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A CONVENIENT SYNTHESIS OF α-AMINO-β-LACTAMS[1,a]

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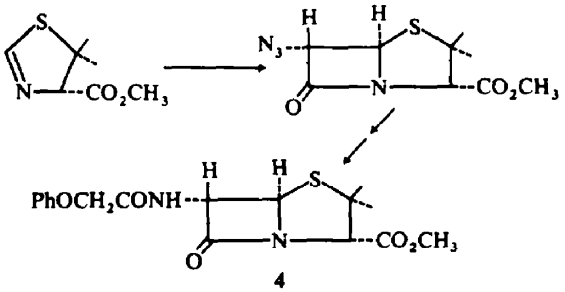
Abstract—A safe and convenient method is described for the synthesis of α-amido-β-lactams starting with glycine and an azomethine. The amino group of glycine is protected by reaction with a β-dicarbonyl compound following the method of Dane *et al.* and the carboxyl group is activated through the formation of a mixed anhydride or an active ester. Condensation between these glycine derivatives and acyclic or cyclic imino compounds (including thioimidates) in presence of triethylamine leads to stereospecific synthesis of 3-(β-carbonyl-vinylamino)-2-azetidinones in 40–60% yield. The vinylamino side chain can be hydrolyzed under mild acid conditions to form 3-amino-2-azetidinones which can be acylated to α-amido-β-lactams. Alternatively, the vinylamino side chain can be converted to an amido side chain by ozonolysis. The molecular parameters of a 3-(β-carbonyl-vinylamino)-2-azetidinone were determined by X-ray crystallography. Usefulness of this α-amido-β-lactam synthesis is illustrated by the preparation of isotope-labeled β-lactams and intermediates for some β-lactam antibiotics.

Penicillins, cephalosporins and other major β-lactam antibiotics in clinical use are characterized by the presence of a 3-amido-2-azetidinone unit. Therefore, synthetic approaches to them and their analogs require an easy access to α-amido-β-lactams under conditions that will not cleave or rearrange the β-lactam ring. To be of practical value such synthetic methods should be safe and economical when attempted on a large scale.

α-Azido-β-lactam approach

In 1967 we[2] reported a method for the synthesis of α-amido-β-lactams that utilizes an azido group as a cryptoamino function. The first step in this synthesis is the reaction between azidoacetyl chloride (**1**) (or mixed anhydride or an active ester) and an azomethine (**2**) in presence of a tertiary amine to produce an α-azido-β-lactam (**3**). Reduction of the azido group and subsequent acylation can be conducted under mild conditions that do not affect the β-lactam ring.

This method was used in our laboratory for a stereospecific, total synthesis of a 6-epi-penicillin ester[3] (**4**).



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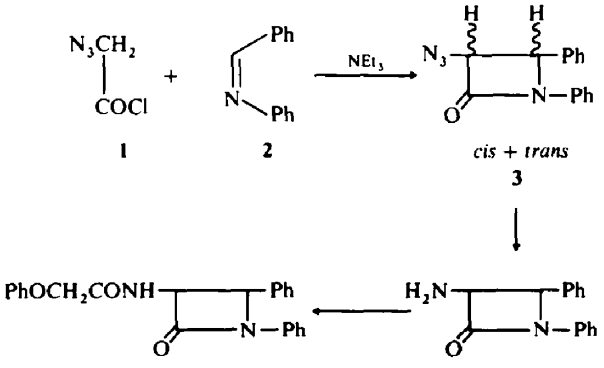
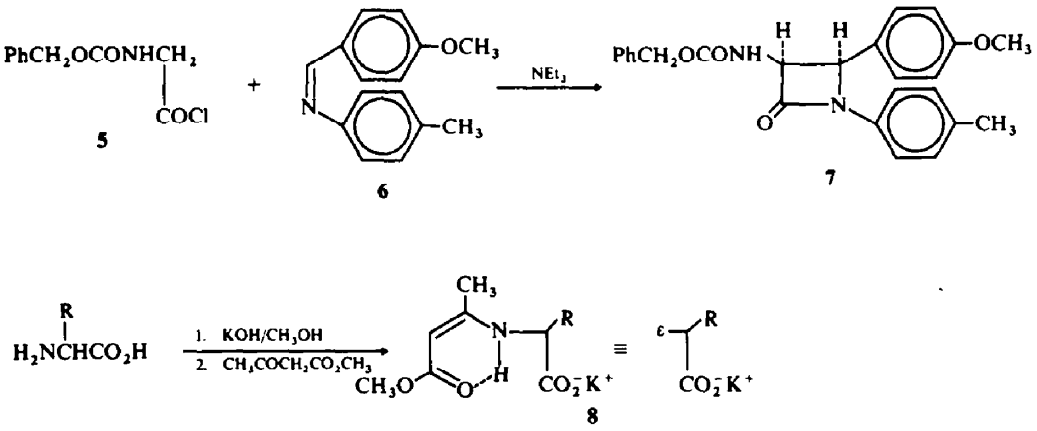
Many other laboratories[4] have adopted the α-azido β-lactam approach for the total synthesis of diverse types of β-lactam antibiotics including penicillins, cephalosporins and nocardicins.

The α-azido-β-lactam approach suffers from a disadvantage in that it is unsuitable for use on a large scale because of the potential of azidoacetic acid and its derivatives for explosive decomposition. To avoid the use of hazardous chemicals, we have attempted to



1 **2** *cis + trans* **3**

* Dedicated to the memory of Robert Burns Woodward, this paper will be included in the Book version of the special Woodward Memorial Supplement.



devise alternative methods for the synthesis of 3-amino-2-azetidinones.

One step α-carbamato-β-lactam synthesis

We[5] have found that N-carbobenzyloxyglycyl chloride (**5**) reacts with a Schiff base (**6**) and a tertiary amine to produce a *cis*-β-lactam (**7**) with a carbamate side chain. Alternatively, t-BOC-glycine can be used in the form of a mixed anhydride in place of N-carbobenzyloxyglycine. The carbamate group can be converted to an amino group under mild conditions. This method has received very limited attention so far.[6] The starting glycine derivatives are not very economical for large scale use.

α-Vinylamino-β-lactam approach

Continuing our search for a safe and economical synthesis of α-amido β-lactams we have investigated the possibility of using a protective group developed by Dane *et al.*[7] for peptide synthesis. The key to this approach is the easy formation of a "Dane salt" (**8**) by allowing methanol solution of the potassium salt of an α-amino acid to react with a β-dicarbonyl compound, for example, methyl acetoacetate. The protective group can be removed efficiently under very mild acid treatment.

Synthesis of 3-(β-carbonyl-vinylamino)-2-azetidinones. We[8] have discovered that Dane salts from glycine can be allowed to react with a chloroformate ester first and then with a Schiff base and triethylamine to produce 3-(β-carbonyl-vinylamino)-2-azetidinones in 40–60% yield. The annelation reaction is stereospecific—only *cis*-β-lactams (**9**) were formed with the Schiff bases studied.

The protective group could be removed by treatment with a weak acid such as, p-toluenesulfonic acid monohydrate to afford *cis*-3-amino-2-azetidinones (**10**) which could be acylated to the desired α-amido-β-lactams (**11**).

We have studied several aspects of this new synthesis of α-amido-β-lactams. Some of our findings are presented here.

Scope of the reaction. There are four essential components of this β-lactam forming reaction each of which is considered below.

(a) *α-Amino acid.* Dane salts from alanine and phenylalanine have been used before for the preparation of esters and peptides. We were unsuccessful in obtaining any β-lactam from the reaction of these two N-protected amino acid salts, ethyl chloroformate, triethylamine and benzalaniline. Under identical conditions the Dane salts from glycine afforded α-vinylamino-β-lactams but the yield did not exceed 60%. The other reaction products have not been identified but it is known that vinylamino ketones are multifunctional, reactive molecules capable of undergoing various types of reaction.

Auricchio *et al.*[9] have reported the formation of substituted aniline as well as pyridine derivatives from 4-ethylamino-3-penten-2-one.

Gupta[10] has found that vinylamino acid salts and alkyl chloroformates react together to produce 1,3-oxazolidin-5-ones in high yield.

