Tetrahedron Vol 44, No 13, pp 4157 to 4172, 1988
Printed in Great Britain

0040-4020/88 $3.00 + .00

SILICON-ASSISTED SYNTHESIS OF β-LACTAMS

ERNEST W. COLVIN*, DANIEL McGARRY, AND MARK J. NUGENT
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, U.K.

(*Received in UK 17 December 1987*)

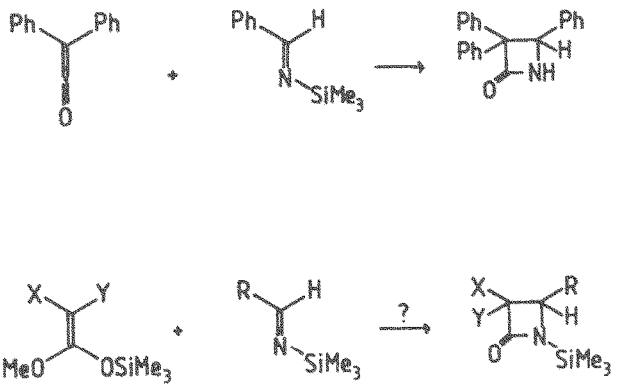
Abstract - Reaction of N-silyl imines with silyl ketene acetals in the presence of ZnI_2 and t-butyl alcohol, followed by treatment *in situ* of the intermediate N-silyl β-aminoesters with MeMgBr, produces N-silyl-azetidin-2-ones in good yield; use of trimethylsilyl triflate as Lewis acid catalyst can be advantageous in some cases. The preparation of the N-t-butyldimethylsilyl imine of ethyl glyoxylate in this context is detailed.

Since the discovery of penicillin, the vast majority of new natural products possessing the β-lactam (azetidin-2-one) ring have fallen into that family of compounds known as the β-lactam antibiotics[1]. In the period up to 1970, β-lactam research concentrated mainly on the penicillin and cephalosporin groups of compounds. Since that time a dramatic expansion in the area has taken place with the discovery of a new generation of β-lactam structures[2]. Monocyclic β-lactams such as the nocardicins, and the monobactams, exemplify this new generation, as do clavulanic acid, a potent β-lactamase inhibitor, and the powerful antibiotic, thienamycin.

With the discovery of these new natural products, substantial efforts have been devoted to the synthesis of β-lactams of varying structures. Most of the successful syntheses of bicyclic β-lactams involve the early creation of a monocyclic β-lactam, followed by substituent elaboration and ultimate cyclisation to form the second ring. With this end in view, N-unsubstituted β-lactams become very attractive synthetic targets. Routes to these valuable intermediates have hitherto involved either creation of an N-functionalised β-lactam followed by liberation of the nitrogen atom, or degradation of a naturally occurring bicyclic β-lactam. Most existing methods either lack generality in the ring assembly, or require often elaborate procedures to deblock the nitrogen atom.

In 1907, Staudinger[3] reported the first synthesis of a β-lactam, by [2+2]-cycloaddition between ketene and benzylidene aniline at 200°C. If a similar sequence could be performed using an N-trimethylsilyl aldimine, this might lead to a useful synthesis of N-unsubstituted β-lactams - the N-trimethylsilyl bond being hydrolytically labile. Indeed, in 1977 Birkofer and Schramm described[4] the reaction between diphenylketene and N-trimethylsilyl benzaldimine to produce the β-lactam (Scheme 1) in 12% yield.

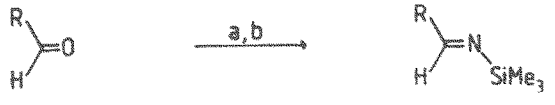
Our plan revolved around the construction of a range of N-silyl aldimines and ketene silyl acetals, followed by an investigation of their possible interaction to form β-lactams. While this work was nearing completion, Hart and co-workers reported[5] on a similar concept using lithium ester enolates in place of ketene silyl acetals. Interesting stereochemical differences are observed between the two sets of conditions, as will be detailed later.



Scheme 1

N-Trimethylsilyl Aldimines

A very limited number of N-silyl imines, particularly those derived from diaryl ketones[6], have been known for some time[7]. A range of silyl aldimines was prepared[8] by a modification of older procedures, a modification which allowed their synthesis and characterisation under mild conditions and in good yield. In detail, treatment of a solution of lithium hexamethyldisilazide in THF at 0°C with one equivalent of a non-enolisable aldehyde (with enolisables, simple deprotonation and tautomeric enamine formation can cause complications[9]), followed by one equivalent of trimethylsilyl chloride, and non-aqueous isolation and distillation (Kugelrohr), gave the imines (Scheme 2), carrying phenyl (1), furyl (2), styryl (3), phenylethynyl (4), trimethylsilylethynyl(5), and trimethylsilyl-ethenyl (6) substituents. In all cases, only one geometric isomer was detected, presumably E. All the imines were pale green/yellow oils, highly sensitive to oxygen and moisture.

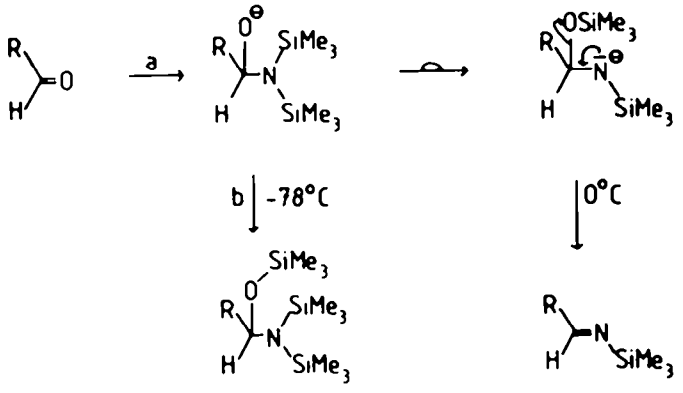


76-95%

(1), R = Ph
(2), = 2-furyl
(3), = PhCH=CH
(4), = PhC≡C
(5), = $Me_3SiC{\equiv}C$
(6), = $Me_3SiCH{=}CH$

Scheme 2: (a) $LiN(SiMe_3)_2$, THF, 0°C; (b) Me_3SiCl

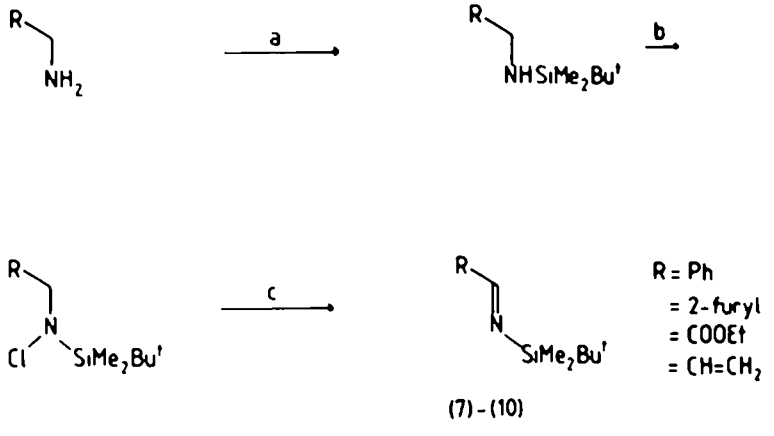
The probable mechanism for this reaction is as shown (Scheme 3), proceeding by a heteroatom variant of Peterson Olefination[10]. N→O Silyl migration does not appear to proceed at a significant rate at -78°C; under those conditions, the aminoacetal adduct can be trapped and isolated as its tris(trimethylsilyl) derivative, a useful precursor for the in situ generation of the N-silyl aldimine.



Scheme 3: (a) $LiN(SiMe_3)_2$; (b) Me_3SiCl

N-t-Butyldimethylsilyl Aldimines

N-t-Butyldimethylsilyl aldimines are of greater potential value than their N-trimethylsilyl analogues - the silyl group is much more resistant to hydrolytic cleavage, and it should survive the β-lactam ring forming conditions just discussed. However, different methodology had to be employed for their synthesis - methodology which also provided access to the hitherto elusive N-t-butyldimethylsilyl imine of ethyl glyoxylate, which cannot be prepared directly.



Scheme 4: (a) $t\text{-}BuMe_2SiCl$, Et_3N, DMAP; (b) t-BuOCl; (c) DBU

In practice (Scheme 4), the starting primary amine was converted into its N-t-butyldimethylsilyl derivative, which on reaction with t-butyl hypochlorite gave the N-chloro-N-silyl species. This, on elimination of HCl using DBU or DBN (other bases were less effective) produced the desired imines (7 - 10) in good yield, i.e., those derived from benzylamine, furfurylamine, ethyl glycinate, and allylamine, the last producing the interesting protected 1-azabutadiene (10).

