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A New Synthetic Method of 3-Formylcephalosporins

Cephalosporin 3′-bromolactones (**3**) were prepared in good yields *via* silyl ethers (**2**) starting from readily available cephalosporin lactones (**1**). Treatment of **3** with dimethyl sulfoxide yielded 3-formylcephalosporins (**4**), a useful intermediate for the chemical modification at the C_3-position of cephalosporins.

Keywords——cephalosporin lactone derivatives; silylation; bromination; 3-formylcephalosporins; silica gel chromatography; separation of epimers

The preceding paper described a new and efficient synthesis of cephalosporins bearing a thiadiazole ring directly attached to the C_3-position starting from 3-formylcephalosporin derivatives.[1] 3-Formylcephalosporins have been obtained from the corresponding 3-hydroxymethyl derivatives by oxidation with DMSO–Ac_2O[2a] or CrO_3–sulfuric acid.[2b,c] However, these oxidation reactions have often been accompanied by side reactions, such as double bond migration ($\Delta^3 \rightarrow \Delta^2$) and lactonization.

This report describes a new and useful synthetic method of 3-formylcephalosporins starting from the readily available cephalosporin lactones.

Direct bromination of 7-phthalimidocephalosporin lactone with NBS has been reported by Bohme *et al.*, but the bromine atom was introduced at the C_2-position.[3] In order to introduce a halogen atom selectively into the $C_{3'}$-position, it was designed to prepare bromolactones (**3**) *via* silyl ethers (**2**) starting from lactones (**1**).

A mixture of a cephalosporin lactone derivative (**1a**), trimethylsilyl chloride (4—8 mol. equiv.) and triethylamine (3—5 mol. equiv.) in DMF was stirred at room temperature to yield the corresponding trimethylsilyl ether (**2a**).[4] Subsequent addition of bromine (1.2 mol. equiv.) at 0° to the reaction mixture afforded the bromolactone (**3a**) as a mixture of

1) T. Sugawara, H. Masuya, T. Matsuo, and T. Miki, *Chem. Pharm. Bull.*, **27**, 2544 (1979).
2) *a*) H. Peter and H. Bickel, *Helv. Chim. Acta*, **57**, 2044 (1974); *b*) Eli Lilly Co., Japan. Patent Provisional Publication, 46-20707 (1971); *c*) Takeda Chem. Co., Japan. Patent Provisional Publication, 49-80097 (1974).
3) E.H. Bohme and J.E. Dolfin, *Chem. Commun.*, **1972**, 941; the methine proton of the C_2-position was observed as a singlet (1H) at 3.53 ppm (DMSO-d_6).
4) *Cf.* Yoshii *et al.* reported that the treatment of but-2-enolides with trimethylsilyl chloride and triethylamine gave 2-trimethylsilyloxyfuranes. E. Yoshii, T. Koizumi, E. Katatsuji, and T. Kaneko, *Heterocycles*, **4**, 1663 (1976).

epimers, and the epimers could be separated from the mixture by silica gel chromatography. Compound **3aA** (less polar epimer, 29.8%); IR ν_{max}^{KBr} cm^{-1}: 1810, 1735, 1670. NMR (DMSO-d_6, ppm): 3.60 (2H, br.s, C_2–H), 5.13 (1H, d, J=5 Hz, C_6–H), 5.84 (1H, q, J=5 Hz and 8 Hz, C_7–H). Compound **3aB** (more polar epimer, 39.7%); IR ν_{max}^{KBr} cm^{-1}: 1810, 1735, 1660. NMR (DMSO-d_6, ppm): 3.68 and 3.85 (2H, ABq, J=18 Hz, C_2–H), 5.15 (1H, d, J=5 Hz, C_6–H), 5.88 (1H, q, J=5 Hz and 8 Hz, C_7–H).

