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A Versatile Approach to *N*-Alkylated 1,4-Dideoxy-1,4-imino-D-arabinitols and 1,4-Dideoxy-1,4-imino-L-xylitols

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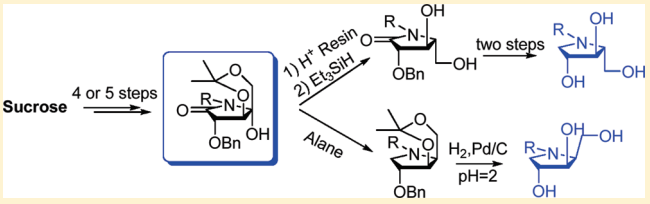
Supporting Information

ABSTRACT: A versatile and concise synthesis of *N*-alkylated 1,4-dideoxy-1,4-imino-D-arabinitol and 1,4-dideoxy-1,4-imino-L-xylitol derivatives is described. These were prepared using pseudohemiketal lactams as key intermediates, which in turn were obtained from sucrose. The key intermediates were prepared by a diastereospecific tandem reaction which facilitated the introduction of various substituents on the nitrogen atom of the iminosugars.



INTRODUCTION

Iminosugars, widespread in plants and microorganisms, are carbohydrate mimetics in which the endocyclic oxygen is replaced by nitrogen.[1] These kinds of compounds raise many synthetic challenges and open the way to treat a wide range of diseases, including diabetes,[2,3] viral infections,[4,5] tumor metastasis,[6] and lysosomal storage disorders.[7] Two iminosugar-based drugs have been approved: *N*-hydroxyethyldeoxynojirimycin (*N*-hydroxyethyl DNJ, Miglitol, Figure 1) in 1996 for the treatment of type II diabetes, and *N*-butyl-deoxynojirimycin (*N*B-DNJ, Miglustat, Figure 1) in 2003 as the first oral treatment for Gaucher disease, a severe lysosomal storage disorder. Both of them are *N*-alkylated iminosugars. *N*-Alkylated iminosugars also show antiviral activities. For instance, the long alkyl-chain compound *N*-nonyl-DNJ (*N*N-DNJ, Figure 1) can block the HCV ion channel p7.[8,9] Compared to the parent iminosugars, the *N*-alkylated structures tend to exhibit better biological activities in vivo, partially due to the improvement of lipophilicity of the compounds, and sometimes because the alkylated chains contribute additional binding to the pocket of the receptor.

1,4-Dideoxy-1,4-imino-D-arabinitol (known as DAB 1, Figure 1), isolated from two types of leguminose plants, *Arachniodes standishii*[10] and *Angylocalyx boutiqueanus*,[11] was shown to be a good inhibitor with a broad inhibitory spectrum toward mammalian glycosidases such as ER α-glucosidase II, Golgi α-mannosidase I/II, intestinal isomaltase, and trehalase.[12,13] In primary rat hepatocytes, DAB 1 was found to be one of the most potent inhibitors of basal- and glucagon-stimulated glycogenolysis ever reported[14] and also one of the most powerful anti-HIV agents.[15] 1,4-Dideoxy-1,4-imino-L-xylitol (Figure 1)[16,17] as the epimer of DAB 1 was also proven to be a potential glycosidase inhibitor.[18] Because of their dazzling activities, several synthetic strategies have been developed to prepare these valuable compounds from both carbohydrate[18−20] and noncarbohydrate sources.[21,22]

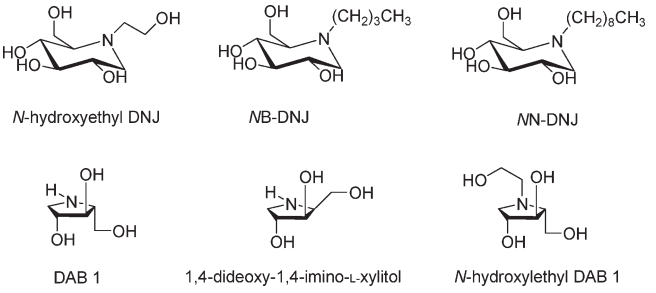


Figure 1. Structures of some iminosugars.

However, more efficient approaches to prepare this type of compounds are still needed. On the other hand, since many iminosugars have better activities after *N*-alkylation, the *N*-alkylated DAB 1 and 1,4-dideoxy-1,4-imino-L-xylitol derivatives could be more active *in vivo*. In fact, some *N*-alkylated DAB 1 analogues are also naturally occurring compounds. For example, the *N*-hydroxyethylated derivative of DAB 1 (*N*-hydroxyethyl DAB 1) (Figure 1) was isolated from the seeds of African legume *Angylocalyx pynaertii*.[23] However, the preparation of these *N*-alkylated iminosugars has not been explored widely to date.

Previously, we reported a concise, one-pot tandem reaction starting from the sugar lactones which provided a facile and efficient approach to construct the *N*-alkylated sugar lactams.[24] On the basis of these findings, we wanted to explore the synthesis of naturally occurring DAB 1 and 1,4-dideoxy-1,4-imino-L-xylitol as well as their *N*-alkylated derivatives. Herein, we describe a short and versatile route to these types of iminosugars using the same lactam, which was prepared from sucrose, as an intermediate.

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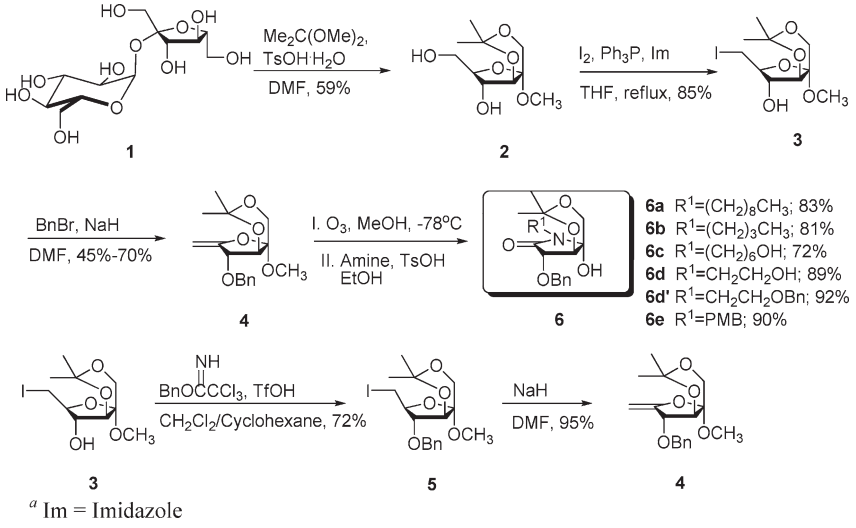
Scheme 1. Synthesis of Compounds 6a−e from Sucrose 1[a]



[a] Im = Imidazole

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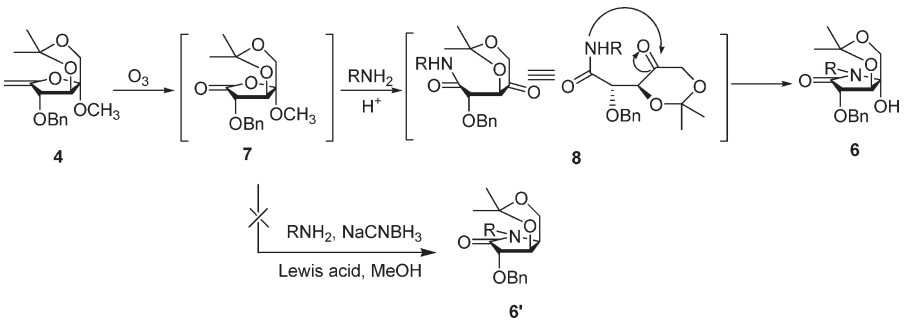
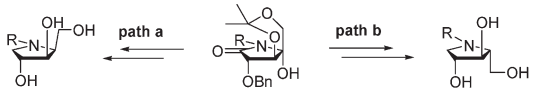
Scheme 2. Proposed Mechanism for the Formation of Compound 6 from Compound 4



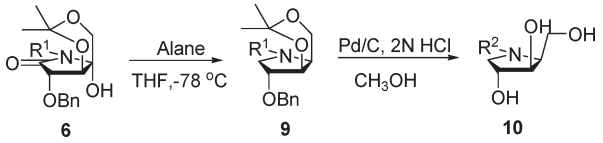
Scheme 3. Switchable Conversion Paths of Compound 6