In another communication Gupta[11] has reported

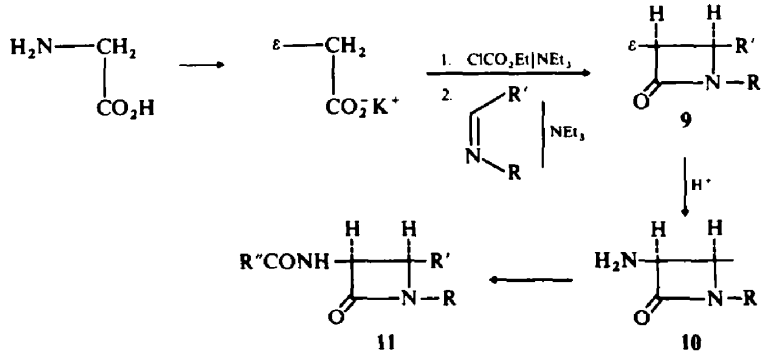
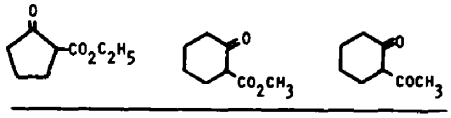


Table 1. β-Dicarbonyl compounds used for β-lactam synthesis R–CO–CH_2–CO–R′

	R	R′
(a)	CH_3	OCH_3
(b)	CH_3	OC_2H_5
(c)	CH_3	$OC(CH_3)_3$
(d)	CH_3	CH_3
(e)	C_6H_5	CH_3



that vinyl-amino acid salts react with trifluoroacetic anhydride to produce pyrrole derivatives.

(b) *β-Dicarbonyl compounds.* Probably the most economical β-dicarbonyl compounds to use for preparing Dane salts from glycine are ethyl and methyl acetoacetates. The size of the ester group does not appear to affect the ring closure reaction: the t-butyl ester of acetoacetic acid produces about the same yield of β-lactam as the methyl ester. Table 1 shows the various β-dicarbonyl compounds used as the protective group for the synthesis of 3-(β-carbonyl-vinyl-amino)-2-azetidinones.

Cyclic β-keto esters also can be used, as can substituted acetoacetate esters, for example, methyl phenylacetoacetate.

β-Diketones, such as acetylacetone and benzoyl-acetone can be employed but β-lactam formation is slower and the yield is smaller.

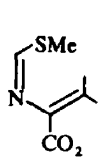
(c) *Reagents for activating the carboxyl group of N-protected glycine.* Haloformate esters, such as, methyl, ethyl, isobutyl or t-butyl chloroformate, in presence of triethylamine were found to be suitable for activating the carboxyl group of the β-carbonyl-vinylamino acetic acid salts. Chloroacetonitrile which has been employed for peptide bond formation reaction of Dane salts was found to be ineffective for β-lactam synthesis.

Table 2 shows the yield of β-lactam obtained from one imino compound using a number of activating agents for the carboxyl group.

Sharma and coworkers[12] have shown that phosphorus oxychloride and triethylamine are suitable for producing β-lactams from "Dane salt" and imino compounds.

An activating agent that is economical as well as very effective is cyanuric chloride. The work-up procedure is easy and the β-lactam product is usually quite pure.[13]

(d) *Azomethines.* We have tested a number of imino compounds (Tables 3a and 3b) and found that the rate of β-lactam formation can vary considerably, but, in every case we have obtained only a single isomer of the β-lactam. Thioimidates (**12**) can also serve as the imino component for the stereoselective β-lactam forming reaction. With Schiff bases the stereochemistry of the β-lactam was *cis*, while with thioimidates only the *trans* isomer (**13**) was formed.



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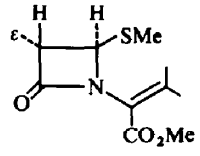

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Bicyclic and tricyclic β-lactams were prepared from cyclic imino compounds (Table 3a, b). The β-lactam formation was again stereospecific but it was not possible in most cases to deduce the stereochemistry of the β-lactam from ^{1}H NMR spectra.

Table 2. Some reagents for activating carboxyl groups

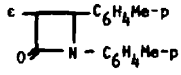
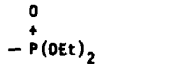
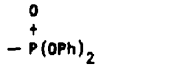
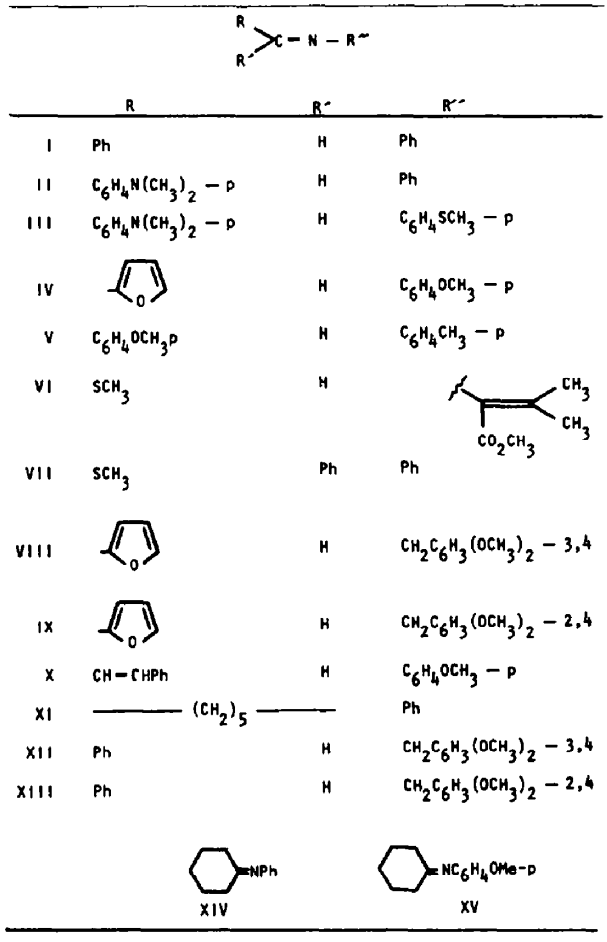
Condensing Agents	Yield of β-lactam
	
ClCO$_2$Me + NEt$_3$ ClCO$_2$Et + NEt$_3$ ClCO$_2$CH$_2$CHMe$_2$ + NEt$_3$ ClCO$_2$CMe$_3$ + NEt$_3$	40 - 60%
	30%
	20%
$(CF_3CO)_2O$	5%

Table 3(a). Some acyclic imines used for β-lactam synthesis

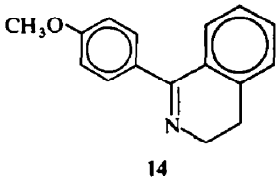


X-ray crystallography of a vinylamino-β-lactam. In the case of the vinylamino-β-lactam (**15**) prepared from the bicyclic imine (**14**), we carried out single crystal X-ray diffraction study to determine the stereochemistry as well as exact molecular parameters. This compound crystallizes as clear, colorless prisms. A crystal having the dimensions 0.30 × 0.30 × 0.30 mm was used for data collection.

Crystal data: $C_{24}H_{26}N_2O_4$, M = 406.5. Monoclinic, $a = 8.913\,(2), b = 9.608\,(2), c = 25.517\,(5)$ Å, $\beta = 96.16\ (2)^0$, Dc = 1.24 g/cm^3, Z = 4. Space Group $P2_1/c$ (hO1:1 = 2n + 1 absent). Ni—filtered CuK_α radiation, $\lambda = 1.5418$ Å, $\mu\,(CuK_\alpha) = 6.98\,cm^{-1}$.

The structure was solved using the direct phasing program *Multan*.[14] The resulting E-map revealed 28 of the 30 non-hydrogen atoms. A difference–electron density map obtained from this phasing model showed the remaining two atoms, as well as the fact that one of these was clearly disordered. Since the two peaks labelled C (17) and C (117) corresponding to this disordered methyl were of equal size, each was assigned an occupation factor of 0.5. Subsequent refinement of these occupation factors gave unreliable results, (probably due to additional disorder in their positions, as evidenced by their high and unsymmetrical thermal parameters) and so the occupation factors were fixed at 0.5.

