Synthesis of Novel Fused β-Lactams by Intramolecular 1,3-Dipolar Cycloadditions. Part 7.[1] (9*RS*,9a*RS*)-9,9a-Dihydro-5-methyl-8-oxo-9-phenoxyacetamido-8*H*-azeto[1,2-*a*]-*v*-triazolo[5,1-*c*]pyrazine-6-carboxylic Acids and (3b*RS*,4*RS*,7*SR*)-4,5-Dihydro-5-oxo-4-phenoxyacetamido-3b*H*-azeto[1′,2′ : 3,4]-imidazo[1,5-*c*]-*v*-triazole-7-carboxylic Acid

Clive L. Branch, Stephen C. Finch, and Michael J. Pearson*
Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ

Addition of the mixed anhydride derived from azidoacetic acid and trifluoroacetic anhydride to benzyl 2-(*N*-phenylpropynylideneamino)-3,3-ethylenedioxybutanoate (**9**) in the presence of triethylamine afforded (3*RS*,4*SR*)-3-azido-1-(1-benzyloxycarbonyl-2,2-ethylenedioxypropyl)-4-phenylethynylazetidin-2-one (**14**), which was converted into (3*RS*,4*SR*)-1-(1-benzyloxycarbonylmethylsulphonyloxyprop-1-enyl)-3-phenoxyacetamido-4-phenylethynylazetidin-2-one (**21**). Treatment of (**21**) with sodium azide, followed by thermolysis in benzene, and de-esterification, provided the desired (9*RS*,9a*RS*)-9,9a-dihydro-5-methyl-9-phenoxyacetamido-1-phenyl-8*H*-azeto[1,2-*a*]-*v*-triazolo-[5,1-*c*]pyrazine-6-carboxylic acid (**26**). A similar reaction sequence yielded the corresponding 1-unsubstituted carboxylic acid (**27**).

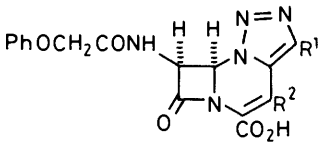
Another totally synthetic approach gave (3*RS*,4*SR*)-4-ethynyl-1-(4-methoxymethoxyphenyl)-3-phenoxyacetamidoazetidin-2-one (**43**), which was converted into (3*RS*,4*SR*)-1-[azido(benzyloxycarbonyl)methyl]-4-ethynyl-3-phenoxyacetamidoazetidin-2-one (**37**). Thermolysis of compound (**37**) in refluxing toluene, followed by removal of the ester protecting group, gave (3b*RS*,4*RS*,7*SR*)-4,5-dihydro-5-oxo-4-phenoxyacetamido-3b*H*-azeto[1′,2′:3,4]imidazo[1,5-*c*]-*v*-triazole-7-carboxylic acid (**48**).

The acid (**27**) showed moderate antibacterial activity against Gram-positive organisms, but the compounds (**26**) and (**48**) were totally inactive.

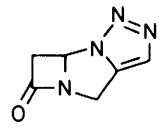
Recent reports[2] from these laboratories have described how the thermally induced intramolecular addition of an azido group to an acetylene was utilized for the synthesis of the tricyclic β-lactams (**1**) and (**3**). The triazolocephem (**1**) was biologically active and this stimulated further investigation into the synthesis of related systems, in the hope of discovering more potent derivatives. Although it was clear that the established methodology could be extended to the preparation of a range of structural types, we were mindful of certain criteria judged necessary to optimise antibacterial activity.[3] Accordingly, triazolocephems and triazolopenams of type (**4**) and (**6**) respectively, were selected as the target molecules.[4]

The initial strategy adopted for the synthesis of triazolocephems (**4**) paralleled the route of the Bristol group[5] who described the use of enol methanesulphonates for the synthesis of a range of nuclear analogues of cephalosporins. It was therefore planned to synthesize a vinyl azide of type (**7**) by reaction of the enol methanesulphonate moiety with sodium azide. Although only a few examples have been reported[6] with regard to the behaviour of vinyl azides as 1,3-dipoles, it was hoped that (**7**) might ring close to provide the tricyclic derivative (**5**). Benzyl was selected as an appropriate carboxyl protecting group since it was surmised that the hydrogenolysis conditions necessary for its removal would be unlikely to disrupt the ring system.

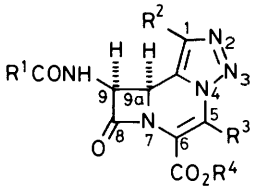
As a first approach the readily available aldehyde, 3-phenylprop-2-ynal was condensed with the amine (**8**)[5] to afford the Schiff base (**9**). In contrast to the corresponding cinnamylidene derivative (**10**)[5] the material (**9**) was a *ca.* 1:1 mixture of *syn* and *anti* isomers. In the n.m.r. spectrum the imine proton of each isomer appeared as a doublet (*J ca.* 0.5 Hz) at δ 7.98, and a singlet at δ 7.78, and the proton α to the ester group gave signals of corresponding multiplicity at δ 4.88 and 4.72.



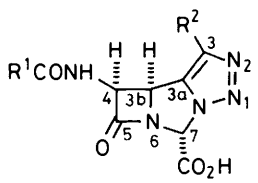
(**1**) R^1 = H, R^2 = Me
(**2**) R^1 = Ph, R^2 = Me



(**3**)



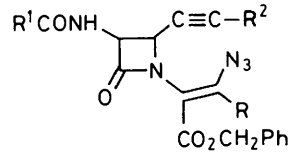
(**4**) R^4 = H
(**5**) R^4 = CH_2Ph



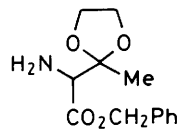
(**6**)

Treatment of the Schiff base (**9**) with the mixed anhydride from azidoacetic acid and trifluoroacetic anhydride, in the presence of triethylamine, gave the *trans* and *cis* β-lactams (**12**) and (**14**).† Both (**12**) and (**14**) were epimeric about the N–C(H)CO_2CH_2Ph centre. In the latter case only, the two epimers could be separated and crystallized. Although exclusive formation of *cis*

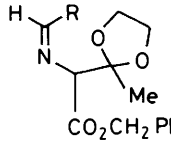
† Unless otherwise stated all synthetic compounds are racemic mixtures, but only one enantiomer is depicted for convenience.



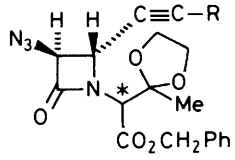
(7)



(8)



(9) R = C≡CPh
(10) R = CH=CHPh
(11) R = C≡C-SiMe$_3$



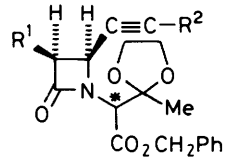
(12) R = Ph
(13) R = SiMe$_3$

products is generally observed with cinnamylidene Schiff bases, the isolation of *cis* and *trans* compounds in our case was not entirely unexpected, since the reaction is known to be sensitive to the substituent on the imine carbon atom, and to the experimental conditions.[3]

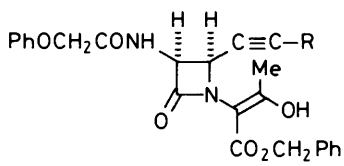
Reduction of either *cis*-epimer (**14**) with triethylamine–hydrogen sulphide[3] in dichloromethane followed by acylation of the crude products with phenoxyacetyl chloride provided the corresponding amides (**15**). Trifluoroacetic acid then smoothly removed the acetal from either amide epimer (**15**) to yield the enol (**19**), which was treated with methanesulphonyl chloride and triethylamine in dichloromethane at −10 °C to give the methanesulphonate (**21**) (78%), as a mixture of geometric isomers (ratio *ca.* 4:1, *E*:*Z*). The methanesulphonate (**21**) was vigorously stirred with powdered sodium azide in dimethylformamide (DMF) to afford the crude vinyl azide (**22**) as an inseparable mixture of geometric isomers. The total crude material was refluxed in benzene for 30 min to give three new products, after silica gel chromatography. The major, least polar material, was the desired triazole (**25**), obtained as a crystalline solid in 71% yield. The ^{1}H n.m.r. of (**25**) was remarkable in that the side-chain methylene, which in most fused β-lactam systems gives a singlet at *ca.* δ 4.5, appeared as an ABq with centres at δ 3.15 and 3.87 (*J* 15 Hz). The shift to high-field provides good evidence for the triazole structure, since a model indicated that the methylene would be heavily shielded by the phenyl group in the triazole ring. The two remaining components (18%) were separable isomers of the azirine (**29**) (2:1). It is presumed that one is derived from the minor *E*-isomer of the vinyl azide (**22**), and the other from the *Z*-isomer, as an alternative to triazole formation.

