

Nitrogen Inversion as a Diastereomeric Relay in Azasugar Synthesis: The First Synthesis of Adenophorine**

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Although amine nitrogen atoms are potential stereogenic centers, their configurational lability arising from lone-pair inversion^[1] has typically prevented their utility in synthesis. *N*-Halogenation can dramatically slow lone-pair inversion^[2] and therefore raise the temperature at which the configurational lability ceases. We therefore considered that if a suitable system could be found, *N*-chloramines might provide a new source of flexible, temperature-dependent stereogenesis. In turn, existing chiral information may then be relayed and exploited such that subsequent reactions are regio- or diastereoselective. Due to the often higher conformational lability of the acyclic *N* lone-pair isomers of *N*-haloamines, we selected cyclic amines for our study, which are typically, but not always, less labile due to angular constraint.^[1] Cyclic systems have often been exploited for intramolecular relay of chirality.^[3]

As our model chiral cyclic *N*-chloramine system we selected *N*-chloropiperidine azasugars. Polyhydroxylated nitrogen heterocycles such as deoxynojirimycin (DNJ, **1** in Scheme 1) may be considered to be mimics of sugars, for example, D-glucose, in which the ring oxygen has been replaced by a nitrogen atom.^[4] The often potent inhibitory activity of many of these compounds towards carbohydrate-processing enzymes has suggested their use in a wide range of potential therapeutic strategies,^[5–8] including the treatment of viral infections^[9,10] and lysosomal storage diseases,^[11,12] and as invaluable tools in the study of enzyme mechanism.^[13]

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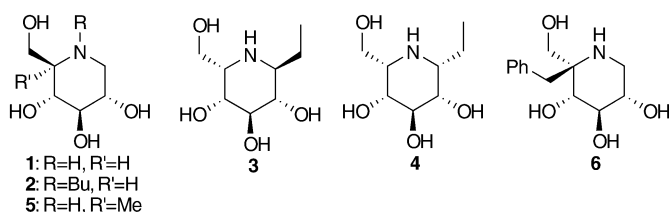
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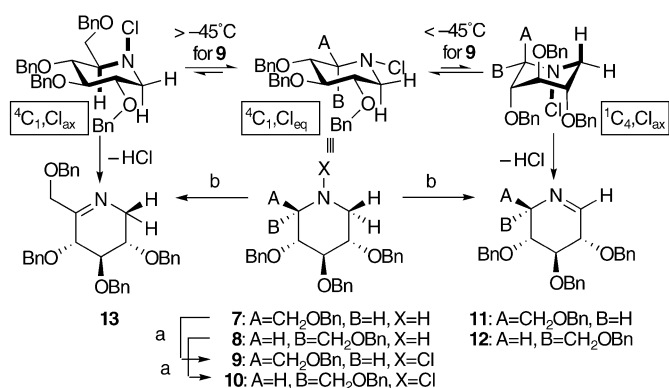


Scheme 1.

Azasugars carrying hydrophobic substituents, such as the butylated azasugar *N*-butyldeoxynojirimycin (**2**, NB-DNJ or Zavesca),^[11] may show increased enzyme inhibition and enhanced bioavailability.^[14] Therefore routes amenable to the ready installation of hydrophobic moieties are of high value.

Adenophorine, a rare example of a naturally occurring azasugar with hydrophobic substituents, was isolated from the roots of *Adenophora* spp. in 2000 by Asano and co-workers and was assigned the ethyl-substituted polyhydroxylated piperidine structure with the relative configuration shown in **3** (Scheme 1) on the basis of NMR investigations; its absolute configuration was not determined.^[15] By virtue of its pseudoanomeric substituent,^[16] adenophorine is a highly α -glycosidase-specific inhibitor (IC₅₀ values for α -glucosidase: 32 μ M, intestinal sucrase: 20 μ M, α -galactosidase: 11 μ M) that displays no detectable inhibition of β -glycosidases.^[15]

We reasoned that for the synthesis of adenophorine (**3**) a two-step process, consisting of regioselective elimination controlled by the switchable configuration at the chloramine nitrogen atom followed by addition of suitable nucleophiles to the resulting imine, might be used as a diastereomeric relay for the ready addition of hydrophobic functionality to a starting azasugar with regio- and stereocontrol (Scheme 2). We have shown previously that the highly functionalized piperidine azasugar **9** can undergo regioselective elimination.^[17] In addition, building on the pioneering work of Horenstein and co-workers^[18] and Furneaux and co-workers,^[19] who demonstrated the addition of organometallic nucleophiles to a single pyrrolidine aldimine, we have

