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A Convergent Total Synthesis of (±)-γ-Rubromycin

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Supporting Information

ABSTRACT: An expeditious convergent total synthesis affords (±)-γ-rubromycin (**1**) in 4.4% overall yield. The longest linear sequence is 12 steps from commercial starting materials. The effort highlights a remarkable late-stage oxidative [3 + 2] cycloaddition for construction of the spiroketal, a regioselective carbonyl methylenation, a boron tribromide promoted deprotection, *ortho*- to *para*- naphthoquinone spiroketal rearrangement, and a tautomerization sequence.

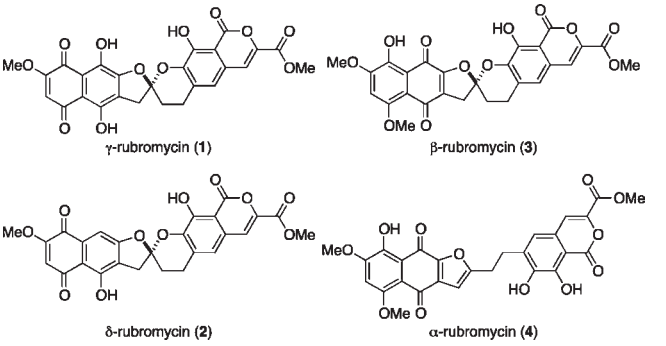


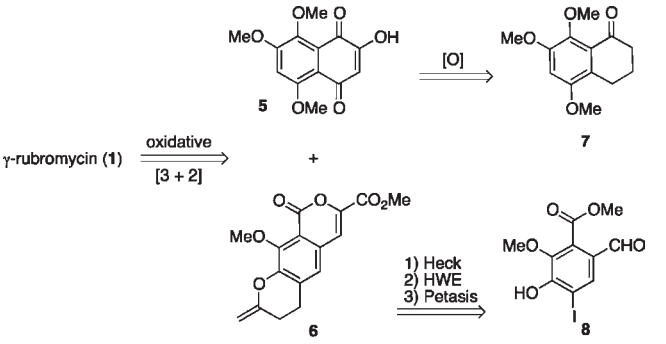
Figure 1. Selected members of the rubromycin family.

The rubromycins represent a small growing family of natural products (**1**−**4**) comprised of a densely oxygenated naphthoquinone moiety linked with an isocoumarin fragment (Figure 1).[1] Other structurally related compounds include the griseorhodins, DK-7814, purpuromycin, and heliquinomycin.[2] These natural products have been shown to display a broad spectrum of assorted bioactivities.[3] In the rubromycin series, studies have revealed that γ-rubromycin (**1**) and β-rubromycin (**3**), which are conjoined through an optically active [5,6]-aryloxy spiroketal, all manifest strong inhibition of human telomerase ($IC_{50} \geq 3\ \mu M$). In contrast, α-rubromycin (**4**), which is missing the [5,6]-aryloxy spiroketal, appears inactive ($IC_{50} > 200\ \mu M$). This contrasting profile of biological activity led Hayashi to propose the [5,6]-spiroketal moiety as the motif responsible for telomerase inhibition.[4]

Accordingly, the rubromycins and the related structures have attracted intensive synthetic interests over the past several decades,[5] culminating first in the total synthesis of the aglycone of (±)-heliquinomycin by Danishefsky in 2001[6] and, more recently, in a total and a formal synthesis of (±)-γ-rubromycin (**1**) by Kita[7] and Brimble,[8] respectively. However, to the best of our knowledge the [5,6]-spiroketal core has never been installed at a late stage with the fully intact naphthoquinone and isocoumarin subunits. The problem surrounding thermodynamic ketalization of the fully elaborated core structure was initially recognized by Kozlowoski[5e] and later substantiated and named by Reissig[9] as the "*Negative Mesomeric & Inductive effects*" (*M&I effects*). The cause principally stems from the electron-withdrawing nature of the isocoumarin moiety, which dramatically diminishes the nucleophilicity of the corresponding phenol moiety.

Our laboratory recently disclosed a facile method for oxidative [3 + 2] cycloadditions between β-diketones and exocyclic enol ethers as a means for fashioning [5,6]-spiroketal frameworks, and we described for the first time a facile rearrangement between *ortho*- and *para*-quinone spiroketals.[10] However, its tolerance of highly functionalized coupling partners was largely untested. Herein, we report its application for a concise synthesis of γ-rubromycin (**1**). The strategy provides convergent synthetic access to all members of the rubromycin family. The general synthetic analysis is depicted in Scheme 1. We aimed to assemble the entire [5,6]-spiroketal core through a late-stage [3 + 2] cycloaddition between the fully mature naphthoquinone **5** and the methylenated chroman **6**. The naphthoquinone **5** would originate from α-tetralone **7**, whereas the chroman **6** could be prepared from Reissig benzaldehyde **8** by sequential Heck, Horner−Wadsworth−Emmons, and Petasis reactions.

