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# Stereoselective Strecker and Carbamate Annulation Methodology for the Synthesis of 1-Amino-1,2,5-trideoxy-2,5-imino-L-iditol

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An efficient and highly stereoselective synthesis of L-*ido*-aminoiminosugar **3** has been described. Key in the synthesis is the application of a diastereoselective Strecker reaction and the extension of our carbamate annulation methodology to protected and functionalized alkenylamines. In addition, the identification of the primary iodide as a key intermediate during the carbamate annulation reaction provides insight into the mechanism of this reaction.

## Introduction

The biological activity of azasugars has been largely attributed to their ability to mimic the oxocarbenium ion intermediate formed during a glycosidase reaction, and for this reason, functional and stereochemical modifications of the azasugar scaffold have led to the development of specific and potent glycosidase inhibitors.[1] Of particular note is the pioneering work of Wong et al. who observed that derivatization of naturally occurring 2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP, **1a**, Figure 1) to the 1-amino-1-deoxy-DMDP analogue (**1b**) resulted in the generation of a compound with pronounced inhibitory activity against *N*-acetylglucosaminidase.[2] The subsequent synthesis of a library of *N*-functionalized DMDP analogues,[3–6] many of which were readily prepared from 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol (**2**),[3,6] then led to the identification of potential drug therapies for the treatment of osteoarthritis,[7,8] and later, bacterial infections.[9] Similarly, the groups of Stütz and Wrodnigg developed a series of functionalized aminoiminohexitols using the Amadori rearrangement.[10–15] They found that one-step *N*-derivatization of amine derivative **2** led to the generation of powerful β-glycosidase inhibitors, whereas aminoiminohexitol **2** itself was a moderate β-glucosidase inhibitor.[10,11,14] More recently, Ramesh and co-workers prepared several selective glycosidase inhibitors based on modifications to L-*ido* azasugar **3**.[16] While the parent compound showed no glycosidase inhibitory activity, *N*-tosyl, *N*-methyl, and *N*-ethyl derivatives all exhibited good, and often selective, activity against the glycosidases tested.

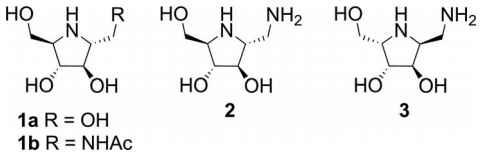


Figure 1. Representative aminoiminohexitols.

Given the potential of aminoiminohexitols as glycosidase inhibitors, we were interested in developing an efficient methodology for their synthesis. To this end, we envisioned using cyclic carbamates **II** as key intermediates, which could be readily hydrolyzed to give target aminoiminohexitols **I** (Scheme 1). These carbamates should be accessible from α-aminonitriles **III** through our recently developed iodine-mediated carbamate annulation reaction.[17–19] Application of this annulation methodology to protected and functionalized alkenylamines, such as **III**, would greatly enhance the scope of the reaction. Nitrile functionalized alkenylamines **III** could in turn be prepared by Strecker reactions[20] using the intermediate aldehydes generated from the Vasella reaction[21] of readily available methyl iodoglycosides **IV**. Here, the inherent chirality of the carbohydrate-derived aldehyde would be used to control the diastereoselectivity of the Strecker reaction. While Strecker reactions have been widely used for the preparation of α-aminonitriles from aldehydes,[22] with stereoselective Strecker-type reactions being developed based on the use of a chiral Lewis acid, reactions in which the chiral matrix is the carbonyl or imine avoids additional steps and the added complexities associated with the use of an auxiliary or a catalyst.

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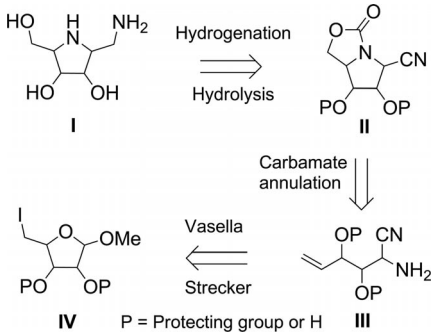
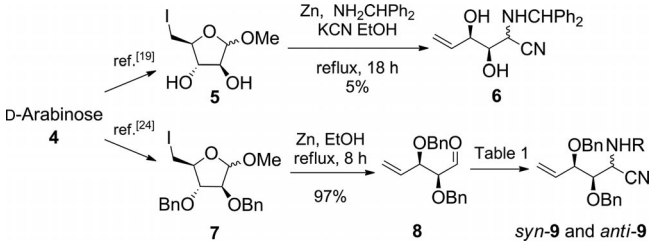



Scheme 1. Retrosynthetic analysis of aminoiminohexitols.

## Results and Discussion

With our synthetic plan in place, we set out to prepare D-arabinose-derived α-aminonitrile **9** (Scheme 2). Initially, attempts were made to perform the Strecker reaction without the use of protecting groups, as this would provide a shorter synthetic route. To this end, methyl iodoglycoside **5**, readily prepared from arabinose (**4**) in 64% yield (two steps),[19,23] was subjected to Vasella conditions. Though a lower running spot was observed by TLC, isolation of the corresponding aldehyde proved futile with product degradation being observed. A two-step, one-pot Vasella/Strecker reaction was then attempted by first treating glycoside **5** with activated zinc in EtOH at reflux, followed by cooling and treatment with amine (either $Ph_2CHNH_2$ or $NH_4Cl$) and nitrile (either KCN or TMSCN). Unfortunately, under these conditions, significant product degradation was observed. At best, only a minor amount (ca. 5%) of desired α-aminonitrile **6** could be obtained when $Ph_2CHNH_2$ was used as the nucleophile.




Scheme 2. Preparation of nitrile-functionalized alkenylamine.

