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Synthesis and Antibacterial Activity of 2α-Functionalized 1β-Methylcarbapenems Related to KR-21012

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Abstract—The 2α-functionalized 1β-methylcarbapenems **3** were synthesized from the 2-formyl 1β-methylcarbapenem intermediate **5**. The best compound in the series of 2α-(hydroxy)alkylcarbapenems, KR-21012, displayed well balanced in vitro and in vivo activity as a parent compound of oral carbapenem.

Introduction

Since the discovery of (+)-thienamycin[1,2] in the early 1980s, the carbapenems have attracted considerable attention as the most promising β-lactam antibiotics due to their chemical and metabolic stabilities as well as their potent antimicrobial activities. For parenteral use, imipenem,[3] panipenem,[4] and meropenem[5] have been launched on the market and sanfetrinem cilexetil,[6] CS-834[7], DZ-2640[8] and L-084[9] are now under clinical stage for oral administration. Our objective has been to find a new oral carbapenem with equal or better activity than that of sanfetrinem cilexetil or faropenem.[10]

It has been demonstrated that good antibacterial potency and stability to DHP-1 are combined in the related sanfetrinem (**1**) and faropenem (**2**) bearing sp^3-hybridized carbon atom at C-2α position. These results prompted us to design 1β-methylcarbapenems having acyclic C-2α functionalized substitutents. As part of a series of investigations,[11] this paper describes the synthesis and antibacterial activity of 2α-functionalized 1β-methylcarbapenems **3** related to KR-21012.[12]

Synthesis

The 2α-functionalized 1β-methylcarbapenems were synthesized from 2-hydroxymethylcarbapenem[13,14] (**4**) as shown in Scheme 1.

2-Hydroxymethylcarbapenem (**4**) was oxidized with MnO_2 to give 2-formylcarbapenem (**5**)[15,16] which was stable in a refrigerator for weeks. The aldehyde **5** was reacted with various organometallic reagents, RM(M = Mg, Li), to provide a diastereomeric mixture of 2α-(hydroxy)alkylcarbapenems(**6*R***, **6*S***), which were readily separable by flash chromatography. The ratio of **6*R*** and **6*S*** was influenced by the steric requirement around the nucleophilic center as shown in Table 1 and the assignment of the absolute stereochemistry of **6*R*** and **6*S*** could be made by the modified Mosher's method.[17,18]

t-Butyldimethylsilyl group was removed by the treatment with *n*-Bu_4NBr in the presence of KF and AcOH.

Subsequent removal of allyl ester with $Pd(PPh_3)_4$ and sodium 2-ethylhexanoate(SEH) provided the corresponding 2α-(hydroxy)alkylcarbapenems(**3*R*** and **3*S***), after purification by reverse phase column chromatography.

Because of the well-balanced antibacterial activity of 2α(*R*)-(hydroxy)isopropylmethycarbapenem (**3Rb**), compound **6Rb** was transformed to the corresponding methoxy, acetoxy and carbamoyloxy derivatives, respectively, as shown in Scheme 2.

Reaction of **6Rb** with methyltriflate in the presence of KHMDS provided 2α(*R*)-methoxy derivatives **8**. Acetylation of **6Rb** with acetic anhydride gave 2α(*R*)-acetoxy derivative and treatment of **6Rb** with trichloroacetyl isocyanate followed by methanolysis in the presence of silicagel afforded the corresponding carbamoyl derivative **9**. Desilylation of these derivatives with KF-*n*Bu_4NBr, followed by allyl ester deprotection with