Full matrix least-squares refinement using isotropic and then anisotropic thermal parameters resulted in an R-factor of 11.3%. The hydrogen atom



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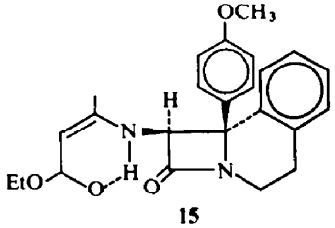

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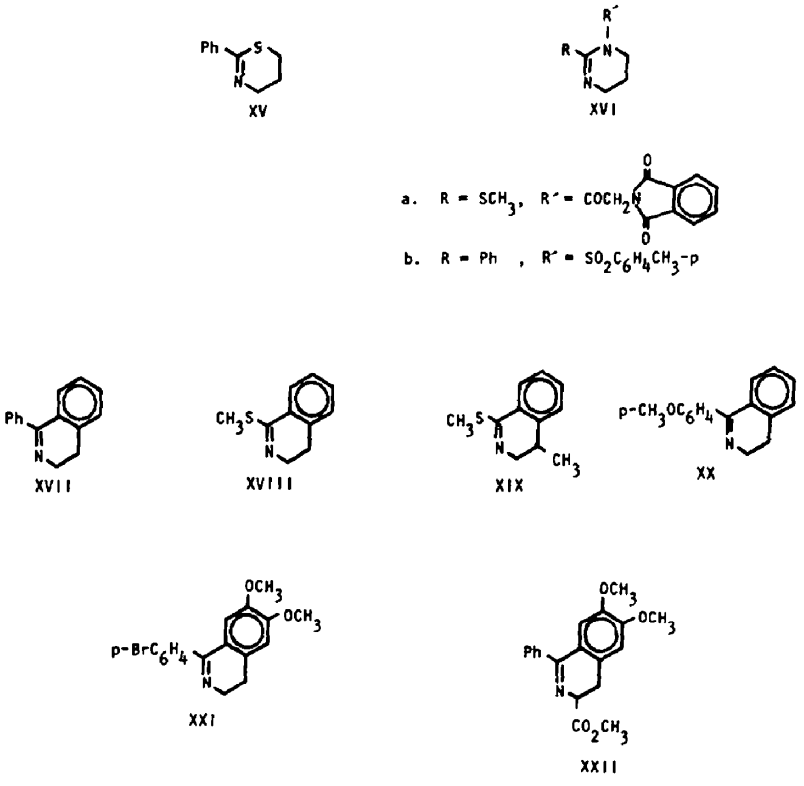
Table 3(b). Some cyclic imines used for β-lactam synthesis



positions were then calculated, when possible, from known atom positions, or else were located on difference electron density map, the hydrogen atoms labelled H (116A) and H (116B) were calculated using the coordinates of C (117). Their positional and thermal parameters were held constant during subsequent refinement, which gave a final R-factor of 9.4% and a weighted R (using unitary weights) of 10.8%. Adopting the weighting scheme:

$$W = [\sigma_F^2 + (0.009F)^2]^{-1}$$

further refinement resulted in an R-factor of 8.8% and a weighted R of 12.9%. H atom positions were not refined as they drifted too much from their original positions.

An ORTEP drawing of the molecule is shown in Fig. 1. Final positional parameters are shown in Table 4a, b. There is a H-bond between atoms N (2) and O (2) with the following parameters.

N(2) – O(2) 2.712(2) Å
H(N2) – O(2) 1.923 Å
∠ N(2) – H(N2) – O(2) 117.2°

The 6-member ring defined by O(2), C (15), C (14), C(13), N(2), H(N2), is planar with the average deviation from planarity of 0.023 Å.

The β-lactam ring defined by N (1), C (2), C (3), C (4) is planar with an average distance from the plane of 0.023 Å. The N (1) atom however lies 0.17 Å above the plane defined by its three substituents. In biologically active penicillins and cephalosporins this nitrogen is 0.40 Å above the equivalent plane and this has been proposed as an essential condition for antibiotic activity.[15]

The X-ray structure established the vinyl amino structure of **15** rather than that of the imine tautomer. This was confirmed by subsequent oxidation of the double bond to yield an amide. The amino groups and anisyl groups are in *cis* configuration as shown in Fig. 1.

Some applications of the α-vinylamino-β-lactam synthesis. (a) *Synthesis of intermediates for β-lactam antibiotics.* In a previous publication we have reported the synthesis of N-unsubstituted *cis*-3-amido-2-azetidinones (**16a**) by using the α-vinyl amino approach[8b] (Scheme 1).

We have also prepared **17** which we have converted to a key intermediate (**16b**) for the synthesis of isocephalosporins by our method.[16] (Scheme 2.)

The α-vinylamino-β-lactam approach has also been used for the synthesis of an intermediate (**18**) for nocardicins.

The thioimidate ester (**12**)[17] which is readily obtained from penicillin was used as the imino component for condensation with the Dane salt. A single isomer of the α-vinylamino-β-lactam (**13**) was

Table 4(a). Fractional atomic coordinates for hydrogen atoms with estimated standard deviations in parentheses

ATOM	X	Y	Z
H N2	.2621	.6878	.0521
H 3	.1334	.7753	.1478
H 5A	.4840	.3979	.2077
H 5B	.4036	.5015	.2544
H 6A	.2617	.2682	.1872
H 6B	.2647	.2928	.2558
H 8	.0079	.3049	.2741
H 9	-.2448	.4084	.2563
H 10	-.3019	.5748	.1846
H 11	-.1003	.6405	.1278
H 14	.1913	1.0393	.0014
H 16A	.3733	.7547	-.1123
H 16B	.1775	.7271	-.1262
H 17A	.1557	.9404	-.1755
H 17B	.3516	.9680	-.1615
H 17C	.2845	.8234	-.1999
H 18A	.2380	.9930	.1390
H 18B	.1580	1.1020	.0880
H 18C	.0450	.9660	.1120
H 20	-.0273	.4261	.0730
H 21	-.0035	.3008	-.0109
H 23	.4757	.3449	.0131
H 24	.4528	.4694	.0981
H 25A	.4411	.3193	-.0722
H 25B	.4469	.1571	-.0397
H 25C	.3814	.1685	-.1066
H 116A	.2811	.6987	-.1073
H 116B	.1715	.8101	-.1510
H 117A	.3866	.9649	-.1530
H 117B	.4962	.8536	-.1092
H 117C	.4231	.7920	-.1724

Table 4(b). Fractional atomic coordinates for non-hydrogen atoms with estimated standard deviations in parentheses

ATOM	X	Y	Z
O 1	0.4570(2)	0.7670(2)	0.19236(8)
O 2	0.2726(2)	0.7109(2)	-0.02231(6)
O 3	0.2379(3)	0.8953(2)	-0.07616(7)
O 4	0.2378(2)	0.2498(2)	-0.05076(6)
N 1	0.3356(2)	0.5532(2)	0.17551(7)
N 2	0.2300(2)	0.7602(2)	0.07973(7)
C 2	0.3605(3)	0.6909(3)	0.17104(8)
C 3	0.2173(2)	0.7098(2)	0.13190(8)
C 4	0.1955(2)	0.5483(2)	0.13891(8)
C 5	0.3811(3)	0.4497(3)	0.2158(1)
C 6	0.2533(3)	0.3458(3)	0.2176(1)
C 7	0.0982(3)	0.4114(3)	0.2099(1)
C 8	-0.0154(4)	0.3771(4)	0.2414(1)
C 9	-0.1573(4)	0.4365(4)	0.2320(1)
C 10	-0.1881(3)	0.5290(3)	0.1921(1)
C 11	-0.0762(2)	0.5669(2)	0.16021(9)
C 12	0.0662(2)	0.5085(2)	0.16968(8)
C 13	0.2027(3)	0.8926(2)	0.06270(9)
C 14	0.2126(3)	0.9308(2)	0.0120(1)
C 15	0.2438(3)	0.8347(3)	-0.02854(9)
C 16	0.2668(6)	0.8086(4)	-0.1196(1)
C 17	0.274(2)	0.893(1)	-0.1664(3)
C 18	0.1646(5)	0.9972(3)	0.1026(1)
C 19	0.2097(2)	0.4601(2)	0.09050(8)
C 20	0.837(2)	0.4096(2)	0.05958(8)
C 21	0.0973(2)	0.3388(2)	0.01350(8)
C 22	0.2386(2)	0.3170(2)	-0.00357(8)
C 23	0.3657(2)	0.3645(2)	0.0269(1)
C 24	0.3510(2)	0.4337(2)	0.07359(9)
C 25	0.3802(4)	0.2233(4)	-0.0695(1)
C 117	0.393(2)	0.860(1)	-0.1419(6)

obtained. Hydrolysis of the side chain with *p*-toluenesulfonic acid monohydrate in acetone–water followed by acylation with phenyl-acetyl chloride provided the amido-β-lactam (**19**). Proton NMR studies established the *trans* stereochemistry of this β-lactam ($J_{3,4}$ = 1.5 Hz).

