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Synthesis of Electron Deficient 5,6-Aryloxy Spiroketals

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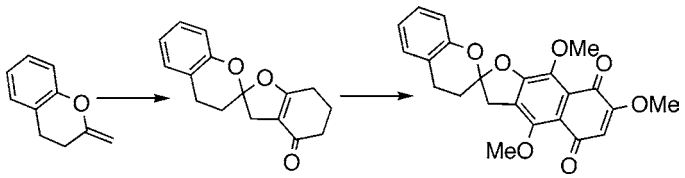
ABSTRACT



A strategy for the construction of electron deficient 5,6-aryloxy spiroketal is reported. The process should prove useful for the synthesis of natural products containing similar spiroketals. The strategy uncovers an unexpected rearrangement between ortho and para quinone spiroketals.

The rubromycin family encompasses three compounds. All were isolated from cultures of Streptomyces and found to inhibit Gram-positive bacteria (Figure 1).[1] All are composed of a naphthoquinone and an iso-coumarin linked through a four carbon atom segment. In the rubromycins designated as β and γ, the hydroxylated aromatic components combine to form a rather unusual optically active 5,6-spiroketal. This structural feature accounts for the human telomerase inhibitory activity of these and related 5,6-aryloxy spiroketal natural products. The original structural assignment for β-rubromycin proposed an *o*-quinone contained within its constitution (cf. **1**). However, this structure was eventually dismissed in favor of the *p*-quinone (cf. **2**).[2] Among the stronger pieces of evidence for structural reassignment was that β-rubromycin proceeds to γ-rubromycin without loss of its optical activity upon treatment with aqueous acid—if the *o*-quinone **1** precedes the *p*-quinone **3**, and the transformation proceeds through an achiral oxonium intermediate, then *rac*-**3** should have formed.

It is easy to imagine generation of an oxonium by protonation of the furan **4** followed by cyclization of the phenol belonging to the iso-coumarin as giving β-rubromycin (**2**) and subsequent hydrolysis of a vinylogous methyl ester in β-rubromycin (**2**) with loss of methanol as leading to γ-rubromycin (**3**). This presumed pathway from α- to β- to

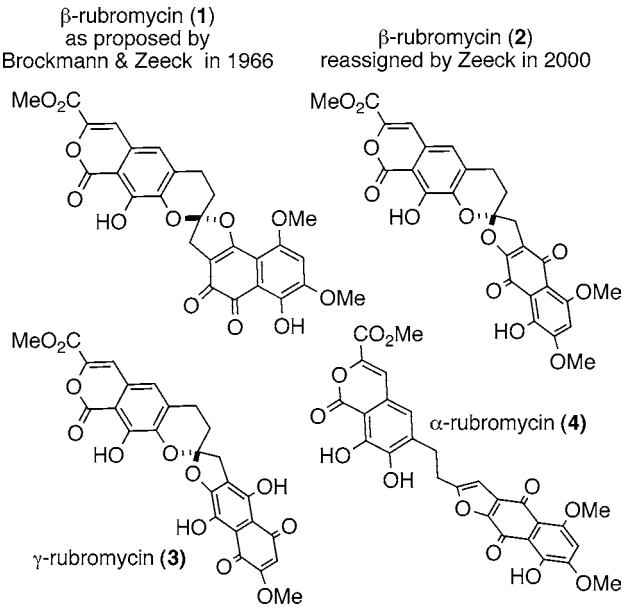


Figure 1. The rubromycin family of natural products.

(1) (a) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Tetrahedron Lett.* **1966**, 3525−3530. (b) Brockmann, H.; Lenk, W.; Schwantje, G.; Zeeck, A. *Chem. Ber.* **1969**, *102*, 126−151. (c) Brockmann, H.; Zeeck, A. *Chem. Ber.* **1970**, *103*, 1709−1726.

(2) Puder, C.; Loya, S.; Hizi, A.; Zeeck, A. *Eur. J. Org. Chem.* **2000**, 729−735.

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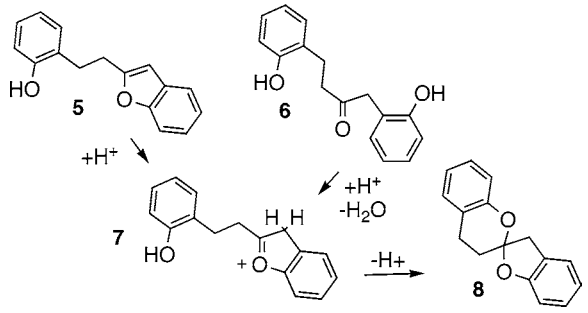
γ-rubromycin (**4** to **2** to **3**) appears to be the foundation for most synthetic approaches. However, given the numerous syntheses of the iso-coumarin[3] and naphthoquinone[4] portions of the family, and the 5,6-aryloxy spiroketalization model studies with simple phenol analogues,[5] we find the absence of a total synthesis of a natural product belonging to the family to be quite conspicuous.[6] Perhaps a conventional thermodynamic spiroketalization (Scheme 1) may be a flawed strategy for constructing spiroketals containing an electron deficient iso-coumarin.[7] Kozlowski and Waters' efforts aimed at constructing purpuromycin derivatives support this conclusion.[8] Furthermore, the fact that β- and γ-rubromycin are themselves optically active argues against a thermodynamic spiroketalization; optical activity cannot be retained or induced during such an event. Thus, the biosynthetic origins of the rubromycins remain unclear and pose an interesting unsolved and enticing problem for organic chemists.

