Synthesis and selective functionalization of enantiomerically pure iminosugars

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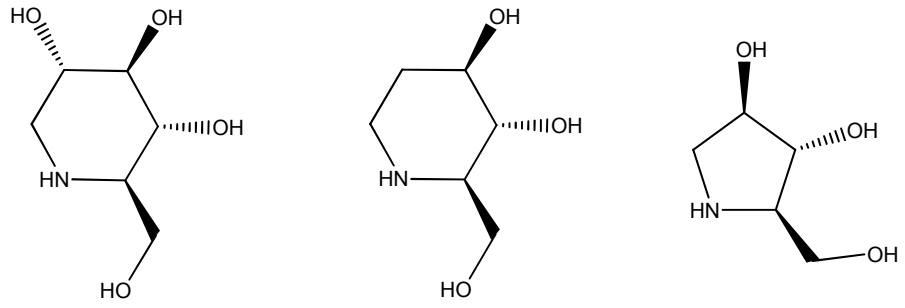
Abstract: The synthesis of iminosugars is one of the most active fields in synthetic organic chemistry. Due to the structural resemblance to sugars, these unique molecules have a tremendous potential in biological functions mediated by carbohydrates and have been postulated in the control of diabetes, Gaucher's disease, cancer, HIV, and viral infections like influenza. A survey of the literature reveals that the synthesis of 2,3,5-substituted pyrrolidines is not a trivial task specially when the attainment of enantiomerically pure compounds is requested. In this work, we describe the synthesis of enantiomerically pure poly(hydroxymethyl)pyrrolidines (iminosugars) and different routes to selective functionalization of –OH and -NH groups. The optically active pyrrolidine derivatives were obtained from 2-azabicyclo[2.2.1]hept-5-enes, which were synthesized in one step according to the literature procedure by an aza-Diels-Alder reaction between protonated glyoxylate imines possessing two chiral auxiliaries, *N*-(*S*)- or *N*-(*R*)-1-phenylethyl and (-)-8-phenylmenthyl or (+)-8-phenylneomenthyl, respectively, and cyclopentadiene. These polycyclic aza-Diels-Alder adducts, trough bis-hydroxylation of the double bond followed by oxidative cleavage of the corresponding diols and in situ reduction of the resulting intermediates, afforded 2,3-bis-(hydroxymethyl)-pyrrolidines from which, application of a selective protection/deprotection methodology provided the possibility of regioselective functionalization at positions 1, 2, 3, and 5 of the pyrrolidine scaffold.

Keywords: Enantioselective aza-Diels-Alder, iminosugars, pyrrolidine derivatives

1. Introduction

Iminosugars are sugar structurally related compounds, polyhydroxylated piperidines and pyrrolidines, in which the oxygen atom is replaced by a nitrogen atom or an amino group. This class of compound is frequently found in bio-systems and its physiologic importance comes through its ability of mimicking a large number of substrates (carbohydrates) during enzymatic processes.[1] Besides, those compounds can act as glycosidases selective inhibitors.[2]

Glycosidases play an important role in sugars metabolism. These enzymes are known for their involvement in the absorption of monosaccharides in the body, as much as the diseases resulting from this metabolic pathway (such as diabetes mellitus) and in the carbohydrate complexes metabolism in the plasmatic membrane. These complexes allow the cell-cell communication and recognition, apart from being involved in important biological functions, such as immunologic response, oncogenesis, tumour metastasis, they can also be anti-bodies, hormones, toxins, drugs, and virus bonding sites. Glycosidase inhibitors allow a better knowledge of important biological processes and have shown application in the control of diabetes, Gaucher's disease, cancer, and viral infections (including influenza) or HIV.[3] Previous reports show that 1-deoxynojirimycin (**A**) has proved to be a powerful inhibitor of α-glycosidases[3c] and its activity is increased by a lipophilic substitute bonded to the iminosugar's nitrogen atom[3a,4], in fact, *N*-butyldeoxynojirimycin is used to treat the Gaucher's disease. Besides, piperidine and pyrrolidine glycomimetics, such as fagomine (**B**) and DAB1 (**C**), showed promising results against the HIV replication.[5] This potentiality, especially as anti-virus agents, encourages the exploration of synthetic routes for the new iminosugars.[6]



A **B** **C**

Figure 1: 1-deoxynojirimycin (A), fagomine (B) and DAB1 (C).

2. Methods and Experimental Procedures

All reagents were purchased from Fluka and/or Aldrich and were used as received, without further purification or distillation. The solvents were purified and dried according to the procedures described in Vogel, A.I., *A textbook of practical Organic Chemistry*, 2ª ed., Longmans, Green & Co., London, **1951**.