Raney nickel hydrogenation led to the desulfurized product (**20**). To obtain the corresponding N-unsubstituted β-lactam, Stoodley's method was used. Treatment of **20** with N-bromosuccinimide under acidic conditions led to the bromohydrin in excellent yield. Subsequent treatment with triethylamine provided the desired lactam **18** in 87% yield. Intermediates such as **18** may be N-alkylated by known methods to nocardicin analogs.[19]

(b) *Synthesis of stable isotope labeled β-lactams.* Concern over radiation hazard from radio isotope labeled compounds for studies in the human—especially, children and women of child-bearing age is reflected in the growing interest in stable isotope labels

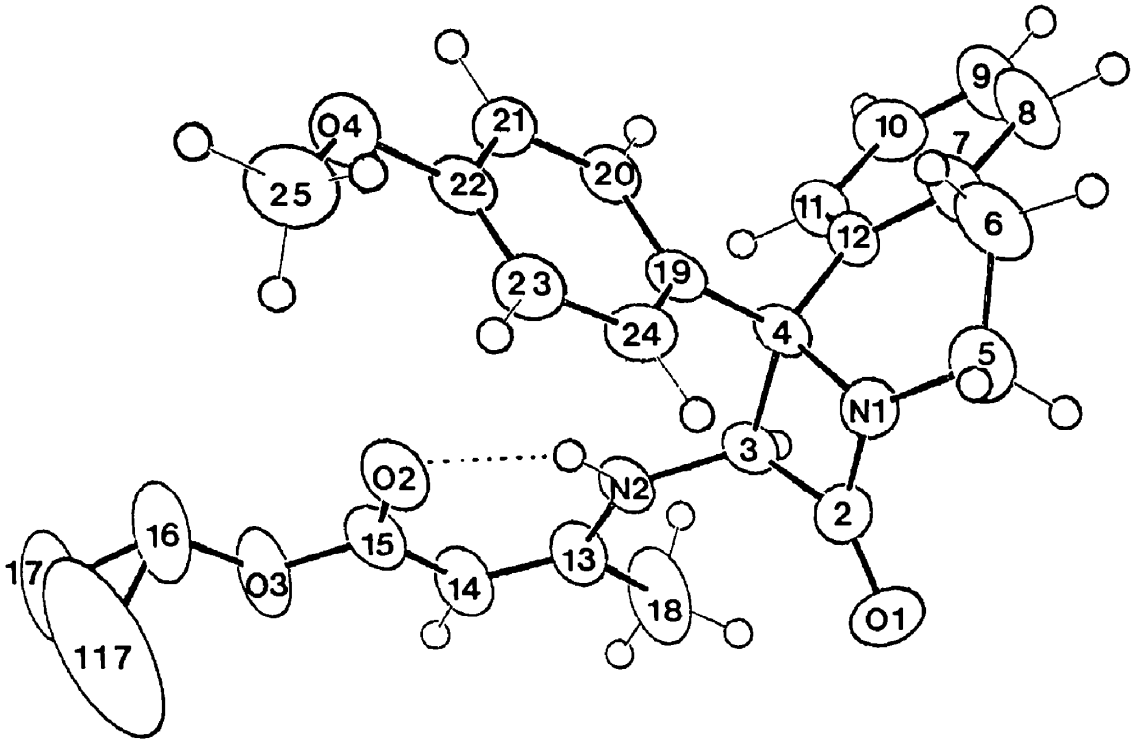
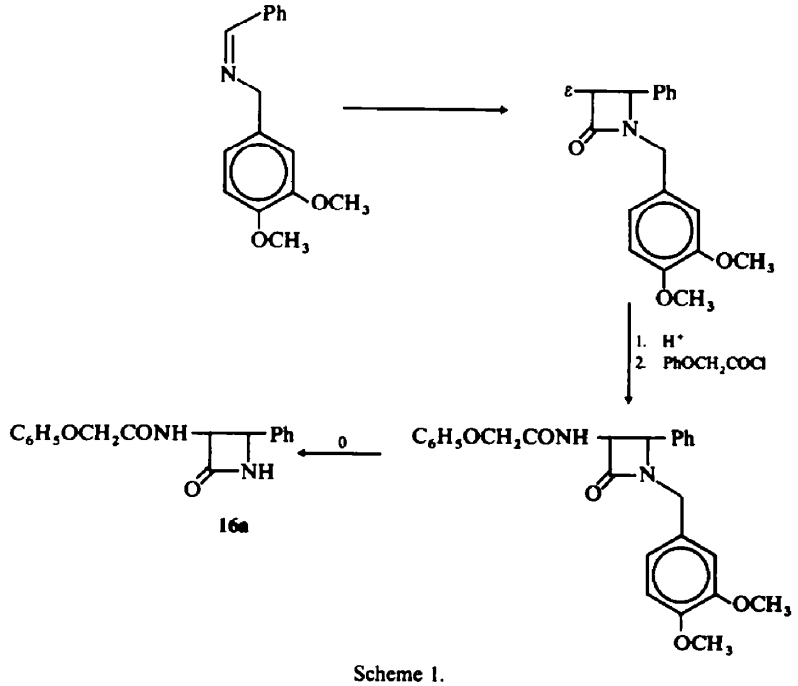
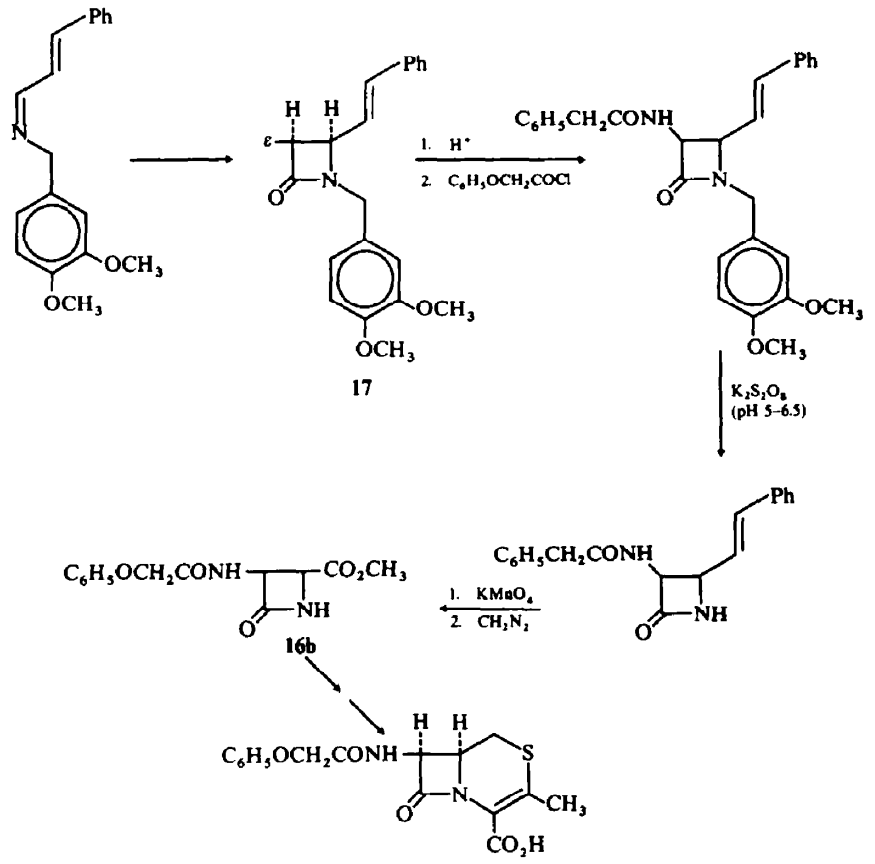


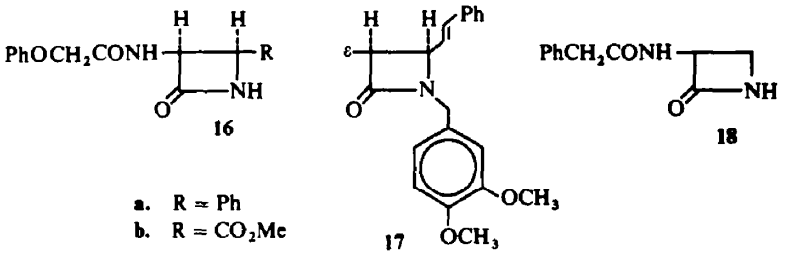
Figure 1.

