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Total Synthesis of Crisamicin A

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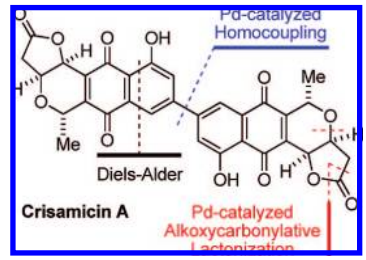
ABSTRACT



Stereoselective total synthesis of natural product crisamicin A (1) was accomplished for the first time via the Pd/TMTU-catalyzed alkoxycarbonylative annulation to generate a unique *cis*-pyran-fused lactone, an intermolecular Diels−Alder reaction to construct the pyranonaphthoquinone unit, and a novel Pd−thiourea pincer complex-catalyzed homocoupling of functionalized naphthoquinones.

Crisamicin A (**1** in Figure 1), a natural product that contains two pyran-fused lactones that are C_2-symmetric to each other, represents a prominent member of the dimeric pyranonaphthoquinone family of antibiotics (**2**−**5**[1] in Figure 1) and was first isolated in 1986 from the micro-organism *Micromonospora purpureochromogenes* that was obtained from a mud sample in the Philippines.[2] Crisamicin A exhibited activity against B16 murine melanoma cells, the herpes simplex, and vesicular stomatitis viruses.[3] A more recent investigation also uncovered important cytotoxic and antimicrobial activities of its close structural analogues; for example, a new pyranonaphthoquinone antibiotic termed GTRI-BB produced by *Micromonospora sp.* SA-246, which is structurally directly derived from crisamicin A through ring opening of one of its two lactone rings, was found to be a stronger inhibitor on the growth of tumor cell lines than the common anticancer compound adriamycin.[4]

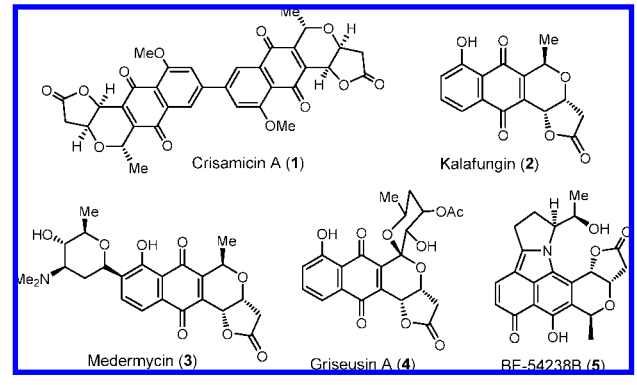


Figure 1. Biologically active pyranonaphthoquinones.

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While the syntheses of several monomeric antibiotics have been reported, the total synthesis of such a dimeric pyranonaphthoquinone as crisamicin A has yet to be achieved.[5] Conceivably, these dimeric structures could be constructed by homocoupling of their monomeric precursors, a particular challenge that has defeated all the attempts so far[6] but, if realized generally, should have greater implication in rapidly assembling these structures. We report herein the identification of a simple and versatile Pd−thiourea catalyst system that improved the carbonylative annulation methodology significantly thus providing an efficient way to construct the pyran-fused lactone ring systems. The successful implementation of this strategy into the context of crisamicin A, in conjunction with the discovery of a remarkably effective Pd−thiourea pincer complex-catalyzed homocoupling protocol, accomplished its stereoselective total synthesis. The work represents the first synthesis of a member of dimeric pyranonaphthoquinone natural products.

As illustrated in Figure 2, a retrosynthetic disconnection of the central aryl−aryl bond in crisamicin A (**1**) yielded a monomeric triflate **A** which in turn could be accessed through

