A Novel Ring-Closure Strategy for the Carbapenems: The Total Synthesis of (+)-Thienamycin

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Received October 18, 1989

Intramolecular Michael cyclization of an *N*-[(alkoxycarbonyl)methyl]-4-(3-nitro-2-propenyl)-3-oxoazetidin-2-one available in optically pure form leads to the corresponding carbapenam skeleton. Further elaboration via oxidative cleavage of an exocyclic nitromethylene group gives an advanced intermediate, which was transformed into (+)-thienamycin. The stereochemistry of the Michael cyclization and the pitfalls of protective group chemistry are discussed.

Introduction

Over the years, the β-lactam group of antibiotics has occupied a fundamental position in the arsenal of chemotherapeutic agents.[1] Indeed, ever since the discovery of penicillin, no other class of antibiotics has been so intensively investigated on so many fronts. Research work in this highly competitive area has been driven by the search for new structural types with improved broad spectrum activity and insensitivity to β-lactamases. Needless to mention, literature coverage has been prolific.

The field of β-lactam antibiotics took a giant step forward with the timely discovery of thienamycin (1) (Figure 1) by scientists at the Merck Laboratories in 1976.[2] Thienamycin exhibited broad spectrum antibacterial activity never before encountered in the β-lactam group, be it natural or semisynthetic. It was also endowed with a number of unusual structural and functional features that rendered its emergence on the scene a unique event. Soon after the discovery of thienamycin, a number of other carbapenem-type[3] β-lactam antibiotics were reported. However, none could rival the outstanding biological properties of thienamycin itself.

In spite of its structural complexity, and considering the delicate balance of functionality, it is remarkable that thienamycin (and its *N*-formimidoyl analogue, imipenem) are manufactured by total synthesis. In fact, the first total synthesis of (+)-thienamycin[4] by the Merck group and subsequent modifications in the process[5] remain as singularly original contributions. While numerous formal syntheses of thienamycin have been reported in recent years,[6] except for the Merck papers, very few have dealt with aspects of the total synthesis of the enantiomerically pure antibiotic from inception to completion.[7] In contrast, total syntheses of several other carbapenems have been described and reviewed.[3]

Examination of the structural intricacies of thienamycin reveals a number of challenges to contend with. The basic skeleton is closely related to a penem,[8] except for the replacement of the sulfur by a methylene group, hence the term carbapenem. As in the case of the penems,[9,10] access to the carbapenems necessitates the development of methodology that addresses the construction of the highly strained bicyclic ring system, as well as designing strategies that accommodate the α-orientated 1-hydroxyethyl side chain harboring a stereogenic center. In general, the synthesis of 6-(1-hydroxyethyl)penems and -carbapenems has involved the building of an appropriate 2-azetidinone, then forming the bicyclic ring systems.[3] The two most frequently used methods for the ring closure of the penem and carbapenem ring systems rely on an intramolecular Wittig-type reaction,[11] or its variants,[12] and on a diazo insertion reaction[4] (Figure 2). Other less frequently used methods are also known.[13] By contrast, there are numerous methods for the synthesis of 4-substituted-3-[(*R*)-1-hydroxyethyl]-2-azetidinones,[14,15] a pivotal inter-

(1) For recent reviews on β-lactam antibiotics, see: *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982–1983; Vol. 1–3. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds., The Royal Society of Chemistry: Burlington House, 1984. Southgate, R.; Elson, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm. Ch., Eds.; Springer Verlag: New York, 1985; p 1. Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180.

(2) Kahan, J. S.; Kahan, F.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapely, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiot.* **1979**, *32*, 1. Albers-Schönberg, G.; et al. *J. Am. Chem. Soc.* **1978**, *100*, 6491.

(3) For recent reviews, see: Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463. Ratcliffe, R. W.; Albers-Schönberg, G. In *Chemistry and Biology of β-Lactam* Antibiotics; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2 pp 227–314.

(4) See: Saltzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.

(5) See, for example: Melillo, D. G.; Cretovich, R. J.; Ryan, K. M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498. Karady, S.; Amato, J.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765.

(6) For an excellent recent review, see: Georg, G. I. In *Studies in Natural Product Chemistry*; Rahman, A-ur, Ed., Elsevier Science: Amsterdam, in press; Vol. 4.

(7) For a recent example, see: Murayama, H.; Hiraoka, T. *J. Org. Chem.* **1986**, *51*, 399.

(8) Ernest, I., Gosteli, I.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6310. Ernest, I. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, p 315.

(9) For a recent total synthesis of penem FCE-22101, see: Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *J. Am. Chem. Soc.* **1985**, *107*, 1438; *Lect. Heterocycl. Chem.* **1985**, *8*, 43; and references cited therein.

(10) Franceschi, G.; Alpegiani, M.; Battistini, C.; Bedeschi, A.; Perrone, E.; Zarini, F. *Pure Appl. Chem.* **1987**, *59*, 467.

(11) Pfaendler, H. R.; Gosteli, J.; Woodward, R. B.; Rihs, G. *J. Am. Chem. Soc.* **1981**, *103*, 4526. Ernest, I.; Gosteli, J.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6310.

(12) See, for example: Battistini, C.; Scarafile, F.; Foglio, M.; Franceschi, G. *Tetrahedron Lett.* **1984**, *25*, 2935. Perrone, E.; Alpegiani, M.; Bedeschi; A.; Giudici, F.; Franceschi, G. *Tetrahedron Lett.* **1984**, *25*, 2939 and previous references. Afonso, A.; Hon, F.; Weinstein, J.; Ganguly, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6138.

(13) For some examples of aldol, Dieckmann, and related methodologies, see: Meyers, A. I.; Sowin, T. J.; Scholz, S.; Ueda, Y. *Tetrahedron Lett.* **1987**, *28*, 5103. Fujimoto, K.; Iwano, Y.; Hirai, K. *Tetraheron Lett.* **1985**, *26*, 4315. Shibuya, M.; Kuretani, M.; Kubota, S. *Tetrahedron* **1982**, *38*, 2659 and preivous references. Hatanaka, Y.; Yamamoto, Y., Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883. Mastalerz, H.; Vinet, V. *Tetrahedron Lett.* **1985**, *26*, 4315.

0022-3263/90/1955-3098$02.50/0

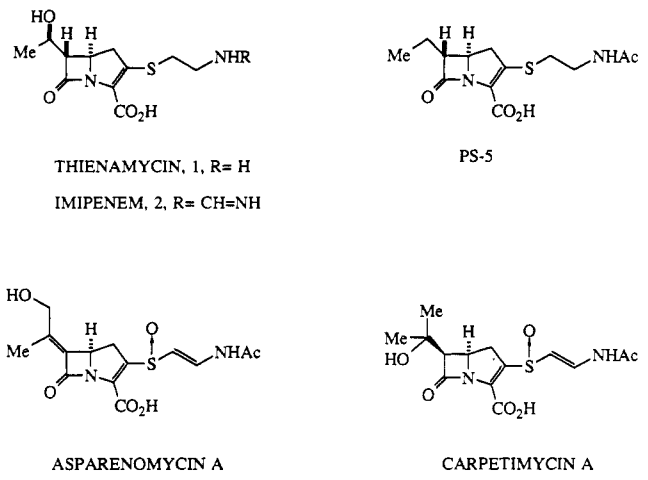


Figure 1.

