Lipophilic iminosugars : synthesis and evaluation as inhibitors of glucosylceramide metabolism

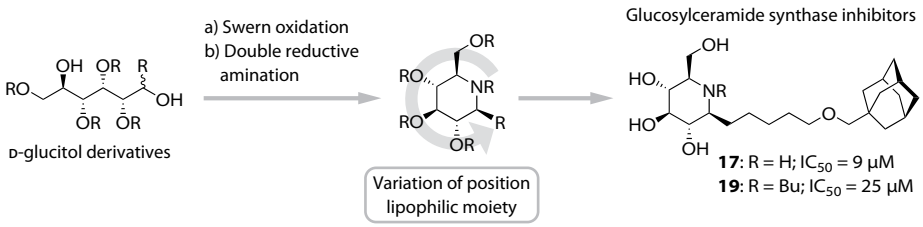
Wennekes, T.

5 Location of the Lipophilic Moiety on the Iminosugar

Influence on Inhibition of Glucosylceramide Metabolism

Abstract

This chapter deals with the influence on inhibition of glucosylceramide metabolism when changing the position of the lipophilic moiety on the 1-deoxynoijirimycin core. D-Glucitol derivatives for each target position were synthesized and transformed into a library of fifteen lipophilic iminosugars. Evaluation of these compounds as inhibitors proved that positioning of the lipophilic moiety on the ring nitrogen atom – as in lead compound **2** – produces the most potent inhibitor of glucosylceramide synthase. However, two β-aza-*C*-glycoside derivatives (**17** and **19**) still considerably inhibited glucosylceramide biosynthesis. Three other compounds (**5**, **6** and **8**) proved to be potent and selective inhibitors of glucocerebrosidase.



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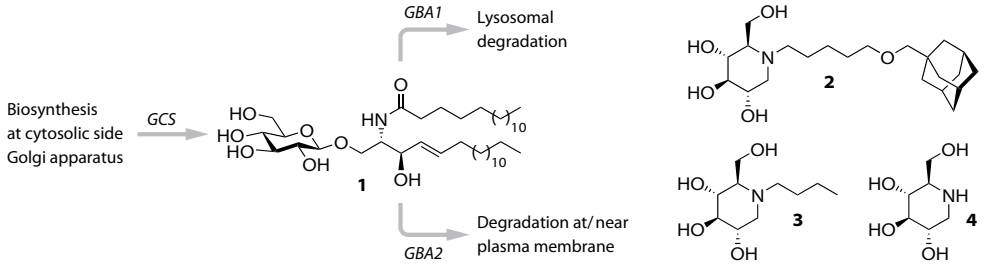
Introduction

Glucosylceramide (**1**) and its additionally glycosylated derivatives are called glycosphingolipids (GSLs). They are components of the outer cellular membrane and are involved in many (patho)physiological processes in humans, such as intercellular recognition, signaling processes (*e.g.* insulin signaling, see Chapter 3)[1] and interactions with pathogens.[2-6] In the metabolism of GSLs, **1** functions as the crucial precursor for the biosynthesis of the majority of the GSLs. The metabolism of **1** itself is summarized in Scheme 1 and involves three enzymes.[7-9] Glucosylceramide synthase (GCS) is responsible for its biosynthesis while glucocerebrosidase (GBA1) carries out its degradation. In a rare recessively inherited disorder – called Gaucher disease – glucosylceramide accumulates inside the lysosomes because of the deficient activity of a mutated GBA1.[10] Furthermore, β-glucosidase 2 (GBA2) has recently been unequivocally identified as being capable of hydrolyzing **1**, although **1** is not its exclusive substrate.[11,12] The biological function of this activity remains unclear.

Scheme 1. The metabolism of glucosylceramide (**1**) (left); Structures of iminosugars **2**, **3** and **4** (right).



In 1998, Aerts *et al.* reported a set of lipophilic GBA2 inhibitors.[13] The most potent of these, **2** (see Scheme 1), proved to be a nanomolar inhibitor of both GBA2, GCS and GBA1. Previously, the work of Platt and Butters had already shown that GCS – to a lesser extent – could be inhibited by **3**.[14] Both these compounds are *N*-alkylated derivatives of the naturally occurring iminosugar – and known glycosidase inhibitor – 1-deoxynojirimycin (**4**).

Selective inhibitors of the enzymes of glucosylceramide metabolism can find an application as tools in the continuing study of the functions of glucosylceramide, complex GSLs and their metabolism.[15,16] Additionally, the crucial role of glucosylceramide synthase (GCS) in glycosphingolipid biosynthesis makes it a interesting drug target for treating diseases in which excessive GSL levels play a role the in the pathology (*e.g.* Gaucher disease and type 2 diabetes, see Chapter 1, section 1.3).[17-20] In 2000, compound **3** received an orphan drug status as a GCS inhibitor for the treatment of Gaucher disease via substrate reduction therapy (see Chapter 1, section 1.3).[21]

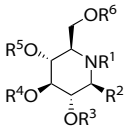
In view of these applications compound **2** is interesting, but also poses a challenge. Besides already inhibiting both GCS, GBA1 and GBA2, **2** also inhibits a number of other

glycosidases not related to the metabolism of **1**. Consequently, more selective inhibitors for each of the targeted three enzymes are needed. In the case of GCS, this search for potent *and* selective inhibitors is hampered by the fact that no structural information of the enzyme and its binding site is available.[22]

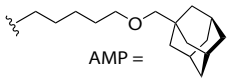
As outlined in Chapter 1, the strategy presented in this thesis for developing inhibitors of glucosylceramide metabolism and a structure–activity–relationship model for GCS inhibition is based on **2** as a lead compound. The structure of **2** can be regarded as possessing a polyhydroxylated iminosugar core to which a hydrophobic group is attached via an aliphatic spacer. The influence on inhibition of the stereochemistry of the iminosugar core and the necessity and nature of the hydrophobic group has been investigated and is described in Chapter 3 – both proved to play an important role.

Table 1. Structures of the lipophilic iminosugar library of Chapter 5.

1-Deoxynojirimycin core:



5-(Adamantan-1-yl-methoxy)-pentyl lipophilic group–spacer moiety:



Compound	R^1	R^2	R^3	R^4	R^5	R^6
2 (lead):	AMP	H	H	H	H	H
5–**7**:	H, Me or Bu	H	H	H	H	AMP
8–**10**:	H, Me or Bu	H	AMP	H	H	H
11–**13**:	H, Me or Bu	H	H	H	AMP	H
14–**16**:	H, Me or Bu	H	H	AMP	H	H
17–**19**:	H, Me or Bu	AMP	H	H	H	H

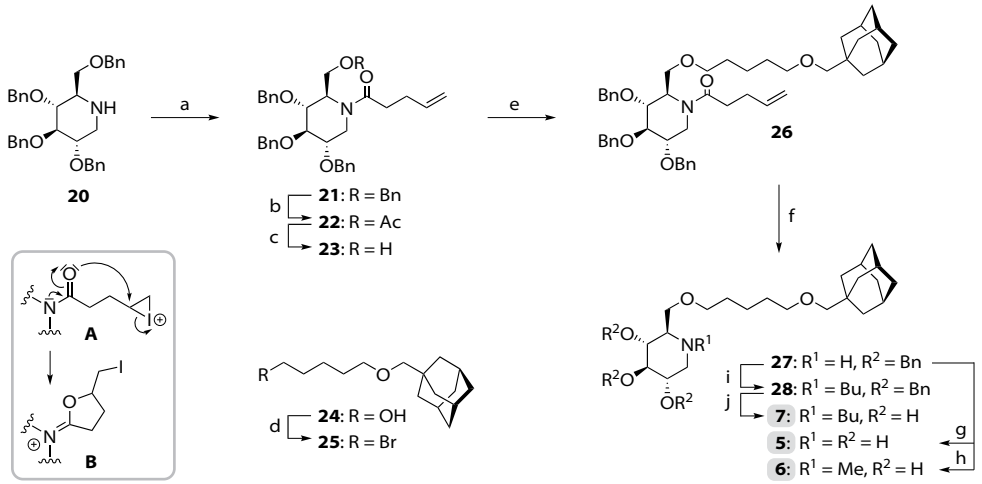
In the research presented in this chapter the attachment site of the hydrophobic moiety on the iminosugar core is varied. The synthesis and biological evaluation of a set of 1-deoxynojirimycin derivatives having the adamantan-1-yl-methoxy-pentyl moiety appended to either the C1 (as a β-aza-*C*-glycoside), O2, O3, O4 or O6 position is reported (see Table 1). Furthermore, in order to assess the influence of the substitution on the endocyclic nitrogen atom, both *N*-methylated and *N*-butylated analogues of each modification were prepared. This library of fifteen lipophilic iminosugars was screened for inhibitory potency against GCS, GBA1 and GBA2. In order to better assess the selectivity of the compounds they were also tested for inhibitory activity against several relevant human glycosidases not related to glucosylceramide metabolism.

Results and Discussion

The general strategy towards the *O*-alkylated iminosugars was to synthesize orthogonally protected 1-deoxynojirimycin derivatives for these four positions via the tandem Swern oxidation/ double reductive amination procedure reported in Chapter 2. Subsequent

selective deprotection followed by alkylation of the free hydroxyl with a suitably activated adamantan-1-yl-methoxy-pentyl moiety would produce the target compounds in protected form. This synthetic strategy would also provide building blocks suitable for straightforward derivitization in the future by alkylation with different lipophilic moieties.

Scheme 2. Synthesis of lipophilic bromide **25** and O6-functionalized iminosugars **5**–**7**.

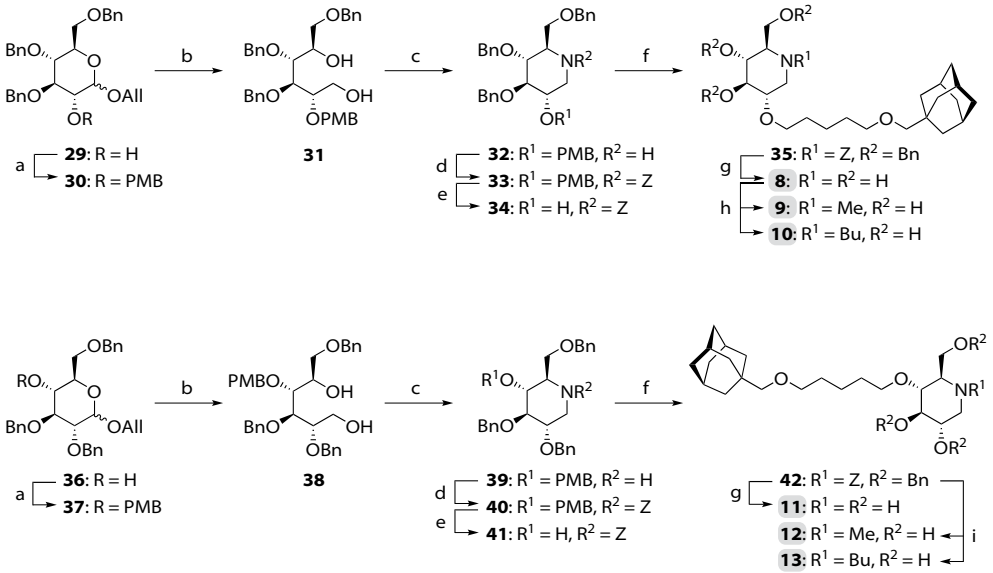


Reagents and conditions: [**a**] 1.5 eq pent-4-enoic anhydride, pyridine, 3h, quantitative. [**b**] $ZnCl_2$, AcOH/Ac_2O (1/2), 20h, 83%. [**c**] cat. NaOMe, MeOH, 90 min, 86%. [**d**] PPh_3, CBr_4, CH_3CN, reflux, 2h, 94%. [**e**] **25**, NaH, DMF, 0 °C to rt, 6h, 92%. [**f**] I_2, THF/H_2O (3/2), 30 min, 81%. [**g**] Pd/C, H_2 atm, EtOH, HCl, 20h, **5**: 75%. [**h**] i: formaldehyde, $NaBH_3CN$, AcOH, ACN, 20h; ii: Pd/C, H_2 atm, EtOH, HCl, 20h, **6**: 83% 2 steps. [**i**] butyraldehyde, $NaBH_3CN$, EtOH/AcOH, 20h, 82%. [**j**] Pd/C, H_2 atm, EtOH, HCl, 20h, **7**: 93%. Bottom left insert: deprotection mechanism of the pent-4-enamide in **26**.

The already optimized synthesis of **20** (see Chapter 2) combined with the possibility of selective deprotection of its primary 6'-benzyl ether made it the starting material of choice for the synthesis of the O6-functionalized iminosugars **5**–**7**. Their synthesis started with protection of the free amine of **20** as a pent-4-enamide to give **21** (see Scheme 2).[23,24] Protection of the amine as a carbamate – *e.g.* Boc or Z – is unfavorable due to their propensity to react intramolecularly upon activation or deprotonation of the 6'-hydroxyl to form a cyclic carbamate/oxazolidinone.[25-31] Next, the primary benzyl ether was selectively cleaved and *in situ* acetylated to **22** by treatment of **21** with zinc chloride in acetic acid/ acetic anhydride.[32] Zemplén deacetylation of **22** thereafter provided **23**. The hydroxyl function of **23** was alkylated by Williamson etherification with bromide **25** to provide protected O6-analogue **26** in 92% yield. Bromide **25** was prepared by subjecting alcohol **24** – from Chapter 2 – to Appel bromination conditions. The pent-4-enoyl group was cleaved by treatment of **26** with excess molecular iodine in THF/water to provide free amine **27**. Deprotection of the pent-4-enoyl group occurs via a cascade of ionic intermediates (see Scheme 2). First the molecular iodine coordinates with the π-bond of

26 and forms iodonium ion **A**. This cyclizes to oxoiminium species **B** and is subsequently hydrolized to the free amine.[23] Deprotection of **27** by Pd-catalyzed hydrogenolysis furnished O6-analogue **5**. Subjecting **27** to formaldehyde and sodium cyanoborohydride treatment followed by hydrogenolysis of the crude intermediate gave *N*-methylated O6-analogue **6**. Reductive amination of **27** with butyraldehyde in the presence of sodium cyanoborohydride and subsequent catalytic hydrogenation of product **28** provided the *N*-butylated O6-analogue **7**.

Scheme 3. Synthesis of O2-functionalized **8**–**10** and O4-functionalized iminosugars **11**–**13**.



Reagents and conditions: [**a**] PMBCl, NaH, DMF, 4h, **30**: 83%; **37**: 90%. [**b**] from **30**: i: $RhCl(PPh_3)_3$, DABCO, EtOH/H_2O, refluxing, 2 days; ii: I_2, THF/H_2O, 6h; iii: $LiAlH_4$, THF, 20h, **31**: 79% 2 steps; from **37**: i: 0.5 eq. KO*t*Bu, DMSO, 100 °C, 30 min; ii: I_2, THF/H_2O, 6h; iii: $LiAlH_4$, THF, 20h, **38**: 82% 2 steps. [**c**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: Et_3N, –75 °C to rt, 1h; iii: $NaBH_3CN$, $HCOONH_4$, 3Å mol. sieves, MeOH, 0 °C to rt, 20h, **32**: 68%; **39**: 48%. [**d**] BnOC(O)Cl, dioxane, aq $NaHCO_3$, 20h, **33**: 99%; **40**: quantitative. [**e**] 2% TFA, DCM, 60 min, **34**: 90%; **41**: 98%. [**f**] **25**, NaH, DMF, 0 °C to rt, 4h, **35**: 91%; **42**: 91%. [**g**] Pd/C, H_2 atm, EtOH, HCl, 20h, **8**: 72%; **11**: 83%. [**h**] Pd/C, H_2 atm, formaldehyde or butyraldehyde, EtOH, HCl, 20h, **9**: quantitative; **10**: 90%. [**i**] i: Pd/C (Degussa-type), H_2 atm, EtOH, 90 min; ii: formaldehyde or butyraldehyde, 90 min; iii: Pd/C, H_2 atm, EtOH, HCl, 20h, **12**: 94%; **13**: 83%.

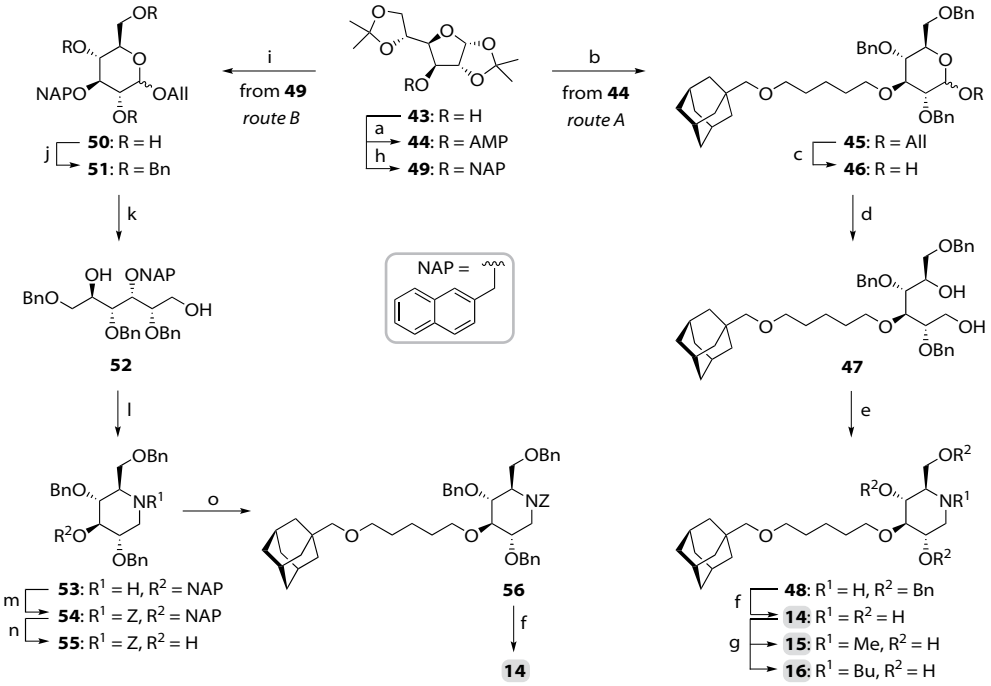
Construction of the O2- and O4-functionalized iminosugars was accomplished following a similar synthetic strategy that entailed the synthesis of O2/O4-orthogonally protected D-glucitol derivates. First the free hydroxyl function of known benzylated allyl glucopyranosides **29**[33]and **36**[34] was protected as a *p*-methoxybenzyl ether (Scheme 3). Next, deallylation of the anomeric position was achieved by isomerization with Wilkinson's catalyst for O2-PMB **30** and KO*t*Bu/DMSO for O4-PMB **37**. For both compounds the generated vinyl-ether was hydrolyzed using molecular iodine in THF/H_2O. The resulting hemiacetal products were not isolated but immediately subjected to $LiAlH_4$ mediated reduction to provide the O2-PMB (**31**) and O4-PMB (**38**) D-glucitol

derivatives. Sequential Swern oxidation and double reductive amination produced orthogonally PMB-protected 1-deoxynojirimycins **32** and **39**. Protection of the amine as a Z-carbamate (**33** and **40**) and subsequent deprotection of the PMB-ethers with 2% TFA provided free 2'-OH **34** and 4'-OH **41**. The liberated hydroxyl functions were alkylated by Williamson etherification with bromide **25** to afford the protected O2-analogue **35** and O4-analogue **42**. Deprotection of the benzyl ethers provided **8** and **11**. *N*-methylated (**9**) and *N*-butylated (**10**) O2-analogues were obtained by Pd-catalyzed hydrogenolysis of **8** in the presence of aqueous HCl and either formaldehyde or butyraldehyde. The *N*-methylated (**12**) and *N*-butylated (**13**) O4-functionalized iminosugars were prepared by a one-pot Z-deprotection and *N*-alkylation with formaldehyde or butyraldehyde, followed by deprotection to yield **12** in **13**.

The synthetic route for the O3-functionalized iminosugars **14–16** started with diacetoneglucose **43** (see Scheme 4). Introduction of the adamantane-spacer moiety at the beginning of the route by alkylation of **43** with bromide **25** provided **44**. Consecutive isopropylidene hydrolysis/Fisher glycosidation with allyl alcohol and benzylation of **44** produced **45**. Isomerization and cleavage of the allyl group in **45** was followed by $LiAlH_4$ mediated reduction of the crude hemiacetal (**46**) to produce **47**. Swern oxidation of **47** produced the hexosulose that was subjected to reductive amination conditions to produce the iminosugar **48**. Hydrogenolysis of **48** with Pd/C and H_2 produced O3-analogue **14**. Reductive amination of **48** with either formaldehyde or butyraldehyde, followed by benzyl ether hydrogenolysis produced *N*-methylated **15** and *N*-butylated O3-analogue **16**.

An O3-orthogonally protected 1-deoxynojirimycin has however not been reported yet and would provide a valuable building block for future research. Initial attempts to produce an O3-orthogonally protected glucitol derivative from **43** were hampered by partial cleavage of most established protecting groups during the initial isopropylidene hydrolysis/Fisher glycosidation steps. The O3 PMB-, TBDPS-, MOM-ethers and pivaloyl ester all proved to be to labile under these conditions. To this end the relatively new 2'-naphthylmethylether protecting group was evaluated. It can be cleaved under similar oxidative conditions as the PMB group, but it is more acid stabile.[35-37] Consequently, **43** was protected by alkylation with commercially available 2'-naphthylmethylbromide to produce **49**[35] (see Scheme 4). In a one-pot procedure under the agency of Amberlite H^+ resin the isopropylidene acetals of **49** could be successfully hydrolyzed with concomitant Fischer glycosidation with allyl alcohol to provide **50** in 50% yield. Consecutive benzylation of **50**, cleavage of the anomeric allyl ether, reduction to **52** and transformation into the iminosugar provided **53**. Protection of endocyclic amine as a Z-carbamate (**54**) made it possible to selectively cleave the O3-NAP ether with DDQ to give **55** in 85% yield.[37] The free OH-3 function in **55** could be alkylated with **25** to give **56**. Penultimate **56** can be exploited via the same procedures as described for the synthesis of the O2- and O4-functionalized iminosugars to give **14–16**, albeit via a lengthier route when starting from **43**.

