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On the nature of the electronic effect of multiple hydroxyl groups in the 6-membered ring – the effects are additive but steric hindrance plays a role too†

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Research during the last two decades has shown a remarkable directional component of the substituent effects of hydroxyl groups, which has a profound effect on the properties of hydroxylated compounds such as carbohydrates. While the epimerisation of a single hydroxyl function is well studied the consequence of multiple epimerisations is more speculative. In this work the effect of three epimerisations was investigated. To this end epimeric 2-phenyl iminoxylitols that have a phenyl group as a conformational anchor and thus hydroxyl groups in the axial or equatorial position, respectively, were synthesized and their pKₐ and conformation were studied. The results show that the large difference in the electronic effect between the axial and equatorial hydroxyls is partially cancelled by counteracting steric hindrance from 1,3-diaxial interactions. Hydrogen bonding does not appear to play any role in the electronic influence of the hydroxyl groups.

Introduction

The profound influence of substituents on the reactivity and properties of organic compounds has been recognized for many years.¹ The effect of substituents on the basicity of simple amines was nicely compiled and discussed more than half a century ago² where it was recognized that the hydroxyl was a particularly influential substituent, but was also fickle with respect to its base decreasing effect which could vary profoundly.²a This was presumed to be due to hydrogen bonding. It was however not until recently that the highly directional and systematic aspect of this substituent effect was recognized and the importance of stereochemistry and conformation was revealed.³ From the synthesis of diastereomeric pairs of hydroxylated piperidines we realized that 1-azafagomine and its galacto isomer have different pKₐ values, which reflect the different stability of the ammonium ions. It was found that the equatorial hydroxyl groups on the piperidine ring decreased the basicity much more than the corresponding axial stereoisomers.³a,4 The substituent effects were also studied for other functional groups and found to be so consistent that the pKₐ can be calculated using the formula 10.7 – ∑σᵣ for piperidines or 7.3 – ∑σᵣ for hexahydropyridazines, where σᵣ is the substituent contribution of the axial or equatorial substituent. The difference in pKₐ values can be attributed to several effects, but charge–dipole interactions are in common for all and provide a satisfactory explanation for the observations: each C–O bond constitutes a dipole while each ammonium group has a positive charge (mainly dispersed on the surrounding atoms) – the closer the negative ends of the dipoles are to the positive charge the more favourable the structure. With this in mind it is not surprising that the stereoelectronic effect is coupled with a conformational effect, which is dependent on the protonation stage of the ring nitrogen, i.e. upon protonation it becomes even more favourable to have electro-negative substituents axially oriented as they effectively are less electron withdrawing than when equatorial due to the charge–dipole interaction. The fact that these stereoelectronic effects are strong enough to introduce conformational changes has been observed in a number of cases⁵ e.g. the hexahydropyridazine derivative (Fig. 1), which shifts conformation from 1 to 2 depending on pH⁶ and also in bicyclic sulfonium salts like 3, which resides in an all axial conformation, which suffers from sterically unfavourable 1,3-diaxial interactions.⁷ Generally, as the C–X dipole increase, with C–F as the extreme,⁸ the conformational change placing the dipole in an axial orientation becomes increasingly important for the stabilization of the piperidinium ion.⁹ In many cases the difference in stability between the two conformations is small and mixtures of conformations are present. The ratio of such mixtures influences the overall pKₐ value and can be determined directly by NMR.
from the intermediate $J$-couplings measured at room temperature$^{10}$ or even from the $pK_a$ itself.$^6$ The $pK_a$ values for the two conformational extremes 1 and 2 (Fig. 1) can be calculated using the formula mentioned above giving $pK_a = 5.5$ and 6.8, respectively, whereas the measured value is 6.2 as a result of both conformers being present. The connection between the substituent effects in nitrogen heterocycles, mainly piperidines, and other heterocycles has been thoroughly studied over the last decade,$^{11}$ and it is well accepted that the stereo-electronic effects observed in piperidines are linearly correlated with the anomic reactivity in e.g. carbohydrates.$^{1b,12}$ As an example it has been revealed that there are linear correlations between the rate in glycoside hydrolysis or glycosylation reactions and the acidity of piperidinium salts, with analogous substituent patterns.$^{12e}$ The generality of these effects is such that they with great success have been used to predict the behaviour and reactivity of carbohydrates such as anhydro-sugars$^{13}$ and axial rich glycosyl donors$^{14}$ as well as hydroxy-methyl conformers.$^{15}$

The $pK_a$-calculations of piperidinium derivatives assume that substituent effects are additive, which for a significant number of reference compounds hold true with a relatively small margin of error. However extreme differences in the basicity of conformers are predicted by this method and such differences have so far not been confirmed experimentally due to the unavailability of appropriate reference compounds. The purpose of this work was to investigate whether such extreme differences in base strength would be observed in diastereoisomers. For this purpose we targeted the two epimers of 5-phenyliminoxylitol, 6 and 7, and determined their $pK_a$ values (Fig. 2). As model compounds 6 and 7 are ideally suited because the very bulky phenyl group in the 5-position (carbo-hydrate numbering) acts as a conformational anchor fixing the conformation so that the three hydroxyl groups will either be all equatorial or all axial, i.e. giving the two extremes. The differences in $pK_a$ values are therefore large and calculated to be $2.0$ $pK_a$ units, with 7 being the most basic amine (Fig. 2).

