SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. PART 3.[1] SYNTHESIS OF 3-TRIFLUOROMETHYL CEPHALOSPORINS FROM PENICILLINS

Sadao Yamamoto, Nobuhiro Haga, Tsutomu Aoki, Sadao Hayashi, Hiroshi Tanida, and Wataru Nagata*

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, 553 Japan

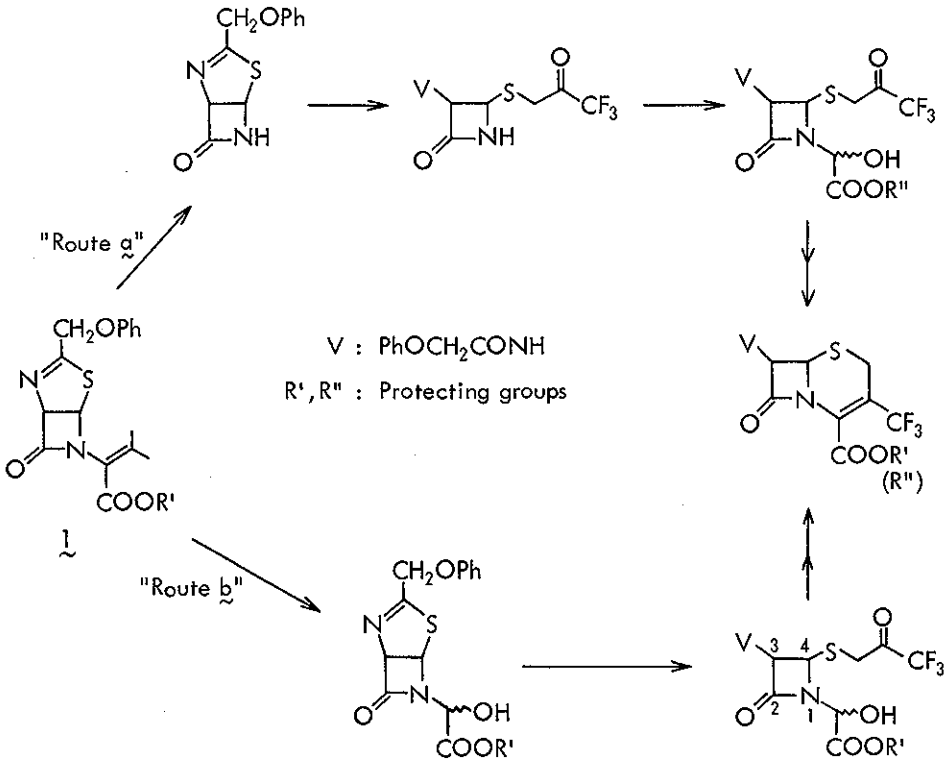
This paper is dedicated to Professor S. Sugasawa on his 80th birthday.

A new synthetic route to 3-trifluoromethyl cephalosporins from penicillin V has been developed. A key intermediate, diphenylmethyl α-{(1R,5R)-3-phenoxymethyl-7-oxa-4-thia-2,6-diazabicyclo[3.2.0]-hept-2-en-6-yl}glycolate (4), was easily obtained by ozonolysis of the known olefin 1 and by zinc-acetic acid reduction of its ozonide. Acid cleavage of the thiazoline ring of 4 followed by alkylation with 1,1,1-trifluoro-3-bromoacetone gave compound 6. Reaction of 6 with thionyl chloride and successive treatment with triphenyl-phosphine afforded the corresponding phosphorane

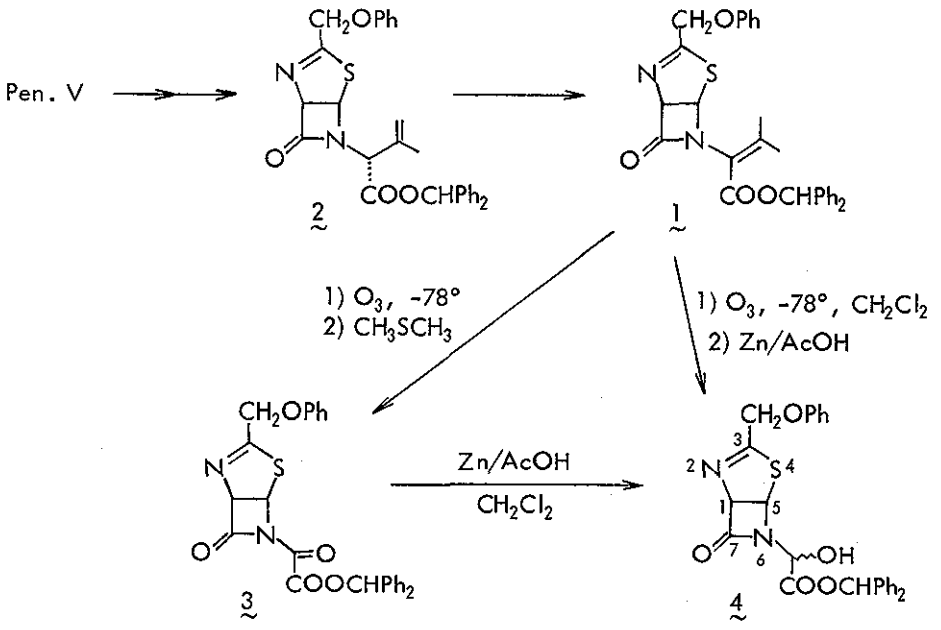
7, which afforded a desired 3-trifluoromethyl-3-cephem compound 8 by intramolecular Wittig cyclization. The new cephalosporins showed interesting *in vitro* and *in vivo* antibacterial activities.

