

# A Convergent Total Synthesis of ( $\pm$ )- $\gamma$ -Rubromycin

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S Supporting Information

**ABSTRACT:** An expeditious convergent total synthesis affords  $(\pm)$ - $\gamma$ -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*- naphtho-quinone spiroketal rearrangement, and a tautomerization sequence.

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).<sup>1</sup> Other structurally related compounds include the griseorhodins, DK-7814, purpuromycin, and heliquinomycin.<sup>2</sup> These natural products have been shown to display a broad spectrum of assorted bioactivities.<sup>3</sup> In the rubromycin series, studies have revealed that  $\gamma$ -rubromycin (1) and  $\beta$ -rubromycin (3), which are conjoined through an optically active [5,6]-aryloxy spiroketal, all manifest strong inhibition of human telomerase (IC<sub>50</sub>  $\geq$  3  $\mu$ M). In contrast,  $\alpha$ -rubromycin (4), which is missing the [5,6]-aryloxy spiroketal, appears inactive (IC<sub>50</sub>  $\geq$  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.<sup>4</sup>

Accordingly, the rubromycins and the related structures have attracted intensive synthetic interests over the past several decades,<sup>5</sup> culminating first in the total synthesis of the aglycone of  $(\pm)$ -heliquinomycin by Danishefsky in 2001<sup>6</sup> and, more recently, in a total and a formal synthesis of  $(\pm)$ - $\gamma$ -rubromycin (1) by Kita<sup>7</sup> and Brimble,<sup>8</sup> 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<sup>5e</sup> and later substantiated and named by Reissig<sup>9</sup> 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  $\beta$ -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.<sup>10</sup> However, its tolerance of



Figure 1. Selected members of the rubromycin family.

Scheme 1. Synthetic Analysis of  $\gamma$ -Rubromycin (1)



highly functionalized coupling partners was largely untested. Herein, we report its application for a concise synthesis of  $\gamma$ -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  $\alpha$ -tetralone 7, whereas the chroman 6 could be prepared from Reissig benzaldehyde 8 by sequential Heck, Horner–Wadsworth–Emmons, and Petasis reactions.

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

Received: December 22, 2010 Published: March 31, 2011 Scheme 2. Synthesis of Naphthoquinone 5 from  $\alpha$ -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<sub>2</sub>O, 0 °C, 60% yield. (c) NaN<sub>3</sub> (1.46 equiv), THF/H<sub>2</sub>O, rt. (d) CsCO<sub>3</sub> (1.5 equiv) PhCH<sub>3</sub>/MeOH, rt, 65% yield for 2 steps. (e) KOH (21.4 equiv), MeOH/H<sub>2</sub>O, 84% yield.

Scheme 3. Preparation of Methylenated Isocoumarin 6



(a) Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, methyl acrylate (1.9 equiv), LiCl, NEt<sub>3</sub> (1.81 equiv), DMF, 80 °C, 93% yield. (b) H<sub>2</sub> (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<sub>2</sub> (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.<sup>13,10d</sup> Hence, we turned our attention toward exploration of an alternative route (Scheme 2). Functionalization of the  $\alpha$ -tetralone 7 using Nicolaou's sequential bromination method provided the desired bromophenol intermediate,<sup>14</sup> 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<sup>16</sup> and subsequently utilized by Brimble,<sup>8</sup> 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  $\beta$ -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).<sup>7</sup> 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.<sup>17</sup> Heck reaction of its aryl iodide with methyl acrylate affords the

Scheme 4. Conclusion of the Total Synthesis of  $(\pm)$ - $\gamma$ -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.<sup>18</sup> 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.<sup>19</sup> 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 bondforming reaction (Scheme 4). Coupling of 5 and 6 in the presence of CAN in THF at room temperature affords a nonequilibrating<sup>10b</sup> 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  $\gamma$ -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<sub>3</sub>) in  $CH_2Cl_2$  (-78 to -20 °C) expectedly provides synthetic (±)- $\gamma$ rubromycin (1), in a respectable 61% yield. This material is indistinguishable from an authentic natural sample (<sup>1</sup>H NMR, IR, TLČ).<sup>1</sup>

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.<sup>7</sup> 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<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (-78 to -20 °C), however, the *o*-napthoquinone spiroketal 17 cleanly provides  $\gamma$ -rubromycin (1) in greater than 50% yield. Although the exact timing of demethylation(s) within this sequence remains unclear, this 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,  $A \rightarrow B \rightarrow C$ ) 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  $(\pm)$ - $\gamma$ -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<sub>3</sub> 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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#### Notes

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(20)  $\gamma$ -Rubromycin is commercially available from Enzo Life Sciences.