β-Lactams. XII.
A study of the synthesis of N-unsubstituted β-lactams, and of 4-styryl monobactams

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This paper is dedicated to Dr. O. E. (Ted) Edwards

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A few types of amines XNH_2 were investigated for the formation of β-lactams via the cycloaddition of the corresponding Schiff bases with azidoacetyl chloride. Among the β-lactams formed, only the *N*-*p*,*p*'-dimethoxybenzhydryl compounds could be transformed to N-unsubstituted azetidinones by removal of the N-substituent with ceric ammonium nitrate. Conversion of those N-unsubstituted intermediates to 3-acylated monobactams was studied in the 4-styryl series.

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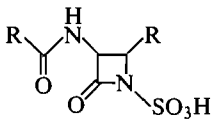
Dans le but de déterminer leur abilité à former des β-lactames, on a étudié la cycloaddition d'un certain nombre de bases de Schiff, dérivées de quelques types d'amines XNH_2, avec le chlorure d'azidoacétyle. Parmi les β-lactames qui se sont formées, seuls les composés *N*-*p*,*p*'-diméthoxybenzhydryles ont pu être transformés, sous l'influence du nitrate d'ammonium cérique, en azétidones ne portant pas de substituants sur le N. Dans la série des dérivés styrylés en position 4, on a étudié la conversion de ces intermédiaires ne portant pas de substituants sur le N en monobactames acylés en position 3.

[Traduit par la revue]

Introduction

We have been interested for some time in the synthesis of monocyclic β-lactams in which ring strain imparted by a second ring in classical β-lactams such as penicillins and cephalosporins was replaced by strain induced by electron withdrawal (1).

Recently, a new class of antibiotics was discovered (2, 3): the monobactam **A** in which this electronic strain is created by *N*-sulfonation of a monocyclic β-lactam.



A

Subsequently, powerful antibiotics were developed by chemical modification of **A** (4, 5). The required β-lactam nucleus has been synthesized by conversion of 6-amino penicillanic acid (5), by cyclization of the appropriate threonine derivative (6) or α,β-diaminocarboxylic acids (7), or by cycloaddition of azidoacetyl chloride with a Schiff base of type **2** and **3** where X is a group that can be subsequently removed without the destruction of the β-lactam ring. Examples of this last approach were mentioned in recently published papers. Thus 2-(phenylselenenyl)ethylamine (8), *p*-anisidine (9), and threonine (10) have been used as the amine from which Schiff bases were derived. The removal of the N-substituents was effected respectively by elimination and oxidative hydrolysis (8), by ceric ammonium nitrate (CAN) oxidation (9), and by oxidation with an excess of Jones reagent (10).

We would like to report our results in this field, which indicate that only certain types of amines may be used for the formation of β-lactams via the cycloaddition reaction pioneered by Bose *et al.* (11) and developed by Doyle *et al.* (12).

In a second part, we describe our studies of the synthesis of 4-styryl monobactams, since some 4-styryl monocyclic β-lactams[1] had shown weak antibacterial properties.

[1]G. Just, W. Y. Liu, and A. Ugolini. Unpublished results.

Results and discussion

Formation of unsubstituted β-lactams

The prototype aldehydes used for this investigation were acetaldehyde and cinnamaldehyde; the amines covered the range described (**1***a*–**1***i*).

The first two amines investigated, hydroxylamine **1***a* and its *O*-benzyl derivative **1***b*, where the X group can be removed by known methods (14), formed oximes **2***a*,*b* and **3***a*,*b*; neither of these underwent cycloaddition with azidoacetyl chloride.

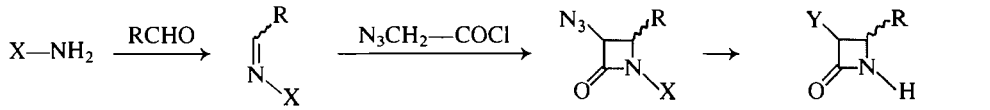
Next, we investigated trityl amine **1***c* and *tert*-butyldimethylsilylamine **1***d* where the X group might be removed by hydrogenolysis or tetra-*n*-butylammonium fluoride; neither amine formed a Schiff base, even under forcing conditions.

The next two amines investigated, trimethylsilylethylamine **1***e* (prepared from vinyltrimethylsilane according to Kabalka *et al.* (15)) and allylamine **1***f*, were found to be too reactive for Schiff base formation with acetaldehyde; they reacted smoothly with cinnamaldehyde to generate the corresponding Schiff bases **3***e*,*f*, which upon reaction with azidoacetyl chloride gave the *cis* β-lactams **5***e*,*f* in good yield. However, the removal of the trimethylsilylethyl group in **5***e*, using a variety of conditions recently described by Lipshutz *et al.* (16), failed. Similarly, the removal of the allyl group in **5***f*, using $(Ph_3P)_3RhCl$, according to Laguzza and Ganem (17), was also unsuccessful.

We finally investigated *l*-methylphenylcarbinyl amine **1***g*, benzhydrylamine **1***h*, and *p*,*p*'-dimethoxybenzhydrylamine **1***i*. All three gave Schiff bases **2***g*,*h*,*i* and **3***g*,*h*,*i* in excellent yield. Cycloaddition of these with azidoacetyl chloride led in good yields to *cis*-styryl β-lactams **5***g*,*h*,*i* and *trans*-methyl β-lactams **4***g*,*h* (12), except in the case of Schiff base **2***i*, which gave in moderate yield the *cis* β-lactam **4***i*.

Hydrogenolysis using a variety of catalysts did not effect the removal of the X group in **4***g*,*h*,*i* and **5***g*,*h*,*i*. The *p*,*p*'-dimethoxybenzhydryl group of **4***i* and **5***i* could be removed in 75% yield by means of ceric ammonium nitrate using a modification of the described conditions (9) (overall from **1**, **6**: 13.5%, **7**: 44%).

We have no explanation for the formation of **4***i* in the *cis* configuration rather than the expected *trans* arrangement.



