Synthesis of Novel Fused β-Lactams by Intramolecular 1,3-Dipolar Cycloadditions. Part 1. Tricyclic Triazoles

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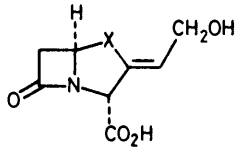
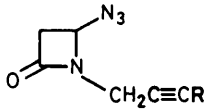
4-Azido-1-alk-2-ynylazetidin-2-ones (3), (14), and (19) when heated in refluxing toluene gave smooth intramolecular cycloaddition of the azido-group to the acetylene function to afford the corresponding 4*H*,7a*H*-azeto[1,2-*a*]-*v*-triazolo[3,4-*c*]imidazol-6(7*H*)-ones (4), (15), and (18). These products were antibacterially inactive, but possessed weak β-lactamase inhibitory properties, particularly against the staphylococcal enzyme. Similar reaction of 4-azido-1-(1-benzyloxycarbonyl-2-hydroxy-2-methylbut-3-ynyl)azetidin-2-one (24) provided benzyl 4,5,7,8-tetrahydro-4-hydroxy-4-methyl-7-oxo-8a*H*-azeto[1,2-*a*]-*v*-triazolo[3,4-*c*]pyrimidine-5-carboxylate (25), which has been converted into 7,8-dihydro-4-methyl-7-oxo-8a*H*-azeto[1,2-*a*]-*v*-triazolo-[3,4-*c*]pyrimidine-5-carboxylic acid (21). The latter was devoid of antibacterial activity, and showed no significant activity as an inhibitor of various β-lactamases.

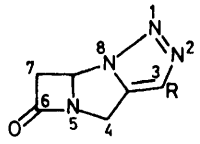
THE intramolecular cycloaddition reaction of suitably functionalised 1,3-dipoles represents a general scheme for the synthesis of novel fused ring heterocycles. In continuation of our research [1] into the potential of such methodology for preparing fused β-lactams, it was surmised that the synthesis of analogues of clavulanic acid (1), a potent β-lactamase inhibitor,[2] in which the ring oxygen is replaced by nitrogen, might be possible.



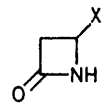
(1) X = O
(2) X = NR



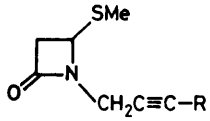
(3) R = H
(13) R = $CH(OEt)_2$
(14) R = CHO
(19) R = CO_2Me



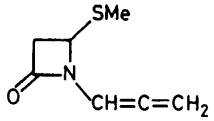
(4) R = H
(15) R = CHO
(16) R = CH_2OH
(17) R = $CH{=}CHCO_2Me$
(18) R = CO_2Me



(5) X = N_3
(6) X = SMe



(7) R = H
(12) R = $CH(OEt)_2$



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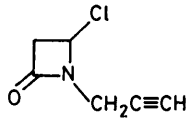
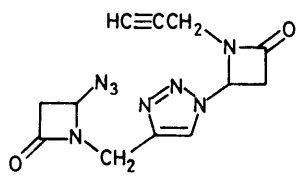


(9)

Considerable effort has been devoted to the preparation of analogues of (1) [3,4] and it has been demonstrated that the C-3 carboxy-group is not essential for activity.[5] Derivatives in which sulphur replaces the ring oxygen have been synthesised,[6] but no aza-analogues have been reported. However, enamine structures of this type (2) might be expected to be rather unstable and, consequently, an intramolecular cycloaddition approach was attractive. Thus, if the azide (3) could be synthesised, such a process ought to provide the tricyclic β-lactam (4), in which the enamine system is stabilised by being part of a triazole ring.

It was not possible to functionalise the β-lactam nitrogen of the 4-azidoazetidinone (5),[7] but the racemic azetidinone (6) [8] proved a suitable starting point for our synthesis. Alkylation of (6) with prop-2-ynyl bromide in the presence of potassium t-butoxide in dimethylformamide (DMF) gave the acetylene (7) (60%), together with the isomeric allene (8) (5%). Following chlorinolysis of (7), the crude chloride (9) was treated with sodium azide in DMF to provide (3) as an unstable gum. The



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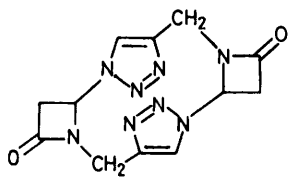


(11)

material was used immediately after isolation, since intermolecular cycloaddition to the dimer (10) occurred even at 0 °C.

