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Synthesis of streptorubin B core

Meng-Yang Chang,[a,*] Chun-Li Pai[b] and Hua-Ping Chen[a]

[a]*Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan*
[b]*Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan*

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Abstract—A straightforward synthesis of streptorubin B core structure has been established starting from *trans*-4-hydroxyproline. The core structure of streptorubin B is constructed in an intramolecular ring-closing metathesis as the key step.

1. Introduction

In view of structural framework of *trans*-4-hydroxyproline (**1**), it possesses three functional groups that can be easily modified, including 1-amino, 2-carboxylate, and 4-hydroxy groups.[1] The skeleton represents the significant feature for producing a series of different carbon frameworks, such as monocycles (pyrrole,[2a] pyrrolidine,[2b,c,l] piperidine,[2d] and azanucleoside,[2e]) fused or bridged bicycles (pyrrolizidine[2f] or azabicycles[2g,h,m]) and polycycles[2i–k,n] etc., using an efficient modification. Recently, we introduced a facile and straightforward approach to the 7-azabicyclo[2.2.1]heptane skeleton[2m] and hexahydro-1*H*-indol-3-one skeleton[2n] ring system via an intramolecular basic alkylation and acidic aldol condensation of the 2-substituted pyrrolidin-4-one framework employing *trans*-4-hydroxyproline (**1**) as the starting material (Fig. 1).

To explore the synthetic application of our methodology, the synthetic study of streptorubin B (**2a**)[3] (butyl-*meta*-cycloheptylprodigiosin) was investigated. In the report, the synthetic study toward streptorubin B (**2a**) has been established by synthesizing core structure **3** (Fürstner's intermediate) from *trans*-4-hydroxyproline (**1**) as shown in Figure 2.

The naturally occurring prodigiosin alkaloids[4] with deeply red colored chromophore, belonging to a series of close relatives with the same prodiginine (pyrrolylpyrromethene) core, were produced by a restricted group of eubacteria and actinomycetes of *Serratia* and *Streptomyces*.[4c] In general, this alkaloid groups[5] possess identical structural features of 4-methoxy-2,2′-bipyrrole ring skeleton system except for different alkyl substitutents in the pyrrole ring C such as streptorubin B (**2a**), prodigiosin (**2b**), undecylprodigiosin (**2c**), nonylprodigiosin (**2d**), metacycloprodigiosin (**2e**), and butylcycloheptylprodiginine (**2f**). The related biochemical functions of the prodigiosin family have been investigated.[6] Roseophilin (**2g**) with a methoxyfuran motif was isolated by Seto in 1992 and it possesses a close structural relative to prodigiosin alkaloids.[7a] Due to its unique structural features and important biological activities, considerable attention is directed from synthetic chemists toward the synthesis of these alkaloids.[8] Rapoport and Holden,[5a] Wasserman et al.,[5c] Boger and Patel,[9a] Fürstner and Krause,[9b] D'Alessio et al.,[7b,c] Fuchs and co-workers,[9c] and Trost and Doherty[9d] have used various key steps,

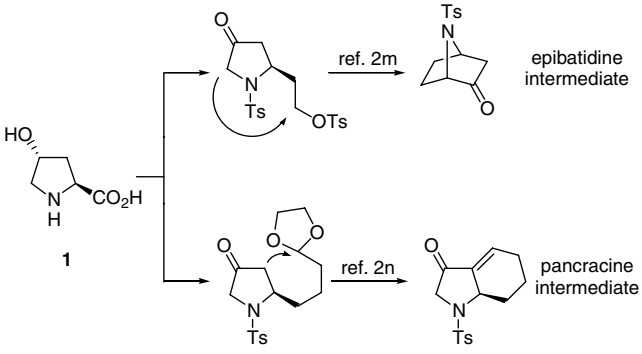

Figure 1. The previous synthetic approaches toward intermediate of epibatidine and pancracine from *trans*-4-hydroxyproline (**1**).

Keywords: Streptorubin B; *trans*-4-Hydroxyproline; Ring-closing metathesis.
* Corresponding author. Tel.: +886 7 5919464; fax: +886 7 5919348; e-mail: mychang@nuk.edu.tw

