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Quantifying Electronic Effects of Common Carbohydrate Protecting Groups in a Piperidine Model System

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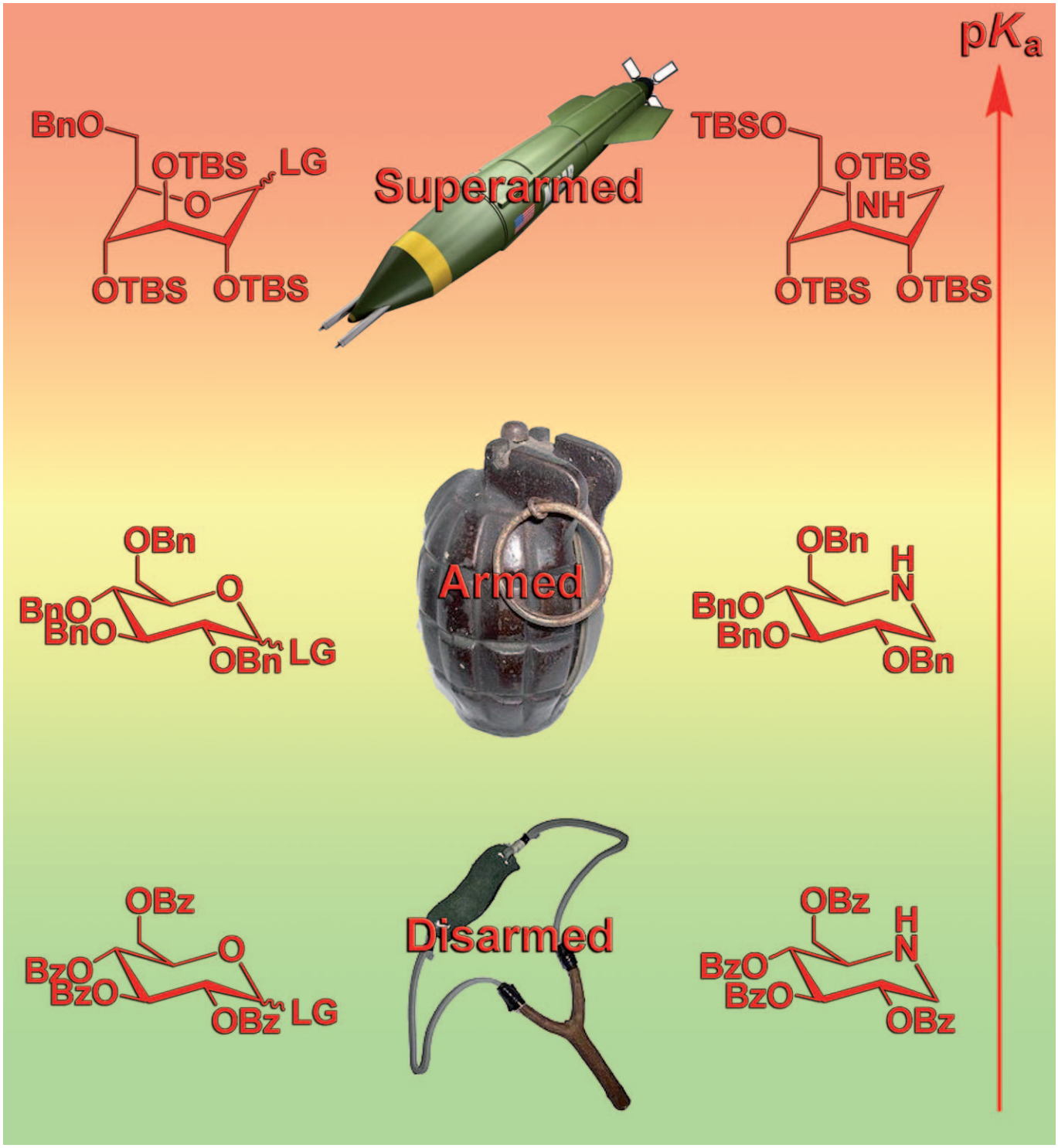

Abstract: A study of the substituent effects of protecting groups in hydroxypiperidines was carried out and compared with the electronic effects in glycosylation chemistry. 1-Deoxynojirimycin, the aza-sugar analogue of 1-deoxy-D-glucose, was used as a carbohydrate model, and protected with the most common carbohydrate protecting groups. The different stabilization of positive charge on the ring heteroatom was determined by pK_a measurements. The protecting groups could be ranked in the following way after their destabilization of the piperidinium ion: benzoyl ≥ acetyl ⩾ 4,6-*O*-benzylidine > benzyl ≈ methyl > H > 3,6-anhydro > *tert*-butyldimethylsilyl. The observed effects of having protecting groups with different electronic characteristics were found to be in agreement with the "armed–disarmed" concept. Comparison of the pK_a of benzylated and benzoylated epimers of 3-hydroxy-6-hydroxymethyl piperidines showed increased stabilization of the piperidinium ion in the axial epimer. The difference between axial and equatorial epimers was larger in the benzylated than in the benzoylated piperidines.

Keywords: basicity · carbohydrates · piperidine · protecting groups · stereoelectronic effects

Introduction

Protecting groups play a central role in carbohydrate chemistry due to the many functional groups present. With increasing need for biologically relevant oligosaccharides and glycoconjugates glycosylation chemistry has been extensively studied[1] and it has become clear that protecting groups do not only protect; they also influence the reactivity of the sugar, its selectivity in glycosylations, and its conformation.[2] The influence on stereoselectivity of an acyl protecting group neighboring the anomeric center has been well understood and exploited in glycosylation for decades,[3] and recently the effect of anchimeric assistance on reactivity has also been studied: the reactivity of 2-acyl donors with a 1,2-*trans* relationship are in fact more reactive than their 1,2-*cis* counterparts.[4]

The influence of protecting groups, remote from the anomeric center, gained significant attention and were subjected to systematic study much later. It was recognized by Hans Paulsen[5] that the protecting groups in glycosyl donors play a role in their reactivity (Scheme 1). By studying the reactivity of 2-azido-2-deoxyglucosyl bromides having different O-3 and O-4 protecting groups it was observed that benzyl (Bn) protection increased the rate, whereas acyl groups decreased the rate; with more electron-withdrawing groups (such as ester protecting groups) causes a decrease in the anomeric reactivity, whereas less electron-withdrawing groups (such as ether protecting groups) increase the relative reactivity of the donors. The effects in this system seemed to be largest on O-3, where the rate was 1.7 with a 3-O-acetyl, compared with 3.0 for the 4-O-acetylated (Scheme 1). Fraser-Reid[6] observed that this phenomena was even more pronounced for *O*-pentenyl glycosyl donors and named it the "armed–disarmed" effect. The glycosyl donor with ether protecting groups was considered armed because it is more reactive, whereas the acyl-group-protected donor is considered disarmed due to its comparatively low reactivity. Hence, Fraser-Reid demonstrated that an armed donor could be selectively activated without activating a disarmed donor and could even be coupled onto the unprotected hydroxyl group of such a donor (Scheme 1). Van Boom and Veeneman observed the same effect in thioglycoside donors.[7] The armed–disarmed concept was later expanded to cover conformational restriction/torsional disarming by using tethering protecting groups, such as acetals, which restrict the sugar to one conformation thereby reducing the reactivity.[6c] In particular, 4,6-benzylidene protection, which has been extensively used in β-mannosylations,[8,9] reduces the reactivity of a glycosyl donor significantly. The effect is partly torsional and partly a stereoelectronic effect of locking the 6-OH in the *tg* conformation.[10] Ley and co-workers have shown that dispiroketal-protected donors are semi-disarmed and have used the concept in one pot assembly of tri-, tetra-, and pentasaccharides from monomeric building blocks.[11]

The stereochemistry of glycosyl donors also influences their reactivity. Paulsen observed that galactosyl donors were more reactive than glucosyl donors,[12] and even before that it was known that carbohydrates with axial OH groups were more reactive than those with equatorial groups.[13] The reason for this difference is electronic effects: from pK_a measurements of hydroxypiperidines,[14] which are excellent mimics of glycoside hydrolysis intermediates, it was shown that axial hydroxyl substituents are less electron withdrawing than equatorial OH groups (Scheme 2), and from linear free energy relationships it was shown that variations in the hydrolysis rate of stereoisomeric glycosides (Scheme 3) are electronically controlled.[15]

Since axial OH groups, in the 3- and 4-position, are 2–3 times less electron withdrawing than equatorial OH groups, relative to the anomeric center, it follows that among chair conformers, the conformer with more axial groups is more

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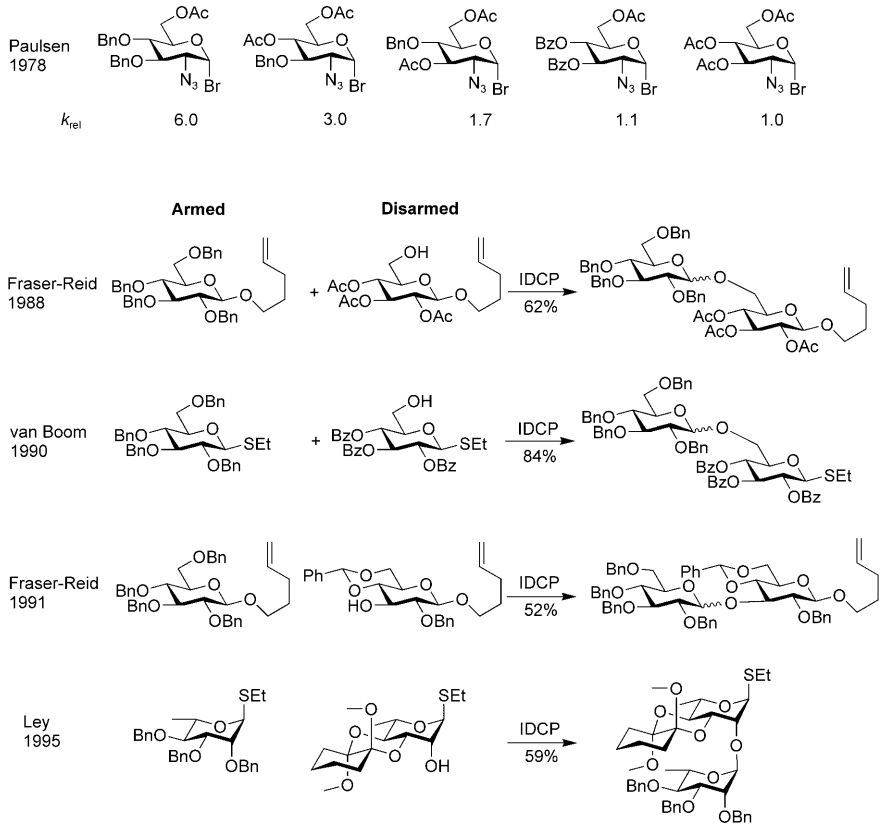
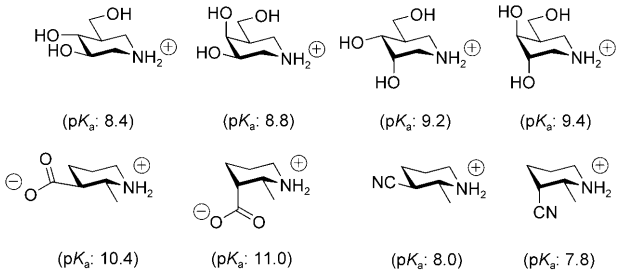
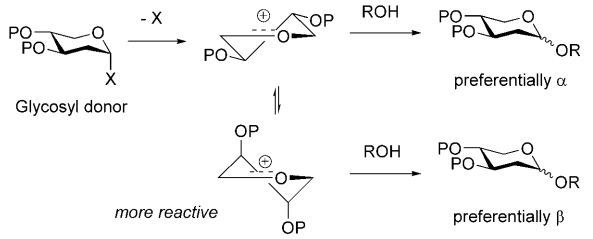


