Transition-Metal-Catalyzed Strategies for the Synthesis of Neocarzinostatin Chromophore and Analogues: Intramolecular Delivery of Palladium Controls Construction of the Biologically Relevant Dienediyne Core

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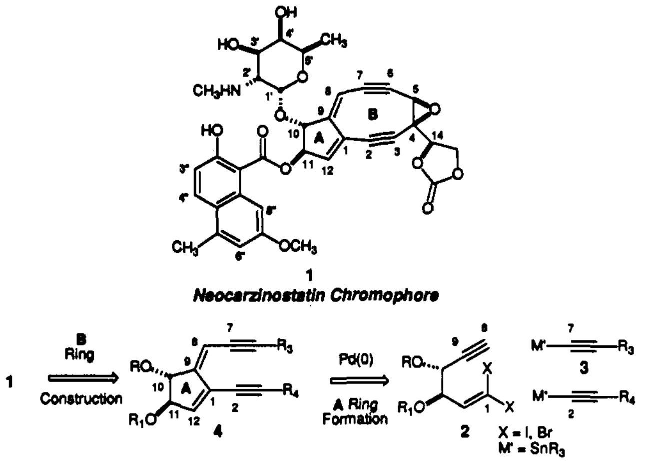
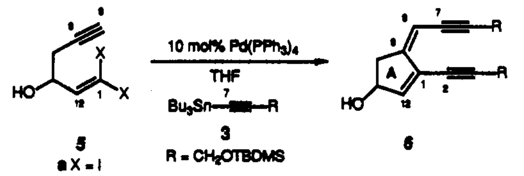
The unique structure and significant biological activity of the powerful antitumor antibiotic Neocarzinostatin Chromophore (NCS-Chr A) (**1**) have made this compound and its functional analogues attractive targets for chemical synthesis.[1] Pharmacodynamic studies have now conclusively shown that the biological activity of this agent is associated with the epoxydienediyne core (C1–C12); **1** exerts its considerable antitumor activity through a novel rearrangement/hydrogen abstraction/DNA cleavage sequence initiated by nucleophilic attack at C12.[1,2] Numerous attempts to prepare congeners of this agent[2,3] have focused on the construction of this dienediyne subunit and the ability of these compounds to cleave DNA in a manner similar to the natural product. The challenge posed to the synthetic chemist by the unprecedented structure of **1** has motivated us to devise a general, expeditious solution to this core functionality applicable to the total synthesis of both **1** and its analogues. Previously, we have established a strategy for the assembly of the A ring of **1** using a transition-metal-catalyzed carbometalation/anion capture sequence,[4,5] the carbometalation affords complete control over the exocyclic C8–C9 olefin geometry[6] while constructing the C7–C8 appendage of the NCS-Chr systems. Herein we report an exceedingly concise "one-pot" approach to these dienediynes that utilizes catalyst delivery by a pendant ligating group to build the A ring, control the C8–C9 exocyclic olefin geometry, and construct the perimeter of the eventual B ring from simple dihaloolefin synthons.

Our two-stage strategy for the construction of these molecules is shown in Scheme I. The first stage takes advantage of the pseudo-C_2 symmetry inherent in **1**, using dihaloenyne **2** as the template for the construction of both the A ring and the perimeter of the B ring via a series of transition-metal-catalyzed carbon–carbon bond-forming events. The second stage of the plan will then involve construction of the B ring from these newly formed appendages (**4** to **1**). To test the viability of this strategy, we have been investigating the chemistry of the readily available model dihaloenynes **5**.[7,8a] Reaction of diiodoenyne **5a** with 5.0 equiv of alkynyl stannane **3**[8b] in the presence of 10 mol % Pd(PPh_3)$_4$ (0.02 M in **5a**, THF, 40–45 °C) affords the cyclic derivative **6**, which possesses the C1–C12 dienediyne core of NCS-Chr, in 32% yield (eq 1).[9] One operation has achieved the

Scheme I





(1)

construction of three carbon–carbon bonds: the C1–C9 bond (A ring formation), the C8–C7 bond of the geometrically defined exocyclic C8–C9 double bond, and the C1–C2 alkynyl appendage. While the overall yield of this process is modest, considered on a per bond basis (ca. 70%) this reaction protocol is quite impressive.

