2,4,5,7-Me_4-1,6,9-$(SO_3^-)_3P$ 3K, 82649-05-6; 3,4,5,6-Me_4-1-SO_3^-P K, 82649-06-7; 3,4,5,6-Me_4-2-SO_3^-P K, 82649-07-8; 3,4,5,6-Me_4-9-SO_3^-P K, 82649-08-9; 3,4,5,6-Me_4-1,7-$(SO_3^-)_2P$ 2K, 82649-09-0; 3,4,5,6-Me_4-1,8-$(SO_3^-)_2P$ 2K, 82649-10-3; 3,4,5,6-Me_4-1,9-$(SO_3^-)_2P$ 2K, 82649-11-4; 4,5-ethano-1,6-$(SO_3^-)_2P$ 2K, 82649-12-5; 4,5-ethano-1,8-$(SO_3^-)_2P$ 2K, 82649-13-6; phenanthrene, 85-01-8; 9-bromophenanthrene, 573-17-1; 4,5-ethanophenanthrene, 6628-98-4; 2-methylnaphthalene, 91-57-6; 1,3-dimethylnaphthalene, 575-41-7; 2,3-dimethylnaphthalene, 581-40-8; 1,2,3-trimethylnaphthalene, 879-12-9; 1,6,7-trimethylnaphthalene, 2245-38-7; naphthalene, 91-20-3; anthracene, 120-12-7; anthracene-9-sulfonic acid, 22582-76-9.

Supplementary Material Available: Table I, listing the ^1H NMR parameters of the phenanthrene substrates, Tables IV and V, listing the mass spectral data of the potassium sulfonate mixtures and of the arenesulfonic acid mixtures, respectively, and Table VI, listing the cation localization energies of the phenanthrenes, obtained by simple Hückel calculation with $\delta\alpha_r = -0.3$ (4 pages). Ordering information is given on any current masthead page.

N-Unsubstituted β-Lactams from β-Hydroxy-α-amino Acids. Facile Preparation of Intermediates for Isocephalosporins[1]

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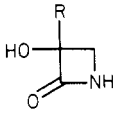
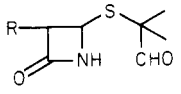
Received January 7, 1982

A facile method has been devised for the synthesis of N-unsubstituted β-lactams. The *cis*-azido β-lactam (**13**) obtained by the reaction of azidoacetyl chloride and the Schiff base (**10**), derived from cinnamaldehyde and a threonine ester, is subjected to controlled oxidation with Jones reagent: the threonine moiety is thereby oxidized to a β-keto ester (**19**), which exists primarily in its enolic form. The use of an excess of the oxidizing agent results in the removal of the threonine moiety and the formation of an N-unsubstituted β-lactam (**22**). Such β-lactams are known key intermediates for the synthesis of isocephalosporins and other β-lactam antibiotics.

N-Unsubstituted β-lactams were first synthesized in the laboratory many years before they were discovered in nature. The first naturally occurring member of this series to be reported in the literature was Wildfire toxin (**1**),[2]



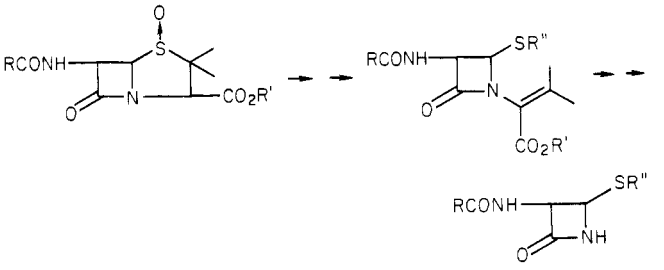
1, R = $CH_2CH_2CH(NH_2)CONHCH(COOH)CH(CH_3)OH$
2, R = $CHClCH_2CH(CO_2H)NHCOCH(CH_3)NH_2$



3a

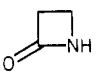
which is a peptide derivative. This β-lactam is produced by the bacterium, *Pseudomonas tabaci*, that causes the "wildfire disease" of tobacco leaves. Another peptide-bearing monocyclic β-lactam (**2**) was isolated from an unidentified *Streptomyces* species 372A.[3]

Sheehan and Brandt[4] cleaved the thiazolidine ring of penicillin and prepared N-unsubstituted β-lactams of type (**3a**). Since then many N-unsubstituted β-lactams (**3b**) have been prepared by the degradation of penicillin sulfoxide via *N*-vinyl β-lactams. Various laboratories have developed their own favorite method for removing the *N*-vinyl group to obtain N-unsubstituted β-lactams.[5]



3b

A number of synthetic approaches to N-unsubstituted β-lactams have been described; all but one[6] of them involve the removal of the N-substituent by some reaction that will not lead to the scission of the β-lactam ring. The one exception is the method first described by Breckpot[7] for the cyclization of β-amino esters directly to N-unsubstituted β-lactams under the influence of an organometallic reagent, such as a hindered Grignard agent[8] or diisobutylaluminum hydride.[9] The parent β-lactam (**4**) was first prepared by this method by Holley and Holley.[10]

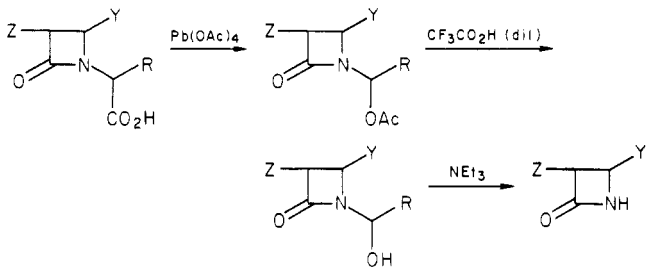


4

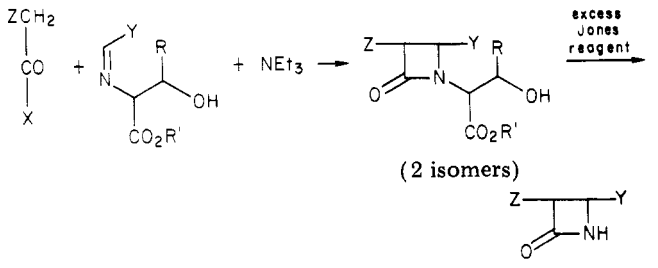
(1) Part 65 in the series "Studies on Lactams". For part 64, see A. K. Bose, M. S. Manhas, J. M. van der Veen, S. G. Amin, I. F. Fernandez, K. Gala, R. Gruska, J. C. Kapur, M. S. Khajavi, J. Kreder, L. Mukkavilli, B. Ram, M. Sugiura, and J. E. Vincent, *Tetrahedron*, **37**, 2321 (1981).
(2) W. W. Stewart, *Nature (London)*, **229**, 174 (1971).
(3) J. P. Scannell, D. L. Pruess, J. F. Blount, H. A. Ax, M. Kellett, F. Weiss, T. C. Demny, T. H. Williams, and A. Stempel, *J. Antibiot*, **28**, 1 (1975).
(4) J. C. Sheehan and K. G. Brandt, *J. Am. Chem. Soc.*, **87**, 5468 (1965).
(5) For example, see (a) A. Suarto, P. Lombardi, C. Galliani, and G. Franceschi, *Tetrahedron Lett.*, 4059 (1978); (b) E. G. Brian, C. L. Branch, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, M. J. Pearson, T. C. Smale, R. Southgate, and P. Tolliday, "Recent Advances in the Chemistry of β-Lactam Antibiotics", J. Elks, Ed., Chemical Society, London, 1977, Special Publication, no. 28, p 204.
(6) G. Cignarelli, G. F. Cristiani, and E. Testa, *Liebigs Ann. Chem.*, **661**, 181 (1963), and subsequent papers in this series.
(7) R. Breckpot, *Bull. Soc. Chim. Belg.*, **32**, 412 (1923); *Chem. Abstr.*, **18**, 1113 (1924).
(8) S. Searles, Jr., and R. E. Wann, *Chem. Ind. (London)*, 2097 (1964).
(9) R. B. Woodward, K. Heusler, J. Gosteil, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Am. Chem. Soc.*, **88**, 852 (1966).

