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Applications and Limitations of the I_2-Mediated Carbamate Annulation for the Synthesis of Piperidines: Five- versus Six-Membered Ring Formation

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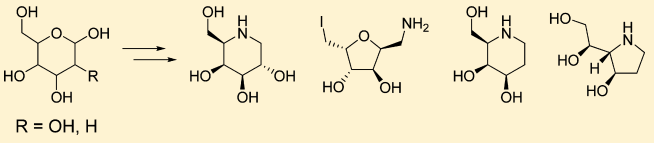
Supporting Information

ABSTRACT: A protecting-group-free synthetic strategy for the synthesis of piperidines has been explored. Key in the synthesis is an I_2-mediated carbamate annulation, which allows for the cyclization of hydroxy-substituted alkenylamines into piperidines, pyrrolidines, and furans. In this work, four chiral scaffolds were compared and contrasted, and it was observed that with both D-galactose and 2-deoxy-D-galactose as starting materials, the transformations into the piperidines 1-deoxygalactonorjirimycin (DGJ) and 4-*epi*-fagomine, respectively, could be achieved in few steps and good overall yields. When D-glucose was used as a starting material, only the furan product was formed, whereas the use of 2-deoxy-D-glucose resulted in reduced chemo- and stereoselectivity and the formation of four products. A mechanistic explanation for the formation of each annulation product could be provided, which has improved our understanding of the scope and limitations of the carbamate annulation for piperidine synthesis.



INTRODUCTION

Iminosugars have enormous therapeutic potential in the treatment of a number of diseases, such as cancer, diabetes, and lysosomal storage disorders.[1] Notable members of the piperidine iminosuguar family include *N*-hydroxyethyl-DNJ (Miglitol, **1**), which has been approved for the treatment of non-insulin-dependent diabetes,[2] and 1-deoxygalactonojirimycin (DGJ, **2**), recently used in a phase-2 clinical trial for the treatment of Fabry's disease (Figure 1).[3] The corresponding 2-deoxypiperidines, fagomine (**3**)[4,5] and the unnatural 4-*epi*-isomer **4**, also exhibit promising biological activities. Fagomine was found to have activity against mammalian gut α-glucosidases and β-galactosidase[6] and a potent antihyperglycemic effect in streptozotocin-induced diabetic mice,[7] while fagomine isomer **4** inhibits lysosomal α-galactosidase A activity in Fabry lymphoblasts.[8]

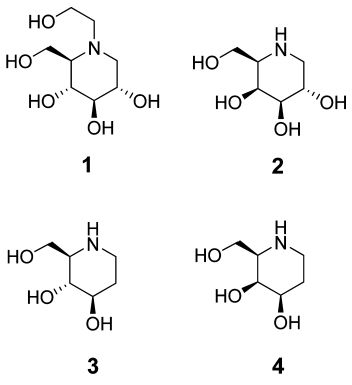


Figure 1. Piperidines.

Given the interesting biological activity of piperidines, we became interested in extending our previously reported protecting-group-free strategy for the synthesis of pyrrolidines[9−11] to the synthesis of piperidines.[12] To this end, we proposed that the target piperidines **I** could be attained following the hydrolysis of the intermediate cyclic carbamate **II**, itself prepared via the I_2-mediated cyclization of alkenylamine precursor **III** (Scheme 1). Alkenylamine **III** would in turn be prepared from methyl iodoglycoside **IV** via our recently reported protecting-group-free Vasella reductive amination methodology.[13] Key in this approach was the provision that when R^1 = OH, alkenylamine **III** should cyclize to form the desired piperidine (N-cyclization) rather than undergoing O-cyclization, which would lead to the undesired aminomethylfuran.

To explore the potential of our annulation methodology for the synthesis of piperidines, we first set out to prepare 1-deoxygalactonojirimycin (DGJ, **2**). As previously described,[14] alkenylamine **5**, itself available in three steps from D-galactose, was subjected to an I_2-mediated carbamate annulation to give, under optimized conditions, piperidine isomers **6a** and **6b** and furan **6c** in a 3:1:1 ratio, respectively (Scheme 2). Whereas our previously reported pyrrolidine annulation methodology

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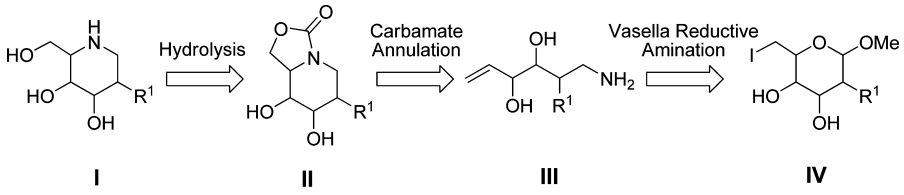
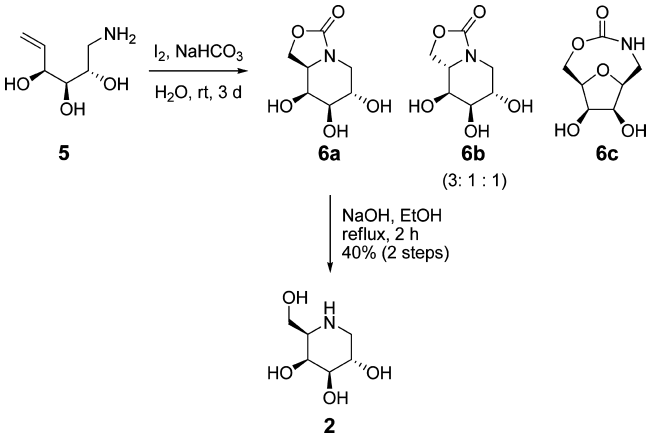
Scheme 1. Retrosynthetic Analysis for the Synthesis of Piperidines



Scheme 2. Synthesis of DGJ (2)



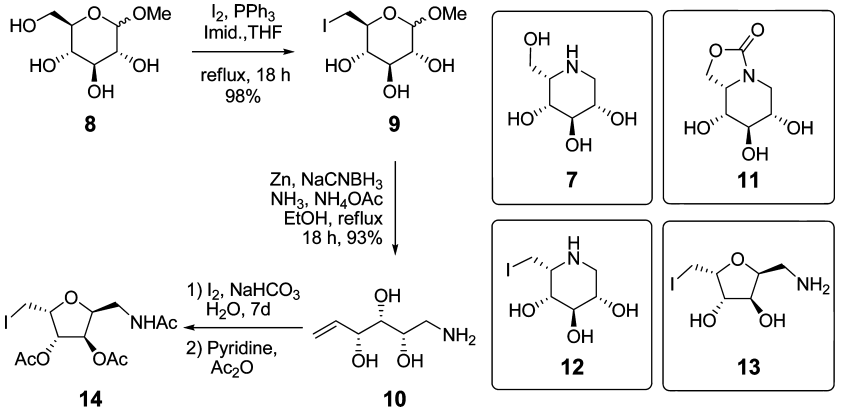
proceeded in 18 h at room temperature and with >95:5 diastereoselectivity in favor of the *cis* product,[9−11] cyclization to the piperidine framework was much slower and resulted in lower stereoselectivity. Hydrolysis of the carbamate and purification by silica gel flash column chromatography, however, allowed **2** to be prepared in a respectable 40% yield (from **5**) and in five steps in total. Given this, we were keen to explore whether a similar methodology could be used for the preparation of other piperidines. The results of our studies in this area are reported herein.

RESULTS AND DISCUSSION

Following our successful synthesis of DGJ, we then explored the potential of our I_2-mediated annulation strategy for the synthesis of 1,5-dideoxy-1,5-imino-L-iditol (**7**) (Scheme 3). To this end, methyl glucopyranoside **8** was subjected to triphenylphosphine, imidazole, and iodine to give the corresponding iodosugar **9** in 98% yield.[13] Subsequent Vasella reductive amination led to the smooth formation of alkenylamine **10**, again in excellent yield (93%) with only minor traces of the secondary amine (<5%).[15] Alkenylamine **10** was then treated with I_2 and $NaHCO_3$ in anticipation that carbamate **11** would be formed. Though TLC analysis revealed the smooth transformation into a higher-running product (R_f = 0.23, DCM/EtOH/MeOH/30% aq. NH_3, 5/2/2/1 v/v/v/v), ^{13}C NMR analysis of the crude reaction mixture revealed the presence of an iodomethylene carbon (−0.3 ppm, $-CH_2I$), thus indicating that the desired carbamate had not been formed. Furthermore, an aminomethylene signal at 39.4 ppm and four oxymethine signals (82−76 ppm) were observed, which indicated the presence of aminomethylfuran **13** rather than piperidine **12**, both of which satisfy the HRMS result ($[M + H]^+$ = 273.9938). Attempts to purify the material to allow for further characterization proved futile, as Dowex-H^+ or silica gel chromatography led to degradation of the product. Full characterization was therefore achieved after acetylation of the crude product with acetic anhydride and pyridine. The ^1H NMR spectral data clearly revealed an NH proton at 5.84 ppm with a COSY correlation to both H1a and H1b and no correlation to H5. In addition, the HMBC correlations between both H1 protons and the NHAc carbonyl were also present. As acetylation of pyran **12** would protect the amine, leaving no observable NH proton, these observations allowed the product of the acetylation reaction to be determined as furan **14**. Following on from this, the product of the I_2-mediated annulation reaction could then be assigned as furan **13**.

In an attempt to encourage attack of the nitrogen atom and formation of the desired carbamate **11** during the annulation reaction, alkenylamine **10** was treated with a stronger base, Na_2CO_3, to favor formation of the free amine. After the reaction mixture was stirred at room temperature overnight, no starting material remained; concentration and NMR analysis of the crude reaction mixture, however, revealed that the carbamic acid derivative of furan **13**, formed via CO_2 absorption onto the amine,[16,17] had been prepared. Numerous other changes were

Scheme 3. Formation of an Undesired Iodofuranoside by I_2-Mediated Annulation



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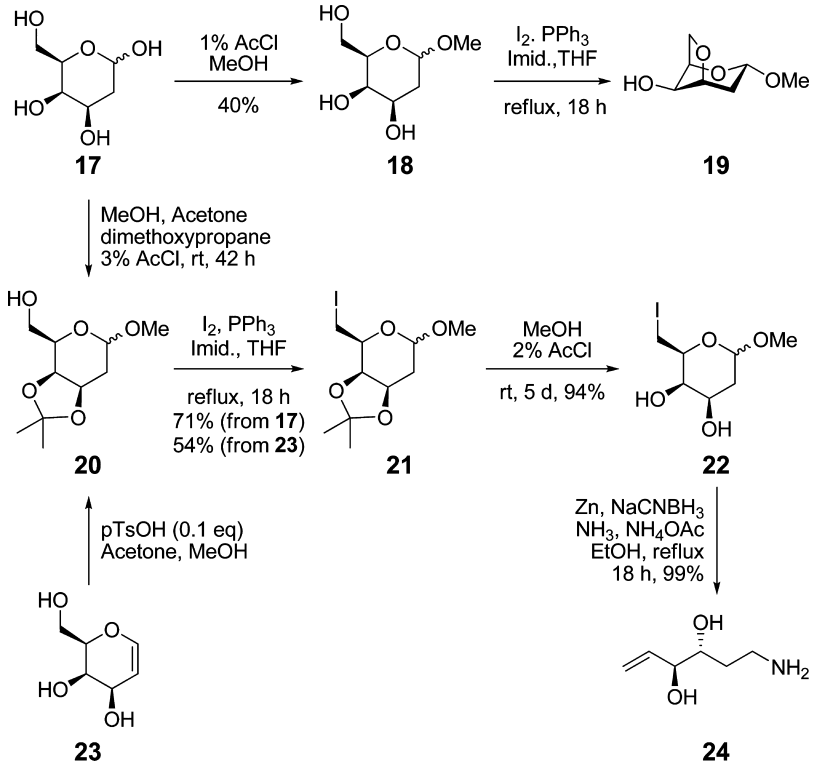
Scheme 4. Formation of Linear Alkenylamine 24



then made to the reaction conditions, including changes to the temperature (0 °C to reflux) and the reagent concentrations. However, under all of the conditions attempted, there was no observable formation of the desired carbamate **11** as determined by ^{1}H NMR analysis of the crude reaction mixture, and furan products always appeared to dominate. Though this result was disappointing, the inherent problem of controlling the chemoselectivity during protecting-group-free syntheses is well-known and thus explains why the development of protecting groups, though undesirable in terms of atom economy, still remains an important objective for the synthetic chemist.[18]

