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A short synthesis of (+)-lycoricidine

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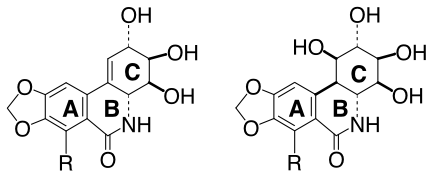
Abstract—A short synthesis of (+)-lycoricidine outlined herein has been accomplished by combining asymmetric chloronitroso cycloaddition with controlled installation of the bromohydrin unit, base-promoted epoxide formation, and $SnCl_4$-catalyzed arene–epoxide cyclization.

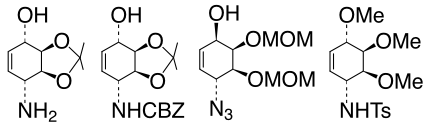
1. Introduction

(+)-Lycoricidine **1** and structurally related alkaloids like (+)-narciclasine **2**, (+)-pancratistatin **3**, and (+)-deoxypancratistatin **4** have attracted considerable interest because of the promising biological activity and natural scarcity.[1] Unsaturated aminocyclitol such as chiral O-isopropylidene-protected 4-aminocyclohexenol **5** is an ideal substrate in the construction of narcissus ring skeleton as it has close relation both structurally and stereochemically. Numerous examples of the use of aminocyclitol derivatives like 4-((benzyloxycarbonyl)amino)cyclohexenol **6**,[2a,b] 4-azidocyclohexenol **7**,[2c] and 4-(tosylamino)cyclohexenol **8**[2d] as key starting materials for the synthesis of (+)-lycoricidine have been reported.[3]



1: R = H
2: R = OH

3: R = OH
4: R = H



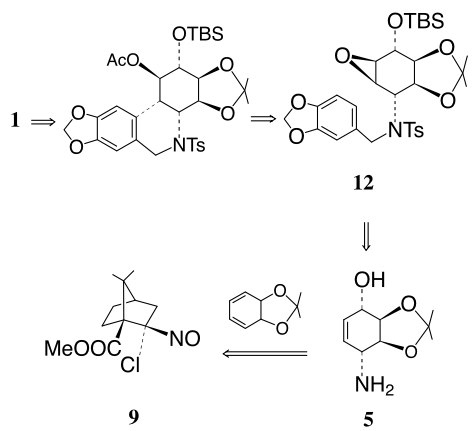
5 **6** **7** **8**

2. Results and discussion

As part of our studies directed toward the development of chiral nitro synthons, we devised an elegant one-pot cycloaddition–reduction procedure for the preparation of enantiopure 4-aminocyclohexenol **5** (86%) by employing camphor-based chloronitroso ester **9**.[4] The ready availability of **5** suggested that an effective asymmetric synthesis of (+)-lycoricidine might emerge. Scheme 1 presents a retrosynthetic analysis.

The successful approach to the synthesis of (+)-lycoricidine reported herein is predicated upon the stereocontrolled conversion of **5** to a suitable epoxide **12** and its participation in the desired carbon–carbon bond construction to connect rings A and C.

The requisite epoxide **12** was prepared according to Scheme 2. Both the amino and hydroxyl functional groups of aminocyclitol **5** were protected as *N*-sulfonylamide and silyl ether, respectively to afford **10** in 78% isolated yield. Exposure of **10** to NBS in aqueous acetone gave rise to bromohydrins **11**. During bromohydrination both the regio



9 **5**

Scheme 1.

Keywords: bromohydrin; cycloaddition.

