Stereoselective Synthesis of *cis*-4-(Substituted) Monobactams from Ethyl Acetoacetate

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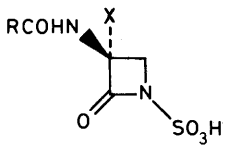
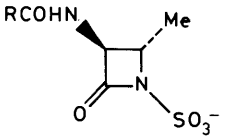
The stereoselective synthesis of *cis*-3-amino-4-methyl-2-oxoazetidine-1-sulphonic acid (**25**) from ethyl acetoacetate is described. Nitrosation of this compound and reduction of the resulting oxime gave the corresponding amine, which after treatment with different acyl halides, yielded the acylamino derivatives (**6**)—(**8**). Condensation with *p*-anisidine gave the enamines (**12**)—(**14**), which were then reduced to the β-amino acid esters (**15**)—(**17**). Stereoselective cyclization with Grignard reagents as base, and appropriate deprotection and sulphonation of the resulting β-lactams (**18**)—(**20**), led to the title compounds.

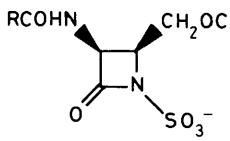
Since the discovery of various 3-acylamino-2-oxoazetidine-1-sulphonic acids (monobactams), a family of monocyclic β-lactam antibiotics isolated from certain gram-negative bacteria,[1] extensive studies have been devoted to the synthesis of both the parent structure (**1**)[2] and its analogues.[3] Some observations[4] revealed that 4-unsubstituted-2-oxoazetidine-1-sulphonic acid derivatives appear to lack activity against β-lactamase producing strains of gram-negative bacteria. Hence, the main synthetic efforts have been directed towards the preparation of monobactams bearing various 4-substituents, with *cis* or *trans* stereochemistry, and with improved antibacterial activity. Among them, aztreonam (**2**),[5] which is on the market for its clinical use, and carumonam (**3**),[6] which has better activity against gram-negative bacteria than the former and is about to be launched.



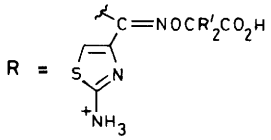
(**1**) X = H, OMe



(**2**)



(**3**)



R′
(**2**) Me
(**3**) H

Following our interest in the synthesis of 4-substituted monobactams,[7] we report here the stereoselective preparation of *cis*-3-amino-4-methyl-2-oxoazetidine-1-sulphonic acid (**25**), the *cis* isomer of the nucleus of aztreonam (**2**), starting from ethyl acetoacetate, a cheap, readily available synthon. Similar reaction sequences could be used for the preparation of other 4-substituted monobactams.

