A Carbon–Carbon Bond Formation Reaction at the C-4 Position of a β-Lactam

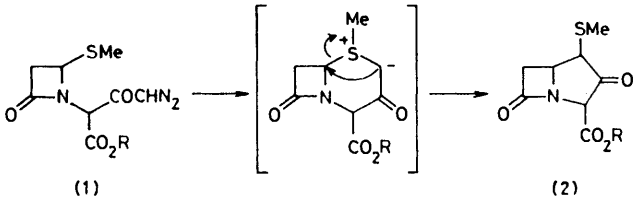
By **Tetsuji Kametani,* Toshio Honda, Junko Sasaki, Hirofumi Terasawa,** and **Keiichiro Fukumoto,** Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Upon treatment with various organolithiums, 4-acetoxyazetidin-2-one (10) afforded the corresponding carbon-displaced compounds (11), (12), and (13). 4-(3-Diazo-3-ethoxycarbonyl-2-oxopropyl)azetidin-2-one (15) was also synthesised from (10) and ethyl α-diazoacetoacetate in the presence of lithium hexamethyldisilazide in one step. The diazo-compound (15) was thermally cyclised to the bicyclic keto-ester (17) in the presence of rhodium acetate.

SINCE the isolation of carbapenem antibiotics such as thienamycin,[1-3] epithienamycin,[4] PS-5,[5,6] and olivanic acid,[7-12] much attention has been focused on their synthesis during the past few years. Interest in the synthesis of new β-lactam antibiotics arose from their reported interesting biological activities and their novel carbapenem ring systems. In continuation of our work on the synthesis of carbapenem antibiotics, we have investigated a carbon–carbon bond formation at the C-4 position of a β-lactam.[13-15] We report here a new carbon–carbon bond formation reaction at the C-4-position of a β-lactam, a reaction which might be very useful in the synthesis of carbapenem and carbacephem type antibiotics.

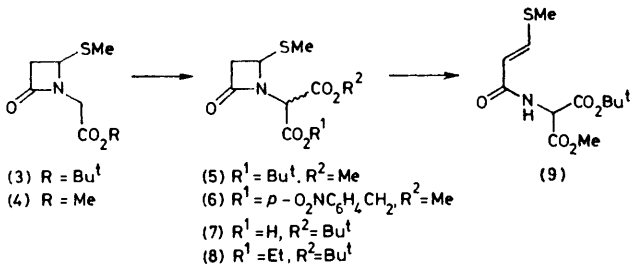
RESULTS AND DISCUSSION

With regard to C-4 substitution of β-lactams, a few papers [16,17] have been published in which the carbenoid reaction to sulphur was used. We first planned to prepare the diazoketone (1) which may produce a carbapenam derivative (2) by decomposition of the diazo-group in the presence of a copper reagent.



(1) (2)

In order to synthesise (1) the ester (3) was prepared from the 4-methylthioazetidin-2-one [18] and t-butyl bromoacetate in the presence of n-butyl-lithium. The ester (3) was then treated with methyl chloroformate in the presence of lithium di-isopropylamide to give an epimeric mixture of the diesters (5) in 78% yield. The attempted hydrolysis of (5) with aqueous basic reagent gave none of the desired product, whereas the ring-opened product (9) was obtained by treatment with trifluoroacetic acid.[19] Deprotection of the *p*-nitrobenzyloxycarbonyl derivatives (6), prepared from (4) [20] and *p*-nitrobenzyl chloroformate, afforded a complicated mixture under the neutral reaction conditions on palladium–carbon in a current of hydrogen. Since all attempts at the conversion of these diesters to half-esters failed, the direct introduction of carboxyl group was examined. Treatment of the ester (3) with carbon dioxide in the presence of lithium hexamethyldisilazide afforded the epimeric desired half-esters (7). The mixed anhydride method [21] was then investigated for the synthesis of the diazo-ketone (1). The reaction of the half-esters (7)



(3) R = Bu^t
(4) R = Me
(5) R^1 = Bu^t, R^2 = Me
(6) R^1 = *p*-$O_2NC_6H_4CH_2$, R^2 = Me
(7) R^1 = H, R^2 = Bu^t
(8) R^1 = Et, R^2 = Bu^t
(9)

