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Stereoselective Chirality Extension of *syn,anti*- and *syn,syn*-Oxazine and Stereochemical Analysis of Chiral 1,3-Oxazines: Stereoselective Total Syntheses of (+)-1-Deoxygalactonojirimycin and (−)-1-Deoxygulonojirimycin

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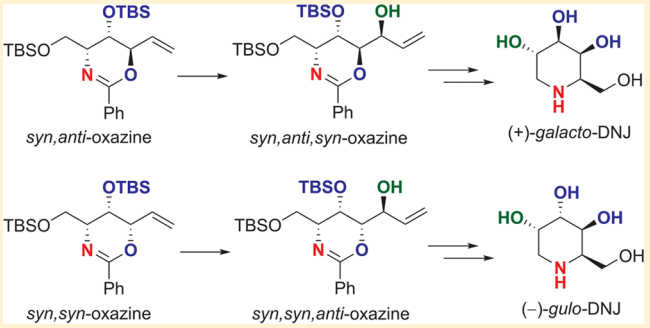
Supporting Information

ABSTRACT: This paper describes the stereoselective total syntheses of (+)-1-deoxygalactonojirimycin and (−)-1-deoxygulonojirimycin via new chiral building blocks *syn,anti,syn*-oxazine **11a** and *syn,syn,anti*-oxazine **13a**. These were accomplished in four steps in 44.1 and 33.7% overall yields, respectively. These chirons were derived from the stereoselective addition of a nucleophile to the corresponding aldehydes of *syn,anti*-oxazine **10** and *syn,syn*-oxazine **12**. Furthermore, this paper describes the stereochemical analysis of three types of chiral 1,3-oxazines; *anti,syn*-, *syn,anti*-, and *syn,syn*-oxazines using the NOESY technique.



INTRODUCTION

Polyhydroxylated piperidines have attracted the attention of organic chemists in recent years because of their promising biological activities and synthetically challenging structural features. They have been especially regarded as possible therapeutics for the treatment of viral infections, diabetes, and cancers. These polyhydroxylated piperidines, also known as iminosugars or azasugars, closely resemble monosaccharides in terms of their shapes and structures.[1,2]

(+)-Nojirimycin (**1**) and its reduced analogue, (+)-1-deoxynojirimycin ((+)-DNJ, **2**),[3] are glucosidase inhibitors and are also analogues of D-glucose. Similarly, (+)-galactonojirimycin (**3**) and its reduced analogue, (+)-1-deoxygalactonojirimycin ((+)-*galacto*-DNJ, **4**),[4] display strong inhibitory activities toward several β-galactosidases and α-galactosidases. In addition, (−)-1-deoxygulonojirimycin ((−)-*gulo*-DNJ, **5**)[5] is a potent and selective inhibitor of fucosidases (Figure 1).[2] Notably, miglitol (**6**)[6a] and miglustat (**7**),[6b] both nojirimycin derivatives, are approved drugs for diabetes.[6]

Over the past several years, we have synthesized efficient chirons through the Pd(0)-catalyzed stereoselective intramolecular cyclization of homoallyl benzamide using a π-allylpalladium complex. We have reported three types of chirons, namely, chiral 1,3-oxazines, *syn,syn*-, *syn,anti*-, and *anti,syn*-oxazines[7,8] (Figure 2a,b), and applied them to the total syntheses of D-*xylo*-, D-*arabino*-, and D-*lyxo*-phytosphingosines[7d,8c] with simple transformations. For the purpose of synthesizing more complicated aminopolyols with four or more contiguous chiral centers, the three chirons are required to be extended.

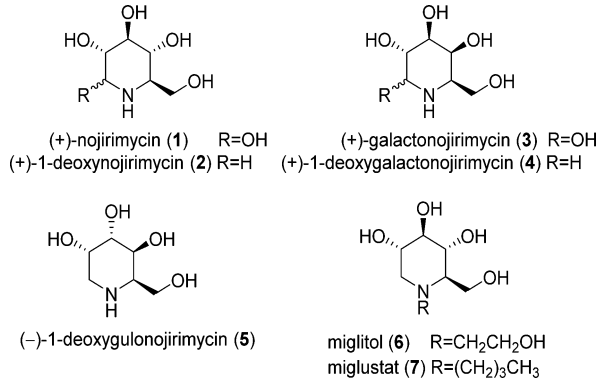


Figure 1. Chemical structures of several nojirimycin derivatives.

Recently, we derived the novel chiron *anti,syn,syn*-oxazine **9a** from *anti,syn*-oxazine **8** (Figure 2c) and successfully applied it to the total syntheses of (−)-conduramine F-1,[9] (+)-hyacinthacine A_2,[10] (−)-sphingofungin B,[10] (+)-DNJ,[3] (2*R*,5*R*)-dihydroxymethyl-(3*R*,4*R*)-dihydroxypyrrolidine ((+)-DMDP),[3] and (+)-radicamine B.[11] As part of a program directed at expanding the synthetic utility of *syn,anti*-oxazine **10** and *syn,syn*-oxazine **12**, we herein report the syntheses of novel chirons *syn,anti,syn*-oxazine **11a** and *syn,syn,anti*-oxazine **13a** and their application to the stereoselective total syntheses of (+)-*galacto*-DNJ (**4**) and (−)-*gulo*-DNJ (**5**).