A successful intramolecular cycloaddition required conditions of high dilution, since compound (3) when heated at normal concentrations (5—10%) in toluene gave a product which has been tentatively assigned the bis-triazole structure (11), based on accurate mass measurement and i.r. spectroscopy [$\nu_{max.}$ (Nujol) 1 760 cm^{-1}]. Accordingly, when the freshly prepared azide (3) was refluxed in toluene (1 mg ml^{-1}) for 40 h, the tricyclic β-lactam (4) was obtained as a white crystalline solid in 20% yield. The product showed high β-lactam

carbonyl group absorptions at 1 805 and 1 795 cm^{-1}, and a sharp singlet at δ 7.43 for the proton in the triazole ring. Although antibacterially inactive, the compound (4) did possess weak β-lactamase inhibitory properties, particularly against the staphylococcal enzyme. This was confirmed in a synergy test with ampicillin (20) against *Staphylococcus aureus* Russell (Table), and we were therefore encouraged to prepare further derivatives.

Inhibitor	Inhibitor conc'n. (μg ml^{-1})	Conc'n. (μg ml^{-1}) of ampicillin (20) to inhibit *Staphylococcus aureus* Russell
None	0	500
(4)	5	3.1
(15)	20	12.5
(16)	20	0.8
(18)	20	50
Clavulanic acid (1)	1	<0.4

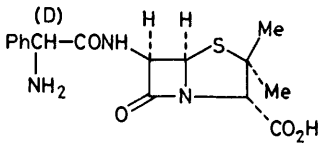
Substitution of the triple bond with alkyl or aryl groups effectively prevented the intramolecular cycloaddition from taking place. However, more success was achieved when small, strongly electron-withdrawing groups were incorporated. Thus, the reaction sequence was repeated starting from the azetidinone (6) and 4,4-diethoxybut-2-ynyl bromide to give the acetal (12). Conversion into the azide (13), followed by removal of the protecting group with formic acid afforded the aldehyde (14). The electron-withdrawing formyl group on the triple bond facilitated the intramolecular cycloaddition reaction which was complete after 12 h in refluxing toluene. The n.m.r. spectrum of triazoloaldehyde (15) is worthy of further comment. The N-CH_2 appears as an AB quartet, J 17 Hz, each peak showing further fine coupling of *ca.* 1.5 Hz. This is due to long-range coupling between the C-4 α-proton and the α-proton at C-7, and coupling of a similar order between the C-7a methine proton and the β-proton at C-4. Corresponding fine coupling is also observed in the lower field part of the C-7 methylene AB quartet, and in the signal due to the C-7a methine proton, the latter appearing as a multiplet and not the expected double doublet.

Reduction of the aldehyde (15) with sodium borohydride gave the alcohol (16), and a Wittig reaction with methoxycarbonylmethylenetriphenylphosphorane in benzene gave the *E*- and *Z*-isomers of the olefin (17) in an isolated ratio of 5 : 1.

Since alkylation of (6) with 3-methoxycarbonylprop-2-ynyl bromide failed, the synthesis of (18) required an indirect approach. Sequential treatment of the unsubstituted prop-2-ynyl derivative (3) with n-butyllithium, carbon dioxide, and methyl iodide, afforded the ester (19), which cyclised in toluene at 110 °C (28 h) to give (18) (50%).

In comparison with (4), compounds (15)—(18) showed broadly similar β-lactamase inhibitory activity. Apart from (17), which was not tested, all were found to synergise the activity of ampicillin (20) against *Staphylococcus aureus* Russell, however the effect was not as dramatic as that of clavulanic acid (Table).

The established methodology could also be successfully extended to the preparation of the azacephem analogue (21). The azetidinone (6) again proved an ideal starting material, and treatment with benzyl bromoacetate and potassium carbonate in DMF gave the ester (22), which was converted into the azide (23) in the usual way.



