Synthesis of Carbacephems from Serine

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Carbacephems have been synthesized from D-serine by two routes involving construction first of the six-membered ring followed by cyclization to give the bicyclic β-lactam. In one route, alkylation of a lactim ether was accomplished with $Ni(Acac)_2$ as a catalyst. The desired R stereochemistry at the carbon corresponding to C-6 of the cephem was obtained by stereospecific hydrogenation of a vinylogous carbamate. The second route involved a stereospecific Michael cyclization to give the same C-6 stereochemistry. Closure of a piperidyl β-amino acid intermediate common to both routes was accomplished using a modified Mukaiyama reagent found to be superior in our system to the traditional reagent. The resulting carbacephem core was stereospecifically substituted at C-7 with an ethyl or amino functionality. The ethylated intermediate was transformed into a stable enol triflate useful for the further elaboration of biologically important carbacephems.

Introduction

Since the discovery of penicillin in 1928, β-lactam antibiotics have remained a premier class of drugs used for the treatment of bacterial infections.[1] Carbacephems represent a recently developed class of this β-lactam type antibiotic closely related to the widely used cephalosporins.[2] While both have similar antibacterial profiles, the carbocyclic 1-carba-1-dethiacephems are chemically more stable and possess enhanced pharmacokinetic properties relative to cephalosporins. These advantageous properties have engendered major interest in carbacephems as clinically viable drugs.

The vast majority of syntheses of carbacephems begin with the formation of the azetidinone, followed by closure of appropriate tethers to form the fused six-membered ring portion of the molecule.[3] A widely used method of forming the initial β-lactam is still the classical (2 + 2) addition of a ketene to an imine,[4] and an extensive number of reports have appeared that elegantly utilize this reaction to enter into the carbacephem framework.[1b] There have been only a few examples, however, of carbacephem syntheses that form the six-membered ring first, followed by the closure of the β-lactam.[5] The advantage of this latter strategy may be that by closing the sensitive four-membered ring later in the synthesis, conditions may be used prior to its closure that otherwise might be incompatible with the labile azetidinone moiety. This strategy has seen limited use, due in part to the perceived difficulty in closing a four-membered ring to form the bicyclic β-lactam.

Our objective was to develop a synthetic route applicable to the carbacephems that would allow control of stereochemistry at C-6 of the carbacephem skeleton, an important chiral center directly related to the biological activity of the carbacephems. In addition, we sought to install an initial functionality from which the double bond and enol ether at C-3 of the carbacephem could be easily generated, thus facilitating further elaboration on the six-membered ring.

Beginning from D-serine, two potential pathways were projected to arrive at the carbacephem skeleton (Figure 1). Both rely on the intermediate **A**, which in path I would be used to form a lactam possessing two chiral centers that would serve as stereochemical directors for inducing the necessary R stereochemistry at C-6 in the carbacephem. For example, hydrogenation of compound **C** should occur preferentially from the rear of the molecule, guided by the bulky protecting groups blocking approach from the front. Conversely, should the opposite (S) stereochemistry at C-6 be desired, this could be effected by starting with L-serine. Also, there is the potential for alkylating compound **B**, perhaps stereoselectively, which would correspond to C-5 of the [4.2.0] carbacephem skeleton (C-1 in cephalosporin numbering regimen).

An alternative strategy involves a potentially stereoselective Michael cyclization utilizing the same chiral directors (path II, Figure 1) as in path I. A suitably protected amine **D** should add in a Michael sense stereoselectively to an ene-ester if the other face of the double bond was sufficiently blocked, thus generating the needed stereochemistry at C-6 of the carbacephem.

Once the six-member ring intermediate **E** is in hand, what remains to complete the carbacephem skeleton is closure of the fused β-lactam. This late closure has proven to be inefficient for many syntheses of the carbacephems using this sequence.[5] We have been able to overcome this hurdle, however, through development of a new carboxylate activating group, which is related to the classical Mukaiyama pyridinium iodides.[6]

(1) Overviews of β-lactam antibiotics are presented in the following: (a) *The Chemistry of* β-Lactams; Page, M. I., Ed.; Blackie Academic & Professional: New York, 1992. (b) *The Organic Chemistry of* β-Lactams; Georg, G. I., Ed.; VCH Press: New York, 1993. (c) Samarendra, C. I.; Maiti, N.; Micetich, R. G.; Daneshtalab, M.; Atchison, K.; Phillips, O. A.; Kunugita, C. *J. Antibiot.* **1994**, *47*, 1030 and references therein.

(2) (a) Hornback, W. J.; Munroe, J. E.; Counter, F. T. *J. Antibiot.* **1994**, *47*, 1052. (b) Cooper, R. D. G. *Am. J. Med.* **1992**, *92*, 6A−2S.

(3) Ternansky, R. J.; Morin, J. M., Jr. Novel Methods for the Construction of the β-Lactam Ring. In *The Organic Chemistry of* β*-Lactams*; Georg, G. I., Ed.; VCH Press: New York, 1993; p 257.

(4) Staudinger, H.; Klever, H. W.; Kober, P. *Liebigs Ann. Chem.* **1910**, *1*, 374.

(5) Benrien, J.-F.; Billion, M.-A.; Husson, H.-P.; Royer, J. *J. Org. Chem.* **1995**, *60*, 2922.

(6) Mukaiyama, T. *Angew. Chem., Int. Ed. Eng.* **1979**, *18*, 707 and references therein.

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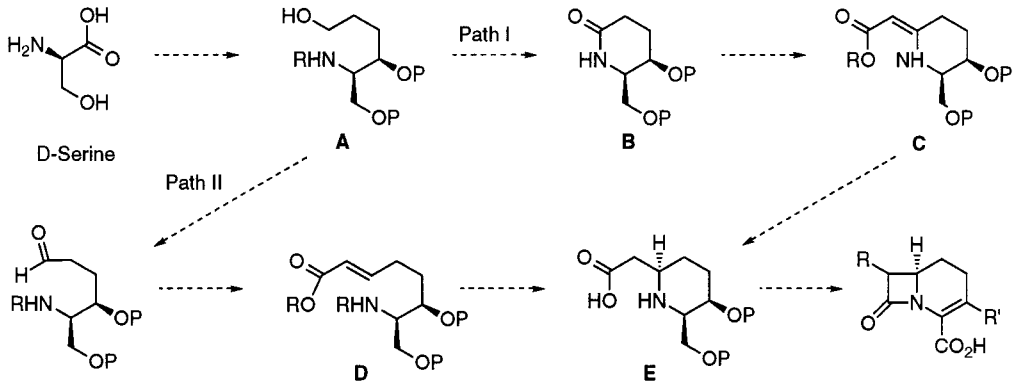
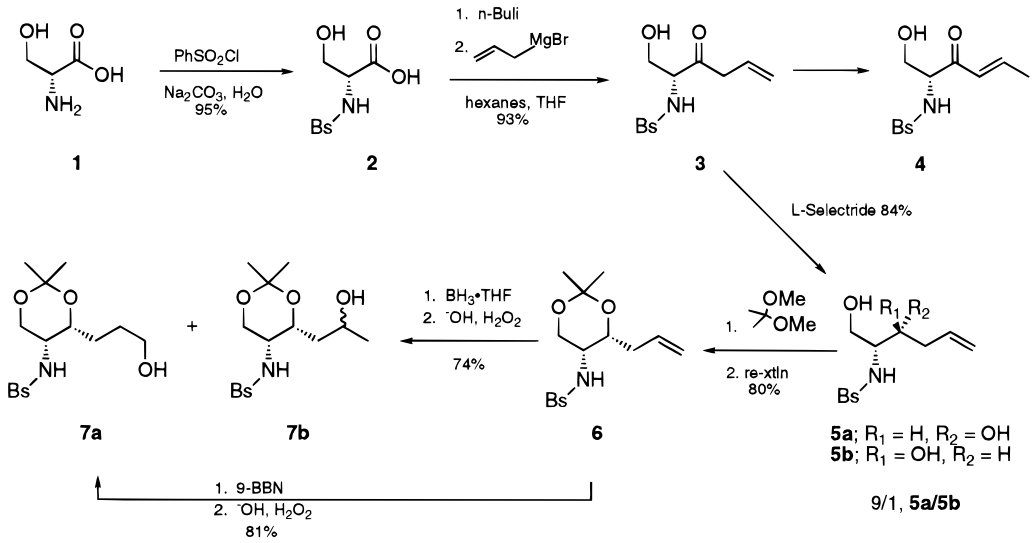


Figure 1. Strategies to the carbacephem core via D-serine.

Scheme 1. Preparation of Amino Alcohol 7 from Serine



Results and Discussion

Preparation of the Common Intermediate (4*R*,5*R*)-5-[(Phenylsulfonyl)amino]-4-(3-hydroxypropyl)-2,2-dimethyl-1,3-dioxane (7a). To explore both synthetic routes depicted in Figure 1, an efficient, high-yielding procedure to generate the amino alcohol **7a** (Scheme 1) was required. This was accomplished by converting the carboxyl group of N-protected D-serine **2** to the allyl ketone **3** under nonracemic conditions, using methodology that had been developed previously, with some important modifications (Scheme 1).[7] Interestingly, the yield in the conversion of acid **2** to ketone **3** was found to be directly related to the proportion of hexane present in the reaction mixture (Table 1).[8] The greater the proportion of hexane in the mixture, resulting from the molarity in hexane of the *n*-BuLi used, the lower the yield of the resultant ketone **3**. For example, using 1.6 M *n*-BuLi as the base gave a yield of 62% (entry 2), but by using 10 M *n*-BuLi as the base (entry 5), the yield of ketone **3** was increased to 90−95%. Initially, it was not clear whether this effect was caused by the presence of hexane in the solvent or the concentration of the *n*-BuLi. Experiments (entries 6 and 7) in which the ratio of hexane in the reaction mixture was kept constant and the concentration of the added *n*-BuLi was varied gave very similar yields, leading to the conclusion that it is the amount of hexane present in the reaction mixture not the concentration of the added *n*-BuLi that influences the yield. Clearly the polarity of the solvent has a major role in the reactivity of the polyanions involved.

Table 1. Allylation of Protected D-Serine (2 → 3) in THF/Hexane

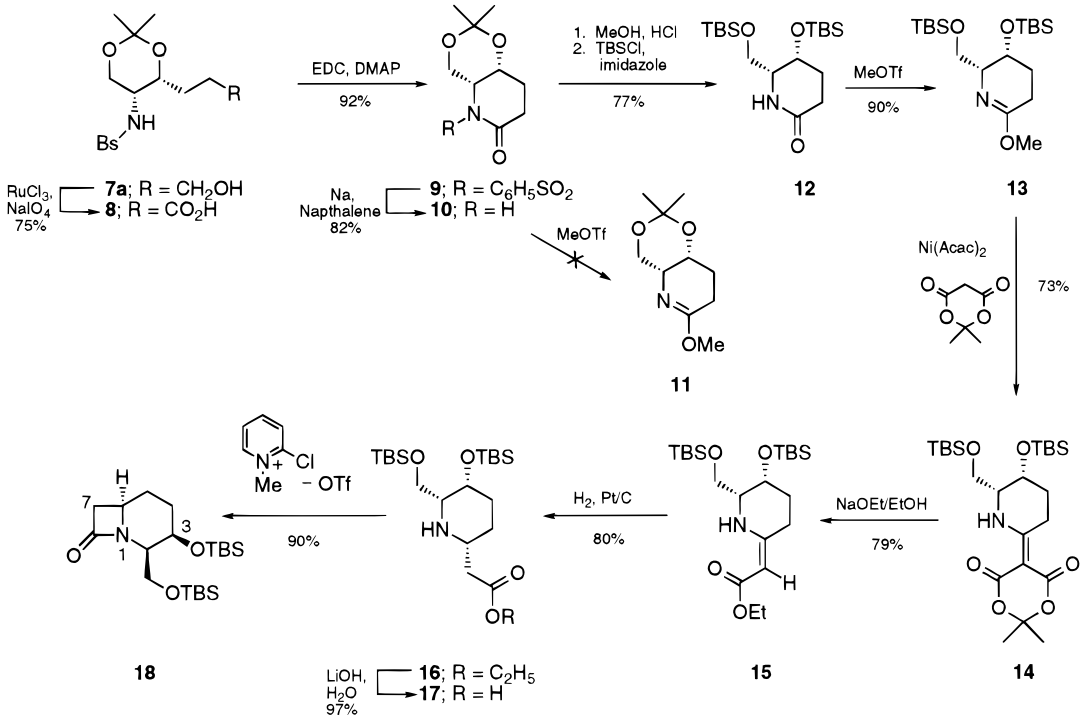
entry	*n*-BuLi (M)	hexane (mL)	% hexane in solvent	% yield
1	1	10	17	46
2	1.6	6.3	11.2	62
3	2.5	4.0	7.4	76
4	5	2.0	3.8	80
5	10	1.0	2	93
6	7.4	1.4	2.6	67
7	1.6	1.4	2.4	71

The mode of quenching in the transformation of **2** to **3** was also found to be pivotal to the success of the reaction. If the quench of the reaction mixture was not kept below 0 °C, a small percentage of the recovered product was the α,β-unsaturated ketone **4**. Also, β,γ-unsaturated ketone **3** slowly isomerizes to conjugated ketone **4** on storage at room temperature for a few months, causing some initially low yields in the reduction of the ketone carbonyl of **3** to form the diols **5a**,**b**. The ease of isomerization of ketone **3** to **4** was demonstrated by treating ketone **3** with 290 mol % of triethylamine in THF for 19 h at room temperature, resulting in complete conversion to the α,β-unsaturated ketone **4**. Subsequent

(7) (a) Knudsen, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260. (b) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866.

(8) Initial observation of this effect was made by N. Atanes of this laboratory.

Scheme 2. Preparation of Carbacephem Core via Lactim Ether Route



NMR doping experiments on stored β,γ-unsaturated ketone **3** revealed that 4−5% of the ketone had undergone double-bond migration over 4 months of storage at room temperature. This small amount of ketone **4** impurity can be diminished by recrystallization from ethyl acetate to <1.5%. Storage, however, at 0 °C for no longer than 2 weeks before use completely eliminates ketone **4**.