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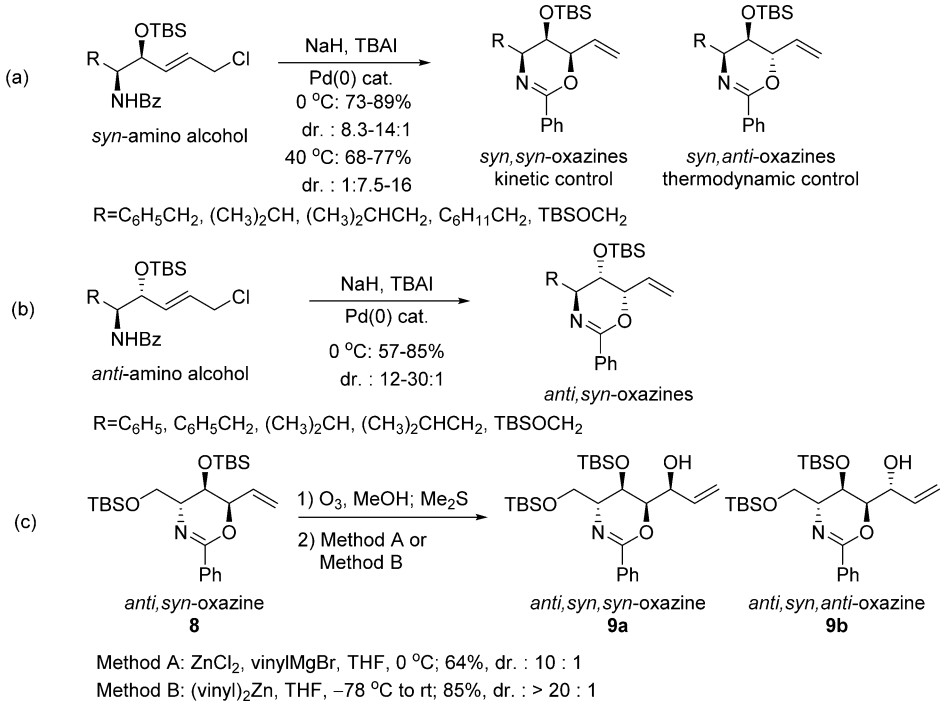
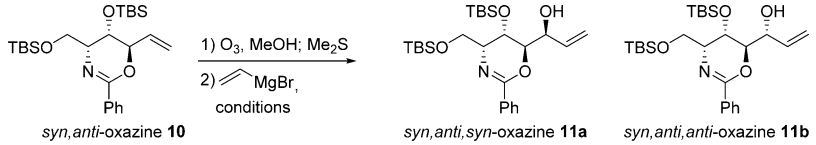


Figure 2. Our previous research on chiral 1,3-oxazines.

Table 1. Stereoselective Chirality Extension of *syn,anti*-Oxazine



entry	Lewis acid	temp	solvent	ratio (**11a**/**11b**)[a,b]	yield (%)[c]
1	N/A	−78 °C	THF	1.2:1	68
2	$BF_3{\cdot}OEt_2$	−78 °C	THF	1:1.3	44
3	$ZnCl_2$	−78 °C	THF	8:1	71
4	$ZnCl_2$	−78 °C	CH_2Cl_2	5:1	63
5	$TiCl_4$	−78 °C	THF	1:2	45
6	$TiCl_4$	−78 °C	CH_2Cl_2	1:3	51
7[d]	N/A	0 °C to rt	THF	1:1	

[a]The ratio was determined by integrating the relevant ^{1}H NMR resonances. [b]The relative stereochemistry was established based on the R_f values from TLC analyses and comparison with ^{1}H and ^{13}C NMR of analogues **9a** and **9b**. [c]Yields refer to isolated mixture of **11a** and **11b** over two steps. [d]Divinylzinc was used instead of vinylmagnesium bromide.

RESULTS AND DISCUSSION

Stereoselective Chirality Extension of *syn,anti*-Oxazine and *syn,syn*-Oxazine. The stereoselective addition of vinylmagnesium bromide to the corresponding aldehyde of *syn,anti*-oxazine **10** under various conditions is summarized in Table 1. The Lewis acid (1.0 equiv) was added dropwise to a solution of the corresponding aldehyde of *syn,anti*-oxazine **10** at −78 °C and stirred for 30 min. This was followed by the addition of vinylmagnesium bromide (3 equiv). Entries 1 and 2 show that *syn,anti*-oxazine **10** does not result in a stereoselective reaction without additional chelating metal. In entries 3 and 4, $ZnCl_2$ gave high *syn*-selectivity and good yield (*syn*/*anti* = 8:1, 71%). $TiCl_4$ resulted in a low *anti*-directed selectivity and low yield (entries 5 and 6). Surprisingly, divinylzinc, which gave excellent *syn*-selectivity with *anti,syn*-oxazine **8**,[8] did not result in a stereoselective reaction (entry 7).

The stereoselective addition of vinylmagnesium bromide to the corresponding aldehyde of **12** is presented in Table 2. Entry 1 indicates that even without a chelating metal, **12** produced **13a** with high selectivity and in moderate yield. Surprisingly, $ZnCl_2$ and divinylzinc gave poor selectivity and low yields (entries 2 and 3). $TiCl_4$, $MgBr_2{\cdot}OEt_2$, and $SnCl_4$ were also examined, and they resulted in *anti*-selective addition, albeit with low yields (entries 4−7). As a long chelation time may result in degraded material, the chelation time was reduced to 15 min, which resulted in a highly *anti*-selective reaction and improved yield (entry 8).

Stereoselective Total Syntheses of (+)-*galacto*-DNJ (4) and (−)-*gulo*-DNJ (5). These results were used for the syntheses of (+)-*galacto*-DNJ (**4**) and (−)-*gulo*-DNJ (**5**) (Scheme 1). Acetate protection of the alcohol functions in *syn,anti,syn*-oxazine **11a** and *syn,syn,anti*-oxazine **13a** and subsequent ring cleavage under Schotten−Baumann conditions

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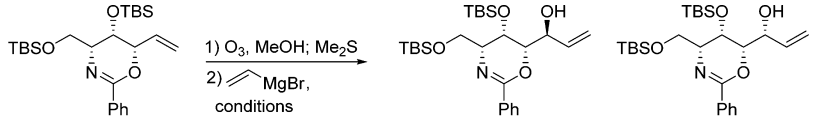
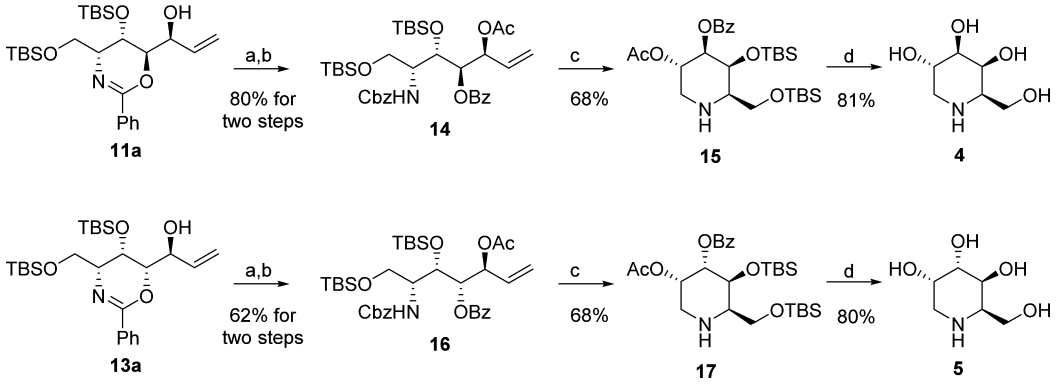
Table 2. Stereoselective Chirality Extension of *syn,syn*-Oxazine



entry	Lewis acid	temp	solvent	ratio (**13a**/**13b**)[a,b]	yield (%)[c]
1	N/A	−78 °C	CH_2Cl_2	6:1	48
2[d]	$ZnCl_2$	−78 °C	THF	1:1.5	12
3[e]	N/A	0 °C	THF	1:1.3	14
4[d]	$TiCl_4$	−78 °C	THF	6:1	20
5[d]	$MgBr_2{\cdot}OEt_2$	−78 °C	THF	6:1	20
6[d]	$SnCl_4$	−78 °C	THF	10:1	18
7[d]	$SnCl_4$	−78 °C	CH_2Cl_2	10:1	18
8[f]	$SnCl_4$	−78 °C	THF	10:1	72

