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# Divergent Synthesis of Solanidine and 22-*epi*-Solanidine

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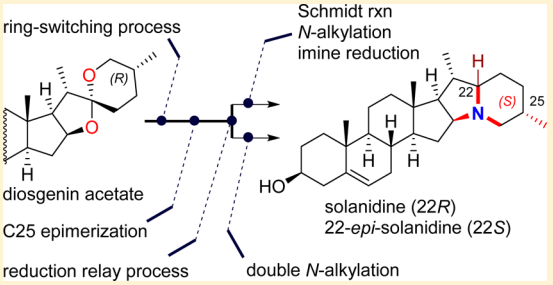
Supporting Information

**ABSTRACT:** A divergent synthesis of solanidine and 22-*epi*-solanidine, two 25*S* natural steroidal alkaloids, from 25*R*-configured diosgenin acetate, is described. Initially, solanidine was synthesized through a series of transformations including a cascade ring-switching process of furostan-26-acid, an epimerization of C25 controlled by the conformation of six-membered lactone ring, an intramolecular Schmidt reaction, and an imine reduction/intramolecular aminolysis process. To address the epimerization issue during Schmidt reaction, an improved synthesis was developed, which also led to a synthesis of 22-*epi*-solanidine. In this synthesis, selective transformation of azido lactone to azido diol and amino diol was realized through a reduction relay tactic. The azido diol was transformed to solanidine via an intramolecular Schmidt reaction/*N*-alkylation/reduction process and to 22-*epi*-solanidine via an intramolecular double *N*-alkylation process.




## INTRODUCTION

Possessing various bioactivities and structures, steroidal alkaloids have drawn great interest from researchers.[1] Solasodine (**2**) and solanidine (**4**) represent two types of cholestane alkaloids isolated from several potato species, mainly present as glycosides. The former is essentially an analogue of diosgenin (**1**), a steroidal sapogenin, and the latter has a different arrangement of rings EF (Figure 1). Solasodine (**2**) and tomatidenol (**3**) are known to act as natural insect deterrents, have antimicrobial properties, can inhibit acetylcholinesterase, and disrupt cell membranes.[2] Solanidine (**4**) and demissidine (**5**) can inhibit proliferation and exhibit obvious antitumor effect.[3]

Needing to replace one oxygen atom of the spiroketal with one nitrogen atom, the synthesis of solasodine (**2**) from diosgenin (**1**) has been widely investigated, resulting in ten syntheses.[4] However, fewer syntheses of solanidine (**4**) and demissidine (**5**) were reported. As shown in Scheme 1, **4** was synthesized from tomatidienol (**3**), a naturally occurring C25*S*-configured steroidal alkaloid, by Schreiber and Rönsch through reduction/oxidation manipulations.[5] Adam and Schreiber prepared **5** from pregnenolone acetate (**8**) by addition of 2-lithio-5-methylpyridine followed by nonstereoselective hydrogenation and Hofmann−Löffler−Freytag cyclization.[6] In 2013, Brewer and co-workers reported a 12-step synthesis of **5** from epiandrosterone, featuring a ring fragmentation 1,3-dipolar cycloaddition approach.[7] The synthesis of **4**/**5** from the corresponding steroidal sapogenin requires the replacement of both oxygen atoms of the spiroketal with one nitrogen atom and the epimerization of C25, which was considered unpractical and therefore less explored. Recently, we developed a synthesis of **4**/**5** from steroidal sapogenins, which, although efficient, suffered from severe epimerization which lowered the overall yield by one-third.[8] Herein, we report an improved synthesis of solanidine, which also enabled a synthesis of 22-*epi*-solanidine (**6**), the first solanidine-type alkaloid with C22*S* configuration discovered from nature.[9]

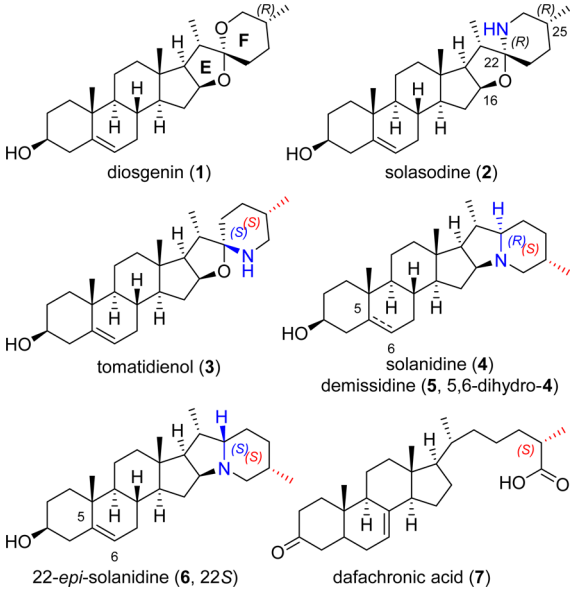



**Figure 1.** Structures of diosgenin and biologically interesting natural products.

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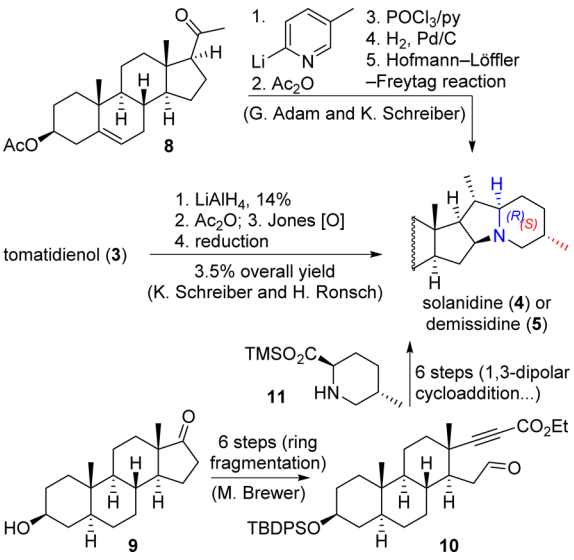
**Scheme 1. Reported Syntheses of Solanidine (4)/Demissidine (5)**



