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Synthesis of 2-aminocyclopropyl pyrrolidines from glycoaminonitriles

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ABSTRACT

We have developed an expedient method for the synthesis of 2-aminocyclopropyl pyrrolidines from carbohydrate-derived α-aminonitriles involving up to five or six steps, the key step being the titanium-mediated aminocyclopropanation on the aminonitrile moiety, followed by cleavage of the protecting groups.

The iminosugar moiety is found in a number of natural products, such as nojirimycin[1] (5-amino-5-deoxy-D-glucose, **1**) and 1-deoxynojirimycin (1,5-dideoxy-1,5-imino-D-glucitol, **2**) (Fig. 1). These compounds are notably reversible glycosidase inhibitors.[2–14] For instance, 2,5-dideoxy-2,5-imino-D-mannitol[15] (DMDP) (**3**) inhibits α- and β-glucosidases.[16] and displays some anti-HIV activity. However its high cytotoxicity has precluded its use as an effective antiviral drug.[17] In this active area of research the development of new, chiral and differently functionalized iminosugars would allow the identification of more potent and selective glycosidase inhibitors.

Cyclopropane rings are present in many bioactive molecules.[18–21] Replacement of a methylene group in an iminosugar by a cyclopropane ring could induce electronic and conformational modifications, and consequently, enhance the binding with biological receptors. Szymoniak and Bertus[22–25] have recently reported a convenient synthesis of cyclopropylamines from nitriles and Grignard reagents in the presence of titanium isopropoxide. In this reaction, a titanacyclopropane intermediate **A** is generated by transmetalation between $Ti(OiPr)_4$ and EtMgBr and subsequent β-hydrogen fragmentation. Insertion of the nitrile into **A** affords the azatitanacycle **B**. Addition of a Lewis acid activates the azatitanacycle, which then undergoes ring-contraction to give the corresponding cyclopropylamine (Scheme 1).

In order to convert tertiary amides into cyclopropylamines, De Meijere and co-workers[26–28] have reported the same strategy, but using of methyltitanium triisopropoxide instead of $Ti(OiPr)_4$, as a more efficient reagent, that in addition requires only 1 equiv of Grignard reagent to generate titanacyclopropane, thus limiting the formation of side reactions (Scheme 2).

Plantier-Royon and co-workers[29] described an original application of this chemistry on a cyanosugar scaffold for the synthesis of α-L-fucosidase inhibitors. The cyclopropanation step occurs in 40–45% yield.

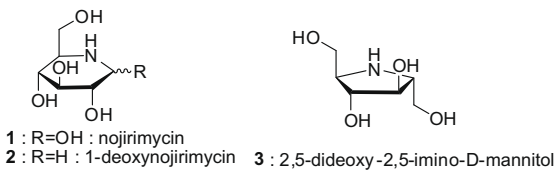
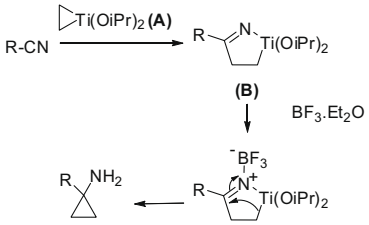
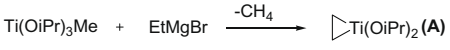


Figure 1.



Scheme 1. Cyclopropanation mechanism.



Scheme 2.

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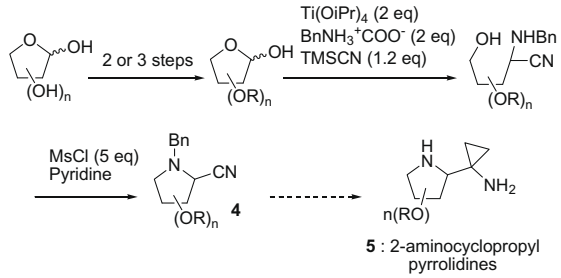
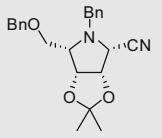
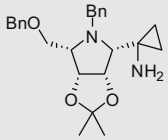
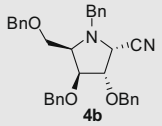
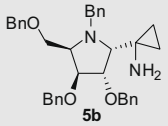
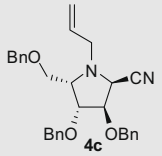
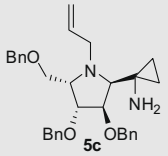
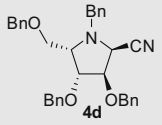
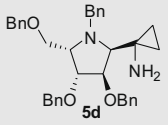
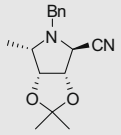
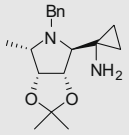
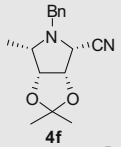
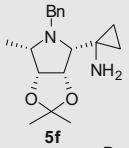
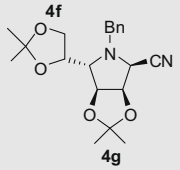
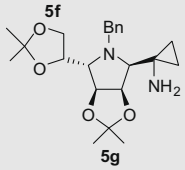
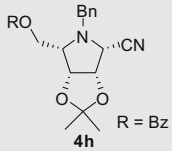
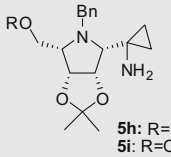


