CONVENIENT SYNTHESIS OF 3'-SUBSTITUTED METHYL 7α-METHOXY-1-OXACEPHEMS[1]

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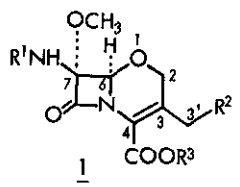
Abstract — A convenient synthesis of the title compounds 1 is achieved by formation of glycols 3, 12, 13 and 14 or chlorohydrins 6 from epioxazolines having pertinent allylic substituents, followed by stereoselective, intramolecular etherification to 4, 7, 15, 16 and 17, elimination to 5, 18 and 19, and further conversions.

Since 7α-methoxy-1-oxacephem 1a was found to possess remarkable antibacterial activity,[2] persistent efforts in our laboratories have been directed towards efficient and industrially feasible synthesis of 3'-substituted methyl derivatives such as 1b and 1c.[2-6] Functionalization at C-3' of 3-methyl 1-oxacephems has not been fruitful[7,8] in contrast to successful allylic bromination at C-3' of the 1-thia congeners.[9] Conversion of epioxazolinoazetidinone allylic chloride 2 into 3-chloromethyl-1-oxacephem 5 is an essential part in our previous promising



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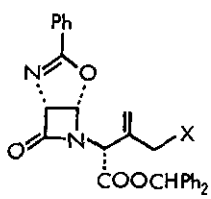
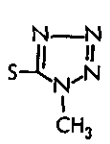
a, R^1 = HO-(4-hydroxyphenyl)-CHCO (COONa) ; R^2 = STet; R^3 = Na
b, R^1 = PhCO; R^2 = Cl; R^3 = $CHPh_2$
c, R^1 = PhCO; R^2 = STet; R^3 = $CHPh_2$
d, R^1 = PhCO; R^2 = $OCOCH_3$; R^3 = $CHPh_2$
e, R^1 = H; R^2 = $OCOCH_3$; R^3 = $CHPh_2$
f, R^1 = H; R^2 = STet; R^3 = $CHPh_2$
g, R^1 = CH_3CO; R^2 = $OCOCH_3$; R^3 = $CHPh_2$

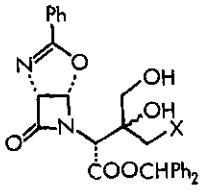


2, X = Cl
8, X = I
9, X = STet
10, X = $OCOCH_3$
11, X = OH

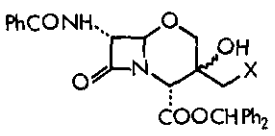
STet = 

synthesis,[5] but it consists of five steps involving an industrially unfavorable photochlorination. We now report a convenient, three-step process for conversion of 2 into 5 utilizing glycol or chlorohydrin formation and application of this process to synthesis of 3'-substituted methyl 7α-methoxy-1-oxacephems.

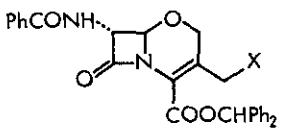
According to a procedure reported from our laboratories for synthesis of 3-methyl 1-oxacephems,[7] allylic chloride 2[5] was oxidized ($KClO_3$/catalytic OsO_4, THF-H_2O, 25 °C) to glycols 3 as an isomeric mixture, which, without separation, underwent stereospecific, intramolecular etherification (catalytic CF_3CO_2H, CH_2Cl_2, 25 °C) to give a mixture of 3-chloromethyl-3-hydroxy-1-oxacephams 4[10] in 72% overall yield. Repeated chromatography[10] of the mixture afforded 3α-hydroxy isomer 4a[11,12] and 3β-isomer 4b[11,13] in 19 and 32% yields, which were dehydrated ($SOCl_2$/α-picoline, CH_2Cl_2, 0 °C) to the same Δ^3-product 5[5,10] in 40 and 63% yields, respectively. This dehydration result contrasts with our earlier observation[5] that the reaction of 3β-hydroxy-3-methyl analog (X = H in 4b) gave a Δ^2-product as a major product. When the above three-step conversion was carried out without separation of the isomers, the product 5[10] was obtained in 40% overall yield from the allylic chloride 2. In an alternative, new approach, 2 was treated with trichloroisocyanuric acid in aq acetone at 20 °C to give an isomeric mixture of chlorohydrins 6,[14] which were cyclized (catalytic $BF_3 \cdot Et_2O$, AcOEt, 20 °C) to an inseparable mixture of 3-chloro-3-chloromethyl compounds 7.[14] Dehydrochlorination (1,5-diazabicyclo[5.4.0]-undec-5-ene, CH_2Cl_2, -20 °C) of the mixture afforded the 1-oxa-3-cephem 5[10] in 32% overall yield



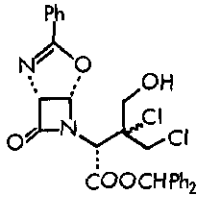
3, X = Cl
12, X = STet
13, X = $OCOCH_3$
14, X = OH



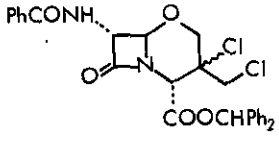
4a; 4b, X = Cl
15a; 15b, X = STet
16a; 16b, X = $OCOCH_3$
17a; 17b, X = OH



5, X = Cl
18, X = STet
19, X = $OCOCH_3$



6a; 6b



7a; 7b

from 2 with no appreciable amount of its Δ^2-isomer being isolated.