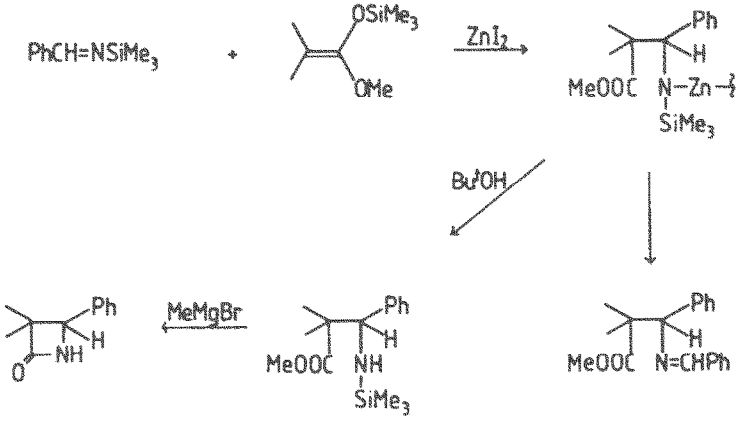
Ketene Silyl Acetals

A range of simple ketene acetals was prepared using standard literature procedures, by deprotonation with lithium di-isopropylamide (LDA) followed by O-silylation. Deprotonation under the conditions of Ainsworth[11] normally leads selectively to the Z-enolate and thence the E-ketene acetal. The separate Z (11) and E (12) ketene t-butyldimethylsilyl acetals of methyl propanoate were prepared using Ireland's procedure[12], where deprotonation in the presence of hexamethylphosphoramide (HMPA) leads, on silylation, to the Z ketene acetal, whereas without the initial presence of HMPA the E isomer is produced preferentially.

Reaction of N-Silyl Aldimines with Ketene Silyl Acetals

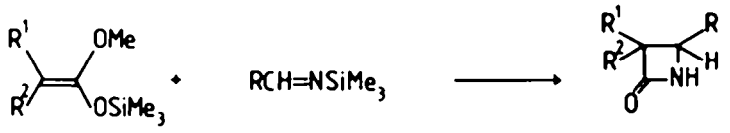
The first catalyst investigated was fluoride ion, present as tetrabutylammonium fluoride. Although successful for the direct production of certain of the target β-lactams, the sequence proved to be irreproducible, possibly due to the difficulties associated[13] in obtaining catalytically active 'anhydrous' tetrabutylammonium fluoride. Other fluoride sources, such as KF-18-crown-6, proved disappointingly slow in effect, with deleterious side reactions competing.

Alternative activation of the imine component with a Lewis acid was initially attempted using $TiCl_4$, a reagent employed successfully by Ojima[14] in a related reaction with N-alkyl and -aryl imines. This and a variety of other Lewis acids proved to be of limited utility, but it was observed that reaction using ZnI_2 in ether produced the imino-ester as sole product and in good yield. On the assumption that this had been formed by competitive trans-amination between unreacted imine and a metallo-amide intermediate, with the zinc atom possibly exerting some template effect, the same reaction was performed in the presence of a weak proton source, t-BuOH, which could cleave the metal-nitrogen bond in such an intermediate. Gratifyingly, this yielded, on work up, β-aminoester as sole product. Indeed, treatment of the reaction mixture prior to work up with MeMgBr under the conditions of Birkofer[15] gave the β-lactams directly (Scheme 5), N-desilylation having occurred on work up.



Scheme 5

Following this general technique of complexation of the imine with ZnI_2 in ether, followed by immediate and sequential addition of the ketene acetal and t-BuOH, and, after 2-3 h, of MeMgBr, a range of β-lactams (Scheme 6), including those shown (Scheme 7), was obtained. All yields were good, except for the preparation of the 3-unsubstituted β-lactam using the O-t-butyldimethylsilyl ketene acetal of methyl acetate, but even this yield of 27% compares favourably with alternatives[15]. All were produced selectively trans [apart from the phenoxy derivative (18)]. This trans-stereoselectivity, which could be enhanced by use of lower temperatures, contrasts with the lithium enolate work of Hart[4] when cis-selectivity prevails.

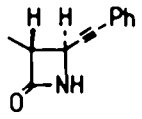


R^1	R^2	Imine	β-Lactam	% Yield	cis:trans ratio
Me	Me	(1)	(13)	75	
		(2)	(14)	76	
		(4)	(15)	78	
		(6)	(16)	75	
H	H	(1)	(17)	27[1]	
H	PhO	(2)	(18)	58	1:0.77
Et	H	(1)	(19)	61	1:9[2]
Me	H	(4)	(20)	82	1:3
		(5)	(21)	62	1:1.5
Ph	H	(5)	(22)	53	1:12[2]
Et	H	(2)	(23)	66	1:2
		(5)	(24)	44	1:2.3
i-Pr	H	(1)	(25)	68	1:5

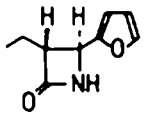
[1] Using t-butyldimethylsilyl ketene acetal

[2] Initial additions at -78°C.

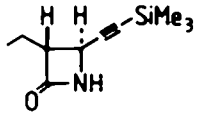
Scheme 6



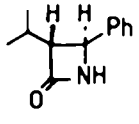
(20)



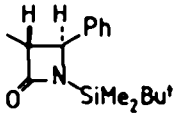
(23)



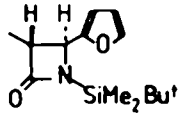
(24)



(25)



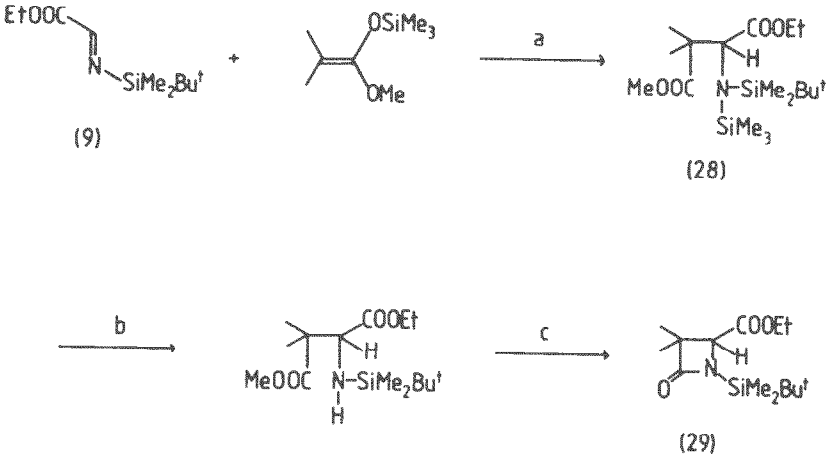
(26)



(27)

Scheme 7

The benzylamine- and furfurylamine-derived N-t-butyldimethylsilyl imines reacted as described above, with the minor difference that trimethylsilyl triflate was the preferred Lewis acid, to give the N-t-butyldimethylsilyl β-lactams (26) and (27). The aldimine derived from ethyl glycinate, i.e. the N-t-butyldimethylsilyl imine (9) of ethyl glyoxylate, also reacted satisfactorily under these conditions, to give the N-trimethylsilyl-N-t-butyldimethylsilyl aminoester (28) (Scheme 8). Selective mono-desilylation using aqueous Na_2HPO_4, followed by Grignard treatment, gave the N-t-butyldimethylsilyl-4-carboethoxy β-lactam (29) in an overall yield of 60%.

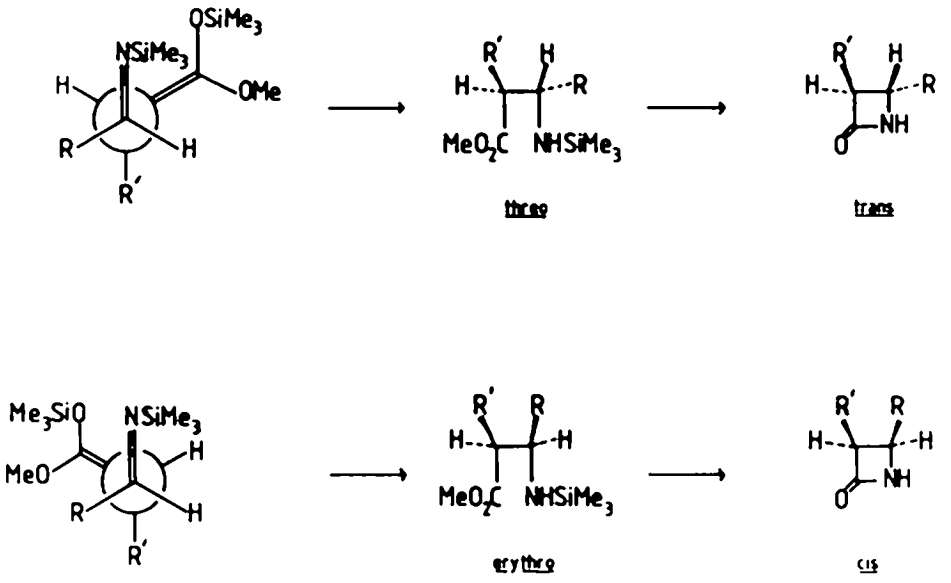


Scheme 8: (a) $Me_3SiOSO_2CF_3$, CH_2Cl_2; (b) Na_2HPO_4 aq.; (c) MeMgBr

Mechanism

The threo diastereoselectivity observed in the initial bond forming step can be explained by invoking transition states such as those shown (Scheme 9). In this interpretation, the reaction course would seem to have a preference to follow a syn-clinal ℓk approach, leading to the threo aminoester and thence the trans β-lactam. It is unlikely that chelation is playing a major role, since the use of trimethylsilyl triflate (vide infra) results in the same stereochemical preference.

