Synthesis of a 4β-(Hydroxymethyl)carbapenem

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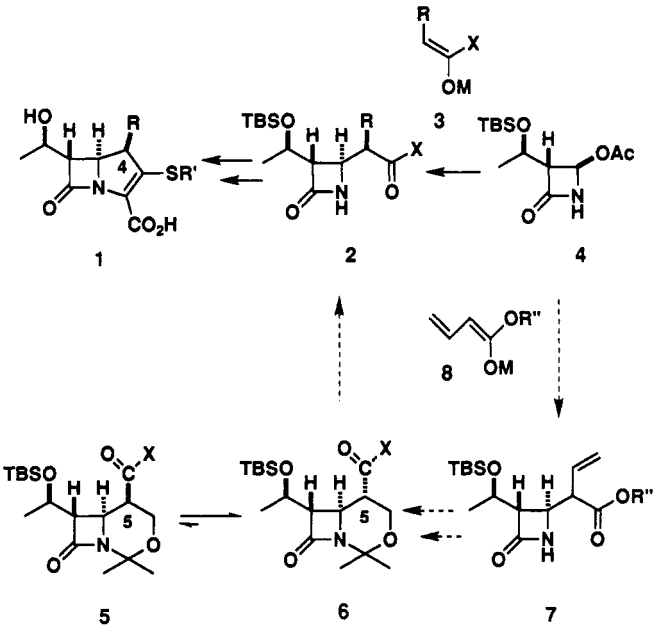
Received December 17, 1993

We undertook the synthesis of the 4β-(hydroxymethyl)-carbapenem (1, R = CH_2OH) as a part of studies that were made to understand the relationship between the structure of carbapenems bearing a heteroatom-substituted 4β-alkyl side chain[2] and their antibacterial activity. A recent report[3] describing the first synthesis of this compound prompted us to disclose our synthesis which was accomplished in a novel manner.

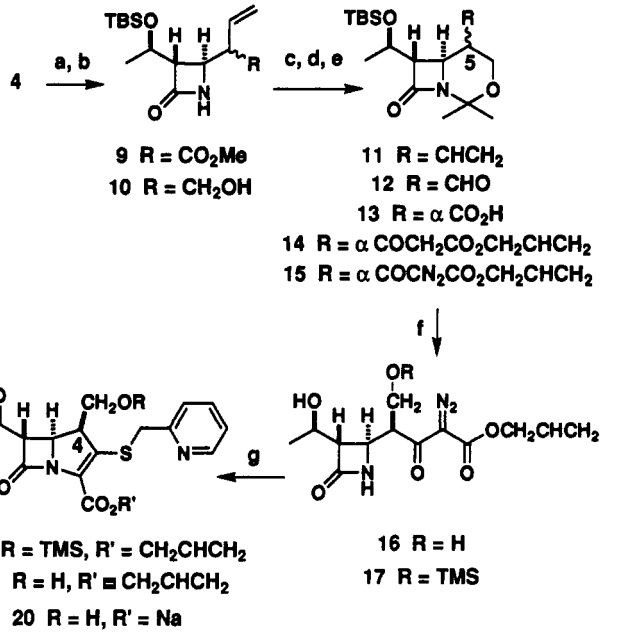
The azetidinone (2) (e.g., X = OH) is a key intermediate in the synthesis of 4β-substituted carbapenems[4] (Scheme 1). It is generally available from the stereoselective reaction of the acetoxyazetidinone 4 with an enolate 3 bearing a special auxiliary.[5] We examined an approach where intermediate 2 is prepared stereoselectively by making use of functionality that is present in the molecule. Specifically, it was thought that base-catalyzed equilibration of the 5-acyl group of a 3-oxa-1-azabicyclo[4.2.0]-octane[6] (5 or 6) should favor the 5α-isomer (6) where this substituent is in the thermodynamically more stable pseudoequatorial configuration. Hydrolysis of the acetonide function in 6 would then furnish intermediate 2 (R = CH_2OH) which could be converted into the desired carbapenem 1 using standard procedures.[4]

It was thought that the required acetonide (5 or 6) could be derived from the α,β-unsaturated ester 7 which, in turn, could be obtained from the reaction of the acetoxyazetidinone 4 with the dienolate 8. For the latter process, a variation[7] of the vinylogous Reformatsky reaction was examined. This was found (Scheme 2) to furnish the desired intermediate 9 as a mixture (9:1 by ^1H NMR) of epimeric esters. These were reduced to the alcohols (10)[8] which were then converted to the acetonides 11. For characterization, a sample of the acetonides 11 was taken and the two isomers were separated by chromatography. The ^1H NMR spectrum of the major isomer showed a small (5.1 Hz) vicinal coupling constant between hydrogen atoms H_a and H_b (Figure 1). This value was found to be larger (9.2 Hz) in the spectrum of the minor isomer and