[a]Ratio was determined from the NMR intensities. [b]The relative stereochemistry was established based on the R_f values from TLC analyses and comparison with ^1H and ^{13}C NMR of analogues **9a** and **9b**. [c]Yields refer to isolated mixture of **11a** and **11b** over two steps. [d]A solution of aldehyde and Lewis acid was stirred for 30 min. [e]Divinylzinc was used instead of vinylmagnesium bromide. [f]A solution of aldehyde and Lewis acid was stirred for less than 15 min.

Scheme 1. Stereoselective Total Syntheses of (+)-*galacto*-DNJ and (−)-*gulo*-DNJ[a]



[a]Reagents and condtions : (a) Ac_2O, 4-DMAP, pyridine, CH_2Cl_2; (b) CbzCl, $NaHCO_3$, CH_2Cl_2/H_2O = 1:1; (c) (i) O_3, MeOH, −78 °C, then Me_2S; (ii) $Pd(OH)_2/C$, H_2, MeOH; (d) 6 N HCl, reflux, then Dowex-50WX8.

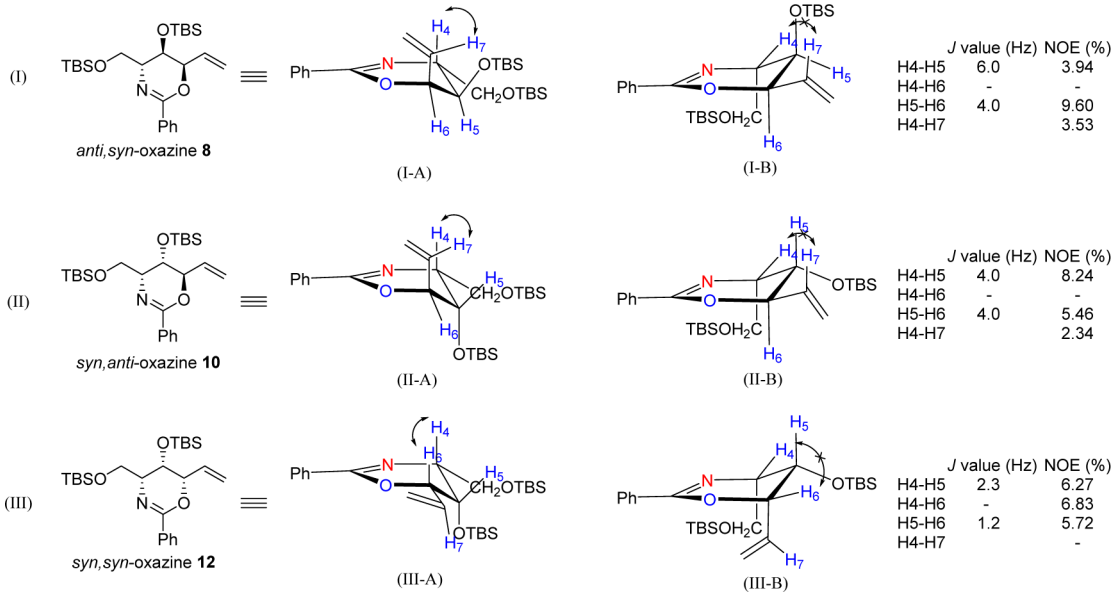


Figure 3. Conformational analysis of chiral oxazines **8**, **10**, and **12** showing two possible isomers.

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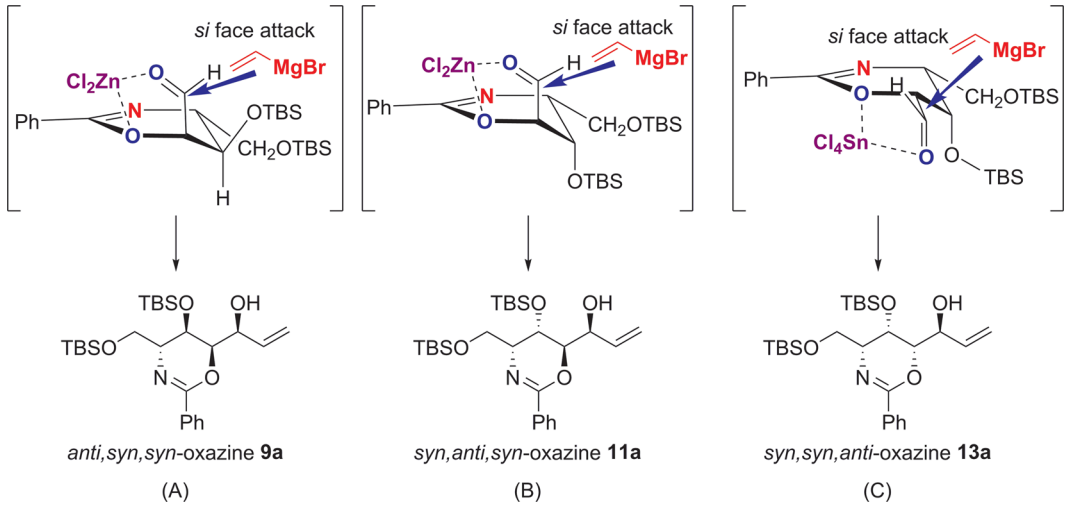

anti,syn,syn-oxazine **9a** (A) syn,anti,syn-oxazine **11a** (B) syn,syn,anti-oxazine **13a** (C)

Figure 4. Proposed mechanisms of addition to the aldehyde of chiral 1,3-oxazines.

produced the desired carbamates **14** and **16** in 80 and 62% yields, respectively. Ozonolysis of the terminal olefin of **14** and **16**, followed by Cbz deprotection, cyclization, and universal deprotection using 6 N HCl produced **4** and **5** in good yields after ion-exchange chromatography.