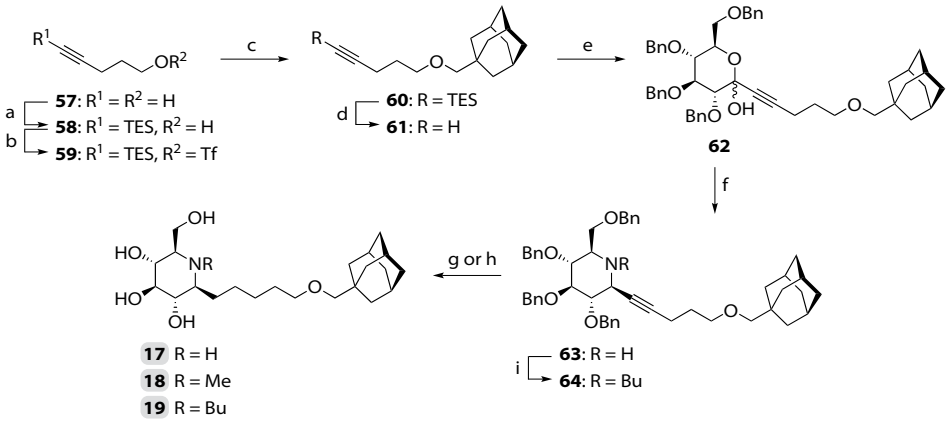
Scheme 4. Synthesis of O3-functionalized iminosugars **14**–**16** via route A and B.



Reagents and conditions: [**a**] **25**, NaH, DMF, 0 °C to rt, 4h, 98%. [**b**] i: AcOH/H_2O, 100 °C, 5h; ii: AllOH, 5 mol% AcCl, reflux, 24h; iii: BnBr, NaH, DMF, 0 °C to rt, 20h, 56% 3 steps. [**c**] i: 0.5 eq. KO*t*Bu, DMSO, 100 °C, 35 min; ii: I_2, THF/H_2O, 6h, 75%. [**d**] $LiAlH_4$, THF, 20h, quantitative. [**e**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: Et_3N, –75 °C to –10 °C, 3h; iii: $NaBH_3CN$, $HCOONH_4$, Na_2SO_4, MeOH, 0 °C to rt, 20h, 67% 2 steps. [**f**] Pd/C, H_2 atm, EtOH, HCl, 20h, from **48**: 86%; **56**: quantitative. [**g**] i: Pd/C (Degussa-type), H_2 atm, 10 eq formaldehyde or butyraldehyde, EtOH, 1h; ii: Pd/C, H_2 atm, EtOH, HCl, 20h, **15**: 83%; **16**: 99%. [**h**] NAP–Br, NaH, DMF, 0 °C to rt, 20h, 98%. [**i**] AllOH, H_2O, Amberlite H^+, 102 °C, 20h, 50%, [**j**] BnBr, NaH, DMF, 0 °C to rt, 20h, 90%. [**k**] i: 0.5 eq. KO*t*Bu, DMSO, 100 °C, 35 min; ii: I_2, THF/H_2O, 20h; iii: $LiAlH_4$, THF, 20h, 68% 2 steps. [**l**] i: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; ii: Et_3N, –75 °C to –10 °C, 3h; iii: $NaBH_3CN$, NH_4HCO_2, Na_2SO_4, MeOH, 0 °C to rt, 20h, 53% 2 steps. [**m**] BnOC(O)Cl, dioxane, aq. $NaHCO_3$, 20h, 81%. [**n**] DDQ, DCM/MeOH (4/1), 5h, 85%. [**o**] **25**, NaH, DMF, 0 °C to rt, 4h, quantitative.

For the preparation of the C1-functionalized iminosugars **17**–**19** established β-aza-*C*-glycoside chemistry could be used. For a concise overview of this class of compounds and their chemistry see Chapter 6. The synthesis of β-aza-*C*-glucosides **17**–**19** commenced with the preparation of alkyne **61** (see Scheme 5 on the next page). Formation of the dianion of pent-4-yn-1-ol **57** with butyllithium followed by successive treatment with triethylsilylchloride and 2M HCl produced **58**. Alkynol **58** was treated with triflic anhydride and triethylamine in DCM to provide triflate **59**. Reaction of the triflate with adamantanemethanol under the agency of potassium carbonate in DCM afforded compound **60**.[38] Installation of various other sulfonate leaving groups on either **58** or adamantanemethanol and alkylations with these under various conditions failed to reproducibly provide **60**. Next, removal of the silyl protective group was accomplished by treatment of **60** with excess NaOMe in MeOH at 90 °C to give alkyne **61**.

Scheme 5. Synthesis of C1-functionalized iminosugars **17**–**18**.



Reagents and conditions: [**a**] i: BuLi, THF, –68 °C, 1h; ii: TESCl, –68 °C to rt, 20h; iii: 2M HCl, 48h, 83%. [**b**] Tf_2O, Et_3N, DCM, –40 °C, 1h. [**c**] adamantanemethanol, K_2CO_3, DCM, reflux, 3 days, 88%. [**d**] 4 eq. NaOMe, THF/MeOH (1/1), 90 °C, 20h, 99%. [**e**] i: BuLi, THF, –50 °C, 1h; ii: 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[39], –50 °C, 2h, 77%. [**f**] i: $NaBH_4$, MeOH/DCM (5/1), 2h; ii: DMSO, $(COCl)_2$, DCM, –75 °C, 2h; iii: Et_3N, –75 °C to rt, 0.5; iv: $NaBH_3CN$, $HCOONH_4$, 3Å mol. sieves, MeOH/DCM (5/1), 0 °C to rt, 20h, 56% 3 steps. [**g**] Pd/C, H_2 atm, EtOH, HCl, 20h, 85% from **63** to **17**; 91% from **64** to **19**. [**h**] i: Pd/C (Degussa-type), H_2 atm, formaldehyde, *n*-propanol, 1h; ii: Pd/C, H_2 atm, EtOH, HCl, 20h, 94% two steps from **63** to **18**. [**i**] Butyraldehyde, $NaBH_3CN$, EtOH/AcOH (3/1), 20h, 80%.

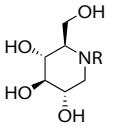
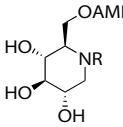
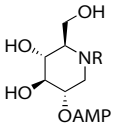
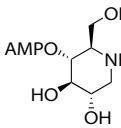
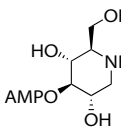
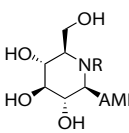
Conversion of **61** into the acetylenic anion with butyllithium in THF at –60 °C was followed by addition of excess 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[39] to produce ketose **62** as an α/β mixture. Reduction of **62** with sodium borohydride in MeOH/DCM was followed by Swern oxidation to give a diketone. The crude diketone was subjected to excess ammonium formate and sodium cyanoborohydride in MeOH/DCM at 0 °C to produce β-aza-*C*-analogue **63** as a single stereoisomer[40,41] in 58% yield over the three steps. Deprotection of the benzyl ethers and reduction of the triple bond under Pd/C catalyzed hydrogenolysis conditions provided C1-analogue **17**. Reductive amination of formaldehyde with the endocyclic amine in **63** with Pd/C (Degussa-type) and subsequent hydrogenolysis after addition of HCl to the reaction mixture yielded *N*-methylated **18** in 94% over the two steps. Sodium cyanoborohydride mediated reductive amination of **63** with butyraldehyde yielded **64**, which was deprotected to produce *N*-butylated **19**.

Biological evaluation

The inhibitory potency and selectivity of the synthesized iminosugars **5**–**19** were assessed by testing the compounds in assays for the three enzymes involved in glucosylceramide metabolism, namely, glucosylceramide synthase (GCS), glucocerebrosidase (GBA1) and β-glucosidase 2 (GBA2) (see Table 2). To further establish the inhibitory profile of iminosugars **5**–**19**, they were also tested for inhibition of the lysosomal α-glucosidase, debranching enzyme, sucrase, lactase and maltase. The lysosomal α-glucosidase was tested as it is known to be strongly inhibited by **3** as well as the lead compound

2 and plays a critical role in lysosomal glycogen degradation during cellular turnover. Debranching enzyme is involved in cytosolic glycogen degradation and it possesses both an α-1,4-transferase and α-1,6-glucosidase catalytic site for its substrate. The intestinal glucosidases are located in the outer membrane of epithelial cells lining the small intestine. The enzymes sucrase, lactase and maltase are responsible for degrading the glucose containing disaccharides (sucrose, lactose and maltose) derived from food and as a side-effect are also inhibited in Gaucher patients receiving substrate deprivation therapy with **3**.[42,43]

Table 2. Enzyme inhibition assay results: apparent IC_{50} values in μM for compounds **2**–**19**.[a,b]

Compound		GCS *in vivo*	GBA1	GBA2	Lysosomal α-gluco-sidase	Sucrase	Lactase	Maltase	De-branching enzyme
	**4**: R = H	> 100	250	21	1.5	2	62	2	10
	3: R = Bu	50	400	0.230	0.1	0.5	> 100	9	10
	2: R = AMP	0.2	0.2	0.001	0.4	4.5	> 100	19	10
	**5**: R = H	> 100	0.5	10	120	25	> 100	> 100	> 100
	6: R = Me	> 100	0.3	250	> 2000	> 100	> 100	> 100	> 100
	7: R = Bu	> 100	2	40	630	39	> 100	> 100	> 100
	**8**: R = H	> 100	0.3	60	~50	57	> 100	> 100	> 100
	9: R = Me	> 100	6	> 100	27	63	> 100	> 100	> 100
	10: R = Bu	> 100	6	5	156	> 100	> 100	> 100	> 100
	**11**: R = H	> 100	25	55	190	50	> 100	> 100	> 100
	12: R = Me	> 100	18	20	1000	50	> 100	> 100	> 100
	13: R = Bu	> 100	250	100	1500	25	> 100	> 100	> 100
	**14**: R = H	> 100	11	60	18	17	> 100	50	> 100
	15: R = Me	> 100	50	50	120	30	> 100	> 100	> 100
	16: R = Bu	> 100	100	40	150	35	> 100	> 100	> 100
	**17**: R = H	9	3	0.04	6.25	> 100	> 100	> 100	> 100
	18: R = Me	> 100	25	1.4	48	> 100	> 100	> 100	> 100
	19: R = Bu	25	40	10	255	> 100	> 100	> 100	> 100

[a]AMP = 5-(adamantan-1-yl-methoxy)-pentyl; [b]Except for GCS all other enzyme assays are *in vitro*.

The apparent IC_{50} values of the newly synthesized iminosugars **5**–**19** for the various enzymes were compared to the values obtained for **2**, **3** and 1-deoxynojirimycin (**4**). When compared to **2**, O6-analogue **5** shows strongly decreased inhibition of GCS and

GBA2, but remains a potent inhibitor of GBA1. The five other human glucose processing enzymes are also inhibited less strongly by this analogue. Its *N*-methylated derivative **6** is even more selective towards GBA1 (IC_{50}: 0.3 μM) as opposed to its *N*-butylated counterpart **7**. O2-analogue **8** has an inhibition profile similar to O6-analogue **5**. Again, both *N*-methylated (**9**) and *N*-butylated (**10**) O2-functionalized iminosugars show a general reduction in inhibitory capacity for all measured enzymes. The inhibitory potency for GCS of both O4-functionalized iminosugars (**11**–**13**) and O3-functionalized iminosugars (**14**–**16**) is very low and a general decrease in inhibition for all the measured enzymes for these compounds is observed. The β-aza-*C*-glycosides **17**–**19** also did not improve upon the potency of GCS inhibition compared to lead compound **2**.

However, compound **17** still shows strong inhibition of GCS, with an *in vivo* IC_{50} of 9 μM. However, it lacks improvement in selectivity for this enzyme when compared to **2**. *N*-methylated analogue **18** showed strongly decreased inhibition of GCS and all other enzymes. Although *N*-butyl analogue **19** also showed decreased inhibition of all tested enzymes, it did show a marked improvement of inhibition of GCS when compared to **18**. Analogue **17** has a fifty times lower potency for GCS inhibition compared to lead compound **2**, but is still a more potent and selective inhibitor than **3**. In a recent paper by Boucheron *et al.*, derivatives of **3** were synthesized bearing one or two additional alkyl chains on the C1, O2 or O4 positions.[44] The outcome of this study corroborates our results in that lipophilic entities are best attached to the endocyclic nitrogen atom.

Conclusion

In this chapter a collection of adamantan-1-yl-methoxy functionalized 1-deoxynojirimycin derivatives is presented in which the attachment site of the hydrophobic moiety is altered compared to lead compound **2**. Determination of their IC_{50} values for the three enzymes involved in glucosylceramide metabolism and comparison with **2** demonstrated that relocating the hydrophobic moiety from the endocyclic nitrogen atom to other positions on the 1-deoxynojirimycin ring system does not lead to a more potent or selective inhibitor of GCS. However, the most potent iminosugar derivative in the presented series, β-aza-*C*-glycoside **17**, still inhibits GCS in the low μM range and shows decreased inhibition of intestinal glucosidases. When combined with the marked improvement of GCS inhibition when lengthening the *N*-alkyl moiety from methyl (**18**) to butyl (**19**), the aza-*C*-glycoside derivatives of **2** may hold potential for development of improved inhibitors of GCS. In chapter 6, the potential and structure–activity relationship of this class of compounds is further explored via the synthesis and evaluation of a diverse library of aza-*C*-glycoside derivatives based on **2**.

Iminosugars **5**, **6** and **8**, although being poor inhibitors of GCS, did show potent and selective inhibition of GBA1. As such, these compounds may find application as potential pharmacological chaperones of the Gaucher disease associated deficient GBA1 (see section 1.3.4 in Chapter 1).[45]

Experimental section

General methods and materials: Reactions were executed at ambient temperature unless stated otherwise. All moisture sensitive reactions were performed under an argon atmosphere and residual water was removed from the starting material by coevaporation with dioxane, toluene or dichloroethane. All solvents were removed by evaporation under reduced pressure. All chemicals and solvents, unless indicated, were acquired from commercial sources and used as received. THF was distilled prior to use from $LiAlH_4$. EtOH was freed of acetaldehyde contamination by distillation from zinc/KOH. DCM was distilled prior to use from P_2O_5. Reaction grade acetonitrile, dimethylsulfoxide, isopropanol and methanol were stored on 3Å molecular sieves. Other reaction grade solvents were stored on 4Å molecular sieves. Reactions were monitored by TLC analysis using silica gel coated aluminum plates (Schleichter & Schuell, F1500, LS254) and technical grade solvents. Compound were detected during TLC analysis by UV absorption (254 nm) where applicable and/ or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\times4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\times2H_2O$ (10 g/L) in 10% sulfuric acid followed by charring at ~150 °C. Visualization of olefins was achieved by spraying with a solution of $KMnO_4$ (5 g/ L) and K_2CO_3 (25 g/ L) in water. Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ~150 °C. Visualization of deprotected iminosugar compounds during TLC analysis was accomplished by exposure to molecular iodine vapor. Column chromatography was performed on silica gel (particle size: 40–63 µm) for all compounds. The ^{1}H- and ^{13}C-NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C HSQC experiments were recorded on a 200/50 MHz, 300/75 MHz, 400/100 MHz, 500/125 MHz or 600/150 MHz spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard for all ^{1}H NMR measurements in $CDCl_3$ and the deuterated solvent signal for all other NMR measurements. Coupling constants (*J*) are given in Hz. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. All presented ^{13}C NMR spectra are proton decoupled ^{13}C-APT measurements. IR spectra were recorded on an apparatus fitted with a single bounce diamond crystal ATR-element and are reported in cm^{-1}. Optical rotations were measured on an automatic polarimeter (Sodium D-line, λ = 589 nm). Mass spectra were recorded an electronspray interface apparatus. High resolution mass spectra were recorded on a mass spectrometer equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 %, capillary temperature 275 °C) with resolution R = 100000 at *m/z* 400. The high resolution mass spectrometer was calibrated prior to measurements with a calibration solution (caffeine, MRFA, Ultramark 1621). Of High resolution mass spectra were recorded by direct injection (2 µL of a 2 µM solution in H_2O/CH_3CN; 50/50; v/v and 0.1% formic acid) on a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at *m/z* 400 (mass range *m/z* = 150–2000) and dioctylpthalate (*m/z* = 391.28428) as a "lock mass".[46] The high resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

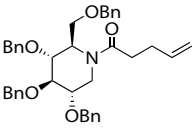
Enzyme Assays: IC_{50} values of compounds for the various enzyme activities were determined by exposing cells or enzyme preparations to an appropriate range of iminosugar concentrations. All iminosugars were tested as their HCl-salt from DMSO stock solutions. IC_{50} values for glucosylceramide synthase were measured using living cells with C_6-NBD-ceramide as substrate.[13] Glucocerebrosidase activity was measured using recombinant enzyme and 4-methylumbelliferyl-beta-glucose as substrate.[13] GBA2 was measured using enzyme-containing membrane preparations from Gaucher spleen and 4-methylumbelliferyl-beta-glucose as substrate.[13] Lysosomal α-glucosidase was measured using purified enzyme from human urine and 4-methylumbelliferyl-alpha-glucoside as substrate.[13] Lactase, maltase and sucrase activities were determined with homogenates of freshly isolated rat intestine by measuring liberated glucose from the corresponding disaccharides.[43] The activity of debranching enzyme (α-1,6-glucosidase activity) was measured by determining liberated glucose from dextrin with an erythrocyte preparation as enzyme source.[47]

General procedure A – $LiAlH_4$ mediated reduction of hemiacetal intermediates.
$LiAlH_4$ (3.5 eq) was added in portions to a cooled (0 °C) and dry solution of the hemiacetal intermediate in THF (0.15 M). The reaction mixture was stirred for 20 h, allowing it to warm to rt. The excess $LiAlH_4$ was quenched with water at 0 °C. The mixture was diluted with EtOAc and washed with sat aq NH_4Cl (3×). The organic phase was dried ($MgSO_4$) and concentrated.

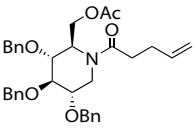
General procedure B – Swern oxidation and double reductive amination:
Swern oxidation: A solution of oxalylchloride (4 eq) in DCM (1 M) was cooled to –78 °C. After dropwise addition of a solution of DMSO (5 eq) in DCM (2 M) over 10 min, the reaction mixture was stirred for 40 min while being kept below –70 °C. Next, a dry solution of the glucitol intermediate in DCM (0.5M) was added dropwise to the reaction mixture over a 15 min period, while keeping the reaction mixture below –70 °C. After stirring the reaction mixture for 2 h below –65 °C, Et_3N (12 eq) was added dropwise over a 10 min period, while keeping the reaction mixture below –65 °C. After addition, the reaction mixture was allowed to warm to –5 °C over 2 h.
Double reductive amination method A: $NaBH_3CN$ (4 eq) and Na_2SO_4 (4 eq) were added to a solution of NH_4HCO_2 (20 eq) in MeOH (0.02M relative to starting compound). The methanolic mixture was cooled to 0 °C, after which the crude Swern oxidation reaction mixture (still at 0 °C) was added under vigorous stirring. The combined mixture was kept at 0 °C for 1 h, after which cooling was ceased and the reaction mixture was stirred for 20 h at rt. The pH of the reaction mixture was adjusted to ~10 by addition of a 1M aq. NaOH solution and the mixture was poured into water (3-fold volume to reaction MeOH). The aqueous phase was extracted repeatedly with DCM (3×), after which the combined organic layers were dried ($MgSO_4$) and concentrated.
Double reductive amination method B: The Swern reaction mixture was concentrated at a moderate temperature (~30 °C) with simultaneous coevaporation of toluene (3×). The residue was dissolved in MeOH (0.05 M relative to starting compound) and NH_4HCO_2 (20 eq) was added. The mixture was cooled to 0 °C and stirred until all NH_4HCO_2 had dissolved. Activated 3Å molsieves (10 g/mmol) were added and reaction mixture was stirred for 15 min, after which $NaBH_3CN$ (4 eq) was added. The reaction mixture was kept at 0 °C for one h after which the cooling source was removed and the reaction was stirred for an additional 20 h. After removal of the molsieves over a glass microfibre filter, the filtrate was concentrated, dissolved in EtOAc and washed with sat aq $NaHCO_3$. The aqueous phase was back-extracted with EtOAc (3×) and the combined organic layers were dried ($MgSO_4$) and concentrated.

*General procedure C – Alkylation with bromide **25***: A combined dry solution of the starting compound and bromide **25** (1.5 eq) in DMF (0.5 M) was cooled to 0 °C. NaH (1.5 eq, 60% wt in mineral oil) was added and the reaction was stirred for 3 h, allowing it to warm to rt. If TLC analysis indicated incomplete conversion, the reaction mixture was cooled to 0 °C and a solution of additional bromide **25** (0.5 eq) in a small amount of DMF and NaH (1 eq, 60% wt in mineral oil) were added. The reaction mixture was stirred for another 3 h at rt, after which it was quenched by addition of water. The mixture was poured into water and extracted repeatedly with Et_2O (3×), after which the combined organic layers were dried ($MgSO_4$) and concentrated.

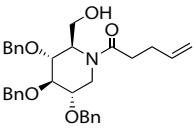
General procedure D – Pd/C catalyzed hydrogenolysis: A solution of compound (~50–250 µmol) in 'acetaldehyde free' EtOH (4 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 min, after which a catalytic amount of Pd/C (50 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 min and the reaction was stirred for 20 h under atmospheric hydrogen pressure. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing of the filter cake with MeOH. The filtrate was concentrated with coevaporation of toluene.



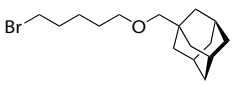
2,3,4,6-Tetra-*O*-benzyl-*N*-pent-4′-enoyl-1-deoxynojirimycin (21)#. A dry solution of **20** (1.05 g, 2.0 mmol) in pyridine was charged with pent-4-enoic anhydride (548 µL, 3.0 mmol) and stirred for 3 h. The reaction mixture was concentrated and coevaporated with toluene. The residue was dissolved in EtOAc (50 mL) and washed with sat aq $NaHCO_3$ (100 mL) and sat aq NaCl (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to quantitatively provide **21** (1.212 mg, 2.0 mmol) as a colorless oil. R_F = 0.71 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, T = 320 K, COSY) δ 7.30 – 7.15 (m, 20H, H_{Ar} Bn), 5.79 (m, 1H CH vinyl), 5.05 – 4.89 (m, 2H, CH_2 vinyl), 4.70 – 4.33 (m, 9H, 4×CH Bn, CH), 3.38 – 2.47 (m, 6H), 2.45 – 2.36 (m, 5H, 2×CH_2 pen-4′-enoyl, CH). ^{13}C NMR (75 MHz, $CDCl_3$, T = 320 K) δ 160.9, (C=O), 138.1 (4×C_q Bn), 137.5 (CH vinyl), 128.1, 127.7, 127.6, 127.5, 127.4, 127.1 (CH_{Ar} Bn), 114.7 (CH_2 vinyl), 74.5 (CH), 73.0, 68.4, 32.1, 29.0 (4×CH_2 Bn, 2×CH_2 pent-4-enoyl, C-1, C-6). IR ν_{max}(thin film)/ cm^{-1}: 3395, 2870, 2106, 1720, 1620, 1450, 1366, 1265, 1211, 1065, 910, 741, 694, 633. [α]$^{20}_D$: 4.6 (*c* 3.9, $CHCl_3$). HRMS: found *m/z* 606.3250 [M+H]$^+$, calcd for [$C_{39}H_{43}NO_5$+H]$^+$ 606.3214. #: NMR characterization suffered from collapsed/multiple signals and severe peak broadening due to rotamers of the *N*-pent-4-enoyl amide.