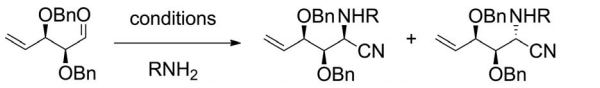
To avoid these issues, D-arabinose (**4**) was converted into benzyl-protected methyl iodoglycoside **7** in five steps and 62% overall yield by following literature procedures.[19,24] Subsequent treatment of iodide **7** with a solution of activated zinc in EtOH, according to the conditions of Vasella, gave corresponding aldehyde **8** in an excellent 97% yield. Given the chirality of **8**, we then envisioned that a diastereoselective Strecker reaction could be developed to favor the selective formation of one α-aminonitrile, either *syn*- or *anti*-**9**, representing the D-*lyxo* and D-*xylo* configurations, respectively.

Aldehyde **8** was first treated with KCN in the presence of $NH_4Cl$ in acetonitrile (Table 1, Entry 1). Unfortunately, the reduced solubility of $NH_4Cl$ in acetonitrile resulted in the formation of the corresponding cyanohydrin, observed by $^1H$ NMR spectroscopy (illustrated by the downfield shift of the α-protons to 4.53 and 4.45 ppm), and the desired α-aminonitrile was not observed. Studies of the Strecker reaction by Taillades and Commeyra demonstrated that cyanohydrin formation is kinetically favored;[25] however, in our hands none of the desired α-aminonitriles **9a** were observed, even after prolonged reaction times (24 h). To prevent formation of the cyanohydrin and other impurities, the much more soluble and nucleophilic $Ph_2CHNH_2$ was utilized,[26,27] which, with increased steric bulk, could also lead to enhanced diastereoselectivity. Aldehyde **8** was thus treated with $Ph_2CHNH_2$, KCN, as the nitrile source, and $Al_2O_3$ (Table 1, Entry 2). The reaction was sluggish, and a reaction time of two weeks was required for the complete disappearance of aldehyde **8** starting material. Although the yield of aminonitriles *syn*- and *anti*-**9b** was poor (ca. 30%), the diastereoselectivity was excellent, being 11:1 in favor of (*R*) diastereomer *syn*-**9b**, and both isomers could be separated by column chromatography. Next, in an attempt to improve the yield and decrease the reaction time, sonication[28] was employed (Table 1, Entry 3). This improved the reaction yield (78%), though the diastereoselectivity was reduced (7:1, *syn*/*anti*). We then explored nitrile sources with improved solubility in organic solvents. When diethyl phosphorocyanidate[29] was added to a solution of aldehyde **8** and $Ph_2CHNH_2$ in acetonitrile (Table 1, Entry 4), the diastereoselectivity (7:1, *syn*/*anti*) was similar to that observed using KCN and sonication (Table 1, Entry 3); however, the yield was only 52%. Changing the solvent to THF (Table 1, Entry 5) improved the overall yield, but led to a dramatic decrease in diastereoselectivity (2:1). The use of TMSCN as a nitrile source was then investigated. First, TMSCN was generated in situ by the addition of KCN to a solution of TMSCl, and this was then added to a solution of the aldehyde in acetonitrile (Table 1, Entry 6). This reaction proved to be slow, taking 2 d to go to completion, and although the diastereoselectivity was good (8.5:1, *syn*/*anti*), the overall yield was modest (49%). Unreacted imine was observed by $^1H$ NMR spectroscopic analysis of the crude reaction mixture. A change to TMSCN,[30] however, led to a rapid improvement in yield (85%) and diastereoselectivity (12.5:1, *syn*/*anti*; Table 1, Entry 7), providing the conditions of choice for the Strecker reaction with $Ph_2CHNH_2$ as the amine source.

Although the initial experiments with $NH_4Cl$ and KCN (Table 1, Entry 1) failed to give the desired aminonitriles, we were keen to explore whether the optimized Strecker conditions, using $Ph_2CHNH_2$ as the nucleophile, were also applicable when using a quaternary ammonium salt. This would allow us to pursue our initial goal of using an unprotected amine source and remove one step from the reaction sequence. To this end, the more soluble $NH_4OAc$ was used in combination with TMSCN as the nitrile source, and to our delight, this resulted in a respectable 80% yield for the

Table 1. Asymmetric Strecker reaction.




| Entry | R–$NH_2$ (equiv.) | Nitrile (equiv.) | Conditions | Ratio[a,b] *syn*/*anti* | Yield [%] |
|---|---|---|---|---|---|
| 1 | $NH_4Cl$ (2.1) | KCN (2) | MeCN, sonication, 50 °C, 18 h | – | 0[c] |
| 2 | $Ph_2CHNH_2$ (2) | KCN (2) | $Al_2O_3$, MeCN, r.t., 14 d | 11:1 | 33 |
| 3 | $Ph_2CHNH_2$ (2) | KCN (2) | $Al_2O_3$, MeCN, sonication, 50 °C, 2 d | 7:1 | 78 |
| 4 | $Ph_2CHNH_2$ (2) | $(EtO)_2P(O)CN$ (1.2) | MeCN, r.t.,2 h | 7:1 | 52 |
| 5 | $Ph_2CHNH_2$ (2) | $(EtO)_2P(O)CN$ (1.2) | THF, r.t., 6 h | 2:1 | 72 |
| 6 | $Ph_2CHNH_2$ (2) | KCN (2) | TMSCl, MeCN, r.t., 2 d | 8.5:1 | 49 |
| 7 | $Ph_2CHNH_2$ (2) | TMSCN (1.2) | MeCN, r.t., 16 h | 12.5:1 | 85 |
| 8 | $NH_4OAc$ (10) | TMSCN (1.2) | MeCN, r.t., 24 h | 5.5:1 | 80 |
| 9 | $NH_4OAc$ (10) | TMSCN (1.2) | THF/$H_2O$, r.t., 18 h | – | 0[c] |
| 10 | $NH_4OAc$ (10) | TMSCN (1.2) | EtOH, r.t., 8 h | 8:1 | 82 |
| 11 | $NH_4OAc$ (10) | TMSCN (1.2) | EtOH, r.t., 8 h | 9:1 | 88 |