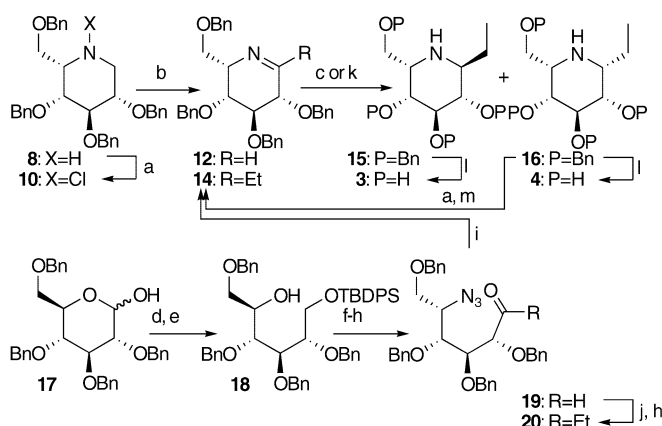


Scheme 2. a) NCS, CH₂Cl₂, 97% for **9**, 93% for **10**; b) Base conditions for **9**→**11** < −45°C: LiTMP, −78°C, Et₂O; Base conditions for **9**→**13** > −45°C: DBU, RT, Et₂O; Base conditions for **10**→**12**: DBU, reflux, Et₂O. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NCS = *N*-chlorosuccinimide, RT = room temperature, TMP = tetramethylpiperidine.

recently shown that this is a general reaction that may be applied with high diastereoselectivity to several pyrrolidine aldimines.^[17,20] We considered that addition of an ethyl nucleophile to idonojirimycin (INJ) aldimine **12** might provide convergent access to adenophorine (**3**) as well as ready access to analogues.^[21]

In this communication, we have applied this stereodynamic strategy to the first synthesis of adenophorine (**3**) and 1-*epi*-adenophorine (**4**) as well as hydrophobically modified DNJ variants **5** and **6**. To our knowledge this is the first example of a *N*-halogen stereogenic center in such a switchable, stereochemical relay.

Central to our approach (vide supra) we established the stereodynamics of the N–Cl bond in two piperidine systems. Tetrabenzyl DNJ **7**^[22] and tetrabenzylidonojirimycin (tetrabenzyl INJ, **8**)^[23] were prepared from D-glucose and smoothly *N*-chlorinated using *N*-chlorosuccinimide (NCS) to give DNJ-Cl **9** and INJ-Cl **10**, respectively, in excellent yields (Scheme 2 and Scheme 3). *N*-configurational exchange was evident by



Scheme 3. a) NCS, CH₂Cl₂, 93% for **10**; b) DBU, Et₂O, reflux; c) **12**→**16**: EtMgBr, Et₂O/dioxane, 47% over two steps from **10**; d) NaBH₄, THF/H₂O, 100%; e) TBDPSCl, imidazole, DMF, 99%; f) Method 1: MsCl, py, 97% then Bu₄N₃, toluene, reflux, 23% or Method 2: HN₃, DIAD, PPh₃, toluene, 87%; g) TBAF, THF, 100%; h) PCC, CH₂Cl₂, mol. sieves, 87% for **19**, 72% for **20**; i) PPh₃, Et₂O; j) EtMgBr, Et₂O, 70%; k) **14**→**15/16**: NaBH₄, MeOH, 17%:32% of **15/16** or LiAlH₄, THF, 69% of **15** only; l) H₂, PdCl₂, EtOH, 100% for **3**, 86% for **4**; m) LiTMP, −78°C, Et₂O. DIAD = diisopropyl azodicarboxylate, PCC = pyridinium chlorochromate, py = pyridine, TBAF = tetrabutylammonium fluoride, TBDPSCl = *tert*-butyldiphenylsilyl chloride.

NMR in both **9** and **10** in the marked broadening of the resonances for C1 and C5 (Figure 1). Encouragingly, variable-temperature NMR experiments (VT-NMR) confirmed the existence at −55°C of two species consistent with *N*-epimers of **9**, one of which was strongly dominant. When the sample was warmed from −55°C to approximately −45°C, a temperature that is accessible in standard synthesis, the signals of **9** started to broaden. Interestingly, signal broadening due to exchange was evident in **10** at much lower temperatures (< −80°C);^[24] only the control of the configurational exchange of **9** was required by our strategy (vide infra).