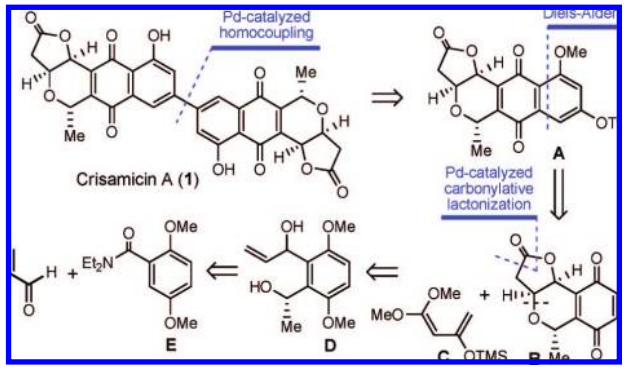
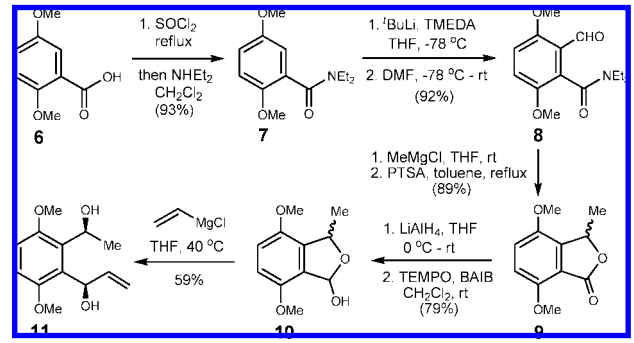


Figure 2. Retrosyntehtic analysis of crisamicin A. Mechanistic pathways involved in Pd-catalyzed alkoxycarbonylative annulation.

a Diels−Alder reaction between a functionalized quinine **B** and an activated diene **C**. The pyran-fused lactone ring in **B** could be constructed by the Pd-catalyzed alkoxycarbonylative annulation of diol **D** that itself could be prepared by a directed *ortho*-metalation−allylation sequence on amide **E**.

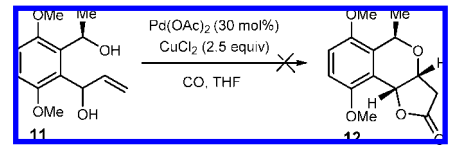
The synthesis of the key precursor **11** is outlined in Scheme 1. The commercially available carboxylic acid **6** was readily transformed into amide **7** in 93% yield. The amide-directed *ortho*-metalation[7] on **7**, followed by formylation with DMF and MeMgCl addition to the resultant aldehyde, delivered lactone **9** in 82% yield over four consecutive manipulations. Reduction of **9** and subsequent diastereoselective ring opening of the hemiacetal by vinyl magnesium chloride provided diol **11** in 59% yield.

Scheme 1. Synthesis of Precursor **11**



With diol **11** in hand, we then set out to evaluate its Pd-catalyzed alkoxycarbonylation−lactonization.[8] Initially, we employed Kraus' annulation conditions[8j] to construct lactone **12**; however, we could not get the desired product according to the published procedure (Scheme 2).

Scheme 2. Pd-Catalyzed Carbonylative Annulation: Total Synthesis of Crisamicin A (**1**)



We reasoned that substrate **11** with a liable benzylic ether moiety might undergo decomposition when exposed to Lewis acid $Pd(OAc)_2$.[9] Thus, electronic tuning of the Pd catalyst through ligation with a certain type of ligand might potentially afford a Pd complex with less Lewis acidity, which in turn could be more compatible with substrates. We therefore started to explore thioureas as ligands in this annulation in consideration of their beneficial role in the metal-catalyzed carbonylative reactions[10] and Au-catalyzed alkylation.[11]

To this end, we profiled the annulation in the presence of various thioureas with **13** as the model substrate with regard

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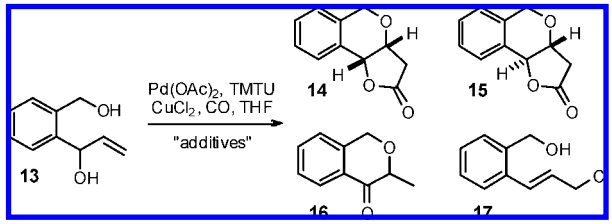
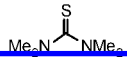
to its easy synthetic accessibility and found that TMTU (tetramethyl thiourea) could give the desired product **14** in 42% yield, together with three other side-products **15**, **16**, and **17** (entry 2 in Table 1). It is worthwhile to mention that the same reaction without the presence of TMTU yielded no desired product (entry 1 in Table 1), indicating the unique role of TMTU in the reaction.

