IMPROVED SYNTHESIS OF 3'-NOR-1-OXACEPHEMS†

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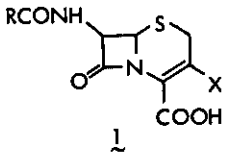
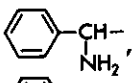
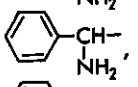
Abstract — Several improved synthetic routes to 7α-unsubstituted and 7α-methoxylated 3'-nor-1-oxacephems, 3 and 4, from 7α-benzoylamino-3-methylene-1-oxacepham 2 were established.

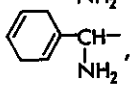
In 1972 Scartazzini and Bickel[1] reported synthesis of 3-unsubstituted cephem compound 1a which represented the first example of the 3'-nor type of cephalosporins showing significant antibacterial activity. Since then much interest has been focused on the synthesis of this type of cephalosporins[2] and several clinically useful antibiotics, such as cefaclor,[3] 1b, cefroxadine,[1] 1c, and ceftizoxime,[4] 1d, have been discovered. With this background it was highly expected that some useful 3'-nor type compounds could be found in the 1-oxacephem series. Synthesis of 3'-nor-1-oxacephems was thus undertaken in our laboratories and the first successful routes, though rather lengthy, were already reported.[5] Very recently synthesis and antibacterial activity of 3-unsubstituted 1-oxacephems with a variety of 7β- side chains of the ceftizoxime type have been

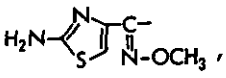


1

a: R =  X = H

b: R =  X = Cl

c: R =  X = OCH_3

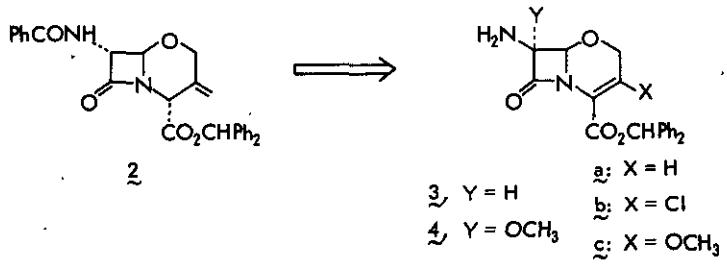
d: R =  X = H

† Dedicated to Dr. Herbert C. Brown, Emeritus Professor of Purdue University, on the occasion of his 70th birthday.

reported by the Fujisawa group.[6]

In this paper we wish to describe improved synthetic routes to 7α-unsubstituted and 7α-methoxylated 3'-nor-1-oxacephem nuclei, 3 and 4, from 7α-benzoylamino-3-methylene-1-oxacepham derivative 2, a key intermediate in the synthesis of our recently developed β-lactam antibiotic 6059-S (latamoxef or moxalactam).[7]

