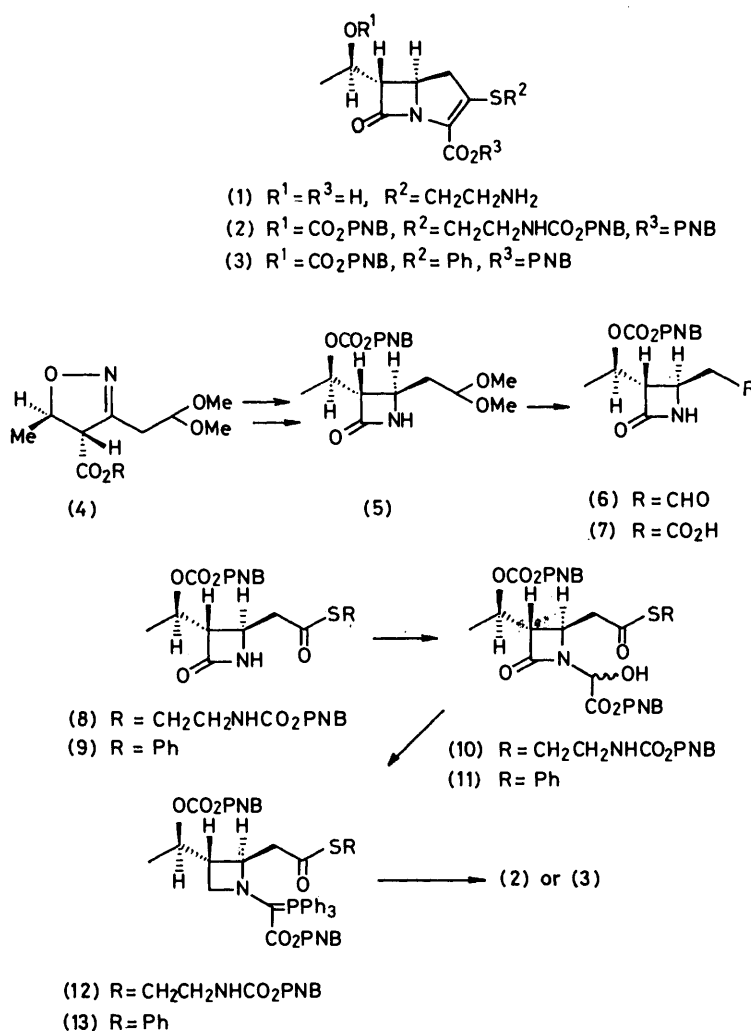


## Studies on the Syntheses of Heterocyclic Compounds. Part 877.<sup>1</sup> An Alternative Synthesis of Protected ( $\pm$ )-Thienamycin and a Related Compound

By Tetsuji Kametani,\* Shyh-Pyng Huang, Takayasu Nagahara, Shuichi Yokohama, and Masataka Ihara, Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

An alternative total synthesis of protected ( $\pm$ )-thienamycin (2) and an analogue is described. ( $\pm$ )-4 $\beta$ -(2,2-Dimethoxyethyl)-3 $\alpha$ -[(1*R*')-1-(*p*-nitrobenzyloxycarbonyloxy)ethyl]azetidin-2-one (5), prepared from isoxazoline derivatives (4), was converted into the 2-(*p*-nitrobenzyloxycarbonylamino)ethyl (12) and phenyl (13) thioester phosphoranes. Intramolecular Wittig reaction of (12) and (13) produced the corresponding carbanions (2) and (3) in poor yield. Effective transformation of (5) into the *p*-nitrobenzyl-protected thienamycin derivative (2) and the analogue (3) was achieved employing a carbene insertion reaction and subsequent introduction of the sulphide moiety.

