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Studies on the transformation of nitrosugars into branched chain iminosugars. Part II: Synthesis of (3*R*,4*R*,5*R*,6*S*)-2,2-bis(hydroxymethyl)azepane-3,4,5,6-tetraol

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ABSTRACT

The first stereocontrolled synthesis of (3*R*,4*R*,5*R*,6*S*)-2,2-bis-(hydroxymethyl)azepane-3,4,5,6-tetraol is described herein. The method involves a novel double Henry reaction of the 3,5-di-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose with formaldehyde followed by a reductive ring closure to give the first branched 1,6-dideoxy-1,6-heptitol described.

1. Introduction

Glycosidase inhibitors have been extensively investigated over the last two decades due to their potential as therapeutic agents.[1] These compounds are involved in several important biological processes, such as digestion, biosynthesis of glycoproteins, and catabolism of glycoconjugates; some examples have already been tested or approved for use in the treatment of various diseases, such as Gaucher's disease,[2] diabetes,[3] cancer,[4] and viral infections,[5] including AIDS.[6]

The most common strategy for the design of such compounds is based on the quest for mimics of the cyclic alkoxycarbenium transition state formed during glycosidic bond cleavage. Thus, imino sugars,[7] which are analogs of furanoses or pyranoses where the ring oxygen is replaced by nitrogen, have been reported in most cases to be almost always inhibitors of the corresponding glycosidases.[8] A great deal of synthetic effort has been focussed on the preparation of substituted pyrrolidine or piperidine mimics of the corresponding sugars.[9] However, only a few syntheses of higher homologues such as azepanes or azocanes have been reported to date, despite such structures being more flexible than the corresponding pyrrolidines and piperidines and their potential to adapt better to the active site of glycosidases.

Tri and tetrahydroxylated azepanes **1** and **2** (Fig. 1) were prepared[10] for the first time by Paulsen and Todt in 1967, and have been extensively studied since then.[11] Some of these derivatives are glycosidase or protease inhibitors, while others exhibited anticancer activity.

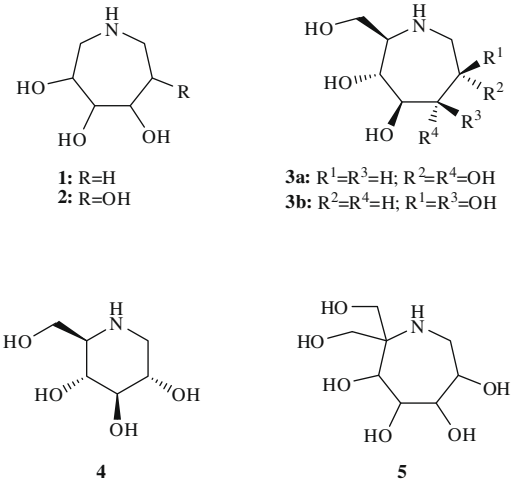

Figure 1.

In 2004, Sinaÿ et al. reported the preparation and biological evaluation of a number of 1,6-dideoxy-1,6-iminoheptitols **3**, a novel family of polyhydroxylated azepanes that are higher homologues of deoxynojirimycin **4** (Fig. 1).[12] Some of these derivatives show potent and specific glycosidase inhibition; for example, compound **3a** is a potent and selective inhibitor of coffee bean α-galactosidase, and compound **3b** strongly inhibits bovine liver β-galactosidase. On the other hand, due to the unusual spatial distribution of the hydroxyl groups,[13] these azepanes not only display a different inhibition profile compared to the previously reported

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polyhydroxylated azepanes but also they are more prone to form hydrogen bonds with nitrogenated bases, thus improving their ability to bind to the minor groove of DNA.[14]

