Synthesis of J-111,347, a Novel 1β-Methylcarbapenem with Broad-spectrum Antibacterial Activity

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Received October 26, 1999; accepted November 27, 1999

Synthesis of J-111,347 (1),[1] a new 1β-methylcarbapenem with broad-spectrum antibacterial activity including that against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, was achieved *via* diastereoselective preparation of a side-chain thiol 3 from an optically active (*R*)-3,4-dihydroxybutanal 4.

Key words J-111,347; carbapenem; MRSA; *P. aeruginosa*; diastereoselective preparation

Several 1β-methylcarbapenems possessing antibacterial activities against MRSA have been reported, although these did not show any appreciable anti-pseudomonal activity.[2] Carbapenems with activity against MRSA and *P. aeruginosa* would be useful for monotherapy in immunocompromised patients with a high risk of polymicrobial infections and would also offer cost-benefit advantages considering the relatively high costs of combination therapy that includes broad-spectrum antibiotics plus vancomycin.

Recently, we identified J-111,347 (**1**) as a new class of 1β-methylcarbapenems since **1** exhibited a broad antibacterial spectrum against MRSA and *P. aeruginosa*.[1] **1** and vancomycin had MIC (μg/ml) values of 0.78 and 0.78 against *S. aureus* pMS/Smith (an MRSA strain), respectively. Also **1** and imipenem had MIC (μg/ml) values of 0.39 and 1.56 against *P. aeruginosa* AK109, respectively. The *trans*-(3*S*,5*R*) pyrrolidinylthio structure of the C-2 side chain of **1** is unique, since the known pyrrolidinylthio-1β-methylcarbapenems such as meropenem, BO-2727, and S-4661 possess *cis*-(3*S*,5*S*) pyrrolidinylthio side chains, which were thought to be indispensable for potent antibacterial activity.[3,4] An aminomethylphenyl group directly attached to the pyrrolidine ring in the *trans*-configuration might play an important role in the remarkable antibacterial activities of **1** against both MRSA and *P. aeruginosa*. In this paper, we describe diastereoselective synthesis of the side-chain thiol **3**, followed by conversion to **1** (Fig. 1).

Aldol reaction of optically active (*R*)-3,4-dihydroxybutanal **4**[5] with substituted phenyllithium yielded an inseparable diastereomeric mixture of alcohols (**5**(*S*) : **5**(*R*)=4 : 3) in 88% yield. To obtain the desired isomer **5**(*S*), we performed diastereoselective reduction of ketone **6** which was formed by the oxidation of **5** with tetrapropylammonium perruthenate (TPAP)-4-methylmorpholine *N*-oxide (NMO) combination in good yield. It is well known that hydride reduction of β-hydroxy- or β-alkoxy-ketones proceeds diastereoselectively in the presence of Lewis acid to provide a 1,3-*syn*-diol system *via* chelating intermediates.[6] Based on this information, ketone **6** was reduced under various conditions with or without Lewis acids, as shown in Table 1. Reduction with $NaBH_4$ did not provide acceptable diastereoselectivity, regardless of the temperature and the presence of Lewis acids such as LiI, $CeCl_3$, $MgCl_2$, and $SmCl_3$. Reduction with $Zn(BH_4)_2$ at low temperature (−78 °C) resulted in good selectivity with moderate yield (entry 2, 76%de, 60% yield). Under the conditions of the $LiAlH_4$–LiI system,[7] good selectivity and acceptable yield (entry 5, 90%de, 76% yield) were obtained by using 10 mol of LiI at −78 °C. When less LiI was used, both selectivity and yield were decreased (entry 3, 4). Subsequently, the optically active alcohol **5**(*S*) was converted to a carbapenem **1**, as shown in Chart 2. The secondary hydroxyl group of **5**(*S*) was substituted with sodium azide *via* its mesylate. Subsequent phosphine reduction of azide and protection of the resulting amino group with allyloxycarbonyl (Alloc) chloride afforded an Alloc-amine **7**. Removal of the *tert*-butyldimethylsilyl (TBS) group of **7** with tetra-*n*-butylammonium fluoride (TBAF) and subsequent introduction of the azide group gave **8** in 91% yield. The azide **8** was transformed to a diol **9** in 78% yield by reduction of the azide, Alloc-protection of the resulting primary amine, and deprotection of the acetonide group under acidic conditions (*p*-TsOH, MeOH).[10] Selective tosylation of the primary hydroxyl group of the 1,2-diol **9** proceeded in good yield (TsCl, triethylamine [TEA], 4-[dimethylamino]pyridine [DMAP], [80%]) to give a tosylate **10**. When **10** was treated under basic conditions, pyrrolidine ring formation did not

