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Letter

Stereoselective Synthesis of (−)-Verazine and Congeners via a Cascade Ring-Switching Process of Furostan-26-acid

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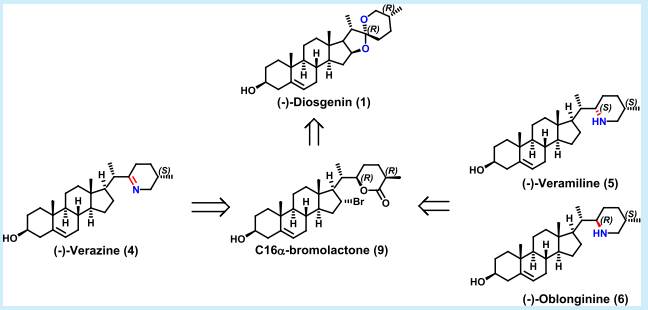
ABSTRACT: An efficient synthetic strategy for three natural *seco*-type cholestane alkaloids isolated from the *Veratrum* plants, based on commercially available naturally occurring and abundant (−)-diosgenin (**1**), as exemplified in the concise asymmetric synthesis of (−)-verazine (**4**), (−)-veramiline (**5**) (proposed structure), and its 22-epimer, (−)-oblonginine (**6**), is presented. This work highlights the application of a cascade ring-switching process of (−)-diosgenin to achieve the E-ring opening and construction of chiral six-membered lactone challenges in *seco*-type cholestane alkaloid synthesis. This approach enables the synthesis of related natural and nature-like novel cholestane alkaloids, opening up opportunities for more extensive exploration of cholestane alkaloid biology.



Part of our research interest has been directed at the development of a general synthetic strategy for cholestane alkaloids with particular emphasis on simplicity, efficiency, and selectivity. (−)-Diosgenin (**1**),[1] a commercially available natural product, was viewed as a versatile platform to devise a conceptionally novel divergent approach toward steroidal alkaloids. To this end, we recently developed a cascade ring-switching process for furostan-26-acids from (−)-diosgenin acetate with E-ring opening and chiral six-membered lactone ring formation as a key step in stereocontrolled synthesis of solanidine (**2**),[2] demissidine (**3**),[3] and other *seco*-cholestane alkaloids[4] (Figure 1). This convenient and efficient activation relay process for the cleavage of the C16−O bond in (−)-diosgenin offers the important building block, a chiral C16α-iodolactone core containing a cholestane ring, by employing the intact (−)-diosgenin skeleton in rapid assembly of the requisite segments in asymmetric synthesis of other natural and nature-like steroidal alkaloids (Scheme 1).

As an initial foray into applications in natural steroidal alkaloid synthesis, *seco*-cholestane alkaloids were chosen as our synthetic targets, as exemplified by (−)-verazine (**4**),[5] (−)-veramiline (**5**),[6] and its 22-epimer, (−)-oblonginine (**6**),[7] a group of *seco*-cholestane-type alkaloids isolated from various species of the *Veratrum* family (Figure 1). The extraordinary range of biological properties exhibited by this class of *seco*-cholestane alkaloids, including antitumor, antimicrobial, and antinociceptive activities,[8] has attracted considerable levels of attention from the medicinal and synthetic communities. However, due to their scarcity in nature, limited pharmacological studies have been employed on these *seco*-cholestane alkaloids and other congeners. In our continuing efforts toward the synthesis of

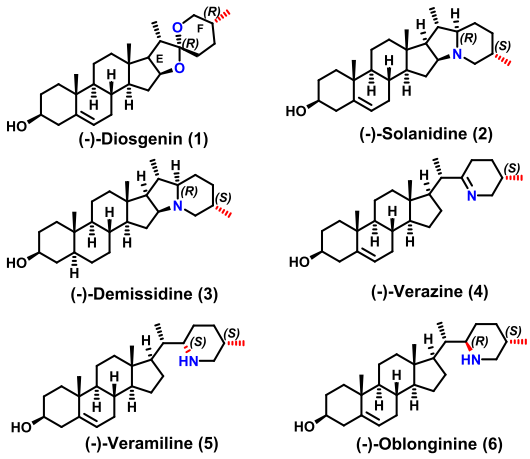


Figure 1. Structures of (−)-diosgenin (**1**) and *seco*-cholestane alkaloids (**2**−**6**).

biologically active steroidal alkaloids, we endeavor to develop efficient strategies that enable the preparation of not only these *seco*-cholestane alkaloids themselves but also various analogues and derivatives for the detailed evaluation of their biological

