

(6*R*,8*S*)-(2-BENZIMIDAZOLYL)HYDROXYMETHYLPENICILLANIC  
ACIDS AS POTENT ANTIBACTERIAL AGENTS AND  
 $\beta$ -LACTAMASE INHIBITORS

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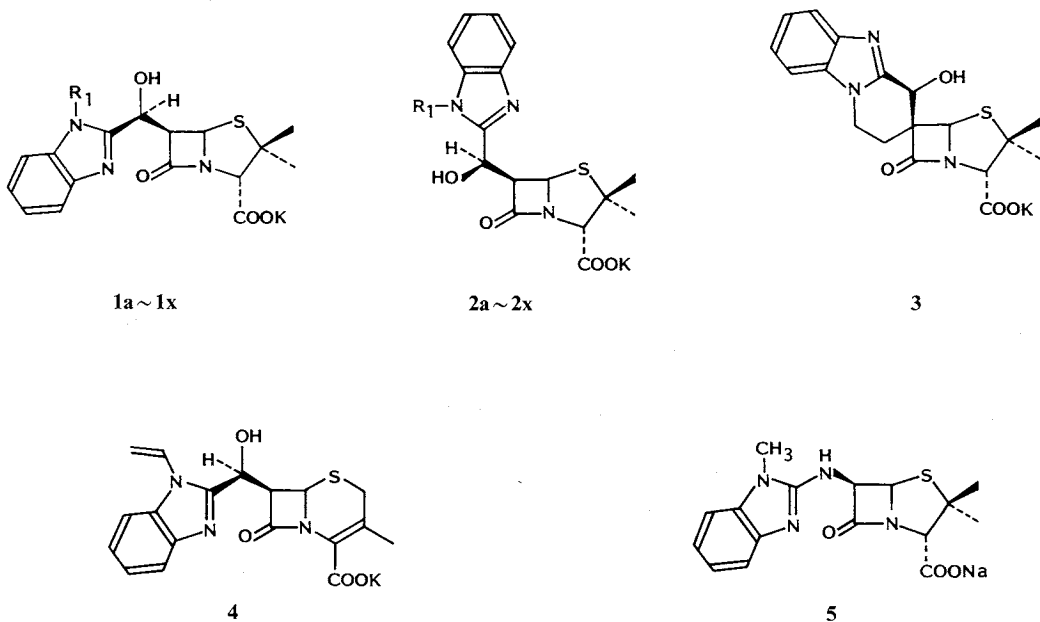
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(6*R*,8*S*)-(2-Benzimidazolyl)hydroxymethylpenicillanic acids (**1a**~**1x**) are potent antibacterial agents and  $\beta$ -lactamase inhibitors against Gram-positive bacteria and *Haemophilus influenzae*. The corresponding (6*R*,8*R*)-isomers (**2a**~**2x**), the 6,6-spiro benzimidazole-penam alcohol (**3**), (7*R*,9*S*)-(2-benzimidazolyl)hydroxymethylcephalosporanic acid (**4**), and 6 $\beta$ -(2-benzimidazolyl)aminopenicillanic acid (**5**) are much less active as antibacterials or  $\beta$ -lactamase inhibitors. The syntheses and structure-activity relationships of these compounds are discussed. Antibacterial activity and  $\beta$ -lactamase inhibition data are presented.

Bacterial resistance to  $\beta$ -lactam antibiotics by virtue of  $\beta$ -lactamase production has become a serious problem. Research to approach this resistance problem has been focused on either development of a  $\beta$ -lactamase inhibitor to inactivate the enzyme or synthesis of new  $\beta$ -lactams with increased stability to  $\beta$ -lactamase hydrolysis. In previous publications from this laboratory, we reported on the  $\beta$ -lactamase

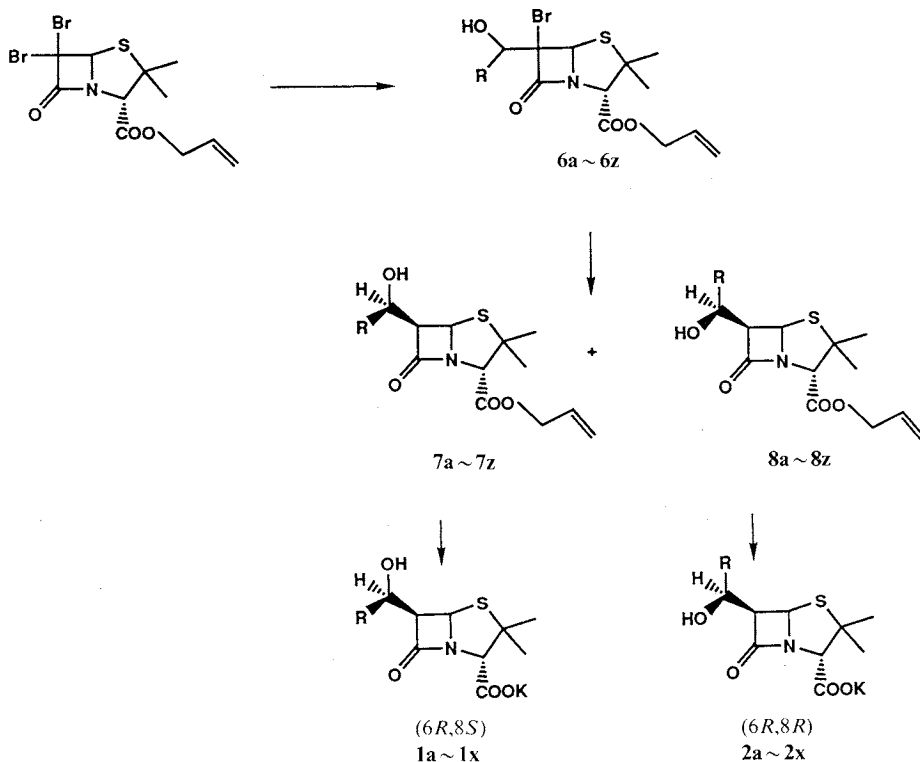


inhibitory activity of a series of 6-(heterocyclyl)-methylene penam sulfones<sup>1,2)</sup> and thiazolyl penam sulfones<sup>3)</sup>. As part of our continuing 6-heterocyclyl  $\beta$ -lactam program, we have synthesized and identified (6*R*,8*S*)-(2-benzimidazolyl)hydroxymethylpenicillanic acids (**1a**~**1x**) as a potent antibacterial against Gram-positive bacteria and *Haemophilus influenzae*, common pathogens of the skin and upper respiratory tract; in addition, **1a**~**1x** is a potent inhibitor of  $\beta$ -lactamases from these organisms. The corresponding (6*R*,8*R*)-isomers (**2a**~**2x**), the spiro compound **3**, and the benzimidazole-cephalosporin alcohol analogue (**4**), were synthesized and found to be much less active as antibiotics and  $\beta$ -lactamase inhibitors. Replacement of the 6-hydroxymethyl group of **1b** with an amino group affords compound **5**<sup>4)</sup>, which has weaker antibacterial and  $\beta$ -lactamase inhibitory activity against these resistant organisms. The syntheses and structure-activity relationships in this series of benzimidazole-penam and benzimidazole-cephalosporin alcohol antibacterials are discussed.

### Chemistry

The syntheses of (2-benzimidazolyl)hydroxymethylpenicillanic acids (**1a**~**1x** and **2a**~**2x**), as well as the spiro analog **3** were accomplished *via* an aldol condensation and tin hydride reduction as outlined in Scheme 1. Reaction of allyl dibromopenicillanate<sup>5)</sup> with methylmagnesium bromide at  $-78^{\circ}\text{C}$ , followed by reaction with a benzimidazole 2-carboxaldehyde at  $-78^{\circ}\text{C}$  produced a mixture of diastereomers (**6a**~**6z**). Stereoselective reduction<sup>6)</sup> of crude compound **6a**~**6z** with tributyltin hydride afforded a mixture of two diastereomers, (6*R*,8*S*)-isomer (**7a**~**7z**) and (6*R*,8*R*)-isomer (**8a**~**8z**). Both **6a**~**6z** and **7a**~**7z** have the (6*R*) stereochemistry which was evident from the coupling constant of  $J=4.6$  and 4.2 Hz, respectively,

