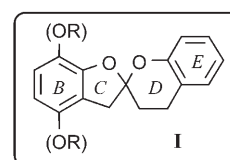
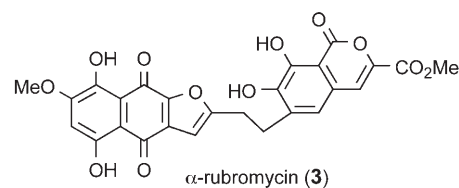
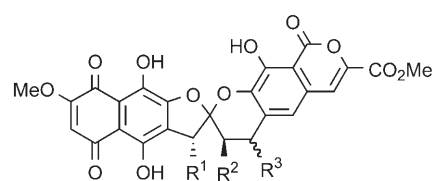
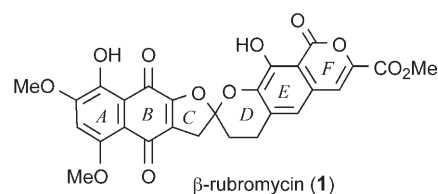


Total Synthesis of ($\pm$)- γ -Rubromycin on the Basis of Two Aromatic Pummerer-Type Reactions**

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The antibiotics β -rubromycin (**1**) and γ -rubromycin (**2**)^[1] contain a highly oxygenated naphthoquinone moiety (A,B rings) and an 8-hydroxyisocoumarin moiety (E,F rings) linked through a 5,6-spiroketal (C,D rings). They exhibit activity against the reverse transcriptase of human immunodeficiency virus-1,^[2] and their inhibition of human telomerase, reported in 2000,^[3] has made these compounds attractive lead compounds for the development of new types of anticancer drugs. The spiroketal unit is essential for their inhibitory activity towards telomerase: The related compound α -rubromycin (**3**), which lacks the spiroketal moiety, exhibits decreased activity. Other natural products have a similar bisbenzannelated spiroketal framework. Typical examples include heliquinomycin (**4**),^[4] an inhibitor of DNA helicase,^[5] and purpuromycin (**5**),^[6] a potential topical agent for vaginal infections (Scheme 1).^[7]

Much effort has been devoted to the synthesis of these compounds,^[8–16] and special attention has been focused on the preparation of the vital bisbenzannelated spiroketal core structure **I**.^[8–13] The reported methods are based on the acid-catalyzed spiroketalization of ketones^[10–12] or a hemiketal,^[9b] the haloetherification of a benzofuran,^[9a] or the oxidative [3+2] cycloaddition of an enol ether with a β -diketone.^[13] However, multiple steps were required to build up the ketals **I** from smaller fragments, and the applicability of these methods to a wide range of analogues has not been demonstrated. Furthermore, the total synthesis of the racemic aglycone of **4** by Danishefsky and co-workers^[9] is the only successful synthesis that has been reported to date for this



Scheme 1. Some typical natural products with bisbenzannelated spiroketal moieties and related compounds.

class of natural products. Therefore, there is a need for the development of more efficient methods for the total synthesis of these natural products and the preparation of diverse analogues with the bisbenzannelated spiroketal moiety **I**. We present herein a convergent synthesis of **I** and the first total synthesis of ($\pm$)- γ -rubromycin (**2**).

First, we developed an effective, convergent route to the pentacyclic ketal **6a**, the core structure of these natural products, on the basis of an unprecedented rearrangement reaction of the spiroketal **10a**. The key precursor **10a** was prepared readily from the sulfoxide **7a** and 2-methylenechroman (**8a**)^[17] by an aromatic Pummerer-type reaction that we had developed previously.^[18–21] The conversion of the “bent”