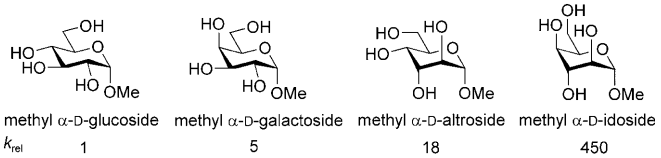
Scheme 1. Substituent effects in glycosyl donors and the armed–disarmed concept. Electron-withdrawing groups, such as ester protecting groups, reduce the reactivity, whereas ether protecting groups (less electron withdrawing) increases the reactivity. IDCP = iodonium dicollidine perchlorate.



Scheme 2. Some examples of the influence of stereoelectronic effects on the pK_a value in piperidines.



Scheme 4. In glycosylation reactions activation of the glycosyl donor leads to intermediate oxocarbenium ions that can adopt two different half-chair conformers each of which has its own stereochemical preference.



Scheme 3. Hydrolysis of methyl glycosides with different configurations—more axial substituents give faster hydrolysis.[15e]

reactive. This was confirmed in the study of 3,6-anhydrides of glucosides: these molecules hydrolyse 200–400 times faster than glucosides.[16] This led to the idea that forcing conformational change in a glycosyl donor with predominantly equatorial OR groups would lead to superior reactivity. This was indeed the case for axial rich silylated glycosyl donors, which have superior reactivity compared with armed donors.[17] The relative reactivity of these "super-armed" glycosyl donors were determined and compared with conventional donors to be 20 fold more reactive than the benzylated analogues. Due to these features "one pot–one addition" reactions with three donors present, in which two of them were acceptors, could be performed giving high yields of the desired trisaccharide donor.[18]

A consequence of the above is that a glycosyl donor may change conformation during a reaction adopting the more reactive conformer (Scheme 4). Woerpel and co-workers have in fact shown this to be the case,[19] pyranosyl oxocarbenium ions with 4-methoxy or 4-methyl substituents react in C-glycosylations with opposite facial selectivity because the former prefer a half-chair conformation with the 4-substituent axial and the latter a half chair with an equatorial substituent,[20] and the nucleophile attacks axially on the ions.[19,20] It has been suggested that this is why glycosylation with mannuronate esters gives the β product. The intermediate adopts the half-chair conformation with a maximal number of axial substituents, which, in this case, upon axial attack gives the observed β anomer.[21]

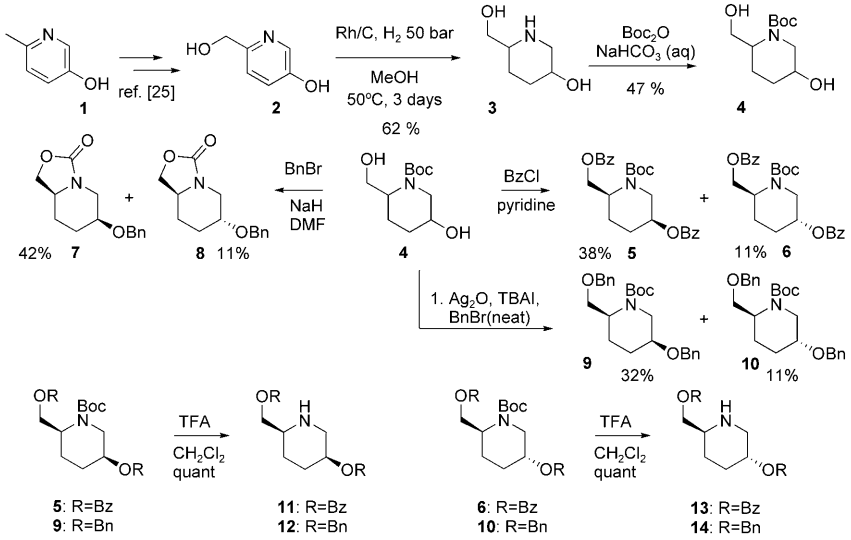
However, despite the clear importance of the different electron-withdrawing effects of protecting groups in glycosylations the actual value is unknown. Though the comparative reactivity of glycosyl donors has been determined by competition reactions between donors,[22,23] or kinetic meas-

urements,[18] these values may or may not be a consequence of electronic effects. The intention with this work was, therefore, to determine the electronic influence of typical carbohydrate protecting groups by determining their influence on the pK_a of a piperidinium ion similar to our previous study of hydroxyl group influence. By using 1-deoxynojirimycin,[24] the 1-deoxy-aza-sugar analogue of D-glucose, as the piperidine scaffold we have studied the influence of benzyl, acetyl, benzoyl, *tert*-butyldimethylsilyl (TBS), benzylidene, and 3,6-anhydro groups. We have also, using a *cis*- and *trans*-3-hydroxy-6-hydroxymethylpiperidine scaffold, determined the difference in electronic effect between an axial and equatorial benzyloxy and benzoxy group.

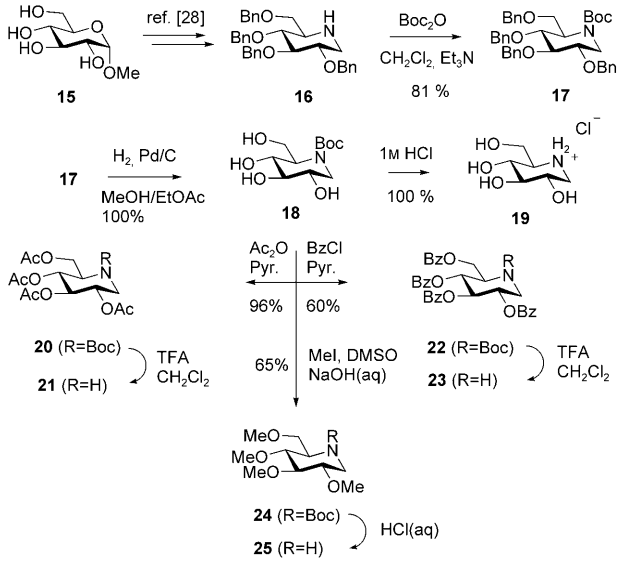
Results

Synthesis: The synthesis of model compounds **11**–**14** was carried out as outlined in Scheme 5. Commercially available 3-hydroxy-6-methyl pyridine **1** was oxidized with *m*-CPBA to give the *N*-oxide followed by acetylation, sigmatropic rearrangement, and deacetylation to give the known compound **2**.[25] Saturation of the pyridine ring catalyzed by rhodium[26] at elevated temperature and hydrogen pressure gave the dihydroxy piperidine **3** as a diastereomeric mixture (*cis*/*trans* 2:1). *tert*-Butoxycarbonyl (Boc) protection followed by benzoylation and separation by dry column chromatography[27] gave the desired diastereomeric pairs **5** and **6**. Attempts to benzylate **4** using standard strong basic conditions resulted in formation of the cyclic carbamates **7** and **8** and hydrolysis of which were unsuccessful. Milder conditions employing Ag_2O in neat benzyl bromide gave the desired product, which could be purified by dry column chromatography to yield the pure diastereoisomers **9** and **10**. Deprotection of the Boc group with trifluoroacetic acid (TFA) in CH_2Cl_2 gave the four target compounds **11**–**14**. In the ^{1}H NMR spectrum the broadness of the H2 multiplet was dependant on the conformation. With a *trans* configuration, that is, both substituents are equatorial, large *trans* vicinal coupling constants to H1, H1′, H3, and H3′ results in a broad multiplet (ca. 34 Hz), as is seen in **13** and **14**. With a *cis* relationship between the substituents, as in **11** and **12**, H2 is equatorial and hence has small *cis* vicinal couplings to its neighbors resulting in a narrow multiplet (ca. 15 Hz). In all of the compounds, the multiplet from H5 has a broad multiplet (30–37 Hz) diagnostic of an axial proton and an equatorial substituent. As expected the major product from the hydrogenation was the *cis*-diol due to the face-selective heterogeneous catalysis with rhodium.

Starting from commercially available methyl α-D-glucopyranoside **15** the O-benzylated 1-deoxynojirimycin **16** was prepared following the procedure by Overkleeft and coworkers Scheme 6.[28] Besides being a target molecule **16** is also a precursor for the remaining compounds and to selectively functionalize the hydroxyl groups a suitable N-protecting group was needed. Due to the straightforward and high yielding way it can be introduced, its stability and its subsequent ease of removal, Boc was the preferred protecting group. Therefore, compound **16** was treated with Boc_2O in CH_2Cl_2 with Et_3N as the base to give the *N*-Boc deriva-



Scheme 5. Synthesis of model compounds **11**–**14**. Bz = benzoyl, TBAI = tetrabutylammonium iodide.



Scheme 6. Synthesis of 1-deoxynojirimycin followed by protecting group manipulations to give the target compounds **16**, **19**, **21**, **23**, and **25**. Pyr = pyridine.

tive **17**, which could then be debenzylated by using Pd/C and hydrogen to give the deblocked *N*-Boc-1-deoxynojirimycin **18** ready for either deprotection to give the unprotected **19** as the HCl salt or further protecting group manipulations of the hydroxyl groups. Acetylation with Ac_2O in pyridine followed by Boc removal using TFA gave the acetylated piperidine **21** as the TFA salt in 96% yield. Similarly, the benzoylated piperidine **23** was prepared from per-benzoylation with BzCl in pyridine followed by TFA-mediated Boc removal to give the desired product in an overall yield of 60%. Methylation of **18** was performed in aqueous DMSO using NaOH as the base and MeI in excess as the reagent[29] giving 65% of **24**, which after Boc removal with HCl (1 M) in THF, afforded **25** as the HCl salt.