All compounds gave satisfactory ^{1}H-NMR (400 MHz) and ESI-MS spectral data.

Procedure for aza-Diels-Alder reaction and the attainment of optically active cyclo-adducts **2a** and **2b** can be found in Tetrahedron, 67 (**2011**) 7162-7172 [ref. 7].

Procedure for di-hydroxylation of Cycloadducts - **3a** ($C_{31}H_{41}NO_4$) – To a solution of **2a** (2.4 g; 5.2 mmol) in water (10 mL) and dioxane (30 mL) was added OsO4 solution (0.02 M; 2.6 mL; 52.0 µmol) and NMMO (0.94 g; 7.8 mmol) at rt. The reaction mixture was stirred for 12 h and then filtered over celite and silica. The filtrate was extracted with AcOEt (3x50 mL) and pooled organic layers were washed with water (2x50 mL) and brine (50 mL) then dried with Na_2SO_4. Removal of solvent left a golden oil that after chromatographed on silica gel, with hexane/AcOEt 1:1, afforded the compound **3a**, as a golden oil (Rf 0.5; 2.3 g; 91%). ^{1}H-RMN (CDCl3): δ = 7.38-6.99 (m,10H), 4.40 (dt, 1H, J 10.8 Hz, J 4.0 Hz), 4.35 (d, 1H, J 6.4 Hz), 3.77 (d, 1H, J 6.0 Hz), 3.60 (s, 1H), 3.54 (q, 1H, J 6.4 Hz), 3.21 (bs, 2H, -OH), 2.28-2.27 (m, 1H), 2.22 (s, 1H), 2.12 (s, 1H), 1.83-1.80 (m, 1H), 1.77-1.71 (m, 3H), 1.50-1,46 (m, 1H), 1.42 (d, 3H, J 6.4 Hz), 1.41-1.29 (m, 2H), 0.86 (s, 3H), 0.80 (d, 3H, J 6.4 Hz), 0.77-0.72 (m, 2H), 0.69 (s, 3H, 8'-CH3). ESI-MS: calculated (M + H^+) 492.3, obtained 492.1. **3b** ($C_{31}H_{41}NO_4$) – Following the same procedure as above, using **2b** (0.80 g; 1.7 mmol), OsO4 solution (0.02 M; 0.90 mL; 18.0 µmol) and NMMO (0.32 g; 2.6 mmol), flash chromatography (hexane/AcOEt 1:1) afforded the compound **3b**, as a white solid (Rf 0.5; 1.4 g; 83%). ^{1}H-RMN (CDCl3): δ = 7.36-7.10 (m, 10H), 4.89 (s, 1H), 4.41 (d, 1H, J 6.0 Hz), 3.94 (d, 1H, J 6.0 Hz), 3.64 (q, 1H, J 6.8 Hz), 3.59 (q, 1H, J 6.4 Hz), 3.23 (bs, 1H), 2.98 (bs, 1H), 2.62 (s, 1H), 2.25 (s, 1H), 1.89-1.77 (m, 3H), 1.61-1.58 (m, 1H), 1.54-1.46 (m, 1H), 1.43 (d, 3H, J 6.8 Hz), 1.39-1.36 (m, 2H), 1.17-1.14 (m, 1H), 0.91-0.84 (m, 2H), 0.84 (s, 3H), 0.78 (s, 3H), 0.77 (d, 3H, J 5.6 Hz). ESI-MS: calculated (M + H^+) 492.3, obtained 492.1.

Procedure for oxidative cleavage of the diols and in situ reduction - **4a** ($C_{31}H_{43}NO_4$) – To a solution of **3a** (2.3 g; 4.7 mmol) in DCM (50 mL) was added silica (5 g) and water (5 mL) followed by slow addition of $NaIO_4$ (3.0 g; 14.0 mmol) at rt. The system was protected from light and vigorously manually shaken, after that the mixture was stirred for 4 h and then filtered over celite. The solvent was evaporated from the filtrate affording a golden oil which was dissolved in MeOH (50 mL). The system was cooled in an ice bath and NaBH4 (1.1 g; 29.1 mmol) was slowly added. The reaction mixture was stirred overnight after that, MeOH

