A Stereocontrolled Synthesis of an Important Intermediate for the Preparation of 1β-Methylcarbapenem Antibiotics

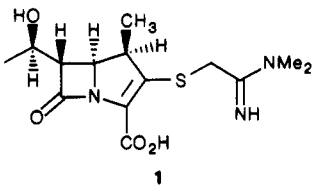
L. M. Fuentes,* I. Shinkai, A. King, R. Purick, R. A. Reamer, S. M. Schmitt,* L. Cama, and B. G. Christensen

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

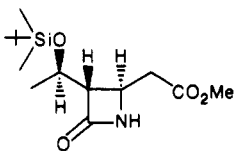
Received February 10, 1987

A stereocontrolled chiral synthesis of the 1β-methylcarbapenem antibiotic precursor **3b** has been accomplished. The factors influencing the stereochemical outcome of the catalytic hydrogenation of the 1-azabicyclo[4.2.0]octanes **4** and **12** are presented.

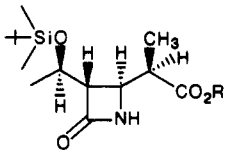
Relative to thienamycin[1] and *N*-formidoylthienamycin (MK-0787)[2] the 1β-methylcarbapenem (−)-(1*R*,1'*R*,5*S*,6*S*)-2-[(2-*N*,*N*-dimethylamino)-2-iminoethyl)-thio]-6-(1-hydroxyethyl)-1-methylcarbapenem (**1**) possesses improved chemical stability at high concentrations and decreased susceptibility to renal dipeptidase-I while it retains an excellent antibacterial profile.[3] Although the synthesis of **1** via the key intermediates **2** and **3a,b** has been reported recently,[3] the methodology employed required epimerization, chromatographic separation, and recycling steps. Thus, stereochemical control of the methylation of **2** remains a critical problem.[4]



1



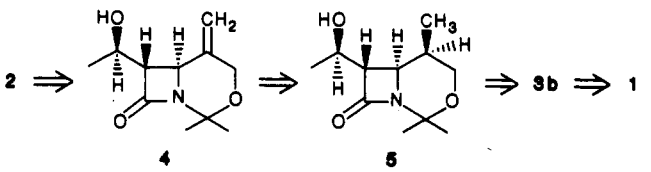
2



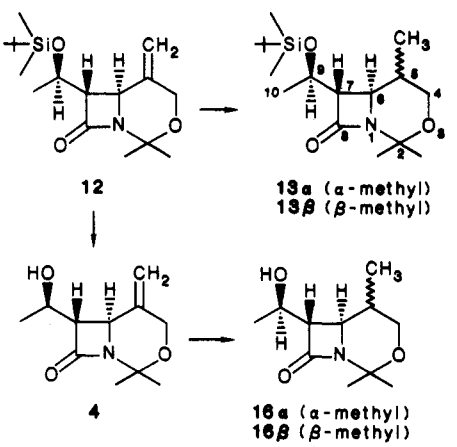
3a, R = Me
b, R = H

We have tried to solve this problem by taking advantage of our previous experience with 1-azabicyclo[4.2.0]octanes.[5a,b] It seemed likely that the catalytic hydrogenation of an exocyclic double bond such as that present in the rigid bicyclic acetonide **4** should proceed at the less sterically hindered α face to give predominantly the 1β-methyl intermediate **5** (Scheme I). Silylation and oxidative hydrolysis of **5** should then give the carboxylic acid **3b**. In this paper, we describe the conversion of the known intermediate **2** to the 1-azabicyclo[4.2.0]octane **4** and the successful application of the strategy depicted in Scheme I which allowed the stereocontrolled synthesis of **3b**, a key intermediate in the preparation of 1β-methylcarbapenem antibiotics.

Scheme I



Scheme II



Results and Discussion

Our synthesis of bicyclic acetonide **4** commenced with the methylation of **2** followed by phenylselenation, thus providing the requisite functionality for later establishment of the exocyclic double bond. Specifically, the dianion of **2**, generated with 2 equiv of lithium diisopropylamide (LDA) in THF containing 1 equiv of HMPA at −78 °C, has been alkylated by using excess methyl iodide to give the α and β isomers **6a,b** (4:1) in 75% yield.[3] When potassium hexamethyldisilazide (KHMD) was used instead of LDA/HMPA, the desired methylation product was obtained in an improved yield of 89.8% (**6a**/**6b**; 93:7). The dianion of **6a**, prepared at −78 °C by using LDA/HMPA was then reacted with diphenyl diselenide[6] to give a

(1) (a) Kropp, H.; Kahan, J. S.; Kahan, F. M.; Sundelof, J.; Darland, G.; Birnbaum, J. *16th Interscience Conference on Antimicrobial Agents and Chemotherapy*, Chicago, IL, 1976; Abstract 228. (b) Kahan, J.; 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. (c) Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirschfield, 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.

(2) Leanza, W. J.; Wildonger, K. J.; Miller, T. W.; Christensen, B. G. *J. Med. Chem.* **1979**, *22*, 1435. Kropp, H.; Sundelof, J. G.; Hajdu, R.; Kahan, F. M. *Antimicrob. Agents Chemother.* **1982**, *22*, 62.

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

(4) Alternate efficient methods to prepare 1β-methylcarbapenems exist: (a) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *19*, 2149. (b) 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. (c) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675.