Scheme 1



Scheme 2[a]



[a] (a) Activated Sn [LAH (1 equiv) and $SnCl_2$ (2 equiv)], methyl 4-bromocrotonate (2 equiv), THF rt, 5 h (55%); (b) LAH (1 equiv), THF, 20 min (75%); (c) 2,2-dimethoxypropane (1.2 equiv), $BF_3{\cdot}Et_2O$ (0.1 equiv), then 2-methoxypropene (1.2 equiv), CH_2Cl_2 (53%); (d) O_3, MeOH, −78 °C, then excess Me_2S, 19 h, then DBU (0.1 equiv), ethyl acetate, 1 h, then Jones reagent, acetone, 4 °C (51% overall); (e) carbonyldiimidazole (1.2 equiv), acetonitrile, 0.5 h, rt, then magnesium monoallylmalonate (1.3 equiv), benzene, reflux, 0.5 h (74%), then toleuenesulfonyl azide (1 equiv), triethylamine (1.0 equiv), acetonitrile, 0.5 h, rt (89% overall); (f) aqueous HOAc, 70 °C, 10 h, (76%); (g) (trimethylsilyl)imidazole (1.0 equiv), CH_2Cl_2, −15 °C to rt; then rhodium(II) octanoate, benzene, reflux, then diphenyl chlorophosphate (1.05 equiv), Hunig's base (1.05 equiv), 4-(dimethylamino)pyridine (catalyst), acetonitrile, 4 °C, 0.5 h, then 2-picolinethiol (1.6 equiv), Hunig's base (1.05 equiv), −20 °C, 18 h, then acetic acid (5 equiv), aqueous THF, 4 °C, 3 h, then *N*-methylaniline (1.5 equiv), bis(dibenzylideneacetone)palladium(0) (0.1 equiv), triphenylphosphine (0.4 equiv), THF, 10 min, then aqueous $NaHCO_3$ (10% overall).

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(2) Menard, M.; Banville, J.; Martel, A.; Desiderio, J.; Fung-Tomc, J.; Partyka, R. In *Recent Advances in the Chemistry of Anti-infective Agents*; Bentley, P. H., Ponsford, R., Eds.; The Royal Society of Chemistry: Cambridge, 1993; p 1.

(3) Sendo, Y.; Kii, M.; Sakanoue, M.; Motokawa, K.; Kimura, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2410.

(4) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.

(5) (a) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (b) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *Ibid.* **1986**, *108*, 4675. (c) Ito, Y.; Terashima, S. *Tetrahedron Lett.* 1987, 28, 6625. (d) Martel, A.; Daris, J.; Bachand, C.; Corbeil, J.; Menard, M. *Can. J. Chem.* **1988**, *66*, 1537.

(6) For a stereoselective synthesis of 4β-methylcarbapenems which also makes use of the 3-oxa-1-azabicyclo[4.2.0]octane system see: Fuentes, L. M.; Shinkai, I.; King, A.; Purick, R.; Reamer, R. A.; Schmitt, S. M.; Cama, L.; Christensen, B. G. *J. Org. Chem.* **1987**, *52*, 2563.

(7) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 161.

(8) The alcohols 10 are reported in ref 2, but without spectral characterization.

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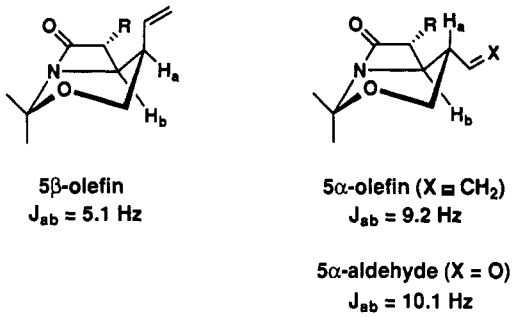

Figure 1. Vicinal coupling constants from the ^1H NMR spectra of the acetonides **11** and **12**.

therefore, based on the coupling data reported for a related acetonide,[9] a pseudoaxial configuration can be assigned to the vinyl group in the major acetonide isomer and a pseudoequatorial configuration for this group in the minor isomer. This allows structures to be assigned to the ester epimers **9** and indicates that the Reformatsky reaction favors formation of the diastereomer that has an *R* configuration at the carbon atom bearing the ester function.

