SYNTHESIS OF 5,6-*cis*-PENEMS

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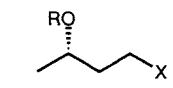
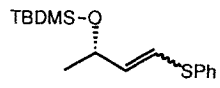
Although the synthesis of naturally occurring 5,6-*cis*-carbapenem antibiotics such as carpetimycins[1] has been extensively studied[2], synthesis of 5,6-*cis*-penem compounds have not been so extensively investigated. A 5,6-*cis*-penem has been obtained as a minor product in the synthesis of thermodynamically stable 5,6-*trans*-penem by intramolecular Wittig reaction[3], and another report described that a kinetically controlled intramolecular substitution reaction at C-4 of azetidinone[4] afforded *cis*-penem. We have observed an effective photoisomerization of (5*R*,6*S*)-5,6-*trans*-penems to thermodynamically unstable and biologically inactive (5*S*,6*S*)-5,6-*cis*-penems *via* inversion of C-5 configuration[5]. This suggests that (5*R*,6*R*)-5,6-*cis*-penem derivatives can be obtained when (5*S*,6*R*)-5,6-*trans*-penem derivatives are isomerized at C-5 by photoirradiation. We herein wish to describe a synthesis of biologically active (5*R*,6*R*)-5,6-*cis*-penems applying a photoisomerization reaction to (5*S*,6*R*)-5,6-*trans*-penem derivatives which were prepared from (4*S*)-4-acetoxyazetidinone (**7**) derived from (*S*)-1,3-butanediol by use of the previously reported method[6,7].

Starting from (*S*)-1,3-butanediol (**1**), (3*R*,4*S*,5*S*)-4-acetoxyazetidinone (**7**) was synthesized by 7 steps involving a coupling reaction of chlorosulfonyl isocyanate (CSI) with vinylsulfide (**5**) as key step[6,7]. Tosylation of butanediol (**1**) with tosylchloride (1.1 equiv) and lutidine (2.1 equiv) gave the monotosylate (**2**). This tosylate (**2**) was converted to phenyl sulfide (**3**) by treatment with sodium phenylsulfide in THF, followed by protection of the hydroxy group by the *tert*-butyldimethylsilyl (TBDMS) group. Chlorination of **4** by *N*-chlorosuccinimide (1.5 equiv) in CCl_4 at room temperature followed by dehydrochlorination by treatment with lithium carbonate (1.5 equiv) lithium iodide (1 equiv) and lithium perchlorate (1 equiv) in DMF afforded a mixture of *cis*/*trans* isomers (**5**) in 1 : 2.5 ratio. This mixture was then reacted with CSI (1.1 equiv) in diisopropyl ether at room temperature for 2 hours to give a mixture of diastereomeric (3*R*,4*S*,5*S*) and

Scheme 1.



1 R=H X=OH
2 R=H X=OTs
3 R=H X=SPh
4 R=TBDMS X=SPh



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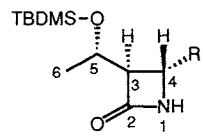
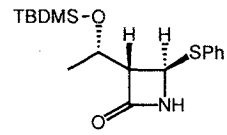
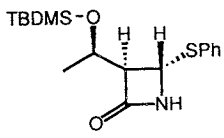


6a R=SPh
7 R=OAc



6b



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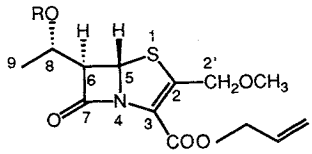
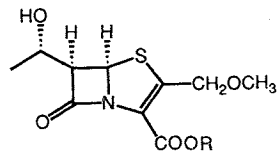
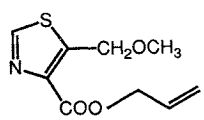


8 R=TBDMS
9 R=H



10 R=Allyl
12 R=H



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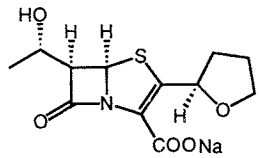
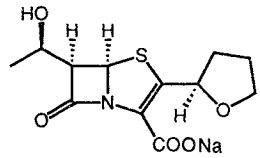


13



14

(3*S*,4*R*,5*S*)-4-phenylthioazetidinone (**6a** and **6b**) in 2:1 ratio after reductive workup with benzenethiol and pyridine in acetone. Washing this mixtute with *n*-hexane to remove a minor diastereoisomer (**6b**) and recrystallization from *n*-hexane gave the pure (3*R*,4*S*,5*S*)-compound (**6a**), $[\alpha]_D$ −63.6° (*c* 0.332, $CHCl_3$). Treatment of phenylthioazetidinone (**6a**) with cupric acetate[7] in acetic acid at reflux for 1 hour povided the desired (3*R*,4*S*,5*S*)-4-acetoxyazetidinone (**7**). Overall yield of the acetoxyazetidinone (**7**) from butanediol (**1**) was about 30%.

