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An Easy Access to 27-Nortomatidine and 27-Norsoladulcidine Derivatives

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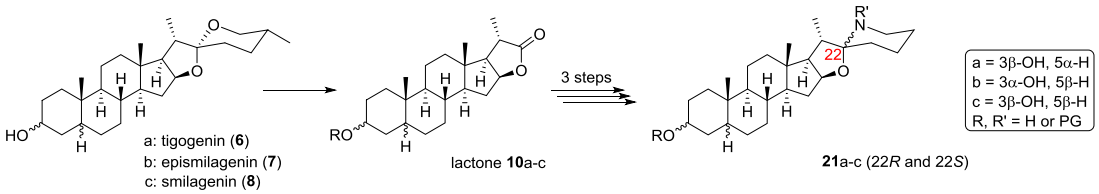


ABSTRACT: Synthesis of (22*R*)- and (22*S*)-27-norspirosolane alkaloids from tigogenin, epismilagenin and smilagenin is described. The alkaloids were prepared from readily available dinorcholanic lactones *via* their reaction with 4-chlorobutyllithium followed by substitution of chloride with azide and reductive *N*-cyclization under the Staudinger conditions.

INTRODUCTION

The use of medicinal plants for treatment of ailments and infections, but also health benefits and disease management is one of the most evolving fields in the pharmaceutical industry.[1] The genus *Solanum* is considered to be of special interest in this matter due to its wide distribution in the plant kingdom. These species occur especially in temperate and tropical region of the world, and constitute excellent source of diverse phytochemicals including steroidal glycoalkaloids (SGAs).[2,3]

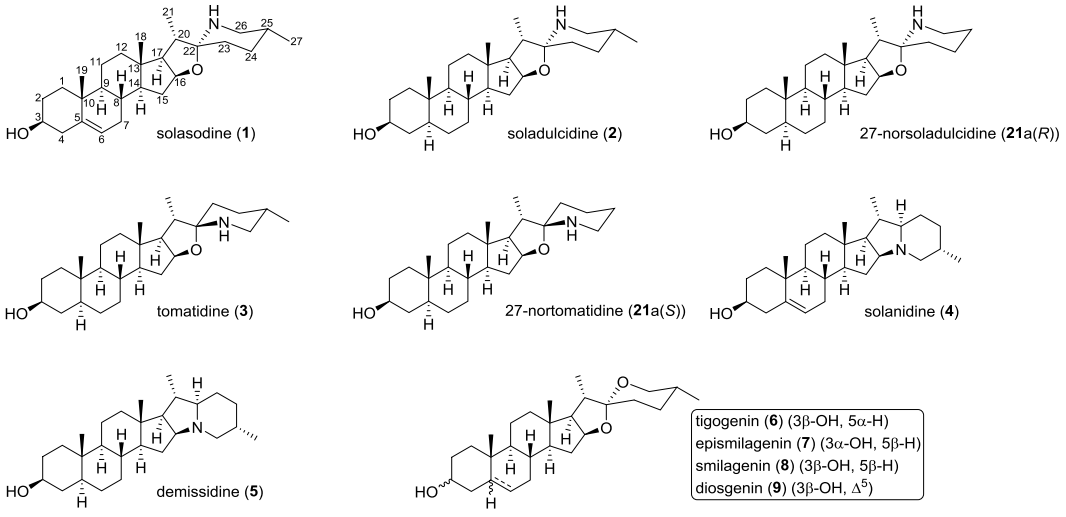


Figure 1. Structures of some *Solanum* alkaloids and related steroidal sapogenins.

As many literature reports reveal, SGAs exhibit remarkable therapeutic properties, i.e. antimicrobial, anticonvulsant, anti-inflammatory, antioxidant and anticancer.[4] Similar activities show their aglycones – direct hydrolysis products, which properties often coincide with those of SGAs.[5] The most studied and well-described compounds belonging to this group are depicted in Figure 1:

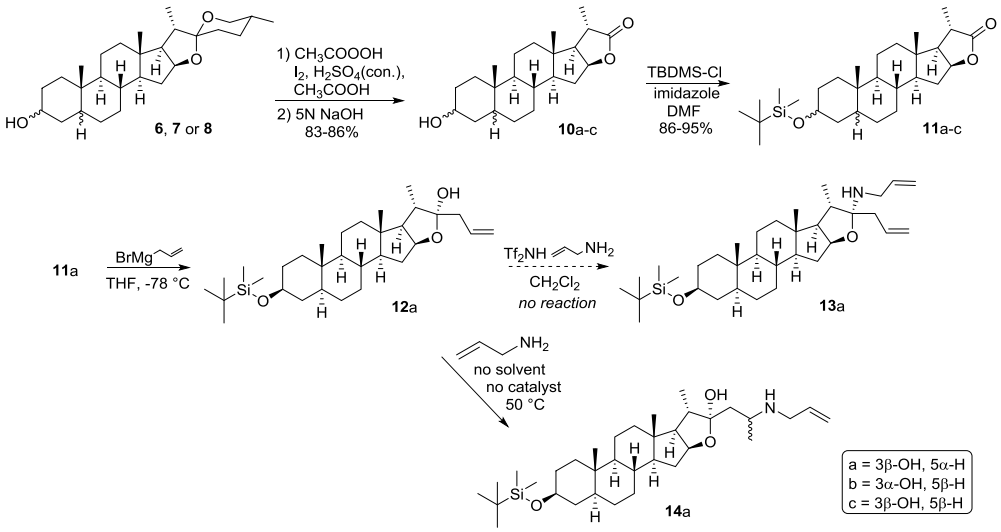
solasodine (**1**), soladulcidine (**2**), tomatidine (**3**), solanidine (**4**), and demissidine (**5**). Admittedly, biological effects of these compounds, as well as the aspects of their extraction and purification are known and well-characterized, but there are only a few described syntheses of these alkaloids.[6] Many of them start from diosgenin (**9**) (Figure 1) and are related to the sequence of the following reactions: acid catalyzed opening of the F-ring, substitution of the side chain leaving group with the nitrogen nucleophile and the F-ring reclosure to build an oxa-aza spiro moiety. Nevertheless, none of these syntheses uses the dinorcholanic lactone, which can be obtained in one step from commercially available tigogenin (**6**), as the starting material (Figure 1).[7]

In 1965, Adam and Schreiber described the first and so far only work on the synthesis of 27-norspirosolane alkaloids from 3β,16β-diacetoxy-5α-pregnan-20-one by addition of 2-lithiopyridine followed by dehydration, catalytic hydrogenation, and cyclization.[8a] The comparison of obtained results with those achieved using 2-lithio-5-methylpyridine[8b] helped to clarify the importance of the 27-methyl group for the stereochemistry of natural spirosolane alkaloids, in particular at the C22 spiro carbon atom (see Scheme S1 in Supporting Information). Herein, we report both a new method of synthesis of the F-ring modified spirosolanes and also confirm the above-mentioned considerations.

RESULTS AND DISCUSSION

Our experience in using the lactone for the reconstruction of heterocyclic ring was reported in our previous work related to the synthesis of "glycospirostanes".[9] We intended to adapt the same methodology to construct the *N*-heterocyclic unsaturated F-ring. For this purpose, tigogenin (**6**), as well as its diastereoisomers – epismilagenin (**7**) and smilagenin (**8**) (Figure 1), were used as starting materials for the synthesis of F-ring modified spirosolane alkaloids. The sapogenins were treated with peroxyacetic acid in the presence of catalytic amounts of H_2SO_4 and iodine (Scheme 1), then saponified with 5N NaOH to afford the corresponding lactones **10**a-c. These compounds reacted, in turn, with *t*-butyldimethylsilyl chloride in the presence of imidazole in DMF to protect the hydroxyl group at C3. Treatment of silyl ether **11**a with allylmagnesium bromide in THF at -78 °C gave the corresponding lactol **12**a stereoselectively in 82% yield. Subsequent reaction with allylamine and Tf_2NH in dichloromethane failed, probably due to the higher basicity of the amine compared to the hemiacetal -OH group and resulted in the reaction of triflimide with allylamine instead of **12**a.

Scheme 1. Unsuccessful attempts to obtain aminal **13**a.