The transition-metal-catalyzed coupling reactions of 1,1-dibromo- and 1,1-dichloroolefins have been thoroughly described by Roush and Tamao, among others.[3c,10] These reports have shown that the sterically less encumbered (*E*)-carbon–halide bond reacts selectively, often affording the resulting monohalogenated products in good yields. Though the reactivity of the analogous 1,1-diiodoolefins in transition-metal-catalyzed coupling reactions

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(1) For a review on Neocarzinostatin Chromophore, see: Goldberg, I. H. *Acc. Chem. Res.*, **1991**, *24*, 191. Isolation of Neocarzinostatin: Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68. Structure elucidation of Neocarzinostatin Chromophore: (a) Edo, K.; Misugaki, M.; Koide, Y.; Seto, H.; Furikata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. (b) Hensens, O. D.; Dewey, R. S.; Liesch, J. M.; Napier, M. A.; Reamer, R. A.; Smith, J. L.; Albers-Schonberg, G.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1983**, *113*, 538. Reactivity of the epoxy dienediyne core: Myers, A. G.; Harrington, P. M.; Kwon, B.-M. *J. Am. Chem. Soc.* **1992**, *114*, 1086 and references therein.

(2) For a comprehensive source of recent references discussing synthetic efforts toward **1**, as well as the molecular pharmacology of this agent, see: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.

(3) Transition-metal couplings used for the synthesis of Neocarzinostatin chromophore analogues: (a) Brückner, R.; Scheuplein, S. W.; Suffert, J. *Tetrahedron Lett.* **1991**, *32*, 1449. (b) Scheuplein, S. W.; Harms, K.; Brückner, R.; Suffert, J. *Chem. Ber.* **1992**, *125*, 27. (c) Torii, S.; Okumoto, H.; Tadokoro, T.; Nishimura, A.; Rashid, M. A. *Tetrahedron Lett.* **1993**, *34*, 2139.

(4) Nuss, J. M.; Levine, B. H.; Rennels, R. A.; Heravi, M. H. *Tetrahedron Lett.* **1991**, *32*, 5243.

(5) For other approaches to carbometalation/anion capture, see: (a) Luo, F.-T.; Chou, F.-L.; Wang, R.-T. *J. Org. Chem.* **1990**, *55*, 4846–4849. (b) Grigg, R.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 2545 and references therein. (c) Negishi, E.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393.

(6) For reviews concerning transition-metal-mediated carbometalation, see: (a) Negishi, E. In *Advances in Metal-Organic Chemistry*; Liebeskind, L., Ed.; Jai Press: London, 1989; Vol. 1. (b) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (c) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323. The carbometalation of alkynes by Ni and Pd aryl complexes has been reported. Ni: Huggins, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 4410. Pd: Arcadi, A.; Cacchi, S; Marinelli, F. *Tetrahedron* **1985**, *41*, 5121.

(7) Compounds **5a** and **5b** are prepared by the addition of propargyl magnesium bromide to 3,3-diiodoacrolein[8a] or 3,3-dibromoacrolein,[8a] respectively, followed by protection with the appropriate protecting group (MOM = methoxymethyl, TBDMS = *tert*-butyldimethylsilyl). This is described in the supplementary material and will be described in more detail in future reports.

(8) (a) Raulet, C.; Levas, M. *Bull. Soc. Chim. Fr.* **1963**, 2147. (b) For a general procedure to prepare compound **3**: see: Bottaro, J. C.; Hanson, R.N.; Seitz, D. E. *J. Org. Chem.* **1981**, *46*, 5221.