X—NH_2	Imines		β-Lactams	
	R = CH_3	R = styryl	R = CH_3	R = styryl
a X = OH	**2***a*	**3***a*	—	—
b X = OCH_2Ph	**2***b*	**3***b*	—	—
c X = CPh_3	—	—	—	—
d X = $SiMe_2t$-Bu	—	—	—	—
e X = $CH_2CH_2SiMe_3$	—	**3***e*	—	**5***e cis*
f X = $CH_2CH{=}CH_2$	—	**3***f*	—	**5***f cis*
g X = CHMePh	**2***g*	**3***g*	**4***g trans*	**5***g cis*
h X = $CHPh_2$	**2***h*	**3***h*	**4***h trans*	**5***h cis*
i X = $CH(p\text{-}C_6H_4OMe)_2$	**2***i*	**3***i*	**4***i cis*	**5***i cis*

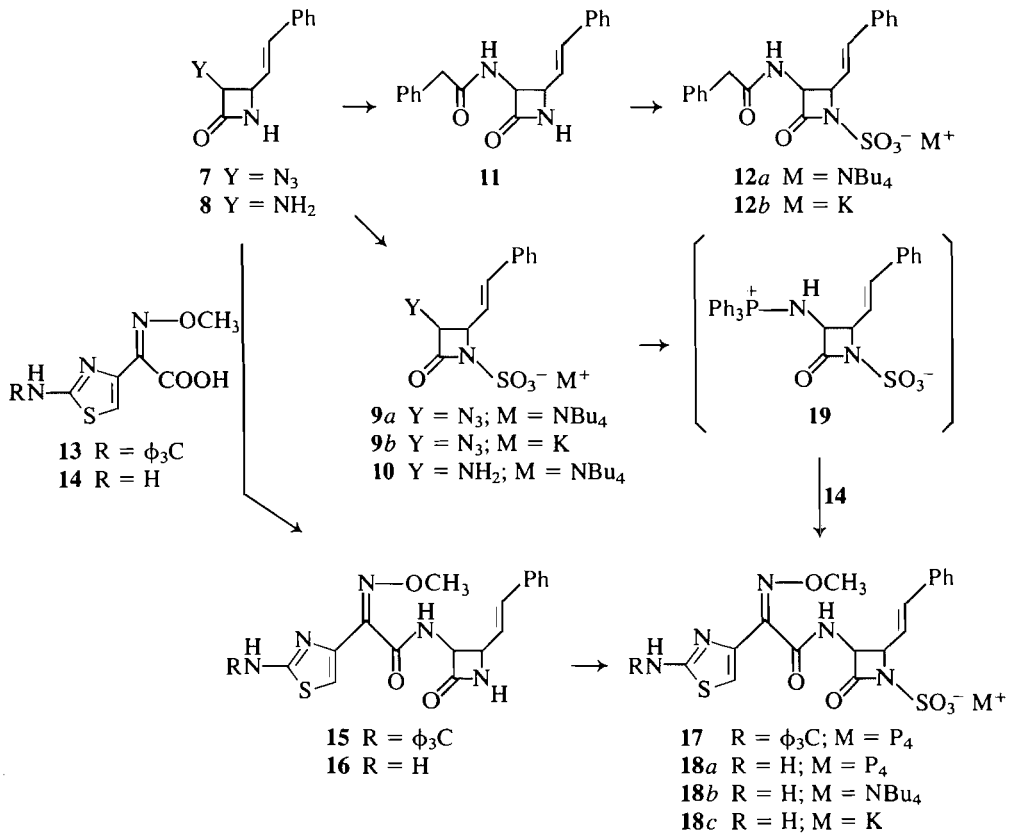
Due to the low yield of **6**, further work was carried out only on 4-styryl β-lactam **7**.

Selective reduction of the azide function in the presence of the styryl group was effected either by catalytic hydrogenation, using nickel boride (18) as catalyst, or by treatment with triphenyl phosphine, followed by aqueous hydrolysis of the resulting iminophosphorane (19), giving amine **8**.

4-Styryl-monobactams

Acylation of **8** with phenylacetyl chloride provided **11** (yield 51%), which was transformed to the *N*-potassium sulfonate **12***b* by sulfonation of **11** with the pyridine – sulfur trioxide complex in pyridine (20), followed by extraction of the sulfonic acid as its tetra-*n*-butylammonium salt **12***a*; passage through an ion-exchange resin gave the potassium salt **12***b* in 48% yield from **11**.

A synthesis of **18***c*, in which the styryl β-lactam **10** was acylated with the aminothiazolylcarboxylic acid **14**, a side chain similar to that used of the highly active aztreonam, has been described in a patent of the Squibb Institute (21), but no information was given concerning its antibacterial activity. We report here two other routes leading to **18***c*.



The first approach reproduces the sequence condensation–sulfonation as developed above for **12***b*. Thus, reaction of **8** with the trityl-amino acid **13** was carried out in CH_2Cl_2/DMF using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (22) as coupling agent (yield of **15**: 62%), and gave better yields than dicyclohexylcarbodiimide (DCC) and *N*-hydroxybenzotriazole. The sulfonation reaction, which required more forcing conditions than before, due to solubility problems, was carried out in DMF/pyridine directly on the trityl-amino β-lactam **15** or on its deprotected amino analogue **16**. Deblocking of the trityl group of **15** and **17** was performed by refluxing for 7 h in a methanolic solution of formic acid. The pyridinium sulfonate **18***a* obtained in both cases could not be isolated and purified as before as its *N*-butylammonium salt **18***b*, because of the low solubility of **18***b* in organic solvents; it was directly converted to potassium salt **18***c* by means of potassium 2-ethyl hexanoate (23), and was obtained with greater purity and better yield in the first sequence (path A) (**15** → **17** → **18**: yield 75%) than in the second one (path B) (**15** → **16** → **18**: yield 50%).

β-Lactam sulfonic salt **18***c* could also be obtained, albeit in lower yield and purity, by another approach involving a modification of the peptide synthesis from an azide and a carboxylic acid, a reaction pioneered by Vilarrasa and co-workers (24) and recently developed by Roberts and co-workers (25). Thus, the tetrabutylammonium salt of 3-azido β-lactam **9***a*, generated from **7** in the conditions previously used, was treated with triphenylphosphine in THF–DMF to form the zwitterion intermediate **19**, which partially precipitated during the reaction (24). Heating of the crude mixture in the presence of carboxylic acid **14** afforded **18***b* contaminated with side products that were difficult to remove. Passage through an ion-exchange resin gave **18***c*.

