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

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

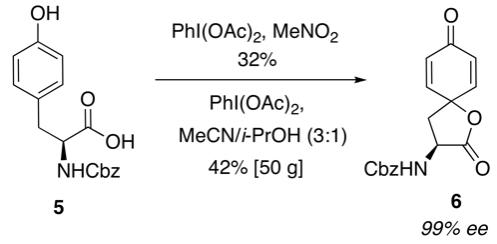
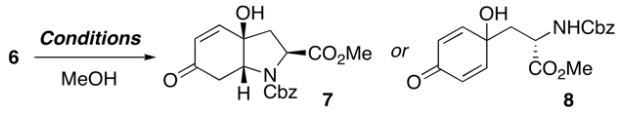


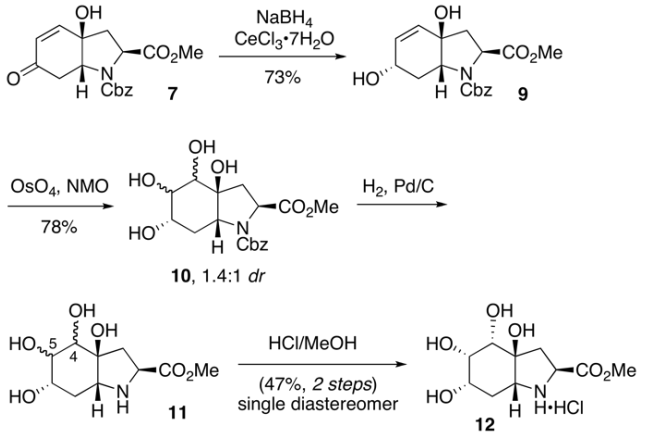
Table 1. Optimization of methanolysis procedure to produce **7**.[2]



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.



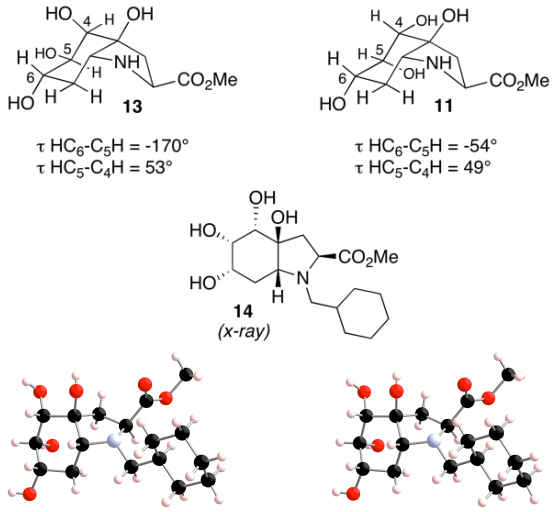
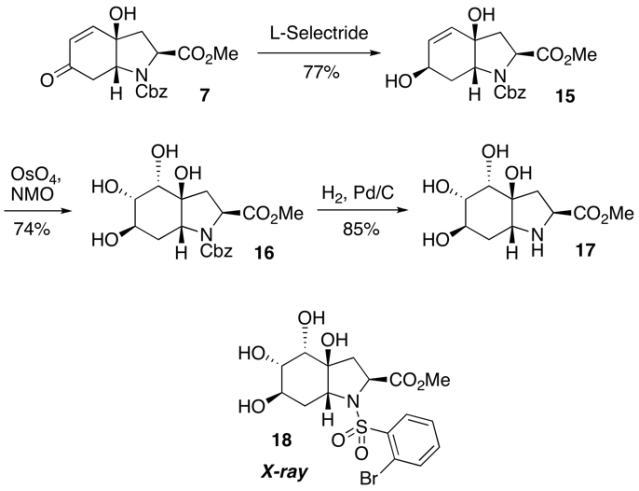


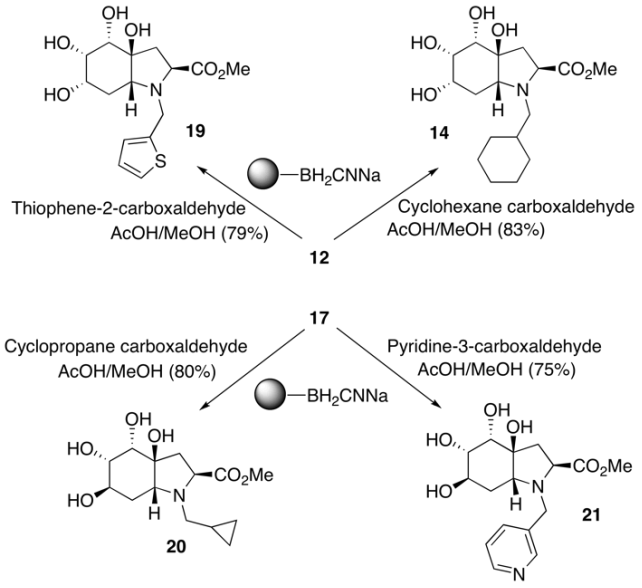
Figure 1. Conformational analysis of **13** and **11** and stereoview of the x-ray structure of **14**.

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

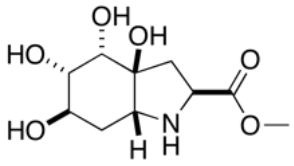


[1] Wipf, P.; Kim, Y. "Synthesis of Stemona Alkaloids; Stereoselective Preparation of the Hydroindole Ring System by Oxidative Cyclization of Tyrosine." *Tetrahedron Lett*. **1992**, *33*, 5477-5480.
[2] Pierce, J. G.; Kasi, D.; Fushimi, M.; Cuzzupe, A.; Wipf, P. "Synthesis of Hydroxylated Bicyclic Amino 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.



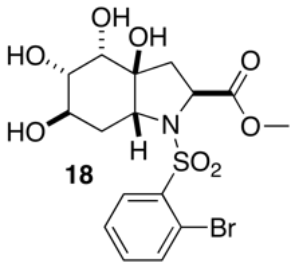
(2*S*,3a*R*,6*R*,7a*R*)-1-Benzyl 2-methyl 3a,6-dihydroxy-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (15). To a solution of **7** (4.42 g, 12.8 mmol) in freshly distilled THF (100 mL) at -78 °C was added L-selectride (19.2 mL, 19.2 mmol, 1.5 eq) dropwise (syringe pump) over 1.5 h. The 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

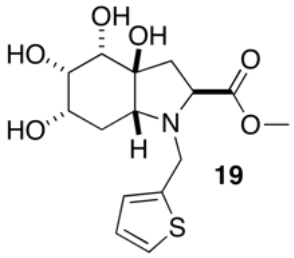
(2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*)-Methyl 3a,4,5,6-tetrahydroxyoctahydro-1*H*-indole-2-carboxylate (17). To a solution of **16** (456 mg, 1.20 mmol) in MeOH (10 mL) was added 10% Pd/C (63.4 mg). The reaction mixture was stirred under an atmosphere of H_2 for 10 h, filtered through a pad of Celite and 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).



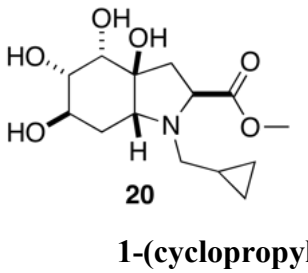
18

(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.