

# Synthesis of ( $\pm$ )- $\gamma$ -Rubromycin via a New Hypoiodite-Catalytic Oxidative Cycloetherification

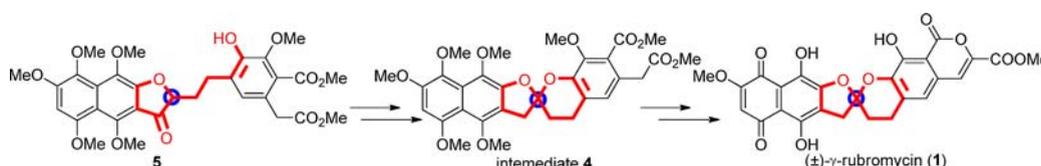
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## ABSTRACT



A new synthesis of  $\gamma$ -rubromycin is presented through a new oxidative, bisbenzannulated spiroketalization as a key step which is catalyzed by an in situ generated hypoiodite species, developed previously by our group. This key transformation has high efficiency and convenient conditions. This is a new and efficient catalytic application for organohypoiodine reagents.

One of the challenges currently facing synthetic chemists is the development of efficient and elegant chemical processes that allow for the rapid synthesis of functional, diverse, and molecularly complex bioactive compounds from simple starting materials.<sup>1</sup> Recently, organohypervalent iodine reagents have attracted significant attention as versatile and environmentally benign oxidants, as well as for their strong potential use in many applications in organic synthesis.<sup>2</sup> The most impressive recent achievements in the field have included the development of new hypervalent iodine reagents and reagent systems and the discovery of catalytic applications for organohypoiodite compounds.<sup>2,3</sup>

Some of these applications include the hypervalent iodine catalytic  $\alpha$ -oxyacetylation and  $\alpha$ -oxyalkylation<sup>4</sup> of carbonyl compounds. Additionally, intramolecular  $\alpha$ -oxyphenylation of carbonyl compounds has proven to be useful in the construction of oxa-benzocycles, but there are few reports on their application in natural product synthesis.

Rubromycins (Figure 1), isolated by Brockmann and co-workers, are a class of antibiotics with a wide spectrum of biological activity, which contain highly functionalized, multiple fused-cyclic scaffolds with bisbenzannulated spiroketal cores.<sup>5</sup> As the typical example,  $\gamma$ -rubromycin (1), traces of which can be isolated from *Streptomyces* cultures, displays potent activity against human telomerase ( $IC_{50} = 3 \mu M$ )<sup>6</sup> and inhibits mammalian DNA-polymerase

(1) (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (b) Wu, C. Y.; Chang, C. F.; Szu, J.; Chen, Y.; Wong, C. H.; Lin, C. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4661. (c) Kodadek, T. *Chem. Commun.* **2011**, *47*, 9757. (d) Duarte, M. J.; Antón-Fos, G. M.; Alemán, P. A.; Gay-Roig, J. B.; González-Rosende, M. E.; Gálvez, J.; García-Domenech, R. *J. Med. Chem.* **2005**, *48*, 1260.

(2) (a) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénéde, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (b) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (c) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175. (d) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (f) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, *16*, 2073. (g) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, *16*, 2086.

(3) (a) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185. (b) Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V. *Tetrahedron* **2010**, *66*, 5745.

(4) (a) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244. (b) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 6193. (c) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Tetrahedron* **2010**, *66*, 5841. (d) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376. (e) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331.

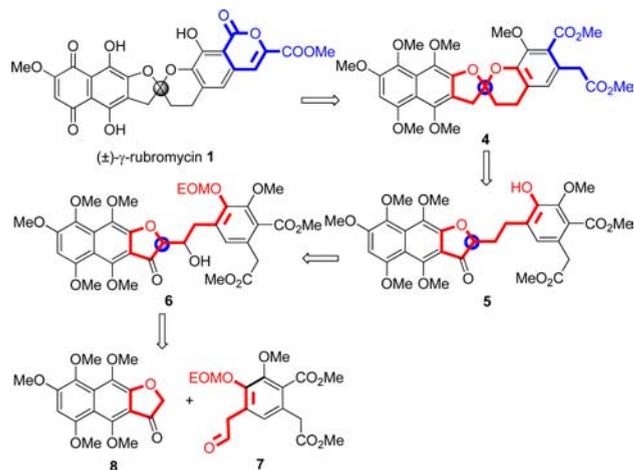
(5) (a) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Tetrahedron Lett.* **1966**, *7*, 3525. (b) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Chem. Ber.* **1969**, *102*, 126. (c) Brockmann, H.; Zeeck, A. *Chem. Ber.* **1970**, *103*, 1709.

