Reagents and Synthetic Methods. Part 58.† Synthesis of β-Lactams from Acetic Acids and Imines promoted by Vilsmeier Type Reagents

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The development of a practical method for the stereospecific preparation of several 3-substituted β-lactams from acetic acids and imines is described. The key step of the method is the activation of the carboxy component by means of Vilsmeier type reagents. The preparation of some *N*-(2′-hydroxyethyl)-β-lactams and *N*-(*p*-dimethyl-t-butylsiloxyphenyl)-β-lactams as intermediates for N–H azetidinones is also reported. For the last compounds the steric bulk of the N-substituent is the key feature for a high *cis*-β-lactam formation.

Since the discovery of non classical β-lactam antibiotics,[1] the development of synthetic methods for the synthesis of 3-substituted β-lactams has been the object of intense study by a number of research groups. Among numerous methods for the synthesis of β-lactams,[2] the annelation of acid chlorides with imines has proved to be a versatile procedure for the construction of the azetidinone ring. However, the acid chloride is not always simple to prepare and/or is not commercially available. An alternative synthesis of β-lactams which circumvents the use of acid halides involves the use of carboxy group-activating agents. Among many useful and reliable activating agents available in the literature,[3] the iminium salts,[4] have received attention, especially those derived from dimethylformamide and inorganic reagents. From this class of reagents the dimethylformiminium chloride (**1**) is the most widely used in organic synthesis. It is known not only as a formylating reagent[5] but also as an activating reagent for carboxylic acids to give esters,[6] amides,[7] and acid chlorides,[8] while the iminium salt is reported also to activate the alcohol moiety yielding alkyl chlorides[9] and nitriles from aldoximes.[10] Also, Fujisawa and co-workers have reported the use of this reagent for the direct conversion of carboxylic acids into alcohols[11] and aldehydes.[12] *N*-Chlorosulphinylmethylene-*N*,*N*-dimethylammonium chloride (**2**),[13] also activates carboxylic acids[14–16] and amino acids[17] and more recently it has been used for the preparation of carboxylic acid anhydrides.[18] This reagent also activates the hydroxy function to give alkyl chlorides from alcohols[19] and gem-dichlorides from aldehydes.[20]

$Me_2\overset{+}{N}{=}CHCl\ Cl^-$ (**1**) $Me_2\overset{+}{N}{=}CHOS(O)Cl\ Cl^-$ (**2**)

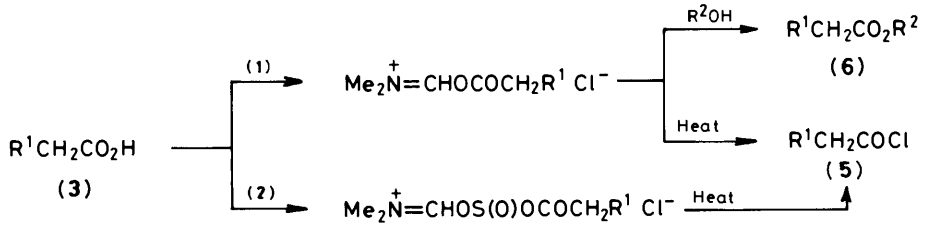
Stadler[6] has reported that activation of carboxylic acids (**3**) by means of reagent (**1**) takes place *via* an active intermediate (**4**) which in the presence of alcohols gives esters (**6**) in good to excellent yields (Scheme 1). In a similar manner, activation of the carboxylic acids (**3**) by means of reagent (**2**) takes place through an active intermediate of type (**7**) which when heated in the appropriate solvent loses hydrogen chloride and yields the corresponding acid chloride.[14]

In a preliminary communication,[21] we have reported some aspects of our studies on the activation of acetic acids promoted by reagent (**2**) for the synthesis of β-lactams. We present here details of these studies as well as new observations made by us.

Results and Discussion

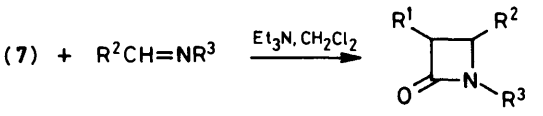
The preparation of the β-lactams (**9**)—(**20**) involves two steps: (*a*) the activation of the carboxy component, *i.e.* generation of the active intermediate (**7**) from (**2**) and the carboxylic acid, and (*b*) cyclocondensation of this activated carbonyl intermediate with a Schiff base in the presence of triethylamine. The first step was carried out by adding the reagent (**2**), prepared from thionyl chloride and dimethylformamide, to a suspension or solution of the corresponding carboxylic acid in methylene dichloride at 0—5 °C. In the case of insoluble carboxylic acids dissolution was observed in a few minutes and, in general, the activation was found to be complete in 15—20 min at 0—5 °C. The second step consists of the addition of the imine (**8**) to a solution of the corresponding active intermediate followed by addition of a solution of triethylamine in methylene dichloride. After the reaction mixture had been stirred at room temperature for 20—24 h the corresponding β-lactams (**9**)—(**20**) were isolated in good yield. β-Lactams have been prepared from a variety of structurally different acids to determine the scope and limitations of this method. Experimental results are summarized in Table 1 and illustrate the efficiency, the applicability, and the scope of the present method. Alkoxyacetic acids, dichloroacetic acid, and phthalimidoacetic acid yielded the corresponding β-lactams in good to excellent yields. Likewise, *p*-methoxyphenylacetic acid was converted, although not as efficiently, into the corresponding β-lactam.

† For Part 57 see J. M. Aizpurua, B. Lecea, and C. Palomo, *Can. J. Chem.*, in press.