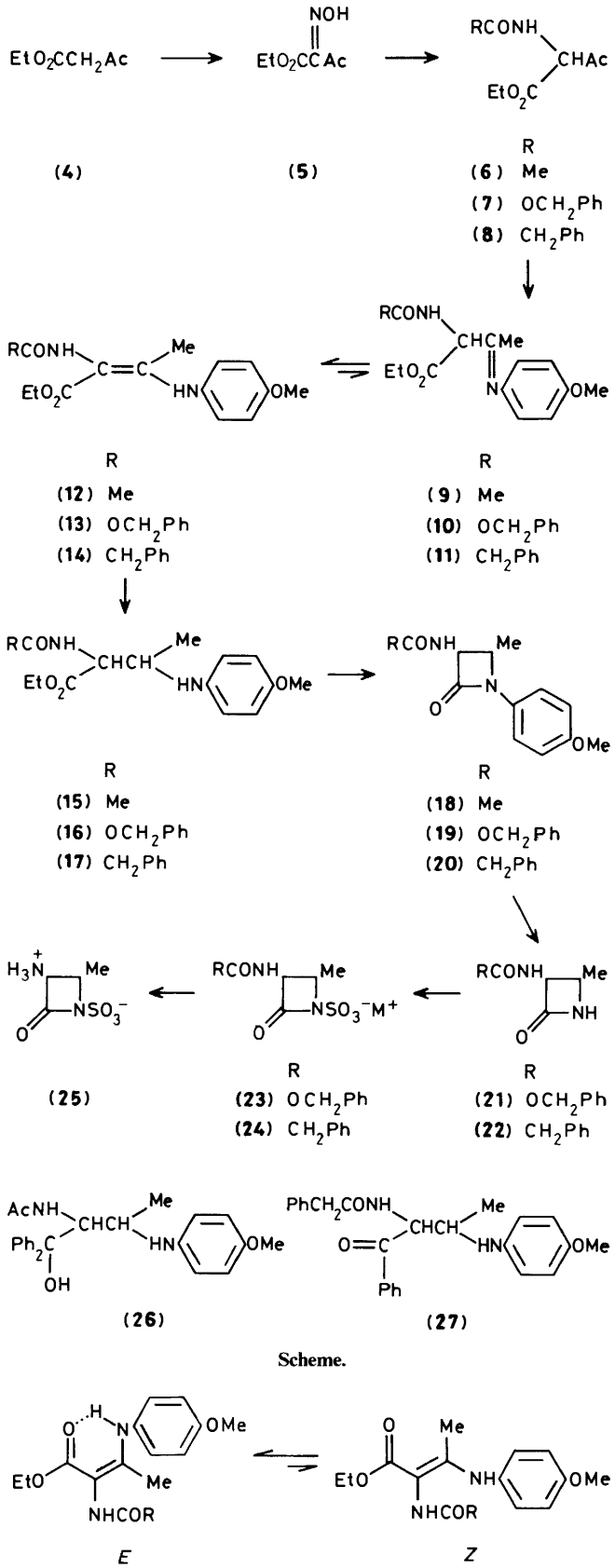
Results and Discussion

As indicated in the Scheme, and following the procedure described by Touster[8] for the nitrosation of hydrogen atoms adjacent to electron-attracting groups, treatment of ethyl acetoacetate (**4**) with sodium nitrite in glacial acetic acid provided ethyl 2-(hydroxyimino)acetoacetate (**5**). Reduction of the oxime group with aluminium amalgam,[9] and treatment *in situ* of the resulting amine with acetyl chloride, benzyl chloroformate, or phenylacetyl chloride, gave the acetyl (**6**), benzyloxycarbonyl (**7**), or phenylacetylamino (**8**) derivatives, respectively.

The next step was treating the acylamino derivatives (**6**), (**7**), and (**8**), with *p*-anisidine and heating the mixture at 110—120 °C under reduced pressure to remove water and shift the equilibrium to the formation of the Schiff bases (**9**), (**11**), and (**12**).[10] Owing to the presence of an ethoxycarbonyl group on the carbon atom adjacent to the imino group, the tautomeric equilibria imine–enamine (as indicated by the n.m.r. data) are completely shifted to the enamine forms (**12**), (**13**), and (**14**), bearing two conjugated double bonds. Similar tautomerizations were observed (*e.g.*, for the benzyl enamine of ethyl acetoacetate)[11] for an intermediate used in the preparation of both (+)-thienamycin[12] and also Dane salts which are useful in the protection of amino groups with ethyl acetoacetate[13] in peptide and penicillin chemistry. In solution, the enamines (**13**) and (**14**) also exist as an equilibrium mixture of the *E*- and *Z*-isomers (in deuteriated chloroform the ratio of *E*:*Z* is *ca.* 5:2 and 7:1, respectively) in which the *E*-isomers, which are stabilized by hydrogen bonds are the predominant species.

From the different reagents suitable for the selective reduction of the carbon–carbon double bond of the enamine esters, sodium cyanoborohydride[14] was chosen due to its remarkable selectivity in mild conditions as well as its stability at low pH. Attempts to use zinc-modified cyanoborohydride, generated from sodium cyanoborohydride and zinc chloride in a 2:1 molar ratio,[15] led to an incomplete reduction of the substrates, and the need for a large excess of reagent. Thus, the reduction of the enamines was carried out with sodium cyanoborohydride in methanol at pH 4, to obtain a mixture of two pairs of diastereoisomers of the corresponding amines (**15**), (**16**), and (**17**).

Cyclization of β-amino acid esters to β-lactams is usually achieved by using Grignard reagents.[16] Thus, treatment of the acetylamino derivative (**15**) with phenylmagnesium bromide in anhydrous tetrahydrofuran (THF) gave a mixture of the *cis*



Scheme.

(63%) and *trans* (10%) β-lactams (**18**), and the tertiary alcohol (**26**) (3%), the latter resulting from the attack of the Grignard reagent on the ester group.[17] The *cis* and *trans* relationship between protons at the 3- and 4-positions of isomers (**18**) was unequivocally established by the value of the coupling constant $J_{3,4}$ measured in their n.m.r. spectra (5.5 and 2 Hz, respectively). In a similar reaction, starting from the benzyloxycarbonyl derivative (**16**), the two isomeric β-lactams (**19**) [*cis* (60%) and *trans* (7%)] were obtained. $J_{3,4}$ Values of 5.5 and 2 Hz, respectively, in the n.m.r. spectra were indicative of the *cis* and *trans* relationship between 3- and 4-protons in both compounds. Finally, from the phenylacetylamino compound (**17**), only the *cis* β-lactam (**20**) (67%) ($J_{3,4}$ 6 Hz), together with the ketone (**27**) (12.4%), resulting from the attack of the organometallic on the ester group,[18] were obtained. No *trans* isomer was detected in the reaction mixture.

In order the obtain the *trans* isomer as major products, we tried to epimerize the 3-position by using several methods as described in the literature, such as: heating the *cis* isomers in benzene solution with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU);[19] treatment of such compounds with butyl-lithium in THF followed by quenching with acetic acid;[20] treatment with trimethylsilyl triflate in the presence of triethylamine followed by *in situ* hydrolysis with aqueous hydrochloric acid;[21] *etc.* Unfortunately, all our attempts were unsuccessful.

The deblocking step of the ring nitrogen of (**19**) and (**20**) was achieved by oxidative removal of the aromatic ring with cerium(IV) ammonium nitrate (CAN).[22] Although the method, performed in acetonitrile–water, has been profusely used in the *N*-dearylation of azetidinones,[22,23] all our attempts to carry out the deprotections under the described conditions were unsuccessful. However, we obtained fairly good results when the deblocking reactions of compounds (**19**) and (**20**) were performed in THF–water with strict control of temperature (63 and 54%, respectively). Unfortunately, in the case of the acetyl derivative (**18**), the *N*-deprotected β-lactam was unobtainable possibly due to its high polarity, which precluded extraction into the organic phase.

