A Synthesis of C-3 Cyclopropylcephem Derivatives

Sung Ho Kang*

Department of Chemistry, Korea Institute of Technology, Taejeon 305-701

Jong-Hoon Oh and Wan Joo Kim

Korea Research Institute of Chemical Technology, Taejeon 305-606. Received June 23, 1989

β-Lactam antibiotics display biological activities by inhibiting the transpeptidase responsible for the final step of bacterial cell wall biosynthesis.[1] Since the action of the antibiotics with the enzyme develops negative charge on the nitrogen atom of the β-lactam ring, the biological activities are believed to depend on their stabilizing ability of the developing charge.

Based on the consideration we planned to develop new cephalosporin derivatives by introducing proper substituents at C-3 position. To attain the intention successfully, some known results related to the modifications at C-3 position merit mention: (1) strong electron-withdrawing substituents may decrease antibacterial activities due to destabilizing β-lactam ring,[2] (2) cephalexin 1 has better oral absorption than cephaloglycin 2,[3] (3) alkoxy substituents improve oral absorption,[4] (4) bulkier alkoxy substituents are more effective against gram-positive bacteria and less effective against gram-negative bacteria,[5] of which the polarity is probably associated with facilitating cell penetration.[6]

Analyzing the aforementioned informations, promising substituents at C-3 position should compromise lipophilicity and hydrophilicity to develop orally administrable cephalosporin derivatives. In this regard we envisioned cyclopropyl group[7] as an adequate choice. We herein wish to describe a synthesis of 3-cyclopropylcephem systems, which have not been reported yet to our knowledge.

Results and Discussion

Although chclopropanation of 3-vinylcephem 3 was unsuccessful with diazomethane in the presence of copper powder or copper salts,[8] employment of palladium acetate[9] as catalyst produced 3-cyclopropylcephem 4 in 70% yield. The formation of the cyclopropyl ring was confirmed by ^{1}H NMR spectrum (CDCl$_3$), in which the cyclopropyl proton signals appear at δ 2.66 (1H, m), 0.78 (2H, m), 0.52 (1H, m) and 0.41 ppm (1H, m). The selective hydrolysis of phenylacetamide group was accomplished with phosphorus pentachloride and pyridine[10] to furnish 3-cyclopropylcephem hydrochloride 5 in 86% yield.

Using 1-methanesulfonyloxy-6-trifluoromethyl benzotriazole (FMS) 7 as a coupling reagent,[11] 3-cyclopropylcephem
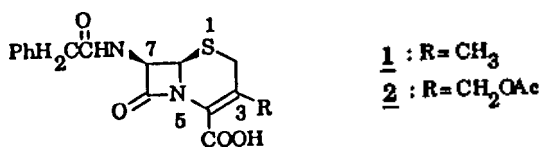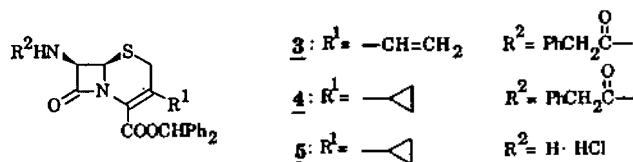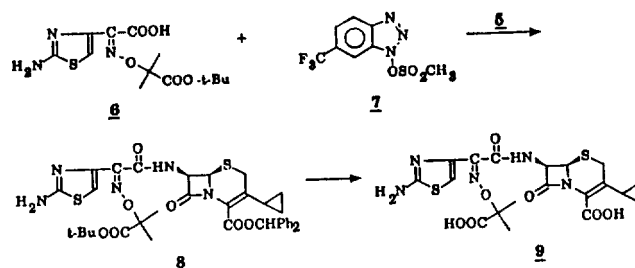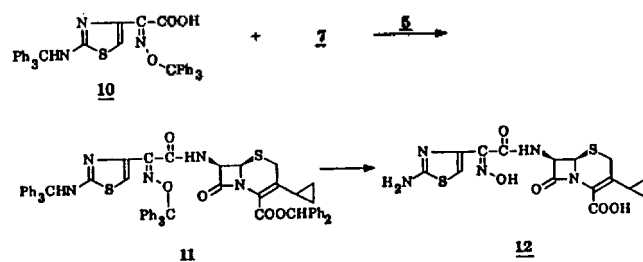
Figure 1