(5) (a) Bouffard, F. A.; Johnston, D. B. R.; Christensen, b. G. *J. Org. Chem.* **1980**, *45*, 1130. (b) Shih, D. H.; Fayter, J. A.; Cama, L. D.; Christensen, B. G.; Hirschfield, J. *Tetrahedron Lett.* **1985**, *26*, 583.

(6) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049 and references therein.

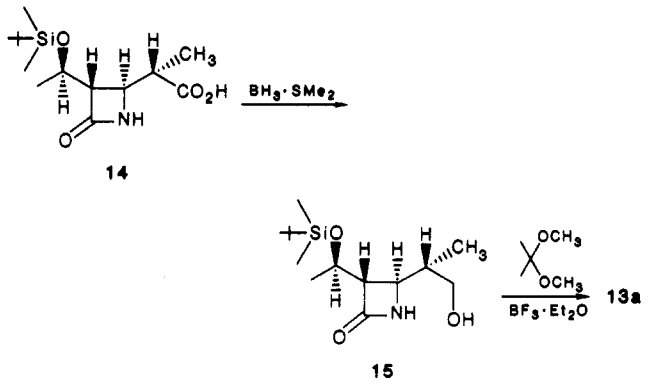
0022-3263/87/1952-2563$01.50/0

Table I. Product Ratios 16β/16α Obtained in the Stereocontrolled Hydrogenation of 4 to 16β under Varying Conditions

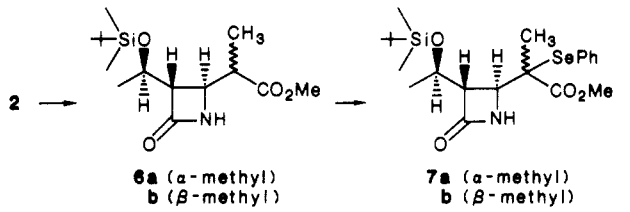
run	press., psig	solv	T,[f] °C	t, h	catal	16β/16α
1	40	EtOAc	r.t.	2.5	PtO_2	60/40[a]
2	40	EtOAc–C_6H_6	r.t.	48	$(Ph_3P)_3RhCl$	65/35[a]
3	40	EtOAc	r.t.	2.5	10% Pd/C	75/25[a]
4	40	Me_2SO	r.t.	24	1,1′-$Cp_2Fe(PH_2P)_2PdCl_2$	[g]
5	40	EtOH	r.t.	22	Ni_2B	[g]
6	40	MeOH	r.t.	6	5% Rh/Al_2O_3	85/15[b]
7	1380	MeOH	−40 to r.t.	22	5% Ru/C[c]	50/50[b]
8	40	EtOH	r.t.	5	RaNi(EtOH)[d]	91/9[b]
9	40	EtOAc	r.t.	4	RaNi(EtOAc)[e]	79/21[b]
10	40	EtOH	r.t.	4	RaNi(EtOAc)[e]	92/8[b]
11	40	MeOH	r.t.	4	RaNi(EtOAc)[e]	92/8[b]
12	2	EtOH	r.t.	5	RaNi(EtOAc)[e]	93/7[b]
13	atmos	MeOH	0	4	RaNi(EtOAc)[e]	95/5[b]
14	atmos	MeOH	−10	3	RaNi(EtOAc)[e]	94/6[b]

[a] Ratio determined by 300-MHz NMR. [b] Ratio determined by 250-MHz NMR and HPLC. [c] Hydrogenation was incomplete; 12.1% of 4 remained. [d] Catalyst washed with EtOH only. [e] Catalyst washed with EtOH and then washed and stored in EtOAc. [f] r.t. = room temperature. [g] No reaction.

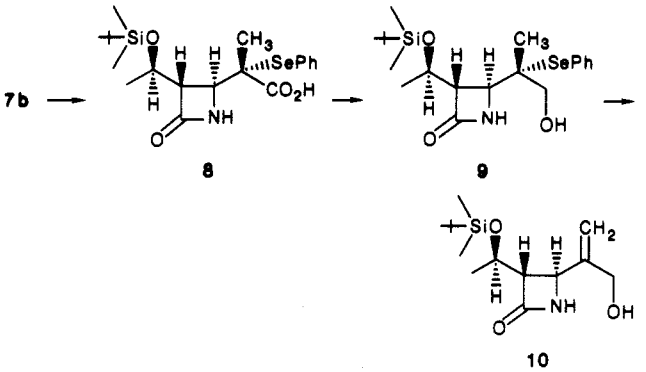
Scheme III



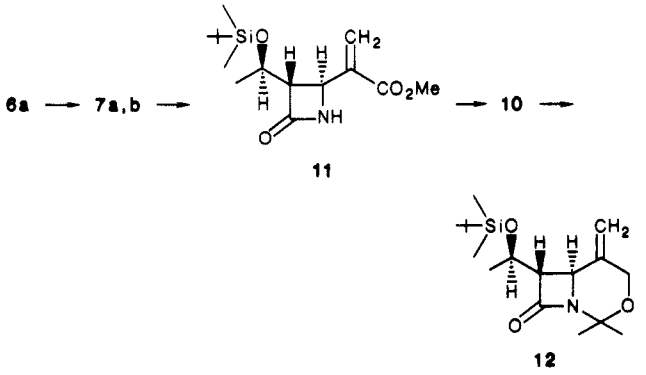
chromatographically separable mixture of diastereomeric phenylselenyl compounds **7a,b** (1:3.4) in 69% yield.



