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Total Synthesis of (±)-δ-Rubromycin

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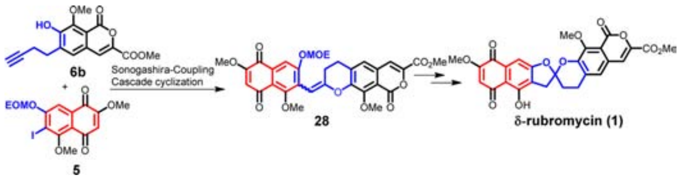
ABSTRACT



Transition-metal-catalyzed spiroketalization cyclization has been performed successfully and has led to the first total synthesis of (±)-δ-rubromycin with a longest linear sequence of 18 steps from commercially available guaiacol in a 2.7% overall yield.

The rubromycin family, although known for more than 50 years,[1] has continued to capture the attention of synthetic chemists because of their range of antitumor effects[2] (see Figure 1). It is the 5,6-spiroketal moiety that is responsible for the biological activity of these compounds.[3]

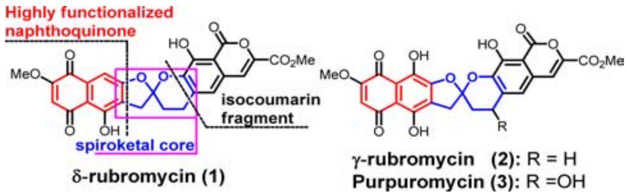


Figure 1. Selected members of the rubromycin family.

In the past few decades, much effort has been devoted to the formation of natural products containing a bisbenzannulated 5,6-spiroketal moiety.[4] Danishefsky,[5] Kita,[6] and Brimble[7] have reported the total synthesis of heliquinomycinone and γ-rubromycin. However, the 5,6-spiroketal core was not installed at a late stage, with the fully intact naphthoquinone and isocoumarin subunits, until 2011 by Pettus in his convergent total synthesis of γ-rubromycin.[8] In spite of this investigation, the most striking problem surrounding spiroketalization of the fully elaborated core structure was "*Electron Withdrawing Resonance & Inductive Effects*."[4e,j] The cause principally stems from the

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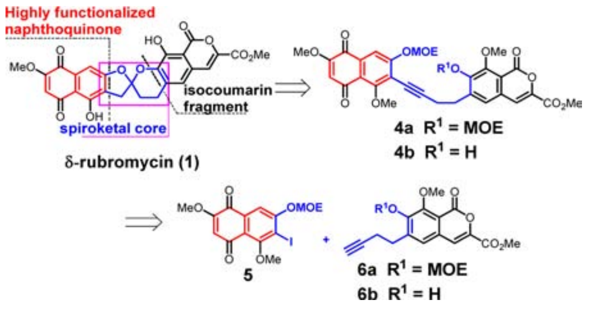
electron-withdrawing nature of the isocoumarin moiety, which dramatically diminishes the nucleophilicity of the corresponding phenol moiety. Difficulties in the application of the convergent route to the natural product have been reported by the research groups of Danishefsky,[5] Kozlowski,[4e] and Reissig[4j,13a] in their respective synthetic efforts toward heliquinomycinone and purpuromycin. Therefore, it is an essential goal in the convergent synthesis of the rubromycin family to find more suitable spiroketalization processes with wider functional group tolerance.

Our investigations into the convergent synthesis of rubromycins have resulted in several novel and efficient processes for the construction of spiroketals, including transition-metal-catalyzed tandem cyclizations,[9] hetero-Diels–Alder cycloadditions,[10] and hypoiodite-catalyzed cycloetherifications.[11] More recently, a formal synthesis of γ-rubromycin was achieved using *in situ* generated hypoiodite-catalytic cycloetherification as a key step in our lab.[12] However, it could not be performed in a really convergent way, so further effort was devoted on the exploration of other more efficient spiroketalization processes.[9a] In continuation of our work on transition-metal-catalyzed cyclizations,[9a] herein we describe the first total synthesis of $(\pm)$-δ-rubromycin through a convergent route. The process not only is highly efficient and elegant but also makes great improvements to late stage spiroketalization with fully intact naphthoquinone and isocoumarin subunits.

