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A NEW METHOD FOR REGIOSELECTIVE SYNTHESIS OF A BROAD-SPECTRUM PARENTERAL S-3578-RELATED CEPHALOSPORIN BEARING AN IMIDAZO[4,5-*b*]PYRIDINIUM DERIVATIVE AT C-3'

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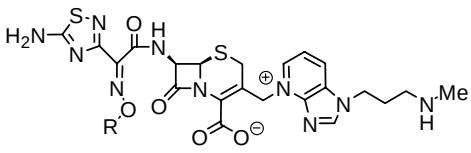
***Abstract*-** A broad-spectrum S-3578-related cephalosporin, 7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-fluoromethoxyiminoacetamido]-3-[1-(3-methylamino-propyl)-1*H*-imidazo[4,5-*b*]pyridinium-4-yl]methyl-3-cephem-4-carboxylate sulfate was regioselectively synthesized in a good yield using diaminopyridine derivative bearing a dimethylformamidine group.

Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* are nosocomial pathogens associated with serious infections and considerable mortality. Also, the incidence of mixed infection by MRSA and *P. aeruginosa* has been increasing,[1] and antibacterial agents having high activity against these pathogens are needed. Therefore, we began a search for novel parenteral C-3' quaternary ammonium cephalosporins exhibiting potent activity against both MRSA and *P. aeruginosa*.



S-3578 (R= Et) H_2SO_4 salt
1 (R= CH_2F) HCl salt

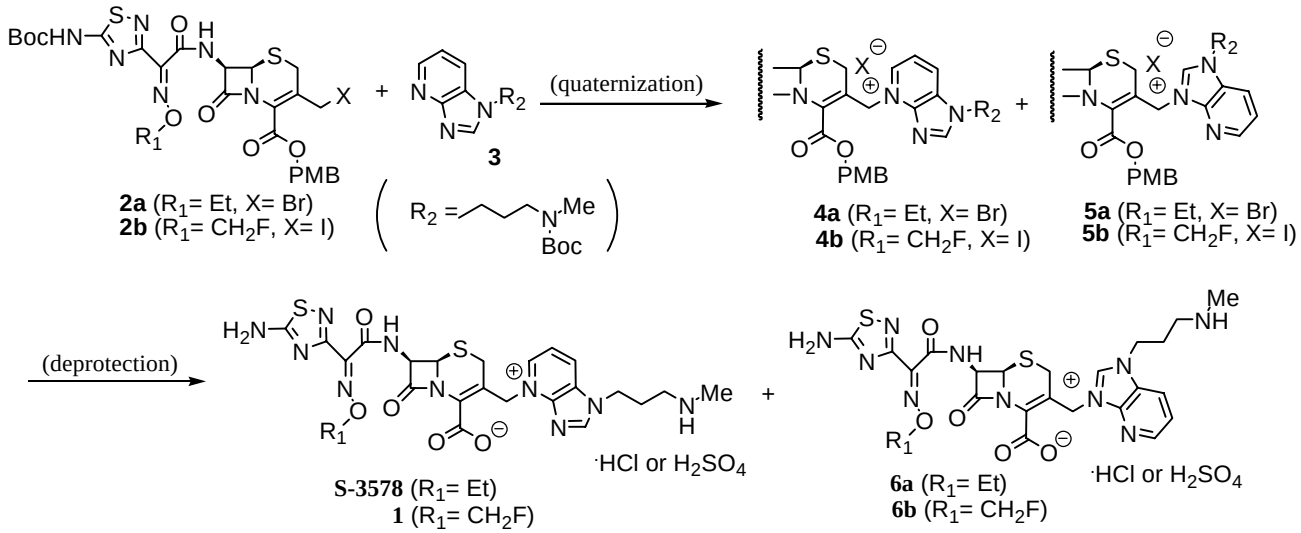
Figure 1. Structures of **S-3578** and **1**

In our previous paper,[2] we reported the synthesis and structure-

activity relationships of a series of C-3' imidazo[4,5-*b*]pyridinium cephalosporins such as **S-3578** and **1** (Figure 1) exhibiting potent antibacterial activity against both MRSA and *P. aeruginosa*.

Scheme 1 shows the earlier reported method for the synthesis of **S-3578** and **1**.

Quaternization of imidazo[4,5-*b*]pyridine derivative (**3**) with the bromide (**2a**) or iodide (**2b**) gave a mixture of imidazopyridinium (**4**) and the undesirable regioisomer (**5**). The ratio of regioisomers (**4**) and (**5**) was usually about 4~5:1 (determined by HPLC).



