), 38.7, 40.1, 51.5, 54.4, 64.0, 65.4, 67.5, 72.9, 128.0, 128.2 (2C), 128.6 (2C), 136.0 (weak), 158.5 (weak), 171.9. Anal. Calcd for $C_{22}H_{35}NO_6Si$: C, 60.4; H, 8.1; N, 3.2. Found: C, 60.1; H, 8.1; N, 3.2.

(2*S*,4*R*,5*R*)-3-*tert*-Butyldimethylsilyloxy-5-methoxycarbonyl-1-benzyloxycarbonylproline *tert*-Butyl Ester (13). To a solution of alcohol **12** (1.06 g, 2.42 mmol) in CH_3CN (11 mL), CCl_4 (11 mL), and H_2O (8.5 mL) were added $NaIO_4$ (1.81 g, 8.5 mmol) and $RuCl_3 \cdot xH_2O$ (50 mg). The biphasic mixture was vigorously stirred (magnetically) for 3 h. The phases were separated, and the aqueous phase was extracted with $CHCl_3$/IPA (4:1, 4 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a dark foam, in nearly quantitative yield. To the crude carboxylic acid dissolved in CH_2Cl_2 (15 mL) were added *tert*-butyl alcohol (38 g, 0.51 mol) and *N*,*N*′-diisopropyl-*O*-*tert* -butylisourea (3 g, 0.015 mol), and the mixture was stirred at room temperature for 2 h. The mixture was evaporated, and to the residue was added H_2O (50 mL) followed by $CHCl_3$/IPA (4:1, 50 mL). The aqueous phase was extracted with additional $CHCl_3$/IPA (4:1, 4 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting solid was dissolved in hexanes/EtOAc (5:1, 10 mL) and filtered. The filtrate was concentrated and chromatographed (4:1 hexanes/EtOAc) to afford 1.12 g (91%) of **13** as a thick, colorless oil: $[\alpha]^{22}_D$ +8.65 (c = 11.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, major rotomer) δ 0.056 (s, 6H), 0.856 (s, 9H), 1.35 (s, 9H), 1.86−1.96 (m, 1H), 2.35−2.41 (m, 1H), 2.69 (dd, J = 16.3, 10.1, 1H), 3.36 (dd, J = 16.3, 4.0, 1H), 3.64 (s, 3H), 4.18−4.24 (m, 1H), 4.31 (d, J = 7.5, 1H), 4.49−4.51 (m, 1H), 5.02−5.17 (m, 2H), 7.27−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CHCl_3$, rotomers) δ −5.0 (6C), −4.9, −4.8, 18.2, 25.8 (3C), 28.1, 28.2, 38.4, 38.8, 39.5 (2C), 51.4, 53.5, 64.9, 65.7, 66.9, 67.1, 71.4, 71.7, 73.4, 74.9, 81.48, 81.53, 127.7, 127.9, 128.4, 128.5, 128.8, 128.9, 136.4, 136.5, 153.9, 154.4, 168.6, 168.9, 172.3 (2C). Anal. Calcd for $C_{26}H_{41}NO_7Si$: C, 61.5; H, 8.1; N, 2.8. Found: C, 61.3; H, 8.2; N, 2.8.

(2*S*,4*R*,5*R*)-3-*tert*-Butyldimethylsilyloxy-5-methoxycarbonyl-proline *tert*-Butyl Ester (14). To a methanolic solution (20 mL) of **13** (565 mg, 1.11 mmol) was added 20% $Pd(OH)_2$/C (255 mg), followed by hydrogenation (1 atm) for 3 h. The heterogeneous mixture was filtered through Celite, and the filter pad was washed copiously with methanol. The combined filtrate was concentrated to an oil, which was diluted with methanol (2 mL) and passed through a cotton plug. Concentration followed by drying on high vacuum gave 410 mg (99%) of **14** as a white foam: $[\alpha]^{22}_D$ −10.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.054 (s, 3H), 0.063 (s, 3H), 0.867 (s, 9H), 1.46 (s, 9H), 1.51−1.58 (m, 1H), 2.13−2.23 (m, 1H), 2.30−2.40 (bs, 1H), 2.53 (dd, J = 15.5, 6.9, 1H), 2.67 (dd, J = 15.5, 7.2, 1H), 3.46−3.51 (m, 1H), 3.58 (d, J = 5.0, 1H), 3.67 (s, 3H), 4.44 (q, J = 4.4, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 18.0, 25.9 28.2, 41.2, 41.3, 51.6, 53.3, 67.6, 74.3, 81.2, 169.8, 172.3. Anal. Calcd for $C_{18}H_{35}NO_5Si$: C, 57.9; H, 9.5; N, 3.8. Found: C, 58.2; H, 9.2; N, 3.6.

