A Short and Efficient Synthesis of 1,5-Dideoxy-1,5-imino-D-galactitol (1-deoxy-D-Galactostatin) and 1,5-Dideoxy-1,5-imino-L-altritol (1-deoxy-L-Altrostatin) from D-Galactose

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Received 16 February 1999

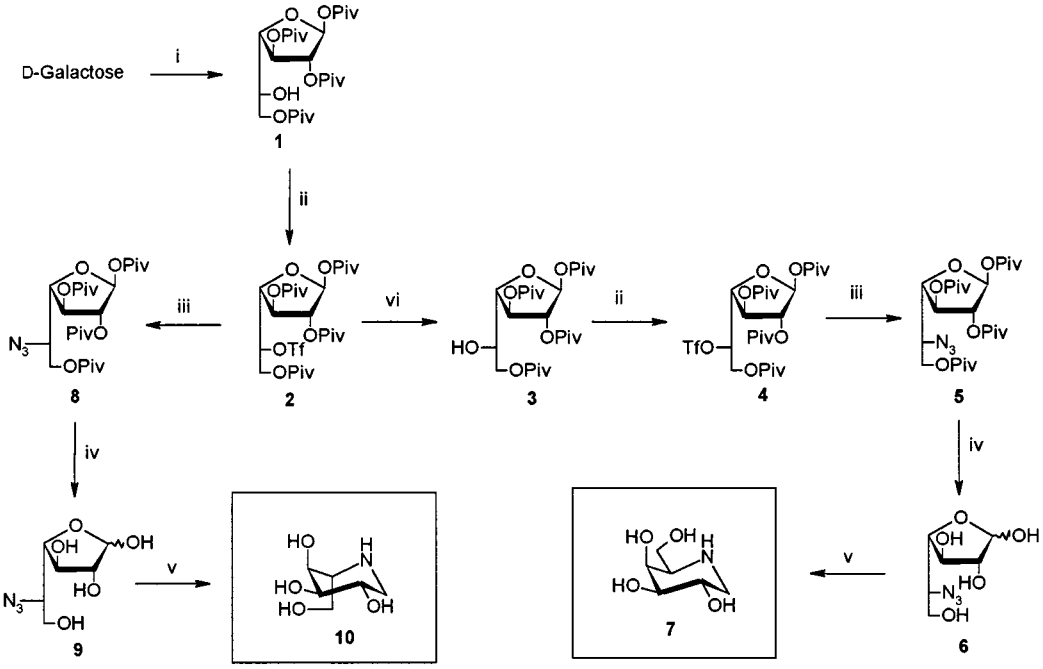
Abstract: A short and efficient route is described for the synthesis of 1-deoxy-D-galactostatin and 1-deoxy-L-altrostatin starting from D-galactose.

Key words: galactostatin, altrostatin, azasugars, galactose, triflation

Polyhydroxypiperidines (also called azasugars, amino sugars or imino alditols) are sugar analogues in which an NH group replaces the oxygen ring. They have become increasingly important targets since they have been shown to possess potent glycosidase inhibitory activity[1-7] and thus have the potential of becoming useful agents for the treatment of several diseases[8-13] such as cancer, viral infections (HIV), inflammation or disorders related to carbohydrate metabolism (diabetes). There is, in fact, considerable efforts in either chemical or enzymatic synthetic procedures to synthesise natural azasugars and their unnatural analogues.

(+)-Galactostatin (also named galacto-nojirimicin or 1,5-imino-D-galactitol) is a natural product isolated[14] from the culture broth of *Streptomyces lydicus PA-5725* and it has been reported to be a potent and specific inhibitor of several α- and β-galactosidases. Its reduced product, 1-deoxy-D-galactostatin (1,5-dideoxy-1,5-imino-D-galactitol) is also a strong galactosidase inhibitor[14-17].