Table 1. Pd/TMTU-Catalyzed Annulation[a]



entry	$Pd(OAc)_2$ (equiv)	TMTU (equiv)	$CuCl_2$ (equiv)	additive (equiv)	time (h)	yield (%)[b] 14	15	16	17
1	0.3	none	2.5	none	24	no products			
2	0.05	0.05	2.5	none	24	42	6	13	10
3	0.05	0.05	2.5	PO (2.0)	4	57	14	11	6
4	0.1	0.1	2.5	PO (2.0)	4	63	4	15	7
5	0.1	0.1	2.5	PO (5.0)	12	78	7	12	0
6	0.1	0.1	2.5	NH_4OAc (1.0)	12	40	5	0	15
7	0.1	0.1	2.5	NH_4OAc (1.0) PO (5.0)	12	83	11	0	0

TMTU:  PO: 

[a] Reaction conditions: substrate **13**, Pd $(OAc)_2$, TMTU, and $CuCl_2$ were combined with or without other additives in THF, and the mixture was allowed to react under a balloon pressure of CO at the indicated time. [b] Isolated yield.

Since the formation of allylic chloride **17** could be attributed to the existence of external chloride, we therefore added propylene oxide (PO)[12] for removal of the Cl^- in situ generated from the oxidative turnover of Pd(0) → Pd(II) assisted by $CuCl_2$. Indeed, when we added 5 equiv of PO, compound **17** was not observed (entry 7 in Table 1).

To eliminate the formation of compound **16** from the annulation reaction, we suspected the base could play a critical role in the formation of **22** (path B). Our earlier work[13] suggested acetates to be a beneficial additive in the Pd-catalyzed carbonylations, thus a few acetates including NaOAc, CsOAc, and NH_4OAc were employed in the reaction. NaOAc and CsOAc, presumably due to their stronger basicity, were found not to be compatible with the substrate. Remarkably, the addition of NH_4OAc (1.0 equiv) to the reaction completely suppressed the formation of **16** (entries 5 and 6). Thus, an optimal catalytic system appeared to consist of 10 mol % of $Pd(OAc)_2$/TMTU, 2.5 equiv of $CuCl_2$, 5.0 equiv of PO, and 1.0 equiv of NH_4OAc.

Thus, under the optimal conditions, substrate **11** was annulated to give the key intermediate **12** in 88% yield (Scheme 3).

With compound **12** in hand, we began to synthesize naphthoquinone **24**. To this end, oxidation of **12** with cerium ammonium nitrate (CAN) gave quinone **23**, which subsequently underwent a Diels−Alder cyclization[14] with diene **H** to furnish phenol **30** under Jones' conditions in 85% yield. It is worthwhile to mention that the regioselectivity in this

We speculated that the overall process may first involve attack of alcohol **13** on the $Pd^{II}X_2Ln$ to generate complex **18**, followed by an alkoxypalladation across the double bond to yield the key pyran-fused metallocycle intermediate **20**, which might first undergo CO insertion to form the acyl palladium intermediate **21**, then reductive elimination to produce the lactones **14** and **15**.

We also envisioned that the complex **18** might undergo an ionization to give the allyl-Pd species **19**, followed by nucleophilic attack of chloride on **19** that would release allylic chloride **17**. On the other hand, due to the existence of an active β-hydrogen, the intermediate **20** could undergo consecutive reductive eliminations to afford alkyl-Pd species **22** and finally ketone **16** (Figure 3).

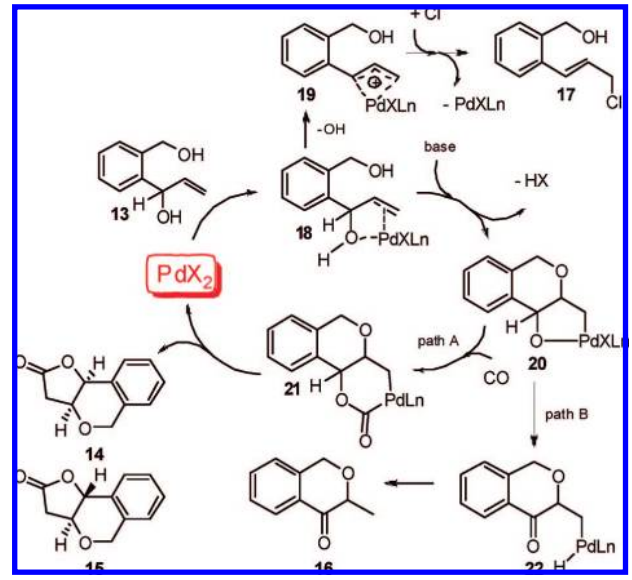


Figure 3. Mechanistic pathways involved in Pd-catalyzed alkoxycarbonylative annulation.