All compounds reported gave good interpretable nmr and mass spectra. Positive-ion fast atom bombardment mass spectra of **18***c* and aztreonam (26) were compared; both are characterized by the following fragments: MK^+, MH^+, $MH^+ - SO_3$, $MH^+ - HSO_3NCHR$ (**18***c*: R = styryl; aztreonam: R = Me), and 126 ($C_4H_4N_3S$).

None of the monobactamates **9***b*, **12***b*, and **18***c* showed notable antibacterial activity when tested against a panel of Gram positive and negative bacteria. The presence of a 4-styryl group seemed to decrease the intrinsic activity of those compounds, especially of aminothiazolyl methoxyimino monobactam **18***c* as compared to its 4-methyl analogue (4, 5).

This result may be explained by either a steric effect, where the antibacterial activity decreases for side chains larger than ethyl (5, 13), or, as suggested by Cimarusti,[2] by the increased lipophilicity of the aromatic ring at an inappropriate binding site.

Experimental

Thin-layer chromatography was performed on Merck Silica Gel 60 F_{254} aluminum-backed plates. Flash chromatography was done with Woelm silica (32–63 μm) using predistilled solvents. Melting points were determined on a Gallenkamp block and are uncorrected. Infrared spectra were run on a Perkin–Elmer 297 spectrophotometer. Nuclear magnetic resonance spectra were recorded on Varian T-60, T-60A, XL-200, and XL-300 spectrometers. Mass spectra were taken on an LKB-9000 and FAB mass spectra on a VG-analytical mass spectrometer.

[2]Personal discussions during the XIth European Heterocyclic Colloquium, Ferrara, Italy, October 1985.

Amines

Trityl amine ***1***c *and* tert-*butyldimethylsilylamine* ***1***d

To a solution of trityl chloride (1.114 g, 4 mmol) or *tert*-butyldimethylsilylchloride (602 mg, 4 mmol) in ether at −50°C was added ether (80 mL) previously saturated by ammonia (at −78°C). After stirring overnight until elimination of excess ammonia, the solvent was removed *in vacuo* to afford the corresponding amines in 90% yield.

Trimethylsilylethylamine ***1***e (ref. 15)

To a solution of vinyltrimethylsilane (900 mg, 9 mmol) in THF (3 mL) was added under nitrogen, at −5°C, BH_3–THF (3 mmol, 3 mL of a 1 *M* solution). The solution was stirred for 2 h and allowed to warm to 10°C. Then, to the organoborane (3 mmol), cooled again to 0°C, was added dropwise under nitrogen aqueous solutions of ammonium hydroxide (3 mmol) and sodium hypochlorite (3.3 mmol). The mixture was stirred for 15 min and allowed to warm to 10°C. The reaction mixture was extracted with ether (3 × 10 mL). The organic layers were combined, washed with brine, and dried on $MgSO_4$. Removal of the solvent gave the expected amine (yield: 65%); ^{1}H nmr (60 MHz, $CDCl_3$) δ: 0.1 (s, 9H, $SiMe_3$), 0.80–1.3 (m, 2H, $SiCH_2$), 1.9 (br s, 2H, NH_2), 3.0 (m, 2H, CH_2—N).

p,p′-*Dimethoxybenzhydrylamine* ***1***i

To a solution of *p,p′*-dimethoxybenzhydrol (1.22 g, 5 mmol) in dry CH_2Cl_2 (100 mL) at −50°C, under nitrogen, was added dropwise mesylchloride (0.87 mL, 1.145 g, 10 mmol) and triethylamine (2.78 mL, 2.20 g, 20 mmol). The mixture was stirred for ½ h and allowed to warm up to −20°C maximum. As shown by tlc, the alcohol was rapidly converted into its mesylate. The reaction mixture was then cooled again to −50°C and THF (100 mL), previously saturated by ammonia (at −78°C), was added. After stirring overnight, the solvents were removed *in vacuo* and replaced with ether (200 mL). The solution was washed with 1 *N* HCl solution (3 × 20 mL); the aqueous layer was then made slightly basic with aqueous sodium hydroxide and extracted several times with ether. The organic extract was dried on $MgSO_4$ and stripped of solvent under reduced pressure to afford the desired amine, which was essentially pure by tlc analysis; yield: 70%; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 2.3 (br s, 2H, NH_2), 3.8 (s, 6H, $2OCH_3$), 5.1 (s, 1H, CH), 7.0 (AB spectra, 8H, 2φ, J = 8.0 Hz, $\Delta\nu$ = 25 Hz).

Schiff bases ***2***a,b,g,h,i, ***3***a,b,e,f,g,h,i

All the Schiff bases were prepared in a similar manner and used without purification. The following is a representative procedure.

A solution of the amine **1***i* (1.21 g, 5 mmol) in dry CH_2Cl_2 (50 mL) was treated with magnesium sulfate (2.4 g, 20 mmol) and cooled to −20°C under a nitrogen atmosphere. Freshly distilled acetaldehyde (660 mg, 15 mmol) or cinnamaldehyde (660 mg, 5 mmol) was added dropwise. The mixture was stirred for 2 h, filtered, and evaporated to give a crude material that was directly used for the next reaction.

2*i*: yield: 90%; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.95 (d, 3H, CH_3, J = 5.0 Hz), 3.7 (s, 6H, $2OCH_3$), 5.35 (br s, 1H, CH), 7.0 (AB spectra, 8H, 2φ, J = 9.0 Hz, $\Delta\nu$ = 21 Hz), 7.85 (q, 1H, CH=, J = 5.0 Hz).

3*i*: yield: 78%; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 3.9 (s, 6H, $2OCH_3$), 5.45 (br s, 1H, CH), 6.8–7.5 (m, 15H, 3φ + C*H*=C*H*), 8.1 (br s, 1H, *H*C=N).