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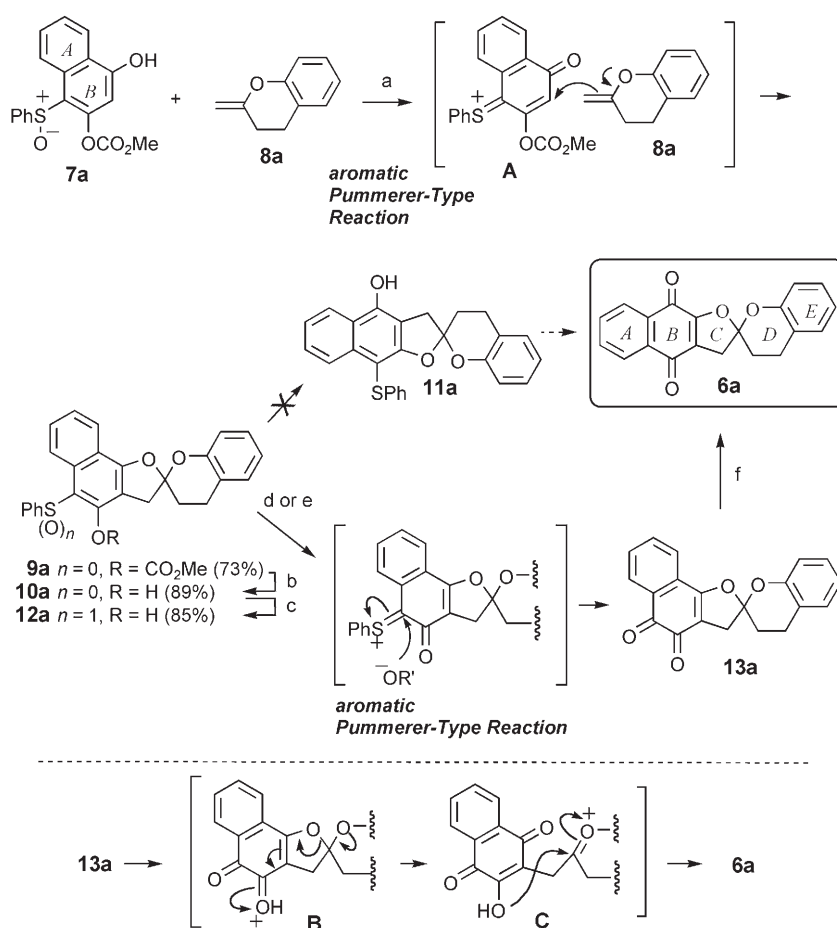
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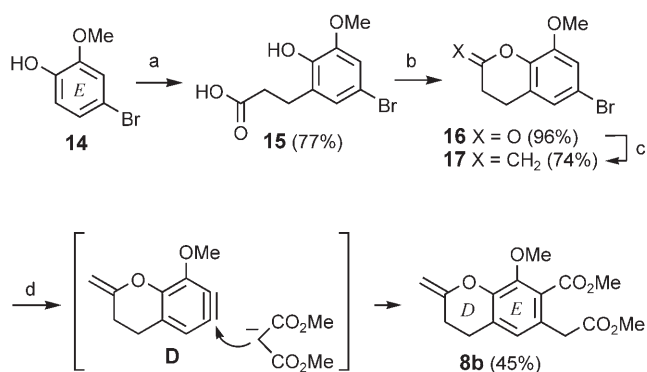
ketal **10a** into the linearly condensed ketal **6a** with a quinone structure at the B ring would complete the preparation of the core structure in a limited number of steps. However, attempts with various acids, such as sulfuric acid, trifluoromethanesulfonic acid, trifluoroacetic acid (TFA), and $\text{BF}_3 \cdot \text{Et}_2\text{O}$, resulted in no transformation. In contrast, when we tried to prepare the orthoquinone **13a** from the sulfoxide derivative **12a** by a second aromatic Pummerer-type reaction^[20] in the presence of trifluoromethanesulfonic anhydride (Tf_2O), we observed the unexpected direct formation of **6a** in 57% yield along with **13a** (27% yield). We investigated the reaction pathway in detail and found that the similar treatment of **12a** with trifluoroacetic anhydride (TFAA) gave **13a** in 82% yield as a single product. We also discovered that the subsequent treatment of **13a** with a strong acid, such as trifluoroacetic acid, afforded **6a** in 87% yield. Probably, the protonation of one carbonyl group in **13a** with the assistance of electron donation by the oxygen atom at the β position (to give intermediate **B**) promotes the cleavage of the ketal, and the oxonium intermediate **C** formed in this way undergoes recyclization to form **6a** (Scheme 2).^[22]

