John Doe
Research Progress Report – 1/1/08-30/6/08

Scheme 1. Oxidative cyclization of *L*-tyrosine.[1]

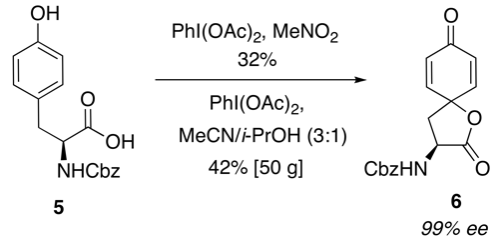
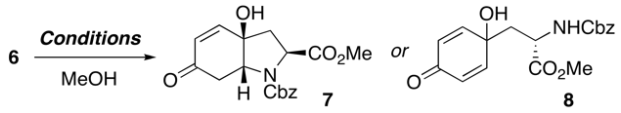


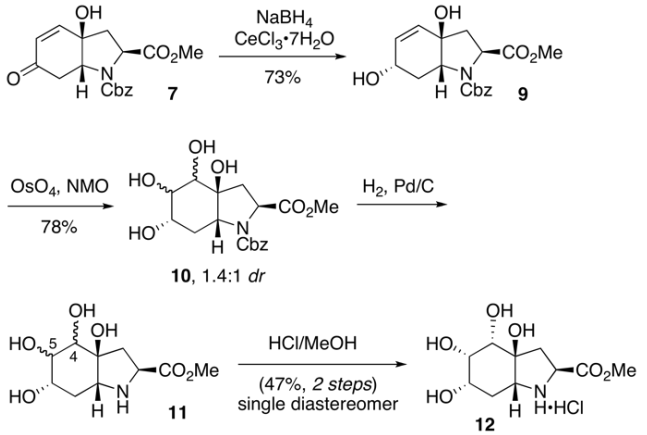
Table 1. Optimization of methanolysis procedure to produce **7**.[2]



entry	conditions	ratio[a]	*ee* (%)[a]
1	Na_2CO_3 (1 eq), rt, 3 h	**7** only	53
2	$NaHCO_3$ (2 eq), rt, 14 h	**7** only	67
3	$NaHCO_3$ (2 eq), MWI, 80 °C, 20 min	**7**:**6**, 6:1	12, 2
4	Na_2HPO_4 (1 eq), rt, 27 h	**8**:**6**, 3.6:1	93, 86
5	NaOAc (1 eq), rt, 12 h	**8**:**6**, 4.6:1	92, 89
6	Li_2CO_3 (1 eq), rt, 16 h	**7** only	50
7	Cs_2CO_3 (1 eq), rt, 5 min	**7** only	51
8	*i*-Pr_2NEt (1 eq), rt, 19 h	**7** only	58
9	DMAP (1 eq), rt, 20 min	**8**:**6**, 2.3:1	97, 93
10	NaOMe (1 eq), -78 °C, 80 min	**8**:**6**, 9:1	99, 99
11	NaOMe (1 eq), - 25 °C, 14 h	**7** only	87
12	3 M KOH/H_2O, -20 °C, 10 min	**7** only	97

[a]Determined by HPLC analysis of crude reaction mixtures using a Chiracel AD-H column; individual yields were not determined. MWI: microwave irradiation.

Scheme 2. Synthesis of polyhydroxylated hydroindoles.