At this point in the synthesis, the vinyl group at C-5 in the acetonides **11** was converted to an aldehyde group. This would make this center epimerizable and should allow us to obtain the required isomer. Indeed, ozonolysis of **11** gave a mixture of aldehydes **12** which underwent isomerization to the thermodynamically more stable 5α-isomer (J_{ab} = 10.1 Hz, Figure 1) on treatment with DBU. The ^1H NMR of the crude reaction mixture did not show signals that could be attributed to the 5-β isomer.

Elaboration of the aldehyde group into the diazo-containing side chain that is required for carbapenem formation was conducted with the acetonide group in place. Oxidation of the 5α-isomer of **12** gave the acid (**13**) and this was converted to the β-keto ester **14** using the procedure of Masamune.[10] Alternatively, the β-keto ester could be obtained directly from the 5α-aldehyde in a 49% yield by treatment of **12** with allyl diazoacetate in the presence of stannous chloride.[11] Conversion of **14** to the diazo derivative **15** followed by the simultaneous hydrolysis of the acetonide and silyl ether functions gave the carbapenem precursor **16**. The primary alcohol was selectively silylated and this derivative (**17**) was converted to the protected carbapenem **18** using the Merck procedure.[4] Hydrolysis of the silyl ether followed by palladium-catalyzed deprotection afforded the 4β-(hydroxymethyl)-carbapenem[12] (**20**). It was found to be less stable[13] and less active *in vitro* than the corresponding 4β-methylcarbapenem. For these reasons further work with 4β-(hydroxymethyl)carbapenems is not planned.

In summary, the synthesis of a 4β-(hydroxymethyl)-carbapenem was achieved using thermodynamic control to obtain the desired stereochemistry at the 4 position. This strategy has been extended to the synthesis of other 4β-substituted carbapenems and this work will be described in the future.

(9) For the structural determination of isomeric 5-methyl 3-oxa-1-azabicyclo[4.2.0]octanes, see: Shih, D. H.; Fayter, J. A.; Cama, L. D.; Christensen, B. G.; Hirshfield, J. *Tetrahedron Lett.* **1985**, *26*, 583. The corresponding coupling constants for the 5α- and 5β-methyl isomers were 10.0 and 5.0 Hz, respectively.

(10) Brooks, D. W.; Lu, L. D.; Masamune, S. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 72.

(11) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

Experimental Section

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. The UV and IR spectra were recorded on Hewlett-Packard 8451 and Perkin-Elmer 781 spectrophotometers, respectively. The ^1H NMR spectra were obtained on a Brucker AC 200 or AMX 400 instrument using tetramethylsilane or sodium 3-(trimethylsilyl)propionate-*2,2,3,3-d*$_4$ as the internal standard. Thin-layer chromatography was performed with Merck Art 5719 Kieselgel 60 F_{254} plates. Flash column chromatography employed Merck Art 9385 Kieselgel 60 (230–400 mesh) with ethyl acetate–hexane mixtures as eluent or Waters C_{18} BondaPak with acetonitrile–water mixtures as eluent. Where necessary, solvents were dried and reactions were conducted under an argon atmosphere.

(3*S*,4*R*)-3-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1′ξ)-1′-(methoxycarbonyl)prop-2′-enyl]azetidin-2-one (9). Lithium aluminum hydride (1.20 g, 20 mmol) was added in small portions to a cooled (5 °C), stirred solution of stannous chloride [(11.4 g, 60 mmol) placed under high vacuum at 120 °C for 1 h before use] in dry THF (50 mL). After H_2 evolution ceased, the reaction flask was purged with Ar and placed in an ambient temperature water bath for 1 h. A solution of (3*R*)-4-acetoxy-3-[(1′*R*)-1′-[(*tert*-butyldimethylsiloxy)ethyl]azetidinone (**4**) (8.40 g, 30 mmol) and freshly distilled methyl 4-bromobut-2-enoate (7.90 mL, 90%, 60 mmol) in dry tetrahydrofuran (25 mL) was added via cannula. The suspension was left stirring for 5 h. An aqueous solution of K_2HPO_4 (40 mL, 1.0 M) was added with vigorous stirring. The suspension was collected by filtration through Celite and was washed with THF. Most of the organic solvent was removed from the filtrate and the residue was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). Removal of the solvent followed by chromatography gave a mixture of the epimeric esters **9** (9:1 by ^1H NMR) as a solid (5.4 g, 55%): R_f (ethyl acetate:hexane = 1:1) 0.64. The major epimer, the 4-[(1′*R*)-1′-(methoxycarbonyl)prop-2′-enyl] compound, could be obtained pure by crystallization from ethyl acetate–hexane: mp 92–93 °C; $[\alpha]^{23}_D$ +6.3° (*c* 2.8, $CHCl_3$); ^1H NMR ($CDCl_3$) 0.05 (s, 6H), 0.85 (s, 9H), 1.12 (d, 3H, *J* = 6.3 Hz), 2.94 (dd, 1H, *J* = 2.2, 6.3 Hz), 3.16 (dd, 1H, *J* = 9.3, 6.5 Hz), 3.70 (s, 3H), 3.90 (dd, 1H, *J* = 2.2, 6.5 Hz), 4.20 (q, 1H, *J* = 6.3 Hz), 5.21–5.98 (m, 3H), 6.03 (br s, 1H); IR (KBr) 3100, 3180, 1765, 1740 cm^{-1}. Anal. Calcd for $C_{16}H_{29}NO_4Si$: C, 58.68; H, 8.93; N, 4.28. Found: C, 58.53; H, 8.95; N, 4.19.

