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Stereoselective Synthesis of Nojirimycin α-*C*-Glycosides from a Bicyclic Acyliminium Intermediate: A Convenient Entry to *N*,*C*-Biantennary Glycomimetics

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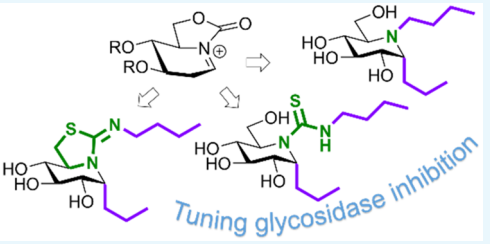
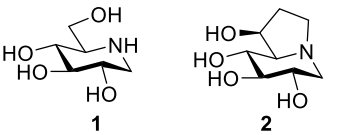
ABSTRACT: A simple and efficient method for the stereoselective synthesis of nojirimycin α-*C*-glycoside derivatives has been developed using a bicyclic carbamate-type sp^2-iminosugar, whose preparation on a gram scale has been optimized, as the starting material. sp^2-iminosugar *O*-glycosides or anomeric esters serve as excellent precursors of acyliminium cations, which can add nucleophiles, including *C*-nucleophiles. The stereochemical outcome of the reaction is governed by stereoelectronic effects, affording the target α-anomer with total stereoselectivity. Thus, the judicious combination of *C*-allylation, carbamate hydrolysis, cross-metathesis, and hydrogenation reactions provides a very convenient entry to iminosugar α-*C*-glycosides, which have been transformed into *N*,*C*-biantennary derivatives by reductive amination or thiourea-forming reactions. The thiourea adducts undergo intramolecular cyclization to bicyclic iminooxazolidine iminosugar α-*C*-glycosides upon acid treatment, broadening the opportunities for molecular diversity. A preliminary evaluation against a panel of commercial glycosidases validates the approach for finely tuning the inhibitory profile of glycomimetics.



INTRODUCTION

Nitrogen-in-the-ring sugar mimetics (iminosugars) have played a prominent role in our understanding of the mechanisms underlying the metabolism and biological functions of carbohydrates during the last five decades.[1−6] By interfering in the biosynthesis or processing of glycans and glycoconjugates, iminosugars enable the regulation of pathological processes resulting from the dysfunction of the intervening enzymes, namely glycosyl hydrolases (glycosidases)[7] and glycosyl transferases.[8] These processes cause from major global health problems, for instance diabetes[9] or cystic fibrosis,[10] to highly disabling rare syndromes such as the lysosomal storage disorders Gaucher, Pompe, G_{M1}-gangliosidosis, and Fabry diseases.[11−14] Disrupting the activity of carbohydrate-processing enzymes in pathogens can be further exploited in fighting infectious diseases: e.g., viral infections.[15,16] Innate immune response signaling routes,[17,18] cell proliferation and metastasis,[19] or age-related neurodegenerative disorders, e.g. Alzheimer and Parkinson diseases,[20,21] can also be targeted with iminosugars. The recent reports on the promise of the piperidine- and indolizidine-type iminosugars 1-deoxynojirimycin (DNJ; **1**) and castanospermine (CS; **2**), respectively, and some of their derivatives for treating patients infected with SARS-CoV-2, the causative agent of the Covid-19 worldwide pandemic, attest to the unrelenting interest in the therapeutic potential of this amazing family of glycomimetics (Figure 1).[22−27]



1 **2**

Figure 1. Structures of the bioactive iminosugars 1-deoxynojirimycin (DNJ, **1**) and castanospermine (CS, **2**).

The sustained success of iminosugars in glycobiology research and drug discovery programs lies, to a great extent, on the large structural variability provided by the naturally occurring representatives and the hundreds of synthetic analogues reported over the years. Most efforts on the chemistry side have been directed to devise efficient strategies matching the stereochemical and substitution profiles of the monosaccharides.[28,29−31] Replicating the glycosidic linkage distinctive of glycoconjugates, however, has proven much more challenging. The intrinsic instability of aminoacetal functionalities makes impractical the synthesis of iminosugar *O*-glycosides or of analogues having other heteroatom sub-

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stituents at the pseudoanomeric position. Instead, aglycon-like appendages have been incorporated through *N*-substitution[32−39] and *C*-branching approaches,[40−47] which accounts for the two major subclasses of iminosugar derivatives on record.

The combination of *N*-substitution and *C*-branching in the same iminosugar scaffold appears to be an obvious strategy for finely tuning the biological activity.[48] Surprisingly, the reported examples of biantennary *N*-substituted iminosugar *C*-glycosides are rather limited.[49−51] An apparent reason is the complexity in accessing the *C*-glycoside precursors in pure diastereoisomeric form. Most of the current protocols involve intramolecular reductive amination[47,52] or aza-Wittig cyclization reactions,[47,50,53] with variable diastereoselectivity outcomes, or the use of 1-*C*-activated precursors that are themselves obtained as mixtures of diastereomers (Figure 2, left panel).[47,54] Sharply different, the 5*N*,6*O*-oxomethylidenenojirimycin derivative **3**[55,56] (ONJ), a member of the sp^2-iminosugar subgroup,[57] is a chemically stable and configurationally defined compound that can be functionalized at the pseudoanomeric position via the corresponding acyliminium cation with total α-stereoselectivity (Figure 2, right panel).[58−62] Since the cyclic carbamate ring can be considered as a protecting group of the vicinal amino alcohol fragment,[63] we conceived that **3** could provide a reliable access to iminosugar α-*C*-glycosides and then to *N*-substituted-α-*C*-glycosides, in both the classical and sp^2-iminosugar series, thereby offering opportunities for molecular diversity. As a proof of concept, here we report (a) an optimized synthesis of **3** on a gram scale, (b) its transformation into NJ α-*C*-glycosides (**I**) by allylation−carbamate hydrolysis−cross-metathesis sequences, (c) the synthesis of *N*-alkyl (**II**) and *N*-(*N*′-alkylthiocarbamoyl) (**III**) biantennary derivatives via an intermolecular reductive amination or a thiourea-forming reaction, respectively, and (d) the cyclization of the last two species to access bicyclic isothiourea analogues (**IV**; Figure 2, right panel). The potential of the strategy to customize the glycosidase inhibition pattern of the glycomimetics is also discussed.

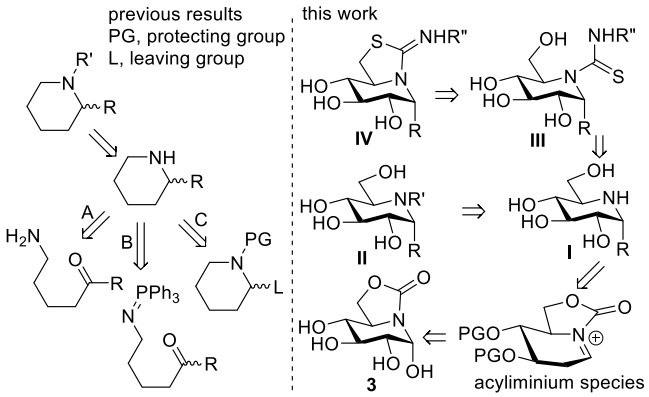
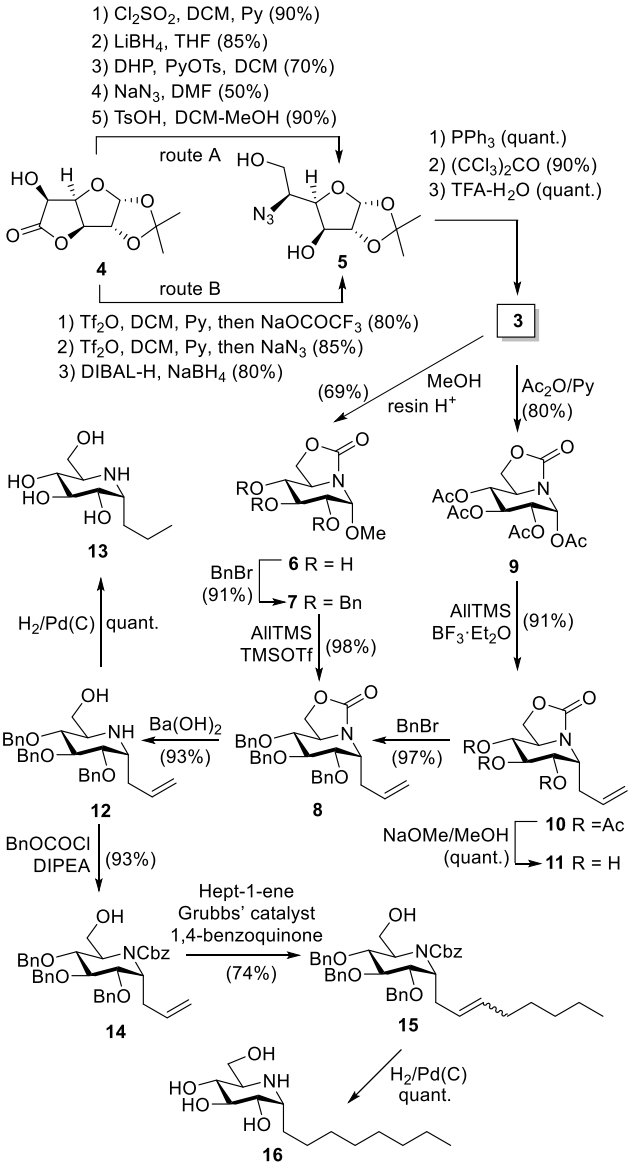


Figure 2. Retrosynthetic analysis commonly used in the synthesis of iminosugar *C*-glycosides and *N*,*C*-biantennary iminosugars via (A) intramolecular reductive amination, (B) aza-Wittig reaction, or (C) 1-*C*-activated precursors the and strategy proposed in this work starting from the bicyclic carbamate sp^2-iminosugar ONJ (**3**).