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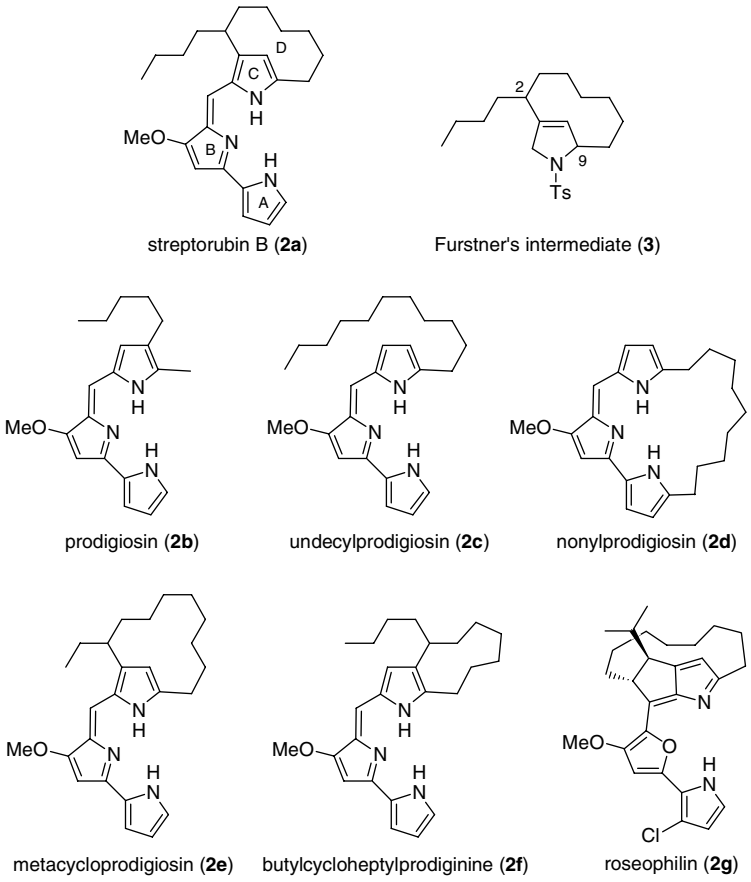


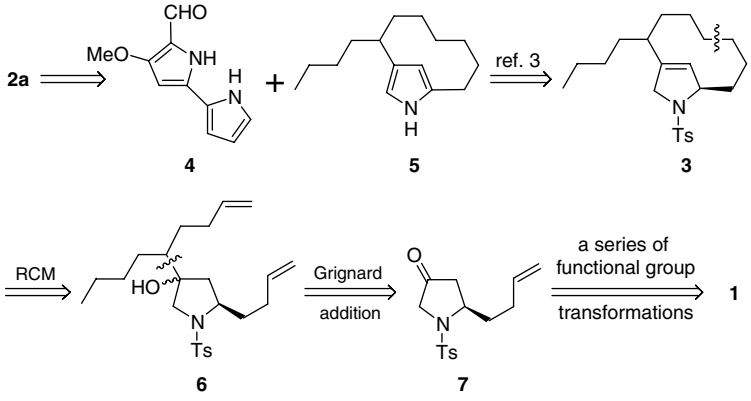
Figure 2. Structural characteristics of streptorubin B (**2a**), Fürstner's intermediate **3**, and their related prodigiosin-group natural products **2b–g**.

for example, Paal–Knorr cyclization and intramolecular diene or enyne ring-closing metathesis, in their respective elaborations of different prodigiosin alkaloids analogs.

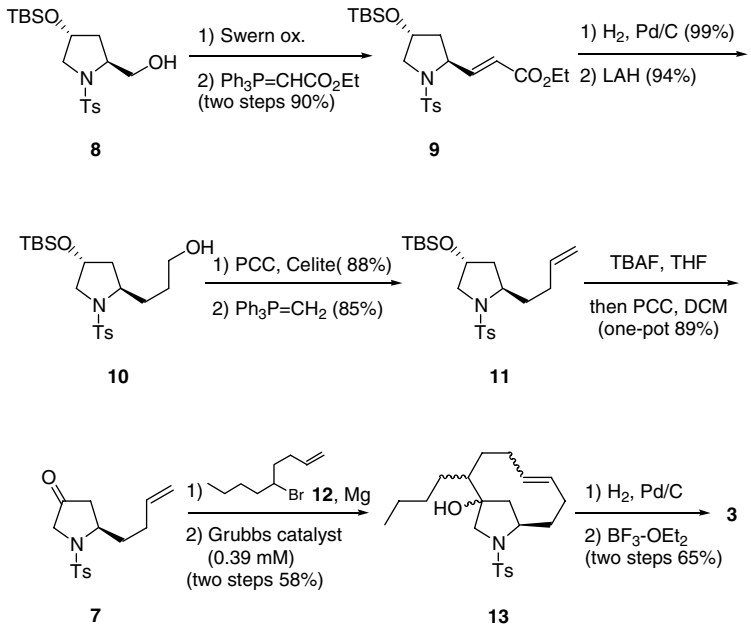
To date, there are few reports for the synthesis of streptorubin B citations. Recently, Fürstner et al. reported the related synthesis of streptorubin B using the intramolecular platinum-catalyzed enyne metathesis and base-induced aromatization as key steps.[3] This nine-steps sequence delivered streptorubin B core structure in 16% overall yield.

