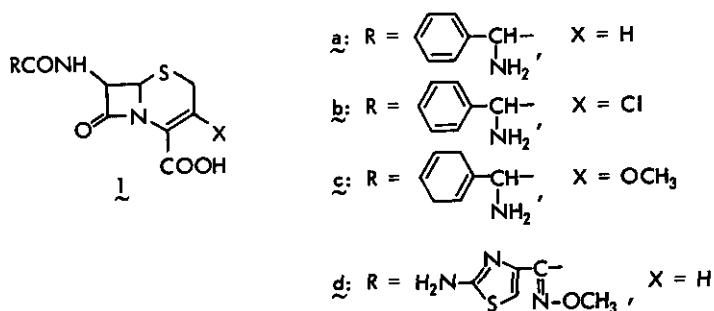


IMPROVED SYNTHESIS OF 3'-NOR-1-OXACEPHEMS[†]

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

In 1972 Scartazzini and Bickel¹ 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 cephalosporins² 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 7 β - side chains of the ceftizoxime type have been

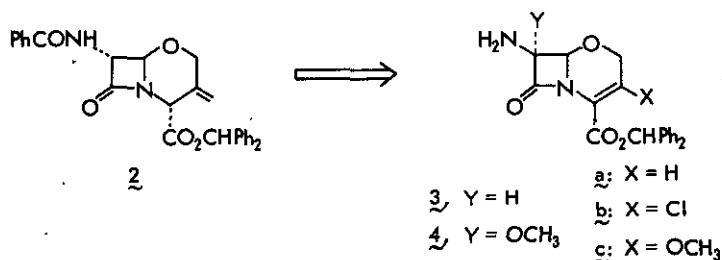


[†] Dedicated to Dr. Herbert C. Brown, Emeritus Professor of Purdue University, on the occasion of his 70th birthday.

reported by the Fujisawa group.⁶

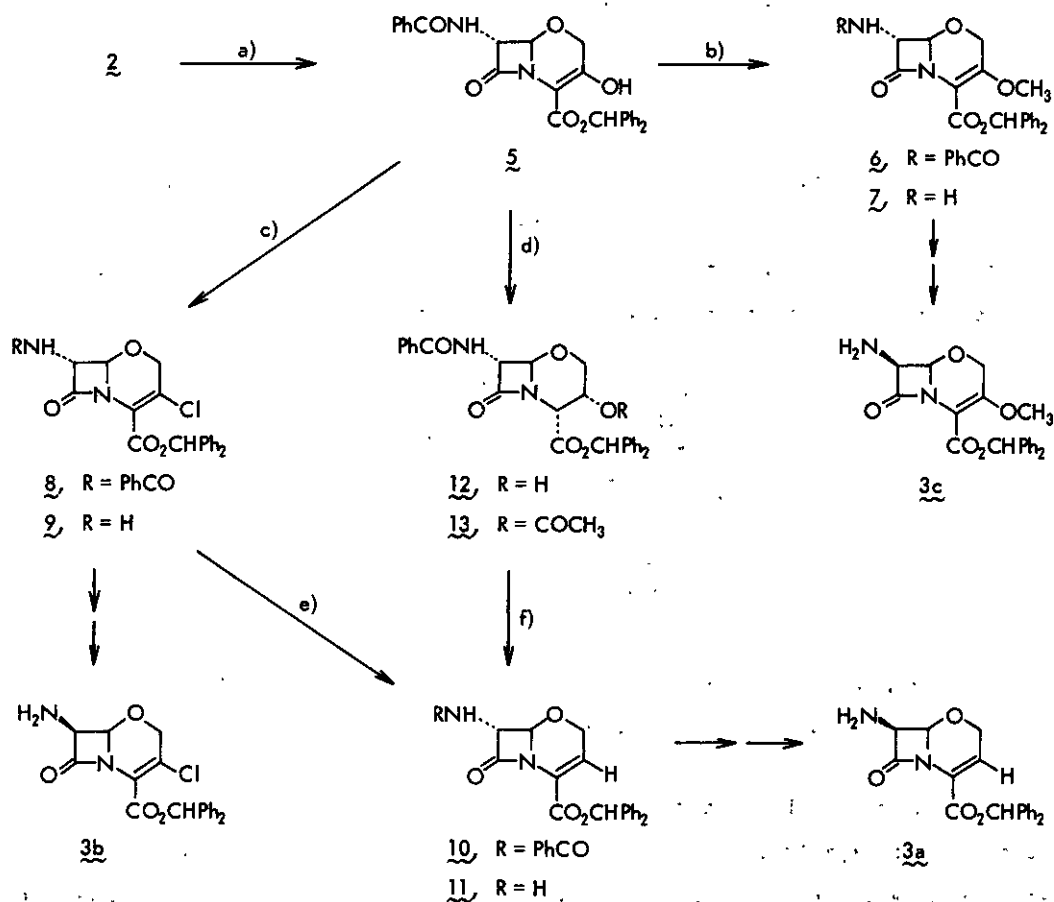
In this paper we wish to describe improved synthetic routes to 7 α -unsubstituted and 7 α -methoxylated 3'-nor-1-oxacephem nuclei, **3** and **4**, from 7 α -benzoylamino-3-methylene-1-oxacephem derivative **2**, a key intermediate in the synthesis of our recently developed β -lactam antibiotic 6059-S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

