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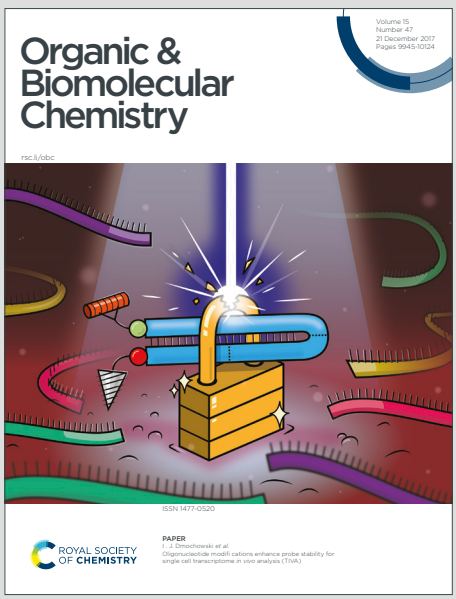

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DOI: 10.1039/D0OB00457J

ARTICLE

Asymmetric Synthesis of (-)-Solanidine and (-)-Tomatidenol

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A concise asymmetric synthesis of two naturally occurring seco-type cholestane alkaloids (-)-solanidine and (-)-tomatidenol from (-)-diosgenin with a linear reaction sequence of 12 steps and 13 steps, respectively is reported. The synthetic strategy includes the highly controlled establishment of highly functionalized octahydroindolizine ((-)-solanidine) and 1-oxa-6-azaspiro[4.5]decane cores ((-)-tomatidenol) with five stereocenters, respectively from (-)-diosgenin, featuring two stereoselective cascade transformations including a modified cascade ring-switching process of furostan-26-acid to open E-ring of (-)-diosgenin and a cascade azide reduction /intramolecular reductive amination to close E and F-rings of (-)-solanidine and (-)-tomatidenol. This work should enable further explorations of chemical and biological spaces based on solanidine, tomatidenol and related natural products.

Introduction

(-)-Solanidine (**1**) and (-)-tomatidenol (**2**) represent two types of *seco*-cholestane alkaloids isolated from various potato species of *solanum* family including *solanum demissum* L.,[1] *solanum acaule* L.,[2] *solanum tubersum* L.,[3] *solanum spirale* L.,[4] and *solanum dulcamara* L.[5] *etc* (Figure 1), mainly present as glycosides. The former has proven to inhibit proliferation and induce apoptosis in various types of cancer cells in vitro,[6] and the latter has been reported to possess antimicrobial,[7] antifungal,[8] *etc* and are used as natural insect deterrents.[9] Structurally, the *seco*-type cholestane alkaloids **1** and **2** possess an unique octahydroindolizine and 1-oxa-6-azaspiro[4.5]decane ring systems with five stereocenters, respectively that lie within a complex cholestane skeleton.

Somewhat surprisingly, there are only three reports of synthesis of the natural alkaloid **1** including the Schreiber's four-step approach starting from naturally occurring product **2**,[10] the Pelletier's three-step route[11] via the reduction cleavage of either isorubijervine mono tosylate or monoiodide from isorubijervine, an alkaloid of *veratrum album* and *veratrum viride*,[12] and recent Tian's eight-step synthesis by an intramolecular Schmidt reaction of chiral azido diol from (-)-diosgenin (**5**).[13] There is no report on the strategy and method for synthesis of natural alkaloid **2**.[14] Considering the scare synthetic achievements of *seco*-cholestane alkaloids and in connection with our long-time research interests to steroidal alkaloids,[13-15] we initiated a long-term research program aiming to the synthesis of this type of natural products to enable further investigation of their bioactive and structure-activity relationship. Herein, we report our efforts that culminated in an improved asymmetric synthesis of (-)-solanidine (**1**) and first formal asymmetric synthesis of (-)-tomatidenol (**2**) from commercially available (-)-diosgenin (**5**) in large bulk in China.

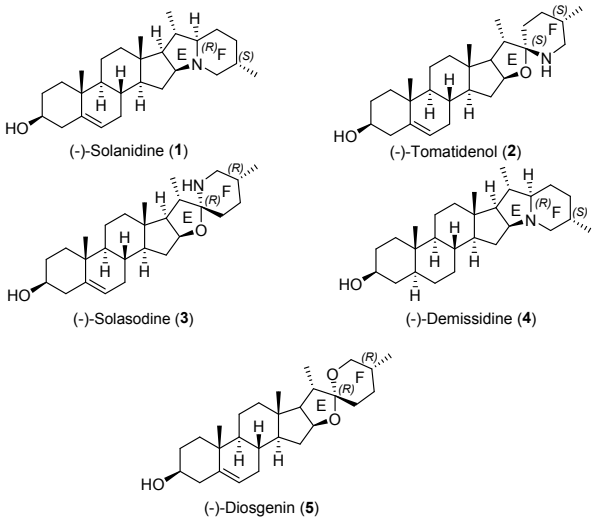

Figure 1. Structures of (-)-solanidine (**1**), (-)-tomatidenol (**2**) and (-)-solasodine (**3**), (-)- demissidine (**4**) and (-)-diosgenin (**5**).

Results and discussion

Our synthetic plan for (-)-solanidine (**1**) and (-)-tomatidenol (**2**) is outlined in Scheme 1. (-)-Solanidine (**1**) and (-)-tomatidenol (**2**) were envisioned to be generated from azidodiketone **6** by construction of octahydroindolizine and 1-oxa-6-azaspiro[4.5]decane units via azide reduction/ stereoselectively intramolecular reductive cascade amination, and stereoselective reduction of the C16-ketone function followed by azide reduction/ intramolecular hemispiroketetal cascade cyclization, respectively. The azidodiketone **6** could be

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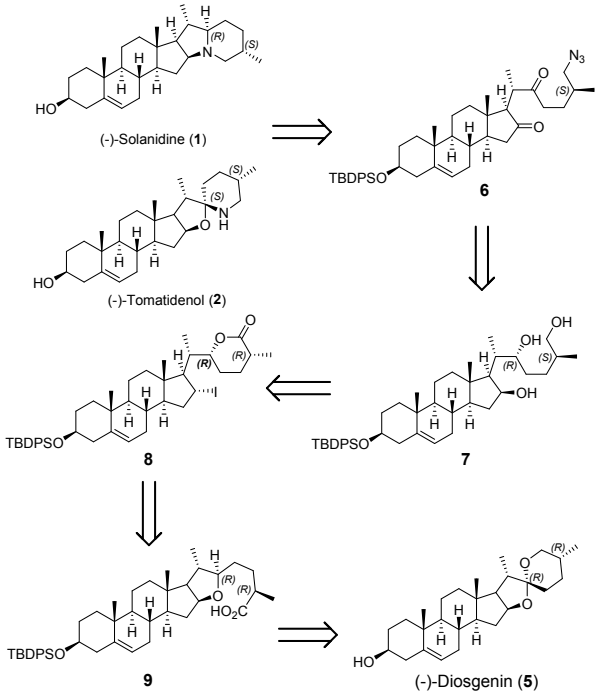
Electronic Supplementary Information (ESI) available: [NMR spectra]. See DOI: 10.1039/x0xx00000x