Recently 3-chloro-7-phenylglycylamino-3-cephem-4-carboxylic acid has been reported to have antibacterial activities superior to those of cephalexin.[2] On the other hand, C-fluorinated D-alanine[3] has been reported to enhance the activity of cycloserine. Thus, introduction of the fluoro atom in the cephalosporin nucleus seemed to be an attractive modification. A consideration that the trifluoromethyl group has an electronegativity similar to the chloro atom prompted us to synthesize 3-trifluoromethyl cephalosporins.[4] We wish to describe a new and useful synthetic route to 3-trifluoromethyl cephalosporins from penicillin V.

In planning the synthesis using the known thiazoline-azetidinone derivative 1 as the suitable starting material, we conceived of two possible routes a and b. Route a would be most promising, since a similar conversion has been developed by Woodward and Ciba-Geigy groups[5] in 1972. However, we did not like to remove the essential carboxylate functionality by the C-N cleavage and restore it later by the reaction with a glyoxylate. Route b in which the two carbon unit is retained would be a simple and more attracting process for the conversion of the penicillin to cephalosporins.



Treatment of thiazoline 2[6] with triethylamine gave the isopropylidene isomer 1. Ozonolysis of 1 proceeded smoothly in methylene chloride at -78° to give alkoxalyl amide 3[7] as crystals in excellent yield. The most important step in our route b was selective reduction of the pyruvic keto group of compound 3. This could be effected simply with zinc-acetic acid reduction. Treatment of 3 in methylene chloride with activated zinc dust and acetic acid (CH_2Cl_2:AcOH = 4:1) at 0° afforded hemi-aminal[8] 4 as a mixture of two stereoisomers (two spots on tlc) in about 90% yield. Crystallization of the mixture from methylene chloride-ethyl ether gave the polar

