

NOVEL 2-METHYL-1-OXACEPHALOSPORINS 1.

SYNTHESIS OF 2-METHYL-3-NOR-1-OXACEPHEM NUCLEUS

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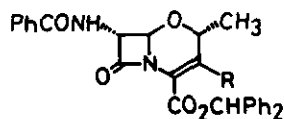
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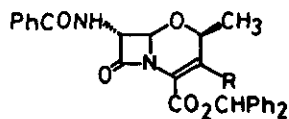
Abstract — The 2 α - and 2 β -methyl-1-oxacephem were synthesized stereoselectively starting from (3R,4S)-oxazolinoazetidinone by reaction with chiral alcohols followed by intramolecular carbene insertion of α -diazo- β -keto intermediates.

1-Oxacephem compounds have received considerable attention since antibacterial activity was found to be enhanced by the nuclear exchange of the sulfur atom of cepheems to oxygen.¹⁻⁵ We assumed that an introduction of α - or β -methyl substituent on C-2 to the 1-oxacephem ring might confer ring constraint and hence might influence the antibacterial activity including β -lactamase stability. Herein we report the stereoselective syntheses of novel 2 α -methyl- (1a and 2a) and 2 β -methyl-3-nor-1-oxacephem (1b and 2b)⁶ having a 7 α -acylamino group.

A chiral building block, (3R,4S)-oxazolinoazetidinone⁷⁻¹⁰ 3 was reacted with neat chiral alcohol (4a or 4b; 300 mg/ml) in the presence of CF₃SO₃H at room temperature for 1.5 h to give crystalline trans-4-alkoxyazetidinone 5a (49%; mp 133-135°C) or 5b (53%; mp 104-105°C) in a stereoselective manner,¹¹ respectively. In these cases the yield of 5 was not improved either with solvent (CHCl₃,

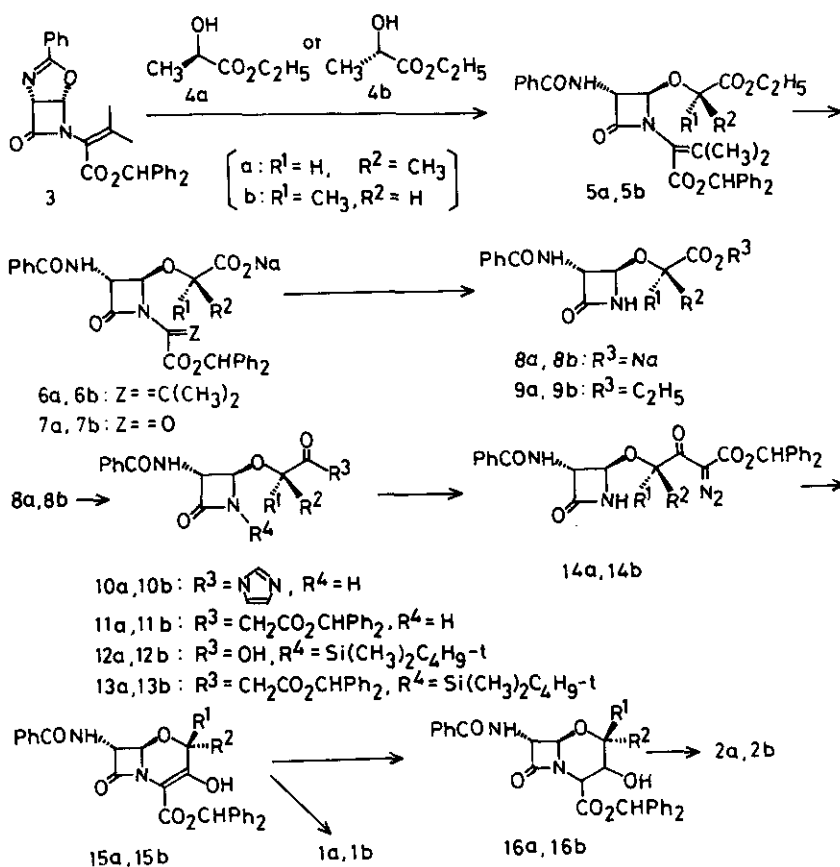
1a: R = OCH₃

2a: R = H

1b: R = OCH₃

2b: R = H

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EtOAc)¹⁰ or with use of Lewis acid as a catalyst ($\text{BF}_3 \cdot \text{Et}_2\text{O}$, ZnCl_2).¹²

