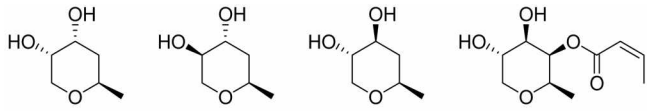
Synthesis of Ophiocerin A and B

Dong-Min Lee and Han-Young Kang*

Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea
**E-mail: hykang@chungbuk.ac.kr*
Received July 7, 2008

Key Words : Tetrahydropyran, Total synthesis, Carbohydrate, Ophiocerin, Natural products

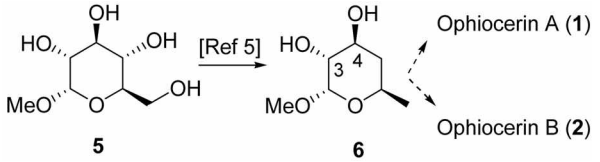
Ophiocerins represents a series of compounds isolated from the fermentation cultures of fresh water fungi *Ophioceras venezuelense* (Figure 1).[1] Due to the interesting array of substituents on the tetrahydropyran rings,[2] Yadav and co-workers studied the synthesis of ophicerin B (**2**) and C (**3**). They used asymmetric dihydroxylation for introducing the required diol stereochemistry.[3]



Ophiocerin A (**1**) Ophiocerin B (**2**) Ophiocerin C (**3**) Ophiocerin D (**4**)

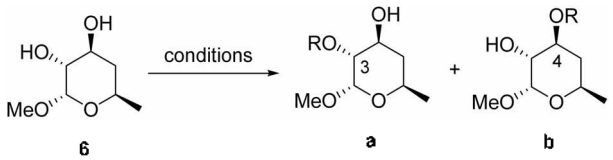
Figure 1. Ophiocerins isolated from cultures of aquatic fungus *Ophioceras venezuelenes*.

We also reported a carbohydrate-based approach to the total synthesis of ophiocerin C (**3**).[4] The commercially available methyl α-D-glucopyranoside (**5**) was converted to the key intermediate **6**, which was then transformed to the target compound **3**. The successful synthesis of ophiocerin C led us to investigate the total synthesis of other ophiocerins. We, herein, report the synthesis of ophiocerin A (**1**) and B (**2**).



First, we investigated the synthesis of ophiocerin B (**2**). Diol **6** was prepared from α-D-glucopyranoside (**5**) by a three-step sequence.[5] Conditions were tested to give rise to the derivatives of **6** with the regioselective protection of its hydroxy groups. The results are summarized in Table 1.

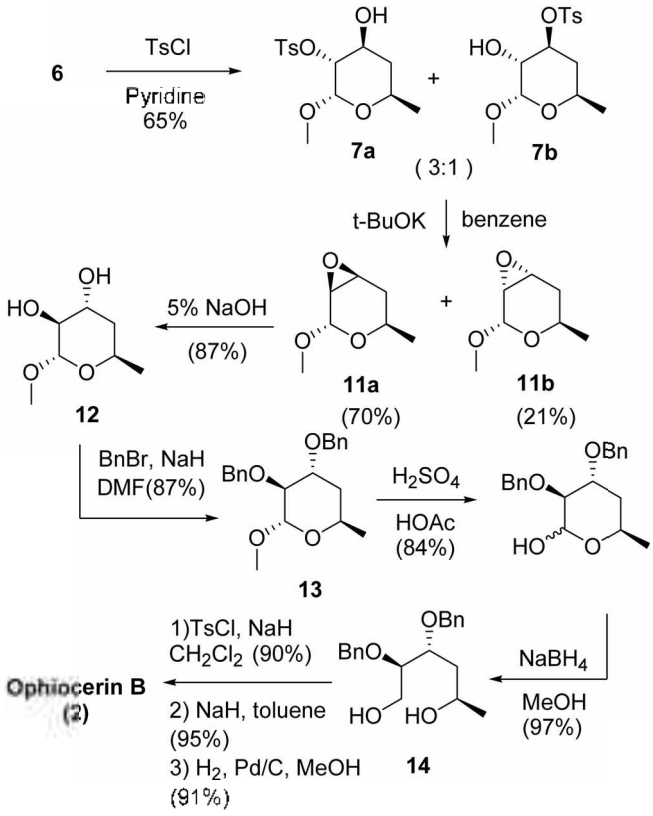
Table 1. Differentiation of the two hydroxy groups



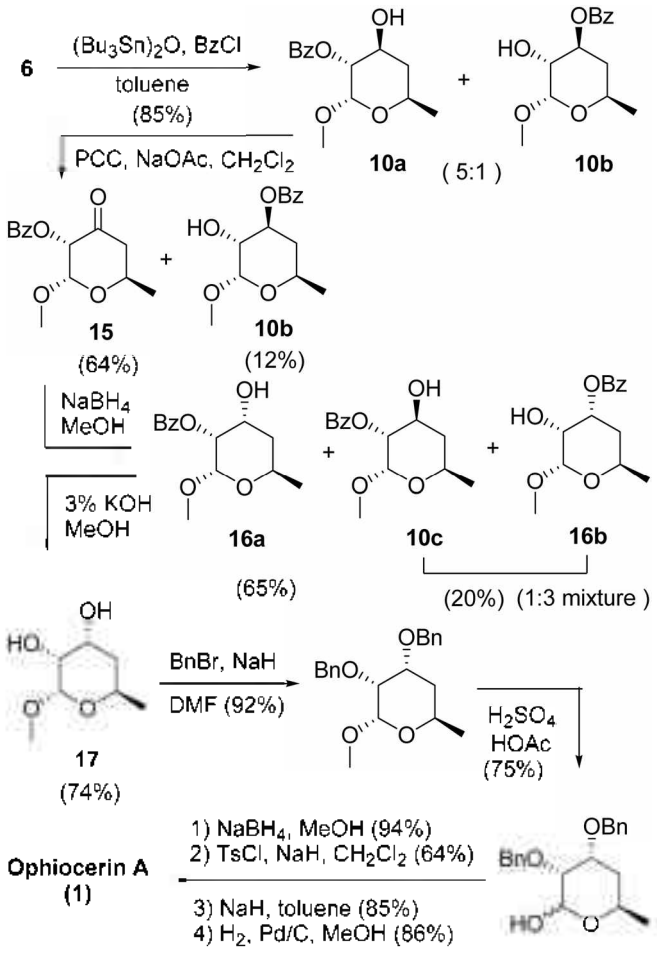
Entry	R	Conditions	Product Ratio (**a**:**b**)
1	Ts	TsCl, Py	**7a**:**7b** = 3:1
2	TBS	TBSCl, Imidazole, DMF	**8a**:**8b** = 1:3
3	Bn	$(Bu_3Sn)_2O$, BnBr	**9a**:**9b** = 3:2
4	Bz	$(Bu_3Sn)_2O$, BzCl	**10a**:**10b** = 5:1

