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A carbohydrate-based approach for the total synthesis of sawaranospirolide C

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ABSTRACT

A diastereoselective carbohydrate-based synthesis of the oxaspirolactone sawaranospirolide C was accomplished by utilizing one-pot cascade of acetonide deprotection/hemiacetal formation/spirolactonization as the key step.

Introduction

The family of sawaranospirolides A-D (1–4) has been isolated by Hasegawa et al. from the heartwood of the Japanese '*Sawara*' tree *Chamaecyparis pisifera* [1,2]. The structure and relative stereochemistry of sawaranospirolides were established based on extensive spectroscopic analysis and the absolute configuration was further confirmed by chemical conversion and degradation. Architecturally, sawaranospirolides family possess unique [6,5]-oxaspirolactone skeleton bearing a highly oxygenated tetrahydropyran ring system and a γ-butyrolactone. These naturally occurring oxaspirolactones [3] contain five contiguous stereogenic centers at C3-C7 and are epimeric with one another at C-3 or C-5.

In 2010, the first synthesis of *ent*-sawaranospirolides C and D was completed by Robertson and co-workers [4]. The absolute configurations were also confirmed by the synthesis and illustrated in Figure 1. The utilization of m-CPBA mediated oxidative spirolactonization enable the successful [6,5]-oxaspirolactone formation and guarantee the total synthesis of *ent*-sawaranospirolide C and D. Although much research has been conducted to date, the biological activities of sawaranospirolides still remain undetermined. As part of our continuing interest in the synthesis of bioactive spiroacetals from naturally abundant carbohydrates, [5] we envisioned that the stereoselective synthesis of sawaranospirolides A and C could be derived from the simple and natural L-sorbose, and the advantage of the existing chirality transfer will be elaborated in the rapid asymmetric synthesis.

Results and discussion

Structurally, sawaranospirolides A and C share the same [6,5]-oxaspirolactone backbone, except for the different stereochemistry of *p*-hydroxyphenyl group at C-3 position of the γ-butyrolactone ring. Structural comparison indicated that the similarities between the natural carbohydrate, L-sorbose and the highly oxygenated tetrahydropyran ring system (C4-C8) of sawaranospirolides A and C. Accordingly, we hypothesized that sawaranospirolides A and C could be prepared from the same precursor, L-sorbose.

Retrosynthetic analysis of sawaranospirolides A (1) and C (3) is summarized in Scheme 1. We envisaged that sawaranospirolides A and C could be generated from multi-functionalized α,β-unsaturated ester **6** via hydrogenation, acetonide deprotection, hemiacetal formation, and spirolactonization cascade (Scheme 1). The key precursor, α,β-unsaturated ester **6**, which contains three desired contiguous stereogenic hydroxyl groups, could be readily accessible from 2,3,4,6-Di-*O*-isopropylidene-L-sorbofuranose **7** via multiple functional group transformations.

Subsequently, the synthesis of the key precursor **6** from L-sorbose is outlined in Scheme 2. The known aldehyde **8** was easily obtained from L-sorbose in excellent yield according to a known

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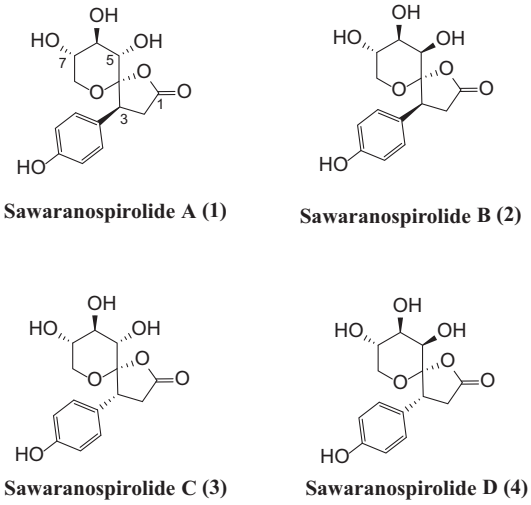


Fig. 1. Structures of Sawaranospirolides A–D.