In 1976, the Merck research group announced the discovery, isolation, and structure elucidation of thienamycin (1) and reported it to possess exceptionally potent and broad-spectrum antibacterial activity.<sup>2</sup> Since then, several analogues, epithienamycins,<sup>3</sup> olivanic acids,<sup>4</sup> PS-5,<sup>5</sup> and MC 696-SY2A,<sup>6</sup> have been isolated from broths



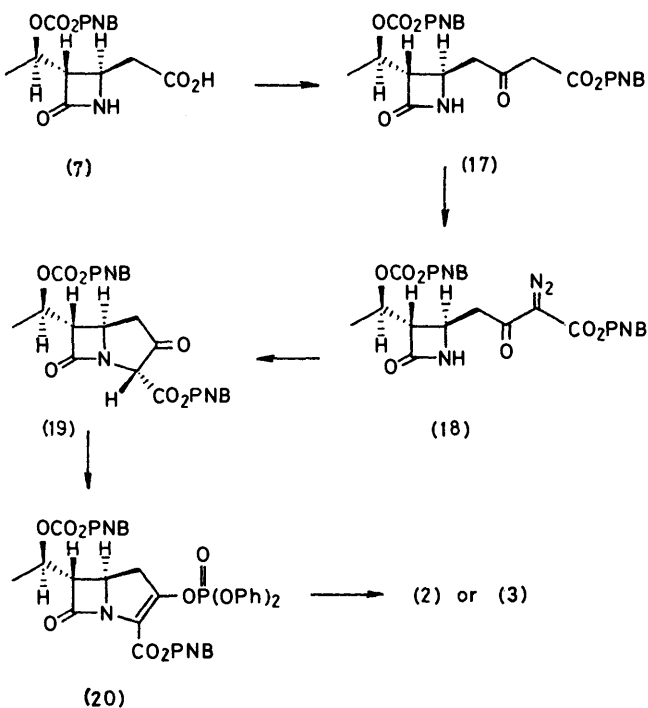
PNB = *p*-nitrobenzyl  
 SCHEME 1

of *Streptomyces* strains and these have also shown interesting biological activity. These discoveries have promoted a considerable amount of synthetic effort resulting in the total synthesis of thienamycin<sup>7,8</sup> and its analogues.<sup>9-12</sup> We have recently developed an efficient synthesis of  $\beta$ -lactam derivatives, through isoxazoline (4), leading to a formal total synthesis of thienamycin.<sup>13,14</sup> Our synthetic intermediate (5) has the following advantages: a hydroxyethyl group at C-3 with the correct stereochemical arrangement, and a 2,2-dimethoxyethyl group at C-4 which is readily convertible, *via* the aldehyde, to the carboxylic acid. We therefore undertook its conversion into the *p*-nitrobenzyl-protected thienamycin derivative (2)<sup>7</sup> employing the intramolecular Wittig reaction<sup>10,15,16</sup> and the carbene insertion reaction.<sup>8,12</sup> We now report the facile synthesis of protected ( $\pm$ )-thienamycin and an analogue.<sup>17</sup>

Hydrolysis of the acetal (5) with hot aqueous acetic acid followed by Jones oxidation of the resulting aldehyde (6) at 0 °C, quantitatively produced the corresponding acid (7). Transformation of (7) to the thioesters (8) and (9) was carried out under a variety of conditions. The best results were obtained from treatment of (7) with thiols in the presence of carbodi-imides and 4-dimethylaminopyridine.<sup>18</sup> *NN'*-Di-isopropylcarbodi-imide was used for the production of the 2-(*p*-nitrobenzyloxycarbonylamino)ethyl thioester (8), while *NN'*-dicyclohexylcarbodi-imide was selected as the condensing agent in the synthesis of the phenyl thioester (9) in order to facilitate the removal of the urea derivative by column chromatography. The phosphoranes (12) and (13) were prepared by established procedures,<sup>15</sup> namely condensation of the thioesters (8) and (9) with *p*-nitrobenzyl

lutidine, and then treatment with triphenylphosphine in the presence of the same base.