was removed. To the crude was added AcOEt (50 mL) and water (50 mL). This system was extracted with AcOEt (2x50 mL) and pooled organic layers were washed with water (50 mL) and brine (50 mL) then dried with Na_2SO_4. Removal of solvent left a golden oil that after chromatographed on silica gel, with hexane/AcOEt 1:1, afforded the compound **4a**, as a golden oil (Rf 0.43; 1.98 g; 85%). ^{1}H-RMN (CDCl3): δ = 7.41-7.23 (m, 10H), 4.78 (dt, 1H, J 10.8 Hz, J 4.4 Hz), 4.30 (bs, 1H), 3.65 (bs, 1H), 3.57 (dd, 1H, J 10.8 Hz, J 5.6 Hz), 3.49 (s, 1H), 2.95 (d, 1H, J 12.4 Hz), 2.73 (dd, 1H, J 12.0 Hz, J 3.2 Hz), 2.31-2.07 (m, 5H), 2,00-1.97 (m,1H), 1.75-1.63 (m, 7H), 1.54-1.48 (m, 4H), 1.29 (s, 3H), 1.26 (s, 3H), 0.92 (d, 3H, J 6.4 Hz). ESI-MS: calculated (M + H^+) 494.3, obtained 494.4. **4b** ($C_{31}H_{43}NO_4$) – Following the same procedure as above, using **3a** (0.63 g; 1.3 mmol), NaIO4 (0.83 g; 3.8 mmol) and NaBH4 (0.33 g; 8.8 mmol), flash chromatography (hexane/AcOEt 1:1) afforded the compound **4b**, as a golden oil (Rf 0.43; 0.61 g; 96%). ^{1}H-RMN (CDCl3): δ = 7.39-7.26 (m, 10H), 5.03 (s,1H), 4.22 (bs, 1H), 3.80 (bs, 1H), 3.73 (dd, 1H, J 10.4 Hz, J 5.2 Hz), 3.51 (s, 1H), 2.96 (d, 1H, J 11.6 Hz), 2.69 (dd, 1H, J 11.6 Hz, J 2.8 Hz), 2.33-2.17 (m, 5H), 2.25 (d, 3H, J 22.8 Hz), 1.95-1.91 (m, 1H), 1.78-1.56 (m, 7H), 1.52-1.42 (m, 4H), 1.34 (s, 3H), 1.32 (s, 3H), 0.85 (d, 3H, J 6.8 Hz). ESI-MS: calculated (M + H^+) 494.3, obtained 494.5.

Procedure for reduction of ester functionality, with LAH - 5a ($C_{15}H_{23}NO_3$) – A solution of **4a** (0.5 g; 1.01 mmol) in dry Et2O (10 mL) was added dropwise under argon to a suspension of $LiAlH_4$ (ca. 6 equiv; 0.23 g; 6.06 mmol) in dry Et2O (10 mL) at 0 °C. The reaction mixture was stirred for 12 h at rt, and then MeOH (20 mL) and H2O (100 mL) were added dropwise at 0 °C. The resulting mixture was extracted with AcOEt (3x100 mL) and the pooled organic layers were washed with brine (100 mL) and dried with Na_2SO_4. Removal of the solvent in a rotary evaporator left a yellow oil that when chromatographed on silica gel with DCM as eluent afforded the chiral auxiliary, (-)-8-phenylmenthol (Rf 0.57 in DCM; 0.22 g; 96%), after that, elution with MeOH afforded **5a** (Rf 0.51 in MeOH; 0.25 g; 94%), as colourless oil. ^{1}H-RMN (CDCl3): δ = 7.51-7.25 (m, 5H), 5.15 (bs, 3H), 4.48-4.46 (m, 1H), 3.90-3.10 (m, 9H), 2.13-1.99 (m, 1H), 1.67-1.77 (m, 1H), 1.60 (d, 3H, J 6.0 Hz). ESI-MS: calculated (M + H^+) 266.3, obtained 266.9. **7a** ($C_{31}H_{41}NO_3Si$) – Following the same procedure as above, using **6a** (1.30 g; 1.34 mmol) and $LiAlH_4$ (0.31 g; 8.17 mmol). Flash chromatography (DCM) afforded the chiral auxiliary, (-)-8-phenylmenthol (Rf 0.57 in DCM; 0.29 g; 93%) after that, elution with AcOEt afforded **7a** (Rf 0.0 in DCM; 0.64 g; 95%),. ^{1}H-RMN (CDCl3): δ = 7.58-7.15 (m, 15H), 3.97 (q, 1H, J 6.4 Hz), 3.61 (dd, 1H, J 10.0 Hz, J 4.4 Hz), 3.50-3.43 (m, 3H), 3.34-3.20 (m, 3H), 3.05 (s, 1H), 2.60 (bs, 2H, 2.26-2.21 (m, 1H), 2.16-2.09 (m, 1H), 1.64 (dt, 1H, J 13.2 Hz, J 10.4 Hz), 1.32 (d, 3H, J 6.4 Hz), 1.0 (s, 9H). ESI-MS: calculated (M + H^+) 504,2, obtained 504.3. **7b** ($C_{31}H_{41}NO_3Si$) – From **6b** (0.39 g; 0.402 mmol) with LAH (0.10 g; 2.64 mmol). Flash chromatography, with DCM and then AcOEt, afforded the chiral auxiliary, (+)-8-phenylneomenthol, (Rf 0.57 in DCM; 0.087g; 93%) and **7b** (Rf 0.0 in DCM; 0.19 g; 95%). ^{1}H-