Alkaline hydrolysis (equimolar NaOH, aq. Me_2CO , 1.5 h) of **5** gave crystalline Na salt of **6** quantitatively. Then, **6** was subjected to the sequence of Cooper¹³ for cleavage of the 3-methyl-2-butenate residue, consisting of ozonolysis (O_3 , MeOH, -60°C), reduction of the ozonide with NaHSO_3 and followed by alkaline hydrolysis (equimolar NaHCO_3 , aq. MeOH, 5°C , 30 min) of oxamide **7**, to afford **8** (93% as the Na salt).¹⁴ The same procedure starting from **5** gave ester **9** in low yield (16%) together with decomposition products.¹⁵

Activation of **8** ($\text{N,N}'$ -carbonyldiimidazole, THF, room temperature, 30 min) to give imidazolide **10**, followed by the reaction with diphenylmethylmagnesium malonate (0°C , 15 h) according to the method of Masamune,¹⁶ gave β -keto ester **11** (23%). β -Keto ester formation was improved starting from N-tert-butyl dimethylsilylazetidione **12** which was prepared from **8** to afford **13** (a: 38%, b: 40%). The diazo-transfer reaction¹⁷ of **11** with p -carboxybenzenesulfonyl azide in MeCN in the presence of Et_3N (0°C , 1 h) gave crystalline α -diazo- β -keto ester **14**. The cycli-

zation via the intramolecular carbene insertion reaction¹⁷ was carried out. Heating of 14 with a catalytic amount of rhodium(II) acetate in EtOAc (60°C, 40 min) under N₂ atmosphere gave 15 quantitatively. The unstable 15 was treated with CH₂N₂ (EtOAc, 5°C, 30 min) to give 1a or 1b,¹⁸ quantitatively from 11. Reduction of 15 with tetrabutylammonium borohydride (THF, 5°C, 30 min) gave 2-methyl-3-hydroxy-1-oxacephams (16a or 16b). Compounds 16a and 16b were mesylated with methanesulfonyl chloride in the presence of Et₃N to give 2a (56% from 15a) and 2b (76% from 15b),¹⁸ respectively. Preparation of further modified 2-methyl-1-oxacephams and their antibacterial profiles will be subjects of a separate paper.¹⁹