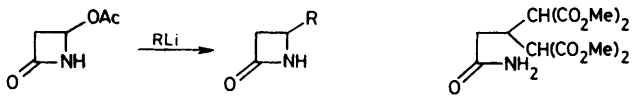
with methyl chloroformate and triethylamine at −30 °C in methylene chloride, followed by treatment of the resulting mixture with diazomethane, gave the diesters (5) instead of the diazo-ketone (1). In order to investigate whether the methoxycarbonyl moiety would form by esterification of the half-ester (7) with diazomethane, or by decarboxylation of the mixed anhydride formed, the half-ester (7) was again treated with ethyl chloroformate, as a result of which compound (8) was obtained. This clearly indicated that the diesters (5) and (8) were formed by decarboxylation of the mixed anhydride intermediates.[22]

Since it is well known [18] that 4-acetoxyazetidin-2-ones are readily displaced by sulphur, nitrogen, and oxygen functions, we investigated the analogous carbon displacement reaction. Thus 4-acetoxyazetidin-2-one (10) was treated with n-butyl-lithium in tetrahydrofuran at −78 °C to give the 4-n-butylazetidin-2-one (11) in 12% yield. The spectroscopic data for all the substituted β-lactams prepared are summarised in the Table. Reaction of (10) with the lithium salt of dimethyl malonate, prepared from n-butyl-lithium and hexamethyldisilazane in tetrahydrofuran, afforded the corresponding C-4-substituted product (12) in 20% yield, together with the cleavage product (16). Introduction of an alkoxycarbonyl group at C-4 was also carried out successfully as follows. The β-lactam (10) was treated with the lithium salt of ethyl acetate in tetrahydrofuran at −78

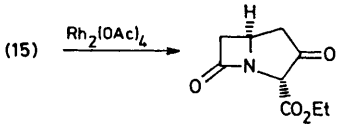
Spectroscopic data for 4-substituted azetidin-2-ones

Compound	$\nu_{max.}$/cm^{-1}	δ ($CDCl_3$)	Mass spectra
(11)	3400 (NH), 1750 (C=O)	0.65—1.25 (3 H, m, Me), 1.05—2.25 (6 H, m, 3 × CH_2), 2.45 (1 H, m, C-3-H), 3.00 (1 H, m, C-3-H), 3.35—3.80 (1 H, m, C-4-H), 7.10—7.60 (1 H, s, NH)	127 (M^+) (Found: M^+ 127.0959. $C_7H_{13}NO$ requires M, 127.0996)
(12)	3425 (NH), 1740 (C=O), 1715 (C=O)	2.40—3.20 (2 H, m, CH_2CO), 3.30 (1 H, m, C-4-H), 3.55 [1 H, d, J 6 Hz, $CH(CO_2Me)_2$], 3.83 (6 H, s, 2 × OMe), 8.66 (1 H, br s, NH)	202 ($M^+ + 1$) (Found: $M^+ + 1$, 202.0688. $C_8H_{12}NO_5$ requires $M + 1$, 202.0653)
(13)	3425 (NH), 1760 (C=O), 1730 (C=O)	1.31 (3 H, t, J 7 Hz, $CHMe$), 2.47—2.87 (1 H, m, C-3-H), 2.68 (2 H, d, J 7 Hz, CH_2CO), 3.20 (1 H, ddd, J 2, 5, and 15 Hz, C-3-H), 3.65—4.10 (1 H, m, C-4-H), 4.30 (2 H, q, J 7 Hz, CH_2Me), 7.67 (1 H, br s, NH)	158 ($M^+ + 1$), 157 (M^+) (Found: M^+ 157.0724. $C_7H_{11}NO_3$ requires M, 157.0737)
(15)	3450 (NH), 2140 (N_2), 1750 (C=O), 1710 (C=O), 1645 (C=O)	1.33 (3 H, t, J 7 Hz, CH_2Me), 2.35—3.65 (4 H, m, C-3-H and CH_2CO), 3.98 (1 H, m, C-4-H), 4.27 (2 H, q, J 7 Hz, CH_2Me), 6.17 (1 H, br s, NH)	

to −30 °C for 3 h to give the desired product (13) in 15% yield. However, attempted introduction of an acetaldehyde unit by treatment of bromoacetaldehyde diethyl acetal and magnesium afforded 4-ethoxyazetidin-2-one (14) as the sole product in 24% yield.



(10) (11) R = Bu^n (12) R = $CH(CO_2Me)_2$ (13) R = CH_2CO_2Et (14) R = OEt (15) R = $CH_2COC(N_2)CO_2Et$ (16)



(17)

Finally, an acetoacetate unit was introduced into (10) to afford the desired product (15), which was then converted to the bicyclic keto-ester (17) by thermal cyclisation in the presence of rhodium acetate.[23-25]

Thus, a new carbon–carbon bond formation reaction at the C-4 position of a β-lactam has been achieved, and its utilisation is expected to provide a useful synthetic pathway to carbapenem antibiotics.