The optical rotation of synthetic **4**, $[\alpha]_D^{20}$ +24.1 (*c* 0.3, MeOH), agreed with the reported values, $[\alpha]_D^{20}$ +24.7 (*c* 0.4, H_2O),[4d] thus confirming the absolute configuration of **4**. Similarly, the optical rotation of synthetic **5**, $[\alpha]_D^{26.4}$ −13.2 (*c* 0.18, MeOH), also agreed with reported values, $[\alpha]_D^{20}$ −13.0 (*c* 0.35, MeOH),[5b] thus confirming its absolute configuration. The spectroscopic (^{1}H and ^{13}C NMR) data and other properties of synthetic (+)-*galacto*-DNJ (**4**) and (−)-*gulo*-DNJ (**5**) showed good agreement with the reported values.[12,5b] The spectra are presented in the Supporting Information.

Analysis of Chiral 1,3-Oxazine Conformations. Following the precedent set by the chiral extension of *anti,syn*-oxazine **8**, which resulted in *anti,syn,syn*-oxazine **9a**, the chiral extension of *syn,anti*-oxazine **10** and *syn,syn*-oxazine **12** was expected to afford *syn,anti,syn*-oxazine **11a** and *syn,syn,syn*-oxazine **13b**. Indeed, *syn,anti*-oxazine **10** gave the expected adduct, namely, *syn,anti,syn*-oxazine **11a**, but, unexpectedly, *syn,syn*-oxazine **12** resulted in *syn,syn,anti*-oxazine **13a**. This contradictory result required a detailed analysis of the 1,3-oxazine starting material conformations as well as the transition states leading to the product. This investigation was carried out by NMR, including NOESY analysis. We conducted our analysis with the assumption that the oxazine ring would have a planar portion because of conjugation between the amide function and the phenyl ring (Figure 3).

In the case of *anti,syn*-oxazine **8**, two oxazine conformations can be considered: (I-A) and (I-B). Since a strong cross-peak between H-4/H-7 in the NOESY spectrum of *anti,syn*-oxazine **8** was observed, both the H-4 and C-6 olefin must be in pseudoaxial positions, which is in accordance with conformation (I-A). In conformation (I-B), the cross-peak between H-4/H-7 could not be observed in the NOESY spectrum as both the H-4 and C-6 olefin are equatorial. Also, the large $J_{4,5}$ value (6.0 Hz) discarded conformation (I-B). Thus, conformation (I-A) is reasonable.

There would also be two possible conformations for *syn,anti*-oxazine **10**. The NOESY spectrum of *syn,anti*-oxazine **10** showed strong interactions between H-4/H-7 and between H-5/H-6, which can only be observed in (II-A) and not in (II-B). Also, the small $J_{5,6}$ value (4.0 Hz) discarded conformation (II-B). Therefore, the (II-A) conformation is reasonable.

In the case of *syn,syn*-oxazine **12**, conformation (III-A) is reasonable because strong cross-peaks between H-4/H-6 and between H-5/H-7 were observed in the NOESY spectrum of *syn,syn*-oxazine **12**. Full details of the NOESY acquisition and analysis are provided in the Supporting Information.

The possible transition states for nucleophilic addition are summarized in Figure 4. Addition to the aldehyde of *anti,syn*-oxazine **8** would proceed via the α-chelation model (A), which would result in *anti,syn,syn*-oxazine **9a**. Addition to the aldehyde of *syn,anti*-oxazine **10** would also proceed via the α-chelation model (B), which would result in *syn,anti,syn*-oxazine **11a**. Experimental observations support this hypothesis. However, the addition to the aldehyde of *syn,syn*-oxazine **12** would proceed via a different mechanism because the pendant aldehyde would be equatorial, not pseudoaxial, as would be the case for **8** and **10**. A possible mechanism (C) is presented, wherein addition to the *si* face of the carbonyl group would result in **13a**.

■ CONCLUSIONS

This study describes a Lewis acid mediated stereoselective nucleophilic addition to the aldehydes derived from *syn,anti*-oxazine **10** and *syn,syn*-oxazine **12**. The diastereoselectivity of the nucleophilic addition to the oxazine ring system is predominantly controlled by a combination of the substrate and the Lewis acid. *syn,anti*-Oxazine **10** reacted in a *syn*-selective manner with $ZnCl_2$ and gave products that were enriched in *syn,anti,syn*-oxazine **11a**. *syn,syn*-Oxazine **12** reacted in an *anti*-selective manner with $SnCl_4$ and gave products that were enriched in *syn,syn,anti*-oxazine **13a**. The resulting chirons **11a** and **13a** were used for the total syntheses of (+)-*galacto*-DNJ (**4**) and (−)-*gulo*-DNJ (**5**), which were achieved in four steps in 44.1 and 33.7% overall yields, respectively. Future applications of these chiral oxazines will be reported in due course.

■ EXPERIMENTAL SECTION

General Experimental Methods. Optical rotations were measured with a polarimeter in the solvent specified. ^{1}H and ^{13}C NMR spectroscopic data were recorded with an FT-NMR

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spectrometer at 125, 175, 500, or 700 MHz. Chemical shift values are reported in parts per million relative to TMS or $CDCl_3$ as the internal standard, and coupling constants are reported in hertz. The IR spectra were measured with an FT-IR spectrometer. The mass spectroscopic data were obtained with a high-resolution mass spectrometer using a magnetic sector−electric sector double focusing analyzer. Flash chromatography was performed using mixtures of ethyl acetate and hexane as the eluents. Unless otherwise noted, all nonaqueous reactions were performed under an argon atmosphere with commercial grade reagents and solvents. THF was distilled from sodium and benzophenone (indicator). Dichloromethane (CH_2Cl_2) was distilled from calcium hydride.

