Stereospecific Synthesis of a Chiral Intermediate for the Preparation of Thienamycin, Penems, and Carbapenems: Use of the Nitro Group as a Hydroxy Protecting Group

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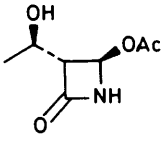
A total stereo- and enantio-controlled synthesis of (3*S*,4*R*)-4-acetoxy-3-[(*R*)-1-hydroxyethyl]azetidin-2-one (**1**) from ethyl (*S*)-3-hydroxybutyrate is reported. A simple method of inversion and concomitant protection of the hydroxy function in the side chain is achieved. The synthesis starts with the conversion of ethyl (*S*)-3-hydroxybutyrate into the azetidinone derivatives (**4**) and (**5**) *via* a stereospecific imine-ester enolate cycloaddition. The resulting azetidinones, with unnatural configuration at C-1′ of the ethyl group were converted into the mesylates (**8**) and (**9**); these were further elaborated into the nitrate esters (**10**) and (**11**) with the natural configuration at C-1′. Sequential treatments of these compounds, with ozone, Jones' reagent, lead tetra-acetate, and cerium ammonium nitrate afforded as a sole product, in 24.8% overall yield, the chiral azetidinone (**17**). Finally, smooth removal of the nitric protecting group of the hydroxy function afforded, quantitatively, the azetidinone (**1**), a key intermediate for the preparation of thienamycin and its biologically active analogues.

In the course of our studies on β-lactam antibiotics,[1] we recently demonstrated the usefulness of ethyl (*S*)-3-hydroxybutyrate as a chiral building block for the stereocontrolled synthesis of (**1**),[1b] which can be converted into thienamycin and related carbapenems by known procedures.[2]



(**1**)

At the same time Hart[3] and Georg,[4] independently, reported similar results on a variety of ester enolates and imines. Since then a number of publications by the above mentioned authors[5] and other research groups[6] have appeared dealing with the synthesis of 3,4-disubstituted azetidinones through the cycloaddition of 3-hydroxybutyrate and suitably functionalized imines.

Here we convey our recent results in this area mainly addressed to finding a more practical synthesis of (**1**), which should avoid the use of expensive protecting groups.

Results and Discussion

Our synthesis started with a cycloaddition between the dilithium enolate of (*S*)-3-alkoxyethyl butyrate (**2**) and *N*-cinnamylidene-*p*-methoxyaniline (**3**).

This imine was preferred for the following reason: (i) its ready availability from *p*-methoxyaniline and cinnamaldehyde in almost quantitative yield;[7] (ii) ease of handling; (iii) the possibility of using the *p*-methoxyphenyl group as a protecting group for the β-lactam nitrogen; (iv) easy removal of *p*-methoxyphenyl and cinnamylidene groups to give the expected azetidinone (**1**).

Reaction of compounds (**2**) and (**3**), under different conditions, gave a mixture of variable amounts of the (3*S*,4*S*)-(**4**), (3*S*,4*R*)-(**5**), (3*R*,4*S*)-azetidin-2-ones (**6**) respectively. It is worth mentioning that there was no trace of the (3*R*,4*R*)-azetidin-2-one (**7**) in any of the product mixtures (Table 1). However, since the differences of the chemical shifts in these compounds are very small, being in the range of 0.03—0.3 p.p.m., it was necessary to prepare compound (**7**) in order to exclude with certainty its presence in the reaction mixture.

The ratios of diastereoisomers were determined by high resolution ^{1}H n.m.r. spectroscopy on a Bruker 300 MHz apparatus by integration of characteristic protons.[8]

The relative stereochemistry at the C-3, C-4, and C-1′, stereocentres was assigned on the basis of the coupling constants and chemical shifts. The *trans* and *cis* isomers were readily distinguished from the value of $J_{3,4}$, the *cis* value always being larger than the *trans* in such compounds.[8] The stereorelationship between C-3 and C-1′ was more difficult to define. Inspection of Dreiding models of compounds (**4**) and (**7**) shows that in the *cis* compounds there is a strong repulsive interaction between the methyl group of the hydroxyethyl side chain and the styryl group. This interaction favours an *anti* H,H conformation in the *cis*-ul isomer (**7**) and a gauche conformation in the *cis*-lk isomer (**4**).[9] On this basis a larger *J* value in the *cis*-ul isomer (**7**) than in *cis*-lk isomer (**4**) is to be expected.

In the case of the *trans* isomers (**5**) and (**6**), where this interaction is absent, the driving effect on the conformation is mainly due to the possibility of formation of a hydrogen bond between the hydroxy group of the chain and β-lactam carbonyl group. This effect favours the *trans*-ul compound (**6**) a conformation in which the angle C(4)H–C(1′)H is near to 90 °C so that the relative *J* has the smallest value of the series.* The structure of compound (**6**) has been further confirmed by its formation from (**4**) *via* basic isomerization.†

The chemical shifts and the *J* values for 3-H, 4-H, 1′-H are reported in Table 2.

