SYNTHESIS OF SULFAZECIN-TYPE 2-AZETIDINONES WITH A CARBON SUBSTITUENT AT THE 4-POSITION

Sir:

As reported in our previous paper,[1] chemical modification of sulfazecin[2] at the 3-position significantly enhanced its antibacterial activity; however, further improvement was desired especially in regard to the stability to some β-lactamases. We focused our attention on modifying the unexplored 4-position, and *cis*-1-(2,4-dimethoxybenzyl)-4-methoxycarbonyl-3-phthalimido-2-azetidinone (**1a**) was selected as a starting material, since the methoxycarbonyl group can be convertible into various kinds of other 4-substituents.[3] Compound **1a**, first synthesized by GLEASON *et al.*,[3] was obtained in 72% yield as colorless needles, mp 172~175°C, by a slightly modified cycloaddition reaction in which the amount of triethylamine was increased to 1.2 molar equivalents. Epimerization[4] of **1a** with 1,8-diazabicyclo[5.4.0]-7-undecene in benzene gave the *trans* isomer (**1b**), and both **1a** and **1b** were converted into 3-acylamino-1-sulfo derivatives (**6a,b**) (Chart 1). Since the antibacterial activity of the 3,4-*cis* compound (**6a**) was higher than that of the *trans* isomer (**6b**), and **6a** was very active against *Escherichia coli* T-7, a producer of TEM-1 β-lactamase, we decided to explore further modification of the *cis* series.

Treatment of **4a** with 25~28% ammonia water or 40% aqueous methylamine in tetrahydrofuran (THF) gave 4-carbamoyl- and 4-methylcarbamoyl-2-azetidinones (**7a,b**) respectively. Hydrolysis of **4a** with K_2CO_3 afforded the 4-carboxy compound (**7c**), which was then converted into 4-dimethylcarbamoyl and 4-methoxycarbamoyl derivatives (**7d,e**). Reduction[5] of **3a** and **4a** with sodium borohydride in THF-water gave alcohols (**8a,b**), from which various 3-amino-4-substituted 2-azetidinones (**9**) were prepared by the conventional methods. For example, compound **9a** was obtained by treating **8a** with chlorosulfonyl isocyanate followed by deprotection (Chart 2). Among the 3-acylamino-1-sulfo derivatives derived from these intermediates in a procedure similar to that of Chart 1, 4-carbamoyl and 4-carbamoyloxymethyl compounds (**11** and **12**) were found to be highly active against Gram-negative bacteria including *Pseudomonas aeruginosa* and some β-lactamase producing strains.

Since ceftazidime has unique antibacterial

Chart 1.

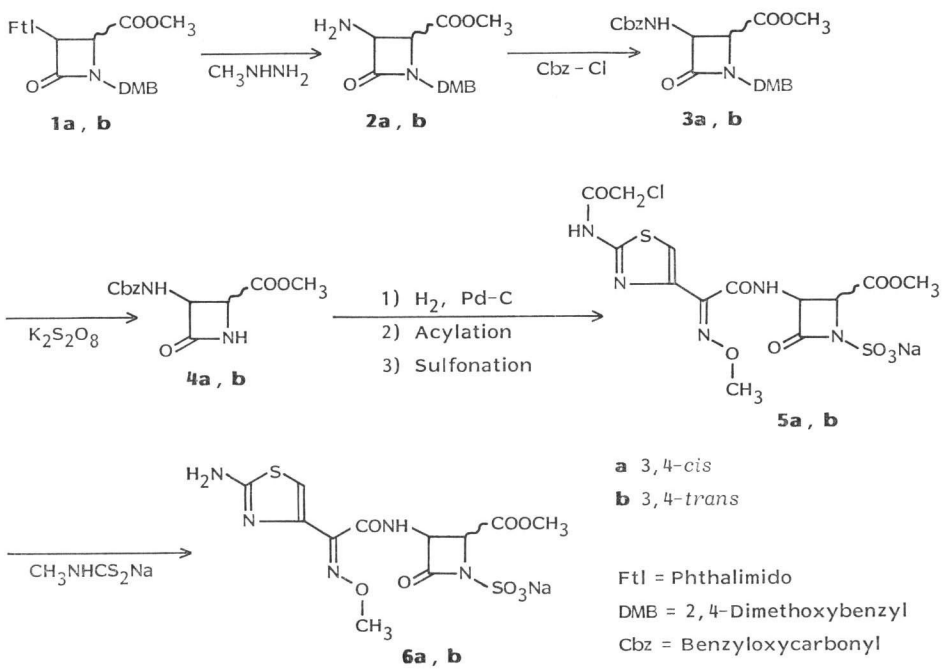


Chart 2.