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. All new compounds were homogeneous on t.l.c. using Merck silica gel $60F_{254}$ in several solvent systems.

N-t-Butoxycarbonylmethyl-4-methylthioazetidin-2-one (3).—To a stirred solution of 4-methylthioazetidin-2-one (1.17 g) in tetrahydrofuran (15 ml) was added n-butyllithium (0.64 g) at −78 °C in a current of nitrogen; and stirring was continued for 1 h at −78 °C; t-butyl bromoacetate (2.14 g) was then added to the solution, and the resulting mixture was warmed up to −10 °C over a period of 1 h and stirred at −10 °C for 2 h. The mixture was treated with water and extracted with ether. The ethereal layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded an oil, which was chromatographed on silica gel using methylene chloride as eluant to give the ester (3) (1.78 g, 78%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 740 cm^{-1} (C=O); δ($CDCl_3$) 1.40 (9 H, s, Bu^t), 2.05 (3 H, s, SMe), 3.57 (1 H, d, J 17 Hz, $CHHCO$), 4.17 (1 H, d, J 17 Hz, $CHHCO$), and 4.91 (1 H, dd, J 2 and 4.5 Hz, C-4-H); m/e 231 (M^+) (Found: M^+, 231.0927. $C_{10}H_{17}NO_3S$ requires M, 231.0900).

t-Butyl Methyl 2-(4-Methylthio-2-oxoazetidin-1-yl)malonate (5).—(a) *By the methoxycarbonylation method.* To a stirred solution of lithium di-isopropylamide [prepared from n-butyl-lithium (0.673 g) and di-isopropylamine (1.2 g)] in tetrahydrofuran (15 ml) was added a solution of the ester (3) (2.31 g) in tetrahydrofuran (10 ml) in a current of nitrogen at −78 °C. The mixture was warmed up to −30 °C and stirred for 1 h. Methyl chloroformate (1.1 g) was then added to the solution, and stirring continued for 2 h at −30 °C. After treatment with water, the mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried (Na_2SO_4). Removal of the solvent gave a yellowish oil which was subjected to silica gel column chromatography. Elution with methylene chloride–acetone (9 : 1 v/v) afforded an epimeric mixture of diesters (5) (2.15 g, 78%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 780 and 1 750 cm^{-1} (C=O); δ($CDCl_3$) 1.53 (9 H, s, Bu^t), 2.10 (0.75 H, s, SMe), 2.17 (2.25 H, s, SMe), 3.83 (1 H, dd, J 3 and 16 Hz, C-3-H), 3.60 (1 H, dd, J 5.5 and 16 Hz, C-3-H), 3.91 (3 H, s, OMe), 4.97 (0.25 H, s, $CH\langle^{CO}_{CO}$), 5.00 (0.75 H, s, $CH\langle^{CO}_{CO}$), and 5.23 (1 H, m, C-4-H); m/e 289 (M^+) (Found: M^+, 289.0974. $C_{12}H_{19}NO_5S$ requires M, 289.0984).

(b) *By the mixed anhydride method.* To a stirred solution of the half-esters (7) (2.7 g) and triethylamine (1.51 g) in methylene chloride (20 ml) was added methyl chloroformate (1.04 g) at −30 °C in a current of nitrogen. After stirring for 1 h at −30 °C, the resulting mixture was treated with an excess of ethereal diazomethane solution and allowed to stand at room temperature for 20 h. Removal of the solvent gave an oil which was subjected to silica gel column chromatography. Elution with methylene chloride–acetone (9 : 1 v/v) afforded the diesters (5), which were identical with an authentic specimen.