After vigorous reflux of the phosphorane (12) for 44 h in dry toluene in the presence of a catalytic amount of



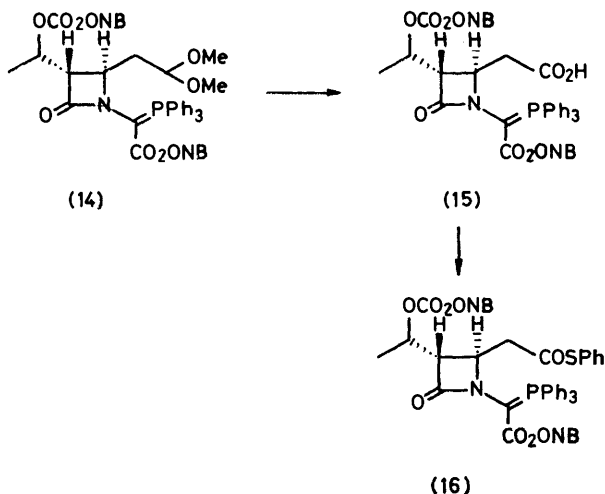
PNB = *p*-nitrobenzyl

SCHEME 2

hydroquinone,<sup>16</sup> the formation of a small amount of the desired carbapenem derivative (2)<sup>7</sup> was detected by t.l.c. and h.p.l.c. analysis. However, the product (2) readily decomposed under these reaction conditions, with unidentified products being obtained on work-up. This method proved more successful for the conversion of the phenyl thioester phosphorane (13) into the corresponding 2-thiophenylcarbapenem (3). Thus, after reflux for 60 h under the above conditions, the carbapenem (3) was obtained along with recovered starting material (13).

Furthermore, transformation of the acetal phosphorane (14), which was prepared as described previously,<sup>13</sup> into the thioester (16) was attempted. After conversion of the acetal group into the aldehyde,<sup>13</sup> Jones oxidation produced the acid (15). Treatment with diethyl chlorophosphate and triethylamine, followed by reaction with thallium(I) phenylthiolate<sup>19</sup> yielded the thioester (16). Because oxidation of the aldehyde phosphorane was difficult, this procedure proved less efficient for the synthesis of thioesters.

A much more effective synthesis of the carbapenems (2) and (3) from the acid (7) was achieved on applying a carbene insertion reaction followed by introduction of the sulphide moiety, a method recently developed by the



ONB = *o*-nitrobenzyl

glyoxylate ethyl hemiacetal in the presence of molecular sieves, followed by chlorination of the resulting epimeric alcohols (10) and (11) with thionyl chloride and 2,6-

Merck research group.<sup>8,12</sup> After treatment of the carboxylic acid (7) with *NN'*-carbonyldi-imidazole,<sup>20</sup> the imidazolide formed was treated with the magnesium salt of the mono-*p*-nitrobenzyl ester of malonic acid<sup>7</sup> to give the  $\beta$ -keto-ester (17) in good yield. By diazo-exchange with toluene-*p*-sulphonyl azide in the presence of triethylamine in acetonitrile, the ester (17) produced the diazo-compound (18). Decomposition of the carbene precursor (18) was carried out by refluxing in benzene in the presence of a catalytic amount of rhodium(II) acetate, leading to quantitative formation of the carbapenam (19). Treatment of (19) with diphenyl chlorophosphate in the presence of 1 molar equivalent of di-isopropylethylamine and a catalytic amount of 4-dimethylaminopyridine in acetonitrile at 0 °C, followed by *in situ* reaction of the resulting phosphate (20) with di-isopropylethylamine and *N*-(*p*-nitrobenzyloxycarbonyl)cysteamine at -15 °C, afforded the protected thienamycin derivative (2)<sup>7</sup> in good yield. The synthetic product (2) was identical with an authentic sample (provided by Dr. B. G. Christensen) by comparison of the i.r. and n.m.r. spectra and t.l.c. and h.p.l.c. behaviours.

Reaction of the above phosphate (20) with thiophenol in the presence of di-isopropylethylamine gave the carbapenam (3).

Thus, facile syntheses of protected ( $\pm$ )-thienamycin and an analogue, through isoxazoline derivatives,<sup>13,14</sup> have been accomplished.