Results and discussion

The two target piperidines have either a $\nu$-gluco or $\nu$-ido stereochemistry if numbered from the CH$_2$ group using carbohydrate numbering. In view of this, diacetone glucose is an obvious starting material as the stereogenic centers at C2, C3 and C4 can be maintained unchanged while phenyl and nitrogen are installed at C5. Using this approach aldehyde 8 was prepared in 3 steps from glucose acetone$^{16}$ and a Grignard addition using phenyl magnesium bromide was carried out to give an approx. $12:1$ ratio of the epimers (9 and 13), with $\nu$-ido (13) being the major product.$^{17}$ Since both were required, a two-step conversion of 13 involving PDC oxidation and NaBH$_4$ reduction provided the $\nu$-gluco derivative 9 as the main product (approx. 10:1 over 13). The $\nu$-ido isomer 13 was readily tosylated followed by nucleophilic substitution using NaN$_3$ in DMF to give the fully protected azide 14. Removal of the isopropylidene group and hydrogenation and benzyl hydrogenolysis over Pd/C afforded the 5-C-phenyl-$\nu$-gluco-1,5-iminopentitol 6. The same approach could however not be applied for the epimeric alcohol 9 as the tosylation did not proceed even under more forcing conditions. This is probably due to steric hindrance. To circumvent this, the 3-O-benzyl group was removed by hydrogenolysis and a cyclic sulfite 11 was prepared using thionyl chloride. Treating this with NaN$_3$ in DMF gave the desired azide 12. The acidic removal of the isopropylidene protective group followed by hydrogenolysis using Pd/C and triethylsilane (TESH) gave the target compound $\nu$-2-phenyl-iminoxylitol 7. The hydrogenation/hydrogenolysis reactions were generally sluggish and attempts to use more forcing conditions mainly gave the pyridine derivative 15. Changing the catalyst to Pearlman’s catalyst (Pd(OH)$_2$) or Raney® Ni did not improve the reaction.

In order to study the influence of internal hydrogen bonding four additional derivatives were synthesized. The H-bond donating capability of the 3-OH group was investigated by preparing the 3-O-methyl derivatives 18 and 20 (Scheme 2). The $\nu$-gluco epimer 18 was synthesized by 3-O-methylation of diacetone glucose followed by selective removal of the 5,6-O-isopropylidene group, periodate cleavage and addition of phenylnitrene bromide to obtain alcohol 16 predominantly as the $\nu$-ido isomer. Tosylation and subsequent $S_n$2 substitution using sodium azide gave azide 17, which was treated with AcOH (75%) to successfully remove the isopropylidene group from where hydrogenolysis to 18 was attempted. Neither hydrogenolysis with H$_2$(g) in the presence of Pd/C, Pearlman’s
catalyst (Pd(OH)₂) or RANEY® Ni gave satisfactory results nor did a two-step procedure of the Staudinger (Ph₃P) reaction and NaBH₄ reduction give satisfactory yield. However, changing the hydrogen source in the catalytic reduction solved the problem and hence using triethylsilane (TESH) in combination with Pd/C gave the 3-O-methyl 2-phenyl-L-iminoxylitol 18 in reproducible good yields. In order to prepare 20 it was necessary to start with the late intermediate 12 (Scheme 1) where the azide was already present. Compound 12 was methylated with MeI/NaH, deprotected with acetic acid and subjected to reductive amination according to the protocol above (Pd/C, TESH) to give 20 (Scheme 2).

The D-glucopyranosyl epimer 23 and the L-ido epimer 27 (Scheme 3) having 2- and 4-hydroxyls protected with methyl groups were prepared starting from the late stage intermediates 14 and 12 (Scheme 1). Compound 12 had to be benzylated to the 3-O-benzyl derivative 24 (Scheme 3). Then both epimers followed the same reaction sequence of removal of isopropylidene with acetic acid followed by reductive amination, which could be performed using Pd/C and TESH without any loss of benzyl ether. The obtained piperidines 21 and 25 were Boc-protected, methylated and the benzyl groups removed using Pearlman’s catalyst and hydrogen. The treatment of the obtained piperidines 22 and 26 with TFA gave the desired compounds 23 and 27 as their corresponding piperidinium trifluoroacetates (Scheme 3).

**Conformational studies**

With the 6 compounds (6, 7, 18, 20, 23 and 27) prepared, their respective conformations were studied using NMR. Since the conformation can be strongly dependent on the pH, as mentioned in the Introduction, the compounds were studied in both their amine and ammonium forms by adding either NaOD or DCl to the NMR sample. As Table 1 shows there is practically no conformational change upon protonation and hence the role of the 2-phenyl group as a conformational anchor that keeps the conformation fixed in one chair form is confirmed. In the D-glucopyranosyl series (6, 18 and 23) the compounds, regardless of pH, show large trans vicinal couplings in the range 9–12 Hz for J₂₃, J₃₄ and J₄₅ showing that these compounds are in the 4C₁ chair conformation (Table 1). The compounds in the L-ido series (7, 20 and 27) display very small couplings (broad singlets – bs) for J₂₃, J₃₄ and J₄₅, which is consistent with a 3C₄ chair conformation (Table 1) and inconsistent with a 4C₁ chair or B₁,₄ boat conformation. In both cases this is as anticipated.
Titrations

The $pK_a$ values of the 6 compounds (6, 7, 18, 20, 23 and 27) were determined using potentiometric titration. At least two titrations were conducted per compound and the average results are presented in Table 2 with the uncertainty being within 0.1 units. From the results we see some general and interesting trends. Firstly, the difference in the $pK_a$ value between the epimeric pairs, 6/7, 18/20 or 23/27, is 1.1 to 1.3 pH units, respectively, with the all axial epimer being more basic. While this qualitatively is the anticipated result it is considerably less than is predicted from calculations as these predict a difference of approximately 2 $pK_a$ units. Secondly O-methylation of the 3-OH has no significant influence on the $pK_a$ value as seen from the essential identical values obtained from the pairs 6/18 and 7/20. Thirdly the 2,4-di-O-methyl derivatives are found consistently less basic than the hydroxylated counterpart as seen from the 0.4 unit lower $pK_a$ value compared to 6 and the 0.6 unit lower $pK_a$ value of 27 compared to 7.