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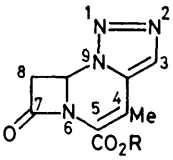
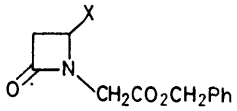
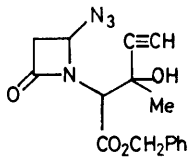


(21) R = H
(26) R = CH_2Ph



(22) X = SMe
(23) X = N_3



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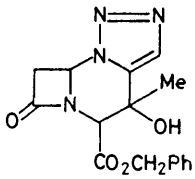

(25)

Reaction of the ester enolate of (23), generated by means of lithium hexamethyldisilazide in tetrahydrofuran (THF) at −76 °C, with but-3-yn-2-one afforded the alcohol (24). As might be expected the product (24) was a mixture of isomers and, although the azide (23) was a contaminant, the material was sufficiently pure for the next stage.

It was anticipated that the intramolecular cycloaddition would be more facile in this case than in the previous series because of the larger ring being formed. Indeed the acetylene (24) cyclised after being heated for only 4.5 h in refluxing toluene, to provide the triazolocepham (25), from which a single isomer could be crystallised.*

* For a more detailed analysis of the products from this type of reaction see following paper.

Successive treatment of compound (25) with thionyl chloride and 2,6-lutidine,* and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), gave the triazolocephem (26) in excellent yield. Catalytic hydrogenation of the ester over 10% palladium–carbon in dry THF removed the benzyl group to provide the acid (21). The product (21) was devoid of antibacterial activity and showed no significant activity as an inhibitor of various β-lactamases.

EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform unless otherwise stated. U.v. spectra were determined for solutions in ethanol unless otherwise stated, with a Unicam SP 1800 spectrometer. ^{1}H N.m.r. spectra were recorded on either a Varian E.M.360 or a Perkin-Elmer R12a 60 MHz instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise; 80 and 90 MHz spectra were obtained on Varian CFT 20 and Perkin-Elmer R32 instruments respectively. Mass spectra were determined with an A.E.I. MS9 machine. M.p.s were determined with a Kofler hot-stage apparatus. Merck Kieselgel 60 (particle size <0.063 mm) was used for column chromatography, with ethyl acetate–light petroleum as eluant. Light petroleum refers to the fraction of b.p. 60—80 °C. Anhydrous magnesium sulphate was used for drying solutions. All the compounds are racemic.

4-Methylthioazetidin-2-one (6).—4-Acetoxyazetidin-2-one[7] (15.3 g) was added in acetone to a mixture of methanethiol (6.6 ml), acetone (60 ml), and 2M-NaOH (60 ml). After 2 h at 15—20 °C the acetone was evaporated, and the residue extracted with ethyl acetate. The extracts were combined, washed with brine, dried, and evaporated. Chromatography and crystallisation from ethyl acetate–light petroleum afforded 4-methylthioazetidin-2-one (6) (12.5 g), m.p. 63—64 °C (lit.,[8] 64—66 °C from chloroform–isopropyl ether).

4-Methylthio-1-prop-2-ynylazetidin-2-one (7) *and 4-Methylthio-1-propadienylazetidin-2-one* (8).—The azetidinone (6) (1.17 g) and prop-2-ynyl bromide (1.22 g) were stirred in dry DMF (50 ml) at −20 °C, and potassium t-butoxide (10.2 ml of a 0.982M solution in t-butyl alcohol) in dimethylformamide (DMF) (10 ml) was added dropwise during 30 min. After a further 5 min at −20 °C the solution was poured into ethyl acetate and brine. The organic layer was separated, washed successively with water and brine and then dried and evaporated. Chromatography of the residue gave the *allene* (8) as a gum (66 mg), $\nu_{max.}$ 1 750 cm^{-1}; δ 2.12 (3 H, s), 3.02 and 3.48 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of 3 and 5 Hz respectively), 4.82 (1 H, dd, *J* 3 and 5 Hz), 5.5 (2 H, d, *J* 7 Hz), and 6.67 (1 H, t, *J* 7 Hz) (Found: M^+, 155.0394. C_7H_9NOS requires *M*, 155.0405).

Further elution provided the *acetylene* (7) as a gum (970 mg), $\nu_{max.}$ 3 310 and 1 755 cm^{-1}; δ 2.12 (3 H, s), 2.32 (1 H, t, X of ABX system, *J* 2 and 2.5 Hz), 2.92 and 3.4 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of 3 and 5 Hz respectively), 3.6 and 4.32 (2 H, AB of ABX system, *J* 18 Hz, each arm showing further coupling of 2 and 2.5 Hz respectively), and 4.83 (1 H, dd, *J* 3 and 5 Hz) and 4.83 (1 H, dd, *J* 3 and 5 Hz) (Found: C, 53.9; H, 5.9; N, 9.3; S, 20.2. C_7H_9NOS requires C, 54.2; H, 5.8; N, 9.0; S, 20.6%).

