Total Synthesis of (±)-Epithienamycins A and B [(±)-Olivanic Acids MM22380 and MM22382] and Derivatives

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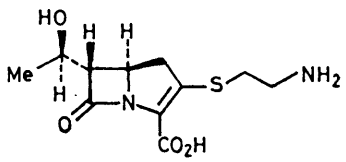
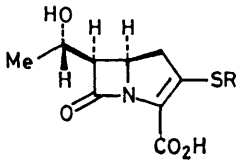
(±)-(3*R**,4*R**)-4-(2,2-Dimethoxyethyl)-3-[(1*S**)-1-hydroxyethyl]azetidin-2-one (7), which has been stereoselectively synthesised *via* the 4-methoxycarbonylisoxazoline (4), was converted into (±)-epithienamycins A (2) and B (3) [(±)-olivanic acids MM22380 and MM22382], (±)-deacetylepithienamycin A (20), and the 2-phenylthio-substituted compound (19). This total synthesis confirms the relative stereochemistry of the natural antibiotics.

A FAMILY of β-lactam antibiotics, having the carbapenem ring system, represented by thienamycin (1),[1-3] has recently attracted much attention because of its potent and broad antibiotic activities. Epithienamycins isolated from the culture broth of *Streptomyces flavogriseus* [4] were identical with some of the olivanic acids independently found in that of *S. olivaceus*.[5,6] Epithienamycins A (2) and B (3) [4] (olivanic acids MM22380 and MM22382,[6] respectively) possessing a *cis*-substituted β-lactam structure showed strong antibacterial properties although they are susceptible to penicillinase, in contrast with the *trans*-isomers. The absolute stereochemistry of (2) and (3) was determined as the (5*R*,6*R*,8*S*)-configuration mainly on the basis of the spectroscopic evidence.[4,6]

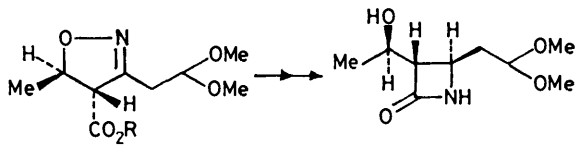


(1)



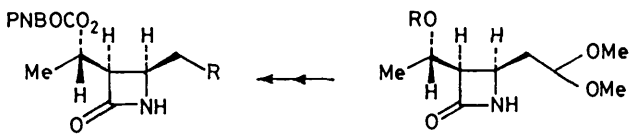
(2) R = CH_2CH_2NHAc
(3) R = CH=CHNHAc

Recently we developed an efficient synthesis of (±)-thienamycin (1) *via* isoxazoline derivatives.[7-9] During this study it was observed that hydrogenolysis of the isoxazoline methyl ester (4), followed by trimethylsilylation of the resulting epimeric amino-alcohols, cyclisation with Grignard reagent, and deblocking had produced the *cis*-azetidinone (7) as the major product in 38% yield along with the *trans*-isomer (6) in 21% yield. The *trans*-compound (6), which could be selectively synthesised from the corresponding t-butyl ester (5) by a similar procedure,[8] had been correlated to (±)-thienamycin (1).[7,9] On the other hand, the relative configuration of the *cis*-β-lactam (7) must be the same as that of epithienamycins A and B. Therefore, by application of the established procedures,[3,9] (7) was



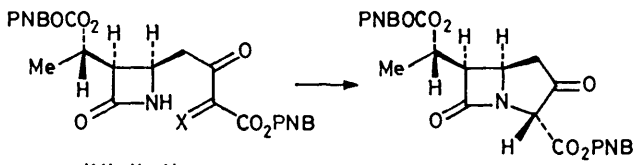
(4) R = Me
(5) R = Bu^t

(6) + (7) R = H



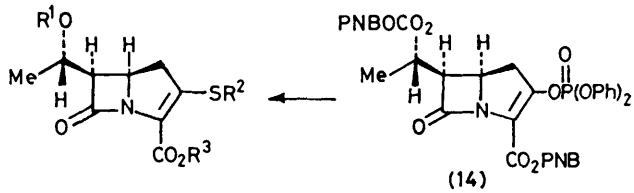
(9) R = CHO
(10) R = CO_2H

(8) R = CO_2PNB



(11) X = H_2
(12) X = N_2

(13)