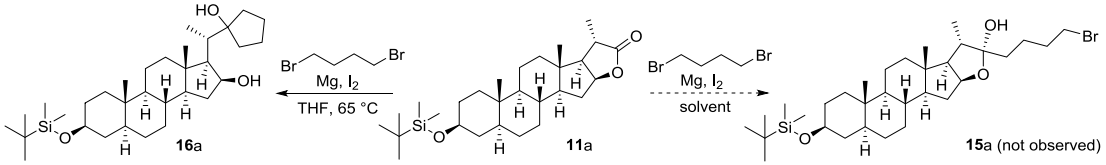


Also attempts to use allylamine neat did not afford **13**a, but yielded lactol **14**a (Scheme 1) as a main reaction product (see Scheme S4 in Supporting Information for the plausible reaction mechanism). Therefore, the basicity of allylamine was later reduced by converting it to an *N*-formyl

derivative. However, the reaction with this reagent did not work either, despite the use of various solvents, temperatures, and catalysts (see Table S2 in Supporting Information).

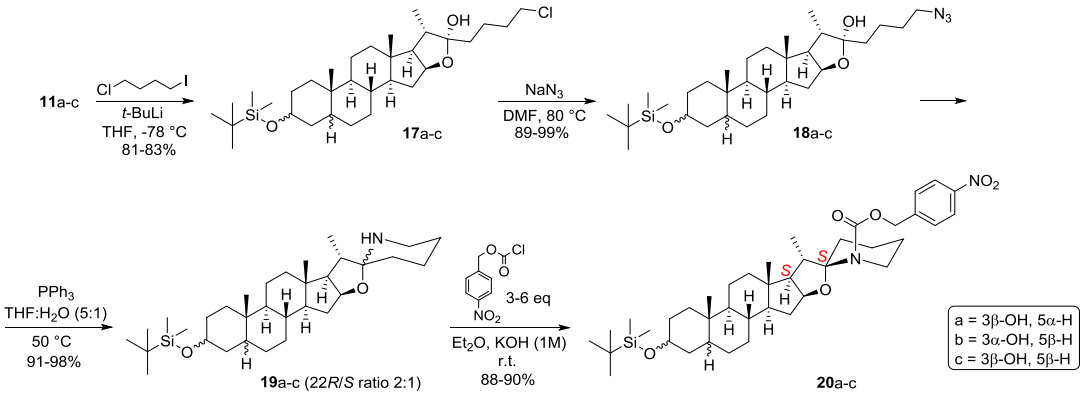
Since we failed to obtain **13**a from **11**a, our synthetic plan was changed. We decided to carry out the reaction of lactones **11**a-c with an organometallic compound to introduce a four carbon atom fragment with a terminal halide (e.g. **15**a), easily convertible to azide, that could be subjected to the reductive cyclization in the presence of triphenylphosphine.[6f,10]

Scheme 2. Synthesis of steroidal diol **16**a form lactone **11**a.



First, the Grignard reaction was attempted with a reagent prepared from 1,4-dibromobutane and magnesium, but an undesirable double addition of the butane-1,4-diyl-magnesium reagent occurred and cyclic steroidal diol **16**a was exclusively formed (Scheme 2).[11] To avoid this problem, an organometallic reagent was chemoselectively prepared from commercially available 1-chloro-4-iodobutane. Knowing that maintaining a relatively low temperature lithiation occurs only at the carbon atom bearing iodine (alkyl chlorides are essentially inert under these conditions[12]), the reagent was treated with *t*-BuLi. And indeed, at -78 °C, 4-chlorobutyllithium was obtained, then it was subjected *in situ* to reaction with lactones **11**a-c to afford the desired steroidal chlorides **17**a-c (Scheme 3). They were subsequently transformed into azides **18**a-c with NaN_3 in DMF, followed by the Staudinger type reaction with PPh_3/THF/H_2O, whereby *N*-cyclization took place. To our disappointment, the reaction provided an inseparable mixture of epimers **19**a-c (22*R* and 22*S*) in ratio of about 2:1. That was due to the lack of C27 methyl group that is crucial for the stereoselectivity control at C22 by assuming an energetically favorable equatorial orientation during cyclization process. The ratio was established by integration of the well resolved signals 16α-H in both epimers (Figure 3). Attempts to avoid the formation of the epimeric mixture by using a more crowded phosphine reagent P(*o*-tol)$_3$ failed, because the reaction did not proceed, even under reflux conditions.

Scheme 3. Synthetic route to 4-nitrobenzyl carbamates **20**a-c from lactones **11**a-c.



To differentiate the epimeric pairs **19**a-c (22*R* and 22*S*), an easily formed and cleavable under mild conditions *p*-nitrobenzyl carbamate (*p*NZ) protection was employed.[13] Initially we expected that due to the steric hindrance only the 22*S* epimer would be transformed into the carbamate (then a separation of two disparate compounds would be trivial). However, both epimers reacted smoothly with 4-nitrobenzyl chloroformate and 1M KOH in diethyl ether affording the same *N*-protected 27-nortomatidine derivatives **20**a-c, verified by representative crystal structures of **20**a and **20**b, which

proved the 22*S* configuration in both compounds (see Figure 2a and 2b, respectively). This unusual transformation of the epimeric mixture into a single stereoisomer of the *p*NZ-derivative is convincingly evidenced by ^{1}H NMR as shown in Figure 3. One of two signals of the 16α-H (δ 4.13 and 4.27 ppm) in the spectrum of 22*R*/*S* epimeric mixture **19**a (22*R* and 22*S*) disappeared and only the upfield shifted signal at δ 4.17 ppm, coming from the 22*S* epimer, was present in the spectrum of compound **20**a. Analogous changes were also observed for other pairs of the spectra of compounds **19**b-c and **20**b-c. For comparison, the literature 16α-H chemical shifts for soladulcidine (**2**) (22*R*) and tomatidine (**3**) (22*S*) are 4.29[6h] and 4.12[14] ppm, respectively.

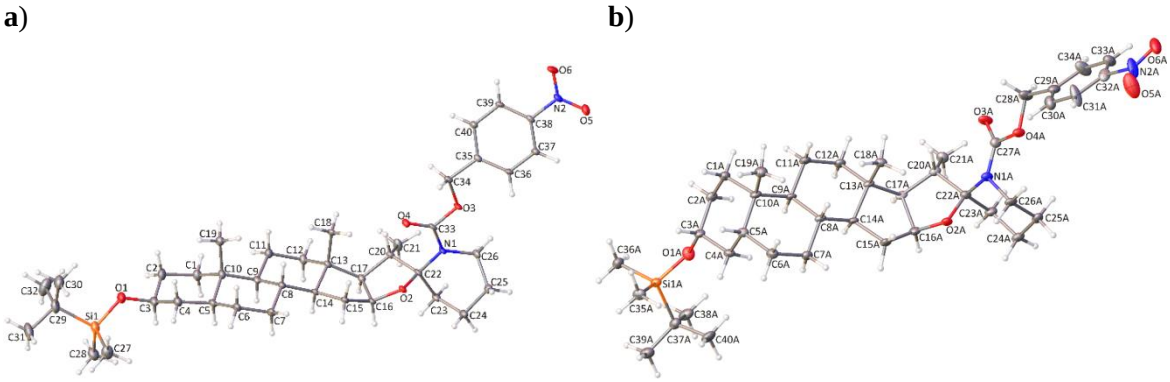


Figure 2. X-ray structures of **20**a (**a**) and **20**b (**b**). Displacement ellipsoids are drawn at the 30% probability level.

These results refer to our recent work where we described *N*-acetylation of solasodine (**1**), proceeding with inversion of configuration at the spiro carbon atom.[15] This is a consequence of existence in the course of the reaction a verazine-type intermediate with an open E-ring, which is based on the 22,26-epimino-27-norcholest-22(*N*)-ene skeleton.[16] The aforementioned partial epimerization is related to the rotation about the C20-C22 single bond followed by recyclization of the E-ring to the energetically favored 22*S* isomer.

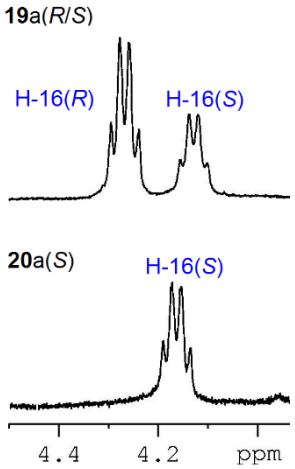
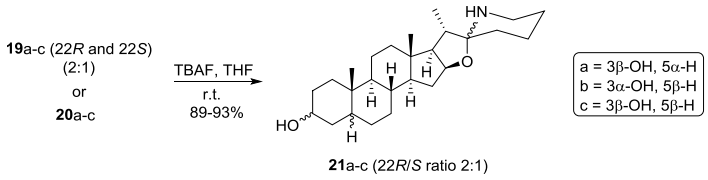


Figure 3. Diagnostic region of ^{1}H NMR spectra of **19**a (*R*/*S*) and **20**a(*S*).

