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First Total Synthesis of 1-*O*-*β*-D-Glucopyranosyl-5-deoxyadenophorine and Its Aglycon Congener: Determination of the Absolute Configuration

François-Xavier Felpin,[†] Kamal Boubekeur,[‡,§] and Jacques Lebreton*[,†]

Laboratoire de Synthèse Organique, CNRS UMR 6513, Université de Nantes, Faculté des Sciences et des Techniques, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France, and Institut des Matériaux Jean Rouxel, CNRS UMR 6502 Université de Nantes, BP 32229, 2 rue de la Houssinière, 44322 Nantes Cedex 03, France

lebreton@chimie.univ-nantes.fr

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The first total synthesis of the potent glycosidase inhibitors 1-*O*-*β*-D-glucopyranosyl-5-deoxyadenophorine and its aglycon congener is described in respectively 13 steps (9% overall yield) and 9 steps (29% overall yield) from (*R*)-Garner aldehyde. The synthesis takes advantage of several key reactions including a diastereoselective allylation of a chiral imine, a stereoselective epoxidation, and a glycoside coupling. In addition this study established unambiguously the absolute configuration of the natural products.

Introduction

Interest in polyhydroxylated piperidines has undergone remarkable expansion in recent years[1] since the discovery of nojirimycin **1**, which displays glycosidase inhibitor activities by glucose **2** mimicry (Figure 1) (by analogy with the glycosyl oxocarbenium intermediate of the enzymatic glycoside cleavage).[2] The biological properties of iminosugars can be explained by their structural resemblance to their oxygenated analogues found in natural substrates. Thus, due to these mimetic properties, iminosugars could be of great interest to treat a variety of diseases such as diabetes,[3] viral infections,[4] and tumor metastasis.[5] As already discussed by Butters and co-workers,[6] hydrophobic substituents on iminosugars can increase enzyme inhibitory activities. For example, *N*-butyldeoxynojirimycin **3** (NB-DNJ) has been approved for use in Europe as therapy for Gaucher disease, a glycolipid lysosomal storage disorder.[7]

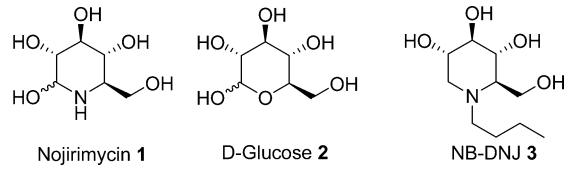

FIGURE 1. Structure of nojirimycin **1**, D-glucose **2**, and NB-DNJ **3**.

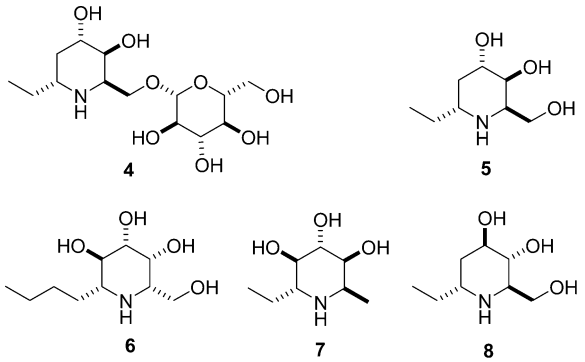

FIGURE 2. Structure of the alkaloids recently isolated by Asano and co-workers.

In this context, Asano and co-workers[8] recently reported the isolation of several new 6-alkyliminosugars from *Adenophora* spp (Figure 2). These compounds are rare examples of natural iminosugars containing hydrophobic α-1-*C*-substituents as the butyl- or ethyl-substituted compounds **4**−**8**. Among them, 1-*O*-*β*-D-glucopy-

* Address correspondence to this author. Phone: + 33 2 51 12 54 03. Fax: + 33 2 51 12 54 02.
† Laboratoire de Synthèse Organique.
‡ Present address: LCIM2, UMR-CNRS 7071, Université Pierre et Marie Curie, 4 Place Jussieu, Case Courrier 42, 75252 Paris Cedex 05. To whom correspondence concerning the X-ray data should be addressed. E-mail: boubekeu@ccr.jussieu.fr.
§ Institut des Matériaux Jean Rouxel.

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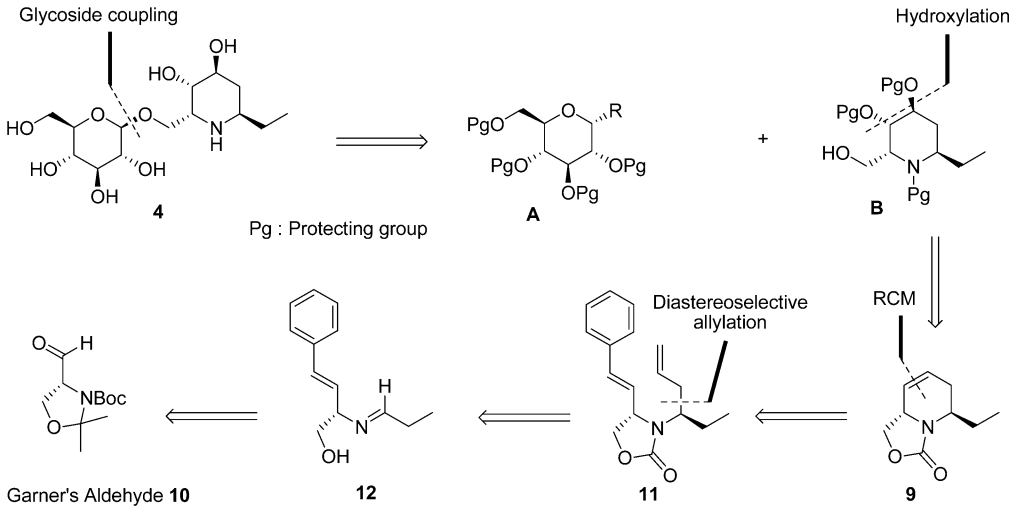
SCHEME 1. Retrosynthetic Analysis



ranosyl-5-deoxyadenophorine **4** was found to be a highly potent α-glycosidase-specific inhibitor (IC_{50} = 0.49−6.1 μM for α-glucosidase and IC_{50} = 1.7 μM for α-galactosidase). The structures as well as the relative configurations of these new iminosugars were established by extensive NMR studies.