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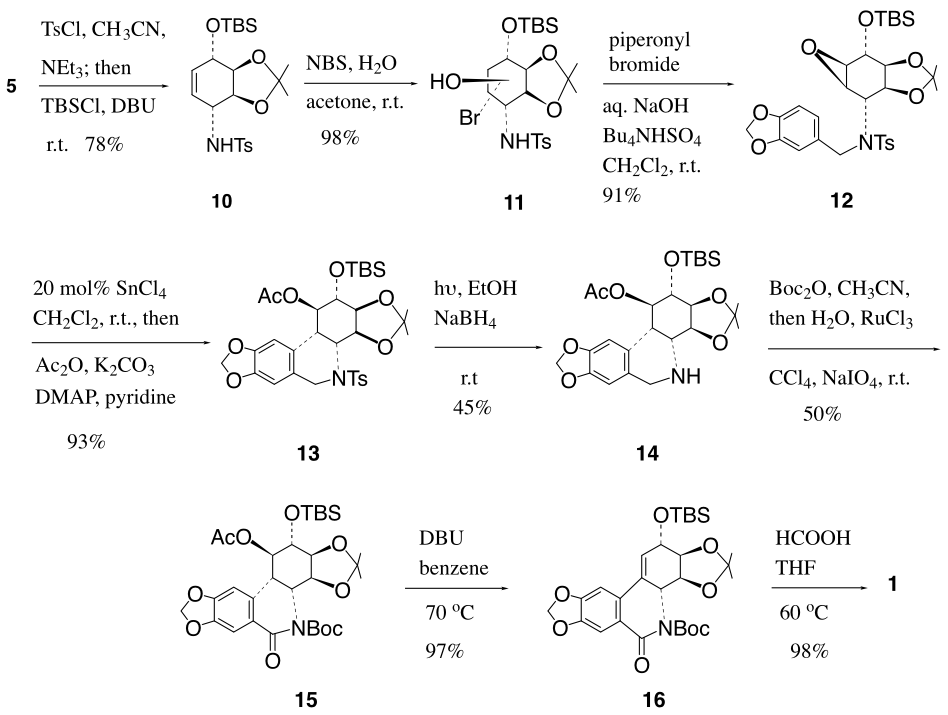

Scheme 2. Asymmetric synthesis of lycoricidine **1**.

isomers are formed and the resulting mixture was used as such for the epoxide formation. Epoxide **12** could be derived in one step from **11** through base-promoted epoxide formation and piperonylation. Thus, treatment of **11** with aqueous NaOH under phase-transfer condition followed by exposing the mixture to piperonyl bromide led to the desired epoxide **12** in 91% isolated yield.[5]

Epoxide ring opening of **12** was initially attempted with boron trifloride etherate. However, all attempts to effect BF_3-promoted arene–epoxide cyclization resulted in deketalization or decomposition. After a good deal of careful experimentation, we observed a facile cyclization with a catalytic amount of $SnCl_4$.[6] Thus treatment of **12** with 20 mol% of $SnCl_4$ in dry CH_2Cl_2 at room temperature for 10 min followed by addition of Ac_2O led to clean intramolecular arylation and O-acylation to give **13** in 93% isolated yield. Cleavage of the *N*-tosyl group of **13** proceeded under the reductive photolytic condition ($h\nu$/$NaBH_4$/EtOH) to generate the free amine **14** in 45% yield,[7] which upon reaction with Boc_2O at room temperature for 4 h followed by immediate oxidation with $RuCl_3$/$NaIO_4$ afforded **15** in 50% yield. The imide **15** possessing the typical framework of deoxypancratistatin is lacking the stereochemistry only at the benzylic position (carbon-10b). In order to obtain the unsaturated alkaloid, treatment of **15** with DBU at 70°C gave **16** in 97% yield. Removal of all the protecting groups with formic acid afforded pure lycoricidine **1** (95%), mp 216–218°C; $[\alpha]_D^{25}=+175°$ (*c* 1.1, MeOH). The spectral properties of **1** are in full agreement with those of the natural product.[2,3] Thus, the asymmetric synthesis of (+)-lycoricidine outlined herein has been accomplished by means of a convergent approach, wherein four steps involved aqueous condition. The overall yield of (+)-lycoricidine from chloronitroso **9** is 13%. By combining asymmetric chloronitroso cycloaddition with controlled installation of the bromohydrin unit, base-promoted epoxide formation and $SnCl_4$-catalyzed arene–epoxide cyclization, we have described a high yield route for the facile construction of the typical framework of narcissus alkaloids. Further studies will determine whether this $SnCl_4$-promoted arene–epoxide cyclization will be generally useful for construction of fused BC ring system. At present, this reaction methodology has been applied to the asymmetric synthesis of (+)-narciclasine.[8] Now the efforts are directed to invert the stereochemistry of the benzylic carbon in **13** for the saturated analogs.

3. Experimental

3.1. General remarks

Reactions were generally conducted under a positive pressure of dry nitrogen within oven-dried glassware. THF and ether were distilled from sodium/benzophenone ketyl prior to use. Methylene chloride and acetonitrile were distilled from CaH_2 prior to use. Flash chromatography was done on E. Merck silica gel 60 (230–400 mesh) Melting points (Pyrex capillary) are uncorrected. Concentrations for rotation data are given as g/100 mL of solvent.