Figure 2

Scheme 1

Scheme 2

hydrochloride 5 and (Z)-2-(2-aminothiazol-4-yl)-2-(1-t-butoxycarbonyl-1-methylethoxyimino)acetic acid 6[12] were condensed to provide 7-acetamido-3-cyclopropylcephemcarboxylate 8 in 74% yield. In the next event diphenylmethyl group and t-butyl group of 8 were hydrolyzed with trifluoroacetic acid in the presence of anisole to afford 7-acetamido-acetic acid in the presence of anisole to afford 7-acetamido-3-cyclopylcephemcarboxylic acid 9 in 71% yield (Scheme 1).

The coupling reaction of 3-cyclopropylcephem hydrochloride 5 with (Z)-2-(2-tritylaminothiazol-4-yl)-2-trityloxyiminoacetic acid 10[13] and the subsequent hydrolysis of triphenylmethyl groups and diphenylmethyl group were also accomplished as described above to give another final target derivative, 7-acetamido-3-cyclopropylcephemcarboxylic acid 12 in 50% overall yield (Schem 2).

The bacteriocidal activities and the oral absorptions of the two 7-acetamido-3-cyclopropylcephemcarboxylic acids 9 and 12 are currently under evaluation.

478 *Bull. Korean Chem. Soc., Vol. 10, No. 5, 1989*

Communications to the Editor

Experimental

3-Vinylcephem 3 was prepared from 7-aminocephalosporanic acid according to the literature.[10] Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer using TMS as an internal standard. Purifications by column chromatography were performed using Merk silica gel 60 (70–230 mesh).

(6R), (7R)-Benzhydryl 7-phenylacetamido-3-cyclopropyl-cephem-4-carboxylate 4. After an excess of diazomethane in ethyl ether was slowly added at room temperature to (6R), (7R)-benzhydryl 7-phenylacetamido-3-vinyl-3-cephem-4-carboxylate 3 (1.04 g, 2 mmol) and 20 mg of palladium acetate in 100 m*l* of THF, the resulting mixture was stirred for 30 min at room temperature. Removal of the volatile meterials under reduced pressure followed by column chromatography (hexane:ethyl acetate = 2:1) of the residue gave 3-cyclopropylcephem 4 (730 mg, 70%) as a white solid (mp 151–153 °C). ^{1}H NMR (CDCl$_3$) δ 7.42–7.26 (15H, m), 6.90 (1H, s), 6.60 (1H, d, J = 8.5 Hz), 5.61 (1H, dd, J = 8.5 and 4.3 Hz), 4.96 (1H, d, J = 4.3 Hz), 3.66 (2H, s), 2.73 (1H, d, J = 16 Hz), 2.66 (1H, m), 2.43 (1H, d, J = 16 Hz), 0.78 (2H, m), 0.52 (1H, m) and 0.41 ppm (1H, m).

(6R), (7R)-Benzhydryl 7-amino-3-cyclopropyl-3-cephem-4-carboxylate hydrochloride 5. To the solution of phosphorus pentachloride (312 mg, 1.5 mmole) and pyridine (118 mg, 1.5 mmole) in 10 m*l* of dichloromethane was 3-cyclopropylcephem 4 (407 mg, 1.0 mmole) added in an ice bath. After the reaction mixture was stirred for 100 min at the temperature followed by the addition of 100 m*l* of methanol at -50 °C, it was warmed up to 0 °C and the reaction was quenched with 5 m*l* of water. The volatile materials were removed under reduced pressure and the addition of ethyl ether induced precipitation of 3-cyclopropylcephem hydrochloride 5 (350 mg, 86%) as a white solid (mp 208–210 °C). ^{1}H NMR (CDCl$_3$) δ 7.43–7.23 (10H, m), 6.89 (1H, s), 5.13 (1H, d, J = 4.3 Hz), 4.78 (1H, d, J = 4.3 Hz), 3.48 (1H, d, J = 15 Hz), 3.04 (1H, m), 2.48 (1H, d, J = 15 Hz), 0.99 (2H, m) and 0.78 ppm (2H, m).