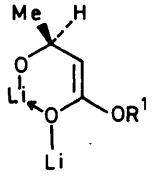
With regard to the diastereoisomer ratios reported in Table

* According this working hypothesis the J_B in compounds (**8**), (**9**), (**10**), and (**11**), where hydrogen bond formation is impossible, is 6.0, 5.3, 10.0, and 4.5 Hz respectively.

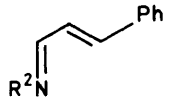
† Upon treatment of (**4**) with 2 equiv. of LDA in THF at −78 °C for 7 h, compound (**6**) was obtained in 22% yield, the rest being starting material.

Table 1. Product ratios of compounds (4), (5), and (6) from compounds (2) and (3) under a variety of conditions

Entry	R^1	Solvent	Ratio (4)	Ratio (5)	Ratio (6)	Method	Yield (%)
1	Me	THF	35.2	59.5	5.3	A	67
2	Et	THF	35.2	55.4	9.4	A	81
3	Bu^t	THF	22.8	65.1	12.1	A	66
4	Menthyl	THF	12.25	84.5	3.25	A	30
5	Et	THF–HMPA	20.76	79.24	—	B	30
6	Et	Toluene	60.16	34.96	4.88	C	60
7	Et	Toluene–HMPA	15.28	76.39	8.33	D	22
8	Bu^t	Toluene–HMPA	21.08	61.59	17.33	D	15



(2)



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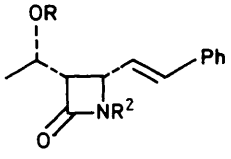

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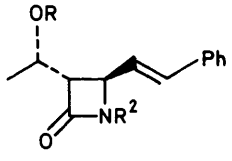
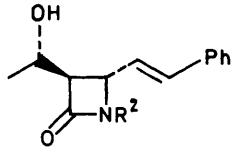
(8) R = Ms



(5) R = H
(9) R = Ms



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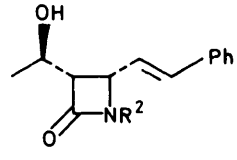

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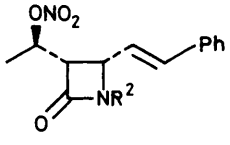

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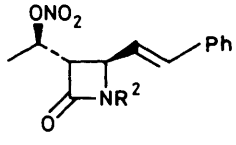

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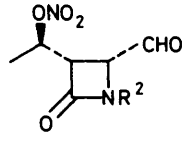

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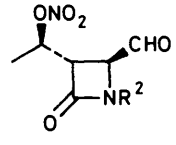

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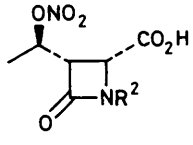

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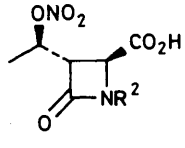

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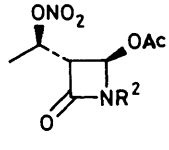

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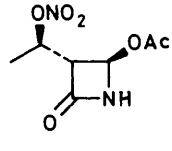


(17)

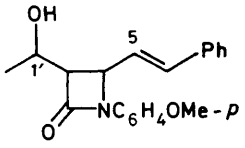
$R^2 = p\text{-MeOC}_6H_4$

1, the condensation leads, in all cases, to a high degree of diastereoselection at C-3 but a much lower degree at C-4.

The high 1,2-lk induction[9] at the C-3 stereocentre resembles the alkylation of the same ester enolate with methyl iodide[10] and may be explained by assuming a cyclic structure for the enolate. This arises as result of the co-ordinating effect of one of the lithium cations, so that a preferred attack of the electrophilic imine from the less hindered face of the diastereotopic plane can take place (Scheme).

