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Stereoselective Total Synthesis of Siladenoserinols A and D

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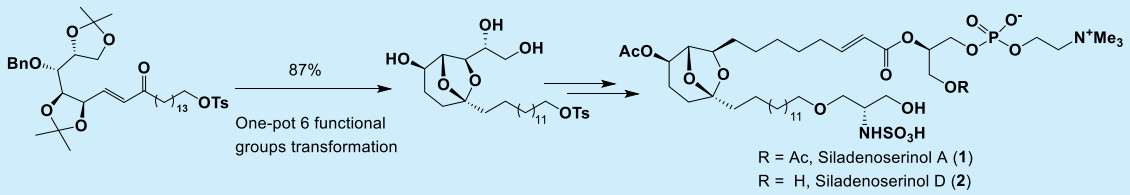

ABSTRACT: The stereoselective total synthesis of siladenoserinols A and D has been accomplished using carbohydrate as a chiral template. The feature of this work is to build the medicinally privileged 6,8-DOBCO scaffold through a cascade reaction of hydrogenation/deacetalization/ketalization in a one-pot process, that is, to take advantage of a thermodynamically controlled bicyclization of polyhydroxyketone under HCl/MeOH reaction conditions. The current cost-effective synthetic strategy could facilitate the bioactivity investigation of siladenoserinols.

Serinolipids have been isolated from *Didemnum* species and exhibit pharmacological interest due to their cell cytotoxicity,[1,2] antibacterial activity,[3] and HIV-1 integrase inhibitory activity.[4] In 2013, Tsukamoto and coworkers discovered a series of siladenoserinol compounds from a tunicate of the family Didemnidae collected in Indonesia,[5] as exemplified by siladenoserinol A (**1**) possessing a 6,8-dioxabicyclo[3.2.1]octane skeleton with two long carbon chains with unique sulfamated serinol and glycerophosphocholine moieties (Figure 1). By 2018, a total of 16 structural analogs of serinol derivatives, namely, siladenoserinols A−P, were isolated from the same natural source by the same research group.[6] Very impressively, siladenoserinol A (**1**) presented potent inhibitory activity against the p53/Hdm2 interaction and could possibly set free the tumor suppressor p53 to induce the apoptosis of cancer cells.[5] It has been well acknowledged that targeting the physical interaction between p53 and Hdm2 would be the most direct of all p53-activating strategies, making it one of the hot research topics in cancer therapeutics.[7] Owing to its unique structural architecture, compelling biological activity, and largely unexplored potential in medicinal chemistry, this type of natural products has become an attractive target for the synthesis.[8] In 2018, the first total synthesis of siladenoserinol A (**1**) was formally documented by Doi and coworkers[9] with 24 steps in the longest linear sequence and 6.04% overall yield, applying $AuCl_3$-catalyzed double hydroalkoxylation and the Masamune−Roush-modified Horner−Wadsworth−Emmons (HWE) reaction as the key steps. In 2019, Tong and coworkers[10] reported their asymmetric total synthesis of siladenoserinols A and H via a cascade Achmatowicz rearrangement and bicycloketalization on a suitable furfuryl diol substrate. Surprisingly, they found that both siladenoserinols A and H were not cytotoxic against A549 and MGC-803 cell lines but exhibited potent and selective antibacterial activity against Gram-positive bacteria. A preliminary structure−activity relationship (SAR) analysis suggested that the reported siladenoserinol compounds containing an acyl group at the C-11 position and an ester linkage at the C-2′ position showed the most potent inhibitory activities against the p53−Hdm2 interaction.[5,6,9] Among these family members, both siladenoserinol A (**1**) and its 1′-deacetylated derivative siladenoserinol D (**2**) exhibited promising inhibitory activity with IC_{50} at 2.0−7.7 μM.

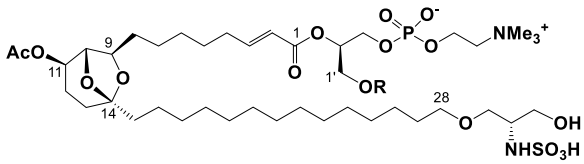

Figure 1. Structures of siladenoserinols A (**1**) and D (**2**).