Selective sulphonation at the 1-position of (**21**) and (**22**) was successfully achieved with dimethylformamide (DMF)–sulphur trioxide (DMF·SO_3) complex[2a] (freshly prepared from trimethylsilyl chlorosulphonate and dry DMF)[24] in DMF. The sulphonates (**23**) and (**24**) were isolated as their tetrabutylammonium salts (M = Bu_4N), which were transformed into the sodium salts (M = Na) by treatment with the sodium form of a Dowex 50W × 4 resin [(**23**), 71% and (**24**), 66%].

The final step was the deprotection of the exocyclic 3-NH of the sulphonates (**23**; M = Na) and (**24**; M = Na). Catalytic hydrogenolysis of the benzyloxycarbonyl-protected compound (**23**; M = Na) with 10% Pd–C in a water–methanol (1:1), followed by treatment of the resulting solution with the acid form of a Dowex 50W × 4 resin, gave, after lyophilization, the desired zwitterion (**25**). The hydrolysis of the phenylacetyl group of (**24**; M = Na) was achieved by taking advantage of the hydrolytic properties of the benzylpenicillin acylase enzyme from different strains of *E. coli*.[25] The enzyme, which selectively transfers the *N*-phenylacetyl moiety of benzylpenicillin to water yielding 6-aminopenicillanic acid, has been shown to possess a variety of hydrolytic[26] capacities and a high substrate specificity to the phenylacetyl moiety has been observed. In our case, the hydrolysis of the sulphonate (**24**; M = Na) was performed by benzylpenicillin acylase immobilized on a porous alumina support treated with polyethylene imine (U.O.P.), at 37 °C and pH 8, leading to complete hydrolysis within 30 min. After acidification, the zwitterion (**25**) was obtained in almost quantitative yield.

In conclusion, the results presented here show the stereoselective synthesis of *cis*-3-amino-4-methyl-2-oxoazetidine-1-sulphonic acid (**25**), an appropriate intermediate for the preparation of various *cis*-monobactams. The method could also be applied to the preparation of a variety of different 4-substituted *cis*-monobactams in addition to other interesting

β-lactams from other β-keto esters with the appropriate functionalization.[27]

Experimental

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 580 Spectrometer. ^{1}H N.m.r. spectra were recorded on a Bruker WP 80 SY using Me_4Si as internal standard. Analytical t.l.c. was performed on Merck silica gel 60 F_{254} pre-coated plates (0.2 mm) and spots were detected in u.v. light, or by spraying with 30% sulphuric acid in ethanol, or ninhydrin reagent. Preparative chromatographic purifications were performed on a medium pressure preparation column of Merck silica gel 60 (230—400 mesh).

General Procedure for the Reduction of the Oxime (**5**) *and Acylation of the Resulting Amine.*—A solution of ethyl 2-(hydroxyimino)acetoacetate[8] (32 g, 200 mmol) in THF (500 ml), was added to aluminium amalgam [obtained[9] from aluminium (8 g)]. The resulting mixture was cooled with ice, diluted with water (15 ml), and stirred at room temperature for 24 h. After further addition of the corresponding acyl halide (200 mmol), the stirring was continued for 24 h. The reaction mixture was then treated with 6M hydrochloric acid (100 ml), and ethyl acetate (500 ml), and the aqueous phase was extracted with ethyl acetate (250 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (100 ml), water (100 ml), and brine (100 ml), dried ($MgSO_4$), and evaporated to dryness. Purification of the resulting product, either by distillation, or by medium pressure chromatography, gave the corresponding acylamino derivative (**6**), (**7**), or (**8**).

Ethyl 2-(acetylamino)acetoacetate (**6**) was obtained from the oxime (**5**), by using acetyl chloride (14.2 ml) as acylating agent. Distillation of the residue (0.2 mm, b.p. 103—105 °C) gave compound (**6**) (23.5 g, 63%) (Found: C, 51.5; H, 7.0; N, 7.4. $C_8H_{13}NO_4$ requires C, 51.3; H, 6.95; N, 7.5%); δ_H(80 MHz; $CDCl_3$) 1.31 (3 H, t, *J* 7 Hz, *Me*CH_2), 2.07 (3 H, s, NH*Ac*), 2.37 (3 H, s, Ac), 4.24 (2 H, q, *J* 7 Hz, MeCH_2), 5.28 (1 H, d, *J* 7.5 Hz, 2-H), and 7.32 (1 H, br d, *J* 7.5 Hz, NH).

Ethyl 2-(benzyloxycarbonylamino)acetoacetate (**7**) was obtained from the oxime (**5**) and benzyl chloroformate (25 ml). Medium pressure chromatography with ethyl acetate–hexane as eluant gave compound (**7**) (41.3 g, 74%) (Found: C, 60.1; H, 6.2; N, 5.2. $C_{14}H_{17}NO_5$ requires C, 60.2; H, 6.1; N, 5.0%); δ_H(80 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 6 Hz, *Me*CH_2), 2.35 (3 H, s, Ac), 4.25 (2 H, q, *J* 6 Hz, MeCH_2), 5.08 (1 H, d, *J* 10 Hz, 2-H), 5.10 (2 H, s, CH_2Ar), 5.94 (1 H, br d, *J* 10 Hz, NH), and 7.28 (5 H, s, Ar).

