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Note

Synthesis of fagopyritols A1 and B1 from D-*chiro*-inositol

M. Belén Cid,*,† Francisco Alfonso and Manuel Martín-Lomas*

Grupo de Carbohidratos, Instituto de Investigaciones Químicas, CSIC, Américo Vespucio s/n, Isla de La Cartuja, 41092 Sevilla, Spain

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Abstract—Fagopyritol A1 (3-*O*-α-D-galactopyranosyl-D-*chiro*-inositol) and fagopyritol B1 (2-*O*-α-D-galactopyranosyl-D-*chiro*-inositol) have been synthesized by glycosylation of the diequatorial diol 1,4,5,6-tetra-*O*-benzoyl-D-*chiro*-inositol, readily obtained from D-*chiro*-inositol, with 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl trichloroacetimidate.

Keywords: Regioselective glycosylation; Glycosyl inositols; Insulin mimetics

Fagopyritols (α-D-galactopyranosyl-D-*chiro*-inositols[1]) have been isolated from the seeds of buckwheat,[1] soybean,[2,3] lupin, lentil, chickpea,[4] sugar beet[5] and jojoba.[6] The first members of the family, fagopyritol A1 (3-*O*-α-D-galactopyranosyl-D-*chiro*-inositol (**1**)[7] and fagopyritol B1 (2-*O*-α-D-galactopyranosyl-D-*chiro*-inositol (**2**),[8] constitute almost 50% of the total soluble carbohydrate of buckwheat embryos (Fig. 1). Higher members, fagopyritols A2, A3, B2 and B3, contain additional α-D-galactopyranosyl units (one in the case of fagopyritols A2 and B2 and two in the case of fagopyritols A3 and B3) elongating the α-D-galactopyranosyl-D-*chiro*-inositol cores.[1]

Substantially pure fagopyritols or mixtures prepared from buckwheat seeds have been reported to lower blood glucose levels.[9] A similar effect has been observed for D-*chiro*-inositol.[10] It is believed that the fagopyritols are digested by bacteria in the digestive tract to release D-*chiro*-inositol for uptake.[7] On the other hand, these fagopyritols present certain structural similarities with the D-*chiro*-inositol containing inositol phosphoglycans (IPGs), which have been proposed as insulin mediators.[11,12] These putative second messengers are thought to be composed of a cyclitol residue, either

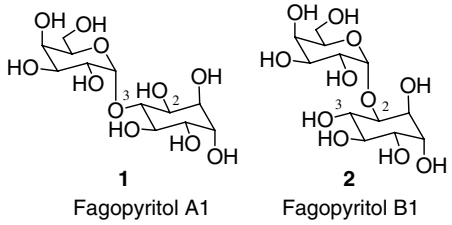

Figure 1.

myo or *chiro* inositol, an aminosugar unit and a glycan chain and could be generated from inositol containing glycolipids through the action of receptor activated phospholipases.[13]

We report in this paper a straightforward synthesis of fagopyritols A1 and B1 starting from D-*chiro*-inositol. A previous synthesis of fagopyritol B1 has been published in which the cyclitol ring was prepared from L-xylose using SmI_2-mediated pinacol coupling.[14]

As a part of a programme on insulin mediators[15] we have synthesized several α and β-D-glucosaminyl and D-galactosaminyl-D- and L-*chiro*-inositols.[16–18] In the course of these studies it was found that 1,4,5,6-tetra-*O*-benzoyl-L-*chiro*-inositol (**3**) could be readily prepared from L-*chiro*-inositol. The glycosylation of **3** with 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-gluco and galactopyranosyl trichloroacetimidates afforded the corresponding 3-*O*-glycopyranosyl derivatives with good regio and stereoselectivity.[18] (Fig. 2). A similar reaction

* Corresponding authors. Tel.: +34-95-4489553; fax: +34-95-4460565; e-mail: manuel.martin-lomas@iiq.csic.es
† Present address: Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain.

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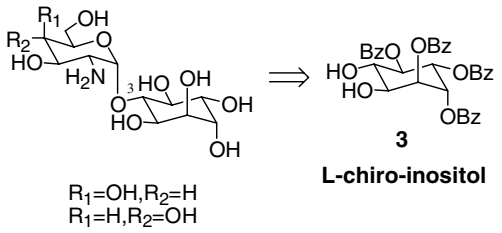


Figure 2.

sequence in the D-*chiro* series using suitable D-galactopyranosyl donors may lead to **1** should the regioselectivity of the glycosylation of the diequatorial D-*chiro* configurated diol (**4**) with these donors be conserved.

