Pergamon

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Tetrahedron Letters 44 (2003) 1075–1077

TETRAHEDRON LETTERS

General entries to *C*-aryl glycosides. Formal synthesis of galtamycinone

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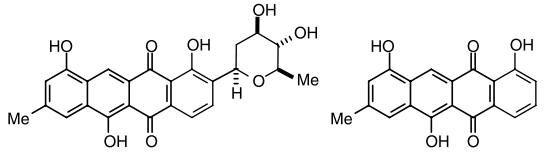
Received 10 August 2002; revised 23 November 2002; accepted 25 November 2002

Abstract—Utilizing a general entry we had developed for the synthesis of *C*-aryl glycosides, we have prepared the juglone derivatives **18**–**20** as well as the juglone precursor **13**. Because **19** had been previously converted in two steps by Suzuki into galtamycinone (**1**), its preparation constitutes a total synthesis of **1**. © 2003 Elsevier Science Ltd. All rights reserved.

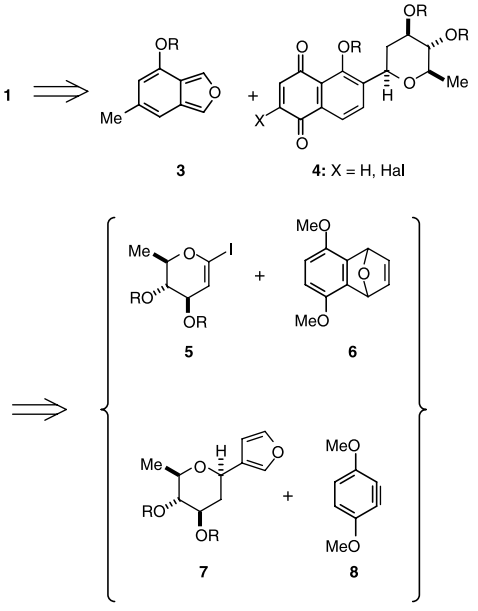
1. Introduction

The *C*-aryl glycoside antibiotics comprise a subclass of the family of naturally occurring *C*-glycosides that have gained considerable attention because of their range of biological activities and their resistance to enzymatic hydrolysis.[1] Consequent to this interest, a number of methods have been developed for their synthesis,[2] and we recently unveiled a unified approach that may be applied to the preparation of each of the four common structural types of *C*-aryl glycosides.[3] Toward establishing these methods in the context of total synthesis, we became interested in galtamycinone (**1**),[4] a member of the angucycline family of *C*-aryl glycosides. Galtamycinone posed a challenge not only with respect to *C*-aryl glycoside synthesis but also for the efficient assembly of the linear tetracyclic framework represented by its aglycone SS-228R (**2**),[5] which is also a natural product.



1 **2**

In developing our approach to **1** (Scheme 1), we were influenced by the prior art. Namely, Suzuki had converted a juglone related to **4** into **1** using the Tamura protocol to annelate the requisite naphthalene subunit.[4,5a] While our primary focus was upon applying our methodology to the syntheses of *C*-glycosylated juglones **4** via combinations of **5** and **6** or **7** and **8**, we were also intrigued by the possibility of developing a different annelation strategy for the end-game of the synthesis. In particular, we wondered whether juglones such as **4** might undergo regioselective Diels–Alder



Scheme 1.

Keywords: *C*-aryl glycosides; Diels–Alder reaction; palladium-catalyzed ring openings.

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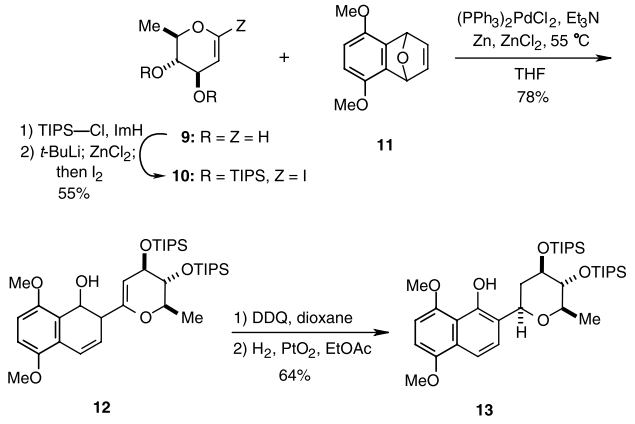
PII: S0040-4039(02)02666-7

cycloadditions with isobenzofurans like **3** to form the requisite tetracyclic framework of **1**. We now report some of the results of these investigations.

