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Stereoselective Synthesis of a Series of New *N*-Alkyl-3-hydroxypiperidine Derivatives Containing a Hemiketal

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A series of new *N*-alkyl-3-hydroxypiperidine derivatives containing a five-membered hemiketal were synthesized from 1-*C*-acetylmethyl sugars. Based on the stereochemistry of the products obtained, a plausible mechanism is illustrated. A new approach to the hemiketal, which has undergone hydrogenation in the presence of Pd/C and β-elimination and intramolecular cycloaddition with 1 % NaOMe in methanol, is reported.

Introduction

In the majority of natural products, polyhydroxypiperidines, also called iminosugars, fully deserve to be one of the privileged scaffolds. Since the discovery of the first polyhydroxypiperidine, nojirimycin (**1a**), as a powerful glycosidase inhibitor in the 1960s,[1] polyhydroxypiperidines have been the subject of enduring scientific interest over recent decades. Extensive work has been devoted to the isolation and synthesis of their analogues and derivatives,[2] many of which have already been tested or approved in the treatment of Gaucher's disease,[3] diabetes,[4] viral infection,[5] HIV infection,[6] or tumor metastasis.[7] For example, *N*-hydroxyethyl-1-deoxynojirimycin (miglitol, **1b**) and *N*-butyl-1-deoxynojirimycin (miglustat, **1c**) have been approved for the treatment of type II diabetes and Gaucher's disease, respectively.[8]

Amongst numerous polyhydroxypiperidines, 3-hydroxypiperidine derivatives attracted our attention. Especially, the two naturally occurring compounds (–)-sedacryptine 2[9] and (+)-isofebrifugine 3[10] (Figure 1) possess a fused five-membered hemiketal motif, and a subgroup of these iminosugars having a bicyclic skeleton and *N*-alkyl-3-hydroxypiperidine substitution pattern frequently found in nature.

However, in the considerable synthetic work for the total synthesis of **2**[11,12] and **3**,[11,12a,13] the construction of the hemiketal was mostly achieved under acidic conditions for the condensation reaction between carbonyl and hydroxy groups in very low yield, which could lead to salification of the alkaloidal products and incur troublesome manipulations for neutralization and extraction. Considering the high potential bioactivity and synthetic interest of this subgroup, we designed and synthesized a series of new *N*-alkyl-3-hydroxypiperidine derivatives that share similar substructures with **3**.

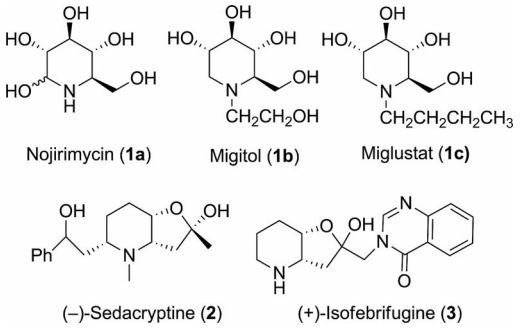

Figure 1. Nojirimycin (**1a**), miglitol (**1b**), miglustat (**1c**), and compounds containing the bicyclic skeleton.

Results and Discussion

It has previously been reported that 1-*C*-(2′-oxoalkyl)glycosides, following base-mediated β-elimination, formed acyclic α,β-conjugates, which enabled an intramolecular hetero-Michael addition through an amino or *N*-substituted amino group to form an iminosugar moiety.[14] This reaction involved 1,4-addition of a nitrogen atom to an α,β-unsaturated carbonyl group with a ring-closure step.[14d] In continuation of our interest in the stereoselective synthesis of *C*-glycosides,[15] we herein report our results concerning the synthesis of iminosugar analogues. The key functional group manipulations for the synthesis of *N*-alkyl-3-hy-

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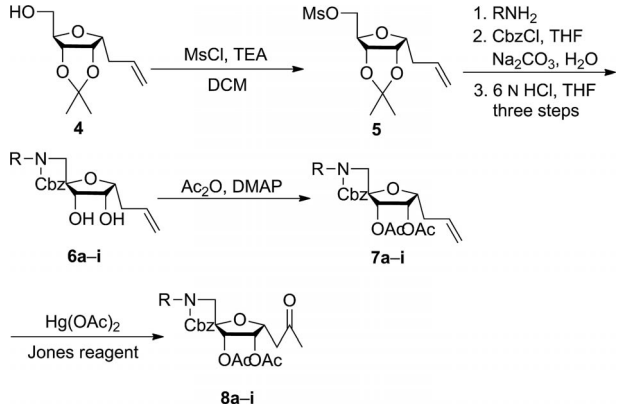
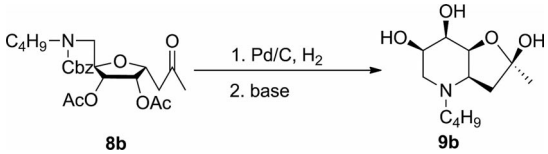
droxypiperidine derivatives **9a**–**i** involved the introduction of 5-substituted amino and 1-*C*-2′-oxoalkyl groups. Starting from D-ribose, the known 1-*C*-allyl glycoside **4** was neatly prepared.[16] Compound **4** was then treated with MsCl/NEt_3 (Ms = mesyl) to provide 5-mesyl-*C*-glycoside **5**. Substitution of the 5-mesyl group by a primary amine and subsequent protection of the amino function with benzyl carbamate (Cbz) gave an intermediate, which afforded the 5-(*N*-alkyl,*N*-Cbz)amino-2,3-diols **6a**–**i** in 72–78% yield for the three steps when the intermediates were treated with aqueous HCl. Reprotection of the resulting diols **6a**–**i** as acetates gave **7a**–**i** in nearly quantitative yields. Afterwards, terminal olefin oxidation of **7a**–**i** with $Hg(OAc)_2$/Jones reagent generated 5-(*N*-alkyl,*N*-Cbz)amino-1-*C*-2′-acetylmethyl glycosides **8a**–**i** (Scheme 1).



