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(*E*)-Bis-1,2-(tributylstannyl)ethylene as a Staple in a Synthetic Approach to Taxol

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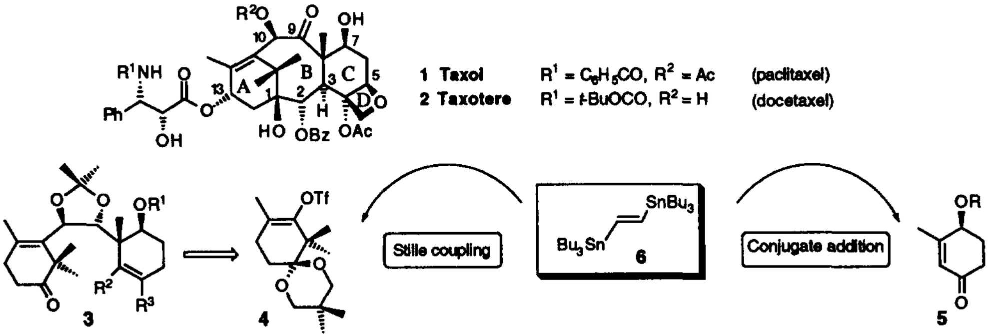
Abstract : An approach of taxol synthesis based on the use of (*E*)-bis-1,2-(tributylstannyl)ethylene **6** as a readily available two-carbon 1,2-link between A and C-ring is described. The conjugate addition of a mixed higher-order stannylvinyl cyanocuprate derived from **6** on chiral cyclohexenone **5** is completely stereoselective. A model study on 3-methylcyclohex-2-enone showed that the afforded stannylvinyl cyclohexenone **12** can be engaged without further transformation in a Stille cross-coupling reaction with the vinyl triflate **4** corresponding to the A-ring of taxol to give *seco*-taxane **14**.

Approval for clinical use of taxol **1** and recently of taxotere **2** shed light on the high pharmaceutical economic and importance of these potent antitumoral molecules that are characterised by a novel mode of action on tubulines.[1]

In addition to their unique biological properties, their unusual complex structure as well as their low natural availability have led to considerable synthetic studies [2] that recently culminated in three total syntheses of taxol **1**.[3] In a program towards the total synthesis of taxol,[4] one of our envisioned approaches was based on the intermediate formation of a *seco*-taxane **3** which would lead to the expected taxol nucleus upon subsequent formation of the C1-C2 bond during the late steps of the synthesis (**Scheme 1**). One example of such a cyclisation step for the construction of the eight-membered B-ring of taxol under SmI_2-promoted intramolecular aldehyde-ketone pinacol coupling conditions was recently described by Swindell *et al.*[5]



Scheme 1

One crucial strategic point for the construction of **3** is the use of vinyl 1,2-distannane as a staple for joining the A and C-rings **4** and **5** of taxol. Bis-1,2-(tributylstannyl)ethylene [6] is a potential two-carbon 1,2-dianion equivalent which can be engaged in either simultaneous [7] or sequential [8] coupling reactions with electrophiles exhibiting similar or complementary reactivities respectively.

The study of molecular models [9] clearly indicates that a good arrangement of the C-1 and C-2 functions to be coupled could be reached through rigidification of the C8-C11 [10] aliphatic segment of the *seco*-ester **3** *via* a cyclic ketal derived from a 1,2-diol at the C9, C10 positions. Although taxol possesses a ketone at C9, other taxoids such as taxusin, baccatin and taxinin, present a *trans* 1,2-diol. Therefore, the *E* double-bond geometry was chosen for **6** because it leads to the required configuration after dihydroxylation.[11]

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For the synthesis of **3**, a reasonable sequence would involve initial cross-coupling reaction of **6** under Stille conditions [12] with vinyltriflate **4**, a suitable precursor for the A-ring. Subsequent conjugate addition of the cuprate derived from the second vinyltin function of the intermediate diene adduct on a convenient C-ring precursor **5** would give the expected *seco*-taxane skeleton. The other sequence where **6** is first condensed with **5** before the Pd (0) catalysed cross-coupling reaction with **4** could not be *a priori* excluded. The present paper deals with our results concerning these alternative approaches for the construction of *seco*-taxane **3**.

