SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. PART 5. A SYNTHESIS OF 7β-ACYLAMINO-3-METHYL-1-OXADETHIA-3-CEPHEM-4-CARBOXYLIC ACIDS[+]

Masayuki Narisada*, Hiroshi Onoue, and Wataru Nagata
Shionogi Research Laboratory, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka, 553 Japan

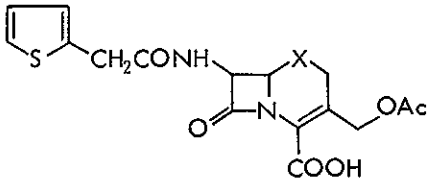
Chloroazetidinone 10, prepared from 6-APA, was etherified with propargyl alcohol and zinc chloride to a 2:1 mixture of cis- and trans-ethers 18. The separated cis-ether 18 was converted into a keto ylide 21d, which was cyclized by intramolecular Wittig reaction to 3-methyl 1-oxacephalosporin 22. From this compound, four optically active 3-methyl oxacephalosporins 25a-d were prepared. Interestingly all of them except 25d, 1-oxacephalexin, exhibited antibacterial activity as four to eight times high as that of the corresponding cephalosporins.

[+] Dedicated to Professor Robert B. Woodward on his sixtieth birthday.

The reports that (±)-1-oxacephalothin 1[1a,c] and (±)-carbacephalothin 2[1b,c] possessed half a potency in antibacterial activity as that of cephalothin have evoked our interest in connection with the question of the extent of the activity of optically active 1-oxacephalosporins with different substituents and the structure-activity relationship among them. In this communication, we describe a synthesis of optically active 3-methyl 1-oxacephalosporin nucleus and its 7-acylamino derivatives.

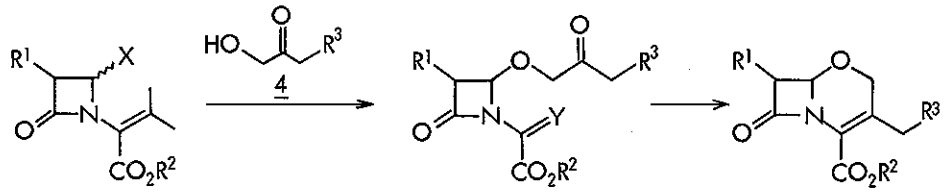
In order to construct the 1-oxacephalosporin nucleus, we first adopted the route shown in Scheme 1 consisting of etherification of an azetidinone 3 with a hydroxyacetone derivative 4, and conversion of the resulting 5 into a ylide 6 and following Wittig cyclization of 6 to the desired nucleus 7.

Etherification of N-substituted azetidinones 8a (X = Cl) with an alcohol using Lewis acid,[2] silver tetrafluoroborate,[1a,c] or stannic chloride[3] is known (Scheme 2). While most phthalimido derivatives 8a (R^1 = phthalimido) gave trans-ethers 9a,[2,3] as major products, an azidoazetidinone 8a ($R^1 = N_3$) yielded a 1:1 mixture of cis- and trans-isomers 9a.[1a,c] Acid alcoholysis of 8a, where R^1 and X forms an oxazoline ring, gave a trans-ether 9a[4] exclusively. Reaction of N-unsubstituted azetidinones 8b proceeded more easily. Methanolysis of a chloro derivative 8b (X = Cl) to trans 9b (R^1 = phthalimido)[5] and a reaction of a compound 8b (X = N_3 or SO_2Et, R^1 = H) giving 9b (R^1 = H)[6] were reported.



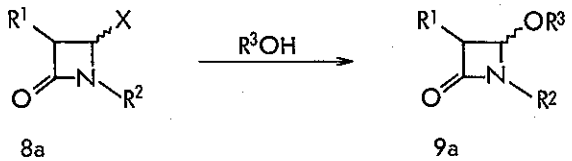
1, X = O(dl-)

2, X = CH_2(dl-)