Ethyl 2-(phenylacetylamino)acetoacetate (**8**) was obtained from the oxime (**5**) with phenylacetyl chloride (28.4 ml) as acylating agent. Medium pressure chromatography with ethyl acetate–hexane as eluant gave compound (**8**) (36.8 g, 70%) (Found: C, 63.7; H, 6.6; N, 5.2. $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%); δ_H(80 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7 Hz, *Me*CH_2), 2.30 (3 H, s, Ac), 3.60 (2 H, s, CH_2Ph), 4.21 (2 H, q, *J* 7 Hz, MeCH_2), 5.23 (1 H, d, *J* 7 Hz, 2-H), 6.85 (1 H, br d, *J* 7 Hz, NH), and 7.3 (5 H, s, Ph).

General Procedure for the Preparation of the Enamines (**12**), (**13**), *and* (**14**).—A mixture of the acylamino derivative (**6**), (**7**), or (**8**) (100 mmol) and *p*-anisidine (12.3 g, 100 mmol) was heated in an oil bath at 120—130 °C, under reduced pressure, for 30 min. The mixture when cooled solidified to a gummy solid which, after crystallization, gave the desired enamine (**12**), (**13**), or (**14**).

Ethyl 2-acetylamino-3-(p-anisidino)but-2-enoate (**12**) was obtained from compound (**6**) (18.7 g). Crystallization from benzene–heptane yielded (**12**) (22.8 g, 78%), m.p. 140—141 °C (Found: C, 61.4; H, 6.9; N, 9.4. $C_{15}H_{20}N_2O_4$ requires C, 61.6; H, 6.85; N, 9.6%); δ_H(80 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 6.5 Hz, *Me*CH_2), 1.90 (3 H, s, MeC=), 1.96 and 2.09 (3 H, 2 s, Ac), 3.78 (3 H, s, OMe), 4.16 (2 H, q, *J* 6.5 Hz, MeCH_2), 6.26 and 6.42 (1 H, 2 br s, NHAr), 6.81 (2 H, d, *J* 9.8 Hz, 2 H *ortho* to OMe), and 6.98 (2 H, d, *J* 9.8 Hz, 2 H *meta* to OMe).

Ethyl 3-(p-anisidino)-2-(benzyloxycarbonylamino)but-2-enoate (**13**) was obtained from compound (**7**) (27.9 g). Medium pressure chromatography with chloroform–acetone as eluant gave (**13**) (38 g, 100%), m.p. 85—88 °C (carbon tetrachloride–hexane) (Found: C, 65.4; H, 6.5; N, 7.0. $C_{21}H_{24}N_2O_5$ requires C, 65.6; H, 6.25; N, 7.3%); δ_H(80 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 6 Hz, *Me*CH_2), 1.96 (3 H, s, MeC=), 3.80 (3 H, s, OMe), 4.15 (2 H, q, *J* 6 Hz, MeCH_2), 5.17 (2 H, s, CH_2Ph), 5.68 (1 H, br s, NHCO), 6.86 (2 H, d, *J* 9.5 Hz, 2 H *ortho* to OMe), 6.99 (2 H, d, *J* 9.5 Hz, 2 H *meta* to OMe), 7.37 (5 H, s, Ph), and 10.55 (1 H, br s, NHAr).

Ethyl 3-(p-anisidino)-2-(phenylacetylamino)but-2-enoate (**14**) was obtained from compound (**8**) (26.3 g). Crystallization from carbon tetrachloride gave (**14**) (29.5 g, 80%), m.p. 140—142 °C (Found: C, 68.4; H, 6.8; N, 7.5. $C_{21}H_{24}N_2O_4$ requires C, 68.5; H, 6.5; N, 7.6%); δ_H(80 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.84 (3 H, s, MeC=), 3.67 (2 H, s, CH_2Ph), 3.78 (3 H, s, OMe), 4.09 (2 H, q, *J* 7 Hz, MeCH_2), 6.20 and 6.27 (1 H, 2 br s, NHCO), 6.80 (2 H, d, *J* 9 Hz, 2 H *ortho* to OMe), 6.93 (2 H, d, *J* 9 Hz, 2 H *meta* to OMe), and 10.47 and 10.63 (1 H, 2 br s, NHAr).

General Procedure for the Preparation of the Amines (**15**), (**16**), *and* (**17**).—A solution of the corresponding enamine (**12**), (**13**), or (**14**) (80 mmol) and 90% sodium cyanoborohydride (5.6 g, 80 mmol) in methanol (300 ml) was treated dropwise with 5M hydrogen chloride in methanol (32 ml), under a nitrogen atmosphere. The mixture was stirred at room temperature, neutralized with 1M sodium hydroxide, and the methanol evaporated off under reduced pressure. The resulting suspension was diluted with water (300 ml) and extracted with ethyl acetate (3 × 250 ml). The combined organic extracts were washed with water (250 ml) and brine (250 ml), dried ($MgSO_4$), and evaporated to dryness. Medium pressure chromatography of the residue, with ethyl acetate–hexane as eluant, gave the amine (**15**), (**16**), or (**17**), as a mixture of two diastereoisomeric pairs of enantiomers, which was used in the next step without additional separation.