Hydrogenolysis of (**25**) over 10% Pd–C in aqueous dioxane provided the free acid (**26**) (90%) as an amorphous solid. The compound (**26**) was anti-bacterially inactive. Although this result was disappointing, a very similar derivative (**2**) in the isomeric series was also inactive, whereas analogues lacking the phenyl group in the triazole ring displayed some activity. Thus, having established the viability of the synthetic route, it was considered worthwhile undertaking the preparation of the unsubstituted derivative (**27**), in the hope that this might show improved biological properties.

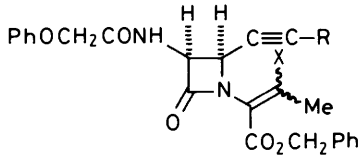
Since instability to mild base precluded the use of prop-2-ynal for Schiff base formation, a suitably protected derivative was utilized. Thus treatment of 3-trimethylsilylprop-2-ynal[7] with the amine (**8**) afforded the Schiff base (**11**). Standard cycloaddition methodology then allowed the preparation of the



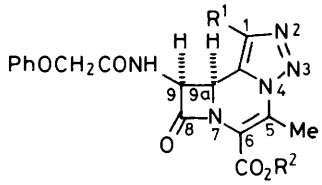
(14) R^1 = N$_3$, R^2 = Ph
(15) R^1 = PhOCH$_2$CONH, R^2 = Ph
(16) R^1 = N$_3$, R^2 = SiMe$_3$
(17) R^1 = N$_3$, R^2 = H
(18) R^1 = PhOCH$_2$CONH, R^2 = H



(19) R = Ph
(20) R = H



(21) R = Ph, X = OSO$_2$Me
(22) R = Ph, X = N$_3$
(23) R = H, X = OSO$_2$Me
(24) R = H, X = N$_3$



(25) R^1 = Ph, R^2 = CH$_2$Ph
(26) R^1 = Ph, R^2 = H
(27) R^1 = R^2 = H
(28) R^1 = H, R^2 = CH$_2$Ph

trans β-lactam (**13**) and the two separable *cis* β-lactam epimers (**16**).

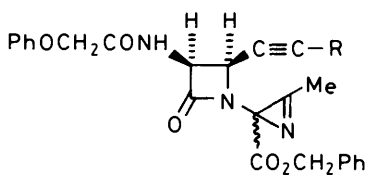
Desilylation of either pure epimer (**16**) with tetraethylammonium fluoride in tetrahydrofuran (THF) was accompanied by epimerisation to give the acetylenes (**17**). The epimers (**17**) were separated and subjected to the usual reduction–acylation sequence to provide the corresponding amides (**18**). Each of these were progressed *via* the enol (**20**) and the methanesulphate (**23**) to provide the vinyl azide (**24**), as a mixture of *E* and *Z* isomers, in excellent overall yield. The crude product was dissolved in benzene and after 17 h at room temperature, the solution was refluxed for 10 min to complete the reaction. Although t.l.c. showed only a single component, silica-gel chromatography, followed by careful ether trituration, allowed partition into two different fractions. The ether-insoluble material was the desired triazole (**28**) (49%), the soluble material (14%) being mainly a mixture of the azirines (**30**), contaminated with *ca.* 30% of the triazole (**28**). In the ^{1}H n.m.r. spectrum of (**28**) the side-chain methylene gave the expected singlet at δ 4.48. Removal of the benzyl ester from the triazole (**28**) then provided the acid (**27**) as a white amorphous solid. In the n.m.r. spectrum of the acid (**27**), the triazole proton, which had been obscured by the benzyl ester signals in (**28**), appeared as a doublet at δ 7.38, the fine coupling of *ca.* 1 Hz being also evident in the signal due to 9a-H at δ 5.25. The

Table. Antibacterial activity*

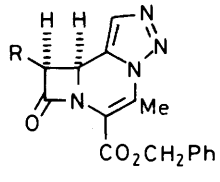
Bacterium	Triazolocephems (1)	(9*RS*,9a*RS*)-(27)	(9*S*,9a*S*)-(27)	(34)	(36)
β-Haemolytic *Streptococcus*	0.5	5.0	2.5	>100	50
Staphylococcus aureus (Oxford)	2.5	25	10	>100	25
Staphylococcus aureus (Russell)†	5.0	100	>50	>100	100
Bacillus subtilis	<0.2	5.0	0.5	100	0.5

* The figures are minimum inhibitory concentrations (μg ml^{-1}) required to inhibit bacterial growth after incubation on nutrient agar for 18 h. † Penicillinase-producing strain.

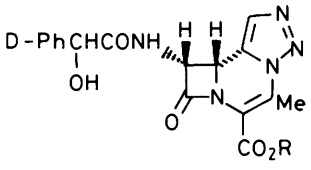
material (**27**) was inactive against Gram-negative bacteria and displayed only moderate activity against Gram-positive organisms (see Table). However, the degree of activity was less than that observed for (**1**) in the isomeric series (see Table) and cannot wholly be accounted for by the racemic nature of the product, since chiral material (**27**) was also less active (*vide infra*). In the i.r. spectrum the β-lactam carbonyl group of (**27**) absorbed at 1 760 cm^{-1}, *ca.* 35 cm^{-1} lower than the corresponding analogue (**1**) in the isomeric series. This decrease in reactivity of the β-lactam carbonyl system may in part explain the reduced anti-bacterial activity. Several acylamino derivatives were synthesized and, although no significant improvement in biological activity was achieved, the preparation of the D-mandelic acid derivative is worthy of mention.



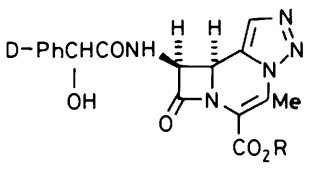
(**29**) R = Ph
(**30**) R = H



(**31**) R = NH_2
(**32**) R = N_3



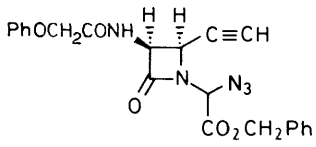
(**33**) R = CH_2Ph
(**34**) R = H



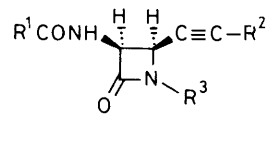
(**35**) R = CH_2Ph
(**36**) R = H

In order to facilitate the preparation of a range of compounds with diverse acylamino side-chains, the amine (**31**) was prepared. Repetition of the usual reaction sequence starting from the epimeric mixture of azides (**17**), without reduction of the azido group, provided the triazole (**32**) in good overall yield. Reduction of the azide (**32**), followed by acylation with D-mandelic *O*-carboxyanhydride allowed chromatographic resolution of the two diastereoisomers (**33**) (29%) and (**35**) (12%). The assignment of relative stereochemistry was made on the basis of the biological activities (see Table) obtained for the corresponding free acids (**34**) and (**36**), prepared by hydrogenation over 10% Pd–C. Some amine (**31**) was also recovered from the original coupling reaction, and was shown to be the natural enantiomorph by re-treatment with D-mandelic *O*-carboxyanhydride which gave only (**35**). Acylation of the resolved amine (**31**) with phenoxyacetyl chloride, followed by removal of the ester protecting group gave (**27**), which showed superior biological activity to the racemic material prepared previously.

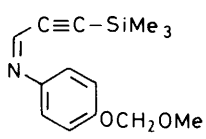
For the synthesis of the triazolopenam ring system, the azido acetylene (**37**) was the key intermediate. The choice was designed to facilitate the intramolecular cycloaddition reaction and hopefully, to optimise the biological activity of the final product. The initial target was the preparation of an azetidinone (**38**), in which the *N*-substituent was compatible with the initial β-lactam forming process, and could be removed under mild conditions, allowing the desired *N*-functionalisation to be achieved. Several potential blocking groups were available, but the *p*-methoxymethoxyphenyl moiety[8] appeared to be the most attractive. Subsequent to the completion of our work the Squibb group[9] have discussed the relative merits of various β-lactam *N*-blocking groups, and described the utility of *p*-methoxyphenyl as a new and particularly efficient alternative.