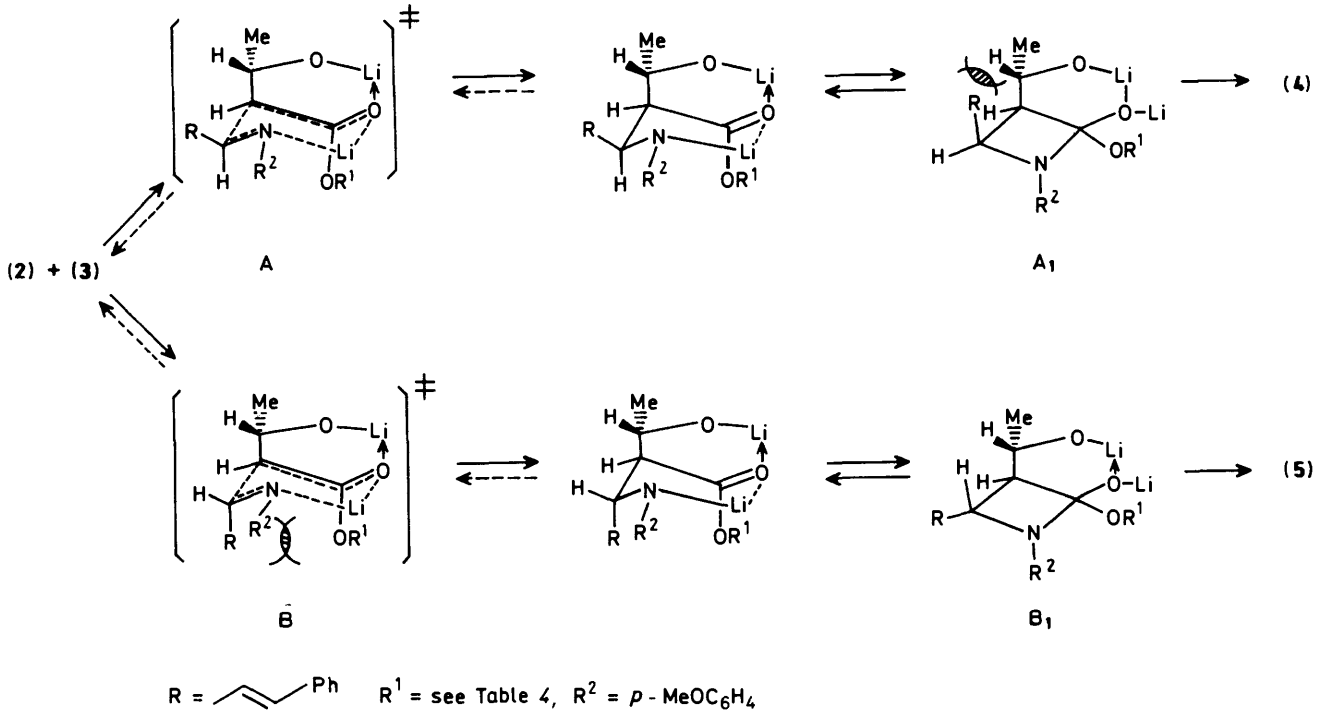
Many factors seem, instead, to play a role in determining the

Table 2. ^{1}H N.m.r. chemical shifts and coupling constants for azetidinones derivative[a,b]



Proton	Compound (4)	(5)	(6)	(7)
3-H	3.42 (J_A 5.6, J_B 6.7)	3.10 (J_A 2.3, J_B 6.0)	3.11 (J_A 2.3, J_B 4.5)	3.45 (J_A 6.0, J_B 9.0)
4-H	4.70 (J_A 5.6, J_C 8.6)	4.48 (J_A 2.3, J_C 8.4)	4.71 (J_A 2.3, J_C 8.2)	4.77 (J_A 6.0, J_C 7.5)
1'-H	4.18 (J_B 6.7, J_D 6.7)	4.22 (J_B 6.0, J_D 6.0)	4.33 (J_B 4.5, J_D 6.7)	4.27 (J_B 9.0, J_D 6.0)
5-H	6.45 (J_C 8.6)	6.24 (J_C 8.4)	6.30 (J_C 8.2)	6.48 (J_C 7.5)

[a] Chemical shifts in p.p.m. downfield from Me_4Si (Δ p.p.m. = 0.02 ΔJ = 0.1 Hz). [b] $J_A = J_{3,4}$; $J_B = J_{3,1'}$; $J_C = J_{4,5}$; $J_D = J_{1',2'}$.



Scheme.

stereochemistry at C-4. In toluene, *cis* β-lactam (entry 6) formation predominates, while with more polar solvents there is a predominance of the more stable *trans* β-lactam (entries 1—5 and 7, 8).

The dependence of the β-lactam *cis–trans* ratio on solvent polarity may be explained in terms of multi-stage formation of the β-lactam-ring: *i.e.* addition of the enolate to the imine to give an acyclic amino ester intermediate and subsequent cyclization of this to give the end product. The addition of the enolate to the imine is generally assumed to proceed *via* a six-centred chair-like transition state.[11] In our case the transition state **B** leading to the *trans*-β-lactam (**5**) appears to be destabilized in comparison to **A** by a 1,3-diaxial interaction between the groups R and OR^1 whilst an analogous repulsion between R and the hydroxy ethyl side chain renders the intermediate $\mathbf{A}_1$, which affords by cyclization the *cis*-β-lactam (**4**), less stable than $\mathbf{B}_1$.

This situation suggests the possibility of a kinetic and thermodynamic control on the first step of the reaction, the second step being irreversible. In apolar solvents the addition is irreversible, leading to the predominance of $\mathbf{A}_1$. With the more polar solvents (toluene/HMPA, THF) the first step becomes reversible favouring the formation of the more stable $\mathbf{B}_1$ intermediate. A further trend noticeable in the results given in Table 1 is the increase of *trans* stereoselectivity, in THF, on increasing the size of the ester alkoxy group.* It is noteworthy that this trend parallels that observed for the basic hydrolysis of the corresponding acetates.[12] Assuming that the transition state of the cyclization is similar to that of the transition state of the basic hydrolysis, it follows that, on going from the methyl ester to the menthyl ester, the cyclization becomes slower, thus favouring equilibration in the first step.