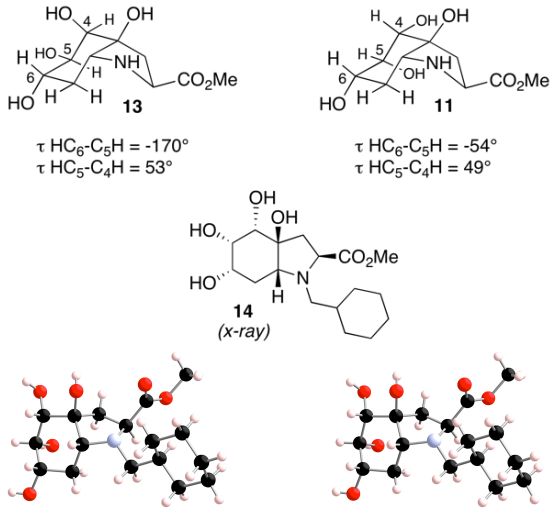
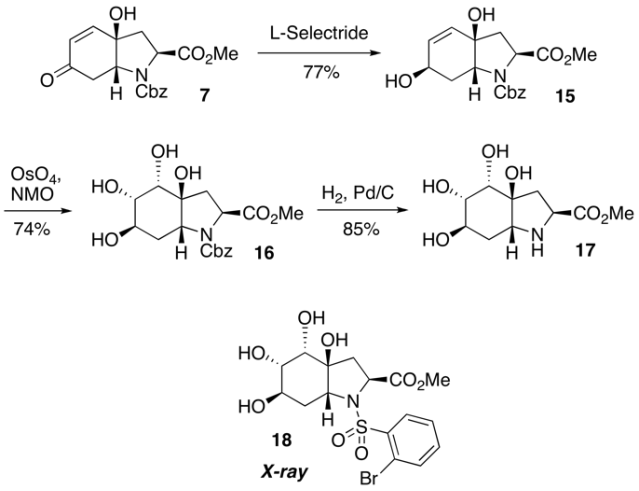


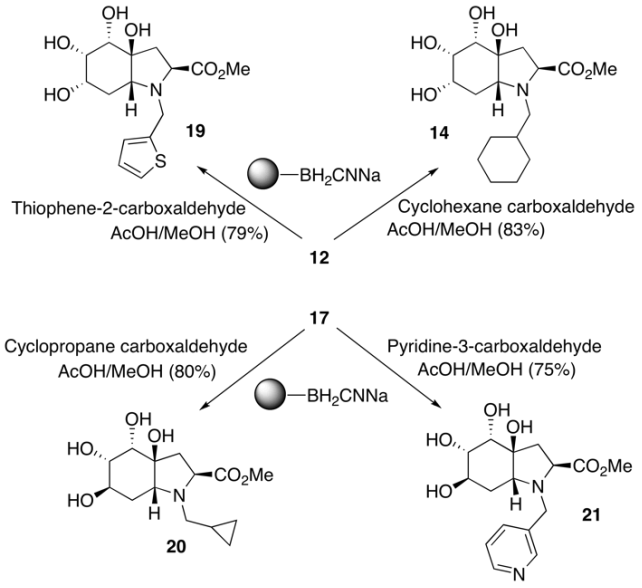
Figure 1. Conformational analysis of **13** and **11** and stereoview of the x-ray structure of **14**.

Scheme 3. Synthesis of polyhydroxylated hydroindoles and stereoview of the x-ray structure of **18**.



[1] Wipf, P.; Kim, Y. "Synthesis of Stemona Alkaloids; Stereoselective Preparation of the Hydroindole Ring System by Oxidative Cyclization of Tyrosine." *Tetrahedron Lett*. **1992**, *33*, 5477-5480.
[2] Pierce, J. G.; Kasi, D.; Fushimi, M.; Cuzzupe, A.; Wipf, P. "Synthesis of Hydroxylated Bicyclic Amino Acids from L-Tyrosine: Octahydro-1H-Indole Carboxylates." *J. Org. Chem.* **2008**, *73*(19), 7807-7810.

Scheme 4. Reductive amination of polyhydroxylated L-Choi scaffolds.



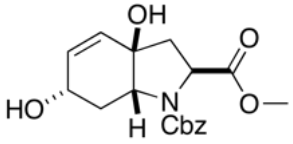
Experimental Part

Contents:

General. All reactions were performed under an N_2 atmosphere and all glassware was dried in an oven at 140 °C for 2 h prior to use. Reactions carried out at -78 °C employed a CO_2/acetone bath. THF and Et_2O were distilled over sodium/benzophenone ketyl, Et_3N was distilled from CaH_2, and CH_2Cl_2 and toluene were purified using an alumina column filtration system.

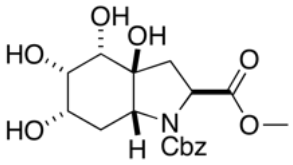
Reactions were monitored by TLC analysis (pre-coated silica gel 60 F_{254} plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a PMA solution (5 g of phosphomolybdic acid in 100 mL of 95% EtOH), *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2 mL of AcOH, and 3.5 mL of conc. H_2SO_4 in 100 mL of 95% EtOH), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\bullet 4\ H_2O$ and 0.2 g of $Ce(SO_4)_2$ in 100 mL of a 3.5 N H_2SO_4 solution) or a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 was used to purify the crude reaction mixtures.