Scheme 1.

Table 1. Preparation of β-lactams



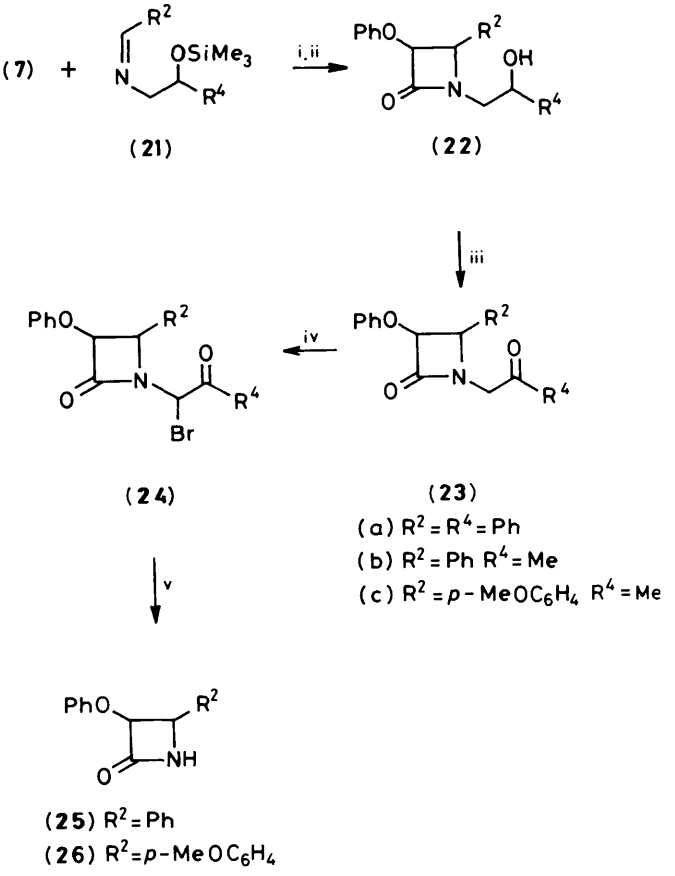
(8) (9)–(20)

Product[a,b]	R^1	R^2	R^3	Yield (%)[c]	M.p. (°C) (lit.)
(9)	Pht	Ph	Ph	65	229–230
(10)	Pht[d]	*p*-$MeOC_6H_4$	α-$C_{10}H_{17}$[e]	75	222—223 (222—223)[31a]
(11)	Pht	C=CHCH=CHO[h]	Ph	65	212—214
(12)	Pht	*p*-$MeOC_6H_4$	OEt	67	140—141
(13)	PhO	*p*-$MeOC_6H_4$	OEt	60	88—89
(14)	Pht	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	71	189—190 (174—175)[31b]
(15)	Pht	Ph	Ph	50	229—230 (230—231)[31a]
(16)	*p*-$MeOC_6H_4$	Ph	Ph	35	200—204 (200—204)[31c]
(17)	Cl_2[f]	Ph	Ph	60	158—160 (164)[31d]
(18)	Pht	*p*-$MeOC_6H_4$	$PhCH_2$	60	181—183
(19)	PhO	C=CHCH=CHO[h]	4-$MeOC_6H_4$	60	154—155
(20)	MeO	Ph	Ph	60[g]	141—142 (141—142)[31e]

[a] Reaction was carried out by addition of triethylamine to a solution of the imine and the activated carboxylic acid. [b] All compounds showed *trans* configuration as was observed by n.m.r. analysis of the crude reaction mixture (*ca.* 2 Hz) except for compound (**19**). Compound (**20**) was obtained as a mixture *cis*:*trans* in a ratio 9:1. [c] Isolated yields after crystallization from ethanol. [d] Pht: phthalimido group. [e] From 1-naphthylamine. [f] From dichloroacetic acid. [g] Prepared from reagent (**1**). Yield of the *cis* isomer is given. [h] From 2-furaldehyde.

Although limitations in this method were found with *N*-acylamino acids such as hippuric acid and aceturic acid, the former upon activation when treated with benzylidene imines and triethylamine yielded the corresponding 4-alkylidene-2-phenyloxazol-5(4*H*)-one. Activation of carboxylic acids carrying other functional groups such as alkyl, cyano, hydroxy and *N*(-α-methyl-β-methoxycarbonylvinyl)amino group (Dane salt of aminoacetic acid),* however did not lead to the formation of the expected β-lactams.

When the method was applied to the imines (**21**) derived from aldehydes and aminoethanol derivatives (Scheme 2) prior protection of the hydroxy group as the trimethylsilyl ether was required,[22] the resulting crude trimethylsiloxy β-lactams, key compounds for the synthesis of NH azetidinones,[23] then being desilylated under mild acidic conditions. Thus, the crude product was dissolved in acetone and a solution of hydrochloric acid was then added; after work-up the resulting oil was treated with ethanol to give the expected β-lactams (**22**). These compounds were obtained as a mixture (*ca.* 1:1) of diastereoisomers as indicated by their n.m.r. spectrum. We have also found that the β-lactams (**22b**) and (**22c**) (Scheme 2) were formed as a mixture of *cis* and *trans* isomers, which were easily separated by column chromatography or recrystallization. However, when phenyl dichlorophosphate, a reagent developed by us in β-lactam synthesis,[22] was used as activating agent of the phenoxyacetic acid, the corresponding *cis* diastereoisomers were formed as sole products as judged by n.m.r. analysis of their crude reaction mixtures. Since we envisaged eventually removing the asymmetric centre in the side chain, no attempt was made to isolate the diastereoisomers. Thus, as shown in Scheme 2, nicotinium dichromate (NDC) oxidation[24] of (**22**) in



Scheme 2. *Reagents*: i, (**4**), (**7**) or $PhOP(O)Cl_2$, NEt_3, CH_2Cl_2; ii, 0.1M HClaq.; iii, NDC-pyr.; iv, $DMAPBr_3H$; v, $NaHCO_3$, H_2O–Me_2CO

* Amino protecting group developed by Dane *et al.*, see E. Dane, F. Drees, P. Konrad, and T. Dockner, *Angew. Chem., Int. Ed. Engl.* 1962, **1**, 658.

