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Palladium-Catalyzed Sequential Bond Formation Leading to Conjugated Ene-Yne System

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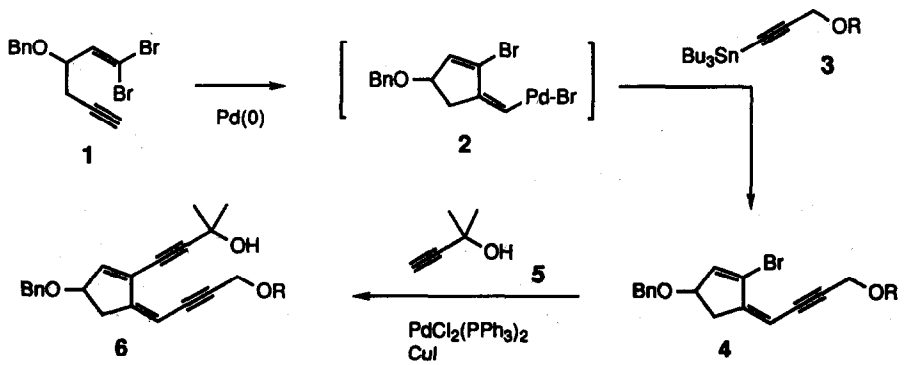
Key Words: Ene-Yne System; Palladium-catalysis; *gem*-Dibromide; Cross-coupling; Neocarzinostatin

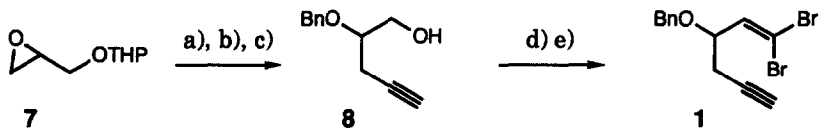
Abstract: Palladium-catalyzed sequential formation of carbon-carbon bonds among sp^2 and sp carbons was performed to construct a highly conjugated ene-yne system aiming neocarzinostatin chromophore.

Neocarzinostatin (NCS) chromophore and its congeners characterized by their ene-yne functionalities are challenging target molecules for synthetic chemists, because of the unique structure and remarkable properties.[1] A variety of excellent approaches to the conjugated cores have been exploited,[1] however such highly conjugated systems still demand a more straightforward assemble method. We have demonstrated that the palladium-catalyzed insertion/cross-coupling sequence can provide a novel method to connect sp^2 and sp carbons.[2] The successful results have stimulated us to explore a direct and potentially more versatile access by palladium-catalyzed processes consisting intramolecular insertion of **1**, ensuing cross-coupling of **2** and **3** leading to an ene-yne system **4**, and further cross-coupling with another acetylene **5** as outlined in Scheme I. A recent work on the insertion/cross-coupling reaction[3] led us to report our preliminary results.



Scheme I

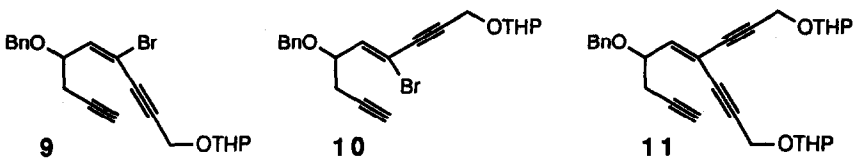
The starting dibromide **1** was readily prepared according to the following Scheme II. Thus, ring opening of epoxide **7** with lithium acetylide in DMSO followed by protection of alcohol with benzyl chloride and removal of THP group gave alcohol **8**. Swern oxidation of **8** and subsequent dibromoolefination[4] with carbon tetrabromide and triphenylphosphine afforded the 1,1-dibromoolefin **1**.



