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The First and Convenient Synthesis of Acyclic Dienediynes Related to Neocarzinostatin Chromophore

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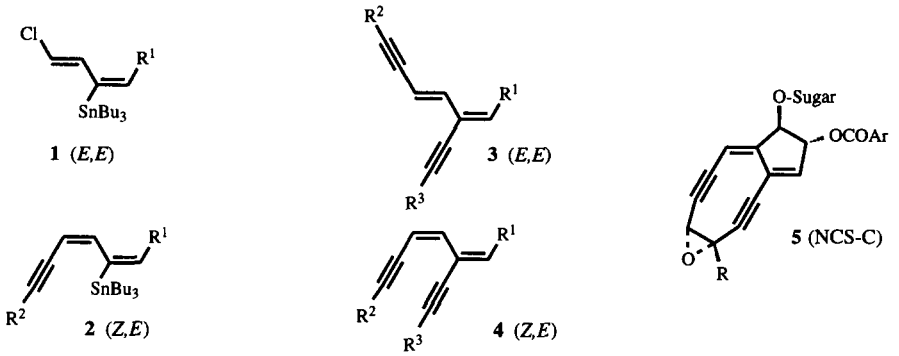
Abstract: A stereocontrolled and flexible synthetic approach to acyclic (*E,E*) and (*Z,E*)-dienediynes, related to the neocarzinostatin chromophore **5**, from readily available stannylated chlorodienes **1** and dienynes **2** is described.

Recently we have shown that under palladium catalysis, the hydrostannation of chloroenynes and enediynes proceeds in a remarkable regio and stereoselectivity to give the corresponding stannylated chlorodienes **1** and dienynes **2** in high yields.[1] An important aspect of our ongoing research on the synthetic utility of **1** and **2** as intermediates in organic synthesis is their elaboration via further reaction into stereodefined dienediynes **3** and **4**. Such highly unsaturated system, found in the natural antitumor antibiotic neocarzinostatin chromophore **5** (NCS-C),[2] have been shown to be responsible of its biological activity including the ability to cleave DNA upon suitable chemical activation.[3]



Scheme 1

Owing to the chemical instability of **5**, great effort has been devoted to the synthesis of new cyclic or bicyclic analogues,[4] having the dienediyne unit, from α-bromocyclopentenone,[5] bis-enol triflates,[6] xylitol[7] or

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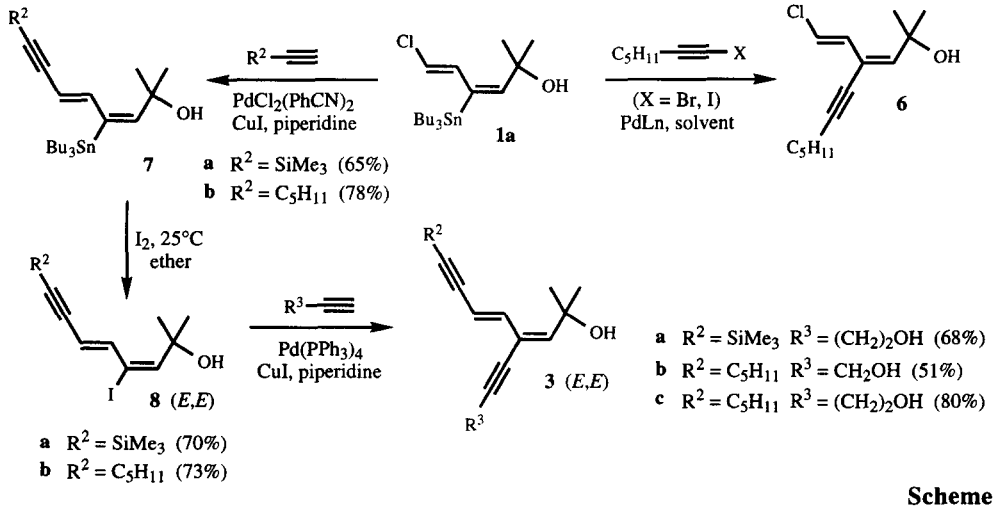
via sequential carbometallation anion capture.[8] However, no acyclic dienediyne derivatives **3** and **4** have so far been reported due to the lack of efficient routes to construct such molecules. Herein, we report a stereocontrolled and flexible strategy for the synthesis of both acyclic (*Z,E*) and (*E,E*)-dienediynes starting from readily available stannylated derivatives **1** and **2**.