[a] As determined from analysis of the crude reaction mixture by $^1H$ NMR spectroscopy. [b] The configurations of *syn*-**9a** and *anti*-**9a** were determined after cyclization by $^1H$ NMR NOE correlations and comparison of the optical rotation values with those of known products. The configuration of *anti*-**9a** was further confirmed through X-ray crystallography. For *syn*-**9b** and *anti*-**9b**, the diphenylmethyl group was removed by treatment with TFA and the resulting $^1H$ NMR spectrum was compared to that of *syn*-**9a** and *anti*-**9a**. [c] Only the cyanohydrin was observed.

two diastereomers and good diastereoselectivity (5.5:1, *syn*/*anti*; Table 1, Entry 8). The stereochemistry of *syn*-**9a** was determined by subsequent NOE correlations and comparison with known optical rotation values following cyclization (vide infra), whereas a crystal structure of *anti*-**9a** was obtained (Figure 2), proving the stereochemistry unambiguously. To further explore the effects of solvent on the reaction yield and diastereoselectivity, the reaction was repeated, this time using a solution of THF/$H_2O$ (1:1) to dissolve both aldehyde **8** and the ammonium salt (Table 1, Entry 9). Unfortunately, these conditions yielded only the cyanohydrin. A change to EtOH, however, led to an improvement in both the yield (82%) and the diastereoselectivity (8:1, *syn*/*anti*; Table 1, Entry 10), with only a minor amount of the cyanohydrin formed. A further improvement was observed with the addition of 2 equiv. of TMSCN (Table 1, Entry 11), which gave the desired α-aminonitrile in excellent (88%) yield and diastereoselectivity (9:1, *syn*/*anti*). This result was remarkable in that both the yield and diastereoselectivity were excellent, and moreover, that the diastereomers were readily separable by flash chromatography [*syn*-**9a**, $R_f$ = 0.47; *anti*-**9a**, $R_f$ = 0.38 (petroleum ether/EtOAc, 1:1)].

The stereochemical outcome of the reaction can be explained by considering the approach of the cyanide nucleophile through a Cram model of a chelation-controlled transition state (Figure 3). Here chelation occurs through the iminium proton and the α-benzyloxy group to give a five-membered ring. The cyanide then attacks from the least hindered *Si* face of the ring.

With the desired α-aminonitriles in hand, an iodine-mediated carbamate annulation was investigated. Previously we illustrated that iodine-mediated cyclizations of hydroxy-functionalized alkenylamines lead to the rapid formation of

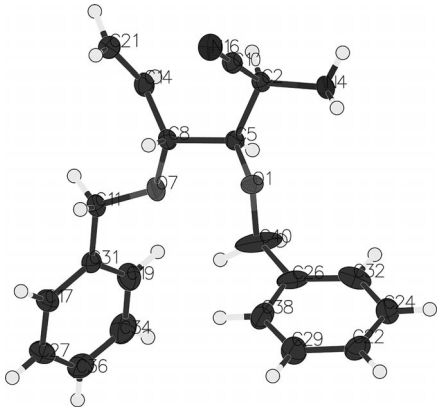


Figure 2. Crystal structure of *anti*-**9a**.[31]

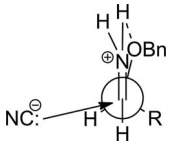
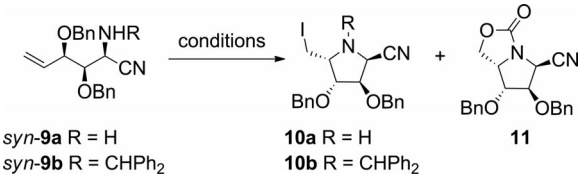



Figure 3. Cram chelate model for the Strecker reaction to give α-aminonitrile *syn*-**9a**.

pyrrolidine-derived cyclic carbamates with excellent diastereoselectivity in favor of the 4,5-*cis* product.[17] These cyclizations were performed in saturated aqueous $NaHCO_3$ and were in contrast to previous scientific dogma whereby iodine-mediated cyclizations of alkenes containing an internal nucleophile (oxygen or nitrogen) were reported to give a halide-functionalized product.[32] Given the limited solubility of benzyl-protected α-aminonitrile *syn*-**9a** in $H_2O$, we were unsure whether our carbamate annulation would

Table 2. Formation of cyclic carbamate **11**.




*syn*-**9a** R = H
*syn*-**9b** R = $CHPh_2$

**10a** R = H
**10b** R = $CHPh_2$

**11**

| Entry | R | Conditions | Ratio[a,b] **10/11** | Yield [%] |
|---|---|---|---|---|
| 1 | $CH_2Ph_2$ | NIS (1.2 equiv.), $CH_2Cl_2$, r.t., 5 h | **10b** only | 79 |
| 2 | H | NIS (1.2 equiv.), $CH_2Cl_2$, r.t., 5 h | >20:1 | 75 |
| 3 | H | $I_2$ (1.1 equiv.), $NaHCO_3$ (1.5 equiv.), THF/$H_2O$ (1:1), r.t., 4 h | 9:1 | 80 |
| 4 | H | $I_2$ (1.1 equiv.), $NaHCO_3$ (1.5 equiv.), THF/$H_2O$ (1:1), r.t., 20 h | 1:1.5 | 76 |
| 5 | H | $I_2$ (2.5 equiv.), $NaHCO_3$ (15 equiv.), THF/$H_2O$ (1:1) r.t., 20 h | 1:20 | 84 |
| 6 | H | $I_2$ (2.5 equiv.), $NaHCO_3$ (20 equiv.), THF/$H_2O$ (1:1), r.t., 20 h | <1:20 | 85 |

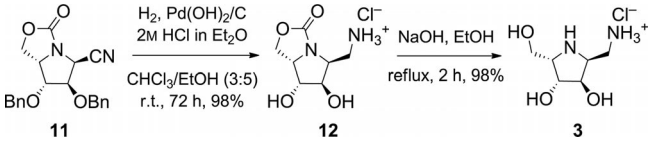
[a] Determined by integration of the relevant signals in the $^1H$ NMR spectrum of the crude reaction mixture. [b] Configuration determined by NOE correlations and comparison of spectra with that of known aminoiminohexitols (vide infra).

occur in a mixed solvent system, and moreover, whether we would generate the primary iodide, as suggested by the literature. To this end, a number of $I_2$-mediated electrophilic cyclizations were performed.