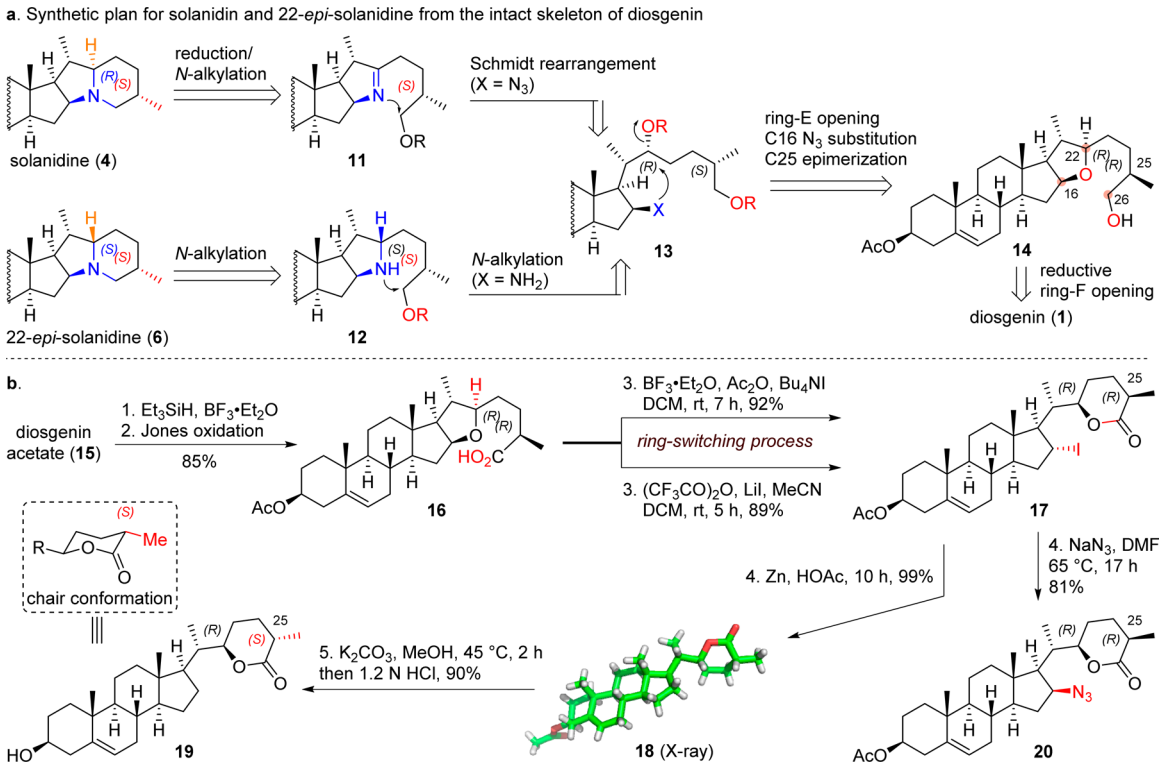

To synthesize **4**/**6** from diosgenin (**1**), we need to replace three C−O bonds (C16−O, C22−O, and C26−O) with C−N bonds, two of which should proceed stereoselectively, and to epimerize the configuration of C25. It was reported that the ring F of diosgenin (**1**) could be opened reductively to give the C22*R*-configured furostanol **14**,[10] based on which we devised our synthetic plan (Scheme 2). We envisioned that the C26−N bond of solanidine (**4**) could be constructed via an intramolecular *N*-alkylation and C22−N be established through an intramolecular Schmidt reaction of azide **13** followed by a substrate-controlled reduction of the resultant imine **11**. Similarly, both C26−N and C22−N bonds of 22-*epi*-solanidine (**6**) could be built via an intramolecular *N*-alkylation of amine **13**. Azide/amine **13** could be prepared from **14** via an epimerization of C25 and a nucleophilic substitution after opening ring E through C16 iodination.

## RESULTS AND DISCUSSION

As depicted in Scheme 2, our synthesis began with the preparation of furostan-26-acid **16** from diosgenin acetate (**15**) through a $BF_3{\cdot}Et_2O/Et_3SiH$ reduction-Jones oxidation process. We then developed a ring-switching process to open the ring E of **16** with the assistance of the C26-acid. Treatment of acid **16** with $BF_3{\cdot}Et_2O$ (12 equiv)/$Ac_2O$ (8 equiv) in the presence of $Bu_4NI$ (6 equiv) provided iodide **17** in high yield on multigram scale.[11] Considering that using excessive amount of $Bu_4NI$ was not convenient in practice, especially on a large scale, we optimized the ring-opening process. Finally, treating **16** with trifluoroacetic anhydride/lithium iodide in dichloromethane (DCM)/MeCN afforded **17** in comparable high yield on multigram scale.[12]

With **17** in hand, we first confirmed the stereochemistry of lactone ring and explored the epimerization of C25. The C16−I bond was reductively cleaved by subjecting **17** to Zn/HOAc in refluxing DCM to provide **18**, which was confirmed to be C22*R*- and C25*R*-configured via an X-ray analysis. Treatment of **18** with $K_2CO_3$ in MeOH at 45 °C for 2 h not only removed the C3-acetate, but also, to our delight, epimerized the C25, providing the 25*S*-configured lactone **19** in 90% yield as a single isomer on multigram scale. In **19**, both substituents (the steroidal backbone and the C26 methyl group) equatorially lie on chair-conformation lactone ring, thus, the epimerization is

**Scheme 2. (a) Synthetic Plan of Solanidine (4) and 22-*epi*-Solanidine (6) and (b) Ring-Switching Process and Epimerization of C25**



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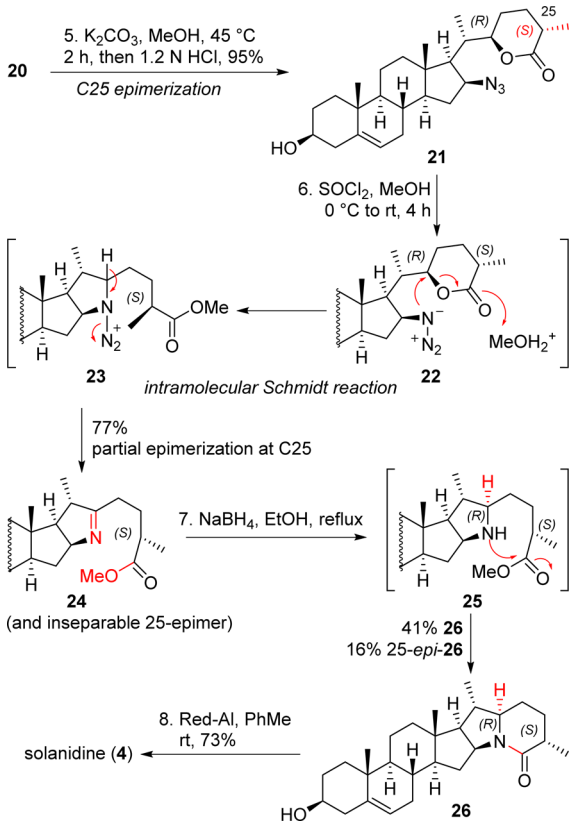
preferred. Lactone **19** is an advanced intermediate in Nishizawa's synthesis of osladin,[13] a plant sweetening agent, and the spectroscopic properties of the synthetic **19** are consistent with those reported, which, therefore, constituted a formal synthesis of osladin.[11]

Treated with sodium azide in DMF at 65 °C, **17** underwent substitution to deliver azide **20** in 81% yield. Likewise, epimerization of its C25 configuration from *R* to *S* was realized by treating with $K_2CO_3$ in MeOH at 45 °C for 2 h and then with 1.2 N HCl, giving **21** in 95% yield (Scheme 3).

