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Synthesis of Demissidine and Solanidine

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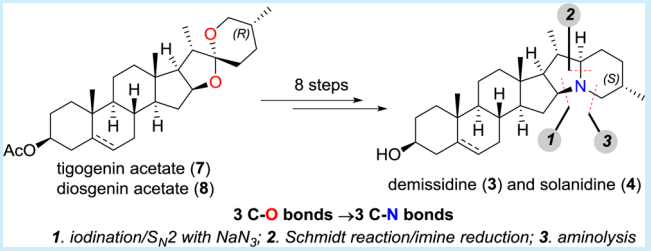
Supporting Information

ABSTRACT: Demissidine and solanidine, two steroidal alkaloids, are synthesized in eight steps from tigogenin acetate and diosgenin acetate, respectively, which involve the replacement of three C−O bonds with C−N bonds. Key transformations include a cascade ring-switching process of furostan-26-acid, an epimerization of C25, an intramolecular Schmidt reaction, and an imine reduction/intramolecular aminolysis process.



Steroidal alkaloids and their glycosides, which occur in many plants of the *Solanaceae*, are known to possess various bioactivities and structures, thus drawing great interest from researchers.[1] Among these alkaloids, solasodine (**1**, Figure 1)

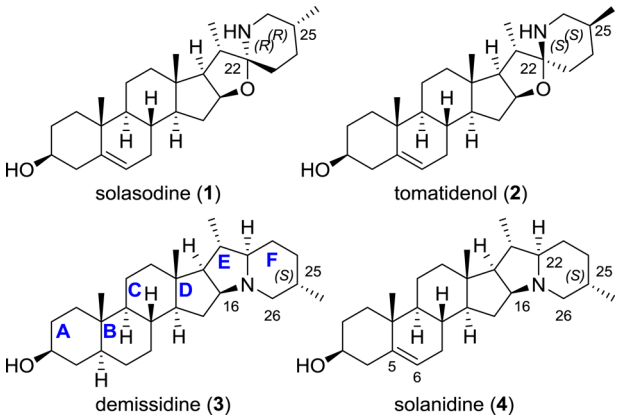


Figure 1. Structures of demissidine (**3**) and solanidine (**4**).

and tomatidenol (**2**) are known to act as natural insect deterrents, have antimicrobial properties, can inhibit acetylcholinesterase, and disrupt cell membranes.[2] Demissidine (**3**) and solanidine (**4**), which are two cholestane alkaloids isolated from several potato species including *Solanum demissum*,[3] *Solanum acaule*,[4] and *Solanum tuberosum*,[5] mainly present as glycosides, can inhibit proliferation and exhibit obvious antitumor effect.[6]

Demissidine (**3**) was synthesized from the related steroidal alkaloid dihydrotomatidine by Kuhn and co-workers in 1952[7] and later by Sato and Latham.[8] In 1963 Adam and Schreiber prepared **3** from pregnenolone acetate by addition of 2-lithio-5-methylpyridine followed by hydrogenation and Hofmann−Löffler−Freytag cyclization.[9] Recently, Brewer and co-workers reported an efficient synthesis of **3** from epiandrosterone by a ring fragmentation 1,3-dipolar cycloaddition approach.[10] Only two syntheses of **4** from **2** and from isorubijervine were reported, both in low yields.[11] Herein, we report an eight-step synthesis of **3** and **4** with the 27C intact skeletons of steroidal sapogenins.