#### EXPERIMENTAL

I.r. spectra were obtained with a Hitachi 260-10 spectrometer, n.m.r. spectra with JEOL-PMX-60 and JEOL-PS-100 spectrometers (tetramethylsilane as internal reference), and mass spectra with Hitachi M-52G and JEOL-JMS-01SG-2 spectrometers. High-pressure liquid chromatography was carried out using a Hitachi 635 instrument monitored by u.v. absorption and refractive index measurements.

( $\pm$ )-4 $\beta$ -Carboxymethyl-3 $\alpha$ -[(1*R*\*)-1-(*p*-nitrobenzyloxy)carbonyloxy]ethyl]azetid-2-one (7).—A solution of the acetal (5)<sup>13</sup> (1.65 g) in 80% acetic acid (30 ml) was stirred for 4 h at 55–60 °C. Evaporation of the solvent afforded the crude aldehyde (6) as a pale yellowish syrup,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 760, 1 750, and 1 720 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.48 (3 H, d, *J* 6.5 Hz, CHMe), 3.00 (3 H, m, CH<sub>2</sub>CHO and 3-H), 4.08 (1 H, m, 4-H), 5.20 (1 H, m, CHMe), 5.30 (2 H, s, CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>), 6.60 (1 H, s, NH), 7.68 (2 H, d, *J* 9 Hz, 2  $\times$  ArH), 8.28 (2 H, d, *J* 9 Hz, 2  $\times$  ArH), and 9.91 (1 H, s, CHO).

To a stirred solution of the above aldehyde (6) in acetone (30 ml) at 0 °C was added 8*N* 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<sub>2</sub>SO<sub>4</sub>), the solvent was evaporated off to give the carboxylic acid (7) (1.40 g) as a syrup (Found: C, 48.65; H, 4.9; N, 7.55. C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>8</sub>·H<sub>2</sub>O requires C, 48.65; H, 4.6; N, 7.9%),  $\nu_{\max}$  (CHCl<sub>3</sub>) 3 420 (NH), 1 755, 1 745, and 1 720 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.40 (3 H, d, *J* 6 Hz, CHMe), 2.40–2.90 (2 H, m, 4-CH<sub>2</sub>), 2.97–3.27 (1 H, m, 3-H), 3.70–4.17 (1 H, m, 4-H), 7.12br (1 H, s, NH),

7.45br (1 H, s, OH), 7.53 (2 H, d, *J* 9 Hz, 2  $\times$  ArH), and 8.18 (2 H, d, *J* 9 Hz, 2  $\times$  ArH).

( $\pm$ )-4 $\beta$ -{[2-(*p*-Nitrobenzyloxycarbonylamino)ethylthio]carbonylmethyl}-3 $\alpha$ -[(1*R*\*)-1-(*p*-nitrobenzyloxy)carbonyloxy]ethyl]azetid-2-one (8).—To a stirred and ice-cooled solution of the carboxylic acid (7) (1.40 g), 4-dimethylaminopyridine (60 mg), and *p*-nitrobenzyloxycarbonylcysteamine (1.53 g) in dry methylene chloride (50 ml) under nitrogen, was slowly added a solution of *NN'*-di-isopropylcarbodi-imide (1.00 g) in dry methylene chloride (10 ml). The mixture was stirred for 30 min at 0 °C and then for 3 h at room temperature. After filtration to remove the urea formed, the combined filtrate and washings were washed with brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of the solvent gave a residue which was chromatographed on silica gel. Elution with benzene–acetone (10 : 1) afforded the thioester (8) (900 mg) as a pale yellowish syrup (Found: C, 50.3; H, 4.45; N, 9.0. C<sub>25</sub>H<sub>26</sub>N<sub>4</sub>O<sub>11</sub>·0.5H<sub>2</sub>O requires C, 50.1; H, 4.55; N, 9.35%),  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 760, 1 750, and 1 680 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.40 (3 H, d, *J* 6 Hz, CHMe), 2.75–3.60 (7 H, m, CH<sub>2</sub>COS-CH<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub> and 3-H), 3.92 (1 H, m, 4-H), 4.65–5.57 (6 H, m, CHMe, 2  $\times$  CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>, and NHCO<sub>2</sub>), 6.53 (1 H, s, NH), and 7.13, 7.16, 8.13, and 8.16 (each 2 H, each d, each *J* 9 Hz, 8  $\times$  ArH); FD mass *m/e* 591 (*M*<sup>+</sup> + 1).