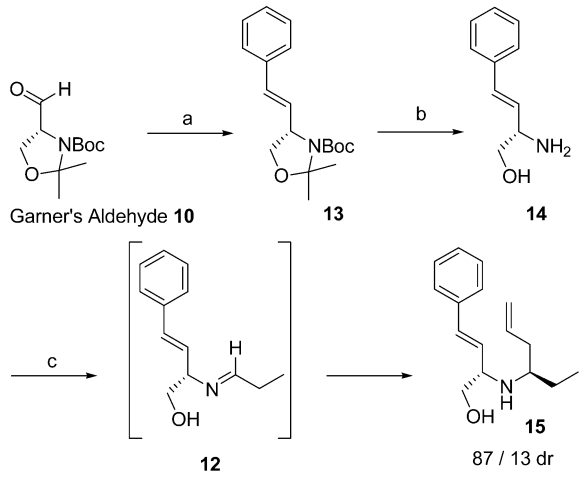
In a previous report, we have developed a novel access to chiral *trans*-2,6-dialkyl-1,2,5,6-tetrahydropyridines.[9] As part of a continuing program directed toward the synthesis of piperidine alkaloids with biological activity,[10] we wished to extend our strategy to the synthesis of iminosugars. Thus, herein we report the asymmetric total synthesis of 1-*O*-*β*-D-glucopyranosyl-5-deoxyadenophorine **4** as well as its aglycon parent 5-named-5-deoxyadenophorine **5**. These first total syntheses confirm the structure assignment and their absolute configuration.

Our plan for preparing our target molecule focused on iminosugar **B**, which should be a key intermediate and on which a glycosidation reaction with glucose derivative **A** would furnish **4** (Scheme 1). It was reasoned that this aglycon compound **B** should be derived from tetrahydropyridine **9** after oxidation of the double bond. According to our recently described methodology,[9] tetrahydropyridine **9** could be obtained from commercially available Garner aldehyde **10** by using two key reactions: a ring-closing metathesis (RCM) reaction on the diethylenic amine **11** and a diastereoselective allylation of a chiral imine **12**.

Results and Discussion

Synthesis of the Iminosugar Moiety. Olefination of the Garner aldehyde **10** by a Horner−Wadworth−Emmons reaction, using the semistabilized benzylphosphonate, furnished (*E*)-olefin **13** and occurred in a highly stereospecific fashion. A subsequent global deprotection of oxazolidine and Boc protecting groups afforded the expected amino alcohol **14** in good yield (74%, 2 steps)

SCHEME 2[a]



[a] Reagents and conditions: (a) diethyl benzylphosphonate, *n*BuLi, THF, −78 °C to room temperature, 14 h, 75%. (b) Concentrated HCl, MeOH, reflux, 4 h, 98%. (c) Propanal, $MgSO_4$, THF, rt, 12 h, then allylmagnesium bromide, THF, Et_2O, −78 to −10 °C, 6 h, 87%.

(Scheme 2). A styryl group, known to be a good substrate for the RCM reaction,[11] was introduced to favorably influence the diastereoselectivity in the allylation step (vide infra). Hence, amino alcohol **14** reacted with propanal to give the corresponding imine **12** on which a diastereoselective allylation (87/13 dr) with allymagnesium bromide led to the diethylenic amino alcohol *trans*-**15**. The minor cis isomer was found to be inseparable from the trans isomer by flash chromatography at this stage and consequently the next step was performed on the diastereoisomeric mixture. Although the stereochemistry at the newly generated stereogenic center could not be determined at this stage, the formation of amino alcohol *trans*-**15** as a major product was deduced from previous results on similar structures[9] and from a mechanistic point of view. Indeed, we anticipated that imino alcohol would react with Grignard reagent via the

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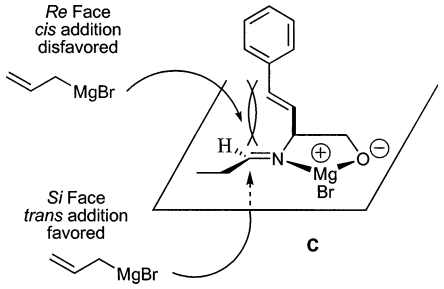


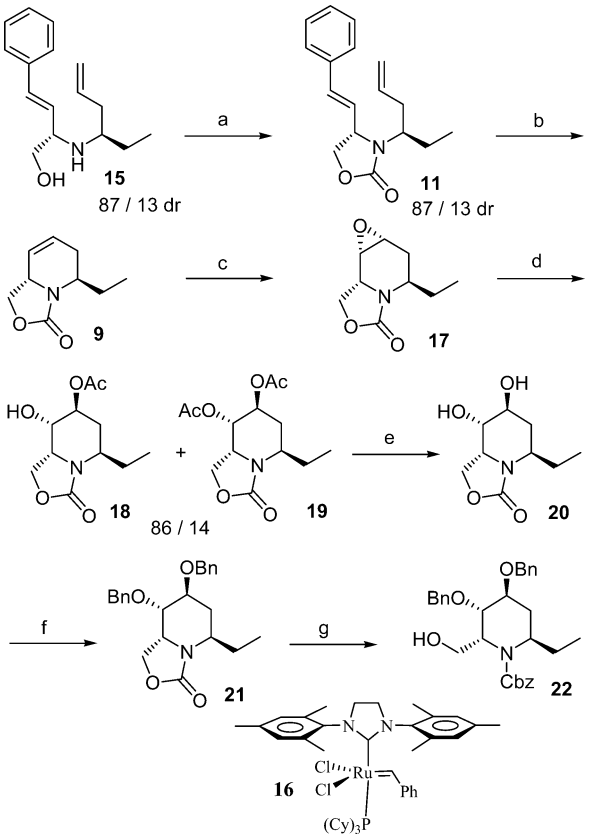
FIGURE 3. Stereoselectivity of the addition of allymagnesium bromide over imino alcohol **12**.

chelation model transition state **C** with a transient five-membered ring, leading to the desired trans-adduct **15** contaminated by less than 13% of the undesired cis isomer. Thus, the Grignard reagent attacks the less hindered face of the imine, the *Si* face for the trans addition (Figure 3).[12] The relative stereochemistry was fully confirmed later by an X-ray crystal structure (vide infra).