^1H spectra were obtained at 300 or 600 MHz in $CDCl_3$ unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were obtained and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). ^{13}C NMR spectra were run at 76 or 125 MHz using a proton-decoupled pulse sequence with a d_1 of 3 sec, and are tabulated by observed peak.



9

(2*S*,3a*R*,6*S*,7a*R*)-1-Benzyl 2-methyl 3a,6-dihydroxy-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (9).[1] To a solution of **7** (1.80 g, 5.21 mmol) in MeOH (35 mL) and THF (35 mL) was added cerium (III) chloride heptahydrate (1.94 g, 5.16 mmol) followed by cooling to 0 °C and addition of sodium borohydride (217 mg, 5.73 mmol) in one portion. The reaction mixture was stirred at 0 °C for 2 h, diluted with EtOAc (200 mL), quenched with water (100 mL) and the layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by chromatography on SiO_2 (EtOAc) to yield 1.32 g (73%) of **9** as a colorless waxy solid: $[\alpha]_D$ -12.4 (*c* 1.16, CH_2Cl_2); IR (CH_2Cl_2) 3417, 3031, 2953, 1754, 1687, 1417, 1355, 1122 cm^{-1}; ^1H NMR (DMSO, 380 K) δ 7.55-7.20 (m, 5 H), 5.67 (d, 1 H, *J* = 9.9 Hz), 5.53 (dd, 1 H, *J* = 10.2, 2.4 Hz), 5.10 (bs, 2 H), 4.61-4.43 (m, 3 H), 4.16 (bd, 1 H, *J* = 6.0 Hz), 3.90 (dd, 1 H, *J* = 12.3, 4.8 Hz), 3.58 (s, 3 H), 2.60-2.40 (m, 1 H), 2.32 (dd, 1 H, *J* = 13.2, 9.6 Hz), 2.14 (app d, 1 H, *J* = 13.5 Hz), 1.37-1.17 (m, 1 H); ^{13}C NMR (DMSO, 380 K) δ 171.2, 153.2, 136.4, 133.1, 128.7, 127.6, 127.0, 126.8, 74.7, 65.6, 64.0, 63.6, 58.1, 50.8, 40.4, 37.1; EIMS *m/z* 347 (M^+, 10), 329 (40), 244 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{21}NO_6$ 347.1369, found 347.1368.

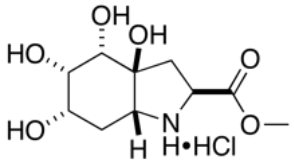


10

(2*S*,3a*S*,4*S*,5*S*,6*S*,7a*R*)-1-Benzyl 2-methyl 3a,4,5,6-tetrahydroxyhexahydro-1*H*-indole-1,2(2*H*,3*H*)-dicarboxylate (10). To a solution of **9** (500 mg, 1.44 mmol) in H_2O/THF (1:10, 15 mL) was added OsO_4 (480 μL, 0.144 mmol), NMO (596 mg, 4.32

[1] Pierce, J. G.; Kasi, D.; Fushimi, M.; Cuzzupe, A.; Wipf, P. "Synthesis of Hydroxylated Bicyclic Amino Acids from L-Tyrosine: Octahydro-1H-Indole Carboxylates." *J. Org. Chem.* **2008**, *73*(19), 7807-7810.