Derivatives of 1,6-dideoxy-1,6-iminoheptitol provide an opportunity to alter and hopefully increase the specificity of inhibition of individual glycosidases. Accordingly, it should be of interest to prepare families of branched 1,6-dideoxy-1,6-iminoheptitols **5** (Fig. 1) in order to test their activity against a range of glycosidases and to determine whether the introduction of a branch can alter the biological activity. As a continuation of work on new synthetic applications of nitrosugars[15] and on new synthetic approaches to branched iminosugars,[16] we herein report the first enantiospecific synthesis of azepane **5a**. The synthesis includes the early introduction of the two hydroxymethyl substituents at C-6 of nitrosugar **6** by means of a double Henry reaction with formaldehyde (Scheme 1), followed by a heteroannulation strategy that was previously used by Fleet et al. in the synthesis of six-membered ring iminosugars.[17]

2. Results and discussion

The Henry reaction of nitrosugar **6** with paraformaldehyde as a source of the hydroxymethyl groups and tetrabutylammonium fluoride as a base afforded dihydroxymethylnitroderivative **7** in good yield. Treatment of **7** with ammonium formate and a catalytic amount of palladium black at 50 °C for 24 h gave amino derivative **8**. Removal of the isopropylidene protecting group in compound **8** under acidic conditions gave a 1.0:0.4 anomeric mixture of amines **9a** and **9b**, after the trifluoroacetic acid present in the reaction mixture was co-evaporated with toluene under reduced pressure. The resulting reaction crude remained unaltered in a sodium bicarbonate solution at room temperature, but compound **10** was obtained when heated at 40 °C for 24 h. The ^{13}C NMR spectrum of this compound showed that only one species was present, and its ^{1}H NMR spectrum showed a coupling constant between the protons H-2 and H-3 ($J_{2,3}$ = 1.2 Hz). This implies a *cis* relationship between the anomeric and adjacent hydroxyl groups. The presence of the *N* bridge in the azepane ring was confirmed by means of an HMBC experiment that showed a signal corresponding to the H-2–C-7 long distance coupling. The structure of compound **10** was additionally supported from its stability in methanol at neutral pH and from that a C-2 epimerization occurred when it was left standing in a methanolic hydrochloric acid solution. This can be explained in terms of a dehydration–hydration equilibrium between compound **10** and its non-isolable derivative **11**.

Finally, treatment of **10** with sodium cyanoborohydride afforded the hydrochloride salt of azepane derivative **5a** in good yield, through imine **11**.