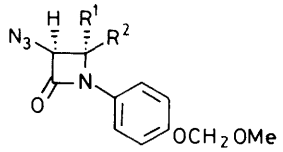
(**37**)



(**38**)



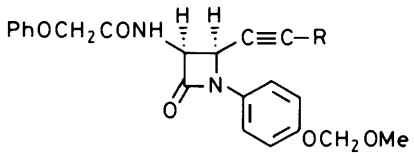
(**39**)



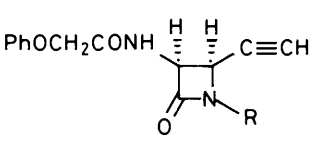
(**40**) R^1 = H, R^2 = C≡C $SiMe_3$
(**41**) R^1 = C≡C $SiMe_3$, R^2 = H

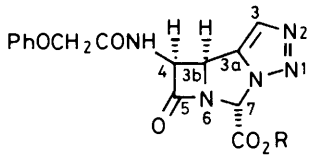
p-Methoxymethoxyaniline[8] was condensed with 3-trimethylsilylprop-2-ynal to give the Schiff base (**39**), a single isomer of undefined stereochemistry. The established cycloaddition procedure yielded the required *cis* β-lactam (**40**), along with traces (0.25%) of the corresponding *trans* isomer (**41**). The standard reduction–acylation procedure on the *cis* derivative (**40**) gave (**42**), and removal of the trimethylsilyl group was accomplished in the usual way to afford (**43**). Cleavage of the *N*-substituent with ceric ammonium nitrate (CAN) in aqueous THF then provided the azetidin-2-one (**44**). Treatment of the lactam (**44**) with benzyl glyoxylate in benzene containing a catalytic quantity of triethylamine,[10] afforded the α-hydroxy-ester (**45**) which was converted into the azide (**37**), *via* the α-chloro-ester (**46**), by successive reaction with thionyl chloride and sodium

azide.[11] The material (**37**) was a mixture of carboxylate diastereoisomers in a ratio *ca.* 1:1.



(**42**) R = $SiMe_3$
(**43**) R = H





(**44**) R = H
(**45**) R = $CH(OH)CO_2CH_2Ph$
(**46**) R = $CH(Cl)CO_2CH_2Ph$

(**47**) R = CH_2Ph
(**48**) R = H

In order to minimise intermolecular reactions, the thermolysis of (**37**) was performed in dilute solution. Accordingly, when the freshly prepared azide (**37**) was refluxed in toluene (1 mg ml^{-1}) for 40 h, the triazolopenam (**47**) was obtained as a white crystalline solid in 18% yield. The material (**47**) displayed a high β-lactam carbonyl absorption at 1 820 cm^{-1}, and although the proton in the triazole ring was obscured by the aromatic signals, its presence was confirmed by the multiplicity of the 3b-H signal, which showed the expected coupling (*J* 5.5 Hz) to 4-H, along with further allylic coupling of 0.8 Hz. Additional long range coupling (*J* 0.9 Hz) between the 3b-H and 7-H was also evident. Such fine coupling has been observed in related systems,[2] and suggested the β-configuration for 7-H. The extremely low-field chemical shift of 7-H at δ 6.49 and the absence of any coupling between 7-H and 4-αH [12,13] corroborated this assignment. Such selectivity in product formation has been reported previously, and has been attributed to steric factors.[13]

Catalytic hydrogenation of the ester (**47**) over 10% Pd–C in anhydrous dioxane afforded the desired free acid (**48**). The material had the expected spectroscopic properties, but was devoid of antibacterial activity.

Experimental

General procedures were as in Part 1[2] except where indicated otherwise. 250 MHz spectra were recorded on a Bruker WM 250 instrument. A Perkin-Elmer 141 polarimeter was used to determine specific rotations. Accurate mass measurements of molecular ions were carried out on compounds shown to be homogeneous by t.l.c. In general, the free acids described in the following experiments were not obtained analytically pure and gave no definitive mass spectral data. However, the antibacterially active compounds showed a single zone of antibacterial activity on biochromatograms and all gave the expected n.m.r., i.r., and u.v. spectra. Ether refers to diethyl ether.

Benzyl 3,3-*Ethylenedioxy*-2-(3-*phenylpropynylideneamino*)*butanoate* (**9**).—Benzyl 2-amino-3,3-ethylenedioxybutanoate (**8**) (16.14 g) (75% pure by n.m.r. spectroscopy) and 3-phenylprop-2-ynal (6.51 g) were stirred in dry dichloromethane (200 ml) containing anhydrous magnesium sulphate (5 g) for 16 h. The mixture was filtered and the solvent evaporated off to give the Schiff base (**9**) as an orange gum (22.2 g), $\nu_{max.}$ 2 200, 1 740, and 1 610 cm^{-1}; δ_H (60 MHz) 1.57 and 1.60 (together 3 H, both s), 4.05 (4 H, AA′ system), 4.72 (0.5 H, s), 4.88 (0.5 H, d, *J ca.* 2 Hz), 5.28 (2 H, AA′ system), 7.42 (10 H, s), 7.78 (0.5 H, s), and 7.98 (0.5 H, d, *J ca.* 2 Hz). The crude material was used directly without purification.

(3RS,4RS) *and* (3RS,4SR)-3-*Azido*-1-(1-*benzyloxycarbonyl*-2,2-*ethylenedioxypropyl*)-4-*phenylethynylazetidin*-2-*one* (**12**) *and* (**14**).—Azidoacetic acid (6.82 g) was dissolved in dry dichloromethane (60 ml) at 0 °C under argon and trifluoroacetic anhydride (9.5 ml) in dry dichloromethane (15 ml) added dropwise over 20 min. After 15 min, triethylamine (9.33 ml) in dry dichloromethane (15 ml) was carefully added dropwise during 15 min and the mixture stirred at 0 °C for a further 45 min. The solution was transferred under argon to a dropping funnel cooled to −76 °C, and added during 1 h to a mixture of the Schiff base (**9**) (22.2 g) and triethylamine (9.33 ml) in dichloromethane (150 ml) at 0 °C. After a further 1 h at 0 °C, the solution was diluted with dichloromethane, washed successively with water, dilute aqueous sodium hydrogen carbonate, and brine, dried, and evaporated. Chromatography of the residue gave the trans-*product* (**12**) as a gum (4.7 g, 17%) (Found: C, 64.6; H, 4.9; N, 12.5. $C_{24}H_{22}N_4O_5$ requires C, 64.5; H, 4.9; N, 12.6%); $\nu_{max.}$ 2 225w, 2 125, 1 780, and 1 750 cm^{-1}. The product was clearly a mixture of isomers, in the ratio *ca.* 3:2 and the ^1H n.m.r. spectrum showed *inter alia* δ (60 MHz) 1.50 and 1.56 (together 3 H, both s), 4.00 and 4.06 (together 4 H, both s), 4.53 (0.7 H, slightly broadened s), 5.21 (0.7 H, d, *J ca.* 1.5 Hz), 5.30 (2 H, s), and 7.38 (10 H, s).

Further elution of the column gave the *less polar isomer* (**14**) as a crystalline solid (1.8 g, 6%), m.p. 84—85 °C (ethyl acetate–light petroleum) (Found: C, 64.4; H, 4.8; N, 12.4%); $\nu_{max.}$ 2 225w, 2 115, 1 775, and 1 740 cm^{-1}; δ_H (90 MHz) 1.57 (3 H, s), 3.9 (4 H, s), 4.6 (1 H, s), 4.62 (1 H, d, *J* 5 Hz), 5.19 (1 H, d, *J* 5 Hz), 5.13 and 5.3 (2 H, ABq, *J* 12 Hz), 7.2—7.5 (10 H, m), and finally the *more polar isomer* (**14**) as a crystalline solid (1.18 g, 4%), m.p. 79—80 °C (ether–light petroleum) (Found: C, 64.7; H, 4.7; N, 12.5%); $\nu_{max.}$ 2 230, 2 120, 1 778, and 1 750 cm^{-1}; δ_H(90 MHz) 1.46 (3 H, s), 3.95 (4 H, s), 4.59 (1 H, s), 4.64 (1 H, d, *J* 5 Hz), 4.98 (1 H, d, *J* 5 Hz), 5.12 (2 H, ABq, *J* 13 Hz), and 7.2—7.5 (10 H, m).