Total Synthesis of (+)-*galacto*-DNJ. *(S)-1-((4R,5S,6R)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-5,6,dihydro-4H-1,3-oxazin-6-yl)prop-2-en-1-ol (**11a**).* *syn,anti*-Oxazine **10** (295 mg, 0.64 mmol) was dissolved in anhydrous MeOH (12.0 mL) and cooled to −78 °C. Ozone was passed through the solution until the reaction was complete. The reaction mixture was quenched with $(CH_3)_2S$ (0.14 mL, 1.92 mmol) and warmed to room temperature. The solvent was evaporated under reduced pressure. The crude aldehyde was immediately used in the next step without further purification. $ZnCl_2$ (0.64 mL of a 1.0 M solution in diethyl ether, 0.64 mmol) was added to a solution of the aldehyde in THF (8.5 mL) at −78 °C and stirred for 30 min. Vinylmagnesium bromide (1.92 mL of a 1.0 M solution in THF, 1.90 mmol) was added and stirred for 12 h. The reaction was quenched with aqueous saturated NH_4Cl and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting mixture was purified by silica gel column chromatography (hexane/EtOAc = 30:1), producing **11a** (198.7 mg, 0.40 mmol) and **11b** (24.8 mg, 0.05 mmol) (71%, **11a**/**11b** = 8:1) as a crude oil, respectively: R_f = 0.4 (hexane/EtOAc = 6:1); $[\alpha]_D^{25}$ +16.1 (*c* 0.5, $CHCl_3$); IR (neat) γ_{max} 3423, 2955, 2930, 2858, 1657, 1472, 1463, 1361, 1348, 1257, 1114, 1030, 1006, 838, 777, 696 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ −0.04−0.15 (m, 12H), 0.80−0.92 (m, 18H), 1.94 (d, *J* = 8.0 Hz, 1H), 3.56 (td, *J* = 5.1, 2.8 Hz, 1H), 3.84 (dd, *J* = 10.0, 5.1 Hz, 1H), 4.07 (dd, *J* = 9.9, 2.8 Hz, 1H), 4.20 (dd, *J* = 7.3, 4.9 Hz, 1H), 4.32−4.36 (m, 1H), 4.51 (dd, *J* = 7.3, 3.4 Hz, 1H), 5.34 (dt, *J* = 10.4, 1.5 Hz, 1H), 5.43 (dt, *J* = 17.2, 1.5 Hz, 1H), 6.02 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 7.35−7.37 (m, 2H), 7.40−7.42 (m, 1H), 7.88−7.89 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.5, −5.4, −5.0, −4.3, 18.0, 56.8, 61.0, 62.8, 71.0, 79.6, 116.9, 127.2, 128.0, 130.4, 133.5, 137.2, 154.6; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{26}H_{46}NO_4Si_2$ 492.2965; found 492.2967.

*(R)-1-((4R,5S,6R)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-5,6,dihydro-4H-1,3-oxazin-6-yl)prop-2-en-1-ol (**11b**):* R_f = 0.47 (hexane/EtOAc = 6:1); $[\alpha]_D^{25}$ +29.1 (*c* 0.23, $CHCl_3$); IR (neat) γ_{max} 2955, 2929, 2888, 2858, 1730, 1659, 1473, 1391, 1365, 1316, 1257, 1100, 1033, 1011, 940, 840, 780, 732, 702 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.02−0.03 (m, 3H), 0.07−0.08 (m, 3H), 0.11−0.12 (m, 6H), 0.86−0.89 (m, 18H), 2.09 (d, *J* = 5.0 Hz, 1H), 3.62 (dt, *J* = 6.8, 3.9 Hz, 1H), 3.84 (dd, *J* = 9.9, 6.7 Hz, 1H), 3.99 (dd, *J* = 9.8, 4.0 Hz, 1H), 4.23 (dd, *J* = 5.3, 4.4 Hz, 1H), 4.28−4.32 (m, 1H), 4.41 (t, *J* = 5.9 Hz, 1H), 5.32 (dt, *J* = 10.5, 1.2 Hz, 1H), 5.40 (dt, *J* = 17.2, 1.4 Hz, 1H), 6.04 (ddd, *J* = 17.1, 10.6, 6.2 Hz, 1H), 7.33−7.37 (m, 2H), 7.39−7.42 (m, 1H), 7.89 (dd, *J* = 8.4, 1.5 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.5, −5.1, −4.0, 18.2, 18.4, 26.1, 56.3, 62.2, 64.1, 73.7, 80.3, 118.5, 128.2, 130.5, 136.5, 154.4; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{26}H_{46}NO_4Si_2$ 492.2965; found 492.2967.

(S)-1-((4R,5S,6R)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-5,6,dihydro-4H-1,3-oxazin-6-yl)allyl Acetate. Acetic anhydride (0.06 mL, 0.63 mmol) and 4-DMAP (6.1 mg, 0.05 mmol) were added to a solution of alcohol **11a** (199.1 mg, 0.40 mmol) in CH_2Cl_2 (1.5 mL) and pyridine (0.06 mL) and stirred for 2 h. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was washed with a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated in vacuo. The resulting material was subjected to oxazine ring cleavage reaction without further purification: R_f = 0.6 (hexane/EtOAc = 6:1); $[\alpha]_D^{25}$ +35.4 (*c* 0.6, $CHCl_3$); IR (neat) γ_{max} 3423, 2955, 2930, 2886, 2858, 1749, 1661, 1472, 1370, 1286, 1255, 1230, 1151, 1116, 1029, 839, 778, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.02−0.10 (m, 12H), 0.77−0.93 (m, 18H), 2.04 (s, 3H), 3.57 (ddd, *J* = 5.9, 4.7, 3.2 Hz, 1H), 3.82 (dd, *J* = 9.7, 5.9 Hz, 1H), 4.03 (dd, *J* = 10.0, 3.2 Hz, 1H), 4.11 (dd, *J* = 6.4, 4.4 Hz, 1H), 4.57 (dd, *J* = 6.4, 4.4 Hz, 1H), 5.37 (dt, *J* = 10.6, 1.2 Hz, 1H), 5.39−5.44 (m, 2H), 5.43 (tt, *J* = 6.4, 4.4 Hz, 1H), 5.92 (ddd, *J* = 17.4, 10.5, 7.0 Hz, 1H), 7.33−7.38 (m, 2H), 7.38−7.43 (m, 1H), 7.87−7.92 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.5, −5.4, −5.2, −4.1, 17.9, 18.0, 20.8, 21.1, 56.4, 56.7, 61.1, 61.2, 62.5, 63.2, 73.3, 78.5, 119.5, 127.3, 128.0, 130.3, 132.6, 133.7, 154.8, 170.0; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{28}H_{48}NO_5Si_2$ 534.3071; found 534.3070.

