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# A Model Study for Constructing the DEF-Benzoxocin Ring System of Menogaril and Nogalamycin via a Reductive Heck Cyclization

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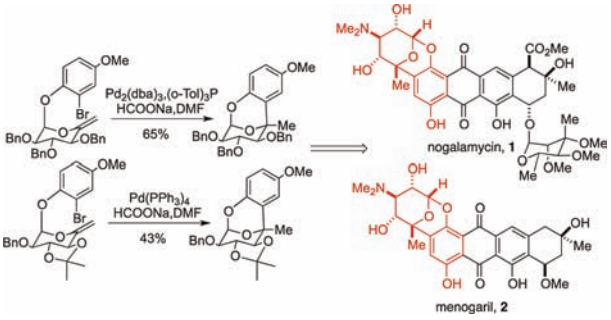
## ABSTRACT




**A novel reductive Heck cyclization approach was developed in order to construct a model DEF-benzoxocin ring system that is present in nogalamycin, menogaril, and related anthracycline antitumor antibiotics.**

The anthracyclines constitute a widely used family of chemotherapeutic agents. Nogalamycin **1**, isolated from *Streptomyces nogalator*,[1] has potent biological activity versus Gram-positive bacteria and shows prominent cytotoxicity against L1210 and KB cell lines *in vitro*. Studies have shown that nogalamycin intercalates DNA with the amino sugar binding in the major groove and the nogalose subunit binding within the minor groove.[2] The binding of nogalamycin to an upstream site can induce highly specific topoisomerase I mediated DNA cleavage.[3] However, nogalamycin was found to show only weak activity against solid tumors *in vivo* and have an unacceptable toxicity profile in large animals.[4] Its semisynthetic derivative, 7-con-*O*-methylnogarol (menogaril) **2**, possessed better antitumor activity and was chosen for evaluation in a clinical trial.[4]

Nogalamycin and menogaril both contain a synthetically interesting DEF-benzoxocin ring system. The F-ring unit, also called nogalamine, has an L-glucose configuration. It is attached to the anthracycline aglycone to form the E-ring by an aryl *C*-glycosidic linkage and an *O*-glycosidic linkage.

Because of their interesting structure, along with their promising antimicrobial and antitumor activities, there has been much effort focused toward the total synthesis of nogalamycin and related congeners. A total synthesis of nogalamycin has yet to be achieved although several model studies, most having focused on the enantioselective synthesis of the DEF-ring system, have been reported.[5]

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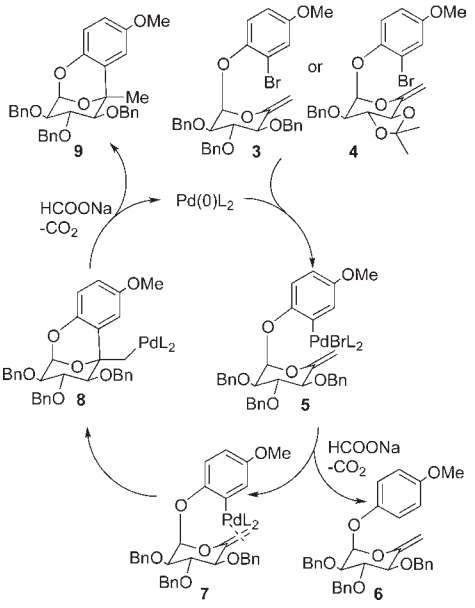
In addition, syntheses of (+)- and (±)-7-con-*O*-methylnogarol (menogaril **2**) have been reported.[5h,6] The overall strategies for most of the reported syntheses are similar. The *C*-glycosidic bond is established first. Subsequent introduction of the *O*-glycosidic bond completes the carbohydrate-bridged DEF-ring system.

An alternative strategy would be to develop an approach wherein the *O*-glycosidic bond is established first. This in turn will allow one to exploit the stereoelectronic preferences dictated by the anomeric effect to install the quaternary aryl-*C*-glycosidic bond with the desired stereochemistry. We are aware of two reports that sought to exploit this strategy. In one report, the formation of the *C*-glycosidic bond was attempted via an intramolecular Friedel–Crafts alkylation onto an electrophile-activated exocyclic 5,6′-olefin.[7] No cyclization was observed, a result ascribed to the insufficient nucleophilicity of the aromatic moiety. In a second report, an aryl radical cyclization onto an exocyclic 5,6′-olefin provided none of the desired cyclization product and afforded predominantly the direct reduction product of the glycosidic aryl bromide radical precursor.[8]

Despite the failures of these attempts, we were intrigued by this strategy since it could leverage the stereoelectronic preference(s) dictated by the anomeric effect to introduce the *C*-glycosidic bond with the desired stereochemistry. In addition, this approach offered the possibility for late-stage introduction of the bridging F-ring carbohydrate if a suitably functionalized aromatic precursor could be prepared. Overman,[9] Grigg,[10] and several others[11] have demonstrated that the Heck cyclization, whether in the normal or reductive mode, is particularly well suited for the construction of quaternary C–C bonds. Successful application of a reductive Heck cyclization may enable late stage introduction of the DEF-ring system on a suitably protected and fully functionalized anthracycline core.