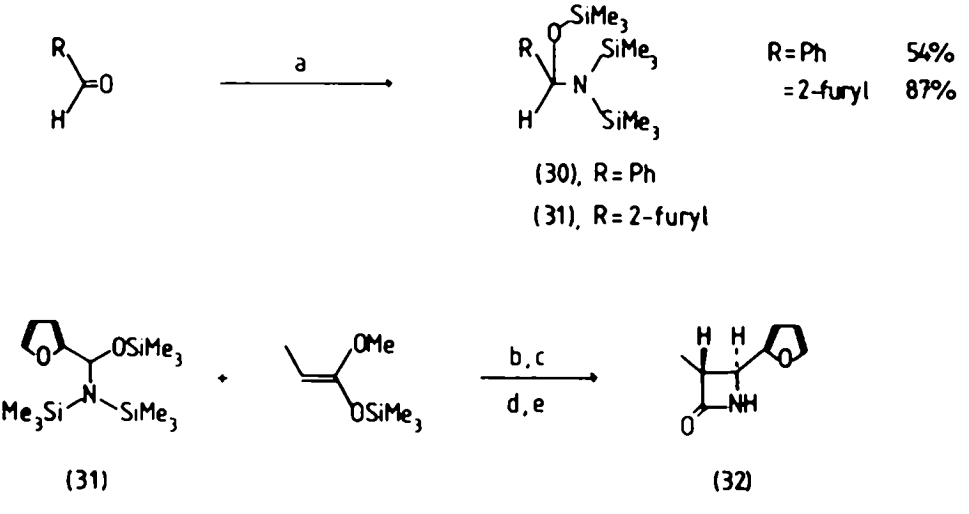
The effect of ketene acetal geometry on diastereoselectivity was examined by reacting separately the Z (11) and E (12) O-t-butyldimethylsilyl ketene acetals of methyl propanoate with the benzaldehyde derived imine (1). These results showed very little dependence on ketene acetal geometry.



Scheme 9

Amine Acetals

Finally, the amine acetals (30) and (31) (Scheme 10) obtained by low temperature silylation could also be employed as satisfactory precursors of the reactive iminium ion species[15]. For example, pre-complexation of the furfural-derived amine acetal (31) with a full equivalent of trimethylsilyl triflate, followed by addition of ketene acetal and subsequent aqueous isolation, gave the aminoester and thence the β-lactam (32), again with a preference for formation of the trans isomer. This process can be achieved equally successfully by a one-pot procedure.



Scheme 10: (a) $LiN(SiMe_3)_2$, Me_3SiCl, THF, -78°C; (b) $Me_3SiOSO_2CF_3$, CH_2Cl_2; (c) Na_2HPO_4 aq.; (d) Me_3SiCl, Et_3N, Et_2O; (e) MeMgBr

EXPERIMENTAL

Melting points are uncorrected. Bulb to bulb distillations were carried out on a Buchi GKR-50 Kugelrohr; recorded boiling ranges refer to the indicated air bath temperatures. ^{1}H n.m.r. spectra were recorded on a Perkin-Elmer R32 spectrometer operating at 90 MHz. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (0.00 ppm). Infra-red spectra were determined on a Perkin-Elmer 580 spectrometer. Low resolution mass spectra were determined on a VG updated MS 12 instrument and high resolution mass spectra were determined on an MS 902S. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser.

Reactions were carried out under an atmosphere of either nitrogen or argon. All reactions involving organo-lithium reagents or trimethylsilyl trifluoromethanesulphonate were carried out under an atmosphere of argon exclusively. Tetrahydrofuran and Et_2O were distilled freshly from sodium/benzophenone. CH_2Cl_2 was distilled from P_2O_5, filtered through basic alumina and stored over 4Å molecular sieves. Triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were distilled from CaH_2.

Unless otherwise stated, solutions of N-trialkylsilyl imines, O-trialkylsilyl ketene acetals and trimethylsilyl trifluoromethanesulphonate of known concentration in CH_2Cl_2 or pentane were utilised instead of the neat materials. The term 'non-aqueous work-up' refers to the process whereby the crude reaction mixture was diluted with either Et_2O or n-pentane, filtered through Celite and evaporated *in vacuo*. This process was repeated until a homogeneous crude product remained. Dry column flash chromatography[17] refer to a technique already described.

N-Trimethylsilyl Aldimines - General Procedure. To hexamethyldisilazane (4.6 ml, 22 mmol) was added n-BuLi (8.0 ml, 2.5 M in hexane, 20 mmol) over 5 min. The solution was stirred for 15 min, then cooled to 0°C and THF (36 ml) added. The solution was stirred for a further 20 min then the appropriate aldehyde, freshly distilled (20 mmol) in THF(5 ml) was added over 7 min. The resulting solution was stirred for 30 min at 0°C then trimethylchlorosilane (2.54 ml, 20 mmol) was added in one portion. Stirring was continued for 30 min. Non-aqueous work-up and Kugelrohr distillation yielded the pure N-trimethylsilyl aldimine.

Utilisation of this general procedure yielded the following N-trimethylsilyl aldimines.

N-Trimethylsilyl benzaldimine (1)[5]. 3.38 g (95%), b.p. 55-60°C/0.05 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3060, 2950, 1640, 1580, and 1250 cm^{-1}; δ ($CDCl_3$) 0.25 (s, 9H, $SiMe_3$), 7.4 (m, 3H, ArH), 7.7 (m, 2H, ArH), 8.93 (s, 1H, CH=N) (Found: M^+, 177.0974. $C_9H_{15}NSi$ requires M, 177.0974).

N-Trimethylsilyl-2-furfuraldimine (2). 3.03 g (91%), b.p. 50-55°C/0.01 mm Hg; $\nu_{max.}$ ($CHCl_3$) 2960, 1640, 1480, 1250 cm^{-1}; δ ($CDCl_3$) 0.25 (s, 9H, $SiMe_3$), 6.5 (dd, J 3 and 2 Hz, 1H, H-4), 6.87 (d, J 3 Hz, 1H, H-3), 7.57 (bs, 1H, H-5), 8.7 (s, 1H, CH=N). (Found: M^+, 167.0766. $C_8H_{13}NOSi$ requires M, 167.0766).

N-Trimethylsilyl cinnamaldimine (3). 4.11 g (95%), b.p. 125-130°C/0.05 mm Hg: $\nu_{max.}$ ($CHCl_3$) 2960, 2810, 1635, 1600, and 1250 cm^{-1}; δ ($CDCl_3$) 0.25 (s, 9H, $SiMe_3$), 6.86 (dd, J 15 and 8 Hz, 1H, C<u>H</u>=CHN), 7.16 (d, J 15 Hz, 1H, PhC<u>H</u>), 7.4 (m, 3H, (ArH), 7.7 (m, 2H, ArH), 8.70 (d, J 8 Hz, 1H, C<u>H</u>=N) (Found: M^+, 203.1126. $C_{12}H_{17}NSi$ requires M, 203.1130).

N-Trimethylsilylpropargylaldimine (4). 3.17 g (79%), b.p. 120-130°C/0.05 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3060, 2960, 2900, 2840, 2200, 1620, 1490, and 1250 cm^{-1}; δ ($CDCl_3$) 0.25 (s, 9H, $SiMe_3$), 7.3 (m, 3H, ArH), 7.5 (m, 2H, ArH), 8.38 (s, 1H, C<u>H</u>=N) (Found: M^+, 201.0968. $C_{12}H_{15}NSi$ requires M, 201.0974).