Scheme 3. General route for cyano pyrrolidine synthesis.[30]

Table 1
Cyclopropanation on cyano pyrrolidine

Entry	Cyano pyrrolidine	2-Amino cyclopropyl pyrrolidine	Yield (%)
1	 **4a**	 **5a**	57
2	 **4b**	 **5b**	45
3	 **4c**	 **5c**	28
4	 **4d**	 **5d**	37
5	 **4e**	 **5e**	38
6	 **4f**	 **5f**	57
7	 **4g**	 **5g**	44
8	 R = Bz **4h**	 **5h:** R= Bz **5i:** R=OH	65

Reagents and conditions: $Ti(OiPr)_3Me$ (1.5 equiv), EtMgBr (1.5 equiv), THF, 1 h, rt then $BF_3{\cdot}OEt_2$ (2 equiv), 1 h, rt.

In our current research programme aimed at the synthesis of glycoaminonitriles and their conversion into new proline derivatives, we chose the cyclopropanation of the cyano-pyrrolidine scaffold **4** (Scheme 3) as the key step. The latter substrates bear an α-aminonitrile moiety, which to the best of our knowledge has not previously been studied in this type of reaction. Cleavage of protective groups should then afford iminosugars of type **5** with potential as glycosidase inhibitors.

Pyrrolidines (**4a**–**h**) with a nitrile group at the anomeric position have been synthesized according to our newly developed methodology (Scheme 3).[30] The cyclopropanation step was performed on pyrrolidines **4a**–**h** using the following synthetic sequence: (i) EtMgBr (1.5 equiv, 2 M in Et_2O) was added at rt to a solution of iminonitrile (1 equiv) and methyltitanium triisopropoxyde (1.5 equiv) in THF, (ii) the reaction mixture was stirred for 1 h before adding $BF_3{\cdot}Et_2O$ (2 equiv), and (iii) after a further hour, a basic work-up followed by extractions with ethyl acetate and flash chromatographic purification afforded 2-aminocyclopropyl pyrrolidines. Cyclopropylamines **5a**–**i**[31] have been obtained following this protocol in moderate to good yields (Table 1). These results allow us to conclude that the reactivity of α-aminonitriles **4** is similar to that reported in the literature for related sugar derivatives.[29] We also observe that cyclopropanation of benzoyl-protected derivative **4h** gives **5i** with a free hydroxyl group on position C5 as the major product (**5h**/**5i**: 1/3).

Finally, and in order to test our derivatives as glycosidase inhibitors, the hydroxyl and amino groups need to be free. Consequently, hydrogenolysis and/or cleavage of the isopropylidene acetals (HCl 3 M) provided the target iminosugars **6**–**10** in 38% to quantitative yields (Fig. 2), isolated as the corresponding chlorhydrate salts as confirmed by spectral analysis.

Of particular interest is the confirmation of the chlorhydrate form of the final products. According to the literature, protonation of amines causes considerable upfield shift of the $^{13}C\alpha$–γ signals and particularly in the position β to the protonated group ($\Delta \approx -1.5$; -5.5; -0.5, respectively).[32] Analyses were performed on the deprotected derivatives as chlorhydrate salts ($1 \leqslant pH \leqslant 4$) and as the neutral form using NaOH to set the pH value to 12. As example the chemical shifts for compound **9** at pH 1 were shifted upfield compared to those in the carbon spectra at pH 12 (Fig. 3), upfield shifts were observed for all the carbon atoms of the pyrrolidine scaffold except for that of the C5 atom (Table 2).

Concerning the C2, C3 and C4, which are in the position β to the protonated cyclopropylamino group and endocyclic amino group, respectively, we observed a sizeable pH dependent shift (Δ = −2.3 to −3.2 ppm).

The signal corresponding to carbon (C7) of the cyclopropane was not influenced by variation in pH.

