



Synthesis of an elaborated heliquinomycin isocoumarin moiety

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Abstract

Synthesis of a fully functionalized isocoumarin moiety **2** of DNA helicase inhibitor heliquinomycin (**1**) is reported. The key step is a modified condensation reaction of diethyl bromomalonate with readily accessible phthalaldehydic acid derivative **3**. Introduction of an allyl side chain is accomplished by Claisen rearrangement of allyl phenyl ether **8**. © 1999 Elsevier Science Ltd. All rights reserved.

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The DNA helicase class of enzymes is responsible for unwinding double stranded DNA in preparation for replication and repair.¹ In a screen for DNA helicase inhibitors, heliquinomycin (**1**, Fig. 1) was isolated from *Streptomyces* sp. MJ929-SF2 by Chino and co-workers.² Compound **1** showed moderate antitumor and antimicrobial activities, but most significantly **1** inhibited human DNA helicase isolated from HeLa S3 cells at concentrations (5–10 µg/mL) that did not inhibit topoisomerases I and II.³ This specificity of **1** for helicase inhibition may allow for the development of novel antitumor agents as well as reagents for elucidating the molecular details of helicase interactions with DNA. The griseorhodins,⁴ purpurumycin⁵ and γ-rubromycin⁶ share a common structural architecture with **1**, the most prominent feature of which is a benzannelated spiroketal linking an isocoumarin moiety with a naphthoquinone ring system. The significant biological activity of **1** and the paucity of synthetic efforts toward this class of compounds have prompted us to pursue a total synthesis of **1**. Herein we report the synthesis of a fully elaborated isocoumarin **2** that provides the requisite functionality to carry out a convergent total synthesis of heliquinomycin (**1**).

Preparation of the fully functionalized heliquinomycin isocoumarin fragment is outlined in Scheme 1. The isocoumarin ring system was constructed under conditions modified from those described by Chatterjea et al.⁷ Treatment of readily accessible phthalaldehydic acid⁸ **3** with a slight excess of NaH in DMPU, followed by addition of diethyl bromomalonate gave a 90% yield of highly pure cyclized intermediate **4**. The excess sodium hydride presumably facilitates a base-catalyzed aldol closure to **4** via the malonate ester of **3**. Ring closure under the original Chatterjea conditions (K₂CO₃, MEK, reflux) resulted in only a 60% yield of a significantly less pure product. Decarboxylative elimination

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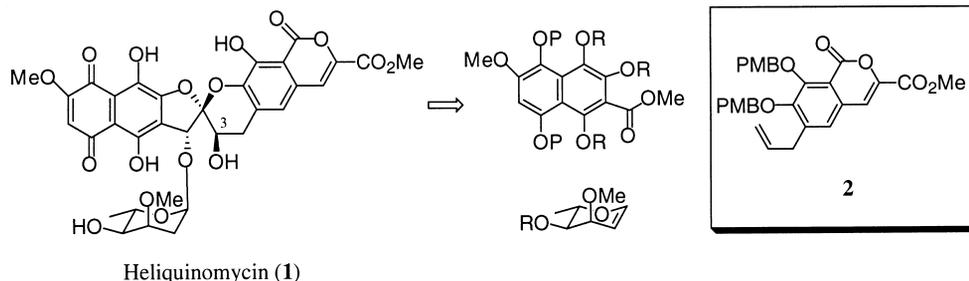
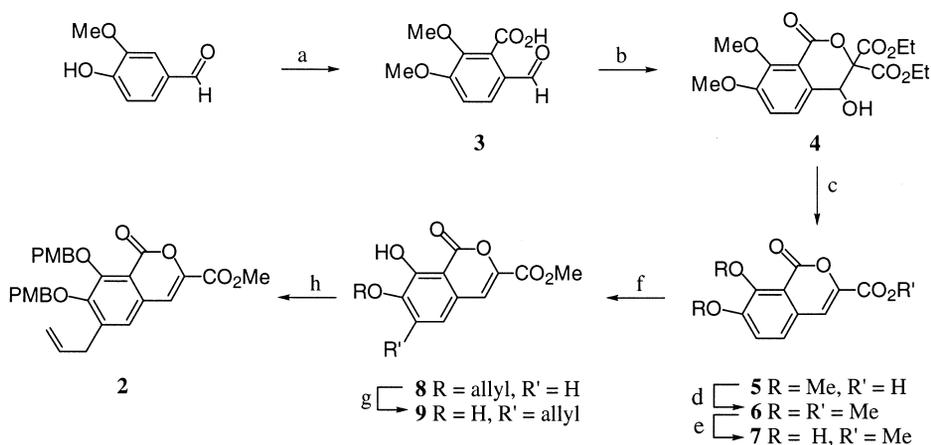


Figure 1. Retrosynthetic fragments for heliquinomycin synthesis

afforded acid **5** (81%), which following Fischer esterification gave known ester **6** in high yield (85%).⁷ Deprotection of the methyl ethers using BBr_3 ⁹ then yielded unstable isocoumarin catechol derivative **7** (98%).



Scheme 1. (a) See Napolitano et al.;⁸ (b) 1.1 equiv. NaH, DMPU, then diethyl bromomalonate, rt; (c) concd HCl/glacial HOAc, reflux; (d) cat. H_2SO_4 , MeOH, reflux; (e) BBr_3 , $\text{ClCH}_2\text{CH}_2\text{Cl}$, rt; (f) 2.2. equiv. NaH, 1.1 equiv. allyl bromide, DMF, -20°C ; (g) PhNEt_2 , reflux; (h) PMBOCl , cat. Et_4NI , K_2CO_3 , acetone, reflux

Selective allylation of the less hindered phenol in **7** was achieved in moderate yield (60% by NMR based on unreacted **7**) using NaH/allyl bromide at -20°C ,¹⁰ and the monoallylated product **8** was then subjected to a thermal Claisen rearrangement in refluxing PhNEt_2 without further purification.¹¹ This resultant unstable catechol **9** was immediately protected as its bis-*p*-methoxybenzyl ether derivative **2** in good yield (70% from **8**). The allyl function in **2** serves as a precursor to a variety of functional groups that may be used to explore coupling strategies to merge the two halves of the heliquinomycin aglycon. This work will be reported in due course.

Acknowledgements

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11. The monoallylated product was only partially stable to chromatography and could not be separated from starting material without significant material losses due to decomposition. However, the mixture obtained from monoallylation could be carried forward directly without reduction in yield through the next two steps (as compared to using purified monoallylated starting material).