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Synthesis of Amphiphilic Polyhydroxylated Pyrrolidines as Potential Glycosidase Inhibitors

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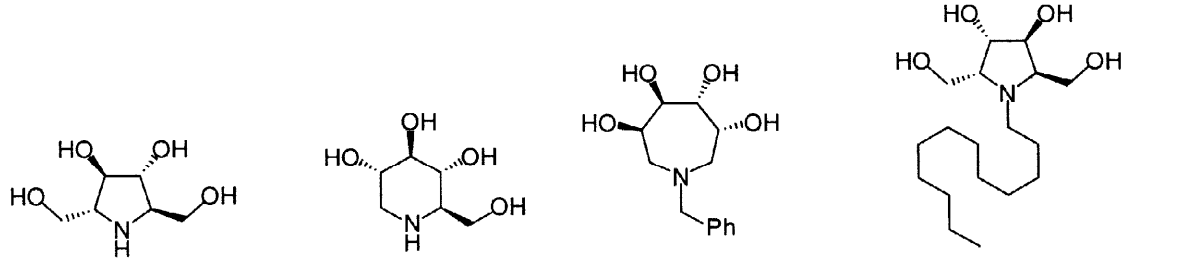
Abstract

Several polyhydroxylated pyrrolidines with an aliphatic long chain on the ring nitrogen were prepared starting from D-mannitol. An amphiphilic bis-azasugar scaffold has been also prepared. These products behave as cationic surfactants and show a promising anti HIV-1 activity.

Keywords: Pyrrolidines; Antivirals; Enzyme inhibitors; Cyclisation.

Polyhydroxylated piperidines and pyrrolidines have potential as therapeutic agents, including the treatment of cancer, diabetes and AIDS [1]. This family of compounds shows a general ability to inhibit the carbohydrate processing enzymes called glycosidases that are involved in several biological phenomena [2]. As these enzymes are responsible for the trimming of cell-surface oligosaccharide recognition, efficient inhibitors may have a role in the cell protection from viral infections [3]. Due to this utility, extensive work has been directed towards the synthesis and the pharmacological studies of five, six and seven membered ring azasugars. Starting from the simple 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine, isolated more than twenty years ago from certain legumes [4,5], all the most effective glycosidase inhibitors reported until now, show a large variety of substituents at the ring carbons but relatively few variations at the nitrogen [5-7].



2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine [4] | 1-Deoxynojirimycin [6] | 1,6-Dideoxy-1,6-imino-N-benzyl-D-manno-azepane [7] | Amphiphilic 2,5-dihydroxy methyl-3,4-dihydroxypyrrolidine [this paper]

Scheme 1

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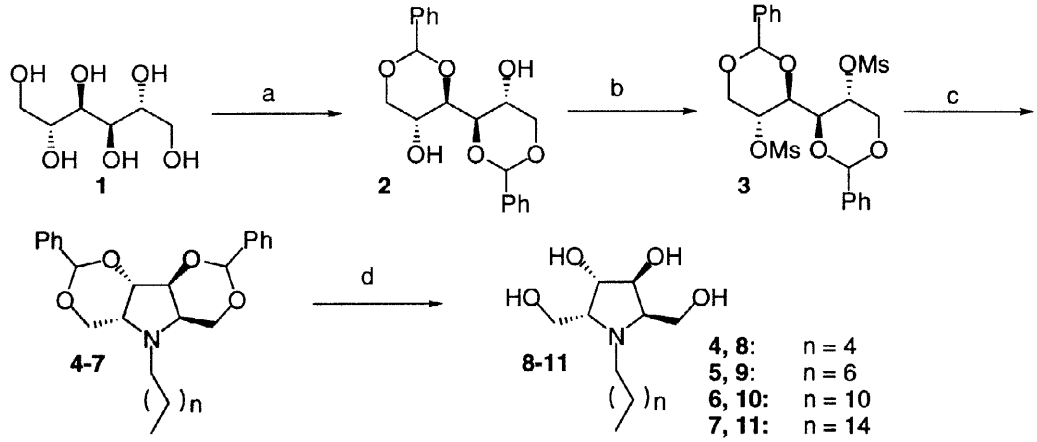
Since it is known that enzymes recognise aggregates of sugars more easily than single molecules [8], we thought that a simple amphiphilic azasugar, able to give aggregates in solution, could have the potential for better recognition and higher activity.