First, we treated protected amine *syn*-**9b** with *N*-iodosuccinimide (NIS) as the source of iodine, and unsurprisingly, in the absence of a "$CO_2$" source, primary iodide **10b** was generated in good yield (79%; Table 2, Entry 1). A similar result was observed when NIS was used with unprotected amine *syn*-**9a** with the corresponding iodoiminosugar **10a** being prepared in 75% yield (Table 2, Entry 2). A change of base to $NaHCO_3$ (1.5 equiv.) and the use of a mixed solvent system, THF/$H_2O$ (1:1), led to the generation of only a minor amount of carbamate **11** (<10%) when the reaction was stirred at room temperature for 4 h (Table 2, Entry 3). Here, the major product was primary iodide **10a**. Increasing the reaction time to 20 h, however, led to a dramatic increase in the yield of **11** (ca. 50%) and suggests that iodoiminosugar **10a** is an intermediate en route to the formation of **11** (Table 2, Entry 4). Only the 4,5-*cis* diastereomer was formed for both **11** and **10a**, as was predicted by our previous carbamate annulations to form dideoxypyrrolidines[17–19] and from literature precedence for the iodocyclization of substrates carrying an alkoxy substituent in the allylic position. Given that the primary iodide appears to be a key intermediate during the carbamate annulation (**9a** → [**10a**] → **11**), it is the formation of the iodide that determines the diastereoselectivity of the reaction. Seminal work by Chamberlin et al.,[33,34] and the more recent theoretical studies by Gouverneur and co-workers,[35] highlight the effects of the substitution pattern on $I_2$-mediated electrophilic halocyclizations and the role that the allylic group has on influencing the diastereoselectivity of the reaction. The attack of the amine on the $I_2$–alkene complex is thought to take place via a five-membered ring transition state in which the internal nucleophile approaches the double bond in an envelope conformation and follows a Bürgi–Dunitz-like trajectory. In our studies, the benzyloxy substituent on the ring would be preferentially positioned in the plane of the double bond, resulting in the 4,5-*cis* product. The addition of "$CO_2$" to **10a** then provides carbamate **11**.

The number of equivalents of iodine and $NaHCO_3$ were then increased to further improve carbamate formation. The use of 2.5 equiv. of iodine and 15 equiv. of $NaHCO_3$ led to the preferential formation of **11** (1:20, **10a/11**) after 20 h (Table 2, Entry 5). Finally, optimal conditions for the formation of carbamate **11** were found when 20 equiv. of $NaHCO_3$ were added to a solution of iodine in THF/$H_2O$ (1:1) so that the final concentration of $NaHCO_3$ in $H_2O$ was approximately 6 M (Table 2, Entry 6). Under these conditions there were no trace amounts of iodide **10a**, as evidenced by $^1H$ NMR spectroscopic analysis of the crude reaction mixture. Again, conversion of iodide **10a** into carbamate **11** was observed by TLC analysis (petroleum ether/ethyl acetate, 2:1; $R_f$ = 0.52 for iodide **10a**, $R_f$ = 0.35 for α-aminonitrile *syn*-**9a**; $R_f$ = 0.24 for carbamate **11**). Here it is important to note that the ability to form carbamate **11**, when starting with a functionalized and protected alkenylamine, greatly expands the scope of this annulation methodology.

To complete the synthesis of target aminoiminohexitol **3** (Scheme 3), carbamate **11** was treated with $Pd(OH)_2$/C in the presence of 2 M HCl and $H_2$ (7 bar) to give amine **12** in 98% yield. NOE correlations between the methylene proton $H_A$ at the C-1 position of **12**, the methine proton at C-4 and the bridge proton at C-5, and between the methylene proton $H_B$ at C-6 and the methine protons at C-2 and C-3 confirmed the stereochemistry of this product. The carbamate in **12** was then hydrolyzed by using a solution of




**11** **12** **3**

Scheme 3. Nitrile reduction and deprotection.

NaOH in EtOH, followed by neutralization with DOWEX-$H^+$ to complete the synthesis and to generate the L-*ido*-aminoiminohexitol **3**[16] in good (39%) overall yield from D-arabinose.

## Conclusions

In summary, an efficient route for the preparation of L-*ido*-aminoiminohexitol (**3**) has been developed. This has been demonstrated through the preparation of aminoiminohexitol **3** in ten steps from D-arabinose and a good 39% overall yield. During the course of this work, the power of a highly diastereoselective Strecker reaction, without the need for chiral Lewis acids or catalysts, has been demonstrated. Moreover, the potential of our novel carbamate annulation for the cyclization of protected and functionalized alkenylamine precursors has greatly expanded the scope of this reaction. A primary iodide has also been identified as a key intermediate in the carbamate annulation reaction. We are currently exploring the scope of this methodology for the synthesis of other aminoiminohexitols and the use of these compounds to prepare *N*-acylated derivatives.

## Experimental Section

**General Methods:** Unless otherwise stated all reactions were performed under atmospheric air. THF was distilled from $LiAlH_4$, and DCM was distilled from $P_2O_5$ prior to use. All chemicals obtained from commercial suppliers were used without further purification. Zn dust was activated by the careful addition of conc. $H_2SO_4$, followed by decantation and washing with EtOH (3×) and hexanes (3×), and storage under dry hexanes. All solvents were removed by evaporation under reduced pressure. Reactions were monitored by TLC analysis on silica gel coated plastic sheets (0.20 mm, Polygram SIL G/UV254) with detection by coating with 20% $H_2SO_4$ in EtOH followed by charring at ca. 150 °C, by coating with a solution of ninhydrin in EtOH followed by charring at ca. 150 °C, by coating with Hanessian's stain followed by charring at ca. 150 °C, or by coating with a solution of 5% $KMnO_4$ and 1% $NaIO_4$ in $H_2O$ followed by heating. Column chromatography was performed on silica gel (40–63 μm). Dowex Monosphere M-31 acidic resin was used for ion-exchange chromatography. Melting points were obtained with a Gallenkamp apparatus. High-resolution mass spectra were recorded with a Waters Q-TOF Premier Tandem Mass Spectrometer using positive electrospray ionization. Optical rotations were recorded by using a Perkin–Elmer 241 or a Rudolf Research Analytical Autopol II polarimeter at the sodium D line. Infrared spectra were recorded as thin films using a Bruker Tensor 27 FTIR spectrometer, equipped with an Attenuated Total Reflectance (ATR) sampling accessory, and are reported in wavenumbers ($cm^{-1}$). Nuclear magnetic resonance spectra were recorded by using a Varian Inova operating at 500 MHz or a Varian Direct Drive operating at 600 MHz. $^1H$ and $^{13}C$ chemical shifts ($\delta$) were internally referenced to the residual solvent peak. NMR peak assignments are based on 2D NMR experiments (COSY, HSQC, and HMBC).

