Polyhydroxylated pyrrolidines. Part 4: Synthesis from d-fructose of protected 2,5-dideoxy-2,5-imino-d-galactitol derivatives

Isidoro Izquierdo,* María T. Plaza, Miguel Rodríguez, Juan A. Tamayo and Alicia Martos

Department of Medicinal and Organic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain

Received 10 November 2005; accepted 13 December 2005

Available online 18 January 2006

Abstract—The readily available 3-O-benzoyl-4-O-benzyl-1,2-O-isopropylidene-5-O-methanesulfonyl-β-D-fructopyranose (5) was straightforwardly transformed into its D-psico epimer (8), after O-debenzoylation followed by oxidation and reduction, which caused the inversion of the configuration at C(3). Compound 8 was treated with lithium azide yielding 5-azido-4-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-L-tagatopyranose (9) that was transformed into the related 3,4-di-O-benzyl derivative 10. Cleavage of the acetonide in 10 to give 11, followed by regioselective 1-O-pivaloylation to 12 and subsequent catalytic hydrogenation gave (2R,3S,4R,5S)-3,4-dibenzyl-2-hydroxymethyl-2'-O-pivaloylpyrrolidine (13). Stereochemistry of 13 could be determined after O-deacylation to the symmetric pyrrolidine 14. Total deprotection of 14 gave 2,5-imino-2,5-dideoxy-D-galactitol (15, DGADP).

© 2005 Elsevier Ltd. All rights reserved.

1. Introduction

In a very recent paper, our group reported on preparation of orthogonally protected derivatives of 2,5-dideoxy-2,5-imino-D-allo- (DADP) and D-altro-hexitol (DALDP),1 in a stereoselective manner, using commercially available D-fructose as the chiral starting material. Continuing with our efforts on this topic, we reported herein on the highly stereoselective synthesis of the D-galacto isomer (13) of the above mentioned 2,5-iminohexitols.

Scheme 1 shows the synthetic potentiality of (2R,3S,4R,5S)-3,4-dibenzyl-2-hydroxymethyl-2'-O-pivaloylpyrrolidine (13) displaying the retrosynthesis of hyacinthacines A4 and 7a-epi-A5, the former recently isolated from Scilla sibirica,2 where clearly is shown that 13 must be considered an appropriate chiral starting material for the synthesis of such target molecules. Thus, O-protecting groups interchange between the hydroxyl groups at C(2')–C(5'), carbon-chain lengthening at either C(2') (the original C(1)) of D-fructose or C(5') in a two more carbon atoms fragment.
suitably functionalized, followed by a further cyclization, could lead to pyrrolizidines, which stereochemistry at C(1,2,3,7a) belonging either to that of the natural hyacinthacine A₄ or the 7a-epi-A₅.

2. Results and discussion

A first attempt of synthesizing the required key intermediate 3,4-di-O-benzyl-1,2,5-isopropylidene-α-L-tagatopyranose (10) according to the synthetic route outlined in Scheme 2, where the well known 3-O-benzoyl-4-O-benzyl-1,2,5-isopropylidene-β-D-fructopyranose (1)¹ was chosen as the chiral starting material was unsuccessful. Even though the transformation of 1 into the already reported 5-azido-5-deoxy-α-L-sorbopyranose derivative 2,⁴ after its treatment with diphenylphosphoryl azide (DPPA)/Ph₃P/DEAD,⁵ occurred with total stereosecontrol and high yield, as well as its 3-O-debenzylation to 3, and subsequent oxidation to the corresponding 2,3-diulose 4, the sodium borohydride reduction of the latter took place with high stereoselectivity but by the α-face regenerating 3.⁶

On the basis of the above results, an alternative synthetic route was explored (see Scheme 3). Thus, 1 was straightforwardly transformed into the corresponding 5-O-methanesulfonyl derivative 5,⁴ which was de-O-benzylated to 6 by standard Zemplen conditions without observing any substitution or elimination of the mesyloxy group at C(5). Oxidation of 6 with the Dess–Martin reagent gave the not fully characterized 2,3-diulose 7, which was exclusively reduced to 4-O-benzyl-1,2,5-isopropylidene-5-O-methanesulfonyl-β-D-psicopyranose (8). Reaction of 8 with lithium azide in DMF gave 5-azido-4-O-benzyl-5-deoxy-1,2,5-isopropylidene-α-L-tagatopyranose (9), which was finally benzylated to the required 10.