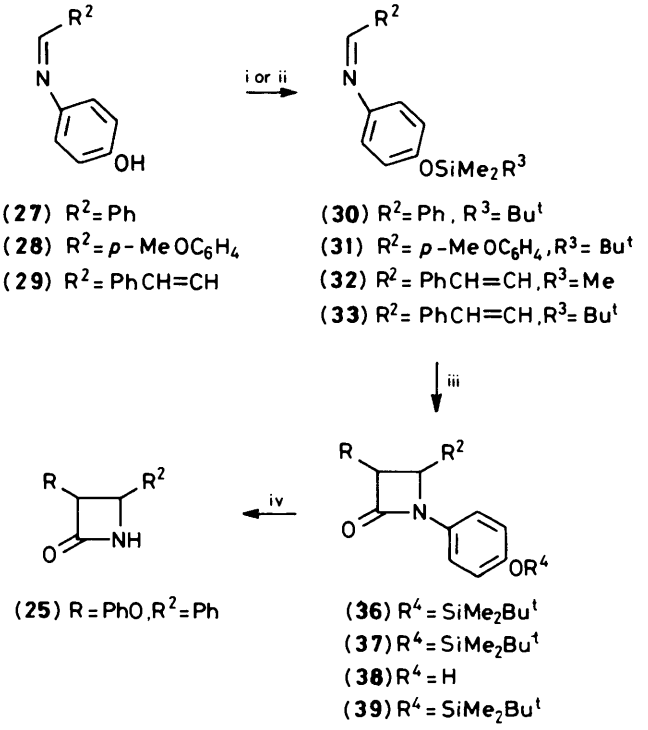
Table 2. Preparation of β-lactams under different conditions (see Scheme 3)

	Product			Conditions[a]	Configuration[b]	
	R	R^2	R^3	reagent, T (°C)	*cis*:*trans*[c]	*cis*:*trans*[d]
(34)	PhO	Ph	Ph	(2), 0—5	95:5(77)	43:57(80)
				(2), 40	95:5(77)	88:12(80)
				(1), 0—5	97:3(99)	90:10(90)
(35)	PhO	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	(2), 0—5	90:10(80)	35:65(85)
				(2), 40	85:15(87)	
				(1), 0—5	90:10(98)	70:30(96)
(36)	PhO	Ph	4-$Bu^tMe_2SiOC_6H_4$	(1), 0—5	100:0(96)	
(37)	PhO	*p*-$MeOC_6H_4$	4-$Bu^tMe_2SiOC_6H_4$	(2), 0—5	100:0(96)	
(38)	Pht	CH=CHPh	4-$Me_3SiOC_6H_4$[e]	(2), 40	50:50(90)	
(39)	Pht	CH=CHPh	4-$Bu^tMe_2SiOC_6H_4$	(2), 40	85:15(96)	

[a] Reaction conditions for activation of carboxylic acid. [b] Configuration of C-3 and C-4 protons in all these monocyclic β-lactams was determined by n.m.r. spectroscopy. The number in parentheses indicate isolated yields of the β-lactams. [c] The activated acid was added to a solution of the imine and triethylamine. [d] The imine and triethylamine were added to a solution of the activated carboxylic acid. [e] The β-lactam was isolated with the free hydroxy group.

methylene dichloride–pyridine gives (**23**) in high isolated yield. Treatment of (**23**) with 4-*N*,*N*-dimethylaminopyridinium bromide perbromide (DMAP·HBr_3)[25] afforded the corresponding α-bromo ketone (**24**) which upon treatment with $NaHCO_3$ in aqueous acetone yielded the desired *N*-unsubstituted β-lactam.