The major phenylselenyl isomer[7] **7b** was saponified with NaOH in aqueous MeOH at 60 °C to give the acid **8** (69%), which was reduced to the alcohol **9** (75%) by using borane–methyl sulfide complex in THF.[8] Oxidative elimination of the selenyl group of **9** with 30% H_2O_2/HOAc[6] in THF at 0 °C provided the allylic alcohol **10** (78%). The minor isomer **7a** was similarly treated to give **10** in comparable yield. The need for a more efficient route to intermediate **10** was clear.



An alternate approach involving the reaction of **6a** with LDA at −40 °C followed by treatment with PhSeX (X = Cl, Br) afforded the phenylselenated material **7a,b** in an improved yield (96%). Oxidation of the crude mixture of diastereoisomers at 0 °C with 30% H_2O_2 in CH_2Cl_2 gave the α,β-unsaturated ester **11** in quantitative yield. Reduction of **11** to **10** with DIBAL proceeded smoothly in 86% yield at ambient temperature.[9] This improved route allowed the preparation of **10** from **2** in 74% overall yield. The reaction of **10** with 2,2-dimethoxypropane in CH_2Cl_2 in the presence of $BF_3{\cdot}Et_2O$[5a] then provided the bicyclic acetonide **12** (89%), a suitable species for the proposed hydrogenation studies.



Our first attempted hydrogenation of the double bond of **12** was run at 40 psig H_2 in ethyl acetate with platinum

(7) Proton NMR NOE difference spectroscopy was used to determine the stereochemistry of the methyl and phenylselenyl moieties in **7a** and **7b**. Experiments were performed on a degassed $CDCl_3$ solution containing both isomers where all pertinent resonances were well resolved. Enhancements at the β-lactam 3- and 4-ring protons upon irradiation of the C-CH_3 adjacent to C-4 were as follows:

	7b (major)[a]	7a (minor)[a]
3-H	12.1%	9.6%
4-H	5.0%	6.6%

[a] Values are corrected for residual signal in NOE difference "on-resonance" spectra.

Since the two ring protons show significant NOE's in both isomers, almost free rotation of the ester side chain is indicated. However, a conformational preference due to hydrogen bonding of the amide NH with the ester carbonyl could explain the incrementally greater enhancement at 3-H in **7b** as the β-methyl isomer. The NOE data for **7a** complement that for **7b** and is consistent with this interpretation.

(8) Lane, C. F.; Myatt, H. L.; Daniels, J.; Hopps, H. B. *J. Org. Chem.* **1974**, *39*, 3052.

(9) When run at −78 °C, the reduction stopped at the aldehyde stage.

oxide as the catalyst (see Scheme II). A mixture of methyl compounds **13α** and **13β** (6:1) resulted. The predominance of the α-methyl product **13α** was evident upon comparison of the 300-MHz NMR of the reduction mixture with that of authentic **13α** derived from the known carboxylic acid **14**[10] via alcohol **15** (see Scheme III). Presuming that the presence of the bulky *tert*-butyldimethylsilyl protecting group has precluded the desired reduction at the α face, **12** was desilylated by treating with Bu_4NF in DMF to give **4** in 73% yield.

The results of a number of catalytic reductions of **4** are presented in Table I. The hydrogenation conditions used in run 1 were identical with those previously used on the *tert*-butyldimethylsilyl-protected species **12**. In the absence of the bulky protecting group, reduction did occur predominantly from the α face to give a much improved β/α product ratio (**16β/16α**; 60:40). A variety of hydrogenation catalysts were then tried as indicated in runs 2–8. Reduction run 8 in the presence of Raney nickel (40 psig H_2, 5 h, EtOH) provided a much improved β/α ratio (**16β/16α**; 90.5:9.5) and established Raney nickel as the catalyst of choice. Variations in solvent, pressure, and temperature were then explored. We speculated that the use of a nonhydroxylic solvent would, by enhancing the intramolecular hydrogen bonding between the hydroxyl group and the β-lactam carbonyl, increase the structural rigidity of the molecule and consequently provide greater stereoselective adsorption onto the surface of the catalyst. Therefore, run 9 was performed in ethyl acetate using Raney nickel, previously washed and aged in ethyl acetate. Contrary to the above theory, the β/α ratio dropped significantly (**16β/16α**; 78.6:21.4). Reductions (runs 10 and 11) with similarly treated Raney nickel but with EtOH or MeOH as the solvent again provided high β/α ratios (**16β/16α**; 91.7:8.3 and 91.5:8.5). These results suggested that interfering with, rather than enhancing, the intramolecular hydrogen bonding was advantageous. Therefore, the disrupting influence of a hydroxylic solvent on intramolecular bonding may give the α-hydroxyethyl side chain freedom to adsorb on the catalyst. Hydrogenation then proceeds predominantly at the α face of the molecule resulting in a much improved β/α product ratio. A decrease in H_2 pressure to 2 psig (run 12) gave a slightly improved ratio (**16β/16α**; 92.8:7.2). Finally, run 13 was carried out at atmospheric pressure and 0 °C and provided the best product ratio yet observed (**16β/16α**; 94.9:6.1). Further lowering of the reduction temperature to −10 °C (run 14) gave no further improvement in the β/α ratio.