Deacetonation of 10 in acid medium (see Scheme 4) yielded the corresponding free hexulose 11 that was shown as the crystalline α-epimer in a 2C₅ conformation with H(4,5,6ax) in trans-diaxial disposition in accordance with the J₄,₅ and J₅,₆ax values of 10.0 and 11.2 Hz, respectively. Reaction of 11 with pivaloyl chloride gave in a highly regioselective manner 5-azido-3,4-di-O-benzyl-5-deoxy-1-pivaloyl-α-L-tagatopyranose (12). Hydrogenation of 12 under the presence of Raney nickel catalyst occurred in moderate yield but with high stereoselectivity affording (2R,3S,4R,5S)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)-2′-O-pivaloyl-pyrrolidine (13). Formation of 13 must occur through the intermediate aminocarbonyl sugar A that reacted in a fast

![Scheme 2](image)

Scheme 2. Synthesis of 3 from 1. Reagents and conditions: (i) Ph₃P/DEAD/ (PhO)₂PON₃/THF; (ii) NaMeO/MeOH; (iii) Dess–Martin periodinane/Cl₂CH₂; (iv) NaBH₄/MeOH.

![Scheme 3](image)

Scheme 3. Synthesis of 10 from 1. Reagents and conditions: (i) MeOH/MeONa (cat.), rt; (ii) Dess–Martin/Cl₂CH₂, rt; (iii) NaBH₄/MeOH, 0 °C; (iv) LiN₃/ DMF, 100 °C; (v) NaH/DMF/BnBr, rt.

![Scheme 4](image)

Scheme 4. Synthesis of polyhydroxylated pyrrolidines 13–15. Reagents and conditions: (i) PivCl/TEA/Cl₂CH₂, rt; (ii) Raney Ni/H₂/MeOH; (iii) NaMeO/MeOH; (iv) 10% Pd–C/H₂/MeOH/HCl.
intramolecular process to its cyclic imine intermediate B, which was finally hydrogenated to 13. The stereochemistry of 13 could be easily established after its 2′-de-O-acetylation to 14, which 1H- and 13C NMR spectra contained signals only consistent with the presence of a symmetry plane in the molecule and hence with a β-galacto configuration in 13. The total removal of the protection group in 14 yielded (2R,3S,4R,5S)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine hydrochloride [2,5-dideoxy-2,5-imino-β-D-galactitol (DGADP)] (15), which analytical and spectroscopic data were in agreement with those previously reported.7 Compound 15 has been described as the free base.8

Comments merit the high stereoselectivity found in the catalytic hydrogenation of intermediate Δ1⁻-pyrroline B (see Scheme 4), where the entry of the hydrogen molecule took place by the β-face resulting in a cis-disposition for all substituents. These results are in accordance with those previously reported, where the authors9 stated that in five-membered ring systems the stereochemistry at the new stereogenic centre [C(2)] is controlled by that existing at C(4), in such a way that the substituents at both carbon atoms resulted cis-positioned.

Compound 15 was also described as the free base.8

3. Conclusions

β-Fructose is an appropriate chiral starting material for the stereoselective synthesis of orthogonally protected polyhydroxylated pyrrolidines alkaloids. Highly diastereoselective hydrogenation of a 5-azido-5-deoxy-α-L-tagatose derivative is an excellent synthetic route to the partially protected target molecule DGADP.

4. Experimental

4.1. General procedures

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over MgSO₄ before concentration under reduced pressure. The 1H and 13C NMR spectra were recorded with Bruker AMX-300, AM-300, and ARX-400 spectrometers for solutions in CDCl₃ (internal Me₄Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Micromass Mod. Platform II and Autospec-Q mass spectrometers. Optical rotations were measured for solutions in CHCl₃ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated E. Merck silica gel 60 F₂₅₄ aluminium sheets with detection by charring with H₂SO₄ or employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulphuric acid containing 0.8% cerium sulphate (w/v) and heating. Column chromatography was performed on silica gel (E. Merck. 7734). The no crystalline compounds, for which elemental analyses were not obtained, were shown to be homogeneous by chromatography and characterized by NMR spectroscopy and FAB-HRMS with thioglycerol matrix.

4.1.1. 5-Azido-3-O-benzoyl-4-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-L-sorbitopyranose (2).