Interestingly, the X-ray structure analysis of *p*-nitrobenzyl carbamates **20**a and **20**b revealed that these compounds have the same *S* configuration at C22, the same *Z* configuration about the amide partial double bond but different conformation of F-ring. It is a slightly distorted chair in **20**b while in **20**a the F-ring assumes a twist-boat conformation in crystalline state. In our previous study on the *N*,*O*-diacetylsolasodine structure[15] it has been shown that there is a low energy difference between the two conformations.

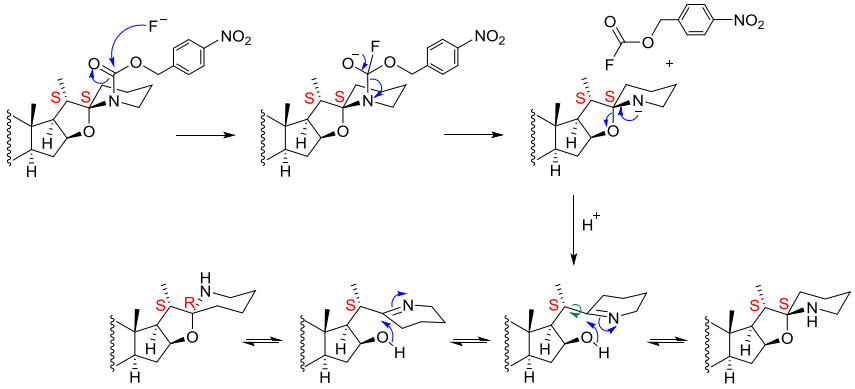
To complete the syntheses of 27-nortomatidine derivatives **21**a-c, deprotection of the secondary amine in the F-ring fragment was needed. For this purpose, mild reaction conditions were applied due to sensitivity of an oxa-aza spiro moiety to acids. Thus, compounds **20**a-c were subjected to hydrogenation over 10 wt % Pd/C under H_2 flow in ethanol. Unexpectedly, the carbamates were converted to the mixture of epimers **19**a-c (22*R* and 22*S*) with approximately the same ratio (2:1) as before, regardless of shortening the reaction time or lowering the temperature. We also tried to perform this transformation by treating *p*-nitrobenzyl carbamates **20**a-c with tetrabutylammonium fluoride (TBAF)[17] in THF, counting on simultaneous cleavage of the 3-hydroxyl group (Scheme 4). As a result, the inseparable mixtures of epimeric compounds – 27-norsoladulcidine (**21**a-c(*R*)) and 27-nortomatidine (**21**a-c(*S*)) derivatives in ratio of about 2:1 ratio were obtained.

Scheme 4. Reaction conditions applied for deprotection of functional groups in epimers **19**a-c (22*R* and 22*S*), and carbamates **20**a-c.



A rationale for this reverse epimerization process can be as follows: an attack of fluoride on the carboxyl group of the carbamate portion (Scheme 5) generated a tetrahedral intermediate which evolved into *p*-nitrobenzyl fluorocarbonate and 27-nortomatidine anion. The latter was transformed into relatively stable alkoxide formed by cleavage of E-ring and then quenched by protonation. In this imine intermediate, a rotation about the C20-C22 bond may occur. Subsequent intramolecular nucleophilic addition of the alcohol to the imine caused E-ring reclosure. Finally, a mixture of 27-norsoladulcidine (**21**a-c(*R*)) and 27-nortomatidine (**21**a-c(*S*)) derivatives in the ratio corresponding to their relative thermodynamic stability was formed.

Scheme 5. Proposed mechanism for the cleavage of *p*NZ group in the presence of fluoride resulting in epimerization at C22.



Inspection of Dreiding models and molecular modeling using the MM+ force-field also confirmed the preference for the *N*-unsubstituted 22*R*-spirosolanes over the 22*S* ones, the difference in steric energies is relatively low and amounts to 1.89 kcal/mol, while for *N*-acyl derivatives the 22*S* configuration is favored and in those cases the difference is up to 3.2 kcal/mol (see Table 1).

Table 1. Steric energies[a] of 22*R*- and 22*S*-spirosolanes and their *N*-acyl derivatives (*E*/*Z* – configuration about the amide partial double bond).

22*R*-Compound	Steric energy (kcal/mol)	22*S*-Compound	Steric energy (kcal/mol)	ΔE (22*R*-22*S*) (kcal/mol)
27-Nor-soladulcidine	57.20	27-Nortomatidine	59.09	-1.89
N-Acetyl-27-norsoladulcidine	61.74 (*Z*)[b]	*N*-Acetyl-27-nortomatidine	58.54 (*Z*)[b]	3.20
N-benzyloxycarbonyl-27-norsoladulcidine	51.77 (*E*) 52.97 (*Z*)	*N*-benzyloxy-carbonyl-27-nortomatidine	50.75 (*E*) 50.93 (*Z*)	1.02 2.02

[a] HyperChem for Windows, Release 7.5, from Hypercube, Inc.; minimizations employed the MM+ force field and the Polak-Ribiere algorithm with RMS gradient 0.001 kcal/A˚ mol.
[b] Steric energies for the *E* isomers were much higher.

CONCLUSIONS

In summary, we have developed a new synthetic route to 27-norspirosolane alkaloids from tigogenin (**6**), epismilagenin (**7**) and smilagenin (**8**) *via* appropriate dinorcholanic lactones. The key transformation was the addition of an organolithium reagent to the lactone followed by the reductive cyclization of an intermediate steroidal azide with PPh_3/H_2O. This methodology provides a convenient and efficient strategy for the synthesis of various F-ring modified spirosolane derivatives.

EXPERIMENTAL SECTION

General Methods. Commercially available reagent grade chemicals were used as received. The solvents were dried prior to use by distillation over the following drying agents: DMF (4Å molecular sieves), THF (Na/benzophenone), Et_2O (Na), CH_2Cl_2 (CaH_2), pyridine (KOH). Flash column chromatography and dry flash chromatography were performed with JT Baker silica gel, pore size 40Å (70-230 mesh), unless otherwise stated. Reactions were monitored by TLC on silica gel plates 60 F_{254} (Merck) and spots were detected either by UV-absorption (UV Emita VP 60, 180 W) and/or by charring with H_2SO_4/ molybdophosphoric acid/cerium(IV) sulfate in H_2SO_4. Some of the reactions were carried out under argon atmosphere using standard Schlenk techniques. ^1H and ^{13}C NMR data for all previously uncharacterized compounds (only selected signals in the ^1H NMR spectra are reported) were recorded at ambient temperature using Brucker Ultrashield Plus 400 spectrometers and are referenced to TMS (0.0 ppm) and $CDCl_3$ (77.0 ppm) respectively, unless otherwise noted. The ATR-IR spectra were recorded with Nicolet 6700 FT-IR Spectrometer (Thermo Scientific, USA) in the 600-4000 cm^{-1} range. Melting points were determined by Kofler bench (Boetius type) melting point apparatus. HRMS were obtained on an Electrospray Ionisation Time of Flight (ESI-TOF) Micromass spectrometer.

General Procedure for Lactone Preparation (10a-c**).** To a mixture of AcOH (22 mL) and concentrated sulfuric acid (0.4 mL), iodine (0.87 mmol) was added and it was stirred for 30 min at room temperature. Then 3 g (7.2 mmol) of sapogenin **6**, **7** or **8** was added and the mixture was stirred for further 10 min. To the reaction mixture peroxyacetic acid in CH_3COOH (39%) (8 mL, 75 mmol)

was added dropwise. After 14 h, the reaction was saponified with 5N NaOH to pH = 13 at room temperature and left overnight. The crude product was filtered off and dried in *vacuo*. Flash chromatography (ethyl acetate/hexane 2:8) provided **10**a-c as white crystalline compounds (83-86%).

*3β-Hydroxy-23,24-dinor-5α-cholano-22,16-lactone (**10**a)*. Yield: 85% (2.12 g); m.p. 237-239 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 3605, 3484, 2934, 1757, 1452, 1189, 1034, 1016, 960; ^1H NMR ($CDCl_3$) δ (ppm): 4.96-4.91 (m, 1H), 3.61-3.56 (m, 1H), 2.57 (dq, *J* = 7.6, 0.9 Hz, 1H), 2.29-2.22 (m, 1H), 1.86 (d, *J* = 7.6 Hz, 1H), 1.31 (d, *J* = 7.6 Hz, 3H), 0.82 (s, 3H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 181.3 (C), 82.8 (CH), 71.1 (CH), 59.0 (CH), 54.6 (CH), 54.4 (CH), 44.8 (CH), 41.7 (C), 38.3 (CH_2), 38.1 (CH_2), 36.9 (CH_2), 36.0 (CH), 35.6 (C), 34.9 (CH), 33.0 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 28.4 (CH_2), 20.5 (CH_2), 17.9 (CH_3), 13.8 (CH_3), 12.3 (CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{22}H_{34}O_3Na$ 369.2406; Found 369.2421.