Azido β-lactams ***4***g–i, ***5***e–i

All β-lactams were prepared in an identical manner. To a solution of Schiff base (2 mmol) and triethylamine (292 μL, 212 mg, 2.1 mmol) in dry CH_2Cl_2 (10 mL) at −30°C, under nitrogen, was added dropwise a solution of azidoacetyl chloride (263 mg, 2.2 mmol) in CH_2Cl_2 (10 mL). The reaction mixture, after stirring for 1 h, was allowed to warm up to 0°C, washed with brine, dried on $MgSO_4$, and evaporated. The crude material was purified by flash chromatography and obtained in approximately 75% yield except for compound **4***i* (yield: 20%); ir ($CHCl_3$) ν_{max}: 2100 (N_3), 1750–1760 (CO β-lactam) cm^{-1}.

Compound *trans* **4***g*: ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.2 and 1.3 (2d, 3H, CH—*C*H_3, J = 6.5 Hz), 1.65 and 1.8 (2d, 3H, CHPh—*C*H_3, J = 8.0 Hz), 3.4 (dg, 1H, C*H*Me, J = 6.5, 2.0 Hz), 4.1 (d, 1H, C*H*N_3, J = 2.0 Hz), 4.4—5.1 (m, 1H, C*H*MePh), 7.3 (s, 5H, φ).

Compound *trans* **4***h*: ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.2 (d, 3H, $CHCH_3$, J = 6.5 Hz), 3.5 (dg, 1H, CHMe, J = 6.5, 2.0 Hz), 4.2 (d, 1H, CHN_3, J = 2.0 Hz), 6.0 (s, 1H, $CHPh_2$), 7.3 (s, 10H, 2φ).

Compound *cis* **4***i*: ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.6 (d, 3H, $CHCH_3$, J = 6.0 Hz), 3.8 (s, 6H, $2OCH_3$), 4.1 (dg, 1H, CHMe, J = 6.0, 5.0 Hz), 4.7 (d, 1H, CHN_3, J = 5.0 Hz), 5.7 (s, 1H, $CH(\phi OMe)_2$), 6.7–7.2 (m, 8H, 2φ).

Compound *cis* **5***e*: ^{1}H nmr (60 MHz, $CDCl_3$) δ: 0.2 (s, 9H, $SiMe_3$), 0.8–1.6 (m, 2H, CH_2—Si), 3.2–3.8 (m, 2H, N—CH_2), 4.6 (dd, 1H, CH—CH=, J = 9.0, 5.5 Hz), 5.0 (d, 1H, CHN_3, J = 5.5 Hz), 6.1–7.1 (m, 2H, CH=CH), 7.6 (s, 5H, φ).

Compound *cis* **5***f*: ^{1}H nmr (60 MHz, $CDCl_3$) δ: 3.4–4.3 (m, 2H, N—CH_2), 4.45 (dd, 1H, CH—CH=, J = 9.0, 5.5 Hz), 4.85 (d, 1H, CHN_3, J = 5.5 Hz), 5.1–6.9 (m, 5H, 3CH= and CH_2=), 7.4 (s, 5H, φ).

Compound *cis* **5***g*: ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.8 and 1.95 (2d, 3H, CHφ—CH_3, J = 8.0 Hz), 4.1 (dd, 1H, CH—CH=, J = 9.5, 5.0 Hz), 4.5–5.1 (m, 2H, CHMePh + CHN_3), 6.2–7.2 (m, 12H, 2φ + CH=CH).

Compound *cis* **5***h*: ^{1}H nmr (60 MHz, $CDCl_3$) δ: 4.3 (dd, 1H, CH—CH=, J = 9.0, 5.5 Hz), 4.7 (d, 1H, CHN_3, J = 5.5 Hz), 6.0 (s, 1H, $CHPh_2$), 6.1–6.7 (m, 2H, CH=CH), 6.9–7.3 (m, 15H, 3φ).

Compound *cis* **5***i*: ^{1}H nmr (60 MHz, $CDCl_3$) δ: 3.7 and 3.8 (2s, 6H, $2OCH_3$), 4.4 (dd, 1H, CH—CH=, J = 9.0, 5.0 Hz), 4.8 (d, 1H, CHN_3, J = 5.0 Hz), 5.8–6.5 (m, 3H, $CH(\phi$-$OMe)_2$ + CH=CH—), 6.7–7.3 (m, 13H, 3φ).

3-Azido N-unsubstituted β-lactams ***6*** *and* ***7*** (ref. 9)

Both β-lactams **6** and **7** were prepared in an identical manner from the corresponding *N*-dimethoxybenzhydryl compounds **4***i* and **5***i*, using the following procedure. A solution of *N*-dimethoxybenzhydryl azetidinone (1 mmol) in acetonitrile (10 mL) was cooled at 0°C and treated with a solution of ceric ammonium nitrate (CAN) (1.64 g, 3 mmol) in water (5 mL) over 5 min. The reaction was stirred at −5° to 0°C for 45 min and diluted with 40 mL of water. The mixture was extracted with ethyl acetate (3 × 15 mL). The organic extracts were washed with 5% sodium bicarbonate (30 mL) and the aqueous extracts back-washed with ethyl acetate (10 mL). The combined organic solutions were washed with 10% sodium sulfite (until the aqueous layer remained colorless), 5% sodium bicarbonate (5 mL), and brine. The resulting solution was swirled over charcoal for 30 min; sodium sulfate was added and the mixture was filtered through Celite. Removal of the solvent yielded a crude material, which was purified by flash chromatography (ethyl acetate – hexane: 30:70) to afford the N-unsubstituted β-lactams in approximately 75% yield.

Compound **6**: ir ($CHCl_3$) ν_{max}: 3400 (NH), 2930 (CH), 2840 (CH_3), 2100 (N_3), 1760 (CO β-lactam) cm^{-1}; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.5 (d, 3H, CH_3, J = 6.0 Hz), 4.2 (dq, 1H, CHMe, J = 6.0, 5.0 Hz), 4.8 (dd, 1H, CHN_3, J = 5.0, 1.0 Hz), 6.7 (br d, 1H, NH, J = 1.0 Hz).

