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Synthesis of anti-tubercular marine alkaloids denigrins A and B

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ABSTRACT

The first synthesis of anti-tubercular marine alkaloids denigrins A and B were accomplished in three and five steps and 62% and 31% overall yields respectively, from maleic anhydride. The key features of the synthesis include efficient Mizoroki-Heck reaction, geometry-controlled vinylogous aldol condensation, and one-pot lactamization. The synthesis first demonstrates the serviceability of maleic anhydride in palladium-catalyzed cross-coupling reactions with diaryliodonium salt.

Tuberculosis (TB), a highly infectious disease caused by the pathogen *M. tuberculosis*, spreads by the air therefore has been one of the leading causes of mortality worldwide for centuries. According to the estimation of WHO, in 2016, 10.4 million people were diagnosed with TB infection, out of which 1.3 million people died [1]. The condition becomes more severe in the case of multi-drug resistant TB, which is difficult to treat with conventional drugs and contributes to the increased mortality. Besides, the adverse effects against epidemic TB are common and thus lead to the problem of nonadherence [2]. Although TB is treatable and preventable, developing nations are still suffering due to the limited resources and the ineffectiveness of first and second line anti-TB drugs [3]. Therefore, safer, inexpensive, and more efficacious new compounds possessing anti-TB activity are urgently needed.

The pyrrole alkaloids exhibit a wide spectrum of bioactivities [4]. Several pyrrole alkaloids, such as denigrins A–C [5], solsodomine A [6], banegasine [7], and celastramycin A [8], exhibit potent anti-TB activity [9]. Among these, denigrins A (**1**), B (**2**) and C (**3**; Fig. 1), isolated from the Indian marine sponge *Dendrilla nigra*, are potent inhibitors of *M. tuberculosis* (MIC of 16.0, 32.0, and 4.0 μg/mL respectively) [5]. Denigrin A (**1**) features the presence of a 3,4-diarylpyrrole structure, with C-3 and C-4 positions of the pyrrole occupied by *p*-hydroxyphenyl groups and C-2 and C-5 positions by imide carbonyls which is closely related to polycitrin A (**4**) isolated from an ascidian *Polycitor* sp. [10]. On the other hand, denigrin B (**2**) features an unusual, densely functionalized (*Z*)-γ-benzylidenelactam motif on one side of the 3,4-diarylpyrrole unit, reminiscent of the telomerase inhibitory secondary metabolite dictyodendrin E [11] (**5**). Although the precise amount of marine organisms used to isolate denigrins A (45 mg) and B (9 mg) was not disclosed [5], as many other marine natural products, denigrins also suffer from short and difficult supply of natural specimens. Furthermore, their total syntheses have not yet been reported to date. These facts as well as the unprecedented structural features of **2** prompted us to undertake the syntheses of denigrins A and B.

Arylated maleic anhydrides are precursors of several biologically important natural products and their artificial congeners [12]. The preparations of mono- and diarylated maleic anhydrides have been well documented in the literature [13]. Among them, the most efficient and direct approach to this class of compounds is the Mizoroki-Heck type arylation of maleic anhydride [14]. In 2006, Correia et al. first reported the Mizoroki-Heck arylation of maleic anhydride using aryldiazonium tetrafluoroborates with moderate to good yields [14a]. However, it has been well established that diaryliodonium salts are more favorable for the coupling of electron-rich aryl groups. Besides, diaryliodonium salts are air- and moisture-stable, easy-to-make compounds that have proved to be mild and non-toxic reagents. Indeed, diazonium and iodonium salts display some similarities in their behavior as outstanding electrophiles which make them highly complementary partners that could be judiciously selected according to the targeted coupling [15]. We therefore sought to suggest a new coupling partner, e.g. diaryliodonium tetrafluoroborate **10**, for our targets, based on the strategy shown in Scheme 1.

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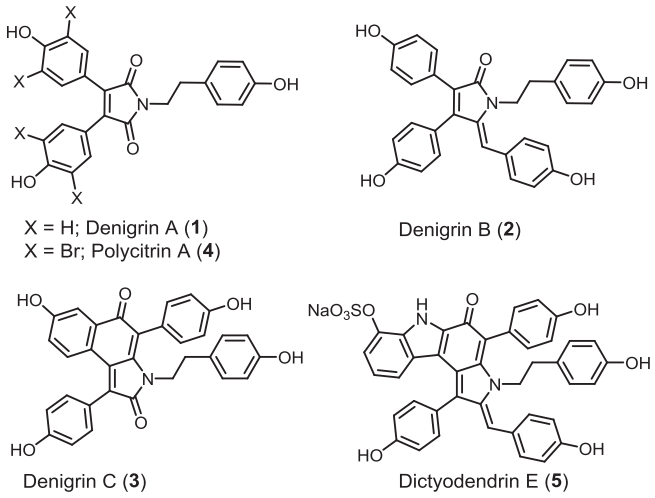
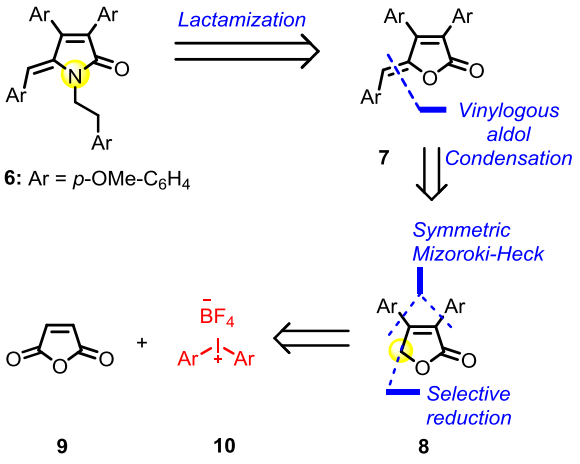


Fig. 1. Structures of denigrin A, B and C and related pyrrole alkaloids.