Silylation of **16β/16α** to **13β/13α** (94.6/5.4) in DMF with *t*-$BuMe_2SiCl/Et_3N$ proceeded smoothly in 82% isolated yield at ambient temperature. Oxidation of **13β/13α** with Jones reagent in acetone at 0 °C provided the key carboxylic acid **3b** (96.8:3.2)[11] in 95% yield after chromatography. No epimerization was observed during the oxidation.

Conclusion

An efficient preparation of intermediate **4** has been described. Conditions have been developed for the hydrogenation of the exocyclic double bond present in **4** to the 1β-methyl species **16β** with excellent stereocontrol. The reduction product was then easily converted to **3b**, an important intermediate for the preparation of 1β-methylcarbapenem antibiotics.

Experimental Section

Instrumentation. Infrared spectra were recorded on Perkin-Elmer 237B and 137 grating spectrophotomers. ^1H NMR spectra were recorded on Bruker WM-250 (250 MHz), Varian XL-200 (200 MHz), and Varian SC-300 (300 MHz) spectrometers. ^{13}C NMR spectra were determined on a Varian CFT-20 (20 MHz) spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane. Melting points and boiling points are uncorrected. Optical rotation measurements were taken on a Perkin-Elmer 241 polarimeter. Mass spectra were obtained on a LKB Model 9000 spectrometer at 70 V ionization energy. All reported elemental analyses are within ±0.4% of the calculated values.

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. THF was freshly distilled from LAH or dried over 3A sieves. Diisopropylamine was distilled from CaH_2 or dried over 3A sieves. Triethylamine was dried over 3A sieves. Alkyllithium reagents were titrated with 2,5-dimethoxybenzyl alcohol.[12]

General Procedures. All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Reaction mixtures were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated by using a Buchi rotatory evaporator at 15–25 mmHg at ambient temperature. Column chromatography was performed with Baker (60–200 mesh) or E. Merck (230–400 mesh) silica gel. Radial preparative thin-layer chromatography was carried out with a Harrison Research, Inc., Chromatotron on plates coated with E. Merck PF-254 silica gel. Normal preparative thin-layer chromatography was performed on 1000 m Analtech silica gel GF plates.

Preparation of the α-Methyl Ester 6. In a 25-mL one-neck round-bottomed flask, equipped with a magnetic stirring bar, septum, and N_2 inlet needle, were placed 193.2 mg (0.640 mmol) of **2** and 3 mL of dry THF. The solution was cooled to −78 °C, and then 2.44 mL of 0.66 M KHMDS in toluene (1.61 mmol, Callery) was added slowly via syringe. After the addition was complete, the temperature was raised to −50 °C. Because the reaction mixture had a jellylike consistency, 2 mL dry THF was added to solubilize the contents. The mixture was stirred at −50 °C for an hour then cooled to −78 °C. To the stirred mixture was added 0.10 mL (227.5 mg, 1.602 mmol) of methyl iodide (Aldrich) over a 25-min period, during which a precipitate was formed. The reaction mixture was then stirred at −78 °C for an additional hour. The reaction was then quenched with 5% aqueous NH_4Cl, warmed to ambient temperature, and transferred to a separatory funnel containing 20 mL of CH_2Cl_2. The layers were separated, and the organic layer was washed with H_2O (20 mL). The organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (230–400 mesh) using 60:40 hexane/ethyl acetate to give 174.2 mg (89.8%) as a white solid. Analysis by liquid chromatography using Altex Ultrasphere-Octyl, 5, 25 cm × 4.6 mm i.d. column and eluting with a solvent system of actonitrile/water/H_3PO_4 (60:40:1) showed a weight ratio of α/β epimers of 93:7. The physical properties of the diastereoisomers were identical with those reported in ref 3.

Preparation of the Phenylselenyl Ester 7. Method A. Diisopropylamine (2.68 mL, 19.2 mmol) and 40 mL dry THF were placed in a 100-mL round-bottom flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C, and 9.2 mL of 2.1 M *n*-BuLi in hexanes (19.3 mmol, Aldrich) was added. The temperature was then lowered to −78 °C, and 3.4 mL of HMPA was added. After 5 min, a solution of **6a** (2.0 g, 6.35 mmol) in dry THF (10 mL) was added dropwise, and the reaction mixture was then aged for 40 min. A solution of PhSeSePh (3.06 g, 9.81 mmol) in THF (8 mL) was added, and stirring was continued for

(10) Shih, D. H.; Cama, L.; Christensen, B. G. *Tetrahedron Lett.* **1985**, *26*, 587.

(11) Separation of the small amount of α isomer present was not necessary since later in the synthesis of 1β-methylcarbapanem antibiotics, only the β-isomer is efficiently converted to the final product via thiol displacement of an enol phosphate (ref 10).

(12) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.

1 h at −78 °C. The reaction mixture was then poured into 1 M KH_2PO_4 (40 mL), H_2O (400 mL) and Et_2O (200 mL). The layers were separated and the aqueous back-extracted with Et_2O (100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give 4.75 g of crude **7** as a mixture of diastereoisomers. The material was purified by chromatography on silica gel (60–200 mesh) gradually eluting with 0–50% EtOAc/CH_2Cl_2 to give 0.47 g of **7a** (16%), 1.58 g of **7b** (53%), and 0.35 g recovered starting material **6** (18%).