Compound **7**: mp 100–102°C (lit. (9) mp 103–105°C); ir ($CHCl_3$) ν_{max}: 3410 (NH), 2920 (CH), 2100 (N_3), 1775 (CO β-lactam), 1650 (w, C=C) cm^{-1}; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 4.5 (dd, 1H, CH—C=, J = 7.5, 5.5 Hz), 4.8 (dd, 1H, CHN_3, J = 5.5, 1.5 Hz), 6.2 (dd, 1H, —CH=CHφ, J = 16.0, 7.5 Hz), 6.5 (d, 1H, CH=$CH\phi$, J = 16.0 Hz), 6.95 (br d, 1H, NH, J = 1.5 Hz), 7.4 (m, 5H, φ).

3-Amino β-lactam ***8***

(a) Method 1

To nickel acetate (249 mg, 1 mmol), in a 2-necked flask equipped with a septum, was added 2 mL of 95% ethanol. The flask was connected to the hydrogenation apparatus and was flushed with hydrogen. The catalyst was produced by injecting 2 mL of a 0.5 *M* solution of sodium borohydride in 95% ethanol to the rapidly stirred solution of nickel acetate. The reaction vessel was reflushed with hydrogen. Hydrogenation was then initiated by introducing 214 mg (1 mmol) of azido β-lactam **7** in 2 mL ethanol via the septum. The reaction was stopped after 2 h, just before that the absorbed quantity of hydrogen was larger than the liberated quantity of nitrogen. The reaction mixture was then filtered through Celite, the ethanol removed under reduced pressure, and the residue diluted in acetone. The solution was filtered again and evaporated. The crude compound was purified on aluminium oxide (eluant: $CHCl_3$–MeOH, 98:2) to give 56 mg of pure β-lactam **8** (yield 30%); ir ($CHCl_3$) ν_{max}: 3420 (NH, NH_2), 2930 (CH), 1760 (CO β-lactam), 1600 (w, C=C) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 1.8 (br s, 2H, NH_2), 4.4–4.5 (m, 2H, CH—CH), 6.22 (dd, 1H, CH=CHφ, J = 16.0, 6.5 Hz), 6.4 (s, 1H, NH), 6.65 (d, 1H, =$CH\phi$, J = 16.0 Hz), 7.25–7.41 (m, 5H, φ); ms (70 eV) *m/e*: 188 (85, M^+), 187 (64), 145 (103, H_2N—CH—CH—CH=$CH\phi^+$), 144 (163), 143 (35), 133 (110), 132 (1000, $M^+ - H_2NCHCO + 1$), 117 (96), 116 (64), 115 (374), 91 (75), 72 (131), 57 (124, H_2N—CH—CO), 51 (150), 43 (60, CONH).

(b) Method 2

To a solution of azido β-lactam **7** (214 mg, 1 mmol) in dry THF (10 mL) was added, under nitrogen and at room temperature, triphenylphosphine (288 mg, 1.1 mmol). After 2 h stirring, 2 or 3 equivalents of water were added and the reaction mixture was stirred overnight. The solvent was then evaporated and the residue dissolved in acetone (5 mL). *para*-Toluenesulfonic acid (209 mg, 1.1 mmol) was added and the solution stirred again for 3 h. The precipitate was filtered and washed with 1 mL of acetone to give 188 mg of the *para*-toluenesulfonate salt of β-lactam **8** (yield: 52%); mp 198–200°C; ir (KBr) ν_{max}: 3400 (NH_3), 2930 (CH), 1750 (CO β-lactam), 1610 (C=C), 1030 (SO_3), 1000, 955 cm^{-1}; ^{1}H nmr (200 MHz, DMSO-d_6) δ: 2.04 (s, 3H, CH_3), 4.48 (dd, 1H, CH—C=, J = 7.5, 5.0 Hz), 4.62 (d, 1H, H_3N—CH, J = 5.0 Hz), 6.34 (dd, 1H, CH=CHφ, J = 16.0, 7.5 Hz), 6.78 (d, 1H, =$CH\phi$, J = 16.0 Hz), 7.04–7.46 (m, 9H, 2φ), 8.42 (br s, 3H, NH_3), 8.85 (s, 1H, NH β-lactam).

4-Styryl 3-azido 2-oxo 1-azetidine sulfonic acid ***9*** (ref. 20)

(a) Tetrabutylammonium salt ***9***a

A solution of 3-azido β-lactam **7** (214 mg, 1 mmol) in 3 mL of pyridine was heated under nitrogen to 80°C, and 477 mg (3 mmol) of pyridine – sulfur trioxide complex added. The mixture, which quickly became homogeneous, was stirred for 2 h and then poured into 35 mL of 0.5 *N* KH_2PO_4. The resulting solution was extracted with CH_2Cl_2 (2 × 10 mL) and EtOAc (1 × 10 mL); the organic extracts were back-washed with phosphate solution (4 × 10 mL). The combined aqueous layers were then treated with 355 mg (1.05 mmol) of tetrabutylammonium hydrogen sulfate (TBAHS) and extracted with methylene chloride (1 × 20 mL and 2 × 10 mL). The organic extract was dried on $MgSO_4$ and concentrated to yield the desired tetra-*n*-butylammonium salt, which was essentially pure by tlc analysis ($CHCl_3$–MeOH, 9:1); yield: 80%; ir (film) ν_{max}: 2960, 2930 and 2875 (CH_3, CH_2), 2100 (N_3), 1770 (CO β-lactam), 1485, 1465, 1380, 1265, 1050 (SO_3), 790, 760 cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.95 (t, 12H, $4CH_3$, J = 7.3 Hz), 1.40 (m, 8H, 4 × CH_2—Me), 1.57 (m, 8H, $4CH_2$), 3.19 (m, 8H, $4NCH_2$), 4.65 (d, 1H, N_3—CH—, J = 5.7 Hz), 4.80 (dd, 1H, CH—C=, J = 5.7, 7.9 Hz), 6.28 (dd, 1H, CH=CHφ, J = 15.9, 7.9 Hz), 6.85 (d, 1H, CH=$CH\phi$, J = 15.9 Hz), 7.25 (m, 5H, φ); ms (70 eV) *m/e*: 242 (1000, NBu_4), 243 (200).