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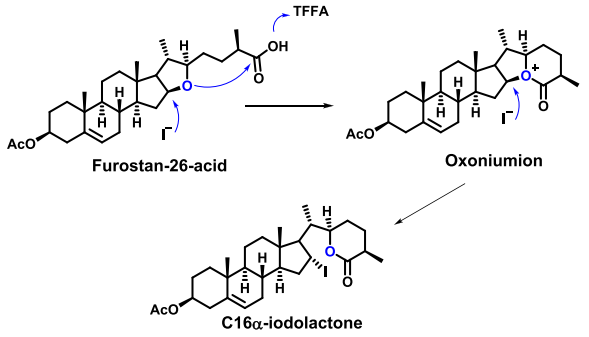
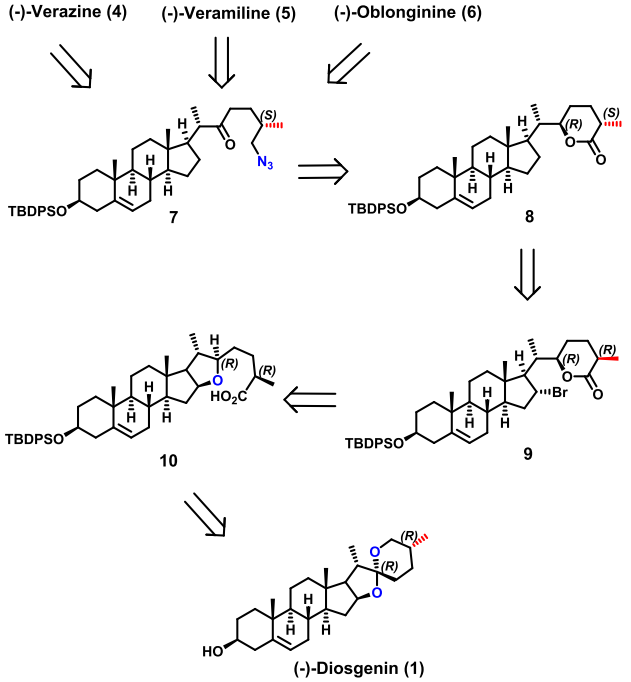
Scheme 1. Cascade Ring-Switching Process of Furostan-26-acid



activities as well as structural activity relationship studies. Starting from commercially available (−)-diosgenin (**1**), we herein describe the application of a convenient entry to a novel key chiral intermediate C16α-bromolactone through the cascade ring-switching process of furostan-26-acid to the first asymmetric synthesis of three natural *seco*-cholastane alkaloids (**4**−**6**).

Our approach toward **4**−**6** is outlined in a retrosynthetic format divergent in Scheme 2. A concise synthesis of **4** is realized

Scheme 2. Retrosynthetic Analysis of *seco*-Cholastane Alkaloids (4−6)



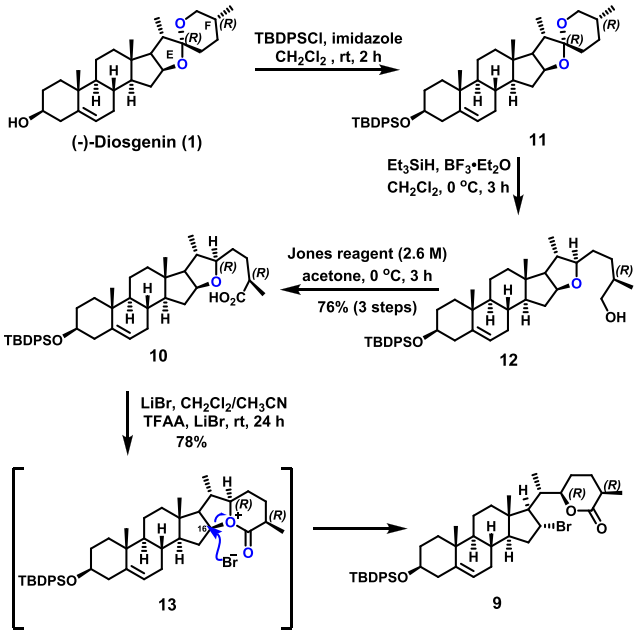
by cascade reduction/cyclization of azidoketone **7**. The azidoketone **7** is synthesized from lactone **8** by a regio- and stereoselective functionalization sequence including lactone reduction, tosylation, and azidation of the primary alcohol and Dess−Martin oxidation of the secondary alcohol. Lactone **8** could, in turn, be accessible from bromolactone **9** through reduction of the C16−Br bond, followed by epimerization of the C25-Me via substrate control. The C16α-bromolactone core structure of **9** could readily be constructed from **1** via furostan-26-acid **10** by using the cascade ring-switching chemistry developed in our asymmetric synthesis of *seco*-cholastane alkaloids (**2** and **3**).