Compounds **3** and **4** differ from steroidal sapogenins in two aspects: the configuration of C25 and the arrangement of the EF rings. The EF rings of steroidal sapogenins are 5,6-spiroketals with two oxygen atoms, while those in **3** and **4** are 5,6-fused bicycles with a nitrogen atom at brighthead. Thus, we needed to replace three C−O bonds (C16−O, C22−O, and C26−O) with C−N bonds and to epimerize the configuration of C25. We envisioned that the C26−N bond of **3**/**4** would be constructed via an intramolecular *N*-alkylation and the C22−N bond would be established stereoselectively via a Schmidt reaction of azide **5** followed by a substrate-controlled reduction of the resulting imine (Scheme 1). Azide **5** would be prepared from iodide **6** through a substitution of C16α-I with sodium azide and an epimerization of C25. Iodide **6**, in turn, would be prepared by a cascade ring-switching process of furostan-26-acid derived from tigogenin acetate (**7**) or diosgenin acetate (**8**), a method we recently developed.[12]

Our synthesis of demissidine (**3**) was depicted in Scheme 2. Furostan-26-acid **9** was prepared from **7** via a reduction−oxidation process, and was then treated with trifluoroacetic anhydride/lithium iodide to afford iodide **6** in high yield. Treated with NaN_3 in DMF at 65 °C, **6** underwent azide-substitution smoothly, delivering **10** in 93% yield. Epimerizing the configuration of C25 from *R* to *S* was then performed, upon treatment with K_2CO_3 (10 equiv) in MeOH at 45 °C for 5 h,[12a] to give **5** in 90% on the multigram scale.

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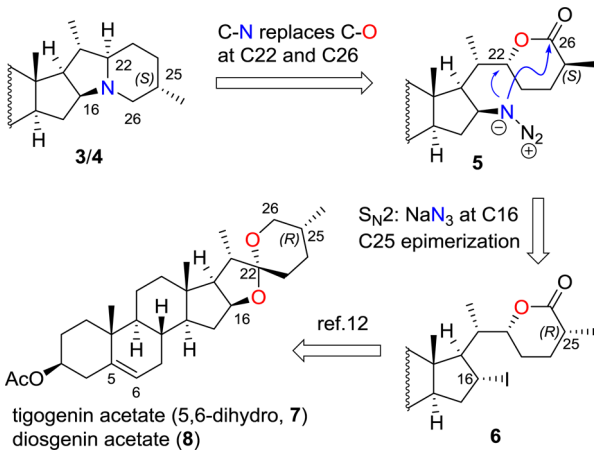
Scheme 1. Synthetic Plan for Demissidine and Solanidine



With **5** in hand, focus turned to stereoselective construction of the required C16N−C22 bond. Both **5** and **3** are *R*-configured at C22. Retaining the configuration might be troublesome during a routine method involving the reduction of the C16-azide to amine and the transformation of the C22−O to a leaving group and the intramolecular substitution. However, it would be more feasible to wipe its stereochemistry by forming an imine and then to restore it through a substrate-controlled reduction. Ideally, the imine could be reached directly from **5** through an intramolecular Schmidt reaction[13] triggered by forming a cation at C22.

We then looked for conditions that could activate C22 and thus trigger the designed Schmidt reaction. It was well-known that lactones could be opened with HBr or HCl to afford the corresponding ω-halo acids or esters.[14] Under these conditions, the intramolecular nucleophilic azido group nearby would outdo the ambient halogen ions in attacking the electrophilic site. After many attempts, we found this hypothesis worked. Treating **5** with $SOCl_2$ in MeOH ($SOCl_2$/MeOH (1/6) *in situ* generates a solution of HCl in MeOH) at ambient temperature delivered the desired imine **13** in good yield, and more importantly, the exposed C3-OH was not affected, thus avoiding the use of protecting groups. We soon found the product was not a single isomer, but a 2/1 inseparable mixture of **13** and its 25-epimer, indicating partial epimerization at C25 under the reaction conditions.[15] Similarly, subjection of **10** to the same conditions caused epimerization at C25, giving a 1/2 inseparable mixture of **13** and 25-*epi*-**13**. Lowering the amount of $SOCl_2$ and using other methods of preparing HCl solution could not inhibit the epimerization. Attempts to convert the unwanted 25-*epi*-**13** to **13** also failed as the C25 is now on a flexible chain where the configurational bias of the C25-epimers no longer exists.

