Synthesis and Biological Activity of New Cephem Compounds with a 3-(2-Butenyl)- and a 3-(1,3-Butadienyl)group at Their 3-Position

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A numbers of cephalosporins have been studied in a semisynthetic approach for developing new and effective drugs. Among them, 3-vinyl cephems have been intensively studied in recent years, and drugs such as cefixime or E1077 are on the market or under extended evaluation[1].

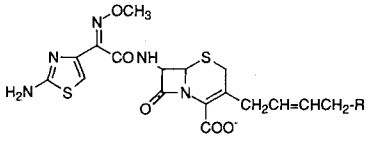
On the other hand, cephems with a homologated 3-substituent, ($-CH_2CH=CHCH_2R$), have been little known[2,3]. Because we were interested in their antibacterial activity, we synthesized 3-(2-butenyl)cephems of type **1** and unexpectedly found a simple process for preparing a novel 3-(1,3-butadienyl)cephem (*E*)-**2**, which has been reported in a communication[4].

In this report, we wish to present the chemistry concerning **1** and **2** as well as their antibacterial activity. Oral absorption data for 3-(1,3-butadienyl)- and 3-(4-hydroxy-2-butenyl)cephems are also given.

Chemistry

Synthesis of the key intermediates, (*E*)- and (*Z*)-**6**, is portrayed in Scheme 1. Acylation of commercially available **3** yielded the amide **4**, which reacted with

Fig. 1. Novel 3-(2-butenyl)- and 3-(1,3-butadienyl)cephalosporin compounds.



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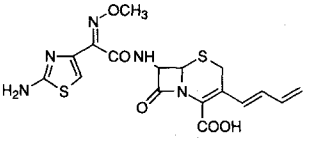
(*E*)-**1a**, (*Z*)-**1a**

(*E*)-**1b**, (*Z*)-**1b**

(*Z*)-**1c** $-N^+(Me)(Et)CH_2CONH_2$

(*E*)-**1d**, (*Z*)-**1d** $-OH$



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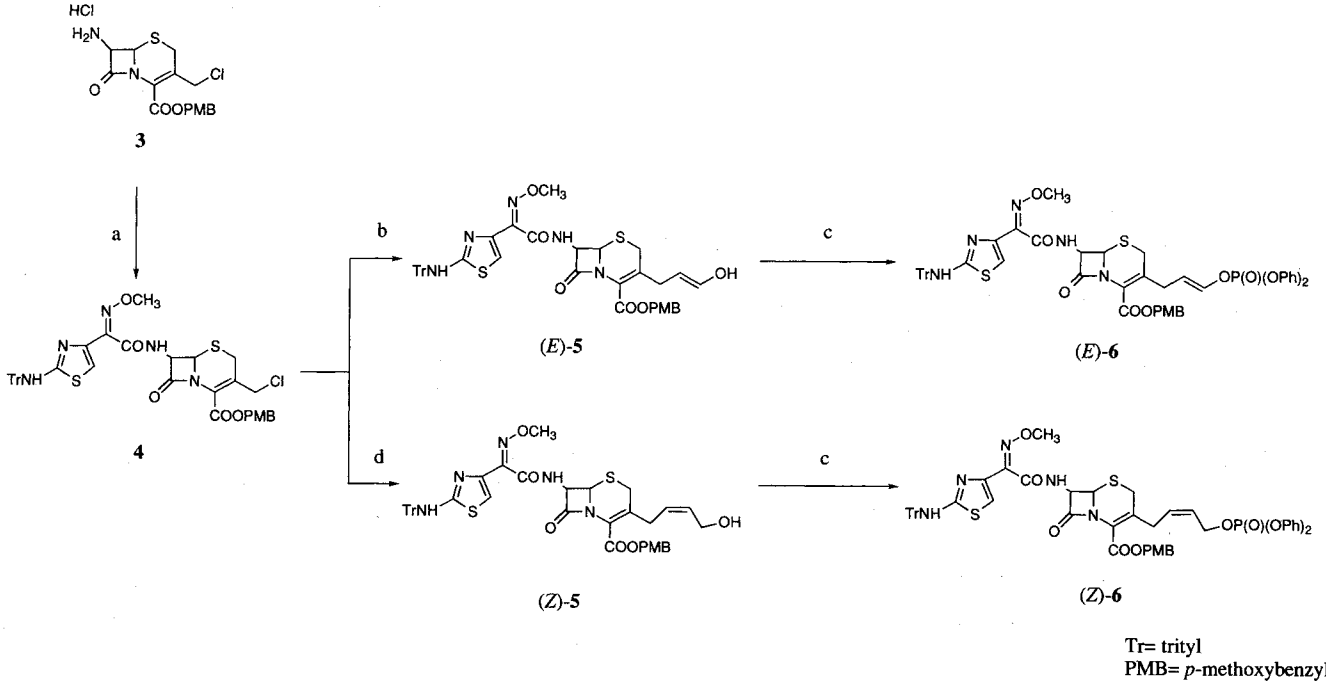
Scheme 1. Synthesis of (*E*)-**6** and (*Z*)-**6**.



