NOVEL 2-METHYL-1-OXACEPHALOSPORINS 1. SYNTHESIS OF 2-METHYL-3-NOR-1-OXACEPHEM NUCLEUS

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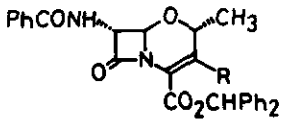
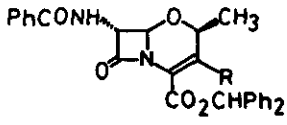
Abstract — The 2α- and 2β-methyl-1-oxacephems were synthesized stereoselectively starting from (3R,4S)-oxazolinoazetidinone by reaction with chiral alcohols followed by intramolecular carbene insertion of α-diazo-β-keto intermediates.

1-Oxacephem compounds have received considerable attention since antibacterial activity was found to be enhanced by the nuclear exchange of the sulfur atom of cephems 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 2α-methyl- (1a and 2a) and 2β-methyl-3-nor-1-oxacephems (1b and 2b)[6] having a 7α-acylamino group.
A chiral building block, (3R,4S)-oxazolinoazetidinone[7-10] 3 was reacted with neat chiral alcohol (4a or 4b; 300 mg/ml) in the presence of CF_3SO_3H 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 ($CHCl_3$,



1a: R = OCH_3
2a: R = H



1b: R = OCH_3
2b: R = H

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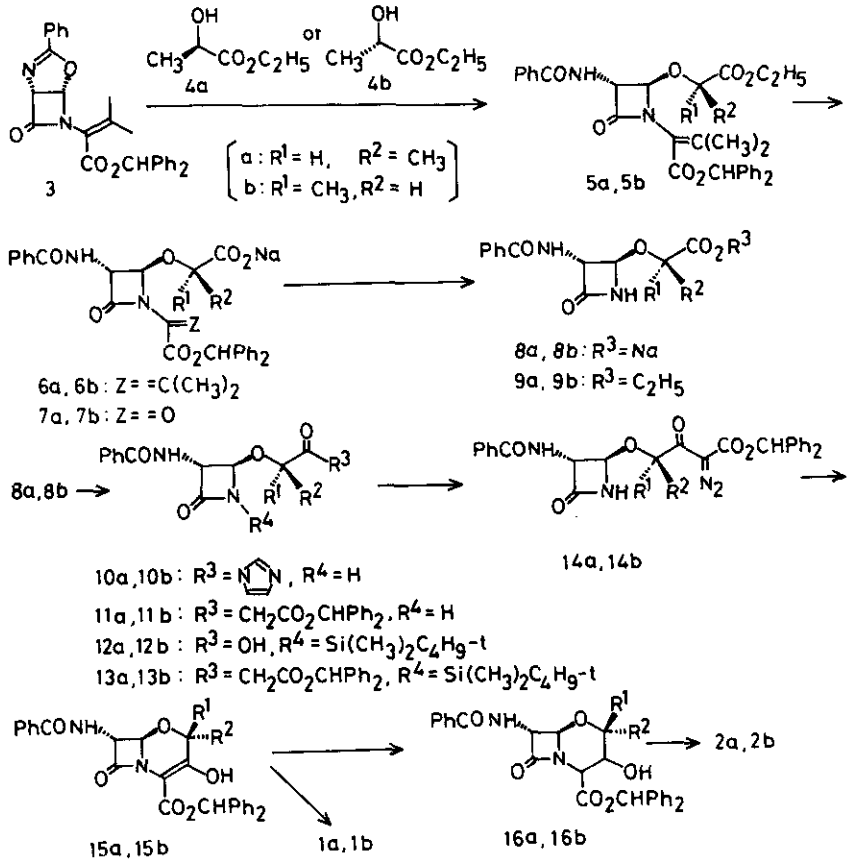

EtOAc)[10] or with use of Lewis acid as a catalyst ($BF_3 \cdot Et_2O$, $ZnCl_2$).[12]