Since the best results, from the chemical point of view, were obtained with experiment 2, we decided to carry out the synthesis of (**1**) utilizing the diastereoisomeric mixture arising from this experiment. Since both condensation products (**4**) and (**5**) possess the unnatural configuration at C-1′, it was necessary to invert the configuration of the side-chain hydroxy group in each. This may be brought about by treatment of the hydroxy-

* Esters of entries 3 and 4 were prepared *via* diketene opening by the corresponding alcohol and reduction of the acetoacetate esters thus obtained with sodium borohydride or H_2/PtO_2.

azetidinones with diethyl azodicarboxylate (DEAD), triphenylphosphine, and formic acid followed by hydrolysis of the inverted formate thus obtained *via* the Mitsunubu procedure.[13] Although this method gives good results, it is unsuitable for large-scale synthesis because of the cost of the reagents and the tedious work-up procedure.

Recently we developed a mild and efficient procedure for inversion of configuration of the hydroxy group in biological systems: it consists of nucleophilic displacement of the sulphonate derivatives by tetrabutylammonium nitrate[14] in hydrocarbons. This procedure seemed to hold promise since not only is the resulting nitrate group retained until the end of our synthetic process, but it also shows remarkable stability to oxidation and hydrolysis, whilst being easily removed under very mild reducing conditions.[15]

Following our synthetic plan, since the C-4 stereocentre of (**4**) will be equilibrated to the more stable (*R*) configuration[1b] at the oxidative decarboxylation stage, a mixture of the intermediates (**4**) and (**5**) was quantitatively converted into the corresponding mesylates (**8**) and (**9**). These on treatment with tetrabutylammonium nitrate in toluene at reflux, afforded the esters (**10**) and (**11**) *via* S_N2 displacement in 79% yield: there was no trace of elimination products.

Ozonolysis of (**10**) and (**11**), followed by reductive work up with dimethyl sulphide (DMS)[16] gave the aldehydes (**12**) and (**13**) which were, after short-column flash chromatography, oxidised, by Jones reagent, to the corresponding acids (**14**) and (**15**) [70% yield from (**10**) and (**11**)]. Treatment of either acid with lead tetra-acetate[2] gave the corresponding 3-acetylazetidin-2-one (**16**) as a single *trans* isomer (77% yield). In this way, (**16**) was prepared from (**4**) and (**5**) in 42% overall yield.

The next phase of the synthesis was the *N*-dearylation of the β-lactam ring and the reduction of the nitric function to give the expected azetidinone (**1**) already transformed in thienamycin by a known procedure.[2]

To achieve this, the intermediate (**16**) was oxidised with cerium ammonium nitrate (CAN)[7] to give the azetidin-2-one (**17**) in 80% yield.

Hydrogenation of (**17**) by H_2/Pd in methanol, in order to remove the nitric protecting group, gave the β-lactam (**1**) in quantitative yield.

We have thus shown that the hydroxybutyric ester-imine condensation is one of the best methods for the enantioselective preparation of carbapenem and penem and that the nitric group can be included in the list of protecting groups for the hydroxylic function in β-lactam synthesis.

Experimental

All m.p.s were uncorrected. Optical rotations were obtained using a Perkin-Elmer 241 Polarimeter. I.r. spectra were recorded on a Perkin-Elmer 710 B spectrophotometer. ^1H and ^{13}C N.m.r. spectra were determined in $CDCl_3$ on Varian EM 390 and Varian FT 80 instruments respectively. High resolution ^1H n.m.r. spectra were recorded on 300 MHz Bruker CXP 300. Chemical shifts are expressed as δ values in p.p.m. from internal standard $SiMe_4$. T.l.c. was performed on silica gel sheets (DC-Plasticfolien Kieselgel 60 F_{253} Merck) and medium-pressure chromatography on a Chromatospac Prep. 10 (Jobin-Yvon instrument) using silica gel (H 60 Merck).

Commercially available starting materials were used without prior purification, unless otherwise stated. THF was obtained anhydrous and oxygen free by distillation over sodium benzophenone ketyl under argon. Methylene dichloride was distilled over P_2O_5. Di-isopropylamine and hexamethyldisilazane were refluxed over molecular sieves (type 4A, Fluka) and distilled at atmospheric pressure.

