Studies on Lactams. Part 74.[1] An Approach to the Total Synthesis of Amino Sugars *via* β-Lactams

Maghar S. Manhas,* Vinod R. Hegde, Dilip R. Wagle, and Ajay K. Bose
Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, NJ 07030, USA

Convenient intermediates for mono- and di-amino sugars related to antibiotics can be prepared in a stereocontrolled fashion by the rearrangement of 3,4-disubstituted azetidin-2-ones which in turn can be synthesized by stereoselective annelation of certain imino compounds by substituted acetic acid derivatives.

In the course of our studies on β-lactams we have conducted stereocontrolled syntheses of various disubstituted azetidin-2-ones (**1**). We have noted previously the potential usefulness of β-lactams as synthons for diverse types of heterocycles.[2] We describe here the use of suitably substituted β-lactams as intermediates for various members of a large and valuable family of compounds: the amino sugars. These are important ingredients of three broad classes of biologically active antibiotics, namely, amino glycosides, macrolides, and anthracyclins, besides some miscellaneous antibiotics.

Many amino glycosides, such as streptomycin, gentamycin, kanamycin, neomycin, sisomycin, *etc.*, are in use as antibacterial drugs. Macrolides constitute a large class of active antibiotics; *e.g.*, erythromycin, oleandomycin, spiramycin, *etc.*, are in clinical use. Anthracyclins, *e.g.* daunomycin, adriamycin, and carminomycin, are highly effective against a wide variety of tumours.

Structural modification of these antibiotics has often involved the synthesis of various amino sugars. Several reviews[3–6] deal with naturally occurring amino sugars and their parent antibiotics. Our goal is to devise stereocontrolled and, preferably, enantioselective synthesis of naturally occurring amino sugars as well as their unusual analogues.

General Strategy.—3,4-Disubstituted azetidin-2-ones (**1**) can be cleaved to provide β-amino acid derivatives (**2**) which can in turn be modified to correspond to the structural features of various amino sugars (Scheme 1). Conversion of the carboxy group into an aldehyde would produce aldoses (**3**) while ketoses (**5**) would be derived from a ketone prepared from the carboxy group. The relative configuration of sugar carbons carrying the Z and NH_2 groups would depend on the *cis* or *trans* configuration of the starting β-lactam. Useful Z groups would be OMe, N_3, and SR; the last two would lead to a diamino sugar and a deoxy sugar (after desulphurization), respectively. The size of the Y group would determine the number of carbons in the sugar backbone.

Reduction of the carboxy group in (**2**) to a primary alcohol and modification of Y would provide a sugar of type (**4**)—a monoamino or diamino aldose. Yet other structural variations could be realized by starting with appropriate 3,3-disubstituted and/or 4,4-disubstituted azetidin-2-ones. The use of optically active β-lactams as starting material would, of course, lead to optically active amino sugars.

Starting Materials.—Previous work in our laboratory and elsewhere has shown that Schiff's bases (**6**) are easily obtained in good yield from α,β-unsaturated aldehydes and arylamines and that annelation of such imino compounds provides stereospecific access to racemic β-lactams (**7a**) (see Scheme 2).

When azido- or methoxy-acetic acid derivatives are used for annelation, *cis* β-lactams are obtained.[7] On the other hand, a *trans* β-lactam is formed if (phenylthio)acetyl chloride is the annelating reagent. If the *N*-aryl group is *p*-methoxyphenyl, oxidation with cerium(IV) ammonium nitrate[8] (CAN) leads to *N*-unsubstituted β-lactams (**7b**).

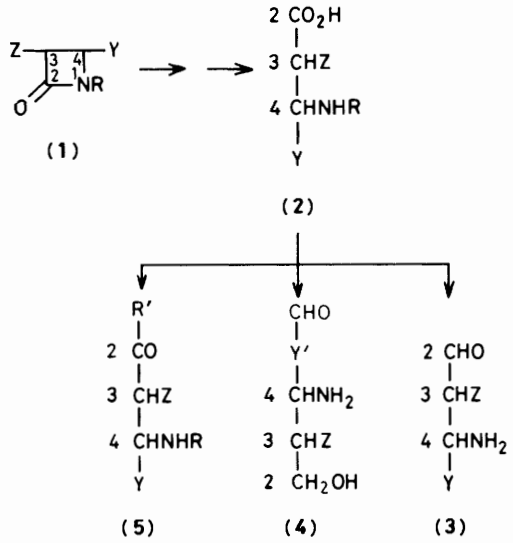
Intermediates for 2,3-*Diamino Sugars.*—As the first step, *cis* α-azido-β-lactams were prepared from appropriate Schiff's bases (Scheme 3). The Schiff's base from crotonaldehyde and *p*-anisidine, which is relatively unstable, was obtained by stirring equimolar amounts of the aldehyde and the amine at 20 °C for 1 h. In view of the hazards of preparing pure azidoacetyl chloride, we employed a method developed recently in our laboratory involving the use of cyanuric chloride to activate the carboxy group of a salt of a substituted acetic acid.[9]

Addition of cyanuric chloride to a solution of the potassium salt of azidoacetic acid, Schiff's base, and triethylamine in methylene dichloride at −20 °C followed by stirring for 8—10 h at room temperature, afforded only *cis*-β-lactams in *ca.* 60—80% yield. *N*-Dearylation of the β-lactams was effected in 70—80% yield by treatment with cerium(IV) ammonium nitrate.

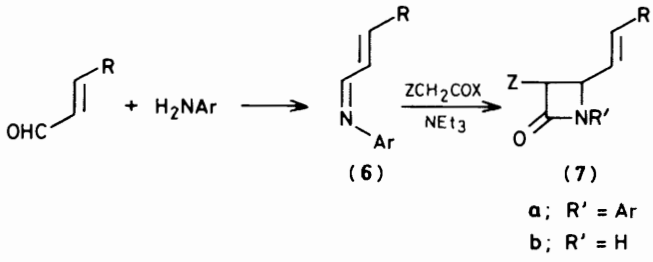
These *N*-unsubstituted β-lactams (**9a**—**c**) were cleaved by alkaline hydrolysis because acid cleavage was not satisfactory. After α-azido-β-lactams had been refluxed in methanol solution with 1.5 equiv. of potassium hydroxide, the β-amino acids formed were *N*-benzoylated by the Schotten–Baumann method. Esterification of β-amido acids in refluxing methanol in the presence of traces of sulphuric acid gave methyl esters (**10**) in good yield (see Scheme 3).