0022-3263/82/1947-4075$01.25/0

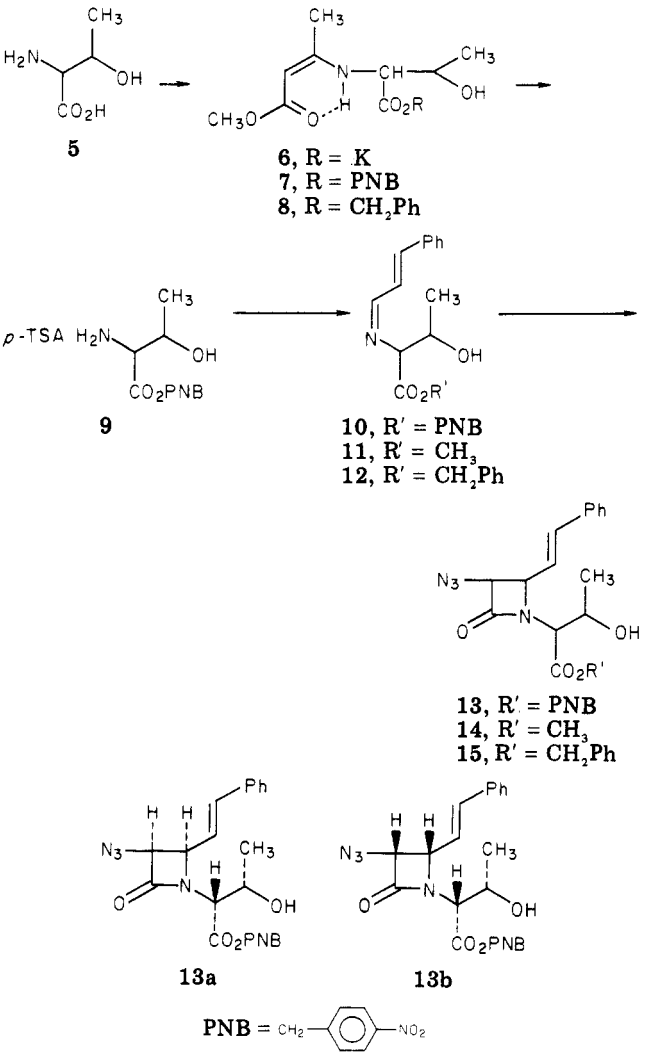
Scheme I



Scheme II



Scheme III



In an earlier publication from our laboratory,[11] we described the synthesis of β-lactams from imino compounds derived from α-amino acid esters and the subsequent conversion of such β-lactams to N-unsubstituted β-lactams. The removal of the α-amino acid residue from the β-lactam nitrogen was achieved by reactions involving a rearrangement under the influence of lead tetraacetate as described in Scheme I. This method was later used by Kamiya et al.[12a] for the synthesis of nocardicins and by Cimarusti et al.[12b] for the preparation of monobactams.

We describe now a different approach to N-unsubstituted β-lactams, which has a potential for producing optically active compounds. This method is based on our observation that 3-substituted 2-azetidinones prepared from imino compounds derived from β-hydroxy-α-amino acids can be directly oxidized to N-unsubstituted β-lactams (Scheme II).

The starting material for our synthesis was threonine (**5**), which is readily available in the racemic, as well as the optically active, form. Much of our work was done with the *p*-nitrobenzyl ester, although we have also used the methyl or other common esters.

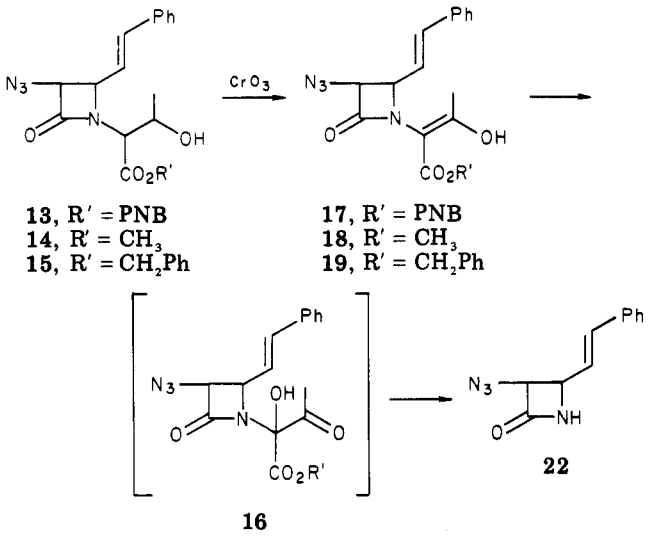
The ester **7** was prepared by first converting threonine to a "Dane salt" (**6**)[13] by reaction with methyl acetoacetate and alkali. Treatment of **6** with *p*-nitrobenzyl chloride gave the ester **7**.[14] Benzyl ester **8** was similarly produced from the Dane salt **6** and benzyl bromide. The protective group was removed from **7** by treatment with a molar equivalent of *p*-toluenesulfonic acid. The crystalline salt of the ester **9** so obtained was converted to the free amino ester by neutralization with potassium carbonate. Heating this ester with cinnamaldehyde in methylene chloride solution for a few minutes resulted in a high yield of the imino compound **10**, which was best used without delay for the β-lactam-forming step. The Schiff bases **11** and **12** were similarly produced from cinnamaldehyde and the methyl and benzyl esters of threonine, respectively.

When **10** was allowed to react with azidoacetyl chloride and triethylamine, two *cis*-β-lactams were obtained in nearly equal amounts. There is no reason to believe that the process of Schiff base formation or reaction with azidoacetyl chloride would epimerize the α carbon of threonine; the carbinol carbon also would be very unlikely to undergo epimerization under the reaction conditions employed. Therefore, we assigned the structures **13a** and **13b** to the two isomeric *cis*-β-lactams (see Scheme III). It was possible to separate them by TLC, but larger scale separation on a chromatographic column proved difficult.

Subsequent studies[19] have shown that better separation of the diastereomeric β-lactams derived from D-threonine can be achieved when in Scheme II Z = $PhOCH_2CONH$, Y = CH=CHPh, and R′ = *p*-CH_2-Ph-NO_2. The N-unsubstituted β-lactams from these isomers have been found to be enantiomeric, as we expected.[19]

(10) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, **71**, 2124 (1949).
(11) A. K. Bose, M. Tsai, S. D. Sharma, and M. S. Manhas, *Tetrahedron Lett.*, 3851 (1973).
(12) (a) T. Kamiya in "Recent Advances in the Chemistry of β-Lactams", J. Elks, Ed., The Chemical Society, London, 1977, Chapter 29. (b) C. M. Cimarusti, H. E. Applegate, H. W. Chang, D. M. Floyd, W. H. Koster, W. A. Slusarchyk, and M. G. Young, *J. Org. Chem.*, **47**, 179 (1982).
(13) E. Dane, F. Dress, P. Konrad, and T. Dockner, *Angew Chem., Intl. Ed. Engl.*, **3**, 440 (1964).
(14) J. A. Maclaren, *Aust. J. Chem.*, **25**, 1293 (1972).
(15) D. B. Bryan, R. F. Hall, K. G. Holden, W. F., Huffman, and M. P. Cunningham, *J. Am. Chem. Soc.*, **99**, 2353 (1977).
(16) T. Wieland and R. Sarges, *Liebigs Ann. Chem.*, **658**, 181 (1962).
(17) Also see G. Just and T. Liak, *Can. J. Chem.*, **56**, 211 (1978).
(18) M. Fieser and L. F. Fieser in "Reagents for Organic Synthesis", Vol. 2, Wiley-Interscience, New York, 1969, p 358.
(19) A. K. Bose et al., paper presented at the 28th IUPAC Meeting, Vancouver, Canada, 1981.