(−)-Veramiline (**5**) and (−)-oblonginine (**6**) posed a significant challenge with respect to diastereocontrol. However, a semisynthesis study from **4** via an imine reduction pathway to **5** in a protocol reported by Kingston and co-workers[9] provides a straightforward but unattractive route due to very poor diastereoselectivity.[10] An attractive solution was found in a tandem azide reduction/diastereoselective double reductive amination, and several successful examples have been reported in its application to the synthesis of deoxy aza sugars and alkaloids.[11] The azide reduction/stereoselective reductive amination cascade reaction derived from **4** was envisaged to lead to the asymmetric synthesis of **5** and **6**, which could be an ideal strategy in terms of both diastereoselectivity and step-economy due to the two-step sequence as noted in our retrosynthetic analysis.

Our synthesis commenced with the protection of the diosgenin (**1**) to afford **11** as its TBDPS ether.[1g] The resulting crude **11** reacted with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$,[12] leading to smoothly reductive cleavage of spiroketal to deliver furostan-26-alcohol **12**, which was directly subjected to Jones oxidation to give furostan-26-acid **10** in 76% yield over three steps. Subjection of **10** to the cascade bromo-lactonization reaction with trifluoroacetic anhydride (TFAA) and lithium bromide resulted in E-ring opening and C16 substitution of a bromide ion within the substrate, thereby generating the anticipated C16-bromolactone **9** in 78% yield in gram quantities.

With gram quantities of C16α-bromolactone **9** in hand, we began to study the hydrogenolysis of its C16−Br bond (Scheme 3). From the outset, we were concerned that the reductive debromination reaction may not exhibit regioselective control during palladium-catalyzed hydrogenolysis (see Tables S1 in the Supporting Information for details). However, when applying 10 atm of H_2, the reaction occurred smoothly with the addition of NaOAc as an additive under 10% Pd/C catalysis in dichloro-

Scheme 3. Synthesis of C16α-Bromolactone 9 by the Cascade Bromo-lactonization Process



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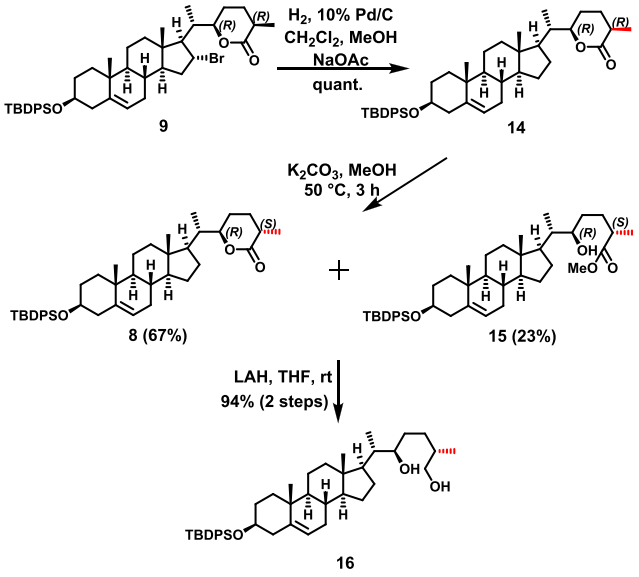
methane/methanol at room temperature for 7 h, resulting in the formation of (25*R*)-lactone **14** in quantitative yield (Scheme 4).

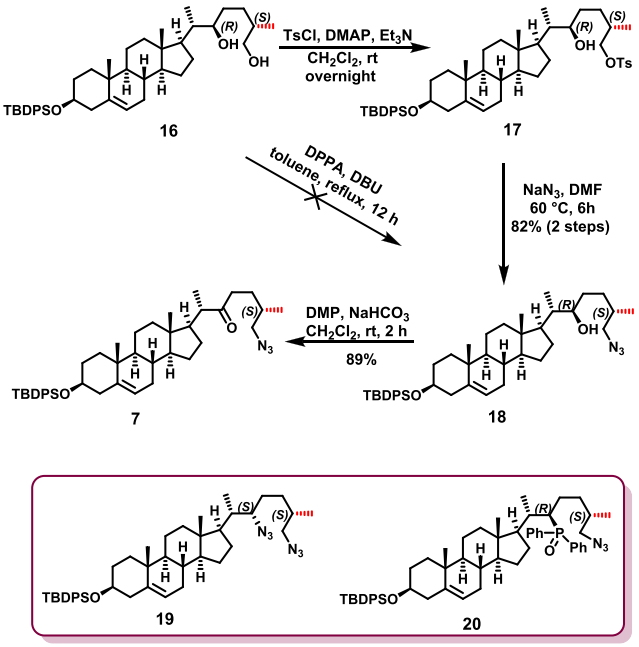
Scheme 4. Synthesis of 22,26-Diol 16 through the Epimerization of (*R*)-Configuration at C25