RESULTS AND DISCUSSION

The structural resemblance makes fructose a potentially good parent structure for DAB 1 and its epimer. However, because of the presence of two primary hydroxyl groups and anomerization, it is difficult to obtain a single protected isomer of fructofuranoside with a defined anomeric configuration. The method originally reported by Richardson et al.[25] and improved by Madsen et al.[26] gave us a solution to this problem and allowed us to choose inexpensive sucrose (**1**) as the starting material. Hence, following the reported procedure, sucrose (**1**) was converted to a fructose derivative in which the two primary hydroxyl groups were differentiated and one primary hydroxyl group, together with the 3-hydroxyl group, was selectively protected with an isopropylidene group, yielding the α-methyl fructofuranoside **2**. The remaining primary hydroxyl group of compound **2** was substituted by an iodine atom to give the iodide **3**; subsequent elimination and benzylation gave compound **4** in 45−70% yields. The yield was lower (45−55%) when this reaction was carried out on a scale greater than 500 mg. Therefore, an alternative stepwise procedure, especially more suitable for a larger scale, was also attempted for the preparation of compound **4**. In this case, the iodide **3** was treated with benzyl trichloroacetimidate

Table 1. Preparation of *N*-Substituted 1,4-Dideoxy-1, 4-imino-L-Xylitols



entry	R^1, R^2	product **9**	product **10**
1	$R^1 = R^2 = (CH_2)_8CH_3$	**9a**, 94%	**10a**, 98%
2	$R^1 = R^2 = (CH_2)_3CH_3$	**9b**, 95%	**10b**, 95%
3	$R^1 = R^2 = (CH_2)_6OH$	**9c**, 87%	**10c**, 97%
4	$R^1 = R^2 = CH_2CH_2OH$	**9d**, 96%	**10d**, 95%
5	R^1 = PMB, R^2 = H	**9e**, 95%	**10e**, 97%

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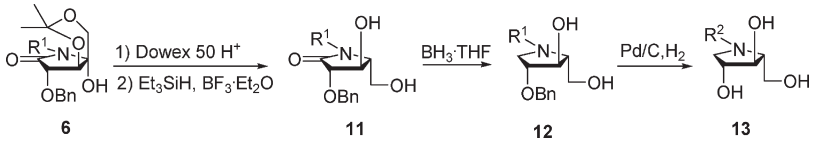
Table 2. Preparation of *N*-Substituted DAB 1



entry	R^1, R^2	product **11**	product **12**	product **13**
1	$R^1 = R^2 = (CH_2)_8CH_3$	**11a**, 91%	**12a**, 95%	**13a**, 98%
2	$R^1 = R^2 = (CH_2)_3CH_3$	**11b**, 84%	**12b**, 96%	**13b**, 97%
3	$R^1 = CH_2CH_2OBn$, $R^2 = CH_2CH_2OH$	**11c**, 94%	**12c**, 98%	**13c**, 98%
4	R^1 = PMB, R^2 = H	**11d**, 74%	**12d**, 75%[a]	**13d**, 97%

[a] $LiAlH_4$ was used instead of $BH_3 \cdot THF$.

under acidic conditions to protect the hydroxyl group; this was followed by a base-promoted elimination of hydrogen iodide, affording compound **4** in 68% overall yield from **3** (Scheme 1).

With compound **4** in hand, the key one-pot tandem reaction was next explored. The sequence began with ozonolysis, followed by a tandem reaction with various amines. In fact, we first tried the reaction with amines using a typical Lewis acid-catalyzed reductive amination procedure (from compound **4** to **6′** via intermediate **7**, Scheme 2). However, the reductive amination of amine ketone was much more difficult than that of amine aldehyde in our previous work;[24] most of the alkylamine did not react with the lactone **7**. Only allylamine provided the reductive amination product in 20% yield as a diastereomeric mixture. When acetic acid was used as catalyst, compound **6** instead of compound **6′** was isolated in moderate yield. Subsequent experiments showed that the reaction is acid-catalyzed ester−amide exchange followed by nucleophilic cyclization and that the use of the reducing reagent $NaCNBH_3$ is not necessary. To increase the reaction yield, a series of acids including both Lewis acids such as $ZnCl_2$ and $AlCl_3$ and protonic acids such as trifluoroacetic acid and toluene sulfonic acid (*p*-TsOH) were also checked, and *p*-TsOH gave the best result. Meanwhile, it was noticed that 1,3-isopropylidene group was partially hydrolyzed during the *p*-TsOH-catalyzed reaction; methanol was replaced by ethanol as the solvent to overcome this problem. A series of *N*-substituted iminosugar precursors **6a**−**e** were then prepared in high yields by the one-pot tandem reaction with the *cis*-1,3-dioxane product as the sole diastereomer (Scheme 1). The mechanism to form pseudohemiketal lactam **6** from lactone **7** was proposed as the following: the lactone ring-opening attacked by amine gave intermediate **8**, and the subsequent intramolecular nucleophilic addition of newly formed amide to the ketone led to the formation of compound **6** (Scheme 2). Theoretically, the nucleophilic addition should result in a pair of diastereomers. However, probably due to the ring strain, the nucleophilic addition tended to selectively take the direction to form less strain ring, which was *cis*-1,3-dioxane isomer.

Generally, the syntheses of *N*-substituted iminosugars starting from commercially available sugars involve the following steps: introduction of an amino functionality in the sugar skeleton, subsequent aminocyclization to generate the imino ring, and finally, at least one more step to introduce the side chain on the nitrogen atom. In contrast, our approach combined amination, cyclization, and installation of *N*-substituents in one step. Furthermore, it should be noted that this tandem reaction is a strain-controlled diastereospecific reaction, and the newly formed hydroxyl group in pseudohemiketal provides an opportunity for making both L-xylo- and D-arabino family of iminosugars.

The unique structure of compounds **6a**−**e** made it possible for further conversion to get the L or D family of *N*-alkylated iminosugars, respectively (Scheme 3). For path a, the carbonyl group of lactam and hydroxyl group in pseudohemiketal were both reduced. When $LiAlH_4$ was used as the reducing reagent and heated in the presence of compound **6** in refluxing THF, high yields were obtained for the compounds bearing *N*-nonyl or *N*-butyl chains; however, the yields were poor for the compounds with *N*-PMB or *N*-hydroxylethyl chains, since the benzyloxy group of C-2 was easily eliminated to afford α,β-unsaturated lactams in these cases. The elimination was avoided by using the alane reagent (3:1 $LiAlH_4/AlCl_3$)[27] as the reductant; when the reaction was performed at −78 °C, compounds **9a**−**e** were isolated in high yields. The protective groups were smoothly removed by hydrogenolysis and hydrolysis, providing the target compounds **10a**−**e** in the form of HCl salts (Table 1).

When we took the other path (path b in Scheme 3) to prepare *N*-substituted DAB 1, the 1,3-isopropylidene group in compound **6** was first removed to provide a diastereomeric mixture of α and β anomers (1:1 ratio). The subsequent $BF_3 \cdot OEt_2$-mediated reductive dehydroxylation of the diastereomeric mixture using the modified procedure originally reported by the Huang group,[22,28] led to the D-arabino-1,4-lactam **11a**−**d** as the sole isolated diastereoisomer in high overall yields (Table 2). It was found that the purity of $BF_3 \cdot OEt_2$ is essential in order to have a high yield, so it was freshly distilled from CaH_2 under reduced pressure before use.

