Syntheses based on 1,2-Secopenicillins. Part II.[1] Preparation of 4-(3-Substituted Prop-2-ynylthio)azetidin-2-ones

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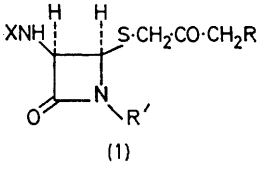
Treatment of benzyl 6β-(triphenylmethylamino)penicillanate with 3-substituted prop-2-ynyl bromides in the presence of strong base gave 1,2-secopenicillanates, which on permanganate oxidation afforded (3*R*,4*R*)-4-(3-substituted prop-2-ynylthio)-3-(triphenylmethylamino)azetidin-2-ones.

As noted in a preliminary communication,[2] our plan to synthesise novel fused β-lactams with potential antibacterial activity from 1,2-secopenicillins[3] included a projected route to new cephalosporin analogues by way of 4-(2-oxoalkylthio)azetidin-2-ones (1). Unfortunately, the desired ketones (1) could not be prepared directly from penicillanates because, although the 1,2-bond in benzyl 6β-(triphenylmethylamino)penicillanate (2) is cleaved selectively by various alkylating agents in the presence of a strong base,[3] the reaction failed in the case of α-bromo-ketones. We therefore conceived the idea of using the acetylenic function as a precursor of the $CO{\cdot}CH_2$ grouping, and in this paper we describe the preparation of a number of 4-(3-substituted prop-2-ynylthio)azetidin-2-ones, (3) and (4). Hydration of the triple bond and its application in the synthesis of a representative cephalosporin analogue is described in the following paper.[4]

The requisite 3-substituted prop-2-ynyl bromides were prepared by treating the corresponding alcohols with phosphorus tribromide. A useful method for preparing certain novel 3-arylprop-2-yn-1-ols proved to be treatment of copper(I) 3-(tetrahydropyran-2-yloxy)prop-1-ynide with the appropriate aryl iodide in boiling pyridine, followed by acidic hydrolysis of the tetrahydropyranyl ether.

Prop-2-ynyl bromide and its analogues substituted in the 3-position by methyl, phenyl, benzyl, *p*-nitrophenyl, *p*-methoxycarbonylphenyl, or 3-pyridyl were each treated with benzyl 6β-(triphenylmethylamino)penicillanate (2) in dry tetrahydrofuran containing a strong base such as sodium hydride, potassium t-butoxide, or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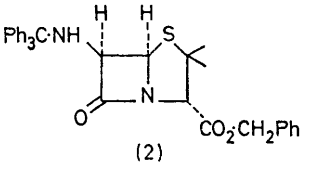
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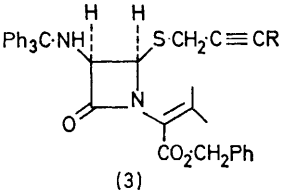
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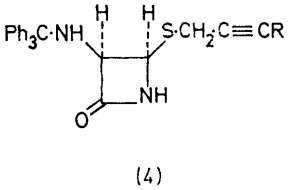
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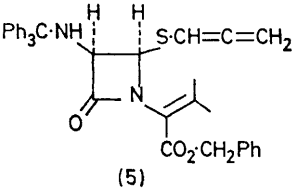
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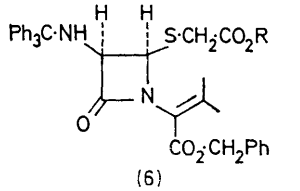
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powdered sodium hydroxide according to the method previously described[3] for non-acetylenic halides. In most cases the desired acetylenic 1,2-secopenicillanate

[1] Part I, E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 447.

[2] J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 57.

[3] E. G. Brain, I. McMillan, J. H. C. Nayler, R. Southgate, and P. Tolliday, *J.C.S. Perkin I*, 1975, 562.

[4] Part III, J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, following paper.

(3) was the only product isolated, but in one experiment with unsubstituted prop-2-ynyl bromide this was accompanied by some of the isomeric allene (5).

Removal of the substituent from the β-lactam nitrogen atom of the 1,2-secopenicillanates (3) was accomplished by the general method described [1] for non-acetylenic analogues. Thus treatment with potassium permanganate in moist pyridine, with or without dimethylformamide as co-solvent, gave benzyl 3-hydroxy-3-methyl-2-oxobutyrate and the required 4-(3-substituted prop-2-ynylthio)-3-(triphenylmethylamino)azetidin-2-ones (4). Oxidative cleavage at the triple bond to give the carboxylic acid (6; R = H) may well be a common side-reaction in this procedure. The acid, characterised as the ester (6; R = Me), was isolated as a by-product from oxidation of the simple prop-2-ynyl sulphide (3; R = H), but was not sought in corresponding oxidations of non-terminal acetylenes.

