Syntheses of sugar-related pyrrolidine derivatives by reductive amination reactions

M. S. Pino-González* and C. Assiego

Departamento de Bioquímica, Biología Molecular y Química Orgánica, Facultad de Ciencias, Universidad de Málaga, 29071 Málaga, Spain

Received 30 October 2004; accepted 22 November 2004
Available online 5 January 2005

Abstract—Several pyrrolidine iminosugar derivatives have been stereoselectively synthesised from a chiral keto-epoxyamide, by reductive amination procedures. An unexpected cyanide addition was observed when a mixture of SnCl₂ and NaCNBH₃ was employed.

© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Iminosugars (or azasugars) represent an important class of transition state analogue inhibitors of glycosidases and glycosyl transferases.¹–³ These compounds can be considered as useful biological tools for a better understanding of glycoconjugate function, because of the key role of carbohydrates in cellular recognition and signalling phenomena. Some iminosugars are arousing great interest as potential therapeutic agents against HIV infection,⁴,⁵ cancer,⁶,⁷ diabetes⁸ and other genetic or metabolic disorders.⁹ Some of them have already found clinical application¹⁰,¹¹ but efforts are still required to create novel structures with improved potency and selectivity towards a target enzyme. Many syntheses of polyhydroxylated pyrrolidines and piperidines have been focused on derivatives of D-gluco, D-manno or D-galacto configurations because their targeting enzymes are essential for living organism, but there are few reports on L-derivatives and other diastereomers.¹²

These antecedents encouraged us to develop our own synthetic approach to these compounds, from chiral epoxyamides as starting materials.¹³,¹⁴ Among the strategies followed by our group to reach several iminosugar types, the most direct synthesis employed reductive amination as the key step (Scheme 1). Several approaches to iminosugars have been described previously using this reaction,¹⁵,¹⁶ and a number of them were based in a double reductive amination,¹⁷,¹⁸ with the possibility of stereoisomer mixtures being formed. We planned to combine reductive amination with intramolecular epoxide opening.

2. Results and discussion

Our strategy starts with the oxidation of the epoxyamide 1a to the ketone 2. The best results were obtained

* Corresponding author. Tel.: +34-952134260; fax: +34-952131941; e-mail: pino@uma.es
treating 1a with DMSO and Ac₂O, although a small quantity of methylthiomethylether 4 was isolated with the oxidation product 2. Both products could be structurally determined by spectroscopy. To test a possible C-5 epimerisation in the oxidation product, we reduced 2 obtaining an inseparable mixture of 1a and its C-6 epimer 5a in approximately 1:1 relation. The epimers were acetylated giving the mixture of 1b and 5b. Thus, it was confirmed that 2 had not epimerised (Scheme 2).

The reductive amination process permitted us to obtain the pyrrolidine products in a one-pot procedure. The ketone 2 was treated with benzylamine and zinc chloride in ethanolic solution in the presence of sodium cyanoborohydride. The reduction of the imine with subsequent regioselective epoxide opening gave the pyrrolidine 3a by a 5-exo intramolecular process. Surprisingly, only a pyrrolidine derivative with the (S)-configuration (L-series) was isolated. The (R)-isomer was not detected. The ¹H NMR data showed the symmetrical structure of 3a, with similar coupling constants $J_{3,4} = 6.3$ Hz and $J_{5,6} = 6.4$ Hz.²⁰ The complete connectivity of the carbon and hydrogen atoms was ascertained by 2D NMR experiments. These signals: C-3 = 67.6 ppm, C-6 = 66.4 ppm, C-4 = 80.56 ppm and C-5 = 78.69 ppm are consistent with a pyrrolidine ring. Additionally, the acetylation of 3a giving 3b, confirmed the structural assignment. Our strategy takes advantage on earlier procedures due to the complete stereoselectivity in both processes: reduction and subsequent oxirane opening.

The low yield in the synthesis of 3a could be due to the formation of hemiacetal 6, formed from 2 after several hours of reaction. This product was isolated in several experiments. The chromatographic mobility of product 6 was similar to that of 2 (slightly more polar), it being sometimes difficult to determine the completion of the reaction with accuracy. NMR experiments permitted us to elucidate the structure of 6 but not the absolute configuration at C-6.