Scheme 1



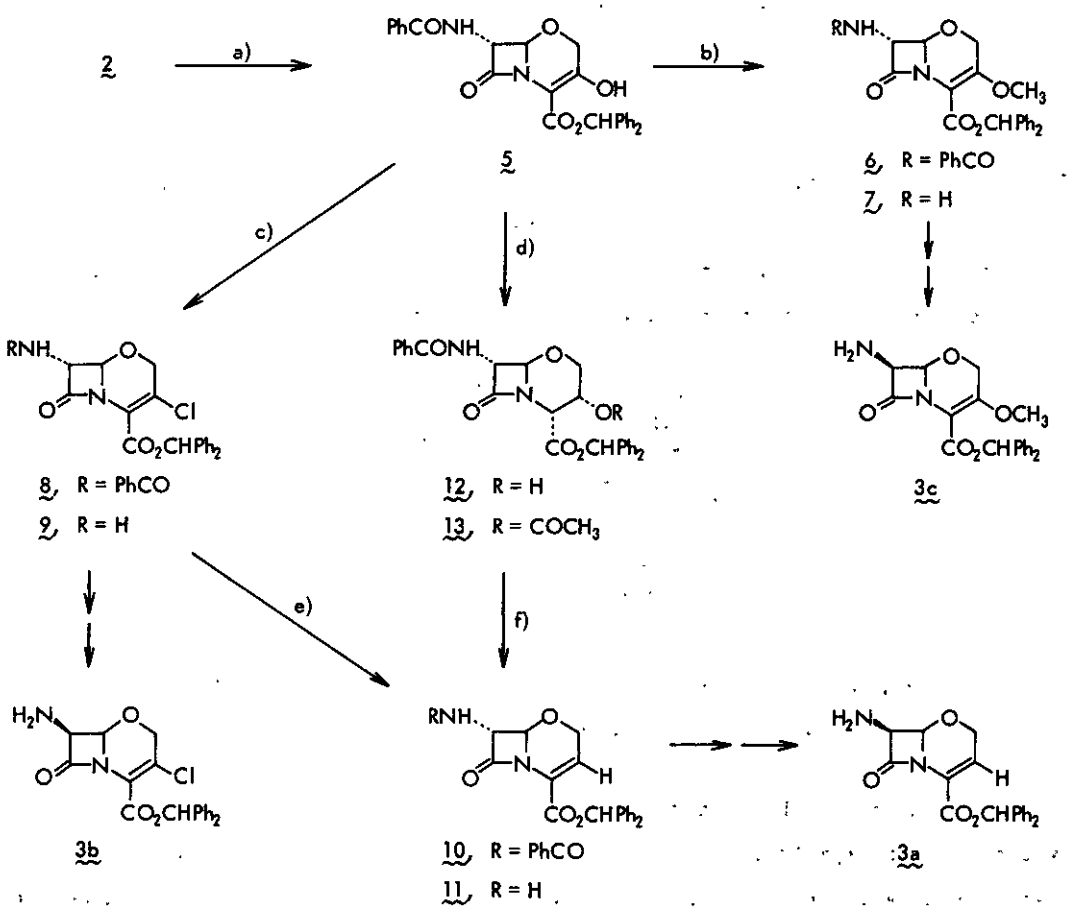
2

3, Y = H
4, Y = OCH_3

a: X = H
b: X = Cl
c: X = OCH_3

Ozonolysis of 2 and subsequent reduction gave 3-hydroxy-3-cephem 5 in almost quantitative yield. The enol structure of the 3-oxo group in this compound is assigned on the basis of its spectral data [IR ($CHCl_3$) 3440, 3330 cm^{-1} (3-OH hydrogenbonded with 4-ester oxygen); NMR ($CDCl_3$) δ 11.03 (enol H)]. In contrast with the case of the corresponding 1-thia analogs[2b] no careful control of the reaction conditions (amount of ozone, reaction temperature, etc.) was necessary owing to lack of the 1-sulfur atom which is very sensitive to various oxidation reagents or more generally various electrophiles. Whereas methylation of 5 with diazomethane proceeded well to give 6 [IR ($CHCl_3$) 3370, 1780, 1710, 1665, 1625 cm^{-1}; NMR ($CDCl_3$) δ 3.65 (3H, s, C_3-OCH_3), 4.37 (2H, d, J = 16 Hz, C_2-H), 4.75 (1H, s, C_6-H), 5.13 (1H, d, J = 7 Hz, C_7-H), 6.83 (1H, s, $CHPh_2$), 7.2-8.0 (16H, m, C_6H_5, NH)] in quantitative yield, chlorination or O-mesylation worked rather sluggishly in contrast with the smooth conversion of the corresponding (1-thia)cephem analogs:[2c,2d] every attempt to obtain the O-mesyl derivative of 5 failed and only the use of chlorine-triphenylphosphine complex and triethylamine was found effective to afford 3-chloro-1-oxacephem 8 [NMR ($CDCl_3$) δ 4.32 (2H, s, C_2-H), 4.75 (1H, s, C_6-H), 5.22 (1H, d, J = 8 Hz, C_7-H), 6.87 (1H, s, $CHPh_2$), 7.2-8.1 (16H, m, C_6H_5, NH)] in 30% yield. This compound underwent dechlorination with zinc and acetic acid to give 3-unsubstituted 1-