EXPERIMENTAL

General experimental procedures were as outlined in Part I.[1]

Copper(I) 3-(*Tetrahydropyran-2-yloxy*)*prop*-1-*ynide*.—This was prepared by the general method of Castro and his co-workers,[5] from 3-(tetrahydropyran-2-yloxy)prop-1-yne instead of phenylacetylene.

3-*Arylprop*-2-*yn*-1-*ols*.—(*a*) Copper(I) 3-(tetrahydropyran-2-yloxy)prop-1-ynide (67.2 g) in pyridine (800 ml) was stirred under nitrogen and heated almost to boiling, then treated with 4-iodonitrobenzene (80 g) and refluxed for 18 h with exclusion of air. The cooled mixture was filtered and the filtrate evaporated to an oil, which was taken up in ether; the solution was shaken with water and filtered. The ether layer of the filtrate was separated, dried, and evaporated, and the residue purified by column chromatography to give 1-*p*-nitrophenyl-3-(tetrahydropyran-2-yloxy)-prop-1-yne (43 g). This ether in methanol (800 ml) and 6M hydrochloric acid (86 ml) was refluxed for 45 min, cooled, and evaporated to low bulk. The residue was dissolved in ethyl acetate, washed with saturated sodium hydrogen carbonate solution, dried, and evaporated. Chromatographic purification of the residue gave 3-p-*nitrophenylprop*-2-*yn*-1-*ol* (11.5 g), m.p. 95—96.5°, $\nu_{max.}$ 3 590, 3 410, 1 603, 1 535, and 1 358 cm^{-1}; δ 2.18br (1 H, exch.), 4.58 (2 H, s), and 7.60 and 8.22 (4 H, ABq, *J* 8 Hz) (Found: C, 61.1; H, 4.2; N, 7.9. $C_9H_7NO_3$ requires C, 61.0; H, 4.0; N, 7.9%).

(*b*) By the same procedure, methyl 4-iodobenzoate (2.25 g) yielded 3-(p-*methoxycarbonylphenyl*)*prop*-2-*yn*-1-*ol* (1.4 g), m.p. 82—83°, $\nu_{max.}$ 3 590, 3 400, 3 000, 1 715, and 1 609 cm^{-1}; δ 2.38br (1 H, exch.), 3.92 (3 H, s), 4.55 (2 H, s), and 7.46 and 8.00 (4 H, ABq, *J* 8 Hz) (Found: C, 69.0; H, 5.5. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%).

(*c*) Similarly 3-iodopyridine (37 g) gave 3-(3-*pyridyl*)*prop*-2-*yn*-1-*ol* (18 g), m.p. 97—98°, $\nu_{max.}$ 3 200, 2 990, 1 589, and 1 565 cm^{-1}; δ 4.50 (2 H, s), 4.92 (1 H, s, exch.), and 7.15—8.0 (4 H, ArH) (Found: C, 71.9; H, 5.2; N, 10.5. C_8H_7NO requires C, 72.2; H, 5.3; N, 10.5%).

3-*Substituted Prop*-2-*ynyl Bromides*.—(*a*) 3-*p*-Nitrophenylprop-2-yn-1-ol (3 g) in dry ether (10 ml) containing pyridine (50 mg) was treated dropwise with phosphorus tribromide (1.7 g) in ether. After 15 min the mixture was poured into ice–water and extracted with ether. Evaporation of the dried extracts gave 3-*p*-nitrophenylprop-2-ynyl bromide (3.2 g) as a solid, which was used without further purification; δ 4.20 (2 H, s), 7.60 (2 H, d, *J* 9 Hz), and 8.23 (2 H, d, *J* 9 Hz). Other neutral acetylenic bromides were prepared similarly.

(*b*) 3-(3-Pyridyl)prop-2-yn-1-ol (36 g) in chloroform (600 ml) was cooled to −10 °C and treated with a solution of phosphorus tribromide (49 g) in chloroform (50 ml), added dropwise during 1 h. The supernatant solution was then decanted from a little gum and stirred at room temperature for 24 h, during which time 3-(3-pyridyl)prop-2-ynyl bromide hydrobromide (60 g) separated as a pale yellow solid, which was collected, washed with dry ether, and used without further purification. The free base was unstable.