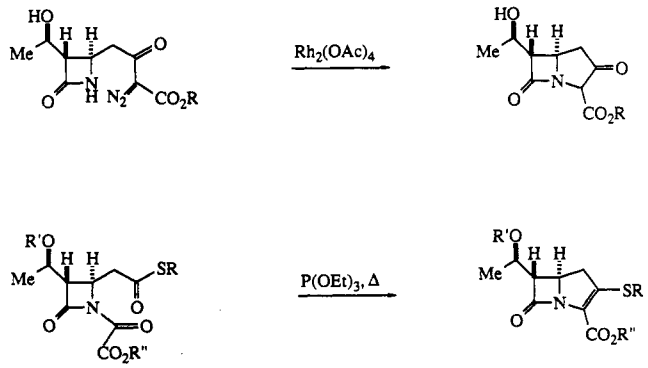


Figure 2.

mediate in the elaboration of the penem or carbapenem systems. We and others have devised protocols for the use of L-threonine as a chiral template in this regard.[9,16] Another practical method involves the use of (*R*)-3-hydroxybutyric acid.[6]

The need to produce optically pure and enantiomerically distinct advanced intermediates, such as the above-mentioned azetidinones, has prompted many groups to devise asymmetric processes[17] or to use readily available chiral

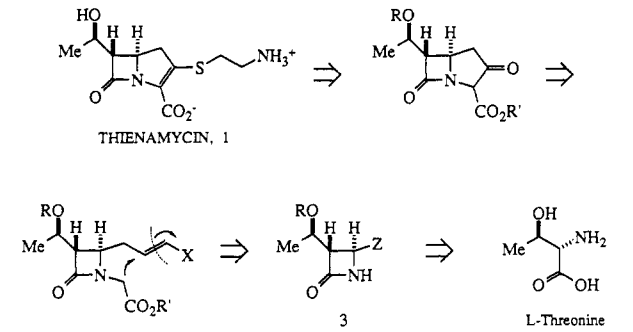


Figure 3.

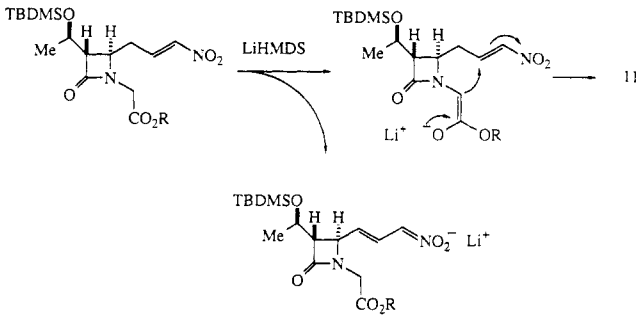


Figure 4.

nonracemic starting materials.[3,6,14,18,19]

Results and Discussion

Our disconnective analysis of the synthesis plan for thienamycin is shown in Figure 3. The azetidinone chiron **3**, readily available commercially[15] or synthesized from our original procedure starting for L-threonine as a chiral template,[9,16] is a pivotal building block. The plan called for a chain extension at C-4, and the construction of a carbapenam bicyclic system via an intramolecular Michael-type ring closure to produce a 3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylic acid system. Surprisingly, such a strategy had not been previously reported to the best of our knowledge. It also presented a number of potential obstacles. We reasoned that the choice of Michael acceptor would be critical particularly because of the reversibility of the reaction. Moreover, successful ring closure would lead to an analogue in which a carbon atom bearing the Michael acceptor group X would have to be excised en route to the desired bicyclic intermediate.

Our synthesis started with the azetidinone **3**, which was transformed into the allyl derivative **4** by treatment with lithium diallylcuprate[20] (Scheme I). The next steps were concerned with the introduction of the acetic acid side chain as the Michael donor and the elaboration of the allyl group into a nitro olefin as the Michael acceptor.[21] Initially, we conducted exploratory studies with the methyl ester **6** in order to avoid possible complications associated with the more commonly used *p*-nitrobenzyl ester especially under basic conditions. Eventually, however, *p*-nitrobenzyl ester derivatives were used since they can be

(14) For an excellent summary, see ref 6. For some representative recent examples, see: Kaga, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 113. Gennari, C.; Cuzzi, P. G. *J. Org. Chem.* **1988**, *53*, 4015. Cainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G. *J. Am. Chem. Soc.* **1988**, *110*, 6879. Tschaen, D. M.; Fuentes, L. M.; Lynch, J. E.; Laswell, W. L.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 2779. Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129. Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4335. Iimori, T.; Ishida, Y.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2153. Chiba, Y.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1985**, 1343. Hart, D. J.; Ha, D.-C. *Tetrahedron Lett.* **1985**, *26*, 5493. Cainelli, G.; Contento, M.; Giacomini, D.; Panunzio, M. *Tetrahedron Lett.* **1985**, *26*, 437. Matsunaga, H.; Sakamati, T.; Nagoaka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 3009. Hubschwerlen, C.; Schmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206. Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. *J. Org. Chem.* **1982**, *47*, 4928. Takano, S.; Kasahara, C.; Ogasawara, K. *Chem. Lett.* **1982**, 631.

(15) For example: 4-acetoxy-3-[(*R*)-1′-hydroxyethyl]-1′-*O*-[*tert*-butyldimethylsilyl)-2-azetidinone (**3**) is commercially available, Kaneka America Corp., NY.

(16) Chackahamannil, S.; Fett, N.; Kirkup, M.; Afonso, A.; Ganguly, A. K. *J. Org. Chem.* **1988**, *53*, 450. Murayama, H.; Shiozaki, M.; Hiroaka, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3264. Yamagisawa, H.; Ando, A.; Shiozaki, M.; Hiraoka, T. *Tetrahedron Lett.* **1983**, *24*, 1037. Shiozaki, M.; Ishida, N.; Hiroaka, T.; Hiroaki, Y. *Tetrahedron Lett.* **1981**, *22*, 5205.

(17) See, for example: Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ohiai, M.; Inone, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. Fuentes, L. M.; Shinkai, I.; Salzmann, T. *J. Am. Chem. Soc.* **1986**, *108*, 4675. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 3119.