In an experiment, the ethanol addition product $6'$ (R = Et) was detected.

To study the influence of the catalyst we repeated the reaction of 2 with BnNH₂ and NaCNBH₃ using SnCl₂ (Scheme 3), isolating 3a as major product (42%) along with an $\alpha$-aminonitrile 7a (12%) that could be formed by cyanide addition to the imine intermediate before cyclisation. The spectroscopy data confirmed this structure, (¹³C NMR: 117.5 ppm, C≡N; quaternary C-6 in SEFT), but not the absolute configuration at C-6. To our knowledge this subproduct type has been not described in literature in reductive amination reactions with NaCNBH₃ as reductor. The $\alpha$-aminonitriles are useful as $\alpha$-aminoacids precursors and among the wide range of synthetic routes to $\alpha$-aminoacids, the related Strecker synthesis is the most predominant (Table 1).

![Scheme 2.](image)

![Scheme 3.](image)

**Table 1.** Isolated products in the reductive amination reactions of Scheme 3²¹

<table>
<thead>
<tr>
<th>Amine</th>
<th>Catalyst</th>
<th>3 (%)</th>
<th>7 (%)</th>
<th>6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BnNH₂</td>
<td>ZnCl₂</td>
<td>3a (60)</td>
<td>—</td>
<td>(25)</td>
</tr>
<tr>
<td>BnNH₂</td>
<td>SnCl₂</td>
<td>3a (42)</td>
<td>7a (12)</td>
<td>Not determined</td>
</tr>
<tr>
<td>(CH₃)₂CH(CH₃)₂NH₂</td>
<td>ZnCl₂</td>
<td>3c (67)</td>
<td>—</td>
<td>(3)</td>
</tr>
<tr>
<td>(CH₃)₂CH(CH₂)₂NH₂</td>
<td>SnCl₂</td>
<td>3c (42)</td>
<td>7c (15)</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

With the object of studying the influence of the nature of protecting group in the stereoselectivity of the reduction process, we tested the reaction with a bulky aliphatic amine. Moreover, $N$-alkylated azasugars have been demonstrated to be stronger glycosidase inhibitors than the corresponding nonalkylated derivatives.²¹ Using isoamylamine we obtained similar results to those of the benzyl amine with ZnCl₂ or SnCl₂ as catalysts (Scheme 3). The formation of the product 3c showed that the complete stereoselectivity, in the reductive amination reaction, cannot be simply justified by a possible


\( \pi-\pi \) stacking interaction between the trityl and benzyl groups as we supposed at first. The role of the free hydroxyl groups in the formation of D-products\(^{22} \) has been previously noted and accordingly, the presence of iso-propylidene group should favour the L-products. In our case, the reaction could not be tested with the deprotected ketone to compare possible changes in the stereoselectivity because the hydrolysis of the protecting groups could provoke secondary reactions. Additionally, some results revealed a discrepancy between the soluble hydride and catalytic hydrogenation methods.\(^{17} \)

In contrast, employing a combination of ammonium formate and sodium cyanoborohydride in methanol, (Scheme 4) we obtained the D-isomer 8a and the direct reduction product 1a. The C-6 epimer was not detected. The structural assignment of 8a and that of its acetate 8b was by NMR data \( (J_{5,6} = 0) \). Compound 1a cyclised easily to the C-glycoside 9.\(^{19} \)

![Scheme 4.](image)

3. Conclusion

In conclusion, with substituted amines and ZnCl\(_2\) or SnCl\(_2\), the hydride delivery is from the least hindered face to afford, after cyclisation, the LL-isomers. With SnCl\(_2\), the hydride delivery is from the least hindered imine is formed, which leads to the product DD-series) with a 5,6-\( \alpha \)-relationship.

We have described a method to achieve pyrrolidine derivatives in a highly stereocontrolled manner, in five steps from D-ribose. Therefore, this methodology can be extended to the synthesis of various pyrrolidine azasugars having suitable side chains for further synthetic elaborations. This research program is underway in our laboratory.

