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An Expeditious Synthesis of Isofagomine

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An expeditious synthesis of isofagomine, from D-arabinose, is reported.

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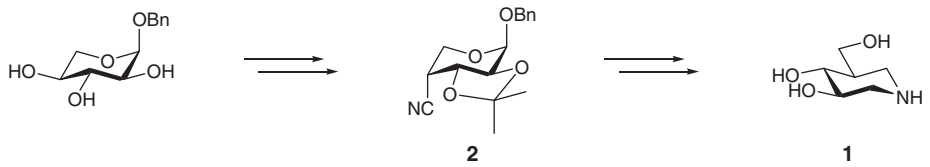
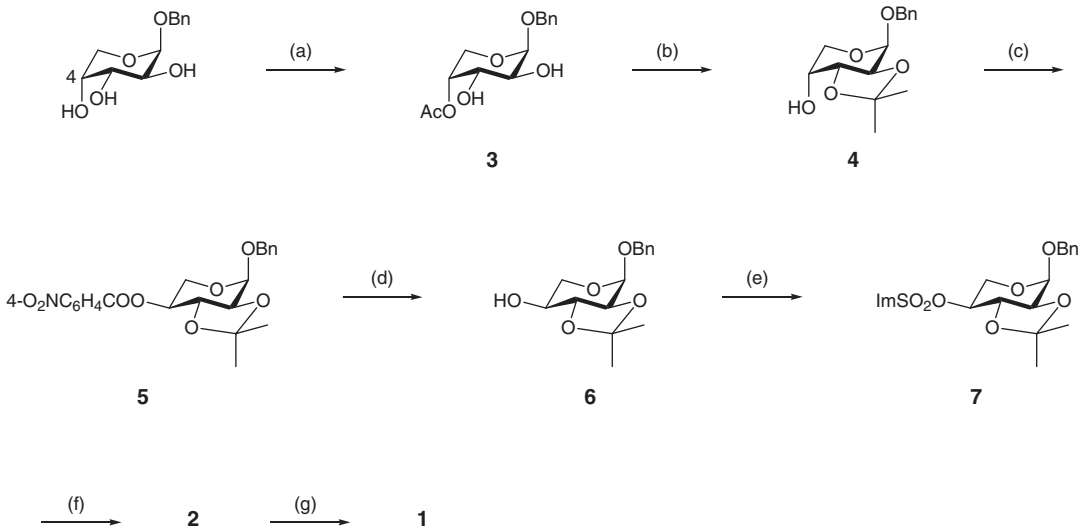
Isofagomine **1** (Scheme 1), a prominent member of the aza sugar family, was proposed and first synthesized by Lundt, Bols, and co-workers in 1994.[1] Subsequently, the molecule attracted considerable synthetic attention[2] owing to its strong inhibition of a range of enzymes that hydrolyze, in particular, the β-glycosidic linkage. One of the most expeditious syntheses of **1** starts from benzyl α-L-xylopyranoside and introduces the required nitrogen and extra carbon atom in the form of the nitrile **2**.[2] This synthesis very closely follows our route to isofagomine, starting with benzyl β-L-xylopyranoside;[3] we have recently reported some improvements to our original synthesis of **1**, as well as related routes to other aza sugars.[4]

It seemed to us, given the importance and general need, including our own, for access to good amounts of isofagomine, that the time was ripe for developing a cheap and easy route to **1**. Undoubtedly the route offered by Fan and co-workers[2] (Scheme 1) was the way to proceed but, like our own synthesis,[3] it suffers from the expense of L-xylose, an inefficient isopropylidenation step and the poor-yielding preparation of benzyl α-L-xylopyranoside.[5] Therefore we decided to start our synthesis of



Scheme 1.



Scheme 2. (a) (i) $MeC(OEt)_3$, CSA, CH_2Cl_2, (ii) Et_3N, (iii) AcOH, H_2O, 87%. (b) (i) $CH_2C(OMe)Me$, CSA, CH_2Cl_2, (ii) NaOH, MeOH, 94%. (c) $4\text{-}O_2NC_6H_4CO_2H$, DEAD, PPh_3, PhMe, 80%. (d) Et_3N, MeOH, 92%. (e) SO_2Cl_2, ImH, C_5H_5N, 94%. (f) KCN, DMF, 76%. (g) $Pd(OH)_2/C$, conc. HCl, MeOH, 81%.