**Scheme 3. Completion of the Synthesis of Solanidine (4)**



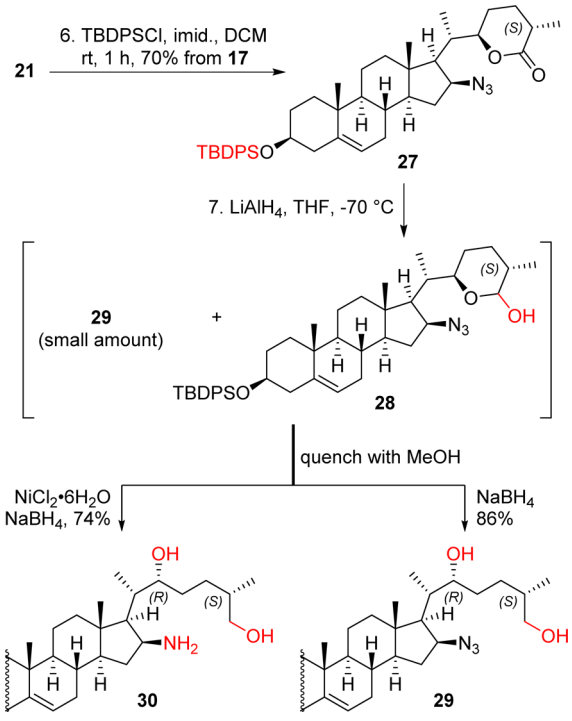

It is well-known that esters could serve as leaving groups under acidic conditions. For example, lactones could be converted to $\omega$-halo acids or esters upon treating with HBr or HCl. This property might be employed to trigger an intramolecular Schmidt reaction,[14] as the C16$\beta$ azido group was close to the electrophilic C22. After many attempts, we found that desired Schmidt reaction proceeded smoothly when **21** was treated with $SOCl_2$ in MeOH (generates in situ a methanolic solution of HCl) at ambient temperature, delivering imine **24** in good yield, with the exposed C3-OH not being affected. To our disappointment, the strong acidic condition caused partial epimerization of C25, and the isolated product was a 2/1 inseparable mixture of **24** and its C25-epimer. Using less amount of $SOCl_2$, conducting the reaction at lower temperatures, and preparing HCl solution by other methods did not provide better results. The mixture of inseparable epimers was therefore used in the next step.

Reduction of imine **24** and its C25-epimer with $NaBH_4$ in ethanol was accompanied by spontaneous intramolecular aminolysis, which was driven to completion by heating the reaction mixture at reflux, giving lactam **26** in 41% yield and 25-*epi*-**26** in 16% yield. Further reduction of **26** with sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) in toluene at ambient temperature gave solanidine (**4**) in 73% yield. Using the same route, demissidine (**5**) was also synthesized from tigogenin acetate in eight steps.[8]

Partial epimerization of the C25 occurred during the course of the $SOCl_2$-activated intramolecular Schmidt reaction of **21** because it is at the $\alpha$ position of a carbonyl group. Converting the lactone of **21** to a 22,26-diol would solve this problem, thus, we altered our synthesis accordingly. As depicted in Scheme 2a, transforming both hydroxyl groups of azido diol **13** (X = $N_3$, R = H) to mesylates would allow us to perform a similar intramolecular Schimdt reaction to form an imine (like **24**), which could undergo *N*-alkylation again and the generated imine salt be reduced to give solanidine **4**. On the other hand, reducing both azide and lactone to amino diol **13** (X = $NH_2$, R = H) and performing *N*-alkylation twice would deliver 22-*epi*-solanidine **6**.

As azides are reactive under reducing conditions and most reagents that could reduce esters also reduce azides, the first challenge of our plan was to convert lactone to diol in the presence of azido group. One advantage we could take is that the C16-azide is a sterically hindered one; chemoselective reduction might be achieved at low temperature. The C3-OH of **21** was protected as TBDPS ether to give **27** in quantitative yield (70% from **17** over 3 steps, Scheme 4). Treatment of **27**

**Scheme 4. Divergent Preparation of 29 and 30 Through a Reduction Relay Procedure**




with diisobutylaluminum hydride (DIBAL-H) in dichloromethane at −70 °C gave a complex mixture. Reduction of **27** with $LiAlH_4$ at 0 °C also gave a mixture of **29**, **30**, and azido hemiacetal **28**. To our delight, at −70 °C, this reaction gave only **29** and **28**, which, we reasoned, could lead to **29** upon further reduction of the crude with $NaBH_4$. We therefore reduced **27** with $LiAlH_4$ at −70 °C, quenched the reaction with MeOH, and added $NaBH_4$ to the mixture to convert **28** to **29**



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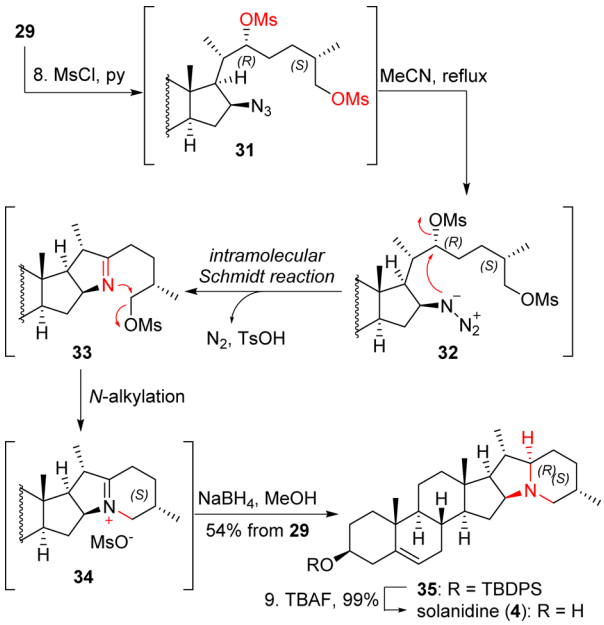
completely. This reduction relay procedure provided the azido diol **29** in one flask with an 86% yield.

Preparation of amino diol **30**, which, we thought at first, could be realized via performing the $LiAlH_4$ reduction of **27** at room temperature, was somewhat problematic. The reduction could not be driven to completion at ambient temperature with excess of $LiAlH_4$ or DIBAL-H. At elevated temperatures, a complex mixture was obtained. Considering $NiCl_2{\cdot}6H_2O$/$NaBH_4$ could also convert azides to amines,[15] we added $NiCl_2{\cdot}6H_2O$ (0.20 equiv) to the previous reduction system and obtained **30** in 74% yield from **27**.