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*prop*-2-*ynylthio*-3-(*triphenylmethylamino*)*azetidin*-2-*one* (3; R = H).—(*a*) Benzyl 6β-(triphenylmethylamino)penicillanate (2) (25 g) in dry tetrahydrofuran (400 ml) was treated with sodium hydride (1.85 g) and prop-2-ynyl bromide (25 ml), then refluxed for 8 h under dry nitrogen, cooled, diluted with ethyl acetate, washed with brine followed by water, and dried. Evaporation, and trituration of the residue with ethyl acetate gave solid starting material (2) (6.22 g), which was removed. Chromatography of the mother liquor gave the *acetylene* (3; R = H) (8.5 g), m.p. 90—92°; $\nu_{max.}$ 3 250, 1 759, 1 718, and 1 622 cm^{-1}; δ 1.98 (3 H, s), 2.28 (3 H, s) (obscuring acetylenic H), 2.67 (2 H, t), 3.6 (1 H, m, exch.), 4.53 (1 H, d, *J* 5 Hz), 4.83 (1 H, d, *J* 5 Hz), 4.98 and 5.22 (2 H, ABq, *J* 12 Hz), and 7.0—7.7 (20 H, m) (Found: C, 75.5; H, 6.2; N, 4.5; S, 5.2. $C_{37}H_{34}N_2O_3S$ requires C, 75.7; H, 5.9; N, 4.8; S, 5.5%).

(*b*) Benzyl 6β-(triphenylmethylamino)penicillanate (2) (54.8 g), powdered sodium hydroxide (4.4 g), and prop-2-ynyl bromide (13.1 g, 8.4 ml) were stirred in tetrahydrofuran (500 ml) for 52 h. Work-up as in (*a*) but without chromatography gave the amorphous product (40 g, 69%) containing *ca.* 5% of starting material (2) (by n.m.r.).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*propa*-1,2-*dienylthio*-3-(*triphenylmethylamino*)*azetidin*-2-*one* (5).—Benzyl 6β-(triphenylmethylamino)penicillanate (2) (5.48 g) in dry tetrahydrofuran (50 ml) and t-butyl alcohol (50 ml) was stirred under nitrogen, and prop-2-ynyl bromide (2.38 g) was added. A solution of potassium t-butoxide (1.3 g) in t-butyl alcohol (12 ml) and tetrahydrofuran (12 ml) was added during 2½ h; then after a further 15 min the mixture was concentrated to small volume, diluted with ethyl acetate, washed, and dried. Chromatography gave the *allene* (5) as a foam (1.58 g), $\nu_{max.}$ 1 940, 1 760, 1 715, and 1 625 cm^{-1}; δ 2.16 (3 H, s), 2.20 (3 H, s), 2.84br (1 H, s, exch.), 4.43 (1 H, m, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.76 (1 H, d, *J* 5 Hz), 4.98 and 5.22 (2 H, ABq, *J* 12 Hz), 4.63—5.5 (3 H, m), and 7.1—7.66 (20 H, m) (Found: C, 75.8; H, 6.0; N, 4.5; S, 5.4. $C_{37}H_{34}N_2O_3S$ requires C, 75.7; H, 5.9; N, 4.8; S, 5.5%). Further elution of the column gave the acetylene (3; R = H) (2.85 g).

Action of 3-*Substituted Prop*-2-*ynyl Bromides on Benzyl* 6β-(*Triphenylmethylamino*)*penicillanate*.—(a) *By use of potassium t-butoxide*. Benzyl 6β-(triphenylmethylamino)penicillanate (2) (3.3 g) and but-2-ynyl bromide [6] (0.9 g) were stirred in tetrahydrofuran (100 ml) under nitrogen. Potassium t-butoxide (6.6 ml of M-solution in t-butyl alcohol) in

[5] C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071.

[6] R. Couffignal, M. Gaudemar, and P. Perrot, *Bull. Soc. chim. France*, 1967, 3909.

tetrahydrofuran (20 ml) was added during 3½ h, then the mixture was stirred for 1½ h more, concentrated to small volume, diluted with ethyl acetate, washed with water, dried, and evaporated. Chromatography of the residue gave unchanged (2) (0.7 g) and (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(*but*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (3; R = Me) (1.81 g) as an amorphous solid, $\nu_{max.}$ 1 760, 1 720, and 1 625 cm^{-1}; δ 1.67 (3 H, t, *J* 2.5 Hz), 2.00 (3 H, s), 2.22 (3 H, s), 2.63 (2 H, q, *J* 2.5 Hz), 2.9br (1 H, d, exch.), 4.50br (1 H, dd, collapsing to d, *J* 5 Hz on D_2O exch.), 4.75 (1 H, d, *J* 5 Hz), 4.95 and 5.22 (2 H, ABq, *J* 12.5 Hz), and 7.1—7.6 (20 H, ArH) (Found: C, 75.5; H, 6.1; N, 4.6. $C_{38}H_{36}N_2O_3S$ requires C, 76.0; H, 6.0; N, 4.7%).