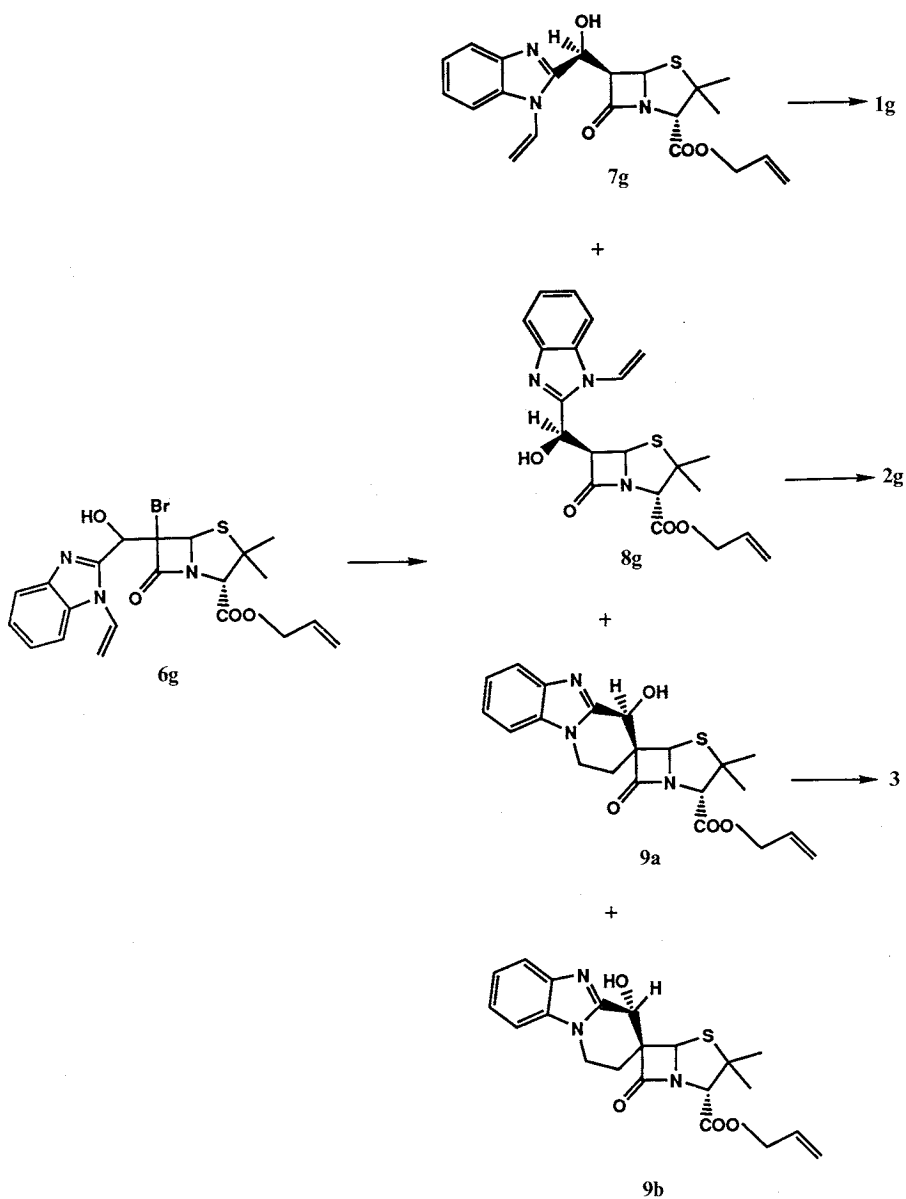
Scheme 1.



indicating a *cis* relationship between C<sub>5</sub> and C<sub>6</sub> protons. The stereochemistry at C<sub>8</sub> was assigned by comparison of the physical properties of each isomer (<sup>1</sup>H NMR, relative HPLC Rt's (the (6*R*,8*S*)-isomer has a longer Rt than the corresponding (6*R*,8*R*)-isomer), and biological activity) to the related analogs, (6*R*,8*S*) and (6*R*,8*R*)-(2-pyrazinyl)hydroxymethylpenicillanic acids, for which the stereochemistry was determined by the X-ray crystallography of a key intermediate.

Because the (6*R*,8*S*) stereochemistry is required for good activity and the desired (6*R*) stereochemistry is obtained selectively *via* the hydride reduction, we examined a variety of conditions for the aldol condensation in order to maximize the stereochemical control at C<sub>8</sub>. Although the conditions explored provided all four possible diastereomers of **6a**~**6z**, the diastereoselectivity was found to be solvent

Scheme 2.



dependent. Methylmagnesium bromide and methyllithium in non-chelating solvents, toluene and methylene chloride, gave a 2:1 mixture in favor of the desired two (8*S*)-diastereomers. In tetrahydrofuran, however, both organometallic agents afforded a mixture of 55:45 in favor of the two undesired (8*R*)-isomers. For synthetic purposes, the crude compound **6a**~**6z**, obtained from aldol condensation using methylmagnesium bromide as a base and methylene chloride or toluene as a solvent, was used directly in the subsequent stereoselective reduction because of its instability. Isomers **7a**~**7z** and **8a**~**8z** were obtained in a ratio of approximately 2:1.

Reduction of **6g** with 2 equiv of tributyltin hydride in benzene gave a mixture of **7g** and **8g**, as well as the spiro compounds (**9a** and **9b**) (Scheme 2). Under the same conditions, reduction of **6e**, **6f** afforded **7e**, **7f** and **8e**, **8f** only. In the case of **6g**, the penam radical, generated by tin hydride, can undergo either an intermolecular hydrogen transfer or intramolecular radical cyclization. In an attempt to increase the formation of the desired reduction products (**7g** and **8g**), we examined the reaction conditions by modifying the amount of tin hydride and solvent. As expected, a large excess of hydride afforded predominately intermolecular hydride reduction, and the reduction in THF favored the undesired spiro compound *via* a radical cyclization. The above results suggest that spiro products (**9a** and **9b**) could probably be largely eliminated by using a large excess of tin hydride reducing agent in benzene. Deallylation of **7a**~**7x**, **8a**~**8x**, and **9a** was achieved in about 90% yield to afford compounds **1a**~**1x**, **2a**~**2x**, and **3** by the method of JEFFREY and McCOMBIE<sup>7)</sup>.

The synthesis of cephalosporin analogue (**4**) is illustrated in Scheme 3. Oxidation of allyl 6,6-dibromopenicillanate was followed by acid rearrangement to afford allyl 7,7-dibromocephalosporinate. Aldol condensation, followed by tin hydride reduction generated all four possible isomers (**11**~**13**). The

Scheme 3.

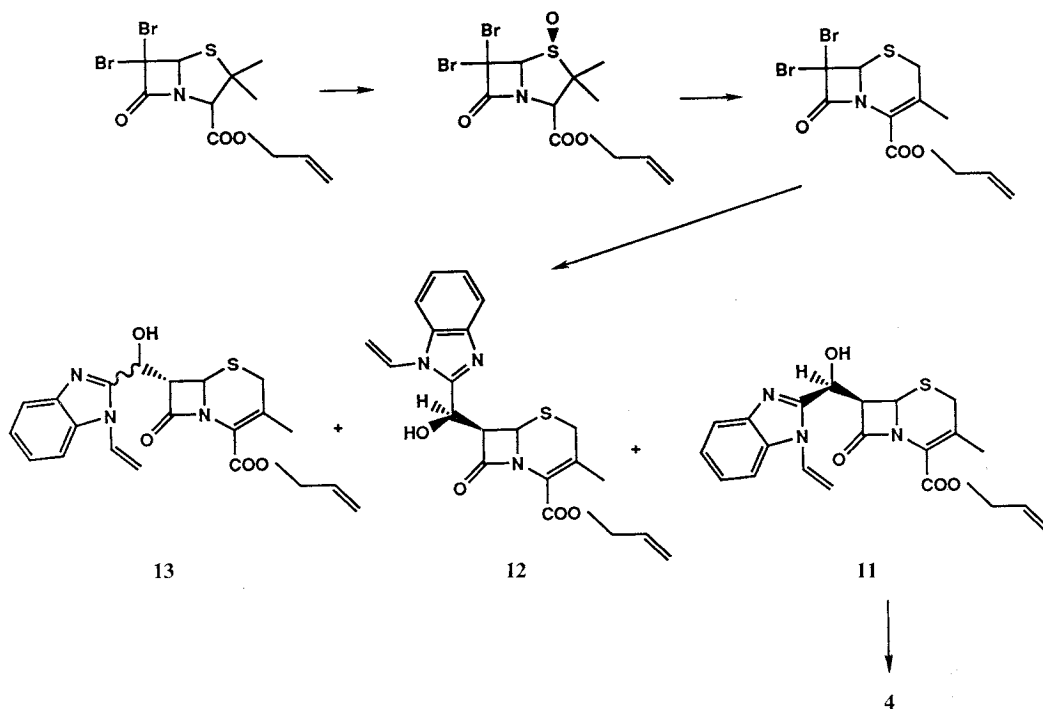
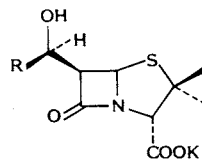
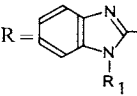

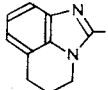
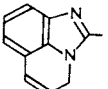

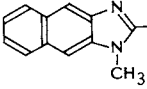


Table 1. MIC data of compound alone and a 1:1 combination of compound with ampicillin.