(3*S*,4*R*)-3-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-[(1′ξ)-1′-(hydroxymethyl)prop-2′-enyl]azetidin-2-one (10). Lithium aluminum hydride (1.55 g, 38.7 mmol) was added in portions over 10 min to a cooled (5 °C) solution of the ester epimers **9** (12.64 g, 38.7 mmol) in dry THF. The bath was then

(12) The spectral data is consistent with the depicted structure. However, it should be noted that the ^1H NMR data does not allow for an unequivocal assignment of configuration at C-4 because the vicinal coupling constant between the methine hydrogen atoms at C-4 and C-5 (9.3 Hz for compound **20**) is not very different for the α and β isomers, i.e., typically 8 Hz or less for the former and 9 Hz or more for the latter (for some examples, see: ref 2). The possibility that **20** is the α-isomer is, however, unlikely. For this to have happened, the asymmetric center at C-4 would have had to undergo complete epimerization during conversion of the diazo intermediate **16** into the protected carbapenem **18**. This should not occur when the standard conditions for this conversion are used (ref 4). Furthermore, it has been our experience, as well as that of others (Shih, S. H.; Cama, L.; Christensen, B. G. *Tetrahedron Lett.* **1985**, *26*, 587), that the last step in this sequence, coupling of the thiol component with the vinyl diphenylphosphate intermediate, is very difficult in the case of the 4α-substituted isomer and typically requires use of the vinyl triflate derivative. In fact, this difference in reactivity often allows one to obtain the 4β-isomer of the coupled product free of the 4α-isomer when beginning with diazo intermediate that is partly epimerized at this center. This is primarily a steric effect and would be expected to be pronounced in the present case with the bulky [(trimethylsilyl)oxy]methyl group at C-4. Since the coupling was found to proceed normally while using the vinyl phosphate intermediate, we feel confident that the stereochemistry of this center was retained in the preceding transformations.

(13) A half-life of 3.8 h (pH 7.4, 37 °C) was determined using the procedure of: Pfaendler, H. R.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 2039.

removed and the reaction was left for 20 min. Careful addition of water (1.6 mL), aqueous NaOH solution (1.6 mL, 15%), water (4.8 mL), and Celite (20 g) left a suspension which was filtered. The solid was washed with THF (3 × 100 mL) and the combined filtrates were concentrated. The residue was chromatographed to afford the alcohol isomers **10** as an oil (8.10 g, 75%): R_f (ethyl acetate:hexane = 1:1) 0.41. The reduction was also conducted with a sample of the major ester epimer to give the 4-[(1′*R*)-1′-(hydroxymethyl)prop-2′-enyl] compound as crystals from hexane: mp 64-65 °C; $[\alpha]^{23}_D$ −9.2° (*c* 3.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$ + 1 drop D_2O) 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.33 (d, 3H, *J* = 6.0 Hz), 2.39 (ddd, 1H, *J* = 15.6, 9.0, 6.6 Hz), 3.13 (dt, 1H, *J* = 8.6, 2.0 Hz), 3.41 (dd, 1H, *J* = 2.0, 9.0 Hz), 3.59 (d, 2H, *J* = 6.6 Hz), 4.14 (dq, 1H, *J* = 6.0, 8.6 Hz), 5.14–5.69 (m, 3H); IR (KBr) 3430, 3180, 3100, 1760, 1720 cm^{-1}. Anal. Calcd for $C_{15}H_{29}NO_3Si$: C, 60,15; H, 9.76; N, 4.68. Found: C, 60.28; H, 10.02; N, 4.49.