Scheme 1



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 (CHCl₃) 3440, 3330 cm⁻¹ (3-OH hydrogenbonded with 4-ester oxygen); NMR (CDCl₃) 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 (CHCl₃) 3370, 1780, 1710, 1665, 1625 cm⁻¹; NMR (CDCl₃) δ 3.65 (3H, s, C₃-OCH₃), 4.37 (2H, d, J = 16 Hz, C₂-H), 4.75 (1H, s, C₆-H), 5.13 (1H, d, J = 7 Hz, C₇-H), 6.83 (1H, s, CHPh₂), 7.2-8.0 (16H, m, C₆H₅, 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 (CDCl₃) δ 4.32 (2H, s, C₂-H), 4.75 (1H, s, C₆-H), 5.22 (1H, d, J = 8 Hz, C₇-H), 6.87 (1H, s, CHPh₂), 7.2-8.1 (16H, m, C₆H₅, NH)] in 30% yield. This compound underwent dechlorination with zinc and acetic acid to give 3-unsubstituted 1-

Scheme 2

a) $\text{O}_3/\text{CH}_2\text{Cl}_2\text{-MeOH}$, -78° ; Zn-HOAc b) CH_2N_2 c) $\text{Ph}_3\text{P}\cdot\text{Cl}_2/(\text{C}_2\text{H}_5)_3\text{N/THF}$ d) $\text{B}_2\text{H}_6/\text{THF}$ e) Zn-HOAc f) $\text{MsCl}/(\text{C}_2\text{H}_5)_3\text{N}$

oxa-3-cephem **10** [IR (CHCl_3) 3380, 1790, 1730, 1670 cm^{-1} ; NMR (CDCl_3) δ 4.23 (2H, br s, $\text{C}_2\text{-H}$), 4.88 (1H, s, $\text{C}_6\text{-H}$), 5.22 (1H, d, $J = 8$ Hz, $\text{C}_7\text{-H}$), 6.27 (1H, br s, $\text{C}_3\text{-H}$), 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-oxacephem derivative **12** [IR (CHCl_3) 3430, 3350 (br), 1778, 1740, 1620 cm^{-1} ; NMR (CDCl_3) δ 3.4-4.2 (4H, m, $\text{C}_2\text{-H}$, $\text{C}_3\text{-H}$, OH), 4.90 (2H, br d, $J = 6$ Hz, $\text{C}_4\text{-H}$, $\text{C}_7\text{-H}$), 5.30 (1H, s, $\text{C}_6\text{-H}$), 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-2 α and H-2 β signals appear as the AB part of an ABX-type system (at δ 3.86 and 3.70, respectively) in C₆D₆. Five percents of nuclear Overhauser effects (NOE) were observed between the H-2 α and H-6 α 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, 3 α configuration of 3-acetoxyl, and 4 α configuration of 4-benzhydryloxycarbonyl, respectively. Thus, diborane reduction occurred stereoselectively from the β -face of the 1-oxacephem molecule.

