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Note

Synthesis of a jojoba bean disaccharide

Alexander Kornienko, Georgia Marnera, Marc d'Alarcao *

Department of Chemistry, Tufts University, Medford, MA 02155, USA

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Abstract

A synthesis of the disaccharide recently isolated from jojoba beans, 2-*O*-α-D-galactopyranosyl-D-*chiro*-inositol, has been achieved. The suitably protected *chiro*-inositol unit was prepared by an enantiospecific synthesis from L-xylose utilizing SmI_2-mediated pinacol coupling as a key step.

Keywords: *chiro*-Inositol; Jojoba beans; Glycosylation; Synthesis; Samarium diiodide

Naturally occurring galactosylcyclitols are believed to play an important role in plant physiology, particularly in seed desiccation tolerance [1]. Several of these natural products incorporate the optically active inositol isomer D-*chiro*-inositol. Examples include ciceritol (**1**) [2], galactopinitol (**2**) [3], and the disaccharide recently isolated from jojoba beans, 2-*O*-α-D-galactopyranosyl-D-*chiro*-inositol (**3**) [4].

The identification of glycosylated *chiro*-inositol in GPI protein membrane anchors [5] and the demonstration of the insulin mimetic activity of some of these compounds [6] have provided additional impetus to develop practical strategies for the synthesis of *chiro*-inositol-containing oligosaccharides [7]. However, the poor availability of differentially protected *chiro*-inositols, has impeded such efforts, and, therefore, has been addressed by several groups including ours [8]. Herein, we demonstrate the utility of our approach by applying it to the first synthesis of the disaccharide **3** from jojoba beans (Scheme 1).

Octadiene **4**, prepared in seven steps from commercially available L-xylose [8], was subjected to ozonolysis followed by SmI_2-mediated pinacol cyclization to obtain *chiro*-inositol **5** as the sole cyclitol product detected in the reaction mixture (40% from **4**). The structure of **5** was assigned by ^{1}H NMR analysis of its diacetyl derivative. The high diastereoselectivity of this cyclization is consistent with previously established patterns [8] and further demonstrates the strength of the technique. Selective *p*-methoxybenzylation of the equatorial hydroxyl group via the dibutylstannyl ester of **5** afforded **6** without any detectable amount of the axially alkylated isomer (77%). The structure of **6** was established by ^{1}H NMR analysis of its acetyl derivative. Benzylation of **6** followed by oxidative removal of the *p*-methoxybenzyl group provided acceptor **7** (59% for two steps). To confirm the assigned structures of **5** and **6** a small sample of **7** was methylated to produce the enantiomer of the previously synthesized pentabenzyl-(-)-quebrachitol (**10**) [8]. Synthetic **10** was identical to that obtained from the natural material by ^{1}H NMR.

Glycosylation of **7** was accomplished by treatment with trichloroacetimidate **8** [9] (2 equivalent) in the presence of 0.15 equivalent of Me_3SiOTf, to produce the α-disaccharide **9** in 70% yield

* Corresponding author.

