

standard based HPLC. HPLC Conditions: Column and Water Associates μ Bondapak C₁₈ 10 μ m, 3.9 mm ID \times 30 cm; mobile phase, 650 mL of CH₃OH (HPLC grade), 350 mL of H₂O (HPLC grade), 1.2 g of Na₂H₂PO₄ (reagent grade); flow rate, 2.0 mL/min.

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Studies on Lactams. 81. Enantiospecific Synthesis and Absolute Configuration of Substituted β -Lactams from D-Glyceraldehyde Acetonide^{†,1}

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Optically active 3,4-disubstituted 2-azetidinones have been prepared in good yield by the annelation of Schiff bases from D-glyceraldehyde acetonide with acid chlorides (or equivalent) and triethylamine. The utility of this enantiospecific synthesis was extended by the stereocontrolled modification of functional groups leading to optically active trans β -lactams. The absolute configuration of some key compounds was determined by chemical degradation. Modification of substituents on the β -lactam ring led to optically active intermediates for a variety of natural products, such as alkaloids, carbohydrates, and amino acids.

Stereocontrolled synthesis of β -lactams continues to be an area of intense activity.² The periodic discovery of new β -lactam antibiotics in nature sustains the interest of synthetic and medicinal chemists.³ The potential of substituted 2-azetidinones for serving as efficient synthons for a variety of natural products has provided added interest.⁴

In the early stages of our studies⁵ on β -lactams, we achieved a completely diastereoselective synthesis of a 6-epipenicillin V methyl ester (**4**) by using a chiral thiazoline (**2**) and an achiral acid chloride (**1**) as the reactants (Scheme I). The stereochemistry at the ring junction carbon (C-5) in **3** is determined by the configuration of the carboxyl group bearing carbon (C-3) since the carboxyl group is sterically less hindered in the exo position. The trans configuration of the β -lactam (resulting in the 6-epi configuration) appears to depend on the directive influence of the sulfur next to the ring junction. For reasons not clear, the presence of sulfur at either C-3 or C-4 induces trans stereochemistry in a 3,4-disubstituted 2-azetidinone.

Annelation of an acyclic imino compound led to β -lactam formation but with reduced diastereoselectivity. Thus, when an acyclic thioimidate, such as **5**⁶ or **8**,⁷ was used as the imino component, two isomeric β -lactams (**6** and **7** or **9** and **10**) were formed but both were trans β -lactams (Scheme II).

In the absence of a thio group in the acyclic imino component, again two β -lactams were formed, but both had the cis geometry (Scheme III). The diastereoselectivity varied depending on the nature of substituents on the amino compound from which the Schiff base was prepared. For instance, we⁸ observed the formation of two cis β -lactams (**12a** and **13a**) in nearly 50:50 proportion by the reaction of an acid chloride (**1**) and triethylamine with a Schiff base (**11a**) from cinnamaldehyde and a D-threonine ester (Scheme III). Tenneson and Belleau⁹ used a *tert*-butyldimethylsilyl ether of a D-threonine ester, e.g., **11b**,

and achieved high diastereoselectivity (e.g., **12b** and **13b** were formed in 90:10 proportion) (Scheme III). This imino compound has two centers of asymmetry. The bulk of the substituents at the chiral center which is not adjacent to the imino group strongly affects the diastereoselectivity for β -lactam formation. When we^{10,31} used the very bulky

(1) Studies on Lactams. 81. For Part 80, see: Wagle, D. R.; Garai, C.; Monteleone, M.; Bose, A. K. *Tetrahedron Lett.* 1988, 29, 1649.

(2) Labia, R.; Morin, C. *J. Antibiot.* 1984, 37, 1103.

(3) See, for example: Chevolut, L.; Chevolut, A. M.; Gajhede, M.; Larsen, C.; Anthoni, U.; Christophersen, C. *J. Am. Chem. Soc.* 1985, 107, 4542.

(4) (a) Manhas, M. S.; van der Veen, J. M.; Wagle, D. R.; Hegde, V. R.; Bari, S. S.; Kosarych, Z.; Ghosh, M.; Krishnan, L. *Indian J. Chem., Sect. B* 1986, 25B, 1095. (b) Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* 1984, 49, 2236. (c) Wasserman, H. H.; Pearce, B. C. *Tetrahedron Lett.* 1985, 26, 2237 and references cited therein. (d) Crombie, L.; Jones, R. C. F.; Mat-Zin, A. R.; Osborne, S. *J. Chem. Soc., Chem. Commun.* 1983, 960. (e) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* 1986, 27, 5147. (f) Fliri, A.; Hohenlohe-Oehringen, D. *Chem. Ber.* 1980, 113, 607. (g) Fukuyama, T.; Frank, R. K.; Jewell, C. F. *J. Am. Chem. Soc.* 1980, 102, 2122. (h) Thomas, E. J.; Williams, A. C. *J. Chem. Soc., Chem. Commun.* 1987, 992. (i) Baldwin, J. E.; Adlington, R. M.; Birch, D. J. *J. Chem. Soc., Chem. Commun.* 1985, 256. (j) Ojima, I. *Asymmetric Reactions and Progress in Chemistry*; ACS Symposium Series; American Chemical Society: Washington, DC, 1982; No. 185, p 109. (k) Duhamel, P.; Goument, B.; Plaquevent, J. C. *Tetrahedron Lett.* 1987, 28, 2595. (l) Kano, S.; Ebata, J.; Shibuya, S. *Heterocycles* 1980, 14, 43.

(5) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *J. Am. Chem. Soc.* 1968, 90, 4506.

(6) Bachi, M. D.; Goldberg, O. *J. Chem. Soc., Perkin Trans. 1* 1972, 2332. See also: Bachi, M. D.; Breiman, R. *J. Chem. Soc., Perkin Trans. 1* 1980, 11.

(7) Kamiya, T. In *Recent Advances in the Chemistry of β -Lactam Antibiotics*; Elks, J., Ed.; spec. publ. no. 28, The Royal Society of Chemistry, June 1976, p 281.

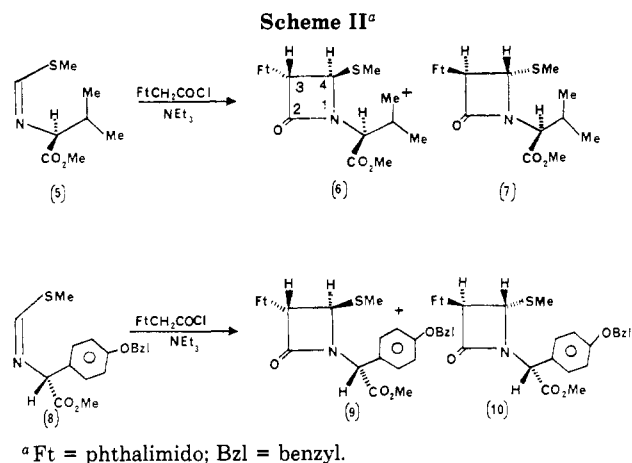
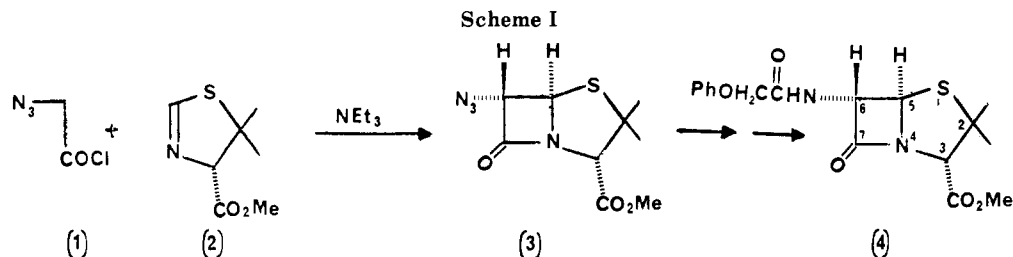
(8) (a) Bose, A. K.; Anjaneyulu, B.; Bhattacharya, S. K.; Manhas, M. S. *Tetrahedron* 1967, 23, 4769. (b) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Amin, S. G.; Fernandez, I. F.; Gala, K.; Gruska, R.; Kapur, J. C.; Khajavi, M. S.; Kreder, J.; Mukkavilli, L.; Ram, B.; Sugiura, M.; Vincent, J. E. *Tetrahedron* 1981, 37, 2321. (c) Vincent, J. E. Ph.D. Thesis, Stevens Institute of Technology, 1979.

(9) Tenneson, S. M.; Belleau, B. *Can. J. Chem.* 1980, 58, 1605.

(10) Hegde, V. R. Ph.D. Thesis, Stevens Institute of Technology, 1984.

(11) Hubschwerlen, C.; Schmidt, G. *Helv. Chim. Acta* 1983, 66, 2206. See also: Hubschwerlen, C.; Schmidt, G. European Patent 0073061, 1983.

[†] Dedicated to the memory of Professor James M. van der Veen.



triphenylsilyl ether of a D-threonine ester (e.g., **11c**), the annelation was almost stereospecific and the β -lactams **12c**

(12) Presented in part at the following: (a) 18th Middle Atlantic Regional Meeting of the American Chemical Society, Newark, NJ, April 1984; paper ORGN 238. (b) 188th National Meeting of the American Chemical Society, Philadelphia, PA, Aug 1984; paper ORGN 116. (c) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R.; Hegde, V. R. In *Third International Symposium on Recent Advances in the Chemistry of β -Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; spec. publ. no. 52, The Royal Society of Chemistry, July 1984, p 387. (d) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R.; Hegde, V. R.; Krishnan, L. *Tetrahedron Lett.* **1985**, *26*, 33. (e) Bose, A. K.; Hegde, V. R.; Wagle, D. R.; Bari, S. S.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1986**, 161.