Reduction of ketone **3** to the diols **5a**,**b** was accomplished using L-selectride in a modification of the reported[7b] procedure, resulting in a 9/1 mixture of diastereomers **5a** and **5b** in 84% yield. The mixture was converted into the corresponding isopropylidine ketals, from which the major diastereomer **6** was easily isolated by crystallization from ethyl acetate in high overall yield. Conversion of olefin **6** to the primary alcohol **7a** by hydroboration was investigated to determine conditions under which minimal secondary alcohol **7b** would be formed. Previous studies[7b] reported only primary alcohol **7a** using borane; however, in our hands, hydroboration with BH_3·THF at room temperature followed by oxidation gave a mixture of alcohols **7a** and **7b** in a ratio of 9.5/1 and an overall yield of 73%. Conducting the hydroboration at −10 to 0 °C decreased the yield to 53% with a **7a**/**7b** ratio of 4.6/1, while hydroboration at 40 °C resulted in a 74% overall yield and a 10/1 ratio. Borane therefore was abandoned, and instead, treatment of **6** with the more hindered 9-BBN at room temperature followed by oxidation gave only primary alcohol **7a** in 81% yield. With **7a** in hand, the two potential routes (I and II, Figure 1) to carbacephem could be explored.

Preparation of the Carbacephem Core by the Lactim Ether Route (Scheme 2). The lactim route to the carbacephem core relies on the generation of the lactim ether **13**, followed by conversion to the amino ene-ester **15** and subsequent stereospecific hydrogenation to the cis ester **16**. A perceived advantage of this route is the potential for incorporation of functionality at C-5 in the [4.2.0] octane system **18** via substitution at the α-methylene in lactam **12**.

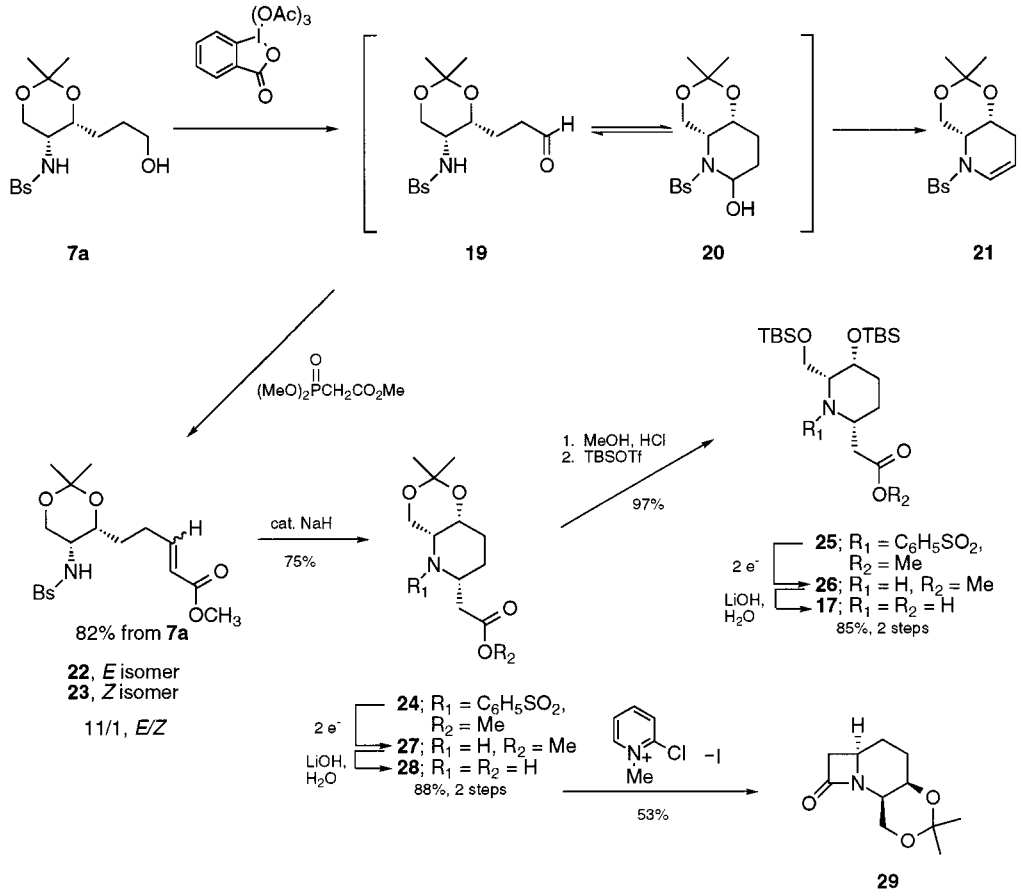
Oxidation of amino alcohol **7a** with catalytic ruthenium trichloride and $NaIO_4$ to amino acid **8** (75% yield) was followed by closure to lactam **9** using EDC/DMAP in 92% yield. Removal of the *N*-benzenesulfonyl group with Na/naphthalene gave the unprotected lactam **10** in 82% yield, but attempted conversion of lactam **10** to lactim ether **11** using methyl triflate failed; only recovered starting material was obtained. On the assumption that lactim ether **11** is formed but because of strain is unstable to the isolation conditions, the isopropylidine ring was opened and the diol was reprotected as silyl ether. Reaction of the resulting disilyl ether lactam **12** with methyl triflate gave the lactim ether **13** in 90% yield.

Conversion of lactim ether **13** to the amino ene-ester **15** was accomplished by first condensing the lactim ether with Meldrum's acid in the presence of catalytic $Ni(Acac)_2$ giving the 2,2-dimethyl-4,6-dioxo-1,3-dioxanylidene derivative **14** in 73% yield;[9] monodecarboxylation using NaOEt/ethanol gave the amino ene-ester **15** (79% yield). Subsequent hydrogenation using Pt as a catalyst gave only the cis diastereomer, 6*R*-ethoxycarbonylmethyl-substituted piperidine **16**, in 80% yield. Hydrolysis of ester **16** with LiOH gave the amino acid **17** in 97% yield.

With the amino acid **17** in hand, the next step was cyclization of the amino acid to form the bicyclic β-lactam **18**. To accomplish this transformation, either the carboxyl or the amino group must be activated. Increasing the nucleophilicity of the nitrogen was explored using various metallo intermediates. Strategies using orga-

(9) Other examples of lactim ether condensations using $Ni(Acac)_2$ are presented in the following: Provot, O.; Celerier, J. P.; Petit, H.; Lhommet, G. *Synthesis* **1993**, 69 and references therein.

Scheme 3. Michael Cyclization Route to Carbacephem Core



noaluminum reagents to activate amines in the formation of amides from carboxylic esters have been reported,[10] and there are also reports of similar aluminum reagents being utilized in β-lactam formation.[11] Other elements that have been utilized to activate amines to induce β-lactam formation include silicon[12] and magnesium.[13] Of particular interest is the use of mesitylmagnesium bromide, which is less likely to attack the carbonyl of the ester moiety.[13d,e] All attempts at using nitrogen activation with amino ester **16**, however, met with limited success, giving low yields of **18** with many side products.

Activation of the carboxyl group was next explored using an activated ester. Both the *p*-nitrophenyl and pentafluorophenyl esters were prepared. In the former case, the amino group was protected as its BOC derivative and in the latter as its CBZ.[14] Subsequent removal of the protecting groups (BOC by acid followed by pyridine; CBZ by hydrogenolysis) under appropriate dilution conditions produced little β-lactam.

A common method for activating carboxylic acids toward nucleophilic substitution is the use of *N*-methyl-2-chloropyridinium iodide (Mukaiyama's reagent). It has also been used to generate monocyclic β-lactams[15] and also a bicyclic β-lactam.[5] Applying Mukaiyama's reagent to amino acid **17** did result in cyclization. Yields, however, were poor; examination of a number of parameters (solvent, dilution, time, and temperature) gave yields in the 50% range at best.

Any further improvement in the cyclization to β-lactam with this reagent probably would require modification of the reagent. What this modification might be was suggested by the reported[16] halogen exchange of *N*-alkyl-2-halopyridinium halides at elevated temperatures. The importance of this report was underlined by the observation that *N*-alkyl-2-iodopyridinium salts are poor carboxylate activating agents.[17] Possibly the Mukaiyama reagent was undergoing this exchange, leading to lower yields of the desired cyclization; even a large excess of *N*-methyl-2-chloropyridinium iodide did not produce higher yields in the closure.

A less nucleophilic anion than iodide in the pyridinium salt would prevent this potentially deactivating halogen exchange and might give higher yields in the cyclization. Although several different counterions have been examined,[6] they did not include triflate. The triflate ion would be the most attractive candidate for use as a counterion due to its lack of nucleophilicity. Thus, *N*-methyl-2-

(10) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989. (c) Sidler, D. R.; Lovelace, T. C.; McNamara, J. M.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 1231.

(11) Vorbrüggen, H.; Woodward, R. B. *Tetrahedron* **1993**, *49*, 1625 and references therein.

(12) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157.

(13) (a) Breckpot, R. *Bull. Soc. Chim. Belg.* **1923**, *32*, 412. (b) Tufariello, J. J.; Lee, G. E.; Senaratne, P. A.; Al-Nuri, M. *Tetrahedron Lett.* **1979**, *20*, 4359. (c) Kametani, T.; Nagahara, T.; Suzuki, Y.; Yokohama, S.; Huang, S.-P.; Ihara, M. *Heterocycles* **1980**, *14*, 403. (d) Searles, S., Jr.; Wann, R. E. *Chem. Ind. (London)* **1964**, 2097. (e) Shibuya, M.; Kuretani, M.; Kubota, S. *Tetrahedron Lett.* **1981**, *22*, 4453.

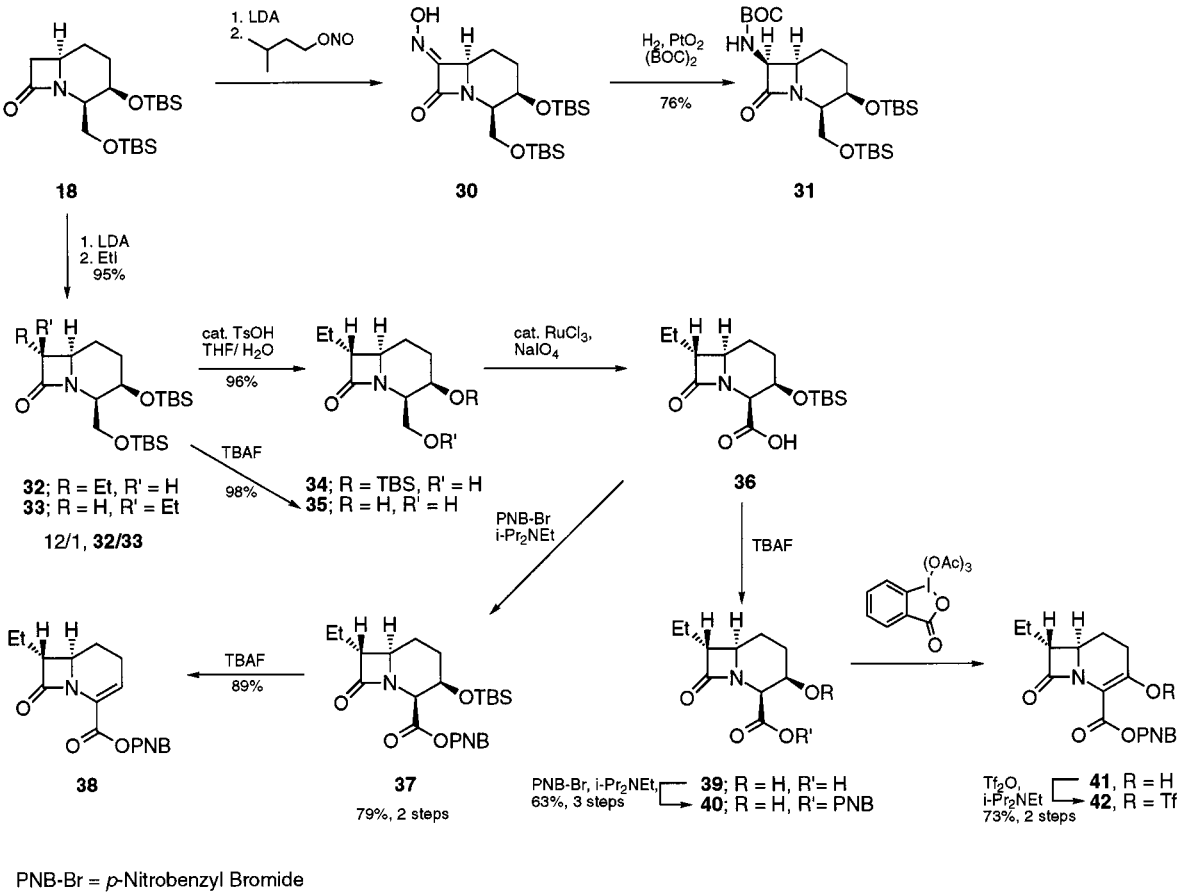
(14) (a) Lagarias, J. C.; Houghten, R. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 8202. (b) Schmidt, U.; Lieberknecht, A.; Bökens, H.; Griesser, H. *J. Org. Chem.* **1983**, *48*, 2680.

(15) (a) Amin, S. G.; Glazer, R. D.; Manhas, M. S. *Synthesis* **1979**, 210. (b) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 1465.

(16) Bradlow, H. L.; Vanderwerf, C. A. *J. Org. Chem.* **1951**, *16*, 1143.

(17) Sutherland, J. K.; Widdowson, D. A. *J. Chem. Soc.* **1964**, 4650.

Scheme 4. Functionalization of the Cephem Core



PNB-Br = *p*-Nitrobenzyl Bromide

chloropyridinium and *N*-methyl-2-bromopyridinium triflates were prepared in quantitative yield using methyl triflate and the respective 2-halopyridine in CH_2Cl_2. *N*-methyl-2-chloropyridinium triflate was indeed superior as a cyclizing agent consistently giving 90% yields in the conversion of amino acid **17** to bicyclic β-lactam **18**.

Preparation of the Carbacephem Core Using a Stereospecific Michael Cyclization (Scheme 3). As a more direct alternative to the lactim ether route (Scheme 2) for the formation of the carbacephem core, we explored the possibility of using a stereocontrolled Michael cyclization on an amino ene-ester such as **22** or **23** (Scheme 3) to generate the piperidine **24** possessing the R stereochemistry of the methoxycarbonylmethyl tether required in the β-lactam. The steric bulk of the isopropylidine ring should block one face of attack onto the ene-ester, giving at the least a favorable mixture of diastereomers.

