

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

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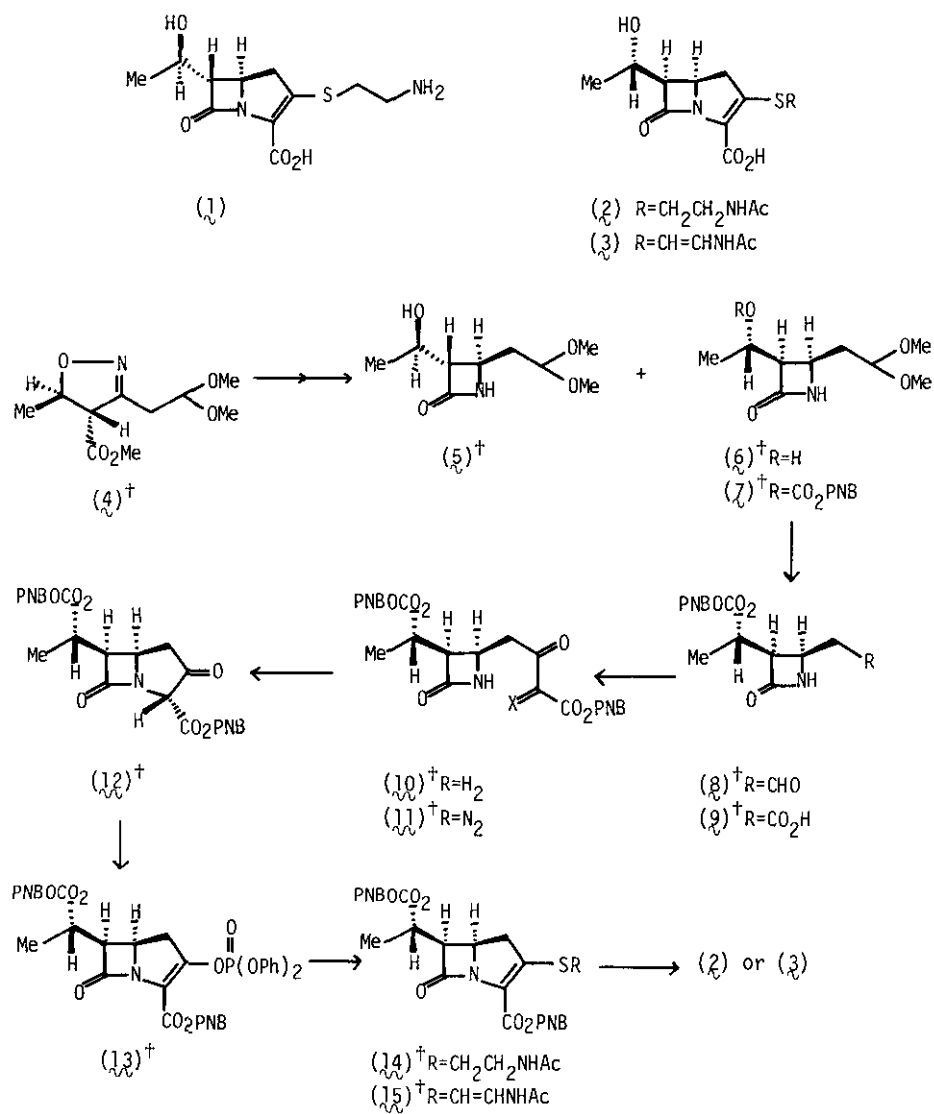
Abstract — (±)-3R*-(1'S*-Hydroxyethyl)-4R*-(2',2'-dimethoxyethyl)-
2-azetidinone (6), which was obtained from the 4-methoxycarbonyl-
isoxazoline (4) as a major product, was converted into (±)-epi-
thienamycins A(2) and B(3) [(±)-olivanic acids MM22380 and 22382]
via the carbene insertion reaction. This 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, epithienamycins⁴
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), ob-
tained 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 (CDCl₃) 1.51 (3H, J = 6.5 Hz, C₁-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, C₃-H), 3.73 ~ 3.97 (1H, m, C₄-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**), ν_{\max} . (KBr) 3240 (NH), 2500 ~ 3000 (CO₂H), 1750 and 1700 cm⁻¹ (C = O); m/e 352 (M⁺), 353 (M⁺ + 1) (FD mass). After treatment of **9** with N,N'-carbonyl-diimidazole,¹⁰ the imidazolide formed was reacted with the magnesium salt of the mono-p-nitrobenzyl ester of malonic acid³ to give the β -keto ester (76 % yield from **9**), ν_{\max} . (CHCl₃) 3410 (NH), 1750 and 1720 cm⁻¹ (C = O); δ (CDCl₃) 1.47 (3H, d, J = 6.5 Hz, C₁-Me), 3.55 (2H, s, COCH₂CO₂); m/e 529 (M⁺), 530 (M⁺ + 1) (FD mass). Treatment of **10** with p-toluenesulphonyl azide in the presence of triethylamine, followed by decomposition³ of the diazo ester (**11**), ν_{\max} . (CHCl₃) 2135 (diazo), with a catalytic amount of rhodium diacetate produced the bicyclic ketone (**12**) (81 % yield from **10**), ν_{\max} . (CHCl₃) 1760 and 1740 (C=O), δ (CDCl₃) 1.52 (3H, d, J = 6.5 Hz, C₈-Me), 2.74 (2H, d, J = 8 Hz, C₁-H₂), 3.92 (1H, dd, J = 5 and 10 Hz, C₆-H), 4.27 (1H, dt, J = 5 and 8 Hz, C₅-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**), ν_{\max} . (CH₂Cl₂) 3450 (NH), 1782, 1750, 1700 and 1675 (C = O); δ (CDCl₃) 1.53 (3H, d, J = 6.5 Hz, C₈-Me), 1.95 (3H, s, NAc), 3.80 (1H, dd, J = 5 and 10 Hz, C₆-H), 4.31 (1H, dt, J = 5 and 9 Hz, C₅-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 (\pm)-epithienamycin A⁴ (**2**) (MM22380⁶) 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-ethenylthiolate¹¹ in the presence of sodium iodide in acetonitrile at 0°C produced the protected epithienamycin B (**15**) (76 % yield from **12**), ν_{\max} . (CHCl₃) 3440 (NH), 1785, 1750 and 1705 cm⁻¹ (C = O); δ 1.56 (3H, d, J = 6.5 Hz, C₈-Me), 2.09 (3H, s, NAc), 2.97 (1H, dd, J = 10 and 19 Hz, C₁-H), 3.17 (1H, dd, J = 9 and 19 Hz, C₁-H), 3.80 (1H, dd, J = 5 and 10 Hz, C₆-H), 4.24 (1H, m, C₅-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