(2*S*,4*R*,5*R*)- 5-Acetic-3-*tert*-butyldimethylsilyloxy-proline *tert*-Butyl Ester (15). To a THF/H_2O solution (4:1, 25 mL) of **14** (667 mg, 1.79 mmol) was added $LiOH \cdot H_2O$ (0.981 g, 23.4 mmol), and the contents were stirred at room temperature for 3 h. The basic mixture was adjusted to pH = 5 with 5% NaH_2PO_4 (65 mL) and extracted with $CHCl_3$/IPA (3:1, 5 × 75 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. After drying on high vaccuum, 566 mg (88%) of **15** was collected as a colorless foam: $[\alpha]^{22}_D$ −53.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.067 (s, 3H), 0.076 (s, 3H), 0.855 (s, 9H), 1.48 (s, 9H), 1.71 (d, J = 13.5, 2H), 2.38 (d, J = 13.5, 2H), 2.80−2.86 (m, 1H), 3.85−3.92 (m, 1H), 4.32 (d, J = 5.2, 1H), 4.66−4.68 (m, 1H), 6.60−6.70 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.7, 17.9, 25.8, 28.1, 40.1, 41.9, 55.3, 65.0, 73.5, 83.3, 166.3 (weak), 176.3 (weak). Anal. Calcd for $C_{17}H_{33}NO_5Si$: C, 56.8; H, 9.3; N, 3.9. Found: C, 56.5; H, 8.9; N, 3.8.

(2*R*,3*S*,7*R*)-3-*tert*-Butyl Ester-2-*tert*-butyldimethylsiloxy-5-oxo-azabicyclo[3.2.0]heptane (16). To a solution of 2-chloro-1-methylpyridinium triflate (2.17 g, 7.90 mmol) and *N*,*N*-diisopropylethylamine (5.20 mL, 29.8 mmol) in CH_3CN (475 mL) was added a CH_3CN/CH_2Cl_2 solution (160 mL:10 mL) of amino acid **15** (0.835 g, 2.32 mmol), dropwise over 4 h at 65 °C. After the addition was complete, the solution was heated at 65 °C for an additional 15 min, allowed to cool to room temperature, and stirred for 12 h. The solution was diluted with CH_2Cl_2 (150 mL) and concentrated to 50% of its original volume. An additional 200 mL of CH_2Cl_2 was added, and the solution was concentrated to 100 mL and then partitioned between CH_2Cl_2 (300 mL) and H_2O (300 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford a dark red oil. Chromatography on silica (4:1 hexanes/EtOAc) gave 0.477 g (60%) of the β-lactam **16** as a white solid: Mp = 41−42 °C; $[\alpha]^{22}_D$

+135.0 ($c = 0.01$, $CHCl_3$); ^1H NMR 0.060 (6H), 0.86 (s, 9H), 1.46 (s, 9H), 2.03−2.15 (m, 2H), 2.89 (dd, $J = 15.6$, 2.7, 1H), 3.09 (dd, $J = 15.6$, 2.7, 1H), 3.52−3.58 (m, 1H), 3.77 (d, $J = 7.0$, 1H), 4.63−4.69 (m, 1H); ^{13}C NMR δ −5.1 (2C), 18.2, 25.7 (3C), 28.0 (3C), 36.7, 43.6, 49.0, 64.7, 79.1, 82.3, 166.3, 172.8. Anal. Calcd for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10. Found: C, 59.90; H, 9.01; N, 3.94.

Acknowledgment. The authors wish to thank colleagues J. Hector Busto, M.N. Atanes, C. Varela, and Larry Anderson for their input on this project and also the University of California, Berkeley. S.K.V. is thankful for fellowship support in the form of a National Research Service Award, NIH, DHHS. B.P.H. and S.K.V. are grateful to Prof. Henry Rapoport for his invaluable tutelage and support.

Supporting Information Available: ^1H and ^{13}C NMR spectra and elemental analysis for compounds **10**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026499S