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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 $\nu_{max}^{KBr}$ $cm^{-1}$: 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 $\nu_{max}^{KBr}$ $cm^{-1}$: 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).

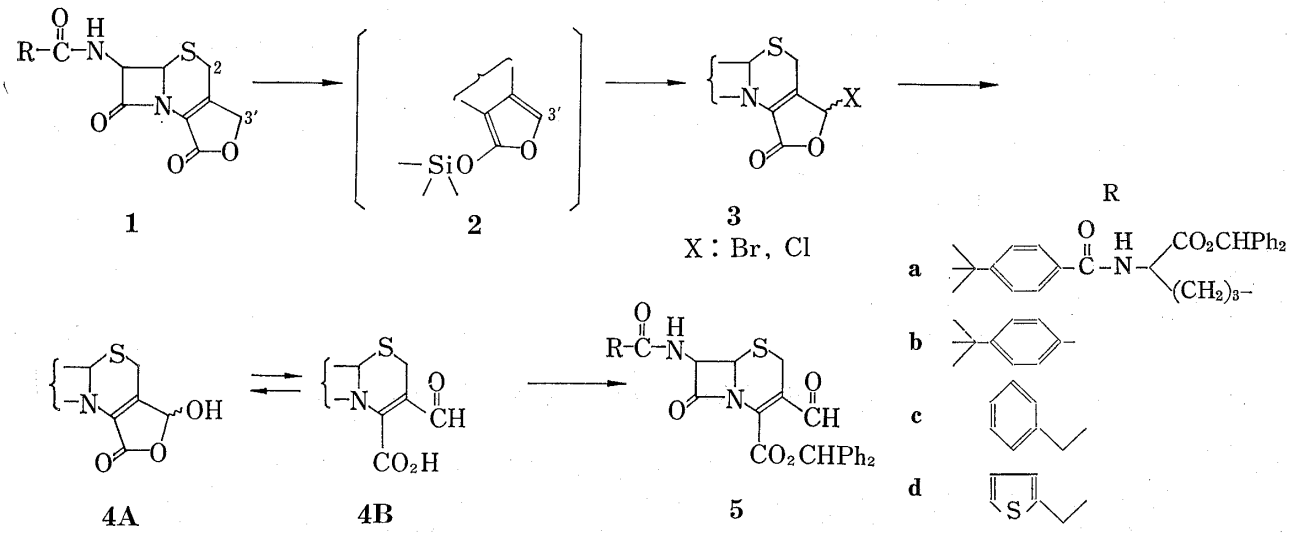


Chart 1

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 $\nu_{max}^{KBr}$ 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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