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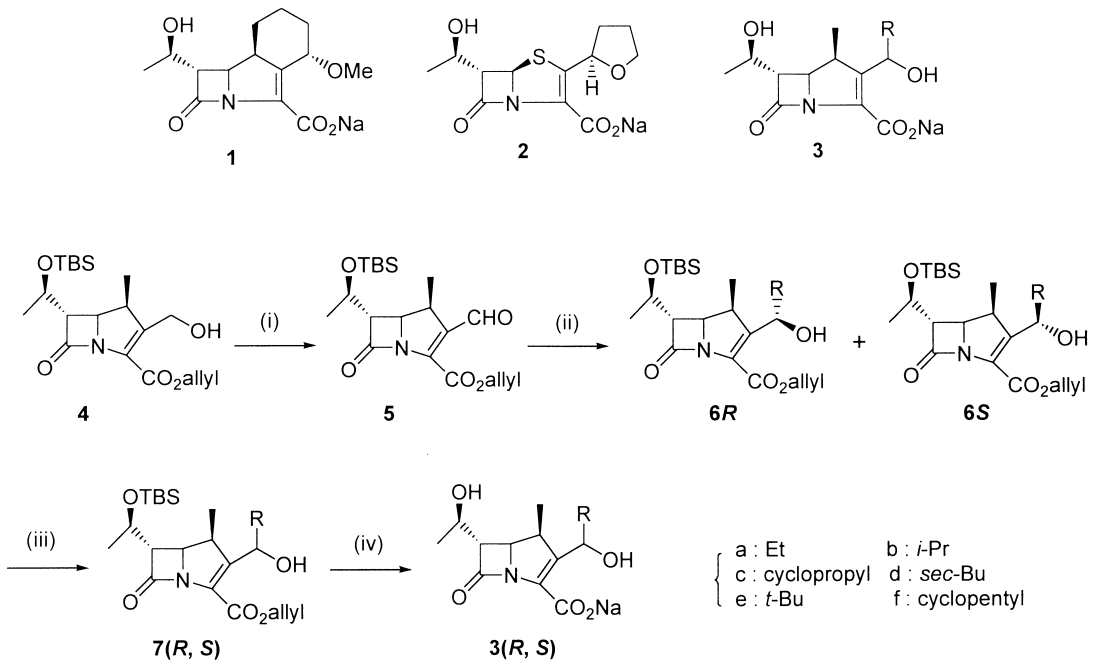
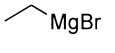
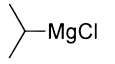
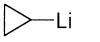
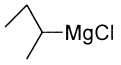
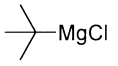
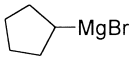


Scheme 1. Reagents and reaction conditions; (i) MnO_2, CH_2Cl_2, reflux (70%); (ii) RMgX or RLi, THF or Et_2O (50–75%); (iii) KF, *n*-Bu_4NBr, →KF, *n*-Bu_4NBr, AcOH, THF (80%); (iv) $Pd(PPh_3)_4$, SHE, THF (62%).

Table 1. Diastereomer ratio of 2α-(hydroxy)methylcarbapenems (**6*R*** and **6*S***) in organometallic addition reaction

Entry	RM	Method[a]	Solvent	Ratio (**6*R*:6*S***)	Yield (% isolated)
1		A	THF	60:40	72
2		A	THF	84:16	68
3		B	Et_2O	75:25	60
4		A	THF	87:13	65
5		A	THF	98:2	63
6		A	THF	79:21	70

[a]Method A: To a solution of **5** in THF with cooling at −78 °C, was added organometallic reagent (RM). The mixture was stirred for 1 h at −78 °C. Method B: To a suspension of lithium metal in Et_2O at 0 °C was added cyclopropylbromide. The mixture was stirred for 2 h at room temperature, and then treated with **5** in Et_2O for 1 h at −78 °C.

$Pd(PPh_3)_4$, gave the methoxy, acetoxy and carbamoyloxy carbapenems(**10**, **11**, **12**), respectively.

Biological Properties

In vitro antibacterial activity and DHP-1 stability of the 2α-functionalized 1β-methylcarbapenems are shown in Table 2. MIC was determined by agar dilution method using Mueller–Hinton. Purified porcine renal enzyme was used for mesurement of DHP-1 stability, which is represented as the relative rate of hydrolysis compared to imipenem(rate = 100). Both sanfetrinem and meropenem are listed as reference drugs.

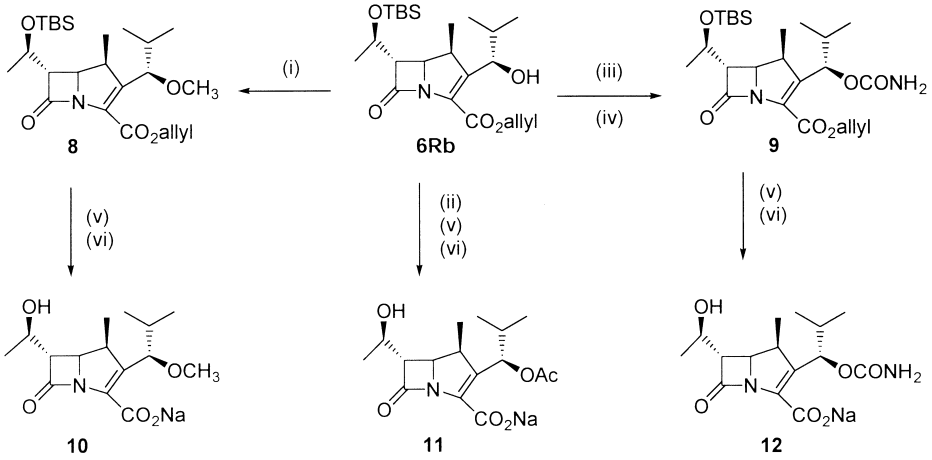
Most of the 2α-(hydroxy)alkylcarbapenems (**3**) are exhibited potent antibacterial activity except against *P. aeruginosa*. Comparison of stereoisomers (**3a-1** and **3a-2**, **3b-1**[19] and **3b-2**[20]) indicates that the *R*-isomer shows better activity than the *S*-isomer. The 2α(*R*)-(hydroxy)isopropylmethyl (**3b-2**) (KR-21012) and 2α(*R*)-(hydroxy) cyclopropylmethyl (**3c-2**)[21] (KR-21011) derivatives showed well-balanced activity similar to that of sanfetrinem.

