http://dx.doi.org/10.5012/bkcs.2013.34.2.357

A Concise and Rapid Approach to the Marine Natural Product Streptochlorin and its Analogues

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Received October 6, 2012, Accepted November 1, 2012

Key Words : Marine natural product, Streptochlorin, van Leusen's oxazole synthesis, Robinson-Gabriel cyclodehydration reaction, Regioselective chlorination

The rich chemical diversity of marine life is the inexhaustible source of drug pipeline.[1] Over the last few decades, great strides have been made in our understanding of marine natural products largely due to dramatic advances in the fields of analytical technology, spectroscopy, synthetic chemistry, and high-throughput screening. Nevertheless, it remains elusive how to secure a supply of rare marine natural products to ensure further study for their biomedical application. Consequently it was driven to develop innovative methods including aquaculture, semi-synthesis, and chemical synthesis to ameliorate the material supply problem. Although the chemical synthesis of natural products is still far from being a mature or applied science, it is an important and reliable tool to attain a target natural product and its analogues for further systematic investigation.

Streptochlorin is a small molecule that was first isolated in 1988 from the lipophilic extract of the mycelium of *Streptomyces* sp. as a new antibiotic (Figure 1).[2]

Compared to other natural products, streptochlorin is a simple molecule. In consequence, this feature can render easy access to diverse analogues by chemical synthesis. Other than the innate antibiotic effect of streptochlorin, it has been revealed that streptochlorin significantly inhibits the growth of cultured human cell lines,[3] suppresses angiogenesis *in vitro* by inhibition of NF-κB,[4] and induces apoptosis in human hepatocarcinoma cells through a reactive oxygen species (ROS)-mediated mitochondrial pathway as well.[5] In addition, a recent study noted that streptochlorin is one of the nine antibiotic substances which confer a potent antimicrobial defense for the wasp larvae that parallels the combination prophylaxis known from human medicine.[6]

Herein, we wish to present a preliminary account of our synthetic efforts toward the marine natural product streptochlorin and its analogues.

The synthesis of streptochlorin began with aldehyde **1a** which was easily prepared from the corresponding indole-3-carboxaldehyde (not shown) in quantitative yield.[7]

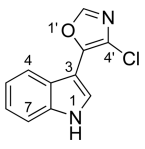
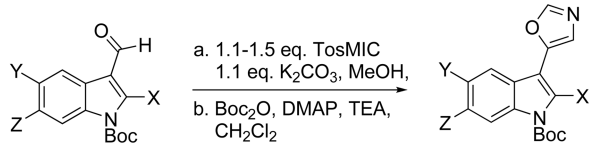


Figure 1. Structure of streptochlorin.

Subsequently aldehyde **1a** was reacted with tosylmethylisocyanide (TosMIC) in the presence of 1.1 eq. of K_2CO_3 in MeOH, namely, 'van Leusen's oxazole synthesis', to provide the desired oxazole compound (not shown) with the Boc protection group lost during this transformation.[8] To compensate the unwanted loss of a Boc protection group, it was reintroduced to the *N*-1 position to give compound **2a** in 11% yield (Scheme 1).

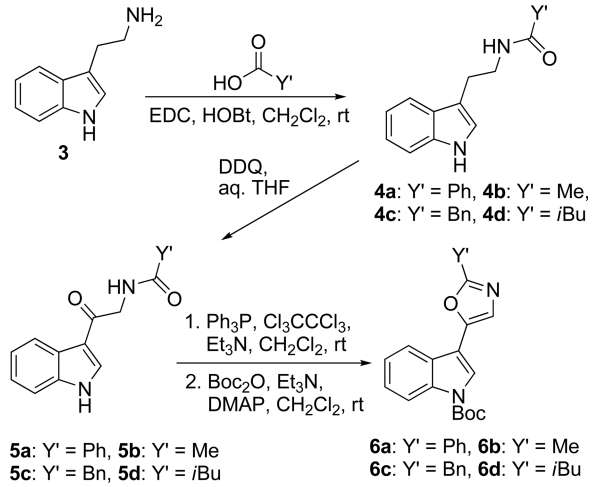
Having achieved the synthesis of the key intermediate **2a** on a comfortable scale, effectiveness of this synthetic sequence was evaluated by applying it to the synthesis of other analogues. Therefore compounds **2b** and **2c** which



1a: X = Y = Z = H
1b: X = Z = H, Y = F
1c: X = Ph, Y = Z = H

2a: X = Y = Z = H
2b: X = Z = H, Y = F
2c: X = Ph, Y = Z = H

Scheme 1. van Leusen's oxazole synthesis reaction of compound **1**.