With both **29** and **30** in hand, we tried to convert them to **4** and **6**, respectively. As shown in Scheme 5, treatment of **29**

**Scheme 5. Improved Synthesis of Solanidine**

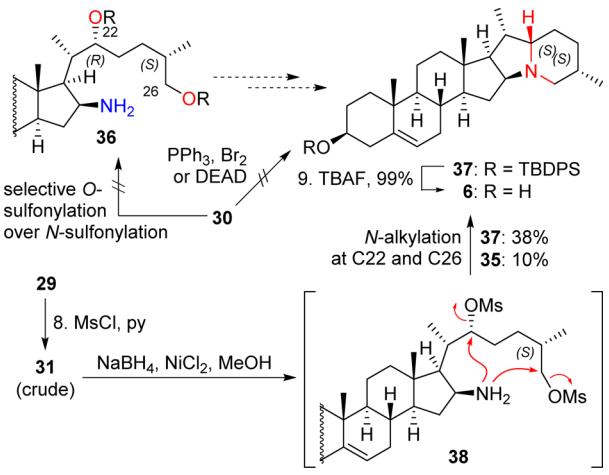



with MsCl (8 equiv) gave bismesylate **31**, which, without purification, was heated at reflux in MeCN to promote the intramolecular Schmidt reaction and the *N*-alkylation. The reaction proceeded smoothly and the newly formed imine salt was treated with $NaBH_4$ in MeOH to set the correct C22 configuration under the control of substrate, delivering the protected solanidine **35** in 54% yield. Removal of the TBDPS group of **35** with TBAF afforded solanidine (**4**), the analytical data of which matched with those reported.[8] In practice, the process of converting **29** to **35** could be carried out in one flask without purification.

We then turned to synthesize 22-*epi*-solanidine (**6**) from the amino diol **30**, which was found difficult to realize (Scheme 6). Selective transformation of C26-OH to 4-methylbenzenesulfonate or of both C22- and C26-OHs in the presence of C16-$NH_2$ to sulfonates (Ms or Ts) were unsuccessful. Other conditions that reportedly could transform amino alcohols to cyclic amines (e.g., $PPh_3$/DEAD;[16] $PPh_3/Br_2$;[17] or $SOCl_2$[18]) also did not work.

Failing to synthesize **6** from **30**, we revisited our plan and considered the azido diol **29** more suitable for our purpose because it did not need selective transformations. We therefore treated **29** with MsCl in pyridine/DCM and the crude azide **31** with $NaBH_4/NiCl_2{\cdot}6H_2O$ in ether/MeOH, and found that the resultant **38** underwent the wanted double *N*-alkylation

**Scheme 6. Completion of the Synthesis of 22-*epi*-Solanidine 6**




spontaneously, delivering **37** in 38% yield, along with **35** in 10% yield.[19] Removal of the TBDPS with TBAF gave 22-*epi*-solanidine (**6**), the analytical data of which matched with those reported.[9]

## CONCLUSION

In summary, we developed an efficient synthesis of solanidine (**4**) from diosgenin acetate, featuring a cascade ring-switching process of the furostan-26-acid **16**, a $SOCl_2$/MeOH-promoted intramolecular Schmidt reaction of the azido lactone **21**, and a substrate-controlled, stereoselective reduction/intramolecular aminolysis. This synthetic route minimized the use of protecting groups, but suffered from severe epimerization in the course of Schmidt reaction.

We then developed an improved route leading to both solanidine **4** (24% overall yield) and 22-*epi*-solanidine **6** (17% overall yield). Selective transformation of the azido lactone **27** to the azido diol **29** and the amino diol **30** was realized via stepwise reduction. Diol **29** was transformed to solanidine (**4**) through an intramolecular Schmidt reaction/*N*-alkylation/reduction process and to 22-*epi*-solanidine (**6**) through an intramolecular double *N*-alkylation, respectively. The strategy and chemistry described herein could also be employed to synthesize other 25*S*-configured steroidal natural products, such as dafachronic acid A and tomatine-related steroidal alkaloids, from steroidal sapogenins.

## EXPERIMENTAL SECTION

**General Methods.** All reactions sensitive to air or moisture were performed in flame-dried round-bottom flasks with rubber septum under a positive pressure of argon or nitrogen atmosphere, unless otherwise noted. Air and moisture-sensitive liquids and solutions were transferred via syringe and stainless steel cannula. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, methylene chloride from calcium hydride, *N*,*N*-dimethylformamide (DMF) from calcium hydride under reduced pressure, others according to the standard procedures described in Purification of Laboratory Chemicals. Yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using an ethanolic solution of phosphomolybic acid, and heat as developing agents. NMR spectra were recorded on 400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference [$^1$H NMR: $CHCl_3$ (7.26), DMSO-$d_6$ (2.50), pyridine-$d_5$ (8.74); $^{13}$C NMR: $CDCl_3$ (77.16), DMSO-$d_6$ (39.52),



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pyridine-$d_5$ (150.35)]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad.

*16α-Iodo Lactone* ***17***.[11] Method 1: To a stirred solution of furostan-26-acid **16** (crude product prepared from diosgenin acetate (15.16 g, 33 mmol) through reduction and Jones oxidation[8]) and LiI (13.15 g, 99 mmol, 3 equiv) in DCM/MeCN (200 mL/50 mL, freshly distilled) at 0 °C was added trifluoroacetic anhydride (9.30 mL, 66 mmol, 2 equiv) slowly. The resulting mixture was stirred for 1 h at ambient temperature and TLC indicated that **16** was completely consumed. The reaction was quenched with saturated aqueous $NaHCO_3$/ $NaSO_3$ solution, and extracted with DCM (3 × 70 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, concentrated under reduced pressure, and purified via flash column chromatography on silica gel (PE/EA: 8/1 to 3/1) to deliver **17** (14.40 g, 75% from **15**) as a white solid. Method 2: To a stirred solution of acid **16** (945 mg, 2 mmol) in DCM (20 mL, freshly distilled) at 0 °C was added a solution of $Bu_4NI$ (4.46 g, 12 mmol, 6 equiv) in DCM (5 mL) solution, $BF_3{\cdot}Et_2O$ (1.6 mL, 16 mmol, 8 equiv, dropwise), and $Ac_2O$ (1.6 mL, 16 mmol, 8 equiv), sequentially. The reaction mixture was stirred for 7 h at 0 °C and TLC indicated that acid **16** was completely consumed. Quenched with saturated aqueous $NaHCO_3$ solution, extracted with DCM (3 × 50 mL), combined organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. Purification via flash column chromatography on silica gel (PE/EA: 10/1−6/1−2/1−1/1) delivered lactone **17** (916 mg, 92%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.38 (s, 1H), 4.73 (d, $J$ = 11.5 Hz, 1H), 4.61 (dt, $J$ = 10.4, 5.3 Hz, 1H), 4.11−4.08 (m, 1H), 2.68 (q, $J$ = 7.4 Hz, 1H), 2.34−2.30 (m, 2H), 2.04 (s, 3H), 1.24 (d, $J$ = 6.8 Hz, 3H), 1.01 (s, 3H), 0.96 (d, J = 6.7 Hz, 3H), 0.72 (s, 3H).