Tosylation of the diol **6** was performed to offer a mixture of 3-tosyloxy product **7a** and 4-tosyloxy product **7b** with a ratio of 3:1 favoring the 3-tosyloxy product **7a** (entry 1). When the bulkier and more stable TBS group was introduced (TBSCl, Imidazole), the corresponding 3- and the 4-protected products were formed with a ratio of 1:3 (entry 2). Since the benzyl was an effective protecting group in our previous synthesis of ophiocerin C, we also sought for the conditions for introducing benzyl groups. Protection with benzyl groups was achieved with benzyl bromide in the presence of $(Bu_3Sn)_2O$.[6] The 3- and the 4-benzyloxy products were formed with relatively poor selectivity (3:2, entry 3). Fortunately, we found that the protection was achieved in a better ratio with benzoyl chloride (5:1, entry 4). With the methods of differentiating hydroxy groups in hand, synthesis of ophiocerin A and B were performed.

The successful synthetic route to the synthesis of ophiocerin B is summarized in Scheme 1. Tosylation (TsCl,



Scheme 1. Synthesis of ophiocerin B (**2**).



Scheme 2. Synthesis of Ophiocerin A (**1**).

Pyridine) gave the regioisomers **7a** and **7b** as a 3:1 mixture, which were, without separation, transformed to the corresponding epoxides **11a** and **11b** by treating with *t*-BuOK. Two isomeric epoxides **11a** and **11b** were obtained in 70 and 21% yield, respectively. After separation, the major epoxide **11a** was subjected to the opening with nucleophiles. Benzyloxide attack (NaOBn, THF) gave the ring-opened product successfully, albeit in poor yield (23%). Alteration of the solvents did not provide any improvement (CH_3CN, DMF, or 1,4-dioxane). Literature survey showed that use of HMPA as a solvent gave a better result.[7] In fact, nucleophilic opening with NaOBz in HMPA proved to be more efficient although it gave the product in still unsatisfactory yield (69%). We also found that NaOBn in HMPA provided a higher yield of the desired ring-opened product (82%). Reluctance to employ HMPA as a solvent due to toxicity led us to find eventually a better condition, that is, nucleophilic opening with 5% aqueous NaOH.[8] Opening with NaOH provided the intermediate **12** with the desired diol stereochemistry in good yield. The diols were, then, protected with benzyl groups (BnBr, NaH) in 87% yield. Cleavage of the methyl group (H_2SO_4, HOAc) followed by $NaBH_4$ reduction provided the ring-opened product **14**. Selective tosylation and subsequent base treatement followed by the debenzylation (H_2, Pd/C) offered ophiocerin B (**2**) which showed the identical spectral properties to those reported in the literature.[1]

We next turned our attention to the synthesis of ophiocerin A (**1**). Our synthetic scheme for the preparation of ophiocerin A is shown in Scheme 2. Treatment of the key starting material **6** with benzoyl chloride in the presence of $(Bu_3Sn)_2O$ led to a regioselective benzoylation (Table 1, entry 4). We successfully obtained the regioisomeric benzoylated alcohol **10a** and **10b** as a mixture of a 5:1 ratio. Without separation the mixture, it was oxidized with PCC to give ketone **15** in 64% of an isolated yield with **10b** unreacted (12%). After separation of ketone **15** a stereoselective reduction was achieved with $NaBH_4$. Thus, the alcohol **16a** with the desired stereochemistry at C-4 was obtained as a major isomer (65%). Besides, we were able to isolate a mixture of two diasteromeric alcohols (in a ratio of 1:3), which were identified as **10c** and **16b** (20% of a combined yield). Formation of **16b** was caused by an acyl group migration during the reduction of **15**. This is not surprising since this acyl group migration is well-known for 6-membered cyclic diols. Alcohol **16a** was, then, converted to diol **17** by hydrolysis (KOH, MeOH).[9] The diol **17** had a correct diol stereochemistry for ophiocerin A. After protecting the diol with benzyl groups, the stage was set for the final synthetic conversion steps to ophiocerin A. By adopting the identical synthetic sequences as used in the synthesis of other ophiocerins, ophiocerin A was completed successfully. The spectroscopic data are consistent with those reported in the literature.[1]

As a summary, ophiocerin A (**1**) and B (**2**) were successfully synthesized via a carbohydrate-based approach starting from methyl α-D-glucopyranoside (**5**). These synthetic routes have been useful for synthesizing ophiocerins and will be of importance for preparing other natural products containing substituted tetrahydropyranes.

Acknowledgments. This work was supported by the research grant of Chungbuk National University in 2006.

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