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Application of differential reactivity towards synthesis of lamellarin and 8-oxoprotoberberine derivatives: Study of photochemical properties of aryl-substituted benzofuran-8-oxoprotoberberines

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ABSTRACT

A unique differential reactivity between dihydroisoquinolines and 3-nitrocoumarins was observed and was exploited for the efficient construction of lamellarins and their isomeric benzofuran-8-oxoprotoberberine derivatives under acid-catalyzed or base-promoted conditions. Further, these prepared aryl-substituted benzofuran-8-oxoprotoberberine derivatives bearing electron-donating substituents on benzofuran moiety are found to be benchtop stable but light-sensitive, and can undergo oxidative ring-opening reaction to give the corresponding keto products when exposed to visible light under aerobic conditions.

1. Introduction

Lamellarins[1] are a diverse family of marine alkaloids. Ever since their first discovery by Faulkner and co-workers[2] in 1985, more than 70 lamellarins and structurally-related pyrrole alkaloids have been isolated from mollusks, ascidians, and sponges so far. Most of lamellarins share a common pyrrolo[2,1-*a*]isoquinoline- and coumarin-fused pentacyclic core structure but differ on their peripheral functional groups. These lamellarin alkaloids have been found to exhibit a variety of biological activities such as antitumor activity,[3] reversal of multidrug resistance,[4] and HIV-1 integrase inhibition activity.[5] Owing to their novel molecular structures and intriguing biological properties, the synthesis of lamellarins and their analogues has continued to attract considerable interest to organic and medicinal chemists. Among these alkaloids, lamellarin D[3a] has received the most attention of all, since it can not only inhibit DNA topoisomerase I (topo I) activity at nanomolar concentration but also exhibit potent anticancer activity against multidrug-resistant cell lines.[6] Previous studies have demonstrated that lamellarin D is capable of promoting DNA cleavage through stabilization of topo I–DNA covalent complexes,[6b-c] a mode of action similar to that of anticancer drug camptothecin[7] and berberines.[8] Camptothecin is a cytotoxic quinoline alkaloid that contains a crucial pyridone moiety, whereas berberines represent a large family of alkaloids that bear an isoquinoline ring-fused system with various biological activities. By comparing the molecular structures of lamellarin D, camptothecin, and berberine (Fig. 1), we speculate that the replacement of the original lamellarin core with its isomeric benzofuran-8-oxoprotoberberine skeleton might potentially provide a new scaffold mimicking the critical interactions of lamellarins with the topo I-DNA complex.

Protoberberines are alkaloids constituting many families of natural products that share similar molecular skeletons such as berberines, tetrahydroprotoberberines, and 8-oxoprotoberberines. Most protoberberines exhibit a wide spectrum of biological activities.[9–12] Mainly due to their potential biological importance, the synthesis of 8-oxoprotoberberines and their derivatives has been well studied by synthetic and medicinal chemists in the past.[13] While previous efforts have been primarily focused on synthesis, biological and therapeutic applications of 8-oxoprotoberberines, their intrinsic photochemical properties,[14] especially visible-light-sensitive properties, were much less explored. Photosensitizer-free, visible-light-mediated organic reactions have recently received increasing attention owing to their simplicity and sustainability.[15] Thus, as a part of our ongoing

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research in pursuit of novel strategy for efficient construction of lamellarin analogues so as to facilitate the process to the development of lamellarin-derived anticancer drugs, here we describe a concise synthesis of lamellarins and their isomeric benzofuran- and pyridone-fused derivatives by acid-catalyzed or base-promoted coupling of dihydroisoquinoline hydrochlorides and 3-nitrocoumarins. The photochemical properties of the benzofuran-8-oxoprotoberberines are then investigated. Some are found to be light-insensitive, whereas others are light-sensitive and can undergo oxidative ring-opening reaction when exposed to visible light under aerobic conditions. A possible mechanism for this photooxygenation is also proposed on the basis of experimental data.

2. Results and discussion

Recently, we have reported[16] the synthesis of lamellarin type II derivatives by Grob-type coupling[17] of 3-nitrocoumarins and papaverine under sealed tube conditions. Success of this coupling reaction serves as a good reference for the current investigation of lamellarin type I synthesis. Scheme 1 outlines the optimized preparation of lamellarin G trimethyl ether (**1a**) by $SnCl_2$-catalyzed direct coupling of **2a** and **3a** in toluene in sealed tube at 140 °C for 8 h (Route I). To the best of our knowledge, this synthetic scheme represents the shortest route for lamellarin G trimethyl ether (**1a**) preparation ever reported in the literature[18] (two steps only with overall yield of 29.7% from commercial 2-hydroxy-4,5-dimethoxybenzaldedyde). Alternatively, **1a** can also be prepared via a stepwise process (Route II) by coupling (**2a**) with 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**3b**) to afford the pentacycle **4**. Bromination of **4** with NBS generated the bromo-substituted pentacycle **5**. Finally, Suzuki coupling between **5** and 3,4-dimethoxyphenylboronic acid afforded **1a**.[19] While Route I is shorter and gives higher overall yields, Route II has the advantage of introducing different aryl groups onto the pentacyclic skeleton. Fig. 2 lists the structures and yields for the prepared lamellarin derivatives **1a**–**f** via Route I. Since substituted 3-nitrocoumarins and 3,4-dihydropapaverines are readily available, this Grob-type coupling reaction provides an easy and rapid access to the biologically important lamellarin type I derivatives.