Scheme IV



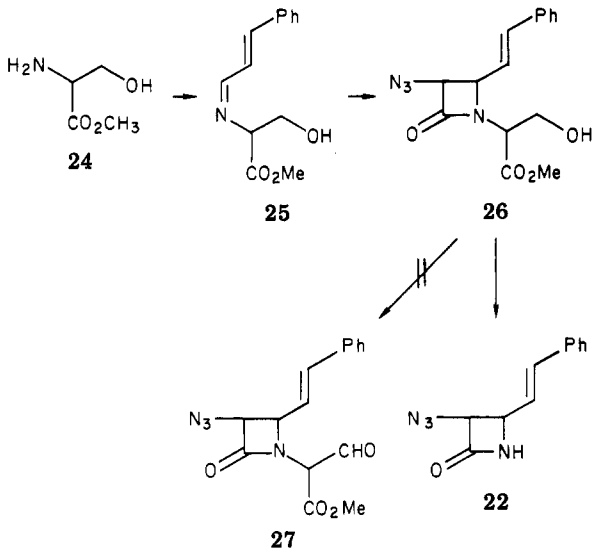
13, R′ = PNB
14, R′ = CH_3
15, R′ = CH_2Ph

17, R′ = PNB
18, R′ = CH_3
19, R′ = CH_2Ph

16

22

Scheme V



24

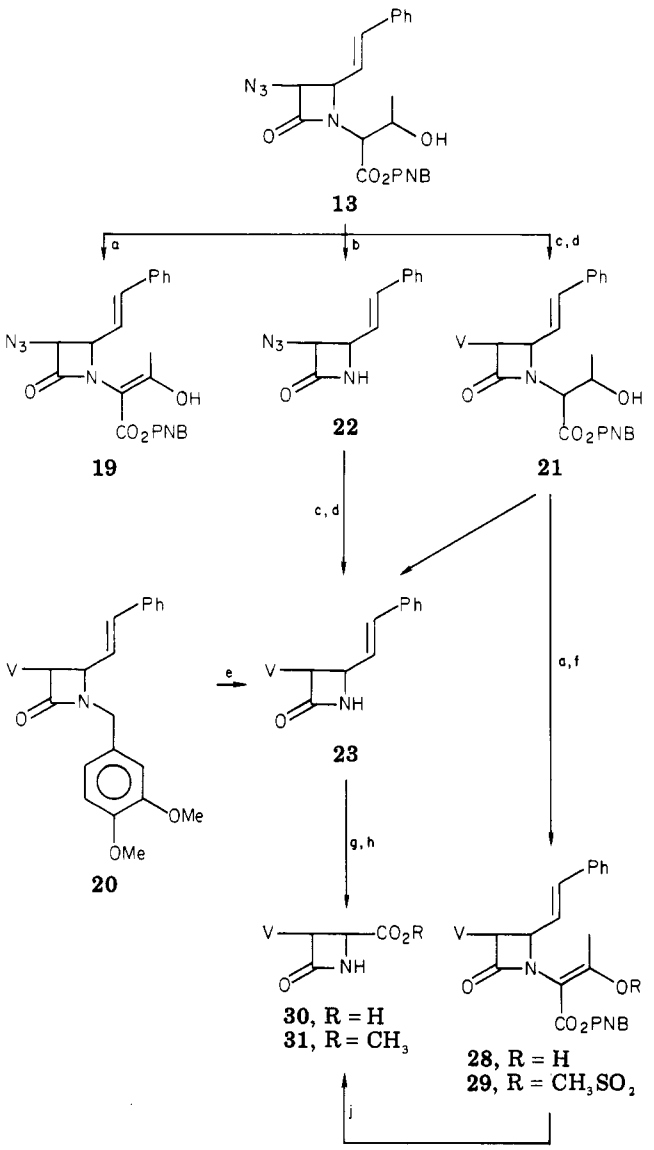
25

26

27

22

Scheme VI[a]



13

19

22

21

20

23

30, R = H
31, R = CH_3

28, R = H
29, R = CH_3SO_2

[a] Reagents and conditions: a limited amount of CrO_3 + H_2SO_4; b, excess CrO_3 + H_2SO_4; c, H_2S; d, $PhOCH_2COCl$ + NEt_3; e, $K_2S_2O_8$; f, CH_3SO_2Cl, NEt_3; g, $KMnO_4$; h, CH_2N_2; j, RuO_4.

It is worthy of note that no protection of the free hydroxy group was necessary during β-lactam formation. Apparently, hydrogen bonding between the hydroxy group and the ester carbonyl provided adequate protection against acylation of the hydroxy group. The reaction of the imines (**11**) and (**12**) with azidoacetyl chloride gave the *cis*-β-lactams **14** and **15**, respectively.

Jones reagent was found to be satisfactory for the oxidation of the hydroxy group of **13**. By monitoring the reaction by TLC, we were able to stop the oxidation at the β-keto ester **19** stage (Scheme IV); however, if an excess of oxidizing agent was employed, the product obtained was the N-unsubstituted β-lactam (**22**).

The mechanism of this cleavage has not been studied. However, it seems possible that further oxidation of the keto ester (**19**) formed initially would lead to an α-hydroxy-β-keto ester (**16**), which would be readily hydrolyzed to the unsubstituted β-lactam (**22**) (see Scheme IV). β-Lactams **14** and **15** were similarly oxidized with Jones reagent to **17**, **18**, or **22** (Scheme IV).

The oxidation of hydroxy β-lactam **26** derived from the reaction of azidoacetyl chloride and the Schiff base **25** from *dl*-serine ester **24** did not result in the formation of the corresponding aldehyde **27**. Only the N-unsubstituted β-lactam **22** could be isolated in this reaction (see Scheme V); the yield of **22** was only 9% using the same conditions as for the oxidation of **13** without trying to find optimum conditions.

The key compound (**13**) with various functional groups can be manipulated in a number of ways (Scheme VI) to reach target compounds, such as **19**, **23**, and **31**.

Reduction of the azido β-lactam **13** with hydrogen sulfide in the presence of triethylamine afforded a 3-amino-2-azetidinone acylation, of which with phenoxyacetyl chloride gave the α-phenoxyacetamido β-lactam **21**. Oxidation of **21** with excess of Jones reagent resulted in the formation of 3-phenoxyacetamido-4-styrylazetidin-2-one (**23**) in 20% yield. The reduction of the β-lactam **22** with hydrogen sulfide in the presence of triethylamine, followed by the acylation of the product with phenoxyacetyl chloride, resulted in the formation of the same amido β-lactam (**23**).

Compound **23** had been obtained in our laboratory earlier by an alternate route[1,20] involving the preparation of an N-unsubstituted β-lactam by the oxidative removal of the dimethoxybenzyl protective group of **20**. The in-

(20) A. K. Bose, M. S. Manhas, S. G. Amin, J. C. Kapur, J. Kreder, L. Mukkavilli, B. Ram, and J. E. Vincent, *Tetrahedron Lett.*, 2771 (1979).

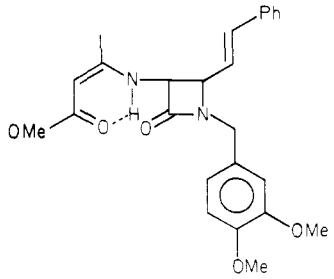
termediate **20** was prepared from the previously described β-lactam **32**[20] by removal of the protective group from the side-chain amino group, followed by acylation.

Oxidation of **23** with potassium permanganate gave the 4-carboxy-2-azetidinone **30**, which was esterified with diazomethane to the known[15] ester **31**. This ester had been prepared previously by the SmithKline group[15] by a longer route that could produce optically active products only through resolution.