1a ~ 1x

Compound No.	R = 	MIC ( $\mu\text{g/ml}$ )									
		<i>S.a.</i>		<i>S.e.</i>	<i>S.p.</i>		<i>St.a.</i>	<i>Haemophilus influenzae</i>			
		01A005 ( $\beta^-$ )	01A400 ( $\beta^+$ )	01B087 ( $\beta^-$ )	01B111 ( $\beta^-$ )	02C054 ( $\beta^-$ )	02B006 ( $\beta^-$ )	54A038 ( $\beta^+$ )	54A042 ( $\beta^+$ )	54A081 ( $\beta^-$ )	54A070 ( $\beta^-$ )
Ampicillin		$\leq 0.39$	12.5	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	50	50	$\leq 0.39$	NT
Cefaclor		3.12	6.25	1.56	0.78	0.10	NT	3.12	1.56	3.12	6.25
<b>1a</b>	H	12.5	12.5	0.78	$\leq 0.39$	$\leq 0.39$	0.78	12.5	6.25	50	50
<b>1a</b> + Amp.			0.78 + 0.78					1.56 + 1.56	0.78 + 0.78		
<b>1b</b>	Me	1.56	1.56	0.39	$\leq 0.05$	0.10	0.10	1.56	1.56	1.56	1.56
<b>1b</b> + Amp.			0.39 + 0.39					0.78 + 0.78	0.78 + 0.78		
<b>1c</b>	Et	0.78	0.78	0.78	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	1.56	0.78	0.78	0.78
<b>1c</b> + Amp.			0.39 + 0.39					0.78 + 0.78	0.78 + 0.78		
<b>1d</b>	Pr	0.78	1.56	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	6.25	6.25	6.25	6.25
<b>1d</b> + Amp.			0.78 + 0.78					3.12 + 3.12	3.12 + 3.12		
<b>1e</b>	CH <sub>2</sub> CH=CH <sub>2</sub>	$< 0.39$	0.78	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	1.56	1.56	1.56	1.56
<b>1e</b> + Amp.			$\leq 0.2 + \leq 0.2$					1.56 + 1.56	1.56 + 1.56		
<b>1f</b>	CH <sub>2</sub> C=CH	0.78	0.78	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	1.56	0.78	1.56	0.78
<b>1f</b> + Amp.			0.39 + 0.39					0.78 + 0.78	0.78 + 0.78		
<b>1g</b>	CH=CH <sub>2</sub>	0.78	0.78	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	0.78	0.78	$\leq 0.39$	0.78
<b>1g</b> + Amp.			$\leq 0.2 + \leq 0.2$					0.78 + 0.78	0.78 + 0.78		
<b>1h</b>	CH <sub>2</sub> OMe	1.56	3.12	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	3.12	1.56	1.56	3.12
<b>1h</b> + Amp.			0.78 + 0.78					1.56 + 1.56	1.56 + 1.56		
<b>1i</b>	CH <sub>2</sub> SMe	0.78	0.78	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	1.56	1.56	1.56	1.56
<b>1i</b> + Amp.			0.78 + 0.78					1.56 + 1.56	1.56 + 1.56		
<b>1j</b>	CH <sub>2</sub> F	0.78	1.56	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	$\leq 0.39$	1.56	1.56	0.78	0.78
<b>1j</b> + Amp.			$\leq 0.2 + \leq 0.2$					0.78 + 0.78	0.78 + 0.78		
<b>1k</b>	CH <sub>2</sub> CH <sub>2</sub> OH	6.25	6.25	3.12	0.39	0.20	0.78	1.56	1.56	1.56	0.78
<b>1k</b> + Amp.			1.56 + 1.56					0.78 + 0.78	0.78 + 0.78		
<b>1l</b>	CH <sub>2</sub> CH <sub>2</sub> F	3.12	3.12	0.78	0.10	$\leq 0.025$	0.20	1.56	1.56	1.56	3.12
<b>1l</b> + Amp.			0.78 + 0.78					1.56 + 1.56	1.56 + 1.56		

<b>1m</b>	CH <sub>2</sub> CH <sub>2</sub> OMe	1.56	3.12	3.12	≤0.39	≤0.39	≤0.39	3.12	3.12	3.12	3.12
<b>1m + Amp.</b>			0.78+0.78					3.12+3.12	3.12+3.12		
<b>1n</b>		6.25	6.25	1.56	≤0.39	≤0.39	0.78	6.25	3.12	6.25	6.25
<b>1n + Amp.</b>			1.56+1.56					1.56+1.56	1.56+1.56		
<b>1o</b>	OMe	3.12	6.25	0.78	≤0.39	≤0.39	0.78	1.56	1.56	1.56	1.56
<b>1o + Amp.</b>			0.78+0.78					0.78+0.78	1.56+1.56		
<b>1p</b>	CH <sub>2</sub> CH <sub>2</sub> NMe <sub>2</sub>	25	25	12.5	≤0.39	≤0.39	3.12	25	25	25	25
<b>1p + Amp.</b>			0.78+0.78					6.25+6.25	6.25+6.25		
<b>1q</b>	R = 	0.78	0.78	≤0.39	≤0.39	≤0.39	≤0.39	1.56	0.78	0.78	NT
<b>1q + Amp.</b>			0.39+0.78					0.78+0.78	0.78+0.78		
<b>1r</b>	R = 	<0.39	≤0.39	≤0.39	≤0.39	≤0.39	≤0.39	0.78	0.78	0.78	NT
<b>1r + Amp.</b>			≤0.2+≤0.2					0.39+0.39	0.78+0.78		
<b>1s</b>	CH <sub>2</sub> COOH	>200	200	200	50	6.25	50	50	50	50	100
<b>1s + Amp.</b>			3.12+3.12					6.25+6.25	6.25+6.25		
<b>1t</b>	CH <sub>2</sub> OCO <sup>t</sup> Bu	12.5	12.5	12.5	0.78	≤0.39	0.78	200	200	200	200
<b>1t + Amp.</b>			1.56+1.56					12.5+12.5	12.5+12.5		
<b>1u</b>	CH <sub>2</sub> Ph- <i>p</i> -OMe	1.56	1.56	0.78	0.10	≤0.05	0.2	100	100	100	100
<b>1u + Amp.</b>			0.39+0.39					3.12+3.12	3.12+3.12		
<b>1v</b>		1.56	1.56	0.78	0.10	≤0.05	0.2	25	50	25	12.5
<b>1v + Amp.</b>			0.39+0.39					1.56+1.56	3.12+3.12		
<b>1w</b>	Ph	1.56	1.56	≤0.39	≤0.39	≤0.39	≤0.39	25	12.5	25	12.5
<b>1w + Amp.</b>			0.39+0.39					1.56+1.56	1.56+1.56		
<b>1x</b>	R = 	0.78	1.56	≤0.39	≤0.39	≤0.39	≤0.39	12.5	12.5	6.25	25
<b>1x + Amp.</b>			0.39+0.39					3.12+3.12	3.12+3.12		
<b>2g</b>	CH=CH <sub>2</sub>	25	25	25	3.12	1.56	6.25	25	25	50	100
<b>2g + Amp.</b>			1.56+1.56					6.25+6.25	6.25+6.25		
<b>3</b>		>200	>200	>200	50	50	200	200	200	100	200
<b>3 + Amp.</b>			12.5+12.5					25+25	25+25		
<b>4</b>		50	100	12.5	3.12	3.12	12.5	100	100	100	200
<b>4 + Amp.</b>			3.12+3.12					25+25	12.5+12.5		
<b>5</b>		0.78	25	3.12	≤0.39	≤0.39	≤0.39	50	50	12.5	NT
<b>5 + Amp.</b>			6.25+6.25					3.12+3.12	12.5+12.5		

Organisms abbreviation: *S.a.*, *Staphylococcus aureus*; *S.e.*, *Staphylococcus epidermidis*; *S.p.*, *Streptococcus pyogenes*; *St.a.*, *Streptococcus agalactiae*.  
 (β-): Sensitive strains which do not produce β-lactamase, (β+): resistant strains; β-lactamase producing strains.  
 NT: Not tested.  
 Amp.: Ampicillin.

desired (7*R*,9*S*)-isomer (**11**) was separated and deblocked to provide compound **4**.

Synthesis of 6-benzimidazolylaminopenicillanic acid (**5**) was accomplished by a method analogous to that reported in literature<sup>4</sup>.

## Results and Discussion

### *In Vitro* Antibacterial Activity

Several analogs in the series of (6*R*,8*S*)-(2-benzimidazolyl)hydroxymethylpenicillanic acid compounds (**1a**~**1x**) possess potent antibacterial activity against both susceptible and ampicillin-resistant strains of Gram-positive bacteria and some of the Gram-negative bacteria such as *H. influenzae*. In fact, these compounds are active against the major etiological agents of otitis media, respiratory tract, and skin and skin structure infections seen in community outpatients. Several analogs (e.g., CP-72,436 (**1b**) and CP-74,833 (**1g**)) are more potent than cefaclor (Table 1). Compounds in series **1a**~**1x** are not active against enteric Gram-negative organisms.

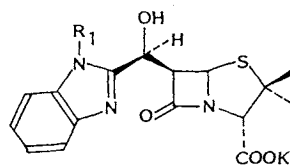
### $\beta$ -Lactamase Inhibitory Activity

Compounds in series **1a**~**1x** were tested against cell free  $\beta$ -lactamase preparations, including *Staphylococcus aureus* and *Escherichia coli*. Many of these compounds are potent inhibitors against both Gram-positive and Gram-negative  $\beta$ -lactamases (e.g., **1b**, **1g**, and **1w** in Table 2); however, a 1:1 combination of compounds in series **1a**~**1x** with ampicillin failed to demonstrate a synergistic effect against *E. coli* 51A129, perhaps these compounds can not penetrate the outer cell membrane of bacteria. Many of these analogs produced synergistic activity against penicillinase producing strains of *S. aureus* 01A400 and *H. influenzae* 54A038 and 54A042 as shown in Table 1. Several analogs (e.g., **1c**, **1e**, **1f**, **1g**, **1i**, **1q** and **1r**) are potent antibacterial agents; thus it is difficult to demonstrate a synergistic effect in combination with ampicillin.

### Structure Activity Relationships

We have previously studied a variety of heteroaryl analogs in a series of penams, penam sulfoxides and penam sulfones. Several penam sulfones were reported previously<sup>1~3</sup>) as potent  $\beta$ -lactamase inhibitors but they are devoid of antibacterial activity. Upon further investigation, we have identified several 6-(2-heteroaryl)hydroxymethylpenicillanic acids which possess potent

Table 2.  $\beta$ -Lactamase inhibitory activity.



