Facile Chemoenzymatic Synthesis of 3-(Hydroxymethyl)-6-epicastanospermine

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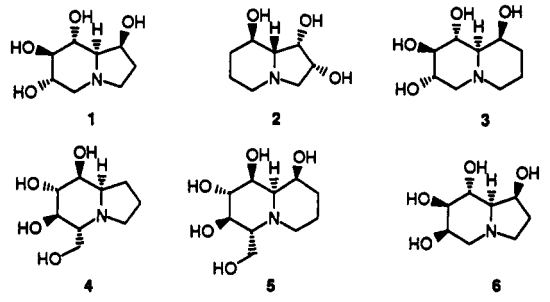
Polyhydroxyindolizidines such as castanospermine (1) and swainsonine (2) have been found in Nature as potent inhibitors of various glycosidases.[1] As a result, such compounds have functioned as probes of the active sites of various glycosidases through enzyme inhibition studies. The emergence of such compounds and their derivatives having anticancer[2] and anti-HIV[3] activities has generated considerable interest and stimulated both the search for superior therapeutic agents and the development of efficient synthetic approaches to such compounds and their analogues. Among recent examples are analogues of castanospermine, namely, 3,[4] 4,[5] 5,[5] and 6,[6] which show



either similar or in fact quite different biological activities compared to the parent compound. For instance, in comparison with castanospermine, 6-epicastanospermine (6) exhibits very different inhibitory effects on certain glycosidases such as β-glucosidase and β-galactosidase and shows no activity against α-mannosidase in contrast to what might be expected from structure–activity relationships.[7] It has been shown that an alteration to any of the five chiral centers in 1 remarkably changes the inhibitory selectivities,[8] and O-acylation of 1 increases the inhibition of glucosidase 10-fold relative to castanospermine itself.[9] These findings suggest that structure–activity relationships for these compounds are more subtle than expected. To determine the structural requirements for optimum glycosidase inhibition, the development of synthetic approaches to novel analogues is essential. A number of synthetic approaches for the construction of the polyhydroxyindolizidine skeleton have been developed,[10] and they all require the protection of hydroxyl groups at various stages. Recently, we began exploting the utilization of aldolases in the synthesis of unnatural polyhydroxyalkaloids to achieve their rapid construction and to evaluate their inhibitory effects on various glycosidases.[11] The effect on biological activity of a 3-substituted polyhydroxyindolizidine skeleton has not been previously reported. In this paper we report a chemoenzymatic method for the construction of the 3-substituted 6-epicastanospermine skeleton, such as **15**, in which the protection and deprotection steps of all hydroxyl groups were not required.

N-Acetylneuraminic acid aldolase (NANA) has been demonstrated to be specific to pyruvate but flexible to various aldoses[12] including the L-sugars.[12,13] This enzyme has been used in the preparation of various analogues of *N*-acetylneuraminic acid. Our present work indicates that the elaboration of neuraminic acids to polyhydroxyindolizidines avoids the protection of hydroxyl groups present, and this approach has led to a rapid synthesis of 3-hydroxy-6-epicastanospermine.

Scheme I illustrates our synthetic route to 3-(hydroxymethyl)-6-epicastanospermine (**15**). Carbobenzyloxy instead of acetyl protection of the amino group in D-mannosamine was necessary to simplify the subsequent intramolecular reductive amination. We found that the enzyme can indeed accommodate the alteration of the acetyl group in the natural substrate to a more sterically demanding group such as the carbobenzyloxy functionality, and we obtained the desired neuraminic acid **9** in 67% yield. The stereochemistry at C(4) in **9** was confirmed to be *S* by the adjacent transaxial coupling constants of H(3ax) and H(4) (J_{3ax-4} = 12 Hz). The adduct **9** was converted to **12** in three steps without purification of intermediates **10** and **11**. Carbobenzyloxy deprotection and cyclization to the proline analogues **10** was accomplished in one step by hydrogenolysis in the presence of 10% Pd/C in water. After removal of Pd/C by filtration, $NaHCO_3$ and benzyl chloroformate were added into the filtrate to produce the *N*-(carbobenzyloxy)proline intermediate **11**. We were not able to separate the two diastereomers resulted from the reductive amination at these stages. However after methyl esterification of **11**, two diastereomers of ester **12** were readily separated by flash chromatography on silica gel. The ratio of **12a** to **12b** is approximately 10 to 1. The overall yield of these three steps (**9** to **12**) was 70%. To determine the stereochemistry at the α-carbon of the proline ring in **12a**