With substrate **15** in hand, we focused our attention on the RCM reaction. However, it is well-known that this reaction was incompatible with free amines.[13] Consequently, the amino alcohol function was protected by simple treatment of the diastereoisomer mixture with carbonyldiimidazole (CDI) to give the corresponding oxazolidinone **11** (86% yield) as its diastereoisomeric mixture, which was not separated at this stage (Scheme 3). The next step was to construct the desired tetrahydropyridine **9** by ruthenium-catalyzed intramolecular cyclization. In this context, the mixture of oxazolidinone **11** treated with second generation Grubbs' catalyst **16** in refluxed dichloromethane featured the formation of tetrahydropyridine **9** in high yield. The minor cis isomer was easily separated by flash chromatography.

A significant goal of this study was the demonstration of the utility of tetrahydropyridine as a key precursor of iminosugar. It was envisaged that the requisite hydroxyl functions of the desired iminosugar would be introduced by functionalization of the olefin. So, epoxidation of the double bond with *m*CPBA proceeded with good diastereoselectivity (9/1 dr) in favor of the desired endo **17** isomer, as determined by extensive NOESY NMR experiments and previous results obtained in our laboratory on a similar structure.[13h] The desired endo-epoxide **17** was separated from its unwanted exo isomers by chromatography on silica gel. In contrast to previous reports in the literature,[14] the opening of epoxide **17** with acetic acid was totally regioselective to give a mixture of

SCHEME 3[a]



[a] Reagents and conditions: (a) CDI, Et_3N, CH_2Cl_2, 18 h, 86%. (b) [Ru]-**16**, CH_2Cl_2, 0.005 M, reflux, 1 h, 83% of *trans*-**9** and 11% of *cis*-**9**. (c) *m*CPBA, CH_2Cl_2, 0 °C to rt, 72 h, 86% of *endo*-**17** and 5% of *exo*-**17**. (d) AcOH, 100 °C, 17 h, 79% of **18** and 10% of **19**. (e) K_2CO_3, MeOH, rt, 3 h, 95%. (f) NaH, BnBr, DMF, 0 °C to rt, 4 h, 93%. (g) 8 N NaOH, MeOH, 95 °C, 24 h, then, Cbz-Cl, CH_2Cl_2, 0 °C to rt, 4 h, 74%.

monoacetate **18** and diacetate **19** (86/14 ratio mixture, 89% combined yield). In fact, compound **19** was formed by in situ esterification of monoacetate **18**. The absolute configuration of **18** was unambiguously confirmed by an X-ray crystal structure (see the Supporting Information). The mixture could easily be separated by flash chromatography for analytical samples, but in our synthetic route, the mixture was directly treated by potassium carbonate in methanol to give quasiquantitatively the diol **20**. To achieve the synthesis of the iminosugar part of **4**, diol **20** was protected as benzyl groups by classical treatment with NaH and BnBr in DMF (93% yield). Finally, opening of the oxazolidinone **21** with NaOH in refluxed MeOH, followed by trapping of the free nitrogen with benzylchloroformate, afforded our key intermediate **22** in 74% yield over the two steps.

Total Synthesis of 5-Deoxyadenophorine 5 and Determination of the Absolute Configuration. At this stage, it was envisaged that **20** should furnish a direct access to 5-deoxyadenophorine **5** by cleavage of the oxazolidinone protecting group. In addition, the optical rotation measurement should enable the absolute configuration of **5** as well as of **4** to be determined. Indeed, by hydrolysis of **4**, Asano and co-workers[8] had shown that the iminosugar part of **4** was identical to **5**. Following our strategy, a basic hydrolysis of the oxazolidinone

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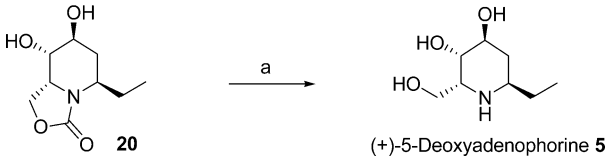
SCHEME 4[a]



[a] Reagents and conditions: (a) 8 N NaOH, MeOH, 95 °C, 24 H, 88%.

function with NaOH in refluxed MeOH led cleanly to **5**. The proton and ^{13}C NMR spectra were identical with those reported for the natural product by Asano et al. Furthermore, the value and sign of the optical rotation were equally in good agreement. Consequently, the configuration of natural 5-deoxyadenophorine **5** was unambiguously assigned as (2*R*,3*S*,4*S*,6*R*).

Glycoside Coupling and Completion of the Synthesis. The major remaining task for the completion of our target was the glycoside coupling between iminosugar **22** and a glucose derivative **23a**,**b** (see Scheme 5 and Table 1). It should be noted that the current literature regarding the coupling of iminosugars with sugar derivatives is limited. First, we opted for a coupling between **22** and bromoglucose **23a**. In this context, according to the procedure described by Liu[15] and co-workers, the coupling of **22** and **23a** in the presence of $Hg(CN)_2$ proceeded with acceptable yield (38%). However, despite several attempts, a mixture of α- and *β*-isomers **24** in an approximate 3/7 ratio was isolated and was found to be inseparable by flash chromatography. Next, we examined a silver-based Lewis acid such as $Ag(OTf)_2$,[16] but without success. Only starting materials were recovered. This failure forced us to plan an alternative strategy based on the coupling of **22** with trichloroacetimidate glucose derivative **23b**. We were very pleased to find that the glycoside coupling in the presence of $BF_3{\cdot}Et_2O$[17] proceeded stereospecifically to give the expected *β*-isomer **24** in 39% yield. In addition, the sole isolated side product was compound **21**, resulting from an intramolecular cyclization, which can be recycled a few steps before.