To an ice-water cooled and stirred solution of 3-O-benzoyl-4-O-benzyl-1,2-O-isopropylidene-β-D-fructopyranose3 (I, 1.1 g, 3.6 mmol) in dry THF (30 mL) were consecutively added triphenylphosphine (1 g, 3.8 mmol), a 40% solution of DEAD in toluene (1.75 mL, 3.8 mmol) and after 10 min DPPA (1 mL, 4.6 mmol). The mixture was allowed to reach room temperature and then left overnight. TLC (3:2, ether/hexane) then revealed a new faster running compound. The mixture was concentrated, supported on silica gel and then submitted to chromatography (1:3, ether/hexane) to afford pure crystalline 2 (1.23 g, 78%), which analytical and spectroscopy data were in accordance with those previously reported.4

4.1.2. 4-O-Benzyl-1,2-O-isopropylidene-5-O-methanesulfonyl-β-D-fructopyranose (6).

To a solution of 3-O-benzoyl-4-O-benzyl-1,2-O-isopropylidene-5-O-methanesulfonyl-β-D-fructopyranose (5, 4.93 g, 10 mmol) in anhydrous methanol (20 mL) was treated with 0.1 M NaOMe in methanol (5 mL) overnight. TLC (4:1, ether/hexane) then revealed the absence of 5 and the presence of a slower-running compound. The reaction mixture was neutralized with AcOH, concentrated and the residue dissolved in CH₂Cl₂ (25 mL) washed with water and concentrated again. Flash chromatography (1:1, ether/hexane) of the residue afforded pure syrupy 6. Flash chromatography (1:1, ether/hexane) of the residue afforded pure syrupy 6 (3.67 g, 94%); [α]D20 -150 (c 1.1); IR (neat): ν 3520 cm⁻¹ (OH). 1H NMR (300 MHz): δ 7.40–7.30 (m, 5H, Ph), 5.10 (dt, 1H, H-5), 4.82 and 4.68 (2d, 2H, J = 11.0 Hz, CH₂Ph), 4.21 and 4.02 (2d, 2H, J₁₁ = 8.8 Hz, H-1,1'), 4.00 (dd, 1H, J₅,₆ = 1.6 Hz, J₆,₆' = 13 Hz, H-6), 3.94 (dd, 1H, J₅,₆ = 1.6 Hz, H-6'), 3.86 (d, 1H, J₃,₃' = 9.8 Hz, H-3), 3.69 (dd, 1H, J₅,₅' = 3.2 Hz, H-4), 3.02 (s, 3H, Ms), 1.90 (br s, 1H, OH), 1.49 and 1.44 (2s, 6H, CMe₂). 13CNMR: δ 137.27, 128.68, and 128.28 (Ph), 112.37 (C₆Me₂), 105.71 (C₆⁻), 77.46 (C₄⁻), 76.79 (C-5), 72.94 (C-4), 71.99 (C-1), 63.12 (C-6), 39.11 (Ms), 26.57 and 26.31 (C₆Me₂). HRMS: m/z 411.1088 [M⁺ + Na]. For C₁₇H₂₄O₄NaS 411.1089 (deviation +0.3 ppm).

4.1.3. 4-O-Benzyl-1,2-O-isopropylidene-5-O-methanesulfonyl-β-D-psicopyranose (8).

To a stirred suspension of Dess–Martin periodinane (5.93 g, 13.9 mmol) in dry CH₂Cl₂ (25 mL) was added dropwise a solution of 6 (4 g, 10.3 mmol) in the same solvent (25 mL) under Ar. The mixture was stirred at room temperature overnight. TLC (4:1, ether/hexane) then revealed the presence of a faster-running product. The reaction mixture was filtered and the filtrate washed with 10% aqueous Na₂CO₃, brine and water, then concentrated. The residue was percolated (3:2, ether/hexane) through a short column of silica gel to afford fractions containing presumably ketone 7 [3.8 mg, 96%; IR (neat): ν 1757 cm⁻¹], that was used in the next step.

