

# Total Synthesis of Aigialomycin D: Surprising Chemoselectivity Dependence on Alkyne Structure in Nickel-Catalyzed Cyclizations

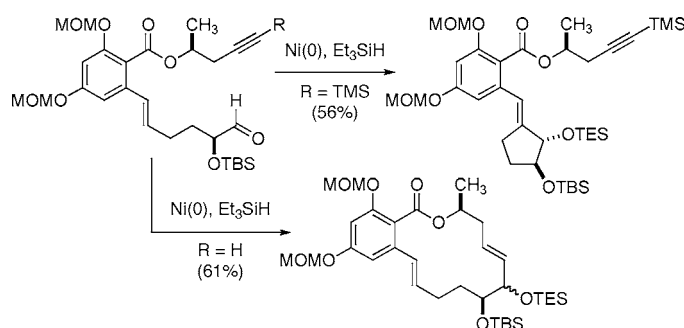
Christa C. Chrovian, Beth Knapp-Reed, and John Montgomery\*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

jmontg@umich.edu

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## ABSTRACT



The total synthesis of aigialomycin D was carried out using a nickel-catalyzed ynal macrocyclization as a key step. This key step allowed macrocycle assembly and formation of a disubstituted alkene and a secondary hydroxyl stereocenter in a single step, although the stereocenter was formed unselectively. An interesting side reaction involving five-membered-ring synthesis by an aldehyde/styrene cyclization was observed when macrocyclization of an alkyne silane was attempted. A mechanistic basis for this surprising process is provided.

Aigialomycin D (**1**) is a resorcinolic macrolide isolated from the marine mangrove fungus *Aigialus parvus*.<sup>1</sup> This compound is part of a larger family of natural products that possess a 14-membered macrolide core structure fused to a benzenoid unit.<sup>2</sup> Extensive studies have examined the ability of the resorcinolic macrolides to degrade oncogenic proteins by targeting the heat shock protein 90 (Hsp90),<sup>3</sup> and other members of the class function as potent kinase inhibitors.<sup>4</sup> Aigialomycin D (**1**) itself has been reported to display antimalarial activity (IC<sub>50</sub>: 6.6 μg/mL against *P. falciparum*) as well as cytotoxicity [IC<sub>50</sub>: 3.0 μg/mL for human epider-

moid carcinoma (KB cells), 1.8 μg/mL for African green monkey kidney fibroblast (Vero cells)].<sup>1</sup> This array of interesting biological properties has stimulated considerable synthetic work directed toward the resorcinolic macrolides and their analogues.

A number of attractive total syntheses of aigialomycin D have been reported, in which assembly of the 14-membered ring was accomplished by ring closing metathesis<sup>5</sup> or by macrolactonization.<sup>6</sup> Our interest in the synthesis of aigia-

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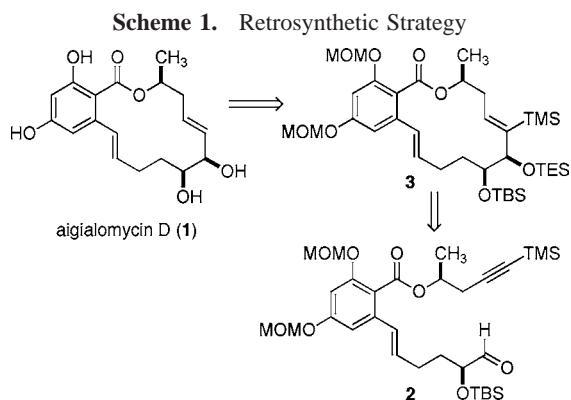
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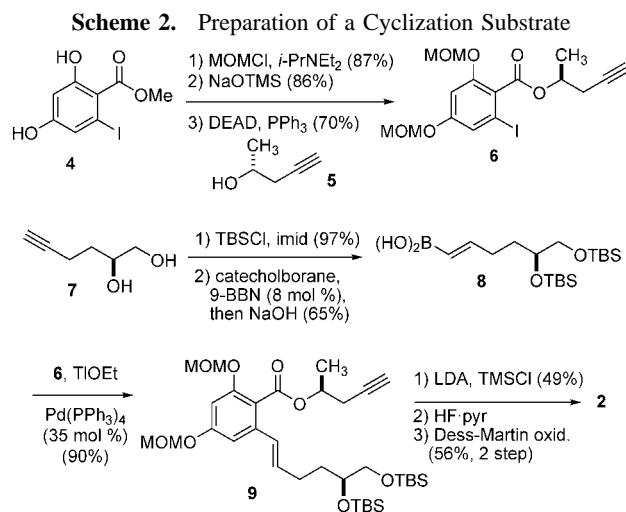
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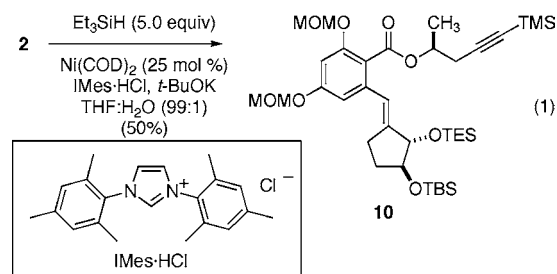
lomycin D stems from our development of a catalytic macrocyclization of ynals<sup>7,8</sup> as well as our more recent studies toward developing intermolecular diastereoselective couplings of alkynyl silanes and  $\alpha$ -silyloxy aldehydes.<sup>9,10</sup> Merging these two developments from our laboratory suggested that a diastereoselective macrocyclization of substrate **2** to afford product **3** could be used as a key feature in an efficient total synthesis of aigialomycin D (**1**) (Scheme 1).