Different strategies have been described for the synthesis of (+)-galactostatin using D-glucose[15], L-tartaric acid[18], L-serine[19], D-serine[20], L-quebrachitol[21] and (+)-diethyl tartrate[22] as starting materials. On the other hand, the first reported synthesis of (+)-deoxygalactostatin started from 1,6-anhydro-α-D-galactofuranose[23]. In addition, it has also been synthesised from D-glucose[15], L-tartaric acid[18], L-quebrachitol[21], benzene[24], L-arabino-hexos-5-ulose[25], 5-azido-1,4-lactones[26], methyl α-D-galactopyranose[16], deoxynojirimicin[27], *N*-acetylglucosamine-derived tetrazole[28] and by enzymatic synthesis[29].



(i) Piv-imidazole, DMF, 60°C, 24h (ii) Tf_2O, Py, CH_2Cl_2 (iii) NaN_3, DMF (iv) NaOMe, MeOH (v) H_2/Pd, MeOH, 12h (vi) $NaNO_2$, DMF

This paper reports the synthesis of 1-deoxy-galactostatin **7** and its L-altro analogue **10** from D-galactose in seven and five steps, respectively, with good overall yields. We envisaged the synthesis of these azasugars from the partly protected galactofuranoside derivative **1**, that is easily obtained in one step from D-galactose following the methodology previously described by us[30], by reaction with *N*-pìvaloyl imidazole. Compound **1**, having the hydroxyl group at C-5 unprotected, allows easy access to the 5-azido-5-deoxy-D-galacto and L-altro derivatives.

For the synthesis of 1-deoxy-L-altrostatin **10** we have followed the route summarised in Scheme 1. Triflation of the free 5-OH group of compound **1** gave **2**[31] in quantitative yield. Subsequent treatment with sodium azide in DMF led to the 5-azido-L-altrofuranose derivative **8**[32] in 85% yield. Removal of the pivaloyl groups from **8** was accomplished by using NaOMe in MeOH (Zémplen conditions) affording 5-azido-5-deoxy-L-altrofuranose **9**[33] in 90% yield[34]. Catalytic hydrogenation of this compound in the presence of palladium black in methanol gave the piperidine derivative **10**[35] in quantitative yield.

For the synthesis of the potent inhibitor 1-deoxy-D-galactostatin **7** a similar approach to that described above could be used but a previous inversion of the configuration at C-5 in **1** is needed. This inversion was achieved by treatment of the triflate derivative **2** with sodium nitrite in DMF affording the L-altro derivative **3**[36] in 55% yield from **1**. Compound **4**[37] was obtained in quantitative yield by reaction of **3** with triflic anhydride-pyridine. Treatment of **4** with sodium azide in DMF gave the 5-azido-5-deoxy-D-galactofuranose derivative **5**[38] in 75% yield. De-*O*-pivaloylation of this compound using NaOMe in MeOH gave **6**[39] (97%) which was hydrogenated under the same conditions as used for **8** leading to the expected 1-deoxy-D-galactostatin **7**[40] being isolated as a hygroscopic solid in quantitative yield.

Acknowledgement

We thank the Comisión Asesora de Investigación Científica y Técnica for financial support (Proyect nº PB97/1207).