Scheme 2



a) O_3/CH_2Cl_2-MeOH, -78°; Zn-HOAc b) CH_2N_2 c) $Ph_3P \cdot Cl_2/(C_2H_5)_3N$/THF d) B_2H_6/THF
e) Zn-HOAc f) $MsCl/(C_2H_5)_3N$

oxa-3-cephem 10 [IR ($CHCl_3$) 3380, 1790, 1730, 1670 cm^{-1}; NMR ($CDCl_3$) δ 4.23 (2H, br s, C_2-H), 4.88 (1H, s, C_6-H), 5.22 (1H, d, J = 8 Hz, C_7-H), 6.27 (1H, br s, C_3-H), 6.90 (1H, s, $CHPh_2$), 7.1-8.3 (16H, m, C_6H_5, NH)] in high yield.[8] An alternative and clearly better route to this compound involves diborane reduction[2b] of 5 to 1-oxacepham derivative 12 [IR ($CHCl_3$) 3430, 3350 (br), 1778, 1740, 1620 cm^{-1}; NMR ($CDCl_3$) δ 3.4-4.2 (4H, m, C_2-H, C_3-H, OH), 4.90 (2H, br d, J = 6 Hz, C_4-H, C_7-H), 5.30 (1H, s, C_6-H), 6.88 (1H, s, $CHPh_2$), 7.1-7.8 (16H, m, C_6H_5, NH)] and subsequent mesylation-elimination reaction with mesyl chloride and triethylamine giving 10 in 80% over-all yield. Stereochemical assignment

of alcohol 12 is based upon the following NMR data of its acetate 13. As shown in Fig., H-2α and H-2β signals appear as the AB part of an ABX-type system (at δ 3.86 and 3.70, respectively) in C_6D_6. Five percents of nuclear Overhauser effects (NOE) were observed between the H-2α and H-6α signals. The $^3J_{2\alpha,3\beta}$, $^3J_{2\beta,3\beta}$ and $^3J_{3\beta,4\beta}$ values were 9.1, 4.8, and 6.9 Hz, respectively. These facts indicate a half chair conformation of the perhydrooxazine ring, 3α configuration of 3-acetoxyl, and 4α configuration of 4-benzhydryloxycarbonyl, respectively. Thus, diborane reduction occurred stereoselectively from the β-face of the 1-oxacephem molecule.