Similar alkylation of the penicillanate (2) (2.74 g) with 3-phenylprop-2-ynyl bromide (1 g) gave (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(3-*phenylprop*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (3; R = Ph) (2.15 g), m.p. 141° (from ethyl acetate–light petroleum), $\nu_{max.}$ 1 760, 1 715, and 1 625 cm^{-1}; δ 2.07 (3 H, s), 2.17 (3 H, s), 2.78 and 3.18 (2 H, ABq, *J* 17 Hz), 2.95br (1 H, s, exch.), 4.55br (1 H, s, collapsing to d, *J* 5 Hz on D_2O exch.), 4.93 (1 H, d, *J* 5 Hz), 4.98 (2 H, s), and 7—7.7 (25 H, m) (Found: C, 77.8; H, 5.8; N, 4.0; S, 4.7. $C_{43}H_{38}N_2O_3S$ requires C, 77.9; H, 5.8; N, 4.2; S, 4.8%).

4-Phenylbut-2-ynyl bromide likewise gave (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(4-*phenylbut*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (3; R = $PhCH_2$) (32%) as an amorphous solid, $\nu_{max.}$ 1 755 and 1 718 cm^{-1}; δ 1.99 (3 H, s), 2.19 (3 H, s), 2.6—3.0 (3 H, m, 1 H exch.), 3.50 (2 H, t, *J* 2 Hz), 4.4—4.6 (1 H, m, collapsing to 4.51, d, *J* 5 Hz on D_2O exch.), 4.81 (1 H, d, *J* 5 Hz), 4.90 and 5.12 (2 H, ABq, *J* 16 Hz), and 7.0—7.7 (25 H, m, ArH) (Found: C, 77.8; H, 6.1; N, 3.9; S, 4.6. $C_{44}H_{40}N_2O_3S$ requires C, 78.1; H, 5.9; N, 4.1; S, 4.7%).

(b) *By use of sodium hydroxide.* The penicillanate (2) (16.4 g) in tetrahydrofuran (300 ml) was treated with 3-*p*-nitrophenylprop-2-ynyl bromide (7.9 g) and powdered sodium hydroxide (2.4 g); the mixture was stirred for 24 h at room temperature, and worked up as in (a) to give (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(3-p-*nitrophenylprop*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (3; R = C_6H_4·NO_2-*p*) (4.16 g) as a yellow amorphous solid, $\nu_{max.}$ 1 770, 1 720, 1 630, 1 520, and 1 345 cm^{-1}; δ 2.02 (3 H, s), 2.17 (3 H, s), 2.82 and 3.15 (2 H, ABq, *J* 17 Hz, covering 1 H exch.), 4.60br (1 H, s, collapsing to d, *J* 5 Hz on D_2O exch.), 4.88 (1 H, d, *J* 5 Hz), 4.90 and 5.13 (2 H, ABq, *J* 12 Hz), 7.0—7.7 (22 H, ArH), and 8.13 (2 H, d, *J* 9 Hz, ArH) (Found: C, 72.8; H, 5.4; N, 5.8; S, 4.4%; M^+, 707. $C_{43}H_{37}N_3O_5S$ requires C, 72.9; H, 5.2; N, 5.9; S, 4.5%; *M*, 707).

3-(*p*-Methoxycarbonylphenyl)prop-2-ynyl bromide similarly gave (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-[3-(p-*methoxycarbonylphenyl*)*prop*-2-*ynylthio*]-3-(*triphenylmethylamino*)*azetidin*-2-*one* (3; R = C_6H_4·CO_2Me-*p*) (62%) as a foam, $\nu_{max.}$ 1 765, 1 720s, and 1 630 cm^{-1}; δ 1.90 (3 H, s), 2.14 (3 H, s), 2.75 and 3.10 (2 H, ABq, *J* 17 Hz covering 1 H exch.), 3.90 (3 H, s), 4.60br (1 H, s, collapsing to d, *J* 5 Hz on D_2O exch.), 4.90 (1 H, d, *J* 5 Hz), 4.85 and 5.09 (2 H, ABq, *J* 12 Hz), 7.0—7.7 (22 H, ArH), and 8.0 (2 H, d, *J* 9 Hz, ArH) (Found: C, 74.4; H, 5.6. $C_{45}H_{40}N_2O_5S$ requires C, 75.0; H, 5.6%).