7 **8** **1**

Scheme II a) Li acetylide b) BnCl c) *p*-TsOH d) $(COCl)_2$, DMSO, Et_3N e) CBr_4, PPh_3

The experimental procedure of the sequential reaction is very simple as follows. A mixture of the dibromide **1** and the alkynylstannane **3** (R=THP, 3 equiv.) in the presence of palladium acetate (5 mol%) and triphenylphosphine (10 mol%) in toluene was stirred at 60 °C for 5 h under argon atmosphere. The cyclization and coupling sequence successfully proceeded to produce the ene-yne system **4** (R=THP) in 51% yield. Another silyl derivative **4** (R=TBDMS) was obtained in 28% yield by using **3** (R=TBDMS) under similar reaction conditions as above. On the other hand, the reaction in acetonitrile afforded mono cross-coupling product **9** or **10** in a good yield. Further treatment of the mono coupling product with **3** (R=THP) gave only diacetylene **11** without any cyclized compounds. If the mono coupling product is the (Z)-bromide **10**, the cyclization may follow.[3] Although the geometry of the olefin has not been confirmed, we suppose the mono coupling product has E-geometry figured as **9**.



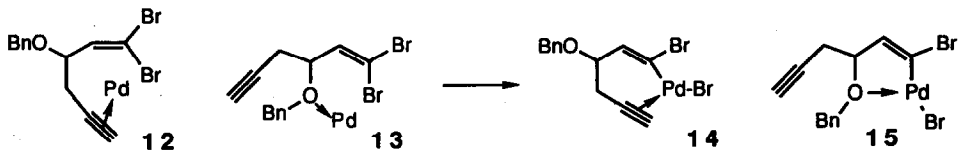
9 **10** **11**

Subsequently, the further carbon-carbon bond formation to elaborate the core framework of the NCS chromophore was performed by the treatment of the bromide **4** (R=THP) with **5** under Sonogashira's conditions.[5] Although decomposition of the product **6** (R=THP) proceeded in some extent during flash chromatography, two different kinds of acetylenic appendages could be introduced into the five-membered skeleton. Other attempts in the presence of hydroquinone did not affect the coupling reaction.[6]

The use of the stannane reagents **3** requires cumbersome purification procedures, because the residue of the stannanes always contaminates the products. Hence, we examined the sequential process in the presence of palladium and copper catalysts, which have successfully been employed in a similar cyclization as previously reported by us.[2] Unfortunately, the reaction of the dibromide **1** and protected propargyl alcohol resulted in only disubstitution of the two bromine atoms to give **11** in a high yield. Transmetalation with copper acetylide was so faster than the intramolecular insertion process that no cyclization product **4** was detected.

Initially, we envisioned that the selective carbon-carbon bond making to produce **10** by the replacement of the (E)-bromine atom of **1** may take place based on the following results. It has been well documented that the palladium-catalyzed cross-coupling reactions of (E)-bromoalkenes are substantially faster than those of (Z)-

bromoalkenes.[7] Selective mono cross-couplings of 1,1-dihaloolefins have also been studied, in which (E)-halogen is exclusively substituted with various nucleophiles.[8] However, the formation of **4** indicates that the actual reaction apparently proceeded through the oxidative addition of the (Z)-bromide in contrast to the above mentioned results. Such a predominant oxidative addition of the (Z)-bromide of **1** would be assisted by the initial coordination of the triple bond[9] or the oxygen atom of the benzyloxy group as illustrated in **12** or **13**, which preferentially delivers the palladium catalyst to the (Z)-bromide.[10] The resulting complex **14** or **15**, stabilized by the intramolecular coordination, is allowed to undergo intramolecular insertion of the acetylene moiety giving rise to the intermediate **2**, or transmetalation leading to the coupling product **9**. A subsequent reaction of the alkenylpalladium **2** with the alkynylstannane **3** afforded the ene-yne **4**. The geometry of the olefin of **4** was assigned on the bases of the recent report[3] as well as precedents involving insertion process,[11] comparison of the NMR data,[1] and the established mechanism that insertion proceeds in a *cis*-fashion.[12]



In conclusion, the palladium-catalyzed sequential formation of contiguous carbon-carbon bonds in a single operation has proved to provide a straightforward and convergent synthetic path to the ene-yne system, the indispensable structure of NCS chromophore, with the desired olefin geometry. The discrimination of the two bromine atoms of the 1,1-dibromide **1** has been accomplished to construct **4**, in which one vinylic bromine atom is still available at the proper position. Since another acetylenic appendage has been introduced into **4** as exemplified in the preparation of **6**, further investigation for the direct construction of the pivotal bicyclic conjugated core is in progress.