(13) Presented in part at the following: (a) 19th Middle Atlantic Regional Meeting of the American Chemical Society, West Long Branch, NJ, May 1985; paper ORGN 192. (b) 15th IUPAC International Symposium on the Chemistry of Natural Products, The Hague, The Netherlands, August 1986. (c) 193rd National Meeting of the American Chemical Society, Denver, CO, April 1987; paper ORGN 215.

(14) Fuganti, C.; Garaselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, *22*, 4017.

(15) Baer, R.; Fischer, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463.

(16) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

(17) (a) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.

(b) Takano, S.; Numata, H.; Ogasawara, K. *Heterocycles* **1982**, *19*, 327.

(c) Hubschwerlen, C. *Synthesis* **1986**, 962.

(18) Kronenthal, K.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.

(19) The formation of β -lactam by the cycloaddition of a Schiff base with azidoacetyl chloride or its equivalent to form 3-azido-2-azetidione has been referred to as the Bose reaction by Sammes. *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Wiley: New York, 1980; Vols. 3 and 4. For a recent review on this reaction, see: Manhas, M. S.; van der Veen, J. M.; Wagle, D. R.; Hegde, V. R.; Bari, S. S.; Kosarych, Z.; Ghosh, M.; Krishnan, L. *Indian J. Chem., Sect. B* **1986**, *25B*, 1095.

(20) Manhas, M. S.; Bose, A. K.; Khajavi, M. S. *Synthesis* **1981**, 209.

(21) (a) Arrieta, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 3365 and references cited therein. (b) Chiang, Y. H. Ph.D. Thesis, Stevens, Institute of Technology, 1989.

(22) (a) Nefkens, G. H. L. *Nature (London)* **1960**, *185*, 309. (b) Nefkens, G. H. L.; Tesser, G. I.; Nivard, R. *J. F. Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 688; *Chem. Abstr.* **1961**, *55*, 1461h.

(23) Sahu, D. P.; Manhas, M. S.; Bose, A. K., unpublished results.

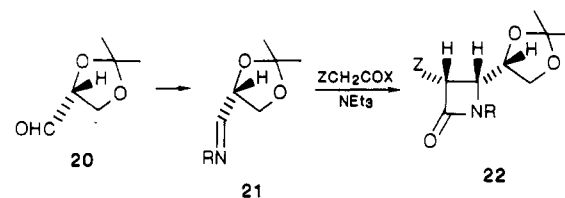
(24) Bose, A. K.; Narayanan, C. S.; Manhas, M. S. *J. Chem. Soc., Chem. Commun.* **1970**, 975.

(25) Kukulja, S.; Lammert, S. R. *J. Am. Chem. Soc.* **1975**, *97*, 5582.

(26) Kemp, J. E. G. In *Second International Symposium on Recent Advances in the Chemistry of β -Lactam Antibiotics*; Gregory, G. I., Ed.; spec. publ. no. 38, The Royal Society of Chemistry, July 1980, p 320.

(27) Kuhlein, K.; Jensen, H. *Justus Liebig's Ann. Chem.* **1974**, 369.

Table I. Enantiospecific Synthesis of Cis-3,4-Disubstituted 2-Azetidinones **22**



serial no.	cis β -lactam 22	Z	R	mp, °C	yield, %
1	a	N ₃	<i>p</i> -anisyl	119–120	55
2	b	Ft ^a	<i>p</i> -anisyl	171	57
3	c	N ₃	CH ₂ COOMe	oil	55
4	d	OMe	<i>p</i> -anisyl	93–94	54
5	e	OMe	CH ₂ COOMe	oil	57
6	f	OAc	<i>p</i> -anisyl	163	70
7	g	OCH ₂ Ph	<i>p</i> -anisyl	120	69
8	h	OPh	<i>p</i> -anisyl	145–146	67
9	i	OMe	benzyl	70–71	55
10	j	OCH ₂ CH=CH ₂	<i>p</i> -anisyl	72	44

^aFt = phthalimido.

and **13c** were formed in the ratio of 95:5 (Scheme III).

Complete diastereoselectivity in β -lactam formation was achieved independently by two laboratories^{11,12} by annealing a Schiff base (**15** or **18**) from optically active aldehydes (**14** or **17**) and an achiral amine (Scheme IV).

Roche scientists¹¹ used acid chlorides (or equivalent) leading to 3-amino-2-azetidiones (**16**). We have conducted more extensive studies directed to the synthesis of a wide variety of 3,4-disubstituted 2-azetidiones (**19** and **22**). Initially we¹² used an optically active threonine derived from D-threonine as the chiral aldehyde component. More recently, we¹³ have utilized a number of other aldehydes including several derived from naturally occurring sugars.

We report here the details of our work on the synthesis of optically active β -lactams (e.g., **22**) using D-glyceraldehyde acetonide (**20**) as the chiral aldehyde for the preparation of Schiff bases (**21**). Also described is the determination of the absolute configuration of some key β -lactams and the steric aspects of the modification of the ring substituents. Some of this work has been published earlier as preliminary communications.¹²

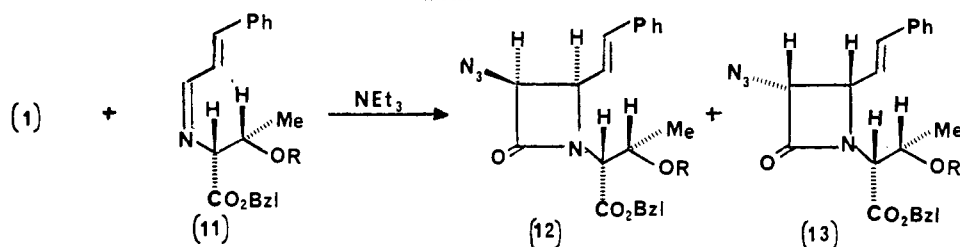
Optically Active Cis β -Lactams. Glyceric acid in either enantiomeric form is available by the diazotization

(28) Latrell, R.; Lohaus, G. *Justus Liebig's Ann. Chem.* **1974**, 901.

(29) The scientists at Hoffman-La-Roche, Basel, Switzerland, prepared the optically active α -amido β -lactams of the type **16** by starting from L-glyceraldehyde acetonide (**14**). They determined the absolute configuration of their β -lactams by single-crystal X-ray crystallography; see ref 11.

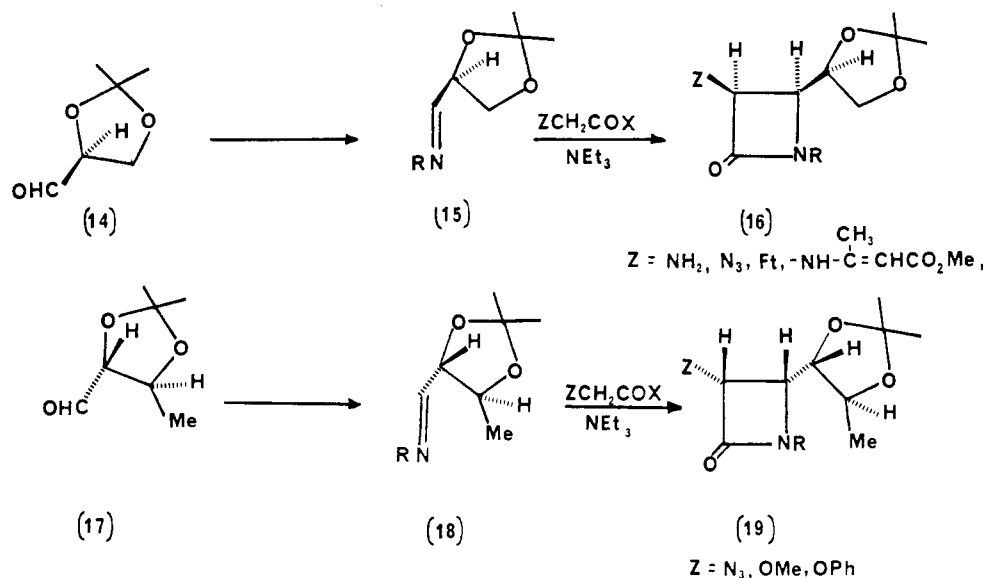
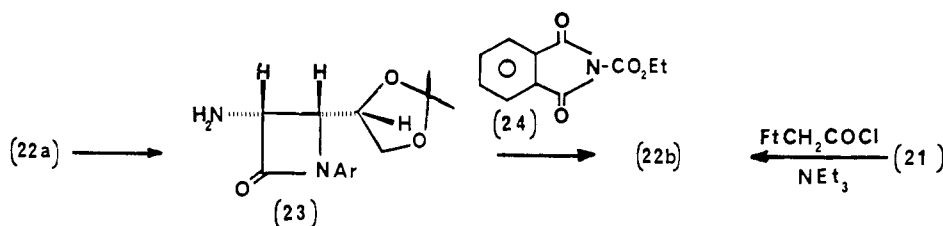
(30) Lee, D. G.; van der Engh, M. In *Oxidation in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic: New York, 1973; Part B, Chapter 4.

(31) Presented in part at the 189th National Meeting of the American Chemical Society, Miami Beach, FL, April 1985; paper MEDI 089. See also ref 10.

Scheme III^a

^a a, R = H; b, R = TBDMS = *tert*-butyldimethylsilyl; c, R = TPS = triphenylsilyl; Bzl = benzyl.