4-Azido-1-prop-2-ynylazetidin-2-one (3).—The lactam (7) (2.06 g) was dissolved in dry carbon tetrachloride (160 ml) and the stirred solution cooled to −20 °C. A solution of chlorine (944 mg) in dry carbon tetrachloride (40 ml) was added dropwise during 30 min and then the mixture was allowed to warm to 0 °C. The solvent was evaporated off, the residue dissolved in carbon tetrachloride, and the mixture evaporated; this procedure was repeated. The product was dried *in vacuo* and then dissolved in dry dimethylformamide (40 ml). Powdered sodium azide (1.7 g) was added to the vigirously stirred solution and after 3 h 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. Chromatography afforded the azide (3) as a gum (1.64 g), $\nu_{max.}$ 3 310, 2 120, and 1 765 cm^{-1}; δ 2.4 (1 H, t, X of ABX system, *J* 2 and 2.5 Hz), 2.92 and 3.35 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of *ca.* 2 and 4 Hz respectively), 3.9 and 4.32 (2 H, AB of ABX system, *J* 18 Hz, each arm showing further coupling of 2 and 2.5 Hz respectively), and 5.12 (1 H, dd, *J ca.* 2 and 4 Hz). The material dimerised with time and was best used immediately after preparation. The *dimer* (10) was obtained as an amorphous solid (*ca.* 10% conversion after five days at 0 °C), $\nu_{max.}$ 3 250, 2 100, and 1 765 cm^{-1}; δ 2.35 (1 H, t, X of ABX system, *J* 2 and 2.5 Hz), 2.95 and 3.4 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of *ca.* 2 and 4 Hz respectively), 3.47—3.8 (2 H, m), 3.77 and 4.33 (2 H, AB of ABX, *J* 18 Hz, each arm showing further coupling of 2 and 2.5 Hz respectively), 4.55—4.77 (2 H, m), 5.13 (1 H, dd, *J ca.* 2 and 4 Hz), 6.23 (1 H, dd, *J* 2 and 4 Hz), and 8.0 (1 H, s) (Found: C, 47.6; H, 3.7; N, 36.9. $C_{12}H_{12}N_8O_2$ requires C, 48.0; H, 4.0; N, 37.3%).

4H,7aH-Azeto[1,2-a]-v-triazolo[3,4-c]imidazol-6(7H)-one (4).—The azide (3) (500 mg) was refluxed in dry toluene (500 ml) under argon for 40 h. The solvent was evaporated off and the residue chromatographed to give the *triazole* (4) as a crystalline solid (69 mg), m.p. 86 °C (ethyl acetate–light petroleum); $\nu_{max.}$ 1 805sh and 1 790 cm^{-1}; δ (90M Hz) 3.36 and 3.77 (2 H, ABq, *J* 16 Hz, higher field arm showing further coupling of 2 Hz, and lower field arm showing further coupling of 3.5 and *ca.* 1 Hz), 4.08 and 4.85 (2 H, ABq, *J* 15 Hz, each arm showing further unresolved fine coupling) 5.75—5.95 (1 H, m), and 7.43 (1 H, s) (Found: C, 48.0; H, 4.2; N, 37.5%; M^+, 150.0553. $C_6H_6N_4O$ requires C, 48.0; H, 4.0; N, 37.3%; *M*, 150.0542).

When the azide (3) (97 mg) was refluxed in toluene (4 ml) under argon for 23 h, a solid was slowly deposited from the solution. Filtration of the cooled reaction mixture afforded the *bistriazole* (11) (62 mg), $\nu_{max.}$ 1 760br cm^{-1}; the compound was too insoluble for a satisfactory n.m.r. spectrum to be obtained (Found: M^+, 300.1092. $C_{12}H_{12}N_8O_2$ requires *M*, 300.1083).

Evaporation of the filtrate and chromatography of the residue gave starting material (3) (13 mg) and the triazole (4) (2 mg).