(b) Potassium salt ***9***b

A solution of tetra-*n*-butylammonium salt (148 mg, 0.28 mmol) in distilled water – methanol (3:1) was applied to a column of ion exchange resin (12 mL) (Dowex: 50 × 8-200) previously charged in K^+ ions with a 1 *N* KCl solution. Elution was made with distilled water. The eluate was freeze-dried to give 44 mg of the desired potassium salt as a yellow powder (yield: 50%); ir (KBr) ν_{max}: 3460 (br, OH), 2100 (N_3), 1765 (CO β-lactam), 1615 (C=C), 1245 and 1050 (SO_3), 970, 755, 695, 650 cm^{-1}; ^{1}H nmr (200 MHz, DMSO-d_6) δ: 4.65 (dd, 1H, CH—C=, J = 7.8, 5.6 Hz), 5.12 (d, 1H, N_3—CH—, J = 5.6 Hz), 6.22 (dd, 1H, —CH=CHφ, J = 16.1, 7.8 Hz), 6.8 (d, 1H, CH=$CH\phi$, J = 16.1 Hz), 7.33 (m, 5H, φ); ms *m/e* (negative FAB): 293 (814, M − K), 265 (161, M − K − N_2), 252 (137), 210 (710, $O_3SNC_9H_8$), 185 (225), 161 (170), 153 (433), 145 (185), 122 (1000,

O_3SNCO); *m/e* (positive FAB): 371 (244, M + K), 332 (71, M), 261 (118), 247 (102), 242 (1000), 168 (457), 158 (496), 142 (275).

4-Styryl 3-phenylacetamido 2-azetidinone ***11***

To a solution of amino β-lactam **8** (34 mg, 0.18 mmol) and pyridine (43 mg, 0.54 mmol) in dry methylene chloride (4 mL) was added dropwise at 0°C, under nitrogen, a solution of phenylacetyl chloride (40 mg, 0.25 mmol) in dry methylene chloride (1 mL). After the addition was complete, the solution was stirred for 3 h, washed with pH 4.5 buffer solution, 5% $NaHCO_3$ solution, and brine. The organic layer was dried on $MgSO_4$ and evaporated. The solid that precipitated was washed with chloroform to give 28 mg (51%) of pure compound, mp 210°C; ir (KBr) ν_{max}: 3280 (NH), 1770 (CO β-lactam), 1660 (CO amide), 1600 (w, C=C), 1540, 1190, 970, 750, 690 cm^{-1}; ^1H nmr (200 MHz, CD_3COCD_3) δ: 3.5 (AB spectra, 2H, CH_2, J = 12.7 Hz, $\Delta\nu$ = 15.5 Hz), 4.47 (ddd, 1H, C*H*—C=, J = 7.0, 5.5, 0.8 Hz), 5.31 (ddd, 1H, NH—C*H*, J = 9.5, 5.5, 1.0 Hz), 6.17 (dd, 1H, —C*H*=CHφ, J = 16.0, 7.0 Hz), 6.71 (dd, 1H, —CH=C*H*φ, J = 16.0, 0.8 Hz), 7.0 (m, 5H, φ), 7.2 (m, 5H, φ), 7.50 (d, 1H, NH β-lactam, J = 1.0 Hz), 7.76 (d, 1H, NH amide, J = 9.5 Hz); ms (70 eV) *m/e*: 306 (1.5, M^+), 289 (5), 263 (15, M^+ − CONH), 188 (19), 187 (20), 175 (23, M^+ − PhCH= − CH—CH—NH), 171 (855), 132 (1000, M^+ − $PhCH_2CONHCHCO$ + 1), 119 (15, $PhCH_2CO$), 115 (309).

4-Styryl 3-phenylacetamido 2-oxo 1-azetidine sulfonic acid ***12*** (ref. 20)

(*a*) *Tetrabutylammonium salt* ***12a***

Tetrabutylammonium salt ***12a*** was prepared from **11** (15 mg, 0.05 mmol) following the procedure described for ***9a***. Yield: 57%; ir ($CHCl_3$) ν_{max}: 3420 (NH), 2960, 2940, 2880 (CH_3, CH_2), 1760 (CO β-lactam), 1670 (CO amide), 1600 (C=C), 1460, 1265 and 1050 (SO_3) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 0.92 (t, 12H, $4CH_3$, J = 7.3 Hz), 1.40 (m, 8H, 4 × CH_2—Me), 1.60 (m, 8H, $4CH_2$), 3.22 (m, 8H, $4NCH_2$), 3.50 (s, 2H, CH_2φ), 4.85 (dd, 1H, C*H*—C=, J = 6.7, 5.9 Hz), 5.33 (dd, 1H, NH—C*H*—, J = 9.7, 5.9 Hz), 5.98 (d, 1H, NH, J = 9.7 Hz), 6.20 (dd, 1H, C*H*=CHφ, J = 16.0, 6.7 Hz), 6.75 (d, 1H, CH=C*H*φ, J = 16.0 Hz), 7.0 (m, 5H, φ), 7.3 (m, 5H, φ); ms *m/e* (positive FAB): 629 (13, MH_2^+), 332 (138), 307 (35, MH_2^+ − NBu_4 − SO_3), 302 (103), 272 (161), 258 (172), 242 (1000, NBu_4), 240 (1000), 212 (63, $HSO_3NC_9H_8$ + H^+), 142 (CH_2NBu_2), 123 (115, HSO_3NCO).