(3RS,4SR)-1-(1-*Benzyloxycarbonyl*-2,2-*ethylenedioxypropyl*)-3-*phenoxyacetamido*-4-*phenylethynylazetidin*-2-*one* (**15**).—To the β-lactam (**14**) (less polar isomer) (1.71 g) in dry dichloromethane (40 ml) at 0 °C was added triethylamine (426 mg). Hydrogen sulphide was bubbled through the mixture for 5 min and the resulting dark solution left at 0 °C for 1 h. The solvent was then removed under reduced pressure and the residue re-evaporated (× 3) from dichloromethane to afford a pale yellow solid. Without further purification, the solid was dissolved in dry dichloromethane (40 ml) at −5 °C and triethylamine (426 mg) added, followed by dropwise addition of phenoxyacetyl chloride (721 mg) in dichloromethane (3 ml) during 5 min. The solution was washed with water, dried and evaporated. Chromatography provided the *product* (**15**) as a white, amorphous solid (2.05 g, 96%) (Found: C, 69.3; H, 5.5; N, 5.0. $C_{32}H_{30}N_2O_7$ requires C, 69.3; H, 5.4; N, 5.1%); $\nu_{max.}$ 3 420, 2 225w, 1 775, 1 745, and 1 695 cm^{-1}; δ_H (90 MHz) 1.58 (3 H, s), 3.92 (4 H, s), 4.52 (2 H, s), 4.58 (1 H, s), 5.20 (1 H, d, *J* 5 Hz), 5.14 and 5.29 (2 H, ABq, *J* 12 Hz), 5.62 (1 H, dd, *J* 5 and 9 Hz), and 6.7—7.5 (16 H, m).

The more polar epimer (**14**) (784 mg) was reduced and acylated using the same procedure to provide the other *amide epimer* (**15**) as a crystalline solid (880 mg, 90%), m.p. 108—109 °C (ethyl acetate–light petroleum) (Found: C, 69.1; H, 5.4; N, 5.0%); $\nu_{max.}$ 3 410, 2 225w, 1 770, 1 750, and 1 690 cm^{-1}; δ_H (90 MHz) 1.44 (3 H, s), 3.95 (4 H, s), 4.51 (2 H, s), 4.66 (1 H, s), 5.1 (1

H, d *J* 5 Hz), 5.13 (2 H, s), 5.68 (1 H, dd, *J* 10 and 5 Hz), and 6.7—7.65 (16 H, m).

E-(3RS,4SR)-1-(1-*Benzyloxycarbonyl*-2-*hydroxyprop*-1-*enyl*)-3-*phenoxyacetamido*-4-*phenylethynylazetidin*-2-*one* (**19**). —The amide (**15**) (2.00 g) [derived from less polar azide (**14**)] was dissolved in 5% aqueous trifluoroacetic acid (15 ml). After 1.5 h the solution was poured into a mixture of dichloromethane and ice–water and the organic layer was separated. The aqueous layer was extracted (×3) with dichloromethane and the combined organic extracts washed with water until neutral. The dichloromethane solution was dried and evaporated. Chromatography on silica-gel afforded the *product* (**19**) as a crystalline solid (1.51 g, 83%), m.p. 124—125 °C (ethyl acetate–light petroleum) (Found: C, 69.9; H, 5.4; N, 5.4; M^+, 510.1771. $C_{30}H_{26}N_2O_6$ requires C, 70.6; H, 5.1; N, 5.5%; *M*, 510.1790); $\nu_{max.}$ 3 420, 2 225w, 1 773, 1 690, and 1 660 cm^{-1}; δ_H (90 MHz) 2.23 (3 H, s), 4.54 (2 H, s), 4.87 (1 H, dd, *J* 5 Hz), 5.14 and 5.31 (2 H, ABq, *J* 12 Hz), 5.5 (1 H, dd, *J* 5 and 9 Hz), 6.7—7.7 (16 H, m), and 12.36 (1 H, s, exch. D_2O).

(3RS,4SR)-1-(1-*Benzyloxycarbonyl*-2-*methylsulphonyloxyprop*-1-*enyl*)-3-*phenoxyacetamido*-4-*phenylethynylazetidin*-2-*one* (**21**).—The enol (**19**) (1.02 g) was dissolved in dry dichloromethane (25 ml) at 0 °C and triethylamine (250 mg) was added, followed by the dropwise addition of methanesulphonyl chloride (286 mg) in dichloromethane (2 ml) during 5 min. The solution was washed with water, dried, and evaporated. Chromatography gave the product (**21**) as an amorphous solid (914 mg), (Found: M^+ 588.1571. $C_{31}H_{28}N_2O_8S$ requires *M* 588.1564); $\nu_{max.}$ 3 400, 2 240w, 1 780, 1 735, 1 695, and 1 640 cm^{-1}; the product was a mixture of *E* and *Z*-isomers (ratio 9:1) and the ^1H n.m.r. spectrum showed, for the major isomer δ (90 MHz) 2.59 (3 H, s), 3.15 (3 H, s), 4.51 (2 H, s), 5.11 (1 H, d, *J* 5 Hz), 5.16 and 5.32 (2 H, ABq, *J* 12 Hz), 5.55 (1 H, dd, *J* 5 and 9 Hz), and 6.7—7.8 (16 H, m). The minor isomer (**21**) gave, *inter alia* δ (90 MHz) 2.45 (3 H, s) and 3.02 (3 H, s).

(9RS,9aRS)-*Benzyl* 9,9a-*Dihydro*-5-*methyl*-8-*oxo*-9-*phenoxyacetamido*-1-*phenyl*-8H-*azeto*[1,2-a]-v-*triazolo*[5,1-c]*pyrazine*-6-*carboxylate* (**25**) *and* (3RS,4SR)-1-(2-*Benzyloxycarbonyl*-3-*methyl*-2H-*azirin*-2-*yl*)-3-*phenoxyacetamido*-4-(3-*phenylethynyl*)-*azetidin*-2-*one* (**29**).—The enol methanesulphonate (**21**) (817 mg) was dissolved in dry DMF (20 ml) and powdered sodium azide (100 mg) was added to the vigorously stirred solution. After 10 min the mixture was poured into ethyl acetate and brine. The organic layer was separated, washed successively with water and brine, and then dried and evaporated to give the crude vinyl azide (**22**). The oily residue was dissolved in dry benzene (20 ml) and the solution refluxed for 30 min. The solvent was evaporated off and the residue was chromatographed to give the *triazole* (**25**) as a white, crystalline solid (384 mg, 71%), m.p. 177—179 °C (decomp.) (ethyl acetate–light petroleum) (Found: C, 67.2; H, 4.7; N, 13.0. $C_{30}H_{25}N_5O_5$ requires C, 67.2; H, 4.6; N, 13.1%); $\lambda_{max.}$ 243, 276, and 312 nm (ε 14 300, 5 600, and 11 500 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$ 3 415, 1 790, 1 712, 1 700, and 1 635 cm^{-1}; δ_H (90 MHz) 2.98 (3 H, s), 3.15 and 3.87 (2 H, ABq, *J* 15 Hz), 5.34 (2 H, s), 5.43 (1 H, d, *J* 5 Hz), 6.11 (1 H, dd, *J* 5 and 10 Hz), 6.4—6.6 (2 H, m), and 6.8—7.6 (14 H, m).

Further elution of the column gave the *less polar isomer* of the *azirine* (**29**) as a crystalline solid (42 mg, 6%), m.p. 127—128 °C (ethyl acetate–light petroleum) (Found: C, 70.6; H, 4.9; N, 8.2. $C_{30}H_{25}N_3O_5$ requires C, 71.0; H, 4.9; N, 8.3%); $\nu_{max.}$ 3 410, 1 780, 1 695, and 1 650 cm^{-1}; δ_H (90 MHz) 2.28 (3 H, s), 4.55 (2 H, s), 4.87 (1 H, d, *J* 5 Hz), 5.38 (2 H, s), 5.65 (1 H, dd, *J* 5 and 9 Hz), and 6.6—7.6 (16 H, m).

The final product eluted was the *more polar isomer* of the *azirine* (**29**), which was obtained as a crystalline solid (77 mg, 11%), m.p. 152 °C (ethyl acetate–light petroleum) (Found: C, 71.1; H, 4.9; N, 8.3%); $\nu_{max.}$ 3 410, 1 780, 1 735, and 1 690 cm^{-1}; δ_H (80 MHz), 2.66 (3 H, s), 4.54 (2 H, s), 4.9 (1 H, d, *J* 5 Hz), 5.18 (2 H, s), 5.56 (1 H, dd, *J* 5 and 9 Hz), and 6.65—7.5 (16 H, m).

