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CHIRAL SYNTHESIS OF IMINOSUGARS

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Abstract – An chiral synthesis of iminosugars such as fagomine, 1-deoxynojirimycine, and isofagomine together with their stereoisomers are described.

INTRODUCTION

Since the discovery of nojirimycin as the first natural glucose mimic, over 200 naturally occurring iminosugars[1] in which the oxygen of the sugar ring is replaced by nitrogen have been reported. The transition states for enzymatic glycosidase and transferase enzymes have considerable oxocarbenium-ion characteristics, in that the anomeric carbon acquires sp^2 hybridization and a partial positive charge develops at the anomeric carbon and the endocyclic oxygen. Therefore, iminosugars as transition-state analogues are of particular interest in terms of inhibitor design. Iminosugars belong to the polyhydroxylated alkaloid family and display a broad range of interesting biological activities that are potentially useful in the treatment of ailments as varied as viral infections,[2] including human immunodeficiency virus (HIV),[2a-e] human hepatitis C (HCV),[2f,g] or dengue virus,[2i] cancer,[3] diabetes,[4] tuberculosis,[5] and lysosomal storage diseases.[6] The tremendous therapeutic potential of this class of compounds has been attributed to their ability to interact with carbohydrate-processing enzymes, where they act as competitive inhibitors of glycosidases and/or glycosyltransferases, a phenomenon that has stimulated much research in this area of glycobiology.[7] Because of the therapeutic importance of these compounds, many synthetic efforts have been directed toward their preparation. In practice, *N*-butyl-1-deoxynojirimycin (DNJ) **1** (Zavesca™) is used in the treatment of Gaucher disease. Another iminosugar, Miglitol (Glycet™) **2**, which is commercially available in the USA and Canada, is used for the treatment of type II diabetes. In addition, *galacto*-DNJ (Migalastat) **3** has been shown to inhibit lysosomal α-galactosidase and is currently in phase III clinical trials for the treatment of Fabry's disease (Figure 1). There are a number of reports and reviews on *in vitro* and *in vivo* glycosidase inhibition by DNJ, *manno-DNJ*, *galacto-DNJ*, and their derivatives. On the other hand, the biological properties of

enantiomers of DNJ, *manno-DNJ*, and *galacto-DNJ*, and other diastereomers of DNJ have not been systematically studied. Therefore, our attention was focused on the syntheses of both enatiomers of several iminosugars such as fagomine, 1-deoxynojirimycine, and isofagomine, together with their congeners.

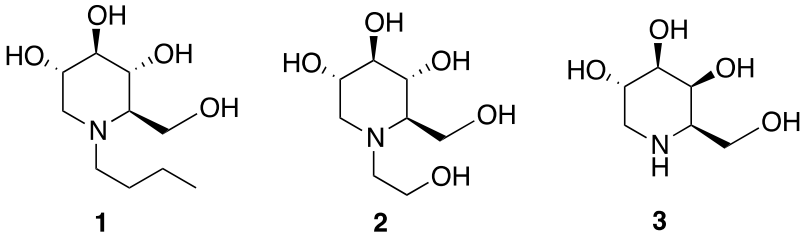


Figure 1. Iminosugars that are clinically used as drugs

SYNTHESIS OF IMINOSUGARS

1. Preparation of Fagomine[8]

Three fagomine isomers **4-6** from *Xanthocercis zambesiaca*, which occurs in dry southern African forests have been isolated (Figure 2).[9] Among these, fagomine **4** and 3-*epi*-fagomine **5** were found to have some activity against mammalian gut α-glucosidase and β-galactosidase.[9] Recently, **4** was reported to have a potent antihyperglycemic effect in streptozocin-induced diabetic mice and the potentiation for the glucose-induced secretion of insulin.[10] In addition, it was reported that the fagomine isomer **7** (not naturally occurring) is an inhibitor of lysosomal α-galactosidase activity in Fabry lymphoblasts.[11] However, most synthetic efforts have been directed towards the synthesis of fagomine derivatives that have a naturally occurring D configuration. Therefore, we embarked on short and efficient syntheses of D-fagomine and its epimers *via* the preparation of a new common chiral building block, hydroxymethylpiperidene **8**, which appears to be an ideal precursor for the synthesis of dihydroxypiperidinols. A new synthesis of all fagomine isomers **4-7** *via* the preparation of **8** in a straightforward and stereoselective manner with Garner aldehyde **9** and catalytic ring-closing metathesis (RCM) of the diene system **12** for the construction of the piperidine ring was achieved.[12]

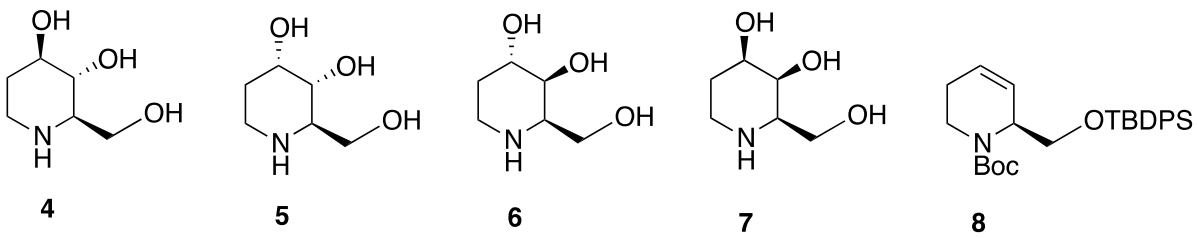
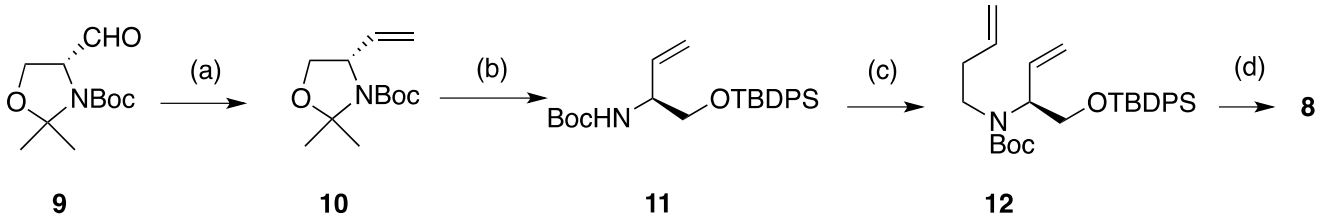


Figure 2. D-Fagomine and its isomers

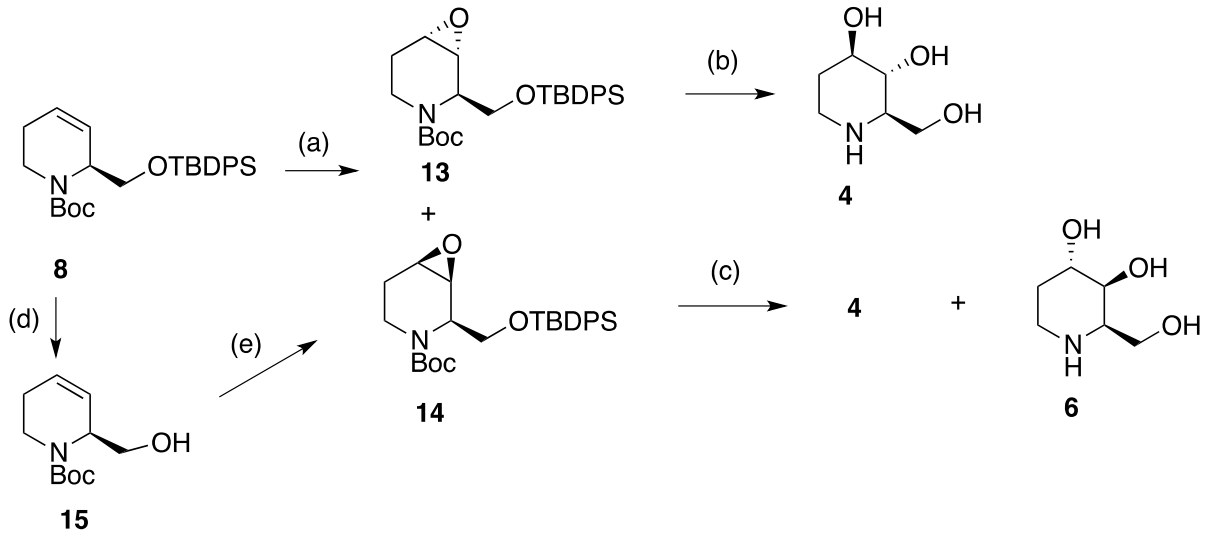
Our synthesis of **8** began with the Wittig reaction of the D-serine-derived Garner aldehyde **9**.[13] Treatment of **9** with methyltriphenylphosphonium iodide in the presence of sodium bis(trimethylsilyl)amide gave olefin **10** in 63% yield. Hydrolysis of **10** with *p*-toluenesulfonic acid in MeOH followed by *O*-silylation afforded **11** in 72% yield. *N*-Alkylation of **11**, using a three-step sequence [(1) deprotection of the *N*-Boc group; (2) alkylation; and (3) *N*-protection] provided the butenylated product **12** in 60% overall yield. RCM of **12** with the Grubbs' 1st generation catalyst, (benzylidine)bis(tricyclohexylphosphine)-ruthenium(IV) dichloride, under the usual conditions gave the desired intermediate **8** in 97% yield (Scheme 1).