These straight-chain compounds (**10**) are suitable intermediates for the preparation of a variety of 2,3-diamino sugars. Because of the *cis* geometry of the starting β-lactams, the stereochemistry of compound (**10**) can be described as (2*SR*, 3*RS*) or *threo*. The ester group would eventually become the aldehyde group of the target sugar; the alkene group would be converted into a vicinal diol of known configuration by such well known methods as osmium tetraoxide oxidation or epoxide formation followed by hydrolysis. The feasibility of this approach was demonstrated by studies on some selected β-lactams as reported below.

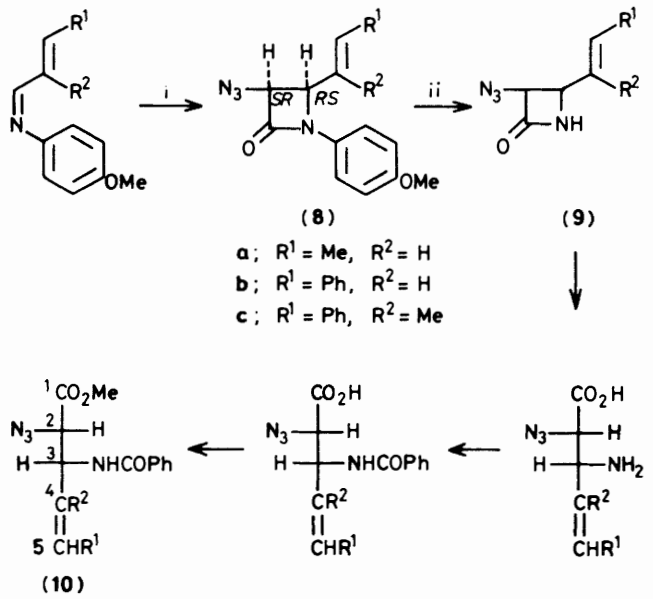
Intermediates for 3-*Amino*-3,6-*dideoxyhexoses.*—The starting material for a 3-amino sugar is a β-lactam with a protected oxygen function at the α-position. One such compound is (**11**), formed by the stereospecific reaction between methoxyacetyl chloride, triethylamine, and the Schiff's base from crotonaldehyde and *p*-anisidine. The *N*-unsubstituted β-lactam (**12**) was obtained readily by the oxidation of compound (**11**) with cerium(IV) ammonium nitrate.



Scheme 1.

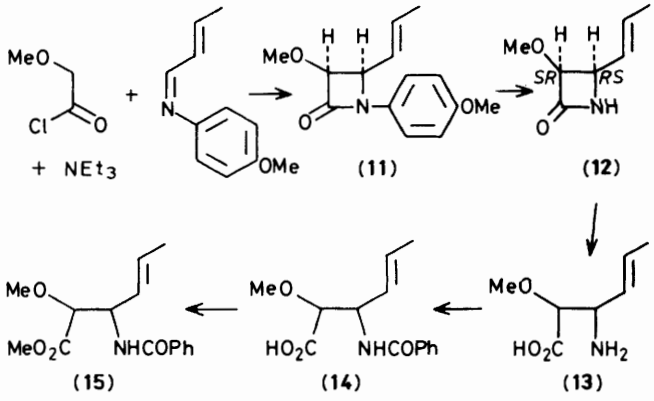


Scheme 2.



Scheme 3. *Reagent:* i, $N_3CH_2CO_2K$, cyanuric chloride, triethylamine; ii, CAN oxidation

The 4-membered ring in compound (**12**) could be cleaved with refluxing dilute alkali to yield a β-amino acid (**13**) in good yield. *N*-Benzoylation of compound (**13**) to give the amide (**14**) was accomplished under Schotten–Baumann conditions. The corresponding methyl ester (**15**) was prepared by refluxing amide (**14**) with methanol and a trace of sulphuric acid (Scheme 4). The *cis* stereochemistry of compound (**11**) led to the *threo* or (2*SR*,3*RS*)-configuration for ester (**15**).



Scheme 4.

The next step in the synthesis was stereocontrolled glycol formation from the double bond in compound (**15**); to this end compound (**15**) was subjected to reaction with osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide. However, the expected diols (**16**) and (**17**) were not obtained; instead, the incipient glycol from the alkene (**15**) underwent rearrangement to form, in 67% yield, two lactones (**18**) and (**19**) in the ratio 1:2. These lactones could be separated by column chromatography.