*3α-Hydroxy-23,24-dinor-5β-cholano-22,16-lactone (**10**b)*. Yield: 83% (2.07 g); m.p. 212-214 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 3605, 3459, 2930, 2859, 1758, 1452, 1189, 1033; ^1H NMR ($CDCl_3$) δ (ppm): 4.98-4.93 (m, 1H), 3.69-3.61 (m, 1H), 2.58 (dq, *J* = 7.6, 0.8 Hz, 1H), 2.31-2.24 (m, 1H), 1.87 (d, *J* = 8.4 Hz, 1H), 1.32 (d, *J* = 7.6 Hz, 3H), 0.95 (s, 3H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 181.3 (C), 82.8 (CH), 71.6 (CH), 59.1 (CH), 54.6 (CH), 41.8 (CH), 41.8 (C), 40.6 (CH), 38.5 (CH_2), 36.3 (CH_2), 36.1 (CH), 35.3 (CH_2), 35.2 (CH), 34.7 (C), 33.0 (CH_2), 30.4 (CH_2), 26.9 (CH_2), 26.6 (CH_2), 23.3 (CH_3), 20.1 (CH_2), 18.0 (CH_3), 13.8 (CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{22}H_{34}O_3Na$ 369.2406; Found 369.2401.

*3β-Hydroxy-23,24-dinor-5β-cholano-22,16-lactone (**10**c)*. Yield: 86% (2.15 g); m.p. 198-200 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 3525, 2923, 1749, 1449, 1187, 1031; ^1H NMR ($CDCl_3$) δ (ppm): 4.97-4.92 (m, 1H), 4.17-4.07 (m, 1H), 2.59 (dq, *J* = 7.6, 0.8 Hz, 1H), 2.31-2.24 (m, 1H), 1.87 (d, *J* = 7.6 Hz, 1H), 1.32 (d, *J* = 7.6 Hz, 3H), 0.99 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 181.3 (C), 82.8 (CH), 66.9 (CH), 59.1 (CH), 54.7 (CH), 41.8 (C), 39.9 (CH), 38.5 (CH_2), 36.3 (CH), 36.0 (CH), 35.2 (C), 35.0 (CH), 33.4 (CH_2), 33.0 (CH_2), 29.9 (CH_2), 27.8 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 23.8 (CH_3), 20.3 (CH_2), 18.0 (CH_3), 13.8 (CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{22}H_{34}O_3Na$ 369.2406; Found 369.2395.

General Procedure for a 3-Hydroxyl Group Protection as TBDMS Ethers in Lactones (11a-c**).** To a solution of compound **10**a, b or c (1050 mg; 3.03 mmol) in dry DMF (20 mL), imidazole (413 mg, 6.07 mmol) and *t*-butyldimethylsilyl chloride (685 mg, 4.54 mmol) were added. The reaction mixture was stirred at room temperature for 3 h, poured into saturated aqueous solution of NaCl and extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated in *vacuo*. The crude product was purified over silica gel with ethyl acetate/hexane (7:93) elution to afford compounds **11**a-c (86-95%).

*3β-t-Butyldimethylsilyloxy-23,24-dinor-5α-cholano-22,16-lactone (**11**a)*. Yield: 95% (1326 mg); m.p. 116-118 °C (ethyl acetate/hexane); IR, ν_{max} ($cm^{-1)}$: 2931, 2855, 1757, 1183, 1092, 1059, 837; ^1H NMR ($CDCl_3$) δ (ppm): 4.96-4.91 (m, 1H), 3.58-3.52 (m, 1H), 2.58 (dq, *J* = 7.6, 1.0 Hz, 1H), 2.30-2.23 (m, 1H), 1.86 (d, *J* = 7.7 Hz, 1H), 1.32 (d, *J* = 7.6 Hz, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.75 (s, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 181.3 (C), 82.8 (CH), 72.0 (CH), 59.1 (CH), 54.7 (CH), 54.5 (CH), 45.0 (CH), 41.7 (C), 38.6 (CH_2), 38.4 (CH_2), 37.1 (CH_2), 36.1 (CH), 35.6 (C), 34.9 (CH), 33.0 (CH_2), 32.2 (CH_2), 31.9 (CH_2), 28.5 (CH_2), 25.9 ($3\times CH_3$), 20.5 (CH_2), 18.2 (C), 18.0 (CH_3), 13.9 (CH_3), 12.4 (CH_3), -4.6 ($2\times CH_3$); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{28}H_{48}O_3SiNa$ 483.3270; Found 483.3283.

*3α-t-Butyldimethylsilyloxy-23,24-dinor-5β-cholano-22,16-lactone (**11**b)*. Yield: 90% (1256 mg); m.p. 127-129 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 2932, 2858, 1758, 1182, 1092, 1068, 837; ^1H NMR ($CDCl_3$) δ (ppm): 4.97-4.92 (m, 1H), 3.63-3.57 (m, 1H), 2.58 (dq, *J* = 7.7, 0.8 Hz, 1H), 2.30-2.23 (m, 1H), 1.86 (d, *J* = 7.0 Hz, 2H), 1.32 (d, *J* = 7.6 Hz, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.73 (s,

3H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 181.4 (C), 82.9 (CH), 72.6 (CH), 59.1 (CH), 54.6 (CH), 42.1 (CH), 41.8 (C), 40.4 (CH), 38.5 (CH_2), 36.9 (CH_2), 36.1 (CH), 35.5 (CH_2), 35.2 (CH_2), 34.7 (C), 33.0 (CH_2), 31.0 (CH_2), 27.0 (CH_2), 26.6 (CH_2), 26.0 (3×CH_3), 23.3 (CH), 20.1 (CH_2), 18.3 (C), 18.0 (CH_3), 13.8 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{28}H_{48}O_3SiNa$ 483.3270; Found 483.3291.

*3β-t-Butyldimethylsilyloxy-23,24-dinor-5β-cholano-22,16-lactone (**11**c)*. Yield: 86% (1200 mg); m.p. 153-155 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 2924, 2855, 1770, 1455, 1176, 1050, 834; ^{1}H NMR ($CDCl_3$) δ (ppm): 4.97‑4.92 (m, 1H), 4.08‑3.99 (m, 1H), 2.59 (dq, *J* = 7.6, 0.8 Hz, 1H), 2.30‑2.23 (m, 1H), 1.87 (d, *J* = 7.2 Hz, 1H), 1.32 (d, *J* = 7.6 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.75 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm): 181.3 (C), 82.9 (CH), 67.3 (CH), 59.2 (CH), 54.8 (CH), 41.9 (C), 40.2 (CH), 38.7 (CH_2), 36.4 (CH), 36.1 (CH), 35.2 (CH), 35.2 (C), 34.4 (CH_2), 33.1 (CH_2), 31.0 (CH_2), 28.6 (CH_2), 26.7 (2×CH_2), 25.8 (3×CH_3), 23.9 (CH_3), 20.4 (CH_2), 18.1 (C), 18.0 (CH_3), 13.9 (CH_3), -4.8 (CH_3), -4.9 (CH_3); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{28}H_{48}O_3SiNa$ 483.3270; Found 483.3283.

Preparation of (22*S*)-3β-*t*-Butyldimethylsilyloxy-26,27-dinor-5α-furost-24-en-22-ol (12a). To a solution of **11**a (1255 mg, 2.72 mmol) in dry THF (15 mL) cooled to −78 °C (dry ice/acetone bath) allylmagnesium bromide solution (2.9 mL 2.90 mmol; 1M in diethyl ether) was added dropwise. The reaction mixture was stirred for 15 min under argon, quenched with saturated aqueous solution of NH_4Cl at −78 °C and allowed to stand at room temperature. The product was extracted three times with diethyl ether (3 x 100 mL). The combined organic extracts were washed with saturated aqueous solution of NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel with ethyl acetate/hexane (6:94) elution to afford compound **12**a in 82% yield (1123 mg,) as white crystals: m.p. 117‑120 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 3582, 3559, 2930, 2855, 1382, 1253, 1093, 1059, 869, 837; ^{1}H NMR ($CDCl_3$) δ (ppm): 5.98‑5.87 (m, 1H), 5.21‑5.15 (m, 2H), 4.61‑4.55 (m, 1H), 3.57‑3.52 (m, 1H), 2.47 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.39 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.19 (s, 1H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.78 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 132.9 (CH), 119.6 (CH_2), 108.9 (C), 81.5 (CH), 72.1 (CH), 62.6 (CH), 56.3 (CH), 54.5 (CH), 45.0 (CH), 43.4 (CH_2), 40.9 (C), 40.2 (CH), 40.0 (CH_2), 38.7 (CH_2), 37.2 (CH_2), 35.6 (C), 35.1 (CH), 32.3 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 28.7 (CH_2), 25.9 (3×CH_3), 21.0 (CH_2), 18.3 (C), 16.5 (CH_3), 15.3 (CH_3), 12.4 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{31}H_{54}O_3SiNa$ 525.3740; Found 525.3757.