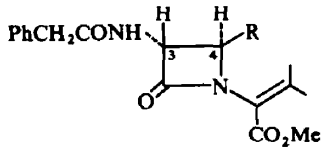


Scheme 1.

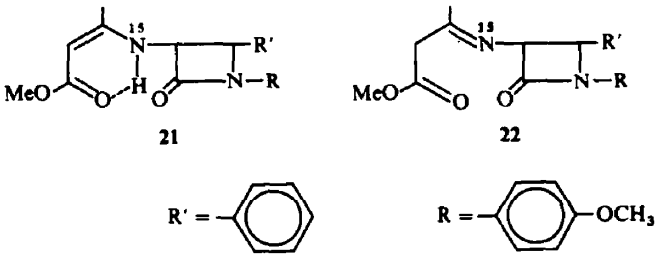


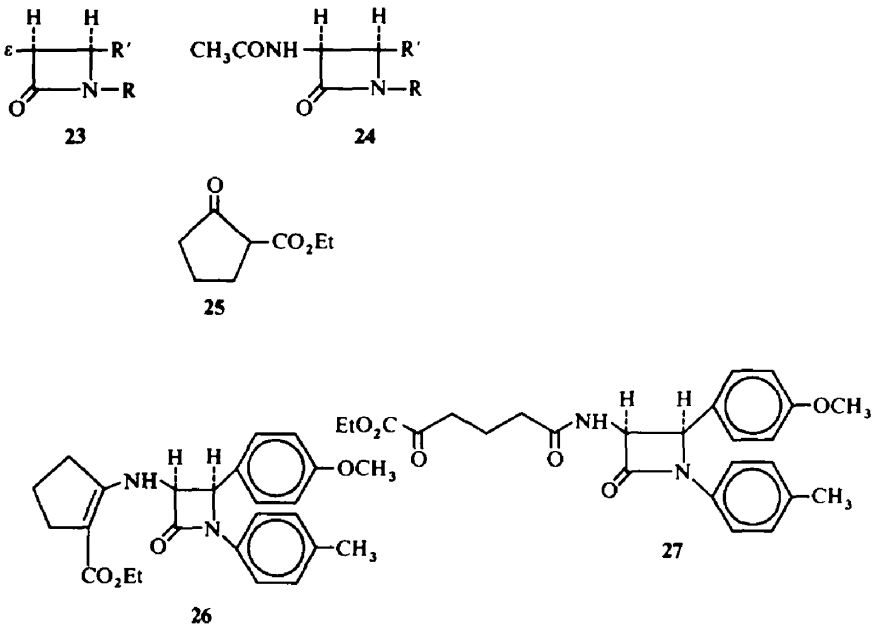
Scheme 2.





19 R = SMe
20 R = H





for metabolic and diagnostic studies. The α-vinylamino-β-lactam synthesis provides a convenient and economical route to α-amino-β-lactams bearing one or more stable isotope labels (^{13}C, ^{2}H, ^{15}N, ^{18}O).

Glycine is commercially available with high levels of stable isotopes. When we condensed the "Dane Salt" from [^{15}N]-glycine with benzylidene-p-anisidine, a labeled β-lactam (**21**) was obtained in about 60% yield. Study of the ^{1}H and ^{13}C NMR spectra of this ^{15}N-labeled β-lactam allowed us to determine that in solution the β-lactam (**21**) exists in a β-oxovinylamine structure rather than the alternative β-oxoimino structure **22**. As mentioned in an earlier section, X-ray diffraction studies have shown that the oxovinylamine structure is favored in the solid state also. A practical use of this structural feature is described in the next section.

(c) *Shortened route to α-amido-β-lactams.* The α-vinylamino-β-lactam structure can be converted to an α-amido-β-lactam in two steps as described earlier. It is possible, however, to obtain an α-amido-β-lactam (**24**) in one step from **23** by ozonation[20] since **23** exists in the β-carbonyl-vinylamino form.[21]

When a cyclic β-keto ester, such as **25**, was employed as the dicarbonyl component, β-lactams of the type **26** were obtained.[20] Ozonation of such vinylamino-β-lactams led to **27** containing an amide side chain with an α-keto ester as an additional functional group. Such α-keto acids can be converted to α-amino acids by known methods. Thus, access to cephalosporin C type of side chain becomes available.

CONCLUSIONS

The synthesis of α-amido β-lactams described here has several advantages over the α-azido-β-lactam approach.

The synthesis of α-amido-β-lactams via 3-(β-carbonyl-vinylamino)-2-azetidinones is a convenient and economical process that can be conducted on a large scale without hazard. The stereospecificity of the annelation reaction is a further advantage in planning synthesis of monocyclic and polycyclic β-lactams. The commercial availability of glycine labeled with one or more stable or radio-isotopes simplifies the preparation of β-lactams with multiple labels of high isotope content. The versatility of this new β-lactam synthesis is under active investigation in our laboratory.

EXPERIMENTAL

All m.ps are uncorrected and were determined in open capillary tubes using a "Mel-Temp" apparatus. IR spectra were obtained with a Perkin–Elmer Infracord. PMR spectra were recorded on a Varian EM 390 NMR spectrometer using TMS as an internal standard in $CDCl_3$. Mass spectra were obtained with a Perkin–Elmer RMU-7 mass spectrometer or CIMS-Biospect mass spectrometer.

General method for the synthesis of "Dane salt"

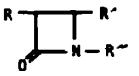
Potassium salt of α-methyl-β-carbomethoxyvinylamino acetic acid. To a soln of KOH (0.25 mol) in anyd MeOH (500 ml) was added 0.25 mol glycine and the mixture stirred till the soln became clear. Methyl aceto-acetate (0.2 mol) was then added to this soln. After 30 min, the solid that separated out was filtered and dried. The title compound was obtained in 75% yield, m.p. 235–237° and was used as such without further purification.

Using the same general conditions, "Dane salts" from other β-keto compounds (see Table 1) were also prepared.

General method for the synthesis of β-lactams

1-(3′,4′-Dimethoxybenzyl)-3-(1′-methyl-2′-carbomethoxy vinylamino)-4-phenyl azetidin-2-one. A soln of St_3N (0.015 mol) in anhyd. ether (10 ml) was added to a stirred suspension of K-salt of α-methyl-β-carbomethyoxyvinylamino acetic acid (0.01 mol) in anhyd. ether (5 ml) at −25° under N_2. To this suspension was added dropwise a soln of ethyl chloroformate (0.015 mol) in ether (10 ml). The mixture was allowed to stir at this temp. for 15 min, followed by a dropwise addition of a soln containing 0.01 mol Schiff base (derived from benzaldehyde and 3,4-dimethoxybenzylamine) and 0.015 mol Et_3N in 100 ml CH_2Cl_2 over a period of 1 hr. The mixture was stirred for 2 hr at 0° and then for 10–12 hr at room temp. The mixture was filtered, and the residue washed

