

NOVEL 2-METHYL-1-OXACEPHALOSPORINS 2.

SYNTHESIS OF 3-SUBSTITUTED 2-METHYL-1-OXACEPHEM NUCLEUS

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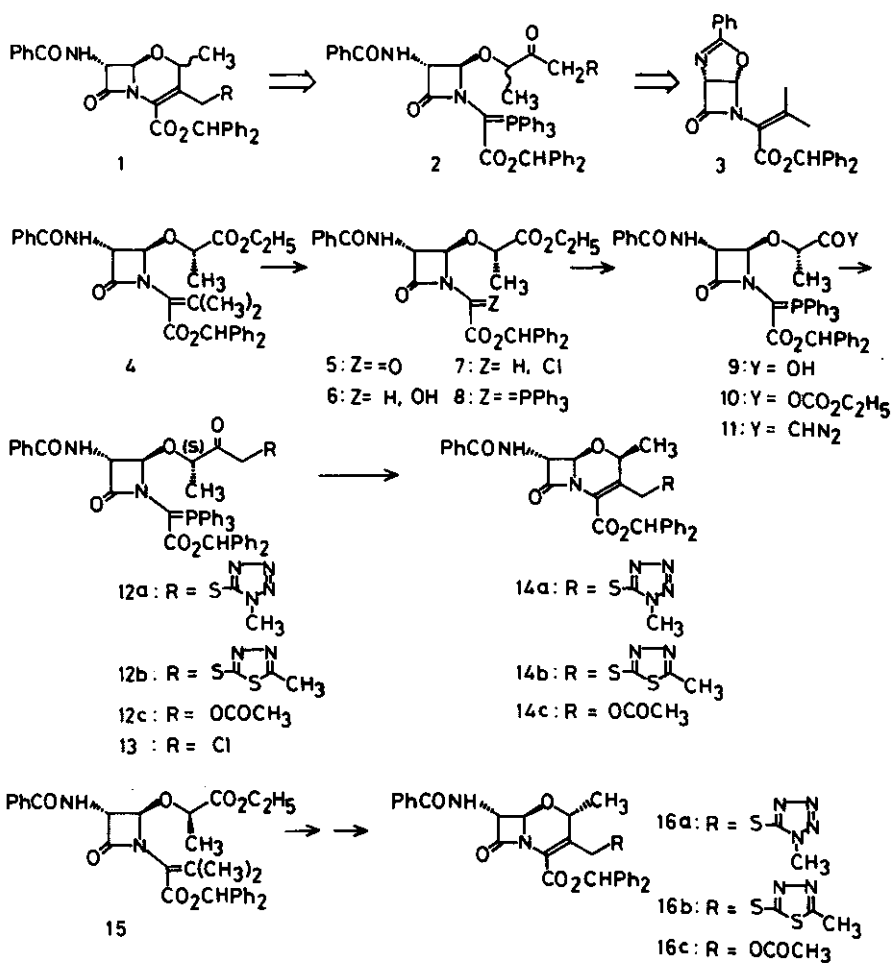
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Abstract — The stereoselective syntheses of 3-substituted 2 α - and 2 β -methyl-1-oxacephems have been achieved through the intramolecular Wittig condensations of 4-(1-methylpropoxy)azetidiones.

In our previous paper¹ the synthesis of 2-methyl-3-nor-1-oxacephems having a 7 α -acylamino group was reported. In this paper we describe a stereoselective synthesis of 3-substituted 1-oxacephems 1 by the intramolecular Wittig condensation² 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)-oxazolinoazetidione 3. As described in the following paper,³ the 7 β -acylamino compounds were derived from 1. Among them, OCP-9-176 (L-656,575) showed especially interesting biological activities.⁴⁻⁶

The synthesis of 2 β -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 Woodward² and applied in the 1-oxacephem series.⁷ Ozonolysis (O₃, CH₂Cl₂, -60°C, 30 min) of 4 followed by reduction (Zn, AcOH/CH₂Cl₂, -10°C, 30 min) afforded diastereoisomeric alcohol 6 (53%) via oxamide 5 which was not isolated.⁸ Chlorination (SOCl₂, pyridine, CH₂Cl₂, 0°C, 30 min, 98%) of 6 followed by treatment of the resulting chloride 7⁹ with triphenylphosphine (CHCl₃, 15h, room temperature, N₂ 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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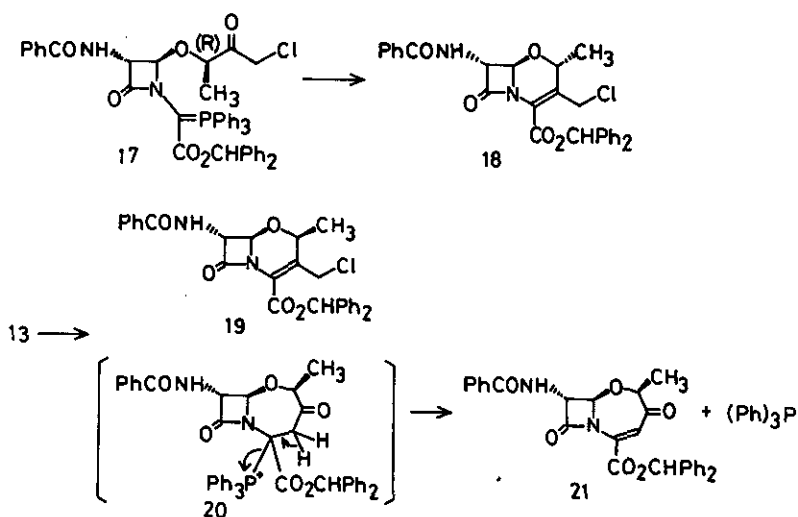