Preparation of Lactol 14a **from 12a.** The solution of **12**a (50 mg, 0.1 mmol) in large excess of allylamine (5 mL) molecular sieves 4 Å were added. The solution was stirred for 2 h at 50 °C before quenching with Et_3N (0.2 mL) at a set temperature. The mixture was cooled down to room temperature and filtered through Celite. After evaporation of the solvent under reduced pressure, the resulting crude product was purified by silica gel column chromatography with methanol/chloroform (1:9) elution to afford lactol **14**a in 63 % yield (35 mg) as white crystals: m.p. 134-136 °C (methanol/dichloromethane); IR, ν_{max} (cm^{-1}): 3170, 2923, 1641, 1456, 1250, 1056, 986, 829; ^{1}H NMR ($CDCl_3$) δ (ppm): 5.93‑5.86 (m, 1H), 5.21‑5.06 (m, 2H), 4.58 (dd, *J* = 14.2, 7.6 Hz, 1H), 3.60‑3.48 (m, 1H), 3.44‑3.36 (m, 1H), 3.36‑3.26 (m, 1H), 3.26‑3.16 (m, 1H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.75 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 136.1 (CH), 116.1 (CH_2), 110.9 (C), 80.5 (CH), 72.1 (CH), 62.3 (CH), 56.2 (CH), 54.4 (CH), 50.6 (CH), 48.6 (CH_2), 45.0 (CH), 42.6 (CH_2), 42.0 (CH), 40.6 (C), 40.1 (CH_2), 38.7 (CH_2), 37.1 (CH_2), 35.6 (C), 35.1 (CH), 32.3 (CH_2), 31.9 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 25.9 (3×CH_3), 21.0 (CH_2), 21.0 (CH_3), 18.3 (C), 16.5 (CH_3), 15.3 (CH_3), 12.4 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{34}H_{61}NO_3SiNa$ 582.4318; Found 582.4347.

Preparation of Diol 16a **from 11a.** Iodine (20 mg, 0.08 mmol, 0.72 eq), magnesium turnings (3.2 mg, 0.13 mmol, 1.2 eq) and dry THF (10 mL) were put into a two necked round-bottomed flask fitted with

reflux condenser. The mixture was heated to 65 °C under argon and a solution of 1,4-dibromobutane (0.033 mL, 59 mg, 0.275 mmol, 2.5 eq) in THF (5 mL) was added dropwise. After 10 minutes of stirring at this temperature lactone **11**a (50 mg, 0.11 mmol) in THF (5 mL) was slowly added and stirring was continued under gentle reflux for another 15 min. Then, the mixture was cooled down to room temperature and quenched with saturated aqueous solution of NH_4Cl. The crude product was extracted three times with diethyl ether (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with ethyl acetate/hexane (1:9) elution to afford diol **16**a in 79% yield (44 mg) as white crystals: m.p. 216-218 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 3264, 2930, 2180, 1456, 1249, 1086, 839, 767; ^1H NMR ($CDCl_3$) δ (ppm): 4.40‑4.28 (m, 1H), 3.62‑3.47 (m, 1H), 3.99 (brs, 1H-OH), 2.43‑2.30 (m, 1H), 2.26‑2.10 (m, 1H), 2.09-1.94 (m, 2H), 1.44 (s, 8H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.81 (s, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 87.5 (C), 72.9 (CH), 72.2 (CH), 59.3 (CH), 54.4 (CH), 54.3 (CH), 45.0 (CH), 43.5 (C), 40.8 (CH_2), 40.4 (CH_2), 38.6 (CH_2), 37.1 (CH_2), 36.8 (CH), 35.5 (C), 35.2 (CH), 34.0 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 26.9 (CH_2), 25.9 (3×CH_3), 24.2 (CH_2), 23.6 (CH_2), 21.1 (CH_2), 18.3 (C), 15.9 (CH_3), 13.1 (CH_3), 12.4 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{32}H_{58}O_3SiNa$ 541.4053; Found 541.4026.

General Procedure for the Synthesis of Steroidal Chlorides 17a-c **from Lactones 11**a-c**.** To a cooled solution (-78 °C; dry ice/acetone bath) of 1-chloro-4-iodobutane (0.16 mL, 1.32 mmol, 3 eq) in dry Et_2O (20 mL) solution of *t*-BuLi (1.55 mL, 1.7 M in pentane, 2.64 mmol, 6 eq) under argon was added. The reaction was allowed to run for further 1 h, and then the solution of lactone **11**a-c (203 mg, 0.44 mmol, 1 eq) in Et_2O (5 mL) cooled to 0 °C (ice/water bath) was dropwise added. After 10 min of stirring at -78 °C, saturated aqueous solution of NH_4Cl (10 mL) was carefully poured into a flask and the reaction mixture was allowed to warm up to room temperature (about 1 h). The product was extracted three times with diethyl ether (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with ethyl acetate/hexane (6:94) elution to afford compound **17**a-c (81-83%).

*(22S)-3β-t-Butyldimethylsilyloxy-26-chloro-27-nor-5α-furost-22-ol (**17a**)*. Yield: 81% (198 mg); amorphous solid; IR, ν_{max} (cm^{-1}): 3399, 2932, 2855, 1456, 1097, 836, 774; ^1H NMR ($CDCl_3$) δ (ppm): 4.59 (dd, *J* = 14.7, 7.6 Hz, 1H), 3.61‑3.50 (m, 1H), 3.55 (t, *J* = 6.6 Hz, 2H), 2.02‑1.93 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.78 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 110.2 (C), 81.5 (CH), 72.1 (CH), 62.7 (CH), 56.3 (CH), 54.4 (CH), 45.0 (CH), 44.9 (CH_2), 41.0 (C), 40.0 (CH_2), 39.8 (CH), 38.6 (CH_2), 38.2 (CH_2), 37.2 (CH_2), 35.6 (C), 35.1 (CH), 32.8 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 25.9 (3×CH_3), 21.3 (CH_2), 21.0 (CH_2), 18.3 (C), 16.4 (CH_3), 15.5 (CH_3), 12.4 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{32}H_{57}ClO_3SiNa$ 575.3663; Found 575.3651.

*(22S)-3α-t-Butyldimethylsilyloxy-26-chloro-27-nor-5β-furost-22-ol (**17b**)*. Yield: 83% (203 mg); amorphous solid; IR, ν_{max} (cm^{-1}): 3427, 2921, 1455, 1247, 1092, 832, 771; ^1H NMR ($CDCl_3$) δ (ppm): 4.60 (dd, *J* = 13.9, 7.8 Hz, 1H), 3.65‑3.49 (m, 1H), 3.55 (t, *J* = 6.6 Hz, 2H), 2.03‑1.93 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.77 (s, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 110.2 (C), 81.6 (CH), 72.7 (CH), 72.7 (CH), 62.8 (CH), 56.2 (CH), 44.8 (CH_2), 42.2 (CH), 41.1 (C), 40.3 (CH), 40.0 (CH_2), 39.8 (CH), 38.2 (CH_2), 36.9 (CH_2), 35.6 (CH_2), 35.5 (CH), 34.7 (C), 32.8 (CH_2), 31.8 (CH_2), 31.0 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 26.0 (3×CH_3), 23.4 (CH_3), 21.3 (CH_2), 20.5 (CH_2),18.3 (C), 16.4 (CH_3), 15.5 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{32}H_{57}ClO_3SiNa$ 575.3663; Found 575.3648.