To a stirred and ice-water cooled solution of 7 (3.8 g, 9.8 mmol) in dry methanol (25 mL) NaBH₄ (0.44 g, 11.5 mmol) was added portionwise. After 1 h, TLC (4:1, ether/hexane) showed no ketone 7 and the presence of a new product of lower mobility. The reaction mixture was neutralized with AcOH, concentrated and the residue was dissolved in CH₂Cl₂, washed with water then concentrated.
Flash chromatography (1:1, ether/hexane) afforded crystalline 8 (2.9 g, 76%); mp 93–94 °C (from ether/hexane); [α]D281 n = −97 (c 1.2); ν (KBr) 3549 (OH), 3089, 726 and 269 cm−1 (aromatic). 1H NMR (300 MHz): δ 7.40–7.30 (m, 5H, Ph), 4.97 (dt, 1H, H-5), 4.73 and 4.66 (2d, 2H, J = 11.3 Hz, CH2Ph), 4.20 and 4.14 (2d, 2H, J1,1′ = 9.6 Hz, H-1,1′), 4.04 (d, 2H, J5,6 = 1.7 Hz, H-6,6′), 3.88–3.83 (m, 2H, H-3, H-4), 3.04 (3s, 3H, Ms), 1.46 and 1.37 (2s, 6H, CH3Me). 13C NMR: δ 136.98, 128.69, 128.32, and 128.12 (Ph), 112.68 (CMe2), 105.47 (C-2), 77.06 (C-5), 73.62 (C-1), 71.90 (C-4), 70.66 (CH2Ph), 70.40 (C-3), 63.33 (C-6), 39.03 (Ms), 26.61 and 26.42 (CMe2). Anal. Calcd for C17H20O6S: C, 52.57; H, 6.23; S, 8.25. Found: C, 52.86; H, 6.53; S, 8.07.

4.1.4. 5-Azido-4-O-benzyl-5-deoxy-1,2,6-isoisopropylidene-α-L-tagatopyranose (9). A stirred solution of 8 (3.8 g, 9.7 mmol) and lithium azide (1.43 g, 29.2 mmol) in dry DMF (20 mL) was heated at 100 °C for 2 h. TLC (1:1, ether/hexane) then revealed a faster-running compound. The mixture was concentrated to a residue that was dissolved in ether (40 mL), washed with brine and concentrated. Flash chromatography (2:1, ether/hexane) of the residue afforded crystalline 9 (2.7 g, 82%); mp 74–76 °C (from ether/hexane); [α]D260 = −112.5 (c 0.9); IR (neat): ν 3492 (OH), 3064 (aromatic), 2105 (N3), 1384 and 1372 (CMe2), 752 and 699 cm−1 (aromatic). 1H NMR (400 MHz): δ 7.45–7.30 (m, 5H, Ph), 4.73 and 4.67 (2d, 2H, J = 11.2 Hz, CH2Ph), 4.11 and 4.02 (2d, 2H, J1,1′ = 9.4 Hz, H-1,1′), 3.87–3.83 (3m, 4H, H-3,4,5,6,5′6′, eq), 3.51 (t, 1H, J5,6ax = J5,6eq = 11.1 Hz, H-6ax), 1.46 and 1.37 (2s, 6H, CH3Me). 13C NMR: δ 137.15, 128.75, 128.40, and 128.22 (Ph), 112.29 (CMe2), 104.54 (C-2), 78.96 (C-3), 73.26 (CH2Ph), 72.31 (C-1), 69.98 (C-4), 61.60 (C-6), 57.10 (C-5), 26.60 and 26.44 (CMe2). HRMS: m/z 358.1377 [M+Na]+. For C16H22N3O6Na 358.1379 (deviation +0.4 ppm).

4.1.5. 5-Azido-3,4-di-O-benzyl-5-deoxy-1,2,6-isopropylidene-α-L-tagatopyranose (10). To an ice-water cooled and stirred solution of 11 (0.5 g, 1.3 mmol) in dry CH2Cl2 (15 mL) were added TEA (200 μL, 1.5 mmol) and pivaloyl chloride (175 μL, 1.5 mmol) and the mixture was left at room temperature for 5 h. TLC (2:1, ether/hexane) then showed a faster-running compound. MeOH (0.5 mL) was added and after 15 min the reaction mixture was washed with water, then concentrated to a residue that was submitted to flash chromatography (1:2, ether/hexane) to afford compound 12 (535 mg, 88%) as a colourless syrup; [α]D281 n = −30 (c 1); ν (neat) 3440 (OH), 3065 (aromatic), 2110 (N3), 1734 (ester C=O), 734 and 698 cm−1 (aromatic). 1H NMR (300 MHz): δ 7.45–7.25 (m, 10H, 2 Ph), 4.92 and 4.56 (2d, 2H, J = 11.0 Hz, CH2Ph), 4.79 and 4.72 (2d, 2H, J = 11.5 Hz, CH2Ph), 4.39 and 4.02 (2d, 2H, J1,1′ = 11.7 Hz, H-1,1′), 4.01 (dt, 1H, H-5), 3.91 (dd, 1H, J3,4 = 2.6 Hz, J5,6 = 9.9 Hz, H-4), 3.76 (dd, 1H, J6,6eq = 5.5 Hz, J6ax,6eq = 11.1 Hz, H-6eq), 3.75 (d, 1H, H-3), 3.58 (t, 1H, J5,6ax = 11.1 Hz, H-6ax), 3.18 (br s, 1H, HO), and 1.20 (s, 9H, CH3Me). 13C NMR (inter alia): δ 179.49 (ester C=O), 97.97 (C-2), 79.52 (C-4), 75.13 and 72.83 (2 CH2Ph), 74.93 (C-3), 65.78 (C-6), 61.81 (C-6), 58.00 (C-5), 39.02 (CMe2) and 27.24 (CMe3). HRMS: m/z 492.2112 [M+Na]+. For C23H23N3O6Na 492.2111 (deviation −0.3 ppm).