*Lactone* ***18***.[11] Iodo lactone **17** was treated with activated zinc powder (488 mg, 7.5 mmol, 15 equiv) in HOAc (10 mL) at ambient temperature for 10 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with DCM for three times. The combined organic layers were dried over $Na_2SO_4$, concentrated under reduced pressure, and purified through flash column chromatography on silica gel (PE/EA: 10/1−8/1−6/1) to produce lactone **18** (228 mg, 99%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.37 (1H, d, $J$ = 4.6 Hz), 4.63−4.57 (1H, m), 4.34 (1H, dt, $J$ = 8.8, 4.1 Hz), 2.61 (1H, dq, $J$ = 14.5, 6.9 Hz), 2.33−2.31 (2H, m), 2.03 (3H, s), 1.22 (3H, d, $J$ = 6.8 Hz), 1.02 (3H, s), 0.98 (3H, d, $J$ = 6.7 Hz), 0.71 (3H, s).

*25S-Lactone* ***19***.[11] Lactone **18** (128 mg, 0.28 mmol) was treated with $K_2CO_3$ (386 mg, 2.8 mmol, 10 equiv) in MeOH (5 mL) at 45 °C for 2 h. The reaction mixture was then acidified with diluted HCl aqueous solution at ambient temperature, and stirred for 2 h. The mixture was diluted with water and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, concentrated, and purified through flash column chromatography on silica gel (PE/EA: 6/1−4/1−3/1) to afford lactone **19** (105 mg, 90%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.35 (1H, d, $J$ = 5.1 Hz), 4.38 (1H, dt, $J$ = 11.6, 3.3 Hz), 3.56−3.48 (1H, m), 2.42−2.36 (1H, m), 1.29 (3H, d, $J$ = 7.0 Hz), 1.01 (3H, s), 0.95 (3H, d, $J$ = 6.7 Hz), 0.71 (s, 3H).

*Azido Lactone* ***20***.[8] A solution of iodide **17** (10.01 g, 17.2 mmol) in dry DMF (75 mL) was treated with $NaN_3$ (3.36 g, 51.6 mmol, 3 equiv) at 65 °C for 15 h. The mixture was quenched with water (300 mL) and extracted with EtOAc (200 mL × 4). The combined organic layers were washed with saturated aqueous LiCl solution (100 mL × 2) and brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude **20** was used in the next step without purification. A 1.50 g (3.1 mmol) scale reaction was performed to give **20** (1.50 g) in 81% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.37 (d, $J$ = 4.7 Hz, 1H), 4.60 (dt, $J$ = 15.7, 7.2 Hz, 1H), 4.55−4.47 (m, 1H), 4.05 (td, $J$ = 8.3, 5.3 Hz, 1H), 2.72−2.59 (m, 1H), 2.04 (s, 3H), 1.23 (d, $J$ = 6.8 Hz, 3H), 1.03 (s, 3H), 1.00 (d, $J$ = 6.8 Hz, 3H), 0.85 (s, 3H).

*25S-Azido Lactone* ***21***.[8] A solution of the crude **20** and $K_2CO_3$ (23.74 mg, 172 mmol, 10 equiv) in MeOH (170 mL) was heated to react at 45 °C for 3 h. Diluted HCl aqueous solution (4.8 M, 200 mL) was added when TLC showed that the starting material was fully consumed, and the reaction was stirred for another 4 h at ambient temperature. The mixture was extracted with $CHCl_2$ (2 × 150 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, concentrated to dryness, and used in the next step without purification. A 500 mg (0.86 mmol) scale reaction was performed to give **21** (406 mg) in 95% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.34 (d, $J$ = 4.9 Hz, 1H), 4.56 (dt, $J$ = 11.4, 3.4 Hz, 1H), 4.03 (dd, $J$ = 8.0, 3.0 Hz, 1H), 3.57−3.46 (m, 1H), 1.31 (d, $J$ = 7.0 Hz, 3H), 1.02 (s, 3H), 0.97 (d, $J$ = 6.8 Hz, 3H), 0.85 (s, 3H).

*Imine* ***24***.[8] To a solution of **21** (1.35 g, 3.0 mmol) in MeOH (30 mL) was added $SOCl_2$ (5 mL) slowly at 0 °C. The resulting solution was stirred at 0 °C for 10 min and then at ambient temperature for 4 h. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with DCM (50 mL × 4). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography on silica gel (PE/EA: 1/1−0/1) to give **24** (1.0 g, 77%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.34 (d, $J$ = 5.2 Hz, 1H), 4.45 (dd, $J$ = 15.1, 7.0 Hz, 1H), 3.67 (d, $J$ = 4.0 Hz, 4H), 3.51 (dt, $J$ = 11.0, 5.8 Hz, 1H), 2.67−2.59 (m, 1H), 2.51 (dq, $J$ = 14.1, 7.0 Hz, 1H), 1.18 (dd, $J$ = 7.0, 2.5 Hz, 4H), 1.06 (d, $J$ = 7.4 Hz, 4H), 0.99 (s, 3H), 0.53 (s, 3H).

*Amide* ***26***.[8] To a solution of **24** (350 mg, 0.8 mmol) in EtOH (10 mL) was added $NaBH_4$ (120 mg, 3.2 mmol) at ambient temperature under argon. The mixture was stirred at ambient temperature for 2 h. Imine **24** disappeared on TLC plate (two sets of products formed) and the mixture was heated at reflux until the more polar products were completely converted to the less polar ones. Concentration under reduced pressure and purification of the crude product (PE/EA: 1/1 to EA) afforded **26** (134 mg, 41%) as a white solid and 25-*epi*-**26** (53 mg, 16%) as a white solid. **26**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.34 (d, $J$ = 4.6 Hz, 1H), 3.91 (dd, $J$ = 17.4, 8.3 Hz, 1H), 3.51 (dd, $J$ = 13.0, 8.7 Hz, 1H), 3.09 (t, $J$ = 9.8 Hz, 1H), 2.37 (dt, $J$ = 14.6, 8.1 Hz, 1H), 2.33−2.18 (m, 3H), 1.17 (d, $J$ = 7.0 Hz, 3H), 1.00 (d, $J$ = 6.1 Hz, 3H), 0.98 (d, $J$ = 6.4 Hz, 3H), 0.76 (s, 3H). 25-*epi*-**26**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.34 (d, $J$ = 3.9 Hz, 1H), 3.98−3.85 (m, 1H), 3.51 (d, $J$ = 4.4 Hz, 1H), 3.10−3.02 (m, 1H), 2.45−2.31 (m, 2H), 2.25 (dd, $J$ = 17.2, 8.0 Hz, 2H), 1.21 (d, $J$ = 7.3 Hz, 3H), 0.99 (d, $J$ = 6.7 Hz, 6H), 0.76 (s, 3H).