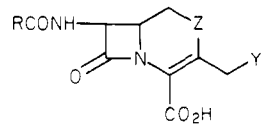
The ester **31** could also be prepared from **13** via the amido β-lactam **21**, which upon controlled Jones oxidation gave the α-keto ester **28**, which exists mainly in its enol form because of strong hydrogen bonding of the OH with the ester moiety (see Scheme VI).

Ruthenium tetroxide oxidation is a convenient way of converting an alkene to a carboxylic acid.[18] In the hope of obtaining **30** directly from **28**, we tried ruthenium tetroxide oxidation but without very satisfactory results. We ascribed our difficulties to the mobile keto–enol form of **28** and decided to immobilize the enolic double bond. The enol mesylate **29** was easily prepared from **28** by reaction with methanesulfonyl chloride in the presence of *N,N*-dimethylaminopyridine. Ruthenium tetroxide oxidation of **29** proceeded smoothly at both double bonds, and the desired β-lactam **30** was obtained as the only product. As before, esterification of **30** with diazomethane gave the known ester[15] **31**.

Compound **31** is a versatile intermediate. The SmithKline group has synthesized a variety of isocephalosporins and analogues, such as **33**, by modifying the carboxy group at C-4, attaching a substituent at the β-lactam nitrogen, and by performing suitable annelation reactions.



32



33, Z = S or O; Y = H or OAc

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 NMR spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane as internal standard, with the downfield direction taken as positive. Mass spectra were taken with a Hitachi RMU-7 mass spectrometer and a CIMS-Biospec instrument. The infrared spectra were recorded on a Perkin-Elmer infracord as Nujol mulls. Microanalyses were performed by Schwarzkopf Microanalytic Laboratory, Inc., Woodside, NY.

***N*-[1-Methyl-2-(methoxycarbonyl)vinyl]-D-threonine Potassium Salt (6).** D-Threonine (39.0 g, 328 mmol) and potassium hydroxide (22.02 g, 393 mmol) were dissolved in absolute methanol (700 mL), and the mixture was stirred at room temperature until it became homogeneous. Methyl acetoacetate (41.82 g, 361 mmol) was then added, and the solution was stirred overnight. This solution was concentrated to dryness under reduced pressure, and the resulting white solid recrystallized from absolute ethanol to yield 78.2 g of **6**. This solid was then suspended in CH_2Cl_2 (500 mL) and stirred vigorously for 1 h. The suspended material was then filtered and dried to yield the pure salt **6** (76.13 g, 91.0%), mp 133–135 °C. Anal. Calcd for $C_9H_{14}NO_5K$: C, 42.35; H, 5.49; N, 5.49. Found: C, 42.61; H, 5.78; N, 5.31.

***p*-Nitrobenzyl-D-threonine *p*-Toluenesulfonate (9).** *p*-Nitrobenzyl bromide (21.6 g, 100 mmol) and the salt **6** (25.5 g, 100 mmol) were dissolved in anhydrous DMF (100 mL), and the solution was stirred at room temperature for 24 h. The reaction mixture was then diluted with ethyl acetate (300 mL), washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under reduced pressure to yield **7** as a viscous oil (36.5 g). This material, quite pure as determined by TLC, was then dissolved in 1,4-dioxane (80 mL), to which was added *p*-toluenesulfonic acid monohydrate (19.2 g, 100 mL). After the mixture was stirred at room temperature for 20 h, the product precipitated from solution and was filtered, and the filtrate was washed with ether and dried to yield **9** (36.04 g, 84.0% from **5**) as a white, fluffy solid, mp 135–137 °C. Anal. Calcd for $C_{18}H_{22}N_2O_8S$: C, 61.36; H, 6.25; N, 7.95. Found: C, 61.55; H, 6.48; N, 7.81.

***cis*-1-[1-[[(*p*-Nitrobenzyl)oxy]carbonyl]-2-hydroxypropyl]-3-azido-4-styrylazetidin-2-one (13).** *p*-Nitrobenzyl-D-threonine *p*-toluenesulfonate (**9**; 34.08 g, 80 mmol) and potassium carbonate (16.56 g, 120 mmol) were suspended in methylene chloride (320 mL) layered with water (160 mL). The mixture was shaken vigorously for 10 min, and the organic layer was separated. The aqueous layer was extracted with additional methylene chloride (160 mL), the organic extracts were combined, dried (K_2CO_3), and filtered, and the filtrate was evaporated at room temperature under reduced pressure to yield the amino ester (18.80 g, 94.0%), which was dissolved in anhydrous methylene chloride (60 mL). To this solution was added *trans*-cinnamaldehyde (10.26 g, 77.7 mmol); the reaction mixture was then refluxed for 3 min and stirred at room temperature for 1 h. The cloudy solution thus obtained was dried (K_2CO_3) and filtered, and the filtrate was diluted to a volume of 200 mL with anhydrous methylene chloride. Triethylamine (14.95 g, 148 mmol) was added to this solution, which was then cooled to 0 °C. Azidoacetyl chloride (17.69 g, 148 mmol) in anhydrous methylene chloride (130 mL) was added dropwise over a period of 1 h. The reactants were allowed to warm to room temperature over a period of 12 h and then evaporated to dryness. The residue was triturated with anhydrous ether (600 mL). The ether layer was filtered and the filtrate was washed with brine (300 mL), dried (Na_2SO_4), and evaporated to yield 34.50 g of a crude oil, which was chromatographed on 600 g of Davison silica gel (100–200 mesh) with an eluent of chloroform–ethyl acetate (10:1), yielding a mixture of diastereomers (1:1 ratio) of **13** (18.16 g, 54.4%). A portion of the mixture was further chromatographed so as to separate the diastereomers. Both compounds exhibited almost identical infrared spectra: IR (neat) 3300–3200, 2110, 1755, 1735, 1520 cm^{-1}; NMR for faster-moving compound ($CDCl_3$) δ 1.35 (d, 3 H, J = 6.0 Hz), 3.95 (d, 1 H, J = 3.0 Hz), 4.30 (s, 1 H), 4.50 (m, 1 H), 4.52 (dd, 1 H, J = 4.5 and 9.0 Hz), 5.00 (d, 1 H, J = 4.5 Hz), 5.28 (d, 2 H, J = 3.0 Hz), 6.75 (d, 1 H, J = 16.0 Hz), 7.35 (s, 5 H), 7.50 (d, 2 H, J = 7.5 Hz), 8.20 (d, 2 H, J = 7.5 Hz); NMR for slower-moving compound ($CDCl_3$) δ 1.35 (d, 3 H, J = 6.0 Hz), 3.98 (d, 1 H, J = 3.0 Hz), 4.45 (m, 1 H), 4.55 (dd, 1 H, J = 4.5 and 9.0 Hz), 4.97 (d, 1 H, J = 4.5 Hz), 5.30 (br s, 2 H), 6.22 (dd, 1 H, J = 9.0 and 16.0 Hz), 6.70 (d, 1 H, J = 16.0 Hz), 7.35 (s, 5 H), 7.40 (d, 2 H, J = 8.0 Hz), 8.10 (d, 2 H, J = 8.0 Hz), OH undetected.