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(31) Trific anhydride (0.41 ml, 2.48 mmol) in anhydrous CH_2Cl_2 (5 ml) was added to a solution of pyridine (1.25 ml, 15.5 mmol) in anhydrous CH_2Cl_2 and the solution was stirred under N_2 at 15ºC. After 15 min., a solution of **1** (1.63 gr, 3.1 mmol) in anhydrous CH_2Cl_2 was added, and stirring was continued for 45 min., the temperature being allowed to rise gradually to 0ºC. After this time, TLC (hexane-AcOEt, 7:3) showed complete disappearance of the starting material. CH_2Cl_2 (100 ml) was added and the solution washed successively with 5% HCl solution (100 ml), aq satd $NaHCO_3$ solution (100 ml) and H_2O (50 ml). The organic phase was dried (Na_2SO_4) and evaporated to give **2** that could be used without purification for the next step.^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18, 1.20, 1.22, 1.24 (4 s, 36H, 4 C(CH_3)$_3$), 4.11 (dd, 1H, *J* = 13.1 and *J* = 6.6 Hz, H-6), 4.30 (t, 1 H, *J* = 7.2 Hz, H-4), 4.53 (dd, 1 H, *J* = 13.1 and 2.8 Hz, H-6'), 5.14 (m, 1 H, H-5), 5.46 (dd, 1 H, *J* = 7.2 and 4.3 Hz, H-2), 5.55 (t, 1 H, *J* = 7.2 Hz, H-3), 6.40 (d, 1 H, *J* = 4.3 Hz, H-1)
(32) Compound **2** (2.5 g, 3.86 mmol) was dissolved in anhydrous DMF (50 ml) and then NaN_3 (1.75 g, 27 mmol) was added. After 2h the solution was diluted with Et_2O (150 ml) and toluene (50 ml) and washed with water (150 ml). The aqueous layer was extracted three times with Et_2O-toluene (150:50 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude product was purified by column chromatography using hexane-ether, 9:1 to give **8** (1.77 g, 85%); mp 62-64 ºC; $[\alpha]_D$+21º (*c* 0.13, chloroform)**.** ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.14, 1.16, 1.18, 1.20 (4 s, 36 H, 4C(CH_3)$_3$), 3.74 (dt, 1 H, *J* = 7.6 and 3.2 Hz, H-5), 3.99 (t, 1 H, *J* = 7.4 Hz, H-4), 4.03 (dd, 1 H, *J* = 11.7 and

7.6 Hz, H-6), 4.29 (dd, 1 H, *J* = 11.7 and 3.2 Hz, H-6'), 5.33 (dd, 1 H, *J* = 7.3 and 4.7 Hz, H-2), 5.63 (t, 1 H, *J* = 7.3 Hz, H-3), 6.29 (d, 1 H, *J* = 4.7 Hz, H-1). ^{13}C NMR($CDCl_3$, 300 MHz): δ 26.8, 26.9, 27.0, 27.1 (4 C(*C*H_3)$_3$), 62.8 (C-5), 63.6 (C-6), 74.4, 75.2, 78.6 (C-2, 3, 4), 93.7 (C-1), 176.4, 176.9, 177.0, 177.7 (4 CO). Anal. Calcd. for $C_{26}H_{43}N_3O_9$: C, 57.64; H, 8.01. Found: C, 57.88; H, 8.27.

(33) A solution of **8** (800 mg, 1.48 mmol) in 0.1M NaOMe in MeOH (10 ml) was stirred for 12h at room temperature. The solution was diluted with MeOH, neutralised with Amberlite IR-120 (H^+) filtered and evaporated. The crude was purified by column chromatography (CH_2Cl_2-MeOH, 9:1) to give **9** (272 mg, 90%) isolated as a syrup.^{1}H NMR (D_2O, 300 MHz) selected signals: δ 5.26 (d, 1 H, *J* = 2.6 Hz, H-1), 5.28 (d, 1 H, *J* = 4.7 Hz, H-1).^{13}C NMR (D_2O, 300 MHz): δ 63.4 (C-6), 66.9, 67.9, 77.4, 78.7, 82.0, 83.9, 84.5 (C-2,3,4,5), 97.9, 103.6 (C-1).

(34) When the reaction time and/or the amount of sodium methoxide are increased, a minor product appears (<10%), that tentatively was assigned as 5-azide-5-deoxy-α,β-L-*arabino*-2-hexo-2-ulopyranose as a result of a Lobry de Bruyn-Van Ekenstein rearrangement. ^{1}H NMR(D_2O, 300 MHz) (selected signals): δ 3.50 (d, 1 H, *J* = 10.4 Hz, H-6), 3.71 (d, 1 H, *J* = 11.7 Hz, H-1'), 3.60 (t, 1 H, *J* = 10.4 Hz, H-6), 3.92 (dd, 1 H, *J* = 9.6 and 3.3 Hz, H-4); ^{13}C NMR(D_2O, 300 MHz): δ 59.9 (C-5), 62.0, 65.4 (C-1, 6), 70.9, 71.5 (C-3,4), 99.8 (C-2).