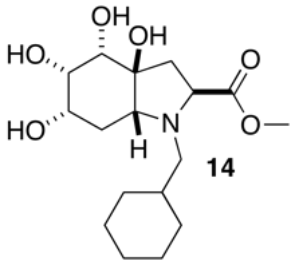
mmol) and methanesulfonamide (154 mg, 1.58 mmol). The reaction mixture was stirred at rt for 72 h, quenched with $NaSO_3$, diluted with H_2O and EtOAc, extracted with EtOAc (4x), washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (EtOAc to 5% MeOH/EtOAc) to yield 426 mg (78%) of **10** as a colorless waxy solid and a 1.4:1 mixture of diastereomers: $[\alpha]_D$ -45.8 (*c* 0.67, MeOH); IR (CH_2Cl_2) 3419, 3033, 2952, 1700, 1417, 1353, 1213, 1069 cm^{-1}; ^1H NMR (MeOD, 600 MHz, rotamers) δ 7.41-7.26 (m, 5 H), 5.20-5.10 (m, 1.60 H), 5.02 (app dd, 0.40 H, *J* = 12.6, 2.4 Hz), 4.48 (app dd, 0.40 H, *J* = 15.0, 9.6 Hz), 4.40 (app dd, 0.60 H, *J* = 15.0, 9.6 Hz), 4.15-3.94 (m, 0.40 H), 3.94-3.89 (m, 0.60 H), 3.85-3.73 (m, 1.60 H), 3.72 (app d, 1.70 H, *J* = 7.2 Hz), 3.67-3.61 (m, 0.60 H), 3.61-3.58 (m, 0.40 H), 3.58-3.54 (m, 1.70 H), 3.46-3.39 (m, 0.40 H), 3.03-2.93 (m, 0.60 H), 2.60-2.50 (m, 0.60 H), 2.45-2.37 (m, 0.14 H), 2.34-2.27 (m, 0.36 H), 2.17 (app dd, 1 H, *J* = 14.4, 7.8 Hz), 2.05 (app dd, 0.40 H, *J* = 13.2, 7.8 Hz); ^{13}C NMR (MeOD, 600 MHz, rotamers) δ 175.1, 174.4, 174.3, 173.9, 156.6, 156.5, 156.2, 156.1, 137.8, 137.8, 129.6, 129.4, 129.2, 129.1, 128.9, 82.2, 81.3, 80.9, 80.1, 75.3, 75.2, 75.1, 75.1, 74.4, 74.3, 73.8, 73.7, 68.4, 68.3, 68.2, 68.1, 68.0, 67.7, 67.6, 64.4, 64.1, 63.4, 63.1, 58.6, 58.5, 52.8, 52.8, 52.7, 38.7, 38.5, 37.7, 37.5, 36.8, 35.9, 33.1, 32.1; ESI-MS *m/z* 404 ($[M+Na]^+$, 100), 365 (25); HRMS (ESI) *m/z* calcd for $C_{18}H_{23}NO_8Na$ (M+Na) 404.1321, found 404.1338.



12

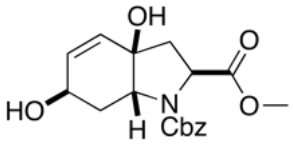
(2*S*,3a*S*,4*S*,5*S*,6*S*,7a*R*)-Methyl 3a,4,5,6-tetrahydroxyoctahydro-1*H*-indole-2-carboxylate hydrochloride salt (12). To a solution of **10** (264 mg, 0.692 mmol) in MeOH (10 mL) was added 10% Pd/C (50 mg). The reaction mixture was stirred under an atmosphere of H_2 for 6 h, filtered though a pad of Celite®, concentrated, and redissolved in MeOH (10 mL). After addition of HCl (5.0 mL, 4.0 M in dioxane), the solution was heated at reflux for 30 min, allowed to cool to rt, and filtered. The solid was dried in vacuo to yield 93 mg (47%) of amine hydrochloride **12** as a colorless powder with a dr of >95:5 as determined by ^1H NMR analysis of the crude reaction mixture: ^1H NMR

(MeOD, 600 MHz, crude) δ 4.61 (dd, 1 H, *J* = 11.4, 3.6 Hz), 3.96-3.89 (m, 1 H), 3.85 (s, 3 H), 3.79-3.71 (m, 1 H), 3.71-3.65 (m, 1 H), 3.63-3.53 (m, 1 H), 3.18 (dd, 1 H, *J* = 14.4, 11.4 Hz), 2.34 (dd, 1 H, *J* = 13.8, 2.4 Hz), 1.99-1.89 (m, 2 H).