4.1.6. Hydrogenation of 12. Compound 12 (1.4 g, 3 mmol) in MeOH (40 mL) was hydrogenated at 60 psi over wet Raney nickel (500 mg, Fluka) for 5 h. TLC (5:1, ether/methanol) then revealed the presence of a slower-running compound. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were concentrated to a residue that was submitted to column chromatography (ether→10:1, ether/methanol) to afford syrup 2(R,3S,4R,5S)-3,4-dibenzylxoy-2,5-bis(hydroxy-methyl)-2′-O-pivaloylpyrrolidine (13, 680 mg, 53%); [α]D281 = −11 (c 0.5); ν (neat) 3268 (OH, NH), 3064, (aromatic), 2981 (C=O), 1792 (ester C=O), 1721 (ester C=O), 1264 (ester C=O), 1119 (ester C=O), 1052 (ester C=O), 980 (ester C=O), 915 (ester C=O), 826 (ester C=O), 749 (ester C=O), 698 (ester C=O), 612 (ester C=O), 564 (ester C=O), 530 (ester C=O), 430 (ester C=O), 343 (ester C=O), 310 (ester C=O), 258 (ester C=O), 204 (ester C=O), 156 (ester C=O), 104 (ester C=O), 97 (ester C=O), 92 (ester C=O), 61 (ester C=O), 52 (ester C=O), 47 (ester C=O), 42 (ester C=O), 36 (ester C=O), 31 (ester C=O), 25 (ester C=O), 20 (ester C=O), 15 (ester C=O), 11 (ester C=O), 8 (ester C=O), 4 (ester C=O), 3 (ester C=O), 1 (ester C=O), 0.3 ppm).
4.1.9. (2R,3S,4R,5S)-3,4-Dibenzyl-2,5-bis(hydroxymethyl)pyrrolidine (14). A solution of 13 (680 mg, 1.59 mmol) in anhydrous MeOH (5 mL), was treated with 0.5 M MeONa in the same solvent (0.3 mL) for 6 h at room temperature. TLC (1:5:1, ether/methanol) then showed the presence of a compound of lower mobility. The catalyst was filtered off, washed with MeOH and the combined filtrate and washings concentrated to a residue that was repeatedly washed with CH2Cl2 to yield 15 hydrochloride (30 mg, 56%) as a colourless foam. 1H NMR (400 MHz, MeOH-d4): δ 4.37 (br d, 2H, J = 5.0 Hz, H-3,4), 3.94 (dd, 2H, J = 4.2 Hz, J2,2a/8 = 4.0 Hz, J2a,2b = 11.7 Hz, H-2,5), 3.89 (dd, 2H, J = 4.2 Hz, J5,5a/8 = 4.0 Hz, J5a,5b = 11.5 Hz, H-5,5a/8), 3.65 (dd, 1H, J = 4.7 Hz, H-2,5), 3.47 (dt, 1H, H = 5, H = 2), 2.35 (br s, 1H, OH), and 1.18 (s, 9H, CMe3). 13C NMR (inter alia): δ 178.44 (COCMes), 81.46 (C-4), 78.36 (C-3), 74.05 and 73.24 (2C, 2,2S,5), 64.29, 60.66, 64.30, 72.86.

Acknowledgements

The authors are deeply grateful to Ministerio de Educación y Cultura (Spain) (Project PPQ2002-01303) and Junta de Andalucía (Group CVI-250) for financial support and for a grant (A. Martos).

References and notes

6. Any attempt of inversion of the configuration at C(3) in 3 by Mitsunobu reaction (n-Bu3P/DEAD/3,5-dinitrobenzoic acid) was unsuccessful.