**(2*S*,3*R*)-2,3-Dibenzyloxypent-4-enal (8):** To a solution of methyl-iodoarabinoside **7**[19,24] (397 mg, 0.87 mmol) in EtOH/$H_2O$/AcOH (40:2:1, 13 mL) was added Zn (284 mg, 4.35 mmol). The mixture was stirred at reflux for 2 h, cooled to room temperature, and filtered through a Celite plug with EtOAc. The resulting mixture was further diluted with EtOAc and washed twice with sat. aq. $NaHCO_3$, then $H_2O$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide aldehyde **8** as a colorless oil (251 mg, 0.85 mmol, 97%), which was used without further purification. $R_f$ = 0.41 [petroleum ether (PE)/EtOAc, 3:1]. $[a]_D^{22}$ = –48.5 (*c* = 0.73, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3064, 3031, 1732, 1454, 1066, 735, 696 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$, 20 °C): $\delta$ = 9.68 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 7.35–7.26 (m, 10 H, H-Ar), 5.94 (ddd, $J_{4,5b}$ = 18.2 Hz, $J_{4,5a}$ = 10.5 Hz, $J_{3,4}$ = 7.8 Hz, 1 H, 4-H), 5.37 (ddd, $J_{4,5a}$ = 10.5 Hz, $^2J_{5a,b}$ = 1.5 Hz, $^4J_{3,5a}$ = 1 Hz, 1 H, 5a-H), 5.35 (ddd, $J_{4,5b}$ = 18.2 Hz, $^2J_{5a,b}$ = 1.5 Hz, $^4J_{3,5b}$ = 1 Hz, 1 H, 5b-H), 4.76 (d, $^2J_{a,b}$ = 11.9 Hz, 1 H, CHa 2-*O*-Bn), 4.64 (d, $^2J_{a,b}$ = 12.2 Hz, 1 H, CHa 3-*O*-Bn), 4.63 (d, $^2J_{a,b}$ = 11.9 Hz, 1 H, CHb 2-*O*-Bn), 4.36 (d, $^2J_{a,b}$ = 12.2 Hz, 1 H, CHb 3-*O*-Bn), 4.17 (ddt, $J_{3,4}$ = 7.8 Hz, $J_{2,3}$ = 4.2 Hz, $^4J_{3,5a}$ = $^4J_{3,5b}$ = 1 Hz, 1 H, 3-H), 3.83 (dd, $J_{2,3}$ = 4.2 Hz, $J_{1,2}$ = 1.6 Hz, 1 H, 2-H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$, 20 °C): $\delta$ = 202.7 (C-1), 137.6 (C-*i* 3-*O*-Bn), 137.2 (C-*i* 2-*O*-Bn), 133.9 (C-4), 128.6 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 128.3 (C-Ar), 128.0 (C-Ar), 127.9 (C-Ar), 120.0 (C-5), 85.3 (C-2), 80.0 (C-3), 73.6 ($CH_2$ 2-*O*-Bn), 70.8 ($CH_2$ 3-*O*-Bn) ppm. HRMS (ESI): calcd. for $[C_{19}H_{20}O_3 + Na]^+$ 319.1305; found 319.1311.