Preparation of 1-p-*Methoxyphenyl* β-*Lactams from an Ester and an Imine.—Method A.* Butyl-lithium in hexane (1.5 M solution; 30.6 ml, 46 mmol) was added to 1,1,1,3,3,3-hexamethyldisilazane (9.59 ml; 46 mmol) at room temperature in one portion. The mixture was stirred for 15 min after which it was diluted with THF (30 ml) and cooled to −78 °C. The appropriate ester (23 mmol) in THF (10 ml) was then added at rate such that the temperature did not exceed −60 °C. The mixture was stirred for 1 h, after which the cinnamylidene imine (5.45 g, 23 mmol) in THF (50 ml) was added *via* a cannula over 10 min. The cold-bath was removed and the mixture was allowed to warm to room temperature when it was stirred overnight. The resulting solution was quenched with 1M HCl (100 ml) and washed with water (2 × 25 ml). The combined aqueous washes were extracted with ethyl acetate (3 × 100 ml) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography over silica gel eluting with a hexane–ethyl acetate (7:3).

Method B. The procedure was identical with that of A, except for the solvent which was a 20% solution of hexamethylphosphoric triamide (HMPA) in THF.

Method C. The imine in toluene (20 ml) was added to a solution of the ester enolate in toluene at −70 °C, prepared as outlined in procedure A.

Method D. The procedure was identical with that of B except for the solvent which was a 20% solution of HMPA in toluene.

(3S,4S)-(**4**), (3S,4R)-(**5**), *and* (3R,4S)-3-[(S)-1-*Hydroxyethyl*]-1-p-*methoxyphenyl*-4-*styrylazetidin*-2-*ones* (**6**).—Following procedure A the organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a dark oil (8.38 g) which was chromatographed over silica gel [methylene dichloride–acetone (95:5)] to give the β-lactams (**4**) (2.12 g, 29%), (**5**) (3.35 g, 45%), and (**6**) (0.54 g, 7%).

Compound (**4**), m.p. 114 °C; $\nu_{max.}$(Nujol) 3 400br s and 1 735br s cm^{-1}; $[\alpha]_D^{20}$ +185 (*c* 8.7; $CHCl_3$); *m/z* 323 (M^+); δ_H (300 MHz) 1.33 (d, *J* 6.7 Hz, 3 H), 2.7 (br s, OH); 3.42 (dd, *J* 5.6 and 6.7 Hz, 1 H), 3.7 (s, 3 H), 4.18 (qt, *J* 6.7, 1 H), 4.70 (dd, *J* 5.6 and 8.6 Hz, 1 H), 6.45 (dd, *J* 8.6 and 16.5 Hz, 1 H), and 6.8—7.4 (m, 10 H); δ_C (20 MHz) 165.2, 155.7, 135.4, 131.2, 128.3, 127.9, 126.3, 124.5; 117.9, 113.8, 64.3, 60.0, 56.8, 54.9, and 21.8 (Found: C, 74.4; H, 6.5; N, 4.2. $C_{20}H_{21}NO_3$ requires C, 74.28; H, 6.55; N, 4.33%).

Compound (**5**), m.p. 110 °C; $[\alpha]_D^{20}$ +13.5 (*c* 2.1; $CHCl_3$); δ_H (300 MHz) 1.39 (d, *J* 6.0 Hz, 3 H), 2.00 (br s, OH), 3.10 (dd, *J* 2.3 and 6.0 Hz, 1 H), 3.76 (s, 3 H), 4.24 (qt, *J* 6.0 Hz, 1 H), 4.50 (dd, *J* 2.3 and 8.4 Hz, 1 H), 6.28 (dd, *J* 8.4 and 16.5 Hz, 1 H), and 6.8—7.4 (m, 10 H); δ_C (20 MHz) 164.9, 155.9, 135.5, 133.9, 131.3, 128.5, 128.2, 126.5, 126.4, 118.1, 114.1, 65.7, 63.3, 56.7, 55.2, 21.1 (Found: C, 74.3; H, 6.5; N, 4.3. $C_{20}H_{21}NO_3$ requires C, 74.28; H, 6.55; N, 4.33%).

Compound (**6**), m.p. 125 °C; $[\alpha]_D^{20}$ −111 (*c* 0.9; $CHCl_3$); δ_H (300 MHz) 1.33 (d, *J* 6.7 Hz, 3 H), 2.6 (br s, OH), 3.11 (dd, *J* 2.3 and 4.5 Hz, 1 H), 3.70 (s, 3 H), 4.33 (dq, *J* 4.5 and 6.7 Hz, 1 H), 4.71 (dd, *J* 2.3 and 8.2 Hz, 1 H), 6.30 (dd, *J* 8.2 and 15.0 Hz, 1 H), and 6.7—7.5 (m, 10 H); δ_C (20 MHz) 164.5, 156.0, 133.8, 128.7, 128.2, 127.1, 126.5, 118.2, 114.2, 64.9, 64.2, 55.8, 55.4, and 21.3 (Found: C, 74.4; H, 6.5; N, 4.2. $C_{20}H_{21}NO_3$ requires C, 74.28; H, 6.55; N, 4.33%).

