NOVEL 2-METHYL-1-OXACEPHALOSPORINS 2. SYNTHESIS OF 3-SUBSTITUTED 2-METHYL-1-OXACEPHEM NUCLEUS

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Abstract — The stereoselective syntheses of 3-substituted 2α- and 2β-methyl-1-oxacephems have been achieved through the intramolecular Wittig condensations of 4-(1-methylpropoxy)azetidinones.

In our previous paper[1] the synthesis of 2-methyl-3-nor-1-oxacephems having a 7α-acylamino group was reported. In this paper we describe a stereoselective synthesis of 3-substituted 1-oxacephems 1 by the intramolecular Wittig condensation[2] of a key intermediate 2. Ylid 2, enantiomerically pure (R or S) at the carbon bearing the methyl group, was prepared in a straightforward manner from (3R,4S)-oxazolinoazetidinone 3. As described in the following paper,[3] the 7β-acylamino compounds were derived from 1. Among them, OCP-9-176 (L-656,575) showed especially interesting biological activities.[4-6]

The synthesis of 2β-methyl-1-oxacephems 14 was initiated by a conversion sequence of the N-isopropenyl residue of 4 which was prepared from 3,[1] to the phosphorous ylid 8. The sequence was initially developed by Woodward[2] and applied in the 1-oxacephem series.[7] Ozonolysis (O_3, CH_2Cl_2, -60°C, 30 min) of 4 followed by reduction (Zn, AcOH/CH_2Cl_2, -10°C, 30 min) afforded diastereoisomeric alcohol 6 (53%) via oxamide 5 which was not isolated.[8] Chlorination ($SOCl_2$, pyridine, CH_2Cl_2, 0°C, 30 min, 98%) of 6 followed by treatment of the resulting chloride 7[9] with triphenylphosphine ($CHCl_3$, 15h, room temperature, N_2 atmosphere) gave 8 (45%).[10] In order to elucidate the structure-activity relationships of the 3-substituted 2-methyl-1-oxacephems, the key intermediates 12 were prepared from 8.

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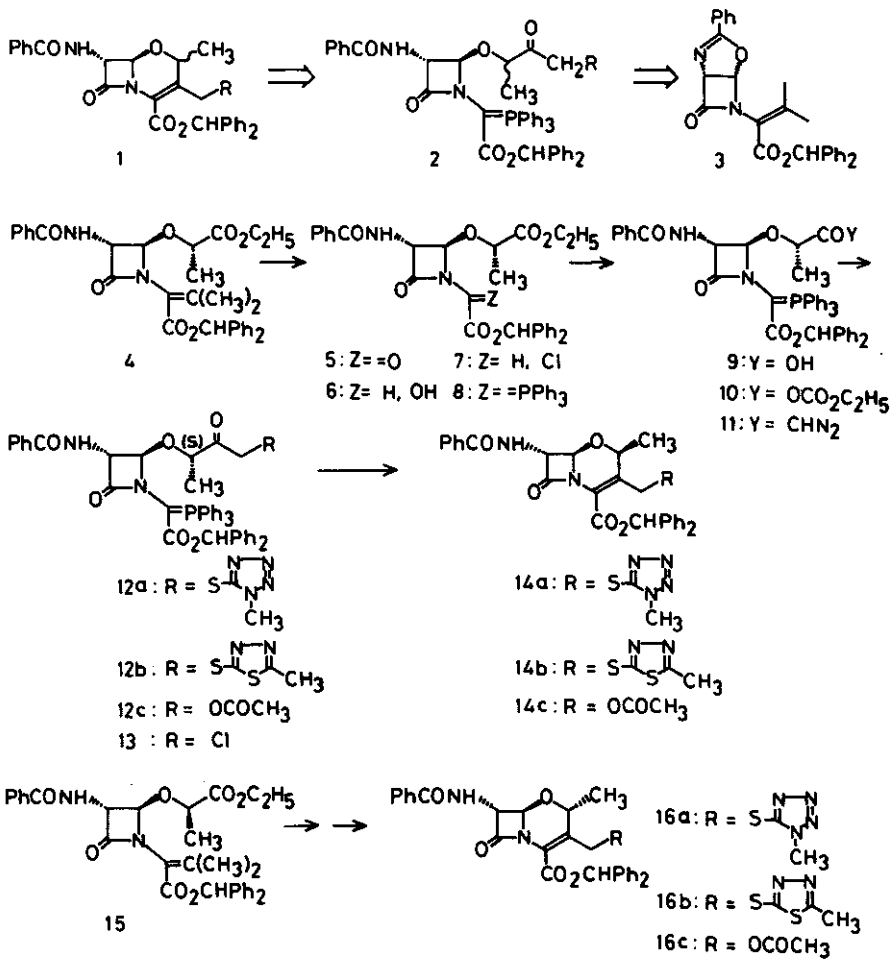
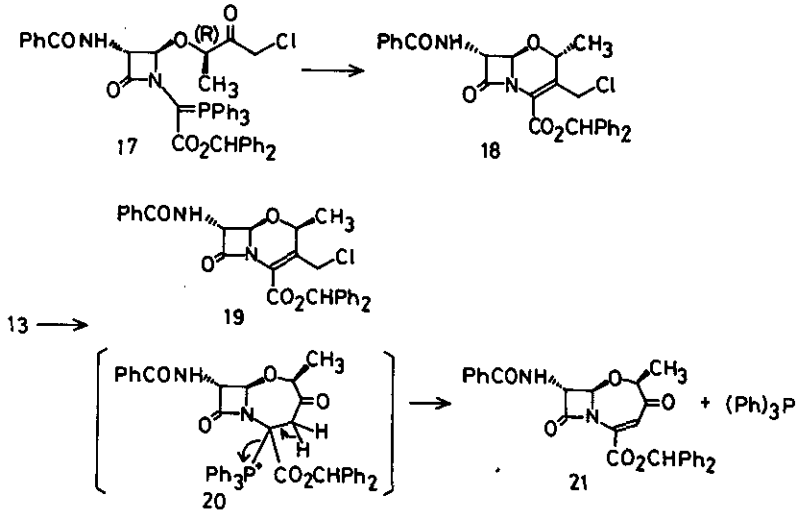