(35) A solution of **9** (220 mg, 1.07 mmol) in MeOH (5 ml) and Pd/C (180 mg), was hydrogenated for 12 h at 25ºC and 50-80 bar. The catalyst was removed by filtering over Celite and evaporated to give **10** (100%) as a hygroscopic solid. $[\alpha]_D$ -7.0º (*c* 0.4, methanol); lit[25] $[\alpha]_D$ -6.8º (*c* 0.9, methanol). ^{1}H NMR(D_2O, 300 MHz): δ 2.91 (d, 1 H, *J* = 13.0 Hz, H-1), 2.99 (m, 1 H, H-5), 3.08 (dd, 1 H, *J* = 13.0 and 1.4 Hz, H-1'), 3.87 (dd, 1 H, *J* = 9.8 and 2.3 Hz), 3.79, 3.96 (m, 4 H, H-2, 4, 6, 6'); ^{13}C NMR(D_2O, 300 MHz): δ 44.6 (C-1), 55.9 (C-5), 60.2 (C-6), 65.5 (C-4), 68.6 (C-2), 70.2 (C-3).

(36) Compound **2** was obtained from **1** (3.1 mmol) and used directly without purification. It was dissolved in anhydrous DMF (8 ml) and then $NaNO_2$ (1 g, 15 mmol) was added. After 18h the reaction mixture was diluted with Et_2O (75 ml) and toluene (25 ml) and then washed with a saturated solution of $NaHCO_3$ (50 ml) and water (50 ml). The organic layer was dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (Et_2O-hexane, 3:1) to give **3** (880 mg, 55% yield from **1**) isolated as a white solid; mp 117 ºC; $[\alpha]_D$+33º (*c* 1, chloroform). ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.18, 1.20, 1.21, 1.22 (s, 36 H, 4 C(CH_3)$_3$), 4.00, 4.09, 4.27 (m, 4 H, H-4, 5, 6, 6'), 5.43 (dd, 1 H, *J* = 7.2 and 4.6 Hz, H-2), 5.59 (dd, 1 H, *J* = 7.2 and 4.6 Hz, H-3), 6.37 (d, 1 H, *J* = 4.6 Hz, H-1). ^{13}C NMR($CDCl_3$, 300 MHz): δ 26.9, 27.0, 27.2 (C(*C*H_3)$_3$), 38.7, 38.8, 38.9 (*C*(CH$_3$)$_3$), 64.6 (C-6), 71.4, 75.4, 75.6, 81.0 (C-2,3,4,5), 93.5 (C-1), 176.3, 177.1, 178.3, 178.6 (4 CO). HRMS (FAB): m/z calcd for $C_{26}H_{44}O_{10}Na$: 539.2832, found: 539.2830

(37) Triflation of **3** under the same conditions as described for **1** gave **4** wich was used in the next step without purification. ^{1}H NMR($CDCl_3$, 300 MHz):1.19, 1.20, 1.24, 1.27 (s, 36 H, 4C(CH_3)$_3$), 4.26 (dd, 1 H, *J* = 13.2 and 6.6 Hz, H-6), 4.34 (t, 1 H, *J* = 7.2 Hz, H-4), 4.56 (dd, 1 H, *J* = 2.3 Hz, H-6), 5.23 (m, 1 H, H-5), 5.44 (dd, 1 H, *J* = 7.2 and 4.4 Hz, H-2), 5.54 (t, 1 H, *J* = 7.2 Hz, H-3), 6.38 (d, 1 H, *J* = 4.4 Hz, H-1)