Scheme 1. Synthetic Analysis of γ-Rubromycin (1)



Our synthesis begins with the preparation of the naphthoquinone **5**, a compound first synthesized by Thomson.[11] In our initial approach, the α-tetralone **7**[12] was prepared in three steps from commercially available 1,2,4-trimethoxybenzene. Further application of oxidative procedures resulted in the corresponding

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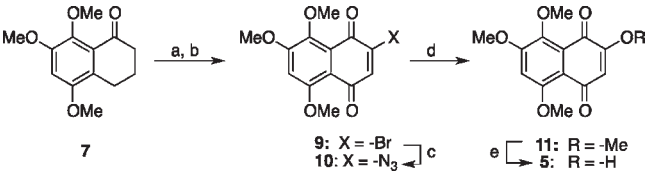
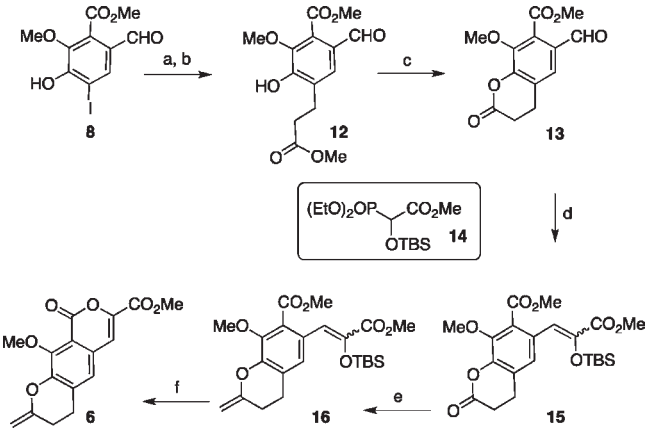
Scheme 2. Synthesis of Naphthoquinone 5 from α-Tetralone 7



(a) LiHMDS (2.4 equiv), THF, −78 °C, then NBS (2.06 equiv); DBU (1.23 equiv), −78 °C to rt, 78% yield. (b) CAN (2.14 equiv), MeCN/H_2O, 0 °C, 60% yield. (c) NaN_3 (1.46 equiv), THF/H_2O, rt. (d) $CsCO_3$ (1.5 equiv) $PhCH_3$/MeOH, rt, 65% yield for 2 steps. (e) KOH (21.4 equiv), MeOH/H_2O, 84% yield.

Scheme 3. Preparation of Methylenated Isocoumarin 6

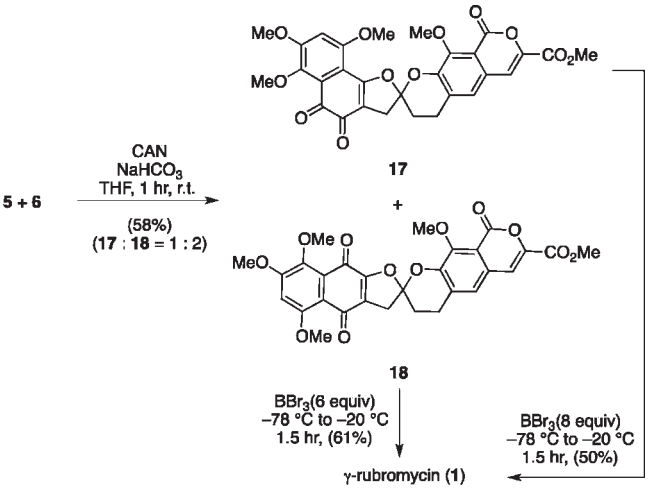


(a) $Pd(OAc)_2$, PPh_3, methyl acrylate (1.9 equiv), LiCl, NEt_3 (1.81 equiv), DMF, 80 °C, 93% yield. (b) H_2 (1 atm), Pd/C, EtOAc, 94% yield. (c) *p*-TsOH (*cat.*), PhMe, reflux, 82% yield. (d) **14** (1.03 equiv), LiHMDS (1.0 equiv), THF, −78 °C, then **13** (1.0 equiv), 60% yield, *E*/*Z* = 6/1. (e) $CpTiMe_2$ (2.19 equiv), PhMe, 70 °C, 72% yield, *E*/*Z* = 8/1. (f) TBAF (1.03 equiv), THF, −78 °C, 94% yield.

naphthoquinone **5**, but in a manner not easily scaled.[13,10d] Hence, we turned our attention toward exploration of an alternative route (Scheme 2). Functionalization of the α-tetralone **7** using Nicolaou's sequential bromination method provided the desired bromophenol intermediate,[14] which was then subjected to cerium ammonium nitrate (CAN) oxidation to provide the bromonaphthoquinone **9** in 47% overall yield from **7**.[15] According to an unusual leaving group effect, previously described by Anufriev[16] and subsequently utilized by Brimble,[8] the vinyl bromide **9** was reformulated into its azide **10** for subsequent displacement. The azide **10** was then subjected to methanol in cesium carbonate thereby resulting in the regioselective formation of the methyl ether **11** in a 65% yield. Subsequent saponification of the vinylogous ester with potassium hydroxide affords the desired naphthoquinone **5** in 84% yield. The naphthoquinone **5** displays a β-diketone of sorts ready for examination in the key oxidative [3 + 2] cycloaddition.