3 4 5, Y = =C< 6, Y = =P< 7

Scheme 1



8a 8b, R^2 = H 9a 9b, R^2 = H

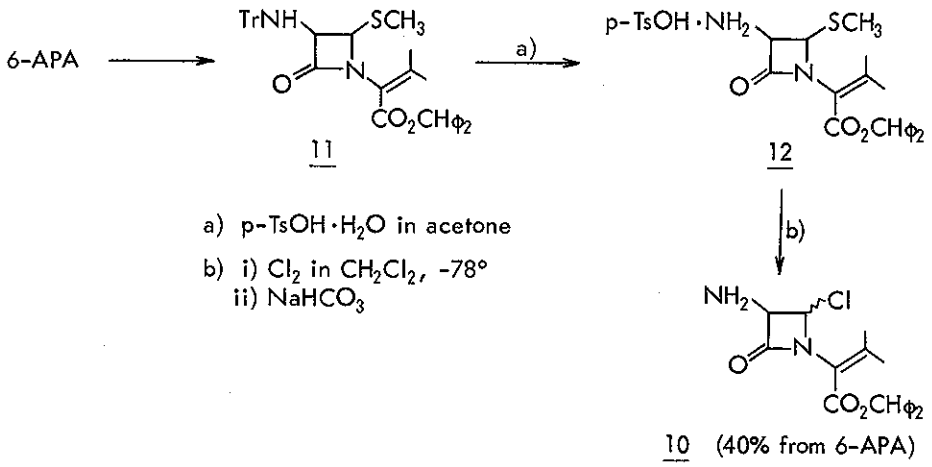
Scheme 2

Concerning preparation of the ylide 6, we planned to follow the method developed in this laboratory.[7] Different from previously reported preparations of ylides used in Wittig cyclization,[8,9] this method effectively converts the α-isopropylideneacetate moiety into the α-ylidoacetate moiety.

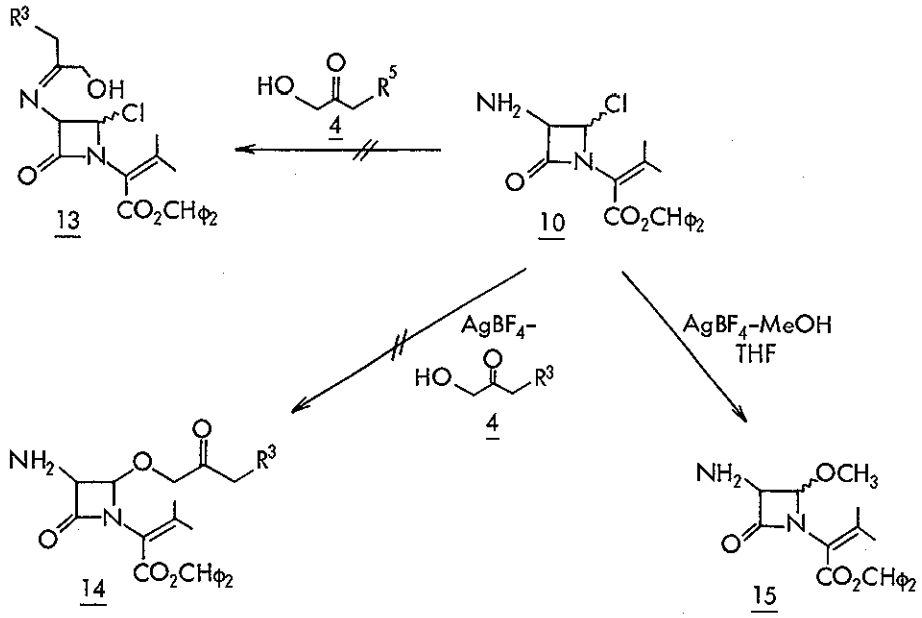
Compound 11, prepared from 6-APA (6-aminopenicillanic acid),[10,11] was deprotected to the amine tosylate 12, which was chlorinated to give a 4 to 1 mixture of cis- and trans-10. The free base 10 was unstable and stored as its tosylate.

First, an intramolecular etherification of an azomethine 13 giving a cis-ether 14 solely was planned. However, several attempts to prepare 13 by condensation of the amino chloride 10 with hydroxyacetones 4 failed (Scheme 4). Then, methoxylation of chloride 10, a model experiment, was carried out. Treatment of 10 with silver tetrafluoroborate and methanol in tetrahydrofuran afforded a 1:1 mixture of cis- and trans-ethers 15. Thus, etherification of the amine 10 with hydroxyacetones 4 (R^3 = OH or OAc) in the presence of silver tetrafluoroborate was attempted. Unfortunately, decomposition of the β-lactam ring resulted.