Ethyl 2-acetylamino-3-(p-anisidino)butanoate (**15**) was obtained from (**12**) (23.4 g) as a syrup (19.5 g, 83%) (Found: C, 60.9; H, 7.55; N, 9.35. $C_{15}H_{22}N_2O_4$ requires C, 61.2; H, 7.5; N, 9.5%); δ_H(80 MHz; $CDCl_3$) 1.15 and 1.20 (3 H, 2 d, *J* 6.5 Hz, 4-H), 1.29 and 1.30 (3 H, 2 t, *J* 6.5 Hz, *Me*CH_2), 2.02 (3 H, s, Ac), 3.26 and 3.32 (1 H, 2 br s, NHAr), 3.72 (3 H, s, OMe), 3.72—4.0 and 3.84—4.11 (1 H, 2 m, 3-H), 4.19 and 4.22 (2 H, 2 q, *J* 6.5 Hz, CH_2), 4.72 and 4.76 (1 H, 2 dd, $J_{2,3}$ 4 and $J_{2,NH}$ 8 Hz, 2-H), 6.35 (1 H, br d, *J* 8 Hz, NHCO), and 6.53—6.80 (4 H, m, Ar).

Ethyl 3-(p-anisidino)-2-(benzyloxycarbonylamino)butanoate (**16**) was obtained from (**13**) (30.7 g) as a syrup (27.8 g, 90%) (Found: C, 65.2; H, 6.85; N, 7.0. $C_{21}H_{26}N_2O_5$ requires C, 65.3; H, 6.7; N, 7.25%); δ_H(80 MHz; $CDCl_3$) 1.05 and 1.14 (3 H, 2 d, *J* 7 Hz, 4-H), 1.25 and 1.30 (3 H, 2 t, *J* 6.5 Hz, *Me*CH_2), 3.73 (3 H, s, OMe), 3.80—4.02 (1 H, m, 3-H), 4.18 and 4.23 (2 H, 2 q, *J* 6.5 Hz, CH_2Me), 4.50 and 4.57 (1 H, 2 dd, $J_{2,3}$ 4 and $J_{2,NH}$ 9 Hz, 2-H), 5.14 and 5.07 (2 H, 2 s, CH_2Ph), 5.65 and 5.51 (1 H, 2 br d, *J* 9 Hz, NHCO), 6.60 and 6.58 (2 H, 2 d, *J* 10 Hz, 2 H *ortho* to OMe), 6.82 and 6.73 (2 H, 2 d, *J* 10 Hz, 2 H *meta* to OMe), and 7.35 and 7.28 (5 H, 2 s, Ph).

Ethyl 3-(p-anisidino)-2-(phenylacetylamino)butanoate (**17**) was obtained from (**14**) (29.4 g) as a white solid (25.7 g, 87%), m.p. 102—104 °C (carbon tetrachloride–hexane) (Found: C, 67.9; H, 7.0; N, 7.5. $C_{21}H_{26}N_2O_4$ requires C, 68.1; H, 7.0; N, 7.6%); δ_H(80 MHz; $CDCl_3$) 1.07 (3 H, d, *J* 6 Hz, 4-H), 1.25 (3 H, t, *J* 7 Hz, *Me*CH_2), 3.29 and 3.47 (1 H, 2 br s, NHAr), 3.60 and 3.57 (2 H, 2 s, CH_2Ph), 3.73 (3 H, s, OMe), 3.80—3.95 and 3.65—

3.93 (1 H, 2 m, 3-H), 4.12 and 4.15 (2 H, 2 q, CH_2Me), 4.69 and 4.70 (1 H, 2 dd, $J_{2,3}$ 3 and $J_{2,NH}$ 8 Hz, 2-H), 6.22 and 6.25 (1 H, 2 br d, *J* 9 Hz, NHCO), 6.62 and 6.54 (2 H, 2 d, *J* 10 Hz, 2 H *ortho* to OMe), and 7.25 and 7.22 (5 H, 2 s, Ph).

General Procedure for the Cyclization of a Mixture of Amines (**15**), (**16**), *and* (**17**) *to the* β-*Lactams* (**18**), (**19**), *and* (**20**).—A solution of the corresponding mixture of amines (**15**), (**16**), or (**17**) (60 mmol) in dry, recently distilled THF (400 ml) was cooled at −20 to −15 °C, and treated under a nitrogen atmosphere, dropwise with phenylmagnesium bromide [prepared from magnesium (4.86 g, 200 mmol) and bromobenzene (21 ml, 200 mmol) in dry ether (50 ml)]. After stirring for 3 h at about 0 °C, the reaction mixture was treated with saturated aqueous ammonium chloride (500 ml) and ether (700 ml). At this point, the desired product partially crystallized spontaneously. The crystals were then filtered and washed with ether, and the aqueous phase was extracted with chloroform (2 × 300 ml). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation to dryness gave a syrup which on treatment with dry ether yielded a second crop of pure product. Finally, the ether solution was evaporated to dryness, and the residue was purified by medium pressure chromatography with mixtures of hexane–ethyl acetate as eluant, to give a third batch of the corresponding β-lactam (**18**), (**19**), or (**20**). Other minor products were also obtained.

