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ATTACHMENT OF THE ANTHRAMYCIN ACRYLAMIDE SIDE CHAIN BY THE PALLADIUM CATALYZED COUPLING REACTION OF A VINYL TRIFLATE

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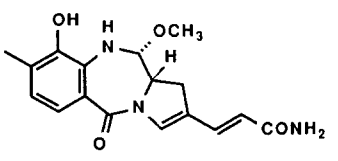
Abstract: Conversion of the 2-keto group in the pyrrolo ring of pyrrolo(1,4)benzodiazepines to the vinyl triflate takes place regiospecifically to yield the enamine. The triflate undergoes palladium catalyzed coupling reactions to attach the acrylamide side chain.

Anthramycin (**1**), an antitumor antibiotic produced by *streptomyces refuineus*[1], belongs to a group of antibiotics all of which share the pyrrolo(1,4)benzodiazepine system.[2] The synthesis of anthramycin by Leimgruber[3] required nine steps to attach the E-acrylamide side chain in an overall 5% yield.

Our recent work showing that carbon-carbon bond formation could be effected by the palladium catalyzed coupling of a vinyl trifluoromethanesulfonate (triflate) either with an organostannane[4] or an olefin[5] (Heck-type reaction) offered a promising route to the attachment of the side chain.



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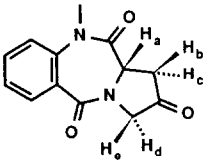

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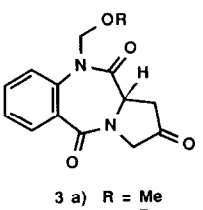
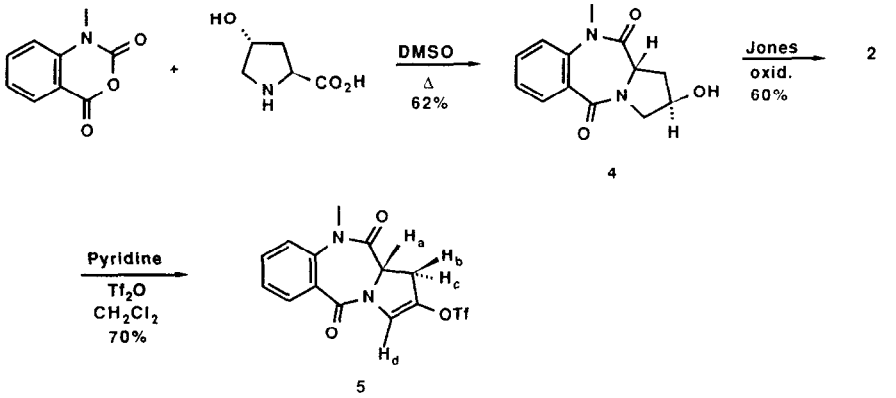


3 a) R = Me
b) R = Et

Two model compounds, **2** and **3**, were prepared to demonstrate the regioselective formation of the vinyl triflate and the viability of the palladium catalyzed coupling reaction with various vinylstannanes and Michael acceptors. The reaction of N-methyl isatoic anhydride[6] with L-hydroxyproline gave the dilactam alcohol **4**, which was oxidized to ketone **2** (Scheme 1). Vinyl triflate **5** was obtained when the ketone was treated with pyridine and triflic anhydride.

Protons H_d and H_e of **2** appear as a pair of doublets at 3.9 and 4.3 ppm with J = 20 Hz. This pattern is absent in vinyl triflate **5**, which shows a vinyl proton (H_d) appearing at 7.1 ppm. Vinyl triflate **5** was then coupled with tributylvinylstannane, E-tributylstannyl ethyl propenoate and with ethyl acrylate (Table 1). A 2-D-COSY[7] spectrum was obtained on **7** (Fig. 1). Protons H_a - H_f have been labeled for clarity.