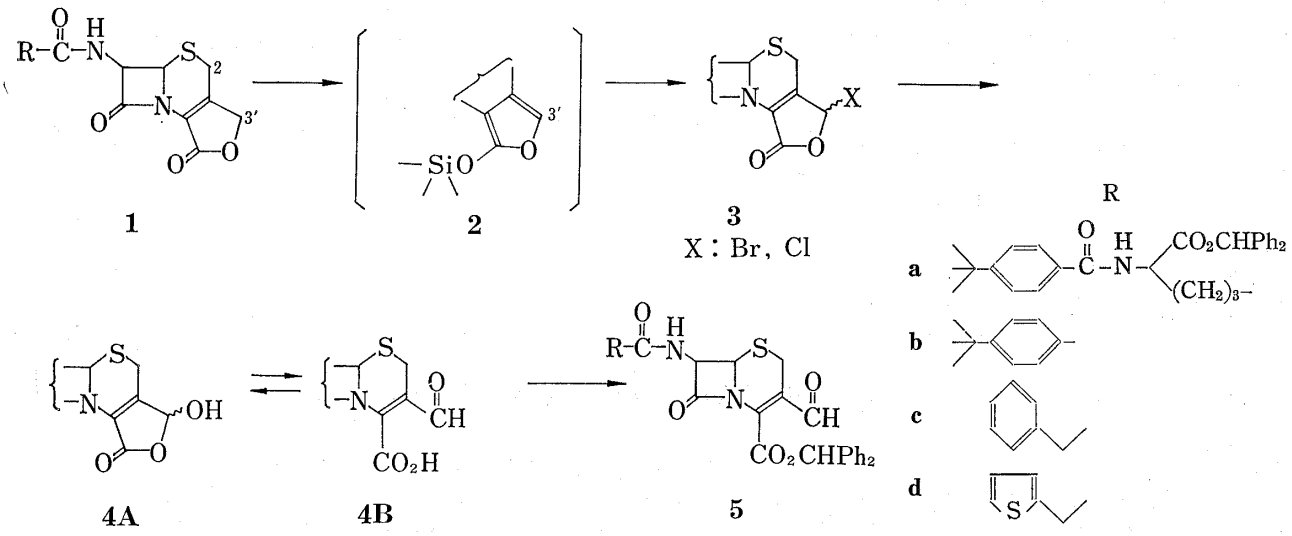

Chart 1

Analogous results were obtained for other lactones (Table I), and, based on the NMR data, the position of the bromine atom was proposed to be $C_{3'}$. Although chlorine was also used as a halogenation reagent, the yield was low (52%).

Table I. NMR Data ($C_{3'}$-H in DMSO-d_6, ppm) and Isolated Yields in the Conversion of Lactones (1) into Bromolactones (3)

Lactone (1)		Bromolactone (3)		
			$C_{3'}$-H (1H)	
	$C_{3'}$-H (2H)	Yield (%)[a]	3A	3B
1a	4.96	78	—[b]	—[b]
1b	5.00	73	7.25	7.15
1c	4.92	78	7.22	7.14
1d	4.98	75	7.23	7.14
		52[c]	7.18	7.16

a) Isolated yields as a mixture of epimers (**3A** and **3B**).
b) $C_{3'}$-H signals were overlapped with aromatic protones.
c) Isolated yield of chlorolactone.

The lactol form (**4A**) is thought to be an equilibrium with 3-formyl form (**4B**).[2a,5] Therefore, next study was focused on converting a bromine atom into a hydroxyl group. It was found that the conversion of **3a** to **4a** proceeded smoothly in a DMSO solution at room temperature in almost quantitative yields and the progress of the reaction was easily visualized by means of the NMR spectra. Compound **4a** (lactol form); NMR (DMSO-d_6, ppm): 3.69 (2H,

5) P.R. Jones, *Chem. Rev.*, **63**, 461 (1963).

br.s, C_2–H), 5.09 (1H, d, J=5 Hz, C_6–H), 5.86 (1H, q, J=5 Hz and 8 Hz, C_7–H), 6.27 (1H, s, $C_{3'}$–H).

Treatment of **4a** with diphenyldiazomethane in THF gave the benzhydryl ester (**5a**). IR and NMR spectral data of **5a** were identical with those of an authentic sample obtained by oxidation of the corresponding 3-hydroxymethylcephalosporin with CrO_3-sulfuric acid.[2b,c] Other bromides (**3b—d**) were also converted into 3-formylcephalosporins, which were isolated as benzhydryl esters (**5**) (Table II).

Table II. Isolated Yield and Spectral Data of 3-Formylcephalosporin Derivatives (**5**)

Compound	Yield (%)[a]	IR ν_{max}^{KBr} cm^{-1}	NMR (DMSO-d_6, ppm)			
			C_2-H[b]	C_6-H[c]	C_7-H[d]	–CHO
5a	97.6	1800, 1735, 1663	3.34, 3.82	5.21	5.86	9.43
5b	95.5	1793, 1725, 1670	3.41, 3.88	5.32	6.04	9.42
5c	92.5	1800, 1735, 1670	3.41, 3.89	5.22	5.87	9.43
5d	81.3	1793, 1733, 1673	3.41, 3.91	5.25	5.90	9.44

a) Overall yields from bromolactones (**3**).
b) ABq, J=18 Hz. *c*) d, J=5 Hz. *d*) q, J=5 Hz and 8 Hz.

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