We report here the synthesis of a new class of simple and scaffolded polyhydroxylated amphiphilic pyrrolidines with the structure of potential glycosidase inhibitors. These products behave as surfactants and show an encouraging anti HIV-1 activity.

The synthesis started from D-mannitol that was selectively protected at positions 1,3 and 4,6 with benzaldehyde, following standard conditions [9]. The two remaining hydroxyl groups were mesylated with methanesulfonyl chloride and Et_3N. The mesylate **2** was further cyclised by heating with several long chain amines to give products **4-7**.



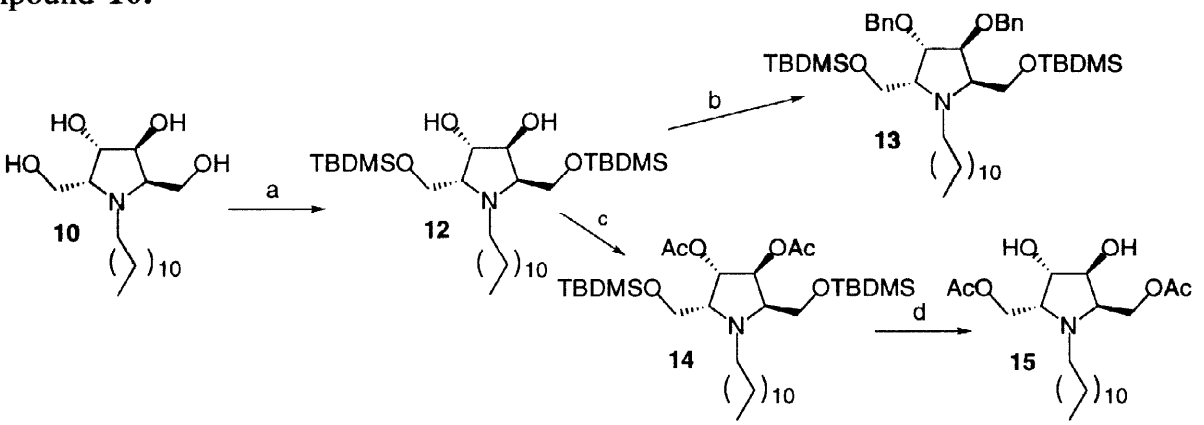
a) PhCHO, DMF, H_2SO_4 , 76 h, 45%. b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C, 90%. c) RNH_2, 135°C, 60-70%. d) HCl 36%, MeOH, 76 h, followed by NH_4OH 5M, 65% .

Scheme 2

The original paper that described the synthesis of N-benzylated pyrrolidines by cyclisation of a mesylate recommended the use of benzylamine (the nucleophile) as the solvent [10]. Following this procedure and using dodecylamine as the nucleophile, we observed the formation of the desired product **10**. However we were not able to separate it from the bulk of the unreacted amine. We tried different strategies to optimise the procedure. The use of 1 or 2 equivalents of the amine in the presence of a base in a high boiling solvent (for example pyridine in xylene or dichlorobenzene or K_2CO_3 in DMF) was completely unsuccessful. Then we tried to decrease the amount of the amine and found that heating **3** at 135°C (oil bath) with not less than 5 eq of the amine for 24 h, gave a crude mixture that could be purified by partition between Et_2O and a saturated solution of Na_2CO_3 followed by separation of the ethereal layer, evaporation of the solvent and filtration on a small path of silica gel with EtOAc/petroleum ether (40-60) 3/1. The yields of products **4-7** obtained with this procedure were always higher than 60%, even though the reaction was performed on multigram scale. The final deprotection was carried out in MeOH/ HCl aq. After stirring for 76 h in the dark under nitrogen, we observed the complete transformation of the starting material. By-products of the deprotection were removed by washing the solution with Et_2O. The aqueous layer was concentrated under vacuum (0.1 mmHg) to give **8-11** hydrochlorides. The corresponding amines were obtained by treatment of the hydrochlorides with a solution of NH_4OH 30%. We obtained compounds **8-11** as solids that were filtered, washed with cold water, crystallised from MeOH and fully characterised by ^1H and ^{13}C NMR spectroscopy.

