

Synthesis of J-111,347, a Novel 1 β -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 1 β -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 1 β -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 1 β -methylcarbapenems since 1 exhibited a broad antibacterial spectrum against MRSA and *P. aeruginosa*.¹⁾ 1 and vancomycin had MIC ($\mu\text{g/ml}$) values of 0.78 and 0.78 against *S. aureus* pMS/Smith (an MRSA strain), respectively. Also 1 and imipenem had MIC ($\mu\text{g/ml}$) 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-1 β -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 4⁵⁾ with substituted phenyllithium yielded an insepara-

ble 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 NaBH₄ did not provide acceptable diastereoselectivity, regardless of the temperature and the presence of Lewis acids such as LiI, CeCl₃, MgCl₂, and SmCl₃. Reduction with Zn(BH₄)₂ at low temperature (−78 °C) resulted in good selectivity with moderate yield (entry 2, 76%de, 60% yield). Under the conditions of the LiAlH₄–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 <i>S</i> and 5 <i>R</i> ^{b)} |
|-------|-----------------------------------|-------------------|-------------------|------------|-------------------------|--|
| 1 | NaBH ₄ | None | MeOH | 0 | 47 | 48:52 |
| 2 | Zn(BH ₄) ₂ | None | Et ₂ O | −78 | 60 | 88:12 |
| 3 | LiAlH ₄ | LiI (2) | Et ₂ O | −78 | 44 | 76:24 |
| 4 | LiAlH ₄ | LiI (5) | Et ₂ O | −78 | 51 | 90:10 |
| 5 | LiAlH ₄ | LiI (10) | Et ₂ O | −78 | 76 | 95:5 |

a) Isolated yield as a mixture of 5*R* and 5*S*. b) Determined by HPLC (DAI-CEL CHIRALPAK AS).⁸⁾

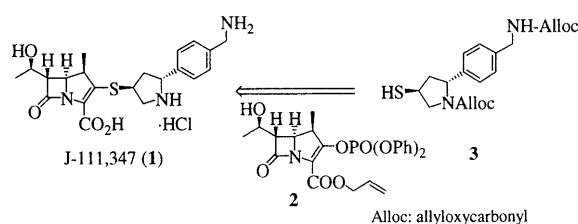
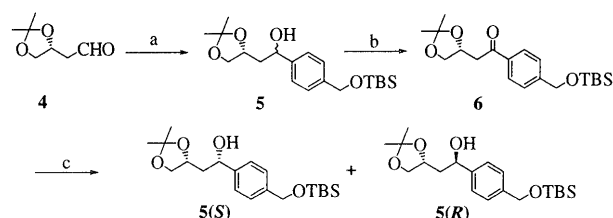


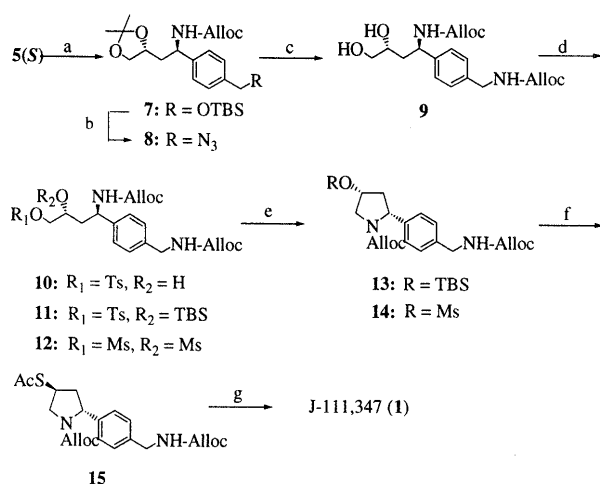
Fig. 1



a) 4-(*tert*-butyldimethylsilyloxymethyl)bromobenzene, *n*-BuLi, THF, −70°C, 88%; b) TPAP, NMO, CH₂Cl₂, 88%; c) Reducing agents (see Table 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 , $\text{THF-H}_2\text{O}$, room temperature; vi) TEA, Alloc-Cl , THF, 0°C , 61%; b) i) $n\text{-Bu}_4\text{NF}$, THF, 0°C ; ii) TEA, MsCl , CH_2Cl_2 , 0°C ; iii) NaN_3 , DMF, room temperature, 91%; c) i) PPh_3 , $\text{THF-H}_2\text{O}$, room temperature; ii) TEA, Alloc-Cl , THF, 0°C ; iii) $p\text{-TsOH}$, MeOH, room temperature, 78%; d) TEA, MsCl , CH_2Cl_2 , 0°C ; e) $t\text{-BuOK}$, THF, -20°C , 97%; f) AcSK , DMF, 65°C , 87%; g) i) NaOH , MeOH, 0°C ; ii) $i\text{-Pr}_2\text{NEt}$, 2, CH_3CN , 0°C , 65%; iii) $(\text{PPh}_3)_2\text{PdCl}_2$, $n\text{-Bu}_3\text{SnH}$, 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-mesyloxy-pyrrolidine **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 product¹²⁾ in the usual manner¹³⁾ afforded the carbapenem **1** in 72% yield.

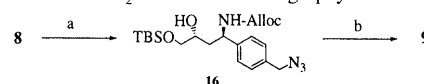
In summary, an efficient method for the synthesis of J-111,347 (**1**), a new carbapenem showing broad-spectrum antimicrobial activity, was established *via* diastereoselective reduction of the ketone **6** and intramolecular cyclization of the dimesylate **12**.

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

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- 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⁾
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- The diol **9** with high purity (>99%de) was obtained *via* separation of compound **16** on SiO_2 column chromatography.



a) i) $p\text{-TsOH}$, MeOH, room temperature; ii) TBS-Cl, imidazole, CH_2Cl_2 , room temperature, 75%; iii) SiO_2 column chromatography; b) i) PPh_3 , $\text{THF-H}_2\text{O}$, room temperature; ii) TEA, Alloc-Cl , 0°C ; iii) HCl-MeOH , 92%.

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- 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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- 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} ; $^1\text{H-NMR}$ (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 $\text{C}_{20}\text{H}_{34}\text{O}_4\text{SiNa}$ ($\text{M}+\text{Na}^+$): 389.2124, Found: 389.2112.
1: IR ν_{max} (KBr) 3421, 1749, 1646, 1558 cm^{-1} ; $^1\text{H-NMR}$ (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 $\text{C}_{21}\text{H}_{28}\text{N}_3\text{O}_4\text{S}$ ($\text{M}+\text{H}^+$): 418.1801, Found: 418.1800; UV λ_{max} 298 (ϵ 9520).