Discussion

The $pK_a$ values of the phenylpiperidines in the $^4C_1$ conformation (6, 18 and 23) are 6.1, 6.1 and 5.7 and are very much in line with the values found in similar compounds or are at least readily explained. A comparison of the $pK_a$ value of 6.1 for compound 6 with that of 1-deoxynojirimycin (28) of 6.7 (Fig. 3) reveals that the value is reasonable since the only difference between these molecules is that the hydroxymethyl group in 28 has been replaced with a phenyl group. This should decrease the basicity since the phenyl group is considerably more electron withdrawing as reflected by its higher inductive substituent constant (0.94 versus 0.66), and this is seen as the $\alpha$-phenyl group reduces the base strength by 1.3 whereas hydroxymethyl only reduces it by 0.7. The influence on the $pK_a$ of O-methylation in compounds 18 and 23 is also in line with what was previously found with 1-deoxynojirimycin derivatives where the tetra-O-methyl derivative 29

\[\text{OH} \quad \text{NH}_2^+ \quad \text{MeO} \quad \text{NH}_2^+ \quad \text{MeO} \quad \text{OH} \]

\[\text{MeO} \quad \text{MeO} \]

Fig. 3 Experimental $pK_a$ values from the literature.
The β-bridge and ammonium hydrogen. Therefore 7, 20 and 27 do not become as basic as one would expect based on electronic effects because they are more difficult to protonate due to hindrance. The base lowering effect from the steric hindrance of the two axial hydroxyl groups is about 0.8, which is very similar to the pKₐ difference in base pairs 36/37 and 38/39. This similarity is reasonable as the methylenes in 37 and 39 should be comparable in size to OH and less bulky than methyl.

**Conclusions**

This work has shown that an all-axial 2,3,4-trihydroxypiperidine has a significantly lower base strength than can be accounted for by the electronic effect. The corresponding all equatorial trihydroxypiperidine, on the other hand, has the pKₐ one would expect based on the electronic effect. The reason for the low pKₐ of the axial isomer is the two unfavourable 1,3-diaxial interactions that is present when the amine is protonated, which makes it more difficult to protonate. Thus the electronic effects are additive but pKₐ is reduced by the counteracting steric effect. Partial O-methylation has no significant effect other than reducing the base strength slightly due to the somewhat higher electron-withdrawing effect of OMe compared to OH.

**Experimental**

5-Azido-5-deoxy-1,2-O-isopropylidene-5-C-phenyl-α-L-idopyranoose (12)

Diol 10 (1.66 g) was dissolved in CH₂Cl₂ (50 mL) together with Et₃N (3.24 mL, 23.3 mmol, 4 eq.) and SOCl₂ (840 μL,
11.6 mmol, 2 eq.) was added slowly. The reaction was followed by TLC (ethyl acetate : petroleum ether 1 : 4, product $R_f = 0.5$) and quenched with water upon completion. The water phase was extracted with CH$_2$Cl$_2$ and the combined organic phases were washed with NH$_4$Cl (aq) and brine, followed by drying (MgSO$_4$) and concentration in vacuo. Flash chromatography yielded 11 (1.77 g, 91%), which was a ratio of 45:55 stereoisomers at sulphur. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.49–7.35 (m, 5H, Ar), 6.15 (d, $J = 3.6$ Hz, 1H, H1), 6.10 (d, $J = 3.7$ Hz, 1H, H3), 5.52 (d, $J = 7.4$ Hz, 1H, H5), 5.16 (d, $J = 3.7$ Hz, 1H, H3'), 4.98 (d, $J = 7.2$ Hz, 1H, H5'), 4.81 (2 d, $J = 3.0$ Hz, 2H, H2', H2'), 4.74 (dd, $J = 7.3$, 3.8 Hz, 1H, H4'), 4.70 (dd, $J = 7.5$, 3.8 Hz, 1H, H4), 4.64 (d, $J = 3.8$ Hz, 1H, H3), 1.46, 1.45, 1.35, 1.34 (4 s, 12 H, Me). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 132.6, 136.1, 129.0, 129.0, 128.8, 128.8, 126.5 (8 Ar C), 113.1 (CMe$_2$), 113.1 (CMe$_2$), 106.4 (C1), 106.0 (C1'), 83.3, 83.0, 83.0, 84.2 (4 C, C2, C2', C4, C4'), 78.7 (C3), 77.0 (C5'), 73.5 (C3'), 71.9 (C5), 27.1, 27.0, 26.5 (4 Me).]

The cyclic sulfite 11 (1.76 g, 5.64 mmol) was dissolved in DMF (25 mL) and NaN$_3$ (2.5 g, 0.038 mmol, 6.8 eq.) was added. The reaction mixture was heated to 105 °C and left overnight. TLC (ethyl acetate–petroleum ether ether 1 : 3) showed full conversion (product $R_f = 0.25$) and the reaction was allowed to cool to room temperature, whereafter it was diluted with water and extracted with ethyl acetate. The organic phases were collected, washed with water and brine followed by drying over MgSO$_4$ and concentration in vacuo. Flash chromatography (ethyl acetate–petroleum ether ether 1 : 3) yielded azide 12 (1.51 g, 92%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.45–7.32 (m, 5H, Ar), 6.01 (d, $J = 3.7$ Hz, 1H, H1), 4.79 (d, $J = 8.9$ Hz, 1H, H5), 4.44 (d, $J = 3.7$ Hz, 1H, H2), 4.35 (dd, $J = 8.7$, 2.7 Hz, 1H, H2), 3.77 (bs, 1H, H3), 2.21 (s, 1H, 3-0H), 1.50 (s, 3H, Me), 1.29 (s, 3H, Me). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 135.9, 129.0, 129.0, 127.8 (4C, Ar), 112.1 (CMe$_2$), 105.1 (C1), 85.1 (C2), 83.2 (C4), 74.7 (C3), 64.7 (C5), 26.8 (Me), 26.2 (Me).