1-(4,4-Diethoxybut-2-ynyl)-4-methylthioazetidin-2-one (12).—The lactam (6) (3 g) and 4,4-diethoxybut-2-ynyl bromide (6 g) were dissolved in dry DMF (100 ml) at −20 °C and treated with potassium t-butoxide (23.1 ml of a 1.11M-solution in t-butyl alcohol) in DMF (10 ml) as described for (7) to provide the *acetylene* (12) as a gum (4.03 g), $\nu_{max.}$ 1 760 cm^{-1}; δ 1.23 (6 H, t, *J* 7.5 Hz), 2.10 (3 H, s), 2.92 and 3.36 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of 3 and 4.5 Hz respectively), 3.4—3.95 (4 H, m), 3.81 and 4.35 (2 H, ABq, *J* 18 Hz, higher field arm showing further coupling of 1.5 and *ca.* 1 Hz and lower field arm showing further coupling of 2 Hz), 4.79 (1 H, dd, *J* 3 and 4.5 Hz,

showing further coupling of *ca.* 1 Hz due to coupling across ring to one of the protons of N-CH_2), and 5.27 (1 H, dd, *J* 1.5 and 2 Hz) (Found: C, 56.0; H, 7.2; N, 5.2; S, 12.5. $C_{12}H_{19}NO_3S$ requires C, 56.0; H, 7.4; N, 5.5; S, 12.5%).

4-*Azido*-1-(4,4-*diethoxybut*-2-*ynyl*)*azetidin*-2-*one* (13).—The azetidinone (12) (3.67 g) in carbon tetrachloride (150 ml) at −20 °C was treated with chlorine (1.014 g) in carbon tetrachloride (50 ml) and the product subsequently treated with powdered sodium azide (1.9 g) in dry DMF (50 ml) as described for (3). Chromatography of the crude product afforded the azide (13) as a pale yellow gum (2.9 g), $\nu_{max.}$ 2 150 and 1 770 cm^{-1}; δ 1.23 (6 H, t, 7.5 Hz), 2.91 and 3.31 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of *ca.* 2 and 4.5 Hz respectively), 3.4—4.0 (4 H, m), 3.93 and 4.35 (2 H, ABq, *J* 18 Hz, further coupling unresolved), 5.07 (1 H, dd, *J ca.* 2 and 4.5 Hz), and 5.3br (1 H, s) (Found: C, 52.8; H, 6.4; N, 22.6. $C_{11}H_{16}N_4O_3$ requires C, 52.4; H, 6.4; N, 22.2%).

4-*Azido*-1-(3-*formylprop*-2-*ynyl*)*azetidin*-2-*one* (14).—The acetal (13) (2 g) was dissolved in toluene (20 ml) at 0 °C and 90% formic acid (25 ml) added. The solution was allowed to warm to room temperature, toluene (50 ml) added, and the volume reduced to *ca.* 10 ml under reduced pressure. Further toluene (50 ml) was added and the solvent evaporated off in the same way. The residue was dissolved in ethyl acetate and the solution washed successively with aqueous $NaHCO_3$, water, and brine. The dried organic layer was evaporated and *rapidly* passed through a short column of silica gel to give the aldehyde (14) as an unstable gum (1.2 g), $\nu_{max.}$ 2 120, 1 775, and 1 680 cm^{-1}; δ (90M Hz) 2.95 and 3.31 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of *ca.* 2 and 4.5 Hz), 4.06 and 4.37 (2 H, ABq *J* 18 Hz), 4.9—5.1 (1 H, m), and 9.14 (1 H, s). The product was used immediately after isolation.

8-*Formyl*-4H,7aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*imidazol*-6(7H)-*one* (15).—The azide (14) (1.2 g) was refluxed in dry toluene (1 300 ml) under argon for 12 h. The solvent was evaporated off and the residue chromatographed. Crystallisation afforded the *aldehyde* (15) as a white solid (260 mg), m.p. 151—153 °C (ethyl acetate–light petroleum), $\nu_{max.}$ 1 815, 1 800, and 1 700 cm^{-1}; δ (90M Hz) 3.43 and 3.84 (2 H, ABq, *J* 18 Hz, higher field arm showing further coupling of 2 Hz, and lower field arm further coupling of 4.5 and *ca.* 1.5 Hz), 4.25 and 5.05 (2 H, ABq, *J* 17 Hz, both arms showing further coupling of *ca.* 1.5 Hz), 5.85—6.0 (1 H, m), and 10.0 (1 H, s) (Found: C, 47.1; H, 3.6; N, 31.8. $C_7H_6N_4O_2$ requires C, 47.2; H, 3.4; N, 31.5%).