3.1.1. (1*S*,2*S*,3*S*,6*R*)-3-((*t*-Butyldimethylsilyl)oxy)-1,2-*O*-isopropylidene-6-(*N*-(*p*-toluenesulfonyl)amino)cyclohexene-1,2-diol 10. To a solution of **5** (1.85 g, 10 mmol) and NEt_3 (4.2 mL, 30 mmol) in CH_3CN (20 mL) was added *p*-toluenesulfonyl chloride (1.9 g, 10 mmol). After stirring at 25°C for 8 h, a solution of DBU (2.3 mL, 15 mmol) and TBS-Cl (1.69 g, 11 mmol) in CH_3CN (10 mL) was added and the mixture was stirred further for a period of 9 h. The reaction mixture was quenched with aqueous $NaHCO_3$ and CH_3CN was removed under vacuum. The aqueous solution

was extracted with CH_2Cl_2 (40 mL×3). The combined organic extracts were washed with dilute HCl, and brine, dried ($MgSO_4$), concentrated in vacuo and purified by flash chromatography (silica gel, 20% EtOAc/hexane) to give 3.58 g (78%) of **10** as a white solid: mp 130–131°C; IR (neat) 3291, 1598, 1328, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=8.4 Hz, 2H), 7.26 (d, J=8.4 Hz, 2H), 5.95 (dd, J=10.0, 5.2 Hz, 1H), 5.77 (dd, J=10.0, 5.6 Hz, 1H), 5.53 (d, J=10.0 Hz, 1H), 4.37 (d, J=2.8 Hz, 1H), 4.35 (d, J=3.2 Hz, 1H), 4.27 (dd, J=6.8, 2.4 Hz, 1H), 4.12 (dd, J=5.2, 2.8 Hz, 1H), 3.89–3.84 (m, 1H), 2.40 (s, 3H), 1.22 (s, 6H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.27, 138.27, 132.30, 130.76, 129.61, 127.08, 108.35, 78.41, 77.32, 66.45, 49.93, 26.16, 25.73, 24.36, 21.48, 17.94, −4.78, −4.91; $[\alpha]_D^{25}=-47.6°$ (c 1.4, CH_2Cl_2); high-resolution MS (FAB+) m/e calcd for $C_{22}H_{35}NO_5SSi$: 454.2079, found: 454.2081. Anal. Calcd for $C_{22}H_{35}NO_5SSi$: C, 58.25; H, 7.78; N, 3.09. Found: C, 58.31; H, 7.76; N, 3.07.

3.1.2. (1*S*,2*S*,3*S*,4*S*,5*S*,6*S*)-5-Bromo-3-((*t*-butyldimethylsilyl)oxy)-1,2-*O*-isopropylidene-6-(*N*-(*p*-toluenesulfonyl)amino)cyclohexane-1,2,4-triol and (1*S*,2*S*,3*R*,4*S*,5*R*,6*R*)-4-bromo-3-((*t*-butyldimethylsilyl)oxy)-1,2-*O*-isopropylidene-6-(*N*-(*p*-toluenesulfonyl)amino)cyclohexane-1,2,5-triol 11. To a solution of **10** (4.53 g, 10.0 mmol) in acetone (10 mL) and water (40 mL) was added NBS (2.67 g, 15 mmol). After stirring at 25°C for 10 h, the reaction mixture was diluted with CH_2Cl_2 (150 mL), washed with water, dried ($MgSO_4$), concentrated in vacuo and purified by flash chromatography (silica gel, 17% EtOAc/hexane) to give 5.4 g (98%) of **11** as a sticky solid: (two regio isomers, found by 400 MHz ^1H NMR to be an 1:1 ratio): IR (neat) 3484, 3279 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=8.4 Hz, 2H), 7.28 (d, J=8.4 Hz, 2H), 5.66 (d, J=12.0 Hz) and 5.51 (d, J=11.6 Hz) (1H total), 4.48–3.52 (m, 6H), 2.41 (s, 3H), 1.42, 1.39, 1.27, and 1.22 (4s, 6H total), 0.90 and 0.88 (2s, 9H total), 0.18 and 0.13 (2s, 6H total); Anal. Calcd for $C_{22}H_{36}BrNO_6SSi$: C, 47.99; H, 6.59; N, 2.54. Found: C, 47.78; H, 6.50; N, 2.63.