Changing the hydroxy group of KR-21012 to the methoxy, acetoxy and carbamoyloxy group was examined in the hope of improving activity. However, none of these derivatives(**10**, **11**, **12**) showed better activity than the parent compound, KR-21012.

In order to select the best parent compound for an oral candidate, pharmacokinetic study and urinary recovery of KR-21011 and KR-21012 were determined after subcutaneous administration to mice as shown in Table 3.

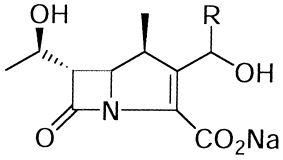
2α(*R*)-(Hydroxy)isopropylmethylcarbapenem (**3b-2**) (KR-21012) showed superior profiles than the 2α(*R*)-(hydroxy)cyclopropylmethyl derivative (**3c-2**) (KR-21011). Urinary recovery of KR-21012 was better than that of sanfetrinem.

The in vivo protective activities of KR-21011 and KR-21012 against *S. pyogenes* 77A, *E. coli* 078 and *En. cloacae* P in ICR mice were investigated. Compounds were administered subcutaneously 1 h after intraperitonial infection with one to five times the minimum



Scheme 2. Reagents and reaction conditions: (i) KHMDS, MeOTf, THF, −78 °C (54%); (ii) Ac_2O, DMAP, pyridine (85%); (iii) $Cl_3CCONCO$; (iv) silicagel, MeOH (75%); (v) KF, *n*-Bu_4NBr, AcOH, THF (80%); (vi) $Pd(PPh_3)_4$, 5EH, THF (61%).

Table 2. In vitro antibacterial activity (MIC, μg/ml) and DHP-1 stability of 2α-functionalized carbapenems



Compound *R*										Sanfe trinem	Mero penem
Strain[a]	**3a-1** (*S*)	**3a-2** (*R*)	**3b-1** (*S*)	**3b-2**[b] (*R*)	**3c-1** (*S*)	**3c-2**[c] (*R*)	**3d** (*R*)	**3e** (*R*)	**3f** (*R*)	(*S*)	
S.p. 77A	0.049	0.625	0.025	0.007	0.098	0.007	0.013	0.049	0.013	0.007	0.013
S.f. MD	12.50	3.125	12.50	1.563	3.125	0.781	1.563	12.50	0.781	1.563	6.250
S.a. SG511	0.391	0.098	0.781	0.098	0.195	0.049	0.098	0.391	0.098	0.098	0.013
S.a. 285	0.391	0.098	0.781	0.098	0.781	0.049	0.098	0.391	0.098	0.049	0.195
E.c. 078	0.391	0.098	1.563	0.049	1.563	0.098	0.195	0.781	0.195	0.049	0.013
E.c. 1507E	0.391	0.098	0.391	0.049	0.195	0.049	0.195	0.781	0.195	0.195	0.025
P.a. 1771	100	100	100	100	100	100	100	100	100	25.0	0.361
P.a. 1771 M	6.250	1.563	1.563	0.781	3.125	1.563	1.563	6.250	0.781	0.391	0.049
S.t.	0.781	0.391	0.781	0.098	1.563	0.098	0.195	1.563	0.195	0.195	0.049
K.o. 1082 E	12.50	3.125	25.00	1.563	6.250	0.781	3.125	12.50	3.125	1.563	0.049
K.a. 1522 E	0.781	0.391	12.50	0.391	0.781	0.195	3.125	6.250	1.563	0.391	0.049
En.c. P99	0.781	0.781	12.50	1.563	0.781	0.781	3.125	6.250	6.250	3.125	0.025
DHP-1 stability	ND	ND	ND	21	ND	38	ND	ND	ND	20	32

[a]*S.p.* = *Streptococcus pyogenes*; *S.a.* = *Staphylococus aureus*; *E.c.* = *Escherichia coli*; *P.a.* = *Pseudomonas aeruginosa*; *S.t.* = *Salmonella typhimirium*; *K.o.* = *Klebsiella oxytoca*; *K.a.* = *Klebsiella aerogenes*; *En.c.* = *Enterobacter cloacae*.
[b]KR-21012.
[c]KR-21011.

