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New strategies for the synthesis and functionalization of tetrahydroxanthones

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ABSTRACT

Two strategies for the functionalization of simple tetrahydroxanthones (THX) on either of the carbocyclic rings are reported. By application of palladium catalysis, concomitant assembly of this heterocyclic scaffold with controlled introduction of substituents on the aromatic ring at C-5, C-6 or C-7 can be achieved. Variation in the nature of the added carbon fragment (aryl, alkenyl and alkynyl) is explored through use of different cross-coupling partners. Separately, functionalization at C-4 of the saturated carbocyclic ring is demonstrated through use of the extended enolate derived from 1-hydroxytetrahydroxanthone.

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1. Introduction

Polycyclic xanthones are an important family of natural products that are based upon a highly oxygenated hexacyclic framework.[1] Based on the oxidation state of the xanthone nucleus, this compound class can be subdivided into fully aromatic-, tetrahydro- and hexahydro-derivatives. Of these, the most synthetically challenging are the tetrahydroxanthone (THX) derivatives due to their increased complexity and potential to aromatize to xanthones by dehydration. Important examples include kigamicin A (**1**),[2] simaomicin α (**2**),[3] kibdelone A (**3**),[4] isokibdelone C (**4**)[5] and albofungin (**5**),[6] which all possess potent bioactivity (Fig. 1). These and other THX natural products show variation in the level of oxidation in the saturated xanthone ring, the relative stereochemistry of the appended alcohol and ether substituents, and how the THX is fused to the remaining rings of the polycyclic xanthone skeleton.

As a consequence of their important biological activities, there is much current interest in the synthesis of THX based natural products and simplified analogues with which to probe structure-activity relationships. For example, Porco and co-workers have recently completed elegant total syntheses of (+)-kibdelone A[7] and (+)-kibdelone C[8] among others[9] whilst Ready has reported efficient

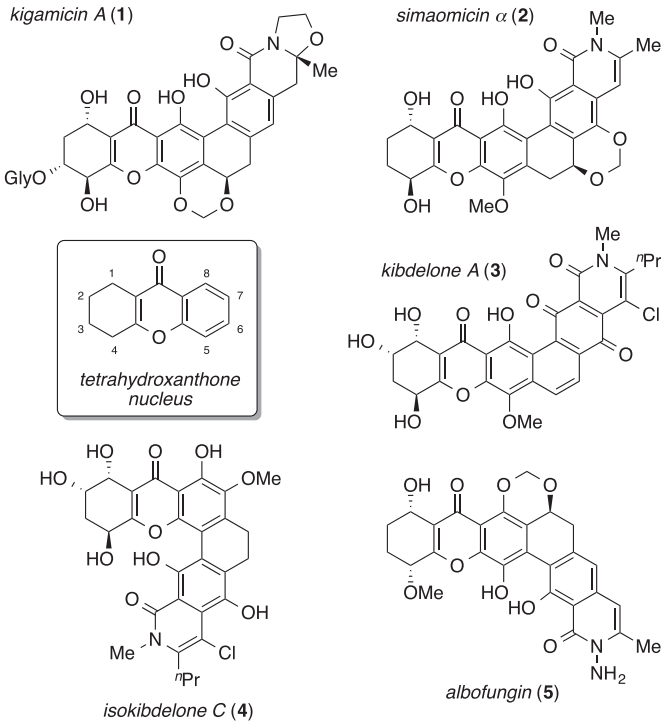

Fig. 1. Tetrahydroxanthone containing natural products.

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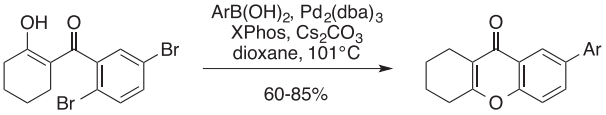
syntheses of (−)-kibdelone C[10] and (−)-simaomicin α.[11] Other groups have devised routes to functionalized THXs related to such natural products.[12–16] In our laboratory, a mild method for the synthesis of 7-arylated THX derivatives by concomitant C–O and C–C bond construction has been developed (Scheme 1). To date, this simple yet powerful methodology has enabled us to identify the minimum *anti*-austerity pharmacophore of the kigamicins,[15] and make glycosylated derivatives for study.[16]



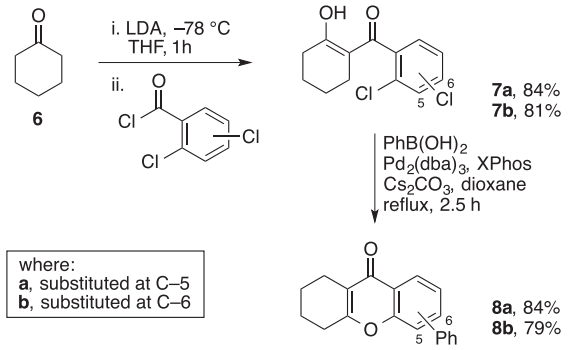
Scheme 1. Previous work towards 7-substituted THXs.