On the basis of the data obtained, the steric course of annelation using reagent (**2**) does not appear to be predictable. Bose *et al.*[26] have shown that in the addition of acid chlorides to a solution of Schiff bases and triethylamine the *cis* stereochemistry generally predominates. However, when triethylamine was added to a solution of the Schiff base and acid chloride, the relative proportions of *cis* and *trans* isomers were reversed. To determine the optimum conditions for the preparation of *cis*-β-lactams employing activating agent (**2**) or (**1**) we examined the reaction under the conditions reported by Bose. Thus, when the activation of phenoxyacetic acid was carried out by means of reagent (**2**) under reflux conditions and the acid chloride formed *in situ* added to a solution of the imine and triethylamine, the corresponding β-lactam was obtained as a mixture of *cis*/*trans* isomers in a ratio of 9:1. From the results outlined in Table 2, the best conditions for a high *cis*-β-lactam formation were obtained when the activation of carboxylic acids was carried out at 0—5 °C and the *in situ* activated carboxylic acids were added to the corresponding imine and triethylamine. Moreover, the *cis*/*trans* ratio is also increased when the size of the substituents at N-1 and C-4 increases.[27] This result has special significance in view of the fact that β-lactam protons in active penicillins, cephalosporins, and other β-lactam antibiotics for clinical use are in a *cis*-relationship. In this manner the β-lactam (**38**) was obtained as an equimolar mixture of *cis* and *trans* isomers but, however, when the bulkiness of the substituent at N-1 was increased such as in the case of β-lactam (**39**) the *cis* isomer was predominantly formed. Likewise, the β-lactams (**36**) and (**37**) were obtained as a single isomer. It is of interest to note that these phenolic β-lactams can serve as precursors of N–H azetidinones. Thus, Kronenthal and coworkers[28] have reported that *N*-*p*-methoxyphenylazetidin-2-ones are useful intermediates for the preparation of *N*-unsubstituted β-lactams through *N*-de-arylation with ceric ammonium nitrate (CAN). We have found that *N*-(4-trimethylsiloxyphenyl)azetidin-2-ones or their corresponding hydroxy derivatives when treated with CAN afforded the corresponding *N*-unsubstituted β-lactams in good yields (Scheme 3). In practice, these β-lactams were prepared from the corresponding trimethylsilyl and dimethyl-t-butylsilyl[29] Schiff bases (**30**)—(**33**) upon reaction with the corresponding activated carboxylic acids. After aqueous work-up, the β-lactams (**36**) and (**39**) were isolated as dimethyl-t-butylsilyl derivatives, however, when the trimethylsilyl group was used in place of the dimethyl-t-butylsilyl moiety as protective group, the unsilylated β-lactam (**38**) was the isolated product. *N*-De-arylation was performed according to the Kronenthal's method but using potassium fluoride as the desilylating reagent in the reaction medium.



Scheme 3. *Reagents*: i, $ClSiMe_3$, Et_3N, CH_2Cl_2; ii, $ClSiMe_2Bu^t$, DBU, CH_2Cl_2; iii, Et_3N; iv, KF, CAN, Me_3CN–H_2O

In conclusion, the present method extends the use of the readily available Vilsmeier type reagents in the synthesis of β-lactams, avoiding the use of acid chlorides as starting materials. The easy preparation of β-lactams from the reagents reported is obvious as demonstrated here by these limited number of examples, and may be readily extended to further applications. Moreover, the choice of Schiff bases with a bulky substituents provided mainly *cis* β-lactams.[30]

Experimental

M.p.s were taken on a Büchi SMP-20 melting point apparatus and are uncorrected. ^{1}H N.m.r. spectra were measured on a Varian EM-360 spectrometer and are reported in p.p.m. downfield from internal tetramethylsilane. All the starting materials used in this work were either commercially available in generally 98% or higher purity and were used without further purification or prepared by literature procedures. Methylene dichloride was purified by the usual method and stored over molecular sieves. Elemental analyses were performed by Departamento de Orgánica, Colegio Universitario de Alava. All the Schiff bases were prepared by conventional procedures.

Preparation of Reagent (**1**).—To a solution of dimethylformamide (0.5 ml, 6 mmol) in methylene dichloride (5 ml) at 0—5 °C, was added dropwise a solution of oxalyl chloride (0.5 ml, 5.75 mmol) in the same solvent (5 ml) over a period of 30 min. During the addition fast evolution of CO_2 and CO was observed. The resulting mixture was stirred at 0—5 °C for a further 30 min, and the reagent used without further purification.

Preparation of Reagent (**2**).—In a 25 ml dropping funnel, benzene (5 ml), dimethylformamide (1 ml, 10.2 mmol), and thionyl chloride (0.8 ml, 11 mmol) were consecutively added; after 3—5 min two phases appeared and the reagent (lower layer) was separated.

Preparation of the β-*Lactams* (**9**)—(**23**): *General Procedure.*—To a solution or suspension of the carboxylic acid (10 mmol) in methylene dichloride (20 ml) was added at 0 °C the reagent (**2**) (10.2 mmol). The mixture was stirred for 10 min at 0—5 °C after which the imine (**8**) (10 mmol) was added; this was followed by dropwise addition of triethylamine (4.2 ml, 30 mmol) in methylene dichloride (10 ml). The resulting mixture was stirred overnight at room temperature and then washed with water (50 ml); the organic layer separated, dried (Na_2SO_4), and evaporated to give an oil which upon treatment with ethanol or ethanol–water afforded the corresponding β-lactam as a single isomer.

4-(2-*Furyl*)-1-*phenyl*-3-*phthalimidoylazetidin*-2-*one* (**11**). From phthalimidoacetic acid (10 mmol) and *N*-(2-furylidene)aniline (10 mmol); yield 2.34 g (65%), m.p. 212—214 °C (from ethanol) (Found: C, 70.4; H, 4.05; N, 7.95. $C_{21}H_{14}N_2O_4$ requires C, 70.38; H, 3.95; N, 7.82%); $\delta_H(CDCl_3)$ 5.4 (1 H, d, *J* 1.8 Hz, CH), 5.5 (1 H, d, *J* 1.8 Hz, CH), 6.25 (1 H, dd, *J* 2, 4 Hz, CH), 6.5 (1 H, d, *J* 4 Hz, CH), 6.7—7.4 (6 H, m, Ar, CH=), and 7.7 (4 H, s br, Ar).