The removal of the acetate groups with potassium carbonate in methanol to give **25** and the subsequent hydrogenolysis of the benzyl protecting groups afforded 1-*O*-*β*-D-glucopyranosyl-5-deoxyadenophorine **4** in 96% yield over the two steps (Scheme 6). The ^1H and ^{13}C NMR spectra and the optical rotation measurement were identical with those reported for natural **4**,[8] and then fully confirmed the assignment previously observed for 5-deoxyadenophorine **5** (vide supra).[18]

Conclusion

We have demonstrated the synthetic utility of *trans*-2,6-dialkyl-1,2,5,6-tetrahydropyridines by the first total syntheses of 1-*O*-*β*-D-glucopyranosyl-5-deoxyadenophorine **4** (13 steps, 9% overall yield) as well as its aglycon congener **5** (9 steps, 29% overall yield) from (*R*)-Garner aldehyde **10**. The stereocenters were successfully accessed by several important steps including a diastereoselective allylation of a chiral imine, a stereoselective epoxidation, and a regioselective opening of the epoxide. The glycoside step was achieved by using the trichloroacetamidate strategy. In addition, our syntheses proved unambiguously the absolute configuration of 1-*O*-*β*-D-glucopyranosyl-5-deoxyadenophorine **4**. Further developments toward the synthesis of iminosugars with intriguing structures remain a major challenge in our laboratory and will be reported in due course.

Experimental Section

(4*S*,1′*E*)-2,2-Dimethyl-4-styryl-3-*tert*-butyloxycarbonyloxazolidine (13). A solution of diethyl benzylphosphonate (6.95 g, 30.48 mmol) in THF (100 mL) was treated with BuLi (15.24 mL, 1.6 M in hexane, 24.38 mmol) at −78 °C. The resulting mixture was stirred for 30 min at −78 °C and then a solution of aldehyde **10** (3.49 g, 15.24 mmol) in THF (35 mL) was slowly added over 30 min. After addition, the mixture was stirred for 2 h at −78 °C and 12 h at room temperature. The mixture was quenched with water and diluted with Et_2O. The aqueous phase was extracted with Et_2O (3×). The combined organic extracts were washed with brine (1×), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (5% EtOAc−petroleum ether) and crystallization in petroleum ether gave (*E*)-**13** (3.46 g, 75%) as colorless crystals. $[\alpha]^{20}_D$ +83.0 (*c* 0.976, $CHCl_3$) [lit.[19] $[\alpha]^{20}_D$ −88.7 (*c* 1, $CHCl_3$) for (*R*)-enantiomer]. Mp 85 °C (lit.[19] mp 81 °C). IR (KBr) 1700, 2977 cm^{-1}. ^1H NMR *δ* 1.46 (s, 9H), 1.57 (s, 3H), 1.68 (s, 3H), 3.85 (dd, 1H, *J* = 2.3, 8.8 Hz), 4.13 (dd, 1H, *J* = 6.1, 8.8 Hz), 4.66 (m, 1H), 6.17 (dd, 1H, *J* = 7.6, 15.1 Hz), 6.52 (d, 1H, *J* = 15.1 Hz), 7.24−7.41 (m, 5H). ^{13}C NMR *δ* 23.9, 26.8, 28.6, 59.6, 68.4, 79.9, 94.4, 126.5, 127.7, 128.7, 131.8, 136.8, 152.1. HRMS (EI) calcd for $C_{18}H_{25}NO_3$ (M^+) 303.1834, found 303.1834.

(2*S*,3*E*)-2-Amino-4-phenylbut-3-en-1-ol (14). A solution of **13** (5.2 g, 17.16 mmol) in MeOH (55 mL) was treated with concentrated HCl (2.7 mL, 5% v/v). After the mixture was stirred at reflux for 4 h, the volatiles were evaporated under reduced pressure. The residue was taken up with CH_2Cl_2 and H_2O and the resulting mixture was basified with solid NaOH. The aqueous layer was extracted with CH_2Cl_2 (5×) and the combined extracts were dried over anhydrous $MgSO_4$. Removal of the solvent left an oil that was precipitated in CH_2Cl_2−petroleum ether to give **14** (2.77 g, 98%) as a white solid. Due to its rapid degradation in air, **14** was used in the next step without further purification. $[\alpha]^{20}_D$ +21 (*c* 0.162, $CHCl_3$). Mp 98 °C. IR (KBr) 1591, 2902, 3060, 3282, 3342 cm^{-1}. ^1H NMR *δ* 1.99−2.06 (m, 3H), 3.42−3.50 (m, 1H), 3.65−3.71 (m, 2H), 6.17 (dd, 1H, *J* = 6.4, 16 Hz), 6.57 (d, 1H, *J* = 16 Hz), 7.20−7.40 (m, 5H). ^{13}C NMR *δ* 55.5, 66.7, 126.5, 127.8, 128.7, 130.8, 131.0, 136.8. HRMS (ESI) calcd for $C_{10}H_{14}NO$ ($M + H^+$) 164.1075, found 164.1076. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.64; H, 7.95; N, 8.49.

2-(1-Ethylbut-3-enylamino)-4-phenylbut-3-en-1-ol (15). To a solution of amino alcohol **14** (1.5 g, 9.20 mmol) in THF (15 mL) was added propanal (534 mg, 9.20 mmol) and anhydrous $MgSO_4$ (2 g). The mixture was stirred overnight and filtered. The resulting mixture was slowly added over 30 min to a solution of allylmagnesium bromide (1 M in Et_2O, 36.81 mmol) in THF (20 mL) cooled to −78 °C. After this addition, the mixture was stirred for 1 h at −78 °C and slowly allowed to warm to −10 °C over 5 h. Then, the reaction mixture

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SCHEME 5

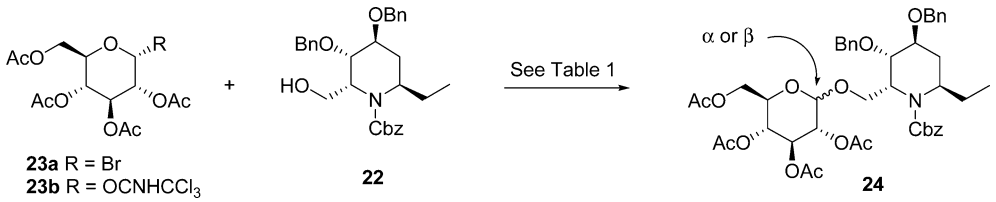
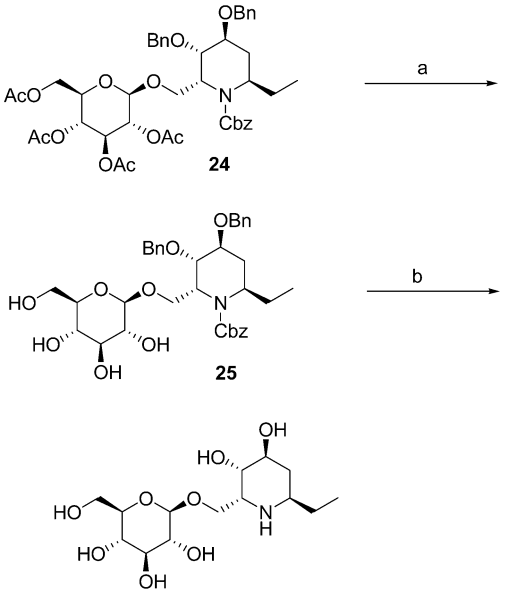