3,N-Bis(trimethylsilyl)propargylamine (5): 3.19 g (81%), b.p. 40-50°C/0.1 mm Hg; $\nu_{max.}$ ($CHCl_3$) 2960, 2900, 2850, 2170, 1615, 1410, and 1250 cm^{-1}; δ ($CDCl_3$) 0.23 (s, 9H, C-$SiMe_3$), 0.25 (s, 9H, N-$SiMe_3$), 8.10 (s, 1H, CH=N) (Found: M^+ 197.1028. $C_9H_{19}NSi_2$ requires M, 197.1056).

2,N-Bis(trimethylsilyl)-2-prop-2-enaldimine (6): 3.76 g (95%), b.p. 100-110°C/12 mm Hg); $\nu_{max.}$ ($CHCl_3$) 2960, 2900, 2850, 1630, 1580, and 1250 cm^{-1}; δ ($CDCl_3$) 0.23 (s, 9H, C-$SiMe_3$), 0.27 (s, 9H, N-$SiMe_3$), 6.7 (m, 2H, C<u>H</u>=C<u>H</u>), 8.45 (dd, J 4.3 and 3 Hz, 1H, C<u>H</u>=N) (Found: M^+, 199.1201. $C_9H_{21}NSi_2$ requires M, 199.1212).

N-t-Butyldimethylsilyl Amines - General Procedure. To a solution of the appropriate freshly distilled/recrystallised amine (20mmol) in Et_2O (10 ml) was added triethylamine (2.78 ml, 22 mmol) and 4-N,N-dimethylaminopyridine (49 mg, 0.40 mmol) in Et_2O (2 ml). The solution was cooled to 0°C and t-butyldimethylchlorosilane (3.01 g, 20 mmol) in Et_2O (10 ml) was added dropwise over 3 min. The resulting heterogeneous solution was warmed to room temperature and stirred for at least a further 12 h. Non-aqueous work-up and Kugelrohr distillation yielded the pure N-t-butyldimethylsilyl amine.

Utilisation of this general procedure yielded the following N-t-butyldimethylsilyl amines:

N-t-Butyldimethylsilyl benzylamine: 3.98 g (90%), b.p. 100-105°C/1.0 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3400, 2940, 2845, 1595, 1445, 1390, and 1110 cm^{-1}; δ ($CDCl_3$) 0.15 (s, 6H, $SiMe_2$), 1.05 (s, 9H, $SiBu^t$), 4.12 (d, J 7 Hz, 2H, CH_2N), 7.4 (m, 5H, ArH) (Found: M^+, 221.1601. $C_{13}H_{23}NSi$ requires M, 221.1600).

N-t-Butyldimethylsilyl furfurylamine: 3.97 g (94%), b.p. 115-123°C/20 mm Hg; $\nu_{max.}$ (CCl_4) 3420, 2940, 1600, 1470, 1460, 1250, 1150, and 840 cm^{-1}; δ ($CDCl_3$) 0.05 (s, 6H, $SiMe_2$), 0.87 (s, 9H, $SiBu^t$), 3.86 (d, J 9 Hz, CH_2N), 6.10 (m, 1H, H-4), 6.28 (m, 1H, H-3), 7.30 (m, 1H, H-5); m/z 196.1153. $C_{11}H_{21}NOSi-CH_3$ requires 196.1153.

N-t-Butyldimethylsilyl glycine ethyl ester: from the hydrochloride as general procedure except utilising 44 mmol triethylamine: 4.30 g (99%), b.p. 100°C/0.8 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3400, 2950, 2850, 1730, 1595, and 1140 cm^{-1}; δ ($CDCl_3$) 0.17 (s, 6H, $SiMe_2$), 1.00 (s, 9H, $SiBu^t$), 1.38 (t, J 7.5 Hz, 3H, CH_3), 3.69 (d, J 8 Hz, 2H, CH_2N), 4.3 (q, J 7.5 Hz, 2H, CH_2); m/z 160.0795. $C_{10}H_{23}NO_2Si-C_4H_9$ requires 160.0794.

N-t-Butyldimethylsilyl allyl amine: 2.70 g (99%), b.p. 100°C/0.8 mm Hg; $\nu_{max.}$ (CCl_4) 3420, 2960, 2940, 2860, 1640, 1470, 1480, 1260, and 840 cm^{-1}; δ ($CDCl_3$) 0.02 (s, 6H, $SiMe_2$), 0.88 (s, 9H, $SiBu^t$), 3.40 (m, 2H, CH_2N), 5.08 (m, 2H, CH=C<u>H</u>$_2$), 5.92 (m, 1H, C<u>H</u>=CH_2) (Found: M^+, 171.1482. $C_9H_{21}NSi$ requires M, 171.1438).

N-t-Butyldimethylsilyl imines - Procedure A. The N-t-butyldimethylsilyl amine (~20 mmol) in THF (30 ml) was cooled to 0°C and t-butyl hypochlorite (1 eq) in THF (5 ml) was added via pipette through a side-arm. The reaction mixture was stirred at 0°C for 2 h before non-aqueous work-up. The crude N-chloro,N-t-butyldimethylsilyl amine was weighed and dissolved in Et_2O (30 ml), cooled to 0°C, and freshly distilled DBU (1 eq) in Et_2O(5 ml)was added dropwise over ~2 min. The resulting heterogeneous reaction mixture was warmed to room temperature and stirred at least a further 12 h. Non-aqueous work-up and Kugelrohr distillation yielded the pure N-t-butyldimethylsilyl imine.

Procedure B. As procedure A, except 1.1 eq. DBU was utilised and the work-up consisted of the reaction mixture being taken up in n-pentane (10 ml), filtered through Celite and concentrated *in vacuo*. The residue was taken up in n-pentane (50 ml), washed with H_2O (2 x 50 ml) and brine (50 ml). Drying over Na_2SO_4 and concentration *in vacuo* afforded the N-t-butyldimethylsilyl imine in a form sufficiently pure for subsequent use.

Utilisation of these general procedures yielded the following N-t-butyldimethylsilyl imines.

N-t-Butyldimethylsilyl benzaldimine (7): Procedure A; 3.31 g (84%), 110-120°C/0.9 mm Hg: $\nu_{max.}$ ($CHCl_3$) 3060, 2950, 2860, 2720, 1645, 1580, and 1250 cm^{-1}; δ ($CDCl_3$) 0.20 (s, 6H, $SiMe_2$), 0.97 (s, 9H, $SiBu^t$), 7.4 (m, 3H, ArH), 7.7 (m, 2H, ArH), 8.94 (s, 1H, CH=N) (Found: M^+ 219.1445. $C_{13}H_{21}NSi$ requires M, 219.1443).

N-t-Butyldimethylsilyl-2-furfuraldimine (8): Procedure A: 2.90 g (74%), b.p. 146-162°C/20 mm Hg; $\nu_{max.}$ (CCl_4) 2960, 2940, 2900, 2860, 1650, and 840 cm^{-1}: δ ($CDCl_3$) 0.20 (s, 6H, $SiMe_2$), 0.93 (s, 9H, $SiBu^t$), 4.48 (dd, J 4 and 2 Hz, H-4), 6.83 (d, J 4 Hz, H-3), 7.52 (d, J 2 Hz, H-5), 8.70 (s, 1H, CH=N) (Found: M^+, 209.1210. $C_{11}H_{19}NOSi$ requires M, 209.1231).

Ethyl N-t-butyldimethylsilyl glyoxaldimine (9): Procedure B: 4.26 g (100%); $\nu_{max.}$ ($CHCl_3$) 2960, 2930, 2860, 1740, 1715, 1665, 1580, and 1250 cm^{-1}; δ ($CDCl_3$) 0.27 (s, 6H, $SiMe_2$), 1.0 (s, 9H, $SiBu^t$), 1.42 (t, J 7 Hz, 3H, CH_3), 4.39 (q, J 7 Hz, 2H, CH_2), 8.26 (s, 1H, CH=N).

N-t-Butyldimethylsilyl-1-azabuta-1,3-diene (10): Procedure B: 2.64 g (99%); $\nu_{max.}$ (CCl_4) 2950, 2920, 2880, 2860, 1650, 1470, 1460, 1250, and 840 cm^{-1}; δ ($CDCl_3$) 0.15 (s, 6H, $SiMe_2$), 0.84 (s, 9H, $SiBu^t$), 6.11 (m, 2H, $CH=C\underline{H}_2$), 6.40 (m, 1H, $C\underline{H}=CH_2$), 8.47 (d, J 8 Hz, 1H, CH=N) Found: M^+, 169.1274. $C_9H_{19}NSi$ requires M, 169.1282).