3.1.3. (1*S*,2*S*,3*S*,4*R*,5*R*,6*S*)-3-((*t*-Butyldimethylsilyl)oxy)-4,5-epoxy-1,2-*O*-isopropylidene-6-(*N*-piperonyl-*N*-(*p*-toluenesulfonyl)amino)cyclohexane-1,2-diol 12. To a solution of **11** (2.75 g, 5.0 mmol) and Bu_4NHSO_4 (50 mg) in CH_2Cl_2 (75 mL) was added 50% aqueous NaOH (45 mL). After stirring at room temperature for 8 h, piperonyl bromide (1.1 g, 5.0 mmol) was added and the mixture was stirred for a further 7 h. The reaction mixture was diluted with CH_2Cl_2 (80 mL), washed with water, aqueous NH_4Cl, and brine, dried ($MgSO_4$), concentrated in vacuo and purified by flash chromatography (silica gel, 15% EtOAc/hexane) to give 2.8 g (91%) of **12** as a white solid: mp 45–46°C; IR (neat) 2930, 1598, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J=8.0 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 6.87 (d, J=1.6 Hz, 1H), 6.79 (dd, J=8.0, 1.6 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 5.90 (s, 2H), 4.40 (d, J=16.0 Hz, 1H), 4.24 (d, J=16.0 Hz, 1H), 4.18 (dd, J=7.6, 6.0 Hz, 1H), 3.99 (dd, J=8.0, 5.2 Hz, 1H), 3.86 (dd, J=4.8, 2.8 Hz, 1H), 3.08 (t, J=3.2 Hz, 1H), 3.01 (t, J=3.2 Hz, 1H), 2.39 (s, 3H), 1.30 (s, 3H), 1.14 (s, 3H), 0.85 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.82, 147.11, 143.47, 137.36, 130.87, 129.56, 127.59, 127.49, 121.57, 114.74, 108.81, 108.73, 107.93, 101.02, 78.51, 73.95, 70.55, 58.84, 55.28, 53.15, 50.07, 26.68, 25.69, 24.17, 21.45, 18.07, −4.87, −5.01; $[\alpha]_D^{25}=-9.3°$ (c 2.2, CH_2Cl_2); high-resolution MS m/e calcd for $C_{30}H_{41}NO_8SSi$: 603.2341, found: 603.2332. Anal. Calcd for $C_{30}H_{41}NO_8SSi$: C, 59.67; H, 6.79; N, 2.32. Found: C, 59.84; H, 7.00; N, 2.12.

3.1.4. (1*R*,2*R*,3*S*,4*R*,4a*R*,10b*S*)-1-Acetoxy-2-((*t*-butyldimethylsilyl)oxy)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-5-(*p*-toluenesulfonyl)-1,1a,2,3,4,4a,6-heptahydrophenanthridine 13. To a solution of epoxide **12** (1.81 g, 3.0 mmol) in CH_2Cl_2 (45 mL) was added $SnCl_4$ (1.0 M in CH_2Cl_2, 0.6 mL). After being stirred at 25°C for 20 min, K_2CO_3 (1.73 g, 12.5 mmol) was added to the reaction mixture followed by the addition of a solution of DMAP (0.13 g, 1.0 mmol), pyridine (30 mmol), and acetic anhydride (1.4 mL, 15 mmol) in CH_2Cl_2. Stirring was continued for 6 h and the reaction mixture was diluted with water (20 mL). The organic layer was washed with dilute HCl and brine. Concentration and purification by flash chromatography (silica gel, 17% EtOAc/hexane) to afford 1.82 g (93%) of **13** as a white solid: mp 115–116°C; IR (neat) 2930, 1747, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 6.64 (s, 1H), 6.31 (s, 1H), 5.83 (s, 2H), 5.08 (t, J=8.4 Hz, 1H), 4.53 (d, J=16.8 Hz, 1H), 4.40 (t, J=6.4 Hz, 1H), 4.33 (t, J=6.4 Hz, 1H), 4.30 (d, J=16.8 Hz, 1H), 4.00 (t, J=6.4 Hz, 1H), 3.90 (dd, J=8.8, 7.2 Hz, 1H), 2.33 (s, 3H), 1.95 (s, 3H), 1.50 (s, 3H), 1.28 (s, 3H), 0.81 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.54, 146.77, 146.43, 143.37, 136.09, 129.23, 127.65, 126.36, 125.69, 109.15, 108.02, 106.29, 100.94, 78.36, 74.50, 73.68, 73.57, 53.27, 44.39, 40.95, 27.68, 25.60, 25.52, 21.35, 21.09, 17.90, −4.37, −4.87; $[\alpha]_D^{25}=-33.1°$ (c 0.2, CH_2Cl_2); high-resolution MS (FAB+) m/e calcd for $C_{32}H_{43}NO_9SSi$: 645.2432, found: 645.2430.

