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Synthesis of Ophiocerins from Non-Carbohydrate Sources†

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Ophiocerins are comprised of four compounds isolated from the aqueous fungi *Ophioceras venezuelense*, each bearing a tetrahydropyran ring with an interesting array of substituents (Figure 1).[1] Since substituted tetrahydropyran rings are found in many biologically important natural products,[2] ophiocerins have attracted the attention of synthetic chemists. The Yadav group recently reported the synthesis of ophiocerin B (**2**) and C (**3**),[3] whereby asymmetric hydroxylation was used as a key reaction to install the requisite stereochemical centers. Recently, the synthesis of ophiocerin D (**4**) was also reported by Sharma and Damera.[4] They employed xylose as a starting material and relied on asymmetric hydroxylation as a key transformation.

We have been interested in the total synthesis of these compounds. Synthesis of all four ophiocerins has been reported. We have used carbohydrates as starting materials.[5] Although use of carbohydrates to install the required stereocenters is a relatively effective strategy, better, more efficient, and unified synthetic pathways to these ophiocerins could be devised if starting materials other than carbohydrates, with set stereochemical centers, were utilized. Since carbohydrate-based approaches must include the destruction or conversion of unnecessary or incorrect stereocenters, more direct synthetic routes were sought out in which ophiocerins could be secured by creating the required stereochemistry after synthesizing the tetrahydropyran ring.

The general synthetic strategy presented herein is shown in the following retrosynthetic analysis (Scheme 1). The ophiocerins could be derived from dihydropyran derivative **5**, which in turn could be prepared from acyclic diene **6**. This strategy could be, in theory, applied to the syntheses of all ophiocerins.

First, the synthesis of ophiocerin D (**4**) that required **6b** as a synthetic intermediate was investigated. The synthetic scheme for the synthesis of ophiocerin D (**4**) is shown in Scheme 2.

The required intermediate **6b** was prepared in two steps from commercially available (*R*)-(+)-methyl lactate according to the reported literature procedure.[6] Intermediate **6b** was obtained as an inseparable mixture (~2.5:1 mixture of stereochemical isomers at C-3). The mixture was subjected to protection (BzCl, DMAP, Et_3N, CH_2Cl_2) to obtain **7** as a mixture. Ring closing metathesis (RCM) was used for preparing dihydropyran derivative **8**, which proceeded in good yield with Grubbs I catalyst. At this stage, the isomers were separated from the mixture and desired isomer **8a** was obtained in 66% yield. Epoxidation was achieved with mCPBA to give a mixture of **9a** and **9b** in 55 and 26% yields, respectively. Opening of the epoxides to install the required stereocenters was the next step. An attempt to open epoxide **9a** with 5% NaOH resulted in hydrolysis of the benzoyl group. Use of an ion exchange resin (Amberlite IR-120) successfully led to opening of the epoxide to provide **10**, the desired product (62%), along with the undesired isomer **11** (17%).[7] The other epoxide **9b** also gave the desired product **10**, albeit in lower selectivity. The benzoyl-protected triol **10** was the intermediate used in the total synthesis of ophiocerin D (**4**) previously, therefore this synthesis comprised a formal synthesis of ophiocerin D (**4**).[8]

After completion of the formal synthesis of ophiocerin D (**4**) from a non-carbohydrate source, attention was directed towards synthesizing other ophiocerins. We thought that other ophiocerins could be obtained from intermediate **5a**, which could be, in turn, derived from **6a** by RCM. The actual starting material was (*R*)-(-)-4-penten-2-ol. We were concerned that the syn-

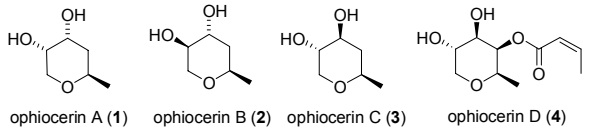
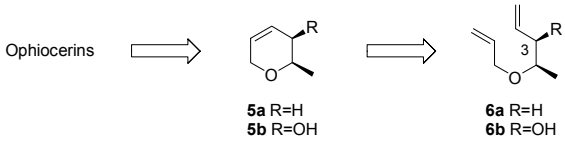
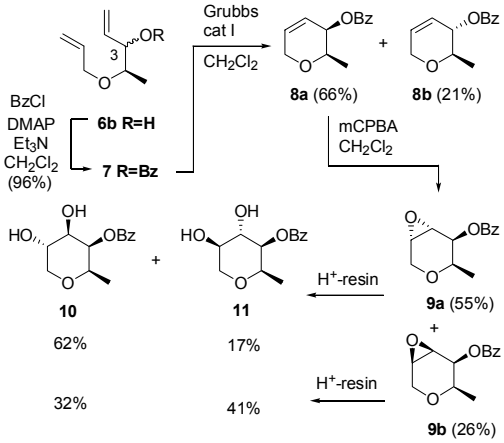


Figure 1. Ophiocerins.