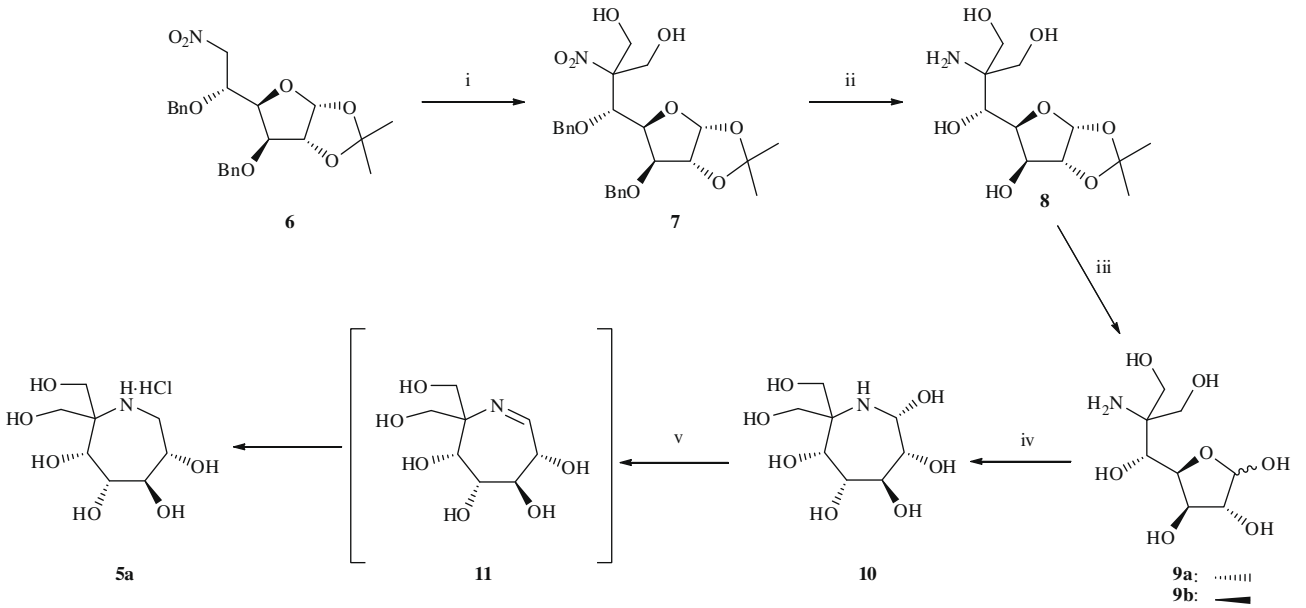
The new iminoheptitols **10** and **5a** were assayed for their inhibitory activity toward commercially available glycosidases. Significant inhibition of the following glycosidases was not observed at a concentration of 143 μg/mL and at optimal pH: α-D-glucosidase from *Saccharomyces cerevisiae*, α-D-glucosidase from *Bacillus stearothermophilus*, α-D-glucosidase from rice (*Oryza sativa*), β-D-glucosidase from Almond (*Prunus* sp.), α-D-galactosidase from green coffee bean (*Coffea* sp.), β-D-galactosidase from bovine liver, α-L-fucosidase from bovine kidney, α-D-mannosidase from jack bean (*Canavalia ensiformis*), β-D-mannosidase from *Cellullomonas fimi*, naringinase from *Penicillium decumbens*, *N*-acetyl-β-D-glucosaminidase from bovine kidney, *N*-acetyl-β-D-glucosaminidase from jack bean, *N*-acetyl-β-D-hexosaminidase from *Aspergillus oryzae*, and amyloglucosidase from *Aspergillus niger*.

3. Conclusion

In conclusion, we have achieved for the first time the efficient preparation of seven-membered ring branched iminoheptitols using a double Henry reaction with formaldehyde as the key step. Our polyhydroxyazepanes have an extra hydroxymethyl group compared to the previously reported 1,6-dideoxy-1,6-iminoheptitols.

Inhibition studies on the branched derivative **5a** showed that the introduction of a second hydroxymethyl substituent at the C-6 position of **3a** or **3b** resulted in the loss of inhibitory activity. This is probably due to the conformational distortion caused by the branched substituent as compared to **3a** and **3b**, which results in **5a** being unable to efficiently bind to the active site of any of the above glycosidases.

Work is now currently in progress in order to extend these studies to hexoses other than D-glucose in order to gain access to



Scheme 1. Reagents and conditions: (i) $(HCHO)_n$, TBAF, THF, rt, 1 h (86%); (ii) Pd black, NH_4HCO_2, MeOH, 50 °C, 24 h (88%); (iii) TFA, H_2O, rt, 4 h; (iv) $NaHCO_3$, THF, 40 °C, 24 h (83%); (v) (1) $NaCNBH_3$, AcOH, MeOH, rt, 30 h; (2) AcCl, MeOH, rt, 30 min (78%).

a wide range of seven-membered ring branched iminosugars like **5a**. Inhibition studies on these targets together with conformational and spectroscopical studies will allow us to confirm the above hypothesis on the relationship between the conformational properties of compounds **5** and the absence of glycosidase inhibition properties.

4. Experimental

Melting points were determined using a Kofler Thermogerate apparatus and are uncorrected. Specific rotations were recorded on a JASCO DIP-370 optical polarimeter. Infrared spectra were recorded on a MIDAC Prospect-IR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker DPX-250 apparatus. Mass spectra were obtained on a Hewlett Packard 5988A mass spectrometer. Elemental analyses results were obtained from the Elemental Analysis Service at the University of Santiago de Compostela. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and ethyl acetate/hexane mixtures as eluants; the TLC spots were visualized with Hanessian mixture. Column chromatography was carried out using Merck type 9385 silica gel.