(6) Ueno, T.; Takahashi, H.; Oda, M.; Mizunuma, M.; Yokoyama, A.; Goto, Y.; Mizushima, Y.; Sakaguchi, K.; Hayashi, H. *Biochemistry* **2000**, *39*, 5995.

(7) Puder, C.; Loya, S.; Hizi, A.; Zeeck, A. *Eur. J. Org. Chem.* **2000**, 729.

and HIV-1 reverse transcriptase.<sup>7</sup> Heliquinomycin (**2**) is a selective inhibitor of a cellular DNA helicase that inhibits the growth of tumor cell lines,<sup>8</sup> and purpuromycin (**3a**) has been considered for use as a topical agent for vaginal infections.<sup>10</sup>

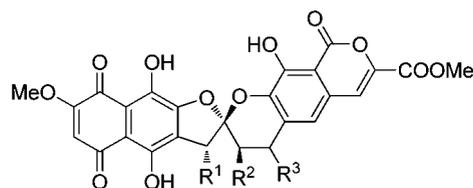
### Scheme 1. Retrosynthetic Analysis



The important biological properties and interesting structures of members of the rubromycin family have made them attractive synthetic targets. In past decades, much effort has been devoted to the formation of natural products on a bisbenzannulated scaffold. Danishefsky,<sup>11</sup> Kita,<sup>12</sup> Brimble,<sup>13</sup> Kozłowski,<sup>14</sup> and Pettus<sup>15</sup> have reported the total synthesis of heliquinomycinone and (±)- $\gamma$ -rubromycin and the formal synthesis of purpuromycin. In these studies, compound **4** was the key intermediate for  $\gamma$ -rubromycin.

In past years, our investigations into the construction of spiroketals has resulted in several new and efficient spiroketalizations that are convenient to use in the construction of natural product spiroketal scaffolds. Some of these

methods have included transition-metal catalyzed spiroketalizations,<sup>16</sup> hetero-Diels–Alder reactions,<sup>17</sup> and hypiodite-catalyzed  $\alpha$ -oxyphenylation.<sup>18</sup> Among them, a new organohypervalent iodine system,<sup>18</sup> generated in situ from the irradiative aerobic oxidation of tetrabutylammonium iodide (TBAI), or the oxidation of peroxy acid, has proved highly useful. In continuation of our investigations into organohypervalent iodine and the total synthesis of natural products, our new catalytic hyperiodite system has been employed in the total synthesis of the rubromycins. In this respect, an efficient synthesis of a key known precursor of  $\gamma$ -rubromycin is described herein.



- $\gamma$ -Rubromycin (**1**):  $R^1 = R^2 = R^3 = H$   
 Heliquinomycin (**2**):  $R^1 = O$ -cymarose,  $R^2 = OH$ ,  $R^3 = H$   
 Purpuromycin (**3a**):  $R^1 = R^2 = H$ ,  $R^3 = OH$   
 Griseorhodin C (**3b**):  $R^1 = R^2 = R^3 = OH$

Figure 1. Selected members of the rubromycin family.

The retrosynthetic analysis outlined in Scheme 1 proceeds from the hypiodite-catalyzed spiroketalization onward toward the synthesis of  $\gamma$ -rubromycin (**1**). The literature reports that compound **4** is the key intermediate in the synthesis of  $\gamma$ -rubromycin.<sup>12,13</sup> Based on our previous experience in the synthesis of bisbenzannulated spiroketal cores, we hypothesized that the [5,6]-spiroketal intermediate **4** could be synthesized by intramolecular cyclization of the phenolic hydroxyl with the  $\alpha$ -oxyphenylation of carbonyl compound **5**, catalyzed by TBAI in the presence of *m*-chlorobenzoic acid (*m*CPBA) and tetrabutylammonium fluoride (TBAF). Compound **5** could be obtained from naphthofuran **8** and isocoumarin precursor **7** through an aldol reaction followed by a reduction.