Table 1. Diastereoselective Reduction of **6**

Entry	Reagent	Additive (equiv.)	Solvent	Temp. (°C)	Yield[a] (%)	Ratio of **5**(*S*) and **5**(*R*)[b]
1	$NaBH_4$	None	MeOH	0	47	48 : 52
2	$Zn(BH_4)_2$	None	Et_2O	−78	60	88 : 12
3	$LiAlH_4$	LiI (2)	Et_2O	−78	44	76 : 24
4	$LiAlH_4$	LiI (5)	Et_2O	−78	51	90 : 10
5	$LiAlH_4$	LiI (10)	Et_2O	−78	76	95 : 5

a) Isolated yield as a mixture of **5**(*R*) and **5**(*S*). *b*) Determined by HPLC (DAICEL CHIRALPAK AS).[8]

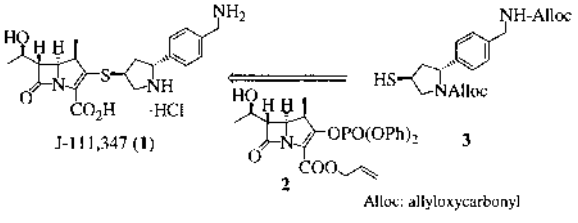

Fig. 1

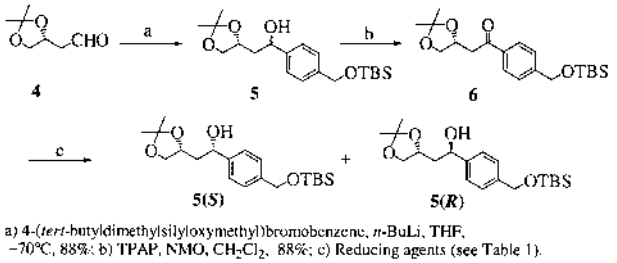

Chart 1

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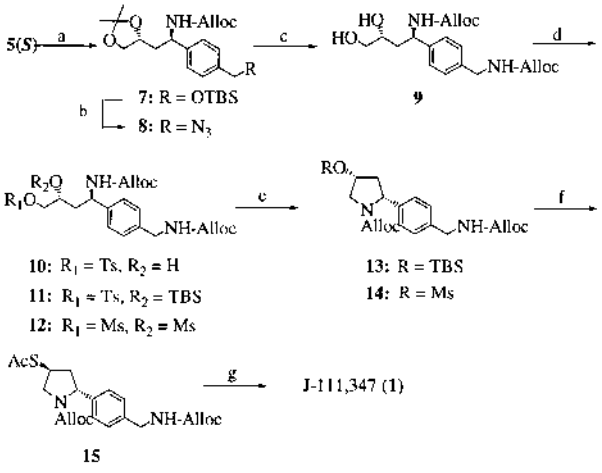

a) i) TEA, MsCl, CH_2Cl_2, 0°C; ii) NaN_3, DMF, 50°C, iii) PPh_3, THF-H_2O, room temperature; vi) TEA, Alloc-Cl, THF, 0°C, 61%; b) i) *n*-Bu_4NF, THF , 0°C; ii) TEA, MsCl, CH_2Cl_2, 0°C; iii) NaN_3, DMF, room temperature, 91%; c) i) PPh_3, THF-H_2O, room temperature; ii) TEA, Alloc-Cl, THF, 0°C; iii) *p*-TsOH, MeOH, room temperature, 78%; d) TEA, MsCl, CH_2Cl_2, 0°C; e) *t*-BuOK, THF, −20°C, 97%; f) AcSK, DMF, 65°C, 87%; g) i) NaOH, MeOH, 0°C; ii) *i*-Pr_2NEt, **2**, CH_3CN, 0°C, 65%; iii) $(PPh_3)_2PdCl_2$, *n*-Bu_3SnH, H_2O, CH_2Cl_2, 72%.