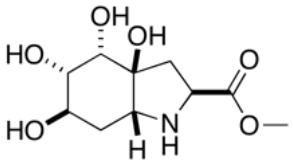
14

(2*S*,3a*S*,4*S*,5*S*,6*S*,7a*R*)-Methyl 1-(cyclohexylmethyl)-3a,4,5,6-tetrahydroxy-octahydro-1*H*-indole-2-carboxylate (14). To a suspension of amine hydrochloride **12** (40.0 mg, 0.141 mmol) in MeOH (2 mL) was added acetic acid (40.7 μL, 0.705 mmol, 5 eq), cyclopropanecarboxaldehyde (26.1 μL, 0.211 mmol, 1.5 eq) and MP-cyanoborohydride resin (2.34 mmol/g, 2.5 eq, 151 mg, 0.352 mmol). The reaction mixture was stirred at rt for 48 h and filtered. The filtrate was neutralized with 2 M NH_3 in MeOH, concentrated and purified by chromatography on SiO_2 (5% MeOH/EtOAc) to provide 40.0 mg (83%) of **14** as a colorless oil that solidified upon standing: $[\alpha]_D$ -53.1 (*c* 0.91, CH_2Cl_2); IR (CH_2Cl_2) 3334, 2919, 2847, 1732, 1196, 1176, 1134, 1114, 1063 cm^{-1}; ^1H NMR (MeOD) δ 3.85 (app t, 1 H, *J* = 2.7 Hz), 3.63 (s, 3 H), 3.58 (app d, 1 H, *J* = 3.9 Hz), 3.52 (dt, 1 H, *J* = 11.4, 3.9 Hz), 3.31 (dd, 1 H, *J* = 11.1, 3.3 Hz), 2.98 (dd, 1 H, *J* = 14.1, 10.8 Hz), 2.92 (dd, 1 H, *J* = 11.1, 5.1 Hz), 2.47 (dd, 1 H, *J* = 12.3, 6.0 Hz), 2.25 (dd, 1 H, *J* = 12.3, 8.7 Hz), 1.86-1.74 (m, 1 H), 1.74-1.53 (m, 6 H), 1.53-1.36 (m, 1 H), 1.35-1.18 (m, 1 H), 1.18-1.00 (m, 3 H), 0.86-0.65 (m, 2 H); ^{13}C NMR (MeOD) δ 178.7, 82.9, 74.4, 73.8, 69.5, 66.9, 63.6, 57.1, 52.9, 38.7, 37.6, 32.9, 32.8, 28.1, 27.4, 27.2, 26.8; ESIMS *m/z* 344 ($[M+H]^+$, 50), 326 (100), 308 (30); HRMS (ESI) *m/z* calcd for $C_{17}H_{30}NO_6$ (M+H) 344.2073, found 344.2090.



15

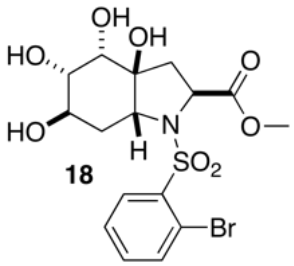
(2*S*,3a*R*,6*R*,7a*R*)-1-Benzyl 2-methyl 3a,6-dihydroxy-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (15). To a solution of **7** (4.42 g, 12.8 mmol) in freshly distilled THF (100 mL) at -78 °C was added L-selectride (19.2 mL, 19.2 mmol, 1.5 eq) dropwise (syringe pump) over 1.5 h. The reaction mixture was stirred for an additional hour at -78 °C, quenched with 10% HCl (10 mL) and warmed to rt. The solution was extracted with EtOAc (2x), washed with brine, dried ($MgSO_4$), filtered and concentrated to provide 3.41 g (77%) of **15** that was carried on without further purification: $[\alpha]_D$ -15.7 (*c* 1.09, CH_2Cl_2); IR (CH_2Cl_2) 3422, 3031, 2952, 1701, 1416, 1353, 1210 cm^{-1}; ^1H NMR (DMSO, 380 K) δ 7.45-7.25 (m, 5 H), 5.79 (dd, 1 H, *J* = 9.9, 3.9 Hz), 5.60 (d, 1 H, *J* = 10.2 Hz), 4.38 (bs, 2 H), 4.24 (dd, 1 H, *J* = 8.7, 4.5 Hz), 4.05-3.93 (m, 2 H), 3.58 (s, 3 H), 2.22 (dd, 1 H, *J* = 12.9, 8.7 Hz), 2.17-2.04 (m, 2 H), 2.01-1.83 (m, 1 H); ^{13}C NMR (DMSO, 380 K) δ 171.5, 153.2, 136.3, 130.5, 130.3, 127.6, 127.0, 126.8, 73.9, 65.5, 61.1, 60.6, 57.6, 50.8, 40.4, 32.9; ESI-MS *m/z* 370 ($[M+Na]^+$, 25), 286 (10); HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO_6Na$ (M+Na) 370.1267, found 370.1287.