***cis*-1-[1-(Methoxycarbonyl)-2-hydroxypropyl]-3-azido-4-styrylazetidin-2-one (14).** The D-threonine methyl ester[16] (9.95 g, 74.8 mmol) and *trans*-cinnamaldehyde (10.37 g, 78.5 mmol) in anhydrous methylene chloride (25 mL) were refluxed together for 5 min and then stirred at room temperature for 1 h. The cloudy solution thus obtained was dried (K_2CO_3) and filtered, and the filtrate was diluted to a volume of 200 mL with anhydrous methylene chloride. Triethylamine (15.11 g, 149.6 mmol) was added to this solution, which was then cooled to 0 °C. Azidoacetyl chloride (17.88 g, 149.6 mmol) in anhydrous methylene chloride (130 mL) was added dropwise over a period of 1 h. The reactants were allowed to warm to room temperature overnight and then evaporated to dryness. The residue was triturated with ether (600 mL). The ether layer was filtered, and the filtrate was washed with brine (300 mL), dried (Na_2SO_4), and evaporated to yield 29.27 g of a crude oil, which was chromatographed on 600 g of Davison silica gel (100–200 mesh) with an eluent of chloroform–ethyl acetate (10:1), yielding a mixture of diastereomers (1:1 ratio) of **14** (13.72 g, 55.6%). A portion of the mixture was further chromatographed so as to separate the diastereomers. Faster-moving compounds: IR (neat) 3250, 2100, 1750, 1725, 1410 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 6.0 Hz), 3.80 (s, 3 H), 3.85 (d,

1 H, J = 5.5 Hz), 4.40 (m, 1 H), 4.55 (dd, 1 H, J = 5.0 and 8.0 Hz), 5.00 (d, 1 H, J = 5.0 Hz), 6.15 (dd, 1 H, J = 8.0 and 16.0 Hz), 6.50 (br s, 1 H), 6.70 (d, 1 H, J = 16.0 Hz), 7.40 (s, 5 H). Slower-moving compound: IR (neat) 3300–3200, 2100, 1750, 1730, 1440 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6.5 Hz), 3.70 (s, 3 H), 3.95 (d, 1 H, J = 4.5 Hz), 4.30 (m, 1 H), 4.55 (dd, 1 H, J = 5.0 and 9.0 Hz), 4.85 (d, 1 H, J = 5.0 Hz), 6.15 (dd, 1 H, J = 9.0 and 16.0 Hz), 6.70 (d, 1 H, J = 16.0 Hz), 7.35 (s, 5 H), OH undetected.

***cis*-1-[1-(Benzyloxycarbonyl)-2-hydroxypropyl]-3-azido-4-styrylazetidin-2-one (15).** Benzyl bromide (5.13 g, 30.0 mmol) and *N*-[1-methyl-2-(methoxycarbonyl)vinyl]-D-threonine potassium salt **6** (7.65 g, 30.0 mmol) were dissolved in anhydrous dimethylformamide (30 mL), and the solution was stirred at room temperature for 24 h. The reaction mixture was then diluted with ethyl acetate (100 mL), washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to yield *N*-[1-methyl-2-(methoxycarbonyl)vinyl]-D-threonine benzyl ester as a viscous oil (9.25 g). This material, quite pure as determined by TLC, was dissolved in 1,4-dioxane (30 mL), to which was added *p*-toluenesulfonic acid monohydrate (5.71 g, 30.0 mmol). After the reaction mixture was stirred at room temperature for 24 h, the 1,4-dioxane was removed under reduced pressure, and the residual oil was heated (70 °C) for 3 h in vacuo (1 mm) to remove the methyl acetoacetate, which was produced as a byproduct. The resulting benzyl D-threonine *p*-toluenesulfonate (10.90 g, 95.4%) as a viscous oil was used as such without further purification. This material (8.56 g, 22.5 mmol) and potassium carbonate (4.65 g, 33.7 mmol) were suspended in methylene chloride (80 mL) layered with water (40 mL) in a separatory funnel. The mixture was shaken vigorously for 10 min, and the organic layer was separated. The aqueous layer was extracted with additional methylene chloride (40 mL), the organic extracts were combined, dried (K_2CO_3), and filtered, and the filtrate was evaporated at room temperature under reduced pressure to yield the benzyl ester (4.15 g, 88.4%) as an amorphous solid. This ester (4.15 g, 19.9 mmol) and *trans*-cinnamaldehyde (2.75 g, 20.8 mmol) were dissolved in anhydrous methylene chloride (20 mL). The solution was refluxed for 5 min and then stirred at room temperature for 1 h. The cloudy solution of **12** thus obtained was dried (K_2CO_3) and filtered, and the filtrate was diluted to a volume of 55 mL with anhydrous methylene chloride. Triethylamine (4.01 g, 39.7 mL) was added dropwise over a period of 1 h. The reactants were allowed to warm to room temperature overnight and then were evaporated to dryness. The residue was triturated with ether (200 mL). The ether layer was filtered, washed with brine (100 mL), dried (Na_2SO_4), and evaporated to yield 8.48 g of **15** as a crude oil, which was chromatographed on 150 g of Davison silica gel (100–200 mesh) with an eluent of chloroform–ethyl acetate (10:1), yielding a mixture of diastereomers (1:1 ratio) of **15** (4.20 g, 52.1%): IR (neat) 3300–3200, 2120, 1755, 1740, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 6.0 Hz), 3.80–4.00 (m, 2 H), 4.50 (m, 1 H), 5.00 (d, 1 H, J = 5.0 Hz), 5.25 (s, 2 H), 6.00–7.10 (m, 2 H), 7.40 (s, 10 H), OH undetected; EIMS, m/e 378 (M^+ − 28).

***cis*-1-[1-[(*p*-Nitrobenzyloxy)carbonyl]-2-hydroxypropenyl]-3-azido-4-styrylazetidin-2-one (19).** To a stirred solution of the diastereomers of **13** (16.62 g, 36.85 mmol) in acetone (1000 mL) at room temperature was added 16.6 mL of Jones reagent, prepared by dissolving CrO_3 (26.72 g) in concentrated H_2SO_4 (23 mL) and diluting the solution to a volume of 100 mL with water. Vigorous stirring was maintained for 1 h, after which time the mixture was filtered to remove the chromous salts. The filtrate (acetone solution) was evaporated, and the residue was taken up in $CHCl_3$ (600 mL). This solution was washed with 5% $NaHCO_3$ (2 × 300 mL), dried (Na_2SO_4), and evaporated to yield 15.95 g of a crude oil. Chromatography on 300 g of Davison silica gel (100–200 mesh) with an eluent of chloroform–ethyl acetate (10:1) afforded the enol **19** (12.86 g, 77.7%): mp 98–101 °C; IR (neat) 2950–2825, 2100, 1762, 1745, 1650, 1605 cm^{-1}; NMR ($CDCl_3$) δ 2.13 (s, 3 H), 4.55 (dd, 1 H, J = 5.5 and 9.0 Hz), 4.90 (d, 1 H, J = 5.5 Hz) 5.33 (s, 2 H), 6.20 (dd, 1 H, J = 9.0 and 16.0 Hz), 6.70 (d, 1 H, J = 16.0 Hz), 7.43 (s, 5 H), 7.55 (d, 2 H, J = 9.0 Hz), 8.25 (d, 2 H, J = 9.0 Hz), 12.30 (s, 1 H).

Using the same reaction conditions, we prepared **17** from **14** in 72.3% yield as an oily product. In this oxidation reaction, 1.2 mol of CrO_3 was used per mole of **14**: IR (neat) 2950–2850, 2110, 1760, 1745, 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3 H), 3.82 (s, 3 H), 4.60 (dd, 1 H, J = 5.0 and 9.0 Hz), 4.90 (d, 1 H, J = 5.0 Hz), 6.20 (dd, 1 H, J = 9.0 and 16.0 Hz), 6.72 (d, 1 H, J = 16.0 Hz), 7.35 (s, 5 H), 12.40 (s, 1 H).

Enol **18** was obtained as an oil from **15** in 67.8% yield (in this reaction, 1.2 mol of CrO_3 was used per mole of β-lactam): IR (neat) 2900–2800, 2110, 1760, 1745, 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (s, 3 H), 4.57 (dd, 1 H, J = 5.0 and 9.0 Hz), 4.92 (d, 1 H, J = 5.0 Hz), 5.25 (s, 2 H), 6.20 (dd, 1 H, J = 9.0 and 16.0 Hz), 6.71 (d, 1 H, J = 16.0 Hz), 7.40 (m, 10 H), 12.40 (s, 1 H).

