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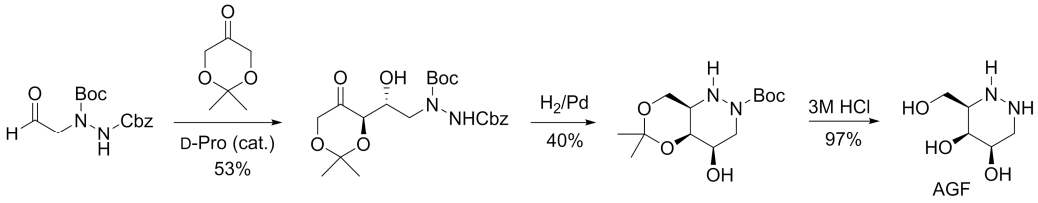

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A Short stereoselective synthesis of (+)-aza-galacto-fagomine (AGF)

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ABSTRACT

A catalytic asymmetric synthesis of (+)-aza-galacto-fagomine (AGF) – the most promising compound for the pharmacological chaperone therapy of Krabbe disease – was accomplished in six steps, in 14% overall yield. The synthesis hinges on the combination of organocatalyzed aldolization and reductive hydrazination.

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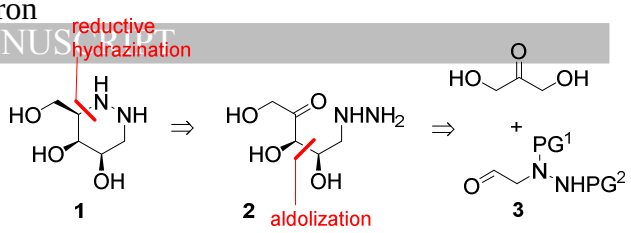
1. Introduction

Sugar processing enzymes play an important role, in both homeostasis and pathological states. Their selective inhibition could provide a basis for the treatment of various diseases, such as diabetes, cancer, obesity, and viral (including HIV) infections.[1] Malfunction of lysosomal glycosphingolipid (GSL) hydrolases that results in the accumulation of substrates in lysosomes, is the cause of a particular class of diseases known under the collective name "lysosomal storage disorders".[2] On the contrary, Krabbe disease, which is also a consequence of the deficiency of lysosomal β-galactocerebrosidase (GALC), does not induce glycolipid precipitation, but leads to progressive demyelination of the white mass in the central nervous system, as well as in peripheral nerves, and neurodegeneration, usually with a fatal outcome.[3] The presumed agent for this destructive process is psychosine, a cytotoxic galactosphingolipid which induces a cascade of events leading to cell death.[4] The enzyme replacement therapy for Krabbe disease is hampered by the fact that GALC does not cross the blood-brain barrier. In a number of cases, the disease is not caused by the complete absence of GALC, but rather by its structural modification, *i. e.* misfolding. The mutated enzyme is not only less efficient, but it cannot leave endoplasmatic reticulum. In such cases, a complex between a small molecule and the protein could stabilize the correctly folded enzyme, thus allowing it to reach lysosome and effect there its glycolytic activity. This effect, known as the active site-specific chaperone effect, provides a basis for the so called pharmacological chaperone therapy (PCT): interestingly (and, maybe, counterintuitively), at subinhibitory concentrations glycosylase inhibitors act as enzyme-rectifying agents. Restoring 10% of the enzyme activity would be enough to prevent the disease. Iminosugars are known to exert strong, yet selective inhibitory activity on sugar-processing enzymes. 1-Deoxygalacto-nojirimycin (DGJ) was shown to enhance α-galactosidase A activity in patients with Fabry disease.[5] Quite recently, a similar approach was proposed for the treatment of Krabbe disease.[6] In a detailed study, a series of azasugars were synthesized and tested for their potential as PCT agents. The most active among them was aza-galacto-fagomine (AGF). This compound was prepared in 16 steps from the commercially available 2,3-*O*-isopropylidene-D-ribofuranose. Chemoenzymatic synthesis of AGF was also described (8 steps, 4% overall yield).[7] Further studies of AGF would require an efficient method of preparation. Several syntheses of diastereoisomeric azafagomine and the derivatives thereof were reported;[8] however, the results of these studies are not directly applicable to the synthesis of AGF. Herein we describe an enantioselective synthesis of AGF that may provide a ready access to this compound.

