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Preparation of Crystalline *p*-Nitrobenzyl 2-Hydroxymethyl Carbapenem as a Key Intermediate for the anti-MRS Carbapenem L-786,392

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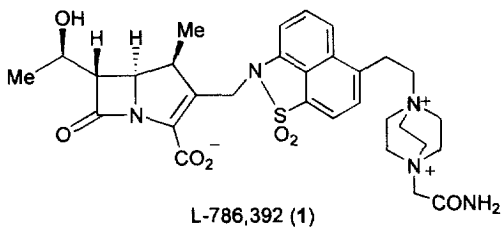
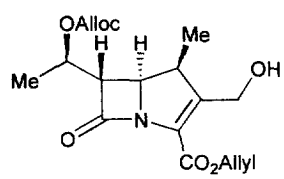
Abstract: Crystalline *p*-nitrobenzyl esters of 2-hydroxymethyl carbapenem derivatives were prepared in one pot from the corresponding diazo compounds and Bu_3SnCH_2OH. The TES protected 2-hydroxymethyl carbapenem was successfully converted to an anti-MRS carbapenem L-786,392.

Keywords: Carbapenems; Coupling reactions; Tin compounds

Recently, L-786,392 (**1**) has drawn great attention due to its potent activities against gram-positive pathogens, especially against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate-resistant *Staphylococcus aureus* (VISA), and vancomycin-resistant *Enterococcus* [1-4]. Previously, **1** was prepared from a 2-hydroxymethyl carbapenem allyl ester (**2**), which is an unstable non-crystalline compound. Furthermore, preparation of **2** required more than 12 steps from the commercially available acetoxyazetidinone according to a modification of the Shionogi procedure [5]. Many other biologically important carbapenems have been prepared from 2-hydroxymethyl intermediates [5-12]. Therefore, a simple and scalable preparation of stable crystalline 2-hydroxymethyl carbapenems is highly desirable. Here, we report a one pot synthesis of crystalline 2-hydroxymethyl carbapenems.



L-786,392 (**1**)



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In 1985, Kosugi *et al.* reported hydroxymethylation by a cross coupling reaction between aryl halides and Bu_3SnCH_2OH [13]. We applied this method to carbapenem 2-triflates (**5**) as shown in Scheme 1. Initial probe studies with isolated enol triflate **5a** produced low yields of the desired product **6** along with substantial quantities of the 2-H (**7**) and 2-Bu (**8**) compounds. As discussed further below, optimization of ligand, halide source, catalyst, solvent, and temperature

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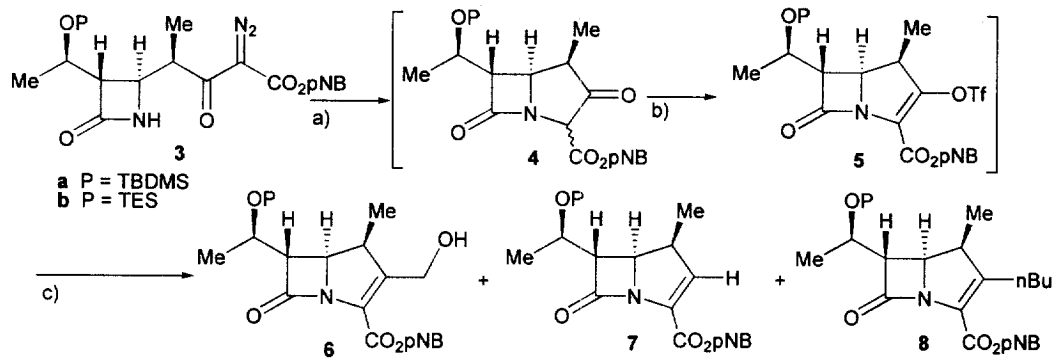
improved the yield to 74%. Given the difficulties encountered with removing the TBDMS group downstream without significant degradation and the instability of the isolated enol triflate, attention was focused on developing a one pot process starting with the open chain diazo compound protected with a TES group (**3b**).

Scheme 1



a) Rodium octanoate, $ZnCl_2$, CH_2Cl_2, reflux; b) Tf_2O, tetramethylpiperidine, DIPA, -40°C; c) Bu_3SnCH_2OH, $ZnCl_2$, $Pd(dba)_2$, tri(2-furyl)phosphine, HMPA, under Ar, 70 °C.

Carbapenem 2-triflates **5** were *in situ* prepared from the corresponding diazo compounds (**3a** and **3b**). However, when a mixture of TEA and diisopropylamine was used during triflation [14], reduction of triflates **5** was the main reaction pathway in the Stille reaction, yielding the 2-protio compound (**7**) and so the use of other bases was investigated. We found that a mixture of tetramethylpiperidine and diisopropylethylamine resulted in a high yield for the triflation and also successfully suppressed the reduction to less than 5 % during the coupling reaction.
Catalysts, ligand, solvent, salt effects and order of addition were optimized as follows.