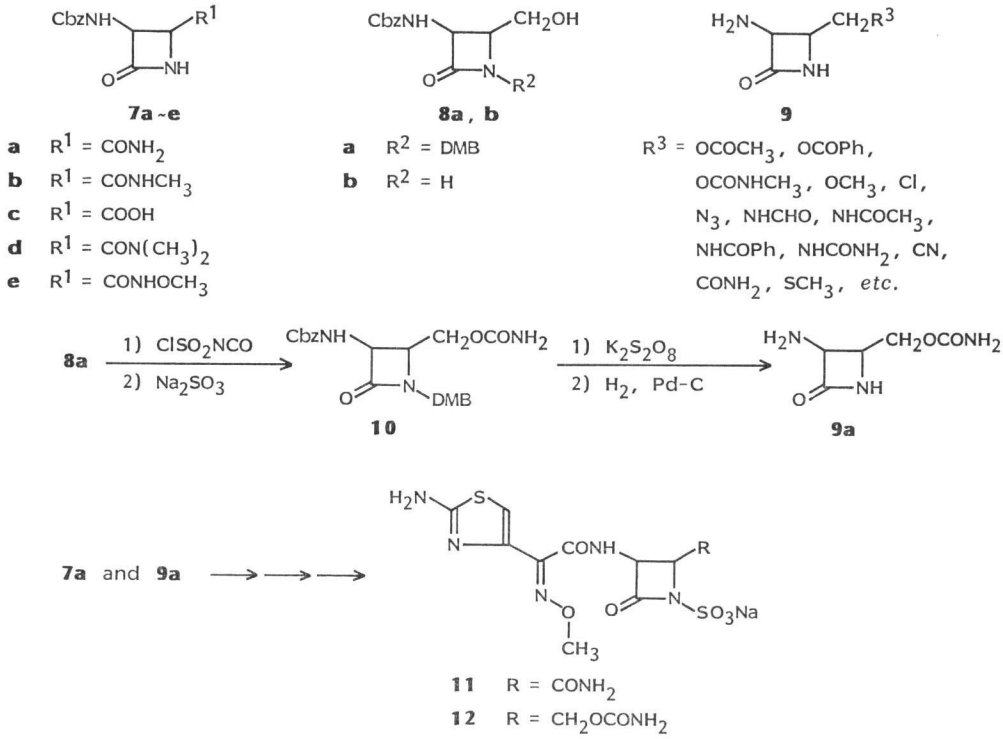


Table 1. Antibacterial activities[a] of AMA-1080 (**21b**), compound **22a** and two reference antibiotics.[b] (MIC: μg/ml)

