TOTAL SYNTHESIS OF (±)-EPITHIENAMYCINS A AND B [(±)-OLIVANIC ACIDS MM22380 AND 22382]

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Abstract —— (±)-3R*-(1'S*-Hydroxyethyl)-4R*-(2',2'-dimethoxyethyl)-2-azetidinone (6), which was obtained from the 4-methoxycarbonyl-isoxazoline (4) as a major product, was converted into (±)-epithienamycins A(2) and B(3) [(±)-olivanic acids MM22380 and 22382] via the carbene insertion reaction. This total synthesis confirms the relative stereochemistry of the natural antibiotics.

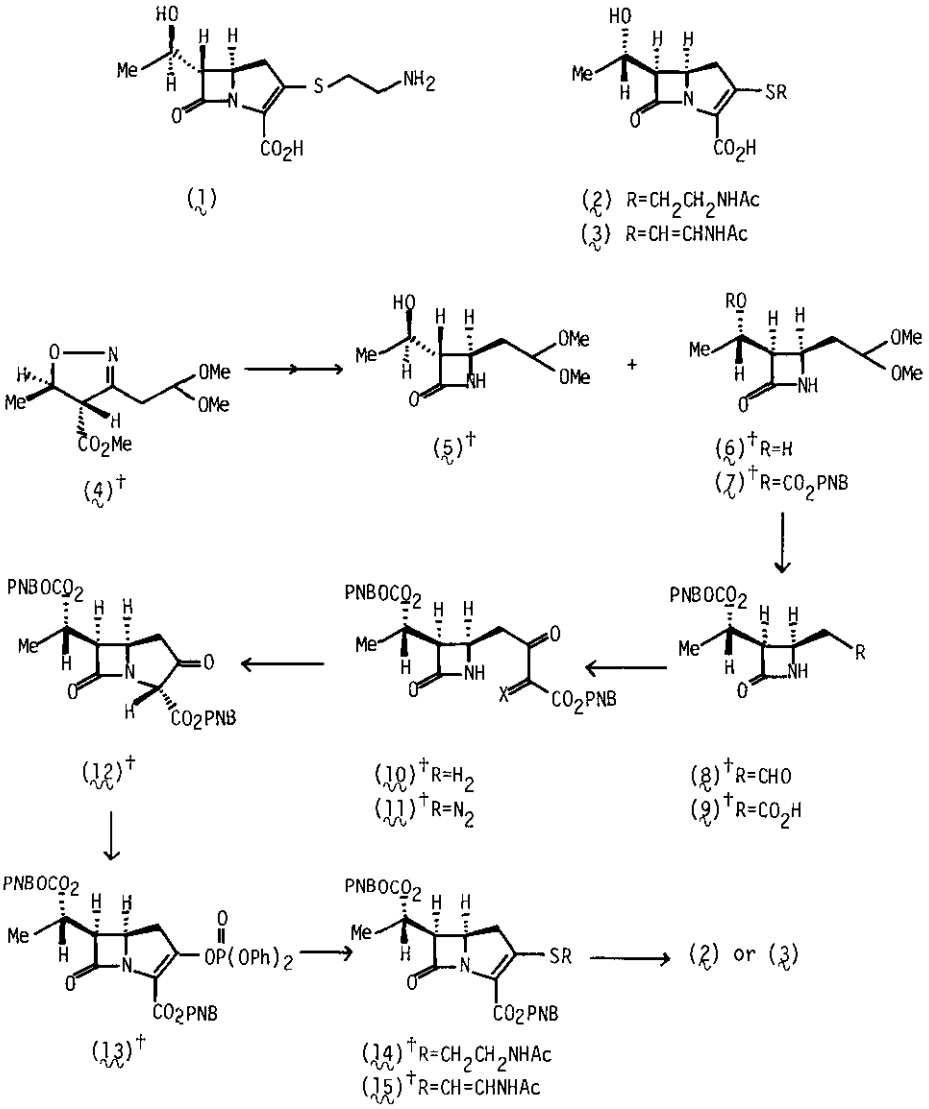
Novel β-lactam antibiotics, possessing the 7-oxa-1-azabicyclo[3.2.0]hept-2-ene ring system, represented by thienamycin (1)[1,2,3], recently attracted a great attention because of their potent and broad antibiotic activities. Among them, epithienamycins[4] isolated from Streptomyces flavogriseus by Merck group were identical with some of olivanic acids[5,6] independently found in the broth of S. olivaceus by Beecham group. The absolute stereochemistry of epithienamycins A(2) and B(3) (olivanic acids MM 22380 and 22382, respectively) was determined as the 5(R), 6(R), 8(S)-configuration mainly on the basis of the spectroscopic evidences.[4,6] Recently we developed an efficient synthesis of (±)-thienamycin (1) via isoxazoline derivatives.[7,8,9] The notice of the identity of the relative configuration of the major product (6), obtained from the isoxazoline methyl ester (4), with that of epithienamycins A and B promoted us to study the synthesis of natural products (2 and 3) from 6.