Having observed competing O-cyclization in an attempt to prepare 1,5-dideoxy-1,5-imino-L-iditol (**7**) and to a lesser extent DGJ (**2**), we thus proposed the synthesis of members of the fagomine family. Fagomine analogues retain interesting biological properties but are devoid of the hydroxyl functionality at C2 (R^1 = H; Scheme 1), and hence, the synthesis would be more readily accomplished. Accordingly, we first set out to synthesize 4-*epi*-fagomine (**4**) (Scheme 4). To this end, 2-deoxy-D-galactose (**17**) was first subjected to a Fischer glycosylation using AcCl and MeOH to give the corresponding methyl glycoside **18** in modest (40%) yield, with a second major product being the kinetically favored furan. Methyl glycoside **18** was then treated with I_2, triphenylphosphine, and imidazole in THF. Under these conditions, however, only bicyclic pyranoside **19** was observed,[19] a consequence of intramolecular substitution of the activated phosphonium group at C6 by the hydroxyl at the 3-position. Indeed, a similar observation was seen en route to the synthesis of DGJ,[14] and given the tendency for this intramolecular cyclization in iodination of methyl glycosides of the *galacto* configuration, we resorted to the installation of an isopropylidine protecting group at the 3- and 4-positions via the treatment of 2-deoxy-D-galactose (**17**) with MeOH, acetone, dimethoxypropane, and AcCl. Conveniently, these conditions led to the concomitant installation of the methyl group at the anomeric position to give galactoside **20** in one step. Galactoside **20** was then subjected to the standard iodination conditions to give the required primary iodide **21** in 71% yield (from **17**), and the isopropylidine group was then removed to give the desired methyl iodoglycoside **22** in 94% yield. Here it is also interesting to note that **20** can be prepared from D-galactal (**23**) by protonation of the alkene with TsOH followed by nucleophilic attack of methanol.[20] Under these conditions, pyranose **20** was formed in ~78% yield with small amounts (ca. 10%) of methyl 5,6-*O*-isopropylidene-D-galactofuranoside, which was more readily separable following conversion of **20** into iodide **21**.

With primary iodide **22** in hand, we then applied the Vasella reductive amination conditions and obtained alkenylamine **24** in excellent yield (99%). Alkenylamine **24** was then subjected to a solution of I_2 and $NaHCO_3$ in H_2O to affect the desired carbamate annulation reaction (Table 1). Again, cyclization to the desired six-membered ring proved to be sluggish, and no appreciable reaction was observed after alkenylamine **24** was stirred in $NaHCO_3$ (sat. aq.) in the presence of excess I_2 (10 equiv) at room temperature (ca. 20 °C) for 7 days (entry 1). When the solution was heated to 50 °C, however, complete conversion of the starting material was observed after 3 days (entry 2), and following filtration, carbamates **25a** and **25b** were observed in a 3:1 ratio, as determined by ^{1}H NMR analysis of the crude reaction mixture. Lowering the reaction temperature to 40 °C resulted in an increased reaction time (5 days) but led to improved diastereoselectivity in favor of the *cis* isomer **25a** (**25a**:**25b** = 9:1; entry 3). Remarkably, a diastereoselectivity of >95:5 was achieved when the reaction was performed at 35 °C with a reaction time of 5 days (entry 4). Indeed, using the latter conditions, carbamate **25a** was

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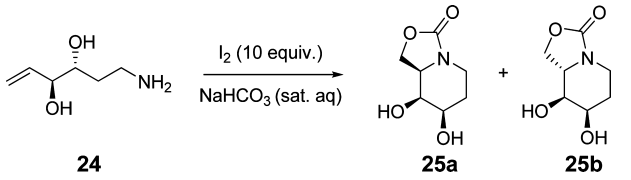
Table 1. Diastereoselectivity of Carbamate Annulation



24 25a 25b

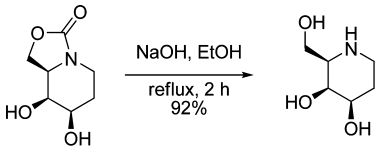
entry	T (°C)	t (days)	25a:25b[a]
1	20	>7	no reaction
2	50	3	3:1
3	40	5	9:1
4	35	5	>95:5[b]

[a]As determined by ^{1}H NMR analysis of the crude reaction mixture. [b]**25a** was isolated in 86% yield.

isolated in 86% yield following silica gel column chromatography.

To complete the synthesis, carbamate **25a** was then hydrolyzed via treatment with NaOH in EtOH at reflux (Scheme 5). This resulted in the smooth formation of 4-*epi*-

Scheme 5. Hydrolysis of *cis*-Carbamate 25a

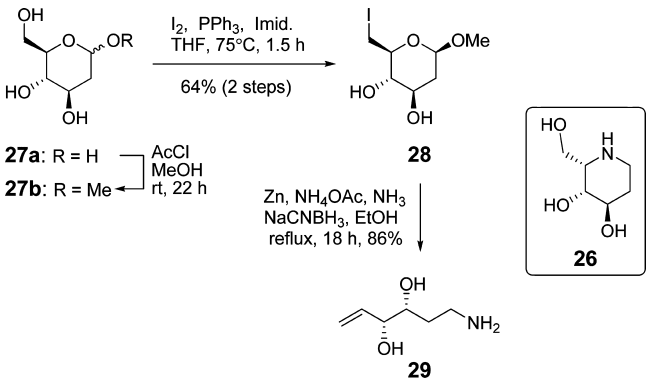


25a 4

fagomine (**4**) in 92% yield, thus completing this remarkably efficient six-step synthesis with an overall yield of 52%. 4-*epi*-Fagomine has been prepared on several other occasions.[21−24] The first synthesis required 10 steps from **3**[21] using the method of Heiker and Schueller[22] (no yield reported), and the synthesis with the best reported yield (28%) proceeded via an asymmetric route from a benzyl-protected galactal.[25] Although the need for a protecting group here was unavoidable because of the inherent reactivity of the *galacto* configuration, protecting group manipulation added just one step to the synthesis, and an expedient synthesis of **4** was achieved with the best yield to date.

To further demonstrate the potential of our strategy for the synthesis of fagomine diastereomers, we then set about to synthesize 5-*epi*-fagomine (**26**) (Scheme 6). 2-Deoxy-D-glucose

Scheme 6. Synthesis of Alkenylamine 29 Derived from 2-Deoxy-D-glucose



(**27a**) was converted to the methyl glycoside (**27b**) under Fischer glycosylation conditions, and subsequent treatment with iodine, triphenylphosphine, and imidazole at 75 °C for 1.5 h gave primary iodide **28** in good overall yield (64% for two steps).[26,27] The reaction times and temperatures were critical to avoid overiodination or incomplete consumption of starting material. Iodide **28** was then treated with Zn, $NaCNBH_3$, NH_3, and NH_4OAc according to the standard Vasella reductive amination protocol to effect its smooth transformation into alkenylamine **29** in good yield (86%).

Alkenylamine **29** was then subjected to a variety of annulation conditions (Table 2). As previously highlighted, slightly warmer temperatures were required for the annulation of alkenylamine **24**, and because of this, alkenylamine **29** was first treated with I_2 and $NaHCO_3$ (sat. aq.) at 40 °C (entry 1). These conditions led to a complex mixture of four carbamate products later identified as pyrrolidine **30**, the two piperidine diastereomers **31a** and **31b**, and iodide **32** (vide infra), with iodide **32** being the major product in this instance. In an attempt to limit the formation of so many carbamate products, the reaction temperature was then lowered and the number of equivalents of $NaHCO_3$ was reduced (entry 2). After the reaction mixture was stirred at room temperature for 9 days, however, no product formation was observed. Next, iodine was added in portions over the course of the reaction while the reaction mixture was stirred at room temperature until all of the starting material was consumed, as gauged by TLC analysis (entry 3). While these conditions invoked annulation reactions and a slight improvement in the ratio of the piperidine carbamate **31a** was observed, iodide **32** was once again the major product and all four carbamates were still formed. The reaction was then attempted at room temperature, again using a saturated solution of $NaHCO_3$ and I_2 (5 equiv) added in one portion at the start of the reaction (entry 4). Under these conditions, the formation of iodide **32** was reduced and pyrrolidine **30** was formed with modest selectivity in a **30**:**31a**:**31b**:**32** ratio of 4:2:2:3. The role of the halide in influencing the ratio of products was then investigated through the use of Br_2 (entry 5); however, this proved futile, with degradation being observed. Further changes were then made to the number of equivalents of reagents and the temperature at which the reaction was performed, but in all instances complex mixtures of products were observed, and the best yield of any single product apart from iodide **32** was still found to be that of pyrrolidine **30** (as highlighted in entry 4). Although the yield was disappointing (10−30%), pyrrolidine **30** could nevertheless be isolated as a pure compound following repeated flash silica gel column chromatography (eluting in 2% MeOH in EtOAc) and reversed-phase column chromatography (C8, H_2O). Here the range of yields reflects the difficulty of this chromatographic separation. Piperidines **31a** and **31b**, however, could not be separated from one another and were isolated in a poor combined yield (ca. 20%). Attempts to separate the products at a later stage in the synthesis (i.e., following hydrolysis) also did not lead to any overall improvement in the isolated yields.

To confirm the structures of pyrrolidine **30** and alkyl iodide **32**, extensive 1D and 2D NMR spectral analysis was undertaken. For pyrrolidine **30**, an HMBC correlation was observed between H4 and C1, thus enabling the 5,6-bicyclic ring system of **30** to be established. Unfortunately, overlapping signals in the proton spectra meant that the configurations of the stereocenters could not be determined unequivocally. However, NMR analysis of the acetylated derivative **33** proved

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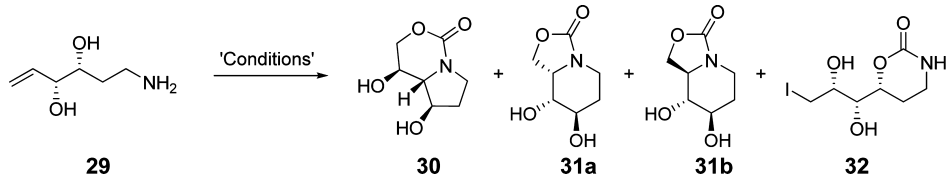
Table 2. Carbamate Annulation Reaction for Alkenylamine 29



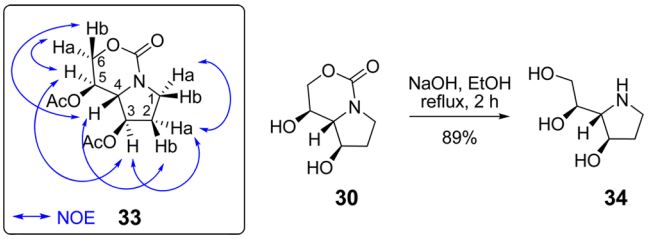
29 30 31a 31b 32

entry	conditions	products (30:31a:31b:32)[a]
1	I_2 (5 equiv), $NaHCO_3$ (sat.), 40 °C, 18 h	3:2:2:8
2	I_2 (5 equiv), $NaHCO_3$ (1.5 equiv), rt, 9 days	starting material
3	I_2 (3 × 1.5 equiv added over 22 days), $NaHCO_3$ (sat.), rt	3:2:1:7
4	I_2 (5 equiv), $NaHCO_3$ (sat.), rt, 5 days	4[b]:2:2:3
5	Br_2 (5 equiv), $NaHCO_3$ (sat.), rt, 3 days	decomposition

[a]As determined by ^{1}H NMR analysis of the crude reaction mixture [b]**30** was isolated as a pure compound in 10−30% yield following column chromatography

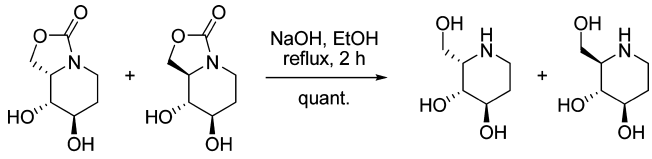
to be more beneficial. The relative configurations of H5, H4, and H6b were apparent through two large *trans*-diaxial couplings ($J_{4,5}$ = $J_{5,6b}$ = 9 Hz), and the coupling constant between H5 and H6a ($J_{5,6a}$ = 4.9 Hz) indicated an axial/equatorial relationship between these two protons. As the stereochemistry at C3 is known, NOEs were then used to determine the stereochemistries of the remaining centers. NOEs were observed between H5 and H3, H3 and H2a, H2a and H1a, and H6a and H5 (Scheme 7), indicating these