2. Results and discussion

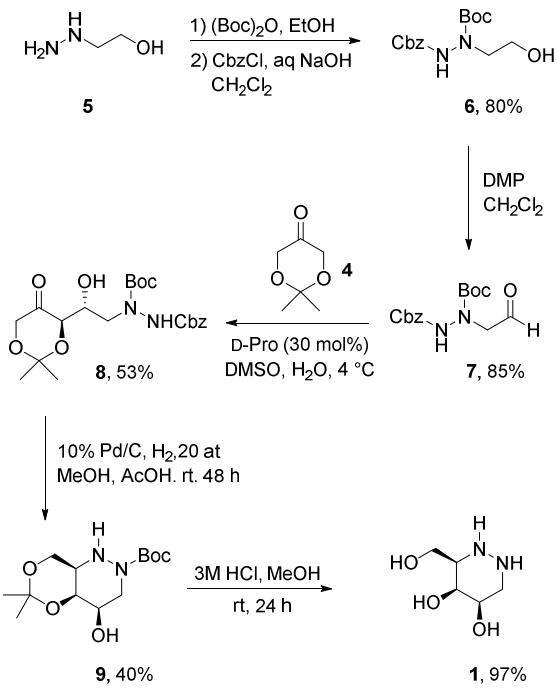
For some time, we have explored a tactical combination of organocatalyzed aldolization with reductive amination, for the efficient construction of polyhydroxylated alkaloids (iminosugars). In this way, optically pure members of pyrrolidine, piperidine,[9] pyrrolizidine[10] and indolizidine[11] series were prepared. We envisaged that a similar approach could be applied to the synthesis of AGF, as outlined in retrosynthetic format (Scheme 1). The piperazine ring in **1** could be formed by "reductive hydrazination" – an analogy of reductive amination applied to hydrazino ketone **2** (whereas intermolecular reductive hydrazinations have been reported recently, we are aware of only a single example of the intramolecular reaction in the literature, so far).[12] Compound **2** could be further disconnected by an *anti*-



Scheme 1

selective aldol transform into dihydroxyacetone and a properly protected hydrazino-acetaldehyde **3**.

Previously, others[13] and our group[9,10,11] have shown dioxanone **4**[14] to be a convenient synthetic equivalent of a dihydroxyacetone enolate in proline-catalyzed enantioselective aldol additions.[15] As the acceptor component we chose hydrazinoaldehyde **7**, whose three-step preparation from the commercially available hydrazinoethanol (**5**) was described earlier (Scheme 2).[16] It is of note that the oxidation step (*i. e.* **6** → **7**) must be performed with freshly prepared Dess-Martin periodinane[17] (DMP); the use of commercial DMP gives rise to impurities in aldehyde **7** that are difficult to remove and which affect the optical rotation of the intermediates and the final product. The key aldol reaction was performed in aqueous DMSO,[18] at 4 °C, to afford the aldol adduct **8** as a single diastereoisomer (98% *ee*, determined by chiral HPLC, see Supplementary material), in 53% yield (comparable results were obtained in DMF as a solvent: 50% yield). Catalytic hydrogenation of aldol **8** in pure ethanol resulted in the removal of the Cbz protecting group (55%); subsequent treatment with $NaCNBH_3$ in the presence of AcOH then gave the cyclic product of reductive hydrazination (**9**; 35%). However, we found that these two operations could be better accomplished as a one-pot procedure, by performing the catalytic hydrogenation of **8** in methanol/AcOH (40% yield for the deprotection/cyclization tandem). Interestingly, palladium catalyst should be added in three portions, as this protocol gives cyclic product **9** of superior purity; addition of Pd/C in a single portion results in side reactions and contamination of product with impurities. Treatment of compound **9** with methanolic HCl effected



Scheme 2

deprotection and provided the target compound – AGF (**1**; 97%) whose physical properties are in agreement with the

literature data.[6,7] The three-step conversion of aldol **8** into AGF (**1**) could be effected as a one-pot operation, in 60% yield; however, although no visible impurities could have been observed in the NMR spectra, the values for optical rotation were low, indicating the presence of trace impurities with strong levorotatory power. Thus, for the AGF to be analytically pure, compound **9** should be purified prior to deprotection.