The major pharmacophore of siladenoserinols is dioxabicyclo[3.2.1]octane (DOBCO), a structurally unique bridge-fused ring system adopting a six-membered chair conformation ring and a seven-membered boat conformation

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ring due to the inherent anomeric effect.[11] Because the intriguing 6,8-DOBCO structure has been found in many biologically active natural products, the synthetic methods toward the efficient preparation of this unique species have been well investigated,[1,2,4,8,12] mainly focusing on the stereocontrolled installation of three consecutive stereogenic centers and the matched hydroalkoxylation method. We are interested in the total synthesis of siladenoserinols due to their challenging 6,8-DOBCO structure, their potential anticancer activity, and our previous experiences of one-pot sequential intramolecular cyclization in natural product syntheses.[13]

Our idea toward the synthesis of 6,8-DOBCO structure was based on the cascade ketalization of ketone-polyols using carbohydrate residues as chiral templates. It is well known that multiple options exist for the intramolecular bicyclization of the ketone−polyol substrate, and thus we started our work from thermodynamic calculation to predict the most favored bicyclic structure of our designed polyhydroxyketone substrate. With the help of Baldwin's rule,[14] we envisaged that dioxabicyclic compounds could be formed from our polyhydroxyketone model substrate in three possible modes (Figure 2). The energy calculation of each of these

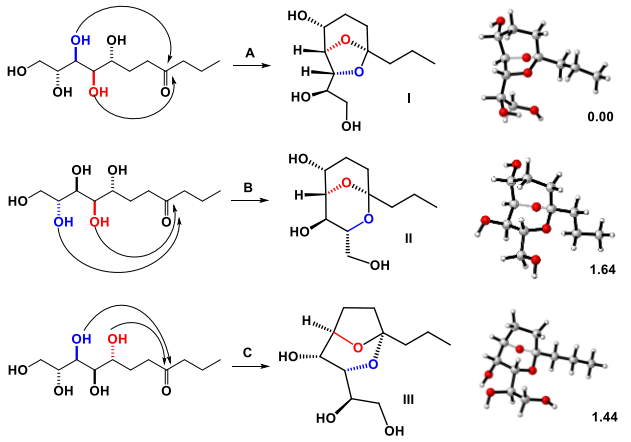
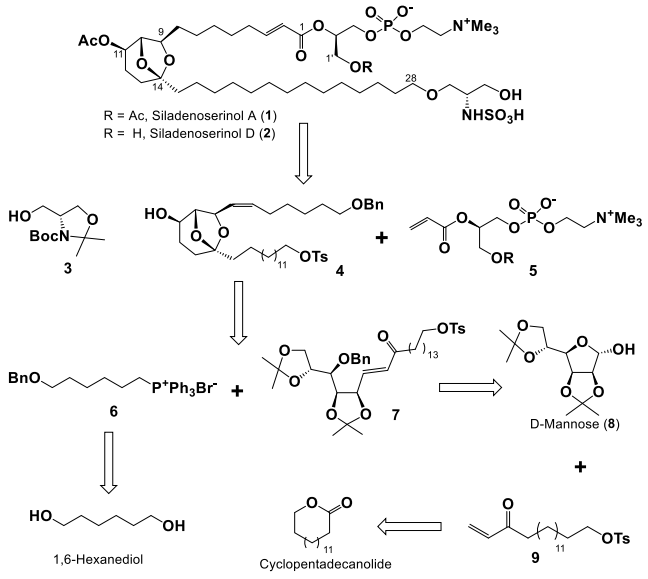


Figure 2. Comparison of the relative energies (kcal/mol) for the three diastereomeric compounds (**I**–**III**).

dioxabicyclic compounds suggested that mode A generated the lowest energy ketal compound possessing the desired 6,8-dioxabicyclo[3.2.1] octane skeleton, whereas the ketals of modes B and C were higher in energy by over 1.64 and 1.44 kcal/mol relative to their counterpart in mode A, respectively.[15] (Full computational details can be found in the Supporting Information.) This result suggested that ketalization of a well-established polyhydroxyketone substrate could be directed to the thermodynamically favored 6,8-DOBCO scaffold.

Encouraged by the above calculation, our retrosynthetic analysis was thus determined, as shown in Scheme 1. The title compounds siladenoserinol A (**1**) and D (**2**) could be assembled from the union of three functionalized fragments, that is , the serinol derivative **3**, the 6,8-DOBCO intermediate **4**, and the glycerophosphocholine-containing α,β-unsaturated ester **5**, through the latent cross-metathesis (CM) reaction and Williamson etherification. According to the prediction of our model polyhydroxyketone substrate, the 6,8-DOBCO backbone **4** could be spontaneously formed from the ketone-polyol **7** via the cascade process of hydrogenation/deacetalization/