Scheme 1. Synthesis of 2′-acetylmethyl glycosides; DMAP: 4-(dimethylamino)pyridine.

To investigate the influence of different bases on the yield of the final product, 1-*C*-[2,3-di-*O*-acetyl-5-(*N*-butyl,*N*-Cbz)amino-5-deoxy-α-D-ribofuranosyl]propan-2-one (**8b**) was tested as a model substrate. After examining various base/solvent combinations, the yields of the final two steps were summarized (Table 1). Inorganic bases, such as Na_2CO_3/H_2O, K_2CO_3/H_2O, and KOH/H_2O, were found to be less effective for the final steps than NaOMe/MeOH. The use of NaOMe/THF, $NaHCO_3/H_2O$, and NEt_3/MeOH (Table 1, Entries 2, 8, and 9) resulted in only a trace amount of the desired product. Thus, with 1% NaOMe/MeOH, we explored the scope of the reaction with different *N*-alkyl-substituted substrates. Exposure of **8** to hydrogen in the presence of Pd/C removed the Cbz protecting group. The

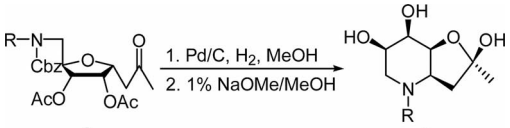
Table 1. Formation of the hemiketal and yield of the products in different bases and solvents.

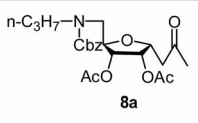
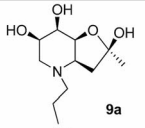
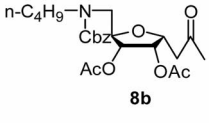
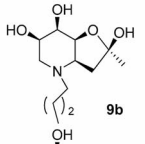
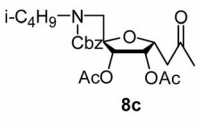
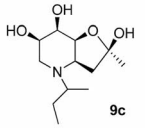
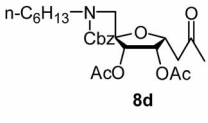
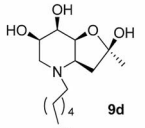
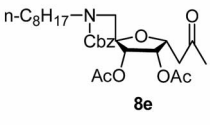
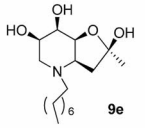
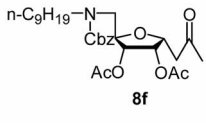
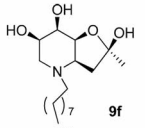
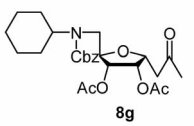
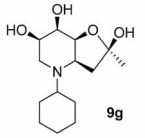
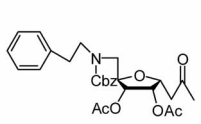
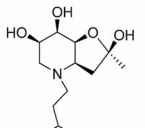
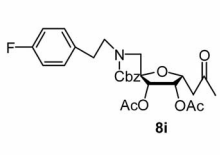
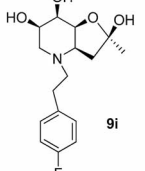


Entry	Base[a]	*t* [h]	Yield[b] [%]
1	NaOMe/MeOH	8	73
2	NaOMe/THF	8	trace
3	NaOMe/MeCN	8	63
4	Na_2CO_3/H_2O	8	46
5	K_2CO_3/H_2O	8	42
6	$NaOH/H_2O$	8	44
7	KOH/H_2O	8	42
8	$NaHCO_3/H_2O$	8	trace
9	NEt_3/MeOH	8	trace

[a] Mass concentration of the basic solution was 1%. [b] Yield after chromatographic purification.

Table 2. Ring-opening reaction of 5-(*N*-alkyl,*N*-Cbz)amino sugars **8** under basic conditions.



Entry	Substrate	Product	Yield
1			72%
2			73%
3			73%
4			70%
5			68%
6			68%
7			71%
8			68%
9			69%

resulting 5-substituted amine, without further purification, was treated with base (1% NaOMe in methanol) to produce aza-*C*-glycosides **9** at room temperature overnight. The final aza-*C*-glycosides were obtained in good yield for those substrates, and the yields of the final two steps under the chosen conditions are outlined in Table 2. As indicated by NMR spectroscopy, signals at δ = 1.48 (s, 3 H) and 106.5 ppm in the ^{1}H and ^{13}C NMR spectra, respectively, supported the presence of a hemiketal unit in the aza-*C*-glycosides **9a**. The stereochemistry of the compounds was further assigned by NOEs, HMBC correlations, and coupling constants.

To ascertain the structure of the bicycles, we tried to obtain single crystals of the final products, and X-ray crystallography analysis was successful for a single crystal of **9g**; this unambiguously confirmed the presence of the key hemiketal group and the stereochemistry of the final products (Figure 2).