cis- *and* trans-3-*Acetylamino*-N-(4-*methoxyphenyl*)-4-*methylazetidin*-2-*one* (**18**) *and* 2-*acetylamino*-3-(p-*anisidino*)-1,1-*diphenylbutanol* (**26**). The *cis* isomer was prepared from (**15**) (17.64 g) as white needles (9.4 g, 63%), m.p. 207—209 °C (methanol) (Found: C, 61.7; H, 6.4; N, 11.4. $C_{13}H_{16}N_2O_3 \cdot 0.2H_2O$ requires C, 62.0; H, 6.5; N, 11.1%); δ_H[80 MHz; $(CD_3)_2SO$] 1.22 (3 H, d, *J* 6 Hz, 4-Me), 1.92 (3 H, s, Ac), 3.75 (3 H, s, OMe), 4.39 (1 H, dq, $J_{4,3}$ 5.5 and $J_{4,Me}$ 6 Hz, 4-H), 5.20 (1 H, dd, $J_{3,NH}$ 9 and $J_{3,4}$ 5.5 Hz, 3-H), 6.95 (2 H, d, *J* 9 Hz, 2 H *ortho* to OMe), 7.35 (2 H, d, *J* 9 Hz, 2 H *meta* to OMe), and 8.65 (1 H, br d, *J* 9 Hz, NH).

From the slower running band in the 'flash' chromatography of the last residue, 1.5 g (10%) of the *trans* isomer were obtained, m.p. 336—337 °C (water–methanol) (Found: C, 62.65; H, 6.75; N, 11.3. $C_{13}H_{16}N_2O_3$ requires C, 62.9; H, 6.45; N, 11.3%); δ_H[80 MHz; $(CD_3)_2SO$] 1.43 (3 H, d, *J* 6 Hz, 4-Me), 1.88 (3 H, s, Ac), 3.77 (3 H, s, OMe), 4.04 (1 H, dq, $J_{4,3}$ 2 and $J_{4,Me}$ 6 Hz, 4-H), 4.50 (1 H, dd, $J_{3,4}$ 2 and $J_{3,NH}$ 8 Hz, 3-H), 6.91 (2 H, d, *J* 9 Hz, 2 H *ortho* to OMe), 7.26 (2 H, d, *J* 9 Hz, 2 H *meta* to OMe), and 8.60 (1 H, br d, *J* 8 Hz, NH).

Along with the two β-lactam products, compound (**26**) was obtained from the fastest running band (0.72 g, 3%), m.p. 218—220 °C (methanol) (Found: C, 74.0; H, 6.8; N, 6.75. $C_{25}H_{28}N_2O_3$ requires C, 74.25; H, 6.9; N, 6.9%); δ_H(80 MHz; $CDCl_3$) 1.05 (3 H, d, *J* 6.5 Hz, 4-H), 1.85 (3 H, s, Ac), 3.41—3.70 (1 H, dq, *J* 6.5 and 2.5 Hz, 3-H), 3.70 (3 H, s, OMe), 5.03 (1 H, dd, *J* 9 and 2.5 Hz, 2-H), 6.18 (1 H, br d, *J* 9 Hz, 2-NH), 6.38 (2 H, d, *J* 9 Hz, 2 H *ortho* to OMe), 6.69 (2 H, d, *J* 9 Hz, 2 H *meta* to OMe), and 7.1—7.53 (12 H, m, 2 × Ph, 3-NH, and OH).

cis- *and* trans-3-*Benzyloxycarbonylamino*-N-(4-*methoxyphenyl*)-4-*methylazetidin*-2-*one* (**19**). The *cis* isomer was obtained from (**16**) (23.2 g) as white needles (12.2 g, 60%), m.p. 193—194 °C (methanol) (Found: C, 67.0; H, 6.1; N, 8.05. $C_{19}H_{20}N_2O_4$ requires C, 67.05; H, 5.9; N, 8.2%); δ_H[80 MHz; $(CD_3)_2SO$] 1.25 (3 H, d, *J* 6 Hz, 4-Me), 3.71 (3 H, s, OMe), 4.36 (1 H, dq, $J_{4,3}$ 5.5 and $J_{4,Me}$ 6 Hz, 4-H), 5.06 (1 H, dd, $J_{3,4}$ 5.5 and $J_{3,NH}$ 10 Hz, 3-H), 5.08 (2 H, s, CH_2), 6.92 (2 H, d, *J* 9 Hz, 2 H *ortho* to OMe), 7.32 (2 H, d, *J* 9 Hz, 2 H *meta* to OMe), and 8.28 (1 H, d, *J* 10 Hz, NH).

From the slowest running band in the 'flash' chromatography of the last residue, the *trans* isomer was isolated (1.4 g, 7%), m.p. 117—118 °C (Found: C, 68.8; H, 6.2; N, 8.0. $C_{19}H_{20}N_2O_4$ requires C, 67.05; H, 5.9; N, 8.2%); δ_H(80 MHz; $CDCl_3$) 1.50 (3 H, d, *J* 6 Hz, 4-Me), 3.82 (3 H, s, OMe), 4.05 (1 H, dq, $J_{4,3}$ 2 and $J_{4,Me}$ 6 Hz, 4-H), 4.48 (1 H, dd, $J_{3,4}$ 2 and $J_{3,NH}$ 7 Hz, 3-H), 5.18 (2 H, s, CH_2), 6.04 (1 H, d, *J* 7 Hz, NH), 6.93 (2 H, d, *J* 9 Hz, 2 H *ortho* to OMe), and 7.34 (2 H, d, *J* 9 Hz, 2 H *meta* to OMe).