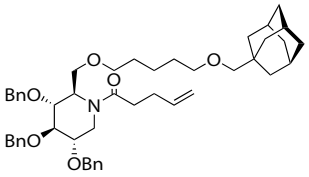
6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-*N*-pent-4′-enoyl-1-deoxynojirimycin (22)#. A dry solution of **21** (1.090 g, 1.80 mmol) in a mixture of AcOH (6 mL) and Ac_2O (12 mL) was charged with anhydrous $ZnCl_2$ (2.46 g, 18.0 mmol) and stirred for 20 h. The reaction was quenched (water, 5 mL) and stirred for 30 min. The reaction mixture was poured into sat aq Na_2CO_3 (100 mL) and extracted with DCM (3×50 mL). The combined organic layers were washed with sat aq NaCl (100 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to afford **22** (832 mg, 1.49 mmol) in 83% yield as a colorless oil. R_F = 0.62 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.35 – 7.17 (m, 15H, H_{Ar} Bn), 5.76 (m, 1H, CH vinyl), 4.99 (d, *J* = 17.4, 1H, C*H*H vinyl), 4.93 (d, *J* = 10.4, 1H, CH*H* vinyl), 4.85 – 4.45 (m, 8H, 3×CH_2 Bn, 2×CH), 4.35 – 4.05 (m, 2H), 3.73 – 3.65 (m, 3H), 3.48 (m, 1H), 2.50 – 2.37 (m, 4H, 2×CH_2 pen-4′-enoyl), 1.95 (s, 3H, CH_3 Ac). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.9 (2×C=O; Ac, pent-4′-enoyl), 137.7, 137.3 (3×C_q Bn), 137.1 (CH vinyl), 128.0, 127.9, 127.6, 127.2 (CH_{Ar} Bn), 114.5 (CH_2 vinyl), 79.0, 76.9, 74.7, 55.7, 51.5 (C-2, C-3, C-4, C-5), 72.5, 72.0, 71.3, 70.7, 70.0, 61.5, 42.7, 34.9, 32.7, 31.8, 31.3, 28.6 (3×CH_2 Bn, 2×CH_2 pent-4-enoyl, C-1, C-6), 20.3 (CH_3 Ac). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1720, 1643, 1450, 1366, 1312, 1265, 1211, 1096, 1072, 910, 741, 702, 617. [α]$^{20}_D$: 2.3 (*c* 6.8, $CHCl_3$). HRMS: found *m/z* 558.2882 [M+H]$^+$, calcd for [$C_{34}H_{39}NO_6$+H]$^+$ 558.2850. #: NMR characterization suffered from collapsed/multiple signals and severe peak broadening due to rotamers of the *N*-pent-4-enoyl amide.



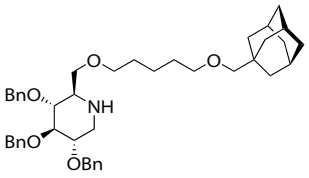
2,3,4-Tri-*O*-benzyl-*N*-pent-4′-enoyl-1-deoxynojirimycin (23)#. NaOMe (20 mg, 0.37 mmol) was added to a dry solution of **22** (810 mg, 1.45 mmol) in MeOH (14.5 mL). The reaction was stirred for 90 min and was subsequently quenched by addition of Amberlite resin (H^+-form) until neutral pH was achieved. The resin was removed by filtration and the filtrate was concentrated. The residue was purified by silica gel column chromatography (33% » 66% EtOAc in PE) to afford **23** (644 mg, 1.25 mmol) in 86% yield as a colorless oil. R_F = 0.15 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 15H, H_{Ar} Bn), 5.76 (m, 1H, CH vinyl), 5.01 – 4.92 (m, 2H, CH_2 vinyl), 4.75 – 4.39 (m, 7H, 3×CH_2 Bn, CH), 3.95 – 3.44 (m, 7H), 2.60 – 2.34 (m, 4H, 2×CH_2 pen-4′-enoyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (C=O), 137.9, 137.8 (3×C_q Bn), 137.2 (CH vinyl), 128.2, 128.1, 127.5, 127.4 (CH_{Ar} Bn), 114.8 (CH_2 vinyl), 75.0 (CH), 72.9 (CH_2), 72.9 (CH_2), 61.4 (CH_2), 32.4 (CH_2), 28.9 (CH_2). IR ν_{max}(thin film)/ cm^{-1}: 3395, 2870, 2106, 1720, 1620, 1450, 1366, 1265, 1211, 1065, 910, 741, 694, 633. [α]$^{20}_D$: –12.5 (*c* 12.6, $CHCl_3$). HRMS: found *m/z* 516.2780 [M+H]$^+$, calcd for [$C_{32}H_{37}NO_5$+H]$^+$ 516.2745. #: NMR characterization suffered from collapsed/multiple signals and severe peak broadening due to rotamers of the *N*-pent-4-enoyl amide.



5-(Adamantan-1-yl-methoxy)-1-bromo-pentane (25). A dry solution of **24** (1.651 g, 6.58 mmol; synthesis described in chapter 2) in acetonitrile (150 mL) was charged with CBr_4 (4.378 g, 13.2 mmol). The solution was heated to reflux at which point a dry solution of PPh_3 (5.194 g, 19.8 mmol) in acetonitrile (50 mL) was added dropwise over 15 min. After addition the reaction mixture was refluxed for 2 h. Next, the solution was concentrated and toluene (100 mL) and sat aq $NaHCO_3$ (100 mL) were added to the residue. The resulting two phase system was vigorously stirred and small portions of molecular iodine were added until the toluene phase obtained a permanent brown color. The mixture was washed with 1M aq $Na_2S_2O_3$ (2×200 mL) after which the organic phase was dried ($MgSO_4$) and concentrated. The residue was dissolved in acetone (5 mL) followed by addition of PE (100 mL). The solids were removed by filtration, washed with PE (2×50 mL) and the combined filtrates were concentrated. The residue was purified by silica gel column chromatography (0% » 10% EtOAc in PE) to provide **25** (1.951 g, 6.21 mmol) in 94% yield as a colorless oil. R_F = 0.89 (1:4; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.44 – 3.36 (m, 4H, CH_2-1, CH_2-5 pentyl), 2.95 (s, 2H, OCH_2-Ada), 1.95 (br s, 3H, 3×CH Ada), 1.89 (m, 2H, CH_2-2 pentyl), 1.74 – 1.62 (m, 6H, 3×CH_2 Ada), 1.61 – 1.48 (m, 10H, 3×CH_2 Ada, CH_2-3, CH_2-4 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 81.9 (OCH_2-Ada), 71.1 (CH_2-5 pentyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 33.8 (C_q Ada), 33.4 (CH_2-1 pentyl), 32.4, 28.5 (CH_2-2, CH_2-4 pentyl), 28.0 (3×CH Ada), 24.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1450, 1358, 1250, 1188, 1157, 1111, 1049, 1011, 910, 810, 733, 640. HRMS: found *m/z* 315.1571 $[M+H]^+$, calcd for $[C_{16}H_{27}OBr+H]^+$ 315.1318.

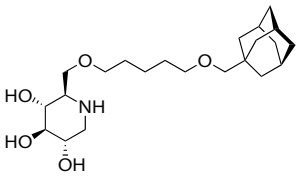


2,3,4-Tri-*O*-benzyl-*N*-pent-4'-enoyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (26)#. General procedure C was applied on compound **23** (322 mg, 0.63 mmol). The resulting residue was purified by silica gel column chromatography (15% » 30% EtOAc in PE) to provide **26** (431 mg, 0.58 mmol) in 92% yield as a colorless oil. R_F = 0.35 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.30 – 7.25 (m, 15H, H_{Ar} Bn), 5.81 (m, 1H CH vinyl), 5.00 (d, *J* = 17.2, 1H, C*H*H vinyl), 4.94 (d, *J* = 10.1, 1H, CH*H* vinyl), 4.80 – 4.40 (m, 7H, 3×CH Bn, CH), 4.07 – 3.94 (m, 1H), 3.70 – 3.45 (m, 6H), 3.36 – 3.30 (m, 4H, 2×OCH_2 pentyl), 2.94 (s, 2H, OCH_2-Ada), 2.50 – 2.30 (m, 4H, 2×CH_2 pen-4'-enoyl), 1.94 (br s, 3H, 3×CH Ada), 1.72 – 1.62 (m, 6H, 3×CH_2 Ada), 1.57 – 1.50 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.34 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) 138.1 (3×C_q Bn), 137.2 (CH vinyl), 128.3, 127.9, 127.7 (CH_{Ar} Bn), 114. 9 (CH_2 vinyl), 82.0 (OCH_2-Ada), 74.4 (CH), 71.5 (CH_2), 39.8 (3×CH_2 Ada), 37.3 (3×CH_2 Ada), 34.1 (C_q Ada), 29.6, 29.4 (2×CH_2 pentyl), 28.3 (3×CH Ada), 22.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2901, 2847, 1643, 1450, 1366, 1211, 1096, 1034, 910, 810, 741, 694, 617. $[\alpha]^{20}_D$: 5.2 (*c* 8.5, $CHCl_3$). MS (ESI): *m/z* 750.5 $[M+H]^+$; 772.6 $[M+Na]^+$. #: NMR characterization suffered from collapsed/multiple signals and severe peak broadening due to rotamers of the *N*-pent-4-enoyl amide.

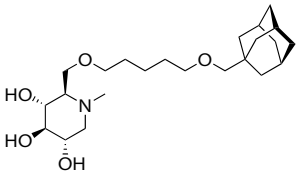


2,3,4-Tri-*O*-benzyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (27). Water (2 mL) was added to a solution of compound **26** (345 mg, 0.46 mmol) in THF (5.5 mL). The solution was charged with molecular iodine (351 mg, 1.38 mmol) and stirred for 30 min when TLC analysis indicated conversion into a lower running product. 1M aq $Na_2S_2O_3$ (10 mL) was added and the mixture was vigorously stirred for 30 min. The suspension was poured into a mixture of 1M aq $Na_2S_2O_3$/sat aq NaCl (100 mL, 1/1) and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (isocratic 25% EtOAc in PE) to yield **27** (246 mg, 0.37 mmol) as a colorless oil in 81% yield. R_F **27** = 0.31; (*R/S*)-γ-Iodomethyl-gamma-butyrolactone = 0.45 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.35 – 7.24 (m, 15H, H_{Ar} Bn), 5.97 (d, *J* = 10.9, 1H, C*H*H Bn), 4.88 (d, *J* = 11.0, 1H, C*H*H Bn), 4.83 (d, *J* = 10.9,

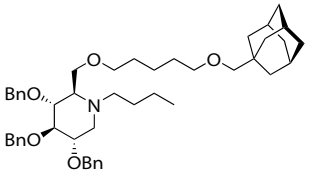
1H, CH*H* Bn), 4.69 (d, *J* = 11.7, 1H, C*H*H Bn), 4.66 (d, *J* = 11.7, 1H, CH*H* Bn), 4.56 (d, *J* = 11.0, 1H, CH*H* Bn), 3.59 (dd, *J* = 2.5, *J* = 9.1, 1H, H-6a), 3.55 – 3.30 (m, 8H, H-2, H-3, H-4, H-6b, 2×OCH_2 pentyl), 3.25 (dd, $J_{H1a\text{-}H2}$ = 4.7, $J_{H1a\text{-}H1b}$ = 12.2, 1H, H-1a), 2.93 (s, 2H, OCH_2-Ada), 2.68 (m, 1H, H-5), 2.51 (dd, $J_{H1b\text{-}H2}$ = 10.2, $J_{H1b\text{-}H1a}$ = 12.2, 1H, H-1b), 2.03 (br s, 1H, NH), 1.94 (br s, 3H, 3×CH Ada), 1.72 – 1.62 (m, 6H, 3×CH_2 Ada), 1.58 – 1.51 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.37 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 138.2 (3×C_q Bn), 128.2, 127.7, 127.6, 127.4, 127.3 (CH_{Ar} Bn), 87.1 (C-3), 81.7 (OCH_2-Ada), 80.4, 79.9 (C-2, C-4), 75.5, 75.0, 72.6, 71.2, 71.1(3×CH_2 Bn, 2×OCH_2 pentyl), 70.4 (C-6), 59.5 (C-5), 47.9 (C-1), 39.5 (3×CH_2 Ada), 37.0 (3×CH_2 Ada), 33.8 (C_q Ada), 29.2 (2×CH_2 pentyl), 28.1 (3×CH Ada), 22.6 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2901, 2847, 1450, 1358, 1258, 1211, 1096, 1065, 903, 741, 694, 610. $[\alpha]^{20}_D$: 18.8 (*c* 4.1, $CHCl_3$). HRMS: found *m/z* 668.4334 $[M+H]^+$, calcd for $[C_{43}H_{57}NO_5+H]^+$ 668.4310.



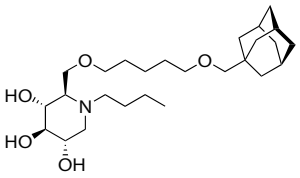
6-*O*-[1-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (5). Compound **27** (56 mg, 84 µmol) was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (0% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **5** (25 mg, 63 µmol) as a colorless oil in 75% yield. R_F = 0.48 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.76 – 3.70 (m, 2H, CH_2-6), 3.56 – 3.43 (m, 3H, H-2, OCH_2 pentyl), 3.39 – 3.34 (m, 3H, H-4 or H-3, OCH_2 pentyl), 3.17 (m, 1H, H-3), 3.02 (m, 1H, H-1a), 2.96 (s, 2H, OCH_2-Ada), 2.49 (br s, 2H, 2×OH), 2.32 (m, 1H, H-5), 2.21 (m, 1H, H-1b), 1.94 (br s, 3H, 3×CH Ada), 1.77-1.55 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.44 (m, 2H, CH_2 pentyl). ^{13}C NMR (50 MHz, MeOD) δ 83.1 (OCH_2-Ada), 80.6, 73.3 (C-2, C-3, C-4), 72.5, 71.7 (C-6, 2×OCH_2 pentyl), 61.3 (C-5), 51.0 (C-1), 40.8 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.2 (C_q Ada), 30.5 (2×CH_2 pentyl), 29.8 (3×CH Ada), 24.0 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2901, 2847, 1674, 1450, 1366, 1319, 1258, 1103, 1042, 671, 610. $[\alpha]^{20}_D$: 16.4 (*c* 0.2, MeOH). HRMS: found *m/z* 398.2910 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.



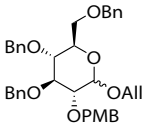
***N*-Methyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (6).** A dry solution of compound **27** (60 mg, 90 µmol) and formaldehyde (100 µL, 1 mmol; 37 wt % in water) in acetonitrile (0.5 mL) was charged with $NaBH_3CN$ (19 mg, 0.3 mmol) and stirred for 15 min, after which AcOH (13 µL) was added. The reaction mixture was stirred for 20 h (R_F intermediate = 0.68 in EtOAc:PE; 1:2), subsequently poured into sat aq $NaHCO_3$ (50 mL) and extracted with Et_2O (3×50 mL). The organic phase was concentrated and coevaporated with EtOH. The crude intermediate product was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **6** (31 mg, 75 µmol) as a colorless oil in 83% yield. R_F = 0.54 (1:2; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.73 (dd, $J_{H6a\text{-}H5}$ = 2.1, $J_{H6a\text{-}H6b}$ = 10.5, 1H, CH-6a), 3.63 (dd, $J_{H6b\text{-}H5}$ = 3.4, $J_{H6b\text{-}H6a}$ = 10.5, 1H, CH-6b), 3.53-3.43 (m, 3H, H-2, OCH_2 pentyl), 3.37 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.32- 3.28 (m, 1H, H-4), 3.12 (dd, *J* = 9.0, 9.0, 1H, H-3), 2.96 (s, 2H, OCH_2-Ada), 2.89 (dd, *J* = 4.8, 11.1, 1H, H-1a), 2.35 (s, 3H, NCH_3), 2.09 (dd, *J* = 10.9, H-1b), 1.98 – 1.88 (m, 4H, H-5, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.60 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.42 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.1 (OCH_2-Ada), 80.5 (C-3), 72.6, 72.4 (2×OCH_2 pentyl), 71.8 (C-4), 70.4 (C-2), 69.2 (C-5), 68.7 (C-6), 62.1 (C-1), 42.7 (NCH_3), 40.9 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.2 (C_q Ada), 30.5, 30.4 (2×CH_2 pentyl), 29.8 (3×CH Ada), 24.1 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3325, 2901, 2847, 2800, 2091, 1612, 1450, 1366, 1250, 1103, 1034, 833, 748. $[\alpha]^{20}_D$: –37.1 (*c* 0.6, MeOH). HRMS: found *m/z* 412.3063 $[M+H]^+$, calcd for $[C_{23}H_{42}NO_5+H]^+$ 412.3058.



2,3,4-Tri-*O*-benzyl-*N*-butyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (28). A dry solution of compound **27** (64 mg, 96 µmol) and butyraldehyde (100 µL, 1 mmol) in EtOH (0.75 mL) and AcOH (0.25 mL) was charged with $NaBH_3CN$ (13 mg, 0.2 mmol). The reaction mixture was stirred for 20 h and subsequently coevaporated with toluene. The residue was dissolved in little EtOAc, poured into sat aq $NaHCO_3$ (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 30% EtOAc in PE) to provide **28** (57 mg, 79 µmol) as a colorless oil in 82% yield. R_F = 0.71 (1:2 EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 15H, H_{Ar} Bn), 4.95 (d, *J* = 11.2, 1H, C*H*H Bn), 4.93 (d, *J* = 11.2, 1H, C*H*H Bn), 4.83 (d, *J* = 11.2, 1H, CH*H* Bn), 4.69 (d, *J* = 11.6, 1H, C*H*H Bn), 4.65 (d, *J* = 11.6, 1H, CH*H* Bn), 4.59 (d, *J* = 11.2, 1H, CH*H* Bn), 3.68 – 3.56 (m, 4H, H-2, H-4, CH_2-6), 3.49 – 3.41 (m, 2H, H-3, OC*H*H pentyl), 3.37 – 3.32 (m, 3H, OCH*H* pentyl, OCH_2 pentyl), 3.09 (dd, J_{H1a-H2} = 4.8, $J_{H1a-H1b}$ = 11.2, 1H, CH-1a), 2.92 (s, 2H, OCH_2-Ada), 2.71 – 2.64 (m, 2H, NCH_2 butyl), 2.30 (d, *J* = 9.2 1H, H-5), 2.25 (dd, *J* = 10.4, 1H, H-1b), 1.93 (br s, 3H, 3×CH Ada), 1.71 – 1.51 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.43 – 1.24 (m, 6H, CH_2 pentyl, 2×CH_2 butyl), 0.92 (t, *J* = 7.2, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 139.0, 138.7, 138.6 (3×C_q Bn), 128.3, 128.2, 127.82, 127.76, 127.71, 127.54, 127.48, 127.3 (CH_{Ar} Bn), 87.3 (C-3), 81.9 (OCH_2-Ada), 78.8, 78.6 (C-2, C-4), 75.3, 75.2 72.7 (3×CH_2 Bn), 71.5 (2×OCH_2 pentyl), 66.5 (C-6), 63.8 (C-5), 54.6 (C-1), 52.1 (NCH_2 butyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 29.4, 29.3 (2×CH_2 pentyl), 28.3 (3×CH Ada), 25.7 (CH_2 butyl), 22.9 (CH_2 pentyl), 20.7 (CH_2 butyl), 14.0 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2901, 2847, 1497, 1458, 1366, 1312, 1265, 1096, 1034, 903, 810, 733, 694. $[\alpha]^{20}_D$: –0.4 (*c* 1.1, $CHCl_3$). HRMS: found *m/z* 724.4905 $[M+H]^+$, calcd for $[C_{47}H_{65}NO_5+H]^+$ 724.4936.

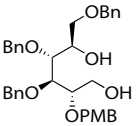


***N*-Butyl-6-*O*-[1-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (7).** Compound **28** (57 mg, 79 µmol) was subjected to General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **7** (33 mg, 74 µmol) as a colorless oil in 93% yield. R_F = 0.68 (1:2; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.74 (d, $J_{H6a-H6b}$ = 10.5, 1H, CH-6a), 3.62 (dd, J_{H6b-H5} = 3.7, $J_{H6b-H6a}$ = 10.5, 1H, CH-6b), 3.45 – 3.43 (m, 3H, H-2, OCH_2 pentyl), 3.37 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.24 (dd, *J* = 9.1, 9.1, 1H, H-4), 3.11 (dd, *J* = 9.1, 9.1, 1H, H-3), 2.98 – 2.93 (m, 3H, H-1a, OCH_2-Ada), 2.78 (m, 1H, NC*H*H butyl), 2.55 (m, 1H, NCH*H* butyl), 2.24 – 2.22 (m, 1H, H-5), 2.16 (dd, *J* = 11.0, 1H, H-1b), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.65 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.48 – 1.43 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.31 (m, 2H, CH_2 butyl), 0.94 (t, *J* = 7.3, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.1 (OCH_2-Ada), 80.6 (C-3), 72.6, 72.3 (2×OCH_2 pentyl), 72.2 (C-4), 70.6 (C-2), 69.4 (C-6), 66.4 (C-5), 57.7 (C-1), 53.9 (NCH_2 butyl), 40.9 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.2 (C_q Ada), 30.5 (2×CH_2 pentyl), 29.8 (3×CH Ada), 27.5 (CH_2 butyl), 24.1 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3364, 2901, 2847, 2106, 1828, 1651, 1458, 1366, 1258, 1103, 1018, 810. $[\alpha]^{20}_D$: –21.8 (*c* 0.7, MeOH). HRMS: found *m/z* 454.3531 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

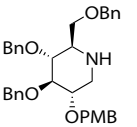


Allyl 3,4,6-tri-*O*-benzyl-2-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (30). A dry solution of compound **29**[33] (112 mg, 0.23 mmol) in DMF (1.5 mL) was cooled to 0 °C, followed by addition of NaH (10 mg, 60% wt in mineral oil, 0.25 mmol). After stirring for 20 min at rt, PMBCl (35 µL, 0.25 mmol) was added and the reaction was stirred for 4 h. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 50% EtOAc in PE) yielded **30** (116 mg, 0.19 mmol) in 83% as a colorless oil. R_F = 0.76 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.25

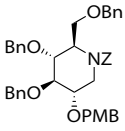
(m, 15H, H_{Ar} Bn), 6.90 – 6.81 (m, 4H, H_{Ar} PMB), 6.01 – 5.93 (m, 1H, CH vinyl; All), 5.38 – 5.19 (m, 2H, CH_2 vinyl; All), 4.95 – 4.39 (m, 8H, 4×CH_2 Bn/PMB), 4.17 – 4.13 (m, 1H), 3.84 – 3.50 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (*p*-C_q PMB), 138.6, 138.0 (3×C_q Bn), 134.0 (CH vinyl; All), 130.5 (C_q PMB), 129.9, 129.8, 129.6, 129.3, 129.2, 128.2, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn, 2× CH_{Ar} PMB), 117.0 (CH_2 vinyl; All), 113.6 (2×CH_{Ar} PMB), 102.6 (C-1), 84.6, 81.7, 77.7, 74.7 (C-2, C-3, C-4, C-5), 75.5, 74.8, 74.4, 71.2, 70.1, 68.8 (CH_2 All, 3×CH_2 Bn, CH_2 PMB, C-6), 55.1 (OCH_3 PMB). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1720, 1612, 1512, 1458, 1358, 1304, 1242, 1173, 1065, 1034, 926, 818, 741, 694. $[\alpha]^{20}_D$: 7.2 (*c* 3.0, $CHCl_3$). HRMS: found *m/z* 633.2868 $[M+Na]^+$, calcd for $[C_{38}H_{42}O_7+Na]^+$ 633.2823.