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1 from inexpensive and readily available D-arabinose, necessitating the replacement of the hydroxyl group at C4 with the required nitrile, and with retention of configuration; our synthesis is outlined in Scheme 2. Such conversions of D-arabinopyranosides into L-xylopyranosides have ample precedent.[6]

Benzyl β-D-arabinopyranoside[7] was converted into the diol **3** using standard orthoester chemistry and thence the alcohol **4**, the configuration of which at C4 was easily inverted by Mitsunobu chemistry, providing the ester **5**; a simple transesterification process then gave the known alcohol **6**.[2] We then found it convenient to avoid the formation of an expensive triflate from the alcohol **6**;[2] instead, the imidazylate **7** allowed for the formation of the nitrile **2**. The described reductive amination then converted **2** into isofagomine **1**.[2]

A gram of isofagomine can now be prepared from D-arabinose, in an overall yield of 30%, in about eight days.

Experimental

General experimental procedures have been described recently.[8]

Benzyl 4-O-Acetyl-β-D-arabinoside ***3***

Camphor-10-sulfonic acid (580 mg, 2.50 mmol) was added to benzyl β-D-arabinopyranoside[7] (21.6 g, 90 mmol) and triethyl orthoacetate (33.0 mL, 180 mmol) in CH_2Cl_2 (350 mL) and the mixture stirred (30°C, 2 h). Triethylamine (5 mL) was added before the solution was washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in $AcOH/H_2O$ (9:1, 200 mL) and the solution stirred (15 min). Concentration of the mixture, co-evaporation with PhMe, and recrystallization gave the diol **3** as colourless needles (22.1 g, 87%). mp 95.0–95.5°C (Et_2O/petrol). $[\alpha]_D$ −213°. δ_H (600 MHz) 1.94–2.67 (2H, br m, OH), 2.14 (s, CH_3), 3.75 (dd, $J_{4,5}$ 2.1, $J_{5,5}$ 13.0, H5), 3.84 (dd, $J_{1,2}$ 3.8, $J_{2,3}$ 9.8, H2), 3.86 (dd, $J_{4,5}$ 1.4, H5), 3.96 (dd, $J_{3,4}$ 3.6, H3), 4.54, 4.76 (ABq, J 11.7, CH_2Ph), 5.02 (d, H1), 5.15 (ddd, H4), 7.28–7.41 (m, Ph). δ_C (150.9 MHz) 21.2 (CH_3), 61.1 (C5), 69.2, 70.0, 71.4 (C2,3,4), 70.1 (*C*H_2Ph), 98.0 (C1), 128.2, 128.3, 128.8, 136.9 (Ph), 171.1 (C=O). *m/z* 283.1179; $[M + H]^+$ requires 283.1182.

Benzyl 2,3-O-Isopropylidene-β-D-arabinopyranoside ***4***

Camphor-10-sulfonic acid (116 mg, 0.50 mmol) was added to the diol **3** (21.2 g, 75.0 mmol) and 2-methoxypropene (12.9 mL, 135 mmol) in CH_2Cl_2 (200 mL), and the mixture stirred (30 min). Triethylamine (1 mL) was added and the solution stirred; saturated methanolic NaOH (30 mL) was added, and the solution again stirred (10 min). The solution was diluted (CH_2Cl_2), washed with water, dried over $MgSO_4$, filtered, and concentrated to give the crude acetonide **4** as a pale yellow oil that was sufficiently pure for the next step of the synthesis. Purification by flash chromatography (EtOAc/petrol/Et_3N, 25:74:1) gave the alcohol **4** as a colourless oil (19.8 g, 94%). $[\alpha]_D$ −255° (MeCN). δ_H (600 MHz, CD_3CN) 1.37, 1.38 (6H, 2s, CH_3), 3.14 (br s, OH), 3.60 (dd, $J_{4,5}$ 1.7, $J_{5,5}$ 12.6, H5), 3.70 (dd, $J_{4,5}$ 1.6, H5), 3.94–4.00 (m, H2,3), 4.20 (ddd, $J_{3,4}$ 2.9, H4), 4.55, 4.75 (ABq, J 12.0, CH_2Ph), 5.26 (d, $J_{1,2}$ 2.8, H1), 7.27–7.42 (m, Ph). δ_C (150.9 MHz, CD_3CN) 27.0 (CH_3), 65.2 (C5), 68.8, 72.2, 74.3 (C2,3,4), 70.2 (*C*H_2Ph), 98.8 (C1), 110.0 [*C*$(CH_3)_2$], 128.6, 129.4, 139.0 (Ph). *m/z* 281.1383; $[M + H]^+$ requires 281.1389.