( $\pm$ )-3 $\alpha$ -[(1*R*\*)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-4 $\beta$ -[(phenylthio)carbonylmethyl]azetid-2-one (9).—To a stirred and ice-cooled solution of the carboxylic acid (7) (106 mg), 4-dimethylaminopyridine (2 mg), and thiophenol (66 mg) in dry methylene chloride under nitrogen, was slowly added a solution of *NN'*-dicyclohexylcarbodi-imide (61.8 mg) in dry methylene chloride (2 ml). The mixture was stirred for 30 min at 0 °C and then for 3 h at room temperature. After filtration followed by evaporation of the filtrate, the residue was subjected to chromatography on silica gel. Elution with benzene–acetone (19 : 1) gave the phenyl thioester (9) (67 mg) as a pale yellowish syrup,  $\nu_{\max}$  (CHCl<sub>3</sub>) 3 440 (NH), 1 765, 1 750, and 1 700 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.43 (3 H, d, *J* 6.5 Hz, CHMe), 2.83–3.26 (3 H, m, 4-CH<sub>2</sub> and 3-H), 3.66–4.16 (1 H, m, 4-H), 6.23br (1 H, s, NH), 7.26–7.63 (7 H, m, 7  $\times$  ArH), and 8.16 (2 H, d, *J* 9 Hz, 2  $\times$  ArH); *m/e* 444 (*M*<sup>+</sup>) (Found: *M*<sup>+</sup>, 444.0946. C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub>S requires 444.0991).

( $\pm$ )-4 $\alpha$ -{[2-(*p*-Nitrobenzyloxycarbonylamino)ethylthio]carbonylmethyl}-3 $\beta$ -[(1*R*\*)-1-(*p*-nitrobenzyloxy)carbonyloxy]ethyl]-1-[*p*-nitrobenzyloxycarbonyl(triphenylphosphoranylidene)methyl]azetid-2-one (12).—A solution of the thioester (8) (414 mg) and *p*-nitrobenzyl glyoxylate ethyl hemiacetal<sup>15</sup> (537 mg) in toluene–dimethylformamide (4 : 1 v/v; 30 ml) was stirred for 12 h at room temperature and then for 4 h at 50 °C in the presence of 3A molecular sieves [2.7 g; activated at 250 °C (2 mmHg)] under nitrogen. After filtration, the filtrate was evaporated to give a residue which was subjected to chromatography on silica gel. Elution with benzene–acetone (19 : 1) yielded the epimeric alcohols (10) (432 mg) as a pale yellowish syrup,  $\nu_{\max}$  (CHCl<sub>3</sub>) 3 425 (OH), 1 750, and 1 670 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.37 (3 H, d, *J* 6 Hz, CHMe), 2.60–3.70 (8 H, m, CH<sub>2</sub>COSCH<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>, 3-H, and OH), 4.10 (1 H, m, 4-H), 4.70–5.67 (8 H, m, CHMe, 3  $\times$  CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>, and NHCO<sub>2</sub>), and 7.45 and 8.12 (each 6 H, each d, *J* 9 Hz, 12  $\times$  ArH).