3.1.5. (1*R*,1a*S*,2*R*,3*S*,4*R*,4a*R*)-1-Acetoxy-2-((*t*-butyldimethylsilyl)oxy)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-1,1a,2,3,4,4a,5,6-octahydrophenanthridine 14. A solution of **13** (0.5 g, 0.77 mmol), $NaBH_4$ (0.45 g, 11.9 mmol), and anisole (0.5 g, 4.6 mmol) in 90% EtOH (67 mL) was put into a Pyrex column (100 mL, OD=20 mm) and degassed by bubbling nitrogen through the solution for 15–20 min. The column was placed ca. 15 cm from a light source and then $NaBH_4$ (0.19 g, 5.0 mmol) was added. After irradiating with 300 nm light for 6 h, the reaction mixture was concentrated in vacuo. The residue was taken in water (20 mL) and extracted with CH_2Cl_2. The organic layer was washed with aqueous NH_4Cl and brine. The organic layer was dried, concentrated, and purified by flash chromatography (silica gel; 10, 15, then 20% EtOAc/hexane) to give 0.18 g (45%) of **14** as a white solid: mp 147–148°C; IR (neat) 3409, 1748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.44 (s, 1H), 5.86 (s, 2H), 5.15 (t, J=10.0 Hz, 1H), 4.16–4.09 (m, 2H), 4.07 (d, J=16.0 Hz, 1H), 4.02 (d, J=16.0 Hz, 1H), 3.80 (dd, J=9.2, 6.0 Hz, 1H), 3.47 (dd, J=1.6, 1.2 Hz, 1H), 2.79 (dd, J=10.4, 3.2 Hz, 1H), 1.94 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H), 0.81 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.47, 146.69, 145.51, 127.98, 126.72, 109.71, 108.56, 106.17, 100.71, 80.29, 78.26, 76.25, 74.52, 53.88, 48.43, 39.49, 28.17, 26.23, 25.66, 21.34, 17.93, −4.20,

−4.86; $[\alpha]_D^{25}$=+27.7° (*c* 0.35, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{25}H_{37}NO_7Si$: 491.2330, found: 491.2335. Anal. Calcd for $C_{25}H_{37}NO_7Si$: C, 61.07; H, 7.58; N, 2.85. Found: C, 61.22; H, 7.54; N, 2.71.

3.1.6. (1*R*,1a*S*,2*R*,3*S*,4*R*,4a*R*)-1-Acetoxy-5-(*t*-butoxycarbonyl)-2-((*t*-butyldimethylsilyl)oxy)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-1,1a,2,3,4,4a-pentatahydrophenanthridone 15. A solution of **14** (0.25 g, 0.5 mmol) and di-*t*-butyl dicarbonate (0.14 g, 0.6 mmol) in CH_3CN (9 mL) was stirred at 25°C till the starting amine disappeared on TLC (ca. 4 h). To this vigorously stirred solution was added CCl_4 (9 mL) followed by aqueous solution of $NaIO_4$ (0.45 g in 13.5 mL H_2O) and $RuCl_3$ (55 mg, 0.29 mmol). After being stirred for 8 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (15 mL×3). The combined organic extracts were dried and concentrated in vacuo. The residue was diluted with ether (20 mL), filtered through a celite pad, concentrated, and purified by flash chromatography (silica gel; 6, 10 and 15% EtOAc/hexane) to afford 0.16 g (50%) of **15** as a white solid: mp 83–84°C; IR (neat) 1747, 1723, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.13 (s, 1H), 5.99 (s, 2H), 5.32 (dd, *J*=8.0, 3.2 Hz, 1H), 4.93 (dd, *J*=8.8, 5.2 Hz, 1H), 4.15 (dd, *J*=8.8, 7.2 Hz, 1H), 3.99 (t, *J*=7.6 Hz, 1H), 3.79 (t, *J*=7.6 Hz, 1H), 3.41 (dd, *J*=4.8, 4.0 Hz, 1H), 2.10 (s, 3H), 1.56 (s, 9H), 1.47 (s, 3H), 1.18 (s, 3H), 0.83 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.12, 161.56, 152.60, 152.15, 147.43, 133.07, 123.37, 109.78, 109.18, 106.13, 101.96, 83.61, 77.57, 75.65, 75.07, 72.82, 53.50, 41.74, 27.97, 27.27, 25.64, 25.03, 21.22, 17.97, −4.44, −4.89; $[\alpha]_D^{25}$=+10.2° (*c* 1.9, $CHCl_3$); high-resolution MS (FAB+) *m/e* calcd for $C_{30}H_{43}NO_{10}Si$: 606.2718, found: 606.2726. Anal. Calcd for $C_{30}H_{43}NO_{10}Si$: C, 59.48; H, 7.15; N, 2.31. Found: C, 59.51; H, 7.19; N, 2.49.