Scheme 1. (a) $Ph_3P^+MeI^-$, $NaN(TMS)_2$, THF. (b) (i) *p*-TsOH, H_2O, MeOH. (ii) TBDPSCl, DMAP, imidazole, CH_2Cl_2. (c) (i) CF_3COOH, CH_2Cl_2. (ii) 4-bromo-1-butene, K_2CO_3, MeCN. (iii) $(Boc)_2O$, Et_3N, THF. (d) Grubbs' catalyst, CH_2Cl_2

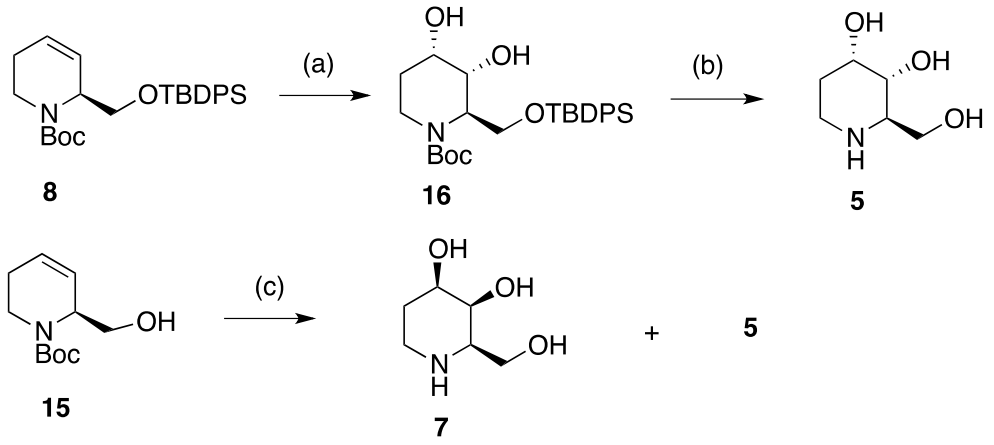
With the promising educt **8** in hand, our interest was then directed to the synthesis of all isomers **4**-**7** of fagomine. We first introduced an epoxy-functionality into the double bond to produce both **4** and **6**, which contain *trans* diols at the 3 and 4 positions. The dioxirane, generated in situ from Oxone® with 1,1,1-trifluoroacetone according to a recent procedure,[14] was reacted with **8** to give a mixture of stereoisomeric epoxy compounds **13** (60%) and **14** (30%) which were separated by medium-pressure chromatography in a high yield of 90% although the diastereoselectivity was low (dr: 33%). The *syn* epoxide **14** was stereoselectively produced by an alternative method. Desilylation of **8** with TBAF was carried out to afford **15** (97% yield). Starting with **15**, hydroxy-directed epoxidation with *m*-CPBA followed by silylation afforded **14** in 64% overall yield. Acid hydrolysis of the epoxy ring of **13** was accomplished using a mixture of H_2SO_4/1,4-dioxane/H_2O in a volume ratio of 0.2/3/2,[15] and further treatment with an ion-exchange resin (Amberlite® IRA-410) gave fagomine **4** exclusievly and in 75% yield. Although the explanation for this high selectivity remains unclear, we consider the following explanation: an attack of H_2O, as a nucleophile with backside displacement of the leaving oxygen in the epoxy-substituted ring, occurs at the more remote site (4 position) because nucleophilic attack at the 3 position has a *syn* orientation with respect to the adjacent siloxymethyl substiuent at the 5 position. In addition, the opening of cyclohexene oxide structures generally proceeds in such a manner that the diaxial

reaction product is usually produced. In contrast, the basic cleavage of epoxide **14** by treatment with a mixture of KOH/1,4-dioxane/H_2O gave **6** preferentially, in a ratio of 5:1 (**6** to **4**) in 99% combined yield.



Scheme 2. (a) Oxone®, CF_3COMe, $NaHCO_3$, aq Na_2EDTA, MeCN. (b) H_2SO_4, 1,4-dioxane, H_2O. (c) KOH, 1,4-dioxane, H_2O. (d) TBAF, THF. (e) (i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2. (ii) TBDPSCl, DMAP, imidazole, CH_2Cl_2

The stereoselective dihydroxylation of the double bond was next examined. Under modified Upjohn conditions,[16] the treatment of **8** with a catalytic amount of $K_2OsO_4 \cdot 2H_2O$ (5 mol%) and 4-methylmorpholine *N*-oxide (1.5 equiv) as a cooxidant gave the diol **16** as a single diastereoisomer in a high yield of 92%. Deprotection of **16** by treatment with 10% hydrochloric acid in 1,4-dioxane followed by treatment with a basic ion-exchange resin (Dowex® 1×2 OH^- form) afforded 3-*epi*-fagomine **5** in 91% yield. Surprisingly, both the AD-mix-α®- and β®-mediated dihydroxylation of **8** provided **16** with no diastereomer being detected, in 94% and 96% yields, respectively. Dihydroxylation exclusively occurred from the less hindered *anti* side of the siloxymethyl substituent, which adopts an axial position due to 1,3-allylic strain. The dihydroxylation of **15** under the above modified Upjohn conditions also took place from the *anti* side of the hydroxymethyl group, followed by the deprotection to give **5** as a single diastereomer in 87% combined yield. Donohoe reported[17] that osmium tetroxide produces a bidendate and reactive complex with TMEDA, which can be utilized in the directed dihydroxylation of homoallyic alcohols. Therefore, the oxidation of **15** with a combination of OsO_4 with TMEDA followed by deprotection gave **7** and **5** in low selectivity (2:1) in 56% and 30% yields, respectively. Since all of the D isomers were obtained, the preparation of L-forms, *ent*-**4-7,** using the L-serine-derived Garner aldehyde *ent*-**9** was accomplished using nearly the same procedure as that reported for the preparations described in Schemes 1 - 3.



Scheme 3. (a) cat. $K_2OsO_4 \cdot 2H_2O$, NMO, H_2O, acetone. (b) 10% HCl, 1,4-dioxane. (c) (i) OsO_4, TMEDA, CH_2Cl_2; (ii) 35% HCl, MeOH

2. Preparation of 1-Deoxynojirimycine and its stereoisomers[18,19]

Four naturally occurring 1-deoxyiminosugars have been isolated to date. 1-Deoxynojirimycin (DNJ) (**17**) and 1-deoxymannojirimycin (*manno*-DNJ) (**19**) have been isolated from many plants and microorganisms.[20] 1-Deoxyaltronojirimycin (*altro*-DNJ) (**18**) and 1-deoxygulonojirimycin (*gulo*-DNJ) were recently isolated from *Scilla sibirica* (Hyacinthaceae)[21] and *Angylocalyx pynaertii* (Leguminosae).[22] Many efforts have been devoted in recent years to develop methodologies for the asymmetric syntheses of iminosugars owing to their promising therapeutic potential in a wide range of diseases. However, many syntheses of iminosugars have been focused on derivatives with D-*gluco*, D-*manno*, or D-*galacto* configurations because their targeting enzymes are essential for survival and the existence of all living organisms.[23,24] There are a number of reports and reviews on *in vitro* and *in vivo* glycosidase inhibition by DNJ, *manno*-DNJ, *galacto*-DNJ, and their derivatives.[25-27] On the other hand, only a few systematic studies of the properties of the enantiomers of DNJ, *manno*-DNJ, and *galacto*-DNJ, and other diastereomers of DNJ have been reported. Herein, we report on the syntheses of both enantiomers of DNJ (**17**), *manno*-DNJ (**19**), *allo*-DNJ (**20**), *galacto*-DNJ (**3**), *altro*-DNJ (**18**), *gulo*-DNJ, and *ido*-DNJ and systematic studies of their inhibitory activities with respect to glycosidases.

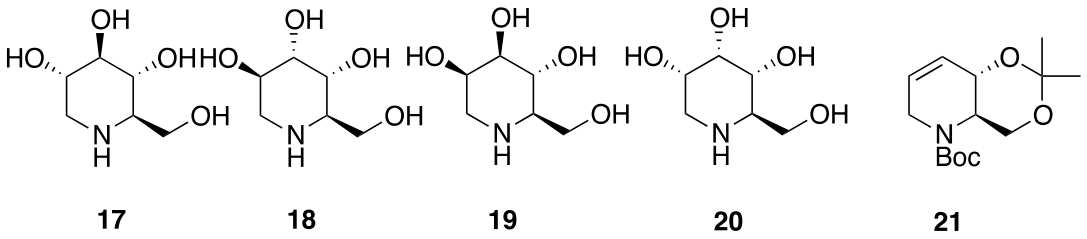
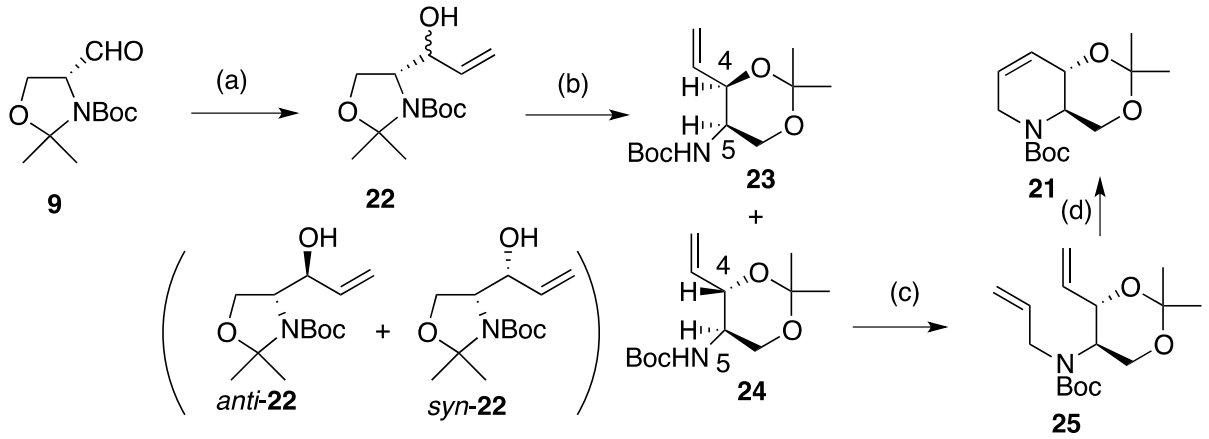