*Solanidine* ***4***.[8] To a solution of amide **26** (50 mg, 0.12 mmol) in toluene (2.0 mL, freshly distilled) was added Red-Al (60 wt% in toluene, 0.22 mL, 1.2 mmol, 10 equiv) at 0 °C under argon. The ice−water bath was removed and the mixture was stirred at ambient temperature until TLC showed complete consumption of **26** (3.5 h). The mixture was quenched with 1 N aqueous NaOH solution and extracted with chloroform (50 mL × 3). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE/EA: 1/1 to EA) afforded solanidine **4** (35 mg, 73%) as a white solid.

*16β-Azido Lactone* ***27***. The crude **21** and imidazole (2.345 g, 34 mmol, 2 equiv) were dissolved in DCM (90 mL), and TBDPSCl (5.40 mL, 20.6 mmol, 1.2 equiv) was added slowly at 0 °C. The reaction was stirred at ambient temperature for 1 h, then quenched with a saturated solution of $NH_4Cl$, diluted with water, and extracted with DCM (100 mL × 3). The combined organic layers were washed with brine, dried over $Na_2SO_4$, concentrated under reduced pressure, and purified through flash column chromatography (PE/EA: 10/1 to 8/1) on silica gel to give **27** (14.40 g, 70% for 3 steps) as a colorless syrup. $R_f$ = 0.40 (silica gel, PE/EA: 5/1); $[\alpha]_D^{22}$ + 6.0 ($c$ 1.00, DCM); IR (film): 2988, 2015, 1728, 1461, 1275, 1260, 1084, 764, 749, 704 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72−7.63 (m, 4H), 7.45−7.32 (m, 6H), 5.14−5.09 (m, 1H), 4.55 (dt, $J$ = 11.4, 3.5 Hz, 1H), 4.06−3.95 (m, 1H), 3.57−3.47 (m, 1H), 1.31 (d, $J$ = 7.1 Hz, 3H), 1.06 (s, 9H), 0.99 (s, 3H), 0.95 (d, $J$ = 6.8 Hz, 3H), 0.82 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.6 (C), 141.5 (C), 135.7 (2CH), 135.7 (2CH), 134.7 (C), 134.7 (C), 129.4 (CH), 129.4 (CH), 127.4 (2CH), 127.4 (2CH), 120.4 (CH), 83.0 (CH), 73.1 (CH), 61.3 (CH), 55.1 (CH), 54.7 (CH), 49.8 (CH), 42.9 (C), 42.4 ($CH_2$), 39.6 ($CH_2$), 37.1 ($CH_2$), 36.4 (CH), 35.1 (CH), 32.8 ($CH_2$), 31.8 ($CH_2$), 31.6 ($CH_2$), 31.4 (CH), 28.5 ($CH_2$), 27.0 ($3CH_3$), 23.0 ($CH_2$), 20.5 ($CH_2$), 19.4



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($CH_3$), 19.1 (C), 17.3 ($CH_3$), 12.6 ($CH_3$), 12.2 ($CH_3$); MS-ESI (*m*/*z*): 732.3 $[M+K]^+$; HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ calcd for $C_{43}H_{59}O_3N_3Si$: 716.4218, found: 716.4215.

*Azido Diol* ***29***. At −70 °C, a solution of lactone **27** (693 mg, 1.0 mmol) in THF (10 mL) was treated with $LiAlH_4$ (133 mg, 3.5 mmol, 3.5 equiv) for 1.5 h. TLC analysis indicated the complete consumption of the starting material. The reaction was quenched with MeOH at −70 °C and treated with $NaBH_4$ (302 mg, 8 mmol, 8 equiv) at 0 °C for 3 h. Then the mixture was quenched with 1.2 N HCl, diluted with MeOH, concentrated under reduced pressure, and purified through flash column chromatography on silica gel (PE/EA: 5/2 to 2/1) to give diol **29** (598 mg, 86%) as a colorless syrup. $R_f$ = 0.33 (silica gel, PE/EA: 1/1); $[\alpha]_D^{22}$ (*c*, DCM); IR (film): 3362, 2933, 2103, 1471, 1462, 1427, 1110 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.72−7.63 (m, 4H), 7.48−7.31 (m, 6H), 5.11 (s, 1H), 4.08−4.01 (m, 1H), 3.72 (d, *J* = 10.3 Hz, 1H), 3.55−3.40 (m, 3H), 1.05 (s, 9H), 0.99 (s, 3H), 0.95 (d, *J* = 7.8 Hz, 3H), 0.94 (d, *J* = 8.0 Hz, 2H), 0.80 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 141.4 (C), 135.7 (2CH), 135.7 (2CH), 134.8 (C), 134.7 (C), 129.4 (CH), 129.4 (CH), 127.4 (2CH), 127.4 (2CH), 120.5 (CH), 73.6 (CH), 73.1 (CH), 67.8 ($CH_2$), 62.1 (CH), 56.1 (CH), 54.7 (CH), 49.8 (CH), 42.7 (C), 42.4 ($CH_2$), 39.5 ($CH_2$), 38.1 (CH), 37.1 ($CH_2$), 36.4 (C), 36.0 (CH), 32.9 ($CH_2$), 31.8 ($CH_2$), 31.6 ($CH_2$), 31.4 (CH), 30.5 ($CH_2$), 27.7 ($CH_2$), 27.0 ($3CH_3$), 20.5 ($CH_2$), 19.4 ($CH_3$), 19.1 (C), 17.1 ($CH_3$), 12.2 ($CH_3$), 12.1 ($CH_3$); MS-ESI (*m*/*z*): 720.3 $[M+Na]^+$; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{43}H_{63}O_3N_3Si$: 698.4711, found: 698.4710.