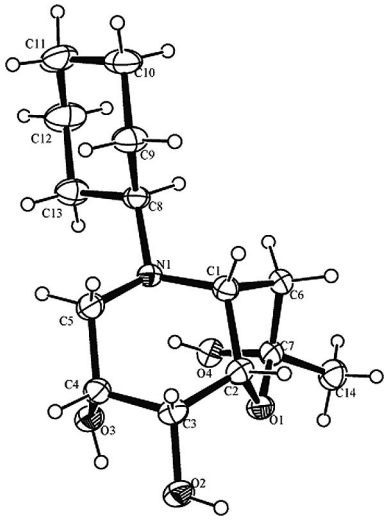
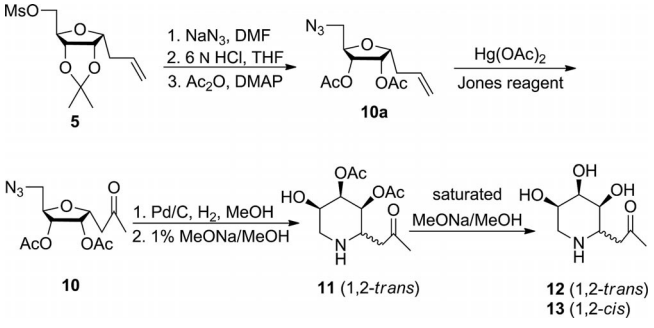


Figure 2. ORTEP drawing of compound **9g**. Ellipsoids are shown at the 50% level of probability.

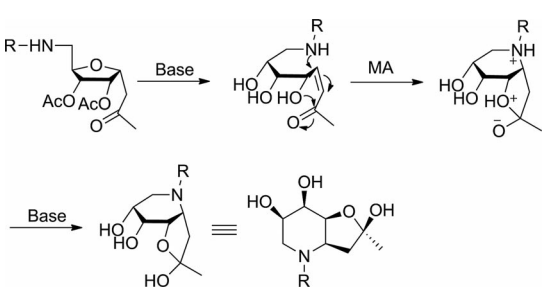
In synthesizing the 5-amino product, we chose 5-azido-*C*-riboside **10** as the substrate (Scheme 2). Reduction of the azido group to the corresponding amine, which was immediately subjected to 1% NaOMe in MeOH at room temperature overnight. The results showed that the acetyl



Scheme 2. Synthesis of piperidine derivatives **12** and **13**.

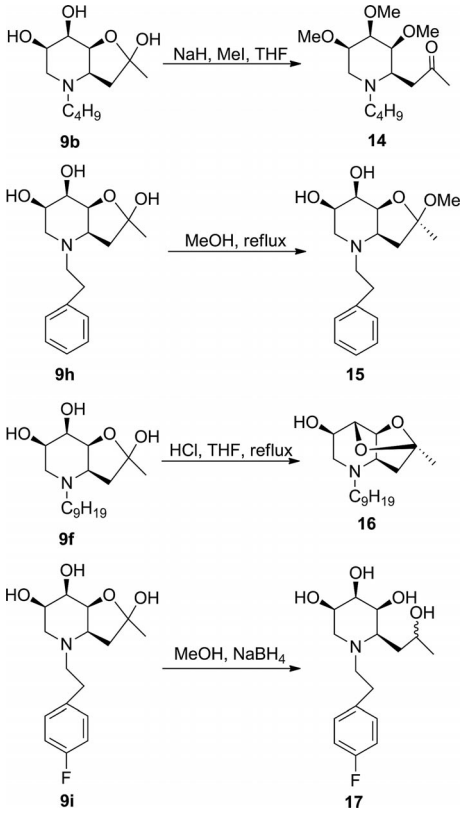
groups were not removed, instead two products were observed by TLC. One of the products was confirmed to be 1,2-*trans*-2,3-di-*O*-acetyl-5-aminoribopyranoside **11a**. Then, we repeated the experiment and the products were not isolated by chromatography, but instead they were treated with a saturated solution of NaOMe/MeOH for 8 h, which gave 1,2-*trans*-5-amino-ribopyranoside **12** ($J_{1,2}$ = 12.1 Hz) and 1,2-*cis*-5-aminoribopyranoside **13**.

Based on the above results, a plausible mechanism is proposed for the formation of the hemiketal under basic conditions. As depicted in Scheme 3, removal of the Cbz protecting group led to the in situ generated amine. The following step involved acetyl group deprotection and ring-opening β-elimination, which produced an acyclic α,β-conjugated ketone as a Michael acceptor.[14] Subsequently, when the conjugate addition of the *N*-substituted amino group to the α,β-unsaturated carbonyl group took place,[14d] the naked, active allylic hydroxy group simultaneously attacked the carbonyl group to give a five-membered hemiketal due to stereochemical factors. However, the unsuccessful deprotection of the acetyl group of compound **10** led to compounds **11** (Scheme 2), which proved that a naked hydroxy group might be necessary for the formation of the hemiketal. Meanwhile, the conversion of **11** to **12** and **13** also demonstrated that the attack of the naked hydroxy group onto the carbonyl group and the *N*-hetero-Michael reaction may be synchronous; otherwise the condensation between the hydroxy and carbonyl groups could not take place under basic conditions.



Scheme 3. Proposed mechanism for the formation of the hemiketal under basic conditions; MA: Michael addition reaction.

Nevertheless, with substrates **9** in hand, to explore the stability and versatility of compounds **9**, our efforts focused on the hemiketal. Reaction of this unit could be accomplished in many different ways (Scheme 4), which generated diverse *N*-substituted iminosugars. Treatment of **9b** with NaH/MeI gave rise to the ring-opened derivative **14** in 81% yield.[17] According to literature procedures,[13c] heating of **9h** in methanol at reflux for 18 h did not provide the ring-opened product, whereas methyl ketal **15** was obtained in moderate yield. However, when **9f** was dissolved in an aqueous solution of HCl and heated at reflux in THF, the intramolecular ketal **16** was obtained. Finally, compound **17** could be readily prepared by reduction of **9i** with $NaBH_4$.[18]



Scheme 4. Synthesis of *N*-substituted iminosugars.