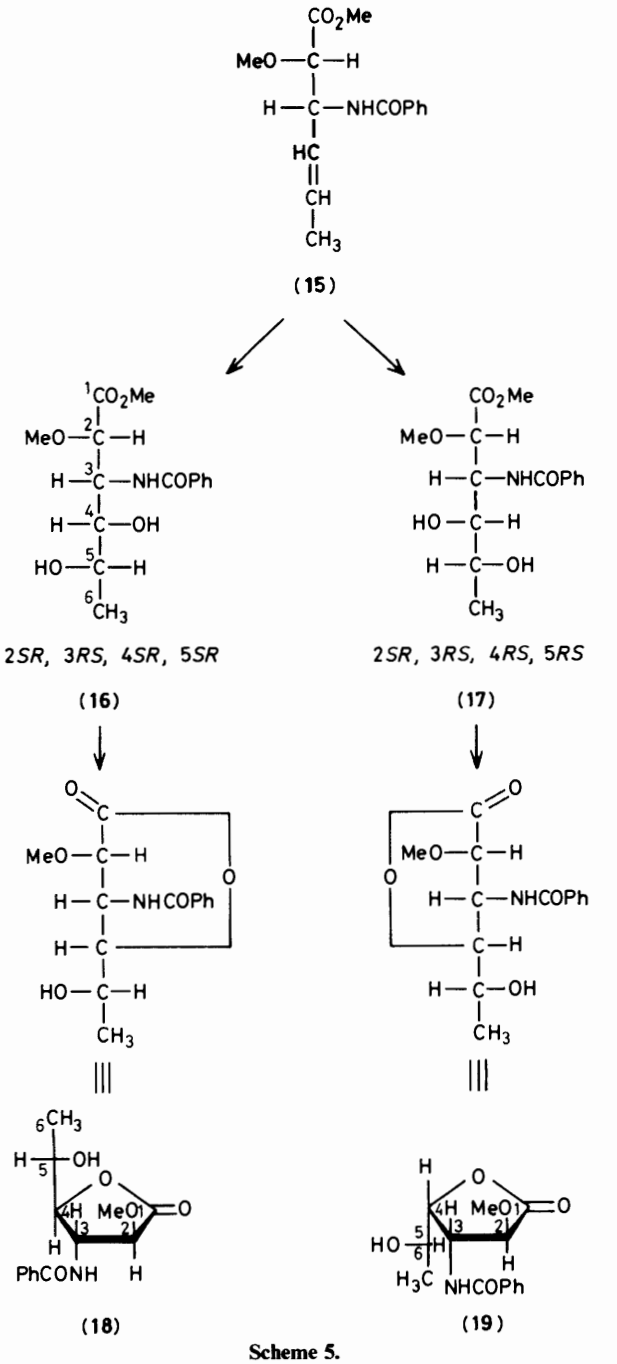
From the i.r. spectra of compounds (**18**) and (**19**) it was apparent that γ-lactones had been formed (amide carbonyl 1 660 cm^{-1}; lactone carbonyl 1 780 cm^{-1}). Cyclization to γ-lactones in preference to δ-lactones is well known in carbohydrate chemistry.

Glycol formation by reaction with osmium tetraoxide is known to produce *cis* glycols only. Since the crotonaldehyde used as an intermediate was of the *trans* (*E*) configuration, the alkene in compound (**15**) was also *trans* (*E*)—a fact confirmed by the size of the coupling (16 Hz) of the olefinic protons in compound (**15**). The configuration of the diols can therefore be predicted to be as shown in structures (**16**) and (**17**). The two corresponding γ-lactones will be (**18**) and (**19**). In the ^1H n.m.r. spectrum the major difference between compounds (**18**) and (**19**) would be due to the relative configuration of their hydrogens at C-3 and C-4 (see Scheme 5).

The assignment of signals in the ^1H n.m.r. spectrum of the lactone (**18**) was based on various coupling constants measured by extensive decoupling experiments. The 2-H signal was assigned to the only low-field doublet. The *J* value of *ca.* 9.6 Hz was consistent with its *trans* coupling with 3-H; the *trans* relationship between the methoxy and the benzamido group follows from their *cis* relationship in the starting β-lactam. The signal at δ 4.2 could be assigned to 5-H because of its multiplet nature. Irradiation of this signal converted the broad doublet signal for 4-H at δ 4.6 into a doublet with a small coupling of *ca.* 2 Hz.

Similar arguments can also be used for the interpretation of the ^1H n.m.r. spectrum of the C-4 epimeric lactone (**19**). The 2-H signal showed the expected *trans* coupling constant of *ca.* 9.6 Hz. Irradiation of this signal helped identify the 3-H signal which appeared as a doublet of doublets (*J* 9.6 and 8.4 Hz). Another proton signal in the form of a doublet of doublets (*J* 3 and 8.4 Hz) must then be assigned to 4-H. The multiplet at δ 3.9 which must be due to 5-H was irradiated, whereupon the 4-H doublet of doublets collapsed to a doublet (*J* 8.4 Hz).

A comparison of the two lactones, (**18**) and (**19**), showed that the *J* value for the diagnostic 3-H and 4-H coupling is 2 Hz in (**18**) and 8.4 Hz in (**19**). The smaller coupling indicates a dihedral angle close to 90°, and the larger coupling, a dihedral



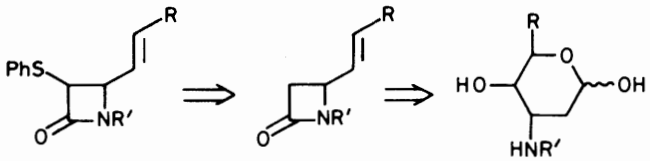
Scheme 5.

angle near 0°. From a model of the lactones it can be seen that compound (**18**) must have a *trans* relationship between 4-H and 3-H while in compound (**19**) this relationship must be *cis*.

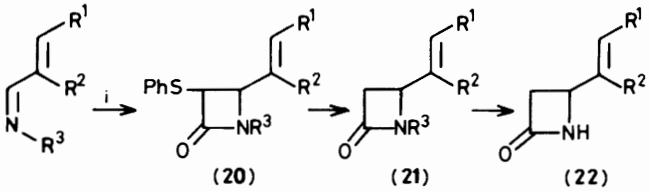
The reduction of γ-lactones to pyranosides with di-isobutylaluminium hydride is well known.[10–16] Therefore, lactones (**18**) and (**19**) are the immediate precursors of (±)-3-amino-3,6-dideoxyhexoses.

Synthesis of 2,3,6-*Trideoxy*-3-*amino Sugars*.—It is well known that thio derivatives of sugars can be converted into deoxy sugars by Raney nickel desulphurization. β-Lactams with a 3-phenylthio group can be desulphurized by Raney nickel to give 3-unsubstituted β-lactams which could serve as intermediates for 2,3,6-trideoxy-3-amino sugars (see Scheme 6).