Treating (25*R*)-lactone **14** with anhydrous K_2CO_3 in methanol at 50 °C for 3 h completely epimerized the configuration from (*R*) to (*S*) to provide a mixture (~3:1) of (25*S*)-lactone **8** and the open-chained methyl ester **15**, which was subjected to lithium aluminum hydride (LAH) reduction without separation to afford 22,26-diol **16** in an overall yield of 94% over the two steps.

We continued with the construction of the azidoketone unit, as illustrated in Scheme 5. Initial attempts at the conversion of diol **16** into the azidoalcohol **18** in a one-step manner using a Merck azidation[13] were unsucessful. Treatment of **16** with

Scheme 5. Synthesis of Azidoketone 7

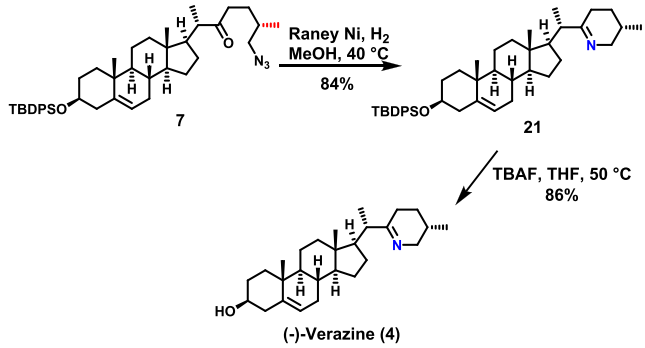


diphenyl phosphorazidate provided diazide product **19** in 15% yield and inseparable product **18** and phosphate **20** in 78% yield by silica gel column chromatography. This depressed result promoted us to opt to employ a stepwise approach for the elaboration of **18**.

Next, the transformation of diol **16** into azido ketone **7** was required, as shown in Scheme 5. Selective tosylation of the primary C26-OH of **16** afforded tosylate **17**, which, without purification, was subjected to NaN_3 substitution reaction to give the azido alcohol **18** in 82% yield. Subsequent oxidation of **18** with Dess-Martin periodinane (DMP) yielded azidoketone **7** in 89% yield.

Having successful access to the requisite azidoketone **7**, we investigated the intramolecular Staudinger aza-Witting reaction[14] to convert the azidoketone **7** into the desired cyclic imine **21**. Initially, our attempts to affect the cyclic imine formation resulted in decomposition of starting **7**, and only complex mixtures were obtained. Therefore, we then turned to the tandem azide hydrogenation/intramolecular cyclization of azidoketone **7** as an alternative tactic (see Table S2 in the Supporting Information for details). To our delight, treatment of **7** with Raney Ni in methanol under a balloon pressure of H_2 at 40 °C initiated this transformation to afford the desired cyclic imine **21** in 84% yield. Upon treating **21** with tetrabutylammonium fluoride (TBAF), the cleavage of the TBDPS ether residue smoothly proceeded to produce (−)-verazine (**4**) in 86% yield (Scheme 6). All the IR, ^1H, and ^{13}C NMR data for synthetic

Scheme 6. Formal Synthesis of (−)-Verazine (4)



(−)-**4** were identical to that reported for the natural product (see Tables S5−6 in the Supporting Information for details).[5a,d,9] Additionally, the specific rotation of (−)-**4**[$[\alpha]_D^{24}$ - 72.0 (*c* 1.50, MeOH)] was in good agreement with [$[\alpha]_D^{26}$ −65.0 (*c* 1.50, MeOH)], which confirmed the stereoconfiguration of (−)-verazine (**4**) assigned by Kingston and co-workers.[9]