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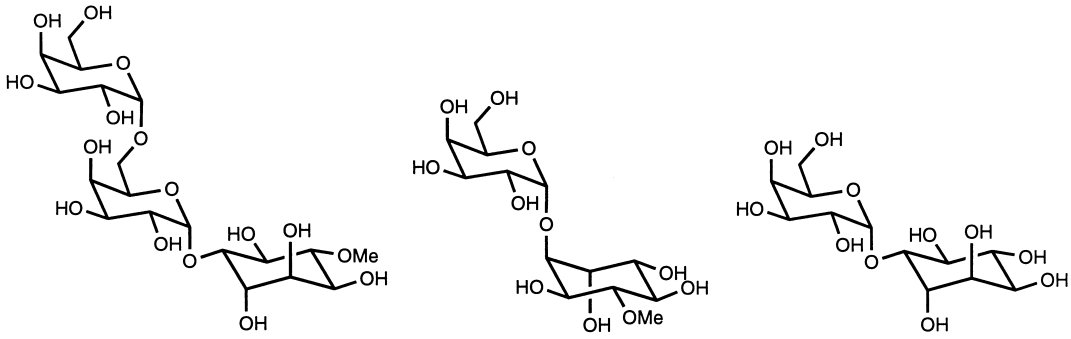
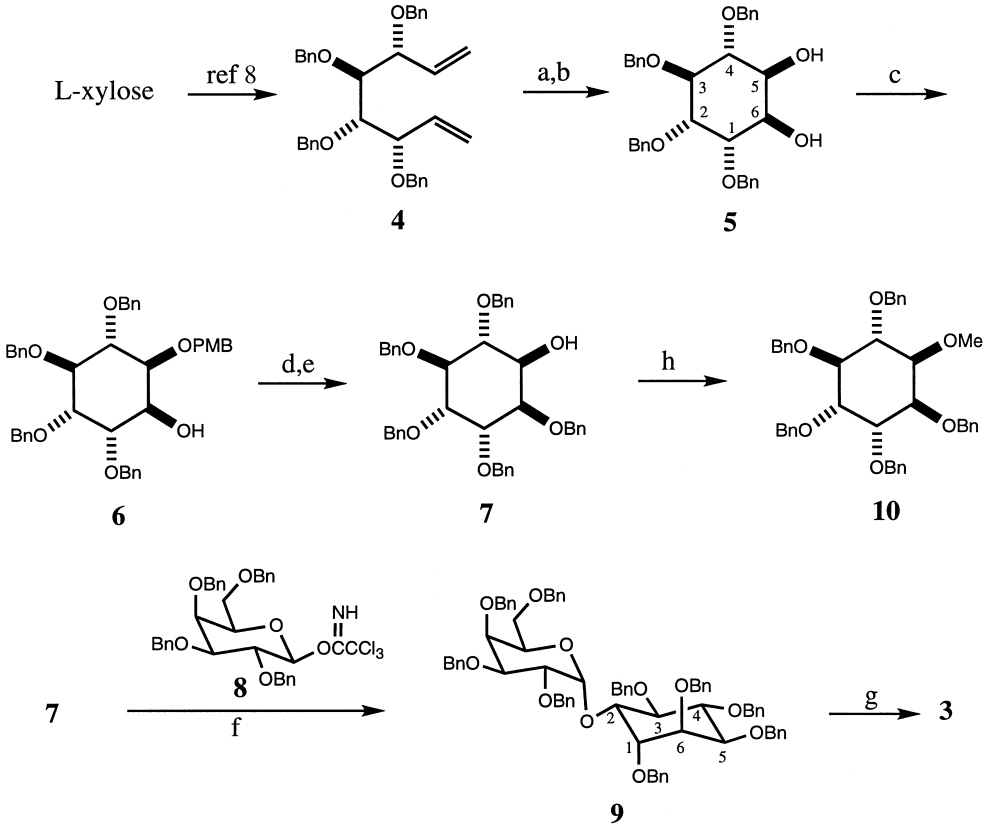


1 2 3

(together with 18% recovered **7**). No β anomer was found in the reaction mixture. Finally, hydrogenolysis afforded pure **3**. Synthetic **3** was identical to a sample of the natural material by ^1H and ^{13}C NMR.

1. Experimental

General methods.—All reactions, with the exception of ozonolysis and hydrogenolysis, were performed under an atmosphere of argon. Solvents were removed in vacuo on a Büchi rotary evaporator. Solvents and reagents obtained from commercial sources were used without further purification with the following exceptions. Tetrahydrofuran (THF) and ether were distilled prior to use from sodium benzophenone ketyl; CH_2Cl_2 was distilled from $CaSO_4$; pyridine and benzene were distilled from CaH_2; Ac_2O was fractionally distilled. Anhydrous reactions were performed with material dried by repeated coevaporation with