RMN (CDCl3): δ = 7.63-7.18 (m, 15H), 4.01 (q, 1H, J 6.8 Hz), 3.65 (dd, 1H, J 10.4 Hz, J 4.8 Hz), 3.54-3.47 (m, 3H), 3.39-3.29 (m, 3H), 3.10 (s, 1H), 2.58 (bs, 2H), 2.32-2.25 (m, 1H), 2.20-2.13 (m, 1H), 1.69 (dt, 1H, J 13.2 Hz, J 4.0 Hz), 1.37 (d, 3H, J 6.8 Hz), 1.04 (s, 9H). ESI-MS: calculated (M + H^+) 504,2, obtained 504.5. **11a** ($C_{27}H_{49}NO_4Si_2$) – From **10a** (0.36 g; 0.49 mmol) with LAH (0.121 g; 3.42 mmol). Flash chromatography with hexane/AcOEt 1:1 afforded the chiral auxiliary (-)-8-phenylmenthol (Rf 0.7; 0.108 g; 95%) and **11a** (Rf 0.3; 0.23 g; 95%). ^{1}H-RMN (CDCl3): δ =7.38-7.26 (m, 5H), 4.12 (q, 1H, J 6.4 Hz), 3.75-3.70 (m, 1H), 3.62-3.57 (m, 2H), 3.54-3.50 (m, 1H), 3.44-3.40 (m, 1H), 3.33 (dd, 1H, J 10.4 Hz, J 6.8 Hz), 3.29-3.24 (m, 1H), 3.17-3.14 (m, 1H), 2.33-2.12 (m + bs, 3H), 1.66-1.60 (m, 1H), 1.48 (d, 3H, J 6.4 Hz), 1.05-0.95 (m, 28H). ESI-MS: calculated (M + H^+) 507.3, obtained 507.6. **11b** ($C_{27}H_{49}NO_4Si_2$) – From **10b** (0.22 g; 0.29 mmol) with LAH (0.09 g; 2.42 mmol). Flash chromatography with hexane/AcOEt 1:1 afforded the chiral auxiliary (+)-8-phenylneomenthol (Rf 0.7; 0.66 g; 96%) and **11b** (Rf 0.3; 0.14 g; 95%). ^{1}H-RMN (CDCl3): δ = 7.33-7.19 (m, 5H), 4.07 (q, 1H, J 6.4 Hz, 3.69-3.65 (m, 1H), 3.55 (dd, 2H, J 10.4 Hz, J 3.2 Hz), 3.48-3.45 (m, 1H), 3.36 (t, 1H, J 7.6 Hz), 3.27 (dd, 1H, J 10.4 Hz, J 6.8 Hz), 3.23-3.19 (m, 1H), 3.12-3.09 (m, 1H), 2.47 (bs, 1H), 2.26-2.20 (m, 1H), 2.15-2.07 (m, 1H), 1.57 (dt, 1H, J 13.2 Hz, J 4 Hz), 1.43 (d, 3H, J 6.4 Hz), 1.03-0.90 (m, 28H). ESI-MS: calculated (M + H^+) 507.3, obtained 507.7.