5a: Y' = Ph, **5b**: Y' = Me
5c: Y' = Bn, **5d**: Y' = *i*Bu

6a: Y' = Ph, **6b**: Y' = Me
6c: Y' = Bn, **6d**: Y' = *i*Bu

Scheme 2. Analogue synthesis *via* Robinson-Gabriel cyclodehydration reaction.

have a substituent in the indole core structure were prepared from compounds **1b** and **1c** in 15-25% yields over 2 steps (Scheme 1).

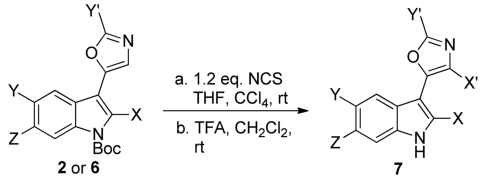
To further broaden the substrate scope, our attention turned to installing a substituent at the C2'-position of the oxazole ring. Wipf's variant of Robinson-Gabriel cyclodehydration reaction was employed as the key reaction, forming oxazole rings.[9]

Hence, amide coupling of tryptamine **3** with 1.1 eq. of benzoic acid (Y' = Ph) in the presence of EDC (1.1 eq.) and HOBt (1.1 eq.), afforded the corresponding amide **4a** in 83% yield.[10] Two-step consecutive reaction of **4a** with DDQ (2.3 eq.) in aqueous THF,[11,9b] followed by Wipf's variant of Robinson-Gabriel cyclodehydration smoothly transformed compound **4a** into the desired oxazole compound (not shown) in 81% overall yield. Then Boc protection of the *N*-1 position of the indole core provided compound **6a** in 87% yield. Instead of phenyl group at the C2'-position of the oxazole ring, other substituents including methyl, benzyl, and isobutyl group were introduced *via* the previously described synthetic sequence (Scheme 2).

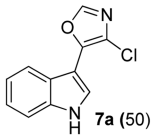
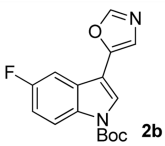
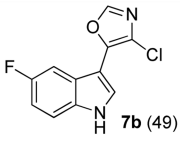
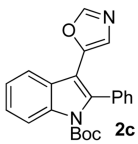
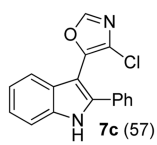
As a result, compounds **6b-6d** were prepared in yields of 11-26% over four steps, starting from the coupling reaction of tryptamine **3** with corresponding coupling counterparts such as acetic acid (Y' = Me), phenyl acetic acid (Y' = Bn), and isovaleric acid (Y' = *i*-Bu).

The completion of the synthesis was accomplished through the regioselective chlorination at the oxazole ring of compounds **2** and **6** using *N*-chlorosuccinimide (NCS) at room temperature, followed by deprotection of the Boc group (Table 1). For example, streptochlorin **7a** was obtained in 50% yield over two steps (entry 1, Table 1). Other analogues were prepared from the above described sequential reactions. Thus NCS-mediated chlorination of compounds **2**, **6** and the subsequent deprotection of the Boc group at the indole nucleus (not shown) gave the target compounds (**7b-7g**) in 47-79% yields (Table 1 and Table S2).

Table 1. Installation of functional groups to the oxazole ring



2 or **6** → **7**

Entry	Reactant	Product (% yield)[a]
1	 **2a**	 **7a** (50)
2	 **2b**	 **7b** (49)
3	 **2c**	 **7c** (57)

[a]Overall isolated yields.

In summary, we have demonstrated a straightforward and efficient synthesis of the marine natural product streptochlorin and its analogues, starting from either 3-formylindole **1** or tryptamine **3**. Notably, our synthesis features a construction of oxazole ring by van Leusen's oxazole synthesis and Wipf's variant of Robinson-Gabriel cyclodehydration reaction depending upon the substituent of the analogues (compounds **2** and **6**). Regioselective halogenation was realized using NCS to furnish compounds **7a-7g**.

In order to construct a streptochlorin-based, focused library and the screening for additional biological activities, we are now focusing on the further extension of the scope of the above described synthetic sequences and the evaluation for additional biological activities.

Acknowledgments. This work was partially supported by the KIOST (PE98833, PE98816, PE99161) and the Ministry of Land, Transport and Maritime Affairs (PM57120), Republic of Korea.

Supporting Information. Supplementary data associated with this article can be found, in the online version, at http://

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