Synthesis of Novel Fused β-Lactams by Intramolecular 1,3-Dipolar Cycloadditions. Part 2.[1] (8*S*,8a*R*)-7,8-Dihydro-7-oxo-8-phenoxyacetamido-8a*H*-azeto[1,2-*a*]-*v*-triazolo[3,4-*c*]pyrimidine-5-carboxylic Acids

By **Michael J. Pearson**, Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ

The penicillin-derived (3*R*,4*R*)-4-methylthio-3-triphenylmethylaminoazetidin-2-one (10) has been converted into (3*S*,4*R*)-4-azido-1-(1-t-butoxycarbonylbut-3-ynyl)-3-triphenylmethylaminoazetidin-2-one (15a), which provided t-butyl(8*S*,8a*R*)-4,5,7,8-tetrahydro-7-oxo-8-triphenylmethylamino-8a*H*-azeto[1,2-*a*]-*v*-triazolo-[3,4-*c*]pyrimidine-5-carboxylate (16a) when heated in refluxing toluene. Conversion of (16a) into t-butyl (8*S*,8a*R*)-7,8-dihydro-7-oxo-8-triphenylmethylamino-8a*H*-azeto[1,2-*a*]-*v*-triazolo[3,4-*c*]pyrimidine-5-carboxylate (14a) was then accomplished *via* an α-selenenylation, oxidation sequence. Removal of the amino-protecting group from (14a), followed by acylation with phenoxyacetyl chloride and de-esterification provided the desired (8*S*,8a*R*)-7,8-dihydro-7-oxo-8-phenoxyacetamido-8a*H*-azeto[1,2-*a*]-*v*-triazolo[3,4-*c*]pyrimidine-5-carboxylic acid (20).

Another intramolecular cycloaddition between an acetylene and an azido-group afforded t-butyl (8*S*,8a*R*)-7,8-dihydro-7-oxo-4-hydroxy-4-methyl-8-triphenylmethylamino-8a*H*-azeto[1,2-*a*]-*v*-triazolo[3,4-*c*]-pyrimidine-5-carboxylate (27). Sequential treatment of (27) with thionyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene gave t-butyl (8*S*,8a*R*)-7,8-dihydro-7-oxo-4-methyl-8-triphenylmethylamino-8a*H*-azeto[1,2-*a*]-*v*-triazolo-[3,4-*c*]pyrimidine-5-carboxylate (34), which was converted into (8*S*,8a*R*)-7,8-dihydro-7-oxo-4-methyl-8-phenoxyacetamido-8a*H*-azeto[1,2-*a*]-*v*-triazolo[3,4-*c*]pyrimidine-5-carboxylic acid (36).

Compounds (20), its 3-phenyl analogue (22), and (36), all showed varying degrees of antibacterial activity.

THE incorporation of one or more nitrogen atoms into the ring fused to the β-lactam has been investigated by various groups. In 1972 Wolfe [2] reported the synthesis of the azacephem (1) and Bose [3] has described various compounds (2) lacking a carboxy-group. More recently a series of β-lactam fused thiadiazine *S*-imides (3) has been described,[4] and Luttringer [5] has synthesised novel β-lactams of type (4). The Bristol workers,[6] as part of their extensive programme directed towards the synthesis of nuclear analogues of cephalosporins, have prepared isoazacephalosporins (5). A recent communication [7] described compounds, (6) and (7), which contained two additional nitrogen atoms in the ring fused to the β-lactam. Modest antibacterial activity and chemical stability have been reported [8] for the bicyclic structure (8).

The triazole (9) has been synthesised [1] and although the compound was antibacterially inactive, it was clear that the established procedure could be extended to the synthesis of acylamino-analogues. It was hoped that these compounds might have antimicrobial properties at least equal to those possessed by the cephalosporins.

Following our earlier investigations, (3*R*,4*R*)-4-methylthio-3-triphenylmethylaminoazetidin-2-one (10) was selected as a suitable starting material. Use of (10) was attractive to us for two reasons. First, the compound was readily available in two steps from benzyl 6β-(triphenylmethylamino)penicillanate [9] and, secondly, the amino-protecting group can be removed from the final tricyclic system under mild conditions, allowing a range of acylated derivatives to be prepared.

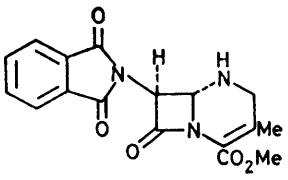
Alkylation of (10) with t-butyl bromoacetate in dry dimethylformamide (DMF) using potassium carbonate gave the crystalline ester (11). The usual chlorinolysis, sodium azide sequence, then provided a 3 : 1 mixture of the *cis*- and *trans*-t-butyl 2-(4-azido-2-oxo-3-triphenylmethylaminoazetidin-1-yl)acetates (12) and (13). These were readily separated by chromatography and the *cis*-isomer was converted into t-butyl (8*S*,8a*R*)-7,8-dihydro-7-oxo-8-triphenylmethylamino-8a*H*-azeto[1,2-*a*]-*v*-triazolo[3,4-c]pyrimidine-5-carboxylate (14a), as depicted in Scheme 1.

Reaction of the ester enolate of (12), generated by means of lithium hexamethyldisilazide in dry tetrahydrofuran (THF) at −76 °C, with prop-2-ynyl bromide afforded the acetylene (15a). When (15a) was refluxed in toluene for 8 h, smooth intramolecular cycloaddition occurred to give the triazolocepham (16a) in 86% yield. The product was a mixture of two isomers, which could be separated by chromatography. However, this was of no real advantage since the stereochemistry at that particular position is subsequently destroyed.

The next synthetic step demanded a mild and efficient procedure for the insertion of the desired double bond. Selenoxide fragmentation constitutes a standard synthetic method for introducing unsaturation into a carbon σ-bond system, and was ideally suited to our requirements.

α-Selenenylation to provide (17a) was successfully accomplished by treatment of the lithium enolate of (16a) with phenylselenenyl bromide [10] in THF at −76 °C. Oxidation of (17a) with *m*-chloroperbenzoic acid at 0 °C then gave the triazolocephem (14a), *via* spontaneous fragmentation of the intermediate selenoxide.