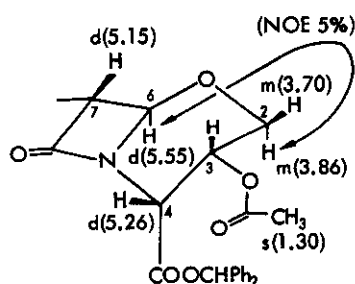


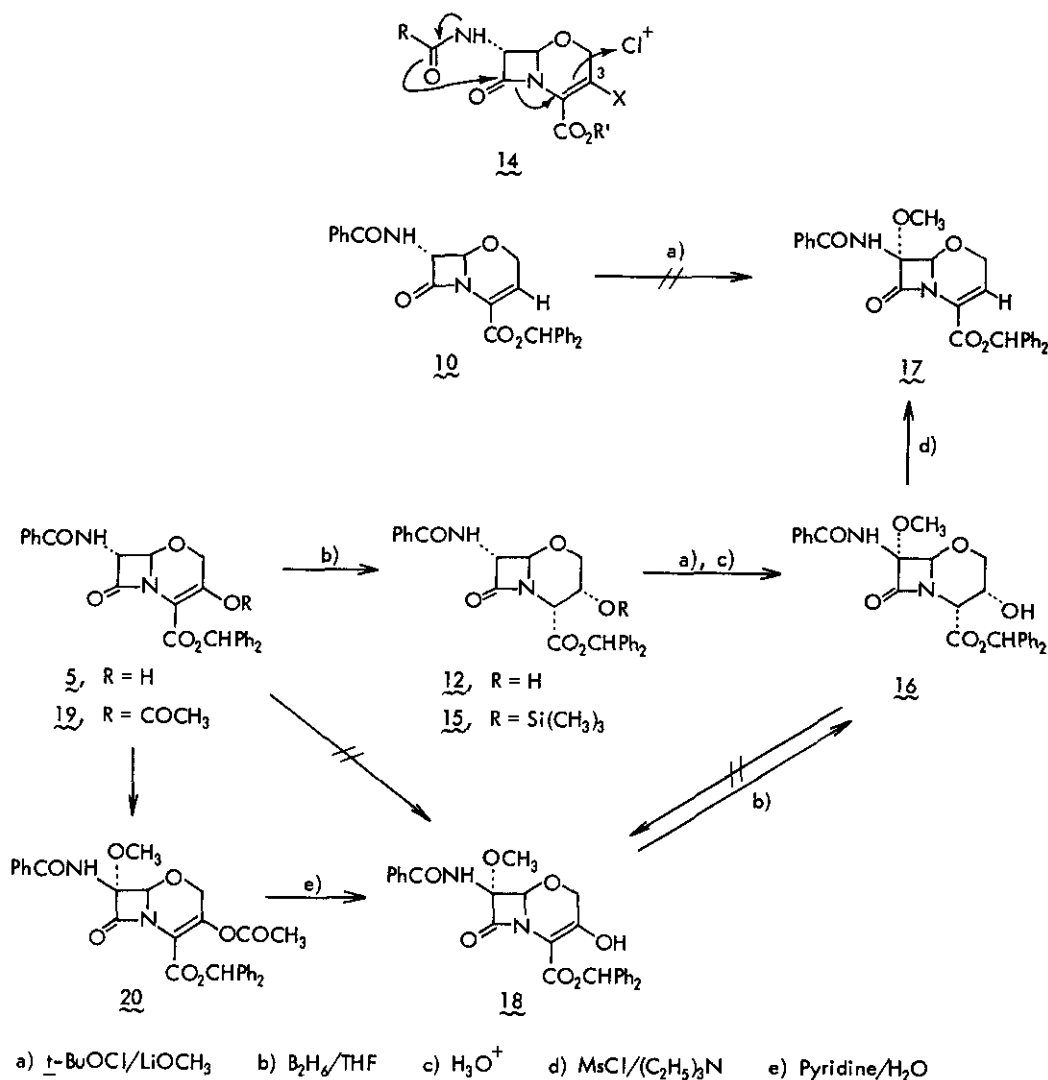
Fig. H¹-Chemical shifts (δ , ± 0.01 ppm), coupling constants ($J_{H,H}$ ± 0.1 Hz), and NOE values ($\pm 2\%$) of 1-oxacephem 13 in C₆D₆.