Therefore, 1,4,5,6-tetra-*O*-benzoyl-D-*chiro*-inositol (**4**) was prepared using the same protocol previously reported for the L-enantiomer.[18] Contrary to expectations, reaction of **4** with 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl trichloroacetimidate (**5**)[19] under the conditions already optimized for the regio and stereoselective glycosylation of **3**[18] (ethyl ether, TMSOTf, −40 to −5 °C, 1 h) gave a mixture of the α(1→2) (**6**, 27%), β(1→2) (**7**, 9%) and α(1→3) (**8**, 17%) pseudodisaccharides (Scheme 1). When the reaction was performed at −78 °C, pseudodisaccharide **6** was isolated in 66% yield as the only glycosylation product. The structures of **6**, **7** and **8** were unequivocally assigned by means of 2D NMR spectroscopy (COSY, HMQC) by identifying the proton coupled to the free hydroxyl group and confirming the downfield shift of the carbon bearing the glycosidic moiety.

These results are difficult to rationalize since the presently available data do not permit an evaluation of the relative importance of the various factors, which may influence the regio and the stereochemical outcome of these glycosylation reactions. It is worthwhile to remark, however, that under identical experimental conditions, the regiochemistry of this glycosylation is reversed as compared to that observed in our previous work.[18] Using an acceptor diol belonging to the D-series (**4**) and a donor lacking the 2-azido functionality (**5**) have an important effect on the subtle reactivity–selectivity balance of these reactions reversing the observed regioselectivity of the glycosylation. It is also important to notice that no transbenzoylation processes were detected to occur in the glycosylation conditions either in this or in the previously studied glycosylation of diol **3**.

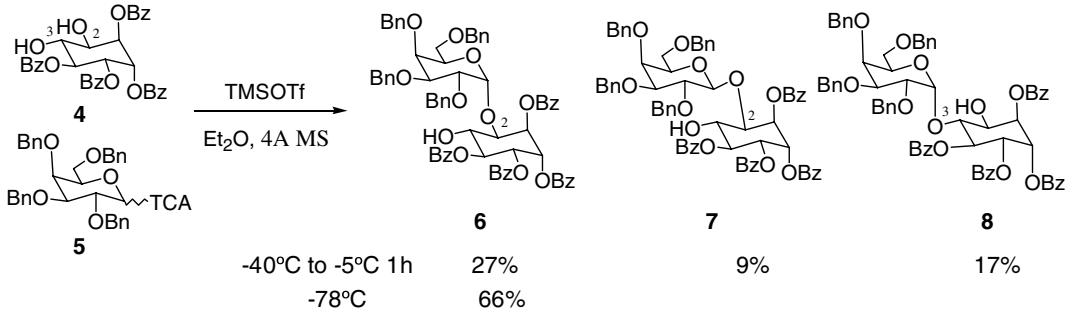
Conventional debenzoylation of **6** and **8** gave the intermediates **9** and **10**, which were submitted to catalytic hydrogenolysis to afford fagopyritol B1 (**2**) and fagopyritol A1 (**1**), respectively, in quantitative yield (Scheme 2). The ^{1}H and ^{13}C NMR spectra of **1** and **2** corresponded to those reported for natural samples of fagopyritol A1 and fagopyritol B1, respectively.[6,7] However, it should be noticed that the $[\alpha]_D$ value found for synthetic **2** was +39.0 while that reported for the natural compound isolated from jojoba beans was +130.[7]

Further studies on the factors, which govern the regiochemical outcome of these glycosylation reactions are presently in progress. The reported results constitute a simple and ready access to pure synthetic samples of both fagopyritols for biological testing.