The ^{1}H n.m.r. spectrum of (14a) has all the resonances in the expected positions. The proton in the triazole ring is characterised by a sharp singlet at δ 7.78. Replacement of sulphur shifts the resonance of the C-8a hydrogen to δ 5.74, *ca.* 1 p.p.m. lower field than the corresponding proton in 7-triphenylmethylaminocephems.[9]



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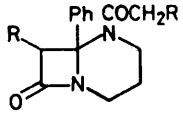

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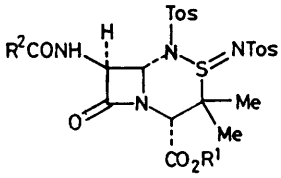

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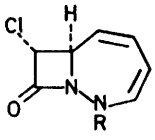

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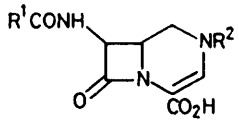

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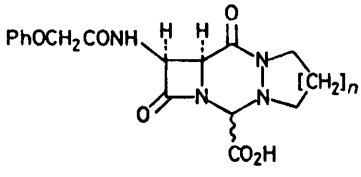
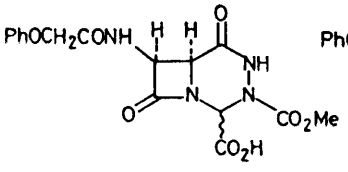


(6) $n = 1, 2$



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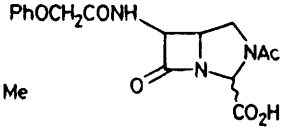

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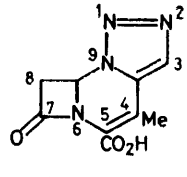
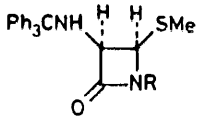


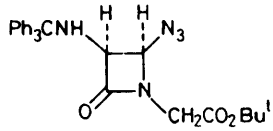
(9)



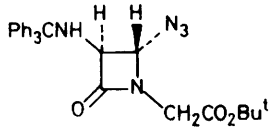
(10) R = H
(11) R = $CH_2CO_2Bu^t$

In the i.r. spectrum, the β-lactam carbonyl group absorbs at *ca.* 1 805 cm^{-1}, higher than most penicillins and cephalosporins, and indicative of a more strained, more reactive β-lactam carbonyl system. The long wavelength maximum at 309 nm (ε 8 700) found in the u.v. spectrum is very similar to that shown by 2-methylenecephalosporins.[11]

Removal of the amino-protecting group from (14a) was achieved by reaction with toluene-*p*-sulphonic acid in methylene dichloride–methanol. Acylation of the resulting primary amine (18) then gave the amide (19), which was finally de-esterified by treatment with trifluoroacetic acid for 0.5 h at room temperature. The



(12)



(13)

free acid (20) was inactive against gram-negative bacteria and displayed only moderate activity against gram-positive organisms (see Table).

Antibacterial activity *

Bacterium	Triazolocephems (20)	(22)	(36)
β-Haemolytic streptococcus	10	>100	0.5
Staphylococcus aureus (Oxford)	10	>100	2.5
Staphylococcus aureus (Russell) †	50	>100	5.0
Bacillus subtilis	2.5	100	<0.2

* 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.

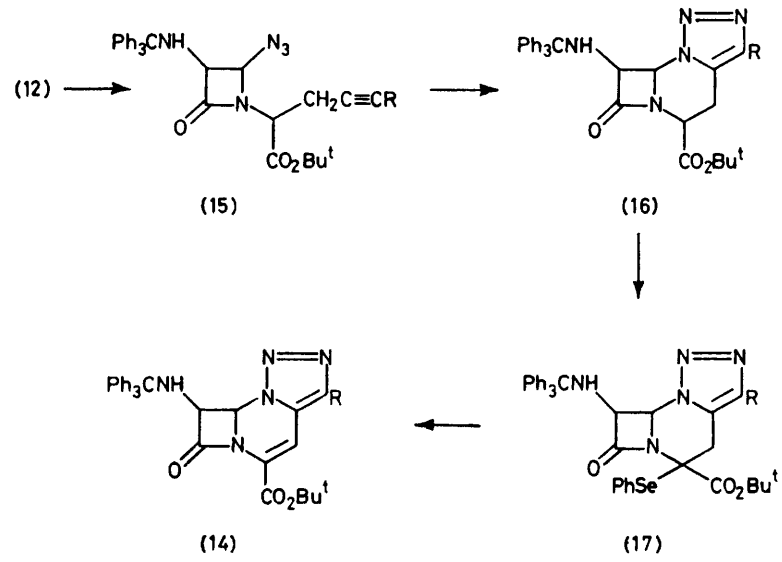
An identical sequence was then repeated using 3-phenylprop-2-ynyl bromide in the initial alkylation of (12). Cyclisation of the acetylene (15b) by refluxing in toluene for 5.75 h then gave the triazolocepham (16b) in 92% yield. Conversion of (16b) into (14b) *via* the selenide (17b) in the usual way, followed by replacement of the triphenylmethyl group by phenoxyacetyl gave (21). Cleavage of the t-butyl ester group then provided the free acid (22). The material was less active than the unsubstituted derivative (20), possessing only marginal gram-positive activity (see Table).

In this particular series two alternative routes to the tricyclic system (14b) were investigated, each of which were minor modifications of Scheme 1.

Scheme 2.—Treatment of the azido-acetylene (15b) with lithium hexamethyldisilazide followed by addition of phenylselenenyl bromide provided the α-seleneno-ester (23). The latter was refluxed in toluene under argon for 16 h and the crude product (17b) oxidised with *m*-chloroperbenzoic acid to yield the triazolocephem (14b).

Scheme 3.—The selenide (23) was treated with *m*-chloroperbenzoic acid to give the olefins (24) and (25) in a ratio of 3 : 1 respectively. Cyclisation of the *Z*-olefin (24) proceeded rapidly (4 h) in refluxing toluene to afford (14b) in 89% yield. However, as might be expected, under the same conditions the *E*-olefin (25) failed to cyclise.

Schemes 1—3 all gave the triazolocephem (14b) in good overall yield, but it does appear that the original Scheme 1 is marginally preferable to Scheme 2. Scheme 3 is less desirable owing to the formation of the *E*-olefin (25) (25%), which does not provide any of the desired

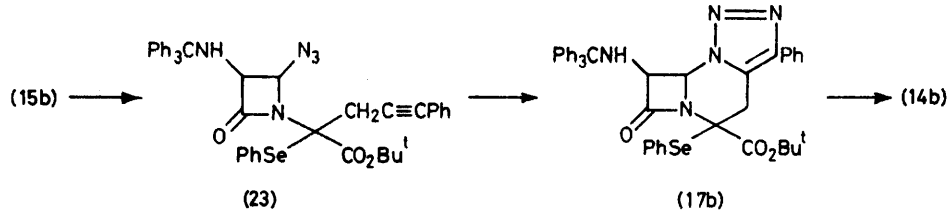


a; R = H b; R = Ph

SCHEME 1

product (14b). However, the three routes do indicate that the rate of cyclisation is (24) ≫ (15b) ≫ (23). Presumably the ene-yne (24) is held in the correct configuration for cycloaddition to occur and the slowness of (23) as compared to the less substituted (15b), is a steric factor, although the phenylseleneno-group might have an adverse electronic effect.

