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Synthesis of Hydroxylated Bicyclic Amino Acids from L-Tyrosine: Octahydro-1*H*-indole Carboxylates

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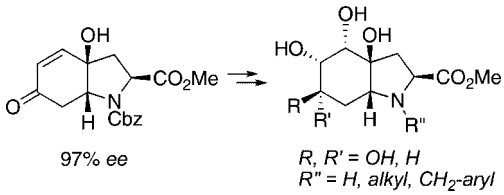

A stereoselective approach to polyhydroxylated L-Choi derivatives has been developed. The oxidative cyclization of L-tyrosine was optimized to avoid partial racemization and to allow a more efficient scale-up.

Aeruginosin 298-A (**1**, Figure 1) is a serine protease inhibitor that was isolated from a fresh water blue green algae in 1994.[1] Approximately 16 members of the aeruginosin family have been identified, and 14 share the unusual bicyclic amino acid L-Choi [(2*S*,3a*S*,6*R*,7a*S*)-2-carboxy-6-hydroxyoctahydroindole] or a close derivative as a common motif.[2] L-Choi is an example of the growing class of sterically encumbered proline analogues that exert a profound influence on the secondary structure when embedded in oligopeptide sequences. Several synthetic approaches to Choi and aeruginosin natural products have been reported.[3]

Many other natural and synthetic compounds contain fused bicyclic scaffolds that closely resemble Choi.[4] The naturally occurring di-, tri-, and tetrahydroxylated indolizidine alkaloids, lentiginosine (an amyloglucosidase inhibitor), swainsonine (an α-mannosidase inhibitor), and castanospermine (**2**, an α-glucosidase inhibitor; analogue **3**[4f]) are particularly noteworthy (Figure 1). Parkacine (**4**) is an alkaloid from *Amaryllis belladonna var. blanda Brunsvigia josephinae*. The significance of these fused bicyclic scaffolds for biologically active natural products has inspired the development of novel chemical libraries.[5]

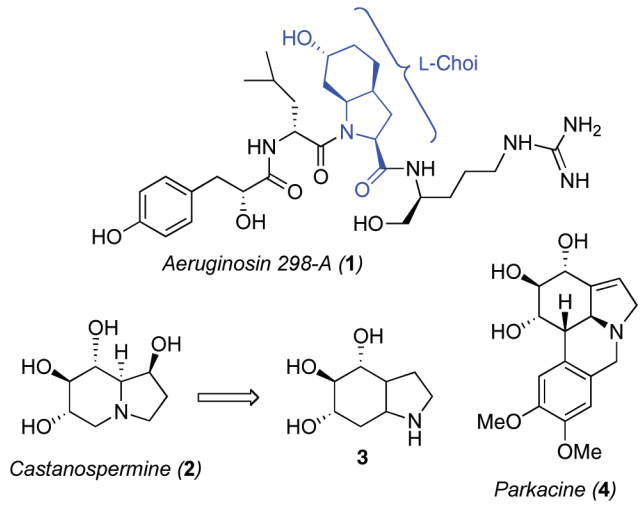

FIGURE 1. Natural products containing L-Choi-like cores.

Our initial studies toward L-Choi derivatives centered around the oxidative cyclization of L-tyrosine previously developed in our laboratory.[3o,6] Although this oxidation was originally

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SCHEME 1. Oxidative Cyclization of L-Tyrosine

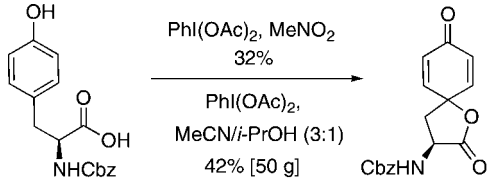
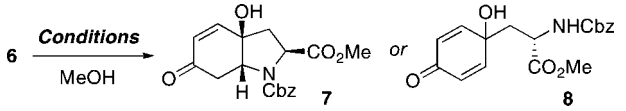


