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Concise Synthesis of the Core Structures of Saundersiosides

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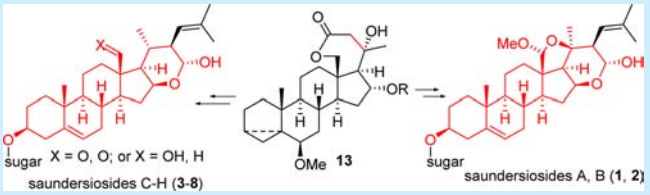
Supporting Information

ABSTRACT: A divergent synthesis of three core pentacyclic lactones of nine rearranged cholestane sapogenins, saundersiosides A–H (**1**–**8**) and candicanoside A (**9**), is reported. Key features include a one-flask CBS reduction/Brown hydroboration–oxidation, a SmI_2-mediated intramolecular Reformatskii reaction, and an intramolecular transesterification. This synthesis provides a general strategy and key precursors for the collective synthesis of natural and designed saundersiosides. An efficient formal synthesis of candicanoside A is also achieved.



The disclosure of the exceptionally potent antitumor activities of OSW sapogenins has triggered a continuous phytochemical investigation of the genus *Ornithogalum*, which resulted in the isolation of more than 100 steroidal glycosides.[1] Among many structurally novel glycosides, a number of them stood out for their rearranged cholestane sapogenins, as depicted in Figure 1. Saundersiosides A–H (**1**–**8**, isolated from *Ornithogalum Saundersiae* bulbs by Mimaki between 1993–1999)[2] and candicanoside A (**9**, isolated from *Galtonia candicans* by Mimaki in 2000)[3] are closely related 24(23 → 22) *abeo*-cholestane glycosides and show potent antitumor activities

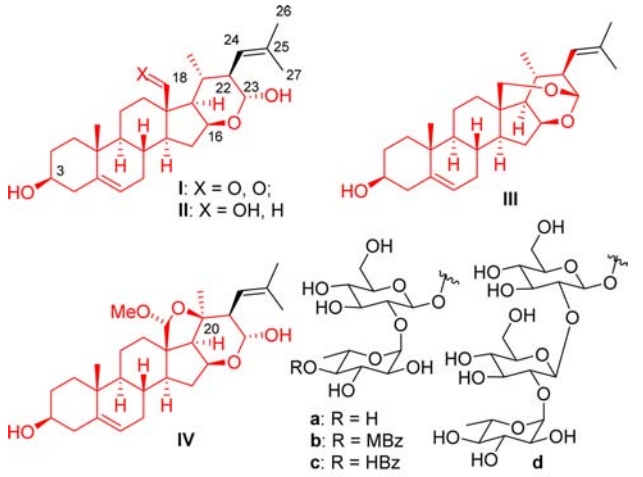
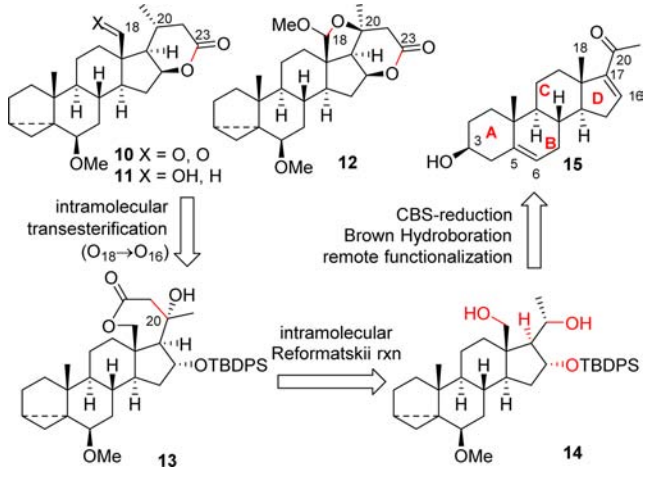


Figure 1. Structures of saundersiosides A–H (**1**–**8**), candicanoside A (**9**), and their analogues.