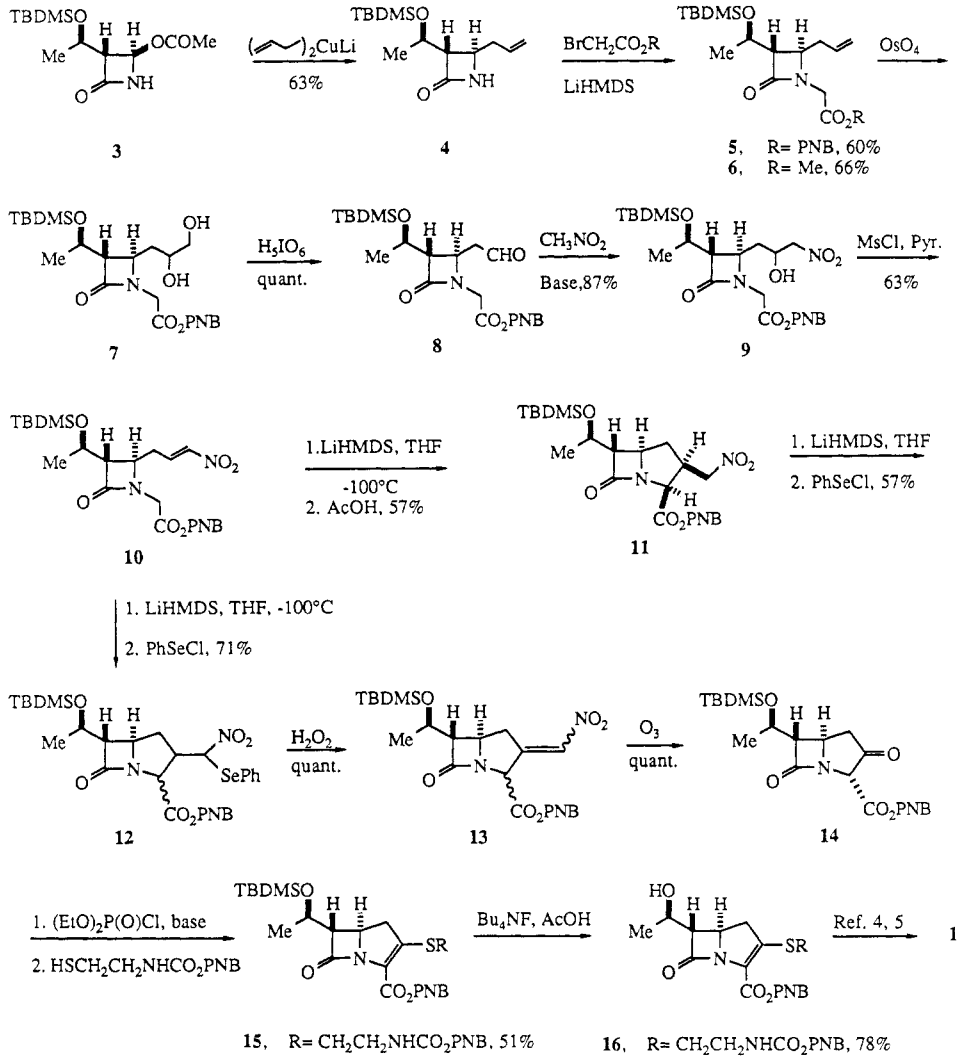
(18) Morin, C.; Labia, R. *Actual. Chim.* **1984**, *31*; Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103.

(19) For a preliminary account, see: Hanessian, S.; Desilets, D. In *Trends in Medicinal Chemistry*; Van der Goot, H., Domany, G., Pallos, L., Timmerman, H., Eds., Elsevier: Amsterdam, 1988; p 165. For another related approach, see: Hanessian, S.; Desilets, D.; Rancourt, G.; Fortin, R. *Can. J. Chem.* **1982**, *60*, 2293.

(20) See, for example: Koller, W.; Linkies, A.; Pietsch, H.; Rehling, H.; Reuschling, D. *Tetrahedron Lett.* **1982**, *23*, 1545.

(21) For other uses of nitroolefins in β-lactam synthesis, see: Barrett, A. G. M.; Graboski, G. G.; Russell, M. A. *J. Org. Chem.* **1985**, *50*, 2603; see also ref 9.

Scheme I



easily transformed into the acid. The allyl group in **5** was hydroxylated to the diol **7**, which was oxidatively cleaved to the aldehyde **8** in excellent overall yield. Treatment of the aldehyde **8** with nitromethane anion generated with 1,1,3,3-tetramethylguanidine led to a mixture of nitro alcohols **9**, which was converted into the nitro olefin **10** in good overall yield using a mesylation/elimination sequence.

We were now poised to attempt the intramolecular ring-closure reaction, but not without some concern. Specifically we were cognizant of the kinetically favored formation of a nitro dienoate anion in addition to the expected enolate anion. The former process could result in the recovery of starting nitro olefin, thus seriously affecting the synthetic plan (Figure 4). Indeed, we were initially disappointed that standard conditions for enolate formation in a model methyl ester (**10**, Me ester) (LDA, LiHMDS, etc. THF, −78 °C) led to the recovery of starting material in over 90% yield. It was after some experimentation that we realized the importance of the temperature during the reaction as well as for the quenching process. By progressively lowering the reaction temperature to −100 °C and the quench temperature to −50 °C, it was possible to obtain the bicyclic product **11** (as the methyl ester) in an isolated yield of 67%. At quench temperatures of −20 °C or −40 °C the yield of the expected product was 48% and 55%, respectively.

Application of the same protocol to the *p*-nitrobenzyl ester analogue **10** gave the bicyclic product **11** as a crystalline substance in 57% yield. X-ray analysis[22] of **11** confirmed its constitutional structure and revealed the syn orientation of the nitromethyl and the ester groups toward the sterically more congested concave face of the bicyclic ring system. This intriguing result was not altogether unexpected since a related Michael cyclization to a penam system in our synthesis of FCE-22101[9] also led to a similar orientation of the bulk groups (Figure 5).[23]

Figure 5.

The reasons for this behavior in the above penam system may be partly steroelectronic, caused by the presence of a mixed dithioacetal function. The outcome of the Michael cyclization of **10** may be rationalized on the basis of a higher reactivity of a nonchelated enolate anion compared to a chelated counterpart (Figure 6).

Assuming the presence of an *E* enolate, a nonchelated enolate with a butane-gauche relationship in the transition state as in B would lead to the observed product. The chelated intermediate A (or a dimeric form) would be

(22) Desilets, D.; Bélanger-Gariépy, F.; Hanessian, S.; Brisse, F. *Acta Crystallogr.* **1987**, *C43*, 919.
(23) Hanessian, S.; Bedeschi, A.; Battistini, C.; Mongelli, N. *Lec. Heterocycl. Chem.* **1985**, *8*, 43.

