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Communications

Synthesis of Quaternary Ammoniocephalosporin Having Two Vinyl Groups Using Radical Promoted Thermal Isomerization

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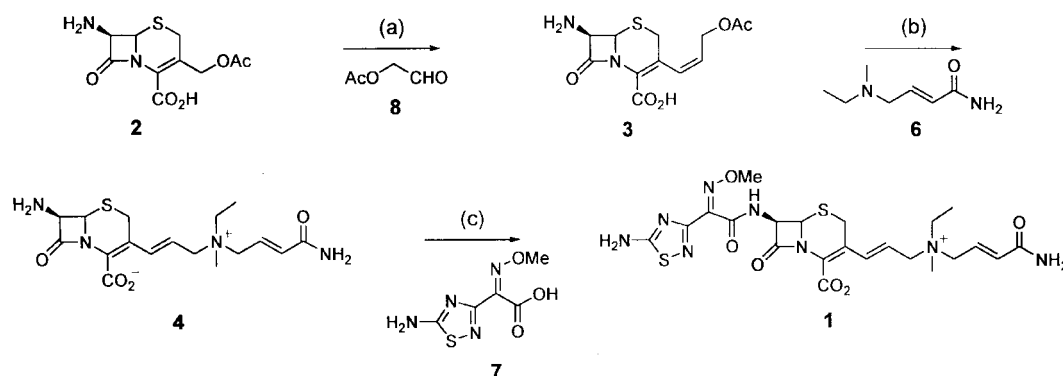
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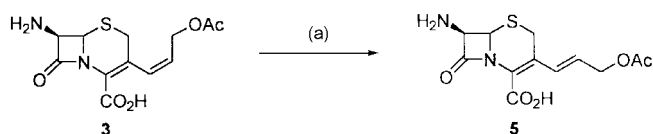
The cephalosporin antimicrobial agents have made remarkable progress and contribution in the treatment of bacterial infections. Recently, many efforts have been made to achieve well balanced broad-spectrum and improve β -lactamase stability. Recently, 3-vinylcephalosporins, such as TOC-39,¹ E-1077,² YM-40220³ and IDC-7181 have been studied intensively.⁴ They show excellent activities against Gram-positive bacteria including *Staphylococcus aureus* and also gram-negative bacteria including *Pseudomonas aeruginosa*. In the previous paper, we described the synthesis and antibacterial activities of IDC-7181, which has two vinyl groups at C-3 side chain. We report herein the result of process

development of novel quaternary ammonio cephalosporins having two vinyl groups (Scheme 1).

(Z)-7-Amino-3-(3-acetoxy-1-propen-1-yl)-3-cephem-4-carboxylic acid **3**⁵ was prepared from 7-ACA **2** using a known procedure (cat. squaric acid, HMDS, iodination with TMSI, ylide generation with PPh₃, and Wittig reaction using LiHMDS and acetoxymethyl aldehyde) in 70% yield (*E*-content: 7.2%).⁶ It has been proved that the vinyl substituted cephalosporin (**1**) has (*E*)-configuration are more potent than the one has (*Z*)-configuration in antibacterial activity against both Gram-positive and Gram-negative bacteria. We focused isomerization to acetoxypentenylcephalosporin having (*E*)-



Scheme 1. Reagents; (a) 1) squaric acid (cat.), HMDS, CH₂Cl₂, reflux (12h), and then TMSI (3h), PPh₃ (3h), 2) BSA, LiHMDS, acetoxymethyl aldehyde, 1N-HCl (b) 1) TMSI (cat.), HMDS, toluene, 4-Me-PhSH, AIBN, reflux (30h), 2) HMDS, CH₂Cl₂, reflux (1h), and then TMSI (7h), **6**, DIPEA (c) FMS, ATDA, Et₃N, DMF.



Scheme 2. Isomerization (a) 4-methylthiophenol, AIBN, toluene.

Table 1. The results of radical promoted thermal isomerization

| No. | Solvent | Radical initiator | Time(h) | Z : E Ratio ^a |
|-----|---------------------------------|----------------------------|---------|--------------------------|
| 1 | CH ₂ Cl ₂ | <i>t</i> -butylperbenzoate | 2 | 28.7 : 71.3 |
| 2 | toluene | <i>t</i> -butylperbenzoate | 12 | 24.5 : 75.5 |
| 3 | toluene | <i>t</i> -butylperbenzoate | 24 | 18.7 : 81.3 |
| 4 | toluene | AIBN | 2 | 38.8 : 61.2 |
| 5 | toluene | AIBN | 12 | 23.5 : 76.5 |
| 6 | toluene | AIBN | 18 | 18.0 : 82.0 |
| 7 | toluene | AIBN | 30 | 2.0 : 98.0 |

^aThe ratio was identified by ¹H-NMR (200 MHz)

configuration and tried radical and thermal isomerization (Scheme 2).⁷

The isomerization reaction of (*Z*)-3-acetoxypropene **3** to (*E*)-3-acetoxypropene cephalosporin **5**⁹ was completed under reflux condition in toluene for 30 h (Z : E = 2 : 98) in the presence of 4-methylthiophenol and AIBN (Table 1). The radical promoted thermal isomerization reaction may proceed by the transition state involving vinylic radical (Figure 1). It is plausible mechanism that vinylic radical is rapidly promoted through addition of generated sulphur-radical from the radical initiator such as AIBN.⁸

The (*E*)-isomer **5** was concentrated in a reduced pressure and reacted with TMSI at -20 °C *in situ* and reacted with (*E*)-4-ethylmethylamino-2-butenamide and DIPEA in CH₂Cl₂ at -10 °C for 3 h to provide (*E*)-7-amino-3-[(*E*)-3-[(*E*)-(1-carbamoyl-1-propen-3-yl)-3-(ethylmethylammonio)-1-propen-1-yl]-3-cephem-4-carboxylate **4**¹⁰ in 75% yield. Acylation of **4** was achieved with ATDA-activated ester [1-methanesulfonyl-6-trifluoromethyl-1H-benzotriazole (FMS)], ATDA **7** and Et₃N in DMF to provide **11** in 35% yield.