To a stirred solution of the above alcohols (10) (388 mg) and 2,6-lutidine (207 mg) in dry tetrahydrofuran (30 ml) at -15 °C under nitrogen was slowly added a solution of thionyl chloride (173 mg) in dry tetrahydrofuran (10 ml). The mixture was stirred for 30 min at -15 °C and then for

30 min at 0 °C. After filtration, the filtrate was evaporated. The residue was dissolved in dry dioxan (30 ml), and triphenylphosphine (254 mg) and 2,6-lutidine (156 mg) were added. The resulting mixture was stirred for 12 h at room temperature and then for 3 h at 50 °C under nitrogen. After filtration, the filtrate was evaporated to give a residue which was subjected to chromatography on silica gel. Elution with benzene-ethyl acetate (4:1) afforded the *phosphorane* (12) (410 mg) as a powder (Found: C, 59.6; H, 4.6.  $C_{52}H_{25}N_5O_{15}$ PS requires C, 59.8; H, 4.45%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1758, 1730, and 1610 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 5.17br (6 H, s, 3 × CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>), 7.45 (15 H, s, 15 × ArH), and 7.18–8.26 (12 H, m, 12 × ArH).

(±)-3 $\alpha$ -[(1R\*)-1-(*p*-Nitrobenzyloxy)ethyl]-1-[*p*-nitrobenzyloxy)carbonyl(triphenylphosphoranylidene)-methyl]-4 $\beta$ -[(phenylthio)carbonylmethyl]azetidin-2-one (13).—A solution of the phenyl thioester (9) (1.56 g) and *p*-nitrobenzyl glyoxylate ethyl hemiacetal (1.79 g) in toluene-dimethylformamide (4:1 v/v; 30 ml) was stirred for 12 h at room temperature and then for 5 h at 50 °C under nitrogen in the presence of activated molecular sieves (10 g). After filtration followed by evaporation of the solvents, the residue was subjected to chromatography on silica gel. Elution with benzene-acetone (19:1) afforded the epimeric alcohols (11) (1.24 g) as a syrup,  $\nu_{\max}$  3500 (OH), 1750, and 1740 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.40 (3 H, d, *J* 6.5 Hz, CHMe), 7.20–7.70 (9 H, m, 9 × ArH), and 8.15 (4 H, d, *J* 9 Hz, 4 × ArH).

To a stirred solution of the above alcohols (11) (65 mg) and 2,6-lutidine (22 mg) in dry tetrahydrofuran (2 ml) at –15 °C under nitrogen, was slowly added a solution of thionyl chloride (23 mg) in dry tetrahydrofuran (0.5 ml). The reaction temperature was allowed to rise to room temperature during 30 min. After filtration followed by evaporation of the filtrate, the residue was dissolved in dry dioxan (2 ml). After addition of 2,6-lutidine (22 mg) and triphenylphosphine (52 mg), the mixture was stirred for 15 h at room temperature and then for 15 h at 50 °C. After filtration, the filtrate was evaporated to give a residue which was subjected to chromatography on silica gel. Elution with benzene-ethyl acetate (4:1) afforded the *phosphorane* (13) (64.5 mg) as a syrup (Found: C, 63.0; H, 4.95; N, 4.55.  $C_{48}H_{46}N_3O_{11} \cdot H_2O$  requires C, 62.95; H, 4.6; N, 4.6%),  $\nu_{\max}$  (CHCl<sub>3</sub>) 1742 and 1620 cm<sup>-1</sup> (C=O).