2a (R_1= Et, X= Br)
2b (R_1= CH_2F, X= I)
3
R_2 = N(Me)Boc
4a (R_1= Et, X= Br)
4b (R_1= CH_2F, X= I)
5a (R_1= Et, X= Br)
5b (R_1= CH_2F, X= I)
S-3578 (R_1= Et)
1 (R_1= CH_2F)
6a (R_1= Et)
6b (R_1= CH_2F)

Abbreviations; PMB: *p*-methoxybenzyl; Boc: *tert*-butoxycarbonyl

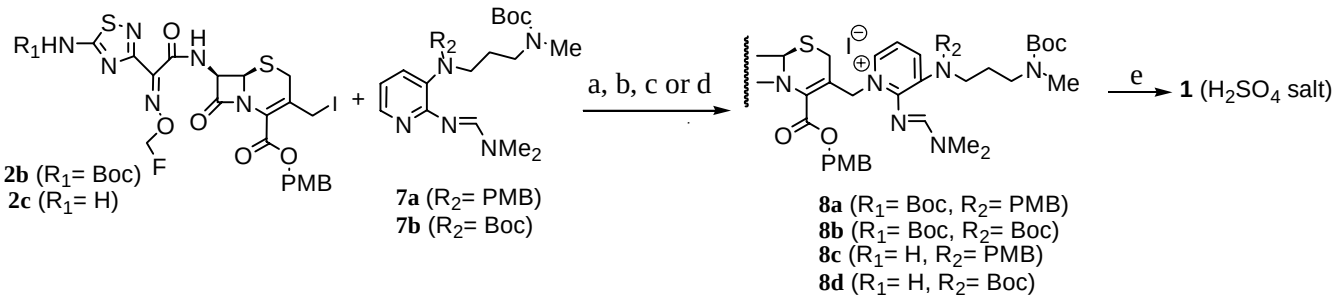
Scheme 1.

Isolation and purification of the desired quaternary imidazopyridinium salts (**4**) by crystallization or chromatography was difficult. Therefore, after deprotection of the mixture of **4** and **5**, the target compound (**S-3578** or **1**) was purified by reversed phase chromatography, although separation of the regioisomeric mixture was troublesome.

In order to facilitate purification of the desired regioisomer such as **S-3578** or **1**, we explored a method for the highly regioselective synthesis of imidazopyridinium cephalosporin. We report herein a new method for the synthesis of imidazopyridinium cephem (**1**) without the formation of undesirable regioisomer (**6b**).

Our approach was based on quaternization of the diaminopyridine derivative followed by cyclization to

form an imidazopyridinium ring under deprotection conditions. We found that the diaminopyridine derivative bearing a dimethylformamidine group is suitable and effective for this purpose.



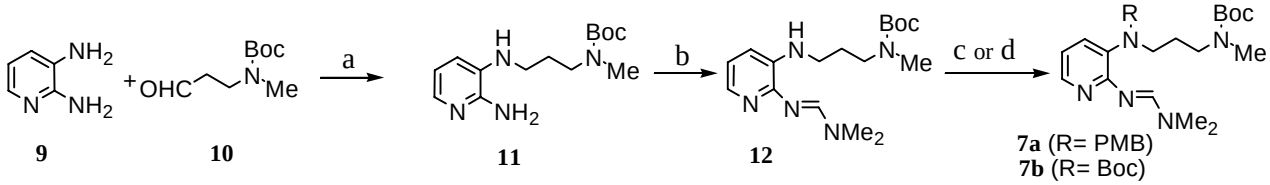
Abbreviations: DMF: *N*,*N*-dimethlyformamide, DMA: *N*,*N*-dimethylacetamide

Scheme 2. *Reagents and conditions*; (a) **2b**+**7a**→**8a**: DMF, rt, 2.5 h; (b) **2b**+**7b**→**8b**: DMF, rt, 17 h; (c) **2c**+**7a**→**8c**: DMA, rt, 3.5 h; (d) **2c** + **7b**→**8d**: DMA, rt, 17 h; (e) i) 62%H_2SO_4-AcOH, 5^oC, 1 h, ii) Purification by HP-20 chromatography, **8a**→**1**: 26% yield from **2b**; **8b**→**1**: 28% yield from **2b**; **8c**→**1**: 49% yield from **2c**; **8d**→**1**: 53% yield from **2c**.

Scheme 2 shows a new method for the synthesis of imidazopyridinium cephem (**1**) using **7**.