The stereochemistry of compounds **11a**−**d** deserved further investigation. The best way to confirm the stereochemistry of the hydroxylmethyl group was to make both diastereoisomers and compare them. For the $BF_3 \cdot OEt_2$-mediated reaction, when compound **6b** reacted with untreated $BF_3 \cdot OEt_2$ and triethylsilane, it provided both D-arabino-1,4-lactam **11b** and L-xylono-1,4-lactam **14b** (Scheme 4). The vicinal coupling constants ($J_{3,4}$ > 6.0 Hz for 3,4-*cis* diastereomers and $J_{3,4}$ < 4.4 Hz for 3,4-*trans* diastereomers) are commonly used to determine the 3,4-relative stereochemistry of γ-lactams.[29,30] However, the configurations of compounds **11b** and **14b** could not be determined by this empirical rule, since they have very similar vicinal coupling constants (compound **11b**, $J_{3,4\text{-}trans}$ = 6.0 Hz; compound **14b**, $J_{3,4\text{-}cis}$ = 7.0 Hz). The assigned stereochemistry was supported by NOESY experiments after confirmation of the proton assignment by $^1H-^1H$ COSY experiments and also further confirmed by converting a series of compounds **11** to compounds **13**. As shown in Figure 2, H-2/H-4 and H-3/H-5 have a long-distance correlation in

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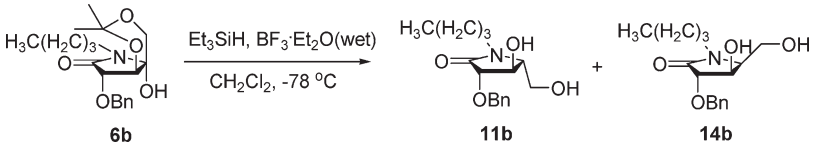
Scheme 4. Reductive Dehydroxylation with Untreated $BF_3 \cdot OEt_2$



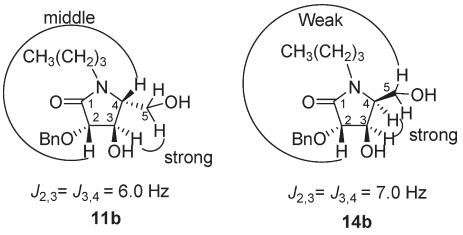


Figure 2. Selective NOE enhancements in NOE experiments.

compound **11b**, which suggests that the lactam has the D-arabino stereochemistry (which is 3,4-*trans* diastereomer), while in compound **14b** H-2/H-5 has a long-distance correlation and H-3/H-4 has a stronger correlation than that in compound **11b**, which suggests that the lactam **14b** has the L-xylono stereochemistry (which is the 3,4-*cis* diastereomer).

Subsequently, the carbonyl groups of lactams **11a**−**d** were reduced by $BH_3 \cdot THF$ or $LiAlH_4$ to obtain compounds **12a**−**d** (Table 2). The product was generated from the product−BH_3 adduct by stirring in methanol for 24−48 h. However, the adduct of *N*-PMB compound **12d** and BH_3 was too tight to release the product **12d** efficiently by stirring in methanol. Therefore, in this case, $LiAlH_4$ was used as reductant instead of $BH_3 \cdot THF$. It should be noticed that the unprotected hydroxyl group in *N*-hydroxylethyl lactam **6d** made the reductive reaction very complicated. Therefore, compound **6d′** instead of compound **6d** was used to prepare *N*-hydroxylethyl DAB 1 (compound **13c**). The aminoethanol was selectively *O*-benzylated using benzyl chloride before the reaction with lactone **7** to afford the desired lactam **6d′**.[31] Finally, compounds **12a**−**d** were subjected to catalytic hydrogenolysis to afford DAB 1 and its *N*-substituted derivatives in nearly quantitative yield. The spectroscopic data of compounds **10e** (1,4-dideoxy-1,4-imino-L-xylitol) and **13d** (DAB 1) coincided with those reported in the literatures,[19,22] which further confirmed the stereochemistry assigned to compounds **11** and **14** by the NOESY experiments.

CONCLUSION

In summary, we have developed a versatile and concise approach to the synthesis of *N*-alkylated 1,4-dideoxy-1,4-imino-D-arabinitol and 1,4-dideoxy-1,4-imino-L-xylitol derivatives starting from sucrose. The key reaction included the tandem transformation from exoglycal to pseudohemiketal lactams, which combined ozonolysis, amination, cyclization, and installation of *N*-substituents in one pot and in a diastereospecific manner. On the basis of the key lactam intermediates, a series of five-membered iminosugar analogues were prepared efficiently. The disclosed approach will facilitate construction of various *N*-alkylated 1,4-dideoxy-1,4-imino-D-arabinitol and 1,4-dideoxy-1,4-imino-L-xylitol derivatives as well as other related iminosugars with biological importance.

EXPERIMENTAL SECTION

Methyl 6-Deoxy-1,3-*O*-isopropylidene-α-D-xylulohex-5,6-enofuranoside (4). *Method 1.* Sodium hydride (60% in mineral oil, 160 mg, 4.0 mmol) was added to the solution of methyl 6-deoxy-6-iodo-1,3-*O*-isopropylidene-α-D-fructofuranoside **3**[26] (344 mg, 1.0 mmol) in dry DMF at 0 °C under argon atmosphere. The mixture was stirred for 15 min, and then benzyl bromide (0.24 mL, 2.0 mmol) was added dropwise. After being stirred for 5 h at 0 °C, the mixture was poured into ice−water and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether−ethyl acetate, 15:1 to 12:1 containing 1% Et_3N) to yield compound **4** as an oil (210 mg, 69%): R_f = 0.65 (petroleum ether−ethyl acetate, 3:1).

Method 2. Trifluoromethanesulfonic acid (50.0 μL) was added to a stirred solution of methyl 6-deoxy-6-iodo-1,3-*O*-isopropylidene-α-D-fructofuranoside **3** (1.0 g, 2.9 mmol), benzyl trichloroacetimidate[32] (2.2 g, 8.7 mmol), and activated 4 Å molecular sieves (powder) in dichloromethane (20 mL) and cyclohexane (40 mL) at 0 °C under argon atmosphere. The solution became light pink. When the color faded away, trifluoromethanesulfonic acid (30.0 μL) was added again until the reaction was completely finished (monitored by TLC). The reaction was quenched by sodium bicarbonate aqueous solution. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed by dichloromethane (10 mL × 3). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether−ethyl acetate, 10:1) to afford compound **5** as a syrup (908 mg, 72%): R_f = 0.75 (petroleum ether−-ethyl acetate, 3:1).

Sodium hydride (60% in mineral oil, 336 mg, 8.4 mmol) was added to a stirred solution of compound **5** (908 mg, 2.1 mmol) in DMF (50 mL) at 0 °C. After being stirred for 4 h, the mixture was poured into ice−water and extracted with ethyl acetate. The organic layer was dried with Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether−ethyl acetate, 15:1 to 12:1 containing 1% Et_3N) to yield compound **4** as an oil (608 mg, 95%): R_f = 0.65 (petroleum ether−ethyl acetate, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.42 (s, 3H), 3.36 (s, 3H), 3.85 (d, J = 12.2 Hz, 1H), 3.94 (d, J = 12.2 Hz, 1H), 4.15 (s, 1H), 4.24 (s, 1H), 4.29 (dd, J = 1.2, 2.4 Hz, 1H), 4.61−4.71 (m, 3H), 7.25−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 26.3, 49.6, 62.08, 62.12, 71.3, 77.3, 81.7, 88.0, 99.2, 104.2, 127.8, 127.9, 128.4, 137.5, 160.1; HRMS calcd for $C_{17}H_{22}O_5Na$ $[M + Na]^+$ 329.1359, found 329.1361.

(4a*S*,7*S*,7a*S*)-7-Benzyloxytetrahydro-4a-methoxy-2,2-dimethylfuro[3,2-*d*][1,3]dioxin-6-one (7). A solution of compound **4** (2.0 g, 6.5 mmol) in MeOH (50 mL) at −78 °C was bubbled with O_3 until the solution became pale blue. The solution was stirred at −78 °C for 3 min and then bubbled with N_2 until the solution became colorless. Methyl sulfide (1.0 mL) was added, and the mixture was stirred at −78 °C for 2 h. The solution was warmed to room temperature and concentrated under reduced pressure to provide lactone **7** (2.0 g, 100%) as a colorless oil, which was stable at −20 °C for several months: R_f = 0.60 (petroleum ether−ethyl acetate, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.41 (s, 3H), 3.44 (s, 3H), 3.82 (d, J = 12.5 Hz, 1H), 4.02 (s, 1H), 4.04 (d, J = 12.5 Hz, 1H), 4.14 (s, 1H), 4.74 (d, J = 11.9 Hz, 1H), 4.92 (d, J = 11.9 Hz, 1H), 7.26−7.41 (m, 5H); ^{13}C NMR

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(75 MHz, $CDCl_3$) δ 21.9, 25.3, 50.5, 61.1, 72.8, 75.1, 78.2, 100.3, 104.4, 128.2, 128.3, 128.5, 136.3, 172.3; HRMS calcd for $C_{16}H_{20}O_6Na$ $[M + Na]^+$ 331.1152, found 331.1147.

