

Communications

Synthesis of Ophiocerin C

Dong-Min Lee, Heesoon Lee,[†] and Han-Young Kang*

Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea

*E-mail: hykang@chungbuk.ac.kr

[†]College of Pharmacy, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea

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Recently, Gloer group isolated several natural products from the solid-substrate fermentation cultures of fresh water fungi *O. venezuelense*.¹ Investigation of the ethyl acetate-extract exhibiting modest activity against *Candida albicans* led to the isolation of the compounds containing the tetrahydropyran core as shown in the following (Figure 1).

Because there exist numerous biologically active natural products that have the substituted tetrahydropyrans and related structures,^{2,3} we decided to study the synthesis of these ophiocerins. The first and only total synthesis of ophiocerin B and C has been reported by Yadav group.⁴ They utilized the Sharpless asymmetric dihydroxylation as a key reaction to establish the diol stereochemistry.

We have been intrigued in ophiocerins due to the interesting array of substituents on the tetrahydropyran ring. Synthesis of these natural products would lead us to establish the routes to many natural products with substituted tetrahydropyran rings. We, therefore, decided to investigate an efficient and practical synthetic route to ophiocerin C starting from the easily available materials. We, herein, report an efficient carbohydrate-based approach to ophiocerin C. Retrosynthetic analysis of ophiocerin C is shown in Scheme 1.

Ophiocerin C could be envisioned to be synthesized from the key intermediate **7** which, in turn, could be easily synthesized from methyl α -D-glucopyranoside (**5**). Synthesis of **7** can be easily achieved by adopting the known transformations of the commercially available methyl α -D-

glucopyranoside (**5**) (Scheme 2).

A known reaction sequence was successfully applied for the conversion of two hydroxy groups to chlorides (reaction of **5** with SO₂Cl₂ followed by the treatment with NaI in MeOH).⁵ Two steps proceeded easily to offer **6** in 98% yield. Dechlorination was performed via a radical process (nBu₃SnH, AIBN, toluene) to provide **7** in reasonable yield (70%).⁶ Two hydroxy groups in diol **7** were successfully protected with benzyl groups (BnBr, NaH, DMF) in excellent yield (98%).

Elimination of the methoxy group at the anomeric position was required for the next synthetic sequences to achieve the synthesis of ophiocerin C. Our synthetic attempt is summarized in Scheme 3.

Dibenzyl-protected compound **8** was subjected to an acidic condition in the presence of acetic anhydride to achieve the conversion of the methoxy group (OMe) at the anomeric position to an acetoxy group (OAc). We realized that in addition to the conversion of the anomeric OMe group, one of the benzyl group was also transformed to an acetyl group.^{7,8} Hydrolysis of the diacetate compound **9** offered **10** which was subjected to reduction (NaBH₄) to give **11**. Selective tosylation of the primary hydroxyl group was successfully conducted (TsCl, Et₃N). Cyclization to the tetrahydropyran ring was examined by treating with NaH.

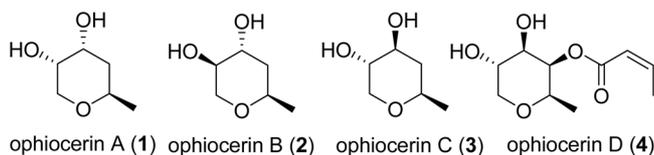
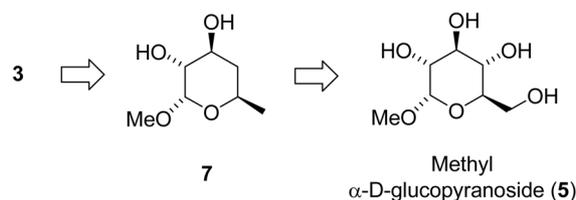
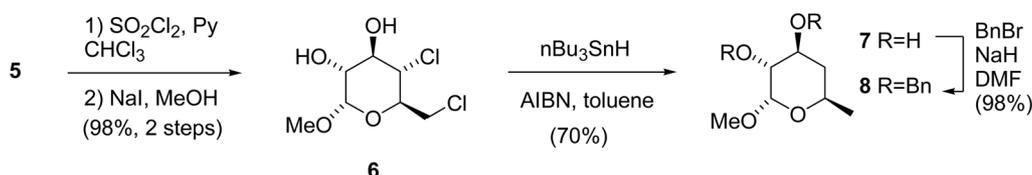


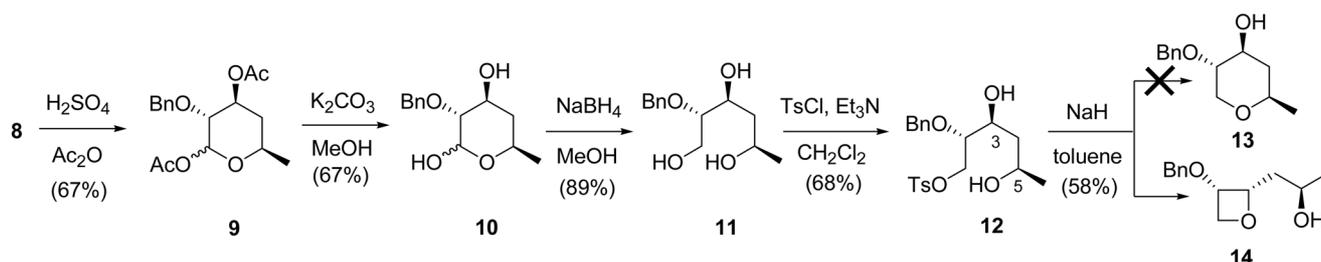
Figure 1. Ophiocerins.