RESULTS AND DISCUSSION

Synthesis. Compound **3** has been previously prepared on a 500 mg scale from commercial 1,2-*O*-isopropylidene-α-D-glucuronolactone (**4**) in 17% overall yield through a nine-step route involving, as the key transformations, nucleophilic substitution of chlorine by azide and OH-6 deprotection to render the D-*gluco* vicinal azido alcohol intermediate **5** (25% over five steps; Scheme 1, route A).[55,56] We have now optimized this critical double-inversion sequence by using triflate as the leaving group and trifluoroacetate and azide as the nucleophiles.[64] Conducting both substitution reactions on the lactone scaffold avoids the need for additional OH-6 protection/deprotection, considerably increasing the efficiency of the **4** to **5** conversion (55% over three steps; Scheme 1, route B). The whole synthetic scheme has been reproducibly scaled up by 20-fold with no significant difference in product yield, providing a very convenient access to the reducing sp^2-

Scheme 1. Optimized Synthesis of the sp^2-Iminosugar Precursor 3 and Its Transformation into the Known NJ α-*C*-Glycosides 13 and 16



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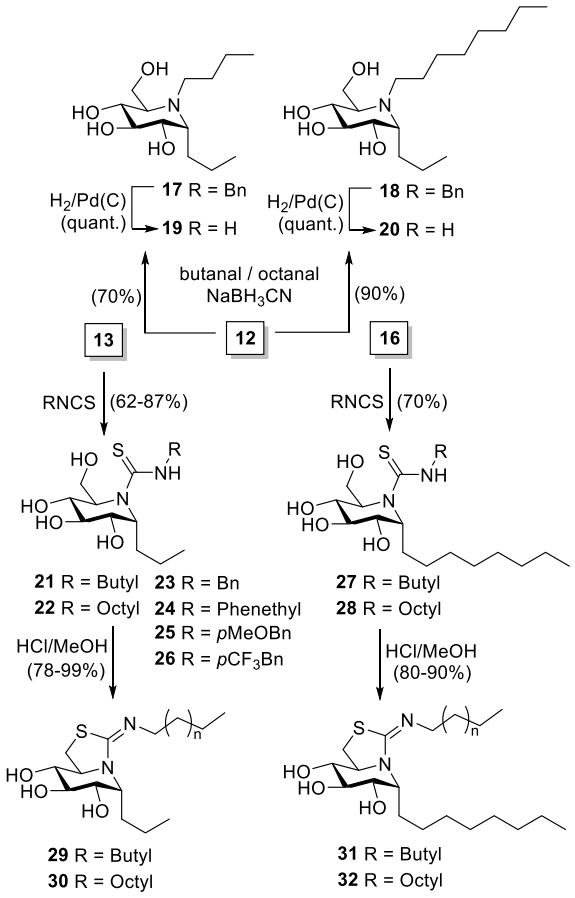
iminosugar **3** in gram quantities (43% over eight steps from commercial **9**; see the Supporting Information for a detailed description of reaction conditions and synthetic intermediates).

En route toward the synthesis of ONJ pseudo-*C*-glycosides, the incorporation of a pseudoanomeric methoxy group followed by *O*-benzylation of the secondary alcohols was first considered. *N*-Acylated aminal derivatives are known to be suitable precursors for acyliminium cation species, which can undergo the addition of a variety of nucleophiles, including carbon nucleophiles.[65−67] Accordingly, a Fischer-type pseudoglycosidation reaction of **3** with methanol, using an acid resin as the promoter, afforded the corresponding ONJ methyl α-*O*-glycoside **6** (69% yield), which upon conventional benzylation afforded the tri-*O*-benzyl derivative **7** (91% yield). *C*-Allylation of **7** by treatment with allyltrimethylsilane (AllTMS) proceeded smoothly in acetonitrile at room temperature in the presence of trimethylsilyl triflate to give the pivotal ONJ allyl α-*C*-glycoside **8** in excellent yield. No trace of the β diastereomer was detected in either the *O*- or the *C*-glycosylation reaction mixtures. However, the relatively modest yield of the *O*-glycosylation reaction was judged to be a limitation. As an alternative, peracetate **9** was prepared and attempted as a pseudoglycosyl donor for *C*-glycosylation. Gratifyingly, the reaction with AllTMS in acetonitrile at 80 °C, using boron trifluoride etherate as a promoter, provided the corresponding allyl α-*C*-glycoside **10** in a remarkable 91% yield. It is worth noting that the α stereoselectivity was preserved despite the participating character of the acetyl group vicinal to the pseudoanomeric center. Compound **10** was next transformed into **8** by standard deacetylation (→**11**)/benzylation protocols (Scheme 1).

Hydrolysis of the cyclic carbamate functionality in **8** was successfully effected by treatment with barium hydroxide in a mixture of methanol and water at 70 °C.[68−70] Partition of the reaction mixture between ethyl acetate and water allowed a very convenient separation of the organic product from the inorganic salts, which was instead very problematic when the base-sensitive triacetate **10** was used as the precursor. The allyl tri-*O*-benzyl-NJ α-*C*-glycoside **12** was thus obtained in 93% yield. Palladium(0)-catalyzed hydrogenation next delivered the known iminosugar propyl α-*C*-glycoside **13**.[53,71,72] Interestingly, protection of the amino group in **12** followed by cross-metathesis with terminal alkenes and final hydrogenation enables a general entry to NJ alkyl α-*C*-glycosides. As a proof of concept, the potent β-glucocerebrosidase inhibitor **16**[72] was synthesized through this procedure via the corresponding *N*-benzyloxycarbonyl **14** and unsaturated *C*-glycoside **15** (mixture of *E* and *Z* isomers in a 5:1 ratio) intermediates in excellent yield (Scheme 1).

Having a general strategy to access iminosugar α-*C*-glycosides in hand, we undertook the preparation of *N*,*C*-biantennary nojirimycin derivatives. Attempts to selectively *N*-alkylate **13** with butyl and octyl bromides using sodium carbonate as a base failed to provide the corresponding tertiary amines in pure form. Alternatively, reductive amination of the partially protected precursor **12** with butanal and octanal furnished the desired *N*-alkyl iminosugars **17** and **18** in 70−90% yield, which after catalytic hydrogenation afforded the target fully unprotected *N*,*C*-dialkyliminosugars **19** and **20**. The propyl and octyl NJ α-*C*-glycosides **13** and **16** were also readily transformed into the corresponding *N*-(*N*′-butyl)-thiocarbamoyl (**21** and **27**) and *N*-(*N*′-octyl)thiocarbamoyl adducts (**22** and **28**) by a thiourea-forming reaction, a click-type conjugation chemistry,[73,74] with butyl and octyl isothiocyanates, respectively. The thiocarbamoylated propyl α-*C*-glycoside series was additionally expanded with the corresponding *N*′-benzyl, *N*′-phenethyl, *N*′-*p*-methoxybenzyl and *N*′-*p*-trifluoromethylbenzyl congeners **23**−**26** to test the generality of the approach and assess the effect of an aromatic moiety on the glycosidase inhibitory properties (Scheme 2).

Scheme 2. Synthesis of NJ *N*-Alkyl α-*C*-Glycosides 19 and 20, *N*-(*N*′-Alkylthiocarbamoyl) α-*C*-Glycosides 21−28, and Bicyclic *N*′-Alkyl Iminothiazolidine α-*C*-Glycosides 29−32



Intramolecular cyclization of **21**, **22**, **27**, and **28** was achieved by heating an acid (HCl) methanolic solution, affording the bicyclic iminothiazolidines **29**−**32** as a novel family of *N*,*C*- biantennary glycomimetics (Scheme 2).[75]

Effect of Structural Modifications in Nojirimycin α-*C*-Glycosides on the Glycosidase Inhibitory Profile. The synthesized compounds were assayed against a panel of glycosidases covering a range of substrate configuration specificities (α- and β-D-glucosidases, α- and β-D-mannosidases and α- and β-D-galactosidases; glcases, Manases, and Galases, respectively). Given the stereochemical complementarity of the ONJ derivatives with D-glucopyranosides, α (baker's yeast, rice, or *Aspergillus niger*)- and β-glcases (*Thermotoga maritima*, almonds, or bovine liver) from diverse origins were included to assess potential selectivity biases. Table 1 displays the corresponding inhibition constant (K_i) values.

The α-C-Propyl NJ **13** is a micromolar inhibitor of the three α-glucosidases tested in this work, exhibiting full configurational and anomeric selectivity and a higher affinity for the rice

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Table 1. Inhibition Constants (K_i, μM) for the Nojirimycin *N,C*-Biantennary Derivatives 19−26 and 27−32, in Comparison with Data for the Nojirimycin α-*C*-Glycosides 13 and 16[a]

compd	α-Glcase baker's yeast	α-Glcase rice	amyloglcase *A. niger*	β-Glcase *T. maritima*	β-Glcase almonds	β-Glcase bovine	α-Galase coffee
13	92 ± 8	11 ± 1	67 ± 5	657 ± 65	ni[b]	ni	ni
19	ni	ni	ni	ni	ni	117 ± 12	ni
20	ni	25 ± 3	ni	ni	ni	358 ± 35	130 ± 12
21	ni	8.2 ± 0.6	ni	ni	ni	136 ± 11	ni
22	ni	11 ± 0.7	ni	ni	ni	ni	ni
23	ni	583 ± 0.2	154 ± 12	ni	ni	ni	ni
24	ni	72 ± 6	455 ± 40	ni	ni	ni	ni
25	ni	340 ± 30	842 ± 75	ni	ni	ni	ni
26	ni	104 ± 9	ni	ni	ni	ni	ni
16	10.7 ± 0.9	0.38 ± 0.04	12.3 ± 2	29 ± 3	28 ± 2	32 ± 3	87 ± 9
27	119 ± 10	3.3 ± 0.5	92 ± 8	293 ± 25	ni	169 ± 15	508 ± 35
28	ni	4.3 ± 0.6	455 ± 40	ni	ni	ni	ni
29	439 ± 35	ni	ni	16 ± 1	75 ± 5	177 ± 14	ni
30	ni	ni	ni	280 ± 25	ni	ni	ni
31	ni	ni	842 ± 80	ni	ni	134 ± 10	ni
32	ni	ni	305 ± 28	ni	ni	ni	ni