Figure 3. Structures of 1-deoxynojirimycin and its congeners

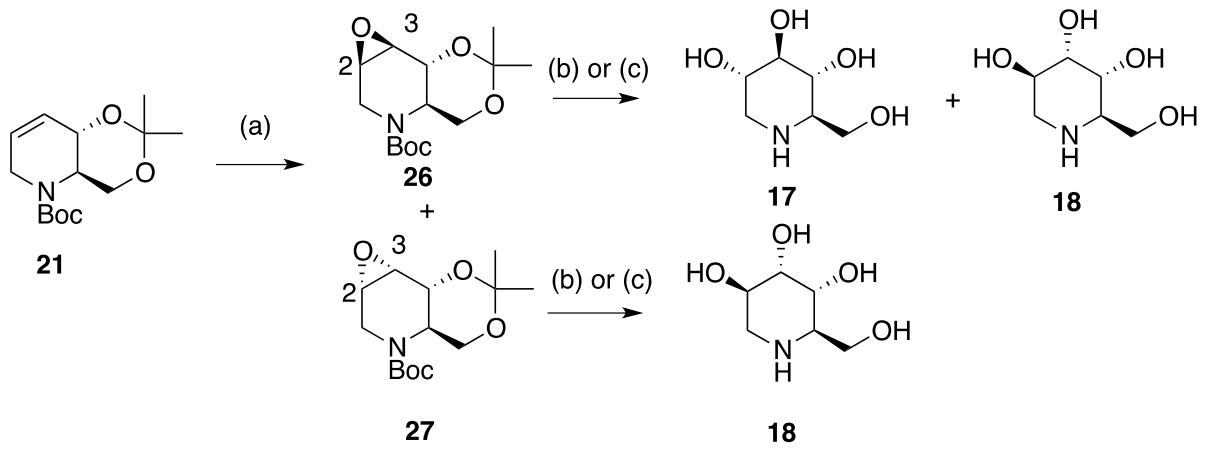
Firstly, DNJ (**17**) and its three stereoisomers, i.e., *altro*-DNJ (**18**), *manno*-DNJ (**19**), and *allo*-DNJ (**20**) of *trans*-4,5-substituted 1-deoxyiminosugars (nojirimycin-type) were synthesized from a common chiral building block **21** (Figure 3). In a project focused on the asymmetric synthesis of glycosidase inhibitors, we envisioned dioxanylpiperidene **21** would serve as a new common chiral building block, which represents an ideal precursor for the synthesis of DNJ (**17**) and its congeners (Figure 3). Herein we describe a straightforward synthesis of DNJ (**17**) and its congeners **18**-**20** via **21** starting from the Garner aldehyde **9** using catalytic RCM to construct the piperidine ring (Scheme 4). The D-serine-derived Garner aldehyde **9** provided an attractive starting point for the synthesis, since it reacts with organometalic reagents with a high degree of diastereoselectivity and racemization is minimal.[28] The diastereoselective addition of vinyl metals to **9** could furnish the *anti*-vinyl alcohol *anti*-**22**, depending on the reaction conditions used.[29] The use of HMPA as a cosolvent gave **22** with high *anti*-selectivity (*anti*:*syn* = 5.2:1) in 91% yield. The diastereoselectivity is convincingly accounted for by considering the preferred transition state in each reaction. According to the well- known Felkin-Anh model, the nucleophile would preferentially attack the *si*-face of aldehyde **9** thereby leading to an *anti*-configuration. The chromatographic separation of a diastereomeric mixture of alcohols **22** was not successful. Accordingly, treatment of **22** (*anti*:*syn* = 5.2:1) with HCl in chloroform afforded the readily separable 1,3-acetonides **23** (1.8%), **24** (47%), and **22** (32%). The relative configuration at the C-4 and C-5 of **24** was confirmed from the H–H-coupling constant (C_4H and C_5H), which is 9.5 Hz for the *trans* configuration. The *N*-allylation of **24** with allyl iodide using NaH as a base gave the diolefin product **25** in 95% yield. Finally, **25** was subjected to RCM in the presence of Grubbs' 1st generation catalyst in dichloromethane. Under these conditions, the desired piperidene **21** was obtained in 97% yield.



Scheme 4. (a) $(CH_2{=}CH)_4Sn$, *n*-BuLi, HMPA, Et_2O, (*anti*:*syn* = 5.2:1). (b) 0.15 N HCI gas in $CHCI_3$, rt, overnight, **23**, **24**, **22**. (c) allyl iodide, NaH, THF, 0 °C. (d) cat. Grubbs' 1st generation, CH_2Cl_2, rt

With the promising chiral building block **21** in hand, our interest was directed to the synthesis of 1-deoxynojirimycin compounds **17**-**20**. We first converted the double bond to an epoxy-functionality to give both **17** and **18** containing a *trans* diol in the 2 and 3 positions. The dioxirane, generated in situ from Oxone® with 1,1,1-trifuluoroacetone was reacted with **21** to give the *anti* epoxide **26** and *syn* epoxide **27** in 45 and 44% yields, respectively. The use of *m*-CPBA also resulted in low stereoselectivity to provide **26** and **27** in a ratio of 47:27 in 74% yield.

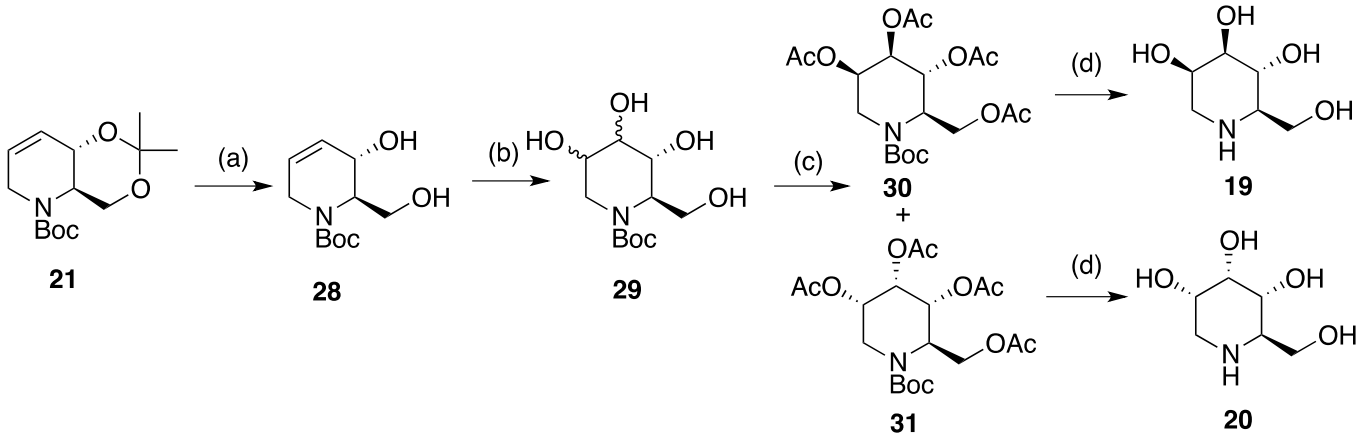
Acid hydrolysis of the epoxy ring of **26** was achieved using a 0.2/3/2 mixture of H_2SO_4/dioxane/H_2O, followed by treatment with an ion-exchange resin to give DNJ (**17**)[30] and *altro*-DNJ (**18**)[31] in a ratio of 1:1 in 89% yield. Base catalyzed cleavage of the epoxide **26** using a mixture of KOH/dioxane/H_2O gave **18**, preferentially, in a ratio of 1:1.5 (**17** to **18**) in 99% yield. In contrast, both acidic hydrolysis and basic cleavage of the *syn* epoxide **27** afforded only *altro*-DNJ (**18**) in 63% and 68% yields, respectively, after treatment with ion-exchange resin. Although the rationale for these stereoselectivities remains unclear, we propose the following explanation. It is known that the opening of cyclohexene oxides generally proceeds via a diaxial reaction.[32] The epoxy substituents at the 3 position of **26** and the 2 position of **27** are in a *quasi*-equatorial orientation, because *anti*-dioxanyl ring has a diequtorial orientation. Accordingly, it would be expected that axial attack would occur at the 3 position of **26** and the 2 position of **27**. In the case of **26**, however, steric repulsion between a nucleophile and substituent at 4 position would exist. Hence, the nucleophile may attack at the more remote site (the 2 position) of **26** (Scheme 5).



Scheme 5. (a) Na_2EDTA, CF_3COMe, $NaHCO_3$, Oxone®, MeCN. (b) (i) H_2SO_4, 1,4-dioxane, H_2O, reflux, (ii), Dowex® 50wX8 1. (c) (i) 3 M KOH, 1,4-dioxane, reflux, (ii) DOWEX® 1X2

The stereoselective dihydroxylation of the double bond was next examined. Deprotection of the acetonide with *p*-TsOH in methanol gave diol **28** (94%), which was treated under modified Upjohn conditions, with a catalytic amount of $K_2OsO_4 \cdot 2H_2O$ (5 mol %) and NMO as a cooxidant to give an inseparable mixture of

tetraols **29** in 87% yield. Fortunately, acetylation of the tetraol gave a mixture of separable tetraacetates **30** and **31**, which were isolated in 45% and 49% yields. Finally, the exposure of **30** and **31** to 6N HCl in methanol followed by treatment with an ion-exchange resin provided *manno*-DNJ (**19**)[33] and *allo*-DNJ (**20**)[34] in 94 and 91% yields, respectively (Scheme 6).



Scheme 6. (a) *p*TsOH·H_2O, MeOH, rt, 2 h. (b) cat. $K_2OsO_4 \cdot 2H_2O$, NMO, acetone, rt, overnight. (c) Ac_2O, pyridine, rt. (d) 6N HCI, MeOH, reflux, 8 h; DOWEX® 50wX8

Thus, the new promising chiral building block **21** for the synthesis of 1-deoxy-4,5-*trans*-oriented iminosugars was prepared in only four steps from the Garner aldehyde **9**. In practice, the first synthesis of all four isomers **17**-**20** of *trans*-4,5-orientated 1-deoxyiminosugars using **21** as a common chiral building block was achieved.

Secondly, *galacto*-DNJ (**3**), *ido*-DNJ (**32**), and *gulo*-DNJ (**33**) of *cis*-4,5-substituted 1-deoxyiminosugars were synthesized from a new common chiral building block, dioxanylpiperidene **34,** which represents an ideal precursor (Figure 4).