Tr= trityl
PMB= *p*-methoxybenzyl

(a) 2-(Methoxyimino)-2-(tritylamino-4-thiazolyl)acetic acid, BSA, PCl_5, Pyr, CH_2Cl_2; (b) (*E*)-$n$$Bu_3SnCH=CHCH_2OH$, $Pd(dba)_2$, tri(2-furyl)phosphine, THF; (c) $P(O)(OPh)_2Cl$, DMAP; (d) (*Z*)-$n$$Bu_3SnCH=CHCH_2OH$, $Pd(dba)_2$, tri(2-furyl)-phosphine, THF.

Scheme 2. Synthesis of novel 3-(2-butenyl)- and 3-(1,3-butadienyl)cephalosporins from (*E*)- or (*Z*)-**6**.

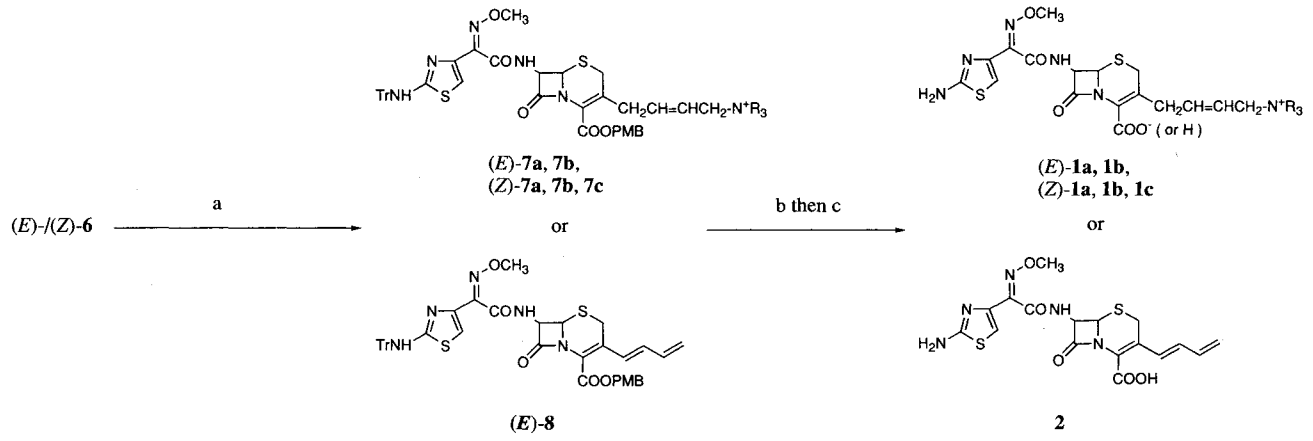


Table 1. Substitution of (*E*)- and (*Z*)-**6** with amines.