Alkaline hydrolysis of 8 (equimolar NaOH, aq. Me_2CO, 5°C, 1.5 h) gave acid 9 (95%).[10] The activation of 9 with ethyl chloroformate in the presence of 4-methylmorpholine (CH_2Cl_2, -10°C, 30 min) gave mixed anhydride 10 which was treated succesively with diazomethane to afford diazomethyl ketone 11 (ir; 2110, 1770 and 1763 cm^{-1}, 80% over 3 steps).

For introduction of substituent R in 12 we tried an intermolecular carbene insertion reaction of 11 with some reagents,[11] expanding our previous studies.[1,12] Heating of 11 with 5-mercapto-1-methyltetrazole (1.8 equimolar, EtOAc, 60°C, 40 min) in the presence of rhodium(II) acetate dimer (1/500 equimolar) smoothly gave 12a (60%). Similar treatment of 11 with 2-mercapto-5-methyl-1,3,4-thiadiazole gave 12b (63%) and moreover with AcOH (5 equimolar) 12c (49%) was obtained. Alternatively preparation of 12a, 12b and 12c was accomplished via 13 which was obtained quantitatively from 11 by treatment with anhydrous HCl (2 equimolar,

dioxane, 5°C, 30 min). Substitution reactions of 13 with the aforementioned mercaptans (DMF, room temperature, 1 h) and with sodium acetate gave 12 in good yields (12a: 95%, 12b: 96% and 12c: 87%), respectively.

The final cyclization by intramolecular Wittig reaction, to give 2β-methyl-1-oxacephems 14 was accomplished by heating of 12 in toluene in the presence of hydroquinone (reflux, N_2 atmosphere, 11 h)[13] followed by chromatographic purification (silicic acid, toluene-EtOAc; 4:1). The 2α-methyl-1-oxacephems 16 were obtained from azetidinone 15,[1] in a similar manner. The cyclization yields were not affected either by the chirality of the 2-methyl group or by the substituent R (14a: 86%, 14b: 67%, 14c: 65%, 16a: 84%, 16b: 81% and 16c: 71%).[14]