**(2*S*,3*R*,4*R*)-2-Amino-3,4-dibenzyloxyhex-5-enenitrile (*syn*-9a) and (2*R*,3*R*,4*R*)-2-Amino-3,4-dibenzyloxyhex-5-enenitrile (*anti*-9a):** To a solution of aldehyde **8** (32.0 mg, 0.11 mmol) in EtOH (2.2 mL) was added $NH_4OAc$ (83.2 mg, 1.07 mmol). The mixture was stirred at room temperature for 15 min, at which point TMSCN (28.9 μL, 0.22 mmol) was added dropwise. The clear colorless solution was stirred at room temperature for 18 h, then diluted with EtOAc, washed with sat. aq. $NaHCO_3$, $H_2O$, and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the α-amino nitriles using silica gel gradient flash chromatography (PE/EtOAc, 10:1 → 1:1) first gave α-amino-nitrile *syn*-**9a** as a pale yellow oil (27.5 mg, 0.09 mmol, 79%) and then α-amino-nitrile *anti*-**9a** as a pale yellow oil (3.06 mg, 0.01 mmol, 9%). Crystallization of *anti*-**9a** (minimum EtOAc/PE) yielded fine colorless needles, which were subjected to single-crystal X-ray diffraction. Data for *syn*-**9a**: $R_f$ = 0.47 (PE/EtOAc, 1:1). $[a]_D^{22}$ = –1.08 (*c* = 0.90, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3393, 3327, 3064, 3031, 2868, 2361, 1497, 1067, 738, 698 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$, 20 °C): $\delta$ = 7.39–7.29 (m, 10 H, H-Ar), 5.86 (ddd, $J_{5,6a}$ = 17.4 Hz, $J_{5,6b}$ = 10.4 Hz, $J_{4,5}$ = 7.7 Hz, 1 H, 5-H), 5.44 (ddd, $J_{5,6a}$ = 17.4 Hz, $^2J_{6a,6b}$ = 1.5 Hz, $^4J_{4,6a}$ = 1 Hz, 1 H, 6a-H), 5.41 (ddd, $J_{5,6b}$ = 10.4 Hz, $^2J_{6a,6b}$ = 1.5 Hz, $^4J_{4,6b}$ = 0.7 Hz, 1 H, 6b-H), 4.91 (d, $^2J_{a,b}$ = 11.0 Hz, 1 H, CHa 3-*O*-Bn), 4.71 (d, $^2J_{a,b}$ = 11.0 Hz, 1 H, CHb 3-*O*-Bn), 4.64 (d, $^2J_{a,b}$ = 11.7 Hz, 1 H, CHa 4-*O*-Bn), 4.40 (d, $^2J_{a,b}$ = 11.7 Hz, 1 H, CHb 4-*O*-Bn), 4.16 (dd, $J_{4,5}$ = 7.7 Hz, $J_{3,4}$ = 6.8 Hz, 1 H, 4-H), 3.89 (d, $J_{2,3}$ = 3.3 Hz, 1 H, 2-H), 3.70 (dd, $J_{3,4}$ = 6.8 Hz, $J_{2,3}$ = 3.3 Hz, 1 H, 3-H), 1.63 (br. s, 2 H, $NH_2$) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$, 20 °C): $\delta$ = 138.0 (C-*i* 4-*O*-Bn), 137.7 (C-*i* 3-*O*-Bn), 134.6 (C-5), 128.6 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 121.3 (C-1), 120.5 (C-6), 81.8 (C-3), 81.0 (C-4), 75.7 ($CH_2$ 3-*O*-Bn), 71.1 ($CH_2$ 4-*O*-Bn), 44.7 (C-2) ppm. HRMS (ESI): calcd. for $[C_{20}H_{22}N_2O_2 + Na]^+$ 345.1573; found 345.1572. Data for *anti*-**9a**: $R_f$ = 0.38 (PE/EtOAc, 1:1). M.p. 64.5–64.7 °C. $[a]_D^{23}$ = –15.5 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3389, 3325, 3064, 3031, 2919, 2870, 2358, 1497, 1068, 737, 698 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$, 20 °C): $\delta$ = 7.36–7.30 (m, 10 H, H-Ar), 5.83 (ddd, $J_{5,6b}$ = 17.5 Hz, $J_{5,6a}$ = 10.5 Hz, $J_{4,5}$ = 7.9 Hz, 1 H, 5-H), 5.49 (dd, $J_{5,6a}$ = 17.5 Hz, $^2J_{6a,6b}$ = 1 Hz, 1 H, 6a-H), 5.44 (dd, $J_{5,6b}$ = 10.5 Hz, $^2J_{6a,6b}$ = 1 Hz, 1 H, 6b-H), 4.96 (d, $^2J_{a,b}$ = 11.4 Hz, 1 H, CHa 3-*O*-Bn), 4.72 (d, $^2J_{a,b}$ = 11.4 Hz, 1 H, CHb 3-*O*-Bn), 4.64 (d, $^2J_{a,b}$ = 11.6 Hz, 1 H, CHa 4-*O*-Bn), 4.41 (d, $^2J_{a,b}$ = 11.6 Hz, 1 H, CHb 4-*O*-Bn), 4.13 (t,

$J_{4,5}$ = 7.9, $J_{3,4}$ = 6.6 Hz, 1 H, 4-H), 3.80 (d, $J_{2,3}$ = 4.4 Hz, 1 H, 2-H), 3.64 (dd, $J_{3,4}$ = 6.6 Hz, $J_{2,3}$ = 4.4 Hz, 1 H, 3-H), 1.68 (br. s, 2 H, $NH_2$) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$, 20 °C): $\delta$ = 138.0 (C-*i* 4-*O*-Bn), 137.9 (C-*i* 3-*O*-Bn), 133.9 (C-5), 128.6 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 121.3 (C-1), 120.4 (C-6), 82.1 (C-3 and C-4), 75.5 ($CH_2$ 3-*O*-Bn), 71.0 ($CH_2$ 4-*O*-Bn), 45.3 (C-2) ppm. HRMS (ESI): calcd. for $[C_{20}H_{22}N_2O_2 + Na]^+$ 345.1573; found 345.1573.

**(2S,3*R*,4*R*,5*R*)-3,4-Bisbenzyloxy-5-iodomethylpyrrolidine-2-carbonitrile (10a):** α-Aminonitrile *syn*-**9a** (30.0 mg, 0.09 mmol) was co-evaporated with toluene and dissolved in DCM (450 μL) under a nitrogen atmosphere. *N*-Iodosuccinimide (25.1 mg, 0.11 mmol) was added, and the pink solution was stirred at room temperature for 5 h, over which time the solution became dark red in color. The solution was quenched with sat. aq. $Na_2S_2O_3$ and extracted with EtOAc, and the organic layer was washed with $H_2O$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified using silica gel gradient flash chromatography (PE/EtOAc, 20:1 → 3:1) to give iodoiminosugar **10a** as a pale orange oil (31.3 mg, 0.07 mmol, 75%). $R_f$ = 0.52 (PE/EtOAc, 2:1). $[\alpha]_D^{20.6}$ = –21.0 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3336, 3062, 3030, 2922, 2867, 2245, 1496, 1454, 1354, 1207, 1091, 1027, 913, 736, 697 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$, 20 °C): $\delta$ = 7.39–7.28 (m, 10 H, H-Ar), 4.66 (d, $^2J_{a,b}$ = 11.8 Hz, 1 H, CHa 3-*O*-Bn), 4.59 (d, $^2J_{a,b}$ = 11.8 Hz, 1 H, CHb 3-*O*-Bn), 4.54 (d, $^2J_{a,b}$ = 11.6 Hz, 1 H, CHa 4-*O*-Bn), 4.51 (d, $^2J_{a,b}$ = 11.6 Hz, 1 H, CHb 4-*O*-Bn), 4.27 (d, $J_{4,5}$ = 5.4 Hz, 1 H, 2-H), 4.09 (dd, $J_{2,3}$ = 5.4 Hz, $J_{3,4}$ = 2.7 Hz, 1 H, 3-H), 4.03 (dd, $J_{4,5}$ = 5.4 Hz, $J_{3,4}$ = 2.7 Hz, 1 H, 4-H) 3.84 (dd, $J_{5,6a,6b}$ = 7.3 Hz, $J_{4,5}$ = 5.4 Hz 1 H, 5-H), 3.27 (dd, $^2J_{6a,6b}$ = 9.6 Hz, $J_{5,6a}$ = 7.3 Hz, 1 H, 6a-H), 3.15 (dd, $^2J_{6a,6b}$ = 9.6 Hz, $J_{5,6b}$ = 7.3 Hz, 1 H, 6b-H), 2.32 (br. s, 1 H, NH) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$, 20 °C): $\delta$ = 137.3 (C-*i* 4-*O*-Bn), 136.8 (C-*i* 3-*O*-Bn), 128.8 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 128.3 (C-Ar), 128.3 (C-Ar), 128.1 (C-Ar), 117.9 (C-1), 82.4 (C-3), 81.8 (C-4), 73.1 ($CH_2$ 3,4-*O*-Bn), 61.5 (C-5), 51.4 (C-2), 4.1 (C-6) ppm. HRMS (ESI): calcd. for $[C_{20}H_{21}IN_2O_2 + Na]^+$ 449.0720; found 449.0726.