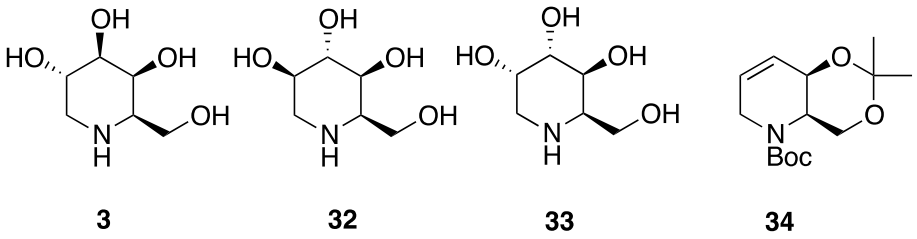
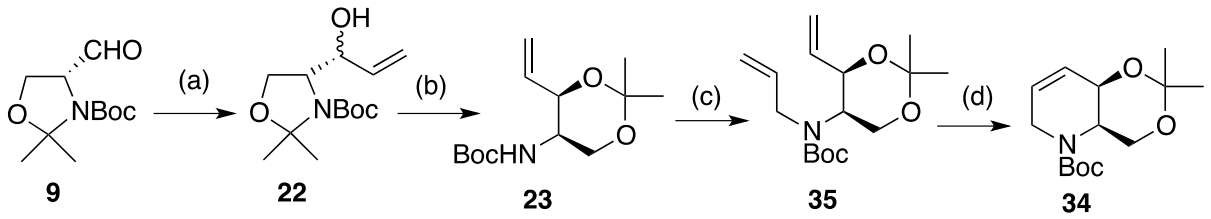


Figure 4. Structures of 1-deoxygalactonojirimycin and its congeners

The common intermediate **34** can be prepared by the RCM of diolefin **37**, produced by the stereoselective coupling of **9** with vinyl metals. The diastereoselective addition of vinyl metals to **9** may furnish the *syn* vinyl alcohol, depending on the reaction conditions.[35] The reagent, formed from *in situ* prepared

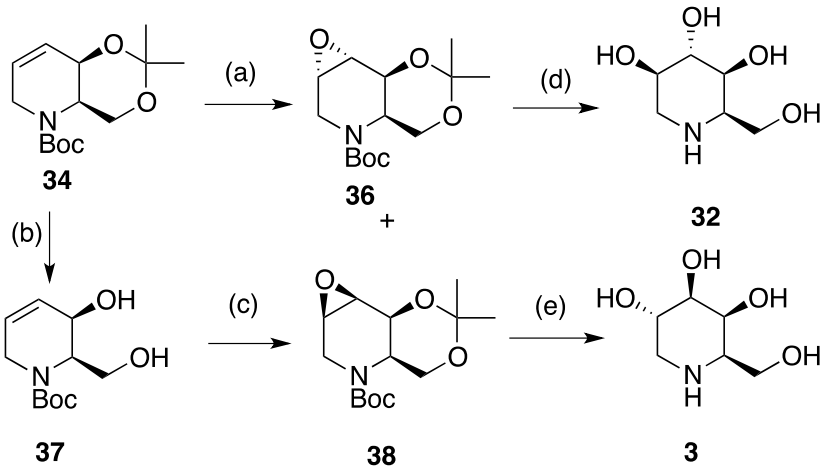
vinyllithium and anhydrous zinc dibromide in diethyl ether was found to provide the *syn* alcohol as a solid with a 5:1 diastereoselectivity (*syn*:*anti*) in 91% yield. The diastereoselectivity can be rationalized by considering the preferred transition state in each reaction. The vinyl zinc bromide complex coordinated with the carbamate carbonyl in the transition state is delivered to the *re* face of the aldehyde carbonyl to afford the vinyl alcohol **22** with *syn* selectivity. The chromatographic separation of the diastereomeric mixture of alcohols **22** was incomplete. However, the 67% de of the *syn*-preferred **22** was improved to 92% de (72%) by one recrystallization. When the recrystallized **22** was treated with HCl gas in chloroform, it was converted to the 1,3-acetonide **23** (69%) together with the recovery of **22** (24%). *N*-Allylation of **23** with allyl iodide using NaH as a base gave the diolefin product **35** in 76%. Finally, **35** was subjected to RCM in the presence of Grubbs' 1st catalyst, in dichloromethane to provide the desired piperidene **34** in excellent yield (Scheme 7).



Scheme 7. (a) vinylzinc bromide, Et_2O, -78 □□□to rt. (b) (i) recrystallization from *n*-hexanes-EtOAc (5:1). (ii) HCl gas, $CHCl_3$, rt. (c) allyl iodide, NaH, THF, 0 □C.□(d) Grubbs' catalyst, CH_2Cl_2, rt

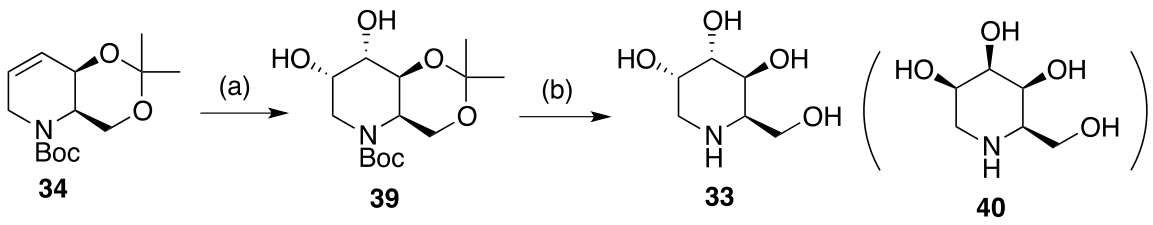
With the promising educt **34** in hand, our interest was directed to the stereoselective synthesis of compounds **3**, **32**, and **33**. We first introduced an epoxy functionality into the double bond to obtain both **3** and **32** containing a *trans* diol in the 3 and 4 positions. The dioxirane, generated in situ from Oxone with 1,1,1-trifuluoroacetone, was reacted with **34** to give the *anti* epoxide **36** as a single diastereomer in 99% yield. This indicates that the epoxidation occurred exclusively from the less hindered convex face, because the concave face is shielded by a methyl substituent. On the other hand, the *syn* epoxide was obtained by the hydroxy-directed epoxidation of diol **37**, prepared by hydrolysis of the acetonide derivative of **34** with *p*-TsOH in methanol. The epoxidation of the diol with *m*-CPBA followed by acetonization afforded the *syn* epoxide **38** in 53% overall yield (Scheme 8).

Acid hydrolysis of the epoxy ring of the *syn* epoxide **41** was accomplished by means of a mixture of H_2SO_4/1,4-dioxane/H_2O in a ratio of 0.2/3/2, and further treatment with an ion-exchange resin (DOWEX® 1x2, OH^- form) gave only *galacto*-DNJ (**3**)[36] in 83% yield. On the other hand, the basic cleavage of the epoxide **36**, accomplished using a mixture of KOH/1,4-dioxane/H_2O, followed by a sequence of deprotection and desalting gave *ido*-DNJ (**32**)[37] exclusively in 87% combined yield.



Scheme 8. (a) Oxone®, CF_3COMe, $NaHCO_3$, aq Na_2EDTA, MeCN, 0 °C. (b) *p*-TsOH, H_2O, MeOH, rt. (c) (i) *m*-CPBA, NaH_2PO_4, CH_2Cl_2, 0 °C to rt. (ii) 2,2-dimethoxypropane, cat. PPTS, acetone, rt. (d) (i) H_2SO_4, 1,4-dioxane, H_2O, reflux. (ii) Amberlite® IRA-410 (OH- form). (iii) DOWEX® 1x2 (OH- form). (e) (i) 0.3 M KOH,1,4-dioxane, H_2O, reflux, (ii) 6 N HCl, MeOH, rt. (iii) Amberlite® IRA-410 (OH- form)

The stereoselective dihydroxylation of the double bond was also examined. Under modified Upjohn conditions, treatment of **34** with a catalytic amount of $K_2OsO_4 \cdot 2H_2O$ (5 mol %) and NMO as a cooxidant gave the diol **39** as a single diastereomer in 85% yield. This remarkably high diastereoselectivity of the dihydroxylation can be attributed to the same steric blocking of the concave face as explained for the epoxidation of **34**. Deprotection of **39** with HCl in methanol followed by treatment with an ion-exchange (DOWEX® 50Wx8 H^+ form) afforded 1-deoxygulonojirimycin (**33**) in 90% combined yield. Unfortunately, the dihydroxylation of **34** or **37** using Donohoe conditions,[17] AD-mix-α®, and AD-mix-β® gave no *syn*-dihydroxyl products, which were converted to *talo*-DNJ (**40**).[38] Thus, a straightforward synthesis of **3**, **32**, and **33** using **34** has been demonstrated in a highly stereocontrolled fashion (Scheme 9).

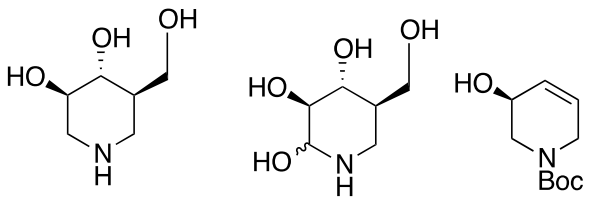


Scheme 9. (a) $K_2OsO_4 \cdot 2H_2O$, NMO, acetone, H_2O, rt. (b) (i) 6N HCl, MeOH, rt. (ii) DOWEX® 50Wx8 (H^+ form)

Since all DNJ isomers of the D-form, except for *talo*-DNJ (**40**), were obtained, the preparation of the L-forms *ent*-**17-20** and **3**, **32**, and **33** using the L-serine-derived Garner aldehyde *ent*-**9** was achieved following almost the same procedure as that reported as shown in Schemes 7-9.