**1a**~**1x**

Compound No.	R <sub>1</sub>	Enzyme inhibition (%) <sup>a</sup>	
		<i>S.a.</i> 01A400	<i>E.c.</i> 51A129
Clavulanic acid		85	81
Sulbactam		46	40
<b>1a</b>	H	95	57
<b>1b</b>	Me	96	72
<b>1c</b>	Et	93	33
<b>1d</b>	Pr	88	58
<b>1g</b>	CH=CH <sub>2</sub>	100	86
<b>1k</b>	CH <sub>2</sub> CH <sub>2</sub> OH	85	43
<b>1l</b>	CH <sub>2</sub> CH <sub>2</sub> F	82	51
<b>1m</b>	CH <sub>2</sub> CH <sub>2</sub> OMe	93	61
<b>1n</b>	Δ	78	23
<b>1s</b>	CH <sub>2</sub> COOH	62	24
<b>1t</b>	CH <sub>2</sub> OCO <sup>t</sup> Bu	92	40
<b>1w</b>	Ph	93	95

<sup>a</sup> The percent inhibition at the enzyme level was obtained at the following indicated concentrations ( $\mu$ M) for inhibitor [I] and substrate [S]:

*Staphylococcus aureus* (*S.a.*) 01A400; [I]/[ampicillin] = 8/32.

*Escherichia coli* (*E.c.*) 51A129; [I]/[ampicillin] = 1/32.

$\beta$ -lactamase inhibitory activity, including several which also show antibacterial activity. Among these, the benzimidazole-penam series is especially interesting because of its antibacterial and  $\beta$ -lactamase inhibitory activity. Our discussion herein is focused on the benzimidazole  $\beta$ -lactam series. The structure-activity relationships are summarized as follows: A) The (6*R*,8*S*) stereochemistry is required for antibacterial activity. The corresponding (6*R*,8*R*)-isomers are much less active (see Table 1 **1g** vs. **2g**); B) A smaller substituent, except hydrogen, at N<sub>1</sub> of the benzimidazole ring showed better antibacterial activity against both Gram-positive bacteria and *H. influenzae*. In general, a lipophilic substituent at the benzimidazole group increases antibacterial activity against Gram-positive bacteria, but decreases activity against *H. influenzae* (e.g., **1u**, **1v**, **1w** and **1x**). Compounds with a polar substituent at N<sub>1</sub> are more potent against *H. influenzae*, but less active against Gram-positive organisms (e.g., **1k**). Compounds with a small substituent at N<sub>1</sub> seem to give the desired broad spectrum (e.g., **1b**, **1c**, **1e**, **1f**, **1g**, **1h**, **1i**, **1j**, **1q** and **1r**); however when the substituent is a hydrogen, the antibacterial activity against both *S. aureus* and *H. influenzae* is unexpectedly decreased (e.g., **1a**); C) As shown above, the benzimidazole-penam alcohol is a unique structure which has antibacterial activity; the corresponding spiro analog (**3**) and cephalosporin (**4**) are weaker antibacterial agents. The classical penam antibacterial structure which possesses a 6-amido side chain is known to be sensitive to many  $\beta$ -lactamase producing bacteria; however, replacement of the 6-amido group with a hydroxymethyl group seems to gain  $\beta$ -lactamase stability as demonstrated in the case of penems and carbapenems, as well as in examples represented here. Replacement of the 6-hydroxymethyl substituent of **1b** with an amino group results in compound **5** which retains Gram-positive activity against sensitive strains, but is inactive against  $\beta$ -lactamase producing strains of *S. aureus* and *H. influenzae* (see Table 1).

### Conclusion

In conclusion, many analogs in series **1a**~**1x** demonstrated antibacterial activity against both sensitive and resistant strains of Gram-positive bacteria and *H. influenzae*. Several of these compounds are more potent antibacterial agents than cefaclor. These agents are also potent  $\beta$ -lactamase inhibitors and are capable of producing synergy in combination with ampicillin. Further biological evaluation of representative compounds (e.g., **1b** and **1g**), as well as their prodrugs will be described in a forthcoming paper.

### Experimental

IR spectra were recorded on Perkin-Elmer model 283 B spectrophotometer. NMR spectra were recorded on a Varian T-60, XL-300, Bruker 250 or 300 spectrometer using TMS as internal standard. Analytical HPLC was carried out with a Waters Associates Instrument using Waters  $\mu$ Bondapak C18 column.

#### Chemicals

Subactam was prepared in the Pfizer laboratories. Cefaclor was a product of Eli Lilly and Co.

#### In Vitro Assays

MICs were determined on Brain Heart Infusion agar (Scott Laboratory Inc., Fiskeville, Rhode Island) as the basal medium<sup>8)</sup> by the method of ERICSSON and SHERRIS<sup>9)</sup> using the multiple inoculator described by STEERS *et al.*<sup>10)</sup>. Synergy was defined as occurring when the MIC of each component in the combination was one-fourth or less than its MIC as a single agent. Cell free extracts of  $\beta$ -lactamase producing organisms were prepared as described previously<sup>8)</sup>. For the percent inhibitory data in Table 2, the rate of hydrolysis was determined by the micro-iodometric assay as described by ZIMMERMANN and ROSSELET<sup>11)</sup>; incubations



were at 37°C for 10 minutes<sup>12)</sup>.

Allyl 6-(2-[1-Methylbenzimidazolyl]hydroxymethyl)-6-bromopenicillanate (6b)

To a solution of allyl 6,6-dibromopenicillanate (21.42 g, 0.053 mol) in 400 ml of methylene chloride cooled to  $-78^{\circ}\text{C}$  was added 17.32 ml (0.053 mol) of a 3.1 M solution of methyl magnesium bromide in diethyl ether over a 5-minute period. After stirring for 30 minutes, 1-methylbenzimidazole-2-carboxaldehyde (8.60 g, 0.053 mol) in 50 ml of methylene chloride was added. After stirring at  $-78^{\circ}\text{C}$  for 1 hour, the mixture was quenched with 3.1 ml (0.053 mol) of acetic acid and allowed to warm to  $0^{\circ}\text{C}$ . The mixture was poured into water and the organic layer was separated, dried and concentrated to give **6b**. The crude material was employed in the subsequent step.

Compounds **6c**~**6j**, **6l**~**6r**, and **6t**~**6z** were prepared from allyl 6,6-dibromopenicillanate and the appropriate aldehyde by a procedure similar to that described for **6b**.

Allyl 6-(2-[1-*tert*-Butyldimethylsiloxyethylbenzimidazolyl]hydroxymethyl)-6-bromopenicillanate (6y)

The title compound was prepared from allyl 6,6-dibromopenicillanate and 1-*tert*-butyldimethylsiloxyethylbenzimidazole-2-carboxaldehyde by a procedure similar to that described for **6b**.

Allyl 6-(2-[1-Allyloxycarbonylmethylbenzimidazolyl]hydroxymethyl)-6-bromopenicillanate (6z)

The title compound was prepared from allyl 6,6-dibromopenicillanate and 1-allyloxycarbonylmethylbenzimidazole-2-carboxaldehyde by a procedure similar to that described for **6b**.

Allyl 6 $\beta$ -(2-[1-Methylbenzimidazolyl]-(*S*) and (*R*)-Hydroxymethyl)penicillanate (7b and 8b)

A mixture of crude **6b** and tri-*n*-butyltin hydride (28.51 ml, 0.106 mol) in 500 ml of benzene was heated at reflux for 6 hours and allowed to stir at room temperature overnight. The solvent was removed and the residue treated with acetonitrile and hexane. The acetonitrile layer was further washed with hexane and the solvent was removed to give 21 g of product as brown oil. The oil was purified by column chromatography on 750 g of silica gel using 25% ethyl acetate in chloroform as eluent to give 3.27 g (17%) of a less polar, (6*R*,8*R*) isomer **8b** as an oil, and 4.08 g (21%) of the more polar, desired (6*R*,8*S*) isomer **7b** as an oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) for **7b**:  $\delta$  1.32 (3H, s), 1.58 (3H, s), 3.71 (3H, s), 4.43 (1H, s), 4.52 (1H, dd), 4.58 (2H, d), 5.16~5.42 (3H, m), 5.49 (1H, d), 5.76~5.94 (1H, m), 7.06~7.26 (3H, m), 7.52~7.60 (1H, m); <sup>1</sup>H NMR (CDCl<sub>3</sub>) for **8b**:  $\delta$  1.50 (3H, s), 1.70 (3H, s), 3.80 (3H, s), 4.38 (1H, dd), 4.44 (1H, s), 4.65 (2H, d), 5.2~5.5 (3H, m), 5.64 (1H, m), 5.8~6.0 (1H, m), 7.2~7.35 (3H, m), 7.7 (1H, m).