Since alkylation of the ester enolate of (12) with 3-bromobut-1-yne failed, an alternative approach was devised in which the acetylenic functionality and the desired potential leaving group were introduced at the same time. Accordingly, treatment of (12) with lithium hexamethyldisilazide, followed by addition of but-3-yn-2-one provided an excellent yield of the alcohol (26).

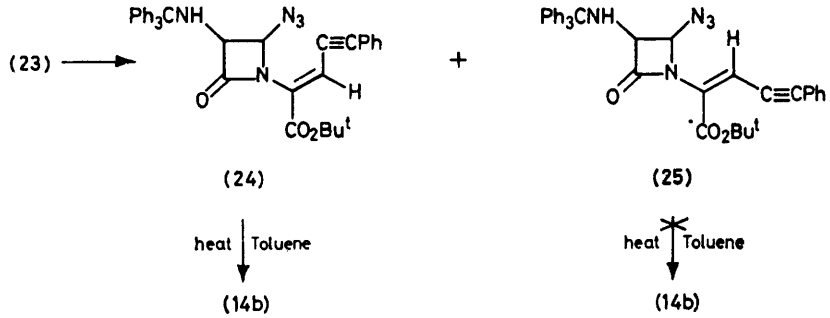


SCHEME 2

The synthesis described here is of considerable generality and has been used to prepare derivatives containing a variety of groups in the triazole ring. However, the best antibacterial activity was observed when the ring was unsubstituted. It was also of interest to synthesise compounds substituted at what would be designated the C-3 position of cephalosporins, in the hope that these might display improved biological activity.

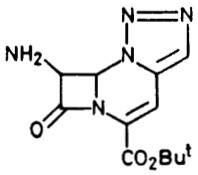
Although four isomers of (26) are possible, it appears that two major isomers are present in a ratio of *ca.* 1 : 1, pairs of singlets at δ 1.43 and 1.47, 1.57 and 1.60, and 2.45 and 2.58 being respectively indicative of $CO_2(CH_3)_3$, $\geq C-CH_3$ and $\equiv C-H$ in each compound.

Cyclisation to (27) was extremely rapid, being achieved by heating in toluene for 2 h at 110 °C. Chromatography on silica gel afforded starting material (26) (10%)



SCHEME 3

the triazolocepham (27) (57%), and another product (25%) which did not contain a β-lactam. The ^1H and ^{13}C n.m.r. spectra of the material were fully consistent with the lactone structure (28). Furthermore, recovered starting material (26) was a single isomer. When the latter was refluxed in toluene and the crude



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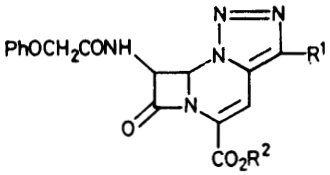
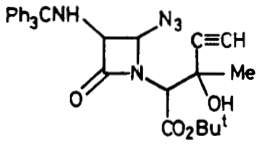
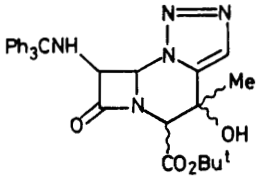


(19) $R^1 = H$, $R^2 = Bu^t$
(20) $R^1 = R^2 = H$
(21) $R^1 = Ph$, $R^2 = Bu^t$
(22) $R^1 = Ph$, $R^2 = H$



(26)



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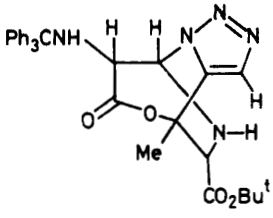

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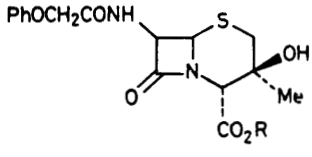
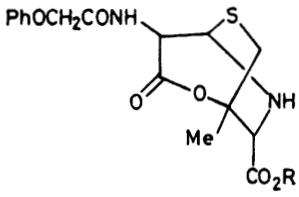


(29)

product examined by i.r. and n.m.r. spectroscopy, the lactone (28) was the only product. Thus it appears that one of the major isomers of the azide (26) gives a cycloaddition product which undergoes immediate thermal rearrangement to the lactone (28). This can be compared to the behaviour of 3β-hydroxy-3-methylcepham derivatives (29) which are reported [13] to be unstable to silica-gel chromatography. Scission of the β-lactam is accompanied by concurrent acylation of the 3β-hydroxy-group, to give a lactone (30).

A more detailed examination of the triazolocepham (27) was possible after recrystallisation from benzene–light petroleum, there being a separation into a major crystalline fraction (85%), and an amorphous solid (mother liquors; 15%). The crystalline material was a single isomer, the C-5 proton appearing as a sharp singlet at δ 4.45 in the n.m.r. spectrum. The chemical shift was not affected by the addition of 1,8-diazabicyclo[5.4.0]-



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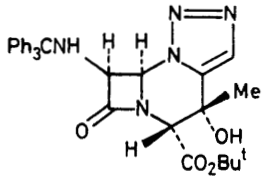
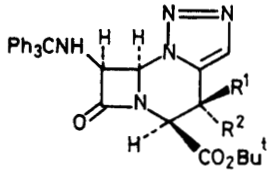
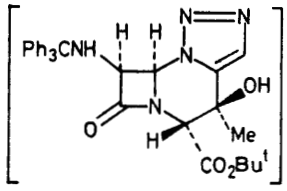


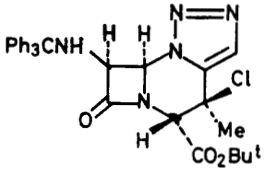
(27a)



(27b) R^1 = Me, R^2 = OH
(27c) R^1 = OH, R^2 = Me



(27d)



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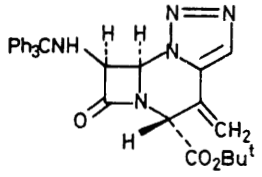

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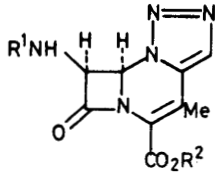


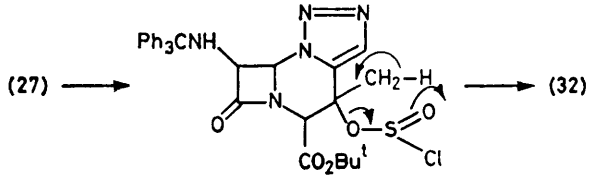
(34) $R^1 = Ph_3C$, $R^2 = Bu^t$
(35) $R^1 = PhOCH_2CO$, $R^2 = Bu^t$
(36) $R^1 = PhOCH_2CO$, $R^2 = H$

undec-7-ene (DBU), and the natural penicillin stereochemistry is therefore assigned to this position.[14] In addition, the stability of the compound indicates that the 4-hydroxy-group must possess the α-configuration, in which lactone formation is not possible. The stereo-

chemistry of the crystalline product is therefore represented by (27a). Intramolecular hydrogen bonding between the *cis*-ester and hydroxy-functionalities could also account for the stability of this isomer.