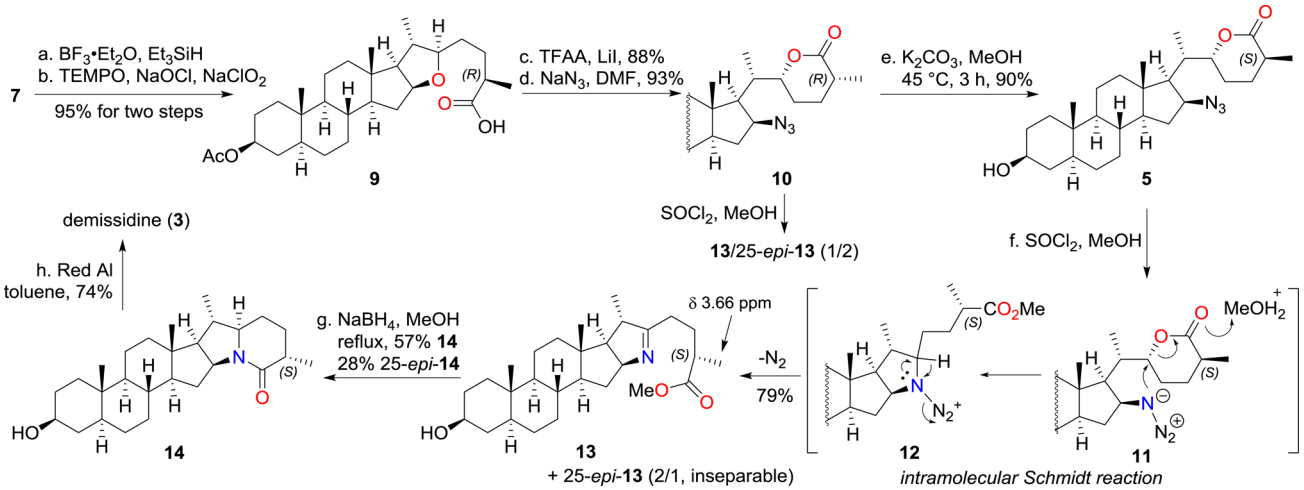
Reduction of the imine group in **13** and 25-*epi*-**13** ($NaBH_4$, EtOH, rt) was therefore performed, and the spontaneous intramolecular aminolysis of the amino-ester was observed, forming a small amount of lactam **14**.[16] Heating at reflux drove the reaction to completion, giving **14** and its 25-epimer in 57% and 28% yield, respectively. The stereochemistry of C22 was assigned as *R* by 2D NOESY analysis (NOEs between C21-Me and C22−H, and between C16α-H and C22−H), thus confirming that the hydride approached the imine from the less hindered face. Treating 25-*epi*-**14** with various bases (K_2CO_3, DBU, NaH, LiHMDS, etc.) could not afford **14** in a reasonable yield.

Reduction of the lactam in **14** to an amine was investigated. To our surprise, treating **14** with $LiAlH_4$ (rt to reflux in THF) only gave demissidine in low yield. Later, reduction of **14** with Red-Al (sodium bis(2-methoxyethoxy)aluminumhydride) in toluene at ambient temperature cleanly gave **3** in 74% yield. The analytical data of synthetic **3** matched with those reported.

Likewise, solanidine **4** was synthesized from diosgenin acetate **8** (Scheme 3). Iodide **6** (with C5−C6 double bond) was prepared from **8** in three steps and 77% yield.[12a] Azide-substitution of C16α-I and epimerization of C25 followed by the intramolecular Schmidt reaction gave imino-ester **16**, which was sequentially reduced with $NaBH_4$ and Red-Al, providing solanidine **4** in 18% overall yield from **6**. The analytical data of synthetic **4** matched with those reported.

