



Synthesis of 6,6-bisbenzannulated spiroketals related to the rubromycins using a double intramolecular hetero-Michael addition (DIHMA)

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ABSTRACT

The synthesis of a series of 6,6-bisbenzannulated spiroketals using a novel microwave-assisted DIHMA approach is reported. Coupling of an aryl acetylene and an aryl aldehyde via acetylide anion addition resulted in the formation of an alkynol which was followed by oxidation to the desired ynone. Spirocyclization using the DIHMA protocol afforded the desired bisbenzannulated spiroketal in good yield.

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Spiroketal is an important subunit present in a broad range of bioactive natural products and are considered a 'privileged scaffold' for drug discovery programs.¹ The rubromycin family of natural products (Fig. 1) are benzannulated spiroketals that have attracted considerable attention. γ -Rubromycin **1** and β -rubromycin **2** exhibit potent inhibition of human telomerase² (IC_{50} $2.64 \pm 0.09 \mu M$ and $3.06 \pm 0.85 \mu M$) and are active against the

reverse transcriptase of human immunodeficiency virus-1.³ Purpuromycin **4** is a potential topical agent for vaginal infections,⁵ whereas heliquinomycin **7** with a rare L-cymarose sugar attached to the 3'-hydroxy functionality is a selective inhibitor of human DNA helicase. The rubromycin family of antibiotics have also been proposed to act as bioreductive alkylating agents.⁷ The unique aromatic spiroketal core present in this class of compounds has been

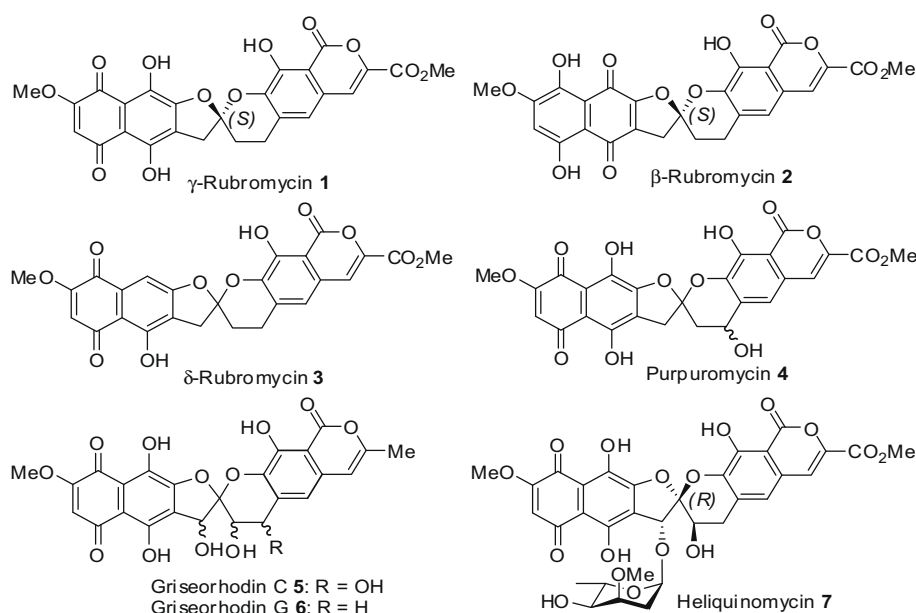


Figure 1. The rubromycin family of antibiotics containing aromatic spiroketal units.

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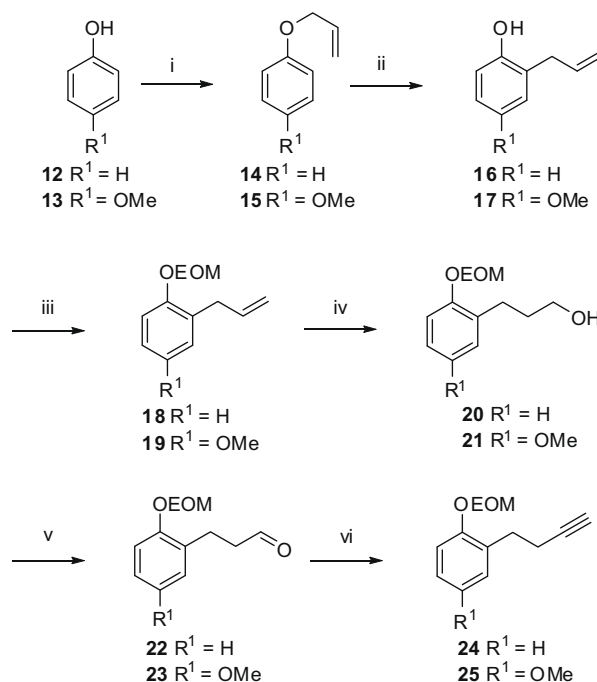
established as the pharmacophore responsible for the observed biological activity.² To date, only a single racemic total syntheses of the aglycon of heliquinomycin **7**⁸ and γ -rubromycin **1**⁹ have been reported. Despite the recent advances in the synthesis of fragments of these natural products,¹⁰ their total synthesis remains a considerable challenge.