[a]The inhibition was competitive in all cases. No inhibitory activity was detected for any of the compounds at 2 mM against jack bean α-mannosidase, *Helix pomatia* β-mannosidase, or *E. coli* β-galactosidase at 2 mM concentration. [b]No inhibition observed at 2 mM concentration.

enzyme (K_i = 11 ± 1 μM). The concurrent presence of the *N*-butyl substituent in **19** totally abolished inhibition of the α-glucosidases, promoting instead weak inhibition of bovine β-glucosidase (K_i = 117 ± 12 μM). Interestingly, the corresponding *N*-octyl derivative **20** recovered the ability to inhibit rice α-glucosidase (K_i = 25 ± 3 μM), showing in this case total selectivity among the α-glucosidase isoenzymes. It also weakly inhibited bovine β-glucosidase and green coffee bean α-galactosidase. The neutral *N*-thiocarbamoyl α-*C*-propyl cognates **21** and **22** preserved the selectivity toward rice α-glucosidase and exhibited even higher inhibitory potencies. Indeed, the *N*′-octyl derivative **22** (K_i = 11 ± 0.7 μM) was as potent as the parent compound **13** and did not show significant inhibition of any other of the tested enzymes at 2 mM concentration. When α-*C*-octyl NJ **16** and the *N*-(*N*′-propyl)- and *N*-(*N*′-octyl)thiocarbamoyl analogues **27** and **28** were compared, a similar narrowing effect in the spectra of responsive glycosidases was observed, the latter being also a powerful and selective inhibitor of rice α-glucosidase (K_i = 4.3 ± 0.6 μM). The effect of the *N*′-substituent nature on the inhibitory activity of thiourea-type NJ *C*-glycosides became much more evident when the above data were compared with data for the aromatic-bearing derivatives **23**−**26**: a drastic increase in the K_i values against rice α-glucosidase was observed in all cases (K_i > 70 μM), accompanied by weak inhibition of amyloglucosidase in the case of compounds **23**−**25**. Transformation of the neutral monocyclic thiourea core into a basic bicyclic isothiourea has been previously found to be a powerful strategy to adjust the enzyme inhibition selectivity of sp^2-iminosugar glycomimetics. In the α-*C*-glycoside series, we encountered that cyclization of **21**, **22**, **27**, and **28** into the corresponding iminothiazolidines **29**−**32** generally shifted the anomeric selectivity from the α- to the β-glucosidases, compound **29** being a strong/modest inhibitor of the three β-glucosidase isoenzymes monitored in this study (K_i = 16 ± 1, 75 ± 5 and 177 ± 14 μM for the *T. maritima*, almonds, and bovine liver isoenzymes, respectively).

CONCLUSIONS

We have developed an efficient tactic for the stereoselective synthesis of iminosugar α-*C*-glycosides that exploits the unique reactivity and stereoelectronic properties of sp^2-iminosugars. The procedures are purposely conceived to be general and translatable to other configurational patterns. Unlike classical iminosugars, reducing carbamate-type bicyclic sp^2-iminosugars can be transformed into stable *O*-glucosides or anomeric esters that serve as suitable precursors for acyliminium cations. The rich chemistry of these intermediates enables mimicking the underlying chemistry of glycosyl oxocarbenium cation species, which has been applied to the case of *C*-glycosidation. An optimized preparation of the nojirimycin-related sp^2-iminosugar ONJ (**3**) demonstrates the feasibility of the strategy. A very efficient reaction sequence employing *C*-allylation, carbamate hydrolysis, and cross-metathesis was then implemented to access nojirimycin α-*C*-glycosides, from which *N,C*-biantennary glycomimetics were readily prepared by reductive amination with aldehydes or by coupling with isothiocyanates. NJ α-*C*-glycoside thiourea adducts have been next transformed into *N*′-substituted iminothiazolidines, the first representatives of bicyclic *N,C*-biantennary iminosugars. A main advantage of the procedure is its rather low synthetic cost, high versatility, and suitability for molecular-diversity-oriented approaches. As a proof of concept, compounds with high inhibition potency and selectivity toward rice α-glcase have been identified.

EXPERIMENTAL SECTION

General Methods. Reagents and solvents were commercial grade and were used without further purification. Optical rotations were measured using a sodium lamp (λ = 589 nm) at 22 °C in 1 cm or 1 dm tubes. Unit for ε values from UV spectra: mM^{-1} cm^{-1}. NMR experiments were performed at 300 (75.5) and 500 (125.7) MHz. 1-D TOCSY as well as 2-D COSY and HSQC experiments were carried out to assist in signal assignments. TLC was performed on precoated plates, silica gel 30F-245. Column chromatography was conducted on Chromagel (silice 60 AC.C 70−200 μm). Elemental analyses were performed at the Servicio de Microanálisis del Instituto de Investigaciones Químicas de Sevilla, Spain. ESI mass spectra

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were recorded for 0.1 pM samples using 50% aqueous MeCN at 0.1 mL min^{-1} as the mobile phase. (1*R*)-2,3,4-Tri-*O*-acetyl-1-*C*-allyl-5*N*,6*O*-oxomethylidene-1-deoxynojirimycin (**10**)[76] and (1*R*)-1-*C*-allyl-5*N*,6*O*-oxomethylidene-1-deoxynojirimycin (**11**)[76] were synthesized using previously described procedures.

(1*R*)-1-*O*-Methyl-5*N*,6*O*-oxomethylidenenojirimycin (6). A solution of ONJ (**3**; 95 mg, 0.46 mmol) in MeOH (2.2 mL) was treated with Amberlite IRA 120 H^+ ion-exchange resin, stirred at RT under Ar for 24 h, filtered, and chromatographed using 70/10/1 → 20/10/1 DCM/MeOH/H_2O as eluent. Yield: 61 mg (60%; white amorphous solid). R_f = 0.62 (40/10/1 DCM/MeOH/H_2O). $[\alpha]_D$ +53.5 (*c* 1.0 in MeOH). ^1H NMR (300 MHz, CD_3OD): δ 4.85 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 4.70 (bs, 3 H, OH), 4.49 (t, 1 H, $J_{5,6a} = J_{6a,6b}$ = 8.6 Hz, H-6a), 4.18 (dd, 1 H, $J_{5,6b}$ = 6.1 Hz, H-6b), 3.46 (ddd, 1 H, $J_{4,5}$ = 9.4 Hz, H-5), 3.52 (dd, 1 H, $J_{2,3} = J_{3,4}$ = 9.4 Hz, H-3), 3.35 (dd, 1 H, H-2), 3.30 (s, 3 H, OMe), 3.25 (t, 1 H, H-4). ^{13}C NMR (75.5 MHz, CD_3OD): δ 158.9 (CO), 84.6 (C-1), 75.7 (C-4), 74.4 (C-3), 73.0 (C-2), 68.5 (C-6), 56.3 (OMe), 54.7 (C-5). ESIMS: *m*/*z* 242.1 $[M + Na]^+$. Anal. Calcd for $C_8H_{13}NO_6$: C, 43.84; H, 5.98; N, 6.39. Found: C, 43.96; H, 6.11; N, 6.21.

(1*R*)-2,3,4-Tri-*O*-benzyl-1-*O*-methyl-5*N*,6*O*-oxomethylidenenojirimycin (7). A solution of **6** (189 mg, 0.86 mmol) in anhydrous DMF (4.3 mL), under Ar at 0 °C, was treated with 95% NaH (155 mg, 6.45 mmol; slow addition) and stirred for 10 min. Benzyl bromide (613 μL, 5.16 mmol) was added dropwise and stirring was continued at RT for 24 h. The reaction mixture was quenched with water (6 mL) and extracted with Et_2O (5 × 5 mL), and the combined organic extracts were washed with water (2 × 10 mL), dried ($MgSO_4$), concentrated, and chromatographed using 1/5 → 1/3 → 1/1 EtOAc/cyclohexane as eluent. Yield: 383 mg (91%; white amorphous solid). R_f = 0.42 (1/2 EtOAc/cyclohexane). $[\alpha]_D$ +86.8 (*c* 1.0 in DCM). ^1H NMR (300 MHz, $CDCl_3$): δ 7.30−7.15 (m, 15 H, Ph), 4.95 (d, 1 H, $J_{1,2}$ = 3.9 Hz, H-1), 4.94, 4.72 (2 d, 2 H, $^2J_{H,H}$ = 10.7 Hz, C*H*Ph), 4.81, 4.52 (2 d, 2 H, $^2J_{H,H}$ = 11.7 Hz, C*H*Ph), 4.66 (s, 2 H, CH_2Ph), 4.24 (t, 1 H, $J_{6a,6a} = J_{5,6a}$ = 8.6 Hz, H-6a), 3.90 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.2 Hz, H-3), 3.69 (m, 1 H, H-5), 3.59 (dd, 1 H, $J_{5,6b}$ = 6.6 Hz, H-6b), 3.44 (dd, 1 H, H-2), 3.31 (s, 3 H, OMe), 3.27 (t, 1 H, H-4). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.4 (CO), 138.4−127.8 (Ph), 81.6 (C-3), 80.9 (C-4), 80.7 (C-1), 79.8 (C-2), 76.1, 74.8, 73.0 (CH_2Ph), 67.0 (C-6), 56.1 (OMe), 52.3 (C-5). ESIMS: *m*/*z* 512.3 $[M + Na]^+$. Anal. Calcd for $C_{29}H_{31}NO_6$: C, 71.15; H, 6.38; N, 2.86. Found: C, 71.25; H, 6.50; N, 2.76.