In summary, 2-aminocyclopropyl pyrrolidines have been synthesized from 2-cyano pyrrolidines. The key step was tita-

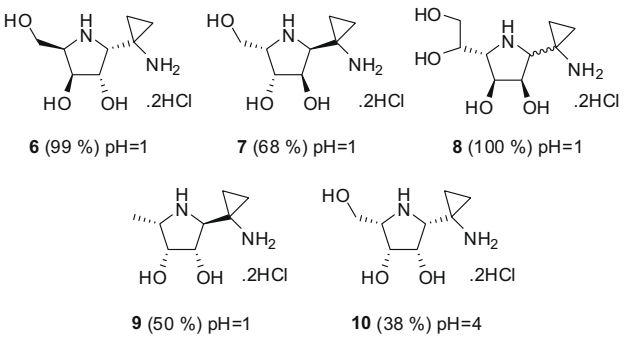


Figure 2. Deprotected 2-amino cyclopropyl pyrrolidines.

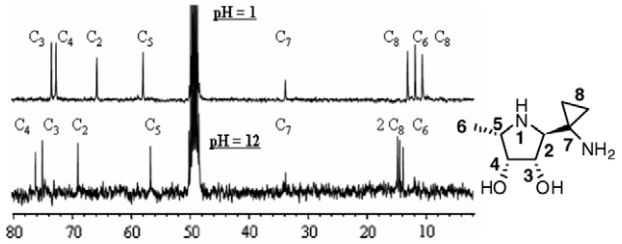


Figure 3. ^{13}C NMR data values at pH 1 and pH 12.

Table 2
^{13}C Chemical shift values for **9**

Carbon	Shift at pH 1	Shift at pH 12	Δ ppm
6	11.6	13.5	1.9
8	12.9–10.4	14.4–14.1	1.5–3.7
4	73.3	76.0	2.7
3	72.5	74.8	2.3
2	65.6	68.8	3.2
5	57.8	56.5	1.3
7	33.6	33.5	0.1

nium-mediated cyclopropanation of nitriles. The subsequent deprotection of hydroxyl and amine groups was carried out by hydrogenolysis followed by acid hydrolysis. Evaluation of the biological activity of the deprotected compounds as glycosidase inhibitors is in progress, and will be reported in due course.

Acknowledgements

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31. *General Procedure for* **5a**: ((2*R*,3*S*,4*R*,5*S*)-6-Benzyloxy-1-*N*-benzyl-3,4-di-*O*-isopropylideneoxy-pyrrolidine-2-aminocyclopropane).
To a solution of azasugar (1 equiv) and $Ti(OiPr)_3Me$ (1.5 equiv) in THF, was slowly added at room temperature EtMgBr (1.5 equiv, 2 M solution in Et_2O). After stirring for 1 h, $BF_3{\cdot}OEt_2$ (2 equiv) was added, and the reaction mixture further stirred for 1 h at room temperature. A solution of HCl 1 M was added until two clear phases were formed. Then, a solution of NaOH (2 M) was added until pH of aqueous layer was basic. The organic layer was extracted with ethyl acetate and dried over Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography using EtOAc.*Formula*: ($C_{25}H_{32}N_2O_3$); **Mw** 408.24; syrup; $[\alpha]_D^{16}$ −3.4° (*c* 1.04; $CHCl_3$); **IR** (**ATR**): ν 2925, 1116, 1094, 1074, 849, 735, 698 cm^{-1}; **^{1}H NMR ($CDCl_3$, 300 MHz)**: δ_H (ppm) 7.35–7.24 (m, 10H, C_6H_5), 4.67–4.59 (m, 2H, H_{6a}+OCH_2Ph), 4.43 (d, 1H, NCH_2Ph, J = 12.0 Hz), 4.33 (d, 1H, NCH_2Ph, J = 12.0 Hz), 3.90–3.74 (m, 3H, H_2+H_3+H_{6b}), 3.48 (dd, 1H, H_4, J = 6.1–9.5 Hz), 2.73 (dt, 1H, H_5, J = 6.1–4.9 Hz), 2.51 (sl, 2H, NH_2), 1.61 (d, 1H, OCH_2Ph, J = 4.3 Hz), 1.55 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 0.78–0.74 (m, 1H, $CH_2\Delta$), 0.54–0.50 (m, 1H, $CH_2\Delta$), 0.42–0.40 (m, 2H, $CH_2\Delta$); **^{13}C NMR ($CDCl_3$, 75 MHz)**: δ_C (ppm) 140.3–138.3 (C^{IV}, C_6H_5), 128.4–126.8 (CH, C_6H_5), 110.8 (C_{iso}), 81.3 (C_3), 78.6 (C_4), 75.0 (C_2), 73.3 (OCH_2Ph), 69.1 (C_6), 68.6 (C_5), 56.3 (NCH_2Ph), 31.4 ($C\Delta$), 26.1 (CH_3), 24.6 (CH_3), 16.8 ($CH_2\Delta$), 10.1 ($CH_2\Delta$); **HRMS** calcd for $C_{25}H_{33}N_2O_3$ $[M+H]^+$: 409.2491, found: 409.2482.
32. *Carbon-13 NMR Spectroscopy*; Breitmaier, E., Voelter, W., Eds.; VCH: New York, 1990.