Allyl 6 $\beta$ -(2-[1-Vinylbenzimidazolyl]-(*S*) and (*R*)-Hydroxymethyl)penicillanate (7g and 8g) and the Spiro Compound 9a and 9b

The title compound were prepared by reduction of **6g** with 10 equiv of tri-*n*-butyltin hydride in benzene by procedure similar to **7b** and **8b**, except this reaction gave a mixture of **7g** (6*R*,8*S*), **8g** (6*R*,8*R*), and two diastereomers of spiro compound **9a** (6*R*,8*S*) and **9b** (6*R*,8*R*). <sup>1</sup>H NMR (CDCl<sub>3</sub>) for **7g**:  $\delta$  1.38 (3H, s), 1.6 (3H, s), 4.46 (1H, s), 4.6 (1H, dd), 4.64 (2H, m), 5.2~5.5 (4H, m), 5.54 (1H, d), 5.86 (1H, d), 5.8~6.0 (1H, m), 7.2~7.4 (3H, m), 7.48 (1H, m), 7.68 (1H, m); <sup>1</sup>H NMR (CDCl<sub>3</sub>) for **8g**:  $\delta$  1.66 (3H, s), 1.86 (3H, s), 4.44 (1H, s), 4.5~4.7 (3H, m), 5.2~5.5 (4H, m), 5.5~5.7 (2H, m), 5.8~6.0 (1H, m), 7.1~7.3 (3H, m), 7.4~7.5 (1H, m), 7.6~7.7 (1H, m); <sup>1</sup>H NMR (CDCl<sub>3</sub>) for **9a**:  $\delta$  1.34 (3H, s), 1.48 (3H, s), 2.42 (1H, m), 3.2 (1H, m), 4.0~4.4 (2H, m), 4.5 (1H, s), 4.6 (2H, m), 5.3 (1H, s), 5.1~5.4 (2H, m), 5.72 (1H, s), 5.75~5.9 (1H, m), 7.1~7.3 (3H, m), 7.7 (1H, m); <sup>1</sup>H NMR (CDCl<sub>3</sub>) for **9b**:  $\delta$  1.42 (3H, s), 1.58 (3H, s), 2.48 (1H, m), 3.0 (1H, m), 4.1~4.24 (1H, m), 4.24~4.34 (1H, m), 4.32 (1H, s), 4.6 (2H, ABq), 5.2~5.4 (2H, m), 5.28 (1H, s), 5.5 (1H, s), 5.8~5.95 (1H, m), 7.1~7.3 (3H, m), 7.6~7.7 (1H, m); MS for **9b** (C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>S): 414 ((M+H)<sup>+</sup>, 48%), 384 (35%), 328 (17%), 231 (41%), 185 (100%).

Compounds with the desired (6*R*,8*S*) stereochemistry, such as **7c**~**7j**, **7l**~**7r**, and **7t**~**7z** were prepared by procedure similar to that described for **7b**. Several analogs of the undesired isomer **8** were also isolated and <sup>1</sup>H NMR data are reported here. The yield over two steps for each pure isomer is reported; the combined yield was not determined.

**7c**: 23%; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.4~1.55 (6H, m), 1.64 (3H, s), 4.14 (1H, q), 4.42 (1H, q), 4.5 (1H, s), 4.64 (2H, m), 5.2~5.5 (2H, m), 5.9 (1H, d), 5.8~6.0 (1H, m), 7.1~7.4 (3H, m), 7.65 (1H, m).

**8c:** 19%;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.40~1.55 (6H, m), 1.75 (3H, s), 4.1~4.4 (2H, m), 4.52 (2H, m), 4.6 (1H, dd), 4.7 (2H, d), 5.2~5.5 (3H, m), 5.8~6.1 (1H, m), 7.2~7.5 (3H, m).

**7d:** 14% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.0 (3H, t), 1.40 (3H, s), 1.64 (3H, s), 1.9 (2H, m), 4.05 (1H, m), 4.3 (1H, m), 4.5 (1H, s), 4.6~4.7 (3H, m), 5.2~5.4 (4H, m), 5.6 (1H, d), 5.84~6.00 (1H, m), 7.1~7.3 (3H, m), 7.6 (1H, m).

**8d:** 7.5% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.98 (3H, t), 1.5 (3H, s), 1.7 (3H, s), 1.87 (2H, m), 4.0~4.4 (2H, m), 4.4~4.6 (2H, m), 4.68 (2H, d), 5.2~5.5 (3H, m), 5.7 (1H, m), 5.84~6.00 (1H, m), 7.2~7.3 (3H, m), 7.66~7.8 (1H, m).

**7e:** 13% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.46 (3H, s), 1.67 (3H, s), 4.54 (1H, s), 4.59 (1H, dd), 4.69 (2H, d), 5.08 (2H, m), 5.2~5.48 (4H, m), 5.46 (1H, d), 5.68 (1H, d), 5.84~6.08 (2H, m), 7.18~7.42 (3H, m), 7.64~7.9 (1H, m).

**8e:** 10% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.47 (3H, s), 1.70 (3H, s), 4.4 (1H, s), 4.60 (3H, m), 4.9 (2H, m), 5.1~5.5 (5H, m), 5.6 (1H, d), 5.8~6.0 (2H, m), 7.1~7.4 (3H, m), 7.6~7.8 (1H, m).

**7f:** 16% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.36 (3H, s), 1.6 (3H, s), 2.33 (1H, t), 4.46 (1H, s), 4.47 (1H, dd), 4.61 (2H, d), 5.05 (2H, ABq), 5.23~5.37 (2H, m), 5.53 (1H, d), 5.58 (1H, d), 5.9~6.0 (1H, m), 7.2~7.26 (2H, m), 7.34~7.37 (1H, m), 7.60~7.64 (1H, m).

**8f:** 8% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.48 (3H, s), 1.69 (3H, s), 2.33 (1H, t), 4.4 (1H, dd), 4.49 (1H, s), 4.65 (2H, d), 5.05 (2H, ABq), 5.2~5.4 (2H, m), 5.4~5.6 (1H, m), 5.77 (1H, d), 5.9~6.0 (1H, m), 7.2~7.3 (2H, m), 7.44 (1H, d), 7.7 (1H, d).

**7h:** 14% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.4 (3H, s), 1.62 (3H, s), 3.32 (3H, s), 4.52 (1H, s), 4.60 (1H, dd), 4.67 (2H, d), 5.26~5.46 (2H, m), 5.46~5.7 (3H, m), 5.74 (1H, d), 5.86~6.04 (1H, m), 7.22~7.37 (2H, m), 7.37~7.52 (1H, m), 7.64~7.83 (1H, m).

**8h:** 6% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.54 (3H, s), 1.76 (3H, s), 3.34 (3H, s), 4.52 (1H, dd), 4.55 (1H, s), 4.72 (2H, ABq), 5.2~5.8 (6H, m), 5.85~6.0 (1H, m), 7.2~7.4 (2H, m), 7.5 (1H, dd), 7.8 (1H, dd).

**7i:** 13% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.36 (3H, s), 1.60 (3H, s), 2.04 (3H, s), 4.45 (1H, s), 4.5 (1H, dd), 4.6 (2H, d), 5.09~5.5 (4H, m), 5.54 (1H, d), 5.62 (1H, d), 5.78~5.96 (1H, m), 7.12~7.3 (2H, m), 7.3~7.48 (1H, m), 7.48~7.8 (1H, m).

**7j:** 17% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.36 (3H, s), 1.59 (3H, s), 2.82 (1H, d), 4.41 (1H, dd), 4.42 (1H, s), 4.60 (2H, d), 5.2~5.36 (2H, m), 5.56 (1H, d), 5.58 (1H, d), 5.78~5.94 (1H, m), 6.29 (2H, m), 7.18~7.42 (3H, m), 7.6~7.74 (1H, m).

**8j:** 12% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.47 (3H, s), 1.67 (3H, s), 4.35 (1H, dd), 4.47 (1H, s), 4.64 (2H, d), 5.22~5.40 (2H, m), 5.46~5.60 (1H, m), 5.70 (1H, d), 5.78~5.96 (1H, m), 6.24 (2H, m), 7.22~7.36 (2H, m), 7.36~7.44 (1H, m), 7.64~7.74 (1H, m).

**7l:** 10% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.4 (3H, s), 1.63 (3H, s), 4.3~4.9 (4H, m), 4.52 (1H, s), 4.58 (1H, dd), 4.68 (2H, m), 5.26~5.44 (2H, m), 5.49 (1H, d), 5.67 (1H, d), 5.8~6.04 (1H, m), 7.2~7.4 (3H, m), 7.63 (1H, d).

**7m:** 14% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.38 (3H, s), 1.63 (3H, s), 3.28 (3H, s), 3.66~3.72 (2H, m), 4.26~4.62 (3H, m), 4.48 (1H, s), 4.6 (2H, d), 5.2~5.44 (3H, m), 5.58 (1H, d), 5.8~6.0 (1H, m), 7.14~7.3 (3H, m), 7.62~7.66 (1H, d).

**8m:** 9% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.46 (3H, s), 1.65 (3H, s), 3.2 (3H, s), 3.6 (2H, t), 4.2~4.5 (3H, m), 4.4 (1H, s), 4.6 (2H, d), 5.2~5.5 (3H, m), 5.6 (1H, d), 5.8~6.0 (1H, m), 7.1~7.3 (3H, m), 7.6~7.7 (1H, m).

**7n:** 12% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.0~1.58 (4H, m), 1.40 (3H, s), 1.69 (3H, s), 3.28~3.44 (1H, m), 4.52 (1H, s), 4.62 (2H, d), 4.68 (1H, dd), 5.20~5.42 (2H, m), 5.46 (1H, d), 5.62 (1H, d), 5.80~5.96 (1H, m), 7.10~7.30 (2H, m), 7.36~7.50 (1H, m), 7.60~7.74 (1H, m).

**7o:** 14% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.36 (3H, s), 1.61 (3H, s), 3.78 (3H, s), 4.45 (1H, s), 4.52 (1H, dd), 4.60 (2H, d), 5.16~5.46 (3H, m), 5.53 (1H, d), 5.78~5.96 (1H, m), 7.10~7.30 (3H, m), 7.56~7.68 (1H, m).