Scheme 7. Synthesis of Previously Undisclosed Trihydroxylated Pyrrolidine 34 and NOE Correlations for Acetylated Carbamate 33



protons to be on the bottom face of the molecule, while NOEs between H2b and H4 and between H4 and H6b identified these protons to be on the opposite face, thereby allowing for the assignment of the L-*allo* stereochemistry. Pyrrolidine **30** was then treated with NaOH in EtOH, which resulted in the smooth hydrolysis of the carbamate and allowed for the synthesis of the previously undisclosed trihydroxylated pyrrolidine **34** in 5−15% yield over five steps. The enantiomer of **34** has been prepared once previously.[28] Comparison of NMR data showed minor differences in the chemical shifts, which can be explained by the use of a different solvent and differences in pH (**34** was treated with conc. DCl to ensure that the amine was fully protonated). The optical rotation of **34** was measured as $[\alpha]_D^{26}$ = −1.8 (*c* = 0.41, MeOH), while that of the enantiomer was of the opposite sign and slightly larger in magnitude, reported as $[\alpha]_D^{22}$ = +4.7 (*c* = 4.0, MeOH), which can be explained by the differences in concentration and protonation state of the two compounds. At this stage, the piperidine carbamates **31a** and **31b** were also hydrolyzed to give 5-*epi*-fagomine (**26**) and fagomine (**3**), which were separated following flash silica gel column chromatography (Scheme 8). The spectral data were similar to those previously reported,[24,29] once again with some variation due to slight differences in pH.[30]

Scheme 8. Hydrolysis of Piperidine Carbamates To Give Fagomine (3) and 5-*epi*-Fagomine (26)



Confirmation of the structure of iodide **32** proved to be more difficult. No HMBC correlation was observed between the carbonyl and H3, and accordingly, the acetylated adduct **35** (Scheme 9) was prepared to aid with structural elucidation. Indeed, upon acetylation, downfield shifts of the resonances for protons H4 (5.34 ppm) and H5 (5.14 ppm), which were previously at ca. 3.76 ppm in the starting material, were observed. Proton H3, which was already at a relatively high chemical shift, did not move significantly upon acetylation. An HMBC correlation between H1 and the carbonyl was observed, though unfortunately, again no HMBC correlation was observed between the carbamate carbonyl and H3. As the stereochemistry of compound **32** also needed to be confirmed, we proposed that the synthesis of the corresponding alkenylamine (Scheme 9) would allow for confirmation of the structure of **32**, including the chirality of all stereogenic centers. To this end, iodide **32** was first converted to the corresponding acetonide **36**, and on the basis of a slightly smaller $\Delta\delta$ of the acetonide methyl group proton signals ($\Delta\delta_{^1H}$ = 0.039 ppm)[31] and diagnostic $\delta_{^{13}C} \approx 27$ ppm for both methyl groups ($\delta_{^{13}C}$ = 27.0 ppm and $\delta_{^{13}C}$ = 27.6 ppm),[32,33] this allowed for the relative stereochemistries of the 4- and 5-substituents to be determined as *trans* in the acetonide five-membered ring, indicating a *syn* relationship in iodide **32**. Opening of the acetonide via oxidative addition of zinc and subsequent reductive ring opening then provided the truncated carbamate **37** in good yield. Finally, hydrolysis of the carbamate in **37** via treatment with NaOH under reflux for 4 h gave the desired alkenylamine **29**. Comparison of the ^{1}H NMR and ^{13}C NMR spectra of the synthesized alkenylamine with those of (+)-**29** revealed them to be identical, and the optical rotations were of the same sign and comparable magnitude {$[\alpha]_D^{27}$ = +37.5 (*c* = 1.0, MeOH) and $[\alpha]_D^{27}$ = +31.8 (*c* = 0.2, MeOH)}, thus

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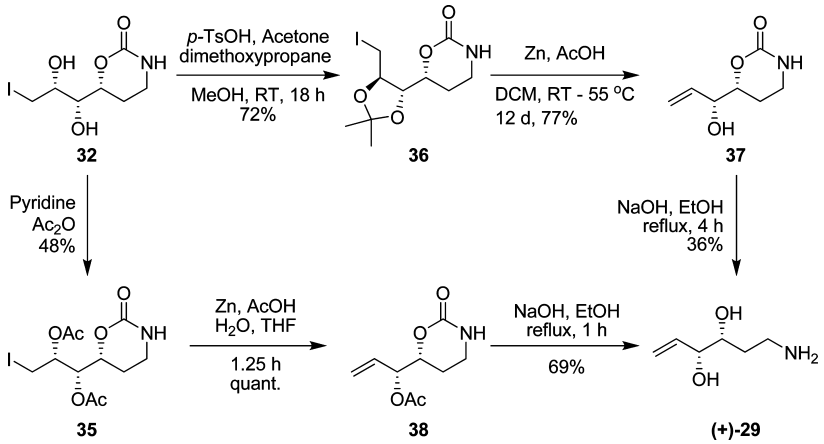
Scheme 9. Determination of the Structure of Iodocarbamate 32 via Transformation into Alkenylamine (+)-29



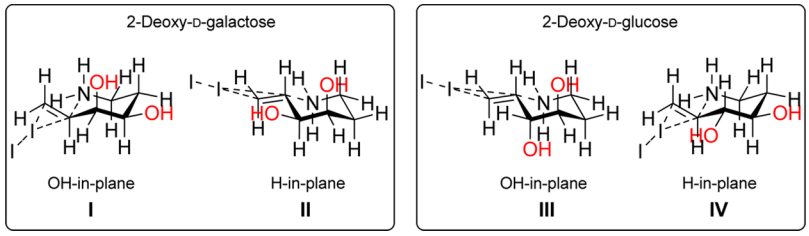


Figure 2. Six-membered iodocyclization transition states for 2-deoxy sugar series.

establishing the structure of the synthesized alkenylamine to be that of the starting material, (+)-**29**. From this information and the previously deduced *trans* relationship in acetonide **36**, the starting iodocarbamate **32** was thus determined to be (3*R*,4*R*,5*R*), as depicted. To confirm our methodology, alkenylamine (+)-**29** was also synthesized from the acetylated adduct **35** by way of reductive elimination of 5-OAc (→**38**) and subsequent carbamate hydrolysis.

Taken as a whole, the range of products formed en route to the synthesis of the target piperidines highlights the inherent problems of chemoselectivity in protecting-group-free chemistry. While we have previously illustrated that the protecting-group-free synthesis of pyrrolidines proceeds relatively smoothly with good to excellent *cis* selectivity for the carbamate annulation,[34] the present results illustrate that this methodology does not always translate readily to the synthesis of piperidines. The first factor to be considered when applying the carbamate annulation methodology to the synthesis of piperidines is O- versus N-cyclization. As illustrated when D-galactose was used as the starting material en route to the synthesis of DGJ,[14] it is possible to favor formation of the desired pyran. This observation is remarkable in its own right given the general preference for five- versus six-membered ring formation. Indeed, when D-glucose was used as the starting material, only the furan was observed.

To eliminate formation of the furan as a competing reaction, the synthesis of piperidines devoid of the hydroxyl functionality at C2 can then be attempted using the corresponding 2-deoxy sugars as starting materials. Here, the chirality of the alkenylamine is crucial in determining the number of products formed during the annulation reaction. While the alkenylamine derived from 2-deoxy-D-galactose was transformed into the 4-*epi*-fagomine carbamate scaffold with excellent chemo- and diastereoselectivity (*cis*:*trans* > 95:5), subjection of the corresponding alkenylamine derived from 2-deoxy-D-glucose to the annulation conditions resulted in poor selectivity and the formation of four products despite much effort to optimize this reaction to favor piperidine formation. The difference in selectivity for the two annulation reactions can be explained by considering the corresponding six-membered iodocyclization transition states, wherein, according to the seminal work of Chamberlin and co-workers,[35] the allylic hydroxyl has a stereodirecting effect in the formation of both five- and six-membered rings. Here, Chamberlin proposed that the unfavorable C−O σ^* to C═C π orbital overlap can be minimized by an OH-in-plane (with the double bond) transition state. In the case of our I_2-mediated carbamate annulations, this is illustrated in Figure 2, wherein transition state **I** for the 2-deoxy-D-galactose series depicts the major OH-in-plane conformer while **II** depicts the unfavorable H-in-plane conformer. Similarly, the OH-in-plane transition state **III** and the H-in-plane transition state **IV** are also given for the 2-deoxy-D-glucose series.

In addition to the conformation of the allylic hydroxyl, for six-membered rings the relative axial or equatorial orientation of the hydroxyl substituents needs to be considered. For the 2-deoxy-D-galactose series, both the OH-in-plane transition state **I** and the H-in-plane transition state **II** have one axial and one equatorial hydroxyl group, and as a consequence, the OH-in-plane transition state is lower in energy because there is no unfavorable C−O σ^* to C═C π orbital overlap. For the 2-deoxy-D-glucose series however, the OH-in-plane transition state **III** has the two hydroxyl substituents placed in an unfavorable axial orientation, thereby increasing the overall energy of this transition state and making it closer in energy to transition state **IV**, which, while having the unfavorable H-in-plane conformation, has the hydroxyl substituents in a more favorable equatorial orientation. In summary, the 2-deoxy-D-galactose series thus leads to the preferential formation of the *cis*-piperidine carbamate, while the 2-deoxy-D-glucose series,

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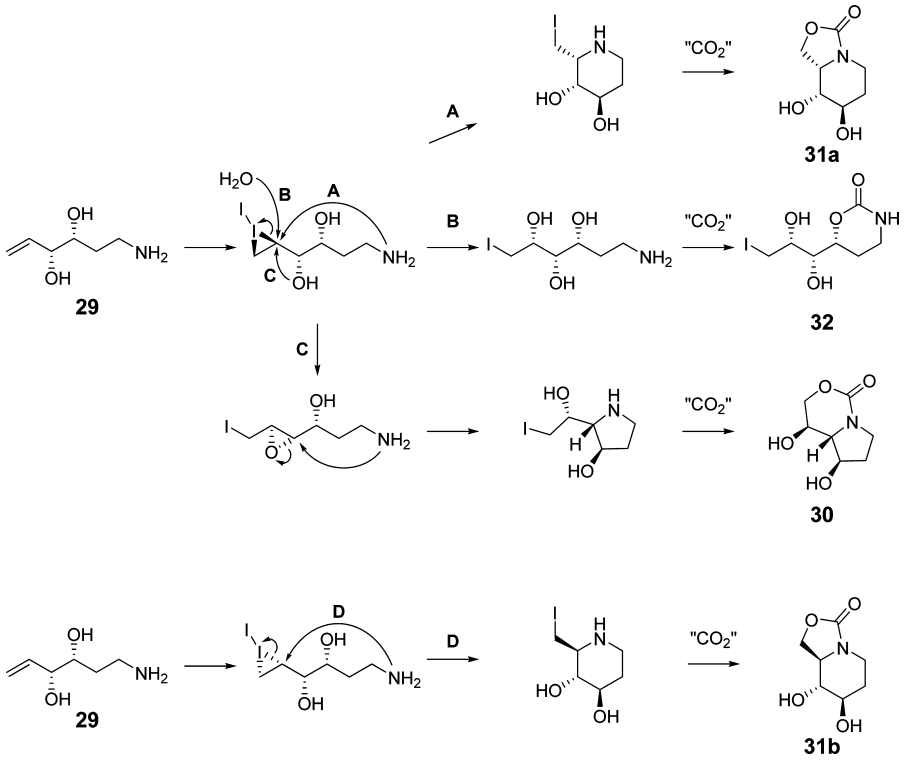
Scheme 10. Proposed Mechanism for the Formation of Pyrrolidine 30, Piperidines 31a and 31b, and Iodide 32



with iodocyclization transition states of similar energy, leads to a variety of products.