The penicillanate (2) (62 g) in tetrahydrofuran (1 l), treated with 3-(3-pyridyl)prop-2-ynyl bromide hydrobromide (34.8 g) and powdered sodium hydroxide (9.95 g) at room temperature for 5 days, gave, after similar work-up, (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-[3-(3-*pyridyl*)*prop*-2-*ynylthio*]-3-(*triphenylmethylamino*)*azetidin*-2-*one* (3; R = 3-pyridyl) as a yellow amorphous solid (17 g, 23%), $\nu_{max.}$ 1 760 and 1 720 cm^{-1}; δ 2.01 (3 H, s), 2.17 (3 H, s), 2.80 and 3.13 (2 H, ABq, *J* 18 Hz, superimposed on 1 H, br, exch.), 4.46—4.74 (1 H, m, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.91 (1 H, d, *J* 5 Hz), 4.40 and 5.13 (2 H, ABq, *J* 12 Hz), 7.0—7.75 (22 H, m, ArH), and 8.45—8.73 (2 H, m, ArH) (Found: C, 76.1; H, 5.8; N, 6.0; S, 4.8. $C_{42}H_{37}N_3O_3S$ requires C, 76.0; H, 5.6; N, 6.3; S, 4.8%).

Oxidative Removal of the N-*Substituent.*—(*a*) The secopenicillanate (3; R = Ph) (6.62 g) in dimethylformamide (60 ml) containing pyridine (2 ml) and water (5 ml) was stirred at 0 °C while powdered potassium permanganate (2.4 g) was added in portions. On completion of the addition, the mixture was held at 0 °C until no permanganate remained (*ca.* 1½ h), then diluted with ether and water, and filtered to remove manganese dioxide. The organic phase of the filtrate was separated, washed successively with dilute hydrochloric acid, sodium hydrogen carbonate solution, and brine, then dried ($MgSO_4$). Evaporation and chromatography gave unchanged (3; R = Ph) (1.81 g) and (3R,4R)-4-(3-*phenylprop*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (4; R = Ph) (1.65 g, 35%), m.p. 121—122° (from ethyl acetate–light petroleum), $\nu_{max.}$ 3 300, 3 230, and 1 765 cm^{-1}; δ 3.05br (1 H, exch.), 3.25 (2 H, s), 4.53 (2 H, m, collapsing to s on D_2O exch.), 6.37br (1 H, exch.), and 7.1—7.7 (20 H, m) (Found: C, 78.4; H, 5.8; N, 5.7; S, 6.5. $C_{31}H_{26}N_2OS$ requires C, 78.4; H, 5.5; N, 5.9; S, 6.8%).

(*b*) Similar oxidation of the secopenicillanate (3; R = CH_2Ph) gave starting material (33%) and (3R,4R)-4-(4-*phenylbut*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (4; R = CH_2Ph) (31%), m.p. 144—145° (from ethyl acetate–light petroleum), $\nu_{max.}$ 3 400 and 1 765 cm^{-1}; δ 2.85—3.20 (3 H, m, collapsing to 3.05, 2 H, t, *J* 2 Hz on D_2O exch.), 3.57 (2 H, t, *J* 2 Hz), 4.4—4.7 (2 H, m), 6.15br (1 H, s, exch.), and 7.0—7.7 (20 H, m) (Found: C, 78.5; H, 5.8; N, 5.6; S, 6.6. $C_{32}H_{28}N_2OS$ requires C, 78.7; H, 5.7; N, 5.7; S, 6.6%).

(*c*) The secopenicillanate (3; R = C_6H_4·CO_2Me-*p*) (1 g) was similarly oxidised to (3R,4R)-4-[3-(p-*methoxycarbonylphenyl*)*prop*-2-*ynylthio*]-3-(*triphenylmethylamino*)*azetidin*-2-*one* (4; R = C_6H_4·CO_2Me-*p*) (0.19 g), amorphous, $\nu_{max.}$ 3 380, 1 770, and 1 723 cm^{-1}; δ 3.30 (2 H, s, covering 1 H, exch.), 3.93 (3 H, s), 4.57br (2 H, s, collapsing to 2 H, sharp s on D_2O exch., β lactam protons), 6.87 (1 H, s, exch.), 7.24—7.70 (17 H, ArH), and 8.10 (2 H, d, *J* 8 Hz, ArH) (Found: C, 74.1; H, 5.3; N, 5.1; S, 6.4. $C_{33}H_{28}N_2O_3S$ requires C, 74.4; H, 5.3; N, 5.3; S, 6.0%).