(14)

(15) R^1 = CO_2PNB, R^2 = CH_2CH_2NHAc, R^3 = PNB
(16) R^1 = CO_2PNB, R^2 = CH=CHNHAc, R^3 = PNB
(17) R^1 = CO_2PNB, R^2 = Ph, R^3 = PNB
(18) R^1 = CO_2PNB, R^2 = $CH_2CH_2NHCO_2$PNB, R^3 = PNB
(19) R^1 = R^3 = H, R^2 = Ph
(20) R^1 = R^3 = H, R^2 = $CH_2CH_2NH_2$

PNB = p-$O_2N{\cdot}C_6H_4{\cdot}CH_2$

transformed into the antibiotics and their related compounds in order to confirm the relative stereochemistry at C-8 of these natural products and to test their biological activities.

The hydroxy-group of the *cis*-azetidinone (7) was protected using *p*-nitrobenzyl chloroformate in the presence of 4-*NN*-dimethylaminopyridine to give the acetal (8) in 60% yield. Hydrolysis of the acetal (8), followed by oxidation of the aldehyde (9) with Jones reagent, produced the *cis*-carboxylic acid (10) in 64% yield from (8). The acid (10) was converted, *via* the imidazolide intermediate,[3,10] into the β-keto-ester (11) in 76% yield. After treatment of (11) with toluene-*p*-sulphonyl azide in the presence of triethylamine, the resulting diazo-ester (12) was subjected to a carbene insertion reaction in the presence of rhodium diacetate [3] in hot benzene. The stereochemistry of the bicyclic product, formed as a single stereoisomer in 81% yield from (11), was assigned as (13), having a α-oriented ester group because (13) is a more stable configuration.[4]

Reaction of (13) with diphenyl chlorophosphate [3,11] in the presence of 1 mol equivalent of di-isopropylethylamine in acetonitrile produced a stable phosphate (14), which was treated, without isolation, with *N*-acetylcysteamine in the presence of the same base to give the diprotected epithienamycin A (15) in 80% yield from (13).

For the purpose of the synthesis of epithienamycin B derivative, silver (*E*)-2-acetamidoethylenethiolate was prepared by a modification of the known method.[12] Reaction of the above phosphate intermediate (14) with the silver salt in the presence of sodium iodide brought about the addition–elimination reaction at 0 °C in acetonitrile to afford the diprotected epithienamycin B(16) in 82% yield from the ketone (13). The structures of these products (15) and (16) were established by spectral analysis (Experimental section). Deprotection of (15) and (16) was carried out by hydrogenolysis using Adams catalyst in the presence of 1 mol equivalent of sodium hydrogen carbonate under hydrogen (40 lbf in^{-2}) in aqueous tetrahydrofuran, respectively. After purification using Sephadex G-10, the sodium salts of (±)-epithienamycins A (2) and B (3) were obtained in good yields. The u.v., i.r., and n.m.r. spectra of the synthetic compounds were consistent with reported data of the natural products.[4,6] Thus the relative configuration of epithienamycins A and B (olivanic acids MM22380 and MM22382) were confirmed as shown in formulae (2) and (3).

Under similar conditions, the 3-phenylthio-derivative (17) and the triprotected (±)-deacetylepithienamycin A (18) were synthesised. The sodium salt of the phenylthio-substituted compound (19) was obtained by the same deprotection procedure as above. On the other hand, (±)-deacetylepithienamycin A (20) was produced by hydrogenolysis using palladium–charcoal.[2] (±)-Epithienamycins A and B and (±)-deacetylepithienamycin A showed similar antibacterial properties as reported,[4,6] while (19) had a lower activity.