The amorphous solid (15%) was an inseparable mixture of three triazolocepham isomers (27), in a ratio of 8 : 3 : 1, the major component being (27a). In the two minor isomers the resonances of the C-5 protons (δ 3.93 and 3.52) are substantially shifted upfield relative to the C-5 hydrogen of (27a) (δ 4.45), indicative of the presence of the unnatural penicillin stereochemistry at C-5. This was confirmed by treatment of the amorphous solid, containing all three isomers, with DBU in deuteriochloroform. The signals at δ 3.93 and 3.52 disappeared and the signal due to (27a) at δ 4.45 was enhanced. The lactone (28) could not be detected, but was shown to be labile to the conditions of the experiment. The two minor isomers can therefore be represented as (27b) and (27c). The former is stable as the 4-hydroxy-function has the α-configuration, and presumably the 4β-hydroxy-group of (27c) can hydrogen bond to the ester carbonyl, precluding β-lactam cleavage. Following these assignments, the lactone (28) must be derived from (27d). In this case no stabilisation by intramolecular hydrogen bonding is possible, and models show that the system is nicely set up for lactone formation.

Treatment of (27a) with thionyl chloride and 2,6-lutidine in THF at −20 °C gave the chloride (31) (30%) and the olefin (32) (50%), each compound being a single C-5 epimer. The formation of the latter was an unexpected bonus, and led to the synthesis of a range of C-4 substituted derivatives, which will be reported in a further paper. The *exo*-methylene compound (32) is assumed to arise *via* the breakdown of the chlorosulphite (33) as shown in Scheme 4. Since C-5 is not involved in the formation of (32), the stereochemistry at that position is unchanged, relative to (27a).



(33)

SCHEME 4

Chloride formation must be accompanied by inversion of configuration at C-4 (retention is only observed in thionyl chloride reactions in the absence of base), to provide the 4β-chloro-derivative (31). Since the configuration at C-5 is not affected, the chlorine and the C-5 proton must be *cis*, and under the reaction conditions no elimination to (34) can occur. In general, if (32) was not required the crude mixture of (31) and (32) was treated directly with DBU to give the fully conjugated compound (34) in excellent overall yield. As in the previous series removal of the protecting groups and introduction of an acyl side-chain provided (36). The latter was *ca.* 10 times more active than the corresponding compound unsubstituted at C-4 (see Table), and this prompted us to prepare a range of acylamino-derivatives. These will be reported at a later date.

EXPERIMENTAL

General procedures were as in Part 1 except where indicated otherwise.

t-Butyl (3R,4R)-2-(4-*Methylthio*-2-*oxo*-3-*triphenylmethylaminoazetidin*-1-*yl*)*acetate* (11).—(3*R*,4*R*)-4-Methylthio-3-triphenylmethylaminoazetidin-2-one (10) (15 g) was dissolved in dry dimethylformamide (225 ml), containing t-butyl bromoacetate (9.24 g) and powdered anhydrous potassium carbonate (9.9 g). The mixture was vigorously stirred at room temperature for 20 h, and then poured into ethyl acetate and brine. The organic layer was separated, washed successively with water and brine, dried, and evaporated. The residual solid was triturated with dry ether and dried *in vacuo* to give the ester (11) (10 g). Chromatography of the ethereal liquors afforded further material (4.8 g), m.p. 147—149 °C (ethyl acetate–light petroleum), $[\alpha]_D^{23}$ −49.9° (*c* 1 in $CHCl_3$); $\nu_{max.}$ (Nujol) 3 300, 1 758, and 1 740 cm^{-1}; δ 1.35 (9 H, s), 1.65 (3 H, s), 2.85 (1 H, d, *J* 7 Hz, exch. D_2O), 3.4 and 4.05 (2 H, ABq, *J* 17 Hz), 4.11—4.58 (2 H, m), and 7.0—7.7 (15 H, m) (Found: C, 71.2; H, 6.4; N, 5.7; S, 6.8. $C_{29}H_{32}N_2O_3S$ requires C, 71.3; H, 6.6; N, 5.7; S, 6.6%).

t-Butyl (3S,4R)- *and* (3S,4S)-2-(4-*Azido*-2-*oxo*-3-*triphenylmethylaminoazetidin*-1-*yl*)*acetate* (12) *and* (13).—The lactam (11) (8.48 g) was dissolved in dry carbon tetrachloride (500 ml) and the solution cooled to −20 °C. A solution of chlorine (1.23 g) in dry carbon tetrachloride (50 ml) was added dropwise during 1 h and then the mixture was allowed to warm to 0 °C. After 30 min the solvent was evaporated off, the residue treated with carbon tetrachloride (100 ml), and the mixture evaporated; this process was repeated. The product was dried *in vacuo* and then dissolved in dry dimethylformamide (400 ml). Powdered sodium azide (2.27 g) was added, the mixture stirred at room temperature for 18 h, and then poured into ethyl acetate and water. The organic layer was separated, washed with brine, dried, and evaporated. Chromatography gave the *cis*-isomer (12) (6.11 g), m.p. 142—143 °C (ethyl acetate–light petroleum), $[\alpha]_D^{23}$ +20.3° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 2 100, 1 770, and 1735 cm^{-1}; δ 1.45 (9 H, s), 2.93 (1 H, d, *J* 11 Hz, exch. D_2O), 3.57 and 4.22 (2 H, ABq, *J* 18 Hz), 4.40—4.77 (2 H, m, becomes 2 H, s, at 4.58 on D_2O exch.), and 7.3—8.0 (15 H, m) (Found: C, 69.7; H, 6.0; N, 14.5. $C_{28}H_{29}N_5O_3$ requires C, 69.6; H, 6.0; N, 14.5%).

Further elution gave the *trans*-isomer (13) (2.2 g), m.p. 135 °C (ethyl acetate–light petroleum), $[\alpha]_D^{23}$ −52.8° (*c* 1.1 in $CHCl_3$); $\nu_{max.}$ 2 075, 1 770, and 1 735 cm^{-1}; δ 1.46 (9 H, s), 2.90 (1 H, d, *J* 10 Hz, exch. D_2O), 3.53 and 4.18 (2 H, ABq, *J* 19 Hz), 4.13 (1 H, s), 4.35 (1 H, s), and 7.1—7.8 (15 H, m) (Found: C, 69.5; H, 6.1; N, 14.5%).