(9RS,9aRS)-9,9a-*Dihydro*-5-*methyl*-8-*oxo*-9-*phenoxyacetamido*-1-*phenyl*-8H-*azeto*[1,2-a]-v-*triazolo*[5,1-c]*pyrazine*-6-*carboxylic Acid* (**26**).—The benzyl ester (**25**) (108 mg) was hydrogenated over 10% Pd–C (50 mg) in a mixture of dioxane (15 ml) and water (3 ml) for 45 min. The catalyst was removed by filtration through Kieselguhr, and the filter cake was thoroughly washed with dioxane. The filtrate was evaporated and the residue dried *in vacuo*. Trituration with ether afforded the *acid* (**26**) as an amorphous solid (81 mg) (Found: C, 61.8; H, 4.5; N, 15.3. $C_{23}H_{19}N_5O_5$ requires C, 62.0; H, 4.3; N, 15.7%); $\lambda_{max.}$ 243, 276, and 296 nm (ε 11 700, 7 900 and 9 200 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$ (KBr) 3 400 br, 1 785, 1 675, and 1 603 cm^{-1}; $\delta_H[(CD_3)_2SO]$ (90 MHz) 2.78 (3 H, s), 3.36 and 3.75 (2 H, ABq, *J* 15 Hz), 4.87b (1 H, s, exch. D_2O), 5.72 (1 H, d, *J* 5 Hz), 6.01 (1 H, dd, *J* 5 and 10 Hz), 6.5—7.7 (10 H, m), and 8.58 (1 H, d, *J* 10 Hz).

Benzyl 3,3-*Ethylenedioxy* 2-(N-*trimethylsilylpropynylideneamino*)*butanoate* (**11**).—Trimethylsilylprop-2-ynal (9 g) (prepared from trimethylsilylethynyl-lithium[14] and ethyl formate according to the procedure of Hauptmann[7]) in dry dichloromethane (250 ml) was converted into the Schiff base (**11**) as described for (**9**). The product (**11**) was a pale orange gum (23 g), $\nu_{max.}$ 1 738 and 1 610 cm^{-1}; δ_H (60 MHz) 0.22 (9 H, s), 1.38 and 1.53 (together 3 H, two s), 4.05 (4 H, s), 4.83, 5.30, and 5.35 (together 4 H, three s), 7.48 (5 H, s), 7.6 (0.5 H, s), and 7.80 (0.5 H, d, *J ca.* 2 Hz). The crude material was used directly without purification.

(3RS,4RS) *and* (3RS,4SR)-3-*Azido*-1-(1-*benzyloxycarbonyl*-2,2-*ethylenedioxypropyl*)-4-*trimethylsilylethynylazetidin*-2-*one* (**13**) and (**16**).—Treatment of the Schiff base (**11**) (23 g) as described for (**9**) gave, after chromatography, the *trans* β-lactam (**13**) as an oil (6.93 g, 18%), which was a mixture of carboxylate diastereoisomers (ratio *ca.* 4:1). Ether trituration afforded the *major isomer* (**13**) as a solid (4.5 g), m.p. 71—72 °C (ethyl acetate–ether) (Found: C, 57.0; H, 5.9; N, 12.7. $C_{21}H_{26}N_4O_5Si$ requires C, 57.0; H, 5.9; N, 12.7%); $\nu_{max.}$ 2 120, 1 780, and 1 745 cm^{-1}; δ_H(90 MHz) 0.18 (9 H, s), 1.53 (3 H, s), 3.9 (4 H, s), 4.38 (1 H, s), 4.48 (1 H, d, *J* 2 Hz), 4.55 (1 H, d, *J* 2 Hz), 5.13 and 5.29 (2 H, ABq, *J* 12 Hz), and 7.35 (5 H, m). The minor isomer (**13**) was never isolated in a pure state but showed δ_H (90 MHz) *inter alia* 1.43 (3 H, s), 3.93 (4 H, s), 4.3 (1 H, d, *J* 2 Hz), 4.47 (1 H, s), and 5.15 (2 H, AA′ system).

Further elution of the column provided the *less polar* cis β-*lactam* (**16**) as an oil (4.85 g, 12%) (Found: C, 57.1; H, 6.0; N, 12.8%); $\nu_{max.}$ 2 120, 1 770, and 1 740 cm^{-1}; δ_H (90 MHz) 0.19 (9 H, s), 1.54 (3 H, s), 3.88 (4 H, s), 4.47 (1 H, d, *J* 5 Hz), 4.52 (1 H, s), 4.92 (1 H, d, *J* 5 Hz), 5.09 and 5.24 (2 H, ABq, *J* 12 Hz), and 7.35 (5 H, s), and the *more polar isomer* (**16**) as a crystalline solid (2.23 g, 6%), m.p. 70—72 °C (ether) (Found: C, 57.1; H, 6.0; N, 12.6%); $\nu_{max.}$(Nujol) 2 130, 1 793, and 1 740 cm^{-1}; δ_H (90 MHz) 0.18 (9 H, s), 1.40 (3 H, s), 3.90 (4 H, s), 4.49 (1 H, d, *J* 5 Hz), 4.50 (1 H, d, *J* 5 Hz), 5.09 and 5.26 (2 H, ABq, *J* 12 Hz), and 7.33 (5 H, s).

(3RS,4SR)-3-*Azido*-1-(1-*benzyloxycarbonyl*-2,2-*ethylenedioxypropyl*)-4-*ethynylazetidin*-2-*one* (**17**).—The major epimer (**16**) (410 mg) in dry THF (10 ml) was treated with tetraethylammonium fluoride (0.14 g). The mixture was vigorously stirred for 20 min, diluted with ethyl acetate, and washed with brine. The organic layer was separated, dried, and

evaporated. Chromatography afforded the *less polar isomer* (**17**) as a white crystalline solid (144 mg, 42%), m.p. 89—91 °C (ethyl acetate–light petroleum) (Found: C, 58.3; H, 4.8; N, 15.0. $C_{18}H_{18}N_4O_5$ requires C, 58.4; H, 4.9; N, 15.1%); $\nu_{max.}$(Nujol) 3 250, 2 100, 1 765, and 1 630 cm^{-1}; δ_H (90 MHz) 1.49 (3 H, s), 2.62 (1 H, d, *J* 2 Hz), 3.87 (4 H, s), 4.52 (1 H, s), 4.58 (1 H, d, *J* 5 Hz), 4.94 (1 H, dd, *J* 2 and 5 Hz), 5.09 and 5.24 (2 H, ABq, *J* 12 Hz), and 7.33 (5 H, s).

Further elution of the column provided the *more polar isomer* (**17**) as a clear oil (86 mg, 25%) (Found: C, 58.5; H, 5.2; N, 15.1%); $\nu_{max.}$ 3 300, 2 120, 1 775, and 1 745 cm^{-1}; δ_H (90 MHz) 1.41 (3 H, s), 2.47 (1 H, d, *J* 2 Hz), 3.93 (4 H, s), 4.56 (1 H, s), 4.61 (1 H, d, *J* 6 Hz), 4.74 (1 H, dd, *J* 2 and 6 Hz), 5.18 (2 H, s), and 7.35 (5 H, s).

Treatment of the minor isomer (**16**) (111 mg) in the same way gave the two carboxylate diastereoisomers of (**17**); less polar isomer (40 mg, 43%), more polar isomer (19 mg, 20%).

(3RS,4SR)-1-(1-*Benzyloxycarbonyl*-2,2-*ethylenedioxypropyl*)-4-*ethynyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**18**).—The lactam (**17**) (2 g) (unseparated epimeric mixture), was reduced and then acylated with phenoxyacetyl chloride as described for (**14**) to give the amide (**18**) as an inseparable epimeric mixture (2.27 g, 90%) (Found: M^+, 478.1708. $C_{26}H_{26}N_2O_7$ requires *M*, 478.1737); $\nu_{max.}$ 3 420, 3 315, 1 780, 1 750, and 1 698 cm^{-1}; δ_H (90 MHz) (deduced from mixture): *major epimer* 1.38 (3 H, s), 2.21 (1 H, d, *J* 2 Hz), 3.92 (4 H, s), 4.54 (2 H, s), 4.62 (1 H, s), 4.83 (1 H, dd, *J* 2 and 5 Hz), 5.18 (2 H, s), 5.58 (1 H, dd, *J* 6 and 10 Hz), and 6.8—7.6 (11 H, m); *minor epimer* 1.51 (3 H, s), 2.36 (1 H, d, *J* 2 Hz), 3.89 (4 H, s), 4.54 (3 H, s, side-chain methylene obscures a methine proton), 4.98 (1 H, d, *J* 2 and 5 Hz), 5.18 (2 H, s), 5.54 (1 H, dd, *J* 6 and 10 Hz), and 6.8—7.6 (11 H, m).