The synthesis of isocoumarin precursor **7** began from phenol **9**, which was prepared in five steps from commercially available guaiacol according to Brimble's protocol (Scheme 2).<sup>13</sup> Alkylation of phenol **9** afforded **10** in an almost quantitative yield. A Claisen rearrangement of **10** in *N,N*-diethylaniline gave rise to product **11** in 95% yield, which was protected as an ethoxymethyl ether under standard conditions. Cleavage of the double bond by ozonolysis in anhydrous MeOH at  $-78^\circ\text{C}$  provided aldehyde **7** in 92% yield.

(8) (a) Ishimi, Y.; Sugiyama, T.; Nakaya, R.; Kanamori, M.; Kohno, T.; Enomoto, T.; Chino, M. *FEBS J.* **2009**, *276*, 3382. (b) Chino, M.; Nishikawa, K.; Yamada, A.; Ohsono, M.; Sawa, T.; Hanaoka, F.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1998**, *51*, 480.

(9) Bardone, M. R.; Martinelli, E.; Zerilli, L. F.; Coronelli, C. *Tetrahedron* **1974**, *30*, 2747.

(10) (a) Waters, S. P.; Kozłowski, M. C. *Tetrahedron Lett.* **2001**, *42*, 3567. (b) Trani, A.; Dallanocce, C.; Panzone, G.; Ripamonti, F.; Goldstein, B. P.; Ciabatti, R. *J. Med. Chem.* **1997**, *40*, 967.

(11) Siu, T.; Qin, D.; Danishefsky, S. *J. Angew. Chem., Int. Ed.* **2001**, *40*, 4713.

(12) Akai, S.; Kakiguchi, K.; Nakamura, Y.; Kuriwaki, I.; Dohi, T.; Harada, S.; Kubo, O.; Morita, N.; Kita, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 7458.

(13) Rathwell, D. C. K.; Yang, S. H.; Tsang, K. Y.; Brimble, M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 7996.

(14) (a) Lowell, A. N.; Fennie, M. W.; Kozłowski, M. C. *J. Org. Chem.* **2011**, *76*, 6488. (b) Bandichhor, R.; Lowell, A. N.; Kozłowski, M. C. *J. Org. Chem.* **2011**, *76*, 6475.

(15) Wu, K. L.; Mercado, E. V.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 6114.

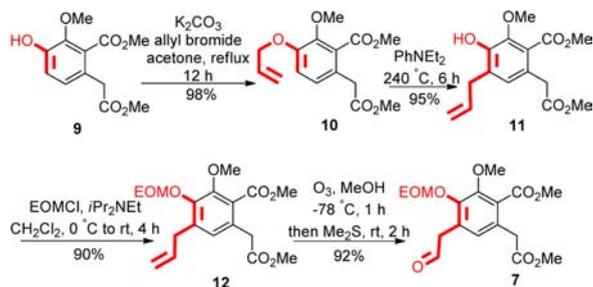
(16) Zhang, Y.; Xue, J.; Xin, Z.; Xie, Z.; Li, Y. *Synlett* **2008**, *2008*, 940.

(17) (a) Zhou, G.; Zheng, D.; Da, S.; Xie, Z.; Li, Y. *Tetrahedron Lett.* **2006**, *47*, 3349. (b) Zhou, G.; Zhu, J.; Xie, Z.; Li, Y. *Org. Lett.* **2008**, *10*, 721.

(18) Wei, W.; Li, L.; Lin, X.; Li, H.; Xue, J.; Li, Y. *Org. Biomol. Chem.* **2012**, *10*, 3494.

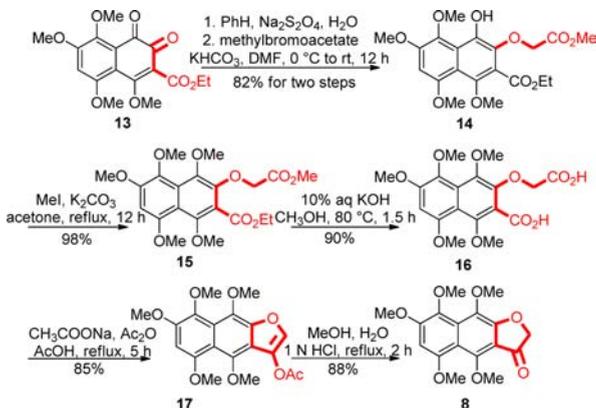
(19) Lowell, A. N.; Fennie, M. W.; Kozłowski, M. C. *J. Org. Chem.* **2008**, *73*, 1911.