*(22S)-3β-t-Butyldimethylsilyloxy-26-chloro-27-nor-5β-furost-22-ol (**17**c)*. Yield: 83% (203 mg); amorphous solid; IR, ν_{max} (cm^{-1}): 3432, 2926, 1454, 1249, 1054, 837, 770; ^1H NMR ($CDCl_3$) δ (ppm): 4.60 (dd, *J* = 14.4, 7.8 Hz, 1H), 4.07‑3.99 (m, 1H), 3.56 (t, *J* = 6.6 Hz, 2H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.78 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 110.2 (C), 81.6 (CH), 67.4 (CH), 62.8 (CH), 56.5 (CH), 44.8 (CH_2), 41.1 (C), 40.2 (CH_2), 40.1 (CH), 39.8 (CH), 38.2 (CH_2), 36.5 (CH), 35.4 (CH), 35.2 (C), 34.4 (CH_2), 32.8 (CH_2), 31.8 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 25.8 (3×CH_3), 24.0 (CH_3), 21.3 (CH_2), 20.9 (CH_2),18.1 (C), 16.4 (CH_3), 15.5 (CH_3), -4.8 (CH_3), -4.9 (CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{32}H_{57}ClO_3SiNa$ 575.3663; Found 575.3677.

General Procedure for the Synthesis of Steroidal Azides 18a-c **from Chlorides 17**a-c. A solution of chloride **17**a-c (165 mg, 0.3 mmol) in dry DMF (11 mL) was placed in round-bottomed flask fitted with reflux condenser, to which sodium azide (35 mg, 0.54 mmol, 1.8 eq) was added. After stirring at 80 °C for 18 h, the reaction mixture was cooled down to room temperature, poured into water and extracted three times with Et_2O (100 mL each). The combined organic layers were dried over Na_2SO_4, and evaporated in *vacuo*. The crude product was purified by dry flash chromatography on silica gel with ethyl acetate/hexane (8:92) elution to afford compound **18**a-c (89-99%).

*(22S)-3β-t-Butyldimethylsilyloxy-26-azido-27-nor-5α-furost-22-ol (**18**a)*. Yield: 99% (165 mg); amorphous solid; IR, ν_{max} (cm^{-1}): 3437, 2925, 2095, 1456, 1251, 1096, 833; ^1H NMR ($CDCl_3$) δ (ppm): 4.59 (dd, *J* = 14.7, 7.6 Hz, 1H), 3.61‑3.50 (m, 1H), 3.29 (t, *J* = 6.7 Hz, 2H), 2.03‑1.94 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.82 (s, 3H), 0.78 (s, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 110.2 (C), 81.5 (CH), 72.1 (CH), 62.7 (CH), 56.3 (CH), 54.5 (CH), 51.4 (CH_2), 45.0 (CH), 41.0 (C), 39.9 (CH_2), 39.8 (CH), 38.6 (CH_2), 38.5 (CH_2), 37.2 (CH_2), 35.6 (C), 35.1 (CH), 32.3 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 25.9 (3×CH_3), 21.1 (CH_2), 21.0 (CH_2), 18.3 (C), 16.4 (CH_3), 15.5 (CH_3), 12.4 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{32}H_{57}N_3O_3SiNa$ 582.4067; Found 582.4048.

*(22S)-3α-t-Butyldimethylsilyloxy-26-azido-27-nor-5β-furost-22-ol (**18**b)*. Yield: 89% (149 mg); m.p. 94-95 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 3507, 2927, 2090, 1456, 1248, 1098, 1059, 833; ^1H NMR ($CDCl_3$) δ (ppm): 4.60 (dd, *J* = 13.9, 7.8 Hz, 1H), 3.65‑3.53 (m, 1H), 3.29 (t, *J* = 6.7 Hz, 2H), 2.02‑1.92 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.77 (s, 3H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 110.2 (C), 81.6 (CH), 72.7 (CH), 62.8 (CH), 56.2 (CH), 51.4 (CH_2), 42.2 (CH), 41.1 (C), 40.3 (CH), 40.0 (CH_2), 39.8 (CH), 38.5 (CH_2), 36.9 (CH_2), 35.6 (CH_2), 35.5 (CH), 34.7 (C), 31.8 (CH_2), 31.0 (CH_2), 29.2 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 26.0 (3×CH_3), 23.4 (CH_3), 21.1 (CH_2), 20.5 (CH_2), 18.3 (C), 16.4 (CH_3), 15.5 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{32}H_{57}N_3O_3SiNa$ 582.4067; Found 582.4040.

*(22S)-3β-t-Butyldimethylsilyloxy-26-azido-5β-27-nor-furost-22-ol (**18**c)*. Yield: 99% (165 mg); m.p. amorphous solid; IR, ν_{max} (cm^{-1}): 3423, 2925, 2093, 1456, 1249, 1053, 831; ^1H NMR ($CDCl_3$) δ (ppm): 4.60 (dd, *J* = 14.5, 7.7 Hz, 1H), 4.07‑4.00 (m, 1H), 3.29 (t, *J* = 6.7 Hz, 2H), 2.03‑1.95 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.78 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 110.2 (C), 81.6 (CH), 67.4 (CH), 62.8 (CH), 56.4 (CH), 51.4 (CH_2), 41.1 (C), 40.2 (CH_2), 40.1 (CH), 39.8 (CH), 38.5 (CH_2), 36.5 (CH), 35.4 (CH), 35.2 (C), 34.4 (CH_2), 31.8 (CH_2), 30.0 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 25.8 (3×CH_3), 24.0 (CH_3), 21.1 (CH_2), 20.9 (CH_2), 18.1 (C), 16.4 (CH_3),15.5 (CH_3), -4.8 (CH_3), -4.9 (CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{32}H_{57}N_3O_3SiNa$ 582.4067; Found 582.4051.

General Procedure for Reductive Cyclization of Azides 18a-c. To a solution of azide **18**a-c (210 mg, 0.38 mmol, 1 eq) in THF (50 mL) and water (10 mL) PPh_3 (300 mg, 1.14 mmol, 3 eq) was added. The mixture was stirred at 50 °C for 19 h, and then it was cooled down to room temperature and poured into saturated solution of NaCl (100 mL). The product was isolated by extracting three times

with diethyl ether (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with methanol/dichloromethane (2.5:97.5) elution to afford the 22*R*/*S* epimeric mixture **19**a-c (2:1) (91-98%).

*Mixture of 22-epimers **19a***. Yield: 91% (176 mg); IR, ν_{max} (cm^{-1}): 3461, 2927, 2854, 1440, 1376, 1252, 1189, 836; ^1H NMR ($CDCl_3$) δ (ppm): 4.27 (dd, *J* = 15.3, 7.4 Hz, 1H), 4.13 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.62-3.49 (m, 2H), 3.17-3.08 (m, 1H), 3.04-2.92 (m, 1H), 2.87-2.77 (m, 1H), 2.77-2.67 (m, 1H), 2.09-1.96 (m, 2H), 0.94 (d, *J* = 7.8 Hz, 6H), 0.89 (s, 6H), 0.89 (s, 18H), 0.81 (s, 3H), 0.79 (s, 3H), 0.05 (s, 12H); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{32}H_{58}NO_2Si$ 516.4231; Found 516.4236.

*Mixture of 22-epimers **19b***. Yield: 93% (179 mg); IR, ν_{max} (cm^{-1}): 3458, 2930, 2857, 1456, 1376, 1252, 1093, 837; ^1H NMR ($CDCl_3$) δ (ppm): 4.28 (dd, *J* = 15.0, 7.3 Hz, 1H), 4.14 (dd, *J* = 14.4, 7.2 Hz, 1H), 3.65-3.53 (m, 2H), 3.18-3.04 (m, 1H), 3.04-2.93 (m, 1H), 2.87-2.78 (m, 1H), 2.78-2.68 (m, 1H), 2.08-1.95 (m, 2H), 0.95 (d, *J* = 7.0 Hz, 6H), 0.93 (s, 6H), 0.90 (s, 18H), 0.81 (s, 3H), 0.79 (s, 3H), 0.07 (s, 12H); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{32}H_{58}NO_2Si$ 516.4231; Found 516.4240.

*Mixture of 22-epimers **19c***. Yield: 98% (189 mg); IR, ν_{max} (cm^{-1}): 3465, 2927, 2855, 1444, 1375, 1249, 1064, 829; ^1H NMR ($CDCl_3$) δ (ppm): 4.41-4.35 (m, 1H), 4.13 (dd, *J* = 13.9, 7.1 Hz, 1H), 4.08-3.98 (m, 2H), 3.18-3.07 (m, 1H), 3.07-2.94 (m, 1H), 2.87-2.71 (m, 2H), 2.06-1.95 (m, 2H), 0.98 (d, *J* = 6.3 Hz, 6H), 0.86 (s, 6H), 0.89 (s, 18H), 0.83 (s, 3H), 0.79 (s, 3H), 0.02 (s, 12H); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{32}H_{58}NO_2Si$ 516.4231; Found 516.4234.