(6R), (7R)-Benzhydryl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-*t*-butoxycarbonyl-1-methylethoxyimino)acetamido]-3-cyclopropyl-3-cephem-4-carboxylate 8. To the solution of aminothiazole derivative 6 (100 mg, 0.30 mmole) and FMS 7 (85 mg, 0.30 mmole) in 2 m*l* of DMF, which were stirred for 30 min at room temperature, were 3-cyclopropylcephem 5 (100 m*l*, 0.27 mmole) and triethylamine (30 mg 0.30 mmole) added, and the reaction mixture was stirred for 3 hours at room temperature. After aqueous work-up with ethyl acetate, the organic layer was washed with saturated aqueous sodium bicarbonate solution three times and dried over magnesium sulfate. Evaporation of the volatile materials and column chromatography (hexane:ethyl acetate = 1:1) of the residue furnished 7-acetamido-3-cyclopropylcephemcarboxylate 8 (140 mg, 74%) as a white solid (mp 108–110 °C). ^{1}H NMR (CDCl$_3$) δ 7.40–7.15 (10H, m), 7.05 (1H, s), 6.94 (1H, s), 5.85 (1H, dd, J = 8.7 and 5.0 Hz), 5.12 (1H, d, J = 5.0 Hz), 2.92 (1H, d, J = 16 Hz), 2.80 (1H, m), 2.73 (1H, d, J = 16 Hz), 1.67 (3H, s), 1.64 (3H, s), 1.42 (9H, s), 0.90 (2H, m), 0.67 (1H, m) and 0.58 ppm (1H, m).

(6R), (7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-(1-carboxyl-1-methylethoxyimino) acetamido]-3-cycloprophyl-3-cephem-4-carboxylic acid 9. After the addition of 1 m*l* of trifluoroacetic acid and 1 m*l* of anisole to 7-acetamido-3-cyclopropylcephemcarboxylate 8 (100 mg, 0.14 mmole) in 10 m*l* of dichloromethane, the reaction mixture was stirred for 3 hours at room temperature. The volatile materials were evaporated *in vacuo* and the residue was crystallized in the mixture of hexane and ethyl ether to afford 7-acetamido-3-cyclopropylcephemcarboxylic acid 9 (50 mg, 71%) as a white solid (decomposed at 155–180 °C). ^{1}H NMR (CDCl$_3$, DMSO-d$_6$) δ 9.15 (1H, d, J = 8.3 Hz), 7.03 (1H, s), 5.76 (1H, dd, J = 8.3 and 4.5 Hz), 5.08 (1H, d, J = 4.5 Hz), 2.87 (2H, br s), 2.71 (1H, m), 1.71 (3H, s), 1.69 (3H, s), 0.88 (2H, m), 0.73 (1H, m) and 0.65 ppm (1H, m).

(6R), (7R)-Benzhydryl 7-[(Z)-2-(2-tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido)-3-cyclopropyl-3-cephem-4-carboxylate 11. To the solution of FMS 7 (280 mg, 1.0 mmole), (Z)-2-(2-tritylaminothiazol-4-yl)-2-trityloxyiminoacetic acid 10 (500 mg, 0.74 mmole) and 0.2 m*l* of triethylamine in 5 m*l* of DMF, which were stirred for 30 min at room temperature, were 3-cyclopropylcephem hydrochloride 5 (200 mg, 0.54 mmole) and 0.12 m*l* of triethylamine added, and the reaction mixture was stirred for 5 hours at room temperature. After aqueous work-up with ethyl acetate, the organic layer was washed with saturated aqueous sodium bicarbonate solution three times and dried over magnesium sulfate. Evaporation of the volatile materials and column chromatography (hexane:ethyl acetate = 1:1) of the residue provided 7-acetamido-3-cyclopropylcephemcarboxylate 11 (400 mg, 75%). ^{1}H NMR (CDCl$_3$) δ 7.40–7.20 (41H, m), 6.95 (1H, s), 5.30 (1H, d, J = 9.5 Hz), 5.20 (1H, dd, J = 9.4 and 4.5 Hz), 5.06 (1H, d, J = 4.5 Hz), 3.16 (2H, br s), 2.71 (1H, m), 0.91 (1H, m), 0.79 (1H, m) and 0.65 ppm (2H, m).

