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Coupling Reactions of 1-Tributylstannyl-1-octen-3-ol Catalyzed by Palladium: The Synthesis of PGB_1 and Coriolic Acid

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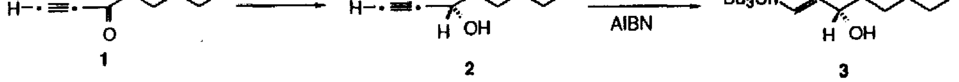
Abstract: The palladium catalyzed coupling of (*S*)-*E*-1-tributylstannyl-1-octen-3-ol (**3**) with 2-(6-carbethoxyhexyl)-3-iodo-2-cyclopenten-1-one gave a 70% yield of the (*S*)-ethyl ester of PGB_1. Coriolic acid was synthesized in 75% yield by coupling **3** with *Z*-10-iodododecenoic acid, demonstrating the tolerance of this coupling reaction to the carboxylic acid function.

The utilization of organotin reagents in place of other main group organometals in the transition metal catalyzed coupling reactions with organic electrophiles enjoys a number of distinct advantages, the most important of which are that the reaction takes place under mild, neutral conditions and tolerates a wide variety of unprotected functional groups on either coupling partner.[1] As a result, the reaction has been of value in the construction of organic molecules containing a multiplicity of functional groups, including alcohol, ester, ketone and aldehyde.

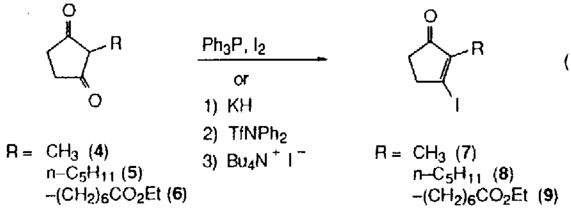
The (*S*)-*E*-1-octenyl-3-ol unit is present in arachidonic acid metabolites and the variety of biosynthetic products that embody the arachidonic cascade.[2] In a number of syntheses of these molecules and their derivatives,[3] the 1-octen-3-ol piece--usually as the protected alcohol--has been introduced through the vinyl halide[4] or the cuprate.[5] In certain synthetic procedures the vinyl cuprate has been generated from the vinylstannane.[5j-m] Because vinyl tin reagents will undergo the palladium catalyzed coupling reaction with vinyl electrophiles[6] in the presence of unprotected alcohols, ketones and esters, the utility of 1-tributylstannyl-1-octen-3-ol in the synthesis of PG's and coriolic acid was explored.

(*S*)-*E*-1-tributylstannyl-1-octen-3-ol was obtained by the asymmetric reduction of the acetylenic ketone (**1**) with (*S*)-β-3-pinanyl-9-borabicyclo[3.3.1]nonane to give (*S*)-1-octyn-3-ol (**2**) in 86% yield and 86% ee.[7] Resolution of this product was accomplished using phthalic anhydride and α-methylbenzylamine to give enantiomerically pure **2**. Hydrostannation[8] of **2** afforded enantiomerically pure (*S*)-*E*-1-tributylstannyl-1-octen-3-ol (**3**).



(Eq. 1)

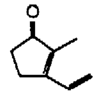
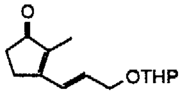
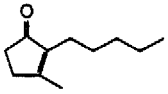
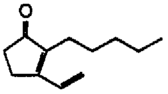
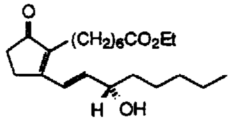
The synthesis of cyclopentenone products of B-type prostaglandins and jasmones shared a common strategy, requiring the synthesis of 2-substituted cyclopentan-1,3-diones and their conversion to the corresponding vinyl triflate or iodide followed by the coupling reactions of these electrophiles with the tin reagents. Both 2-methylcyclopentane-1,3-dione (**4**) and 2-pentylcyclopentane-1,3-dione (**5**)[9] were converted to vinyl iodides **7** and **8** in 92 and 90% yield, respectively, by reaction with triphenylphosphine diiodide[10] (Eq. 2). Conversion of the 1,3-diketones to the corresponding vinyl triflate[11] by quenching the potassium enolate with N-phenyltriflamide followed by reaction with tetrabutylammonium iodide also gave vinyl iodides. Thus diketones **5**,[9] and **6**[12] were converted to iodides **8** and **9**, respectively, using this procedure (100% and 76%, respectively).