3. Preparation of Isofagomine[39-42]

The search for anomer selective β-glycosidase inhibitors has led to a new class of sugar-mimics, 1-*N*-iminosugars with a nitrogen atom at the anomeric position. The representative 1-*N*-iminosugar isofagomine **41** was first designed by Bols *et al*.[43] as an apparent transition state analog mimicking the carbocationic form of the oxycarbenium-like transition state in which the positive charge resides at the anomeric carbon. Isofagomine was found to be a selective and very strong inhibitor of β-glucosidase [K_i = 0.11 μM, sweet almonds][43,44] and its 2-hydroxy analog noeuromycin **42** functions as a β-glucosidase inhibitor in the nanomolar range.[45] Isofagomine derivatives have recently received a great deal of attention because they are new candidates for the therapeutic treatment of Gaucher's disease and are currently in Phase II of clinical development. Due to the pronounced and selective inhibition activities of isofagomine and its congeners, an increased interest has developed in the synthesis of such 1-*N*-iminosugars (Figure 5).[46]

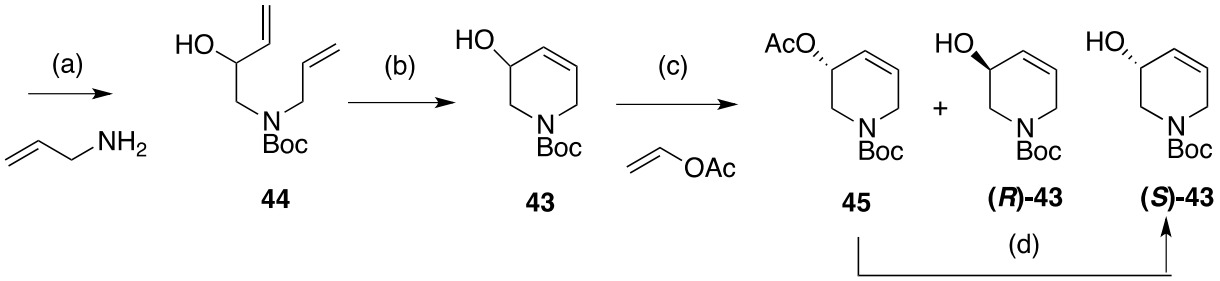


41 **42** **43**

Figure 5. Structures of a common building block **43** and 1-iminosugars

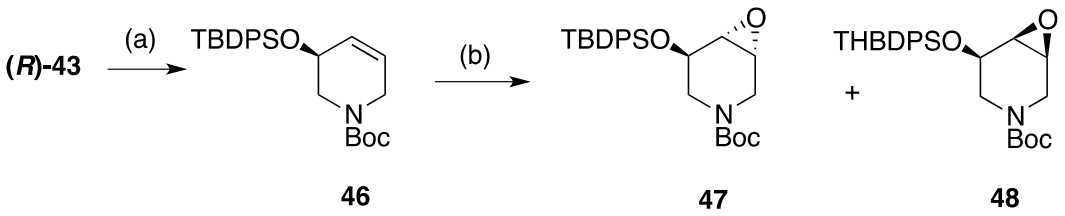
We envisioned the use of *N*-Boc-5-hydroxy-3-piperidene (**43**) as a general representative chiral building block that might permit easy access to these classes of compounds. The synthesis of racemic **43** as the starting material began with the regioselective opening of butadiene monoxide with allylamine followed by protection of the secondary amine to afford the metathesis precursor **44** (66%). The Grubbs' catalysts could be used directly on **44** to afford the ring-closing metathesis product **43** in 99% yield. Ogasawara reported[47] on the lipase-catalyzed transesterification of *N*-Cbz-5-hydroxy-3-piperidene with vinyl acetate. We applied this method to racemic **43** using lipase and vinyl acetate. Of the various lipases tested, resolution was best achieved with lipase PS (Pseudomonas *cepacia)*, immobilized on ceramic particles, in *tert*-butyl methyl ether at 40 °C, which gave the acetate **45** in 49% yield, along with the unreacted alcohol (*R*)-**43**, in 48% (>99% ee) yield. In addition, the enzymatic hydrolysis of the acetate **45** with the same lipase in 0.1 M phosphate buffer afforded the enantiomeric alcohol (*S*)-**43**, in 98% (>99% ee) yield

(Scheme 10). In addition, (*R*)- or (*S*)-**43** was prepared by the palladium-catalyzed deracemization of the methyl carbonate derivative of racemic **43**.[48]



Scheme 10. (a) (i) cat. H_2O, 100 °C, (ii) Boc_2O, NaOH. (b) Grubbs' catalyst, CH_2Cl_2, rt. (c) vinyl acetate, lipase PS (immobilized on ceramic particles), *tert*-BuOMe, 40 °C. (d) lipase PS (immobilized on ceramic particles), 0.1 M phosphate buffer (pH 7), acetone, 40 °C

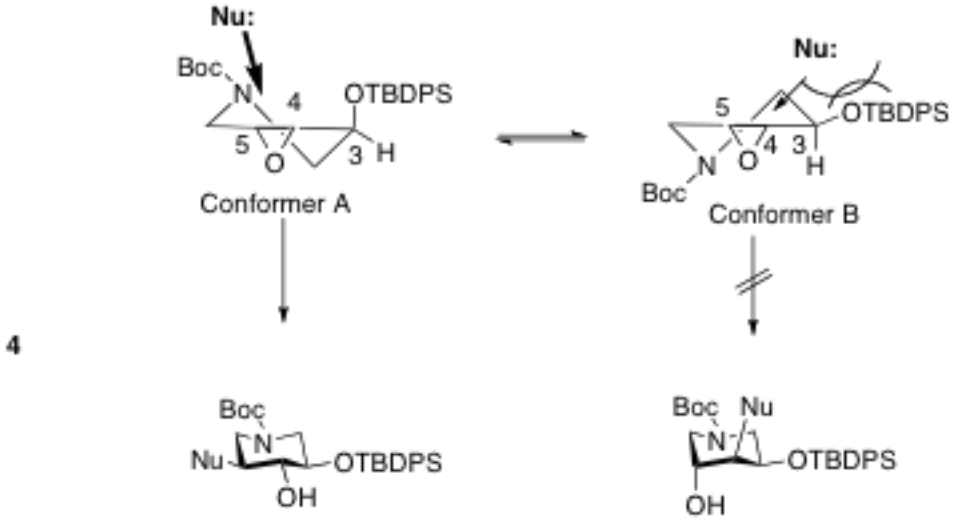
Alcohol (*R*)-**43** was initially converted into the TBDPS derivative **46**, thus avoiding the possible assistance of the hydroxyl group in the favored approach of the oxidant. Treatment of (*R*)-**43** with *tert*-butyldiphenylsilyl chloride under basic conditions gave the TBDPS derivative **46** in 99% yield. The dioxirane, generated in situ[49] from Oxone with 1,1,1-trifluoroacetone, was subsequently reacted with **46** to give the *anti* epoxide **47** and the *syn* epoxide **48** in 72% and 17% yields, respectively (Scheme 11).



Scheme 11. (a) TBDPSCl, imidazole, cat. DMAP, CH_2Cl_2, rt. (b) Oxone®, aq Na_2EDTA, $NaHCO_3$, CF_3COMe, MeCN, 0 °C

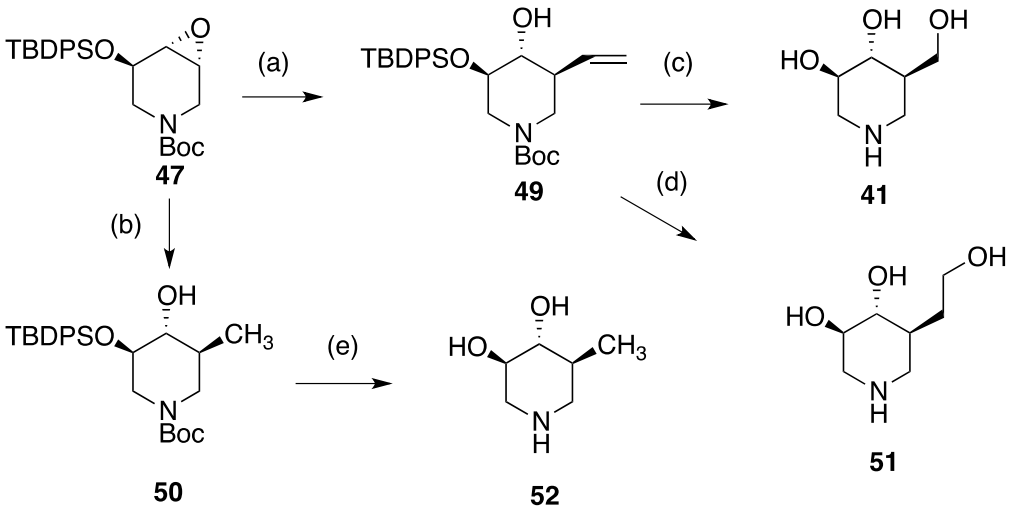
The nucleophilic opening of the *anti* epoxide **47** with "higher order" cuprate[50] free halide ions in the presence of boron trifluoride etherate as the activating species was carried out as follows: treatment of **47** with $(CH_2{=}CH)_2CuCNLi_2$ in the presence of $BF_3{\cdot}OEt_2$ at −78 °C for 2 h gave **49** as the sole isolable product in 74% yield. Analogously, the reaction of **47** with $Me_2CuCNLi_2$ afforded only **50** in 71% yield. An attempt to employ Grignard reagents in the presence of cuprous bromide[51] resulted in no reaction. Although the rationale for this high selectivity remains unclear, the following mechanism is consistent with the results. The regiochemistry of the nucleophilic opening of the epoxide on a six-membered ring is

mainly subject to *trans* diaxial opening (Fürst−Plattner rule).[32] Consequently, a high regioselectivity would result if the opening proceeded through only one of the two possible half-chair conformations (**A** and **B**). Thus, the exclusive attack of the nucleophile at C-5 as conformer **A** would involve a *trans* diaxial opening. On the other hand, if a nucleophile attacked at C-4 of **47** through conformer **B** steric hindrance by the pseudoequatorial OTBDPS group at C-3 would be in play. Therefore, a *trans* diaxial opening through one of the half-chair conformers, namely conformer **A**, would occur (Scheme 12). A similar regioselectivity has been reported for ring-opening reactions of *trans*-3-(benzyloxy)-1,2-epoxycyclohexane derivatives.[52]



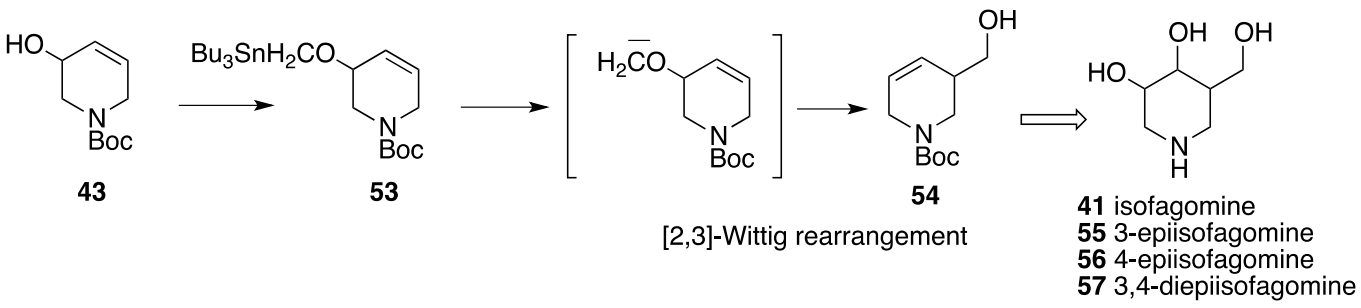
Scheme 12. Regiochemistry of nucleophilic opening of the epoxide **47**