Scheme 1. (a) O_3, CH_2Cl_2, Py, 78 °C, 15 min; DMS, rt, 5 h; (b) SmI_2, *t*-BuOH, THF, 78°C, 3 h; (c) Bu_2SnO, benzene, reflux; PMBCl, TBABr, reflux, 45 min; (d) NaH, BnBr, DMF, 12 h; (e) DDQ, CH_2Cl_2–H_2O, rt, 1.5 h; (f) TMSOTf, ether, 78 °C, 10 min; (g) H_2 (40 psi), Pd black, THF–ethanol–H_2O, 30 h; (h) NaH, MeI, DMF, 1 h.

toluene. TLC and preparative TLC were performed using Baker glass-backed silica gel plates (0.25 mm thickness) with 254-nm fluorescent indicator. The chromatograms were visualized by (a) ultraviolet illumination and (b) dipping in the Hanes–Isherwood solution (1 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 10 mL of 1N HCl, 3 mL of $HClO_4$ in 90 mL of H_2O) followed by heating. Flash chromatography was performed on Baker silica gel (40 mesh). Ozone was generated using an ozonator purchased from Ozone Pure Water, Inc. (model 2HD). NMR spectra were recorded on a Bruker AM300 spectrometer using Me_4Si as an internal standard for ^1H in $CDCl_3$, DOH (4.65 ppm) for ^1H in D_2O, and 1,4-dioxane (67.4 ppm) for ^{13}C in D_2O. Solutions of SmI_2 were titrated with I_2 prior to use.

1,2,3,4-Tetra-O-*benzyl*-D-chiro-*inositol* (**5**).—Due to the low ozone flux of the ozonator 400 mg (0.75 mmol) of **4** were ozonolyzed in eight portions. In each case a solution containing 50 mg of **4** and 20 μL of pyridine in 3 mL of CH_2Cl_2 was treated with ozone at −78 °C until TLC (8:2 hexane–EtOAc) showed complete disappearance of the starting material (R_f 0.6), at which point 200 μL of Me_2S were added. All eight solutions were kept at rt for 5 h, pooled and treated with water (15 mL). After the separation of the organic layer the aqueous phase was extracted with additional CH_2Cl_2 (15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The residue was diluted with *t*-butanol (0.22 mL, 2.25 mmol) in THF (25 mL) and added dropwise over a period of 30 min to a cold (−78 °C) solution of SmI_2 (5.1 mmol) in THF (85 mL). The mixture was stirred for 3 h at −78 °C and then overnight at rt. Sat. $NaHCO_3$ solution (30 mL) was added and the white slurry was extracted with EtOAc (2×50 mL). The organic layer was washed with 10% $Na_2S_2O_3$ (50 mL), sat. NaCl (50 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography (7:3 hexane–EtOAc) afforded pure **5** (160 mg, 40% yield); ^1H NMR ($CDCl_3$): δ 7.4–7.22 (m, 20 H, aromatic), 5.02, 4.81 (2d, 2 H, J_{gem} 11.3 Hz, CH_2Ph), 4.99, 4.65 (2d, 2 H, J_{gem} 10.5 Hz, CH_2Ph), 4.81, 4.65 (2d, 2 H, J_{gem} 10.7 Hz, CH_2Ph), 4.72, 4.61 (2d, 2 H, J_{gem} 11.7 Hz, CH_2Ph), 4.07–3.86 (m, 5 H, CH-OR), 3.64 (ψt, 1 H, $J_{3,4}$ 9.1 Hz, H-3 or H-4), 2.31, 2.32 (2 br d, 2 OH); FAB HRMS (NBA/NaI) *m/z* 563.2434, $M+Na^+$ calcd for $C_{34}H_{36}O_6$ 563.2411. A sample of **5** (5 mg) was treated with Ac_2O (10 μL) and pyridine (0.2 mL) for 2 h at rt. After aqueous work-up, 5 mg of sufficiently pure diacetate **5** was obtained; ^1H NMR ($CDCl_3$, inositol numbering is the same as in **5**): δ 7.42–7.28 (m, 20 H, aromatic), 5.41 (ψt, 1 H, $J_{5,6}$, $J_{6,1}$ 3.6 Hz, H-6), 5.34 (dd, 1 H, $J_{4,5}$, 9.5 Hz, $J_{5,6}$ 3.6 Hz, H-5), 4.93, 4.82 (2d, 2 H, J_{gem} 10.4 Hz, CH_2Ph), 4.86, 4.70 (2d, 2 H, J_{gem} 11.6 Hz, CH_2Ph), 4.73 (s, 2 H, CH_2Ph), 4.69, 4.57 (2d, 2 H, J_{gem} 11.7 Hz, CH_2Ph), 4.04 (ψt, 1 H, $J_{2,3}$, $J_{3,4}$ 9.5 Hz, H-3), 3.79 (ψt, 1 H, $J_{3,4}$, $J_{4,5}$ 9.5 Hz, H-4), 3.72 (dd, 1 H, $J_{1,2}$ 3.6, $J_{2,3}$ 9.5 Hz, H-2), 3.70 (ψt, 1 H, $J_{6,1}$, $J_{1,2}$ 3.6 Hz, H-1), 2.00 (s, 3 H, OAc), 1.97 (s, 3 H, OAc).