General Procedure for the Synthesis of *N*-Substituted Lactams 6a−e. Amine (NH_2R^1, 1.3 mmol) and toluenesulfonic acid (5.6 mg, 64.9 μmol) were added to a stirred solution of lactone **7** (200 mg, 0.65 mmol) in absolute ethyl alcohol (40 mL) at room temperature. The mixture was allowed to stir for 12−24 h (monitored by TLC) followed by quenching with saturated $NaHCO_3$ aqueous solution. After removal of the solvent, the product mixture was dissolved in ethyl acetate (80 mL) and washed with brine (20 mL × 2). The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel to provide the products **6a**−**e**.

(4a*R*,7*S*,7a*S*)-7-Benzyloxytetrahydro-4a-hydroxy-2,2-dimethyl-5-nonyl[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (6a): yield 83%; white foam after column chromatography (petroleum ether−ethyl acetate, 8:1 containing 1% Et_3N); R_f = 0.55 (petroleum ether−ethyl acetate, 3:1); IR ν_{max} (KBr)/cm^{-1}: 3379, 3065, 3032, 2993, 2927, 2856, 1685, 1497, 1457, 1427, 1377, 1341, 1272, 1226, 1203, 1158, 1099, 957, 859, 738, 700, 612, 519; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3H) 1.26−1.32 (m, 15H), 1.48 (s, 3H), 1.62 (brs, 2H), 2.94 (s, 1H), 3.21−3.38 (m, 2H), 3.81 (s, 1H), 3.90 (s, 2H), 4.04 (s, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.89 (d, J = 11.4 Hz, 1H), 7.32−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.8, 22.7, 27.1, 27.6, 28.9, 29.3, 29.5, 31.8, 39.0, 61.7, 72.8, 74.3, 79.4, 84.9, 98.9, 128.2, 128.3, 128.5, 136.7, 171.8; ESI-MS 420 $[M + H^+]$. Anal. Calcd for $C_{24}H_{37}NO_5$: C, 68.71; H, 8.89; N, 3.34; Found: C, 68.63; H, 8.94; N, 3.29.

(4a*R*,7*S*,7a*S*)-7-Benzyloxytetrahydro-4a-hydroxy-2,2-dimethyl-5-butyl[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (6b): yield 81%; colorless oil after column chromatography (petroleum ether−ethyl acetate, 6:1 containing 1% Et_3N); R_f = 0.3 (petroleum ether−ethyl acetate, 2:1); IR ν_{max} (KBr)/cm^{-1} 3369, 3064, 3031, 2959, 2934, 2873, 1686, 1497, 1455, 1428, 1377, 1334, 1271, 1226, 1201, 1164, 1096, 937, 858, 738, 700, 611, 519; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3H), 1.31 (s, 3H), 1.26−1.42 (m, 2H), 1.47 (s, 3H), 1.52−1.66 (m, 2H), 3.22 (brs, 1H, OH), 3.27−3.34 (m, 2H), 3.83 (s, 1H), 3.89 (s, 2H), 4.04 (s, 1H), 4.72 (d, J = 11.4 Hz, 1H), 4.88 (d, J = 11.4 Hz, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.0, 20.2, 27.4, 30.9, 38.7, 61.9, 72.8, 74.4, 79.4, 85.0, 99.0, 128.1, 128.2, 128.5, 136.7, 171.7; ESI-MS 372 $[M + Na^+]$. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.04; H, 7.58; N, 3.84.

(4a*R*,7*S*,7a*S*)-7-Benzyloxytetrahydro-4a-hydroxy-5-(6-hydroxyhexyl)-2,2-dimethyl[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (6c): yield 72%; colorless oil after column chromatography (petroleum ether−ethyl acetate, 1:1 to 1:2 containing 0.5% Et_3N); R_f = 0.2 (petroleum ether−ethyl acetate-methanol, 10:10:1); IR ν_{max} (KBr)/cm^{-1}: 3393, 3064, 3032, 2989, 2935, 2861, 1687, 1496, 1455, 1427, 1377, 1272, 1225, 1152, 1097, 962, 930, 857, 740, 700, 612, 520; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H, CH_3), 1.36−1.68 (m, 8H), 1.48 (s, 3H), 1.95 (brs, 1H), 3.21−3.37 (m, 2H), 3.57 (t, J = 6.3 Hz, 3H), 3.82−3.92 (m, 3H), 4.04 (s, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.90 (d, J = 11.4 Hz, 1H), 7.31−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 25.1, 26.5, 27.2, 28.7, 32.3, 38.7, 62.2, 62.5, 73.0, 74.7, 79.6, 85.3, 99.1, 128.2, 128.3, 128.5, 136.6, 171.8; ESI-MS 416 $[M + Na^+]$. Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.86; H, 7.70; N, 3.36.

(4a*R*,7*S*,7a*S*)-7-Benzyloxytetrahydro-4a-hydroxy-5-(2-hydroxyethyl)-2,2-dimethyl[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (6d): yield 89%; colorless oil after column chromatography (petroleum ether−ethyl acetate, 1:1.5 to 1:2 containing 1% Et_3N); R_f = 0.2 (petroleum ether−ethyl acetate−methanol, 10:15:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.47 (s, 3H), 3.18−3.27 (m, 1H), 3.65−3.79 (m, 4H), 3.87−3.90 (m, 3H), 4.10 (s, 1H), 4.74 (d, J = 11.7 Hz, 1H), 4.88 (d, J = 11.7 Hz, 1H), 7.29−7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 27.0, 41.9, 60.8, 62.8, 73.0, 74.3, 79.7, 84.9, 99.5, 128.2, 128.3, 128.5, 136.6, 172.4. ESI-MS 360 $[M + Na^+]$. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.38; H, 6.77; N, 4.07.

(4a*R*,7*S*,7a*S*)-7-Benzyloxy-5-(2-benzyloxyethyl)tetrahydro-4a-hydroxy-2,2-dimethyl[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (6d′). Compound **6d′** was prepared by lactone **7** and 2-(benzyloxy) ethanamine[31] as general procedure for the synthesis of *N*-substituted lactams: yield 92%, colorless oil after column chromatography (petroleum ether−ethyl acetate, 3:1 containing 0.5% Et_3N); R_f = 0.30 (petroleum ether−ethyl acetate, 2:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.44 (s, 3H), 3.10−3.19 (m, 1H), 3.56−3.61 (m, 1H), 3.68 (dt, J = 3.0, 9.9 Hz, 1H), 3.78−3.96 (m, 4H), 4.08 (s, 1H), 4.48−4.59 (ABq, J = 11.4 Hz, 2H), 4.75 (d, J = 12.0 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 7.25−7.41 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 26.3, 39.3, 64.0, 67.7, 72.6, 73.5, 74.6, 79.8, 85.1, 99.6, 127.8, 128.1, 128.3, 128.5, 136.4, 137.1, 171.9; HRMS calcd for $C_{24}H_{29}NO_6Na$ $[M + Na^+]$ 450.1887f ound 450.1890.

(4a*R*,7*S*,7a*S*)-5-(4-Methoxybenzyl)-7-benzyloxytetrahydro-4a-hydroxy-2,2-dimethyl[1,3]dioxino[5,4-*b*]pyrrol-6(4*H*)-one (6e): yield 90%; white amorphous solid after column chromatography (petroleum ether−ethyl acetate, 3:1 containing 0.5% Et_3N); R_f = 0.55 (petroleum ether−ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.42 (s, 3H), 3.00 (s, 1H), 3.69 (s, 2H), 3.77 (s, 3H), 3.93 (s, 1H), 4.05 (s, 1H), 4.32 (d, J = 15.4 Hz, 1H), 4.64 (d, J = 15.4 Hz, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.92 (d, J = 11.4 Hz, 1H), 6.82 (d, J = 8.1 Hz, 2H), 7.23−7.35 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 26.8, 41.8, 55.2, 62.7, 72.9, 74.9, 79.3, 86.0, 99.3, 113.8, 128.2, 128.3, 128.5, 129.0, 129.2, 136.7, 158.9, 171.8; ESI-MS: 413 $[M + Na^+]$. Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.56. Found: C, 66.89; H, 6.50; N, 3.34.