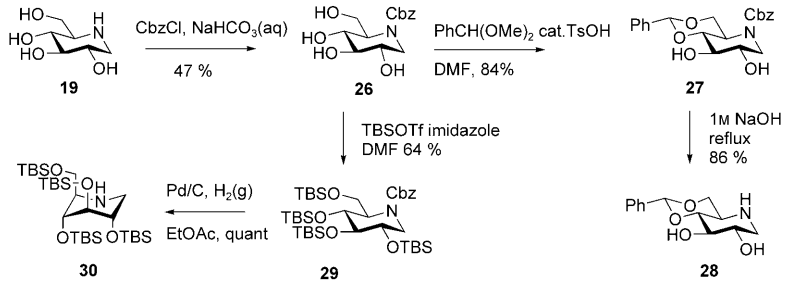
An important target was the silylated piperidine **30**, due to the profound reactivity of TBS-protected glycosyl donors.[17] Introduction of 4 TBS groups in the Boc-protected 1-deoxynojirimycin was performed in a satisfying 55% yield, but unfortunately it was not possible to remove the Boc protection without partial deprotection of the TBS groups. Neither TFA in CH_2Cl_2 or HCl in dry EtOAc gave any amount of the desired product.

As a consequence another N-protecting group, which could be orthogonally removed in the presence of acid-labile TBS groups, was needed. Several candidates were investigated but only benzyloxycarbonyl chloride CbzCl[30] gave reasonable yields in the N-protection and excellent yields in the final removal (Scheme 7). 1-Deoxynojirimycin was protected using CbzCl in $NaHCO_3$ (aq) to give the tetrol **26**, which could then be further protected. Treatment with benzaldehyde dimethylacetal and a catalytic amount of *para*-toluenesulfonic acid gave the benzylidene acetal **27** in an improved yield, compared with a previous synthesis,[30] of 84%. Upon base treatment of **27** the 4,6-*O*-benzylidene-1-deoxynojirimycin **28** was obtained in 86% yield. Silylation of **26** with *tert*-butyldimethylsilyl triflate (TBSOTf) in DMF containing imidazole gave the fully protected **29** in 64% yield. Due to rotamers of the Boc substituent it was not possible to determine the exact conformation from ^{1}H NMR spectroscopy, but mass spectrometry revealed that a compound with the right mass had been formed. The Cbz protecting group could then be removed using Pd/C and hydrogen in EtOAc under neutral conditions to give the free amine **30** in an excellent yield without losing any silyl protecting groups. The structure of **30** was analyzed by ^{1}H NMR spectroscopy and was, from the small intraring coupling constants, found to be in a $^1C_4$ conformation with all the substituents axial (Table 1).

Table 1. NMR spectroscopic data of the model compounds; δ [ppm] (J [Hz]).

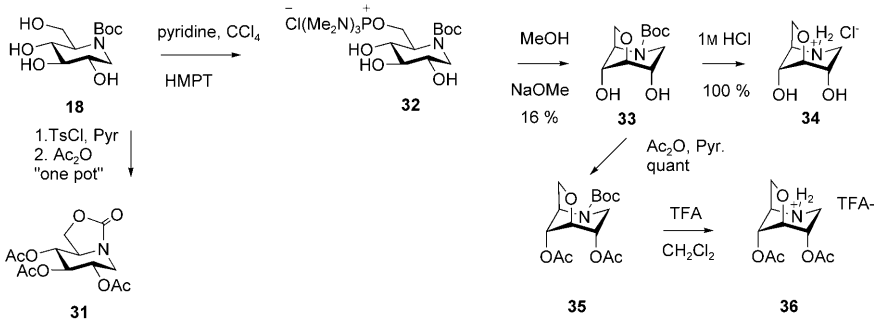
	H5	H4	H3	H2	H1	H1
30[a]	2.79	3.68	3.66	3.48	3.01	2.57
	(m)	(brs, 0)	(brs, 0)	(d, 2.7)	(dd, 14.0, 2.7)	(d, 14.0)
34[a]	3.28	4.20	3.97	3.66	3.30	2.84
	(dt, 3.2, 1.6)	(dd, ≈3.8)	(dd, 5.2)	(dd, 4.0)	(dd, 10.1, 3.8)	(d, 14.6)
21[a]	2.92	4.89	5.13	4.83	3.35	2.60
	(ddd, 10.0, 4.4, 3.3)	(t, 9.9)	(t, 9.6)	(dt, 10.3, 5.0)	(dd, 12.7, 5.4)	(dd, 12.7, 10.7)
11	3.53	n.d.	n.d.	5.29	3.42	3.13
	(brm, 37.2)			(brs, 15.5)	(d, 13.5)	(d, 13.5)
13[a]	3.02	1.90	n.d.	4.99	3.45	2.75
	(brm, 30.0)	(dd, 12.5, 3.2)		(brm, 34.2)	(ddd, 11.2, 4.5, 1.8	(dd, 11.2, 10.4)
12[a]	2.83	n.d.	n.d.	3.46	3.20	2.74
	(brm, 31.4)			(brm, 14.5)	(dt, 13.2, 2.3)	(dd, 13.2, 1.8)
14[a]	2.75	1.63	2.16	3.45	3.35	2.49
	(brm, 31.9)	(dd, 12.8, 2.9)	(d, 12.3)	(brm, 33.5)	(m)	(dd, 10.2, 9.8)

[a] Free amine, brm = broad multiplet (broadness in Hz), n.d. = not determined.



Scheme 7. Cbz protection and introduction of acid-labile protecting groups followed by selective deprotection of the Cbz group.

Attempts to synthesize the all axial 3,6-anhydro-1-deoxynojirimycin **34** from the standard procedures used for 3,6-anhydro sugars were not successful (Scheme 8). Activation of the 6-OH with a leaving group, for example, tosyl, followed by acetylation resulted in attack from the *N*-Boc protecting group leading to the cyclic carbamate **31**.[31] However, when using activation with the bulky *N,N,N′,N′,N″,N″*-hexamethylphosphinetriamine (HMPT) in tetrachloromethane and pyridine to give the intermediate **32**, followed by treatment with sodium methoxide, the desired 3,6-anhydro compound with an intact Boc protection could be isolated in a modest yield. Due to rotamers from the Boc group in **33** a small amount was acetylated to confirm the structure. Further insight into the conformation was achieved by Boc removal, as a result of which the NMR spectrum showed small coupling constants within the piperidine ring confirming a $^1C_4$ conformation with the O-2 and O-4 positions acetylated. N-Deprotection of **33** with HCl



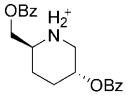
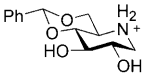
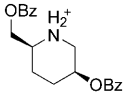
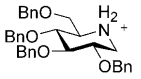
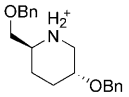
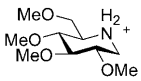
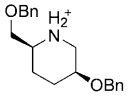
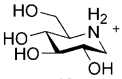
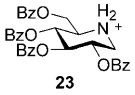
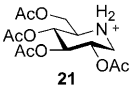
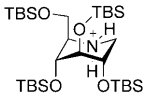
Scheme 8. Synthesis of 3,6-anhydro-1-deoxynojirimycin.

gave the desired 3,6-anhydro derivative **34**. Again ^{1}H NMR spectroscopy (Table 1) was diagnostic for the conformation, with small coupling constants (smaller than 5 Hz) between the ring protons comparable with those observed in 3,6-anhydroglucoside derivatives.[16]

Determination of the base strength: With the target compounds in hand the pK_a values were determined by titration using an acetonitrile/water mixture (50% by mass). The compounds were titrated with NaOH in water with simultaneous addition of equal amounts of acetonitrile (2 burette system). The data are the average of 2 determinations (error $\pm$0.1) and after end titration the compounds were isolated to confirm their stability under the applied conditions.

Table 2 lists the measured pK_a values starting from the simple difunctionalized piperidines (entry 1–4) followed by the functionalized 1-deoxynojirimycin derivatives ranked after increasing basicity. The silylated derivative (entry 12), created more troubles: first due to its low solubility in polar solvents (50 mg could not be dissolved in 50 mL MeCN) a more apolar solvent system had to be used. THF/water (65 vol%) was able to dissolve the compound, but upon titration no reasonable result could be obtained and only decomposed material could be isolated. Neither titration with base nor titration with acid within the pH range 4–10 gave any useful result, and no starting material was left after titration. The surprising lability of **30** in aqueous media required other ways to determine the pK_a. It was clear that water had to be avoided, which precluded a normal determination of pK_a. It was therefore decided to estimate pK_a in an inert solvent by using NMR spectroscopy. In this approach the ability of the piperidine to deprotonate an acid with similar pK_a was used to give an estimate of the pK_a in $CDCl_3$ and by comparison with other amine bases in the same range an estimated pK_a could be obtained. 4-Hydroxy acetophenone (pK_a=8.0) was selected as the acid and titrated with 1,8-diazbicyclo[5.4.0]undec-7-ene (DBU) (pK_a= 11.0) to get a standard curve. By adding one equivalent of the amine the amount of deprotonation can be directly found from the standard curve. It was anticipated that **30** would have a pK_a between 8 and 9, since 1-deoxynojirimycin in $^1C_4$ conformation is predicted as 8.8 by our pK_a model.[15b] Morpholine (pK_a=8.4), *N*-methylmorpholine (pK_a=7.4), *N*-ethoxycarbonylpiperazine (pK_a=8.3), and *N*-methylpiperazine (pK_a=9.0) were used as amine bases with basicity in the range of the pK_a expected for **30**. Morpholine and *N*-ethoxycarbonylpiperazine deprotonated about 30% of the acid when one equivalent was added, this is in agreement with their similar pK_a values in water. *N*-Methylmorpholine, however, turned out to be a stronger base in $CDCl_3$ than in water, and a deprotonation degree of 35% was observed. This suggests that the hydration effect of solvation plays a major role for the lower pK_a value in water, whereas this effect is diminished in $CDCl_3$. Finally, 1 equivalent of *N*-methylpiperazine was able to deprotonate 45% of the acid in agreement with it being the strongest of the amines selected. One equivalent of **30** was able to deprotonate about 35% showing that it is a stronger base in $CDCl_3$ than morpholine and *N*-ethoxycarbonylpiperazine, but weaker than methyl piperazine. From the pK_a values of the selected amines the pK_a of **30** was estimated to be about 8.5 in water. It should be underlined that this is a rough estimation from values ob-

Table 2. Measured pK_a values for the synthesized piperidine model compounds.

Entry	Structure	pK_a	Entry	Structure	pK_a
1	 **13**	6.4	7	 **28**	5.3
2	 **11**	6.9	8	 **16**	6.0
3	 **14**	7.7	9	 **25**	6.0
4	 **12**	8.7	10	 **19**	6.7 6.7[a]
5	 **23**	3.4	11	 **34**	7.2
6	 **21**	3.5	12	 **30**	≈8.5[b]

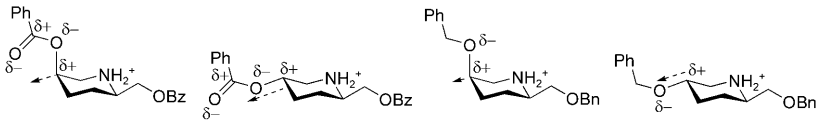
[a] In THF/water (65%). [b] Estimated from NMR spectroscopy titrations.

tained in $CDCl_3$ and it might deviate from a value, if possible, obtained by titration in water.