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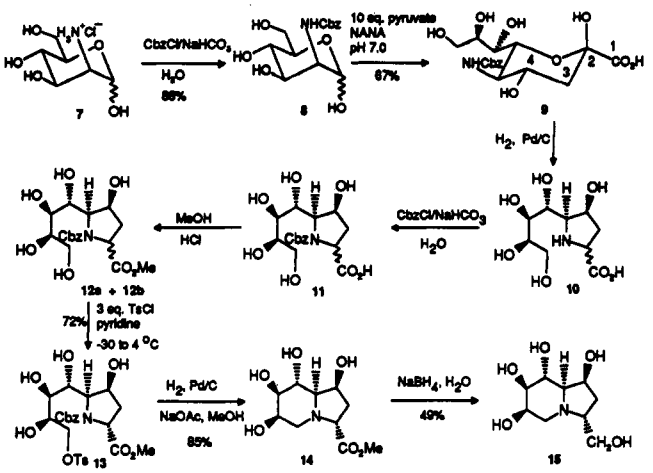
Scheme I



and **12b**, the two isomers **12a** and **12b** were degraded[14] to bulgecinine epimers. By comparing the optical rotations of degradation products with that of known epibulgecinine **17**,[15] the absolute configuration of the α-carbon in major isomer **12a** was assigned as *R*.[14] The primary hydroxyl group of **12a** was selectively tosylated with *p*-toluenesulfonyl chloride in pyridine at −30 to 4 °C to give the monotosylate **13** in 72% yield after flash chromatographic purification on silica gel. Cyclization to the fused six-membered ring was effected by removal of the carbobenzyloxyl group by hydrogenolysis in the presence of 10% Pd/C in methanol to afford **14** in 85% yield. The ester **14** was subjected to reduction with $NaBH_4$ in water to afford the final product **15** in 80% yield after considering the recovery of 38% of starting material **14**.

It has been reported that 6-epicastanospermine is a potent inhibitor of amyloglucosidase with 50% inhibition occurring at approximately 0.02 mM.[7] In contrast to this, 3-(hydroxymethyl)-6-epicastanospermine (**15**) was a poor inhibitor of amyloglucosidase and showed less than 20% inhibition of this enzyme at levels as high as 1 mM. It is now apparent that a hydroxymethyl group at the 3-position in **15** drastically reduces binding of this analogue to amyloglucosidase. In addition compound **15** showed no potent inhibitory activity when tested at 1 mM against the following enzymes: bakers' yeast invertase, bovine epididymis α-L-fucosidase, bakers' yeast α-glucosidase, almonds α-mannosidase, *E. coli* β-galactosidase, snail β-mannosidase, almonds β-glucosidase, *Aspergillus niger* α-galactosidase, *Aspergillus niger* hesperidinase, and *Penicillium decumbens* naringinase.

This paper describes the facile synthesis of the first 3-substituted analogue of castanospermine via a neuraminic acid derivative and sets the stage for the synthesis of more complex analogues of other naturally occurring polyhydroxylated bicyclic alkaloids[16] using an approach which accommodates the principle of atom economy.[17]

Experimental Section

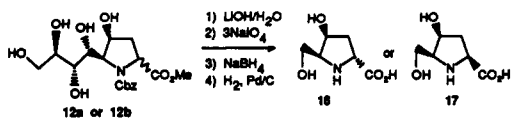
General Methods. Pyridine was distilled from CaH_2 and kept under nitrogen in the presence of molecular sieves (4A). *N*-Acetylneuraminic acid aldolase (EC 4.1.3.3) was purchased from Toyobo Co., Ltd, Osaka, Japan. All NMR spectra taken in D_2O, $(CD_3)_2SO$, CD_3CN, or $(CD_3)_2CO$, the signal of HDO, CHD_2SOCD_3, CHD_2CN, or CHD_2COCD_3 were set to 4.63, 2.49, 1.93, or 2.04, respectively. For ^{13}C NMR spectra taken in D_2O, sodium 3-(trimethylsilyl)-1-propanesulfonate was used as an external reference. For ^{13}C NMR spectra taken in $(CD_3)_2SO$, CD_3CN, or $(CD_3)_2CO$, the signal of $(CD_3)_2SO$, CD_3 in CD_3CN, or CD_3 in $(CD_3)_2CO$ was set to 39.5, 1.3, or 29.8, respectively. Mass spectra were recorded at the McMaster Regional Centre For Mass Spectrometry at the Department of Chemistry, McMaster University, Hamilton, Ontario, Canada. IR spectra were obtained using KBr pellets. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Elemental analyses were performed by the M-H-W Laboratories, Phoenix, AZ.