The 3-(phenylthio)azetidin-2-ones suitable for the projected synthesis were obtained in good yield by the annelation of



Scheme 6.



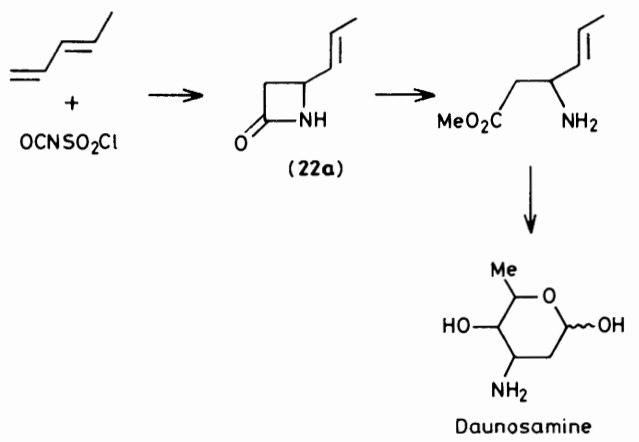
a; R^1 = Me, R^2 = H, R^3 = $C_6H_4OMe(p)$
b; R^1 = Ph, R^2 = H R^3 = $C_6H_4OMe(p)$
c; R^1 = Ph, R^2 = Me, R^3 = $C_6H_4OMe(p)$

Scheme 7. *Reagent:* i, $PhSCH_2COCl$

Schiff's bases prepared from *p*-anisidine (Scheme 7). Thus, the addition of cyanuric chloride to a mixture of the potassium salt of (phenylthio)acetic acid, triethylamine, and a Schiff's base gave only *trans* β-lactams as indicated by the coupling constants of 2 Hz for 3-H and 4-H protons in the n.m.r. spectra of compound (**20**).

The conversion of these β-lactams into 3-unsubstituted β-lactams was achieved by Raney nickel desulphurization. Thus, refluxing the β-lactam (**20a**) in acetone solution with W_2 Raney nickel for half an hour resulted in a clean reaction, (monitored by t.l.c.) to afford a 3-unsubstituted β-lactam (**21a**). This was converted into the *N*-unsubstituted β-lactam (**22a**)[17] by oxidation with cerium(IV) ammonium nitrate.

The β-lactam (**22a**) has been converted by Hauser *et al.*[18] into (±)-daunosamine. They prepared compound (**22a**) by the cycloaddition of chlorosulphonyl isocyanate to (*E*)-penta-1,3-diene (obtained by careful separation of the commercially available mixture of *Z* and *E* dienes) followed by reductive removal of the *N*-chlorosulphonyl group (Scheme 8).



Scheme 8.

The synthesis by Hauser *et al.* can generate only (±)-compounds because the starting β-lactam was derived from achiral components. Recently we[19] have devised highly enantioselective syntheses of β-lactams which can lead to

compounds closely related to (**7**), (**16**), (**17**), and (**20**). The synthesis of optically active amino sugars from such β-lactam intermediates using the general strategy discussed above will be described in a future communication.

Experimental

M.p.s were taken for samples in open capillary tubes (Mel. Temp apparatus) and were uncorrected. I.r. spectra were obtained on a Perkin-Elmer 1310 i.r. spectrophotometer. N.m.r. spectra were recorded on a Varian EM-390 spectrometer or Bruker WP200 SY spectrometer in CCl_4, $CDCl_3$, or [$^2H_6$]acetone with $SiMe_4$ 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. Elemental analyses were determined by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, New York.

N-(*But*-2-*enylidene*)-4-*methoxyaniline* (**6**; R = CH_3, Ar = *p*-methoxyphenyl). To a stirred solution of 85% crotonaldehyde (in water) (9 ml, 0.11 mol) and *p*-anisidine (12.3 g) in methylene dichloride (150 ml) was added an excess of molecular sieves at 20 °C. The reaction mixture was stirred for 1 h and filtered, and the solvent was evaporated off at low temperature from the filtrate to give the desired Schiff's base in 85% yield. It was used as such in the next step; $\nu_{max.}$(Nujol) 1 640 and 1 500 cm^{-1}; δ_H($CDCl_3$) 7.9 (1 H, *J* 8 Hz), 7.0—6.1 (6 H, m), 3.7 (3 H, s), and 1.9 (3 H, d, *J* 6 Hz).

General Procedure for the Preparation of α-*Azido*-β-*lactams*.—A solution of the potassium salt of azidoacetic acid (0.06 mol), an imine (0.03 mol) (**6**), and triethylamine (0.12 mol) in dry methylene dichloride (150 ml) was cooled to −20 °C under nitrogen and a solution of cyanuric chloride[9] (0.045 mol) in methylene dichloride (100 ml) was added dropwise. The reaction mixture was allowed to come to room temperature and was then stirred overnight. It was then diluted with methylene dichloride (75 ml), and washed successively with water (2 × 150 ml), 5% aqueous sodium hydrogen carbonate (2 × 100 ml), and brine (100 ml). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography over silica gel (eluted with an appropriate hexane–ethyl acetate mixture) and recrystallization.

cis-3-*Azido*-1-(4-*methoxyphenyl*)-4-(*prop*-1-*enyl*)*azetidin*-2-*one* (**8a**) was prepared by the action of the mixed anhydride of azidoacetic acid and cyanuric chloride[9] on *N*(but-2-enylidene)-*p*-anisidine (**6a**) in the presence of triethylamine in 68% yield, m.p. 69 °C; $\nu_{max.}$(Nujol) 2 100 and 1 740 cm^{-1}; δ_H($CDCl_3$) 7.1 and 6.75 (4 H, dd, ArH), 6.4—5.35 (2 H, m), 4.8 (1 H, d, *J* 5 Hz), 4.65 (1 H, m), 3.8 (3 H, s), and 1.85 (3 H, d, *J* 6 Hz); CIMS (NH_3 reagent gas) *m*/*z* 259, $(M + 1)^+$ and 276 $(M + 18)^+$ (Found: C, 60.3; H, 5.3; N, 21.5. $C_{13}H_{14}N_4O_2$ requires C, 60.46; H, 5.46; N, 21.69%).