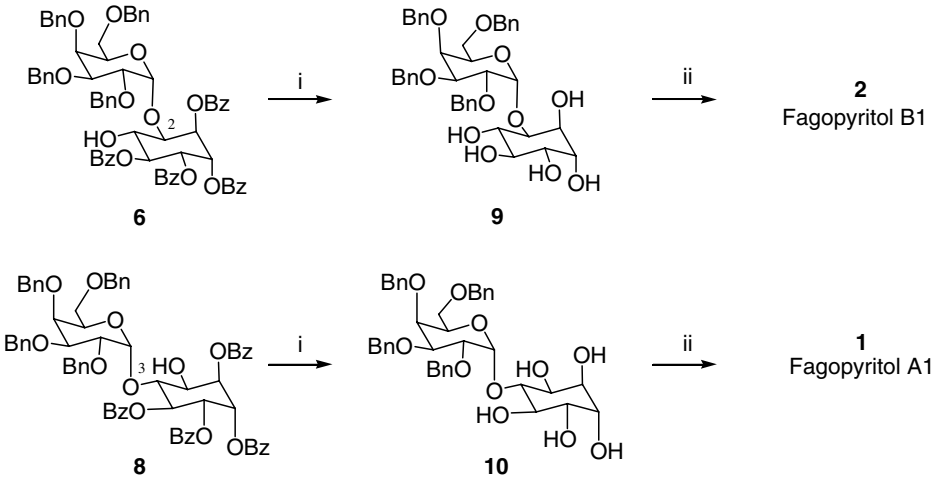
1. Experimental

1.1. General methods

Dichloromethane was distilled from calcium hydride and diethyl ether from sodium/benzophenone. D-*chiro*-Inositol was provided by New Zealand Pharmaceuticals Limited (NZP). Molecular sieves (4 Å, powdered) were dried in an oven and activated for 5 min under vacuum at 300 °C. All aqueous (aq) solutions were saturated unless otherwise stated. All reactions were carried out under argon in dried glassware. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on Bruker Avance DRX500 (^{1}H, 500 MHz) spectrometers. Chemical shifts are given in ppm (δ) relative to tetramethylsylane as an internal reference. Signals were assigned by means of 2D spectra (COSY, HMQC). Microanalyses were determined in a Leco CHNS-932 apparatus. Optical rotations were measured with an optical activity Perkin–Elmer 341 polarimeter. Purifications by column chromatography



Scheme 1.



Scheme 2. Reagents and conditions: (i) MeONa/MeOH 1 M, MeOH/THF, rt, 10 min, quantitative; (ii) H_2 Pd/C, EtOH/MeOH/H_2O, rt, overnight, quantitative.

were carried out under pressure with Merck silica gel 60 (15–200 mesh). Chromatography eluents are given as volume ratios (v/v). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel $60F_{254}$ with detection by charring with oleum.

1.2. 1,4,5,6-Tetra-*O*-benzoyl-D-*chiro*-inositol (4)

This compound was prepared from D-*chiro*-inositol following the experimental procedure previously reported for the L-enantiomer (**3**).[18] $[\alpha]_D^{20}$ +68.0 (*c* 0.7, $CHCl_3$).

1.2.1. 2,3,4,6-Tetra-*O*-benzyl-D-galactopyranosyl-α(1→2)-1,4,5,6-tetra-*O*-benzoyl-D-*chiro*-inositol (6), 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl-β(1→2)-1,4,5,6-tetra-*O*-benzoyl-D-*chiro*-inositol (7) and 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl-α(1→3)-1,4,5,6-tetra-*O*-benzoyl-D-*chiro*-inositol (8). Toluene was evaporated three times from a mixture of 1,4,5,6-tetra-*O*-benzoyl-D-*chiro*-inositol (**4**) (52 mg, 0.087 mmol, 1 equiv) and 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-trichloroacetimidate (59 mg, 0.087 mmol, 1 equiv) and the residue was dried under vacuum overnight. Freshly activated 4 Å molecular sieves and diethyl ether (2 mL) were added under argon and the mixture was stirred for 15 min at room temperature. A solution of TMSOTf in diethyl ether (0.1 M, 70 μL, 0.08 equiv) was added at −40 °C and the reaction mixture was stirred for 1 h allowing to reach −5 °C. The suspension was quenched with Et_3N and the solvent evaporated under vacuum to give a residue that was purified by flash chromatography (hexane/EtOAc 6:1–2:1) to obtain pseudodisaccharides **6** (26 mg, 27%), **7** (9 mg, 9%) and **8** (17 mg, 17%).

When the reaction was carried out at −78 °C for 1 h, the α(1→2) pseudodisaccharide **6** was obtained as the only product (34 mg, 66%).