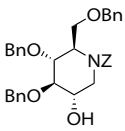
3,4,6-Tri-*O*-benzyl-2-*O*-*p*-methoxybenzyl-D-glucitol (31). Compound **30** (486 mg, 0.8 mmol) and DABCO (29 mg, 0.26 mmol) were combined, dissolved in EtOH/water (12.7 mL/ 0.6 mL) and argon was passed through the solution for 15 min. Wilkinson's catalyst (56 mg, 0.06 mmol) was added and the reaction mixture was refluxed for 48 h. The reaction mixture was concentrated with coevaporation of dioxane and redissolved in THF/water (6 mL/ 1 mL). Molecular iodine (407 mg, 1.6 mmol) was added to the solution and the reaction was stirred for 6 h's, after which TLC indicated the appearance of a lower running hemiacetal product mixture (R_F = 0.49; 0.42 in EtOAc:PE; 1:1). 1M aq $Na_2S_2O_3$ (4 mL) was added to the reaction, stirred for 15 min and poured into a mixture of sat aq NaCl/ 1M aq $Na_2S_2O_3$ (40 mL; 1/1). The aqueous phase was extracted with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude hemiacetal was used in General procedure A. The resulting residue was purified by silica gel column chromatography (20% » 50% EtOAc in PE) to give **31** (362 mg, 0.63 mmol) in 79% over two steps as a colorless oil. R_F = 0.56 (2:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.47 – 7.24 (m, 17H, H_{Ar} Bn, H_{Ar} PMB), 6.87 (m, 2H, H_{Ar} PMB), 4.74 (d, *J* = 11.3, 1H, C*H*H Bn/PMB), 4.68 (d, *J* = 11.3, 1H, CH*H* Bn/PMB), 4.66 – 4.52 (m, 6H, 3×CH_2 Bn/PMB), 4.05 (m, 1H, H-5), 3.89 (dd, *J* = 3.6, 6.3, 1H, H-3), 3.85 – 3.78 (m, 5H, H-2, H-4, OCH_3 PMB), 3.74 (dd, $J_{H1a\text{-}H2}$ = 4.5, $J_{H1a\text{-}H1b}$ = 11.8, 1H, H-1a), 3.70 – 3.66 (m, 2H, CH_2-6), 3.58 (dd, $J_{H1b\text{-}H2}$ = 4.8, $J_{H1b\text{-}H1a}$ = 11.8, 1H, H-1b), 3.01 (br s, 1H, OH), 2.11 (br s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (*p*-C_q PMB), 138.0, 137.9, 137.8 (3×C_q Bn), 130.2 (C_q PMB), 130.0, 129.9, 129.8, 129.7, 129.6, 129.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.91, 127.88, 128.82, 127.76 (CH_{Ar} Bn, 2×CH_{Ar} PMB), 113.9 (2×CH_{Ar} PMB), 79.1, 79.0 (C-2, C-3), 77.5 (C-4), 74.4, 73.5, 73.3, 72.7 (3×CH_2 Bn, CH_2 PMB), 71.1 (C-6), 70.7 (C-5), 61.9 (C-1), 55.3 (OCH_3 PMB). IR ν_{max}(thin film)/ cm^{-1}: 3410, 2870, 1713, 1612, 1512, 1458, 1250, 1072, 1034, 826, 741, 702, 625. $[\alpha]^{20}_D$: 10.0 (*c* 0.2, $CHCl_3$). MS (ESI): *m/z* 573.3 $[M+H]^+$; 595.3 $[M+Na]^+$.



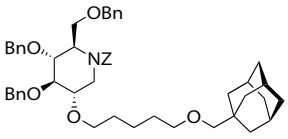
3,4,6-Tri-*O*-benzyl-2-*O*-*p*-methoxybenzyl-1-deoxynojirimycin (32). Compound **31** (994 mg, 1.74 mmol) was used in General procedure B with double reductive amination method B. The resulting residue was purified by silica gel column chromatography (25% » 75% EtOAc in PE) to provide **32** (654 mg, 1.18 mmol) in 68% yield as a light yellow crystalline solid. R_F = 0.19 (2:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.36 – 7.18 (m, 17H, H_{Ar} Bn, H_{Ar} PMB), 6.85 (m, 2H, H_{Ar} PMB), 4.96 (d, *J* = 11.0, 1H, C*H*H Bn/PMB), 4.85 (d, *J* = 11.2, 1H, C*H*H Bn/PMB), 4.82 (d, *J* = 11.2, 1H, CH*H* Bn/PMB), 4.62 (d, *J* = 11.3, 1H, C*H*H Bn/PMB), 4.58 (d, *J* = 11.3, 1H, CH*H* Bn/PMB), 4.48 (d, *J* = 11.0, 1H, CH*H* Bn/PMB), 4.47 (d, *J* = 11.8, 1H, CH*H* Bn/PMB), 4.42 (d, *J* = 11.8, 1H C*H*H Bn/PMB), 3.79 (s, 3H, OCH_3 PMB), 3.67 (dd, $J_{H6a\text{-}H5}$ = 2.5, $J_{H6a\text{-}H6b}$ = 9.0, 1H, H-6a), 3.55 – 3.45 (m, 3H, H-2, H-3, H-6b), 3.35 (dd, *J* = 8.9, 8.9, 1H, H-4), 3.22 (dd, $J_{H1a\text{-}H2}$ = 4.8, $J_{H1a\text{-}H1b}$ = 12.2, 1H, H-1a), 2.72 (ddd, *J* = 2.5, 5.9, 9.0, 1H, H-5), 2.48 (dd, $J_{H1b\text{-}H2}$ = 10.3, $J_{H1b\text{-}H1a}$ = 12.2, 1H, H-1b), 2.06 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 159.2 (*p*-C_q PMB), 139.0, 138.4, 137.9 (3×C_q Bn), 130.6 (C_q PMB), 129.4, 128.4, 128.35, 128.33, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn, 2×CH_{Ar} PMB), 113.8 (2×CH_{Ar} PMB), 87.2 (C-3), 80.2, 80.0 (C-2, C-4), 75.6, 75.2, 73.4, 72.5 (3×CH_2 Bn, CH_2 PMB), 70.2 (C-6), 59.7 (C-5), 55.2 (OCH_3 PMB), 48.1 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 2932, 2862, 1728, 1612, 1512, 1458, 1358, 1250, 1096, 1072, 1034, 818, 741, 702, 633. $[\alpha]^{20}_D$: 18.8 (*c* 1.1, $CHCl_3$). HRMS: found *m/z* 554.2930 $[M+H]^+$, calcd for $[C_{35}H_{39}NO_5+H]^+$ 554.2901.



3,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-2-*O*-*p*-methoxybenzyl-1-deoxynojirimycin (33). To a solution of compound **32** (654 mg, 1.18 mmol) in dioxane (12 mL), 10 wt % aq $NaHCO_3$ (4 mL) was added. Next, benzyloxychloroformate (253 µL, 1.77 mmol) was added and the reaction was stirred for 20 h. The reaction mixture was poured into water (40 mL) and extracted with Et_2O (3×50mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (15% » 33% EtOAc in PE) to provide **33** (808 mg, 1.17 mmol) in 99% yield as a colorless oil. R_F = 0.69 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.32 – 7.19 (m, 22H, H_{Ar} Bn, H_{Ar} Z, H_{Ar} PMB), 6.81 (d, *J* = 8.6, 2H, H_{Ar} PMB), 5.14 (d, *J* = 12.3, 1H, C*H*H Z), 5.08 (d, *J* = 12.3, 1H, CH*H* Z), 4.72 (d, *J* = 11.6, 1H, C*H*H Bn/PMB), 4.62 – 4.55 (m, 3H, 3×CH Bn/PMB), 4.51 (d, *J* = 11.6, 1H, CH*H* Bn/PMB), 4.43 (d, *J* = 12.1, 1H, C*H*H Bn/PMB), 4.39 (d, *J* = 11.5, 1H, CH Bn/PMB), 4.33 (d, *J* = 12.1, 1H, CH*H* Bn/PMB), 4.20 – 4.18 (m, 1H, H-5), 4.13 (br d, $J_{H1a\text{-}H1b}$ = 14.4, 1H, H-1a), 3.90 (dd, *J* = 6.5, 1H, H-4), 3.78 (s, 3H, OCH_3 PMB), 3.71 (dd, *J* = 4.4, *J* = 6.9, 1H, H-3), 3.73 – 3.60 (m, 3H, H-2, CH_2-6), 3.32 (dd, $J_{H1b\text{-}H2}$ = 3.4, $J_{H1b\text{-}H1a}$ = 14.4, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 159.1 (*p*-C_q PMB), 155.8 (C=O Z), 138.3, 138.2, 136.6 (3×C_q Bn, C_q Z), 130.1 (C_q PMB), 129.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.57, 127.49, 127.46 (CH_{Ar} Bn, 2×CH_{Ar} PMB, CH_{Ar} Z), 113.7 (2×CH_{Ar} PMB), 81.8 (C-3), 77.8 (C-2), 74.1 (C-4), 73.2, 72.9, 72.8, 70.2 (3×CH_2 Bn, CH_2 PMB), 68.4 (C-6), 67.2 (CH_2 Z), 55.7 (C-5), 55.2 (OCH_3 PMB), 41.3 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1697, 1612, 1512, 1420, 1358, 1304, 1242, 1072, 1026, 910, 818, 740, 694. $[\alpha]^{20}_D$: 7.0 (*c* 1.5, $CHCl_3$). HRMS: found *m/z* 688.3298 $[M+H]^+$, calcd for $[C_{43}H_{45}NO_7+H]^+$ 688.3269.

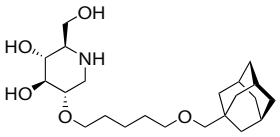


3,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-deoxynojirimycin (34)#. Trifluoroacetic acid (600 µL) was slowly added to a dry solution of compound **33** (601 mg, 0.87 mmol) in DCM (29 mL), under rapid stirring. The reaction mixture was stirred for 60 min, after which it was poured into sat aq $NaHCO_3$ (50 mL) and extracted with DCM (3×50mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (20% » 33% EtOAc in PE) to provide **34** (446 mg, 0.79 mmol) in 90% yield as a colorless oil. R_F = 0.51 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.60 – 7.28 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.32 (d, *J* = 12.8, 1H, C*H*H Z), 5.27 (d, *J* = 12.8, 1H, CH*H* Z), 5.08 (m, 1H), 4.79 – 4.53 (m, 6H, 3×CH_2 Bn), 3.31 (m, 1H, H-1a), 3.98 (m, 1H), 3.92 – 3.81 (m, 5H), 3.37 (d, *J* = 14.0 , 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 156.6 (C=O Z), 138.0, 137.4, 136.7, 136.6 (3×C_q Bn, C_q Z), 128.32, 128.28, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3 (CH_{Ar} Bn, CH_{Ar} Z), 74.3, 72.5, 66.5 (C-2, C-3, C-4, C-5), 72.6, 71.9, 71.4, (CH_2 Bn), 67.1 66.8 (CH_2 Z, C-6), 42.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3503, 3032, 2870, 1697, 1605, 1450, 1427, 1358, 1319, 1250, 1172, 1072, 1026, 818, 733, 694. $[\alpha]^{20}_D$: –35.6 (*c* 1.3, $CHCl_3$). HRMS: found *m/z* 568.2668 $[M+H]^+$, calcd for $[C_{35}H_{37}NO_6+H]^+$ 568.2694. #: NMR characterization suffered from collapsed signals and peak broadening due to rotamers of the benzyloxycarbamate.

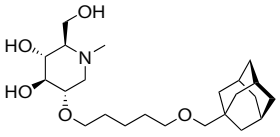


3,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-2-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (35). Compound **34** (148 mg, 0.26 mmol) was alkylated with bromide **25** using General procedure C. The resulting residue was purified by silica gel column chromatography (5% » 33% EtOAc in PE) to provide **35** (186 mg, 0.24 mmol) in 91% yield as a colorless oil. R_F = 0.50 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.31 – 7.25 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.14 (d, *J* = 12.4, 1H, C*H*H Z), 5.07 (d, *J* = 12.4, 1H, CH*H* Z), 4.74 (d, *J* = 11.6, 1H, C*H*H Bn), 4.65 (s, 2H, CH_2 Bn), 4.51 (d, *J* = 11.6, 1H, CH*H* Bn), 4.42 (d, *J* = 12.0, 1H, C*H*H Bn), 4.32 (d, *J* = 12.0, 1H, CH*H* Bn), 4.13 (m, 1H, H-5), 3.99 (dd, *J* = 14.2, 4.6, 1H, H-1a), 3.91 (dd, *J* = 6.7, 6.7, 1H, H-4), 3.67 – 3.54 (m, 4H, H-2, H-3, CH_2-6), 3.38 – 3.31 (m, 5H, H-1b, 2×OCH_2 pentyl), 2.93 (s, 2H, OCH_2-Ada), 1.94 (br s, 3H, 3×CH Ada), 1.72 – 1.52 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.36 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.7 (C=O Z), 138.2, 136.6 (3×C_q Bn, 1×C_q Z), 128.4, 128.2, 127.9, 127.7, 127.5, 127.4 (CH_{Ar} Bn, CH_{Ar} Z), 82.4, 79.5, 74.3 (C-2, C-3, C-4), 81.9 (OCH_2-Ada), 73.2, 72.9, 72.8, 71.5, 70.0, 68.5, 67.1 (CH_2

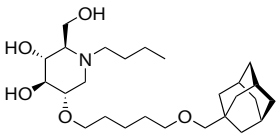
Z, 3×CH_2 Bn, 2×OCH_2 pentyl, C-6), 55.8 (C-5), 41.7 (C-1), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 29.7, 29.4 (2×CH_2 pentyl), 28.2 (3×CH Ada), 22.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1697, 1450, 1420, 1358, 1312, 1250, 1219, 1088, 1026, 910, 810, 733, 694, 617. $[\alpha]^{20}_D$: –3.7 (*c* 3.7, $CHCl_3$). HRMS: found *m/z* 802.4694 $[M+H]^+$, calcd for $[C_{51}H_{63}NO_7+H]^+$ 802.4677.



2-*O*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (8). Compound **35** (94 mg, 236 µmmol) was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **8** (72 mg, 181 µmol) as an off-white solid in 72% yield. R_F = 0.35 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.82 (dd, $J_{H6a\text{-}H5}$ = 2.8, $J_{H6a\text{-}H6b}$ = 10.9, 1H, H-6a), 3.65 – 3.56 (m, 3H, H-6b, OCH_2 pentyl), 3.37 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.28 – 3.22 (m, 2H, H-3, H-1a), 3.18 – 3.12 (m, 2H, H-2, H-4), 2.96 (s, 2H, OCH_2-Ada), 2.44 (m, 1H, H-5), 2.35 (dd, *J* = 10.2, 10.2, 1H, H-1b), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.63 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.42 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.0 (OCH_2-Ada), 80.8 79.6 (C-2, C-3), 73.4 (C-4), 72.6, 71.7 (2×OCH_2 pentyl), 63.0 (C-6), 62.7 (C-5), 48.6 (C-1), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.1 (C_q Ada), 31.0, 30.5 (2×CH_2 pentyl), 29.7 (3×CH Ada), 23.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3333, 2901, 2847, 2476, 1450, 1366, 1258, 1096, 1049, 880, 841, 710. $[\alpha]^{20}_D$: 28.2 (*c* 1.4, $CHCl_3$). HRMS: found *m/z* 398.2921 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

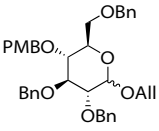


***N*-Methyl-2-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (9).** A solution of compound **8** (36 mg, 90 µmol) and formaldehyde (0.5 mL, 6.2 mmol; 37 wt % in water) in EtOH (4 mL) was acidified to pH ~2 with 1M aq HCl. Argon was passed through the solution for 5 min, after which a catalytic amount of Pd/C (30 mg, 10 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 10 min and stirring was continued under atmospheric hydrogen pressure for 20 h. Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH. The filtrate was concentrated and coevaporated with toluene. The residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **9** (37 mg, 90 µmol) as a light yellow oil in quantitative yield. R_F = 0.49 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.84 – 3.83 (m, 2H, CH_2-6), 3.40 – 3.36 (m, 3H, H-4, OCH_2 pentyl), 3.25 – 3.17 (m, 2H, H-2, H-3), 3.04 (dd, $J_{H1a\text{-}H2}$ = 4.4, $J_{H1a\text{-}H1b}$ = 11.3, 1H, H-1a), 2.96 (s, 2H, OCH_2-Ada), 2.35 (s, 3H, NCH_3), 2.00 (dd, *J* = 9.0, 12.2, H-1b), 1.95 – 1.93 (m, 4H, H-5, 3×CH Ada), 1.79 – 1.66 (m, 6H, 3×CH_2 Ada), 1.61 – 1.53 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.43 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.0 (OCH_2-Ada), 79.5, 78.8 (C-2, C-3), 72.6, 71.9 (2×OCH_2 pentyl), 71.6, 70.3 (C-4, C-5), 59.6, 59.2 (C-6, C-1), 42.5 (NCH_3), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.0, 30.5 (2×CH_2 pentyl), 29.7 (3×CH Ada), 23.8 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3302, 2901, 2847, 2353, 2106, 1659, 1612, 1450, 1366, 1234, 1234, 1096, 1049, 910, 826. $[\alpha]^{20}_D$: 6.3 (*c* 0.8, $CHCl_3$). HRMS: found *m/z* 412.3076 $[M+H]^+$, calcd for $[C_{23}H_{41}NO_5+H]^+$ 412.3058.

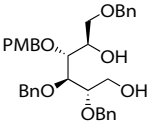


***N*-Butyl-2-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (10).** Compound **8** (24 mg, 60 µmol) was transformed into **10** using the procedure as described for **9**, but substituting formaldehyde for butyraldehyde (0.1 mL, 1.1 mmol). The crude product was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **10** as a light yellow oil (24 mg, 54 µmol) in 90% yield. R_F = 0.59 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.84 – 3.83 (m, 2H, CH_2-6), 3.65 – 3.56 (m, 2H, OCH_2 pentyl), 3.40 – 3.33 (m, 3H, H-4, OCH_2 pentyl),

3.24 – 3.15 (m, 2H, H-2, H-3), 3.08 (dd, $J_{H1eq\text{-}H2}$ = 4.2, $J_{H1eq\text{-}H1ax}$ = 11.2, 1H, H-1a), 2.96 (s, 2H, OCH_2-Ada), 2.78 (m, 1H, NC*H*H butyl), 2.59 (m, 1H, NCH*H* butyl), 2.12 – 2.07 (m, 2H, H-1b, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.63 – 1.53 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.50 – 1.40 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.30 (m, 2H, CH_2 butyl), 0.94 (t, *J* = 7.4, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.0 (OCH_2-Ada), 79.6, 79.2 (C-2, C-3), 72.6 (OCH_2 pentyl), 72.1 (C-4), 71.7 (OCH_2 pentyl), 67.1 (C-5), 59.4 (C-6), 55.2 (C-1), 53.6 (NCH_2 butyl), 40.9 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.1 (C_q Ada), 31.0, 30.7 (2×CH_2 pentyl), 29.8 (3×CH Ada), 27.3 (CH_2 butyl), 23.9 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3371, 2901, 2847, 2091, 1690, 1458, 1366, 1150, 1103, 903, 826, 664. $[\alpha]^{20}_D$: 28.1 (*c* 0.3, $CHCl_3$/MeOH; 2/1). HRMS: found *m/z* 454.3551 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

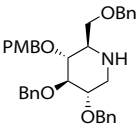


α/β-Mixture of allyl 2,3,6-tri-*O*-benzyl-4-*O*-*p*-methoxybenzyl-D-glucopyranoside (37). Compound **36**[34] (2.328 g, 4.75 mmol) was protected with a PMB-group using the same procedure as described for the synthesis of **30**. The crude product was purified by silica gel column chromatography (15% » 33% EtOAc in PE) to yield **37** (2.617 g, 4.29 mmol) in 90% as a crystalline solid. R_F = 0.68 (1:2; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) α/β mixture δ 7.38 – 7.23 (m, 15H, H_{Ar} Bn), 7.07 – 7.02 (m, 2H, H_{Ar} PMB), 6.78 – 6.76 (m, 2H, H_{Ar} PMB), 5.97 – 5.87 (m, 1H, CH vinyl; All), 5.35 – 5.17 (m, 2H, CH_2 vinyl; All), 5.01 – 4.39 (m, 8H, 4×CH_2 Bn/PMB), 4.16 – 4.10 (m, 1H), 4.03 – 3.97 (m, 1H), 3.81 – 3.42 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) α/β mixture δ 159.0 (*p*-C_q PMB), 138.7, 138.4, 138.2, 138.0, 137.0 (3×C_q Bn α+β), 133.9, 133.5 (CH vinyl; All α+β), 130.2, 130.0 (C_q PMB α+β) 129.4, 129.3, 128.1, 127.9, 127.8, 127.63, 127.60, 127.56, 127.53, 127.50, 127.4, 127.3 (CH_{Ar} Bn, 2×CH_{Ar} PMB; α+β), 117.8, 116.8 (CH_2 vinyl; All α+β), 113.6 (2×CH_{Ar} PMB α+β), 102.5(C-1 β), 95.4 (C-1 α), 84.5, 82.0, 81.9, 79.7, 77.3, 77.2, 74.6, 70.0 (C-2, C-3, C-4, C-5; α+β), 75.4, 74.6, 74.4, 73.2, 72.9, 69.9, 68.7, 68.2, 67.9 (CH_2 All, 3×CH_2 Bn, CH_2 PMB, C-6; α+β), 54.9 (OCH_3 PMB; α+β). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2862, 1720, 1612, 1512, 1458, 1358, 1304, 1250, 1157, 1065, 1034, 926, 818, 741, 694. $[\alpha]^{20}_D$: 15.6 (c = 5.5, $CHCl_3$). HRMS: *M/Z* found 633.2883 $[M+Na]^+$, calcd for $[C_{38}H_{42}O_7+Na]^+$ 633.2823.