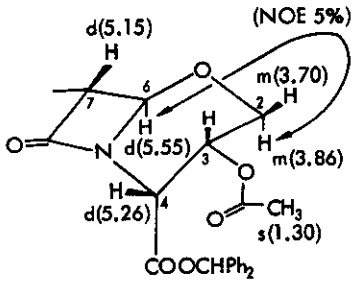


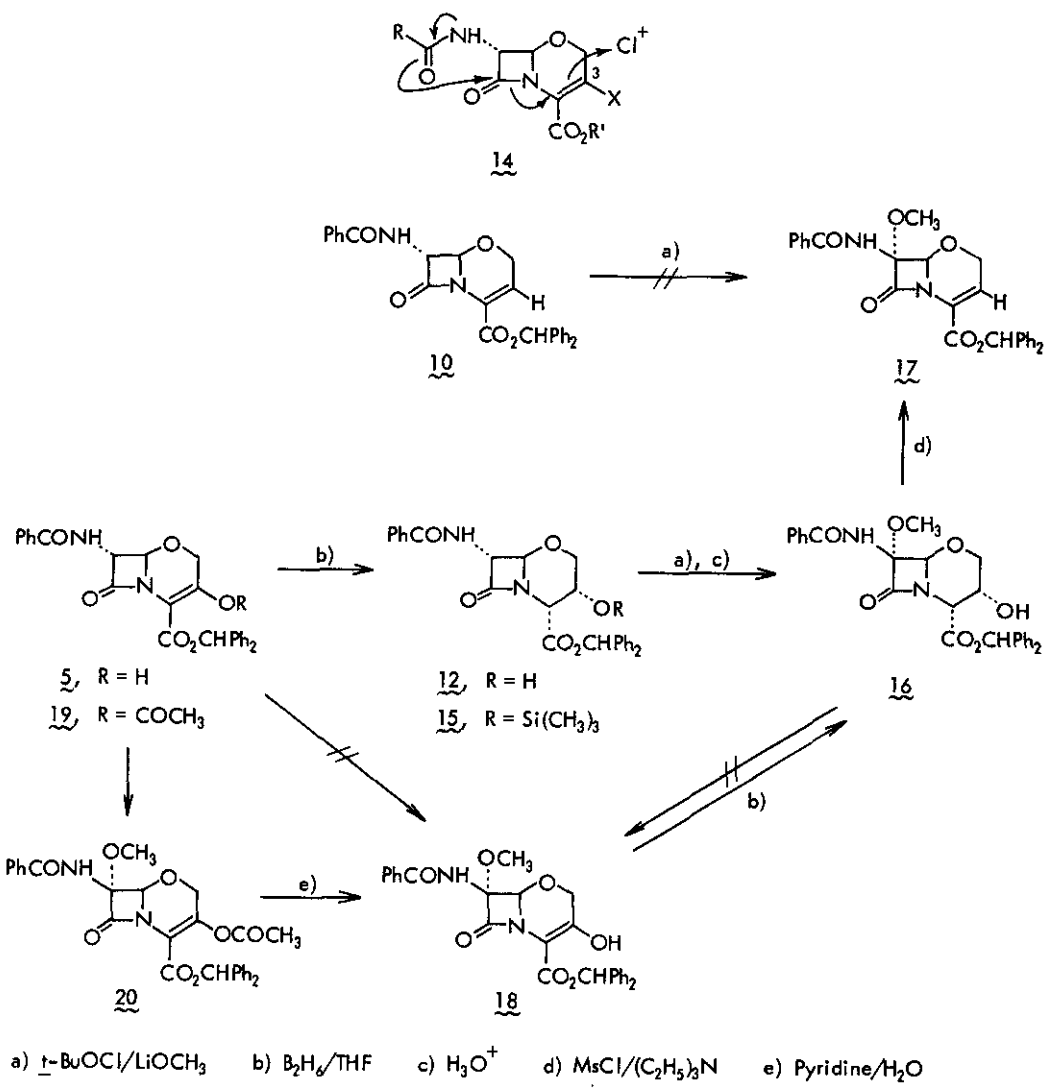
Fig. H¹-Chemical shifts (δ, ±0.01 ppm), coupling constants ($J_{H,H}$ ±0.1 Hz), and NOE values (±2%) of 1-oxacepham 13 in C_6D_6.

Deacylation of the 7α-benzoylamino side chains in 6, 8, and 10 was effected by a conventional method using phosphorus pentachloride and pyridine followed by a sequential addition of methanol and water to give 7α-amino-3'-nor-1-oxacephems 7 [IR ($CHCl_3$) 3550, 3400, 1775, 1715, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.06 (2H, br s, NH_2), 3.70 (3H, s, C_3-OCH_3), 3.97 (1H, br s, C_7-H), 4.40 (2H, s, C_2-H), 4.72 (1H, s, C_6-H), 7.00 (1H, s, $CHPh_2$), 7.2-7.7 (10H, m, C_6H_5)], 9 [NMR ($CDCl_3$) δ 2.22 (2H, br s, NH_2), 4.03 (1H, br s, C_7-H), 4.32 (2H, s, C_2-H), 4.73 (1H, s, C_6-H), 6.97 (1H, s, $CHPh_2$), 7.1-7.6 (10H, m, C_6H_5)], and 11 [IR ($CHCl_3$) 3400, 3340, 1785, 1730, 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.87 (2H, br s, NH_2), 3.72 (1H, s, C_7-H), 4.38 (2H, d, J = 3 Hz, C_2-H), 4.65 (1H, s, C_6-H), 6.35 (1H, t, J = 3 Hz, C_3-H), 7.00 (1H, s, $CHPh_2$), 7.1-7.7 (10H, m, C_6H_5)], respectively, each in high yield. These 7α-amino compounds were finally subjected to epimerization by our newly developed procedure[9] [borohydride reduction of 7-(2,2-dichlorovinylimino derivatives)] giving 7β-amino-3'-nor-1-oxacephem 3c [IR (Nujol) 3520, 3400, 1785, 1725, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (2H, br s, NH_2), 3.77 (3H, s, OCH_3), 4.48 (1H, d, J = 4