To study the solvent influence on the pK_a values, the pK_a of 1-deoxynojirimycin in THF/water (65 vol%) was determined (Table 2, entry 10) and found to be identical to that in the MeCN/water mixture and in water.[15b,32]

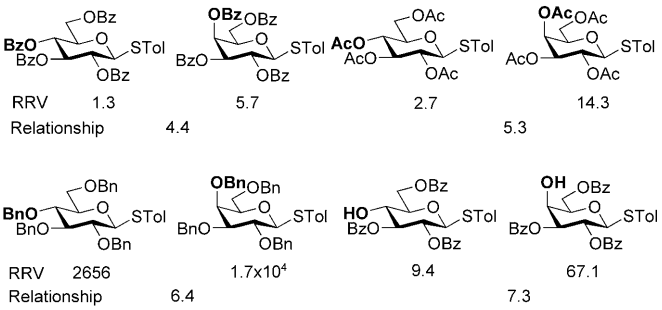
Discussion

Titration of diastereomers **11** and **13** (Table 2, entries 1 and 2) showed a difference of 0.5 pK_a units with the equatorial **13** being, as expected, the least basic with a pK_a of 6.4 compared with 6.9 for **11**. The pK_a values of the benzylated analogues **12** and **14** were higher than the benzoylated and again it was observed that the axial isomer **12** was more basic that the equatorial counterpart **14**. The difference from having two equatorial benzyl groups to two benzoyl groups is 1.3 pK_a units (benzyl being less acidic than benzoyl) in agreement with the reactivity increase observed in sugars that have alkyl protecting groups. The difference is somewhat larger between the compounds that have a *cis* relationship (O-2 is axial) **11** and **12**, here the benzylated is 1.8 pK_a units more basic than the benzoylated. The difference is only 0.5 pK_a units for benzoylated epimers compared with 1.0 for the benzylated pair of epimers. The explanation for this is likely to be that the charge is more distributed in the ester groups, which gives rise to more dipole vectors. The carbonyl group can freely rotate around the O–C bond, but due to 1,3-diaxial interactions the conformation with the benzoyl group pointing away from the piperidine ring must be the most favorable. This results in a pseudo-equatorial dipole-moment vector. When projecting this vector in the plane of the piperidine ring this must be slightly shorter than the one from the equatorial benzoyl group, but the in-between difference is smaller than that between the benzyl-protected epimers with only one dipole moment—axial or equatorial (Scheme 9).



Scheme 9. Projection of dipole moment vectors in the piperidine plane.

The fact that less electron-withdrawing benzyl groups show a larger difference between the epimers has also been observed in glycosylation reactions. In work by Wong and co-workers the same trend can be observed between different gluco- and galactopyranosyl donors (Scheme 10),[23] for which the difference in relative reactivity values (RRV) gets larger as the substituent gets less electron withdrawing and smaller. The biggest difference is observed with OH groups, followed by benzyl, which is in agreement with the Pauling scale, in which hydrogen is more electropositive compared



Scheme 10. Glucosyl and galactosyl donors reactive reaction value (RRV) and the relationship between axial and equatorial substituents. Tol = tolyl.

with carbon, directing more negative charge onto the oxygen. The difference in RRV for acyl-protected epimers is smaller, by a factor of 4.4 for benzoyl and 5.3 for acetyl, hence, a more delocalized negative charge reduces the stereoelectronic effect of having an axial electron-withdrawing group compared with an equatorial one. A more delocalized and therefore more remote charge will also reduce the effect in the ester groups, both in the axial and equatorial epimer.

The resemblance between 1-deoxynojirimycin and D-glucose makes it a unique model compound to study the effects of substituents on the stabilization of a positive charge at the ring heteroatom (N vs. O) and to quantify these effects. By obtaining a measurement for the stability of the positive charge, here the pK_a value, it would be possible to rank the substituents (or protecting groups) by their stereoelectronic influences. This can be done without the influence of other effects observed in glucosylations, such as reactivity dependence on the anomeric leaving group, neighboring group effects, choice of promoter system, and effects related to the reactivity of the incoming nucleophile (the acceptor). The direct quantification of stereoelectronic effects measured in the model system is summarized in Table 2, in which some of the most common carbohydrate protecting groups have been applied to protect 1-deoxynojirimycin and their respective pK_a values determined and compared. As one would expect the acyl protecting groups are the least stabilizing and hence give the most acidic pyridonium ion (Table 2, entry 5 and 6). The difference between benzoyl and acetyl protecting groups is marginal, with 0.1 pK_a unit between them (3.4 and 3.5, respectively). They are however almost 2 pK_a units more acidic than the benzylidine-protected analogue **28**, which has a pK_a value of 5.3. The perbenzylated compound **16** and methylated analogue **25** are very similar in their ability to stabilize the piperidonium ion (Table 2, entry 8 and 9). Both are significantly less acidic than the benzylidene **28**, which is to be

expected from glycosylation chemistry, where benzylidene is considered to be both torsionally and stereoelectronically disarming. In this model system only the stereoelectronic effect of the benzylidene is observed, since the torsional effect will not affect the basicity of the ring nitrogen. The lower pK_a value of **28** compared with **19** once again underlines the fact that a benzylidene, besides affecting torsional factors, is electronically disarming. 1-Deoxynojirimycin **19**, having no protecting groups, was found to be 0.7 pK_a units less acidic compared with the alkylated compounds **16** and **25** (Table 2). This can be explained by the fact that hydrogen is less electronegative compared with carbon (according to the Pauling scale) and is therefore less destabilizing towards the positive charge on the nitrogen. This observation can also explain why the difference between the benzylidene **28** and the benzylated **16** is relatively small, benzylating O-2 and O-3 would decrease the pK_a further. Changing the solvent system from acetonitrile/water to THF/water did not influence the measurement and the exact same pK_a value was obtained.

The 3,6-anhydro **34** was found to be 0.5 pK_a units less acidic compared with **19**, this is in agreement with the observed increased reactivity of 3,6-anhydro glucosyl donors and glucosides, but significantly smaller than expected from earlier studies of 3,6-anhydro sugars.[16] When calculating[15b] the pK_a of an all axial 1-deoxynojirimycin and of 1,6-dideoxynojirimycin pK_a values of 8.8 and 9.5, respectively, are found. This considerable divergence from the measured value suggests that other effects contribute to destabilization of the piperidinium ion, it cannot, however, be distinguished, what effects are involved and dominant in this context. As demonstrated in Table 2 (entries 1–4), axial oxygen atoms are less electron withdrawing and hence destabilize the positive charge less, but **34** is also missing an oxygen atom, which might contribute to the increased stabilization. There is, however, also one additional bond (3-O to 6-C) giving an extra inductive effect, which would destabilize a positive charge on N. Finally, the pK_a measurement of the axial-rich per-O-silylated **30** by a ^{1}H NMR spectroscopic study gave a pK_a value of about 8.5. This value is close to the one expected from calculations (8.8 for all axial 1-deoxynojirimycin[15b]) and gives a good correlation when plotted, together with the pK_a values of the acetylated and benzylated 1-deoxynojirimycin, against log k in a linear free energy diagram (Figure 1). The method for determining the pK_a was further evaluated by testing the method with other known secondary amines with similar pK_a values and it was shown to be reliable; factors such as hydration can, however, not be observed in this study.

A free energy relationship plot between the obtained pK_a values and the kinetic data obtained with thioglycosides[18a] gives a good correlation with a slope of 0.6 (Figure 1). One explanation for the relatively small slope suggests that the charge in glycosylations is distributed between C1 and O, which gives a dampening of the substituent effects.

Plotting the measured pK_a values with the known RRVs obtained from glycosylation reactions using data from Wong and co-workers[23] and supplemented with values for phenylthio 4,6-*O*-benzylidene-β-D-glucopyranoside (RRV = 664) and tolylthio-6-*O*-benzyl-2,3,4-tri-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranoside (RRV = 29000) obtained with Wong's method gave a good correlation (R^2 = 0.99, Figure 2). The plot convincingly shows that superarmed–armed–disarmed effects are due to electronic effects.

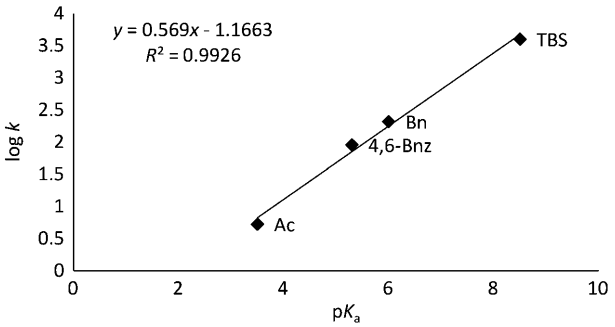


Figure 1. Relationship between log k, in which k is the rate constant for NIS/TfOH-promoted methanolysis of acetylated, 4,6-benzylidene, benzylated, and TBS-protected thioglycosides, and the measured pK_a of corresponding 1-deoxynojirimycins with acetates, 4,6-benzylidene, benzyl, and TBS groups.

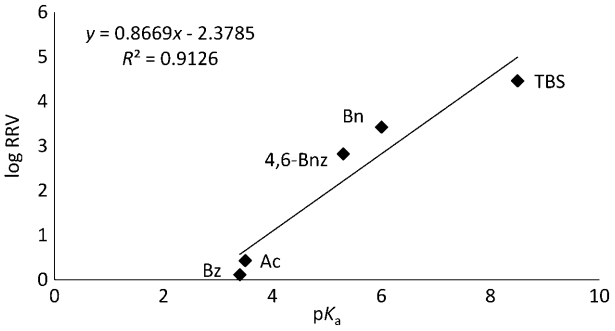


Figure 2. Relationship between log RRV partly from ref. [23] and from our own data of NIS/TfOH-promoted methanolysis of benzoylated, acetylated, 4,6-benzylidene, benzylated, and TBS-protected thioglycosides and the pK_a values for benzoylated, acetylated, 4,6-benzylidene, benzylated, and TBS-protected 1-deoxynojirimycin.

By comparing the measured pK_a values with known σ_I values[33] a linear relationship and good correlation (R^2 = 0.95) is observed showing that the difference between the substituents is mainly an inductive effect (Figure 3). The negative ρ value (−22) indicates that electron-releasing groups greatly increase the reaction rate, and support a mechanism with ionization in the rate-determining step. The large ρ value shows that the reaction is very sensitive to substituent effects and implies that there is a large redistribution of charge in the transition state.