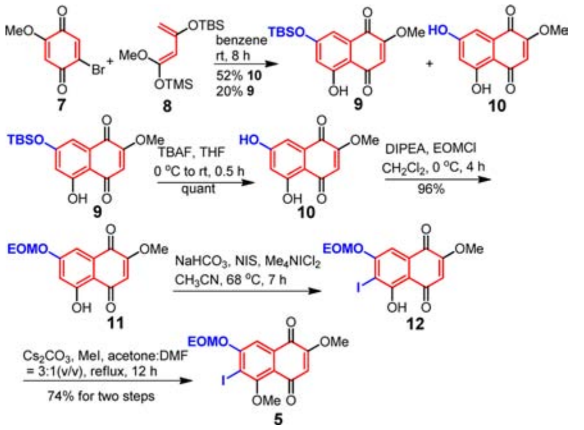
Our retrosynthetic analysis is outlined in Scheme 1. We hypothesized that the entire 5,6-spiroketal moiety of $(\pm)$-δ-rubromycin could be prepared from the alkyne **4** through a transition-metal-catalyzed cascade spiroketalization reaction,[9a] which might avoid the "*Electron Withdrawing Resonance & Inductive Effects*" and result in nucleophilic attack of the complete isocoumarins. Obviously, alkyne **4** could be convergently synthesized from the isocoumarin fragment **6** and the naphthalene fragment **5** by a Sonogashira coupling reaction.

Naphthoquinone fragment **5** is a highly functionalized compound, and several research groups have already encountered difficulties in the synthesis of its analogs.[4e,13] The Diels–Alder reaction is an effective method for creating naphthalene rings in a regioselective manner.[14] A new strategy was therefore designed for the synthesis of naphthoquinone **5** (see Scheme 2), from the known quinone **7**[15] and diene **8**.[16] Gratifyingly, this reaction in benzene at rt afforded a mixture of naphthoquinones **10** and **9** in 72% total yield and 2.6:1 ratio. Furthermore, naphthoquinone **9** could be isolated and converted to phenol **10** in quantitative yield. The selective reprotection of phenol **10** with ethoxymethyl chloride (EOMCl) also provided **11** in almost quantitative yield. The subsequent ortho-selective iodination of phenol **11** proceeded to give iodophenol **12**, which was then methylated to yield naphthoquinone **5** in a 74% yield for two steps and a 51% total yield from **7**.

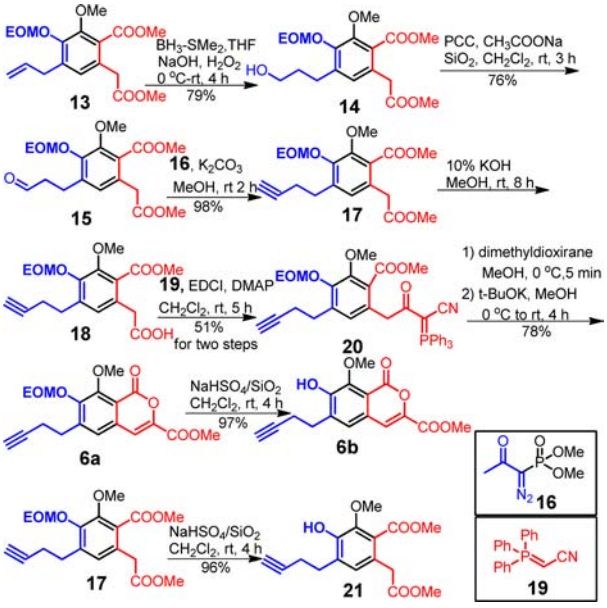
Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of the Naphthoquinone **5**



Scheme 3. Synthesis of Isocoumarin Moiety **6b** and **21**



For the isocoumarin alkyne **6b**, its synthesis has not been reported to date. However, there are several reported