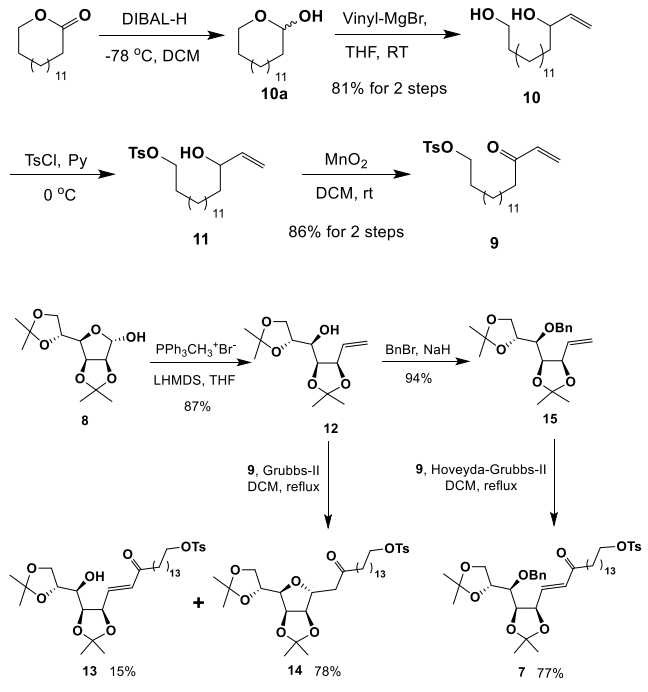
Scheme 1. Retrosynthetic Analysis of Siladenoserinols A (1) and D (2)



selective ketalization in one pot. The stereochemically well-defined ketone **7**, in which four consecutive stereocenters were in place, could be readily accessible from the commercial carbohydrate chiral template 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**8**). Two side chains of **4** could be loaded up with the ylide **6** and the α,β-unsaturated ketone **9** derived from the commercially available 1,6-hexanediol and cyclopentadecanolide, respectively.

Our formal synthesis commenced with the transformation of cyclopentadecanolide to diol **10** through diisobutylaluminum hydride (DIBAl-H) reduction and the Grignard addition of vinyl magnesium bromide in good yield over two steps (Scheme 2). Selective tosylation of the primary alcohol at 0 °C

Scheme 2. Synthesis of Fragment 7



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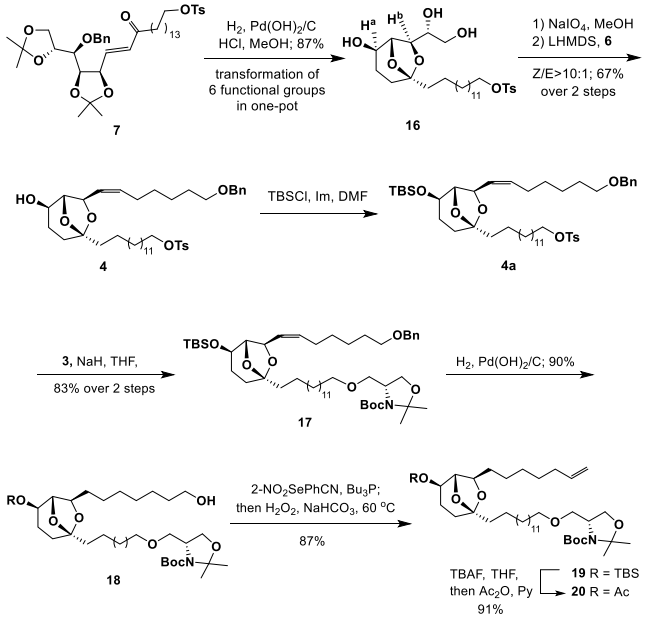
provided **11**, followed by a subsequent oxidation of the crude allylic alcohol with MnO_2, which produced the α,β-unsaturated ketone **9** in a yield of 86%. Convergently, Wittig methylenation of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**8**) on the anomeric carbon in the presence of lithium hexamethyldisilazide (LHMDS) afforded the terminal alkene **12** in 87% yield. However, the Grubbs-II-catalyzed[16] CM reaction of **12** with **9** generated the undesired furanosyl *C*-glycoside **14** as a major product alone with the desired product **13** in only 15% yield.[17] It is noteworthy that 1,2-*trans* furanosyl *C*-glycoside was obtained as a single diastereomer, and the other isomer was not observed. This stereoselectivity might have originated from the steric interaction of two adjacent bulky cyclic acetonides. Attempts to improve the reaction outcome by decreasing the reaction temperature and using other Grubbs catalysts[18] were fruitless. We believe that the enhanced oxa-conjugate reactivity[19] in hydroxy-enone **13** would facilitate the formation of tetrahydrofuran **14** under these reaction conditions. Therefore, the free hydroxyl group of **12** was temporarily blocked with a benzyl group using BnBr and NaH in dry THF to give the intermediate **15** in excellent yield. The following CM of **15** and **9** in the presence of Hoveyda−Grubbs-II catalyst proceeded smoothly to give the desired α,β-unsaturated ketone **7** in 77% yield with excellent E/Z selectivity (>20:1).