Quaternization of **7a-b** with iodomethyl **2b** or **2c** at room temperature gave the corresponding imidazopyridinium salts (**8a-d**) respectively, of which purification by crystallization or chromatography was difficult. The crude compounds (**8a-d**) were treated with a mixture of 62% H_2SO_4 and AcOH (at 5^oC for 1 h) to obtain the target material (**1**) in moderate to good yields (26%~53% yield from **2**),[3] involving both deprotection and cyclization.

Diaminopyridine derivatives (**7a-b**) were readily prepared from 2,3-diaminopyridine (**9**) in good yields as shown in Scheme 3. Pyridine derivative (**11**)[2] was obtained by reductive alkylation of **9** and aldehyde **10** using borane-pyridine complex as a reductant. The pyridine derivative (**11**) was treated with *N*,*N*-dimethylformamide dimethyl acetal to yield the amidine derivative (**12**) in a quantitative yield, followed by protection of the amino group at the 3-position of **12** to give **7a** and **7b**.[4]



Scheme 3. *Reagents and conditions*; (a) BH_3-Py (1 eq.), CH_2Cl_2 / AcOH (1 / 1), -15^oC, 69.6%; (b) *N*,*N*-dimethylformamide dimethyl acetal (1.5 eq.), 70^oC, 4 h, quant.; (c) **7a**: *p*-methoxybenzyl bromide(1.1 eq.), $NaHCO_3$, rt, 3.5 h, 73%; (d) **7b**: Boc_2O (1.2 eq.), THF, 3.5 h, reflux, 82%.

In conclusion, the new method presented in this paper offers the advantages of a good yield, high regioselectivity and easy purification. It could be applied to the synthesis of other imidazopyridinium cephalosporins including S-3578.

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2. H.Yoshizawa, H. Itani. K, Ishikura, T. Irie, K. Yokoo, T. Kubota, K. Minami, T. Iwaki, H. Miwa, and Y. Nishitani, *J. Antibiotics*, 2002, **55**, 975.
3. A typical procedure for the synthesis of **1** using **7a** is as follows.

   To a solution of iodomethyl **2b** (19.1 g, 25 mmol) in DMF (40 mL) was added pyridine derivative (**7a**) (14.4 g, 30 mmol), and the reaction mixture was stirred at rt for 2.5 h. The mixture was poured into 5% NaCl. The precipitate was filtered, washed with EtOAc and dried *in vacuo* to give quaternary ammonium (**8a**) (27.4 g) as an amorphous solid. The crude product (**8a**) was used directly in the next reaction. A sample of the crude **8a** was analyzed by ^{1}H-NMR, IR and HRMS; ^{1}H-NMR (DMSO-d_6) δ 1.32 (9H, s), 1.51 (9H, s), 2.71 (3H, s), 2.89 (3H, s), 3.10 (3H, s), 3.72 (3H, s), 3.76 (3H, s), 4.02 (2H, m), 5.10 (1H, d, *J* = 4.8 Hz), 5.20 (4H, m), 5.82 (2H, d, *J* = 54.6 Hz), 5.96 (1H, dd, *J* = 8.1 Hz, 4.8 Hz), 6.87 (2H, q, *J* = 8.4 Hz), 6.95 (2H, d, *J* = 8.7 Hz), 7.00 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.7 Hz), 7.22 (1H, m), 7.78 (1H, m), 8.16 (1H, m), 8.43 (1H, m); IR ($CHCl_3$) cm^{-1} 1775, 1720, 1695, 1640, 1555, 1520; HRMS Found: 1090.4277 ($[M-I]^+$). Calcd for $C_{51}H_{65}N_{11}O_{11}FS_2$:1090.4291.

   To 62% H_2SO_4 (42 mL) was added a solution of the crude compound (**8a**) (9.99 g, 8.2 mmol) in AcOH (18 mL) at 5^{o}C, and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was poured into 2-propanol. The precipitate was collected by filtration and