Thus, the amino alcohol **7a** was oxidized to aldehyde **19** using the Dess−Martin periodinane.[18] Attempted purification of aldehyde **19** using SiO_2, neutral alumina, or Florisil led to the recovery of enamine **21**, presumably due to dehydration of the hemiaminal form **20** of the aldehyde; a similar observation has been reported recently.[19] If crude aldehyde **19**, however, is used directly in the next step, no enamine is formed. In this manner, reaction of crude aldehyde **19** with the potassium salt of trimethoxy phosphonoacetate gave the diastereomeric amino ene-esters **22** and **23** in a ratio of 11/1 in 82% yield from amino alcohol **7a**.[20] Reaction of either diastereomer **22** or **23** with catalytic NaH in DME at 50 °C gave only a single diastereomeric product, in 50−60% overall yield, as well as recovered starting material.[21] The mass balance for the conversion was 97−100%. If higher temperatures were used, the mass balance decreased considerably and the reaction mixture became more complicated. With one recycling of the recovered starting material **22** or **23**, the yield for the cyclization is 75%, with 20−25% recovered starting material. The structure of the cyclized product was determined by single-crystal X-ray analysis to be as shown in **24** (Scheme 3).

The next step in the sequence required the removal of the benzenesulfonyl moiety in **24** in the presence of the methyl ester. Classical cleavage methods for arylsulfonamides such as Na/naphthalene led to reduction of the ester as well as removal of the benzenesulfonyl group. However, an electrochemical method for removing arylsulfonyl groups from amines has been described[22] in which phenol is used to quench the amine anion as well as the arylsulfonyl anion and to absorb any bromine liberated from the electrolyte. Use of this protocol led to a mixture of amino acid **28**, amino ester **27**, and unchanged substrate **24**, undoubtedly due to the presence of moisture that caused ester hydrolysis. The difficulty in working with the very hygroscopic phenol was overcome by simply changing the proton source to the

(18) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(19) Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180.

(20) A critical review of Wittig chemistry is presented in the following: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(21) A related example is presented in the following: Shishido, K.; Sukegawa, Y.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 993.

(22) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367.

nonhygroscopic 4-phenylphenol. With this change, the benzenesulfonyl group could be removed electrolytically from **24** to produce amino ester **27** in 90% yield. Using 4-phenylphenol as the proton source has been found to be of general use in the electrolysis of a variety of different substrates and is a significant improvement to the published procedure using phenol, especially for compounds possessing other sensitive functionalities.

Hydrolysis of the ester in **27** to acid **28** with LiOH proceeded in 98% yield. Isolation of the zwitterionic species **28**, however, was difficult and capricious. Nonetheless, once in hand, cyclization of the amino acid **28** with *N*-methyl-2-chloropyridinium iodide gave the β-lactam **29** in 53% yield. The difficulties in handling **28** led us to abandon this path and attempt a crossover route from amino ester **24** to the disilyl protected amino acid **17** (Scheme 3). An interchange at this point would allow determination of the absolute stereochemistry of compound **17** obtained from the lactim ether route (Scheme 2) based on the X-ray crystal structure of compound **24** and also would allow the use of the more efficient Michael cyclization chemistry in the preparation of amino acid **17**. Following this plan, cleavage of the isopropylidine group in acetonide **24** with HCl/MeOH, followed by reprotection of the intermediate diol with TBSOTf, gave the piperidine derivative **25** in 97% yield. Electrolytic removal of the benzenesulfonyl group in bissilyl ether **25** followed by hydrolysis of the resultant amino ester **26** using LiOH gave the amino acid **17** in 85% yield for the two steps. The amino acid **17** obtained from this route was identical to amino acid **17** obtained from the lactim ether route.

Preparation of C-7-Substituted Analogues (Scheme 4). The three chiral centers at C-2, C-3, and C-6 in β-lactam **18** should be dominant in directing the stereochemistry of any substitution at C-7. For example, deprotonation at C-7 in β-lactam **18** with LDA, followed by reaction with isoamyl nitrite, gave the oxime **30** as a mixture of isomers.[23] The oxime was hydrogenated using PtO_2 as a catalyst, and the resultant amine was protected as the *tert*-butyl carbamate in 76% overall yield. The stereochemistry at C-7 was determined to be S based on the coupling constants between H-6 and H-7. This is also the predicted stereochemistry based on the fact that the C-2 and C-3 silyloxy moieties and the C-6 alkyl group block attack from the β face of the molecule. While compound **31** was not carried further, the methodology developed for the preparation of the target enol triflate from disilyl **32** bearing a C-7 alkyl substituent should be applicable to the 7β-amino-substituted carbacephem.

On the basis of these steric considerations, alkylation at C-7 was predicted to provide the α-alkyl derivative. When β-lactam **18** was ethylated using LDA followed by EtI, a 12/1 mixture was obtained of 7*R*-ethyl **32** and its 7*S*-epimer **33** in 95% overall yield. The diastereomers could be easily separated by chromatography, and it was found that **33** fortuitously could be obtained in crystalline form, suitable for X-ray analysis. The X-ray crystal structure of **33** (Figure 2) thus confirms all previous stereochemical assignments.

The β-hydroxy ester **40** is a crucial intermediate in the preparation of the target molecule. Two possible routes

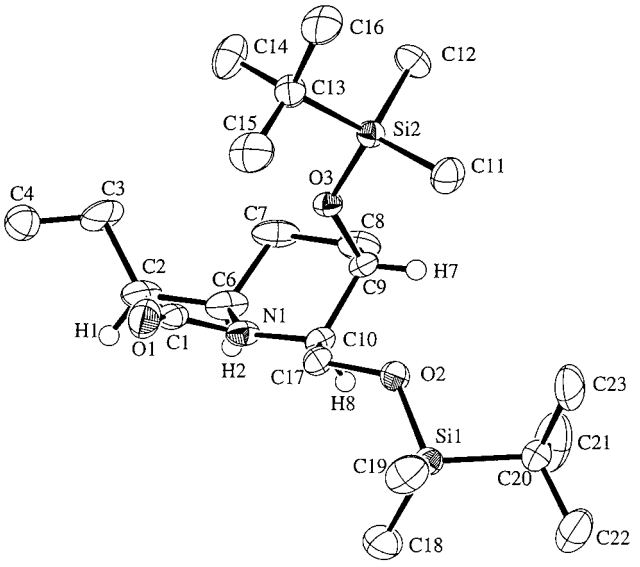


Figure 2. Structure of (2*R*,3*R*,6*R*,7*S*)-3-*tert*-butyldimethylsiloxy-2-*tert*-butyldimethylsiloxymethyl-7-ethyl-8-oxo-1-azabicyclo[4.2.0]octane (**33**) as determined by X-ray crystallography (arbitrary numbering system).

to this hydroxy ester were envisioned from disilyl **32**. The first route involved removal of both protecting groups with excess TBAF in THF to give diol **35** in 98% yield. Selective oxidation of the primary alcohol in the presence of the secondary hydroxyl group to give hydroxy acid **39** was attempted using a Pt/O_2 protocol previously applied to similar systems.[7b] While Pt/O_2 oxidation was successful in the synthesis of cyclic and acyclic β-hydroxy α-amino acids, we were unable to obtain **39** by this method. Alternatively, monodeprotection of the primary silyl group of **32** with catalytic *p*-TsOH in THF/H_2O gave the alcohol **34** in 96% yield.[24] Ruthenium-catalyzed oxidation[25] of **34** followed by esterification of acid **36** using excess *p*-nitrobenzyl bromide gave PNB ester **37** in 79% yield. Attempts to remove the silyl ether of **37** in the presence of the *p*-nitrobenzyl ester using TBAF led to elimination and formation of the α,β-unsaturated ester **38**. Reversing the sequence from **36** by first removing the silyl ether and then esterifying hydroxy acid **39** provided hydroxy ester **40** in 63% overall yield from **35**.

With the key intermediate **40** in hand, completion of the synthesis of the target carbacephem only required oxidation to the β-keto ester. The objective was to obtain the enol triflate **42** protected as a *p*-nitrobenzyl ester, since structurally related carbacephems are known to be stable intermediates useful for extrapolation to biologically active β-lactam antibiotics.[26] Oxidations of β-hydroxy esters to β-keto esters are challenging because of the potential fragmentation of the C-C bonds α and β to the ester.[27] This was readily apparent when application of a DMSO-based oxidation led to a very complex reaction mixture containing very minor amounts of **41**. On the other hand, β-keto esters have been successfully prepared

(23) For a related example, see: Yamashita, H.; Minami, N.; Sakakibara, K.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1988**, *36*, 469.

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under mild conditions using Dess−Martin periodinane.[28] With this reagent, β-keto ester **41** was obtained as an unstable mixture of keto and enol forms from 200 mol % of the periodinane in CH_2Cl_2. After an aqueous wash, the isolated oil was treated with 200 mol % of triflic anhydride to trap the enol form and to give the target carbacephem **42** in 73% yield from hydroxy ester **40**.

Conclusion

A process has been developed for the synthesis of carbacephems from D-serine. The process proceeds by preparing the suitably substituted piperidine-2-acetic acid, which is then very efficiently cyclized to the β-lactam. Both the relative and absolute stereochemistry are specifically controlled, with the prospect for inversion, should L-serine be used as the educt. The process presents various opportunities for introduction of substituents.

Experimental Section

General. All reactions were conducted under an atmosphere of nitrogen or argon, and solvents were distilled immediately before use unless otherwise noted. THF and diethyl ether were distilled from sodium/benzophenone, CH_3CN was distilled from P_2O_5 and then from CaH_2, DMF was dried over 4 Å molecular sieves, methylene chloride and toluene were distilled from CaH_2, and ethyl acetate, hexanes, 2-propanol, and chloroform were used as purchased. Tetraethylammonium bromide (TEAB) was recrystallized 4 times from abs EtOH, and 4-phenylphenol was recrystallized from abs EtOH then sublimed at 100 °C/25 Torr. ^{1}H and ^{13}C NMR were taken in $CDCl_3$ unless otherwise stated, and chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. Numbers in parentheses following the chemical shifts in ^{13}C NMR data correspond to the number of hydrogens attached to that carbon atom, as determined by DEPT 90 and DEPT 135 NMR experiments. Column chromatography was performed using EM Science silica gel 60 (70−230 mesh). Preparative TLC was carried out using preformed plates (Analtech) of 250−2000 μm thickness. All final organic extracts were dried over Na_2SO_4 and filtered before evaporation unless otherwise noted. Melting points are uncorrected. Elemental analyses were determined by the Microanalytical Laboratories, University of California, Berkeley.

***N*-Phenylsulfonyl-D-serine (2).** **2** was prepared by treating D-serine (50.0 g, 476 mmol) with $Na_2CO_3 \cdot H_2O$ (148 g, 1.19 mol) and phenylsulfonyl chloride (100 g, 563 mmol) as described for L-serine[29] with the following changes. The reaction mixture was stirred at room temperature for 24 h and then was washed with hexanes (3 × 300 mL). The aqueous phase was acidified to pH 1.2 with 85% H_3PO_4 whereupon a white precipitate formed. After being stored at 0 °C for 24 h, the mixture was filtered, and the crystals were washed with Et_2O (400 mL) and air-dried to give the protected serine **2** as fluffy white crystals (110 g, 95%): mp 232−233 °C (lit.[7b] 222−224 °C, dec); $[\alpha]^{22}_D$ −10.3 (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, Me_2SO-*d*6) δ 3.48−3.52 (m, 2H), 3.71−3.80 (m, 1H), 7.53−7.61 (m, 3H), 7.79 (d, *J* = 7.1 Hz, 2H), 8.0 (d, *J* = 8.4 Hz, 1H) [lit.[25] δ 3.56 (d, *J* = 6 Hz, 2H), 3.83 (m, 1H), 7.5−8.2 (m, 7H)].

(*R*)-5-[(Phenylsulfonyl)amino]-6-hydroxy-4-hexenone (3). A mixture of the protected d-serine **2** (70.1 g, 286 mmol) in 2.3 L of dry THF in a 5 L three-neck Morton flask equipped with a mechanical stirrer, a reflux condenser, and a gas inlet was heated at reflux for 45 min until the solution became homogeneous. The solution was then cooled to −75 °C, and *n*-BuLi (70.0 mL, 10.0 M in hexanes, 0.7 mol, 245 mol %) was added dropwise over 35 min, keeping the temperature of the reaction mixture below −69 °C. The orange mixture was stirred an additional 20 min and allowed to warm to 0 °C over 1 h. Allylmagnesium bromide (950 mL, 0.85 M in Et_2O, 0.81 mol, 282 mol %) was added dropwise over 1.5 h. After the addition was complete, the olive-green mixture was stirred for an additional 25 min at 0 °C and allowed to warm to room temperature over 1 h. Stirring was continued at room temperature for 17 h, and the mixture was then cooled to 0 °C and cannulated below the surface of 3 L of a 0.75 M solution of H_3PO_4 at 0 °C at such a rate as to keep the temperature of the quenched mixture below 2 °C. The layers were separated, and the aqueous phase was extracted with Et_2O (4 × 500 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 300 mL) and brine (300 mL), dried, and evaporated, leaving a white solid, which as determined by NMR analysis, was pure ketone **3** (71.7 g, 93%): mp 110−111 °C (lit.[7b] mp for *S*-**3**, 1.09−110 °C); $[\alpha]^{22}_D$ −99.4 (*c* 1, $CHCl_3$); (lit.[7b] for *S*-**3**, $[\alpha]^{20}_D$ +72.4 (*c* 2, $CHCl_3$); ^{1}H NMR δ 2.19 (bs, 1H), 3.14−3.26 (m, 2H), 3.82−3.99 (m, 3H), 5.02−5.15 (m, 2H), 5.65−5.71 (m, 1H), 5.81−5.83 (m, 1H), 7.48−7.62 (m, 3H), 7.79−7.83 (m, 2H). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.6; N, 5.2. Found: C, 53.7; H, 5.7; N, 5.2.

(*R*,*E*)-5-[(Phenylsulfonyl)amino]-6-hydroxy-2-hexen-4-one (4). To a solution of β,γ-unsaturated ketone **3** (0.995 g, 3.7 mmol) in 40.0 mL of dry THF was added Et_3N (1.50 mL, 10.8 mmol). The yellow solution was stirred at room temperature for 19.5 h and then quenched with 10 mL of saturated aqueous KH_2PO_4. The quenched mixture was stirred for an additional 5 min, then evaporated, and the aqueous residue was extracted with Et_2O (50 mL) and EtOAc (50 mL). The pH of the aqueous phase was adjusted to 4.0 with 1 M H_3PO_4, and the solution was extracted with EtOAc (2 × 20 mL). The combined organic phase was dried and evaporated, leaving an off-white solid, which as determined by NMR analysis, was the α,β-unsaturated ketone **4** (0.980 g, 98%): recrystallization from EtOAc, mp 122−123 °C; $[\alpha]^{24}_D$ −53.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 1.89 (dd, *J* = 6.9, 1.6 Hz, 3H), 2.37 (bs, 1H), 3.80−3.90 (m, 2H), 4.13−4.16 (m, 1H), 5.97 (d, *J* = 6.7 Hz, 1H), 6.19 (dq, *J* = 15.5, 1.6 Hz, 1H), 6.97 (dq, *J* = 15.5, 6.9 Hz, 1H), 7.48−7.60 (m, 3H), 7.84−7.86 (m, 2H); ^{13}C NMR δ 18.6 (3), 61.8 (1), 63.4 (2), 127.07 (1), 127.10 (1), 129.2 (1), 133.0 (1), 139.4 (0), 146.9 (1), 193.7 (0). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.6; N, 5.2. Found: C, 53.5; H, 5.7; N 5.1.