Similarly, Scheme 2 shows the two synthetic routes for the preparation of benzofuran-8-oxoprotoberberine **6a**. In Route I, **6a** was synthesized by Cs_2CO_3-mediated coupling reaction between 6,7-dimethoxy-3-nitrocoumarin (**2a**, prepared from condensation of 2-hydroxy-4,5-dimethoxybenzaldedyde with ethyl nitroacetate) and 3,4-dihydropapaverine hydrochloride (**3a**) in sealed tube in 18% yield (27% of **3a** was recovered). Alternatively, compound **6a** can also be prepared via a stepwise process (Route II, Scheme 2) by first coupling of **2a** with 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride (**3b**) in sealed tube to afford the pentacycle **7**. The subsequent bromination of **7** with NBS generated the bromo-substituted pentacycle **8**. Final Suzuki coupling of **8** with 3,4-dimethoxyphenylboronic acid afforded the target **6a**.[13] While Route I is shorter and gives a higher overall yield, Route II is capable of incorporating different aryl groups onto the pentacyclic skeleton.

In order to prove that the formation of this oxoprotoberberine scaffold is not a random process but follows a pattern that can be applied to a large substrate scope, we have prepared a series of 3-nitrocomarin and 3,4-dihydropapaverine derivatives with electron-donating ($N(Et)_2$, OMe) and electron-withdrawing (Cl, NO_2) substituents as the substrates. Fig. 3 lists the structures and

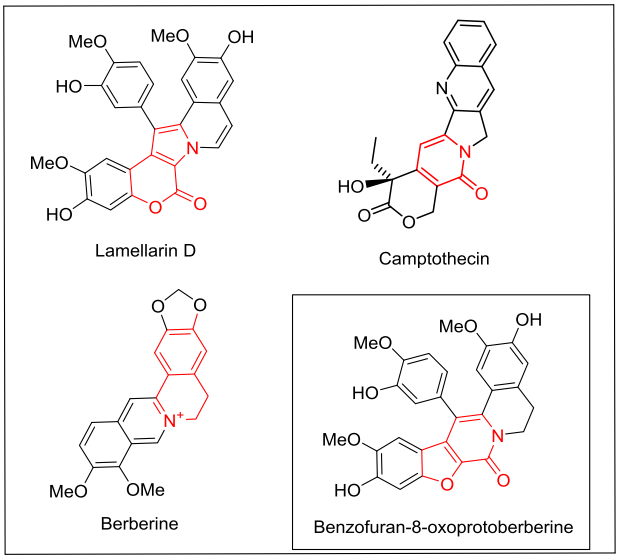
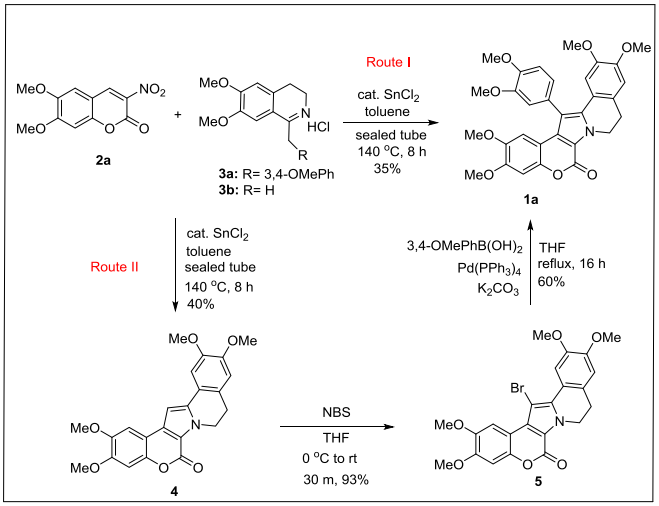


Fig. 1. Structures of lamellarin D, camptothecin, berberine, and benzofuran-8-oxoprotoberberine.



Scheme 1. Synthesis of lamellarin **1a**.

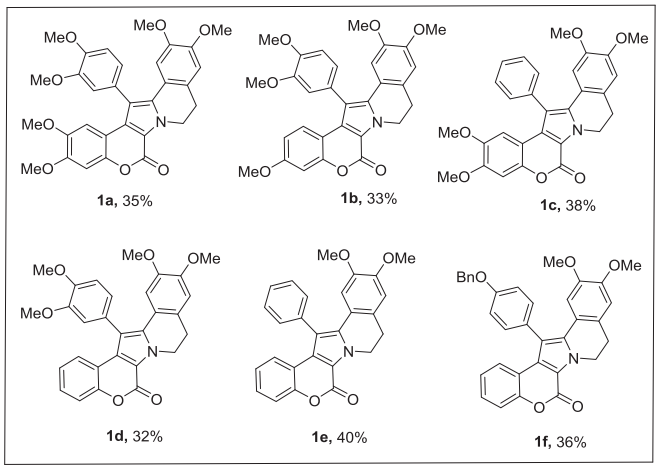


Fig. 2. Structures of the prepared lamellarins **1a**–**f**.