(*b*) *Potassium salt* ***12b***

Potassium salt ***12b*** was prepared from ***12a*** (11 mg, 0.017 mmol) as described for ***9b***. However, in the present case the tetrabutylammonium salt was dissolved in distilled water – methanol (1:1). Elution of the ion-exchange resin was made first with a MeOH–H_2O (1:1) solution, then distilled water. The eluate was partially evaporated *in vacuo* and freeze-dried to afford 6 mg of potassium salt. Yield: 83%; ir (KBr) ν_{max}: 3485, 3310 (NH), 1760 (CO β-lactam), 1660 (CO amide), 1600 (C=C), 1540, 1295, 1240, 1050 and 1040 (SO_3) cm^{-1}; ^1H nmr (200 MHz, DMSO-d_6) δ: 3.38 (AB spectra, 2H, CH_2, J = 12 Hz, $\Delta\nu$ = 16 Hz), 4.53 (dd, 1H, C*H*—C=, J = 8.4, 5.7 Hz), 5.13 (dd, 1H, NH—C*H*, J = 9.4, 5.7 Hz), 6.31 (dd, 1H, C*H*=CHφ, J = 16.0, 8.4 Hz), 6.60 (d, 1H, CH=C*H*φ, J = 16.0 Hz), 6.95–7.40 (m, 10H, 2φ), 8.92 (d, 1H, NH, J = 9.4 Hz).

4-Styryl 3[[(2-trityl-amino 4-thiazolyl)(methoxyimino)acetyl]amino] 2-azetidinone ***15***

To a solution of (2-trityl-amino 4-thiazolyl)(methoxyimino) acetic acid **13** (443 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise, at 0°C under nitrogen, a solution of EEDQ (296 mg, 1.2 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 1 h. Simultaneously, to a solution of *para*-toluenesulfonate salt of β-lactam **8** (360 mg, 1 mmol) in 6 mL CH_2Cl_2–DMF (4:1) was added dropwise, at 0°C under nitrogen, triethylamine (167 μL, 121 mg, 1.2 mmol). The mixture was allowed to warm up to 25°C over 1 h and was then added dropwise to the first solution at 0°C. After stirring overnight, the precipitate was filtered and washed with 1 mL CH_2Cl_2 to give 380 mg of trityl β-lactam **15** (yield: 62%); mp 235°C; ir (KBr) ν_{max}: 3410 (w, NH β-lactam), 3280 (br, NH), 1780 (CO β-lactam), 1670 (CO amide), 1590 (C=C) cm^{-1}; ^1H nmr (200 MHz, DMSO-d_6) δ: 3.6 (s, 3H, OCH_3), 4.4 (dd, 1H, C*H*—C=, J = 8.0, 5.0 Hz), 5.22 (dd, 1H, NH—C*H*—, J = 9.0, 5.0 Hz), 6.1 (dd, 1H, C*H*=CHPh, J = 16.0, 8.0 Hz), 6.34 (s, 1H, S—C*H*=), 6.6 (d, 1H, =C*H*Ph, J = 16.0 Hz), 7.26 (m, 20H, $4C_6H_5$), 8.48 (s, 1H, NH β-lactam), 8.78 (s, 1H, ϕ_3C—N*H*), 9.24 (d, 1H, NH amide, J = 9.0 Hz); ms (70 eV) *m/e*: 614 (9, M^+ + 1), 483 (9, M^+ − φCH=CH—NH + 1), 244 (1000, ϕ_3CH), 243 (195, ϕ_3C), 223 (110), 207 (235), 205 (101), 183 (128), 165 (167), 153 (104), 131 (147, C_6H_5—CH=CH—CH—NH), 115 (387).

4-Styryl 3[[(2-amino 4-thiazolyl)(methoxyimino)acetyl]amino] 2-azetidinone ***16***

Trityl β-lactam **15** (306 mg, 0.5 mmol) in 40 mL methanol – formic acid (2:1) was refluxed for 7 h. After evaporation of the solvent, the crude material was washed with chloroform (3 × 2 mL) and MeOH (1 × 1 mL) to give 173 mg (93%) of amino β-lactam **16**; mp 226–229°C; ir (KBr) ν_{max}: 3400 (NH β-lactam), 3300, 3200 (NH_2), 1770 (CO β-lactam), 1660 (CO amide), 1590 (C=C) cm^{-1}; ^1H nmr (200 MHz, DMSO-d_6) δ: 3.6 (s, 3H, OCH_3), 4.46 (dd, 1H, C*H*—C=, J = 8.0, 5.0 Hz), 5.26 (dd, 1H, NH—C*H*—, J = 9.0, 5.0 Hz), 6.26 (dd, 1H, C*H*=CHφ, J = 16.0, 8.0 Hz), 6.4 (s, 1H, S—C*H*=), 6.64 (d, 1H, C*H*φ, J = 16.0 Hz), 7.13 (s, 2H, NH_2), 7.24–7.44 (m, 5H, φ), 8.5 (s, 1N, NH β-lactam), 9.26 (d, 1H, NH amide, J = 9.0 Hz); ms (70 eV) *m/e*: 371 (3, M^+), 328 (3, M^+ − CONH), 240 (M^+ − PhCH=CH—CHNH), 210 (169), 181 (182), 156 (209, $C_5H_6N_3OS$), 131 (346, C_6H_5—CH=CH—CH—NH), 130 (1000), 126 (218, $C_4H_4N_3S$), 125 (349), 115 (224), 103 (230), 84 (307), 43 (353, CHNO).

4-Styryl 3-[[(2-amino 4-thiazolyl)(methoxyimino)acetyl]amino] 2-oxo 1-azetidine sulfonic acid, potassium salt ***18c***

(a) Method 1 (path A)

A solution of trityl-amino azetidinone **15** (184 mg, 0.3 mmol) in 2 mL pyridine–DMF (1:1) was heated under nitrogen to 80°C, and 215 mg (1.35 mmol) of pyridine – sulfur trioxide complex was added. The mixture was stirred at 80°C for 15 h until tlc showed no more starting material. Evaporation of the solvents *in vacuo* afforded **17** as a crude material; ir ($CHCl_3$) ν_{max}: 3500–2500 (br), 1770 (CO β-lactam), 1385, 1255 (SO_3), 1100, 1050 (SO_3), 920, 760, 730 cm^{-1}; ^1H nmr (60 MHz, $CDCl_3$) δ: 3.7 (s, 3H, OCH_3), 4.5–5.2 (m, 2H, N—C*H*—C*H*—), 6.1–7.0 (m, 3H, 3CH=), 7.2 and 8.0 (m, φ).