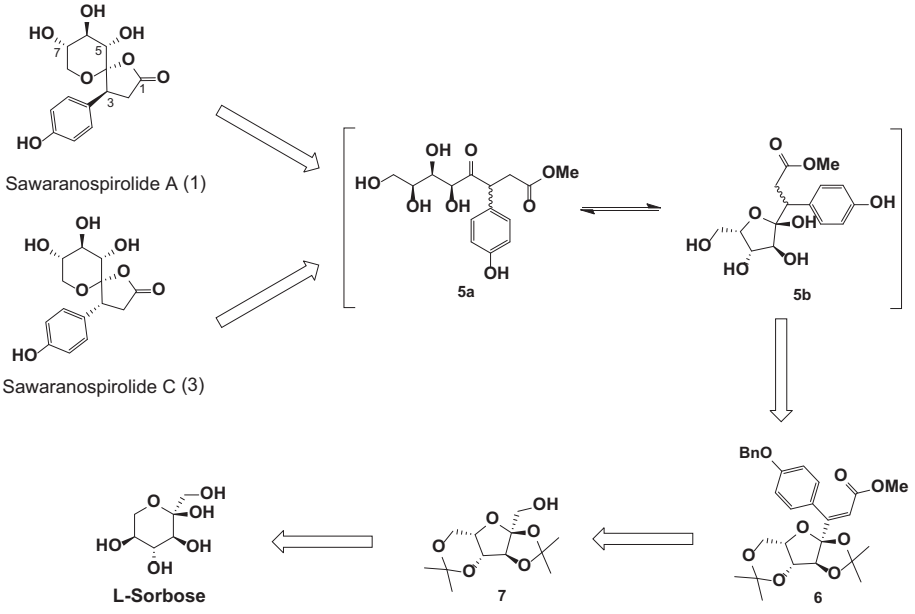
procedure [6,7]. Aryllithium reagent, which is *in situ* generated from 4-benzyloxybromobenzene and *n*-BuLi, was added to aldehyde **8** to give diastereomeric alcohol **9** as an inseparable mixture. [8] However, in the case of the nucleophilic addition by Grignard reagent, which is also derived from 4-benzyloxybromobenzene, lower yield (<40%) was obtained. Dess-Martin oxidation of the resulting secondary alcohol of **9** gave the corresponding ketone **10** in 71% yield over three steps. Homologation of the ketone **10** by Horner-Wadsworth-Emmons [9] reaction with triethyl phosphonoacetate in the presence of a variety of bases (eg. $Ba(OH)_2$, DBU, *t*-BuOK or LiHMDS) were explored; however, the desired α, β-unsaturated ester **6** was formed in a very low yield and significant substrate decomposition was observed. Alternatively, when the ketone **10** was subjected to Wittig olefination with, the corresponding α,β-unsaturated ester **6** was successfully synthesized in 69% isolated yield (Table 1). Due to the low reactivity of this stabilized ylide prolonged heating up to 125 °C for several days was necessary, during which considerable decomposition occurred. The stereochemistry of ester **6** was confirmed on the basis of its NOESY correlations.

With the key precursor **6** in hand, we then focused on the final stage of the total synthesis of sawaranospirolides A (**1**) and C (**3**) according to the retrosynthetic design. Hydrogenation of α,β-unsaturated ester **6** over palladium on activated charcoal (Pd/C, 10%) under high pressure hydrogen atmosphere (4 atm) removed the benzyl group and reduced the conjugate double bond to afford the saturated ester **11** along with significant quantities of a byproduct **12**, which is the partial hydrolysis product of the acetonide group. [10] It was noteworthy that 3*R* isomer of the saturated ester was obtained as a single diastereomer. The excellent selectivity probably originated from the steric interactions of two adjacent bulky cyclic acetonides. Facial selective hydrogenation of the double bond proceeded only on the less hindered face of the α, β-unsaturated ester to give exclusively 3*R* isomer.

