Natural Products Synthesis

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

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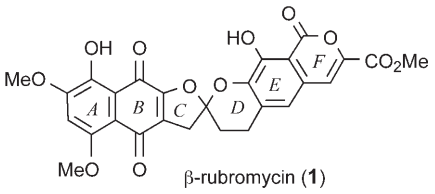
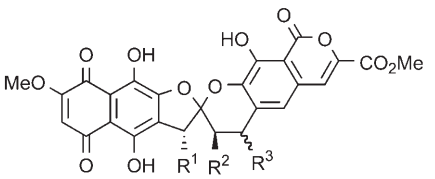
The antibiotics β-rubromycin (**1**) and γ-rubromycin (**2**)[1] contain a highly oxygenated naphthoquinone moiety (A,B rings) and an 8-hydroxyisocoumarin moiety (E,F rings) linked through a 5,6-spiroketal (C,D rings). They exhibit activity against the reverse transcriptase of human immunodeficiency 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]

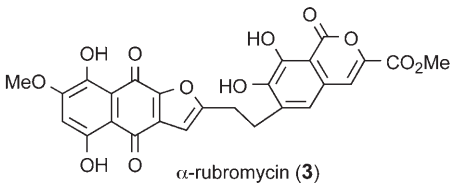
Much effort has been devoted to the synthesis of these compounds,[8–16] and special attention has been focused on the preparation of the vital bisbenzannelated spiroketal core structure **I**.[8–13] The reported methods are based on the acid-catalyzed spiroketalization of ketones[10–12] or a hemiketal,[9b] 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 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 (±)-γ-rubromycin (**2**).



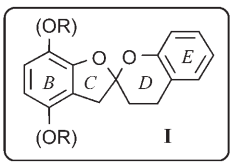
β-rubromycin (**1**)



γ-rubromycin (**2**): $R^1 = R^2 = R^3 = H$
heliquinomycin (**4**): R^1 = *O*-cymarose, R^2 = OH, R^3 = H
purpuromycin (**5**): $R^1 = R^2$ = H, R^3 = OH



α-rubromycin (**3**)



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

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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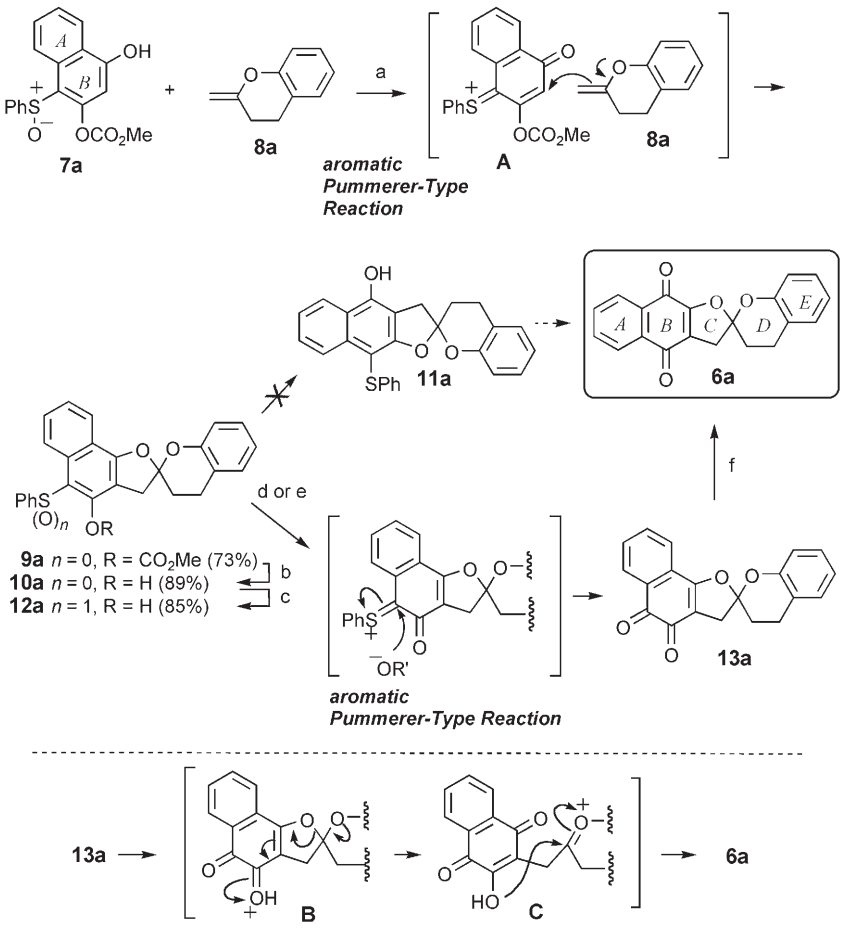
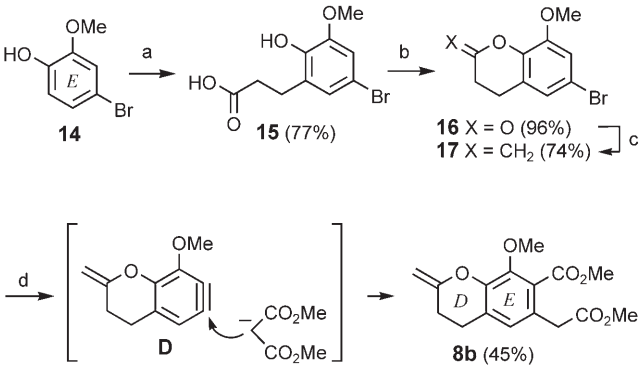
ketal **10a** into the linearly condensed ketal **6a** with a quinone structure at the B ring would complete the preparation of the core structure in a limited number of steps. However, attempts with various acids, such as sulfuric acid, trifluoromethanesulfonic acid, trifluoroacetic acid (TFA), and $BF_3.Et_2O$, 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]