**7p:** 8% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.32 (3H, s), 1.6 (3H, s), 2.15 (6H, s), 2.5~2.7 (2H, m), 4.2~4.35 (2H, m), 4.48 (1H, s), 4.6 (3H, m), 5.1~5.4 (3H, m), 5.65 (1H, d), 5.78~6.0 (1H, m), 7.1~7.4 (3H, m), 7.7 (1H, m).

**7q:** 14% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.34 (3H, s), 1.59 (3H, s), 2.0~2.1 (2H, m), 2.64~2.86 (2H, m), 4.1~4.2 (2H, m), 4.44 (1H, s), 4.52 (1H, dd), 4.59 (2H, d), 5.2~5.34 (2H, m), 5.34 (1H, d), 5.46 (1H, d),

5.75~5.95 (1H, m), 6.87 (1H, d), 7.04 (1H, t), 7.39 (1H, d).

**8q:** 17% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.42 (3H, s), 1.70 (3H, s), 2.0~2.2 (2H, m), 2.75~2.9 (2H, m), 4.0~4.2 (2H, m), 4.34 (1H, dd), 4.4 (1H, s), 4.62 (2H, d), 5.24~5.38 (2H, m), 5.37 (1H, d), 5.56 (1H, d), 5.7~5.9 (1H, m), 6.9 (1H, d), 7.07 (1H, t), 7.43 (1H, d).

**7r:** 16% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.37 (3H, s), 1.61 (3H, s), 4.45 (1H, s), 4.45 (1H, dd), 4.61 (2H, d), 5.0~5.4 (5H, m), 5.53 (1H, d), 5.7~5.8 (1H, m), 5.8~5.9 (1H, m), 6.42~6.5 (1H, m), 6.75 (1H, d), 6.97 (1H, t), 7.34 (1H, d).

**7t:** 17% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.12 (9H, s), 1.38 (3H, s), 1.62 (3H, s), 4.46 (1H, s), 4.48 (1H, dd), 4.62 (2H, d), 5.2~5.4 (2H, m), 5.6~5.7 (2H, m), 5.8~6.0 (1H, m), 6.24 (2H, ABq), 7.2~7.35 (2H, m), 7.48 (1H, m), 7.66 (1H, m).

**7u:** 21% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.4 (3H, s), 1.45 (3H, s), 3.82 (3H, s), 4.5 (1H, s), 4.63 (1H, dd), 4.72 (2H, ABq), 5.3~5.64 (5H, m), 5.7 (1H, d), 5.9~6.1 (1H, m), 6.9 (2H, d), 7.2 (2H, d), 7.2~7.4 (3H, m), 7.8 (1H, d).

**8u:** 7% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.52 (3H, s), 1.64 (3H, s), 3.8 (3H, s), 4.5 (2H, m), 4.7 (2H, ABq), 5.2~5.55 (5H, m), 5.7 (1H, d), 5.9~6.1 (1H, m), 6.88 (2H, d), 7.1 (2H, d), 7.2~7.4 (3H, m), 7.78 (1H, d).

**7v:** 5% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.38 (3H, s), 1.52 (3H, s), 4.48 (1H, s), 4.52 (1H, dd), 4.64 (2H, ABq), 5.1~5.5 (5H, m), 5.64 (1H, d), 5.8~6.0 (1H, m), 6.35 (1H, s), 7.2~7.4 (5H, m), 7.7 (1H, m).

**7w:** 9% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.3 (3H, s), 1.32 (3H, s), 4.34 (1H, s), 4.53~4.60 (2H, m), 4.66 (1H, dd), 5.04~5.34 (3H, m), 5.38 (1H, d), 5.69~5.82 (1H, m), 7.08~7.34 (3H, m), 7.42~7.64 (5H, m), 7.80 (1H, d).

**8w:** 14% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.40 (3H, s), 1.43 (3H, s), 4.30 (1H, dd), 4.37 (1H, s), 4.60 (2H, d), 4.18~4.40 (3H, m), 4.56 (1H, d), 5.80~5.96 (1H, m), 7.12~7.34 (3H, m), 7.42~7.66 (5H, m), 7.80 (1H, d).

**7x:** 9% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.34 (3H, s), 1.60 (3H, s), 3.74 (3H, s), 4.46 (1H, s), 4.6 (3H, m), 5.2~5.4 (2H, m), 5.42 (1H, d), 5.58 (1H, d), 5.8~6.0 (1H, m), 7.2 (1H, m), 7.25~7.5 (2H, m), 7.74 (1H, d), 7.84 (1H, d), 8.0 (1H, s).

**7y:** 21% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  -0.26 (3H, s), 0 (3H, s), 0.76 (9H, s), 1.4 (3H, s), 1.66 (3H, s), 4.1 (2H, m), 4.2~4.4 (2H, m), 4.52 (1H, s), 4.6 (1H, dd), 4.68 (2H, ABq), 5.0 (1H, br s), 5.2~5.5 (3H, m), 5.66 (1H, d), 5.86~6.0 (1H, m), 7.2~7.4 (3H, m), 7.7 (1H, m).

**7z:** 29% yield;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.44 (3H, s), 1.64 (3H, s), 4.40 (1H, dd), 4.48 (1H, s), 4.98~5.42 (6H, m), 5.49 (1H, d), 5.64 (1H, d), 5.74~6.00 (2H, m), 7.14~7.36 (3H, m), 7.62~7.78 (1H, m).

Allyl 6 $\beta$ -(2-[1-(2-Hydroxyethyl)benzimidazolyl]-(*S*)-hydroxymethyl)penicillanate (**7k**)

Allyl 6 $\beta$ -(2-[1-(2-*tert*-butyldimethylsilyloxyethyl)benzimidazolyl]-(*S*)-hydroxymethyl)penicillanate (**7y**) (600 mg, 1.1 mmol) and 0.13 ml (2.2 mmol) of acetic acid were added to 6.6 ml (6.6 mmol) of 1 M solution of tetrabutylammonium fluoride in THF and the reaction mixture was stirred overnight at room temperature under  $\text{N}_2$ . The reaction mixture was diluted with ethyl acetate and after washing with water and saturated sodium bicarbonate, the organic layer was separated, dried and concentrated to give compound **7k** (474 mg, 100% yield) which was used directly for the next step.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.4 (3H, s), 1.64 (3H, s), 3.8~4.1 (2H, m), 4.3~4.6 (3H, m), 4.52 (1H, s), 4.68 (2H, d), 5.1~5.5 (3H, m), 5.62 (1H, dd), 5.86~6.04 (1H, m), 7.1~7.4 (3H, m), 7.6~7.7 (1H, m).

Potassium 6 $\beta$ -(2-[1-Methylbenzimidazolyl]-(*S*)-hydroxymethyl)penicillanate (**1b**)

A solution of allyl 6 $\beta$ -(2-[1-methylbenzimidazolyl]-(*S*)-hydroxymethyl)penicillanate (**7b**) (1.45 g, 3.9 mmol) in 5 ml of ethyl acetate was treated with  $\text{Pd}(\text{PPh}_3)_4$  (120 mg),  $\text{PPh}_3$  (120 mg) and 0.5 M solution of potassium 2-ethylhexanoate in ethyl acetate (7.8 ml, 3.9 mmol) and the mixture was stirred at room temperature for 45 minutes. A precipitate formed and was filtered to give **1b** (1.25 g, 87%) as a pale-yellow solid which is reasonably pure. For analytical purity, the solid was purified by medium pressure  $\text{C}_{18}$  silica gel column chromatography eluting with 15% acetonitrile in water to give a white solid. The analytical purity was determined by HPLC using 1:1 mixture of MeOH-0.02 M ammonium acetate as eluent with 1.5 ml/minute of flow rate.  $^1\text{H NMR}$  ( $\text{D}_2\text{O}$ )  $\delta$  1.26 (3H, s), 1.48 (3H, s), 3.76 (3H, s), 4.16 (1H, s), 4.36 (1H, dd), 5.3~5.45 (2H, m), 7.2~7.35 (2H, m), 7.45 (1H, d), 7.58 (1H, d).

Compounds **1c~1x**, **2g** and **3** were prepared by a procedure similar to that described for **1b**.

**1c:** 89% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.4~1.45 (6H, m), 1.6 (3H, s), 4.3 (1H, s), 4.3~4.75 (3H, m), 5.4~5.6 (2H, m), 7.3~7.5 (2H, m), 7.6 (1H, d), 7.7 (1H, d).

**1d:** 90% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  0.95 (3H, t), 1.42 (3H, s), 1.62 (3H, s), 1.9 (2H, m), 3.39 (1H, s), 4.3 (2H, m), 4.5 (1H, dd), 5.4~5.6 (2H, m), 7.3~7.5 (2H, m), 7.6 (1H, m), 7.7 (1H, m); IR (KBr)  $\text{cm}^{-1}$  3437, 1756, 1604.

**1e:** 81% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.34 (3H, s), 1.52 (3H, s), 4.22 (1H, s), 4.38 (1H, dd), 4.8~5.04 (3H, m), 5.1~5.22 (1H, m), 5.4 (1H, d), 5.47 (1H, d), 5.9~6.1 (1H, m), 7.24~7.42 (2H, m), 7.42~7.54 (1H, m), 7.64~7.76 (1H, m); IR (KBr)  $\text{cm}^{-1}$  3434, 1754, 1606.

**1f:** 72% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.42 (3H, s), 1.63 (3H, s), 2.83 (1H, m), 4.31 (1H, s), 4.46 (1H, dd), 5.23 (2H, s), 5.55 (1H, d), 5.6 (1H, d), 7.36~7.5 (2H, m), 7.68~7.8 (2H, m).