With the vinyl product **49** in hand, our interest was directed to its conversion to isofagomine (**43**) and homoisofagomine (**51**). Oxidative cleavage of the vinyl group of **49** with OsO_4 and $NaIO_4$ afforded the aldehyde, which without purification, and after reduction with $NaBH_4$ followed by deprotection, afforded isofagomine (**41**) in 85% combined yield.[53] Next, the hydroboration of the vinyl group of **49** with 9-BBN followed by treatment with hydrogen peroxide gave the corresponding primary alcohol. Deprotection of the alcohol with 10% HCl in 1,4-dioxane afforded **51** in 86% combined yield. Conversion of **50** to 5'-deoxyisofagomine (**52**) was accomplished by deprotection. The complete deprotection of **50** by treatment with 10% HCl in 1,4-dioxane afforded **52** in 92% yield. Thus, the first synthesis of **51** and **52** was achieved. Enantiomers of **41**, **51**, and **52** were also prepared starting from (-)-**43**, following the same procedure as above (Scheme 13).



Scheme 13. (a) $(CH_2{=}CH)_2CuCNLi_2$ (5 equiv), $BF_3{\cdot}OEt_2$ (2 equiv), Et_2O, -78 °C. (b) $Me_2CuCNLi_2$ (5 equiv), $BF_3{\cdot}OEt_2$ (2 equiv), Et_2O, -78 °C. (c) (i) cat. OsO_4, $NaIO_4$, 50% EtOH, rt. (ii) $NaBH_4$, 50% EtOH, rt. (iii) 10% HCl, dioxane, reflux. (d) (i) 9-BBN, THF, rt. (ii) H_2O_2, 3 M NaOH, THF, rt. (iii) 10% HCl, dioxane, reflux. (e) 10% HCl, 1,4-dioxane, reflux

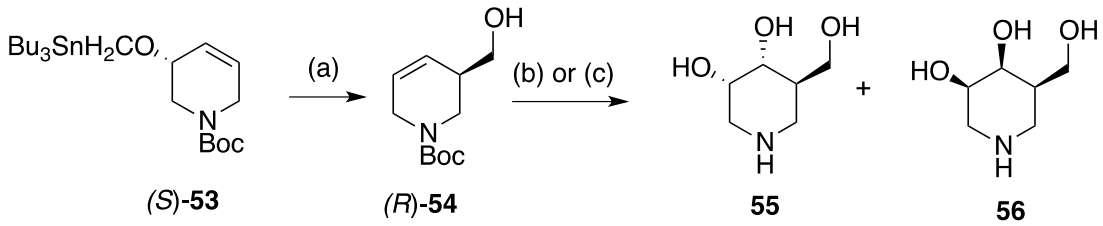
Next, we report on the asymmetric synthesis of all stereoisomers of 1-iminosugars such as isofagomine (**41**), using the [2,3]-Wittig rearrangement[54] as a key step starting from the chiral *N*-Boc-5-hydroxy-3-piperidene (**43**) as depicted in Scheme 14. We began with the synthesis of a precursor **53** for the [2,3]-Wittig rearrangement from **43**. *O*-Alkylation of (*S*)-**43** with tributyl(iodomethyl)stannane[55] in the presence of KH and *n*-Bu_4NI gave the stannane product (*S*)-**53** in 98% yield. With (*S*)-**53** in hand, the [2,3]-Wittig rearrangement of (*S*)-**53** was examined by transmetallation using *n*-BuLi, producing the requisite hydroxymethyl substituent (*R*)-**54**[56] with no racemization ([1,2]-Wittig rearrangement).[57] The use of less polar solvents such as *n*-pentane and *n*-hexane resulted in yields of 65% and 53%, respectively.



Scheme 14. Synthesis of isofagomine and its stereoisomers using [2,3]-Wittig rearrangement

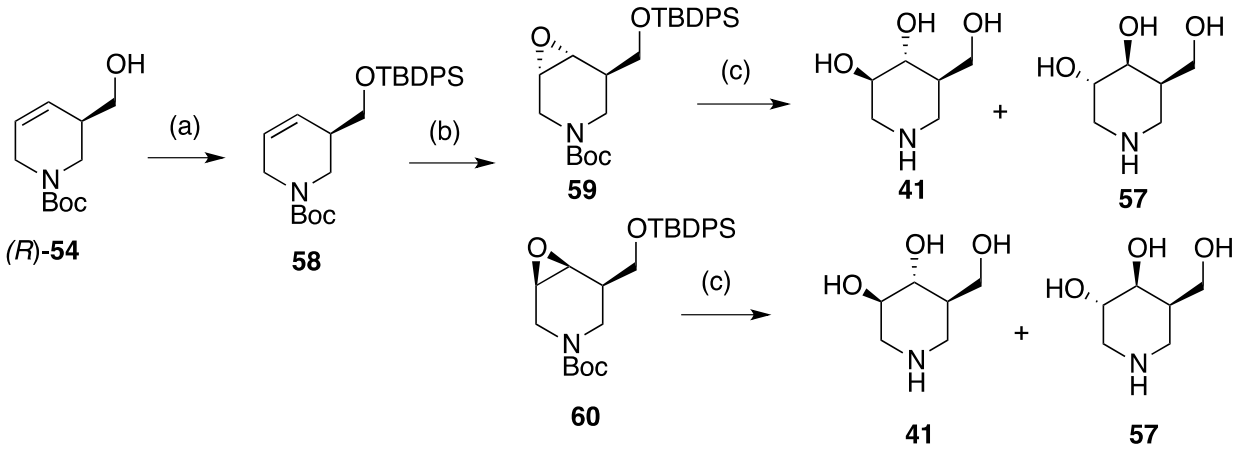
Having the key intermediate (*R*)-**54** in hand, the stereoselective dihydroxylation of the double bond was examined. Treatment of (*R*)-**54** with a catalytic amount of OsO_4 (5 mol%) and NMO as a cooxidant gave

an inseparable mixture of diastereomeric diols, which, after deprotection with 10% HCl in dioxane, followed by silica gel column chromatography using an eluent comprised of a mixture of solvents (methanol:10% NH_4OH), gave 3-*epi*isofagomine (**55**) (75%) and 4-*epi*isofagomine (**56**) (14%). Donohoe reported that osmium tetroxide produces a bidendate and reactive complex with TMEDA, that can be used in the directed dihydroxylation of cyclic homoallylic alcohols.[58] Under these conditions, control via hydrogen bonding preferentially led to the formation of the *syn* isomer in almost every case. However, the oxidation of (*R*)-**54** with a combination of OsO_4 with TMEDA gave **55** and **56** in 61% and 37% yields, respectively. Although the yield of **56** was increased, reversal of the ratio was not observed in any case.

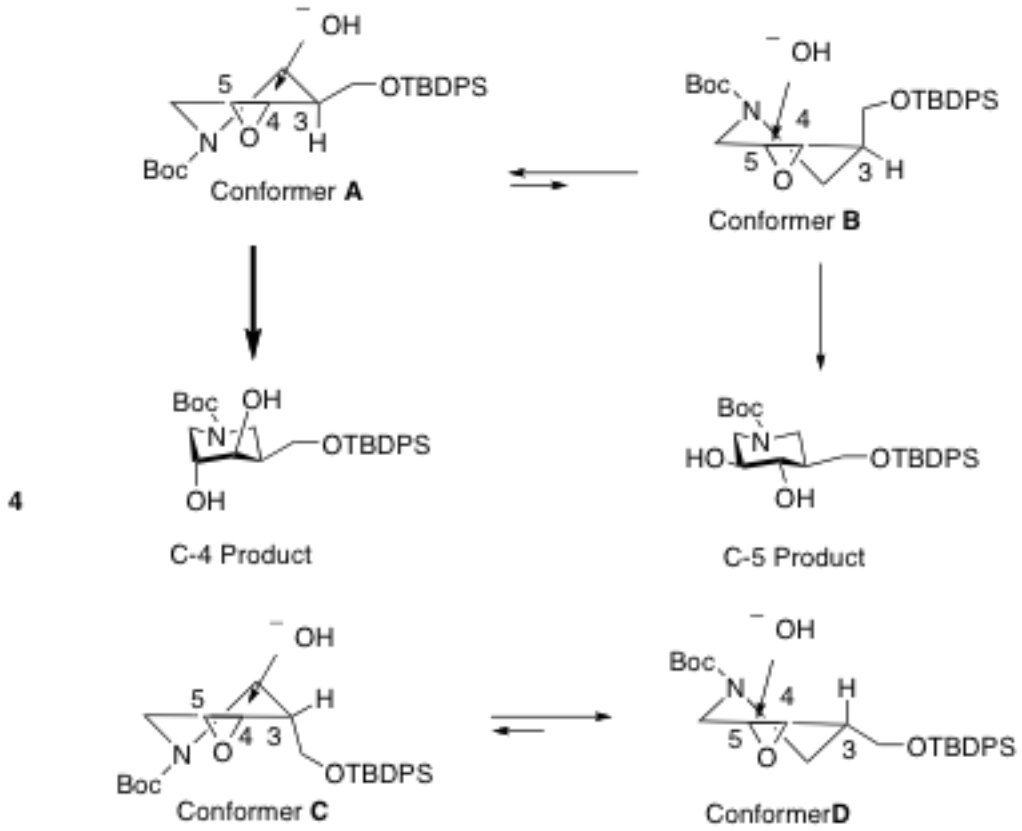


Scheme 15. (a) *n*-BuLi, *n*-pentane, -80 °C. (b) (i) cat. OsO_4, NMO, acetone. (ii) 10% HCl, 1,4-dioxane, reflux, (iii) NH_4OH (c) i) OsO_4-TMEDA complex, CH_2Cl_2. (ii) *c.* HCl, MeOH. (iii) NH_4OH