To pursue the line of work proposed above, we prepared the known resorcinylic iodide **4** (Scheme 2).<sup>11</sup> Protection as the bis-methoxymethyl ether, followed by ester hydrolysis and Mitsunobu esterification with alcohol **5** produced compound **6** in 70% isolated yield. Alkenyl boronic acid **8** was then prepared from the known diol **7**<sup>12</sup> by bis-silylation, followed by treatment of the protected alkyne with catecholborane and catalytic 9-BBN.<sup>13</sup> Palladium-catalyzed cross-coupling of boronic acid **8** with aryl iodide **6** afforded **9** in 90% yield.<sup>13b,c</sup> Compound **9** thus serves as a common intermediate for strategies involving macrocyclization of either a terminal alkyne or alkynyl silane. Preparation of the alkynyl silane cyclization precursor **2** was accomplished by treatment of **9** with LDA and TMSCl, followed by selective monodeprotection with HF·pyridine and Dess–Martin oxidation.



With structure **2** in hand, we examined macrocyclization with Et<sub>3</sub>SiH as reducing agent (5.0 equiv), Ni(COD)<sub>2</sub> (25 mol %), IMes·HCl (25 mol %), and *t*-BuOK (25 mol %) (eq 1). Whereas conversion was sluggish in THF, addition



of water to give a 99:1 THF:water solvent system promoted substrate consumption at 60 °C.<sup>14</sup> Under these conditions, no evidence for macrocyclization was obtained; however, a new product was observed that maintained the alkynyl silane unit but involved disappearance of the aldehyde. Upon evaluating the COSY, HMQC, and NOE data, it became apparent that the major product of the cyclization was compound **10**, formed in 50% yield, with an anti relationship of the newly formed cyclopentane diol unit and the *E*-configuration of the newly formed trisubstituted alkene.

Product **10** is not derived from a reductive cyclization as typically seen in nickel-catalyzed processes involving triethylsilane. Instead, the product is analogous to the known nickel-catalyzed silyl triflate-promoted couplings of aldehydes and alkenes that involve loss of HOTf (with neutralization by triethylamine) during the coupling event.<sup>15,16</sup> This

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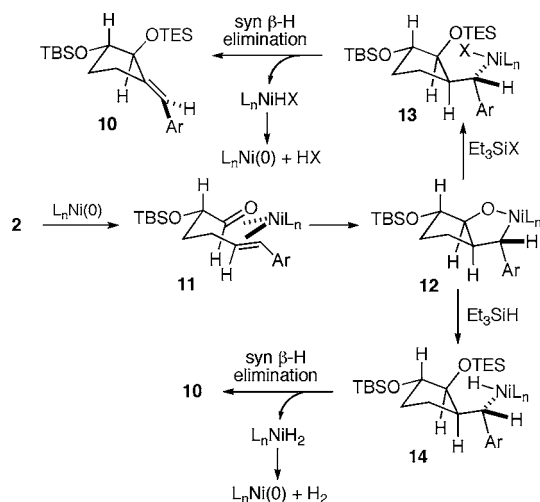
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non-reductive cyclization mode utilizing a silyl hydride rather than silyl triflate is, to our knowledge, unprecedented. One possibility is that triethylsilane modification to an electrophilic silylating agent involving the trace water additive occurs under the reaction conditions,<sup>14,17</sup> which then promotes a cyclization directly analogous to the silyl triflate procedure previously described (Scheme 3).<sup>16</sup> Coordination of Ni(0)

**Scheme 3.** Mechanism of the Formation of **10**



to the aldehyde and styrene unit of **2**, with the silyloxy unit positioned in a pseudo-equatorial position, would result in structure **11**. Oxidative cyclization would produce metallacycle **12**, most likely promoted by silyl activation of the aldehyde.<sup>15,18</sup> Ni–O bond dissociation to **13**, followed by bond rotation and  $\beta$ -hydride elimination, would afford product **10**.

Alternatively, direct involvement of unmodified triethylsilane in the reaction mechanism would require extrusion of H<sub>2</sub> during the cyclization event (Scheme 3). Formation of metallacycle **12**, followed by  $\sigma$ -bond metathesis with Et<sub>3</sub>SiH would result in nickel hydride **14**. *syn*- $\beta$ -Hydride elimination of **14** would afford the observed *E*-alkene of product **10** and a nickel dihydride species, which could produce H<sub>2</sub> upon regeneration of the catalytically active Ni(0) species. The importance of the precise aromatic ring functional group arrangement has not been established, and the generality of this transformation remains to be determined.<sup>19</sup> Details of the mechanism of the formation of **10** including the nature of the active silyl species are under study.