PNB = p-nitrobenzyl group

\dagger 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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REFERENCES

1. 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. Morisn and B. G. Christensen, J. Amer. Chem. Soc., 1978, 100, 6491.
2. D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, J. Amer. Chem. Soc., 1978, 100, 313; S. M. Schmitt, D. B. R. Johnston, and B. G. Christensen, J. Org. Chem., 1980, 45, 1142.
3. T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, and F. A. Bouffard, Phil. Trans. Roy. Soc. London, 1980, 289, 1036; J. Amer. Chem. Soc., 1980, 102, 6161; D. G. Melillo, I. Shinkai, T. Liu, K. Ryan, and M. Sletzingler, Tetrahedron Letters, 1980, 21, 2783.
4. E. O. Stapley, P. J. Cassidy, J. Tunac, R. L. Monaghan, M. Jackson, S. Hernandez, S. B. Zimmerman, J. M. Mata, S. A. Currie, D. Daoust, and D. Hendlin, J. Antibiotics, in press; P. J. Cassidy, G. Albers-Schönberg, R. T. Goegelman, T. Miller, B. Arison, E. O. Stapley, and J. Birnbaum, J. Antibiotics, in press.
5. A. G. Brown, D. F. Corbett, A. J. Eglinton, and T. T. Howarth, J. C. S. Chem. Comm., 1977, 523; D. F. Corbett, A. J. Eglinton, and T. T. Howarth, J. C. S. Chem. Comm., 1977, 953; D. Butterworth, M. Cole, G. Hornscomb, and G. N. Robinson, J. Antibiotics, 1979, 32, 287; J. D. Hood, S. J. Box, and M. S. Verrall, J. Antibiotics, 1979, 32, 295.
6. A. G. Brown, D. F. Corbett, A. J. Eglinton, and T. T. Howarth, J. Antibiotics, 1979, 32, 961; S. J. Box, J. D. Hood, and S. R. Spear, J. Antibiotics, 1979, 32, 1239.
7. T. Kametani, S.-P. Huang, and M. Ihara, Heterocycles, 1979, 12, 1183 and 1189; T. Kametani, S.-P. Huang, Y. Suzuki, S. Yokohama, and M. Ihara, Heterocycles, 1979,

- 12, 1301; T. Kametani, S.-P. Huang, S. Yokohama, Y. Suzuki, and M. Ihara, J. Amer. Chem. Soc., 1980, ~~102~~, 2060.
8. T. Kametani, T. Nagahara, Y. Suzuki, S. Yokohama, S.-P. Huang, and M. Ihara, Heterocycles, 1980, ~~14~~, 403; Tetrahedron, in press.
9. T. Kametani, S.-P. Huang, T. Nagahara, and M. Ihara, Heterocycles, 1980, ~~14~~, 1305; J. C. S. Perkin I, in press.
10. D. W. Broocks, L. D.-D. Lu, and S. Masamune, Angew. Chem. Int. Ed. Engl., 1979, ~~18~~, 72.
11. R. J. Ponsford, R. Southgate, P. M. Roberts, A. J. G. Baxter, Japan Kokai, 1979, ~~112~~, 887.

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