(1*R*)-1-*C*-Allyl-2,3,4-tri-*O*-benzyl-5*N*,6*O*-oxomethylidene-1-deoxynojirimycin (8). *From* ***7****.* A solution of 7 (105 mg, 0.2 mmol) in anhydrous MeCN (1.1 mL) at RT, under Ar, was treated with allylTMS (341 μL, 2.2 mmol), stirred for 30 min, and cooled to 0 °C. TMSOTf (195 μL, 1.1 mmol) was added dropwise, and the mixture was further stirred for 19 h at RT, diluted with DCM (10 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), water (10 mL), and brine (10 mL). The organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (1/4 EtOAc/cyclohexane). Yield: 108 mg (98%; white amorphous solid).

From ***11****.* A solution of **11** (607 mg, 2.65 mmol) in anhydrous DMF (14 mL), under Ar at 0 °C, was treated with 95% NaH (477 mg, 19.9 mmol, slow addition) and stirred for 10 min. Benzyl bromide (1.9 mL, 15.9 mmol) was added dropwise, and stirring was continued at RT for 24 h. The reaction mixture was quenched by addition of water (6 mL) and extracted with Et_2O (5 × 5 mL), and the combined organic extracts were washed with water (2 × 10 mL), dried ($MgSO_4$), concentrated, and chromatographed using 1/5 → 1/3 → 1/1 EtOAc/cyclohexane as eluent. Yield: 1.29 g (97%; white amorphous solid). R_f = 0.50 (1/2 EtOAc/cyclohexane). $[\alpha]_D$ +74.9 (*c* 1.0 in DCM). ^1H NMR (300 MHz, $CDCl_3$): δ 7.30−7.15 (m, 15 H, Ph), 5.71−5.60 (m, 1 H, C*H*=CH_2), 5.05−4.99 (m, 2 H, CH = CH_2), 4.93, 4.70 (2 d, 2 H, $^2J_{H,H}$ = 10.3 Hz, C*H*Ph), 4.82, 4.52 (2 d, 2 H, $^2J_{H,H}$ = 11.4 Hz, C*H*Ph), 4.62, 4.56 (2 d, 2 H, $^2J_{H,H}$ = 11.4 Hz, C*H*Ph), 4.17 (m, 2 H, H-1, H-6a), 3.68 (t, 1 H, $J_{2,3} = J_{3,4}$= 9.5 Hz, H-3), 3.68 (dd, 1 H, $J_{6a,6b}$ = 9.1 Hz, $J_{5,6b}$ = 4.5 Hz, H-6b), 3.57 (dd, 1 H, $J_{1,2}$ = 5.9 Hz, H-2), 3.52 (m, 1 H, H-5), 3.26 (dd, 1 H, $J_{4,5}$ = 8.8 Hz, H-4), 2.59 (m, 1 H, C$H_a$$H_b$CH = CH_2), 2.21−2.09 (m, 1 H, $CH_a$$H_b$CH=$CH_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 156.9 (CO), 138.3−137.6 (Ph), 133.9 (*C*H=CH_2), 128.7−127.8 (Ph), 117.8 (CH = *C*H_2), 81.9 (C-3), 80.8 (C-4), 79.5 (C-2), 75.8, 75.1, 72.9 (CH_2Ph), 66.1 (C-6), 52.9 (C-5), 50.7 (C-1), 30.3 (CH_2CH=CH_2). ESIMS: *m*/*z* 522.4 $[M + Na]^+$. Anal. Calcd for $C_{31}H_{33}NO_5$: C, 74.53; H, 6.66; N, 2.80. Found: C, 74.70; H, 6.83; N, 2.87.

(1*R*)-1-*C*-Allyl-2,3,4-tri-*O*-benzyl-1-deoxynojirimycin (12). To a solution of **8** (171 mg, 0.34 mmol) in MeOH/H_2O (5/1, 3.6 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (1.07 g, 3.4 mmol). The suspension was heated at 70 °C for 18 h, diluted with 1/1 H_2O/EtOAc (20 mL), and filtered, and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed using 2/1 → 4/1 → 1/0 EtOAc/cyclohexane as eluent. Yield: 149 mg (93%; white amorphous solid). R_f = 0.34 (2/1 EtOAc/cyclohexane). $[\alpha]_D$ +34.3 (*c* 1.0 in DCM). IR (ATR): ν_{max} 3333, 1750, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.28 (m, 15 H, Ph), 5.75 (m, 1 H, C*H*=CH_2), 5.16−5.10 (m, 2 H, CH=CH_2), 4.96, 4.82 (2 d, 2 H, $^2J_{H,H}$ = 10.9 Hz, C*H*Ph), 4.92, 4.66 (2 d, 2 H, $^2J_{H,H}$ = 10.7 Hz, C*H*Ph), 4.71, 4.67 (2 d, 2 H, $^2J_{H,H}$ = 11.6 Hz, C*H*Ph), 3.78 (t, 1 H, $J_{2,3} = J_{3,4}$= 8.4 Hz, H-3), 3.72 (dd, 1 H, $J_{1,2}$ = 5.0, H-2), 3.69 (m, 1 H, H-6a), 3.66 (dd, 1 H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6b}$ = 4.8, H-6b), 3.42 (dd, 1 H, $J_{4,5}$ = 9.1 Hz, H-4), 3.24 (m, 1 H, H-1), 2.91 (m, 1 H, H-5), 2.50 (m, 1 H, $CH_a$$H_b$CH=$CH_2$), 2.33 (m, 1 H, $CH_a$$H_b$CH=$CH_2$), 2.20 (bs, 2 H, OH, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.7−127.6 (Ph), 135.6 (*C*H=CH_2), 117.9 (CH=*C*H_2), 82.5 (C-3), 81.1 (C-2), 79.4 (C-4), 75.4, 75.1, 72.6 (CH_2Ph), 62.7 (C-6), 54.2 (C-5), 53.0 (C-1), 30.5 (CH_2CH=CH_2). ESIMS: *m*/*z* 473.26 $[M + Na]^+$. Anal. Calcd for $C_{30}H_{35}NO_4$: C, 76.08; H, 7.45; N, 2.96. Found: C, 74.21; H, 7.51; N, 2.96.

Synthesis of (1*R*)-1-*C*-Propyl-1-deoxynojirimycin (13). A solution of **12** (0.32 mmol) in degassed MeOH (3.0 mL) was acidified with HCl (300 μL, 6.0 M) and hydrogenated at atmospheric pressure (balloon) for 24 h using 10% Pd/90% C (30 mg). The mixture was filtered (Celite), concentrated, and chromatographed using 10/1/1 → 10/2/1 MeCN/H_2O/NH_4OH as eluent. Yield: 66 mg (quantitative; colorless oil). The analytical and spectroscopical data of **13** were in agreement with those in the literature.[71]

Synthesis of (1*R*)-1-*C*-Allyl-2,3,4-tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-deoxynojirimycin (14). To a solution of **12** (322 mg, 0.68 mmol) in anhydrous DCM (13.8 mL), under Ar, at RT were added DIPEA (470 μL, 2.72 mmol) and benzyl chloroformate (530 μL, 3.74 mmol). The mixture was stirred for 3 h, diluted with DCM (10 mL), and washed with water

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(10 mL), and the organic extracts were dried ($MgSO_4$), concentrated, and chromatographed using 1/5 EtOAc/cyclohexane as eluent. Yield: 384 mg (93%; colorless oil). R_f = 0.50 (1/3 EtOAc/cyclohexane). $[\alpha]_D$ −27.0 (*c* 0.8 in DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.28 (m, 20 H, Ph), 5.62 (m, 1 H, C*H*=CH_2), 5.16, 5.10 (2 d, 2 H, $^2J_{H,H}$ = 12.4 Hz, C*H*Ph), 5.05 (m, 2 H, CH=CH_2), 4.90, 4.82 (2 d, 2 H, $^2J_{H,H}$ = 10.4 Hz, C*H*Ph), 4.87, 4.81 (2 d, 2 H, $^2J_{H,H}$ = 11.0 Hz, C*H*Ph), 4.66, 4.61 (2 d, 2 H, $^2J_{H,H}$ = 11.6 Hz, C*H*Ph), 4.57 (m, 1 H, H-1), 4.12 (m, 2 H, H-6a, H-6b), 3.80 (m, 2 H, H-3, H-4), 3.61 (dd, 1 H, $J_{2,3}$ = 8.4 Hz, $J_{1,2}$ = 6.1 Hz, H-2), 3.33 (m, 1 H, H-5), 2.57 (dt, 1 H, $^2J_{Ha,Hb}$ = 15.0 Hz, $J_{Ha,1}$ = $J_{Ha,CH}$ = 5.2 Hz, C$H_a$$H_b$CH=CH), 2.40 (ddd, 1 H, $J_{1'b,1}$ = 10.9 Hz, $J_{1'b,2'}$ = 8.5 Hz, $CH_a$$H_b$CH=$CH_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 155.9 (CO), 138.6−136.2 (Ph), 134.1 (*C*H=CH_2), 129.4−127.6 (Ph), 117.4 (CH=CH_2), 82.7 (C-3), 79.5 (C-2), 77.8 (C-4), 75.1, 74.9, 72.7, 67.6 (CH_2Ph), 59.3 (C-6), 57.2 (C-5), 54.4 (C-1), 30.0 (CH_2CH=CH_2). ESIMS: *m*/*z* 630.3 [M + Na]$^+$. Anal. Calcd for $C_{38}H_{41}NO_6$: C, 75.10; H, 6.80; N, 2.30. Found: C, 75.21; H, 6.93; N, 2.19.