The inhibitory activities were measured as described previously.[11]

***N*-(Carbobenzyloxy)-D-mannosamine (8).** Benzyl chloroformate (3.7 mL, 26.2 mmol) was added dropwise to a solution of D-mannosamine hydrochloride (4.7 g, 22.9 mmol) and $NaHCO_3$ (5.8 g, 68.7 mmol) in distilled water (150 mL) at 0 °C with stirring. The mixture was warmed to room temperature and stirred overnight. The reaction mixture was then neutralized to pH 5–6 with 1 N HCl and washed with diethyl ether three times (50 mL each time). The aqueous solution was freeze-dried after evaporation of dissolved diethyl ether. The solid residue was triturated with absolute ethanol (100 mL), and the insoluble material was removed by filtration. Silica gel (5 g) was added into the filtrate to adsorb the crude product. Ethanol was removed under vacuum, and the residue was purified by flash chromatography (70–230-mesh silica gel, 2% water and 25% methanol in ethyl acetate) to give the product **8** (6.34 g, 88%): white powder; ^1H NMR (200 MHz, DMSO-d_6 with D_2O wash) δ 7.34 (m, 5 H, aromatic), 4.99 (br s, 2 H, benzylic), 4.94 (d, J = 3.3 Hz, 1 H, H1), 3.8–2.9 (m, 6 H); ^{13}C NMR (50.3 MHz, DMSO-d_6 with D_2O wash) δ 156.2 (OCONH), 137.2 (aromatic C1), 128.5 (aromatic), 127.9 (aromatic), 90.7 (C1), 72.1, 71.0, 70.3, 65.4, 61.1, 56.4 ($PhCH_2O$); IR 3353 s, 1682 s, 1549 s, 1323 m, 1289 m, 1253 m, 1130 m, 1084 m, 1050 m, 1018 m cm^{-1}. MS (FAB+) *m/e* 314 (M + H). Anal. Calcd for $C_{14}H_{19}O_7N$: C, 53.7; H, 6.1; N, 4.5. Found: C, 53.7; H, 6.3; N, 4.4.

***N*-(Carbobenzyloxy)neuraminic Acid (9).** To an aqueous solution of *N*-(carbobenzyloxy)-D-mannosamine (5.9 g, 18.7 mmol), sodium pyruvate (20.6 g, 18.7 mmol), and sodium azide (100 mg) in distilled water (200 mL) was added to sodium phosphate buffer (0.1 M, pH = 7.5, 15 mL) and *N*-acetylneuraminic acid aldolase (200 units). The reaction mixture was incubated at 35 °C for 48 h and chromatographed in 70-mL portions (3- X 42-cm gravity column, 200–400-mesh Bio-Rad AG 1-X8-HCO_2^-) eluting with a linear gradient of distilled water (600 mL) and 2 N formic acid (600 mL), followed by 2 N formic acid to give the starting material **8** (1.3 g) and the adduct **9** (5 g, 67%): white fluffy powder; ^1H NMR (200 MHz, D_2O) δ 7.28 (br s, 5 H, aromatic), 4.98 (AB q, J = 12.5 Hz, 2 H, benzylic), 4.0–3.3 (m, 7 H), 2.14 (dd, J = 4.8, 13.0 Hz, 1 H, H3eq), 1.71 (dd, J = 12.0 Hz, 1 H, H3ax); ^{13}C NMR (50.3 MHz, D_2O) δ 179.5 (C1), 161.1 (OCONH), 139.2 (aromatic C1) 131.5 (aromatic), 131.1 (aromatic C4), 130.4 (aromatic), 99.1 (C2), 73.2, 73.0, 71.3, 70.0, 69.7, 66.1, 56.4 (CH_2Ph), 41.5 (C3); IR 3573 s, 3297 s, 2920 s, 1709 s, 1530 s, 1451 m, 1386 m, 1316 m, 1235 s, 1123 m, 1040 s cm^{-1};

(14) The degradation of **12a** and **12b** was illustrated by the following scheme:



The optical rotation ($[\alpha]^{22}_D$ +8°) of the degradation product from minor isomer **12b** is close to the reported value ($[\alpha]^{28}_D$ +5.7°) for **17**. This tentatively set the configuration of the α-carbon in minor isomer **12b** as *S* and consequently that in major isomer **12a** as *R*. This was further confirmed by the very different optical rotation (−34°) of the degradation product from **12a**.

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MS (FAB$^+$) m/e 402 (M + H). Anal. Calcd for $C_{17}H_{23}O_{10}N$: C, 50.9; H, 5.8; N, 3.5. Found: C, 51.0; H, 5.9; N, 3.5.

