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Cyclization of 1,4-dihydroxyanthraquinone with α,β-unsaturated aldehyde: a new strategy for the synthesis of cyclopentanoids

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ABSTRACT

A cascade cyclization strategy has been developed for the synthesis of cyclopentane-fused anthraquinones through the condensation of 1,4-dihydroxyanthraquinone with α,β-unsaturated aldehydes in the presence of common inorganic base NaOH. These fused-tetracyclic anthraquinone products are formed in a single step from readily accessible starting materials under very mild conditions without the use of any expensive or complex reagents. This method represents an unprecedented example of a base-promoted protocol to access five-membered carbocyclic rings in a single step. Moreover, this chemistry also provides useful guidance for the preparation of 6,5-fused ring systems.

Many naturally occurring and biologically active molecules with structures based on the fusion of one or more five-membered carbocyclic rings are known,[1] including the steroids and cyclopentanoid monoterpenes (Fig. 1). Owing to the importance of these ring systems in drug discovery and biological studies, many approaches have been developed to access the valuable five-membered cyclopentane unit.[2] The two main strategies that have been developed for constructing such carbocycles are the [3+2] annulation[3] and cyclopentane annellation.[4] The former requires polarized cyclopropanes as synthons, whereas the latter, mainly based on the cyclic α,β-unsaturated carbonyl compounds as the key components, requires an additional step to introduce a three-carbon unit onto a pre-existing ring unit before intramolecular cyclization. Despite the efficiency of these two approaches, simple and convenient methods are more desirable in view of the pharmaceutical applications.

Fused anthraquinones are also of much importance because they are present in a variety of bioactive compounds and drugs (Fig. 2).[5] In particular, anthracycline antibiotics such as doxorubicin and daunomycin are widely used in the treatment of all kinds of human cancers.[6] The outstanding potencies of anthracycline antibiotics as anticancer drugs motivate the discovery of the next generation of these drugs. Most of the reported synthetic tetracyclic anthraquinones contain a fused six-membered ring.[7] Analogues made by changing the six-membered ring to a five-membered one are particularly rare.[8] We have initiated a project that aims to explore new carbon–carbon bond forming reactions of anthraquinones.[9] As part of those efforts, we are interested in cyclopentane-fused anthraquinones because tetracyclic anthraquinones contain a fused five-membered ring that possesses more planar conformation and might therefore be a better fit into the DNA double helix and remain electronic and spatial characteristics of the anthraquinone that believed to a bioactive moiety. Herein we wish to disclose our recent findings on the assembly of cyclopentane-fused anthraquinones in a simple manner.

The selection of a suitable three-carbon unit is crucial for a successful synthesis of the cyclopentanoids when using anthraquinone as the pre-existing ring skeleton in a single reaction. Taking into account the potential of α,β-unsaturated carbonyl compounds for sequential 1,2- and 1,4-addition reactions with two nucleophiles, we decided to employ α,β-unsaturated aldehyde as a three-atom reagent to examine the feasibility of constructing of the five-membered carbocycle in a single step (Table 1). We previously reported on the C–C bond formation reaction of anthraquinone with different aldehydes.[9a] Thus, the cyclization behavior of anthraquinone with cinnamaldehyde was initially examined under reaction conditions similar to those that were employed previously.[9a] To our delight, the desired product was obtained in 58% yield, although 30% of unreacted **1** was recovered (entry 1). To improve the yield of **3a** and the conversion of **1**, the reaction temperature was raised to room temperature. However,

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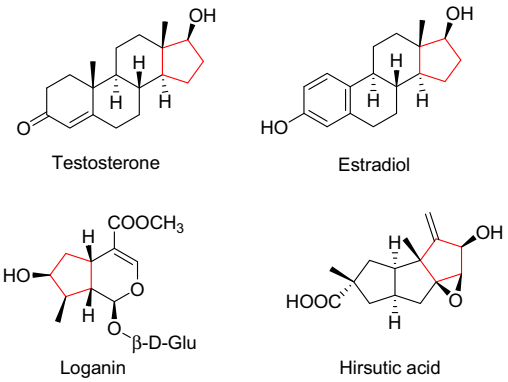


Figure 1. Representative example of biologically important cyclopentanoids.

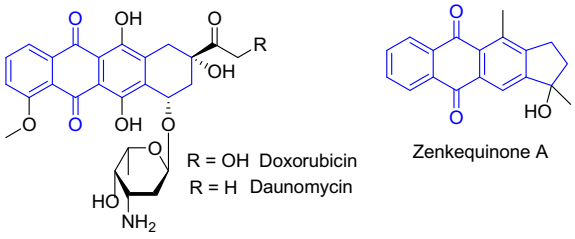


Figure 2. Selected drugs and natural products containing fused anthraquinones.