TABLE 1. Optimization of Methanolysis Procedure To Produce 7



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

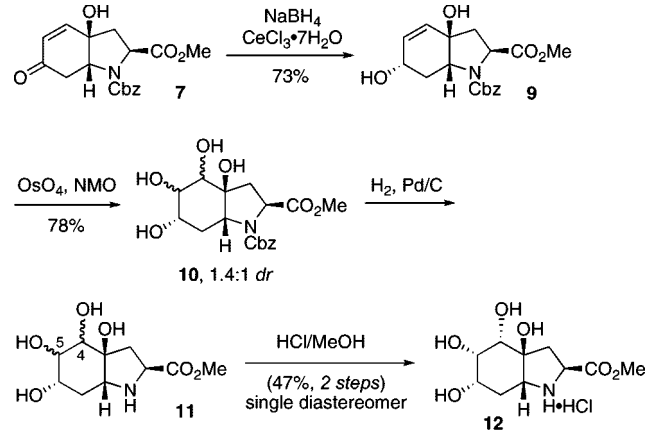
[a] Determined by HPLC analysis of crude reaction mixtures using a Chiracel AD-H column; individual yields were not determined. MWI: microwave irradiation.

performed in methanol and subsequently nitromethane, a 3:1 mixture of acetonitrile:isopropanol has proven more successful upon scale-up (Scheme 1). This optimized procedure led to spirocycle **6** in 42% yield and >99% ee. Subsequent methanolysis of the spirocycle was performed according to a literature procedure.[6] While at first not immediately apparent, we came to realize that the conversion of the spirocycle **6** to hydroxyhydroindole **7** occurred in a mediocre 53% ee (Table 1, entry 1). This partial racemization is likely to occur at the lactone stage prior to methanolysis. We screened a variety of bases and measured product ratios and enantiomeric excess by chiral HPLC analysis. Stronger bases and/or extended reaction times gave products with further deteriorated enantiomeric purity, while weak bases promoted only spirocycle opening to generate hydroxydienone **8**. Gratifyingly, lowering the reaction temperature and using NaOMe had a beneficial effect, providing **7** in 87% ee (Table 1, entry 11). Addition of water and switching the base to KOH not only improved the ee further to 97%, but also decreased the reaction time to 10 min and increased the yield to 80%.[7] Utilizing this protocol, **7** could be prepared in overall 34% yield and 97% ee from L-tyrosine on a 50 g scale.

After identifying a stereoselective protocol to the desired hydroindole **7**, our focus turned toward the synthesis of hydroxylated L-Choi derivatives. Realizing the potential to generate a number of stereoisomers from the common intermediate **7**, we first subjected the enone to $NaBH_4$ at 0 °C to provide in 73% yield the axial alcohol **9**, which upon dihydroxylation led to tetrol **10** in 1.4:1 facial selectivity and 78% yield (Scheme 2).[3o,6] The Cbz group was removed by hydrogenolysis to yield a mixture of amines (**11**), and separation of

(7) Quenching with aqueous HCl at −20 °C was essential for high ee's.

SCHEME 2. Synthesis of Polyhydroxylated Hydroindoles



diastereomers was achieved by formation of their hydrochloride salts in methanol, followed by selective precipitation to generate **12** as a single diastereomer in 47% yield based on **10**.

The configuration at the C_4 and C_5 positions of **11** was initially assigned based on ^1H NMR analysis; specifically, the hydrogen atoms were assigned by COSY and HMQC, and the relative configuration was determined in ^1H NMR double resonance experiments from the coupling constants $J_{4,5} = 3.5$ Hz and $J_{5,6} = 2.4$ Hz for **11** (Figure 2). Among the C_6-α-hydroxy isomers **13** and **11**, only **11** provided a good agreement between the dihedral angles of the minimized structure and these coupling constants.[8] This assignment was further confirmed by an X-ray analysis of the N-alkylated derivative **14**. In the solid state, this compound adopted a conformation closely analogous to the calculated structure of **11** shown in Figure 2, with dihedral angles τ $HC_6-C_5H = -63.3°$ and τ $HC_5-C_4H = 53.7°$. It is interesting to note that the osmate in the dihydroxylation step favors an approach from the concave α-face in spite of the syn-orientation to the equatorial secondary alcohol.[9] This result demonstrates the role of the tertiary alcohol at the bridgehead position in controlling the *anti*-approach of osmium tetraoxide to the allylic double bond.

The synthesis of the C_6-epimer **15** began with a reduction of enone **7** with L-Selectride at −78 °C to give the axial alcohol in 77% yield and in >95:5 selectivity when the reagent was added by syringe pump (Scheme 3).[3o,6,10] Subsequent dihydroxylation of the diol gave **16** as a single diastereomer by ^1H NMR analysis. Tetrol **16** was subsequently deprotected to provide hydroindole **17**.