We thank the SC-NMR Laboratory of Okayama University for obtaining 500 MHz NMR spectra.[13]

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13. The selected NMR data (500 MHz for ^{1}H and 125 MHz for ^{13}C, $CDCl_3$) δ (ppm).
4 (R=THP): 2.67 (d, *J*=16.87 Hz, 1H, =CCH_2), 2.97 (ddd, *J*=1.80, 6.78, 16.87 Hz, 1H, =CCH_2), 3.53 (dt, *J*=4.51, 11.24 Hz, 1H, OCH_2), 3.85 (dt, *J*=3.14, 11.24 Hz, 1H, OCH_2), 4.44 (brs, 2H, CH_2OTHP), 4.53 (s, 2H, CH_2Ph), 4.57 (dt, *J*=2.45, 6.78 Hz, 1H, BnOCH), 4.88 (t, *J*=3.48 Hz, 1H, OCHO), 5.53 (d, *J*=1.80 Hz, 1H, CH=), 6.51 (brs, 1H, CH=CBr), 7.25-7.42 (m, 5H, Ar).; ^{13}C NMR 19.16, 25.37, 30.27, 38.79, 54.90, 62.09, 70.80, 78.94, 81.73, 93.21, 96.69, 101.64, 125.18, 127.76, 127.84, 128.48, 137.82, 142.64, 148.47.
6 (R=THP): 2.62 (d, *J*=17.1 Hz, 1H, =CCH_2), 2.92 (dd, *J*=6.81, 17.2 Hz, 1H, =CCH_2), 3.53-3.59 (m, 1H, OCH_2), 3.82 (t, *J*=10.0 Hz, 1H, OCH_2), 4.40 (d, *J*=15.9 Hz, 1H, CH_2OTHP), 4.49 (d, *J*=15.9 Hz, 1H, CH_2OTHP), 4.52 (s, 2H, CH_2Ph), 4.65-4.69 (m, 1H, BnOCH), 4.93-4.97 (m, 1H, OCHO), 5.50 (brs, 1H, CH=C-C≡), 6.54 (brs, 1H, =CH-C≡). ^{13}C NMR 18.62, 25.26, 29.92, 31.14, 31.20, 31.29, 31.36, 38.61, 38.69, 53.38, 55.10, 55.15, 61.63, 64.82, 70.78, 70.80, 75.48, 79.44, 79.48, 82.93, 90.20, 96.30, 96.39, 100.33, 100.38, 127.73, 128.43, 128.79, 138.13, 146.05, 146.13, 151.34, 151.38
9: 2.03 (t, *J*=2.98 Hz, 1H, ≡CH), 2.53 (dt, *J*=2.98, 5.91 Hz, 2H, ≡CCH_2), 3.49-3.58 (m, 1H, OCH_2), 3.82-3.88 (m, 1H, OCH_2), 4.39-4.65 (m, 5H, 2XCH_2OTHP, BnOCH), 4.82 (t, *J*=3.42 Hz, 1H, OCHO), 6.36 (d, *J*=8.36 Hz, 1H, CH=CBr), 7.25-7.38 (m, 5H, Ar).
11: 2.02 (t, *J*=2.63 Hz, 1H, ≡CH), 2.50 (ddd, *J*=2.63, 5.92, 16.5 Hz, 1H, ≡CCH_2), 2.55 (ddd, *J*=2.63, 5.92, 16.5 Hz, 1H, ≡CCH_2), 3.50-3.58 (m, 2H, OCH_2), 3.80-3.89 (m, 2H, OCH_2), 4.49-4.55 (m, 1H, BnOCH), 4.31-4.64 (m, 6H, 2XCH_2OTHP, CH_2Ph), 4.78 (dt, *J*=3.04, 3.31 Hz, 1H, OCHO), 4.83 (t, *J*=3.41 Hz, 1H, OCHO), 6.31 (d, *J*=9.27 Hz, 1H, CH=), 7.24-7.38 (m, 5H, Ar).

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