Scheme 1

Table 1

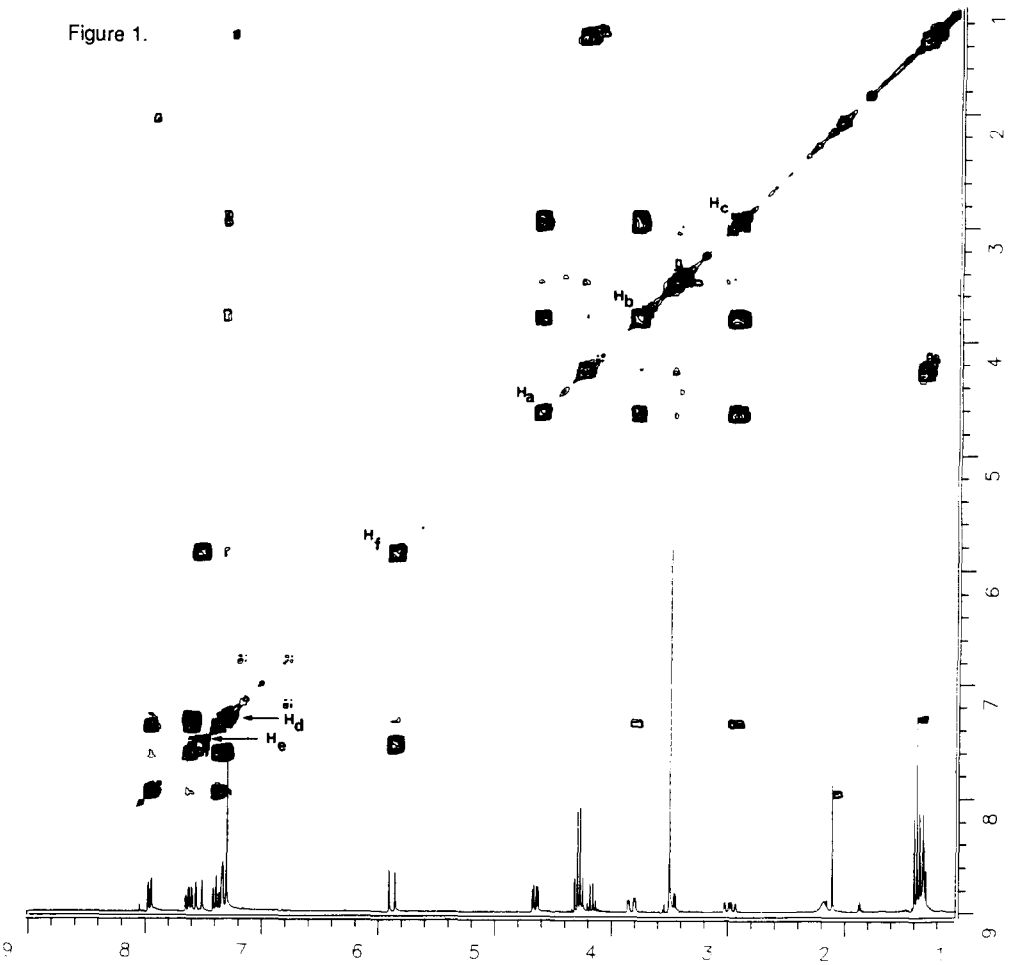
Coupling Reactions of Vinyl Triflate 5

Coupling Partners	Product	% Yield	Reaction Conditions
Bu_3Sn	6	60	a
Bu_3Sn CO_2Et	7	78	a
CO_2Et	7	40	b

a) 3 mol % $(Ph_3P)_4Pd$, 3 eq LiCl, THF, 65°C

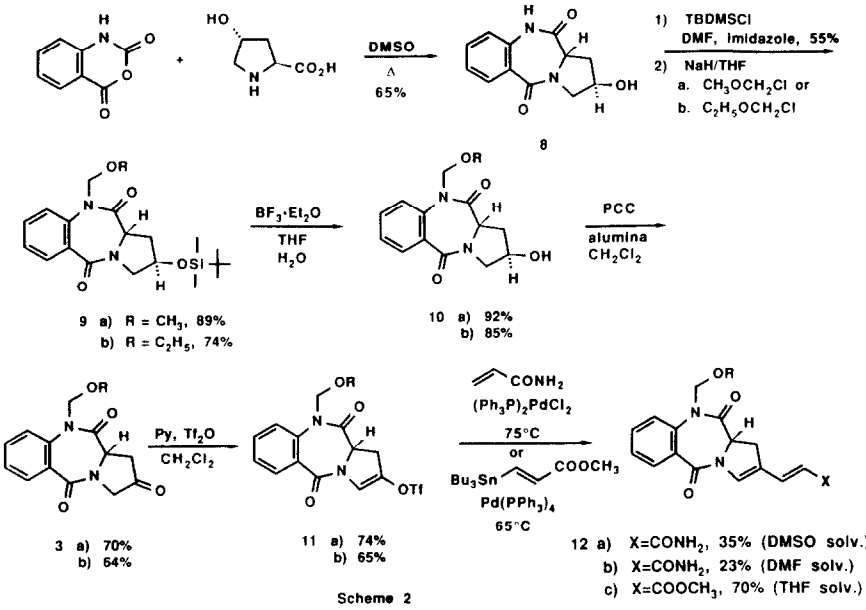
b) 4 mol % $(Ph_3P)_2PdCl_2$, DMF, TEA, 75°C

Figure 1.



Recently, the conversion of the secondary amide to an imine (as in anthramycin) has been effected by the reaction of the MOM-protected amide with sodium borohydride.[8] Despite the difficulties other workers[9] have reported, this series of reactions--formation of the vinyl triflate and coupling--was carried out on the protected amide (**3**). The formation of the vinyl triflate and the coupling reaction takes place under mild conditions.

Condensation of isatoic anhydride[10] with L-hydroxyproline gave the dilactam alcohol **8** (Scheme 2), which was silylated and alkylated with chloromethyl methyl ether or chloromethyl ethyl ether to give **9**. Selective deprotection (BF_3•Et_2O)[11] gave **10**, which was oxidized to ketone **3** with PCC on alumina.[12] Conversion of **3** to **11** by the rapid addition of triflic anhydride to a solution of **3**



Scheme 2

and pyridine gave the best yields. Vinyl triflate **11** underwent the Heck-type coupling with acrylamide to give the coupled product **12** in a relatively low yield. However, the coupling reaction with a vinyl tin reagent was much more satisfactory.

Overall this methodology provides a rapid entry into the pyrrolo(1,4)benzodiazepine structure bearing the side chain. The generation of the vinyl triflate and the coupling reaction offers a convenient procedure for the construction of a variety of anthramycin derivatives. The synthesis of anthramycin **1** will be reported separately.

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References and Notes

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