(*d*) The secopenicillanate (3; R = 3-pyridyl) (22.3 g) in pyridine (200 ml) and water (20 ml) was stirred at 0 °C while powdered potassium permanganate (8 g) was added during 15 min, and kept thus for 1 h more. The mixture was then diluted with ethyl acetate (500 ml) and brine (400 ml), and filtered through kieselguhr. The organic layer of the filtrate was separated, washed with brine, dried, and evaporated. Chromatography gave unchanged (3; R = 3-pyridyl) (5.83 g, 26%) and (3R,4R)-4-[3-(3-*pyridyl*)*prop*-2-*ynylthio*]-3-(*triphenylmethylamino*)*azetidin*-2-*one* (4; R = 3-pyridyl) (4.57 g, 29%), m.p. 96—99° (from benzene–ether), $\nu_{max.}$ 3 380 and 1 765 cm^{-1}; δ 3.25 (3 H, s, 1 H, exch.), 4.60br (2 H, s), 6.61 (1 H, s, exch.), 7.1—7.9 (17 H, m), and 8.4—8.8 (2 H, m) (Found: C, 73.1; H, 5.7; N, 8.3; S, 6.3.

$C_{30}H_{25}N_3OS,H_2O$ requires C, 73.0; H, 5.5; N, 8.5; S, 6.5%).

(*e*) Oxidation of the secopenicillanate (3; R = H) (2.88 g) as in (*d*) gave starting material (1.22 g) and (3R,4R)-4-*prop*-2-*ynylthio*-3-(*triphenylmethylamino*)*azetidin*-2-*one* (4; R = H) (0.54 g), m.p. 58—60° (from aqueous ethanol), $\nu_{max.}$ 3 395, 3 295, and 1 768 cm^{-1}; δ 2.22 (1 H, t, *J* 2.5 Hz), 3.03 (2 H, d, *J* 2.5 Hz), 3.00 (1 H, s, exch.), 4.62br (2 H, s), 6.43br (1 H, s, exch.), and 7.0—7.6 (15 H, m) (Found: C, 72.5; H, 5.8; N, 6.8; S, 8.0. $C_{25}H_{22}N_2OS,H_2O$ requires C, 72.1; H, 5.8; N, 6.7; S, 7.7%). Elution of the chromatography column with neat ethyl acetate afforded a fraction (0.144 g) consisting mainly of the carboxylic acid (6; R = H), $\nu_{max.}$ 2 500—3,500br, 1 760, 1 720, and 1 630 cm^{-1}; δ 1.95 (3 H, s), 2.14 (3 H, s), 2.4 and 2.77 (2 H, ABq, *J* 15 Hz), 4.5 (1 H, d, *J* 5 Hz), 4.74 (1 H, d, *J* 5 Hz), 4.92 and 5.18 (2 H, ABq, *J* 12 Hz), 6.54br (2 H, s, exch.), and 7.0—7.6 (20 H, m). Ethereal diazomethane converted this acid into (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methoxycarbonylmethylthio*-3-(*triphenylmethylamino*)*azetidin*-2-*one* (6; R = Me) (56 mg), m.p. 120—121°, $\nu_{max.}$ 1 775, 1 730br, and 1 630 cm^{-1}; δ 1.99 (3 H, s), 2.23 (3 H, s), 2.48 and 2.84 (2 H, ABq, *J* 15 Hz), 3.0br (1 H, s, exch.), 3.58 (3 H, s), 4.50br (1 H, collapses to d, *J* 5 Hz, on D_2O exch.), 4.78 (1 H, d, *J* 5 Hz), 4.98 and 5.23 (2 H, ABq, *J* 12 Hz), and 7.1—7.7 (20 H, m) (Found: C, 71.4; H, 6.0; N, 4.4; S, 5.2. $C_{37}H_{36}N_2O_5S$ requires C, 71.6; H, 5.9; N, 4.5; S, 5.2%). The same product was obtained by treating benzyl 6β-triphenylmethylaminopenicillanate with methyl bromoacetate, as previously described [3] for the t-butyl analogue.

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