Methyl *N*-(Carbobenzyloxy)-4-hydroxy-5-(1′,2′,3′,4′-tetrahydroxybutyl)prolinate 12. (A) The mixture of **9** (1.1 g, 2.7 mmol) and 10% Pd/C (1 g) in distilled water (150 mL) was shaken under hydrogen (60 psi) at room temperature for 20 h. The Pd/C was removed by filtration with the aid of Celite.

(B) To the filtrate, $NaHCO_3$ (0.68 g, 8.1 mmol) and benzyl chloroformate (0.5 mL, 3.2 mmol) were added subsequently at 0 °C with stirring. The mixture was warmed to room temperature and stirred overnight. It was then neutralized to pH 5–6 with 2 N HCl and washed with diethyl ether twice. The aqueous solution was freeze-dried after evaporation of dissolved diethyl ether. The solid residue was triturated with absolute ethanol (50 mL), and the insoluble material was removed by filtration.

(C) After the filtrate was concentrated to dryness, the solid residue was added to a solution of acetyl chloride (1.79 mL, 25 mmol) in dry methanol (50 mL) with stirring at room temperature. The mixture was stirred for 3 h and evaporated to dryness under vacuum at room temperature. The residue was chromatographed on silica gel, eluting with 10% methanol in ethyl acetate to give the minor isomer **12b** (71 mg, 6.6%): white powder; ^{1}H NMR (250 MHz, CD_3CN with D_2O wash) δ 7.40 (m, 5 H, aromatic), 5.10 (AB q, J = 12.0 Hz, 2 H, benzylic), 4.6–3.7 (m, 8 H), 3.60 (s, 3 H, Me), 2.55 (m, 1 H, H3′), 2.05 (m, 1 H, H3″); ^{13}C NMR (62.9 MHz, CD_3CN with D_2O wash) δ 177.0 and 176.8 (CO_2Me, splitting due to the rotamers), 159.6 (OCONH), 138.5 (aromatic C1), 131.6 (aromatic), 131.4 (aromatic C4), 130.5 (aromatic), 73.0, 72.7, 71.0 (2 C), 70.7, 69.3, 62.5, 60.1, 55.6 (Me), 37.5 (ring CH_2); MS (FAB$^+$) m/e 400 (M + H). Then the column was eluted with 25% methanol in ethyl acetate to give the major isomer **12a** (675 mg, 62%): white powder; ^{1}H NMR (250 MHz, D_2O) δ 7.10 (m, 5 H), 4.80 (AB q, J = 12.0 Hz, 2 H, benzylic), 4.4–3.3 (m, 8 H), 3.35 (s, 3 H, Me), 2.28 (m, 1 H, H3′), 1.90 (m, 1 H, H3″); ^{13}C NMR (62.9 MHz, D_2O) δ 177.0 and 176.8 (CO_2Me, splitting due to rotamers), 159.2 (OCONH), 138.4 (aromatic tertiary C), 131.3 (aromatic), 131.1 (aromatic C4), 130.3 (aromatic), 73.3, 73.1, 73.0, 71.1, 70.7, 66.3, 62.6, 59.5, 55.4 (Me), 37.4 (ring CH_2); IR 3412 s, 1744 s, 1687 s, 1419 s, 1355 s, 1177 s, 1089 s cm^{-1}; MS (FAB$^+$) m/e 400 (M + H). Anal. Calcd for $C_{18}H_{25}O_9N$: C, 54.1; H, 6.3; N, 3.5. Found: C, 54.1; H, 6.2; N, 3.4.