(IC_{50} from nM to μM against HL-60 human promyelocytic leukemia cells). The first and only synthesis of candicanoside A by the Yu group[4] is elegant but not flexible to the synthesis of saundersiosides. Our goal is to provide a unified solution to these natural products and their analogues. Herein we report a divergent synthesis of the core structures of their sapogenins (compounds **10**–**12**, Scheme 1).

Scheme 1. Retrosynthesis Analysis of the Core Structures



The steroidal sapogenins of **1**–**9** differed with each other mainly in the oxidative states and assembly patterns of C18, C20, and C23. Since the Yu group has successfully introduced the C24–C27 side chain at the late stage of the candicanoside A synthesis, we likewise identified lactones **10**–**12** as the core structures and thus planned our synthesis toward them. We envisaged that the six-membered lactones of **10**–**12** could be

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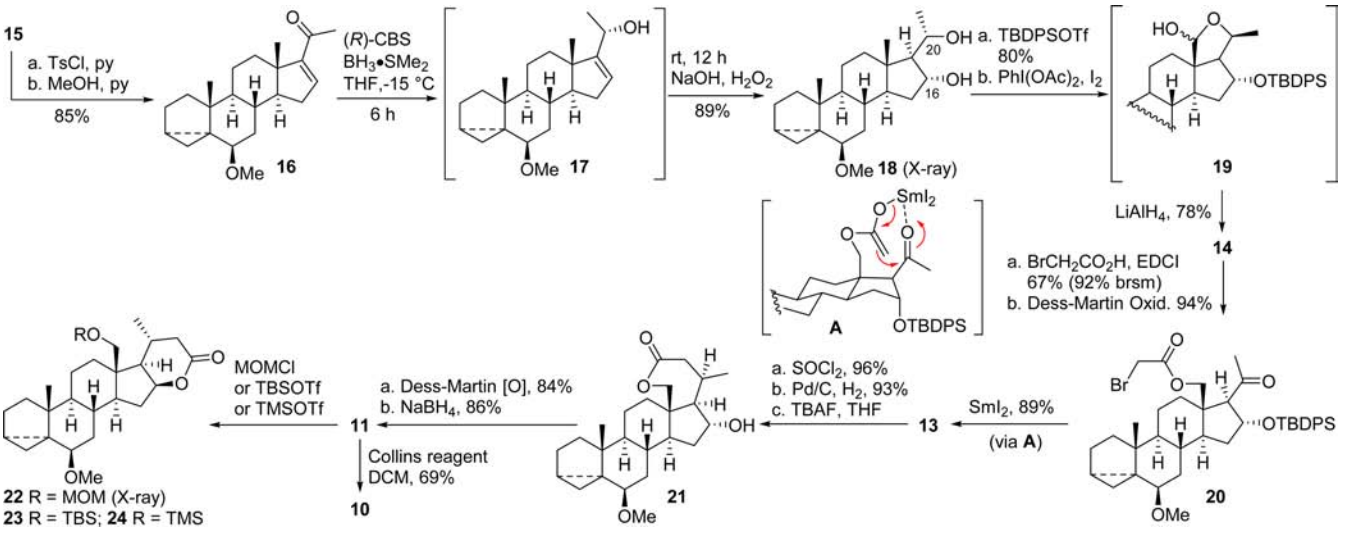
Scheme 2. Synthesis of the Core Structures of I–III



obtained through an intramolecular transesterification of the seven-membered lactone of **13** ($O_{18} \rightarrow O_{16}$) and the oxidative states of C18/C20 could be easily modified via simple transformations. In turn, **13** could be prepared by an intramolecular Reformatskii reaction from the triol derivative **14** which was designed to be prepared from dihydropregnenolone **15** through reduction (C20-OH), hydroboration–oxidation (C16-OH), and remote functionalization (C18-OH).