dissolved in H_2O. The solution was chromatographed on HP-20 resin. The target product was eluted with 3% MeCN/0.001 N H_2SO_4. The solution containing the target product was concentrated *in vacuo*, and compound (**1**) was crystallized as a sulfate salt (1.90 g, 26% from **2b**); mp >200°C (decomp); ^{1}H-NMR (D_2O) δ 2.42 (2H, m), 2.73 (3H, s), 3.17 (2H, t, *J* = 7.6 Hz), 3.30 and 3.64 (2H, ABq, *J* = 18.3 Hz), 4.62 (2H, t, *J* = 7.4 Hz), 5.25 (1H, d, *J* = 4.8 Hz), 5.70 and 5.91 (2H, ABq, *J* = 13.0 Hz), 5.82 (2H, d, *J* = 54.6 Hz), 5.86 (1H, d, *J* = 4.8 Hz), 7.87 (1H, dd, *J* = 8.2 Hz, 6.4 Hz), 8.80 (1H, d, *J* = 8.2 Hz), 8.83 (1H, d, *J* = 6.4 Hz); ^{13}C-NMR (D_2O) δ 28.6, 28.8, 35.7, 46.4, 48.7, 57.3, 60.1, 61.7, 105.6, 108.6, 117.7, 122.4, 131.7, 133.8, 136.0, 141.0, 150.8, 152.6, 153.4, 162.5, 165.1, 166.5, 169.4, 187.0; IR (KBr) cm^{-1} 1774, 1720, 1679, 1631, 1577, 1529, 1495, 1463, 1417; MS *m*/*z* 605 ([M+H]$^+$, 40), 604 (4), 557 (2), 531 (2), 456(2), 429 (2), 329 (5), 303 (2), 191 (100), 189 (10), 146 (8); HRMS Found: 605.1521. Calcd for $C_{23}H_{26}N_{10}O_5FS_2$: 605.1513. *Anal*. Calcd for $C_{23}H_{25}N_{10}O_5FS_2 \cdot 1.0H_2SO_4 \cdot 8.2H_2O$: C 32.48, H 5.14, N 16.47, F 2.23, S 11.31. Found: C 32.57, H 5.00, N 16.49, F 2.22, S 11.31.

4. The method for the syntheses of **7a** and **7b** is as follows.

[3-(2-Aminopyridin-3-ylamino)propyl]methylcarbamic acid *tert*-butyl ester (**11**)

2,3-Diaminopyridine (**9**) (161.5 g, 1.48 mol) was dissolved in a mixture of CH_2Cl_2 (1.6 L) and AcOH (1.6 L), and the solution was cooled to –15°C. To this was added borane-pyridine complex (150 mL, 1.48 mol), followed by addition of a solution of 3-*tert*-butoxycarbonylmethylamino-propionaldehyde (**10**) (360.2 g, 1.92 mol) in CH_2Cl_2 (300 mL). The reaction mixture was stirred at –15°C for 1 h. The organic layer was washed with 5% NaOH and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (**11**) (289 g, 69.6%) as a pale yellow crystal which was crystallized from Et_2O; mp 103-104°C; ^{1}H-NMR ($CDCl_3$) δ 1.44 (9H, s), 1.83 (2H, m), 2.85 (3H, s), 3.1 (2H, t, *J* = 6.3 Hz), 3.36 (2H, t, *J* = 6.6 Hz), 4.13 (1H, s), 4.58 (2H, bs), 6.66 (1H, m), 6.75 (1H, m), 7.55 (1H, d, *J* = 4.3 Hz); ^{13}C-NMR ($CDCl_3$) δ 26.1, 28.3, 34.0, 40.0, 45.1, 79.6,

115.2, 116.4, 131.5, 135.6, 148.6, 156.0; MS *m*/*z* 281 ($[M+H]^+$, 100), 280 (64), 225 (18), 224 (15), 181 (17), 122 (18), 57 (19). HRMS Found: 281.1974. Calcd for $C_{14}H_{25}N_4O_2$: 281.1978. *Anal*. Calcd for $C_{14}H_{24}N_4O_2$: C 59.98, H 8.63, N 19.98. Found: C 59.98, H 8.65, N 19.88.

{3-[2-(Dimethylaminomethyleneamino)pyridin-3-ylamino]propyl}methylcarbamic acid *tert*-butyl ester (**12**)

A mixture of **11** (200 g, 0.713 mol) and *N*,*N*-dimethylfolmamide dimethyl acetal (142 mL, 1.06 mol) was stirred at 70°C for 4 h. The reaction mixture was poured into a mixture of EtOAc and H_2O, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (**12**) (239 g). A portion (3.9 g) of the crude product was chromatographed on silica gel with chloroform-methanol (9:1) as eluent to give pure **12** as a reddish oil (3.9 g, quantitative yield); ^{1}H-NMR ($CDCl_3$) δ 1.45 (9H, s), 1.87 (2H, m), 2.87 (3H, s), 3.09 (6H, s), 3.13 (2H, t, *J* = 6.4 Hz), 3.34 (2H, t, *J* = 6.9 Hz), 6.74 (2H, m), 7.56 (1H, dd, *J* = 4.8 Hz, 1.6 Hz), 8.44 (1H, s); ^{13}C-NMR ($CDCl_3$) δ 27.2, 28.3, 34.2, 34.5, 40.5, 46.1, 46.8, 79.1, 114.1, 118.3, 134.0, 137.1, 149.0, 153.7, 155.5; IR ($CHCl_3$) cm^{-1} 1680, 1485, 1460, 1405; MS *m*/*z* 336 ($[M+H]^+$, 87), 335 (**100**), 291 (8), 280 (6), 235 (12), 191 (19), 177 (15), 57 (12). HRMS Found: 335.2311. Calcd for $C_{17}H_{30}N_5O_2$: 335.2321.