The preparation of the other coupling partner, the fully elaborated isocoumarin **6**, was much more challenging (Scheme 3).[7] After considering several new strategies, we decided to begin with Reissig's aldehyde **8**, which was prepared in four steps and 42% overall yield from vanillin according to literature protocol.[17] Heck reaction of its aryl iodide with methyl acrylate affords the

Scheme 4. Conclusion of the Total Synthesis of (±)-γ-Rubromycin (1)



corresponding *E*-unsaturated ester, which succumbs to catalytic hydrogenation to afford the saturated ester **12** in 87% overall yield. Subsequent acid-promoted lactonization provides the dihydrocoumarin **13** in 82% yield. The aldehyde in this material undergoes a Horner−Wadsworth−Emmons reaction with Thompson's phosphonate **14** to afford the unsaturated triester **15** as a 6:1 mixture of *E*/*Z* isomers.[18] Interestingly, the dihydrocoumarin carbonyl in compound **15** undergoes selective methylenation upon treatment with the Petasis reagent to cleanly afford the exocyclic enol ether **16** as an 8:1 mixture of *E*/*Z* isomers.[19] Further treatment of the silyl enol ether of compound **16** with *tert*-butyl ammonium fluoride (TBAF) causes sequential deprotection and cyclization to furnish the desired methylenated isocoumarin **6** in 94% yield.

Having successfully prepared both the naphthoquinone **5** and the isocoumarin **6**, we were eager to implement the key bond-forming reaction (Scheme 4). Coupling of **5** and **6** in the presence of CAN in THF at room temperature affords a nonequilibrating[10b] separable 1:2 mixture of regioisomers in 58% combined yield (*o*-naphthoquinone spiroketal **17** and *p*-naphthoquinone spiroketal **18**, respectively). From a synthetic perspective, the [3 + 2] oxidative cycloaddition fashions the most challenging aspect of the framework of γ-rubromycin (**1**) in a single step. Given the success of this unprecedented strategy, we next investigated the individual deprotection of each of the valence tautomers. Gratifyingly, exposure of the *p*-naphthoquinone spiroketal **18** to an excess of boron tribromide (BBr_3) in CH_2Cl_2 (−78 to −20 °C) expectedly provides synthetic (±)-γ-rubromycin (**1**), in a respectable 61% yield. This material is indistinguishable from an authentic natural sample (^1H NMR, IR, TLC).[19]

We next considered the application of protic conditions with the *o*-naphthoquinone ketal **17**, as previously used by Kita to catalyze a similar rearrangement for a simplified albeit related system.[7] To our surprise, all attempts to induce rearrangement on **17** with acid were unsuccessful and they resulted in unchanged starting material. Upon subjection of compound **17** to an excess of BBr_3 in CH_2Cl_2 (−78 to −20 °C), however, the *o*-napthoquinone spiroketal **17** cleanly provides γ-rubromycin (**1**) in greater than 50% yield. Although the exact timing of demethylation(s) within this sequence remains unclear, this

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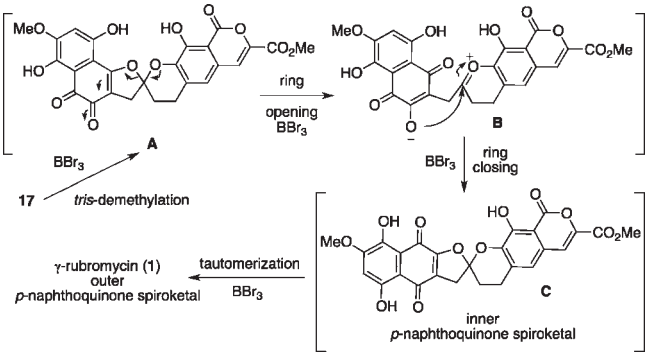
Scheme 5. *tris*-Deprotection/*ortho*- to *para*-Naphthoquinone Spiroketal Rearrangement/Tautomerization



overall transformation is quite unusual as it involves deprotection of three methoxy substituents, an *ortho*- to *para*-naphthoquinone rearrangement, and an inner to outer naphthoquinone tautomerization (Scheme 5, A→B→C) all in a single pot.

In conclusion, by exploiting a last stage oxidative [3 + 2] cycloaddition, we have completed a significantly shorter total synthesis of (±)-γ-rubromycin (**1**) than previously realized. The highly convergent strategy provides the target molecule in a 4.4% overall yield. The naphthoquinone and isocoumarin components (**5** and **6**) employed in the oxidative [3 + 2] cycloaddition are respectively prepared from 1,2,4-trimethoxybenzene and vanillin. Both are inexpensive and readily available. The strategy highlights a regioselective Petasis carbonyl methylenation and a rather unusual BBr_3 promoted *ortho*- to *para*-naphthoquinone spiroketal rearrangement/deprotection/tautomerization in the case of the *o*-naphthoquinone **17**. Further efforts toward the synthesis of optically enriched rubromycins and the biological evaluation of rubromycins and their analogs will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, structural proofs, and full spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) γ-Rubromycin is commercially available from Enzo Life Sciences.