1-*Ethoxy*-4-(p-*methoxyphenyl*)-3-*phthalimidoylazetidin*-2-*one* (**12**). From phthalimidoacetic acid (2.05 g, 10 mmol) and ethyl *N*-(*p*-methoxyphenyl)formimidate (1.79 g, 10 mmol); yield 2.45 g (67%), m.p. 140—141 °C (lit.,[31f]) (Found: C, 65.4; H, 5.05; N, 7.6. $C_{20}H_{18}N_2O_5$ requires C, 65.56; H, 4.96; N, 7.65%); $\delta_H(CDCl_3)$ 1.35 (3 H, t, Me), 3.75 (2 H, q, CH_2), 3.8 (3 H, s, OMe), 5.25 (1 H, d, *J* 2 Hz, CH), 5.7 (1 H, d, *J* 2 Hz, CH), 6.85 (2 H, d, ArH), 7.4 (2 H, d, ArH), and 7.8 (4 H, s, ArH).

1-*Ethoxy*-4-(p-*methoxyphenyl*)-3-*phenoxyazetidin*-2-*one* (**13**). From phenoxyacetic acid (15.2 g, 100 mmol) and ethyl *N*-(-*p*-methoxyphenyl)formimidate (17.9 g, 100 mmol); yield 18.7 g (60%), m.p. 88—89 °C (lit.,[31f]) (Found: C, 69.10; H, 6.15; N, 4.50. $C_{18}H_{19}NO_4$ requires C, 69.21; H, 6.14; N, 4.48%); $\delta_H(CDCl_3)$ 1.2 (3 H, t, Me), 3.7 (2 H, q, CH_2) 3.8 (3 H, s, OMe), 5.1 (1 H, s br, CH), 5.4 (1 H, s br, CH), and 6.8—7.8 (9 H, m, ArH).

1-*Benzyl*-4-(p-*methoxyphenyl*)-3-*phthalimidoylazetidin*-2-*one* (**18**). From phthalimidoacetic acid (10 mmol) and *N*-(*p*-methoxybenzylidene)benzylamine (10 mmol); yield 2.47 g (60%), m.p. 181—183 °C (Found: C, 72.3; H, 4.25; N, 6.5. $C_{25}H_{20}N_2O_4$ requires C, 72.79; H, 4.65; N, 6.79%); $\delta_H(CDCl_3)$ 3.7 (3 H, s, OMe), 3.8 (1 H, d, *J* −14 Hz, CH), 4.6 (1 H, d, *J* 2 Hz, CH), 4.8 (1 H, d, *J* −14 Hz, CH), 5.1 (1 H, d, *J* 2 Hz, CH), 6.4—7.3 (9 H, m, ArH), and 7.56 (4 H, s, ArH).

4-(2-*Furyl*)-1-(p-*methoxyphenyl*)-3-*phenoxyazetidin*-2-*one* (**19**). From phenoxyacetic acid (10 mmol) and *N*-(-2-furylidene)-4-methoxyaniline (10 mmol); yield 3.3 g (60%), m.p. 154—155 °C (Found: C, 71.5; H, 5.05; N, 4.3. $C_{20}H_{17}NO_4$ requires C, 71.62; H, 5.12; N, 4.18%); $\delta_H(CDCl_3)$ 3.6 (3 H, s, OMe), 5.05 (1 H, d, *J* 5 Hz, CH), 5.2 (1 H, d, *J* 5 Hz, CH), 6.0 (1 H, dd, *J* 2, 4 Hz, CH=), 6.15 (1 H, d, *J* 4 Hz, CH), and 6.3—7.1 (10 H, m, ArH).

Preparation of β-*Lactams* (**22**): *General Procedure.*—Method A. The aldehyde (50 mmol) was added to the (*R,S*)-1-aminopropan-2-ol (50 mmol) giving a slight exothermic reaction. The mixture was set aside at room temperature and then diluted with methylene dichloride (75 ml) and dried ($MgSO_4$); the solution was stirred for 30 min and then filtered. To this solution of the Schiff base (**21**), triethylamine (7 ml, 50 mmol), and chlorotrimethylsilane (6.4 ml, 50 mmol) were successively added at 0 °C. The resulting mixture was stirred at room temperature for 60 min after which time triethylamine (21 ml, 150 mmol) was added to it; the activated acid from reagent (**2**) (50 mmol) was then added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 20—24 h and then washed with water (75 ml) and evaporated to give an oil. This dissolved in acetone (125 ml), was stirred with solution of 1M HCl (60 ml) at room temperature for 30 min, after which time the mixture extracted with methylene dichloride. The organic layer was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated to give (**22**) as a mixture of diastereoisomers which were crystallized from ethanol.

Method B. To the corresponding trimethylsiloxy Schiff base in methylene dichloride prepared as above, was added at 0 °C triethylamine (21 ml, 150 mmol), the carboxylic acid (50 mmol), and phenyl dichlorophosphate (7.5 ml, 50 mmol). The same procedure as described in method A was found to give the corresponding *cis* β-lactam (**22**) as single isomer.

1-(2-*Hydroxypropyl*)-3-*phenoxy*-4-*phenylazetidin*-2-*one* (**22b**). By method A. From *N*-benzylidene-2-trimethylsiloxypropylamine (50 mmol) and phenoxyacetic acid (50 mmol), yield (10 g, 67%); *cis*:*trans* ratio 75:25; m.p. 138—141 °C (crystallization from ethanol–water gives the *cis* isomer) (Found: C, 72.6; H, 6.5; N, 4.8. $C_{18}H_{19}NO_3$ requires C, 72.69; H, 6.45; N, 4.72%); $\delta_H(CDCl_3)$ 1.05, 1.15 (3 H, d, *J* 7 Hz each, Me both diastereoisomers), 2.6—4.2 (4 H, m, CH_2, CH, OH), 4.85 (1 H, d, *J* 4 Hz, CH), 5.35 (1 H, d, *J* 4 Hz, CH), and 6.3—7.4 (10 H, m, ArH).