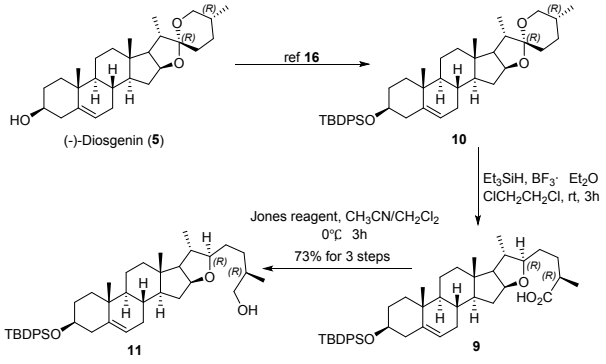
obtained from the corresponding triol **7** by SN2 azido nucleophilic displacement, selective tosylation and Swern oxidation. The triol **7** would be derived from C16α-iodolactone **8** by nucleophilic substitution with CsOAc followed by C25 epimerization and C16-OAc reduction/ deacetylation. The six-membered lactone with two stereocenters and C16α-I bond of **8** could conveniently be constructed using a modified tetrabutylammonium iodide (TBAI)-catalyzed trifluoroacetic anhydride(TFAA)-LiI promoted cascade ring-switching process of furostan-26-acid **9**, which could be originated from (-)-diosgenin (**5**) through a route largely similar to the one previously used in this laboratory in the asymmetrie of (-)-solasodine (**3**), (-)- demissidine (**4**) and other related cholestane alkaloids[15].

Scheme 1. Retrosynthetic analysis for (-)-solanidine (**1**) and (-)-tomatidenol (**2**).



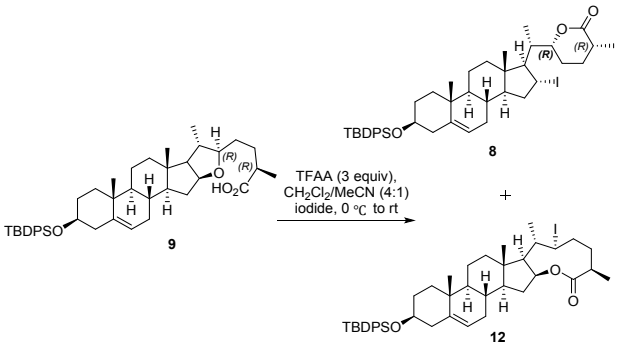
Our synthesis began with efficient synthesis of furostan-26-acid **9,** and its synthesis route is depicted in Scheme **2**, starting from (-)-diosgenin (**5**), the (-)-diosgenin TBDPS ether **10** was be easily prepared in our multigram scale following the known procedure.[16] Then, regioseletive spiroketal cleavage of the resulting crude **10** using $Et_3SiH/BF_3{\cdot}Et_2O$ reduction[17] at room temperature stereospecifically delivered primary alcohol **11** without purification and further underwent Jones oxidation to yield the corresponding furostan-26-acid **9** in 73% overall yield over three steps.

Scheme 2. Synthesis of furostan-26-acid **9**



The next stage of the synthesis involved an intramolecular ring-switching process to assemble chiral six-membered lactone ring and C16α-I bond of C16α-iodolactone **8** (Table 1) in according with similar reaction in our prior art.[13, 15a, 15c] The first attempt at an intramolecular ring-switching reaction of **9** with 3 equiv of TBAI as nucleophile under TFAA (activator)-free condition resulted in no reaction and 95% of recovery unreactive **9** (entry 1). However, employing 5 equiv of TBAI as nucleophile in the reaction of **9** in the presence of 3 equiv of TFAA in CH_2Cl_2/MeCN provided the desired C16α-iodolactone **8** for 24 h in 67% yield along with macrolide product **12** in 10% yield after silica gel column chromatography (entry 2).

Table 1. Synthesis of C16 α-iodolactone **8** by the ring-switching reaction of **9** under different conditions



Entry	Iodide (equiv)	Time (h)	Yield(%)[b] (**8**/**12**)
1	TBAI [a] (3)	4	none
2	TBAI (5)	24	67/10
3	LiI (3)	3.5	72/13
4	NaI (3)	4	71/14
5	NH_4I (3)	4	70/13
6	LiI/TBAI (3/0.5)	4	72/13
7	LiI/TBAI (4/0.5)	4	74/8

[a] No activator TFAA was added. [b] Yield of isolate after silica gel column chromatography.

Armed with this result, we queried whether we might optimize this transformation to further decrease the formation of the by-product **12**. The use of other nucleophiles such as 3 equiv of LiI, NaI, NH_4I and LiI/TBAI (3/0.5 equiv) (entries 3-6) led to the disappointing reaction results analogous to that of TBAI as in entry 1. To our delight, simply switching the nucleophile for this transformation to LiI (4 equiv) and TBAI (0.5 equiv) afforded **8** in 74% yield, only 8% of **12** was isolated (entry 7).

After accomplishing C16α-iodolactone **8**, the next stage was set for the installation of C16β-hydroxyl functionality through the nucleophilic substitution of C16α-I in **8** by a suitable acetate (Scheme 3). Initially, nucleophilic substitution using KOAc in DMF at 60 °C for 15 h restore the C16β-O functional group to give C16β-ester **13** in 83% yield along with 16% of the thermodynamically favored elimination product **14** (Table 2, entry 1). To solve this problem, we elected to conduct this transformation using CsOAc as the nucleophiles. As expected, heating **8** with CsOAc in DMF at 60 °C for 15 h gave rise to C16β-ester **13** in 91% yield, accompanied by a negligible amount of

14 for ready C25 epimerization reaction (entry 2). Consistent with our previous studies,[13, 15a] treating **13** with K_2CO_3 in MeOH underwent C25-epimerization followed by LAH reduction delivered 16, 22, 26-triol **7** in 92% yield over the two steps.