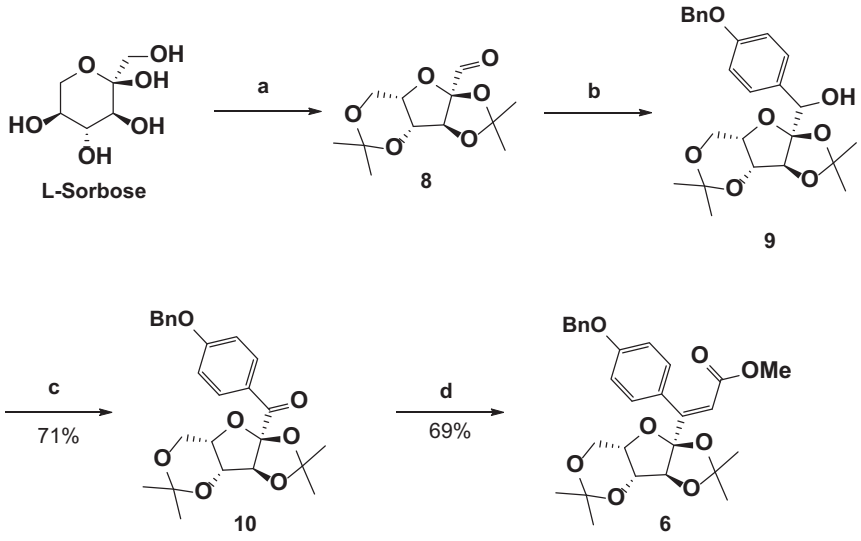
Finally, one-pot acetonide deprotection/ hemiacetal formation / spirolactonization was achieved with 70% TFA *via* spirohemiacetal intermediates (**5a-b**), delivering the [6,5]-oxaspirolactone sawaranospirolide C (**3**) in 67% overall yield (Scheme 3). The optical rotation and spectroscopic data (^1H and ^{13}C NMR, HRMS) of our synthetic sample were in good agreement with natural product sawaranospirolide C [1,11].

In view of the structural similarities between sawaranospirolides A and C, we designed the divergent synthesis of both natural products from the same precursor **6**. Results were detailed in Table 2. We began our investigation by the reduction of **6** with metal hydride species (e.g. $NaBH_4$-$NiCl_2$, [12] $NaBH_4$-$CuCl_2$ and Mg-MeOH [13], entries 5–6, Table 2), however only complex mixture was obtained or low conversion was observed with recovered starting materials. Other reaction conditions were also attempted, such as hydosilylation, Crabtree's reduction, and Stryker's reduction $[Ph_3PCuH]_6$, [14] no desired product was observed. (entries 7–8, Table 2)

Since the previous synthetic strategy for sawaranospirolide A was failed, we then revised our plan at this stage. The conjugate addition of organometallic reagents to electron-deficient alkenes might be a possible solution due to its high electrophilic reactivity. Robertson and co-workers reported the synthesis of sawaranospirolides with the similar synthetic strategy to introduce the

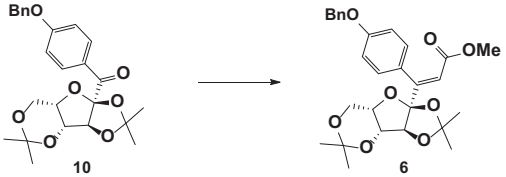


Scheme 1. Retrosynthetic analysis of sawaranospirolides A (1) and C (3).



Scheme 2. Synthesis of **6**. *Reagents and conditions:* (a) Ref 6; (b) 4-benzyloxybromobenzene, *n*-BuLi, then **8**, THF, −78 °C; (c) Dess-Martin periodinane, $NaHCO_3$, DCM, 71% over three steps; (d) See Table 1, $Ph_3P = CHCO_2Me$, Toluene, 125 °C, 110 h, 69%.