Method B. In a 250-mL round-bottom flask, equipped with a magnetic stirring bar, septum, dropping funnel, and N_2 inlet, were placed 21.6 mL of diisopropylamine (153.9 mmol) and 80 mL dry THF. The solution was cooled to 0 °C, and 70 mL of 1.84 M *n*-BuLi in hexanes (128.8 mmol) was added via syringe. The temperature was then lowered to −50 °C, and 16.2 g of **6a** (51.4 mmol) was added as a solid, via a side arm. Dry THF (40 mL) was then added to aid dissolution, and the reaction mixtures was aged at −45 °C (±5 °C) for 3.5 h. A solution of PhSeCl (24.6 g, 128 mmol) in dry THF (40 mL) was added dropwise over 25 min at −70 to −75 °C. After the mixture was stirred for 15–20 min at −78 °C, 0.5 N HCl (150 mL) was added, and the reaction contents were allowed to warm to room temperature. An additional 100 mL of 0.5 N HCl was then added, and the reaction mixture was poured into a separatory funnel containing Et_2O (200 mL). The organic layer was separated and the aqueous back-extracted with Et_2O (100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure to give crude **7**. The crude material was treated with hexane at ambient temperature to yield 8.7 g of the major isomer **7b** (crystallized out). The hexane filtrate was concentrated and purified by chromatography on silica gel (60–200 mesh) gradually eluting with hexane and then with 1:1 EtOAc/hexanes to provide a mixture of the diastereoisomers **7a**/**7b** in 55:45 ratio (14.5 g). The total weight of **7** was 23.2 g (96%).

7a: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67–7.32 (m, 5 H, Ar H), 6.05 (br s, 1 H, NH), 4.27 (m, 1 H, CH_3CHOSi), 4.00 (d, 1 H, *J* = 2 Hz, H_4), 3.68 (s, 3 H, OCH_3), 3.18 (m, 1 H, H_3), 1.48 (s, 3 H, CH_3CSePh), 1.22 (d, 3 H, CH_3CHOSi), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); IR (CH_2Cl_2) 3400 (NH), 1769 (β-lactam C=O), 1725 ester C=O) cm^{-1}; mp 128–130 °C (hexane). Anal. Calcd for $C_{21}H_{33}NO_4SeCi$: C, 53.60; H, 7.07; N, 2.98. Found: C, 53.68; H, 7.2; N, 2.91.

7b: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69–7.30 (m, 5 H, Ar H); 5.80 (br s, 1 H, NH), 4.26 (m, 1 H, CH_3CHOSi), 4.22 (d, 1 H, *J* = 2 Hz, H_4), 3.62 (s, 3 H, OCH_3), 3.06 (m, 1 H, H_3), 1.53 (s, 3 H, CH_3CSePh), 1.31 (d, 3 H, CH_3CHOSi), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.04 and 0.08 (2 s, 6 H, $Si(CH_3)_2$); IR (CH_2Cl_2) 3400 (NH), 1769 (β-lactam C=O), 1725 (ester C=O) cm^{-1}; mp 115–118 °C (hexane). Anal. Calcd for $C_{21}H_{33}NO_4SeSi$: C, 53.60; H, 7.07; N, 2.98. Found: C, 53.76; H, 7.28; N, 2.87.

Preparation of the Phenylselenyl Acid 8. A solution of **7b** (0.89 g, 1.9 mmol) in 23 mL of 4:1 MeOH/H_2O was placed in a 50-mL, one-neck, round-bottom flask, equipped with a magnetic stirring bar, a condenser, and N_2 inlet. To the solution was added 1.6 mL of 2.8 N NaOH (4.5 mmol) and the resultant mixture heated at 60 °C for 2 h. Upon cooling to ambient temperature, the reaction was poured into 2 N HCl (5 mL), H_2O (60 mL), and EtOAc (60 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (60 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide 0.84 g of crude **8**. Crude **8** was dissolved in $CHCl_3$, decolorized with charcoal and concentrated under reduced pressure. Recrystallization of the residue from Et_2O provided 0.43 g of **8** (50%). A second crop afforded 0.16 g (19%) additional material: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.31 (m, 5 H, Ar H), 6.31 (br s, 1 H, NH), 4.25 (m, 1 H, CH_3CHOSi), 4.17 (d, 1 H, *J* = 2 Hz, H_4), 3.15 (m, 1 H, H_3), 1.52 (s, 3 H, CH_3CSePh), 1.27 (d, 3 H, CH_3CHOSi), 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.06 and 0.02 (2 s, 6 H, $Si(CH_3)_2$); IR (CH_2Cl_2) 1760, 1740 (carbonyls) cm^{-1}; mp 172–176 °C (ether). Anal. Calcd for $C_{20}H_{31}NO_4SeSi$: C, 52.62; H, 6.85; N, 3.07. Found: C, 52.77; H, 6.82; N, 2.93.