(3S,4R)-4-*Azido*-1-(1-*t*-*butoxycarbonylbut*-3-*ynyl*)-3-*triphenylmethylaminoazetidin*-2-*one* (15a).—n-Butyl-lithium (0.44 ml of a 2.5M-solution in hexane) was added dropwise to a solution of hexamethyldisilazane (177 mg) in dry THF (2 ml), under argon at 0 °C. After 10 min the solution was cooled to −76 °C and the lactam (12) (483 mg) in dry THF (5 ml) added during 5 min. After a further 10 min a solution of prop-2-ynyl bromide (600 mg) in dry THF (3 ml) was added dropwise during 5 min. The reaction mixture was

stirred for a further 15 min and was then poured into ethyl acetate and aqueous citric acid. The organic layer was separated, washed with brine, dried, and evaporated. Chromatography afforded the product (15a) as an amorphous solid (350 mg), $\nu_{max.}$ 3 270, 2 100, 1 770, and 1 735 cm^{-1}; δ (90M Hz) the n.m.r. spectrum was complex but indicated that the product was a mixture of epimers (Found: C, 71.6; H, 5.9; N, 13.6. $C_{31}H_{31}N_5O_3$ requires C, 71.4; H, 6.0; N, 13.4%).

t-Butyl (8S,8aR)-4,5,7,8-*Tetrahydro*-7-*oxo*-8-*triphenylmethylamino*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (16a).—The lactam (15a) (1.28 g) was refluxed in dry toluene (750 ml) under argon for 8 h. The solvent was evaporated and the residue chromatographed to give the less-polar isomer (16a) (781 mg) as an amorphous solid, $[\alpha]_D^{23}$ −31° (*c* 1.09 in $CHCl_3$); $\nu_{max.}$ 3 315, 1 783, and 1 738 cm^{-1}; δ (90M Hz) 1.32 (9 H, s), 2.40br (1 H, s, exch. D_2O), 3.21 (1 H, d, *J* 4 Hz), 4.63 (1 H, t, *J* 4 Hz), the latter resonance obscures the signal due to the C-8 β-lactam, 5.78 (1 H, d, *J* 4 Hz), and 7.1—7.7 (16 H, m) (Found: C, 71.4; H, 6.1; N, 13.3. $C_{31}H_{31}N_5O_3$ requires C, 71.4; H, 6.0; N, 13.4%). Further elution gave the more-polar isomer (16a) (320 mg) as an amorphous solid, $[\alpha]_D^{23}$ −15° (*c* 1.13 in $CHCl_3$); $\nu_{max.}$ 3 300, 1 788, and 1 740 cm^{-1}; δ (90 MHz) 1.49 (9 H, s), 2.3br (1 H, s, exch. D_2O), 3.10—3.3 (2 H, m), 3.56—3.8 (1 H, m), 4.63br (1 H, s, becomes d, *J* 4 Hz on D_2O exch.), 5.38 (1 H, d, 4 Hz), and 7.0—7.55 (16 H, m) (Found: C, 71.9; H, 6.0; N, 13.3%).

t-Butyl (8S,8aR)-7,8-*Dihydro*-7-*oxo*-8-*triphenylmethylamino*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (14a).—Hexamethyldisilazane (177 mg) in dry THF (3 ml) was cooled to 0 °C under argon and n-butyl-lithium (0.44 ml of 2.5M in hexane) added. After 10 min the stirred solution was cooled to −76 °C and a solution of the lactam (16a) (521 mg; mixed isomers) in dry THF (5 ml) was added dropwise during 10 min. After a further 10 min phenylselenenyl bromide in dry THF [0.8 ml of a solution freshly prepared by addition of bromine (0.162 ml) to diphenyl diselenide (0.94 g) in THF (4 ml)] was added dropwise during 5 min. The solution was poured into ethyl acetate–brine and the organic layer separated; this was then washed successively with dilute aqueous $NaHCO_3$ and brine. The dried organic layer was evaporated and the residue filtered through a short silica column to give the selenenotriazole (17a) (448 mg), $\nu_{max.}$ 3 360, 1 795, and 1 725 cm^{-1}.

The product (17a) (448 mg) was dissolved in ethyl acetate (10 ml) at 0 °C and *m*-chloroperbenzoic acid (226 mg) added portionwise during 2 min. The solution was allowed to warm to room temperature and was then washed successively with aqueous $NaHCO_3$ and brine. The dried organic layer was evaporated and the residue chromatographed to give the *triazole* (14a) (265 mg) as an amorphous solid; $\lambda_{max.}$ (EtOH) 309 nm (ε 8 700) $[\alpha]_D^{23}$ +1.12° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 360, 1 806, 1 720, and 1 620 cm^{-1}; δ (90 MHz) 1.51 (9 H, s), 3.24br (1 H, s, exch. D_2O), 5.09br (2 H, s, becomes sharp 2 H, s, on D_2O exch.), 7.0—7.7 (16 H, m), and 7.78 (1 H, s) (Found: C, 72.0; H, 5.9; N, 13.4. $C_{31}H_{29}N_5O_3$ requires C, 71.7; H, 5.6; N, 13.5%).

t-Butyl (8S,8aR)-7,8-*Dihydro*-7-*oxo*-8-*phenoxyacetamido*-8aH-*azeto*[1,2-a]-v-*triazolo*[3.4-c]*pyrimidine*-5-*carboxylate* (19).—The lactam (14a) (100 mg) was dissolved in dry methylene dichloride (3 ml) at −20 °C and toluene-*p*-sulphonic acid (40 mg) added dropwise in the minimum volume of methanol (0.5 ml). After 2.5 h at +5 °C the solvents were evaporated and the residue dried *in vacuo*.

The crude toluene-*p*-sulphonic acid salt of the free base (18) was dissolved in dry methylene dichloride (7 ml) at −20 °C and triethylamine (80 mg) added in methylene dichloride (0.5 ml), followed by phenoxyacetyl chloride (64 mg) in methylene dichloride (1 ml). The reaction mixture was allowed to warm to ambient temperature and was then washed successively with aqueous $NaHCO_3$ and brine, and then dried and evaporated. Chromatography of the residue afforded the *acylamino-derivative* (19) as a white amorphous solid (71 mg), $\lambda_{max.}$ (EtOH) 313 nm (ε 9 600); $\nu_{max.}$ (Nujol) 3 315, 1 805, 1 718, 1 680, and 1 625 cm^{-1}; δ (90 MHz) 1.55 (9 H, s), 4.37 (2 H, s), 5.78 (1 H, dd, *J* 4 and 8 Hz), 5.89 (1 H, d, *J* 4 Hz), 6.7—7.5 (7 H, m), and 7.77 (1 H, s) (Found: C, 58.2; H, 5.2; N, 16.7. $C_{20}H_{21}N_5O_5$ requires C, 58.4; H, 5.1; N, 17.0%).