Data for the α(1→2) pseudodisaccharide (**6**): $[\alpha]_D^{20}$ +46.7 (*c* 1.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 8.01–7.77 (4H*ortho*, 8H); 7.60–7.10 (m, 20H, 4Bn and 12H, 4Bz); 5.96 (t, 1H, J = 10.3 Hz, H_4); 5.94–5.91 (m, 2H, H_6 and H_1); 5.82 (dd, 1H, J = 10.4 and 2.7 Hz, H_5); 5.04 (d, 1H, J = 3.6 Hz, $H_{1'}$); 4.85–4.30 (4 AB syst, 8H); 4.39 (br t, 1H, J = 9.5 Hz, H_3); 4.15 (dd, 1H, J = 9.5 and 2.7 Hz, H_2); 4.06 (t, 1H, J = 6.4 Hz, $H_{5'}$); 3.98 (dd, 1H, J = 9.9 and 3.6 Hz, $H_{2'}$); 3.80 (br d, 1H, J = 3.6 Hz, OH_3); 3.71 (dd, 1H, J = 9.9 and 3.6 Hz, $H_{3'}$); 3.67 (br s, 1H, $H_{4'}$); 3.43 (dd, 1H, J = 9.9 and 7.5 Hz, $H_{6a'}$) and 3.23 (dd, 1H, J = 9.3 and 5.1 Hz, $H_{6b'}$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 165.8, 165.0 and 165.0 (4CO), 138.9, 138.8, 138.7 and 137.9 (4C, Bn), 134.0, 133.8, 133.5 and 133.4 (4CH*para*), 130.1–127.8 (20CH, Bn and 16CH, Bz), 129.9, 129.7, 129.3 and 129.2 (4C, Bz), 98.1 ($C_{1'}$), 78.8 (CH), 78.4 (C_2), 76.7 (CH), 75.4 (CH), 74.8 (CH_2), 73.8 (CH_2), 73.7 (CH_2), 73.6 (CH_2), 72.4 (CH), 71.5 (CH), 70.9 (CH), 70.4 (CH), 69.5 (CH_2), 69.2 (CH) and 68.9 (CH). Anal. Calcd for $C_{68}H_{62}O_{15}$+$2H_2O$: 70.74% C and 5.64% H. Found: 70.74% C and 5.64% H.

Data for the β(1→2) pseudodisaccharide (**7**): $[\alpha]_D^{20}$ +20.2 (*c* 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 8.13–7.77 (4H*ortho*, 8H); 7.60–7.20 (m, 20H, 4Bn and 12H, 4Bz); 5.97 (t, 1H, J = 3.6 Hz, H_6); 5.88 (t, 1H, J = 10.4 Hz, H_4); 5.72 (t, 1H, J = 3.7 Hz, H_1); 5.69 (dd, 1H, J = 10.6 and 3.5 Hz, H_5); 4.78 (d, 1H, J = 7.9 Hz, $H_{1'}$); 4.86–4.29 (4 AB syst, 8H); 4.29–4.23 (m, 2H, H_2 and H_3); 3.87 (d, 1H, J = 2.7 Hz, $H_{4'}$); 3.82 (dd, 1H, J = 9.7 and 7.9 Hz, $H_{2'}$); 3.72 (s, 1H,

OH_3) and 3.54–3.45 (m, 4H, 2$H_{6'}$, $H_{5'}$ and $H_{3'}$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 165.7, 165.1 and 165.0 (4CO), 138.8, 138.4, 138.2 and 138.1 (4C, Bn), 133.9, 133.9, 133.7 and 133.4 (4CH*para*), 130.3–127.8 (20CH, Bn and 16CH, Bz), 129.9, 129.9, 129.4 and 129.2 (4C, Bz), 104.7 ($C_{1'}$), 82.8 (CH), 79.9 (CH), 79.2 (C_2), 76.2 (CH_2), 74.9 (CH_2), 73.9 (CH), 73.8 (CH_2), 73.5 (CH), 72.7 (CH_2), 72.5 (CH), 71.9 (CH), 71.2 (CH), 70.2 (CH), 68.7 (CH) and 68.5 (CH_2); Anal. Calcd for $C_{68}H_{62}O_{15}$: 72.97% C and 5.58% H. Found: 72.89% C and 5.55% H.

