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# Synthesis of an Anti-Methicillin-Resistant *Staphylococcus aureus* (MRSA) Carbapenem via Stannatrane-Mediated Stille Coupling

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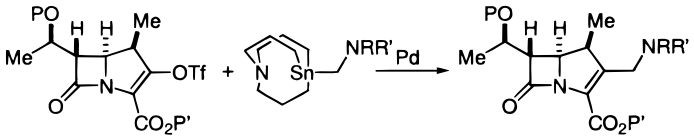
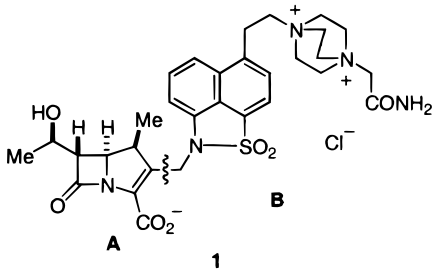
## ABSTRACT




**A short synthesis of carbapenem 1 is described. The key step involves the cross-coupling of an enol triflate with an amino-substituted sp$^3$ carbon. This cross-couping, which allows the introduction of the complete side chain in one step, utilizes a stannatrane as the heteroalkyl transfer reagent.**

Recently, $\beta$-lactam **1** was identified as a clinical candidate for the treatment of serious bacterial infections, including those caused by strains resistant to current therapeutic protocols.[1] Here we report a short synthesis of **1** that utilizes an unprecedented cross-coupling of an enol triflate with an amino-substituted methylene to join the two fragments of the molecule. This cross-coupling was mediated by a stannatrane as the heteroalkyl transfer agent.

While **1** can be disconnected in several ways, among the most convergent disconnects is the C−C bond between the




**1**

carbapenem core **A** and the side chain **B**, as shown in structure **1**. While several cross-coupling reactions using Stille or Suzuki conditions with similar carbapenems have been reported in recent years,[2,3] that required for construction of **1** would involve the cross-coupling of enol triflate **3** with

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(2) Yasuda, N.; Huffman, M. A.; Ho, G.-J.; Xavier, L. C.; Yang, C.; Emerson, K. M.; Tsay, F.-R.; Li, Y.; Kress, M. H.; Rieger, D. L.; Karady, S.; Sohar, P.; Abramson, N. L.; DeCamp, A. E.; Mathre, D. J.; Douglas, A. W.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 5438.

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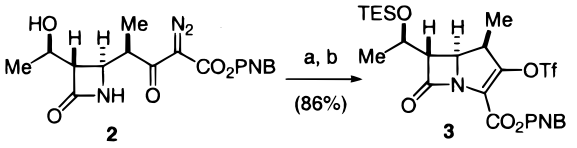
an amino-substituted $sp^3$ carbon, a coupling for which we could find no precedence. This Letter discloses a route to **1** that makes this key bond connection and yields **1** in protected form in one step from **3**.[4]

Scheme 1 depicts the preparation of the enol triflate

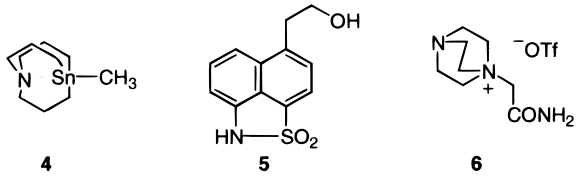
**Scheme 1.** Enol Triflate Preparation




a. imidazole, TESCl, THF. b. $Rh_2(octa)_4$, $ZnCl_2$, $CH_2Cl_2$, Δ; $Et_3N$, $i$-$Pr_2NH$, -70 °C; $Tf_2O$, -70 to -20 °C.

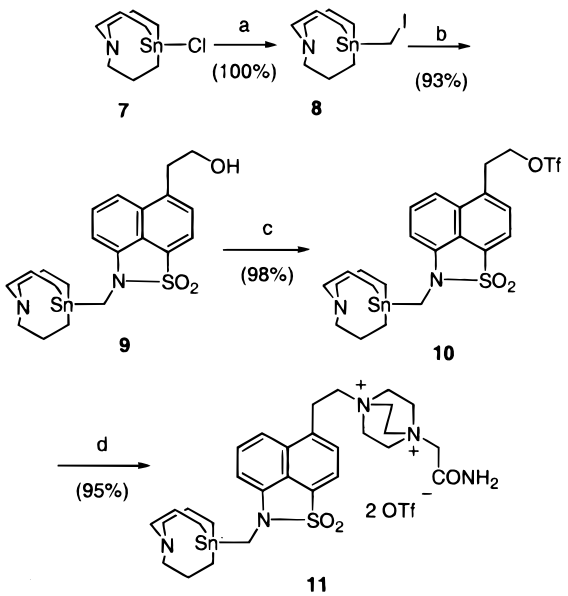
coupling partner. Protection of the alcohol function of **2**[5] was required for the successful preparation and isolation of **3**. Thus, O-silylation was favored over N-silylation when imidazole was used as base with TESCl. TES-protected **2** was isolated in crystalline form from IPAC and heptane. Reaction of this compound with 0.5 mol % of rhodium octanoate and 1 mol % of zinc chloride in refluxing methylene chloride gave quantitative conversion to the $\beta$-keto ester. The crude solution was treated at −70 °C with 0.35 equiv of triethylamine and 1.0 equiv of diisopropylamine followed by 1.05 equiv of trifluoromethanesulfonic anhydride. Enol triflate **3** was then isolated as a crystalline compound after passing through a short plug of silica gel, eluting with methylene chloride and then switching the solvent to heptane.