(38) Compound **4** (650 mg, 1 mmol) was treated with NaN_3 (455 mg, 7 mmol) in anhydrous DMF as described for **8** to give **5** (406 mg, 75% from **1**); mp 101-102ºC; $[\alpha]_D$+24º (*c* 0.1, chloroform); IR: ν_{max} (Nujol) 2098 cm^{-1}. ^{1}H NMR($CDCl_3$, 300 MHz): δ 1.19, 1.20, 1.22, 1.25, (s, 36 H, 4 C(CH_3)$_3$), 3.81 (ddd, 1 H, *J* = 7.8, 4.7 and 4.1 Hz, H-5), 4.03 (dd, 1 H, *J* = 6.7 and 4.7 Hz, H-4), 4.15 (dd, 1 H, *J* = 11.7 and 7.8 Hz, H-6'), 4.31 (dd, 1 H, *J* = 11.7 and 4.1 Hz, H-6), 5.40 (dd, 1 H, *J* = 7.9 and 4.6 Hz, H-2), 5.59 (m, 1 H, H-3), 6.32 (d, 1 H, *J* = 4.6 Hz, H-1). ^{13}C NMR($CDCl_3$, 300 MHz): δ 27.0, 27.1, 27.1 (4 C(*C*H_3)$_3$), 38.9, 41.7 (4 *C*(CH$_3$)$_3$), 61.6 (C-5), 63.4 (C-6), 74.1, 74.6, 79.8 (C-2,3,4), 93.0 (C-1), 172.2, 177.8 (4 CO). Anal. Calcd. for $C_{26}H_{43}N_3O_9$: C, 57.64; H, 8.01; N, 7.76. Found: C, 57.41; H, 8.39; N, 7.52.

(39) Compound **5** (325 mg, 0.6 mmol) was de-*O*-pivaloylated as described for **9**. The crude product was purified by column chromatography (CH_2Cl_2-MeOH, 4:1) to give **6** (119 mg, 97%). IR: ν_{max} (Nujol) 2118 cm^{-1}; ^{1}H NMR(300 MHz, D_2O) selected signals: δ 5.24 (d, 1 H, *J* = 3.1 Hz, H-1), 5.30 (d, 1 H, *J* = 4.6 Hz, H-1);^{13}C NMR (300 MHz, D_2O): δ 62.4, 63.0 (C-6), 65.1, 66.7, 76.6, 77.6, 78.1, 81.5, 82.8, 82.9 (C-2,3,4,5), 96.8, 102.5 (C-1)

(40) A solution of **6** (185 mg, 0.9 mmol) was hydrogenated as described for **10** to give **7** as a hygroscopic solid (quantitative yield). $[\alpha]_D$+61.3º (*c* 0.4, H_2O); (lit[18] $[\alpha]_D$+52.6º (*c* 1.3, H_2O); lit[21] $[\alpha]_D$+52º (*c* 0.4, H_2O); lit[24] $[\alpha]_D$+53.7º (H_2O); lit[25] $[\alpha]_D$+40.5º (*c* 1.5, H_2O); ^{1}H NMR(300 MHz, D_2O): δ 2.39 (dd, 1 H, *J* = 12.6 and 10.8 Hz, H-1), 2.77 (dt, 1 H, *J* = 6.7 and 1.4 Hz, H-5), 3.13 (dd, 1 H, *J* = 12.6 and 5.3 Hz, H-1'), 3.47 (dd, 1 H, *J* = 9.7 and 3.2 Hz, H-3), 3.59 (dd, 1 H, *J* = 11.2 and 6.7 Hz, H-6), 3.64 (dd, 1 H, *J* = 6.7 and 1.2 Hz, H-6'), 3.75 (ddd, 1 H, *J* = 10.8, 9.7 and 5.3 Hz, H-2), 3.99 (dd, 1 H, *J* = 3.2 and 1.4 Hz, H-4); ^{13}C NMR(300 MHz, D_2O): 49.1 (C-1), 61.5 (C-6), 59.2, 68.2, 69.3, 75.2 (C-2,3,4,5).

Article Identifier:
1437-2096,E;1999,0,05,0593,0595,ftx,en;L00499ST.pdf