8-*Hydroxymethyl*-4H,7aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]-*imidazol*-6(7H)-*one* (16).—The aldehyde (15) (100 mg) was dissolved in THF (12.5 ml) and propan-2-ol (12.5 ml) at 0 °C and sodium borohydride in propan-2-ol–water (4 : 1) (1 ml of 1% solution) added. After 15 min glacial acetic acid (3 drops) was added, the solution evaporated to low volume and rapidly chromatographed to give the *alcohol* (16) as a white solid (70 mg), m.p. 116—118 °C (ethyl acetate); $\nu_{max.}$ (Nujol) 3 300br, and 1 790 cm^{-1}; δ (90M Hz) [$(CD_3)_2CO$] 3.05br (1 H, s, exch. D_2O), 3.32 and 3.84 (2 H, ABq, *J* 17 Hz, higher field arm showing further coupling of *ca.* 1.5 Hz, and lower field arm showing further coupling of *ca.* 1 and 4 Hz), 4.11 and 4.80 (2 H, ABq, *J* 15 Hz, each peak being slightly broadened indicating further unresolved coupling) 4.60 (2 H, s), and 5.89—6.02 (1 H, m) (Found: C, 46.9; H, 4.7; N, 31.4. $C_7H_8N_4O_2$ requires C, 46.7; H, 4.4; N, 31.1%).

8-(2-*Methoxycarbonylvinyl*)-4H,7aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*imidazol*-6(7H)-*one* (17).—The aldehyde (15) (50 mg) and methoxycarbonylmethylenetriphenylphosphorane (100 mg) were dissolved in benzene (12 ml). After 1 h the solvent was evaporated off and the residue chromatographed to give the (*Z*)-isomer (17) as a white crystalline solid (9 mg), m.p. 135—136 °C (ethyl acetate–light petroleum); $\lambda_{max.}$ 270 nm (ε 11 100); $\nu_{max.}$ 1 805, 1 800, 1 720, and 1 650 cm^{-1}; δ (90M Hz) 3.37 and 3.78 (2 H, ABq, *J* 16 Hz, higher field arm showing further coupling of *ca.* 1.5 Hz, and lower field arm showing further coupling of *ca.* 1 and 4 Hz), 3.70 (3 H, s), 4.37 and 5.04 (2 H, ABq, *J* 17 Hz, each arm showing further unresolved fine coupling), *ca.* 5.85 (1 H, m), 5.93 (1 H, d, *J* 12 Hz), and 7.04 (1 H, d, *J* 12 Hz) (Found: C, 51.4; H, 4.2; N, 24.1. $C_{10}H_{10}N_4O_3$ requires C, 51.3; H, 4.3; N, 23.9%).

Further elution gave the (*E*)-isomer (17) as needles (45 mg), m.p. 158—160 °C (ethyl acetate–light petroleum), $\lambda_{max.}$ 272 nm (ε 17 380); $\nu_{max.}$ 1 810, 1 805, 1 710, 1 665, and 1 655 cm^{-1}; δ (90M Hz) 3.41 and 3.80 (2 H, ABq, *J* 17 Hz, higher field arm showing further coupling of *ca.* 1.5 Hz, and lower field arm showing further coupling of *ca.* 1 Hz and 4 Hz), 3.77 (3 H, s,) 4.17 and 4.94 (2 H, ABq, *J* 16 Hz, higher field arm showing further coupling of *ca.* 1 Hz, further fine coupling of lower field arm not resolved), 5.81—5.95 (1 H, m), 6.34 (1 H, d, *J* 16 Hz), and 7.55 (1 H, d, *J* 16 Hz) (Found: C, 51.3; H, 4.4; N, 24.2%).

