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An Approach to the A Ring of Neocarzinostatin Chromophore *via* Sequential Carbometalation/Anion Capture

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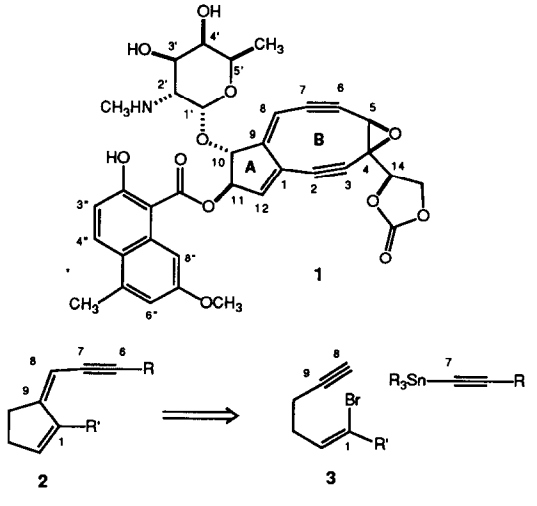
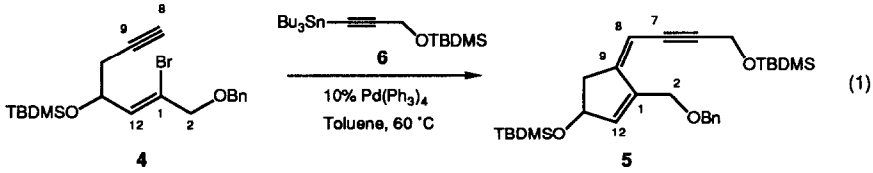
Abstract: An intramolecular palladium catalyzed carbometalation followed by anion capture achieves construction of a model comprising the A ring of the proposed structure of Neocarzinostatin Chromophore-A with sufficient functionality to elaborate the B ring and explore the likely mode of biological action.

The highly interesting structure[1] and novel mode of biological action[2] of the powerful antitumor antibiotic Neocarzinostatin Chromophore (NCS-Chr), **1**, have made it an attractive target for both total synthesis and for the design of analogues which mimic its considerable biological activity.[3] Important subgoals subsumed in this exotic target are the labile array of unsaturation, control of olefin geometry and position, formation of the strained bicyclo[7.3.0]dodecadienediyne nucleus and the installation of four stereogenic centers on the C_{12} core. We perceived that by exploiting the known selectivities of transition metal mediated carbometalation, along with the entropic advantage of intramolecular formation of five membered rings, an acyclic precursor could be transformed in one operation to the NCS-Chr A ring with proper appendages for elaboration of the B ring.[4] Our strategy is described in Scheme 1. This synthetic approach can easily access structurally modified analogues for the further elucidation of the biological action. The plan involves utilizing an intramolecular carbometalation to form the bond between C1 and C9; this is immediately followed by intermolecular capture of the resultant (Z)-organometallic by an alkynyl tin to form the C7-C8 bond.[5,6]

Scheme 1. Structure of Neocarzinostatin Chromophore and Plan for Assembly of the A Ring



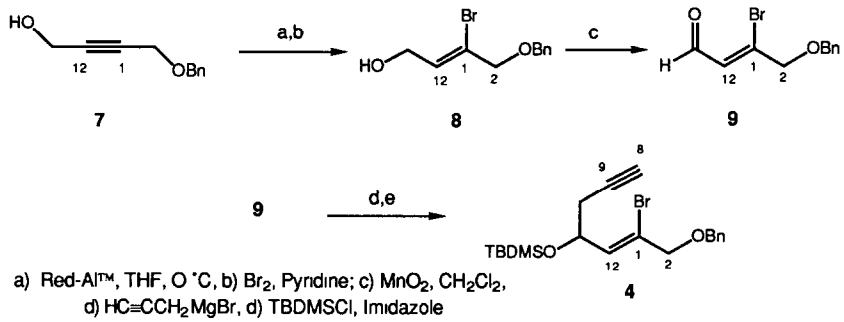
The successful implementation of this strategy in the synthesis of the A ring model, **5**, is described in Equation 1 (the numbering system refers to that of NCS-Chr, **1**). Reaction of bromoeneyne **4** with two to three equivalents of the alkynyl stannane **6** in the presence of a catalytic amount of $Pd(Ph_3)_4$ (10 mol%, 70 °C, 5-6 hr) results in the complete conversion of **4** to a single product, assigned from spectroscopic data as the desired cyclization product **5**.[7] Capillary gas chromatographic examination of the crude reaction mixture reveals **5** and *n*-Bu_3SnBr as the only volatile products (86% yield by GC, 75% after chromatography). This two component reaction has led, in a single operation, to the construction of the C1-C9 and C7-C8 bonds, with complete control of the C8-C9 exocylic olefin geometry, based on the literature precedent for *syn*-carbometalation of alkynes.[4,5,8].



