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SYNTHESIS OF CASTANOSPERMINE GLUCOSIDES

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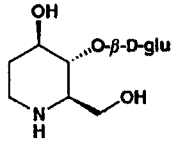
ABSTRACT: Glucosides of the indolizidine alkaloid, castanospermine, were prepared by condensation reactions employing glucosyl imidates.

Glucosides of polyhydroxylated alkaloids have been found naturally [e.g., 4-*O*-β-D-glucopyranosylfagomine (1)[1]] or synthesized [e.g., 7-*O*-β-D-glucopyranosylhomonojirimycin (2)[2], 4-*O*-α-D-glucopyranosyldeoxynojirimycin (3),[3] 4-*O*-β-D-glucopyranosyl-1,6-dideoxynojirimycin (4),[4] and D-glucopyranosylcastanospermine (5a-f)[5]]. Compounds 2, 3, and 5 are potent and selective inhibitors of intestinal sucrase and are potentially useful as therapeutic agents for the treatment of diabetes mellitus. Compound 4 is a potent inhibitor of the endocellulase E_1 from *T. fusca*.[4]



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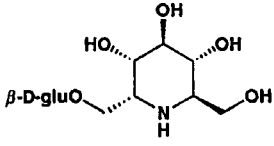

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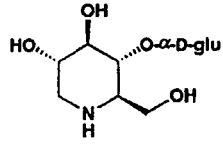

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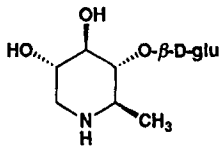

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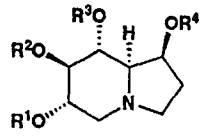
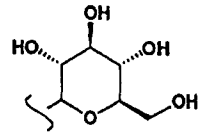


D-glu =



5a : R^1 = α-D-glu; other R's = H
5b : R^2 = α-D-glu; other R's = H
5c : R^2 = β-D-glu; other R's = H
5d : R^3 = α-D-glu; other R's = H
5e : R^3 = β-D-glu; other R's = H
5f : R^4 = α-D-glu; other R's = H

In the course of synthesizing various glucosyl derivatives of castanospermine,[5] we observed that the conventional Koenigs-Knorr procedure[6] (glucosyl halide, Lewis acid catalyst) failed to provide any appreciable amount of the glycosylated product. The difficulty of condensing amino sugars with glucosyl halide is evident from the synthesis of Carbomycin B, a mycaminose-containing antibiotic.[7] The amino group in these sugars competes with the alcohol function in the coupling process. Herein, we describe our finding that Schmidt's glycosyl imidate procedure[8] is well suited for glucosidation of the alkaloidal castanospermine.

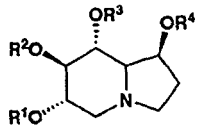
The results of the glucosidation reactions are summarized in Table. The glucosidation of 1,6,8-tri-*O*-benzoylcastanospermine (**6b**, Entry II) is given as a typical example: To a stirred cold (-20 °C) solution of 1,6,8-tri-*O*-benzoylcastanospermine (**6b**, 5.2 g, 10.4 mmol)[9] in CH_2Cl_2 (150 mL) under nitrogen was added 2,3,4,6-tetra-*O*-(benzyl)-α-D-glucopyranosyl trichloroacetimidate (**7b**, 8.5 g, 12.4 mmol)[8]. After dropwise addition of $BF_3{\cdot}Et_2O$ (3.46 g, 24.6 mmol) the reaction mixture was kept at -10 °C for 4 d. After warming to ambient temperature, the mixture was washed successively with aq. $NaHCO_3$ solution (200 mL) and brine (200 mL). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to provide a syrupy residue which was purified *via*

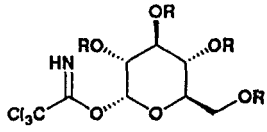
Table. Results of the Glucosidation and the Subsequent Deprotection Reactions.[10]