Palladium-catalyzed cross-coupling of **3** with $Bu_3SnCH_2OH$ was successful;[3] however, attempts at attaching any $CH_2NRR'$ to the carbapenem using either a typical Suzuki or Stille approach failed. The transmetalation step of the catalytic cycle was viewed as the problem in this case.[6] If this is true, a potential solution for the Stille approach would be lengthening the Sn−$CH_2$ bond. Long Sn−C bonds were reported by Tzschach when he disclosed the preparation and properties of methylstannatrane **4**.[7] In fact, this critical bond distance is 2.214 Å which is about 0.1 Å longer than that in the typical alkylstannane.[8] Vedejs capitalized on this characteristic when he demonstrated the palladium-catalyzed transfer of $CH_3$ and $CH_2OMOM$ to aryl halides;[9] however, no other reports of cross-coupling using this type of organostannane have appeared.




Preliminary cross-coupling studies of enol triflate **3**, protected with TBS, with the methylstannatrane **4** indicated that the desired C−C bond could be made under mild conditions. This provided impetus to investigate the coupling of the entire side chain with the enol triflate using stannatrane **11**. Using this highly convergent approach, the sensitive carbapenem core would be required to survive relatively few steps, as **1**, in protected form, would be prepared in a single reaction from **3**. Scheme 2 outlines the synthesis of the fully

**Scheme 2.** Preparation of the Stannatrane Coupling Partner




a. $Et_2Zn$, $CH_2I_2$, THF. b. **5**, $K_2CO_3$, DMF. c. $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$. d. **6**, MeCN.

elaborated stannatrane coupling partner **11**.

Stannatrane chloride **7** was treated with the zinc reagent prepared by combining 1 equiv of diethylzinc and 2 equiv of diiodomethane to provide iodomethylstannatrane **8** in quantitative yield.[10] Treatment of **8** with **5**[11] in the presence

(4) An elegant synthesis of **1** that starts from a commercially available acetoxyazetidinone was recently disclosed by colleagues in these laboratories. Humphrey, G. R.; Miller, R. A.; Pye, P. J.; Rossen, K.; Reamer, R. A.; Maliakal, A.; Ceglia, S. S.; Grabowski, E. J. J.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1999**, *121*, 11261.

(5) Compound **2** is available from Kanegafuchi, Nippon Soda, and Takasago.

(6) For a thorough discussion of the mechanism of the Stille cross-coupling, see: Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978 and references therein.

(7) (a) Jurkschat, K.; Tzschach, A. *J. Organomet. Chem.* **1984**, *272*, C13. (b) Jurkschat, K.; Tzschach, A.; Meunier-Piret, J. *J. Organomet. Chem.* **1986**, *315*, 45.

(8) (a) Ross, J.; Wardell, J. L.; Ferguson, G.; Low, J. N. *Acta Crystallogr., C* **1994**, *50*, 1703. (b) Belanger-Gariepy, F.; Leger, R.; Hanessian, S. *Acta Crystallogr., C* **1992**, *48*, 1309. (c) Cox, P. J.; Wardell, J. L. *Acta Crystallogr., C* **1995**, *51*, 2037.

(9) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556.