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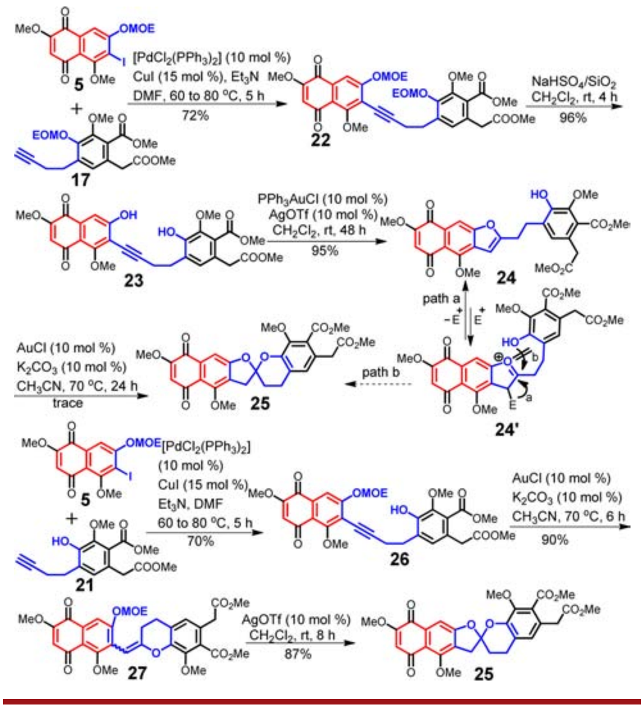
methods for the construction of similar isocoumarin fragments.[5,6,17] Accordingly, the synthesis of **6b** was designed as shown in Scheme 3, where a modified Seyferth–Gilbert reaction was used to construct the alkyne, and the isocoumarin ring was synthesized following Kita's method.[6] From alkene **13**, prepared previously by our group in 7 steps and 40% overall yield from commercially available guaiacol,[12] alcohol **14** was synthesized in a 79% yield through hydroboration–oxidation. After compound **14** was oxidized to the aldehyde **15** with PCC, **15** was treated with **16** in the presence of K_2CO_3; the modified Seyferth–Gilbert homologation proceeded, and the alkyne **17** was efficiently obtained in a 98% yield.[18] Selective hydrolysis of the aliphatic ester **17** to the carboxylic acid **18** was completed with 10% aqueous KOH solution. Then the condensation of **18** and (triphenylphosphoranylidene)acetonitrile **19** gave **20** in a moderate yield. It was oxidized by dimethyldioxirane. The cyclization of the intermediate progressed immediately, following treatment with potassium *tert*-butoxide, to afford isocoumarin **6a** in a 78% yield. Final deprotection with $NaHSO_4/SiO_2$ produced **6b**. Similarly, alkyne **17** could also be converted to compound **21**.

Scheme 4. Model Studies for the Spiroketal Scaffold



With the "*Electron Withdrawing Resonance & Inductive Effects*" taken into consideration, elimination of the electron-withdrawing mesomeric effect of the isocoumarin precursor **17** from the advanced alkyne **6a** was expected to increase the nucleophilicity of the phenol.[7] With this in mind, construction of the spiroketal core was attempted initially using **5** with **17** as a model study. First, a trial Sonogashira coupling of **5** and **17** was attempted under various conditions[7,19] (Scheme 4). Under strictly anhydrous conditions, the alkyne **22** was synthesized in a 72% yield. After removing the EOM group, compound **23** was formed and used in the construction of the spiroketal. To our dismay, the aromatic spiroketal **25** could not be obtained using our previously reported conditions.[9a] Following treatment of $PPh_3AuCl/AgOTf$ in CH_2Cl_2, benzofuran **24** formed in a high yield. Therefore, attempts were devoted solely to the conversion of **24** to **25** using various acids, such as TfOH, TFA, $BF_3.Et_2O$, CSA, NIS, NBS, PPh_3AuCl, AgOTf, $PdCl_2$, and $CuCl_2$, which resulted in no conversion at all. These findings were attributed to impaired nucleophilic attack of the isocoumarin phenolic oxygen atom. During this process, benzofuran **24** would cyclize in the presence of acid to intermediate oxonium ion **24′**. In this intermediate, elimination to the benzofuran derivative **24** would be much faster than nucleophilic attack by the isocoumarin precursor hydroxy function (Scheme 4). Finally, only a trace of the desired spiroketal **25** was found by treating **24** with catalytic amounts of AuCl and K_2CO_3.