17

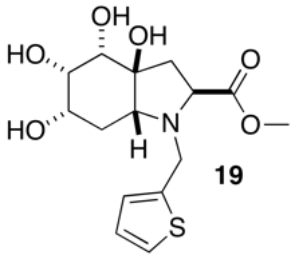
(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*)-Methyl 3a,4,5,6-tetrahydroxyoctahydro-1*H*-indole-2-carboxylate (17). To a solution of **16** (456 mg, 1.20 mmol) in MeOH (10 mL) was added 10% Pd/C (63.4 mg). The reaction mixture was stirred under an atmosphere of H_2 for 10 h, filtered through a pad of Celite and concentrated to provide 251 mg (85%) of amine **17** as an off-white solid that was carried on without further purification: ^1H NMR (MeOD, 600 MHz, crude) δ 3.95-3.87 (m, 1 H), 3.87 (app d, 1 H, *J* = 3.6 Hz), 3.81 (dd, 1 H, *J* = 10.2, 4.2 Hz), 3.77 (dd, 1 H, *J* = 5.4, 3.6 Hz), 3.73 (s, 3 H), 3.37-3.27 (m, 1 H), 2.83 (dd,

1 H, *J* = 13.8, 10.2 Hz), 1.99 (dd, 1 H, *J* = 13.8, 4.2 Hz), 1.86-1.76 (m, 1 H), 1.76-1.67 (m, 1 H).



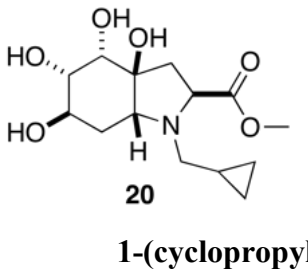
18

(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*)-Methyl 1-(2-bromophenylsulfonyl)-3a,4,5,6-tetrahydroxy-octahydro-1*H*-indole-2-carboxylate (18). To a solution of **17** (24.7 mg, 0.100 mmol) in THF (2 mL) at rt was added Et_3N (15.3 μL, 0.110 mmol), 2-bromobenzenesulfonylchloride (25.6 mg, 0.100 mmol) and DMAP (2.44 mg, 0.0200 mmol). The reaction mixture was stirred at this temperature for 17 h, quenched with 1 M HCl, extracted with EtOAc (4x), washed with brine, dried ($MgSO_4$) and concentrated. The crude residue was purified by chromatography on SiO_2 (EtOAc to 5% MeOH/EtOAc) to yield 26.3 mg (56%) of **18** as a colorless solid: Mp 182 ˚C (MeOH); $[\alpha]_D$ +7.6 (*c* 1.8, MeOH; obtained for an 58% *ee* sample); IR (CH_2Cl_2) 3650-2800 (br), 1725, 1434, 1323, 1158, 1102, 1054 cm^{-1}; ^1H NMR (MeOD) δ 8.24 (dd, 1 H, *J* = 7.5, 1.8 Hz), 7.81 (dd, 1 H, *J* = 7.5, 1.8 Hz), 7.57-7.43 (m, 2 H), 4.74 (dd, 1 H, *J* = 10.2, 1.5 Hz), 4.22 (dd, 1 H, *J* = 10.8, 5.7 Hz), 3.96 (d, 1 H, *J* = 3.9 Hz), 3.82 (appt, 1 H, *J* = 3.9 Hz), 3.75-3.67 (m, 1 H), 3.54 (s, 3 H), 3.09 (dd, 1 H, *J* = 14.1, 10.2 Hz), 2.15 (d, 1 H, *J* = 13.8 Hz), 1.90-1.63 (m, 2 H); ^{13}C NMR (MeOD) δ 175.6, 142.4, 136.8, 135.2, 133.3, 129.0, 122.1, 82.9, 73.4, 73.3, 70.7, 67.0, 61.6, 53.1, 38.9, 32.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}NO_8NaSBr$ (M+Na) 487.9991, found 487.9994.