**1g:** 91% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.34 (3H, s), 1.54 (3H, s), 4.24 (1H, s), 4.44 (1H, dd), 5.45 (2H, m), 5.55 (1H, d), 5.72 (1H, d), 7.24 (1H, m), 7.4 (2H, m), 7.7 (2H, m).

**1h:** 88% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.34 (3H, s), 1.53 (3H, s), 3.28 (3H, s), 4.22 (1H, s), 4.37 (1H, dd), 5.4~5.54 (2H, m), 5.54~5.76 (2H, m), 7.22~7.44 (2H, m), 7.44~7.80 (2H, m).

**1i:** 65% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.42 (3H, s), 1.64 (3H, s), 2.10 (3H, s), 4.29 (1H, s), 4.42 (1H, dd), 5.51 (2H, s), 5.55 (1H, d), 5.62 (1H, d), 7.34~7.48 (2H, m), 7.68~7.78 (2H, m); IR (KBr)  $\text{cm}^{-1}$  3400, 1750, 1600.

**1j:** 100% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.42 (3H, s), 1.62 (3H, s), 4.29 (1H, s), 4.44 (1H, dd), 5.46~5.68 (2H, m), 6.47 (2H, d), 7.35~7.60 (2H, m), 7.62~7.84 (2H, m); IR (KBr)  $\text{cm}^{-1}$  3401, 1748, 1601.

**1k:** 100% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.42 (3H, s), 1.62 (3H, s), 4.0~4.1 (2H, m), 4.32 (1H, s), 4.4~4.7 (3H, m), 5.5~5.6 (2H, m), 7.36~7.5 (2H, m), 7.68 (1H, d), 7.76 (1H, d).

**1l:** 78% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.35 (3H, s), 1.49 (3H, s), 3.86 (1H, s), 4.2 (1H, dd), 4.5~4.94 (4H, m), 5.24 (1H, d), 5.39 (1H, d), 7.18~7.34 (2H, m), 7.56~7.7 (2H, m).

**1m:** 85% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.36 (3H, s), 1.57 (3H, s), 3.23 (3H, s), 3.8~3.9 (2H, m), 4.24 (1H, s), 4.4 (1H, dd), 4.46~4.6 (2H, m), 5.46 (1H, d), 5.5 (1H, d), 7.3~7.44 (2H, m), 7.58 (1H, d), 7.68 (1H, d).

**1n:** 72% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.06~1.46 (4H, m), 1.36 (3H, s), 1.60 (3H, s), 3.38~3.48 (1H, m), 4.27 (1H, s), 4.41 (1H, dd), 5.40 (1H, d), 5.66 (1H, d), 7.25~7.46 (2H, m), 7.60~7.80 (2H, m); IR (KBr)  $\text{cm}^{-1}$  3410, 1751, 1600.

**1o:** 76% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.40 (3H, s), 1.62 (3H, s), 3.92 (3H, s), 4.28 (1H, s), 4.43 (1H, dd), 5.48~5.54 (2H, m), 7.24~7.48 (2H, m), 7.52~7.64 (1H, m), 7.64~7.76 (1H, m); IR (KBr)  $\text{cm}^{-1}$  3400, 1750, 1610.

**1p:** A precipitate did not form. The reaction mixture was treated with water and ethyl acetate. The water layer was separated, freeze dried and purified through  $\text{C}_{18}$  column chromatography using medium pressure liquid chromatography (MPLC) and eluting with 10% acetonitrile in water to give a golden solid (21% yield);  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.38 (3H, s), 1.58 (3H, s), 2.54 (6H, s), 3.1~3.3 (2H, m), 4.26 (1H, s), 4.4 (1H, dd), 4.5~4.7 (2H, m), 5.4 (1H, d), 5.52 (1H, d), 7.3~7.5 (2H, m), 7.5 (1H, d), 7.72 (1H, d); IR (KBr)  $\text{cm}^{-1}$  3410, 1757, 1612.

**1q:** 96% yield; 64% yield after  $\text{C}_{18}$  column chromatography;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.39 (3H, s), 1.61 (3H, s), 2.22 (2H, m), 2.98 (2H, m), 4.26 (1H, s), 4.2~4.3 (2H, m), 4.4 (1H, dd), 5.41 (1H, d), 5.44 (1H, d), 7.14 (1H, d), 7.26 (1H, t), 7.49 (1H, d).

**1r:** 100% yield; 57% after  $\text{C}_{18}$  column chromatography;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.41 (3H, s), 1.62 (3H, s), 4.28 (1H, s), 4.41 (1H, dd), 5.20 (2H, s), 5.32 (1H, d), 5.46 (1H, d), 5.9~6.0 (1H, m), 6.58~6.68 (1H, m), 6.94 (1H, d), 7.13 (1H, t), 7.4 (1H, d); IR (KBr)  $\text{cm}^{-1}$  3411, 1752, 1602.

**1s** was prepared by a method analogous to that of **1b** except 2 equiv of potassium 2-ethylhexanoate were employed; 92% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.45 (3H, s), 1.65 (3H, s), 4.31 (1H, s), 4.46 (1H, dd), 4.97 (2H, s), 5.46 (1H, d), 5.53 (1H, d), 7.36~7.58 (3H, m), 7.60~7.82 (1H, m); IR (KBr)  $\text{cm}^{-1}$  1745, 1600.

**1t:** 100% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.02 (9H, s), 1.42 (3H, s), 1.62 (3H, s), 4.28 (1H, s), 4.44 (1H, dd), 5.58 (1H, d), 5.63 (1H, d), 6.38 (2H, ABq), 7.33~7.5 (2H, m), 7.7~7.8 (2H, m); IR (KBr)  $\text{cm}^{-1}$  3399, 1746, 1608.

**1u:** 83% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.22 (6H, d), 3.56 (3H, s), 4.12 (1H, s), 4.42 (1H, dd), 5.0~5.5 (4H, m), 6.68 (2H, m), 6.9~7.3 (5H, m), 7.7 (1H, m); IR (KBr)  $\text{cm}^{-1}$  3428, 1753, 1613.

**1v:** 49% yield;  $^1\text{H NMR (D}_2\text{O)}$   $\delta$  1.32 (3H, s), 1.46 (3H, s), 4.2 (1H, s), 4.4 (1H, dd), 5.4 (2H, s), 5.46 (2H, m), 6.3 (1H, s), 7.25~7.6 (5H, m), 7.7 (1H, m); IR (KBr)  $\text{cm}^{-1}$  3385, 1750, 1607.

**1w**: 71% yield; 30% yield after  $C_{18}$  column chromatography:  $^1H$  NMR ( $D_2O$ )  $\delta$  1.33 (3H, s), 4.14 (1H, s), 4.42 (1H, dd), 5.07 (1H, d), 5.40 (1H, d), 7.26~7.43 (3H, m), 7.52~7.72 (6H, m), 7.76 (1H, d); IR (KBr)  $cm^{-1}$  3411, 1746, 1605.

**1x**: 87% yield;  $^1H$  NMR ( $D_2O$ )  $\delta$  1.34 (3H, s), 1.58 (3H, s), 3.82 (3H, s), 4.24 (1H, s), 4.43 (1H, dd), 5.46 (1H, d), 5.49 (1H, d), 7.3~7.5 (2H, m), 7.7 (1H, s), 7.8~7.96 (2H, m), 8.0 (1H, s); IR (KBr)  $cm^{-1}$  3390, 1747, 1604.

**2g** was prepared from compound **8g** in 96% yield;  $^1H$  NMR ( $D_2O$ )  $\delta$  1.54 (3H, s), 1.65 (3H, s), 4.2 (1H, s), 4.56~4.60 (1H, m), 5.5~5.8 (4H, m), 7.1~7.3 (1H, m), 7.3~7.5 (2H, m), 7.6~7.8 (2H, m); IR (KBr)  $cm^{-1}$  3452, 1759, 1644.

**3** was prepared from compound **9a** in 93% yield;  $^1H$  NMR ( $D_2O$ )  $\delta$  1.42 (3H, s), 1.6 (3H, s), 2.5~2.6 (1H, m), 2.85~3.0 (1H, m), 4.18~4.3 (1H, m), 4.28 (1H, s), 4.35~4.5 (1H, m), 5.38 (1H, s), 5.48 (1H, s), 7.25~7.42 (2H, m), 7.42~7.6 (1H, m), 7.6~7.75 (1H, m).

#### Potassium 6 $\beta$ -(2-[Benzimidazolyl]-(*S*)-hydroxymethyl)penicillanate (**1a**)

A solution of **1g** (232 mg, 0.56 mmol) in 20 ml MeOH was cooled to  $-78^\circ C$  and treated with a saturated  $O_3$  in methylene chloride (15 ml, about 0.85 mmol) at  $-78^\circ C$ . The reaction was monitored by HPLC. Upon completion, the resulting mixture was quenched with dimethyl sulfide and evaporated to dryness. The residue was treated with water and ethyl acetate. The water layer was separated and freeze dried to give a yellow solid which was purified through medium pressure  $C_{18}$  column chromatography using 10% acetonitrile in water as eluent to afford compound **1a** (135 mg, 63% yield) as a white solid;  $^1H$  NMR ( $D_2O$ )  $\delta$  1.42 (3H, s), 1.63 (3H, s), 4.26 (1H, s), 4.30 (1H, dd), 5.43 (1H, d,  $J=4$  Hz), 5.43 (1H, d,  $J=10$  Hz), 7.3~7.4 (2H, m), 7.6~7.7 (2H, m);  $^{13}C$  NMR ( $D_2O$ )  $\delta$  27.0, 30.9, 56.2, 63.8, 64.8, 65.9, 73.0, 116.0, 116.1, 124.1, 153.9, 175.6, 176.1; IR (KBr)  $cm^{-1}$  3404, 1744, 1599.