(9) Consistent with published examples of transition-metal-mediated carbometalation,[6] only adducts having the (*Z*)-exocyclic olefin geometry are produced during these reactions. These compounds do not isomerize under the reaction conditions, though photolysis of these compounds (benzene, 3.0 equiv benzophenone, Pyrex filter, ca. 0.003 M in substrate) does eventually produce the corresponding (*E*)-isomer. These are readily distinguishable by the presence of a NOE of ca. 3–5% between the C10 methylene protons and the C8 olefin resonance of the (*Z*)-isomer, an effect missing in the (*E*)-isomer. This has been observed by others.[3a,b]

(10) (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509. (b) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (c) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 710.

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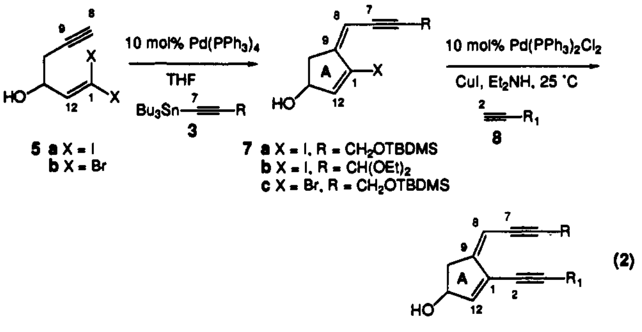
had not been reported at the outset of our studies, we felt that these compounds would react under less forcing conditions than the corresponding dibromide and dichloride compounds, a critical consideration when dealing with thermally labile compounds typified by **1** and **4**. Our investigations have found that the chemistry of 1,1-diiodoolefins is not analogous to that seen for either the 1,1-dichloro or 1,1-dibromo derivatives. For example, reaction of **5a** with only 2.2 equiv of **3** surprisingly results in the selective reaction of the ostensibly more sterically demanding (*Z*)-C1–I bond, to afford the cyclized product **7a**, possessing only the (*Z*)-C8–C9 olefin geometry, in high yields (70–80%, eq 2).[11]



5 **a** X = I
b X = Br

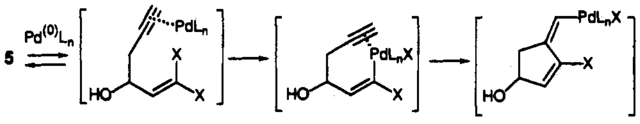
7 **a** X = I, R = CH$_2$OTBDMS
b X = I, R = CH(OEt)$_2$
c X = Br, R = CH$_2$OTBDMS

9 **a** R$_1$ = CH(OEt)$_2$
b R$_1$ = CH$_2$OTBDMS
c R$_1$ = C$_6$H$_5$

To further explore the chemistry of 1,1-diiodolefins, we have studied a number of simple 1,1-diiodoolefins and have found these compounds to be *unreactive* toward alkynylstannanes such as **3** under the influence of the Pd(0)-catalyzed reaction conditions which convert **5a** to **6** or **7**.[12] This lack of reactivity is quite astounding, given the general pattern of reactivity of C-I, C-Br, and C-Cl bonds observed in transition-metal-catalyzed coupling reactions.[14] This must, we feel, point to the importance of the pendant alkyne functionality in **5a** as playing a critical role in initiating this cyclization.[15] The adducts produced here, **7**, can then be coupled in quite good yields (ca. 70–75%) with a series of alkynes to give dienediynes **9** having differentiated C1–C2 and C8–C7 alkynyl appendages.[13]