Preparation of the Phenylselenyl Alcohol 9. At 0 °C under N_2, a 10 M solution of BH_3·SMe_2 complex (0.38 mL, 3.80 mmol, Aldrich) was added to a solution of **8** (0.4 g, 0.88 mmol) in 8.5 mL of dry THF. After 5 min the reaction mixture was stirred at ambient temperature for 2.5 h. After recooling to 0 °C, MeOH (4.6 mL) was carefully added to destroy the excess BH_3. The cooling bath was removed after the initial gas evolution, and stirring was continued for 15 min. The reaction was concentrated under reduced pressure and then partitioned between CH_2Cl_2 and brine. The organic phase was separated and the aqueous back-extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.37 g crude **9**. Preparative TLC eluting with 20% EtOAc/CH_2Cl_2 and extracting with 10% MeOH/CH_2Cl_2 provided 0.29 g of **9** (75%) as a white foam: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74–7.32 (m, 5 H, Ar H), 5.64 (br s, 1 H, NH), 4.22 (m, 1 H, CH_3CHOSi), 3.80 (d, 1 H, *J* = 2 Hz, H_4), 3.66 (m, 2 H, CH_2OH), 3.40 (m, 1 H, H_3), 2.76 (dd, 1 H, CH_2OH), 1.35 (d, 3 H, CH_3CHOSi), 1.26 (s, 3 H, CH_3CSe), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.12 and 0.09 (2 s, Si $(CH_3)_2$); IR (CH_2Cl_2) 1760 (β-lactam C=O) cm^{-1}; mass spectrum [of $(Me_3Si)_2$ derivative], *m/z* 530 (MI − *t*-Bu).

Preparation of the Allylic Alcohol 10. Method A. To a solution of **9** (0.29 g, 0.65 mmol) in THF (3.3 mL) at 0 °C were added acetic acid (0.1 mL, 1.7 mmol) and 30% H_2O_2 (0.45 mL, 4.0 mmol). After being stirred at 0 °C for 5 h, the reaction mixture was carefully added to cold, saturated, aqueous $NaHCO_3$ (10 mL) and Et_2O (25 mL). The organic phase was separated and the aqueous back-extracted with Et_2O. The combined organic layers were washed with brine (2×), dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure to give 0.19 g of crude **10**. Preparative TLC eluting with 20% EtOAc/CH_2Cl_2 and extracting with 10% MeOH/CH_2Cl_2 provided 140 mg of **10** (78%) as a crystalline material.

Method B. At −78 °C, 2.8 mL of 1.51 M DIBAL in toluene (4.23 mmol, Aldrich) was added via syringe under moisture exclusion conditions to **11** (320.0 mg, 1.02 mmol) in 5 mL of dry THF. The cooling bath was removed, and the contents were stirred at ambient temperature for 1 h. Isopropyl alcohol (1.0 mL) was added at 0–5 °C, followed by 5% aqueous NH_4Cl, to give a pH 3.5–4.0, and EtOAc was then added to thin the resulting gelatinous mass. After the addition of filter gel and water, the reaction mixture was filtered, and the organic phase was separated. The filter cake was washed with EtOAc. The original organic phase and the EtOAc washings were combined, washed with saturated $NaHCO_3$, brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to yield 250 mg (86%) of **10**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.05 (br s, 1 H, NH), 5.23 and 5.20 (2 br s, CH_2=C), 4.29–4.10 (m, 4 H, H_4, CH_2OH and CH_3CHOSi), 3.05 (m, 1 H, H_3), 2.30 (m, 1 H, CH_2OH), 1.30 (d, 3 H, CH_3CHOSi), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.13 (s, 6 H, $Si(CH_3)_2$); IR (CH_2Cl_2) 1770 (β-lactam C=O) cm^{-1}; mp 130–133.5 °C. Anal. Calcd for $C_{14}H_{27}NO_3Si$: C, 58.89; H, 9.55; N, 4.91. Found: C, 58.85; H, 9.23; N, 4.86.

Preparation of the α,β-Unsaturated Ester 11. To a stirred solution of **7** (0.50 g, 1.06 mmol) in CH_2Cl_2 (15 mL), at ambient temperature, was added 1.0 mL of 30% H_2O_2 dropwise. The reaction proceeded instantly as indicated by the loss of the yellow color. After the addition was completed, the reaction mixture was aged for 0.5 h. The organic phase was separated and washed with 5% $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 320 mg (96.1%) of **11**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.49 (br s, 1 H, NH), 6.35, 5.92 (br s, 2 H, CH_2=C), 4.58 (br s, 1 H, H_4), 4.27 (q of d, 1 H, CH_3CHOSi, *J* = 6.3, 3.6 Hz), 3.80 (s, 3 H, OCH_3), 3.0 (br s, 1 H, H_3) 1.29 (d, 3 H, CH_3CHOSi, *J* = 6.3 Hz), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.07 and 0.06 (s, 6 H, $Si(CH_3)_2$). Anal. Calcd for $C_{15}H_{27}NO_4Si$: C, 57.46; H, 8.70; N, 4.47. Found: C, 57.51; H, 8.54; N, 4.49.

Preparation of Acetonide 12. To a solution of **10** (6.9 g, 24.2 mmol) in sieve-dried CH_2Cl_2 (17.8 mL) were added 2,2-dimethoxypropane (3.5 mL; 28.4 mmol) and BF_3·OEt_2 (0.31 mL). After the mixture was stirred at room temperature under N_2 for 30 min, Et_3N (1.6 mL) was added to complex the BF_3. The reaction mixture was filtered through silica gel (60–200 mesh, eluting with CH_2Cl_2) and the filtrate concentrated in vacuo to give 6.98 g (89%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.08 and 4.96 (2 br s, CH_2=C), 4.34–4.16 (m, CH_3CHOSi, CH_2O, H_6), 3.04 (dd, *J* = 2, 4 Hz, H_7), 1.71 and 1.44 (2 s, $(CH_3)_2C$), 1.25 (d, CH_3CHOSi), 0.88 (s, SiC-

(CH_3)$_3$, 0.08 and 0.07 (2 s, Si(CH_3)$_2$); IR (CH_2Cl_2) 1750 (β-lactam C=O) cm^{-1}; mp 46–48 °C; mass spectrum, m/z 268 (MI – t-Bu), 166 (MI – CH_3CHO-t-BDMSi).