(4a*S*,7*R*,7a*R*)-7-Benzyloxyhexahydro-2,2-dimethyl-5-nonyl [1,3]dioxino[5,4-*b*]pyrrole (9a). Preparation of Alane. A cooled (0 °C) solution of anhydrous $AlC1_3$ (13.3 mg, 0.1 mmol) was added to anhydrous THF (5 mL) via syringe under a static argon atmosphere. The resulting clear and colorless solution was allowed to stir at 0 °C for 5 min, and lithium aluminum hydride (12 mg, 0.3 mmol) was added. Bubbling was observed. The resulting clear and colorless solution was allowed to warm to room temperature and stir for 20 min to give a solution of alane (0.4 mmol).

To a stirred, cooled (−78 °C) solution of alane (0.4 mmol) in dry THF (5 mL) was added a solution of lactam **6a** (42 mg, 0.1 mmol) in dry THF (5 mL) under an argon atmosphere. The mixture was allowed to stir for 45 min at −78 °C, then warmed to room temperature over 20 min, and stirred for additional 15 min. The mixture was recooled to 0 °C and quenched with by careful addition of 0.5 N NaOH aqueous solution (30 μL). The precipitate was filtered off and washed with dichloromethane (5 mL × 3). The solvent was evaporated in vacuo, and the residue was dissolved in dichloromethane (30 mL). This solution was washed with brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (petroleum ether−ethyl acetate, 6:1 containing 0.5% Et_3N) to provide **9a** (36.7 mg, 94%) as a colorless oil: R_f = 0.45 (petroleum ether−ethyl acetate, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.26 (s, 12H), 1.37 (s, 3H), 1.39 (s, 3H), 1.44 (m, 2H), 2.20−2.30 (m, 2H), 2.49−2.58 (m, 1H), 2.67 (dd, J = 5.7, 12.0 Hz, 1H), 3.45 (dd, J = 6.3, 9.3 Hz, 1H), 3.66 (dd, J = 6.6, 11.4 Hz, 1H), 3.89 (dd, J = 5.7, 11.4 Hz, 1H), 4.05 (dt, J = 1.8, 6.9 Hz, 1H), 4.20 (dd, J = 2.4, 6.0 Hz, 1H), 4.55 (ABq, J = 11.7 Hz, 2H), 7.28−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.1, 22.7, 26.4, 27.6, 28.2, 29.3, 29.5, 31.9, 55.4, 57.2, 61.4, 62.5, 71.9, 75.8, 83.1, 98.9, 127.8, 128.4, 138.0; HRMS calcd for $C_{24}H_{40}NO_3$ $[M + H^+]$ 390.3003, found 390.3001.

(4a*S*,7*R*,7a*R*)-7-Benzyloxy-5-butylhexahydro-2,2-dimethyl [1,3]dioxino[5,4-*b*]pyrrole (9b). Compound **9b** was prepared from

compound **6b** as described in the preparation of compound **9a**, yielding **9b** as a colorless oil (95% yield): R_f = 0.35 (petroleum ether−ethyl acetate, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3H, CH_3), 1.25−1.48 (m, 10H), 2.20−2.31 (m, 2H), 2.50−2.57 (m, 1H), 2.67 (dd, J = 6.3, 12.3 Hz, 1H), 3.45 (dd, J = 6.6, 9.3 Hz, 1H), 3.66 (dd, J = 6.6, 11.4 Hz, 1H), 3.89 (dd, J = 6.0, 11.4 Hz, 1H), 4.05 (dt, J = 2.3, 6.9 Hz, 1H), 4.20 (dd, J = 2.3, 6.0 Hz, 1H), 4.50−4.61 (ABq, J = 11.7 Hz, 2H), 7.26−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.7, 22.1, 26.4, 30.4, 55.0, 57.2, 61.3, 62.5, 71.9, 75.9, 83.1, 98.9, 127.7, 127.8, 128.4, 138.0; HRMS calcd for $C_{19}H_{30}NO_3$ [M + H$^+$] 320.2220, found 320.2219.

6-((4a*S*,7*R*,7a*R*)-7-Benzyloxytetrahydro-2,2-dimethyl[1,3]dioxino[5,4-*b*]pyrrol-5(6*H*)-yl)hexan-1-ol (9c). Compound **9c** was prepared from compound **6c** as described in the preparation of compound **9a**, yielding **9c** (87% yield) after column chromatography (petroleum ether−ethyl acetate, 1:1 containing 0.5% Et_3N): R_f = 0.3 (petroleum ether−ethyl acetate/methanol, 10:10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32−1.48 (m, 10H), 1.50−1.58 (m, 4H), 2.20−2.31 (m, 2H), 2.52−2.61 (m, 1H), 2.65 (dd, J = 6.0, 11.7 Hz, 1H), 3.46 (dd, J = 6.3, 9.6 Hz, 1H), 3.61−3.70 (m, 3H), 3.90 (dd, J = 5.4, 11.7 Hz, 1H), 4.04 (dt, J = 2.4, 6.9 Hz, 1H), 4.20 (dd, J = 2.4, 6.0 Hz, 1H), 4.50−4.60 (ABq, J = 11.7 Hz, 2H), 7.26−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 25.4, 26.5, 27.2, 28.1, 32.6, 55.1, 57.2, 61.2, 62.3, 62.8, 71.8, 75.7, 83.1, 98.9, 127.8, 128.4, 138.0; HRMS calcd for $C_{21}H_{34}NO_4$ [M + H$^+$] 364.2482, found 364.2487.

2-((4a*S*,7*R*,7a*R*)-7-Benzyloxytetrahydro-2,2-dimethyl[1,3]dioxino[5,4-*b*]pyrrol-5(6*H*)-yl)ethanol (9d). Compound **9d** was prepared from compound **6d** as described in the preparation of compound **9a**, yielding **9d** (96% yield) without chromatography: R_f = 0.25 (petroleum ether−ethyl acetate−methanol, 10:10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.41 (s, 3H), 2.42 (dd, J = 5.4, 10.2 Hz, 1H), 2.57 (td, J = 3.5, 12.9 Hz, 2H), 2.79−2.87 (m, 2H), 3.51−3.57 (m, 2H), 3.59 (dd, J = 3.5, 9.3 Hz, 1H), 3.66−3.73 (m, 1H), 3.91−4.01 (m, 2H), 4.25 (dd, J = 1.5, 5.1 Hz, 1H), 4.51−4.60 (ABq, J = 11.7 Hz, 2H), 7.29−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 27.2, 56.0, 57.1, 59.6, 60.5, 60.9, 71.7, 75.1, 82.9, 98.5, 127.7, 127.8, 128.4, 137.8; HRMS calcd for $C_{17}H_{26}NO_4$ [M + H$^+$] 308.1856, found 308.1856.

(4a*S*,7*R*,7a*R*)-5-(4-Methoxybenzyl)-7-benzyloxyhexahydro-2,2-dimethyl[1,3]dioxino[5,4-*b*]pyrrole (9e). Compound **9e** was prepared from compound **6e** as described in the preparation of compound **9a**, yielding **9e** (95% yield) after column chromatography (petroleum ether−ethyl acetate, 5:1): R_f = 0.55 (petroleum ether−ethyl acetate, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.36 (s, 3H), 2.30 (t, J = 8.4 Hz, 1H), 2.79 (dd, J = 6.3, 12.6 Hz, 1H), 3.30 (t, J = 8.1 Hz, 1H), 3.46−3.62 (m, 4H), 3.79 (s, 3H), 4.05 (t, J = 6.9 Hz, 1H), 4.19 (d, J = 5.7 Hz, 1H), 4.47−4.58 (ABq, J = 11.7 Hz, 2H), 6.83 (d, J = 7.8 Hz, 2H), 7.19−7.32 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 26.1, 55.2, 57.1, 58.4, 61.3, 62.0, 71.9, 76.1, 82.8, 99.1, 113.6, 127.7, 127.8, 128.4, 130.2, 130.3, 138.0, 158.9; HRMS calcd for $C_{23}H_{30}NO_4$ [M + H$^+$] 384.2169, found 384.2162.