In summary, we developed an eight-step synthetic route to demissidine and solanidine from tigogenin acetate (**7**) and diosgenin acetate (**8**). Key transformations include the cascade ring-switching process of furostan-26-acid, the intramolecular Schmidt reaction of azido-lactones **5**/**15** to provide imino-esters **13**/**16**, and the stereoselective reduction/intramolecular aminolysis of **13**/**16** to give lactams **14**/**17**. It was also noteworthy that our synthesis minimized the use of protecting groups except the acetate in starting materials. Applying the

Scheme 2. Eight-Step Synthesis of Demissidine from Tigogenin Acetate



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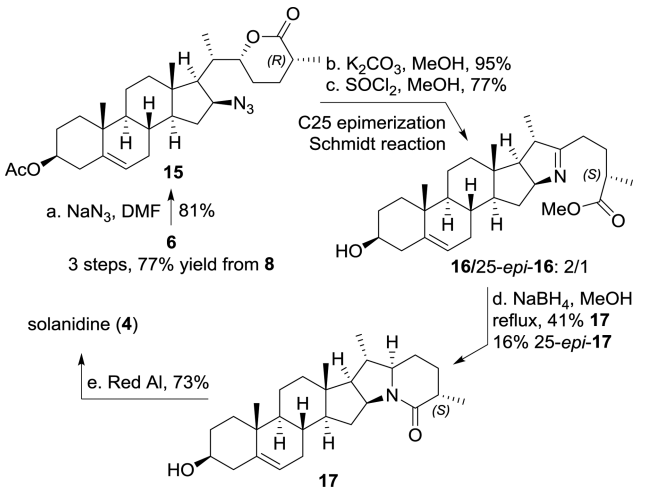
Scheme 3. Synthesis of Solanidine



reactions used herein to the synthesis of other natural products is ongoing in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01320.

Experimental details, spectral data, ^1H and ^{13}C NMR spectra of all the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Jiang, Q.-W.; Chen, M.-W.; Cheng, K.-J.; Yu, P.-Z.; Wei, X.; Shi, Z. *Med. Res. Rev.* **2016**, *36*, 119−143. (b) Heretsch, P.; Tzagkaroulaki, L.; Giannis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3418−3427. (c) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148−3149. (d) Lee, S. T.; Welch, K. D.; Panter, K. E.; Gardner, D. R.; Garrossian, M.; Chang, C.-W. T. *J. Agric. Food Chem.* **2014**, *62*, 7355−7362. (e) Keyzers, R. A.; Daoust, J.; Davies-Coleman, M. T.; Soest, R. V.; Balgi, A.; Donohue, E.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2008**, *10*, 2959−2962. (f) Moore, K. S.; Wehrli, S.; Roder, H.; Rogers, M.; Forrest, J. N.; McCrimmon, D.; Zasloff, M. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 1354−1358. (g) Zasloff, M.; Adams, A. P.; Beckerman, B.; Campbell, A.; Han, Z.; Luijten, E.; Meza, I.; Julander, J.; Mishra, A.; Qu, W.; Taylor, J. M.; Weaver, S. C.; Wong, G. C. L. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 15978−15983. (h) Milner, S. E.; Brunton, N. P.; Jones, P. W.; O' Brien, N. M.; Collins, S. G.; Maguire, A. R. *J. Agric. Food Chem.* **2011**, *59*, 3454−3484.

(2) (a) Chauhan, K.; Sheth, N.; Ranpariya, V.; Parmar, S. *Pharm. Biol.* **2011**, *49*, 194−199. (b) Lecanu, L.; Hashim, A. I.; McCourty, A.; Giscos-Douriez, I.; Dinca, I.; Yao, W.; Vicini, S.; Szabo, G.; Erdélyi, F.; Greeson, J.; Papadopoulos, V. *Neuroscience* **2011**, *183*, 251−264. (c) Pandurangan, A.; Khosa, R. L.; Hemalatha, S. *Nat. Prod. Res.* **2011**, *25*, 1132−1141. (d) Lee, K.-R.; Kozukue, N.; Han, J.-S.; Park, J.-H.; Chang, E.-Y.; Baek, E.-J.; Chang, J.-S.; Friedman, M. *J. Agric. Food Chem.* **2004**, *52*, 2832−2839. (e) Friedman, M. *J. Agric. Food Chem.* **2006**, *54*, 8655−8681.