cis-3-*Azido*-1-(4-*methoxyphenyl*)-4-*styrylazetidin*-2-*one* (**8b**) was prepared in 73% yield from the mixed anhydride of azidoacetic acid and cyanuric chloride, the Schiff's base from cinnamaldehyde and *p*-anisidine, and triethylamine, m.p. 117 °C; $\nu_{max.}$(KBr) 2 100 and 1 755 cm^{-1}; δ_H($CDCl_3$) 7.5—7.66 (10 H, m), 6.4 (1 H, dd, *J* 10 and 16 Hz), 4.8 (2 H, m), and 3.7 (3 H, s); CIMS (CH_4 reagent gas) *m*/*z* 321 $(M + 1)^+$ (Found: C, 67.6; H, 5.2; N, 17.6. $C_{18}H_{16}N_4O_2$ requires C, 67.48; H, 5.46; N, 17.49%).

cis-3-*Azido*-1-(4-*methoxyphenyl*)-4-(α-*methylstyryl*)*azetidin*-2-*one* (**8c**) was obtained (77% yield) by the action of cyanuric chloride on a mixture of potassium azidoacetate, *N*-(2-methyl-3-phenylprop-2-enylidene)-*p*-anisidine, and triethylamine in methylene dichloride; m.p. 93—94 °C $\nu_{max.}$(KBr) 2 100 and 1 720 cm^{-1}; δ_H($CDCl_3$) 7.48—6.66 (10 H, m), 4.92 (1 H, d, *J* 4.5 H), 4.85 (1 H, d, *J* 4.5 Hz), 3.78 (3 H, s), and 1.92 (3 H, s); CIMS (NH_3 reagent gas) *m*/*z* 335 $(M + 1)^+$ (Found: C, 68.0; H, 5.45; N, 17.3. $C_{19}H_{18}N_4O_2$ requires C, 68.26; H, 5.43; N, 16.76%).

General Procedure for the Preparation of N-*Unsubstituted*-β-*Lactams* (**9**).—To a solution of an *N*-(4-methoxyphenyl)-β-lactam (0.015 mol) in acetonitrile (150 ml) cooled to 0 °C was added during 5 min a solution of cerium(IV) ammonium nitrate (0.045 mol) in water (200 ml). The mixture was stirred at 0 °C for 1 h, diluted with water (1 l), and extracted with ethyl acetate (3 × 200 ml). The organic layer was washed with 5% aqueous sodium hydrogen carbonate (500 ml) and the aqueous layer was back-washed with ethyl acetate (100 ml). The combined organic layers were washed successively with 10% aqueous sodium sulphite (until the aqueous layer remained colourless), 5% aqueous sodium hydrogen carbonate (100 ml), and brine. The resulting solution was dried (Na_2SO_4) and filtered through Florisil. Removal of the solvent yielded the *N*-unsubstituted β-lactam (**9**) which was purified either by chromatography over silica gel (hexane–ethyl acetate mixture as eluant) or by recrystallization.

cis-3-*Azido*-4-(*prop*-1-*enyl*)*azetidin*-2-*one* (**9a**) was obtained by the oxidation of compound (**8a**) with cerium(IV) ammonium nitrate; yield 79%, m.p. 71 °C; $\nu_{max.}$(KBr) 3 250, 2 100, and 1 740 cm^{-1}; δ_H($CDCl_3$) 6.40 (1 H, br s), 5.9—5.25 (2 H, m), 4.65 (1 H, d, *J* 6 Hz), 4.25 (1 H, m), and 1.8 (3 H, d, *J* 6 Hz); CIMS (CH_4 reagent gas) *m*/*z* 153 $(M + 1)^+$.

cis-3-Azido-4-styrylazetidin-2-one (**9b**) was prepared in 72% yield by the oxidation of compound (**8b**) with cerium(IV) ammonium nitrate; m.p. 104 °C; $\nu_{max.}$(KBr) 3 250, 2 100, and 1 750 cm^{-1}; δ_H($CDCl_3$) 7.4—7.15 (6 H, m), 6.5 (1 H, m), 6.25 (1 H, dd, *J* 15 and 2 Hz), 4.75 (1 H, br d, *J* 6 Hz), and 4.45 (1 H, m); CIMS (CH_4 reagent gas) *m*/*z* 215 $(M + 1)^+$.

cis-3-Azido-4-(α-methylstyryl)azetidin-2-one (**9c**). Oxidation of compound (**8c**) with cerium(IV) ammonium nitrate in acetonitrile gave the product (**9c**) in 89% yield; oil, $\nu_{max.}$(KBr) 3 400, 2 100, 1 730, and 1 660 cm^{-1}; δ_H($CDCl_3$) 6.8—7.4 (5 H, m), 6.77 (1 H, br s), 6.58 (1 H, s), 4.70 (1 H, d, *J* 5 Hz), 4.4 (1 H, d, *J* 5 Hz), and 1.9 (3 H, s).