Scheme IV

Scheme V^a

^a Ar = *p*-anisyl.

of optically active serine.¹⁴ Methods are known for the conversion of glyceric acid to glyceraldehyde acetonide.¹⁴ It is more convenient, however, to prepare D-glyceraldehyde acetonide from D-mannitol^{15,16} and the L enantiomer from L-ascorbic acid.¹⁷

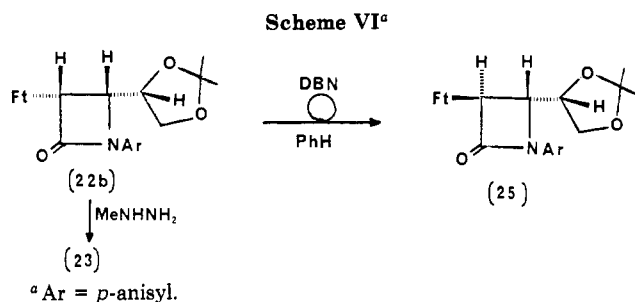
Both aliphatic and aryl amines can be used for preparing Schiff bases from D-glyceraldehyde acetonide. The Schiff base (21, R = *p*-anisyl) was preferred for our work because the *N*-(*p*-anisyl) group can be removed under mild conditions by oxidation of 1-(*p*-anisyl)-2-azetidinones with cerium(IV) ammonium nitrate (CAN).¹⁸

Optically active β -lactams **22** which are intermediates for 3-amino-2-azetidinones are obtained by the reaction of **21** with azidoacetyl chloride¹⁹ (or equivalent)²⁰ or phthalimidoacetyl chloride (or a carboxyl activated form of an enamino acetic acid)^{11,12} and triethylamine (Table I).

It is worth noting that the α -phthalimido β -lactam **22b** is obtained exclusively in the *cis* form although phthalimidoacetyl chloride is known to produce a *trans* β -lactam from benzylideneaniline.²¹ Reduction of the α -azido β -lactam **22a** with hydrogen sulfide gave an α -amino β -lac-

tam **23**, which upon reaction with Nefkens reagent (**24**)²² led to the same *cis* α -phthalimido β -lactam (**22b**) as was obtained by direct synthesis (Scheme V).

We had been interested in 3-hydroxy-2-azetidinones as intermediates for other β -lactam and non- β -lactam natural products. We found it possible to prepare optically active α -hydroxy β -lactams by a process similar to that we have used for preparing α -amino β -lactams. Thus, condensation of the chiral Schiff base **21** with methoxy- and phenoxyacetyl chloride led to single isomers of *cis* β -lactams. However, these were not suitable for conversion to α -hydroxy β -lactams. Several other derivatives of *cis* α -hydroxy β -lactams were obtained by the annelation of **21** with the appropriate acid derivatives. Again, a single, *cis* β -lactam was formed in each case in good yield (e.g., **22e-g**, Table I). We prepared a *cis* α -allyloxy β -lactam (**22j**)²³ again as a single isomer. This β -lactam was converted to an α -hydroxy β -lactam by treatment with 10% Pd/C and *p*-toluenesulfonic acid. Under these conditions, the double bond of the allyl group undergoes rearrangement to produce a vinyl ether, which is easily cleaved to an α -hydroxy β -lactam. The benzyloxy β -lactam **22g** can be hydroge-



nolyzed to the α -hydroxy β -lactam **26** but only under 50 psi of pressure. A more convenient access is provided by the acetoxy β -lactam **22f** prepared in 70% yield from **21**. It was possible to hydrolyze the acetoxy group without cleavage of the β -lactam ring by using very mild basic conditions to form β -lactam **26**. The α -hydroxy β -lactam in turn could be converted into *cis* mesyloxy β -lactam **27**, which proved useful for preparing several *trans* β -lactams (Scheme VII).

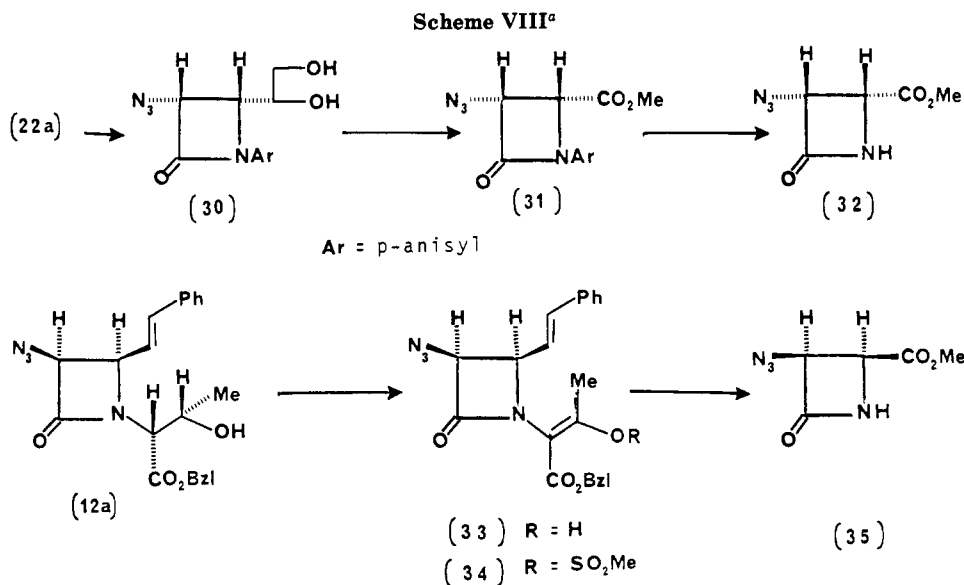
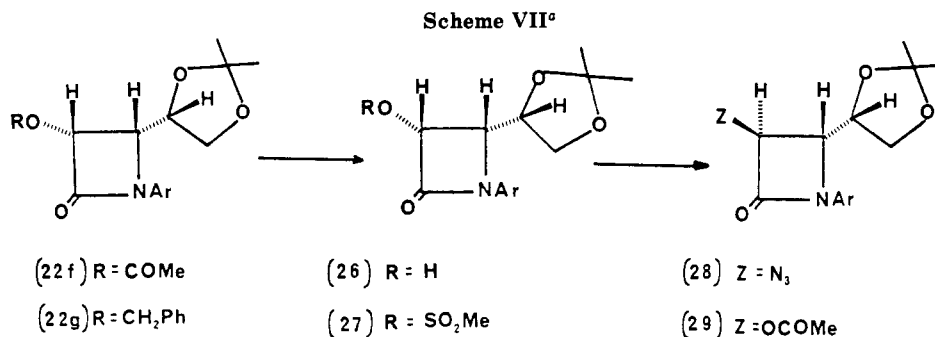
Optically Active Trans β -Lactams. Convenient methods have been developed for the conversion of *cis* β -lactams to *trans* β -lactams without loss of optical purity. Depending on the nature of the substituents at C-3 and C-4, different approaches have to be used as illustrated below.

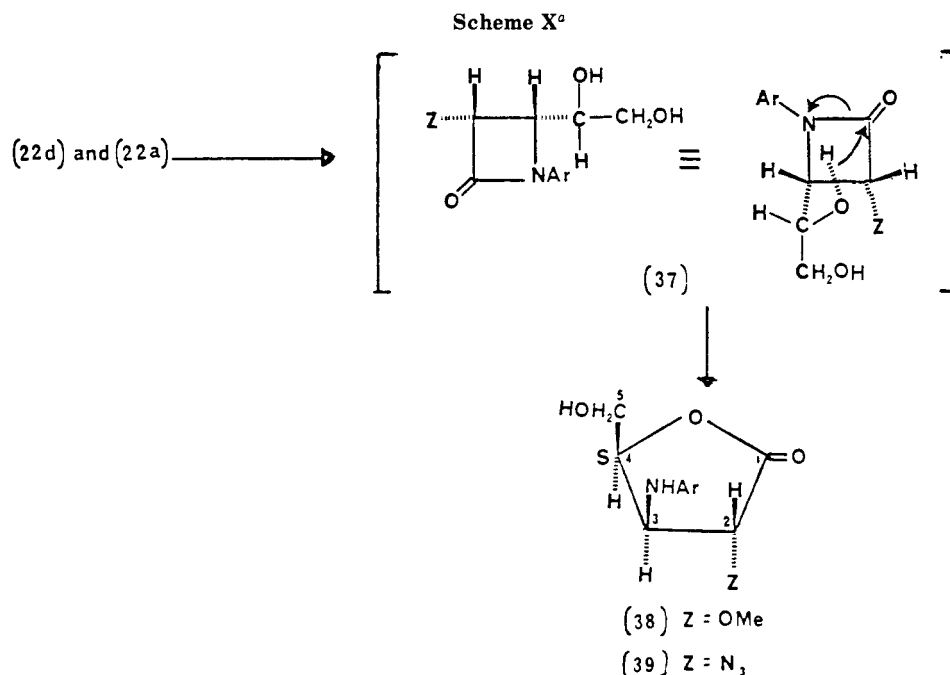
1. Trans β -Lactams via Epimerization at C-3. Taking advantage of a method²⁴ developed in our laboratory some years ago, we heated the *cis* α -phthalimido β -lactam **22b**—prepared directly or derived from **22a**—under

reflux with 1,3-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene solution. Epimerization at C-3 was essentially complete under these conditions, and the *trans* phthalimido β -lactam **25** could be isolated in high yield (Scheme VI). Methods are available for converting the phthalimido group to an amino group without scission of the β -lactam ring^{11,25} (e.g., **23**, Scheme VI).