Hz, C_7-H), 4.52 (2H, s, C_2-H), 4.98 (1H, d, J = 4 Hz, C_6-H), 6.98 (1H, s, $CHPh_2$), 7.2-7.6 (10H, m, C_6H_5)], 3b [IR (Nujol) 3520, 1785, 1720, 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.07 (2H, br s, NH_2), 4.40 (2H, s, C_2-H), 4.45 (1H, d, J = 4 Hz, C_7-H), 4.98 (1H, d, J = 4 Hz, C_6-H), 6.97 (1H, s, $CHPh_2$), 7.2-7.6 (10H, m, C_6H_5)] and 3a [IR (Nujol) 3530, 3400, 1785, 1725, 1640 cm^{-1}] respectively, in acceptable yields.

In contrast with the synthesis of 7α-unsubstituted 3'-nor-1-oxacephems, the way to 7α-methoxylated 3'-nor-1-oxacephems was not plain, since, in general, 3'-*nor*-1-oxacephems are sensitive to attack by a cationic reagent such as Cl^+ undergoing severe decomposition as indicated in formula 14. Thus, attempted methoxylation of 3-unsubstituted 1-oxacephem 10 by a conventional method using t-butyl hypochlorite and lithium methoxide resulted in formation of a mixture of non-β-lactams and no desired product 17 was obtained. Therefore, an indirect and lengthy way was necessary to prepare this compound; 3α-hydroxy-1-oxacepham 12 obtained by diborane reduction of 5 as described earlier, was first trimethylsilylated giving 15 [mp 157-158°. Anal. Calcd. $C_{30}H_{32}O_6N_2Si$: C, 66.15; H, 5.92; N, 5.14. Found: C, 66.16; H, 5.90; N, 5.10. $[\alpha]_D^{23}$ +2.1 ± 0.4 (c = 1.016, $CHCl_3$); IR ($CHCl_3$) 3430, 1778, 1740, 1673 cm^{-1}; NMR ($CDCl_3$) δ 0.0 (9H, s, Si-CH_3), 3.6-4.2 (3H, m, C_2-H, C_3-H), 4.80 (1H, d, J = 6 Hz, C_3-H or C_7-H), 4.91 (1H, d, J = 6 Hz, C_7-H or C_3-H), 5.30 (1H, s, C_6-H), 6.87 (1H, s, $CHPh_2$), 6.9-7.8 (16H, m, C_6H_5, NH)] which was then subjected to the conventional 7α-methoxylation followed by hydrolysis to afford the 7α-methoxy 1-oxacepham 16 [IR ($CHCl_3$) 3430, 1781, 1740, 1683 cm^{-1}; NMR ($CDCl_3$) δ 3.47 (3H, s, C_7-OCH_3), 3.7-4.3 (4H, m, C_2-H, C_3-H, C_3-OH), 4.97 (1H, d, J = 5 Hz, C_4-H), 5.40 (1H, s, C_6-H), 6.93 (1H, s, $CHPh_2$), 7.1-7.9 (16H, m, C_6H_5, NH)] in 83% yield. This compound was now led to 3-*unsubstituted* 7α-methoxy-1-oxa-3-cephem 17 [IR ($CHCl_3$) 3440, 1790, 1734, 1695 cm^{-1}; NMR ($CDCl_3$) δ 3.57 (3H, s, C_7-OCH_3), 4.41 (2H, d, J = 2 Hz, C_2-H), 5.13 (1H, s, C_6-H), 6.45 (1H, t, J = 2 Hz, C_3-H), 6.97 (1H, s, $CHPh_2$), 7.1-8.0 (16H, m, C_6H_5, NH)] in 93% yield. Despite the success it appeared most desirable to have 7α-methoxy-3-hydroxy-1-oxacephem 18 as a common intermediate as can be easily understood from the above discussion about the synthesis of 7α-unsubstituted 3'-nor-1-oxacephems. Unfortunately direct methoxylation of 5 or oxidation of 16 did not give 18 at all and so some device was necessary. It was anticipated that acylation of the 3-hydroxy group in 5 would reduce the nucleophilic susceptibility of the Δ^3-double bond to prevent