(3S,4S)-3-[(R)-1-*Hydroxyethyl*]-1-p-*methoxyphenyl*-4-*styrylazetidin*-2-*one* (**7**).—A solution of compound (**10**) (0.820 g, 2.3 mmol) in AcOH (15 ml), was stirred and treated with Zn powder (0.400 g, 6.1 mmol) for 6 h at room temperature. The mixture was filtered, the filtrate evaporated under reduced pressure, and the residue diluted with ethyl acetate. The solution was then washed with 5% aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to give the title compound (**7**) (0.69 g,

93%), m.p. 133 °C; $[\alpha]_D^{20}$ +193 (*c* 2.25; $CHCl_3$); *m/z* 323 (M^+); δ_H (90 MHz) 1.40 (d, *J* 6.0 Hz, 3 H), 2.15 (br s, OH), 3.45 (dd, *J* 6.0 and 9.0 Hz, 1 H), 3.73 (s, 3 H); 4.27 (dq, *J* 6.0 and 9.0 Hz, 1 H), 4.77 (dd, *J* 6.0 and 7.5 Hz, 1 H), 6.48 (dd, *J* 7.5 and 15.0 Hz, 1 H); and 6.7—7.5 (m, 10 H); δ_C (20 MHz) 163.9, 156.0, 135.6, 135.2, 131.5, 128.6, 128.3, 126.6, 124.4, 118.2, 114.2, 64.4, 61.6, 56.7, 55.3, and 21.56 (Found: C, 74.3; H, 6.5; N, 4.3. $C_{20}H_{21}NO_3$ requires C, 74.28; H, 6.55; N, 4.33%).

(3S,4S)-1-p-*Methoxyphenyl*-3-[(S)-1-*methylsulphonyloxyethyl*]-4-*styrylazetidin*-2-*one* (**8**) *and* (3S,4R)-1-p-*Methoxyphenyl*-3-[(S)-1-*methylsulphonyloxy*]-4-*styrylazetidin*-2-*one* (**9**).—Triethylamine (0.64 ml, 4.6 mmol) and methanesulphonyl chloride (0.36 ml, 4.6 mmol) were added to a solution of the mixture of the hydroxy β-lactams (**4**) and (**5**) (1 g, 3.1 mmol) in dry methylene dichloride (30 ml) at 0 °C. The mixture was stirred at 0 °C for 2 h after which it was quenched with cold dilute 1M HCl and extracted with methylene dichloride. The combined organic layers were washed several times with water, dried ($MgSO_4$), and evaporated under reduced pressure; the residue was chromatographed at medium pressure (hexane–ethyl acetate, 8:2) to give the mesylates (**8**) and (**9**) in quantitative yield.

Compound (**8**), $\nu_{max.}$(film) 1 740 cm^{-1}; *m/z* 401 (M^+); δ_H (90 MHz) 1.57 (d, *J* 6.4 Hz, 3 H), 3.11 (s, 3 H), 3.62 (dd, *J* 6.0 and 6.4 Hz, 1 H), 3.76 (s, 3 H), 4.79 (dd, *J* 6.0 and 8.2 Hz, 1 H), 5.13 (qt, *J* 6.4 Hz, 1 H), 6.38 (dd, *J* 8.2 and 15.7 Hz, 1 H), and 6.7—7.4 (10 H) (Found: C, 62.7; H, 5.6; N, 3.6. $C_{21}H_{23}NO_5S$ requires C, 62.83, H, 5.77; N, 3.49%).

Compound (**9**), $\nu_{max.}$(film) 1 740 (cm^{-1}); *m/z* 401 (M^+); δ_H (90 MHz) 1.64 (d, *J* 6.0 Hz, 3 H), 3.06 (s, 3 H), 3.36 (dd, *J* 3.0 and 4.5 Hz, 1 H), 3.77 (s, 3 H), 4.61 (dd, *J* 3.0 and 7.5 Hz, 1 H), 5.21 (dq, *J* 6.0 and 4.5 Hz, 1 H), 6.23 (dd, *J* 7.5 and 15.6 Hz, 1 H) and 6.7—7.4 (9 H, Ar) (Found: C, 62.8; H, 5.8; N, 3.5. $C_{21}H_{23}NO_5S$ requires C, 62.83; H, 5.77; N, 3.49%).

(3S,4S)-1-p-*Methoxyphenyl*-3-[(R)-1-*nitroxyethyl*]-4-*styrylazetidin*-2-*one* (**10**) *and* (3S,4R)-1-p-*methoxyphenyl*-3-[(R)-1-*nitroxyethyl*]-4-*styrylazetidin*-2-*one* (**11**).—A solution of the mesylates (**8**) and (**9**) (3 g, 7.5 mmol) and anhydrous tetrabutylammonium nitrate (2.74 g, 9 mmol) in toluene (60 ml) was heated under reflux for 2 h. The toluene solution was washed with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give (**10**) and (**11**) (2.17 g) with a good degree of purity for subsequent elaboration. A portion of the mixture (0.100 g) was purified by column chromatography to give the pure isomers (**10**) and (**11**). The spectral data were as follows.