(5ξ, 6*R*,7*S*)-6-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2,2-dimethyl-3-oxa-7-oxo-5-vinyl-1-azabicyclo[4.2.0]octane (11). A solution of the alcohol isomers **10** (6.79 g, 22.7 mmol) and 2,2-dimethoxypropane (3.35 mL, 27.2 mmol) in CH_2Cl_2 (17 mL) was treated with $BF_3{\cdot}Et_2O$ (0.28 mL, 2.3 mmol). After 0.5 h, 2-methoxypropene (2.60 mL, 27.2 mmol) was added and , after an additional 0.5 h, the reaction was worked up by the addition of triethylamine (2 mL) and filtration through a short column of silica gel. Removal of the solvent followed by chromatography afforded the acetonides **11** (4.06 g, 53%). Careful chromatography of a sample of this mixture allowed for the separation of the two isomers. The major, less-polar component (**11**, 5*R*) was obtained as a crystalline solid: mp 59–60 °C; $[\alpha]^{23}_D$ 12° (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.06 (s, 6H), 0.87 (s, 9H), 1.14 (d, 3H, *J* = 6.2 Hz), 1.42 (s, 3H), 1.73 (s, 3H), 2.35 (m, 1H), 3.73 (dd, 1H, *J* = 2.7, 12.0 Hz), 3.83 (dd, 1H, *J* = 2.0, 5.1 Hz), 4.03 (dd, 1H, *J* = 2.4, 12.0 Hz), 4.17 (dq, 1H, *J* = 6.2, 3.8 Hz), 5.13–5.28 (m, 2H), 6.02–6.21 (m, 1H); IR (KBr) 1740 (br) cm^{-1}. Anal. Calcd for $C_{18}H_{33}NO_3Si$: C, 63.67; H, 9.80; N, 4.13. Found: C, 64.04; H, 9.81; N, 4.17. The minor isomer (**11**, 5*S*) was also a crystalline solid: mp 64–67 °C; $[\alpha]^{23}_D$ −14° (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.06 (s, 6H), 0.89 (s, 9H), 1.13 (d, 3H, *J* = 6.3 Hz), 1.39 (s, 3H), 1.74 (s, 3H), 2.33 (m, 1H), 2.79 (dd, 1H, *J* = 1.8, 3.6 Hz), 3.42 (dd, 1H, *J* = 1.8, 9.2 Hz), 3.68 (dq, 2H, δ_A = 3.74, δ_B = 3.63, J_{AB} = 12.1 Hz, J_{AX} = 4.6 Hz, J_{BX} = 11.2 Hz), 4.17 (dq, 1H, *J* = 6.3, 3.6 Hz), 5.14–5.69 (m, 3H); IR (KBr)1740 (br) cm^{-1}. Anal. Calcd for $C_{18}H_{33}NO_3Si$: C, 63.67; H, 9.80; N, 4.13. Found: C, 63.41; H, 9.92; N, 3.93.

(5*S*,6*R*,7*S*)-6-[(1′*R*)-1′-*tert*-Butyldimethylsilyl)oxy]ethyl]-2,2-dimethyl-3-oxa-7-oxo-1-azabicyclo[4.2.0]octan-5-oic acid (13). A solution of the 5-vinyl isomers **11** (5.14 g, 15.1 mmol) in methanol (50 mL) was cooled to −78 °C. Ozone was bubbled through the solution until a blue coloration persisted. The excess ozone was then removed with argon and dimethyl sulfide (20 mL) was added. The reaction was then left at rt for 19 h after which the solvent was removed. The residue was taken up in ethyl acetate (25 mL) and diazabicyclo[5.4.0]undec-7-ene (0.23 mL, 1.5 mmol) was added. TLC indicated that essentially all of what was initially the major component of the reaction mixture [R_f 0.56 (ethyl acetate:hexane = 1:1)] is converted into what was initially the minor component (R_f 0.43) within 1 h at rt. The reaction was diluted with hexane (50 mL) and was washed with aqueous HCl solution (5%, 5 mL), saturated aqueous $NaHCO_3$ solution (10 mL), water (10 mL), and brine (10 mL). Drying (Na_2SO_4) and removal of the solvent left the crude 5*S*-aldehyde **12** as an oil. A sample was purified by chromatography: ^{1}H NMR ($CDCl_3$) 0.05 (s, 3H), 0.07 (s, 3H) 0.86 (s, 9H), 1.20 (d, 1H, *J* = 6.3 Hz), 1.38 (s, 3H), 1.74 (s, 3H), 2.80 (ddt, 1H, *J* = 10.1, 4.5, 1.1 Hz), 2.90 (dd, 1H, *J* = 3.6, 1.7 Hz), 3.75-3.87 (m, 2H), 4.09 (dd, 1H, *J* = 12.2, 4.5 Hz), 4.20 (dq, 1H, *J* = 6.3, 3.6 Hz), 9.77 (br s, 1H). The crude 5*S*-aldehyde **12** was taken up in acetone (50 mL). This was cooled in an ice bath and Jones reagent (5 mL) was added portionwise. After 15 min, the reaction was partitioned between ethyl acetate (100 mL) and water (25 mL). Sufficient solid $NaHSO_3$ was added to decolorize the aqueous phase. The latter was separated and extracted with ethyl acetate. The combined organic phases were washed with brine and dried (Na_2SO_4), and the solvent was removed. The residual material was dissolved in ethyl acetate (25 mL) and extracted with quantities of saturated aqueous $NaHCO_3$ solution. The pH of the combined aqueous extracts was adjusted to 2.5 by the addition of aqueous HCl solution (10%). This was extracted with ethyl acetate and the combined extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent left the acid **13** as an oil which crystallized on standing (2.76 g, 51%): mp 115–117 °C; $[\alpha]^{23}_D$ −48° (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$ + 1 drop D_2O) 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 1.19 (d, 3H, *J* = 6.4 Hz), 1.41 (s, 3H), 1.74 (s, 3H), 2.73 (ddd, 1H, *J* = 11.0, 10.2, 4.5 Hz), 2.96 (dd, 1H, *J* = 1.5, 2.8 Hz), 3.89 (dd, 1H, *J* = 12.2, 11.0 Hz), 4.06 (dd, 1H, *J* = 12.2, 4.5 Hz), 4.23 (dq, 1H, *J* = 6.4, 2.8 Hz); IR (KBr) 3000 (br), 1740 (br) cm^{-1}. Anal. Calcd for $C_{17}H_{31}NO_5Si$: C, 57.11; H, 8.74; N, 3.93. Found: C, 56.85; H, 8.31; N, 3.99.