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 Cooper[13] for cleavage of the 3-methyl-2-butenoate 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 (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-butyldimethylsilylazetidinone 12 which was prepared from 8 to afford 13 (a: 38%, b: 40%). The diazo-transfer reaction[17] 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 reaction[17] was carried out. Heating of 14 with a catalytic amount of rhodium(II) acetate in EtOAc (60°C, 40 min) under N_2 atmosphere gave 15 quantitatively. The unstable 15 was treated with CH_2N_2 (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 Et_3N to give 2a (56% from 15a) and 2b (76% from 15b),[18] respectively. Preparation of further modified 2-methyl-1-oxacephems and their antibacterial profiles will be subjects of a separate paper.[19]

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6. Our prototype synthesis was achieved on 2-unsubstituted 1-oxacephems: Jpn. Pat. Kokai 58-103391 (Chem. Abstr., 1983, 99, 139636z). And the same strategic syntheis was reported by two other groups. a) D. Habich and W. Hartwig, Tetrahedron, 1984, 40, 3667. b) S. Yamamoto, H. Itani, H. Takahashi, T. Tsuji, and W. Nagata, Tetrahedron Lett., 1984, 25, 4545.
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14. The catalyst for the hydrolysis of 7 was critical: known catalysts (silicic acid[11] and CH_3ONa[14,16]) gave by-products and $NaHCO_3$ gave the best result.

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18. Selected Physical Data. 1a: oil, nmr δ (400 MHz, $CDCl_3$) 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 ($CHCl_3$) 1780, 1720, 1670 cm^{-1}. 1b: oil, nmr δ ($CDCl_3$) 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 ($CHCl_3$) 1770, 1715, 1663 cm^{-1}. 2a: oil, nmr δ ($CDCl_3$) 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 ($CHCl_3$) 1782, 1725, 1664 cm^{-1}. 2b: oil, nmr δ ($CDCl_3$) 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 ($CHCl_3$) 1781, 1727, 1665 cm^{-1}. 5a: colorless leaflets, mp 133-135°C (from ethyl ether), $[\alpha]_D^{25}$-2.1° (c 1, $CHCl_3$); EI-ms 570 (M^+); nmr δ ($CDCl_3$) 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° (c 1, $CHCl_3$); nmr δ (CDC_3) 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-d_6) 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 ($CDCl_3$) 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 ($CDCl_3$) 1.40(3H, d, J=6.7 Hz), 4.57(1H, dd, J=6.7, 0.7 Hz),

5.13(1H, q, J=6.7 Hz), 5.29(1H, d, J=0.7 Hz), 6.46(1H, s), 6.67(1H, d, J=6.7 Hz), 6.96(1H, s), 7.10-7.60(15H, m); ir ν ($CHCl_3$) 2130, 1775, 1758, 1708 cm^{-1}. 15a: colorless crystals, mp 111-112°C (decomp) (from acetonitrile), nmr δ ($CDCl_3$) 1.51(3H, d, J=6.9 Hz), 4.56(1H, q, J=6.9 Hz), 5.02(1H, dd, J=7.4, 0.6 Hz), 5.20(1H, d, J=0.6 Hz), 6.78(1H, d, J= 7.4 Hz), 6.98(1H, s), 7.10-7.80 (15H, m) ; ir ν ($CHCl_3$) 3440, 1779, 1664 cm^{-1}. 15b: colorless crystals, mp 175-177°C (decomp) (from acetonitrile), nmr δ ($CDCl_3$) 1.41(3H, d, J=6.8 Hz), 4.54(1H, q, J=6.8 Hz), 5.02(1H, dd, J=6.9, 0.7 Hz), 5.02(1H, d, J=0.7 Hz), 6.89(1H, d, 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 ($CDCl_3$) 1.27(3H, d, J=6.4 Hz), 3.99(1H, q, J=6.4 Hz), 4.19(1H, d, J=5.9 Hz), 4.67(1H, d, J=5.9 Hz), 5.17(1H, dd, J=7.9, 0.8 Hz), 5.31(1H, d, J=0.8 Hz), 6.92(1H, s), 7.10-7.80(16H, m).

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