EXPERIMENTAL

U.v. spectra were measured with a Hitachi 124 spectrophotometer, i.r. spectra with a Hitachi 260-10 spectrophotometer, and n.m.r. spectra with JEOL-PMX-60 and JEOL-PS-100 spectrometers. Ordinary mass spectra were obtained with a Hitachi M-52G while FD and accurate mass spectra were taken with a JEOL-JMS-01SG-2 spectrometer.

(±)-4β-(2,2-*Dimethoxyethyl*)-3β-[(1S*)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]*azetidin*-2-*one* (8).—To a mixture of the azetidinone (7) [8] (2.09 g, 10.3 mmol) and 4-dimethylaminopyridine (3.66 g, 30 mmol) in dry methylene chloride (30 ml), was added a solution of *p*-nitrobenzyl chloroformate (3.23 g, 15 mmol) in dry methylene chloride (10 ml) at −5 °C with stirring. The mixture was stirred for 1 h at −5 to 0 °C under nitrogen. After filtration followed by evaporation of the filtrate, the residue was dissolved in methylene chloride. The extract was washed with saturated aqueous potassium hydrogen sulphate and water, dried (Na_2SO_4), and evaporated. The residue was subjected to chromatography on silica gel. Elution with benzene–acetone (17 : 3 v/v) afforded the azetidinone (8) (2.39 g, 60%) as a solid, which was recrystallised from benzene to give (8) as needles, m.p. 125.5—126.5 °C (Found: *m/e*, 383.1454. $C_{17}H_{23}N_2O_8$ requires $M^+ + 1$, 383.1419), $\nu_{max.}$ ($CHCl_3$) 3 415 (NH), and 1 758 cm^{-1} (C=O); δ($CDCl_3$) 1.51 (3 H, d, *J* 6.5 Hz, CH*Me*), 1.74—1.91 (2 H, m, 4-CH_2), 3.29 and 3.31 (each 3 H, each s, 2 × OMe), 3.41 (1 H, ddd, *J* 10.1, 5.1, and 1.4 Hz, 3-H), 3.73—3.97 (1 H, m, 4-H), 4.43 [1 H, t, *J* 4.9 Hz, *CH*($OMe)_2$], 5.06 (1 H, dq, *J* 10.1 and 6.5 Hz, *CH*Me), 5.22 (2 H, s, $CH_2C_6H_4NO_2$), 6.23 (1 H, s, NH), 7.51 (2 H, d, *J* 9.1 Hz, 2 × ArH), and 8.20 (2 H, d, *J* 9.1 Hz, 2 × ArH); *m/e* 383 ($M^+ + 1$).

(±)-4β-*Formylmethyl*-3β-[(1S*)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]*azetidin*-2-*one* (9).—A solution of the acetal (8) (1 g) in 80% acetic acid (30 ml) was stirred for 4 h at 55—60 °C. Evaporation of the solvent afforded a pale yellowish syrup which was subjected to chromatography on silica gel. Elution with benzene–acetone (9 : 1 v/v) gave the *aldehyde* (9) (695 mg, 79%) as needles, m.p. 133—134 °C (from n-hexane–ethyl acetate) (Found: C, 53.15; H, 4.9; N, 7.85. $C_{15}H_{16}N_2O_7$ requires C, 53.55; H, 4.8; N, 8.35%), $\nu_{max.}$ ($CHCl_3$) 3 420 (NH), 1 765, 1 750, and 1 720 cm^{-1} (C=O); δ($CDCl_3$) 1.51 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.63—2.98 (2 H, m, CH_2CHO), 3.50 (1 H, ddd, *J* 10.5, 5.2, and 1.4 Hz, 3-H), 4.04—4.27 (1 H, m, 4-H), 5.04 (1 H, dq, *J* 10.5 and 6.5 Hz, *CH*Me), 5.24 (2 H, s, CH_2-$C_6H_4NO_2$), 6.21 (1 H, s, NH), 7.50 (2 H, d, *J* 9.1 Hz, 2 × ArH), 8.21 (2 H, d, *J* 9.1 Hz, 2 × ArH), and 9.74 (1 H, s, CHO); *m/e* 337 ($M^+ + 1$).