Synthesis of azetidin-2-ones from N-Trimethylsilyl Imines and O-Trimethylsilyl Ketene Acetals - Procedure A. To a solution of ZnI_2 (640 mg, 2 mmol) in Et_2O (20 ml) was added an ethereal solution of the appropriate N-trimethylsilyl imine (2 mmol). The resulting yellow-green solution was stirred for 30 sec then an ethereal solution of the appropriate ketene acetal (2 mmol) was added, followed immediately by t-BuOH (148 mg, 2 mmol) in Et_2O (0.75 ml). This solution was stirred for a prescribed number of hours then cooled to 0°C and MeMgBr (2 ml, 3M in ether, 6 mmol) added over 5 sec. The mixture was then allowed to warm to room temperature and stirred for a prescribed number of hours before being poured into saturated aqueous NH_4Cl (10 ml) and shaken thoroughly. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then purified by flash chromatography.

Procedure B. All operations were identical to procedure A except that t-BuOH (222 mg, 3 mmol) in Et_2O (1 ml) and MeMgBr (2.33 ml, 3M in ether, 7 mmol) were added at the appropriate times.

Procedure C. To a solution of ZnI_2 (640 mg, 2 mmol) in Et_2O (20 ml) was added an ethereal solution of the appropriate N-trimethylsilyl imine (2 mmol). The resulting yellow/green solution was cooled to -78°C over 20 min then an ethereal solution of the appropriate ketene acetal (2 mmol) was added, followed immediately by t-BuOH (148 mg, 2 mmol) in Et_2O (0.75 ml). This solution was stirred for 3 h then allowed to warm to room temperature and stirred for a stated number of hours before being cooled to 0°C and MeMgBr (2 ml, 3M in ether, 6 mmol) added over 5

sec. The ice bath was removed and the mixture was allowed to warm to room temperature and stirred for a stated number of hours then worked up as in A.

Procedure D. All operations were identical to procedure C except that t-BuOH (222 mg, 3 mmol) in Et_2O (1 ml) and MeMgBr (2.33 ml, 3M in ether, 7 mmol) were added at the appropriate times.

Utilisation of these general methods produced the following azetidin-2-ones.

3,3-Dimethyl-4-phenylazetidin-2-one (13). Procedure A: stirred for 3 h at room temperature then 14 h after Grignard addition, gave 266 mg (75%) of β-lactam, m.p. 104-105°C (lit.[1] m.p. 104-105°C); $\nu_{max.}$ ($CHCl_3$) 3410, 2970, 2930, 1760, 1610, and 1495 cm^{-1}; δ ($CDCl_3$) 0.72 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 4.48 (s, 1H, CHPh), 6.6 (bs, 1H, NH), 7.28 (m, 5H, ArH) (Found: C, 75.49; H, 7.62; N, 7.99. $C_{11}H_{13}NO$ requires: C, 75.4; H, 7.48; N, 7.99%. Found: M^+, 175.0998. Required M, 175.0994).

3,3-Dimethyl-4-(2-furyl)azetidin-2-one (14). Procedure A; stirred for 3 h at room temperature then 16 h after Grignard addition, gave 240 mg (76%) of the β-lactam, m.p. 106.5°C; $\nu_{max.}$ ($CHCl_3$) 3420 and 1765 cm^{-1}; δ ($CDCl_3$) 0.96 (s, 3H, Me), 1.40 (s, 3H, Me), 4.43 (s, 1H, CHN), 6.35 (m, 2H, H-3, H-4), 6.5 (bs, 1H, NH), 7.38 (bs, 1H, H-5) (Found: C, 65.39; H, 6.61; N, 8.44. $C_9H_{11}NO_2$ requires C, 65.44; H, 6.71; N, 8.48%. Found: M^+, 165.0791. Required M, 165.0787).

3,3-Dimethyl-4-(phenylethynyl)azetidin-2-one (15). Procedure A: stirred for 6 h at room temperature then 17 h after Grignard addition, gave 313 mg (78%) of the β-lactam, m.p. 117.5-118.5°C; $\nu_{max.}$ ($CHCl_3$) 3410, 3080, 2970, 2230, 1765, 1600 and 1370 cm^{-1}; δ ($CDCl_3$) 1.36 (s, 3H, Me), 1.39 (s, 3H, Me), 4.19 (s, 1H, CHN), 6.6 (bs, 1H, NH), 7.3 (m, 5H, ArH) (Found: C, 78.60; H, 6.49; N, 7.00. $C_{13}H_{13}NO$ requires C, 78.36; H, 6.58; N, 7.03%. Found: M^+, 199.0996. Required M, 199.0997).

3,3-Dimethyl-4-(2-E-trimethylsilylethenyl)azetidin-2-one (16): Procedure A: stirred for 2 h at room temperature then for 16 h after Grignard addition gave 277 mg (75%) of the β-lactam, m.p. 58-59°C; $\nu_{max.}$ ($CHCl_3$) 3410, 2960, 1755, 1618, and 1250 cm^{-1}; δ ($CDCl_3$) 0.03 (s, 9H, $SiMe_3$), 0.98 (s, 3H, Me), 1.28 (s, 3H, Me), 3.79 (d, J 4 Hz, 1H, CHN), 5.79 (d, J 24 Hz, 1H, C=CHSi), 6.01 (dd, J 24 and 3 Hz, 1H, CH=CSi), 6.70 (bs, 1H, NH) (Found: C, 60.91; H, 9.66; N, 7.08. $C_{10}H_{19}NOSi$ requires: C, 60.84; H, 9.71; N, 7.10%. Found: M^+, 197.1234. Required M, 197.1236).

4-Phenylazetidin-2-one (17): Procedure A: on a 1 mmol scale, stirred for 4 h at room temperature then 17 h after Grignard addition gave 41 mg (27%) of the β-lactam, m.p. 106.5-108°C (lit.[15] m.p. 107-108°C); $\nu_{max.}$ ($CHCl_3$) 3420, 3060, 2960, 1760, and 1605 cm^{-1}; δ ($CDCl_3$) 2.79 [dd, J 15 and 2 Hz, 1H, CH-CPh(cis)], 3.38 [ddd, J 15, 5 and 2 Hz, 1H, CH-CPh(trans)], 4.77 (dd, J 5 and 2 Hz, 1H, CHN), 7.30 (m, (5H, ArH).

3-Phenoxy-4-(2-furyl)azetidin-2-one (18): Procedure A: stirred for 2 h at room temperature then 16 h after Grignard addition, gave 149 mg (32%) of cis-β-lactam and 116 mg (26%) of trans-β-lactam.

Trans-(18): $\nu_{max.}$ ($CHCl_3$) 3420, 3020, 1785, 1600, and 1595 cm^{-1}; δ ($CDCl_3$) 4.70 (d, J 2 Hz, 1H, CHN), 5.28 (d, J 2 Hz, 1H, CHOPh), 6.39 (m, 2H, H-3 , H-4), 6.9 (m, 3H, ArH), 7.0 (bs, 1H, NH), 7.22 (m, 2H, ArH), 7.41 (m, 1H, H-5) (Found: M^+, 229.0739. $C_{13}H_{11}NO_3$ requires M, 229.0739).

Cis-(18): m.p. 154.5-155.5°C; $\nu_{max.}$ (KBr) 3400, 3200, 3120, 2910, 1750, 1725, 1700, 1595 cm^{-1}; δ (d_6-acetone) 5.23 (d, J 5 Hz, 1H, CHN), 5.64 (dd, J 5.2 Hz, 1H, CHOPh), 6.32 (dd, J 3 and 2 Hz, 1H, H-4), 6.44 (d, J 3 Hz, 1H, H-3), 6.9 (m, 3H, ArH), 7.25 (m, 2H, ArH), 7.44 (m, 1H, H-5), 7.85 (bs, 1H, NH) (Found: C, 68.26; H, 5.03; N, 6.06. $C_{13}H_{11}NO_3$ requires: C, 68.11; H, 4.84; N, 6.11%. Found: M^+, 229.0740).

3-Ethyl-4-phenylazetidin-2-one (19): Procedure D; stirred for 1 h at room temperature then 3 h after Grignard addition, gave 221 mg (63%) of trans-β-lactam

and 25 mg (7%) cis-β-lactam.

Trans-(19): $\nu_{max.}$ ($CHCl_3$) 3410, 2960, 1755, 1600, 1455 cm^{-1}; δ ($CDCl_3$) 1.05 (t, J 7 Hz, 3H, Me), 1.84 (m, 2H, CH_2Me), 2.96 (dt, J 7 and 2 Hz, 1H, CHEt), 4.36 (d, J 2 Hz, 1H, CHN), 6.65 (bs, 1H, NH), 7.3 (m, 5H, ArH).

Cis-(19): m.p. 122-123°C (lit.[1] m.p. 123-124°C); $\nu_{max.}$ ($CHCl_3$) 3410, 2970, 2880, 1765, and 1350 cm^{-1}; δ ($CDCl_3$) 0.74 (t, J 7 Hz, 3H, Me), 1.25 (m, 2H, CH_2Me), 3.36 (m, 1H, CHEt), 4.86 (d, J 5 Hz, 1H, CHN), 6.34 (bs, 1H, NH), 7.3 (m, 5H, ArH).