(4*R*/*S*,5*R*)-5-[(Phenylsulfonyl)amino]-4,6-dihydroxy-2-hexene (5a,b). To a 500 mL three-neck flask equipped with a magnetic stirrer and an addition funnel was added a solution of l-selectride (96 mL, 96 mmol, 1.0 M in THF) followed by an additional 140 mL of THF, and the solution was cooled to −78 °C. The addition funnel was charged with a solution of ketone **3** (12.0 g, 44.56 mmol)[30] in 60 mL of THF, which was added to the vigorously stirred L-selectride solution, keeping the temperature of the reaction mixture below −73 °C. After the addition was complete (ca. 15 min), the reaction mixture was stirred at −78 °C for 2 h, 200 mL of a 1/1 solution of glacial acetic acid and water was added to the cold reaction mixture over 1 min, the cold bath was removed, and the mixture was allowed to warm to room temperature over 1 h. The mixture was concentrated to 40% of its original volume and diluted with saturated aqueous $NaHCO_3$ (196 mL), the pH (4.5) was adjusted to 10.5 using 6 M NaOH (ca. 220 mL), and 70 mL of 30% H_2O_2 was added. (Caution! exothermic reaction.) The warm mixture was stirred at room temperature for 1 h and washed with hexanes (2 × 75 mL); this wash was set aside. The aqueous layer was next extracted with a 1/3 IPA/$CHCl_3$ (4 × 150 mL), and the combined organic layer was dried and evaporated to give 7.68 g (63%) of the diastereomeric diols **5a**,**b** as a thick, colorless oil, which slowly crystallized under high vacuum. The hexanes wash was evaporated to a thick, opaque residue, which was diluted with 50 mL of saturated aqueous

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(30) Ketone **3** was recrystallized from EtOAc prior to use in order to remove any traces of the α,β-unsaturated ketone **4**. The presence of as little as 4% of conjugated ketone **4** in a sample of ketone **3** produces significantly lower yields of diol.

$NaHCO_3$. The pH was adjusted to 10.5 by the addition of 17 mL of 6 M NaOH, 8 mL of 30% H_2O_2 was added, and the mixture was stirred at room temperature overnight (12 h). The mixture was then extracted with 1/3 IPA/$CHCl_3$ (3 × 50 mL), and the combined organic phases were dried and evaporated to a yellow oil. Chromatography (40/1, w/w) using 2/1 EtOAc/hexanes as an eluent afforded the diols **5a**,**b** as a thick, colorless oil, which solidified under high vacuum (2.37 g, 20%). As a precaution, the combined aqueous layers were allowed to stand at room temperature overnight and re-extracted with IPA/$CHCl_3$ 1/3 (75 mL). The organic layer was dried and evaporated to yield a small amount of diols **5a**,**b**, as a white solid (0.062 g, 0.5%); ^{1}H NMR was identical to that reported.[7b] The total yield of diols **5a**,**b** was 84%, and the product was used in the next step without further purification.

(4*R*,5*R*)-5-[(Phenylsulfonyl)amino]-4-allyl-2,2-dimethyl-1,3-dioxane (6). To a solution of diols **5a**,**b** (8.40 g, 31.0 mmol) in 400 mL of THF at room temperature was added *p*-toluenesulfonic acid (0.41 g, 2.20 mmol), followed by 2,2-dimethoxypropane (39.0 g, 46.0 mL, 374 mmol, 1200 mol %). The reaction mixture was stirred at room temperature for 48 h, 250 mL of saturated aqueous $NaHCO_3$ was added, and stirring was continued for an additional 1 h; then, it was poured into 200 mL of Et_2O. The aqueous phase was extracted with Et_2O (2 × 100 mL), and the combined organic phase was washed with brine (150 mL), dried, and evaporated to give 9.70 g of a white solid, which was recrystallized from EtOAc to give the cis diastereomer **6** (5.79 g, 60%): mp 140−142 °C (lit. mp 143−144 °C); $[\alpha]^{22}_D$ −15.6 (*c* 1, $CHCl_3$); [lit.,[7b] enantiomer of **6**, $[\alpha]^{22}_D$ +13.6 (*c* 2.12, $CHCl_3$)]. The ^{1}H NMR and analytical data for **6** were identical to reported values.[7b] The mother liquor from the recrystallization above was stored and combined with the mother liquors of subsequent runs, from which more of the cis diastereomer **6** was obtained by further recrystallizations or by chromatography (80/1, w/w) using EtOAc/hexanes 1/9 as eluent, for a total yield of 80%.

(4*R*,5*R*)-5-[(Phenylsulfonyl)amino]-4-(3-hydroxylpropyl)-2,2-dimethyl-1,3-dioxane (7a) and (4*R*,5*R*)-5-[(Phenylsulfonyl)amino]-4-(2-hydroxylpropyl)-2,2-dimethyl-1,3-dioxane (7b). On the basis of the reported procedure,[7b] to a solution of olefin **6** (4.0 g, 12.9 mmol) in 250 mL of THF at room temperature was added BH_3·THF (6.0 mL, 1.0 M in THF, 47 mol %). The colorless solution was stirred at room temperature for 2.5 h then quenched by the addition of 38 mL of H_2O. The mixture was heated at reflux for 25 min, and 42 mL of 3 M aqueous NaOH was added. The heating bath was removed, and 48 mL of 30% H_2O_2 was added carefully to the warm mixture over 5 min. The mixture was again heated at reflux for 1.5 h and cooled to room temperature over 1 h, after which the aqueous layer was extracted with 1/4 IPA/$CHCl_3$ (3 × 75 mL) and the combined organic phase was washed with H_2O (25 mL), dried, and evaporated to give a crude white solid (4.0 g). This crude product was recrystallized from EtOAc to give pure primary alcohol **7a** (2.39 g). The mother liquor was purified by chromatography using EtOAc/hexanes, 3/2, as an eluent to give secondary alcohol **7b** (270 mg, 6.4%) followed by additional **7a** (420 mg). The combined yield of **7a** was 66%. Primary alcohol **7a**: mp 124−126 °C (lit.,[7b] reported as an oil); $[\alpha]^{22}_D$ −15.9 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.38 (s, 3H), 1.40 (s, 3H), 1.42−1.76 (m, 5H), 3.15−3.19 (m, 1H), 3.33−3.38 (m, 1H), 3.55−3.57 (m, 2H), 3.84−3.88 (m, 2H), 5.32−5.35 (m, 1H), 7.48−7.61 (m, 3H), 7.88−7.92 (m, 2H); ^{13}C NMR δ 18.4 (3), 28.1 (2), 28.5 (2), 29.4 (3), 50.2 (1), 62.3 (2), 64.1 (2), 71.5 (1), 99.2 (0), 126.8 (1), 129.1 (1), 132.6 (1), 141.2 (0). Anal. Calcd for $C_{15}H_{23}NO_5S$: C, 54.7; H, 7.0; N, 4.2. Found: C, 54.3; H, 6.9; N, 4.2. Secondary alcohol **7b**: mp 118−119 °C; ^{1}H NMR δ 1.14 (d, *J* = 6.3, 3H), 1.34 (s, 3H), 1.40 (s, 3H), 1.61 (d, *J* = 6.9 Hz, 1H), 1.65−1.68 (m, 1H), 3.17 (d, *J* = 10.0 Hz, 1H), 3.27 (d, *J* = 12.1 Hz, 1H), 3.86 (d, *J* = 12.1 Hz, 2H), 4.15 (m, 1H), 5.30 (d, *J* = 10.1 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR δ 18.5 (3), 24.2 (3), 29.5 (3), 40.8 (2), 51.0 (1), 64.2 (2), 64.7 (1), 68.8 (1), 99.3 (0), 126.9 (1), 129.2 (1), 132.7 (1), 141.1 (0). Anal. Calcd for $C_{15}H_{23}NO_5S$: C, 54.7; H, 7.0; N, 4.2. Found: C, 54.8; H, 7.2; N, 4.0.

(4*R*,5*R*)-5-[(Phenylsulfonyl)amino]-4-(3-hydroxypropyl)-2,2-dimethyl-1,3-dioxane (7a). Alternatively, **7a** was prepared by adding to a solution of 9-BBN (2.68 g, 11 mmol, 190 mol %) in 20 mL of THF a solution of olefin **6** (1.80 g, 5.8 mmol) in 20 mL of THF dropwise over 5 min at room temperature. The mixture was stirred for 4 h at room temperature then quenched at 0 °C with 8 mL of EtOH, followed by careful addition of 4.5 mL of 3 M aqueous NaOH and 4.5 mL of 30% H_2O_2. The mixture was allowed to reach room temperature, heated at reflux for 90 min, cooled to room temperature, concentrated to 40% of its original volume, and diluted with 200 mL of Et_2O. The aqueous phase was diluted with 10 mL of H_2O, the pH was adjusted from 11.6 to 7 using 0.5 M H_3PO_4, and the solution was extracted with IPA/$CHCl_3$, 1/4 (4 × 30 mL). The combined organic phase was dried and evaporated, and the residue was chromatographed (130 g SiO_2) using 1−2% MeOH/CH_2Cl_2 (gradient elution) as an eluent to afford the alcohol **7a** as a white solid (1.55 g, 81%): mp 124−126 °C.

(4*R*,5*R*-5-[Phenylsulfonyl)amino]-4-(2-carboxyethyl)-2,2-dimethyl-1,3-dioxane (8). To the vigorously stirred mixture of alcohol **7a** (2.94 g, 8.92 mmol) in 330 mL of CH_3CN/CCl_4/phosphate buffer (pH 7.0) (4/4/5) was added $NaIO_4$ (8.81 g, 41.2 mmol, 462 mol %), followed by $RuCl_3$·$3H_2O$ (55 mg, 0.24 mmol, 2.7 mol %). The mixture was stirred at room temperature for 90 h, 150 mL of CH_2Cl_2 was added, stirring was continued for 1 h, and the layers were separated. The aqueous layer was extracted with IPA/$CHCl_3$, 1/4 (4 × 50 mL), and the combined organic phase was filtered through a fritted glass disk and evaporated to a gray foam, which was diluted with Et_2O (30 mL) and filtered through Celite. The filtrate was washed with 5% aqueous $NaHSO_3$ (2 × 15 mL), dried, and evaporated. Chromatography (SiO_2, 45/1, w/w) of the residue using 2−10% MeOH/CH_2Cl_2 (gradient elution) afforded acid **8** (2.32 g, 75%): mp 45 °C (dec); ^{1}H NMR δ 1.36 (s, 3H), 1.38 (s, 3H), 1.65 (m, 1H), 1.85 (m, 1H), 2.37 (t, *J* = 7.1 Hz, 2H), 3.17 (m, 1H), 3.32 (dd, *J* = 11, 1.6 Hz, 1H), 3.86 (dd, *J* = 11, 1.6 Hz, 1H), 3.95 (m, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 7.55 (m, 3H), 7.90 (m, 2H); ^{13}C NMR δ 18.4, 26.7, 29.0, 29.3, 50.1 (1), 64.1 (2), 70.1 (1), 99.4 (1), 126.8 (1), 129.2 (1), 132.7 (1), 141.1, 178.8. Acid **8** is hygroscopic; it was immediately converted to lactam **9**.

(2*R*,3*R*)-6-Oxo-3-hydroxy-2-hydroxymethyl-1-phensylsulfonylpiperidine Acetonide (9). To a solution of acid **8** (1.11 g, 3.23 mmol) in 315 mL of CH_2Cl_2 was added 4-(dimethylamino)pyridine (0.380 g, 3.1 mmol, 96 mol %), followed by a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.750 g, 3.91 mmol, 121 mol %) in 25 mL of CH_2Cl_2. The mixture was stirred at 0 °C for 12 h, diluted with 100 mL of CH_2Cl_2, washed with 0.5 M HCl (4 × 40 mL), saturated aqueous $NaHCO_3$ (40 mL), and brine (40 mL), dried, and evaporated. Sublimation of the residue (140 °C, 0.3 Torr) afforded lactam **9** (0.970 g, 92%): mp 176−178 °C; $[\alpha]^{23}_D$ −136.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.34 (s, 3H), 1.42 (s, 3H), 1.81 (m, 1H), 2.03 (m, 1H), 2.34 (m, 1H), 2.76 (ddd, *J* = 12, 5 Hz, 1H), 3.84 (dd, 1H, *J* = 12, 7 Hz, 1H), 4.24 (dd, *J* = 12.6 Hz, 1H), 4.47 (m, 1H), 4.56 (m, 1H), 7.52 (m, 2H), 7.59 (m, 1H), 8.01 (m, 2H); ^{13}C NMR δ 22.3 (3), 24.6 (2), 25.4 (3), 29.0 (2), 56.1 (1), 62.2 (2), 62.9 (1), 99.9 (0), 128.6 (1), 128.7 (1), 133.6 (1), 139.7 (0), 171.2 (0). Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.4; H, 5.9; N, 4.3. Found: C, 55.3; H, 6.1; N, 4.2.

(2*R*,3*R*)-6-Oxo-3-hydroxy-2-hydroxymethylpiperidine Acetonide (10). To a solution of naphthalene (1.65 g, 12.9 mmol) in 20 mL of DME was added sodium (0.49 g, 21.5 mmol). The mixture was stirred at room temperature for 3 h, giving a green-black suspension. A solution of lactam **9** (1.16 g, 3.56 mmol) in 42 mL of THF was cooled to −78 °C, and the solution of sodium naphthalenide was added via syringe until a green-black color persisted (ca. 15 mL). During the addition, the internal temperature of the reaction mixture was maintained just below −75 °C. The mixture was stirred at −78 °C for 2.5 h, and then 2.3 g of NH_4Cl was added quickly, followed by removal of the cooling bath. The mixture, which warmed to room temperature over 45 min, was filtered, the filtrate was evaporated, and the residue was chromatographed (SiO_2, 230−400 mesh, 40 g) eluting with hexanes to 15% MeOH/CH_2Cl_2.