1,4-Dideoxy-l,4-(nonylimino)-L-xylitol (10a). A methanolic solution (4 mL) of compound **9a** (39 mg, 0.10 mmol) was adjusted to pH = 2 with 2 N HCl and stirred at rt in the presence of 10% Pd/C (5 mg) under 4 atm hydrogen pressure for 48 h. The catalyst was then removed by filtration through Celite, and the filtrate was concentrated. The residue was subjected to a C-18 reversed-phase column chromatography (eluent: H_2O) to give compound **10a** (29 mg, 98% yield, in the form of HCl salt) as a colorless oil: IR ν_{max} (KBr)/cm^{-1} 3326, 2927, 2855, 2685, 1680, 1640, 1465, 1377, 1264, 1091, 1057, 784, 724, 599, 479; ^{1}H NMR (400 MHz, D_2O) δ 0.79 (t, J = 6.8 Hz, 3H), 1.21−1.28 (m, 12H), 1.69 (brs, 2H), 3.09−3.16 (m, 1H), 3.21 (d, J = 13.2 Hz, 1H), 3.4−3.49 (m, 1H), 3.77 (m, 1H), 3.89 (dd, J = 4.0, 13.2 Hz, 1H), 3.94−4.03 (m, 2H), 4.30 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 13.9, 22.6, 25.4, 26.2, 28.6, 28.87, 28.93, 31.6, 57.4, 58.3, 59.1, 70.9, 74.2, 75.7; HRMS calcd for $C_{14}H_{30}NO_3$ [M + H$^+$] 260.2220, found 260.2222.

1,4-Dideoxy-l,4-(butylimino)-L-xylitol (10b). Compound **10b** was prepared from compound **9b** as described in the preparation of compound **10a**, yielding **10b** (95% yield, in the form of HCl salt) as a colorless oil: IR ν_{max}(KBr)/cm^{-1} 3357, 2961, 2876, 2697, 1634, 1462, 1415, 1305, 1258, 1116, 1085, 1057, 991, 783, 737, 584, 478; ^{1}H NMR (300 MHz, D_2O) δ 0.74 (t, J = 7.2 Hz, 3H), 1.14−1.23 (m, 2H), 1.49−1.57 (m, 2H), 2.96−3.06 (m, 1H), 3.10 (d, J = 12.9 Hz, 1H), 3.29−3.39 (m, 1H), 3.65−3.67 (m, 1H), 3.76 (dd, J = 4.2, 12.9 Hz, 1H), 3.85−3.90 (m, 2H), 4.16−4.18 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 13.3, 19.8, 27.3, 57.4, 58.1, 59.1, 70.9, 74.2, 75.72; HRMS calcd for $C_9H_{20}NO_3$ [M + H$^+$] 190.1438, found 190.1443.

1,4-Dideoxy-l,4-(6-hydroxyhexylimino)-L-xylitol (10c). Compound **10c** was prepared from compound **9c** as described in the preparation of compound **10a**, yielding **10c** (97% yield, in the form of HCl salt) as a colorless oil: IR ν_{max} (KBr)/cm^{-1} 3332, 3047, 2939, 2862, 1641, 1407, 1083, 1055, 727, 600; ^{1}H NMR (300 MHz, D_2O) δ 1.21 (m, 4H), 1.34−1.38 (m, 2H), 1.59 (m, 2H), 2.97−3.03 (m, 1H), 3.10 (d, J = 13.1 Hz, 1H), 3.30−3.42 (m, 3H), 3.67 (m, 1H), 3.77 (dd, J = 4.2, 13.1 Hz, 1H), 3.85−3.92 (m, 2H), 4.16−4.18 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 25.0, 25.3, 26.0, 31.5, 57.4, 58.2, 59.1, 62.1, 70.9, 74.2, 75.7; HRMS calcd for $C_{11}H_{24}NO_4$ [M + H$^+$] 234.1700, found 234.1701.

1,4-Dideoxy-l,4-(2-hydroxyethylimino)-L-xylitol (10d). Compound **10d** was prepared from compound **9d** as described in the preparation of compound **10a**, yielding **10d** (95% yield, in the form of HCl salt) as a colorless oil: IR ν_{max} (KBr)/cm^{-1} 3418, 2956, 1635, 1441, 1406, 1312, 1257, 1094, 1047, 593; ^{1}H NMR (300 MHz, D_2O) δ 3.22−3.30 (m, 2H), 3.53−3.61 (m, 1H), 3.77−3.88 (m, 4H), 3.92−3.94 (m, 2H), 4.22−4.26 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 57.1, 57.4, 59.5, 60.2, 71.7, 74.6, 75.5; HRMS calcd for $C_7H_{16}NO_4$ [M + H$^+$] 178.1074, found 178.1078.

1,4-Dideoxy-l,4-imino-L-xylitol (10e). Compound **10e** was prepared from compound **9e** as described in the preparation of compound **10a**, yielding **10e** (97% yield, in the form of HCl salt) as a colorless oil: IR ν_{max} (KBr)/cm^{-1} 3421, 2935, 1635, 1407, 1316, 1049, 987, 780, 609; ^{1}H NMR (300 MHz, D_2O) δ 2.90 (d, J = 12.8 Hz, 1H), 3.32 (dd, J = 4.5, 12.8 Hz, 1H), 3.46−3.51 (m, 1H), 3.63 (dd, J = 7.8, 11.6 Hz, 1H), 3.76 (dd, J = 5.7, 11.6 Hz, 1H), 4.06−4.07 (m, 1H), 4.12−4.13 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 51.1, 58.9, 62.7, 75.8, 76.0; HRMS calcd for $C_5H_{12}NO_3$ [M + H$^+$] 134.0812, found 134.0815; $[\alpha]_D^{29}$ −2.9 (c 0.17, H_2O) [lit[19]. $[\alpha]_D^{20}$ −4.3 (c 0.38, H_2O)].

(3*S*,4*R*,5*R*)-3-Benzyloxy-4-hydroxy-5-(hydroxymethyl)-1-nonylpyrrolidin-2-one (11a). Dowex 50 H$^+$ resin was added to the solution of lactam **6a** (45 mg, 0.11 mmol) in methanol (8 mL) at room temperature. The mixture was alowed to stir slowly for 24 h. The resin was then filtered off, and the filtrate was concentrated to afford the product with the isopropylidene group removed as a diastereomeric mixture, which was used in the next step without further purification. To the cooled (−78 °C) solution of diastereomeric mixture in dry dichloromethane (10 mL) were added under argon atmosphere triethylsilane (140 μL, 0.88 mmol) and freshly distilled boron trifluoride etherate (34 μL, 0.275 mmol). After being stirred at −78 °C for 8 h, the mixture continued to stir for 8 h at room temperature. The reaction was quenched with saturated sodium bicarbonate aqueous solution (1.0 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether− ethyl acetate, 1:1) on silica gel to provide the compound **11a** (35.3 mg, 91% yield over two steps) as a white amorphous solid: R_f = 0.65 (petroleum ether−ethyl acetate−methanol, 5:5:2); IR ν_{max} (KBr)/cm^{-1} 3402, 2926, 2855, 1669, 1459, 1376, 1336, 1262, 1097, 1076, 802, 737, 698, 607, 473; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.25 (s, 12H), 1.44−1.49 (m, 2H), 2.55 (brs, 1H), 2.84−2.93

(m, 2H), 3.31−3.36 (m, 1H), 3.62−3.72 (m, 1H), 3.77 (brs, 2H), 4.04 (d, J = 6.0 Hz, 1H), 4.18 (t, J = 6.0 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 5.10 (d, J = 11.7 Hz, 1H), 7.29−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 26.8, 27.3, 29.2, 29.3, 29.5, 31.8, 40.2, 59.5, 61.7, 72.8, 73.2, 81.8, 128.1, 128.3, 128.5, 137.5, 171.0; HRMS calcd for $C_{21}H_{34}NO_4$ [M + H$^+$] 364.2482, found 364.2489.