Having developed this successful protocol, we began the total synthesis of **2** with the attempted functionalization of the E ring to build up the F ring. Reported methods for the installation of the F ring include carbon–carbon bond formation of phthalaldehyde derivatives with malonates^[14] or Horner–Wadsworth–Emmons reagents,^[9,15] and the Heck reaction of an aryl iodide.^[16] However, our attempts to use these methods for the functionalization of 2-methylenechroman (**8a**) were unsuccessful, and we took a different approach based on the benzyne intermediate **D**. Thus, the commercially available bromophenol **14** was converted into the bromolactone **16** by using the method described by Panetta and Rapoport,^[23] and **16** was then treated with the Tebbe reagent^[17] to give the 2-methylenechroman **17**. The treatment of **17** with dimethyl malonate in the presence of lithium 2,2,6,6-tetramethylpiperidide afforded the highly functionalized bicyclic compound **8b** as a single regioisomer. This exclusive regioselectivity is probably a result of the strong inductive effect of the methoxy group (Scheme 3).^[24,25]

The functionalized AB-ring fragment **7b** was prepared from the known compound **18**^[26] and subjected to spiroketal formation with **8b** by the aromatic Pummerer-type reaction to give the pentacyclic ketal **9b**. The sulfoxide **10b** derived from **9b** by treatment with $i\text{Pr}_2\text{NH}$ and oxidation underwent a second aromatic Pummerer-type reaction in the presence of TFAA, and the resulting orthoquinone was converted into the

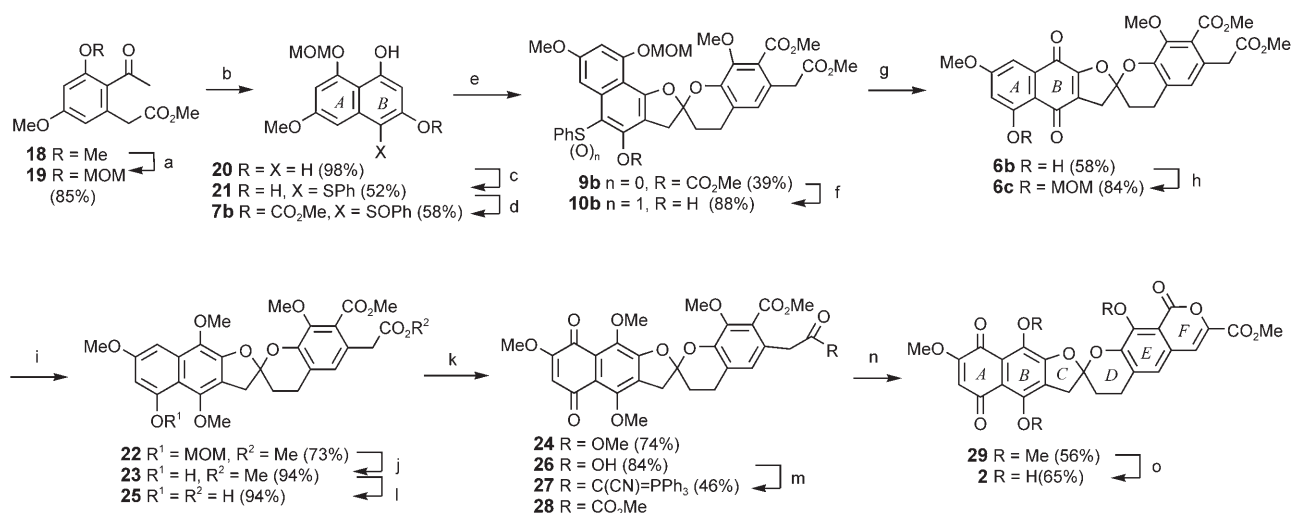


Scheme 2. Preparation of **6a** by two aromatic Pummerer-type reactions: a) 1) methyl trimethylsilyl dimethylketene acetal, MeCN, RT; 2) **8a**, Tf_2O , 2,4,6-collidine, MeCN, -40°C ; b) $i\text{PrNH}_2$, MeCN, RT; c) MCPBA, CH_2Cl_2 , $-78 \rightarrow -35^\circ\text{C}$; d) Tf_2O , CH_2Cl_2 , 0°C ; e) TFAA, CH_2Cl_2 , 0°C ; f) TFA, CH_2Cl_2 , 0°C . MCPBA = *m*-chloroperbenzoic acid.