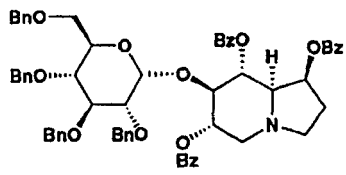
Entry	Alcohol Donor	Glucosyl Imidate	Protected Glucoside (% Yield)	Castanospermine Glucoside (% Yield)[a]
I	**6a**[11]	**7b**[8]	6-*O*-α-glucoside **8a** (35%)	**5a** (87%)
II	**6b**[9]	**7b**	7-*O*-α-glucoside **8b** (54%)	**5b** (80%)
III	**6b**	**7a**[8]	7-*O*-β-glucoside **8c** (62%)	**5c** (81%)
IV	**6c**[12]	**7b**	8-*O*-α-glucoside **8d** (15%)[b]	**5d** (65%)
			8-*O*-β-glucoside **8e** (4%)[b]	**5e** (74%)
			1-*O*-α-glucoside **8f** (4%)[b]	**5f** (65%)

[a] Compounds were obtained after the deprotection.
[b] Compounds were isolated from the product mixture of Entry IV.

preparative medium-pressure liquid chromatography (SiO_2 with 1:3 EtOAc:hexane as eluent) to provide 5.7 g (54%) of the protected 7-*O*-α-glucoside **8b** as a thick colorless syrup (R_f=0.44, SiO_2 TLC, 1:3 EtOAc:hexane). Stepwise deprotection of the glucoside **8b** with base ($KOH/H_2O/CH_3OH$) and catalytic hydrogenation (H_2, Pd/C, HOAc, 55 °C) provided 7-*O*-α-glucoside **5b** in 80% yield.







6a : R^1 = H, R^2 = Bz, R^3 = R^4 = Ac
6b : R^2 = H, R^1 = R^3 = R^4 = Bz
6c : R^3 = R^4 = H, R^1 = R^2 = Bz

7a : R = Ac
7b : R = Bn

8b

In general, moderate yields of the desired glucosides were obtained. Acetyl-protected imidate **7a** (Entry III) gave only β-glucoside in the glycosidation reaction.

Benzyl-protected imidate **7b**, however, provided α-glucoside and sometime β-glucoside as the minor product (Entry IV).

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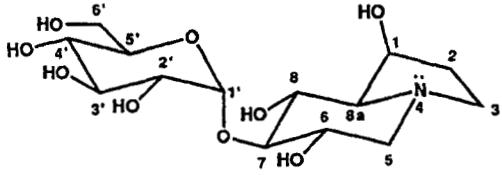
10. The spectral data (300 MHz NMR, MS, IR) obtained for all new compounds corroborate the proposed structures.
    5a: m.p. 88-90 °C (hygroscopic). ^{1}H NMR (D_2O) δ 5.03 (d, J=3.8 Hz, 1H, $H_{1'}$), 4.4 (m, 1H, H_1), 3.9 (m, 1H), 3.5-3.9 (m, 8H), 3.44 (t, J=10.0 Hz, 1H, H_7), 3.4 (m, 1H, $H_{5\beta}$), 3.1 (m, 1H, $H_{3\beta}$), 2.3 (m, 2H, $H_{2\beta}$ & $H_{3\alpha}$), 2.1 (m, 2H, H_{8a} & $H_{5\alpha}$), 1.7 (m, 1H, $H_{2\alpha}$).
    ^{13}C NMR (D_2O) δ 98.9, 79.8, 77.6, 75.7, 74.6, 74.2, 74.0, 72.4, 72.3, 71.7, 63.2, 54.9, 54.4, 35.4. MS (CI, CH_4) m/z (rel. intensity) 352 (MH^+, 16), 190 (30), 172 (100).
    5b: m.p. 207-209 °C. ^{1}H NMR (D_2O) δ 5.35 (d, J=3.9 Hz, 1H, $H_{1'}$), 4.4 (m, 1H, H_1),

3.5-3.9 (m, 8H), 3.31 (t, J=9.4 Hz, 1H, H_7), 3.2 (m, 1H, $H_{5\beta}$), 3.1 (m, 1H, $H_{3\beta}$), 2.3 (m, 2H, $H_{2\beta}$ & $H_{3\alpha}$), 2.2 (m, 1H, H_{8a}), 2.06 (t, J=10.3 Hz, 1H, $H_{5\alpha}$), 1.7 (m, 1H, $H_{2\alpha}$). ^{13}C NMR (D_2O) δ 103.6, 82.5, 81.1, 76.4, 76.0, 75.2, 73.5, 73.3, 73.2, 72.9, 63.9, 58.5, 54.9, 36.1. MS (CI, CH_4) m/z (rel. intensity) 352 (MH^+, 84), 334 (14), 190 (100), 172 (40), 154 (20), 136 (12).