The glycol process was extended to synthesis of 3-(1-methyl-1H-tetrazol-5-ylthio)methyl and 3-acetoxymethyl derivatives 18 and 19. Since the allylic chloride 2 is not reactive enough for nucleophilic substitution without double bond migration, the starting olefins 9 and 10 were prepared by treatment of more reactive allylic iodide 8[5] with sodium 1-methyl-1H-tetrazole-5-thiolate (TetSNa) (Me_2CO-MeOH, 20 °C) and with $AgBF_4$ in DMA at 20 °C in 92 and 82% yields, respectively. An alternative preparation of the allylic acetate 10 (43% yield) without using the expensive silver reagent is acetylation (AcCl/$PhNEt_2$, CH_2Cl_2, 20 °C) of allylic alcohol 11,[5] which itself serves as a starting material for synthesis of the 3-acetoxymethyl compound 19 via diols 17. Oxidation of olefins 9, 10, and 11 as described above gave glycols 12 and 13 as isomeric mixtures and triol 14 as a crystalline single isomer (mp 134-136 °C), which on intramolecular etherification (catalytic $BF_3 \cdot Et_2O$, AcOEt, 20 °C) were converted into epimeric mixtures of 3-hydroxy derivatives 15, 16, and 17,[15] respectively. The 3-hydroxymethyl derivatives 17 were quantitatively acetylated (Ac_2O/pyridine, 0 °C) to 16. Dehydration ($SOCl_2$/pyridine, CH_2Cl_2, 25 °C) of 15 and 16 gave 1-oxa-3-cephem derivatives 18[10,16] and 19[10,17] in overall yields of 22% from 9 and 32% from 10 (35% from 11 via 17), respectively.

The above synthesis of the 3-acetoxymethyl-1-oxacephem 19 is significant, since substitution of the 3-chloromethyl derivative 5 did not proceed smoothly under usual conditions (NaOAc/DMF, AgOAc/HOAc etc.) in contrast to facile conversion of 5 ino 18 (TetSNa/catalytic Bu_4NBr, CH_2Cl_2-H_2O, 25 °C; 80% yield).

The acetate 19 underwent 7α-methoxylation (t-BuOCl-LiOMe, CH_2Cl_2, -40 °C) to 1d[10,18] (81% yield) followed by the side-chain cleavage (PCl_5/pyridine, CH_2Cl_2, 25 °C; MeOH, 0 °C; Et_2NH, -8 °C) to give methoxy amine 1e,[19] the nucleus for preparation of various 3-acetoxymethyl-7α-methoxy-1-oxacephem antibiotics.[20] On the other hand, the 7α-methoxylation of the tetrazolylthiomethyl derivative 18 was difficult owing to its low solubility in an applicable solvent such as CH_2Cl_2. Conversion of the 3-chloromethyl compound 5 into 1f and further into the antibiotic 1a has been reported.[5,2]

In conclusion, the present approach provides an alternative, convenient synthesis of the antibiotic 1a in the shortest steps and of 3-acetoxymethyl-7α-methoxy-1-oxacephems. Successful application to synthesis of other 3'-substituted methyl derivatives will be highly feasible.

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10. The product(s) was separated or purified by chromatography (silica gel, C_6H_6-AcOEt) and/or crystallization.

11. The α or β configuration of the 3-substituent was determined by ^1H- and ^{13}C-NMR studies which will be published in a separate paper.

12. 4a,[11] 3α-hydroxy isomer: foams; ir ($CHCl_3$) 3550 (br), 3440-3200, 1782, 1745, 1670 cm^{-1}.

13. 4b,[11] 3β-hydroxy isomer: mp 132-134 °C (ether-acetone); $[\alpha]_D^{25}$ +48.8 ± 0.9° (c 1.020, $CHCl_3$); ir ($CHCl_3$) 3550 (br), 3450-3200, 1780, 1740, 1665 cm^{-1}.