Gratifyingly and consistent with these observations, treatment of DNJ-Cl **9** with the base DBU at room temperature,

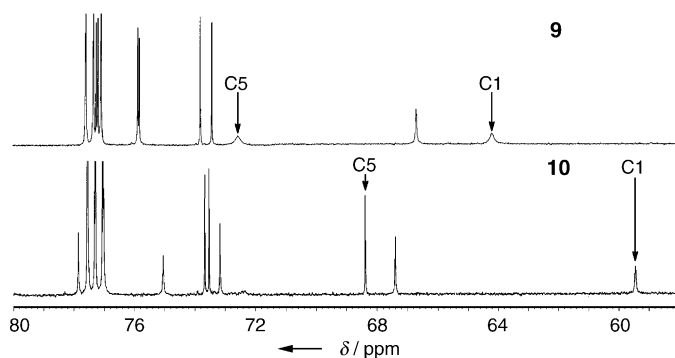


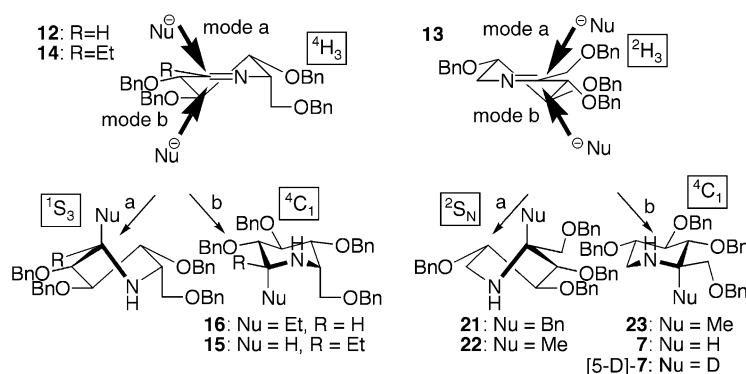
Figure 1. ^{13}C NMR spectra (CDCl_3 , 125 MHz, 294 K) illustrating the dramatic broadening of the signals of the carbon atoms flanking the configurationally labile nitrogen atom in chloramines **9** and **10**.

above the point of N-configurational lability, yielded ketimine **13** (Scheme 2) (IR: $\tilde{\nu} = 1667\text{ cm}^{-1}$ ($\text{C}=\text{N}$), ^{13}C NMR: $\delta = 168.5\text{ ppm}$ (s, C5)), whereas treatment with LiTMP at -78°C yielded DNJ-aldimine **11** (IR: $\tilde{\nu} = 1654\text{ cm}^{-1}$ ($\text{C}=\text{N}$), ^{13}C NMR: $\delta = 162.3\text{ ppm}$ (d, C1), ^1H NMR: $\delta = 7.60\text{ ppm}$ (brs, 1 H, H1)). We interpret these results as being due to the relative accessibility of the conformational and configurational manifolds shown in Scheme 2. Above -45°C elimination proceeds according to Curtin–Hammett principles via the $^4\text{C}_1, \text{Cl}_{\text{ax}}$ conformation that allows antiperiplanar elimination of H5_{ax} and Cl_{ax} .^[25] However, below -45°C the $^4\text{C}_1, \text{Cl}_{\text{eq}} \rightleftharpoons ^4\text{C}_1, \text{Cl}_{\text{ax}}$ configurational manifold is inaccessible, and elimination proceeds via a conformation such as $^1\text{C}_4, \text{Cl}_{\text{ax}}$,^[26,27] which allows elimination of H1_{ax} and Cl_{ax} . To test these interpretations we studied the elimination of INJ-Cl **10**, for which the antiperiplanar elimination of H5 and Cl is not possible from its preferred $^4\text{C}_1$ conformation by virtue of the opposite configuration of **10** at C5. In accord with this model, elimination with DBU at reflux gave INJ-aldimine **12** as the exclusive product. To further confirm their identities imines **12** and **13** were also independently synthesized by novel routes employing Staudinger aza-Wittig reactions (Scheme 3).

Addition of EtMgBr to imine **12**, with the aim of synthesizing adenophorine, initially provided disappointing results, yielding only products consistent with intermediate tautomerization and/or elimination. To reduce the likelihood of these base-catalyzed processes, we added imine **12** to a solution of EtMgBr that had been pretreated with dioxane,^[28] and gratifyingly obtained **16**. Subsequent deprotection gave protected 1-*epi*-adenophorine **4** as a single diastereomer (*de* > 98%). Although we were pleased by the level of diastereoselectivity, our goal, the synthesis of adenophorine, required the opposite sense of selectivity, and this stimulated an investigation of the determining factors. An investigation of different nucleophile additions to ketimine **13**, as a near-enantiomeric substrate to INJ-aldimine **12**, revealed a graduation in the sense of selectivity (from mode a to b, Scheme 4) as the size of the nucleophile decreased, although electronic