This acetoxyazetidinone (**7**) was then converted to 5*S*,6*R*,8*S*-penem compounds by use of a conventional method[6,8]. Treatment of **7** with sodium methoxyacetyl thiolate in aqueous acetone, and subsequent treatment with allyl oxallyl chloride (1.1 equiv) gave the oxamate derivative which was heated with triethyl phosphite in xylene at 140°C to give (5*S*,6*R*,8*S*)-2-methoxymethyl penem (**8**) in 40% yield, which showed a characteristic coupling constant (J=1 Hz) between C-5 and C-6 protons for *trans*-penem structure. In this reaction, no thermal isomerization was observed in contrast to the case of 2-alkylthiopenem compounds[3], suggesting an important role of the alkylthiol group attached to C-2 to assist thermal opening of the 5-membered ring. After deprotection of the alcohol by treatment with tetra-*n*-butylammonium fluoride in THF, a solution of the compound **9** in ethyl acetate (2 mM) was irradiated by use of high pressure UV lamp (Hanovia) through Pyrex filter[5] for 50 minutes to afford the isomerized 5,6-*cis*-penem (**10**) together with unchanged *trans*-penem (**9**) in 2:1 ratio in good yield and a minor amount of further degradated thiazole compound **11** (<5%)[5]. Further irradiation increased the *cis*/*trans* ratio, but the yield was reduced because of a rapid degradation of *cis*-penem to compound **11**. Then, removal of the allyl group of 5,6-*cis*-penem (**10**) by treatment with tetrakistriphenylphosphine palladium[9] and sodium 2-ethylhexanoate in ethyl acetate provided the carboxylic acid (**12**). IR (ν_{max} cm^{-1} 3466, 1782, 1697) and UV (λ_{max} nm 303) spectra, and FAB-MS (m/z 260, $(M+H)^+$) of the compound **12**, indicat-

Table 1. *In vitro* activity of *cis* and *trans* penem derivatives.

Organism	MIC (μg/ml)				
	12	**13**	**14**	SUN5555	*trans*-**12**[a]
Staphylococcus aureus 209P JC-1	1.56	0.78	3.13	0.10	0.10
S. aureus Smith	1.56	0.78	6.25	0.10	—
S. aureus S-14	3.13	1.56	6.25	0.39	0.20
S. epidermidis ATCC 14990	0.78	0.78	3.13	0.10	—
Bacillus subtilis ATCC 6633	0.20	0.39	0.39	<0.025	0.05
Micrococcus luteus ATCC 9341	0.20	0.20	3.13	0.05	0.05
Escherichia coli NIHJ JC-2	1.56	0.78	6.25	0.78	0.39
E. coli KC-14	0.78	0.39	1.56	0.20	0.20
E. coli KC-14/RGN823	50	50	25	0.20	0.20
E. coli KC-14/Rms213	1.56	1.56	6.25	0.78	0.78
E. coli KC-14/RGN238	1.56	1.56	6.25	0.39	0.39
Klebsiella pneumoniae PCI 602	1.56	3.13	3.13	0.20	0.39
K. pneumoniae KC-1	1.56	0.78	6.25	0.39	—
Serratia marcescens IAM 1136	25	6.25	25	3.13	1.56
S. marcescens GN 10857	>50	>100	>100	50	25
Proteus mirabilis GN 79	6.25	6.25	25	3.13	0.78
P. vulgalis GN 7919	>50	50	6.25	0.78	0.39
P. vulgalis GN 76	50	25	25	6.25	3.13
Morganella morganii IFO 3848	6.25	1.56	12.50	0.78	1.56
Providencia rettgeri GN 624	>50	25	50	3.13	—
Salmonella typhi O 901	0.78	0.78	3.13	0.10	0.20
Citrobacter freundii GN 7391	>50	>100	>100	25	6.25
Enterobacter cloacae 91	12.50	6.25	6.25	0.39	0.39
Pseudomonas aeruginosa No. 12	>50	>100	>100	>100	>100
P. aeruginosa PAO-1	>50	>100	>100	>100	—
Acinetobacter calcoaceticus AC 54	6.25	6.25	100	12.50	12.50

Medium: Sensitivity disk agar, inoculum size: 10^6 cfu/ml.

[a] (5*R*,6*S*,8*R*)-5,6-*trans* isomer of **12**.

ed penem structure, and its characteristic coupling constant ($J=4$ Hz) between C-5 and C-6 protons in its ^{1}H NMR and the positive Cotton effect (λ_{max} nm 250, $\theta=1.75\times10^5$) in the CD spectrum[5] confirmed its 5*R*,6*R* configuration.

As described above, this synthetic route offers a new and convenient approach to the synthesis of *cis*-penem derivatives. Thus, we could synthesize the other derivatives such as **13** and **14**, the latter of which was derived from (3*R*,4*S*,5*R*)-4-phenylthioazetidinone (**15**)[6] in similar fashion.

Penem derivatives (**12**, **13** and **14**) showed good activities against various Gram-positive and Gram-negative bacteria. However, these were less active than the corresponding (5*R*,6*S*,8*R*)-5,6-*trans* isomers[6] as shown in the Table 1.

Acknowledgments

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