4.1. 3,5-Di-*O*-benzyl-6-deoxy-6-*C*-hydroxymethyl-1,2-*O*-isopropylidene-6-nitro-α-D-*gluco*-heptofuranose 7

A 1.0 M solution of tetrabutylammonium fluoride in dry tetrahydrofuran (1.34 mL, 1.34 mmol) was added to a suspension of paraformaldehyde (0.41 g, 13.5 mmol) and 3,5-di-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-6-nitro-α-D-glucofuranose **6** (0.29 g, 0.67 mmol) in anhydrous tetrahydrofuran (3.5 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1 h. Dichloromethane (10 mL) was added, and the organic layer was washed with saturated aqueous ammonium chloride (3 × 5 mL), dried with anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting crude product was purified by flash column chromatography (dichloromethane/methanol 50:1) to give 3,5-di-*O*-benzyl-6-deoxy-6-*C*-hydroxymethyl-1,2-*O*-isopropylidene-6-nitro-α-D-*gluco*-heptofuranose **7** (0.29 g, 0.58 mmol, 86% yield) as an amorphous white solid. $[\alpha]_D^{20} = -67.8$ (*c* 1.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ = 1.32 (s, 3H, CH_3); 1.49 (s, 3H, CH_3); 2.72 (br s, 1H, OH); 2.95 (br s, 1H, OH); 4.10 (d, 1H, $J_{4,5}$ = 3.1 Hz, H-5); 4.21–4.28 (m, 4H, 2 × CH_2-Ph); 4.37–4.47 (m, 4H, 2 × CH_2–OH); 4.64 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-2); 4.66–4.71 (m, 2H, H-3 + H-4); 5.91 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1); 7.10–7.39 (m, 10H, 10 × H-Ph). ^{13}C NMR ($CDCl_3$) δ = 26.2; 26.7; 62.3; 63.6; 71.2; 75.1; 77.1; 78.5; 80.1; 81.7; 95.9; 104.9; 112.3; 127.3; 127.6; 127.9; 128.2; 128.4; 128.6; 136.6; 137.1. IR (NaCl) $\bar{\nu}$ = 3472 (br, OH); 1546 (st, NO_2). MS (CI) *m*/*z* (%) = 491 (1, $[M+H_2]^+$); 91 (100, $[PhCH_2]^+$). Anal. Calcd for $C_{25}H_{31}NO_9$: C, 61.34; H, 6.38; N, 2.86. Found: C, 60.98; H, 6.23; N, 2.82.

4.2. 6-Amino-6-deoxy-6-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranose 8

Palladium black (0.11 g, 20% w/w) and ammonium formate (2.09 g, 33.11 mmol) were added to a degassed solution of 3,5-di-*O*-benzyl-6-deoxy-6-*C*-hydroxymethyl-1,2-*O*-isopropylidene-6-nitro-α-D-*gluco*-heptofuranose **7** (0.54 g, 1.10 mmol) in methanol (11 mL), and the resulting mixture was stirred under a nitrogen atmosphere at 50 °C for 24 h. The suspension was then filtered through a CELITE® pad, and the solvent was evaporated in vacuo, to give 6-amino-6-deoxy-6-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*gluco*-heptofuranose **8** (0.27 g, 0.97 mmol, 88% yield) as a yellow oil. $[\alpha]_D^{20} = -20.3$ (*c* 2.33, CH_3OH). ^{1}H NMR (CD_3OD) δ = 1.31 (s, 3H, CH_3); 1.47 (s, 3H, CH_3); 3.74 (d, 1H, $J_{7,7}$ = 11.5 Hz, H-7); 3.76 (d, 1H, $J_{7,7}$ = 11.5 Hz, H-7); 3.86 (d, 1H, $J_{7,7}$ = 11.5 Hz, H-7); 3.91 (d, 1H, $J_{7,7}$ = 11.5 Hz, H-7); 4.14 (d, 1H, $J_{3,4}$ = 10.3 Hz, H-3); 4.22–4.28 (m, 2H, H-4 + H-5); 4.48 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-2); 5.92 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1); 8.51 (br s, 2H, NH_2). ^{13}C NMR (CD_3OD) δ = 26.7; 27.3; 61.1; 64.2; 66.9; 75.6; 81.2; 85.5; 106.8; 113.1. IR (NaCl) ν = 3425 (br, OH + NH_2). MS (CI) *m*/*z* (%) = 280 (100, MH^+); 263 (46, $[M-NH_2]^+$); 222 (27, $[M-C_3H_6O]^+$).