In contrast to **11**, the differentiation of the two possible diastereomers of **17** by coupling constant analysis was not possible since the two energy minimized structures had very similar dihedral angles. Fortunately, sulfonylation of **17** provided the crystalline material **18** which enabled the unambiguous

(8) Conformational analysis of tetrahydroxy hydroindole scaffolds was performed with MOE 2005.06/MMFF94 force field/10 000 step stochastic conformational search. Only the lowest-energy conformations and the corresponding dihedral angles are shown for each diastereomer.

(9) In general, the double bond in allylic alcohols is dihydroxylated on the face opposite to the hydroxyl group, mainly driven by repulsive steric interactions: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. (b) Cha, J. K.; No-Soo, K. *Chem. Rev.* **1995**, *95*, 1761. See also: (c) Donohoe, T. J. *Synlett* **2002**, 1223. However, there is very limited precedence on the facial selectivity of dihydroxylation of *anti*-1,4-cyclohexenediols; for the *cis*-1,4-diol configuration the preferred stereoselectivity is also *anti*: (d) Carless, H. A. J.; Busia, K.; Oak, O. Z. *Synlett* **1993**, 672.

(10) For selectivities of reducing compounds analogous to **7** with $NaBH_4$, Dibal-H, and L-Selectride, see: Hanessian, S.; Guillemette, S.; Ersmark, K. *Chimia* **2007**, *61*, 361.

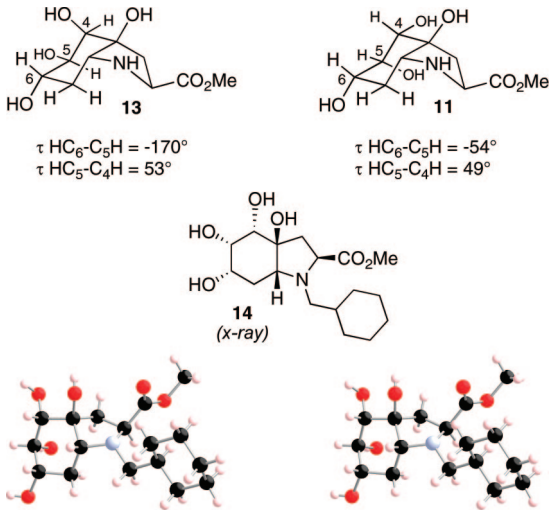
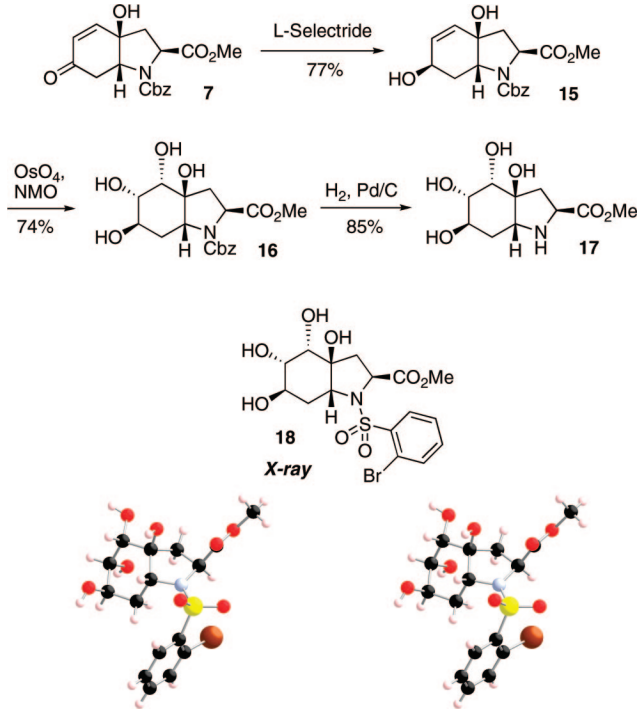


FIGURE 2. Conformational analysis of **13** and **11** and stereoview of the X-ray structure of **14**.