Sublimation (110 °C, 0.3 Torr) gave lactam **10** (0.541 g, 82%): mp 165 °C (dec); $[\alpha]^{23}_D$ −64.1 (*c* 0.6, $CHCl_3$); IR 3020, 1700, 1450, 1360, 1220, 1170 cm^{-1}; ^1H NMR δ 1.40 (m, 3H), 1.49 (m, 3H), 1.83 (m, 1H), 2.02 (m, 1H), 2.26 (ddd, J = 12.8, 1H), 2.59 (m, 1H), 3.27 (m, 1H), 3.75 (dd, J = 1.7, 12.8, 1H), 4.09 (dd, J = 2.4, 12.8, 1H), 4.22 (m, 1H), 6.88 (bs, 1H); ^{13}C NMR δ 18.8 (3), 25.7 (2), 25.8 (2), 29.0 (3), 49.0 (1), 61.9 (1), 63.0 (2), 98.2 (0), 173.1 (0). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.4; H, 8.2; N, 7.6. Found: C, 58.4; H, 8.4; N, 7.4.

(2*R*,3*R*)-6-Oxo-3-*tert*-butyldimethylsilyloxy-2-(*tert*-butyldimethylsilyloxymethyl)piperidine (12). To a solution of lactam **10** (0.420 g, 2.27 mmol) in 6 mL of MeOH was added concd HCl (0.1 mL). The mixture was stirred at room temperature for 15 h, the solvent was evaporated, and the residue was diluted with MeOH (5 mL) and evaporated; this addition−evaporation was repeated twice. The oily residue was dissolved in 3 mL of DMF, imidazole (0.770 g, 11.3 mmol) and TBDMSCl (1.01 g, 6.70 mmol) were added, and the mixture was stirred at room temperature for 72 h then extracted with hexanes (5 × 10 mL). The combined organic phase was washed with pH 4 phosphate buffer (3 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried, and evaporated. The residue was chromatographed (SiO_2, 40 g) using EtOAc/hexanes, 1/1, as an eluent to give lactam **12** (0.650 g, 77%): mp 48−51 °C; $[\alpha]^{23}_D$ +21.3 (*c* 1.4, $CHCl_3$); ^1H NMR δ 0.05 (s, 6H), 0.07 (s, 6H), 0.87 (s, 9H), 0.88 (s, 9H), 1.72 (m, 2H), 2.2−2.4 (m, 1H), 2.5−2.65 (m, 1H), 3.4−3.5 (m, 1H), 3.6−3.7 (m, 2H), 4.03 (m, 1H), 5.93 (s, 1H); ^{13}C NMR δ −5.8 (3), −5.79 (3), −5.5 (3), −4.8 (3), 17.7, 17.9, 25.3 (3), 25.4, 25.5, 25.6 (3), 26.2, 27.8, 58.5 (1), 63.7 (1), 171.1 (0). Anal. Calcd for $C_{18}H_{39}NO_3Si_2$; C, 57.9; H, 10.5; N, 3.8. Found: C, 58.1; H, 10.5; N, 3.7.

(5*R*,6*R*)-2-Methoxy-5-*tert*-butyldimethylsilyloxy-6-*tert*-butyldimethylsilyloxymethyl-1,2-didehydropiperidine (13). To a solution of lactam **12** (0.500 g, 1.34 mmol) in 5 mL of CH_2Cl_2 was added methyl triflate (0.17 mL, 1.50 mmol, 112 mol %), and the mixture was stirred at room temperature for 8 h. The solvent and excess methyl triflate were evaporated, and to the residue was added 10 mL of cold 5% aqueous Na_2CO_3 followed by extraction with CH_2Cl_2 (4 × 10 mL). Evaporation gave crude lactim ether **13**, which was used without further purification (0.468 g, 90%): ^1H NMR δ 0.04 (s, 6H), 0.05 (s, 6H), 0.85 (s, 9H), 0.88 (s, 9H), 1.63−1.71 (m, 1H), 1.88−1.95 (m, 1H), 2.04−2.1 (m, 1H), 2.29−2.39 (m, 1H), 3.30 (m, 1H), 3.59 (s, 3H), 3.60−3.65 (m, 1H), 3.69−3.75 (m, 1H), 4.03−4.08 (m, 1H); ^{13}C NMR δ −5.2 (3), −5.19 (3), −5.0 (3), −4.6 (3), 18.0 (0), 18.2 (0), 22.0 (2), 25.8 (3), 25.9 (3), 27.7 (2), 51.8 (3), 61.9 (1), 63.7 (1), 63.9 (2), 162.6 (0).

(2*R*,3*R*)-6-[5-(2,2-Dimethyl-4,6-dioxo-1,3-dioxanylidene)]-3-*tert*-butyldimethylisilyloxy-2-*tert*-butyldimethylsilyloxymethylpiperidine (14). To a solution of lactim ether **13** (0.520 g, 1.34 mmol) in 5 mL of $CHCl_3$ was added 2,2-dimethyl-4,6-dioxo-1,3-dioxane (0.220 g, 1.53 mmol, 114 mol %) and nickel acetylacetonate monohydrate (4 mg, 0.015 mmol, 1 mol %). The mixture was heated at reflux for 22 h and evaporated to a yellow residue, which was chromatographed (SiO_2, 35 g) using EtOAc/hexanes as an eluent to give the enamine **14** (0.490 g, 73%): mp 142−144 °C; $[\alpha]^{23}_D$ +39.6 (*c* 1.2, $CHCl_3$); ^1H NMR δ 0.05 (s, 6H), 0.07 (s, 6H), 0.85 (s, 9H), 0.91 (s, 9H), 1.64 (s, 3H), 1.66 (s, 3H), 1.7−1.8 (m, 1H), 1.9−2.0 (m, 1H), 3.0−3.15 (m, 1H), 3.4−3.5 (m, 1H), 3.5−3.6 (m, 1H), 3.65−3.8 (m, 2H), 4.08−4.15 (m, 1H), 9.84 (s, 1H); ^{13}C NMR δ −5.8 (3), −5.5 (3), −5.2 (3), −4.5 (3), 17.9 (0), 18.2 (0), 24.6 (2), 25.6 (3), 25.8 (3), 26.0 (3), 26.4 (2), 26.7 (3), 58.8 (1), 62.9 (1), 63.4 (2), 82.9 (0), 102.2 (0), 163.1 (0), 166.9 (0), 172.9 (0). Anal. Calcd for $C_{24}H_{45}NO_6Si_2$: C, 57.7; H, 9.1; N, 2.8. Found: C, 57.4; H, 9.2; N, 2.7.

(2*R*,3*R*)-6-Ethoxycarbonylmethylidene-3-*tert*-butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethylpiperidine (15). To a solution of enamine **14** (0.260 g, 0.52 mmol) in 4 mL of absolute EtOH was added a freshly made solution of sodium ethoxide (1 mL, 0.56 M in EtOH, 0.56 mmol). The mixture was heated at reflux for 40 h, the solvent was evaporated, the residue was diluted with 10 mL of H_2O, and the pH of the mixture was adjusted to 5 using 0.5 M HCl. The mixture was extracted with CH_2Cl_2 (4 × 10 mL), followed by washing the combined organic phase with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (10 mL). The organic phase was dried and evaporated to a yellow oil, which was chromatographed (SiO_2, 73/1, w/w) using EtOAc/hexanes, 1/2, as an eluent to afford the enamine **15** as a light-yellow oil (0.182 g 79%): $[\alpha]^{23}_D$ +6.5 (*c* 0.85, $CHCl_3$); ^1H NMR δ 0.07 (s, 6H), 0.09 (s, 6H), 0.88 (s, 9H), 0.91 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H), 1.6−1.9 (m, 2H), 2.15−2.25 (m, 1H), 2.6−2,75 (m, 1H), 3.25−3.35 (m, 1H), 3.55−3.75 (m, 2H), 4.08 (q, J = 7.1 Hz, 2H), 4.12 (s, 1H), 4.39 (s, 1H), 8.74 (s, 1H); ^{13}C NMR δ −5.5 (3), −5.4 (3), −5.1 (3), −4.6 (3), 14.7 (0), 18.0 (0), 18.3 (0), 24.3 (2), 25.7 (1), 25.9 (1), 27.6 (2), 57.6 (1), 58.1 (2), 63.7 (2), 64.4 (1), 80.3 (1), 161.3 (0), 170.3 (0). Anal. Calcd for $C_{22}H_{45}NO_4Si_2$: C, 59.5; H, 10.2; N, 3.2. Found: C, 59.6; H, 10.3; N, 3.3.

(2*R*,3*R*,6*R*)-6-Ethoxycarbonylmethyl-3-*tert*-butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethylpiperidine (16). A solution of enamine **15** (0.182 g, 0.41 mmol) in 4 mL of EtOAc was degassed with N_2, and 5% Pt/C (0.060 g, 1.6% w/w) was added. The mixture was agitated under an atmosphere of H_2 (50 psi) for 30 h, and the catalyst was removed by filtration through Celite. Evaporation of the solvent afforded amino ester **16** as a light-yellow oil (0.146 g, 80%): $[\alpha]^{23}_D$ +13.2 (*c* 1.04, $CHCl_3$); ^1H NMR δ −0.05−0.05 (m, 12H), 0.80 (s, 9H), 0.83 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H), 1.40−1.70 (m, 3H), 1.70−1.85 (m, 1H), 2.40−2.62 (m, 2H), 2.65−2.74 (m, 1H), 3.0−3.1 (m, 1H), 3.40−3.50 (m, 1H), 3.55−3.65 (m, 1H), 3.91 (bs, 1H), 4.05 (q, J = 7.1 Hz, 2H); ^{13}C NMR δ −5.3 (3), −5.29 (3), −4.8 (3), −4.6 (3), 14.2, 18.1, 18.2, 25.9 (3), 26.6 (2), 32.1 (2), 41.9 (2), 53.4 (1), 60.2 (2), 61.9 (1), 63.7 (2), 63.9 (1), 172.0 (0). Anal. Calcd for $C_{22}H_{47}NO_4Si_2$: C, 59.3; H, 10.6; N, 3.1. Found: C, 59.5; H, 11.0; N, 3.2.

(2*R*,3*R*,6*R*)-6-Carboxymethyl-3-*tert*-butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethylpiperidine (17). A solution of amino ester **16** (30 mg, 0.067 mmol) in 2 mL of a 4/1 MeOH/H_2O solution was cooled to 0 °C and LiOH·H_2O (15 mg, 0.36 mmol, 537 mol %) was added. The mixture was warmed to room temperature and stirred for 12 h. The pH of the solution was adjusted to pH 7 using pH 4 phosphate buffer and extracted with IPA/$CHCl_3$ (1/4), and the combined layers were dried and evaporated to afford the amino acid **17** (27 mg, 97%): mp 108−110 °C; ^1H NMR δ 0.04−0.1 (m, 12H), 0.89 (s, 9H), 0.91 (s, 9H), 1.5−1.95 (m, 4H), 2.31 (dd, J = 16.9, 9.2 Hz, 1H), 2.54 (dd, J = 16.9, 3.2 Hz, 1H), 2.76 (t, J = 7 Hz, 1H), 2.92−3.05 (m, 1H), 3.51−3.69 (m, 2H), 3.96 (bs, 1H); ^{13}C NMR δ −5.4 (3), −5.3 (3), −5.1 (3), −4.5 (3), 18.0 (0), 18.1 (0), 24.5 (2), 25.8 (3), 25.9 (3), 31.0 (2), 39.2 (2), 53.8 (1), 61.1 (1), 61.4 (2), 63.2 (1), 174.4 (0).

***N*-Methyl-2-chloropyridinium Triflate.** In a resealable tube was placed a solution of 2-chloropyridine (2.0 mL, 2.4 g, 21.1 mmol) in 3.5 mL of CH_2Cl_2. The solution was degassed by three freeze/thaw cycles, and the tube was then purged with Ar. The colorless solution was cooled to −78 °C, and with stirring, methyl trifluoromethanesulfonate (2.4 mL, 3.48 g, 21.2 mmol) was added over 45 s, as a white precipitate began to form. The cooling bath was removed, the tube was closed under Ar, and the cloudy mixture was stirred for 16 h. Toluene (20 mL) was added to the white mixture, and after stirring for 30 min more, the precipitate slowly settled to the bottom of the tube, leaving a clear supernatant, which was removed via syringe. An additional 20 mL of dry toluene was added to wash the precipitate, and the toluene was removed via syringe, with all operations being done under a stream of Ar. The washed precipitate was dried under high vacuum for 48 h at room temperature to afford 5.5 g (94%) of *N*-methyl-2-chloropyridinium triflate: mp 162−164 °C; ^1H NMR (CD_3CN) δ 4.30 (s, 3H), 7.93−7.96 (m, 1H), 8.12−8.14 (m, 1H), 8.45−8.49 (m, 1H), 8.78−8.80 (m, 1H); ^{13}C NMR (CD_3CN) δ 48.7 (3), 126.6 (0), 123.8 (0), 127.4 (1), 131.0 (1), 148.4 (1), 149.1 (1). Anal. Calcd for $C_7H_7C1F_3NO_3S$: C, 30.3; H, 2.5; N, 5.0. Found: C, 30.0; H, 2.5; N, 4.9.

(2*R*,3*R*,6*R*)-8-Oxo-3-*tert*-butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethyl-1-azabicyclo[4.2.0]octane (18). To a solution of 2-chloro-1-methylpyridinium triflate (1.08 g, 3.90 mmol) in 230 mL of dry CH_3CN was added *N*,*N*-

diisopropylethylamine (2.0 mL, 1.48 g, 11.5 mmol), and the colorless solution was heated at 65−70 °C as a solution of the amino acid **17** (0.50 g, 1.2 mmol) in 230 mL of dry CH_3CN was slowly added via syringe pump over 4 h. After the addition was complete, the slightly yellow solution was heated at 65−70 °C for an additional 15 min and then was stirred at room temperature for 12 h. The solution was diluted with 150 mL of CH_2Cl_2 and concentrated to 5% of its original volume. An additional 200 mL of CH_2Cl_2 was added, and the solution was concentrated to 10 mL and partitioned between 500 mL of CH_2Cl_2 and 400 mL of H_2O. The cloudy aqueous phase was extracted with CH_2Cl_2 (4 × 120 mL), and the combined organic layer was washed with brine (100 mL), dried, and evaporated to a dark-red oil, which was chromatographed on a 7 cm × 15 cm plug of SiO_2 using EtOAc/hexanes, 1/3, as an eluent to give the *β*-lactam **18** (433 mg, 90%): mp 58−59 °C; $[\alpha]^{22}_D$ −1.5 (*c* 1, $CHCl_3$); ^{1}H NMR *δ* 0.02−0.1 (m, 12H), 0.88 (s, 9H), 0.91 (s, 9H), 1.48−1.55 (m, 1H), 1.68−1.94 (m, 3H), 2.49 (dd, *J* = 14.3, 1.6 Hz, 1H), 2.98−3.03 (m, 2H), 3.25−3.28 (m, 1H), 4.0−4.02 (m, 1H), 4.1−4.19 (m, 2H); ^{13}C NMR *δ* −5.4 (3), −5.2 (3), −5.1 (3), −4.5 (3), 18.0 (0), 18.1 (0), 23.6 (2), 25.7 (3), 25.9 (3), 30.0 (2), 44.0 (2), 46.5 (1), 59.0 (2), 62.6 (1), 63.4 (1), 166.3 (0). Anal. Calcd for $C_{20}H_{41}NO_3Si_2$: C, 60.1; H, 10.3; N, 3.5. Found: C, 60.1; H, 10.7; N, 3.5.