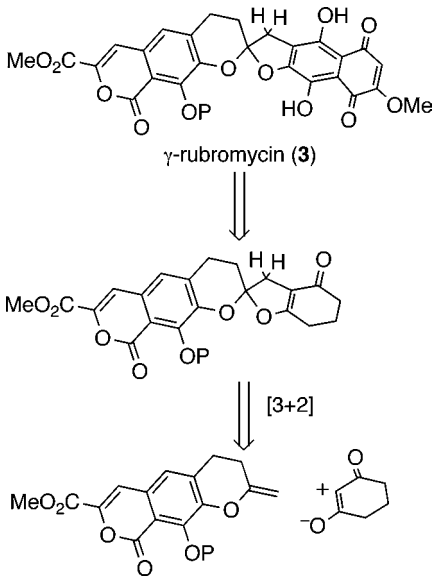
Scheme 1. Thermodynamic Ketalization[a]



[a] Classical thermodynamic ketalization, while successful with simpler analogues, is unsuitable for the assembly of electron deficient nonracemic spiroketals. The transformation is not amenable to enantiocontrol and the oxonium **7** is subject to elimination.

We chose to employ a [3+2] cycloaddition between an enol ether and a zwitterion to form the spiroketal in a single step and thereby provide a scaffold, which can be further transformed into the electron deficient naphthoquinone found in **3** (Scheme 2). This strategy seemed amenable to enantiocontrol and could avoid the elimination that has presumably stalled other efforts.

Scheme 2. Strategy Envisioned To Avoid Furan Formation



To test this strategy, Petasis's methylenation conditions are applied to dihydrocoumarin (Scheme 3). The reaction affords the known enol ether **9** in 80% yield.[9] Next, the enol ether **9**, the β-diketone **10**, and cerium ammonium nitrate are combined with use of Roy's conditions. A smooth [3+2] cycloaddition ensues at 0 °C and affords the 5,6-spiroketal **11** in 56% yield.[10] Aromatization of this material with DDQ provides the phenol **12** in 64% yield.

Oxidation of the phenol **12** (0.063 M in DMF) with IBX (1.02 equiv) affords the unstable *o*-quinone **13**, which slowly converts into the more stable *p*-quinone **14**.[11] Immediate treatment of the crude mixture (0.063 M in DMF) with $BnNEt_3Cl$ (4.8 equiv) and TMSCl (10 equiv) affords the chloride ion that participates in a 1,4-conjugate addition.[12] Upon workup, the hydroquinone **15** and the catechol **16** are isolated separately in a combined 54% yield and 1.0:2.3 ratio. Alternatively, exposure of the purified quinone **14** to similar conditions affords the hydroquinone **15** and the catechol **16** in a combined 60% yield and 2.0:1.0 ratio.

Oxidation of either regioisomer (**15** or **16**) with DDQ affords the *p*-quinone **18**. These results clearly suggest an equilibrium between the *p*-quinones **18** and **14** and their respective *o*-quinone counterparts **17** and **13**.

The mixed ketene acetal **19**[13] (3.2 equiv) combines with the chloroquinone **18** (0.1 M in CH_2Cl_2) in a regioselective [4+2] cycloaddition to produce the naphthoquinone **20** in a 53% isolated yield. The free phenol (0.1 M in THF) is protected with NaH (1.3 equiv) and MOMCl (2.0 equiv) providing the aryl ether **21** in 80% yield. Reduction of the

(3) (a) Thrash, T. P.; Welton, T. D.; Behar, V. *Tetrahedron Lett.* **2000**, *41*, 29−31. (b) Waters, S. P.; Kozlowski, M. C. *Tetrahedron Lett.* **2001**, *42*, 3567−3570. (c) Brasholtz, M.; Reissig, H.-U. *Synlett* **2004**, *15*, 2736−2738.

(4) (a) Stevens, J. L.; Welton, T. D.; Deville, J. P.; Behar, V. *Tetrahedron Lett.* **2003**, *44*, 8901−8903. (b) Xie, X.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 2661−2663.

(5) (a) Capecchi, T.; de Koning, C. B.; Michael, J. P. *Tetrahedron Lett.* **1998**, *39*, 5429−5432. (b) Capecchi, T.; de Koning, C. B.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2681−2688. (c) Tsang, K. Y.; Brimble, M. A.; Bremner, J. B. *Org. Lett.* **2003**, *5*, 4425−4427.

(6) The strategy, which delivered the aglycon of heliquinomycin [Siu, T.; Qin, D. H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4713], employs a naphthafuran-3-one nucleus in the spiroketalization. Without the carbonyl, this related system undergoes elimination to the naphthafuran and therefore this strategy is not well suited for the rubromycins that exist in a lower oxidation state.