2. Trans β -Lactams via Inversion at C-3. The halogen in 6-halopenams is not easily replaced via S_N2 reactions. Recently, Kemp et al.²⁶ used the very reactive triflate ester group at 6α - and 6β -positions for replacement by halogen with inversion at C-6 in several penicillin derivatives. Kuhlein and Jensen²⁷ have prepared a few *cis* α -azido β -lactams—both monocyclic and bicyclic—by S_N2 replacement of a halogen group by an azido group. Latrell and Lohaus²⁸ synthesized *cis*-3-azido-2-azetidiones by an S_N2 reaction of *trans*-3-[(substituted-sulfonyl)oxy]-2-azetidiones with sodium azide.

We have observed that monocyclic *cis* β -lactams of type **26** can be converted in good yield and without loss of optical purity to *trans* α -azido β -lactams **28**. Thus, *cis*-3-acetoxy-2-azetidione **22f** was converted to 3-hydroxy-2-azetidione **26** by treatment with methanolic sodium hydroxide at 0 °C and then to 3-(mesyloxy)-2-azetidione **27** under conditions that should not affect the absolute configuration at C-3. The mesyloxy group was then replaced by an azido group to obtain *trans* α -azido β -lactam **28** by reaction with lithium azide. The *cis* 3-benzyloxy β -lactam **22g** was hydrogenated in the presence of catalytic amounts of 10% Pd/C at 50 psi at room temperature to give **26** in quantitative yield; mesylation to **27** followed by treatment





^a Ar = *p*-anisyl.

rule,³³ it was concluded that the α -methoxy β -lactam **22d** had the $3R,4S$ configuration. The J values in the NMR spectrum of **39** were very similar to those of **38**.

It may be noted that the NMR method led to the same absolute configuration for **39** as for **22a** that was derived by the chemical correlation method. The assignment of the absolute configuration for **22d** by the NMR method may therefore be considered reliable.

Appropriately substituted β -lactams can undergo rearrangement to various heterocycles³⁶ (for example, see Scheme X for the preparation of a sugar lactone). Several laboratories including ours have transformed β -lactams to sugars, alkaloids, amino acids, etc.³⁷

Conclusions. Comparison of the absolute configurations of **22a**, **22b**, and **19** show that the secondary hydroxyl group as a chiral center in the threose-derived Schiff base **18** did not affect the steric course of β -lactam formation. Apparently, the chiral center proximate to the C=N group alone controls the diastereoselectivity of the annelation reaction. It may be noted that the nature of the achiral substituent on the Schiff base nitrogen or the nitrogen function (azido, phthalimido, or enamino) at C-3 of the 2-azetidinone did not influence the steric course of ring formation.

Interestingly, the steric course of β -lactam formation is the same for oxygen functions at C-3 as for nitrogen functions at the same carbon.

It has been noted in an earlier section that when a D-threonine derivative is used as the amino component of the Schiff base **11** (Scheme III), the absolute configuration at C-3 and C-4 of the major product is as shown in **12**. When an aldehyde derived from D-threonine or D-serine is used for preparing the Schiff bases **18** and **21**, the absolute configuration of the β -lactam formed (**19** and **22**) is opposite to that for **12**. Thus, the same optically active α -amino acid can provide the two opposite enantiomers of a cis β -lactam depending on whether it is used for preparing the aldehyde or the amino component of the Schiff base required for annelation.

Recently a few syntheses of optically active β -lactams have been reported.³⁸ Compared to them, the method described here appears to be more versatile and more convenient. It is remarkable that this particular β -lactam formation reaction proceeds with complete diastereoselectivity and leads to cis stereochemistry in every case.

The optically active β -lactams described here have multiple functional groups which can be manipulated to generate other functional groups of interest or to alter the configuration. Thus a wide variety of optically active β -lactams are conveniently and readily available. Synthesis of diverse natural products in either enantiomeric form by transformations and/or molecular rearrangements of β -lactams will be described in future publications.

Experimental Section

Melting points were taken for samples in open capillary tubes (Mel-Temp apparatus) and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1310 IR spectrophotometer. NMR spectra were recorded on a Varian EM-390 spectrometer or Bruker WP200 SY spectrometer in appropriate NMR solvents with SiMe₄ as internal standard. Mass spectra [chemical-ionization mass spectra (CIMS) and fast-atom bombardment (FAB)] were recorded on a CIMS Biospect Instrument and a Finnigan MAT 312 spectrometer. Optical rotations were measured on an Autopol III automatic polarimeter. CD spectra were obtained on a JASCO J-SOOA CD spectrophotometer with a DP-SOON data processor. Elemental analyses were determined by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY.

General Procedure for the Synthesis of Schiff Bases **21**.

To a stirred solution of the amine (10 mmol) in ether (20 mL) at 0 °C was added a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (**20**)¹⁵ (10 mmol) in ether (20 mL). After 1–3 h, the reaction mixture was dried over anhydrous magnesium sulfate, filtered, and evaporated to give the crude Schiff base **21**, which was used as such in the next step.

General Procedure for the Synthesis of β -Lactams **22a–j**. Method A. Mixed Anhydride Method Using Cyanuric Chloride.

To a solution of the potassium salt of the acid (20 mmol), triethylamine (40 mmol), and Schiff base **21** (10 mmol) in dry methylene chloride (100 mL) at –20 °C under a nitrogen

(36) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* 1976, 5, 669.

(37) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles*, in press.

(38) For example, see: (a) Kaneko, T.; Okamoto, Y.; Hatada, K. *J. Chem. Soc., Chem. Commun.* 1987, 1511. (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* 1986, 27, 3119.

atmosphere was added with stirring a solution of cyanuric chloride (15 mmol) in dry methylene chloride (100 mL) during 30 min. The reaction mixture was stirred overnight at room temperature, washed with saturated sodium bicarbonate solution and brine, and dried (Na_2SO_4). Evaporation of the solvent gave the crude β -lactam. Further purification of the β -lactam was done by column chromatography (silica gel, 230–400 mesh; appropriate mixture of hexane/ethyl acetate) and recrystallization.

Method B. Acid Chloride–Imine Method. A solution of the acid chloride (15 mmol) in dry methylene chloride (50 mL) was added dropwise to a stirred solution containing the Schiff base **21** (13 mmol) and triethylamine (30 mmol) in dry methylene chloride (100 mL) under a nitrogen atmosphere at -20°C . The resulting reaction mixture was stirred overnight at room temperature and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give the crude β -lactam, which was further purified by silica gel (230–400 mesh) column chromatography, using an appropriate mixture of hexane/ethyl acetate as eluent, and recrystallization.

(3R,4R)-cis-1-(p-Anisyl)-3-azido-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22a): prepared from **21** (R = *p*-anisyl) and potassium azidoacetate in 55% yield by method A; mp 119–120 $^\circ\text{C}$; $[\alpha]_D^{26} +224.5^\circ$ (c 0.5, MeOH); IR (KBr) 2140, 1750 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.64–6.8 (dd, AB pattern, 4 H), 4.82 (d, $J = 6$ Hz, 1 H), 4.34–4.20 (m, 4 H), 3.8 (s, 3 H), 1.52 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 161.25, 156.98, 130.73, 119.97, 114.14, 110.34, 76.79, 66.83, 64.02, 60.79, 55.50, 26.65, 24.86 ppm; CIMS (NH_3 reagent gas), m/e 319 ($M + 1$)⁺. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_4$: C, 56.60; H, 5.66; N, 17.61. Found: C, 56.75; H, 5.72; N, 17.63.

(3R,4R)-cis-1-(p-Anisyl)-3-phthalimido-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22b): prepared from **21** (R = *p*-anisyl) and phthalimidoacetyl chloride³⁹ in 57% yield by method B; mp 174 $^\circ\text{C}$; $[\alpha]_D^{26} -30.4^\circ$ (c 0.53, MeOH); IR (KBr) 1750, 1710 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 8.0–6.8 (aromatic protons, 8 H), 5.5 (d, $J = 6$ Hz, 1 H), 4.6–4.3 (m, 2 H), 3.8 (s, 3 H), 3.8–3.35 (m, 2 H), 1.5 (s, 3 H), 1.29 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 167.01, 160.70, 156.64, 134.88, 131.28, 131.21, 124.02, 119.75, 114.04, 110.09, 75.89, 65.91, 62.81, 55.45, 54.43, 26.56, 25.05 ppm; EIMS, m/e 422 (M)⁺. Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_6$: C, 65.4; H, 5.21; N, 6.63. Found: C, 65.3; H, 5.28; N, 6.54.

(3R,4R)-cis-1-(Carbomethoxymethyl)-3-azido-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22c): prepared in 55% yield from **21** (R = $\text{CH}_2\text{CO}_2\text{Me}$) and potassium azidoacetate by method A; oil; $[\alpha]_D^{26} +93.4^\circ$ (c 0.5, MeOH); IR (neat) 2105, 1765, 1740 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 4.87 (d, $J = 5$ Hz, 1 H), 4.35–3.75 (m, 6 H), 3.73 (s, 3 H), 1.35 (s, 3 H), 1.3 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 168.35, 164.22, 110.04, 76.58, 76.44, 66.45, 64.87, 59.62, 42.81, 26.73, 25.11 ppm; MS (FAB), m/e 285 ($M + 1$)⁺.

