

SYNTHETIC STUDIES ON β -LACTAM ANTIBIOTICS. PART 3.¹⁾

SYNTHESIS OF 3-TRIFLUOROMETHYL CEPHALOSPORINS
FROM PENICILLINS

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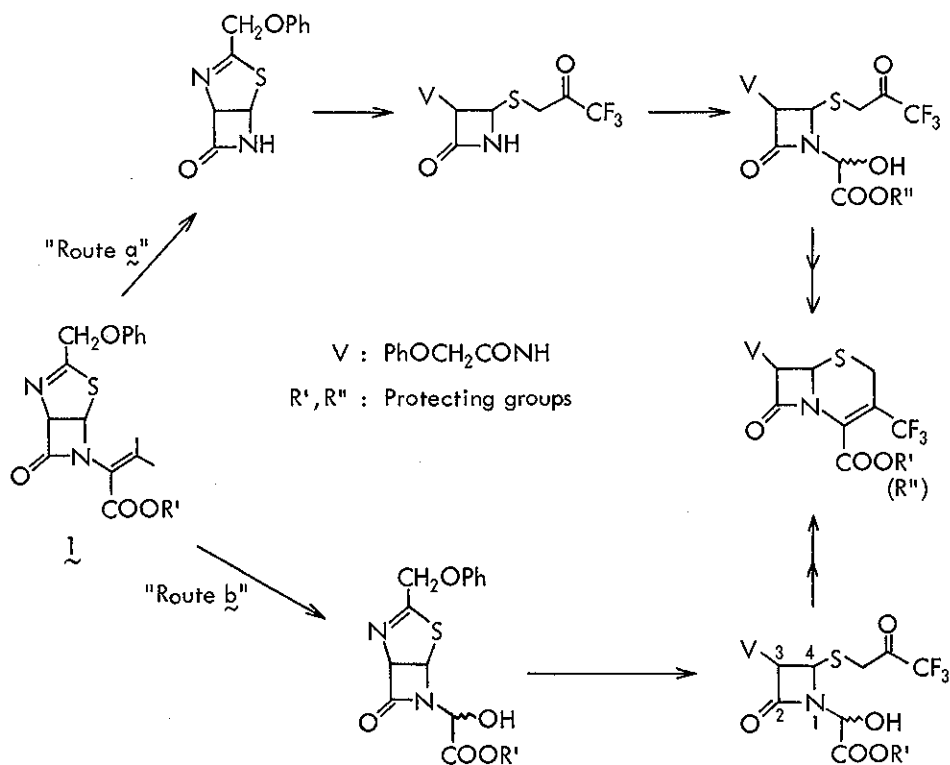
This paper is dedicated to Professor S. Sugasawa on his 80th birthday.

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 triphenylphosphine afforded the corresponding phosphorane

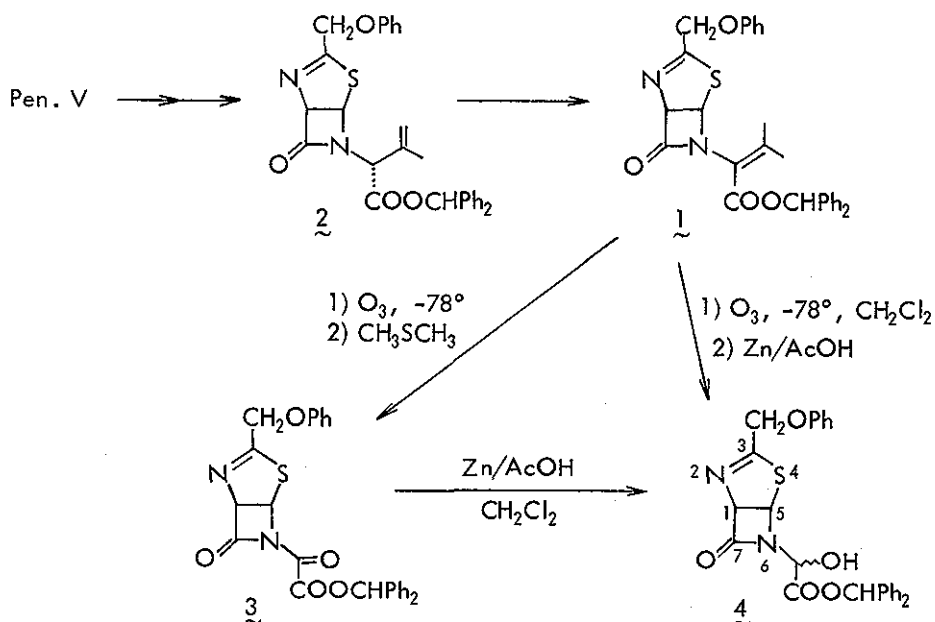
7, which afforded a desired 3-trifluoromethyl-3-cephem compound 8 by intramolecular Wittig cyclization. The new cephalosporins showed interesting in vitro and in vivo antibacterial activities.