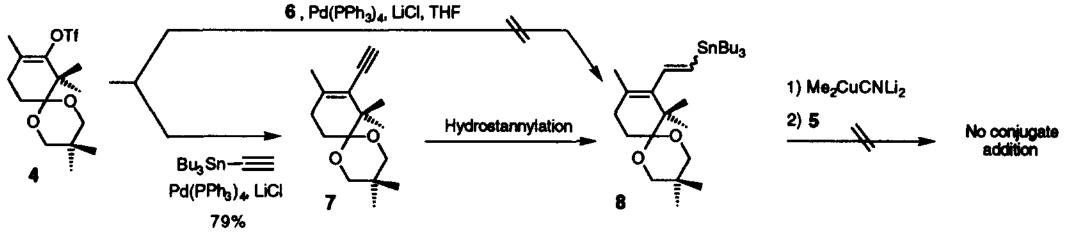
As no example of coupling reaction of **6** with vinyltriflates was known, it was initially decided to experiment its condensation with vinyltriflate **4** under Pd(0) catalysis (**Scheme 2**). Vinyltriflate **4** was prepared from the corresponding ketone in 95% yield.[13] Unfortunately, when **4** was submitted to Stille conditions in presence of **6** [$Pd(PPh_3)_4$, LiCl, THF, reflux], no trace of diene **8** was detected.

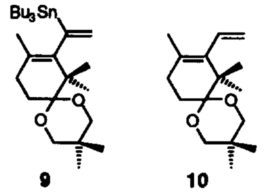
We then decided to prepare **8** by hydrostannylation of enyne **7** which was easily obtained in 79% yield by condensation of vinyltriflate **4** with tributylstannylacetylene under Pd(0) catalysis [$Pd(PPh_3)_4$, LiCl, THF, reflux]. Several hydrostannylation conditions were experimented:

- the reaction at -30°C of enyne **7** with the mixed higher order cyanocuprate $(Bu_3Sn)BuCu(CN)Li_2$ [14] did not afford, after aqueous work-up, the expected distal stannyldiene **8**. The regioisomeric tin derivative **9** was obtained in 52% yield together with the destannylated diene **10** in 24% yield.

- Similar results were obtained under Bu_3SnH/ $Pd(Ph_3)_4$ conditions.[15] In this case, stannyldiene **9** and diene **10** were obtained in 25% and 50% yield respectively.

- By contrast, classical direct hydrostannylation conditions (Bu_3SnH, AIBN, tol, 80°C, 3h) gave the required stannyldiene regioisomer **8** in 50% yield. *E/Z* ratios up to 100:0 were obtained, depending on the quality of the tributyltin hydride.





Hydrostannylation conditions	8	9	10
$(Bu_3Sn)BuCu(CN)Li_2$, 3 eq, THF/H_2O 2/1, -30°C; H^+	0%	52%	25%
Bu_3SnH, $Pd(PPh_3)_2Cl_2$, THF, 20°C	0%	25%	50%
Bu_3SnH, AIBN, Toluene, 80°C	50% *	-	-

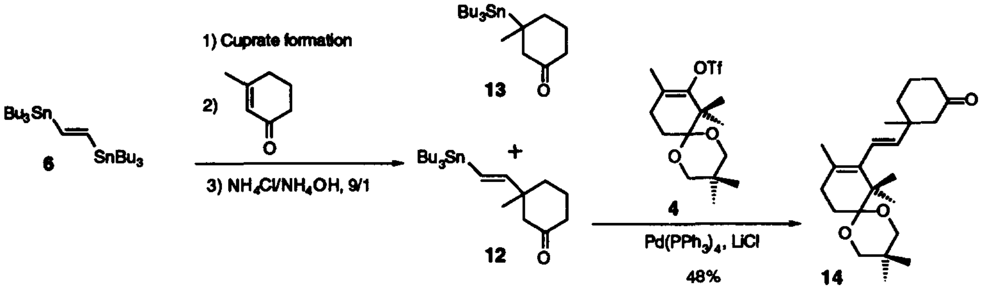
* *E/Z* mixture from 55/45 to 100/0

Scheme 2

We next turned to the conjugate addition of the cuprates derived from **8** on hydroxyenones **5** (R=H or TES) that were readily prepared according to described procedures.[16] Treatment of pure stannyldiene **8*E*** with $Me_2Cu(CN)Li_2$ (THF, 20°C, 1.5h) according to the Lipshutz exchange method [17] followed by *in situ* addition of a solution of enone **5** (R=TES) failed to give any trace of expected 1,4-addition product. The enone was recovered unchanged together with diene **10**. Carrying out this reaction with a 55:45 mixture of **8*E*** and **8*Z*** isomers led to the isolation of diene **10** and stannyldiene **8*Z*** in 39% and 41% yield respectively. The **8*Z*** isomer is obviously not affected by the tin/copper exchange conditions whereas obtention of destannylated diene **10** is in agreement with the formation of the corresponding higher order cuprate from the **8*E*** isomer.