E-(3RS,4SR)-1-(1-*Benzyloxycarbonyl*-2-*hydroxyprop*-1-*enyl*)-4-*ethynyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**20**).—The amide (**18**) (464 mg) was treated with trifluoroacetic acid as described for (**15**) to give the *enol* (**20**) as a crystalline solid (170 mg, 39%), m.p. 115—116 °C (ethyl acetate–light petroleum) (Found: C, 66.2; H, 4.8; N, 6.3. $C_{24}H_{22}N_2O_6$ requires C, 66.4; H, 5.1; N, 6.5%); $\nu_{max.}$(Nujol) 3 345, 3 260, 1 780, 1 755, 1 695, 1 660, and 1 620 cm^{-1}; δ_H (90 MHz) 2.16 (3 H, s), 2.31 (1 H, d, *J* 2 Hz), 4.56 (2 H, a), 4.59 (1 H, dd, *J* 2 and 5 Hz), 5.18 (2 H, s), 5.38 (1 H, dd, *J* and 9 Hz, collapses to d, *J* 5 Hz on exch. D_2O), 6.8—7.4 (11 H, m), and 12.32 (1 H, s, exch. D_2O).

(3RS,4SR)-1-(1-*Benzyloxycarbonyl*-2-*methylsulphonyloxyprop*-1-*enyl*)-4-*ethynyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**23**).—The enol (**20**) (217 mg) was converted to the methanesulphonate (**23**) as described for (**19**). The product (**23**), isolated as an amorphous solid (181 mg), was a mixture of geometrical isomers (Found: M^+, 512.1253. $C_{25}H_{24}N_2O_8S$ requires *M*, 512.1251); $\nu_{max.}$ 3 420, 3 310, 1 785, 1 750, 1 695, and 1 645 cm^{-1}; δ_H (90 MHz) *major* E-*isomer* (**23**) 2.32 (1 H, d, *J* 2 Hz), 2.57 (3 H, s), 3.14 (3 H, s), 4.51 (2 H, s), 4.83 (1 H, dd, *J* 2 and 5 Hz), 5.2 (2 H, s), 5.47 (1 H, dd, *J* 5 and 9 Hz), and 6.8—7.5 (11 H, m); *minor* Z-*isomer* (**23**) *inter alia* 2.39 (3 H, s), and 2.99 (3 H, s).

Benzyl 9,9a-*Dihydro*-5-*methyl*-8-*oxo*-9-*phenoxyacetamido*-8H-*azeto*[1,2-a]-v-*triazolo*[5,1-c]*pyrazine*-6-*carboxylate* (**28**) *and* (3RS,4SR)-1-(2-*Benzyloxycarbonyl*-3-*methyl*-2H-*azirin*-2-*yl*)-3-*phenoxyacetamido*-4-*ethynylazetidin*-2-*one* (**30**).—(a). (9*RS*,9a*RS*)-(**28**). The methanesulphonate (**23**) (142 mg) was converted into the vinyl azide (**24**) as described for (**21**). The crude product (**24**) was then dissolved in benzene (5 ml). After 17 h, the solution was refluxed for 10 min and the solvent evaporated off. Chromatography of the crude product on silica-gel, followed by trituration of the eluted material with ether gave the (9RS,9aRS)-*triazole* (**28**) as an amorphous solid (62 mg; 49%) (Found: C, 62.4; H, 4.4; N, 14.7. $C_{24}H_{21}N_5O_5$ requires C, 62.7; H, 4.6; N, 15.3%); $\lambda_{max.}$ 268, 275, and 301 nm (ε 6 700, 6 900, and 9 500 dm^{-3} mol^{-1} cm^{-1}); $\nu_{max.}$ 3 410, 1 790, 1 720, 1 690, and 1 630 cm^{-1}; δ_H (90 MHz) 2.9 (3 H, s), 4.48 (2 H, s), 5.1 (1 H, d, *J* 5 Hz), 5.3 (2 H, s), 5.84 (1 H, dd, *J* 5 and 8 Hz), and 6.7—7.5 (12 H, m); The C.I. mass spectrum showed (M^+ + H) 460.

The ^1H n.m.r. spectrum of the ether soluble material (17 mg) indicated that the product contained the triazole (**28**) (30%), and the two isomers of the azirine (**30**) (70%). Singlets at δ 2.22 and δ 2.59 were assignable to the methyl groups of the minor and major azirines (**30**) respectively. (b). (9*S*,9a*S*)-(**28**). The (9*S*,9a*S*)-amine (**31**) (14 mg) (*vide infra*) was dissolved in dry dichloromethane (2 ml) at −20 °C and triethylamine (5 mg) and phenoxyacetyl chloride (8 mg) added in the minimum volume of dichloromethane. The solution was diluted with dichloromethane, washed with brine, dried and evaporated. Chromatography on silica-gel afforded the (9*S*,9a*S*)-amide (**28**) as an amorphous solid (19 mg; 99%), $[\alpha]_D^{22}$ −5.15° (*c* 3.25 in $CHCl_3$).

9,9a-*Dihydro*-5-*methyl*-8-*oxo*-9-*phenoxyacetamido*-8H-*azeto*-[1,2-a]-v-*triazolo*[5,1-c]*pyrazine*-6-*carboxylic Acid* (**27**).—(a). (9*RS*,9a*RS*)-(**27**). The (9*RS*,9a*RS*)-ester (**28**) (40 mg) was hydrogenated as described for (**25**) to give the (9*RS*,9a*RS*)-acid (**27**) as an amorphous solid (30 mg, 94%), $\lambda_{max.}$ 269, 275, and 288 nm (ε 5 600, 6 300, and 6 400 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$ (KBr) 3 400br, 1 760, 1 675, and 1 630 cm^{-1}; δ_H(CD_3OD–D_2O) (80 MHz) 2.81 (3 H, s, $-CH_2$-obscured by solvent peaks), 5.25 (1 H, dd, *J ca.* 1 and 5 Hz), 5.67 (1 H, d, *J* 5 Hz), 6.8—7.3 (5 H, m), and 7.38 (1 H, d, *J ca.* 1 Hz). (b). (9*S*,9a*S*)-(**27**). The (9*S*,9a*S*)-ester (**28**) (18 mg) was hydrogenated as described for (9*RS*,9a*RS*)-ester (**25**) to provide the (9*S*,9a*S*)-acid (**27**) as a white solid (10 mg), $[\alpha]_D^{22}$ −21.1° (*c* 1.2 in DMSO).

(9RS,9aRS)-*Benzyl* 9-*azido*-9,9a-*dihydro*-5-*methyl*-8-*oxo*-8H-*azeto*[1,2-a]-v-*triazolo*[5,1-c]*pyrazine*-6-*carboxylate* (**32**).—The mixture of epimeric azides (**17**) was converted *via* the usual sequence into the *triazole* (**32**) which was isolated as an amorphous solid (Found: M^+ 351.1073. $C_{16}H_{13}N_7O_3$ requires *M*, 351.1077); $\lambda_{max.}$ 298 nm (ε 10 650 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$ 2 125, 1 795, 1 725, and 1 630 cm^{-1}; δ_H (90 MHz) 2.92 (3 H, s), 5.02 (1 H, dd, *J* 1.8 and 4.9 Hz), 5.31 (2 H, s), 5.34 (1 H, d, *J* 4.9 Hz), 7.39 (5 H, s), and 7.65 (1 H, d, *J* 1.8 Hz).