HRMS calculated C$_{13}$H$_{23}$N$_2$O$_4$Na $= 314.1117$ found: 314.1112.

**5-Azido-3-O-benzyl-5-deoxy-1,2-O-isopropylidene-5-C-phenyl-$\alpha$-$\delta$-gluco-pentofuranose (14)**

Alcohol 13 (1.66 g, 4.66 mmol) was dissolved in pyridine (25 mL) and TsCl (2.0 g, 10.2 mmol, 2.2 eq.) was added. The reaction mixture was heated to 90 °C and left for 18 h. TLC (ethyl acetate–petroleum ether ether 1 : 3; $R_f = 0.2$) showed full conversion and the reaction was cooled to room temperature followed by dilution with ethyl acetate washing with water and brine. After concentration the crude product was dissolved in DMF (25 mL) and NaN$_3$ (5 eq.) was added. The reaction was stirred at 105 °C for 18 h whereafter TLC (ethyl acetate–petroleum ether ether 1 : 3; $R_f = 0.45$) showed full conversion. The reaction was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic phases were washed with water (5 times) and finally brine. After concentration the crude product was purified by flash chromatography (ethyl acetate–petroleum ether ether 5 : 1 to 3 : 1) to give the product (1.23 g; 69% over 2 steps).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.48–7.30 (m, 10H, Ar), 5.87 (d, $J = 3.7$ Hz, 1H, H1), 4.84 (d, $J = 10.0$ Hz, 1H, H5), 4.76 (d, $J = 11.4$ Hz, 1H, PhCH$_2$), 4.68 (d, $J = 11.4$ Hz, 1H, PhCH$_2$), 4.64 (d, $J = 3.7$ Hz, 1H, H2), 4.33 (dd, $J = 10.0$, 3.1 Hz, 1H, H4), 4.14 (d, $J = 3.1$ Hz, 1H, H3), 1.47 (s, 3H, Me), 1.30 (s, 3H, Me).

$^{13}$C NMR (126 MHz, CDCl$_3$): δ 137.3, 136.9, 128.8, 128.6, 128.1, 127.8 (12C, 2 Ar), 111.9 (CMe$_2$), 105.3 (C1), 81.9 (C2), 81.6 (C3), 81.5 (C4), 72.4 (PhCH$_2$), 62.9 (C5), 26.9 (Me), 26.3 (Me).

HRMS calculated C$_{21}$H$_{23}$N$_2$O$_4$Na $= 404.1586$ found: 404.1580.

**1,5-Dideoxy-1,5-imino-5-phenyl-$\alpha$-$\delta$-gluco-pentitol (6)**

Azide 14 (0.127 g, 0.33 mmol) was treated with TFA and water in THF (5 mL) until the TLC showed full conversion of the starting material (ethyl acetate–petroleum ether ether 1 : 3; $R_f = 0.45$). The solvents were removed in vacuo and the crude was dissolved in ethyl acetate–MeOH (1 : 1, 5 mL) and Pd/C (ca. 25 mg) was added. The reaction was stirred under a hydrogen atmosphere (1 atm) O.N. TLC (EtOH : CHCl$_3$) showed the formation of the product ($R_f = 0.2$). Yield $= 79$ mg (77%).

$^1$H NMR (500 MHz, D$_2$O) δ 7.55–7.48 (m, 5H, Ph), 4.23 (d, $J = 10.8$ Hz, 1H, H1), 4.02 (dd, $J = 9.3$, 10.8 Hz, 1H, H2); 3.99 (dd, $J = 5.1$, 9.3, 11.6, 1H, H4), 3.68 (t, $J = 9.3$ Hz, 1H, H3), 3.58 (dd, $J = 5.1$, 12.4 Hz, 1H, H5), 3.15 (dd, $J = 11.6$, 12.4 Hz, 1H, H5').

$^{13}$C NMR (126 MHz, D$_2$O) δ 131.9 (Ph), 130.3 (Ph), 129.6 (Ph), 128.3 (Ph), 76.3 (C3), 70.9 (C2), 67.0 (C4), 62.9 (C1), 46.5 (C6).

HRMS calculated C$_{14}$H$_{15}$N$_2$O$_3$ $= 210.1125$ found: 210.1136.
5-Azido-5-deoxy-1,2-O-isopropylidene-3-O-methyl-5-C-phenyl-α-D-glucopyranose (17)

1,2-O-Isopropylidene-3-O-methyl-α-D-glucopyranose (4.75 g, 20.3 mmol) was dissolved in EtOH : water (9 : 1) and NaIO₄ (6.5 g, 30.4 mmol; 1.5 eq.) was added in portions. After 2 h the reaction mixture was diluted with CH₂Cl₂, filtered and concentrated in vacuo. The crude was dried by azeotropic co-evaporation using toluene, whereafter it was dissolved in dry THF (30 mL) followed by the addition of PhMgBr (ca. 40 mmol in THF) at 0 °C. The reaction was quenched with NH₄Cl (aq) and extracted with ethyl acetate. The combined organic phases were washed with brine and concentrated in vacuo followed by purification using flash chromatography (ethyl acetate : petroleum ether 1 : 3; Rf = 0.3). A mixture of the two diastereomers of 16 was isolated (5.0 g; 88%).