Compound (**10**), $\nu_{max.}$(film) 1 750 and 1 635 cm^{-1}; *m/z* 368 (M^+); δ_H (90 MHz) 1.55 (d, *J* 6.7 Hz, 3 H); 3.59 (dd, *J* 6.0 and 10.5 Hz, 1 H), 3.72 (s, 3 H), 4.76 (dd, *J* 6.0 and 6.7 Hz, 1 H), 5.44 (dq, *J* 6.7 and 10.5 Hz, 1 H), 6.19 (dd, *J* 6.7 and 15.7 Hz, 1 H), and 6.7—7.4 (9 H, Ar) (Found: C, 65.3; H, 5.5; N, 7.5. $C_{20}H_{20}N_2O_5$ requires C, 65.21; H, 5.47; N, 7.60%).

Compound (**11**), $\nu_{max.}$(film) 1 750 and 1 635 cm^{-1}; *m/z* 368 (M^+); δ_H (90 MHz) 1.59 (d, *J* 6.4 Hz, 3 H), 3.29 (dd, *J* 2.5 and 7.5 Hz, 1 H), 3.76 (s, 3 H), 4.59 (dd, *J* 2.5 and 7.5, 1 H), 5.51 (dq, *J* 6.4 and 7.5 Hz, 1 H), 6.24 (dd, *J* 7.5 and 15.7 Hz, 1 H), 6.7—7.4 (9 H, Ar) (Found: C, 65.2; H, 5.5; N, 7.5. $C_{20}H_{20}N_2O_5$ requires C, 65.21; H, 5.47; N, 7.6%).

(3S,4S)- *and* (3S,4R)-4-*Formyl*-1-p-*methoxyphenyl*-3-[(R)-1-*nitroxyethyl*]*azetidinone* (**12**) *and* (**13**).—A mixture of compounds (**10**) and (**11**) (2.20 g, 5.97 mmol) in dry methylene dichloride (50 ml) was cooled to −78 °C. Ozone was passed for 10 min through the solution which turned light blue. While still at −78 °C the system was flushed with nitrogen to give a light yellow solution; the temperature was then allowed to rise to 0 °C when dimethyl sulphide (DMS) (5 ml) was added. The mixture was stirred overnight, washed with water, dried, and evaporated under reduced pressure to give an oily residue which was used in the subsequent Jones' oxidation. A portion of the residue on chromatography afforded the aldehydes (**12**) and (**13**).

Aldehyde (**12**), m.p. 156 °C, $[\alpha]_D^{20}$ +121.2 (*c* 2.5; $CHCl_3$); $\nu_{max.}$($CHCl_3$) 2 910, 2 830, 1 760, 1 740, and 1 645 cm^{-1}; *m/z* 294 (M^+); δ_H (90 MHz) 1.57 (d, *J* 6.0 Hz, 3 H), 3.81 (br s, 4 H), 4.69 (dd, *J* 3.0 and 6.0 Hz, 1 H), 5.38 (dq, *J* 6.0 and 9.0 Hz, 1 H), 6.9—7.4 (4 H, Ar), and 9.90 (d, *J* 3.0 Hz, 1 H); δ_C (20 MHz) 197.4, 118.2, 114.7, 75.7, 59.5, 56.2, 55.6, 17.9.

Aldehyde (**13**), δ_H (90 MHz) 1.55 (d, *J* 6.0 Hz, 3 H), 3.47 (dd, *J* 3.0 and 7.5 Hz, 1 H), 3.77 (s, 3 H), 4.46 (m, 1 H), 5.51 (quintet, *J* 6.0 Hz, 1 H), 6.7—7.2 (4 H, Ar), and 9.75 (d, *J* 3 Hz, 1 H); δ_C (20 MHz) 196.7, 117.9, 114.2, 76.3, 59.8, 55.3, 55.3, and 17.1.

(3S,4S)- *and* (3S,4R)-1-p-*Methoxyphenyl*-3-[(R)-1-*nitroxyethyl*]-2-*oxoazetidine*-4-*carboxylic Acids* (**14**) *and* (**15**).—Jones reagent (2.67M; 1 ml) was added dropwise at 0 °C to a solution of the aldehydes (**12**) and (**13**) (0.20 g) in acetone (15 ml). After 1 h, methanol (1 ml) was added and the mixture was filtered, washed with brine, and evaporated under reduced pressure to give the acids (**14**) and (**15**) (0.15 g, 70.6%).

Acid (**14**), δ_H (90 MHz) 1.60 (d, *J* 6.0 Hz, 3 H), 3.65 (complex pattern, 4 H), 4.70 (d, *J* 5.0 Hz, 1 H), 5.54 (dq, *J* 6.0 and 11.2, Hz, 1 H), 6.7—7.3 (4 H, Ar), and 11.0 (br s, 1 H).