To gain further insight into how to better design starting materials to favor the formation of the desired piperidine or pyrrolidine, reaction mechanisms have been proposed to explain the formation of the four products following the subjection of alkenylamine **29** to the carbamate annulation conditions (Scheme 10). First, attack of iodine from the top face of alkenylamine **29** (via transition state **III** in Figure 2) leads to an intermediate that can be transformed into piperidine **31a**, iodide **32**, and pyrrolidine **30**. Here, pathway A involves amine attack on the iodine complex at C5 followed by the addition of CO_2 to give *cis*-carbamate **31a** in accordance with our previously published annulation methodology.[34] The synthesis of iodocarbamate **32**, which contains a chiral backbone with a C5 stereocenter that differs from the parent alkenylamine **29**, is proposed to occur via S_N2 attack of water on the iodine complex (pathway B) followed by the addition of CO_2 to the linear iodoamine, which itself can be formed via the dissociation of carbonic acid. While there is no literature precedent for the reaction of terminal unsubstituted allylic alcohols with iodine, a number of halohydrin reactions have been performed on similar substrates with both the substitution pattern and the accessibility of the halonium ion effecting regio-[36−38] and stereochemical[39,40] outcomes. In the most closely related system involving hydrobromination, a variety of products were observed.[41,42] In our case, however, ^{1}H NMR analysis revealed no product that could have arisen from opening of the iodine complex by water at the terminal carbon or from attack on the diastereomeric iodine complex. The observed regioselectivity can be explained by Markovnikov's rule, while the stereoselectivity is more difficult to rationalize but is correlated to the relative reaction rates for formation of the intermediate iodine complex and the subsequent intramolecular or intermolecular nucleophilic ring opening. It is also conceivable that formation of a cyclic carbamate at the 3-position takes place prior to halohydrin formation[43] and that this provides an alternative route to **32**. The possibility that **32** is formed via a Payne rearrangement[44] of the intermediate epoxide is unlikely, as this reaction would require strongly basic conditions.[45] Such a cyclic carbamate intermediate, however, does not add to a conceivable mechanism for the formation of either **31a** or **30**.

To explain the formation of pyrrolidine **30**, a mechanism that supports the inversion of the C4 and C5 chiral centers is required, and thus an iodoepoxide (pathway C) is proposed as a key intermediate.[42,46] Nucleophilic 5-*exo-tet* ring opening of the epoxide followed by the addition of CO_2 then allows for the formation of **30**.[47] Finally, the formation of *trans*-piperidine **31b** can be envisioned to occur via S_N2 attack of the diastereomeric iodine complex (pathway D), with the iodine complex itself arising from transition state **IV** (Figure 2). Subsequent addition of CO_2 to the intermediate cyclic iodoamine then gives the piperidine. Here it should also be noted that attack at the 5-position of the intermediate epoxide discussed in pathway C (6-*endo-trig*) could also lead to **31b**, but this is less favored than the corresponding 5-*exo-trig* cyclization (→**31b**),[47] especially in the absence of a bulky group α to the nitrogen.[48]

Taken together, a number of factors should thus be considered before using the carbamate annulation reaction as a key step in the synthesis of piperidines containing multiple reactive sites. First, the orientations of the ring substituents affect the relative energies of the OH-in-plane or H-in-plane transition states, and where there is no obvious low-energy conformer, this can lead to a variety of products. One could thus envisage the use of judiciously placed bulky substituents to favor one conformer over the other, while the positioning of a

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protecting group at the 4-position of the alkenylamine could be used to inhibit formation of the intermediate epoxide and hence the associated pyrrolidine products (e.g., **30**). We have previously shown that the carbamate annulation can occur in the presence of protecting groups,[49,50] which supports the validity of installing one or more protecting groups to control the chemoselectivity of the annulation when required.

CONCLUSION

We have presented two highly efficient syntheses of the biologically important piperidines DGJ (**2**) and 4-*epi*-fagomine (**4**) in good overall yields. Key in these reactions is the use of an I_2-mediated carbamate annulation. The use of the carbamate annulation for the synthesis of other piperidines, however, was less successful, as either O-cyclization or a series of competing intramolecular reactions occurred. To this end, trihydroxypyrrolidine **34** was prepared in five steps and modest overall yield (up to 15%). These studies highlight the limitations of using the carbamate annulation for the preparation of piperidines in protecting-group-free syntheses, although the work also points to the potential of this methodology for the synthesis of interesting chiral scaffolds when either protected or suitably functionalized alkenylamines are used as starting materials.

EXPERIMENTAL SECTION

General Procedures. Unless otherwise stated, all reactions were performed under atmospheric air. THF was distilled from $LiAlH_4$ prior to use. Pyridine was distilled over KOH prior to use. All chemicals obtained from commercial suppliers were used without further purification. Zn dust was activated by the careful addition of concentrated H_2SO_4 followed by decantation, 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 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, or by coating with a solution of 5% $KMnO_4$ and 1% $NaIO_4$ in H_2O followed by heating. ^1H and ^{13}C chemical shifts (δ) were internally referenced to the residual solvent peak. NMR peak assignments are based on 2D NMR experiments (COSY, HSQC, and HMBC). High-resolution electrospray ionization mass spectrometry [HRMS(ESI)] was performed on a Q-TOF instrument.

1-Amino-2,5-anhydro-1,6-dideoxy-6-iodo-L-iditol (13). To a solution of alkenylamine **10**[13] (310 mg, 1.69 mmol) in sat. aq. $NaHCO_3$ (7 mL) was added I_2 (645 mg, 2.54 mmol), and the solution was stirred for 7 days. The reaction mixture, a crude oil, was concentrated and used without further purification. R_f = 0.23 (DCM/EtOH/MeOH/30% aq. NH_3, 5/2/2/1 v/v/v/v); ^1H NMR (500 MHz, D_2O) δ 4.45 (dt, $J_{4,5}$ = 3.1, $J_{5,6a}$ = $J_{5,6b}$ = 7.3 Hz, 1H, H5), 4.40 (ddd, $J_{2,3}$ = 3.8, $J_{1a,2}$ = 4.4, $J_{1b,2}$ = 5.6 Hz, 1H, H2), 4.38 (dd, $J_{3,4}$ = 1.3, $J_{2,3}$ = 3.8 Hz, 1H, H3), 4.28 (dd, $J_{3,4}$ = 1.3, $J_{4,5}$ = 3.1 Hz, 1H, H4), 3.27 (dd, $J_{5,6a}$ = 7.3, $J_{6a,6b}$ = 9.8 Hz, 1H, H6a), 3.26 (dd, $J_{5,6b}$ = 7.3, $J_{6a,6b}$ = 9.8 Hz, 1H, H6b), 3.258 (dd, $J_{1a,2}$ = 4.4, $J_{1a,1b}$ = 13.6 Hz, 1H, H1a), 3.23 (dd, $J_{1b,2}$ = 5.6, $J_{1a,1b}$ = 13.6 Hz, 1H, H1b); ^{13}C NMR (125 MHz, D_2O) δ 81.7 (C5), 77.5 (C3), 76.52, 76.50 (C2 and C4), 39.4 (C1), 0.6 (C6); HRMS(ESI) m/z calcd for $[C_6H_{12}O_3NI + H]^+$ 273.9935, found 273.9938.

1-Acetamido-3,4-di-*O*-acetyl-2,5-anhydro-1,6-dideoxy-6-iodo-L-iditol (14). A solution of iditol **13** was stirred overnight at rt in a solution of acetic anhydride (4 mL) and pyridine (4 mL). The reaction mixture was concentrated, dissolved in EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give acetylated iditol **14** as a colorless oil. R_f = 0.12 (EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (t, $J_{1a,NH}$ = $J_{1b,NH}$ = 6.2 Hz, 1H, NH), 5.38 (dd, $J_{3,4}$ = 1.4, $J_{4,5}$ = 4.0 Hz, 1H, H4), 5.27 (dd, $J_{3,4}$ = 1.4, $J_{2,3}$ = 3.4 Hz, 1H, H3), 4.52 (ddd, $J_{4,5}$ = 4.0, $J_{5,6a}$ = 6.3, $J_{5,6b}$ = 8.8 Hz, 1H, H5), 4.30 (ddd, $J_{2,3}$ = 3.4, $J_{1b,2}$ = 6.2, $J_{1a,2}$ = 7.3 Hz, 1H, H2), 3.47 (ddd, $J_{1a,NH}$ = 6.2, $J_{1a,2}$ = 7.3, $J_{1a,1b}$ = 14.0 Hz, 1H, H1a), 3.27 (td, $J_{1b,NH}$ = $J_{1b,2}$ = 6.2, $J_{1a,1b}$ = 14.0 Hz, 1H, H1b), 3.21 (dd, $J_{5,6a}$ = 6.3, $J_{6a,6b}$ = 9.7 Hz, 1H, H6a), 3.17 (dd, $J_{5,6b}$ = 8.8, $J_{6a,6b}$ = 9.7 Hz, 1H, H6b), 2.16 (s, 3H, Ac), 2.15 (s, 3H, Ac), 2.00 (s, 3H, NH*Ac*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C═O, NHAc), 170.1 (C═O, Ac), 169.4 (C═O, Ac), 79.6 (C5), 78.9 (C2), 76.4 (C3), 76.1 (C4), 38.1 (C1), 23.5 (CH_3, NHAc), 20.9 (CH_3, Ac), 20.8 (CH_3, Ac), −0.6 (C6); HRMS(ESI) m/z calcd for $[C_{12}H_{18}O_6NI + Na]^+$ 422.0076, found 422.0076.

Methyl 3,6-Anhydro-2-deoxy-α-D-galactopyranoside (19). To a solution of methyl glycoside **18** (28 mg, 0.16 mmol) in dry THF (3 mL) were added PPh_3 (83 mg, 0.32 mmol), imidazole (43 mg, 0.63 mmol), and I_2 (80 mg, 0.32 mmol). The mixture was refluxed overnight (18 h) and then cooled and concentrated. The resulting oil was purified by flash column chromatography (petroleum ether/EtOAc, 5/1 to 1/1 v/v) to give bicyclic galactoside **19**. R_f = 0.3 (EtOAc/MeOH, 98/2 v/v); ^1H NMR (500 MHz, D_2O) δ 4.69 (d, $J_{1,2b}$ = 6.2 Hz, 1H, H1), 4.31−4.32 (m, 2H, H3 and H6a), 4.27−4.28 (m, 1H, H5), 4.02 (d, $J_{3,4}$ = 1.8 Hz, 1H, H4), 3.98 (dd, $J_{5,6b}$ = 3.4, $J_{6a,6b}$ = 9.9 Hz, 1H, H6b), 3.40 (s, 3H, OMe), 2.19 (dd, $J_{2a,3}$ = 4.6, $J_{2a,2b}$ = 14.5 Hz, 1H, H2a), 2.02 (ddd, $J_{2b,3}$ = 1.6, $J_{1,2b}$ = 6.2, $J_{2a,2b}$ = 14.5 Hz, 1H, H2b); ^{13}C NMR (125 MHz, D_2O) δ 97.2 (C1), 77.8 (C3), 77.3 (C5), 74.8 (C4), 70.2 (C6), 55.7 (OMe), 37.6 (C2); HRMS(ESI) m/z calcd for $[C_7H_{12}O_4 + Na]^+$ 183.0633, found 183.0631.

Methyl 2-Deoxy-3,4-*O*-isopropylidene-α/β-D-galactopyranoside (20). *From* ***17***. AcCl (180 μL) was added to a solution of 2-deoxy-D-galactose (**17**) (200 mg, 0.61 mmol) in MeOH/acetone/dimethoxypropane (6 mL, 2/2/2 v/v/v), and the solution was stirred for 18 h at room temperature. The reaction was quenched with Dowex−OH^-, and the mixture was filtered and concentrated. The resulting oil, **20**, was used without purification.

From ***23***. To a solution of D-galactal **23** (200 mg, 1.36 mmol) in MeOH (8 mL) and acetone (8 mL) was added pTsOH·H_2O (24 mg, 0.14 mmol), and the reaction was stirred at room temperature for 18 h. The reaction mixture was then neutralized by the addition of Dowex−OH^-, filtered, and concentrated in vacuo. The crude reaction product, **20**, was used in the iodination reaction without further purification.