Table 5. Analytical and spectral data on monocyclic β-lactams



No.	R	R′	R″	mp °C	Yield	Molecular Formula	Analysis C	H	N	Spectral Data
1	c	Ph	$CH_2C_6H_3(OCH_3)_2$-3,4	155-156	65	$C_{23}H_{26}N_2O_5$	67.25 (67.30)	6.48 (6.38)	6.73 (6.82)	IR: 1740, 1655 cm^{-1}; NMR: 1.7 (s,3H), 3.4 (s,3H), 3.7 (s,3H), 3.8 (s,3H), 4.25 (s,1H), 4.6-5.2 (m,4H) 6.7-7.4 (m,8H), 8.5 (d,1H);mass spec.:M^+ at m/e 410.
2	c	Ph	$C_6H_3(OCH_3)_2$-2,4	135-136	60	$C_{22}H_{24}N_2O_5$	66.49 (66.65)	6.18 (6.10)	7.04 (7.07)	IR: 1740, 1660 cm^{-1}; NMR: 1.9 (s,3H), 3.5 (s,3H), 3.65 (s,3H), 5.2 (q,1H), 5.65 (d,1H), 6.4-7.8 (m,8H), 8.5 (d,1H); mass spec.: M^+ at m/e 396.
3	c		$CH_2C_6H_3(OCH_3)_2$-3,4	116	50	$C_{21}H_{24}N_2O_6$	62.89 (62.99)	6.08 (6.04)		IR: 1740, 1640 cm^{-1}; NMR: 1.8 (s,3H), 3.55 (s,3H), 3.83 (s,3H), 3.86 (s,3H), 4.45 (s,1H), 4.6 (d,1H), 4.7 (q,2H), 5.1 (d,1H), 6.4-7.7 (m,6H), 8.7 (d,1H), mass spec.: M^+ at m/e 400.
4	c		$CH_2C_6H_3(OCH_3)_2$-2,4	100-101	50	$C_{21}H_{24}N_2O_6$	62.98 (62.99)	6.06 (6.04)		IR: 1740, 1650 cm^{-1}; NMR: 1.9 (s,3H), 3.6 (s,3H), 3.75 (s,3H), 3.85 (s,3H), 4.3 (q,2H), 4.7 (s,1H), 4.85 (d,1H), 5.0 (q,1H), 6.3-7.6 (m,6H), 8.8 (d,1H).
5	c	$-C_5H_{10}-$	Ph	164	60	$C_{19}H_{24}N_2O_3$	68.24 (69.49)	7.19 (7.37)		IR: 1740, 1660 cm^{-1}; NMR: 2.15 (s,3H), 1.2-2.1 (m,10H), 3.7 (s,3H), 4.55 (d,1H, J=8 Hz), 4.7 (s,1H), 7.1-7.7 (m,5H), 9.3 (d,1H), J=8 Hz); mass spec.: M^+ at m/e 328.
6	c		$C_6H_4OCH_3$-p	174-175	50	$C_{19}H_{20}N_2O_5$	63.85 (64.04)	5.63 (5.66)	7.74 (7.86)	IR: 1740, 1650, 1600 cm^{-1}; NMR: 2.0 (s,3H), 3.7 (s,3H), 3.85 (s,3H), 4.6 (s,1H), 5.2 (d,1H), 5.4 (m,1H), 6.3-7.6 (m,7H), 8.9 (d,1H); mass spec.: M^+ at m/e 356.
7	$NHCOCH_2OPh$	Ph	$CH_2C_6H_3(OCH_3)_2$-3,4	130	50	$C_{26}H_{26}N_2O_5$	69.79 (69.94)	5.92 (5.87)		IR: 3200, 1750, 1660 cm^{-1}; NMR: 3.8 (s,3H), 3.9 (s,3H), 4.3 (q,2H), 4.9 (s,2H), 5.05 (d,1H), 5.7 (q,1H), 6.7-7.6 (m,14H).
8	$NHCOCH_2OPh$		$CH_2C_6H_3(OCH_3)_2$-3,4	128	50	$C_{24}H_{24}N_2O_6$	66.07 (66.05)	5.52 (5.54)		IR: 3200, 1745, 1660 cm^{-1}
9	$NHCOCH_2Ph$		$CH_2C_6H_3(OCH_3)_2$-3,4	138	60	$C_{24}H_{24}N_2O_5$	68.38 (68.56)	5.80 (5.75)		IR: 3150, 1745, 1640 cm^{-1}; NMR: 3.5 (s,2H), 3.75 (s,3H), 3.85 (s,3H), 4.2 (q,2H), 4.7 (d,1H), 5.6 (q,1H), 6.0-7.5 (m,12H), mass spec.: M^+ at m/e 420.
10	$NHCOCH_2OPh$	$-C_5H_{10}-$	Ph	140	65	$C_{22}H_{24}N_2O_3$	72.49 (72.51)	6.63 (6.64)		IR: 3500, 1765, 1660 cm^{-1}; NMR: 1.3-2.0 (m,10H), 4.55 (s,2H), 5.1 (d,1H), J=8 Hz), 6.9-7.6 (m,11H).

with CH_2Cl_2. The combined organic phase was washed with water and dried ($MgSO_4$). Removal of the solvent provided the title compound in 65% yield, m.p. 155–156° (CH_2Cl_2 + n-hexane).

IR (Nujol): 1740, 1655 cm^{-1}; NMR ($CDCl_3$) δ: 1.7 (s, 3H), 3.4 (s, 3H), 3.7 (s, 3H), 3.8 (s, 3H), 4.25 (s, 1H), 4.6–5.2 (m, 4H), 6.7–7.4 (m, 8H), 8.5 (d, 1H); mass spectrum: M^+ at *m/e* 410. (Found: C, 67.25,, H, 6.48, N, 6.73. Calc. for $C_{23}H_{26}N_2O_5$: C, 67.30, H, 6.38, N, 6.82%.)

Cleavage of vinylaminocarbonyl side chain

1-(3',4'-*Dimethoxy benzyl*)-3-*amino*-4-*phenylazetidin*-2-*one*. A soln of **1g** described above in acetone (15 ml) was treated with 2N HCl (10 ml) and stirred for 15 min at room temp. and filtered. The filtrate was diluted with water, neutralized with Na HCO_3 aq and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to obtain the title compound (520 mg, 65% yield), IR (Nujol), 1730 cm^{-1}. This compound was used as such for the next step.

Acylation of α-amino-β-lactam

1-(3',4'-*Dimethoxy benzyl*)-3-*phenoxyacetamido*-4-*phenylazetidin*-2-*one*. A soln of 0.01 mol of the above α-amino-β-lactam in 20 ml CH_2Cl_2 was stirred with 0.01 mol Et_3N and 0.01 mol phenoxyacetyl chloride at 0°. The mixture was stirred for about 3 hr and filtered through celite. The filtrate was washed with water, dried ($MgSO_4$), concentrated under reduced pressure, and passed through a short Florisil column using CH_2Cl_2 as the eluant. The product crystallized as white needles (CH_2Cl_2-n-hexane) m.p. 130° (50% yield).

IR (Nujol): 3200, 1750, 1660 cm^{-1}; NMR ($CDCl_3$) δ: 3.8 (s, 3H), 3.9 (s, 3H), 4.3 (q, 2H), 4.9 (s, 2H), 5.05 (d, 1H), 5.7 (q, 1H), 6.7–7.6 (m, 14H). (Found: C, 69.79, H, 5.92. Calc. for $C_{26}H_{26}N_2O_5$: C, 69.94, H, 5.87.)

3-*Phenoxyacetamido*-4-*phenylazetidin*-2-*one*. To a refluxing soln of 1-(3',4'-dimethoxy benzyl) β-lactam (0.004 mol) in acetonitrile (100 ml) was added a soln of $Na_2HPO_4 \cdot 7H_2O$ (0.008 mol) and $K_2S_2O_8$ (0.016 mol) in water (50 ml).[22] The progress of the oxidative cleavage was monitored through tlc. The starting N-substituted β-lactam disappeared after approximately 1.5 hr. The acetonitrile was then evaporated under reduced pressure and the aqueous phase extracted with CH_2Cl_2 (2 × 50 ml). The combined organic extract was evaporated to afford the title compound, m.p. 134–136°[23] (yield, 35%).

Using a similar sequence of reactions 3-phenylacetamido-4-phenylazetidin-2-one was also prepared, m.p. 187–188°.[23]

Following essentially the same conditions, **15** was obtained in 80% yield from the Dane salt derived from glycine and ethylacetoacetate and 1-*p*-methoxyphenyl-3, 4-dihydroisoquinoline, m.p. 165°. IR (Nujol): 1750, 1640 cm^{-1}; NMR ($CDCl_3$) δ: 1.15 (t, 3H), 2.0 (s, 3H), 7.5–2.9 (m, 2H), 3.4–3.65 (m, 2H), 3.75 (s, 3H), 3.95 (g, 2H), 4.4 (s, 1H), 5.05 (d, 1H), 6.7–7.5 (m, 8H), 8.6 (d, 1H).