Methyl 2-*Azido*-3-*benzamidohex*-4-*enoate* (**10a**).—A solution of the β-lactam (**9a**) (1.52 g, 0.01 mol) and potassium hydroxide (1 g, 0.015 mol; 85% purity) in methanol (150 ml) was refluxed overnight. The cooled solution was evaporated to afford the potassium salt of a β-amino acid as a black, gummy solid. This was dissolved in a mixture of water (40 ml) and acetone (50 ml) and the solution was cooled to 0 °C. To this stirred solution was added potassium hydroxide (0.66 g, 0.01 mol; 85% purity) and then a solution of benzoyl chloride (1.75 g, 0.015 mol) in acetone (20 ml). This solution was stirred for 4 h at room temperature. After evaporation of acetone the residue was washed with chloroform (2 × 50 ml). The aqueous layer was acidified and re-extracted with ethyl acetate (3 × 100 ml). The ethyl acetate extract was washed with brine, dried, and evaporated to give a crude β-amino acid as a dark solid. This was dissolved in methanol (150 ml) and refluxed overnight in the presence of a few drops of conc. H_2SO_4. The cooled reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate, the methanol was evaporated off, and the residue was extracted with ethyl acetate (3 × 100 ml). The organic layer was washed with brine, dried, and evaporated to afford the crude β-amido ester (**10a**) which was further purified by passage through a silica gel column (50 g) and elution with ethyl acetate–hexane (1:9) to yield (83%) pure compound (**10a**) m.p. 67 °C; $\nu_{max.}$(KBr) 3 280, 2 160, 1 740, and 1 630 cm^{-1}; δ_H($CDCl_3$) 7.3—7.9 (5 H, m), 6.6 (1 H, br), 5.3—6.0 (2 H, m), 5.2 (1 H, br), 4.1 (1 H, d, *J* 2 H), 3.8 (3 H, s), and 1.75 (3 H, d, *J* 7 Hz); CIMS (NH_3 reagent gas) *m*/*z* 289 $(M + 1)^+$ and 306 $(M + 18)$ (Found: C,

58.3; H, 5.7; N, 19.4. $C_{14}H_{16}N_4O_3$ requires C, 58.33; H, 5.55; N, 19.44%).

Methyl 2-Azido-3-benzamido-5-phenylpent-4-enoate (**10b**).—This was prepared according to the procedure used for the synthesis of compound (**10a**) in 82% yield; m.p. 125—126 °C; $\nu_{max.}$(KBr) 3 400, 2 200, 1 800, 1 700, and 1 500 cm^{-1}; $\delta_H(CDCl_3)$ 7.8—7.3 (5 H, m), 6.6 (1 H, br), and 5.9—5.3 (2 H, m); CIMS (CH_4 reagent gas) *m/z* 351 $(M + 1)^+$ (Found: C, 65.15; H, 5.1.; N, 16.0. $C_{19}H_{18}N_4O_3$ requires C, 65.13; H, 5.18; N, 15.99%).

Methyl 2-Azido-3-benzamido-4-methyl-5-phenylpent-4-enoate (**10c**).—This was prepared in 59% yield from compound (**9c**) according to the procedure used for the preparation of ester (**10a**); m.p. 97—99 °C; $\nu_{max.}$(KBr) 3 320, 2 100, 1 730, 1 630, and 1 515 cm^{-1}; $\delta_H(CDCl_3)$ 7.1—7.9 (10 H, m), 6.7 (1 H, br), 6.55 (1 H, s), 5.25 (2 H, br d), 4.6 (1 H, d, *J* 3 Hz), 3.75 (3 H, s), and 1.9 (3 H, s); CIMS (CH_4 reagent gas) *m/z* 365 $(M + 1)^+$ (Found: C, 65.8; H, 5.55; N, 15.2. $C_{20}H_{20}N_4O_3$ requires C, 65.93; H, 5.49; N, 15.38%).

cis-3-*Methoxy*-1-(4-*methoxyphenyl*)-4-(*prop*-1-*enyl*)*azetidin*-2-*one* (**11**).—This was prepared by the reaction of methoxyacetyl chloride with *N*-(but-2-enylidene)-*p*-anisidine (**6a**) in the presence of triethylamine (yield 71%), m.p. 103 °C; $\nu_{max.}$(KBr) 1 720 cm^{-1}; $\delta_H(CDCl_3)$ 7.4—6.85 (4 H, dd, ArH), 6.0 (1 H, m), 5.6 (1 H, dd, *J* 15.5 and 7.1 Hz), 4.6 [2 H, m, splits on addition of Eu(fod)$_3$ to give one doublet *J* 5.5 Hz and other dd, *J* 5.5 and 2 Hz], 3.8 (3 H, s), 3.5 (3 H, s), and 1.8 (3 H, d, *J* 7 Hz); CIMS (CH_4 reagent gas) *m/z* 248 $(M + 1)^+$ (Found: C, 68.0; H, 6.9; N, 5.6. $C_{14}H_{17}NO_3$ requires C, 68.1; H, 6.88; N, 5.66%).

cis-3-*Methoxy*-4-(*prop*-1-*enyl*)*azetidin*-2-*one* (**12**).—This was prepared by oxidation of compound (**11**) with cerium(IV) ammonium nitrate (83% yield), $\nu_{max.}$(CCl_4) 3 300, 1 765, and 810 cm^{-1}; $\delta_H(CCl_4)$ 7.45 (1 H, br), 5.95—5.35 (2 H, m), 4.45 (1 H, dd, *J* 5 and 1 Hz), 4.1 (1 H, dd, *J* 5 and 6 Hz), 3.4 (3 H, s), and 1.75 (1 H, d, *J* 6 Hz); CIMS (CH_4 reagent gas) *m/z* 156 $(M + 1)^+$.

Methyl-3-*benzamido*-2-*methoxyhex*-4-*enoate* (**15**).—A solution of the β-lactam (**12**) (1.41 g, 0.01 mol) and KOH (1 g, 0.015 mol; 85% purity) in methanol (150 ml) was refluxed overnight. The cooled solution was evaporated to afford the potassium salt of the β-amino acid (**13**) as a dark, gummy solid. This was dissolved in a mixture of water (40 ml) and acetone (50 ml) and cooled to 0 °C. To this stirred solution was added potassium hydroxide (0.66 g, 0.01 mol; 85% purity) and then a solution of benzoyl chloride (1.75 g, 0.015 mol) in acetone (20 ml). This solution was stirred for 4 h at room temperature. After evaporation of the acetone the aqueous solution was extracted with chloroform (2 × 50 ml). The aqueous layer was acidified and re-extracted with ethyl acetate (3 × 100 ml). The ethyl acetate extract was washed with brine, dried, and evaporated to give the crude β-amido acid (**14**) as a dark solid which was dissolved in methanol (150 ml) and the solution was refluxed overnight in the presence of a few drops of conc. H_2SO_4. The cooled reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate, the methanol was evaporated off, and the residue was extracted with ethyl acetate (3 × 100 ml). The organic layer was washed with brine, dried, and evaporated to afford the crude β-amido ester (**15**) which was further purified by passage through a silica gel column (50 g) and eluted with 1:9 ethyl acetate–hexane mixture to yield (73%) pure ester (**15**), m.p. 81 °C; $\nu_{max.}$(Nujol) 3 200, 1 720, and 1 640 cm^{-1}; $\delta_H(CDCl_3)$ 7.35—7.8 (5 H, m), 6.6 (1 H, br d), 5.95—5.35 (2 H, m), 5.05 (1 H, br), 4.9 (1 H, d, *J* 2 Hz), 3.7 (3 H, s), 3.5 (3 H, s), and 1.7 (3 H, d, *J* 5 Hz) (Found: C, 64.9; H, 6.8; N, 4.9. $C_{15}H_{19}NO_4$ requires C, 64.98; H, 6.86; N, 5.05%).