By method B. From *N*-benzylidene-2-trimethylsiloxypropylamine (50 mmol) and phenoxyacetic acid (50 mmol: yield 11.1 g (75%), m.p. 138—141 °C (ethanol–water).

1-(2-*Hydroxypropyl*)-3-*phenoxy*-4-(*p-methoxyphenyl*)-*azetidin*-2-*one* (**22c**). By method A. From *N*-(4-methoxybenzylidene)-2-trimethylsiloxypropylamine (50 mmol) and phenoxyacetic acid (50 mmol); yield 9.8 g (60%), *cis*:*trans* proportion 1:1; $\delta_H(CDCl_3)$ 4.6 (1 H, s br, CH *trans*), 4.9 (1 H, s br, CH *trans*), 4.95 (1 H, d, *J* 4 Hz, CH), and 5.5 (1 H, d, *J* 4 Hz, CH).

By method B. From *N*-(4-methoxybenzylidene)-2-trimethylsiloxypropylamine (50 mmol) and phenoxyacetic acid (50 mmol); yield 10.6 g (65%), m.p. 141—143 °C (ethanol–water) (Found: C, 69.75; H, 6.4; N, 4.35. $C_{19}H_{21}NO_4$ requires 69.69; H, 6.48; N, 4.28%); $\delta_H(CDCl_3)$ 1.0, 1.1 (3 H, d, *J* 7 Hz each, Me both diastereoisomers), 2.8—4.5 (7 H, m, CH_2CH, OH, OMe), 5.0 (1 H, d, *J* 4 Hz, CH), 5.4 (1 H, d, *J* 4 Hz, CH), and 6.6—7.5 (9 H, m, ArH).

Preparation of β-*Lactams* (**23**): *General Procedure.*—To a suspension of NDC (27.84 g, 60 mmol) in methylene dichloride (125 ml), pyridine (9.6 ml, 120 mmol) was added at room

temperature with mechanical stirring. The suspension was cooled at 0—5 °C and the β-lactam (**22**) (20 mmol) was added. The reaction mixture was stirred at room temperature until the oxidation was complete and was then filtered off through a pad of silica gel 230—400 mesh. The organic layer was washed with water (30 ml), 6M HCl (30 ml) and saturated aqueous $NaHCO_3$ (30 ml), dried (Na_2SO_4), and evaporated to give fairly pure β-lactam (**23**).

1-*Benzoylmethyl*-3-*phenoxy*-4-*phenylazetidin*-2-*one* (**23a**). From (**22a**)[32] (10 mmol) after 3 h at room temperature; yield 3.4 g (95%), m.p. 165—167 °C (Found: C, 77.85; H, 5.7; N, 4.1. $C_{23}H_{19}NO_3$ requires C, 77.28; H, 5.37; N, 3.92%); $\delta_H(CDCl_3)$ 4.0 (1 H, d, *J* −18 Hz, CH), 5.0 (1 H, d, *J* −18 Hz, CH), 5.2 (1 H, d, *J* 5 Hz, CH), 5.5 (1 H, d, *J* 5 Hz, CH), and 6.4—7.4 (15 H, m, Ar).

1-*Acetonyl*-3-*phenoxy*-4-*phenylazetidin*-2-*one* (**23b**). From (**22b**) (5.9 g, 20 mmol) after 5 h at room temperature; yield 5.2 g (88%), m.p. 129—130 °C (ethanol) (Found: C, 73.2; H, 5.8; N, 4.7. $C_{18}H_{17}NO_3$ requires C, 73.19; H, 5.81; N, 4.74%); $\delta_H(CDCl_3)$ 2.0 (3 H, s, Me), 3.5 (1 H, d, *J* −18 Hz, CH), 4.5 (1 H, d, *J* −18 Hz, CH), 5.2 (1 H, d, *J* 5 Hz, CH), 5.5 (1 H, d, *J* 5 Hz, CH), and 6.7—7.5 (10 H, m, ArH).

1-*Acetonyl*-4-(p-*methoxyphenyl*)-3-*phenoxyazetidin*-2-*one* (**23c**). From (**22c**) (4.6 g, 14 mmol) after 7 h at room temperature; yield 3.8 g (83%) (syrup), $\delta_H(CDCl_3)$ 2, 2.1 (3 H, s, Me, both diastereoisomers), 3.5 (1 H, d, *J* −19 Hz, CH), 3.7 (3 H, s, OMe), 4.5 (1 H, d, *J* −19 Hz, CH), 5.1 (1 H, d, *J* 5 Hz, CH), 5.5 (1 H, d, *J* 5 Hz, CH), and 6.6—7.3 (9 H, m, ArH).

3-*Phenoxy*-4-*phenylazetidin*-2-*one* (**25**). Method A. 1-Benzoylmethyl-3-phenoxy-4-phenylazetidin-2-one (**23a**) (1.8 g, 5 mmol) was disolved in acetic acid (20 ml) and 4-*N,N*-dimethylaminopyridinium bromide perbromide (1.81 g, 5 mmol) was added to it; the mixture was then stirred at room temperature for 15 min. The solid residue was filtered off and dissolved in acetone (60 ml) and sodium hydrogen carbonate (1 g, 12 mmol) in water (35 ml) was added to it. The mixture was stirred at room temperature for 48 h and then methylene dichloride (3 × 20 ml) was added. The organic layer was washed with water (20 ml), dried (Na_2SO_4) and evaporated to give the β-lactam (**25**) (0.5 g, 42%), m.p. (174—175 °C) (lit.,[23] 174—176 °C).