(3*S*,4*R*,5*R*)-3-Benzyloxy-4-hydroxy-5-(hydroxymethyl)-1-butylpyrrolidin-2-one (11b). Compound **11b** was prepared from compound **6b** as described in the preparation of compound **11a**, yielding **11b** (84% yield) as a white amorphous solid: R_f = 0.55 (petroleum ether−ethyl acetate−methanol, 5:5:2); IR ν_{max} (KBr)/cm^{-1} 3395, 3064, 3032, 2959, 2930, 2873, 1682, 1458, 1378, 1345, 1282, 1214, 1155, 1101, 1028, 981, 787, 740, 699, 605, 514; ^{1}H NMR (500 MHz, $CDCl_3$, after D_2O shake) δ 0.92 (t, J = 7.5 Hz, 3H, CH_3), 1.26−1.35 (m, 2H, CH_2CH_3), 1.39−1.55 (m, 2H, NCH_2CH_2), 2.40 (m, 1H, OH-5), 2.69 (d, J = 4.0 Hz, 1H, OH-3), 2.88−2.94 (m, 1H, NCH_2 × 1), 3.33−3.36 (m, 1H, H-4), 3.65−3.71 (m, 1H, NCH_2 × 1), 3.74−3.81 (m, 2H, H-5), 4.04 (d, J = 6.0 Hz, 1H, H-2), 4.16−4.19 (td, J = 4.0, 6.0 Hz, 1H, H-3), 4.78 (d, J = 11.5 Hz, 1H, $PhCH_2$ × 1), 5.10 (d, J = 11.5 Hz, 1H, $PhCH_2$ × 1), 7.29−7.42 (m, 5H, Ph); deuterium exchange ^{1}H NMR (500 MHz, $CDCl_3$ containing 2 drops of D_2O) δ 0.91 (t, J = 7.5 Hz, 3H, CH_3), 1.26−1.34 (m, 2H, CH_2CH_3), 1.38−1.54 (m, 2H, NCH_2CH_2), 2.87−2.93 (m, 1H, NCH_2 × 1), 3.31−3.34 (m, 1H, H-4), 3.65−3.71 (m, 1H, NCH_2 × 1), 3.75−3.78 (m, 2H, H-5), 4.05 (d, J = 6.0 Hz, 1H, H-2), 4.17 (t, J = 6.0 Hz, 1H, H-3), 4.78 (d, J = 11.5 Hz, 1H, $PhCH_2$ × 1), 5.10 (d, J = 11.5 Hz, 1H, $PhCH_2$ × 1), 7.28−7.42 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.0, 29.3, 39.8, 59.5, 61.7, 72.8, 73.2, 81.7, 128.1, 128.3, 128.5, 137.5, 171.0; HRMS calcd for $C_{16}H_{24}NO_4$ [M + H$^+$] 294.1700, found, 294.1699.

(3*S*,4*R*,5*R*)-3-Benzyloxy-1-(2-(benzyloxy)ethyl)-4-hydroxy-5-(hydroxymethyl)pyrrolidin-2-one (11c). Compound **11c** was prepared from compound **6d′** as described in the preparation of compound **11a**, yielding **11c** (94% yield) as a colorless oil: R_f = 0.30 (petroleum ether−ethyl acetate−methanol, 5:5:2); IR ν_{max} (KBr)/cm^{-1} 3404, 3064, 3031, 2924, 2854, 1678, 1496, 1457, 1357, 1333, 1264, 1204, 1151, 1085, 1045, 1028, 908, 806, 738, 698, 607, 531, 460; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (brs, 1H), 3.18−3.28 (m, 2H), 3.53−3.62 (m, 3H), 3.81−3.94 (m, 3H), 4.07 (d, J = 6.9 Hz, 1H), 4.31−4.32 (m, 1H), 4.43−4.55 (ABq, J = 11.4 Hz, 2H), 4.79 (d, J = 11.7 Hz, 1H), 5.08 (d, J = 11.7 Hz, 1H), 7.29−7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.9, 58.0, 63.6, 68.5, 71.9, 72.7, 73.6, 82.0, 127.9, 128.2, 128.3, 128.5, 128.6, 136.5, 137.8, 172.3; HRMS calcd for $C_{21}H_{26}NO_5$ [M + H$^+$] 372.1805, found 372.1806.

(3*S*,4*R*,5*R*)-1-(4-Methoxybenzyl)-3-(benzyloxy)-4-hydroxy-5-(hydroxymethyl)pyrrolidin-2-one (11d). Compound **11d** was prepared from compound **6e** as described in the preparation of compound **11a**, yielding **11d** (74% yield) as a white amorphous solid: R_f = 0.30 (petroleum ether−ethyl acetate−methanol, 5:5:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (brs, 1H), 2.87 (d, J = 3.9 Hz, 1H), 3.16−3.21 (m, 2H), 3.67 (m, 2H), 3.77 (s, 3H), 4.09−4.14 (m, 2H), 4.20−4.25 (m, 1H), 4.73 (d, J = 15.0 Hz, 1H), 4.80 (d, J = 11.7 Hz, 1H), 5.11 (d, J = 11.7 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.29−7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.7, 55.3, 59.0, 61.8, 72.7, 72.9, 77.2, 81.8, 114.3, 128.0, 128.1, 128.3, 128.5, 129.2, 137.5, 159.2, 171.4; HRMS calcd for $C_{20}H_{24}NO_5$ [M + H$^+$] 358.1649, found 358.1642.

1,4-Dideoxy-l,4-(nonylimino)-D-arabinitol (13a). BH_3·THF (1M, 0.44 mL, 0.44 mmol) was added dropwise to the solution of lactam **11a** (40 mg, 0.11 mmol) in anhydrous THF (10 mL) at 0 °C, and after being stirred for 20 min at room temperature, the mixture was heated under reflux for 4 h. The mixture was cooled to 0 °C, treated with methanol dropwise (5 mL), and allowed to stir for 36 h at room temperature. The mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether−ethyl acetate−methanol, 10:10:1) on silica gel to provide compound **12a** (36.5 mg, 95%) as a colorless oil: R_f = 0.25 (petroleum ether−ethyl acetate−methanol, 5:5:1); ^{1}H NMR (500 MHz, CD_3OD) δ 0.89 (t, J = 7.0 Hz, 3H), 1.28−1.30 (m, 12H), 1.49−1.53 (m, 2H), 2.26−2.32 (m, 1H), 2.44 (m, 1H), 2.62 (dd, J = 6.0, 11.0 Hz, 1H), 2.83−2.89 (m, 1H), 3.18−3.21 (m, 1H), 3.64 (dd, J = 5.0, 11.0 Hz, 1H), 3.70 (dd, J = 5.5, 11.0 Hz, 1H), 3.84 (td, J = 2.5, 6.5 Hz, 1H), 4.07 (dd, J = 2.5, 5.5 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.59 (d, J = 11.5 Hz, 1H), 7.24−7.36 (m, 5H); ^{13}C NMR (125 MHz, CD_3OD) δ 14.4, 23.7, 28.6, 28.7, 30.4, 30.6, 30.7, 33.1, 56.8, 58.3, 62.4, 72.2, 74.4, 78.6, 84.9, 128.6, 128.9, 129.3, 139.6; HRMS calcd for $C_{21}H_{36}NO_3$ [M + H$^+$] 350.2690, found 350.2692.

The methanolic solution (4 mL) of compound **12a** (36.5 mg, 0.10 mmol) was stirred at room temperature in the presence of 10% Pd/C (5 mg) under 4 atm of hydrogen pressure for 48 h. The catalyst was then removed by filtration through Celite, and the filtrate was concentrated. The residue was subjected to a C-18 reversed-phase column chromatography (methanol−water, 1:1) to give **13a** (25.4 mg, 98%) as a colorless oil: IR ν_{max} (KBr)/cm^{-1} 3347, 2926, 2855, 2694, 1640, 1466, 1381, 1257, 1068, 1019, 895, 721, 605; ^{1}H NMR (300 MHz, CD_3OD) δ 0.89 (t, J = 7.2 Hz, 3H), 1.30−1.37 (m, 12H), 1.75 (m, 2H), 3.08−3.24 (m, 1H), 3.39−3.49 (m, 3H), 3.58 (d, J = 11.7 Hz, 1H), 3.80−4.02 (m, 3H), 4.19 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 13.9, 22.6, 25.3, 26.2, 28.6, 28.9, 31.7, 57.4, 58.3, 59.1, 70.9, 74.2, 75.7; HRMS calcd for $C_{14}H_{30}NO_3$ [M + H$^+$] 260.2220, found 260.2215.

1,4-Dideoxy-l,4-(butylimino)-D-arabinitol (13b). Compound **12b** was prepared from compound **11b** as described in the preparation of compound **12a**, R_f = 0.15 (petroleum ether−ethyl acetate-methanol, 5:5:3). After concentration, without chromatography, catalytic hydrogenolysis was conducted to **12b** as described in the preparation of compound **13a**, yielding **13b** (93% yield over two steps) as a colorless oil: IR ν_{max} (KBr)/cm^{-1} 3356, 2962, 2876, 2711, 1639, 1465, 1410, 1346, 1258, 1078, 1017, 906, 739, 572; ^{1}H NMR (300 MHz, CD_3OD) δ 0.98 (t, J = 7.2 Hz, 3H), 1.37−1.44 (m, 2H), 1.74 (m, 2H), 3.10−3.15 (m, 1H), 3.43−3.61 (m, 4H), 3.87−4.03 (m, 3H), 4.20 (brs, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 13.9, 20.9, 28.3, 58.7, 60.7, 60.9, 75.7, 77.7, 78.5; HRMS calcd for $C_9H_{20}NO_3$ [M + H$^+$] 190.1438, found 190.1442.