The mixture of alcohols (16, 2.00 g; 7.13 mmol) was dissolved in pyridine (30 mL) and TsCl (4.08 g; 21.4 mmol; 3 eq.) was added together with DMAP (87 mg; 0.1 eq.). The reaction was stirred at 90 °C for 2.5 h, additional 2 g of TsCl was added and stirring was continued for 2 days at room temperature. After concentration the crude residue was diluted with ethyl acetate. The ethyl acetate phase was washed with water, HCl (1 M in water), NaHCO₃ and finally brine. After concentration the crude residue was diluted with ethyl acetate 3 : 1) to give tosylate (1.36 g, 70%).

HRMS calculated C₁₅H₂₆N₅O₅ + Na⁺ = 328.1268 found: 328.1288.

1,5-Dideoxy-1,5-imino-3-O-methyl-5-C-phenyl-D-ido-pentofuranose (18)

Azide 17 (562 mg; 1.84 mmol) was dissolved in AcOH (75% in water) and refluxed for 2 h. TLC (ethyl acetate–petroleum ether 1 : 4) showed full conversion of the starting material and the solvent was removed under vacuum. The residue was purified by chromatography (ethyl acetate : petroleum ether 1 : 1) to give 5-azido-5-deoxy-3-O-methyl-5-C-phenyl-D-ido-pentofuranose (404 mg, 1.52 mmol, 83%). This compound was dissolved in MeOH (20 mL) and Pd/C (162 mg) was added. To the reaction mixture was then added Et₃SiH (2.65 g; 22.8 mmol, 15 eq.) in portions via syringe. Pd/C was removed by filtration through Celite, which was then washed carefully with MeOH. The filtrate was concentrated and purified by chromatography (CH₂Cl₂–MeOH 9 : 1) to give 18 (144 mg, 42%).

1H NMR (500 MHz, DMSO-d₆) δ 7.49–7.35 (m, 5H, Ar), 3.72 (dd, J = 11.1, 9.1, 5.3 Hz, 1H, H1), 3.64 (dd, J = 10.0, 9.1 Hz, 1H, H3), 3.62 (s, 3H, Me), 3.50 (d, J = 10.0 Hz, 1H, H2), 3.21 (t, J = 9.1 Hz, 1H, H4), 3.14 (dd, J = 12.1, 5.3 Hz, 1H, H6), 2.61 (dd, J = 12.1, 1.1 Hz, 1H, H6).

13C NMR (126 MHz, DMSO-d₆) δ 138.3 (Ar), 127.9 (Ar), 127.3 (Ar), 127.0 (Ar), 87.3 (C4), 73.3 (C3), 69.4 (C5), 64.2 (C2), 58.9 (Me), 48.7 (C6).

[1] 45.0° (c 1.0, MeOH).

HRMS calculated C₁₅H₁₉N₃O₅ = 224.1281 found: 224.1264.

1,5-Dideoxy-1,5-imino-3-O-methyl-5-C-phenyl-D-ido-pentitol (20)

Azide 12 (1.323 g; 4.61 mmol) was dissolved in DMF (25 mL) cooled to 0 °C, where Na₂B₃H₆ (211 mg; 60% dispersion; 2 eq.) was added after MeI (0.6 mL; 1.31 g; 9.22 mmol; 2 eq.). After 1 h the reaction was quenched with water and diluted with EA. The phases were separated and the organic phase was washed with water (5 times) followed by brine and drying over MgSO₄. The crude 19 was concentrated on Celite and purified by flash chromatography (petroleum ether : ethyl acetate 1 : 1). Yield 1.28 g (91%).

1H NMR (500 MHz, DMSO-d₆) δ 7.46–7.29 (m, 5H, Ar), 5.99 (d, J = 3.8 Hz, 1H, H1), 4.82 (d, J = 9.5 Hz, 1H, H5), 4.50 (d, J = 3.8 Hz, 1H, H2), 4.33 (dd, J = 9.5, 3.1 Hz, 1H, H4), 3.16 (s, 3H, OMe), 3.11 (d, J = 3.1 Hz, 1H, H3), 1.51 (s, 3H, Me), 1.31 (s, 3H, Me). 13C NMR (126 MHz, DMSO-d₆) δ 136.4 (Ar), 128.8 (Ar), 128.8 (Ar), 127.8 (Ar), 112.0 (CMe₂), 105.6 (C1), 83.8 (C3), 83.5 (C4), 81.2 (C2), 64.9 (C5), 57.4 (OMe), 26.9 (Me), 26.7 (Me), 26.3 (Me).

HRMS calculated C₁₁H₁₄N₂O₄ + Na⁺ = 212.0952 found: 212.0950.

1,5-Dideoxy-3-O-methyl-5-C-phenyl-α-D-idopyranose (0.76 g; 1.74 mmol) was dissolved in DMF (10 mL) and NaN₃ (0.454 g, 7 mmol, 4 eq.) was added. The mixture was stirred at 70 °C for 24 h. The reaction mixture was diluted with ethyl acetate and washed with water (4 times) and brine. After concentration in vacuo the residue was purified using flash chromatography (ethyl acetate–petroleum ether 1 : 4) to give 17 (0.43 g, 80%).

1H NMR (500 MHz, CDCl₃) δ 7.42–7.30 (m, 5H, Ar), 5.89 (d, J = 3.8 Hz, 1H, H1), 4.77 (d, J = 10.0 Hz, 1H, H5), 4.61 (d, J = 3.7 Hz, 1H, H2), 4.30 (dd, J = 10.0, 3.1 Hz, 1H, H4), 3.90 (d, J = 3.1 Hz, 1H, H3), 3.42 (s, 3H, OMe), 3.14 (s, 3H, Me), 1.30 (s, 3H, Me).