With the knowledge gained from this prior attempt, it was clear that nucleophilicity of the isocoumarin precursor was not the only factor controlling the spiroketalization. To circumvent formation of the benzofuran before nucleophilic attack of the isocoumarin phenolic oxygen atom we designed a second-generation model study, in which the construction of benzopyran was prior to the construction of benzofuran (see Scheme 4). Naphthoquinone portion **5** and isocoumarin precursor **21** provided alkyne **26** via Sonogashira coupling. In the presence of catalytic amounts of AuCl and K_2CO_3, the benzopyran **27** was synthesized from compound **26** as a 5:1 mixture of Z/E isomers in an excellent yield. We were pleased that treatment of the

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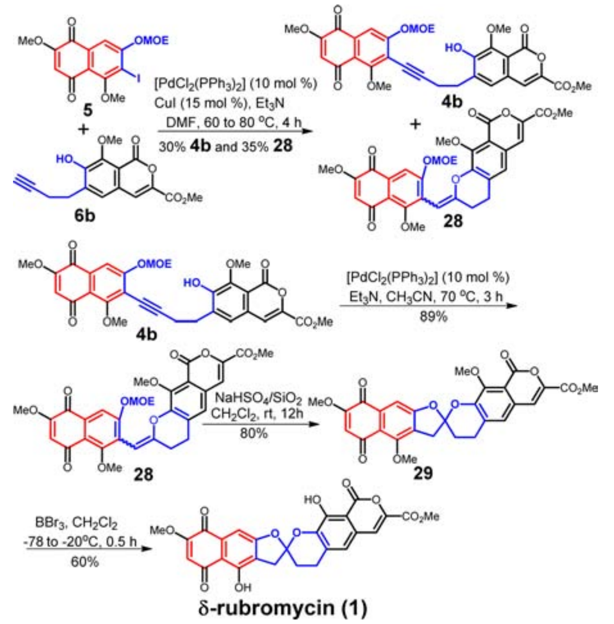
benzopyran **27** with 10 mol % AgOTf afforded the desired spiroketal **25** in 87% yield. Following reduction and permethylation,[20] the spiroketal **25** could perhaps be converted to the natural product (±)-δ-rubromycin according to the procedure reported by Brimble[7] and Kita.[6]

Scheme 5. Convergent Total Synthesis of (±)-δ-Rubromycin



Encouraged by the successful spiroketalization of compound **26** to **25**, a more convergent strategy for the first total synthesis of (±)-δ-rubromycin was designed (see Scheme 5). According to the successful Sonogashira coupling conditions of **5** and **17**/**21**, the benzopyran **28** resulted along with **4b**, as a 4:1 mixture of *E*/*Z* isomers in a 35% yield. Unfortunately, transformation of the alkyne **4b** to benzopyran **28** gave no desired product with the AuCl/K_2CO_3 catalyst, even over a very long time. With formation of **28** in mind, $PdCl_2(PPh_3)_2$ was taken into consideration as a possible Sonogashira catalyst. With satisfaction, compound **28** was obtained by the intramolecular cyclization of the alkyne **4b** catalyzed by $PdCl_2(PPh_3)_2$. As opposed to the problem seen with "*Electron Withdrawing Resonance & Inductive Effects*," nucleophilic attack of the phenolic hydroxyl group of isocoumarin proceeded efficiently. The effect of the isocoumarin electron-withdrawing groups has also been studied by Kozlowski and co-workers recently.[4k] Failure to spiroketalize was shown to be a result of oxidation of a naphthalene subunit to the naphthaquinone, not the nucleophilicity of the isocoumarin phenol. Attention was now paid to the conversion of compound **28** to **29**. The conditions that were used to convert **27** to **25** failed in the transformation of the benzopyran **28** to the spiroketal **29**. Therefore, alternate conditions for the deprotection and cyclization were explored. TsOH, PPh_3AuCl, $PdCl_2(PPh_3)_2$, and $Pd(OAc)_2$ did not give any of the desired product. Similar to the removal of the EOM group of **22**, the benzopyran **28** was treated with $NaHSO_4/SiO_2$ in dichloromethane, and the desired spiroketal **29** formed in 80% yield. Final deprotection with BBr_3 produced **1**.[8] The spectroscopic data were identical to those reported in the literature.[2a]

In summary, the first total synthesis of (±)-δ-rubromycin has been achieved through a convergent strategy with a longest linear sequence of 18 steps from commercially available guaiacol in a 2.7% overall yield. Palladium, gold, and silver reagents were screened in the spiroketalization of different precursors. A Danishefsky-type Diels–Alder reaction was employed to install the requisite highly functionalized aromatic ring system of the naphthalene portion **5**, in a very short sequence, which makes the total synthesis of this natural product more efficient and elegant. This synthesis avoids the "*Electron Withdrawing Resonance & Inductive Effects*" and provides a new idea for the construction of spiroketals, as well as an efficient and convergent approach to synthesizing rubromycins.

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

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The authors declare no competing financial interest.