General Procedure for the Synthesis of Carbamates 20a-c **from Mixtures of *22R/S* Isomers 19**a-c**.** To a solution of the mixture of C22-epimers **19**a-c (40 mg, 0.07 mmol, 1 eq) in Et_2O (15 mL) and 1M KOH (0.1 mL) 4-nitrobenzyl chloroformate (80 mg, 0.37 mmol, 5.3 eq) was added. The mixture was stirred at room temperature for 16 h. Then it was diluted with an additional portion (10 mL) of diethyl ether and filtered through a fritted funnel containing Al_2O_3 and powdered KOH. The funnel was washed with two portions of diethyl ether (50 mL each), and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography with ethyl acetate/hexane (6:94) elution to afford compound **20**a-c as white crystalline materials (88-90%).

*(3β-t-Butyldimethylsilyl)-N-(4-p-nitrobenzyloxycarbonyl)-27-nortomatidine (**20a**)*. Yield: 90% (49 mg); m.p. 179-181 °C (methanol/dichloromethane); IR, ν_{max} (cm^{-1}): 2929, 2854, 1703, 1603, 1522, 1342, 1254, 1161, 1061, 836; ^1H NMR ($CDCl_3$) δ (ppm): 8.22 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 5.24 (d, *J* = 13.7 Hz, 1H), 5.18 (d, *J* = 13.6 Hz, 1H), 4.17 (dd, *J* = 14.5, 7.3 Hz, 1H), 3.87-3.77 (m, 1H), 3.68-3.59 (m, 1H), 3.59-3.48 (m, 1H), 3.27-3.16 (m, 1H), 2.03-1.94 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.83 (s, 3H), 0.82 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 154.0 (C), 147.5 (C), 144.5 (C), 127.9 (2×CH), 123.7 (2×CH), 100.8 (C), 79.0 (CH), 72.1 (CH), 65.1 (CH_2), 63.4 (CH), 56.0 (CH), 54.5 (CH), 45.1 (CH), 43.8 (CH_2), 41.4 (C), 40.1 (CH_2), 38.7 (CH_2), 38.1 (CH), 37.2 (CH_2), 35.6 (C), 35.1 (CH), 32.4 (CH_2), 31.9 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 25.9 (3×CH_3), 24.4 (CH_2), 21.0 (CH_2), 18.4 (CH_2), 18.3 (C), 16.8 (CH_3), 16.5 (CH_3), 12.4 (CH_3), -4.6 (2×CH_3); HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{40}H_{62}N_2O_6SiNa$ 717.4275; Found 717.4289.

*(3α-t-Butyldimethylsilyl)-N-(4-p-nitrobenzyloxycarbonyl)-27-nor-5β-spirosolane (**20b**)*. Yield: 88% (48 mg); m.p. 170-172 °C (dichloromethane/methanol/acetone); IR, ν_{max} (cm^{-1}): 2929, 2856, 1700, 1604, 1521, 1342, 1254, 1166, 1064, 834; ^1H NMR ($CDCl_3$) δ (ppm): 8.23 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 5.24 (d, *J* = 13.6 Hz, 1H), 5.19 (d, *J* = 13.7 Hz, 1H), 4.17 (dd, *J* = 14.9, 7.2 Hz, 1H), 3.88-3.76 (m, 1H), 3.69-3.54 (m, 2H), 3.29-3.17 (m, 1H), 2.04-1.93 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 9H), 0.81 (s, 3H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 154.0 (C),

147.5 (C), 144.5 (C), 127.9 (2×CH), 123.7 (2×CH), 100.8 (C), 79.0 (CH), 72.7 (CH), 65.1 (CH_2), 63.4 (CH), 55.9 (CH), 43.8 (CH_2), 42.2 (CH), 41.4 (C), 40.4 (CH), 40.2 (CH_2), 38.0 (CH), 36.9 (CH_2), 35.6 (CH_2), 35.4 (CH), 34.7 (C), 32.4 (CH_2), 31.0 (CH_2), 27.8 (CH_2), 27.2 (CH_2), 26.7 (CH_2), 26.0 ($3\times CH_3$), 24.4 (CH_2), 23.4 (CH_3), 20.6 (CH_2), 18.3 (CH_2), 18.3 (C), 16.8 (CH_3), 16.5 (CH_3), -4.6 ($2\times CH_3$); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{40}H_{62}N_2O_6SiNa$ 717.4275; Found 717. 4284.

*(3β-t-Butyldimethylsilyl)-N-(4-p-nitrobenzyloxycarbonyl)-27-nor-5β-spirosolane (**20**c)*. Yield: 90% (49 mg); m.p. 153‑155 °C (ethyl acetate/hexane); IR, ν_{max} (cm^{-1}): 2927, 2856, 1703, 1603, 1522, 1342, 1254, 1166, 1066, 832; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.23 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 5.25 (d, *J* = 13.7 Hz, 1H), 5.19 (d, *J* = 13.7 Hz, 1H), 4.18 (dd, *J* = 14.8, 7.2 Hz, 1H), 4.07‑4.00 (m, 1H), 3.88‑3.76 (m, 1H), 3.69‑3.59 (m, 1H), 3.28-3.16 (m, 1H), 2.04‑1.93 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.96 (s, 3H), 0.90 (s, 9H), 0.83 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 154.0 (C), 147.5 (C), 144.5 (C), 127.9 (2×CH), 123.7 (2×CH), 100.8 (C), 79.1 (CH), 67.4 (CH), 65.1 (CH_2), 63.5 (CH), 56.2 (CH), 43.8 (CH_2), 41.5 (C), 40.4 (CH_2), 40.1 (CH), 38.1 (CH), 36.5 (CH), 35.3 (CH), 35.2 (C), 34.4 (CH_2), 32.4 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 26.8 ($2\times CH_2$), 25.8 ($3\times CH_3$), 24.4 (CH_2), 24.0 (CH_3), 20.9 (CH_2), 18.4 (CH_2), 18.1 (C), 16.8 (CH_3), 16.5 (CH_3), -4.8 (CH_3), -4.9 (CH_3); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{40}H_{62}N_2O_6SiNa$ 717.4275; Found 717.4282.

General Procedure for the Deprotection of Carbamates 20a-c**.** A solution of carbamate **20**a-c (35 mg, 0.05 mmol) in dry THF (12 mL) was placed in a round-bottomed flask, to which tetrabutylammonium fluoride (TBAF) (0.5 mL, 1 M in THF, 0.5 mmol, 10 eq) was dropwise added. After stirring at room temperature for 24 h, the reaction mixture was poured into water (20 mL) and extracted three times with Et_2O (50 mL each). The combined organic layers were dried over Na_2SO_4, and evaporated in *vacuo*. The crude product was purified by silica gel column chromatography with ethyl acetate (100%) or methanol/dichloromethane (1:9) elution to afford compounds **21**a-c (89-93%).

*Mixture of 22-epimers **21**a*. Yield: 91% (18 mg); IR, ν_{max} (cm^{-1}): 3434, 2925, 2852, 1449, 1367, 1261, 1043, 884; ^{1}H NMR ($CDCl_3$) δ (ppm): 4.27 (dd, *J* = 14.8, 7.7 Hz, 1H), 4.18‑4.07 (m, 1H), 3.65-3.53 (m, 2H), 3.17-3.04 (m, 1H), 3.04-2.91 (m, 1H), 2.85-2.76 (m, 1H), 2.76-2.67 (m, 1H), 2.10‑1.94 (m, 2H), 0.99 (s, 6H), 0.94 (d, *J* = 7.0 Hz, 6H), 0.83 (s, 3H), 0.79 (s, 3H); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{44}NO_2$ 402.3367; Found 402.3371.

*Mixture of 22-epimers **21**b*. Yield: 93% (19 mg); IR, ν_{max} (cm^{-1}): 3431, 2930, 2857, 1456, 1376, 1252, 1093, 1008, 837; ^{1}H NMR ($CDCl_3$) δ (ppm): 4.28 (dd, *J* = 14.9, 7.4 Hz, 1H), 4.13 (dd, *J* = 14.9, 7.4 Hz, 1H), 3.70-3.57 (m, 2H), 3.19-3.04 (m, 1H), 3.04-2.93 (m, 1H), 2.87-2.77 (m, 1H), 2.77-2.68 (m, 1H), 2.08‑1.95 (m, 2H), 0.96 (s, 6H), 0.95 (d, *J* = 7.2 Hz, 6H), 0.82 (s, 3H), 0.78 (s, 3H); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{44}NO_2$ 402.3367; Found 402.3375.