13C NMR (126 MHz, CDCl₃) δ 137.1 (Ar), 128.9 (Ar), 128.9 (Ar), 128.7 (Ar), 127.9 (Ar), 111.9 (CMe₂), 105.4 (C1), 83.7 (C3), 81.8 (C4), 81.3 (C2), 63.1 (C5), 57.9 (OMe), 27.0 (Me), 26.4 (Me).
the reaction was allowed to stir for 2 h where TLC (ethyl acetate : petroleum ether 1 : 1 and CH₂Cl₂ : MeOH 9 : 1) showed full conversion. The reaction mixture was filtered through Celite, which was then washed carefully with MeOH. The filtrate was concentrated in vacuo and purified by chromatography (CH₂Cl₂ : MeOH 9 : 1). Yield 243 mg (38%).

¹H NMR (500 MHz, D₂O) δ 7.70-7.39 (m, 5H, Ar), 4.62 (bs, 1H, H2), 4.30 (bs, 1H, H5), 4.25 (d, J = 3 Hz, 1H, H3), 3.79 (dd, J < 3 Hz, 1H, H4), 3.60 (bd, J = 13.7 Hz, 1H, H6), 3.53 (s, 3H, Me), 3.53 (bd, J = 13.7 Hz, 1H, H6).

¹³C NMR (126 MHz, D₂O) δ 133.6 (Ar), 129.1 (Ar), 129.1 (Ar), 126.9 (Ar), 76.4 (C4), 68.4 (C3), 63.2 (C5), 58.7 (C2), 57.8 (Me), 46.9 (C6).

[a]D 56.8° (c 1.0, MeOH).

HRMS calculated C₁₂H₁₈NO₃ = 224.1281 found: 224.1301.

3-O-Benzyl-1,5-dideoxy-1,5-imino-5-C-phenyl-D-glucopentitol (21)

Azide 14 (0.88 g; 2.31 mmol) was dissolved in 50 mL acetic acid (75% in water) and refluxed for 1.5 h, where TLC (PE–EA 4 : 1) showed full conversion of the starting material. The reaction was concentrated in vacuo and purified by flash chromatography (ethyl acetate : petroleum ether 1 : 1) to give 5-azido-3-O-benzyl-1,5-dideoxy-1,5-imino-5-C-phenyl-D-glucopentofuranose (0.61 mg; 77%). A portion of this material (102 mg; 0.30 mmol) was dissolved in 5 mL MeOH and Pd/C (32 mg) was added under a nitrogen atmosphere followed by Et₃SiH (0.9 mL; 4.5 mmol; 1.0 eq.; 1.1 mmol) was added followed by Boc-anhydride (75% in water) and refluxed for 1.5 h, where TLC (ethyl acetate : petroleum ether 1 : 1 and CH₂Cl₂ : MeOH 9 : 1) showed full conversion, and the reaction was stirred for 2 h, where TLC (ethyl acetate–petroleum ether 1 : 1) indicated full conversion of the starting material. The reaction was quenched with water and the aqeous phase was extracted with CH₂Cl₂ (3 × 60 mL). The combined organic phases were washed with water (2 times), brine and dried (MgSO₄) followed by concentration in vacuo to give the title product (250 mg; 83%).

¹H NMR (500 MHz, CDCl₃) δ 7.43–6.94 (m, 10H, Ar), 4.62 (m, 3H, Bn, H2), 4.17 (dd, J = 14.4, 3.1 Hz, 1H, H6), 3.53 (dd, J = 7.8, 3.7 Hz, 1H, H4), 3.46 (ddd, J = 3.7, 3.2, 3.1 Hz, 1H, H5), 3.41 (t, J = 7.8 Hz, 1H), 3.32 (s, 3H, OMe), 3.31 (d, J = 14.4, 3.2 Hz, 1H, H6), 3.16 (s, 3H, OMe), 1.18 (s, 9H, CMe₃).

¹³C NMR (126 MHz, CDCl₃) δ 155.5 (C = O), 142.0 (Ar), 138.5 (Ar), 128.4 (Ar), 128.3 (Ar), 128.3 (Ar), 127.6 (Ar), 127.0 (Ar), 126.5 (Ar), 83.6 (C4), 83.4 (C3), 81.4 (C5), 80.1 (CMe₃), 72.9 (Bn), 60.1 (OMe), 59.6 (C2), 56.6 (OMe), 40.8 (C6), 28.3 (CMe₃).

HRMS calculated for C₁₈H₂₃NO₅Na = 450.2256 found: 450.2247.

1,5-Dideoxy-1,5-imino-2,4-di-O-methyl-5-C-phenyl-D-glucopentitol (23)

Compound 22 (235 mg; 0.55 mmol) was dissolved in 10 mL MeOH : acetic acid (1 : 1) and the solution was saturated with hydrogen gas using a balloon equipped with a long needle. The atmosphere in the flask was then exchanged with nitrogen and Pd(OH)₂ (50 mg) was added followed by flushing with hydrogen gas. After 24 h under a hydrogen atmosphere TLC showed that the reaction was incomplete and an additional 50 mg Pd(OH)₂ was added. This was repeated after additional 24 h, whereafter the reaction was left for further 72 h with 50 mg fresh catalyst. The crude reaction mixture was filtered through Celite, which was then washed carefully with MeOH. The filtrate was concentrated in vacuo and purified by flash chromatography (CH₂Cl₂–MeOH 9 : 1) to give the product (69 mg; 77%).

¹H NMR (500 MHz, CDCl₃) δ 7.75–7.01 (m, 10H, Ar), 4.94 (d, J = 11.5 Hz, 1H, Bn), 4.81 (d, J = 11.5 Hz, 1H, Bn), 3.74 (ddd, J = 9.7, 9.1, 5.3 Hz, 1H, H5), 3.57 (t, J = 9.1 Hz, 1H, H3), 3.44 (d, J = 9.1 Hz, 1H, H2), 3.32 (t, J = 9.1 Hz, 1H, H4), 3.20 (dd, J = 11.3, 5.3 Hz, 1H), 2.62 (ddd, J = 11.3, 9.7, 9.1 Hz, 1H, H6).