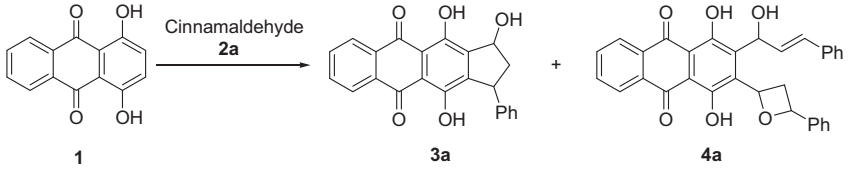
increasing the temperature resulted in the formation of anthraquinone **4a** as the main product in 39% yield along with the recovery of 40% of unreacted **1** (entry 2). The formation of **4a** was likely due to the overreaction of **1** with **2a** as described in the literature.[10] These results indicated that a low temperature was sufficient to conduct the cyclization and circumvent the formation of byproduct. Switching the solvent from MeOH to EtOH gave evidence of the facile consumption of **1**, and the cyclized product was obtained in 74% isolated yield after 50 min at 0 °C (entry 3). Increasing the reaction temperature to room temperature in EtOH gave a similar result with entry 2 (entry 4). Subsequently, further screening of reaction times and temperatures was performed, but furnished **3a** only in 21% and 53% yields, respectively (entries 5 and 6). Eventually, attempts to perform the reaction in water failed to produce any desired product (entry 7). Therefore, the optimized conditions for the one-pot annulation that worked best were anthraquinone (1.0 equiv), aldehyde (4.0 equiv), NaOH (6.0 equiv), and $Na_2S_2O_4$ (2.0 equiv) at 0 °C for 50 min in EtOH.

With the optimized reaction conditions in hand, we explored other α,β-unsaturated aldehydes to examine the scope and limitations of the reaction. The results are summarized in Table 2. A variety of cyclopentane-fused anthraquinones **3** were readily accessible by taking advantage of this strategy. All substituted cinnamaldehydes **2**, regardless of whether electron-withdrawing or electron-donating substituents were attached to the phenyl rings, could react with anthraquinone **1** to afford the desired fused-tetracyclic anthraquinone products **3** in moderate to good yields (42–82%) (entries 1–18). It seems that the electronic properties and varied positions of the substituents on the phenyl ring had little impact on the product formation. Furthermore, a variety of substituents on the aromatic ring were tolerated under the optimized conditions, including methyl (entries 1–3), methoxy (entries 4–6), fluoro (entries 7–9), chloro (entries 10–12), bromo (entries 13–15), and cyano (entries 16–18). A heterocyclic α,β-unsaturated aldehyde **2t** was also a suitable substrate, as compound **3t**, in which the phenyl ring was replaced by fural, was obtained in 49% yield under the optimized conditions (entry 19). Unfortunately, attempts to use aliphatic α,β-unsaturated aldehydes such as acrylaldehyde or crotonaldehyde did not provide the desired cyclized products (data not shown). It is worth noting that, although limitations on the substrate scope were noted, our method presents several advantages over alternative procedures: (i) it avoids the use of the expensive and complex reagents necessary for [3+2] annulation[3] and cyclopentane annellation[4]; (ii) the completion of the reaction is achieved in only 50 min in comparison to several hours or even days with catalysts[3d–g,4b–f]; (iii) the cyclization requires only NaOH in the presence of $Na_2S_2O_4$ without the necessity of adding any ligands and additives; (iv) the formation of two C–C bonds was accomplished in a single operation under mild conditions; and (v) the hydroxyl group that simultaneously formed in the carbocycle is a useful handle for further structural manipulations, which can be variously derivatized to produce a wide variety of interesting structures.

The structures of all the products **3** were determined by ^1H NMR, ^{13}C NMR, and HRMS. The structure of compound **3a** was further confirmed by X-ray analysis of crystals grown from dichloromethane (see the Supporting information).

On the basis of the above results and previous studies reported by us,[9a] we propose a possible mechanism (Scheme 1) to explain the cyclization behavior of anthraquinone with α,β-unsaturated

Table 1
Optimization of reaction conditions[a]



Entry	Solvent	T (°C)	t (min)	**3a** (%)[b]	**4a** (%)[b]	Recovery of **1** (%)[b]
1	MeOH	0	50	58	0	30
2	MeOH	r. t.	50	0	39	40
3	EtOH	0	50	74	0	9
4	EtOH	r. t.	50	Trace	44	7
5	EtOH	−10	50	21	0	75
6	EtOH	0	30	53	0	38
7	H_2O	0	50	0	0	66

[a] Reactions were performed with **1** (0.5 mmol), **2a** (2.0 mmol), NaOH (3.0 mmol) and $Na_2S_2O_4$ (1.0 mmol) in 10.0 mL of solvent.
[b] Isolated yields.