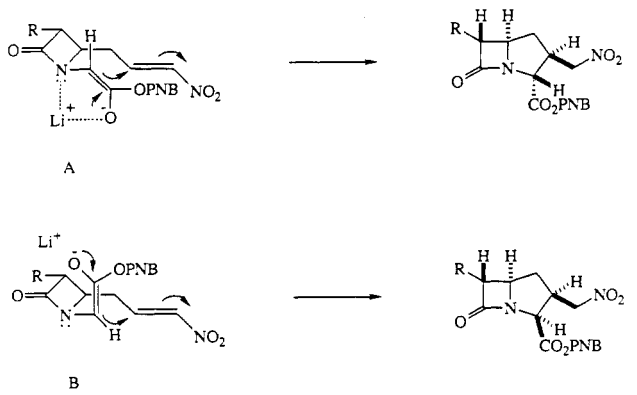


Figure 6.

somewhat less reactive, even with an apparently more favorable butane-anti relationship. These speculative arguments do not take into account possible aggregation states of these anionic species.

Having secured a method for the formation of the bicyclic ring system, the next issue to be addressed was the one-carbon excision of the nitromethyl group en route to 2-oxocarbapenam intermediate **14**. Considering the type of functionality present, it was anticipated that an oxidative elimination of a nitro(α-phenylseleno)methyl derivative would lead to the corresponding nitro olefin, which in turn could be cleaved by ozonolysis.[9] Once again, the question of site-selective proton abstraction was raised as an issue, since phenylselenylation at a site other than the nitromethyl group would result in a serious setback of the final steps of the synthesis. Treatment of **11** with LiHMDS in THF and quenching the resulting anionic species with benzeneselenenyl chloride gave the selenide **12** in good yield with no apparent contamination from other byproducts. In this regard it was gratifying to find that the nitronate anion resulting from the intramolecular Michael reaction of **10** could be directly quenched with benzeneselenenyl chloride to afford **12** in 71% overall yield from the nitro olefin **10**.

Oxidative elimination of the bicyclic ester **12** gave a mixture of exocyclic nitro olefin isomers **13**. There now remained to excise the nitromethyl group, which was done by oxidation with ozone to give the bicyclic ketone **14** in excellent yield. Since the NMR parameters of **14** were very similar to those reported for the corresponding des-TBDMS compound,[5] we can assume that epimerization at C_2 had taken place in the transformations of **12** to **14**.[24] At this stage we were in a position to converge with a known intermediate in the Merck synthesis,[4,5] namely, the desilylated oxo intermediate corresponding to **14**.

Unfortunately, all attempts at desilylation of **14** or the corresponding methyl ester resulted in the gradual destruction of the substrate. It was soon found that these compounds underwent very facile retro-Dieckmann opening of the β-keto ester even in the presence of alcohols and under neutral conditions.[25] After our work was completed we became aware of similar problems in the de-O-silylation of 2-oxocarbapenems as encountered by other groups.[26] Faced with this untimely impasse, it was decided to attempt the desilylation at a penultimate stage of the synthesis. Thus, the cysteamino group was introduced, based on methodology already developed in the Merck laboratories[4,5] that involved the intermediacy of an enol phosphate derived from **14**. The much maligned desilylation of **15** was the only obstacle left en route to the intended title. Once again, the seemingly trivial removal of the silyl group in **15** presented difficulties. Numerous attempts using aqueous mineral acids, Lewis acids, HF–pyridine, HF–acetonitrile, Bu_4NF, etc., led to decomposition. Ultimately, successful desilylation was possible with Bu_4NF in aqueous acetic acid–THF by allowing a long contact time (48 h) and monitoring the progress of the reaction by HPLC. The desired compound **16** was isolated by preparative HPLC with recovery of starting material. By this process it was possible to obtain the desired protected ester derivative **16** in 40% isolated yield (78% based on recovered starting material), which has been previously transformed into thienamycin.[4] Compound **16** was identical in all respects with a sample provided by Dr. D. Melillo of the Merck laboratories.[5]

Thienamycin and imipenem are currently among a small number of complex natural products that are manufactured by total synthesis. In this regard, a large-scale process developed at the Merck laboratories[5] starts with acetonedicarboxylic acid. This achiral starting material is cleverly transformed into an optically active azetidinone intermediate, via an asymmetric hydrogenation of an enamino derivative. The bicyclic ring system is constructed using the diazo insertion methodology referred to earlier[4] (Figure 2). A strong attribute of this process is the avoidance of the use of a protective group for the C-8 alcohol group during the diazoinsertion reaction.

Our synthetic approaches to the penems and carbapenems as exemplified by the total syntheses of FCE-22101[9] and thienamycin[19] have resulted in the development of a viable process for the production of the azetidinone **3** from L-threonine and of novel stereocontrolled Michael-type ring closures. These results should also find utility in the synthesis of other members of these important chemotherapeutic agents.[27]

Experimental Section

^1H NMR spectra were recorded on a Bruker 90, a Bruker WH-400, or 250- and 300-MHz VARIAN instruments using deuteriochloroform as solvent ($CHCl_3$ standard, δ = 7.26) (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Infrared spectra were recorded with a Perkin-Elmer 781 infrared spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Combustion analyses were performed by Guelph Laboratories Ltd, Guelph, Ontario, Canada. Column chromatography was done by the flash method.[28] HPLC was performed on μ-Porasil steel columns (P/N 27477 and P/N 84175 for preparative scale) on a Waters Model 440 chromatograph. Melting points were not corrected. X-ray analysis was done on a NONIUS-ENRAF CAD-4 diffractometer using graphite-monochromatized Cu Kα radiation and the structure solved using the MULTAN program.

(3*S*,4*R*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-(2-propenyl)-2-azetidinone (4). To a stirred suspension of cuprous iodide (2.65 g) in 80 mL of THF was added 54 mL of a 0.43 M solution of allyllithium in THF at −15 °C under argon over 20 min. The mixture was stirred at −15 °C for 15 min and then cooled to −30 °C. A solution of **3** (1.66 g) in 50 mL of THF was added, and the mixture was stirred at −30 °C for 10 min and then at 10 °C for 1 h. The mixture was poured into saturated NH_4Cl (150 mL) and extracted with ether, and the extracts were processed in the usual manner. The crude syrup was chromatographed on silica gel (EtOAc–hexanes, 2.5:10) to give 980 mg (63% yield) of

(24) We thank one of the referees for bringing this point to our attention.

(25) See, for example: deVries, J. G.; Hauser, G.; Sigmund, G. *Heterocycles* **1985**, *23*, 1081.

(26) Oina, H.; Uyeo, S.; Fikao, T.; Doi, M.; Yoshida, T. *Chem. Pharm. Bull.* **1985**, *33*, 4382. Satoh, H.; Tsuji, T. *Heterocycles* **1988**, *27*, 2803.

(27) Since the completion of our work, we became aware of a patent in which 6-(nitromethyl)carbapenems are cited as novel, biologically active analogues. Yoshioka, T.; Yamamoto, K.; Fukagawa, Y.; Shimauchi, Y.; Ishikura, T.; European Pat. No. 111286 A1, 1984.