(Eq. 2)

The palladium catalyzed coupling reactions of cyclopentenone electrophiles **7-9** with various tin reagents generally give high yields of coupled products (Table 1). The coupling reaction of **8** with tetramethyltin at 55°C in HMPA gave a 95% yield of dihydrojasmone (**13**) while the coupling with various vinyl tin reagents, including (*S*)-*E*-1-tributylstannyl-1-octen-3-ol (**3**) provided the

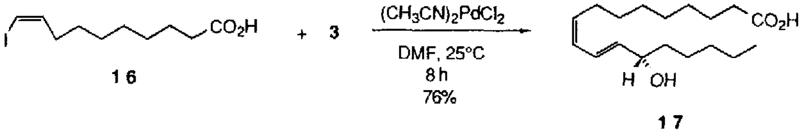
Table 1. Coupling Reactions of Vinyl Electrophiles with Vinyl Reagents[a]

Entry	Electrophile	Tin Reagent	Yield (%)	Product
1	**7**		85	 **11**
2			80	 **12**
3	**8**	Me$_4$Sn	95	 **13**
4			90	 **14**
5	**9**	**3**	70	 **15**

[a] Generally, coupling reactions were carried out on a 1 mmol scale in 10 ml THF with 3% benzylchlorobis(triphenylphosphine)palladium(0) at 55°C, except entry 3, which was carried out in HMPA. For various reaction conditions in the coupling of vinyl iodides with vinylstannanes, see ref. 6b.

expected products. However, when the alcohol function in vinyl tin reagent **3** is protected with the *t*-butyldimethylsilyl group, little coupling takes place with **9**, presumably because the coupling reaction is somewhat sterically demanding,[6a,b] either as a result of a difficult transmetallation reaction or a difficult trans to cis isomerization of the divinylpalladium(II) complex (*vide infra*). The coupling reaction of (*S*)-*E*-1-tributylstannyl-1-octen-3-ol with electrophile **9** gave a good yield of the ester of prostaglandin B_1 (**15**). Thus the ethyl ester of PGB_1 could be obtained in a 55% overall yield from the 2-substituted cyclopentane-1,3-dione (**6**). This overall yield is 2.5-9 times greater than those that have been achieved utilizing Grignard reactions to transform **6** into **15**.[12,13] Furthermore, procedures utilizing the Grignard reagents require between 3 and 5 equivalents of the non-racemic 1-octyn-3-ol.[13d,e]

Since the palladium catalyzed coupling reaction takes place under *neutral*, mild reaction conditions with the vinyl tin reagent (**3**) bearing the unprotected alcohol, it was of interest to determine if a direct synthesis of coriolic acid (**17**) could be achieved by coupling the free acid, (Z)-10-iodo-9-decenoic acid (**16**) with **3**. Vinyl iodide **16** was obtained by the diimide reduction[14] of 10-iodo-9-decynoic acid.[15] The coupling reaction was carried out in DMF with a bis(acetonitrile)dichloropalladium(II) catalyst to give a 76% yield of coriolic acid, (Eq. 3).



(Eq. 3)

This reaction is remarkable in that not only does coupling take place in *the presence of a free acid*, but also good yields are obtained under mild reaction conditions. It is noteworthy that after this work was completed, the synthesis of coriolic acid by the palladium catalyzed coupling reaction of the *methyl ester* of **16** with *t*-butyldimethylsilyl-protected **3** was reported.[16] This coupling reaction gave a 60% yield of the silyl protected methyl ester of coriolic acid but required 4 days at 60°C, as compared with 8 h at 25°C for the tin reagent but **3** with an unprotected alcohol.

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