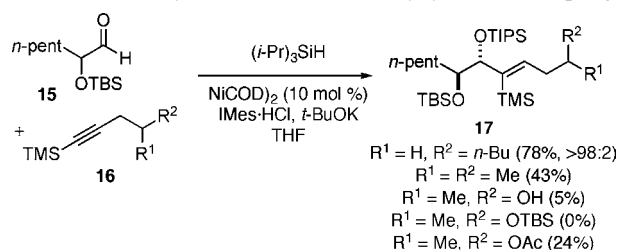
Given the failure of the alkynyl silane of **2** to participate in the desired macrocyclization, we examined a few simple

(17) A tentative possibility is that triethylsilane undergoes nickel-catalyzed conversion to triethylsilanol in the presence of water to generate the Et<sub>3</sub>SiX species depicted in Scheme 3. Control experiments illustrated that Et<sub>3</sub>SiOH is slowly produced under the reaction conditions in the absence of substrate **2**.

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model systems involving the intermolecular coupling of alkynyl silanes with  $\alpha$ -silyloxy aldehydes. From our previous study, nickel-catalyzed couplings of aldehyde **15** with alkyne **16** bearing an unbranched alkyl chain (R<sup>1</sup> = H) afforded high yields of **17** with exceptional diastereoselectivity.<sup>9</sup> However, as the examples illustrate (Scheme 4), even modest

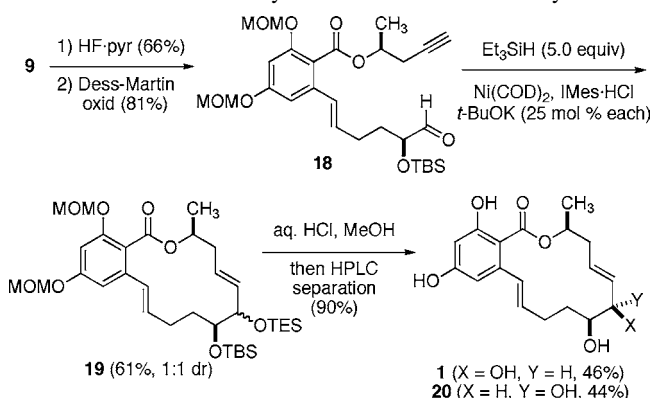
**Scheme 4.** Study of Intermolecular Alkynyl Silane Couplings



branching at the homopropargylic position led to considerably lower yields, with substrates oxygenated at that position being particularly poor substrates. Given these results, and knowing that the internal styrene of substrate **2** was capable of undergoing undesired five-membered-ring cyclization, we abandoned attempts to effect the desired alkynyl silane macrocyclization.

Although we knew from our prior studies that terminal alkynes undergo intermolecular couplings with  $\alpha$ -silyloxy aldehydes with considerably lower diastereoselection than alkynyl silanes, we nonetheless opted to examine a terminal alkyne macrocyclization since that material was easily accessible from our studies described above. To pursue this strategy, selective monodesilylation of **9** with HF·pyridine followed by Dess–Martin oxidation afforded compound **18** in good yield (Scheme 5). Cyclization of **18** with Ni(COD)<sub>2</sub>

**Scheme 5.** Macrocyclization of a Terminal Alkyne



and IMeS (25 mol % each) in THF afforded the desired macrocycle **19** in 61% isolated yield as a 1:1 mixture of

(19) Simple intermolecular reductive couplings of benzaldehyde with either styrene or allyl benzene are not promoted by either Et<sub>3</sub>SiH in wet THF or Et<sub>3</sub>SiOH in dry THF with use of the catalyst and reaction conditions used in the production of **10**.

diastereomers. Similar chemical yield and diastereoselectivity for formation of **19** were observed with the 99:1 THF:water solvent composition that afforded the five-membered-ring **10** from alkynyl silane **2**. Deprotection of the diastereomeric mixture with 0.5 M HCl afforded aigialomycin D (**1**) in 46% yield and epimeric structure **20** in 44% yield after preparative HPLC separation. Synthetic data for **1** were identical in all respects with data previously reported for synthetic and natural material.<sup>1,5,20</sup>

In summary, the total synthesis of aigialomycin D has been accomplished by a short sequence involving a nickel-catalyzed ynol macrocyclization. Initial attempts to accomplish ring closure via an alkynyl silane macrocyclization uncovered a surprising styrene–aldehyde five-membered-ring cyclization using triethylsilane as a promoter for a non-reductive transformation. These studies shed light on the

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(20) Additional synthetic manipulations of compounds derived from **19** were performed for the confirmation of structure **20**. See the Supporting Information for details.

scope of macrocyclizations involving different classes of alkynes and suggest interesting new cyclization modes available for Ni(0)/trialkylsilane reagent combinations.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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