(8S,8aR)-7,8-*Dihydro*-7-*oxo*-8-*phenoxyacetamido*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylic Acid* (20).—The ester (19) (47 mg) was dissolved in trifluoroacetic acid (2 ml) and the pale yellow solution left at room temperature for 35 min. The solvent was evaporated off, the residue treated with toluene, and the mixture evaporated; this procedure was repeated. Trituration of the residue with ether gave the free acid (20) as a white amorphous solid (36 mg), $\lambda_{max.}$ (EtOH) 327 nm (ε 6 500); $\nu_{max.}$ (Nujol) 3 350br, 1 810, 1 720sh, 1 690, and 1 623 cm^{-1}; δ [$CDCl_3$ + two drops $(CD_3)_2SO$] (90 MHz) 4.43 (2 H, s), 5.2—5.7br (1 H, s, exch. D_2O), 5.95 (2 H, m, collapses to two d's at 5.91 and 6.03, both *J* 4 Hz, on exch. D_2O), 6.8—7.6 (6 H, m), 7.88 (1 H, s), and 8.55 (1 H, d, *J* 8 Hz, exch. D_2O).

(3S,4R)-4-*Azido*-1-(1-*t-butoxycarbonyl*-4-*phenylbut*-3-*ynyl*)-3-*triphenylmethylaminoazetidin*-2-*one* (15b).—Reaction of the lactam (12) (3.59 g) with 3-phenylprop-2-ynyl bromide as described for (15a) gave the acetylene (15b) as an amorphous solid (3.59 g), $[\alpha]_D^{25.5}$ −25.6° (*c* 1.57 in $CHCl_3$); $\nu_{max.}$ 2 125, 1 770, and 1 740 cm^{-1}; δ (the product was a single isomer) 1.41 (9 H, s), 2.69 and 3.11 (2 H, ABq, *J* 18 Hz, each arm showing further coupling of *ca.* 1 and 2 Hz respectively), 4.4—4.7 (2 H, m), 4.76 (1 H, d, *J* 4 Hz), and 6.9—7.8 (20 H, m) (Found: C, 74.1; H, 6.1; N, 11.6. $C_{37}H_{35}N_5O_3$ requires C, 74.3; H, 5.9; N, 11.7%).

t-Butyl (8S,8aR)-4,5,7,8-*Tetrahydro*-7-*oxo*-3-*phenyl*-8-*triphenylmethylamino*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (16b).—The lactam (15b) (1.5 g) was refluxed in toluene (500 ml) under argon for 5.75 h. The solvent was evaporated off, and the residue chromatographed to give the *phenyltriazole* (16b) as an amorphous solid (1.37 g), $[\alpha]_D^{25.5}$ −5.7° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 3 355, 1 785, and 1 738 cm^{-1}; δ (250 MHz) 1.32 (9 H, s), 2.53br (1 H, s, exch. D_2O), 3.39 and 3.52 (2 H, ABq, *J* 16.7 Hz, higher field arm shows further coupling of 1.8 and *ca.* 0.5 Hz, the latter due to long range coupling with the proton at C-8a, lower field arm shows further coupling of 7.5 Hz), 4.74 (1 H, dd, *J* 1.8 and 7.5 Hz), 4.77 (1 H, broad signal, collapses to d, *J* 3.9 Hz on exch. D_2O), 5.74 (1 H, dd, *J* 3.9 and *ca.* 0.5 Hz), and 7.15—7.75 (20 H, m) (Found: C, 74.0; H, 6.0; N, 11.6. $C_{37}H_{35}N_5O_3$ requires C, 74.3; H, 5.9; N, 11.7%).

t-Butyl (8S,8aR)-7,8-*Dihydro*-7-*oxo*-3-*phenyl*-8-*triphenylmethylamino*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (14b).—*Method A*. The triazolocepham (16b) (1.452 g) was treated with phenylselenenyl bromide and the product oxidised with *m*-chloroperbenzoic acid as described for (16a) to give the triazolocephem (14b) as an amorphous solid (932 mg), $[\alpha]_D^{23}$ +172.6° (*c* 1.37 in

$CHCl_3$); $\lambda_{max.}$ (EtOH) 333 nm (ε 17 900); $\nu_{max.}$ 3 355, 1 805, 1 715, and 1 605 cm^{-1}; δ (90 MHz) 1.52 (9 H, s), 3.3br (1 H, s, exch. D_2O), 5.1 (2 H, slightly broadened d, collapses to s on exch. D_2O) and, 6.8—7.8 (21 H, m) (Found: C, 74.7; H, 5.8; N, 11.7. $C_{37}H_{33}N_5O_3$ requires C, 74.6; H, 5.5; N, 11.8%).

Method B. The azide (15b) (1.41 g) was treated with phenylselenenyl bromide as described for (16a) to afford the selenide (23) as an amorphous solid (1.48 g), $\nu_{max.}$ 3 340, 2 125, 1 765, and 1 730 cm^{-1}; δ 1.48 (9 H, s), 2.72br (1 H, s, exch. D_2O), 3.07 and 3.89 (2 H, ABq, *J* 16 Hz), 3.43br (1 H, s, becomes d, *J* 4 Hz on exch. D_2O), 4.19 (1 H, d, *J* 4 Hz), and 6.8—7.6 (25 H, m).

The selenide (23) (1.2 g) was refluxed in dry toluene for 16 h. The solvent was evaporated off and the residue dissolved in ethyl acetate at +5 °C. *m*-Chloroperbenzoic acid (302 mg) was added and after 10 min the solution was washed successively with aqueous $NaHCO_3$ and brine, dried, and evaporated. Chromatography gave the required triazolocephem (14b) (306 mg).