Chart 2

take place to recover **10**, probably due to inactivation of the carbamate group by intramolecular hydrogen bonding. Therefore the secondary hydroxyl group of **10** was protected with a TBS group (TBS-Cl, imidazole, room temperature, 60%), giving **11** prior to the cyclization reaction. The desired pyrrolidine **13** was obtained in quantitative yield by treatment of **11** with *tert*-BuOK at −20 °C. Next, pyrrolidine ring formation was carried out using a dimesylate of the diol **9**. As expected, the dimesylate **12** was easily cyclized under the same conditions to afford 4-mesyloxypyrrolidine **14** (97% yield), which was then treated with potassium thioacetate in DMF at 70 °C to produce the thioacetate **15** (87% yield). Coupling reaction of the carbapenem enolphosphate **2**[11] and the thiol **3** derived by alkaline hydrolysis of the thioacetate **15** followed by deprotection of the coupling product[12] in the usual manner[13] afforded the carbapenem **1** in 72% yield.

In summary, an efficient method for the synthesis of J-111,347 (**1**), a new carbapenem showing broad-spectrum antimicrobial activity, was established *via* diastereoselective reduction of the ketone **6** and intramolecular cyclization of the dimesylate **12**.

Acknowledgment We are grateful to Ms. A. Dobbins, Merck & Co., for her critical reading of this manuscript.

References and Notes

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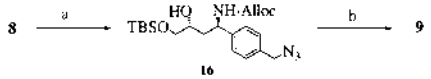
8) HPLC analysis: column, DAICEL CHIRALPAK AS (250×4.6 mm); detection, 254 nm; eluent, *n*-hexane/isopropanol=90 : 10; flow rate, 0.5 ml/min; t_R of **5**(*S*), 9.1 min; t_R of **5**(*R*), 8.6 min. The stereochemical structure of **5**(*R*) was determined by the advanced Mosher method with the corresponding MTPA ester.[9]
9) Ohtani I., Kusumi T., Kashman Y., Kakisawa H., *J. Am. Chem. Soc*., **113**, 4092—4096 (1991).
10) The diol **9** with high purity (>99%de) was obtained *via* separation of compound **16** on SiO_2 column chromatography.



a) i) *p*-TsOH, MeOH, room temperature; ii) TBS-Cl, imidazole, CH_2Cl_2, room temperature, 75%, iii) SiO_2 column chromatography; b) i) PPh_3, THF-H_2O, room temperature; ii) TEA, Alloc-Cl, 0°C; iii) HCl-MeOH, 92%

11) *a*) Berks A. H., *Tetrahedron*, **52**, 331—375 (1996); *b*) Deziel R., Endo M., *Tetrahedron Lett*. **29**, 61—64 (1988); *c*) Shih D. H., Baker F., Cama L., Christensen B. G., *Heterocycles*, **21**, 29—40 (1984).
12) The coupling product derived from the diol **9** (90%de) could be purified by separation of its diastereomer on SiO_2 column chromatography.
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14) Spectral data were obtained for new compounds.
5(*S*): $[\alpha]_D^{25}$ −27.4 (*c* 1.0, $CHCl_3$); IR λ_{max} (Nujol) 3461, 1257 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.92 (9H, s), 1.36 (3H, s), 1.44 (3H, s), 1.86 (1H, m), 1.97 (1H, m), 3.53 (1H, t, *J*=8.1 Hz), 4.03 (1H, dd, *J*=8.1, 5.9 Hz), 4.23 (1H, m), 4.70 (2H, s), 4.89 (1H, dd, *J*=8.5, 4.2 Hz), 7.27 (2H, d, *J*=8.5 Hz), 7.32 (2H, d, *J*=8.5 Hz); FAB-HRMS *m*/*z* Calcd for $C_{20}H_{34}O_4SiNa$ $(M+Na)^+$: 389.2124, Found: 389.2112.
1: IR ν_{max} (KBr) 3421, 1749, 1646, 1558 cm^{-1}; ^{1}H-NMR (300 MHz, D_2O) δ 1.22 (3H, d, *J*=7.0 Hz), 1.27 (3H, d, *J*=6.5 Hz), 2.51 (1H, m), 2.73 (1H, m), 3.40 (3H, m), 3.86 (1H, dd, *J*=12.5, 6.0 Hz), 4.25 (5H, m), 5.03 (1H, dd, *J*=10.5, 7.0 Hz), 7.20 (4H, m); FAB-HRMS *m*/*z* Calcd for $C_{21}H_{28}N_3O_4S$ $(M+H)^+$: 418.1801, Found: 418.1800; UV λ_{max} 298 (ε 9520).