After the access to the key fragment **7**, we next focused our attention on the synthesis of the 6,8-dioxabicyclo[3.2.1]octane skeleton (Scheme 3). The hydrogenation of **7** over 20% $Pd(OH)_2/C$ in methanol removed both the benzyl group and the conjugate double bond, affording the saturated ketone intermediate in excellent yield. This ketone intermediate, without further purification, was subjected to acid hydrolysis at ambient temperature for 4 h to deliver the intramolecular bicyclized compound **16**. We found that hydrochloric acid (1 M, a few drops) in methanol was the best reaction conditions for triggering the deacetalization and ketalization in one pot, leading to the desired 6,8-DOBCO structure **16** in 87% yield as a single diastereoisomer,[20] whereas the same reaction in the TFA/CH_2Cl_2 system gave a messy thin layer chromatography (TLC) result. The stereochemistry of **16** was confirmed by the nuclear Overhauser effect (NOE) between H^a and H^b and the structure assignments from the following derivatives. Moreover, when we reinvestigated the thermodynamic stability on all potential products of **7**, as described in Figure 2, the 6,8-DOBCO structure **16** displayed the lowest energy with consideration of the solvation effect, matching our experimental results in methanol.

Scheme 3. Synthesis of Fragment 20

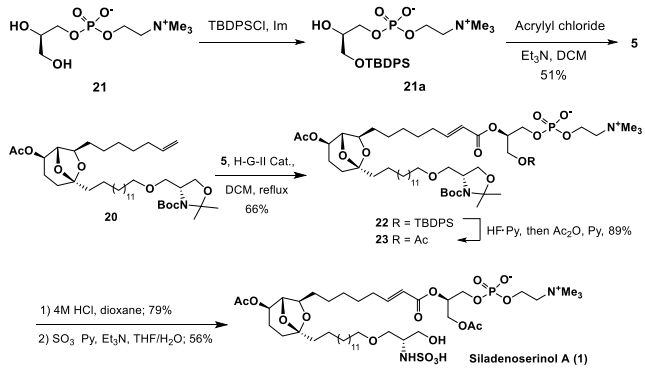


Oxidative cleavage of the adjacent hydroxyls in **16** with sodium periodate, followed by Wittig olefination with ylide **6** (see the Supporting Information),[21] predominantly afforded (*Z*)-olefin **4** in 67% yield with Z/E > 10:1. The free hydroxyl group of **4** was protected with TBDMS, then subjected to Williamson etherification with serinol derivative **3**[22] to give the DOBCO−serinol moiety **17** in 83% isolated yield. The hydrogenation of **17** with $Pd(OH)_2/C$ under a hydrogen atmosphere simultaneously saturated the double bond and removed the benzyl protecting group. The formation of terminal alkene **19** from alcohol **17** was carried out smoothly under the modified Grieco−Nishizawa procedure,[23] involving the introduction of 2-nitrophenyl selenide and the subsequent oxidative elimination with H_2O_2 in a one-pot procedure, to give **19** in 87% yield. Desilylation of **19** with TBAF followed by acetylation with acetic anhydride in one pot[24] provided the advanced intermediate **20** in 91% yield.

With the key intermediate **20** in hand, we were ready to complete the total synthesis of siladenoserinol A (**1**), as summarized in Scheme 4. The functionalized α,β-unsaturated ester **5** was prepared in two steps and in 51% overall yield from the commercially available glycerophosphocholine **21**. CM between **20** and the α,β-unsaturated ester **5** in the presence of the second-generation Hoveyda−Grubbs catalyst afforded **22** in 66% yield without our worrying about the sensitive choline moiety. Next, a two-step, one-pot sequence reaction was used to convert TBDPS silyl ether **22** into diacetate **23**, involving the selective removal of the TBDPS protecting group with HF·Py followed by acetylation with acetic anhydride in pyridine. Finally, removal of the acid-labile 2,2-dimethyloxazolidine ring from **23** with 4 M HCl in dioxane followed by a regioselective sulfamation on the serinol moiety with SO_3·Py in THF/H_2O (v/v 1:1) provided siladenoserinol A (**1**) in 56% yield.