(3R,4S)-cis-1-(p-Anisyl)-3-methoxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22d): prepared (54% yield) from **21** (R = *p*-anisyl) and methoxyacetyl chloride by method B; mp 93–94 $^\circ\text{C}$; $[\alpha]_D^{26} +142.4^\circ$ (c 0.5, MeOH); IR (KBr) 1750 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.69–6.87 (dd, AB pattern, 4 H), 3.8 (s, 3 H), 3.6 (s, 3 H), 1.52 (s, 3 H), 1.31 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 164.86, 156.50, 131.26, 119.56, 113.97, 109.68, 82.23, 77.14, 66.96, 61.82, 59.29, 55.3, 26.68, 24.98 ppm; CIMS (NH_3 reagent gas), m/e 308 ($M + 1$)⁺. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.45; H, 6.88; N, 4.45.

(3R,4S)-cis-1-(Carbomethoxymethyl)-3-methoxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22e): prepared in 57% yield from **21** (R = $\text{CH}_2\text{CO}_2\text{Me}$) and methoxyacetyl chloride by method B; oil; $[\alpha]_D^{26} +62.6^\circ$ (c 0.5, MeOH); IR (neat) 1750, 1730 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 4.55 (d, $J = 5$ Hz, 1 H), 4.36–3.6 (m, 6 H), 3.73 (s, 3 H), 3.53 (s, 3 H), 1.35 (s, 3 H), 1.3 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 168.53, 167.42, 109.46, 83.61, 76.67, 66.66, 60.72, 59.10, 52.12, 42.31, 26.82, 25.21 ppm; MS (FAB), m/e 274 ($M + 1$)⁺.

(3R,4S)-cis-1-(p-Anisyl)-3-acetoxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22f): prepared in 70% yield by the reaction of **21** (R = *p*-anisyl) with acetyl glycolyl chloride⁴⁰

by method B; mp 163 $^\circ\text{C}$; $[\alpha]_D^{26} +101.3^\circ$ (c 0.5, MeOH); IR (CHCl_3) 1750 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.75–6.9 (dd, AB pattern, 4 H), 6.05 (d, $J = 5.7$ Hz, 1 H), 4.45 (m, 2 H), 4.05 (m, 1 H), 3.8 (s, 3 H), 3.65 (m, 1 H), 2.15 (s, 3 H), 1.50 (s, 3 H), 1.30 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 169.3, 161.8, 157.0, 119.8, 114.0, 76.55, 73.11, 66.39, 61.53, 55.46, 26.52, 24.89, 20.45 ppm; CIMS (NH_3 reagent gas), m/e 353 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_6$: C, 60.89; H, 6.26; N, 4.17. Found: C, 60.86; H, 6.35; N, 3.81.

(3R,4S)-cis-1-(p-Anisyl)-3-(benzyloxy)-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22g): prepared in 69% yield according to method B by using **21** (R = *p*-anisyl) and (benzyloxy)acetyl chloride; mp 120 $^\circ\text{C}$; $[\alpha]_D^{26} +109.2^\circ$ (c 0.541, MeOH); IR (CH_2Cl_2) 1740 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.65 (d, 2 H), 7.39 (s, 5 H), 6.85 (d, 2 H), 5.0 (d, 1 H), 4.8–3.7 (m, 6 H), 3.8 (s, 3 H), 1.62 (s, 3 H), 1.35 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 165.00, 156.51, 136.75, 128.58, 128.20, 127.98, 119.57, 113.99, 109.79, 79.71, 77.20, 77.16, 73.20, 67.12, 61.83, 55.44, 26.72, 24.93 ppm; CIMS (NH_3 reagent gas), m/e 401 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_5$: C, 68.92; H, 6.52; N, 3.65. Found: C, 68.68; H, 6.36; N, 3.63.

(3R,4S)-cis-1-(p-Anisyl)-3-phenoxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22h): prepared from **21** (R = *p*-anisyl) and phenoxyacetyl chloride in 67% yield by using method B; mp 145–146 $^\circ\text{C}$; $[\alpha]_D^{26} +185.4^\circ$ (c 0.5, MeOH); IR (KBr) 1730 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.67–6.84 (aromatic protons, 9 H), 5.29 (d, $J = 6$ Hz, 1 H), 4.75–4.19 (m, 4 H), 3.79 (s, 3 H), 1.53 (s, 3 H), 1.34 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 163.34, 157.47, 156.75, 131.09, 129.74, 122.80, 119.78, 115.96, 114.07, 109.99, 79.56, 77.18, 67.19, 61.65, 55.47, 26.70, 24.92 ppm; EIMS, m/e 369 M^+ . Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5$: C, 68.29; H, 6.23; N, 3.79. Found: C, 68.39; H, 6.26; N, 3.61.

(3R,4S)-cis-1-Benzyl-3-methoxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22i): prepared from **21** (R = benzyl) and methoxyacetyl chloride in 55% yield by using method B; mp 70–71 $^\circ\text{C}$; $[\alpha]_D^{26} -1.3^\circ$ (c 0.45, CHCl_3); IR (Nujol) 1760 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.3 (s, 5 H), 4.8 (d, $J = 14.65$ Hz, 2 H), 4.4 (d, $J = 4.48$ Hz, 1 H), 4.3 (m, 1 H), 4.1 (m, 2 H), 3.5 (m, 4 H), 1.35 (s, 3 H), 1.32 (s, 3 H); CIMS (NH_3 reagent gas), m/e 309 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$: C, 65.97; H, 7.21; N, 4.81. Found: C, 65.75; H, 7.23; N, 4.63.

(3R,4S)-cis-1-(p-Anisyl)-3-(allyloxy)-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22j): prepared from **21** (R = *p*-anisyl) and (allyloxy)acetyl chloride⁴¹ in 44% yield by using method B; mp 72 $^\circ\text{C}$; $[\alpha]_D^{26} +125.8^\circ$ (c 0.5, MeOH); IR (CH_2Cl_2) 1740 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.65–6.9 (dd, AB pattern, 4 H), 5.95 (m, 1 H), 5.3 (t, 2 H), 4.8 (d, $J = 5.6$ Hz, 1 H), 4.5–3.7 (m, 6 H), 3.8 (s, 3 H), 1.55 (s, 3 H), 1.35 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 164.96, 156.44, 133.31, 131.18, 119.53, 118.09, 113.95, 109.75, 80.00, 77.15, 72.27, 67.01, 61.84, 55.43, 26.69, 24.88 ppm; CIMS (NH_3 reagent gas), m/e 351 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_5$: C, 64.86; H, 6.90; N, 4.20. Found: C, 64.59; H, 6.99; N, 4.09.

(3R,4R)-cis-1-(p-Anisyl)-3-amino-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (23). Hydrogen sulfide gas was bubbled through a cooled (0 $^\circ\text{C}$) solution of **22a** (500 mg, 16 mmol) in dry methylene chloride (50 mL) for 30 min. The reaction mixture was quenched with triethylamine (0.6 mL, 43 mmol) in methylene chloride (5 mL) and was stirred at 0 $^\circ\text{C}$ for 1 h. The solvent was then evaporated under reduced pressure. The residue was triturated with benzene (10 mL) and filtered. The filtrate was evaporated, and the crude product was crystallized from methylene chloride/petroleum ether to obtain the pure α -amino β -lactam **23**: yield 460 mg (95%); mp 169 $^\circ\text{C}$; $[\alpha]_D^{26} +81.9^\circ$ (c 0.5, MeOH); IR (Nujol) 3420, 1730 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 7.5–6.8 (AB pattern, 4 H), 4.4–4.15 (m, 4 H), 3.9 (m, 1 H), 3.7 (s, 3 H), 1.8 (s, 2 H), 1.45 (s, 3 H), 1.3 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 168.60, 156.85, 131.82, 120.16, 114.46, 110.00, 76.73, 67.28, 61.77, 60.99, 55.79, 26.82, 25.50 ppm; CIMS (NH_3 reagent gas), m/e 310 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_4$: C, 61.64; H, 6.85; N, 9.59. Found: C, 61.38; H, 7.00; N, 9.20.

(3R,4R)-cis-1-(p-Anisyl)-3-phthalimido-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (22b). The β -lactam **23** (400 mg, 14 mmol) was dissolved in tetrahydrofuran 25 mL,

(39) Gabriel, S. *Chem. Ber.* 1907, 40, 2648.

(40) Friedman, O. M.; Seligman, A. M. *J. Am. Chem. Soc.* 1954, 76, 658. See also: Anschutz, R.; Bertram, W. *Chem. Ber.* 1903, 36, 467.

(41) Fridman, S. G. *Zh. Obshch. Khim.* 1954, 24, 642; *Chem. Abstr.* 1955, 49, 6231a.

and to this was added a saturated sodium carbonate solution (5 mL) followed by Nefkens reagent²² (500 mg, 22 mmol). The reaction mixture was stirred at room temperature for 45 min and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, and evaporated to afford crude β -lactam **22b**. It was purified by column chromatography using 1:1 ethyl acetate/petroleum ether as a solvent to yield **22b** as a bright yellow crystalline solid in 70% yield (410 mg): mp 174 °C; $[\alpha]_D^{26} -33.2^\circ$ (c 0.52, MeOH); IR (KBr) 1750, 1710 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 8.0–6.8 (aromatic protons, 8 H), 5.5 (d, $J = 6$ Hz, 1 H), 4.6–4.3 (m, 2 H), 3.8 (s, 3 H), 3.8–3.32 (m, 2 H), 1.5 (s, 3 H), 1.29 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 167.01, 160.70, 156.64, 134.88, 131.28, 131.21, 124.02, 119.75, 114.04, 110.09, 75.89, 65.91, 62.81, 55.45, 54.43, 26.52, 25.05 ppm; CIMS (NH_3 reagent gas), m/e 423 ($M + 1$)⁺. Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_6$: C, 65.4; H, 5.21; N, 6.63. Found: C, 65.3; H, 5.28; N, 6.54.