Starting material	Amine	Additive	Product	Yield (%)
(*E*)-**6**	Pyridine	NaI	(*E*)-**7a**	32
(*E*)-**6**	2,3-Cyclopentenopyridine	NaI	(*E*)-**7b**	77
(*E*)-**6**	2-(Ethylmethylamino)acetamide	NaI	(*E*)-**8**	63
(*Z*)-**6**	Pyridine	NaI	(*Z*)-**7a**	28
(*Z*)-**6**	2,3-Cyclopentenopyridine	NaI	(*Z*)-**7b**	59
(*Z*)-**6**	2-(Ethylmethylamino)acetamide	NaI	(*Z*)-**7c**	73
(*Z*)-**6**	Diisopropylethylamine	—	N.R.	—
(*E*)-**6**	Diisopropylethylamine	—	(*E*)-**8**	94

N.R.; No reaction.

(*E*)-3-tributylstannyl-2-propen-1-ol[5] under Pd(0)-catalyzed coupling conditions[2,6] to give (*E*)-**5**. (*E*)-**5** was then treated with diphenyl chlorophosphate to afford (*E*)-**6**. (*Z*)-**6** was synthesized in a similar way.

Reactions of (*E*)- and (*Z*)-**6** with *N*-nucleophiles are summarized in Scheme 2 and Table 1. Pyridine and 2,3-cyclopentenopyridine reacted with (*E*)-**6** in the presence of NaI to give the corresponding quaternary ammonio compounds (*E*)-**7a** and (*E*)-**7b**, while 2-(ethylmethylamino)acetamide afforded (*E*)-butadiene **8**. With the geometric isomer, (*Z*)-**6**, these amines yielded (*Z*)-**7a**~**c** and no butadienyl compound was obtained. These results indicate that the products are contingent upon the proportion of amine basicity to nucleophilicity as well as the olefin geometry. Actually, the use of (*E*)-**6** and diisopropylethylamine, a hindered base, improved the yield of (*E*)-**8** to 94%: IR (KBr) cm^{-1} 1780, 1724, 1686, 1520, 1306, 1248, 1168, 1038, 702; ^1H NMR (DMSO-d_6) δ 3.61 (1H, d, J=18 Hz, 2-C*H*H), 3.75 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.89 (1H, d, J=18 Hz, 2-CH*H*), 5.18 (1H, d, J=5 Hz, 6-CH), 5.20 (2H, s, CH_2Ar), 5.26 (1H, d, J=12 Hz, CH=CHCH=C*H*H), 5.39 (1H, d, J=18 Hz, CH=CHCH=CH*H*), 5.69 (1H, dd, J=8 and 5 Hz, 7-CH), 6.40 (1H, dt, J=18 and 12 Hz, CH=CHC*H*=CH_2), 6.70 (1H, dd, J=15, 12 Hz, CH=C*H*CH=CH_2), 6.72 (1H, s, thiazole), 6.75 (1H, d, J=15 Hz, C*H*=CHCH=CH_2), 6.9~7.2 (19H, m, Ph), 8.85 (1H, s, TrNH), 9.59 (1H, d, J=8 Hz, CONH); FAB-MS (positive) m/z 798 $(M+H)^+$. Under the same conditions, (*Z*)-**6** was recovered intact.

Finally, deprotection of cephems (either (*E*)- or (*Z*)-of **5**, **7a**, **7b**, (*Z*)-**7c** and (*E*)-**8**) was performed using a stepwise procedure (trifluoroacetic acid-anisole, then trifluoroacetic acid-H_2O) to yield the novel cephems.

Biological Activity and Discussion

The *in vitro* antibacterial activity of the novel cephalosporins ((*Z*)-**1a**~**d**, (*E*)-**1a**, **b**, **d** and **2**) against selected Gram-positive and Gram-negative bacteria is displayed in Table 2. For comparison, the MICs of ceftazidime (CAZ) and cefpirome (CPR) are also shown.

In a series of 3-(2-butenyl)cephems ((*E*)- or (*Z*)-**1a**, **b** and **d**), the (*Z*)-isomers showed more potent activity than the corresponding (*E*)-isomers against Gram-positive bacteria. However, this tendency was even reversed in most of the cases against Gram-negative bacteria: the (*E*)-isomers displayed much better activity. These compounds (**1a**, **b** and **d**) have a partial structure (–CH_2CH=CH–) at their 3-positions in common, which is a C-congener of a thiovinyl (–S–CH=CH–) structure. Interestingly, (*Z*)-isomers were reported to have more potent activity against Gram-negative bacteria in the thiovinyl

Table 2. Comparative activity (MIC, μg/ml) of 3-(2-butenyl)- and 3-(1,3-butadienyl)cephem compounds.