TABLE 1

entry	substrates	conditions	product	yield, %
1	**23a** + **22**	$HgCN_2$, 4 Å Ms, $MeNO_2$, toluene, 60 °C, 5 h	**24** 60%β/40%α	38
2	**23a** + **22**	$AgOTf_2$, CH_2Cl_2, −20 °C, 12 h	starting materials	
3	**23b** + **22**	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C, 2 h	**24** 100%β/0%α	39

SCHEME 6[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH, THF, H_2O, rt, 3 h, 98%. (b) H_2, $Pd(OH)_2$, MeOH, CH_2Cl_2, rt, 4 h, 98%.

was hydrolyzed with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O (4×). The combined organic extracts were washed with brine (1×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (40% EtOAc−petroleum ether then pure EtOAc) affording the diethylenic amino alcohols **15** (1.96 g, 87%) as an inseparable mixture of diastereoisomers (trans/cis: 87/13). Pale yellow oil. IR (KBr) ν 1599, 1639, 2963, 3314 cm^{-1}.

Alcohol *trans*-**15**: ^1H NMR δ (ppm) 0.91 (t, 3H, J = 7.2 Hz), 1.34−1.55 (m, 2H), 2.18−2.22 (m, 2H), 2.61−2.70 (m, 1H), 3.32−3.48 (m, 2H), 3.60−3.66 (m, 1H), 5.07 (s, 1H), 5.10−5.13 (m, 1H), 5.75−5.87 (m, 1H), 6.01 (dd, 1H, J = 7.8, 15.9 Hz), 6.54 (d, 1H, J = 15.9 Hz), 7.24−7.40 (m, 5H). ^{13}C NMR δ (ppm) 10.4, 27.6, 38.0, 55.5, 59.9, 65.2, 117.3, 126.5, 127.8, 128.7, 129.8, 132.3, 135.5, 136.8.

Alcohol *cis*-**15**: ^1H NMR δ (ppm) 0.91 (t, 3H, J = 7.2 Hz), 1.34−1.55 (m, 2H), 2.00−2.33 (m, 2H), 2.61−2.70 (m, 1H), 3.32−3.48 (m, 2H), 3.60−3.66 (m, 1H), 5.07 (s, 1H), 5.10−5.13 (m, 1H), 5.58−5.70 (m, 1H), 5.90 (dd, 1H, J = 7.6, 16 Hz), 6.50 (d, 1H, J = 16 Hz), 7.30−7.41 (m, 5H). ^{13}C NMR δ (ppm) 9.6, 26.7, 38.9, 54.6, 59.6, 65.0, 117.9, 126.5, 127.8, 128.7, 129.7, 132.3, 135.9, 136.8.

3-(1-Ethyl-but-3-enyl)-4-styryloxazolidin-2-one (11). To a solution of the diethylenic amino alcohols **15** (3.68 g, 15.02 mmol) in CH_2Cl_2 (120 mL) was added Et_3N (2.09 mL, 15.02 mmol) and carbonyldiimidazole (CDI) (4.87 g, 30.04 mmol). The mixture was stirred overnight and then an additional portion of CDI (2.44 g, 15.02 mmol) was added and the mixture was stirred for 6 h. The solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.5 N aqueous HCl solution (2×). The combined aqueous phases were extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc−petroleum ether) gave carbamate **11** (3.48 g, 86%) as an inseparable mixture of diastereoisomers (trans/cis: 87/13). Pale yellow oil. IR (KBr) ν 1734, 2965 cm^{-1}.

trans-**11**: ^1H NMR δ (ppm) 0.95 (t, 3H, J = 7.5 Hz), 1.55−1.88 (m, 2H), 2.23−2.32 (m, 1H), 2.44−2.55 (m, 1H), 3.53−3.64 (m, 1H), 3.95−4.04 (m, 1H), 4.39−4.49 (m, 2H), 5.06−5.08 (m, 1H), 5.10 (s, 1H), 5.75−5.87 (m, 1H), 6.10 (dd, 1H, J = 8.4, 15.6 Hz), 6.61 (d, 1H, J = 15.6 Hz), 7.30−7.41 (m, 5H). ^{13}C NMR δ (ppm) 11.4, 24.7, 38.2, 56.2, 58.8, 67.3, 117.6, 126.7, 127.2, 127.3, 128.7, 129.0, 134.8, 135.5, 158.0.

cis-**11**: ^1H NMR δ (ppm) 0.97 (t, 3H, J = 7.9 Hz), 1.51−1.78 (m, 2H), 2.23−2.55 (m, 2H), 3.67−3.73 (m, 1H), 3.95−4.04 (m, 1H), 4.39−4.49 (m, 1H), 5.10−5.12 (m, 1H), 5.19 (s, 1H), 5.75−5.87 (m, 1H), 6.10 (dd, 1H, J = 8.4, 15.6 Hz), 6.62 (d, 1H, J = 15.6 Hz), 7.30−7.41 (m, 5H). ^{13}C NMR δ (ppm) 11.4, 26.9, 36.4, 56.2, 58.4, 67.3, 117.6, 126.7, 127.2, 127.3, 128.7, 129.0, 134.5, 135.5, 158.2.