3-*Benzamido*-5-*hydroxy*-2-*methoxyhexan*-4-*olides* (**18**) *and* (**19**).—To a solution of the ester (**15**) (2.8 g, 10 mmol) in aqueous acetone (30 ml) (acetone–water 2:1) was added osmium tetraoxide (*ca.* 25 mg) and *N*-methylmorpholine *N*-oxide (1.2 g, 10 mmol). The solution was stirred for 24 h. Then another batch (1.2 g, 10 mmol) of *N*-methylmorpholine *N*-oxide was added and the mixture was stirred for an additional 24 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was chromatographed over a silica gel column which was eluted with hexane–ethyl acetate (1:1) to obtain the two isomeric lactones (**18**) and (**19**) (1:2 proportions) in 67% yield.

Spectral data for compound (**18**): m.p. 171 °C; $\nu_{max.}$(Nujol) 3 400, 3 290, 1 770, 1 655, and 1 530 cm^{-1}; δ_H([$^2H_6$]acetone) 8.15 (1 H, br d), 8.0—7.4 (5 H, m, ArH), 4.9 (1 H, m), 4.6 (2 H, m), 4.5 (1 H, d, *J* 6 H), 4.05 (1 H, m), 3.6 (3 H, s), and 1.25 (3 H, d, *J* 7 Hz); δ_C ([$^2H_6$]acetone) 173.46, 167.35, 133.59, 131.68, 128.36, 127.46, 80.74, 76.95, 63.42, 57.74, 54.07, and 19.26 p.p.m.; FAB *m/z* 280 $(M + 1)^+$ (Found: C, 60.1; H, 6.3; N, 4.9. $C_{14}H_{17}NO_5$ requires C, 60.21; H, 6.09; N, 5.02%).

Spectral data for compound (**19**): m.p. 142 °C; $\nu_{max.}$(Nujol) 3 400, 3 290, 1 780, 1 655, and 1 540 cm^{-1}; δ_H ([$^2H_6$]acetone) 8.44 (1 H, br d), 8.0—7.5 (5 H, m), 4.9 (1 H, q, *J* 8.4 Hz), 4.65 (1 H, d, *J* 9.6 Hz), 4.35 (1 H, dd, *J* 8.4 and 3 Hz), 4.3 (1 H, d, *J* 10 Hz), 3.95 (1 H, m), 3.6 (3 H, s), and 1.25 (3 H, d, *J* 7 Hz); δ_C ([$^2H_6$]acetone) 170.26, 164.59, 131.79, 129.70, 126.45, 125.23, 80.46, 77.60, 62.77, 55.45, 49.97, and 17.11 p.p.m.; FAB ms *m/z* 280 $(M + 1)^+$ (Found: C, 59.9; H, 6.1; N, 4.8%).

trans-1-(4-*Methoxyphenyl*)-3-*phenylthio*-4-(*prop*-1-*enyl*)-*azetidin*-2-*one* (**20a**).—To a constantly stirred, refluxing solution of potassium(phenylthio)acetate (4.1 g, 20 mmol), triethylamine (5.5 ml, 40 mmol), and *N*-(but-2-enylidene)-*p*-anisidine (1.75 g, 10 mmol) in carbon tetrachloride (100 ml) was added dropwise a solution of cyanuric chloride (2.76 g, 15 mmol) in carbon tetrachloride (100 ml) under nitrogen. The reaction mixture was refluxed for 8—10 h, cooled, and extracted successively with saturated aqueous sodium hydrogen carbonate (3 × 50 ml) and brine (3 × 50 ml), dried (Na_2SO_4), and stripped of solvent to yield a dark, gummy solid. After chromatography over a Florisil column, yellow, crude β-lactam was obtained which, on further chromatography on a silica gel column and elution with ether–hexane, gave the pure β-lactam (**20**) as an oil, yield 29%; $\nu_{max.}$ (neat) 1 740 and 1 590 cm^{-1}; $\delta_H(CDCl_3)$ 7.6—6.7 (9 H, m, ArH), 6.5—5.3 (2 H, m), 4.25 (1 H, d, *J* 2 Hz), 4.15 (1 H, m), 3.7 (3 H, m), and 1.7 (3 H, d, *J* 7 Hz); CIMS (He reagent gas) *m/z* 325 $(M + 1)^+$.

trans-1-(4-*Methoxyphenyl*)-3-*phenylthio*-4-*styrylazetidin*-2-*one* (**20b**).—This was prepared from the Schiff's base derived from cinnamaldehyde and *p*-anisidine, potassium(phenylthio)acetate, cyanuric chloride and triethylamine in 32% yield as an oil; $\nu_{max.}$(Nujol) 1 745 cm^{-1}; $\delta_H(CDCl_3)$ 7.6—6.6 (15 H, m), 6.2 (1 H, dd, *J* 15.5 and 7.0 Hz), 4.65 (2 H, dd, *J* 7 and 2 Hz), 4.15 (2 H, d, *J* 2 Hz) and 3.62 (3 H, s); CIMS (CH_4 reagent gas) *m/z* 388.