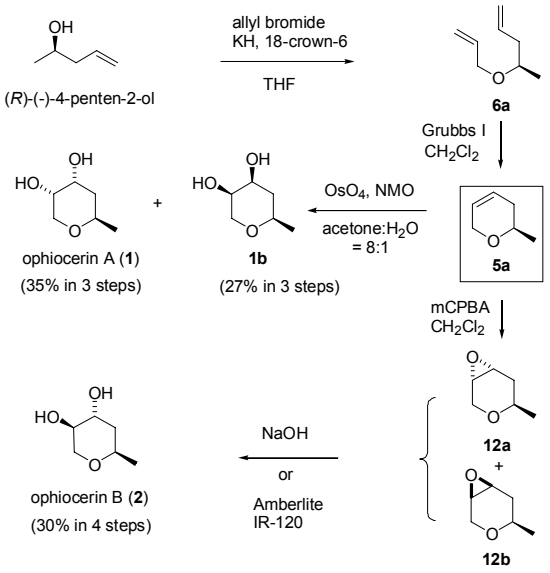


Scheme 1. Retrosynthesis of ophiocerins

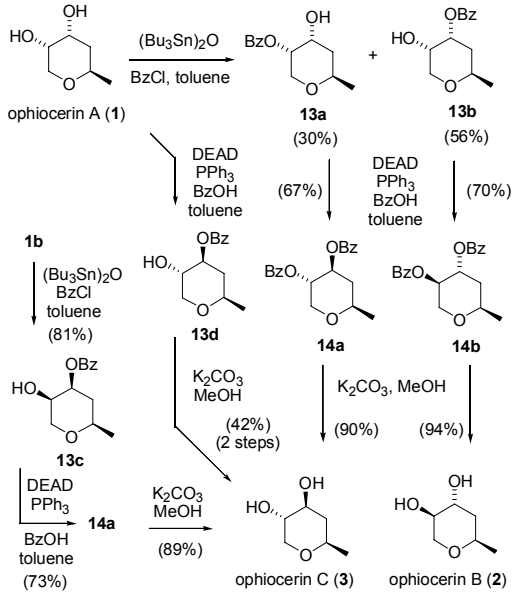


Scheme 2. Synthesis of the intermediate **10** for ophiocerin D

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.



Scheme 3. Synthesis of ophiocerin A and B



Scheme 4. Synthesis of ophiocerin C

thesis might suffer from low yield due to the volatility of the intermediates. To overcome this handling problem caused by volatility of the intermediates, we avoided complete concentration of the product mixture by removing solvents under vacuum until we reached the synthetic step in which the intermediates involved became relatively less volatile. Synthesis of ophiocerin A (**1**) was easily accomplished as shown in Scheme 3. The (*R*)-(-)-4-penten-2-ol was treated with allyl bromide in the presence of KH with 18-crown-6 to provide allylated product **6a**. After separation by chromatography, it was subjected to RCM with Grubbs catalyst I. After the RCM reaction, some of the solvent was removed and product **5a** was dihydroxylated (OsO_4, NMO). The desired ophiocerin A (**1**) was thus obtained in three steps (35% overall yield, unoptimized) from (*R*)-(-)-4-penten-2-ol. The other dihydroxylated isomer **1b** was also obtained in 27% yield.

A similar synthetic procedure was applied to the synthesis of ophiocerin B (**2**), as summarized in Scheme 3. After **5a** was obtained, it was subjected to epoxidation using mCPBA to give a mixture of epoxides (**12a** and **12b**). Opening of both epoxides (**12a** and **12b**) with NaOH (5%) provided the identical product, ophiocerin B (**2**). With Amberlite resin (IR-120), both of the epoxides also gave ophiocerin B (**2**). During the first three steps, only the allylated product was separated by chromatography. Epoxides **12a** and **12b** did not require separation as both compounds offered ophiocerin B (**2**).

Synthesis of ophiocerin C (**3**), summarized in Scheme 4, was achieved using ophiocerin A (**1**) as a starting material. Benzoylation provided a mixture of monobenzoylated products (~ 1:2 mixture of **13a** and **13b**). The major product **13b** was transformed to ophiocerin B (**2**) by a two-step procedure, that is, the Mitsunobu reaction to invert the stereochemistry of the carbon bearing unprotected hydroxy group followed by hydrolysis (K_2CO_3, MeOH). We were also able to convert the minor product **13a** to ophiocerin C (**3**) *via* the same two-step procedure. When we started from **1b**, benzoylation ($(Bu_3Sn)_2O$, BzCl) proceeded regioselectively to form **13c** as a single isomer. The Mitsunobu reation and basic hydrolysis provided ophiocerin C (**3**). We also examined the possibility of converting ophiocerin A (**1**) to ophiocerin C (**3**) in shorter steps. Thus, a direct Mitsunobu reaction on ophiocerin A (**1**) was attempted for a selective benzoylation with inversion. However, purification of **13d** was unfortunately problematic. We were able to isolate the desired ophiocerin C (**3**) only after basic hydrolysis of the mixture, albeit in rather low yield (42% in two steps, unoptimized).

In summary, direct and unified synthetic routes to ophiocerin A, B, C, and D have been successfully developed. These syntheses are based on ring-closing metathesis and non-carbohydrate starting materials and are simpler and more efficient than the previous syntheses, as demonstrated in the case of ophiocerin B (**2**) (eleven steps from methyl α-D-glucopyranoside *vs.* four steps from 4-penten-2-ol) and ophiocerin A (**1**) (twelve steps from methyl α-D-glucopyranoside *vs.* three steps from 4-penten-2-ol). These routes will be useful for the practical synthesis of related natural products.

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8. The spectral and physical properties of **12** were identical to the intermediate prepared in the our previous synthesis of ophiocerin D.[5c]