The hydroxyl group of the cis-azetidinone (6), prepared in 38 % yield along with the trans isomer (5) in 21 % yield from the isoxazoline derivative (4) by hydrogenation followed by trimethylsilylation, cyclisation with ethylmagnesium bromide and deblocking as described earlier,[8] was protected, in 60 % yield, with p-nitrobenzyloxycarbonyl group to afford 7, δ ($CDCl_3$) 1.51 (3H, J = 6.5 Hz, $C_{1'}$-Me),

3.29 and 3.31 (each 3 H, each s, 2 x OMe), 3.41 (1H, ddd, J = 10.1, 5.1 and 1.4 Hz, C_3-H), 3.73 ∿ 3.97 (1H, m, C_4-H), m/e 383 ($M^+ + 1$). Hydrolysis of the acetal group of 7 with hot aqueous acetic acid yielded the corresponding aldehyde (8), m/e 337 ($M^+ + 1$), which was then oxidised with Jones reagent to the carboxylic acid (9) (64 % yield from 7), $\nu_{max.}$ (KBr) 3240 (NH), 2500 ∿ 3000 (CO_2H), 1750 and 1700 cm^{-1} (C = O); m/e 352 (M^+), 353 ($M^+ + 1$) (FD mass). After treatment of 9 with N,N'-carbonyldiimidazole,[10] the imidazolide formed was reacted with the magnesium salt of the mono-p-nitrobenzyl ester of malonic acid[3] to give the β-keto ester (76 % yield from 9), $\nu_{max.}$ ($CHCl_3$) 3410 (NH), 1750 and 1720 cm^{-1} (C = O); δ ($CDCl_3$) 1.47 (3H, d, J = 6.5 Hz, C_1-Me), 3.55 (2H, s, $COCH_2CO_2$); m/e 529 (M^+), 530 ($M^+ + 1$) (FD mass). Treatment of 10 with p-toluenesulphonyl azide in the presence of triethylamine, followed by decomposition[3] of the diazo ester (11), $\nu_{max.}$ ($CHCl_3$) 2135 (diazo), with a catalytic amount of rhodium diacetate produced the bicyclic ketone (12) (81 % yield from 10), $\nu_{max.}$ ($CHCl_3$) 1760 and 1740 (C=O), δ ($CDCl_3$) 1.52 (3H, d, J = 6.5 Hz, C_8-Me), 2.74 (2H, d, J = 8 Hz, C_1-H_2), 3.92 (1H, dd, J = 5 and 10 Hz, C_6-H), 4.27 (1H, dt, J = 5 and 8 Hz, C_5-H); m/e 527 (M^+)(FD mass), as a single stereoisomer.

Reaction of 12 with diphenyl chlorophosphate in the presence of one molar equivalent of diisopropylethylamine and a catalytic amount of 4-dimethylaminopyridine in acetonitrile,[3] followed by *in situ* reaction of the resulting phosphate (13) with diisopropylethylamine and N-acetylcysteamine afforded the protected epithienamycin A (14) (79 % yield from 12), $\nu_{max.}$ (CH_2Cl_2) 3450 (NH), 1782, 1750, 1700 and 1675 (C = O); δ ($CDCl_3$) 1.53 (3H, d, J = 6.5 Hz, C_8-Me), 1.95 (3H, s, NAc), 3.80 (1H, dd, J = 5 and 10 Hz, C_6-H), 4.31 (1H, dt, J = 5 and 9 Hz, C_5-H); m/e 628 (M^+), 629 ($M^+ + 1$) (FD mass). Deprotection of 14 in the presence of Adams catalyst and one equivalent of sodium hydrogen carbonate under hydrogen (40 psi) in aqueous tetrahydrofuran gave (±)-epithienamycin A[4] (2) (MM22380[6]) in 85 % yield based on the hydroxylamine extinguishable absorption at 299 nm. After purification using Sephadex G-10, the uv, ir and nmr spectra of the isolated product was identical with the reported ones.[4,6]

Reaction of the above phosphate (13) without isolation with silver (E)-2-acetamido-1-ethenylthiolate[11] in the presence of sodium iodide in acetonitrile at 0°C produced the protected epithienamycin B (15) (76 % yield from 12), $\nu_{max.}$ ($CHCl_3$) 3440 (NH), 1785, 1750 and 1705 cm^{-1} (C = O); δ 1.56 (3H, d, J = 6.5 Hz, C_8-Me), 2.09 (3H, s, NAc), 2.97 (1H, dd, J = 10 and 19 Hz, C_1-H), 3.17 (1H, dd, J = 9 and 19 Hz, C_1-H), 3.80 (1H, dd, J = 5 and 10 Hz, C_6-H), 4.24 (1H, m, C_5-H), 5.86 (1H, d, J = 13.5 Hz, SCH=CH-), 7.18 (1H, dd, J = 11.5 and 13.5 Hz, -CH=CHNH). Deprotection of 15 under



(1)

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

(4)† (5)† (6)† R=H
(7)† R=CO_2PNB

(8)† R=CHO
(9)† R=CO_2H
(10)† R=H_2
(11)† R=N_2

(12)† (13)†

(14)† R=CH_2CH_2NHAc
(15)† R=CH=CHNHAc

PNB = p-nitrobenzyl group

† one of enantiomers is described as a representative.

the same condition as above formed (±)-epithienamycin B(3) (MM22382) in good yield, whose uv and nmr spectra were consistent with the reported ones.[4,6] Thus the relative configurations of epithienamycins A and B were confirmed as the formulae (2 and 3). Preparation of epithienamycin derivatives and their biological properties will be published somewhere in the future.

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