(3S,4R)-trans-1-(p-Anisyl)-3-phthalimido-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidid-2-one (25). A mixture of the β -lactam **22b** (50 mg, 1.2 mmol) and DBN (14.7 mg, 1.2 mmol) in dry benzene (9 mL) was refluxed under a nitrogen atmosphere. The reaction was monitored by proton NMR. At the end of 24 h, the solvent was evaporated and the crude reaction mixture was passed over Florisil and eluted with 2:8 ethyl acetate/hexanes. The β -lactam **25** was then obtained as a white crystalline solid: 38 mg (75%); mp 127 °C; $[\alpha]_D^{26} +11.6^\circ$ (c 0.5, MeOH); IR (Nujol) 1745, 1720 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 8.05–7.05 (aromatic protons, 8 H), 5.3 (d, $J = 2.4$ Hz, 1 H), 4.5–4.7 (m, 2 H), 4.2–4.3 (m, 1 H), 3.8–3.9 (m, 1 H), 3.8 (s, 3 H), 1.52 (s, 3 H), 1.4 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 166.70, 161.36, 157.00, 134.56, 131.71, 123.80, 120.32, 114.37, 110.94, 75.90, 65.48, 60.73, 55.51, 55.38, 26.52, 24.98 ppm; EIMS, m/e 422 M^+ . Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_6$: C, 65.4; H, 5.21; N, 6.63. Found: C, 65.66; H, 5.54; N, 6.56.

(3R,4R)-cis-1-(p-Anisyl)-3-amino-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidid-2-one (23). To a solution of the β -lactam **22b** (0.5 g, 1.18 mmol) in methylene chloride (10 mL) was added, at 0 °C and under a nitrogen atmosphere, *N*-methylhydrazine (0.12 g, 2.6 mmol) in methylene chloride (10 mL). The reaction mixture was stirred at room temperature overnight. The white precipitate was filtered and the filtrate washed successively with water (10 mL \times 2) and saturated sodium bicarbonate solution (10 mL \times 2) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure yielded **23** (0.23 g, 67%), mp 167 °C (crystallized from methylene chloride/petroleum ether). This compound was found to be identical with the one described above on the basis of their IR, NMR and mass spectral data.

(3R,4S)-cis-1-(p-Anisyl)-3-hydroxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidid-2-one (26). The acetoxy β -lactam **22f** (3.35 g, 10 mmol) was dissolved in a mixture of tetrahydrofuran (25 mL) and methanol (5 mL) and cooled to 0 °C. Sodium hydroxide (440 mg, 10 mmol) was dissolved in methanol (25 mL) and added dropwise to the above solution, the temperature being maintained at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and extracted with methylene chloride. The organic layer was washed with water (30 mL \times 3), dried (Na_2SO_4), and concentrated to give a white solid, which was crystallized from ethyl acetate/hexanes (2.7 g, 93%): mp 199–201 °C; $[\alpha]_D^{26} +90.9^\circ$ (c 0.5, MeOH); IR (Nujol) 3350, 1750 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.51–6.8 (dd, AB pattern, 4 H), 5.0 (d, $J = 5.7$ Hz, 1 H), 4.42 (m, 1 H), 4.25 (m, 2 H), 4.09–3.85 (m, 2 H), 3.76 (s, 3 H), 1.42 (s, 3 H), 1.3 (s, 3 H); CIMS (NH_3 reagent gas), m/e 311 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_5$: C, 61.43; H, 6.48; N, 4.77. Found: C, 60.94; H, 6.52; N, 4.82.

(3R,4S)-cis-1-(p-Anisyl)-3-hydroxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidid-2-one (26). The β -lactam **22g** (3.83 g, 10 mmol) was dissolved in absolute ethanol (50 mL), and a catalytic amount of 10% Pd/C was added. Hydrogenation of this reaction mixture at room temperature at 45 psi for 8 h yielded the 3-hydroxy β -lactam **26** (2.9 g, 100%), which was isolated by filtering the reaction mixture and evaporating the solvent. This compound was found to be identical with the one described above on the basis of their mp, specific rotation, IR, NMR, and mass spectral analysis.

(3R,4S)-cis-2-(p-Anisyl)-3-(mesyloxy)-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidid-2-one (27). A mixture of hydroxy β -lactam **26** (2.93 g, 10 mmol), triethylamine (4.04 g, 40

mmol), and 4-(dimethylamino)pyridine (310 mg, 2.5 mmol) in dry methylene chloride was cooled to 0 °C, and methanesulfonyl chloride (2.28 g, 20 mmol) in methylene chloride (10 mL) was added dropwise with stirring under a nitrogen atmosphere. The reaction mixture was allowed to come to room temperature and was stirred overnight. The reaction mixture was washed with dilute hydrochloric acid (50 mL \times 2) and brine, dried (Na_2SO_4), filtered, and evaporated to give the crude mesylate **27**, which was purified by flash chromatography (silica gel, 230–400 mesh, hexanes/ethyl acetate, 7:3) (3.5 g, 95%): mp 133 °C; $[\alpha]_D^{26} +97.4^\circ$ (c 0.3, MeOH); IR (Nujol) 1740 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.6–6.9 (dd, AB pattern, 4 H), 5.65 (d, $J = 5$ Hz, 1 H), 4.37 (m, 4 H), 3.7 (s, 3 H), 3.3 (s, 3 H), 1.55 (s, 3 H), 1.35 (s, 3 H); $^{13}\text{C NMR}$ 160.27, 157.13, 130.28, 119.91, 114.11, 110.39, 77.93, 76.30, 66.61, 61.54, 55.47, 39.40, 26.58, 24.77 ppm; CIMS (NH_3 reagent gas), m/e 389 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_5\text{S}$: C, 51.75; H, 5.66; N, 3.77; S, 8.63. Found: C, 51.06; H, 5.36; N, 3.72; S, 8.69.

(3S,4R)-trans-1-(p-Anisyl)-3-azido-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidid-2-one (28). The mesylate **27** (3.5 g, 11 mmol) was dissolved in dry *N,N*-dimethylformamide (20 mL), and lithium azide (2.45 g, 50 mmol) was added to the reaction mixture under nitrogen. The reaction mixture was then heated at 80 °C with continuous stirring under a nitrogen atmosphere for 2 days. The mixture was poured onto ice water and extracted with methylene chloride (20 mL \times 8). The combined organic extracts were washed with water (100 mL \times 5), dried over Na_2SO_4 , and evaporated to give the title compound as an oil, which was purified by flash chromatography (silica gel, 230–400 mesh, hexanes/ethyl acetate, 1:1) (2.59 g, 91%): mp 96–98 °C; $[\alpha]_D^{26} -119.8^\circ$ (c 0.5, MeOH); IR (neat) 2105, 1750 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.45–6.8 (dd, AB pattern, 4 H), 4.5 (d, $J = 2.5$ Hz, 1 H), 4.02 (m, 4 H), 3.8 (s, 3 H), 1.52 (s, 3 H), 1.34 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 161, 157, 130.5, 120, 114, 110.5, 76.5, 66.8, 64, 60.75, 55.5, 26.5, 24.8 ppm; CIMS (NH_3 reagent gas), m/e 336 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_4$: C, 56.60; H, 5.66; N, 17.61. Found: C, 56.80; H, 5.96; N, 17.47.

(3S,4S)-trans-1-(p-Anisyl)-3-acetoxy-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidid-2-one (29). To a solution of mesylate **27** (1.5 g, 4 mmol) in dry dimethyl sulfoxide (50 mL) was added anhydrous sodium acetate (1.65 g, 20 mmol). The reaction mixture was heated at 100 °C with continuous stirring and under a nitrogen atmosphere for 50 h. The mixture was poured onto ice water and extracted with methylene chloride (100 mL \times 3). The combined organic extracts were washed with water (10 mL \times 5), dried over Na_2SO_4 , filtered, and evaporated to give **29**, which was purified by flash column chromatography using silica gel (230–400 mesh) and hexanes/ethyl acetate (2:1) as eluent (974 mg, 69%): mp 113 °C; $[\alpha]_D^{26} +46.1^\circ$ (c 0.4, MeOH); IR (Nujol) 1750 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.55–6.9 (dd, AB pattern, 4 H), 5.5 (d, $J = 1.95$ Hz, 1 H), 4.35 (q, 1 H), 4.2–4.05 (m, 3 H), 3.8 (s, 3 H), 2.15 (s, 3 H), 1.5 (s, 3 H), 1.3 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 169.65, 161.23, 156.98, 150.17, 120.37, 114.18, 110.53, 75.95, 75.81, 66.15, 62.96, 55.44, 26.50, 25.16, 20.10 ppm; CIMS (NH_3 reagent gas), m/e 353 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_6$: C, 60.89; H, 6.17; N, 4.18. Found: C, 60.57; H, 6.17; N, 4.02.

(3R,4R)-cis-1-(p-Anisyl)-3-azido-4-(1,2-dihydroxyethyl)azetidid-2-one (30). The β -lactam **22a** (3.18 g, 10 mmol) and *p*-toluenesulfonic acid monohydrate (560 mg, 2.9 mmol) were added to a mixture of tetrahydrofuran (40 mL) and water (15 mL) and refluxed for 24 h. The reaction mixture was neutralized with saturated sodium bicarbonate solution, extracted with ethyl acetate (25 mL \times 3), and dried (Na_2SO_4). Evaporation of the solvent gave **30** in quantitative yield: IR (neat) 3450 (br), 2120, 1740 cm^{-1} ; CIMS (NH_3 reagent gas), m/e 269 ($M + 18$)⁺. This compound was used directly in the next step without further purification.