Our proposed model for a reductive Heck cyclization construct, along with pertinent mechanistic considerations, is illustrated in Scheme 1. We envisaged aryl glycosides **3** and **4** as model substrates for these reactions. Although each is a D-sugar (the nogalamine residue in nogalamycin has the L-configuration), like nogalamine, each has the gluco relative

**Scheme 1.** Proposed Catalytic Cycle for Reductive Heck Cyclization of **3**




configuration and each is readily accessible from commercially available precursors. In addition, the dimethyl ketal present in **4** confers an added element of rigidity, relative to **3**, that could impact the efficiency of the cyclization reaction.

The desired reaction would take place via initial oxidative addition of the Pd(0) catalyst to the aryl-Br bond generating an arylpalladium(II) intermediate (e.g., **5** or **7**). This intermediate would then undergo an olefin insertion reaction with the exocyclic olefin and generate an alkylpalladium(II) intermediate (**8**). Capture of this intermediate by a suitable hydride source, to generate a palladium hydride, followed by reductive elimination would provide the desired cyclization product and regenerate the Pd(0) catalyst.

Several mechanistic aspects of this reaction must work in our favor in order for this construct to be successful. First, the olefin insertion reaction must proceed at a favorable rate, relative to direct capture of the arylpalladium(II) intermediate (e.g., **5**) by hydride, in order to suppress formation of the direct reduction product **6**. Second, the olefin insertion reaction must take place preferentially in a 6-exo mode relative to the alternative 7-endo mode (intermediate not shown). Our intuition suggested that the desired mode of olefin insertion ought to be intrinsically favored on both kinetic and thermodynamic grounds. Finally, our construct required a kinetically competent hydride source in order to ensure efficient capture of the alkylpalladium(II) intermediate **8** and enable catalyst turnover; however, if the olefin insertion reaction is sluggish, the reactivity of the hydride source must be sufficiently moderate in order to avoid direct capture of the arylpalladium(II) intermediate that would lead to the reduction product **6**.

The synthesis of **3** (Scheme 2) began with sulfoxide **10**, which was prepared in four steps from commercially

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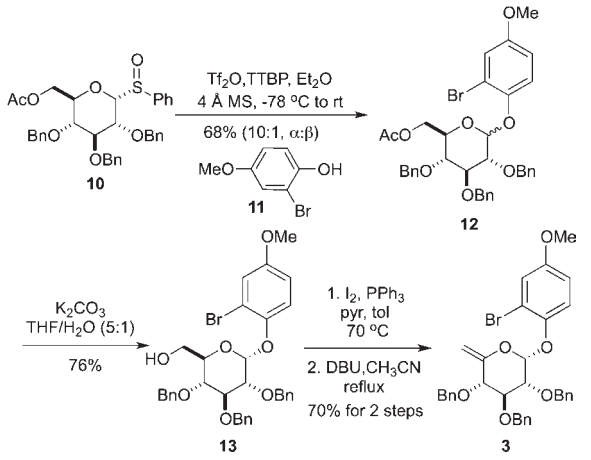
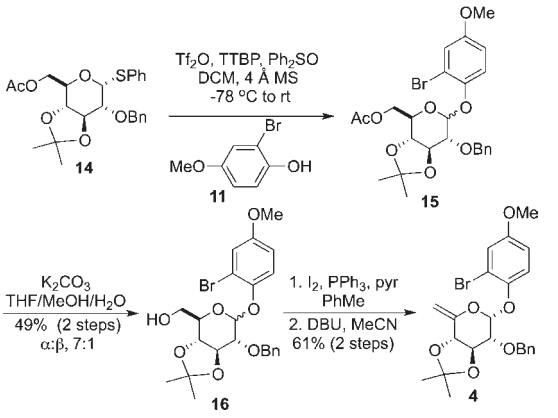
**Scheme 2.** Synthesis of **3**




**Scheme 3.** Synthesis of **4**

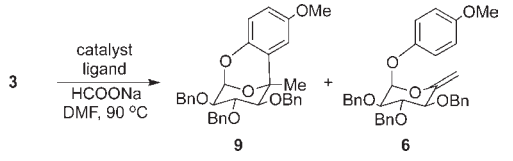



available methyl-α-D-glucopyranoside.[12] Sulfoxide **10** was then subjected to Kahne glycosylation conditions ($Tf_2O$, TTBP, $Et_2O$, **11**, 68%) to give an inseparable mixture of *O*-aryl glycosides **12**.[13] After cleavage of the acetate protecting group ($K_2CO_3$, THF/$H_2O$, 76%), the respective anomers were cleanly separated by chromatographic purification. The α-anomer **13** was subjected to iodination ($I_2$, $PPh_3$, pyridine, toluene) followed by elimination of the primary iodide to provide **3** in good overall yield (70% for two steps).