1,4-Dideoxy-l,4-(2-hydroxyethylimino)-D-arabinitol (13c). Compound **12c** was prepared from compound **11c** as described in the preparation of compound **12a**, yielding **12c** as a colorless oil: R_f = 0.65 (petroleum ether−ethyl acetate−methanol, 5:5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (brs, 2H), 2.53−2.62 (m, 2H), 2.83 (dd, J = 6.9, 10.8 Hz, 1H), 2.95−3.04 (m, 1H), 3.26 (dd, J = 2.7, 10.8 Hz, 1H), 3.55 (t, J = 5.7 Hz, 2H), 3.65−3.75 (m, 2H), 3.87−3.91 (m, 1H), 4.23 (dd, J = 3.6, 5,7 Hz, 1H), 4.52−4.57 (m, 4H), 7.29−7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.2, 57.6, 59.5, 68.7, 71.3, 71.4, 73.2, 83.2, 127.7, 127.8, 128.4, 138.0; HRMS calcd for $C_{21}H_{28}NO_4$ [M + H$^+$] 358.2013, found 358.2017. Compound **13c** was prepared from compound **12c** as described in the preparation of compound **13a**, yielding **13c** (96% yield over two steps) as a colorless oil: IR ν_{max} (KBr)/cm^{-1} 3357, 2935, 1611, 1408, 1265, 1072, 892, 655, 613; ^{1}H NMR (400 MHz, D_2O) δ 2.58−2.62 (m, 2H), 2.81 (m, 1H), 2.97−3.05 (m, 2H), 3.56−3.64 (m, 4H), 3.81−3.83 (m, 1H), 4.01 (t J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ 59.3, 61.5, 63.1, 75.3, 77.9, 81.0; HRMS calcd for $C_7H_{16}NO_4$ [M + H$^+$] 178.1074, found 178.1078.

(2*R*,3*R*,4*R*)-1-(4-Methoxybenzyl)-4-benzyloxy-2-(hydroxymethyl)pyrrolidin-3-ol (12d). A mixture of **11d** (46 mg, 0.13 mmol) and $LiAlH_4$ (31 mg, 0.78 mmol) in THF (10 mL) was heated to reflux for 16 h. The mixture was cooled to 0 °C, treated with H_2O dropwise (60 μL), and stirred at room temperature until the gray powder completely turned to white. The solids were filtered off and washed with ethyl acetate (20 mL). After evaporation of the filtrate, the residue was subjected to column chromatography (petroleum ether−ethyl acetate 1:1) to afford **12d** (33 mg, 75% yield) as a white amorphous solid: R_f = 0.35 (petroleum ether−ethyl acetate−methanol, 5:5:1); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 2.66−2.77 (m, 2H), 3.06 (dd, J = 2.1, 11.1 Hz, 1H), 3.40 (d, J = 12.9 Hz, 1H), 3.46−3.56 (m, 2H), 3.71−3.86 (m, 6H), 3.94 (d, J = 12.9 Hz, 1H), 4.29 (dd, J = 3.0, 5.1 Hz, 1H), 4.46−4.55 (m, 2H), 6.85 (d, J = 8.4 Hz, 2H), 7.19−7.34 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 56.2, 57.5, 59.3, 71.3, 71.7, 77.9, 82.6, 113.8, 127.8, 128.4, 129.0, 130.2, 137.8, 159.0; HRMS calcd for $C_{20}H_{26}NO_4$ [M + H$^+$] 344.1856, found 344.1851.

1,4-Dideoxy-l,4-imino-D-arabinitol Hydrochloride (DAB 1·HCl) (13d). Compound **13d** was prepared from compound **12d** as described in the preparation of compound **13a**, yielding **13d** (97% yield) as a colorless oil. To the solution of compound **13d** in methanol was slowly added 1 N HCl (0.5 mL) at 0 °C. After being stirred for 30 min at 0 °C, the resulting mixture was evaporated in vacuo, and further evaporation under high vacuo gave DAB 1 in the form of hydrochloride salt: IR ν_{max}(KBr)/cm^{-1} 3424, 3381, 3286, 3030, 2972, 2943, 2764, 1632, 1578, 1450, 1399, 1378, 1360, 1326, 1301, 1261, 1216, 1167, 1110, 1077, 1040, 1009, 967, 918, 765, 611, 567; ^{1}H NMR (400 MHz, D_2O) δ 3.26 (dd, J = 2.8, 12.8 Hz, 1H), 3.46−3.54 (m, 2H), 3.73 (dd, J = 8.0, 12.0 Hz, 1H), 3.85 (dd, J = 4.8, 12.0 Hz, 1H), 3.98−4.00 (m, 1H), 4.22−4.24 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 52.7, 61.6, 69.4, 77.0, 78.4; HRMS calcd for $C_5H_{12}NO_3$ [M + H$^+$] 134.0812, found 134.0814; $[\alpha]_D^{27}$ +33.3 (c 0.18, H_2O) [lit.[22] $[\alpha]_D^{20}$ +36.1 (c 0.2, H_2O)].

(3*S*,4*R*,5*S*)-3-(Benzyloxy)-4-hydroxy-5-(hydroxymethyl)-1-butylpyrrolidin-2-one (14b). To a cooled (−78 °C) solution of compound **6b** (40 mg, 0.11 mmol) in dichloromethane (10 mL) were added under argon atmosphere triethylsilane (183 μL, 1.10 mmol) and untreated boron trifluoride etherate (116 μL, 0.88 mmol). After being stirred at −78 °C for 8 h, the mixture was continuously stirred for 8 h at room temperature. The reaction was quenched with saturated sodium bicarbonate aqueous solution (1.0 mL) and extracted with dichloromethane (3 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether−ethyl acetate, 1:1) on silica gel to provide the compound **14b** (5.0 mg, 15% yield) as a colorless oil [R_f = 0.50 (petroleum ether−ethyl acetate−methanol, 5:5:2)] and **11b** (9.0 mg, 27% yield) as a white amorphous solid [R_f = 0.55 (petroleum ether−ethyl acetate−methanol, 5:5:2)]. Spectral data for compound **14b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 3H, CH_3), 1.28−1.35 (m, 2H, CH_2CH_3), 1.47−1.56 (m, 2H, NCH_2CH_2), 2.34 (t, J = 6.5 Hz, 1H, OH-5), 2.47 (d, J = 6.0 Hz, 1H, OH-3), 2.92−2.98 (m, 1H, NCH_2 × 1), 3.60−3.66 (m, 2H, H-4, NCH_2 × 1), 3.79−3.83 (m, 1H, H-5a), 3.85−3.89 (ddd, J = 2.0, 6.5, 12.0 Hz, 1H, H-5b), 4.21 (d, J = 7.0 Hz, 1H, H-2), 4.45 (m, 1H, H-3), 4.77 (d, J = 11.8 Hz, 1H), 5.13 (d, J = 11.8 Hz, 1H), 7.29−7.44 (m, 5H); deuterium exchange ^{1}H NMR (500 MHz, $CDCl_3$ containing 2 drops of D_2O) δ 0.93 (t, J = 7.0 Hz, 3H, CH_3), 1.29−1.34 (m, 2H, CH_2CH_3), 1.47−1.57 (m, 2H, NCH_2CH_2), 2.92−2.97 (m, 1H, NCH_2 × 1), 3.60−3.66 (m, 2H, H-4, NCH_2 × 1), 3.79 (dd, J = 4.0, 12.0 Hz, 1H, H-5a), 3.86 (dd, J = 2.0, 12.0 Hz, 1H, H-5b), 4.22 (d, J = 7.0 Hz, 1H, H-2), 4.44 (t, J = 7.0 Hz, 1H, H-3), 4.78 (d, J = 12.0 Hz, 1H, $PhCH_2$ × 1), 5.12 (d, J = 12.0 Hz, 1H, $PhCH_2$ × 1), 7.29−7.44 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 20.1, 29.2, 40.6, 58.7, 58.8, 72.8, 74.0, 81.9, 127.9, 128.2, 128.5, 138.0, 171.0; HRMS calcd for $C_{16}H_{24}NO_4$ [M + H$^+$] 294.1700, found 294.1701.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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