Preparation of Acetonide 4. To a solution of **12** (6.98 g, 21.5 mmol) in anhydrous DMF (70 mL) at 0 °C under N_2 was added 1 N tetrabutylammonium fluoride in THF (23.7 mL), and stirring was continued for 3 h at room temperature. The DMF was removed in vacuo, and the crude product was treated with 150 mL of Et_2O and 100 mL of saturated ammonium chloride. The organic phase was separated and the aqueous back-extracted with Et_2O (100 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography eluting with 40% Hex/EtOAc provided 3.3 g of **4** (73%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.05 (m, CH_2=C), 4.22 (m, CH_3CHOH, CH_2O, H_6), 3.08 (dd, J = 2, 5 Hz, H_7), 2.62 (br, OH), 1.73 and 1.47 (2 s, (CH_3)$_2$C), 1.33 (d, J = 6 Hz, CH_3CHOH); IR (CH_2Cl_2) 3650 (OH), 1746 (β-lactam C=O) cm^{-1}.

Hydrogenation of 12 with PtO_2 to 13α/13β. A mixture of **12** (32 mg, 0.1 mmol), PtO_2 (7 mg), and EtOAc (4 mL) was shaken on a Parr apparatus at room temperature under 40 psig H_2 for 2.5 h. The reaction mixture was then filtered through Celite, rinsing in with additional EtOAc. The filtrate was concentrated in vacuo to provide 31 mg of a mixture of **13α/13β** in a 6:1 ratio: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (m, CH_3CHOSi, of **13α** and **13β**), 3.91 (dd, $J_{4,4}$ = 12.5 Hz, $J_{4,5}$ = 3 Hz, H_4 of **13β**), 3.77 (dd, $J_{6,7}$ = 2 Hz, $J_{6,5}$ = 5 Hz, H_6 of **13β**), 3.66 (dd, $J_{4,4}$ = 12.5 Hz, $J_{4,5}$ = 4 Hz, H_4 of **13α**), 3.54 (dd, $J_{4,4}$ = 12.5 Hz, $J_{4,5}$ = 3 Hz, H_4 of **13β**), 3.41 (t, $J_{4,4}$ = $J_{4,5}$ = 12.5 Hz, H_4 of **13α**), 3.13 (dd, $J_{6,7}$ = 1.5 Hz, $J_{6,5}$ = 10.5 Hz, H_6 of **13α**), 2.94 (dd, $J_{6,7}$ = 2 Hz, $J_{7,9'}$ = 4.5 Hz, H_7 of **13β**), 2.70 (dd, $J_{6,7}$ = 1.5 Hz, $J_{7,9'}$ = 4.5 Hz, H_7 of **13α**), 1.68 and 1.31 (2 s, 2,2-dimethyl of **13α**), 1.67 and 1.32 (2 s, 2,2-dimethyl of **13β**), 1.14 (d, J = 6 Hz, CH_3CHOSi of **13α**), 1.12 (d, J = 6 Hz, CH_3CHOSi of **13β**), 1.04 (d, β-CH_3), 0.84–0.81 (s's and d, (CH_3)$_3$CSi and α-CH_3), 0.01 (s, Si(CH_3)$_2$); IR (CH_2Cl_2) 1750 (β-lactam C=O) cm^{-1}; mass spectrum m/z 328 (MI + 1), 312 (MI – CH_3), 270 (MI – t-Bu).

Preparation of Acetonide 13α from the Known Carboxylic Acid 14.[10] To a solution of **14** (103 mg, 0.34 mmol) in THF (3 mL) at 0 °C under N_2 was added 10 M BH_3·Me_2S (0.14 mL, 1.4 mmol). Stirring was then continued for 1.5 h at room temperature. After the mixture was recooled to 0 °C, MeOH (3 mL) was carefully added to destroy the excess BH_3, and the reaction was again brought to room temperature for 10 min. After concentration under a stream of N_2 and then in vacuo, the residue was partitioned between CH_2Cl_2 and brine. After phase separation and back-extraction with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 91 mg crude **15**. Crude **15** (131 mg, 0.46 mmol) was then reacted with 2,2-dimethoxypropane (73 L, 0.6 mmol) and BF_3·OEt_2 (6 μL) in CH_2Cl_2 at room temperature under N_2 for 1 h. The reaction mixture was added to additional CH_2Cl_2, 1 M K_2HPO_4 (2 mL), and brine. After phase separation and back extraction of the aqueous with additional CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **13α** (136 mg). Chromatography on silica gel (eluting with 0–10% EtOAc/CH_2Cl_2) provided 97 mg of **13α** (65%) identical in R_f and NMR with the major isomer produced in the above hydrogenation of **12**.