Method B. 1-Acetonyl-3-phenoxy-4-phenylazetidin-2-one (**23b**) (2.95 g, 10 mmol) in acetic acid (30 ml) and 4-*N,N*-dimethylaminopyridinium bromide perbromide (3.63 g, 10 mmol) was stirred for 1 h and then diluted with methylene dichloride (50 ml). The resulting solution was successively washed with water (3 × 40 ml) and 5% aqueous $NaHCO_3$; the organic layer was dried (Na_2SO_4) and evaporated to give a syrup. To this dissolved in acetone (45 ml) was added sodium hydrogen carbonate (1 g, 12 mmol) in water (50 ml), and the mixture was stirred at room temperature for 2 h. Following the above work-up the β-lactam (**25**) was obtained (1 g, 40%), m.p. 174—176 °C.

4-(p-*Methoxyphenyl*)-3-*phenoxyazetidin*-2-*one* (**26**). By method B. From 1-acetonyl-3-phenoxy-4-(*p*-methoxyphenyl)-azetidin-2-one (3.25 g, 10 mmol) the β-lactam (**26**) was obtained, yield 0.67 g (25%), m.p. 165—167 °C (lit.,[33] 166—167 °C).

General Procedure for the Preparation of Schiff Bases (**27**)—(**29**).—To a solution of *p*-aminophenol (1.09 g, 10 mmol) in hot ethanol (15 ml) the aldehyde (11 mmol) was added and the mixture was heated at 70—75 °C. After being set aside at room temperature overnight, the resulting precipitate was filtered off to give the Schiff bases (**27**)—(**29**) which were used without further purification.

General Procedure for the Preparation of Schiff Bases (**30**), (**31**), *and* (**33**).—To a suspension of the Schiff bases (**27**)—(**29**) (5 mmol) and dimethyl-t-butylchlorosilane (0.9 g, 6 mmol) in dry methylene dichloride (10 ml), was added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.2 ml, 8 mmol). The resulting mixture was stirred at room temperature for 60 min and then diluted with methylene dichloride (20 ml), and washed with water (15 ml), 0.1M HCl (15 ml), and finally with saturated aqueous $NaHCO_3$ (15 ml). The organic layer was separated, dried (Na_2SO_4), and evaporated to give a solid crude product, which was used without further purification.

N-(p-*Dimethyl-t-butylsiloxybenzylidene*)*aniline* (**30**). From *N*-(*p*-hydroxybenzylidene)aniline (**27**); yield 95% as syrup; $\delta_H(CDCl_3)$ 0.15 (6 H, s, $SiMe_2$), 0.95 (9 H, s, $SiCMe_3$), 6.71—8.30 (9 H, m, ArH), and 8.43 (1 H, s, HC=N).

N-(p-*Dimethyl-t-butylsiloxybenzylidene*)-p-*methoxyaniline* (**31**). From *N*-(*p*-hydroxybenzylidene)-4-methoxyaniline (**28**); yield 97% as syrup; $\delta_H(CDCl_3)$ 0.07 (6 H, s, $SiMe_2$), 0.87 (9 H, s, $SiCMe_3$), 3.7 (3 H, s, OMe), 6.73—7.03 (4 H, ArH), 6.83—7.70 (4 H, ArH), and 8.27 (1 H, s, HC=NH).

N-(p-*Dimethyl-t-butylsiloxybenzylidene*)*styrylamine* (**33**). From *N*-(*p*-hydroxybenzylidene)styrylamine (**29**), yield 95% as syrup; $\delta_H(CDCl_3)$ 0.1 (6 H, s, $SiMe_2$), 0.87 (9 H, s, $SiCMe_3$), 6.63—7.53 (11 H, m, ArH and CH=), and 8.14 (1 H, t br, HC=N).

General Procedure for the Preparation of the β-*Lactams* (**34**)—(**39**).—Method A. To a suspension of the reagent (**1**) prepared as above, was added the corresponding carboxylic acid (5 mmol) and the resulting solution was stirred at room temperature for 15 min. Each of the corresponding crude Schiff bases (**30**)—(**33**) (5 mmol) was dissolved in methylene dichloride (8 ml) and triethylamine (2.1 ml, 15 mmol) was added; the mixture was cooled to 0 °C and the solution of the above activated carboxylic acid was added dropwise. After being stirred at room temperature for 20—24 h the reaction mixture was washed with water (20 ml), 1M HCl (20 ml), and 5% aqueous $NaHCO_3$ (20 ml). The organic layer was separated, dried (Na_2SO_4), and evaporated to give a solid product which was treated with hexane and filtered off to yield the corresponding β-lactams (**36**)—(**39**) which were analysed by ^1H n.m.r. spectroscopy.