3-(Methoxycarbonyl)-6-epicastanospermine (14). (A) *p*-Toluenesulfonyl chloride (159 mg, 0.83 mmol) was added to a solution of **12a** (150 mg, 0.38 mmol) in dry pyridine (20 mL) at −30 to −40 °C with stirring. The mixture was warmed to 4 °C and kept at this temperature overnight. After the excess toluenesulfonyl chloride was decomposed by slow addition of methanol (0.5 mL), the pyridine was evaporated under vacuum at room temperature. The residue was purified by flash chromatography (silica gel, 10% methanol in ethyl acetate) to give the monotosylate **13** (151 mg, 72%): white powder; ^{1}H NMR (250 MHz, acetone-d_6 with D_2O wash) δ 7.70 (d, J = 8.7 Hz, 2 H, H3 on tosyl), 7.30 (d, 2 H, H2 on tosyl), 7.21 (m, 5 H, Cbz), 5.00 (AB q, J = 13.0 Hz, 2 H, benzylic), 4.52 (m, 1 H), 4.25 (m, 2 H), 4.10 (m, 1 H), 3.95 (m, 3 H), 3.50 (m, 1 H), 3.46 (s, 3 H, OMe), 2.45 (m, 1 H), 2.30 (s, 3 H, Me), 1.95 (m, 1 H); ^{13}C NMR (62.9 MHz, acetone-d_6 with D_2O wash) δ 173.2 (CO_2Me), 156.9 (OCONH), 145.5, 137.0, 134.0, 130.6, 129.1, 128.7, 128.6, 128.2, 74.2, 71.2, 70.7, 69.3, 68.9, 68.2, 60.2, 57.8, 52.5 (OMe), 36.2 ($PhCH_2O$), 21.4 (Me); IR 3418 s, 1743 s, 1684 s, 1419 s, 1356 s, 1176 s, 1090 s cm^{-1}; MS (FAB$^+$) m/e 554 (M + H). Anal. Calcd for $C_{25}H_{31}O_{11}NS$: C, 54.2; H, 5.6; N, 2.5. Found: C, 54.2; H, 5.8; N, 2.5.

(B) The monotosylate **13** (130 mg, 0.24 mmol) and sodium acetate (197 mg, 2.4 mmol) were dissolved in methanol (50 mL), and the solution was shaken in the presence of 10% Pd/C (60 mg) under hydrogen (60 psi) for 20 h. The Pd/C was removed by filtration with the aid of Celite, and the filtrate was refluxed for 10 min and concentrated to dryness. The residue was chromatographed (1- X 40-cm gravity column, 200–400-mesh Bio-Rad AG 1-X8 HCO_2^-, distilled water) to give the desired compound **14** (50 mg, 85%): white powder; ^{1}H NMR (200 MHz, D_2O) δ 4.21 (m, 1 H, H1), 3.83 (br s, 1 H, H6), 3.74 (dd, J = 9.6, 9.6 Hz, 1 H, H8), 3.62 (s, 3 H, Me), 3.37 (dd, J = 3.4 Hz, 1 H, H7), 3.12 (dd, J = 6.5, 10.6 Hz, 1 H, H3), 3.00 (dd, J = 12.2, 3.0 Hz, 1 H, H5′), 2.51 (ddd, J = 14.7 Hz, 1 H, H2′), 2.24 (d, 1 H, H5″), 2.10 (dd, 1 H, H8a), 1.72 (dd, 1 H, H2″); ^{13}C NMR (50.3 MHz, D_2O) δ 178.6 (CO_2Me), 77.8, 74.0, 71.5, 71.3, 69.9, 66.1, 56.9, 55.5, 40.4; IR 3360 s, 1719 s, 1447 m, 1327 m, 1287 m, 1238 s, 1186 m, 1087 s cm^{-1}; MS (FAB$^+$) m/e 248 (M + H).

3-(Hydroxymethyl)-6-epicastanospermine (15). A solution of **14** (20 mg, 0.08 mmol) in distilled water (5 mL) was added slowly to $NaBH_4$ (27 mg, 0.72 mmol) at 0 °C with stirring. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The mixture was cooled to 0 °C and adjusted to pH 2–3 with 2 N HCl. The water was lyophilized, and the residue was purified by flash chromatography (silica gel, 30% water in methanol) to give the starting material **14** (7.7 mg) and the product **15** (8.5 mg, 49%): white powder; ^{1}H NMR (250 MHz, D_2O) δ 4.19 (m, 1 H, H1), 3.87 (br, 1 H, H6), 3.73 (dd, J = 9.6, 9.6 Hz, 1 H, H8), 3.50 (d, J = 4.3 Hz, 2 H, CH_2OH), 3.40 (dd, J = 3.5, 1 H, H7), 3.18 (dd, J = 12.3, 3.0 Hz, 1 H, H5′), 2.6 (br, 1 H, H2′) 2.38–2.20 (m, 2 H, H3 and 5″), 2.01 (dd, J = 3.72 Hz, 1 H, H8a), 1.44 (ddd, J = 1.1 Hz, 1 H, H2″); ^{13}C NMR (50.3 MHz, D_2O) δ 78.1, 74.9, 71.7, 71.4, 70.1, 66.0, 64.9, 56.7, 39.1; IR 3354 s cm^{-1}; HRMS (CH_4, DCI/CI) calcd 220.1185 (M + H), found 220.1189.

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Supplementary Material Available: ^{1}H NMR spectra for the compounds **14** and **15** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.