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

the title compound, mp 84–85 °C: $[\alpha]^{25}_D$ −16.6° (*c* 1.01, $CHCl_3$); IR (CCl_4) 3220 (NH), 1760 (C=O) cm^{-1}; MS *m/e* 270 (MH^+), 212 (MH^+ − *t*-BuH); ^1H NMR (90 MHz, $CDCl_3$) δ 6.33 (br s, 1 H, NH), 5.72 (m, 1 H, C*H*=CH_2), 5.10 (m, 2 H, C=CH_2), 4.16 (m, 1 H, C*H*OSi), 3.70 (dt, 1 H, *J* = 6.6 Hz, J_{trans} = 2.0 Hz, H_4), 2.76 (dd, 1 H, *J* = 5.6 Hz, J_{trans} = 2.0 Hz, H_3), 2.44–2.29 (m, 2 H, C_4-CH_2), 1.20 (d, 3 H, *J* = 6.5 Hz, C_3-C-CH_3), 0.87 (s, 9 H, C_4H_9Si), 0.06 (s, 6 H, 2 × CH_3Si). Anal. Calcd for $C_{14}H_{27}NO_2Si$ (269.45): C, 62.41; H, 10.11; N, 5.19. Found: C, 62.08; H, 9.81; N, 5.11.

p-Nitrobenzyl (3*S*,4*R*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-oxo-4-(2-propenyl)-1-azetidineacetate (5). To a suspension of (freshly sublimed) potassium *tert*-butoxide, 416 mg, 3.71 mmol) in 4.5 mL of anhydrous toluene at 0 °C under argon was added dropwise 400 mg (1.48 mmol) of the azetidinone **4** in 8 mL of anyhydrous toluene. The solution was stirred for 30 min at 0 °C, then cooled to −35 °C, and rapidly treated with *p*-nitrobenzyl bromoacetate (2.04 g, 7.42 mmol) in 4.5 mL of toluene. The red-brick solution was stirred for an additional 20 min at −30 °C and then poured into a saturated NH_4Cl solution (70 mL) with vigorous sitrring. The aqueous layer was extracted with 3 × 70 mL of EtOAc, and the organic layer was processed in the usual manner. The residue thus obtained was chromatographed on silica gel, using a mixture of 10:2.5 hexanes–EtOAc as eluant to give 413 mg (60% yield) of the expected product **5** as an oil; $[\alpha]^{25}_D$ −32.1° (*c* 1.24, $CHCl_3$); IR (film) 1755, 1610, 1530, and 1350 cm^{-1}; MS *m/e* 463 (MH^+), 405 (MH^+ − *t*-BuH); ^1H NMR (90 MHz, $CDCl_3$) δ 8.29–7.48 (m, 4 H, 4 × ArH), 5.75 (m, 1 H, C*H*=CH_2), 5.26 (s, 2 H, ArCH_2), 5.26–5.00 (m, 2 H, C=CH_2), 4.16 (m, 1 H, *J* = 6.2 Hz, C*H*OSi), 4.05 (m, 2 H, NCH_2), 3.86 (m, 1 H, *J* = 6.5 Hz, J_{trans} = 2.1 Hz, H_4), 2.86 (dd, 1 H, *J* = 5.9, J_{trans} = 2.1 Hz, H_3), 2.44 (t, 2 H, *J* = 6.5 Hz, C_4-CH_2), 0.86 (s, 9 H, C_4H_9Si), 1.22 (d, 3 H, *J* = 6.2 Hz, C_3-CHCH_3), 0.06 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3'Si). Anal. Calcd for $C_{23}H_{34}N_2O_6Si$ (462.61): C, 59.71; H, 7.41; N, 6.05. Found: C, 59.53; H, 7.03; N, 5.77.

Methyl (3*S*,4*R*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-oxo-4-(2-propenyl)-1-azetidineacetate (6). To a stirred solution of LiHMDS (4.0 mmol) (prepared from 672 mg of hexamethyldisilazane in 4.0 mL of THF and 2.75 mL of 1.45 M *n*-BuLi in hexanes at 0 °C, 30 min) was added a solution of **4** (1.02 g, 3.8 mmol) in 10 mL of dry THF at −78 °C. After being stirred at −78 °C for 10 min, a solution of (freshly distilled) methyl bromoacetate (696 mg, 4.55 mmol) in 10 mL of THF was added. The reaction mixture was warmed to −20 °C over 45 min and stirred at this temperature for 15 min. The solution was poured into a saturated solution of NH_4Cl (50 mL) and then extracted with 400 mL and 200 mL of CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and then concentrated. The residue was purified by flash chromatography using a mixture of hexanes–EtOAc (10:2) as eluant to give 848 mg (66% yield) of **6** as an oil: $[\alpha]^{25}_D$ −31.6° (*c* 0.91, $CHCl_3$); IR (film) 1765, 1750 cm^{-1}; MS *m/e* 342 (MH^+), 284 (MH^+ − *t*-BuH); ^1H NMR (90 MHz, $CDCl_3$) δ 5.78 (m, 1 H, C*H*=CH_2), 5.17 (m, 2 H, C=CH_2), 4.18 (m, 1 H, *J* = 6.2 Hz, CHOSi), 4.08 (A of AB, 1 H, J_{gem} = 17.9 Hz, NCH_A), 3.88 (B of AB, 1 H, J_{gem} = 17.9 Hz, NCH_B), 3.80 (m, 1 H, H_4), 3.74 (s, 3 H, CO_2CH_3), 2.85 (dd, 1 H, *J* = 6.0 Hz, J_{trans} = 2.2 Hz, H_3), 2.45 (t, 2 H, *J* = 6.6 Hz, C_4-CH_2), 1.23 (d, 3 H, *J* = 6.2 Hz, C_3-C-CH_3), 0.88 (s, 9 H, C_4H_9Si), 0.08 (s, 6 H, 2 × CH_3Si).

p-Nitrobenzyl (2*R*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-(2,3-dihydroxypropyl)-4-oxo-1-azetidineacetate (7). To a solution of **5** (910 mg, 1.96 mmol) in 15 mL of anhydrous dioxane under argon was added (525 mg, 2.06 mmol) of osmium tetraoxide dissolved in 16 mL of dioxane. The mixture was stirred at room temperature for 20 h, hydrogen sulfide was bubbled through for 30 min, and the precipitate was filtered on a Celite pad and washed with dioxane, followed by evaporation of the solvent to give 970 mg (quant.) of **7** as a colorless oil: IR (film) 3420, 1740, 1610, 1525, and 1350 cm^{-1}; MS *m/e* 497 (MH^+), 439 (MH^+ − *t*-BuH); ^1H NMR (90 MHz, $CDCl_3$) δ 8.26–7.44 (m, 4 H, 4 x ArH), 5.23 and 5.17 (s, 2 H, ArCH_2), 4.41–2.78 (m, 10 H, H_2, H_3, NCH_2, CHOSi, CHOH, and CH_2OH), 1.40–1.15 (m, 5 H, C_2-CH_2, C_3-C-CH_3), 0.87 and 0.82 (s, 9 H, C_4H_9Si), 0.15 and 0.13 (s, 3 H, CH_3Si), 0.09 and 0.06 (s, 3 H, CH_3'Si). The corresponding methyl ester was similarly prepared (89%): MS *m/e* 344 (MH^+).