Crude **17** was dissolved in 16 mL methanol – formic acid (3:1); the solution was refluxed for 7 h and evaporated to dryness. The residue was washed with chloroform (5 × 2 mL), dissolved in methanol (0.5 mL), and 2 mL of potassium 2-ethyl hexanoate (0.5 *M* in ethyl acetate) was added. The slurry was cooled to 0°C, filtered, washed with ethyl acetate, and dried to give 105 mg of potassium salt ***18c***; yield ~ 75–80%; mp 200°C (dec.); pH = 4.5; ir (KBr) ν_{max}: 3650–2800 (br), 1770 (CO β-lactam), 1670 (CO amide), 1635, 1535, 1250 (SO_3), 1130 (strong), 1050 (SO_3), 980, 620 cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6) δ: 3.9 (s, 3H, OCH_3), 4.64 (dd, 1H, C*H*—CH=, J = 8.0, 5.0 Hz), 5.3 (dd, 1H, NH—C*H*—, J = 10.0, 5.0 Hz), 6.37 (dd, 1H, C*H*=CHφ, J = 16.0, 8.0 Hz), 6.45 (s, 1H, S—C*H*=), 6.68 (d, 1H, C*H*φ, J = 16.0 Hz), 7.25 (br s, 2H, NH_2), 7.29–7.5 (m, 5H, φ), 9.2 (d, 1H, NH, J = 10.0 Hz); ms *m/e* (positive FAB): 529 (55, MH^+ + K), 528 (151, MK^+), 490 (151, MH^+), 452 (82), 451 (94, MH^+ − K), 410 (166, MH^+ − SO_3), 390 (121), 359 (272), 353 (121), 343 (91), 329 (70, MH^+ − KSO_3NCO), 321 (145), 279 (151, MH^+ − $HSO_3NC_9H_8$), 242 (1000), 240 (91, 279 − K), 165 (424, $C_4H_4N_3S$ + K), 126 (575, $C_4H_4N_3S$), 91 (363, $C_6H_5CH_2$).

(b) Method 1 (path B)

A solution of amino β-lactam **16** (93 mg, 0.25 mmol) in 1.5 mL pyridine–DMF (1:2) was heated under nitrogen to 80°C and 159 mg (1 mmol) of pyridine – sulfur trioxide complex was added. The mixture was stirred at 80°C for 10 h. Evaporation of the solvents *in vacuo* gave a crude material, which was washed with chloroform (5 × 1.5 mL) and dissolved in methanol (0.5 mL). A solution of potassium 2-ethyl hexanoate in ethyl acetate (1.5 mL, 0.5 *M*) was added. The slurry was cooled to 0°C, filtered, and dissolved in distilled water (1 mL). The

aqueous solution was washed with ethyl acetate (2 × 0.5 mL), partially evaporated *in vacuo*, and freeze-dried to afford 62 mg of potassium salt **18***c* as a white powder (yield: 51%).

(c) Method 2 (refs. 24, 25)

To a solution of triphenylphosphine (208 mg, 0.8 mmol) in 1.5 mL THF–DMF (2:1) was added a solution of 3-azido *N*-sulfonyl β-lactam **9***a* (390 mg, 0.73 mmol) in 1 mL THF. The mixture was stirred for 1 h at room temperature. A light precipitate of zwitterion **19** appeared during the reaction; ir (KBr) ν_{max}: 3480 (br), 3080, 2895, 2790, 1780 (CO β-lactam), 1590 (C=C), 1480, 1440, 1290, 1230 (SO_3), 1180, 1120, 1050 (SO_3), 990 cm^{-1}; ^1H nmr (300 MHz, DMSO-d_6) δ: 4.44 (m, 1H, C*H*—CH=), 4.88 (br s, 1H, N—C*H*), 6.48 (m, 2H, C*H*=), 7.4–8.1 (m, 22H); ms *m/e* (positive FAB): 551 (6, MNa^+), 529 (14, MH^+), 450 (12), 449 (27, $MH^+ - SO_3$), 406 (10, $MH^+ - HSO_3NCO$), 332 (20), 318 (10, $MH^+ - HSO_3C_9H_8$), 262 (47, $P\phi_3$), 242 (1000), 142 (322), 91 (57), 90 (161).

Thereupon, a solution of amino-thiazolyl acid **14** (147 mg, 0.73 mmol) in 2 mL THF–DMF (1:1) was added to the above solution and the mixture was heated to 50°C for 8 h. The solution was then cooled, filtered, and evaporated *in vacuo* to afford 500 mg of crude *N*-butylammonium salt **18***b*; ir (film) ν_{max}: 3380 (br), 2940, 2880 (CH_3, CH_2), 1750 (CO β-lactam), 1640 (CO amide), 1460, 1240 and 1040 (SO_3), 880, 750 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.05 (t, 12H, $4CH_3$, J = 7.3 Hz), 1.5 (m, 8H, $4CH_2Me$), 1.7 (m, 8H, $4CH_2$), 3.34 (m, 8H, $4CH_2N$), 3.40 (s, 3H, OCH_3), 4.8–5.5 (m, 2H, C*H*—C*H*), 6.35–7.8 (m, 11H, φ, 3CH=, NH_2, NH); ms *m/e* (positive FAB): 332 (14, 240 + G), 242 (1000, NBu_4), 240 (72, $MH^+ - NBu_4$—$HSO_3NC_9H_8$), 165 (9, $C_4H_4N_3S$ + K), 142 (287, CH_2NBu_2), 126 (8, $C_4H_4N_3S$), 100 (46), 98 (40), 91 (9).

The *N*-butylammonium salt **18***b* was dissolved in distilled water – methanol (2:1) and the solution was applied to a column of ion-exchange resin (12 mL) (Dowex 50 × 8-200) previously charged in K^+ ions with a 1 *N* KCl solution. Elution was made first with a MeOH–H_2O solution (1:1) and then distilled water. The eluate was washed with chloroform (2 × 0.5 mL) to remove the small amount of unexchanged *N*-butylammonium salt (18 mg). The aqueous layer was partially evaporated *in vacuo* and freeze-dried to afford 36 mg of potassium salt **18***c* in 11% overall yield from **9***a*.

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