Our synthesis of **4** (Scheme 3) began with thioglycoside **14** that was readily available in eight steps from pentaacetyl-α-D-glucopyranoside.[14] Glycosylation with **11** ($Tf_2O$, TTBP, $Ph_2SO$, DCM)[15] followed by cleavage of the acetate protecting group provided **16** in good overall yield (49% for two steps). Iodination of **16** ($I_2$, $PPh_3$, pyridine, toluene) followed by elimination (DBU, MeCN, 61% overall) and chromatographic separation of the respective α- and *β*-anomers provided exocyclic olefin **4** in good overall yield.

Our initial experiments (summarized in Table 1) utilized **3** and were designed in order to identify an optimal source of Pd(0). Catalytic $Pd(PPh_3)_4$ (0.1 equiv) gave a 70% conversion of the substrate and provided a 4:1 ratio of the cyclization (**9**)/direct reduction (**6**) products (entry 1). Stoichiometric $Pd(PPh_3)_4$ reduced the ratio of **9**/**6** to approximately 2.5:1, again with complete consumption of **3** (entry 2). Increasing the temperature to 125 °C led to decomposition. Common Heck reaction additives such as silver salts or tetraethylammonium chloride resulted in low conversions and undesirable product ratios.[16] A large increase in yield and product ratio was realized by using $Pd_2(dba)_3$/(*o*-Tol)$_3$P as the catalyst (entry 3). In this example, the desired cyclization product was obtained in 65% isolated yield. We also found that mixtures of DMF and water gave poorer product ratios while little or no reaction was observed in dioxane and toluene. With (*o*-Tol)$_3$P as the ligand, neither $Pd(OAc)_2$ (entry 4) nor the Herrmann catalyst [*trans*-di-(*μ*-acetate)-bis-[*o*-(di-*o*-tolylphosphine)-benzyl]dipalladium(II)] (entry 5) provided a significant improvement in product ratios or conversion when compared to $Pd_2(dba)_3$. Other hydride donors, such as ammonium formate or triethylsilane, gave undesirable product ratios and/or decomposition.[16] Product ratios (**9:6**) were unchanged by running the reactions at higher dilution.

**Table 1.** Conditions for Reductive Heck Cyclization of **3**




| entry | catalyst | ligand | ratio[a] | yield[b] (%) |
|---|---|---|---|---|
| 1 | 0.1 equiv $Pd(PPh_3)_4$ | none | 30:56:14 | ND[c] |
| 2 | 1 equiv $Pd(PPh_3)_4$ | none | 0:73:27 | 38 |
| 3 | 0.1 equiv $Pd_2(dba)_3$, | 0.8 equiv (*o*-Tol)$_3$P | 0:88:12 | 68(65[d]) |
| 4 | 0.2 equiv $Pd(OAc)_2$, | 0.8 equiv (*o*-Tol)$_3$P | 0:73:27 | 43 |
| 5 | 0.1 equiv Herrmann catalyst | 0.4 equiv (*o*-Tol)$_3$P | 0:78:22 | 49 |

[a] Ratio of **3:9:6**, determined by comparing the anomeric proton peak area of each compound in crude $^1$H NMR. [b] NMR yield. [c] Not determined. [d] Isolated yield. All reactions were carried out with 1.2 equiv of sodium formate (HCOONa).

Using the results above, a series of phosphine ligands was screened with the $Pd_2(dba)_3$ catalyst (Table 2). (1-Naphthyl)$_3$P (entry 4) gave a comparable result to (*o*-Tol)$_3$P. All the other

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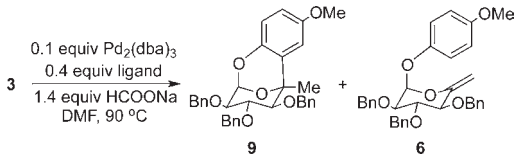
(16) Complete experimental details are reported in the Supporting Information.