The resemblance of the piperidine model system to the glycosyl donors makes it possible to obtain σ values for common carbohydrate substituents, in this case protected hydroxy groups, and use these to predict the reactivity of a

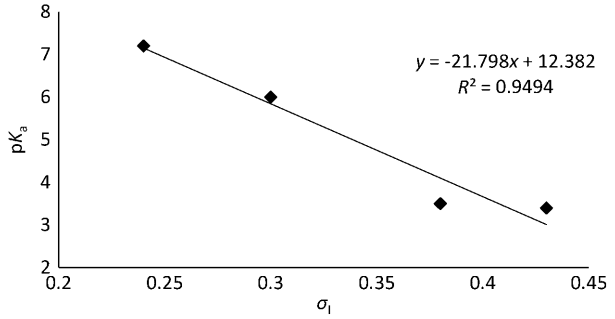


Figure 3. Plot of σ_I values from ref. [33] of OH, MeO, AcO, and BzO versus the pK_a values for unprotected, and methyl-, acetate-, and benzoate-protected 1-deoxynojirimycin.

glycosyl donor. This is of major importance in the synthesis of oligosaccharides, in one-pot multiple glycosylations and for the development of new methodologies in glycosylation chemistry.

As an example the benzylidene **28** has a pK_a value 2 units larger than the acetylated analogue **21**, this implies that the 4,6-*O*-benzylideneglucosyl donor is about 100 times more reactive than the acylated donor analogue.

Conclusion

This work has quantified the electron-withdrawing effect of various common protecting groups in carbohydrates. The results show an order of electron-withdrawing power of OBz $\geq$ OAc $\gg$ 4,6-di-*O*-benzylidene > OBn $\approx$ OMe > OH $\gg$ OTBS. Tetra-O-acylation (OAc/OBz, $\Delta pK_a \approx 2.5$) is found to be 300–400 times more electron withdrawing than tetra-O-alkylation (OMe/OBn). Noteworthy, is firstly that benzylidene ($\Delta pK_a = 0.7$) is found to be 5 times more electron withdrawing than perbenzyl, which confirms the electron-withdrawing effect of locking the 6-OH in a *tg* conformation.[10] Secondly, the results show a difference between benzyl/methyl and hydroxyl with the former more electron withdrawing, a difference that can be related to the difference in inductive effects between OH and OMe. It nevertheless means that unprotected sugars are somewhat more reactive than armed sugars. Thirdly, we observe that TBS protection is 300–400 times less electron withdrawing than benzyl protection. This is roughly consistent with the anticipated effect of the conformational change induced in this molecule by the protecting groups leading to an all-axial conformation. A 3,6-anhydro derivative that shares the $^1C_4$ conformation was more basic than comparable $^1C_4$ derivatives but the difference was smaller than anticipated.

The results also show, perhaps unsurprisingly, that the difference in electron-withdrawing power between axial and equatorial hydroxyl substituents depends on whether the hydroxyl group is protected and in that case, which protecting group. Although for unprotected OH groups in the β position the ΔpK_a(ax/eq) value is 0.8,[15b] it is 1.0 for OBn and 0.5 for OBz. This means that the reactivity difference between stereoisomeric glycosyl donors is larger when they are armed than for unprotected carbohydrates; for disarmed glycosyl donors the relative difference is smaller. It also means that, during a reaction, a conformational change of a glycosyl donor towards a half-chair conformation with axial substituents, as observed by Woerpel et al.[19,20] and suggested by van der Marel et al.,[21] is less likely to be favored in a disarmed donor.

Experimental Section

Compound 3: 6-(Hydroxymethyl)pyridine-3-ol (2.76 g, 22 mmol) was dissolved in methanol (50 mL) and Rh/C (5%, 2.75 g) was added. A hydrogen pressure of 50 bar was applied and the reaction vessel was heated to 50°C for 3 days. The reaction mixture was filtered and concentrated to give the crude product (1.8 g, 62%). ^{1}H NMR (very complicated, see the Supporting Information); ^{13}C NMR (75 MHz, CD_3OD) δ = 67.7, 65.5, 64.3, 63.6, 58.9, 58.5, 52.9, 51.0, 33.6, 30.1, 27.1, 21.9 ppm; HRMS: *m*/*z*: calcd for $C_6H_{13}NO_2Na$: 154.0844; found: 154.0840.

Compound 4: Crude 6-(hydroxymethyl)piperidine-3-ol (1.76 g, 13.5 mmol) was dissolved in sat. bicarbonate solution (20 mL) and Boc anhydride was added (4.40 g, 20.2 mmol). The reaction was followed by TLC and when finished, the reaction mixture was carefully extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography with 9:1 ethyl acetate/methanol to give the product (1.47 g, 47%). ^{1}H NMR (complex, see the Supporting Information); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.7 (C=O), 155.6 (C=O), 80.1 (C-Boc), 77.4, 66.5, 64.0, 60.2, 59.8, 52.1, 50.9, 45.8, 28.5, 28.3 (CH_3-Boc), 25.8, 23.1, 18.8 ppm; HRMS: *m*/*z*: calcd for $C_{11}H_{22}NO_4$: 232.1549; found: 232.1556.

Compounds 5 and 6: *N*-Boc-6-(hydroxymethyl)piperidine-3-ol (0.533 g, 2.30 mmol) was dissolved in pyridine (5 mL) followed by the addition of benzoyl chloride (0.81 g, 5.76 mmol). The reaction mixture was stirred for 2 h. The solvent was evaporated and the crude products were carefully separated by dry column chromatography with heptane as the eluent with a gradient of ethyl acetate to give each product. Compound **5** (0.383 g, 38%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13–7.96 (m, 4H, Ar), 7.63–7.30 (m, 6H, Ar), 4.97 (tt, *J* = 10.2, 4.9 Hz, 1H, H5), 4.60–4.38 (b, 4H, H1, H2, H6), 3.01 (dd, *J* = 12.5, 11.3 Hz, 1H, H6), 2.15 (dd, *J* = 11.9, 3.0 Hz, 1H, H4), 1.93–1.85 (m, 2H, H3), 1.74 (dt, *J* = 18.0, 10.9 Hz, 1H, H4), 1.37 ppm (s, 9H, Boc); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.4 (C=O, Bz), 165.6 (C=O, Bz), 154.7 (C=O, Boc), 133.2, 130.1, 129.9, 129.8, 129.7, 128.4, 128.4 (Ar), 80.4 (C-Boc), 69.3 (C5), 62.0 (C1), 48.6–47.4 (C2), 43.2–41.6 (C6), 28.3 (CH_3-Boc) 25.9 (C4), 23.7 ppm (C3); HRMS: *m*/*z*: calcd for $C_{25}H_{29}NO_6Na$: 462.1893; found: 462.1885. Compound **6** (0.116 g, 11%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 7.2 Hz, 4H, Ar), 7.54 (t, *J* = 7.4 Hz, 2H, Ar), 7.42 (t, *J* = 7.6 Hz, 4H, Ar), 5.16–4.85 (2 × br s, 2H, H5, H2), 4.60 (t, *J* = 9.6 Hz, 1H), 4.50–4.29 (m, 2H), 3.20 (dd, *J* = 15.0, 1.0 Hz, 1H), 2.18 (dt, *J* = 13.1, 7.0 Hz, 1H), 2.08–1.86 (m, 2H), 1.65 (dd, *J* = 13.9, 1.4 Hz, 1H), 1.25 ppm (s, 9H, Boc); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.5 (C=O, Bz), 165.8 (C=O, Bz), 155.2 (C=O, Boc), 133.2, 133.1, 130.4, 130.0, 129.8, 129.7, 128.4 (Ar), 80.0 (C-Boc), 67.6, 62.1, 48.2, 42.7, 28.2, 24.1, 20.3 ppm; HRMS: *m*/*z*: calcd for $C_{25}H_{29}NO_6Na$: 462.1893; found: 462.1904.

Compounds 7 and 8: *N*-Boc-6-(hydroxymethyl)piperidine-3-ol (0.543 g, 2.35 mmol) was dissolved in dry DMF (5 mL) and NaH (60% 0.38 g, 9.4 mmol) was added. Then benzyl bromide was added (1 g, 5.9 mmol) and the reaction mixture was stirred for 2 h. Water was then added carefully to the reaction mixture, which was then extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude product, which was purified by dry column chromatography with heptane as the eluent with a gradient of ethyl acetate to give each product. Compound **7** (0.245 g, 42%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44–7.15 (m, 5H, Ar), 4.67 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.37 (t, *J* = 8.3 Hz, 1H, H6), 4.40 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.12 (dt, *J* = 14.1, 2.1 Hz, 1H,

H1), 3.91 (dd, $J=8.5$, 5.3 Hz, 1H, H6), 3.77–3.63 (m, 1H, H5), 3.60 (dd, $J=3.4$, 1.9 Hz, 1H, H2), 2.88 (dd, $J=14.2$, 1.9 Hz, 1H, H1), 2.14–1.99 (m, 1H, H3), 1.99–1.78 (m, 1H, H4), 1.65–1.47 ppm (m, 2H, H3, H4); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=157.8$ (C=O), 138.2, 128.4, 127.7, 127.5 (Ar), 70.1 (C6), 69.5 (C2), 68.1 (C6), 53.9 (C5), 43.2 (C1), 27.5 (C3), 24.5 ppm (C4); elemental analysis calcd (%) for C 68.00, H 6.93, N 5.66; found: C 67.89, H 6.86, N 5.60. Compound **8** (0.065 g, 11%): ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.52$–7.09 (m, 5H), 4.59 (d, $J=11.7$ Hz, 1H, $PhCH_2$), 4.54 (d, $J=11.7$ Hz, 1H, $PhCH_2$), 4.37 (t, $J=8.4$ Hz, 1H, H6), 4.15 (ddd, $J=12.6$, 5.2, 1.7 Hz, 1H, H1), 3.85 (dd, $J=8.6$, 5.8 Hz, 1H, H6), 3.67–3.50 (m, 1H, H5), 3.47–3.30 (m, 1H, H2), 2.67 (dd, $J=12.6$, 10.3 Hz, 1H, H1), 2.29–2.14 (m, 1H, H3), 1.95–1.79 (m, 1H, H4), 1.53–1.25 ppm (m, 2H, H3, H4); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=156.9$ (C=O), 138.0, 128.5, 127.8, 127.6 (Ar), 72.5 (C2), 70.9 ($PhCH_2$), 67.7 (C6), 53.7 (C5), 45.5 (C1), 29.5 (C3), 29.1 ppm (C4); HRMS: *m/z*: calcd for $C_{14}H_{17}NO_3Na$: 270.1106; found: 270.1106.

