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Use of a Sonogashira–Acetylide Coupling Strategy for the Synthesis of the Aromatic Spiroketal Skeleton of γ-Rubromycin

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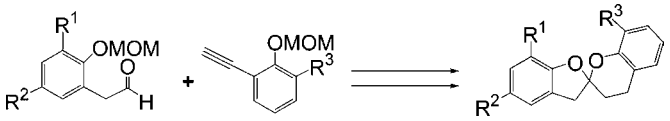
ABSTRACT



The synthesis of the fused aromatic spiroketal core of γ-rubromycin is described via addition of an aryl acetylide fragment to an aryl acetaldehyde fragment. In turn, the aryl acetylene precursor was readily prepared with use of a Sonogashira reaction.

While spiroketal ring systems are present as subunits in a diverse range of bioactive natural products, thereby attracting considerable attention[1] from synthetic chemists, the presence of spiroketals in which the oxygen atoms are derived from two aromatic hydroxy groups is less common. The rubromycins **1**−**3** (Figure 1) are a class of antibiotics isolated from cultures of *Streptomyces*[2] that exhibit activity against Gram-positive bacteria. β-Rubromycin **2** and γ-rubromycin **3** exhibit potent inhibition of human telomerase,[3] with IC_{50} values of 3 μM, and are active against the reverse transcriptase of human immunodeficiency virus-1.[4] These compounds possess a unique aromatic spiroketal ring system in which benzannelated furan and pyran rings share one carbon atom to form a spiroketal system. The fact that α-rubromycin **1**, which lacks this aryl spiroketal moiety, exhibits substantially decreased inhibitory potency toward telomerase (IC_{50} > 200 μM), suggests that this spiroketal system plays an essential role in the observed inhibition of telomerase. Structurally related to the rubromycins are purpuromycin **4**,[5] a potential topical agent for vaginal infections,[6] heliquino-

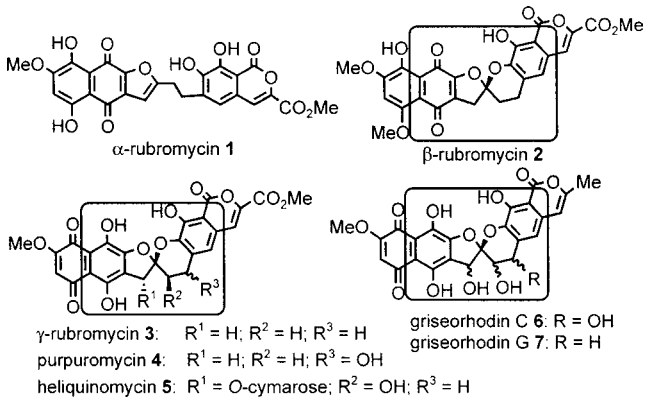


Figure 1.

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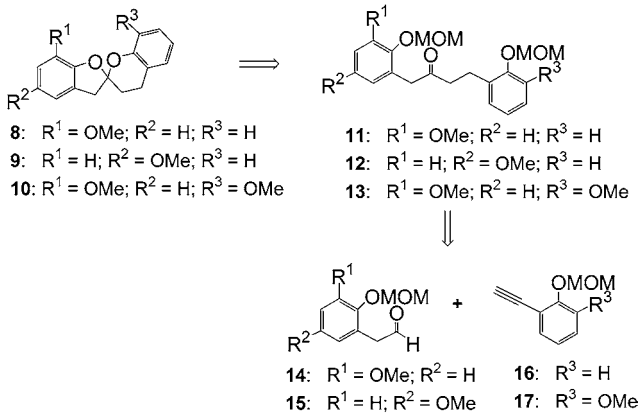
mycin **5**,[7] an inhibitor of DNA helicase, and griseorhodins C **6**[8] and G **7**. All of these compounds can act as bioreductive alkylating agents as postulated by Moore.[9]