4.3. 6-Amino-6-deoxy-6-*C*-hydroxymethyl-α-D-*gluco*-heptofuranose 9a and 6-amino-6-deoxy-6-*C*-hydroxymethyl-β-D-*gluco*-heptofuranose 9b

A solution of 6-amino-6-deoxy-6-*C*-hydroxymethyl-1,2-*O*-isopropylidene-D-*glycero*-α-D-*gluco*-heptofuranose **8** (0.17 g, 0.61 mmol) in a mixture of trifluoroacetic acid and water (2:1, 9 mL) was stirred at room temperature for 4 h. The solvents were removed in vacuo, and the residue co-evaporated with toluene (3 × 5 mL) to afford a crude yellow oil formed for a 1.0:0.4 anomeric mixture of 6-amino-6-deoxy-6-*C*-hydroxymethyl-α-D-*gluco*-heptofuranose **9a** and 6-amino-6-deoxy-6-*C*-hydroxymethyl-β-D-*gluco*-heptofuranose **9b** (0.15 g, 0.61 mmol). ^{1}H NMR (CD_3OD) δ = 3.19–3.34 (m, 0.8H, 2 × **9b**-H); 3.34–3.50 (m, 1.4H, **9a**-H + **9b**-H); 3.60–3.92 (m, 6.2H, 5 × **9a**-H + 3 × **9b**-H); 3.97–4.13 (m, 2.8H, 2 × **9a**-H + 2 × **9b**-H); 4.57 (d, 0.4H, $J_{1,2}$ = 7.9 Hz, **9b**-H-1); 5.21 (d, 1H, $J_{1,2}$ = 3.6 Hz, **9a**-H-1). ^{13}C NMR (CD_3OD) δ = 60.9 (**9b**); 61.0 (**9a**); 61.1 (**9b**); 61.2 (**9a**); 63.3 (**9a**); 63.4 (**9b**); 69.2 (**9a**); 71.8 (**9b**); 72.0 (**9a**); 73.0 (**9a**); 73.6 (**9b**); 75.0 (**9a**); 75.7 (**9b**); 78.0 (**9b**); 93.8 (**9a**); 98.6 (**9b**). IR (NaCl) ν = 3327 (br, OH + NH_2). MS (CI) *m*/*z* (%) = 240 (7, MH^+); 223 (4, $[M-NH_2]^+$); 222 (16, $[M-OH]^+$).

4.4. (2*R*,3*R*,4*S*,5*R*,6*R*)-7,7-Bis-(hydroxymethyl)azepane-2,3,4,5,6-pentaol 10