4. Experimental

4.1. General

All reactions were carried out under argon or nitrogen atmosphere using distilled solvents. Reactions were monitored by thin layer chromatography (TLC) on E. Merck silica gel plates (0.25 mm) and visualised using UV light (254 nm) and/or heating with 7% ethanolic phosphomolybdic acid solution. Flash chromatography was performed on E. Merck silica gel (60, particle size 0.040–0.063 mm). After chromatographic purification, the formation of solid foam is favoured solving syrupy products in some of Et\(_2\)O and evaporating. NMR spectra were recorded at on a Bruker WP200SY spectrometer at room temperature. Chemical shifts (ppm) are reported relative to the residual solvent peak. Multiplicities are designated as: singlet (s), doublet (d), triplet (t) and multiplet (m). Coupling constants are expressed as \( J \) values in Hertz units. Mass spectra (EI, CI and FAB) were recorded with a Kratos MS-80RFA or a Micromass AutoSpecQ instrument with a resolution of 1000 or 6000 (10\% valley definition). For the FAB spectra, ions were produced by a beam of xenon atoms (67 keV), using 3-nitrobenzyl alcohol or thioglycerol as matrix and Na\(_2\) as salt. Exact masses were recorded on a Kratos MS-80RFAa instrument of the University of Seville. Specific rotations were measured with a Perkin-Elmer 241 polarimeter.

4.2. N,N-Diethyl 2,3-anhydro-4,5-O-isopropylidene-7-O-trityl-D-altro-6-heptulosonamide 2

To a solution of 1a\(^{19} \) (0.7 g, 1.3 mmol) in DMSO (3.6 mL, 51.3 mmol) cooled with ice bath was added Ac\(_2\)O (2.4 mL, 25.6 mmol). The mixture was allowed to reach room temperature and stirred for 24 h. TLC (CHCl\(_3\)-hexanes-MeOH, 10:10:1) showed the depletion of 1a and the formation of two faster-running compounds. Ethyl ether was added (10 mL) and the reaction mixture washed with water and the aqueous layer extracted with Et\(_2\)O (2\times 10 mL). The combined organic layers were dried over anhyd MgSO\(_4\) and concentrated. The residue was chromatographed (AcOEt-hexanes, 4:6) to give 4 (123 mg, 27\%) and the ketone 2 (430 mg, 61\%) as a white foam.

\( ^{1}H \) NMR \( \delta \) (400 MHz, CDCl\(_3\)); 1.09 (t, 3H, CH\(_2\)C\(_3\)); 1.19 (t, 3H, CH\(_2\)C\(_3\)); 1.29 (s, 3H, C(CH\(_3\))\(_2\)); 1.44 (s, 3H, C(CH\(_3\))\(_2\)); 1.44–1.60 (m, 7H, H-7, J\(_{3,2} = 8.0, J_{5,6} = 7.0\), J\(_{7,7} = 6.6\), J\(_{8,8} = 7.6\), J\(_{9,9} = 3.0\); 3.18 (dd, 1H, H-5, J\(_{3,4} = 5.4, J_{2,3} = 1.1\), 3.30–3.46 (m, 4H, C\(_3\)); 3.49 (d, 1H, H-2), 4.04 (d, 2H, H-7, H-7, J\(_{7,7} = 6.9\), 4.39 (dd, 1H, H-4, J\(_{4,5} = 7.5\), 4.84 (d, 1H, H-5), 7.21–7.43 (m, 15H, Tr). 13C NMR \( \delta \) (100 MHz, CDCl\(_3\)); 26.9, 28.0, 31.4 (CH\(_3\)); 51.5 (C-2), 55.2 (C-3), 69.3 (C-4), 76.2 (C-5), 110.5 (C\(_4\)), 127.4, 128.1, 128.6, 142.9 (Ph), 165.1 (C\((CH\(_3\))+\), 193.1 (C\(_3\)).