The remote functionalization of the angular C18 methyl group often requires a C20-OH or a C11β-OH to perform the transformation,[5] and the C16-substituent, if there was one, at the α face of the D-ring to minimize side reactions.[6] Therefore, diol **18**, with the C20(S)-[7] and C16α-hydroxyl groups and the 3,5-cyclo-6-methoxy-protected AB ring, was prepared from **15**, as shown in Scheme 2. Through a slightly modified two-step procedure,[8,9] the C5–C6 double bond of **15** was protected, affording enone **16** in 85% yield on the 60 g scale. Then the C20 ketone of **16** was stereoselectively transformed into the C20(S)-OH of **17** through Corey–Bakshi–Shibata (CBS) reduction,[4b,10] and the C16α-OH was introduced through a substrate-controlled Brown hydroboration–oxidation to provide diol **18**. Since both CBS reduction and Brown hydroboration–oxidation use borane as a stoichiometric reagent, we envisioned that incorporation of them in one flask would simplify the operation. As expected, performing the reduction at −15 °C for 6 h, and then keeping the reaction at 25 °C for 12 h before $NaOH/H_2O_2$ was added, effectively delivered diol **18** (89% yield, 50 g scale). The structure of **18** was secured by an X-ray analysis (Figure 2). In this manner, three contiguous stereocenters (C16, C17, and C20) were established in one flask.

Before remote functionalization of the C18-Me was performed on **18**, the C16-OH was selectively protected as the TBDPS ether in 80% yield (TBDPSOTf, iPr$_2$NEt, DCM, 0 °C to rt, 10 h). Employing Meystre's hypoiodite method[11] ($Pb(OAc)_4/I_2$, hv) we obtained the desired diol **14** in 40% yield after $LiAlH_4$ reduction,[12] along with the cyclic ether in 42% yield. Owing to the inefficiency in converting the byproduct to **14** through $RuCl_3$–$NaIO_4$ oxidation/$LiAlH_4$ reduction, we investigated other C18-oxidation methods. Finally, the combination of a Suárez iodine(III) oxidation[13] ($PhI(OAc)_2/I_2$, hv) and a $LiAlH_4$ reduction was employed to give **14** in 78%

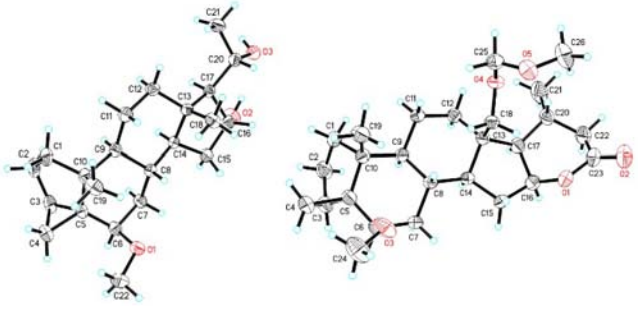


Figure 2. Ortep structures of **18** (left) and **22** (right).

yield on the 20 g scale. It was noted that the transformation required 3 equiv of $PhI(OAc)_2$ and 2 equiv of iodine. Furthermore, despite being widely used in steroid synthesis, the free radical remote functionalization of C18-Me was never followed by a direct reduction step to provide 18,20-diol; therefore, our method provided an important complement to the existing protocol especially for the acid-labile substrates.

We then entered the next stage of the synthesis. A selective esterification of the C18-OH in **14** with bromoacetic acid (EDCI, DMAP, CH_2Cl_2, rt, 1 h) and a Dess–Martin oxidation of the C20-OH gave **20** in good yield.[14] Compound **20** quite smoothly underwent the key transformation, an intramolecular Reformatskii reaction mediated by SmI_2[15] at ambient temperature, to form the seven-membered lactone **13** in 89% yield as a single isomer. In contrast, at −78 °C, this reaction only gave the debromination product of **20**, as did the reaction at ambient temperature using additives or cosolvents such as HMPA, LiCl, MeOH, and t-BuOH. We reasoned that the reductive debromination of **20** occurred swiftly to form the Sm^{III} enolate, but it failed to attack the C20 carbonyl group at low temperature because the reaction sites were seven atoms away from each other. This distance was shortened through the chelation of the Sm^{III} ion with the reacting functional groups, an effect which was fortunately achieved by running the reaction at ambient temperature but was broken by using additives or cosolvents. The high stereoselectivity was also viewed as a consequence of chelation (as in structure **A**).[16]