(5*S*,6*R*,7*S*)-6-[(1′*R*)-1′-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-5-[2′-(allyloxycarbonyl)-2′-diazo-1′-oxoethyl]-2,2-dimethyl-3-oxa-7-oxo-1-azabicyclo[4.2.0]octane (15). Carbonyldiimidazole (1.20 g, 8.95 mmol) was added to a solution of the acid (**13**) (2.66 g, 7.46 mmol) in dry acetonitrile (10 mL) and a gentle evolution of gas ensued. After 0.5 h, the solvent was removed and the residue was dissolved in dry benzene (20 mL). Magnesium monoallyl malonate (3.00 g, 9.70 mmol) was suspended in benzene (75 mL) and about 25 mL of the solvent was removed by distillation. The resulting clear solution was added to the solution of the acylimidazole and the mixture was heated at reflux for 0.5 h. After cooling to rt, the reaction was diluted with ethyl acetate (50 mL) and washed with an aqueous HCl solution (20 mL, 5%), a saturated aqueous $NaHCO_3$ solution (5 mL), water (10 mL), and brine (10 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed. Chromatography afforded (5*S*,6*R*,7*S*)-6-[(1′*R*)-1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]-5-[2′-(allyloxycarbonyl)-1′-oxoethyl]-2,2-dimethyl-3-oxa-7-oxo-1-azabicyclo-[4.2.0]octane (**14**) (2.42 g, 74%) as an oil: R_f (ethyl acetate:hexane = 1:2) 0.59; ^{1}H NMR ($CDCl_3$, 1:2 mixture of keto:enol isomers) 0.03, 0.04, and 0.05 (3S, 6H), 0.84 and 0.85 (2S, 9H), 1.13 (2d, 3H), 1.38 (s, 1H), 1.42 (s, 2H), 1.73 (s, 3H), 2.41 (dt, 0.3H, *J* = 10.2, 4.9 Hz), 2.83 (dd, 0.3H, *J* = 3.9, 1.5 Hz), 2.89 (dd, 0.7H, *J* = 4.0, 1.6 Hz), 3.03 (dt, 0.7H, *J* = 10.4, 4.3 Hz), 3.53 (s, 1.3H), 3.63–4.04 (m, 3H), 4.15 (dq, 1H, *J* = 4.0, 6.2 Hz), 4.63 (m, 2H), 5.10 (s, 0.7H), 5.23–6.00 (m, 3H); IR (film) 1755, 1710, 1635 cm^{-1}. This was mixed with a solution of toluenesulfonyl azide (5.5 mL, 1.0 M in acetonitrile, 5.5 mmol) and cooled in an ice bath. Triethylamine (0.77 mL, 5.5 mmol) was added and, after a few minutes, the reaction was removed from the bath. After 0.5 h, the solvent was removed and the residue was suspended in hexane. This was filtered and the solid was washed with hexane. The solvent was removed from the filtrate and the residue was chromatographed to afford the diazo derivative (**15**) (2.28 g, 89%) as an oil: $[\alpha]^{23}_D$ −46° (*c* 6.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 0.04 (s, 3H), 0.45 (s, 3H), 0.85 (s, 9H), 1.10 (d, 3H, *J* = 6.2 Hz), 1.42 (s, 3H), 1.75 (s, 3H), 2.78 (dd, 1H, *J* = 0.9, 4.1 Hz), 3.71–3.96 (m, 4H), 4.13 (dq, 1H, *J* = 6.2, 4.1 Hz), 4.73–6.04 (m, 5H); IR (film) 2140, 1760, 1720, 1650 cm^{-1}. Anal. Calcd for $C_{22}H_{35}N3O_6Si$: C, 56.73; H, 7.58; N, 9.03. Found: C, 56.82; H, 7.53; N, 8.60.