p-Nitrobenzyl (3*S*,4*R*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-oxo-4-(2-oxoethyl)-1-azetidineacetate (8). To a solution of diol **7** (923 mg, 1.86 mmol) in 15 mL of THF at 0 °C was added (445 mg, 1.95 mmol) of periodic acid in 30 mL of THF. The solution was stirred for 30 min at 0 °C, and the acid was neutralized by using basic Amberlite IR-45 (OH^-). Filtration, washing with CH_2Cl_2, and evaporation of solvent gave 752 mg (87% yield) of aldehyde **8** as an oil: IR (film) 1755, 1725, 1610, 1530, and 1350 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.76 (s, 1 H, CHO), 8.31–7.48 (m, 4 H, 4 x ArH), 5.24 (s, 2 H, ArCH_2), 4.23 (A of AB, 1 H, J_{gem} = 18 Hz, NCH_A), 4.21 (m, 1 H, *J* = 6.0 Hz, CHOSi), 4.20 (m, 1 H, H_4), 4.01 (B of AB, 1 H, J_{gem} = 18.0 Hz, NCH_B), 3.00 (m, 2 H, C_4-CH_2), 2.90 (dd, 1 H, *J* = 5.6 Hz, J_{trans} = 2.3 Hz, H_3), 1.25 (d, 3 H, *J* = 6.2 Hz, C_3-C-CH_3), 0.87 (s, 9 H, C_4H_9Si), 0.09 (s, 3 H, CH_3Si), and 0.06 (s, 3 H, CH_3'Si).

p-Nitrobenzyl (2*R*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-(2-hydroxy-3-nitropropyl)-4-oxo-1-azetidineacetate (9). To a solution of aldehyde **8** (380 mg, 1.10 mmol) in 20 mL of anhydrous nitromethane at −20 °C under argon was added 1,1,3,3-tetramethylguanidine (94 mg, 1.10 mmol) in 10 mL of anhydrous nitromethane. The solution was stirred for 30 min at −20 °C and then treated with 10 μL of AcOH and diluted with 10 mL of a saturated solution of NaCl. Extraction with 3 × 15 mL of EtOAc, washing with water, and evaporation of the organic layer after drying ($MgSO_4$) gave a residue, which was chromatographed on silica gel using 10:9 hexanes–EtOAc as eluant to give 270 mg (63% yield) of nitro alcohol product **9** as an oil: IR (film) 3400, 1745, 1610, 1555, 1525, 1380, and 1350 cm^{-1}; MS *m/e* 526 (MH^+) and 465 (MH^+ − CH_3NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 8.23–7.41 (m, 4 H, 4 × ArH), 5.21 and 5.19 (s, 2 H, ArCH_2), 4.48–3.68 (m, 7 H, H_2, CHOSi, CH_2NO_2, NCH_2, C_2-C-CH), 3.15 and 2.87 (dd, 1 H, *J* = 9.7 Hz and 6.7 Hz, J_{trans} = 2.1 Hz and 2.3 Hz, H_3), 2.06–1.47 (m, 2 H, C_2-CH_2), 1.30 and 1.23 (d, 3 H, *J* = 7 Hz and 5.6 Hz, C_3-C-CH_3), 1.26 (m, 1 H, OH), 0.84 and 0.81 (s, 9 H, C_4H_9Si), 0.08 (s, 3 H, CH_3Si), and 0.03 (s, 3 H, CH_3'Si).

p-Nitrobenzyl (2*R*,3*S*)-3-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2-[(*E*)-3-nitro-2-propenyl]-4-oxo-1-azetidineacetate (10). A solution of mesyl chloride (2.1 mL from a 1.0 mL of MsCl in 50 mL of CH_2Cl_2 solution) was added to 260 mg (0.5 mmol) of nitro alcohol **9** in 10 mL of CH_2Cl_2 at 0 °C under argon. The mixture was stirred for 5 min at 0 °C and treated with 140 μL (1.1 mmol) of Et_3N. After 45 min, AcOH was added until pH 6 and the solution was diluted with 15 mL of CH_2Cl_2. The organic layer was washed with 2 × 30 mL of a half saturated NaCl solution and processed in the usual manner. The residue was chromatographed on silica gel using a mixture of 2:1 hexanes–EtOAc as eluant to give 201 mg (80% yield) of product **10** as an oil: $[\alpha]^{25}_D$ −24.9° (*c* 1.0, $CHCl_3$); IR (film) 1760, 1610, 1530, 1350 cm^{-1}; MS *m/e* 508 (MH^+), 450 (MH^+ − *t*-BuH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.26–7.50 (m, 4 H, 4 × ArH), 7.23 (m, 1 H, C*H*=CNO_2), 7.05 (td, 1 H, J_{trans} = 13.6 Hz, J_{allyl} = 1.3 Hz, C=C*H*NO_2), 5.25 (s, 2 H, ArCH_2), 4.19 (m, 1 H, *J* = 6.0 Hz, C*H*OSi), 4.09 (A of AB, 1 H, J_{gem} = 18.2 Hz, NCH_A), 4.02 (B of AB, 1 H, J_{gem} = 18.2 Hz, NCH_B), 3.97 (td, 1 H, *J* = 6.2 Hz, *J* = 2.3 Hz, H_2), 2.91 (dd, 1 H, *J* = 5.5 Hz, *J* = 2.3 Hz, H_3), 2.78–2.62 (m, 2 H, C_2-CH_2), 1.22 (d, 3 H, *J* = 6.2 Hz, C_3-C-CH_3), 0.85 (s, 9 H, C_4H_9Si), 0.08 (s, 3 H, CH_3Si) 0.04 (s, 3 H, CH_3'Si). Anal. Calcd for $C_{23}H_{33}N_3O_8Si$ (507.61): C, 54.42; H, 6.55; N, 8.28. Found: C, 54.30; H, 6.31; N, 7.96.