**Scheme 2.** Synthesis of Isocoumarin Precursor 7



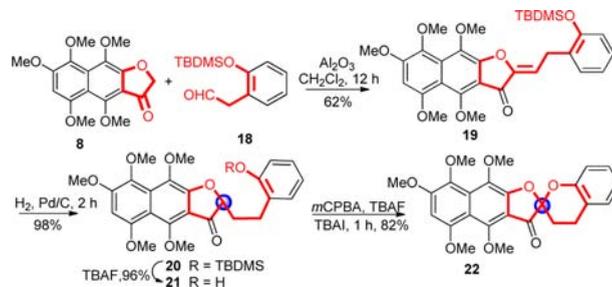
Due to its highly functionalized structure, the synthesis of precursor **8** remained a challenge. Our synthetic route to **8** utilized the Dieckmann condensation as a key step and began from readily prepared Kozlowski's *ortho*-quinone **13** (Scheme 3).<sup>19</sup> First, **13** was reduced under the conditions described by Kozlowski,<sup>19</sup> and the formed naphthodiol was reacted with methyl bromoacetate in the presence of potassium bicarbonate and DMF, to generate **14** in 82% yield. Methylation of **14** and hydrolysis using 10% aqueous potassium hydroxide formed the diacid **16**. A Dieckmann condensation of **16**, carried out in the presence of acetic anhydride, fused sodium acetate, and boiling acetic acid, gave **17** in 85% yield.<sup>20</sup> Subsequent conversion to ketone **8** was accomplished by boiling **17** in 1 N aqueous HCl in MeOH.

**Scheme 3.** Synthesis of Naphthofuran Ketone 8



With the two key precursors in hand, a trial condensation and cyclization was tried using compound **8** and **18** as substrates (Scheme 4). Under neutral  $\text{Al}_2\text{O}_3$  conditions, **8** condensed with **18** and formed **19** in 62% yield. This was followed by Pd–C catalyzed hydrogenation that yielded compound **20** quantitatively. After the removal of the

**Scheme 4.** Model Synthesis of the Scaffold



*tert*-butyldimethylsilyl (TBDMS) protecting group with TBAF in tetrahydrofuran (THF), the key precursor **21** was formed in 96% yield. Using our previously reported conditions,<sup>18</sup> compound **21** was treated with TBAI and *m*CPBA, in the presence of TBAF, to produce the desired spiroketal **22** in 82% yield.