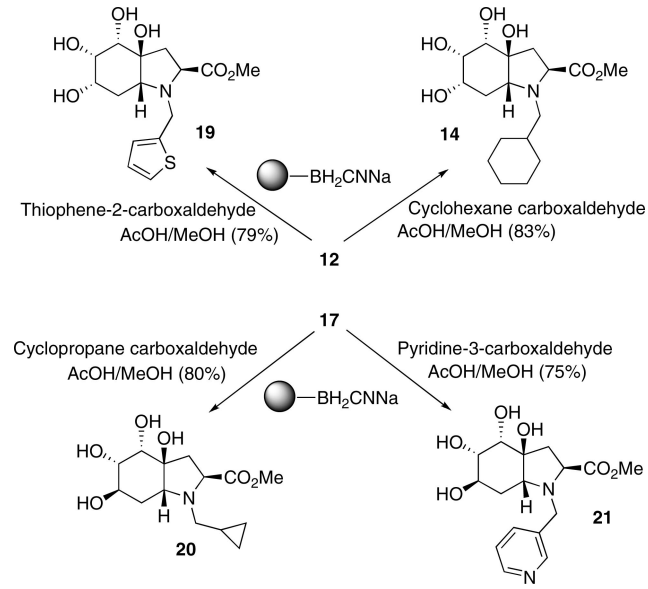
SCHEME 3. Synthesis of Polyhydroxylated Hydroindoles and Stereoview of the X-ray Structure of 18



assignment of the relative configuration through X-ray analysis. On the basis of our previous result, it was not surprising that the approach of the osmium reagent occurred opposite to the *cis*-1,4-diol functionality, exclusively from the α-face of alkene **15**.

After establishing a facile approach to hydroxylated L-Choi derivatives, we pursued a reductive amination as a way to install diverse functionality onto the secondary amine. To this end, a number of conditions were screened to achieve high yields in the amination. MP-cyanoborohydride resin[11] was found to be the most effective reducing agent, which we attributed to its greater stability in methanol. Applying these optimized conditions to both intermediates **12** and **17**, we produced tertiary amines bearing thiophene (**19**), cyclohexyl (**14**), cyclopropyl (**20**), and pyridine (**21**) hetero- and carbocyclic ring functionality (Scheme 4). These conversions illustrate the broad substituent diversity that can be introduced with this transformation.

SCHEME 4. Reductive Amination of Polyhydroxylated L-Choi Scaffolds



In conclusion, we have developed an improved protocol for our tyrosine oxidation−methanolysis methodology that not only provides a higher yield but also prevents the potential for deterioration of enantiomeric excess that had previously gone unnoticed. The conversion of this hydroindole scaffold to ring- and side-chain-functionalized L-Choi derivatives was achieved in a stereoselective and high-yielding sequence, and the relative configuration of all derivatives was confirmed through NMR and X-ray analyses. The biological evaluation of this class of compounds is currently in progress.

Experimental Section

Oxidative Spirocyclization of Tyrosine. (*S*)-Benzyl 2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-3-ylcarbamate (6). To a solution of $PhI(OAc)_2$ (39.1 g, 119 mmol) in MeCN/*i*-PrOH (4:1, 130 mL) was added a solution of Cbz-tyrosine (25.0 g, 79.3 mmol) in MeCN/*i*-PrOH (4:1, 150 mL) dropwise over 1 h. The reaction mixture was stirred for an additional 2 h, quenched with saturated aq $NaHCO_3$ (500 mL), and extracted with EtOAc (2 × 500 mL). The combined organic layers were washed with $NaHCO_3$ (3 × 500 mL) and brine, dried ($MgSO_4$), and concentrated. A heterogeneous mixture of the crude residue in 80% EtOAc/hexanes (400 mL) was filtered though a pad of SiO_2. The resulting solution was concentrated and purified by chromatography on SiO_2 (45% EtOAc/hexanes to 60% EtOAc/hexanes). The orange solid was recrystallized from hot EtOAc/hexanes (at −20 °C overnight after being dissolved in boiling solvent) to yield 9.57 g (39%) of spirocycle **6** as colorless needles: $[\alpha]_D$ −26.0 (*c* 1.08, CH_2Cl_2); IR (CH_2Cl_2) 3060, 2956, 1789, 1710, 1674, 1635, 1523, 1198 cm^{-1}; ^1H NMR δ 7.53−7.20 (m, 5 H), 6.86 (br d, 2 H, J = 7.5 Hz), 6.43−6.20 (m, 2 H), 5.59 (br s, 1 H), 5.14 (br s, 2 H), 4.70−4.54 (m, 1 H), 2.74 (dd, 1 H, J = 11.1, 10.2 Hz), 2.49 (app t, 1 H, J = 12.3 Hz); ^{13}C NMR δ 184.2, 173.8, 156.1, 146.3, 144.4, 135.8, 129.8, 129.2, 128.8, 128.6, 128.3, 67.7, 50.5, 38.0; EIMS *m/z* 313 (M^+, 15), 269 (15), 226 (15), 107 (95), 91 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{15}NO_5$ 313.0950, found 313.0940.