Compounds 9 and 10: *N*-Boc-6-(hydroxymethyl)piperidine-3-ol (0.293 g, 1.26 mmol) was dissolved in benzyl bromide (7 mL) and tetrabutylammonium iodide (TBAI) (48 mg, 0.13 mmol) was added. The mixture was stirred for 20 min followed by the addition of freshly prepared Ag_2O (1.17 g, 5.1 mmol). The reaction mixture was stirred for 12 h followed by the addition of DMF (5 mL) and NaOH (aq, 50%, 5 mL) and then stirring for another 12 h. The reaction mixture was then filtered through Celite, diluted with 50 mL of water, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The crude products were carefully separated by dry column chromatography with heptane as eluent with a gradient of ethyl acetate to give each product. Compound **10** (0.061 g, 11%): ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.50$–7.16 (m, 10H, Ar), 4.71–4.40 (m, 5H, $PhCH_2$, H5), 4.34 (d, $J=14.4$ Hz, 1H, H1), 3.61–3.49 (m, 2H, H2, H6), 2.84 (d, $J=14.5$ Hz, 1H, H1), 2.16–1.97 (m, 1H, H4), 1.85–1.53 (m, 3H, H3, H4), 1.50–1.41 ppm (m, 9H, Boc); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=155.6$(C=O), 138.9, 138.5, 128.5, 128.4, 127.7, 127.6, 127.5 (Ar), 79.6 (C-Boc), 73.0 ($PhCH_2$), 70.8 (C2), 69.8 ($PhCH_2$), 68.5 (C6), 49.2 (C5), 41.7 (C1), 28.6 (CH_3-Boc), 24.7 (C3), 19.9 (C4); HRMS: *m/z*: calcd for $C_{25}H_{33}NO_4Na$: 434.2307; found: 434.2321. Compound **9** (0.166 g, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.57$–7.09 (m, 10H, Ar), 4.58 (s, 2H, $PhCH_2$), 4.53 (s, 2H, $PhCH_2$), 4.51–4.01 (m, 2H, H1, H5), 3.54 (d, $J=6.9$ Hz, 2H, H6), 3.37 (s, 1H, H2), 2.59 (s, 1H, H1), 2.06–1.79 (m, 2H, H3, H4), 1.73–1.50 (m, 2H, H3, H4), 1.45 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=155.2$ (C=O), 138.5, 138.4, 128.5, 128.5, 127.7, 127.6 (Ar), 79.9 (C-Boc), 74.1 (C2), 73.0, 70.7 ($PhCH_2$), 67.7 (C6), 49.6, 47.9 (C5), 44.6, 43.4 (C1), 28.5 (CH_3-Boc), 26.41, 23.77 (C3, C4); HRMS: *m/z*: calcd for $C_{25}H_{33}NO_4Na$: 434.2307; found: 434.2326.

Compound 11: (2*S*,5*S*),(2*R*,5*R*)-*N*-Boc-2,6-dibenzoyloxopiperidine (0.383 g, 0.871 mmol) was dissolved in CH_2Cl_2 and an excess of TFA was added. When the reaction was finished the mixture was evaporated to dryness to give the product (0.422 g, quantitative yield, with small excess of TFA). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=10.06$–9.76 (br m, 2H, NH), 8.16 (d, $J=7.7$ Hz, 2H, Ar), 7.97 (d, $J=7.7$ Hz, 2H Ar), 7.55 (t, $J=7.4$ Hz, 2H, Ar), 7.46 (t, $J=7.4$ Hz, 2H, Ar), 7.39 (t, $J=7.7$ Hz, 2H, Ar), 7.30 (t, $J=7.6$ Hz, 2H, Ar), 5.29 (s, 1H, H2), 4.53 (ddd, $J=15.1$, 12.4, 5.0 Hz, 2H, H6), 3.61–3.44 (s, 1H, H5), 3.42 (d, $J=13.5$ Hz, 1H, H1), 3.13 (d, $J=13.5$ Hz, 1H, H1), 2.31 −1.79 ppm (m, 4H, H3, H4); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=166.1$ (C=O), 165.5 (C=O), 133.7, 133.5, 130.2, 130.0, 129.1, 128.9, 128.6, 128.5 (Ar), 64.4 (C2), 64.1 (C6), 55.3 (C5), 46.9 (C1), 26.4, 20.5 ppm (C1, C2); HRMS: *m/z*: calcd 340.1549; found: 340.1545.

Compound 12: (2*S*,5*S*),(2*R*,5*R*)-*N*-Boc-2,6-dibenzyloxopiperidine (0.166 g, 0.403 mmol) was dissolved in CH_2Cl_2 and an excess of TFA was added. The reaction was stirred until finished (TLC) and then evaporated to dryness. The compound was then dissolved in CH_2Cl_2 and extracted with 1 M NaOH. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give the product (0.123 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.50$–7.15 (m, 10H, Ar), 4.67–4.37 (m, 4H, $PhCH_2$), 3.51–3.39 (m, 3H, H6, H2), 3.20 (dt, $J=13.2$, 2.3 Hz, 1H, H1), 2.88–2.78 (m, 1H, H5), 2.74 (dd, $J=13.2$, 1.8 Hz, 1H, H1), 2.11 (s, 1H, NH), 2.09–1.98 (m, 1H, H3), 1.72–1.39 ppm (m, 3H, H3, H4); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=139.06$, 138.45, 128.39, 128.34, 127.71, 127.58, 127.54, 127.41 (Ar), 74.4 (C6), 73.2 ($PhCH_2$), 71.1 (C2), 69.9 ($PhCH_2$), 55.8 (C5), 49.3 (C1), 27.8 (C3), 24.1 (C4); HRMS: *m/z*: calcd for $C_{20}H_{26}NO_2$: 312.1964; found: 312.1970.

Compound 13: (2*R*,5*S*),(2*S*,5*R*)-*N*-Boc-2,6-dibenzoyloxopiperidine (0.116 g, 0.378 mmol) was dissolved in CH_2Cl_2 and an excess of TFA was added. When the reaction was finished (TLC) the mixture was evaporated to dryness to give the product (0.120 g, 100%). Elemental analysis calcd (%): C 70.78, H 6.24, N 4.1; found: C 70.70, H 6.78, N 3.79. Free amine: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=8.11$–7.99 (m, 4H, Ar), 7.64–7.38 (m, 6H, Ar), 5.07–4.90 (m, 1H, H2), 4.40 (dd, $J=11.1$, 4.1 Hz, 1H, H6), 4.22 (dd, $J=11.1$, 7.2 Hz, 1H, H6), 3.45 (ddd, $J=11.2$, 4.5, 1.8 Hz, 1H, H1), 3.07–2.97 (m, 1H, H5), 2.75 (dd, $J=11.2$, 10.4 Hz, H1), 2.57 (s, 1H), 2.37–2.23 (m, 1H, H3), 1.90 (dd, $J=12.5$, 3.2 Hz, 1H, H4), 1.57 ppm (m, 2H, H3, H4); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=166.5$ (C=O), 165.9 (C=O), 133.3, 133.1, 130.5, 130.0, 129.8, 129.7, 128.6, 128.5 (Ar), 70.7 (C2), 68.2 (C6), 54.7 (C5), 49.8 (C2), 29.9 (C3), 27.6 ppm (C2).

Compound 14: (2*R*,5*S*),(2*S*,5*R*)-*N*-Boc-2,6-dibenzyloxopiperidine (0.061 g, 0.148 mmol) was dissolved in CH_2Cl_2 and an excess of TFA was added. The reaction was stirred until it was finished (TLC) and then evaporated to dryness. The compound was then dissolved in CH_2Cl_2 and extracted with 1 M NaOH. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give the product (0.045 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.71$–6.88 (m, 10H, Ar), 4.56 (s, 2H, $PhCH_2$), 4.50 (s, 2H, $PhCH_2$), 3.51–3.39 (m, 2H, H2, H6), 3.39–3.31 (m, 1H, H1), 3.27 (t, $J=8.7$ Hz, 1H, H6), 2.80–2.69 (m, 1H, H5), 2.49 (dd, $J=10.2$, 9.8 Hz, 1H, H1), 2.16 (d, $J=12.3$ Hz, 2H, NH, H3), 1.63 (dd, $J=12.8$, 2.9 Hz, 1H, H4), 1.48–1.30 (m, 1H, H3), 1.25–1.06 ppm (m, 1H, H4); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=138.9$, 138.3, 128.6, 128.5, 127.9, 127.8, 127.7, 127.7 (Ar), 75.3 (C2), 74.7 (C6), 73.6 ($PhCH_2$), 70.6 ($PhCH_2$), 55.8 (C5), 51.1 (C1), 31.0 (C3), 27.5 ppm (C4); HRMS: *m/z*: calcd for $C_{20}H_{26}NO_2$: 312.1964; found: 312.1960.

Compound 17: A solution of tetra-*O*-benzyl-1-deoxynojirimycin (1.491 g, 2.85 mmol) in CH_2Cl_2 was cooled to 0°C and one equivalent of triethylamine was added. Then a solution of Boc anhydride in CH_2Cl_2 was added. The solution was stirred at 0°C for 0.5 h and then allowed to reach room temperature over 2 h. The solution was washed with 1 M HCl, a saturated aqueous solution of bicarbonate, brine, and dried over $MgSO_4$. The organic layer was evaporated and the crude compound was purified by flash column chromatography. The eluent was pentane with a gradient of ethyl acetate (1.35 g, 81%). $[\alpha]_D^{RT}=12.8°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.3$ (20H, Ar), 4.7–4.4 (8H, $PhCH_2$), 4.1 (m, 2H, H1, H5), 3.9 (t, $J=6.4$ Hz, 1H, H4), 3.7 (1H, H3), 3.6 (m, 4H, H2, H6), 3.3 (dd, $J=3.3$, 14.2 Hz, 1H, H1), 1.4 ppm (s, 9H, Boc); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=155.3$ (C=O), 138.4 (Ar-C), 128.7–127.3 (Ar), 82.7 (C-Boc), 80.0 (C3), 78.2 (C2), 76.8 (C4), 73.1–72.9 ($PhCH_2$), 68.9 (C6), 55.6 (C5), 41.0 (C1), 28.6 ppm (CH_3-Boc); HRMS: *m/z*: calcd for $C_{39}H_{45}NO_6Na$: 646.3145; found: 646.3127.

Compound 18: *N*-Boc-tetra-*O*-benzyl-1-deoxynojirimycin (1.31 g, 2.1 mmol) was dissolved in 1:1 mixture of methanol and ethyl acetate (20 mL) and Pd/C was added (10%, 0.2 g), the flask was flushed with hydrogen and the solution was then stirred overnight. The reaction mixture was filtered and evaporated to give the product (0.553 g, 100%). $[\alpha]_D^{RT}=-15.9°$ ($c=1.0$, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=4.15$ (m, 1H, H5), 3.9 (d, 1H, $J=13.9$ Hz, H1), 3.85–3.82 (m, 2H, H6), 3.79 (m, 1H, H4), 3.70 (m, 2H, H2, H3), 3.40 (dd, 1H, $J=3,4$, 13,8 Hz, H1), 1.51 (s, 9H, Boc); ^{13}C NMR (75 MHz, CD_3OD) $\delta=156.9$ (C=O), 80.1 (C-Boc), 71.0, 70.1, 69.2, 60.2, 59.8, 43.0, 27.5 (CH_3-Boc); HRMS: *m/z*: calcd for $C_{11}H_{21}NO_6Na$: 286.1267; found: 286.1268.