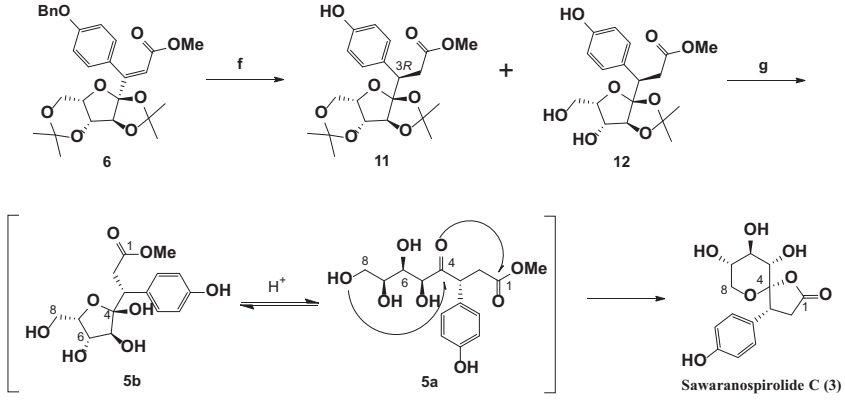
Table 1
Homologation of ketone **10** under various conditions.



Entry	Reagents and conditions	Time	Yield
1	triethyl phosphonoacetate, $Ba(OH)_2$, THF, rt to reflux	62 h	-[a]
2	triethyl phosphonoacetate, DBU, THF, rt	56 h	-[a]
3	triethyl phosphonoacetate, ^{t}BuOK, THF, 0 °C to reflux	40 h	<5%[b]
4	triethyl phosphonoacetate, LiHMDS, THF, −78 °C to rt	5 h	<5%[b]
5	methyl (triphenylphosphoranylidene) acetate, DCM, 40 °C	80 h	9%
6	methyl (triphenylphosphoranylidene) acetate, toluene, 125 °C	110 h	69%

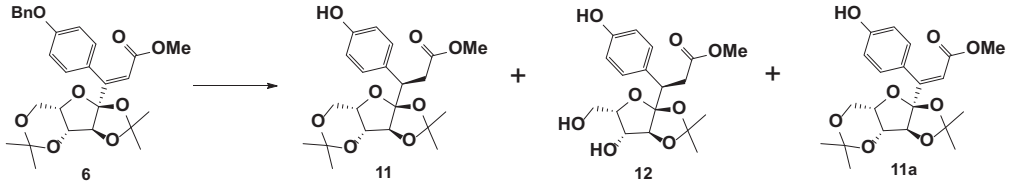
[a] No reaction occured with complete recovery of the starting material.
[b] With considerable unidentified decomposition products.

p-hydroxyphenyl substituent at the 3-position of the oxaspirolactone backbone. In their study, [4] they used Meyers' dienyloxazoline chiral auxiliary with *p*-(benzyloxy)phenyllithium for the key conjugate addition. Accordingly, α,β-unsaturated ester **14**, readily prepared from **7**, was used as an appropriate substrate for this addition. One-pot oxidation/olefination of the primary alcohol in **7** using Dess-Martin periodinane and the stabilized ylide ($Ph_3P = CH_2CO_2Me$) furnished the unsaturated ester **14** in 71% yield [15]. Initially, the conjugate addition of *4*-(benzyloxy)phenyllithium to ester **14** in THF at low temperature led to unidentified decomposition products along with the 1,2-addition product (10–20%) (Scheme 4). Treatment of ester **14** with corresponding phenyl Grignard reagent in the presence of cuprous chloride salt was also unfruitful. In 2012, Fukuyama *et al.* [16] reported an elegant total synthesis of the indole alkaloid isoschizogamine. One of the key steps in their synthesis is a Rh (I)-catalyzed Michael addition of arylboronic acid to *α, β*-unsaturated lactone. Encouraged by their result, we decided to extend the Rh (I)-catalyzed strategy to our substrate **14**. Unfortunately, the conjugate addition reactions of arylboronic acids to acyclic α, β-unsaturated ester **14** did not yield the 1,4-addition product under various conditions, only resulted in unidentified decomposition product and the recovery of major starting material. These results demonstrate that α, β-unsaturated