(±)-4β-*Carboxymethyl*-3β-[(1S*)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]*azetidin*-2-*one* (10).—To a stirred solution of the aldehyde (9) (695 mg) in acetone (30 ml) at 0 °C was added 8N-Jones reagent dropwise until the orange colour persisted. After addition of an excess of isopropyl alcohol, the solvent was evaporated off. The residue was taken up in chloroform and washed with brine. After drying (Na_2SO_4), the solvent was evaporated off and the residue was subjected to chromatography on silica gel. Elution with benzene–acetone (17 : 3 v/v) afforded the *acid* (10) (590 mg, 81%) as a powder (Found: C, 49.9; H, 4.45; N, 7.35. $C_{15}H_{16}N_2O_8 \cdot 0.5H_2O$ requires C, 49.85; H, 4.75; N, 7.75%), $\nu_{max.}$ ($CHCl_3$) 3 240 (NH), 3 000—2 500 (CO_2H), 1 750, and 1 700 cm^{-1} (C=O); δ{$CDCl_3$–[$^2H_6$]DMSO (6 : 1 v/v)} 1.43

(3 H, d, *J* 6.5 Hz, CH*Me*), 2.50 (2 H, d, *J* 7 Hz, CH_2CO_2H), 3.80—4.20 (1 H, m, 4-H), 5.03 (1 H, dq, *J* 10.1 and 6.5 Hz, *CH*Me), 5.27 (2 H, s, $CH_2C_6H_4NO_2$), 7.60 (2 H, d, *J* 9 Hz, 2 × ArH), 7.97 (1 H, s, NH), and 8.18 (2 H, d, *J* 9 Hz, 2 × ArH); *m/e* (FD) 352 (M^+) and 353 ($M^+ + 1$).

(±)-3β-[(1S*)-1-(p-*Nitrobenzyloxycarbonyloxy*)*ethyl*]-4β-(3-p-*nitrobenzyloxycarbonyl*-2-*oxopropyl*)*azetidin*-2-*one* (11).—To a solution of the acid (10) (526 mg, 1.5 mmol) in dry tetrahydrofuran (20 ml) was added *NN'*-carbonyldiimidazole (300 mg, 1.9 mmol). After stirring for 4 h at room temperature under nitrogen, a solution of the magnesium salt of the mono-*p*-nitrobenzyl ester of malonic acid (822 mg, 1.6 mmol) in dry tetrahydrofuran (10 ml) was added and the resulting mixture was stirred for 12 h at room temperature under nitrogen. After filtration followed by evaporation of the filtrate, the residue was subjected to chromatography on silica gel. Elution with benzene–acetone (9 : 1 v/v) gave the β-*keto-ester* (11) (600 mg, 76%) as a powder (Found: C, 54.2; H, 4.3; N, 7.75. $C_{24}H_{23}N_3O_{11}$ requires C, 54.45; H, 4.4; N, 7.95%), $\nu_{max.}$ 3 410 (NH), 1 750, and 1 720 cm^{-1} (C=O); δ($CDCl_3$) 1.49 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.79 (1 H, dd, *J* 18.2 and 9.1 Hz, 4-CH_2CO), 2.99 (1 H, dd, *J* 18.2 and 4.7 Hz, 4-CH_2CO), 3.40—3.60 (1 H, m, 3-H), 3.50 (2 H, s, $COCH_2CO_2$), 3.97—4.23 (1 H, m, 4-H), 4.86—5.29 (1 H, m, *CH*Me), 5.24 (4 H, s, 2 × $CH_2C_6H_4NO_2$), 6.10 (1 H, s, NH), 7.50 (2 H, d, *J* 9.1 Hz, 2 × ArH), 7.54 (2 H, d, *J* 9.1 Hz, 2 × ArH), and 8.21 (4 H, d, *J* 9.1 Hz, 4 × ArH); *m/e* (FD) 529 (M^+) and 530 ($M^+ + 1$).