Scheme 3. Synthesis of 16, 22, 26-triol **7**

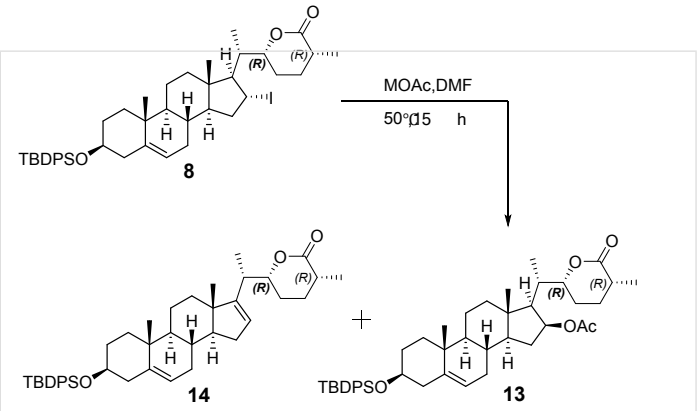


Table 2. Results of reactions using MOAc

entry	MOAc	Yield (%) [a] **13/14**
1	KOAc	83/16
2	CsOAc	91/0 [b]

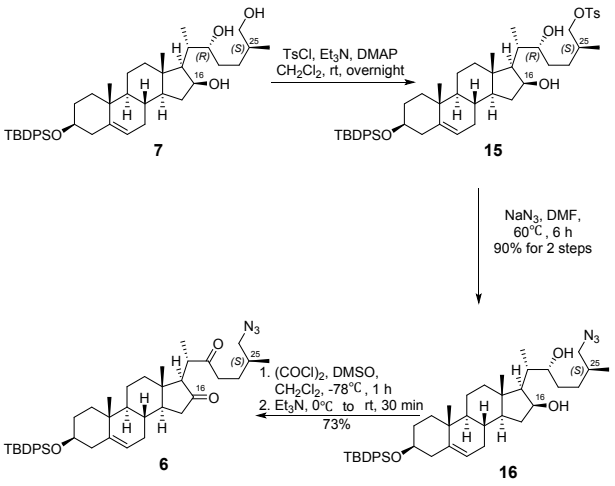
[a] Isolate yield. [b] Almost no visible trace of **14**.

Prior to further construction of the E- and F-ring of **1** and **2**, we focused on forming azidodiketone framework through a three-step sequence of tosylation of C26-OH in **7** azide displacement to tosylate **15** and Swern oxidation of C16β-OH in **16** as illustrated in Scheme 4. Regioselective tosylation of the C26-OH in **7** with *p*-toluene sulfonyl chloride (*p*-TsCl) and Et_3N generated a tosylate **15** to be azide displacement by NaN_3, providing the corresponding azidodidiol **16** in 90% yield over the two steps. Oxidation to **16** proved to be less straightforward than anticipated. Oxidation using Dess-Martin periodinane (DMP) led to formation of a complex mixture of products. Pleasingly, treatment of **16** with large excess of oxalyl chloride (8 equiv) and DMSO (12 equiv) in CH_2Cl_2 at -78°C for 2 h for Swern oxidation of the exposed C16β-OH and C22-OH efficiently supplied azidodiketone **6** in 73% yield.

With the key intermediate **6** in hand, we directed our attention to the construction of E- and F-ring for the synthesis of (-)-solanidine (**1**) and (-)-tomatidenol (**2**). One-pot three-step transformation (namely, azide reduction and double reductive amination) using Raney Ni-catalyzed hydrogenation was first tested on the azidodiketone **6**. In this event, the treatment of **2** with Raney Ni in MeOH at 40 °C produced the desired (-)-solanidine (**1**) TBDPS ether **17** in 64% yield.

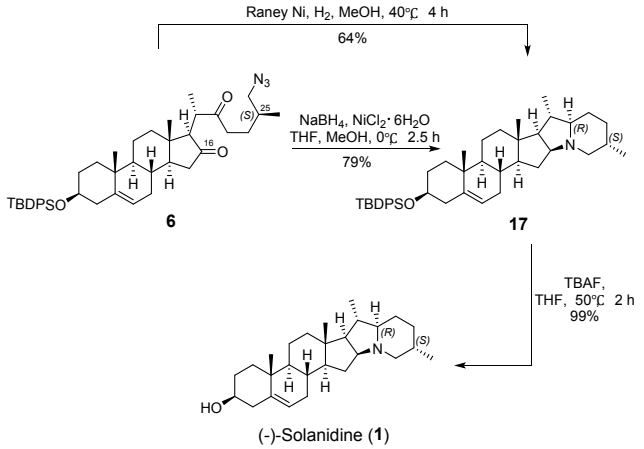
When performing the reaction using $NaBH_4$ and $NiCl_2{\cdot}6H_2O$ in mixed THF and MeOH at 0°C, the yield of **17** was increased to 79%. The final desilylation proceeded without incident. The TBDPS group in **17** was clearly removed by treatment of TBAF in THF at 50 °C for 2 h, (-)-solanidine (**1**) was obtained in essentially quantitative yield[15a] (Scheme 5). The spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS and specific rotation of the synthetic product) are in excellent agreement with those reported.[13,18]

Scheme 4. Synthesis of azidodiketone **6.**



The synthesis of (-)-tomatidenol (**2**) is described in Scheme 6. Reduction of **6** with $NaBH_4$ in THF/methanol at room temperature gave the desired hemiketal **18** in 61% yield along with 22% of azidoalcohol **22-*epi*-16**. After separation, the undesired azidoalcohol **22-*epi*-16** was oxidized back to the azidodiketone **6** in 75% yield by Swern oxidation and was recycled. The hemiketal **18** was treated with iodotrimethylsilane,[19] (*in situ* prepared by trimethyl chlorosilane (TMSCl) and NaI) in MeCN to generate (-)-tomatidenol TBDPS ether **19** through the cascade azide reduction/stereoselective hemispiroketal cyclization, which was directed cleaved by TBAF in THF to afford the expected (-)-tomatidenol (**2**) in 75% yield. The synthetic product exhibited identical spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS and IR) with those of we previously synthesized.[14]

Scheme 5. Complete the synthesis of (-)-solanidine (**1**)



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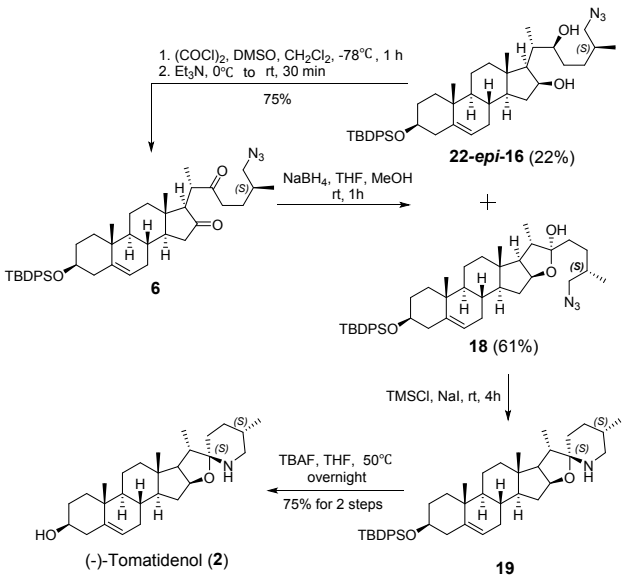
DOI: 10.1039/D0OB00457J

Scheme 6. Complete the synthesis of (-)-tomatidenol (**2**).