Scheme 3

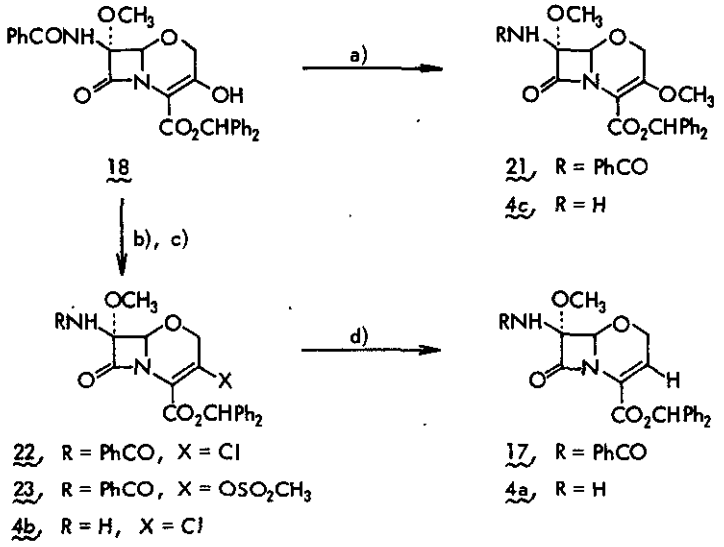


the decomposition with the chlorinating agent as depicted in 14. Thus, 5 was first acetylated to enol acetate 19 [mp 135-137°. Anal. Calcd. $C_{29}H_{24}O_7N_2$: C, 67.96; H, 4.72; N, 5.47. Found: C, 67.66; H, 4.67; N, 5.39. $[\alpha]_D^{23}$ +10.2 ± 0.5° (c = 1.037, $CHCl_3$); IR ($CHCl_3$) 3430, 3380, 1790, 1730, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.83 (3H, s, $COCH_3$), 4.27 (2H, s, C_2-H), 4.80 (1H, s, C_6-H), 5.13 (1H, d, J = 8 Hz, C_7-H), 6.87 (1H, s, $CHPh_2$), 7.1-8.0 (16H, m, C_6H_5, NH)] which was now subjected to 7α-methoxylation using t-butyl hypochlorite and lithium

methoxide. As expected methoxylation of this compound was very successful, giving in 85% yield 7α-methoxy enol acetate 20 [IR ($CHCl_3$) 3425, 1790, 1733, 1683 cm^{-1}; NMR ($CDCl_3$) δ 1.92 (3H, s, $COCH_3$), 3.55 (3H, s, C_7-OCH_3), 4.33 (2H, s, C_2-H), 5.28 (1H, s, C_6-H), 6.95 (1H, s, $CHPh_2$), 7.1-8.1 (16H, m, C_6H_5, NH)] which on treatment with wet pyridine was converted into the desired compound 18 [IR ($CHCl_3$) 3430, 3325, 1785, 1735, 1680, 1625 cm^{-1}; NMR ($CDCl_3$) δ 3.58 (3H, s, C_7-OCH_3), 4.28 (2H, s, C_2-H), 5.22 (1H, s, C_6-H), 6.98 (1H, s, $CHPh_2$), 7.1-8.1 (17H, m, C_6H_5, NH, C_3-OH)] in almost quantitative yield. It may be noteworthy that this compound was reduced with diborane giving in good yield a 1-oxacepham compound which proved to be identical with 16 obtained from 5 via 12. This result indicates that diborane reduction occurred from the β face, irrespective of the substituent at C_7.