Data for the α(1→3) pseudodisaccharide (**8**): $[\alpha]_D^{20}$ + 37.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13–7.77 (4H*ortho*, 8H); 7.60–7.10 (m, 20H, 4Bn and 12H, 4Bz); 6.12 (t, 1H, *J* = 10.3 Hz, H_4); 5.91 (t, 1H, *J* = 3.5 Hz, H_6); 5.84 (dd, 1H, *J* = 10.4 and 3.5 Hz, H_5); 5.75 (t, 1H, *J* = 3.5 Hz, H_1); 4.96 (d, 1H, *J* = 3.6 Hz, $H_{1'}$); 4.85–4.10 (4 AB syst, 8H); 4.38 (m, 1H, $H_{5'}$); 4.34–4.30 (m, 2H, H_2 and H_3); 3.92 (dd, 1H, *J* = 10.4 and 2.9 Hz, $H_{3'}$); 3.86 (dd, 1H, *J* = 10.2 and 3.6 Hz, $H_{2'}$); 3.79 (s, 1H, $H_{4'}$); 3.39 (dd, 1H, *J* = 9.5 and 7.8 Hz, $H_{6'a}$) and 3.19 (dd, 1H, *J* = 9.5 and 4.4 Hz, $H_{6'b}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 165.8, 165.3 and 165.1 (4CO), 139.1, 138.7, 138.5 and 137.7 (4C, Bn), 133.9, 133.9, 133.5 and 133.3 (4CH*para*), 130.4–127.8 (20CH, Bn and 16CH, Bz), 130.3, 129.6, 129.4 and 129.3 (4C, Bz), 99.6 ($C_{1'}$H), 80.9 (C_3), 79.2 (CH), 76.0 (CH), 75.4 (CH), 74.7 (CH_2), 73.9 (CH_2), 73.7 (CH_2), 73.3 (CH_2), 71.3 (C_2), 71.1 (CH), 70.9 (CH), 70.6 (CH), 69.9 (CH_2), 69.8 (CH) and 68.8 (CH). Anal. Calcd for $C_{68}H_{62}O_{15}$+5H_2O: 67.60% C and 5.49% H. Found: 67.69% C and 5.49% H.

1.2.2. 2,3,4,6-Tetra-*O*-benzyl-D-galactopyranosyl-α(1→2)-D-*chiro*-inositol (9). To a solution of **6** (16.1 mg, 0.014 mmol) in a mixture of dry methanol and THF (8:1) (2 mL), MeONa in MeOH (0.5 mL, 1 M) was added at room temperature. The solution was stirred for 30 min, whereupon it was quenched with Amberlite IR-120H^+ resin. The solvent and the liquid BzOMe were removed by heating at 50 °C under vacuum to give **9** (10 mg, quantitative); $[\alpha]_D^{20}$ + 72.0 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, MeOD): δ = 7.40–7.20 (m, 20H, 4Bn); 4.99 (d, 1H, *J* = 3.6 Hz, $H_{1'}$); 4.85–4.40 (4 AB syst, 8H); 4.41 (m, 1H, $H_{5'}$); 4.10–4.05 (m, 2H, $H_{3'}$ and $H_{4'}$); 4.04 (t, 1H, *J* = 3.3 Hz, H_1); 4.01 (dd, 1H, *J* = 9.9 and 3.6 Hz, $H_{2'}$); 3.94 (t, 1H, *J* = 3.4 Hz, H_6); 3.76 (dd, 1H, *J* = 9.5 and 3.2 Hz, H_2); 3.67 (dd, 1H, *J* = 9.6 and 3.3 Hz, H_5); 3.64 (t, 1H, *J* = 9.3 Hz, H_3); 3.56 (t, 1H, *J* = 9.3 Hz, H_4); and 3.54–3.52 (m, 2H, 2$H_{6'}$); ^{13}C NMR (125 MHz, MeOD): δ = 138.3, 138.2, 137.6 and 137.5 (4C, Bn), 127.8–126.8 (20CH, Bn), 95.0 ($C_{1'}$), 78.3 (CH), 77.3 (CH), 75.8 (CH), 74.6 (CH), 74.2 (CH_2), 73.2 (CH_2), 72.7 (CH), 72.4 (CH_2), 71.8 (CH_2), 71.4 (CH), 71.0 (CH), 70.5 (CH), 68.7 (CH), 68.5 (CH) and 67.9 (CH_2); Anal. Calcd for $C_{40}H_{46}O_{11}$: 68.36% C and 6.59% H. Found: 68.35% C and 6.60% H.