Experimental

General Methods. All reactions sensitive to air or moisture were performed in flame-dried flasks with rubber septum under a positive pressure of argon atmosphere, unless otherwise noted. Air and moisture-sensitive liquids and solutions were transferred via syringe and stainless-steel cannula. 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); ^{13}C NMR: $CDCl_3$ (77.16)]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad.

Compound (9)

To a solution of diosgenin (**5**, 10.0 g, 24 mmol) in dry DMF (60 mL) were added imidazole (4.93 g, 72 mmol, 3 equiv) and then TBDPSCl (9.4 mL, 36 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature for 2 h. The mixture was quenched with water and extracted with EtOAc (3×50 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo.* The crude and Et_3SiH (7.7 mL, 48 mmol, 2 equiv) were dissolved in dry $ClCH_2CH_2Cl$ (65 mL), and boron trifluoride etherate (9.1 mL, 72 mmol, 3 equiv) was added dropwise at 0 °C. The resulting mixture was warmed to room temperature and stirred for 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was dissolved in CH_3CN (160 mL) and CH_2Cl_2 (30 mL) was added Jones reagent (2.6 M, 17 mL, 48 mmol, 2 equiv) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and was quenched with *i*-PrOH and filtered. The filtrate was concentrated *in vacuo* and diluted with EtOAc (200 mL), washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 2/1) to give **9** (11.8 g, 73% for 3 step) as a white foam. $[\alpha]_D^{26}$ -47.3 (*c* 0.65, $CHCl_3$); IR (cm^{-1}): 3070, 2932, 2898, 2856, 1706, 1110, 1088, 740, 702, 509; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.70 (m, 4H), 7.33-7.48 (m, 6H), 5.14 (d, *J* = 5.0 Hz, 1H), 4.33 (td, *J* = 7.7, 5.1 Hz, 1H), 3.50-3.60 (m, 1H), 3.32-3.40 (m, 1H), 2.47-2.62 (m, 1H), 2.29-2.43 (m, 1H), 2.10-2.22 (m, 1H), 1.88-2.05 (m, 2H), 1.54-1.83 (m, 11H), 1.37-1.51 (m, 3H), 1.25-1.36 (m, 1H), 1.18-1.22 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.08 (s, 9H), 1.02 (s, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.82-0.93 (m, 2H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9 (C), 141.4 (C), 135.9 (2CH), 135.9 (2CH), 134.93 (C), 134.9 (C), 129.6 (CH), 129.5 (CH), 127.6 (2CH), 127.6 (2CH), 121.0 (CH), 90.3 (CH), 83.6 (CH), 73.3 (CH), 65.0 (CH), 57.1 (CH), 50.1 (CH), 42.6 (CH_2), 40.8 (C), 39.6 (CH), 39.5 (CH_2), 38.1 (CH), 37.3 (CH_2), 36.7 (C), 32.3 (CH_2), 32.1 (CH_2), 32.0 (CH_2), 31.7 (CH), 31.4 (CH_2), 31.1 (CH_2), 27.1 ($3CH_3$), 20.8 (CH_2), 19.6 (CH_3), 19.3 (C), 19.0 (CH_3), 17.3 (CH_3), 16.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_{43}H_{60}O_4SiNa$ $[M+Na]^+$: 691.4153, found: 691.4139.

Compound (8) and Compound (12)

To a solution of **9** (10 g, 15 mmol) and lithium iodide (8 g, 60 mmol, 4 equiv) and TBAI (2.76 g, 7.5 mmol, 0.5 equiv) in dry CH_2Cl_2/CH_3CN (100 mL/25 mL) was added TFAA (6.3 mL, 45 mmol, 3 equiv) at 0 °C. The resulting mixture was vigorously stirred at ambient temperature for 4 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$, and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 20/1-8/1) to give **8** (8.6 g, 74%) as a white foam and **12** (933 mg, 8%) as a yellow foam. **8:** $[\alpha]_D^{25}$ -33.8 (*c* 1.09, $CHCl_3$); IR (cm^{-1}): 2936, 2897, 2854, 1736, 1589, 1474, 1187, 1110, 1073, 706, 511; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.72 (m, 4H), 7.33-7.45 (m, 6H), 5.11 (d, *J* = 5.0 Hz, 1H), 4.71 (dt, *J* = 11.5, 2.8 Hz, 1H), 4.04-4.10 (m, 1H), 3.49-3.59 (m, 1H), 2.59-2.73 (m, 1H), 2.27-2.38 (m, 1H), 1.92-2.27 (m, 7H), 1.80-1.92 (m, 2H), 1.63-1.74 (m, 2H), 1.25-1.63 (m, 10H), 0.74-0.91 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H), 0.97 (s, 3H), 0.94 (d, *J*=6.7 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (C), 141.4 (C), 135.9 (2CH), 135.9 (2CH), 134.9 (C), 134.8 (C), 129.6 (CH), 129.6 (CH), 127.6 (2CH), 127.6 (2CH), 120.6 (CH), 79.7 (CH), 73.2 (CH), 64.8 (CH), 53.4 (CH), 49.7 (CH), 45.3 (C), 42.5 (CH_2), 41.9 (CH_2), 39.7 (CH_2), 39.4 (CH), 37.2 (CH_2), 36.5 (C), 33.2 (CH), 31.9 (CH_2), 31.7 (CH_2), 30.6 (CH), 28.8 (CH), 27.1 ($3CH_3$), 25.2 (CH_2), 20.9 (CH_2), 20.8 (CH_2), 19.5 (CH_3), 19.3 (C), 16.5 (CH_3), 13.9 (CH_3), 12.6 (CH_3); HRMS (DART) *m/z* calcd for $C_{43}H_{63}NO_3ISi$ $[M+NH_4]^+$: 796.3616, found: 796.3622. **12:** $[\alpha]_D^{25}$ -52.6 (*c* 1.00, $CHCl_3$); IR (cm^{-1}): 2934, 2856, 1731, 1459, 1110, 759, 702, 510; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.72 (m, 4H), 7.32-7.45 (m, 6H), 5.30 (td, *J*=8.4, 6.0 Hz, 1H), 5.11 (d, *J* = 5.3 Hz, 1H), 4.23-4.31 (m, 1H), 3.48-3.58 (m, 1H), 2.40-2.54 (m, 1H), 2.00-2.39 (m, 6H), 1.83-1.98 (m, 2H), 1.49-1.75 (m, 6H), 1.33-1.49 (m, 6H), 1.21-1.33 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 1.07 (d, *J*=10.0 Hz, 3H), 1.06 (s, 9H), 0.99 (s, 3H), 0.91 (s, 3H), 0.75-0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (C), 141.4 (C), 135.9 (2CH), 135.9 (2CH), 134.9 (C), 134.9 (C), 129.6 (CH), 129.6 (CH), 127.6 (2CH), 127.6 (2CH), 120.8 (CH), 76.2 (CH), 73.3 (CH), 58.5 (CH), 54.1 (CH), 49.8 (CH), 42.9 (CH), 42.6 (CH_2), 41.9 (C), 41.6 (CH), 39.7 (CH_2), 39.1 (CH_2), 37.2 (CH_2), 36.6 (C), 34.1 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 31.9 (CH_2), 31.2 (CH), 30.7 (CH), 27.2 ($3CH_3$), 24.2 (CH_3), 20.8 (CH_2), 19.6 (CH_3), 19.3 (C), 18.6 (CH_3), 13.3 (CH_3); HRMS (DART) *m/z* calcd for $C_{43}H_{63}NO_3ISi$ $[M+NH_4]^+$: 796.3616, found: 796.3601.