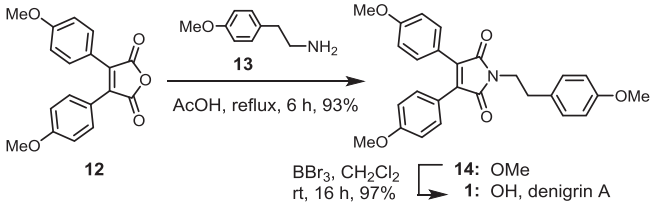


Scheme 1. Retrosynthetic analysis of denigrin B.

We considered that methyl-protected denigrin B (**6**) would be obtained from lactamization of **7**, whose benzylidene moiety can be installed via vinylogous aldol condensation, following to the selective reduction of the anhydride moiety. If the two aryl groups of **8** are envisaged to be introducible by Mizoroki-Heck reaction, our synthesis was retrosynthetically analyzed to start with maleic anhydride **9** and diaryliodonium tetrafluoroborate **10**. Herein, we report the successful implementation of this plan to the first syntheses of denigrins A and B.

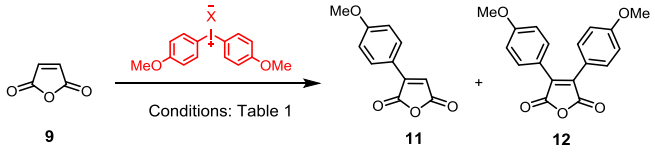
Our investigation began with the synthesis of 3,4-diaryl maleic anhydride **12**, which was previously reported via Mizoroki-Heck arylation of maleic anhydride using aryldiazonium tetrafluoroborate [14a]. We started evaluating the scope of this reaction by employing diaryliodonium salts as new coupling partners under various reaction parameters such as palladium sources, solvents, and bases (Table 1).

The reaction of the maleic anhydride and diaryliodonium tosylate, catalyzed by $Pd_2(dba)_3$/NaOAc, was found only modestly effective in providing the mixture of mono- and di-arylated products **11** and **12** (36%, entry 1). Changing the catalyst to $Pd(OAc)_2$ did not improve the yield although the diarylated product **12** was found as a major product (43%, entry 2). A slight improvement in the yield of desired product **12** was observed when diaryliodonium tetrafluoroborate was used under the catalysis of $Pd_2(dba)_3$/NaOAc (49%, entry 3). The use of $PdCl_2$/NaOAc (entry 4), other bases (e.g. NaOTs and Na_2CO_3) and solvents (e.g. DMF and MeOH) with $Pd(OAc)_2$ seems hopeless to the arylation of maleic anhydride (entries 7–10). Much to our delight, the best yield was achieved by $Pd(OAc)_2$/NaOAc in acetonitrile, i.e., only the diarylated compound **12** was formed as a sole detectable product in good yield (69%,



Scheme 2. Synthesis of denigrin A.

Table 1
Optimization of Mizoroki-Heck arylation of maleic anhydride with iodonium salts.[a]



Entry	X	Pd-source (equiv)	Base (equiv)	Solvent	Yield (10:11)[b]
1	OTs	$Pd_2(dba)_3$ (0.05)	NaOAc (4.0)	MeCN	36 (60:40)
2	OTs	$Pd(OAc)_2$ (0.05)	NaOAc (3.0)	MeCN	43 (10:90)
3	BF_4	$Pd_2(dba)_3$ (0.1)	NaOAc (3.0)	MeCN	49 (10:90)
4	BF_4	$PdCl_2$ (0.05)	NaOAc (3.0)	MeCN	Trace
5	BF_4	$Pd(OAc)_2$ (0.05)	NaOAc (4.0)	MeCN	69 (4:96)
6	BF_4[c]	$Pd(OAc)_2$ (0.05)	NaOAc (3.0)	MeCN	72 (84:16)
7	BF_4	$Pd(OAc)_2$ (0.05)	NaOTs (3.0)	MeCN	Trace
8	BF_4	$Pd(OAc)_2$ (0.05)	Na_2CO_3 (3.0)	MeCN	No reaction
9	BF_4	$Pd(OAc)_2$ (0.1)	NaOAc (3.0)	DMF	Trace
10	BF_4	$Pd(OAc)_2$ (0.05)	NaOAc (3.0)	MeOH	No reaction

[a] In all cases, 4.5 equiv of iodonium salts and 0.005 equiv of anisole were used and the reaction was conducted at 70 °C for 24 h.
[b] Isolated yield. The ratio of mono- and diarylated products was determined by ^1H NMR.
[c] The reaction was stopped after 3 h.