Acid (**15**), δ_H (90 MHz) 1.62 (d, *J* 6.0 Hz, 3 H), 3.74 (complex pattern 4 H), 4.54 (d, *J* 3.0 Hz, 1 H), 5.56 (quintet, *J* 6.0 Hz, 1 H), 6.7—7.3 (4 H, Ar), and 11.0 (br s, 1 H).

(3S,4R)-4-*Acetoxy*-1-p-*methoxyphenyl*-3-[(R)-1-*nitroxyethyl*]*azetidin*-2-*one* (**16**).—A solution of the acids (**14**) and (**15**) (0.150 g, 0.48 mmol) in acetonitrile (20 ml) was treated with catalytic amount of cupric acetate [$Cu(OAc)_2 \cdot H_2O$ ground in a mortar] and $Pb(OAc)_4$ (dried *in vacuo* to remove AcOH) (0.50 g, 1.1 mmol). The slurry was immersed in an oil-bath at 60 °C and stirred by passage of N_2 through it. After t.l.c. showed the absence of starting material (only traces remained after 2 h), the slurry was filtered on Celite. The solid was washed with EtOAc and the combined filtrate and washings were evaporated under reduced pressure and the residue chromatographed (hexane–ether, 3:2) to give the title compound (**16**) (0.12 g, 77%), m.p. 102 °C, $[\alpha]_D^{20}$ −32.4 (*c* 2.5; $CHCl_3$); $\nu_{max.}$ 1 760 and 1 640 cm^{-1}; *m/z* 324 (M^+); δ_H (90 MHz) 1.57 (d, *J* 6.0 Hz, 1 H), 2.14 (s, 3 H), 3.46 (dd, *J* 1.5 and 6.0 Hz, 1 H), 3.81 (s, 3 H), 5.51 (qt, *J* 6.0 Hz, 1 H), 6.45 (d, *J* 1.5 Hz, 1 H), and 6.7—7.4 (m, 4 H, Ar); δ_C (20 MHz) 170.0, 160.2, 119.0, 118.3, 114.6, 77.5, 75.7, 61.8, 55.5, 20.8, and 17.2 (Found: C, 52.0; H, 4.7; N, 8.6. $C_{14}H_{16}N_2O_7$ requires C, 51.85; H, 4.97; N, 8.64).

(3S,4R)-3-[(R)-1-*Nitroxyethyl*]-4-*styrylazetidin*-2-*one* (**17**).—A solution of compound (**16**) (0.120 g, 0.37 mmol) in MeCN (10 ml) at 0 °C was treated with a solution of cerium ammonium nitrate (CAN) (0.67 g, 1.2 mmol) in water (10 ml). After 30 min the reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (3 × 20 ml). The organic layers were washed with 5% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel (hexane–ethyl acetate 7:3) to give the title compound (**17**) (0.065 g, 81%), $[\alpha]_D^{20}$ +46.8 (*c* 3.3; $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 420, 1 790, 1 740, and 1 640 cm^{-1}; *m/z* 218 (M^+); δ_H (90 MHz) 1.52 (d, *J* 6.0 Hz, 3 H), 2.10 (s, 3 H), 3.37 (dd, *J* 1.5 and 6.0 Hz, 1 H), 5.41 (qt, *J* 6.0 Hz, 1 H), 5.78 (d, *J* 1.5 Hz, 1 H), and 6.96 (br s, NH); δ_C (20 MHz) 75.5, 75.4, 60.9, 20.7, and 17.2 (Found: C, 38.5; H, 4.5; N, 12.8. $C_7H_{10}N_2O_6$ requires C, 38.54; H, 4.62; N, 12.84).

(3S,4R)-4-*Acetoxy*-3-[(R)-1-*hydroxyethyl*]*azetidin*-2-*one* (**1**).—A slurry of Pd/C (10%; catalytic quantity) and compound

(**17**) (0.065 g, 0.3 mmol), in MeOH (30 ml) was stirred under an atmosphere of H_2 (30 p.s.i.) for 2 h. Filtration and evaporation gave the title compound (**1**) in quantitative yield; $[\alpha]_D^{20}$ +32.2 (*c* 2.05 $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 500, 3 420, 1 780, and 1 740 cm^{-1}; *m/z* 173 (M^+); δ_H (300 MHz) 1.32 (d, *J* 0.6 Hz, 1 H), 2.10 (s, 3 H), 2.80 (br s, OH), 3.21 (dd, *J* 1.5 and 6.0 Hz, 1 H), 4.21 (qt, *J* 6.0 Hz, 1 H), 5.91 (d, *J* 1.5 Hz, 1 H), and 6.98 (br s, NH); δ_C (20 MHz) 75.3, 64.9, 63.5, 21.0, and 20.7 (Found: C, 48.6; H, 6.3; N, 8.0. $C_7H_{11}NO_4$ requires C, 48.55; H, 6.40; N, 8.09).

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