Benzyl 2,3-O-Isopropylidene-4-O-(4-nitrobenzoyl)-α-L-xyloside ***5***

Diethyl azodicarboxylate (30.6 mL, 196 mmol) in dry PhMe (25 mL) was added dropwise with stirring to the alcohol **4** (19.6 g, 70.0 mmol), PPh_3 (50.5 g, 192 mmol), and 4-$O_2NC_6H_4CO_2H$ (32.2 g, 192 mmol) in dry PhMe (175 mL) at 0°C. The resulting mixture was warmed and stirred (40°C, 12 h). The dark mixture was concentrated and rapid silica gel filtration (EtOAc/petrol/Et_3N, 5:94:1 then 10:89:1) gave the 4-nitrobenzoate **5** as pale yellow needles (24.0 g, 80%). mp 104–105°C (EtOAc/petrol). $[\alpha]_D$ −38.0° (MeCN). δ_H (600 MHz, CD_3CN) 1.41 (6H, 2s, CH_3), 3.57 (dd, $J_{4,5}$ 10.7, $J_{5,5}$ 11.2, H5), 3.68 (dd, $J_{1,2}$ 3.1, $J_{2,3}$ 9.6, H2), 3.97 (dd, $J_{4,5}$ 5.5, H5), 4.27 (dd, $J_{3,4}$ 9.9, H3), 4.61, 4.81 (ABq, J 12.0, CH_2Ph), 5.28 (d, H1), 5.32 (ddd, H4), 7.32–7.44 (m, Ph), 8.16–8.29 (4H, m, Ar). δ_C (150.9 MHz, CD_3CN) 26.8, 27.0 (2C, CH_3), 60.3 (C5), 70.5 (*C*H_2Ph), 73.3, 74.8, 76.8 (C2,3,4), 97.3 (C1), 111.6 [*C*$(CH_3)_2$], 124.7–151.9 (Ar, Ph), 164.7 (C=O). *m/z* 430.1477; $[M + H]^+$ requires 430.1502.

Benzyl 2,3-O-Isopropylidene-α-L-xylopyranoside ***6***

Triethylamine (10 mL) was added to the 4-nitrobenzoate **5** (21.5 g) in MeOH (250 mL), and the mixture stirred (40°C, 30 min). The solution was concentrated and flash chromatography (EtOAc/petrol/Et_3N, 25:74:1) gave the alcohol **6** as a colourless oil (12.9 g, 92%). $[\alpha]_D$ −115° (MeOH; lit.[2] −119.0° (MeOH)). The ^1H and ^{13}C NMR spectra were consistent with those previously reported.[2]

Benzyl 4-O-(Imidazolyl-1-sulfonyl)-2,3-O-isopropylidene-α-L-xylopyranoside ***7***

Sulfuryl chloride (2.41 mL, 30.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the alcohol **6** (7.01 g, 25.0 mmol) and pyridine (4.85 mL, 60.0 mmol) in CH_2Cl_2 (100 mL) at −35°C and the mixture stirred (1 h). Imidazole (7.49 g, 110 mmol) was added, the mixture allowed to warm to room temperature, and stirred (16 h). The solution was diluted (CH_2Cl_2), washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (EtOAc/petrol/Et_3N, 15:84:1) to give the imidazylate **7** as colourless needles (9.64 g, 94%). mp 80–81°C (Et_2O/petrol). $[\alpha]_D$ −115° (MeCN). δ_H (600 MHz, CD_3CN) 1.29, 1.32 (6H, 2s, CH_3), 3.52 (dd, $J_{4,5}$ 9.9, $J_{5,5}$ 11.3, H5), 3.53 (dd, $J_{1,2}$ 3.1, $J_{2,3}$ 9.5, H2), 3.71 (dd, $J_{4,5}$ 5.6, H5), 4.00 (dd, $J_{3,4}$ 9.6, H3), 4.56, 4.74 (ABq, J 12.0, CH_2Ph), 4.93 (ddd, H4), 5.21 (d, H1), 7.13–7.14 (1H, m, Im), 7.30–7.41 (m, Ph), 7.47–7.48 (1H, m, Im), 8.03–8.04 (1H, m, Im). δ_C (150.9 MHz, CD_3CN) 26.5, 26.7 (2C, CH_3), 59.8 (C5), 70.7 (*C*H_2Ph), 74.2, 76.3, 82.3 (C2,3,4), 96.9 (C1), 112.0 [*C*$(CH_3)_2$], 119.3–138.5 (Im, Ph). *m/z* 411.1226; $[M + H]^+$ requires 411.1226.

Benzyl 4-C-Cyano-4-deoxy-2,3-O-isopropylidene-β-D-arabinoside ***2***

Potassium cyanide (6.3 g, 96 mmol) was added to the imidazylate **7** (4.9 g, 12 mmol) in DMF (150 mL) and the mixture stirred (50°C, 48 h). The mixture was then concentrated, diluted (CH_2Cl_2), washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash chromatography (EtOAc/petrol/Et_3N, 5:94:1) to give the nitrile **2** as a colourless oil (2.6 g, 76%). $[\alpha]_D$ −198° (MeOH; lit.[2] −204.6° (MeOH)). The ^1H and ^{13}C NMR spectra were consistent with those previously reported.[2]

Acknowledgments

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