As noted in our retrosynthetic analysis, the azidoketone **7** could serve as a common intermediate for the efficient synthesis of (−)-**5** and (−)-**6**, as shown in Scheme 7. A novel procedure for a one-pot three-step sequence including azide reduction, ketone amine cyclization, and imine reduction by treatment of **7** with $NaBH_4$ in the presence of $NaBH_4/NiCl_2{\cdot}6H_2O$ in methanol under mild conditions for 4 h resulted in the formation of the desired (−)-veramiline TBDPS ether **22** and its 22-epimer, (−)-oblonginine TBDPS ether **23**, which were isolated in 25 and 45% yield, respectively, by silica gel column chromatography. The structures of **22** and **23** were unambiguously confirmed by X-ray crystallographic analysis (Scheme 7 and Tables S3 and S4). In the final step of the

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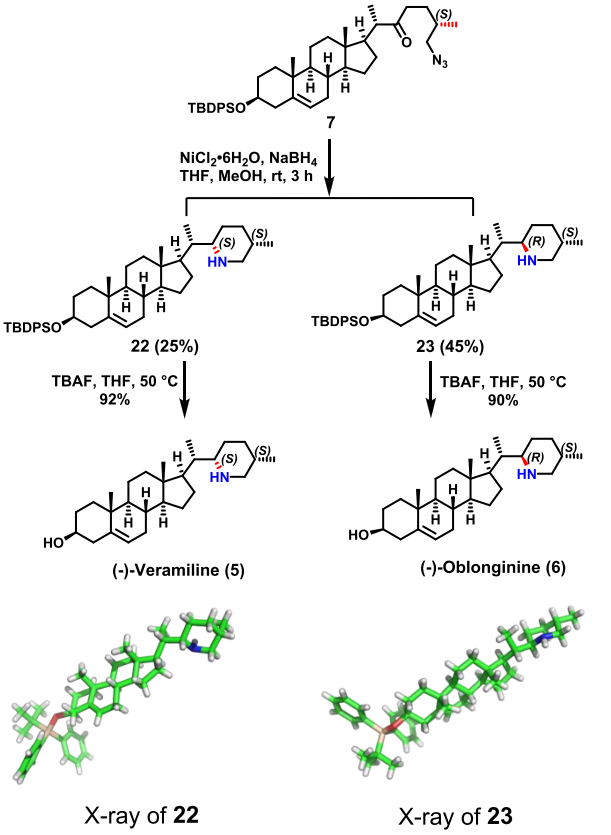
Scheme 7. Formal Synthesis of (−)-Veramiline (5) and (−)-Oblonginine (6)



synthesis, compounds **22** and **23** were treated with TBAF, which chemoselectively afforded cleavage of the TBDPS ether and produced (−)-veramiline (**5**) (proposed structure) and (−)-oblonginine (**6**) in 92 and 90% yield, respectively. The specific rotations, $[\alpha]_D^{25}$, of synthetic (−)-veramiline (**5**) (proposed structure), −43.5 (*c* 0.7, MeOH), compared to that of synthetic product (−)-**5**, −43 (*c* 0.7, MeOH),[9] and (−)-oblonginine (**6**), −37.2 (*c* 1.17, MeOH), compared to that of natural product (−)-**6**, −40.7 (*c* 0.11, $CHCl_3$),[7a] were identical. Surprisingly, comparison of the spectroscopic data of synthetic (−)-**5** with those reported by Kingston indicated a few differences,[9] especially in the ^{13}C NMR data regarding C16, C17, and C24−C27 (see Tables S7 and S8 in the Supporting Information for details). The ^{1}H and ^{13}C NMR spectra and specific rotation of the synthesized (−)-oblonginine (**6**) were in good agreement with those of natural (−)-**6**, as reported by Kadoto and co-workers in 1995 and Salder and co-workers in 1998 (see Tables S9 and S10 in the Supporting Information for details).[7]

In summary, we utilized our TFAA/LiBr-promoted cascade bromo-lactonization process of the furostan-26-acid to yield a chiral C16α-bromolactone building block with high regio- and stereoselectivity in facile asymmetric synthesis of naturally occurring *seco*-type cholestane alkaloids. We believe that the described strategy and methodologies should be widely applicable to the asymmetric synthesis of other related cholestane alkaloids. These studies are currently underway in our laboratory and will be reported 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.0c00747.

Detailed experimental procedures and ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

Accession Codes

CCDC 1900504−1900505 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(10) Applying Kingston's reaction condition ($NaBH_4$/MeOH/H_2O), it was found that this condition affected the reduction of (−)-**4** to provide a diastereoisomeric mixture of (−)-**5** and its 22-epimer (−)-**6** in a 1:1.3 ratio, which could not be separated by silica gel chromatography after our experimentation.

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