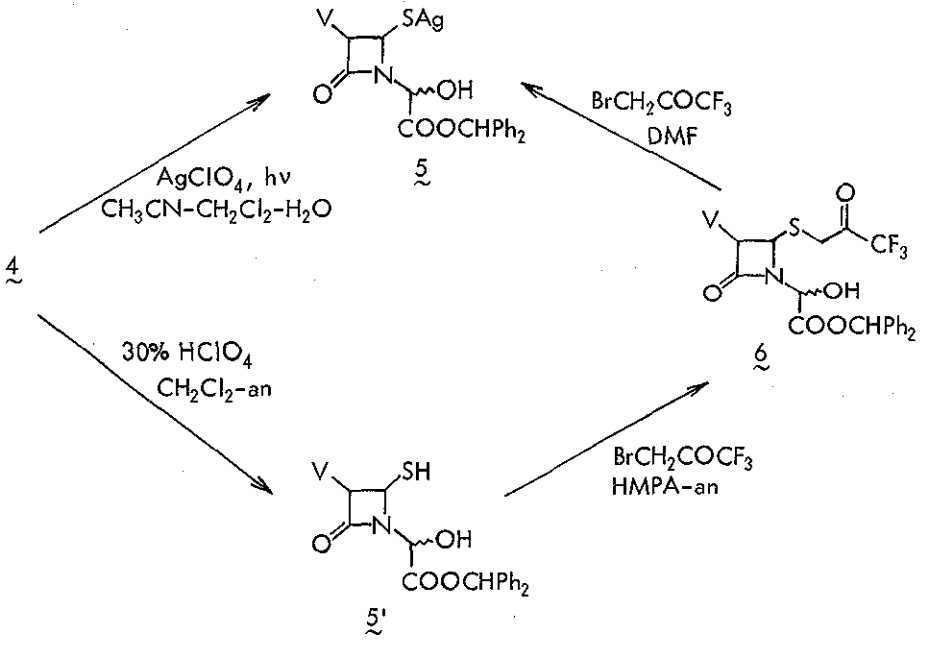


isomer as crystals, mp 172-175°; ir ($CHCl_3$) 3515, 1784, 1746 cm^{-1}; nmr δ($CDCl_3$) 4.37, 4.82 (ABq, CH_2OPh, J = 15 Hz), 5.63 (d, glycolate α-H, J = 7.0 Hz), 5.87 (d, C_5-H, J = 4.0 Hz), 6.15 (d, C_1-H, J = 4.0 Hz). The other isomer was obtained by column chromatography[9] of the residue from the mother liquor as a foam; ir ($CHCl_3$) 3525, 1784, 1747 cm^{-1}; nmr δ($CDCl_3$) 4.90, 5.03 (ABq, CH_2OPh, J = 15 Hz), 5.52 (d, glycolate α-H, J = 7.0 Hz), 5.73 (d, C_5-H, J = 4.0 Hz), 6.12 (d, C_1-H, J = 4.0 Hz). Furthermore, the hemi-aminal 4 could be prepared in high yield from 1 in a one-pot procedure by the successive zinc-acetic acid reduction of the ozonide.

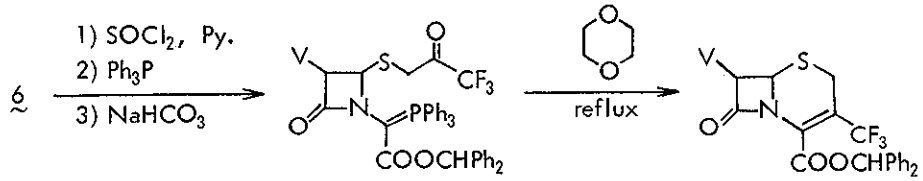
Ring cleavage of the thiazoline[10] of 4 was smoothly accomplished by treatment with silver perchlorate under irradiation (300W tungsten lamp) in a mixture of water,

acetonitrile and methylene chloride at 0° to give silver thiolate 5 in nearly quantitative yield; ir ($CHCl_3$) 3409, 1776, 1743, 1663, 1522 cm^{-1}. Alternatively, direct acid cleavage of the thiazoline was nicely achieved by reaction with 30% perchloric acid in a mixture of methylene chloride and acetone at room temperature to give thiol 5' in good yield; ir (Nujol) 2555, 1752, 1672, 1522 cm^{-1}. Treatment of 5 (or 5') with 1,1,1-trifluoro-3-bromoacetone[11] in dimethylformamide (or HMPA and acetone for 5') at 0° gave the trifluoroacetonylthio derivative 6 in nearly quantitative yield; ir ($CHCl_3$) 3410, 1782, 1750, 1512, 1172, 1079 cm^{-1}.

Chlorination of 6 with thionyl chloride and pyridine in



methylene chloride at 0° followed by treatment with triphenylphosphine in refluxing methylene chloride and then with sodium bicarbonate gave a stable phosphorane 7. Chromatographic separation afforded a pure sample of 7 in 40% yield; ir ($CHCl_3$) 3422, 1772, 1680, 1633, 1526, 1174, 1080 cm^{-1}. Intramolecular Wittig cyclization of ketone 7 by refluxing in dioxane gave the desired 3-trifluoromethyl-3-cephem compound.*



7 8

After chromatography, pure 8 was obtained in 83% yield, mp 156-157°C; ir ($CHCl_3$) 3417, 1802, 1746, 1697, 1652, 1511, 1160 cm^{-1}; nmr δ ($CDCl_3$) 3.47 (br s, C_2-CH_2), 4.57 (s, $PhOCH_2$), 5.03 (d, C_6-H, J = 5.5 Hz), 5.98 (dd, C_7-H, J = 5.5, 10 Hz). The pure sample gave satisfactory elemental analyses.

The side-chain cleavage[12] of 8 by treatment with phosphorus pentachloride and dry pyridine in dry benzene at room temperature followed by addition of dry methanol gave a versatile 7-amino-3-trifluoromethyl-3-cephem nucleus 9, which was isolated as a hydrochloride directly from the reaction