(11) Le Bourdonnec, B.; Goodman, A. J.; Graczyk, T. M.; Belanger, S.; Seida, P. R.; DeHaven, R. N.; Dolle, R. E. *J. Med. Chem.* **2006**, *49*, 7290.

Indoline Scaffold. (2*S*,3a*R*,7a*R*)-1-Benzyl 2-methyl 3a-hydroxy-6-oxo-3,3a,7,7a-tetrahydro-1*H*-indole-1,2(2*H*,6*H*)-dicarboxylate (7). To a solution of KOH (3.0 M in H_2O, 200 mL) and MeOH (200 mL) at −20 °C was added a solution of **6** (6.48 g, 20.7 mmol) in 150 mL of MeOH in one portion. The reaction mixture was allowed to stir at −20 °C for 20 min during which time the solution became brown in color. The mixture was quenched by addition of 10% HCl (100 mL), extracted with EtOAc (3 × 150 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by chromatography on SiO_2 (60% EtOAc/hexames to 80% EtOAc/hexanes) to yield 5.68 g (80%) of methyl ester **7** as a colorless waxy solid: $[\alpha]_D$ −130 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) 3034, 2953, 1756, 1686, 1415, 1351, 1124 cm^{-1}; ^1H NMR (DMSO-d_6, 380 K) δ 7.43−7.26 (m, 5 H), 6.76 (d, 1 H, J = 10.2 Hz), 5.90 (d, 1 H, J = 10.5 Hz), 5.40 (br s, 1 H), 5.18−5.03 (m, 2 H), 4.50 (dd, 1 H, J = 9.3, 3.0 Hz), 4.24 (dd, 1 H, J = 9.3, 5.7 Hz), 3.61 (s, 3 H), 2.93 (dd, 1 H, J = 15.9, 5.4 Hz), 2.62 (dd, 1 H, J = 16.2, 9.6 Hz), 2.58 (dd, 1 H, J = 13.2, 9.3 Hz), 2.29 (ddd, 1 H, J = 13.2, 3.0, 0.6 Hz); ^{13}C NMR (DMSO-d_6, 380 K) δ 195.4, 170.9, 153.0, 148.8, 136.1, 127.7, 127.6, 127.2, 126.9, 126.9, 73.9, 65.8, 63.7, 58.0, 51.0; ESI-MS *m*/*z* 368 ([M + Na]$^+$, 50), 302 (10); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}NO_6Na$ (M + Na) 368.1110, found 368.1121.