R_f = 0.13 (petroleum ether/EtOAc, 1/1 v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 4.86 (dd, $J_{1,2a}$ = 5.1, $J_{1,2b}$ = 6.0 Hz, 1H, H1), 4.47 (ddd, $J_{2b,3}$ = 4.1, $J_{2a,3}$ = 5.1, $J_{3,4}$ = 6.9 Hz, 1H, H3), 4.16 (dd, $J_{4,5}$ = 1.7, $J_{3,4}$ = 6.9 Hz, 1H, H4), 3.89 (dd, $J_{5,6a}$ = 5.6, $J_{6a,6b}$ = 10.6 Hz, 1H, H6a), 3.80 (ddd, $J_{4,5}$ = 1.7, $J_{5,6b}$ = 4.3, $J_{5,6a}$ = 5.6 Hz, 1H, H5), 3.77 (dd, $J_{5,6b}$ = 4.3, $J_{6a,6b}$ = 10.6 Hz, 1H, H6b), 3.37 (s, 3H, OMe), 2.17 (dt, $J_{2a,2b}$ = 14.8, $J_{1,2a}$ = $J_{2a,3}$ = 5.1 Hz, 1H, H2a), 1.73 (ddd, $J_{2b,3}$ = 4.1, $J_{1,2b}$ = 6.0, $J_{2a,2b}$ = 14.8 Hz, 1H, H2b), 1.47 (s, iPr), 1.31 (s, iPr); ^{13}C NMR (75 MHz, $CDCl_3$) 109.2 (iPr-$C(CH_3)_2$) 97.4 (C1), 73.4 (C4), 70.5 (C3), 68.5 (C5), 62.8 (C6), 55.0 (OMe), 30.8 (C2), 26.8, 25.3 (iPr-$C(CH_3)_2$); HRMS(ESI) m/z calcd for $[C_{10}H_{18}O_5 + Na]^+$ 241.1052, found 241.1046.

Methyl 2,6-Dideoxy-6-iodo-3,4-*O*-isopropylidene-α/β-D-galactopyranoside (21). *From* ***17***. To a solution of **20** (0.61 mmol) in dry THF (7 mL) were added PPh_3 (456 mg, 1.74 mmol), imidazole (180 mg, 2.62 mmol), and I_2 (442 mg, 174 mmol). The mixture was refluxed for 18 h and then cooled and concentrated. The syrup was redissolved in ethyl acetate (20 mL), washed with sat. aq. $Na_2S_2O_3$ (2 × 15 mL) and then brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by flash column chromatography (petroleum ether/EtOAc, 15/1 v/v) followed by crystallization from hexanes to give iodogalactoside **21** as white crystals (142 mg, 0.434 mmol, 71% from **17**).

From ***23***. Iodination of **20** performed as above yielded iodogalactoside **21** as white crystals (241 mg, 0.73 mmol, 54% over two steps from **23**).

R_f = 0.77 (petroleum ether/EtOAc, 1/1 v/v); Mp 91−92 °C; $[\alpha]_D^{21}$ = +72.4 (c = 1.0, $CHCl_3$); IR (film) 2982, 2936, 2912, 2833, 1439, 1373, 1246, 1214, 1186, 1088, 1047, 969, 880, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.86 (dd, $J_{1,2a}$ = 5.4, $J_{1,2b}$ = 6.6 Hz, 1H, H1), 4.49 (ddd, $J_{2b,3}$ = 3.7, $J_{2a,3}$ = 4.6, $J_{3,4}$ = 7.3 Hz, 1H, H3), 4.26 (dd, $J_{4,5}$ = 2.0, $J_{3,4}$ = 7.3 Hz, 1H, H4), 3.86 (ddd, $J_{5,4}$ = 2.0, $J_{5,6a}$ = 5.8, $J_{5,6b}$ = 8.1 Hz, 1H, H5), 3.47 (s, 3H, OMe), 3.34 (dd, $J_{5,6a}$ = 5.8, $J_{6a,6b}$ = 10.2 Hz, 1H,

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H6a), 3.28 (dd, $J_{5,6b}$ = 8.1, $J_{6a,6b}$ = 10.2 Hz, 1H, H6b), 2.24 (ddd, $J_{2a,3}$ = 4.6, $J_{1,2a}$ = 5.4, $J_{2a,2b}$ = 15.1 Hz, 1H, H2a), 1.64 (ddd, $J_{2b,3}$ = 3.7, $J_{1,2b}$ = 6.6, $J_{2a,2b}$ = 15.1 Hz, 1H, H2b), 1.48 (s, 3H, iPr), 1.34 (s, 3H, iPr); ^{13}C NMR (75 MHz, $CDCl_3$) 109.3 (iPr-C(CH_3)$_2$) 97.6 (C1), 73.4 (C4), 70.9 (C3), 70.0 (C5), 55.2 (OMe), 30.2 (C2), 26.6, 25.2 (iPr-C(CH_3)$_2$), 3.2 (C6); HRMS(ESI) *m*/*z* calcd for $[C_{10}H_{17}O_4I + Na]^+$ 351.0069, found 351.0072.

Methyl 2,6-Dideoxy-6-iodo-α/β-D-galactopyranoside (22). To a solution of iodogalactoside **21** (237 mg, 0.79 mmol) in MeOH (10 mL), at 0 °C was added AcCl (200 μL). The reaction mixture was stirred at room temperature for 5 days, after which the reaction was quenched with Dowex−OH^- and the mixture was concentrated in vacuo. The product was purified via gradient flash column chromatography (petroleum ether/EtOAc, 3/1 to 1/1 v/v) to provide galactoside **22** as a colorless oil (200 mg, 0.69 mmol, 94%). R_f = 0.11 (EtOAc); $[\alpha]_D^{21}$ = +0.11 (*c* = 1.0, MeOH); IR (film) 3292, 2925, 2854, 1735, 1457, 1209, 1130, 1034, 668 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 4.71 (d, $J_{1,2a}$ = 3.6 Hz, 1H, H1), 3.81 (ddd, $J_{3,4}$ = 3.2, $J_{2b,3}$ = 4.1, $J_{2b,3}$ = 12.6 Hz, 1H, H3), 3.78−3.72 (m, 2H, H4 and H5), 3.31 (s, 3H, OMe), 3.30−3.22 (m, 2H, H6a and H6b), 1.82 (td, $J_{2a,2b}$ = $J_{2a,3}$ = 12.6, $J_{1,2a}$ = 3.6 Hz, 1H, H2a), 1.62 (dd, $J_{2b,3}$ = 5.1, $J_{2a,2b}$ = 12.6 Hz, 1H, H2b); ^{13}C NMR (125 MHz, CD_3OD) δ 100.3 (C1), 72.9 (C4), 70.5 (C5), 66.7 (C3), 55.5 (OCH_3), 33.1 (C2), 4.5 (C6); HRMS(ESI) *m*/*z* calcd for $[C_7H_{13}O_4I + Na]^+$ 310.9756, found 310.9756.

(3*R*,4*S*)-1-Aminohex-5-ene-3,4-diol (24). To a solution of iodogalactoside **22** (58 mg, 0.21 mmol) in a saturated solution of NH_4OAc in EtOH (3 mL) were added activated Zn (36 mg, 0.55 mmol), $NaCNBH_3$ (21 mg, 0.33 mmol), and 30% aq. NH_3 (1 mL). The mixture was stirred at reflux for 18 h, filtered, and concentrated in vacuo. The mixture was loaded on a Dowex-H^+ column, eluted in 15% aq. NH_3, and concentrated in vacuo. Acidification with 1 M HCl yielded alkenylamine **24**, a white solid, as the HCl salt (35 mg, 0.21 mmol, 99%). R_f = 0.11 (DCM/EtOH/MeOH/30% aq. NH_3, 5/2/2/1 v/v/v/v); $[\alpha]_D^{25}$ = −114 (*c* = 0.1, EtOH); IR (film) 3370, 3321, 2962, 2836, 1642, 1504, 1435, 1378, 1025, 652 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 5.87 (ddd, $J_{4,5}$ = 6.2, $J_{5,6\text{-}cis}$ = 10.3, $J_{5,6\text{-}trans}$ = 17.1 Hz, 1H, H5), 5.30 (d, $J_{5,6\text{-}trans}$ = 17.1 Hz, 1H, H6-*cis*), 5.27 (d, $J_{5,6\text{-}cis}$ = 10.3 Hz, 1H, H6-*trans*), 4.03 (dd, $J_{3,4}$ = 4.6, $J_{4,5}$ = 6.2 Hz, 1H, H4), 3.69 (ddd, $J_{2a,3}$ = 3.2, $J_{3,4}$ = 4.6, $J_{2b,3}$ = 9.6 Hz, 1H, H3), 2.85 (ddd, $J_{1a,2b}$ = 5.9, $J_{1a,2a}$ = 8.5, $J_{1a,1b}$ = 12.8 Hz, 1H, H1a), 2.77 (ddd, $J_{1b,2a}$ = 7.0, $J_{1b,2b}$ = 8.0, $J_{1a,1b}$ = 12.8 Hz, 1H, H1b), 1.72 (dddd, $J_{2a,3}$ = 3.2, $J_{1b,2a}$ = 7.0, $J_{1a,2a}$ = 8.5, $J_{2a,2b}$ = 17.5 Hz, 1H, H2a), 1.55 (dddd, $J_{1a,2b}$ = 5.9, $J_{1b,2b}$ = 8.0, $J_{2b,3}$ = 9.6, $J_{2a,2b}$ = 17.5 Hz, 1H, H2b); ^{13}C NMR (75 MHz, D_2O) δ 135.5 (C5), 118.0 (C6), 75.4 (C4), 71.6 (C3), 37.1 (C1), 28.9 (C2); HRMS(ESI) *m*/*z* calcd for $[C_6H_{13}O_2N + H]^+$ 132.1025, found 132.1022.

1-*N*,6-*O*-Carbonyl-4-*epi*-fagomine (25a). To a solution of alkenylamine hydrochloride **24** (17 mg, 0.13 mmol) in saturated $NaHCO_3$ (aq) (0.6 mL) was added I_2 (32 mg, 0.25 mmol). The solution was stirred for 5 days at 35 °C and then filtered and concentrated in vacuo. Purification by flash chromatography (EtOAc/MeOH, 99/1 v/v) yielded carbamate **25a** as a white solid (15.1 mg, 0.0873 mmol, 86%). $[\alpha]_D^{19}$ = +4.0 (*c* = 1, MeOH); IR (film) 3338, 2945, 2833, 2360, 2342, 1653, 1449, 1417, 1114, 1021 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 4.48 (t, $J_{5,6}$ = $J_{6a,6b}$ = 9.0 Hz, 1H, H6a), 4.37 (dd, $J_{5,6}$ = 5.5, $J_{6a,6b}$ = 9.0 Hz, 1H, H6b), 4.03 (ddd, $J_{4,5}$ = 1.8, $J_{5,6b}$ = 5.5, $J_{5,6a}$ = 9.0 Hz, 1H, H5), 3.89 (m, 1H, H4), 3.86 (dd, $J_{3,4}$ = 2.5, $J_{2,3}$ = 5.5 Hz, 1H, H3), 3.76 (ddd, $J_{1a,2a}$ = 1.8, $J_{1a,2b}$ = 5.5, $J_{1a,1b}$ = 13.5 Hz, 1H, H1a), 3.06 (app dt, $J_{1b,2a}$ = $J_{1b,2b}$ = 4.5, $J_{1a,1b}$ = 13 Hz, 1H, H1b), 1.70−1.80 (m, 2H, H2a and H2b); ^{13}C NMR (125 MHz, D_2O) δ 159.2 (C═O) 68.6 (C3), 67.9 (C4), 64.1 (C6), 57.0 (C5), 38.5 (C1), 25.1 (C2); HRMS(ESI) *m*/*z* calcd for $[C_7H_{11}NO_4 + Na]^+$ 196.0586, found 196.0590.

4-*epi*-Fagomine (4). To a solution of carbamate **25a** (11 mg, 0.06 mmol) in EtOH (2 mL) was added NaOH (32 mg, 0.80 mmol). The solution was stirred at reflux for 2 h and then cooled and purified directly using a Dowex-H^+ column. The product was eluted in 5 to 15% aq. NH_3 and concentrated in vacuo. Purification by flash chromatography (DCM/EtOH/MeOH/30% aq. NH_3, 25/2/2/1 to 5/2/2/1 v/v/v/v) yielded piperidine **4** as a white solid (8.1 mg, 0.055 mmol, 92%). $[\alpha]_D^{19}$ = +11.8 (*c* = 0.1, MeOH); IR (film) 3286, 2923, 1653, 1398, 1145, 1100, 1046, 1022 cm^{-1}; ^{1}H NMR (600 MHz, D_2O) δ 3.92 (bs, 1H, H4), 3.76 (ddd, *J* = 2.8, *J* = 8.4 Hz, *J* = 10.5 Hz, 1H, H3), 3.69 (dd, *J* = 5.8, *J* = 11.7 Hz, 1H, H6a), 3.65 (dd, *J* = 7.6, *J* = 11.6 Hz, 1H, H6b), 3.17 (dt, *J* = 3.6, *J* = 12.7 Hz, 1H, H1a), 2.92 (app t, *J* = 7.1 Hz, 1H, H5), 2.73 (m, 1H, H1b), 1.74−1.79 (m, 2H, H2a and H2b); ^{13}C NMR (150 MHz, D_2O) δ 67.4 (C3), 65.8 (C4), 60.0 (C6), 59.4 (C5), 42.1 (C1), 24.0 (C2); HRMS(ESI) *m*/*z* calcd for $[C_6H_{13}NO_3 + H]^+$ 148.0974, found 148.0974.