Conclusions

We have developed an NaOMe/MeOH-catalyzed ring-opening reaction using 5-(*N*-alkyl,*N*-Cbz)amino sugars as a new type of reactant. The reaction is efficient and provides a method for stereoselective synthesis of new *N*-alkyl-3-hydroxypiperidine derivatives containing a hemiketal. Furthermore, our approach could facilitate the synthesis of other alkaloid products containing a hemiketal. Further investigations of the scope of this reaction and of the biological activities of these compounds are in progress.

Experimental Section

General Procedures: All reactions sensitive to air or moisture were carried out under nitrogen or argon with anhydrous solvents. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. TLC was performed by using silica gel 60 F254 precoated plates (0.20–0.25 mm thickness) with a fluorescent indicator. Visualization of TLC plates was achieved by UV light (254 nm) and a typical TLC indicator solution (10% sulfuric acid/ethanol solution). Column chromatography was performed on silica gel 90, 200–300 mesh. Melting points were determined with an X-6 (Beijing Fukai Co. Ltd.) melting point apparatus. Optical rotations were measured with a Perkin–Elmer M341 digital polarimeter. ^{1}H and ^{13}C NMR spectra (600 and 150 MHz, respectively) were recorded with a Bruker Avance 600 spectrometer. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants [Hz]. ^{13}C NMR chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ESI-HRMS data were recorded with a BioTOF Q instrument.