(3R,4R)-cis-1-(p-Anisyl)-3-azido-4-carbomethoxyazetidid-2-one (31). To a solution of sodium periodate (7.0 g, 31 mmol) in acetone (70 mL) and water (35 mL) cooled to 0 °C was added ruthenium dioxide (70 mg, 0.522 mmol). The reactants were stirred for 1 h. During this period, all the ruthenium oxide dissolved and the solution developed a yellow color. This solution was added with stirring to a solution of crude **30** (2.78 g, 10 mmol) in acetone (60 mL). A solution of sodium periodate (19.3 g, 8.5 mmol) in water (90 mL) was added in portions, and the course of the reaction was monitored by TLC. Reactants were stirred

overnight and filtered, and the acetone was removed under reduced pressure. The resulting aqueous solution was extracted with ethyl acetate (100 mL \times 2). The organic layer was washed with water and extracted with saturated sodium bicarbonate solution (50 mL). The aqueous layer was acidified and extracted with ethyl acetate (80 mL \times 2). The organic layer was washed with brine (30 mL \times 1) and dried (Na_2SO_4) and the solvent evaporated to afford the crude acid, which was converted to its methyl ester by treatment with diazomethane. Pure methyl ester **31** was obtained by preparative TLC (ethyl acetate/hexane, 2:8). The solid obtained on crystallization with ether/petroleum ether gave **31** in 57% yield (1.4 g): mp 121 °C; $[\alpha]_D^{26} +169.8^\circ$ (c 0.5, MeOH); IR (KBr) 2100, 1740 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.38–6.75 (dd, AB pattern, 4 H), 5.0 (d, $J = 6$ Hz, 1 H), 4.43 (d, $J = 6$ Hz, 1 H), 3.9 (s, 3 H), 3.77 (s, 3 H); $^{13}\text{C NMR}$ ($n\text{CDCl}_3$) 167.37, 159.50, 157.17, 129.95, 118.51, 114.61, 65.93, 57.80, 57.80, 55.52, 52.97 ppm; CIMS (NH_3 reagent gas), m/e 277 ($M + 1$)⁺. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_4\text{O}_4$: C, 52.17; H, 4.34; N, 20.28. Found: C, 51.68; H, 4.30; N, 20.48.

(3R,4R)-cis-3-Azido-4-carbomethoxyazetidid-2-one (32). To a solution of β -lactam **31** (1.2 g, 4.3 mmol) in acetonitrile (50 mL) cooled to 0 to –5 °C was added with stirring cerium(IV) ammonium nitrate (7.15 g, 13 mmol) in water (50 mL) during 5 min. The reaction mixture was stirred for 2 h, diluted with water (200 mL), and extracted with ethyl acetate (100 mL \times 3). The combined ethyl acetate extracts were washed with 5% sodium bicarbonate (100 mL). The sodium bicarbonate extract was again washed with ethyl acetate (20 mL \times 2). The organic layer was washed successively with sodium bisulfite (till a colorless aqueous extract was obtained), 5% sodium bicarbonate (50 mL \times 1), and brine (50 mL \times 1), dried (Na_2SO_4), and evaporated to give **32**. The crude product was purified by silica gel column chromatography using an ethyl acetate/hexanes gradient. β -Lactam **32**, which elutes with 1:1 ethyl acetate/hexanes, was crystallized from ether/petroleum ether to give colorless crystals, yield 450 mg (26%): mp 70–71 °C; $[\alpha]_D^{26} +48.9^\circ$ (c 0.5, MeOH); IR (KBr) 2100, 1720 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 6.99 (br s, 1 H), 5.0 (br d, $J = 6$ Hz, 1 H), 4.43 (d, $J = 6$ Hz, 1 H), 3.85 (s, 3 H); $^{13}\text{C NMR}$ (CDCl_3) 168.65, 163.65, 68.31, 54.49, 52.81 ppm; EIMS, m/e 170 M^+ ; MS (FAB) (glycerol), m/e 263 ($M + 1$ + glycerol)⁺. Anal. Calcd for $\text{C}_9\text{H}_9\text{N}_4\text{O}_3$: C, 35.29; H, 3.53; N, 32.94. Found: C, 35.71; H, 3.5; N, 32.50.

(3S,4R)-cis-1-[1-(Carbobenzyloxy)-2-hydroxyprop-1-enyl]-3-azido-4-styrylazetidid-2-one (33). To a stirred solution of β -lactam **12a**⁴² (1.1 g, 2.84 mmol) in acetone (70 mL) at 10 °C was added dropwise Jones reagent (1.3 mL) [prepared by dissolving chromium trioxide (2.68 g) in concentrated sulfuric acid (2.3 mL) and diluting the solution to 10 mL with water]. The reactants were stirred vigorously for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the chromous salt was filtered. The filtrate was evaporated under vacuum and the residue dissolved in ethyl acetate (120 mL). This solution was washed with 5% sodium bicarbonate (50 mL \times 2) and brine 50 mL, dried (Na_2SO_4), and evaporated to yield an oily residue (1.2 g), which on passing through a silica gel column (200–400 mesh, 30 g) and eluting with ethyl acetate/hexanes (1:4) afforded the enol **33** (890 mg, 81%): IR (neat) 3300, 2100, 1755 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 12.40 (s, 1 H), 7.5–7.2 (m, 10 H), 6.53 (d, $J = 15.9$ Hz, 1 H), 6.15 (dd, $J = 15.9$ and 9.5 Hz, 1 H), 5.27 (m, 2 H), 4.85 (d, $J = 4.9$ Hz, 1 H), 4.55 (dd, $J = 4.9$ Hz, 1 H), 2.12 (s, 3 H).

(3S,4R)-cis-1-[1-(Carbobenzyloxy)-2-(mesyloxy)prop-1-enyl]-3-azido-4-styrylazetidid-2-one (34). To a stirring solution of the enol **33** (800 mg, 2.05 mmol) and *N,N*-dimethylamino-pyridine (500 mg, 4.10 mmol) in dry methylene chloride (40 mL) at 0 °C was added a solution of methanesulfonyl chloride (350 mg, 1.30 mmol) in methylene chloride (5 mL) over a period of 10 min. The progress of the reaction was checked by TLC. After the completion of the reaction, the organic layer was washed with 3% hydrochloric acid (30 mL \times 3) and brine (30 mL) and dried (Na_2SO_4). Evaporation of the solvent afforded the crude mesylate **34** as an oil, which was used for the next reaction without further

purification: yield 910 mg (94%); IR (neat) 2100, 1740, 1720 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.55–7.25 (m, 10 H), 6.51 (d, $J = 15.9$ Hz, 1 H), 6.18 (dd, $J = 15.9$ and 9.5 Hz, 1 H), 3.3 (s, o H).

(3S,4S)-cis-3-Azido-4-carbomethoxyazetidid-2-one (35). A solution of ruthenium tetroxide, formed by adding sodium periodate (2.5 g, 11.7 mmol) to a suspension of ruthenium dioxide (15 mg, 0.112 mmol) in a 1:1 mixture of acetone/water (50 mL), was added to a solution of mesylate **35** (350 mg, 1.89 mmol) in acetone (10 mL). The reaction mixture was stirred for 2 h at room temperature, and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was filtered, and acetone was evaporated from the filtrate. The aqueous solution was extracted with ethyl acetate (50 mL \times 5). The ethyl acetate extract was dried (Na_2SO_4). Evaporation of the solvent afforded the crude acid as a semisolid. This acid on treatment with excess diazomethane gave the methyl ester **35** as an oil. It was purified by flash chromatography [silica gel, 70–200 mesh, ethyl acetate/hexanes (1:1)]: yield 115 mg (35%); mp 70–71 °C; $[\alpha]_D^{26} -46.0^\circ$ (c 0.5, MeOH); IR (KBr) 3215, 2110, 1785, 1740 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 6.85 (br s, 1 H), 5.03 (d, $J = 5.37$ Hz, 1 H), 4.47 (d, $J = 5.4$ Hz, 1 H), 3.86 (s, 3 H); $^{13}\text{C NMR}$ ($n\text{CDCl}_3$) 168.61, 163.61, 68.26, 54.45, 52.80 ppm; CIMS (NH_3 reagent gas), m/e 171 ($M + 1$)⁺, 188 ($M + 18$)⁺.

(3S,4R)-trans-1-(p-Anisyl)-3-phthalimido-4-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidid-2-one (25). Hydrogen sulfide gas was bubbled through a solution of **28** (0.5 g, 16 mmol) in dry methylene chloride (20 mL) at 0 °C for 30 min. The reaction mixture was quenched with triethylamine (0.6 mL, 43 mmol) in methylene chloride (5 mL). The reaction mixture was stirred at 0 °C for an additional 1 h. Evaporation of the solvent under reduced pressure afforded a solid residue, which was triturated with benzene (10 mL) and filtered. The filtrate was evaporated, and the crude product was crystallized from ethyl acetate/petroleum ether to obtain the pure amino β -lactam (0.45 g, 95%): mp 150 °C; $[\alpha]_D^{26} +29.9^\circ$ (c 0.5, MeOH); IR (Nujol) 1725, 3400 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.55–6.85 (AB pattern, 4 H), 4.4 (m, 1 H), 4.15 (m, 1 H), 3.9 (m, 3 H), 3.8 (s, 3 H), 1.5 (s, 3 H), 1.35 (s, 3 H). Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_4$: C, 61.64; H, 6.85; N, 9.59. Found: C, 61.47; H, 6.78; N, 9.52.