Table 3. Phamacokinetic parameters[a] and urinary recovery of selected carbapenems

Parameter	KR-21011	KR-21012	Sanfetrinem	Meropenem
C_{max} (μg/mL)	18.1	24.98	28.79	7.6
T_{max}	0.17	0.25	0.37	0.21
$T_{\frac{1}{2}}$ (h)	0.31	0.69	0.55	0.24
AUC (μg/mL)	6.86	20.90	27.39	3.29
UR[b] (%)	14.26	25.14	20.49	—

[a]At a single subcutaneous administration of 40 mg/kg in mice ($n = 4$).
[b]Urinary recovery by disk method using *S. pyogenes* 77A ($n = 4$, 0–24 h).

Table 4. In vivo protective activity[a] of selected carbapenems

Strain	KR-21011	KR-21012	Sanfetrinem	Meropenem
S. pyogenes 77A	7.94	1.19	1.46	4.60
E. coli 078	23.05	1.30	3.13	1.24
E. cloacae P	12.57	1.37	1.18	ND

[a]PD_{50} (mg/kg) with 95% confidence limits.

lethal dose. Activity was calculated by the probit method from the survival rates for 5 days after infection. Compound KR-21012 displayed similar protective activity with sanfetrinem as shown in Table 4.

Through these experiments KR-21012, which has α(*R*)-(hydroxy)isopropylmethyl group at C-2 position, has been selected as the best parent compound for the following prodrug approach and further evaluation.

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19. ^{1}H NMR of **3b-1**; (200 MHz, D_2O) δ 4.07(m, 1H), 3.96(dd, J=2.5, 9.0 Hz, 1H), 3.77(d, J=6.5 Hz, 1H), 3.20(dd, J=2.5, 6.5 Hz, 1H), 2.92(m, 1H), 1.76(m, 1H), 1.13(d, J=6.1 Hz, 3H), 1.00(d, J=7.2 Hz, 3H), 0.77(d, J=6.8 Hz, 6H); ^{13}C NMR (50 MHz, D_2O) δ 177.7, 169.4, 146.6, 134.3, 74.1, 66.2, 57.8, 39.7, 33.3, 21.1, 19.5, 19.3, 17.9; IR (D_2O) 3435, 2958, 1735, 1636, 1380, 1324 cm^{-1}; HRMS (EI, 70 eV) calcd for $C_{14}H_{20}NaO_5$ 305.1239, found 305.1237.
20. ^{1}H NMR of **3b-2** (KR-21012); (200 MHz, D_2O) δ 4.55(d, J=10.0 Hz, 1H), 4.45(d, J=8.9 Hz, 1H), 4.01–4.11(m, 1H), 3.97(dd, J=2.8, 10.0 Hz, 1H), 3.21(dd, J=2.8, 6.5 Hz, 1H), 2.96–3.08(m, 1H), 1.62–1.77(m, 1H), 1.11(d, J=6.2 Hz, 3H), 1.00(d, J=7.2 Hz, 3H), 0.82(d, J=6.7 Hz, 3H), 0.62(d, J=6.7 Hz, 3H); ^{13}C NMR (50 MHz, D_2O) δ 177.6, 169.4, 146.5, 134.3, 74.1, 66.0, 57.8, 57.7, 39.7, 33.1, 21.0, 19.4, 19.3, 17.9; IR (D_2O) 3390, 2965, 1733, 1600, 1412 cm^{-1}; HRMS (EI, 70 eV) calcd. for $C_{14}H_{20}NaO_5$ 305.1239, found 305.1237.
21. ^{1}H NMR of **3c-2** (KR-21011); (200 MHz, D_2O) δ 4.18–4.23(m, 2H), 4.14(d, J=3.2 Hz, 1H), 3.37(dd, J=2.2, 10.4 Hz, 1H), 3.23(d, J=4.1 Hz, 1H), 2.33–2.53(bs, 1H), 1.30(d, J=6.3 Hz, 3H), 1.24(d, J=7.4 Hz, 3H), 1.01(m, 1H), 0.65(m, 1H), 0.33–0.54(m, 2H), 0.09(m, 1H).