(1)

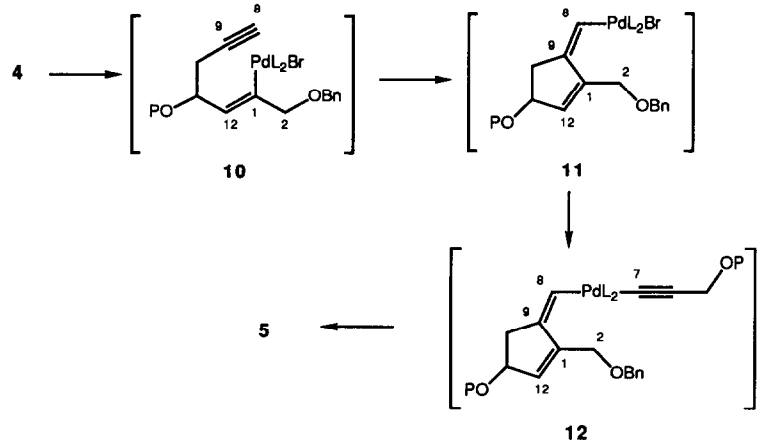
The requisite substrate **4** was synthesized from 2-butyne-1,4-diol *via* the known benzyl ether, **7**.[9] Directed hydrometalation with Red-Al™ at 0 °C followed by brominolysis in pyridine at -78°C provided a 98% yield of the fragile vinyl bromide **8** as a single geometric isomer.[10] Oxidation of **8** (MnO_2, CH_2Cl_2, 56%) afforded aldehyde **9.** Addition of propargyl magnesium bromide (-78°C, 70%) and protection of the resultant alcohol (TBDMSCl, Imidazole, DMF, 68%) provided the model substrate **4**. The C5-C7 fragment, **6**, was prepared from propargyl alcohol in two steps (TBDMSCl protection, then *n*-BuLi/*n*-Bu_3SnCl) in 66% overall yield.

Scheme 2. Preparation of the Substrate **4**



It is our operating presumption (Scheme 3) that the reaction proceeds by initial oxidative addition of palladium(0) to the C1-Br bond to afford **10**; complexation of the pendant alkyne and migratory insertion, proceeding in a *syn* fashion, then give a second vinyl palladium species, **11**, having the correct C8-C9 olefin geometry.[4,5,8] Note that the high effective concentration of the alkyne proximal to the metal-carbon bond in **10** has made intramolecular carbometalation rapid compared to intermolecular capture of **10** by **6** (Stille type coupling);[6] this phenomena has been noted previously.[5] Transmetalation of **11** with the alkynyl tin, **6**, provides **12**; reductive elimination affords **5** and regenerates palladium (0).[6]

Scheme 3 Mechanistic Hypothesis for Formation of **5**.



In summary, we have developed an expeditious and versatile route for construction of a key portion of the biologically relevant core of Neocarzinostatin Chromophore-A. Further studies, now in progress, are aimed at elaborating the nine-membered ring and at performing an intramolecular carbometalation/intramolecular capture sequence in which both rings are formed at once.

Acknowledgments

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7 The experimental procedure: A solution of 158 mg (0.386 mmol) of **4** dissolved in 1.5 ml of toluene was added to 45 mg of tetrakis(triphenylphosphine)palladium(0) (0.0386 mmol) followed by 443 mg (0.965 mmol) of **6** dissolved in 1.0 ml of toluene. The resulting solution was then heated to 70°C for 6 h; higher temperatures resulted in faster conversion. The solution was directly chromatographed on SiO_2 using 40 : 1 (petroleum ether : ether) to give 144 mg (75% yield) of spectroscopically pure **5**; the remainder of the product is contaminated with **6**. Selected spectral data for **5**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H, arom), 6.27 (bs, 1H, H_{12}), 5.32 (d, J = 1.2 Hz, 1H, H_8); 4.88-4.86 (m, 1H, H_{11}), 4.66-4.48 (m, 4H, benzyl and H_2 and $H_{2'}$), 4.37 (d, J = 2.3 Hz, 2H, H_5 and $H_{5'}$), 2.96 (ddd, J = 1.2 Hz, 7.1 Hz, 16.8 Hz, 1H, *anti* H_{10}), 2.51 (ddd, J = 2.0 Hz, 2.0 Hz, 16.9 Hz, 1H, *syn* H_{10}) 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 6H) , 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.75, 143.92, 140.22, 138.36, 128.35, 127.69, 127.59, 97.45, 90.97, 82.98, 73.36, 73.06, 67.53, 52.34, 43.16, 25.90, 25.87, 18.33, -4.57, -4.63, -5.11; IR (film) 2955, 2929, 2886, 2857, 1472, 1463, 1361, 1255, 1078, 836, 777 cm^{-1}, HRMS m/z, M^+, calcd. for $C_{29}H_{46}O_2Si_2$ 498.2987, found 498.2981.

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