Benzyl 9-*Amino*-9,9a-*dihydro*-5-*methyl*-8-*oxo*-8H-*azeto*[1,2-a]-v-*triazolo*[5,1-c]*pyrazine*-6-*carboxylate* (**31**) *and*, (9R,9aR) *and* (9S,9aS)-*Benzyl* 9,9a-*Dihydro*-9-(D-α-*hydroxyphenylacetamido*)-5-*methyl*-8-*oxo*-8H-*azeto*[1,2-a]-v-*triazolo*[5,1-c]*pyrazine*-6-*carboxylate* (**33**) *and* (**35**).—The azido triazole (**32**) (75 mg) in dichloromethane (3 ml) was reduced as described for (**14**) to give the crude (9*RS*,9a*RS*)-amine (**31**) as a solid. Without further purification the (9*RS*,9a*RS*)-amine (**31**) was dissolved in dichloromethane (3 ml) at −20 °C, and D-mandelic *O*-carboxyanhydride (42 mg) added. After 1 h, the reaction mixture was diluted with dichloromethane, washed successively with dilute aqueous sodium hydrogen carbonate solution and brine, dried, and evaporated. Chromatography afforded the *first diastereoisomer* (**33**) as a white solid (29 mg, 30%), $[\alpha]_D^{22}$ −21.6° (*c* 2.9 in $CHCl_3$) [Found: $M^+ - H_2O$, 441.1445. $C_{24}H_{19}N_5O_4$ requires $M - H_2O$, 441.1433. The C.I. mass spectrum gave (M^+ + H) 460]; $\lambda_{max.}$ 301 nm (ε 9 450 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$ 3 400br, 1 790, 1 725, 1 690, and 1 630 cm^{-1}; δ_H (90 MHz) 2.87 (3 H, s), 4.0—4.3 (1 H, br s, exch. D_2O), 4.94 (1 H, d, *J* 5 Hz), 5.10 (1 H, s), 5.29 (2 H, s), 5.69 (1 H, dd, *J* 5 and 8 Hz), 6.91 (1 H, s), 7.34 (10 H, s), and 7.60 (1 H, d *J* 8 Hz).

Further elution of the column gave the *more polar*

diastereoisomer (**35**) as an amorphous solid (12 mg, 12%), $[\alpha]_D^{22}$ −22.2° (*c* 1.2 in $CHCl_3$) (Found: M^+, 459.1544. $C_{24}H_{21}N_5O_5$ requires *M*, 459.1540); $\lambda_{max.}$ 302 nm (ε 9 010 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$ 3 400br, 1 790, 1 725, 1 690, and 1 630 cm^{-1}; δ_H (90 MHz) 2.79 (3 H, s), 4.1—4.5 (1 H, br s, exch. D_2O), 4.94 (1 H, d, *J* 5 Hz), 5.06 (1 H, s), 5.26 (2 H, s), 5.68 (1 H, dd, *J* 5 and 8 Hz), 6.91 (1 H, s), and 7.34 (11 H, m, 1 H lost on exchange with D_2O).

The last product eluted was the (9*S*,9a*S*)-*amine* (**31**), isolated as a white solid (25 mg), $[\alpha]_D^{22}$ −52.97° (*c* 1.5 in $CHCl_3$) (Found: M^+, 325.1169. $C_{16}H_{15}N_5O_3$ requires *M*, 325.1173); $\lambda_{max.}$ 300 nm (ε 7 905 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$(Nujol) 3 380, 1 770, 1 718, and 1 630 cm^{-1}; δ_H[$(CD_3)_2CO$] (90 MHz) 2.87 (3 H, s), 5.24 (1 H, d, *J* 5 Hz), 5.32 (2 H, s), 5.7 (1 H, d, *J* 5 Hz), 7.3—7.6 (5 H, m), and 7.57 (1 H, s).

Treatment of the (9*S*,9a*S*)-amine (**31**) with D-mandelic *O*-carboxyanhydride for 3 h as described above gave only (**35**).

(9R,9aR) *and* (9S,9aS) 9,9a-*Dihydro*-(D-α-*hydroxyphenylacetamido*)-5-*methyl*-8-*oxo*-8H-*azeto*[1,2-a]-v-*triazolo*[5,1-c]-*pyrazine*-6-*carboxylic Acids* (**34**) *and* (**36**).—The ester (**33**) (15 mg) was hydrogenated as described for (**25**) to give the acid (**34**) as a white amorphous solid (10 mg, 79%), $\lambda_{max.}$ 287 nm (ε 4 800 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$(KBr) 3 400, 1 765, 1 670, and 1 640 cm^{-1}.

Similar treatment of the other diastereoisomer (**35**) (23 mg) provided the acid (**36**) as an amorphous solid (13 mg, 68%), $\lambda_{max.}$ 290 nm (ε 6 490 dm^3 mol^{-1} cm^{-1}); $\nu_{max.}$(KBr) 3 400, 1 750, 1 675, and 1 640 cm^{-1}. The free acids (**34**) and (**36**) were re-esterified to provide the substantially pure (t.l.c.) benzyl esters (**33**) and (**35**).

N-(3-*Trimethylsilylprop*-2-*ynylidene*)-4-*methoxymethoxyaniline* (**39**).—Trimethylsilylprop-2-ynal (5.8 g) and 4-methoxymethoxyaniline (7 g) were dissolved in dry dichloromethane (100 ml) containing anhydrous magnesium sulphate (5 g). After 16 h the mixture was filtered and the filtrate evaporated to give the Schiff base (**39**) as an orange oil (11.9 g), $\nu_{max.}$ 1 605 cm^{-1}; δ_H (60 MHz) 0.27 (9 H, s), 3.5 (3 H, s), 5.25 (2 H, s), 7.15 (AA' system, 4 H), and 7.8 (1 H, s). The crude material was used directly without purification.

(3RS,4RS) *and* (3RS,4SR)-3-*Azido*-1-(4-*methoxymethoxyphenyl*)-4-*trimethylsilylethynylazetidin*-2-*one* (**40**) *and* (**41**).—The Schiff base (**39**) (11.9 g) was converted into the title compounds as described for (**9**). Chromatography of the crude product gave the trans-*isomer* (**40**) as a crystalline solid (385 mg, 2%), m.p. *ca.* 112 °C (dependent on the rate of heating) (light petroleum) (Found: C, 55.6; H, 6.0; N, 15.9. $C_{16}H_{20}N_4O_3Si$ requires C, 55.8; H, 5.9; N, 16.3%); $\nu_{max.}$ 2 110, and 1 760 cm^{-1}; δ_H (60 MHz) 0.25 (9 H, s), 3.46 (3 H, s), 4.4 (1 H, d, *J ca.* 2 Hz), 4.76 (1 H, d, *J ca.* 2 Hz), 5.16 (2 H, s), 7.03 and 7.48 (4 H, ABq, *J* 9 Hz).

Further elution of the column afforded the cis-*isomer* (**41**) as a crystalline solid (11.2 g, 57%), m.p. *ca.* 125 °C (dependent on the rate of heating) (ethyl acetate–light petroleum) (Found: C, 55.7; H, 6.0; N, 16.0%); $\nu_{max.}$ 2 110 and 1 760 cm^{-1}; δ_H (60 MHz) 0.25 (9 H, s), 3.25 (3 H, s), 4.43 (1 H, d, *J* 5 Hz), 4.62 (1 H, d, *J* 5 Hz), 4.94 (2 H, s), 6.82 and 7.27 (2 H, ABq, *J* 9 Hz).

(3RS,4SR)-1-(4-*Methoxymethoxyphenyl*)-3-*phenoxyacetamido*-4-*trimethylsilylethynylazetidin*-2-*one* (**42**).—The lactam (**41**) (3.44 g) was reduced and then acylated with phenoxyacetyl chloride as described for (**14**) to give the *amide* (**42**) as a crystalline solid (4.38 g, 97%), m.p. 202—203 °C (ethyl acetate) (Found: C, 63.8; H, 6.3; N, 6.1. $C_{24}H_{28}N_2O_5Si$ requires C, 63.7; H, 6.2; N, 6.2%); $\nu_{max.}$(Nujol) 3 280, 1 760, and 1 670 cm^{-1}; δ_H[$(CD_3)_2SO$] (90 MHz) 0.13 (9 H, s), 3.36 (3 H, s), 4.58 (2 H, s), 5.08 (1 H, d, *J* 5.5 Hz), 5.17 (2 H, s), 5.4 (1 H, dd, *J* 5.5 and 9 Hz), 6.85—7.5 (9 H, m), and 9.1 (1 H, d, *J* 9 Hz).