(3) Osman, S. F.; Sinden, S. L. *Phytochemistry* **1982**, *21*, 2763−2764.

(4) Gregory, P. *Am. Potato J.* **1984**, *61*, 115−122.

(5) (a) Stankovic, M. Z.; Nikolic, N. C.; Palic, R.; Cakic, M. D.; Veljkovic, V. B. *Potato Res.* **1994**, *37*, 271−278. (b) Attoumbre, J.; Giordanengo, P.; Baltora-Rosset, S. *J. Sep. Sci.* **2013**, *36*, 2379−2385.

(6) (a) Zupkó, I.; Molnár, J.; Réthy, B.; Minorics, R.; Frank, É.; Wölfling, J.; Molnár, J.; Ocsovszki, I.; Topcu, Z.; Bitó, T.; Puskás, L. *Molecules* **2014**, *19*, 2061−2076. (b) Shih, Y.-W.; Chen, P.-S.; Wu, C.-H.; Jeng, Y.-F.; Wang, C.-J. *J. Agric. Food Chem.* **2007**, *55*, 11035−11043. (c) Lu, M.-K.; Shih, Y.-W.; Chang Chien, T.-T.; Fang, L.-H.; Huang, H.-C.; Chen, P.-S. *Biol. Pharm. Bull.* **2010**, *33*, 1685−1691. (d) Yamashoji, S.; Matsuda, T. *Food Chem.* **2013**, *141*, 669−674.

(7) Kuhn, R.; Löw, I.; Trischmann, H. *Angew. Chem.* **1952**, *64*, 397−397.

(8) Sato, Y.; Latham, H. G. *J. Am. Chem. Soc.* **1956**, *78*, 3146−3150.

(9) Adam, G.; Schreiber, K. *Tetrahedron Lett.* **1963**, *4*, 943−948.

(10) Zhang, Z.; Giampa, G. M.; Draghici, C.; Huang, Q.; Brewer, M. *Org. Lett.* **2013**, *15*, 2100−2103.

(11) (a) Pelletier, S. W.; Jacobs, W. A. *J. Am. Chem. Soc.* **1953**, *75*, 4442−4446. (b) Schreiber, K.; Rönsch, H. *Tetrahedron* **1965**, *21*, 645−650.

(12) (a) Zhang, X.-F.; Wu, J.-J.; Shi, Y.; Lin, J.-R.; Tian, W.-S. *Tetrahedron Lett.* **2014**, *55*, 4639−4642. (b) Wu, J.-J.; Shi, Y.; Tian, W.-S. *Chem. Commun.* **2016**, *52*, 1942−1944.

(13) (a) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146−156. (b) Sun, X.; Gao, C.; Zhang, F.; Song, Z.; Kong, L.; Wen, X.; Sun, H. *Tetrahedron* **2014**, *70*, 643−649. (c) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **1995**, *60*, 4960−4961. (d) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W. K.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183−10194. (e) Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583−585.

(14) (a) Gimazetdinov, A. M.; Gataullin, S. S.; Loza, V. V.; Miftakhov, M. S. *Tetrahedron* **2013**, *69*, 9540−9543. (b) Wolfe, S.; Wilson, M.-C.; Cheng, M.-H.; Shustov, G. V.; Akuche, C. I. *Can. J. Chem.* **2003**, *81*, 937−960. (c) Kad, G. L.; Kaur, I.; Bhandari, M.; Singh, J.; Kaur, J. *Org. Process Res. Dev.* **2003**, *7*, 339−340.

(15) The ^1H NMR of **13** and 25-*epi*-**13** were almost the same, except the signals of methyl ester. The chemical shift of the methoxyl group in **13** is 3.66 ppm and in 25-*epi*-**13** is 3.65 ppm. The ratio of the two epimers was thus identified.

(16) (a) Gardette, D.; Gramain, J. C.; Sinibaldi, M. E. *Heterocycles* **1990**, *31*, 1439−1444. (b) Choi, J.-R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469−6472.

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Org. Lett. XXXX, XXX, XXX−XXX