(±)-4β-(3-*Diazo*-3-p-*nitrobenzyloxycarbonyl*-2-*oxopropyl*)-3β-[(1S*)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]*azetidin*-2-*one* (12).—To an ice-cooled solution of the above β-keto-ester (11) (500 mg, 0.9 mmol) and toluene-*p*-sulphonyl azide (205 mg, 1 mmol) in dry acetonitrile (20 ml) under nitrogen, was added a solution of triethylamine (334 mg, 3.3 mmol) in dry acetonitrile (3 ml) and the resulting mixture was stirred for 1.5 h at room temperature. Evaporation of the solvent gave a residue which was subjected to chromatography on silica gel. Elution with benzene–acetone (9 : 1 v/v) afforded the diazo-compound (12) (490 mg, 93%) as a powder, $\nu_{max.}$ ($CHCl_3$) 3 410 (NH), 2 135 (diazo), 1 760, 1 750, and 1 710 cm^{-1} (C=O); δ{$CDCl_3$–[$^2H_6$]DMSO (5 : 1 v/v)} 1.50 (3 H, d, *J* 6.5 Hz, CH*Me*), 3.41 (1 H, dd, *J* 10.4 and 5.1 Hz, 3-H), 3.97—4.25 (1 H, m, 4-H), 5.05 (1 H, dq, *J* 10.4 and 6.5 Hz, *CH*Me), 5.25 and 5.33 (each 2 H, each s, 2 × $CH_2C_6H_4NO_2$), 7.54 (4 H, d, *J* 9 Hz, 4 × ArH), 8.18 (2 H, d, *J* 9 Hz, 2 × ArH), and 8.20 (2 H, d, *J* 9 Hz, 2 × ArH).

p-*Nitrobenzyl* (±)-cis-6β-[(1S*)-1-(p-*Nitrobenzyloxycarbonyloxy*)*ethyl*]-3,7-*dioxo*-1-*azabicyclo*[3.2.0]*heptane*-2-*carboxylate* (13).—A mixture of the diazo-compound (12) (490 mg, 0.88 mmol) and a catalytic amount of rhodium(II) acetate in dry benzene (30 ml) was heated for 0.5 h at 80 °C under nitrogen. After cooling to room temperature followed by filtration, evaporation of the solvent gave a residue which was subjected to chromatography on silica gel. Elution with benzene–acetone (9 : 1 v/v) gave the 3-*oxocarbapenam* (13) (430 mg, 92%) as a syrup (Found: C, 54.6; H, 4.05; N, 7.75. $C_{24}H_{21}N_3O_{11}$ requires C, 54.65; H, 4.0; N, 7.95%), $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 740 cm^{-1} (C=O); δ($CDCl_3$) 1.52 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.74 (2 H, d, *J* 8 Hz, 4-H_2), 3.92 (1 H, dd, *J* 10 and 5 Hz, 6-H), 4.27 (1 H, dt, *J* 5 and 8 Hz, 5-H), 4.69 (1 H, s, 2-H), 5.00—5.46 (5 H, m, 2 × $CH_2C_6H_4NO_2$ and *CH*Me), 7.48 (2 H, d, *J* 9 Hz, 2 × ArH), 7.50 (2 H, d, *J* 9 Hz, 2 × ArH), and 8.22 (4 H, d, *J* 9 Hz, 4 × ArH); *m/e* (FD) 527 (M^+).

