# SYNTHESIS OF 1-OXA ANALOGUES OF NATURALLY OCCURRING CEPHALOSPORINS AND CEPHAMYCINS

Yuji Sendo,* Toshiro Konoike, Masayuki Murakami, and Mitsuru Yoshioka*
Shionogi Research Laboratories, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka, 553 Japan

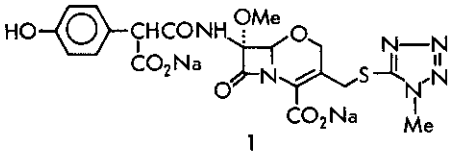
Abstract — The title compounds 15a-c and 16a-c were synthesized from a 3-exomethylene-1-oxacepham compound 4. Its chlorohydroxylation provided a key intermediate 5e in synthesis of the 3'-oxygen-functionalized 1-oxacephems.

1-Oxacephem antibiotics including the clinically important compound 1 (code number 6059-S)[1] have been obtained by multi-step semi-syntheses[2] starting from naturally abundant penicillins. In connection with a search for naturally occurring 1-oxacephem compounds, we have synthesized novel 1-oxacephem derivatives, 15a-c and 16a-c, which possess the C-7 and C-3 side chains of naturally occurring cephalosporins and cephamycins.[3,4]

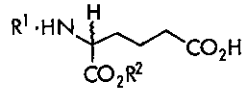
The acid 3 to be used for the 7β side chain was prepared from D,L-2-aminoadipic acid 2 by a modification of Christensen's method[5] ($PhCH_2OH$, concd $H_2SO_4$, 0°; t-$BuOCO_2$-N=C(CN)Ph,[6] 25% KOH-20% $K_3PO_4$, aq acetone; $Cl_3CCH_2OH$, DCC-pyridine, $CH_2Cl_2$, 25°; $H_2$-10% Pd-C, AcOEt; 23.5% from 2).

As the starting material for preparation of the necessary 1-oxacephem nuclei 8 and 9 we have chosen the 3-exomethylene derivative 4 which is available on an industrial scale.[2] Thus our synthetic routes involve conversion of the 3-exomethylene group into the 3-methyl or 3'-functionalized-methyl group (4→6), 7α-methoxylation (6→10), side-chain cleavage (6→7 or 10→9), and inversion of the 7α-amino group to the 7β-amino (7→8) or the 7β-amino-7α-methoxy (7→9) groups.

Treatment of 4 with $Et_3N$ ($CH_2Cl_2$, 25°, 1.5 hr) gave a single product 6a, which underwent side-chain cleavage by the $PCl_5$-Py-i-BuOH procedure[7] ($PCl_5$-pyridine, $CH_2Cl_2$, 25°; HCl, i-BuOH-$CH_2Cl_2$, 25°) to give the 3-methyl-7α-amino derivative 7a (55% from 4). Inversion of the 7α-amino group in 7a was effected by a novel method developed in our laboratories,[8] giving the 3-methyl nucleus 8a (63%). Methoxylation of 6a by the t-BuOCl-LiOMe method[9] (t-BuOCl-LiOMe,