5-Ethyl-4,5,6,8a-tetrahydroxazolidino[3,4-*a*]pyridin-3-one (9). To a solution of carbamates **11** (1.8 g, 6.64 mmol) in CH_2Cl_2 (1400 mL) was added [Ru]-**16** (284 mg, 0.33 mmol) at room temperature. After being stirred for 1 h at reflux, the solution was allowed to warm to room temperature and DMSO was added (177 μL, 16.5 mmol). The solution was stirred overnight, concentrated under reduced pressure, and purified by flash chromatography (20% EtOAc−petroleum ether) to give tetrahydropyridines *trans*-**9** (921 mg, 83%) and *cis*-**9** (122 mg, 11%) as pale yellow oils.

trans-**9**: $[\alpha]^{20}_D$ +195.7 (*c* 1.555, $CHCl_3$). IR (KBr) 1750, 2966 cm^{-1}. ^1H NMR δ 0.95 (t, 3H, J = 7.2 Hz), 1.43−1.60 (m, 1H), 1.60−1.70 (m, 1H), 1.89−1.97 (m, 1H), 2.46−2.57 (m, 1H), 3.88−3.96 (m, 1H), 3.96 (dd, 1H, J = 6.6, 8.1 Hz), 4.27−4.31 (m, 1H), 4.48 (app t, 1H, J = 8.7 Hz), 5.59−5.64 (m, 1H), 5.82−5.87 (m, 1H). ^{13}C NMR δ 10.8, 24.6, 27.8, 49.3, 49.5, 67.9, 124.5, 126.4, 157.9. HRMS (EI) calcd for $C_9H_{13}NO_2$ (M^+) 167.0946, found 167.0947.

cis-**9**: $[\alpha]^{20}_D$ −5.8 (*c* 0.748, $CHCl_3$). IR (KBr) 1750, 2966 cm^{-1}. ^1H NMR δ 1.00 (t, 3H, J = 7.5 Hz), 1.72−1.86 (m, 1H), 2.04−2.10 (m, 1H), 2.23−2.97 (m, 2H), 3.11−3.21 (m, 1H), 3.96−3.99 (m, 1H), 4.33−4.38 (m, 2H), 5.61 (dt, 1H, J = 1.5, 10.2 Hz), 5.91−5.95 (m, 1H). ^{13}C NMR δ 11.5, 24.6, 29.7, 56.4, 57.2, 67.0, 127.2, 129.5, 157.6.

(5*R*,7*R*,8*S*,8a*R*)-5-Ethyl-7,8-epoxyoxazolidino[3,4-*a*]piperidine-3-one (17). To a solution of tetrahydropyridine *trans*-**9** (1.0 g, 5.99 mmol) in CH_2Cl_2 (80 mL) cooled to 0 °C was added *m*CPBA (70%, 5.97 g, 23.95 mmol). The solution was stirred for 72 h at room temperature and then hydrolyzed with 1/1 saturated aqueous $NaHCO_3$/10% aqueous $Na_2S_2O_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (3×),

washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (80% EtOAc−petroleum ether) gave *endo*-**17** (0.942 g, 86%) as a colorless crystal and *exo*-**17** (54.8 mg, 5%) as a colorless oil.

endo-**17**: $[\alpha]^{20}_D$ −13.9 (*c* 0.720, $CHCl_3$). Mp 86 °C. IR (KBr) 1742, 2974 cm^{-1}. ^1H NMR δ 0.93 (t, 3H, J = 7.5 Hz), 1.46−1.64 (m, 2H), 1.76 (ddd, 1H, J = 1.2, 6.3, 15.6 Hz), 2.27 (dd, 1H, J = 5.4, 15.6 Hz), 3.11−3.12 (m, 1H), 3.32 (app t, 1H, J = 4.8 Hz), 3.71 (app q, 1H, J = 7.5 Hz), 4.14 (ddd, 1H, J = 1.2, 5.4, 8.7 Hz), 4.33 (dd, 1H, J = 5.4, 8.7 Hz), 4.50 (app t, 1H, J = 8.7 Hz). ^{13}C NMR δ 10.7, 25.5, 26.1, 47.1, 48.9, 50.0, 50.2, 65.2, 157.8. HRMS (EI) calcd for $C_9H_{13}NO_3$ (M^+) 183.0895, found 183.0886. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15.; N, 7.65. Found: C, 58.89; H, 7.04; N, 7.83.

exo-**17***:* $[\alpha]^{20}_D$ +3.1 (*c* 0.381, $CHCl_3$). IR (KBr) 1742, 2974 cm^{-1}. ^1H NMR δ 0.87 (t, 3H, J = 7.2 Hz), 1.44−1.59 (m, 1H), 1.74−1.91 (m, 1H), 2.07 (d, 1H, J = 15.6 Hz), 2.19 (ddd, 1H, J = 2.4, 7.2, 15.6), 3.11−3.21 (m, 1H), 3.32−3.33 (m, 1H), 3.72−3.80 (m, 1H), 4.15−4.24 (m, 2H), 4.55−4.64 (m, 1H). ^{13}C NMR δ 11.3, 25.7, 26.7, 48.9, 49.3, 51.5, 53.7, 65.0, 157.4.

Compounds 18 and 19. A solution of epoxide *endo*-**17** (700 mg, 3.83 mmol) was heated at 100 °C in AcOH for 17 h. Then, solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (80% EtOAc−petroleum ether) to give acetate **18** (734 mg, 79%) and diacetate **19** (109 mg, 10%). Acetate **18** and diacetate **19** were independently recrystallized in benzene to give colorless crystals.

Acetate **18**: Mp 116 °C. $[\alpha]^{20}_D$ −15.3 (*c* 0.433, $CHCl_3$). IR (KBr) ν 1711, 1730, 2926, 3355 cm^{-1}. ^1H NMR δ (ppm) 0.91 (t, 3H, J = 7.2 Hz), 1.49−1.63 (m, 1H), 1.73 (dd, 1H, J = 2.7, 15.3 Hz), 1.76−1.90 (dm, 1H, J = 2.7 Hz), 2.07 (s, 3H), 2.27 (ddd, 1H, J = 15.3, 3.3, 6.9 Hz), 3.66 (s, broad, 1H), 3.79 (dt, 1H, J = 15.9, 6.6 Hz), 4.04 (s broad, 1H), 4.07−4.13 (m, 1H), 4.35 (app t, 1H, J = 8.5 Hz), 4.44 (dd, 1H, J = 8.5, 5.1 Hz), 5.06−5.06 (m, 1H). ^{13}C NMR δ (ppm) 11.3, 21.4, 25.5, 26.2, 49.8, 50.3, 63.4, 65.4, 70.5, 158.3, 170.0. HRMS (ESI) calcd for $C_{11}H_{18}NO_5$ ($M + H^+$) 244.1185, found 244.1190. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04.; N, 5.76. Found: C, 54.34; H, 7.21; N, 5.93.