cis-N-(4-*Methoxyphenyl*)-4-*methyl*-3-(*phenylacetylamino*)-*azetidin*-2-*one* (**20**) *and* 3-(p-*anisidino*)-2-(*phenylacetylamino*)-*butyrophenone* (**27**). Compound (**20**) was obtained from (**17**) (22.2 g) as white needles (13 g, 67%), m.p. 199—200 °C (methanol) (Found: C, 70.1; H, 6.5; N, 8.65. $C_{19}H_{20}N_2O_3$ requires C, 70.4; H, 6.2; N, 8.6%); δ_H[80 MHz; $(CD_3)_2SO$] 1.18 (3 H, d, *J* 7 Hz, 4-Me), 3.52 (2 H, s, CH_2), 3.74 (3 H, s, OMe), 4.35 (1 H, dq, $J_{4,3}$ 6 and $J_{4,Me}$ 7 Hz, 4-H), 5.20 (1 H, dd, $J_{3,4}$ 6 and $J_{3,NH}$ 11 Hz, 3-H), 6.93 (2 H, d, *J* 11 Hz, 2 H *ortho* to OMe), 7.34 (2 H, d, *J* 11 Hz, 2 H *meta* to OMe), and 7.26 (5 H, s, Ph).

From the fastest running band compound (**27**) was isolated as a white solid (3 g, 12.4%), m.p. 120—124 °C (decomp.) (carbon tetrachloride–hexane) (Found: C, 74.6; H, 6.7; N, 7.0. $C_{25}H_{26}N_2O_3$ requires C, 74.6; H, 6.5; N, 7.0%); δ_H(80 MHz; $CDCl_3$) 0.9 (3 H, d, *J* 6 Hz, 4-H), 3.62 (2 H, s, CH_2), 3.72 (3 H, s, OMe), 3.82 (1 H, dq, *J* 2.5 and 6 Hz, 3-H), 5.72 (1 H, dd, *J* 2.5 and 8 Hz, 2-H), 6.58 (2 H, d, *J* 9 Hz, 2 H *ortho* to OMe), 6.71 (2 H, d, *J* 9 Hz, 2 H *meta* to OMe), 6.5—6.8 (1 H, br s, 3-NH), 7.28 (5 H, s, $PhCH_2$), 7.28—7.58 (4 H, m, 2 H *meta* and 1 H *para* to CO and NHCO), and 7.90 and 8.0 (2 H, 2 d, *J* 2 Hz, 2 H *ortho* to CO).

General Procedure for the Preparation of the N-*Deprotected* β-*Lactam Compounds* (**21**) *and* (**22**).—A suspension of the *N*-protected *cis* β-lactams (**19**) and (**20**) (30 mmol) in THF (500 ml) was cooled to 0 °C, and treated with an aqueous solution of CAN (48.6 g, 88.6 mmol; 300 ml) dropwise, the temperature being kept between −3 and 0 °C. The resulting solution was then stirred for 30 min at below 3 °C. Ethyl acetate (250 ml) was quickly added to the mixture and the aqueous phase was extracted several times with THF–ethyl acetate (2:1) (150 ml). The combined organic extracts were successively washed with 5% aqueous sodium hydrogen carbonate (150 ml), 10% aqueous sodium sulphite (150 ml), 5% aqueous sodium hydrogen carbonate (150 ml), and brine (150 ml), and dried ($MgSO_4$). Evaporation to dryness gave a dark solid residue which was carefully washed with anhydrous ether to give a yellowish solid, chromatographically homogeneous, which was used in the next step without additional purification.

cis-3-*Benzyloxycarbonylamino*-4-*methylazetidin*-2-*one* (**21**) was obtained from (**19**) (10.20 g), as white needles after crystallization (4.42 g, 63%), m.p. 179—180 °C (ethyl acetate–hexane) (Found: C, 61.3; H, 5.9; N, 12.1. $C_{12}H_{14}N_2O_3$ requires C, 61.5; H, 6.0; N, 12.0%); δ_H[80 MHz; $(CD_3)_2SO$] 1.07 (3 H, d, *J* 6 Hz, 4-Me), 3.60—3.90 (1 H, m, *J* 6 and 6 Hz, 4-H), 4.81 (1 H, dd, *J* 6 and 10 Hz, 3-H), 5.07 (2 H, s, CH_2), 7.36 (5 H, s, Ph), 8.0 (1 H, d, *J* 10 Hz, 3-NH), and 8.08 (1 H, br s, 1-NH).

cis-4-*Methyl*-3-(*phenylacetylamino*)*azetidin*-2-*one* (**22**) was obtained from (**20**) (9.72 g), as white needles after crystallization (3.53 g, 54%), m.p. 219—220 °C (propanol) (Found: C, 66.0; H, 6.6; N, 12.95. $C_{12}H_{14}N_2O_2$ requires C, 66.05; H, 6.4; N, 12.8%); δ_H[80 MHz, $(CD_3)_2SO$] 1.0 (3 H, d, *J* 6 Hz, 4-Me), 3.49 (2 H, s, CH_2), 3.57—3.87 (1 H, m, *J* 6 and 6 Hz, 4-H), 4.97 (1 H, dd, *J* 6 and 9 Hz, 3-H), 7.27 (5 H, s, Ph), 8.16 (1 H, br s, 1-NH), and 8.57 (1 H, d, *J* 9 Hz, 3-NH).