Deacylation of the 7 α -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 7 α -amino-3'-nor-1-oxacephems 7 [IR (CHCl₃) 3550, 3400, 1775, 1715, 1620 cm⁻¹; NMR (CDCl₃) δ 2.06 (2H, br s, NH₂), 3.70 (3H, s, C₃-OCH₃), 3.97 (1H, br s, C₇-H), 4.40 (2H, s, C₂-H), 4.72 (1H, s, C₆-H), 7.00 (1H, s, CHPh₂), 7.2-7.7 (10H, m, C₆H₅)], 8 [NMR (CDCl₃) δ 2.22 (2H, br s, NH₂), 4.03 (1H, br s, C₇-H), 4.32 (2H, s, C₂-H), 4.73 (1H, s, C₆-H), 6.97 (1H, s, CHPh₂), 7.1-7.6 (10H, m, C₆H₅)], and 11 [IR (CHCl₃) 3400, 3340, 1785, 1730, 1635 cm⁻¹; NMR (CDCl₃) δ 1.87 (2H, br s, NH₂), 3.72 (1H, s, C₇-H), 4.38 (2H, d, J = 3 Hz, C₂-H), 4.65 (1H, s, C₆-H), 6.35 (1H, t, J = 3 Hz, C₃-H), 7.00 (1H, s, CHPh₂), 7.1-7.7 (10H, m, C₆H₅)], respectively, each in high yield. These 7 α -amino compounds were finally subjected to epimerization by our newly developed procedure⁹ [borohydride reduction of 7-(2,2-dichlorovinylimino derivatives)] giving 7 β -amino-3'-nor-1-oxacephem 3c [IR (Nujol) 3520, 3400, 1785, 1725, 1630 cm⁻¹; NMR (CDCl₃) δ 1.75 (2H, br s, NH₂), 3.77 (3H, s, OCH₃), 4.48 (1H, d, J = 4

Hz, C₇-H), 4.52 (2H, s, C₂-H), 4.98 (1H, d, J = 4 Hz, C₆-H), 6.98 (1H, s, CHPh₂), 7.2-7.6 (10H, m, C₆H₅), 3b [IR (Nujol) 3520, 1785, 1720, 1710 cm⁻¹; NMR (CDCl₃) δ 2.07 (2H, br s, NH₂), 4.40 (2H, s, C₂-H), 4.45 (1H, d, J = 4 Hz, C₇-H), 4.98 (1H, d, J = 4 Hz, C₆-H), 6.97 (1H, s, CHPh₂), 7.2-7.6 (10H, m, C₆H₅)] 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-oxacephem 12 obtained by diborane reduction of 5 as described earlier, was first trimethylsilylated giving 15 [mp 157-158°. Anal. Calcd. C₃₀H₃₂O₆N₂Si: C, 66.15; H, 5.92; N, 5.14. Found: C, 66.16; H, 5.90; N, 5.10. [α]_D²³ +2.1 ± 0.4 (c = 1.016, CHCl₃); IR (CHCl₃) 3430, 1778, 1740, 1673 cm⁻¹; NMR (CDCl₃) δ 0.0 (9H, s, Si-CH₃), 3.6-4.2 (3H, m, C₂-H, C₃-H), 4.80 (1H, d, J = 6 Hz, C₃-H or C₇-H), 4.91 (1H, d, J = 6 Hz, C₇-H or C₃-H), 5.30 (1H, s, C₆-H), 6.87 (1H, s, CHPh₂), 6.9-7.8 (16H, m, C₆H₅, NH)] which was then subjected to the conventional 7α-methoxylation followed by hydrolysis to afford the 7α-methoxy 1-oxacephem 16 [IR (CHCl₃) 3430, 1781, 1740, 1683 cm⁻¹; NMR (CDCl₃) δ 3.47 (3H, s, C₇-OCH₃), 3.7-4.3 (4H, m, C₂-H, C₃-H, C₃-OH), 4.97 (1H, d, J = 5 Hz, C₄-H), 5.40 (1H, s, C₆-H), 6.93 (1H, s, CHPh₂), 7.1-7.9 (16H, m, C₆H₅, NH)] in 83% yield. This compound was now led to 3-unsubstituted 7α-methoxy-1-oxa-3-cephem 17 [IR (CHCl₃) 3440, 1790, 1734, 1695 cm⁻¹; NMR (CDCl₃) δ 3.57 (3H, s, C₇-OCH₃), 4.41 (2H, d, J = 2 Hz, C₂-H), 5.13 (1H, s, C₆-H), 6.45 (1H, t, J = 2 Hz, C₃-H), 6.97 (1H, s, CHPh₂), 7.1-8.0 (16H, m, C₆H₅, 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 Δ³-double bond to prevent

