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Expeditious Stereo and Regioselective Synthesis of Stannylated Dienynes: Versatile Precursors of Dienediynes Related to Neocarzinostatin Chromophore

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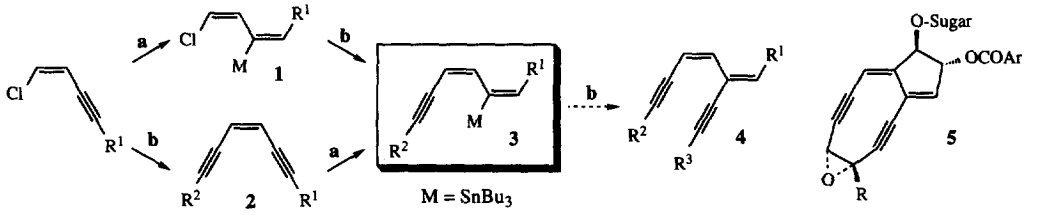
Abstract: Hydrostannation of readily available (*Z*) or (*E*)-enediynes is described. This reaction allows an expeditious stereo- and regioselective construction of stannylated dienyne derivatives **3**, suitable for the synthesis of dienediyne systems **4** related to NCS-C **5**. Copyright © 1996 Elsevier Science Ltd

Neocarzinostatin chromophore **5** (NCS-C),[1] a remarkably powerful antitumor antibiotic, has generated considerable interest towards its synthesis and the design of analogues which mimic its DNA cleaving properties.[2] The antitumor activity of NCS is proposed to be associated with the dienediyne core. Several approaches to such highly conjugated system have been described from α-bromocyclopentenone,[3] bis-enol triflates,[4] xylitol[5] or via sequential carbometallation anion capture.[6] Furthermore to our knowledge, synthesis of acyclic dienediyne system **4** has not been realized due to the lack of efficient routes to construct such molecules.



a: hydrostannation step **b**: coupling step

Scheme 1

A straightforward approach to **4** *via* **3** could be the sequential Pd-mediated coupling reaction of (*Z,E*)-stannylated chlorodienes[7] **1** with 1-alkynes (Scheme 1, path ab). However, **3** (M = $SnBu_3$) could not be obtained in satisfactory yield through this pathway, presumably due to the steric hindrance exerted by tributyl tin groups. In contrast, the cross coupling reaction[8] of (*E,E*)-stannylated chlorodienes **6** with alkynes occurs readily and gives (*E,E*)-stannylated dienynes **7** in good isolated yields (70-90%, Table I).

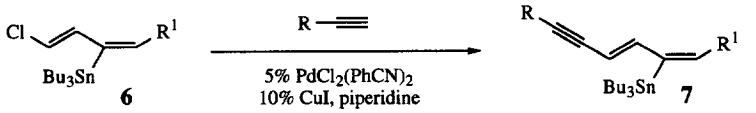


Table I

Entry	R^1	R	Isolated yield of **7** (%)	Product
1	$(CH_2)_2OH$	C_5H_{11}	90	**a**
2	CH(OH)Me	"	80	**b**
3	CH_2NMe_2	"	90	**c**
4	"	$(CH_2)_2OH$	70	**d**
5	"	$CH(OH)C_5H_{11}$	77	**e**

We therefore turned our attention to the introduction of the acetylenic group before the hydrostannation step (Scheme 1, path ba). If the tributyltin hydride is regioselectively added to (*Z*)-enediynes[9] **2**, this reaction will be useful and convenient for the preparation of stannylated dienynes **3**. We report herein a stereo and regioselective synthesis of stannylated dienyne derivatives **3** involving the palladium-catalyzed hydrostannation of (*Z*)-enediynes **2**.

Thus, symmetrical (*Z*)-enediynes[10] **8** undergo rapid addition (20 min) of *n*-Bu_3SnH (1.1 equiv.) in the presence of $PdCl_2(PPh_3)_2$ (5%) to give stannylated dienynes **9**[11] in good isolated yields as a single regioisomer in which the tributyl tin group is introduced at the α carbon (Table II). It must be outlined, that no β-regioisomer **10** was formed.

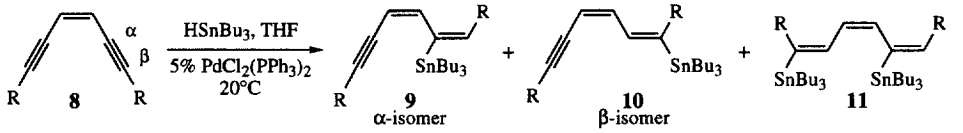
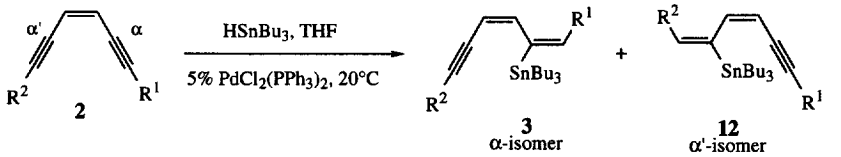


Table II

Entry	R	Isolated yield of (%)			Product
		9	**10**	**11**	
6	$(CH_2)_2OH$	78	0	8	**a**
7	$CH(OH)C_5H_{11}$	50	0	-[a]	**b**
8	C_5H_{11}	82	0	-[a]	**c**
9	C_6H_5	77	0	-[a]	**d**

[a] less than 2% of an other isomer were obtained whose structure could not be assigned.