(3RS,4SR)-4-*Ethynyl*-1-(4-*methoxymethoxyphenyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (**43**).—The lactam (**42**) (1.81 g) was treated with tetraethylammonium fluoride (815 mg) as described for (**16**). Chromatography of the crude product on silica-gel eluting with ethyl acetate–dichloromethane mixtures gave the *ethynyl derivative* (**43**) as a crystalline solid (1.38 g, 91%), m.p. 153 °C (ethyl acetate–light petroleum) (Found: C, 66.3; H, 5.4; N, 7.2. $C_{21}H_{20}N_2O_5$ requires C, 66.3; H, 5.3; N, 7.4%); $\nu_{max.}$ 3 400, 3 290, 1 760, and 1 690 cm^{-1}; δ_H (90 MHz) 2.4 (1 H, d, *J* 2 Hz), 3.44 (3 H, s), 4.58 (2 H, s), 4.85 (1 H, dd, *J* 2 and 5.5 Hz), 5.12 (2 H, s), 5.66 (1 H, dd, *J* 5.5 and 10 Hz), and 6.85—7.5 (10 H, m).

(3RS,4SR)-4-*Ethynyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**44**).—The lactam (**43**) (340 mg) was dissolved in THF (10 ml) and the solution cooled to 0 °C. Ceric ammonium nitrate (2.45 g) in water (4 ml) was added dropwise during 10 min. After a further 10 min solid sodium sulphite was added to discharge the orange-red colour, and the mixture poured into ethyl acetate–brine. After filtration through Kieselguhr the organic layer was separated, washed with brine, dried, and evaporated. Chromatography on silica-gel gave recovered starting material (**43**) (30 mg, 9%) and the *azetidin*-2-*one* (**44**) as a crystalline solid (75 mg, 35%), m.p. 190—191 °C (ethyl acetate–light petroleum) (Found: C, 64.0; H, 5.1; N, 11.3. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 5.0; N, 11.5%); $\nu_{max.}$(Nujol) 3 280, 3 250, 3 225sh, 1 768, and 1 675 cm^{-1}; δ_H[$(CD_3)_2SO$] (90 MHz) 3.47 (1 H, d, *J* 2 Hz), 4.48 (1 H, dd, *J* 1.9 and 4.5 Hz), 4.57 (2 H, s), 5.19 (1 H, dd, *J* 4.5 and 8 Hz), 6.8—7.4 (5 H, m), 8.68 (1 H, s, exch. D_2O), and 8.92 (1 H, d, *J* 8 Hz, exch. D_2O).

(3RS,4SR)-1-[*Benzyloxycarbonyl*(*hydroxy*)*methyl*]-4-*ethynyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**45**).—The β-lactam (**44**) (25 mg) and benzyl glyoxylate monohydrate (20 mg) were refluxed in benzene (10 ml) for 1 h. The solution was cooled to room temperature and triethylamine (1 mg) added. After 1 h the solvent was evaporated and the residue chromatographed on silica to provide the less polar isomer (**45**) as an amorphous solid (16 mg; 40%), $\nu_{max.}$ 3 420, 3 310, 1 780, 1 750, and 1 695 cm^{-1}; δ_H (250 MHz) 2.38 (1 H, d, *J* 2 Hz), 4.26 (1 H, d, *J* 8 Hz), 4.48 (1 H, dd, *J* 2 and 5 Hz), 4.56 (2 H, s), 5.26 and 5.32 (2 H, ABq, *J* 11.5 Hz), 5.47 (1 H, d, *J* 8 Hz), 5.50 (1 H, dd, *J* 5 and 9.6 Hz), 6.87—7.42 (10 H, m), and 7.47 (1 H, d, *J* 9.6 Hz).

Further elution gave the more polar isomer (**45**) (11 mg; 28%), $\nu_{max.}$ 3 420, 3 310, 1 780, 1 750, and 1 695 cm^{-1}; δ_H (250 MHz) 2.11 (1 H, d, *J* 2 Hz), 4.13 (1 H, d, *J* 7 Hz), 4.53 and 4.60 (2 H, ABq, *J* 15 Hz), 4.69 (1 H, dd, *J* 2 and 5 Hz), 5.21 and 5.30 2 H, ABq, *J* 11.5 Hz), 5.56 (1 H, d, *J* 7 Hz), 5.57 (1 H, dd, *J* 5.0 and 9.5 Hz), and 6.87—7.43 (11 H, m). Each isomer (**45**) contained 5—10% of the other, and they were normally not separated but progressed directly to the next stage.

(3RS,4SR)-1-[*Azido*(*benzyloxycarbonyl*)*methyl*]-4-*ethynyl*-3-*phenoxyacetamidoazetidin*-2-*one* (**37**).—The alcohol (**45**) (396 mg) was dissolved in dry THF (10 ml) at −15 °C and 2,6-dimethylpyridine (156 mg) was added, followed by thionyl chloride (173 mg) in THF (2 ml). The mixture was filtered and the filtrate evaporated; the residue was dissolved in toluene and the solution evaporated to afford the chloride (**46**) as an amorphous solid (400 mg). This was dissolved in dry DMF (5 ml) and powdered sodium azide (66 mg) added to the vigorously stirred solution. After 5 min the mixture was poured into ethyl acetate–dilute aqueous citric acid, the organic phase separated, and washed with brine. The solution was dried and evaporated. Chromatography gave the azide (**37**) as an inseparable mixture of isomers (319 mg, 76%), $\nu_{max.}$ 3 410, 3 300, 2 120, 1 790, 1 760, and 1 695 cm^{-1}; δ_H (250 MHz) (1:1 mixture of isomers) 2.21 and 2.43 (together 1 H, two d, *J* 2 Hz), 4.55 (2 H,

s), 4.72 (1 H, dd, *J* 2 and 5.5 Hz), 5.26 (2 H, s), 5.42 and 5.59 (together 1 H, two s), 5.60 (1 H, m), and 6.80—7.5 (11 H, m). The material (**37**) was best used immediately after purification.

(3bRS,4RS,7SR)-*Benzyl* 4,5-*Dihydro*-5-*oxo*-4-*phenoxyacetamido*-3bH-*azeto*[1′,2′:3,4]*imidazo*[1,5-c]-v-*triazole*-7-*carboxylate* (**47**).—The azide (**37**) (265 mg) was dissolved in degassed toluene (250 mg) and the solution was refluxed under argon for 36 h. The solvent was evaporated off and the residue chromatographed. The *triazole* (**47**) was isolated as a crystalline solid (47 mg; 18%), m.p. 168—170 °C (ethyl acetate–hexane) (Found: C, 61.0; H, 4.4; N, 15.8. $C_{22}H_{19}N_5O_5$ requires C, 61.0; H, 4.4; N, 16.2%); $\nu_{max.}$ 3 400, 1 820, 1 765, and 1 595 cm^{-1}; δ_H (250 MHz) 4.52 (2 H, AA′), 5.23 and 5.28 (2 H, ABq, *J* 12.2 Hz), 5.33 (1 H, ddd, *J* 0.8, 0.9, and 5.5 Hz), 5.72 (1 H, dd, *J* 5.5 and 7.5 Hz), 6.49 (1 H, d, *J* 0.9 Hz), 6.91 (1 H, d, *J* 7.5 Hz), and 6.8—7.4 (11 H, m).

(3bRS,4RS,7SR) 4,5-*Dihydro*-5-*oxo*-4-*phenoxyacetamido*-3bH-*azeto*[1′,2′:3,4]*imidazo*[1,5-c]-v-*triazole*-7-*carboxylic Acid* (**48**).—The benzyl ester (**47**) (35 mg) was hydrogenated as described for (**25**) to give the acid (**48**) as an amorphous solid (**21** mg; 72%); $\nu_{max.}$(KBr) 3 400, 1 805, 1 745sh, and 1 675 cm^{-1}; $\delta_H[(CD_3)_2SO]$ (250 MHz) 4.49 (2 H, AA′ system), 5.28 (1 H, s, *J* 5.6 Hz), 5.64 (1 H, dd, *J* 5.6 and 8 Hz), 6.45 (1 H, s), 6.85—7.36 (5 H, m), 7.51 (1 H, s), and 8.88 (1 H, d, *J* 8.0 Hz).

Acknowledgements

We thank Dr. J. H. C. Nayler for his interest in this work, Mr. M. J. Basker for the microbiological data and Dr. J. Gower, Mr. J. W. Tyler, and Mr. A. Cutmore for the spectral data.

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Received 7th November 1984; *Paper* 4/1898