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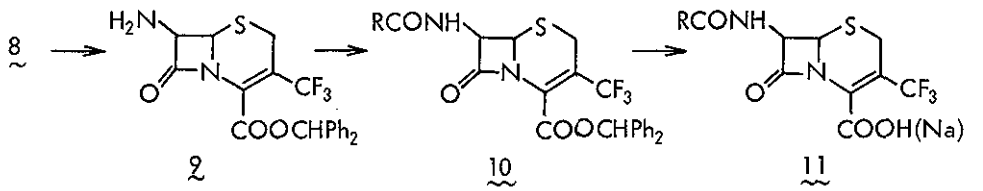
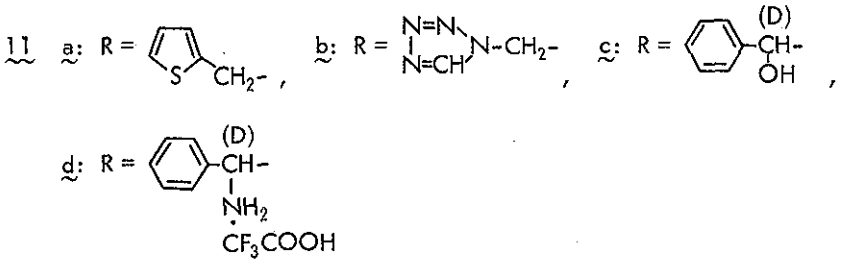
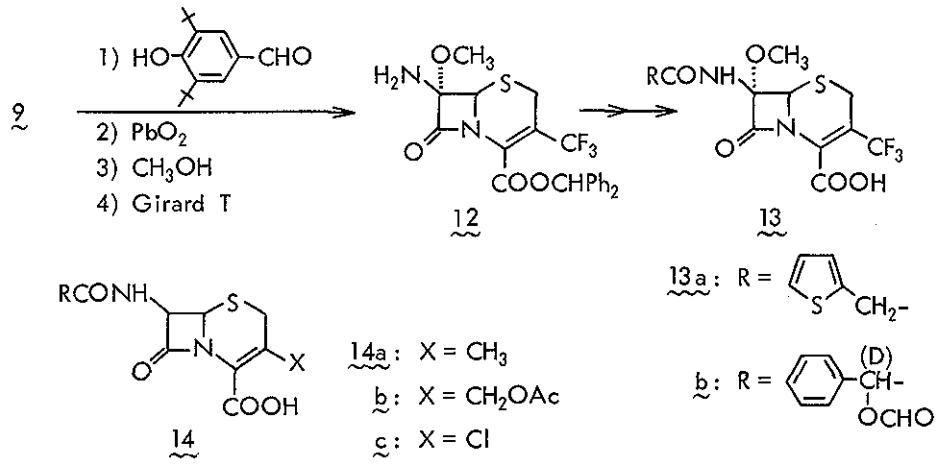
*Hereafter the cephalosporin numbering is used.





mixture in 85% yield; ir ($CHCl_3$) 1798, 1746, 1648, 1162, 1125 cm^{-1}; nmr δ ($CDCl_3$) 1.78 (br s, NH_2), 3.48 (br s, C_2-CH_2), 4.78 (d, C_6-H, J = 5.5 Hz), 4.97 (d, C_7-H, J = 5.5 Hz), 7.07 (s, $CHPh_2$). This amino ester 9 was stable and reacylated in the usual way. Removal of the benzhydryl protecting group from 7-acylamino derivatives 10 by treatment with trifluoroacetic acid and anisole afforded 7-acylamino-3-trifluoromethyl-3-cephem-4-carboxylic acids[13] 11a-11d.

We also prepared the 7β-amino-7α-methoxy-3-trifluoromethyl-3-cephem nucleus 12 from 9 by the Sankyo method.[14] Its nmr spectrum ($CDCl_3$) showed signals at δ 2.17 (br s, NH_2), 3.4-3.5 (s, OCH_3 and C_2-CH_2), and 4.83 (s, 6α-H). Reacylation of 7β-amino group followed by removal of the protecting group gave 7β-acylamino-7α-methoxy-3-trifluoromethyl-3-cephem-4-carboxylic acids[13] 13a and 13b.



Biological tests showed that the electron-withdrawing 3-trifluoromethyl group enhanced both gram positive and negative activities as compared to the activities of the corresponding 3-methyl analog 14a. 3-Trifluoromethyl cephalosporins are more active against the gram positive bacteria, especially against Streptococcus pyogenes and Staphylococcus aureus than the corresponding 3-acetoxymethyl and 3-chloro derivatives 14b and 14c, whereas their gram negative activities are comparable. On the other hand, 7α-methoxy derivatives 13 showed enhanced activities against penicillinase-producing strains but slightly reduced activities against sensitive gram positive and negative bacteria.

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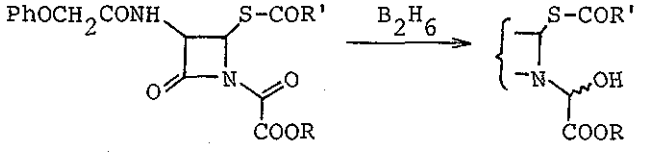

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