p-Nitrobenzyl (2*S*,3*S*,5*R*,6*S*)-6-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3-(nitromethyl)-7-oxo-1-azabicyclo-[3.2.0]heptane-2-carboxylate (11). To a solution of 54 mg of hexamethyldisilazane in 1.5 mL of THF was added 0.25 mL of *n*-BuLi (1.36 M in hexanes) at 0 °C. The solution was stirred for 20 min at 0 °C and then cooled to −100 °C. A solution of **10** (153 mg in 3 mL of THF) was added from a jacketed and cooled (−78 °C) dropping funnel. After being stirred for 20 min at −100 °C, the internal temperature was raised to −50 °C and 0.045 mL of acetic acid in 1 mL of THF was added with a styringe. The reaction mixture was warmed to room temperature and filtered through a pad of Celite, and the filtrate and washings (CH_2Cl_2) were evaporated to dryness. The residue was purified by flash chromatography (hexanes–EtOAc, 10:3), to give 90 mg (57%) of the crystalline carbapenam **11**, mp 104–105 °C $[\alpha]^{25}_D$ +75.4° (*c* 1.4, $CHCl_3$); MS *m/e* 449 (MH^+ − *t*-BuH); IR (film) 1770, 1740, 1610, 1560, 1380 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25–7.55 (m, 4 H, 4 × ArH), 5.32 (A of AB, 1 H, J_{gem} = 13.0 Hz, $ArCH_A$), 5.22 (B of AB, 1 H, *J* = 13.0 Hz, $ArCH_B$), 4.52 (dd, 1 H, J_{gem} =

14.2 Hz, J = 8.6 Hz, $CHNO_2$), 4.48 (dd, 1 H, J_{gem} = 14.2 Hz, J = 6.6 Hz, $CH'NO_2$), 4.21 (d, 1 H, J = 7.6 Hz, H_2), 4.18 (m, 1 H, J = 6.0 Hz, CHOSi), 3.84 (ddd, 1 H, J = 9.8 Hz, J = 5.3 Hz, J_{trans} = 2.3 Hz, H_5), 3.52 (m, 1 H, H_3), 3.02 (dd, 1 H, J = 5.3 Hz, J_{trans} = 2.3 Hz, H_6), 2.22 (td, 1 H, J = 11.9 Hz, $J_{4,3}$ = $J_{4,5}$ = 5.4 Hz, H_4), 1.82 (td, 1 H, J_{gem} = $J_{4,3}$ = 12.4 Hz, $J_{4,5}$ = 9.8 Hz, H_4'), 1.22 (d, 3 H, J = 6.2 Hz, C_6-C-CH_3), 0.88 (s, 9 H, C_4H_9Si), 0.08 (s, 3 H, CH_3Si), 0.07 (s, 3 H, $CH_3'Si$). Anal. Calcd for $C_{23}H_{33}N_3O_8Si$ (507.60): C, 54.42; H, 6.55; N, 8.28. Found: C, 54.37; H, 6.51; N, 8.11. The yield varied between 57 and 60% (three runs).

p-Nitrobenzyl (2*S*,3*S*,5*R*,6*S*)-6-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3-[nitro(phenylseleno)methyl]-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (12). To a solution of 69 mg of hexamethyldisalazane in 1.0 mL of THF at 0 °C under argon was added 0.32 mL of 1.29 M n-BuLi in hexanes and the mixture was stirred at 0 °C for 20 min. The solution was cooled at −100 °C and treated with 198 mg of compound **11** in 6 mL of THF at −78 °C. After being stirred at −100 °C for 15 min, the solution was slowly warmed to −80 °C and treated with 90 mg of benzeneselenenyl chloride in 2 mL of THF. The mixture was warmed to −40 °C, acetic acid was added until pH 5, and then the solution was diluted with 30 mL of a half saturated NaCl solution. Extraction with 2 × 25 mL of EtOAc and processing of the organic layer in the usual manner, followed by chromatography on silica gel using a mixture of 10:2 hexanes–EtOAc as eluant gave 184 mg (71% yield) of product **12** as an oil: IR (film) 1770, 1740, 1610, 1560, and 1525 cm^{-1}; MS m/e 664 and 662 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 8.23–7.34 (m, 9 H, C_6H_5Se, 4 × ArH), 5.76 and 5.45 (d, 1 H, J = 11.7 Hz, C_3-CH), 5.30 and 5.25 (A of AB, 1 H, J_{gem} = 13.0 Hz and 12.9 Hz, $ArCH_A$), 5.18 and 5.05 (B of AB, 1 H, J_{gem} = 13.0 Hz and 12.9 Hz, $ArCH_B$), 4.17 and 4.13 (m, 1 H, J = 6.2 Hz, CHOSi), 4.03 (d, 1 H, J = 7.3 Hz, H_2), 3.80 (m, 1 H, H_5), 3.44 (m, 1 H, H_3), 3.04 and 2.96 (dd, 1 H, J = 5.1 Hz, J_{trans} = 2.3 Hz, H_6), 2.51 and 2.16 (td, 1 H, J_{gem} = 12.1 Hz and 11.7 Hz, $J_{4,3}$ = $J_{4,5}$ = 5.4 Hz, H_4), 1.99 (td, 1 H, J_{gem} = $J_{4,3}$ = 12.6 Hz, $J_{4,5}$ = 9.9 Hz, H_4'), 1.22 and 1.19 (d, 3 H, J = 6.2 Hz, C_6-C-CH_3), 0.88 and 0.86 (s, 9 H, C_4H_9Si), 0.08 and 0.07 (s, 3 H, CH_3Si), 0.06 and 0.05 (s, 3 H, $CH_3'Si$).

p-Nitrobenzyl (5*R*,6*S*)-6-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3-(nitromethylene)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (13). To a solution of compound **12**, 84.0 mg in 6 mL of CH_2Cl_2 at 0 °C, was added 39 μL of a 30% hydrogen peroxide solution with vigorous stirring. The mixture was warmed to 10 °C and stirred for an additional 45 min. The solution was diluted with 80 mL of CH_2Cl_2 and successively washed with 20 mL of H_2O, 2 × 20 mL of saturated $NaHCO_3$, and 20 mL of H_2O. Processing of the organic phase in the usual manner gave 64.1 mg (quant.) of compound **13** as an oil: IR (film) 1765, 1730, 1610, 1525, and 1350 cm^{-1}; MS m/e 448 (MH^+ − t-BuH); ^1H NMR (90 MHz, $CDCl_3$) δ 8.28–7.55 (m, 4 H, 4 × ArH), 7.20 (br, s, 1 H, $CHNO_2$), 5.34 (s, 2 H, $ArCH_2$), 5.15 (br s, 1 H, H_2), 4.22 (m, 1 H, J = 6.1 Hz, CHOSi), 3.89 (m, 1 H, H_5), 3.23–2.83 (m, 3 H, 2 × H_4, H_6), 1.24 (d, 3 H, J = 6.0 Hz, C_6-C-CH_3), 0.87 (s, 9 H, C_4H_9Si), 0.07 (s, 6 H, 2 × CH_3-Si).