4-*Azido*-1-(3-*methoxycarbonylprop*-2-*ynyl*)*azetidin*-2-*one* (19).—The lactam (3) (1.11 g) in dry THF (40 ml) at −76 °C under argon, was treated with n-butyl-lithium (3.26 ml of a 2.5M-solution in hexane). After 5 min, dry carbon dioxide was rapidly passed through the solution for 30 min. The mixture was allowed to warm slowly to −20 °C and methyl iodide (7 ml) in DMF (15 ml) was added to it. After the mixture had warmed to room temperature it was stirred for 18 h and then poured into ethyl acetate and brine. The organic layer was separated, washed successively with water and brine, dried, and evaporated. Chromatography of the residue gave the ester (19) as an unstable gum (190 mg), $\nu_{max.}$ 2 250, 2 120, 1 770, and 1 710 cm^{-1}; δ 2.97 and 3.37 (2 H, ABq, *J* 16 Hz, each arm showing further coupling of 2 and 5 Hz, respectively), 3.78 (3 H, s), 4.17 and 4.42 (2 H, ABq, *J* 18 Hz), and 5.13 (1 H, dd, *J* 2 and 5 Hz). The material was too labile for any further analytical characterisation, and was generally used immediately after isolation.

8-*Methoxycarbonyl*-4H-7aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]-*imidazol*-6(7H)-*one* (18).—The azide (19) (190 mg) was refluxed in dry toluene (200 ml) under argon for 28 h. The solvent was evaporated off and the residue chromatographed to afford the *triazole* (18) as a white crystalline solid (90 mg), m.p. 139.5—141 °C (ethyl acetate–light petroleum), $\nu_{max.}$ 1 810 and 1 740br cm^{-1}; δ (90M Hz), 3.41 and 3.82 (2 H, ABq, *J* 18 Hz, each arm showing further coupling of *ca.* 1.5 and 4 Hz respectively), 3.89 (3 H, s), 4.23 and 5.02 (2 H, ABq, *J* 16 Hz, further fine coupling poorly resolved), and 5.85—6.05 (1 H, m) (Found: C, 46.4; H, 4.0; N, 26.9. $C_8H_8N_4O_3$ requires C, 46.4; H, 3.9; N, 26.9%).

Benzyl 2-(4-*Methylthio*-2-*oxoazetidin*-1-*yl*)*acetate* (22).—The lactam (6) (3.51 g) was dissolved in dry DMF (50 ml) containing benzyl bromoacetate (7.56 g) and powdered anhydrous potassium carbonate (4.6 g). The mixture was vigorously stirred at room temperature for 24 h and then poured into ethyl acetate–5% aqueous citric acid. The organic layer was separated, washed with brine, dried, and

evaporated. Chromatography afforded the *ester* (22) as a thick oil (4.6 g), $\nu_{max.}$ 1 760 and 1 745 cm^{-1}; δ 2.0 (3 H, s), 2.97 and 3.41 (2 H, ABq, *J* 16 Hz, showing further coupling of *ca.* 2.5 and 5 Hz respectively), 3.7 and 4.32 (2 H, ABq, *J* 18 Hz), 4.9 (1 H, dd, *J* 2.5 and 5 Hz), 5.19 (2 H, s), and 7.38 (5 H, s) (Found: C, 58.6; H, 5.5; N, 5.0; S, 11.7. $C_{13}H_{15}NO_3S$ requires C, 58.9; H, 5.7; N, 5.3; S, 12.0%).

Benzyl 2-(4-*Azido*-2-*oxo*-*azetidin*-1-*yl*)*acetate* (23).—The ester (22) (2.56 g) in carbon tetrachloride (500 ml) at −20 °C was treated with chlorine (690 mg) in carbon tetrachloride (25 ml) and the product subsequently treated with powdered sodium azide (715 mg) as described for (3). Chromatography gave the azide (23) as an oil (1.85 g), $\nu_{max.}$ 2 125, 1 775, and 1 745 cm^{-1}; δ 2.93 and 3.36 (2 H, ABq, *J* 15 Hz, showing further coupling of 2 and 4 Hz respectively) 3.78 and 4.31 (2 H, ABq, *J* 18 Hz), 5.12 (1 H, m) 5.18 (2 H, s), and 7.36 (5 H, s) (Found: C, 55.1; H, 4.4; N, 21.1. $C_{12}H_{12}N_4O_3$ requires C, 55.4; H, 4.6; N, 21.5%).

Benzyl 4,5,7,8-*Tetrahydro*-4-*hydroxy*-4-*methyl*-7-*oxo*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (25).—Hexamethyldisilazane (1.198 g) was dissolved in dry THF (10 ml), under argon, at 0 °C and n-butyl-lithium (4.65 ml; 1.6M-solution in hexane) was added. After 10 min the solution was cooled to −76 °C and the azide (23) (1.76 g) in dry THF (20 ml) added dropwise during 10 min. The mixture was stirred for a further 15 min and then but-3-yn-2-one (800 mg) in THF (5 ml) added dropwise during 10 min. After 30 min the solution was neutralised with glacial acetic acid and then poured into ethyl acetate and brine. The organic layer was separated, washed successively with water and brine, and then dried and evaporated. Chromatography afforded the product (24) contaminated with starting material (23) (25%), but sufficiently pure for the cycloaddition reaction.