Compounds **10** and **11** behave as single chain cationic surfactants. Determining the surface pressure of a monolayer against the surface area (π=f(A)) and from the results of light scattering analyses of solutions of **10** and **11**, we found that compound **10** forms micelles in diluted solution and compound **11** forms a monolayer on the interphase air-water [11].

With the idea of synthesising a bis- (or an oligo-) azasugar scaffold [12] with amphiphilic properties, we tried to selectively protect the hydroxymethyl groups in position 3 and 4 of compound **10.**

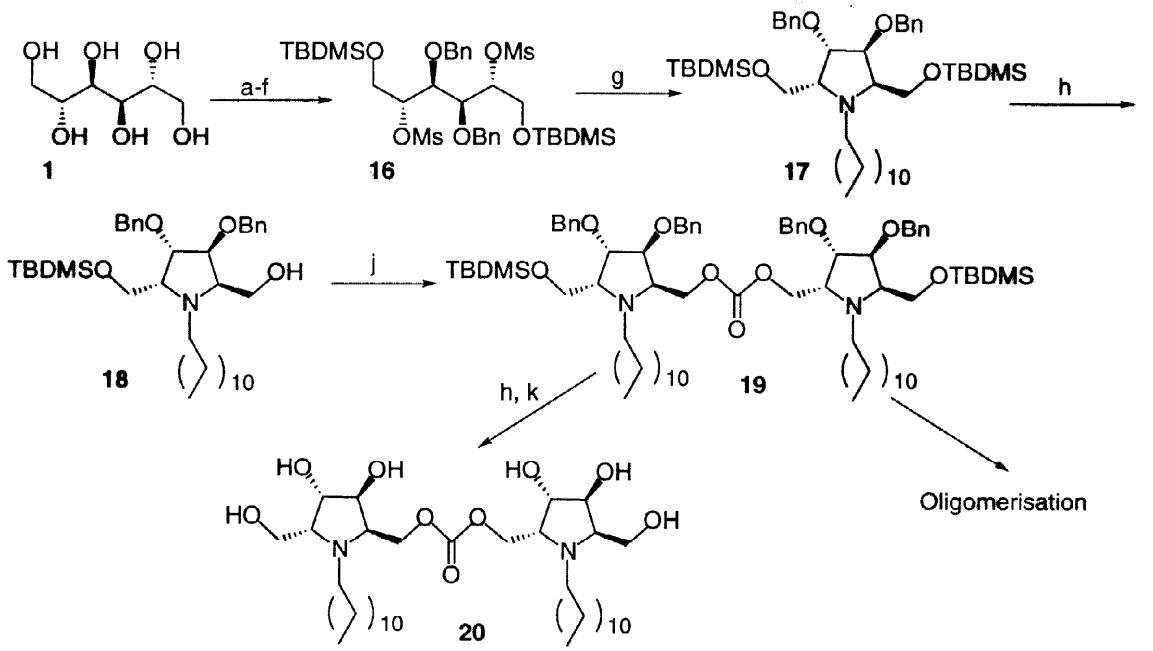


a) TBDMSCl, imidazole, DMF (60 % after separation from 20% of the monosilylated compound).
b) Benzyl-Br, NaOH, 5-10% c) Ac_2O, AcONa , 52% d) TBAF, THF, 58%.

Scheme 3

The primary OH functions were protected with TBDMSCl/imidazole/DMF to give compound **12** together with a relatively high amount of the monosilylated derivative that was separated by column chromatography on silica gel. Unfortunately the benzylation of the secondary OH functions of **12** was not possible. We tried several procedures (e.g. BnBr, TBAI, NaOH; BnBr, NaH, TBAI, DMF) but obtained just 5-10% of **13**. Acetylation of **12** (Ac_2O/AcONa) worked much better but, as soon as we tried to desilylate product **14**, we obtained exclusively compound **15** in which the acetate group migrated on to the primary alcohol. This transesterification occured so rapidly that it could not be avoided even at low temperature.