1,2,3,4-Tetra-O-*benzyl-5*-O-p-*methoxybenzyl*-D-chiro-*inositol* (**6**).—A suspension of **5** (20 mg, 37 μmol) and dibutyltin oxide (10 mg, 41 μmol) in 20 mL of benzene was fitted with a distillation head and placed in an oil bath at 110 °C until most of the benzene had distilled. An additional portion of benzene (10 mL) was added to the residue and the mixture was heated until again most of the benzene had distilled. The reaction mixture was cooled and treated with *p*-methoxybenzyl chloride (7.5 μL, 55 μmol) and tetrabutylammonium bromide (13 mg, 41 μmol). The mixture was then heated at reflux for 45 min more, then $NaHCO_3$ (2 mL of 1 M solution) was added and the mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. Preparative TLC (1:1 hexanes–ether) gave 18.7 mg of **6** (77% yield); ^1H NMR ($CDCl_3$): δ 7.35–7.2 (m, 22 H, aromatic), 6.85–6.78 (d, 2 H, aromatic), 4.94–4.47 (m, 10 H, CH_2Ar), 3.94 (dd, 1 H, *J* 9.3, 8.8 Hz, H-3 or H-4), 3.95–3.90 (m, 2 H, CHOR), 3.85 (dd, 1 H, *J* 10.3, 2.6 Hz, H-2 or H-5), 3.80–3.72 (m, 2 H, CHOR), 3.79 (s, 3 H, OCH_3), 2.41 (br s, 1 H, OH); Anal calcd for $C_{42}H_{44}O_7$: C, 76.34; H, 6.71. Found: C, 75.98; H, 6.84. A solution of **6** (3.3 mg, 5 μmol) in pyridine (192 μL), was treated with Ac_2O (3.3 μL, 35 μmol). After aqueous work-up, 2.7 mg of acetylated product was obtained; ^1H NMR ($CDCl_3$, inositol numbering is the same as in **6**): δ 7.35–7.2 (m, 22 H, aromatic), 6.85–6.78 (d, 2 H, aromatic), 5.32 (ψt, 1 H, $J_{6,1}$ and $J_{5,6}$ 3.4 Hz, H-6), 4.93–4.40 (m, 10 H, CH_2Ar), 3.97–3.85 (m, 2 H, CHOR), 3.77 (s, 3 H, OCH_3), 3.78–3.68 (m, 4 H, CHOR), 2.0 (s, 3 H, OAc).

1,2,3,4,6-Penta-O-*benzyl*-D-chiro-*inositol* (**7**).—A solution of **6** (14.2 mg, 21.5 μmol) in DMF (190 μL) at 0 °C was treated with NaH (3.4 mg of a 60% oil dispersion, 86 μmol). After 0.5 h, the mixture was treated with benzyl bromide (7.7 μL, 65 μmol) and allowed to warm to room temperature.