¹³C NMR (126 MHz, CDCl₃) δ 140.0 (Ar), 138.9 (Ar), 128.8 (Ar), 128.7 (Ar), 128.7 (Ar), 128.3 (Ar), 128.1 (Ar), 128.0 (Ar), 128.0 (Ar), 87.6 (C4), 76.3 (Bn), 75.1 (C3), 71.2 (C5), 66.6 (C2), 50.7 (C6).

HRMS calculated for C₁₈H₂₃NO₅Na = 300.1594 found: 300.1592.

3-O-Benzyl-N-tert-butoxycarbonyl-1,5-dideoxy-1,5-imino-2,4-di-O-methyl-5-C-phenyl-D-glucopentitol (22)

Diol 21 (300 mg; 1.0 mmol) was dissolved in THF : water (1 : 1; 10 mL), cooled to 0 °C in an ice bath. NaHCO₃ (152 mg; 1.1 eq.; 1.1 mmol) was added followed by Boc-anhydride (327 mg; 1.50 mmol, 1.5 eq.) and additional 1.1 eq. of NaHCO₃ in 6 mL THF : water (1 : 1). The reaction was allowed to reach room temperature, where it was kept stirred for 24 h. TLC (CH₂Cl₂–MeOH 9 : 1) indicated full conversion, and the reaction mixture was concentrated to remove THF and then diluted with ethyl acetate. The organic phase was washed with water three times, brine, dried over MgSO₄ and concentrated in vacuo. Flash chromatography (CH₂Cl₂–MeOH 19 : 1) yielded the Boc protected piperdine (289 mg, 72%). Most of this compound (280 mg; 0.70 mmol) was dissolved in dry DMSO (30 mL) and added to degreased NaH (7.4 mmol; 10 eq.) followed by MeI (450 μL; 7.4 mmol; 10 eq.). The reaction was stirred for 2 h, where TLC (ethyl acetate–petroleum ether 1 : 1) indicated full conversion of the starting material. The reaction was quenched with water and the aqueous phase was extracted with CH₂Cl₂ (3 × 60 mL). The combined organic phases were washed with water (2 times), brine and dried (MgSO₄) followed by concentration in vacuo to give the title product (250 mg; 83%).

¹H NMR (500 MHz, CDCl₃) δ 7.40 (m, 5H, Ar), 4.27 (d, J = 10.3 Hz, 1H, H5), 3.83 (dd, J = 9.2, 10.3 Hz, 1H, H4), 3.82 (dd, J = 12.5, 5.2 Hz, 1H, H1a); 3.79 (dd, J = 9.2, 9.2 Hz, 1H, H3), 3.73 (ddd, J = 11.2, 9.2, 5.2 Hz, 1H, H2), 3.56 (s, 3H, Me), 3.12 (s, 3H, Me), 3.08 (dd, J = 12.5, 11.2 Hz).

¹³C NMR (126 MHz, D₂O, DMSO log tube) δ 131.0 (Ar), 129.4 (Ar), 128.7 (Ar), 127.3 (Ar), 80.0 (C3), 75.5 (C2), 74.0 (C4), 60.9 (C5), 59.2 (Me), 57.6 (Me), 43.0 (C1).

[a]D 33.4° (c 1.0, MeOH).
HRMS calculated for $\text{C}_{13}\text{H}_{20}\text{NO}_3 = 238.1438$ found: 238.1437.

5-Azido-3-0-benzyl-5-deoxy-1,2-O-isopropylidene-5-C-phenyl-α-L-id-o-pentofuranose (24)

Compound 12 (105 mg; 0.36 mmol) was dissolved in dry DMF (2.5 mL) and cooled to 0 °C in an ice bath, and NaH (60% dispersion) (19 mg; 0.79 mmol; 2.2 eq.) was added. BnCl (0.5 mL) was added under an atmosphere of nitrogen, and the reaction was stirred for 1 h at 0 °C followed by 1.5 h at room temperature, where TLC (petroleum ether:ethyl acetate 3:1) showed full conversion. The reaction was quenched with water and diluted with ethyl acetate. The phases were separated, and the crude residue was purified by flash chromatography (petroleum ether:ethyl acetate 6:1) to give the product (128 mg; 93%).

$^1$H NMR (500 MHz, chloroform-d) $\delta$ 7.41–7.22 (m, 10H, Ar), 6.04 (d, J = 3.8 Hz, 1H, H1), 4.88 (d, J = 9.6 Hz, 1H, H5), 4.57 (d, J = 3.8 Hz, 1H, H2), 4.49 (dd, J = 9.6, 3.2 Hz, 1H, H4), 4.43 (d, J = 11.3 Hz, 1H, Bn), 4.09 (d, J = 11.3 Hz, 1H, H3), 3.47 (d, J = 3.2 Hz, 1H, H3), 1.55 (s, 3H, Me), 1.32 (s, 3H, Me).

$^{13}$C NMR (126 MHz, CDCl3) $\delta$ 136.9 (Ar), 136.0 (Ar), 128.7 (2 × C, Ar), 128.4 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 111.8 (CMe3), 105.3 (C1), 83.4 (C3), 81.6 (C4), 81.5 (C2), 71.8 (Bn), 64.7 (C5), 26.8 (Me), 26.2 (Me).

HRMS calculated $\text{C}_{21}\text{H}_{33}\text{NO}_5 + \text{Na}^+ = 404.1586$ found: 404.1556.