#### Allyl 6,6-Dibromopenicillanate Sulfoxide

To a solution of allyl 6,6-dibromopenicillanate (7.98 g, 0.02 mol) in 140 ml of methylene chloride at  $0^\circ C$  was added dropwise a solution of *m*-chloroperbenzoic acid (4.2 g, 0.0206 mmol, 80% pure) in methylene chloride over 15 minutes. The ice-bath was removed and the mixture was stirred for an additional 30 minutes, then washed with saturated sodium bicarbonate to pH 7.5 and brine. The organic layer was dried and concentrated to give the title compound (7.523 g, 91% yield) as a yellow solid;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.5 (3H, s), 1.65 (3H, s), 4.65 (1H, s), 4.8 (2H, m), 5.2~6.1 (3H, m), 5.35 (1H, s).

#### Allyl 7,7-Dibromo-3-methylcephalosporanate

Allyl 6,6-dibromopenicillanate sulfoxide (4.23 g, 10.2 mmol) was dissolved in 100 ml xylene and treated with *p*-TsOH  $\cdot$   $H_2O$  (140 mg). The mixture was heated at reflux for 1 hour and xylene was removed under reduced pressure. The residue was diluted with ethyl acetate and saturated sodium bicarbonate and the organic layer was washed with brine, dried and concentrated to give a black oil. The oil was purified by silica gel column chromatography using chloroform as eluent to give 1.823 g (45%) of yellow oil;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  2.3 (3H, s), 3.3 (2H, s), 4.75 (2H, m), 6.25 (1H, s), 5.1~6.3 (3H, m).

#### Allyl 7-(2-[1-Vinylbenzimidazolyl]hydroxymethyl)-7-bromo-3-methylcephalosporanate

A solution of allyl 7,7-dibromo-3-methylcephalosporanate (1.67 g, 4.21 mmol) in 40 ml methylene chloride was cooled to  $-78^\circ C$  and treated with a 2.8 M solution of methylmagnesium bromide in ether (1.5 ml, 4.2 mmol). After stirring at  $-78^\circ C$  for 5 minutes, a solution of *N*-vinylbenzimidazole-2-carboxaldehyde (0.724 g, 4.2 mmol) in 10 ml of methylene chloride was added at  $-78^\circ C$ . The resulting mixture was stirred at that temperature for 30 minutes and quenched with saturated ammonium chloride. The organic layer was washed with brine, dried and concentrated to give 1.649 g (80%) of the title compound as a yellow glass, which was used directly for the next step.

#### Allyl 7-(2-[1-Vinylbenzimidazolyl]hydroxymethyl)-3-methylcephalosporanate **11**, **12** and **13**

Allyl 7-(2-[1-vinylbenzimidazolyl]hydroxymethyl)-7-bromo-3-methylcephalosporanate (1.649 g, 3.365 mmol) was dissolved in 40 ml of benzene, treated with tri-*n*-butyl tin hydride (8.9 ml, 33.65 mmol) and the resulting mixture was heated at reflux for 4 hours. Benzene was removed and the residue was

treated with acetonitrile and hexane. The acetonitrile layer was separated, washed three more times with hexane and concentrated to dryness to give a yellow oil which was subjected to silica gel column chromatography using 10% ethyl acetate in chloroform as eluent to give 60 mg of 7 $\alpha$ -isomer **13**, 155 mg of (7 $\beta$ ,9S)-isomer **11**, and a mixture of **11**, **12**, and **13** (450 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>) for **11**:  $\delta$  2.04 (3H, s), 3.1 (2H, ABq), 4.68 (1H, dd), 4.7 (2H, m), 4.97 (1H, d,  $J=4$  Hz), 5.1~5.7 (5H, m), 5.9 (1H, m), 7.25 (3H, m), 7.5 (1H, m), 7.7 (1H, m); <sup>1</sup>H NMR (CDCl<sub>3</sub>) for **13**:  $\delta$  2.02 (3H, s), 3.3 (2H, ABq), 3.80 (1H, dd,  $J=2$  and 4 Hz), 4.68 (1H, d,  $J=5$  Hz), 4.98 (1H, d,  $J=2$  Hz), 5.1~5.7 (4H, m), 5.52 (1H, d,  $J=4$  Hz), 5.86 (1H, m), 7.08 (1H, dd), 7.24 (2H, m), 7.48 (1H, m), 7.7 (1H, m).

#### Potassium (7R,9S)-(2-[1-Vinylbenzimidazolyl]hydroxymethyl)-3-methylcephalosporanate (**4**)

A solution of **11** (152 mg, 0.37 mmol) in 2 ml of ethyl acetate was treated with Pd(PPh<sub>3</sub>)<sub>4</sub> (15 mg), PPh<sub>3</sub> (15 mg) and potassium 2-ethylhexanoate (0.5 M solution in ethyl acetate, 0.74 ml, 0.37 mmol), and stirred at room temperature for 1 hour. The mixture was treated with ether to form a precipitate and filtered to give 98 mg (65%) of yellow solid which was purified through C<sub>18</sub> silica gel column chromatography using MPLC and eluting with 15% acetonitrile in water to give 38 mg of **4** as a yellow solid; <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  1.8 (3H, s), 2.93 (2H, ABq,  $J_{AB}=18$  Hz), 4.53 (1H, dd,  $J=5$  and 8 Hz), 4.98 (1H, d,  $J=5$  Hz), 5.55 (1H, d,  $J=8$  Hz), 5.55 (1H, d,  $J=9$  Hz), 5.7 (1H, d,  $J=13$  Hz), 7.21 (1H, dd,  $J=13$  and 9 Hz), 7.4 (2H, m), 7.7 (2H, m); IR (KBr) cm<sup>-1</sup> 3373, 1744, 1643, 1592.

#### Benzimidazole *N*-Oxide

Formic acid (12.3 ml, 0.32 mol) was added to acetic anhydride (25 ml, 0.26 mol) at 0°C and then warmed to 60°C for 2 hours, cooled to room temperature and treated with 20 ml of THF. A solution of *o*-nitroaniline (13.8 g, 0.1 mol) in 40 ml of THF was added to the resulting anhydride solution and stirred at room temperature overnight. Solvents were removed under reduced pressure to give 16.723 g of *o*-formylnitroaniline as a yellow solid. The solid was dissolved in 300 ml EtOH and treated with ammonium hydroxide (20.4 ml) and H<sub>2</sub>S was bubbled into the reaction mixture for 2 hours at 0°C. The resulting mixture was warmed to room temperature, stirred overnight and concentrated to dryness to give a yellow solid which was washed with ethyl acetate to give a white solid (10.5 g, 78% overall yield); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  7.06~7.22 (2H, m), 7.4 (1H, d), 7.54 (1H, d), 8.18 (1H, s).

#### 1-Methoxybenzimidazole

A 50% NaH (1.397 g, 29 mmol) was added portionwise to a solution of benzimidazole *N*-oxide (4.2 g, 31.3 mmol) in 50 ml DMF. After stirring for 30 minutes, methyl iodide (1.95 ml, 31.3 mmol) was added and the mixture was stirred at room temperature overnight. DMF was evaporated and the residue was quenched with water, adjusted to pH 2, and extracted with ethyl acetate. The water layer was adjusted to pH 12 and extracted with ethyl acetate. This organic layer was dried and concentrated to give an oil which was purified through silica gel column chromatography to give 2.578 g (56%) of desired 1-methoxybenzimidazole as a yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  4.16 (3H, s), 7.26~7.32 (2H, m), 7.47 (1H, d), 7.75 (1H, d), 8.06 (1H, s).

#### 1-Methoxy-3-methylbenzimidazolium Methanesulfonate

A solution of 1-methoxybenzimidazole in 25 ml acetonitrile was treated with methyl methanesulfonate (0.57 ml, 6.76 mmol) and heated to reflux for 2 hours. Solvent was evaporated and the residue was treated with ether, stirred for 30 minutes, and filtered to give 1.05 g (60% yield) of brown solid which was used directly for the next reaction.

#### Sodium 6 $\beta$ -(2-[1-Methylbenzimidazolyl]amino)penicillanate (**5**)

6 $\beta$ -Aminopenicillanate (432 mg, 2 mmol) was dissolved in 4 ml of pH 7 phosphate buffer, treated with sodium bicarbonate (0.168 g, 2 mmol) and stirred for 10 minutes. 1-Methoxy-3-methylbenzimidazolium methanesulfonate (0.516 g, 2 mmol) was added to the reaction mixture and stirred at room temperature for 6 hours. Precipitate formed and was filtered, washed with ice-water and dried *in vacuo* to give 147 mg of white solid. The solid was dissolved in 4 ml of water and sodium bicarbonate was added to pH 7.5. The solution was purified through C<sub>18</sub> column chromatography using MPLC and eluting with 10%

acetonitrile in water to give 52 mg of **5** as a white solid;  $^1\text{H NMR}$  ( $\text{DMSO-}d_6$ )  $\delta$  1.44 (3H, s), 1.58 (3H, s), 3.56 (3H, s), 3.87 (1H, s), 5.40~5.44 (2H, m), 6.94~7.4 (4H, m).

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