Scheme 3. Preparation of the DE-ring moiety **8b**: a) 1) triethyl orthoacrylate, $t\text{BuCO}_2\text{H}$, toluene, reflux; 2) HCl (1 N), Et_2O , RT; 3) 10% KOH, MeOH, RT; b) Ac_2O , reflux; c) Tebbe reagent, THF, $-78 \rightarrow -40^\circ\text{C}$; d) lithium 2,2,6,6-tetramethylpiperidide, dimethyl malonate, THF, -78°C .

linearly condensed paraquinone **6b** with concomitant removal of the MOM group. After reprotection of the phenol with a MOM group, the quinone **6c** was converted into the corresponding dihydroquinone dimethyl ether **22**,



Scheme 4. Completion of the total synthesis of **2**: a) 1) BCl₃, CH₂Cl₂, 0°C; 2) MOMCl, *i*Pr₂NEt, CH₂Cl₂, 0°C; b) NaOMe, MeOH, reflux; c) 1) PhICl₂, Pb(SCN)₂, CH₂Cl₂, RT; 2) PhLi, THF, −78°C; d) 1) ClCO₂Me, *i*Pr₂NEt, CH₂Cl₂, 0°C; 2) MCPBA, CH₂Cl₂, −78 → −5°C; e) 1) methyl trimethylsilyl dimethylketene acetal, MeCN, RT; 2) **8b**, Tf₂O, 2,4,6-collidine, MeCN, −78°C; f) 1) *i*Pr₂NH, MeCN, RT; 2) MCPBA, CH₂Cl₂, −78 → −20°C; g) 1) TFAA, CH₂Cl₂, 0°C; 2) TFA, CH₂Cl₂, 0°C; h) MOMCl, *i*Pr₂NEt, CH₂Cl₂, 0°C; i) Na₂S₂O₄, Me₂SO₄, K₂CO₃, acetone, reflux; j) TFA, CH₂Cl₂, 0°C; k) [Co(salen)₂], O₂, DMF, RT; l) 10% KOH, MeOH, RT; m) (triphenylphosphoranylidene)acetonitrile, EDCI, DMAP, CH₂Cl₂, RT; n) dimethyldioxirane, MeOH, 0°C; o) BBr₃, CH₂Cl₂, −78 → 0°C. DMAP = 4-(dimethylamino)pyridine, DMF = *N,N*-dimethylformamide, EDCI = *N*-ethyl-*N'*-(3-(dimethylamino)propyl)carbodiimide hydrochloride, MOM = methoxymethyl.

and the MOM group was removed to give **23**. The [Co(salen)₂]-catalyzed oxidation^[13a] of the A ring of **23** gave the quinone **24**; however, subsequent hydrolysis of the ester group of the α -arylaceto moiety caused decomposition. When the hydrolysis step (**23** → **25**) was carried out prior to the oxidation, **26** was obtained in 79% overall yield. The method of Wong et al.^[27] was used to transform the carboxylic acid moiety into the α -keto ester **28**. Thus, the condensation of **26** with (triphenylphosphoranylidene)acetonitrile gave **27**, which was oxidized by dimethyldioxirane. The intermediate **28** underwent immediate cyclization to produce the lactone **29**. Final deprotection by BBr₃ delivered **2**, which was identical to authentic natural γ -rubromycin by direct comparison (¹H NMR, IR, TLC; Scheme 4).

In conclusion, we have completed the total synthesis of racemic **2** by the successful application of two kinds of aromatic Pummerer-type reactions of sulfinyl naphthol derivatives. The first enabled the novel one-step construction of the bisbenzannelated spiroketal unit, and the second involved the unique rearrangement of a “bent” pentacyclic ketal to a linearly fused pentacyclic ketal with the concurrent formation of the B-ring paraquinone. This methodology offers convenient access to a wide range of substituted bisbenzannelated spiroketals from naphthol derivatives **7** and 2-methylenechroman derivatives **8** and has potential for use in the development of new drugs derived from natural products that contain bisbenzannelated spiroketal structures.