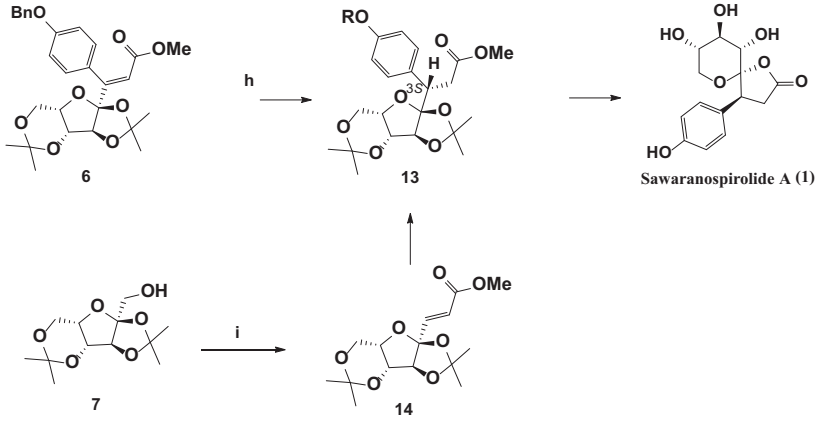
Scheme 3. Synthesis of sawaranospirolide C (**3**). *Reagents and conditions:* (f) H_2 (4 atm), 10% Pd/C, EtOAc, MeOH, 30 h; (g) 70% trifluoroacetic acid, rt, 67% over two steps.

Table 2
Reduction of α, β-unsaturated ester **6** under various conditions.



Entry	Reagents and conditions	Time	Product (Yield)
1	H_2 (1 atm), Pd/C, EtOAc, MeOH	12 h	**11a** (99%)
2	H_2 (1 atm), $Pd(OH)_2$/C, EtOAc, MeOH	12 h	**11a** (95%)
3	H_2 (4 atm), Pd/C, EtOAc, MeOH	12 h	**11** (>40%)[a]
4	H_2 (4 atm), Pd/C, EtOAc, MeOH	30 h	**11** + **12** (>90%)
5	$NaBH_4$-$NiCl_2$ or $NaBH_4$-$CuCl_2$, −40 °C to rt	24 h	-[b]
6	Mg-MeOH, 0 °C to rt	24 h	-[c]
7	$[Ir(cod)(Py)(PCy_3)]PF_6$, H_2 (1 atm), DCM	24 h	-[d]
8	Stryker's reagent, $PhSiH_3$, 0 °C to rt	24 h	-[c]

[a] With debenzylation product **11a** in 50%.
[b] No reaction occured with complete recovery of the starting material.
[c] Starting material **6**was recovered with unidentified mixtures.
[d] No desired product was observed.



Scheme 4. Attempted synthesis of sawaranospirolide A (**1**). *Reagents and conditions:* (h) See the text; (i) Dess-Martin periodinane, solid $NaHCO_3$, then Ph_3P = $CHCO_2Me$, DCM, 71%.

ester **14** is exceptionally sterically hindered thus the desired conjugate addition is highly impeded and challenging.

Conclusion

In summary, an efficient total synthesis of spiroacetal butyrolactone sawaranospirolide C was achieved in seven linear steps from L-sorbose. Our highly efficient synthesis demonstrated the powerful application of easily accessible carbohydrate as chiral pool. Synthetic efforts toward sawaranospirolide A were also described. However, the effort was compromised by the inability to effect reduction or conjugate addition of the remarkably unreactive intermediates (**6** or **14**). Further studies toward the synthesis of other sawaranospirolides are currently in progress and will be reported in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153072.

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[11] Our synthetic sawaranospirolide C exhibited physical properties that consistent with that for natural sawaranospirolide C and Robertson's synthetic sawaranospirolide C. See Supporting Information for detailed spectroscopic comparisons (1H, 13C NMR and COSY in CD3OD or DMSO-d6) of synthetic and natural sawaranospirolide C. The observed optical rotation values for our synthetic sawaranospirolide C ([α]D25 -19.4(c 0.1, MeOH)) was the same sign as the isolated sawaranospirolide C ([α]D25 -36 (c 2.25, MeOH)) 1 and opposite to Robertson's synthetic ent-sawaranospirolide C ([α]D23 +40.5 (c 1.4, MeOH))4.
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