With **13** in hand, we began to explore the synthesis of **10** and **11**. Replacement of the C20-OH with hydrogen through a

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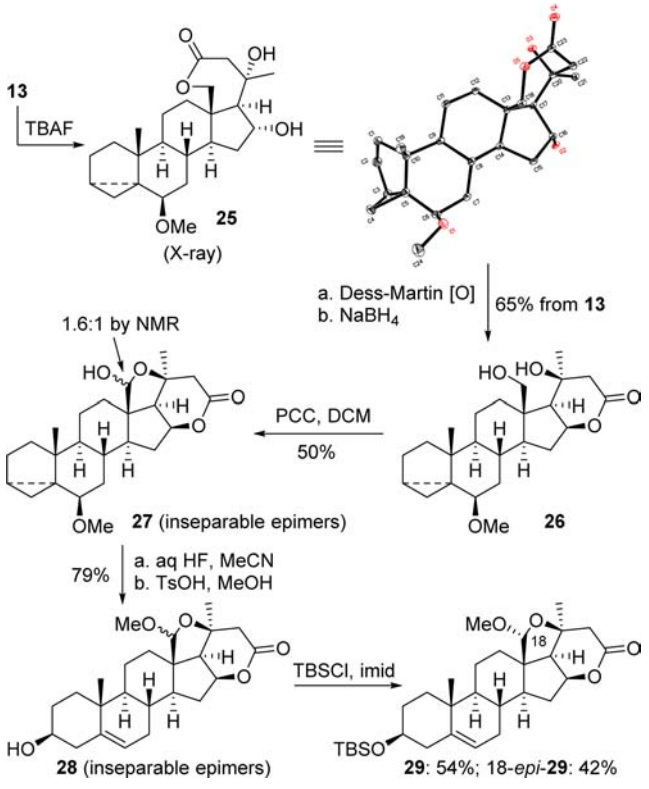
dehydration−hydrogenation process ($SOCl_2$, pyridine, 0 °C, 30 min; 10% Pd/C, 20 atm, EtOH-EtOAc, rt, 24 h[17]) and deprotection of the TBDPS ether on the resulting product with TBAF provided compound **21**. Then, inverting the configuration of the C16α-OH was achieved through a Dess−Martin oxidation/$NaBH_4$ reduction process, which was accompanied by a spontaneous intramolecular transesterification of the C22 carboxyl group from the C18-OH to the newly generated C16β-OH, thus providing the desired lactone **11** (five steps, 64% overall yield from **13**). The exposed C18-OH was oxidized with Collins reagent to give aldehyde **10** in 69% yield.[18]

Yu and Tang have used the TBS-protected **11** (**23**) as an intermediate in their synthesis, so we decided to obtain a formal synthesis of candicanoside A. Interestingly, we found that **23**, prepared from **11** (TBSOTf, 2,6-lutidine, DCM, 0 °C, 69%), is acid-labile and partly desilylated in neutralized $CDCl_3$, presumably owing to the steric crowding of this position, and that the TMS-protected product **24** (TMSOTf, Et_3N, DCM, 0 °C, 90%) is much more stable. Moreover, compound **11** was protected as the MOM ether (MOMCl, iPr_2NEt, Bu_4NI, DCM, 83%) and the resulting **22** generated a crystal suitable for X-ray analysis, thereby securing the stereochemistry. Until then we have achieved a formal synthesis of candicanoside A in 16% yield over 15 steps from dihydropregnenolone **15**, which is apparently superior to the previous route in efficiency (4% yield over 18 steps from dehydroisoandrosterone).