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- [1] a) H. Brockmann, W. Lenk, G. Schwantje, A. Zeeck, *Chem. Ber.* **1969**, *102*, 126–151; b) H. Brockmann, A. Zeeck, *Chem. Ber.* **1970**, *103*, 1709–1726.
- [2] M. E. Goldman, G. S. Salituro, J. A. Bowen, J. M. Williamson, D. L. Zink, W. A. Schleif, E. A. Emini, *Mol. Pharmacol.* **1990**, *38*, 20–25.
- [3] T. Ueno, H. Takahashi, M. Oda, M. Mizunuma, A. Yokoyama, Y. Goto, Y. Mizushima, K. Sakaguchi, H. Hayashi, *Biochemistry* **2000**, *39*, 5995–6002.
- [4] a) M. Chino, K. Nishikawa, M. Umekita, C. Hayashi, T. Yamazaki, T. Tsuchida, T. Sawa, M. Hamada, T. Takeuchi, *J. Antibiot.* **1996**, *49*, 752–757; b) M. Chino, K. Nishikawa, T. Tsuchida, R. Sawa, H. Nakamura, K. T. Nakamura, Y. Muraoka, D. Ikeda, H. Naganawa, T. Sawa, T. Takeuchi, *J. Antibiot.* **1997**, *50*, 143–146.
- [5] M. Chino, K. Nishikawa, A. Yamada, M. Ohsono, T. Sawa, F. Hanaoka, M. Ishizuka, T. Takeuchi, *J. Antibiot.* **1998**, *51*, 480–486.
- [6] a) C. Coronelli, H. Pagani, M. R. Bardone, G. C. Lancini, *J. Antibiot.* **1974**, *27*, 161–168; b) M. R. Bardone, E. Martinelli, L. F. Zerilli, C. Coronelli, *Tetrahedron* **1974**, *30*, 2747–2754.
- [7] A. Trani, C. Dallanocce, G. Panzone, F. Ripamonti, B. P. Goldstein, R. Ciabatti, *J. Med. Chem.* **1997**, *40*, 967–971.
- [8] For a review on the rubromycins, see: M. Brasholz, S. Sörgel, C. Azap, H.-U. Reißig, *Eur. J. Org. Chem.* **2007**, 3801–3814.
- [9] a) D. Qin, R. X. Ren, T. Siu, C. Zheng, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4845–4849; *Angew. Chem. Int. Ed.* **2001**, *40*, 4709–4713; b) T. Siu, D. Qin, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4849–4852; *Angew. Chem. Int. Ed.* **2001**, *40*, 4713–4716.
- [10] a) T. Capecchi, C. B. de Koning, J. P. Michael, *Tetrahedron Lett.* **1998**, *39*, 5429–5432; b) T. Capecchi, C. B. de Koning, J. P. Michael, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2681–2688; c) S. Sörgel, C. Azap, H.-U. Reißig, *Org. Lett.* **2006**, *8*, 4875–4878.
- [11] K. Y. Tsang, M. A. Brimble, J. B. Bremner, *Org. Lett.* **2003**, *5*, 4425–4427.