5b

5c: m.p. 205-207 °C. ^1H NMR (D_2O) δ 4.69 (d, J=7.8 Hz, 1H, $H_{1'}$), 4.4 (m, 1H, H_1), 3.9 (m, 1H), 3.6-3.9 (m, 4H), 3.4-3.5 (m, 4H), 3.31 (t, J=9.4 Hz, 1H, H_7), 3.2 (m, 1H, $H_{5\beta}$), 3.1 (m, 1H, $H_{3\beta}$), 2.1-2.4 (m, 3H), 2.06 (t, J=10.3 Hz, 1H, $H_{5\alpha}$), 1.7 (m, 1H, $H_{2\alpha}$). ^{13}C NMR (D_2O) δ 105.9, 82.3, 80.9, 79.5, 79.1, 76.9, 73.7, 73.4, 73.0, 72.9, 64.1, 58.6, 55.0, 36.2. MS (CI, CH_4) m/z (rel. intensity) 352 (MH^+, 55), 334 (8), 190 (100), 172 (100), 163 (10), 154 (72), 145 (40), 136 (25).

5d: m.p. 205-207 °C. ^1H NMR (D_2O) δ 5.36 (d, J=3.9 Hz, 1H, $H_{1'}$), 4.4 (m, 1H, H_1), 3.5-3.9 (m, 8H), 3.41 (t, J=10.0 Hz, 1H, H_7), 3.2 (m, 1H, $H_{5\beta}$), 3.1 (m, 1H, $H_{3\beta}$), 2.1-2.4 (m, 3H, $H_{2\beta}$, $H_{3\alpha}$ & H_{8a}), 2.06 (t, J=11.2 Hz, 1H, $H_{5\alpha}$), 1.7 (m, 1H, $H_{2\alpha}$). ^{13}C NMR (D_2O) δ 102.8, 81.7, 80.2, 75.7, 75.2, 74.4, 72.7, 72.5, 72.4, 72.1, 63.1, 57.7, 54.1, 35.3. MS (CI, CH_4) m/z (rel. intensity) 352 (MH^+, 100), 334 (10), 190 (35), 172 (12).

5e: m.p. 198-200 °C. ^1H NMR (D_2O) δ 4.70 (d, J=8.1 Hz, 1H, $H_{1'}$), 4.5, (m, 1H, H_1), 3.9 (m, 1H), 3.6-3.8 (m, 3H), 3.4-3.5 (m, 4H), 3.30 (t, J=10.0 Hz, 1H, H_7), 3.0-3.2 (m, 2H, $H_{5\beta}$ & $H_{3\beta}$), 2.1-2.4 (m, 3H), 2.06 (t, J=11.2 Hz, 1H, $H_{5\alpha}$), 1.7 (m, 1H, $H_{2\alpha}$). ^{13}C NMR (D_2O) δ 105.2, 81.6, 80.1, 78.7, 78.4, 76.1, 72.9, 72.6, 72.2, 72.1, 63.3, 57.8, 54.2, 35.4. MS (CI, CH_4) m/z (rel. intensity) 352 (MH^+, 15), 334 (5), 190 (40), 172 (100).

5f: m.p. 120-123 °C (hygroscopic). ^1H NMR (D_2O) δ 5.02 (d, J=3.6 Hz, 1H, $H_{1'}$), 4.5 (m, 1H, H_1), 3.6-3.9 (m, 6H), 3.6 (m, 1H), 3.3-3.5 (m, 4H), 2.7 (m, 2H), 2.42 (t, J=11.2 Hz, 1H, $H_{5\alpha}$), 2.2 (m, 1H), 2.1 (m, 1H). ^{13}C NMR (D_2O) δ 96.7, 81.2, 76.0, 74.7, 74.1, 74.0, 72.8, 72.0, 71.7, 70.4, 63.0, 56.9, 54.1, 30.7. MS (CI, CH_4) m/z (rel. intensity) 352 (MH^+, 12) 190 (100) 172 (10), 154 (18), 136 (30).

11. 1,8-Di-*O*-acetyl-7-*O*-benzoylcastanospermine (**6a**) was prepared from 7-*O*-benzoyl-6-*O*-carbobenzyloxy-1,8-*O*-cyclohexylidenylcastanospermine[12] in 3 steps.

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