Methyl p-Nitrobenzyl 2-(4-Methylthio-2-oxoazetidin-1-yl)-

malonate (6).—The ester (4) (0.945 g) was treated with *p*-nitrobenzyl chloroformate (1.08 g) in the presence of lithium di-isopropylamide [prepared from n-butyl-lithium (0.32 g) and di-isopropylamine (505 mg)] as in the case of (5) to give an epimeric mixture of the diesters (6) (1.14 g, 62%) as a colourless powder; $\nu_{max.}$ ($CHCl_3$) 1 760 cm^{-1} (C=O); δ($CDCl_3$) 2.10 (0.75 H, s, SMe), 2.12 (2.25 H, s, SMe), 3.87 (3 H, s, OMe), 7.64 (2 H, d, *J* 8 Hz, aromatic protons), and 8.33 (2 H, d, *J* 8 Hz, aromatic protons). Field-desorption mass *m/e* 368 (M^+).

t-Butyl Hydrogen 2-(4-*Methylthio*-2-*oxoazetidin*-1-*yl*)*malonate* (7).—To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (1.61 g) and n-butyl-lithium (0.54 g)] in tetrahydrofuran (20 ml) was added a solution of the ester (3) (2.31 g) in tetrahydrofuran (10 ml) at −78 °C in a current of nitrogen. After stirring for 1 h at −30 °C, carbon dioxide was bubbled through the above solution for 2 h. The mixture was treated with water and washed with ether. The aqueous layer was acidified with 10% hydrogen chloride solution, extracted with methylene chloride, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave an epimeric mixture of the acids (7) (2.06 g, 75%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 760 (C=O); δ($CDCl_3$) 1.48 (9 H, s, Bu^t), 2.14 (0.75 H, s, SMe), 2.17 (2.25 H, s, SMe), 4.88 (0.25 H, s, $CH\langle^{CO}_{CO}$), 4.92 (0.75 H, s, $CH\langle^{CO}_{CO}$), and 5.13 (1 H, m, C-4-H), which was used in the following reaction without further purification.

Ethyl t-Butyl 2-(4-*Methylthio*-2-*oxoazetidin*-1-*yl*)*malonate* (8).—To a stirred solution of the half-esters (7) (2.7 g) and triethylamine (1.51 g) in methylene chloride (30 ml) was added ethyl chloroformate (1.2 g) at −30 °C in a current of nitrogen. The mixture was further stirred at −30 °C for 1 h, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed on silica gel using methylene chloride–acetone (9 : 1 v/v) as eluant to afford an epimeric mixture of the esters (8) (2.15 g, 72%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 770 and 1 740 cm^{-1} (C=O); δ($CDCl_3$) 1.56 (9 H, s, Bu^t), 1.38 (3 H, t, *J* 7 Hz, CH_2*Me*), 2.19 (3 H, s, SMe), 3.08 (1 H, dd, *J* 3 and 16 Hz, C-3-H), 3.50 (1 H, dd, *J* 5 and 16 Hz, C-3-H), 4.38 (2 H, q, *J* 7 Hz, C*H*$_2$Me) 4.94 (0.33 H, s, $CH\langle^{CO}_{CO}$), 4.96 (0.67 H, s, $CH\langle^{CO}_{CO}$), and 5.23 (1 H, dd, *J* 3 and 5 Hz, C-4-*H*). Field-desorption mass *m/e* 303 (M^+).

The Ring-opened Amide (9).—To a stirred solution of the diesters (5) (1.36 g) in methylene chloride (20 ml) was added dropwise trifluoroacetic acid (3 ml) at 0 °C. After stirring for 3 h, the mixture was washed with water and dried (Na_2SO_4). Removal of the solvent gave an oil which was chromatographed on silica gel using methylene chloride–acetone (9 : 1 v/v) to afford the amide (9) (1.13 g, 83%) as a pale yellow oil; $\nu_{max.}$ ($CHCl_3$) 3 420 (NH), 1 750, and 1 660 cm^{-1} (C=O); δ($CDCl_3$) 1.51 (9 H, s, Bu^t), 2.37 (3 H, s, SMe), 3.83 (3 H, s, OMe), 5.78 (1 H, d, *J* 15 Hz, =CHCON), 6.58 (1 H, br s, NH), and 7.74 (1 H, d, *J* 15 Hz, =C*H*SMe). Field-desorption mass *m/e* 289 (M^+).

4-*n-Butylazetidin*-2-*one* (11).—n-Butyl-lithium (0.64 g) was added to a solution of 4-acetoxyazetidin-2-one (10) (1.27 g) in tetrahydrofuran (20 ml) with stirring at −78 °C in a current of nitrogen. After stirring for 2 h at −78 °C, the mixture was treated with water and extracted with methylene chloride. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was chromatographed on silica gel using methylene chloride–acetone (8 : 2 v/v) as eluant to afford the β-lactam (11) (230 mg, 12%) as a colourless oil (see Table).