*Amino Diol* ***30***. At −70 °C, a solution of **27** (346 mg, 0.5 mmol) in THF (10 mL) was treated with $LiAlH_4$ (57 mg, 1.5 mmol, 3 equiv) for 2 h. TLC analysis indicated the complete consumption of the starting material. The reaction was quenched with MeOH (5 mL) at −70 °C; $NiCl_2{\cdot}6H_2O$ (23 mg, 0.1 mmol, 0.2 equiv) and $NaBH_4$ (156 mg, 4 mmol, 8 equiv) were added at 0 °C and the mixture was stirred at ambient temperature for 14 h. Then the mixture was diluted with MeOH, concentrated under reduced pressure, and purified through flash column chromatography on silica gel (PE/EA: 10/1 to 1/1) to give diol **30** (247 mg, 74%) as a colorless syrup. $R_f$ = 0.17 (silica gel, DCM/MeOH: 9/1); $[\alpha]_D^{22}$ −24.1 (*c* 1.00, DCM); IR (film): 3365, 2932, 1729, 1462, 1427, 1110, 1087 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-*d6*) $\delta$ 7.64−7.53 (m, 4H), 7.46−7.34 (m, 6H), 5.09−5.01 (m, 1H), 4.36 (br s, 1H), 3.66−3.55 (m, 1H), 3.51−3.38 (m, 1H), 3.28−3.20 (m, 2H), 3.19−3.07 (m, 1H), 2.25 (t, *J* = 11.6 Hz, 1H), 2.14−1.97 (m, 2H), 0.97 (s, 9H), 0.89 (s, 3H), 0.86 (d, *J* = 6.2 Hz, 3H), 0.80 (d, *J* = 7.8 Hz, 3H), 0.78 (s, 3H);$^{13}C$ NMR (100 MHz, DMSO-*d6*) $\delta$ 140.5 (C), 135.2 (4CH), 133.85(2C), 129.8 (2CH), 127.8 (4CH), 120.8 (CH), 73.5 (CH), 72.9 (CH), 66.1 ($CH_2$), 54.7 (CH), 53.5 (CH), 51.6 (CH), 49.0 (CH), 42.5 ($CH_2$), 40.4 ($CH_2$), 36.6 (CH), 35.9 (CH), 35.6 (C), 31.9 ($CH_2$), 31.5 ($CH_2$), 31.0 ($CH_2$), 30.5 (CH), 29.4 ($CH_2$), 29.1 ($CH_2$), 26.8 (CH), 20.1 ($CH_2$), 19.0 (CH), 18.7 (C), 17.3 ($CH_3$), 14.0 ($CH_3$), 12.7 (CH); MS-ESI (*m*/*z*): 672.4 $[M+H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{43}H_{65}O_3NSi$: 672.4806, found: 672.4802.

*Protected Solanidine* ***35***. To a solution of diol **29** (100 mg, 0.14 mmol) and DMAP (2.0 mg, 0.014 mmol, 0.1 equiv) in DCM/pyridine (2.0 mL/0.50 mL) was added MsCl (0.090 mL, 1.1 mmol, 8 equiv) at 0 °C. The resulting mixture was stirred at ambient temperature for 9 h, then quenched with a saturated solution of $NaHCO_3$ (5 mL), diluted with water (10 mL), and extracted with DCM (5 mL × 3). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The crude was dissolved in MeCN (5 mL) and the solution was stirred at reflux for 7 h. The solvent was switched to MeOH (10 mL) and the resulting solution was treated with $NaBH_4$ (42 mg, 1.1 mmol, 8 equiv) at ambient temperature for 10 h. The reaction was quenched with water, diluted with MeOH, concentrated under reduced pressure, and purified through flash column chromatography on silica gel (PE/EA: 6/1 to 2/1) to afford the protected solanidine **35** (51 mg, 54%) as a white solid. $R_f$ = 0.50 (silica gel, PE/EA: 3/1); mp: 139.5−141.3 °C; $[\alpha]_D^{22}$ −15.1 (*c* 0.45, DCM); IR (film): 3070, 2929, 2856, 1472, 1427, 1261, 1110, 1087 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.70−7.64 (m, 4H), 7.45−7.32 (m, 6H), 5.12 (d, J = 5.1 Hz, 1H), 3.58−3.46 (m, 1H), 2.83 (dd, *J* = 10.2, 3.1 Hz, 1H), 2.59 (dt, *J* = 7.4, 6.4 Hz, 1H), 2.38−2.27 (m, 1H), 2.13 (dd, *J* = 13.3, 2.9 Hz, 1H), 1.95−1.87 (m, 1H), 1.05 (s, 9H), 0.99 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 8.7 Hz, 3H), 0.82 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 141.3 (C), 135.8 (2CH), 135.7 (2CH), 134.8 (C), 134.8 (C), 129.4 (CH), 129.4 (CH), 127.4 (2CH), 127.4 (2CH), 121.1 (CH), 74.6 (CH), 73.2 (CH), 69.0 (CH), 63.0 (CH), 60.3 ($CH_2$), 57.6 (CH), 50.1 (CH), 42.5 ($CH_2$), 40.2 ($CH_2$), 39.9 (C), 37.2 ($CH_2$), 36.6 (CH), 33.4 ($CH_2$), 32.0 ($CH_2$), 31.9 ($CH_2$), 31.6 (CH), 31.3 ($CH_2$), 31.1 (CH), 29.3 ($CH_2$), 27.0 ($3CH_3$), 20.9($CH_2$), 19.5 ($CH_3$), 19.4 ($CH_3$), 19.1 (C), 18.3 ($CH_3$), 16.9 ($CH_3$); MS-ESI (*m*/*z*): 636.4 $[M+H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{43}H_{61}ONSi$: 636.4595, found: 636.4593.

*Solanidine (****4****)*. A solution of **35** (38 mg, 0.06 mmol) in THF (3.0 ML) was treated with TBAF (1.0 M, 1.0 mL, 1.0 mmol) at 50 °C for 2 h. The reaction was quenched with water, concentrated under reduced pressure, and purified through column chromatography on silica gel (PE/EA: 5/2 to 2/1) to afford solanidine **4** (24 mg, 99%) as a white solid. $R_f$ = 0.83 (silica gel, PE/EA: 1/1); mp: 208.3−209.5 °C; $[\alpha]_D^{22}$ −20.8 (*c* 0.50, DCM); IR (film): 3246, 2927, 1453, 1372, 1053, 1009 $cm^{-1}$; $^1H$NMR (400 MHz, $CDCl_3$) $\delta$ 5.35 (d, *J* = 5.1 Hz, 1H), 3.57−3.46 (m, 1H), 2.91−2.81 (m, 1H), 2.68−2.57 (m, 1H), 2.36−2.15 (m, 2H), 1.02 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.84 (s, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 140.9 (C), 121.8 (CH), 74.8 (CH), 71.9 (CH), 69.2 (CH), 63.2 (CH), 60.4 ($CH_2$), 57.8 (CH), 50.4 (CH), 42.5 ($CH_2$), 40.4 (C), 40.1 ($CH_2$), 37.4 ($CH_2$), 36.8 (CH), 36.8 (C), 33.5 ($CH_2$), 32.2 ($CH_2$), 31.8 (CH), 31.5 ($CH_2$), 31.2 (CH), 31.2 ($CH_2$), 29.5 ($CH_2$), 21.1 ($CH_2$), 19.7 ($CH_3$), 19.6 ($CH_3$), 18.5 ($CH_3$), 17.1 ($CH_3$); MS-ESI (*m*/*z*): 398.3 $[M+H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{27}H_{43}ON$: 398.3417, found: 398.3416.