Our interest in the synthesis of spiroketal natural products,¹¹ in particular the spiroketal core of the rubromycins,¹² has prompted the synthesis of aryl-fused spiroketals. Although several syntheses of 5,6-bisbenzannulated¹³ and 6,6-bisbenzannulated¹⁴ spiroketals related to the rubromycins have been reported, syntheses of bisbenzannulated spiroketals are less common than their aliphatic counterparts. The synthesis of aliphatic spiroketals using a double intramolecular hetero-Michael addition (DIHMA) strategy, in which double conjugate addition of a diol to an ynone system provides an effective method to generate 5,6-spiroketals, has been explored by various research groups.¹⁵ To our knowledge, the use of a DIHMA approach for the synthesis of a bisbenzannulated spiroketal core has not previously been reported. Therefore, we herein propose that bisbenzannulated spiroketal **8** could be assembled via DIHMA of dihydroxy ynone **9** (Fig. 2). In turn, access to the spiroketal precursor **9** is readily achieved by addition of the acetylide anion generated from acetylene **11** to aldehyde **10**. The efficient synthesis of several bisbenzannulated 6,6-spiroketals using a novel microwave-assisted DIHMA protocol is then realized.

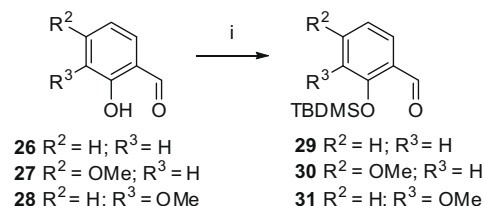
Acetylenes **24** and **25** were prepared from commercially available phenols **12** and **13** via Claisen rearrangement of the derived allyl ethers **14** and **15** (Scheme 1). Protection of the allylphenols as ethoxymethyl (EOM) ethers followed by hydroboration with borane-dimethylsulfide complex afforded the primary alcohols **20** and **21**. Subsequent oxidation using 2-iodoxybenzoic acid (IBX) produced the desired aldehydes **22** and **23** that were readily converted to their respective acetylenes using the Ohira–Bestmann reagent.¹⁶

Aldehydes **29–31** were easily prepared by *tert*-butyldimethylsilyl chloride protection of the readily available salicylaldehydes **26–28** (Scheme 2).

With acetylenes **24–25** and aldehydes **29–31** in hand, coupling of the two subunits was undertaken (Scheme 3). Generation of the acetylide anions of **24–25** using *n*-BuLi and reaction with aldehydes **29–31** gave the desired alkynols **32–36**. Subsequent oxidation of the secondary alcohols **32–36** to the desired ynones **37–41** was achieved in good yields using IBX. Addition of diethylamine to a dichloromethane solution of ynones **37–41** led to the deprotection of the TBDMS group with concomitant formation of the isolable enamino-ketone intermediate after 30 min. Intramolecular 6-endo-dig cyclization of this intermediate can lead to the formation of the desired benzopyrone intermediate via an addition–elimination sequence.¹⁷ The crude enamino-ketones were, therefore, heated under reflux for 16 h, resulting



Scheme 1. Reagents, conditions, and yields: (i) allyl bromide, K_2CO_3 , acetone, reflux, **14**, 97%; **15**, 92%; (ii) neat, microwave, 210 °C, 300 W, **16**, 92%; **17**, 90%; (iii) ethoxymethyl chloride, iPr_2NEt , CH_2Cl_2 , 0 °C, **18**, 85%; **19**, 86%; (iv) BH_3-SMe_2 , NaOH, H_2O_2 , **20**, 81%; **21**, 80%; (v) IBX, DMSO, **22**, 84%; **23**, 78%; (vi) diethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3 , MeOH, **24**, 94%; **25**, 90%.



Scheme 2. Reagents, conditions, and yields: (i) TBDMS-Cl, imidazole, DMAP, CH_2Cl_2 , **29**, 85%; **30**, 88%; **31**, 90%.

in formation of the desired benzopyrones **42–46** in excellent yields.

Benzopyrones **44**, **45**, and **46** underwent deprotection of the phenolic EOM ether with carbon tetrabromide in isopropanol with concomitant spirocyclization affording spiroketals **51**, **52** and **53**, respectively (Scheme 3). However, in the case of benzopyrones **42** and **43** final spirocyclization to the desired 6,6-spiroketal ring system proved challenging, only furnishing the deprotected phenols **47** and **48** upon treatment with carbon tetrabromide. Attempts to effect the efficient conversion of deprotected phenol **47** to spiroketal **49** were conducted using various reaction conditions (Table 1). After intense experimentation, cyclization of **47–49** using microwave irradiation in the presence of potassium carbonate proved to be the most reliable method.¹⁸ This procedure was, therefore, applied to benzopyrone **48** affording the desired bisbenzannulated 6,6-spiroketal **50**.

In conclusion, an efficient method for the construction of bisbenzannulated 6,6-spiroketals related to the rubromycin family of antibiotics has been developed. The methodology involves the union of an aryl acetylene with an aryl aldehyde followed by oxidation to an ynone intermediate in preparation for DIHMA to form a bisbenzannulated spiroketal. Application of this DIHMA protocol

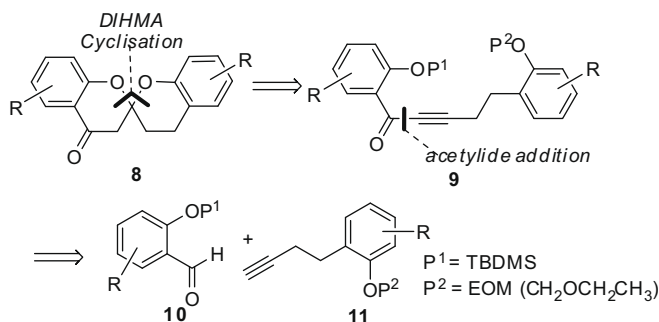


Figure 2. Retrosynthesis of 6,6-bisbenzannulated spiroketals.

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