(6R), (7R)-7-[(Z)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-cyclopropyl-3-cephem-4-carboxylic acid 12. After the addition of 3 m*l* of trifluoroacetic acid and 3 m*l* of anisole to 7-acetamido-3-cyclopropylcephem carboxylate 11 (400 mg, 0.37 mmole) in 20 m*l* of dichloromethane, the reaction mixture was stirred for 3 hours at room temperature. The volatile materials were evaporated *in vacuo* and the residue was crystallized in the mixture of hexane and ethyl ether to yield 7-acetamido-3-cyclopylcephemcarboxylic acid 12 (100 mg, 66%) as a white solid (decomposed at 135–155 °C). ^{1}H NMR (CDCl$_3$, DMSO-d$_6$) δ 8.40 (1H, d, J = 10.0 Hz), 7.75 (1H, s), 6.61 (2H, s), 5.20 (1H, dd, J = 10.0 and 4.6 Hz), 5.03 (1H, d, J = 4.6 Hz), 2.99 (1H, d, J = 16.7 Hz), 2.89 (1H, d, J = 16.7 Hz), 2.69 (1H, m), 0.89 (2H, m), 0.75 (1H, m) and 0.68 ppm (1H, m).

References

1. (a) J. L. Strominger, *The Harvey Lectures*, **64**, 179 (1970); (b) J. L. Strominger, P. M. Blumberg, H. Suginaka, J. Umbreit and G. G. Wickus, *Proc. Roy. Soc.*, **B179**, 369 (1971).
2. (a) H. Peter, B. Muller and H. Bickel, *Helv. Chim. Acta.*, **58**, 2450 (1975); (b) J. L. Fahey, R. A. Firestone and B. G. Christenson, *J. Med. Chem.*, **19**, 562 (1976).

3. R. Scartazzini and H. Bickel, *Heterocycles*, **7**, 1165 (1977).

4. O. Zak, W. A. Vischer, C. Schenk, W. Tosch, W. Zimmermann, J. Regos, E. R. Suter, F. Kradolfer and J. Gelzer, *J. Antibiot.*, **29**, 653 (1976).

5. J. Gosteli, *Chimia*, **30**, 13 (1976).

6. M. Gorman and C. W. Ryan, *"Cephalosporins and Penicillins-Chemistry and Biology"*, ed. E. H. Flynn, Academic Press, New York, p. 532 (1972).

7. M. Charton, *"The Chemistry of Alkenes"*, ed. J. Zabicky, Interscience, New York, Vol. 2, pp. 511-610

8. S. D. Burke and P. A. Grieco, *Org. React.*, **26**, 361 (1979).

9. M. Suda, *Synthesis*, 714 (1981).

10. H. Yamanaka, T. Chiba, K. Kawabata, H. Takasugi, T. Masugi and T. Takaya, *J. Antibiot.*, **38**, 1738 (1985).

11. C. H. Lee, C. J. Moon, K. S. Kim, J. H. Kim and D. W. Kim, *Bull. Korean Chem. Soc.*, **8**, 336 (1987).

12. C. N. Herbschwerlen and G. Schmid, EP 73061; *Chem. Abstr.*, **99**, 38291 C (1983).

13. R. Bucourt, R. Heymes, A. Lutz, L. Penasse and J. Perronet, *Tetrahedron*, **34**, 2233 (1978).

(1970).