We next set out to synthesize **41** and **57** from the *O*-TBDPS protected intermediate (*R*)-**58**. The silylation of (*R*)-**54** followed by epoxidation was attempted. Thus, the dioxirane, generated *in situ*[59] from Oxone by treatment with 1,1,1-trifluoroacetone was reacted with (*R*)-**58** to give the *anti* epoxide **59** and the *syn* epoxide **60** in 52% and 34% yields, respectively, which were tentatively assigned based on steric considerations between the allylic substitutent of the six membered cyclic alkene and a substituent of dioxrane.[60] Subsequently, the basic cleavage of the epoxy ring of **59** was accomplished using a mixture of KOH/1,4-dioxane/H_2O at reflux followed by a sequence of deprotection with 6 N HCl and desalting to give **41** and **57**, 28% and 62% yields, respectively (Scheme 16). The regiochemistry of the nucleophilic opening of the epoxide on a six-membered ring is mainly subject to *trans* diaxial opening (Fürst-Plattner rule). Consequently, this regioselectivity would result, if the opening proceeded through the two possible half chair conformations (**A** and **B**). A substituent at C-3 would be preferentially located in a pseudoequatrial orientation compared with a pseudoaxial substituent. Thus, the somewhat preferential attack of the hydroxide anion at C-4 through conformer **A** would occur by *trans* diaxial opening. On the other hand, a similar reaction using **60** somewhat preferentially gave **41** (53%) together with **57** (37%). On the basis of the above reasoning, the existence of conformer **D** would be major species and conformer **C**, the minor species (Scheme 17).



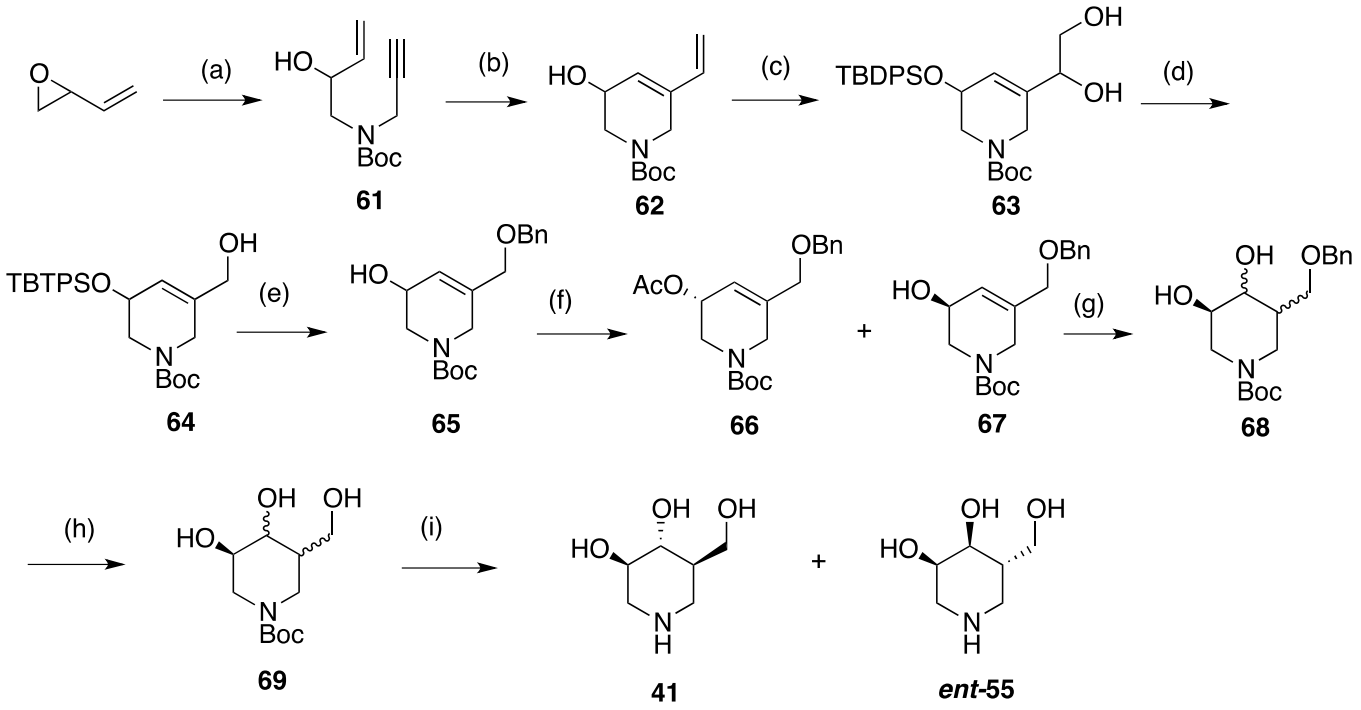
Scheme 16. (a) TBDPSCl, imidazole, cat. DMAP, CH_2Cl_2. (b) Oxone®, CF_3COMe, $NaHCO_3$, aq Na_2EDTA, MeCN, 0 °C. (c) (i) 0.3 M KOH, 1,4-dioxane, (ii) NH_4OH



Scheme 17. Basic cleavage of epoxide

In addition, four enantiomers of **41**, **55**, **56**, and **57** were prepared from (*R*)-**43** according to the above described procedure.

An interesting acceleration effect of an allylic hydroxy group on ring-closing enyne metathesis has been recently found by us.[41] Ring-closing enyne metathesis of terminal alkynes with an allylic hydroxy group

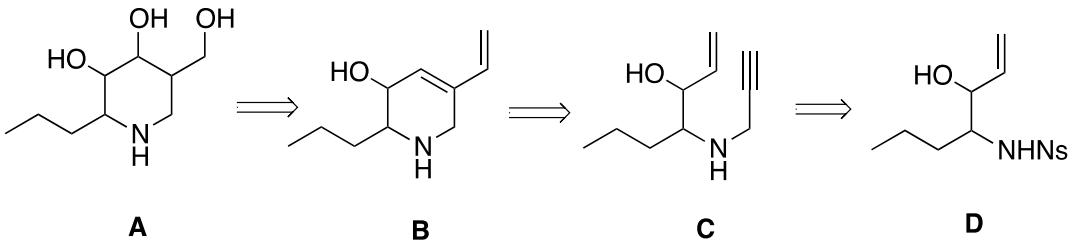


Scheme 18. (a) (i) propargylamine, cat. H_2O, 100 °C. (ii) Boc_2O, NaOH, 1,4-dioxane/H_2O, rt (b) Grubbs' 1st catalyst, CH_2Cl_2, rt. (c) (i) TBDPSCl, imidazole, cat. DMAP, CH_2Cl_2, ii) AD-mix-α®, methanesufonamide, *tert*-BuOH/H_2O, (d) (i) $NaIO_4$, EtOH/H_2O, rt. (ii) $NaBH_4$, EtOH/H_2O. (e) (i) NaH, BnBr, cat. Bu_4NI. (ii) TBAF, THF, rt. (f) lipase PS-C, vinyl acetate, diisopropyl ether, 30 °C. (g) (i) BH_3·THF, THF, 70 °C. (ii) 3 M NaOH, 30% H_2O_2, THF, rt. (h) H_2, Pd/C, MeOH, rt, (i) (i) 10% HCl, dioxane reflux. (ii) NH_4OH

proceeded smoothly without ethylene atmosphere, which is generally necessary to promote the reaction. Utilizing this efficient ring-closing enyne metathesis based on the acceleration effect of an allylic hydroxy group, the synthesis of (+)-isofagomine was achieved (Scheme 18). The enyne substrate with an allylic hydroxy group, **61**, was synthesized by means of an addition reaction between propargyl amine and butadiene monoxide followed by protection of the imino group with a *tert*-butoxycarbonyl (Boc) group (71% for 2 steps). The allylic hydroxy group-accelerated ring-closing enyne metathesis (AHA-RCEM) of **61** efficiently gave the cyclic product **62** (>99%) in a short reaction time. The hydroxyl group of **62** was then protected with a *tert*-butyldiphenylsilyl (TBDPS) group (99%). The TBDPS-protected product was treated with AD-mix-α®. The highly regioselective dihydroxylation of the terminal olefin proceeded to provide diol **63** (78%). Oxidative cleavage of the diol **63** with $NaIO_4$ followed by reduction with $NaBH_4$ gave the allyl alcohol **64** (98% in 2 steps). Protection of the hydroxy group of **64** with a benzyl group (92%) and subsequent deprotection of the TBDPS group (98%) gave the benzylated product **65**. The kinetic transesterification of **65** with vinyl acetate using lipase PS-C permitted the excellent resolution of

the enantiomers, giving almost enantiomerically pure **67** (46%, 99% ee) together with acetate **66**. Hydroboration of the internal olefin of **67** followed by oxidation with $NaOH/H_2O_2$ afforded diol **68** (67% for 2 steps). After both deprotection of the benzyl group (99%) and the Boc group, (+)-isofagomine (**41**) (78%) and (-)-3-*epi*-isofagomine (*ent*-**55**) (20%) were obtained. (+)-Isofagomine was synthesized in 11.5% total yield from commercially available 1,3-butadiene monoxide.