Compound 20: Pyridine (1 mL) and acetic acid anhydride (1 mL) were added to *N*-Boc-1-deoxynojirimycin (0.157 g, 0.596 mmol). The reaction mixture was stirred for 24 h and the solvents were removed by co-evaporation with toluene. The crude product was purified by flash chromatography with pentane as the eluent with a gradient of ethyl acetate to give the product (0.247 g, 96%). $[\alpha]_D^{RT}=1.9°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=4.97$ (t, $J=3.8$ Hz, 1H, H3), 4.84 (t, $J=3.8$ Hz, 1H, H4), 4.70 (d, $J=2.9$ Hz, 1H, H2), 4.50 (m, 1H, H5), 4.30–4.17 (m, 3H, H6, H1), 3.22 (dd, $J=15.4$, 2.1 Hz, 1H), 2.03–1.99 (m, 12H, Ac), 1.39 ppm (s, 12 H CH_3-Boc); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=170.4$, 169.6,

169.4, 168.8 (C=O, Ac), 155.0 (C=O, Boc), 80.5 (C-Boc), 68.3–68.1 (C3,C4), 66.6 (C2), 60.5 (C6), 52.9 (C5), 39.3 (C1), 28.2 (CH_3-Boc), 20.8–20.7 (Ac); HRMS: *m/z*: calcd for $C_{19}H_{30}NO_{10}$: 432.1870; found: 432.1875.

Compound 21: *N*-Boc-2,3,4,6-tetra-*O*-acetyl-1-deoxynojirimycin (0.247 g, 0.573 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (0.5 mL) was added. The reaction mixture was stirred for 24 h and evaporated to dryness to give the product (0.255 g, 100%). Salt: $[\alpha]_D^{RT}=23.9°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=9.11$ (br m, 2H, NH_2), 5.28 (m, 3H, H2, H3, H4), 4.32 (dd, $J=34.0$, 10.9 Hz, 2H, H6), 3.76 (d, $J=10.4$ Hz, 1H, H1), 3.50 (d, $J=8.4$ Hz, 1H, H5), 2.91 (br m, 1H, H1), 2.06, 2.05, 2.04, 2.03 ppm (Ac); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=171.2$, 170.1, 160.0, 169.2 (C=O, Ac), 162.1, 161.6, 117.7, 114.0 (TFA), 71.8, 66.4, 66.3 (C2,C3,C4), 59.0 (C6), 56.7 (C2), 43.8 (C1), 20.5, 20.4, 20.4, 20.2 ppm (Ac); free amine: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=5.13$ (t, $J=9.6$ Hz, 1H, H3), 4.89 (t, $J=9.9$ Hz, 1H, H4), 4.83 (dt, $J=15.4$, 5.0 Hz, 1H, H2), 4.09 (dd, $J=3.7$, 2.6 Hz, 2H, H6), 3.35 (dd, $J=12.7$, 5.4 Hz, 1H, H1), 2.92 (ddd, $J=10.0$, 4.4, 3.3 Hz, 1H, H5), 2.60 (dd, $J=12.7$, 10.7 Hz, 1H, H2), 2.56, 2.08, 2.03, 2.02 ppm (Ac); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=170.7$, 170.4, 170.2, 169.9 (C=O, Ac), 74.5 (C3), 71.4 (C2), 70.6 (C4), 63.3 (C6), 57.4 (C5), 47.0 (C1), 21.0, 20.9, 20.9, 20.8 ppm (Ac); HRMS: *m/z*: calcd for $C_{14}H_{22}NO_8$: 332.1340; found: 332.1328.

Compound 22: *N*-Boc-1-deoxynojirimycin (0.3 g, 1.14 mmol) was dissolved in pyridine (3 mL) and benzoyl chloride was added (0.8 g, 5.7 mmol). The reaction mixture was stirred overnight. Pyridine was removed by evaporation and the crude mixture was dissolved in ethyl acetate and washed 3 times with 1 M HCl (aq), once with sat. bicarbonate solution and once with brine. The organic layer was dried ($MgSO_4$) and the solvent evaporated and flash chromatography of the residue with pentane with a gradient of ethyl acetate gave the product (0.47 g, 60%). $[\alpha]_D^{RT}=19.1°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=8.18$–7.83 (m, 10H, Ar), 7.77–7.14 (m, 10H, Ar), 5.68 (s, 1H, H5), 5.39 (s, 1H, H6), 5.22 (s, 2H, H2, H6), 5.06–4.96 (m, 1H, H3), 4.74–4.46 (m, 2H, H1, H4), 3.66 (dd $J=1.9$, 15.6, 1H, H1), 1.18 ppm (s, 9H, Boc); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=166.3$, 165.6, 165.5, 164.7, 155.4 (C=O), 134.0–133.4 (Ar-C), 130.3–128.5 (Ar), 80.8 (C-Boc), 67.9–67.6 (C5,C6), 60.6 (C3,C4), 53.3 (C2), 38.7 (C1), 28.1 ppm (CH_3-Boc); HRMS: *m/z*: calcd $C_{39}H_{37}NO_{10}Na$: 702.2315; found: 702.2292.

Compound 23: *N*-Boc-2,3,4,6-tetra-*O*-benzoyl-1-deoxynojirimycin (0.1 g, 0.15 mmol) was dissolved in CH_2Cl_2 (10 mL) and an excess of TFA was added. The solution was stirred until the reaction was finished (TLC). The solution was evaporated to dryness to give the product (0.102, 100%); $[\alpha]_D^{RT}=49.3°$ ($c=1.0$, CH_3CN); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=$ 8.10–7.83 (m, 10H, Ar), 7.45–7.26 (m, 10H, Ar), 5.96 (m, 2H, H3, H4), 5.68 (m, 1H, H2), 4.8 (dd $J=2,3$, 12,8 Hz, 1H, H6), 4.6 (dd, $J=5,5$, 12,8 Hz, 1H, H6), 4.09 (dd, $J=5,0$ 12,8 1H, H5), 3.97 (m, 1H, H1), 3.27 ppm (t, 1H, $J=11,5$ H1); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=166.6$, 165.7, 165.4, 165.0 (C=O), 134.1–128.7 (Ar), 71.9 (C3), 67.3 (C4), 67.0 (C2), 60.1 (C6), 57.4 (C5), 44.1 (C1); HRMS: *m/z*: calcd for $C_{34}H_{30}NO_8$: 580.1971; found: 580.1956.

Compound 24: *N*-Boc-1-deoxynojirimycin (0.182 g, 0.691 mmol) was dissolved in DMSO (4 mL) and a solution of NaOH was added (50%, 0.2 mL). Methyl iodide was added dropwise (0.59 g, 4.15 mmol). The reaction mixture was stirred for 8 h and poured into water (25 mL). The mixture was extracted 3 times with diethyl ether and the combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to dryness. The crude product was purified by flash chromatography with pentane as the eluent with a gradient of ethyl acetate to give the product (0.143 g, 65%). $[\alpha]_D^{RT}=-7.6°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=4.06$ (dd, $J=10.8$, 5.3 Hz, 1H, H4), 3.86 (dd, $J=14.3$, 3.8 Hz, 1H, H1), 3.50–3.45 (3H, H3, H6), 3.44–3.32 (12H, Me), 3.29–3.28 (m, 2H, H2, H5), 3.12 (dd, $J=14.2$, 2.8 Hz, 1H, H1), 1.43 ppm (9H, CH_3-Boc); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=155.3$ (C=O), 82.5 (C-Boc), 79.9–79.5 (C2,C5), 76.3 (C3), 70.9 (C6), 59.0 (Me), 58.6 (Me), 58.3 (Me), 56.8 (Me), 54.0 (C4), 39.4 (C1), 28.5 (CH_3-Boc); HRMS: *m/z*: calcd for $C_{15}H_{29}NO_6Na$: 342.1893; found: 342.1910.

Compound 25: *N*-Boc-2,3,4,6-tetra-*O*-methyl-1-deoxynojirimycin (0.143 g, 0.448 mmol) was dissolved in a 1:1 mixture of THF and 1 M HCl (10 mL). The reaction mixture was refluxed for 1 h at 80°C. The mixture was evaporated and purified by flash chromatography with ethyl acetate and 1% triethylamine to give the product (0.075 mg, 65%). $[\alpha]_D^{RT}=51.6°$ ($c=1.0$, MeOH) (HCl salt); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=3.56$ (s, 3H, Me.), 3.51 (dd, $J=9.1$, 2.4 Hz, 1H, H6), 3.45 (s, 3H, Me), 3.39 (s, 3H, Me), 3.34 (dd, $J=9.0$, 6.5 Hz, 1H, H6), 3.29 (s, 3H, Me), 3.18 (dd, $J=$ 11.9, 4.7 Hz, 1H, H1), 3.10–3.02 (m, 1H, H2), 2.97 (t, $J=8.8$ Hz, 1H, H3), 2.83 (t, $J=9.0$ Hz, 1H, H4), 2.54–2.43 (m, 1H, H5), 2.28 (dd, $J=$ 11.2, 10.5 Hz, 1H, H1), 1.86 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=88.8$ (C3), 82.1 (C4), 82.0 (C2), 73.0 (C6), 61.0 (Me.), 60.6 (Me.), 59.8 (C5), 59.0 (Me.), 58.3 (Me.), 47.7 (C1); HRMS: *m/z*: calcd for $C_{10}H_{22}NO_4$: 220.1543; found: 220.1538.

Compound 28: *N*-Cbz-4,6-*O*-benzylidene-1-deoxynojirimycin (0.818 g, 2.12 mmol) was dissolved in 1:1 ethanol/water (30 mL) and NaOH (1 g) was added. The reaction mixture was stirred at 80°C for 12 h. The reaction mixture was cooled and extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and purified by flash chromatography with ethyl acetate as the eluent with a gradient of methanol to give the product (0.46 g, 86%). $[\alpha]_D^{RT}=-27.4°$ ($c=1.0$, CH_3OH); m.p. 176–177°C; ^{1}H NMR (300 MHz, CD_3OD) $\delta=7.66$–7.23 (m, 5H, Ar), 5.58 (s, 1H, PhCH), 4.23 (ddd, $J=10.5$, 4.7, 1.2 Hz, 1H, H6), 3.65 (tt, $J=4.4$, 2.2 Hz, 1H, H6), 3.60–3.32 (m, 3H, H2, H3, H4), 3.15 (ddd, $J=12.5$, 4.9, 1.4 Hz, 1H, H1), 2.74–2.63 (m, 1H, H5), 2.61–2.51 ppm (m, 1H, H1); ^{13}C NMR (75 MHz, CD_3OD) $\delta=139.4$, 129.9, 129.0, 127.5 (Ar), 102.9 (PhCH), 83.8, 77.0, 73.0, 70.5 (C6), 55.0 (C5), 51.4 (C1); HRMS: *m/z*: calcd for $C_{13}H_{17}NO_4Na$: 274.1055 [$M+Na^+$]; found 274.1061; elemental analysis calcd (%) for $C_{13}H_{17}NO_4$: C 62.14, H 6.82, N 5.57; found: C 61.91, H 6.76, N 5.52.