Method C. The selenide (23) (570 mg) in ethyl acetate at 0 °C was treated with *m*-chloroperbenzoic acid (260 mg). The solution was washed successively with aqueous $NaHCO_3$ and brine, dried, and evaporated. The crude product was chromatographed to give the minor *E*-isomer (25) (90 mg), $\nu_{max.}$ 3 350, 2 190w, 2 150, 1 770, and 1 710 cm^{-1}; δ (90 MHz) 1.48 (9 H, s), 2.95br (1 H, s, exch. D_2O), 4.45br (1 H, s, becomes d, *J* 4 Hz on exch. D_2O), 4.96 (1 H, d, *J* 4 Hz), 7.02 (1 H, s), and 7.1—7.6 (20 H, m) (Found: C, 74.1; H, 5.6; N, 11.7. $C_{37}H_{33}N_5O_3$ requires C, 74.6; H, 5.5; N, 11.8%). Further elution gave the major *Z*-isomer (24) (270 mg), $\nu_{max.}$ 3 340, 2 205, 2 125, 1 785, 1 715, and 1 608 cm^{-1}; δ (90 MHz) 1.48 (9 H, s), 2.96br (1 H, s, exch. D_2O), 4.47br (1 H, s, becomes d, *J* 4 Hz on exch. D_2O), 4.95 (1 H, d, *J* 4 Hz), 6.49 (1 H, s), and 7.0—7.6 (20 H, m) (Found: C, 74.4; H, 5.4; N, 11.6%).

The *Z*-isomer (24) (245 mg) was refluxed under argon in toluene (120 ml) for 4 h. The solvent was evaporated off and the residue chromatographed to provide the triazolocephem (14b) (219 mg). The *E*-isomer (25) (70 mg) slowly decomposed when refluxed under argon in toluene (40 ml).

t-Butyl (8S,8aR)-7,8-*Dihydro*-7-*oxo*-8-*phenoxyacetamido*-3-*phenyl*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (21).—The lactam (14b) (298 mg) was detritylated and acylated as described for (14a) to give the acylated derivative (21) as an amorphous solid (156 mg), $\lambda_{max.}$ (EtOH) 336 nm (ε 14 300); $\nu_{max.}$ 3 380, 1 810, and 1 710br cm^{-1}; δ (90 MHz) 1.56 (9 H, s), 4.39 (2 H, s), 5.8—5.97 (2 H, m), and 6.7—7.8 (12 H, m) (Found: C, 63.8; H, 5.0; N, 14.1. $C_{26}H_{25}N_5O_5$ requires C, 64.1; H, 5.1; N, 14.4%).

(8S,8aR)-7,8-*Dihydro*-7-*oxo*-8-*phenoxyacetamido*-3-*phenyl*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylic Acid* (22).—The ester (21) (107 mg) was deprotected as described for (19) to give the free acid (22) as a pale yellow amorphous solid (75 mg), $\lambda_{max.}$ (EtOH) 260 (ε 11 400) and 324 nm (14 500); $\nu_{max.}$ (KBr) 3 370, 1 800, and 1 700 cm^{-1}; δ [$(CD_3)_2SO$] very broad signal at *ca.* 4.0 (1 H, CO_2H), 4.39 (2 H, s), 5.91 (1 H, dd, *J* 4 and *J* 9 Hz), 6.14 (1 H, d, *J* 4 Hz), 6.7—7.9 (11 H, m), and 8.99 (1 H, d, *J* 9 Hz).

(3S,4R)-4-*Azido*-1-(1-*t-butoxycarbonyl*-2-*hydroxy*-2-*methylbut*-3-*ynyl*)-3-*triphenylmethylaminoazetidin*-2-*one* (26).—Hexamethyldisilazane (0.88 g) was dissolved in dry THF at 0 °C under argon and n-butyl-lithium (2.2 ml; 2.5M-solution in hexane) added. The solution was stirred for 10 min and then cooled to −76 °C and the lactam (12) (2.42 g) in THF (30 ml) added dropwise during 20—25 min. A further 20 min later but-3-yn-2-one (400 mg) in THF (10 ml) was added dropwise during 10 min. The reaction mixture was neutralised with acetic acid and then poured into ethyl acetate. The mixture was washed with brine (×2), dried, and evaporated. Chromatography gave the amorphous product (26) as a mixture of isomers (2.325 g), $\nu_{max.}$ 3 500, 3 310, 1 770, and 1 730 cm^{-1}; δ, *inter alia*, 1.43 and 1.47 (s, together 9 H), 1.57 and 1.60 (s, together 3 H), 2.45 and 2.58 (s, together 1 H), and 2.8—3.2 (1 H, m, exch. D_2O) (Found: C, 69.3; H, 5.9; N, 12.3. $C_{23}H_{33}N_5O_4$ requires C, 69.7; H, 6.0; N, 12.7%).

t-Butyl (8S,8aR)-7,8-*Dihydro*-7-*oxo*-4-*hydroxy*-4-*methyl*-8-*triphenylmethylamino*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]-*pyrimidine*-5-*carboxylate* (27).—The lactam (26) (2.265 g) was refluxed under argon in toluene (300 ml) for 2 h. The solvent was evaporated off and the residue chromatographed. The material first eluted was the acetylene (26) (207 mg), which was shown by n.m.r. to be a single isomer, δ 1.47 (9 H, s), 1.57 (3 H, s), 2.45 (1 H, s), 2.96 (1 H, d, *J* 9 Hz, exch. D_2O), 4.15 (1 H, s), 4.38—4.7 (3 H, m, 1 H exch. D_2O), and 7.1—7.7 (15 H, m).

Further elution gave the major product (27) which was recrystallised from benzene–light petroleum to give white crystals (27a) (1.072 g), m.p. 165—167 °C $[\alpha]_D^{20}$ −36.9° (*c* 0.78 in $CHCl_3$); $\nu_{max.}$ 3 350, 1 780, and 1 718 cm^{-1}; δ 1.38 (9 H, s), 1.69 (3 H, s), 2.65 (1 H, d, *J* 9 Hz, exch. D_2O), 3.66 (1 H, s, exch. D_2O), 4.45 (1 H, s), 4.77 (1 H, dd, *J* 4 Hz and 9 Hz, collapsing to d, *J* 4 Hz on D_2O exch.), 5.60 (1 H, d, *J* 4 Hz), 7.1—7.7 (15 H, m), and 7.81 (1 H, s) (Found: C, 69.4; H, 6.1; N, 12.6. $C_{32}H_{33}N_5O_4$ requires C, 69.7; H, 6.0; N, 12.7%).

The mother liquors from the recrystallisation (200 mg) were an amorphous solid which were shown by n.m.r. to be a mixture of three isomers (27a—c). . The relative intensities of the resonances due to the C-5 protons at δ 4.45, 3.93, and 3.52 being 8 : 3 : 1.