Procedure for *O*-protection with TBDPS - 6a ($C_{63}H_{79}NO_4Si_2$) – To a cooled (ice bath) solution of **4a** (0.66 g; 1.34 mmol) and Et_3N (0.37 mL; 2.68 mmol) in dry DCM (50 mL), TBDPS (0.70 mL; 2.68 mmol) was added dropwise under argon atmosphere. The mixture was stirred at rt over 72 h, and then saturated aqueous $NaHCO_3$ solution (50 mL) was added. The resulting mixture was extracted with DCM (2x50 mL) and the pooled organic layers were washed with water (50 mL) and brine (50 mL), and dried over Na_2SO_4. Removal of solvents left a dark yellow oil that when chromatographed on silica gel with DCM as eluent afforded **6a** (Rf 0.8, 1.17 g, 90%) as a colourless oil. ^{1}H-RMN (CDCl3): δ = 7.53-7.09 (m, 30H), 4.86 (dt, 1H, J 10.4 Hz, J 4 Hz), 4.23 (q, 1H, J 6.8 Hz), 3.93 (s, 1H), 3.71 (t, 1H, J 9.6 Hz), 3.57-3.45 (m, 3H), 2.88 (dd, 1H, J 10 Hz, J 4.4 Hz), 2.70 (t, 1H, J 9.6 Hz), 2.31-2.18 (m, 2H), 2.09-2.04 (m, 1H), 1.99-1.93 (m, 1H), 1.60-1.44 (m, 6H), 1.39 (s, 3H), 1.32 (s, 3H,), 1.29 (d, 3H, J 6.8 Hz), 1.16 (s, 9H), 0.97 (d, 3H, J 6.4 Hz), 0.95 (s, 9H). **6b** ($C_{63}H_{79}NO_4Si_2$) – Following the same procedure as above, using **4a** (0.203 g; 0.41 mmol), Et3N (0.11 mL; 0.82 mmol) and TBDPS (0.21 g; 0.82 mmol). Flash chromatography (DCM) afforded **6b** (Rf 0.8; 0.38 g; 96%). ^{1}H-RMN (CDCl3): δ = 7.45-7.06 (m, 30H), 5.05 (s, 1H), 4. 25 (s, 1H), 4.13 (q, 1H, J 8.8 Hz), 3.71 (t, 1H, J 12.8 Hz), 3.51-3.42 (m, 3H), 2.77 (dd, 1H, J 13.2 Hz, J 5.6 Hz), 2.59 (t, 1H, J 12.4 Hz), 2.33-2.15 (m, 2H), 1.99-1.92 (m, 1H), 1.75-1.67 (m, 5H), 1.48-1.41 (m, 3H), 1.37 (s, 3H), 1.32 (d, 3H, J 8.8 Hz), 1.27 (s, 3H), 1.10 (s, 9H), 0.88 (d, 3H, J 6.4 Hz), 0.86 (s, 3H).

Procedure for *O*-protection with acetyl chloride - 8a ($C_{35}H_{45}NO_5Si$) – To a cooled (icebath) solution of **7a** (0.15 g; 0.29 mmol) and Et_3N (0.103 mL; 0.74 mmol) in dry DCM (50

mL), AcCl (0.05 mL; 0.74 mmol) was added under argon atmosphere. The mixture was stirred for 1 h and then saturated aqueous $NaHCO_3$ solution (50 mL) was added. The resulting mixture was extracted with DCM (2x50 mL) and pooled organic layers were washed with water (50 mL) and brine (50 mL), and dried over Na_2SO_4. Removal of solvent left a dark yellow oil that when chromatographed on silica gel with hexane/AcOEt 1:1, afforded **8a** (Rf 0.8; 0.17g; 98%). ^{1}H-RMN (CDCl3): δ = 7.58-7.16 (m, 15H), 4.14-4.05 (m, 3H), 3.99-3.92 (m, 2H), 3.27-3.23 (m, 2H), 3.20-3.16 (m, 2H), 2.27-2.23 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.65-1.61 (m, 1H), 1.36 (d, 3H, J 6.8 Hz), 1.02 (s, 9H). ESI-MS: calculated (M + H^+) 588.3, obtained 588.4. **8b** ($C_{35}H_{45}NO_5Si$) – Following the same procedure as above, using 7b (0.07 g; 0.13 mmol), Et3N (0.05 mL; 0.34 mmol) and AcCl (0.025 mL, 0.34 mmol). Flash chromatography with hexane/AcOEt 1:1 afforded **8b** (Rf 0.8; 0.07 g; 92%). ^{1}H-RMN (CDCl3): δ = 7.58-7.15 (m, 15H), 4.11-4.04 (m, 3H), 3.99-3.92 (m, 2H), 3.28-3.23 (m, 2H), 3.20-3.10 (m, 2H), 2.27-2.22 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.67-1.59 (m, 1H), 1.36 (d, 3H, J 6.4 Hz), 1.01 (s, 9H). ESI-MS: calculated (M + H^+) 588.3, obtained 588.3.