Hydrogenation of 4 with Raney Nickel to 16β/16α (Run 13). Raney nickel from W.R. Grace Co. [Grace No. 28 Raney nickel (W-4)] was washed repeatedly with EtOAc and then with MeOH. The catalyst (1.14 g wet) was added to a solution of **4** (1.14 g, 5.4 mmol) in MeOH (50 mL), and the reaction mixture was stirred under an atmosphere pressure of H_2 for 4 h at 0 °C. The reaction mixture was then filtered through Celite, rinsing in with additional MeOH. Concentration of the filtrate in vacuo gave a quantitative yield of **16β/16α** in a 95:5 molar ratio as approximated by 300-MHz NMR and HPLC analysis. Additional runs were made for comparison purposes in which the catalyst, solvent, pressure, temperature, and catalyst loading and reaction time were varied. The results are listed in Table I. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (m, CH_3CHOH), 3.98 (dd, $J_{4,4}$ = 12 Hz, $J_{4,5}$ = 2 Hz, H_4 of **16β**), 3.80 (dd, J = 2, 5 Hz, H_6 of **16β**), 3.73 (dd, $J_{4,4}$ = 12 Hz, $J_{4,5}$ = 4.5 Hz, H_4 of **16α**), 3.60 (dd, $J_{4,4}$ = 12 Hz, $J_{4,5}$ = 3 Hz, H_4 of **16β**), 3.46 (t, $J_{4,4}$ = $J_{4,5}$ = 12 Hz, H_4 of **16α**), 3.18 (dd, J = 2, 10 Hz, H_6 of **16α**), 3.06 (dd, J = 2, 6 Hz, H_7 of **16β**), 2.83 (dd, J = 2, 5.5 Hz, H_7 of **16α**), 1.96 (m, H_5), 1.87 (d, OH), 1.42 and 1.74 (2 s, (CH_3)$_2$C of **16β**), 1.41 and 1.75 (2 s, (CH_3)$_2$C of **16α**), 1.31 (d, CH_3CHOH of **16α**), 1.30 (d, CH_3CHOH of **16β**), 1.12 (d, β-CH_3), 0.91 (d, α-CH_3); mass spectrum [of Me_3Si derivative], m/z 285 (M^+), 270 (M^+ – CH_3).

TBDMS Protection of 16β. The 1.14 g (5.4 mmol) mixture of **16β/16α** (95:5) was treated with 1.0 g (6.7 mmol) of TBDMSCl and 1.5 mL of Et_3N in 10 mL of DMF. The reaction mixture was stirred at room temperature for 6 h. At 0 °C, 50 mL of CH_2Cl_2 was added followed by 25 mL of 1 N HCl. After phase separation, the CH_2Cl_2 layer was washed with 25 mL of H_2O, 25 mL of saturated $NaHCO_3$, and 25 mL of H_2O. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography on silica gel (eluting with 20% EtOAc/Hex) provided 1.45 g of **13β** (82.4%): ^{1}H NMR (250 MHz, $CDCl_3$ δ 4.17 (qd, CH_3CHOSi, J = 6.2, 1.9 Hz), 3.96 (dd, J = 12.1, 2.4 Hz, H_4), 3.82 (dd, J = 5.1 2.0 Hz, H_6), 3.58 (dd, J = 12.1, 3.0 Hz, H_4), 2.98 (dd, J = 4.3, 2.0 Hz, H_7), 1.89 (m, H_5), 1.72, 1.40 (2 s, 2,2-dimethyl), 1.18 (d, J = 6.2 Hz, CH_3CHOSi), 1.11 (d, J = 7.1 Hz, β-CH_3), 0.88 (s, CH_3)$_3$Si), 0.08 and 0.07 (2 s, Si(CH_3)$_2$).

Jones Oxidation of 13β to 3b. Jones reagent was added to a stirred solution of **13β** (500.0 mg, 1.53 mmol) in 15 mL of Et_2O at 0 °C until a permanent orange color was attained. After the addition, H_2O (10 mL) and CH_2Cl_2 (10 mL) were added, the phases were separated, and the aqueous was back-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered through silica gel, and concentrated in vacuo to give 439.1 mg of **3b**, which crystallized upon standing: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.19 (qd, J = 6.2, 4.5 Hz, CH_3CHOSi), 3.93 (dd, J = 5.0, 2.2 Hz, H_4), 3.01 (dd, J = 4.3, 2.2 Hz, H_3), 2.73 (qd, J = 7.0, 5.0 Hz, CHCO$_2$H), 1.26 (d, J = 7 Hz, β-CH_3), 1.18 (d, J = 6.2 Hz, CH_3CHOSi), 0.86 (s, (CH_3)$_3$CSi), 0.06 and 0.05 (2 s, (CH_3)$_2$Si); mp 143.5–144.0 °C (lit.[3] mp 144 °C); specific rotation $[\alpha]^{25}_{589}$ –36.9°, $[a]^{25}_{578}$ –37.3°, $[\alpha]^{25}_{546}$ –42.6°, $[\alpha]^{25}_{436}$ –76.3°, $[\alpha]^{25}_{365}$ –132.6° (c 0.469, MeOH). Anal. Calcd for $C_{14}H_{27}SiNO_4$: C, 55.77; H, 9.04; N, 4.65. Found: C, 55.95; H, 8.64; N, 4.29.

Acknowledgment. we thank H. Flynn for obtaining the 300-MHz ^{1}H NMR spectra, Lisa DiMichele for recording and interpreting the ^{13}C NMR and 250-MHz ^{1}H NMR spectra, Jack Smith for obtaining the mass spectral data, J. P. Gilbert and his associates for the elemental analyses, Dr. C. H. Shunk for supplying intermediates, and M. T. Spears for preparing this manuscript. We are also grateful to Drs. D. H. Shih and T. N. Salzmann for helpful discussions during this work.