(4*R*,5*R*,*E*/*Z*)-5-[(Phenylsulfonyl)amino]-4-(methoxycarbonyl-3-butenyl)-2,2-dimethyl-1,3-dioxane (22/23). To 180 mL of CH_2Cl_2 was added fresh Dess−Martin reagent (13.6 g, 32.0 mmol) followed, after 5 min of stirring, by pyridine (4.92 mL, 61.4 mmol) and, after 5 min of stirring, a solution of alcohol **7a** (10.0 g, 30.4 mmol) in 40 mL of CH_2Cl_2; the cloudy mixture was stirred at room temperature for 2 h. After the addition of 90 mL of EtOH, the mixture was evaporated to a white residue. To this residue was added 500 mL of Et_2O and 400 mL of a 1/1 solution of 10% aqueous $Na_2S_2O_3{\cdot}5H_2O$ (w/w) and saturated aqueous $NaHCO_3$, and the organic phase was washed with H_2O (100 mL). The combined aqueous phase was stirred with Et_2O (400 mL), the aqueous layer was extracted with Et_2O (2 × 200 mL), and the combined organic phase was washed with H_2O (2 × 200 mL) and brine (200 mL), dried, and evaporated (bath at room temperature) to afford aldehyde **19** as a colorless, thick oil after 2 h under high vacuum (10.3 g): ^{1}H NMR *δ* 1.35 (s, 6H), 1.54−1.72 (m, 1H), 1.83−2.06 (m, 1H), 2.38−2.50 (m, 1H), 3.15 (dd, *J* = 12.2, 1.9 Hz, 1H), 3.30 (dd, *J* = 10.2, 1.8 Hz, 1H), 3.80−3.98 (m, 3H), 5.29 (d, *J* = 10.2 Hz, 1H), 7.50−7.63 (m, 3H), 7.88−7.98 (m, 2H), 9.68 (t, *J* = 1.5 Hz, 1H); ^{13}C NMR *δ* 18.4 (3), 24.6 (2), 29.4 (3), 39.1 (3), 39.1 (2), 50.1 (1), 64.1 (2), 70.3 (1), 99.4 (0), 126.8 (1), 129.3 (1), 132.8 (1), 201.7 (0).

Crude aldehyde **19** (10.3 g), as a solution in 180 mL of THF, was added to a pre-formed mixture of the potassium trimethylphosphonoacetate [prepared by the addition of trimethyl phosphonoacetate (10.0 mL, 61.8 mmol) to a −78 °C solution of KHMDS (67.0 mL, 0.92 M in toluene, 61.6 mmol) in 180 mL of THF, followed by stirring at −78 °C for 15 min, then at 0 °C for 6 h, then cooling to −78 °C] over 30 min followed by stirring at −78 °C for 3 h. The reaction mixture was then slowly warmed to 0 °C over 2 h and stirred at 0 °C for 12 h, followed by addition at 0 °C of 140 mL of saturated aqueous KH_2PO_4 and 200 mL of brine. After 15 min at 0 °C, organic volatile components were evaporated and 500 mL of EtOAc was added to the remaining aqueous layer. The aqueous phase was extracted with EtOAc (3 × 150 mL), and the combined organic phase was dried and evaporated to an orange oil. Chromatography using EtOAc/hexanes, 2/3 then 1/1, as an eluent afforded an 11/1 mixture of the E isomer **22** and the Z isomer **23** (9.55 g, 82% from **7a**). E isomer **22**: bp 180 °C/1.2 Torr; mp 82−84 °C; $[\alpha]^{24}_D$ −2.1 (*c* 1, $CHCl_3$); ^{1}H NMR *δ* 1.37 (s, 6H), 1.40−1.52 (m, 1H), 1.65−1.74 (m, 1H), 2.09−2.24 (m, 2H), 3.12 (dd, *J* = 10.1, 1.8 Hz, 1H), 3.36 (dd, *J* = 12.1, 1.8 Hz, 1H), 3.73 (s, 3H), 3.79−3.91 (m, 2H), 5.33 (d, *J* = 10.1 Hz, 1H), 5.74 (dt, *J* = 15.7, 1.5 Hz, 1H), 6.86 (dt, *J* = 15.7, 7.0 Hz, 1H), 7.49−7.60 (m, 3H), 7.87−7.89 (m, 2H); ^{13}C NMR *δ* 18.4 (3), 27.2 (2), 29.5 (3), 30.0 (2), 50.2 (1), 51.4 (3), 64.2 (2), 70.3 (1), 99.3 (0), 121.4 (1), 126.8 (1), 129.2 (1), 132.7 (1), 141.2 (0), 148.3 (1), 166.9 (0). Anal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.4; H, 6.6; N, 3.6. Found: C, 56.4; H, 6.8; N, 3.5. Z isomer **23**: ^{1}H NMR *δ* 1.36 (s, 6H), 1.45−1.54 (m, 1H), 1.59−1.68 (m, 1H), 2.53−2.72 (m, 2H), 3.19 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.34 (dd, *J* = 12.1, 1.8 Hz, 1H), 3.70 (s, 3H), 3.83−3.86 (m, 2H), 5.30 (d, *J* = 10.1 Hz, 1H), 5.76 (d, *J* = 11.5 Hz, 1H), 6.11 (dt, *J* = 11.5, 3.9 Hz, 1H), 7.48−7.62 (m, 3H), 7.88−7.90 (m, 2H); ^{13}C NMR *δ* 18.4 (3), 24.5 (2), 29.5 (3), 31.0 (2), 50.1 (1), 51.0 (3), 64.2 (2), 71.0 (1), 99.3 (0), 119.7 (1), 126.8 (1), 129.1 (1), 132.6 (1), 141.3 (0), 149.5 (1), 166.7 (0).

(2*R*,3*R*,6*R*)-6-(Methoxylcarbonylethyl)-3-hydroxy-2-hydroxymethyl-1-phenylsulfonylpiperidine Acetonide (24). To a solution of the amino ester **22** (0.993 g, 2.59 mmol) in 67 mL of DME was added NaH (17 mg, 95%, as a powder, 0.71 mmol, 27 mol %). Using an air condenser, the reaction mixture was heated at 50−55 °C for 2.5 days, then cooled to 0 °C, and 4 mL of saturated aqueous KH_2PO_4 was added. After being stirred for 10 min, the mixture was concentrated, and the aqueous residue was diluted with 60 mL of CH_2Cl_2 and stirred with 1.5 g of anhydrous Na_2SO_4 for 15 min, filtered through a fritted glass disk, and evaporated to an orange oil. Chromatography (SiO_2, 82 g, 3 cm × 4 cm plug) using EtOAc/hexanes, 1/3, as an eluent afforded the cyclized product **24** as a single diastereomer (0.63 g, 64%) as well as unreacted **22** (0.230 g, 23%). Resubjection of the recovered amino ester **22** to the above conditions gave an additional amount of the cyclized product **24** (110 mg, 11%) as well as unreacted **22** (93 mg, 9%). The total yield of **24** was 75%: mp 104−105 °C; $[\alpha]^{22}_D$ +19.6 (*c* 1, $CHCl_3$); ^{1}H NMR *δ* 0.56−0.63 (m, 1H), 1.34 (s, 3H), 1.37 (s, 3H), 1.51−1.61 (m, 2H), 1.82−1.88 (m, 1H), 2.70−2.76 (m, 1H), 2.97−3.02 (m, 1H), 3.70−3.74 (m, 4H), 3.84−3.88 (m, 1H), 4.02−4.07 (m, 2H), 4.26−4.31 (m, 1H), 7.52−7,62 (m, 3H), 7.83−7.86 (m, 2H); ^{13}C NMR *δ* 21.6 (2), 23.1 (3), 24.1 (2), 25.9 (3), 44.2 (2), 29.5 (3), 44.2 (2), 29.5 (1), 51.7 (3), 51.9 (1), 62.5 (2), 63.2 (1), 99.5 (0), 126.9 (1), 129.3 (1), 1.32.8 (1), 139.6 (0), 171.3 (0), 171.3 (0). Anal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.4; H, 6.6; N, 3.6. Found: C, 56.7; H, 6.6; N, 3.6.

(2*R*,3*R*,6*R*)-6-Methoxycarbonylethyl)-3-hydroxy-2-hydroxymethyl-1-phenylsulfonylpiperidine Acetonide (24). **24** also was prepared from the Z isomer. To a solution of *Z*-amino ester **23** (27 mg, 0.07 mmol) in 2.0 mL of dry DME was added NaH (∼1 mg, 95%, as a powder). The reaction mixture was stirred at room temperature for 6 days, and then 0.5 mL of saturated aqueous KH_2PO_4 was added. The mixture was evaporated, to the white residue was added 10 mL of CH_2Cl_2 and 1 g of solid Na_2SO_4, the mixture was filtered through a small plug of $MgSO_4$ using 20 mL of CH_2Cl_2 as an eluent, and the filtrate was evaporated. Preparative TLC (SiO_2, 250 *μ*m) using EtOAc/hexanes, 1/3, as an eluent gave the cyclized product **24** (13 mg, 48%) and recovered **23** (8 mg, 30%). The yield of **24** based on recovered starting material was 68%. Spectral data (^{1}H NMR, ^{13}C NMR) for the product obtained from Z isomer **23** were identical to those for the product obtained from E isomer **22**. Alternatively, a mixture of *E*/*Z* isomers **22** and **23** was subjected to the process described for the preparation of acetonide **24** from pure *E*-**22**, giving **24** in 75% yield.

(2*R*,3*R*,6*R*)-6-Methoxycarbonylmethyl-3-*tert*-butyldimethylsilyloxy-2-butyldimethylsilyloxymethyl-1-phenylsulfonylpiperidine (25). To a solution of ester **24** (0.425 g, 1.11 mmol) in 35 mL of MeOH was added concd HCl (0.15 mL). The mixture was stirred at room temperature for 14 h then evaporated, and 5 mL of MeOH was added and evaporated. This addition/evaporation process was repeated once with MeOH (5 mL) and twice with benzene (5 mL). The residual oil was dissolved in 25 mL of CH_2Cl_2 and cooled to −10 °C, and 2,6-lutidine (0.60 mL, 5.15 mmol) was added, followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.65 mL, 2.83 mmol). The reaction mixture was stirred at −10 °C for 2 h, 30 mL of 1/1 EtOAc/H_2O was added, the mixture was allowed to reach room temperature and then extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layer was washed with pH 4 phosphate buffer (2 × 15 mL) and brine (15 mL), dried, and evaporated. Chromatography (SiO_2, 66 g) of the residue using EtOAc/hexanes, 1/4, as an eluent gave ester **25** as an oil (0.62 g, 97%): $[\alpha]^{23}_D$ −6.9 (*c* 1.3,

$CHCl_3$); ^1H NMR δ 0.001−0.1 (m, 12H), 0.86 (s, 9H), 0.92 (s, 9H), 1.30−1.50 (m, 2H), 1.51−1.60 (m, 1H), 1.70−1.90 (m, 3H), 2.75 (dd, J = 16.2, 3.5 Hz, 1H), 2.85−3.0(m, 1H), 3.45−3.59 (m, 1H), 3.65 (s, 3H), 3.85−3.95 (m, 2H), 4.05−4.15 (m, 1H), 4.25−4.37 (m, 1H), 7.40−7.60 (m, 3H), 7.80−7.90 (m, 2H); ^{13}C NMR δ −5.6 (3), −5.5 (3), −5.2 (3), −4.9 (3), 17.9 (0), 18.3 (0), 24.8 (2), 25.6 (3), 25.9 (3), 26.5 (2), 38.8 (2), 47.5 (1), 51.5 (3), 57.7 (1), 61.5 (2), 68.9 (1), 126.8 (1), 128.9 (1), 132.2 (1), 141.1 (0), 171.8 (0). Anal. Calcd for $C_{27}H_{49}NO_6Si_2S$: C, 56.7; H, 8.6; N, 2.5. Found: C, 56.9; H, 8.7; N, 2.5.

(2*R*,3*R*,6*R*)-6-Methoxycarbonylmethyl-3-*tert*-butyldimethylsilyloxy-2-(*tert*-butyldimethylsilyloxymethyl)piperidine (26). The ester **25** (2.60 g, 4.55 mmol) was electrolyzed at −1.73 V [in 200 mL of 0.1 M TEAB in CH_3CN containing 4-phenylphenol (2.02 g, 11.9 mmol)] for 26 h as described for the formation of amino ester **27** (see below). The isolated residue was chromatographed (SiO_2, 150 g) using CH_2Cl_2 followed by 4% MeOH/CH_2Cl_2 as an eluent to give the amino ester **26** as an oil (1.69 g, 86%): ^1H NMR δ 0.005−0.015 (m, 12H), 0.84 (s, 9H), 0.86 (s, 9H), 1.35−1.60 (m, 3H), 1.70−1.85 (m, 1H), 2.25−2.47 (m, 2H), 2.55−2.65 (m, 1H), 2.85−3.0 (m, 1H), 3.35−3.50 (m, 2H), 3.62 (s, 3H), 3.84 (bs, 1H); ^{13}C NMR δ −5.6 (3), −5.5 (3), −5.2 (3), −4.9 (3), 18.0 (0), 18.1 (0), 25.8 (3), 26.6 (2), 32.0 (2), 41.6 (2), 51.4 (3), 53.2 (1), 61.8 (1), 63.6 (2), 63.8 (1), 172.4 (0). This material was used directly for the preparation of **17**.

(2*R*,3*R*,6*R*)-6-Methoxycarbonylmethyl-3-*tert*-butyldimethylsilyloxy-2-(*tert*-butyldimethylsilyloxymethyl)piperidine (17). **17** was prepared from a solution of ester **26** (105 mg, 0.24 mmol) in 7 mL of 4/1 MeOH/H_2O at 0 °C, to which was added LiOH·H_2O (60 mg, 1.43 mmol, 595 mol %). The mixture was warmed to room temperature and stirred for 12 h, and the pH was adjusted to 7.0 using 0.5 M aqueous H_3PO_4. The reaction mixture was extracted with IPA/$CHCl_3$, 1/4 (4 × 10 mL), and the combined organic phase was dried and evaporated to give the amino acid **17** as a white solid (99 mg, 99%). The analytical data for this product were identical to those for amino acid **17** obtained from the lactim ether route (cf **15** → **17**, Scheme 2).