Organism	*S. a. 1*	*S. a. 2*	*S. e.*	*S. p.*	*E. co. 1*	*E. co. 2*	*K. p.*	*E. cl.*	*S. m.*	*P. r.*	*P. a. 1*	*P. a. 2*
(*E*)-**1a**	0.78	1.56	0.78	0.39	0.39	0.39	0.39	0.78	0.78	0.39	12.5	>25
(*Z*)-**1a**	0.39	0.78	0.39	0.1	0.39	0.39	0.39	0.78	0.78	0.2	25	>25
(*E*)-**1b**	0.78	6.25	0.78	0.39	0.2	1.56	0.2	0.78	0.39	1.56	>25	>25
(*Z*)-**1b**	0.39	0.78	0.39	0.2	0.78	1.56	0.2	1.56	0.78	0.78	>25	>25
(*Z*)-**1c**	1.56	1.56	0.39	0.2	1.56	3.13	0.78	6.25	6.25	3.13	>25	>25
(*E*)-**1d**	12.5	12.5	3.13	1.56	0.39	1.56	0.05	3.13	0.78	1.56	>25	>25
(*Z*)-**1d**	12.5	6.25	1.56	0.025	1.56	3.13	0.2	6.25	1.56	1.56	>25	>25
2	6.25	6.25	6.25	0.1	0.39	1.56	0.1	1.56	0.39	1.56	25	>25
CPR	0.39	0.39	0.2	0.05	0.025	0.013	0.025	0.05	0.025	0.2	0.78	50
CAZ	6.25	6.25	3.13	0.78	0.05	0.1	0.05	0.2	0.05	1.56	0.78	50

Abbreviations: *S. a. 1*, *Staphylococcus aureus* FDA209P JC-1; *S. a. 2*, *S. aureus* Smith; *S. e.*, *Streptococcus epidermidis* IID866; *S. p.*, *S. pyogenes* Cook; *E. co. 1*, *Escherichia coli* 0-1; *E. co. 2*, *E. coli* NY-17; *K. p.*, *Klebsiella pneumoniae* ATCC10031; *E. cl.*, *Enterobacter cloacae* 963; *S. m.*, *Serratia marcescens* IID620; *P. r.*, *Providencia rettgeri* Y-1; *P. a. 1*, *Pseudomonas aeruginosa* NCTC10490; *P. a. 2*, *P. aeruginosa* ATCC8689; CPR, cefpirome; CAZ, ceftazidime.

series according to the studies done by the Taisho and Fujisawa groups[7,8].

Among the 3-(2-butenyl)cephems, (*Z*)-**1a** was the most well-balanced, but its activity against Gram-negative bacteria was less than that of CPR. We considered that this comparatively weak activity was attributed to the reduced reactivity of the β-lactam ring caused by deconjugation of the amide carbonyl with the side chain double bond. Therefore, we expected a better activity of 3-(1,3-butadienyl)cephem **2**, but its activity was almost equal to that of CAZ against Gram-positive bacteria and inferior to those of CPR and CAZ against Gram-negative bacteria. These results suggest that steric bulkiness or spatial orientation of the substituent is another contributory factor in the antibacterial activity of these cephems.

Compounds ((*E*)-**2**, (*E*)- and (*Z*)-**1d**) were poorly absorbed by the oral route in rats. The absorbability of (*E*)-**2**, (*E*)-**1d** and (*Z*)-**1d** in rats were 4.4%, 6.6% and 14.2%, respectively. Comparing (*E*)-**1d** with (*Z*)-**1d**, the (*Z*)-isomer exhibited somewhat higher absorption.

Disappointingly, the antibacterial activity and the oral absorbability of all tested compounds were insufficient for further development. Therefore, we turned our attention to the synthesis of new derivatives using the novel butadienyl cephem, (*E*)-**8**, as an intermediate, which will be described in subsequent articles.

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