The above β -lactam (0.4 g, 14 mmol) was dissolved in tetrahydrofuran (25 mL), and to this was added saturated sodium carbonate solution (5 mL) followed by Neffkens reagent (0.5 g, 22 mmol). The reaction mixture was stirred at room temperature for 45 min and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, and evaporated to afford the crude β -lactam **25**, which was purified by silica gel column chromatography using 1:1 ethyl acetate/petroleum ether as solvent to give **25** in 70% yield, which was identical with the one described above on the basis of their mp, IR, NMR, and mass spectral analysis.

(3R,4S)-cis-1-(p-Anisyl)-3-hydroxy-4-(1,2-dihydroxyethyl)azetidid-2-one (36). The acetoxy β -lactam **22f** (1 g, 2.9 mmol) was dissolved in a mixture of tetrahydrofuran (20 mL) and water (10 mL), and *p*-toluenesulfonic acid monohydrate (200 mg, 1 mmol) was added. The reaction mixture was refluxed overnight, allowed to come to room temperature, neutralized with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give **36** (700 mg, 93%). The crude product was crystallized from a mixture of methanol/acetone/ethyl acetate (2:1:2): mp 177 °C; $[\alpha]_D^{26} +104.8^\circ$ (c 0.3, MeOH); IR (Nujol) 3380, 1720 cm^{-1} ; $^1\text{H NMR}$ ($\text{CD}_3\text{OD} + \text{DMSO}-d_6$) δ 7.6–6.87 (dd, AB pattern, 4 H), 4.92 (d, $J = 5$ Hz, 1 H), 4.35 (t, 1 H), 3.98 (q, 1 H), 3.75 s, 3 H), 3.65 (m, 2 H); $^{13}\text{C NMR}$ ($\text{CD}_3\text{OD} + \text{DMSO}-d_6$) 169.15, 157.57, 132.96, 120.82, 114.69, 75.59, 72.65, 64.22, 60.63, 55.72 ppm; CIMS (NH_3 reagent gas), m/e 271 ($M + 18$)⁺. Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_5$: C, 56.92; H, 5.93; N, 5.53. Found: C, 56.76; H, 5.93; N, 5.64.

(3R,4S)-cis-1-(p-Anisyl)-3-hydroxy-4-(1,2-dihydroxyethyl)azetidid-2-one (36). The 3-hydroxy β -lactam **26** (1 g, 3.5 mmol) was dissolved in tetrahydrofuran/water (2:1) (60 mL), and *p*-toluenesulfonic acid monohydrate (90 mg, 0.047 mmol) was added. The mixture was refluxed for 17 h, cooled to room temperature, and neutralized with saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate, dried (Na_2SO_4), filtered, and evaporated to give **36**, which was crys-

(42) This β -lactam was prepared by the annelation of **11c** and **1** in the presence of triethylamine according to the procedure described by Tenneson and Belleau; see ref 9.

tallized from methanol/acetone/ethyl acetate (2:1:2) (723 mg, 83%). This β -lactam was found to be identical with the one described above on the basis of their mp, specific rotation, IR, NMR, and mass spectral analysis.

(3*R*,4*S*)-*cis*-1-(*p*-Anisyl)-3-hydroxy-4-(1,2-dihydroxyethyl)azetid-2-one (36). To a solution of 22j (150 mg, 0.045 mmol) in absolute methanol (25 mL) were added *p*-toluenesulfonic acid monohydrate (10 mg, 0.052 mmol) and 10% Pd/C (15 mg). The solution was refluxed overnight under a nitrogen atmosphere and filtered through Celite. Evaporation of the solvent gave 36 (95 mg, 83%) identical with the one described earlier on the basis of their mp, specific rotation, IR, NMR, and mass spectral analysis.

2-Methoxy-3-[(4-methoxyphenyl)amino]-5-hydroxy- γ -valerolactone (38). β -Lactam 22d (3.0 g, 10 mmol) was refluxed in 90% trifluoroacetic acid (20 mL) for 12 h under a nitrogen atmosphere. The reaction mixture was then cooled and dried in vacuum and the residue chromatographed over a silica gel column (1:1 ethyl acetate/hexane) to afford lactone 38 (1.70 g, 64%) as an oil: $[\alpha]_D^{26} +86.9^\circ$ (*c* 0.5, MeOH); IR (CDCl₃) 3380, 1780, 1690 cm⁻¹; ¹H NMR (CDCl₃) δ 6.9–6.6 (dd, aromatic, 4 H), 4.7 (d, *J* = 7.3 Hz, 1 H), 4.45–4.25 (m, 2 H), 4.0–3.7 (m, 4 H), 3.75 (s, 3

H), 3.6 (s, 3 H); ¹³C NMR (CDCl₃) 174.11, 153.11, 140.29, 115.20, 114.93, 8.20, 78.87, 60.57, 58.98, 58.77, 55.71 ppm; MS (FAB), *m/e* 268 (*M* + 1)⁺.

2-Azido-3-[(4-methoxyphenyl)amino]-5-hydroxy- γ -valerolactone (39) was prepared from 22a in 63% yield as an oil by using the same procedure as above: $[\alpha]_D^{26} +74.5^\circ$ (*c* 0.5, MeOH); IR (neat) 3290, 2100, 1760 cm⁻¹; ¹H NMR (CDCl₃) δ 6.85–6.6 (dd, AB pattern, 4 H), 4.75 (d, *J* = 7.6 Hz, 1 H), 4.6 (d, *J* = 9.6 Hz, 1 H), 4.3 (dd, *J* = 7.6 Hz and 9.6 Hz, 1 H), 4.0–3.8 (m, 3 H), 3.75 (s, 3 H); ¹³C NMR (CDCl₃) 172.2, 153.2, 139.8, 115.3, 79.4, 62.8, 60.88, 58.7, 55.8 ppm; MS (FAB), *m/e* 279 (*M* + 1)⁺.

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Reduction of Lactams and Thiolactams by Sodium Borohydride: Application in the Synthesis of Some Alkaloids

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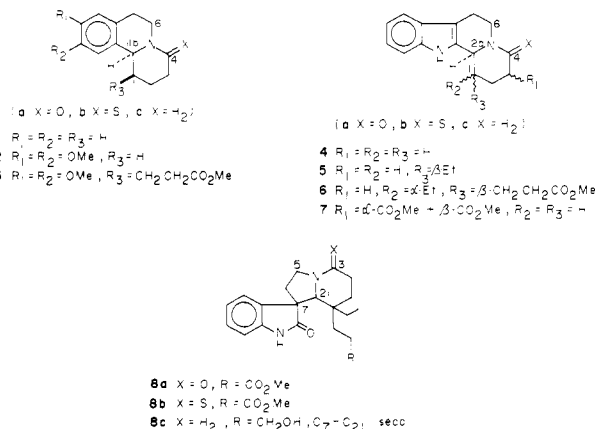
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Lactams 1a–8a and thiolactams 1b–8b, 9a, 10b–12b, and 13 could be reduced to their corresponding amines in 70–98% yield by using sodium borohydride-*tert*-butyl alcohol-methanol mixtures under reflux. Even the vinylogous amide 19 underwent reduction to afford deplancheine (18) in 53% yield. The use of this reagent has also been extended to the synthesis of bharatamine (10d), aspidospermidine (12d), and quebrachamine (17).

Introduction

Deoxygenation of lactams to their respective amines is usually brought about by direct reduction with lithium aluminum hydride¹ or diborane² or indirectly by desulfurization of the corresponding thiolactams³ with Raney nickel and in some cases with aluminum amalgam in neutral alcoholic solution. Sodium borohydride itself was not known so far to effect such transformation, though it reduces⁴ imino ethers and imino chlorides of the amides and lactams to the corresponding amines, and in combination with anhydrous AlCl₃ in diglyme,⁵ it reduces many functional groups, including some open-chain amides. We, therefore, tried to use NaBH₄-*t*-BuOH-MeOH for the preferential reduction of an ester⁶ in the presence of an amide group in compound 7a in connection with the synthesis of (\pm)-deplancheine (18), an indole alkaloid. To our surprise, the lactam moiety also underwent simultaneous reduction. Subsequently, we extended the use of this reagent to the reduction of a series of lactams (1a–8a) and thiolactams (1b–8b, 9a, 10b–12b, 13), the preliminary accounts of which have been published.^{7,8} (The structures given for 8 and 12 are shown with alternate biosynthetic numbering.)

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We now report further application of this reagent in the synthesis of some more alkaloids, including deplancheine

- (1) Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* 1960, 82, 5941.
(2) Brown, H. C.; Heim, P. *J. Org. Chem.* 1973, 38, 912.
(3) (a) Kuehne, M. E. *J. Am. Chem. Soc.* 1964, 86, 2946. (b) Johnson, W. R.; Buchanan, J. B. *J. Am. Chem. Soc.* 1953, 75, 2103.
(4) (a) Borch, R. F. *Tetrahedron Lett.* 1968, 61. (b) Aimi, N.; Yamana, E.; Endo, J.; Sakai, S.; Haginiwa, J. *Tetrahedron Lett.* 1972, 1081.
(c) Rahman, A.; Basha, A.; Waheed, N. *Tetrahedron Lett.* 1976, 219. (d) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* 1977, 42, 2082.
(5) Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* 1956, 78, 2582.
(6) Soai, K.; Oyamada, H.; Ookawa, A. *Synth. Commun.* 1982, 12, 463.