CCDC-823764 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthetic Procedures for Compounds 9a–i: A solution of compound **8a**–**i** (1 mmol) in methanol (8 mL) was bubbled with hydrogen in the presence of Pd/C catalyst (200 mg) and stirred at room temperature for 8 h. Then, the solution was filtered and concentrated to give a yellow oil, which was immediately treated with 1% MeONa in methanol at room temperature for 8 h. The reaction mixture was concentrated to give a yellow crude product, which was purified by silica gel flash column chromatography (petroleum ether/acetone, 10:1 → 1:1) to give the final product **9a**–**i**.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-2,6,7-Trihydroxy-2-methyl-4-propyltetrahydrofuro[3,2-*b*]piperidine (9a): Yield 72%, over two steps. Yellow oil. $[\alpha]_D^{20}$ = –68.8 (*c* = 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 4.12 (br. s, 1 H), 3.94 (br. s, 1 H), 3.62 (t, *J* = 7.7 Hz, 1 H), 3.30 (dd, *J* = 3.6, 12.6 Hz, 1 H), 2.93 (t, *J* = 6.2 Hz, 1 H), 2.83–2.73 (m, 1 H), 2.37 (d, *J* = 13.6 Hz, 1 H), 2.24–2.15 (m, 2 H), 1.91 (dd, *J* = 3.6, 13.2 Hz, 1 H), 1.63–1.56 (m, 1 H), 1.54–1.45 (m, 1 H), 1.48 (s, 3 H), 0.92 (t, *J* = 14.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$) δ = 106.5, 80.3, 69.6, 68.7, 63.0, 55.7, 55.2, 42.9, 25.5, 19.6, 11.5 ppm. ESI-HRMS: calcd. for $C_{11}H_{22}NO_4$ [M + H]$^+$ 232.1543; found 232.1538.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-4-Butyl-2,6,7-trihydroxy-2-methyltetrahydrofuro[3,2-*b*]piperidine (9b): Yield 73%, over two steps. Yellow oil. $[\alpha]_D^{20}$ = –90.0 (*c* = 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 4.12 (br. s, 1 H), 3.94 (br. s, 1 H), 3.62 (t, *J* = 7.3 Hz, 1 H), 3.55 (br. s, 1 H), 3.30 (dd, *J* = 3.6, 12.6 Hz, 1 H), 2.93 (t, *J* = 6.2 Hz, 1 H), 2.84–2.79 (m, 1 H), 2.36 (d, *J* = 13.6 Hz, 1 H), 2.25–2.18 (m, 2 H), 1.91 (dd, *J* = 3.6, 13.5 Hz, 1 H), 1.54–1.46 (m, 2 H), 1.48 (s, 3 H), 1.44–1.34 (m, 1 H), 1.35–1.25 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 106.0, 80.3, 69.6, 68.8, 63.0, 55.2, 53.7, 42.9, 28.6, 25.5, 20.4, 13.9 ppm. ESI- HRMS: calcd. for $C_{12}H_{24}NO_4$ [M + H]$^+$ 246.1688; found 246.1700.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-2,6,7-Trihydroxy-4-isobutyl-2-methyltetrahydrofuro[3,2-*b*]piperidine (9c): Yield 73%, over two steps. Yellow oil. $[\alpha]_D^{20}$ = –92.4 (*c* = 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 4.13 (br. s, 1 H), 3.94 (br. s, 1 H), 3.62 (br. s, 1 H), 3.53 (d, *J* = 10.2 Hz, 1 H), 3.31 (dd, *J* = 3.6, 12.6 Hz, 1 H), 2.85 (t, *J* = 6.6 Hz, 1 H), 2.47 (t, *J* = 22.7 Hz, 1 H), 2.36 (d, *J* = 13.2 Hz, 1 H), 2.09 (d, *J* = 12.4 Hz, 1 H), 2.05 (dd, *J* = 4.4, 12.4 Hz, 1 H), 1.94–1.97 (m, 1 H), 1.92 (dd, *J* = 3.6, 6.7 Hz, 1 H), 1.48 (s, 3 H), 0.92 (q, *J* = 9.9 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 105.9, 80.2, 69.5, 68.7, 64.0, 62.5, 55.4, 43.0, 25.5, 25.4, 21.2, 19.9 ppm. ESI-HRMS: calcd. for $C_{12}H_{24}NO_4$ [M + H]$^+$ 246.1700; found 246.1696.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-4-Hexyl-2,6,7-trihydroxy-2-methyltetrahydrofuro[3,2-*b*]piperidine (9d): Yield 70%, over two steps. Yellow oil. $[\alpha]_D^{20}$ = –65.6 (*c* = 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 4.12 (br. s, 1 H), 3.94 (br. s, 1 H), 3.62 (t, *J* = 7.3 Hz, 1 H), 3.30 (dd, *J* = 3.6, 12.6 Hz, 1 H), 2.93 (pt, *J* = 6.2 Hz, 1 H), 2.82–2.77 (m, 1 H), 2.20–2.24 (m, 2 H), 1.90 (dd, *J* = 3.3, 5.6 Hz, 1 H), 1.55–1.53 (m, 1 H), 1.48–1.45 (m, 1 H), 1.48 (s, 3 H), 1.29–1.26 (m, 6 H), 0.88 (t, *J* = 13.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 106.0, 80.3, 69.6, 68.8, 63.0, 55.2, 54.0, 42.9, 31.6, 26.8, 26.4, 25.5, 22.4, 13.9 ppm. ESI-HRMS: calcd. for $C_{14}H_{28}NO_4$ [M + H]$^+$ 274.2013; found 274.2000.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-2,6,7-Trihydroxy-2-methyl-4-octyltetrahydrofuro[3,2-*b*]piperidine (9e): Yield 68%, over two steps. Yellow oil. $[\alpha]_D^{20}$ = –57.4 (*c* = 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 4.12 (br. s, 1 H), 3.94 (br. s, 1 H), 3.62 (t, *J* = 7.3 Hz, 1 H), 3.54 (br. s, 1 H), 3.30 (dd, *J* = 3.6, 12.8 Hz, 1 H), 2.93 (pt, *J* = 6.2 Hz, 1 H), 2.82–2.77 (m, 1 H), 2.36 (d, *J* = 13.2 Hz, 1 H), 2.24–2.20 (m, 2 H), 1.90 (dd, *J* = 3.6, 13.2 Hz, 1 H), 1.59–1.51 (m, 1 H), 1.48–1.43 (m, 1 H), 1.48 (s, 3 H), 1.29–1.26 (m, 12 H), 0.88 (t, *J* = 13.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 106.0, 80.3, 69.6, 68.8, 63.0, 55.2, 54.0, 42.9, 31.7, 29.4, 29.1, 27.2, 26.4, 25.5, 22.5, 14.0 ppm. ESI-HRMS: calcd. for $C_{16}H_{32}NO_4$ $[M + H]^+$ 302.2326; found 302.2330.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-2,6,7-Trihydroxy-2-methyl-4-nonyltetrahydrofuro[3,2-*b*]piperidine (9f): Yield 68%, over two steps. Yellow oil. $[\alpha]_D^{20}$ = –47.8 (*c* = 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 4.12 (br. s, 1 H), 3.94 (br. s, 1 H), 3.62 (br. s, 1 H), 3.30 (dd, *J* = 2.9, 12.4 Hz, 1 H), 2.93 (t, *J* = 5.8 Hz, 1 H), 2.82–2.77 (m, 1 H), 2.36 (d, *J* = 13.2 Hz, 1 H), 2.24–2.16 (m, 2 H), 1.90 (dd, *J* = 5.8, 13.3 Hz, 1 H), 1.58–1.53 (m, 1 H), 1.48–1.37 (m, 1 H), 1.48 (s, 3 H), 1.29–1.26 (m, 12 H), 0.88 (t, *J* = 13.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 106.0, 80.3, 69.6, 68.8, 63.0, 55.3, 54.1, 42.9, 31.8, 29.48, 29.42, 29.2, 27.2, 26.4, 25.5, 22.6, 14.0 ppm. ESI-HRMS: calcd. for $C_{17}H_{34}NO_4$ $[M + H]^+$ 316.2484; found 316.2494.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-4-Cyclohexyl-2,6,7-trihydroxy-2-methyltetrahydrofuro[3,2-*b*]piperidine (9g): Yield 71%, over two steps. White powder. $[\alpha]_D^{20}$ = –93.5 (*c* = 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 4.13 (br. s, 1 H), 3.94 (br. s, 1 H), 3.58 (t, *J* = 7.3 Hz, 1 H), 3.45 (br. s, 1 H), 3.32 (t, *J* = 5.8 Hz, 1 H), 3.14 (dd, *J* = 3.6, 12.4 Hz, 1 H), 2.80–2.76 (tt, *J* = 6.2, 11.5, 21.4 Hz, 1 H), 2.45 (d, *J* = 13.6 Hz, 1 H), 2.40 (d, *J* = 12.4 Hz, 1 H), 1.85 (dd, *J* = 3.3, 13.5 Hz, 2 H), 1.82–1.78 (m, 2 H), 1.68–1.66 (m, 1 H), 1.61–1.60 (m, 1 H), 1.52–1.49 (m, 1 H), 1.48 (s, 3 H), 1.37–1.05 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 105.8, 80.6, 69.7, 68.8, 59.0, 57.5, 49.0, 42.7, 31.1, 26.3, 26.0, 25.9, 25.4, 24.5 ppm. ESI-HRMS: calcd. for $C_{14}H_{26}NO_4$ $[M + H]^+$ 272.1856; found 272.1863.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-2,6,7-Trihydroxy-2-methyl-4-phenethyltetrahydrofuro[3,2-*b*]piperidine (9h): Yield 68%, over two steps. Yellow oil. $[\alpha]_D^{20}$ = –59.0 (*c* = 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 7.32–7.29 (t, *J* = 15.0 Hz, 2 H), 7.23 (t, *J* = 14.7 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 4.09 (br. s, 1 H), 3.96 (br. s, 1 H), 3.62 (br. s, 1 H), 3.44 (dd, *J* = 3.3, 12.4 Hz, 2 H), 3.07–3.02 (m, 2 H), 2.95 (br. s, 1 H), 2.89–2.85 (m, 1 H), 2.79–2.72 (m, 1 H), 2.55–2.50 (m, 1 H), 2.29 (dd, *J* = 12.4, 26.5 Hz, 2 H), 2.16 (d, *J* = 5.4 Hz, 1 H), 1.89 (dd, *J* = 3.7, 13.5 Hz, 1 H), 1.43 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 139.0, 128.7, 128.7, 128.6, 128.6, 126.6, 105.7, 80.1, 69.5, 68.8, 62.9, 55.8, 55.7, 43.1, 32.9, 25.7 ppm. ESI-HRMS: calcd. for $C_{16}H_{24}NO_4$ $[M + H]^+$ 294.1700; found 294.1695.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-4-(*p*-Fluorophenethyl)-2,6,7-trihydroxy-2-methyltetrahydrofuro[3,2-*b*]piperidine (9i): Yield 69%, over two steps. Yellow oil. $[\alpha]_D^{20}$ = –64.2 (*c* = 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 7.16–7.13 (m, 2 H), 7.00–6.97 (m, 2 H), 4.11 (br. s, 1 H), 3.97 (m, 1 H), 3.63 (t, *J* = 7.3 Hz, 1 H), 3.50 (br. s, 1 H), 3.41 (dd, *J* = 3.6, 12.4 Hz, 1 H), 3.07–2.99 (m, 1 H), 2.95 (t, *J* = 6.2 Hz, 1 H), 2.87–2.84 (m, 1 H), 2.77–2.70 (m, 1 H), 2.52–2.47 (m, 1 H), 2.28 (dd, *J* = 12.4, 24.1 Hz, 2 H), 2.16 (s, 1 H), 1.90 (dd, *J* = 3.6, 13.5 Hz, 1 H), 1.44 (s, 3 H), 1.23 (d, *J* = 17.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 162.4, 160.8, 134.6, 130.0, 129.9, 115.5, 105.8, 80.1, 69.5, 68.7, 62.9, 55.9, 43.1, 43.1, 32.2, 25.6 ppm. ESI-HRMS: calcd. for $C_{16}H_{23}NFO_4$ $[M + H]^+$ 312.1606; found 312.1607.