(2*R*,3*R*,6*R*)-6-(Methoxycarbonylmethyl)-3-hydroxy-2-hydroxymethylpiperidine Acetonide (27). By use of a 250 mL capacity H-cell fitted with a Pt foil anode, a 3 mm deep Hg pool cathode, and a Ag wire reference electrode, the amino ester **24** (0.400 g, 1.04 mmol) was electrolyzed at 1.73 V in 180 mL of a 0.12 M solution of TEAB in CH_3CN containing 4-phenylphenol (0.444 g, 2.61 mmol, 250 mol %) for 12.7 h, during which time the current flowing through the cell dropped from an initial 14 mA to 0.8 mA. The contents of the cathode chamber were decanted from the Hg, the Hg was washed with CH_2Cl_2 (3 × 30 mL), and this wash was combined with the cathode solution, which was then evaporated (at or slightly below room temperature) to a grayish solid residue. This residue was dissolved in 350 mL of CH_2Cl_2, which was washed with cold 0.1 M KOH (3 × 100 mL, then 1 × 30 mL) and brine (150 mL). The organic phase was dried and evaporated to a residue (400 mg of a yellow-white solid), which was chromatographed (90/1, w/w) using 3% MeOH/CH_2Cl_2 as an eluent to give amino ester **27** as a clear, colorless oil (0.220 g, 87%): $[\alpha]^{22}_D$ −1.3 (*c* 1, $CHCl_3$); ^1H NMR δ 1.43 (s, 3H), 1.45 (s, 3H), 1.63−1.72 (m, 1H), 1.87−1.93 (m, 1H), 2.07 (bs, 2H), 2.40−2.52 (m, 3H), 2.99−3.06 (m, 1H), 3.69−3.75 (m, 4H), 3.87−3.91 (m, 1H), 4.08−4.12 (m, 1H); ^{13}C NMR δ 18.6 (3), 25.7 (2), 29.8 (3), 29.8 (2), 41.5 (2), 51.5 (3), 51.8 (1), 63.8 (1), 64.9 (2), 98.4 (0), 172.4 (0). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.2; H, 8.7; N, 5.8. Found: C, 59.1; H, 8.8; N, 5.7.

(2*R*,3*R*,6*R*)-6-(Carboxymethyl)-3-hydroxy-2-hydroxymethylpiperidine Acetonide (28). To a solution of amino ester **27** (0.130 g, 0.53 mmol) in 4 mL of 10/1 MeOH/H_2O at 0 °C was added LiOH·H_2O (48 mg, 1.14 mmol, 214 mol %). The mixture was stirred at 0 °C for 20 min, warmed to room temperature, and stirred for an additional 15 h, then diluted with H_2O (7 mL) and Et_2O (5 mL). The aqueous layer was acidified to pH 6.2 with 0.4 M H_3PO_4, extracted with 1/4 IPA/$CHCl_3$ (4 × 5 mL), stirred with 1 g of NaCl and 10 mL of 1/4 IPA/$CHCl_3$ for 12 h, and then filtered through a cotton plug. The combined organic phase was evaporated to a white solid, to which was added 20 mL of benzene, and the solvent was evaporated again, affording amino acid **28** (0.119 g, 98%), sufficiently pure to be used in the next step: mp 55−57 °C (dec); ^1H NMR (MeOH-d_4) δ 1.46 (s, 3H), 1.51 (s, 3H), 1.70−1.96 (m, 4H), 2.61−2.73 (m, 2H), 3.24−3.25 (m, 1H), 3.46−3.52 (m, 1H), 3.83−3.87 (m, 1H), 4.28−4.34 (m, 2H); ^{13}C NMR (MeOH-d_4) δ 18.9 (3), 23.4 (2), 28.7 (2), 29.4 (3), 38.2 (2), 53.3 (1), 55.1 (1), 62.2 (2), 64.1 (1), 101.1 (0), 175.6 (0).

(2*R*,3*R*,6*R*)-8-Oxo-3-hydroxy-2-hydroxymethyl-1-azabicyclo[4.2.0]octane Acetonide (29). To 2-chloro-1-methylpyridinium iodide (0.17 g, 0.66 mmol, 372 mol %) was added 30 mL of CH_3CN and Et_3N (0.21 mL, 0.152 g, 1.50 mmol, 838 mol %). The resulting yellow solution was heated at 70−73 °C (oil bath), and to this was slowly added a solution of **28** (41 mg, 0.18 mmol) in 17 mL of CH_3CN over the course of 11 h. The deep-red reaction mixture was cooled to room temperature and stirred for an additional 14 h, whereupon the solvent was evaporated, leaving a reddish residue. The residue was diluted with 50 mL of EtOAc, filtered through a cotton plug, concentrated under reduced pressure, and applied directly to a 1 × 15 cm plug of SiO_2. Elution with EtOAc/hexanes, 1/1, afforded β-lactam **29** as a yellowish oil, which solidified upon standing (20 mg, 53%): mp 122−125 °C; $[\alpha]^{22}_D$ +19.8 (*c* 0.55, $CHCl_3$); ^1H NMR δ 1.43 (s, 3H), 1.46 (s, 3H), 1.51−1.59 (m, 1H), 1.70−1.79 (m, 2H), 1.94−2.00 (m, 1H), 2.69 (dd, J = 14.4, 2.0 Hz, 1H), 2.98−3.03 (m, 1H), 3.05−3/06 (m, 1H), 3.27−3.33 (m, 1H), 3.94−3.96 (m, 1H), 4.05 (dd, J = 12.7, 3.4 Hz, 1H), 4.67 (dd, J = 12.7, 1.6 Hz, 1H): ^{13}C NMR δ 19.0 (3), 23.4 (2), 27.8 (2), 29.2 (3), 44.3 (2), 47.2 (1), 50.5 (1), 59.0 (2), 63.2 (1), 98.2 (0), 165.8 (0); FABMS, 212 (MH+). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.5; H, 8.1; N, 6.6. Found: C, 62.6; H, 8.1; N, 6.4.

(2*R*,3*R*,6*R*)-3-*tert*-Butyldimethylsilyloxy-2-(*tert*-butyldimethylsilyloxymethyl)-7-hydroxyimino-8-oxo-1-azabicyclo[4.2.0]octane (30). To a solution of diisopropylamine (26 μL, 19 mg, 0.19 mmol) in 3.5 mL of dry THF at −78 °C was added *n*-BuLi (0.016 mL, 1.6 M in hexanes, 0.19 mmol). The solution was stirred at −78 °C for 35 min, a solution of β-lactam **18** (57 mg, 0.14 mmol) in 1.2 mL of THF was added dropwise, the resulting yellow solution was stirred at −78 °C for 1 h, and isoamyl nitrite (25 μL, 22 mg, 0.19 mmol) was added. The reaction mixture was stirred at −78 °C for 4 h, 1 mL of saturated aqueous KH_2PO_4 and 3.5 mL of brine were added, the cooling bath was removed, and the mixture was warmed to room temperature. After dilution with 15 mL of EtOAc, the aqueous layer was extracted with EtOAc (3 × 7 mL) and the combined organic layer was washed with 5 mL of brine, dried, and evaporated to an oil. Chromatography (1 cm × 9.5 cm plug of SiO_2) using EtOAc/ hexanes, 1/3, as an eluent afforded the oxime **30** as a mixture of isomers (20 mg, 33%).

(2*R*,3*R*,6*R*,7*S*)-7-(*tert*-Butyloxycarbonyl)amino]-3-*tert*-butyldimethylsilyloxy-2-(*tert*-butyldimethylsilyloxymethyl)-8-oxo-1-azabicyclo[4.2.0]octane (31). To a solution of oxime **30** (20 mg, 0.047 mmol) in 5 mL of EtOAc was added 1 mg of PtO_2 followed by di-*tert*-butyl dicarbonate (30 mg, 0.14 mmol). The mixture was stirred vigorously under an atmosphere of H_2 (balloon) for 4 h and filtered through Celite using an additional 15 mL of EtOAc, and the resultant filtrate was evaporated to an oil. Chromatography (SiO_2, EtOAc/hexanes, 1/3, as an eluent) gave carbamate **31** as an oil (18 mg, 76%): $[\alpha]^{22}_D$ +4.2 (*c* 0.9, $CHCl_3$); ^1H NMR δ 0.055−0.087 (m, 12H), 0.88 (s, 9H), 0.92 (s, 9H), 1.44 (s, 9H), 1.57−1.60 (m, 1H), 1.64−1.82 (m, 1H), 1.90−2.01 (m, 1H), 2.96−3.02 (m, 1H), 3.49−3.52 (m, 1H), 3.96−4.08 (m, 4H), 4.78−4.88 (m, 1H), 4.92−4.95 (m, 1H); ^{13}C NMR δ −5.4 (3), −5.3 (3), −5.1 (3), −4.5 (3), 17.3 (2), 18.1 (0), 18.2 (0), 25.8 (3), 28.2 (3), 29.3 (2), 53.0 (1), 59.2 (2), 59.3 (1), 62.2 (1), 63.8 (1), 80.2 (0), 155.2 (0), 166.1 (0). Anal. Calcd for $C_{25}H_{50}N_2O_5Si_2$: C, 58.3; H, 9.8; N, 5.4. Found: C, 58.2; H, 9.8; N, 5.1.

(2*R*,3*R*,6*R*,7*R*)-3-*tert*-Butyldimethylsilyloxy-2-(*tert*-butyldimethylsilyloxymethyl)-7-ethyl-8-oxo-1-azabicyclo-[4.2.0]octane (32) and Diastereomer (2*R*,3*R*,6*R*,7*S*)-33. To a −78 °C solution of diisopropylamine (0.195 mL, 0.141 g, 1.39

mmol) in 10 mL of THF was slowly added a solution of *n*-BuLi (0.867 mL, 1.6 M in hexanes, 1.39 mmol). After being stirred at −78 °C for 1 h, a solution of *β*-lactam **18** (0.482 g, 1.21 mmol) in 3 mL of dry THF was added over 5 min. The solution gradually turned yellow and was stirred at −78 °C for 1 h, followed by the addition of EtI (0.125 mL, 0.247 g, 1.56 mmol). The reaction mixture was stirred at −78 °C for 3.5 h, 8 mL of saturated aqueous KH_2PO_4 was added, and the mixture was partitioned between 100 mL of EtOAc and 20 mL of brine. The aqueous phase was extracted with EtOAc (4 × 30 mL), the combined yellow organic phase was washed with saturated aqueous $Na_2S_2O_3$ (2 × 30 mL), and the resulting colorless organic phase was washed with brine (60 mL), dried, and evaporated to an oil. Chromatography over SiO_2, using EtOAc/hexanes, 1/9, as an eluent, afforded the ethylated *β*-lactams **32** and **33**. **7**α-Ethyl (**32**), slightly yellow oil (0.455 g, 88%): $[\alpha]^{22}_D$ −8.8 (*c* 1.7, $CHCl_3$); ^{1}H NMR *δ* 0.056−0.084 (m, 12H), 0.88 (s, 9H), 0.90 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H), 1.45−1.93 (m, 6H), 2.62−2.66 (m, 1H), 2.96−3.00 (m, 2H), 4.00−4.01 (m, 1H), 4.10−4.18 (m, 2H); ^{13}C NMR *δ* −5.4 (3), −5.2 (3), −5.1 (3), −4.5 (3), 11.7 (3), 18.0 (0), 18.1 (0), 21.8 (2), 23.1 (2), 25.7 (3), 25.9 (3), 36.0 (2), 52.9 (1), 58.9 (2), 59.3 (1), 62.3 (1), 63.3 (1), 169.1 (0). Anal. Calcd for $C_{22}H_{45}NO_3Si_2$: C, 61.8; H, 10.6; N, 3.3. Found: C, 61.6; H, 10.7; N, 3.2. **7***β*-Ethyl (**33**), white solid (40 mg, 7%): mp 90−92 °C; $[\alpha]^{24}_D$ −4.2 (*c* 1, $CHCl_3$); ^{1}H NMR *δ* 0.056−0.083 (m, 12H), 0.88 (s, 9H), 0.91 (s, 9H), 0.97 (t, *J* = 7.4 Hz, 3H), 1.41−1.66 (m, 3H), 1.71−1.78 (m, 1H), 1.93−1.99 (m, 2H), 2.97−3.02 (m, 2H), 3.35−3.41 (m, 1H), 3.98−3.99 (m, 1H), 4.08−4.18 (m, 2H); ^{13}C NMR *δ* −5.3 (3), −5.2 (3), −5.1 (3), −4.6 (3), 12.7 (3), 17.9 (2), 18.1 (0), 18.17 (0), 18.2 (2), 25.8 (3), 25.9 (3), 29.7 (2), 50.6 (1), 54.3 (1), 59.2 (2), 62.1 (1), 63.8 (1), 169.5 (0). Anal. Calcd for $C_{22}H_{45}NO_3Si_2$: C, 61.7; H, 10.6; N, 3.3. Found: C, 61.8; H, 10.4; N, 3.2.

(2*R*,3*R*,6*R*,7*R*)-3-*tert*-Butyldimethylsilyloxy-7-ethyl-2-hydroxymethyl-8-oxo-1-azabicyclo[4.2.0]octane (34). To a solution of *β*-lactam **32** (455 mg, 1.06 mmol) in 15 mL of a 40/1 solution of THF/H_2O was added *p*-TsOH (60 mg, 0.32 mmol). The reaction mixture was stirred at room temperature for 37.5 h then partitioned between 15 mL of H_2O and 75 mL of Et_2O. The aqueous layer was extracted with EtOAc (4 × 20 mL), and the combined organic phase was washed with brine (30 mL), dried, and evaporated to an oil. Chromatography (SiO_2, 3.5 cm × 10 cm plug), using EtOAc/hexanes, 1/3, as an eluent gave the monodeprotected *β*-lactam **34** as an oil (320 mg, 96%): $[\alpha]^{22}_D$ +52.8 (*c* 1 $CHCl_3$); ^{1}H NMR *δ* 0.039−0.044 (m, 6H), 0.89 (s, 9H), 1.00 (t, *J* = 7.4 Hz, 3H), 1.50−1.92 (m, 6H), 2.83−2.87 (m, 1H), 3.06−3.11 (m, 1H), 3.23−3.27 (m, 1H), 3.53−3.60 (m, 1H), 3.82−3.83 (m, 1H), 4.15−4.21 (m, 1H), 4.29−4.33 (m, 1H); ^{13}C NMR *δ* −5.1 (3), −4.5 (3), 11.6 (3), 18.0 (0), 21.2 (2), 22.5 (2), 25.7 (3), 30.6 (2), 54.0 (1), 58.6 (1), 61.6 (1), 61.7 (2), 64.8 (1), 169.8 (0). Anal. Calcd for $C_{16}H_{31}NO_3Si$: C, 61.3; H, 10.0; N, 4.5. Found: C, 61.0; H, 10.2; N, 4.8.