Methyl 2-Deoxy-α/β-D-glucopyranoside (27b). To a solution of AcCl (240 μL) in MeOH (240 mL) was added 2-deoxy-D-glucose (**27a**) (1200 mg, 7.3 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was then neutralized by the addition of Dowex−OH^-, filtered, and concentrated. The resulting oil was used without further purification. Methyl 2-deoxy-α/β-D-glucopyranoside (**27b**) was obtained as a colorless oil in an 8:1 α:β ratio.

Data for the α isomer: R_f = 0.27 (10% MeOH in EtOAc); ^{1}H NMR (600 MHz, D_2O) δ 4.86 (d, $J_{1,2b}$ = 3.5 Hz, 1H, H1), 3.83 (dd, $J_{5,6a}$ = 2.1, $J_{6a,6b}$ = 12.0 Hz, 1H, H6a), 3.79−3.87 (m, 1H, H3), 3.73 (dd, $J_{5,6b}$ = 5.5, $J_{6a,6b}$ = 12.0 Hz, 1H, H6b), 3.56 (ddd, $J_{5,6a}$ = 2.1, $J_{5,6b}$ = 5.5, $J_{4,5}$ = 9.6 Hz, 1H, H5), 3.32 (s, 3H, OMe), 3.31 (m, 1H, H4), 2.10 (dd, $J_{2a,3}$ = 5.3, $J_{2a,2b}$ = 13.5 Hz, 1H, H2a), 1.67 (ddd, $J_{1,2b}$ = 3.5, $J_{2b,3}$ = 12.0, $J_{2a,2b}$ = 13.5 Hz, 1H, H2b); ^{13}C NMR (150 MHz, D_2O) δ 98.1 (C1), 71.9 (C5), 70.8 (C4), 68.0 (C3), 60.5 (C6), 54.2 (OMe), 36.4 (C2); HRMS(ESI) *m*/*z* calcd for $[C_7H_{14}O_5 + Na]^+$ 201.0733, found 201.0735.

Data for the β isomer: R_f = 0.27 (10% MeOH in EtOAc); ^{1}H NMR (600 MHz, D_2O) δ 4.59 (dd, $J_{1,2a}$ = 1.8, $J_{1,2b}$ = 9.9 Hz, 1H, H1), 3.89 (dd, $J_{5,6a}$ = 2.0, $J_{6a,6b}$ = 12.0 Hz, 1H, H6a), 3.65−3.72 (m, 2H, H3 and H6b), 3.48 (s, 3H, OMe), 3.32 (m, 1H, H5), 3.21 (t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, 1H, H4), 2.21 (ddd, $J_{1,2a}$ = 1.8, $J_{2a,3}$ = 5.1, $J_{2a,2b}$ = 12.9 Hz, 1H, H2a), 1.43 (ddd, $J_{1,2b}$ = 9.9, $J_{2b,3}$ = 12.0, $J_{2a,2b}$ = 12.9 Hz, 1H, H2b); ^{13}C NMR (150 MHz, D_2O) δ 100.6 (C1), 75.9 (C5), 70.9 (C4), 70.2 (C3), 60.8 (C6), 56.4 (OMe), 38.0 (C2); HRMS(ESI) *m*/*z* calcd for $[C_7H_{14}O_5 + Na]^+$ 201.0739, found 201.0735.

Methyl 2,6-Dideoxy-6-iodo-α-D-glucoside (28). To a solution of methyl 2-deoxy-D-glucoside (70.1 mg, 0.4 mmol) in dry THF (4 mL) under an atmosphere of argon were added imidazole (81.6 mg, 1.2 mmol), PPh_3 (157 mg, 0.6 mmol), and I_2 (152 mg, 0.6 mmol). The reaction mixture was heated to 75 °C for 1.5 h and then cooled and concentrated. The product was purified by silica gradient flash column chromatography (petroleum ether/EtOAc, 2/1 v/v) and then reversed-phase HP20 chromatography (MeOH/water, 1/5 v/v) to give methyl 2,6-dideoxy-6-iodo-α-D-glucopyranoside (**28**) as a colorless oil (74.1 mg, 0.26 mmol, 64% over two steps from 2-deoxyglucose **27**). R_f = 0.42 (1% MeOH in EtOAc); $[\alpha]_D^{23}$ = +84.0 (*c* = 1.0, $CHCl_3$) (lit $[\alpha]_D^{27}$ = +97, *c* = 0.9 in chloroform[51]); IR (film) 3387, 2934, 1442, 1377, 1211, 1128, 1044, 966, 938 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (d, $J_{1,2b}$ = 3.4 Hz, 1H, H1), 3.97 (ddd, $J_{2a,3}$ = 5.1, $J_{3,4}$ = 8.7, $J_{2b,3}$ = 11.7 Hz, 1H, H3), 3.57−3.62 (m, 1H, H6a), 3.40 (s, 3H, OMe), 3.35−3.41 (m, 2H, H5 and H6b), 3.24−3.30 (m, 1H, H4), 2.16 (ddd, $J_{1,2a}$ = 1.0, $J_{2a,3}$ = 5.1, $J_{2a,2b}$ = 12.9 Hz, 1H, H2a), 1.71 (ddd, $J_{1,2b}$ = 3.2, $J_{2b,3}$ = 11.7, $J_{2a,2b}$ = 12.9 Hz, 1H, H2b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.7 (C1), 77.6 (C4), 70.4 (C5), 69.1 (C3), 55.3 (OMe), 37.8 (C2), 7.9 (C6); HRMS(ESI) *m*/*z* calcd for $[C_7H_{13}O_4I + Na]^+$ 310.9756, found 310.9751.

(3*R*,4*R*)-1-Amino-hex-5-ene-3,4-diol Hydrochloride (29). To a solution of methyl 2,6-dideoxy-6-iodo-α-D-glucoside (**28**) (111 mg, 0.39 mmol) in a saturated solution of NH_4OAc in EtOH (7.3 mL) were added activated Zn (450 mg, 6.9 mmol), $NaCNBH_3$ (85 mg, 1.3 mmol), and 30% aq. NH_3 (2.9 mL). The mixture was stirred at reflux for 4.5 h, cooled to room temperature, filtered through Celite, and concentrated under reduced pressure. HCl (30 mL, 2 M) was added, and AcOH was removed by evaporation. Coevaporation with water/EtOH was performed to remove traces of AcOH, after which an aqueous solution of NaOH (40 mL, 1.25 M) was added and the NH_3 was evaporated. The resulting solid was filtered and washed with EtOH to remove the bulk of the insoluble NaCl salt, and the filtrate and combined washings were concentrated and then dry-loaded on silica for column chromatography (DCM/EtOH/MeOH/35% aq.

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NH_3, 55/2/2/1 to 5/2/2/1 v/v/v/v). Alkenylamine **29** was obtained as the HCl salt after the addition of aq. HCl (1.2 M) and concentration to obtain a white solid (55.5 mg, 0.33 mmol, 86%). R_f = 0.16 (DCM/EtOH/MeOH/35% aq. NH_3, 5/2/2/1 v/v/v/v); $[\alpha]_D^{27}$ = +37.5 (*c* = 1.0, MeOH); IR (film) 3336, 2924, 1621, 1505, 1468, 1396, 1312, 1255, 1122, 1020, 997, 931, 854 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.87 (ddd, $J_{4,5}$ = 6.7, $J_{5,6\text{-}cis}$ = 10.5, $J_{5,6\text{-}trans}$ = 17.3 Hz, 1H, H5), 5.34 (d, $J_{5,6\text{-}trans}$ = 17.3 Hz, 1H, H6-*trans*), 5.28 (d, $J_{5,6\text{-}cis}$ = 10.5 Hz, 1H, H6-*cis*), 4.03 (dd, $J_{4,5}$ = 6.7, $J_{3,4}$ = 6.8 Hz, 1H, H4), 3.70 (ddd, $J_{2a,3}$ = 2.9, $J_{2b,3}$ = 5.4, $J_{3,4}$ = 6.8 Hz, 1H, H3), 3.13 (m, 2H, H1), 1.89 (m, 1H, H2a), 1.77 (m, 1H, H2b); ^{13}C NMR (125 MHz, D_2O) δ 136.1 (C5), 118.1 (C6), 75.4 (C4), 71.7 (C3), 37.2 (C1), 29.4 (C2); HRMS(ESI) *m*/*z* calcd for $[C_6H_{13}O_2N + H]^+$ 132.1025, found 132.1031.

Iodocyclization/Carbamate Annulation. To a solution of alkenylamine hydrochloride **29** (240 mg, 1.4 mmol) in saturated aq. $NaHCO_3$ (7.2 mL) (made fresh immediately prior to use) were added I_2 (1900 mg, 7.5 mmol) and $NaHCO_3$ (1400 mg, 17 mmol). The solution was stirred at room temperature for 5 days, filtered, and concentrated under reduced pressure. The products, all as white solids, were separated by repeated use of silica plug (MeOH in EtOAc, 0−10% v/v) and reversed-phase columns (octyl-bonded end-capped silica beads) eluting in H_2O (for carbamates **30**, **31a**, and **31b**) and MeOH (for iodide **32**). Yield of **30** = 10−30%.

1-N,6-O-Carbonyl-1,2,4-trideoxy-1,4-imino-L-allitol (30). $[\alpha]_D^{25}$ = −0.5 (*c* = 0.4, MeOH); IR (film) 3390, 3331, 2965, 2914, 1719, 1634, 1517, 1477, 1455, 1133, 1110, 1070 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.19−4.27 (m, 2H, H3 and H6a), 3.94−4.03 (m, 2H, H5 and H6b), 3.47 (dd, $J_{1,2a}$ = 6.1, $J_{1,2b}$ = 9.0 Hz, 2H, H1), 3.28 (t, $J_{4,5}$ = $J_{3,4}$ = 7.7 Hz, 1H, H4), 2.24 (dq, $J_{1,2a}$ = $J_{2a,3}$ = 6.1, $J_{2a,2b}$ = 12.6 Hz, 1H, H2a), 1.80 (dq, $J_{1,2b}$ = $J_{2b,3}$ = 9.0, $J_{2a,2b}$ = 12.6 Hz, 1H, H2b); ^{13}C NMR (150 MHz, D_2O) δ 154.4 (C═O), 74.0 (C3), 69.2 (C6), 64.8 (C4), 64.2 (C5), 44.2 (C1), 30.2 (C2); HRMS(ESI) *m*/*z* calcd for $[C_7H_{11}O_4N + Na]^+$ 196.0586, found 196.0579.

1-N,6-O-Carbonyl-5-epi-fagomine (31a) and 1-N,6-O-Carbonylfagomine (31b). IR (film) 3409, 2948, 2840, 1632, 1462, 1403, 1092, 1010 cm^{-1}.

Data for the major isomer (**31a**): ^1H NMR (500 MHz, D_2O) δ 4.53 (t, $J_{5,6a}$ = $J_{6a,6b}$ = 9.0 Hz, 1H, H6a), 4.34 (dd, $J_{5,6b}$ = 6.0, $J_{6a,6b}$ = 9.0 Hz, 1H, H6b), 4.23 (ddd, $J_{4,5}$ = 2.5, $J_{5,6b}$ = 6.0, $J_{5,6a}$ = 9.0 Hz, 1H, H5), 4.06 (dd, $J_{3,4}$ = 3.2, $J_{2a,3}$ = 6.3 Hz, 1H, H3), 3.73 (m, 1H, H4), 3.56 (dd, $J_{1a,2a}$ = 6.3, $J_{1a,1b}$ = 13.5 Hz, 1H, H1a), 3.23 (td, $J_{1b,2a}$ = 3.7, $J_{1a,1b}$ = $J_{1b,2b}$ = 13.5 Hz, 1H, H1b), 1.95−2.02 (m, 1H, H2a), 1.64 (d, $J_{2a,2b}$ = 15.0 Hz, 1H, H2b); ^{13}C NMR (125 MHz, D_2O) δ 159.2 (C═O), 66.5 (C3), 66.5 (C4), 64.1 (C6), 53.2 (C5), 35.2 (C1), 24.4 (C2); HRMS(ESI) *m*/*z* calcd for $[C_7H_{11}O_4N + Na]^+$ 196.0586, found 196.0587.