p-*Nitrobenzyl* (±)-cis-3-(2-*Acetamidoethylthio*)-6β-[(1S*)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (15).—To a stirred and ice-cooled solution of the above 3-oxocarbapenam (13) (120 mg, 0.23 mmol) in dry acetonitrile (2 ml) under nitrogen, was added a solution of di-isopropylethylamine (45.4 mg, 0.34 mmol) in dry acetonitrile (2 ml), and a solution of diphenyl chlorophosphate (18.9 mg, 0.28 mmol) in dry acetonitrile (2 ml) was then added to the above mixture. After stirring for 10 min at 0 °C, solutions of di-isopropylethylamine (121.1 mg, 0.94 mmol) in dry acetonitrile (2 ml) and of *N*-acetylcysteamine (34.1 mg, 0.32 mmol) in dry acetonitrile (2 ml) were added. The resulting mixture was stirred for 1 h at 0 °C. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with benzene–ethyl acetate (7 : 3 v/v) afforded a syrup, which was further chromatographed on Bio-Beads S-X3 (Bio-Rad Laboratories) using acetone as eluant to give the *epithienamycin A derivative* (15) (114 mg, 80%) as a pale yellowish syrup (Found: C, 53.25; H, 4.4; N, 8.65. $C_{28}H_{28}N_4O_{11}S$ requires C, 53.5; H, 4.5; N, 8.9%), $\nu_{max.}$ (CH_2Cl_2) 3 450 (NH), 1 782, 1 750, 1 700, and 1 675 cm^{-1} (C=O); δ($CDCl_3$) 1.53 (3 H, d, *J* 6.5 Hz, CH*Me*), 1.95 (3 H, s, COMe), 2.72—3.54 (6 H, m, SCH_2CH_2N and 4-H_2), 3.80 (1 H, dd, *J* 10 and 5 Hz, 6-H), 4.31 (1 H, dt, *J* 9 and 5 Hz, 5-H), 4.94—5.57 (5 H, m, 2 × $CH_2C_6H_4NO_2$ and *CH*Me), 5.76—6.05 (1 H, m, NH), 7.52 (2 H, d, *J* 9 Hz, 2 × ArH), 7.60 (2 H, d, *J* 9 Hz, 2 × ArH), 8.18 (2 H, d, *J* 9 Hz, 2 × ArH), and 8.21 (2 H, d, *J* 9 Hz, 2 × ArH); *m/e* (FD) 628 (M^+) and 629 ($M^+ + 1$).

p-*Nitrobenzyl* (±)-cis-3-[(E)-2-*Acetamidovinylthio*]-6β-[(1S*)-1-(p-*nitrobenzyloxycarbonyloxy*)*ethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (16).—To a stirred and ice-cooled solution of the 3-oxocarbapenam (13) (40 mg, 0.076 mmol) and a catalytic amount of 4-dimethylaminopyridine in dry acetonitrile (5 ml) under nitrogen, was added a solution of di-isopropylethylamine (12.1 mg, 0.094 mmol) in dry acetonitrile (0.5 ml) followed by a solution of diphenyl chlorophosphate (22.1 g, 0.082 mmol) in dry acetonitrile (0.5 ml). After stirring for 10 min at 0 °C, an excess of sodium iodide (114 mg, 0.76 mmol) and silver (*E*)-2-acetamidoethylenethiolate [12] (25 mg, 0.112 mmol) were added. The mixture was stirred for 2.5 h at 0 °C. After filtration followed by evaporation of the filtrate, the residue was subjected to chromatography on silica gel. Elution with benzene–ethyl acetate (7 : 3 to 6 : 4 v/v) afforded the *epithienamycin B derivative* (16) (39 mg, 82%) as a pale yellowish syrup (Found: C, 53.85; H, 4.35; N, 8.55. $C_{28}H_{26}N_4O_{11}S$ requires C, 53.65; H, 4.2; N, 8.95%), $\nu_{max.}$ ($CHCl_3$) 3 440 (NH), 1 785, 1 750, and 1 705 cm^{-1} (C=O); δ($CDCl_3$) 1.56 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.09 (3 H, s, COMe), 2.97 (1 H, dd, *J* 10 and 19 Hz, 4-H), 3.17 (1 H, dd, *J* 9 and 19 Hz, 4-H), 3.80 (1 H, dd, *J* 5 and 10 Hz, 6-H), 4.24 (1 H, m, 5-H), 4.96—5.55 (5 H, m, 2 × CH_2-$C_6H_4NO_2$ and *CH*Me), 5.86 (1 H, d, *J* 13.5 Hz, SC*H*=CH), 7.18 (1 H, dd, *J* 11.5 and 13.5 Hz, HNC*H*=CH), 7.40—7.72 (5 H, m, 4 × ArH and NH), 8.18 (2 H, d, *J* 9 Hz, 2 × ArH), and 8.20 (2 H, d, *J* 9 Hz, 2 × ArH).