*(3S,4R,5S,6R)-3-Acetoxy-6-(benzyloxycarbonylamino)-5,7-bis-(tert-butyldimethylsilyloxy)hept-1-en-4-yl Benzoate (**14**).* A solution of allyl acetate (225.3 mg, 0.42 mmol) in CH_2Cl_2 (2.8 mL) was treated with $NaHCO_3$ (2.8 mL of a 0.60 M aqueous solution, 1.68 mmol), and the resulting mixture was cooled to 0 °C. A solution of benzyl chloroformate (0.12 mL, 0.84 mmol) was added dropwise. The resulting mixture was stirred at 40 °C for 24 h, and additional benzyl chloroformate (0.12 mL, 0.84 mmol) was added. The resulting mixture was stirred for another 24 h until the reaction was complete, as monitored by TLC. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with water, dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel column chromatography afforded carbamate **14** (206.1 mg, 0.32 mmol) in 80% yield for two steps as a crude oil: R_f = 0.5 (hexane/EtOAc = 6:1); $[\alpha]_D^{25}$ −2.6 (*c* 0.6, $CHCl_3$); IR (neat) γ_{max} 3454, 2955, 2930, 2886, 2858, 1498, 1269, 1258, 1228, 1110, 1027, 839, 779, 712 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.07−0.17 (m, 12H), 0.86−0.95 (m, 18H), 1.96 (s, 3H), 3.41 (t, *J* = 9.7 Hz, 1H), 3.68 (dd, *J* = 9.9, 5.2 Hz, 1H), 4.01 (dddd, *J* = 9.8, 8.2, 5.1, 1.5 Hz, 1H), 4.42 (dd, *J* = 3.9, 1.3 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 5.15 (d, *J* = 8.2 Hz, 1H), 5.31 (d, *J* = 10.8 Hz, 1H), 5.42 (d, *J* = 17.2 Hz, 1H), 5.46 (dd, *J* = 6.9, 3.9 Hz, 1H), 5.55 (t, *J* = 6.7 Hz, 1H), 5.88 (ddd, *J* =17.2, 10.8, 6.4 Hz, 1H), 7.27−7.35 (m, 7H), 7.48−7.51 (m, 1H), 7.97−7.99 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.4, −5.3, −4.7, −4.6, −4.5, 18.1, 20.9, 52.7, 61.2, 66.7, 67.3, 73.2, 76.1, 119.8, 128.0, 128.1, 128.3, 128.4, 128.5, 129.8, 132.0, 133.0, 136.4, 155.7, 165.5, 169.6; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{36}H_{56}NO_8Si_2$ 686.3545; found 686.3542.

*(2R,3S,4R,5S)-5-Acetoxy-3-(tert-butyldimethylsilyloxy)-2-((tert-butyldimethylsilyloxy)methyl)piperidin-4-yl Benzoate (**15**).* Carbamate **14** (246 mg, 0.36 mmol) was dissolved in anhydrous methanol (12 mL) and cooled to −78 °C. Ozone was passed through the solution until the reaction was completed. The reaction mixture was quenched with $(CH_3)_2S$ (0.08 mL, 1.08 mmol) and warmed to room temperature. The solvents were evaporated under reduced pressure. The crude aldehyde was immediately used for the next step without further purification. A solution of aldehyde in anhydrous methanol (3.6 mL) was treated with 20% $Pd(OH)_2/C$ (126 mg), and the resulting mixture was vigorously shaken under 75 psi of H_2 for 24 h at ambient temperature. The mixture was filtered through a pad of Celite, concentrated in vacuo, and purified by silica gel column chromatography, affording piperidine **15** (131 mg, 0.24 mmol) in 68% yield: R_f = 0.6 (hexane/EtOAc = 2:1); $[\alpha]_D^{25}$ +13.8 (*c* 0.6, $CHCl_3$); IR (neat) γ_{max} 3317, 2955, 2930, 2885, 2858, 1747, 1723, 1471, 1372, 1282, 1256, 1234, 1107, 1071, 1045, 837, 776, 714, 678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.00−0.08 (m, 12H), 0.88−0.91 (m, 18H), 1.93 (s, 3H), 2.63 (dd, *J* = 13.4, 10.7 Hz, 1H), 2.76 (dd, *J* = 9.4, 6.2 Hz, 1H), 3.33 (dd, *J* = 13.5, 5.6 Hz, 1H), 3.43 (t, *J* = 9.5 Hz, 1H), 3.63 (dd, *J* = 10.0, 5.9 Hz, 1H), 4.44 (dd, *J* = 2.0, 0.6 Hz, 1H), 5.04 (dd, *J* = 10.1, 2.5 Hz, 1H), 5.42 (td, *J* = 10.4, 5.6 Hz, 1H), 7.45 (m, 2H), 7.56−7.59 (m, 1H), 8.01−8.03 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.3, −5.2, −4.8, −4.6, 18.3, 18.4, 48.2, 60.7, 61.7, 68.5, 69.1, 128.5, 129.8, 129.9, 132.2, 166.3, 170.5; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{27}H_{48}NO_6Si_2$ 538.3020; found 538.3019.

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*(2R,3S,4R,5S)-2-(Hydroxymethyl)piperidine-3,4,5-triol, (+)-1-Deoxygalactonojirimycin (**4**).* A solution of **15** (131 mg, 0.24 mmol) in methanol (1.6 mL) was acidified with 6 N HCl (0.60 mL, 3.60 mmol). The reaction mixture was heated at reflux for 24 h and concentrated. The resulting aqueous residue was washed with EtOAc and the separated aqueous layer evaporated to dryness to afford the HCl salt of (+)-*galacto*-DNJ. Further purification of the salt using an ion-exchange resin (DOWEX 50WX8 H+ form) column afforded (+)-galacto-DNJ (**4**)[4d,11] (31.5 mg, 0.19 mmol) in 81% yield: R_f = 0.15 ($CHCl_3$/MeOH = 1:1); $[\alpha]_D^{20}$ +24.1 (*c* 0.3, MeOH) [lit.[4d] $[\alpha]_D^{20}$ +24.7 (*c* 0.4, H_2O)]; IR (neat) γ_{max} 3356, 2925, 2834, 1597, 1557, 1452, 1391, 1250, 1151, 1100, 1066, 1033, 941, 918, 864, 816, 726, 694, 650, 599, 513 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 2.35 (dd, *J* = 12.5, 11.3 Hz, 1H), 2.73 (t, *J* = 6.4 Hz, 1H), 3.08 (dd, *J* = 12.6, 5.3 Hz, 1H), 3.40 (dd, *J* = 9.7, 3.2 Hz, 1H), 3.56 (qd, *J* = 11.3, 6.8 Hz, 2H), 3.70 (td, *J* = 10.3, 5.3 Hz, 1H), 3.93 (dt, *J* = 2.2, 1.2 Hz, 1H) [lit.[12] ^1H NMR (D_2O) δ 2.41(dd, *J* = 13, 11 Hz, 1H), 2.79 (brt, 1H), 3.15 (dd, *J* = 13, 5.3 Hz, 1H), 3.49 (dd, *J* = 9.8, 3.1 Hz, 1H), 3.62 (dd, *J* = 11, 7.0 Hz, 1H) 3.67(dd, *J* = 11, 6.5 Hz, 1H) 3.78 (ddd, *J* = 11, 9.8, 5.3 Hz, 1H), 4.02 (dd, *J* = 3.1, 1.4 Hz, 1H)]; ^{13}C NMR (125 MHz, D_2O) δ 48.9, 59.2, 61.3, 68.0, 69.2, 75.0 [lit.[12] ^{13}C NMR (D_2O) δ 49.4,59.4, 61.8, 68.5, 69.7, 75.5]; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_6H_{14}NO_4$ 164.0923; found 164.0921.