Compound (13)

To a solution of **8** (3.00 g, 3.85 mmol) in dry DMF (15 mL) was added CsOAc (3.70 g, 19.3 mmol, 5 equiv). The resulting mixture was stirred at 60 °C for 15 h, and was

View Article Online DOI: 10.1039/D0OB00457J

quenched with waterand extracted with EtOAc (3×50 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (petroleum ether/EtOAc: 5/1) to give **13** (2.51 g, 91%) as a white foam. $[\alpha]_D^{24}$ -22.8 (*c* 1.58, $CHCl_3$); IR (cm^{-1}): 2934, 1738, 1241, 703, 510; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.69 (m, 4H), 7.32-7.43 (m, 6H), 5.10 (d, *J* = 5.0 Hz, 1H), 5.06-5.17 (m, 1H), 4.12-4.22 (m, 1H), 3.45-3.58 (m, 1H), 2.50-2.60 (m, 1H), 2.41-2.49 (m, 1H), 2.28-2.38 (m, 2H), 2.01-2.17 (m, 1H), 1.93-2.08 (m, 3H), 2.02 (s, 3H), 1.80-1.92 (m, 1H), 1.55-1.74 (m, 6H), 1.34-1.55 (m, 6H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.10-1.17 (m, 2H), 1.05 (s, 9H), 1.03-1.09 (m, 2H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.89 (s, 3H), 0.78-0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (C), 171.0 (C), 141.5 (C), 135.9 (2CH), 135.9 (2CH), 134.9 (C), 134.9 (C), 129.6 (CH), 129.6 (CH), 127.6 (2CH), 127.6 (2CH), 120.7 (CH), 79.0 (CH), 74.3 (CH), 73.3 (CH), 55.5 (CH), 54.8 (CH), 50.0 (CH), 43.0 (C), 42.5 (CH_2), 39.7 (CH_2), 37.2 (CH_2), 36.6 (C), 35.3 (CH_2), 33.7 (CH), 33.1 (CH), 31.9 (CH_2), 31.7 (CH_2), 31.5 (CH), 27.1 ($3CH_3$), 25.6 (CH_2), 21.5 (CH_3), 20.8 (CH_2), 19.9 (CH_2), 19.5 (CH_3), 19.3 (C), 16.4 (CH_3), 12.5 (CH_3), 12.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{45}H_{62}O_5SiNa$ $[M+Na]^+$: 733.4259, found: 733.4251.

Compound (7)

To a solution of **13** (3.60 g, 5.06 mmol) in MeOH (80 mL) was added K_2CO_3 (7.00 g, 50.7 mmol, 10 equiv). The resulting mixture was stirred at 50 °C for 5 h and its pH value was adjusted to 2 with HCl aqueous solution. The mixture was extracted with EtOAc (3×60 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. A mixture of the crude and $LiAlH_4$ (577 mg, 15.2 mmol, 3 equiv) in dry THF (60 mL) was stirred at room temperature overnight. The mixture was quenched with water slowly and filtered. The filtrate was extracted with EtOAc (3×60 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 1/3) to give **7** (3.13 g, 92%) as a white foam. $[\alpha]_D^{26}$ -29.0 (*c* 0.83, $CHCl_3$); IR (cm^{-1}): 3361, 2933, 2857, 1110, 701, 509; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.71 (m, 4H), 7.32-7.44 (m, 6H), 5.12 (d, *J* = 5.0 Hz, 1H), 4.29 (td, *J* = 7.6, 4.8 Hz, 1H), 3.61-3.68 (m, 1H), 3.38-3.57 (m, 3H), 2.91 (s, br, 2H), 2.28-2.40 (m, 1H), 2.03-2.23 (m, 3H), 1.85-2.02 (m, 2H), 1.78 (s, 1H), 1.52-1.73 (m, 6H), 1.24-1.51 (m, 6H), 1.10-1.24 (m, 2H), 1.05 (s, 9H), 1.00-1.03 (m, 1H), 0.98 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 5.9 Hz, 3H), 0.88 (s, 3H), 0.73-0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (C), 135.9 (2CH), 135.9 (2CH), 135.0 (C), 134.9 (C), 129.6 (CH), 129.6 (CH), 127.6 (2CH), 127.6 (2CH), 121.0 (CH), 76.1 (CH), 73.4 (CH), 72.6 (CH), 67.8 (CH_2), 59.9 (CH), 54.6 (CH), 50.1 (CH), 42.9 (C), 42.6 (CH_2), 40.2 (CH_2), 37.3 (CH_2), 36.6 (CH), 36.5 (CH_2), 36.0 (CH), 32.0 (CH_2), 31.9 (CH_2), 31.6 (CH), 30.0 (CH_2), 29.6 (CH_2), 27.2 ($3CH_3$), 20.9 (CH_2), 19.5 (CH_3), 19.3 (C), 17.2 (CH_3), 14.1 (CH_3), 13.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{45}H_{65}O_4Si$ $[M+H]^+$: 673.4647, found: 673.4633.