However Wittig reactions of 13 and its R isomer 17 were not equivalent. The reaction of 17 gave 18[15] in 85% yield. Tlc (Merck silica gel plate, toluene-EtOAc; 2:1) of the reaction mixture showed the presence of 18 (Rf 0.69) and $(Ph)_3PO$ (Rf 0.13). While, the reaction mixture of 13 showed three new spots (Rf 0.62, 0.70 and 0.95) with $(Ph)_3PO$. Purification by column chromatography on silica gel gave 19[16] (18%, Rf 0.70), $(Ph)_3P$ (Rf 0.95) and 7-membered homooxacephem 21[17] (13%, Rf 0.62). The formation[18] of 21 is likely to pass through Hoffmann type elimination[19] of 20. Compound 20 was formed by the attack of the ylid carbon to the intramolecular methylene carbon bearing chlorine atom of 13. Bestmann et al.[20] reported, a similar but intermolecular, reaction of bromo or iodomethyl ketones with stabilized ylids. We propose that the stabilized ylid carbon of 13 attacked the less reactive chloromethyl group than ketone, intramolecularly. Compound 20 is susceptible to another 13 molecule which acts as a base to give the

elimination product 21, the phosphonium chloride of 13 and eliminated $(Ph)_3P$.

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8. 6: oil, ir ν ($CHCl_3$) 3440, 1771, 1727, 1660, 1600 cm^{-1}; nmr δ (90 MHz, $CDCl_3$) 1.17 and 1.20(3H, t, J=7.2 Hz, $-CH_2CH_3$), 1.20 and 1.47(3H, d, J=7.0 Hz, $-CHCH_3$), 4.03 and 4.12(2H, q, J=7.2 Hz, $-CH_2CH_3$), 4.32 and 4.43(1H, q, J=7.0 Hz, -CH-), 4.75 and 4.80(1H, dd, J=6.5, 0.9 Hz, 3-H), 4.90 and 4.99(1H, d, J=0.9 Hz, 4-H), 5.05 and 5.41(1H, br s, -CH-OH), 6.87 and 6.92(1H, s, $-CHPh_2$), 7.00-7.80(15H, m, -Ph). ^1H Nmr spectra of 6 and 7 showed a typical pattern of diastereoisomeric mixture and the two respective chemical shifts were observed.
9. 7: oil, ir ν ($CHCl_3$) 1785, 1738, 1667 cm^{-1}; nmr δ (90 MHz, $CDCl_3$) 1.23(3H, t, J=7.2 Hz, $-CH_2CH_3$), 1.36 and 1.47(3H, d, J=7.0 Hz, $-CH_3$), 4.12(2H, q, J=7.2 Hz, $-CH_2-$), 4.43 and 4.52(1H, q, J=7.0 Hz, -CH-), 4.72 and 4.73(1H, dd, J=6.6, 0.9 Hz, 3-H), 5.32 and 5.38(1H, d, J=0.9 Hz, 4-H), 6.17 and 6.22(1H, s, -CH-Cl), 6.88 and 6.93(1H, s, $-CHPh_2$), 7.10-7.70(15H, m, -Ph).
10. 8: amorphous solid, FD-ms 790 (m/z, M^+); ir ν ($CHCl_3$) 1760, 1740, 1650, 1615 cm^{-1}. 9: colorless leaflets, mp 139-141°C (from methyl alcohol); ir ν ($CHCl_3$) 1765, 1730, 1658, 1617 cm^{-1}. Compounds 8 and 9 showed broad spectra by the presence of phosphorous.[2]
11. Reactions were reported; a) R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert, and P. Teyssie, Tetrahedron Lett., 1973, 2233. b) M. A. Mckervey and

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12. By the reaction of 11 with AcOH for 10 days at room temperature in the absence of rhodium(II) acetate the only starting material was recovered.