**Table 2.** Ligand Screening for the Reductive Heck Cyclization of **3**




| entry | ligand | ratio[a] | yield[b] (%) |
|---|---|---|---|
| 1 | $(p\text{-Tol})_3P$ | 38:40:22 | 31 |
| 2 | $(p\text{-F-phenyl})_3P$ | 41:26:33 | 20 |
| 3 | $(o\text{-OMe-phenyl})_3P$ | 0:68:32 | 55 |
| 4 | $(1\text{-Naphthyl})_3P$ | 0:93:7 | 65 |
| 5 | $(2,4,6\text{-tri-OMe-Ph})_3P$ | 17:0:83 | 0 |
| 6 | $(2,4,6\text{-tri-Me-Ph})_3P$ | 25:3:72 | ND[c] |
| 7 | $(CyHex)_3P$ | 0:13:87 | 9 |
| 8 | $^nBu_3P$ | 90:1:9 | ND |
| 9 | $^tBu_3P$ | 0:14:86 | 11 |
| 10 | dppp[d] | 67:9:24 | 8 |
| 11 | dppf[d] | 53:0:47 | 0 |
| 12 | DPEphos[d] | 21:0:79 | 0 |

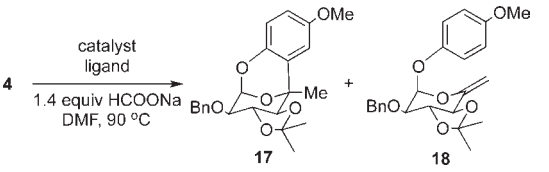
[a] Ratio of **3:9:6**, determined by integration of the anomeric proton peak area of each compound in crude $^1H$ NMR. [b] NMR yield. [c] Not determined. [d] 0.2 equiv of ligand was used.

phosphines, triarylphosphines (entries 1−3, 5−6), trialkylphosphines (entries 7−9), or bidentate phosphines (entries 10−12), resulted in incomplete conversions or undesirable product ratios.

The optimal reductive Heck cyclization conditions were then tried on substrate **4** (Table 3). Under these conditions (0.1 equiv $Pd_2(dba)_3$, 0.8 equiv $(o\text{-Tol})_3P$, DMF), the reaction of **4** gave incomplete conversion and a 2:1 ratio of products favoring the direct reduction product (entry 1). With stoichiometric $Pd_2(dba)_3$, complete consumption of starting material was observed, but the ratio of direct reduction to cyclization product (**18**/**17**) increased (entry 2). A reaction employing stoichiometric $Pd(PPh_3)_4$ resulted in a complete reversal of product selectivity; the desired cyclization product (**17**) was isolated as the major product of a 72:28 product mixture (entry 3).

It is interesting to note that the results obtained with **3** and **4** are qualitatively identical with respect to the extent of conversion and product yields/ratios when stoichiometric $Pd(PPh_3)_4$ was used (cf., Table 1, entry 2 and Table 3, entry 3). When substoichiometric amounts of catalyst were used, substrates **3** and **4** showed opposing product preferences; **3** preferentially provided the desired cyclization product while reactions with **4** resulted in preferential formation of a direct reduction product (e.g., **18**). This observation may be the result of additional strain energy in **4** due to the fused five-membered ketal ring that is exacerbated as

**Table 3.** Reductive Heck Cyclization of **4**




| entry | catalyst | ligand | ratio[a] | yield (%) |
|---|---|---|---|---|
| 1 | 0.1 equiv $Pd_2(dba)_3$ | 0.8 equiv $(o\text{-Tol})_3P$ | 10:32:68 | ND[b] |
| 2 | 0.5 equiv $Pd_2(dba)_3$ | 4 equiv $(o\text{-Tol})_3P$ | 0:22:78 | ND |
| 3 | 1 equiv $Pd(PPh_3)_4$ | none | 0:72:28 | 44[c] |

[a] Ratio of **4:17:18**, determined by integration of the anomeric proton peak area of each compound in crude $^1H$ NMR. [b] Not determined. [c] Isolated yield.

the arylpalladium(II) intermediate tries to access the transition state for olefin insertion (e.g., as in the conversion of **7** to **8**).

Table 2 also reveals that ligand selection may also exert a significant influence on product ratios. Reactions using bidentate and bulky monodentate ligands gave the direct reduction product (**6**) almost exclusively. This may reflect the lack of an accessible coordination site for the olefin prior to olefin insertion. Alternatively, it may also suggest steric implications for the catalyst ensemble that suppress access to the transition state for olefin insertion.

In conclusion, we have developed a novel approach for the construction of the DEF-benzoxocin ring system of nogalamycin, and related congeners, via a reductive Heck cyclization. The product ratios obtained from these reactions show a marked dependence on the choice of catalyst precursor, ligand, and substrate. The successful construction of a model DEF-benzoxocin ring system has catalyzed subsequent efforts in our laboratory directed at the total synthesis of the nogalamycin family of anthracycline antitumor antibiotics. The results of these studies will be presented in due course.

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

The authors declare no competing financial interest.