β-Lactam **17** was prepared from the Schiff base derived from cinnamaldehyde and 3,4-dimethoxybenzylamine in 46% yield as a viscous oil. IR (Nujol): 2900, 1720, 1250 cm^{-1}; NMR ($CDCl_3$) δ: 1.9 (s, 3H), 3.7 (s, 3H), 3.9 (s, 6H), 4.35 (dd, 1H, J = 4.5 Hz and 9 Hz), 4.6 (d, 2H, J = 5H), 4.9 (dd, 1H, J = 4.5 Hz and 9 Hz), 6.05 (dd, 1H, J = 9 Hz and 16 Hz), 6.7 (s, 1H), 6.85 (d, 1H, J = 16 Hz), 6.9 (s, 3H), 7.35 (s, 5H), 9,1 (d, 1H, J = 9 Hz).

Using similar reaction conditions, the Dane salt derived from ^{15}N-glycine (Bio–RAD) was used to synthesize **21** in 50% yield, m.p. 165°.

IR (Nujol): 1730, 1655 cm^{-1}; NMR ($CDCl_3$) δ: 1.89 (s, 3H), 3.47 (s, 3H), 3.79 (s, 3H), 4.40 (d, 1H, J = 6 Hz), 6.78–7.50 (m. 9H), 8.52 (dd, 1H, $J_{^{15}N-H}$ = 93 Hz, J_{NH,C_3H} = 9 Hz).

Synthesis of 3-phenylacetamidoazetidin-2-one (**18**)

(a) 1-(2'-*Methyl*-1'-*carbomethoxy*) *propenyl*-3-(α-*methyl*-β-*carbomethoxy*-*vinylamino*)-4-*methylthioazetidin*-2-*one* (**13**). This compound was prepared as a viscous oil from **12**[15] and the Dane salt as described above.

IR (Nujol): 1770, 1725, 1660 cm^{-1}; NMR ($CDCl_3$) δ: 2.0 (s, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 2.26 (s, 3H), 3.63 (s, 3H), 3.82 (s, 3H), 4.66 (s, 1H), 4.5–4.9 (m, 2H), 9.1 (d, 1H, J = 9 Hz); Mass spectrum: M^+ at *m/e* 342.

(b) The β-lactam (**13**) was hydrolyzed to the 3-amino-β-lactam by the method described earlier, IR. 1760 cm^{-1}, EI–MS: *m/e* 244. The structure of this compound which was obtained as an oily liquid was further confirmed through its alternative synthesis. The Schiff base (**12**) on treatment with azidoacetyl chloride in the presence of Et_3N afforded the α-azido β-lactam which on catalytic reduction (H_2/Pd–C) gave an amino compound which was identical to the one obtained through the vinylamino sequence.

(c) *The α-amino-β-lactam* (200 mg) described above was acylated with phenylacetyl chloride (127 mg) in the presence of triethylamine (83 mg) at 0° in CH_2Cl_2 to obtain 200 mg of **19** (67% yield), m.p. 87–91° (ether).

IR (Nujol): 1765, 1720, 1660 cm^{-1}; NMR ($CDCl_3$) δ: 1.93 (s, 3H), 2.12 (s, 3H), 2.23 (s, 3H), 3.6 (s, 2H), 3.73 (s, 3H), 4.77 (q, 1H), 4.95 (d, 1H, J = 2 Hz), 7.35 (s, 6H); Mass spectrum: M^+ at *m/e* 362.

(d) 1-(1'-*Methoxycarbonyl*-2'-*methylprop*-1-*enyl*) - 3 - *phenylacetamidoazetidin*-2-*one* (**20**). To a soln of 67 mg of **19** in 20 ml acetone was added prewashed activated Raney Ni (1 g). The mixture was refluxed with stirring for 20 min, cooled and filtered. The filtrate was evaporated under reduced pressure. The residual oil was redissolved in $CHCl_3$ (20 ml) and this soln was washed with brine (3 × 10 ml), dried (Na_2SO_4) and evaporated to yield 35 mg of **20** as an oil sufficiently pure for further use.

IR (neat): 3300–3200, 2900, 1760, 1720, 1660, 1540 cm^{-1}; NMR ($CDCl_3$) δ: 1.95 (s, 3H), 2.20 (s, 3H), 3.50 (s, 2H), 3.60 (m, 2H), 3.65 (s, 3H), 5.00 (m, 1H), 6.90 (m, 1H), 7.30 (s, 5H); mass spectrum: CIMS (NH_3), peaks at *m/e* 316 (M^+), 334 ($M^+ + NH_4^+$).

(e) To a cooled (0°) soln of (20, 35 mg) in water (0.9 ml) and acetone (5 ml) was added IN H_2SO_4 (0.032 ml) followed by a dropwise addition of a soln of N-bromosuccinimide (23 mg) in acetone (0.5 ml). The mixture was stirred at room temp. for 1 hr. Acetone was evaporated under reduced pressure. The remaining aqueous soln was extracted with $CHCl_3$ (2 × 5 ml). The combined organic layers were washed with 10% Na_2SO_3 (5 ml), dried (Na_2SO_4) and evaporated to yield the bromohydrin (40 mg, 87% yield) as an oil.

IR (neat): 3300–3100, 2900, 1755, 1720, 1660, 1520 cm^{-1}; CIMS (CF_2Cl_2): *m/e* 447, 449 (1:1) [M^+ + 35].

This bromohydrin (40 mg) was dissolved in anhyd CH_2Cl_2 (5 ml) containing Et_3N (25 mg). The soln was stirred overnight at room temp. The mixture was then washed with brine (20 ml), dried (Na_2SO_4) and evaporated to yield 15 mg (76% yield) of **18**.

IR (neat): 3250, 2900, 1745, 1660, 1540 cm^{-1}; NMR ($CDCl_3$) δ: 3.50 (s, 2H), 3.60 (m, 2H), 5.00 (m, 1H), 6.90 (m, 1H), 7.30 (s, 6H); CIMS (NH_3): *m/e* at 220 ($M^+ + NH_4^+$); (High resolution): 204.2272. Calc. for $C_{11}H_{12}N_2O_2$: 204.2280.

cis-1-p-*Tolyl*-4-p-*anisyl*-3-*acetamidoazetidin*-2-*one* (**24**). Ozo was bubbled through a precooled soln (−78°) of the corresponding O_3 **23**, (300 mg); derived from the Dane salt and *p*-anisylidin-*p*-toluidine) in dry CH_2Cl_2 for approximately 20 min until the soln was saturated with O_3 (tested with KI soln). The blue soln obtained was transferred to a round bottom flask and the solvent evaporated carefully under reduced pressure. The resulting slurry was dissolved in acetone (25 ml), cooled to 0° and treated with Jones reagent to cleave this ozonide. The mixture was stirred for another 15 min. This soln was diluted with water and extracted with $CHCl_3$ (3 × 100 ml). The $CHCl_3$ extract was dried ($MgSO_4$) and evaporated. The resulting solid was chromatographed over Florisil using CH_2Cl_2 as an eluant. The title compound was obtained as brownish crystals (125 mg) m.p. 171°.

IR (Nujol): 3200, 1720, 1640 cm^{-1}; NMR ($CDCl_3$) δ: 1.70 (s, 3H), 2.30 (s, 3H), 3.75 (s, 3H), 5.3 (d, 1H), 5.6 (q, 1H), 6.1 (d, 1H), 6.7–7.3 (m, 8H).

Using similar ozonolysis conditions, **27** was prepared from

the β-lactam derived from the Dane salt of **25** and *p*-anisidin-*p*-toluidine in 50% yield, m.p. 129–131°.

IR (Nujol): 3200, 1760, 1640 cm^{-1}; NMR ($CDCl_3$) δ: 1,3 (s, 2H), 1.8 (t, 3H), 1.95 (s, 2H), 2.3 (s, 3H), 2.7 (s, 2H), 2.9 (q, 2H), 3.7 (s, 3H), 5.3 (d, 1H), 5.6 (m, 1H), 6.0 (d, 1H), 6.8–7.4 (m, 8H); mass spectrum: M^+ at *m/e* 452.