Compound 29: *N*-Cbz-1-deoxynojirimycin (200 mg, 0.673 mmol) was dissolved in dry DMF (5 mL) and imidazole (0.37 g, 5.38 mmol) was added. TBSOTf (1.07, 4.04 mmol) was then added to the mixture under nitrogen. The reaction was followed by TLC and, if necessary, more TBSOTf was added to complete the reaction. Methanol was added to the reaction mixture to react with any unreacted TBSOTf. Ethyl acetate was then added and the mixture was washed 6 times with brine, once with 1 M HCl, once with sat. bicarbonate solution, and once more with brine. The combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography with petroleum ether as eluent with a gradient of ethyl acetate to give the product (0.327 g, 64%). $[\alpha]_D^{RT}=-2.3°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=$ 7.36–7.25 (m, 5H, Ar), 5.26–4.97 (m, 2H, $PhCH_2$), 4.34 (t, $J=6.9$ Hz), 4.24 (t, $J=7.9$ Hz), 3.95 (dd, $J=13.8$, 3.6 Hz), 3.89–3.80 (m), 3.80–3.69 (m), 3.62 (d, $J=2.0$ Hz), 3.27 (dd, $J=13.8$, 2.4 Hz), 3.19 (dd, $J=13.8$, 2.0 Hz), 0.92–0.76 (m, 36H, $(CH_3)_3CSi$), 0.09–00.4 ppm (m, 24H, CH_3Si); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=156.8$, 137.2, 128.4, 129.0, 127.8, 74.2, 73.8, 70.6, 69.8, 67.0, 61.3, 59.8, 59.2, 41.3, 26.1, 26.1, 26.0, 26.0, 25.9, 18.4, 18.0, −4.4, −4.4, −4.6, −4.6, −4.6, −4.8, −4.8, −5.1, −5.2 ppm; HRMS: *m/z*: calcd for $C_{38}H_{75}NO_6Si_4Na$: 776.4569; found: 776.4542.

Compound 30: *N*-Cbz-tetra-*O*-(tert-butyldimethylsilyl)-1-deoxynojirimycin (250 mg, 0.332 mmol) was dissolved in ethyl acetate (10 mL) and Pd/C was added (10%, 250 mg) together with a drop of acetic acid. The flask was flushed with hydrogen and the solution was then stirred overnight. The solution was filtered and evaporated to dryness to give the product (0.206 mg, 100%). $[\alpha]_D^{RT}=9.2°$ ($c=1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta=3.88$ (dd, $J=9.7$, 7.5 Hz, 1H, H6), 3.74 (dd, $J=9.7$, 5.7 Hz, 1H, H6), 3.69 (m, 1H), 3.66 (m, 1H), 3.48 (d, $J=2.7$ Hz, 1H, H2), 3.01 (dd, $J=14.0$, 2.7 Hz, 1H, H1), 2.79 (m, 1H, H5), 2.57 (d, $J=$ 14.0 Hz, 1H, H1), 2.43–1.92 (b, 1H, NH), 0.89 (m, 36H, $(CH_3)_3CSi$), 0.11–−0.01 ppm (m, 24H,CH_3Si); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta=74.1$, 69.9 (C2), 69.7, 63.2 (C6), 60.9 (C5), 44.8 (C1), 26.2–18.0 ($(CH_3)_3CSi$), −3.9–−5.13 ppm (CH_3Si); HRMS: *m/z*: calcd for $C_{30}H_{69}NO_4Si_4Na$: 620.4382; found: 620.4372.

Compound 31: *N*-Boc-1-deoxynojirimycin (0.130 g, 0.494 mmol) was dissolved in pyridine and cooled to 0°C, then tosyl chloride was added (0.104 g, 0.543 mmol). The reaction was followed by TLC and when the starting material was consumed, acetic acid anhydride was added (1 mL). The reaction was stirred overnight and the solvents were evaporated, the crude product was purified by flash chromatography with pentane as the eluent with a gradient of ethyl acetate (0.015 g, 10%). $[\alpha]_D^{RT}=19.4°$ ($c=$

1.0, $CHCl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.20 (t, J = 9.7 Hz, 1H, H3), 4.95 (m, 2H, H2, H4), 4.39 (t, J = 8.6 Hz, 1H, H6), 4,22 (m, 2H, H1, H6), 3.87–3.61 (m, 1H, H5), 2.89 (dd, J = 13.0, 10.6 Hz, 1H, H1), 2.07, 2.05, 2.04 ppm (3s, 9H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.1, 167.0, 169.4 (C=O, Ac), 156.1 (C=O), 72.9 (C3), 71.5 (C4), 67.9 (C2), 65.5 (C6), 56.0 (C5), 42.1 (C1), 20.7, 20.7, 20.7 (CH_3, Ac); HRMS: m/z: calcd for $C_{13}H_{18}NO_8$: 316.1032; found: 316.1044.

Compound 33: *N*-Boc-1-deoxynojirimycin (0.165 g, 0.627 mmol) was dissolved in pyridine (5 mL) and CCl_4 (0.193 g, 1.254 mmol) in pyridine (0.62 mL) was added. The mixture was cooled to −35 °C and HMPT (0.166 g, 1.02 mmol) was added over a period of 15 min. The reaction mixture was stirred for 30 min at −35 °C and then slowly allowed to reach RT. The solvents were removed by evaporation and the product dissolved in methanol (3.2 mL) followed by addition of NaOMe (0.317 g, 1.467 mmol). The reaction mixture was refluxed for 2 h, and then neutralized by adding ammonium chloride. The solvent was evaporated and purified by flash chromatography with petroleum ether as the eluent with a gradient of ethyl acetate to give the product (0.025 g. 16 %). $[\alpha]_D^{RT} = -2.8°$ (c = 1.0, $CHCl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.68–4.59 (brm, 1H, H5), 4.43(brm, 1H, H6), 4.25(b, 1H, H6), 4.17 (t, J = 5.0 Hz, 1H, H3), 4.12–4.02 (2H, H1,H4), 3.77 (brm, 1H, H2), 3.50 (brm, 1H, H1), 1.49 ppm (s, 9H, Boc); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.4 (C=O), 80.9 (C-Boc), 72.8 (C6), 72.0 (C3), 69.6 (C2), 69.5 (C2), 69.2 (C4), 56.3 (C5), 55.2 (C5), 47.5 (C1), 28.49 ppm (CH_3-Boc); HRMS: m/z: calcd for $C_{11}H_{19}NO_5Na$: 268.1161; found: 268.1145.

Compound 34: *N*-Boc-3,6-anhydro-1-deoxynojirimycin (25 mg, 0.102 mmol) was dissolved in 1 M HCl (aq). The reaction mixture was stirred until the reaction was finished (TLC). The mixture was evaporated to dryness to give the product (0.0185 g, 100 %). $[\alpha]_D^{RT} = 26.5°$ (c = 1.0, MeOH); salt: ^{1}H NMR (300 MHz, CD_3OD) δ = 4.62 (t, J = 4.8 Hz, 1H) 4.27–4.16(m, 3H), 4.01(m, 1H), 3.66 (dd, J = 14.3, 4.3 Hz, 1H, H1), 3.35–3.31 ppm (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ = 71.9, 71.3, 68.6, 66.7, 57.7, 46.2 ppm; free amine: ^{1}H NMR (500 MHz, CD_3OD) δ = 4.20 (dd, J = 3.8 Hz, 1H, H4), 4.07 (d, J = 9.9 Hz, 1H, H6), 4.02 (dd, J = 9.9, 3.8 Hz, 1H, H6), 3.97 (dd, J = 5.2 Hz, 1H, H3), 3.66 (dd, J = 4.0 Hz, 1H, H2), 3.30 (dd, J = 10.1, 3.7 Hz, 1H, H1), 3.28 (dt, J = 3.2, 1.6 Hz, 2H, H5, NH), 2.84 ppm (d, J = 14.6 Hz, 1H, H1); ^{13}C NMR (126 MHz, CD_3OD) δ = 73.2 (C4), 72.5 (C3), 71.0 (C2), 69.1 (C6), 57.1 (C5), 46.9 ppm (C1); HRMS: m/z: calcd for $C_6H_{12}NO_3$: 146.0817; found: 146.0809.

Compound 35: *N*-Boc-3,6-anhydro-1-deoxynojirimycin (5.6 mg, 0.023 mmol) was dissolved in pyridine and an excess of acetic acid anhydride was added. The reaction mixture was stirred overnight and the solvent was then evaporated, to give the product (7.5 mg, 100 %); $[\alpha]_D^{RT}$ = 58.3° (c = 1.0, $CHCl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.91–4.81(m, 3H, H2, H4, H5), 4.51 (t, J = 4.6 Hz, 1H, H3), 4.21–4.02 (m, 3H, H1, H6), 3.60 (dd, J = 15.5, 4.5 Hz, 1H, H1), 3.51 (dd, J = 15.4, 4.7 Hz, 1H, H1), 2.10, 2.09, 2.05, 2.03 (Ac), 1.48 ppm (Boc); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.4, 170.3, 169.9, 169.8 (C=O, Ac), 154.8, 154.5 (C=O, Boc), 80.4 (C-Boc), 71.7, 69.9, 69.8, 69.0, 68.7, 68.6, 53.6 (C5), 52.7 (C5), 43.3 (C1), 42.0 (C1), 28.4 (CH_3-Boc), 21.0, 20.9, 20.8 ppm (CH_3, Ac); HRMS: m/z: calcd for $C_{15}H_{23}NO_7Na$: 352.1372; found: 352.1367.

Compound 36: *N*-Boc-2,4-di-*O*-acetyl-3,6-anhydro-1-deoxynojirimycin (7.5 mg, 0.023 mmol) was dissolved in CH_2Cl_2 and an excess of TFA was added. When the reaction was finished the mixture was evaporated to dryness to give the product (7.5 mg, 100 %). $[\alpha]_D^{RT} = 46.5°$ (c = 1.0, $CHCl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.06–5.02 (m, 2H, H2, H4), 4.66 (t, J = 4.7 Hz, 1H, H3), 4.38–4.17 (m, 3H, H5, H6), 3.67–3.51 (m, 2H, H1), 2.19, 2.06 ppm (6H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.1, 169.6 (C=O), 69.5 (C2), 68.7 (C3), 66.3 (C4), 65.3 (C6), 54.3 (C5), 41.7 (C1), 20.5, 20.3 ppm (Ac); HRMS: m/z: calcd for $C_{10}H_{16}NO_5$: 230.1028; found: 230.1037.

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