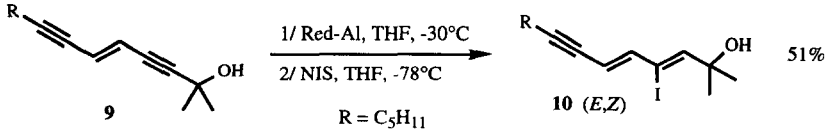
(*E,E*)-Dienediynes **3** could be obtained from (*E,E*)-stannylated chlorodienes **1** via sequential Pd-mediated coupling reactions (Scheme 1). As a model, we first investigated the coupling of 1-haloheptyne with stannylated chlorodiene **1a**, readily obtained by hydrostannation[1a] of the corresponding chloroenyne (94%). However, the coupling product **6** could not be obtained in satisfactory yield[9] (15 to 20%) even by using various combinations of Pd/solvent/additive mixtures (e.g., $Pd(PPh_3)_4$, $PdCl_2L_2$ (L = MeCN or PPh_3), $Pd(dba)_2$/$(furyl)_3P$ or $AsPh_3$ in DMF or NMP, with or without CuI).



Scheme 2

Difficulties in coupling **1a** with 1-haloalkynes led us to explore a second synthetic approach starting from the (*E,E*)-stannylated dienynes **7** easily prepared[10] from **1a** as outlined in scheme 2. Stereospecific iodo-destannylation of **7** under appropriate reaction conditions provided cleanly the corresponding unsaturated (*E,E*)-vinyl iodides **8** which afforded after coupling with 1-alkynes under palladium-copper catalysis[11] stereodefined (*E,E*)-dienediynes **3a-c**[12] in moderate to good yields (51-80%, scheme 2).

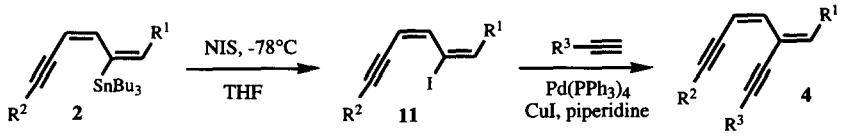
It may be pointed out that vinyl iodides **8** were found to contain only one stereoisomer (≥98%) assigned as (*E,E*) based upon comparison (^1H and ^{13}C-NMR spectra) to the (*E,Z*)-isomer easily obtainable from the enediyne **9**[13] according to scheme 3.



Scheme 3

We next investigated the synthesis of stereodefined (*Z,E*)-dienediynes **4** under similar conditions starting from (*Z,E*)-stannylated dienynes **2** (scheme 4). Thus, the required compounds **2** were obtained by hydrostannation of the corresponding (*Z*)-enediynes.[1b] Iododestannylation of **2** with iodine in ether at room

temperature lead to a mixture of stereoisomers ((*Z,E*)/(*Z,Z*): 50/50 to 70/30 determined by ^{1}H-NMR) fortunately, utilization of NIS in THF at -78°C obviated the problem. However, purification of the compounds **11** by chromatography on silica gel resulted in their partial isomerization. Therefore, the crude unsaturated vinyl iodides **11** were treated directly with 1-alkynes under Pd-Cu catalysis to accomplish coupling reactions. Workup and chromatography of the concentrated reaction mixtures on deactivated silica gel (pretreated with 25% aq. $NaHCO_3$) afforded the pure (*Z,E*)-dienediynes[14] **4** in good overall yields.

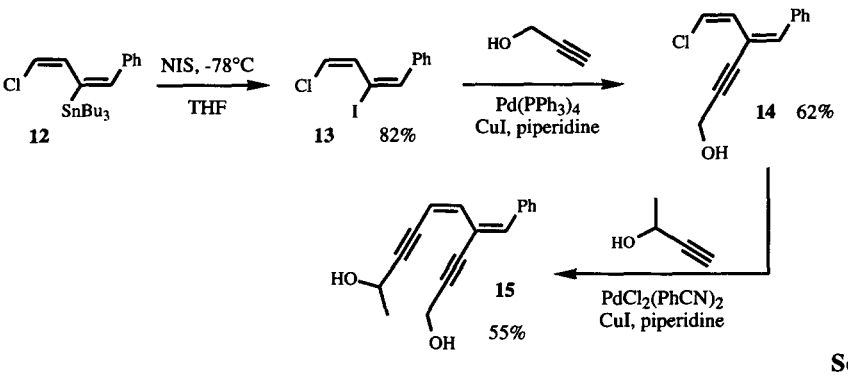


a $R^1 = R^2 = Ph$
b $R^1 = Ph$ $R^2 = SiMe_3$

a $R^1 = R^2 = Ph$ $R^3 = (CH)OHMe$ (51%)
b $R^1 = Ph$ $R^2 = SiMe_3$ $R^3 = (CH)OHMe$ (49%)
c $R^1 = Ph$ $R^2 = SiMe_3$ $R^3 = (CH_2)_2OH$ (47%)

Scheme 4

It is interesting to note that (*Z,E*)-dienediynes **4** may also be prepared in a similar way from **13** by sequential coupling reactions. Thus, reaction of **12** with NIS in THF at -78°C affords stereospecifically (*Z,E*)-1,3-chloroiododiene **13**. Sequential coupling of **13** with 1-alkynes under palladium-copper catalysis[11] provided stereodefined (*Z,E*)-dienediyne **15**[15] (Scheme 5).