In the case of the unsymmetrial (*Z*)-enediyne alcohol **2a**, the reaction gives a mixture (1:1) of unseparable α and α' isomers since the tributyltin hydride does not discriminate in its addition between the two triple bonds.



a $R^1 = C_5H_{11}$, $R^2 = (CH_2)_2OH$ (77%) 50 50

More interestingly, palladium-catalyzed hydrostannation of unsymmetrical (*Z*)-enediynes **13** bearing a trimethylsilyl group was remarkably regio and stereoselective and gives exclusively stannylated dienynes **14** in excellent isolated yields[12] (79-96%, Table III). It is worthy to note that only the α-isomer *versus* α'-isomer was obtained since the two triple bonds exhibit appreciably different reactivities toward Bu_3SnH.[13]

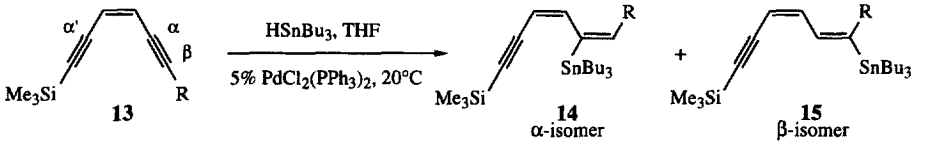


Table III

Entry	R	Isolated yield of (%)		Product
		14	**15**	
10	$(CH_2)_2OH$	96	0	**a**
11	CH_2OH	90	0	**b**
12	CH_2NMe_2	96	0	**c**
13	C_6H_5	79	0	**d**
14	C_5H_{11}	92	0	**e**

It is interesting to note that the geometry of the double bond in the enediyne derivatives has a significant influence on the formation of the α-isomers. Thus, when performing the hydrostannation of unsymmetrical (*E*)-enediynes **16** containing a trimethylsilyl group, the addition of Bu_3SnH was less regioselective and gives a mixture of α and β-isomers. The two geometric isomers **17a-d** and **18a-d** were obtained in a ratio ranging from 64:36 to 94:6 depending on the nature of the R group (Table IV).

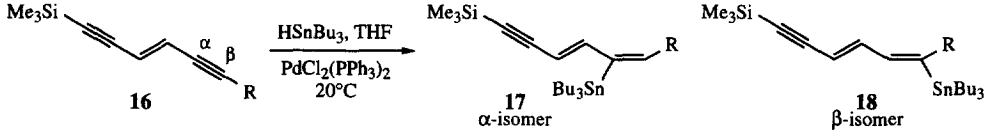


Table IV

Entry	R	Isolated yield of (%)		Product
		17	**18**	
15	$(CH_2)_2OH$	61	34	**a**
16	C_5H_{11}	59	23	**b**
17	$CH(OH)C_5H_{11}$	58	11	**c**
18	CH_2NMe_2	82	5	**d**

In conclusion, this reaction provides an efficient and regioselective route to stannylated dienynes from the corresponding enediyne derivatives. These alkenyl stannanes **9** and **14** are potentially suitable reagents for the stereoselective construction of dienediyne compounds **4** related to NCS-C. Additional developments will be reported in due course.

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11. Satisfactory spectral data were obtained for all new compounds.
12. *Typical procedure: preparation of (3E,5Z)-4-tributyltin-8-trimethylsilyl-octa-3,5-dien-7-yn-1-ol (**14a**, Table III, entry 10)*: To a solution of (*Z*)-enediyne **13a** (179 mg, 0.93 mmol) and $PdCl_2(PPh_3)_2$ (32 mg, 0.0465 mmol) in THF (2 mL), under an argon atmosphere, was added dropwise tributyltin hydride (0.28 mL, 1.023 mmol) and the reaction was stirred at room temperature and monitored by TLC analysis until complete consumption of the starting material (15 to 30 min). After evaporation of the solvent *in vacuo*, the crude material was purified by filtration through silica gel (petroleum ether:ethyl acetate 9:1) and gave 428 mg (96%) of pure stannylated dienyne **14a**: ^{1}H-NMR (250 MHz) δ: 6.50 (1H, dd, J = 12 and 1 Hz), 5.60 (1H, td, J = 6.5, 1.5 and 63 Hz), 5.37 (1H, d, J = 11.5 Hz), 3.65 (2H, q, J = 6 Hz), 2.38 (2H, q, J = 6.5 Hz), 1.60 to 1.19 (13H, m), 0.96 to 0.83 (15H, m), 0.13 (9H, s); ^{13}C-NMR (50 MHz) δ: 144.70, 144.50, 138.10, 106.55, 103.80, 99.90, 62.00, 34.60, 29.00, 27.30, 13.65, 10.60, 0.05.
13. Similar deactivation of the acetylenic bond by trimethylsilyl group toward hydrostannation has been reported, see: ref. 9b.

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