Sodium bicarbonate (0.077 g, 0.915 mmol) was added to a solution of hemiacetals **9a** and **9b** (0.15 g, 0.61 mmol) in tetrahydrofuran (9 mL), and the resulting solution was heated at 40 °C for 24 h, after which TLC (chloroform/methanol/water/acetic acid 60:30:5:3) showed that the starting material had been consumed. The solvent was evaporated in vacuo, and the resulting residue dissolved in acetone. The solution was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (chloroform/methanol/water 40:10:1) to give (2*R*,3*R*,4*S*,5*R*,6*R*)-7,7-bis-(hydroxymethyl)azepane-2,3,4,5,6-pentaol **10** (0.12 g, 0.51 mmol, 83% yield) as a yellow oil. $[\alpha]_D^{20} = -13.9$ (*c* 1.32, CH_3OH). ^{1}H NMR (D_2O) δ = 3.39 (s, 1H, NH); 3.46 (d, 1H, $J_{6,6}$ = 8.4 Hz, H-6); 3.57 (dd, 1H, $J_{2,3}$ = 1.2 Hz, $J_{3,4}$ = 7.3 Hz, H-3); 3.71 (dd, 1H, $J_{8,8}$ = 2.3 Hz, $J_{8,8}$ = 10.4 Hz, H-8); 3.77–3.80 (m, 3H, H-5 + 2 × H-8); 3.87–3.91 (m, 2H, H-4 + H-8); 4.99 (d, 1H, $J_{2,3}$ = 1.2 Hz, H-2). ^{13}C NMR (D_2O) δ = 61.4; 67.0; 69.0; 69.3; 71.6; 72.2; 77.3; 94.4. IR (NaCl) ν = 3420 (br, OH + NH). MS (ES) *m*/*z* (%) = 240 (100, MH^+); 222 (34, $[M-H_2O]^+$). HRMS calculated for $C_8H_{18}NO_7$ $[MH]^+$: 240.1083. Found: 240.1077, $\Delta m = 6 \times 10^{-4}$.

4.5. (3*R*,4*R*,5*R*,6*S*)-2,2-Bis-(hydroxymethyl)azepane-3,4,5,6-tetraol hydrochloride 5a

Sodium cyanoborohydride (0.045 g, 0.71 mmol) was added to a solution of (2*R*,3*R*,4*S*,5*R*,6*R*)-7,7-bis-(hydroxymethyl)azepane-2,3,4,5,6-pentaol **10** (0.034 g, 0.14 mmol) in a mixture of methanol and acetic acid (98:2, 1 mL). The mixture was stirred at room temperature for 24 h. The solvents were removed in vacuo, after which the residue was dissolved in anhydrous methanol (1 mL) and acetyl chloride (0.1 mL) was added dropwise. The mixture was stirred

for 30 min, and the white solid was filtered off and was washed with diethyl ether (5 mL) to afford the (3*R*,4*R*,5*R*,6*S*)-2,2-bis-(hydroxymethyl)-azepane-3,4,5,6-tetraol hydrochloride **5a** (0.028 g, 0.11 mmol, 78% yield). $[\alpha]_D^{20} = -5.6$ (*c* 1.07, CH_3OH). ^1H NMR (D_2O) δ = 3.41–3.58 (m, 3H, 2 × H-7 + H-6); 3.89–4.18 (m, 7H, H-3 + H-4 + H-5 + 4 × H-8). ^{13}C NMR (D_2O) δ = 44.1; 59.5; 59.9; 66.4; 70.0; 71.8; 72.4; 74.6. IR (NaCl) ν = 3323 (br, OH + NH). MS (CI) *m/z* (%) = 224 (60, $[M-Cl]^+$); 206 (100, $[M-Cl\ H_2O]^+$). HRMS calculated for $C_8H_{18}NO_6$ $[M-Cl]^+$: 224.1134. Found: 224.1133, $\Delta m = 1 \times 10^{-4}$.

4.6. Biological assays

All enzymes and *para*-nitrophenyl substrates were purchased from Sigma, with the exception of β-mannosidase, which came from Megazyme. Enzymes were assayed at 27 °C in 0.1 M citric acid/0.2 M disodium hydrogen phosphate buffers at the optimum pH for the enzyme. The incubation mixture consisted of 10 μL of enzyme solution, 10 μL of 1 mg/mL aqueous inhibitor solution, and 50 μL of the appropriate 5 mM *para*-nitrophenyl substrate made up in buffer at the optimum pH for the enzyme. The reactions were stopped by the addition of 70 μL of 0.4 M glycine (pH 10.4) during the exponential phase of the reaction, which had been determined at the beginning using uninhibited assays in which water replaced inhibitor. Final absorbances were read at 405 nm using a Versamax microplate reader (Molecular Devices). Assays were carried out by triplicate.

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