A Convenient Synthesis of 1-Triacontanol, A Plant Growth Regulator

Suk-Ku Kang* and **Joon-Sang Cho**[†]

*Department of Chemistry, Sung Kyun Kwan University, Natural Science Campus, Suwon 440-746*

[†]*Graduate Student for M. Sc. on leave from Cheil Sugar Company, Korea*

1-Triacontanol (1) is a naturally occuring fatty alcohol with extremely long chain length isolated as a principal contituent of wax derived from alfalfa leaves (*Medicago sativa L.*).[1] It was reported by Ries *et al.*[2] that 1-triacontanol (1) is a plant growth regulator for several crop species including rice. Recently, triacontyn-1-ols and triacenten-1-ols which have double or triple bond in the straight carbon skeleton have been reported[3] to be better plant growth regulators. Other higher saturated alcohols (C-26 and C-28) were also reported to possess biological activity such as insect feeding stimulant[4]. Several syntheses of 1 have been reported.[5]

We have investigated a general and practical procedure for the synthesis of the long chain saturated and unsaturated alcohols. Herein, we wish to report a convenient synthesis of 1-triacontanol (1) which is simple, uses cheap raw mateials, and is well suited for large scale preparations for 1 and other saturated and unsaturated long chain alcohols.

By the conventional method, 7-octyn-1-ol (4) was easily prepared. Alkylation of dianion of propargyl alcohol (2) with 1-bromopentane gave 2-octyn-1-ol (3), which was converted to 7-octyn-1-ol (4)[6] using Brown's acetylene-zipper KAPA in which the triple bond was shifted to the terminal position in 77% overall yield from propargyl alcohol (2) (Scheme 1). Chain elongation of 7-octyn-1-ol (4) by alkylation with 1-bromodecane furnished 7-octadecyn-1-ol (5) in 75% yield. The acetylenic alcohol 5 was subjected to another acetylene-zipper reaction using potassium hydride in 1,3-diaminopropane (KAPA) to provide 17-octadecyn-1-ol (6) in 88% yield. Further alkylation of dianion of the terminal acetylene 6 with 1-bromododecane gave 17-triacontyl-1-ol (7) having the desired number of carbon atoms (C-30 unit), which was directly subjected to catalytic hydrogenation in ethyl acetate using 10% Pd/C at room temperature for 24h to afford 1-triacontanol (1) (Scheme 1). The synthetic com-
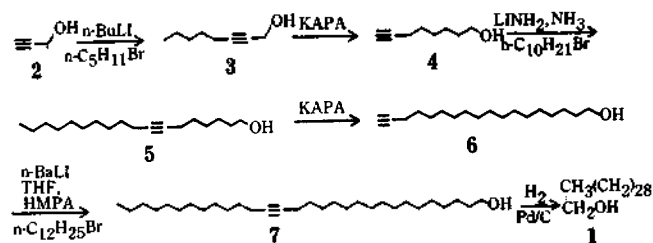
Scheme 1

pound 1 was identical in every respect (mp, ¹H-NMR, IR, MS) with an authentic sample purchased from Aldrich Chem. Co.,

Thus, the above synthetic sequence of 1 does not involve protection and deprotection and thus offers a facile route for the synthesis of other inaccessible long chain fatty alcohols.

Experimental Section

All chemicals and solvents were analytical grade. IR spectra were recorded on a Shimadzu IR-440 spectrophotometer and were calibrated with the 1601 cm⁻¹ absorption of polystyrene. ¹H-NMR spectra were taken in chloroform-d at 80MHz on a Bruker WP 80 SY spectrometer. Chemical shifts are reported in ppm relative to internal tetramethylsilane. ¹³C-NMR spectra (¹H-decoupled) were taken in CDCl₃ solutions at 22.6MHz using Me₄Si as an internal standard. Mass spectra were obtained using Hewlett-Packard 5890 GC/MS system at 70 eV. Column chromatography was performed using silica gel (Merck 60, 70-230 mesh) as adsorbent. 7-Octadecyn-1-ol (5)-To a suspension of lithium (1.40g, 200mmol) in liquid ammonia (ca, 200ml) in the presence of ferric nitrate (0.50g) was added 7-octyn-1-ol (4) (12.6 g, 100mmol) in THF (100ml) followed by 1-bromodecane