Our working hypothesis for the conversion of **5** to **6** (via **7**) is given in Scheme II. Complexation of the pendant alkyne with the reactive organometallic species initiates this process to produce a transient π-complex (**10**);[3c,15] oxidative addition to the proximal (*Z*)-C1–I bond then provides the critical Pd-C σ-bonded species **11**. This intermediate then undergoes rapid carbometalation (migratory insertion) of the precoordinated alkyne, resulting in formation of the A ring and (*Z*)-vinylorganometallic **12**; indeed, oxidative addition is believed to be the product-determining step in this sequence. This exocyclic intermediate, **12**, then undergoes intermolecular reaction with the alkynylstannane **3**, delivering the alkyne which will be the C7–C5 appendage, to afford **7**. Attachment of the C2–C4 appendage to vinyl iodide **7** is then smoothly achieved via Stille[17] coupling with excess alkynylstannane to produce **6**. If lower concentrations of alkynylstannane are used, then the subsequent coupling of the vinyl iodide **7** is slow, thus permitting its isolation. We feel that the chemoselective oxidative addition to the (*Z*)-C1–I bond observed here (**5** to **11**), in contrast to previous work on 1,1-dihaloolefins, *reflects a directing role of the pendant alkyne (C8–C9) as a ligand for the Pd(0) catalyst.*[15] Though intramolecular ligand-directed processes are well known in transition-metal-catalyzed reactions,[18] this serves as an example of such a directing effect in an oxidative addition; thus precomplexation of the pendant alkyne serves to activate the otherwise quiescent 1,1-diiodoolefin. This exploitation of the existing C8–C9 alkyne functionality to direct subsequent chemistry (oxidative addition/carbometalation) permits the rapid synthesis of intricate, highly unsaturated structures from synthons of very low complexity. This promises to prove a general route to NCS-Chr analogues and to the parent natural product.

Scheme II



10 **11** **12**

In summary, we have developed an expeditious and versatile route for construction of the critical, biologically relevant core of Neocarzinostatin Chromophore A. Further studies, also now in progress, are aimed at elaborating the nine-membered ring and utilizing this reaction sequence to construct both the A and B rings of **1** in one operation.

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Supplementary Material Available: Experimental procedures and spectral data for compounds **5a–c**, **6**, **7a–c**, and **9a–c** (14 pages). Ordering information is given on any current masthead page.

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(11) Our initial experiments focused on the dibromide **5b**, which undergoes an analogous cyclization (**5b** to **7c**), albeit in lower yields and at higher temperatures and dilutions. Considerable amounts of uncyclized coupling products were obtained in these studies and in no case was **5b** found to convert directly to **6**. Subsequent success with the diiodides led us to abandon the dibromides.

(12) The reaction of 1,1-diidoolefins in transition-metal-catalyzed coupling reactions has not been reported. We have prepared 1,1-diiodo-1-hexene and β,β-diiodo-3,4-dimethoxystyrene and have found them to be unreactive under the conditions sufficient to convert **5a** to **6**. These compounds, as well as 3,3-diidoacrolein, do undergo alkyne coupling reactions under Sonagashira coupling conditions.[13] The 1,1-diiodoolefins were synthesized according to: Gavina, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Marco, J. A. *J. Chem. Soc., Chem. Commun.* **1985**, 296.

(13) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

(14) For a review of oxidative addition, see: Stille, J. K. In *Chemistry of the Metal-Carbon Bond*; Hartley, F., Ed.; John Wiley and Sons: New York, 1987; Vol. 1.

(15) Both the methoxymethyl (MOM)- and *tert*-butyldimethylsilyl (TBDMS)-protected derivatives of **5a** give the adducts corresponding to **7a** in good yields. The similar reactivity between the free alcohol and these protected derivatives would seem to preclude chelation of the oxygen as being critical in directing the oxidative addition.[16]

(16) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, 265. (b) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, 3223. (c) Keck, G. E.; Hehre, W. J.; Kahn, S. D. *Tetrahedron Lett.* **1987**, 279.

(17) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(18) For other ligand-directed transition-metal processes, see: (a) Holton, R. A.; Zoeller, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 2124. (b) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237. (c) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917. (d) Zhang, W.; Jakiela, D. J.; Maul, A.; Knors, C.; Lauher, J. W.; Helquist, P.; Enders, D. *J. Am. Chem. Soc.* **1988**, *110*, 4652. (e) Stary, I.; Zacicek, J.; Kocovsky, P. *Tetrahedron* **1992**, *48*, 7229.