14. Chromatographic separation[10] gave 6a and 6b, the latter being partly changed into the corresponding lactone. The acid-catalyzed cyclization of the isomers afforded the epimeric dichloride 7a and 7b. 7a,[11] 3α-chloroisomer: mp 190-191 °C (decomp) (ether); $[\alpha]_D^{25}$ +15.6 ± 1° (c 0.537, $CHCl_3$); ir ($CHCl_3$) 3444, 1787, 1749, 1680 cm^{-1}. 7b,[11] 3β-chloro isomer: foams; ir ($CHCl_3$) 3430, 3325, 1785, 1740, 1675 cm^{-1}.

15. The α and β epimers were separated[10] and characterized[11] except for 15a and 15b whose NMR spectra were too complicated for interpretation. 15a: foams; ir ($CHCl_3$) 3435, 3300 (br), 1780, 1745, 1675 cm^{-1}. 15b: foams; ir ($CHCl_3$) 3525, 3410, 1780, 1743, 1679 cm^{-1}. 16a,[11] 3α-hydroxy isomer: foams; ir ($CHCl_3$) 3580, 3440, 1785, 1752, 1675 cm^{-1}. 16b,[11] 3β-hydroxy isomer: mp 142-143 °C (CH_2Cl_2-ether); $[\alpha]_D^{25.5}$ +29.2 ± 1.3 (c 0.501, acetone); ir ($CHCl_3$) 3560 (br), 3430 (br), 1784, 1750, 1710 (sh), 1675 cm^{-1}. 17a, 3α-hydroxy isomer: foams; ir ($CHCl_3$) 3450 (br), 1790-1760, 1665 cm^{-1}; nmr ($CDCl_3$) δ 3.4-4.3 (m, 6, C_2 H, $C_{3'}$ H, OH), 4.86 (br s, 1, C_4 H), 4.96 (d, 1, J = 8 Hz, C_7 H), 5.36 (br s, 1, C_6 H), 6.90 (s, 1,

$CHPh_2$), 7.1-7.9 (m, 16H, ArH and NH). 17b, 3β-hydroxy isomer: foams; ir ($CHCl_3$) 3425 (br), 1790, 1745 (sh), 1715, 1675 cm^{-1}; nmr ($CDCl_3$) δ 3.26 (br s, 3, C_3, H, OH), 3.75 (br s, 2, C_2 H), 4.71 (s, 1, C_4 H), 5.08 (d, 1, J = 7 Hz, C_7 H), 5.46 (s, 1, C_6 H), 6.90 (s, 1, $CHPh_2$), 7.2-7.9 (m, 16, ArH and NH).

16. 18: mp 203-205 °C; $[\alpha]_D^{22}$ -116.1 ± 3.2° (c 0.492, dioxane); ir ($CHCl_3$) 3450, 1792, 1725, 1680 cm^{-1}; nmr ($CDCl_3$) δ 3.77 (s, 3, NCH_3), 4.20 (s, 2, C_3, H), 4.57 (s, 2, C_2 H), 4.90 (d, 1, J = 7 Hz, C_7 H), 5.07 (s, 1, C_6 H), 6.93 (s, 1, $CHPh_2$), 7.2-7.9 (m, 16, ArH and NH).
17. 19: foams; ir ($CHCl_3$) 3380 (br), 1785, 1735 (br), 1665 cm^{-1}; nmr ($CDCl_3$) δ 2.00 (s, 3, $COCH_3$), 4.41 (s, 2, C_2 H), 4.92 (s, 3, C_3, H, C_6 H), 5.06 (d, 1, J = 8 Hz, C_7 H), 6.88 (s, 1, $CHPh_2$), 7.15-7.90 (m, 16, ArH and NH).
18. 1d: foams; ir ($CHCl_3$) 3425, 1785, 1740, 1685 cm^{-1}; nmr ($CDCl_3$) δ 1.96 (s, 3, $COCH_3$), 3.56 (s, 3, OCH_3), 4.41 (s, 2, C_2 H), 5.00 (s, 2, C_3, H), 5.15 (s, 1, C_6 H), 6.90 (s, 1, $CHPh_2$), 7.00 (s, 1, NH), 7.2-7.5 and 7.7-7.9 (m, 15, ArH).
19. This amine is somewhat unstable and usually used for acylation without purification. For example, treatment with AcCl-py at 0 °C afforded acetylamino derivative 1g (45%). 1g: nmr ($CDCl_3$) δ 2.00 (s, 6, $OCOCH_3$, $NHCOCH_3$), 3.55 (s, 3, OCH_3), 4.48 (s, 2, C_2 H), 5.03 (br s, 2, C_3, H), 5.06 (s, 1, C_6 H), 6.40 (br s, 1, NH), 6.91 (s, 1, $CHPh_2$), 7.2-7.6 (m, 10H, ArH).
20. Synthesis and biological activity of the antibiotics will be published in separate papers.

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