***cis*-1-(3,4-Dimethoxybenzyl)-3-(phenoxyacetamido)-4-styrylazetidin-2-one (20).** To a solution of **32**[20] (1.00 g, 2.3 mmol) in 1,4-dioxane (20 mL) was added *p*-toluenesulfonic acid monohydrate (0.87 g, 4.6 mmol). The reaction mixture was stirred at room temperature overnight, after which time it was evaporated under reduced pressure. The residual oil was redissolved in anhydrous methylene chloride (50 mL) to which was then added triethylamine (0.465 g, 4.6 mmol). The solution was stirred at room temperature for 1 h, at which point it was cooled to 0 °C, and additional triethylamine (0.280 g, 2.8 mmol) was added. Phenoxyacetyl chloride (0.47 g, 2.8 mmol) in anhydrous methylene chloride (5 mL) was then slowly added dropwise with stirring. After 2 h, the solution was washed with 5% $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated to yield 1.50 g of a crude oil. Chromatographic purification of this oil on 100 g of Davison silica gel (100–200 mesh), with chloroform–ethyl acetate (10:5) as eluent, provided the amide **20** (0.580 g, 53.6% yield) as an oil: IR (neat) 3170, 2850, 1750, 1670 cm^{-1}; NMR ($CDCl_3$) δ 3.85 (s, 3 H), 3.90 (s, 3 H), 4.40 (dd, 2 H, J = 15.0 and 48.0 Hz), 4.50 (s, 2 H), 5.40 (dd, 1 H, J = 5.0 and 9.0 Hz), 5.95 (dd, 1 H, J = 7.5 and 16.0 Hz), 6.60 (d, 1 H, J = 16.0 Hz), 6.80–7.35 (m, 13 H), 7.40 (d, 1 H, J = 9.0 Hz).

***cis*-1-[1-[[(*p*-Nitrobenzyl)oxy]carbonyl]-2-hydroxypropyl]-3-(phenoxyacetamido)-4-styrylazetidin-2-one (21).** Hydrogen sulfide was passed through a cooled (0 °C) solution of **13** (18.04 g, 40 mmol) in anhydrous CH_2Cl_2 (400 mL) for 20 min. Triethylamine (10.10 g, 100 mmol) in anhydrous CH_2Cl_2 (25 mL) was then added dropwise with stirring, and the reaction mixture was maintained at 0 °C for 1 h. The solvent was evaporated, and the residual solid was triturated with benzene (250 mL) and filtered. The filtrate was evaporated, and the residue of the crude diastereomeric amines was dissolved in anhydrous CH_2Cl_2 (300 mL). Triethylamine (4.85 g, 48 mmol) was added, and the solution was cooled to 0 °C. Phenoxyacetyl chloride (8.19 g, 48 mmol) in anhydrous CH_2Cl_2 (25 mL) was slowly added dropwise to the stirred solution. The mixture was allowed to stir with warming to room temperature over 3 h, washed with 5% $NaHCO_3$ (150 mL) and brine (150 mL), dried (Na_2SO_4), and evaporated to yield 21.80 g of a crude oil. Chromatographic purification of this oil on 500 g of Davison silica gel (100–200 mesh) with an eluent of chloroform–ethyl acetate (10:3) provided the diastereomeric amides **21** (15.32 g, 68.5%): mp 130–132 °C; IR (neat) 3250–3100, 1755, 1738, 1655, 1525, 1360 cm^{-1}; NMR ($CDCl_3$): δ 1.40 (d, 3 H, J = 6.0 Hz), 3.95 (d, 1 H, J = 3.0 Hz), 4.45 (s, 2 H), 4.55 (m, 2 H), 5.29 (d, 2 H, J = 2.5 Hz), 5.30 (m, 1 H), 6.10 (dd, 1 H, J = 9.0 and 16.0 Hz), 6.60–7.31 (m, 12 H), 7.55 (d, 2 H, J = 9.0 Hz), 8.22 (d, 2 H, J = 9.0 Hz), O*H* undetected. Anal. Calcd for $C_{30}H_{29}N_3O_8$: C, 64.39; H, 5.22; N, 7.51. Found: C, 63.92; H, 5.40; N, 7.30.

***cis*-3-Azido-4-styryl-2-azetidinone (22).** An excess of Jones reagent (3.6 equiv of CrO_3 per equivalent of β-lactam) was added to a solution of **13** in dry acetone. The reaction time was monitored by TLC (reaction was stopped at the time when the intensity of the spot corresponding to the desired product was maximum). The compound **22** was obtained as an oil in 37% yield after the usual workup: IR (neat) 3200–3100, 2120, 1760 cm^{-1}; NMR ($CDCl_3$) δ 4.55 (dd, 1 H, J = 4.5 and 7.0 Hz), 4.90 (dd, 1 H, J = 2.0 and 4.5 Hz), 6.25 (dd, 1 H, J = 7.0 and 16.0 Hz), 6.80 (d, 1 H, J = 16.0 Hz), 7.40 (m, 6 H).

***cis*-3-(Phenoxyacetamido)-4-styrylazetidin-2-one (23). Method A.** To a solution of **21** (3.0 g, 0.0054 mol) in 10 mL of acetone was added 11 mL of Jones reagent (3.6 equiv of CrO_3) in a dropwise manner. This reaction mixture was stirred for another 2 h and then evaporated to dryness. An ethyl acetate extract of the residue was washed with 5% $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated to an oil, which was chromatographed (chloroform–ethyl acetate, 10:3) to give a white solid,

which was triturated with methylene chloride to obtain a crystalline product (0.34 g, 20%), mp 191–193 °C, which was used directly for the preparations of **31**, a known compound.

Method B. Hydrogen sulfide was passed through a cooled (0 °C) solution of **22** (100 mg, 0.47 mmol) in anhydrous CH_2Cl_2 (5 mL) for 15 min. Triethylamine (472 mg, 4.70 mmol) was then added, and the reaction mixture was stirred at 0 °C for 1 h. The solvent was evaporated under reduced pressure, and the residue triturated with benzene (15 mL). The insoluble salts were removed by filtration. The filtrate on evaporation gave the crude amine, which was dissolved in anhydrous CH_2Cl_2 (5 mL). Triethylamine (57 mg, 0.56 mmol) was added, and the solution was cooled to 0 °C. Phenoxyacetyl chloride (96 mg, 0.56 mmol) was slowly added to a stirred solution. The mixture was allowed to stir with warming to room temperature over 1 h, after which time it was washed with 5% $NaHCO_3$ (3 mL) and brine (3 mL), dried (Na_2SO_4), and evaporated to yield the crude amide. Crystallization with methylene chloride–ether afforded **23** (108 mg, 71.8%) as a white solid, mp 191–193 °C. This sample was identical with that prepared from **21**: IR (neat) 3400–3300, 1755, 1680 cm^{-1}; NMR ($CDCl_3$) δ 4.40 (s, 2 H), 4.40 (m, 1 H), 5.30 (dd, 1 H, J = 5.0 and 9.0 Hz), 6.20 (dd, 1 H, J = 7.0 and 16.0 Hz), 6.55 (d, 1 H, J = 16.0 Hz), 6.80–7.25 (m, 11 H, N*H* of the β-lactam hidden), 8.20 (d, 1 H, J = 9.0 Hz, N*H* of the amide); CIMS, m/e 323 ($M^+ + 1$).