3-Methyl-4-(phenylethynyl)azetidin-2-one (20): Procedure B, stirred for 4 h then 16 h after Grignard addition, gave 229 mg, (62%) of trans-β-lactam and 74 mg (20%) of cis-β-lactam.

Trans-(20): m.p. 116.5-117.5°C; $\nu_{max.}$ ($CHCl_3$) 3418, 3050, 2930, 2230, 1765, 1600, and 1490 cm^{-1}; δ ($CDCl_3$) 1.39 (d, J 7.5 Hz, 3H, Me), 3.40 (dq, J 7.5 and 2 Hz, 1H, $CHCH_3$), 4.0 (d, J 2 Hz, 1H, CHN), 6.41 (bs, 1H, NH), 7.3 (m, 5H, ArH) (Found: C, 77.66; H, 5.81; N, 7.40. $C_{12}H_{11}NO$ requires: C, 77.81; H, 5.99; N, 7.56%. Found: M^+, 185.0839. Required M, 185.0840).

Cis-(20): m.p. 68-71°C; $\nu_{max.}$ ($CHCl_3$) 3410, 3020, 2930, 2225, 1765, 1595, and 1345 cm^{-1}; δ ($CDCl_3$) 1.41 (d, J 7.5 Hz, 3H, Me), 3.48 (m, 1H, CHMe), 4.58 (d, J 5 Hz, 1H, CHN), 6.3 (bs, 1H, NH), 7.3 (m, 5H, ArH) (Found: C, 77.79; H, 5.97; N, 7.56%. Found: M^+, 185.0838).

3-Methyl-4-(trimethylsilylethynyl)azetidin-2-one (21): Procedure B: stirred for 2 h at room temperature then 3 h after Grignard addition, gave 134 mg (37%) trans-β-lactam and 89 mg (25%) cis-β-lactam.

Trans-(21): b.p. (Kugelrohr) 110-115°C/0.04 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3418, 2960, 2900, 2175, 1765, and 1340 cm^{-1}; δ ($CDCl_3$) 0.19 (s, 9H, $SiMe_3$), 1.34 (d, J 8 Hz, Me), 3.31 (dq, J 8 and 2 Hz, CHMe), 3.87 (d, J 2 Hz, CHN), 6.38 (bs, 1H, NH) (Found: C, 59.77; H, 8.29; N, 7.59. $C_9H_{15}NOSi$ requires: C, 59.64; H, 8.35; N, 7.73%. Found: m/z 166.0693. M-CH_3 requires 166.0688).

Cis-(21): b.p. (Kugelrohr) 100°C/0.04 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3418, 3005, 2960, 2165, 1765, 1335, and 1250 cm^{-1}; δ ($CDCl_3$) 0.20 (s, 9H, $SiMe_3$), 1.32 (d, J 8 Hz, 3H, Me), 3.41 (m, 1H, CHMe), 4.35 (d, J 5 Hz, 1H, CHN), 6.31 (bs, 1H, NH) (Found: C, 59.70; H, 8.22; N, 7.73%. Found: m/z 166.0690).

3-Phenyl-4-(trimethylsilylethynyl)azetidin-2-one (22): Procedure C: stirred for 1 h at room temperature then 16 h after Grignard addition, gave 239 mg (49%) trans-β-lactam and 20 mg (4%) cis-β-lactam.

Trans-(22): m.p. 113-114°C; $\nu_{max.}$ ($CHCl_3$) 3410, 3090, 3010, 2960, 2180, 1770, 1605, and 1500 cm^{-1}; δ $CDCl_3$) 0.08 (s, 9H, $SiMe_3$), 3.06 (d, J 2 Hz, 1H, CHPh), 3.30 (d, J 2 Hz, 1H, CHN), 6.72 (bs, 1H, NH), 7.16 (m, 5H, ArH) (Found: C, 68.88; H, 6.93; N, 5.64. $C_{14}H_{17}NOSi$ requires: C, 69.07; H, 7.05; N, 5.76%. Found M^+, 243.1091. Required M, 243.1080).

Cis-(22): m.p. 129-130°C; $\nu_{max.}$ ($CHCl_3$) 3418, 3010, 2960, 2180, 1765, 1600, and 1500 cm^{-1}; δ ($CDCl_3$) 0.08 (s, 9H, $SiMe_3$), 3.68 (d, J 5 Hz, 1H, CHPh), 3.77 (d, J 5 Hz, CHN), 6.52 (bs, 1H, NH), 7.38 (m, 5H, ArH) (Found: C, 68.97; H, 7.8; N, 5.61%. Found: m/z 228.0869. M-CH_3 requires 228.0845).

3-Ethyl-4-(2-furyl)azetidin-2-one (23): Procedure B: stirred for 3 h at room temperature then stirred for 2 h at -5°C after Grignard addition, gave 145 mg (44%) trans-β-lactam and 72 mg (22%) cis-β-lactam.

Trans-(23): b.p. (Kugelrohr) 70-80°C/0.005 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3410, 3020, 2965, 1760, 1665, and 1500 cm^{-1}; δ ($CDCl_3$) 1.02 (t, J 7 Hz, 3H, Me), 1.80 (m, 2H, CH_2Me), 3.25 (dt, J 7 and 2 Hz, 1H, CHEt), 4.35 (d, J 2 Hz, 1H, CHN), 6.30 (m, 2H, H_3, H_4), 6.6 (bs, 1H, NH), 7.37 (m, 1H, H_5) (Found: C, 65.57; H, 6.59; N, 8.75. $C_9H_{11}NO_2$ requires, C, 65.44; H, 6.71; N, 8.48%. Found: M^+, 165.0793. Required M, 165.0790).

Cis-(23): m.p. 92.5-93.5°C; $\nu_{max.}$ ($CHCl_3$) 3410, 2975, 2940, 1765, 1345 cm^{-1}; δ ($CDCl_3$) 0.78 (t, J 7 Hz, 3H, Me), 1.65 (m, 2H, CH_2Me), 3.40 (m, 1H, CHEt), 4.78 (d, J 5 Hz, 1H, CHN), 6.3 (m, 2H, H_3, H_4), 6.81 (bs, 1H, NH), 7.36 (m, 1H, H_5) (Found: C, 65.32; H, 6.58; N, 8.43%. Found: M^+, 165.0793).

3-Ethyl-4-(trimethylsilylethynyl)azetidin-2-one (24): Procedure D: stirred for 2 h at room temperature, then 2 h after Grignard addition, gave 120 mg (31%) trans-β-lactam and 52 mg (13%) cis-β-lactam.

Trans-(24): b.p. (Kugelrohr) 115°C/0.04 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3429, 2960, 2180, 1765, and 1460 cm^{-1}; δ ($CDCl_3$) 0.17 (s, 9H, $SiMe_3$), 1.02 (t, J 7 Hz, 3H, Me), 1.77 (m, 2H, CH_2Me), 2.24 (dt, J 7 and 2 Hz, 1H, CHEt), 3.92 (d, J 2 Hz, 1H, CHN), 6.4 (bs, 1H, NH) (Found: C, 61.32; H, 8.59; N, 7.12. $C_{10}H_{17}NOSi$ requires: C, 61.36; H, 8.62; N, 7.11%).

Cis-(24): b.p. (Kugelrohr) 100-105°C/0.04 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3410, 2960, 2870, 2170, 1760, and 1330 cm^{-1}; δ ($CDCl_3$) 0.18 (s, 9H, $SiMe_3$), 1.05 (t, J 7 Hz, 3H, Me), 1.83 (dq, J 7 and 7 Hz, 2H, CH_2Me), 3.24 (dt, J 7 and 5 Hz, 1H, CHEt), 4.34 (d, J 5 Hz, 1H, CHN), 6.28 (bs, 1H, NH) (Found: C, 61.36; H, 8.62; N, 7.11%).

3-Isopropyl-4-phenylazetidin-2-one (25): Procedure B: stirred for 2 h at room temperature then 2 h after Grignard addition, gave 217 mg (57%) of trans-β-lactam and 43 mg (11%) of cis-β-lactam.

Trans-(25): m.p. 120-121°C (lit.[5] 112-113°C); $\nu_{max.}$ ($CHCl_3$) 3410, 3010, 2980, 2880, 1760, and 1600 cm^{-1}; δ($CDCl_3$) 0.90 (d, J 7 Hz, 3H, Me), 0.95 (d, J 7 Hz, 3H, Me), 1.99 (m, 1H, $CHMe_2$), 2.70 (dd, J 8 and 2 Hz, 1H, CHCO), 4.34 (d, J 2 Hz, 1H, CHN), 6.5 (bs, 1H, NH), 7.26 (m, 5H,ArH).