Sodium (6*S*,5*S*,4*S*)-6-[(1′(*R*)-Hydroxyethyl)-4-(hydroxymethyl)-8-oxo-3-[2-pyridinylmethyl)thio]-1-azabicyclo[3.2.0]-hept-2-en-2-oate (20). The diazo compound **15** (2.28 g, 4.90 mmol) was dissolved in a mixture of acetic acid (24 mL) and water (6 mL). This was heated at 70 °C for 10 h. The solvents were removed and the residue was chromatographed to afford (3*S*,3*R*)-4-[(1′*S*)-3′-(allyloxycarbonyl)-3′-diazo-1′-(hydroxymethyl)-2′-oxopropyl]-3-[(1′*R*)-1′-hydroxyethyl]azetidin-2-one (**16**) (1.16 g, 76%) as an oil: $[\alpha]^{23}_D$ −83° (*c* 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$ + 1 drop D_2O) 1.32 (d, 3H, *J* = 6.4 Hz), 3.07 (dd, 1H, *J* = 8.2, 1.4 Hz), 3.40–4.01 (m, 4H), 4.10 (dq, 1H, *J* = 6.4, 8.2 Hz), 4.73–6.04 (m, 5H); IR (film) 3360, 2150, 1730, 1640 cm^{-1}. A solution of this diol (**16**) (2.46 g, 0.79 mmol) in dry CH_2Cl_2 (3 mL) was cooled to −15 °C and *N*-(trimethylsilyl)imidazole (116 μL, 0.79 mmol) was added. The reaction was allowed to warm to rt, diluted with CH_2Cl_2, and washed with water. After drying with Na_2SO_4, the solvent was removed and the residue was rapidly chromatographed to give (3*S*,3*R*)-4-[(1′*S*)-3′-(allyloxycarbonyl)-3′-diazo-1′-[(trimethylsilyl)oxy]-2′-oxopropyl]-3-[(1′*R*)-1′-hydroxyethyl]-azetidin-2-one (**17**) as an oil (185 mg): R_f (ethyl acetate:methanol = 9:1) 0.78. This derivative (185 mg, 0.48 mmol) and rhodium-(II) octanoate dimer (10 mg) were dissolved in benzene (10 mL) and the solution was brought to a gentle reflux. After 5 min, the solvent was removed and the residue was dissolved in dry