(±)-3 $\alpha$ -[(1R\*)-1-(*p*-Nitrobenzyloxy)ethyl]-4 $\beta$ -(3-*p*-nitrobenzyloxy)carbonyl-2-oxopropyl)azetidin-2-one (17).—To a solution of the carboxylic acid (7) (90 mg) in dry tetrahydrofuran (3 ml) was added *NN'*-carbonyldiimidazole (46 mg). After stirring for 6 h at room temperature under nitrogen, a solution of the magnesium salt of the mono-*p*-nitrobenzyl ester of malonic acid<sup>8</sup> (77 mg) in dry tetrahydrofuran (3 ml) was added and the resulting mixture was stirred for 18 h at room temperature under nitrogen. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with benzene-acetone (17:3) gave the  $\beta$ -keto-ester (17) (96 mg) as a syrup (Found: C, 51.8; H, 4.7; N, 7.55.  $C_{24}H_{23}N_3O_{11} \cdot 1.5H_2O$  requires C, 51.5; H, 4.5; N, 7.6%),  $\nu_{\max}$  (CHCl<sub>3</sub>) 3420 (NH), 1765, 1750, and 1720 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.42 (3 H, d, *J* 6.5 Hz, CHMe), 3.57 (2 H, s, COCH<sub>2</sub>CO<sub>2</sub>), 3.70–4.15 (1 H, m, 4-H), 5.23 (4 H, s, 2 × CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>), 6.50br (1 H, s, NH), 7.48 (4 H, d, *J* 9 Hz, 4 × ArH), and 8.15 (4 H, d, *J* 9 Hz, 4 × ArH); FD mass *m/e* 530 (*M*<sup>+</sup> + 1).

(±)-*p*-Nitrobenzyl 6 $\alpha$ -[(1R\*)-1-(*p*-Nitrobenzyloxy)ethyl]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate

(19).—To an ice-cooled solution of the above  $\beta$ -keto-ester (17) (40 mg) and toluene-*p*-sulphonyl azide (16.4 mg) in dry acetonitrile (2 ml) under nitrogen, was added a solution of triethylamine (30.6 mg) in dry acetonitrile (1 ml). Evaporation of the solvent gave a residue which was subjected to chromatography on silica gel. Elution with benzene-acetone (19:1) afforded the diazo-compound (18) (40 mg) as a syrup,  $\nu_{\max}$  (CHCl<sub>3</sub>) 3420 (NH), 2130 (diazo), 1765 and 1720 (C=O), and 1350 cm<sup>-1</sup> (NO<sub>2</sub>);  $\delta$  (CDCl<sub>3</sub>) 1.45 (3 H, d, *J* 6.5 Hz, CHMe), 2.57–3.63 (3 H, m, 3-H and 4-CH<sub>2</sub>), 3.70–4.18 (1 H, m, 4-H), 5.25 (2 H, s, CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>), 5.37 (2 H, s, CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>), 6.30br (1 H, s, NH), 7.52 (4 H, d, *J* 9 Hz, 4 × ArH), 8.20 (2 H, d, *J* 9 Hz, 2 × ArH), and 8.23 (2 H, d, *J* 9 Hz, 2 × ArH).

A mixture of the above diazo-compound (18) (40 mg) and a catalytic amount of rhodium(II) acetate in dry benzene (5 ml) was heated for 1 h at 80 °C under nitrogen. After cooling to room temperature followed by filtration, evaporation of the solvent gave the 3-oxocarbapenam (19) (38 mg) as a syrup (Found: C, 54.35; H, 4.05; N, 7.7.  $C_{24}H_{21}N_3O_{11}$  requires C, 54.65; H, 4.0; N, 7.95%),  $\nu_{\max}$  (CHCl<sub>3</sub>) 1770 and 1750 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.52 (3 H, d, *J* 6.5 Hz, CHMe), 2.45 (1 H, dd, *J* 8 and 19 Hz, 4-H), 2.97 (1 H, dd, *J* 7 and 19 Hz, 4-H), 3.38 (1 H, dd, *J* 2 and 7 Hz, 6-H), 3.92–4.33 (1 H, m, 5-H), 4.77 (1 H, s, 2-H), 5.28br (4 H, s, 2 × CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>), 7.52 (4 H, d, *J* 9 Hz, 4 × ArH), and 8.22 (4 H, d, *J* 9 Hz, 4 × ArH); FD mass *m/e* 527 (*M*<sup>+</sup>).