To summarize the above results, we developed an efficient method for the synthesis of novel quaternary ammoniocephalosporins having two vinyl groups by a radical promoted thermal isomerization.

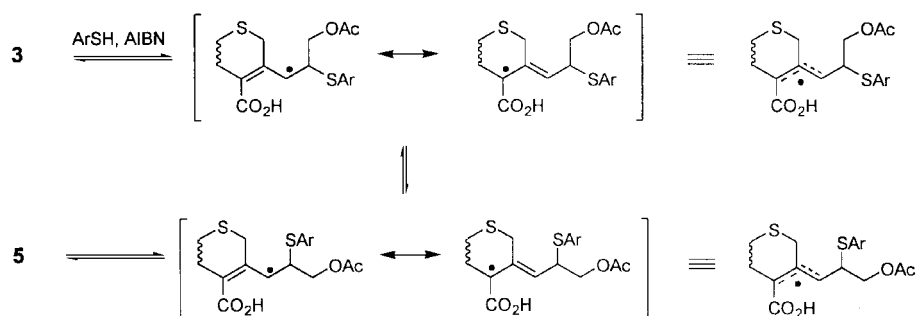


Figure 1. Possible mechanism for the radical promoted thermal isomerization.

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- Compound **3**: ¹H-NMR (DMSO-d₆, 200 MHz) δ 6.32 (d, *J* = 11.8 Hz, 1H), 5.58 (dt, *J* = 11.8, 6.1 Hz, 1H), 5.02 (d, *J* = 5.0 Hz, 1H), 4.78 (d, *J* = 5.0 Hz, 1H), 4.64-4.47 (m, 2H), 3.50 (q, *J* = 17.7 Hz, 2H), 2.00 (s, 3H) ¹³C-NMR (DMSO-d₆, 50 MHz) δ 170.1, 169.6, 163.6, 129.1, 127.1, 125.9, 122.1, 63.5, 60.9, 59.2, 26.5, 20.6 HRMS (EI) Calcd for C₁₂H₁₄N₂O₅S; 298.0623, Found 298.0618.
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- Compound **5**: ¹H-NMR (DMSO-d₆, 200 MHz) δ 6.82 (d, *J* = 15.8 Hz, 1H), 6.13-6.02 (dt, *J* = 15.8, 6.1 Hz, 1H), 5.00 (d, *J* = 5.4 Hz, 1H), 4.78 (d, *J* = 4.8 Hz, 1H), 4.61 (d, *J* = 5.9 Hz, 2H), 3.83-3.48 (q, *J* = 17.1 Hz, 2H), 2.01 (s, 3H).
- Compound **4**: ¹H-NMR (D₂O, 200 MHz) δ 6.75 (d, *J* = 15.6 Hz, 1H), 6.63 (dt, *J* = 15.6, 7.6 Hz, 1H), 6.34 (d, *J* = 15.4 Hz, 1H), 5.73 (dt, *J* = 15.4, 6.3 Hz, 1H), 4.84 (d, *J* = 5.1 Hz, 1H), 4.18 (d, *J* = 5.1 Hz, 1H), 3.90 (dd, *J* = 7.0, 4.0 Hz, 2H), 3.85 (dd, *J* = 7.5, 3.5 Hz, 2H), 3.23 (q, *J* = 17.3 Hz, 2H), 2.86 (s, 3H), 1.22 (t, *J* = 7.3 Hz, 3H) ¹³C-NMR (D₂O, 50 MHz) δ 185.0, 170.2, 169.3, 139.9, 134.4, 134.2, 130.5, 116.2, 115.2, 64.3, 63.4, 61.3, 59.4, 58.0, 47.7, 23.9, 8.2 HRMS (FAB) Calcd for C₁₇H₂₅N₄O₄S; 381.1597, Found 381.1596.
- Compound **1**: ¹H-NMR (D₂O, 200 MHz) δ 6.76 (d, *J* = 15.6 Hz, 1H), 6.63 (dt, *J* = 15.6, 7.5 Hz, 1H), 6.31 (d, *J* = 15.3 Hz, 1H), 5.73 (dt, *J* = 15.3, 7.2 Hz, 1H), 5.69 (d, *J* = 4.9 Hz, 1H), 5.10 (d, *J* = 4.9 Hz, 1H), 3.92 (s, 3H), 3.91-3.78 (m, 4H), 3.52 (q, *J* = 17.3 Hz, 2H), 3.20 (q, *J* = 7.3 Hz, 2H), 2.85 (s, 3H), 1.10 (t, *J* = 7.3 Hz, 3H) ¹³C-NMR (D₂O, 50 MHz) δ 185.0, 169.1, 164.4, 164.3, 161.8, 147.4, 139.8, 134.5, 134.1, 132.2, 130.3, 116.5, 115.5, 64.3, 61.3, 59.8, 58.4, 58.1, 56.2, 47.7, 23.9, 8.2 HRMS (FAB) Calcd for C₂₂H₂₉N₈O₆S₂; 565.1651, Found 565.1653.