p-*Nitrobenzyl* (±)-cis-6β-[(1S*)-1-(p-*Nitrobenzyloxycarbonyloxy*)*ethyl*]-7-*oxo*-3-*phenylthio*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (17).—The 3-oxocarbapenam (13) (34 mg, 0.065 mmol) was treated with di-isopropylethylamine (10.3 mg, 0.08 mmol) and diphenyl chlorophosphate (19 mg, 0.071 mmol) in dry acetonitrile (4 ml) as for compound (15). After formation of the phosphate, di-

isopropylethylamine (33 mg, 0.256 mmol) and a solution of thiophenol (7.5 mg, 0.068 mmol) in dry acetonitrile (2 ml) were added, and the mixture was stirred for 1 h at 0 °C. After evaporation of the solvent, the residue was purified by chromatography on silica gel. Elution with benzene–acetone (49 : 1 v/v) gave the carbapenem (17) (32 mg, 80%) as a yellowish syrup, $\nu_{max.}$ ($CHCl_3$) 1 785, 1 750, and 1 700 cm^{-1} (C=O); δ($CDCl_3$) 1.46 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.44 (1 H, dd, *J* 10 and 19 Hz, 4-H), 2.90 (1 H, dd, *J* 9 and 19 Hz, 4-H), 3.74 (1 H, dd, *J* 5.5 and 10 Hz, 6-H), 4.18 (1 H, ddd, *J* 5.5, 9, and 10 Hz, 5-H), 4.97—5.15 (1 H, m, C*H*Me), 5.15 (2 H, s, $CH_2C_6H_4NO_2$), 5.26 (1 H, d, *J* 12.5 Hz, $CH_2C_6H_4NO_2$), 5.52 (1 H, d, *J* 12.5 Hz, CH_2-$C_6H_4NO_2$), 7.21—7.76 (9 H, m, 4 × ArH and 5 × ArH), 8.18 (2 H, d, *J* 9 Hz, 2 × ArH), and 8.22 (2 H, d, *J* 9 Hz, 2 × ArH); *m/e* (FD) 619 (M^+) and 620 (M^+ + 1).

p-*Nitrobenzyl* (±)-cis-3-[2-(p-*Nitrobenzyloxycarbonylamino*)*ethylthio*]-6β-[(1S*)-1-(p-*nitrobenzyloxycarbonyloxy*)-*ethyl*]-7-*oxo*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (18).—The 3-oxocarbapenam (13) (100 mg, 0.19 mmol) was treated with di-isopropylethylamine (30.3 mg, 0.23 mmol) and diphenyl chlorophosphate (63.1 mg, 0.23 mmol) in dry acetonitrile (9 ml) as for compound (15). After formation of the phosphate, di-isopropylethylamine (101 mg, 0.78 mmol) in dry acetonitrile (2 ml) and a solution of *N*-*p*-nitrobenzyloxycarbonylcysteamine (67 mg, 0.26 mmol) in dry acetonitrile (2 ml) were added. The mixture was stirred for 1 h at 0 °C. Evaporation of the solvent gave a syrup which was subjected to chromatography on silica gel. Elution with benzene–ethyl acetate (4 : 1 v/v) afforded a syrup which was further chromatographed on Bio-Beads S-X3 (Bio-Rad Laboratories) using acetone as eluant to give the *epithienamycin A derivative* (18) (120 mg, 83%) as a pale yellowish syrup (Found: C, 53.1; H, 4.05; N, 9.05. $C_{34}H_{31}N_5O_{14}S$ requires C, 53.3; H, 4.1; N, 9.15%), $\nu_{max.}$ (CH_2Cl_2) 3 450 (NH), 1 782, 1 750, 1 730, and 1 700 cm^{-1} (C=O); δ($CDCl_3$) 1.53 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.61—3.64 (6 H, m, SCH_2CH_2N and 4-H), 3.82 (1 H, dd, *J* 9.7 and 5.1 Hz, 6-H), 4.13—4.43 (1 H, m, 5-H), 4.97—5.60 (7 H, m, 3 × $CH_2C_6H_4NO_2$ and C*H*Me), 7.35—7.69 (6 H, m, 6 × ArH), 8.19 (4 H, d, *J* 9 Hz, 4 × ArH), and 8.20 (2 H, d, *J* 9 Hz, 2 × ArH); *m/e* (FD) 765 (M^+).