4-[*Bis*(*methoxycarbonyl*)*methyl*]*azetidin*-2-*one* (12).—To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (1.61 g) and n-butyl-lithium (0.64 g)] was added dimethyl malonate (1.32 g) at −78 °C in a current of nitrogen. After stirring for 0.5 h, a solution of 4-acetoxyazetidin-2-one (10) (1.29 g) in tetrahydrofuran (10 ml) was added to the above solution at −78 °C, and the resulting mixture was warmed up to −20 °C during 3 h. The mixture was then treated with water and extracted with methylene chloride. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was subjected to silica gel column chromatography. Elution with methylene chloride–acetone (8 : 2 v/v) afforded first the β-lactam (12) (see Table) (402 mg, 20%) as a colourless oil, and then the *amide* (16) (510 mg) as needles, m.p. 152 °C (benzene–n-hexane) (Found: C, 46.55; H, 5.6; N, 4.25. $C_{13}H_{19}NO_9$ requires C, 46.85; H, 5.75; N, 4.2%); $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 680 cm^{-1} (C=O); δ($CDCl_3$) 2.68 (2 H, d, *J* 6 Hz, 2 × $CH\langle^{CO}_{CO}$), 3.33 (1 H, m, C*H*–CH_2), 3.78 (12 H, s, 4 × OMe), and 6.03 (2 H, br s, NH_2); *m/e* 334 (M^+).

4-*Ethoxycarbonylmethylazetidin*-2-*one* (13).—The reaction of 4-acetoxyazetidin-2-one (10) (1.29 g) with ethyl acetate (0.88 g) in tetrahydrofuran in the presence of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (1.61 g) and n-butyl-lithium (0.64 g)] was carried out as above to yield the β-lactam (13) (236 mg, 15%) as a colourless powder (see Table).

4-*Ethoxyazetidin*-2-*one* (14).—A mixture of bromoacetaldehyde diethyl acetal (1.97 g) and magnesium turnings (240 mg) in tetrahydrofuran (10 ml) was stirred at ambient temperature until the mixture became homogeneous. A solution of 4-acetoxyazetidin-2-one (10) (1.29 g) in tetrahydrofuran (10 ml) was added to the above solution at 0 °C, and the resulting mixture was further stirred for 2 h at 0 °C. After addition of water the mixture was extracted with ether. The ethereal layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded an oil which was chromatographed on a silica gel column, using methylene chloride–acetone (8 : 2 v/v) as eluant, to give the β-lactam (14) (276 mg, 24%) as a colourless oil; $\nu_{max.}$ ($CHCl_3$) 3 245 (NH) and 1 770 cm^{-1} (C=O); δ($CDCl_3$) 1.27 (3 H, t, *J* 7 Hz, CH_2*Me*), 2.83 (1 H, dd, *J* 3 and 15 Hz, C-3-H), 3.58 (2 H, q, *J* 7 Hz, C*H*$_2$Me), 5.10 (1 H, dd, *J* 2 and 4 Hz, C-4-H), and 7.40 (1 H, br s, NH); *m/e* 116 ($M^+ + 1$) (Found: $M^+ + 1$, 116.0703. $C_5H_{10}NO_2$ requires 116.0710).

4-(3-*Diazo*-3-*ethoxycarbonyl*-2-*oxopropyl*)*azetidin*-2-*one* (15).—To a stirred solution of lithium hexamethyldisilazide [prepared from n-butyl-lithium (0.64 g) and hexamethyldisilazane (1.84 g)] in tetrahydrofuran (10 ml) was added ethyl α-diazoacetoacetate (1.56 g) at −78 °C in a current of nitrogen. After stirring for 1.5 h at −78 °C, a solution of 4-acetoxyazetidin-2-one (10) (1.29 g) in tetrahydrofuran (5 ml) was added and the resulting mixture was further stirred at −78 °C for 2 h. After the addition of water, the mixture was extracted with methylene chloride. The extract was washed with water and dried (Na_2SO_4). Removal of the solvent at 35 °C gave a reddish gum which was subjected to silica gel column chromatography. Elution

with methylene chloride–acetone (95 : 5 v/v) afforded the diazo-compound (15) (247 mg, 11%) as a colourless oil (see Table).