\( ^{31}P \) NMR (200 MHz, CDCl\(_3\)); 0.46 (m, 1H, H-6, J\(_{4,5} = 6.4\), 4.06 (m, 1H, H-6), 4.55 (dd, 1H, H-5, J\(_{5,6} = 5.4\), J\(_{6,7} = 3.0\)).

Compound 4: \( R_\text{e} \); 0.7 (AcOEt–hexanes, 4:6) \( ^{1}H \) NMR \( \delta \) (400 MHz, CDCl\(_3\)); 1.14 (t, 3H, CH\(_2\)C\(_3\)); 1.25 (t, 3H, CH\(_2\)C\(_3\)); 1.37 (s, 3H, C(CH\(_3\))\(_2\)); 1.40 (s, 3H, C(CH\(_3\))\(_2\)); 2.10 (s, 3H, CH\(_2\)SCH\(_3\)); 3.37 (dd, 1H, H-3, J\(_{3,2} = 6.3, J_{2,3} = 1.8\), 3.4–3.52 (m, 6H, H-7, H-7, 2CH\(_2\)C\(_3\)); 3.54 (d, 1H, H-2), 4.02 (t, 1H, H-4, J\(_{4,5} = 6.4\), 4.06 (m, 1H, H-6), 4.55 (dd, 1H, H-5, 

\( J_{5,6} = 6.4\).
To a cooled solution (0 °C) of 2 (70 mg, 0.13 mmol) in EtOH (0.5 mL) was added NaBH₄ (4.8 mg, 0.13 mmol) stirring for 15 min. The reaction mixture was diluted with aq KHSO₄ and extracted with Et₂O. The organic layer was dried over anhyd MgSO₄, filtered and evaporated and later purified. The residue was purified by preparative TLC (AcOEt–hexanes, 1:1), yielding an inseparable mixture of 1a and 5a (50 mg, 71%). A solution of the mixture 1a and 5a (42 mg, 0.08 mmol) and Ac₂O (0.02 mL, 0.15 mmol) in pyridine (0.5 mL) was stirred for 48 h at room temperature. After addition of cold water and extraction with Et₂O. The organic layer was dried over anhyd MgSO₄, filtered and evaporated. The residue was purified in preparative TLC (hexanes–EtOEt, 3:7), yielding an inseparable mixture of 19 and 3a (23 mg, 0.4 mmol) and SnCl₂ (17.24 mg, 0.08 mmol, 0.15 equiv) in EtOH (0.4 mL), stirring the resulting mixture for 7 h at room temperature. After following the work-up procedure for reductive amination reactions, the residue was purified by preparative TLC (hexanes–EtOEt, 5:10:2), yielding a mixture (Rf: 0.4) of the acetylated products 1b and 5b (1:1, 30 mg, 65%).

Selected ¹H NMR data for compound 5a: 3.48 (d, H-2), 3.55 (m, H-3), 3.80 (t, H-4, 4.05 (m, H-6), 4.42 (dd, H-5). Compound 5b: 4.72 (m, 2H, H-5 of 5a and 5b), 5.39 (m, H-6).

4.4. Typical procedure for reductive amination reaction with metal chlorides

To a solution of the carbonyl compound 2 in EtOH was added the amine and then a solution of NaCNBH₃ and the catalyst (ZnCl₂ or SnCl₂) in EtOH, stirring the mixture at rt. After completion of the reaction, the mixture was diluted with water and extracted with Et₂O (2×). The combined organic layers were dried over anhyd MgSO₄, filtered and evaporated and later purified.