The final product eluted was the lactone (28) (611 mg), which was isolated as an amorphous solid, $\nu_{max.}$ 3 360br and 1 725 cm^{-1}; δ (90 MHz) 1.35 (9 H, s), 1.98 (3 H, s), 2.47br (1 H, s, exch. D_2O), 3.1 (1 H, poorly resolved doublet, D_2O exch.), 3.43br (1 H, s, becomes sharp s on D_2O exch.), 4.44 (1 H, d, *J ca.* 1.5 Hz, becomes sharp s on D_2O exch.), 7.1—7.7 (16 H, m); C13 ($CDCl_3$) fully proton decoupled spectrum had lines at the following p.p.m., downfield relative to $SiMe_4$ (multiplicity of off-resonance spectrum shown in brackets) 22.224 (q), 27.796 (q), 62.979 (d), 64.825 (d), 69.740 (d), 72.056 (s), 74.404 (s), 83.700 (s), 127.115 (d), 128.18 (d), 129.43 (d), 129.557 (d), 133.814 (s), 145.364 (s), 168.214 (s), and 170.718 (s) (Found: C, 69.7; H, 6.3; N, 12.6. $C_{32}H_{33}N_5O_4$ requires C, 69.7; H, 6.0; N, 12.7%).

t-Butyl (8S,8aR)-7,8-*Dihydro*-7-*oxo*-4-*chloro*-4-*methyl*-8-*triphenylmethylamino*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]-*pyrimidine*-5-*carboxylate* (31) and *t-Butyl* (8S,8aR)-7,8-*Dihydro*-7-*oxo*-4-*methylene*-8-*triphenylmethylamino*-8aH-*azeto*-[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (32).—The lactam (27; recrystallised) (1.102 g) was dissolved in dry tetrahydrofuran (50 ml) and the solution cooled to −20 °C. Dry 2,6-lutidine (0.51 ml) was added followed by the dropwise addition of thionyl chloride (0.315 ml) in tetrahydrofuran (5 ml). After 5 min the precipitate was removed and the filtrate evaporated and redissolved in ethyl acetate. The solution was washed successively with very dilute hydrochloric acid and brine, dried, and evaporated. The residue was chromatographed to provide the *chloride* (31)

as an amorphous solid (335 mg), $[\alpha]_D^{24}$ −27° (*c* 0.81 in $CHCl_3$); $\nu_{max.}$ 3 350, 1 788, and 1 735 cm^{-1}; δ 1.4 (9 H, s), 2.05 (3 H, s), 2.89 (1 H, d, *J* 9 Hz, exch. D_2O), 4.57 (1 H, s), 4.78 (1 H, dd, *J* 5 and 9 Hz, collapsing to d, 5 Hz on D_2O exch.), 5.67 (1 H, d, *J* 5 Hz), 7.1—7.7 (15 H, m), and 7.87 (1 H, s) (Found: C, 67.7; H, 5.8; Cl, 5.8; N, 11.9. $C_{32}H_{32}ClN_5O_3$ requires C, 67.4; H, 5.7; Cl, 6.2; N, 12.3%).

Further elution gave the 8-*methylene derivative* (32) as an amorphous solid (475 mg) $[\alpha]_D^{24}$ −22.5° (*c* 0.96 in $CHCl_3$); $\lambda_{max.}$ (EtOH) 256 nm (ε 10 300); $\nu_{max.}$ 3 350, 1 790, and 1 735 cm^{-1}; δ 1.42 (9 H, s), 2.55 (1 H, d, *J* 9 Hz, exch. D_2O), 4.73 (1 H, dd, *J* 4 and 9 Hz, collapsing to d, 4 Hz on D_2O exchange), 5.08br (1 H, s), 5.57br (1 H, s), 5.77 (1 H, d, *J* 4 Hz), 5.85br (1 H, s), 7.1—7.7 (15 H, m), and 7.95 (1 H, s) (Found: C, 71.7; H, 6.2; N, 12.7. $C_{32}H_{31}N_5O_3$ requires C, 72.0; H, 5.9; N, 13.1%).

Generally the two products were not separated, but the mixture used directly for the preparation of compound (34).

t-Butyl (8S,8aR)-7,8-*Dihydro*-7-*oxo*-4-*methyl*-8-*triphenylmethylamino*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (34).—The mixture of (31) and (32) (810 mg) was dissolved in dry methylene chloride (30 ml) at −20 °C and DBU (200 mg) added. The reaction mixture was allowed to warm to room temperature and the volume reduced to *ca.* 10 ml. The solution was filtered through a short column of silica gel to give the product (34) as a glass (679 mg), $[\alpha]_D^{23.5}$ +2.5° (*c* 0.74 in $CHCl_3$); $\lambda_{max.}$ (EtOH) 231 (ε 18 500) and 310 nm (9 100); $\nu_{max.}$ 3 350, 1 800, and 1 709 cm^{-1}; δ 1.5 (9 H, s), 2.4 (3 H, s), 3.27 (1 H, d, *J* 10 Hz, exch. D_2O), 4.85—5.15 (2 H, m, collapses to 2 H, s on D_2O exch.), 7.1—7.8 (15 H, m), and 7.83 (1 H, s) (Found: C, 71.6; H, 6.2; N, 12.9. $C_{32}H_{31}N_5O_3$ requires C, 72.0; H, 5.9; N, 13.1%).

t-Butyl (8S,8aR)-7,8-*Dihydro*-7-*oxo*-4-*methyl*-8-*phenoxyacetamido*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (35).—Detritylation and acylation of (34) (533 mg) as described for compound (14a) gave the *acylated derivative* (35) as an amorphous solid (334 mg), $[\alpha]_D^{21.5}$ −82.2° (*c* 1.19 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 310 nm (ε 9 500); $\nu_{max.}$ 3 425, 1 805, and 1 700 cm^{-1}; δ 1.5 (9 H, s), 2.48 (3 H, s), 4.45 (2 H, s), 5.68—6.03 (2 H, m), 6.7—7.7 (6 H, m), and 7.88 (1 H, s) (Found: C, 59.3; H, 5.5; N, 16.2. $C_{21}H_{23}N_5O_5$ requires C, 59.3; H, 5.5; N, 16.5%).

(8S,8aR)-7,8-*Dihydro*-7-*oxo*-4-*methyl*-8-*phenoxyacetamido*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylic Acid* (36).—The ester (35) (216 mg) was deprotected as described for (19) to give the free acid (36) as a white amorphous solid (174 mg), $[\alpha]_D^{20.5}$ −61.5° (*c* 0.93 in DMSO); $\lambda_{max.}$ (EtOH) 301 nm (ε 7 950); $\nu_{max.}$ (KBr) 3 370, 1 795, and 1 690 cm^{-1}; δ [$CDCl_3$ + $(CD_3)_2SO$] (90 MHz) 2.46 (3 H, s), 4.35 (2 H, s), 5.77 (1 H, dd, *J* 3 and 8 Hz, collapses to d, 3 Hz on exch. D_2O), 5.97 (1 H, d, *J* 3 Hz), 6.7—7.4 (6 H, m, 1 H exch. D_2O), 7.88 (1 H, s), and 8.79 (1 H, d, *J* 8 Hz, exch. D_2O).

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