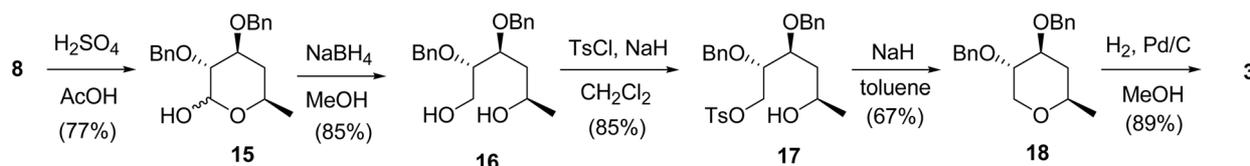
Scheme 1. Retrosynthetic analysis of ophiocerin C (**3**).



Scheme 2. Synthesis of the key intermediate **7**.



Scheme 3. Attempt to eliminate the methoxy group at the anomeric position.



Scheme 4. Total synthesis of ophiocerin C.

Unfortunately, according to ^1H and ^{13}C NMR analyses, the product was not identified as the anticipated tetrahydropyran **13**. The product was believed to be a four-membered cyclic ether, that is, compound **14** which could be formed by an attack of the oxygen atom of the C-3 hydroxy group instead of the C-5 hydroxy group.

To circumvent the undesired cyclization we decided to adopt the reaction condition for eliminating OMe group without causing the unnecessary removal of the benzyl group. The right condition for the selective removal of methyl group eventually led to the total synthesis of ophiocerin C as summarized in Scheme 4.

We found that use of acetic acid and 3 M H_2SO_4 (2 eq) successfully eliminate the methyl group in **8** to give compound **15** (1:1 anomeric mixture).^{8,9} Reduction with NaBH_4 generated the diol **16** which was subjected to monotosylation to produce **17**. Tosylation was too slow when triethylamine was used as a base. Stronger base (NaH) was needed to achieve a successful selective tosylation of the primary hydroxy group.¹⁰ Thus, tetrahydropyran **18** with the correct stereochemistry at the carbons bearing hydroxy groups was prepared by cyclization with NaH . Finally, removal of the benzyl group (H_2 , Pd/C) completed the total synthesis of ophiocerin C. The synthetic ophiocerin C showed identical spectroscopic properties with those reported in the literature.¹

In conclusion, we have successfully attained a total synthesis of a tetrahydropyran-containing natural product, ophiocerin C. The synthesis was conducted in 9 steps with a total of 22% yield starting from the readily available methyl α -D-glucopyranoside (**5**). This successful synthetic route could be easily expanded and applied to the synthesis of other structurally related natural products.

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- Procedure for the preparation of **9** and **15**: **Compound (9)**. Compound **8** (550 mg, 1.47 mmol) was suspended in Ac_2O (5 mL) and stirred under nitrogen at 0°C . Ac_2O solution (0.5 mL) of concentrated H_2SO_4 (5 drops in 0.7 mL of Ac_2O) was added, and the cooling bath was removed. Stirring was continued until completion of the reaction (0.5~1 h), after which the reaction was quenched with solid anhydrous NaHCO_3 (0.2 g). The mixture was stirred for 10 min at 25°C . Then, the mixture was diluted with ether (80 mL) and saturated aqueous NaHCO_3 solution (150 mL). After the bubbling ceased, the organic phase was separated and the aqueous layer was reextracted with ether (50 mL). The combined ethereal solution was washed with H_2O (25 mL) and brine (25 mL), dried (MgSO_4), and concentrated. Purification by flash column chromatography (20-50% ether in petroleum ether) provided the desired compound **9** (320 mg, 67%, 3:1 anomeric mixture) as a crystalline solid: mp $75\text{--}77^\circ\text{C}$. **Compound (15)**. Compound **8** (3.6 g, 10.5 mmol) are dissolved in acetic acid (15 mL) and H_2SO_4 (3 M, 7 mL) and stirred at 85°C for 4.5 h. Then cold H_2O (20 mL) and toluene (20 mL) are added. The aqueous phase is extracted with toluene (3×30 mL). The combined organic phases are washed with saturated aqueous NaCl solution, dried (MgSO_4), and concentrated. Purification of the residue by flash chromatography (hexane:EtOAc = 5:1) to yield the desired compound **15** (2.65 g, 77%, 1:1 anomeric mixture) as a colorless syrup.
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