{3-[[2-(Dimethylaminomethyleneamino)pyridin-3-yl]-(4-methoxybenzyl)amino]propyl}methyl-carbamic acid *tert*-butyl ester (**7a**)

To a solution of the crude compound (**12**) (50.8 g, 0.151 mol) in DMF (250 mL) was added $NaHCO_3$ (38.17 g, 0.454 mol) and subsequently *p*-methoxybenzyl bromide (33.5 g, 0.166 mol) at 25°C. The reaction mixture was stirred at the same temperature for 3.5 h. After addition of EtOAc, the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude compound (**7a**) (59.46 g). A portion (12.1 g) of the crude product (**7a**) was chromatographed on silica gel with EtOAc as eluent to give pure **7a** as a reddish oil (11.0 g, 73%);

^{1}H-NMR ($CDCl_3$) δ 1.39 (9H, s), 1.65 (2H, m), 2.70 (3H, s), 3.03 (3H, s), 3.07 (3H, s), 3.10 (4H, m), 3.78 (3H, s), 4.37 (2H, s), 6.80 (3H, m), 7.03 (1H, dd, *J* = 7.9 Hz, 1.7 Hz), 7.23 (2H, d, *J* = 8.7 Hz), 7.87 (1H, dd, *J* = 4.7 Hz, 1.6 Hz), 8.33 (1H, s); ^{13}C-NMR ($CDCl_3$) δ 25.4, 28.3, 34.1, 34.6, 40.4, 47.1, 47.4, 55.0, 56.2, 78.9, 113.1, 113.5, 117.4, 129.3, 131.1, 138.5, 140.7, 153.5, 155.4, 155.9, 158.1; IR ($CHCl_3$) cm^{-1} 1685, 1635, 1580, 1520, 1405; MS *m*/*z* 456 ([M+H]$^{+}$, 55), 334 (35), 297 (3), 283 (35), 203 (9), 191 (13), 177 (4), 121 (100), 57 (11). HRMS Found: 456.2972. Calcd for $C_{25}H_{38}N_5O_3$: 456.2975,

[3-(*tert*-Butoxycarbonylmethylamino)propyl]-[2-(dimethylaminomethyleneamino)pyridin-3-yl-carbamic acid *tert*-butyl ester (**7b**)

To a solution of **12** (312 g, 0.92 mol) in THF (624 mL) was added di-*tert*-butyldicarbonate (243 g, 1.11 mol) and then the reaction mixture was refluxed for 3.5 h. After evaporation of the solvent, EtOAc and 10% oxalic acid were added to the residue. The aqueous layer was alkalinized with 4 N NaOH and subsequently extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude compound (**7b**) (356.9 g). A portion (2.1 g) of the crude product (**7b**) was chromatographed on silica gel with EtOAc as eluent to give pure **7b** as a reddish oil (1.99 g, 82%); ^{1}H-NMR (DMSO-d_6) δ 1.21 (9H, s), 1.35 (9H, s), 1.59 (2H, m), 2.70 (3H, s), 2.96 (3H, s), 3.08 (3H, s), 3.15 (2H, t, *J* = 7.1 Hz), 6.89 (1H, dd, *J* = 7.6 Hz, 4.8 Hz), 7.42 (1H, dd, *J* = 7.6 Hz, 1.6 Hz), 8.08 (1H, dd, *J* = 4.8 Hz, 1.6 Hz), 8.44 (1H, s); ^{13}C-NMR (DMSO-d_6) δ 26.1, 27.6, 27.8, 33.5, 338, 45.9, 47.0, 78.0, 78.5, 116.8, 129.7, 136.2, 137.2, 145.7, 153.7, 154.2, 154.3, 158.0; IR ($CHCl_3$) cm^{-1} 1690, 1638, 1585, 1465, 1405; MS *m*/*z* 436 ([M+H]$^{+}$, 100), 291 (20), 235 (11), 191 (30), 177 (12), 57 (39). HRMS Found: 436.2927. Calcd for $C_{22}H_{38}N_5O_4$: 436.2924.