- Of the palladium catalysts screened, which included $Pd_2(dba)_3 \bullet CHCl_3$, $Pd(dba)_2$ and $Pd(OAc)_2$, $Pd(dba)_2$ was found to be more robust for this reaction.
- The Stille reaction does not take place without a ligand. The best ligand is tri(2-furyl)phosphine. The ratio between Pd and ligand was briefly studied and 1 : 2.5 ratio provided consistent results. Tri(2-thienyl)phosphine, triphenylphosphine, and triphenylarsine retarded the reaction and provided **6** in lower yield. All bidentate ligands examined, such as BINAP, DPPF, DPPE and DPPP, were less effective, providing only trace amount of product.
- HMPA is essential for this coupling reaction. The coupling reaction in all other solvents, such as DMPU, DMF, THF, NMP, NEP, DMSO, gave **6** in only 25 - 30 % yield. The reaction in 10 : 1 mixture of DMPU and HMPA gave the same yield (45 - 55 %) as the reaction in neat HMPA.
- Liebeskind *et al.* reported copper catalyzed cross coupling reaction with organotin compounds [16]. However, addition of copper catalysts to the reaction mixture totally suppressed the reaction.
- In solution, **6a** and **6b** are stable from pH 4-7 but are unstable in basic media due to intramolecular nucleophilic attack of the primary alcohol on the ester (generation of *p*NBOH was observed upon decomposition of **6**). On the other hand, carbapenem 2-triflates (**5**) are stable in base but are unstable in neutral or acidic media [14]. If isolated 2-triflates **5** are used as starting materials, the coupling reaction does not require halide sources (such as LiCl, $ZnCl_2$) [15]. However, $ZnCl_2$ is essential when *in situ* prepared **5** is used in order to maintain the reaction

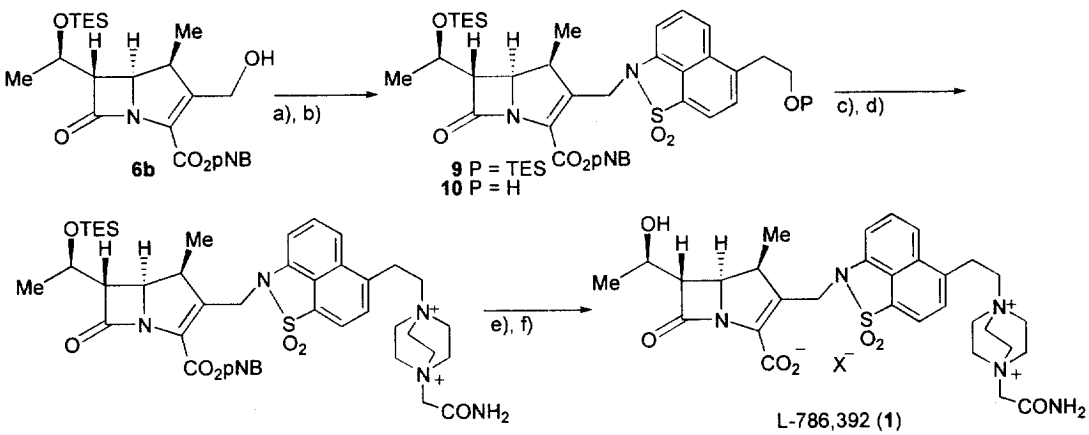
mixture at acidic pH where the product **6** is stable. In order to maximize stability of both **5** and **6**, a mixture of *in situ* prepared **5** and Bu_3SnCH_2OH in HMPA (basic conditions) was slowly added to a mixture of $Pd(dba)_2$, tri(2-furyl)phosphine, and $ZnCl_2$ (acidic conditions) in HMPA at 70 °C. The reaction was typically complete in 2 h at 70 °C.

• This reaction is very sensitive to oxygen, so operations were carried out under an argon atmosphere. Using these reaction conditions, TES protected 2-hydroxymethyl carbapenem *p*-nitrobenzyl (*p*NB) ester **6b** could be isolated in the 3-step one-pot process in 45 - 55 % yield as a stable crystalline compound.

In order to stabilize the 2-hydroxymethyl carbapenem **6**, the coupling reaction between **5** and Bu_3SnCH_2OTMS was attempted. This reaction gave the 2-butyl compound **8** as the major product together with **6**. [Typically, the ratio **6/8** is 7-8 : 1]. Since the addition of excess bis(trimethylsilyl)acetamide to the reaction mixture (with Bu_3SnCH_2OH) dramatically slowed the reaction and gave predominately the butyl compound **8**, the reaction apparently proceeded only after desilylation of Bu_3SnCH_2OTMS by $ZnCl_2$. A similar phenomenon was observed when $B(OR)_3$ was added to the reaction mixture to protect the 2-hydroxymethyl group.