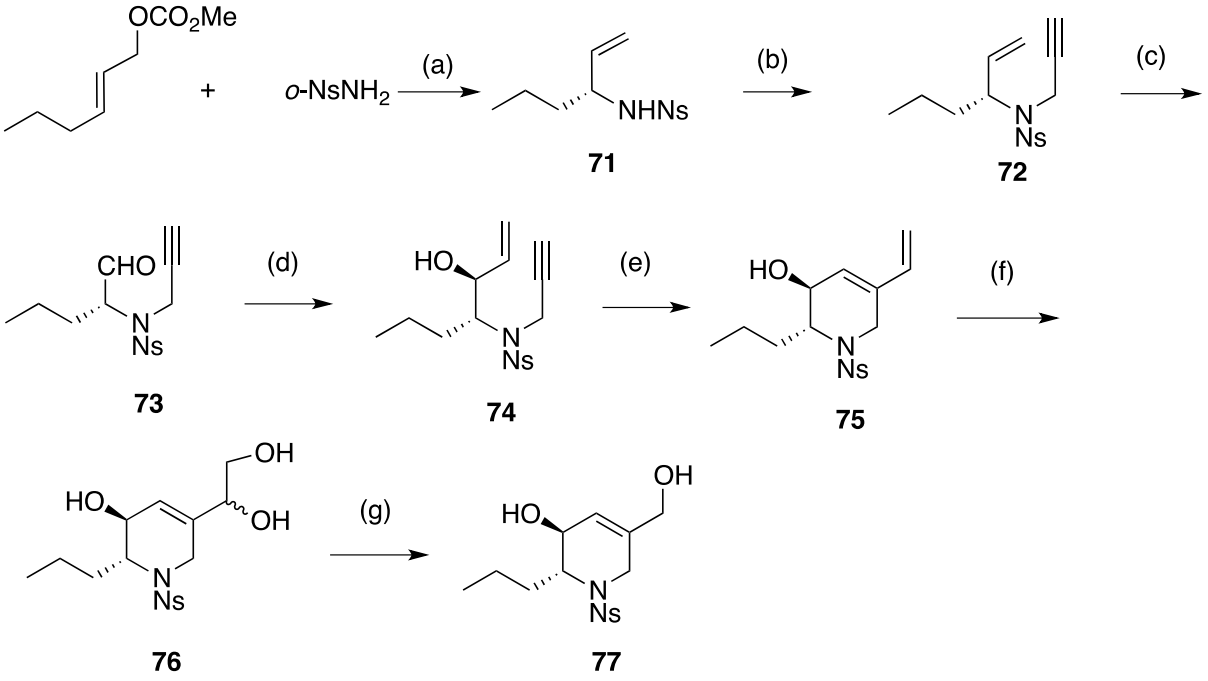
Our attention was next focused on the synthesis of 2-propylisofagomine **70** using allylic hydroxy group accelerated ring-closing enyne methasesis, since the synthesis of 2-alkyl isofagomines remains unexplored.[61] Our strategy for the synthesis of 2-propylisofagomine is outlined in Scheme 19, which shows that the desired iminosugars **A** can be produced from the cyclic diene **B** by an operation similar to that described above. The piperidene core could be prepared by the AHA-RCEM of the terminal alkyne **C** as a key step. Hence, we began with a synthesis of the precursor **C**, which is available from the known chiral *N*-nosyl allylic amine **D** (Scheme 19).



Scheme 19. Retrosynthesis of 2-propylisofagomines

In initial experiments, an asymmetric allylic amination between *N*-(*o*-nosyl)amine and carbonate provided *N*-hexenylnosylamide **71** in 82% yield with 94% ee using the procedure reported by Weihofen *et al*.[62] The propargylation of **71** with propargyl bromide in the presence of potassium carbonate gave the acetylene product **72** in quantitative yield, which, on ozonolysis, afforded the aldehyde **73** in 88% yield. The vinylation of **73** with vinylmagnesium chloide in THF at –78 °C proceeded stereoselectively to give the allyl alcohol **74** as a single diastereomer in 66% yield. Although the stereochemistry of **74** remains unclear in this stage, we tentatively concluded that it is 3*S*,4*R* in the light of the Felkin-Anh model. Having the precursor **74**, the AHA-RCEM of **74** was carried out using Grubbs' 1st catalyst (10 mol %) as a catalyst at room temperature in a short reaction time to afford cyclic diene **75** in 85% yield. Treatment of **75** with AD-mix-β® as a bulky oxidant resulted in the highly regioselective dihydroxylation of the terminal olefin to provide diol **76** (81%). Oxidative cleavage of the diol **76** with $NaIO_4$, followed by reduction with $NaBH_4$, gave the allyl alcohol **77** (94% over two steps) (Scheme 20). At this stage, the

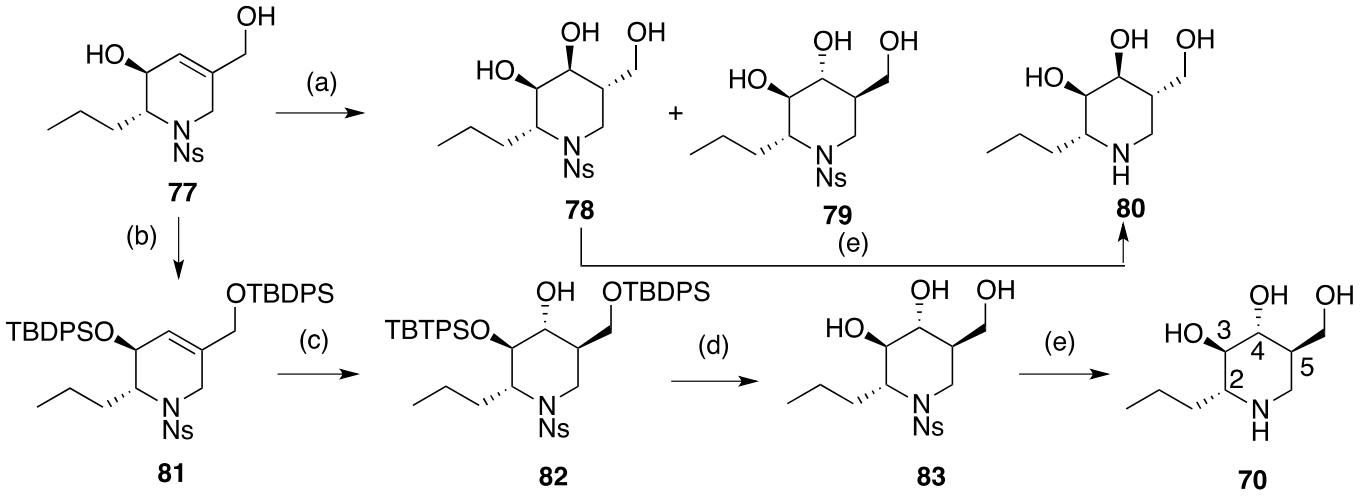
stereochemistry of **77** was determined to be *2R,3S*, by an X ray crystallographic analysis of the di-*p*-nitrobenzoate of **77**.



Scheme 20. (a) 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD), cat. $[Ir(COD)Cl]_2$, (*S,S,S*)-(+)-(3,5-dioxa-4-phosphacyclohepta[2,1-3,4-*a*']dinaphtalen-4-yl)bis(1-phenylethyl)amine, Et_3N, THF. (b) propargyl bromide, K_2CO_3, MeCN. (c) O_3, Me_2S, CH_2Cl_2. (d) vinylmagunesium chloride, THF. (e) cat. Grubbs'1st, CH_2Cl_2. (f) AD-mix-β®, *tert*-BuOH-H_2O. (g) (i) $NaIO_4$, EtOH-H_2O. (ii) $NaBH_4$, EtOH-H_2O

With **77** in hand, we attempted to hydroxylate the 4 position of **77** by hydroboration followed by oxidation. The olefin **77** was treated with a BH_3·THF complex (6 equiv.) at room temperature for 13 h, followed by oxidation with 3M NaOH and 30% H_2O_2 to give a separable mixture of triols **78** and **79** in 72% yield. Unfortunately, the ratio of the two diastereomeric triols was about 1:1 with no selectivity. We concluded that **78** was produced *via* transition state **A** with chelation between the hydroxy group at the 3 position and the borane reagent. Therefore, we hypothesized that the hydroboration of a protected silyl ether **81** could preferentially produce the desired isomer via transition state **B** due to steric repulsion between the boron reagent and the bulky *O*-silylated group (Figure 6). In practice, the hydroboration-oxidation of **81** produced the expected product **82** as a single isomer in 60% yield. Removal of the TBDPS groups by treatment with TBAF smoothly furnished the triol **83** in 96% yield. Finally, deprotection of the Ns group with benzenethiol in the presence of K_2CO_3 gave the desired 2-propylisofagomine **70** in 82% yield. Since a nuclear Overhauser effect (NOE) was observed between axial hydrogens at the 2 and 4 positions and also between axial hydrogens at the 3 and 5 positions, the

stereochemistry of **70** was confirmed to be 2*R*,3*R*,4*R*,5*R*. In addition, **78** was transformed by denosylation into **80** in 90% yield. Thus, 2-propylisofagomine **70** was stereoselectively prepared from the carbonate in 13% overall yield using AHA-RCEM as the key step.



Scheme 21. (a) (i)BH_3·THF, THF. (2) 3M NaOH, 30% H_2O_2, 37% for **78**, 35%, for **79**. (b) TBDPSCl, imidazole, DMAP, CH_2Cl_2. (c) (i) BH_3·THF, THF. (ii) 3M NaOH, 30% H_2O_2. (d) TBAF, THF. (e) benzenethiol, K_2CO_3, MeCN, 82% for **70**, for 90% for **80**

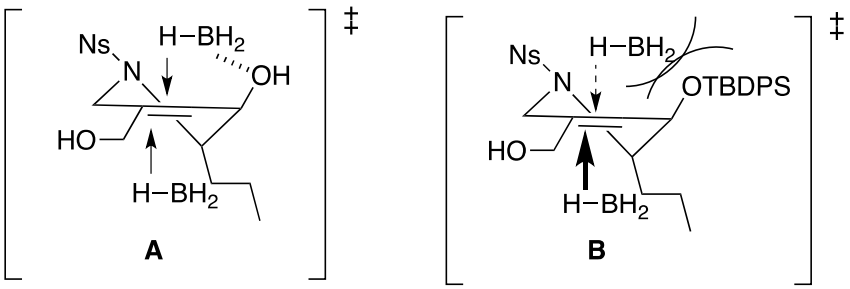


Figure 6. Transition state in the hydroboration of **77** and **81**

SUMMARY

In summary, we report herein on the synthesis of both enantiomers of iminosugars such as fagomine, 1-deoxynojirimycine, and isofagomine accompanied by their congeners. Although systematic studies of their glycosidase inhibitory activities are not described in this review, some quite interesting results have been observed.[63] In addition, 1-*C*-alkyl-L-arabinoimonofuranoses, potential α-glucosidase inhibitors, were prepared and have potential for use in the treatment of type 2 diabetes.[64]

ACKNOWLEDGEMENT

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