To date the only synthesis of a naturally occurring bisbenzannelated spiroketal is the elegant total synthesis of heliquinomycin **5** reported by Danishefsky et al.[10] In this case the key aromatic 1,6-dioxaspiro[4.5]decane ring system was assembled via electrophilic spiroketalization of a naphthofuran bearing a phenolic hydroxyl group as the nucleophilic partner. This particular strategy was complicated by the limited choice of a suitable electrophile that was compatible with the highly electron-rich naphthalene ring. The only other synthesis of a bisbenzannelated spiroketal as present in γ-rubromycin **3** was reported by de Koning et al.[11] in which a Henry reaction was used to couple two aryl moieties followed by use of a Nef reaction to liberate the masked carbonyl group that induces the spiroketalization step. In this case the Henry condensation and the Nef-type reaction proceeded in moderate yield. We therefore herein report the synthesis of several bisbenzannelated spiroketal analogues of the naturally occurring antibiotic γ-rubromycin **3** (and related compounds) thereby adding to the synthetic armory for construction of this important structural unit such that its effect on the inhibition of human telomerase can be probed.

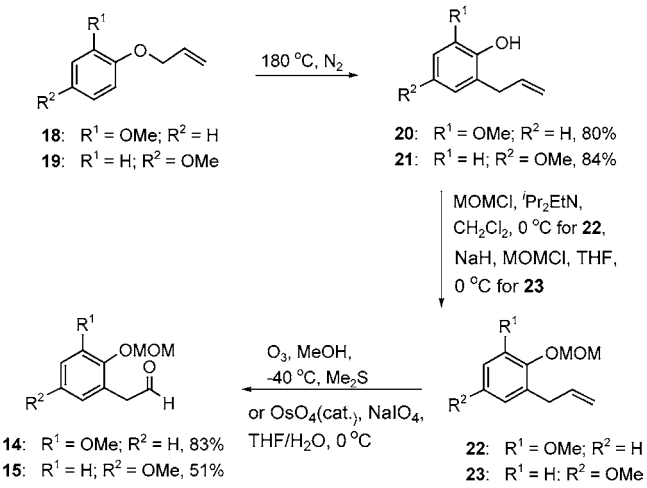
As part of our synthetic program directed toward the synthesis of bioactive spiroketal-containing natural products we investigated the assembly of the tetracyclic aryl spiroketals **8**−**10** via disconnection to the methoxymethyl-protected diphenolic ketones **11**−**13** (Scheme 1).

Scheme 1

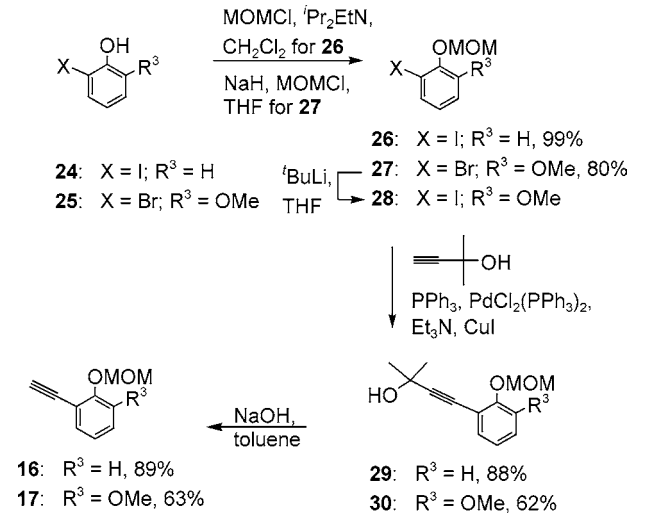


The strategy for assembly of these spiroketal precursors **11**−**13** focused on the addition of the aryl acetaldehydes **14** and **15** (Scheme 2) to the acetylides derived from acetylenes **16** and **17**. The versatility of this approach was further realized by the facile preparation of acetylenes **16** and **17** via Sonogashira reaction[12] with an appropriate readily available aromatic halide (Scheme 3).