3-O-Benzyl-1,5-dideoxy-1,5-imino-5-C-phenyl-α-L-glucopyranosyl (25)

Compound 24 (461 mg; 1.21 mmol) was dissolved in 60 mL 75% aqueous acetic acid and refluxed for 2 h, where TLC (petroleum ether:ethyl acetate 4:1) showed full conversion. After concentration in vacuo the residue was purified by flash chromatography (petroleum ether:ethyl acetate 2:1) to give 5-azido-3-O-benzyl-5-deoxy-5-C-phenyl-α-L-id-o-pentofuranose (292 mg; 71%). This was then dissolved in MeOH (15 mL) and Pd/C (10%; 90 mg) was added followed by Et3SiH (2mL; 12.8 mmol; 15 eq.). After 2 h TLC (petroleum ether:ethyl acetate:petroleum ether 1:1) showed full conversion and was then quenched with water. The reaction mixture was extracted with CH2Cl2, and the combined organic phases were washed with water (3 times), brine and dried over MgSO4, filtered and concentrated in vacuo. The reaction was left for 20 h under a hydrogen atmosphere. THF and water were partly removed by evaporation and the rest were diluted with ethyl acetate followed by washing the organic phase with water (3 times) and brine before drying it (MgSO4). Concentration in vacuo and subsequent purification by flash chromatography (CH2Cl2:MeOH 29:1) gave the Boc derivative (104 mg; 0.26 mmol; 77%). This intermediate was redissolved in dry DMSO (10 mL) and added to a flask containing degreased NaH (110 mg as 60% dispersion; 10 eq.) together with MeI (170 μl; 2.72 mmol; 10 eq.). The reaction was stirred for 1.5 h where TLC (ethyl acetate–petroleum ether 1:1) showed full conversion and was then quenched with water. The reaction mixture was extracted with CH2Cl2, and the combined organic phases were washed with water (2 times) and brine followed by drying over MgSO4, and concentration in vacuo to give the title product 26 (99 mg; 89%).

$^1$H NMR (500 MHz, CDCl3) $\delta$ 7.54–7.39 (m, 2H), 7.37–7.11 (m, 8H), 5.70 (s, 0.5H), 5.38 (s, 0.5H), 4.86–4.70 (m, 2H), 4.22 (s, 0.5H), 3.94 (s, 0.5H), 3.76 (s, 1H), 3.54–3.44 (m, 1H), 3.45–3.13 (m, 7H), 2.47 (m, 1H), 1.38 (m, 9H).

$^{13}$C NMR (126 MHz, CDCl3) $\delta$ 155.0 (C=O), 139.0, 138.1 (broad), 137.4 (broad), 128.6 (broad), 128.4, 128.1 (broad), 128.0, 127.6, 127.2, 83.0 (broad), 82.1 (broad), 81.3 (broad), 80.7 (broad), 80.6 (CMe3), 80.3 (broad), 75.3 (broad), 74.7 (broad), 58.8 (broad), 58.5 (broad), 55.3 (broad), 53.7 (broad), 41.8 (broad), 41.0 (broad), 28.4 (CMe3).

$[\text{R}]_\infty 27.0^\circ$ (c 1.0, CHCl3).

HRMS calculated for $\text{C}_{25}\text{H}_{33}\text{NO}_5\text{Na} = 450.2251$ found: 450.2249.

1,5-Dideoxy-1,5-imino-2,4-di-O-methyl-5-C-phenyl-α-L-id-o-pentitol (27)

26 (84 mg; 0.20 mmol) was dissolved in MeOH:AcOH (1:1; 3 mL) and the solution was saturated with hydrogen gas before 50 mg Pd(OH)2 was added under an atmosphere of nitrogen. The reaction was left for 20 h under a hydrogen atmosphere. TLC (petroleum ether–ethyl acetate 1:1 + 1% Et3N) showed full conversion, and the reaction was filtered through Celite, which was then washed carefully with MeOH. The solution was concentrated in vacuo to give the debenzylated product (50 mg; 76%).

$^1$H NMR (500 MHz, CDCl3) $\delta$ 7.46–7.34 (m, 3H, Ar), 4.22 (bs, 1H, H2), 4.22 (bs, 1H, H4), 3.46 (bm, 1H, H3), 3.44 (s, 3H, Me), 3.33 (bm, J = 3.6 Hz, 1H, H5), 3.10 (s, 3H, Me), 3.09–3.04 (bm, J = 14.4, 3.6 Hz, 2H, H6, H6').

$^{13}$C NMR (126 MHz, DMSO-d6) $\delta$ 138.6 (Ar), 127.5 (Ar), 126.3 (Ar), 126.1...
(Ar), 80.5 (C3), 76.5 (C4), 65.5 (C5), 57.5 (Me), 55.7 (C2), 55.6 (Me), 51.7 (C6), [α]D 39.9° (c 1.0, CHCl₃).]

The Boc-protected intermediate (50 mg; 0.15 mmol) was treated with TFA (400 μl) in CH₂Cl₂ (4 ml containing 1% water) and concentrated to give the title product 27 (60 mg, quantitative).

1H NMR (500 MHz, D₂O) δ 7.61–7.52 (m, 5H, Ar), 4.76 (d, J = 1.9 Hz, 0H), 4.43 (dd, J = 3.1, 1.4 Hz, 1H), 3.83–3.74 (m, 3H), 3.62 (d, J = 2.3 Hz, 1H), 3.60–3.57 (m, 0H), 3.54 (d, J = 1.9 Hz, 3H), 3.18 (d, J = 1.9 Hz, 3H).

13C NMR (126 MHz, D₂O) δ 163.1, 162.8 (Cα), 138.3 (Ar), 128.6 (Ar), 127.6 (Ar), 127.1 (Ar), 116.4 (q, J = 292 Hz, 1 C, TFA), 80.9, 76.8, 65.9, 58.7 (Me), 56.9 (C1), 56.8 (Me), 42.6 (C6).

[a]D 23.8° (c 1.0, MeOH).

HRMS calculated for \( \text{C}_{13}\text{H}_{20}\text{NO}_3 \) = 238.1438 found: 238.1439.

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