In this article, we extend our investigations to a range of functionalized THXs beyond C-7 substitution, which has the potential to provide analogues with which to reveal insights into the biology of other polycyclic xanthone natural products. Specifically, we explore the feasibility of accessing derivatives functionalized on either carbocyclic ring of the THX. Two strategies are explored that are highly complementary and allow access to a range of simple derivatives. To make compounds substituted on the aromatic ring, further development of our Pd catalyzed methodology is explored. Additionally, the feasibility of making di- and tri-hydroxylated derivatives by controlled hydroxylation of the saturated ring of the THX is examined, through the use of extended enolates of this heterocycle nucleus.

2. Results and discussion

2.1. Assembly of functionalized THXs using Pd catalysis

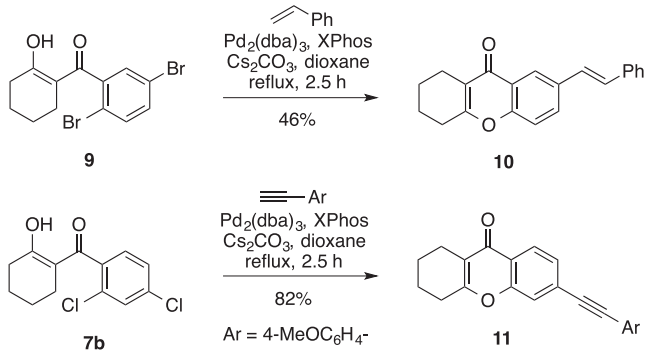
Building on the initial findings depicted in Scheme 1, we set out to ascertain if this chemistry could be extended to different substitution patterns, by location of the second halogen at other sites on the benzene ring, and to other types of cross-coupling reactions. First, we examined if we could make THXs bearing substituents at C-5 and C-6, mapping over, for example, the structures of isokibdelone C (**4**) and albofungin (**5**), respectively (Fig. 1). Thus, cyclohexanone (**6**) was *C*-acylated with the appropriate acid chlorides to give **7a**,**b** in good yield which, in $CDCl_3$, exist exclusively in the enol form (Scheme 2). Treatment of these substrates with phenylboronic acid under our optimized conditions smoothly provided **8a**,**b** by way of concomitant C–O and C–C bond formation. Clearly, the Suzuki–Miyaura reactions work well with aryl chlorides under these conditions. While the transition metal is essential for the cross-coupling, we should stress that in recent work directed towards glycosylated THXs, we have noted that Pd catalysis is not



Scheme 2. Synthesis of THXs substituted at C-5 and C-6.

always essential for the C–O bond construction.[16] However, the reaction times are longer and the reactions less clean without it.

To extend the scope of this chemistry still further, we examined if Pd-catalyzed Heck and Sonogashira cross-couplings could be combined with THX assembly. These reactions were performed under our standard conditions, without further optimization. Two illustrative systems were explored (Scheme 3). Reaction of dibromide **9**[15] with styrene yielded C-7 substituted THX **10** by way of a Heck coupling (Scheme 3). Similarly, treatment of dichloride **7b** with 4-ethynylanisole provided C-6 substituted THX **11** in excellent yield by way of a Sonogashira reaction.



Scheme 3. THX assembly combined with Heck and Sonogashira couplings.

2.2. Use of extended enolates derived from THX nucleus

Complex THX natural products such as **1**–**5** possess a variety of hydroxylation patterns within the saturated six-membered ring, and the role of these alcohol and ether substituents on bioactivity is poorly understood (Fig. 1). Consequently, strategies for the assembly of hydroxylated THXs are of much interest.[13,16] Since all these natural products contain a hydroxyl group at C-1, a potentially simple and direct approach for the introduction of diol and triol motifs would be to generate and exploit the extended enolate derived from 1-hydroxy-tetrahydroxanthone.

To explore this idea, we began with an examination of the enolate chemistry of (±)-**12a**[17] (Scheme 4). Generation of the potassium enolate from **12a** was readily achieved by deprotonation with 2.1 equiv of potassium *tert*-butoxide in THF at low temperature. Quenching of the presumed dianion intermediate **13** with PhSeCl provided selenide **14** as a mixture of diastereomers through selective functionalization at C-4. The use of the unprotected hydroxyl group at C-1 proved critical to success. Using **12b** or **12c**, in which the hydroxyl group was protected as the TBS or PMB ether, respectively, led only to recovery of starting materials upon addition of PhSeCl.[18] Moreover, no improvements were seen using LDA as base with **12b**. Selenide **14**, as a mixture of diastereomers, was converted to the corresponding PMB ether which was further transformed into dihydroxanthone **15** by oxidation to the selenoxide and *syn*-elimination. Despite concerns that this material might be prone to elimination to the aromatic xanthone, it proved reasonably stable. *syn*-Dihydroxylation of olefin **15** under Upjohn conditions gave diol **16** as a single diastereomer in 53% yield. Quantities of xanthone (20%) were isolated alongside this diol as a result of elimination of PMBOH under the reaction conditions. To our surprise, **16** has all the ring substituents on the same face, as a result of dihydroxylation from the seemingly more hindered face of the olefin. To confirm our assignments, the structures of both alkene **15** and diol **16** were established by single crystal XRD (Scheme 4 and Supplementary data).[19] It is known that hydroxyl groups can direct dihydroxylation of allylic and homoallylic

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