Alkaline hydrolysis of 8 (equimolar NaOH, aq. Me₂CO, 5°C, 1.5 h) gave acid 9 (95%).¹⁰ The activation of 9 with ethyl chloroformate in the presence of 4-methylmorpholine (CH₂Cl₂, -10°C, 30 min) gave mixed anhydride 10 which was treated successively with diazomethane to afford diazomethyl ketone 11 (ir; 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, N₂ 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** (R_f 0.69) and (Ph)₃PO (R_f 0.13). While, the reaction mixture of **13** showed three new spots (R_f 0.62, 0.70 and 0.95) with (Ph)₃PO. Purification by column chromatography on silica gel gave **19**¹⁶ (18%, R_f 0.70), (Ph)₃P (R_f 0.95) and 7-membered homooxacephem **21**¹⁷ (13%, R_f 0.62). The formation¹⁸ of **21** is likely to pass through Hoffmann type elimination¹⁹ 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 $(\text{Ph})_3\text{P}$.

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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, $\underline{J}=7.2$ Hz, $-\text{CH}_2\text{CH}_3$), 1.20 and 1.47(3H, d, $\underline{J}=7.0$ Hz, $-\text{CHCH}_3$), 4.03 and 4.12(2H, q, $\underline{J}=7.2$ Hz, $-\text{CH}_2\text{CH}_3$), 4.32 and 4.43(1H, q, $\underline{J}=7.0$ Hz, $-\text{CH}-$), 4.75 and 4.80(1H, dd, $\underline{J}=6.5, 0.9$ Hz, 3-H), 4.90 and 4.99(1H, d, $\underline{J}=0.9$ Hz, 4-H), 5.05 and 5.41(1H, br s, $-\text{CH}-\text{OH}$), 6.87 and 6.92(1H, s, $-\text{CHPh}_2$), 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, $\underline{J}=7.2$ Hz, $-\text{CH}_2\text{CH}_3$), 1.36 and 1.47(3H, d, $\underline{J}=7.0$ Hz, $-\text{CH}_3$), 4.12(2H, q, $\underline{J}=7.2$ Hz, $-\text{CH}_2-$), 4.43 and 4.52(1H, q, $\underline{J}=7.0$ Hz, $-\text{CH}-$), 4.72 and 4.73(1H, dd, $\underline{J}=6.6, 0.9$ Hz, 3-H), 5.32 and 5.38(1H, d, $\underline{J}=0.9$ Hz, 4-H), 6.17 and 6.22(1H, s, $-\text{CH}-\text{Cl}$), 6.88 and 6.93(1H, s, $-\text{CHPh}_2$), 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 (CHCl₃) 1782, 1720, 1670 cm⁻¹; nmr δ (400 MHz, CDCl₃) 1.53(3H, d, $J=6.7$ Hz, 2-CH₃), 3.80(3H, s, N-CH₃), 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, -CHPh₂), 7.10-7.90(16H, m, -Ph and -CONH-). 14b: amorphous solid, ir ν (CHCl₃) 1785, 1720, 1670 cm⁻¹; nmr δ (400 MHz, CDCl₃) 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 (CHCl₃) 1786, 1738, 1672 cm⁻¹; nmr δ (400 MHz, CDCl₃) 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 (CHCl₃) 1788, 1718, 1670 cm⁻¹; nmr δ (400 MHz, CDCl₃) 1.52(3H, d, $J=6.7$ Hz, 2-CH₃), 3.81(3H, s, N-CH₃), 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, -CHPh₂), 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 (CHCl₃) 1785, 1720, 1670 cm⁻¹; nmr δ (400 MHz, CDCl₃) 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 (CHCl₃) 1785, 1735, 1667 cm⁻¹; nmr δ (400 MHz, CDCl₃) 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 (CHCl₃) 3450, 1784, 1728, 1662 cm⁻¹; nmr δ (90 MHz, CDCl₃) 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,

- \underline{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 (CHCl₃) 3450, 1787, 1724, 1670 cm⁻¹; nmr δ (90 MHz, CDCl₃) 1.49(3H, d, \underline{J} =6.6 Hz), 4.08, 4.93(2H, ABq, \underline{J} =12.3 Hz), 4.73(1H, q, \underline{J} =6.6 Hz), 4.91 (1H, dd, \underline{J} =7.2, 0.9 Hz), 5.10(1H, d, \underline{J} =0.9 Hz), 6.82(1H, d, \underline{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 (CHCl₃) 3400, 1792, 1731, 1658 cm⁻¹; nmr δ (90 MHz, CDCl₃) 1.43(3H, d, \underline{J} =6.8 Hz), 5.21(1H, dd, \underline{J} =7.9, 2.0 Hz), 5.34(1H, d, \underline{J} =2.0 Hz), 5.98(1H, s), 6.84(1H, s), 7.10-7.80(15H, m).
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