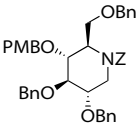


2,3,6-Tri-*O*-benzyl-4-*O*-*p*-methoxybenzyl-D-glucitol (38). A dry solution of **37** (1.221 mg, 2.00 mmol) in DMSO (4 mL) was charged with KO*t*Bu (112 mg, 1.00 mmol) and heated at 100 °C for 30 min, after which it was quenched by addition of water (1 mL). The reaction mixture was poured into water (150 mL) and extracted with Et_2O (3×100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was dissolved in THF/water (8.5 mL/ 1.5 mL). Molecular iodine (1 g, 4 mmol) was added to the solution and the reaction was stirred for 6 h, after which TLC indicated the appearance of a lower running hemiacetal product mixture (R_F = 0.67; 0.60 in EtOAc:PE; 1:1). 1M aq $Na_2S_2O_3$ (10 mL) was added to the reaction, stirred for 15 min and poured into a mixture of sat aq NaCl/ 1M aq $Na_2S_2O_3$ (80 mL; 1/1). The aqueous phase was extracted with EtOAc (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude hemiacetal intermediate was reduced to **38** using General procedure A. The resulting residue was purified by silica gel column chromatography (25% » 66% EtOAc in PE) to give **38** (940 mg, 1.64 mmol) in 82% over two steps as a colorless oil. R_F = 0.40 (1:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.35 – 7.23 (m, 15H, H_{Ar} Bn), 7.13 (dd, *J* = 3.9, 11.4, 2H, H_{Ar} PMB), 6.80 (dd, *J* = 3.0, 11.4, 2H, H_{Ar} PMB), 4.71 (d, *J* = 11.3, 1H, C*H*H Bn/PMB), 4.66 (d, *J* = 11.6, 1H, C*H*H Bn/PMB), 4.64 (d, *J* = 11.3, 1H, CH*H* Bn/PMB), 4.61 (d, *J* = 11.6, 1H, CH*H* Bn/PMB), 4.55 (d, *J* = 11.9, 1H, C*H*H Bn/PMB), 4.51 (d, *J* = 11.0, 1H, C*H*H Bn/PMB), 4.50 (d, *J* = 11.9, 1H, CH*H* Bn/PMB), 4.46 (d, *J* = 11.0, 1H, CH*H* Bn/PMB), 4.02 (m, 1H, H-5), 3.87 (dd, *J* = 3.6, 6.4, 1H, H-3), 3.80 – 3.74 (m, 5H, H-2, H-4, OCH_3 PMB), 2.71 (dd, $J_{H1a\text{-}H2}$ = 4.3, $J_{H1a\text{-}H1b}$ = 11.9, 1H, H-1a), 3.66 – 3.58 (m, 2H, CH_2-6), 3.55 (dd, $J_{H1b\text{-}H2}$ = 4.5, $J_{H1b\text{-}H1a}$ = 11.9, 1H, H-1b), 2.98 (br s, 1H, OH), 2.16 (br. s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 159.3 (*p*-C_q PMB), 138.1, 137.9, 137.8 (3×C_q Bn), 129.9 (C_q PMB), 129.8, 128.4, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar} Bn, 2×CH_{Ar} PMB), 113.8 (2×CH_{Ar} PMB), 79.4 (C-2), 79.1 (C-3), 76.8 (C-4), 74.4, 73.4, 73.0, 72.8 (3×CH_2 Bn, CH_2 PMB), 71.1 (C-6),

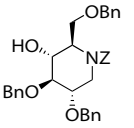
70.7 (C-5), 61.8 (C-1), 55.2 (OCH_3 PMB). IR ν_{max}(thin film)/ cm^{-1}: 3433, 3032, 2924, 2870, 1713, 1612, 1512, 1458, 1358, 1288, 1250, 1065, 1034, 918, 818, 733, 694. $[\alpha]^{20}_D$: 4.3 (*c* 13.1, $CHCl_3$). HRMS: found *m/z* 573.2698 $[M+H]^+$, calcd for $[C_{35}H_{40}O_7+H]^+$ 573.2666.



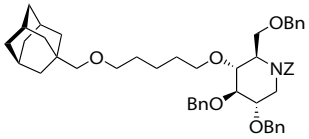
2,3,6-Tri-*O*-benzyl-4-*O*-*p*-methoxybenzyl-1-deoxynojirimycin (39). Compound **39** was synthesized from **38** (469 mg, 0.82 mmol) using General procedure B with double reductive amination method B. The crude product was purified by silica gel column chromatography (25% » 75% EtOAc in PE) to provide **39** (218 mg, 0.39 mmol) in 48% yield as a light yellow crystalline solid. R_F = 0.14 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.38 – 7.24 (m, 15H, H_{Ar} Bn), 7.09 (m, 2H, H_{Ar} PMB), 6.80 (m, 2H, H_{Ar} PMB), 4.98 (d, *J* = 11.0, 1H C*H*H Bn/PMB), 4.85 (d, *J* = 11.0, 1H CH*H* Bn/PMB), 4.78 (d, *J* = 10.5, 1H CH Bn/PMB), 4.66 (m, 2H, CH_2 Bn/PMB), 4.51 – 4.39 (m, 3H, 3×CH Bn/PMB), 3.73 (s, 3H, OCH_3 PMB), 3.64 (dd, *J* = 2.3, 8.9, 1H, H-6a), 3.57 – 3.43 (m, 3H, H-2, H-3, H-6b), 3.33 (dd, *J* = 8.8, 9.3, 1H, H-4), 3.21 (dd, $J_{H1a\text{-}H2}$ = 4.6, $J_{H1a\text{-}H1b}$ = 12.2, 1H, H-1a), 2.69 (m, 1H, H-5), 2.48 (dd, $J_{H1b\text{-}H2}$ = 10.2, $J_{H1b\text{-}H1a}$ = 12.2, 1H, H-1b), 2.00 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1 (*p*-C_q PMB), 138.8, 138.4, 137.8 (3×C_q Bn), 130.4 (C_q PMB), 129.5, 128.2, 127.7, 127.6, 127.5, 127.3 (CH_{Ar} Bn, 2×CH_{Ar} PMB), 113.6 (2×CH_{Ar} PMB), 87.2, 80.5, 79.6 (C-2, C-3, C-4), 75.5, 74.6, 73.2, 72.6, 70.1 (3×CH_2 Bn, CH_2 PMB, C-6), 59.6 (C-5), 55.1 (OCH_3 PMB), 48.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2862, 1612, 1512, 1458, 1358, 1304, 1250, 1096, 1034, 910, 818, 741, 702. $[\alpha]^{20}_D$: 17.4 (*c* 2.6, $CHCl_3$). HRMS: found *m/z* 554.2954 $[M+H]^+$, calcd for $[C_{35}H_{39}NO_5+H]^+$ 554.2901.



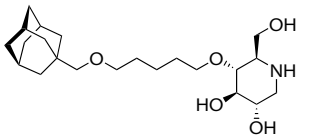
2,3,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-4-*O*-*p*-methoxybenzyl-1-deoxynojirimycin (40). Compound **39** (218 mg, 0.39 mmol) was protected with a Z-carbamate function using the same procedure as described for the synthesis of **33**. The crude product was purified by silica gel column chromatography (15% » 33% EtOAc in PE) to provide **40** (268 mg, 0.39 mmol) quantitatively as a colorless oil. R_F = 0.78 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.33 – 7.20 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 7.14 (d, *J* = 8.5, 2H, H_{Ar} PMB), 6.77 (d, *J* = 8.5, 2H, H_{Ar} PMB), 5.09 (d, *J* = 12.4, 1H C*H*H Z), 5.03 (d, *J* = 12.4, 1H CH*H* Z), 4.65 – 4.38 (m, 7H, 7×CH Bn/PMB), 4.29 (d, *J* = 12.0, 1H, CH Bn/PMB), 4.19 – 4.11 (m, 2H, H-5, H-1a), 3.88 (dd, *J* = 6.3, 6.3, 1H, H-4), 3.75 – 3.62 (m, 7H, H-2, H-3, CH_2-6, OCH_3 PMB), 3.30 (dd, *J* = 2.9, 14.4, 1H, H-1b). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9 (*p*-C_q PMB), 155.7 (C=O Z), 138.0, 137.9, 137.8, 136.3 (3×C_q Bn, C_q Z), 130.0 (C_q PMB), 129.5, 128.1, 127.6, 127.5, 127.3, 127.2, 127.1, 126.6 (CH_{Ar} Bn, 2×CH_{Ar} PMB, CH_{Ar} Z), 113.5 (2×CH_{Ar} PMB), 81.4, 77.8, 73.3 (C-2, C-3, C-4), 72.6, 72.5, 70.3, 68.0, 67.1, 64.6 (3×CH_2 Bn, CH_2 PMB, CH_2 Z, C-6), 55.4 (C-5), 54.9 (OCH_3 PMB), 41.0 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 2932, 2870, 1697, 1612. 1512, 1450, 1358, 1250, 1072, 1034, 826, 741, 694. $[\alpha]^{20}_D$: 5.7 (*c* 2.0, $CHCl_3$). HRMS: found *m/z* 688.3287 $[M+H]^+$, calcd for $[C_{43}H_{45}NO_7+H]^+$ 688.3269.



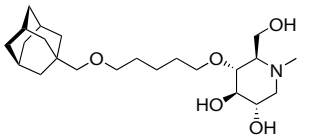
2,3,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-deoxynojirimycin (41)#. The PMB-function in **40** (268 mg, 0.39 mmol) was cleaved using the same procedure as described for the synthesis of **34**. The crude product was purified by silica gel column chromatography (20% » 33% EtOAc in PE) to provide product **41** (217 mg, 0.38 mmol) in 98% yield as a colorless oil. R_F = 0.71 (1:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.19 (d, *J* = 12.5, 1H, C*H*H Z), 5.14 (d, *J* = 12.5, 1H, CH*H* Z), 4.75 – 4.65 (m, 2H), 4.70 – 4.37 (m, 6H, 3×CH_2 Bn), 3.96 (m, 1H), 3.81 – 3.63 (m, 5H), 3.15 (d, *J* = 14.7, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.5, 136.9 (C_q Bn), 128.4, 128.3, 128.2, 127.9, 127.8, 127.5, 127.4 (CH_{Ar} Bn, CH_{Ar} Z), 75.2, 66.0 (CH), 72.6, 72.2, 70.8, 67.3, 67.0 (CH_2). IR ν_{max}(thin film)/ cm^{-1}: 3502, 3032, 2870, 1697, 1504, 1450, 1427, 1358, 1312, 1250, 1096, 1026, 741, 694. $[\alpha]^{20}_D$: 19.3 (*c* 2.1, $CHCl_3$). HRMS: found *m/z* 568.2725 $[M+H]^+$, calcd for $[C_{35}H_{37}NO_6+H]^+$ 568.2694. #: NMR characterization suffered from collapsed signals and peak broadening due to rotamers of the benzyloxycarbamate.



2,3,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-4-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (42). Compound **41** (102 mg, 0.18 mmol) was alkylated with bromide **25** using General procedure C. The resulting residue was purified by silica gel column chromatography (5% » 33% EtOAc in PE) to provide product **42** (132 mg, 0.16 mmol) in 91% yield as a colorless oil. R_F = 0.60 (1:3; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.32 – 7.21 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.13 (d, *J* = 12.4, 1H, C*H*H Z), 5.08 (d, *J* = 12.4, 1H, CH*H* Z), 4.68 (d, *J* = 11.6, 1H, C*H*H Bn), 4.64 – 4.61 (m, 3H, 2×CH Bn), 4.51 (d, *J* = 12.0, 1H, C*H*H Bn), 4.43 (d, *J* = 11.7, 1H, CH Bn), 4.42 (d, *J* = 12.0, 1H, CH*H* Bn), 4.12 – 4.05 (m, 2H, H-1a, H-5), 3.75 (dd, *J* = 6.7, 6.7, 1H, H-4), 3.69 – 3.65 (m, 5H, H-2, H-3, CH_2-6, OC*H*H pentyl), 3.42 (m, 1H, OCH*H* pentyl), 3.36 – 3.31 (m, 3H, H-1b, OCH_2 pentyl), 2.93 (s, 2H, OCH_2-Ada), 1.94 (br s, 3H, 3×CH Ada), 1.71 – 1.62 (m, 6H, 3×CH_2 Ada), 1.55 – 1.47 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.32 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (C=O Z), 138.3, 138.0, 136.6 (3×C_q Bn, 1×C_q Z), 128.3, 128.3, 127.79, 127.76, 127.69, 127.59, 127.53, 127.46 (CH_{Ar} Bn, CH_{Ar} Z), 82.2, 78.6, 75.0 (C-2, C-3, C-4), 81.8 (OCH_2-Ada), 73.0, 72.9, 71.6, 71.4, 70.5, 68.5, 67.1 (CH_2 Z, 3×CH_2 Bn, 2×OCH_2 pentyl, C-6), 56.0 (C-5), 41.4 (C-1), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 29.8, 29.4 (2×CH_2 pentyl), 28.2 (3×CH Ada), 22.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1697, 1497, 1450, 1420, 1358, 1312, 1219, 1096, 1026, 910, 741, 694. $[\alpha]^{20}_D$: 5.8 (*c* 2.5, $CHCl_3$). HRMS: found *m/z* 802.4639 $[M+H]^+$, calcd for $[C_{51}H_{63}NO_7+H]^+$ 802.4677.

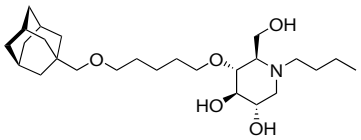


4-*O*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (11). Compound **42** (132 mg, 164 µmol) was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in EtOAc with 0.5% NH_4OH) to give **11** (54 mg, 136 µmol) as an off-white solid in 83% yield. R_F = 0.22 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.89 – 3.85 (m, 1H, OC*H*H pentyl), 3.79 (dd, *J* = 2.5, 10.8, 1H, H-6a), 3.62 – 3.52 (m, 2H, H-6b, OCH*H* pentyl), 3.42 – 3.36 (m, 3H, H-2, OCH_2 pentyl), 3.28 (dd, *J* = 9.4, 9.4, 1H, H-3), 3.07 (dd, J_{H1a-H2} = 5.1, $J_{H1a-H1b}$ = 12.2, 1H, H-1a), 3.00 (dd, *J* = 9.4, 9.4, 1H, H-4), 2.96 (s, 2H, OCH_2-Ada), 2.47 (ddd, *J* = 2.5, 5.6, 9.6, 1H, H-5), 2.40 (dd, J_{H1b-H2} = 10.8, $J_{H1b-H1a}$ = 12.2, 1H, H-1b), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 6H, 3×CH_2 Ada), 1.64 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.43 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.0 (OCH_2-Ada), 81.2 (C-4), 80.6 (C-3), 72.8 (C-2), 73.9, 72.6 (2×OCH_2 pentyl), 62.4 (C-6), 62.3 (C-5), 50.8 (C-1), 40.4 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.1 (C_q Ada), 31.2, 30.5 (2×CH_2 pentyl), 29.7 (3×CH Ada), 23.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3371, 2901, 2847, 2476, 2068, 1674, 1450, 1366, 1258, 1196, 1096, 1049, 980, 880, 841, 718. $[\alpha]^{20}_D$: 16.9 (*c* 1.1, MeOH). HRMS: found *m/z* 398.2905 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

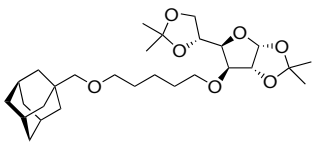


***N*-Methyl-4-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (12).** Argon was passed through a solution of compound **42** (54 mg, 67 µmol) in MeOH (3 mL) for 15 min, after which a catalytic amount of Pd/C Degussa type (50 mg, 5 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 30 min. After stirring the reaction under atmospheric hydrogen pressure for 60 min, TLC analysis indicated full conversion to the Z-deprotected intermediate product (R_F = 0.04 in 3:1; PE:EtOAc). At this point a solution of formaldehyde (0.7 mL; 37 wt % in water) in MeOH (1.4 mL), through which argon had been passed for 5 min, was added to the reaction mixture. After stirring under a hydrogen atmosphere for another 90 min, TLC analysis indicated full conversion to the *N*-methylated intermediate (R_F intermediate = 0.36 in PE:EtOAc; 2:1). The Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH. The filtrate was concentrated and coevaporated once with toluene. The crude intermediate product was deprotected using General procedure

D. The resulting residue was purified by silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **12** (26 mg, 63 µmol) as a colorless oil in 94% yield. R_F = 0.42 (1:4; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD, COSY) δ 3.94 – 3.89 (m, 1H, OC*H*H pentyl), 3.82 (dd, $J_{H6a\text{-}H5}$ = 2.3, $J_{H6a\text{-}H6b}$ = 11.9, 1H, CH-6a), 3.74 (dd, $J_{H6b\text{-}H5}$ = 2.1, $J_{H6b\text{-}H6a}$ = 11.9, 1H, CH-6b), 3.65 – 3.60 (m, 1H, OCH*H* pentyl), 3.47 (m, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.23 – 3.21 (m, 2H, H-3, H-4), 2.96 (s, 2H, OCH_2-Ada), 2.89 (dd, *J* = 4.8, 11.1, 1H, H-1a), 2.33 (s, 3H, NCH_3), 2.03 (dd, *J* = 10.8, 1H, H-1b), 1.93 (br s, 3H, 3×CH Ada), 1.76 – 1.65 (m, 7H, H-5, 3×CH_2 Ada), 1.63 – 1.55 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.44 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, MeOD) δ 83.1 (OCH_2-Ada), 80.7, 79.5 (C-3, C-4), 74.1, 72.6 (2×OCH_2 pentyl), 70.7, 69.8 (C-2, C-5), 62.1, 58.5 (C-1, C-6), 42.3 (NCH_3), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.2, 30.6 (2×CH_2 pentyl), 29.6 (3×CH Ada), 23.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3387, 2901, 2847, 2793, 2106, 1666, 1458, 1358, 1250, 1096, 1042, 988, 918, 826. $[\alpha]^{20}_D$: 11.5 (*c* 0.4, $CHCl_3$/MeOH; 2/1). HRMS: found *m/z* 412.3074 $[M+H]^+$, calcd for $[C_{23}H_{42}NO_5+H]^+$ 412.3058.

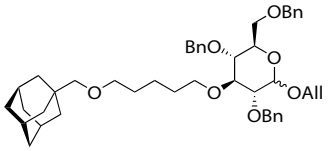


***N*-Butyl-4-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (13).** Compound **42** (83 mg, 104 µmol) was *N*-butylated and deprotected using the same procedure as described above for the synthesis of **12**, but substituting formaldehyde for butyraldehyde (200 µL, 2 mmol). The crude product was purified by silica gel column chromatography (0% » 10% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **13** (39 mg, 86 µmol) as a colorless oil in 83%. R_F = 0.72 (1:3; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 3.94 – 3.89 (m, 1H, OC*H*H pentyl), 3.83 (dd, $J_{H6a\text{-}H5}$ = 2.1, $J_{H6a\text{-}H6b}$ = 11.8, 1H, CH-6a), 3.75 (dd, $J_{H6b\text{-}H5}$ = 2.2, $J_{H6b\text{-}H6a}$ = 11.8, 1H, CH-6b), 3.65 – 3.59 (m, 1H, OCH*H* pentyl), 3.44 (ddd, *J* = 4.7, 10.0, 14.6, 1H, H-2), 3.38 (t, *J* = 6.3, 2H, OCH_2 pentyl), 3.24 – 3.19 (m, 2H, H-3, H-4), 2.97 – 2.93 (m, 3H, H-1a, OCH_2-Ada), 2.76 (m, 1H, NC*H*H butyl), 2.58 (m, 1H, NCH*H* butyl), 2.15 – 2.07 (m, 2H, H-1b, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.55 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.48 – 1.41 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.30 (m, 2H, CH_2 butyl), 0.94 (t, *J* = 7.2, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.0 (OCH_2-Ada), 80.7, 79.9 (C-3, C-4), 74.0, 72.6 (2×OCH_2 pentyl), 71.0 (C-2), 66.6 (C-5), 58.5 (C-6), 57.5 (C-1), 53.3 (NCH_2 butyl), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.2, 30.6 (2×CH_2 pentyl), 29.8 (3×CH Ada), 27.3 (CH_2 butyl), 23.9 (CH_2 pentyl), 21.8 (CH_2 butyl), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3364, 2901, 2847, 1666, 1458, 1366, 1250, 1103, 1042, 903, 818. $[\alpha]^{20}_D$: –2.5 (*c* 0.4, $CHCl_3$/MeOH; 1/1). HRMS: found *m/z* 454.3539 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

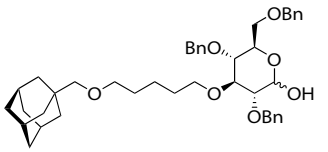


1,2:5,6-Di-*O*-isopropylidene-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-α-D-glucofuranoside (44). 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**43**: 222 mg, 0.85 mmol) was alkylated with bromide **25** using General procedure C. The resulting residue was purified by silica gel column chromatography (0% » 20% EtOAc in PE) to furnish **44** (413 mg, 0.84 mmol) in 98% yield as a colorless oil. R_F = 0.61 (1:4; EtOAc:PE). ^{1}H NMR (600 MHz, $CDCl_3$, COSY) δ 5.87 (d, *J* = 3.7, 1H, H-1), 4.53 (d, $J_{H2\text{-}H1}$ = 3.7, 1H, H-2), 4.30 (m, 1H, H-5), 4.12 (dd, *J* = 3.0, 7.6, 1H, H-4), 4.08 (dd, $J_{H6a\text{-}H6b}$ = 8.5, $J_{H6a\text{-}H5}$ = 6.3, 1H, H-6a), 3.99 (dd, $J_{H6b\text{-}H6a}$ = 8.5, $J_{H6b\text{-}H5}$ = 6.0, 1H, H-6b), 3.85 (d, *J* = 3.0, 1H, H-3), 3.61 (m, 1H, OC*H*H pentyl), 3.52 (m, 1H, OCH*H* pentyl), 3.40 (m, 2H, OCH_2 pentyl), 3.00 (s, 2H, OCH_2-Ada), 1.95 (br s, 3H, 3×CH Ada), 1.68 (m, 6H, 3×CH_2 Ada), 1.58 (m, 4H, 2×CH_2 pentyl) 1.52 (br d, 6H, 3×CH_2 Ada), 1.50 (s, 3H, CH_3 isopropylidene), 1.43 (s, 3H, CH_3 isopropylidene), 1.40 (m, 2H, CH_2-3 pentyl), 1.35 (s, 3H, CH_3 isopropylidene), 1.32 (s, 3H, CH_3 isopropylidene). ^{13}C NMR (150 MHz, $CDCl_3$) δ 111.6, 108.8 (2×C_q isopropylidene), 105.1 (C-1), 82.5, 82.0, 81.1 (C-2, C-3, C-4), 81.8 (OCH_2-Ada), 72.4 (C-5), 71.3, 70.4 (2×OCH_2 pentyl), 67.1 (C-6), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 34.0 (C_q Ada), 29.5, 29.3 (2×CH_2 pentyl), 28.2 (3×CH Ada), 26.7, 26.6, 26.1, 25.3 (4×CH_3 isopropylidene), 22.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1454, 1369, 1254, 1215, 1157, 1072, 1018, 957, 914, 849, 637. $[\alpha]^{20}_D$:

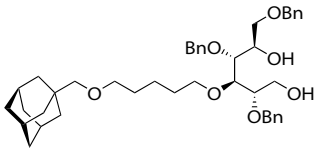
–16.7 (*c* 0.5, $CHCl_3$). HRMS: found *m/z* 495.3341 $[M+H]^+$; 512.3598 $[M+NH_4]^+$, calcd for $[C_{28}H_{46}O_7+H]^+$ 495.3316; $[C_{28}H_{46}O_7+NH_4]^+$ 512.3582.