Scheme 2



Scheme 3



The aryl acetaldehydes **14**[11] and **15** were readily prepared from allyl ethers **18** and **19** (Scheme 2) via Claisen

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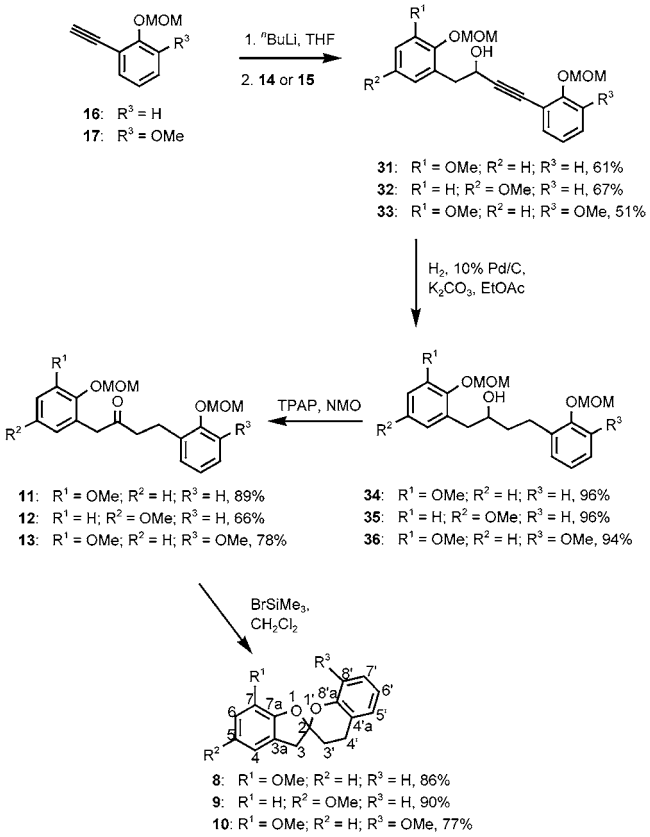
rearrangement to phenols **20** and **21**, protected as methoxymethyl ethers **22** and **23**, followed by either ozonolysis or oxidative cleavage to aldehydes **14** or **15**, respectively. Sodium periodate cleavage of a diol was required in the latter case to avoid the undesired formation of quinone byproducts that were observed when ozonolysis was used.

The acetylenes **16** and **17** were prepared (Scheme 3) by Sonogashira coupling[12] of methoxymethyl-protected aryl iodides **26** (prepared from iodophenol **24**) and **28** (prepared from bromophenol **25**[13] via **27**[13]) with 2-methyl-3-butyn-2-ol followed by elimination of acetone from the resulting acetylenes **29** and **30** upon heating with sodium hydroxide in toluene. This two-step procedure provided a convenient preparation of the desired acetylenes **16** and **17**.

With the aryl acetaldehydes **14**,**15** and acetylenes **16**,**17** in hand, attention was directed to their union and subsequent elaboration to the desired benzannelated spiroketals **8**−**10** (Scheme 4). Treatment of acetylenes **16** or **17** with *n*-butyllithium (1.1 equiv) in THF at −78 °C for 30 min followed by addition of the appropriate aldehyde **14** or **15** afforded the acetylenic alcohols **31**−**33** in moderate yield. Oxidation of the propargylic alcohol proved problematic hence the acetylenes were subjected to hydrogenation over palladium on charcoal affording the saturated alcohols **34**−**36** in high yield. Subsequent oxidation with tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide then proceeded uneventfully, providing the desired spiroketal precursors **11**−**13**. The final deprotection and spirocyclization step necessitated considerable experimentation with our efforts leading to the use of bromotrimethylsilane as the optimum reagent to effect deprotection of the methoxymethyl ether groups and concomitant spirocyclization. Compatibility of the reagent with the sensitivity of the bisbenzannelated aryl spiroketals **8**−**10** thus formed was a key issue in the present work.

In summary, an efficient method for the construction of the benzannelated spiroketal core of β-rubromycin **2**, γ-rubromycin **3**, and related antibiotics has been developed. The methodology combines the use of a Sonogashira reaction to prepare an aryl acetylene fragment from, which the derived acetylide readily adds to an aryl acetaldehyde fragment. Subsequent oxidation and deprotection of the phenolic groups under acidic conditions leads to formation of the aryl spiroketal. The methodology provides ready access to a range of benzannelated spiroketals to evaluate their inhibitory activity against human telomerase.

Scheme 4



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Supporting Information Available: Experimental procedures and MS andNMR data for compounds **8** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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