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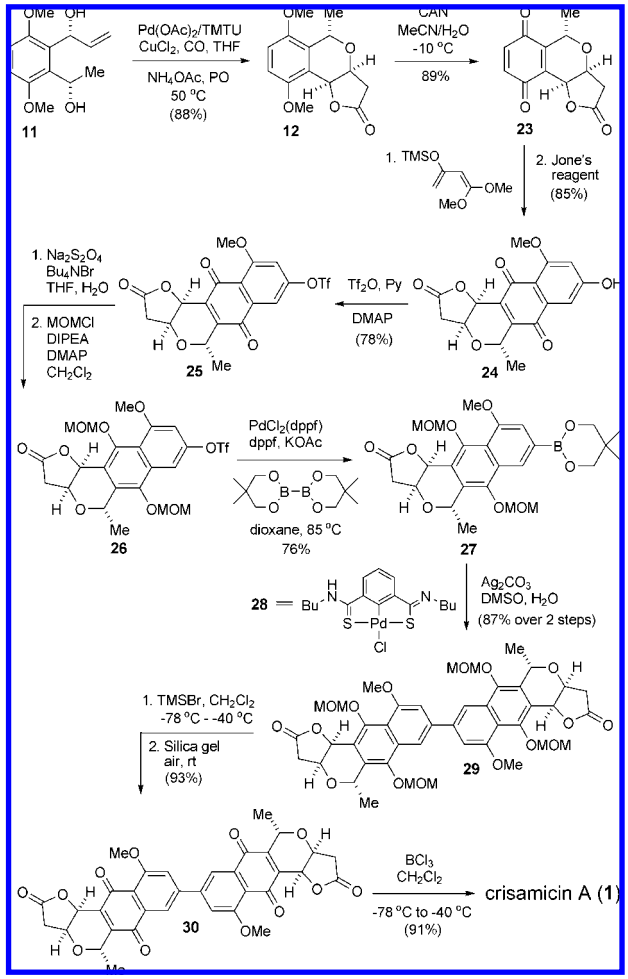
Scheme 3. Total Synthesis of Crisamicin A (**1**)



step was remarkably high (>20:1), presumably due to the stereoelectronic differentiation of the two quinone carbonyls that was dictated by the pyran-fused lactone moieties.

To complete the total synthesis, a triflation−reductive protection sequence efficiently transformed **24** into **26** which was then employed in a Pd-catalyzed borylation to give boronic ester **27**. Without further purification, **27** was directly treated with a catalytic amount (2% mol) of a newly discovered Pd−thiourea pincer complex **28**[15] to give the homocoupling product **29**, a full and functionalized crisamicin A skeleton, in 87% yield over two steps. It should be noted that an extensive range of existing homocoupling protocols reported in the literature,[16] including those employing various Pd, Ni, and Cu catalysts and aryl halides, triflates, mesylates, and boronic esters as substrates, had been screened in this transformation. Although several of them promoted homocoupling on simpler naphthoquinone and naphthohydroquinone model compounds with various degrees of success, none of them was found to be capable of effecting such a reaction on more functionalized entities **24**−**27**, a fact that could be reflective of these dimeric pyranonaphthoquinones' unique, highly oxygenated structural characteristic and echoed with a previous finding by Brimble and coworkers.[6a] In sharp contrast, the catalyst **28** proved to be generally successful with both simple and functionalized substrates. Thus, the inherent robustness of **28** in overriding a substrate's individual reactivity profile promises further applications in the context of natural product synthesis involving homocoupling as a key strategy. Deprotection of the hydroquinone moiety of **29** and its subsequent air oxidation yielded bisquinone **30** in 93% yield. Finally, demethylation of **30** by the action of BCl_3 gave crisamicin A in 91% yield. Overall, the synthesis consisted of 19 steps in its linear sequence, and the overall yield was 10%. The synthetic material was fully characterized, and its ^1H and ^{13}C NMR spectra were found to be identical to those of the natural product.

In summary, we have demonstrated Pd/TMTU to be an efficient and general catalytic system in the Pd-catalyzed alkoxycarbonylative annulation to generate pyran-fused lactones in high yields. We also uncovered a robust Pd−thiourea pincer complex that was capable of homocoupling functionalized naphthoquinones and naphthahydroquinones. Implementation of these discoveries into the context of crisamicin A has yielded its first stereoselective total synthesis successfully.

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Supporting Information Available: Experimental procedure and NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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