Scheme 5

In conclusion, we have succeeded in developing an efficient and flexible synthetic route to acyclic (*E,E*) and (*Z,E*)-dienediyne compounds **3** and **4** starting from readily available stannylated derivatives **1** and **2**. Investigations toward the cycloaromatization of these compounds are currently in progress and will be reported in due course.

The following procedure for the preparation of ***4c*** *is representative*: To a stirred solution of stannylated **2b**[1b] (1.6 mmol, 825 mg) in dry THF (3 mL) under an argon atmosphere was added at -78°C NIS (2.4 mmol, 544 mg) in THF (2 mL) and the dark wine solution was stirred until all of the substrate had been consumed (1h). After concentration of THF *in vacuo*, the ^{1}H-NMR of the crude material (oil) showed the presence of only one stereoisomer[16] (≥ 98%). To a mixture of this crude material in piperidine (5 mL) were added successively, under an argon atmosphere, $Pd(PPh_3)_4$ (0.08 mmol, 93 mg), 3-butyn-1-ol (3.2 mmol, 224 mg) and CuI (0.16 mmol, 31 mg). The reaction was stirred at room temperature and monitored by TLC analysis until complete consumption of the unsaturated vinyl iodide **11b** (4h) before to be treated with a saturated aqueous solution of ammonium chloride and extracted with Et_2O. The organic extract was dried over $MgSO_4$ and the solvent was

removed *in vacuo*. Filtration through deactivated silica gel (pretreated with 25% aq. $NaHCO_3$ (petroleum ether/AcOEt 5%) gave 221 mg (47%) of pure **4c**: ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.32 to 7.27 (5H m), 6.95 (1H, s), 6.50 (1H, d, J = 11.9 Hz), 5.68 (1H, d, J = 11.9 Hz), 3.78 (2H, q, J = 6.1 Hz), 2.66 (2H, t, J = 6.1 Hz), 2.02 (1H, t, J = 6.2 Hz), 0.20 (9H, s); ^{13}C-NMR (63 MHz, $CDCl_3$): δ 140.35, 135.25, 129.55, 128.30, 128.15, 117.75, 111.50, 103.80, 102.50, 88.50, 82.20, 61.00, 24.20, -0.05; CIMS (NH_3) m/e: 312 ($M+NH_4^+$, 8%), 295 (M^+, 100%), 205 (20%).

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11. Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *40*, 6403-6406.
12. **3c:** ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.44 (1H, d, J = 15.0 Hz), 6.07 (1H, dt, J = 15.0 and 2.3 Hz), 5.94 (1H, s), 3.72 (2H, t, J = 6.3 Hz), 2.58 (2H, t, J = 6.3 Hz), 2.30 (2H, td, J = 7.0 and 2.3 Hz), 1.56 to 1.45 (2H, m), 1.38 (6H, s), 1.36 to 1.27 (4H, m), 0.87 (3H, t, J = 7.1 Hz); ^{13}C-NMR (63 MHz, $CDCl_3$): δ 144.45, 134.85, 121.90, 113.60, 95.20, 86.60, 80.10, 79.75, 71.85, 61.10, 31.35, 31.00, 28.40, 22.20, 19.65, 13.90; CIMS (NH_3) m/e: 292 ($M+NH_4^+$, 2%), 275 ($(M+H)^+$, 1%), 257 ($(M+H)^+-H_2O$, 100%), 173 (20%).
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14. Satisfactory spectral data were obtained for all new compounds.
15. During the purification step, a partial isomerization of the trisubstituted double bond of the compound **15** was observed: *Z,E*/*Z,Z* = 85/15 determined by ^{1}H NMR.
16. ^{1}H-NMR (250 MHz, $CDCl_3$) of the crude unsaturated vinyl iodide **11b:** δ 7.26 (6H, m), 6.44 (1H, dd, J = 11.8 and 2.0 Hz), 5.53 (1H, d, J = 11.9 Hz), 0.13 (9H, s).