(±)-*Epithienamycin A* (2).—A mixture of the diprotected epithienamycin A (15) (30 mg) in tetrahydrofuran (3 ml), 0.0319M-aqueous sodium hydrogencarbonate (1.5 ml) and Adams catalyst (10 mg) was shaken for 1.5 h under hydrogen (40 lbf in^{-2}) at room temperature. After filtration, the filtrate was washed with ether at <5 °C and then evaporated to remove any residual organic solvents. The aqueous solution, containing the sodium salt of epithienamycin A (2) (13.6 mg, 85%) (based on hydroxylamine-extinguishable u.v. absorption at 298 nm), was subjected to a Sephadex G-10 (Pharmacia Fine Chemicals) chromatography using water as eluant. The fractions ($\lambda_{max.}$ 298 nm) were combined and lyophilized to give (2) (8 mg, 50%) as a pale brownish solid, identical (i.r., n.m.r., and u.v. spectra) with an authentic sample.[4,6]

(±)-*Epithienamycin B* (3).—A mixture of the diprotected epithienamycin B (16) (30 mg) in tetrahydrofuran (2 ml), 0.048M-aqueous sodium hydrogencarbonate (1 ml), and Adams catalyst (10 mg) was shaken for 1 h under hydrogen (40 lbf in^{-2}) at room temperature. After work-up and purification as above, the fractions ($\lambda_{max.}$ 308 nm) gave the sodium salt of epithienamyin B (3) (10 mg, 62.5%) as a pale brownish solid, identical (i.r., n.m.r., and u.v. spectra) with an authentic sample.[4,6]

Sodium (±)-cis-6β-[(1S*)-1-*Hydroxyethyl*]-7-*oxo*-3-*phenylthio*-1-*azabicyclo*[3.2.0]*hept*-2-*ene*-2-*carboxylate* (19).—A mixture of the carbapenem (17) (42 mg) in tetrahydrofuran (2 ml), 0.068M-aqueous sodium hydrogen carbonate (1 ml) and Adams catalyst (10 mg) was shaken for 40 min under hydrogen (40 lbf in^{-2}) at room temperature. Work-up and purification as for epithienamycin A afforded the sodium salt of the carbapenem acid (19) ($\lambda_{max.}$ 302 nm) (15 mg, 68.2%) as a pale brownish solid, δ(D_2O) 1.31 (3 H, d, *J* 6.5 Hz, CH*Me*), 2.56 (1 H, dd, *J* 10 and 18.5 Hz, 4-H), 2.96 (1 H, dd, *J* 9 and 18.5 Hz, 4-H), 3.59 (1 H, dd, *J* 5.5 and 10 Hz, 6-H), 3.81 (s, D_2O), 3.90—4.39 (2 H, m, 5-H and C*H*Me), and 7.07—7.98 (5 H, m, 5 × ArH).

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