3. Conclusions

To summarize, the catalytic asymmetric synthesis of (+)-aza-galacto-fagomine (AGF, **1**) was accomplished in 6 steps from the commercially available alcohol **5**, in 14% overall yield, which makes this compound readily accessible for further medical research.

4. Experimental section

4.1. General experimental

All chromatographic separations were performed on silica gel, 10–18, 60 Å (dry-flash), 100–200, 60Å (column chromatography), ICN Biomedicals, 60 (0.063-0.200 mm) (column chromatography), and ion exchange column chromatography (acidic resin DOWEX 50WX8-100). Standard techniques were used for the purification of reagents and solvents.[19] Petroleum ether (PE) refers to the fraction boiling at 70–72 °C. ^{1}H NMR spectra were recorded at 500 MHz, ^{13}C NMR at 126 MHz. Chemical shifts are expressed in ppm (δ) using TMS as the internal standard. IR spectra were recorded on a FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on TOF LC/MS instrument. Melting points are uncorrected.

2-Benzyl 1-*tert*-butyl 1-(2-hydroxyethyl)hydrazine-1,2-dicarboxylate (6)[16]

A solution of $(Boc)_2O$ (2.87 g, 13.15 mmol) in dry ethanol (8.0 mL) was added dropwise to a cold (0 °C) solution of *N*-2-hydroxyethylhydrazine **5** (1.00 g, 13.14 mmol) in dry ethanol (10.0 mL). After 30 min, cooling bath was removed and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure and the residue was further used without purification.

A solution of the crude product from the previous experiment (2.30 g, 13.05 mmol) in CH_2Cl_2 (13.6 mL) was added to a solution of NaOH (0.57 g, 14.25 mmol) in water (13.6 mL), at 0 °C, followed by a dropwise addition of benzyl chloroformate (1.86 mL, 2.23 g, 13.07 mmol). After 10 min, cooling bath was removed and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with water and 20% citric acid aq. solution, dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (SiO_2; eluent: petroleum ether/EtOAc = 8/2) afforded the title alcohol **6** (3.26 g, 80 %) as a white solid. mp 58-59 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 65 °C):[20] δ_H 9.21 (bs, 1H), 7.40-7.30 (m, 5H), 5.11 (s, 2H), 4.29 (t, *J* 5.6 Hz, 1H), 3.50 (q, *J* 6.3 Hz, 2H), 3.40 (bs, 2H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6, 65 °C): δ_C 155.8 (C), 154.5 (C), 136.3 (C), 128.0 (CH), 127.6 (CH), 127.4 (CH), 79.8 (C), 65.8 (CH_2), 57.9 (CH_2), 51.7 (CH_2), 27.6 (3 × CH_3); IR (ATR) ν_{max} 3362, 3198, 3009, 2980, 2886, 1716, 1422, 1364, 1288, 1138, 1061, 737 cm^{-1}; HRMS (ESI) for $C_{15}H_{22}N_2NaO_5$ $[M+Na]^+$ calculated: 333.1421; found: 333.1422.