**(5*S*,6*R*,7*R*,7a*S*)-6,7-Dibenzyloxy-3-oxotetrahydropyrrolo[1,2-*c*]oxazole-5-carbonitrile (11):** To a solution of α-aminonitrile *syn*-**9a** (34.0 mg, 0.11 mmol) in THF (0.4 mL) was added $I_2$ (66.9 mg, 0.26 mmol), $H_2O$ (0.4 mL), and $NaHCO_3$ (177 mg, 2.11 mmol). The reaction mixture was stirred at room temperature for 20 h, quenched by the addition of sat. aq. $Na_2S_2O_3$, and extracted with EtOAc. The organic layer was washed with $H_2O$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue using silica gel gradient flash chromatography (PE/EtOAc, 10:1 → 1:1) provided carbamate **11** as a colorless viscous oil (32.6 mg, 0.09 mmol, 85%). $R_f$ = 0.24 (PE/EtOAc, 2:1). $[\alpha]_D^{20}$ = +23.7 (*c* = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3064, 3032, 2925, 2872, 2254, 1755, 1469, 1316, 1216, 1093, 1051, 1001, 814, 736, 698 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$, 20 °C): $\delta$ = 7.43–7.32 (m, 8 H, H-Ar), 7.16 (m, 2 H, H-Ar), 4.75 (d, $^2J_{a,b}$ = 12 Hz, 1 H, CHa 3-*O*-Bn), 4.76 (d, $J_{2,3}$ = 5.2 Hz, 1 H, 2-H), 4.56 (d, $^2J_{a,b}$ = 12 Hz, 1 H, CHb 3-*O*-Bn), 4.50 (d, $^2J_{a,b}$ = 12.6 Hz, 1 H, CHa 4-*O*-Bn), 4.45 (t, $^2J_{6a,6b}$ = 8.7 Hz, $J_{5,6a}$ = 8.2 Hz, 1 H, 6a-H), 4.38 (t, $^2J_{6a,6b}$ = 6.2 Hz, $J_{5,6b}$ = 3.0 Hz, 1 H, 6b-H), 4.35 (d, $^2J_{a,b}$ = 12.6 Hz, 1 H, CHb 4-*O*-Bn), 4.27 (dt, $J_{5,6a}$ = 8.2 Hz, $J_{5,6b}$ = $J_{4,5}$ = 3.0 Hz, 1 H, 5-H), 4.23 (dd, $J_{2,3}$ = 5.2 Hz, $J_{3,4}$ = 1.0 Hz, 1 H, 3-H), 3.77 (dd, $J_{4,5}$ = 3.0 Hz, $J_{3,4}$ = 1.0 Hz, 1 H, 4-H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$, 20 °C): $\delta$ = 161.0 (C-7), 136.5 (C-*i* 4-*O*-Bn), 136.3 (C-*i* 3-*O*-Bn), 128.9 (C-Ar), 128.9 (C-Ar), 128.7 (C-Ar), 128.6 (C-Ar), 128.3 (C-Ar), 127.9 (C-Ar), 115.4 (C-1), 81.6 (C-3), 79.9 (C-4), 73.8 ($CH_2$ 3-*O*-Bn), 72.0 ($CH_2$ 4-*O*-Bn), 63.2 (C-6), 61.3 (C-5), 53.2 (C-2) ppm. HRMS (ESI): calcd. for $[C_{21}H_{20}N_2O_2 + Na]^+$ 387.1315; found 387.1317.