(1*R*)-2,3,4-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-(octa-2-en-1-yl)-1-deoxynojirimycin (15). To a solution of **14** (98 mg, 0.16 mmol) in anhydrous degassed DCM (2.3 mL), under Ar, were added hept-1-ene (113 μL, 0.8 mmol), 1,4-BQ (3.5 mg, 0.032 mmol), and the Grubbs II catalyst (14 mg, 0.016 mmol), and the mixture was stirred under Ar at RT for 5 h. A second portion of Grubbs II catalyst (7 mg, 0.008 mmol) was added, and stirring was continued for 18 h. The solvent was evaporated, and the residue was chromatographed using 1/6 EtOAc/cyclohexane as eluent to afford **15** as a mixture of *E*/*Z* isomers (5/1 ratio). Yield: 80 mg (74%; colorless oil). R_f = 0.32 (1/4 EtOAc/cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.18 (m, 20 H, Ph), 5.34 (m, 1 H, =CH), 5.11 (m, 1 H, =CH), 5.05, 4.99 (2 d, 2 H, $^2J_{H,H}$ = 12.4 Hz, C*H*Ph), 4.74 (m, 4 H, C*H*Ph), 4.52, 4.50 (2 d, 2 H, $^2J_{H,H}$ = 11.7 Hz, C*H*Ph), 4.47 (m, 1 H, H-1), 4.00 (m, 2 H, H-6a, H-6b), 3.68 (m, 2 H, H-3, H-4), 3.48 (dd, 1 H, $J_{2,3}$ = 8.7 Hz, $J_{1,2}$ = 6.1 Hz, H-2), 3.18 (m, 1 H, H-5), 2.40−2.16 (m, 2 H, CH_2CH=CH), 1.84 (m, 2 H, CH_2CH=CH), 1.18 (m, 6 H, CH_2), 0.80 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 155.9 (CO), 138.7−136.2 (Ph), 133.8, 132.8 (=CH), 128.6−127.6 (Ph), 125.0, 124.4 (=CH), 82.8, 82.7 (C-3), 79.6, 79.5 (C-2), 77.9 (C-4), 75.2−67.4 (CH_2Ph), 59.2 (C-6), 57.3, 57.2 (C-5), 55.1, 54.7 (C-1), 32.6 (CH_2CH=CH), 31.5, 31.3, 29.3, 29.1 (CH_2), 28.7 (CH_2CH=CH), 27.6, 22.6, 22.5 (CH_2), 14.1 (CH_3). ESIMS: *m*/*z* 700.4 [M + Na]$^+$. Anal. Calcd for $C_{43}H_{51}NO_6$: C, 76.19; H, 7.58; N, 2.07. Found: C, 76.07; H, 7.44; N, 1.85.

Synthesis of (1*R*)-1-*C*-Octyl-1-deoxynojirimycin (16). A solution of **15** (0.32 mmol) in degassed MeOH (3.0 mL) was acidified with HCl (300 μL, 6.0 M) and hydrogenated at atmospheric pressure for 24 h using 10% Pd/90% C (30 mg). The mixture was filtered (Celite), concentrated, and chromatographed using 10/1/1 → 10/2/1 MeCN/H_2O/NH_4OH as eluent to afford **16**. Yield: 88 mg (quantitative; colorless oil). The analytical and spectroscopical data of **16** were in agreement with those reported in the literature.[72]

General Procedure for the Synthesis of (1*R*)-*N*-Alkyl-1-*C*-allyl-2,3,4-tri-*O*-benzyl-1-deoxynojirimycin Derivatives 17 and 18. A solution of **12** (60 mg, 0.13 mmol) and the corresponding aldehyde (1.3 mmol, 10 equiv) in 5/1 MeCN/MeOH (1.3 mL), under Ar, was acidified to pH 5−6 with AcOH (3 μL). Sodium sulfate (32 mg, 0.26 mmol, 2 equiv) and sodium cyanoborohydride (33 mg, 0.52 mmol, 4 equiv) were added, the mixture was heated to 65 °C for 18 h and then diluted with saturated aqueous $NaHCO_3$ (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated, and chromatographed with the indicated eluent.

*(1R)-1-C-Allyl-2,3,4-tri-O-benzyl-N-butyl-1-deoxynojirimycin (**17**).* Column chromatography (1/4 EtOAc/cyclohexane). Yield: 48 mg (70%; colorless oil). R_f = 0.51 (1/3 EtOAc/cyclohexane). $[\alpha]_D$ +6.4 (*c* 0.8 in DCM). IR (ATR): ν_{max} 1637, 1453, 1092, 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28−7.18 (m, 15 H, Ph), 5.68 (m, 1 H, C*H*=CH_2), 4.98−4.91 (m, 2 H, CH=CH_2), 4.84, 4.71 (2 d, 2 H, $^2J_{H,H}$ = 10.9 Hz, C*H*Ph), 4.78, 4.48 (2 d, 2 H, $^2J_{H,H}$ = 11.0 Hz, C*H*Ph), 4.61, 4.54 (2 d, 2 H, $^2J_{H,H}$ = 11.6 Hz, C*H*Ph), 3.72 (dd, 1 H, $J_{6a,6b}$ = 10.8 Hz, $J_{5,6a}$ = 4.5 Hz, H-6a), 3.69−3.64 (m, 2 H, H-2, H-3), 3.50 (dd, 1 H, $J_{5,6b}$ = 7.5 Hz, H-6b), 3.39 (m, 1 H, H-4), 3.03 (m, 1 H, H-1), 2.84 (ddd, 1 H, $J_{4,5}$ = 10.3 Hz, H-5), 2.51 (m, 1 H, C$H_a$$H_b$N), 2.40 (m, 2 H, C$H_a$$H_bN, CH_a$$H_b$CH=$CH_2$), 2.21 (m, 2 H, C$H_a$$H_b$CH=$CH_2$, OH), 1.18 (m, 4 H, CH_2), 0.81 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 138.8−127.6 (Ph), 136.9 (*C*H=CH_2), 115.9 (CH=CH_2), 83.7 (C-2), 79.0 (C-3), 78.5 (C-4), 75.4, 75.1, 72.9 (CH_2Ph), 59.5 (C-6), 58.3 (C-5), 56.9 (C-1), 46.5 (CH_2N), 31.6 (CH_2), 29.6 (CH_2CH=CH_2), 20.3 (CH_2), 14.0 (CH_3). ESIMS: *m*/*z* 530.33 [M + H]$^+$. HRMS (ESI) [M + H]$^+$ calcd for $C_{34}H_{44}NO_4$ *m*/*z* 530.3265; found *m*/*z* 530.3258.

*(1R)-1-C-Allyl-2,3,4-tri-O-benzyl-N-octyl-1-deoxynojirimycin (**18**).* Column chromatography (1/5 EtOAc/cyclohexane). Yield: 69 mg (90%; colorless oil). R_f = 0.49 (1/5 EtOAc/cyclohexane). $[\alpha]_D$ +16.5 (*c* 1.0 in $CHCl_3$). IR (ATR): ν_{max} 925, 2854, 1453, 1027, 749, 696 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28−7.18 (m, 15 H, Ph), 5.68 (m, 1 H, C*H*=CH_2), 4.98−4.91 (m, 2 H, CH=CH_2), 4.84, 4.71 (2 d, 2 H, $^2J_{H,H}$ = 10.9 Hz, C*H*Ph), 4.78, 4.48 (2 d, 2 H, $^2J_{H,H}$ = 11.0 Hz, C*H*Ph), 4.61, 4.54 (2 d, 2 H, $^2J_{H,H}$ = 11.6 Hz, C*H*Ph), 3.72 (dd, 1 H, $J_{6a,6b}$ = 10.9 Hz, $J_{5,6a}$ = 4.5 Hz, H-6a), 3.69−3.64 (m, 2 H, H-2, H-3), 3.50 (dd, 1 H, $J_{5,6b}$ = 7.5 Hz, H-6b), 3.39 (m, 1 H, H-4), 3.03 (m, 1 H, H-1), 2.84 (ddd, 1 H, $J_{4,5}$ = 10.2 Hz, H-5), 2.50 (m, 1 H, C$H_a$$H_b$N), 2.37 (m, 2 H, C$H_a$$H_bN, CH_a$$H_b$CH=$CH_2$), 2.22 (m, 2 H, C$H_a$$H_b$CH = CH_2, OH), 1.30−1,10 (m, 12 H, CH_2), 0.82 (t, 3 H, $^3J_{H,H}$ = 6.9 Hz, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 138.8−127.6 (Ph), 136.9 (*C*H=CH_2), 115.9 (CH=CH_2), 83.7 (C-2), 79.0 (C-3), 78.5 (C-4), 75.4, 75.1, 72.9 (CH_2Ph), 59.5 (C-6), 58.3 (C-5), 56.9 (C-1), 46.7 (CH_2N), 31.8 (CH_2), 29.6−29.3 (CH_2, CH_2CH=CH_2), 27.1, 22.7 (CH_2), 14.1 (CH_3). ESIMS: *m*/*z* 586.39 [M + H]$^+$, 589.40 [M + Na]$^+$. HRMS (ESI) [M + H]$^+$ calcd for $C_{34}H_{44}NO_4$ *m*/*z* 586.3891; found *m*/*z* 586.3885.

General Procedure for the Synthesis of (1*R*)-*N*-Alkyl-1-*C*-propyl-1-deoxynojirimycin Hydrochloride Derivatives 19 and 20. A solution of **17** or **18** (0.094 mmol) in degassed MeOH (1.0 mL) was acidified with HCl (94 μL, 6.0 M) and hydrogenated at atmospheric pressure for 24 h using 10% Pd/C (9 mg). The mixture was filtered (Celite), concentrated, and chromatographed with the indicated eluent.