- [12] a) S. P. Waters, M. W. Fennie, M. C. Kozlowski, *Tetrahedron Lett.* **2006**, 47, 5409–5413; b) S. P. Waters, M. W. Fennie, M. C. Kozlowski, *Org. Lett.* **2006**, 8, 3243–3246.
- [13] a) C. C. Lindsey, K. L. Wu, T. R. R. Pettus, *Org. Lett.* **2006**, 8, 2365–2367; b) for a related synthesis of bisbenzannelated 6,6-spiroketal, see: G. Zhou, D. Zheng, S. Da, Z. Xie, Y. Li, *Tetrahedron Lett.* **2006**, 47, 3349–3352.
- [14] T. P. Thrash, T. D. Welton, V. Behar, *Tetrahedron Lett.* **2000**, 41, 29–31.
- [15] a) M. Brasholz, X. Luan, H.-U. Reissig, *Synthesis* **2005**, 3571–3580; b) M. Brasholz, H.-U. Reissig, *Synlett* **2004**, 2736–2738.
- [16] S. P. Waters, M. C. Kozlowski, *Tetrahedron Lett.* **2001**, 42, 3567–3570.
- [17] The 2-methylenechromans **8** were prepared readily by the methylenation of the corresponding lactones with the Tebbe reagent; for related examples, see: S. H. Pine, R. J. Pettit, G. D. Geib, S. G. Cruz, C. H. Gallego, T. Tijerina, R. D. Pine, *J. Org. Chem.* **1985**, 50, 1212–1216.
- [18] a) S. Akai, T. Takeda, K. Iio, Y. Yoshida, Y. Kita, *J. Chem. Soc. Chem. Commun.* **1995**, 1013–1014; b) S. Akai, Y. Takeda, K. Iio, K. Takahashi, N. Fukuda, Y. Kita, *J. Org. Chem.* **1997**, 62, 5526–5536; for recent reviews on aromatic Pummerer-type reactions, see: c) K. S. Feldman, *Tetrahedron* **2006**, 62, 5003–5034; d) S. Akai, Y. Kita, *Top. Curr. Chem.* **2007**, 274, 35–76.
- [19] Owing to its poor solubility in acetonitrile, **7a** was converted in situ into a silyl ether by using methyl trimethylsilyl dimethylketene acetal: Y. Kita, J. Haruta, J. Segawa, Y. Tamura, *Tetrahedron Lett.* **1979**, 20, 4311–4314. The subsequent aromatic Pummerer-type reaction proceeded via the paraquinone sulfonium intermediate **A**,^[20] the regioselective nucleophilic addition^[21] of **8a** to which led to the formation of the spiroketal **9a**.
- [20] For paraquinone formation from parasulfinylphenols via paraquinonesulfonium intermediates, such as **A**, generated by an aromatic Pummerer-type reaction, see: Y. Kita, Y. Takeda, M. Matsugi, K. Iio, K. Gotanda, K. Murata, S. Akai, *Angew. Chem.* **1997**, 109, 1525–1527; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1529–1531; see also ref. [18].
- [21] For related nucleophilic carbon–carbon bond-forming reactions with paraquinonesulfonium intermediates, such as **A**, see: a) S. Akai, N. Morita, K. Iio, Y. Nakamura, Y. Kita, *Org. Lett.* **2000**, 2, 2279–2282; for related studies, see: b) M. Matsugi, K. Murata, K. Gotanda, H. Nambu, G. Anilkumar, K. Matsumoto, Y. Kita, *J. Org. Chem.* **2001**, 66, 2434–2441; c) S. Akai, N. Kawashita, N. Morita, Y. Nakamura, K. Iio, Y. Kita, *Heterocycles* **2002**, 58, 75–78; d) S. Akai, N. Kawashita, H. Satoh, Y. Wada, K. Kakiguchi, I. Kuriwaki, Y. Kita, *Org. Lett.* **2004**, 6, 3793–3796; e) S. Akai, N. Kawashita, Y. Wada, H. Satoh, A. H. Alinejad, K. Kakiguchi, I. Kuriwaki, Y. Kita, *Tetrahedron Lett.* **2006**, 47, 1881–1884.
- [22] For a related rearrangement of β -lapachone to α -lapachone, see: R. H. Thomson in *Naturally Occurring Quinones*, Butterworths, London, **1957**.
- [23] J. A. Panetta, H. Rapoport, *J. Org. Chem.* **1982**, 47, 946–950.
- [24] For a recent review on benzyne chemistry, see: H. Pellissier, M. Santelli, *Tetrahedron* **2003**, 59, 701–730.
- [25] For examples of the nucleophilic addition of malonates to benzyne, see: Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, K. Ueda, S. Akai, H. Fujioka, *J. Am. Chem. Soc.* **2001**, 123, 3214–3222.
- [26] M. W. B. McCulloch, R. A. Barrow, *Tetrahedron Lett.* **2005**, 46, 7619–7621.
- [27] M.-K. Wong, C.-W. Yu, W.-H. Yuen, D. Yang, *J. Org. Chem.* **2001**, 66, 3606–3609.