Recently 3-chloro-7-phenylglycylamino-3-cephem-4-carboxylic acid has been reported to have antibacterial activities superior to those of cephalixin.²⁾ On the other hand, C-fluorinated D-alanine³⁾ 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 groups⁵⁾ 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 2⁶⁾ with triethylamine gave the isopropylidene isomer 1. Ozonolysis of 1 proceeded smoothly in methylene chloride at -78° to give alkoxalyl amide 3⁷⁾ 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 ($\text{CH}_2\text{Cl}_2:\text{AcOH} = 4:1$) at 0° afforded hemi-aminal⁸⁾ 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

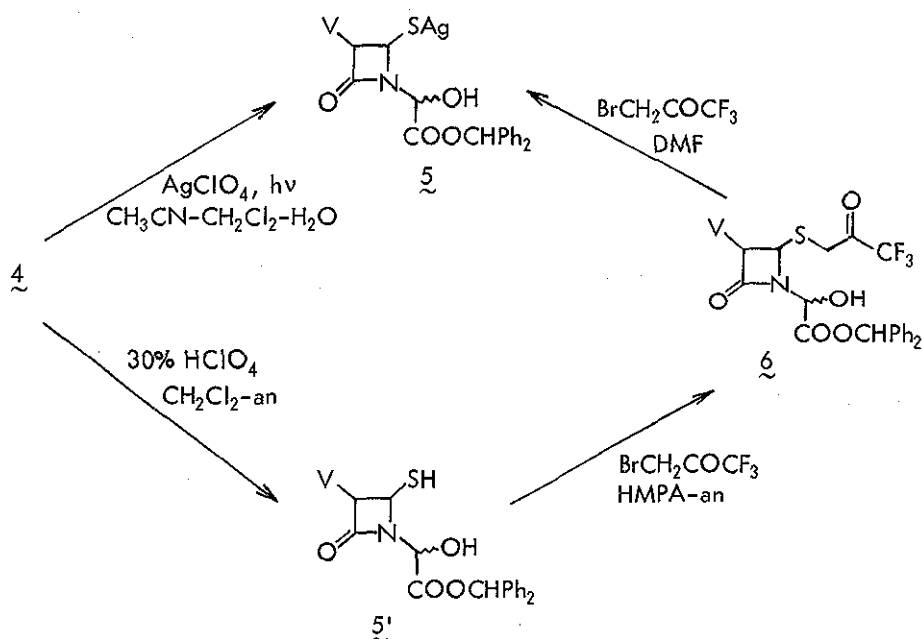


isomer as crystals, mp $172-175^\circ$; ir ($CHCl_3$) 3515 , 1784 , 1746 cm^{-1} ; nmr δ ($CDCl_3$) 4.37 , 4.82 (ABq, CH_2OPh , $J = 15$ Hz), 5.63 (d, glycolate α -H, $J = 7.0$ Hz), 5.87 (d, C_5 -H, $J = 4.0$ Hz), 6.15 (d, C_1 -H, $J = 4.0$ Hz). The other isomer was obtained by column chromatography⁹⁾ 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.

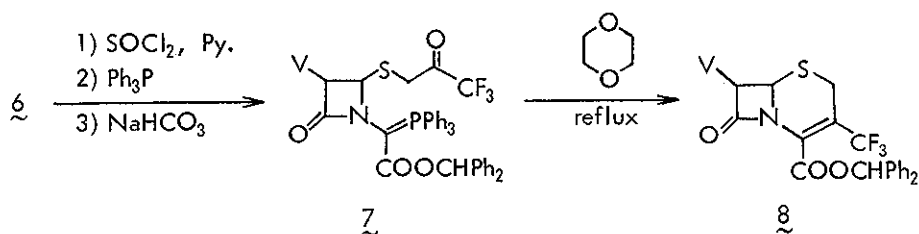
Ring cleavage of the thiazoline¹⁰⁾ of 4 was smoothly accomplished by treatment with silver perchlorate under irradiation (300W tungsten lamp) in a mixture of water,

acetonitrile and methylene chloride at 0° to give silver thiolate 5 in nearly quantitative yield; ir (CHCl₃) 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-bromoacetone¹¹ in dimethylformamide (or HMPA and acetone for 5') at 0° gave the trifluoroacetylthio derivative 6 in nearly quantitative yield; ir (CHCl₃) 3410, 1782, 1750, 1512, 1172, 1079 cm⁻¹.