Total Synthesis of (−)-*gulo*-DNJ. The experimental details are identical to those for *galacto*-DNJ unless otherwise indicated.

*(S)-1-((4R,5S,6S)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-5,6,dihydro-4H-1,3-oxazin-6-yl)prop-2-en-1-ol (**13a**).* *syn,syn*-Oxazine **12** (653.1 mg, 1.41 mmol) was dissolved in anhydrous MeOH (14.1 mL) and cooled to −78 °C. Ozone was passed through the solution until the reaction was complete. The reaction mixture was quenched with $(CH_3)_2S$ (311 μL, 4.24 mmol) and warmed to room temperature. The solvent was evaporated under reduced pressure. The crude aldehyde was immediately used in the next step without further purification. $SnCl_4$ (1.41 mL of a 1.0 M solution in dichloromethane, 1.414 mmol) was precomplexed to a solution of the aldehyde in THF (14.1 mL) at −78 °C and stirred for less than 15 min. Vinylmagnesium bromide (4.24 mL of a 1.0 M solution in THF, 4.24 mmol) was added and stirred for 12 h. The reaction was quenched with aqueous saturated NH_4Cl and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting mixture was purified by silica gel column chromatography (hexane/EtOAc = 30:1), producing **13a** (455.2 mg, 0.93 mmol) and **13b** (45.5 mg, 0.09 mmol) (72%, **13a**/**13b** = 10:1) as a crude oil, respectively: R_f = 0.48 (hexane/EtOAc = 6:1); $[\alpha]_D^{25}$ +46.2 (*c* 0.43, $CHCl_3$); IR (neat) γ_{max} 3068, 2952, 2927, 2855, 1657, 1471, 1361, 1258, 1110, 838, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.09−0.21 (m, 12H), 0.84−0.94 (m, 18H), 3.60 (td, *J* = 5.0, 2.9 Hz, 1H), 3.88 (dd, *J* = 10.0, 5.1 Hz, 1H), 4.10 (dd, *J* = 9.9, 3.0 Hz, 1H), 4.24 (dd, *J* = 7.3, 4.9 Hz, 1H), 4.37 (ddt, *J* = 5.6, 3.4, 1.4 Hz, 1H), 4.54 (dd, *J* = 7.3, 3.4 Hz, 1H), 5.37 (dt, *J* = 10.6, 1.4 Hz, 1H), 5.46 (dt, *J* = 17.2, 1.5 Hz, 1H), 6.05 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 7.37−7.41 (m, 2H), 7.43−7.47 (m, 1H), 7.92 (dd, *J* = 8.4, 1.5 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.4, −5.0, −4.3, 18.0, 25.7, 25.8, 29.7, 56.8, 61.0, 62.7, 70.9, 76.8, 77.0, 77.2, 79.7, 116.9, 127.3, 128.0, 130.4, 137.2; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{26}H_{46}NO_4Si_2n$ 492.2965; found 492.2966.

*(R)-1-((4R,5S,6S)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-5,6,dihydro-4H-1,3-oxazin-6-yl)prop-2-en-1-ol (**13b**):* Crude oil; R_f = 0.39 (hexane/EtOAc = 6:1); $[\alpha]_D^{25}$ −10.0 (*c* 0.52, $CHCl_3$); IR (neat) γ_{max} 3389, 2951, 2927, 2855, 1649, 1471, 1252, 1117, 1092, 1032, 833, 776, 704 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.08−0.14 (m, 6H), 0.15−0.19 (m, 6H), 0.80−0.86 (m, 9H), 0.89−0.97 (m, 9H), 3.52 (dddd, *J* = 10.1, 5.4, 2.3, 1.2 Hz, 1H), 3.72 (t, *J* = 10.1 Hz, 1H), 3.87 (dd, *J* = 10.1, 5.4 Hz, 1H), 3.93 (ddd, *J* = 9.4, 1.2, 0.9 Hz, 1H), 4.37 (dddd, *J* = 9.4, 5.9, 1.4, 1.3 Hz, 1H), 4.53 (dd, *J* = 2.3, 0.9 Hz, 1H), 5.36 (dt, *J* = 10.6, 1.3 Hz, 1H), 5.45 (dt, *J* = 17.2, 1.4 Hz, 1H), 6.20 (ddd, *J* = 17.3, 10.6, 5.9 Hz, 1H), 7.30−7.36 (m, 2H), 7.36−7.42 (m, 1H), 7.80−7.88 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.1, −4.5, −4.3, 18.3, 18.5, 26.0, 26.1, 29.7, 59.8, 60.7, 63.3, 69.7, 80.5, 116.7, 127.2, 127.9, 130.3, 133.5, 138.5, 154.7; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{26}H_{46}NO_4Si_2$ 492.2965; found 492.2963.