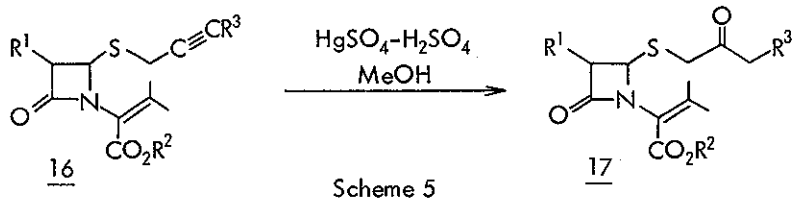
Next, etherification of 10 with propargyl alcohol was examined. Nayler et al. utilized a propargyl group as a synthon for an acetonyl group exemplified by a successful conversion of a propargyl ether 16 into a ketone 17 (Scheme 5).[9,12] The amine 10 was treated with silver tetrafluoroborate in propargyl alcohol to give a 1:1 mixture of cis- and trans-ethers 18 (Scheme 6). By using less expensive anhydrous zinc



Scheme 3

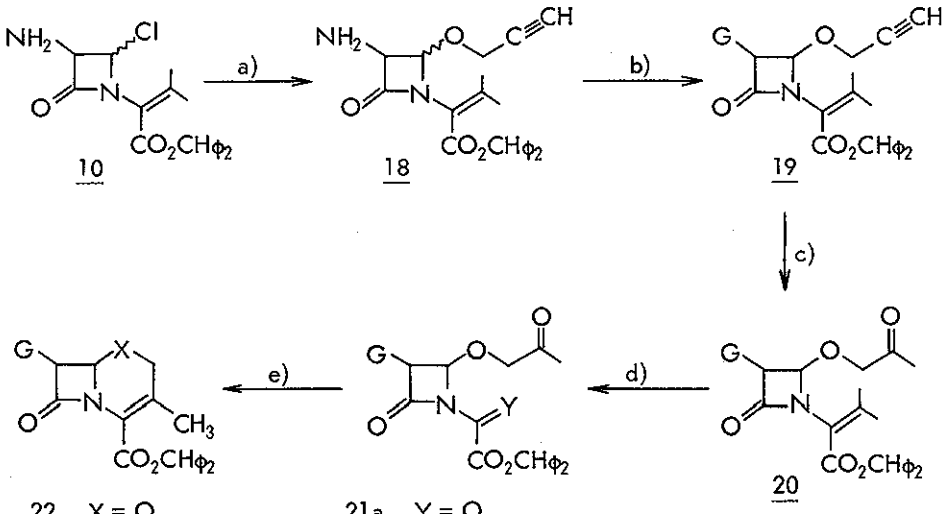


Scheme 4



16 17

Scheme 5



10 18 19 20

22, X = O

23, X = S

21a, Y = O

21b, Y = H, OH

21c, Y = H, Cl

21d, Y = =Pφ3

G: φ-CH2CONH-

a)

	reagent	yield	cis-trans
a-1	$AgBF_4$	38%	1 : 1
a-2	$ZnCl_2$	39%	2 : 1
a-3	$SnCl_2$	14%	3 : 2

b) $C_6H_5CH_2COCl$, pyridine

c) H_2SO_4-$HgSO_4$-MeOH-H_2O

d)

	reagent	product
1°	i) O_3, ii) Me_2S	21a
2°	Zn-HOAc	21b
3°	$SOCl_2$-py	21c
4°	ϕ_3P	21d