2. Results and discussion

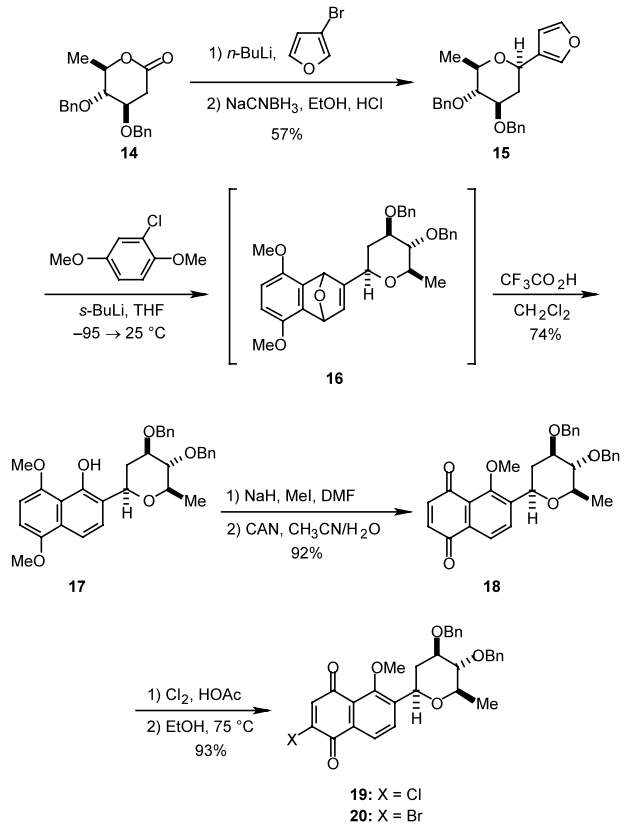
In our first entry to a potential precursor of a juglone of general type **4**, D-olivose glycal (**9**)[6] was converted into the protected iodo glycal **10** according to the protocol of Friesen (Scheme 2).[7] The Pd-catalyzed opening of **11** with **10** then furnished **12**,[8] which was transformed into the desired *C*-aryl glycoside **13** in 50% overall yield from **10** by sequential oxidation of the dihydronaphthol moiety and stereoselective reduction of the glycal.[3,9]



Scheme 2.

One may easily envision ways of transforming **13** into a juglone derivative related to **4** that could be elaborated into galtamycinone by straightforward modifications of the prior art of Suzuki.[4] However, we opted instead to prepare the corresponding dibenzyl ether as this intermediate would bear protecting groups identical to those previously reported. In this way, we would also be able to highlight the effectiveness of an alternative entry to juglones like **4** that features our benzyne–glycosyl furan Diels–Alder approach to *C*-aryl glycosides.[3]

In the event, the lactone **14**, which was prepared by the same procedure reported for its enantiomer,[10] was first converted into the furyl glycoside **15** (Scheme 3). The subsequent reaction of **15** with the benzyne generated in situ from 2-chloro-1,4-dimethoxybenzene furnished a mixture of the diastereomeric Diels–Alder adducts **16**. These compounds were not separated because they converged to the desired *C*-aryl glycoside **17** (74% overall yield from **15**) upon acid-catalyzed rearrangement. *O*-Methylation of **17** followed by selective oxidation of the dimethyl hydroquinone ring gave the juglone **18**. Sequential chlorination–dehydrochlorination of **18** proceeded with essentially complete regioselectivity to give chlorojuglone **19** in 93% yield.[11] Bromination–dehydrobromination (Br_2, $CHCl_3$, 0°C; EtOH, AcOH, reflux; 61%) of **18** similarly gave **20**. Because **19** had been efficiently converted in two steps