*(1R)-1-C-Propyl-N-butyl-1-deoxynojirimycin Hydrocloride (**19**).* Column chromatography (40/10/1 DCM/MeOH/H_2O). Yield: 27 mg (97%; white amorphous solid). R_f = 0.49 (60/10/1 DCM/MeOH/H_2O). $[\alpha]_D$ −6.5 (*c* 1.0 in MeOH). ^{1}H NMR (500 MHz, 5/1 CD_3OD/$CDCl_3$): δ 3.76 (dd, 1 H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 4.2 Hz, H-6a), 3.70 (m, 1 H,

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H-6b), 3.61 (dd, 1 H, $J_{2,3}$ = 9.3 Hz, $J_{1,2}$ = 5.4 Hz, H-2), 3.37 (t, 1 H, $J_{3,4}$ = 9.3 Hz, H-3), 3.31 (t, 1 H, $J_{4,5}$ = 9.3 Hz, H-4), 2.94 (bs, 1 H, H-1), 2.63 (m, 3 H, H-5, CH_2N), 1.50−1.19 (m, 8 H, CH_2), 0.85 (t, 3 H, $^3J_{H,H}$ = 7.1 Hz, CH_3), 0.84 (t, 3 H, $^3J_{H,H}$ = 7.4 Hz, CH_3). ^{13}C NMR (125.7 MHz, 5/1 $CD_3OD/CDCl_3$): δ 76.6 (C-3), 72.4 (C-2), 71.5 (C-4), 61.0 (C-1, C-5, C-6), 48.8 (CH_2N), 27.3, 22.4, 21.3 (CH_2), 14.6, 14.4 (CH_3). ESIMS: *m/z* 262.20 $[M + H - Cl]^+$. HRMS (ESI) $[M + H - Cl]^+$ calcd for $C_{13}H_{28}ClNO_4$ *m/z* 262.2013; found *m/z* 262.2014.

*(1R)-1-C-Propyl-N-octyl-1-deoxynojirimycin Hydrochloride (**20**).* Column chromatography (80/10/1 DCM/MeOH/H_2O). Yield: 27 mg (80%; white amorphous solid). R_f = 0.23 (80/10/1 DCM/MeOH/H_2O). $[\alpha]_D$ +16.6 (*c* 1.0 in MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 3.85 (dd, 1 H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 4.1 Hz, H-6a), 3.78 (dd, 1 H, $J_{5,6b}$ = 5.5 Hz, H-6b), 3.68 (dd, 1 H, $J_{2,3}$ = 9.1 Hz, $J_{1,2}$ = 5.4 Hz, H-2), 3.44 (t, 1 H, $J_{3,4}$ = 9.0 Hz, H-3), 3.37 (t, 1 H, $J_{4,5}$ = 9.0 Hz, H-4), 3.01 (m, 1 H, H-1), 2.71 (m, 3 H, H-5, CH_2N), 1.60−1.31 (m, 16 H, CH_2), 0.93 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_3), 0.89 (t, 3 H, $^3J_{H,H}$ = 6.9 Hz, CH_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 76.7 (C-3), 72.5 (C-2), 71.7 (C-4), 61.2 (C-1, C-5, C-6),48.9 (CH_2N), 33.0, 30.6, 30.4, 28.3, 27.4, 23.9, 23.7, 22.5 (CH_2), 14.7, 14.4 (CH_3). ESIMS: *m/z* 318.26 $[M + H - Cl]^+$. HRMS (ESI) $[M + H - Cl]^+$ calcd for $C_{17}H_{36}ClNO_4$ *m/z* 318.2639; found *m/z* 318.2639.

General Procedure for the Synthesis of (1*R*)-*N*-(*N*′-Alkylthiocarbamoyl)-1-*C*-propyl-1-deoxynojirimycin Derivatives 21−26. To a solution of **13** (66 mg, 0.32 mmol) in pyridine (5.0 mL) were added Et_3N (53 μL, 0.38 mmol) and the isothiocyanate reagent (0.35 mmol, 1.1 equiv). The mixture was stirred at RT for 18 h, concentrated, coevaporated with toluene, and chromatographed with the indicated eluent. Line broadening was observed in the ^{1}H and ^{13}NMR spectra of these compounds and even line splitting in the case of the ^{13}C NMR spectrum of compound **25**; this effect is not a sign of the presence of impurities but the consequence of slow rotation about the N−C(=S) thiourea bonds.

*(1R)-N-(N′-Butylthiocarbamoyl)-1-C-propyl-1-deoxynojirimycin (**21**).* Column chromatography (100/10/1 → 80/10/1 DCM/MeOH/H_2O). Yield: 80 mg (78%; colorless oil). R_f = 0.27 (80/10/1 DCM/MeOH/H_2O). UV (MeOH): 253 nm (ε_{mM} 11.7). $[\alpha]_D$ −236.1 (*c* 1.0 in MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 3.92 (m, 4 H, H-4, H-5, H-6a, H-6b), 3.55 (m, 3 H, H-1, CH_2NH), 3.39 (m, 2 H, H-2, H-3), 2.02 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.76 (m, 1 H, CH$_a$H$_b$CH$_2$CH$_3$), 1.61 (m, 2 H, CH_2), 1.42 (m, 2 H, CH_2), 1.33 (m, 2 H, CH_2), 0.97 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH_3), 0.96 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH_3). ^{13}C NMR (100.6 MHz, CD_3OD): δ 186.4 (CS), 79.0 (C-2), 75.9 (C-1), 71.2 (C-3, C-4), 62.0 (C-5), 60.3 (C-6), 46.8 (CH_2NH), 32.0, 29.7, 21.2, 20.5 (CH_2), 14.2, 14.0 (CH_3). ESIMS: *m/z* 343.3 $[M + Na]^+$. Anal. Calcd for $C_{14}H_{28}N_2O_4S$: C, 52.47; H, 8.81; N, 8.74; S, 10.00. Found: C, 52.36; H, 9.00; N, 8.70; S, 9.88.

*(1R)-N-(N′-Octylthiocarbamoyl)-1-C-propyl-1-deoxynojirimycin (**22**).* Column chromatography (20/1 → 7/1 DCM/MeOH). Yield: 89 mg (74%; colorless oil). R_f = 0.48 (15/1 DCM/MeOH). UV (MeOH): 253 nm (ε_{mM} 9.3). $[\alpha]_D$ −221.4 (*c* 1.0 in MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 3.92 (m, 4 H, H-4, H-5, H-6a, H-6b), 3.54 (m, 3 H, H-1, CH_2NH), 3.56 (m, 2 H, H-2, H-3), 2.03 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.76 (m, 1 H, CH$_a$H$_b$CH$_2$CH$_3$), 1.61 (m, 2 H, CH_2), 1.34 (m, 12 H, CH_2), 0.97 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH_3), 0.92 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_3). ^{13}C NMR (75.5 MHz, CD_3OD): δ 186.1 (CS), 79.0 (C-2), 75.7 (C-1), 71.0 (C-3, C-4), 61.9 (C-5), 60.3 (C-6), 47.0 (CH_2NH), 33.0, 30.4, 30.3, 30.0, 29.6, 28.2, 23.7, 20.5 (CH_2), 14.4, 14.3 (CH_3). ESIMS: *m/z* 399.4 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{36}N_2O_4S$: C, 57.41; H, 9.64; N, 7.44; S, 8.51. Found: C, 57.44; H, 9.72; N, 7.65; S, 8.30.

*(1R)-N-(N′-Benzylthiocarbamoyl)-1-C-propyl-1-deoxynojirimycin (**23**).* Column chromatography (100/10/1 DCM/MeOH/H_2O). Yield: 70 mg (62%; colorless oil). R_f = 0.57 (70/10/1 DCM/MeOH/H_2O). UV (MeOH): 252 nm (ε_{mM} 13.1). $[\alpha]_D$ −254.4 (*c* 1.1 in MeOH). ^{1}H NMR (500 MHz, CD_3CN): δ 7.37−7.26 (m, 5 H, Ph), 4.83, 4.74 (2 d, 2 H, $^2J_{H,H}$ = 14.3 Hz, CH_2NH), 4.01 (bs, 1 H, H-4), 3.94−3.87 (m, 3 H, H-5, H-6a, H-6b), 3.57 (m, 1 H, H-1), 3.41 (m, 2 H, H-2, H-3), 1.96 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.70 (m, 1 H, CH$_a$H$_b$CH$_2$CH$_3$), 1.31 (m, 2 H, CH_2), 0.92 (t, 3 H, $^3J_{H,H}$ = 7.4 Hz, CH_3). ^{13}C NMR (125.7 MHz, CD_3CN): δ 185.0 (CS), 138.0, 128.2, 127.6, 127.0 (Ph), 77.6 (C-2), 74.5 (C-1), 69.6 (C-3, C-4), 60.6 (C-6), 59.2 (C-5), 49.4 (CH_2NH), 28.3 (CH_2), 19.1 (CH_2CH_3), 12.9 (CH_3). ESIMS: *m/z* 377.1 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{26}N_2O_4S$: C, 57.60; H, 7.39; N, 7.90; S, 9.04. Found: C, 57.45; H, 7.12; N, 7.69; S, 8.80.

*(1R)-N-[N′-(2-Phenyl)ethylthiocarbamoyl]-1-C-propyl-1-deoxynojirimycin (**24**).* Column chromatography (100/10/1 → 80/10/1 DCM/MeOH/H_2O). Yield: 86 mg (73%; colorless oil). R_f = 0.42 (70/10/1 DCM/MeOH/H_2O). UV (MeOH): 251 nm (ε_{mM} 10.5). $[\alpha]_D$ −240.1 (*c* 1.0 in MeOH). ^{1}H NMR (500 MHz, CD_3CN): δ 8.19 (bs, 1 H NH), 7.36−7.22 (m, 5 H, Ph), 4.17 (bs, 1 H, OH), 3.92 (bs, 1 H, H-4), 3.83−3.73 (m, 5 H, CH_2NH, H-5, H-6a, H-6b), 3.49 (m, 1 H, H-1), 3.31 (dd, 1 H, $J_{2,3}$ = 9.4 Hz, $J_{1,2}$ = 6.1 Hz, H-2), 3.26 (m, 1 H, H-3), 2.93 (t, 2 H, $^3J_{H,H}$ = 7.5 Hz, CH_2Ph), 1.97 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.66 (m, 1 H, CH$_a$H$_b$CH$_2$CH$_3$), 1.23 (m, 2 H, CH_2), 0.90 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH_3). ^{13}C NMR (125.7 MHz, CD_3CN): δ 185.9 (CS), 139.9, 129.5, 129.1, 126.9 (Ph), 78.2 (C-2), 75.1 (C-1), 70.3 (C-3, C-4), 61.4 (C-6), 58.7 (C-5), 47.5 (CH_2NH), 35.0 (CH_2Ph), 28.8 (CH_2), 19.8 (CH_2CH_3), 13.8 (CH_3). ESIMS: *m/z* 391.2 $[M + Na]^+$, 369.2 $[M + H]^+$. Anal. Calcd for $C_{18}H_{28}N_2O_4S$: C, 58.67; H, 7.66; N, 7.60; S, 8.70. Found: C, 58.77; H, 7.78 N, 7.42; S, 8.46.