Typical Procedure for the Dihydroxylation of 1,4-Dihydroxy-2-cyclohexenes. (2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*)-1-Benzyl 2-methyl 3a,4,5,6-tetrahydroxyhexahydro-1*H*-indole-1,2(2*H*,3*H*)-dicarboxylate (16). To a solution of **15** (1.00 g, 2.88 mmol in THF (25 mL)) and water (2.5 mL) were added methanesulfonamide (307 mg, 3.17 mmol, 1.1 equiv), NMO-H_2O (1.19 g, 8.64 mmol, 3.0 equiv), and osmium tetraoxide (0.3 M in toluene, 747 mg, 0.288 mmol, 0.960 mL), and the reaction mixture was stirred at rt for 48 h. After this time, additional osmium tetraoxide (0.3 M in toluene, 747 mg, 0.288 mmol, 0.960 mL) was added and the mixture was stirred for an additional 72 h. The solution was quenched with Na_2SO_3, diluted with H_2O and EtOAc, extracted with EtOAc (4×), 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 810 mg (74%) of tetraol **16** as a colorless waxy solid: $[\alpha]_D$ −33.4 (*c* 0.44, MeOH); IR (CH_2Cl_2) 3410, 3063, 2952, 2901, 1686, 1419, 1216, 1056 cm^{-1}; ^1H NMR (methanol-d_4, 600 MHz, rotamers) δ 7.42−7.26 (m, 5 H), 5.18 (d, 0.5 H, J = 12.6 Hz), 5.15 (d, 0.5 H, J = 12.6 Hz), 5.14 (d, 0.5 H, J = 12.6 Hz), 4.99 (d, 0.5 H, J = 12.6 Hz), 4.41 (app ddd, 1 H, J = 19.8, 10.2, 1.2 Hz), 4.12−4.04 (m, 1 H), 3.96 (app dd, 1 H, J = 16.8, 3.6 Hz), 3.92−3.87 (m, 0.5 H), 3.87−3.82 (m, 1.5 H), 3.71 (s, 1.5 H), 3.56 (s, 1.5 H), 2.92 (app ddd, 1 H, J = 13.8, 10.8, 1.2 Hz), 2.37−2.29 (m, 0.5 H), 2.25−2.18 (m, 0.5 H), 2.15 (app dd, 1 H, J = 14.4, 0.6 Hz), 1.63 (ddd, 0.5 H, J = 13.8, 10.8, 2.4 Hz), 1.59 (ddd, 0.5 H, J = 13.8, 10.8, 2.4 Hz); ^{13}C NMR (methanol-d_4, 150 MHz, rotamers) δ 175.3, 174.9, 156.6, 156.0, 138.0, 137.8, 129.5, 129.4, 129.1, 129.0, 129.0, 128.9, 82.3, 81.3, 73.6, 70.6, 70.5, 68.2, 68.1, 63.6, 63.4, 58.8, 58.7, 52.8, 52.7, 38.5, 37.4, 32.1, 31.3; ESIMS *m*/*z* 404 ([M + Na]$^+$, 100), 365 (15); HRMS (ESI) *m*/*z* calcd for $C_{18}H_{23}NO_8Na$ (M + Na) 404.1321, found 404.1305.

Typical Procedure for Reductive Amination. (2*S*,3a*S*,4*S*,5*S*,6*R*,7a*R*)-Methyl 3a,4,5,6-tetrahydroxy-1-(pyridin-3-ylmethyl) octahydro-1*H*-indole-2-carboxylate (21). To a solution of **17** (50.0 mg, 0.202 mmol) in MeOH (2 mL) were added acetic acid (57.9 μL, 1.01 mmol, 5 equiv), pyridine-3-carboxaldehyde (29.1 μL, 0.303 mmol, 1.5 equiv), and MP-cyanoborohydride resin (2.34 mmol/g, 2.5 equiv, 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 in vacuo, and purified by chromatography on SiO_2 (short plug, 5% MeOH/EtOAc to 10% MeOH/EtOAc) to yield 51.0 mg (75%) of **21** as a colorless oil: $[\alpha]_D$ −32.6 (*c* 0.95, CH_2Cl_2); IR (CH_2Cl_2) 3319, 2949, 1730, 1432, 1365, 1211, 1063 cm^{-1}; ^1H NMR (methanol-d_4) δ 8.40 (br s, 1 H), 8.30 (d, 1 H, J = 3.9 Hz), 7.78 (d, 1 H, J = 7.5 Hz), 7.27 (dd, 1 H, J = 7.5, 4.8 Hz), 3.92−3.64 (m, 5 H), 3.52−3.40 (m, 1 H), 3.44 (s, 3 H), 3.30−3.21 (m, 1 H), 2.87 (dd, 1 H, J = 13.8, 10.5 Hz), 1.80−1.61 (m, 3 H); ^{13}C NMR (methanol-d_4) δ 177.4, 150.5, 149.0, 139.1, 136.7, 125.3, 81.8, 74.6, 74.2, 69.7, 66.0, 62.6, 52.5, 51.1, 39.6, 27.5; ESI-MS *m*/*z* 339 ([M + H]$^+$, 10), 321 (100), 261 (30), 246 (40); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{22}N_2O_6$ (M + H) 339.1556, found 339.1544.

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Supporting Information Available: Experimental procedures for compounds **9**,**10**, **12**, **14**, **15**, and **17**−**20**, copies of ^1H and ^{13}C NMR spectra for **6**, **7**, **9**, **10**, **12**, and **14**−**21**, and CIF files for **14** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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