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14. 14a: amorphous solid, ir ν ($CHCl_3$) 1782, 1720, 1670 cm^{-1}; nmr δ (400 MHz, $CDCl_3$) 1.53(3H,d, J=6.7 Hz, 2-CH_3), 3.80(3H, s, N-CH_3), 4.06 and 4.67(2H, ABq, J=13 Hz, 3'-H), 4.81(1H, q, J=6.7 Hz, 2-H), 4.91(1H, dd, J=7.2, 1.0 Hz, 7-H), 5.12(1H, d, J=1.0 Hz, 6-H), 6.94(1H, s, -C<u>H</u>Ph_2), 7.10-7.90(16H, m, -Ph and -CONH-). 14b: amorphous solid, ir ν ($CHCl_3$) 1785, 1720, 1670 cm^{-1}; nmr δ (400 MHz, $CDCl_3$) 1.53(3H, d, J=6.7 Hz), 2.65(3H, s), 4.01 and 4.79(2H, ABq, J=14 Hz), 4.80(1H, q, J=6.7 Hz), 4.93(1H, dd, J=7.2 and 1.0 Hz), 5.07(1H, d, J=1.0 Hz), 6.87(1H, d, J=7.2 Hz), 6.95(1H, s), 7.20-7.80(15H, m). 14c: amorphous solid, ir ν ($CHCl_3$) 1786, 1738, 1672 cm^{-1}; nmr δ (400 MHz, $CDCl_3$) 1.45(3H, d, J=6.7 Hz), 1.96(3H, s), 4.57(1H, q, J=6.7 Hz), 4.65 and 5.16(2H, ABq, J=14 Hz), 4.99(1H, dd, J=7.2, 1.0 Hz), 5.03(1H, d, J=1.0 Hz), 6.92(1H, s), 7.20-7.90(16H, m). 16a: colorless leaflets, mp 155-158°C (decomp) (from methyl alcohol), ir ν ($CHCl_3$) 1788, 1718, 1670 cm^{-1}; nmr δ (400 MHz, $CDCl_3$) 1.52(3H, d, J=6.7 Hz, 2-CH_3), 3.81(3H, s, N-CH_3), 4.21 and 4.39 (2H, ABq, J=13 Hz, 3'-H), 4.82(1H, dd, J=7.2, 1.0 Hz, 7-H), 4.83(1H, q, J=6.7 Hz, 2-H), 5.30(1H, d, J=1.0 Hz, 6-H), 6.95(1H, s, -C<u>H</u>Ph_2), 7.05(1H, d, J=7.2 Hz, -CONH-), 7.20-7.90(15H, m, -Ph). 16b: colorless leaflets, mp 189-191°C (decomp) (from methyl alcohol), ir ν ($CHCl_3$) 1785, 1720, 1670 cm^{-1}; nmr δ (400 MHz, $CDCl_3$) 1.52(3H, d, J=6.9 Hz), 2.70(3H, s), 4.35(2H, s), 4.83(1H, q, J=6.9 Hz), 4.90(1H, dd, J=7.4, 1.0 Hz), 5.25(1H, d, J=1.0 Hz), 6.95(1H, d, J=7.4 Hz), 6.96(1H, s), 7.10-7.82(15H, m). 16c: colorless leaflets, mp 177-179°C (decomp) (from methyl alcohol), ir ν ($CHCl_3$) 1785, 1735, 1667 cm^{-1}; nmr δ (400 MHz, $CDCl_3$) 1.41(3H, d, J=6.9 Hz), 1.99(3H, s), 4.66(1H, q, J=6.9 Hz), 4.81 and 4.96(2H, ABq, J=13 Hz), 4.98(1H, dd, J=7.4, 1.0 Hz), 5.21(1H, d, J=1.0 Hz), 6.92(1H, s), 7.17(1H, d, J=7.4 Hz), 7.20-7.80(15H, m).
Chemical shifts of the 3-methylene protons of 14a are different from those of 16a.

15. 18: colorless needles, mp 130-132°C (decomp) (from ethyl acetate); ir ν ($CHCl_3$) 3450, 1784, 1728, 1662 cm^{-1}; nmr δ (90 MHz, $CDCl_3$) 1.46(3H, d, J=6.9 Hz), 4.22, 4.53(2H, ABq, J=11.5 Hz), 4.78(1H, q, J=6.9 Hz), 4.95(1H, dd,

J=7.5, 1.0 Hz), 5.23(1H, d, J=1.0 Hz), 6.95(1H, s), 7.10-7.80(15H, m).

16. 19: oil, ir ν ($CHCl_3$) 3450, 1787, 1724, 1670 cm^{-1}; nmr δ (90 MHz, $CDCl_3$) 1.49(3H, d, J=6.6 Hz), 4.08, 4.93(2H, ABq, J=12.3 Hz), 4.73(1H, q, J=6.6 Hz), 4.91 (1H, dd, J=7.2, 0.9 Hz), 5.10(1H, d, J=0.9 Hz), 6.82(1H, d, J=7.2 Hz), 6.90 (1H, s), 7.10-7.80(15H, m).
17. 21: oil, FD-ms m/z 496 (M^+); ir ν ($CHCl_3$) 3400, 1792, 1731, 1658 cm^{-1}; nmr δ (90 MHz, $CDCl_3$) 1.43(3H, d, J=6.8 Hz), 5.21(1H, dd, J=7.9, 2.0 Hz), 5.34(1H, d, J=2.0 Hz), 5.98(1H, s), 6.84(1H, s), 7.10-7.80(15H, m).
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