(7) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227−256.

(8) Waters, S. P. Ph.D. Thesis, University of Pennsylvania, Philidelphia, PA, 2004.

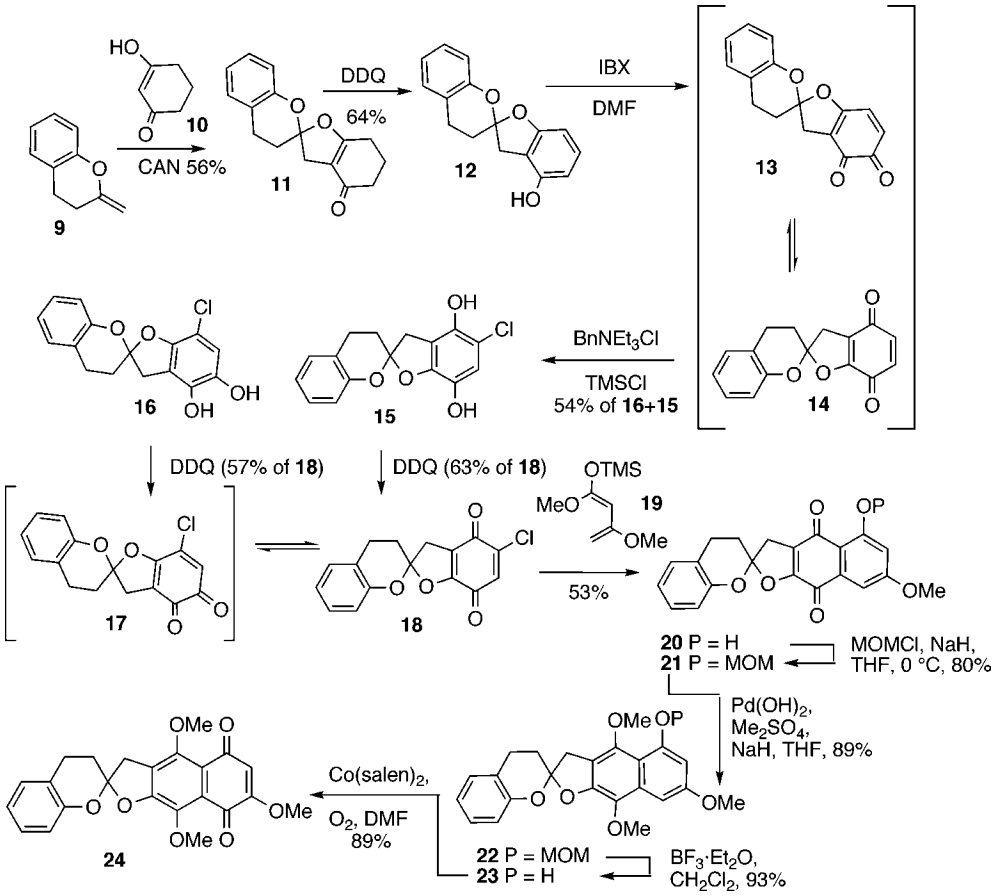
(9) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394

(10) Roy, S. C.; Mandal, P. K. *Tetrahedron* **1996**, *52*, 12495−12498.

(11) (a) Huang, Y. D.; Zhang, J. S.; Pettus, T. R. R. *Org. Lett.* **2005**, *7*, 5841−5844. (b) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285−288.

(12) Miller, L. L.; Stewart, R. F. *J. Org. Chem.* **1978**, *43*, 3078−3079.

Scheme 3. A Rearrangement Uncovered



quinone **21** (0.1 M in THF) with Pearlman's catalyst (0.2 equiv) and a hydrogen balloon gives the corresponding hydroquinone. This intermediate is protected *in situ* (4.0 equiv of Me_2SO_4 and NaH) yielding the methylated naphthazarin **22** in 89% yield. Cleavage of the MOM ether (0.01 M in CH_2Cl_2) with $BF_3{\cdot}Et_2O$ (1.5 equiv) affords the phenol **23** in 93% yield. Oxidation with $Co(salen)_2$ and oxygen completes the model study and provides the fully elaborated naphthoquinone **24** in an 89% yield.

The facile quinone rearrangement suggests that β-rubromycin (**1**) as originally proposed may convert into the more recently assigned structure **2**. This rearrangement, and the ease with which it occurs, may have implications regarding the origins of the optical activity in rubromycins, griseorhodins, purpuromycin, and heliquinomycin and the design of future synthetic strategies. We speculate that *rac*-β rubromycin (**1**) may be a biosynthetic progenitor of the nonracemic compounds **2**−**4.** Our next goal will be to determine the fate of optical activity in this rearrangement.[14]

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Supporting Information Available: Experimental procedures and key spectral data for all new isolable compounds **9**−**12**, **14**−**16**, and **20**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0606886

(13) Donner, D. C.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 938−948.

(14) While the rearrangement reported herein seems to resemble the conversion of β-lapachone into α-lapachone, the latter rearrangement requires elevated temeperature and harsh contions and results in a loss of optical activity. Bock, K.; Jacobsen, N.; Terem, B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 659−664.