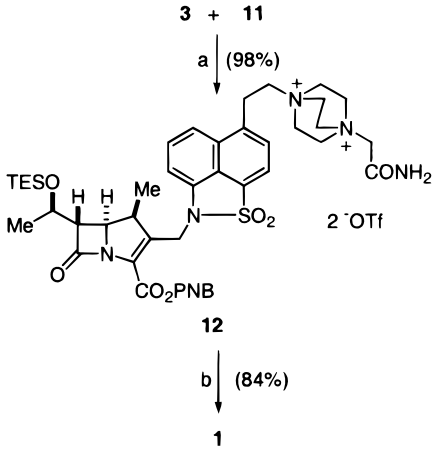
(10) This preparation of the organozinc reagent is a modification of Knochel's procedure (Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956) by J. C. McWilliams, unpublished results. To THF (33 mL) under nitrogen at −60 °C were added diethylzinc (2.56 mL, 25.0 mmol) and then diiodomethane (4.02 mL, 50.0 mmol), maintaining an internal temperature below −55 °C. After 1 h at −40 °C, stannatrane chloride (**7**,

of potassium carbonate and DMF provided **9**, which was isolated as a crystalline solid from EtOAc. The alcohol was activated by conversion to triflate **10** using standard conditions. When **10** was treated with **6**[2] at ambient temperature in acetonitrile, **11** was produced in high yield. This compound was isolated as an amorphous ditriflate salt by precipitation with ether.

Alternatively **11** could be prepared as a different salt form by simply changing the order of reactions. First combining the triflate of **5** with **6**, followed by coupling with **8**, provided **11** as the monoiodide monotriflate salt.

With the coupling partners **3** and **11** in hand, the key cross-coupling reaction was explored (Scheme 3). The use of

**Scheme 3.** Coupling and Deprotection Sequence




a. $Pd_2dba_3$·$CHCl_3$, tris-2-furylphosphine, *i*-$Pr_2NEt$, NMP, 60 °C, 3h. b. HCl, isopropylacetate, isoamyl alcohol, rt; pH 7.0 MOPS buffer, 5% Pd/C, $H_2$; Amberchrome CG-161m resin column.

HMPA as solvent or cosolvent with DMPU, which was required for the cross-coupling of **3** with $Bu_3SnCH_2OH$,[3] is not needed in this case. In fact, NMP was found to give superior yields. When the cross-coupling was attempted between the monoiodide monotriflate salt of **11** and **3**, no reaction occurred. The technique of adding silver triflate or silver nitrate to the reaction mixture to sequester the halide also failed. The reaction of **3** with the ditriflate salt **11**, however, performed well.

The preferred catalyst was prepared by the combination of $Pd_2(dba)_3$·$CHCl_3$ and tri-2-furylphosphine[12] in warm NMP. This was added to a solution of coupling partners **3**, **11**, diisopropylethylamine, and NMP. The tertiary amine was required to maintain basic conditions during the reaction. Decomposition was observed when the mixture was allowed to become acidic during the course of this cross-coupling. After 3 h at 60 °C, the assay yield was 98% (HPLC).[13]

A workup procedure was devised that allowed the quantitative recovery of the stannatrane as chloride **7** as well as the isolation of **12** as a crystalline solid in high yield. The transmetalation step of the Stille coupling catalytic cycle returns the stannatrane as its triflate. This compound was converted to chloride **7** by diluting the crude reaction mixture with THF and washing with 20% aqueous NaCl. A solvent switch from THF to acetonitrile provided a slurry which, when filtered, gave 61% of the stannatrane as crystalline **7** and a clear mother liquor. When 2-propanol was added dropwise to this mother liquor, **12** crystallized and was isolated in 98% yield by filtration. This mother liquor was concentrated to dryness and the residue triturated with methanol to return the remaining 39% of stannatrane chloride **7**.

To complete the preparation of drug candidate **1**, all that remained was the removal of the triethylsilyl and 4-nitrobenzyl blocking groups from **12**. This was accomplished using a procedure that avoided any intermediate isolation. Treatment of **12** with 0.06 M HCl removed the triethylsilyl moiety. The pH was then adjusted to 7.0 using a 4-morpholinepropanesulfonic acid/NaOH buffer system. The mixture was hydrogenated at 40 psi using 5% Pd/C as catalyst to remove the 4-nitrobenzyl group. Carbapenem **1** was isolated in pure form as the chloride salt using Amberchrome CG-161m resin followed by lyophilization.

With this work we have demonstrated a brief and efficient route to **1** that highlights the versatility of the stannatrane in palladium-catalyzed cross-coupling reactions. The stannatrane was quantitatively recovered leaving residual tin in

2.94 g, 10.0 mmol) was added in one portion and the resulting suspension was stirred at 0 °C for 3 h and then rt for 0.5 h. The solution was poured onto heptanes (100 mL) and water (33 mL) and then 2 M aqueous HCl (18 mL) was added (pH now 2.5); both phases were clear. The layers were partitioned, and the organic phase was washed with water (2 × 30 mL) and then brine (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to provide **8** (3.98 g, 100%) as colorless crystals. An analytical standard was prepared by recrystallization from methanol: mp 40−55 °C;$^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 2.37 (m, 6H), 1.67 (m, 6H), 1.66 (s, 2H), 0.82, (m, 6H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) $\delta$ 54.6, 23.3, 7.2, −13.5. Anal. Calcd for $C_{10}H_{20}INSn$: C, 30.04; H, 5.04; I, 31.75; N, 3.50. Found: C, 30.20; H, 4.88; I, 31.45; N, 3.41.