(±)-*p*-Nitrobenzyl 3-[2-(*p*-Nitrobenzyloxy)carbonylamino-ethylthio]-6 $\alpha$ -[(1R\*)-1-(*p*-nitrobenzyloxy)ethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (2).—To a stirred and ice-cooled solution of the above 3-oxocarbapenam (19) (40 mg) and a catalytic amount of 4-dimethylaminopyridine in dry acetonitrile (2 ml) under nitrogen, was added a solution of di-isopropylethylamine (11.8 mg) in dry acetonitrile followed by a solution of diphenyl chlorophosphate (21.5 mg) in dry acetonitrile. After stirring for 1 h at 0 °C, di-isopropylethylamine (39.2 mg) and a solution of *N*-(*p*-nitrobenzyloxy)carbonyl)cysteamine (20.5 mg) in dry acetonitrile (2 ml) were added at –5 °C. The mixture was allowed to stand for 20 h at –15 °C. After evaporation of the solvent, the residue was subjected to chromatography on silica gel. Elution with benzene-acetone (9:1) afforded the *p*-nitrobenzyl-protected thienamycin (2) (41.5 mg) as a yellowish syrup, which was identical to an authentic sample (donated by Dr. B. G. Christensen) {n.m.r. (CDCl<sub>3</sub>) and i.r. (CH<sub>2</sub>Cl<sub>2</sub>) spectra and t.l.c. and h.p.l.c. [ $\mu$ -Bondapak-C<sub>18</sub> (1 ft × 1/4 in); methanol-water containing 0.5% ammonium carbonate (3:1 v/v), 1.2 ml min<sup>-1</sup>; *R*<sub>t</sub> 5.44 min]}.

(±)-*p*-Nitrobenzyl 6 $\alpha$ -[(1R\*)-1-(*p*-Nitrobenzyloxy)ethyl]-7-oxo-3-phenylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3).—(A) The 3-oxocarbapenam (19) (34 mg) was treated with a catalytic amount of 4-dimethylaminopyridine, di-isopropylethylamine (10.3 mg) and diphenyl chlorophosphate (19 mg) in dry acetonitrile (2 ml) as above. After formation of the phosphate (20), di-isopropylethylamine (33 mg) and a solution of thiophenol (7.5 mg) in dry acetonitrile (2 ml) were added, and the mixture was allowed to stand for 20 h at –15 °C. After evaporation of the solvent, the residue was purified by chromatography on silica gel. Elution with benzene-acetone (49:1) gave the carbapenam (3) (32 mg) as a yellowish syrup (Found: C, 55.7; H, 4.35; N, 6.5.  $C_{30}H_{25}N_3O_{10}S \cdot 1.5H_2O$  requires C, 56.0; H, 4.15; N, 6.2%),  $\nu_{\max}$  (CHCl<sub>3</sub>) 1780, 1745, and 1700 cm<sup>-1</sup> (C=O);  $\delta$  (CDCl<sub>3</sub>) 1.44 (3 H, d, *J* 6.5 Hz, CHMe),

2.69 (2 H, d,  $J$  10 Hz, 4-H<sub>2</sub>), 3.27 (1 H, dd,  $J$  2.5 and 8 Hz, 6-H), 4.07 (1 H, dt,  $J$  2.5 and 10 Hz, 5-H), 4.74—5.70 (5 H, m,  $2 \times \text{CH}_2\text{C}_6\text{H}_4\text{NO}_2$  and CHMe), 7.30—7.83 (9 H, m,  $9 \times \text{ArH}$ ), 8.20 (2 H, d,  $J$  9 Hz,  $2 \times \text{ArH}$ ), and 8.23 (2 H, d,  $J$  9 Hz,  $2 \times \text{ArH}$ );  $m/e$  619 ( $M^+$ ).

(B) A mixture of the phosphorane (13) (100 mg) and hydroquinone (5 mg) in dry toluene (60 ml) was degassed under reduced pressure and then vigorously refluxed for 60 h in a Dean-Stark apparatus under nitrogen. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with benzene-acetone (49:1) afforded the carbapenem (3) (4.6 mg) as a yellowish syrup, the i.r. and n.m.r. spectra and t.l.c. behaviour of which were identical to those of the sample prepared by Method (A).

Further elution with benzene-acetone (19:1—9:1) yielded starting material (13) (75 mg).

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