2-Benzyl 1-*tert*-butyl 1-(2-oxoethyl)hydrazine-1,2-dicarboxylate (7)[16]

Freshly prepared Dess-Martin's periodinane (3.00 g, 7.07 mmol) was added to a solution of alcohol **6** (0.95 g, 3.06 mmol) in water-saturated dichloromethane (28.0 mL) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane, washed with 10% $Na_2S_2O_3$ (2 × 50 mL), sat. aq. $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by dry-flash chromatography (SiO_2; eluent: petroleum ether/EtOAc = 7/3) afforded aldehyde **7** (0.80 g, 85 %) as a pale yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$; at room temperature the compound exists as a mixture of rotamers[21]): δ_H 9.66 (bs, 1H), 7.35 (s, 5H), 7.02 (bs, NH, 1H; minor rotamer) and 6.91 (bs, NH, 1H; major rotamer), 5.16 (s, 2H), 4.33 (bs, 2H; major rotamer), and 4.24 (bs, 2H, minor rotamer), 1.45 (s, 9H; minor rotamer) and 1.39 (s, 9H; major rotamer); ^{13}C NMR (126 MHz, $CDCl_3$): δ_C 197.9 (CH), 156.2 and 155.7 (C), 155.0 and 154.6 (C), 135.5 and 135.4 (C), 128.6 and 128.5 (CH), 128.4 and 128.3 (CH), 128.2 and 128.2 (CH), 83.1 and 82.5 (C), 67.8 and 67.7 (CH_2), 61.2 and 59.5 (CH_2), 28.0 and 27.9 (3 × CH_3); IR (ATR) ν_{max} 3302, 2979, 2935, 1714, 1501, 1371, 1259, 1154, 1067, 756 cm^{-1}; HRMS (ESI) for $C_{15}H_{20}N_2NaO_5$ $[M+Na]^+$ calculated: 331.1264; found: 331.1270.

2-Benzyl 1-*tert*-butyl 1-((*R*)-2-((*R*)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-2-hydroxyethyl)hydrazine-1,2-dicarboxylate (8)

Aldehyde **7** (800 mg, 2.59 mmol) was added to a solution of D-proline (90.0 mg, 0.78 mmol, 30 mol %) in DMSO (9.0 mL). Next, dioxanone **4** (900 mg, 6.92 mmol) and water (206.0 μL, 11.44 mmol) were added to the flask and the mixture was vigorously stirred for 48 h at 4 °C. The reaction mixture was diluted with EtOAc and washed with water (50 mL). The aqueous phase was back-extracted with EtOAc (2 × 50 mL). The combined organic extract was dried over anh. $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by column chromatography (SiO_2; eluent: petroleum ether/acetone = 8/2) afforded the title aldol **8** (604.0 mg, 53%) as a pale yellow, viscous oil. $[\alpha]_D^{20}$ +70.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 65 °C) δ_H 9.15 (bs, NH, 1H), 7.38-7.32 (m, 5H), 5.12 (s, 2H), 4.39 (s, 1H), 4.26 (dd, *J* 16.7, 1.2 Hz, 1H), 4.06 (td, *J* 6.5, 3.0 Hz, 1H), 3.93 (d, *J* 16.7 Hz, 1H), 3.55 (bs, 2H), 3.15 (bs, OH, 1H), 1.41 (s, 6H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6, 65 °C) δ_C 206.9 (C), 155.7 (C), 154.5 (C), 136.2 (C), 128.0 (CH), 127.6 (CH), 127.3 (CH), 99.6 (C), 79.9 (C), 76.2 (CH), 67.5 (CH), 66.5 (CH_2), 65.8 (CH_2), 51.8 (CH_2), 27.5 (3 × CH_3), 24.3 (CH_3), 22.8 (CH_3); IR (ATR) ν_{max} 3306, 2984, 2938, 1743, 1714, 1374, 1224, 1158, 1086, 859, 754 cm^{-1}; HRMS (ESI) for $C_{21}H_{30}KN_2O_8$ $[M+K]^+$ calculated: 477.1634; found: 477.1635. The optical purity of compound **8** was determined by chiral HPLC as >98% ee (See the Supplementary material for details, page S12).