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14. The catalyst for the hydrolysis of 7 was critical: known catalysts (silicic acid¹¹ and CH₃ONa^{14,16}) gave by-products and NaHCO₃ gave the best result.
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18. Selected Physical Data. 1a: oil, nmr δ (400 MHz, CDCl₃) 1.42(3H, d, $J=7.0$ Hz), 3.67(3H, s), 4.63(1H, q, $J=7.0$ Hz), 5.06(1H, dd, $J=7.0, 0.9$ Hz), 5.11(1H, d, $J=0.9$ Hz), 6.95(1H, s), 7.10-7.80(16H, m); ir ν (CHCl₃) 1780, 1720, 1670 cm⁻¹. 1b: oil, nmr δ (CDCl₃) 1.43(3H, d, $J=6.7$ Hz), 3.57(3H, s), 4.47(1H, q, $J=6.7$ Hz), 4.90(1H, d, $J=0.7$ Hz), 5.04(1H, s), 6.91(1H, s), 7.10-7.80(16H, m); ir ν (CHCl₃) 1770, 1715, 1663 cm⁻¹. 2a: oil, nmr δ (CDCl₃) 1.33(3H, d, $J=6.9$ Hz), 4.69(1H, dq, $J=6.9, 3.7$ Hz), 5.06(1H, s), 5.06(1H, dd, $J=6.8, 0.7$ Hz), 6.44(1H, d, $J=3.7$ Hz), 6.97(1H, s), 7.10-7.80(16H, m); ir ν (CHCl₃) 1782, 1725, 1664 cm⁻¹. 2b: oil, nmr δ (CDCl₃) 1.39(3H, d, $J=7.0$ Hz), 4.50(1H, dq, $J=7.0, 1.7$ Hz), 5.03(1H, d, $J=1.0$ Hz), 5.07(1H, dd, $J=7.9, 1.0$ Hz), 6.21(1H, d, $J=1.7$ Hz), 6.92(1H, s), 7.10-7.90(16H, m); ir ν (CHCl₃) 1781, 1727, 1665 cm⁻¹. 5a: colorless leaflets, mp 133-135°C (from ethyl ether), $[\alpha]_D^{25} -2.1^\circ$ (c 1, CHCl₃); EI-ms 570 (M⁺); nmr δ (CDCl₃) 1.19(3H, t, $J=7.2$ Hz), 1.25(3H, d, $J=7.0$ Hz), 2.08(3H, s), 2.27(3H, s), 4.03(1H, q, $J=7.0$ Hz), 4.10(2H, q, $J=7.2$ Hz), 4.89(1H, dd, $J=6.7, 1.1$ Hz), 5.30(1H, d, $J=1.1$ Hz), 6.55(1H, d, $J=6.7$ Hz), 6.92(1H, s), 7.00-7.77(15H, m). 5b: colorless prisms, mp 104-106°C (from ethyl ether), $[\alpha]_D^{25} -75^\circ$ (c 1, CHCl₃); nmr δ (CDCl₃) 1.12(3H, t, $J=7.2$ Hz), 1.42(3H, d, $J=7.0$ Hz), 2.06(3H, s), 2.28(3H, s), 3.97(2H, q, $J=7.2$ Hz), 4.40(1H, q, $J=7.0$ Hz), 4.79(1H, dd, $J=6.7, 1.1$ Hz), 5.07(1H, d, $J=1.1$ Hz), 6.67(1H, d, $J=6.7$ Hz), 6.85(1H, s), 7.00-7.60(15H, m). 6a: colorless crystals, mp 160-162°C (from ethyl alcohol). 6b: colorless crystals, mp 163-166°C (from ethyl acetate). 8a: nmr δ (DMSO-d₆) 1.20(3H, d, $J=6.8$ Hz), 3.75(1H, q, $J=6.8$ Hz), 4.61(1H, d, $J=8.1$ Hz), 5.32(1H, d, $J=1.3$ Hz), 7.20-7.80(5H, m), 8.90(1H, s), 9.19(1H, d, $J=8.1$ Hz). 11a: oil, nmr δ (CDCl₃) 1.34(3H, d, $J=6.9$ Hz), 3.70(2H, s), 4.27(1H, q, $J=6.9$ Hz), 4.57(1H, dd, $J=7.0, 0.7$ Hz), 5.13(1H, d, $J=0.7$ Hz), 6.82(1H, s), 6.85(1H, s), 7.06(1H, d), 7.10-7.80(15H, m). 14a: oil, nmr δ (CDCl₃) 1.40(3H, d, $J=6.7$ Hz), 4.57(1H, dd, $J=6.7, 0.7$ Hz),

5.13(1H, q, \underline{J} =6.7 Hz), 5.29(1H, d, \underline{J} =0.7 Hz), 6.46(1H, s), 6.67(1H, d, \underline{J} =6.7 Hz), 6.96(1H, s), 7.10-7.60(15H, m); ir ν (CHCl₃) 2130, 1775, 1758, 1708 cm⁻¹.

15a: colorless crystals, mp 111-112°C (decomp) (from acetonitrile), nmr δ (CDCl₃) 1.51(3H, d, \underline{J} =6.9 Hz), 4.56(1H, q, \underline{J} =6.9 Hz), 5.02(1H, dd, \underline{J} =7.4, 0.6 Hz), 5.20(1H, d, \underline{J} =0.6 Hz), 6.78(1H, d, \underline{J} =7.4 Hz), 6.98(1H, s), 7.10-7.80

(15H, m) ; ir ν (CHCl₃) 3440, 1779, 1664 cm⁻¹. 15b: colorless crystals, mp 175-177°C (decomp) (from acetonitrile), nmr δ (CDCl₃) 1.41(3H, d, \underline{J} =6.8 Hz),

4.54(1H, q, \underline{J} =6.8 Hz), 5.02(1H, dd, \underline{J} =6.9, 0.7 Hz), 5.02(1H, d, \underline{J} =0.7 Hz),

6.89(1H, d, \underline{J} =6.6 Hz), 6.93(1H, s), 7.10-7.80(15H, m). 16a: colorless crystals,

mp 106-109°C (from ethyl acetate), nmr δ (CDCl₃) 1.27(3H, d, \underline{J} =6.4 Hz),

3.99(1H, q, \underline{J} =6.4 Hz), 4.19(1H, d, \underline{J} =5.9 Hz), 4.67(1H, d, \underline{J} =5.9 Hz), 5.17(1H,

dd, \underline{J} =7.9, 0.8 Hz), 5.31(1H, d, \underline{J} =0.8 Hz), 6.92(1H, s), 7.10-7.80(16H, m).

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