Procedure for *O*-desilylation with TBAF - 9a ($C_{19}H_{27}NO_5$) – To a solution of **8a** (0.18 g; 0.30 mmol) in acetone (20 mL) was added a solution of TBAF (75% in H_2O; 0.27 mL; 0.75 mmol). The mixture was stirred for 72 h and then AcOEt (100 mL) and water (100 mL) were added. This system was extracted with AcOEt (2x100 mL) and the pooled organic layers were washed with water (100 mL) and brine (100 mL), and dried over Na2SO4. Removal of solvent left a yellow oil that when chromatographed on silica gel with hexane/AcOEt 1:1 afforded **9a** (Rf 0.35; 0.08 g; 80 %). ^{1}H-RMN (CDCl3): δ = 7.38-7.29 (m, 5H), 4.25 (dd, 1H, J 11.2 Hz, J 2.8 Hz), 4.15-4.10 (m, 1H), 4.06-3.99 (m, 3H), 3.35-3.34 (m, 1H), 3.21-3.18 (m, 1H), 3.07 (d, 1H, J 11.2 Hz), 2.87-2.84 (m, 1H), 2.28-2.22 (m, 2H), 2.10 (s, 3H), 2.06 (s, 3H), 1.82 (bs, 1H), 1.63-1.59 (m, 1H), 1.49 (d, 3H, J 6.4 Hz). **9b** ($C_{19}H_{27}NO_5$) – Following the same procedure as above with 8b (0.08 g; 0.14 mmol) and TBAF (0.12 mL; 0.34 mmol). Flash chromatography with hexane/ACOEt 1:1 afforded **9b** (Rf 0.35; 0.05 g; 98 %). ^{1}H-RMN (CDCl3): δ = 7.38-7.29 (m, 5H), 4.25 (dd, 1H, J1=11.2 Hz, J2=2.8 Hz), 4.15-4.10 (m, 1H), 4.06-3.99 (m, 3H), 3.35-3.34 (m, 1H), 3.21-3.14 (m, 1H), 3.07 (d, 1H, J 10.8 Hz), 2.87-2.84 (m, 1H), 2.31-2.24 (m, 2H), 2.10 (s, 3H), 2.06 (s, 3H), 1.82 (bs, 1H), 1.63-1.59 (m, 1H), 1.49 (d, 3H, J 6.4 Hz).

Procedure for *O*-protection with TIPDS - 10a ($C_{43}H_{69}NO_5Si_2$) – To a cooled (ice bath) solution of **4a** (0.66g; 1.34 mmol) and imidazole (0.46 g, 6.7 mmol) in dry DCM (50 mL), TIPDS was added dropwise (0.47 mL; 1.47 mmol) under argon atmosphere. The mixture was stirred for 72 h then saturated aqueous $NaHCO_3$ solution (50 mL) was added. This system was extracted with DCM (2x50 mL) and the pooled organic layers were washed with water (50 mL) and brine (50 mL), and dried over Na_2SO_4. Removal of solvent left a dark yellow oil that when chromatographed on silica gel with DCM afforded **10a** (Rf 0.75; 0.71 g; 72 %). ^{1}H-RMN (CDCl3): δ = 7.39-7.17 (m, 10H), 4.72 (dt, 1H, J 10.4 Hz, J 4.0 Hz), 4.24 (q, 1H, J 6.8 Hz), 3. 99