(4*R*,4a*S*,8a*R*)-*tert*-Butyl 4-hydroxy-6,6-dimethyltetrahydro-1*H*-[1,3]dioxino[5,4-c]pyridazine-2(3*H*)-carboxylate (9)

10% Pd/C (4.4 mg, 0.004 mmol, 7.5 mol %) was added to a solution of aldol **8** (23.1 mg, 0.053 mmol) in a solvent mixture methanol/acetic acid (3.7 mL, v/v= 7/1), and the reaction mixture was stirred at room temperature under a hydrogen atmosphere (20 at). After 2 h a second portion of Pd/C (8.8 mg, 0.008 mmol,

15 mol %) was added, and after 24 h a third portion of Pd/C (4.4 mg, 0.004 mmol, 7.5 mol %) was added. The total time of the reaction was 48 h. The mixture was filtered through celite and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; eluent: petroleum ether/EtOAc = 1/2) afforded the title compound (**9**) (6.0 mg, 40%) as a white solid. mp 180-181 °C; $[\alpha]_D^{20}$ +50.9 (*c* 1.20, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6, 65 °C) δ_H 4.59 (d, *J* 5.7 Hz, 1H), 4.23 (d, *J* 11.4 Hz, 1H), 4.07-4.00 (m, 2H), 3.81 (dd, *J* 12.2, 5.2 Hz, 1H), 3.60 (dd, *J* 12.3, 1.6 Hz, 1H), 3.49-3.42 (m, 1H), 2.90 (t, *J* 11.7 Hz, 1H), 2.54-2.50 (m, 1H), 1.41 (s, 3H), 1.40 (s, 9H), 1.35 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6, 65 °C) δ_C 154.4 (C), 97.9 (C), 78.5 (C), 66.5 (CH), 65.8 (CH), 61.3 (CH_2), 51.3 (CH), 45.0 (CH_2), 28.9 (CH_3), 27.8 (3 x CH_3), 18.5 (CH_3); IR (ATR) ν_{max} 3417, 3250, 2983, 2973, 1695, 1502, 1385, 1177, 1066, 993, 853 cm^{-1}; HRMS (ESI) for $C_{13}H_{24}N_2NaO_5$ $[M+Na]^+$ calculated: 311.1577; found: 311.1584.

(3*R*,4*S*,5*R*)-3-(hydroxymethyl)piperazine-4,5-diol (aza-galacto-fagomine) (1)

A solution of compound **9** (21.0 mg, 0.07 mmol) in a solvent mixture methanol/3M HCl (3.6 mL, v/v= 1/1) was stirred at room temperature for 24 h. After the volatiles were removed under reduced pressure, the residue was purified by ion exchange column chromatography (acidic resin DOWEX 50WX8-100) to give (+)-aza-galacto-fagomine (AGF, **1**) (10.5 mg, 97%) as a colorless film. $[\alpha]_D^{20}$ +10.4 (*c* 1.00, H_2O), [lit.[7] $[\alpha]_D^{20}$ +11.9 (*c* 1.00, H_2O)]; [lit.[6] $[\alpha]_D^{20}$ +9.0 (*c* 1.00, H_2O)]; ^{1}H NMR (500 MHz, D_2O) δ_H 4.02-3.99 (m, 1H), 3.79 (ddd, *J* 11.0, 5.2, 3.0 Hz, 1H), 3.64 (d, *J* 6.3 Hz, 2H), 2.96-2.87 (m, 2H), 2.81 (dd, *J* 12.6, 11.1 Hz, 1H); ^{13}C NMR (126 MHz, D_2O) δ_C 64.9 (CH), 63.7 (CH), 58.1 (CH), 57.6 (CH_2), 43.5 (CH_2); IR (ATR) ν_{max} 3274, 2932, 1570, 1413, 1102, 1029, 817, 657 cm^{-1}; HRMS (ESI) for $C_5H_{13}N_2O_3$ $[M+H]^+$ calculated: 149.0921; found: 149.0924.

5. Acknowledgments

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6. Supplementary Material

Supplementary material available (copies of ^{1}H and ^{13}C NMR spectra for all compounds).

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20. There is no perfect matching of *J* values for coupled protons because multiplets are somewhat deformed due to the existence of rotamers.

21. Aldehyde **7** decomposes on heating, so NMR spectra could not be recorded at elevated temperature.