Diacetate **19**: Mp 121 °C. $[\alpha]^{20}_D$ +36.9 (*c* 0.913, $CHCl_3$). IR (KBr) ν 1731, 1747, 2973 cm^{-1}. ^1H NMR δ (ppm) 0.92 (t, 3H, J = 7.5 Hz), 1.50−1.65 (m, 1H), 1.81−1.86 (m, 2H), 2.09 (s, 3H), 2.12 (s, 3H, 3.83−3.93 (m, 1H), 4.07 (dd, 1H, J = 3.9, 8.7 Hz), 4.23−4.27 (m, 1H), 4.36 (app t, 1H, J = 9 Hz), 4.90−4.91 (m, 1H), 5.00−5.03 (m, 1H). ^{13}C NMR δ (ppm) 11.2, 20.8, 21.1, 26.1, 49.1, 49.7, 63.1, 66.6, 67.3, 157.4, 169.1, 170.0. HRMS (ESI) calcd for $C_{13}H_{20}NO_6$ ($M + H^+$) 286.1291, found 286.1288.

Compound 20. A solution of acetate **18** (703 mg, 2.89 mmol) and diacetate **19** (94 mg, 0.330 mmol) in MeOH (50 mL) and H_2O (2 mL) was treated with K_2CO_3 (1.33 g, 9.66 mmol). The resulting mixture was stirred for 3 h at room temperature. Then, the solvent was evaporated under reduced pressure and the residue was taken up in dry MeOH (10 mL) and filtered. The solution was concentrated under reduced pressure and purified by flash chromatography (EtOAc, then 80% EtOAc−MeOH) to yield **20** (615 mg, 95%) as a white solid. Mp 157 °C. $[\alpha]^{20}_D$ −21.4 (*c* 1.177, $CHCl_3$). IR (KBr) ν 1719, 2972, 3365, 3391 cm^{-1}. ^1H NMR (MeOD) δ (ppm) 0.90 (t, 3H, J = 7.5 Hz), 1.59−1.70 (m, 2H), 1.93−2.09 (m, 1H), 2.11 (ddd, 1H, J = 3.3, 7.2, 14.7 Hz), 3.52−3.54 (m, 1H), 3.69 (dt, 1H, J = 6.3, 9.9 Hz), 3.93 (dd, 1H, J = 3, 6.6 Hz), 4.21−4.26 (m, 1H), 4.36−4.39 (m, 1H). ^{13}C NMR (MeOD) δ (ppm) 11.7, 27.8, 29.3, 51.2, 51.8, 65.1, 68.9, 69.3, 160.6. HRMS (ESI) calcd for $C_9H_{16}NO_4$ ($M + H^+$) 202.1079, found 202.1066.

Compound 21. To a stirred solution of diol **20** (450 mg, 2.24 mmol) in dry DMF (25 mL) at 0 °C was added NaH (60% in oil, 537 mg, 13.43 mmol). After the evolution of H_2 had ceased (30 min), benzyl bromide (1.07 mL, 8.96 mmol) was added. After being stirred for 4 h 30 at room temperature, the mixture was quenched with water (15 mL). The aqueous layer was extracted with ether (3×). The combined organic extracts were washed with brine (3×), dried over anhydrous $MgSO_4$, and filtered. Removal of the solvent left an oil that was purified by flash chromatography (20% EtOAc−petroleum ether, then 40% EtOAc−petroleum ether), affording compound **21** (793 mg, 93%) as a colorless oil. $[\alpha]^{20}_D$ +6.0 (*c* 1.433, $CHCl_3$). IR (KBr) ν 1734, 2965, 3031 cm^{-1}. ^1H NMR δ (ppm) 0.95 (t, 3H, J = 7.2 Hz), 1.61−1.75 (m, 1H), 1.84 (dm, 1H, J = 15 Hz), 1.89−2.04 (m, 1H), 2.08 (ddd, 1H, J = 3.3, 6.9, 14.7 Hz), 3.37−3.39 (m, 1H), 3.80−3.88 (m, 2H), 4.17−4.29 (m, 3H), 4.45 (d, 2H, J = 12.3 Hz), 4.64 (dd, 2H, J = 1.5, 11.7 Hz), 7.26−7.42 (m, 10H). ^{13}C NMR δ (ppm) 11.5, 25.4, 26.4, 49.9, 50.1, 63.4, 71.3, 72.0, 72.1, 73.2, 127.4, 127.8, 128.0, 128.1, 128.6, 137.5, 138.0, 158.0. HRMS (ESI) calcd for $C_{23}H_{27}NO_4$ ($M + H^+$) 382.2019, found 382.2015.

Compound 22. To a solution of oxazolidinone **21** (750 mg, 1.97 mmol) in MeOH (30 mL) was added 8 N aqueous NaOH (10 mL). After being stirred at 95 °C for 24 h, the resulting mixture was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (30 mL) and H_2O (10 mL) and cooled to 0 °C. To this solution was added benzyl chloroformate (0.31 mL, 2.17 mmol) and stirring was continued for 4 h at room temperature. The aqueous phase was extracted with CH_2Cl_2 (4×). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (20% EtOAc−petroleum ether) gave **22** (712 mg, 74%) as a colorless oil. $[\alpha]^{20}_D$ +45.8 (*c* 0.467, $CHCl_3$). IR (KBr) ν 1684, 2964, 3063, 3447 cm^{-1}. ^1H NMR δ (ppm) 0.90 (t, 3H, J = 7.2 Hz), 1.56−1.71 (m, 1H), 1.80−2.10 (m, 3H), 3.21 (s broad, 1H), 3.80−3.94 (m, 5H), 4.28 (dd, 1H, J = 6.0, 10.5 Hz), 4.53 (d, 1H, J = 12.0 Hz), 4.62−4.72 (m, 3H), 5.13−5.22 (m, 2H), 7.26−7.36 (m, 15H). ^{13}C NMR δ (ppm) 11.5, 27.6, 28.2, 53.6, 54.5, 63.8, 67.4, 71.4, 72.7, 75.9, 79.1, 127.5, 127.7, 127.9, 127.9, 128.1, 128.5, 128.6, 136.6, 138.0, 138.4, 156.8. HRMS (ESI) calcd for $C_{30}H_{36}NO_5$ ($M + H^+$) 490.2594, found 490.2598.