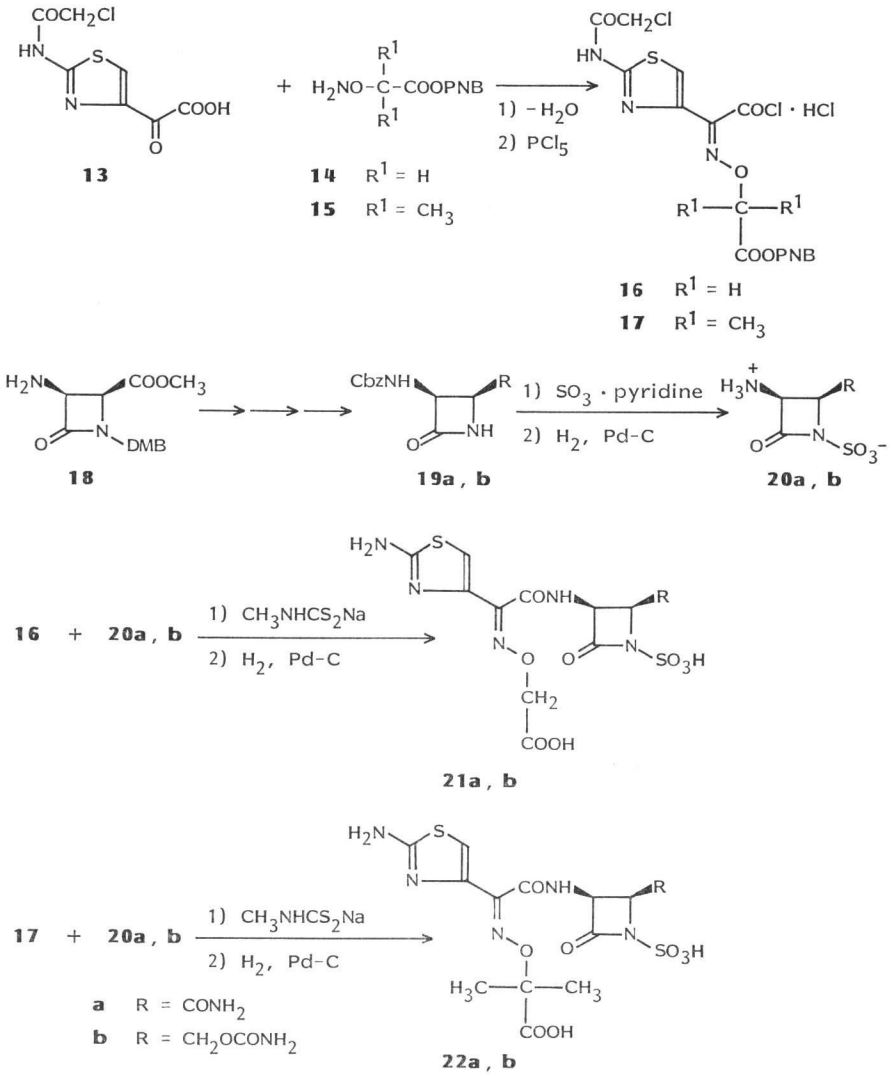
Organism	β-Lactamases type	AMA-1080 (**21b**)	**22a**	Aztreonam	Ceftazidime
Escherichia coli NIHJ JC-2	—	0.1	0.2	0.1	0.39
E. coli T-7	TEM-1[d]	0.2	0.39	0.39	0.78
Klebsiella pneumoniae TN 1711[c]	IV[e]	0.1	0.2	25	0.39
Enterobacter cloacae IFO 12937	Ia[e]	0.78	0.39	3.13	6.25
Serratia marcescens IFO 12648	Ia[e]	0.05	0.2	0.1	0.2
Proteus vulgaris IFO 3988	Ic[e]	0.05	0.2	0.013	0.2
Pseudomonas aeruginosa IFO 3455	Ia[e]	1.56	1.56	3.13	1.56
P. aeruginosa GN 3407	PSE-1[d]	6.25	6.25	6.25	6.25

[a] Activities were determined by the agar dilution method using an inoculum of 10^5 cfu/ml.
[b] Reference compounds were prepared according to the reported procedure.
[c] Indole positive.
[d] Plasmid-mediated β-lactamases.
[e] Chromosomal β-lactamases (RICHMOND classification).

activity especially against Gram-negative bacteria, we tried* to synthesize new compounds having the analogous acyl groups at the 3-position of **11** and **12**. The acylating agents (**16** and **17**) were prepared as shown in Chart 3. To protect the carboxy groups, 4-nitrobenzyl esters were conveniently prepared. Optical resolution of **2a** was carried out by the use of di-(4-toluoyl)-D-tartaric acid to give the (3*S*,4*S*)-3-amino compound (**18**), which was then converted into four sulfazecin-type 2-azetidinones (**21a,b** and **22a,b**)

* The independent work of SYKES *et al.*[6] led to the development of a clinical candidate, aztreonam, having the ceftazidime side-chain.

Chart 3.



(Chart 3). Selective sulfonation at the 1-position of **19a,b** was successfully achieved with sulfur trioxide-pyridine complex in dioxane; after hydrogenolysis the products were isolated as crystalline zwitter ions (**20a,b**).*

As shown in Table 1, AMA-1080 (**21b**) was highly active against Gram-negative bacteria and the protective effect on experimental intraperitoneal infection in mice reflected the *in vitro* activity. Further evaluation of this compound as a possible clinical candidate is now in progress. Compound **22a** also exhibited good antibacterial activity and high stability to β-lactamases produced by various bacterial species. Chiral syntheses of **21b** and **22a** have been extensively investigated from the practical point of view, and several pathways to prepare the important intermediates (**20a,b**) have been established starting from penicillin, L-tartaric acid and (2*R*,3*R*)-epoxysuccinic acid,[7] which will be reported elsewhere.

* The absolute structure of **20b** was confirmed by X-ray analysis, and the details will be published elsewhere.

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