With the complete synthesis of siladenoserinol A, we thought it would be straightforward to finish the first total synthesis of siladenoserinol D (**2**) (Scheme 5). Thus global deprotection was routinely performed on **22** with TFA in THF at room temperature to afford the precursor **24**,[25] which was

Scheme 4. Total Synthesis of Siladenoserinol A (1)



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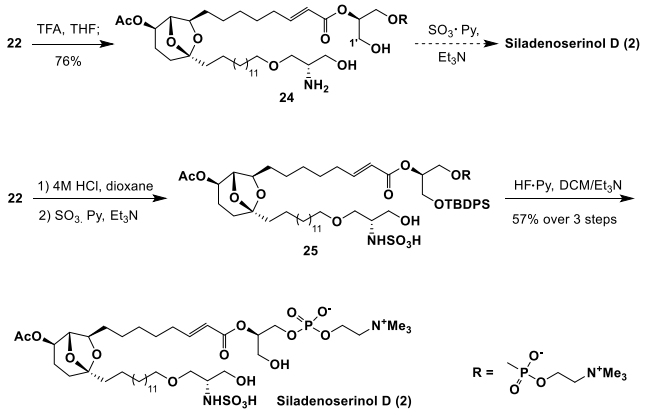
Scheme 5. Completion of the First Total Synthesis of Siladenoserinol D (2)



subsequently subjected to Doi's selective sulfamation protocol,[9] however, leading to 1′-*O*-monosulfate product as the only detectable component based on mass and ^{1}H NMR analysis of the crude product. The mass spectrum ($[M - H]^+$ = 915.4654) of this side product corresponded to the monosulfated product, whereas chemical shifts of H-1′ and H-2′ moved to 4.26 and 5.34 ppm from 3.72 and 5.08 ppm, respectively, pointing to the possible 1′-*O*-monosulfated structure of **24**. This unexpected result could be ascribed to the competitive sulfation and sulfamation between 1′-OH and the serinol moiety. Attempts to improve the reaction outcome with different sulfamation conditions, such as Ley's microwave protocol,[2,12d] failed to give the expected product and afforded several unidentified products. Alternatively, the HCl-catalyzed cleavage of oxazolidine and the Boc group set free the serinol unit, which was treated with the SO_3·Py complex in THF/H_2O cosolvent system later on to afford the regioselectively sulfamated residue **25**. The THF/H_2O cosolvent system was found to be essential for this selective sulfamation; otherwise, it would be very sluggish in an anhydrous environment. It is also worth noting that the desilylation of **25** with TBAF in THF could lead to a partial epimerization on the chiral sulfamate carbon of the serinol moiety. Fortunately enough, deprotection of the silyl group was completed with the HF·Py complex at room temperature to give siladenoserinol D (**2**) in 57% yield over three steps. The spectroscopic data of the synthetic siladenoserinols A (**1**) and D (**2**) were in good accordance with those reported for the natural products.[26]

In summary, we have accomplished the stereoselective total synthesis of siladenoserinols A and D in 15 steps in the longest linear sequence in 6.01 and 6.19% overall yield, respectively. The distinguishing feature of this work is to build the medicinally privileged 6,8-DOBCO scaffold from a predetermined polyhydroxyketone substrate through a cascade reaction of hydrogenation/deacetalization/selective ketalization in a one-pot process. Our work indicated that the desired 6,8-DOBCO scaffold is a thermodynamically controlled product of polyhydroxyketone under HCl/MeOH reaction conditions, whereas the polyhydroxyketone precursor can be quickly assembled from carbohydrate chiral building blocks. Because the 6,8-DOBCO core structure appears in many natural products, we believe that our strategy will have some potential advantages in the preparation of the related target molecules.[27] Extending this strategy to the construction of siladenoserinol congeners, as well as other structurally related bioactive natural products, is favorably underway in our laboratory and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00720.

Complete experimental procedures and characterization data for new compounds, ^{1}H and ^{13}NMR spectra for new compounds, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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(20) An attempt to convert triol **16** to the corresponding mono- or di-*p*-bromobenzoates failed to afford a crystal for single-crystal X-ray analysis.
(21) The Wittig salt **6** was readily prepared in three steps (67% overall yield) from commercially available 6-hexanediol. See the Supporting Information for details.
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(25) It is worth mentioning that compound **24** was very sensitive and partially epimerized during the purification process by silica gel flash chromatography. The crude product was purified by column chromatography on neutral alumina to prevent epimerization.
(26) See the Supporting Information for detailed comparisons of the ^{1}H and ^{13}C NMR of natural and synthetic siladenoserinols A and D.
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