The bis-azasugar **20** was obtained by changing the order of events in the protection-cyclisation sequence of D-mannitol (scheme 4). We protected mannitol **1** at position 1,2 and 5,6 with 2,2 dimethoxypropane and p-TsOH in DMSO [13] followed by benzylation at position 3 and 4 with benzyl bromide/NaOH and selective deprotection at 1,2 and 5,6 with acetic acid in H_20.[14] The primary hydroxyl groups were selectively protected with TBDMSCl/imidazole/ DMF and the secondary OH mesylated to give product **16** (18% overall yields from **1**). Compound **16** was cyclised in the presence of dodecylamine at 135° C following our standard procedure to give **17** in 70% yield. Treatment of **17** with 0.8 eq of TBAF in THF at room temperature gave the monosilylated compound **18** together with less of 5% of the diol. Product **18** was reacted with 2 eq of 1,1'-carbonyldiimidazole in $CHCl_3$ at room temperature to give the corresponding acyl-imidazole derivative. The crude intermediate was heated at 110°C with one additional eq of **18** in pyridine for 5 h to give the dimer **19.** This product could be selectively deprotected with TBAF (as before) to continue the oligomerisation with 1,1'-carbonyldiimidazole or fully deprotected (TBAF/THF and H_2 Pd/C) to give the bis- azasugar carbonate **20.**



a) 2,2-Dimethoxypropane, p-TsOH, DMSO, 16h rt 70%. b) BnBr, NaOH, $TBAHSO_4$, 22h, 40°C, 61% . c) AcOH 80% in H_2O, 75%. e) TBDMSCl, imidazole, DMF, 65%. f) MsCl, Et_3N, CH_2Cl_2, 0°C, 90% . g) $C_{12}H_{25}NH_2$, 135°C, 18h, 70%. h) 0.8 TBAF, THF rt, 35%.j) 1,1'-Carbonyldiimidazole, $CHCl_3$, pyridine, 110°C, 35%. k) H_2 Pd/C, MeOH.

Scheme 4

Compounds **8-11** and **20** were tested in experiments of protection of MT4 cells from the HIV-1 induced cytopathogenicity, obtaining EC_{50} values between 8 and 12 μM.

Further experiments for the synthesis of oligomers (linear and cyclic) and for the optimisation of the structures for anti HIV-1 activity are in progress and will be reported in due course.

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References and Notes.

[1] Jacob GS. Current Opinion in Structural Biology 1995; 5: 605.
[2] See for example Look GC, Fotsch CH, Wong CH. Acc. Chem. Res. 1993; 26: 182
[3] Winkler DA. J. Med. Chem. 1996; 39: 4332 and references therein.
[4] Welter A, Dardenne G, Marlier M, Casimir J. Phytochemistry 1976; 25: 747
[5] Johnson CR, Johns BA. J. Org. Chem. 1997, 62, 6046.
[6] Fleet GWJ, Nicholas SJ, Smith PW, Evans SV, Fellows LE, Nash RJ. Tetrahedron Lett. 1985; 26: 3127.
[7] Qian X, Moris-Varas F, Wong CH. Bioorg. Med. Chem. Lett. 1996; 6: 1117.
[8] Lee YC, Lee RT. Acc. Chem. Res. 1995; 28: 321.
[9] Bagget N, Stribblehill J. J. Chem. Soc. Perkin Trans. I 1977; 1123.
[10] Masaky Y, Oda H, Kazuta K, Usui A, Itho A, Xu F. Tetrahedron Lett. 1992; 35: 5089.
[11] Full details of surface area, light scattering and data analysis will be presented elsewhere.
[12] Johns BA, Johnson CR. Tetrahedron Lett. 1998; 39: 749.
[13] Kierstead RW, Faraone A, Mennona F, Mullin J, Guthrie RW, Crowley H, Simko B, Blaber LC. J. Med. Chem. 1983; 26: 1561.
[14] Jurkzak J, Bauer T, Chmielewski M. Carbohydr. Res. 1987; 164: 493.