General Procedure of Sulphonation and Conversion into Sodium Salts of β-*Lactams* (**21**) *and* (**22**).—A solution of the *N*-deprotected β-lactams (**21**) and (**22**) (20 mmol) in dry DMF (15 ml) was cooled to 0 °C, and 1M DMF·SO_3 complex in DMF (25 ml) was added dropwise under nitrogen. The reaction mixture was stirred for 1 h at room temperature and poured over 0.5M aqueous potassium dihydrogen phosphate. The solution was extracted with dichloromethane (3 × 250 ml), the

aqueous phase was treated with solid tetrabutylammonium hydrogen sulphate (6.9 g, 20 mmol), and extracted several times with dichloromethane. The organic phase was repeatedly washed with water and brine, and dried ($MgSO_4$). Evaporation to dryness gave the corresponding tetrabutylammonium salts (**23**; M = Bu_4N) and (**24**; M = Bu_4N) as analytical t.l.c. homogeneous foams. These were converted into the corresponding sodium salts on being stirred with the sodium form of Dowex 50W × 4 resin (100—200 mesh) (100 ml) in ethanol–water (1:2) (100 ml) for 30 min. The resin was filtered off and washed with water. The filtrate was concentrated to about half of the original volume and washed with ethyl acetate (2 × 30 ml). The aqueous solution was evaporated to dryness under highly reduced pressure, and the residue crystallized from methanol to give the corresponding sodium salts (**23**; M = Na) and (**24**; M = Na).

cis-3-*Benzyloxycarbonylamino*-4-*methyl*-2-*oxoazetidine*-1-*sulphonic acid sodium salt* (**23**; M = Na) was obtained from (**21**)(4.68 g) as the tetrabutylammonium salt (**23**; M = Bu_4N) in 88% yield, which was transformed into the sodium salt in 81% yield, m.p. 203—204 °C (decomp.) (from methanol) (Found: C, 42.9; H, 4.0; N, 8.4; S, 9.3. $C_{12}H_{13}N_2NaO_6S$ requires C, 42.85; H, 3.9; N, 8.3; S, 9.5%); δ_H[80 MHz; $(CD_3)_2SO$] 1.18 (3 H, d, *J* 6 Hz, 4-Me), 3.83—4.13 (1 H, m, *J* 6 and 6 Hz, 4-H), 4.80 (1 H, dd, *J* 6 and 10 Hz, 3-H), 5.11 (2 H, s, CH_2), 7.37 (5 H, s, Ph), and 8.13 (1 H, d, *J* 10 Hz, NH).

cis-4-*Methyl*-3-*phenylacetylamino*-2-*oxoazetidine*-1-*sulphonic acid sodium salt* (**24**; M = Na) was obtained from (**22**) (4.36 g) as the tetrabutylammonium salt (**24**; M = Bu_4N) in 80% yield, which was transformed into the sodium salt in 82% yield, m.p. 210—213 °C (from methanol) (Found: C, 45.3; H, 4.4; N, 8.75; S, 9.80. $C_{12}H_{13}N_2NaO_5S$ requires C, 45.0; H, 4.1; N, 8.75; S, 10.0%); δ_H[80 MHz; $(CD_3)_2SO$] 1.11 (3 H, d, *J* 6 Hz, 4-Me), 3.48 (2 H, s, CH_2), 3.78—4.08 (1 H, m, *J* 6 and 6 Hz, 4-H), 4.93 (1 H, dd, *J* 6 and 9 Hz, 3-H), 7.27 (5 H, s, Ph), and 8.84 (1 H, d, *J* 9 Hz, NH).

cis-3-*Amino*-4-*methyl*-2-*oxoazetidine*-1-*sulphonic Acid* (**25**).—(A) *From* (**23**; M = Na). A solution of compound (**23**; M = Na) (3.36 g, 10 mmol) in a (1:1) methanol–water mixture (200 ml) was stirred under hydrogen at atmospheric pressure and room temperature for 2 h, in the presence of 10% palladium–charcoal (1.2 g). The catalyst was filtered off, washed with water, and the filtrate was evaporated to dryness. The residue was redissolved in water (100 ml) and treated with the acidic form of Dowex 50W × 4 resin (200—400 mesh), for 30 min. After the resin was filtered off, the filtrate was lyophilyzed to give compound (**25**) (1.14 g, 78%) as a white, crystalline solid, m.p. 205—206 °C (Found: C, 26.4; H, 4.4; N, 15.3; S, 17.6. $C_4H_8N_2O_4S$ requires C, 26.7; H, 4.4; N, 15.55; S, 17.8%); δ_H[80 MHz; $(CD_3)_2SO$] 1.36 (3 H, d, *J* 6.5 Hz, 4-Me), 4.03 (1 H, dq, *J* 6.5 and 6 Hz, 4-H), and 4.47 (1 H, d, *J* 6 Hz, 3-H).

(B) *From* (**24**; M = Na). A small amount of immobilized Penicillin G acylase was added to a solution of compound (**24**; M = Na) (0.32 g, 1 mmol) in a pH 8 buffer phosphate (2 ml). The mixture was incubated with stirring at 37 °C for 30 min. After this time, the reaction mixture pH is 7. The enzyme was filtered off and the aqueous solution acidified to pH 3.7 and lyophilyzed to give a white solid (0.18 g, 100%), identical in all respects with compound (**25**), obtained by hydrogenolysis of compound (**23**; M = Na).

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