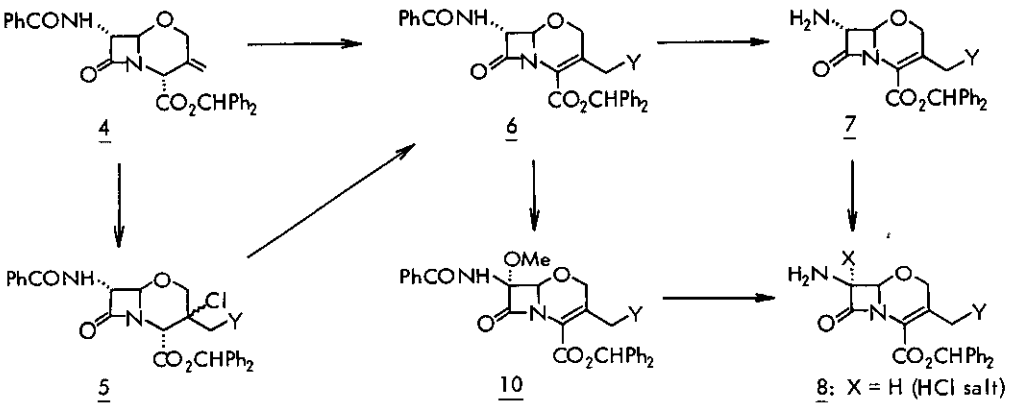


1

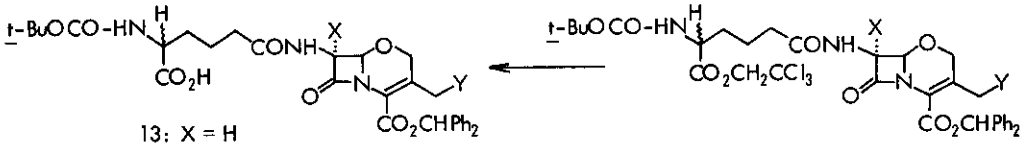


2: $R^1 = R^2 = H$

3: $R^1$ = t-BuOCO, $R^2 = CH_2CCl_3$

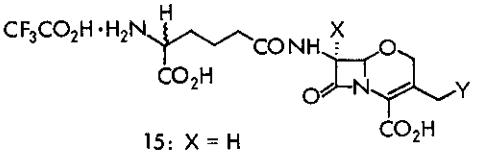


4 5 6 7 8: X = H (HCl salt) 9: X = OMe 10



11: X = H

12: X = OMe



13: X = H

14: X = OMe



15: X = H

16: X = OMe

a: Y = H

b: Y = OAc

c: $Y = OCONH_2$

d: $Y = OCOCH_2Cl$

e: Y = OH

f: $Y = OCONHCOCCl_3$

g: Y = Cl

$CH_2Cl_2$-MeOH, -40°; AcOH, -40°; aq $Na_2S_2O_3$, 10°) gave 10a (65% from 6a), which was deacylated to methoxy amine 9a (53%) by the $PCl_5$-Py-MeOH process[2] ($PCl_5$-pyridine, $CH_2Cl_2$, 0°; MeOH, 0-25°; $Et_2NH$, -10°).

After attempts were made unsuccessfully to obtain 3'-oxygen-functionalized compounds such as 6b and 6c from allylic chloride 6g,[2] we turned our attention to convert exomethylene 4 into its chlorohydrin 5e. Among the known chlorohydroxylation reagents, trichloroisocyanuric acid[10] [0.5 equiv, 60% $HClO_4$ (0.05 equiv), aq acetone, 25°] was most efficient in giving 5e[11] (~100%). Acetylation of 5e ($CH_3COCl$-pyridine, $CH_2Cl_2$, 0-25°) was accompanied by dehydrochlorination giving 3'-acetoxy-1-oxacephem 6b (66%), which was converted into the 3'-acetoxy nuclei 8b (37%) and 9b (crude, 81%) by the same processes as described above for preparing 8a and 9a from 6a. Acylation of 5e with trichloroacetyl isocyanate followed by dehydrochlorination {$Cl_3CCONCO$, $CH_2Cl_2$, 25°; 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), $CH_2Cl_2$, -35°} gave 6f (71% from 5e), which was converted into 7β-amine 8f (54% from 6f) by the same processes via 7f as described for preparation of 8a. Since the deprotection of the trichloroacetyl group in 8f and its amide 11f was unsuccessful, we planned to introduce the carbamoyl group at a later stage for synthesis of 13c while protecting the 3'-hydroxy group of 5e as the chloroacetate. Chloroacetylation of 5e followed by dehydrochlorination ($ClCH_2COCl$-pyridine, $CH_2Cl_2$, 0°; DBU, $CH_2Cl_2$, -30°) gave 6d (70% from 5e), which was converted into 7α-amine 7d (85%) by the $PCl_5$-Py-i-BuOH method.[7] Inversion of 7d to its 7β-epimer 8d by the above-mentioned method[8] was accompanied with partial deprotection of the chloroacetyl group, giving a mixture of 8d and 8e (53% from 7d). Because the side-chain cleavage of methoxy amide 10f, prepared from the trichloroacetate 6f by the t-BuOCl-LiOMe method,[9] was unsuccessful, the 7α-amine 7f was methoxylated by a modification[1] of Yanagisawa's method[12] (3,5-di-t-butyl-4-hydroxybenzaldehyde, molecular sieves 4A, $CH_2Cl_2$, reflux; nickel peroxide, 25°, MeOH, 25°; aq $NaHCO_3$-MeOH, 25°; Girard's reagent T, MeOH, 0°). During this methoxylation step, the trichloroacetyl group was removed to give the 3'-carbamoyloxy-7α-methoxy nucleus 9c (40% from 7f).

Further conversion of these 1-oxacephem nuclei 8 and 9 to the final products 15 and 16 were straightforward except for preparation of the 3'-carbamoyloxy derivative 15c. Thus, the amines, 8a-b and 9a-c, were coupled with the acid 3 [$(COCl)_2$-DMF, benzene, 10°; $Et_3N$-pyridine, $CH_2Cl_2$, 0°] to give 11a (76%), 11b (68%), 12a (40%), 12b (45%), and 12c (56%), respectively, which underwent the trichloroethyl deprotection (Zn, 90% AcOH, 25°) to monoacids, 13a-b and 14a-c,[13] followed by further deprotection with $CF_3CO_2H$-anisole ($CH_2Cl_2$, 0°) giving the desired compounds, 15a[14] (76%), 15b[15] (53%), 16a[16] (79%), 16b[17] (62%), and 16c[18] (62% overall yield), respectively. On the other hand, the mixture of 8e and 8d was condensed with 3 as described above to afford a

5:7 mixture of 11e and 11d (78%), which was converted into the 3'-carbamoyloxy compound 11c (46% overall yield) by a sequence of reactions [$(H_2N)_2CS$, EtOH, 25°; $ClSO_2NCO$, AcOEt, 0°; HCl, $H_2O$-AcOEt, 25°]. Further deprotections via 13c[13] by the above two-step process gave 15c[19] (60% overall yield).