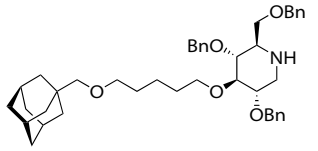
α/β-Mixture of allyl 2,4,6-tri-*O*-benzyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-D-glucopyranoside (45). Compound **44** (383 mg, 0.77 mmol) was dissolved in AcOH (6 mL) and water (2 mL). The resulting solution was refluxed for 5 h at 105 °C. The reaction mixture was concentrated and coevaporated with allyl alcohol. The residue was dissolved in allyl alcohol (1.6 mL), which contained 5 mol % HCl (generated by prior addition of AcCl). The reaction mixture was refluxed for 24 h, after which TLC analysis showed disappearance of the starting material (R_F = 0.07 in EtOAc:PE; 3:1) and the appearance two products (R_F = 0.85; 0.76 in MeOH:EtOAc; 1:4). The reaction was quenched (Et_3N, 0.3 mL), concentrated and coevaporated with toluene. The residue was dissolved in DMF (4 mL) and BnBr (380 µL, 3.2 mmol) was added. The reaction mixture was cooled to 0 °C and NaH (128 mg; 60% wt in mineral oil, 3.2 mmol) was added. The reaction was stirred for 20 h, warming to rt, after which TLC analysis indicated incomplete conversion. Additional BnBr (48 µL, 0.40 mmol) was added, the reaction mixture was cooled to 0 °C and additional NaH was added (16 mg; 60% wt in mineral oil, 0.40 mmol). After stirring for 20 h at rt, the reaction was quenched (water, 1 mL) and poured into water (100 mL). The aqueous layer was extracted repeatedly with Et_2O (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 15% EtOAc in PE) yielding **45** (313 mg, 0.43 mmol) as an α/β mixture in 56% over three steps as a colorless oil. R_F = 0.37; 0.33 (1:10; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) α/β mixture δ = 7.48 – 7.17 (m, 15H, H_{Ar} Bn), 5.97 – 5.85 (m, 1H, CH vinyl), 5.35 – 5.17 (m, 3H), 4.93 – 4.38 (m, 6H, 3×CH_2 Bn), 4.13 – 3.20 (m, 13H), 2.96 – 2.89 (m, 3H), 1.93 (br s, 3H, 3×CH Ada), 1.71 – 1.21 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) α/β mixture δ = 138.4, 138.2, 138.1, 137.7 (3×C_q Bn, α/β), 133.9, 133.6 (CH vinyl, α/β), 128.2, 128.0, 127.8, 127.7, 127.6, 127.5 (CH_{Ar}, Bn), 117.9, 116.9 (CH_2 vinyl, α/β), 102.5, 95.7 (C-1, α/β), 84.6, 82.0, 79.6, 77.6, 70.0 (CH, α/β), 81.7 (OCH_2-Ada), 77.6, 74.8, 73.6, 73.5, 73.3, 73.1, 71.3, 68.8, 68.3, 67.9 (CH_2, α/β), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 30.3, 29.4 (2×CH_2 pentyl), 28.1 (3×CH Ada), 22.8 (CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1724, 1497, 1454, 1362, 1312, 1273, 1150, 1092, 1069, 1030, 930, 748, 698. $[\alpha]^{20}_D$: 26.1 (*c* 0.4, $CHCl_3$). HRMS: found *m/z* 747.4255 $[M+Na]^+$, calcd for $[C_{46}H_{60}O_7+Na]^+$ 747.4231.



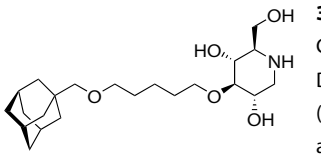
α/β-Mixture of 2,4,6-tri-*O*-benzyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-D-glucopyranose (46). The allyl-function in compound **45** (295 mg, 0.41 mmol) was cleaved using the same procedure as described for the synthesis of **38**. The crude product was purified by silica gel column chromatography (10% » 40% EtOAc in PE) to furnish **46** (211 mg, 0.31 mmol) as an α/β mixture in 75% yield as a colorless oil. R_F = 0.20 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$) major α-anomer δ = 7.36 – 7.17 (m, 15H, H_{Ar} Bn), 5.15 (d, $J_{H1\text{-}H2}$= 3.2, 1H, H-1), 4.84 – 4.42 (m, 6H, 3×CH_2 Bn), 3.86 – 3.31 (m, 10H, H-2, H-3, H-4, H-5, CH_2-6, 2×OCH_2 pentyl), 2.93 (s, 2H, OCH_2-Ada), 1.93 (br s, 3H, 3×CH Ada), 1.71 – 1.38 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (50 MHz, $CDCl_3$) α/β mixture δ = 138.4, 138.2, 138.0, 137.7 (3×C_q Bn, α+β), 128.3, 128.2, 127.9, 127.8, 127.6 (CH_{Ar}, Bn), 97.3, 91.2 (C-1 α+β), 84.6, 82.9, 81.6, 79.7, 77.7, 74.4, 70.0 (CH, α+β), 81.8 (OCH_2-Ada), 74.8, 74.6, 73.6, 73.3, 73.1, 71.3, 68.8, 68.5 (CH_2, α+β), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 34.0 (C_q Ada), 30.4, 29.5 (2×CH_2 pentyl), 28.2 (3×CH Ada), 22.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1724, 1497, 1454, 1362, 1315, 1258, 1207, 1153, 1073, 911, 733, 698. $[\alpha]^{20}_D$: 26.0 (*c* 0.2, $CHCl_3$). HRMS: found *m/z* 707.3930 $[M+Na]^+$, calcd for $[C_{43}H5_6O_7+Na]^+$ 707.3918.



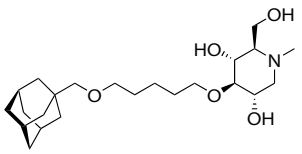
2,4,6-Tri-*O*-benzyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-D-glucitol (47). Compound **46** (211 mg, 0.31 mmol) was subjected to General procedure A. The resulting residue was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to give **47** (211 mg, 0.31 mmol) in quantitative yield as a colorless oil. R_F = 0.15 (1:3; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 15H, H_{Ar} Bn), 4.69 – 4.49 (m, 6H, 3×CH_2 Bn), 4.04 (m, 1H, H-5), 3.73 – 3.51 (m, 9H, CH_2-1, H-2, H-3, H-4, CH_2-6, OCH_2 pentyl), 3.32 (t, *J* = 6.5, 2H, OCH_2 pentyl), 2.93 (s, 2H, OCH_2-Ada), 2.44 (br s, 2H, OH-1, OH-5), 1.94 (br s, 3H, 3×CH Ada), 1.72 – 1.28 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.8, 137.7 (3×C_q Bn), 128.2, 128.0, 127.8, 127.7, 127.6 (CH_{Ar}, Bn), 81.8 (OCH_2-Ada), 80.1, 79.1, 76.9 (C-2, C-3, C-4), 73.3, 73.0, 72.9, 72.7, 71.3, 71.1 (3×CH_2 Bn, 2×OCH_2 pentyl, C-6), 70.6 (C-5), 61.7 (C-1), 39.6 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 29.9, 29.3 (2×CH_2 pentyl), 28.2 (3×CH Ada), 22.5 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3464, 2901, 2847, 1497, 1454, 1358, 1315, 1207, 1088, 1026, 910, 814, 733, 694. [α]$^{20}_D$: 1.3 (*c* 1.2, $CHCl_3$). HRMS: found *m/z* 687.4270 [M+H]$^+$; 709.4063 [M+Na]$^+$, calcd for [$C_{43}H_{58}O_7$+H]$^+$ 687.4255; [$C_{43}H_{58}O_7$+Na]$^+$ 709.4075.



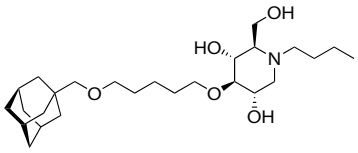
2,4,6-Tri-*O*-benzyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (48). Compound **47** (132 mg, 0.20 mmol) was treated according to General procedure B and double reductive amination method A. The crude product was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to provide **48** (89 mg, 0.13 mmol) in 67% yield as a colorless oil. R_F = 0.32 (1:2; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.53 – 7.23 (m, 15H, H_{Ar} Bn), 4.86 (d, *J* = 10.9, 1H, C*H*H Bn), 4.70 (d, *J* = 11.7, 1H, C*H*H Bn), 4.63 (d, *J* = 11.7, 1H, CH*H* Bn), 4.49 (d, *J* = 10.9, 1H, CH*H* Bn), 4.42 (d, *J* = 11.8, 1H, CH Bn), 4.40 (d, *J* = 11.8, 1H, CH Bn), 3.90 (dt, *J* = 9.0, 6.8, 1H, OC*H*H pentyl), 3.78 (dt, *J* = 9.0, 6.8, 1H, OCH*H* pentyl), 3.64 (dd, $J_{H6a\text{-}H5}$ = 2.4, $J_{H6a\text{-}H6b}$ = 9.0, 1H, H-6a), 3.49 (dd, $J_{H6b\text{-}H5}$ = 5.9, $J_{H6b\text{-}H6a}$ = 9.0, 1H, H-6b), 3.43 – 3.23 (m, 5H, H-2, H-3, H-4, OCH_2 pentyl), 3.19 (dd, $J_{H1a\text{-}H2}$ = 4.8, $J_{H1a\text{-}H1b}$ = 12.1, 1H, H-1a), 2.92 (s, 2H, OCH_2-Ada), 2.67 (ddd, $J_{H5\text{-}H6a}$ = 2.4, $J_{H5\text{-}H6b}$ = 5.9, $J_{H5\text{-}H4}$ = 9.2, 1H, H-5), 2.45 (dd, $J_{H1b\text{-}H2}$ = 10.2, $J_{H1b\text{-}H1a}$ = 12.1, 1H, H-1b), 2.40 (br s, 1H, NH), 1.93 (br s, 3H, 3×CH Ada), 1.72 – 1.35 (m, 18H, 6×CH_2 Ada, 3×CH_2 pentyl). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.4, 137.9 (3×C_q Bn), 128.3, 128.0, 127.8, 127.6, 127.5 (CH_{Ar}, Bn), 87.3, 80.4, 80.0 (C-2, C-3, C-4), 81.8 (OCH_2-Ada), 75.1, 73.7, 73.3, 72.8, 71.5, 70.2 (3×CH_2 Bn, 2×OCH_2 pentyl, C-6), 59.6 (C-5), 48.1 (C-1), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 30.5, 29.6 (2×CH_2 pentyl), 28.3 (3×CH Ada), 22.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 1724, 1497, 1454, 1362, 1265, 1096, 1069, 1026, 733, 698. [α]$^{20}_D$: 19.9 (*c* 1.8, $CHCl_3$). HRMS: found *m/z* 668.4319 [M+H]$^+$, calcd for [$C_{43}H_{57}NO_5$+H]$^+$ 668.4310.



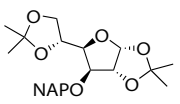
3-*O*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (14). Compound **48** (53 mg, 80 μmol) was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in EtOAc with 0.5% NH_4OH) to give **14** (28 mg, 69 μmol) as an off-white solid in 86% yield. R_F = 0.22 (1:3; MeOH:EtOAc + 0.5% NH_4OH). ^{1}H NMR (400 MHz, $CDCl_3$:MeOD; 2:1, COSY) δ 3.93 – 3.80 (m, 4H, CH_2-6, OCH_2 pentyl), 3.76 (m, 1H, H-2), 3.57 (dd, *J* = 9.1, 9.1, 1H, H-4), 3.42 (t, *J* = 6.5, 2H, OCH_2 pentyl), 3.31 (dd, $J_{H1a\text{-}H2}$ = 4.4, $J_{H1a\text{-}H1b}$ = 12.4, 1H, H-1a), 3.19 (m, 1H, H-3), 2.99 (s, 2H, OCH_2-Ada), 2.98 (m, 1H, H-5), 2.78 (dd, *J* = 11.9, 1H, H-1b), 1.96 (br s, 3H, 3×CH Ada), 1.75 – 1.57 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.54 (br d, *J* = 2.3, 6H, 3×CH_2 Ada), 1.42 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (100 MHz, $CDCl_3$:MeOD; 2:1) δ 84.2 (C-3), 81.5 (OCH_2-Ada), 72.8, 71.2 (2×OCH_2 pentyl), 67.7, 67.0 (C-2, C-4), 60.3 (C-5), 57.7 (C-6), 46.0 (C-1), 39.1 (3×CH_2 Ada), 36.6 (3×CH_2 Ada), 33.6 (C_q Ada), 29.4, 28.7 (2×CH_2 pentyl), 27.8 (3×CH Ada), 21.9 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3358, 2901, 2847, 1674, 1597, 1448, 1344, 1186, 1103, 1026, 733, 623. [α]$^{20}_D$: 17.4 (*c* 0.5, MeOH). HRMS: found *m/z* 398.2892 [M+H]$^+$, calcd for [$C_{22}H_{39}NO_5$+H]$^+$ 398.2901.



***N*-Methyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-nojirimycin (15).** Argon was passed through a solution of compound **48** (42 mg, 63 µmol) and formaldehyde (160 µL, 2 mmol; 37 wt % in water) in MeOH (2 mL) for 5 min, after which a catalytic amount of Pd/C Degussa type (30 mg, 5 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 10 min. After stirring the reaction under atmospheric hydrogen pressure for 1 h, TLC analysis full conversion to the intermediate product (R_F = 0.54 in PE:EtOAc; 1:1). The Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH. The filtrate was concentrated and coevaporated once with toluene. The crude intermediate product was deprotected using General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in EtOAc with 0.5% NH_4OH) to give **15** (22 mg, 52 µmol) as an off-white solid in 83% yield. R_F = 0.38 (1:3; MeOH:EtOAc + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD) δ 4.04 (d, $J_{H6a\text{-}H6b}$ = 12.2, 1H, H-6a), 3.88 (dd, $J_{H6b\text{-}H6a}$ = 12.2, $J_{H6b\text{-}H5}$ = 2.7, 1H, H-6b), 3.85 (m, 2H, OCH_2 pentyl), 3.70 (m, 1H, H-2), 3.60 (dd, *J* = 9.4, 9.4, 1H, H-4), 3.38 (t, *J* = 6.4, 2H, OCH_2 pentyl), 3.32 (dd, $J_{H1a\text{-}H2}$ = 4.7, $J_{H1a\text{-}H1b}$ = 12.1, 1H, H-1a), 3.15 (dd, *J* = 9.4, 9.4, 1H, H-3), 2.96 (s, 2H, OCH_2-Ada), 2.95 – 2.83 (m, 5H, H-1b, NCH_3, H-5), 1.93 (br s, 3H, 3×CH Ada), 1.7 – 1.63 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.60-1.55 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.44 (m, 2H, CH_2-3 pentyl). ^{13}C NMR (150 MHz, MeOD) δ 86.6 (C-3), 83.1 (OCH_2-Ada), 74.5, 72.7 (2×OCH_2 pentyl), 69.3, 68.7, 68.0 (C-2, C-4, C-5), 58.9 (C-6 and C-1 overlap), 41.3 (NCH_3), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.1, 30.5 (2×CH_2 pentyl), 29.7 (3×CH Ada), 23.7 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3351, 2903, 2847, 1657, 1454, 1358, 1101, 1040, 1020, 959, 611. $[\alpha]^{20}_D$: 6.9 (*c* 0.6, MeOH). HRMS: found *m/z* 412.3047 $[M+H]^+$, calcd for $[C_{23}H_{42}NO_5+H]^+$ 412.3058.

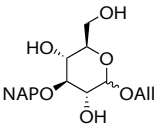


***N*-Butyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxy-nojirimycin (16).** Compound **48** (42 mg, 63 µmol) was *N*-butylated and deprotected using the same procedure as described above for the synthesis of **15**, but substituting formaldehyde for butyraldehyde (80 µL, 1 mmol). The resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in EtOAc with 0.5% NH_4OH) to give **16** (28 mg, 63 µmol) as an off-white solid in 99% yield. R_F = 0.74 (1:3; MeOH:EtOAc + 0.5% NH_4OH). ^{1}H NMR (600 MHz, MeOD:acetone-*d6*; 3:1) δ 4.09 (m, 1H, H-6a), 3.90 (m, 1H, H-6b), 3.83 (m, 2H, OCH_2 pentyl), 3.77 (m, 1H, H-2), 3.66 (m, 1H, H-4), 3.43 (m, 1H, H-1a), 3.38 (m, 3H, OCH_2 pentyl, NC*H*H butyl), 3.24 – 3.20 (m, 2H, H-3, NCH*H* butyl), 3.09 (m, 1H, H-5), 3.01 (m, 1H, H-1b), 2.96 (s, 2H, OCH_2-Ada), 1.94 (br s, 3H, 3×CH Ada), 1.76 – 1.64 (m, 10H, 3×CH_2 Ada, CH_2 pentyl, CH_2 butyl), 1.58 – 1.55 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.43 (m, 4H, CH_2 pentyl, CH_2 butyl), 1.00 (t, *J* = 7.1, 3H, CH_3 butyl). ^{13}C NMR (150 MHz, $CDCl_3$:MeOD; 2:1) δ 81.6 (OCH_2-Ada), 71.3 (OCH_2 pentyl), 66.8, 65.8 (2×CH), 39.2 (3×CH_2 Ada), 36.7 (3×CH_2 Ada), 33.7 (C_q Ada), 29.5, 28.8 (2×CH_2 pentyl), 27.9 (3×CH Ada), 22.0 (CH_2), 19.4 (CH_2), 12.8 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3341, 2903, 2847, 1672, 1456, 1364, 1103, 1030, 1030, 608. $[\alpha]^{20}_D$: 2.8 (*c* 0.5, MeOH). HRMS: found *m/z* 454.3509 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

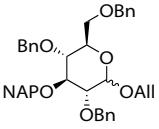


1,2:5,6-Di-*O*-isopropylidene-3-*O*-(2-naphthylmethyl)-α-D-glucofuranoside (49). A dry solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoside (**43**: 2.140 g, 8.22 mmol) in DMF (16.4 mL) was cooled to 0 °C. The solution was charged with NaH (362 mg, 60% wt in mineral oil, 9.04 mmol) and stirred at 0 °C for 30 min after which 2-bromomethylnaphthalene (2 g, 9.04 mmol) was added. The reaction mixture was stirred for 20 h, warming to rt. The reaction mixture was quenched (water, 1 mL), concentrated and redissolved in Et_2O (100 mL). The organic layer was washed successively with water (50 mL) and sat aq NaCl (50 mL), dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (5% » 25% EtOAc in PE) to furnish **49**[35] (3.224 g, 8.06 mmol) in 98% yield as a colorless

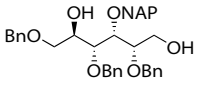
oil. R_F = 0.74 (1:6; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.77 – 7.75 (m, 4H, H_{Ar} NAP), 7.45 – 7.39 (m, 3H, H_{Ar} NAP), 5.91 (d, *J* = 3.7, 1H, H-1), 4.78 (d, *J* = 12.1, 1H, C*H*H NAP), 4.71 (d, *J* = 12.1, 1H, CH*H* NAP), 4.59 (d, $J_{H2\text{-}H1}$ = 3.7, 1H, H-2), 4.43 (m, 1H, H-5), 4.18 (dd, *J* = 3.1, 7.8, 1H, H-4), 4.13 (dd, $J_{H6a\text{-}H6b}$ = 8.5, $J_{H6a\text{-}H5}$ = 6.3, 1H, H-6a), 4.06 (d, *J* = 2.5, 1H, H-3), 4.04 (dd, $J_{H6b\text{-}H6a}$ = 8.5, $J_{H6b\text{-}H5}$ = 5.8, 1H, H-6b), 1.47 (s, 3H, CH_3 isopropylidene), 1.42 (s, 3H, CH_3 isopropylidene), 1.37 (s, 3H, CH_3 isopropylidene), 1.26 (s, 3H, CH_3 isopropylidene). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 134.9, 133.0, 132.8 (3×C_q NAP), 127.9, 127.6, 127.4, 126.1, 125.9, 125.7, 125.4 (7×H_{Ar} NAP), 111.4, 108.7 (2×C_q isopropylidene), 105.1 (C-1), 82.4 (C-2), 81.4 (C-3), 81.1 (C-4), 72.3 (C-5), 72.0 (CH_2 NAP), 67.1 (C-6), 26.6, 26.5, 26.0, 25.2 (4×CH_3 isopropylidene). IR ν_{max}(thin film)/ cm^{-1}: 2986, 2932, 1454, 1369, 1339, 1254, 1211, 1165, 1126, 1069, 1015, 953, 887, 845, 818, 748, 637. $[\alpha]^{20}_D$: –30.0 (*c* 4.1, $CHCl_3$). HRMS: found *m/z* 401.1951 $[M+H]^+$, calcd for $[C_{23}H_{28}O_6+H]^+$ 401.1959.