Data for the minor isomer (**31b**): ^1H NMR (500 MHz, D_2O) δ 4.53 (t, $J_{5,6a}$ = $J_{6a,6b}$ = 9.0 Hz, 1H, H6a), 4.31 (dd, $J_{5,6b}$ = 5.0, $J_{6a,6b}$ = 9.0 Hz, 1H, H6b), 3.68−3.71 (m, 1H, H1a), 3.67 (ddd, $J_{5,6b}$ = 5.0, $J_{5,6a}$ = 9.0, $J_{4,5}$ = 9.5 Hz, 1H, H5), 3.62 (ddd, $J_{2b,3}$ = 5.0, $J_{3,4}$ = 9.5, $J_{2a,3}$ = 11.5 Hz, 1H, H3), 3.34 (t, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, 1H, H4), 3.03 (td, $J_{1b,2a}$ = 3.2, $J_{1a,1b}$ = $J_{1b,2b}$ = 13.0 Hz, 1H, H1b), 1.92−1.98 (m, 1H, H2a), 1.51 (ddt, $J_{2b,3}$ = 5.0, $J_{1a,2b}$ = 11.7, $J_{1b,2b}$ = $J_{2a,2b}$ = 13.0 Hz, 1H, H2b); ^{13}C NMR (125 MHz, D_2O) δ 158.7 (C═O), 74.5 (C4), 71.4 (C3), 66.5 (C6), 57.6 (C5), 38.7 (C1), 30.8 (C2); HRMS(ESI) *m*/*z* calcd for $[C_7H_{11}O_4N + Na]^+$ 196.0586, found 196.0587.

1-Amino-1-N,3-O-carbonyl-1,2,6-trideoxy-6-iodo-L-gulitol (32). R_f = 0.26 (10% MeOH in EtOAc); $[\alpha]_D^{26}$ = −8.9 (*c* = 0.67, MeOH); IR (film) 3367, 2928, 1680, 1488, 1457, 1300, 1223, 1108, 1021, 523 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.50 (dt, *J* = 3.3, *J* = 9.9 Hz, 1H, H3), 3.72−3.81 (m, 2H, H4 and H5), 3.44 (dd, *J* = 3.9, *J* = 10.5 Hz, 1H, H6a), 3.29−3.37 (m, 3H, H1a,b and H6b), 1.90−2.01 (m, 2H, H2a,b); ^{13}C NMR (125 MHz, D_2O) δ 154.7 (C═O), 76.1 (C3), 71.8, 68.1 (C4 and C5), 35.8 (C1), 19.6 (C2), 6.2 (C6); HRMS(ESI) *m*/*z* calcd for $[C_7H_{12}O_4NI + H]^+$ 301.9889, found 301.9888.

3,5-Di-*O*-acetyl-1-*N*,6-*O*-carbonyl-1,2,4-trideoxy-1,4-imino-L-allitol (33). Carbamate (**30**) (124.7 mg, 0.7 mmol) was subjected to dry pyridine (1.0 mL) and acetic anhydride (1.0 mL) at rt under an argon atmosphere overnight (14 h). After concentration, the crude compound was dry-loaded on silica before gradient column chromatography (petroleum ether to petroleum ether/EtOAc, 1/1 v/v). Acetylated carbamate **33** was recovered as a white solid. R_f = 0.44 (5% MeOH in EtOAc); $[\alpha]_D^{27}$ = +19.9 (*c* = 0.1, MeOH); IR (film) 2957, 2925, 1741, 1711, 1430, 1367, 1238, 1070, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.16 (dt, $J_{3,4}$ = 6.5, $J_{2a,3}$ = $J_{2b,3}$ = 7.5 Hz, 1H, H3), 5.06 (td, $J_{5,6a}$ = 4.9, $J_{4,5}$ = $J_{5,6b}$ = 9.0 Hz, 1H, H5), 4.32 (dd, $J_{5,6a}$ = 4.9, $J_{6a,6b}$ = 11.0 Hz, 1H, H6a), 4.05 (dd, $J_{5,6b}$ = 9.0, $J_{6a,6b}$ = 11.0 Hz, 1H, H6b), 3.79 (dt, $J_{1a,2a}$ = $J_{1a,2b}$ = 7.5, $J_{1a,1b}$ = 11.0 Hz, 1H, H1a), 3.50−3.57 (m, 2H, H1b and H4), 2.32 (dt, $J_{1a,2a}$ = $J_{1b,2a}$ = $J_{2a,3}$ = 7.5, $J_{2a,2b}$ = 14.5 Hz, 1H, H2a), 2.11 (s, 3H, Me), 2.08 (s, 3H, Me), 1.88 (dt, $J_{1a,2b}$ = $J_{1b,2b}$ = $J_{2b,3}$ = 7.5, $J_{2a,2b}$ = 14.5 Hz, 1H, H2b); ^1H NMR (300 MHz, CD_3OD) δ 5.19 (dd, $J_{3,4}$ = 7.2, $J_{2b,3}$ = 7.9 Hz, 1H, H3), 5.12 (dd, $J_{5,6a}$ = 4.7, $J_{4,5}$ = $J_{5,6b}$ = 8.7 Hz, 1H, H5), 4.32 (dd, $J_{5,6a}$ = 4.7, $J_{6a,6b}$ = 10.8 Hz, 1H, H6a), 4.11 (dd, $J_{5,6b}$ = 8.7, $J_{6a,6b}$ = 10.8 Hz, 1H, H6b), 3.66 (dt, $J_{1a,2a}$ = $J_{1a,2b}$ = 8.0, $J_{1a,1b}$ = 11.1 Hz, 1H, H1a), 3.62 (dd, $J_{3,4}$ = 7.2, $J_{4,5}$ = 8.7 Hz, 1H, H4), 3.49 (ddd, $J_{1b,2b}$ = 4.7, $J_{1b,2a}$ = 9.1, $J_{1a,1b}$ = 11.1 Hz, 1H, H1b), 2.34 (dddd, $J_{1b,2b}$ = 4.7, $J_{2b,3}$ = 7.9, $J_{1a,2b}$ = 8.0, $J_{2a,2b}$ = 12.9 Hz, 1H, H2a), 2.07 (s, 3H, Me), 2.05 (s, 3H, Me), 1.88 (ddt, $J_{1a,2b}$ = $J_{2b,3}$ = 7.9, $J_{1b,2b}$ = 9.1, $J_{2a,2b}$ = 12.9 Hz, 1H, H2b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1 (C═O, Ac), 169.9 (C═O, Ac), 151.6 (C═O), 75.2 (C3), 66.7 (C6), 65.7 (C5), 63.2 (C4), 44.9 (C1), 28.8 (C2), 20.9 (CH_3, Ac), 20.8 (CH_3, Ac); HRMS(ESI) *m*/*z* calcd for $[C_{11}H_{15}O_6N + Na]^+$ 280.0797, found 280.0791.

1,2,4-Trideoxy-1,4-imino-L-allitol (34). Carbamate (**30**) (10.6 mg, 0.061 mmol) was dissolved in EtOH (1 mL), and NaOH (26 mg, 0.6 mmol) was added. The solution was refluxed for 2 h, neutralized with aq. HCl (1 M), and loaded on silica for chromatography (DCM/EtOH/MeOH/35% aq. NH_3, 55/2/2/1 to 15/2/2/1 v/v/v/v). Product **34** was obtained as a white solid (8.0 mg, 0.054 mmol, 89%). R_f = 0.19 (DCM/EtOH/MeOH/35% aq. NH_3, 5/2/2/1 v/v/v/v); $[\alpha]_D^{26}$ = −1.8 (*c* = 0.41, MeOH); IR (film) 3309, 2956, 2927, 1629, 1420, 1089, 1041 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.33 (dt, $J_{2b,3}$ = $J_{3,4}$ = 4.3, $J_{2a,3}$ = 6.2 Hz, 1H, H3), 3.78 (dd, $J_{4,5}$ = 4.3, $J_{5,6}$ = 10.3 Hz, 1H, H5), 3.44−3.52 (m, 2H, H6), 3.35 (t, $J_{3,4}$ = $J_{4,5}$ = 4.3 Hz, 1H, H4), 3.21 (dd, $J_{1,2b}$ = 6.3, $J_{1,2a}$ = 8.1 Hz, 2H, H1), 2.02 (ddd, $J_{2a,3}$ = 6.2, $J_{1,2a}$ = 8.1, $J_{2a,2b}$ = 14.2 Hz, 1H, H2a), 1.78 (ddd, $J_{2b,3}$ = 4.3, $J_{1,2b}$ = 6.3, $J_{2a,2b}$ = 14.2 Hz, 1H, H2b); ^{13}C NMR (125 MHz, D_2O) δ 69.4 (C3), 68.4 (C5), 67.1 (C4), 62.5 (C6), 44.1 (C1), 32.6 (C2); HRMS(ESI) *m*/*z* calcd for $[C_6H_{13}O_3N + H]^+$ 148.0974, found 148.0978.

5-*epi*-Fagomine (26) and Fagomine (3). Carbamates **31a** and **31b** (11.7 mg, 0.07 mmol) were dissolved in EtOH (1 mL), and NaOH (80 mg, 2 mmol) was added. The solution was refluxed for 2 h, neutralized with aq. HCl (1 M), and concentrated in vacuo. Purification by gradient silica column chromatography (DCM/EtOH/MeOH/35% aq. NH_3, 45/2/2/1 to 15/2/2/1 v/v/v/v) gave the products **3** and **26** as a white solid and a mixture of diastereomers (12.4 mg, 0.07 mmol, quant.).

Data for 5-*epi*-fagomine (**26**): R_f = 0.24 (DCM/EtOH/MeOH/35% aq. NH_3, 5/2/2/1 v/v/v/v); $[\alpha]_D^{29}$ = −8.9 (*c* = 0.63, MeOH); IR (film) 3364, 2970, 1425, 1366, 1217, 1079 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.02 (m, 1H, H3), 3.93 (m, 1H, H4), 3.85 (dd, $J_{5,6a}$ = 4.9, $J_{6a,6b}$ = 12.0 Hz, 1H, H6a), 3.80 (dd, $J_{5,6b}$ = 8.5, $J_{6a,6b}$ = 12.0 Hz, 1H, H6b), 3.54 (dd, $J_{5,6a}$ = 4.9, $J_{5,6b}$ = 8.5 Hz, 1H, H5), 3.20−3.31 (m, 2H, H1a,b), 2.16−2.24 (m, 1H, H2a), 1.84 (d, $J_{2a,2b}$ = 14.5 Hz, 1H, H2b); ^{13}C NMR (125 MHz, D_2O) δ 65.8 (C4), 64.8 (C3), 59.5 (C6), 55.8 (C5), 38.9 (C1), 23.6 (C2); HRMS(ESI) *m*/*z* calcd for $[C_6H_{13}O_3N + H]^+$ 148.0974, found 148.0968.