*Mixture of 22-epimers **21**c*. Yield: 89% (17 mg); IR, ν_{max} (cm^{-1}): 3432, 2925, 2859, 1449, 1376, 1262, 1036, 891; ^{1}H NMR ($CDCl_3$) δ (ppm): 4.28 (dd, *J* = 15.1, 7.6 Hz, 1H), 4.20-4.05 (m, 3H), 3.17-3.04 (m, 1H), 3.04-2.92 (m, 1H), 2.88-2.78 (m, 1H), 2.78-2.67 (m, 1H), 0.99 (s, 6H), 0.95 (d, *J* = 7.3 Hz, 6H), 0.82 (s, 3H), 0.79 (s, 3H); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{44}NO_2$ 402.3367; Found 402.3379.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

X-ray crystallographic data and copies of spectra for all key compounds (PDF)

Crystal data for **20**a (CIF) and **20**b (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Jayakumar, K.; Murugan, K. *Solanum* Alkaloids and their Pharmaceutical Roles: A Review. *J. Anal. Pharm. Res.* **2016**, *3*, 00075.

(2) Heretsch, P.; Giannis, A. *The Alkaloids*, **2015**, vol. 74, 1st Ed., chapter 4, p. 201–232, Elsevier Inc.

(3) Al Sinani, S. S. S.; Eltayeb, E. A. *S.* The Steroidal Glycoalkaloids Solamargine and Solasonine in *Solanum* Plants. *Afr. J. Bot.* **2017**, *112*, 253–269.

(4) (a) Yuan, B.; Byrnes, D.; Giurleo, D.; Villani, T.; Simon, J. E.; Wu, Q. Rapid Screening of Toxic Glycoalkaloids and Micronutrients in Edible Nightshades (*Solanum spp.*). *J. Food Drug Anal*. **2018**, *26*, 751–760. (b) Milner, S. E.; Brunton, N. P.; Jones,P. W.; O' Brien, N. M.; Collins, S. G.; Maguire, A. R. Bioactivities of Glycoalkaloids and Their Aglycones from *Solanum* Apecies. *J. Agric. Food Chem.* **2011**, *59*, 3454–3484. (c) Ikeda, T.; Tsumagari, H,; Honbu, T.; Nohara, T. Cytotoxic Activity of Steroidal Glycosides from Solanum Plants. *Biol. Pharm. Bull*. **2003**, *26*, 1198–1201.

(5) Friedman, M. Chemistry and Anticarcinogenic Mechanisms of Glycoalkaloids Produced by Eggplants, Potatoes, and Tomatoes. *J. Agric. Food Chem.* **2015**, *63*, 3323–3337.

(6) (a) Hou, L. L.; Shi, Y.; Zhang, Z.D.; Wu, J. J.; Yang, Q. X.; Tian, W. S. Divergent Synthesis of Solanidine and 22-*epi*-Solanidine. *J. Org. Chem*. **2017**, *82*, 7463–7469. (b) Zhang, Z.-D.; Shi, Y.; Wu, J.-J.; Lin, J.-R.; Tian, W.-S. Synthesis of Demissidine and Solanidine. *Org. Lett.* **2016**, *18*, 3038–3040. (c) Wu, J.-J.; Gao, R.; Shi, Y.; Tian, W.-S. Direct Amination of EF Spiroketal in Steroidal Sapogenins: an Efficient Synthetic Strategy and Method for Related Alkaloids. *Tetrahedron Lett*. **2015**, *56*, 6639–6642. (d) Wu, J.-J.; Gao, R.; Shi, Y.; Tian, W.-S. Facile Synthesis of Solasodine Based on a Mild Halogenation-Ring Opening Reaction of Spiroketals in Steroidal Sapogenins. *Tetrahedron Lett*. **2015**, *56*, 1215–1217. (e) Zhang, Z.; Giampa, G. M.; Draghici, C.; Huang, Q.; Brewer, M. Synthesis of Demissidine by a Ring Fragmentation 1,3-Dipolar Cycloaddition Approach. *Org. Lett.* **2013**, *15*, 2100–2103. (f) Wei, G.-H.; Wei, D.-B.; Du, Y.-G. An Alternative Total Synthesis of Solamargine. *Sci. China Chem.* **2012**, *55*, 1247–1251. (g) Zhang, G.-P.; Shen, S.-D.; Lei, M.; Hu, L.-H. A Facile and Efficient Method for the Synthesis of Solasodine from Diosgenin. *Tetrahedron*, **2011**, *67*, 5894–5896. (h) Zha, X.; Sun, H.; Hao, J.; Zhang, Y. Efficient Synthesis of Solasodine, *O*-Acetylsolasodine, and Soladulcidine as Anticancer Steroidal Alkaloids. *Chem. Biodivers*. **2007**, *4*, 25–31.

(7) Jiang, B.; Shi, H.; Tian, W.; Zhou, W. The Convergent Synthesis of Novel Cytotoxic Certonardosterol D_2 from Diosgenin. *Tetrahedron* **2008**, *64*, 469–476.

(8) (a) Schreiber, K.; Horstmann, C.; Adam, G. Synthese von 27-Nor-spirosolan-Alkaloiden. *Chem. Ber*. **1965**, *98*, 1061–1973. (b) Schreiber, K.; Adam, G. Synthese von Solanum-Alkaloiden aus 3β-Acetoxy-5α-pregn-16-en-20-on. *Tetrahedron Lett.* **1960**, *1*, 5–8.

(9) Czajkowska, D.; Morzycki, J. W.; Santillan, R.; Siergiejczyk, L. Synthesis of "Glycospirostanes" *via* Ring-Closing Metathesis. *Steroids* **2009**, *74*, 1073–1079.

(10) Wei, G.; Wang, J.; Du, Y. Total Synthesis of Solamargine. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2930–2933.

(11) Canonne, P.; Foscolos, G. B.; Belanger D. One-step annulation. A convenient method for the preparation of diols, spirolactones, and spiroethers from lactones. *J. Org. Chem.*, **1980**, *45*, 1828–1835.

(12) Rappoport, Z.; Marek, I. *The Chemistry of Organolithium Compounds: R-Li*, **2004**, vol. 2, chapter 4, p. 315, Wiley.

(13) (a) Ferreira, P. M. T.; Monteiro, L. S. Synthesis and Reactivity of β-Bromo-β-Substituted Dehydroalanines. *Eur. J. Org. Chem.* **2006**, 3226–3234. (b) Sato, H.; Sakoh, H.; Hashihayata, T.; Imamura, H.; Ohtake, N.; Shimizu, A.; Sugimoto, Y.; Sakuraba, S.; Bamba-Nagano, R.; Yamada, K.; Hashizume, T.; Morishima, M. Structure–Activity Relationships of 1β-Methyl-2-(5-phenylpyrrolidin-3-ylthio)carbapenems. *Bioorg. Med. Chem.* **2002**, *10*, 1595–1610. (c) Hashiguchi, S.; Natsugari, H.; Ochiai, M. Synthesis of γ-Lactam Analogues of Carbapenems with Substituted-thio Groups at the C-3 Position. *J. Chem. Soc., Perkin Trans. I* **1988**, 2345–2352.

(14) Matsushita, S.; Yanai, Y.; Fusyuku, A.; Fujiwara, Y.; Ikeda, T.; Ono, M.; Han, C.; Ojika, M.; Nohara, T. Efficient Conversion of Tomatidine into Neuritogenic Pregnane Derivative. *Chem. Pharm. Bull.* **2007**, *55*, 1077−1078.

(15) Czajkowska-Szczykowska, D.; Jastrzebska, I.; Rode, J. E.; Morzycki. J. W. Revision of the Structure of *N*,*O*-Diacetylsolasodine. Unusual Epimerization at the Spiro Carbon Atom during Acetylation of Solasodine. *J. Nat. Prod.* **2019**, *82*, 59−65.

(16) (a) Munafo Jr, J. P.; Gianfagna, T. J. Chemistry and Biological Activity of Steroidal Glycosides from the *Lilium* Genus. *Nat. Prod. Rep.* **2015**, *32*, 454–477. (b) Ripperger, H. 22, 26-Epiminocholestane Alkaloids with Unusual (20*R*)-Configurations from *Solanum* Species. *Phytochemistry* **1996**, *41*, 1629–1631. (c) Bird, G. J.; Collins, D. J.; Eastwood, F. W.; Exner, R. H. Assignment of the ^{13}C N.M.R. Spectra of Some 22,26-Epiminocholestanes 22,26-Epiminocholest-22(*N*)-enes and Some 3β-Amino Steroidal Alkaloids. *Aust. J. Chem.* **1979**, *32*, 797–816. (d) Uhle, F. C. *N*-Methylsolasodine. *J. Org. Chem.* **1967**, *32*, 792–797.

(17) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. Mild and Selective Deprotection of Carbamates with Bu_4NF. *Tetrahedron*, **2004**, *60*, 10039–10047.