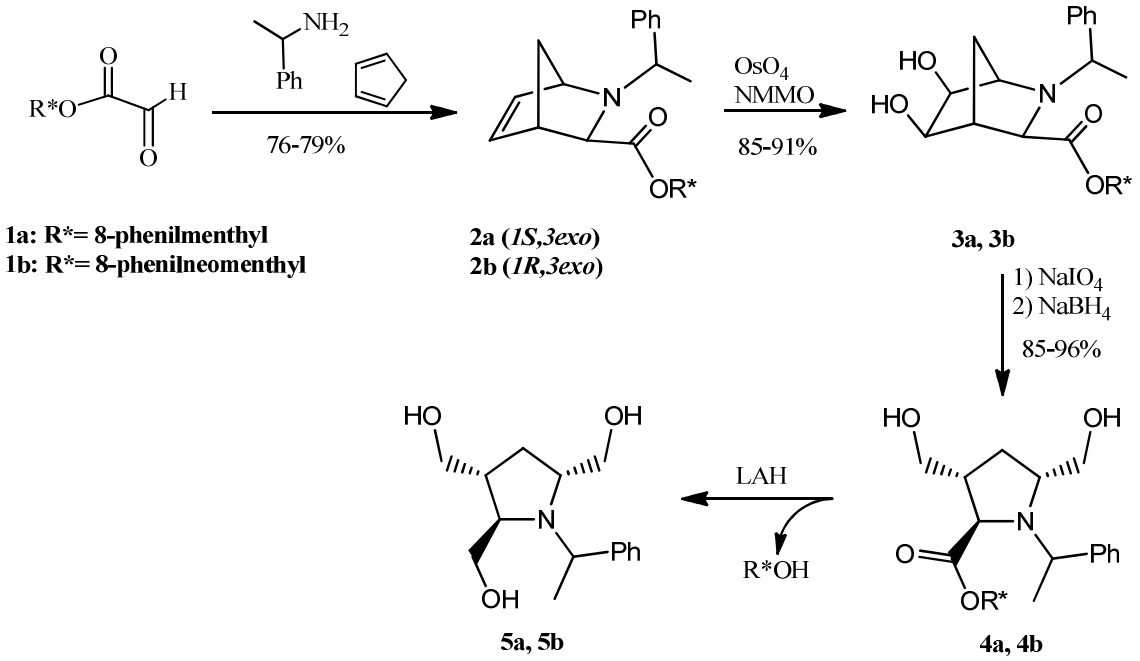
(dd, 1H, J 11.2 Hz, J 9.6 Hz), 3.87-3.81 (m, 2H), 3,71 (dd, 1H, J 9.2 Hz, J 4.0 Hz), 3.36-3.11 (m, 1H), 3.15 (s, 1H), 2.98 (dd, 1H, J 10.8 Hz, J 3.2 Hz), 2.89 (dd, 1H, J 10.8 Hz, J 5.6 Hz), 2.16-2.11 (m, 1H), 2.07-1.81 (m, 4H), 1.65-1.46 (m, 4H), 1.35 (s, 3H), 1.30 (d, 3H, J 6.8 Hz), 1.25 (s, 3H), 1.09-0.96 (m, 28H), 0.90 (d, 3H, J 6.4 Hz). ESI-MS: calculated (M + H^+) 736.4, obtained 736.5. **10b** ($C_{43}H_{69}NO_5Si_2$) – Following the same procedure as above, with **4b** (0.26 g; 0.53 mmol), imidazole (0.18 g; 2.65 mmol) and TIPDS (0.19 mL; 0.58 mmol). Flash chromatography with DCM afforded **10b** (Rf 0.75; 0.26 g; 67%). ^{1}H-RMN (CDCl3): δ = 7.41-7.20 (m, 10H), 5.05 (s, 1H), 4.21 (q, 1H, J 6.8 Hz), 4.15 (dd, 1H, J 10.8 Hz, J 9.6 Hz), 3.95 (dd, 1H, j 9.6 Hz, J 5.2 Hz), 3.70 (s, 1H), 3.43-3.38 (m, 1H), 3.03 (dd, 1H, J 10.8 Hz, J 3.6 Hz), 2.95 (dd, 1H, J 10.8 Hz, J 5.6 Hz), 2.30-2.24 (m, 1H), 2.14 (dd, 1H, J 13.2 Hz, J 2.4 Hz), 2.10-1.99 (m, 3H), 1.80-1.77 (m, 1H), 1.71-1.63 (m, 4H), 1.39 (d, 3H, J 6.8 Hz), 1.36 (s, 3H), 1.34 (s, 3H), 1.17-0.99 (m, 28H), 0.89 (d, 3H, J 6.4 Hz). ESI-MS: calculated (M + H^+) 736.4, obtained 736.5

3. Results and Discussion

The enantiomerically pure *N*-alkylated 2,3,5-poly(hydroxymethyl)pyrrolidines (**5a**,**5b**) were prepared from 2-azabicyclo[2.2.1]hept-5-enes (**2a**,**2b**). These aza-Diels-Alder cycloadducts contain a highly functionalized bridged ring system that may undergo further transformations and their synthesis was carried out, according to the reported method,[7] in order to afford a pair of enantiomers separately. Oxidation of the double bond, ring opening of the vicinal-diol, and reduction of the ester functionality lead to chiral non-natural amino alcohols (pyrrolidine derivatives) while allowing quantitative recovery of the chiral auxiliaries with retention of configuration in both cases (scheme 1).

The pyrrolidines **5a** and **5b**, besides being optical active iminosugars, show great synthetic versatility due to the hydroxyl groups therein. These structures can be functionalized in order to furnish, for example, non-natural aza-nucleosides (by nitrogenous base condensation). To reach this goal, it is necessary a route that selective functionalise the hydroxyl groups of this compounds.

We previously reported assays involving a racemic mixture of 2,3-bis(hydroxymethyl)pyrrolidines,[6d] which allow the complete and selective functionalization of all groups in any position of the scaffold. The same methodology has been applied to the separated enantiomers and the preliminary results are summarized hereafter.



1a: R*= 8-phenilmenthyl
1b: R*= 8-phenilneomenthyl

2a (*1S,3exo*)
2b (*1R,3exo*)