After these disappointing results we decided to test the alternative strategy where (*E*)-bis-1,2-(tributylstannyl)ethylene **6** would be first condensed, *via* its mono-high order cuprate **11**, with conjugated α,β-cyclohexenone precursors of the C-ring of Taxoids. Subsequent cross-coupling of the remaining vinyltin end with vinyltriflate **4** according to the above Stille conditions would lead to *seco*-taxane **3**.

As very few results deal with conjugate addition reactions of the mono higher-order cuprate **11** derived from **6**,[18] preliminary studies were done with 3-methylcyclohex-2-enone. Surprisingly, under classical conditions, two stannylated compounds 12 and 13 were obtained in various proportions as depicted on **Scheme 3**. Beside the expected vinyl derivative 12, non negligeable amounts of the product of 1,4-addition of tributyltin 13 were isolated. Unfortunately, attempts to limit the formation of 13, for example by addition of HMPT [19] or starting from the vinyllithium derivative obtained from Sn/Li exchange,[20] were fruitless. The best conditions (entry 1) led to the formation of 12 in 45% yield.

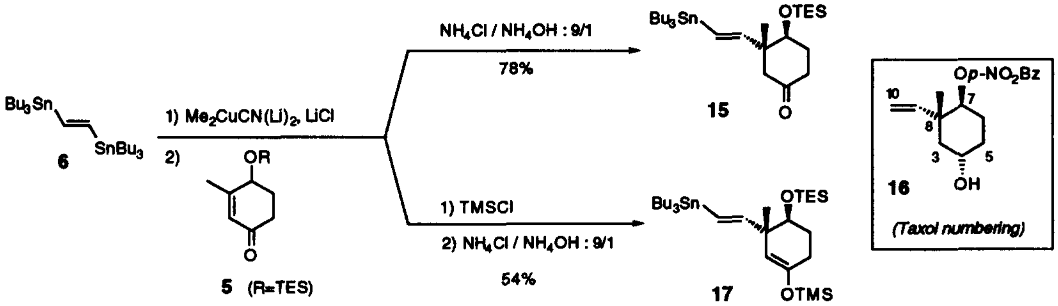


Entry	Cuprate 1,4-addition conditions	12	13
1	$Me_2CuCNLi_2$ (1.6 eq), THF	45%	17%
2	ibid. + HMPT (10 eq)	0%	55%
3	ibid. + LiCl (2 eq)	30%	12%
4	BuLi, THF, then CuCN	31%	16%

Scheme 3

In a preliminary attempt to test our "staple" strategy, a Stille cross-coupling reaction was then carried out between vinylstannane 12 and enoltriflate 4. In presence of freshly prepared $Pd(PPh_3)_4$ [21] and LiCl (THF, reflux, 36 h) the *seco*-taxane derivative 14 was produced in 48% yield.

Having demonstrated the validity of our synthetic approach starting from 3-methylcyclohex-2-enone, we next turned to the more synthetically significant C-ring precursors 5 and the results are summarized on **Scheme 4**. [22] Addition of the mixed higher-order cuprate derived from 6 on γ-hydroxycyclohexenone 5 (R=TES) led to the formation of the expected vinylstannyl adduct 15 in 78% yield after NH_4Cl/NH_4OH workup.



Scheme 4

This conjugate addition is stereoselective. A single diastereomer was isolated and no addition of tributylstannyl residues was observed in this case. The relative *cis* stereochemistry of the methyl and hydroxyl groups has been established by NMR studies on protected diol 16 derived from 15.[23] A 2D NOESY experiment performed on the major 4α-OH isomer allowed an unambiguous elucidation of the relative configuration.

A synthesis of the taxol skeleton would require a further substitution at the C-3 centre. Cuprate conjugate addition followed by direct trapping of the resultant enolate would represent a straightforward solution to this problem. However no such direct condensations were reported in the case of conjugate additions of stannylvinylcuprates and preliminary disappointing results prompted us to address the more reliable route *via* the corresponding silyl enol ether which would be later engaged in a Mukaiyama aldol reaction.[24] Direct addition of trimethylsilylchloride at the end of the above conjugate addition reaction afforded enol ether **17** in 54% yield. Further work is still in progress to improve these results towards a total synthesis of taxol.

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