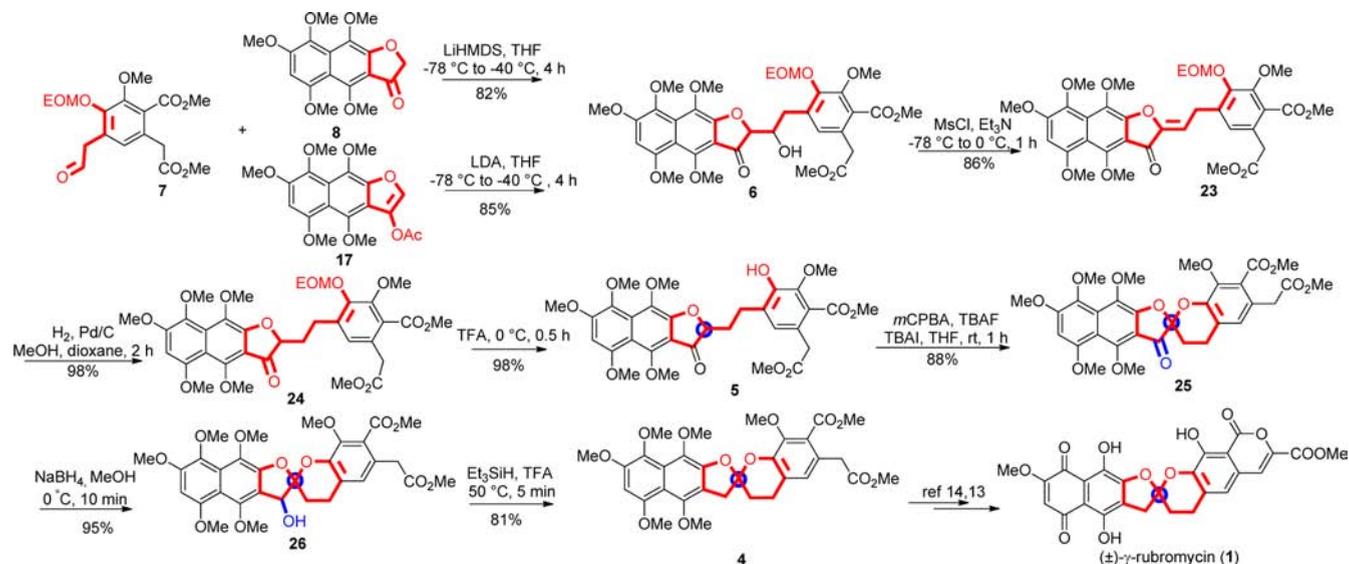
The final phase of our formal synthesis involved the synthesis of compound **4** (Scheme 5). The synthesis of **6** revealed that the condensations of **7** with **17** and of **7** with **8** were efficient. In the presence of lithium diisopropylamide (LDA), the aldol condensation of **7** and **17** provided **6** in 85% yield. By using lithium hexamethyldisilylamide (LHMDS) instead of LDA as a base, the reaction of **7** and **8** produced **6** in 82% yield. Removal of the hydroxyl group was attempted under various conditions, including acid-promoted dehydration,  $\text{Al}_2\text{O}_3$ -mediated elimination, mesylation–reduction, and so on.<sup>21</sup> Finally, dehydration succeeded with methanesulfonyl chloride and triethylamine; it produced olefin **23** with high efficiency in 86% yield. Olefin **23** was then hydrogenated to afford **24** in almost quantitative yield. After removal of the ethoxymethyl (EOM) group with trifluoroacetic acid, compound **5** was formed, allowing the key spirocyclization step to be attempted. Effective cyclization of **5** was accomplished with TBAI as the catalyst, *m*CPBA as the oxidant, TBAF as the additive, and THF as the solvent. At room temperature, bisbenzannulated spiroketal **25** was generated in 88% yield after 1 h. The last step was reduction of the ketone. In the presence of sodium borohydride, spiroketal **25** was first reduced to the alcohol **26**, which was further reduced with trifluoroacetic acid and triethylsilane at 50 °C, forming the known advanced intermediate **4** in 81% yield. Compound **4** can be converted to the target natural product easily according to Kita's<sup>12</sup> and Brimble's<sup>13</sup> procedure. It will be noted that the structures of intermediates **5**, **6**, **25**, and **26** are related to those of heliquinomycin (**2**) and griseorhodin (**3b**). Therefore, they are potentially useful in the total synthesis of these natural products.

In summary, a formal synthesis of  $\gamma$ -rubromycin has been achieved with a longest linear sequence of only 12

(20) (a) Maya, Y.; Ono, M.; Watanabe, H.; Haratake, M.; Saji, H.; Nakayama, M. *Bioconjugate Chem.* **2008**, *20*, 95. (b) Venkatesan, A. M.; Dos Santos, O.; Ellingboe, J.; Evrard, D. A.; Harrison, B. L.; Smith, D. L.; Scerni, R.; Hornby, G. A.; Schechter, L. E.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 824.

(21) In both acid-promoted dehydration and  $\text{Al}_2\text{O}_3$ -mediated elimination, the substrates failed to dehydrate, which instead resulted in complex mixtures.  $\text{MsCl}$  (1.2 equiv) and pyridine at 0 °C for 2 h afforded compound **23** in a low yield.

**Scheme 5.** Completion of Advanced Spiroketal Intermediate 4



steps and 24% overall yield, using in situ generated hypiodite-catalytic cycloetherification as a key step. The synthesis gave a good overall yield, and all the reactions were not overly difficult to execute. This work presents a novel catalytic application of hypiodite reagents, which represents a substantial achievement in the field of organohypervalent iodine chemistry. These results provide a new and efficient approach to synthesizing  $\gamma$ -rubromycin, as well as possible intermediates for other natural products. Further investigations in this field are underway.

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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>.

The authors declare no competing financial interest.