(2*R*,3*R*,6*R*,7*R*)-7-Ethyl-3-hydroxy-2-hydroxymethyl-8-oxo-1-azabicyclo[4.2.0]octane (35). To a solution of diprotected lactam **32** (55 mg, 0.129 mmol) in 2 mL of THF was added TBAF (0.283 mL, 1.0 M in THF, 220 mol %). The solution was stirred at room temperature for 2 h and diluted with EtOAc (25 mL) and saturated aqueous KH_2PO_4 (25 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL), dried, and evaporated to a white residue. Chromatography of the residue on SiO_2 using EtOAc/hexanes, 2/1, as an eluent afforded diol **35** as an opaque oil (25 mg, 98%): ^{1}H NMR *δ* 1.03 (t, *J* = 7.2 Hz, 3H), 1.51 (t, *J* = 13.7 Hz, 1H), 1.67−2.03 (m, 5H), 2.81−2.85 (m, 1H), 2.99−3.01 (m, 1H), 3.14−3.18 (m, 1H), 3.99−4.08 (m, 2H), 4.19−4.24 (m, 1H), 4.40 (br s, 1H), 4.94 (dd, *J* = 4.5, 10.6 Hz, 1H); ^{13}C NMR *δ* 11.4 (3), 21.5 (2), 22.3 (2), 29.1 (2), 53.5 (1), 58.1 (1), 58.9 (1), 62.3 (2), 68.0 (1), 171.1 (0).

(2*S*,3*R*,6*R*,7*R*)-3-*tert*-Butyldimethylsilyloxy-2-carboxyl-7-ethyl-8-oxo-1-azabicyclo[4.2.0]octane (36). To a solution of monoprotected lactam **34** (115 mg, 0.367 mmol) in 4 mL of a 2/2/3 mixture of $CH_3CN/CCl_4/H_2O$ was added $NaIO_4$ (314 mg, 1.47 mmol), followed by $RuCl_3 \cdot 3H_2O$ (2 mg). The tan mixture was stirred vigorously at room temperature for 3 h, and 20 mL of CH_2Cl_2 was added. The aqueous layer was extracted with CH_2Cl_2 (4 × 15 mL), and the combined organic layer was evaporated to a dark-gray residue, which was diluted with Et_2O (50 mL) and filtered through a plug of Celite. The Et_2O was evaporated, and the resulting residue was redissolved in EtOAc (25 mL) and extracted with 5% Na_2CO_3 (6 × 15 mL). The alkaline layer was acidified to pH 3.0 with concd H_3PO_4 and extracted with IPA/$CHCl_3$, 1/3 (5 × 20 mL), and the organic layer was dried and evaporated to provide **36** as a colorless oil (110 mg); ^{1}H NMR *δ* 0.005 (s, 3H), 0.014 (s, 3H), 0.819 (s, 9H), 0.982 (t, *J* = 7.4 Hz, 3H), 1.55−1.91 (m, 6H), 2.82 (t, *J* = 7.3 Hz, 1H), 3.17−3.21 (m, 1H), 3.95 (d, *J* = 1.9 Hz, 1H), 4.35 (t, *J* = 1.9 Hz, 1H); ^{13}C NMR *δ* −5.6 (3), −4.8 (3), 11.2 (3), 17.7 (0), 21.4 (2), 22.4 (2), 25.5 (3), 29.4 (2), 54.7 (1), 57.6 (1), 66.3 (1), 67.4 (1), 168.4 (0), 173.4 (0). This material was used in the next reaction without further purification.

(2*S*,3*R*,6*R*,7*R*)-2-Carboxyl-7-ethyl-3-hydroxy-8-oxo-1-azabicyclo-[4.2.0]octane (39). To a solution of crude acid **36** (110 mg) in 8 mL of THF was added TBAF (0.505 mL, 1.0 M in THF, 150 mol %), the reaction was stirred at room temperature for 18 h, saturated $NaHCO_3$ solution (5 mL) was added, and the THF was evaporated. The resulting solution was diluted with 5% Na_2CO_3 (15 mL) and EtOAc (25 mL), and the EtOAc layer was washed with 5% Na_2CO_3 (4 × 15 mL). The combined alkaline layer was acidified at 0 °C to pH 2.5 with concd H_3PO_4 and extracted with IPA/$CHCl_3$, 1/3 (5 × 15 mL), and the combined organic phase was dried and evaporated to provide **39** as a colorless oil (80 mg); ^{1}H NMR *δ* 1.04 (t, *J* = 7.4 Hz, 3H), 1.60−1.66 (m, 2H), 1.69−1.81 (m, 1H), 1.82−1.87 (m, 2H), 2.11−2.18 (m, 1H), 2.95 (t, *J* = 7.4 Hz, 1H), 3.19−3.26 (m, 2H), 4.05 (d, *J* = 2.1 Hz, 1H), 4.42 (t, *J* = 1.9 Hz, 1H); ^{13}C NMR *δ* 11.3 (3), 21.3 (2), 22.1 (2), 28.6 (2), 55.1 (1), 57.6 (1), 64.2 (1), 65.4 (1), 169.4 (0), 172.7 (0). This material was used in the next reaction without further purification.

(2*S*,3*R*,6*R*,7*R*)-2-(*p*-Nitrobenzyloxycarbonyl)-7-ethyl-8-oxo-3-hydroxy-1-azabicyclo-[4.2.0]octane (40). To a solution of crude hydroxy acid **39** (80 mg) in 4 mL of DMF was added *N*,*N*-diisopropylethylamine (0.160 mL, 119 mg, 0.919 mmol), followed by *p*-nitrobenzyl bromide (0.159 g, 0.734 mmol). The reaction mixture was stirred for 16 h at room temperature and then suspended between EtOAc (30 mL) and saturated $NaHCO_3$ (30 mL). The aqueous layer was extracted with EtOAc (4 × 20 mL), and the combined organic layer was washed with 0.1 M H_3PO_4 (2 × 20 mL) and brine (3 × 20 mL), dried, and evaporated to an orange oil. Chromatography of the residue on SiO_2 using EtOAc/hexanes, 3/2, as an eluent afforded ester **40** as a yellow solid (80 mg, 63% from **34**): mp 113−114 °C; $[\alpha]^{22}_D$ +61.7 (*c* 1, $CHCl_3$); ^{1}H NMR *δ* 1.02 (t, *J* = 7.4 Hz, 3H), 1.67−2.01 (m, 4H), 2.10−2.15 (m, 1H), 2.84−2.89 (m, 1H), 3.18−3.22 (m, 1H), 3.71−3.72 (m, 1H), 3.80 (bs, 1H), 4.16 (bs, 1H), 5.35 (s, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 8.22 (d, *J* = 8.8 Hz, 2H); ^{13}NMR *δ* 11.5 (3), 21.7 (2), 22.2 (2), 28.0 (2), 53.5 (1), 57.5 (1), 60.8 (1), 63.6 (1), 66.5 (2), 123.7 (1), 129.0 (1), 142.0 (0), 147.9 (0), 169.2 (0), 169.9 (0). Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.6; H, 5.8; N, 8.0. Found: C, 58.4; H, 5.5; N, 7.8.

(2*S*,3*R*,6*R*,7*R*)-3-*tert*-Butyldimethylsilyloxy-2-(*p*-nitrobenzyloxycarbonyl)-7-ethyl-8-oxo-1-azabicyclo[4.2.0]-octane (37). To a solution of crude acid **36** (66 mg in 3 mL of DMF) was added *N*,*N*-diisopropylethylamine (53 *μ*L, 39 mg, 0.30 mmol), followed by *p*-nitrobenzyl bromide (65 mg, 0.30 mmol). The reaction mixture was stirred for 24 h at room temperature then suspended between EtOAc (20 mL) and saturated $NaHCO_3$ (40 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed with 0.2 M HCl (50 mL), dried, and evaporated to a yellow oil. Chromatography on SiO_2 using EtOAc/hexanes, 1/4, as an eluent afforded ester **37** as an oil (84 mg, 79% from **34**): $[\alpha]^{22}_D$ +23.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR *δ* 0.030 (s, 3H), 0.071 (s, 3H), 0.84 (s, 9H), 1.02 (t, *J* = 7.4 Hz, 3H), 1.60−1.94 (m, 6H), 2.73−2.77 (m, 1H), 3.15−3.18 (m, 1H), 3.83 (d, *J* = 2.3 Hz, 1H), 4.31−4.33 (m, 1H), 5.23 (d, *J* = 13.4 Hz, 1H), 5.37 (d, *J* = 13.4 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR *δ* −5.3 (3), −4.6 (3), 11.6 (3), 17.9 (0), 21.9 (2), 23.3 (2), 25.5 (3), 29.8 (2), 52.8 (1), 60.3 (1), 61.0 (1), 65.2 (1),

65.7 (2), 123.6 (1), 128.6 (1), 142.9 (0), 147.6 (0), 166.8 (0), 168.9 (0). Anal. Calcd for $C_{23}H_{34}N_2O_6Si$: C, 59.7; H, 7.4; N, 6.1. Found: C, 59.6; H, 7.6; N, 5.8.

(6*R*,7*R*)-2-(*p*-Nitrobenzyloxycarbonyl)-7-ethyl-8-oxo-1-azabicyclo[4.2.0]-2-octene (38). To a solution of ester **37** (0.140 g, 0.30 mmol) in 10 mL of dry THF was added TBAF (0.32 mL, 0.320 mmol). The colorless solution immediately darkened and was stirred for 1 h at room temperature then cooled to 0 °C, and H_2O (2 mL) and Et_2O (40 mL) were added. The mixture was warmed to room temperature, H_2O (5 mL) was added, the aqueous phase was extracted with EtOAc (4 × 10 mL), and the combined organic phase was washed with H_2O (2 × 10 mL) and brine (10 mL), dried, and evaporated. Chromatography on SiO_2 (3 cm × 12 cm) using EtOAc/hexanes, 1/3 then 1/1, gave the olefin **38** as a solid (89 mg, 89%): mp 83−86 °C; ^{1}H NMR δ 1.07 (t, J = 7.4 Hz, 3H), 1.46−1.50 (m, 1H), 1.79−1.95 (m, 2H), 2.26−2.33 (m, 2H), 2.33−2.45 (m, 1H), 2.83−2.87 (m, 1H), 3.28−3.31 (m, 1H), 5.29−5.45 (m, 2H), 6.38−6.40 (m, 1H), 7.64 (d, J = 8.9 Hz, 2H), 8.23 (d, J = 8.9 Hz, 2H); ^{13}C NMR δ 11.6 (3), 21.7 (2), 22.8 (2), 25.4 (2), 52.0 (1), 59.6 (1), 65.6 (2), 123.3 (1), 123.7 (1), 127.9 (1), 128.4 (0), 142.9 (0), 161.7 (0), 167.5 (0).

(6*R*,7*R*)-2-(*p*-Nitrobenzyloxycarbonyl)-7-ethyl-8-oxo-3-trifluoromethanesulfonyloxy-1-azabicyclo[4.2.0]-2-octene (*p*-Nitrobenzyl 7α-Ethyl-3-trifluoromethanesulfonyloxy-1-carba-1-dethia-3-cephem-4-carboxylate) (42). To a solution of hydroxy ester **40** (40 mg, 0.115 mmol) in CH_2Cl_2 (2.5 mL) was added solid Dess−Martin reagent (100 mg, 0.234 mmol). The reaction mixture was stirred for 3 h at room temperature then suspended between CH_2Cl_2 (40 mL) and a 1/1 solution of 10% $Na_2S_2O_3$ and saturated $NaHCO_3$ (30 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layer was washed with a 1/1 solution of 10% $Na_2S_2O_3$ and saturated $NaHCO_3$ (2 × 20 mL), dried, and evaporated to afford enol **41** as a crude yellow oil (60 mg): ^{1}H NMR δ 1.05 (t, J = 7.4 Hz, 3H), 1.72−1.91 (m, 2H), 2.02−2.13 (m, 1H), 2.38−2.51 (m, 1H), 2.69−2.72 (m, 2H), 2.89−2.93 (m, 1H), 3.72−3.76 (m, 1H), 5.29 (d, J = 13.0 Hz, 1H), 5.47 (d, J = 13.0 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 8.23 (d, J = 8.7 Hz, 2H).

Crude enol **41** (60 mg) was dissolved in CH_2Cl_2 (4.0 mL), the solution was cooled to −40 °C in a dry ice/CH_3CN bath, and to this solution was added *N*,*N*-diisopropylethylamine (44 μL, 32.6 mg, 0.25 mmol) followed by triflic anhydride (39 μL, 65.4 mg, 0.232 mmol). The reaction mixture turned yellow and was stirred at −40 °C for 20 min. Aqueous saturated $NaHCO_3$ (15 mL) was added, the solution was allowed to warm to room temperature, it was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic layer was washed with 0.1 M HCl (2 × 20 mL) and brine (20 mL). Drying and evaporating gave an orange oil, which was chromatographed on SiO_2 using hexanes/EtOAc, 3/1, as an eluent to give enol triflate **42** as a yellow oil (40 mg, 73% from **40**): $[\alpha]^{22}_D$ +20.1 (*c* 1, $CHCl_3$); ^{1}H NMR δ 1.06 (t, J = 7.4 Hz, 3H), 1.71−1.96 (m, 3H), 2.35−2.41 (m, 1H), 2.62−2.65 (m, 2H), 2.88−2.93 (m, 2H), 3.42−3.46 (m, 1H), 5.36 (d, J = 13.2 Hz, 1H), 5.47 (d, J = 13.2 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 8.23 (d, J = 8.6 Hz, 2H); ^{13}C NMR δ 11.5 (3), 21.7 (2), 26.0 (2), 26.6 (2), 52.1 (1), 58.9 (1), 66.6 (2), 120.0 (q, J = 318.4 Hz), 122.8 (0), 123.8 (1), 142.0 (0), 142.4 (0), 148.0 (0), 159.1 (0), 168.2 (0). Anal. Calcd for $C_{18}H_{17}F_3N_2O_8S$: C, 45.2; H, 3.6; N, 5.9. Found: C, 45.0; H, 3.3; N, 5.5.

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