5-Deoxyadenophorine 5. A solution of 8 N aqueous NaOH (2 mL) was added to a solution of diol **20** (50 mg, 0.249 mmol) in MeOH (3 mL). The solution was stirred for 24 h at 95 °C then evaporated under reduced pressure. The residue was purified by flash chromatography (5% MeOH−1% Et_3N−CH_2Cl_2) to give 5-deoxyadenophorine **5** (38 mg, 88%) as a colorless oil. $[\alpha]^{20}_D$ +52.3 (*c* 0.382, H_2O) [lit.[8] $[\alpha]^{20}_D$ +50.1. (*c* 0.32, H_2O)]. ^1H NMR D_2O δ (ppm) 0.90 (t, 3H, J = 7.5 Hz), 1.09−1.18 (m, 1H), 1.37−1.47 (m, 2H), 2.07 (ddd, 1H, J = 2.7, 4.5, 12.9 Hz), 2.81−2.87 (m, 1H), 3.25−3.32 (m, 1H), 3.65−3.85 (m, 4H). ^{13}C NMR D_2O δ (ppm) 12.4, 30.9, 40.5, 51.7, 59.4, 60.4, 71.6, 76.2.

Compound 24. To a solution of alcohol **22** (100 mg, 0.204 mmol) and trichloroacetimidate **23b** (151 mg, 0.307) in CH_2Cl_2 (5 mL) at −30 °C was added $BF_3{\cdot}Et_2O$ (33.7 μL, 0.266 mmol). After being stirred at −30 °C for 2 h, the resulting mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ (2×) and brine (1×), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (30% EtOAc−petroleum ether) gave **24** (65 mg, 39%) as a colorless oil and **21** (35 mg, 45%). $[\alpha]^{20}_D$ −5.8 (*c* 0.380, $CHCl_3$). IR (KBr) ν 1695, 1750, 2963, 3032 cm^{-1}. ^1H NMR δ (ppm) 0.87 (t, 3H, J = 7.2 Hz), 1.55−1.65 (m, 1H), 1.77−2.20 (m, 15H), 3.50−4.39 (m, 10H), 4.47−4.66 (m, 4H), 4.94−5.17 (m, 5H), 7.26−7.37 (m, 15H). ^{13}C NMR δ (ppm) 11.4, 20.7, 27.3, 28.3, 52.6, 53.6, 61.9, 67.2, 68.4, 71.2, 71.3, 71.7, 72.5, 73.1, 100.7, 127.5, 127.6, 127.7, 128.1, 128.5, 128.6, 136.8, 138.5, 138.7, 156.2, 169.5, 170.4, 170.8. HRMS (ESI) calcd for $C_{44}H_{54}NO_5$ ($M + H^+$) 820.3544, found 820.3570.

Compound 25. To a solution of compound **24** (60 mg, 73.3 μmol) in a mixture of MeOH (5 mL), THF (2 mL), and H_2O (0.2 mL) was added K_2CO_3 (50.5 mg, 0.366 mmol). After being stirred at room temperature for 3 h, the mixture was diluted with water and extracted with CH_2Cl_2 (4×). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography gave **25** (47 mg, 98%) as a colorless oil. $[\alpha]^{20}_D$ +10.3 (*c* 1.05 $CHCl_3$). IR (KBr) ν 1683, 292, 3065, 3419 cm^{-1}. ^1H NMR δ (ppm) 0.86 (t, 3H, J = 7.2 Hz), 1.56−1.69 (m, 1H),

1.73−1.88 (m, 3H), 2.05−2.15 (m, 1H), 2.25 (s broad, 1H), 2.97 (s broad, 1H), 3.23 (s broad, 1H), 3.27−3.32 (m, 1H), 3.46−3.58 (m, 2H), 3.76−3.91 (m, 6H), 4.07 (s broad, 1H), 4.19−4.31 (m, 4H), 4.49−4.70 (m, 4H), 5.08 (d, J = 15.7 Hz), 5.12 (d, J = 15.7 Hz), 7.25−7.31 (m, 15H). ^{13}C NMR δ (ppm) 11.4, 27.9, 28.7, 53.1, 53.5, 62.1, 67.5, 69.2, 70.2, 71.4, 72.6, 73.8, 75.8, 78.6, 103.5, 127.6, 127.8, 128.1, 128.2, 12.5, 128.6, 136.6, 138.2, 138.6, 156.7. HRMS (ESI) calcd for $C_{36}H_{45}NO_{10}$ ($M + H^+$) 652.3122, found 652.3126.

1-*O*-*β*-D-Glucopyranosyl-5-deoxyadenophorine 4. To a solution of compound **25** (40 mg, 61.4 μmol) in a mixture of MeOH (2 mL) and CH_2Cl_2 (1 mL) was added $Pd(OH)_2$ (5 mol %) under an atmosphere of H_2. After being stirred for 48 h at room temperature, the catalyst was filtered and the solvent was concentrated. The residue was taken up in CH_2Cl_2 (0.5 mL) and $NaHCO_3$ (5.2 mg, 61.4 μmol) was added. The solution was filtered on Millipore and the filtrate was evaporated under reduced pressure to give 1-*O*-*β*-D-glucopyranosyl-5-deoxyadenophorine **4** (20.1 mg, 98%) as a colorless oil. $[\alpha]^{20}_D$ +17.6 (*c* 0.87, H_2O) [lit.[8] $[\alpha]^{20}_D$ +11.4 (*c* 0.33, H_2O)]. ^{1}H NMR D_2O δ (ppm) 0.92 (t, 3H, J = 7.5 Hz), 1.09−1.18 (m, 1H), 1.38−1.47 (m, 2H), 2.09 (dm, 1H, J = 12.6 Hz), 2.82−2.87 (m, 1H), 3.29−3.57 (m, 5H), 3.67−3.78 (m, 3H), 3.89−3.96 (m, 2H), 4.11 (dd, 1H, J = 3.6, 10.5 Hz), 4.48 (d, 1H, J = 7.8 Hz). ^{13}C NMR D_2O δ (ppm) 12.4, 30.9, 40.7, 51.6, 58.9, 63.5, 68.6, 71.6, 72.4, 75.9, 76.1, 78.4, 78.7, 106.0.

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

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