Cis-(25): m.p. 129-130°C (lit.[5] m.p. 129-130°C; $\nu_{max.}$ ($CHCl_3$) 3410, 3020, 2930, 1760, and 1600 cm^{-1}; δ ($CDCl_3$ 0.44 (d, J 6 Hz, 3H, Me), 1.03 (d, J 6 Hz, 3H, Me), 2.1 (m, 1H, $CHMe_2$), 3.13 (ddd, J 12, 6 and 1 Hz, 1H, CHCO), 4.81 (d, J 6 Hz, 1H, CHN), 6.5 (bs, 1H, NH), 7.32 (m, 5H, ArH).

Synthesis of Azetidin-2-ones using N-t-butyldimethylsilyl Imines.-
N-t-Butyldimethylsilyl-3-methyl-4-phenylazetidin-2-one (26): To N-t-butyldimethylsilyl benzaldimine (7) (698 mg, 3.187 mmol), in CH_2Cl_2 (31.9 ml) at 0°C was added a pentane solution of trimethylsilyl trifluoromethanesulphonate (708 mg, 3.187 mmol) in a dropwise manner over 2 min. The mixture was stirred for 10 min before addition of the E-trimethylsilyl ketene acetal of methyl propanoate (510 mg, 3.187 mmol) in one portion followed immediately by t-BuOH (236 mg, 3.187 mmol), also in one portion. The mixture was warmed to room temperature and stirred for 2.5 h. After cooling to 0°C, MeMgBr (3.19 ml, 3M in ether, 9.6 mmol) was added in a dropwise manner over 2 min and the mixture warmed to room temperature and stirred for 17 h.

The mixture was poured into sat. aq. Na_2HPO_4 (100 ml) and extracted with Et_2O (2 x 100 ml) and the Et_2O extracts washed with sat. aq. NaCl (100 ml) and dried over Na_2SO_4. Concentration in vacuo and flash chromatography of the

residual oil afforded the N-t-butyldimethylsilyl β-lactam, 377 mg (43%) as a 5.6:1 mixture of trans and cis diastereoisomers, and 86 mg (17%) of N-unsubstituted β-lactam in the same diastereomeric ratio.

Trans-(26): δ ($CDCl_3$)-0.20 (s, 3H, SiMe), 0.22 (s, 3H, SiMe), 0.93 (s, 9H, $SiBu^t$), 1.37 (d, J 8 Hz, 3H, Me), 3.07 (dq, J 8 and 2 Hz, 1H, MeCH), 4.10 (d, J 2 Hz, 1H, CHN), 7.32 (bs, 5H, ArH).

Cis-(26): δ ($CDCl_3$)-0.20 (s, 3H, SiMe), 0.22 (s, 3H, SiMe), 0.62 (d, J 7 Hz, 3H, Me), 0.93 (s, 9H, $SiBu^t$), 3.57 (m, 1H, MeCH), 4.70 (d, J 5 Hz, 1H, CHN), 7.32 (bs, 5H, ArH).

N-t-Butyldimethylsilyl-3-methyl-4-(2-furyl)azetidin-2-one (27): To N-t-butyldimethylsilyl furfuraldimine (8) (406 mg, 1.943 mmol) in CH_2Cl_2 (19.4 ml) at 0°C was added a pentane solution of trimethylsilyl trifluoromethanesulphonate (431 mg, 1.943 mmol) in a dropwise manner over 2 min. The mixture was stirred for 10 min before addition of the E-trimethylsilyl ketene acetal of methyl propanoate (311 mg, 1.943 mmol) in one portion followed immediately by t-BuOH (144 mg, 1.943 mmol), also in one portion. The mixture was warmed to room temperature and stirred for 2.5 h. After cooling to 0°C, MeMgBr (1.94 ml, 3M in ether, 5.828 mmol) was added in a dropwise manner over 2 min and the mixture warmed to room temperature and stirred for 17 h.

The mixture was poured into sat. aq. Na_2HPO_4 (100 ml) and extracted with Et_2O (2 x 100 ml). The Et_2O extracts were washed with sat. aq. NaCl (100 ml) and dried over Na_2SO_4. Concentration in vacuo and flash chromatography of the residual oil afforded the N-t-butyldimethylsilyl β-lactam, 251 mg (49%) as a 3:1 mixture of trans and cis diastereoisomers, and 124 mg (24%) of N-unsubstituted β-lactam in the same diastereomeric ratio.

Trans-(27): δ $CDCl_3$-0.07 (s, 3H, SiMe), 0.10 (s, 3H, SiMe), 0.80 (s, 9H, $SiBu^t$), 1.30 (d, J 8 Hz, 3H, Me), 3.30 (dq, J 8 and 2 Hz, 1H, MeCH), 4.03 (d, J 2 Hz, 1H, CHN), 6.22 (m, 2H, H_3, H_4), 7.25 (m, 1H, H_5).

Cis-(27): δ ($CDCl_3$)-0.07 (s, 3H, SiMe), 0.10 (s, 3H, SiMe), 0.80 (s, 9H, $SiBu^t$), 0.98 (d, J 7 Hz, 3H, Me), 3.65 (m, 1H, MeCH), 4.66 (d, J 4 Hz, 1H, CHN), 6.22 (m, 2H, H_3, H_4), 7.25 (m, 1H, H_5).

Methyl 2,2-Dimethyl-3-(N-t-butyldimethylsilyl amino)-3-(ethoxycarbonyl)propanoate: To 4 Å molecular sieves (0.25 g) was added N-t-butyldimethylsilyl glyoxaldimine (13) (123 mg, 0.572 mmol) in CH_2Cl_2 (5.7 ml) and the O-trimethylsilyl ketene acetal of methyl isobutyrate (100 mg, 0.572 mmol) as a CH_2Cl_2 solution. The reaction mixture was cooled to 0°C before addition of a solution of trimethylsilyl trifluoromethanesulphonate (12.7mg, 0.06 mmol) in CH_2Cl_2. The reaction mixture was warmed to room temperature and stirred for 19 h. It was then diluted with Et_2O (50 ml), filtered through Celite, and washed with saturated aqueous Na_2HPO_4 (50 ml). The aqueous portion was extracted with Et_2O (50 ml), and the combined organic extracts were dried over Na_2SO_4. Concentration in vacuo and flash chromatographic purification of the residual oil yielded methyl 2,2-dimethyl-3-(N-t-butyldimethylsilyl amino)-3-(ethoxycarbonyl)propanoate, 129 mg (71%), b.p. 85-94°C/0.1 mm Hg; $\nu_{max.}$ (CCl_4) 3380, 2980, 2950,2930, 2900, 2880, 2860, 1740, 1470, 1460, 1260, 1190, 1140, 1120, and 830 cm^{-1}; δ ($CDCl_3$) 0.02 (s, 6H, $SiMe_2$), 0.88 (s, 9H, $SiBu^t$), 1.14 (s, 3H, CH_3CCH_3), 1.21 (s, 3H, CH_3CCH_3), 1.28 (t, J 7 Hz, 3H, CH_2CH_3), 3.72 (s, 3H, CO_2Me), 4.17 (q, J 7 Hz, 2H, CH_2CH_3) (Found: m/z, 260.1325. $C_{15}H_{31}NO_4Si-C_4H_9$ requires m/z 260.1312).

N-t-Butyldimethylsilyl-3,3-dimethyl-4-(ethoxycarbonyl)azetidin-2-one (29): To methyl 2,2-dimethyl-3-(N-t-butyldimethylsilylamino)-3-ethoxycarbonyl) propanoate (129 mg, 0.407 mmol) in CH_2Cl_2 (4.1 ml) at 0°C was added MeMgBr (0.27 ml, 3M in ether, 0.814 mmol). The resulting solution was warmed to room temperature and stirred for 19 h. Dilution with Et_2O (50 ml), washing with saturated aqueous ammonium chloride (50 ml), extraction of the aqueous portion with Et_2O (50 ml), drying of the combined organic extracts over Na_2SO_4, concentration in vacuo and flash chromatographic purification of the residual oil afforded N-t-butyldimethylsilyl-3,3-dimethyl-4-(ethoxycarbonyl)azetidin-2-one, 99 mg (85%), b.p. 130°C/1 mm Hg; $\nu_{max.}$ ($CHCl_3$) 3010, 2950, 2920, 2850, 1735, 1250, 835, and 820 cm^{-1}; δ ($CDCl_3$) 0.12 (s, 3H, SiMe), 0.32 (s, 3H, SiMe), 0.98 (s, 9H, $SiBu^t$), 1.13 (s, 3H, $C\underline{H}_3CCH_3$), 1.32 (t, J 7 Hz, 3H, $CH_2C\underline{H}_3$), 1.43 (s, 3H, $CH_3C\underline{H}_3$), 3.84 (s, 1H, CHN), 4.26 (q, J 7 Hz, 2H, $C\underline{H}_2CH_3$) (Found: m/z, 228.1054. $C_{14}H_{27}NO_3Si-C_4H_9$ requires m/z 228.1051).