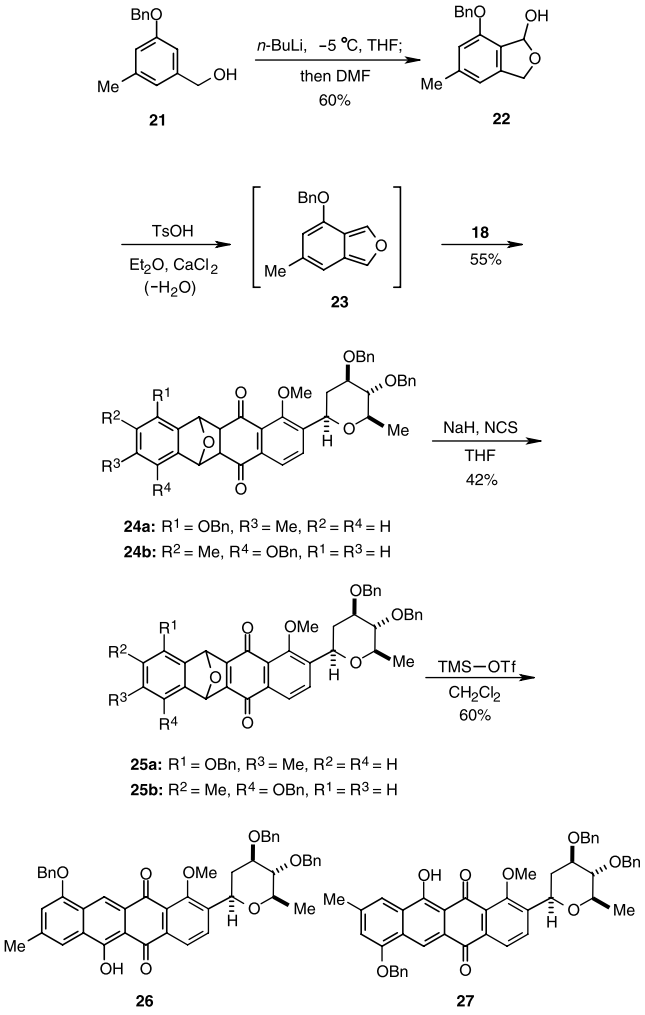


Scheme 3.

into galtamycinone by Suzuki,[4] its preparation constitutes a formal synthesis of **1**.

With the successful application of our methodology for preparing *C*-aryl glycosides to the formal synthesis of **1**, a major goal had been achieved. However, we wanted to explore the annelation strategy depicted in Scheme 1 to see if a more concise route to the tetracyclic aromatic core of **1** might be developed. The central question was whether glycosylated juglones as **18**–**20** would undergo a regioselective Diels–Alder reaction with an isobenzofuran related to **3**.

In order to address this question, we conducted an exploratory study in which **18** was allowed to react with the isobenzofuran **23**, which was generated in situ by dehydration of **22**. Unfortunately this reaction gave an uncharacterized mixture of regio- and stereoisomeric products of general structures **24a**,**b** (Scheme 4). The composition of this mixture was simplified by treating **24a**,**b** with *N*-chlorosuccinimide (NCS) in the presence of NaH to introduce a double bond and form the central quinone ring in **25a**,**b**. Reaction of **23** with the bromojuglone derivative **20** also gave a mixture of **25a**,**b**, albeit in lower overall yield. The TMS–OTf induced opening of the oxabicyclic rings in **25a**,**b** was directed by the proximal benzyloxy group to give a separable mixture (ca 1.1:1) of the regioisomers **26** and **27**. The *C*-aryl glycoside **26** thus obtained exhibited spectral properties consistent with those reported by Suzuki for the penultimate intermediate in his synthesis of galtamycinone (**1**).[4]



Scheme 4.

The preparation of the chlorojuglone **19** constitutes a formal synthesis of galtamycinone (**1**) and clearly demonstrates the viability of our methodology for the facile synthesis of naturally occurring *C*-aryl glycosides. However, the lack of significant regioselectivity in the Diels–Alder reaction to assemble the tetracyclic core of **1** illustrates the need for developing methods to control the regiochemistry of benzyne–furan cycloadditions. We are presently examining a number of tactics to address this problem and will report the results of these investigations in due course.

Acknowledgements

We thank the National Institutes of Health (GM 31077), the Robert A. Welch Foundation, Pfizer, Inc., and Merck Research Laboratories for their generous support of this research.

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