1-*Thia*-6-*phenyl*-7-(1'-*methyl*-2'-*carbomethoxyvinylamino*) *octam* was prepared from 5,6-dihydro-2-phenyl-4H-1,3-thiazine and Dane salt, m.p. 162–163°, (55% yield); IR: 1760, 1660 cm^{-1}.

1-*Thia*-6-*phenyl*-7-*phenoxyacetamidooctam*, m.p. 151–152°[24] and 1-*thia*-6-*phenyl*-7-*phenylacetamidooctam*, m.p. 175–176° were prepared by acylation of the corresponding 7-aminooctam.

1,1-*Dimethyl*-2-*thia*-6-*phenyl*-7-*phenoxyacetamidooctam*, m.p. 173–174°[25] was similarly prepared by the reaction of 5,6-dihydro-2,2-dimethyl-3-phenyl-1,4-thiazine with Dane salt followed by cleavage of the amino protective group and acylation of the resulting amino compound with phenoxyacetyl chloride.

1-*Phthalimidoacetyl*-1-*aza*-6-*methylthio* - 7 - *phenoxyacetamido octam*, m.p. 241–243° was obtained by the reaction of Dane salt with 2-methylthio-3-phthalimidoacetyl-3,4,5,6-tetra hydropyrimidine followed by acid hydrolysis of the vinyl amino product and acylation to the resulting amino compound with phthalimidoacetyl chloride.

1-p-*Toluenesulfonyl*-1-*aza*-6-*methylthio* - 7 - (1' - *methyl* - 2' - *carbomethoxyvinylamino*) *octam* was prepared by the condensation of the Dane salt with 2-methyl-mercapto-1-(*p*-toluenesulfonyl)-Δ^2-tetrahydropyrinidine, m.p. 161–162°; IR ($CHCl_3$): 1770, 1650 cm^{-1}.

1,2-*Benzo*-6-*phenyl*-7-(1'-*methyl*-2'-*carbomethoxyvinylamino*)-*octam*; m.p. 148–150° was prepared in 45% yield by treating 1-phenyl-3,4-dihydroisoquinoline with Dane salt, IR: 1760, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.75 (m, 2H), 3.45 (s, 3H), 3.75 (m, 2H), 4.45 (s, 1H), 5.0 (d, 1H), 7.1–7.6 (b, 9H), 8.45 (d, 1H).

1,2-*Benzo*-6-*phenyl*-7-(1'-*methyl*-2'-*carbo* - *t* - *butoxylvinylamino*) *octam* was prepared in 33% yield from 1-phenyl-3,4-dihydroisoquinaline and the Dane salt derived from t-butyl acetoacetate and glycine, m.p. 149–150°; NMR: 1.3 (s, 9H), 1.9 (s, 3H), 2.7 (m, 2H), 3.6 (b, 2H), 4.3 (s, 1H), 5.1 (b, 1H), 7.3–7.5 (b, 9H), 8.6 (b, 1H); mass spectrum: M^+ at *m/e* 405 (CIMS).

1,2-*Benzo*-6-*methylthio*-7-(1' - *methyl* -2' - *carbomethoxyvinylamino*) *octam*, m.p. 117°, was prepared from 1-methylthio-3,4-dihydroiso-quinoline and Dane salt in 40% yield, IR: 1760, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.1 (s, 3H), 3.0 (m, 2H), 3.65 (s, 3H), 3.3 (m, 2H), 4.7 (b, 1H), 4.9 (s, 1H), 7.1–7.3 (b, 4H), 9.3 (b, 1H).

1,2-*Benzo*-3-*methyl*-6-*thiomethyl*-7-(1' - *methyl* - 2' - *carbomethoxyvinylamino*) *octam* was prepared by the method described earlier from Dane salt (8, R = H) and 1-thiomethyl-4-methyl-3,4-dihydroisoquinoline in 60% yield, m.p. 102–104°; IR: 1760, 1660 cm^{-1}; NMR: 1.4 (d, 3H), 2.05 (s, 3H), 2.2 (s, 3H), 3.7 (s, 3H), 3.0–4.0 (m, 3H), 4.7 (s, 1H), 4.9 (d, 1H), 7.4 (s, 4H).

1,2-*Benzo*-6-p-*methoxyphenyl*-7-(1' - *methyl* - 2' - *carbethoxyvinylamino*) *octam* was prepared from the Dane salt derived from glycine and ethyl acetoacetate and 1-*p*-methoxyphenyl-3,4-dihydroisoquinoline, m.p. 165° (80% yield); IR: 1750, 1640 cm^{-1}; NMR: 1.15 (t, 3H), 2.0 (s, 3H), 7.5–2.9 (m, 2H), 3.4–3.65 (m, 2H), 3.75 (s, 3H); 3.95 (q, 2H), 4.4 (s, 1H), 5.05 (d, 1H), 6.7–7.5 (m 8H), 8.6 (d, 1H).

1,2-*Benzo*-6-p-*methoxyphenyl*-7-(1' - *methyl* - 2' - *carbomethoxyvinylamino*) *otcam* was prepared in 80% yield from the Dane salt (8, R = H) and the appropriate dihydroisoquinoline, m.p. 149–150°; IR: 1760, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.7 (m, 2H), 3.45 (s, 3H), 3.6 (m, 2H), 3.75 (s, 3H), 4.4 (s, 1H), 5.0 (d, 1H, J = 10 Hz), 6.75–7.45 (m, 8H), 8.45 (d, 1H), J = 10 Hz).

1,2-(4",5"-*dimethoxybenzo*)-4-*carbomethoxy* - 6 - *phenyl* - 7 - (1' - *methyl* - 2' - *carbomethoxyvinylamino*) *octam* was prepared in 80% yield from the appropriate dihydroisoquinoline and Dane salt **8** (R = H); IR: 1760, 1750, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.7 (m, 2H), 3.45 (s, 3H), 3.85 (s, 3H), 3.9 (s, 3H), 4.05 (s, 3H), 4.2 (m, 1H), 5.1 (d, 1H, J = 10 Hz), 6.66–7.50 (m, 7H).

1,2-(4",5"-*Dimethoxybenzo*)-4-*carbomethoxy* - 6 - *phenyl* - 7 - *phenylacetamidooctam* was obtained by the acid cleavage of the amino protective group of the above compound followed by acylation with phenylacetyl chloride as described earlier, m.p. 188–190.[26]

1,2-(4",5"-*Dimethoxybenzo*)-6-p-*bromophenyl* - 7 - (1' - *methyl* - 2' - *carbomethoxyvinylamino*) *octam* was obtained in 55% yield, m.p. 188–190° from Dane salt (8, R = H) and 1-*p*-bromophenyl-3,4-dihydro-6,7-dimethoxyisoquinoline, IR: 1760, 1660 cm^{-1}; NMR: 2.0 (s, 3H), 2.7 (m, 2H), 3.5 (s, 3H), 3.5 (m, 2H), 3.85 (s, 3H), 3.95 (s, 3H), 4.5 (s, 1H), 5.1 (d, 1H, J = 10 Hz), 6.7–7.6 (m, 6H), 8.5 (d, 1H, J = 10 Hz).

Hydrolysis of this octam with dil HCl followed by acylation with phenylacetyl chloride afforded the corresponding 7-phenylacetamido octam in 60% yield, m.p. 170°.

1,2-*Benzo*-6-*phenyl*-7-(1'-*methyl*-2'-*acetylvinylamino*) *octam* was prepared by treating 1-phenyl-3,4-dihydroisoquinoline and Dane salt derived from glycine and acetylacetone in 40% yield, m.p. 167–169°.

1,2-*Benzo*-6-*phenyl*-7(2'-*acetylcyclohexenylamino*) *octam* was similarly prepared from the potassium salt of 2'-acetylcyclohexenylamino acetic acid and 1-phenyl-3,4-dihydroisoquinoline in 54% yield, m.p. 166° (CH_2Cl_2 + n-hexane); NMR: 1.4–2.8 (b, 11H), 3.5–3.88 (b, 4H), 5.15 (d, 1H), 7.1–7.6 (b, 9H), 8.2 (b, 1H).

Spectral and other properties of some representative monocyclic β-lactams and their derivatives synthesized by the Dane salt method are presented in Table 5.

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