Method C. To a solution of **20** (560 mg, 1.19 mmol) in 40% aqueous acetonitrile (50 mL) was added $K_2S_2O_8$ (1.280 g, 4.70 mmol) and $Na_2HPO_4 \cdot 7H_2O$ (640 mg, 2.40 mmol). The mixture was refluxed with stirring for 1 h, cooled to room temperature, and evaporated to yield an aqueous residue. This residue was then extracted with methylene chloride (110 mL), and the organic solution was washed with 1 N HCl (50 mL) and brine (50 mL), dried ($NaSO_4$), and evaporated to yield a crude oil, which, when triturated with ether, afforded **23** (80 mg, 20.9%) as a white solid, mp 190–193 °C.

***cis*-1-[1-(Methoxycarbonyl)-2-hydroxyethyl]-3-azido-4-styrylazetidin-2-one (26).** DL-Serine methyl ester hydrochloride (15.56 g, 100 mmol), triethylamine (12.12 g, 120 mmol), and anhydrous tetrahydrofuran (35 mL) were stirred for 1 h at room temperature. The reaction mixture was then filtered, and the tetrahydrofuran filtrate was evaporated under reduced pressure to yield DL-serine methyl ester (11.45 g, 96.2%) as a viscous oil. This unpurified amino ester (11.45 g, 96.2 mmol) and *trans*-cinnamaldehyde (13.34 g, 101.0 mmol) were dissolved in anhydrous methylene chloride (40 mL). The solution was refluxed for 5 min and then stirred at room temperature for 1 h. The cloudy solution of the Schiff base **25** thus obtained was dried (K_2CO_3) and filtered, and the filtrate was diluted to a volume of 250 mL with anhydrous methylene chloride. Triethylamine (19.43 g, 192.4 mmol) was added to this solution, which was then cooled to 0 °C. Azidoacetyl chloride (22.99 g, 192.4 mmol) in anhydrous methylene chloride (170 mL) was added dropwise over a period of 1 h. The reactants were allowed to warm to room temperature overnight and then evaporated to dryness. The residue was triturated with ether (700 mL). The ether layer was filtered, the filtrate was washed with brine (350 mL), dried (Na_2SO_4), and evaporated to yield 33.20 g of a crude oil, which was chromatographed on 600 g of Davison silica gel (100–200 mesh) with an eluent of chloroform–ethyl acetate (10:1), yielding a mixture of diastereomers (1:1 ratio) of **26** (17.76 g, 56.2% from DL-serine methyl ester hydrochloride). A portion of the mixture was further chromatographed to separate the diastereomers as oily liquids. Both compounds exhibited almost identical infrared spectra: IR (neat) 3250–3050, 2110, 1745, 1725, 1410, 1260 cm^{-1}; NMR for faster-moving compound ($CDCl_3$) δ 3.72 (s, 3 H), 3.75 (m, 1 H), 4.02 (m, 2 H), 4.58 (dd, 1 H, J = 5.0 and 9.0 Hz), 4.95 (d, 1 H, J = 5.0 Hz), 5.75 (br s, 1 H), 6.12 (dd, 1 H, J = 9.0 and 16.0 Hz), 6.72 (d, 1 H, J = 16.0 Hz), 7.35 (m, 5 H); NMR for slower-moving compound ($CDCl_3$) δ 3.66 (s, 3 H), 3.90 (d, 2 H, J = 5.0 Hz), 4.26 (m, 2 H), 4.60 (dd, 1 H, J = 5.0 and 9.0 Hz), 4.87 (d, 1 H, J = 5.0 Hz), 6.22 (dd, 1 H, J = 9.0 and 16.0 Hz), 6.72 (d, 1 H, J = 16.0 Hz), 7.35 (m, 5 H).

When the same general conditions as described under the conversion of **13** to **22** were used, the serine-derived β-lactam **26** on oxidation with 3.6 equiv of Cr_2O_3 with an equivalent of **26** gave **22** as an oil in only 9% yield. The IR and NMR spectra of the two N-unsubstituted β-lactams derived from **13** and **26** were identical.

***cis*-1-[1-[[(*p*-Nitrobenzyl)oxy]carbonyl]-2-hydroxypropenyl]-3-phenoxyacetamido-4-styryl-2-azetidinone (28).** Amido β-lactam **21** was dissolved in 460 mL of dry acetone, and Jones reagent (2.67 mol of H_2CrO_4), 8.89 mL, was added dropwise with vigorous stirring. After 2 h, the reaction mixture was filtered through a coarse scintered glass funnel, the filtrate was concentrated, and the residual oil was taken up in ethyl acetate. This solution was washed with 3 × 250 mL of 5% $NaHCO_3$, dried (Na_2SO_4), and evaporated to yield the title compound **28** (4 g, 44% yield): mp 125–127 °C (ethyl acetate–petroleum ether); IR 1740, 1670, 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (s, 3 H), 4.25 (s, 2 H), 4.62 (dd, 1 H, J = 5.5 Hz, J' = 9.0 Hz), 5.32 (dd, 1 H, hidden), 5.35 (s, 2 H), 6.15 (dd, 1 H, J = 7.0 Hz, J' = 16.0 Hz), 6.50 (d, 1 H, J = 16.0 Hz), 6.75–7.45 (m, 11 H), 7.52 (d, 2 H, J = 8.0 Hz), 8.25 (d, 2 H, J = 8.0 Hz), NH hidden in 6.75–7.45, 13.00 (s, broad, 1 H); CIMS, m/e 558 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{27}N_3O_8$: C, 64.63; H, 4.88; N, 7.54. Found: C, 64.41; H, 5.07; N, 7.23.

***cis*-1-[1-[[(*p*-Nitrobenzyl)oxy]carbonyl]-2-mesylpropenyl]-3-phenoxyacetamido-4-styryl-2-azetidinone (29).** To a solution of 1.0 g (0.0018 mol) of **28** in 25 mL of dry dichloromethane was added 0.439 g (0.0036 mol) of *N*,*N*-dimethylaminopyridine (DMAP) in 10 mL of dichloromethane. A solution of 0.302 g (0.0027 mol) of mesyl chloride in 10 mL of dichloromethane was added at once, and the reaction mixture was stirred for 5 min. TLC of the reaction mixture after 5 min showed the disappearance of the starting material. The organic layer was washed with 3 × 20 mL of 3% HCl and once with brine and dried (Na_2SO_4). Evaporation of the solvent afforded an amorphous powder, which was redissolved in ethyl acetate–dichloromethane (1:1) and filtered through silica gel (10 g), and the filtrate was evaporated to obtain 0.85 g (74.5%) of **29**: IR (film) 3200, 2900, 1758, 1735, 1675, 1520 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (s, 3 H), 3.30 (s, 3 H), 4.40 (s, 2 H), 4.75 (dd, 1 H, J = 5.0 Hz), 5.25 (s, 2 H), 5.45 (dd, hidden), 6.20 (dd, 2 H, J = 7.0 Hz), 6.80 (d, 1 H, J = 9.0 Hz), 6.10–7.30 (m, 11 H), 7.50 (d, J = 8.0 Hz), 8.20 (d, 2 H, J = 8.0 Hz).

***cis*-3-(Phenoxyacetamido)-4-carboxy-2-azetidinone (30).** A solution of ruthenium tetroxide was prepared by adding 2.5 g of sodium periodate to a suspension of 15 mg of ruthenium dioxide in 50 mL of (1:1) acetone–water. This solution was added to 500 mg of **29** dissolved in 10 mL of acetone. The reaction mixture was stirred for 1 h at room temperature and filtered, and the filtrate was then stripped of solvent under reduced pressure. The residue was extracted with ethyl acetate, and this organic solution was washed with 30 mL of 5% $NaHCO_3$. The aqueous layer was separated and then acidified with 1 N HCl and extracted with ethyl acetate. The organic phase was separated and evaporated, and the residual solid was triturated with ether and filtered when the acid **30** was obtained as a colorless solid. This acid was used as such for the synthesis of **31**: NMR ($CDCl_3$–Me_2SO-d_6) δ 4.35 (d, 1 H, J = 5.0 Hz), 4.50 (s, 2 H), 5.50 (dd, 1 H, J = 5.0 and 9.0 Hz), 6.70–7.60 (m, 6 H), 7.80 (d, 1 H, J = 9.0 Hz), 8.20 (s, 1 H); CIMS, m/e 245 ($M^+ - H_2O$).