19

(2*S*,3a*S*,4*S*,5*S*,6*S*,7a*R*)-Methyl 3a,4,5,6-tetrahydroxy-1-(thiophen-2-ylmethyl) octahydro-1*H*-indole-2-carboxylate (19). A suspension of amine hydrochloride **12** (40.0 mg, 0.141 mmol) in MeOH (2 mL), acetic acid (40.7 μL, 0.705 mmol, 5 eq), thiophene-2-carboxaldehyde (20.0 μL, 0.211 mmol, 1.5 eq) and MP-cyanoborohydride resin (2.34 mmol/g, 2.5 eq, 151 mg, 0.211 mmol) was stirred at rt for 48 h. The reaction mixture was filtered, neutralized with 2 M NH_3 in MeOH, concentrated and purified by chromatography on SiO_2 (5% MeOH/EtOAc) to provide 38.2 mg (79%) of **19** as a colorless oil: $[\alpha]_D$ -64.8 (*c* 1.06, CH_2Cl_2); IR (CH_2Cl_2) 3357, 2949, 1731, 1438, 1213, 1068 cm^{-1}; ^1H NMR (MeOD) δ 7.34 (dd, 1 H, *J* = 5.1, 1.2 Hz), 7.06-6.99 (m, 1 H), 6.96 (dd, 1 H, *J* = 5.1, 3.6 Hz), 4.13, 4.07 (AB, 2 H, *J* = 13.8 Hz), 3.98 (app t, 1 H, *J* = 2.7 Hz), 3.73-3.57 (m, 3 H), 3.66 (s, 3 H), 3.24-3.07 (m, 2 H), 1.95-1.67 (m, 3 H); ^{13}C NMR (MeOD) δ 177.9, 143.3, 127.3, 127.3, 126.4, 82.4, 74.8, 73.6, 69.4, 66.5, 62.4, 52.7, 39.1, 27.2; ESI-MS *m/z* 366 ($[M+Na]^+$, 30), 344 ($[M+H]^+$, 10); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NO_6S$ (M+H) 344.1168, found 344.1184.



20

(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*)-Methyl 1-(cyclopropylmethyl)-3a,4,5,6-tetrahydroxy octahydro-1*H*-indole-2-carboxylate (20). To a solution of **17** (50.0 mg, 0.202 mmol) in MeOH (2 mL) was added acetic acid (57.9 μL, 1.01 mmol, 5 eq), cyclopropanecarboxaldehyde (23.1 μL, 0.303 mmol, 1.5 eq) and MP-cyanoborohydride resin (2.34 mmol/g, 2.5 eq, 216 mg, 0.506 mmol). The reaction mixture was stirred at rt for 48 h, filtered, neutralized with 2 M NH_3 in MeOH, concentrated and purified by chromatography on SiO_2 (5% MeOH/EtOAc) to provide 49.0 mg (80%) of **20** as a

colorless oil: $[\alpha]_D$ -69.1 (*c* 1.05, CH_2Cl_2); IR (CH_2Cl_2) 3334, 3001, 2950, 1733, 1438, 1213, 1062 cm^{-1}; ^1H NMR (MeOD) δ 3.97-3.75 (m, 4 H), 3.77 (s, 3 H), 3.51 (app t, 1 H, *J* = 6.0 Hz), 2.99 (dd, 1 H, *J* = 13.8, 10.5 Hz), 2.80 (dd, 1 H, *J* = 12.6, 5.7 Hz), 2.35 (dd, 1 H, *J* = 12.6, 7.8 Hz), 1.99-1.71 (m, 3 H), 1.00-0.81 (m, 1 H), 0.63-0.40 (m, 2 H), 0.24-0.06 (m, 2 H); ^{13}C NMR (MeOD) δ 177.1, 80.9, 75.8, 74.4, 69.1, 66.6, 62.2, 54.6, 52.8, 39.9, 27.8, 10.7, 4.6; EIMS *m/z* 302 ($[M+H]^+$, 5), 284 (100), 230 (50), 224 (70); HRMS (EI) *m/z* calcd for $C_{14}H_{23}NO_6$ 302.1604, found 302.1615.