4.5. N,N-Diethyl 3,6-dideoxy-3,6-imino-N′-benzyl-4,5-O-isopropylidene-7-O-trityl-l-glycero-o-manno-heptonamide 3a

To a solution of 2 (200 mg, 0.37 mmol) in EtOH (1.2 mL) were successively added benzylamine (0.16 mL, 1.47 mmol) and a mixture of NaBH₄ (4.8 mg, 0.13 mmol) in EtOH (0.4 mL), stirring the mixture for 7 h at room temperature. After following the work-up procedure for reductive amination reactions, the residue was purified by preparative TLC (MeOH–AcOEt–hexanes, 1:1:8), obtaining pure 3a (120 mg, 60%) and 6 (28 mg, 25%) as white foams. Compound 3a: [α]_D²⁰ +16 (c 1, CHCl₃). ¹H NMR δ (400 MHz, CDCl₃): 1.08 (t, 3H, CH₃CH₂), 1.07 (t, 3H, CH₃CH₂), 1.33 (s, 3H, C(CH₂)₃), 1.41 (s, 3H, C(CH₂)₃), 2.66–2.72 (m, 2H, H₃, H-6), 3.06–3.21 (m, 3H, H-7, CH₂CH₂), 3.33–3.51 (m, 3H, H-7', CH₂CH₂, CH₂Ph), 3.56 (d, 1H, CH₂Ph), 4.57 (d, 1H, H-2, J₂₂ = 5.3), 4.70 (dd, 1H, H-4, J₄₃ = 6.4, J₄₅ = 5.2), 4.93 (dd, 1H, H-5, J₅₆ = 6.4), 6.98 (m, 2H, CH₂Ph), 7.15 (m, 3H, CH₂Ph), 7.18–7.41 (m, 15H, Tr). ¹³C NMR δ (100 MHz, CDCl₃): 12.6 and 14.2 (2CH₂CH₃), 25.1 and 26.0 (C(CH₃)₂), 40.0 and 41.6 (2CH₂CH₃), 54.4 (CH₂Ph), 61.6 (C-7), 66.4 (C-6), 67.5 (C-3), 67.7 (C-2), 78.7 (C-4), 80.6 (C-5), 86.8 (CPh₃), 110.9 (C(CH₂)₂), 126.8, 127.6, 128.7, 137.0, 144.1 (Ph), 171.9 (COEt₂). FAB HRMS m/z: 635.3456 [MH⁺] C₄₀H₃₂N₂O₅ requires 635.3484.

4.6. Acetylation of 3a

A solution of 3a (100 mg, 0.16 mmol) and Ac₂O (0.5 mL) in 1.2 mL of pyridine was stirred for 48 h at rt. After addition of cold water and extraction with Et₂O (2×5 mL), the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by preparative TLC (AcOEt–hexanes, 1:1, Rf: 0.5) afforded pure 3b (74 mg, 80%) as a foam. ¹H NMR δ (400 MHz, CDCl₃): 0.91 (t, 3H, CH₃CH₂), 1.20 (t, 3H, CH₃CH₂), 1.32 (s, 3H, C(CH₂)₃), 1.40 (s, 3H, C(CH₂)₃), 2.06 (s, 3H, COC(CH₃)₂), 2.73 (m, 1H, H₆), 3.06 (dd, 1H, H-3, J₃₂ = 8.2, J₃₄ = 4.6), 3.10–3.17 (m, 2H, CH₂CH₂), 3.29–3.35 (m, 3H, H-7, CH₂CH₂), 3.35 (d, 1H, CH₂Ph), 3.43 (t, 1H, H-7, J₇₇ = 8.3), 3.53 (d, 1H, CH₂Ph), 3.70–3.77 (m, 1H, CH₂CH₃), 4.60 (dd, 1H, H-5, J₄₅ = 6.0), 4.72 (dd, 1H, H-4), 5.51 (d, 1H, H-2), 6.93 (m, 2H, CH₂Ph), 7.14 (m, 3H, CH₂Ph), 7.20–7.40 (m, 15H, Tr). ¹³C NMR δ (100 MHz, CDCl₃): 12.3 and 13.3 (2CH₂CH₃), 20.8 (OOC(CH₃)₂), 25.4 and 26.1 (C(CH₃)₂), 40.9 and 42.2 (2CH₂CH₃), 54.2 (CH₂Ph), 61.2 (C-7), 65.1 (C-6), 65.7 (C-5), 69.3 (C-3), 78.8 (C-4), 79.5 (C-5), 86.7 (CPh₃), 110.8 (C(CH₂)₂), 126.8–144.1 (Ph), 168.7 (COEt₂), 170.1 (COEt₂).