**(5*S*,6*R*,7*R*,7a*S*)-5-Aminomethyl-6,7-dihydroxytetrahydropyrrolo-[1,2-*c*]oxazol-3-one Hydrochloride (12):** Carbamate **11** (100 mg, 0.27 mmol) was dissolved in $CHCl_3$ (4.5 mL) and transferred into a Fischer-Porter bottle, EtOH (7.5 mL), HCl in diethyl ether (1.4 mL, 2 M), and $Pd(OH_2)$/C (230 mg) were then added, and the vessel was charged with $H_2$ (7 bar). The reaction mixture was stirred vigorously at room temperature for 3 d. After releasing the $H_2$ pressure, the reaction mixture was filtered through a plug of Celite, washing with EtOH and $H_2O$, and concentrated in vacuo to provide amine **12** as the HCl salt (50.1 mg, 0.26 mmol, 98%). $R_f$ = 0.25 (DCM/MeOH/EtOH/30% aq. $NH_3$, 5:2:2:1). $[\alpha]_D^{19}$ = –50.0 (*c* = 0.1, $H_2O$). IR (film): $\tilde{\nu}$ = 3928, 2925, 2854, 1727, 1642, 1404, 1243, 1083, 1014, 783 $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$, HCl salt, 20 °C): $\delta$ = 4.64 (t, $^2J_{6a,6b}$ = 9.2 Hz, $J_{5,6a}$ = 8.9 Hz, 1 H, 6a-H), 4.52 (dd, $^2J_{6a,6b}$ = 9.2 Hz, $J_{5,6b}$ = 3.3 Hz, 1 H, 6b-H), 4.49 (dd, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$ = 0.5 Hz, 1 H, 3-H), 4.36 (dt, $J_{5,6a}$ = 8.9 Hz, $J_{5,6b}$ = 3.3, $J_{4,5}$ < 1 Hz, 1 H, 5-H), 4.09 (br. s, 1 H, 4-H), 4.04 (dt, $J_{1b,2}$ = 8.5 Hz, $J_{2,3}$ = $J_{1a,2}$ = 4.4 Hz, 1 H, 2-H), 3.30 (dd, $^2J_{1a,1b}$ = 13.4 Hz, $J_{1a,2}$ = 4.4 Hz, 1 H, 1a-H), 3.21 (dd, $^2J_{1a,1b}$ = 13.4 Hz, $J_{1b,2}$ = 8.5 Hz, 1 H, 1b-H) ppm. $^{13}C$ NMR (150 MHz, $D_2O$, HCl salt, 20 °C): $\delta$ = 164.9 (C-7), 77.7 (C-3), 75.1 (C-4), 64.4 (C-6), 61.8 (C-5), 58.8 (C-2), 39.3 (C-1) ppm. HRMS (ESI): calcd. for $[C_7H_{12}N_2O_4 + Na]^+$ 211.0689; found 211.0684.

**1-Amino-1,2,5-trideoxy-2,5-imino-L-iditol (3):** A solution of NaOH in EtOH (0.5 mL, 2 M) was added to amino carbamate **12** (16.0 mg, 0.09 mmol) and stirred at reflux for 2 h. The resulting reaction mixture was loaded directly onto a Dowex $H^+$ ion-exchange resin column and washed with $H_2O$ to remove the excess amount of salt. The hydrolyzed amine was then eluted with 30% aq. $NH_3$ and concentrated in vacuo to provide amino hexitol **3** (13.5 mg, 0.08 mmol, 98%). $R_f$ = 0.01 (DCM/MeOH/EtOH/30% aq. $NH_3$, 5:2:2:1); (HCl salt) $[\alpha]_D^{26}$ = +6.0 (*c* = 1.0, $H_2O$). IR (film, free base): $\tilde{\nu}$ = 3376, 2881, 2854, 1651, 1549, 1393, 1218, 1115, 1059, 946, 836 $cm^{-1}$. $^1H$ NMR (500 MHz, 2% NaOD in $D_2O$, 20 °C): $\delta$ = 4.14 (d, $J_{2,3}$ = 4 Hz, $J_{3,4}$ < 1 Hz, 1 H, 3-H), 4.09 (d, $J_{4,5}$ = 4 Hz, $J_{3,4}$ < 1 Hz, 1 H, 4-H), 3.73 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $J_{5,6a}$ = 6.5 Hz, 1 H, 6a-H), 3.64 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $J_{5,6b}$ = 6.5 Hz, 1 H, 6b-H), 3.35 (td, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, $J_{4,5}$ = 4 Hz, 1 H, 5-H), 3.28 (td, $J_{1a,2}$ = $J_{1b,2}$ = 6.9 Hz, $J_{2,3}$ = 4 Hz, 1 H, 2-H), 2.77 (dd, $^2J_{1a,1b}$ = 12.7 Hz, $J_{1a,2}$ = 6.9 Hz, 1 H, 1a-H), 2.66 (dd, $^2J_{1a,1b}$ = 12.7 Hz, $J_{1b,2}$ = 6.9 Hz, 1 H, 1b-H) ppm. $^{13}C$ NMR (125 MHz, 2% NaOD in $D_2O$, 20 °C): $\delta$ = 77.3 (C-3), 77.0 (C-4), 61.1 (C-5), 59.9 (C-6), 40.1 (C-1) ppm. HRMS (ESI): calcd. for $[C_6H_{14}N_2O_3 + H]^+$ 163.1077; found 163.1077. $^1H$ NMR (500 MHz, $D_2O$, 2HCl salt, 20 °C): $\delta$ = 4.41 (dd, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 1.7 Hz, 1 H, 3-H), 4.40 (dd, $J_{4,5}$ = 3.6 Hz, $J_{3,4}$ = 1.7 Hz, 1 H, 4-H), 4.17 (td, $J_{1a,2}$ = $J_{1b,2}$ = 6.8 Hz, $J_{2,3}$ = 3.4 Hz, 1 H, 2-H), 4.07 (ddd, $J_{5,6a}$ = 8.8 Hz, $J_{5,6b}$ = 4.6 Hz, $J_{4,5}$ = 3.6 Hz, 1 H, 5-H), 4.00 (dd, $^2J_{6a,6b}$ = 12.2 Hz, $J_{5,6a}$ = 4.6 Hz, 1 H, 6a-H), 4.91 (dd, $^2J_{6a,6b}$ = 12.2 Hz, $J_{5,6b}$ = 8.8 Hz, 1 H, 6b-H), 3.58 (dd, $^2J_{1a,1b}$ = 13.7 Hz, $J_{1a,2}$ = 6.8 Hz, 1 H, 1a-H), 3.49 (dd, $^2J_{1a,1b}$ = 13.7, $J_{1b,2}$ = 6.8 Hz, 1 H, 1b-H) ppm. $^{13}C$ NMR (125 MHz, $D_2O$, 2HCl salt, 20 °C): $\delta$ = 74.5 (C-3), 74.2 (C-4), 63.8 (C-5), 58.2 (C-2), 57.2 (C-6), 35.8 (C-1) ppm.

**Supporting Information** (see footnote on the first page of this article): Copies of the $^1H$ and $^{13}C$ NMR spectra.

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