*Protected 22-epi-Solanidine* ***37***. To a solution of diol **29** (100 mg, 0.14 mmol) and DMAP (2.0 mg, 0.014 mmol, 0.1 equiv) in DCM/pyridine (2.0 mL/0.50 mL) was added MsCl (0.090 mL, 1.1 mmol, 8 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 7 h, then quenched with a saturated solution of $NaHCO_3$ (5 mL), and extracted with ether (2 mL × 3). To the combined organic layers were added sequentially MeOH (3.0 mL), $NiCl_2{\cdot}6H_2O$ (7.0 mg, 0.029 mmol, 0.2 equiv), and $NaBH_4$ (42 mg, 1.1 mmol, 8 equiv) at 0 °C. The mixture was stirred at ambient temperature for 10 h and another portion of $NaBH_4$ (42 mg, 1.1 mmol, 8 equiv) was added. The reaction mixture was stirred for another 5 h, quenched with water, diluted with MeOH, concentrated under reduced pressure, and purified via flash column chromatography on silica gel (PE/EA: 6/1 to 2/1) to furnish the protected 22-*epi*-solanidine **37** (34 mg, 38%) as a yellow syrup and the protected solanidine **35** (9.1 mg, 10%). $R_f$ = 0.33 (silica gel, DCM/MeOH: 15/1); $[\alpha]_D^{22}$ −11.9 (*c* 0.30, DCM); IR (film): 3070, 2929, 2855, 1460, 1427, 1378, 1110, 864 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (dd, *J* = 6.0, 1.6 Hz, 4H), 7.44−7.31 (m, 6H), 5.12−5.09 (m, 1H), 3.69−3.57 (m, 1H), 3.59−3.46 (m, 1H), 2.62 (d, *J* = 11.3 Hz, 1H), 2.51 (d, *J* = 9.8 Hz, 1H), 2.33 (t, *J* = 10.9 Hz, 2H), 2.13 (dd, *J* = 13.4, 3.0 Hz, 1H), 1.06 (d, *J* = 7.2 Hz, 1H), 1.05 (s, 9H), 0.99 (s, 3H), 0.88 (d, *J* = 7.1 Hz, 3H), 0.75 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 141.3 (C), 135.7 (2CH), 135.7 (2CH), 134.8 (2C), 129.4 (CH), 129.4 (CH), 127.4 (2CH), 127.4 (2CH), 121.0 (CH), 73.2 (CH), 67.5 (CH), 64.9 (CH), 60.7 (CH), 54.6 (CH), 50.1 (CH), 42.5 ($CH_2$), 41.1 (C), 40.6 ($CH_2$), 37.1 ($CH_2$), 36.7 (CH), 35.4 ($CH_2$), 32.3 ($CH_2$), 31.8 ($CH_2$), 30.6 (CH), 30.3 ($CH_2$), 28.1 (CH), 27.0 ($3CH_3$), 26.4 ($CH_2$), 21.7 ($CH_2$), 20.9 ($CH_2$), 19.4 ($CH_3$), 19.1 (C), 18.5 ($CH_3$), 17.8 ($CH_3$), 14.7 ($CH_3$); MS-ESI (*m*/*z*): 636.4 $[M+H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{43}H_{61}ONSi$: 636.4595, found: 636.4587.

*22-epi-Solanidine (****6****)*. A solution of **37** (10.0 mg, 0.016 mmol) in THF (1.0 ML) was treated with TBAF (0.5 M, 1.0 mL, 0.5 mmol) at 60 °C for 4 h. The reaction was quenched with water, concentrated under reduced pressure, and purified through column chromatography on silica gel (PE/EA: 5/2 to 2/1) to afford 22-*epi*-solanidine **6** (6.0 mg, 99%) as a white solid. $R_f$ = 0.50 (silica gel, DCM/MeOH: 15/1); mp: 140.3−141.5 °C; $[\alpha]_D^{22}$ −8.6 (*c* 0.30, DCM), − 30.8 (*c* 0.11, MeOH) (ref −35.6 (*c* 0.11, MeOH)); IR (film): 3566, 2925, 2867, 1456, 1374, 1361, 1060, 1011 $cm^{-1}$; $^1H$NMR (400 MHz, pyridine-d5)



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δ 5.53 (d, J = 4.9 Hz, 1H), 4.02−3.91 (m, 1H), 3.88−3.79 (m, 1H), 2.79 (d, J = 11.2 Hz, 1H), 2.76−2.70 (m, 2H), 2.67−2.59 (m, 1H), 2.53−2.42 (m, 1H), 2.23−2.15 (m, 1H), 2.13−2.05 (m, 2H), 1.24 (d, J = 7.1 Hz, 3H), 1.17 (s, 3H), 1.08 (d, J = 7.1 Hz, 3H), 0.90 (s, 3H); $^{13}$C NMR (100 MHz, pyridine-d5) δ 142.5 (C), 121.7 (CH), 71.8 (CH), 68.2 (CH), 65.4 (CH), 61.7 (CH), 55.2 (CH), 54.3 ($CH_2$), 51.0 (CH), 44.1 ($CH_2$), 41.9 (C), 41.3 ($CH_2$), 38.3 ($CH_2$), 37.6 (C), 36.2 (CH), 33.1 ($CH_2$), 31.4 ($CH_2$), 31.2 (CH), 30.5 ($CH_2$), 29.1 (CH), 27.0 ($CH_2$), 22.8 ($CH_2$), 21.8 ($CH_2$), 20.1 ($CH_3$), 19.0 ($CH_3$), 18.7 ($CH_3$), 15.2 ($CH_3$); MS-ESI (*m*/*z*): 398.4 $[M+H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{27}H_{43}ON$: 398.3417, found: 398.3414.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01133.

$^1$H NMR spectra for known compounds and $^1$H and $^{13}$C NMR spectra of all new compounds (PDF)

X-ray crystallographic data for **18** (CIF)

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### Notes

The authors declare no competing financial interest.

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