With the common intermediate 18 in hand, synthesis of the representative 7α-methoxylated 3'-norcephems proceeded smoothly an analogous way to that of 7α-unsubstituted analogs. Compound 18 was converted on treatment with diazomethane into 3-methoxy-3'-nor-1-oxacephem 21 [IR ($CHCl_3$) 3425, 1780, 1725, 1682, 1625 cm^{-1}; NMR ($CDCl_3$) δ 3.57 (3H, s, C_7-OCH_3), 3.61 (3H, s, C_3-OCH_3), 4.33 (2H, s, C_2-H), 5.18 (1H, s, C_6-H), 6.88 (1H, s, $CHPh_2$), 7.2-8.1 (16H, m, C_6H_5, NH)], with triphenylphosphine-chlorine complex in the presence of triethylamine into 3-chloro-3'-nor-1-oxacephem 22 [IR ($CHCl_3$) 3430, 1792, 1735, 1688 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (3H, s, C_7-OCH_3), 4.33 (2H, s, C_2-H), 5.25 (1H, s, C_6-H), 6.83 (1H, s, $CHPh_2$), 7.2-8.1 (16H, m, C_6H_5, NH)], and with mesylchloride and pyridine into 3-mesyloxy-3'-nor-1-oxacephem 23 [NMR ($CDCl_3$) δ 2.97 (3H, s, SO_2CH_3), 3.58 (3H, s, C_7-OCH_3), 4.52 (2H, s, C_2-H), 5.22 (1H, s, C_6-H), 6.90 (1H, s, NH), 6.97 (1H, s, $CHPh_2$), 7.2-7.9 (15H, m, C_6H_5)] each in good yield. The latter two compounds, 22 and 23, were further reduced with zinc and acetic acid to give 3-unsubstituted analog 17 smoothly. This transformation provided a better route to 17 in comparison with that described above. Finally the side chain cleavage by a modification of the phosphorus pentachloride method[10] converted 17, 22, and 21 smoothly into 3'-nor-methoxyamines 4a [IR ($CHCl_3$) 3410, 3330, 1790, 1732 cm^{-1}; NMR ($CDCl_3$) δ 2.21 (2H, br s, NH_2), 3.45 (3H, s, C_7-OCH_3), 4.40 (2H, d, J = 3 Hz, C_2-H), 4.75 (1H, s, C_6-H), 6.40 (1H, t, J = 3 Hz, C_3-H), 6.96 (1H, s, $CHPh_2$), 7.2-7.7 (10H, m, C_6H_5)], 4b [IR ($CHCl_3$) 3420, 3340, 1790, 1732 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (2H, br s, NH_2), 3.50 (3H, s, C_7-OCH_3), 4.40 (2H, s, C_2-H),

Scheme 4



18

21, R = PhCO

4c, R = H

22, R = PhCO, X = Cl

23, R = PhCO, X = OSO_2CH_3

4b, R = H, X = Cl

17, R = PhCO

4a, R = H

a) CH_2N_2 b) $Ph_3P \cdot Cl_2/(C_2H_5)_3N/THF$ c) MsCl/Pyridine

d) Zn/HOAc

4.91 (1H, s, C_6-H), 7.00 (1H, s, $CHPh_2$), 7.2-7.7 (10H, m, C_6H_5)], and 4c [IR ($CHCl_3$) 3410, 1785, 1723 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (2H, br s, NH_2), 3.47 (3H, s, C_7-OCH_3), 3.70 (3H, s, C_3-OCH_3), 4.47 (2H, s, C_2-H), 4.86 (1H, s, C_6-H), 6.95 (1H, s, $CHPh_2$), 7.2-7.6 (10H, m, C_6H_5)].

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