effects cannot be excluded.^[29] Thus, addition of the bulky nucleophile BnMgCl yielded, exclusively by means of mode a, the highly substituted piperidine **21** as the only addition product albeit in low yield (19%). The reaction with the smaller nucleophile MeMgBr yielded a mixture of products from mode a and mode b (d.r. 1:8, 17%) **22** and **23**. Finally, reaction of **13** with yet smaller nucleophiles hydride and deuteride from LiAlH_4 and LiAlD_4 yielded, exclusively by means of mode b, **7** and [5-D]-**7** in 87% and 93% yield, respectively. We speculate that the two opposing modes may be influenced by two opposing factors: steric approach control^[30] (mode a, $\text{H} \rightarrow \text{S}$ thereby developing strain, Scheme 4) and stereoelectronic control coupled with strain relief^[31,32] (mode b, $\text{H} \rightarrow \text{C}$, Scheme 4).^[29]

The formation of protected *epi*-adenophorine **16** had indicated that Et_2Mg added to **12** exclusively by mode b.



Scheme 4. Competing modes a and b for the attack on polyhydroxylated imines are modulated by the size of the nucleophile (see Supporting Information for discussion).

Armed with the above information, we considered that only nucleophiles larger than Et^- would favor the desired addition mode a, and this appeared to block our convergent approach to the synthesis of adenophorine through addition of Et^- to **12**. However, according to this size-dependent model, addition of the small nucleophile hydride, again by means of mode b, to ethyl ketimine **14** as an alternative substrate would yield adenophorine. Ethyl ketimine **14** was synthesized in two ways: from **16** by our two-step chlorination–elimination approach and independently by means of a Staudinger aza-Wittig cyclization from ethylazidoketone **20**, which was in turn synthesized efficiently in 38% yield from **17** in eight steps. Although the former provided a convenient way of converting **16** to **14**, the regioselectivity of the elimination step was poor and the latter route **17**→**14** was more efficient (overall yields: **16**→**15** 24% over three steps, **17**→**15** 26% over ten steps, vide infra). Reduction of **14** under various standard conditions ($\text{NaBH}_3\text{CN}/\text{AcOH}$, H_2/Pd , K-selectride) failed due to degradation or protecting-group incompatibilities. However, reduction with $\text{NaBH}_4/\text{MeOH}$ yielded a mixture of mode-a and mode-b products (d.r. 1:2) **15** and **16**. The formation of **16** as a major mode b product highlighted the need for a yet smaller source of hydride. Gratifyingly, the use of LiAlH_4 yielded tetrabenzyladenophorine **15**

in 69% yield ($de > 98\%$). Deprotection of **15** yielded (–)-adenophorine (**3**) ($[\alpha]_D^{22} = -52.3$ ($c = 0.20$ in water)) which was identical in all respects to a sample of the natural product save its opposite sense of rotation ($[\alpha]_D = +59.7$ ($c = 1.0$ in water)). On the basis of these results we have assigned the absolute configuration of the natural product (+)-adenophorine to the enantiomer of **3**.

In summary, we have exploited configurational dynamics at the nitrogen atom in azasugar chloramines to control the regiochemistry of elimination. Moreover, after the factors controlling stereoselectivity were determined, subsequent nucleophilic additions to the resulting imines were achieved with excellent diastereoselectivity. Together these represent, to the best of our knowledge, the first examples of a switchable, stereochemical relay from N to neighboring C1 or C5 positions. Furthermore, this imine methodology has enabled us to synthesize a number of novel hydrophobically modified azasugars. We were able to identify a good and highly selective inhibitor of human α -glucosidase^[33] and completed the first synthesis of (–)-adenophorine, thereby allowing assignment of the configuration of the natural (+) isomer.

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- [33] The deprotected piperidine adducts produced here as hydrophobically modified azasugars were evaluated for their inhibitory activity towards panels of human glycoprocessing enzymes. These revealed that **5** is a good and highly selective inhibitor of human α -glucosidase (IC_{50} : $1 \mu\text{M}$ but no inhibition of GCS at 0.1 mM) that is more potent than the archetypal azasugar DNJ **1** (IC_{50} : $1.4 \mu\text{M}$ towards human α -glucosidase^[14d]). This high α -glucosidase inhibitory power of **5** suggests it as a potential broad-spectrum antiviral agent.^[9c] Further details will be published in due course.