1-*C*-Acetylmethyl 2,3-Di-*O*-acetyl-5-azido-5-deoxy-α-D-ribfuranoside (10): A solution of **5** (0.8 g, 2.7 mmol) in DMF (10 mL) was treated with NaN_3 (0.5 g, 8.2 mmol) at 80 °C for 8 h. Then, the mixture was poured into cold water (30 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was successively washed with water (2 × 50 mL) and brine (3 × 100 mL), then dried with anhydrous Na_2SO_4. The filtrate was concentrated to give a colorless oil, which was subsequently heated with 6 N HCl/THF (1:1; 20 mL) at 50 °C. After 18 h, the aqueous mixture was neutralized with $NaHCO_3$ powder and extracted with EtOAc (3 × 60 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated to give a brown oil. Without further purification, the obtained oil was dissolved in Ac_2O (6 mL) at 0 °C and treated with DMAP (8 mg). The ice bath was removed, and the solution was stirred at room temperature for 5 h. The mixture was poured into cold water (30 mL), washed with 1 N HCl, brine, and water, and dried with Na_2SO_4. The filtrate was concentrated in vacuo and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate, 5:1) to afford compound **10a** as a colorless oil (0.6 g, 2.1 mmol, 78%, over three steps). $[\alpha]_D^{20}$ = +70.0 (*c* = 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 5.74–5.68 (m, 1 H), 5.41 (t, *J* = 7.9 Hz, 1 H), 5.25 (dd, *J* = 4.6, 7.8 Hz, 1 H), 5.07 (dd, *J* = 1.5, 17.2 Hz, 1 H), 5.05 (dd, *J* = 0.9, 9.8 Hz, 1 H), 4.22 (td, *J* = 3.4, 6.9, 14.1 Hz, 1 H), 4.15–4.12 (m, 1 H), 3.55 (dd, *J* = 3.2, 13.2 Hz, 1 H), 3.27 (dd, *J* = 4.2, 13.2 Hz, 1 H), 2.42–2.37 (m, 1 H), 2.34–2.29 (m, 1 H), 2.10 (s, 3 H), 2.00 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.8, 159.5, 133.0, 117.7, 79.0, 78.2, 72.7, 72.4, 52.0, 33.8, 20.5, 20.4 ppm. ESI-HRMS: calcd. for $C_{12}H_{17}N_3O_5Na$ $[M + Na]^+$ 306.1060; found 306.1063. A solution of Jones reagent (2 M, 6 mL) was added dropwise to a solution of **10a** (0.6 g, 2.1 mmol) and $Hg(OAc)_2$ (200 mg, 0.6 mmol) in acetone/water (4:1, 20 mL) at 0 °C. The dark greenish-brown mixture was stirred at 0 °C to room temperature overnight and then poured into cold water (40 mL). The aqueous mixture was extracted with EtOAc (3 × 60 mL). The organic layer was successively washed with water (2 × 50 mL) and brine (5 × 100 mL) and dried with anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate, 2:1) to afford compound **10** as a colorless oil (0.47 g, 1.6 mmol, 76%). $[\alpha]_D^{20}$ = +66.0 (*c* = 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 5.51 (t, *J* = 8.7 Hz, 1 H), 5.29 (dd, *J* = 4.8, 7.3 Hz, 1 H), 4.70–4.67 (m, 1 H), 4.14–4.12 (m, 1 H), 3.54 (dd, *J* = 6.3, 13.1 Hz, 1 H), 3.33 (dd, *J* = 4.6, 13.1 Hz, 1 H), 2.82 (dd, *J* = 7.3, 16.9 Hz, 1 H), 2.69 (dd, *J* = 5.9, 16.9 Hz, 1 H), 2.19 (s, 3 H), 2.11 (s, 3 H), 3.11 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 204.9, 169.6, 169.5, 78.4, 75.2, 72.7, 72.4, 52.1, 43.5, 30.3, 20.4, 20.4 ppm. ESI-HRMS: calcd. for $C_{12}H_{17}N_3O_6Na$ $[M + Na]^+$ 322.1010; found 322.1016.