The product (24) (1.28 g) was dissolved in dry toluene (300 ml) and the solution was refluxed under argon for 4.5 h. The solvent was evaporated and the residue crystallised from ethyl acetate–light petroleum to give the *triazole* (25) as white crystals (554 mg), m.p. 171—178 °C, $\nu_{max.}$ (Nujol) 3150br, 1 790sh, 1 780, and 1 735 cm^{-1}; δ (90M Hz) [$(CD_3)_2SO$] 1.63 (3 H, s), 3.25 (1 H, s, exch. D_2O) 3.38 and 3.82 (2 H, ABq, *J* 16 Hz, showing further coupling of 2 and 4 Hz respectively), 4.6 (1 H, s), 5.12 (2 H, s), 6.05 (1 H, dd, *J* 2 and 4 Hz), 7.3 (5 H, s), and 7.78 (1 H, s) (Found: C, 58.6; H, 4.7; N, 16.8. $C_{16}H_{16}N_4O_4$ requires C, 58.5; H, 4.9; N, 17.1%).

Benzyl 7,8-*Dihydro*-4-*methyl*-7-*oxo*-8aH-*azeto*[1,2-a]-v-*triazolo*[3,4-c]*pyrimidine*-5-*carboxylate* (26).—The lactam (25) (164 mg) was dissolved in dry THF (15 ml) at −20 °C and 2,6-lutidine (118 mg) was added, followed dropwise by thionyl chloride (131 mg) in THF (2 ml) during 2—3 min. The mixture was filtered and the filtrate evaporated. The residue was dissolved in methylene chloride (10 ml) at −20 °C and DBU (152 mg) added. The temperature was allowed to warm to 0 °C after which the solution was washed successively with dilute HCl (0.5N) and brine, dried, and evaporated. The residue was chromatographed and crystallisation of the *product* (26) from ethyl acetate–light petroleum gave white crystals (150 mg), m.p. 166—167 °C, $\lambda_{max.}$ 309 nm (ε 6 900); $\nu_{max.}$ 1 795 and 1 715 cm^{-1}; δ (80MHz) 2.51 (3 H, s), 3.72 and 4.05 (2 H, ABq, *J* 16 Hz, showing further coupling of 1.4 and 3.5 Hz, respectively), 5.32 (2 H, s), 5.88 (1 H, dd, *J* 1.4 and 3.5 Hz), 7.39 (5 H, s), and 7.88 (1 H, s) (Found: C, 61.6; H, 4.5; N, 17.9. $C_{16}H_{14}N_4O_3$ requires C, 61.9; H, 4.7; N, 18.1%).

7,8-*Dihydro*-4-*methyl*-7-*oxo*-8aH-*azeto*[1,2-a]-v-*triazolo*-[3,4-c]*pyrimidine*-5-*carboxylic Acid* (21).—The benzyl ester (26) (100 mg) was hydrogenated over 10% Pd–C (25 mg) in THF (15 ml) for 1 h. The catalyst was removed by filtration through Kieselguhr, the filter cake being thoroughly washed with acetone. The filtrate was evaporated and the residue triturated with ether to afford the *acid* (21) as an amorphous solid (55 mg), $\lambda_{max.}$ (0.3% w/v $NaHCO_3$ solution) 294 nm (ε 10 100); $\nu_{max.}$ (Nujol) 2 500br, 1 802, and 1 690 cm^{-1}; δ (80 MHz) [$(CD_3)_2SO$] 2.43 (3 H, s), 3.67 and 4.13 (2 H, ABq, *J* 17 Hz, showing further coupling of 1.5 and 3.5 Hz, respectively), 4.0—6.0 (1 H, very broad s, exch. D_2O), 6.14 (1 H, dd, *J* 1.5 and 3.5 Hz), and 8.18 (1 H, s) (Found: C, 48.9; H, 3.5; N, 25.1. $C_9H_8N_4O_3$ requires C, 49.1; H, 3.6; N, 25.5%).

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