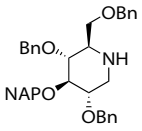
α/β-Mixture of allyl 3-*O*-(2-naphthylmethyl)-D-glucopyranoside (50). To a solution of compound **49** (404 mg, 1.01 mmol) in allylalcohol (10 mL), water (37 µL, 2.02 mmol) and Amberlite resin (170 mg, IR-120 H^+-form) were added. The reaction mixture was heated at 102 °C for 20 h. The reaction was filtered and the resin was washed with MeOH. The filtrate was concentrated and the resulting residue was purified by silica gel column chromatography (50% » 100% EtOAc in PE) yielding a 2:1 α/β mixture of **50** (182 mg, 0.51 mmol) in 50% as a white solid. R_F = 0.29; 0.23 (3:1; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) α/β mixture δ = 7.78 – 7.76 (m, 4H, H_{Ar} NAP, α/β), 7.49 – 7.40 (m, 3H, H_{Ar} NAP, α/β), 5.92 – 5.81 (m, 1H, CH vinyl, α/β), 5.29 – 5.16 (m, 2H, CH_2 vinyl, α/β), 5.08 (d, *J* = 11.7, 1H, C*H*H NAP, α), 5.06 (d, *J* = 11.7, 1H, C*H*H NAP, β), 4.92 (d, *J* = 11.7, 1H, CH*H* NAP, β), 4.90 (d, *J* = 11.7, 1H, CH*H* NAP, α), 4.82 (s, 1H, H-1, α), 4.28 (m, 1H, OC*H*H Allyl, β), 4.26 (d, *J* = 7.6, 1H, H-1, β), 4.12 (dd, *J* = 5.3, 12.8, 1H, OC*H*H Allyl, α), 4.12 (dd, *J* = 6.3, 12.8, 1H, OCH*H* Allyl, β), 3.94 (dd, *J* = 6.3, 12.8, 1H, OCH*H* Allyl, α), 3.80 – 3.70 (m, 4H, CH_2-6, α+β), 3.64 – 3.60 (m, 5H, H-2, H-3, H-4, H-5, α; H-4, β), 3.51 (dd, 1H, H-2, β), 3.42 (m, 1H, H-3, β), 3.21 (m, 1H H-5, β), 3.04 – 2.59 (3×br s, 3H, OH). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) α/β mixture δ = 135.9, 135.8, 133.2, 132.9 (3×C_q NAP, α/β), 133.6, 133.4 (CH vinyl, α/β), 128.2, 128.1, 127.8, 127.6, 126.7, 126.5, 126.2, 126.0, 125.8 (CH_{Ar} NAP, α/β), 117.9 (CH_2 vinyl, α/β), 101.8 (C-1, β), 97.6 (C-1, α), 83.6 (C-3, β), 82.6 (C-3, α), 75.3, 74.1 (C-2, C-5, β), 74.9 (CH_2 NAP, α), 74.6 (CH_2 NAP, β), 72.5 (C-2, α), 71.3, 69.7 (C-4, C-5, α), 70.3 (OCH_2 Allyl, β), 68.4 (OCH_2 Allyl , α), 61.9 (C-6, β), 61.7 (C-6, α). IR ν_{max}(thin film)/ cm^{-1}: 3387, 2924, 2874, 1508, 1458, 1346, 1273, 1026, 926, 895, 857, 814, 748, 621. $[\alpha]^{20}_D$: 62.6 (*c* 3.6, $CHCl_3$). HRMS: found *m/z* 383.1447 $[M+Na]^+$, calcd for $[C_{20}H_{24}O_6+Na]^+$ 383.1465.



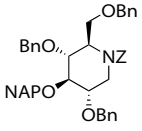
α/β-Mixture of allyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-naphthylmethyl)-D-glucopyranoside (51). A dry solution of compound **50** (182 mg, 0.51 mmol) in DMF (5 mL) was charged with BnBr (198 µL, 1.67 mmol). The reaction mixture was cooled to 0 °C and NaH (67 mg; 60% wt in mineral oil, 1.67 mmol) was added. The reaction was stirred for 20 h, warming to rt, after which TLC analysis indicated complete conversion and the reaction was quenched (water, 0.2 mL). The mixture was poured into water (50 mL) and the aqueous layer was extracted repeatedly with Et_2O (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 15% EtOAc in PE) giving an α/β mixture of **51** (286 mg, 0.45 mmol) in 90% as a colorless oil. R_F = 0.62; 0.58 (1:3; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) α/β mixture δ 7.75 – 7.67 (m, 4H, H_{Ar} NAP, α/β), 7.47 – 7.07 (m, 18H, H_{Ar} Bn/NAP, α/β), 5.98 – 5.87 (m, 1H, CH vinyl, α/β), 5.35 – 4.41 (m, 11H, α/β), 4.15 – 4.31 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) α/β mixture δ 139.3, 139.2, 138.9, 137.4, 135.1, 134.8, 134.7, 134.4, 133.9, 129.2, 128.5, 127.0, 126.7, 119.1, 118.1, 104.4, 103.7, 97.7, 96.7, 85.7, 83.3, 83.1, 82.9, 81.0, 80.2, 79.6, 78.9, 78.8, 76.7, 76.6, 76.1, 76.0, 75.9, 75.8, 74.4, 74.0, 71.3, 71.2, 70.7, 69.5, 69.3, 69.2, 63.7. IR ν_{max}(thin film)/ cm^{-1}: 2866, 1497, 1454, 1362, 1269, 1207, 1069, 1026, 930, 856, 818, 733, 694. $[\alpha]^{20}_D$: 19.4 (*c* 0.4, $CHCl_3$). HRMS: found *m/z* 653.2828 $[M+Na]^+$, calcd for $[C_{41}H_{42}O_6+Na]^+$ 653.2874.



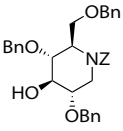
2,4,6-Tri-*O*-benzyl-3-*O*-(2-naphthylmethyl)-D-glucitol (52). The allyl-function in **51** (397 mg, 0.63 mmol) was cleaved using the same procedure as described for the synthesis of **38**. The crude hemiacetal intermediate was reduced with $LiALH_4$ using General procedure A (R_F hemiacetal = 0.21; 0.15 in EtOAc:PE; 1:4). The resulting residue was purified by silica gel column chromatography (25% » 50% EtOAc in PE) to give product **52** (254 mg, 0.43 mmol) over two steps in 68% yield as a colorless oil. R_F = 0.1 (1:2; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 – 7.70 (m, 4H, H_{Ar} NAP), 7.48 – 7.41 (m, 3H, H_{Ar} NAP), 7.34 – 7.17 (15H, H_{Ar} Bn), 4.86 (d, *J* = 11.5, 1H, C*H*H Bn/NAP), 4.80 (d, *J* = 11.5, 1H, CH*H* Bn/NAP), 4.66 (d, *J* = 11.6, 1H, CH Bn/NAP), 4.63 – 4.50 (m, 4H, 4×CH Bn), 4.46 (d, *J* = 11.9, 1H, CH Bn/NAP), 4.05 (m, 1H, H-5), 3.95 (dd, *J* = 3.7, 6.3, 1H), 3.84 – 3.72 (m, 3H), 3.68 – 3.55 (m, 3H), 3.04 (br s, 1H, OH-1 or OH-5), 2.22 (br s, 1H, OH-1 or OH-5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.9, 137.8, 135.3, 133.1, 132.9 (3×C_q Bn, 3×C_q NAP), 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.1, 126.2, 126.1, 125.9 (CH_{Ar} Bn/NAP), 79.5, 79.2, 77.3 (C-2, C-3, C-4), 74.6, 73.4, 73.2, 73.0 (3×CH_2 Bn, CH_2 NAP), 71.1 (C-6), 70.7 (C-5), 61.8 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3445, 3032, 2870, 1497, 1454, 1362, 1207, 1065, 1026, 952, 895, 856, 818, 733, 694. $[\alpha]^{20}_D$: 10.5 (*c* 2.7, $CHCl_3$). HRMS: found *m/z* 593.2872 $[M+H]^+$, calcd for $[C_{38}H_{40}O_6+H]^+$ 593.2898.



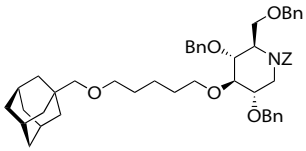
2,4,6-Tri-*O*-benzyl-3-*O*-(2-naphthylmethyl)-1-deoxynojirimycin (53). Compound **53** was synthesized from **52** (142 mg, 0.24 mmol) via General procedure B with double reductive amination method A. The crude product was purified by silica gel column chromatography (33% » 75% EtOAc in PE) to provide **53** (89 mg, 0.13 mmol) in 53% yield as a crystalline solid. R_F = 0.61 (2:1; EtOAc:PE). ^{1}H NMR (300 MHz, $CDCl_3$, COSY) δ 7.82 – 7.71 (m, 4H, H_{Ar} NAP), 7.48 – 7.42 (m, 3H, H_{Ar} NAP), 7.34 – 7.16 (15H, H_{Ar} Bn), 5.13 (d, *J* = 11.2, 1H, C*H*H Bn/NAP), 4.97 (d, *J* = 11.2, 1H, CH*H* Bn/NAP), 4.87 (d, *J* = 11.0, 1H, CH Bn/NAP), 4.71 (d, *J* = 12.0, 1H, C*H*H Bn/NAP), 4.67 (d, *J* = 12.0, 1H, CH*H* Bn/NAP), 4.56 – 4.41 (m, 3H, 3×CH Bn), 3.69 (dd, $J_{H6a\text{-}H5}$ = 2.2, $J_{H6a\text{-}H6b}$ = 9.0, 1H, H-6a), 3.61 (dd, *J* = 9.0, 9.0, 1H, H-3), 3.57 – 3.53 (m, 2H, H-2, H6b), 3.41 (dd, *J* = 9.1, 9.1, 1H, H-4), 3.29 (dd, $J_{H1a\text{-}H2}$ = 4.6, $J_{H1a\text{-}H1b}$ = 12.2, 1H, H-1a), 2.76 (ddd, $J_{H5\text{-}H6a}$ = 2.4, $J_{H5\text{-}H6b}$ = 5.7, $J_{H5\text{-}H4}$ = 9.8, 1H, H-5), 2.53 (dd, $J_{H1b\text{-}H2}$ = 10.2, $J_{H1b\text{-}H1a}$ = 12.1, 1H, H-1b), 2.23 (br s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.3, 137.9, 135.3, 133.0 (3×C_q Bn, 3×C_q NAP), 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 126.4, 126.1, 125.9, 125.7 (CH_{Ar} Bn/NAP), 87.1, 80.3, 79.8 (C-2, C-3, C-4), 75.7, 75.2, 73.4, 72.8 (3×CH_2 Bn, CH_2 NAP), 69.9 (C-6), 59.7 (C-5), 47.9 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3028, 2858, 1497, 1454, 1362, 1269., 1207, 1092, 1061, 1026, 949, 895, 856, 818, 733, 694. $[\alpha]^{20}_D$: 10.0 (*c* 0.1, $CHCl_3$). HRMS: found *m/z* 574.2928 $[M+H]^+$, calcd for $[C_{38}H_{39}NO_4+H]^+$ 574.2952.



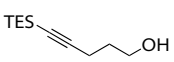
2,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-3-*O*-(2-naphthylmethyl)-1-deoxynojirimycin (54). Compound **53** (89 mg, 0.13 mmol) was protected with a Z-carbamate function using the same procedure as described for the synthesis of **33**. The resulting residue was purified by silica gel column chromatography (15% » 25% EtOAc in PE) to provide **54** (72 mg, 0.10 mmol) in 81% yield as a colorless oil. R_F = 0.35 (1:4; EtOAc:PE). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) δ 7.82 – 7.65 (m, 4H, H_{Ar} NAP), 7.48 – 7.34 (m, 3H, H_{Ar} NAP), 7.32 – 7.22 (20H, H_{Ar} Bn, H_{Ar} Z), 5.13 (d, *J* = 12.4, 1H, C*H*H Bn/NAP/Z), 5.08 (d, *J* = 12.4, 1H, CH*H* Bn/NAP/Z), 4.78 – 4.42 (m, 7H, 7×CH Bn/NAP/Z), 4.34 (d, *J* = 12.0, 1H, CH Bn/NAP/Z), 4.23 – 4.14 (m, 2H, H-1a, H-5), 3.94 (dd, *J* = 6.3, 1H, H-4), 3.79 (dd, *J* = 4.3, 6.5, 1H, H-3), 3.71-3.62 (m, 3H, H-2, CH_2-6), 3.36 (dd, $J_{H1b\text{-}H2}$ = 3.3, $J_{H1b\text{-}H1a}$ = 14.4, 1H, H-1b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (C=O Z), 138.3, 138.2, 138.0, 136.6, 135.6, 133.1 (3×C_q Bn, 3×C_q NAP, C_q Z), 128.4, 128.3, 128.0, 127.8, 127.6, 127.5, 127.4, 126.4, 126.0, 125.8, 125.7 (CH_{Ar} Bn, CH_{Ar} NAP, CH_{Ar} Z), 81.6, 78.1, 74.1 (C-2, C-3, C-4), 73.1, 72.9, 70.6 (3×CH_2 Bn, CH_2 NAP), 68.4 (C-6), 67.2 (CH_2 Z), 55.7 (C-5), 41.2 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 2858, 1693, 1497, 1455, 1424, 1354, 1312, 1250, 1219, 1069, 1026, 964, 910, 856, 818, 733, 694. $[\alpha]^{20}_D$: 4.3 (*c* 0.1, $CHCl_3$). HRMS: found *m/z* 708.3288 $[M+H]^+$, calcd for $[C_{46}H_{45}NO_6+H]^+$ 708.3320.



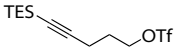
2,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-deoxynojirimycin (55). A dry solution of compound **54** (72 mg, 102 µmol) in a mixture of DCM (4.8 mL) and MeOH (1.2 mL) was charged with DDQ (69 mg, 306 µmol). The reaction mixture was stirred for 5 h, after which TLC analysis showed complete consumption of **54**. The reaction mixture was diluted with DCM (15 mL) and washed successively with sat aq $NaHCO_3$ (20 mL) and sat aq NaCl (20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (20% » 50% EtOAc in PE) to furnish **55** (49 mg, 86 µmol) in 85% yield as a colorless oil. R_F = 0.25 (1:3; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$, COSY) δ 7.33 – 7.23 (m, 20H, H_{Ar} Bn, H_{Ar} Z), 5.12 (d, *J* = 12.3, 1H, C*H*H Z), 5.07 (d, *J* = 12.3, 1H, CH*H* Z), 4.67 – 4.51 (m, 4H, 4×CH Bn), 4.47 (d, *J* = 11.8, 1H, C*H*H Bn), 4.38 (d, *J* = 11.8, 1H, CH*H* Bn), 4.16 (br s, 1H, H-5), 4.09 (d, *J* = 14.0, 1H, H-1a), 3.87 (m, 1H, H-3), 3.75 – 3.56 (m, 3H, H-2, CH_2-6), 3.44 (dd, $J_{H1b\text{-}H2}$ = 3.9, $J_{H1b\text{-}H1a}$ = 14.3, 1H, H-1b), 3.10 (br s, 1H, OH-3). ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) δ 155.7 (C=O Z), 138.2, 138.0, 137.4, 136.5 (3×C_q Bn, C_q Z), 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 127.5 (CH_{Ar} Bn, CH_{Ar} Z), 78.4 (C-2), 77.4 (C-4), 73.3 (C-3), 73.4, 73.2, 70.8 (3×CH_2 Bn), 70.2 (C-6), 67.2 (CH_2 Z), 56.2 (C-5), 42.5 (C-1). IR ν_{max}(thin film)/ cm^{-1}: 3418, 3032, 2866, 1670, 1497, 1454, 1427, 1354, 1250, 1215, 1069, 1026, 910, 733, 694. $[\alpha]^{20}_D$: –14.0 (*c* 0.1, $CHCl_3$). HRMS: found *m/z* 568.2671 $[M+H]^+$, calcd for $[C_{35}H_{37}NO_6+H]^+$ 568.2694.



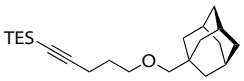
2,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-3-*O*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (56). Compound **55** (45 mg, 0.08 mmol) was alkylated with bromide **25** using General procedure C. The resulting residue was purified by silica gel column chromatography (5% » 33% EtOAc in PE) to provide product **56** (64 mg, 0.08 mmol) in quantitative yield as a colorless oil. Compound **56** could be deprotected using General procedure D to quantitatively yield **14**. R_F = 0.78 (1:2; EtOAc:PE). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 20H, H_{Ar} Bn/ Z), 5.11 (d, *J* = 12.3, 1H, C*H*H Z), 5.08 (d, *J* = 12.3, 1H, CH*H* Z), 4.72 (d, *J* = 11.6, 1H, C*H*H Bn), 4.68 – 4.64 (m, 1H, C*H*H Bn), 4.55 (d, *J* = 11.6, 1H, CH*H* Bn), 4.49 – 4.31 (m, 3H, CH*H* Bn, CH_2 Bn), 4.28 – 4.07 (m, 3H), 3.82 (dd, *J* = 6.0, 6.0, 1H), 3.63 (s, 1H), 3.60 – 3.49 (m, 4H, OCH_2 pentyl, 2×CH), 3.32 (t, *J* = 6.5, 2H, OCH_2 pentyl), 3.29 (dd, *J* = 2.9, 14.5, 1H), 2.93 (s, 2H, OCH_2-Ada), 1.94 (s, 3H, 3×CH Ada), 1.66 (dd, *J* = 11.9, 34.5, 6H, 3×CH_2 Ada), 1.57 – 1.48 (m, 10H, 3×CH_2 Ada, 2×CH_2 pentyl), 1.40 – 1.22 (m, 2H, CH_2-3 pentyl).^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0 (C(O) Z), 138.5, 138.3, 136.8 (C_q Bn/ Z), 128.6, 128.5, 128.1, 128.0, 127.7, 127.7 (CH_{Ar} Bn/ Z), 82.1, 78.3, 74.3, 73.3, 73.1, 71.6, 71.2, 70.8, 68.5, 68.3, 67.4, 55.7, 39.9 (CH_2 Ada), 37.4 (CH_2 Ada), 34.3 (C_q Ada), 30.1, 29.6 (2×CH_2 pentyl), 28.5 (CH Ada), 23.0 (CH_2-3 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 2900, 2847, 1697, 1497, 1450, 1421, 1359, 1310, 1219, 1096, 1026, 910, 741, 694 cm^{-1}. MS (ESI): *m/z* 802.5 $[M+H]^+$.



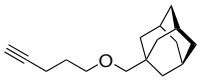
5-(Triethylsilyl)pent-4-yn-1-ol (58). A dry and cooled (–68 °C) solution of pent-4-yn-1-ol (**57**:1.85 mL, 20 mmol) in THF (20 mL) was charged with BuLi (27.5 mL, 44 mmol, 1.6M in toluene) and stirred at –68 °C for 1 h. Triethylsilylchloride (10 mL, 59.5 mmol) was added dropwise to the reaction and the mixture was stirred at –68 °C for 1 h, after which cooling was ceased and the solution was stirred for 18 h. 2M aq HCl (100 mL) was added and the reaction mixture was stirred for 48 h. The mixture was extracted with Et_2O (2×100 mL) and the combined organic layers were washed with water (2×100 mL). The organic phase was dried ($MgSO_4$), concentrated and the resulting residue was purified by silica gel column chromatography (5% » 25% EtOAc in PE) to provide product **58** (3.276 g, 16.50 mmol) in 83% yield as a colorless oil. R_F = 0.53 (3:7; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.75 (t, *J* = 6.2, 2H, $HOCH_2$-1 pent-4-yn), 2.44 (m, 1H, OH-1), 2.36 (t, *J* = 7.3, 2H, CH_2-3 pent-4-yn), 1.77 (m, 2H, CH_2-4 pent-4-yn), 0.98 (t, *J* = 8.0, 9H, 3×CH_3 $SiEt_3$), 0.57 (m, 6H, 3×CH_2 $SiEt_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 107.5, 81.4 (2×C_q pent-4-yn), 60.6 (OCH_2-1 pent-4-yn), 31.2 (CH_2-2 pent-4-yn), 16.0 (CH_2-3 pent-4-yn), 7.0 (3×CH_3 $SiEt_3$), 4.2 (3×CH_2 $SiEt_3$). IR ν_{max}(thin film)/ cm^{-1}: 3319, 2953, 2936, 2912, 2876, 2172, 1458, 1414, 1379, 1348, 1319, 1067, 1051, 1016, 982, 924, 845, 721, 635, 610. MS (ESI): *m/z* 199.3 $[M+H]^+$.



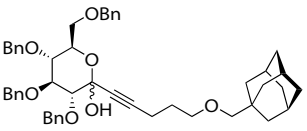
5-(Triethylsilyl)pent-4-ynyl trifluoromethanesulfonate (59). A dry solution of **58** (594 mg, 3 mmol) in DCM (30 mL) was cooled to –40 °C followed by addition of Et_3N (416 µL, 3 mmol). Next, Tf_2O (555 µL, 3.3 mmol) was added dropwise and the reaction mixture was stirred at –40 °C for 1 h. Cooling was ceased and the reaction mixture was concentrated at rt by means of a nitrogen flow. The residue was purified by silica gel column chromatography (isocratic 10% EtOAc in PE) and the product containing factions were concentrated under a nitrogen flow at rt to furnish **59** (885 mg, 2.68 mmol) in 89% yield as a colorless oil. R_F = 0.84 (EtOAc:PE; 3:7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (t, *J* = 6.1, 2H), 2.44 (t, *J* = 6.7, 2H), 2.02 (m, 2H), 0.98 (t, *J* = 7.9, 9H), 0.59 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.6 (q, $J_{C\text{-}F}$ = 319.7, 1C), 104.5, 84.0, 75.6, 28.2, 15.8, 7.2, 4.3. IR ν_{max}(thin film)/ cm^{-1}: 1462, 1416, 1246, 1204, 1142, 1069, 1007, 926, 806, 721.



[5-(Adamantan-1-yl-methoxy)-pent-1-ynyl]-triethylsilane (60). Compound **59** (885 mg, 2.68 mmol) was dissolved in DCM (54 mL), to which adamantanemethanol (2.23 g, 13.4 mmol) and K_2CO_3 (1.83 g, 13.4 mmol) were successively added. The reaction mixture was refluxed for 3 days, after which the solids were removed via filtration and the filtrate was concentrated. The residue was purified by silica gel column chromatography (0% » 10% EtOAc in toluene) to provide **60** (900 mg, 2.6 mmol) in 97% yield as a colorless oil. R_F = 0.84 (1:9; EtOAc:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.46 (t, *J* = 6.2, 2H, OCH_2-5 pentynyl), 2.96 (s, 2H, OCH_2-Ada), 2.33 (t, *J* = 7.3, 2H, CH_2-3 pentynyl), 1.95 (br s, 3H, 3×CH Ada), 1.83 – 1.60 (m, 8H, 3×CH_2 Ada, CH_2-4 pentynyl), 1.52 (br d, *J* = 3.0, 6H, 3×CH_2 Ada), 0.98 (t, *J* = 8.0, 9H, 3×CH_3 $SiEt_3$), 0.56 (m, 6H, 3×CH_2 $SiEt_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 108.1 (C_q-1 pentynyl), 82.0 (OCH_2-Ada), 81.4 (C_q-2 pentynyl), 69.8 (OCH_2-5 pentynyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.1 (C_q Ada), 29.0 (CH_2-4 pentynyl), 28.3 (3×CH Ada), 16.6 (CH_2-3 pentynyl), 7.4 (3×CH_3 $SiEt_3$), 4.5 (3×CH_2 $SiEt_3$). IR ν_{max}(thin film)/ cm^{-1}: 2901, 2847, 2176, 1458, 1420, 1366, 1234, 1150, 1111, 1018. HRMS: found *m/z* 347.2751 $[M+H]^+$, calcd for $[C_{22}H_{38}OSi+H]^+$ 347.2765.