1-*C*-Acetylmethyl 2,3-Di-*O*-acetyl-5-deoxy-5-amino-β-D-ribopyranoside (11a): A solution of compound **10** (0.4 g, 1.3 mmol) in methanol (8 mL) was bubbled with hydrogen in the presence Pd/C catalyst (200 mg) and stirred at room temperature for 8 h. Then, the solution was filtered and concentrated to give a yellow oil, which was immediately treated with 1% MeONa in methanol at room temperature for 8 h. The reaction mixture was concentrated to give a yellow crude product. The crude product was purified by silica gel flash column chromatography (ethyl acetate/methanol, 10:1) to give the final product **11a** as a yellow oil (0.27 g, 1.0 mmol, 75%). $[\alpha]_D^{20}$ = –28.2 (*c* = 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 5.43 (d, *J* = 2.2 Hz, 1 H), 4.50 (br. dd, *J* = 2.9, 10.3 Hz, 1 H), 3.79–3.77 (m, 1 H), 3.28–3.25 (m, 1 H), 2.92–2.89 (m, 1 H), 2.81 (dd, *J* = 2.6, 11.7 Hz, 1 H), 2.78 (d, *J* = 2.9 Hz, 1 H), 2.73 (br. s, 1 H), 2.61 (br. dd, *J* = 2.6, 17.6 Hz, 1 H), 2.35 (m, 1 H), 2.12 (s, 3 H), 2.11 (s, 3 H), 1.96 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 207.7, 171.0, 169.9, 71.8, 71.2, 67.5, 49.5, 46.3, 44.8, 30.8, 30.5, 20.8, 20.7 ppm. ESI-HRMS: calcd. for $C_{12}H_{20}NO_6Na$ $[M + H]^+$ 274.1285; found 274.1286.

1-*C*-Acetylmethyl 5-Amino-5-deoxy-β-D-ribopyranoside (12) and 1-*C*-Acetylmethyl 5-Amino-5-deoxy-α-D-ribopyranoside (13): A solution of **11** (0.1 g, 0.36 mmol) was treated with a saturated solution of MeONa in methanol at room temperature for 8 h. The reaction mixture was concentrated to give the yellow crude product. The crude product was purified by silica gel flash column chromatography (ethyl acetate/methanol, 2:1 → 1:1) to give the final products **12** (0.03 g, 0.15 mmol, 49%) and **13** (0.026 g, 0.14 mmol, 46%) as yellow oils.

12: $[\alpha]_D^{20}$ = –21.6 (*c* = 0.6, MeOH). ^{1}H NMR (CD_3OD): δ = 3.99 (s, 1 H), 3.62–3.59 (m, 1 H), 3.23 (dd, *J* = 2.6, 10.3 Hz, 1 H), 3.03 (t, *J* = 17.2 Hz, 1 H), 2.69 (dd, *J* = 4.7, 12.1 Hz, 1 H), 2.61 (t, *J* = 23.5 Hz, 1 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (D_2O): δ = 214.4, 71.7, 71.4, 68.2, 50.4, 45.3, 44.0, 29.7 ppm. ESI-HRMS: calcd. for $C_8H_{16}NO_4$ $[M + H]^+$ 190.1074; found 190.1092.

13: $[\alpha]_D^{20}$ = –20.5 (*c* = 0.2, MeOH). ^{1}H NMR (CD_3OD): δ = 3.77 (s, 1 H), 3.66 (s, 1 H), 3.49 (s, 1 H), 3.02–2.96 (m, 2 H), 2.77–2.59 (m, 3 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (CD_3OD): δ = 208.5, 71.6, 69.6, 69.2, 54.5, 49.9, 44.9, 29.1 ppm. ESI-HRMS: calcd. for $C_8H_{16}NO_4$ $[M + H]^+$ 190.1074; found 190.1092.

1-*C*-Acetylmethyl 5-Butylamino-5-deoxy-2,3,4-trimethoxy-α-D-ribopyranoside (14): A solution of **9b** (30 mg, 0.12 mmol) in THF (5 mL) was treated with NaH (10 mg, 0.4 mmol) at 0 °C under argon for 1 h. Then MeI (0.5 mL) was added dropwise, and the solution was stirred overnight. The mixture was quenched with water, and the solvent was evaporated to give a yellow residue, which was subsequently purified by silica gel flash column chromatography (petroleum ether/ethyl acetate, 3:1 → 1:1) to give compound **14** as a yellow oil (28 mg, 0.1 mmol, 81%). $[\alpha]_D^{20}$ = +44.1 (*c* = 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 3.86 (br. s, 1 H), 3.78 (q, *J* = 5.5 Hz, 1 H), 3.57 (s, 3 H), 3.40 (s, 3 H), 3.33 (s, 3 H), 3.32–3.23 (m, 2 H), 2.90 (dd, *J* = 5.1, 16.8 Hz, 1 H), 2.63–2.56 (m, 2 H), 2.48–2.41 (m, 2 H), 2.39–2.31 (m, 1 H), 2.19 (s, 3 H), 1.43–1.25 (m, 4 H), 0.88 (t, *J* = 15.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.4, 79.7, 77.6, 77.5, 60.8, 57.1, 56.5, 54.8, 53.9, 44.6, 36.8, 30.9, 29.9, 20.4, 13.9 ppm. ESI-HRMS: calcd. for $C_{15}H_{30}NO_4$ $[M + H]^+$ 288.2169; found 288.2180.