3.1.7. (2*S*,3*S*,4*R*,4a*R*)-5-(*t*-Butoxycarbonyl)-2-((*t*-butyldimethylsilyl)oxy)-3,4-(isopropylidenedioxy)-8,9-(methylenedioxy)-2,3,4,4a-tetrahydrophenanthridone 16. To a solution of **15** (0.3 g, 0.5 mmol) in benzene (3 mL) was added DBU (0.75 mL, 5 mmol). After being heated at 70°C for 40 h, the reaction mixture was cooled, diluted with ether (15 mL), and washed with aqueous $NaHCO_3$ followed by brine. Drying, solvent evaporation, and silica gel chromatography (elution with 15% EtOAc/hexane) gave 0.26 g (97%) of **16** as a white solid: mp 58–59°C; IR (neat) 1756, 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.99 (s, 1H), 6.20 (t, *J*=3.2 Hz, 1H), 6.01 (s, 2H), 4.78 (dt, *J*=8.4, 2.8 Hz, 1H), 4.36 (dt, *J*=5.6, 2.4 Hz, 1H), 4.12 (t, *J*=8.8 Hz, 1H), 4.01 (dd, *J*=8.0, 5.6 Hz, 1H), 1.58 (s, 9H), 1.46 (s, 3H), 1.29 (s, 3H), 0.93 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.02, 153.61, 152.16, 148.59, 128.39, 127.15, 126.78, 120.62, 111.48, 107.88, 101.96, 100.89, 84.01, 79.86, 79.56, 73.55, 58.38, 27.69, 26.96, 25.87, 25.13, 18.22, −4.48, −5.00; $[\alpha]_D^{25}$=−14.8° (*c* 0.7, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{28}H_{39}NO_8Si$: 545.2445, found: 545.2448.

3.1.8. (+)-Lycoricidine 3. To a solution of **16** (0.10 g, 0.18 mmol) in THF was added 60% HCOOH (8 mL) at 25°C. After heated at 60°C for 1 h, the solvent was evaporated and the residue was purified by flash chromatography (silica gel, 15% EtOAc/hexane) to give 0.05 g (98%) of **3** as a white solid: mp 216–218°C [lit.[2c] mp 217–221°C; lit.[3c] mp 224–226°C]; IR (neat) 3390, 1679 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.29 (s, 1H), 7.06 (s, 1H), 6.07 (dd, *J*=4.0, 2.8 Hz, 1H), 5.97 (d, *J*=1.2 Hz, 1H), 5.95 (d, *J*=1.2 Hz, 1H), 4.29 (dt, *J*=9.2, 1.6 Hz, 1H), 4.15 (dt, *J*=4.4, 2.0 Hz, 1H), 3.85–3.81 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.53, 153.44, 150.11, 133.41, 132.63, 123.34, 122.83, 107.71, 104.40, 103.56, 74.37, 70.94, 53.90; $[\alpha]_D^{25}$=175° (*c* 1.1, MeOH) [lit.[2b] $[\alpha]_D^{25}$=+170° (*c* 1.0, MeOH); lit.[2c] $[\alpha]_D^{25}$=+204° (*c* 0.21, pyridine); lit.[3c] $[\alpha]_D^{25}$=+180° (*c* 0.21, pyridine)].

Acknowledgments

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