*(1R)-N-(N′-p-Methoxybenzylthiocarbamoyl)-1-C-propyl-1-deoxynojirimycin (**25**).* Column chromatography (100/10/1 DCM/MeOH/H_2O). Yield: 107 mg (87%; colorless oil). R_f = 0.45 (80/10/1 DCM/MeOH/H_2O). UV (MeOH): 252 nm (ε_{mM} 15.0). $[\alpha]_D$ −309.9 (*c* 1.0 in MeOH). ^{1}H NMR (500 MHz, CD_3CN): δ 8.48 (bs, 1 H NH), 7.28−6.92 (m, 4 H, Ph), 4.72, 4.65 (2 dd, 2 H, $^2J_{H,H}$ = 14.6 Hz, $^3J_{H,H}$ = 5.2 Hz, CH_2NH), 4.24 (bs, 1 H, OH), 4.01 (bs, 1 H, H-4), 3.84−3.80 (m, 3 H, H-5, H-6a, H-6b), 3.79 (s, 3 H, OMe), 3.68 (bs, 2 H, OH), 3.53 (m, 1 H, H-1), 3.35 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 6.0 Hz, H-2), 3.31 (m, 1 H, H-3), 2.33 (bs, 1 H, OH), 2.01 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.68 (m, 1 H, CH$_a$H$_b$CH$_2$CH$_3$), 1.26 (m, 2 H, CH_2), 0.90 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH_3). ^{13}C NMR (125.7 MHz, CD_3CN): δ 186.0 (CS), 159.7, 131.1, 130.0, 114.6 (Ph), 78.4 (C-2), 75.4 (C-1), 70.5 (C-3, C-4), 61.7 (C-6), 59.0 (C-5), 55.6 (OMe), 49.6 (CH_2NH), 29.1 (CH_2), 19.9 (CH_2CH_3), 14.0 (CH_3). ESIMS: *m/z* 407.2 $[M + Na]^+$, 385.2 $[M + H]^+$. Anal. Calcd for $C_{18}H_{28}N_2O_5S$: C, 56.23; H, 7.34; N, 7.29; S, 8.34. Found: C, 55.99; H, 7.20; N, 7.04; S, 8.01.

*(1R)-N-(N′-p-Trifluoromethylbenzylthiocarbamoyl)-1-C-propyl-1-deoxynojirimycin (**26**).* Column chromatography (100/10/1 → 80/10/1 DCM/MeOH/H_2O). Yield: 88 mg

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(65%; colorless oil). R_f = 0.54 (80/10/1 DCM/MeOH/H_2O). UV (MeOH 253 nm (ε_{mM} 13.2). $[\alpha]_D$ −190.6 (*c* 1.0 in MeOH). ^{1}H NMR (300 MHz, CD_3CN): δ 8.459 (bs, 1 H NH), 7.60, 7.44 (2 d, 4 H, $^3J_{H,H}$ = 8.1 Hz, Ph), 4.80 (d, 2 H, $^3J_{H,H}$ = 5.6 Hz, CH_2NH), 3.94 (bs, 1 H, H-4), 3.83−3.78 (m, 3 H, H-5, H-6a, H-6b), 3.46 (m, 1 H, H-1), 3.28 (m, 2 H, H-2, H-3), 1.97 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.65 (m, 1 H, CH$_a$$H_bCH_2CH_3$), 1.22 (m, 2 H, CH$_2$), 0.84 (t, 3 H, $^3J_{H,H}$ = 7.4 Hz, CH$_3$). ^{13}C NMR (125.7 MHz, CD_3CN): δ 186.5 (CS), 144.1, 128.7, 125.8 (Ph), 78.2 (C-2), 75.1 (C-1), 70.3 (C-3, C-4), 61.4 (C-6), 59.3 (C-5), 49.1 (CH$_2$NH), 28.9 (CH$_2$), 19.8 (CH$_2$CH$_3$), 13.8 (CH$_3$). ESIMS: *m*/*z* 445.14 [M + Na]$^+$, 423.16 [M + H]$^+$. Anal. Calcd for $C_{18}H_{25}F_3N_2O_4S$: C, 51.18; H, 5.97; N, 6.63; S, 7.59. Found: C, 50.88; H, 5.76; N, 6.37; S, 7.31.

General Procedure for the Synthesis of (1*R*)-5-*N*,6-*S*-(*N*′-Alkyliminomethylidene)-1-*C*-propyl-6-thio-1-deoxynojirimycin Hydrochloride Derivatives 29 and 30. To a solution of **21** or **22** (0.14 mmol) in MeOH (5.0 mL) was added concentrated HCl (pH 1), and the reaction mixture was stirred at RT for 18 h and evaporated. The residue was coevaporated with MeOH (3 × 10 mL) and chromatographed with the indicated eluent.

*(1R)-5-N,6-S-(N′-Butyliminomethylidene)-1-C-propyl-6-thio-1-deoxynojirimycin Hydrochloride (**29**).* Column chromatography (70/10/1 → 60/10/1 → 40/10/1 DCM/MeOH/H_2O). Yield: 37 mg (78%; white amorphous solid). R_f = 0.30 (70/10/1 DCM/MeOH/H_2O). $[\alpha]_D$ +23.9 (*c* 1.0 in MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 4.28 (ddd, 1 H, $J_{1,CH}$ = 11.3 Hz, $J_{1,2}$ = 5.0 Hz, $J_{1,CH}$ = 3.2 Hz, H-1), 4.15 (ddd, 1 H, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 8.4 Hz, $J_{5,6b}$ = 4.9 Hz, H-5), 3.70 (dd, 1 H, $J_{6a,6b}$ = 11.6 Hz, H-6a), 3.50 (dd, 1 H, H-6b), 3.49 (m, 2 H, H-2, H-3), 3.32 (m, 3 H, H-4, CH_2NH), 1.85 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.57 (m, 3 H, CH$_a$$H_bCH_2CH_3$, CH$_2$), 1.26 (m, 4 H, CH$_2$), 0.89 (t, 3 H, $^3J_{H,H}$ = 7.2 Hz, CH$_3$), 0.88 (t, 3 H, $^3J_{H,H}$ = 7.3 Hz, CH$_3$). ^{13}C NMR (75.5 MHz, CD_3OD): δ 172.5 (CN), 74.8 (C-3), 73.8 (C-4), 71.2 (C-2), 65.1 (C-5), 59.6 (C-1), 49.8 (CH$_2$NH), 32.1 (CH$_2$), 31.1 (C-6), 28.3, 20.8, 20.2 (CH$_2$), 14.2, 13.9 (CH$_3$). ESIMS: *m*/*z* 303.3 [M - Cl]$^+$. Anal. Calcd for $C_{14}H_{27}ClN_2O_3S$: C, 49.62; H, 8.03; N, 8.27; S, 9.56. Found: C, 49.86; H, 8.30; N, 8.43; S, 9.54.

*(1R)-5-N,6-S-(N′-Octyliminomethylidene)-1-C-propyl-6-thio-1-deoxynojirimycin Hydrochloride (**30**).* Column chromatography (50/10/1 DCM/MeOH/H_2O). Yield: 55 mg (quant; white amorphous solid). R_f = 0.44 (50/10/1 DCM/MeOH/H_2O). $[\alpha]_D$ +48.4 (*c* 1.0 in MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 4.35 (ddd, 1 H, $J_{1,CH}$ = 11.4 Hz, $J_{1,2}$ = 5.2 Hz, $J_{1,CH}$ = 3.9 Hz, H-1), 3.98 (m, 1 H, H-5), 3.60 (dd, 1 H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 7.9 Hz, H-6a), 3.57 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 3.53 (dd, 1 H, H-2), 3.46 (dd, 1 H, $J_{5,6b}$ = 4.0 Hz, H-6b), 3.30 (m, 3 H, H-4, CH_2NH), 1.90 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.63 (m, 3 H, CH$_a$$H_bCH_2CH_3$, CH$_2$), 1.35 (m, 12 H, CH$_2$), 0.98 (t, 3 H, $^3J_{H,H}$ = 7.4 Hz, CH$_3$), 0.92 (t, 3 H, $^3J_{H,H}$ = 7.2 Hz, CH$_3$). ^{13}C NMR (125.7 MHz, CD_3OD): δ 167.2 (CN), 75.2 (C-3), 73.7 (C-4), 71.5 (C-2), 63.1 (C-5), 58.2 (C-1), 52.7 (CH$_2$NH), 32.9, 31.0, 30.3 (CH$_2$), 30.2 (C-6), 28.3, 27.9, 23.6, 20.4 (CH$_2$), 14.4, 14.3 (CH$_3$). ESIMS: *m*/*z* 359.4 [M - Cl]$^+$. Anal. Calcd for $C_{18}H_{35}ClN_2O_3S$: C, 54.73; H, 8.93; N, 7.09; S, 8.12. Found: C, 54.49; H, 9.12; N, 6.86; S, 7.81.

General Procedure for the Synthesis of (1*R*)-*N*-(*N*′-Alkylthiocarbamoyl)-1-*C*-octyl-1-deoxynojirimycin Derivatives 27 and 28. To a solution of **16** (55 mg, 0.2 mmol) in DMF (2.0 mL) were added Et_3N (56 μL, 0.4 mmol) and the isothiocyanate reagent (0.24 mmol, 1.2 equiv). The mixture was stirred at 40 °C for 18 h, concentrated, and chromatographed using 100/10/1 DCM/MeOH/H_2O as eluent.