Scheme 3

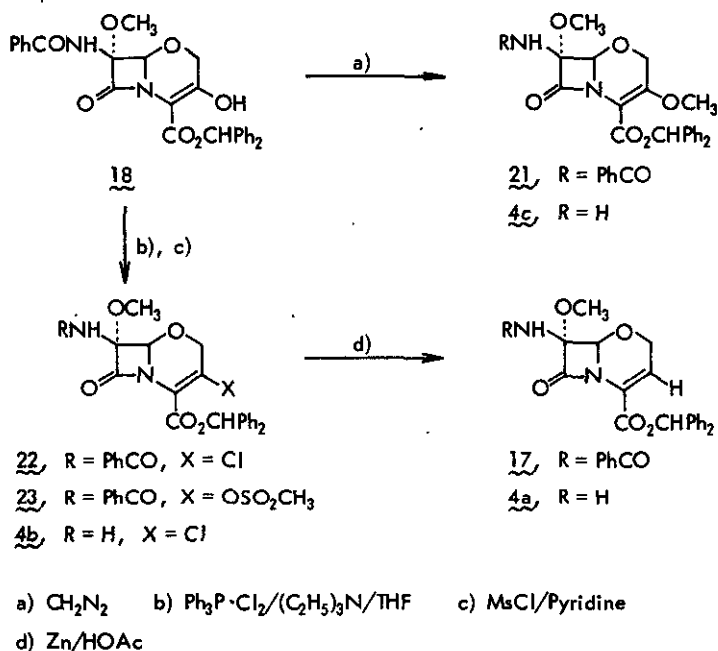


the decomposition with the chlorinating agent as depicted in 14. Thus, 5 was first acetylated to enol acetate 19 [mp 135-137°. Anal. Calcd. $\text{C}_{29}\text{H}_{24}\text{O}_7\text{N}_2$: C, 67.96; H, 4.72; N, 5.47. Found: C, 67.66; H, 4.67; N, 5.39. $[\alpha]_D^{23} +10.2 \pm 0.5^\circ$ ($c \approx 1.037$, 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, $\text{C}_2\text{-H}$), 4.80 (1H, s, $\text{C}_6\text{-H}$), 5.13 (1H, d, $J = 8$ Hz, $\text{C}_7\text{-H}$), 6.87 (1H, s, CHPh_2), 7.1-8.0 (16H, m, C_6H_5 , NH)] which was now subjected to 7 α -methoxylation using t -butyl hypochlorite and lithium