1.2.3. 2,3,4,6-Tetra-*O*-benzyl-D-galactopyranosyl-α(1→3)-D-*chiro*-inositol (10). This compound has been prepared from **8** (16.1 mg, 0.014 mmol) following the same experimental procedure described for the preparation of (**9**). Compound **10** was obtained in quantitative yield (10 mg). $[\alpha]_D^{20}$ + 24.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 20H, 4Bn); 4.93 (d, 1H, *J* = 3.9 Hz, $H_{1'}$); 4.90–4.13 (4 AB syst, 8H); 4.13 (m, 2H, H_6 or H_1 and $H_{5'}$); 4.09 (br t, 1H, *J* = 3.3 Hz, H_6 or H_1); 4.07 (dd, 1H, *J* = 9.8 and 3.7 Hz, $H_{2'}$); 3.93 (dd, 1H, *J* = 9.9 and 3.6 Hz, $H_{3'}$); 3.87–3.80 (m, 3H, 2$H_{6'}$, $H_{4'}$ and H_2 or H_5); 3.56–3.49 (m, 2H, H_4 and H_3); 3.22 (dd, 1H, *J* = 9.5 and 3.4 Hz, H_2 or H_5) and 2.78 (br s, 5H, 5O*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.2, 138.1, 137.4 and 137.3 (4C, Bn), 128.6–127.5 (20CH, Bn), 99.1 ($C_{1'}$), 79.6 (CH), 75.9 (CH), 74.6 (CH_2), 74.5 (CH_2), 74.5 (CH), 73.6 (CH_2), 72.8 (CH_2), 71.5 (CH), 71.2 (CH), 71.1 (CH), 70.9 (CH), 70.7 (CH), 69.7 (CH_2), 69.2 (CH) and 67.5 (CH); Anal. Calcd for $C_{40}H_{46}O_{11}$: 68.36% C and 6.59% H. Found: 68.33% C and 6.54% H.

1.2.4. D-Galactopyranosyl-α(1→2)-D-*chiro*-inositol. Fagopyritol B1 (2). A slurry of compound **9** (10 mg, 0.014 mmol) and Pd/C 10% in MeOH/EtOH/water 10:3:1 (2 mL) was saturated with a stream of H_2 for 30 min, and stirred under H_2 overnight. The reaction mixture was filtrated through Celite and the solvent evaporated to give 5 mg of **2** (quantitative). $[\alpha]_D^{20}$ + 39.0 (*c* 0.3, H_2O). ^{1}H NMR (500 MHz, D_2O): δ = 4.94 (d, 1H, *J* = 3.8 Hz, $H_{1'}$); 4.06–4.02 (m, 2H, $H_{5'}$ and H_1), 3.88 (t, 1H, *J* = 3.4 Hz, H_6); 3.84 (d, 1H, *J* = 2.7 Hz, $H_{4'}$); 3.78 (dd, 1H, *J* = 10.3 and 3.7 Hz, $H_{3'}$); 3.68 (dd, 1H, *J* = 10.2 and 3.8 Hz, $H_{2'}$); 3.61 (dd, 1H, *J* = 9.7 and 3.3 Hz, H_5); 3.64 (dd, 1H, *J* = 9.5 and 3.2 Hz, H_2); 3.55 (m, 2H, $H_{6'}$); 3.54 (t, 1H, *J* = 9.5 Hz, H_3) and 3.45 (t, 1H, *J* = 9.6 Hz, H_4). ^{13}C NMR (125 MHz, D_2O): δ = 95.2, 75.1, 72.3, 70.8, 70.6, 70.4, 70.0, 68.9, 68.8, 67.7, 67.3 and 60.5. Anal. Calcd for $C_{12}H_{22}O_{11}$: 42.10% C and 6.47% H. Found: 42.08% C and 6.44% H.

1.2.5. D-Galactopyranosyl-α(1→3)-D-*chiro*-inositol. Fagopyritol A1 (1). This compound has been prepared from **10** (16.1 mg, 0.014 mmol) following the same experimental procedure described for the preparation of **2** to yield 10 mg of **1** (quantitative). $[\alpha]_D^{20}$ + 57.5 (*c* 0.4, H_2O); ^{1}H NMR (500 MHz, D_2O): δ = 5.17 (d, 1H, *J* = 3.9 Hz, $H_{1'}$); 4.08 (t, 1H, *J* = 6.1 Hz, $H_{5'}$), 3.87–3.81 (m, 3H, $H_{4'}$, H_6 and H_1); 3.74 (dd, 1H, *J* = 10.4 and 3.3 Hz, $H_{3'}$); 3.69–3.66 (m, 2H, $H_{2'}$ and H_2); 3.62 (m, 2H, H_4 and H_5) and 3.57–3.53 (m, 3H, 2$H_{6'}$ and H_3). ^{13}C NMR (125 MHz, D_2O): δ = 99.1, 80.6, 72.4, 71.3, 70.9,

70.6, 69.8, 69.0, 68.8, 68.7, 68.3 and 60.6. Anal. Calcd for $C_{12}H_{22}O_{11}$: 42.10% C and 6.47% H. Found: 42.13% C and 6.48% H.

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