*(R)-N-(N′-Butylthiocarbamoyl)-1-C-octyl-1-deoxynojirimycin (**27**).* Yield: 55 mg (70%; colorless oil). R_f = 0.38 (100/10/1 DCM/MeOH/H_2O). UV (MeOH): 252 nm (ε_{mM} 14.1). $[\alpha]_D$ −212.5 (*c* 1.0 in MeOH). ^{1}H NMR (500 MHz, CD_3CN, 303 K): δ 8.16 (bs, 1 H, NH), 4.54 (bs, 1 H, OH), 4.18 (m, 1 H, H-6a), 3.97 (m, 1 H, H-4), 3.82 (m, 2 H, H-5, H-6b), 3.63−3.40 (m, 6 H, H-1, OH, CH_2NH), 3.29 (m, 2 H, H-2, H-3), 2.01 (m, 1 H, CH_aH$_b$CH$_2$), 1.76 (m, 1 H, CH$_a$$H_bCH_2$), 1.59 (m, 2 H, CH$_2$), 1.40 (m, 2 H, CH$_2$), 1.37−1.22 (m, 12 H, CH$_2$), 0.97 (t, 3 H, $^3J_{H,H}$ = 7.4 Hz, CH$_3$), 0.92 (t, 3 H, $^3J_{H,H}$ = 7.1 Hz, CH$_3$). ^{13}C NMR (125.7 MHz, CD_3CN, 303 K): δ 185.7 (CS), 77.8 (C-2), 74.8 (C-1), 70.1 (C-3, C-4), 61.1 (C-5), 58.2 (C-6), 45.5 (CH$_2$NH), 31.6, 30.7, 29.2, 29.1, 28.9, 26.3, 26.0, 22.3, 19.9 (CH$_2$), 13.3, 13.0 (CH$_3$). ESIMS: *m*/*z* 413.2 [M + Na]$^+$. Anal. Calcd for $C_{19}H_{38}N_2O_4S$: C, 58.43; H, 89.81; N, 7.17; S, 8.21. Found: C, 58.31; H, 9.66; N, 6.92; S, 8.01.

*(1R)-N-(N′-Octylthiocarbamoyl)-1-C-octyl-1-deoxynojirimycin (**28**).* Yield: 63 mg (70%; colorless oil). R_f = 0.41 (100/10/1 DCM/MeOH/H_2O). UV (MeOH): 251 nm (ε_{mM} 11.6). $[\alpha]_D$ −178.6 (*c* 1.0 in MeOH). ^{1}H NMR (500 MHz, 17:3 CD_3CN-$CDCl_3$): δ 8.15 (bs, 1 H, NH), 4.57 (bs, 1 H, OH), 4.18 (m, 1 H, H-6a), 4.00 (bs, 1 H, H-4), 3.79 (m, 2 H, H-5, H-6b), 3.59−3.44 (m, 6 H, H-1, OH, CH_2NH), 3.34 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 6.0 Hz, H-2), 2.78 (bt, 1 H, H-3), 2.08 (m, 1 H, CH_aH$_b$CH$_2$), 1.77 (m, 1 H, CH$_a$$H_bCH_2$), 1.60 (m, 2 H, CH$_2$), 1.35−1.24 (m, 22 H, CH$_2$), 0.93 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH$_3$), 0.92 (t, 3 H, $^3J_{H,H}$ = 7.1 Hz, CH$_3$). ^{13}C NMR (125.7 MHz, 17:3 CD_3CN-$CDCl_3$): δ 184.8 (CS), 77.7 (C-2), 74.3 (C-1), 69.4 (C-3, C-4), 60.6 (C-5), 57.6 (C-6), 45.3 (CH$_2$NH), 31.2, 31.1, 28.8, 28.7, 28.6, 28.5, 28.1, 26.3, 25.8, 25.5, 22.0, 21.9 (CH$_2$), 13.1 (CH$_3$). ESIMS: *m*/*z* 469.3 [M + Na]$^+$. Anal. Calcd for $C_{23}H_{46}N_2O_4S$: C, 61.84; H, 10.38 N, 6.27; S, 7.18. Found: C, 61.69; H, 10.30; N, 6.04; S, 6.89.

General Procedure for the Synthesis of (1*R*)-5-*N*,6-*S*-(*N*′-Alkyliminomethylidene)-1-*C*-octyl-6-thio-1-deoxynojirimycin Hydrochloride Derivatives 31 and 32. To a solution of **27** or **28** (0.14 mmol) in MeOH (5.0 mL) was added concentrated HCl (pH 1), and the reaction mixture was further stirred at RT for 18 h. The solvent was removed, and the residue was coevaporated several times with MeOH (neutral pH) and purified by column chromatography with the eluent indicated in each case.

*(1R)-5-N,6-S-(N′-Butyliminomethylidene)-1-C-octyl-6-thio-1-deoxynojirimycin Hydrochloride (**31**).* Column chromatography (60/10/1 DCM/MeOH/H_2O. Yield: 46 mg (80%; white amorphous solid). R_f = 0.64 (60/10/1 DCM/MeOH/H_2O). $[\alpha]_D$ +35.9 (*c* 1.0 in MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 4.32 (ddd, 1 H, $J_{1,CH}$ = 11.3 Hz, $J_{1,2}$ = 5.1 Hz, $J_{1,CH}$ = 4.0 Hz, H-1), 4.05 (bs, 1 H, H-5), 3.66 (dd, 1 H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6a}$ = 8.5 Hz, H-6a), 3.58 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 3.55 (dd, 1 H, H-2), 3.49 (dd, 1 H, $J_{5,6b}$ = 4.3 Hz, H-6b), 3.40−3.30 (m, 3 H, H-4, CH_2NH), 1.98 (m, 1 H, CH_aH$_b$CH$_2$CH$_3$), 1.65 (m, 3 H, CH$_a$$H_bCH_2CH_3$, CH$_2$), 1.45−1.30 (m, 14 H, CH$_2$), 0.99 (t, 3 H, $^3J_{H,H}$ = 7.4 Hz, CH$_3$), 0.93 (t, 3 H, $^3J_{H,H}$ = 7.1 Hz, CH$_3$). ^{13}C NMR (125.7 MHz, CD_3OD): δ 169.4 (CN), 75.3 (C-3), 73.9 (C-4), 71.6 (C-2),

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63.7 (C-5), 58.8 (C-1), 51.8 (CH_2NH), 33.0, 32.9, 30.7, 30.5 (CH_2), 30.4 (C-6), 27.3, 26.2, 23.7, 21.1 (CH_2), 14.4, 14.1 (CH_3). ESIMS: m/z 373.3 $[M - Cl]^+$. HRMS (ESI) $[M + Na]^+$ calcd for $C_{19}H_{37}ClN_2O_3NaS$ m/z 431.2106; found m/z 431.2103.

*(1R)-5-N,6-S-(N′-Octyliminomethylidene)-1-C-octyl-6-thio-1-deoxynojirimycin Hydrochloride (**32**).* Column chromatography (70/10/1 DCM/MeOH/H_2O). Yield: 4659 mg (90%; white amorphous solid). R_f = 0.45 (70/10/1 DCM/MeOH/H_2O). $[\alpha]_D$ +24.8 (c 1.0 in MeOH). ^{1}H NMR (500 MHz, 6/1 $CD_3OD/CDCl_3$): δ 4.20 (ddd, 1 H, $J_{1,CH}$ = 11.3 Hz, $J_{1,2}$ = 5.3 Hz, $J_{1,CH}$ = 4.0 Hz, H-1), 3.87 (m, 1 H, H-5), 3.50 (m, 1 H, H-6a), 3.47 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.7 Hz, H-3), 3.43 (dd, 1 H, H-2), 3.35 (dd, 1 H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6b}$ = 4.3 Hz, H-6b), 3.27−3.15 (m, 3 H, H-4, CH_2NH), 1.86 (m, 1 H, $CH_aH_bCH_2CH_3$), 1.51 (m, 3 H, $CH_aH_bCH_2CH_3$, CH_2), 1.22 (m, 22 H, CH_2), 0.80 (t, 3 H, $^3J_{H,H}$ = 7.2 Hz, CH_3), 0.79 (t, 3 H, $^3J_{H,H}$ = 7.0 Hz, CH_3). ^{13}C NMR (125.7 MHz, 6/1 $CD_3OD/CDCl_3$) δ 167.0 (CN), 75.3 (C-3), 74.0 (C-4), 71.6(C-2), 63.5 (C-5), 58.6 (C-1), 52.6 (CH_2NH), 33.1, 33.0, 31.1, 30.8, 30.6 (CH_2), 30.5 (C-6), 30.4, 28.1, 27.4, 26.3, 23.8, 23.7 (CH_2), 14.7, 14.6 (CH_3). ESIMS: m/z 429.3 $[M - Cl]^+$. HRMS (ESI) $[M + Na]^+$ calcd for $C_{23}H_{45}ClN_2O_3NaS$ m/z 487.2732; found m/z 431.2723.

Inhibitory Activity Screening toward Commercial Glycosidases. Kinetic K_i values were determined from the residual activities of the enzymes at their optimal pHs using *o* (for β-galactosidase from *E. coli*)- or *p*-nitrophenyl α- or β-D-glycopyranoside (for other glycosidases) in the presence of increasing concentrations of the inhibitors. Approximate values were first obtained using a fixed concentration of substrate close to the K_M value for the corresponding glycosidase. Lineweaver−Burk plots and a double-reciprocal analysis provided accurate K_i values and confirmed the inhibition mode.[76,77]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01469.

Optimized synthesis of the sp^2-iminosugar precursor **3**, ^{1}H and ^{13}C NMR spectra for all compounds, and experimental details for glycosidase inhibition studies (PDF)

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Notes

The authors declare no competing financial interest.

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