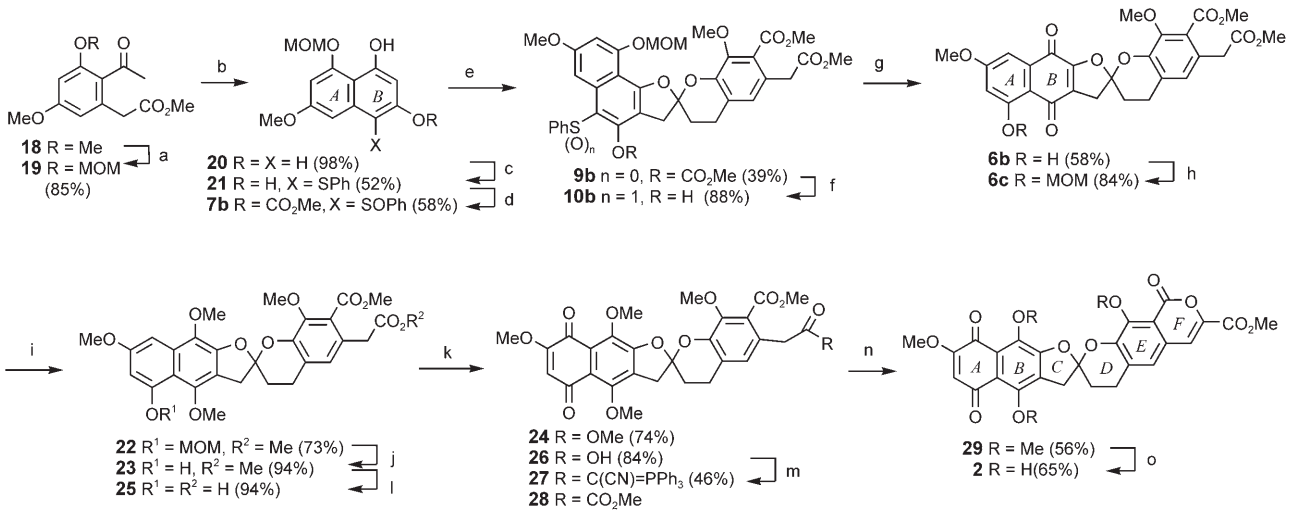
Scheme 2. Preparation of **6a** by two aromatic Pummerer-type reactions: a) 1) methyl trimethylsilyl dimethylketene acetal, MeCN, RT; 2) **8a**, Tf_2O, 2,4,6-collidine, MeCN, −40°C; b) *i*PrNH$_2$, MeCN, RT; c) MCPBA, CH_2Cl_2, −78→−35°C; d) Tf_2O, CH_2Cl_2, 0°C; e) TFAA, CH_2Cl_2, 0°C; f) TFA, CH_2Cl_2,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

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]



Scheme 3. Preparation of the DE-ring moiety **8b**: a) 1) triethyl orthoacrylate, *t*BuCO$_2$H, toluene, reflux; 2) HCl (1 N), Et$_2$O, RT; 3) 10% KOH, MeOH, RT; b) Ac$_2$O, reflux; c) Tebbe reagent, THF, −78→−40°C; d) lithium 2,2,6,6-tetramethylpiperidide, dimethyl malonate, THF, −78°C.

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*Pr$_2$NH and oxidation underwent a second aromatic Pummerer-type reaction in the presence of TFAA, and the resulting orthoquinone was converted into the 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) BCl_3, CH_2Cl_2, 0 °C; 2) MOMCl, iPr_2NEt, CH_2Cl_2, 0 °C; b) NaOMe, MeOH, reflux; c) 1) $PhICl_2$, $Pb(SCN)_2$, CH_2Cl_2, RT; 2) PhLi, THF, −78 °C; d) 1) $ClCO_2Me$, iPr_2NEt, CH_2Cl_2, 0 °C; 2) MCPBA, CH_2Cl_2, −78→−5 °C; e) 1) methyl trimethylsilyl dimethylketene acetal, MeCN, RT; 2) **8b**, Tf_2O, 2,4,6-collidine, MeCN, −78 °C; f) 1) iPr_2NH, MeCN, RT; 2) MCPBA, CH_2Cl_2, −78→−20 °C; g) 1) TFAA, CH_2Cl_2, 0 °C; 2) TFA, CH_2Cl_2, 0 °C; h) MOMCl, iPr_2NEt, CH_2Cl_2, 0 °C; i) $Na_2S_2O_4$, Me_2SO_4, K_2CO_3, acetone, reflux; j) TFA, CH_2Cl_2, 0 °C; k) [Co(salen)$_2$], O_2, DMF, RT; l) 10% KOH, MeOH, RT; m) (triphenylphosphoranylidene)acetonitrile, EDCI, DMAP, CH_2Cl_2, RT; n) dimethyldioxirane, MeOH, 0 °C; o) BBr_3, CH_2Cl_2, −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-arylacetate 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 BBr_3 delivered **2**, which was identical to authentic natural γ-rubromycin by direct comparison (^{1}H 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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