L-786,392 was prepared from 2-hydroxymethyl **6b** as shown in Scheme 2. Under Mitsunobu conditions, a naphthosultam side chain was installed on the 2-hydroxymethyl moiety. The naphthosultam ring was further modified by coupling with a DABCO derivative. Finally, the two protective groups, namely TES and pNB, were sequentially removed under standard conditions yielding L-786,392 (**1**) after purification by resin column chromatography and lyophilization.

Scheme 2



a) Ph_3P, DEAD, 4-[2-(triethylsilyloxy)ethyl]-1,8-naphthosultam, THF, -25~-30 °C; b) aq. THF, pH 2.3, r.t.; c) Lutidine, Tf_2O, CH_2Cl_2, -10 °C; d) acetamide DABCO triflate salt [5], ACN; e) aq. THF, HCl; f) 5 % Pd/C, H_2 (40psi), MOPS buffer, iPA, THF, r.t.

In conclusion, stable crystalline TES protected 2-hydroxymethyl carbapenem **6b** was prepared for the first time in one pot in a reasonable yield. The compound **6b** is a versatile intermediate for many biologically important compounds including L-786,392 (**1**).

Preparation of 2-hydroxymethyl carbapenem 6b: Diazo compound **3b** [14] (2.70 kg, 5.35 mol), rhodium octanoate (21.4 g, 0.027 mol), $ZnCl_2$ (10.7 g, 0.079 mol), and dry CH_2Cl_2 (13.5 L) were charged to a dry reactor. The solution was heated to reflux under nitrogen for 90 min. When complete conversion of **3b** to **4b** was confirmed by HPLC analysis, the CH_2Cl_2 solution was cooled to -50 °C. A combined mixture of 2,2,6,6-tetramethylpiperidine (0.910 L, 5.39 mol) and diisopropylethylamine (0.325 L, 2.32 mol) was added, maintaining the batch temperature below -40 °C. After a 30 min age, Tf_2O (0.990 L; 5.88 mol) was added slowly, maintaining the batch temperature below -40 °C. The resulting suspension was stirred at -40 °C for 60 min. Dry HMPA (5.35 L) was added and the mixture was stirred at 30 °C under vacuum for 30 min to remove CH_2Cl_2 from the mixture. In a separate flask, tri(2-furyl)phosphine (400 g, 1.72 mol), $Pd(dba)_2$ (400 g, 0.7 mol), $ZnCl_2$ (730 g, 5.60 mol), and dry HMPA (16.0 L) were charged and heated to 70 °C under an argon atmosphere. To the solution of **5b** in HMPA was added Bu_3SnCH_2OH (6.02 L, 88.8 wt % purity, 21.2 mol). The resulting solution was added to the catalyst solution over 40 - 60 min maintaining 70 °C. The reaction was complete in a total of 2 h at 70 °C yielding **6b** in 46 % yield by HPLC assay. The reaction mixture was diluted with MTBE (32 L) and water (32 L) at 5 °C. The organic layer was separated and washed with 32 L of water. The organic layer was concentrated and the resulting residue was purified on a silica gel (20 kg) column using AcOEt/hexanes (1 : 9 to 4 : 6). The fractions containing **6b** were combined and concentrated to give crystalline **6b** (1.54 kg, 80 wt %, 46.7 % isolated yield). A pure sample was prepared by recrystallization from hexane.

^1H NMR ($CDCl_3$, 250 MHz) δ 8.22 (m, 2H), 7.64 (d, *J*=8.7 Hz, 2H), 5.47 (AB d, *J*=13.9 Hz, 1H), 5.27 (AB d, *J*=13.9 Hz, 1H), 4.54 (AB dd, *J*=14.9, 6.6 Hz, 1H), 4.38 (AB dd, *J*=14.9, 5.9 Hz, 1H), 4.25 (m, 1H), 4.22 (dd, *J*=7.0, 3.0 Hz, 1H), 3.27 (dd, *J*=5.7, 3.0 Hz, 1H), 3.24 (m, 1H), 3.09 (m, 1H), 1.26 (d, *J*=6.2 Hz, 3H), 1.21 (d, *J*=7.4 Hz, 3H), 0.94 (t, *J*=7.9 Hz, 9H), 0.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 175.1, 161.8, 153.5, 147.6, 142.4, 128.0, 127.3, 123.7, 65.8, 65.6, 60.3, 57.6, 55.9, 41.6, 22.5, 15.3, 6.7, 4.9; mp 98 °C.

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