Chlorination of 6 with thionyl chloride and pyridine in



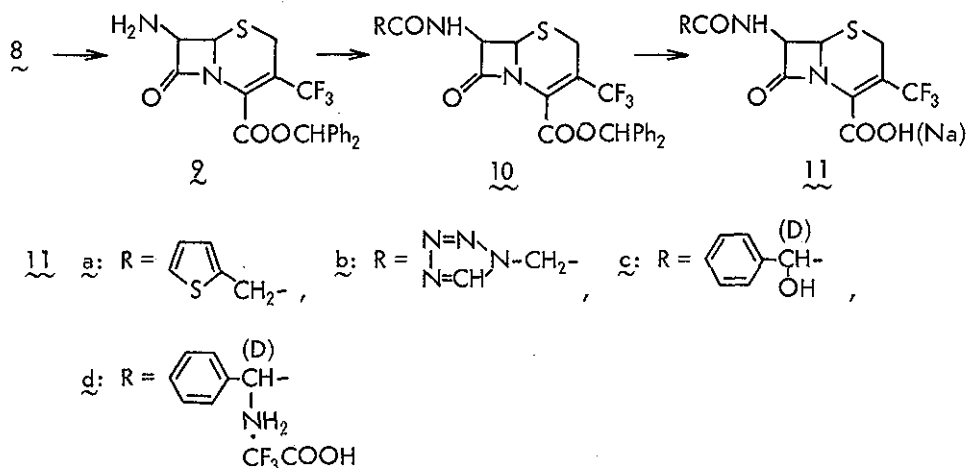
methylene chloride at 0° followed by treatment with triphenylphosphine in refluxing methylene chloride and then with sodium bicarbonate gave a stable phosphorane 7. Chromatographic separation afforded a pure sample of 7 in 40% yield; ir (CHCl₃) 3422, 1772, 1680, 1633, 1526, 1174, 1080 cm⁻¹. Intramolecular Wittig cyclization of ketone 7 by refluxing in dioxane gave the desired 3-trifluoromethyl-3-cephem compound.*



After chromatography, pure 8 was obtained in 83% yield, mp 156-157°C; ir (CHCl₃) 3417, 1802, 1746, 1697, 1652, 1511, 1160 cm⁻¹; nmr δ (CDCl₃) 3.47 (br s, C₂-CH₂), 4.57 (s, PhOCH₂), 5.03 (d, C₆-H, J = 5.5 Hz), 5.98 (dd, C₇-H, J = 5.5, 10 Hz). The pure sample gave satisfactory elemental analyses.

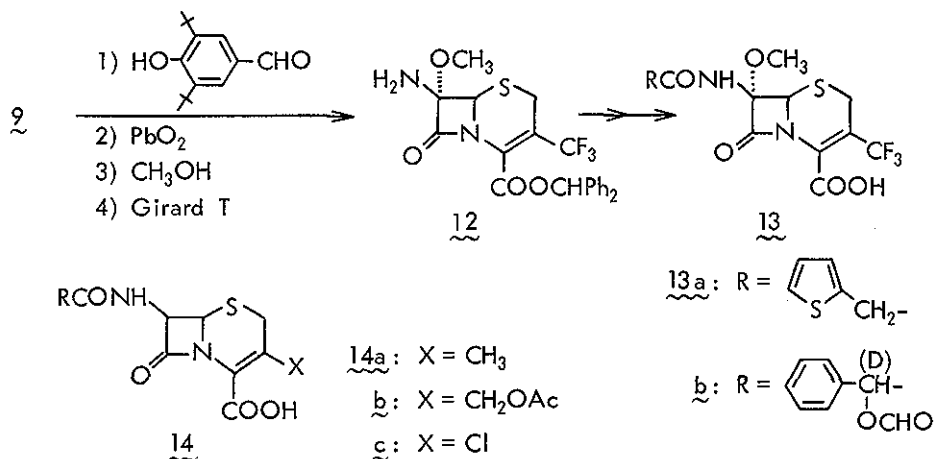
The side-chain cleavage¹²⁾ of 8 by treatment with phosphorus pentachloride and dry pyridine in dry benzene at room temperature followed by addition of dry methanol gave a versatile 7-amino-3-trifluoromethyl-3-cephem nucleus 9, which was isolated as a hydrochloride directly from the reaction

*Hereafter the cephalosporin numbering is used.



mixture in 85% yield; ir (CHCl₃) 1798, 1746, 1648, 1162, 1125 cm⁻¹; nmr δ (CDCl₃) 1.78 (br s, NH₂), 3.48 (br s, C₂-CH₂), 4.78 (d, C₆-H, J = 5.5 Hz), 4.97 (d, C₇-H, J = 5.5 Hz), 7.07 (s, CHPh₂). 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 acids¹³⁾ 11a-11d.

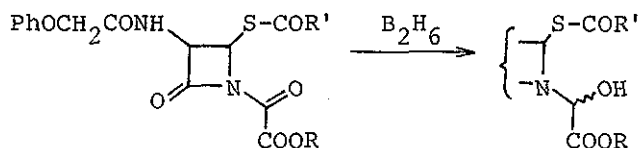
We also prepared the 7β-amino-7α-methoxy-3-trifluoromethyl-3-cephem nucleus 12 from 9 by the Sankyo method.¹⁴⁾ Its nmr spectrum (CDCl₃) showed signals at δ 2.17 (br s, NH₂), 3.4-3.5 (s, OCH₃ and C₂-CH₂), and 4.83 (s, 6α-H). Reacylation of 7β-amino group followed by removal of the protecting group gave 7β-acylamino-7α-methoxy-3-trifluoromethyl-3-cephem-4-carboxylic acids¹³⁾ 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, 7 α -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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