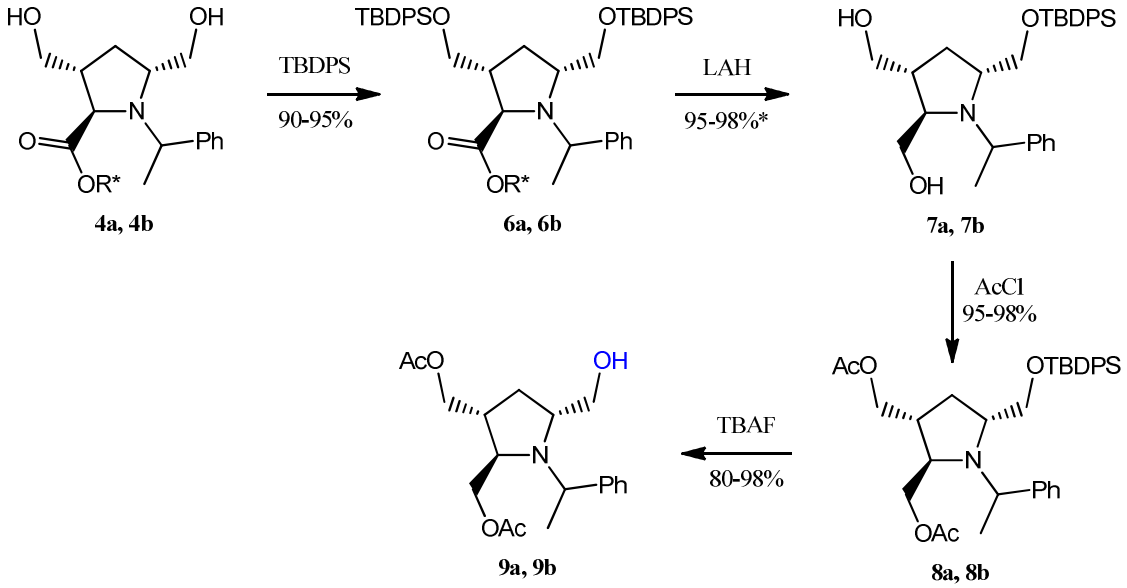
3a, 3b

5a, 5b

4a, 4b

Scheme 1

Starting from pyrrolidines **4a** and **4b**, protection of hydroxyl groups was performed by using twice the equimolar amount of tert-butylchlorodiphenylsilane (TBDPS). The *O*-protected compounds (**6a,b**) were treated with lithium aluminum hydride (LAH) in order to reduce the ester group, recover the chiral auxiliaries, and get a free –OH group at C2-position. At this step the nearest TBDPS group was removed[6d] affording the 2,3-bis(hydroxymethyl)pyrrolidines **7a** and **7b**. These, after reaction with acetyl chloride (AcCl) followed by selective *O*-deprotection with tetrabutylammonium fluoride (TBAF), generate the compounds **9a** and **9b**, in which only one –OH remains to further reactions (scheme 2).



4a, 4b

6a, 6b

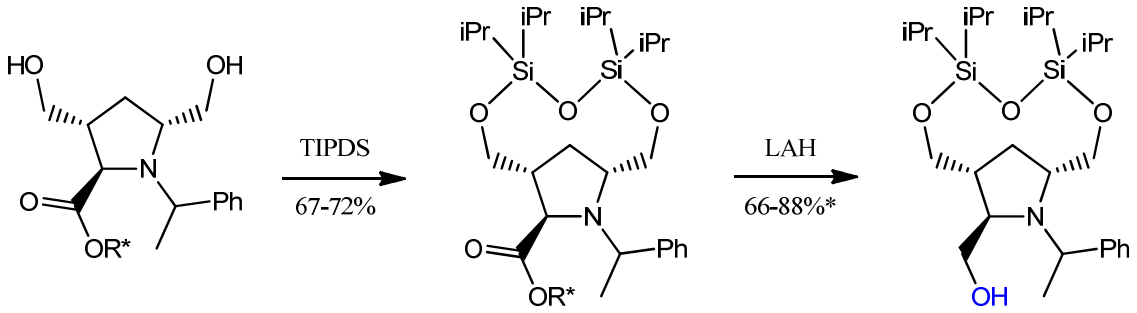
7a, 7b

8a, 8b

9a, 9b

Scheme 2:

Several assays were performed to selective reduce the carbonyl group in order to guarantee the C2-OH group. Different silyl protecting and reducing agents were used. Trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBDMS) showed the same results as TBDPS and borohydrides were ineffective in the reduction assays. Best results appeared when 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[8] (TIPDS) was used, where it was possible to perform the reduction getting both monohydroxilated compounds **11a** and **11b** with moderated to high yields (scheme 3).



4a, 4b **10a, 10b** **11a, 11b**

Scheme 3

Those results encouraged us to perform all the remaining processes in these enantiomers, as previously reported to the racemic mixture. In this way, it is expected to perform the *N*-deprotection from **6a** and **6b** and, using equimolar amount of silyl protecting agent with **4a** and **4b**, get a free hydroxyl group in C3-postion.

4. Conclusion

In conclusion, it was possible to, applying an efficient and straight forward orthogonal protection/deprotection methodology, selectively introduce functional groups in chiral iminosugars. Through the method described in the scheme 2, it was possible to achieve a C5-monohydroxylated compound with 68-91% yield over 4 steps. The C5-monohydroxylated ones were achieved using TIPDS as protecting agent with 44-63% yield over two steps.

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