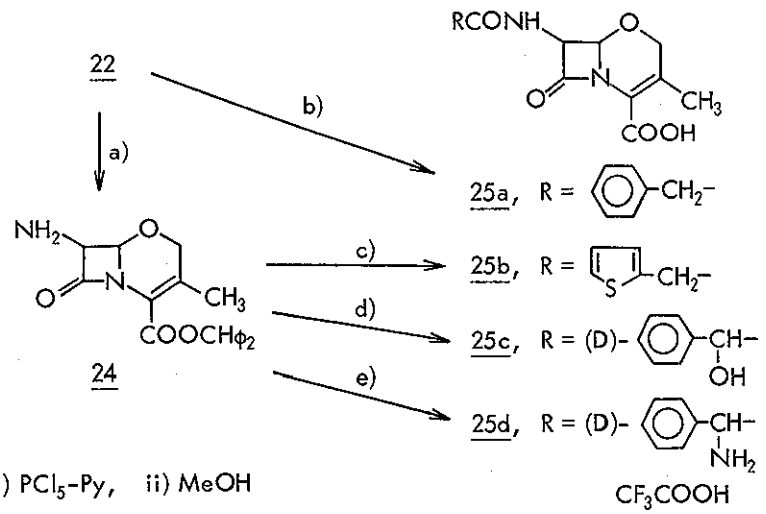
e) dioxane, reflux

Scheme 6

chloride as the condensing agent, the cis-trans ratio was improved to 2:1. The reaction in the presence of stannic chloride was sluggish and the yield was less satisfactory. The resulting cis- and trans-ethers were separated by silica gel chromatography. The pure cis-18 was acylated to give amide 19. Mercuric sulfate catalyzed hydration of the propargyl group of 19 proceeded well as expected to yield a ketone 20. Smooth conversion of the isopropylideneacetate 20 into ylide 21d via 21a, 21b, and 21c, was performed by following the method developed in this laboratory.[7] Wittig cyclization of 21d proceeded slowly but cleanly in refluxing dioxane to give the cyclized product 22 in good yield. The structure of 22 was confirmed by similarity of its spectra to those of the corresponding cephalosporin 23 (Table 1). A higher reactivity of the β-lactam ring in 22 was suggested from its slightly higher carbonyl stretching frequency and lower electron densities on the carbon atoms at 6 and 7 positions were indicated from a smaller coupling constant $J_{6,7}$. Side chain cleavage of 22 with phosphorous pentachloride proceeded satisfactorily to produce amine 24 (Scheme 7).

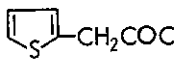
The usual methods used in modification of the C_7-side chain and deprotection of the ester group of cephalosporins were applied to the oxa-series without any difficulties and four 1-oxa-cephalosporins 25a-d were obtained. The compound 25a-c showed antibacterial activity[13] against Gram-positive and -negative bacteria as four to eight times high as that of

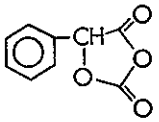
		22	23
ir ($CHCl_3$) cm^{-1}		1792	1785
nmr ($CDCl_3$) δ, ppm	C_{10}	1.97s	2.06s
	C_2	4.15s	3.03, 3.39 ABq
	C_6	4.97d (3.5 Hz)	4.92d (4.5 Hz)
	C_7	5.65dd (3.5, 9 Hz)	5.73dd (4.5, 9 Hz)
uv (CH_2Cl_2) nm (ε)		267.5 (7,760)	264 (6,500)

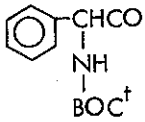


a) i) PCl_5-Py, ii) MeOH

b) CF_3COOH-anisole

c) i)  ii) CF_3COOH-anisole

d) i) (D)-  ii) CF_3COOH-anisole

e) i) (D)-  ii) CF_3COOH-anisole

cephalosporin analogs, whereas the cephalexin analog 25d was almost inactive. Although 25d as its trifluoroacetate was stable, the free base was proved to be unstable. The ultraviolet absorption maximum of 25d (255 nm, ε 7,080) in a slightly alkaline solution disappeared with a half life time of about 3 hr. This contrasted with the stability of cephalexin under the same conditions where the absorption maximum remained unchanged. Accordingly, we concluded that 25d was decomposed by intramolecular aminolysis of the reactive β-lactam ring during the in vitro assay.

Christensen et al.[14] further reported a synthesis of (±)-1-oxacefamandol, which showed doubled activity of that of cefamandol. Recently, Nayler et al.[15] reported a synthesis of several optically active amides 25 by a method similar to that described in this report. In this case, the etherification was carried out by refluxing 8b (R^1 = tritylamino, X = SO_2CH_3 or R^1 = phenoxyacetamido, X = OAc) in propargyl alcohol and toluene in the presence of zinc acetate.

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