p-Nitrobenzyl (2*R*,5*R*,6*S*)-6-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (14). To a solution of compound **13** (64.1 mg) in 12 mL of CH_2Cl_2 cooled at −50 °C was added 84 μL of dry MeOH, and ozone was bubbled in during 25 min at −78 °C. After passing a flow or argon for 10 min, 84 μL of Me_2S was added, and the solution was warmed at 0 °C over 15 min and stirred at 0 °C for 45 min. The mixture was then diluted with 35 mL of CH_2Cl_2 and washed with 5 mL of saturated $NaHCO_3$ and then 5 mL of H_2O. The aqueous layer was re-extracted with 2 × 20 mL of CH_2Cl_2, and the organic layers were combined and concentrated to give 59 mg (quant.) of the title compound **14** as an oil: $[\alpha]^{25}_D$ +49.5° (c 0.44, EtOAc); IR (film) 1760, 1720, 1610, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25–7.51 (m, 4 H, ArH), 5.31 (A of AB, 1 H, J_{gem} = 13.2 Hz, $ArCH_A$), 5.26 (d, 1 H, J_{gem} = 13.2 Hz, $ArCH_B$), 4.75 (s, 1 H, H_2), 4.31 (m, 1 H, J = 5.6 Hz, CHOSi), 4.14 (td, 1 H, J = 7.4 Hz, J_{trans} = 1.9 Hz, H_5), 3.15 (dd, 1 H, J = 5.1 Hz, J_{trans} = 1.9 Hz, H_6), 2.89 (dd, 1 H, J = 18.8 Hz, 6.9 Hz, H_4), 2.45 (dd, 1 H, J = 18.8 Hz, J = 7.8 Hz, H_4'), 1.28 (d, 3 H, J = 6.0 Hz, C_6-C-CH_3), 0.87 (s, 9 H, C_4H_9Si), 0.09 (s, 3 H, CH_3Si), 0.07 (s, 3 H, $CH_3'Si$). Anal. Calcd for $C_{22}H_{30}N_2O_7Si$ (462.56): C, 57.12; H, 6.53; N, 6.05. Found: C, 56.94; H, 6.03; N, 5.77.

p-Nitrobenzyl (5*R*,6*S*)-6-[(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-3-[[2-[[[(p-nitrobenzyl)oxy]carbonyl]amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (15). To a solution of β-keto ester **14** (46 mg, 0.1 mmol) in 1.5 mL of anhydrous CH_3CN were added 16 μL of diisopropylethylamine at 0 °C followed by diethyl chlorophosphate (64 μL). After stirring for 1 h, 24.0 mg of thiol ($HSCH_2CH_2N$-HCO_2PNB) in 7 mL of CH_3CN was added, followed by 16 μL of diisopropylethylamine. The mixture was stirred at 25 °C for 20 h, diluted with 15 mL of EtOAc, and washed with 2 × 5 mL of H_2O. The organic layer was processed as usual and the residue obtained upon evaporation was chromatographed using 10:7 hexanes–EtOAc to give 33 mg of **15** (51% yield, 2 steps) as an oil: $[\alpha]^{25}_D$ +31.71° (c 0.7, $CHCl_3$); IR (film) 3416, 1780, 1726, 1708 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6) δ 8.20 (m, 4 H, ArH), 7.66 (m, 2 H, 2 × ArH), 7.50 (m, 2 H, 2 × ArH), 5.45 (A of AB, 1 H, J_{gem} = 14 Hz, $ArCH_A$), 5.36 (br t, 1 H, J = 6.3 Hz, NH), 5.26 (B of AB, H, J_{gem} = 14 Hz, $ArCH_B$), 5.19 (s, 2 H, $ArCH_2$), 4.29–4.20 (m, 2 H, H_5,CH_3CH), 3.57–2.81 (m, 6 H, H_4, H_4', CH_2N, CH_2S), 3.17 (dd, 1 H, J = 5.3 Hz, J = 2.8 Hz, H_6), 1.25 (d, 3 H, J = 6.2 Hz, C_6-C-CH_3), 0.87 (s, 9 H, C_4H_9Si), 0.09 (s, 3 H, CH_3Si), 0.08 (s, 3 H, $CH_3'Si$).

p-Nitrobenzyl (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3-[[2-[[[(p-nitrobenzyl)oxy]carbonyl]amino]ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (*N*-[[(p-Nitrobenzyl)oxy]carbonyl]thienamycin p-Nitrobenzyl Ester) (16). To a solution of **15** (30 mg) in 12 mL of dry THF was added 1.26 mL of a freshly prepared solution containing tetra-n-butylammonium fluoride (360 mg) and 90 μL of acetic acid in 16 mL of THF. After stirring at room temperature for 24 h, another 1.26 mL of the fluoride reagent solution was added. The solution was stirred for another 24 h, concentrated to 0.5 mL, and charged onto a Waters μPorasil P/N 84175 normal phase column using EtOAc–hexanes (9:1). The retention time for **16** was 16.01 min, while that of **15** was 4.94 min. Evaporation of the fractions containing **16** gave 10.5 mg (40% yield, 78% based on recovered starting material) of a white solid, mp 184–185 °C: $[\alpha]^{25}_D$ +39.3° (c 0.15, THF); IR (Nujol mull) 2773, 1690 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 8.24 (m, 4 H, 4 × ArH), 7.80 (m, 2 H, 2 × ArH), 7.63 (m, 2 H, 2 × ArH), 6.88 (br s, 1 H, NH), 5.40 (dd, 2 H, J = 14 Hz, C*H*Ar), 5.24 (s, 2 H, 2 × C*H*Ar), 4.25 (ddd, 1 H, J = 10 Hz, 10 Hz, 2.8 Hz, H_5), 4.12 (dq, 1 H, J = 6.2 Hz, 6.1 Hz, CH_3CH), 3.25–3.55 (m, 5 H, H_6, H_4, H_4', CH_2N), 3.07 (m, 2 H, CH_2S), 1.26 (d, 3 H, J = 6.2 Hz, CH_3CHOH); reported[4] ^1H NMR (acetone-d_6) δ 8.28, 7.85, 7.69 (8 H, aromatic), 6.94 (1 H, br s, NH), 5.45 (2 H, AB, J = 14 Hz, C*H*Ar), 5.29 (2 H, s, C*H*Ar), 4.29 (1 H, ddd, J = 10 Hz, 10 Hz, 2.8 Hz, H_5), 4.16 (1 H, dq, J = 6.2 Hz, 6 Hz, CH_3CH), 3.3–3.6 (5 H, m, H_6, H_4, H_4', CH_2N), 3.1 (2 H, m, CH_2S), 1.29 (3 H, d, J = 6 Hz, CH_3CHOH).

Acknowledgment. We thank NSERCC and FCAR for financial support. We also thank Farmitalia Carlo-Erba for a sample of 4-acetoxy-3-[(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-azetidinone and Dr. D. G. Melillo, Merck & Co., for an authentic sample of compound **14** (as the 8-hydroxy analogue).