Finally, we moved on toward another target **12**. As depicted in Scheme 3, deprotection of the TBDPS group on **13** with TBAF in THF gave diol **25** whose crystal was suitable for X-ray analysis. The stereochemistry of C20 was secured as the *R* configuration. Again, the Dess−Martin oxidation/$NaBH_4$ reduction process, accompanied by an intramolecular transesterification, provided another diol **26** with C18-OH exposed for further transformation.

Scheme 3. Synthesis of the Core Structure of IV



Oxidation of the C18-OH of **26** with PCC reagent directly gave hemiacetal **27** as an inseparable mixture of epimers (1.6/1 at C18 by ^1H NMR) in moderate yield. The 3,5-cyclo-6-methoxy protection of **27** was then removed with aqueous HF in MeCN because it is acid-sensitive and apt to react with MeOH in an acidic medium. The resulting crude was treated with *p*-toluenesulfonic acid in MeOH to deliver the desired acetal **28** in 79% yield, also as an inseparable mixture of epimers. To render the chromatographic separation of the epimers, the C3-OH of **28** was protected as the TBS ether, giving acetal **29** in 54% yield and 18-*epi*-**29** in 42% yield. Acetal **29** is a more advanced intermediate than **12**; therefore, we accomplished the synthesis of the core structure of **IV** in 5% (9% as mixture) yield over 15 steps.

In summary, we have achieved a divergent and effective route for the core structures of saundersiosides and candicanoside A, with lactone **13** as a common intermediate. The key transformations featured herein include a one-flask CBS reduction/Brown hydroboration−oxidation to install three stereocenters from the starting enone, a SmI_2-mediated intramolecular Reformatskii reaction to connect the C20−C22 bond in a highly stereoselective manner, and an intramolecular transesterification to furnish the desired six-membered lactone and to expose the C18-OH for further manipulations. Our synthesis also exhibits an efficient formal synthesis of candicanoside A. Installation of the C24−C27 side chain and progress toward the natural products and the designed analogues are ongoing in this laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data, ^1H and ^{13}C NMR spectra of all the new compounds, the X-ray crystallographic data and cif files for **18**, **22**, and **25**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00821.

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Notes

The authors declare no competing financial interest.

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(7) Our experience suggests that C20(*S*)-OH is more suitable for C18-Me remote functionalization than its C20(*R*)-OH counterpart, owing to the faster reaction rate and higher yield (see ref 6).

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(9) By employing pyridine as the base instead of KOAc in the 3,5-cyclo-6-methoxy-forming step, our procedure eliminates the generation of the 3,5-cyclo-6-acetoxy compound as a side product, which is difficult to remove from **16**.

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(12) Jones oxidation was frequently performed after the remote funtionalization of the C18-Me group to give a lactone in good yield. As in our case, 3,5-cyclo-6-methoxy protection of the AB ring is acid-labile and cannot survive Jones oxidation, so direct reduction of the intermediate **19** was investigated.

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(14) The outcome of the selective esterification of the C18-OH group in **14** was unstable. We found that Dess-Martin oxidation of the unwanted C20-OH protected byproduct also provided the desired ketone **20** in 50% yield which might be caused by the shift of the bromoacetyl group from C20-OH to C18-OH. So direct oxidation of the crude product in esterification step gave an reasonable yield of ketone **20**.

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(17) Hydrogenation with $NaBH_4/NiCl_2$ gave a 1/1 mixture of 20(*S*)- and 20(*R*)-epimers. The high stereoselectivity of the Pd/C catalyzed hydrogenation was realized in a substatrate-controlled manner. The catalyst approached the double bond from the less hindered convex face.

(18) Dess−Martin, Swern, and Parikh−Doering oxidations only provided aldehyde **10** in less than 20% yield.

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