Data for fagomine (**3**): R_f = 0.33 (DCM/EtOH/MeOH/35% aq. NH_3, 5/2/2/1 v/v/v/v); $[\alpha]_D^{29}$ = +8.4 (*c* = 0.27, MeOH); IR (film) 3367, 2930, 1461, 1271, 1073 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 3.93 (dd, $J_{5,6a}$ = 3.2, $J_{6a,6b}$ = 12.5 Hz, 1H, H6a), 3.88 (dd, $J_{5,6b}$ = 5.5, $J_{6a,6b}$ = 12.5 Hz, 1H, H6b), 3.71 (ddd, $J_{2a,3}$ = 4.9, $J_{3,4}$ = 9.0, $J_{2b,3}$ = 11.7 Hz, 1H, H3), 3.52 (t, $J_{3,4}$ = $J_{4,5}$ = 9.0 Hz, 1H, H4), 3.44 (ddd, $J_{1a,2a}$ = 2.5, $J_{1a,2b}$ = 4.1, $J_{1a,1b}$ = 13.5 Hz, 1H, H1a), 3.12−3.16 (m, 1H, H5), 3.10 (dd, $J_{1b,2a}$ = 2.5, $J_{1b,2b}$ = $J_{1a,1b}$ = 13.5 Hz, 1H, H1b), 2.21 (ddd, *J* = 2.5, $J_{2a,3}$ = 4.9, $J_{2a,2b}$ = 13.5 Hz, 1H, H2a), 1.72 (ddt, $J_{1a,2b}$ = 4.1, $J_{2b,3}$ = 11.7, $J_{1a,2b}$ = $J_{2a,2b}$ = 13.5 Hz, 1H, H2b); ^{13}C NMR (125 MHz, D_2O) δ 70.4 (C3), 69.5 (C4), 60.0 (C5), 57.6 (C6), 41.8 (C1), 28.5 (C2); HRMS(ESI) *m*/*z* calcd for $[C_6H_{13}O_3N + H]^+$ 148.0974, found 148.0968.

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4,5-Di-*O*-acetyl-1-amino-1-*N*,3-*O*-carbonyl-1,2,6-trideoxy-6-iodo-L-gulitol (35). Iodide **32** (20.4 mg, 0.07 mmol) was subjected to dry pyridine (0.5 mL) and acetic anhydride (0.5 mL) at room temperature under an argon atmosphere overnight (9 h). After concentration and repeated coevaporation with toluene to remove pyridine, the crude compound was dry-loaded on silica before gradient column chromatography (petroleum ether to petroleum ether/EtOAc, 1/1 v/v). Acetylated iodide **35** was recovered as a white solid in 48% yield (12.5 mg, 0.03 mmol). R_f = 0.44 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = +6.6 (c = 0.23, $CHCl_3$); IR (film) 3266, 3056, 2927, 1742, 1716, 1373, 1266, 1219, 1117, 1059, 1024, 598.7 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (br s, 1H, NH), 5.34 (dd, $J_{3,4}$ = 3.7, $J_{4,5}$ = 5.5 Hz, 1H, H4), 5.14 (dd, $J_{5,6a}$ = 4.5, $J_{4,5}$ = $J_{5,6b}$ = 5.5 Hz, 1H, H5), 4.47 (d, $J_{2b,3}$ = 10.8 Hz, 1H, H3), 3.46 (dd, $J_{5,6a}$ = 4.5, $J_{6a,6b}$ = 11.4 Hz, 1H, H6a), 3.37−4.43 (m, 2H, H1a,b), 3.36 (dd, $J_{5,6b}$ = 5.5, $J_{6a,6b}$ = 11.4 Hz, 1H, H6b), 2.16 (s, 3H, 4-OAc), 2.13 (s, 3H, 5-OAc), 2.00 (d, $J_{2a,2b}$ = 14.2 Hz, 1H, H2a), 1.79−1.89 (m, 1H, H2b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2 (C═O, 4-Ac), 169.9 (C═O, 5-Ac), 152.9 (C═O), 75.0 (C3), 73.4 (C4), 70.4 (C5), 38.9 (C1), 22.8 (C2), 20.9 (CH_3, Ac), 20.6 (CH_3, Ac), 3.3 (C6); HRMS(ESI) m/z calcd for $[C_{11}H_{16}O_6NI + H]^+$ 386.0101, found 386.0094.

1-Amino-1-*N*,3-*O*-carbonyl-1,2,6-trideoxy-6-iodo-4,5-*O*-isopropylidene-L-gulitol (36). Iodide **32** (8.8 mg, 0.3 mmol) was dissolved in acetone (0.45 mL), dimethoxypropane (0.45 mL), and MeOH (0.25 mL). A 100 μL aliquot of pTsOH·H_2O in acetone (2.85 mg/mL) was added, and the reaction mixture was stirred at room temperature overnight (17 h). The mixture was then neutralized with Dowex−OH^-, filtered, and concentrated to give a white solid **36** (7.2 mg, 0.02 mmol, 72%) that was used without further purification. R_f = 0.49 (10% MeOH in EtOAc); $[\alpha]_D^{23}$ = −23.0 (c = 0.48, $CHCl_3$); IR (film) 3282, 2985, 2930, 1700, 1487, 1456, 1421, 1372, 1294, 1239, 1214, 1107, 1069, 554 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3/CD_3OD$ 95/5) δ 4.40 (app dt, $J_{3,4}$ = 2.2, $J_{2a,3}$ = 10.0 Hz, 1H, H3), 4.20 (dt, $J_{5,6a}$ = $J_{5,6b}$ = 4.7, $J_{4,5}$ = 7.5 Hz, 1H, H5), 3.83 (dd, $J_{3,4}$ = 2.2, $J_{4,5}$ = 7.5 Hz, 1H, H4), 3.41 (ddd, $J_{1a,2b}$ = 3.7, $J_{1a,2a}$ = 5.8, $J_{1a,1b}$ = 11.0 Hz, 1H, H1a), 3.36 (m, 1H, NH), 3.31−3.35 (m, 1H, H1b), 3.31 (dd, $J_{5,6a}$ = 4.7, $J_{6a,6b}$ = 10.8 Hz, 1H, H6a), 3.28 (dd, $J_{5,6b}$ = 4.7, $J_{6a,6b}$ = 10.8 Hz, 1H, H6b), 2.06 (dtd, $J_{1a,2a}$ = 5.8, $J_{1b,2a}$ = $J_{2a,3}$ = 10.0, $J_{2a,2b}$ = 14.0 Hz, 1H, H2a), 1.98 (m, 1H, H2b), 1.43 (s, 3H, Me), 1.40 (s, 3H, Me); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$ 95/5) δ 154.4 (C═O), 110.7 (iPr-$C(CH_3)_2$), 82.4 (C4), 75.1 (C3), 74.6 (C5), 38.7 (C1), 27.6, 27.0 (iPr-$C(CH_3)_2$), 23.3 (C2), 6.1 (C6); HRMS(ESI) m/z calcd for $[C_{10}H_{16}O_4NI + H]^+$ 342.0202, found 342.0201.

D-*threo*-1-Amino-1-*O*,3-*N*-carbonyl-1,2,5,6-tetradeoxyhex-5-enose (37). Iodoacetonide **36** (6.8 mg, 0.02 mmol) was subjected to DCM (0.3 mL), AcOH (0.1 mL), and zinc (27.6 mg, 0.2 mmol) and stirred at 40−55 °C for 12 days. The reaction mixture was filtered through silica and concentrated to remove zinc. The crude product was purified by silica column chromatography (petroleum ether to petroleum ether/EtOAc, 1/3 v/v), yielding **37** as a white solid (2.4 mg, 0.015 mmol, 77%). R_f = 0.22 (10% MeOH in EtOAc); $[\alpha]_D^{29}$ = −12.8 (c = 0.16, MeOH); IR (film) 3373, 2926, 2856, 1682, 1489, 1459, 1294, 1108, 1071, 1028, 946 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.92 (ddd, $J_{4,5}$ = 6.6, $J_{5,6\text{-}cis}$ = 10.5, $J_{5,6\text{-}trans}$ = 17.3 Hz, 1H, H5), 5.40 (app dt, $J_{4,6\text{-}trans}$ = 1.2, $J_{5,6\text{-}trans}$ = 17.3 Hz, 1H, H6-*trans*), 5.32 (app dt, $J_{4,6\text{-}cis}$ = 1.2, $J_{5,6\text{-}cis}$ = 10.5 Hz, 1H, H6-*cis*), 4.35 (ddd, $J_{2a,3}$ = 3.0, $J_{3,4}$ = 5.7, $J_{2b,3}$ = 10.5 Hz, 1H, H3), 4.24 (ddt, $J_{4,6\text{-}trans}$ = $J_{4,6\text{-}cis}$ = 1.2, $J_{3,4}$ = 5.7, $J_{4,5}$ = 6.6 Hz, 1H, H4), 3.33 (ddd, $J_{1a,2a}$ = 3.0, $J_{1a,2b}$ = 6.9, $J_{1a,1b}$ = 12.0 Hz, 1H, H1a), 3.32 (ddd, $J_{1b,2a}$ = 4.5, $J_{1b,2b}$ = 10.5, $J_{1a,1b}$ = 12.0 Hz, 1H, H1b), 1.99 (ddt, $J_{2a,3}$ = $J_{1a,2a}$ = 3.0, $J_{1b,2a}$ = 4.5, $J_{2a,2b}$ = 14.1 Hz, 1H, H2a), 1.84 (dtd, $J_{1a,2b}$ = 6.9, $J_{1b,2b}$ = $J_{2b,3}$ = 10.5, $J_{2a,2b}$ = 14.1 Hz, 1H, H2b); ^{13}C NMR (150 MHz, D_2O) δ 156.8 (C═O), 134.9 (C5), 118.4 (C6), 80.2 (C3), 73.5 (C4), 37.8 (C1), 21.7 (C2); HRMS(ESI) m/z calcd for $[C_7H_{11}O_3N + H]^+$ 158.0817, found 158.0805.

D-*threo*-4-*O*-Acetyl-1-amino-1-*O*,3-*N*-carbonyl-1,2,5,6-tetradeoxyhex-5-enose (38). Iodide **35** (10.7 mg, 0.03 mmol) was dissolved in THF (0.3 mL), and H_2O (0.06 mL), AcOH (0.06 mL), and zinc (62 mg, 0.6 mmol) were added. The resulting mixture was then stirred at room temperature for 1 h. The reaction mixture was filtered through Celite, washed with DCM and EtOH, and concentrated before coevaporation with H_2O and toluene to remove traces of AcOH. The crude product was purified by silica column chromatography (petroleum ether to petroleum ether/EtOAc, 1/3 v/v) to give **38** as a white solid (5.5 mg, 0.03 mmol, quant.). R_f = 0.38 (10% MeOH in EtOAc); $[\alpha]_D^{25}$ = −11.0 (c = 0.13, $CHCl_3$); IR (film) 3278, 2925, 2854, 1703, 1489, 1459, 1424, 1372, 1294, 1227, 1104, 1023, 950, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddd, $J_{4,5}$ = 6.5, $J_{5,6\text{-}cis}$ = 10.5, $J_{5,6\text{-}trans}$ = 17.0 Hz, 1H, H5), 5.51 (br s, 1H, NH), 5.44 (d, $J_{4,5}$ = 6.5 Hz, 1H, H4), 5.43 (d, $J_{5,6\text{-}trans}$ = 17.0 Hz, 1H, H6-*trans*), 5.37 (d, $J_{5,6\text{-}cis}$ = 10.5 Hz, 1H, H6-*cis*), 4.39 (ddd, J = 2.5, J = 5.5, $J_{2b,3}$ = 10.5 Hz, 1H, H3), 3.35−3.45 (m, 2H, H1a,b), 2.13 (s, 3H, Me), 1.94−2.01 (m, 1H, H2a), 1.86 (dtd, J = 6.5, J = $J_{2b,3}$ = 10.5, $J_{2a,2b}$ = 14.0 Hz, 1H, H2b); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (C═O, Ac), 153.8 (C═O), 131.5 (C5), 120.4 (C6), 77.5 (C3), 74.5 (C4), 39.0 (C1), 22.5 (C2), 21.2 (CH_3, Ac); HRMS(ESI) m/z calcd for $[C_9H_{13}O_4N + H]^+$ 200.0923, found 200.0918.

(3*R*,4*R*)-6-Aminohex-1-ene-3,4-diol Hydrochloride (29). Acetylated alkene carbamate **38** (5.7 mg, 0.03 mmol) was dissolved in EtOH (1 mL), and NaOH (80 mg, 2 mmol) was added. The solution was refluxed for 1 h, neutralized with aq. HCl (1.2 M), and then concentrated in vacuo. Purification by gradient silica column chromatography (DCM/EtOH/MeOH/35% aq. NH_3, 65/2/2/1 to 5/2/2/1 v/v/v/v) gave the alkenylamine, which was converted into the HCl salt **29** as a white solid (3.3 mg, 0.02 mmol, 69%) by the addition of HCl (1.2 M, aq.) and concentration. R_f = 0.16 (DCM/EtOH/MeOH/35% aq. NH_3, 5/2/2/1 v/v/v/v); $[\alpha]_D^{27}$ = +31.8 (c = 0.2, MeOH).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra (^1H and ^{13}C) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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