acetonitrile (2 mL). The reaction was cooled in an ice bath and diphenyl chlorophosphate (103 μL, 0.50 mmol), diisopropylethylamine (89 μL, 0.50 mmol), and *p*-(dimethylamino)pyridine (pinch) were added. After 0.5 h, 2-picolinethiol (97 μL, 0.77 mmol) and diisopropylethylamine (89 μL, 0.50 mmol) were added and the reaction was cooled to −20 °C. After 18 h, the reaction was diluted with ethyl acetate and washed with water (3 mL) and a phosphate buffer solution (pH 7.0, 0.05 M, 3 mL). Drying (Na_2SO_4) followed by removal of the solvent left an oil which was chromatographed [silica gel, elution with cold (4 °C) mixtures of ethyl acetate:hexane = 1:1 followed by ethyl acetate:methanol = 9:1] to give slightly impure allyl (6*S*,5*S*,4*S*)-6-[(1′*R*)-hydroxyethyl]-8-oxo-3-[(2-pyridinylmethyl)thio]-4-[[(trimethylsilyl)oxy]methyl]-1-azabicyclo[3.2.0]hept-en-2-oate (**18**) (96 mg, 0.21 mmol): R_f (ethyl acetate) 0.30. A solution of **18** in a mixture of tetrahydrofuran and water (1.5 mL, 2:1) was cooled in an ice bath and acetic acid (60 μL, 5 equiv) was added. After 3 h, a solution of phosphate buffer (1.5 mL, 0.2 M, pH 8.0) was added and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and dried (Na_2SO_4). Removal of the solvents followed by flash chromatography [silica gel, eluted with a cold (4 °C) mixture of ethyl acetate:methanol = 9:1) afforded slightly impure allyl (6*S*,5*S*,4*S*)-6-[(1′*R*)-hydroxyethyl]-4-(hydroxymethyl)-8-oxo-3-[(2-pyridinylmethyl)thio]-1-azabicyclo[3.2.0]hept-2-en-2-oate (**19**) (32 mg, 0.11 mmol) as an oil: R_f (ethyl acetate:methanol = 9:1) 0.02. The allyl ester **19** and *N*-methylaniline (18 μL, 0.17 mmol) were dissolved in dry tetrahydrofuran (1.5 mL) and this was added via cannula to a yellow solution of bis(dibenzylideneacetone)palladium(0) (6.3 mg, 0.01 mmol) and triphenylphoshine (12 mg, 0.04 mmol) in THF (1.5 mL) under Ar. After 10 min, the reaction was cooled in an ice bath, and diethyl ether (4 mL) and water (4 mL) were added. The pH of the aqueous phase was adjusted to 7.0 by the addition of saturated aqueous $NaHCO_3$. The aqueous phase was separated, residual organic solvent was removed under high vacuum, and the water was removed by lyophilization. The residue was chromatographed (reverse phase silica gel, eluted with cold water (4 °C) and then a cold mixture of acetonitrile:water = 1:9) to afford, after lyophilization, the product (**20**) (about 90% pure by ^1H NMR) as a tan-colored solid (17 mg, 10%): R_f (reverse phase TLC, acetonitrile:water = 1:9) 0.72; ^1H NMR (D_2O) 1.28 (d, 3H, J = 6.3 Hz), 3.35 (m, 1H, J = 5.7, 2.1, 9.3 Hz), 3.55 (dd, 1H, J = 6.1, 2.6 Hz), 3.77 (dq, 2H, δ_A=3.78, δ_B=3.76, J_{AB} = 1.2 Hz, J_{AX} = 5.7 Hz, J_{BX} = 2.1 Hz), 4.70 (dd, 1H, J = 2.6, 9.3 Hz), 4.11 (d, 1H, J = 14.3 Hz), 4.21 (d, 1H, 14.3 Hz), 4.23 (dq, 1H, J = 6.3, 6.1 Hz), 7.35–8.47 (m, 4H); IR (KBr disk) 3499 (br), 1750, 1600 cm^{-1}; UV (phosphate buffer, 0.07 M, pH 7.4) 304 nm (ε 6600).

Alternative Synthesis of (5*S*,6*R*,7*S*)-5-[2′-(allyloxycarbonyl)-1′-oxoethyl]-2,2-dimethyl-3-oxa-7-oxo-1-azabicyclo[4.2.0]octane (14). A solution of 3-(allyloxycarbonyl)-3-diazo-2-oxopropane (6.9 g, 41 mmol) and allyl alcohol (8.4 mL, 123 mmol) in dry THF (100 mL) under Ar was cooled to −78 °C. A solution of *n*-butyllithium (2.57 mL, 1.6 M in hexanes, 41 mmol) was added slowly and the reaction was left for 1 h. The reaction was then allowed to warm to rt over 0.5 h. Saturated aqueous NH_4Cl solution (200 mL) was added and the mixture was extracted with diethyl ether (3 × 100 mL). The combined extracts were washed with brine (3 × 50 mL) and dried (Na_2SO_4) and the solvents were removed. The residue was chromatographed to afford allyl diazoacetate (3.87 g, 75%) as a pale orange oil: R_f (ethyl acetate:hexane = 1:4) 0.57; ^1H NMR ($CDCl_3$) 4.66 (dt, 2H, J = 1.4, 5.7 Hz), 4.77 (s, 1H), 5.21–6.02 (m, 3H). A solution of the 5*S*-aldehyde **12** (239 mg, 0.71 mmol) in dry CH_2Cl_2 (2 mL) was added to a mixture of allyl diazoacetate (97 mg, 0.78 mmol) and stannous chloride (133 mg, 0.71 mmol) in dry CH_2Cl_2 (2 mL). A slow evolution of nitrogen was observed and the reaction was left for 5 h. Brine (5 mL) was added and the reaction was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and filtered through a Celite plug. Removal of the solvent followed by chromatography (preparative silica gel TLC developed with ethyl acetate:hexane = 1:4) afforded the keto ester **14** (152 mg, 49%).

Supplementary Material Available: Copy of the ^1H NMR spectrum of **20** (1 page). 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.