Compound (16)

To a solution of **7** (1.10 g, 1.63 mmol) and DMAP (20 mg, 0.16 mmol, 0.1 equiv) in dry CH_2Cl_2 (20 mL) were added Et_3N (0.91 mL, 6.54 mmol, 4 equiv) and TsCl (623 mg, 3.27 mmol, 2 equiv) successively. The resulting mixture was stirred at room temperature overnight, and was quenched with water and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. A mixture of the crude product and NaN_3 (318 g, 4.90 mmol, 3 equiv) in dry DMF (10 mL) was stirred at 60 °C for 6 h. The mixture was quenched with water and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 8/1) to give **16** (1.03 g, 90%) as a white foam. $[\alpha]_D^{24}$ -20.3 (*c* 0.91, $CHCl_3$); IR (cm^{-1}): 3389, 2931, 2856, 2096, 1110, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.71 (m, 4H), 7.31-7.43 (m, 6H), 5.12 (d, *J* = 5.0 Hz, 1H), 4.23-4.34 (m, 1H), 3.60-3.69 (m, 1H), 3.47-3.58 (m, 1H), 3.25 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.11 (dd, *J* = 12.1, 6.8 Hz, 1H), 2.95 (s, 1H), 2.88 (s, 1H), 2.25-2.34 (m, 1H), 2.03-2.25 (m, 3H), 1.83-2.03 (m, 2H), 1.56-1.81 (m, 6H), 1.25-1.55 (m, 8H), 1.10-1.24 (m, 2H), 1.05 (s, 9H), 0.99 (s, 3H), 0.98 (d, *J* = 8.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 3H), 0.73-0.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (C), 135.9 (2CH), 135.9 (2CH), 134.9 (C), 134.9 (C), 129.6 (CH), 129.5 (CH), 127.6 (2CH), 127.6 (2CH), 121.0 (CH), 75.8 (CH), 73.3 (CH), 72.6 (CH), 59.8 (CH), 57.8 (CH_2), 54.5 (CH), 50.0 (CH), 42.9 (C), 42.6 (CH_2), 40.1 (CH_2), 37.2 (CH_2), 36.6 (CH), 36.5 (CH_2), 34.0 (CH), 32.0 (CH_2), 31.9 (CH_2), 31.6 (CH), 30.6 (CH_2), 30.1 (CH_2), 27.1 ($3CH_3$), 20.8 (CH_2), 19.5 (CH_3), 19.3 (C), 18.1 (CH_3), 14.0 (CH_3), 13.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{43}H_{63}N_3O_3SiNa$ $[M+Na]^+$: 720.4531, found: 720.4528.

Compound (6)

To a solution of $(COCl)_2$ (0.10 mL, 1.15 mmol, 8 equiv) and DMSO (0.12 mL, 1.72 mmol, 12 equiv) in dry CH_2Cl_2 (2 mL) was stirred at -78 °C for 30 min. A solution of **16** (100 mg, 0.14 mmol) in dry CH_2Cl_2 (4 mL) at -78 °C was added to the solution. The resulting mixture was stirred at -78 °C for 1 h, then Et_3N (0.40 mL, 2.87 mmol, 20 equiv) was added and the mixture was stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 15/1) to give **6** (73 mg, 73%) as a white foam. $[\alpha]_D^{24}$ -125.8 (*c* 0.98, $CHCl_3$); IR (cm^{-1}): 2932, 2097, 1735, 1715, 1110, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.70 (m, 4H), 7.32-7.44 (m, 6H), 5.11 (d, *J* = 5.1Hz, 1H), 3.49-3.58 (m, 1H), 3.26 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.12 (dd, *J* = 12.1, 6.7 Hz, 1H), 2.68-2.80 (m, 1H), 2.53-2.66 (m, 3H), 2.28-2.39 (m, 1H), 2.09-2.23 (m, 1H), 1.94-2.03 (m, 1H), 1.64-1.92 (m, 6H), 1.39-1.63 (m, 9H), 1.06 (s, 9H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.01 (s, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.82-0.94 (m, 2H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.3 (C), 213.4 (C), 141.6 (C), 135.9 (2CH), 135.9 (2CH), 134.9 (C), 134.8 (C), 129.6 (CH), 129.6 (CH), 127.6 (2CH), 127.6 (2CH), 120.4 (CH), 73.2 (CH), 66.4 (CH), 57.9 (CH_2), 51.4 (CH), 49.7 (CH), 43.5 (CH), 42.5 (CH_2), 41.8 (C), 39.7 (CH_2), 38.7 (CH_2), 37.3 (CH_2), 37.0 (CH_2), 36.7 (C), 33.1 (CH), 31.9 (CH_2), 31.8 (CH_2), 31.0 (CH), 27.7 (CH_2), 27.1 ($3CH_3$), 20.6 (CH_2), 19.6 (CH_3), 19.3 (C), 17.7 (CH_3), 15.6 (CH_3), 13.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{43}H_{60}N_3O_3Si$ $[M+H]^+$: 694.4398, found: 694.4386.

Compound (17)

a) To a solution of **6** (50 mg, 0.07 mmol) in MeOH (2 mL) and THF (1 mL) were added $NiCl_2{\cdot}6H_2O$ (3.0 mg, 0.01 mmol, 0.2 equiv) and $NaBH_4$ (22 mg, 0.6 mmol, 8 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 2.5 h, and was quenched with water and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 6/1) to give **17** (36 mg, 79%) as a white foam. b) To a solution of 6 (110 mg, 0.16 mmol) in MeOH (6 mL) and EtOAc (2 mL) was added Raney-Ni (220 mg). The resulting mixture was stirred under H_2 at 40 °C for 4 h and was filtered. The filtrate was concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum

ether/EtOAc: 6/1) to give **17** (65 mg, 64%) as a white foam. $[\alpha]D^{22}$ −15.1 (c 0.45, DCM); IR (film): 3070, 2929, 2856, 1472, 1427, 1261, 1110, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.71 (m, 4H), 7.32-7.44 (m, 6H), 5.12 (d, *J* = 5.0 Hz, 1H), 3.47-3.58 (m, 1H), 2.83 (dd, *J* = 10.7, 3.8 Hz, 1H), 2.50-2.67 (m, 1H), 2.28-2.38 (m, 1H), 2.08-2.18 (m, 1H), 1.85-1.95 (m, 1H), 1.62-1.75 (m, 6H), 1.48-1.62 (m, 6H), 1.29-1.48 (m, 5H), 1.10-1.29 (m, 2H), 1.05 (s, 9H), 1.00-1.09 (m, 3H), 0.99 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 8.6 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (C), 135.9 (2CH), 135.9 (2CH), 135.0 (C), 135.0 (C), 129.6 (CH), 129.6 (CH), 127.6 (2CH), 127.6 (2CH), 121.2 (CH), 74.8 (CH), 73.4 (CH), 69.2 (CH), 63.2 (CH), 60.4 (CH_2), 57.8 (CH), 50.3 (CH), 42.7 (CH_2), 40.4 (CH_2), 40.1 (C), 37.4 (CH_2), 36.8 (CH), 33.6 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 31.5 (CH), 31.3 (CH_2), 31.1 (CH), 29.5 (CH_2), 27.2 ($3CH_3$), 21.1 (CH_2), 19.7 (CH_3), 19.6 (CH_3), 19.3(C), 18.4 (CH_3), 17.0 (CH_3); HRMS (ESI-TOF) *m/z* calcd for $C_{43}H_{61}NSi$ $[M+H]^+$: 636.4595, found: 636.4593.

(-)-Solanidine (1)

To a solution of **17** (80 mg, 0.13 mmol) in THF (4 ML) was added TBAF (1.0 M, 1.89 mL, 1.89 mmol, 15 equiv) at 50 °C for 2 h. The reaction was quenched with water and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 1/1) to give **1** (50 mg, 99%) as a white solid; 208-210 °C; $[\alpha]_D^{22}$ -20.8 (*c* 0.50, CH_2Cl_2); IR (cm^{-1}): 3246, 2927, 1453, 1372, 1053, 1009; ^1H NMR (400 MHz, CDCl3) δ 5.35 (d, *J* = 5.1 Hz, 1H), 3.46-3.57 (m, 1H), 2.81-2.91 (m, 1H), 2.57-2.68 (m, 1H), 2.15-2.36 (m, 2H), 1.93-2.04 (m, 1H), 1.80-1.90 (m, 2H), 1.66-1.80 (m, 4H), 1.40-1.65 (m, 10H), 1.30-1.39 (m, 1H), 1.25 (s, 1H), 1.05-1.21 (m, 5H), 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, $CDCl_3$) δ 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 (CH3); HRMS (ESI-TOF) *m/z* calcd for $C_{27}H_{43}NO$ $[M+H]^+$: 398.3417, found: 398.3416.

Compound (18) and Compound (22-*epi*-16).

To a solution of **6** (300 mg, 0.43 mmol) in THF (4 mL) and MeOH (4 mL) was added $NaBH_4$ (25 mg, 0.65 mmol, 1.5 equiv) at room temperature. The resulting mixture was stirred for 1 h, and was quenched with water and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 10/1-6/1) to give **18** (183 mg, 61%) as a white foam and **22-*epi*-16**, 67 mg, 22%) as a white foam. To a solution of $(COCl)_2$ (65 µL, 0.77 mmol, 8 equiv) and DMSO (82 µL, 1.15 mmol, 12 equiv) in dry CH_2Cl_2 (2 mL) was stirred at -78 °C for 30 min. A solution of **22-*epi*-16** (67 mg, 0.10 mmol) in dry CH_2Cl_2 (4 mL) at -78 °C was added to the solution. The resulting mixture was stirred at -78 °C for 1 h, then Et_3N (0.27 mL, 1.92 mmol, 20 equiv) was added and the mixture was stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was chromatographed on silica gel (petroleum ether/EtOAc: 15/1) to give **6** (50 mg, 75%) as a white foam **18**: $[\alpha]_D^{24}$ -38.4 (*c* 0.72, $CHCl_3$); IR (cm^{-1}): 3436, 2932, 2902, 2096, 1110 702, 510; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.71 (m, 4H), 7.32-7.44 (m, 6H), 5.11 (d, *J* = 5.1 Hz, 1H), 4.57 (q, *J* = 7.6 Hz, 1H), 3.47-3.57 (m, 1H), 3.22 (dd, *J* = 12.0, 5.9 Hz, 1H), 3.13 (dd, *J* = 12.0, 6.8 Hz, 1H), 2.27-2.37 (m, 1H), 2.10-2.19 (m, 1H), 1.99-2.09 (m, 1H), 1.87-1.99 (m, 2H), 1.84 (s, 1H), 1.63-1.79 (m, 6H), 1.51-1.63 (m, 5H), 1.38-1.50 (m, 3H), 1.19-1.37 (m, 3H), 1.09-1.16 (m, 1H), 1.05 (s, 9H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.80-0.90 (m, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (C), 135.9 (2CH), 135.9 (2CH), 135.0 (C), 134.9 (C), 129.6 (CH), 129.6 (CH), 127.6 (2CH), 127.6 (2CH), 120.9 (CH), 110.4 (C), 81.6 (CH), 73.3 (CH), 62.8 (CH), 57.9 (CH_2), 56.6 (CH), 50.1 (CH), 42.6 (CH_2), 40.8 (C), 40.0 (CH), 39.8 (CH_2), 37.3 (CH_2), 36.8 (C), 36.4 (CH_2), 34.0 (CH), 32.2 (CH_2), 32.0 (CH_2), 32.0 (CH_2), 31.5 (CH), 28.1 (CH_2), 27.2 ($3CH_3$), 20.9 (CH_2), 19.6 (CH_3), 19.3 (C), 17.7 (CH_3), 16.4 (CH_3), 15.7 (CH_3); HRMS (DART) *m/z* $[M-H]^-$ calcd for $C_{43}H_{60}N_3O_3Si$ $[M-H]^-$: 694.4409, found: 694.4410. **22-*epi*-16**: $[\alpha]_D^{25}$ -39.4 (*c* 1.58, $CHCl_3$); IR (cm^{-1}): 3323, 2933, 2096, 1110, 702, 512; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.70 (m, 4H), 7.32-7.44 (m, 6H), 5.12 (d, *J* = 4.9 Hz, 1H), 4.32 (td, *J* = 7.6, 4.6 Hz, 1H), 3.59-3.64 (m, 1H), 3.47-3.57 (m, 1H), 3.07-3.27 (m, 2H), 2.10-2.39 (m, 4H), 1.93 (s, 1H), 1.90 (s, 1H), 1.56-1.80 (m, 5H), 1.30-1.55 (m, 8H), 1.12-1.30 (m, 3H), 1.05 (s, 9H), 0.93-1.00 (m, 1H), 0.98 (d, *J* = 7.5 Hz, 3H), 0.98 (s, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 3H) 0.78-0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (C), 135.9 (2CH), 135.9 (2CH), 135.0 (C), 134.9 (C), 129.6 (CH), 129.5 (CH), 127.6 (2CH), 127.6 (2CH), 121.0 (CH), 73.3 (CH), 72.1 (CH), 57.9 (CH), 57.3 (CH_2), 54.8 (CH), 50.2 (CH), 42.6 (C), 42.6 (CH_2), 40.1 (CH_2), 37.3 (CH_2), 36.6 (CH_2), 36.2 (CH), 35.1 (CH), 33.7 (CH), 32.0 (CH_2), 31.9 (CH_2), 31.6 (CH), 31.4 (CH_2), 29.6 (CH_2), 27.2 ($3CH_3$), 20.8 (CH_2), 19.5 (CH_3), 19.3 (C), 17.8 (CH_3), 16.3 (CH_3), 13.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{43}H_{64}N_3O_3Si$ $[M+H]^+$: 698.4711, found: 698.4709.