4.7. Synthesis of 3a and N,N-diethyl 6(R or S)-cyano-3-dideoxy-3,6-imino-N′-benzyl-4,5-O-isopropylidene-7-O-trityl-D-glycero-O-manno-heptonamide 7a

Following the general procedure were mixed: 2 (100 mg, 0.18 mmol), EtOH (1 mL) and benzylamine (0.2 mL, 1.08 mmol) with a solution of NaBH₄ (23 mg, 0.4 mmol) and SnCl₂ (17.24 mg, 0.08 mmol, 0.5 equiv) in EtOH (0.4 mL), stirring the resulting mixture at room temperature. After 24 h, TLC (AcOEt–hexanes, 4:6) indicated the complete conversion of the starting material. After work-up as usual, the residue was subjected to flash chromatography on silica (AcOEt–hexanes, 3:7) to afford 3a (49 mg, 42%) and 7a (15 mg, 12%) as white foams. Compound 7a: Rf:
4.8. N,N-Diethyl 3,6-dideoxy-3,6-imino-3′-(3′-methylbutyl)-4,5-O-isopropylidene-7-O-trityl-L-glycero-d-manno-heptonamide 3c

Isoamylamine (0.04 mL, 0.36 mmol) was added to a solution of 2 (50 mg, 0.09 mmol) in EtOH (0.4 mL) with stirring at room temperature. Then was added a solution of NaBH3CN (25.9 mg, 0.41 mmol). After stirring for 3 h, TLC (AcOEt–hexanes, 4:6) showed a more faster-running compound (Rf: 0.45). The reaction was worked up as above and the residue subjected to flash chromatography on silica (AcOEt–hexanes, 4:6) to afford 3c (38 mg, 67%) as white foam, and 10 mg of 3d [25] (20 mg, 42%) as white foams. Compound 3c: Rf: 0.45. 

4.9. Synthesis of 3c and N,N-dietethyl 6(R or S)-cyano-3,6-dideoxy-3′-(3′-methylbutyl)-4,5-O-isopropylidene-7-O-trityl-d-manno-heptonamide 7c

Isoamylamine (0.08 mL, 0.73 mmol) was added to a solution of 2 (100 mg, 0.18 mmol) in EtOH (1 mL) with stirring at room temperature. Then was added a solution of NaBH3CN (11.5 mg, 0.18 mmol) and SnCl2 (17.3 mg, 0.09 mmol) in EtOH (0.4 mL). After stirring for 3 h, TLC (AcOEt–hexanes, 4:6) showed two new less polar products than 2. The reaction was worked up as above and the residue subjected to flash chromatography on silica (AcOEt–hexanes, 4:6) to afford 3c (47 mg, 42%) and 7c (18 mg, 15%) as white foams. Compound 7c: Rf: 0.7 (AcOEt–hexanes, 4:6). 

4.10. N,N-Diethyl 3,6-dideoxy-3,6-imino-4,5-O-isopropylidene-7-O-trityl-L-glycero-d-manno-heptonamide 8a

In a flask containing 14 mg of dried molecular sieves that was washed with methanol. The filtrates were concentrated under vacuo that was washed with methanol. The filtrates were concentrated under vacuo and the residue subjected to flash chromatography on silica (AcOEt–hexanes, 1:3) to afford 8a (15 mg, 14%), pure 8a (40 mg, 40%) as white foam, and 10 mg (8a + degradation products). Compound 8a: Rf: 0.3 (AcOEt–hexanes, 6:4). 

4.11. Acetylation of 8a

To a solution of 8a (30 mg, 0.05 mmol) in pyridine (1 mL) was added Ac2O (0.2 mL) with stirring at rt. TLC showed the slow formation of a new compound.
After 5 days, cold water was added and the mixture extracted with Et₂O (2 × 5 mL). The organic layers were dried (anhyd MgSO₄) and concentrated to give a residue that was subjected to flash chromatography on silica (AcOEt–hexanes, 1:1) to afford 8b (25 mg, 80%) as a white foam.

References

3. Asano, N. Glycobiology 2003, 13, 93R–104R.
23. Yields are given after purification. Partial hydrolysis was observed with prolonged exposure to silica.