***cis*-3-(Phenoxyacetamido)-4-(methoxycarbonyl)-2-azetidinone (31). Method A.** Amido β-lactams **23** (65 mg, 0.0002 mol) was placed in 5 mL of 60% aqueous acetone to which was added 6 drops of 1,4-dioxane to facilitate complete dissolution of the starting material. To this was then added 64 mg (0.0004 mol) of $KMnO_4$. After the reaction mixture was stirred at room temperature for 2 h, it was filtered and evaporated to an aqueous residue, which was then acidified with 1 N HCl (20 mL). The aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated to yield 55 mg of a crude acid. This crude product was then dissolved in anhydrous dichloromethane (5 mL) to which was then added 0.30 mL of an ethereal solution of diazomethane. The solution was stirred at room temperature for 15 min, after which time it was evaporated to dryness. Chromatography of the residual oil on the thin-layer plates afforded the pure ester **31** (15 mg, 26.7%) as a white solid, crystallized from a dichloromethane–ether: mp 138–139 °C (lit.[15] mp 140–141 °C); IR (neat) 3250–3200, 1770, 1740, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.60 (s, 3 H), 4.45 (m, 1 H), 4.48 (s, 2 H), 5.23 (dd, 1 H, J = 5.0 and 10.0 Hz), 6.80–7.40 (m, 7 H).

Method B. To a suspension of 30 mg of the β-lactam acid **30** was added an excess of diazomethane in ether solution. After stirring at room temperature for some time, the reaction mixture

was filtered, and the filtrate was evaporated to an oil, which was purified by thin-layer chromatography (silica gel, 150 g, eluent: ethyl acetate). The material (**31**) was obtained (7 mg) was crystallized from methylene chloride–ether: mp 139–140 °C (lit.[15] mp 140–141 °C); CIMS, m/e 278 ($M^+ + 1$).

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Registry No. **5**, 632-20-2; **6**, 79006-99-8; **7**, 82679-67-2; **8**, 82679-57-0; **9**, 79006-98-7; **13a**, 82730-04-9; **13b**, 82730-05-0; **14a**, 82679-56-9; **14b**, 82730-06-1; **15a**, 82679-60-5; **15b**, 82730-07-2; **17**, 82730-08-3; **18**, 82679-62-7; **19**, 82679-61-6; **20**, 82730-10-7; **21** (isomer 1), 82730-13-0; **21** (isomer 2), 82730-14-1; **21** (amino derivative isomer 1), 82730-11-8; **21** (amino derivative isomer 2), 82730-12-9; **22**, 78905-28-9; **23**, 80024-26-6; **23** amino derivative, 82730-15-2; **24**, 2104-89-4; **24**·HCl, 5619-04-5; **25**, 82679-63-8; **26** (isomer 1), 82679-64-9; **26** (isomer 2), 82730-16-3; **28**, 82730-17-4; **29**, 82730-18-5; **30**, 82679-65-0; **31**, 82679-66-1; **32**, 82730-09-4; methyl acetoacetate, 105-45-3; *p*-nitrobenzyl bromide, 100-11-8; *p*-nitrobenzyl-D-threonine, 78963-69-6; *trans*-cinnamaldehyde, 14371-10-9; azidoacetyl chloride, 30426-58-5; D-threonine methyl ester, 82679-55-8; benzyl D-threonine-*p*-toluenesulfonate, 82679-59-2; D-threonine benzyl ester, 82679-58-1; phenoxyacetyl chloride, 701-99-5.

Synthesis of Optically Active Spirohydantoins by Asymmetric Induction. Hydantoin Formation from Amino Nitriles and Chlorosulfonyl Isocyanate

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Conversion of 6-chloro- or 6-fluoro-2,3-dihydro-4*H*-1-benzopyran-4-one with optically active (*S*)-α-methylbenzylamine in the presence of $TiCl_4$ to the ketimine followed by treatment in EtOH with HCN gas gives excellent yields of crystalline, enantiomerically pure (4*S*)-4-cyano-2,3-dihydro-6-chloro(or 6-fluoro)-4-[(*S*)-(1-phenylethyl)amino]-4*H*-1-benzopyran. These sterically hindered amino nitriles react smoothly with chlorosulfonyl isocyanate to give, after hydrolysis, the hydantoins (4*S*)-2,3-dihydro-6-chloro(or 6-fluoro)-3′-[(*S*)-1-phenylethyl]spiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione. The α-methylbenzyl groups can be removed by aqueous HBr/acetic acid to give the unprotected spirohydantoins.

Compounds that inhibit the enzyme aldose reductase are of potential value in the therapy of chronic complications of diabetes mellitus because they inhibit the conversion of glucose to sorbitol. Formation of sorbitol, for instance in lens and nerve, is believed to contribute to certain late-stage complications (e.g., cataracts and neuropathy) in diabetics. We have previously reported on potent in vitro and in vivo aldose reductase inhibitory activity is spirohydantoins derived from 1-tetralones, 1-indanones, 4-thiochromanones, and 4-chromanones.[1] In the chroman series the biological activity was found to reside predominantly in the *S* enantiomers, and one of these compounds, (4*S*)-2,3-dihydro-6-fluorospiro[4*H*-1-benzopyran-4,4′-imidazolidine]-2′,5′-dione (**17a**; CP-45,634; USAN, sorbinil), is currently undergoing clinical evaluation.[1,2] Although this compound has been obtained by resolution of its racemic form with brucine,[3] certain congeners could not be obtained by standard resolution techniques. This prompted us to examine alternative synthetic approaches to these spirohydantoins involving asymmetric induction, and the results of these studies are reported here.

Our initial strategy envisioned as the first step the addition of HCN to an imine prepared from an optically active benzylamine derivative; this was to be followed by hydrolysis and debenzylation of the amino nitrile to the amino acid, in analogy to published asymmetric induction syntheses,[4,5] and conversion to the hydantoin, as shown in Scheme I.

Indeed, treatment of 2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-one[3] (**1**) with (*R*)-(+)-α-methylbenzylamine in the presence of $TiCl_4$[6] gave the imine **2** (attempts to form **2** by using molecular sieves or toluenesulfonic acid in place of $TiCl_4$ were unsatisfactory and led to substantial dimerization of the ketone). Treatment of a solution of **2** in EtOH with HCN precipitated the crystalline and diastereomerically pure 4*R* amino nitrile **3** in very good yield. However, attempted hydrolysis of **3** under acidic conditions[4,5] gave ketone **1** instead of the expected **4**, presumably via a stabilized benzylic carbonium ion intermediate at C-4. Initial attempts to convert **3** into a hydantoin or a potential hydantoin precursor were also unsuccessful: treatment of **3** with $(NH_4)_2CO_3$ in aqueous EtOH[7] at 65 °C caused partial conversion to ketone **1**, as did treatment of **3** with KNCO in glacial AcOH[8] or with NaNCO in trifluoroacetic acid.[9] Similar results were obtained in acylation experiments with **3** and CS_2,[10] phosgene, or methyl or ethyl chloroformate.[11] No reaction occurred between **3** and CO_2[7] or methyl isocyanate. Presumably, steric hindrance around the benzylic amine nitrogen is too severe in all of these cases.

This problem was solved by the use of highly reactive chlorosulfonyl isocyanate,[12] which reacted cleanly with **3** in CH_2Cl_2 to give, after treatment with water, the iminohydantoin **11**. Hydrolysis of **11** with aqueous acid resulted in the hydantoin **12** (Scheme II). Attempts to remove the α-methylbenzyl group from **12** by hydrogenation failed under a variety of conditions, a finding con-

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