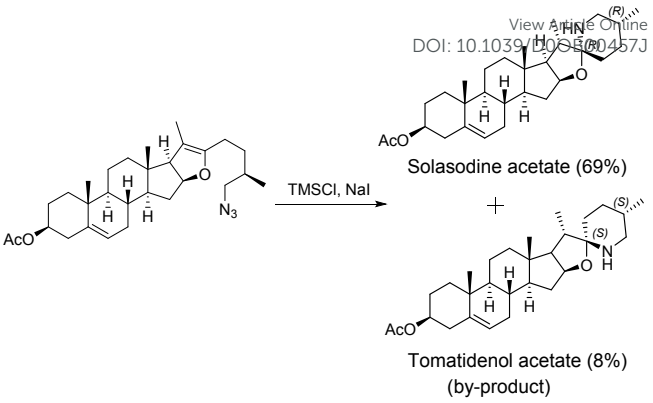
(-)-Tomatidenol (2).

To a solution of **18** (100 mg, 0.14 mmol) in dry CH_3CN (4 mL) were added NaI (65 mg, 0.43 mmol, 3 equiv) and TMSCl (91 µL, 0.72 mmol, 5 equiv) at room temperature. The resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude was dissolved in THF (4 mL) was added a 1.0 mol/L TBAF solution in THF (0.72 mL, 0.72 mmol, 5 equiv). The mixture was stirred at 50 °C overnight, and was quenched with water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (petroleum ether/EtOAc: 1/1) to give **2** (45 mg, 75%) as a white solid. mp. 215–217 °C; $[\alpha]_D^{25}$ -35.4 (*c* 0.75, $CHCl_3$) IR (cm^{-1}): 3314, 2927, 2856, 1462, 1450, 1068, 758; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (d, *J* = 5.4 Hz, 1H), 4.14 (q, *J* = 7.4 Hz, 1H), 3.46-3.57 (m, 1H), 2.66-2.76 (m, 2H), 2.20-2.37 (m, 2H), 1.97-2.09 (m, 2H), 1.79-1.89 (m, 2H), 1.59-1.79 (m, 10H), 1.40-1.58 (m, 6H), 1.22-1.40 (m, 4H), 1.03 (s, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0 (C), 121.5 (CH), 100.1 (C), 78.6 (CH), 71.9 (CH), 62.0 (CH), 56.2 (CH), 50.4 (CH_2), 50.3 (CH), 43.2 (CH), 42.4 (CH_2), 40.8 (C), 40.1 (CH_2), 37.4 (CH_2), 36.8 (C), 32.9 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 31.5 (CH), 31.2 (CH), 28.7 (CH_2), 26.8 (CH_2), 21.0 (CH_2), 19.6 (CH_3), 19.5 (CH_3), 16.9 (CH_3), 16.1 (CH_3); HRMS (DART) *m/z* calcd for $C_{27}H_{44}NO_2$ $[M+H]^+$: 414.3367, found: 414.3367.

Conclusions

In summary, we have achieved the formal asymmetric synthesis of (-)-solanidine (**1**) in 12 steps with 32% overall yield and (-)-tomatidenol (**2**) in 13 steps with 18.7% overall yieldby employing the

intact skeleton of (-)-diosgenin (**5**). The synthetic strategy described herein is concise and could also be used for the synthesis of 25-configuration solanidine and tomatidenol-related steroidal alkaloids, as well as analogues from steroidal sapogenins. The synthesis of other tomatidenol congeners, in particular (+)-tomatidine along this line, are now under investigation in our laboratory, and will be reported in due course.



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Prof. Jing-Han Gui and Dr. Jing-jing Wu (Shanghai Institute of Organic Chemistry) for helpful discussions.

Notes and references

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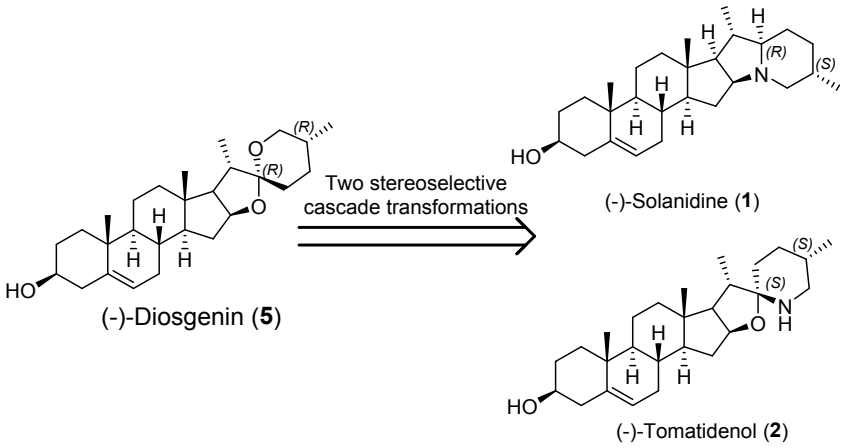
DOI: 10.1039/D0OB00457J



The asymmetric synthesis of (-)-solanidine (**1**) and (-)-tomatidenol (**2**) has been achieved by employing two cascade reactions including a modified cascade ring-switching reaction of furstan-26-acid and a cascade azide reduction/intramolecular reductive amination as key transformations. This synthesis of (-)-solanidine (**1**) and (-)-tomatidenol (**2**) was completed in 12 steps with 32% overall yield and 13 steps with 18.7% overall yield, respectively.