After overnight stirring, the mixture was cooled to 0 °C, and water (1 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under diminished pressure. To the residue was added CH_2Cl_2 (544 μL), H_2O (60 μL) and DDQ (5.2 mg, 22 μmol) and the mixture was stirred at room temperature for 1.5 h. Sat. $NaHCO_3$ solution (1 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL) the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. Preparatative TLC (2:1 hexanes–ether) gave 7.9 mg of **7** (58% yield for two steps); ^{1}H NMR ($CDCl_3$): δ 7.35–7.2 (m, 25 H, aromatic), 4.96–4.29 (m, 10 H, CH_2Ph), 3.97 (dd, 1 H, *J* 3.4, 9.2 Hz, H-2 or H-5), 3.93 (dd, 1 H, *J* 9.3, 9.2 Hz, H-3 or H-4), 3.79 (dd, 1 H, *J* 2.8, 9.3 Hz, H-2 or H-5), 3.75 (dd, 1 H, *J* 3.8, 3.4 Hz, H-1 or H-6) 3.71 (dd, 1 H, *J* 3.8, 2.8 Hz, H-1 or H-6), 3.65 (dd, 1 H, *J* 9.3, 9.2 Hz, H-3 or H-4); FAB HRMS (NBA/NaI) *m/z* 653.2883, $M+Na^+$ calcd for $C_{41}H_{42}O_6$ 653.2880.

To confirm unequivocally the structure of **7**, 2.6 mg of **7** was treated with NaH (1 mg) and MeI (12 μL) in DMF (0.1 mL) for 1 h. Aqueous work-up gave 2.6 mg of **10**; ^{1}H NMR ($CDCl_3$): δ 7.5–7.12 (m, 25 H, aromatic), 4.93–4.76 (m, 5 H, CH_2Ph), 4.67, 4.48 (2d, 2 H, J_{gem} 11.8 Hz, CH_2Ph), 4.63, 4.41 (2d, 2 H, J_{gem} 12.3 Hz, CH_2Ph), 4.32 (d, 1 H, J_{gem} 12.2 Hz, CH_2Ph), 3.92–3.77 (m, 3 H, CH-OR), 3.71 (dd, 1 H, *J* 3.0, 4.0 Hz, CH-OR), 3.66 (dd, 1 H, *J* 2.7, 4.0 Hz, CH-OR), 3.55 (dd, 1 H, *J* 3.0, 9.7 Hz, CH-OR), 3.40 (s, 3 H, OCH_3).

1,3,4,5,6-Penta-O-*benzyl-2*-O-*(2,3,4,6-tetra*-O-*benzyl*-α-D-*galactopyranosyl)*-D-chiro-*inositol* (**9**).—To a cold (78 °C) solution of **7** (15 mg, 24 μmol) and **8** (35 mg, 51 μmol) in dry ether (1.5 mL) was added trimethylsilyl triflate (0.65 μL, 3.6 μmol). The mixture was stirred at 78 °C for 10 min and allowed to warm to room temperature. Sat. aqueous NH_4Cl (1 mL) was added and the mixture was extracted with ether (2×1.5 mL). The ethereal layers were combined, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by preparative TLC (4:1 hexane–EtOAc) to give 19 mg (70% yield) of pure **9** (R_f 0.5) and 2.5 mg of recovered **7** (R_f 0.3); ^{1}H NMR ($CDCl_3$) δ 7.35–7.2 (m, 43 H, aromatic), 7.0–6.96 (m, 2 H, aromatic), 5.07 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.91–4.40 (m, 18 H, CH_2Ph), 4.39–3.42 (m, 12 H, CH-OR); Anal calcd for $C_{75}H_{76}O_{11}$: C, 78.10; H, 6.64. Found: C, 77.64; H, 6.74.

2-O-α-D-*Galactopyranosyl*-D-chiro-*inositol* (**3**).—A solution of **9** (15 mg, 13 μmol) in THF–ethanol–H_2O (1:1:1) was hydrogenolyzed with Pd black (28 mg) at 40 psi for 30 h. The mixture was filtered through Celite and concentrated to produce **3** (4.4 mg, 100% yield); m.p. 140–180 °C (dec) [lit. 165–170 (dec)] [4], ^{1}H and ^{13}C NMR (D_2O) were identical of those of an authentic sample of natural **3** [4], generously provided by Professor S. Kondo.

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