Method B. To a solution or suspension of the carboxylic acid (10 mmol) in methylene dichloride (20 ml) was added at 0 °C the reagent (**2**) (10.2 mmol) the resulting solution refluxed for 30 min. Each of the corresponding crude Schiff bases (**30**)—(**33**) (10 mmol) was dissolved in methylene dichloride (15 ml) and triethylamine (4.2 ml, 30 mmol) was added; the mixture was then cooled to 0 °C and a solution of the above activated carboxylic acid was added dropwise. The same work-up as described in method A gave the corresponding β-lactams (**36**)—(**39**) which were analysed by ^1H n.m.r. spectroscopy.

cis-1-(p-*Dimethyl-t-butylsiloxyphenyl*)-3-*phenoxy*-4-*phenylazetidin*-2-*one* (**36**). By method A. Phenoxyacetic acid (0.76 g, 5 mmol), reagent (**1**), and the Schiff base (**30**); yield 2.14 g (96%), m.p. 180—181 °C (from ethanol) (Found: C, 71.95; H, 7.1; N, 3.15. $C_{27}H_{31}NO_3Si$ requires C, 72.77; H, 7.01; N, 3.14%); $\delta_H(CDCl_3)$ 0.86 (6 H, s, $SiMe_2$), 0.88 (9 H, s, $SiCMe_3$), 5.23 (1 H, d, *J* 5 Hz, CH), 5.48 (1 H, d, *J* 5 Hz, CH), and 76.5—7.6 (14 H, m, ArH).

cis-1-(p-*Dimethyl-t-butylsiloxyphenyl*)-4-(p-*methoxyphenyl*)-3-*phenoxyazetidin*-2-*one* (**37**). By method A. Phenoxyacetic acid (0.76 g, 5 mmol), reagent (**1**), and the Schiff base (**31**); yield 2.27 g (95.5%), m.p. 159—160 °C (from ethanol) (Found: C, 70.1; H, 6.85; N, 3.05. $C_{28}H_{33}NO_4Si$ requires C, 70.70; H, 6.99; N, 2.84%); $\delta_H(CDCl_3)$ 0.1 (6 H, s, $SiMe_2$), 0.8 (9 H, s, $SiCMe_3$), 3.71 (3 H, s, OMe), 5.25 (1 H, d, *J* 5 Hz, CH), 5.47 (1 H, d, *J* 5 Hz, CH), and 6.6—7.43 (13 H, m, ArH.)

1-(p-*Hydroxyphenyl*)-3-*phthalimidoyl*-4-*styrylazetidin*-2-*one* (**38**). To a solution of the Schiff base (**32**) (2.23 g, 10 mmol) and triethylamine (2.1 ml), 15 mmol) in methylene dichloride (15 ml)

trimethylchlorosilane (1.2 ml, 10 mmol) was added. The resulting mixture was stirred at room temperature for 60 min after which time triethylamine (4.2 ml, 30 mmol) was added; the activated phthalimidoacetic acid (10 mmol) (from Method B) was then added dropwise. The reaction mixture was stirred at room temperature for 20—24 h and then washed with water (20 ml), 1M HCl (20 ml), and 5% aqueous $NaHCO_3$ (20 ml) and evaporated to give a residue. This, dissolved in acetone (50 ml), was then stirred with 1M HCl (20 ml) at room temperature for 30 min; the mixture was extracted with methylene dichloride and the extract dried (Na_2SO_4) and evaporated to give an equimolar mixture of *cis*/*trans* β-lactam (**38**) (3.48 g, 90%); $\delta_H(CDCl_3)$ 5.23 (1 H, d, *J* 3 Hz, CH *trans*) and 5.56 (1 H, d, *J* 5 Hz, CH *cis*).

1-(p-*Dimethyl-t-butylsiloxyphenyl*)-3-*phthalimidoyl*-4-*styryl-azetidin*-2-*one* (**39**). By method B. Phthalimidoacetic acid (2.05 g, 10 mmol), reagent (**2**), and the Schiff base (**33**), gave a mixture (4.32 g, 86%) of *cis*/*trans* β-lactam (**39**) in 85:15 ratio. Recrystallization from ethanol yielded pure *cis* β-lactam, m.p. 200—202 °C (Found: C, 70.95; H, 5.95; N, 5.1. $C_{31}H_{32}N_2O_4Si$ requires C, 70.95; H, 6.16; N, 5.34%); $\delta_H(CDCl_3)$ 0.1 (6 H, s, $SiMe_2$), 0.9 (9 H, s, $SiCMe_3$), 4.95 (1 H, dd, *J* 5 Hz, *J'* 8 Hz, CH), 5.6 (1 H, d, *J* 5 Hz, CH), 6.2 (1 H, dd, *J* 8, 16 Hz, CH), 6.76 (1 H, d, *J* 16 Hz, CH), 6.74 (2 H, ArH), 7.22 (5 H, s, ArH), and 7.4 (2 H, ArH).

cis-3-*Phenoxy*-4-*phenylazetidin*-2-*one* (**25**). To a suspension of *cis*-3-phenoxy-4-phenyl-1-(*p*-dimethyl-t-butylsiloxyphenyl)-azetidin-2-one (**37**) (4.46 g, 10 mmol) and potassium fluoride (1.16 g, 20 mmol) in acetonitrile (250 ml), CAN (16.44 g, 30 mmol) in water (150 ml) was added dropwise at 70 °C over 20 min. The reaction was stirred at room temperature for 1.25 h and then diluted with water (700 ml). The mixture was extracted with ethyl acetate (4 × 150 ml) and the combined extracts were washed with 5% aqueous $NaHCO_3$ (350 ml), 1M Na_2SO_3 (100 ml), 5% aqueous $NaHCO_3$ (100 ml), and aqueous NaCl (100 ml), dried, and evaporated to give an orange-red oil which was purified by column chromatography (methylene dichloride–hexane and then with ether) to yield the β-lactam (**25**) (1.28 g, 54%), m.p. 176 °C (lit.,[23]); $\delta_H(CDCl_3)$ 4.9 (1 H, d, *J* 5 Hz, CH) 5.35 (2 H, dd, *J* 5, 2 Hz, CH), 6.45—7.5 (10 H, m, ArH), and 8.23 (1 H, s br, NH).

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