Studies related to the search for the naturally occurring 1-oxacephem compounds will be published elsewhere.[20]

The authors thank Dr. Wataru Nagata of our laboratories for his helpful advice.

References and Notes

(1) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, J. Med. Chem. 22, 757 (1979).

(2) M. Yoshioka, T. Tsuji, S. Uyeo, S. Yamamoto, T. Aoki, Y. Nishitani, S. Mori, H. Satoh, Y. Hamada, H. Ishitobi, and W. Nagata, Tetrahedron Lett. 21, 351 (1980) and references cited therein.

(3) E. P. Abraham and P. B. Loder; R. Nagarajan in "Cephalosporins and Penicillins: Chemistry and Biology," E. H. Flynn, Ed., Academic, New York, 1972, Chapter 1; Chapter 15.

(4) C. E. Higgens, R. L. Hamill, T. H. Sands, M. M. Hochn, N. E. Davis, R. Nagarajan, and L. D. Bocck, J. Antibiotics 27, 298 (1974).

(5) R. W. Ratcliffe and B. G. Christensen, Tetrahedron Lett. 2907 (1972).

(6) M. Itoh, D. Hagiwara, and T. Kamiya, Tetrahedron Lett. 4393 (1975).

(7) R. R. Chauvette and P. A. Pennington, J. Med. Chem. 18, 403 (1975).

(8) T. Aoki, N. Haga, Y. Sendo, T. Konoike, M. Yoshioka, and W. Nagata, to be published.

(9) G. A. Koppel and R. E. Koehler, Tetrahedron Lett. 1943 (1973).

(10) F. Mukawa, Nippon Kagaku Zasshi 78, 450 (1957); Chem. Abstr. 53, 5338ae (1959).

(11) 5e: foams; IR ($CHCl_3$) 3590, 3440, 1781, 1742, 1676; NMR ($CDCl_3$) δ 2.43 (1H, br s), 3.50 (2H, s), 3.77, 4.10 (2H, ABq, J = 12 Hz), 4.87 (1H, s), 4.97 (1H, d, J = 7 Hz), 5.38 (1H, s), 6.85 (1H, s), 7.2-7.9 (16H, m).

(12) H. Yanagisawa, M. Fukushima, A. Ando, and H. Nakano, Tetrahedron Lett. 2705 (1975).

(13) Every compound included in the type of 13 and 14 shows reasonable $^1H$ NMR and IR spectra and has satisfactory elemental analysis.

(14) 15a: powder; IR (KBr) 3420, 1770, 1715, 1660; NMR ($D_2O$, DSS) δ 1.88 (4H, br s), 1.83 (3H, s), 2.42 (2H, br s), 4.1 (1H, br s), 4.48 (2H, s), 5.23 (1H, d, J = 3 Hz), 5.48 (1H, d, J = 3 Hz).

(15) 15b: powder; IR (KBr) 3360, 1780, 1720, 1660; NMR ($D_2O$, DSS) δ 1.88 (4H, br s), 2.10 (3H,

s), 2.42 (2H, br s), 4.0 (1H, br s), 4.60 (2H, s), 5.02 (2H, s), 5.22 (1H, d, J = 3.5 Hz), 5.48 (1H, d, J = 3.5 Hz).

(16) 16a: powder; IR (KBr) 3400, 1773, 1720, 1670; NMR ($D_2O$, DSS) δ 1.90 (4H, br s), 1.98 (3H, s), 2.45 (2H, br s), 3.50 (3H, s), 4.1 (1H, br s), 4.42 (2H, s), 5.17 (1H, s).

(17) 16b: powder; IR (KBr) 3400, 1780, 1730, 1670; NMR ($D_2O$, DSS) δ 1.92 (4H, br s), 2.10 (3H, s), 2.50 (2H, br s), 3.55 (3H, s), 4.10 (1H, br s), 4.60 (2H, s), 5.03 (2H, s), 5.22 (1H, s).

(18) 16c: powder; IR (KBr) 3370, 1780, 1712, 1675; NMR ($D_2O$, ext TMS) δ 2.33 (4H, br s), 2.90 (2H, br s), 3.95 (3H, s), 4.43 (1H, br s), 4.98 (2H, s), 5.27, 5.53 (2H, ABq, J = 14 Hz), 5.63 (1H, s).

(19) 15c: powder; IR (KBr) 3380, 1780, 1710, 1670; NMR ($D_2O$, ext TMS) δ 2.32 (4H, br s), 2.85 (2H, br s), 4.43 (1H, br s), 5.03 (2H, s), 5.30, 5.58 (2H, ABq, J = 15 Hz), 5.65 (1H, d, J = 4 Hz), 5.93 (1H, d, J = 4 Hz).

(20) e.g., R. D. Miller, C. Affolder, and N. Neuss, submitted for publication in Experientia.

Received, 14th January, 1981