methoxide. As expected methoxylation of this compound was very successful, giving in 85% yield 7 α -methoxy enol acetate 20 [IR (CHCl₃) 3425, 1790, 1733, 1683 cm⁻¹; NMR (CDCl₃) δ 1.92 (3H, s, COCH₃), 3.55 (3H, s, C₇-OCH₃), 4.33 (2H, s, C₂-H), 5.28 (1H, s, C₆-H), 6.95 (1H, s, CHPh₂), 7.1-8.1 (16H, m, C₆H₅, NH)] which on treatment with wet pyridine was converted into the desired compound 18 [IR (CHCl₃) 3430, 3325, 1785, 1735, 1680, 1625 cm⁻¹; NMR (CDCl₃) δ 3.58 (3H, s, C₇-OCH₃), 4.28 (2H, s, C₂-H), 5.22 (1H, s, C₆-H), 6.98 (1H, s, CHPh₂), 7.1-8.1 (17H, m, C₆H₅, NH, C₃-OH)] in almost quantitative yield. It may be noteworthy that this compound was reduced with diborane giving in good yield a 1-oxacephem 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 C₇.

With the common intermediate 18 in hand, synthesis of the representative 7 α -methoxylated 3'-norcephems proceeded smoothly an analogous way to that of 7 α -unsubstituted analogs. Compound 18 was converted on treatment with diazo-methane into 3-methoxy-3'-nor-1-oxacephem 21 [IR (CHCl₃) 3425, 1780, 1725, 1682, 1625 cm⁻¹; NMR (CDCl₃) δ 3.57 (3H, s, C₇-OCH₃), 3.61 (3H, s, C₃-OCH₃), 4.33 (2H, s, C₂-H), 5.18 (1H, s, C₆-H), 6.88 (1H, s, CHPh₂), 7.2-8.1 (16H, m, C₆H₅, NH)], with triphenylphosphine-chlorine complex in the presence of triethylamine into 3-chloro-3'-nor-1-oxacephem 22 [IR (CHCl₃) 3430, 1792, 1735, 1688 cm⁻¹; NMR (CDCl₃) δ 3.55 (3H, s, C₇-OCH₃), 4.33 (2H, s, C₂-H), 5.25 (1H, s, C₆-H), 6.83 (1H, s, CHPh₂), 7.2-8.1 (16H, m, C₆H₅, NH)], and with mesylchloride and pyridine into 3-mesyloxy-3'-nor-1-oxacephem 23 [NMR (CDCl₃) δ 2.97 (3H, s, SO₂CH₃), 3.58 (3H, s, C₇-OCH₃), 4.52 (2H, s, C₂-H), 5.22 (1H, s, C₆-H), 6.90 (1H, s, NH), 6.97 (1H, s, CHPh₂), 7.2-7.9 (15H, m, C₆H₅)] 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 method¹⁰ converted 17, 22, and 21 smoothly into 3'-nor-methoxyamines 4a [IR (CHCl₃) 3410, 3330, 1790, 1732 cm⁻¹; NMR (CDCl₃) δ 2.21 (2H, br s, NH₂), 3.45 (3H, s, C₇-OCH₃), 4.40 (2H, d, J = 3 Hz, C₂-H), 4.75 (1H, s, C₆-H), 6.40 (1H, t, J = 3 Hz, C₃-H), 6.96 (1H, s, CHPh₂), 7.2-7.7 (10H, m, C₆H₅)], 4b [IR (CHCl₃) 3420, 3340, 1790, 1732 cm⁻¹; NMR (CDCl₃) δ 2.15 (2H, br s, NH₂), 3.50 (3H, s, C₇-OCH₃), 4.40 (2H, s, C₂-H),

Scheme 4



4.91 (1H, s, C₆-H), 7.00 (1H, s, CHPh₂), 7.2-7.7 (10H, m, C₆H₅), and **4c** [IR (CHCl₃) 3410, 1785, 1723 cm⁻¹; NMR (CDCl₃) δ 2.50 (2H, br s, NH₂), 3.47 (3H, s, C₇-OCH₃), 3.70 (3H, s, C₃-OCH₃), 4.47 (2H, s, C₂-H), 4.86 (1H, s, C₆-H), 6.95 (1H, s, CHPh₂), 7.2-7.6 (10H, m, C₆H₅)].

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