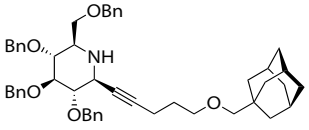


5-(Adamantan-1-yl-methoxy)-pent-1-yne (61). A dry solution of **60** (2.74 g, 7.92 mmol) in a mixture of THF (40 mL) and MeOH (40 mL) was charged with NaOMe (2.23 g, 41.2 mmol) and refluxed at 90 °C for 20 h. The reaction was quenched (water, 0.5 mL) and concentrated. The residue was dissolved in EtOAc (200 mL) and washed with water (2×200 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (2% » 10% acetone in PE) to provide **61** (1.70 g, 7.33 mmol) in 93% yield as a colorless oil. R_F = 0.80 (1:19; acetone:PE). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.48 (t, *J* = 6.3, 2H, OCH_2-5 pentynyl), 2.96 (s, 2H, OCH_2-Ada), 2.28 (dt, *J* = 2.9, 7.3, 2H, CH_2-3 pentynyl), 1.95 – 1.92 (m, 4H, 3×CH Ada, CH-1 pentynyl), 1.83 – 1.60 (m, 8H, 3×CH_2 Ada, CH_2-4 pentynyl), 1.48 (br d, *J* = 3.0, 6H, 3×CH_2 Ada). ^{13}C NMR (50 MHz, $CDCl_3$) δ 84.0 (C_q-2 pentynyl), 81.8 (OCH_2-Ada), 69.5 (OCH_2-5 pentynyl), 68.1 (CH-1 pentynyl), 39.5 (3×CH_2 Ada), 37.1 (3×CH_2 Ada), 33.9 (C_q Ada), 28.6 (CH_2-4 pentynyl), 28.2 (3×CH Ada), 15.6 (CH_2-3 pentynyl). IR ν_{max}(thin film)/ cm^{-1}: 3310, 2901, 2847, 2669, 1450, 1366, 1234, 1157, 1111, 9910, 725, 625. HRMS: found *m/z* 233.1897 $[M+H]^+$, calcd for $[C_{16}H_{24}O+H]^+$ 233.1900.

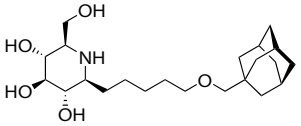


α/β-Mixture of 2,3,4,6-tetra-*O*-benzyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pent-1-ynyl)-D-glucose (62). A dry solution of **61** (536 mg, 2.31 mmol) in THF (12.5 mL) was cooled to –50 °C and BuLi (1.73 mL, 2.77 mmol, 1.6M in toluene) was added slowly to the solution. After stirring for 1 h at –50 °C, a dry solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone[39] (2.49 g, 4.62 mmol) in THF (12.5 mL) was slowly added and the reaction was stirred at –50 °C for 2 h. The reaction mixture was quenched (sat aq NH_4Cl, 1 mL), warmed to rt and poured into sat aq NH_4Cl (100 mL). The aqueous layer was extracted with Et_2O (3×50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (0% » 10% EtOAc in toluene) to provide **62** (1.364 g, 1.77 mmol) as an 1:1 anomeric mixture in 77% yield as a colorless oil. R_F = 0.68 (1:3; EtOAc:toluene). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) α/β mixture

δ = 7.42 – 7.11 (m, 40H, H_{Ar} Bn α+β), 5.05 – 4.48 (m, 16H, 4×CH_2 Bn α+β), 4.03 (m, 1H, H-5 α or β), 3.92 (m, 1H, H-5 α or β), 3.90 (dd, *J* = 9.2, 9.2, 1H, H-3 α or β), 3.78 (dd, *J* = 9.2, 9.2, 1H, H-3 α or β), 3.74 – 3.62 (m, 7H, CH_2-6 α+β, H-4 α+β, H-2 α or β), 3.50 (d, $J_{H2\text{-}H3}$ = 9.5, 1H, H-2 α or β), 3.44 (t, *J* = 6.1, 2H, CH_2-5 pentynyl α or β), 3.39 (t, *J* = 6.0, 2H, CH_2-5 pentynyl α or β), 2.91 (s, 2H, OCH_2-Ada α or β), 2.89 (s, 2H, OCH_2-Ada α or β), 2.37 (t, *J* = 7.1, 2H, CH_2-3 pentynyl α or β), 3.31 (t, *J* = 7.3, 2H, CH_2-3 pentynyl α or β), 1.93 (br s, 6H, 3×CH Ada α+β), 1.80-1.72 (m, 4H, CH_2-4 pentynyl α+β), 1.70-1.60 (m, 12H, 3×CH_2 Ada α+β), 1.48 (br s, 12H, 3×CH_2 Ada α+β). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) α/β mixture δ = 138.6, 138.5, 138.1, 138.04, 138.02, 137.9 (8×C_q Bn α+β), 130.0, 128.2, 128.1, 128.0, 127.9, 127.85, 127.83, 127.74, 127. 71, 127.6, 127.5, 127.46, 127.40, 127.33 (CH_{Ar} Bn α+β), 95.5, 91.6 (2×C-1 α+β), 88.9, 84.7, 79.7, 76.2 (4×C_q pentynyl α+β), 84.3, 84.2 (2×C-2 α+β), 83.7, 82.4 (2×C-3 α+β), 81.9, 81.7 (2×OCH_2-Ada α+β), 77.7, 77.4 (2×C-4 α+β), 75.7, 75.6, 75.0, 74.8, 74.5, 73.3 (8×CH_2 Bn α+β), 73.6, 71.6 (2×C-5 α+β), 69.7, 69.6 (2×OCH_2-5 pentynyl α+β), 68.53, 68.49 (2×C-6 α+β), 39.6 (6×CH_2 Ada α+β), 37.1 (6×CH_2 Ada α+β), 34.0 (2×C_q Ada α+β), 28.5 (2×CH_2-4 pentynyl α+β) 28.2 (6×CH Ada α+β), 15.5, 15.4 (2×CH_2-3 pentynyl α+β). IR ν_{max}(thin film)/ cm^{-1}: 3348, 3032, 2901, 2847, 2373, 1728, 1605, 1497, 1450, 1358, 1265, 1211, 1072, 910, 810, 741, 694, 602, 571, 525. $[\alpha]^{20}_D$: 30.5 (*c* 18.5, $CHCl_3$). HRMS: found *m/z* 793.4057 $[M+Na]^+$, calcd for $[C_{50}H_{58}O_7+Na]^+$ 793.4075.

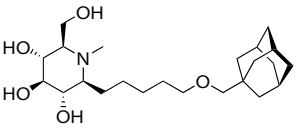


(1*S*)-2,3,4,6-Tetra-*O*-benzyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pent-1-ynyl]-1-deoxynojirimycin (63). A dry solution of **62** (549 mg, 0.71 mmol) in MeOH (5 mL) and DCM (1 mL) was cooled to 0 °C and $NaBH_4$ (134 mg, 3.57 mmol) was added. After stirring for 2 h at 0 °C, TLC analysis indicated full conversion to a lower running product. The reaction was quenched by addition of acetone (1 mL) and stirring for 15 min. The reaction mixture was concentrated, dissolved in little EtOAc, poured into sat aq NH_4Cl (100 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to provide the glucitol-derivative, which was used without further purification in the next reaction (ESI-MS found 795.6 $[M+Na]^+$; R_F diol = 0.45/ 0.35 in EtOAc:toluene; 1:3). The crude product was subjected to General procedure B and double reductive amination method B (R_F diketone = 0.80 in EtOAc:toluene; 1:3). However during the double reductive amination a mixture of MeOH/DCM (0.02M; 5/1) was used. The crude product was purified by silica gel column chromatography (0% » 25% EtOAc in toluene) to provide **63** (303 mg, 0.40 mmol) in 56% yield as a colorless oil. R_F = 0.55 (1:3; EtOAc:toluene). ^{1}H NMR (600 MHz, $CDCl_3$, COSY) δ 7.39 – 7.16 (m, 20H, H_{Ar} Bn), 5.03 (d, *J* = 10.5, 1H, C*H*H Bn), 4.91 (d, *J* = 10.9, 1H, C*H*H Bn), 4.83 (d, *J* = 10.9, 1H, C*H*H Bn), 4.82 (d, *J* = 10.5, 1H, CH*H* Bn), 4.80 (d, *J* = 10.9, 1H, CH*H* Bn), 4.48 (d, *J* = 10.9, 1H, CH*H* Bn), 4.47 (d, *J* = 11.8, 1H, C*H*H Bn), 4.43 (d, *J* = 11.8, 1H, CH*H* Bn), 3.68 (dd, $J_{H6a\text{-}H5}$ = 2.5, $J_{H6a\text{-}H6b}$ = 9.0, 1H, H-6a), 3.49 – 3.24 (m, 5H, H-1, H-2, H-3, H-6b), 3.41 (t, *J* = 6.1, 2H, OCH_2-5 pentynyl), 3.37 (dd, *J* = 9.3, 9.3, 1H, H-4), 2.90 (s, 2H, OCH_2-Ada), 2.76 (ddd, $J_{H5\text{-}H6a}$ = 2.5, *J* = 6.4, 9.7, 1H, H-5), 2.30 (t, *J* = 7.2, 2H, CH_2-3 pentynyl), 2.22 (br s, 1H, NH), 1.93 (br s, 3H, 3×CH Ada), 1.74 (m, 2H, CH_2-4 pentynyl), 1.71-1.61 (m, 6H, 3×CH_2 Ada), 1.49 (br d, *J* = 2.9, 6H, 3×CH_2 Ada). ^{13}C NMR (100 MHz, $CDCl_3$, HSQC) δ 138.7, 138.4, 138.2, 137.9 (4×C_q Bn), 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.67, 127.62, 127.5 (CH_{Ar}, Bn), 86.9 (C-3), 84.5 (C-2), 84.0 (C_q pentynyl), 81.8 (OCH_2-Ada), 79.9 (C-4), 78.9 (C_q pentynyl), 75.7, 75.4, 75.1, 73.4 (4×CH_2 Bn), 70.1 (C-6), 69.9 (OCH_2-5 pentynyl), 58.7 (C-5), 51.7 (C-1), 39.6 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 28.7 (CH_2-4 pentynyl), 28.2 (3×CH Ada), 15.6 (CH_2-3 pentynyl). IR ν_{max}(thin film)/ cm^{-1}: 3032, 2901, 2847, 1497, 1450, 1358, 1265, 1211, 1072, 1018, 910, 741, 694. $[\alpha]^{20}_D$: 9.5 (*c* 5.3, $CHCl_3$). HRMS: found *m/z* 754.4421 $[M+H]^+$, calcd for $[C_{50}H_{59}NO_5+H]^+$ 754.4466.

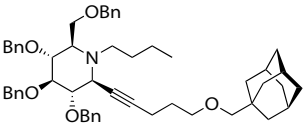


(1*S*)-1-*C*-[5-(Adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (17). Compound **63** (87 mg, 115 µmol) was subjected to Pd/C catalyzed hydrogenolysis according to General procedure D. The resulting residue was purified by silica gel column chromatography (5% » 15% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **17** (39 mg, 98 µmol) as a colorless oil in 85% yield. R_F = 0.38 (1:2; MeOH:$CHCl_3$ + 0.5%

NH_4OH). ^1H NMR (300 MHz, MeOD, COSY) δ 3.91 (dd, $J_{H6a\text{-}H5}$ = 3.0, $J_{H6a\text{-}H6b}$ = 10.9, 1H, H-6a), 3.49 (dd, $J_{H6b\text{-}H5}$ = 7.8, $J_{H6b\text{-}H6a}$ = 10.9, 1H, H-6b), 3.38 (t, *J* = 6.4, 2H, OCH_2-5′pentyl), 3.19 (dd, *J* = 9.0, 9.0, 1H, H-3), 3.10 (dd, *J* = 9.0, 9.0, 1H, H-4), 3.00 – 2.96 (m, 3H, H-2, OCH_2-Ada), 2.53 (m, 1H, H-5), 2.41 (m, 1H, H-1), 1.95 – 1.85 (m, 5H, 3×CH Ada, CH_2 pentyl), 1.76 – 1.66 (m, 6H, 3×CH_2 Ada), 1.58 – 1.50 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.45 – 1.25 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (75 MHz, MeOD, HSQC) δ 83.1 (OCH_2-Ada), 79.1 (C-3), 74.2 (C-2), 72.5 (OCH_2-5′pentyl), 70.4 (C-4), 62.2 (C-5), 60.7 (C-1), 60.1 (C-6), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 35.2 (C_q Ada), 31.7, 30.5 (2×CH_2 pentyl), 27.8 (3×CH Ada), 27.4, 26.7 (2×CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3310, 2901, 2847, 1450, 1366, 1312, 1258, 1150, 1096, 1018, 910, 826, 733, 671. $[\alpha]^{20}_D$: –12.5 (*c* 0.4, $CHCl_3$). HRMS: found *m/z* 398.2905 $[M+H]^+$, calcd for $[C_{22}H_{39}NO_5+H]^+$ 398.2901.

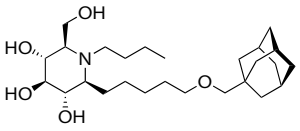


(1*S*)-*N*-Methyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (18). Argon was passed through a solution of compound **63** (70 mg, 93 μmol) and formaldehyde (1 mL; 37 wt % in water) in *n*-propanol (4 mL) for 5 min, after which a catalytic amount of Pd/C Degussa type (50 mg, 5 wt % on act. carbon) was added. Hydrogen was passed through the reaction mixture for 15 min. After stirring the reaction under atmospheric hydrogen pressure for 1 h, Pd/C was removed by filtration over a glass microfibre filter, followed by thorough rinsing with MeOH. The filtrate was concentrated and the resulting residue was subjected to General procedure D. The crude product was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **18** (36 mg, 88 μmol) as a colorless oil in 94% yield. R_F = 0.50 (1:2; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^1H NMR (400 MHz, MeOD, COSY) δ 3.90 (dd, $J_{H6a\text{-}H6b}$ = 11.8, $J_{H6a\text{-}H5}$ = 3.0, 1H, H-6a), 3.82 (dd, $J_{H6b\text{-}H6a}$ = 11.8, $J_{H6b\text{-}H5}$ = 3.9, 1H, H-6b), 3.40 – 3.35 (m, 3H, H-3, OCH_2-5 pentyl), 3.22 (dd, *J* = 9.2, 9.2, 1H, H-2), 3.15 (dd, *J* = 9.1, 9.1, 1H, H-4), 2.96 (s, 2H, OCH_2-Ada), 2.29 (s, 3H, NCH_3), 2.08 – 2.03 (m, 2H, H-1, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.66 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.61 – 1.55 (m, 8H, 3×CH_2 Ada, CH_2 pentyl), 1.43 – 1.35 (m, 4H, 2×CH_2 pentyl). ^{13}C NMR (100 MHz, MeOD, HSQC) δ 83.1 (OCH_2-Ada), 80.5 (C-3), 72.8 (C-2), 72.7 (OCH_2-5 pentyl), 70.9 (C-4), 69.8 (C-5), 67.9 (C-1), 60.4 (C-6), 40.8 (3×CH_2 Ada), 38.3 (3×CH_2 Ada), 36.1 (NCH_3), 35.2 (C_q Ada), 30.7, 29.8 (2×CH_2 pentyl), 29.8 (3×CH Ada), 27.8, 25.4 (2×CH_2 pentyl). IR ν_{max}(thin film)/ cm^{-1}: 3348, 2901, 2847, 2793, 2677, 2499, 1664, 1450, 1366, 1234, 1103, 1011, 864, 810, 687, 617. $[\alpha]^{20}_D$: 2.3 (*c* 0.5, $CHCl_3$). HRMS: found *m/z* 412.3064 $[M+H]^+$, calcd for $[C_{23}H_{42}NO_5+H]^+$ 412.3058.



(1*S*)-2,3,4-Tri-*O*-benzyl-*N*-butyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pent-1-ynyl]-1-deoxynojirimycin (64). A dry solution of compound **63** (75 mg, 100 μmol) and butyraldehyde (100 μL, 1 mmol) in EtOH (0.75 mL) and AcOH (0.25 mL) was charged with $NaBH_3CN$ (19 mg, 0.3 mmol). The reaction mixture was stirred for 20 h and subsequently concentrated with coevaporation of toluene. The residue was dissolved EtOAc, poured into sat aq $NaHCO_3$ (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (8% » 20% EtOAc in PE) to provide **64** (65 mg, 80 μmol) as a colorless oil in 80% yield. R_F = 0.45 (1:4 EtOAc:PE). ^1H NMR (400 MHz, $CDCl_3$, COSY) δ 7.41 – 7.13 (m, 20H, H_{Ar} Bn), 5.00 (d, *J* = 10.5, 1H, C*H*H Bn), 4.90 – 4.78 (m, 4H, 2×CH Bn, CH_2 Bn), 4.54 – 4.44 (m, 3H, CH Bn, CH_2 Bn), 3.72 (dd, $J_{H6a\text{-}H5}$ = 2.4, $J_{H6a\text{-}H6b}$ = 10.4, 1H, H-6a), 3.62 (dd, *J* = 9.2, 9.2, 1H, H-4), 3.58 (dd, *J* = 9.3, 9.6, 1H, H-2), 3.55 (dd, $J_{H6b\text{-}H5}$ = 2.4, $J_{H6b\text{-}H6a}$ = 10.4, 1H, H-6b), 3.45 – 3.40 (m, 3H, H-3, OCH_2-5 pentynyl), 3.34 (m, 1H, NC*H*H butyl), 3.31 (dt, $J_{H1\text{-}H3'}$ = 2.0, $J_{H1\text{-}H2}$ = 9.6, 1H, H-1), 2.91 (s, 2H, OCH_2-Ada), 2.79 (m, 1H, NCH*H* butyl), 2.45 (m, 1H, H-5), 2.30 (dt, *J* = 2.0, 7.2, 2H, CH_2-3 pentynyl), 1.94 (br s, 3H, 3×CH Ada), 1.79 – 1.61 (m, 8H, 3×CH_2 Ada, CH_2-4 pentynyl), 1.49 (br s, 6H, 3×CH_2 Ada), 1.39 (m, 1H, C*H*H butyl), 1.26 – 1.17 (m, 3H, CH*H* butyl, CH_2 butyl), 0.85 (t, *J* = 7.2, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.6, 138.5, 137.7 (4×C_q Bn), 128.4, 128.3, 128.0, 127.8, 127.54, 127.50, 127.4 (CH_{Ar} Bn), 86.8 (C-3), 85.1 (C_q pentynyl), 82.8, 78.3 (C-2, C-4), 81.9 (OCH_2-

Ada), 77.7 (C_q pentynyl), 75.5, 75.4, 75.0, 73.4, 70.0 (4×CH_2 Bn, OCH_2-5 pentynyl), 65.9 (C-6), 61.9, 56.7 (C-1, C-5), 48.0 (NCH_2 butyl), 39.7 (3×CH_2 Ada), 37.2 (3×CH_2 Ada), 34.0 (C_q Ada), 28.3 (3×CH Ada), 28.8, 23.5, 20.4, 15.6 (4×CH_2 butyl/ pentynyl), 14.0 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3063, 3024, 2901, 2847, 1728, 1666, 1497, 1450, 1358, 1288, 1211, 1157, 1088, 1026, 903, 841, 741, 694. $[\alpha]^{20}_D$: 2.3 (*c* 1.3, $CHCl_3$). HRMS: found *m/z* 810.5037 $[M+H]^+$, calcd for $[C_{54}H_{67}NO_5+H]^+$ 810.5092.



(1*S*)-*N*-Butyl-1-*C*-[5-(adamantan-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (19). General procedure D was applied to compound **64** (65 mg, 80 µmol) and the resulting residue was purified by silica gel column chromatography (5% » 20% MeOH in $CHCl_3$ with 0.5% NH_4OH) to give **19** (33 mg, 73 µmol) as a colorless oil in 91% yield. R_F = 0.60 (1:2; MeOH:$CHCl_3$ + 0.5% NH_4OH). ^1H NMR (400 MHz, MeOD, COSY) δ 3.90 – 3.80 (m, 2H, CH_2-6), 3.40 – 3.25 (m, 3H, H-4, OCH_2-5 pentyl), 3.20 – 3.09 (m, 2H, H-2, H-3), 2.96 (s, 2H, OCH_2-Ada), 2.82 (m, 1H, NC*H*H butyl), 2.68 (m, 1H, NCH*H* butyl), 2.39 – 2.32 (m, 2H, H-1, H-5), 1.94 (br s, 3H, 3×CH Ada), 1.77 – 1.55 (m, 16H, 6×CH_2 Ada, 2×CH_2 pentyl), 1.50 – 1.30 (m, 4H, CH_2 butyl, CH_2 pentyl), 1.25 (m, 2H, CH_2 butyl), 0.93 (t, *J* = 7.1, 3H, CH_3 butyl). ^{13}C NMR (100 MHz, MeOD) δ 81.0 (OCH_2-Ada), 80.5 (C-3), 72.9, 71.6 (C-2, C-4), 72.5 (OCH_2-5 pentyl), 65.8, 63.7 (C-1, C-5), 60.2 (C-6), 47.3 (NCH_2 butyl), 40.9 (3×CH_2 Ada), 38.4 (3×CH_2 Ada), 35.0 (C_q Ada), 30.7, 29.1, 27.9, 25.8, 24.5, 21.6 (6×CH_2 butyl/pentyl), 29.8 (3×CH Ada), 14.4 (CH_3 butyl). IR ν_{max}(thin film)/ cm^{-1}: 3364, 2901, 2847, 2098, 1728, 1450, 1366, 1258, 1111, 1011, 926. $[\alpha]^{20}_D$: 1.2 (*c* 0.3, $CHCl_3$). HRMS: found *m/z* 454.3543 $[M+H]^+$, calcd for $[C_{26}H_{47}NO_5+H]^+$ 454.3527.

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