(S)-1-((4R,5S,6S)-5-(tert-Butyldimethylsilyloxy)-4-((tert-butyldimethylsilyloxy)methyl)-2-phenyl-5,6,dihydro-4H-1,3-oxazin-6-yl)allyl Acetate: Crude oil; R_f = 0.68 (hexane/EtOAc = 6:1); $[\alpha]_D^{25}$ −3.3 (*c* 0.59, $CHCl_3$); IR (neat) γ_{max} 3727, 3698, 3623, 3593, 2953, 2885, 2856, 1750, 1657, 1472, 1369, 1253, 1226, 1164, 1113, 1028, 938, 836, 772, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01−0.16 (m, 12H), 0.81−0.95 (m, 18H), 2.11 (s, 3H), 3.55 (ddt, *J* =10.3, 5.3, 1.5 Hz, 1H), 3.66 (t, *J* = 10.4 Hz, 1H), 3.88 (dd, *J* = 10.1, 5.4 Hz, 1H), 4.21 (dt, *J* = 9.7, 1.2 Hz, 1H), 4.39 (d, *J* = 2.3 Hz, 1H), 5.33 (ddt, *J* = 9.7, 6.5, 0.9 Hz, 1H), 5.41 (d, *J* = 0.9 Hz, 1H), 5.44 (dt, *J* = 7.3, 1.0 Hz, 1H), 5.98 (ddd, *J* = 17.3, 10.9, 6.5 Hz, 1H), 7.30−7.45 (m, 3H), 7.80−7.88 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.4, −5.1, −3.9, 18.2, 18.4, 21.2, 25.7, 26.0, 59.9, 60.6, 62.9, 72.0, 119.1, 127.1, 128.0, 130.4, 133.1, 133.7, 154.6, 169.4; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{28}H_{48}NO_5Si_2$ 534.3071; found 534.3074.

*(3S,4S,5S,6R)-3-Acetoxy-6-(benzyloxycarbonylamino)-5,7-bis-(tert-butyldimethylsilyloxy)hept-1-en-4-yl Benzoate (**16**):* 62% yield for two steps as a crude oil; R_f = 0.44 (hexane/EtOAc = 6:1); $[\alpha]_D^{25}$ +106.6 (*c* 0.03, $CHCl_3$); IR (neat) γ_{max} 3447, 2952, 2928, 2856, 1725, 1497, 1471, 1270, 1253, 1225, 1095, 1067, 1024, 834, 709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.02−0.10 (m, 12H), 0.79−0.85 (m, 18H), 1.97 (s, 3H), 3.45 (t, *J* = 9.7 Hz, 1H), 3.64 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.91 (tdd, *J* = 9.4, 5.3, 1.5 Hz, 1H), 4.32 (dd, *J* = 6.7, 1.8 Hz, 1H), 5.12−5.18 (m, 3H), 5.32 (dt, *J* = 10.6, 1.5 Hz, 1H), 5.44 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.49 (dd, *J* = 6.7, 4.1 Hz, 1H), 5.55 (dd, *J* = 7.6, 4.1 Hz, 1H), 5.95 (ddd, *J* = 17.3, 10.3, 7.3 Hz, 1H), 7.28−7.41 (m, 5H), 7.42−7.47 (m, 2H), 7.54−7.60 (m, 1H), 8.00−8.07 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.2, −4.5, −4.3, −0.2, 18.2, 18.3, 21.2, 25.9, 26.0, 29.9, 53.4, 61.0, 67.1, 67.5, 68.3, 73.4, 75.2, 121.1, 128.3, 128.4, 128.5, 128.7, 130.0, 130.4, 131.4, 133.3, 136.6, 156.2, 166.0, 169.7; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{36}H_{56}NO_8Si_2$ 686.3545; found 686.3548.

*(2R,3S,4R,5S)-5-Acetoxy-3-(tert-butyldimethylsilyloxy)-2-((tert-butyldimethylsilyloxy)methyl)piperidin-4-yl Benzoate (**17**):* 68% yield as a crude oil; R_f = 0.64 (hexane/EtOAc = 2:1); $[\alpha]_D^{25}$ −115.0 (*c* 0.1, $CHCl_3$); IR (neat) γ_{max} 2953, 2928, 2884, 2856, 1726, 1472, 1363, 1251, 1230, 1106, 1068, 1049, 835, 710 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 0.01−0.23 (m, 12H), 0.81−0.99 (m, 18H), 1.98 (s, 3H), 3.00−3.13 (m, 3H), 3.50 (dd, *J* = 10.0, 8.5 Hz, 2H), 3.63 (dd, *J* = 10.0, 6.2 Hz, 1H), 4.09 (dd, *J* = 4.4, 1.8 Hz, 1H), 5.25 (ddd, *J* = 10.7, 5.7, 3.2 Hz, 1H), 5.45 (t, *J* = 3.5 Hz, 1H), 7.44−7.51 (m, 3H), 7.55−7.63 (m, 1H), 8.04−8.09 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ −5.3, −5.2, −4.7, 18.0, 18.2, 20.1, 25.8, 26.0, 44.2, 50.9, 56.5, 62.0, 67.6, 67.9, 71.0, 128.4, 129.6, 129.8, 129.9, 133.2, 165.4, 170.2; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_{27}H_{48}NO_6Si_2$ 538.3020; found 538.3019.

*(2R,3S,4S,5S)-2-(Hydroxymethyl)piperidine-3,4,5-triol, (−)-1-Deoxygulonojirimycin (**5**):* 80% yield, as a white solid; R_f = 0.17 ($CHCl_3$/MeOH = 1:1); $[\alpha]_D^{26.4}$ −13.2 (*c* 0.18, MeOH) [lit.[5b] $[\alpha]_D^{20}$ −13.0 (*c* 0.35, MeOH)]; IR (neat) γ_{max} 3415, 2955, 2925, 2851, 1737, 1633, 1463, 1261, 1081 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 2.73 (dd, *J* = 12.6, 10.6 Hz, 1H), 2.89 (dd, *J* = 12.0, 4.7 Hz, 1H), 2.97 (td, *J* = 6.6, 2.1 Hz, 1H), 3.64 (qd, *J* = 9.8, 6.2 Hz, 2H), 3.92−3.99 (m, 3H) [lit.[5b] ^1H NMR (600 MHz, D_2O) δ 2.82 (t, *J* = 11.6 Hz, 1H), 2.99 (dd, *J* = 12.4, 4.9 Hz, 1H), 3.12 (t, *J* = 6.6 Hz, 1H), 3.65 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.70 (dd, *J* = 11.6, 5.9 Hz, 1H); 3.96 (t, *J* = 6.6 Hz, 2H), 4.00−4.03 (m, 1H)]; ^{13}C NMR (175 MHz, D_2O) δ 44.2, 53.8, 61.1, 65.7, 69.3, 70.3 [lit.[5b] ^{13}C NMR (150 MHz, D_2O) δ 43.4, 54.2, 60.3, 64.6, 68.5, 69.6]; HRMS (FAB+) $[M^+ + H]$ *m*/*z* calcd for $C_6H_{14}NO_4$ 164.0923; found 164.0921.

■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C NMR for **11a**, **11b**, **13a**, **13b**, **14**, **15**, **16**, **17**, **4**, and **5**; NOESY data for **8**, **10**, and **12** (PDF)

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Notes

The authors declare no competing financial interest.

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