2. Results and discussion

The retrosynthetic approach is shown in Scheme 1. Streptorubin B (**2a**) with prodiginine framework is easily formed by acid-catalyzed condensations[8] of the known bipyrrole aldehyde **4** with a bicyclic pyrrole segment **5**. Therefore, the preparation of the core structure constitutes the prime challenge. We envisioned the streptorubin B core structure **3** could be achieved via a series of functional group transformation to 2-substituted pyrrolidin-4-one **7** from *trans*-4-hydroxyproline (**1**), Grignard addition of ketone **7**, intramolecular ring-closing



Scheme 1. Retrosynthetic analysis of streptorubin B (**2a**).



Scheme 2. Synthesis of streptorubin B core structure (Fürstner's intermediate **3**).

metathesis reaction of diene **6**, and followed by hydrogenation and dehydration.

We first studied the approach to streptorubin B core structure **3** from prolinol **8** as shown in Scheme 2. Synthesis of prolinol **8** contains the following four-step reactions from *trans*-4-hydroxyproline (**1**): (i) esterification with thionyl chloride and methanol, (ii) tosylation with *p*-toluenesulfonyl chloride and triethylamine, (iii) silylation with *tert*-butyldimethylsilyl chloride and imidazole, and (iv) reduction of the resulting ester with sodium borohydride in the presence of lithium chloride. Thus, prolinol **8** was given in 90% overall yield with only once purification.[2m,n]

Prolinol **8** was transformed into α,β-unsaturated ethyl ester **9** by Swern oxidation and Wittig olefination under the standard conditions. Compound **10** was hydrogenated with hydrogen and a catalytic amount of 10% palladium on activated carbon followed by reduction of the resulting ester with lithium aluminum hydride. Alcohol **10** was transformed to olefin **11** by oxidation with pyridinium chlorochromate and olefination with *n*-butyllithium and methyltriphenylphosphonium iodide. The overall yield of the easy six-step approach was approximately provided 62%. For shortening the synthesis of olefin **11**, two-step synthetic route[10] of O-tosylation and allyl group elongation was also studied. The poor yield (<30%) was provided in our case. Although the synthetic efficiency is decreased, we believe the rather lengthy six-step route with good yield will be valuable to report. To synthesize ketone **7** easily, compound **11** was desilylated with tetra-*n*-butylammonium fluoride in tetrahydrofuran followed by oxidation with pyridinium chlorochromate in dichloromethane in one-pot conditions.

Grignard addition of ketone **11** with 1-nonenyl-5-magnesium bromide gave diene **6** as the mixture product. Bromide **12** was prepared from Grignard addition of valeraldehyde with the freshly prepared 1-butenyl-4-magnesium bromide followed by bromination of the corresponding secondary alcohol with carbon tetrabromide and triphenylphosphine in overall 75% yield. With diene **6** in hand, we turn the attentions to build up the bicyclic pyrrolophane skeleton **13** via intramolecular ring-closing metathesis reaction. The reaction has been established as a powerful method for the elaboration of medium-sized rings, including carbohydrates, heterocycles, and alkaloids.[11,12] When diene **6** was subjected to a ring-closing metathesis reaction employing the first generation Grubbs catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$], the expected macrocyclic skeleton **13** was generated in trace yield (<5%).

We next turn our focus to examine the second generation Grubbs catalyst with higher thermal stability and lower sensitivity to double bond migration.[11c] Following a similar approach, attempts to form compound **13** using second generation Grubbs catalyst under a variety of conditions (prolonged reaction time, elevated temperature, different solvents) were unsuccessful. Finally, the product **13** was obtained in 58% yield in the diluted solution (0.39 mM). In order to simplify the complexity of bicyclic skeleton, product **13** was further transformed to known Fürstner's intermediate **3** by hydrogenation with 10% palladium on activated carbon followed by dehydration of the resulting compound with boron triflouride etherate.

The major signal peaks in ^{1}H NMR spectral data of compound **3** were in accordance with those reported in the literature.[3] In our technology, we cannot separate the diastereomers **3** with a pair of (2*S*,9*R*) and (2*R*,9*R*) chiral centers such that correct stereochemistry of major product cannot be addressed. According to the report,[3] the related stereochemistry

of diastereomers **3** is not an important factor to yield a sole compound **5** in the following base-induced aromatization for the synthesis of the streptorubin B (**2a**).

3. Conclusion

In summary, we have developed a straightforward approach to the bicyclic pyrrolophane skeleton ring system based on the intramolecular ring-closing metathesis reaction as the key step and applied this route to synthesize Fürstner's intermediate **3** toward the study of streptorubin B (**2a**). For the application and investigation of *trans*-4-hydroxyproline (**1**), synthetic study toward macrocyclic framework has not been reported in the literature. In the objective of our paper, a novel approach for synthesis of streptorubin B core structure based on the *trans*-4-hydroxyproline (**1**) has been explored. We are currently studying the scope of this process as well as additional applications of this approach to the synthesis of various potential biological activity compounds using *trans*-4-hydroxyproline (**1**) as the starting material.

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Supplementary data

Experimental procedures and photocopies of ^{1}H and ^{13}C NMR ($CDCl_3$) spectral data were supported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.024.

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