cis-1-(4-*Methoxyphenyl*)-4-(α-*methylstyryl*)-3-*phenylthio*-*azetidin*-2-*one* (**20c**).—This was prepared from the Schiff's base derived from *p*-anisidine and 2-methylcinnamaldehyde in 37% yield; m.p. 146 °C; $\delta_H(CDCl_3)$ 7.6—6.8 (14 H, m, ArH), 6.6 (1 H, s), 4.9 [2 H, m, resolves into two doublets having *ca.* 5.4 Hz coupling on addition of Pr(fod)$_3$], 3.8 (3 H, s), and 1.98 (3 H, s) (Found: C, 75.0; H, 5.9; N, 3.5; S, 8.2. $C_{25}H_{23}NO_2S$ requires C, 74.81; H, 5.73; N, 3.49; S, 7.98%).

1-(4-*Methoxyphenyl*)-4-(*prop*-1-*enyl*)*azetidin*-2-*one* (**21a**).—To a solution of the β-lactam (**20a**) (0.325 mg, 1 mmol) in acetone (50 ml) was added prewashed, freshly prepared, activated W_2 Raney nickel (4.0 g). The mixture was refluxed and stirred for 30 min, cooled to room temperature, and filtered. The acetone was evaporated off under reduced pressure from the filtrate and the crude residue was purified by preparative t.l.c. to give 160 mg of the pure β-lactam (**21a**) (160 mg, 73.7%), $\nu_{max.}$ (neat) 1 740 cm^{-1}; $\delta_H(CDCl_3)$ 7.3—6.8 (4 H, dd, ArH), 6.1—5.2 (2 H, m), 4.35 (1 H, br), 3.75 (3 H, s), 3.3 (1 H, dd, *J* 15 and 6 Hz), 2.7 (1 H, dd, *J* 15 and 2 Hz), and 1.7 (3 H, d, *J* 6 Hz).

4-(*Prop*-1-*enyl*)*azetidin*-2-*one* (**22a**).—This was obtained in 59% yield as an oil by the reaction of cerium(IV) ammonium nitrate with the β-lactam (**21a**); $\nu_{max.}$ (neat) 3 220 and 1 750 cm^{-1}; $\delta_H(CCl_4)$ 7.52 (1 H, br), 6.20—5.22 (2 H, m), 4.43 (1 H, br), 3.3 (1 H, dd, *J* 15 and 6 Hz), 2.6 (1 H, dd, *J* 15 and 2 Hz), and 1.7 (3 H, d, *J* 6 Hz).

Acknowledgements

We are indebted to the Stanley Funds and Stevens Institute of Technology for the support of this research, and to Dr. F. T. Jones, Dean J. Fajans, and Dean S. Sylvester for their interest.

1 For Part 73 see A. K. Bose, M. S. Manhas, J. M. van der Veen, S. S. Bari, D. R. Wagle, V. R. Hegde, and L. Krishnan, *Tetrahedron Lett.*, 1985, **26**, 33.

2 M. S. Manhas, S. G. Amin, and A. K. Bose, *Heterocycles*, 1976, **5**, 669; T. Kamiya in 'Recent Advances in the Chemistry of β-lactam Antibiotics,' Cambridge University Press, London, 1976, p. 281.

3 'Topics in Antibiotic Chemistry,' ed. P. G. Sammes, Ellis Horwood Limited, Chichester and London, 1977, vol. 1.

4 J. D. Dutcher, *Adv. Carbohydr. Chem.*, 1963, **18**, 259.

5 A. B. Foster and D. Horton, *Adv. Carbohydr. Chem.*, 1959, **14**, 213.

6 S. Umezawa, *Adv. Carbohydr. Chem.*, 1974, **30**, 111.

7 A. K. Bose, Y. H. Chiang, and M. S. Janhas, *Tetrahedron Lett.*, 1972; 4091; A. K. Bose, G. Spiegelman, and M. S. Manhas, *ibid.*, 1971, 3167.

8 D. R. Kronethal, C. V. Han, and M. K. Taylor, *J. Org. Chem.*, 1982, **47**, 2765.

9 M. S. Manhas, A. K. Bose, and M. S. Khajavi, *Synthesis*, 1981, 290.

10 T. Mukaiyama, Y. Goto, and S. Shoda, *Chem. Lett.*, 1983, 671.

11 T. Hiyama, K. Nishide, and K. Kobayashi, *Tetrahedron Lett.*, 1984, **25**, 569.

12 T. Mukaiyama, T. Miwa, and T. Nakatsuka, *Chem. Lett.*, 1982, 145.

13 I. Dyong and H. Bendlin, *Chem. Ber.*, 1978, **111**, 1677.

14 I. Dyong and H. Bendlin, *Chem. Ber.*, 1977, **110**, 2721.

15 H. Grisebach, W. Hufheinz, and N. Doerr, *Chem. Ber.*, 1963, **96**, 1823.

16 G. Fronaz, C. Fuganti, P. Grasselli, and G. Marinoni, *Tetrahedron Lett.*, 1975, 3883.

17 P. Goebel and K. Clauss, *Justus Liebigs Ann. Chem.*, 1969, **122**, 722; E. J. Moriconi and E. J. Mayer, *J. Org. Chem.*, 1971, **36**, 2841.

18 F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, 1981, **46**, 227; F. M. Hauser, R. P. Rhee, and S. R. Ellenberger, *ibid.*, 1984, **49**, 2236.

19 Presented at the 188th ACS National Meeting at Philadelphia, Pennsylvania, August 26—31, 1984, ORGN-116; A. K. Bose, M. S. Manhas, J. M. van der Veen, S. S. Bari, D. R. Wagle, V. R. Hegde, and L. Krishnan, *Tetrahedron Lett.*, in the press.

Received 12*th December* 1984; *Paper* 4/2104