Ethyl 3,7-Dioxo-1-azabicyclo[3.2.0]*heptane-2-carboxylate* (17).—A solution of the diazo-compound (15) (100 mg) in dry benzene in the presence of a catalytic amount of rhodium acetate was warmed at 80 °C for 0.5 h. After filtration, the filtrate was evaporated to give the bicyclic keto-ester (17) (81.4 mg, 93%) as an unstable colourless oil; $\nu_{max.}$ ($CHCl_3$) 1 775 and 1 740 cm^{-1} (CO); δ($CDCl_3$) 1.32 (3 H, t, *J* 7 Hz, CH_2Me), 2.46 (1 H, dd, *J* 8 and 18 Hz, C-4-H), 2.90 (1 H, dd, *J* 6 and 18 Hz, C-4-H), 3.01 (1 H, dd, *J* 2 and 16 Hz, C-6-H), 3.63 (1 H, dd, *J* 2 and 16 Hz, C-6-H), 4.23 (2 H, q, *J* 7 Hz, CH_2Me), 4.65 (1 H, s, C-2-H); *m/e* 197 (M^+) (Found: M^+ 197.0912. $C_9H_{11}NO_4$ requires *M*, 197.0920).

We thank Mr. K. Kawamura, Miss Y. Enomoto, Mrs. C. Koyanagi, Mrs. R. Kobayashi, Miss K. Kikuchi, Miss Y. Katoh, Miss K. Ohtomo, Miss A. Hareyama, and Miss Y. Watanabe for microanalyses and spectral measurements.

[0/1750 *Received*, 13*th November*, 1980]

REFERENCES

[1] J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, *J. Antibiot.*, 1979, **32**, 1.

[2] F. P. Tally, N. V. Jacobus, and S. L. Gorbach, *Antimicrob. Agents Chemother.*, 1978, **14**, 436.

[3] G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, *J. Am. Chem. Soc.*, 1978, **100**, 6491.

[4] P. J. Cassidy, E. O. Stapley, R. Goegelman, T. W. Miller, B. Arison, G. Albers-Schönberg, S. B. Zimmerman, and J. Birnbaum, 17*th Intersci. Conference Antimicrobial Agents and Chemotherapy*, New York, N.Y., 1977, No. 81.

[5] K. Okamura, S. Hirata, A. Koki, K. Hori, N. Shibamoto, Y. Okamura, M. Okabe, R. Okamoto, K. Kouno, Y. Fukagawa, Y. Shimauchi, T. Ishikura, and J. Lein, *J. Antibiot.*, 1979, **32**, 262.

[6] K. Yamamoto, T. Yoshioka, Y. Kato, N. Shibamoto, K. Okamura, Y. Shimauchi, and T. Ishikura, *J. Antibiot.*, 1980, **33**, 796.

[7] D. Butterworth, M. Cole, G. Hanscomb, and G. N. Robinson, *J. Antibiot.*, 1979, **32**, 287.

[8] J. D. Hood, S. S. Box, and M. S. Verrall, *J. Antibiot.*, 1979, **32**, 295.

[9] A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Antibiot.*, 1979, **32**, 961.

[10] S. J. Box, J. D. Hood, and S. R. Spear, *J. Antibiot.*, 1979, **32**, 1239.

[11] A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, 523.

[12] D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Chem. Soc., Chem. Commun.*, 1977, 953.

[13] T. Kametani, S. Hirata, H. Nemoto, M. Ihara, and K. Fukumoto, *Heterocycles*, 1979, **12**, 523.

[14] T. Kobayashi, N. Ishida, and T. Hiraoka, *J. Chem. Soc., Chem. Commun.*, 1980, 736.

[15] M. Shibuya and S. Kubota, *Heterocycles*, 1979, **12**, 1315.

[16] J. Ernest, *Tetrahedron*, 1977, **33**, 547.

[17] M. D. Bachi, O. Goldberg, and A. Gross, *Tetrahedron Lett.*, 1978, 4167.

[18] K. Clauss, D. Grimm, and G. Prossel, *Liebigs Ann. Chem.*, 1974, 539.

[19] A. K. Bose, J. L. Fakey, and M. S. Manhas, *J. Heterocycl. Chem.*, 1973, **10**, 791.

[20] P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *J. Chem. Soc., Chem. Commun.*, 1977, 905.

[21] B. G. Ramsay and R. J. Stoodley, *J. Chem. Soc. C*, 1969, 1319.

[22] C. K. Sauers and R. J. Cotter, *J. Org. Chem.*, 1961, **26**, 6.

[23] T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and F. A. Bouffard, *J. Am. Chem. Soc.*, 1980, **102**, 6161.

[24] R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, *Tetrahedron Lett.*, 1980, 31.

[25] D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzinger, *Tetrahedron Lett.*, 1980, 2783.