(11) Miller, R. A.; Humphrey, G. R.; Lieberman, D. R.; Ceglia, S. S.; Grabowski, E. J. J. *J. Org. Chem.* **2000**, *65*, 1399.

(12) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(13) A suspension of $Pd_2(dba)_3$·$CHCl_3$ (31.6 mg, 0.031 mmol), tri-2-furylphosphine (35.4 mg, 0.153 mmol), and NMP (2 mL) was degassed and then warmed to 60 °C for 30 min. The catalyst solution was added to a degassed solution of **3** (743 mg, 1.22 mmol), **11** (972 mg, 1.00 mmol), diisopropylethylamine (47 mg, 0.37 mmol), and NMP (10 mL) at 60 °C. The mixture was stirred for 3 h at 60 °C (98% assay yield). The crude reaction was diluted with THF (50 mL) and washed with 20% aqueous NaCl (3 × 50 mL). The THF was removed in vacuo, and the residue was diluted with acetonitrile (5 mL). The resulting crystalline solids (**7**, 179 mg, 0.61 mmol) were collected on a frit. 2-Propanol (20 mL) was added dropwise to the mother liquor, and the resulting crystalline solid was collected by filtration to provide **12** (1.243 g) as a crystalline solid. The mother liquor was concentrated to dryness and then triturated with methanol (2 mL) to provide the remaining **7** (116 mg, 0.39 mmol). **12**: $^1$H NMR ($CD_3CN$, 250 MHz) $\delta$ 8.19 (dt, $J$ = 8.8, 1.9 Hz, 2H), 8.06 (d, $J$ = 7.5 Hz, 1H), 7.80 (d, $J$ = 7.5 Hz, 1H), 7.73 (dt, $J$ = 8.8, 1.9 Hz, 2H), 7.76−7.57 (m, 2H), 6.94 (bs, 1H), 6.87 (dd, $J$ = 6.0, 2.1 Hz, 1H), 6.44 (bs, 1H), 5.52 (d, $J$ = 13.9 Hz, 1H), 5.37 (d, $J$ = 13.9 Hz, 1H), 5.31 (d, $J$ = 17.0 Hz, 1H), 4.68 (d, $J$ = 17.0 Hz, 1H), 4.28 (m, 1H), 4.27 (s, 2H), 4.23 (m, 1H), 4.21 (m, 6H), 4.17 (m, 6H), 3.82 (m, 2H), 3.63 (m, 2H), 3.39 (m, 1H), 3.34 (m, 1H), 1.23 (d, $J$ = 7.0 Hz, 3H), 1.15 (d, $J$ = 6.2 Hz, 3H), 0.90 (t, $J$ = 8.0 Hz, 9H), 0.56 (q, $J$ = 8.0 Hz, 6H); $^{13}$C NMR ($CD_3CN$, 62.9 MHz) $\delta$ 175.9, 164.9, 162.0, 148.7, 147.2, 144.2, 138.2, 138.1, 131.3, 130.5, 130.4, 130.3, 130.1, 129.4, 124.5, 122.0 (q, $J$ = 320 Hz), 121.0, 120.1, 116.3, 105.6, 66.5, 66.1, 65.0, 63.0, 61.2, 56.0, 52.9, 52.1, 41.5, 39.1, 25.4, 22.3, 15.9, 7.1, 5.5. Anal. Calcd for $C_{46}H_{58}N_6O_{15}F_6S_3Si$·0.5IPA: C, 47.41; H, 5.19; F, 9.47; N, 6.98. Found: C, 47.20; H, 5.30; F, 9.16; N, 6.69.

the drug substance at acceptable levels. Iodomethylstannatrane **8** should be viewed as a versatile reagent for the preparation of numerous Sn-$CH_2X$ compounds that will function well in currently difficult cross-coupling reactions. This promising approach using the stannatrane in Stille cross-coupling reactions adds versatility to this already powerful reaction.

**Acknowledgment.** We thank Drs. G. R. Humphrey and R. A. Miller for a generous supply of naphthosultam **5**. We acknowledge Dr. E. J. J. Grabowski for helpful discussions and Mr. R. A. Reamer and Ms. L. M. DiMichele for NMR support. Expert hydrogenation assistance was provided by Mr. C. Bazaral, Mr. A. L. Houck, and Mr. A. Newell.

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