(2*R*,3a*R*,6*R*,7*R*,7a*S*)-6,7-Dihydroxy-2-methoxy-2-methyl-4-(phenethyl)tetrahydrofuro[3,2-*b*]piperidine (15): Compound **9h** (30 mg, 0.1 mmol) was dissolved in MeOH (5 mL) and heated to reflux with anhydrous HCl under argon for 18 h. The solution was then concentrated to give a yellow residue, which was subsequently purified by silica gel flash column chromatography (petroleum ether/ethyl acetate, 3:1) to give compound **15** as a yellow oil (16 mg, 0.052 mmol, 52%). $[\alpha]_D^{20}$ = –16.2 (*c* = 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.28–7.26 (m, 2 H), 7.18–7.17 (m, 2 H), 4.12 (br. s, 1 H), 3.84 (d, *J* = 11.0 Hz, 1 H), 3.60 (br. s, 1 H), 3.24 (dd, *J* = 3.6, 12.3 Hz, 1 H), 3.17 (s, 3 H), 2.91–2.78 (m, 3 H), 2.77–2.68 (m, 2 H), 2.47–2.43 (m, 1 H), 2.24 (d, *J* = 12.4 Hz, 1 H), 1.98 (dd, *J* = 5.5, 13.7 Hz, 1 H), 1.86 (d, *J* = 13.6 Hz, 1 H), 1.09 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 140.2, 128.8, 128.4, 126.1, 106.7, 78.7, 69.0, 68.7, 63.3, 55.2, 54.6, 48.9, 44.8, 33.2, 29.6, 22.7 ppm. ESI-HRMS: calcd. for $C_{17}H_{26}NO_4$ $[M + H]^+$ 308.1856; found 308.1855.

Tricyclic Compound 16: Compound **9e** (25 mg, 0.08 mmol) was treated with a 3 N aqueous solution of HCl (5 mL) in THF (5 mL) and the mixture heated to reflux for 24 h. The solution was then extracted with EtOAc (3 × 20 mL). The organic layer was successively washed with water (2 × 20 mL) and brine (5 × 20 mL) and dried with anhydrous Na_2SO_4. The filtrate was concentrated in vacuo, and the residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate, 3:1) to give compound **16** as a colorless oil (21.7 mg, 0.073 mmol, 92%). $[\alpha]_D^{20}$ = –45.4 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 4.51–4.44 (m, 1 H), 4.43–4.37 (m, 1 H), 3.67 (s, 1 H), 3.20 (dd, *J* = 12.7, 3.0 Hz, 1 H), 2.89 (d, *J* = 1.8 Hz, 1 H), 2.60 (dd, *J* = 9.0, 6.3 Hz, 2 H), 2.51 (d, *J* = 12.7 Hz, 1 H), 1.97 (dd, *J* = 14.1, 4.6 Hz, 1 H), 1.74 (d, *J* = 14.2 Hz, 1 H), 1.47 (s, 3 H), 1.44 (t, *J* = 10.8 Hz, 2 H), 1.27 (dd, *J* = 21.1, 6.7 Hz, 13 H), 0.87 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 106.3, 75.4, 74.0, 64.0, 56.5, 55.5, 49.5, 37.7, 31.8, 29.5, 29.2, 27.9, 27.2, 22.9, 22.6, 14.0 ppm. ESI-HRMS: calcd. for $C_{17}H_{32}NO_3$ $[M + H]^+$ 298.2377; found 298.2386.

1-*C*-2-Hydroxypropyl 5-Deoxy-5-[(*p*-fluorophenethyl)amino]-α-D-ribopyranoside (17): A solution of **9i** (40 mg, 0.12 mmol) in MeOH (5 mL) was treated with $NaBH_4$ (6 mg, 0.15 mmol) at 0 °C for 1 h. The mixture was quenched with water, and the solvent was evaporated to give a yellow residue, which was subsequently purified by silica gel flash column chromatography ($CHCl_3$/MeOH, 5:1 → 2:1) to give compound **17** as a colorless oil (27.4 mg, 0.087 mmol, 73%). $[\alpha]_D^{20}$ = –31.8 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.13–7.07 (m, 2 H), 6.96–6.91 (m, 2 H), 4.07–3.54 (m, 4 H), 2.86–2.50 (m, 6 H), 1.91–1.47 (m, 2 H), 1.23–1.16 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 162.2, 160.6, 135.4, 130.0, 115.3, 115.2, 70.7, 66.4, 66.0, 60.5, 54.9, 51.2, 51.0, 33.4, 24.2, 24.1 ppm. ESI-HRMS: calcd. for $C_{16}H_{25}NFO_4$ $[M + H]^+$ 314.1762; found 314.1759.

Supporting Information (see footnote on the first page of this article): Characterization data of compounds **5**, **6a**–**i**, **7a**–**i**, **8a**–**i**, characterization data and NMR spectra of the new compounds.

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