Benzaldehyde-N,N,O-Tris(trimethylsilyl)amine Acetal (30): To hexamethyldisilazane (2.32 ml, 11 mmol) was added n-BuLi (4.00 ml, 2.5M in hexane, 10 mmol) over 5 min. The solution was stirred for 15 min, THF (18 ml) was then added and the mixture was cooled to -78°C over 20 min. Trimethylchlorosilane (1.27 ml, 10 mmol) was added dropwise over 5 min and stirring continued at -78°C for 10 min. Freshly distilled benzaldehyde (1.06 g, 10 mmol) in THF (10 ml) was added dropwise over 7 min, and the reaction mixture was stirred at -78°C for a further 30 min before being allowed to warm to room temperature over 30 min. Non-aqueous work-up and Kugelrohr distillation afforded pure benzaldehyde N,N,O-tris(trimethylsilyl)-amine acetal, 1.82 g (54%), b.p. 100-110°C/0.04 mm Hg; $\nu_{max.}$ (CCl_4) 2960, 2900, 1265, 1255, and 920 cm^{-1}; δ ($CDCl_3$) 0.10 [s, 18H, $-N(SiMe_3)_2$], 0.22 (s, 9H, $-OSiMe_3$), 5.85 (s, 1H, CHPh), 7.30 (m, 5H, Ph) (Found: M^+, 339.1848. $C_{16}H_{33}NOSi_3$ requires M, 339.1861).

Furfural N,N,O-Tris(trimethylsilyl)amine Acetal (31).: All operations were identical with the procedure described above for benzaldehyde N,N,O-tris(trimethylsilyl)amine acetal except that freshly distilled furfural (0.96 g, 10 mmol) in THF (10 ml) was employed. Kugelrohr distillation of the crude product afforded furfural N,N,O-tris(trimethylsilyl)amine acetal, 2.86 g (87%), b.p. 90-110°C/0.3 mm Hg; $\nu_{max.}$ (CCl_4) 2960, 2900, 1260, 1250, 870, and 850 cm^{-1}; δ ($CDCl_3$) 0.11 [s, 18H, $-N(SiMe_3)_2$], 0.26 (s, 9H, $OSiMe_3$), 5.75 (s, 1H, $C\underline{H}NSi_2$), 6.10 (m, 1H, H-4), 6.25 (m, 1H, H-3), 7.28 (s, 1H, H-5) (Found: M^+, 329.1661. $C_{14}H_{31}NO_2Si_3$ requires M, 329.1654).

3-Methyl-4-(2-furyl)azetidin-2-one (32): Furfural N,N,O-tris(trimethylsilyl)amine acetal (329 mg, 1.00 mmol) was dissolved in CH_2Cl_2 (3.5 ml) and the solution cooled to 0°C. A solution of trimethylsilyl trifluoromethanesulphonate (222 mg, 1.00 mmol) in CH_2Cl_2 was added dropwise over 2 min and the mixture stirred at 0°C for 10 min before addition of the E-O-trimethylsilyl ketene acetal of methyl propanoate (480 mg, 3.00 mmol) in one portion. The mixture was warmed to room temperature and stirred for 19 h. It was diluted with Et_2O (50 ml) and filtered through Celite. The organic solution was washed with saturated aqueous Na_2HPO_4 (50 ml), the aqueous portion extracted with Et_2O (50 ml), and the combined organic extracts were dried over Na_2SO_4. Concentration in vacuo and flash chromatography of the residual oil afforded methyl 2-methyl-3-amino-3-(2-furyl)propanoate, 117 mg (64%) as a 2:1 mixture of threo and erythro diastereoisomers.

To a solution of this diastereoisomeric mixture (117 mg, 0.639 mmol) in Et_2O (4 ml) was added Et_3N (94 μl, 0.671 mmol) and the mixture was cooled to 0°C.

Trimethylchlorosilane (85 µl, 0.671 mmol) was then added, and the heterogeneous reaction mixture allowed to warm to room temperature with stirring over 24 h. The mixture was re-cooled to 0°C, MeMgBr (0.54 ml, 3M in ether, 1.630 mmol) was added dropwise over 2 min, and the mixture was allowed to warm to room temperature with stirring over 15 h. It was then diluted with Et_2O (30 ml) and washed with 1N HCl (30 ml). The aqueous portion was extracted with Et_2O (30 ml) and the combined organic extracts were dried over Na_2SO_4. Concentration *in vacuo* followed by flash chromatographic separation yielded 61 mg (63%) of the β-lactam (32) as a 2:1 mixture of *trans* and *cis* diastereoisomers.

Trans-(32): m.p. 113-114°C; $\nu_{max.}$ ($CHCl_3$) 3418, 3120, 2880, 1770, 1670, 1600, and 1350 cm^{-1}; δ ($CDCl_3$) 1.35 (d, J 7 Hz, 3H, Me), 3.34 (dq, J 7 and 2 Hz, 1H, CHMe), 4.27 (d, J 2 Hz, 1H, CHN), 6.30 (m, 2H, H_3H_4), 5.53 (bs, 1H, NH), 7.36 (m, 1H, H_5) (Found: C, 63.63; H, 5.90, N, 9.30. $C_8H_9NO_2$ requires: C, 63.56; H, 6.00; N, 9.27%. Found: M^+, 151.0628. Required M, 151.0634).

Cis-(32): m.p. 82-83.5°C; $\nu_{max.}$ ($CHCl_3$) 3420, 3020, 2980, 2940, 1765, and 1340 cm^{-1}; δ ($CDCl_3$) 0.96 (d, J 8 Hz, 3H, Me), 3.48 (m, 1H, CHMe), 4.77 (d, J 5 Hz, CHN), 6.30 (m, 2H, H_3, H_4), 6.8 (bs, 1H, NH), 7.37 (m, 1H, H_5) (Found: C, 63.64; H, 5.94; N, 9.33%. Found: M^+, 151.0633).

REFERENCES

1. Southgate, R. and Elson, S., 'Naturally Occurring β-Lactams', *Prog. Chem. Org. Nat. Prods.*, 1985, **47**, 1.
2. 'Chemistry and Biology of β-Lactam Antibiotics', Vol. 2, eds. Morin, R.B. and Gorman, M., Academic Press, New York and London, 1982.
3. Staudinger, H., *Liebigs Ann. Chem.*, 1907, **356**, 51.
4. Birkofer, L. and Schramm, J., *Liebigs Ann. Chem.*, 1977, 760.
5. Ha, D.-C., Hart, D.J., and Yang, T.-K., *J. Am. Chem. Soc.*, 1984, **106**, 4819 and references therein; see also Cainelli, G., Contento, M., Giacomini, G., and Panunzio, M., *Tetrahedron Letters*, 1985, **26**, 937; Chiba, T., Nagatsuma, M., and Nakai, T., *Chemistry Letters*, 1984, 1927; Chiba, T. and Nakai, T., *Chemistry Letters*, 1985, 651; Chiba, T., Nakai, T., and Nagatsuma, M., *Chemistry Letters*, 1985, 1343.
6. Chan, L.-H., and Rochow, E.G., *J. Organomet. Chem.*, 1967, **9**, 231.
7. Krüger, C., Rochow, E.G., and Wannagat, U., *Chem. Ber.*, 1963, **96**, 2132.
8. For a preliminary account of a portion of this work, see Colvin, E.W. and McGarry, D.G., *J. Chem. Soc., Chem. Commun.*, 1985, 539.
9. See however Cainelli, G., Giacomini, D., Panunzio, M., Martelli, G., and Spunta, G., *Tetrahedron Letters*, 1987, **28**, 5369.
10. Ager, D.J., *Synthesis*, 1984, 384; Colvin, E., 'Silicon in Organic Synthesis', Krieger Press, Florida, 1985.
11. Ainsworth, C., Chen, F., and Kuo, Y.N., *J. Organomet. Chem.*, 1972, **46**, 59.
12. Ireland, R.E., Mueller, R.H., and Willard, A.K., *J. Am. Chem. Soc.*, 1976, **98**, 2868.
13. Sharma, R.K. and Fry, J.L., *J. Org. Chem.*, 1983, **48**, 2112.
14. Ojima, I. and Inaba, S., *Tetrahedron Letters*, 1980, **21**, 2077, 2081.
15. Birkofer, L. and Schramm, J., *Liebigs Ann. Chem.*, 1975, 2195.
16. Okano, K., Morimoto, T., and Sekiya, M., *J. Chem. Soc., Chem. Commun.*, 1984, 883.
17. Harwood, L.M., *Aldrichimica Acta*, 1985, **18**, 25.